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Common comorbidities and survival in MS: Risk for stroke, type 1 diabetes and infections

Annukka Murtonen, MD[1], Samu Kurki, PhD[2], Katariina Hänninen, BM[3], Merja Soilu-Hänninen, MD[3], PhD, Marja-Liisa Sumelahti, MD, PhD[1]

[1] University of Tampere, 33014- TaY, Finland and Tampere University Hospital, Department of Neurology, PL 2000,33521 Tampere, Finland.
Murtonen.Annukka.S@student.uta.fi
[2]Auria Biobank, University of Turku and Turku University Hospital, PL 52, 20521 Turku, Finland.
Samu.Kurki@tyks.fi
[3]Turku University Hospital, Division of Clinical Neurosciences and University of Turku, PL 52, 20521
Turku, Finland
Katariina.Hanninen@utu.fi
Merja.Soilu-Hanninen@tyks.fi

Address for correspondence:
Marja-Liisa Sumelahti
e-mail: Marja-Liisa.Sumelahti@uta.fi.
Postal address: Arvo, 33014 SF-University of Tampere.
Tel. +358 40 587 4149

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1. Introduction

Multiple sclerosis (MS) is a progressive autoimmune disease causing disability and premature mortality. Pathologically MS is characterized by inflammation, demyelination and neurodegeneration in the central nervous system (CNS). (1) Other mechanisms in CNS include changes in vascular perfusion, activation of microglia and intracerebral vascular changes like blood-brain barrier leakage. (2,3)

Autoimmune disorders, infections and circulatory diseases are common in MS population. (4,5,6) Several disorders in these disease groups affect brain and the nervous system in MS, such as cardio- and cerebrovascular diseases, hypertension and diabetes. (7)

There is a risk for premature mortality in MS (8,9) and the major cause of death are infections. It is increasingly recognized that the common causes of death observed in general population are present also in MS, such as cardiovascular causes and stroke (8-11). At the same time findings regarding the prevalence of several vascular comorbidities in MS are conflicting (12). An almost two-fold increased risk for cerebrovascular comorbidity and a significant risk for cardiovascular comorbidity after MS onset has been recently reported (13). This observation has raised a question of converging causal pathways of the coexisting diseases and a need to study the effects in a broader spectrum of comorbidities in MS. Vascular aspects in MS are thus recognized and the reported risk may be explained on basis of the inflammatory and vascular mechanisms present in both MS and circulatory diseases, in addition to suspected effect of shared genetic and life-style risk factors. (14, 15)

Our study bases on these observations and hypotheses. We studied the age- and gender adjusted risk for circulatory diseases in an MS population diagnosed and followed-up in a large university hospital district in Southwest Finland. We focused on ischemic cerebro- and cardiovascular diseases and related disorders, diabetes and acute and chronic infections. An established public health care system and population registers in Finland form a reliable basis in our survey. By access to administrative and patient specific data from the Hospital District of Southwest Finland we studied the coincident risk and survival effect for circulatory diseases

and related comorbidities in MS, to assess the need of preventive actions and practical treatment strategies.

2. Materials and methods

This study was registered and approved by the Turku Clinical Research Center, Finland. Ethical committee approval was obtained from the joint Ethics Committee of the Tampere University and Pirkanmaa Hospital District, Finland.

For data mining, we used the administrative Clinical Data Repository of the University Hospital of Turku containing electronic health records at the Hospital District of Southwest Finland. These are collected directly and retrospectively monthly from the operational patient data systems from the central and university hospitals of the region by using ICD-10 codes (International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-WHO Version for 2016) from 1.1.2004 to 31.12.2012.

All resident cases with MS (ICD-10 code G35) were included. The catchment of data concerned both alive and deceased MS patients followed from 1.1.2004. Case ascertainment followed the initial data mining by scrutiny of each patient document by author K.H. to meet the study inclusion criteria of definite MS by McDonald criteria (16). Patient documents of the confirmed MS cases with diagnoses for cardiac (acute myocardial infarct I21), ischemic stroke (cerebral infarct, I62) and other vascular diseases of the brain were next scrutinized by the authors (M-L.S, A.M, M.S-H) for diagnostic ascertainment, including information on paraclinical diagnostics (date and results of brain CT or MRI scans, ECG and specific laboratory results). The ICD codes for causes of death among the deceased MS cases were collected from the patient records. Comorbidities diagnosed both before and after the date of diagnosis of definite MS were included in the analysis.

Confirmed MS cases in this nested case control study were gender- and age matched to controls drawn from the same population cohort. A 10-fold gender- and age (based on birth year) -matched control population was randomly chosen from the CDR patient pool and another

separate age- and gender-matched 10-fold control population was used to verify the stability of the results in the district.

All ICD-10 codes for each hospital visit were available for MS and control cases residing in the catchment area from 1.1.2004 to 31.12.2012. We collected data for ICD codes I06-I71 in Diseases of Circulatory Disease group, Chapter IX, I00-I71 and for other specific diagnoses under the study irrespective of time or age at each diagnosis. Dates of death were available from CDR.

2.1. Statistical analyses

Kaplan-Meier (KM) survival analysis was applied to study the mean survival times. A separate KM analysis was performed to study the effect of CD morbidity (I00-I71 codes). Significance was assessed by log-rank test.

The odds ratios, OR's, were calculated with 95% confidence intervals (95% CI) and p-values were calculated using Pearson's χ^2 test. All statistical tests were two-tailed and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using R Statistics version 3.0.2 with standard packages.

3. Results

A total of 1074 confirmed MS cases, 315 men and 759 women, were identified in a population of 472 139. The distribution of prevalent cases in 2004 and new incident cases from 2004 to 2012 by sex and age at entry is shown in Table 1. The date of entry is the first hospital visit due to any cause.

During the follow-up death in MS occurred in 5.9% (n 70, 34 women and 36 men). The main cause of death was infections (n 38, 54.3%). Other specific causes in the circulatory diseases group (n 5, 7.1%) were one case of acute myocardial infarct, four cases of ischemic stroke and one case of subarachnoid haemorrhage. Causes in other disease groups were respiratory insufficiency (n 6, 8.6%), cancer (n 3, 4.3%) and intoxication (n 2, 2.9%). The rest of the death causes represented other causes of death (n 16, 22.9%).

The mean survival time in MS was 82.4 years compared to 85.6 years in the age and gender matched control population, difference was statistically significant (KM log rank p <0.001), KM curve shown in Figure 1.

The MS prevalence in 31.12.2012 was 212.6 / 10^5 (95% CI 199.5-225.8), 121.4 (114.5-128.4) for men and 258.3 (247.9-268.6) for women (17).

The diagnosed concomitant circulatory system diseases in ICD I06-I71 at any point of disease trajectory including death during the follow-up in 2004-2012 were included in the second KM analysis shown in Figure 2. The risk related to circulatory disease diagnoses in MS was statistically significant, log rank p<0.001: the mean survival time among MS cases with circulatory diseases was 79.5 years and without circulatory diseases 85.4 years. Survival among controls was 85.6 years. The odds ratios (OR) concerning MS and control cases in specific circulatory diseases ICD- groups I06-I71 (n=340) are shown in the additional data.

The number of MS, age- and gender matched control cases and OR's for specific circulatory diseases diagnoses are presented in Table 2. An almost 50% greater risk for ischemic cerebral infarct in MS (n 25), OR 1.49 (95% CI 1.03-2.35), was statistically significant. A statistically significant and over two-fold risk was observed also for other strokes (n 9) including both subarachnoid and intracerebral haemorrhages: OR 2.5 (1.24-5.06). Acute myocardial infarct (n 18, 1.85%) showed no increased risk in MS, OR was 1.49 (0.91-2.43). Diagnoses with other

cerebrovascular diseases by code I67 (n 9) and sequelae of cerebrovascular disease I69 (n 18) may overlap the acute stroke diagnoses why they were assessed separately. Respective OR's were high, 2.5 (1.24-5.06) and 1.73 (1.06-2.83).

Ischemic stroke (cerebral infarct, I63) was confirmed either as a comorbid diagnosis (n 21) or an immediate cause of death (n 4). Case ascertainment was based on findings in CT scan or MRI in 92% (23/25 cases), location was mainly parietal in middle artery region (n 11), posterior (n 6) and subcortical (n 6). Female to male ratio was 0.79 (11/13 cases). Mean age at cerebral infarct was 69.5 years, median 69 years (SD 10.58), 71.6/71 years (SD 9.93) for women and 67.86/67.5 years (SD 11.15) for men (χ^2 p=0.23, statistically nonsignificant). All cases in I67 (subarachnoid and intracerebral haemorrhage) were radiologically confirmed. Diagnosis of acute myocardial infarct ~~diagnosis~~ based on ECG and blood tests.

The number of MS, age- and gender matched control cases and OR's for common circulatory disease related risk factors are presented in Table 3. Type 1 diabetes showed a two-fold risk, OR 2.1 (1.3-3.36). A statistically nonsignificant risk was observed for type 2 diabetes, transient ischemic attack (TIA), atrial fibrillation, other cardiac arrhythmia, hypertension, hyperlipidaemia and obesity in MS.

The number of MS, age- and gender matched control cases and OR's for a number of acute and chronic infections are presented in Table 4. with detailed results. The coincident risk for the hospital treated infections showed an increased risk for urinary, respiratory and periodontal infections in MS.

4. Discussion

The lower mean survival time of 82.4 years in MS compared to 85.6 years in the control population was statistically significant. However, life expectancy was reduced much less than in earlier studies showing 6-7 years shorter life expectancy in MS (8, 9, 18). This supports improved survival in patient cohorts from the era of disease modifying therapies and is in line with the

recent study from Norway showing a near normal standardised mortality ratio in the patient cohort monitored from 1997 to 2012 (18).

The high mortality of cerebrovascular diseases in the Finnish general population (19) was here shown to concern also the MS population. Result supports the Danish study (5) and corroborates survival disadvantage reported for cerebrovascular diseases among MS patients. (10-13) Survival disadvantage related to circulatory disease comorbidity was significant in our study. The mean survival time was lower for MS cases with any circulatory diseases related diagnosis in ICD-10 I06-I71 group, 79.5 years, in comparison with the 85.4 years in MS patients without it. The specific risk for the common risk factors for these diseases, such as hypertension, hyperlipidaemia or cardiac disorders and arrhythmias, were low also in our MS population (20) along with other risk factors for ischemic stroke, except for type 1 diabetes.

MS patients were followed up during a 9-year period in 2004-2012. The catchment area in the Hospital District of Southwest Finland represents a high-risk region of MS, where prevalence was $212/10^5$ in 2012. (17) MS cohort originated from an administrative database and after confirmation of MS diagnosis 9.6% of cases were excluded, which amount is similar to other reports using administrative catchment. (5, 20) Patient records were examined for confirmation of MS, ischemic brain and myocardial infarcts and for causes of death, why we believe to have reliable data for the statistical assessment concerning these diagnoses. The diagnosis of type 1 diabetes was considered reliable in this population due to regular hospital controls.

Strength of our study is the public health care system, where health care is available for all Finnish citizen and an equal treatment practice is followed. The national and hospital registers in Finland base on personalized identification code and are regarded reliable. The administrative health registry covers almost the entire population of the study region and provides objective data avoiding bias related to patient recall. MS is diagnosed and treated by neurologist in central and university hospitals why we believe to have a representative sample of MS patients from a large hospital district. A 10-fold sample of the general non-MS population ensure that study observations reflect general patterns of co-occurrence of health problems among MS patients, which may not be accurate in small clinical samples, due to sampling, or referral biases.

We observed an increased risk for circulatory diseases in MS population as compared to age- and sex matched control population during the follow-up. Evidence that autoimmunity may play an

essential role in the pathogenesis of atherosclerosis (21) is supported by reports on increased risk for cerebro- and cardiovascular disorders in several immune-mediated diseases, such as MS (22), rheumatoid arthritis (23, 24) and type 1 diabetes (25). These results suggest that these inflammatory diseases may share pathological links with cerebrovascular diseases. However, although inflammation is shown to contribute to stroke risk (26), other typical risk factors may be absent in MS. (25, 27) This view was supported by observations in our data, as other common cerebrovascular risk factors, such as TIA, atrial fibrillation and other arrhythmias, showed no increased risk, nor was there any risk for secondary hypertension, hyperlipidaemia or obesity. Result differs from observations in rheumatoid arthritis and type 1 diabetes populations, where several common risk factors exist, but corroborates observations in other MS populations where prevalence of diabetes, hypertension, and hyperlipidaemia have been similar to rates in general population. (20)

Given the observation of increased risk for stroke, which is diagnosed in hospital, and the low comorbidity for some of the most common vascular disease risk factors, our results are discordant but in accordance with other studies. (20) Limitation in our study population however concerns the catchment of these risk diagnoses from the tertiary care hospital data, as most of these conditions are recognized and treated mainly in the primary care. It also remains unknown to what content the observed circulatory disease risk is related to metabolic syndrome in MS, a question which has remained open also in other studies addressing this relation and the increased risk of obesity or changes in body composition, hypertension, dyslipidaemia or type II diabetes in MS (27). Although administrative data are considered a valid means of tracking diabetes, hypertension, and hyperlipidaemia in MS (27) the so far inconclusive results from hospital data regarding common circulatory disease risk factors in MS as shown here could be elaborated by linkage to other databases and primary care data.

Respiratory infections were the major cause of death and the high rates of acute and chronic respiratory, urinary and periodontal infections were present also in our MS cohort. (8, 11, 28) Acute and chronic infectious diseases are related to risk of stroke (29) and infections may be a specific risk factor in MS population. There is a connection between the immunological and vascular factors (30), which supports the suggested hypothesis on the shared inflammatory mechanisms in MS and ischemic stroke (31). The control of inflammation and infections appear as important modifiable factors in MS related circulatory disease risk. Evidence from observational studies shows that vaccination against influenza is associated with a reduced risk

of stroke, myocardial infarction and all-cause mortality. (32) The preventive seasonal and H1N1 vaccines are safe and efficacious also among MS patients, nor is there any reduced response to vaccination against influenza associated to majority of immunomodulatory drugs used in MS. (33)

The independent coincident relative risk for type 1 diabetes in our MS population was high and corroborates results in other studies (34). In Finland, the incidence of both type 1 diabetes and MS are high (35). The autoimmune pathogenesis of MS and type 1 diabetes (6) as well as socioeconomic, environmental and latitude correlated factors may contribute to the predisposition of these immune-mediated diseases. The global and steep increase in both type 1 and 2 diabetes (36) and MS incidences recorded in the last half of the 1990's may be a serious signal of unhealthy changes in the environment and life style. These may affect the penetrance of disease susceptibility genes in autoimmune diseases and may also be involved in the high circulatory disease risk observed in MS and type 1 diabetes in Finland. The modifiable risk factors in type 1 diabetes, MS and circulatory diseases include childhood obesity and smoking. (37)

MS patients today expect a longer survival. The long disease trajectory combines an increased risk for comorbidities common in the general population, as shown here for ischemic stroke risk along with other studies. Consistent with other reports, limitation for information regarding circulatory disease mortality related life-style factors here concerns the lack of socioeconomic and lifestyle information in MS cohorts. At the moment, we have no information on the changes in occupational status, medication, weight, serum lipid status or on individual lifestyle factors such as smoking, dietary habits, physical activity or health behaviour in general, but evidence on accumulating comorbidity risk in MS supports the importance of dealing with these factors. Life style interventions are justifiable as the key findings in comorbidity studies in MS have been association of life-style related type 2 diabetes, hypertension, dyslipidaemia or peripheral vascular disease at any point in the disease course with a greater progression in disability. (20) These factors may add to complex risk for circulatory diseases in MS and have implications for prevention and treatment in the recognized risk groups. Disadvantages in administrative databases such as ours include the lack of structured data on life style factors. We expect to expand the information in our databases in the future with the application of text mining tools to patient reports and linkage to other governmental health registries such as the medication reimbursement registry of social insurance institution of Finland.

The immortal time bias is a limitation for inferences in cohort and case-control study designs, however a nested case-control analysis as chosen here, and matching by age and sex, may be much less susceptible to selection bias than the other approaches since controls are known to represent the source population that gave rise to the cases and the analysis can include all the cases from the source population. (38) This analytical technique has not only been shown to provide an unbiased estimate of the hazard ratio that would be obtained from a traditional time to event analysis of the full cohort (39, 40, 41) and its inherent time dependent nature means that it is also free of immortal time bias.

In conclusion, the overall survival advantage in MS was related to lack of circulatory disease diagnoses at any point during the follow-up. Further knowledge on influences of comorbidities on the course and outcome of MS is important for better clinical care and optimized life style interventions in the individual patients.

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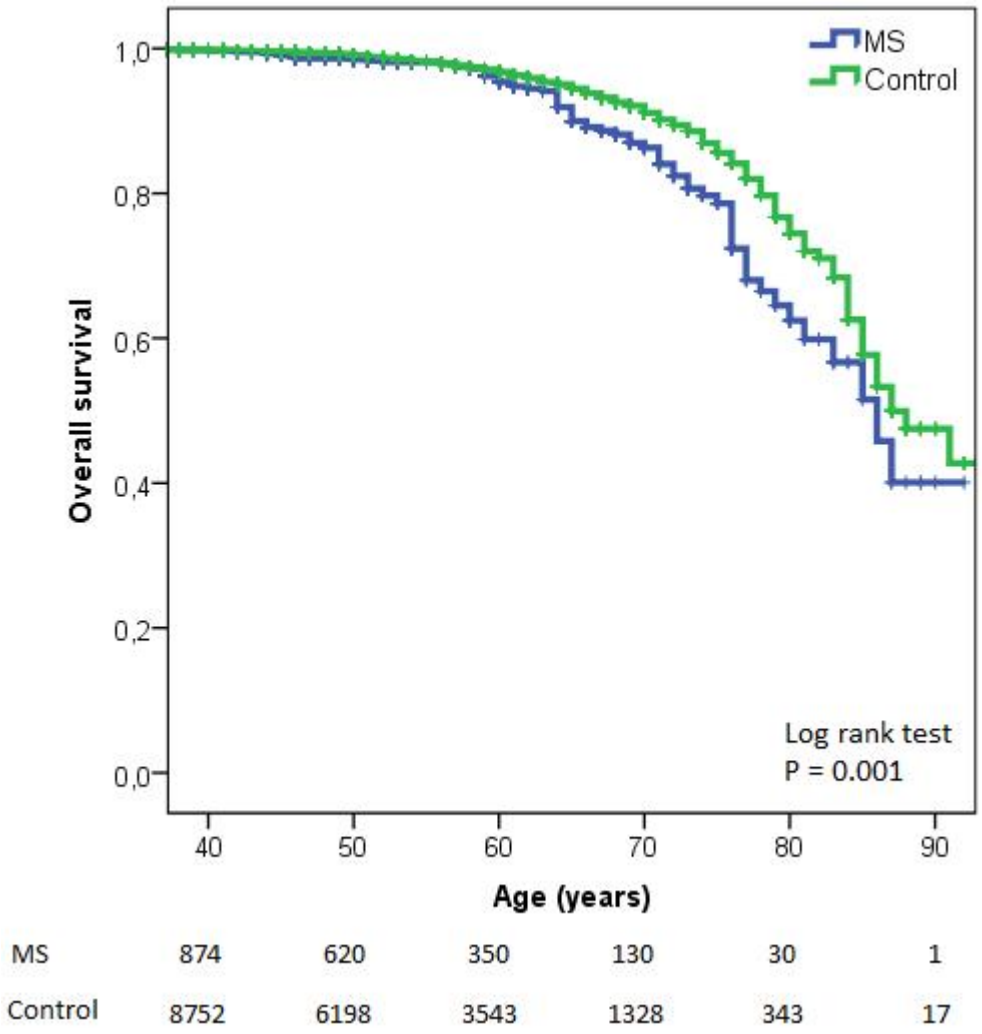

Figure 1. Kaplan-Meier survival curve from birth up to end of follow-up or at the point of death due to any cause for MS and age- and gender matched control cases. MS cases were enrolled from 1.1.2004 to 31.12.2012 in the Hospital District of Southwest Finland. The numbers below refer to the number of cases in each group that are still part of the follow-up at that time and have not experienced an event.

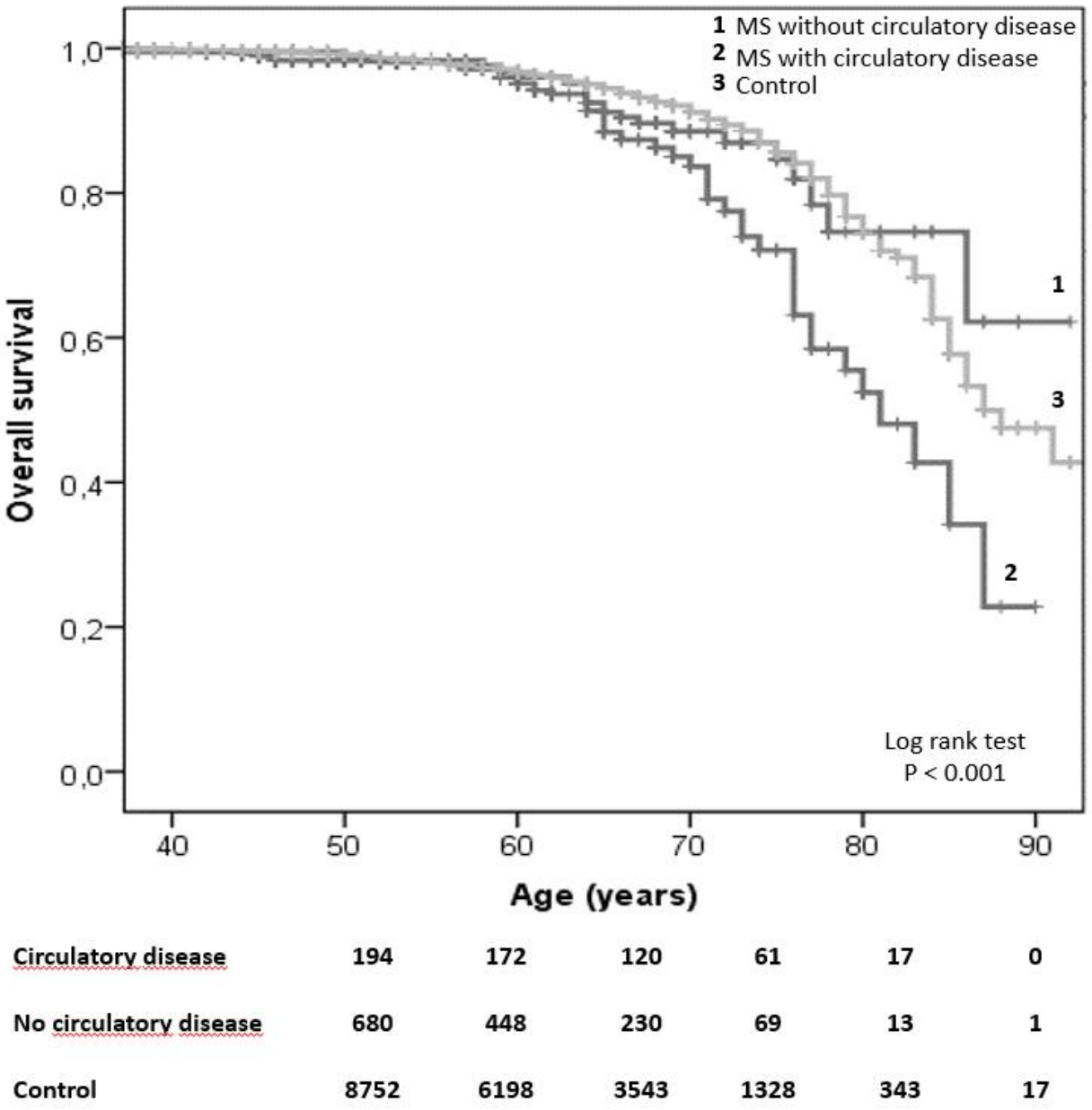

Figure 2. Kaplan-Meier survival curve for MS cases with and without circulatory disease diagnosis and for the age- and gender matched controls from birth up to end of follow-up or at the point of death due to any cause. Cases were enrolled from 1.1.2004 to 31.12.2012 in the Hospital District of Southwest Finland. The numbers below refer to the number of cases in each group that are still part of the follow-up at that time and have not experienced an event.

Table 1. Number, mean age and standard deviation (years) at enrollment from 1.1.2004 to 31.12.2012 among the 1074 MS cases (ICD-10 G35) by gender in the Hospital District of Southwest Finland.

Female				Male			
Year of entry	Mean age	Std dev	Number of cases	Year of entry	Mean age	Std dev	Number of cases
2004	44.6	12.0	212	2004	47.7	13.8	111
2005	46.8	13.2	159	2005	50.3	14.1	53
2006	44.4	12.7	79	2006	48.2	14.4	34
2007	42.6	14.3	50	2007	49.2	14.5	26
2008	45.4	15.7	61	2008	42.7	13.1	33
2009	44.9	17.6	52	2009	45.1	13.9	18
2010	48.7	14.2	49	2010	49.1	15.1	14
2011	41.9	14.5	52	2011	45.9	15.1	16
2012	45.9	18.5	45	2012	49.6	18.6	10
Total	44.9	13.8	759	Total	47.5	14.1	315

Table 2. The number, percentage and coincident odds ratio (OR) with 95% confidence interval (CI) for the diagnosed and confirmed cases in acute myocardial infarct, cerebral infarct and other vascular disease of the brain for MS cases compared to age- and gender matched control cases from 1.1.2004 to 31.12.2012 in the Hospital Distict of Southwest Finland.

ICD-10 code	Disease	MS (n)	%	Controls (n)	%	OR	95% CI
I21	Acute myocardial infarct	18	1.7	121	1.1	1.49	0.91 – 2.43
I63	Cerebral infarct	25	2.3	161	1.5	1.55	1.03 – 2.35
I67	Other vascular disease of the brain	9	0.8	36	0.3	2.50	1.24 – 5.06

Table 3. The number, percentage and coincident odds ratio (OR) with 95% confidence interval (CI) for the common circulatory diseases diagnosed in hospitals for MS cases compared to age- and gender matched control cases from 1.1.2004 to 31.12.2012 in the Hospital Distict of Southwest Finland.

ICD-10 code	Disease	MS	%	Controls	%	OR	95% CI
G45	TIA	12	1.1	136	1.3	0.88	0.49-1.59
I48	Atrial or fibrillation or flutter	18	1.7	350	3.3	0.51	0.33-0.81
I49	Other cardiac arrythmia	18	1.7	189	1.8	0.95	0.59-1.54
I10	Essential hypertension	93	8.7	1034	9.6	0.90	0.74-1.10
I70	Atherosclerosis	12	1.1	102	1.0	1.18	0.65-2.13
E10	Type I diabetes mellitus	20	1.9	95	0.9	2.11	1.32-3.36
E11	Type II diabetes mellitus	39	3.6	391	3.6	1.00	0.72-1.38
E78	Hyperlipidemia	17	1.2	336	3.1	0.51	0.32-0.81
E66	Obesity	21	2.0	328	3.1	0.64	0.42-0.99

Table 4. The number, percentage and coincident odds ratio (OR) with 95% confidence interval (CI) for common acute and chronic infections diagnosed in hospital for MS cases compared to age- and gender matched control cases from 1.1.2004 to 31.12.2012 in the Hospital Distict of Southwest Finland.

ICD -10 code	Disease	MS (n)	%	Controls (n)	%	OR	95% CI
N10	Acute pyelonephritis	88	8.2	116	1.1	7.59	6.01 - 9.57
J22	Unspecified acute lower respiratory infection	7	0.7	10	0.1	7.0	3.06 - 16.03
N30	Cystitis	81	7.5	116	1.1	6.98	5.48 - 8.89
J41	Simple and mucopurulent chronic bronchitis	4	0.4	7	0.1	5.71	1.93 - 16.92
A41	Other sepsis	29	2.7	62	0.6	4.68	3.14 - 6.97
J18	Pneumonia, unspecified organism	100	9.3	297	2.8	3.37	2.73 - 4.15
K02	Dental caries	25	2.3	90	0.8	2.78	1.82 - 4.24
J20	Acute bronchitis	25	2.3	102	0.95	2.45	1.61 - 3.73
K05	Gingivitis and periodontal diseases	23	2.1	101	0.94	2.28	1.47 - 3.53
A04	Other bacterial intestinal infections	14	1.3	62	0.6	2.26	1.29 - 3.96
K08	Other disorders of teeth and supporting structures	18	1.7	86	0.8	2.09	1.28 - 3.43
L02	Cutaneous abscess, furuncle and carbuncle	15	1.4	77	0.7	1.95	1.13 - 3.35
A09	Infectious gastroenteritis and colitis, unspecified	29	2.7	164	1.5	1.77	1.20 - 2.60
J06	Acute upper respiratory infections of multiple and unspecified sites	41	3.8	237	2.2	1.73	1.25 - 2.39

ICD code	Disease	MS	%	Controls	%	OR	95% CI
I06	Rheumatic aortic valve diseases	1	0.09	6	0.06	1.67	0.21 - 13.52
I10	Essential (primary) hypertension	93	8.66	1034	9.63	0.90	0.74 - 1.10
I11	Hypertensive heart disease	2	0.19	35	0.33	0.57	0.14 - 2.33
I12	Hypertensive chronic kidney disease	1	0.09	3	0.03	3.33	0.40 - 28.10
I15	Secondary hypertension	7	0.65	23	0.21	3.04	1.36 - 6.79
I20	Angina pectoris	12	1.12	141	1.31	0.85	0.47 - 1.53
I21	Acute myocardial infarction	18	1.68	121	1.13	1.49	0.91 - 2.43
I22	Subsequent myocardial infarction	2	0.19	2	0.02	10.00	2.05 - 48.82
I23	Certain current complications following myocardial infarction	1	0.09	2	0.02	5.00	0.58 - 43.34
I25	Chronic ischemic heart disease	25	2.33	259	2.41	0.97	0.64 - 1.45
I26	Pulmonary embolism	11	1.02	52	0.48	2.12	1.12 - 3.99
I33	Acute and subacute endocarditis	1	0.09	4	0.04	2.50	0.30 - 20.75
I34	Nonrheumatic mitral valve disorders	5	0.47	63	0.59	0.79	0.32 - 1.96
I35	Nonrheumatic aortic valve disorders	4	0.37	65	0.61	0.62	0.23 - 1.67
I36	Nonrheumatic tricuspid valve disorders	1	0.09	4	0.04	2.50	0.30 - 20.75
I40	Acute myocarditis	1	0.09	6	0.06	1.67	0.21 - 13.52
I42	Dilated cardiomyopathy	2	0.19	26	0.24	0.77	0.18 - 3.22
I44	Atrioventricular and left bundle-branch block	6	0.56	42	0.39	1.43	0.61 - 3.34
I45	Other conduction disorders	6	0.56	41	0.38	1.46	0.63 - 3.42
I46	Cardiac arrest	1	0.09	4	0.04	2.50	0.30 - 20.75
I47	Paroxysmal tachycardia	9	0.84	84	0.78	1.07	0.54 - 2.12
I48	Atrial fibrillation and flutter	18	1.68	350	3.26	0.51	0.33 - 0.81
I49	Other cardiac arrhythmias	18	1.68	189	1.76	0.95	0.59 - 1.54
I50	Heart failure	19	1.77	124	1.15	1.53	0.95 - 2.47
I60	Nontraumatic subarachnoid hemorrhage	5	0.47	24	0.22	2.08	0.81 - 5.34
I61	Nontraumatic intracerebral hemorrhage	4	0.37	26	0.24	1.54	0.54 - 4.37
I63	Cerebral infarction	25	2.33	161	1.50	1.55	1.03 - 2.35
I67	Other cerebrovascular diseases	9	0.84	36	0.34	2.50	1.24 - 5.06
I69	Sequelae of cerebrovascular disease	18	1.68	104	0.97	1.73	1.06 - 2.83
I70	Atherosclerosis	12	1.12	102	0.95	1.18	0.65 - 2.13
I71	Aortic aneurysm and dissection	3	0.28	26	0.24	1.15	0.35 - 3.80

Additional table. The number, percentage and coincident odds ratio (OR) with 95% confidence interval (CI) for the ICD-10 circulatory disease diagnoses I06-I71 for the MS and age- and gender matched control cases from 1.1.2004 to to 31.12.2012 in the Hospital Distict of Southwest Finland.