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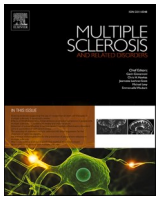

Association of age and disease duration with comorbidities and disability: A study of the Swiss Multiple Sclerosis Registry

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ABSTRACT

Background: While comorbidities increase with age, duration of multiple sclerosis (MS) leads to disability accumulation in persons with MS. The influence of ageing vis-a-vis MS duration remains largely unexplored. We studied the independent associations of ageing and MS duration with disability and comorbidities in the Swiss MS Registry participants.

Methods: Self-reported data was cross-sectionally analyzed using confounder-adjusted logistic regression models for 6 outcomes: cancer, type 2 diabetes (T2D), hypertension, cardiac diseases, depression, and having at least moderate or severe gait disability. Using cubic splines, we explored non-linear changes in risk shapes.

Results: Among 1615 participants age was associated with cardiac diseases (OR 1.05, 95% CI [1.02, 2.08]), hypertension (OR 1.08, 95% CI [1.06, 2.10]), T2D (OR 1.10, 95%CI [1.05, 1.16]) and cancer (OR 1.04, 95% CI [1.01, 1.07]). MS duration was not associated with comorbidities, except for cardiac diseases (OR 1.03, 95% CI [1.00, 1.06]). MS duration and age were independently associated with having at least moderate gait disability (OR 1.06, 95% CI [1.04, 1.07]; OR 1.04, 95% CI [1.02, 1.05], respectively), and MS duration was associated with severe gait disability (OR 1.05, 95% CI [1.03, 1.08]). The spline analysis suggested a non-linear increase of having at least moderate gait disability with age.

Conclusions: Presence of comorbidities was largely associated with age only. Having at least moderate gait disability was associated with both age and MS duration, while having severe gait disabity was associated with MS duration only.

Abbreviations: MS, multiple sclerosis; PwMS, persons with multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; CIS, clinically isolated syndrome; SPMS, secondary progressive multiple sclerosis; BMI, body mass index; T2D, type 2 diabetes; SMSR, Swiss Multiple Sclerosis Registry; SRDSS, Self-reported Disability Status Scale; DMT, disease modifying therapy; Mini-SPIKE, short form of Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology Questionnaire; AIC, Akaike information criterion; VIF, variance inflation factor; OR, odds ratio; CI, confidence interval; IQR, interquartile range.

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1. Introduction

Life expectancy of persons with multiple sclerosis (PwMS) is only slightly reduced compared to the general population, and is gradually increasing (Lunde et al., 2017). This leads to increased average age of PwMS and a growing population of elderly with multiple sclerosis (MS) (Marrie et al., 2010), many of whom have been living with the disease for several decades.

Physiological ageing is characterized by substantial changes in immune system, such as reduced capacity of providing an adequate immune response and inflammageing or chronic low-grade inflammation with increased levels of proinflammatory cytokines (Cevenini et al., 2013; Grebenciucova and Berger, 2017). These processes, referred to as immunosenescence, prompt the underlying mechanisms of MS, inflammation and oxidative stress, hampering lesion repair and leading to increased loss of neuronal synaptic plasticity and neuro-axonal injury (Vaughn et al., 2019).

Changes in the immune system are also responsible for many age-related comorbidities (Cevenini et al., 2013; Ferrucci and Fabbri, 2018). Comparable to the general population, old age in PwMS is accompanied by a greater multimorbidity risk. Depression, anxiety, and hypertension were recently identified as the three most commonly observed comorbidities in PwMS (Marrie et al., 2015).

Presence of comorbidities is associated with worse MS-related outcomes, as well as mortality in PwMS. Cardiovascular diseases may worsen clinical and MRI-derived MS outcomes (Jakimovski et al., 2019), while cardiovascular disease, type 2 diabetes (T2D), cancer and psychiatric disorders were found to be associated with increased mortality in PwMS (Thormann et al., 2017). Nevertheless, less is known about the possible interplay of ageing and disease duration on the occurrence of comorbidities in PwMS.

Thus, we explored the association of ageing and MS duration with comorbidities and gait disability. We aimed to identify whether increasing age or longer MS duration (or both) are associated with a higher gait disability or comorbidity risk. In addition, we aimed to explore the association between presence of comorbidities and having different gait disability levels.

2. Materials and methods

2.1. Data source

This study used data from the Swiss Multiple Sclerosis Registry (SMSR), a nation-wide self-reported registry for PwMS. SMSR is a prospective longitudinal study open to all interested adults with MS residing or receiving care in Switzerland who provided written informed consent. Detailed information on SMSR is provided elsewhere (Steinemann et al., 2018; Puhan et al., 2018). The SMSR was approved by the Ethics Committee of the Canton of Zurich (PB-2016-00894; BASEC-NR 2019-01027).

The present study used self-reported data on comorbidity and gait disability outcomes from the baseline assessments, which were complemented by follow-up questionnaires (self-administered 6, 12, 18, 24 and 36 months after the baseline questionnaire) (Fig. 1, Supplementary Fig. 1). Due to the short follow-up time (up to five years) in terms of chronic diseases and ageing research and the lack of repeated measurements in large majority of the participants we adopted a “hybrid” approach, combining the longitudinal aspect of data collection and cross-sectional analysis. To increase statistical power, outcome data from all available questionnaires were merged into a single data set and data were treated cross-sectionally. To be included in the analysis, participants had to fill in at least the baseline questionnaire. A sensitivity analysis included only baseline outcome data.

2.2. Variables of interest

MS duration and age were variables of interest in this study. MS duration was measured from the self-reported symptom onset. Sensitivity analysis using MS duration calculated from the date of diagnosis was conducted. Age was calculated from the year of birth to the year in which the baseline questionnaire was completed.

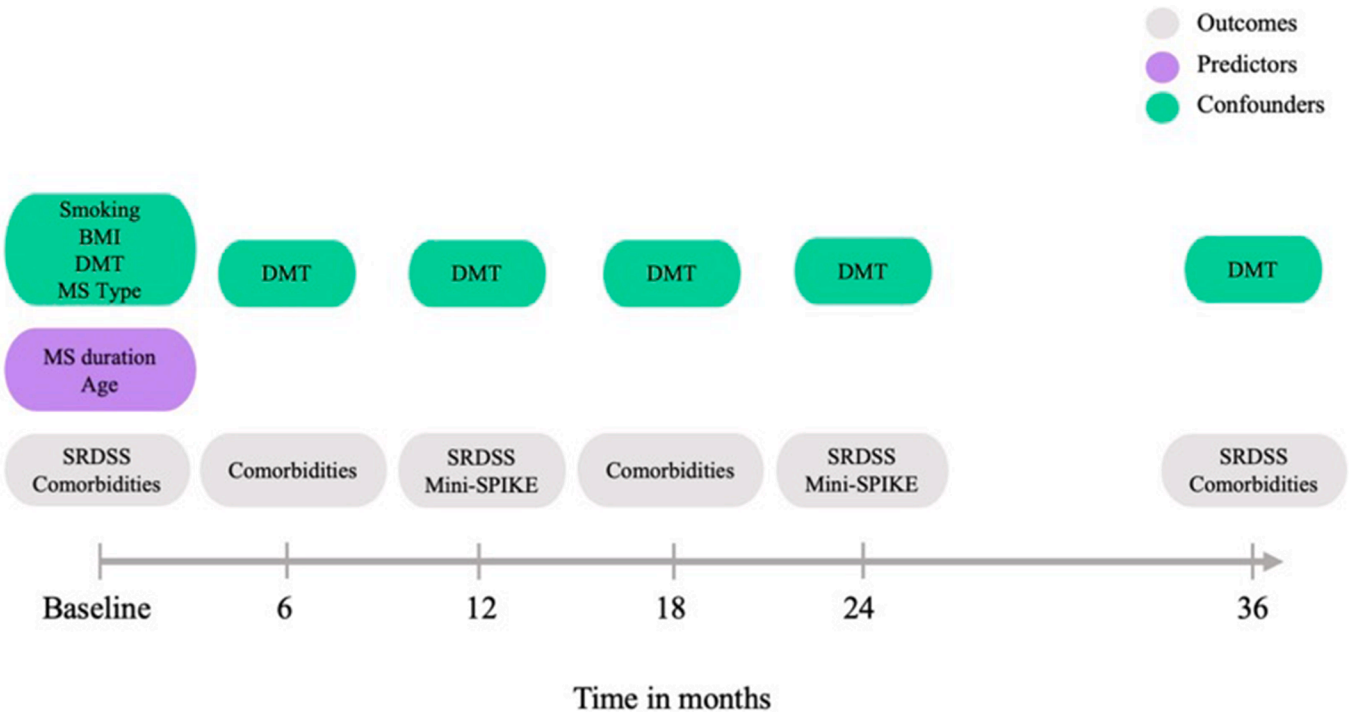


Fig. 1. Schematic diagram of used questions per follow-up. BMI – body mass index, DMT – disease modifying therapy, MS – multiple sclerosis, SRDSS – Self-reported disability status scale, Mini-SPIKE - short form of the structured psychopathological interview and rating of the social consequences for epidemiology questionnaire.

2.3. Outcome variables

The following outcomes were of interest: cancer, depression, hypertension, cardiac diseases, T2D and Self-reported Disability Status Scale (SRDSS) assessments (henceforth gait disability).

Gait disability was measured using SRDSS, a proxy measure for Expanded Disability Status Scale (EDSS) based on 3 questions on mobility (Kaufmann et al., 2020). Details are given in the Supplementary Material. Gait disability levels of SRDSS ≥ 4 (at least moderate) and ≥ 7 (severe) were of interest in this study.

Presence of comorbidities was established using answers to a multiple-choice question on diseases present in addition to MS. The baseline question referred to the comorbidities diagnosed up until the date of questionnaire administration, while the follow-up questions concerned comorbidities newly diagnosed in the last 6 or 12 months. The following answers were of interest: "Increased blood pressure", "Heart problems", "Diabetes Type 2", "Depression" and "Cancer". An outcome was registered as present when it was reported at least once at baseline or over the course of the follow-up. If the outcome was not reported at any time point, the outcome was considered as not present.

Additionally, presence of cancer and depression was measured using methods other than self-reports and was used for sensitivity analysis. Presence of cancer was established using clinically verified cancer diagnoses. Presence of depression was measured using the short form of the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology Questionnaire (Mini-SPIKE) (Angst et al., 2005). Details are given in the Supplementary Material.

2.4. Statistical analysis

Descriptive analyses included calculation of frequencies for the outcomes of interest within discrete categories of MS duration (0–9, 10–19, 20–29 and 30+ years) and age at baseline (18–29, 30–39, 40–49, 50–59, 60–69 and 70+ years), as well as frequencies and means or medians with regards to the sociodemographic characteristics. Multivariable logistic regression models were used for analysing the association of age and MS duration with the outcomes of interest. Age and MS duration were treated as continuous variables. A two-way interaction between age and MS duration was added to the models and maintained if resulted in model fit improvement of Akaike Information Criterion (AIC) of at least 2, as the rule of thumb (Burnham and Anderson, 2004). All models were corrected for the following, a-priori fixed confounders: sex, MS type (RRMS, PPMS, SPMS, CIS or transition), body mass index (BMI) (continuous variable) and smoking ("never", "formerly" or "currently"), all reported in the entry and baseline questionnaires, and use of disease modifying therapy (DMT, "never" or "anytime"). "Transition" by convention refers to the transition stage between RRMS and SPMS. However, the SMSR questionnaire does not include a definition of transition, and examination of the MS stages reported at follow-up by participants who initially reported transition stage suggests a broad understanding of the term by the participants. Therefore, for participants who reported transition in the entry questionnaire, the MS type was replaced with the stage reported in the baseline questionnaire whenever possible.

Additionally, we visually explored the functional shape of the relationship between age and MS duration and specific outcomes of interest. To this end, we re-estimated the multivariable models by including restricted cubic spline transformed age and MS duration variables. Next, we plotted age and MS duration dependent outcome risks by holding the values of confounding variables fixed at means for continuous and modes for categorical variables (sex: female, smoking: never, MS type: RRMS, DMT: previous or current use). Three internal knots were supplied per spline transformation, each positioned at 25th, 50th and 75th quantile of age or MS duration.

No data imputation was performed and only cases with all required data available were included in the analysis. All analyses were performed using R (version 4.2.0) and R Studio (version 2022.02.3 + 492) software and the following packages: tidyverse, stats, splines, performance (R Core Team, 2020).

3. Results

As of March 12th 2021, 1876 participants had completed the baseline assessment. Of those, 261 were excluded due to missing values (Fig. 2) and a total of 1,615 participants were included in the analysis. Details on excluded participants can be found in Supplementary Table 1. Overall, 1134 (70.2%) of 1615 had at least one follow-up survey covering comorbidities and 1063 (65.8%) had an updated SRDSS score.

Women accounted for 73.3% of the final sample. Median [interquartile range (IQR)] age was 47 [37 to 55] and median [IQR] MS duration was 11 [4 to 19] years. At baseline most participants reported having RRMS (69.2%), followed by SPMS (13.1%) and PPMS (9.70%). Depression was the most frequently reported comorbidity (13.8%), followed by hypertension (12.5%), while cancer, T2D and cardiac diseases were reported by less than 5% of participants. Almost one third (31.3%) of the participants had at least moderate gait disability milestone, while only 8.9% had severe gait disability (Table 1).

Frequencies of reported comorbidities and disability levels per age and disease duration categories are presented in Table 2 and in Supplementary Fig. 2.

3.1. Association of age and MS duration with gait disability and comorbidity

Participants became 4% more likely to have at least moderate gait disability (OR 1.04, 95% CI [1.02, 1.05]) with each year of MS duration, and 6% more likely with each year of age (OR 1.06, 95% CI [1.04, 1.07], Table 3). On the other hand, MS duration was not significantly associated with having a comorbidity, except for cardiac diseases (OR 1.03, 95% CI [1.00, 1.05]). Age was associated with hypertension and diabetes, with close to 10% increase in odds per year of age (OR 1.08, 95%

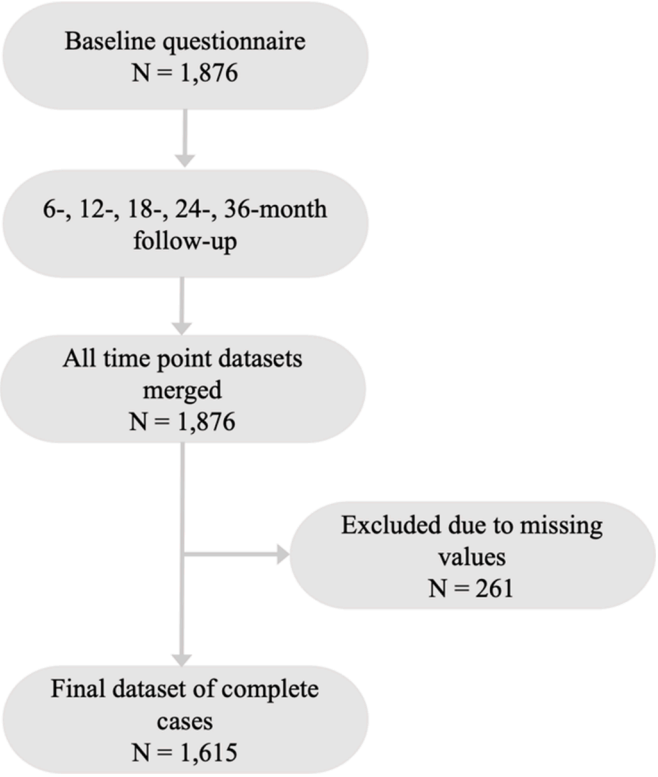


Fig. 2. Study design flowchart.

Table 1
Description of the study sample with regards to demographic characteristics, confounders, and outcomes.

Characteristic	$N = 1,615$
Age, median [interquartile range]	47 [37 to 55]
Women, N (%)	1,184 (73.3%)
MS type, N (%)	
CIS	71 (4.4%)
RRMS	1,141 (70.7%)
PPMS	158 (9.8%)
SPMS	236 (14.6%)
Transition	9 (0.6%)
MS duration, median [interquartile range]	11 [4 to 20]
Smoking, N (%)	
Never	706 (43.7%)
Formerly	552 (34.2%)
Currently	357 (22.1%)
BMI, N (%)	
Underweight	68 (4.2%)
Normal weight	896 (55.5%)
Preobesity	420 (26.0%)
Obesity I-III	231 (14.3%)
DMT use, N (%)	
Never	194 (12.0%)
Anytime	1,421 (88.0%)
Comorbidities, N (%)	
Cancer	44 (2.7%)
Clinically verified cancer	28 (1.7%)
Depression	223 (13.8%)
Depression per Mini-SPIKE †	39 (4.96%)
Hypertension	202 (12.5%)
Cardiac problems	65 (4.0%)
T2D	25 (1.5%)
Gait disability milestones, N (%)	
At least moderate	506 (31.3%)
Severe	143 (8.9%)

†Mini-SPIKE was only included in 12- and 24-month follow-up, thus limiting the number of participants to whom it was distributed to a total of $N = 697$.
MS – multiple sclerosis, CIS – clinically isolated syndrome, RRMS – relapsing-remitting MS, SPMS – secondary progressive MS, BMI – body mass index, DMT – disease modifying therapy, T2D – type 2 diabetes, Mini-SPIKE – short form of Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology Questionnaire

CI [1.06, 1.10] and OR 1.10, 95% CI [1.05, 1.16], respectively). The likelihood of having cancer increased by 4% per year (OR 1.04, 95% CI [1.01, 1.07]). Variance inflation factor (VIF) calculations suggested no substantial multicollinearity (all VIF < 2) across all main analysis models (Supplementary material, Table 2). Inclusion of the two-way interaction between age and MS duration did not improve fit in any of the outcomes.

Male participants were shown more likely to have a cardiac disease (OR 2.25, 95% CI [1.32, 3.81]) than females, but not T2D (OR 1.51, 95% CI [0.63, 3.66]) and hypertension (OR 1.18, 95% CI [0.83, 1.69]). Furthermore, BMI was positively associated with reporting hypertension (OR 1.12, 95% CI [1.09, 1.15]), cardiac disease (OR 1.04, 95% CI [1.00, 1.09]), T2D (OR 1.15, 95% CI [1.09, 1.22]), depression, (OR 1.03, 95% CI [1.0, 1.06]), having at least moderate (OR 1.04, 95% CI [1.01, 1.06]) and severe gait disability (OR 1.04, 95% CI [1.01, 1.08]).

Depression was the only comorbidity significantly associated with having at least moderate gait disability (OR 1.57, 95% CI [1.09, 2.24], Supplementary Table 3).

3.2. Exploration of functional shape of age/MS duration and outcome association

By plotting spline-based risk functions we examined the age- and MS duration relationships with specific outcomes. This approach helps to identify non-linear changes across age- and MS duration profiles. Fig. 3 shows risk functions derived from models with cubic spline transformed age and MS duration. While predicted probability of having cancer

Table 2
Frequency of reported or diagnosed comorbidities over years of age and years of disease duration groups.

	Years since MS onset				
	0–9	10–19	20–29	30+	Total
Age group 18–29 years (N)	**145**	**12**			**157**
Cancer	2 (1.4%)	0			2 (1.3%)
Clinically verified cancer	0	0			0
Depression	14 (9.7%)	1 (8.3%)			15 (9.6%)
Hypertension	2 (1.4%)	0			2 (1.3%)
Cardiac problems	2 (1.4%)	1 (8.3%)			3 (1.9%)
T2D	1 (0.7%)	0			1 (0.6%)
At least moderate gait disability	9 (6.2%)	1 (8.3%)			10 (6.4%)
Severe gait disability	2 (1.4%)	1 (8.3%)			3 (1.9%)
Age group 30–39 years (N)	**257**	**88**	**10**		**355**
Cancer	1 (0.4%)	0	0		1 (0.3%)
Clinically verified cancer	2 (0.8%)	0	0		2 (0.6%)
Depression	29 (11.3%)	13 (14.8%)	4 (40.0%)		46 (13.0%)
Hypertension	8 (3.1%)	4 (4.5%)	0		12 (3.4%)
Cardiac problems	1 (0.4%)	3 (3.4%)	0		4 (1.1%)
T2D	3 (1.2%)	0	0		3 (0.8%)
At least moderate gait disability	25 (9.7%)	21 (23.9%)	1 (10.0%)		47 (13.2%)
Severe gait disability	2 (0.8%)	4 (4.5%)	0		6 (1.7%)
Age group 40–49 years (N)	**180**	**153**	**89**	**10**	**432**
Cancer	3 (1.7%)	4 (2.6%)	1 (1.1%)	1 (10.0%)	9 (2.10%)
Clinically verified cancer	2 (1.1%)	2 (1.3%)	1 (1.1%)	0	5 (1.2%)
Depression	18 (10.0%)	30 (19.6%)	13 (14.6%)	3 (30.0%)	64 (14.8%)
Hypertension	23 (12.8%)	12 (7.8%)	6 (6.7%)	0	41 (9.5%)
Cardiac problems	5 (2.8%)	4 (2.6%)	5 (5.6%)	1 (10.0%)	15 (3.5%)
T2D	2 (1.1%)	0	1 (1.1%)	0	3 (0.7%)
At least moderate gait disability	17 (9.4%)	35 (22.9%)	36 (40.4%)	7 (70.0%)	95 (22.0%)
Severe gait disability	2 (1.1%)	9 (5.9%)	6 (6.7%)	3 (30.0%)	20 (4.6%)
Age group 50–59 years (N)	**116**	**170**	**95**	**47**	**428**
Cancer	3 (2.6%)	8 (4.7%)	9 (9.5%)	0	20 (4.7%)
Clinically verified cancer	4 (3.4%)	2 (1.2%)	6 (6.3%)	0	12 (2.8%)
Depression	25 (21.6%)	18 (10.6%)	24 (25.3%)	6 (12.8%)	73 (17.1%)
Hypertension	23 (19.8%)	32 (18.8%)	16 (16.8%)	13 (27.7%)	86 (19.4%)
Cardiac problems	3 (2.6%)	4 (2.4%)	4 (4.2%)	4 (8.5%)	15 (3.5%)
T2D	1 (0.9%)	5 (2.9%)	1 (1.1%)	0	7 (1.6%)
At least moderate gait disability	40 (34.5%)	74 (43.5%)	48 (50.5%)	33 (70.2%)	195 (45.6%)
Severe gait disability	7 (6.0%)	19 (11.2%)	21 (22.1%)	14 (29.8%)	61 (14.3%)
Age group 60–69 years (N)	**23**	**53**	**44**	**63**	**183**
Cancer	3 (13.0%)	2 (3.8%)	2 (4.5%)	3 (4.8%)	10 (5.5%)

(continued on next page)

Table 2 (*continued*)

	Years since MS onset				
	0–9	10–19	20–29	30+	Total
Clinically verified cancer	2 (8.7%)	0	2 (4.5%)	4 (6.3%)	8 (4.6%)
Depression	4 (17.4%)	7 (13.2%)	3 (6.8%)	7 (11.1%)	21 (11.5%)
Hypertension	3 (13.0%)	11 (20.8%)	14 (31.8%)	15 (23.8%)	43 (23.5%)
Cardiac problems	1 (4.3%)	5 (9.4%)	4 (9.1%)	6 (9.5%)	16 (8.7%)
T2D	1 (4.3%)	3 (5.7%)	1 (2.3%)	2 (3.2%)	7 (3.8%)
At least moderate gait disability	10 (43.5%)	29 (54.7%)	32 (72.7%)	44 (69.8%)	115 (62.8%)
Severe gait disability	2 (8.7%)	9 (17.0%)	9 (20.5%)	18 (28.6%)	38 (20.8%)
Age group 70+ years (N)	**4**	**8**	**19**	**29**	**60**
Cancer	0	0	2 (10.5%)	0	2 (3.3%)
Clinically verified cancer	1 (25.0%)	0	0	0	1 (1.7%)
Depression	0	1 (12.5%)	0	3 (10.3%)	4 (6.7%)
Hypertension	1 (25.0%)	4 (50.0%)	5 (26.3%)	10 (34.5%)	20 (33.3%)
Cardiac problems	1 (25.0%)	1 (12.5%)	6 (31.6%)	4 (13.8%)	12 (20.0%)
T2D	1 (25.0%)	0	1 (5.3%)	2 (6.9%)	4 (6.6%)
At least moderate gait disability	3 (75.0%)	3 (37.5%)	12 (63.2%)	26 (89.7%)	44 (73.3%)
Severe gait disability	2 (50.0%)	0	3 (15.8%)	10 (34.5%)	15 (25.0%)

MS – multiple sclerosis, T2D – type 2 diabetes.

Table 3
Odds ratios (OR) and 95% confidence intervals (95% CI) for basic models for all six outcomes of interest. All models were adjusted for sex, MS type, use of DMT, BMI, and smoking habits.

Outcome	AgeOR [95% CI]	MS durationOR [95% CI]
Cancer	1.04 [1.01, 1.07]	1.00 [0.97, 1.03]
Hypertension	1.08 [1.06, 1.10]	1.00 [0.99, 1.02]
Cardiac problems	1.05 [1.02, 1.08]	1.03 [1.00, 1.06]
T2D	1.10 [1.05, 1.16]	0.97 [0.93, 1.01]
Depression	1.01 [0.99, 1.02]	1.01 [0.99, 1.03]
At least moderate gait disability	1.04 [1.02, 1.05]	1.06 [1.04, 1.07]
Severe gait disability	1.00 [0.98, 1.02]	1.05 [1.03, 1.08]

MS – multiple sclerosis; DMT – disease modifying treatment, BMI – body mass index, T2D – type 2 diabetes.

started to increase mildly around the age of 50, a marginal increase in probability followed by a further decline was predicted around 5th and 20th year of MS duration (Fig. 3a)). The predicted probability of having other comorbidities, T2D, hypertension and a cardiac disease, remained fairly stable and low throughout the spectrum of MS duration, while an almost linear increase of the predicted probability after the age of around 40 was observed in the case of hypertension (Fig. 3b, c and d)). The probability of having T2D and cardiac diseases increased only after the age of 60 (Fig. 3c and d)). Finally, the predicted probability of having at least moderate gait disability increased almost linearly at comparable rates with both age and MS duration, except for a modest decline around the age of 40 (Fig. 3e).

3.3. Sensitivity analyses

Models using clinically confirmed instead of self-reported cancer yielded similar results to the ones reported above, while models using depression measured through Mini-SPIKE resulted in significant association between having depression and MS duration, but not age (Supplementary Material).

Sensitivity analyses using self-reported outcomes at baseline only or MS duration calculated from the year of diagnosis showed results comparable to the main analysis (Supplementary Tables 5 and 6).

4. Discussion

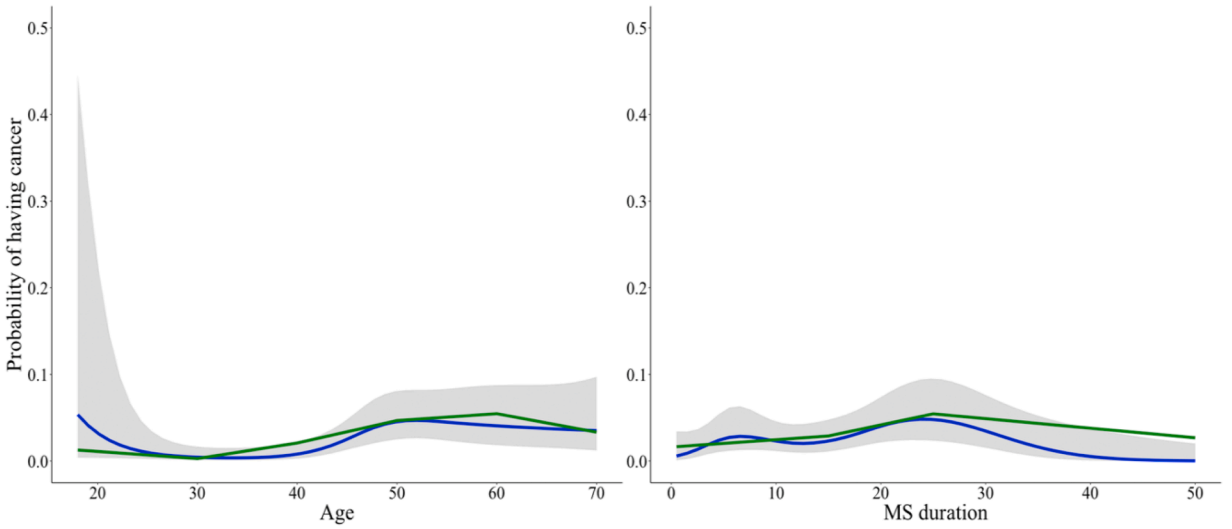
This cross-sectional study explored age and MS duration in association with self-reported comorbidities and gait disability using data of the SMSR, a real-world longitudinal study in PwMS in Switzerland. The analysis of 1,615 participants' data showed statistically significant association of both age and MS duration with having at least moderate gait disability, while only MS duration was associated with having severe gait disability. Having a comorbidity tended to be associated with age only, as was the case for cancer, hypertension and T2D, while both age and MS duration were associated with having cardiac diseases. No statistically significant associations were found in the case of depression. We identified several non-linear changes across different MS duration and age profiles, albeit modest in size.

The observed prevalence of comorbidities in different studies including PwMS varies substantially, depending on the study design and setting, as well as demographic and health-related population characteristics. Several studies have found hypertension to be among the most often reported or diagnosed comorbidities in PwMS at approximately 15% (Ciampi et al., 2020; Hauer et al., 2021). Prevalence of hypertension in our study was within the range of most reports. Conversely, the prevalence of depression in our study was markedly lower compared with the prevalence of 18% to more than 35% in other studies (Hauer et al., 2021). Considerable fluctuations in prevalence of depression are a recognized phenomenon and are largely attributed to numerous measurement instruments used to identify presence of depression. Thus, the markedly lower prevalence of depression in our study may be attributed to methodological differences in depression evaluation, different definitions of depression, and demographic and health-related differences in the PwMS population. In general, PwMS are considered to have higher prevalence of various comorbidities in comparison to the general population, included those of interest in our study (Hauer et al., 2021; Tettey et al., 2016).

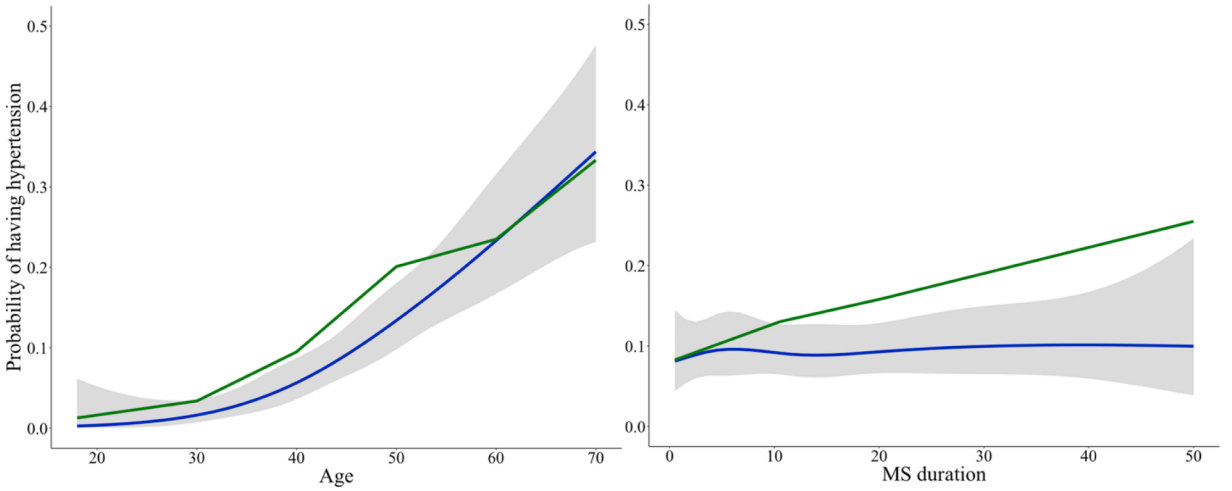
While numerous studies described the prevalence of various comorbidities in PwMS, using a "checkerboard" approach (Table 2 and Supplementary Fig. 2) for descriptive analysis of the comorbidities and their association with age or disease duration is less commonly seen. This approach enables preliminary visual inspections of patterns along the horizontal (MS duration), vertical (age) and diagonal (interaction) axes. In general, while a steady increment in the prevalence of comorbidity can be seen across increasing age groups, this is rarely observed when looking at increasing MS duration. By contrast, having disability levels of interest tended to become more frequent both along the vertical (age) and horizontal (MS duration) axes.

Preliminary findings from the "checkerboard" approach were confirmed by use of multivariable logistic regression models. These models suggest that mainly age was associated with the presence of comorbidity. Age was previously found to be independently and positively associated with several comorbidities, including hypertension and diabetes (Edwards et al., 2018). The same study found PwMS under 65 years more likely to have depression in comparison to those under 34 years. However, this association was inverted in case of PwMS older than 65 years. Similarly, in our study the frequency of depression increased until the age of 60 and was then followed by a decline. Self-reported cardiac disease was the only comorbidity for which both age and disease duration were positively and independently associated, after adjusting for major confounders such as BMI and smoking. While we should be cautious to assume any causality from this finding, a number of cross-sectional and longitudinal studies established an association between vascular comorbidities and MS-associated disability

a) Cancer



b) Hypertension



c) Cardiac disease

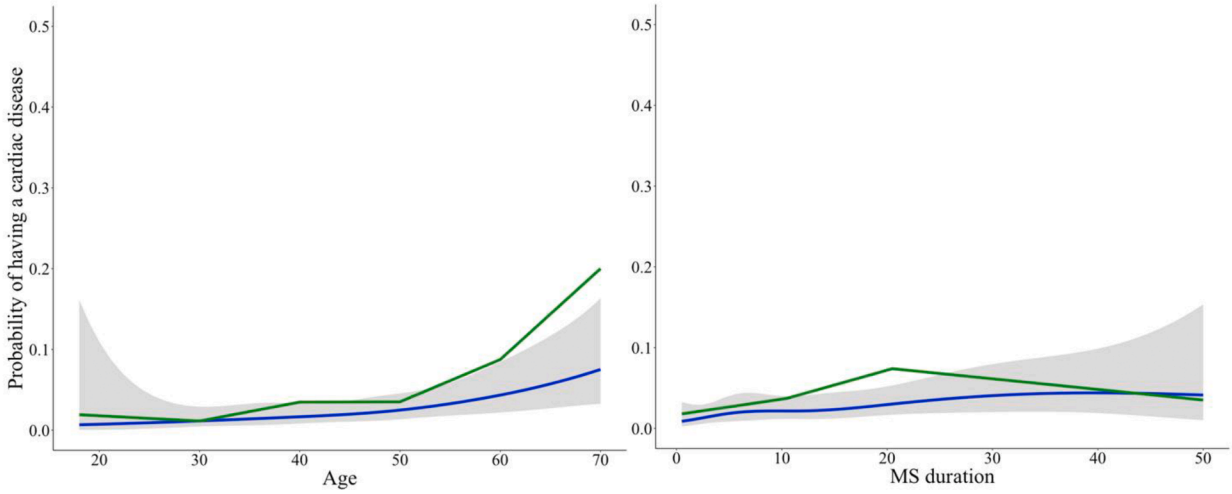
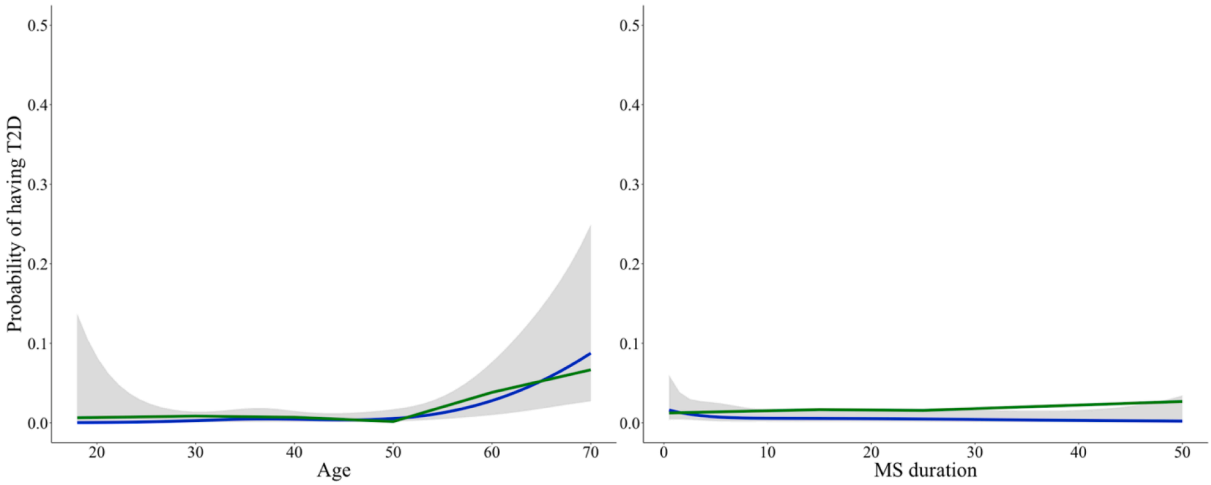
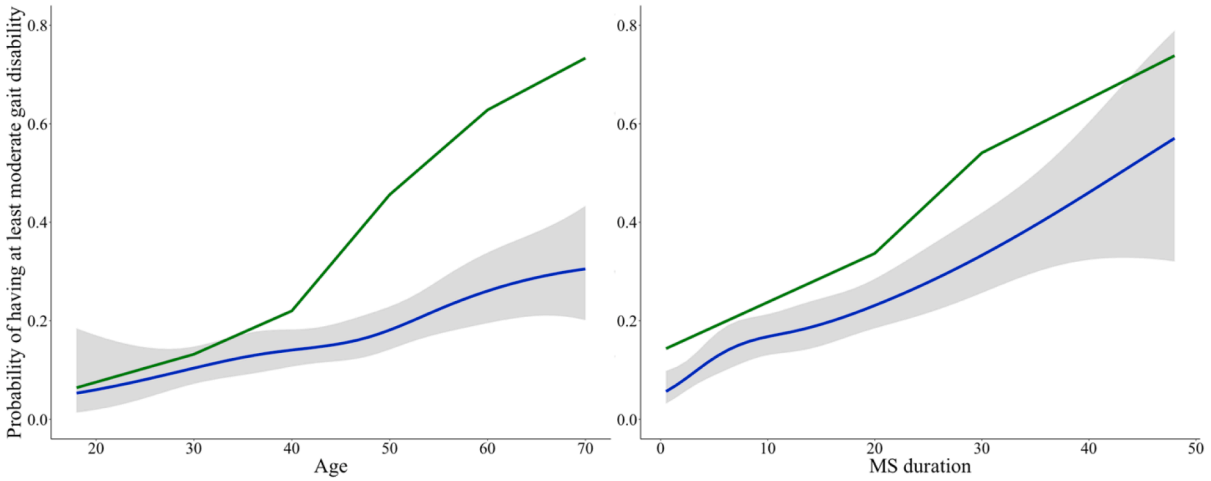


Fig. 3. (a–f). Risk functions derived from the extended models with age or MS duration transformed using cubic splines. Observed frequencies per age and MS group are shown in green, whereas predicted probabilities from models corrected for confounders are shown in blue with 95% confidence intervals in grey.

d) Type 2 diabetes



e) At least moderate gait disability



f) Severe gait disability

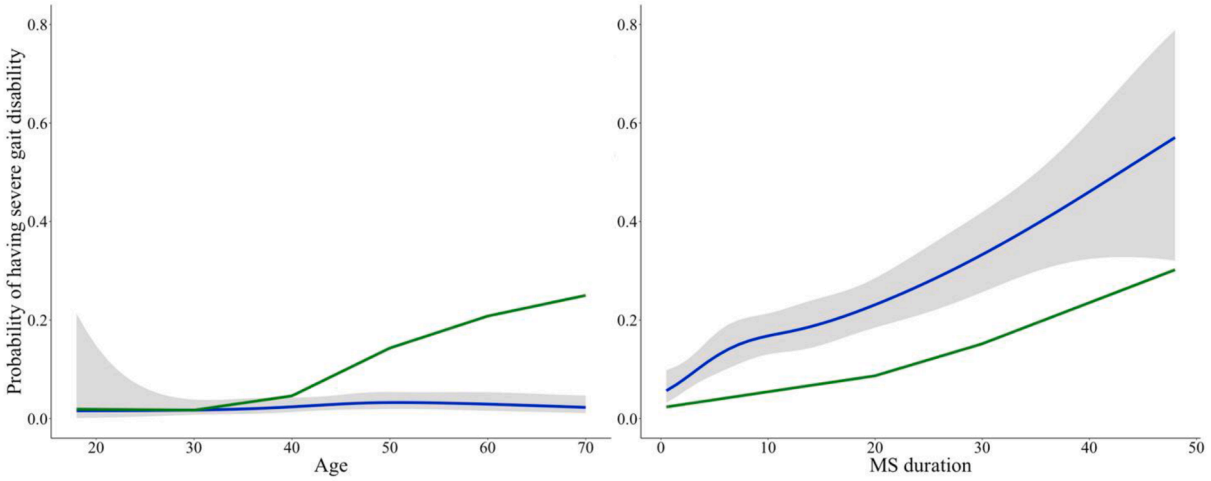


Fig. 3. (*continued*).

(Moss et al., 2017). It is speculated that the association could reflect reduced physical activity and aggravated sedentary behavior, yet the causality could go either way. A pronounced association of higher BMI and increased risk of gait disability in our study fits into this theory and underlines the importance of obesity prevention and treatment in PwMS. Finally, we found late-life increases in predicted probability of T2D and cardiac diseases, which is in line with the age groups most often diagnosed with those diseases in general population (Zhou et al., 2016; Benjamin et al., 2019; Centers for Disease Control and Prevention, 2014).

Having severe gait disability was found to be primarily associated with MS duration, while significant associations with having at least moderate gait disability were found in case of both age and MS duration. This is expected, since PwMS with longer disease course show accumulation of disability (DiLorenzo et al., 2004). A recent cross-sectional study found a significant and positive association between MS duration and clinically estimated EDSS $\geq$ 6, albeit the association was rather modest in magnitude (Ciampi et al., 2020). On the other hand, and in line with our finding concerning at least moderate gait disability, progression of motor decline in PwMS was found to be amplified by ageing (Roy et al., 2017). We found a plateau in the otherwise increasing probability of having at least moderate disability between the ages of 30 and 40, followed by another one after the age of 60. The first plateau could relate to the shorter disease duration, and thus lesser chances of aggravated disability in persons diagnosed with MS in their third life decade, when the disease onset usually peaks. While the second plateau could suggest diminishing role of ageing in disability accumulation after certain age, it more likely reflects an attrition bias, as more severely disabled elderly population would be more likely to discontinue participation in the SMSR or to have never participated.

The lack of an association of most comorbidities (except depression) with disability levels is somewhat contradictory to the previously published studies. Specifically, several studies observed greater frequencies of physical disability, as well as an acceleration of disability accumulation in the presence of comorbidities such as cardiovascular diseases or T2D (Zhang et al., 2018; Marrie et al., 2010; Maric et al., 2022). By contrast, studies exploring psychiatric comorbidities and their association with disability in PwMS are less common and showing conflicting results. While one study found no relationship between baseline depression and disability progression 10 years later (Koch et al., 2008), other studies found mood disorders and anxiety to be associated with disability progression (McKay et al., 2018; Binzer et al., 2019). The latter could be understood as comparable to our results, although we only investigated having certain disability levels and not progression.

While our study cannot provide evidence for causal interpretations, future research should strive for establishing causality. Attributing comorbidities to ageing and disability to MS with certainty could enable better distinguishing between overlapping symptoms of comorbidities and MS itself, thus facilitating adequate management. Furthermore, special attention should be given to preventive measures in middle aged and ageing PwMS.

5. Strengths and limitations

Strengths of our study are a large sample size with relatively low prevalence of missing data, a diverse population with clinically confirmed MS diagnoses and a variety of available outcomes. In addition to these hallmarks of SMSR methodology, the use of cubic splines to inspect non-linear risk shapes presents an important added value to our analysis. The confirmation of our main results in several sensitivity analyzes speaks for robustness of our results. Still, our data may suffer from information bias, an expected flaw of self-reported measurements. Due to the formulation of the question and given answers, decision on what constitutes a "heart problem" was left to the discretion of the participants and may have varied across participants with different characteristics. As SMSR is collecting data longitudinally, our results may have been affected by attrition bias. Finally, the cross-sectional design of our analysis prohibits any causal interpretation, which calls for future longitudinal analysis.

6. Conclusions

Both age and MS duration were associated with having at least moderate gait disability, while only MS duration was associated with having severe gait disability. Presence of comorbidities was associated mainly with age, but not MS duration. However, both age and MS duration were associated with having cardiac diseases. MS-management should take these associations into account and strive to prevent comorbidity occurrence in middle-aged and older PwMS.

Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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CRediT authorship contribution statement

Mina Stanikić: Conceptualization, Formal analysis, Writing – original draft. **Anke Salmen:** Conceptualization, Methodology, Writing – original draft. **Andrew Chan:** Resources, Writing – review & editing. **Jens Kuhle:** Resources, Writing – review & editing. **Marco Kaufmann:** Resources, Writing – review & editing. **Sabin Ammann:** Investigation. **Sandra Schafroth:** Investigation. **Stephanie Rodgers:** Resources, Writing – review & editing. **Christina Haag:** Resources, Writing – review & editing. **Caroline Pot:** Resources, Writing – review & editing. **Christian P Kamm:** Resources, Writing – review & editing. **Chiara Zecca:** Resources, Writing – review & editing. **Claudio Gobbi:** Resources, Writing – review & editing. **Pasquale Calabrese:** Resources, Writing – review & editing. **Zina-Mary Manjaly:** Resources, Writing – review & editing. **Viktor von Wyl:** Conceptualization, Methodology, Supervision, Resources, Writing – review & editing.

Declaration of Competing Interest

Mina Stanikić reports employment by Roche branch in Serbia, Roche d.o.o., from February 2019 to February 2020. Anke Salmen has received speaker honoraria and/or travel compensation for activities with Bristol Myers Squibb, Novartis, Roche and research support of Baasch Medicus Foundation and the Swiss MS society, not related to this work. Andrew Chan has served onadvisory boards for, and received funding for travel or speaker honoraria from Actelion-Janssen,Almirall, Bayer, Biogen, Celgene, Sanofi-Genzyme, Merck, Novartis, Roche and Teva, all for hospitalresearch funds; and research support from Biogen, Genzyme and UCB. Andrew Chan is associate editor ofthe European Journal of Neurology and serves on the editorial board for Clinical and Translational Neuroscience and as topic editor for the Journal of International Medical Research. Jens Kuhle has received speaker fees, research support, travel support, and/or served on advisory boards by Swiss MS Society, Swiss National Research Foundation (320030_189140/1), University of Basel, Progressive MS Alliance, Bayer, Biogen, Bristol Myers Squibb, Celgene, Merck, Novartis, Octave Bioscience, Roche, Sanofi. Christian P Kamm has received honoraria for lectures as well as research support from Biogen, Novartis, Almirall, Teva, Merck, Sanofi Genzyme, Roche, Janssen, Eli Lilly, Celgene and the Swiss MS Society (SMSG). The employer of Caroline Pot has received speaker honoraria and/or travel compensation for her activities with Biogen, Merck, Novartis, Roche and Sanofi Genzyme, and research support of SFNS,

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104084.

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