Decline in PPMS Diagnosis? – The German View

D. Ellenberger[1], P. Flachenecker[2], T. Friede[1], J. Haas[3], C. Kleinschnitz[4], D. Pöhlau[5], O. Rienhoff[1], P.S. Rommer[6,7], A. Stahmann[8], U.K. Zettl[6]

for the German Multiple Sclerosis Register of the German National MS Society

1: University Medical Center Göttingen, Georg August University Göttingen

2: Neurological Rehabillitation Center Quellenhof, Bad Wildbad

3: MS-Center, Jewish Hospital Berlin

4: Department of Neurology, University Hospital Essen

5: Department of Neurology, German Red Cross - Kamillus-Clinic, Asbach

6: Department of Neurology, University of Rostock

7: Department of Neurology, Medical University of Vienna

8: MS-Forschungs- und Projektentwicklungs-gGmbH, Hannover

Background

In Germany approximately 6-9% of people with MS (PwMS) suffer from primary progressive MS (PPMS) (1). In 2016 Westerlind et al. (2) reported a significant decrease in the proportion of PPMS in Sweden.

Aims and Hypotheses:

We analysed data of the German MS-Register with regard to the findings of Westerlind et al. (2) to evaluate whether we can confirm the Swedish data also in Germany.

Methods and Material:

- Data from the German MS-Registry was extracted in May 2017.
- Only patients with a confirmed disease course and who were born between 1946 and 1980 were analysed (N=30,195).
- Birth and diagnosis cohorts were defined as in Westerlind et al. 2016.
- Statistical analyses included Age-Period-Cohort Models based on smoothed cubic regression splines (3).
- Additional adjustment for sex, diagnosis delay and the date of entry into the registry has been carried out.

Results:

56.8% of our analysed patients with PPMS were females and mean age was 51.3 (±7.7) years at time of analyses. Mean age at diagnosis was 42.7(±9.7). Crude estimates of PPMS prevalence ranges from 19% for the late 1940s birth cohort to less than 3% for the early 1970s birth cohort.
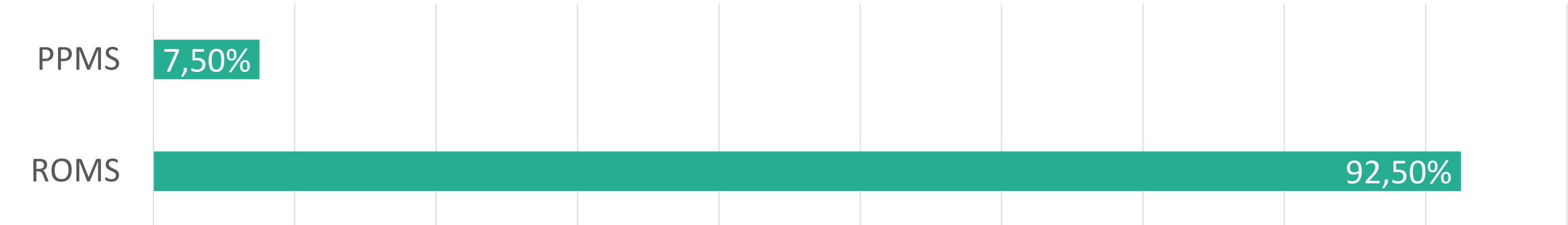

Figure 1: Ratio of PPMS and ROMS Patients in the analysed dataset

Age-Period-Cohort models reveal that this decline seems to be occurring rapidly in calendar time. The underlying temporal trend is described best by the birth cohort only (p<0.001). The trends in the date of diagnosis reported by Westerlind et al. were not replicated (p=0.71) and the narrow 95%-confidence bounds show that no substantial effects are present. The variables age at diagnosis (p<0.001), gender (odds ratio 1.8; p<0.001) and diagnostic delay (p<0.001) were also found to be significant while the entry date into the register was not (p=0.91). Sensitivity analyses by regional strata showed coherent results.

Birth-cohort	Rate	95%-CI (%)	Rate ratio	95%-CI	Adj. rate	95%-CI (%)
1946-1950	19.3%	[17.4,21.2]	Reference		14.2%	[11.7,17.0]
1951-1955	15.9%	[14.6,17.2]	0.82	[0.7, 0.9]	11.4%	[10.0,13.0]
1956-1960	11.5%	[10.6,12.4]	0.59	[0.5, 0.7]	8.9%	[8.2, 9.7]
1961-1965	6.7%	[6.1, 7.4]	0.34	[0.3, 0.4]	6.6%	[6.1, 7.1]
1966-1970	4.5%	[4.0, 5.1]	0.24	[0.2, 0.3]	4.6%	[4.2, 5.1]
1971-1975	2.6%	[2.2, 3.1]	0.14	[0.1, 0.2]	3.0%	[2.6, 3.6]

Table 2: Proportion of PPMS by birth cohorts

Diagnosis-cohort	Rate	95%-CI (%)	Rate ratio	95%-CI	Adj. rate	95%-CI (%)
1980-1984	6.9%	[5.1, 9.1]	Reference		5.9%	[5.2, 6.6]
1985-1989	8.0%	[6.8, 9.4]	1.17	[0.8, 1.6]	5.8%	[5.1, 6.7]
1990-1994	6.9%	[6.0, 7.8]	1.00	[0.7, 1.4]	5.8%	[5.1, 6.7]
1995-1999	7.0%	[6.4, 7.8]	1.02	[0.8, 1.4]	5.9%	[5.3, 6.5]
2000-2004	7.2%	[6.6, 7.8]	1.05	[0.8, 1.4]	6.0%	[5.5, 6.4]
2005-2009	7.7%	[7.1, 8.4]	1.27	[0.8, 1.5]	6.0%	[5.5, 6.7]
2010-2014	8.4%	[7.7, 9.3]	1.23	[0.9, 1.7]	6.2%	[5.1, 7.4]

Table 3: Proportion of PPMS by diagnostic cohorts

	% Females	Ø-Duration at register entry (years)	Ø-Age at diagnosis (years)	Ø-Diagnostic Delay (years)
ROMS (n=27,926)	71.4%	9.0 (±7.8)	36.3 (±9.1)	2.83 (±5.0)
PPMS (n=2,269)	56.8%	8.6 (±7.7)	42.7 (±9.7)	3.31 (±4.7)

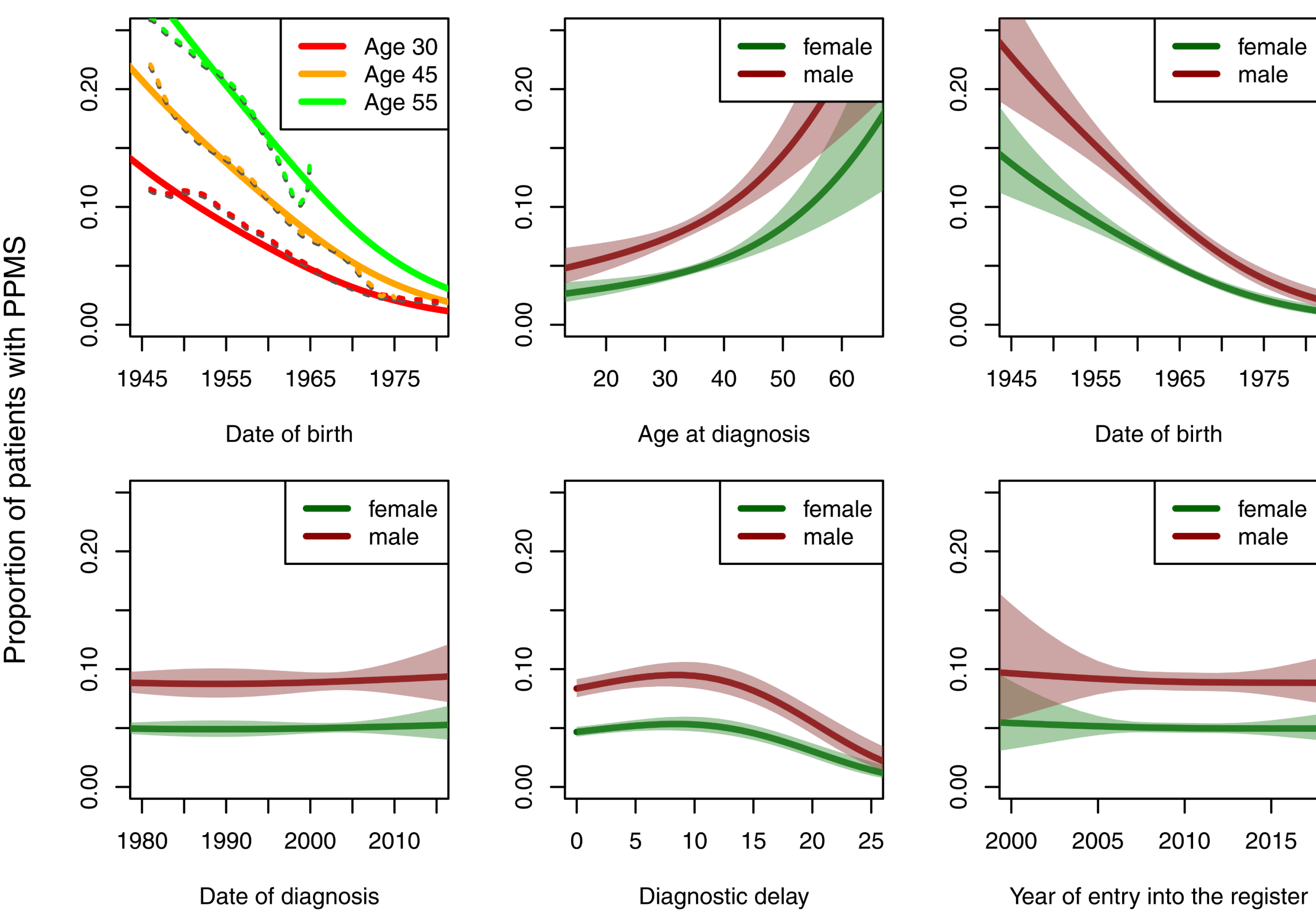Table 1: Demographics (%, mean, and standard deviations)

Figure 2: Predicted likelihood of a diagnosis of a PPMS disease course is given along with pointwise confidence bands (95%). Dotted lines in the first graph show true relative frequencies by age groups.

Conclusions:

- Strong temporal trend as reported by Westerlind et al. were found in Germany
- Swedish and German data suggest the date of birth as a strong explanatory variable, thus epidemiological reasons must be considered
- Changes in diagnostic criteria did not show a large influence in the German data

References:

(1) Petersen G, Wittmann R, Arndt V, Göpffarth D. *Epidemiologie der Multiplen Sklerose in Deutschland*. Nervenarzt. 2014;85(8):990–998.

(2) Westerlind H, Stawiarz L, Fink K, Hillert J, Manouchehrinia A. *A significant decrease in diagnosis of primary progressive multiple sclerosis: A cohort study*. Mult Scler J. 2016; 22(8): 1071-1079.

(3) Wood, Simon N. *Generalized additive models: an introduction with R*. CRC press, 2017.

Abstract