

Decline in PPMS Diagnosis? – The German View

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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.

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.

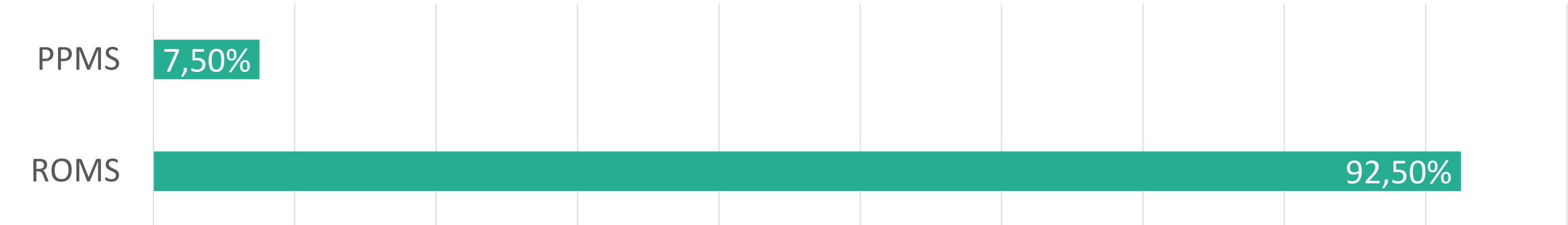


Figure 1: Ratio of PPMS and ROMS Patients in the analysed dataset

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

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.

| | % 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)

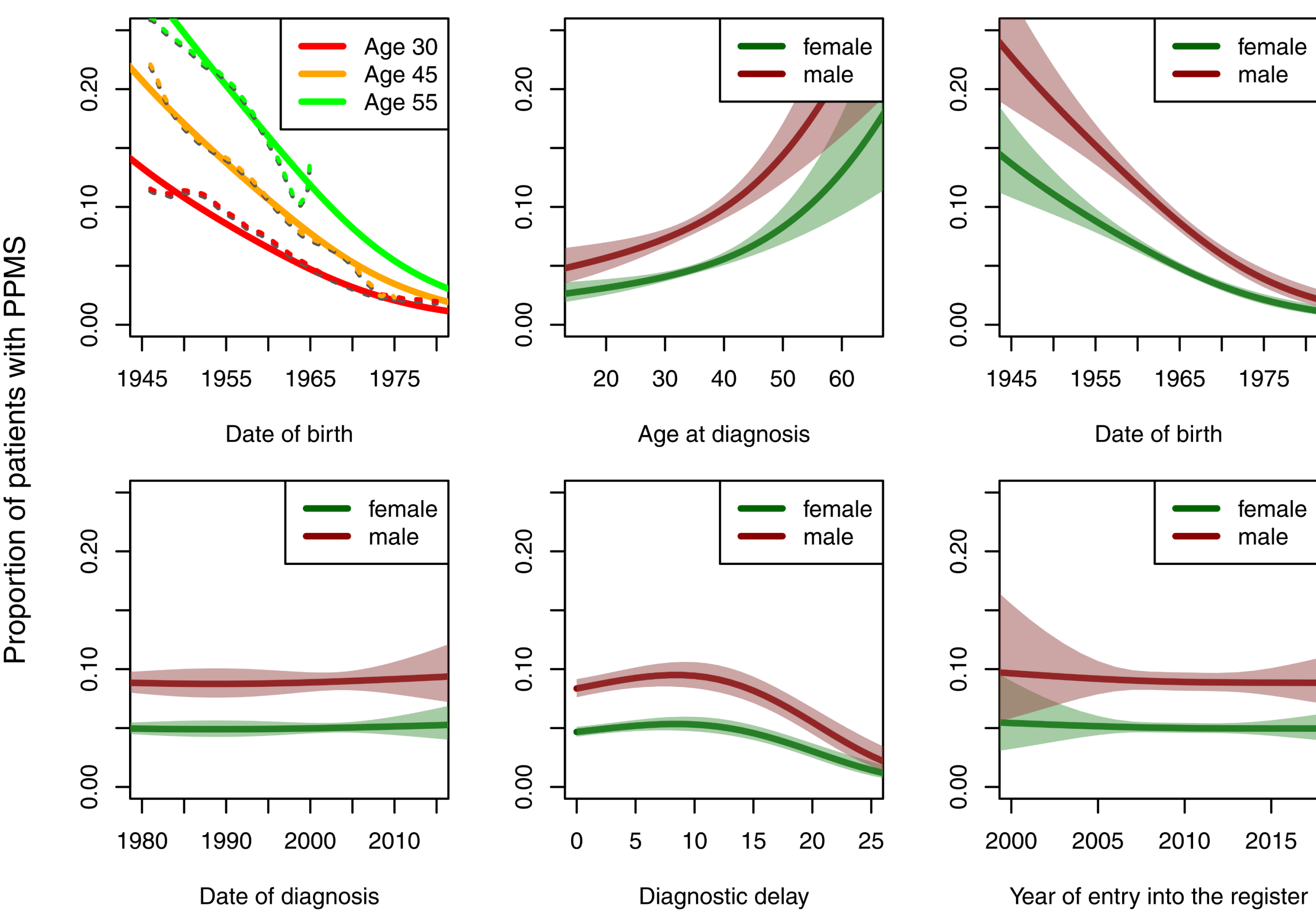


Figure 2: Predicted likelihood of a diagnosis of a PPMS disease course is given along with pointwise confidence bands (95%). Dotted lines in the first graph show true relative frequencies by age groups.

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

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Abstract

Disclosure – Declaration of Interest

David Ellenberger, Christoph Kleinschnitz, Otto Rienhoff and Alexander Stahmann have nothing to disclose.
Peter Flachenecker has received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen, Genzyme, Merck-Serono, Novartis, Roche and Teva. He has participated in pharmaceutical company sponsored trials by Almirall, Biogen Idec and Novartis. None resulted in a conflict of interest.
Tim Friede has received personal fees for consultancies (including data monitoring committees) in the past three years from AstraZeneca, Bayer, Boehringer Ingelheim, CTCT, DaiichiSankyo, Feldmann Patent Attorneys, Grünenthal, Janssen, Mediconomics, Novartis, Pharmalog, Roche, SGS, UCB; all outside the submitted work.
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