1. Background
Benign MS (BMS) was defined as patients that are fully functional in all neurologic systems 15 years after onset (Lubin and Reingold, 1996). Amato et al. (2006) described the most commonly used definition of patients (PwMS) not exceeding an EDSS of 3.0 after 15 years of disease duration (DD). The definition and existence of BMS is still a matter of debate. In the age of earliest possible MS diagnosis, individual prognosis and initiation of DMT - the clinical relevance of a 'benign' disease course is a pressing question.

2. Aims and Hypotheses:
This study aims to provide quantitative and qualitative analysis on BMS in Germany.

3. Methods and Material:
- Data [extract date: 13.08.2019] of 28,595 PwMS from the German MS-Register was analysed. Subsequently, only PwMS with a DD of ≥15 years were included. These were divided into "benign" with documented EDSS ≤ 3 at any visit later than 15 years disease duration and "non-benign" with EDSS > 3 at all visits after 15 years and beyond.
- Descriptive analyses were performed using Fisher’s exact test ($p_f$) for categorical data, t-test ($t_p$) for metric outcomes and Wicoxon test ($w_p$) for ordinal outcomes considering $p$-values $p < 0.05$ as statistically significant. No adjustments for multiple comparisons were made due to the exploratory nature of the study.
- Kaplan-Meier (KM) analyses using interval censored data were used to model and to test time to EDSS > 3. The left side of the interval is the last (sustained) measurement of EDSS ≤ 3 if existing and the right side the first visit with EDSS > 3.

4. Results:
We identified 9,398 PwMS with a disease duration ≥15 years of which 3,794 patients (40.4%) fulfilled the criteria of EDSS ≤ 3 at least one visit. Follow-up by exact years of disease duration shows that up to half of PwMS are 'benign':

- Figure 1: Proportion of EDSS ≤ 3.0 after exactly 15, 20, and 30 years of disease duration. We analysed the BMS group for survival (defined as EDSS ≤ 3; interval-censored Kaplan-Meier estimation), showing that 57% of the benign PwMS stayed benign for further 10 years, with males having less chances and PwMS with progressive onset (POMS) only being very rarely benign.

- Figure 2: Kaplan-Meier estimates of proportion of PwMS with EDSS≤3.0 in the period from 15 to 55 years of disease duration.

5. Conclusions:
- With 40% a high number of the patients did fulfil the most commonly used definition of benign MS.
- In contrast, the low number of benign-PwMS with DD of 20 or 30 years shows that the time to measure 'true benignity' of a MS might no longer be at DD of 15 years.
- In contrast to the low EDSS a high number (30%) of 'benign' patients is unemployed (already 15 years).
- The focus on the EDSS in today’s definition of BMS, which disregards 'soft/hidden' symptoms like fatigue, cognition and emotions could be a possible explanation.
- A revision of the definition for 'benign' MS is due.

6. References