Title: Month of birth effects on the risk of MS in the European Register for Multiple Sclerosis (EUReMS): Study protocol of the Epi-1s study

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Acknowledgements:
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Background: Associations between the month of birth and the risk of developing MS were observed for the first time in the Danish MS registry in 1992 with an increased risk for those born around May and a decreased risk for those born around November. Numerous studies could replicate these findings, but since effects are small and appear to be inhomogeneous concerns regarding their robustness remain. Recently, it has also been suggested that the observed effects are arte facts due to inappropriate choice of reference populations. Therefore, large scale databases with appropriate analyses are required to settle the debate.

Objectives: To combine European MS registers to form a large scale database including over 70,000 persons with MS and to build statistical models appropriately controlling for confounding factors such as socioeconomics, migration or latitude to assess the MoB effects across Europe.

Methods: MS registries and MS societies across Europe were contacted and their ability to provide data for this study was investigated by structured telephone interviews. Statistical analyses compare the observed distribution of the month of birth with those from national birth statistics, adjusting for the year of birth. Potential confounding is adjusted for through meta-regression modelling.

Results: Out of 37 MS societies in Europe, 15 were considered as potential data providers. Three of them were not willing to participate in the Epi-1s study due to problems in feasibility or conflict of interest, resulting in 12 data providers: Catalonia, Croatia, Czech republic, Finland, Germany, Italy, Liguria, Norway, Poland, Sweden, Tuscany and UK. A EUReMS-Epi-1s database was set up, and import frameworks were developed providing information on specifications and definitions for data items, guidance on data anonymization and data transfer, and supported export formats.

Conclusions: Data integration of many registers with different data architectures as well as different legal underpinnings have turned out to be a great challenge. However, the experiences of this study show that this can be mastered. Not only the large number of total cases was worth the effort, but also the fact that data was gathered independently in different heterogeneous settings. With this methodology, the risk of systematic biases is substantially reduced resulting in a high degree of evidence of our findings.