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Letter to the Editor

Comments on the review article 'Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades'

This article is a commentary to the Review article by Grytten et al, published in Supplement 132:29–36 (DOI: 10.1111/ane.12428).

A step back for MS prevalence studies in Norway

The article gives an overview of time trends in prevalence and incidence of multiple sclerosis (MS) in the different regions in Norway (1). The authors also intend to provide an update on the MS prevalence in Norway, compared to the first nationwide prevalence study published in 2014 (2). Grytten et al. estimate a nationwide prevalence of MS in Norway of 208 per 100,000 on 31 December 2013, which is not far from our reported 203 per 100,000 on 1 January 2012 (although confidence intervals were not given for the newly estimated 2013 data in the review article). Even if the main finding is similar, the methodologies used in the two studies are not comparable. As stated by the authors: 'The numbers were not adjusted, neither reduced for deaths, nor increased for those who were not treated during the period'.

In our study from 2014, data were retrieved from five different sources: in addition to data from the Norwegian MS Registry and Biobank (NMSRB) and the Norwegian Patient Register (NPR), we also included information from the Norwegian Prescription Database (NPD), Statistics Norway and Oslo MS Registry (OMSR). The patients included in the NMSRB and OMSR were diagnosed according to the Poser (3) or the McDonald (4–6) criteria by Norwegian neurologists. However, the coverage in the NMSRB was low (approximately 50% in our study), and we developed a set of inclusion criteria to exclude possible cases included in NPR due to misclassification: (i) more than one visit registered in NPR with MS as main or codiagnosis or (ii) MS and optic neuritis (ON) or (iii) MS *or* ON in combination with the prescription of a MS drug from NPR/NPD or (iv) MS *or* ON in combination with code from a rehabilitation institution.

The coverage of Oslo was higher from the validated sources (>80% of the MS patients in Oslo were included in NMSRB and/or OMSR), and we used this as a test of sensitivity (as described in the original paper). In order to adjust for differences in age and gender distribution between the regions, and to be able to compare our data with findings from other countries, the prevalence adjusted to the European Standard Population was also given. By including information from Statistics Norway, we were able to exclude those who were deceased or had emigrated during the study period (approximately 10%).

As required, our study of prevalence was in advance approved by the Regional Committee for Research Ethics and the Review Board for Oslo University Hospital, Ullevål, and the Norwegian Data Protection Authority.

We question how the prevalence figures were calculated in the review article. Cited from the abstract: 'The nationwide crude prevalence in Norway, based on the Norwegian Patient Registry, was 208 per 100,000 on December 31, 2013'. From the Methods: 'Furthermore, we retrieved data on people with MS from the Norwegian Multiple Sclerosis Registry and Biobank and from the Norwegian Patient Registry on December 31, 2013 to calculate updated figures for the prevalence of MS in Norway'. From the Results: 'To follow up on the nationwide prevalence of MS in Norway and to estimate the prevalence in the counties, we retrieved data from the Norwegian Multiple Sclerosis Registry and Biobank and the Norwegian Patient Registry'.

If data from the two sources were combined, the process of excluding duplicates, which requires unique personal identification numbers, was not described.

Prevalence on county level

The review article also gives estimates for the prevalence in the individual counties in Norway, presumably based on the same methodology as for the national prevalence figures. The authors presented similar data at the annual meeting of Norwegian neurologists on 11 March 2015 and confirmed that these data were based on hospital contacts and not the patients' place of residence (Aarseth, JH, Grytten N, Torkildsen Ø, Myhr KM: Norsk MS-Register og Biobank; registerdekningsgrad og behandlingsfrekvens. Nevrodagene 2015). In addition (cited and translated from Norwegian from the abstract): 'The number of treated patients per county and the total number of patients (prevalence) per 2013 was retrieved from NPR'. In the abstract, the reported prevalence in Norway (208 per 100,000) and in Møre and Romsdal (275/100,000) was identical to that presented in the review article, thus strongly suggesting that also these data were based solely on the numbers from NPR and not linked with the NMSRB. Identical prevalence estimates for Norway and for the Norwegian counties as to those given in the review article were presented as a poster at 'Kvalitetsregisterkonferansen in 2015', based on data from NPR (http://www.helse-bergen.no/no/OmOss/Avdelinger/ms/Documents/Kvalitetsregisterkonferansen_Poster_MS_5_11.pdf). In table 1 from the poster (cited and translated from Norwegian): 'Troms and Finnmark, Vest-Agder and Aust-Agder and Oppland and Hedmark are combined as diagnosing and treating patients goes across the county borders'. This indicates that the estimates for the prevalence by county were based on the county where the patients were followed up and not where they were residing, as is crucial both for giving reliable prevalence estimates for the counties and particularly for estimating the fraction of patients receiving disease-modifying treatment in each county.

Prevalence for each county based on county of residence has, however, also been calculated based on data from the 2014 nationwide prevalence study and presented in the doctoral thesis by Pål Berg-Hansen (Clinical and epidemiological studies of immigrants with multiple sclerosis in Norway, University of Oslo, 2015. ISBN 978-82-8333-004-5). These data are shown in Table 1. The most striking dissimilarity is found for Akershus county, which had a reported prevalence of 142/100,000 in the review article compared to 192/100,000 in our study, indicating that a significant number of patients from Akershus are followed up in the neighbouring counties.

Table 1 Most recent Norwegian MS prevalence studies by county and year compared to data adapted from the 2014 Norwegian prevalence study

County	Prevalence[a]	Year[b]	Author (year)	Prevalence 1 January 2012[c]
Finnmark	51.3	1993	Grønlie et al. (2000) (14)	167
Troms	84.0	1993	Grønlie et al. (2000) (14)	180
Nordland	105.6	2000	Alstadhaug et al. (2005) (15)	206
Nord-Trøndelag	163.6	2000	Dahl et al. (2004) (16)	215
Sør-Trøndelag	–	–	–	247
Møre and Romsdal	329.2	2014	Willumsen and Midgard (2014)[d] (17)	269
Sogn and Fjordane	–	–	–	238
Hordaland	211.2	2013	Grytten et al. (2015) (19)	190
Rogaland	–	–	–	168
Vest-Agder	180	2007	Vatne et al. (2011) (18)	237
Aust-Agder	–	–	–	216
Telemark	–	–	–	194
Vestfold	166.8	2003	Lund et al. (2014) (20)	195
Buskerud	–	–	–	180
Oppland	174.1	2002	Risberg et al. (2011) (21)	243
Hedmark	–	–	–	247
Oslo	148/170[e]	2006	Smestad et al. (2008) (12)	182
Akershus	–	–	–	192
Østfold	–	–	–	191

[a]Per 100,000 inhabitants.
[b]Prevalence year, 1 January.
[c]Prevalence per 100,000 inhabitants calculated from the 2014 Norwegian prevalence study.
[d]Poster presented at ACTRIMS/ECTRIMS 2014.
[e]Norwegian/Western population.

No nationwide prevalence studies were published in Norway until 2014

From the Introduction: 'Several publications have since reported an increased prevalence and incidence of MS in Norway, and the most recent nationwide publication concluded that the MS prevalence in Norway is among the highest reported worldwide and that there is no longer any evidence of a latitude gradient'.

And from the Results: 'In 1952, Swank et al. published the first nationwide study on the incidence of MS in Norway during 1935–1948'. Although Swank was an important pioneer in MS epidemiology in Norway, patients were not included 'nationwide' but only from selected areas (7). Our 2014 study is the first and so far the only true nationwide publication.

Comments on the latitude gradient

The authors repeatedly state that a latitude gradient was previously found for the prevalence of MS in Norway. This hypothesis was, however, based on studies from different counties at dif-

ferent time points and with varying methodology, as there was no previous nationwide prevalence study performed until 2012. We did therefore not contradict any previous findings, as it is not clear whether any such gradient has ever existed.

Some comments might give the impression that our studies were performed in Oslo and not in the whole country

From the Results: 'The latest report corroborating a trend toward increasing prevalence was reported from Oslo: 203 per 100,000 population in 2014. The recent Oslo study no longer found any evidence for the latitude gradient in MS prevalence in Norway... In 2014, a follow-up study on immigration and prevalence was published, detecting a prevalence of 162 per 100,000 population among first-generation Iranian immigrants in Oslo vs the prevalence of 99 per 100,000 population in Iran'. The data were based on the same sample as the 2014 nationwide prevalence study, including immigrants from the whole country and not only Oslo (8).

Additional comments

Some of the statements in the review article might be misleading or even erroneous. From the Results: 'Increased disease severity and younger age at onset were also detected among non-Western immigrants with MS, as measured by the Multiple Sclerosis Severity Score'. Age at onset is not included in this score, which is a measure of disease disability in relation to disease duration (9).

In the Conclusion, the authors claim that 'The prevalence of MS in Norway has increased 10-fold during the past five decades, the female-male sex ratio has increased, and second-generation immigrants have an increased risk of MS compared with native populations in their countries of origin'. Given that the only nationwide prevalence study performed in Norway to date presented data from 2012, this statement could be questioned. In line with studies from Canada (10), Sweden (11) and Oslo (12), Iranian immigrants have a higher prevalence of MS than reported from their country of origin. Our study indicates that second-generation immigrants from Pakistan have a considerably higher prevalence compared to the first-generation Pakistani immigrants; however, we lack reliable data on the prevalence of MS from Pakistan.

Well-done prevalence studies are encouraged

Our nationwide prevalence study published in 2014 received an editorial comment, encouraging well-done prevalence studies (13). Utilization of several different sources whilst maximizing capture allows validation of diagnoses. Applying specific criteria makes a good compromise and 'balance' between incorrect diagnosis and incomplete case ascertainment. Age and sex standardization must be applied for a prevalence estimate to be compared with other regions and nations. Well-done prevalence studies should, to provide useful data, meet the criteria outlined in the editorial comment. Work like ours, particularly from regions such as northern Scandinavia was strongly encouraged. Unfortunately, we consider the review by Grytten et al. a major step back from this scientific goal.

Conclusion

The review article intends to give an update on the prevalence of MS in Norway 31 December 2013, 2 years after the data from 1 January 2012, which was published in 2014. Although the main findings are in part similar, the methodology used is poor or only vaguely described. We identify some major dissimilarities concerning the prevalence in the counties between the two studies. We are concerned that future reports based on the paper by Grytten et al. might be highly biased. Some of the statements are also misleading and some directly erroneous and cannot pass without being commented on.

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None.

Conflict of interest

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P. Berg-Hansen[1,2], *S. M. Moen*[1,2], *H. F. Harbo*[1,2], *E. G. Celius*[1,2]
[1]Department of Neurology, Oslo University Hospital, Oslo, Norway; [2]Institute of Clinical Medicine, University of Oslo, Norway
e-mail: pberghansen@gmail.com

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