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Sporadic cases of chronic wasting disease in old moose – an epidemiological study

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Abstract

Transmissible spongiform encephalopathies or prion diseases comprise diseases with different levels of contagiousness under natural conditions. The hypothesis has been raised that the chronic wasting disease (CWD) cases detected in Nordic moose (*Alces alces*) may be less contagious, or not contagious between live animals under field conditions. This study aims to investigate the epidemiology of CWD cases detected in moose in Norway, Sweden and Finland using surveillance data from 2016 to 2022.

In total, 18 CWD cases were detected in Nordic moose. All moose were positive for prion (PrP^{res}) detection in the brain, but negative in lymph nodes, all were old (mean 16 years; range 12–20) and all except one, were female. Age appeared to be a strong risk factor, and the sex difference may be explained by few males reaching high age due to hunting targeting calves, yearlings and males.

The cases were geographically scattered, distributed over 15 municipalities. However, three cases were detected in each of two areas, Selbu in Norway and Arjeplog-Arvidsjaur in Sweden. A Monte Carlo simulation approach was applied to investigate the likelihood of such clustering occurring by chance, given the assumption of a non-contagious disease. The empirical *P*-value for obtaining three cases in one Norwegian municipality was less than 0.05, indicating clustering. However, the moose in Selbu were affected by different CWD strains, and over a 6 year period with intensive surveillance, the apparent prevalence decreased, which would not be expected for an ongoing outbreak of CWD. Likewise, the three cases in Arjeplog-Arvidsjaur could also indicate clustering, but management practices promotes a larger proportion of old females and the detection of the first CWD case contributed to increased awareness and sampling.

The results of our study show that the CWD cases detected so far in Nordic moose have a different epidemiology compared to CWD cases reported from North America and in Norwegian reindeer (*Rangifer tarandus tarandus*). The results support the hypothesis that these cases are less contagious or not contagious between live animals under field conditions. To enable differentiation from other types of CWD, we support the use of sporadic CWD (sCWD) among the names already in use.

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Keywords: *Alces alces*; epidemiology; Nordic countries; prion disease; sporadic chronic wasting disease (sCWD); transmissible spongiform encephalopathies.
Abbreviations: BSE, bovine spongiform encephalopathy; CNS, central nervous system; CWD, chronic wasting disease; DNA, deoxyribonucleic acid; EEA, European Economic Area; ELISA, enzyme-linked immunoassay; EU, European Union; 109K, lysine at codon 109; PCR, polymerase chain reaction; *PRNP*, prion protein gene; prob, probability; PrP, prion protein; PrP^{res}, prion (resistant prion protein); 109Q, glutamine at codon 109; sCWD, sporadic chronic wasting disease; TSE, transmissible spongiform encephalopathy.
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Three supplementary figures and one supplementary table is available with the online version of this article.

Impact Statement

Chronic wasting disease (CWD) in Nordic moose has been found in old animals and all, except one male, were females. Previous studies of Norwegian moose cases have reported detection of prions (PrP^{res}) in the central nervous system only. The epidemiological findings in this study, in combination with the biochemical properties and the strain typing results, support a different aetiology of CWD in Nordic moose compared to CWD in North American cervids and Norwegian reindeer. Although the number of moose CWD cases is limited in comparison with other ruminant TSEs, our findings support the hypothesis that these Nordic cases occur sporadically and not contagious or only contagious to a low degree between live animals under field conditions. Knowledge of the epidemiology is fundamental for disease control, as different epidemiological patterns require different control measures. Among the different names already being used, we support the use of the name *sporadic chronic wasting disease* (sCWD) to facilitate distinction from CWD as currently observed in cervids in North America and Norwegian reindeer.

INTRODUCTION

Transmissible spongiform encephalopathies (TSE) or prion diseases, are characterized by misfolding of cellular prion protein into prions (PrP^{res}), which accumulate in the central nervous system, causing neurodegeneration and eventually death. Although all TSEs are associated with a transmissible agent, the group comprises diseases with different aetiology and different modes of transmission. Some of the diseases are hypothesized to be spontaneous, i.e. without known cause, for example, 90% of the prion diseases in human [1], and Nor98 scrapie, also called atypical scrapie, in small ruminants [2]. Atypical scrapie occurs in approximately 6 to 8 animals per 10000 slaughtered adult sheep, and in older sheep compared to classical scrapie [3] (Table 1). In contrast, classical scrapie shows a clear contagious pattern with prions being transmitted horizontally between individuals by direct contacts or indirectly through contaminated environment [4, 5]. Classical scrapie can be detected in both young and adult individuals, and the prevalence in affected flocks can be more than 20% [5]. A key feature of contagious forms of TSEs is detectable prions in lymphoid tissue, and the presence of prions in excretions and/or amniotic fluid thus enabling exposure to other animals. In contrast, for TSEs that are hypothesized to be spontaneous, prions are only detected in the central nervous system (CNS) and not in lymphoid tissue when using traditional diagnostic methods, limiting the potential for prions to be transmitted horizontally between live animals under field conditions (Table 1).

Epidemiology and routes of transmission are fundamental aspects to determine efficient strategies for prevention, surveillance and control of disease. Bovine spongiform encephalopathy (BSE) or 'mad cow disease', was transmitted through use of meat and bone meal in cattle feed resulting in bovine-to-bovine transmission of prions [6]. The insight in 1996, that BSE could be transmitted to humans causing a fatal disease named variant Creutzfeldt-Jacob disease [7] resulted in strict control measures (e.g. prohibition to use ruminant meat and bone meal in feed for all farmed species), and extensive surveillance in cattle and small ruminants [8].

Surveillance contributed to detection and understanding of previously unknown TSEs in ruminants. In 1998, an unusual type of scrapie was discovered in Norway and designated Nor98 scrapie or atypical scrapie [9]. When analysing surveillance data, two different epidemiological patterns of scrapie in small ruminants became clear. Atypical scrapie occurs as sporadic cases, which do not cluster within flocks or countries and is now hypothesized to be spontaneously occurring and not contagious or only contagious to a low degree between live animals under field conditions [2]. The same happened in 2004, when atypical BSE was described [10, 11]. As more cases were detected, in most of the European countries, it became clear that they had a different aetiology compared to classical BSE and are now hypothesized to be spontaneous [12]. The findings also led to new nomenclature separating scrapie into classical scrapie (contagious) and atypical scrapie (hypothesized spontaneous), and BSE into classical BSE (acquired through prion contaminated meat and bone meal) and atypical BSE (hypothesized spontaneous). Accordingly, the different types of disease were distinguished in relation to reporting, control and international trade [13–15].

Chronic wasting disease (CWD) is a TSE affecting species in the Cervidae family. It was first diagnosed among mule deer (*Odocoileus hemionus*) in 1967 in Colorado, USA and has since then spread extensively within North America [16]. The disease is contagious, with prions detectable in lymphoid tissue and are excreted in saliva, urine and faeces. Moreover, cases are spatially clustered with a rising prevalence in most of the affected populations unless management actions are taken.

In May 2016, the first European case of CWD was detected in Norwegian wild reindeer (*Rangifer tarandus tarandus*) [17]. Following this detection, Norway initiated extensive CWD surveillance in all cervid species. In May 2016, two cases were detected in moose (*Alces alces*) [18]. The findings in Norway led to mandatory surveillance within the European Union (EU)/the European Economic Area (EEA), in countries with reindeer and/or moose populations, i.e. Estonia, Finland, Latvia, Lithuania, Norway, Poland and Sweden [19]. The aim was to confirm or exclude the presence of CWD. This surveillance has led to detection of further cases in moose in Norway, Sweden and Finland and in red deer (*Cervus elaphus*) in Norway [20].

Table 1. Characteristics of some animal TSEs; PrP^{res} distribution, age and sex of cases, observed clustering of cases and assumed aetiology. CNS: central nervous system; RLN: retropharyngeal lymph nodes; F: female; M: male

Disease	Sub-category of disease	PrP^{res} distribution		Age in year	Sex	Spatial clustering	Transmission	References
		RLN	CNS	Mean (range)	Ratio (F/M)			
Scrapie in sheep	Classical scrapie	+	+	‡	F>M *	Herd/country	Contagious	[5, 13, 56]
	Atypical scrapie	–	+	6.9	F>M *	No, sporadic occurrence	Hypothesized spontaneous	[13, 14, 56]
BSE in cattle	Classical BSE	–	+	Approx. 5†	F>M *	Country	Feed borne	[6, 57, 58]
	Atypical BSE	–	+	12 (5.5–18.5)	F>M *	No, sporadic occurrence	Hypothesized spontaneous	[13, 15, 58]
CWD in cervids	White tailed deer North America	+	+	2–3 (1–10)	F<M	Area	Contagious	[37, 38]
	Mule deer North America	+	+	5–6 (1–10)	F<M	Area	Contagious	[39]
	Elk/wapiti North America	+	+	3‡ (2–17)	F≤M	Area	Contagious	[59, 60]
	Cases detected in wild reindeer Norway	+	+	4 (1.5–8.5)	6 F / 13 M	Area	Contagious	[36]
	Cases detected in Nordic moose	–	+	16 (12–20)§	17 F / 1 M	Yes/no, sporadic occurrence	Hypothesized spontaneous or low contagiousness	[18], this paper

*The sex ratio in production animals is dependent on husbandry practices, which gives more females than males.
†Based on age data from 1988 to 2002 as reported by Prince *et al*. [57].
‡Calculated excluding one moose with uncertain age.
§Median.

The post-harvest moose population size was estimated to 107000 in Norway, 265000 in Sweden and 96000 in Finland around 2010 [21]. Moose are solitary animals and have varying migration patterns. In Fennoscandia, the proportion that migrates between separate winter and summer ranges have been found to vary from 0% to almost 100%, with migration distances up to 150–200 km [22, 23]. In 2010, about 200000 moose were harvested in the Nordic countries [21]. The harvest focuses on calves, yearlings and males (> 50%) [24], which impact the age and sex distribution of the population. The population sex ratio has been skewed in favour of females [24]. Most males are shot before their prime (about 5–9 years old). Conversely, female moose survive longer and the average age at death is higher than for males [25, 26]. In a sample of 14736 harvested and age-determined moose (including calves) in Norway during 2010–2016, less than 0.01% of males and 4.5% of females were 12 years or older [27]. See Supplementary Material for details, available with the online version of this article.

Large-scale surveillance and analysis of both case data and surveillance data were pivotal to understanding the epidemiology of BSE and scrapie, and how they could be separated in different subgroups. With the accumulating number of cases in moose and ongoing surveillance efforts, available data is increasing. Analysis of these can contribute to the understanding of the underlying epidemiology of these cases in moose. Whereas a first joint analysis was recently published [28], this study contribute to further analyses, including Monte Carlo simulation of the probability of detection of cases and analysis of age data of surveyed moose.

The aim of this paper was to describe and analyse available CWD surveillance and case data related to the CWD detections in moose in Norway, Sweden and Finland and thus contribute to the understanding of the epidemiology.

METHODS

Surveillance

In all countries, there has been a general CWD surveillance covering all relevant cervid species from before 2016. From 2016, Norway implemented an extensive surveillance programme and all countries implemented surveillance based on EU regulation [19] from 2018. When positive cases were detected, intensified surveillance was performed in areas surrounding the cases sampling all available adult cervids regardless whether hunted or found dead. From 2016 to June 2022, more than 160100 cervids have been

Table 2. Surveillance for CWD in Norway, Sweden and Finland from 2016 to June 2022. Number of moose that tested negative and positive per country and target group as defined in EU commission regulation [19]. Neg: negative; Pos: positive

		Norway				Sweden				Finland				Sum	
Risk		**Ordinary**		**Intensified**		**Ordinary**		**Intensified**		**Ordinary**		**Intensified**			
Category	**Target group**	**Neg**	**Pos**	**Neg**	**Pos**	**Neg**	**Pos**	**Neg**	**Pos**	**Neg**	**Pos**	**Neg**	**Pos**	**Neg**	**Pos**
Risk	Clinical suspect animals	–	–	–	–	78	1*	1	–	–	–	–	–	79	1
Risk	Fallen/culled	1841	10*	256	0	701	2‡	7	0	297	2	6	0	3108	14
Risk	Road/predator killed	1675	0	433	0	19	0	2	0	187	0	6	0	2322	0
Risk	Hunted, not fit for human consumption	75	0	17	0	40	0	0	0	39	0	2	0	173	0
Hunted	Hunted, fit for human consumption	13123	0	9808	1†	80	0	1034	1†	110	0	132	0	24287	2
Hunted	Unspecified, within hunting season	3502	0	1874	0	–	–	–	–	–	–	–	–	5376	–
Risk	Unspecified, outside hunting season	751	0	256	0	–	–	–	–	–	–	–	–	1007	–
	Total	20967	**10**	12644	**1**	**918**	**3**	**1044**	**1**	**633**	**2**	**146**	**0**	36352	**17**

*One of the cases was found in the same area as a previous case, but it was detected before an intensified surveillance area was formally established, see Table 3.
†Would have been considered fit for human consumption if CWD had not been diagnosed.
‡The group includes animals with signs of disease, which were culled.

tested, of which 33622 (28319), 1966 (1126) and 781 (242) moose (hunted in brackets) have been tested in Norway, Sweden and Finland, respectively (Table 2). See Supplementary Material for details.

Sampling and diagnostic tests

Samples of brain tissue (*medulla oblongata*) and lymphoid tissue, if available, were collected. The samples were tested for the detection of PrP^{res} using an ELISA as primary test and Western-blot for confirmation in accordance with EU Regulation [8]. The analyses were performed at the national reference laboratories in the respective countries. See Supplementary Material for details.

Age determination

The surveillance focused on animals above 1 year of age. The age category was reported by the person collecting the sample or performing necropsy based on eruption of teeth. In Norway, the animals were categorized as yearling or adult ≥2 years when possible.

All countries made efforts to retrieve the mandibula from positive cases to enable age determination in cases when the whole head was not initially submitted to the laboratory. In four areas of intensified surveillance, i.e. Arjeplog-Arvidsjaur and Robertsfors in Sweden, Laukaa in Finland and Selbu in Norway, part of the mandibula was submitted to enable age determination also of the CWD negative animals. As age determination is resource demanding, this was restricted to these areas. The age in years was estimated by counting annual cementum growth layers in stained tooth sections from incisors (Norway), unstained sections from incisors (Finland), or stained sections from either molars or incisors (Sweden) [29, 30].

Prion protein genotyping

In short, genomic DNA was extracted from brain. Prion protein (PrP) coding region was amplified, and the amplicons were sequenced with primers used in the PCR and the polymorphisms at codons 36, 100, 109 and 209 were determined. The readings were compared to GenBank accession no. MH230115 that was considered the 'wild-type' [31]. See Supplementary Material for details.

Description of data

Data on all individual moose analysed for CWD in the period 2016 to June 2022 were provided from the national reference laboratories for TSE. For each case, the data included information on area of origin, date, risk category ('healthy hunted animals', 'risk animals', see Table 2), age category, sex and CWD result. For Norway, when data was missing on risk category, sex and/or age category, the missing data was imputed. For details, see Supplementary Material.

In addition, detailed data on all positive cases in the study period plus an additional case detected in October 2022 (Table 3) as well as age data for sampled moose in the areas of intensified surveillance as detailed above.

Prevalence estimates

The apparent prevalence with 95% confidence intervals was estimated for each country and risk category assuming a binomial distribution. Fisher's exact test was used to estimate the *P*-value when comparing different proportions. To explore development over time, the annual apparent prevalence was estimated for areas with at least one positive case from 2016 to 2020. Only areas where the number of tested animals was large enough to give meaningful confidence limits for several years were included. The estimation was performed using 'base::binom.test' and 'stats::fisher.test' in R version 4.0.2 [32].

Spatial analysis

As of June 2022, a total number of 17 CWD-positive moose had been detected, which were considered too few to obtain stable results from a traditional cluster analysis. Instead, Monte Carlo simulation was used to compute empirical *P*-values [33] of obtaining two or more cases within a municipality or within neighbour municipalities. We simulated the distribution of positive cases on municipalities for the risk categories: hunted, road/predator killed, other risk animals using the actual number of tested per municipality, for the corresponding risk category and sex for each country. When the empirical *P*-value for the observed number within an area was less than 0.05, it was considered to indicate clustering. The simulations were performed in R version 4.2.1 [32] using 'base::sample' sampling without replacement, and 100000 iterations of each simulation were performed.

Age analysis

The probability that a moose sampled within the intensified surveillance was ≥12 years was estimated using a generalized linear model using R version 4.2.2 'stats::glm', predicted values were calculated with the package 'ggeffects' [34].

Table 3. Description of the chronic wasting disease cases in moose detected in Norway, Sweden and Finland from 2016 to 2022. NA = material not available

								Result PrP^{res}		
Case N°	**Country**	**Municipality**	**Dead month**	**Category**	**Sex**	**Age* (years)**	**Genotype†**	***Medulla oblongata***	**Lymph nodes**	**Observations/ findings**
NO-1	Norway	Selbu	May 2016	Clinically sick	F	13	Wild type	Positive	Negative	
NO-2	Norway	Selbu¶	May 2016	Found dead	F	14	Wild type	Positive	NA	
NO-3	Norway	Lierne	Oct 2017	Abnormal behaviour	F	13	Wild type	Positive	Negative	Hip joint luxation
NO-4	Norway	Flesberg	Oct 2018	Abnormal behaviour	F	15	109Q/109Q	Positive	Negative	Ethmoid tumour and hip joint luxation
NO-5	Norway	Selbu	Sep 2019	Hunted‡	F	20	Wild type	Positive	Negative	
NO-6	Norway	Sigdal	Nov 2019§	Found dead‡	F	12	109Q/109Q	Positive	Negative	
NO-7	Norway	Steinkjer	Apr 2020§	Found dead	F	17	Wild type	Positive	Negative	
NO-8	Norway	Bamble	Jan 2021	Clinically sick	M	13	Wild type	Positive	Negative	Hind limb fracture
NO-9	Norway	Vinje	Oct 2021	Found dead	F	17	Wild type	Positive	Negative	
NO-10	Norway	Tynset	Dec 2021††	Clinically sick	F	20	109Q/109Q	Positive	Negative	
NO-11	Norway	Nord-Odal	Nov 2021††	Found dead	F	19	Wild type	Positive	Negative	
SE-1	Sweden	Arjeplog	Mar 2019	Clinically sick	F	16	Wild type	Positive	Negative	Observed emaciated, walking in circles
SE-2	Sweden	Arvidsjaur¶	May 2019	Clinically sick	F	16	Wild type	Positive	Negative	Observed with neurological symptoms
SE-3	Sweden	Arjeplog	Sep 2019	Hunted‡	F	>10**	Wild type	Positive	Negative	Observed standing still and didn't move when hunters approached
SE-4	Sweden	Robertsfors	Sep 2020	Clinically sick	F	14	Wild type	Positive	Negative	Observed lame
FI-1	Finland	Kuhmo	Feb 2018	Found dead	F	15	NA	Positive	Negative	
FI-2	Finland	Laukaa/ Laukas	Oct 2020	Clinically sick	F	18	Wild type	Positive	Negative	Observed lying down, emaciated
FI-3	Finland	Kyyjärvi	Oct 2022	Clinically sick	F	15	Wild type	Positive	Negative	In poor condition, did not move when hunters approached

*Methods for age determination varies between countries, see Methods.
†Wild-type = 36T, 100S, 109K and 209M (GenBank accession no. MH230115) [31]. Genotypes for the eight first Norwegian cases have been reported previously [18, 55].
‡Found or hunted within an intensified surveillance area.
§Exact month of death is uncertain.
¶Case found in the same area as a previous case, but it was detected before an intensified surveillance area was formally established.
**Difficult to determine age, at least 10 years.
††Samples received in 2022 and registered in 2022 statistics.

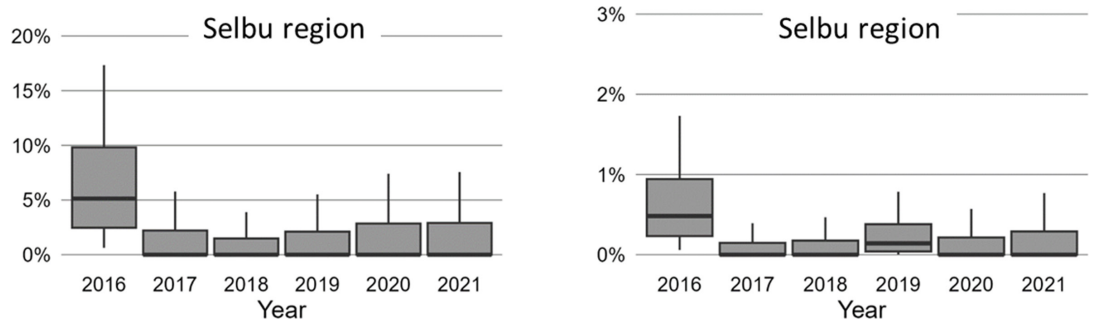

Fig. 1. Apparent annual prevalence of CWD in moose from the Selbu region, Norway, from 2016 to 2021. (a) Prevalence in adult risk animals. (b) Prevalence in all adult animals (risk animals and hunted animals). Box plots where the thick line depicts the median, the box the 25 and the 75% percentiles and the whiskers the 2.5 and 97.5% percentiles.

RESULTS

Description of the cases

In addition to the 17 cases detected during the study period, a case detected in October 2022 is included in the description of cases. There where 11 cases in Norway, four in Sweden and three in Finland (Table 3). All cases were in old individuals, and all, except one, were female (Tables 1 and 3). Age was estimated to 12–20 years (mean 16 years, Table 1). One moose was not included in the calculation of mean as the age could not be estimated with certainty, but it was at least 10 years old based on cementum annulations in the fourth molar.

Fifteen (83%) moose were animals that either showed abnormal behaviour or clinical signs compatible with CWD, were clinically ill or found dead. The main clinical or pathological findings per case, if known, are given in Table 3.

Variation in the prion protein gene (*PRNP*) in Nordic moose has only been detected at codon 109 expressing 109K (wild-type) or 109Q (GenBank accession no. JQ290077.1). Of the 17 cases with known genotype, all were homozygous, 14 were 109K/109K and three were 109Q/109Q (Table 3).

Prevalence estimates

In total, 0.27% of the risk animals were positive for CWD with 0.23, 0.35 and 0.43% being positive in Norway, Sweden, and Finland, respectively (Table 2). When imputing risk category, age and sex for Norwegian moose lacking such information, 0.19% of the Norwegian risk animals were CWD positive. When stratifying on sex, the prevalence was higher in female risk animals (0.48) than in male risk animals (0.07). This difference was borderline significant (P-value=0.048).

In the Selbu region, a region where data over several years was available and where more than one positive case had been detected, the prevalence did not increase during the intensified surveillance (Fig. 1). Corresponding figures for four regions in Norway are available in the Supplementary Material (Figs S1 and S2).

Spatial distribution

The positive moose were distributed in 15 different municipalities in three countries. The cases occurred geographically scattered and, except for cases within same municipality or neighbour municipalities, there was no known connection between the areas, such as known moose migration routes (Fig. 2).

Five of the cases were found in the same or neighbouring municipality of a previous case (Table 3). The empirical probability estimated by Monte Carlo simulation of having two or more cases within a single municipality or a group of neighbour municipalities are presented in (Tables 4 and 5), respectively. In Norway, there were a total of 11 cases from 2016 to 2022 and three Norwegian cases were found within a single municipality (Selbu). The empirical P-value of a single municipality having three cases or more was 2.0% indicating clustering (Table 4). In Sweden a total of four cases have been detected, with two cases found in Arjeplog municipality and one case found in the neighbour municipality Arvidsjaur. The empirical P-value of a single municipality having at least two cases was 5.5% (Table 4) while it was 0.7% for having three cases within neighbour municipalities indicating clustering (Table 5). In Finland, as of June 2022, two cases were detected in two different municipalities and a third Finnish case was detected in another municipality in October 2022. There were no indication of clustering in the Finnish data.

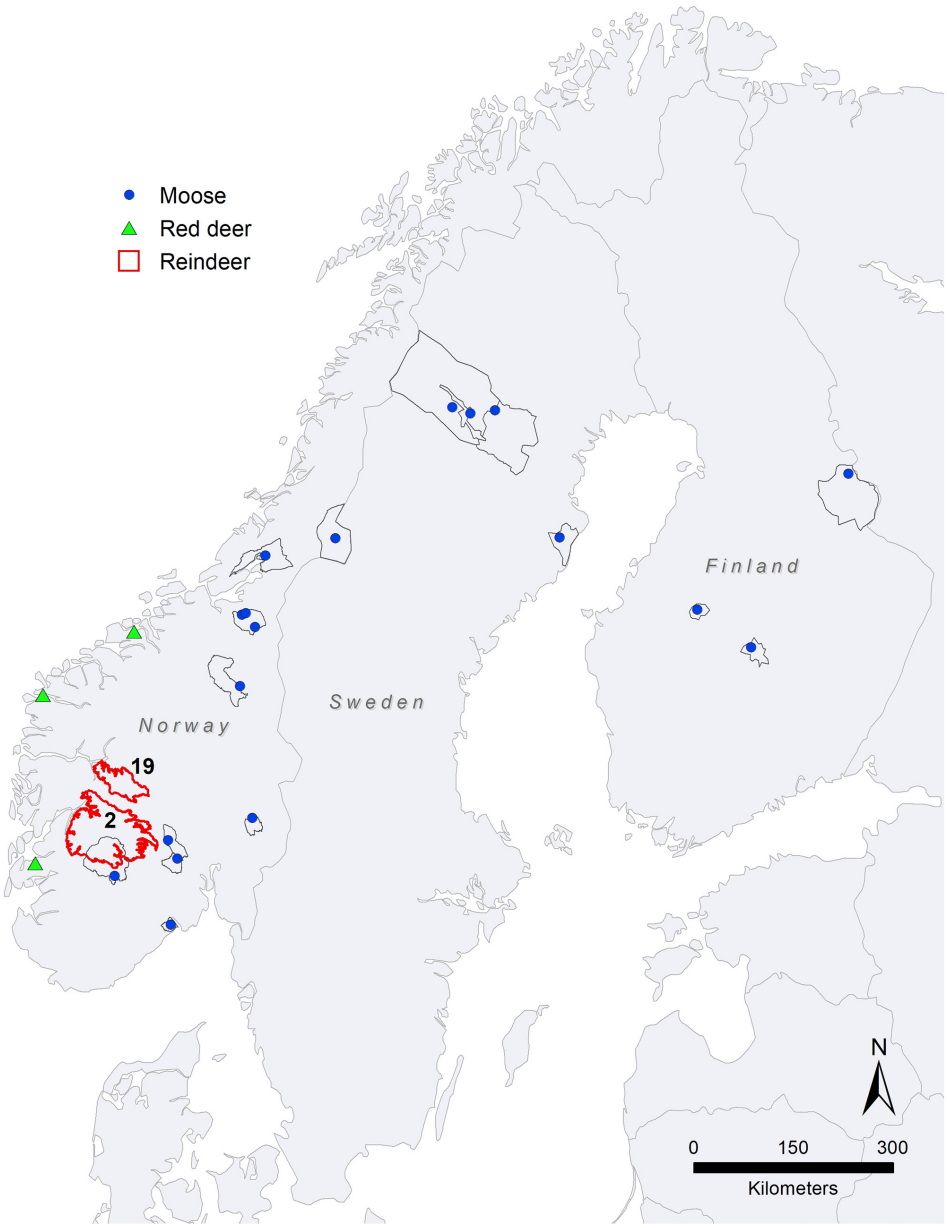

Fig. 2. Location of detected cases of chronic wasting disease in the Nordic countries from 2016 to 2022 by species. For wild moose and wild red deer, the location is described using the geo-coordinates of the places where they have been discovered deceased or hunted. The grey borders mark the municipality in which the moose cases were found. For wild reindeer, the animals are assigned to the wild reindeer management area.

Age distribution in intensified surveillance area

There was a clear difference in age between female and male moose sampled within the intensified surveillance, and a difference between the four areas (Fig. 3 and Table S1) where age determination was performed. The probability that a female moose was ≥12 years varied from 0.17 in Arjeplog-Arvidsjaur to 0.06 in Robertsfors. The probability that a male moose was ≥12 years was 0.01 or less in all areas. The age distribution of the sampled female and male moose are shown in the Supplementary Material (Fig. S3).

DISCUSSION

CWD is known as a contagious disease among cervids in North America. The disease is characterized by the detection of prions in lymphoid tissue and at a later stage in CNS tissue, cases occurring spatially clustered, usually with increasing prevalence over time, affecting all age classes (rarely calves), and often with higher prevalence in males compared to females (Table 1). We here

Table 4. Empirical *P*-value estimated by Monte Carlo simulation of having multiple cases within a single municipality. The probability was computed by simulating the distribution per municipality of the national number of CWD cases, accounting for the number of moose tested in each municipality. The observed cases are added for comparison

	Empirical *P*-value (in percent) of a single municipality having a certain no. of cases or more given that it has at least one case.					**Observed no. of municipalities with one or more cases**		
No. of cases per municipality country, strategy	≥1 case	≥2 cases	≥3 cases	≥4 cases	≥5 cases	1 case	2 cases	3 cases
Norway excluding animals with missing data	100	38.9	2.0	0.08	0.003	8		1*
Norway, including animals with missing data	100	36.2	1.7	0.07	0.001	8		1*
Sweden	100	5.5	0.05	–	–	2	1	
Finland	100	1.1	–	–	–	2		

*Observations for which the empirical *P*-value was less than 5%.

document the epidemiological differences between the contagious CWD in North America and in Norwegian wild reindeer compared to CWD as detected in moose in the Nordic countries. In CWD cases in Nordic moose, prions were detectable only in CNS tissue when using traditional diagnostic methods [ELISA, Western-blot (Table 2) and immunohistochemistry [35]], cases have occurred geographically scattered, there were no signs of increasing prevalence over time, only cases in old animals have been detected, and there was a notably higher prevalence in females compared to males (Table 1).

All CWD cases in Nordic moose have been detected in old animals, with a mean age of 16 years, and a minimum age of at least 10 years. Given the age structure of the moose population, the findings show that the cases are overrepresented in old moose and either not present among younger adults, or present at an early stage and not yet detectable. These findings contrast with CWD detected in Norwegian wild reindeer and CWD in North America where cases usually are adult animals not being particularly old (Table 1).

All detected CWD moose cases so far, except one, were females. However, the high prevalence in female moose compared to male moose likely reflects that more females reach old age and therefore are at higher risk compared to males, rather than being female *per se* giving higher risk for developing CWD. This pattern contrast to the findings in Norwegian reindeer with higher prevalence in adult males (1.2%) compared to adult females (0.5%) [36], and to CWD in North American cervids, where several studies in mule deer and white-tailed deer have reported higher prevalence in males [37–40]. In North America, this uneven distribution between sexes has been explained by different behaviour of males and females. Adult males are expected to have more contacts and fighting between males facilitates closer contact and possibly higher exposure to the CWD agent [41].

All cases except two, were detected in moose found dead or euthanized due to clinical signs of disease. This contrasts with the findings in wild reindeer in Norway where 18 of 19 cases were animals shot without prior observation of clinical signs [42]. Most moose are removed from the population through hunt. However, the moose which are not harvested and survive long enough to reach their full lifespan will by the end of their life likely display age-related signs (e.g. emaciation due to worn teeth) increasing

Table 5. Empirical *P*-value estimated by Monte Carlo simulation of having multiple cases within a group of neighbouring municipalities. The probability was computed by simulating the distribution per municipality of the national number of CWD cases, accounting for the number of moose tested in each municipality. The observed cases are added for comparison

	Empirical *P*-value (in percent) of a group of neighbour municipalities having a certain no. of cases or more given that it has at least one case								**Observed no. of groups of neighbour municipalities with one or more cases**		
Number of cases per neighbour group country, strategy	≥1 case	≥2 cases	≥3 cases	≥4 cases	≥5 cases	≥6 cases	≥7 cases	≥8 cases	one case	2 cases	3 cases
Norway, excluding animals with missing data	100	89.4	32.0	6.2	0.8	0.09	0.005	–	6	1	1
Norway, including animals with missing data	100	89.1	32.3	6.4	0.9	0.1	0.008	0.001	6	1	1
Sweden	100	19.3	0.7	0.009	–	–	–	–	1		1*
Finland	100	3.9	–	–	–	–	–	–	2		

*Observations for which the empirical *P*-value was less than 5%.

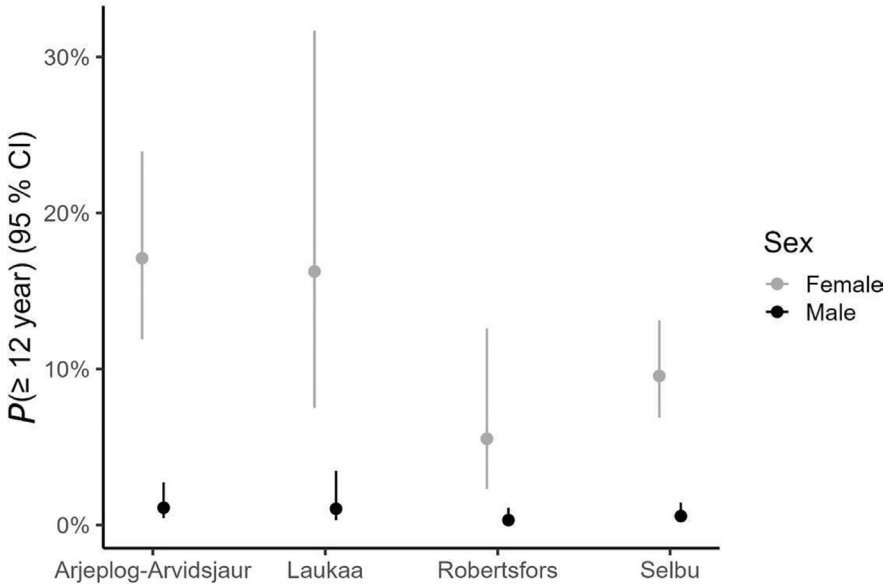

Fig. 3. Probability that female and male moose were 12 years or older in the four areas with intensified CWD surveillance with age determination of sampled moose: Arjeplog-Arvidsjaur (Sweden), Laukaa (Finland), Robertsfors (Sweden) and Selbu (Norway). The figure presents the probability (*P*) of an animal being 12 years or more with 95% confidence interval (CI).

the likelihood that they will be observed in a poor condition and culled, or die a natural death and end up in the category fallen moose. Consequently, the found dead and euthanized animals are expected to have a higher proportion of old animals [43]. Therefore, the finding that the majority of CWD cases were detected in found dead or euthanized moose may be a consequence of this group having a higher proportion of old animals. In contrast, the target group road kills, in which no CWD cases were found, will be expected to have an age distribution comparable to the general (hunted) population [43]. These observations are also of relevance for design and interpretation of future surveillance, i.e. inclusion of fallen cervids in surveillance is likely to increase the detection of cases.

The demographic pattern of CWD in Nordic moose, with predominantly old females being affected and most cases being fallen moose or animals with clinical signs, indicates that it has a different epidemiology than CWD in wild reindeer in Norway and CWD in North America. Accordingly, the mechanisms for acquiring CWD in Nordic moose seem to be different from those behind transmission of CWD between cervids in Norwegian wild reindeer and in cervids in North America.

In contrast to the cases detected in wild reindeer (Fig. 2), the CWD cases detected in moose were scattered in the Nordic countries. However, in three regions more than one positive CWD case were found within the same municipality or within neighbour municipalities in Norway (Selbu and Flesberg-Sigdal) and Sweden (Arjeplog-Arvidsjaur). According to the Monte Carlo simulation, the probability of finding three or more cases within one municipality or within neighbour municipalities, was less than 0.05. Thus, the clustering of these cases within the same or neighbouring municipalities cannot be rejected as simply a matter of chance, but merits further discussion.

Clustering of cases can be indicative of an outbreak of a contagious disease. However, of the three cases within Selbu municipality, material from two have been strain-typed by inoculation in rodents and they were found to be affected by different CWD strains [44, 45]. It is therefore unlikely that these two different cases were the result of a common infection cluster. During the intensified surveillance in the Selbu-region there was no increase in the annual apparent prevalence of CWD as usually seen during an outbreak of CWD in North America. The establishment phase of CWD could last for 10 years or more. An outbreak is difficult to detect in this phase and usually CWD is well established when detected in active surveillance [46]. Although theoretically possible, it is unlikely that the eighteen CWD cases scattered around in 14 different Nordic municipalities should belong to 14 different outbreaks in the establishment phase and no outbreak in a later phase. On the other hand, the epidemiological pattern is in agreement with a spontaneous origin of the disease as previously hypothesized [45, 47].

Clustering of cases could also indicate uneven distribution of risk factors for the disease or uneven detection probability. In the Nordic countries, the number and distribution of hunting permits are usually determined at the local level, and variation in age (calves, yearlings, adults) and sex-specific number of permits have substantial effects of the population age- and sex-structure. As age seems to be a significant risk factor, harvest-induced differences in population age structure could therefore have contributed

to the observed clustering. This fits the pattern observed in Sweden where the probability of female moose being ≥12 years old was higher in the Arjeplog-Arvidsjaur area (prob=0.17) where three cases were detected, compared to Robertsfors (prob=0.06) where one case was detected (Fig. 3). More studies are needed to document whether differences in age structure are large enough to explain a certain clustering of what in other areas appears as sporadic cases of CWD linked to old age.

The number of cases in an area could also be affected by probability of detection. After the detection of a CWD case, intensified surveillance was implemented in the area. This included education and facilitating sampling, which has been shown to enhance reporting and sampling from both hunted and risk animals [28]. There was also an increased testing of hunted animals. In Selbu and Arjeplog-Arvidsjaur, which were the areas with the potential clusters, the third case in each of these areas was detected in hunted animals. It would have been unlikely to detect these cases unless an intensified sampling had been established and thereby increased the detection probability.

The results gave no indications of an increasing prevalence in any area with positive cases, despite the intensified surveillance implemented in such areas. Nor has there been any indication of CWD being transmitted between species. Despite intensive sampling of all cervid species in these areas, only a few positive moose cases have been found. The CWD strains detected in moose differ from the CWD strain detected in wild reindeer [18, 44, 45], and the biochemical characteristics of the red deer prions are different from both reindeer and moose detected in Norway (and North American CWD) (Sylvie L. Benestad, Norwegian Veterinary Institute, personal communication). Furthermore, CWD in red deer and reindeer has been detected in geographical areas separated from the areas where the moose cases were detected (Fig. 2). Although one should be cautious concluding based on a relatively short time span [48], this contrasts with the situation in North America where the prevalence usually has increased within a few years after detection of the first cases [37], and where CWD has been found to be contagious between cervid species living in the field [37]. Furthermore, in North America the CWD strains found in moose are identical to CWD strains in other cervid species [49]. These differences in epidemiological patterns strengthen the hypothesis that the cases of CWD detected in Nordic moose so far, have a different aetiology compared to CWD in North America, and that the former is less contagious, if contagious at all, between live animals under field conditions.

While being clearly different from CWD in North America and CWD in wild reindeer, the features of the CWD cases so far detected in Nordic moose show similarities with other ruminant TSEs. The pattern with cases observed in old animals, PrP^{res} only detectable in CNS but not in lymphoid tissues when using traditional diagnostic methods, geographically scattered and widespread, and no increase in prevalence over years, agrees with observations in atypical scrapie and atypical BSE (Table 1). After many years of intensive surveillance, neither of these diseases have shown evidence of being contagious between live animals, nor can they be explained by exposure to contaminated meat and bone meal, and they are hypothesized to have a spontaneous origin [2, 12]. Regarding contagiousness, the differences in distribution of PrP^{res} is of special interest. Prions in CWD cases observed in Nordic moose, in atypical scrapie, and atypical BSE are only detected in the CNS. In contrast, prions are present both in the CNS and in lymphoid tissue in classical scrapie and CWD observed in North America, both of which are contagious. Presence of PrP^{res} in lymphoid tissues likely reflects dissemination of prions in the body and natural shedding, which may be a prerequisite for being contagious between live animals under field conditions. One could hypothesize that the relatively high crude prevalence of CWD detected in Nordic moose, as compared to other ruminant TSEs, would imply contagiousness. However, it is also worth mentioning that there is more than 100-fold difference in observed prevalence between atypical scrapie and atypical BSE [13]. When comparing prevalences, it is relevant to consider age structure and life-length at the population level, since age and time seem important for developing sporadic forms of TSEs. The cases in moose were detected in the second half of their expected life span. Despite a small proportion of moose reaching such high age, the selection pressure on livestock is even higher. When fertility or milk production drops, livestock are sent to slaughter or culled, and an even lower proportion of livestock may live as long as moose compared to their full potential lifespan. This would merit further investigation and could contribute to a better understanding of the underlying factors that contribute to moose developing the disease.

Susceptibility for developing TSEs is shown to be related to variations in the prion protein gene (*PRNP*) for both classical scrapie and atypical scrapie in sheep [50, 51], and for CWD in mule deer, white-tailed deer and elk [52, 53]. However, *PRNP* variation seems to be limited in moose [31]. In Europe there is a common 'wild-type' and only two alleles have been reported [54]. CWD in Nordic moose have been found in the two homozygous forms of these three possible genotypes [55]. Currently, there is no indication that variation in PrP-genotype can explain the geographical distribution of CWD in Nordic moose.

In scientific communication, as well as in communication related to management and control and standards for trade with animals and animal products, there is a need for a terminology which differentiate diseases with different characteristics, this includes CWD. In the scientific literature, CWD in Nordic moose has been considered one entity based on prion properties of which the two main important common features are (1) a truncated c-terminal of the prion [18] and (2) no detection of prions in lymphoid tissue with traditional diagnostic methods (Table 3) [28]. We have shown that these cases also have an epidemiological pattern that differs from CWD as observed in North America and Norwegian reindeer. The terms 'Nor-16CWD', 'atypical CWD', 'sporadic CWD' and 'Ly-' have been used for the CWD cases as observed in Nordic moose [18, 28, 47]. We support the use of the term 'sporadic chronic wasting disease' (with acronym sCWD) for these cases. The term agrees with the term sporadic

Creutzfeldt-Jakob disease in humans. We prefer sporadic rather than 'atypical' as used for scrapie and BSE, as sporadic is more informative towards the observed epidemiological pattern.

CONCLUSION

The epidemiological findings in this study, in combination with the biochemical properties and strain-typing results previously reported, support that the epidemiology of CWD in Nordic moose differs from CWD in North American cervids and CWD in Norwegian wild reindeer. Furthermore, the findings in Nordic moose have similarities with atypical scrapie and atypical BSE, which both are sporadically occurring and hypothesized to have a spontaneous aetiology. The findings in moose support that these cases occur sporadically and are not contagious or only contagious to a low degree between live animals under field conditions. The disease may have a spontaneous aetiology (with unknown cause). Knowledge of the epidemiology is fundamental for disease prevention and control. It is necessary to distinguish different variants of the disease in scientific communication, for authorities and stakeholders. To facilitate such distinction we support the use of the previously suggested name *sporadic chronic wasting disease* (*sCWD*) [47].

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Author contributions
P.H. and M.N. conceived the study and drafted the first version of the manuscript and C.M.R., E.J.S., A.M., S.L.B., D.G.W., S.L.K., J.P. gave substantial contribution to the manuscript. J.V., C.M.R., P.H., S.L.B., M.N., T.R., .K.S., G.A., E.Å., S.L.K., M.H., M.I. designed and implemented the surveillance programmes and C.M.R., E.J.S., A.M., J.P., G.E. contributed with population understanding. K.M., M.I., D.G.W. followed up the positive cases. C.M.R., G.A., M.I. performed the age analyses. P.H., M.N., T.R., S.L.K. curated the data and P.H., H.C.B., C.M.R. performed the statistical analyses. All authors critically reviewed the manuscript and approved the final manuscript for submission.

Conflicts of interest
The authors declare that there are no conflicts of interest.

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