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Disease patterns and incidence of immune-mediated disease in insured Swedish Nova Scotia Duck Tolling Retrievers

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In this study, morbidity in insured Nova Scotia Duck Tolling Retriever (NSDTR) dogs from Sweden was investigated and compared with all other breeds and other retriever breeds. In addition to describing common morbidities in NSDTRs, the hypotheses that NSDTRs are predisposed to lymphoma, immune-mediated rheumatic disease (IMRD) and steroid-responsive meningitis-arteritis (SRMA) were tested. Included in the study were 445,336 dogs; of which, 2890 were NSDTRs that had been covered by veterinary insurance from the Agria Insurance Company (Stockholm, Sweden) at some point during the years 1995–2006. Incidences of various health problems were calculated using the number of veterinary visits as the numerator and the exact time at risk as the denominator. Overall, morbidity was higher in NSDTRs compared with all other breeds, but similar compared with other retriever breeds. The most common causes of veterinary visits in NSDTRs were injuries, gastrointestinal disease and locomotor disorders, with NSDTRs at increased risk of these compared with all other breeds. The incidences for IMRD, SRMA and lymphoma were significantly higher in NSDTRs than in all other dog breeds and all other retriever breeds. The study describes morbidity in NSDTRs, and identifies several disorders to which the breed is predisposed.

Introduction

Nova Scotia Duck Tolling Retriever (NSDTR) dogs can be affected by several immune-mediated disorders, in particular immune-mediated rheumatic disease (IMRD) and steroid-responsive meningitis-arteritis (SRMA) (Redman 2002, Hansson-Hamlin and Lilliehöök 2009, 2013). Dogs affected by IMRD are normally middle-aged, and the most prevalent clinical finding is chronic pain and stiffness from multiple joints caused by non-erosive polyarthritis. Sometimes, organ systems other than the joints can be affected, most commonly the skin. Most cases are shown to have antinuclear antibodies on indirect immunofluorescence (Hansson-Hamlin and Lilliehöök 2009). The clinical signs of IMRD in NSDTRs resemble those seen in the chronic autoimmune disease, systemic lupus erythematosus (SLE) or SLE-related disorders; diseases well described in both human beings and dogs (Lewis and others 1965, Tan 1989, Fournel and others 1992, Rahman and Isenberg 2008). In human beings, a diagnosis of SLE is made based on defined criteria (Tan and others 1982, Hochberg 1997). Similar criteria for the diagnosis of canine SLE have been proposed (Halliwell 1978, Grindem and Johnson 1983, Bennett 1987), but they are not well established, and there is an overlap of clinical and diagnostic findings between SLE and SLE-related disorders like IMRD. Overall, the clinical features of SLE are similar in dogs and human beings. Similarly, canine lymphoma resembles human lymphoma in many ways (Richards and Suter 2015). Human patients with SLE are known to have an increased risk of lymphoma (Pettersson and others 1992, Mellemkjaer and others 1997), whether this is the case in dogs, is not known, but the similarities for the disorders between dogs and human beings evoke the question of whether a similar association can be found in dogs.

SRMA is a disease primarily affecting young dogs. The typical, acute form is characterised by pain, cervical rigidity, pyrexia and polymorphonuclear pleocytosis of the cerebrospinal fluid (Tipold and Jaggy 1994, Tipold and Schatzberg 2010, Hansson-Hamlin and Lilliehöök 2013). A high prevalence of SRMA in Norwegian NSDTRs has been reported, suggesting a breed predisposition (Anfinsen and others 2008).

Genome-wide association studies in NSDTRs have shown that IMRD and SRMA are diseases with complex inheritance patterns. Loci associated with IMRD and/or SRMA contain strong candidate genes that are involved in immune regulation (Wilbe and others 2010). In addition, a particular major histocompatibility complex class II haplotype is a genetic risk factor for IMRD (Wilbe and others 2009).

Previous published studies on immune-mediated diseases in NSDTRs are mainly case reports or case-control studies (Hansson-Hamlin and Lilliehöök 2009, 2013; Wilbe and others 2009; Wilbe and others 2010). Such studies can be important in highlighting a problem within a breed; however, they do not give any information about the frequency of disease, and do not prove a breed predisposition. The disease frequency of SRMA in the Norwegian population of NSDTRs has previously been

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estimated (Anfinsen and others 2008), but the relative risk (RR) compared with dogs of other breeds was not investigated. Morbidity associated with IMRD has not previously been investigated. To fully understand the impact of a possible predisposition to a disease in a breed, the disease frequency should be compared with other breeds and also with other disorders within the breed.

Population-based epidemiological studies of morbidity in dog breeds can provide valuable information about genetic predisposition for disease and support disease-prevention strategies. Insurance data have proven to be a valuable tool for epidemiological studies since it contains information about the background population as well as the disease events (Egenvall and others 2009). In Sweden, most dogs are covered by an insurance plan, and over one-third of the dog population is insured by Agria Insurance Company, Stockholm, Sweden (Egenvall and others 1998, Agria 2013).

This study assessed morbidity in NSDTRs using Agria insurance data from the years 1995 to 2006. The first aim was to describe the disease pattern in NSDTRs. The second aim was to test the hypothesis that NSDTRs are predisposed to IMRD, SRMA and lymphoma compared with other breeds.

Material and methods

Study population

A retrospective cohort was assembled from insurance data from Agria Insurance Company. The study population included all dogs insured before one year of age during the years 1995–2006. Data were included on 445,336 dogs (219,201 females, 226,135 males, neutering status not available), of which 2890 (1408 females, 1482 males) were NSDTRs. Two comparison groups were created; the first consisting of all dogs except NSDTRs (442,446 dogs) and the other of all retrievers except NSDTRs (52,073 dogs).

Information on dog identity, breed, sex, date of birth, dates when dogs entered and left insurance database, diagnostic codes for veterinary visits and dates of veterinary visits were collected. The diagnostic code, best describing the cause of the veterinary visit, was selected from a standard national diagnostic registry (Swedish Animal Hospital Organisation 1993) by the attending veterinarian. If the owner was reimbursed for the cost of the veterinary visit, the cause of visit (the diagnostic code) was registered in the insurance database. The diagnostic registry and the insurance process in Agria have previously been described in detail (Egenvall and others 2000a, b).

Diagnostic classification

To describe morbidity in NSDTRs at both general and detailed levels, diagnostic codes were grouped into 24 level-1 categories based on organ systems and disease processes. Every category was further divided into level-2 categories that were further divided into level-3 categories containing 1–390 diagnostic codes. The subdivision is exemplified in Table 1.

There is no single diagnostic code for either IMRD or SRMA in the national diagnostic registry. Therefore, diagnostic codes that could represent IMRD and SRMA, respectively, were combined to create these classifications. Two diagnostic groups were created for each disorder; the first, designated 'IMRD' and 'SRMA', included codes most likely to be used by veterinarians for these disorders. The second group, designated 'IMRD/SRMA possibly' included, in addition to those in 'IMRD/SRMA' groups, additional codes that may have also been used for dogs suspected to have these disorders. These non-specific codes could have been used for other disorders as well. A table containing all of the diagnostic codes is included in the online supplementary material Table S1.

For the purpose of studying lymphoma, two diagnostic codes 'lymphosarcoma/malignant lymphoma' and 'malignant lymphoma' were grouped together since veterinary clinicians may use them interchangeably.

TABLE 1: Hierarchical distribution of original diagnostic codes and level-3 categories within autoimmune causes* (level 2) of veterinary visits

Level 2	Level 3	Diagnostic code
Autoimmune	Autoimmune blood	Autoimmune haemolytic anaemia
		Autoimmune thrombocytopenia
	Autoimmune skin	Autoimmune skin diseases
		Cold haemagglutinin disease
		Dermatomyositis
		Pemphigus
		Pemphigus vulgaris
		Pemphigus vegetans
		Pemphigus foliaceus
		Pemphigus erythematosus
		Bullous pemphigoid
	Lupus	Discoid lupus erythematosus
		Systemic lupus erythematosus
	Myasthenia gravis	Myasthenia gravis
	Rheumatological	Immune-related condition, specified by each joint†
		Immune-related condition, several joints
		Rheumatoid arthritis, specified by each joint†
		Rheumatoid arthritis, several joints
		Signs of rheumatological disease

*From level-1 category 'Immunological' disorders
†Several diagnostic codes available, specified by the joint affected

There was no information on whether or how diagnosis was confirmed.

Statistical analysis

Incidences were calculated using the number of veterinary visits as the numerator and the exact time at risk as the denominator. Prophylactic visits were not counted for. Time at risk for the dogs was calculated as time from the start of the insurance policy (or January 1, 1995, if it started earlier) until a disease event occurred for the particular diagnosis or disease category studied, or until withdrawal from insurance cover (or at the end of the study period, ie, December 31, 2006). The incidence was multiplied by 10,000 and presented as number of cases per 10,000 dog years at risk (DYAR). If a dog had more than one claim for the investigated diagnosis or disease category, only the first claim was counted.

Since it is rare to diagnose primary cases of SRMA in dogs older than two years of age (Lowrie and others 2009, Tipold and Schatzberg 2010, Hansson-Hamlin and Lilliehöök 2013), a conditional analysis for SRMA was also performed, including only veterinary visits and time at risk for dogs up to two years of age.

Incidences were calculated for NSDTRs as well as for the two comparison groups, for each sex separately as well as for the two sexes combined. Calculations were performed using the software SAS V.9.3 (SAS Institute, Cary, North Carolina, USA). Exact CIs for incidences were constructed using the epi.conf function in the R package epiR V.0.9–59 in R V.3.0.2 (R core team 2013). RR values for NSDTRs were calculated by dividing incidence for NSDTRs by incidence for the respective comparison group. CIs and P values for RR were constructed using the R package exactci V.1.2–1 (Fay 2010) in R V.3.0.2. The level of significance was set to 0.05. For a description of the disease pattern, correction for multiple comparisons with Bonferroni correction was performed in addition to calculating raw P values.

Results

Of the 2890 NSDTRs in the study, 51 per cent had at least one veterinary visit between 1995 and 2006. For all other breeds combined, the proportion of dogs with at least one veterinary visit was 43 per cent. For retrievers, the proportion was 52 per cent. The average number of veterinary visits per dog was 2.2 for NSDTRs, 1.7 for all other breeds combined and 2.1 for other retrievers. Excluding the 49 per cent of NSDTRs that did not experience a veterinary visit, the number of visits per dog was 4.3. The incidence for veterinary visits in NSDTRs was 1300 cases per 10,000 DYAR, with a RR of 1.1 (95 per cent CI 1.0 to 1.1, P=0.0075) compared with all other breeds combined. Compared with other retrievers combined, the RR was 0.96 (95 per cent CI 0.91 to 1.0, P=0.091).

In Table 2, incidences and RR in NSDTRs for level-1 categories are presented. The most common level-1 causes of veterinary visits in NSDTRs were injuries, gastrointestinal disease and locomotor disorders, with an increased risk among NSDTRs evident compared with all other breeds (also after Bonferroni correction). Compared with all other breeds, NSDTRs were at decreased risk of ear and heart disorders, heart disorders being less common in NSDTRs (also after Bonferroni correction).

The incidence for the level-1 category immunological disorders in NSDTRs was approximately the same as in all other breeds and retriever breeds (Tables 2 and 3). Immunological disorders consisted of three level-2 categories, 'allergic', 'autoimmune' and 'immune, various', which are presented in Table 3. 'Allergic' was the most common level-2 category of immunological disorders in NSDTRs, with a similar incidence in NSDTRs compared with other breeds and retrievers. Autoimmune disorders and remaining immunological disorders, not classified as autoimmune or allergies (named 'immune, various'), were significantly more common in NSDTRs than in other breeds and retrievers (Table 3).

The incidence for the level-1 category neurological disorders was higher in NSDTRs than in other breeds and retrievers (Tables 2 and 4). Neurological infection/inflammation was the most common level-2 category of neurological disorders in NSDTRs, and was nine times more common in NSDTRs than in other breeds (Table 4). Epilepsy was less common in NSDTRs, and the risk was significantly decreased compared with retrievers (Table 4).

Morbidity was assessed on a more detailed level where level-2 categories were divided into level-3 categories. Table 5 includes incidences and RRs in NSDTRs for the 15 most common level-3 categories. The most common was 'vomiting/diarrhoea/gastroenteritis', which had an incidence similar to all other breeds and retriever breeds. Among the top 15 most common level-3 categories, NSDTRs had the highest RR for 'pain/stiffness' (RR 2.7 compared with other breeds, RR 2.4 compared with retrievers).

Presented in Fig 1 are the 15 level-3 categories with the highest RRs in NSDTRs compared with all other breeds. Only significant ($P<0.05$) findings are presented, and categories significantly more common in NSDTRs than in other breeds and retriever breeds after Bonferroni corrections are marked in the figure. Compared with all other breeds, NSDTRs had the highest risk of unspecified immune disorders and CNS infections/inflammations (Fig 1). Unspecified immune disorders included various immune disorders, not autoimmune or allergic, and not related to the skin, muscle, eyes or claws. The most common diagnostic codes of unspecified immune disorders in NSDTRs were 'immune-related conditions, oral cavity/throat' followed by 'immunological changes, whole animal' and 'immune-related conditions, spinal cord membranes'.

Immune-mediated rheumatic disease

Of the 2890 NSDTRs in the study, 0.35 per cent had an 'IMRD' diagnosis, and 3.3 per cent had an 'IMRD possibly' diagnosis. The most common diagnostic codes in the 'IMRD possibly' group were 'signs of generalised pain' and 'signs of general stiffness', both codes being significantly more common ($P=6.5\times10^{-7}$; 1.1×10^{-5}) in NSDTRs than in other breeds, when analysed individually.

The incidence in NSDTRs and RR values for the diagnostic groups representing IMRD (see online supplementary Table S1) are presented in Table 6. The incidence for 'IMRD' was 6.8 cases per 10,000 DYAR with an 18 times increased risk in NSDTRs compared with all other breeds (95 per cent CI 8.5 to 36) and a 30 times increased risk compared with other retriever breeds (95 per cent CI 9.9 to 100). For 'IMRD possibly', which included some non-specific diagnostic codes, incidence was higher and RR

TABLE 2: Incidences and relative risk for level-1 causes of veterinary visits in NSDTRs

	Incidence, NSDTR Cases/10,000 DYAR (95% CI)	Relative risk/all other breeds (95% CI)	P value	Relative risk/retrievers (95% CI)	P value
Injury*†	310 (280 to 340)	1.4 (1.2 to 1.5)	4.4×10^{-9}	1.3 (1.2 to 1.4)	6.7×10^{-7}
Gastrointestinal*	310 (270 to 340)	1.2 (1.1 to 1.3)	0.0012	1.1 (1.0 to 1.3)	0.017
Locomotor*	270 (240 to 300)	1.2 (1.1 to 1.4)	2.5×10^{-4}	0.94 (0.84 to 1.0)	0.23
Neoplasia	250 (230 to 280)	1.1 (1.1 to 1.3)	0.021	0.87 (0.78 to 0.97)	0.013
Skin	250 (220 to 280)	1.2 (1.1 to 1.3)	0.0028	1.1 (0.97 to 1.2)	0.16
Signs/whole body*†	190 (170 to 220)	1.4 (1.2 to 1.6)	5.8×10^{-7}	1.3 (1.1 to 1.4)	4.4×10^{-4}
Reproductive/female‡	140 (120 to 160)	0.88 (0.76 to 1.0)	0.061	0.72 (0.63 to 0.83)	2.8×10^{-6}
Eyes	91 (77 to 110)	1.2 (0.97 to 1.4)	0.11	1.2 (0.99 to 1.4)	0.063
Respiratory/upper	76 (63 to 92)	0.90 (0.74 to 1.1)	0.27	1.0 (0.84 to 1.3)	0.82
Infection	76 (63 to 91)	1.3 (1.1 to 1.6)	0.0048	0.99 (0.81 to 1.2)	0.98
Ear‡	71 (59 to 87)	0.77 (0.63 to 0.94)	0.0074	0.47 (0.39 to 0.58)	$<2.2\times10^{-16}$
Neurological*†	68 (56 to 83)	1.7 (1.4 to 2.1)	7.6×10^{-7}	1.6 (1.3 to 2.0)	3.8×10^{-5}
Urinary/lower	52 (41 to 65)	0.82 (0.65 to 1.0)	0.093	0.95 (0.75 to 1.2)	0.75
Reproductive/male	46 (36 to 58)	1.3 (1.0 to 1.7)	0.029	2.0 (1.5 to 2.6)	9.2×10^{-7}
Immunological	44 (35 to 56)	1.3 (0.99 to 1.6)	0.064	1.2 (0.91 to 1.5)	0.20
Blood/vascular*†	34 (26 to 45)	2.1 (1.5 to 2.7)	6.5×10^{-6}	1.7 (1.3 to 2.3)	7.3×10^{-4}
Endocrine	30 (22 to 40)	0.96 (0.69 to 1.3)	0.83	0.86 (0.62 to 1.2)	0.37
Respiratory/lower	20 (14 to 29)	0.76 (0.51 to 1.1)	0.15	1.1 (0.71 to 1.5)	0.77
Heart§	20 (14 to 29)	0.55 (0.37 to 0.78)	3.7×10^{-4}	0.86 (0.59 to 1.2)	0.50
Urinary/upper	14 (9.4 to 22)	0.77 (0.48 to 1.2)	0.26	0.75 (0.46 to 1.2)	0.22
Operation/complication	9.5 (5.7 to 16)	1.3 (0.70 to 2.2)	0.42	1.4 (0.73 to 2.3)	0.33
Claw	7.5 (4.2 to 13)	1.0 (0.52 to 1.9)	0.96	0.90 (0.44 to 1.6)	0.88
Behaviour	2.7 (1.1 to 6.9)	1.9 (0.52 to 5.0)	0.32	2.5 (0.63 to 7.1)	0.19
Respiratory/thoracic	2.0 (0.74 to 5.9)	0.79 (0.16 to 2.3)	0.95	0.62 (0.13 to 1.9)	0.59

Ranked by incidence
Relative risk=incidence for NSDTR/incidence for comparison group
*Increased risk in NSDTRs compared with all breeds after correction for multiple comparisons (Bonferroni n=24)
†Increased risk in NSDTRs compared with retrievers after correction for multiple comparisons (Bonferroni n=24)
‡Decreased risk in NSDTRs compared with retrievers after correction for multiple comparisons (Bonferroni n=24)
§Decreased risk in NSDTRs compared with all breeds after correction for multiple comparisons (Bonferroni n=24)
DYAR, dog years at risk; NSDTR, Nova Scotia Duck Tolling Retriever

TABLE 3: Incidences and relative risk for immunological causes of veterinary visits in NSDTRs

	Incidence, NSDTR Cases/10,000 DYAR (95% CI)	Relative risk/all other breeds (95% CI)	P value	Relative risk/retrievers (95% CI)	P value
Level 1					
Immunological	44 (35 to 56)	1.3 (0.99 to 1.6)	0.064	1.2 (0.91 to 1.5)	0.20
Level 2					
Allergic	22 (16 to 31)	0.78 (0.53 to 1.1)	0.18	0.72 (0.50 to 1.0)	0.068
Autoimmune	13 (8.3 to 20)	2.7 (1.3 to 5.1)	2.5×10^{-4}	2.7 (1.6 to 4.3)	5.9×10^{-4}
Immune, various	8.8 (5.1 to 15)	3.9 (2.1 to 6.7)	1.1×10^{-4}	3.8 (1.9 to 7.1)	2.4×10^{-4}

Level-2 categories in the level-1 category 'immunological' are presented
Relative risk=incidence for NSDTR/incidence for comparison group
DYAR, dog years at risk; NSDTR, Nova Scotia Duck Tolling Retriever

lower than for 'IMRD', but still significantly higher than in all other breeds (Table 6).

The incidence for 'IMRD' was higher in female NSDTRs than in male NSDTRs (RR 8.9, 95 per cent CI 1.3 to 390, P=0.023), but no sex difference were observed in the 'IMRD possibly' category. In all other breeds combined, and in all other retriever breeds combined, there was no sex difference in incidence for 'IMRD', but the incidence for 'IMRD possibly' was higher in males (RR all other breeds 1.4, 95 per cent CI 1.3 to 1.5, $P=2.2\times10^{-16}$; RR in other retrievers 1.4, 95 per cent CI 1.2 to 1.7, $P=7.9\times10^{-16}$).

Steroid-responsive meningitis-arteritis

Of the 2890 NSDTRs, 1.0 per cent had an 'SRMA' diagnosis, and 1.2 per cent had an 'SRMA possibly' diagnosis. The diagnostic code 'meningitis' was the most common code in the two diagnostic groups.

The incidences in NSDTRs and RR values for the diagnostic groups representing SRMA (see online supplementary Table S1) are presented in Table 7. The incidence for 'SRMA' in NSDTRs was 20 per 10,000 DYAR, 12 times higher than in all other breeds (95 per cent CI 7.6 to 17) and 21 times higher than in other retriever breeds (95 per cent CI 12 to 37). When excluding cases and time at risk in dogs above two years of age, the incidence for 'SRMA' was 53 cases per 10,000 DYAR.

There was no difference in incidences between females and males for 'SRMA' in NSDTRs, in all other breeds combined or in all other retriever breeds. The incidence for 'SRMA possibly' was 1.2 times higher in males than in females (95 per cent CI 1.0 to 1.5, P=0.041) of all other breeds combined. There was no sex difference for 'SRMA possibly' in NSDTRs or in other retrievers.

Lymphoma

The incidence for lymphoma ('lymphosarcoma/malignant lymphoma' and 'malignant lymphoma' combined) in NSDTRs was 15 cases per 10,000 DYAR (95 per cent CI 9.9 to 23). NSDTRs had a significant increased risk compared with all other breeds (RR 2.8, 95 per cent CI 1.8 to 4.3, $P=4.9\times10^{-5}$) as well as to other retriever breeds (RR 2.0, 95 per cent CI 1.2 to 3.1, P=0.0067). None of the NSDTR dogs with a lymphoma diagnosis did have an IMRD or SRMA diagnosis.

Discussion

Immune-mediated diseases have previously been reported to be a problem in NSDTRs, with two disorders being particularly recognised: IMRD and SRMA (Redman 2002, Anfinsen and others 2008, Hansson-Hamlin and Lilliehöök 2009, 2013). Although previous studies have suggested that NSDTRs are predisposed to IMRD and SRMA, the RR compared with other dog breeds has not been evaluated.

The Swedish dog population has been estimated to be 700,000 to 800,000 individuals (Egenvall and others 1999, Agria 2013, Swedish Board of Agriculture 2014); of which, approximately 0.5 per cent were NSDTRs at the end of 2013 (Swedish Board of Agriculture 2014). The number of dogs included in the present study was over 400,000. Hence, it represented a large proportion of the Swedish dog population over several years, and the proportion of NSDTRs was approximately the same as previously published.

The main advantage of using insurance data is that it is possible to estimate incidence of disease. The Agria insurance database is validated for epidemiological studies, and it has been used in multiple studies to assess morbidity in dogs (Egenvall and others 1998, 1999, 2009; Nodtvedt and others 2006; Fall and others 2007; Vilson and others 2013). Even so, the database was not developed to study morbidity primarily for research purposes, and limitations have to be recognised. First of all, the diagnostic codes used to assess morbidity are assigned by the attending veterinarian, and no information about diagnostic accuracy is available. However, the agreement between the database and veterinary records has been evaluated and considered fair and similar across breeds (Egenvall and others 1998). It is unknown to what extent morbidity findings based on insurance data can be applied to an uninsured population.

The general description of disease patterns presented here provides unique information about morbidity in NSDTRs. High-risk disorders were identified, and also the most common disorders in the breed. The purpose of comparing NSDTRs with other retrievers was to create a comparison group with dogs that live under similar environmental conditions, and are used for similar activities. NSDTRs had a slightly increased risk of disease compared with all other dog breeds combined, but a similar risk compared with other retrievers. Increased risk for several groups

TABLE 4: Incidences and relative risk for neurological causes of veterinary visits in NSDTRs

	Incidence, NSDTR Cases/10,000 DYAR (95% CI)	Relative risk/all other breeds (95% CI)	P value	Relative risk/retrievers (95% CI)	P value
Level 1					
Neurological	68 (56 to 83)	1.7 (1.4 to 2.1)	7.6×10^{-7}	1.6 (1.3 to 2.0)	3.8×10^{-5}
Level 2					
Neurological inf/infl	28 (21 to 39)	9.0 (6.4 to 12)	$<2.2\times10^{-16}$	12 (8.0 to 18)	$<2.2\times10^{-16}$
Neurological, various	25 (18 to 35)	1.7 (1.2 to 2.3)	0.0042	1.6 (1.1 to 2.2)	0.017
Epilepsy	16 (10 to 23)	0.70 (0.44 to 1.1)	0.092	0.61 (0.39 to 0.93)	0.018

Level-2 categories in the level-1 category 'neurological' are presented
Relative risk=incidence for NSDTR/incidence for comparison group
DYAR, dog years at risk; inf/infl, infection/inflammation; NSDTR, Nova Scotia Duck Tolling Retriever

TABLE 5: Most common level-3 causes of veterinary visits in NSDTR

	Incidence, NSDTR Cases/10,000 DYAR (95% CI)	Relative risk/all other breeds (95% CI)	P value	Relative risk/retrievers (95% CI)	P value
Vomiting/diarrhoea/gastroenteritis	170 (150 to 190)	1.1 (0.92 to 1.2)	0.46	0.97 (0.85 to 1.1)	0.70
Locomotor pain/signs*	120 (100 to 140)	1.5 (1.3 to 1.7)	7.8×10^{-7}	1.0 (0.85 to 1.2)	1
Skin trauma	110 (97 to 130)	1.3 (1.1 to 1.5)	0.0019	1.3 (1.1 to 1.5)	0.0034
Pyometra/endometritis†	110 (95 to 130)	0.89 (0.76 to 1.0)	0.17	0.70 (0.59 to 0.82)	2.5×10^{-6}
Skin tumour	100 (89 to 120)	1.2 (1.0 to 1.4)	0.043	0.80 (0.67 to 0.93)	0.0047
Anal/perianal*‡	82 (68 to 98)	1.8 (1.5 to 2.1)	1.6×10^{-8}	2.8 (2.3 to 3.4)	$<2.2\times10^{-16}$
Dermatitis/pyoderma/folliculitis†	78 (65 to 93)	0.88 (0.73 to 1.1)	0.20	0.64 (0.52 to 0.77)	6.2×10^{-7}
Mammary tumour	66 (53 to 80)	1.0 (0.83 to 1.3)	0.86	1.3 (1.0 to 1.6)	0.026
Otitis†	65 (53 to 80)	0.80 (0.65 to 0.98)	0.028	0.58 (0.47 to 0.72)	3.2×10^{-8}
Respiratory upper inf/infl	61 (50 to 75)	0.90 (0.72 to 1.1)	0.35	1.1 (0.85 to 1.3)	0.58
Teeth*	61 (49 to 75)	1.6 (1.3 to 1.9)	9.8×10^{-5}	1.4 (1.1 to 1.8)	0.0030
Claw trauma	52 (41 to 65)	1.6 (1.3 to 2.0)	1.6×10^{-4}	1.1 (0.84 to 1.4)	0.61
Signs of tiredness	45 (36 to 58)	1.5 (1.2 to 1.9)	0.0023	1.1 (0.81 to 1.4)	0.70
Pain/stiffness*‡	40 (31 to 52)	2.7 (2.0 to 3.5)	1.4×10^{-10}	2.4 (1.8 to 3.2)	1.3×10^{-8}
Itching	40 (31 to 51)	0.95 (0.72 to 1.3)	0.75	0.89 (0.67 to 1.2)	0.41

Ranked by incidence, top 15 shown
Relative risk=incidence for NSDTR/incidence for comparison group
*Increased risk in NSDTRs compared with all breeds after correction for multiple comparisons (Bonferroni n=339)
†Decreased risk in NSDTRs compared with retrievers after correction for multiple comparisons (Bonferroni n=339)
‡Increased risk in NSDTRs compared with retrievers after correction for multiple comparisons (Bonferroni n=339)
DYAR, dog years at risk; inf/infl, infection/inflammation; NSDTR, Nova Scotia Duck Tolling Retriever

of disorders were found; however, the RR values have to be considered when interpreting the results; in some instances, the incidence was only slightly higher than in other breeds, and the lower confidence limit was close to 1.0. This study was an observational study, and it was not the aim, and it is not possible, to draw definite conclusions about the cause of increased risk. Increased risk in a breed can reflect a genetic predisposition, but can, sometimes, be explained by lifestyle factors or owners' attitudes to seeking veterinary care, factors that can vary between breeds. In the case of reproductive disorders, the incidence is affected by neutering, and neutering frequency might vary between breeds.

The incidences for IMRD, SRMA and lymphoma, which were significantly higher in NSDTRs than in other breeds and other retrievers, show that these disorders are more common in NSDTRs. The high RRs observed and the fact that heritable risk factors contribute to these disorders (Wilbe and others 2009, 2010; Richards and Suter 2015) indicate a breed predisposition. However, point estimates for RRs should be extrapolated cautiously, given

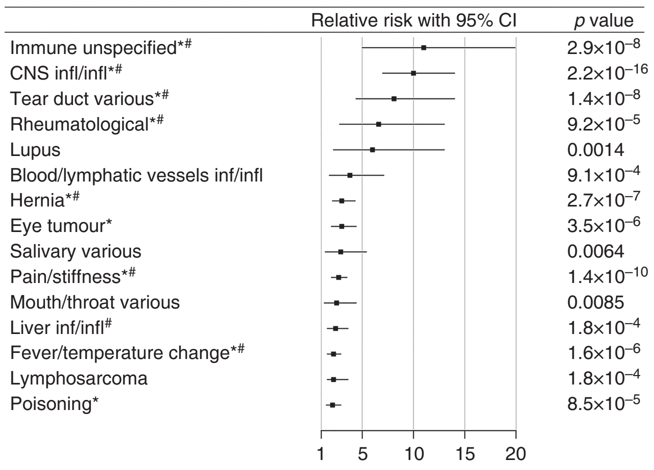

FIG 1: Relative risk for level-3 categories in Nova Scotia Duck Tolling Retrievers compared with all other breeds. Top 15 level-3 categories for those with rates different (P<0.05) from other breeds. inf/infl, infection/inflammation. *Increased risk compared with all other breeds after correction for multiple comparisons (Bonferroni n=339). #Increased risk compared with retrievers after correction for multiple comparisons (Bonferroni n=339)

that the CIs may be rather wide. The authors could not find an association between lymphoma and IMRD at an individual level as hypothesised, but they think that a possibly defective immune regulation in the NSDTR breed makes them predisposed to both immune-mediated disorders and lymphoma.

IMRD was more common in female NSDTRs than in males, but was equally common in both sexes in all other breeds. Previous studies on this disorder in NSDTRs have not indicated a sex predisposition (Hansson-Hamlin and Lilliehöök 2009). In human beings, autoimmune disease in general, and SLE in particular, is more common in females than in males (Whitacre and others 1999).

The general lack of population-based epidemiological studies for immune-related disorders like IMRD and SRMA makes comparisons of incidences difficult. The cumulative prevalence of SRMA in Norwegian NSDTRs has been estimated to be 2.5 per cent, 95 per cent CI 0.9 to 4.1 per cent (Anfinsen and others 2008). It is difficult to exactly compare disease frequency in this study with the cumulative prevalence of 2.5 per cent, but 1 per cent of NSDTRs in this study had an SRMA diagnosis, which is within the confidence limits of the Norwegian study.

The incidences in this study may be lower than the true incidence. One reason is that only veterinary visits for which the owner was reimbursed for the cost of the visit were included. If the cost of the veterinary visit was low or if the owners had not sought veterinary care, the visit was not counted. In this study, only the first claim for a particular diagnosis or group of disorders was counted, which might underestimate the total disease burden of the population, although presumably not the incidence. The comparison between breeds should not be affected, since the effects should be similar across breeds. There could be a risk that the knowledge about SRMA and IMRD in NSDTRs could lead to some NSDTRs being misdiagnosed on the basis of diagnostic suspicion bias, but since the disorders were first reported in NSDTRs in 2002 (Redman 2002) and 2009 (Hansson-Hamlin and Lilliehöök 2009), and the study period is 1995–2006, the authors do not think this factor has affected the results. Further support for the present study finding is that the authors can show predisposition at different levels for immune-mediated and neurological disease, not just particular diagnoses.

The choice of diagnostic codes to be included to represent IMRD and SRMA was challenging. This is particularly true for IMRD where strict criteria for disease are lacking, and the clinical signs of SLE, IMRD and other SLE-related diseases may be similar. It should be noted that some diagnostic codes included were descriptions of clinical signs, rather than aetiology, which

TABLE 6: Incidence and relative risk for IMRD in NSDTR compared with all other breeds and all other retrievers

	Number of NSDTRs	Incidence for NSDTR Cases/10,000 DYAR (95% CI)	Relative risk/all other breeds (95% CI)	P value	Relative risk/retrievers (95% CI)	P value
IMRD	10	6.8 (3.7 to 12)	18 (8.5 to 36)	1.4×10^{-9}	30 (9.9 to 100)	1.9×10^{-9}
IMRD possibly	94	65 (53 to 80)	3.2 (2.4 to 4.4)	$<2.2\times10^{-16}$	2.6 (1.9 to 3.6)	7.1×10^{-15}

Relative risk=incidence for NSDTR/incidence for comparison group
DYAR, dog years at risk; IMRD, immune-mediated rheumatic disease; NSDTR, Nova Scotia Duck Tolling Retriever

TABLE 7: Incidence and relative risk for SRMA in NSDTR compared with all other breeds and all other retrievers

	Number of NSDTRs	Incidence, NSDTR Cases/10,000 DYAR (95% CI)	Relative risk/all other breeds (95% CI)	P value	Relative risk/retrievers (95% CI)	P value
SRMA	29	20 (14 to 28)	12 (7.6 to 17)	$<2.2\times10^{-16}$	21 (12 to 37)	$<2.2\times10^{-16}$
SRMA possibly	35	24 (17 to 33)	12 (8.2 to 17)	$<2.2\times10^{-16}$	21 (13 to 36)	$<2.2\times10^{-16}$
SRMA ≤2 years	18	53 (34 to 83)	13 (7.5 to 21)	6.2×10^{-14}	31 (13 to 83)	1.4×10^{-15}
SRMA possibly ≤2 years	22	65 (43 to 98)	14 (8.7 to 22)	$<2.2\times10^{-16}$	38 (16 to 99)	$<2.2\times10^{-16}$

SRMA ≤2 years only includes dogs less than two years of age
Relative risk=incidence for NSDTR/incidence for comparison group
DYAR, dog years at risk; NSDTR, Nova Scotia Duck Tolling Retriever; SRMA, steroid-responsive meningitis-arteritis

could have led to misclassification of some cases. The diagnostic codes representing SRMA and IMRD were chosen based on published descriptions of the diseases in NSDTRs and the authors' clinical experience. The choices were also validated by checking the diagnostic codes in primary clinical records from NSDTRs with a high suspicion of IMRD or SRMA. These records, which contained information from the years 2002 to 2013, have been collected with the owner's consent, and used for the purpose of previous studies (Hansson-Hamlin and Lilliehöök 2009, 2013). This validation revealed that dogs with SRMA often receive the diagnostic code 'meningitis'. In contrast, dogs with IMRD are assigned a variety of diagnostic codes, the most common being 'lameness'. In the Agria database, 'lameness' was the most common diagnostic code in all NSDTRs (data not shown), probably reflecting a large range of different disorders. Some dogs with IMRD might have been assigned this diagnostic code, but the authors decided it to be too unspecific to be included in 'IMRD possibly'.

NSDTRs had significantly higher incidences for IMRD and SRMA than other breeds for both the more and less specific diagnostic classifications (Tables 6 and 7). The purpose of creating two diagnostic groups for each disease was to estimate a valid range for the incidence. The results from the study can be interpreted such that the true incidence for IMRD and SRMA is in the range between the incidence for 'IMRD/SRMA' and the incidence for 'IMRD/SRMA possibly'. Only one diagnosis within the 'IMRD/SRMA possibly' group was sufficient to make a diagnosis, meaning this group probably includes dogs with other disorders as well. The RR for 'IMRD/SRMA possibly' was lower than for 'IMRD/SRMA', which is expected when including more unspecific diagnoses that can equally affect or be more common in some other breeds.

Unfortunately, it was not possible to differentiate SRMA from meningitis of other origins due to a lack of a more specific diagnostic code in the registry. Conditional analyses, which only included dogs diagnosed before two years of age, were performed to increase the specificity. This approach produced increased incidences, but the RR was basically unaffected. Given that the diagnostic accuracy should not differ between NSDTRs and other breeds, the RR values should be valid.

The authors think that the disease patterns and breed predispositions described here are still relevant in the Swedish dog population today. The present study results, which are based on insurance data from 1995 to 2006, have been compared with newer insurance data from Agria (data not presented), and the authors found agreement at various levels. For example, similar to results in the present study (Table 2), the most common causes of veterinary visits in NSDTRs in the years 2006–2011 were neoplasia, gastrointestinal and locomotor disorders, followed by trauma (B. N. Bonnett, personal communication). Causes of veterinary visits with the highest RR values were unspecified immune disorders and CNS infection/inflammation, also in agreement with the results of the present study (Fig 1).

In conclusion, the results show that NSDTRs are at similar risk of disease, in general, to other retriever breeds, and are at a slightly higher risk of disease compared with all other breeds combined. The authors describe morbidity in NSDTRs, and show that NSDTRs are predisposed to autoimmune and neurological disorders in general and particularly to IMRD and SRMA. The authors further show that NSDTRs have an increased risk of lymphoma compared with other breeds. The information gained is of value to breeders, dog owners and veterinarians, and can be used for preventive measures as well as in disease investigations. Research to functionally characterise the genetic risk factors for IMRD and SRMA in NSDTRs is in progress.

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Contributors All the authors conceived and designed the study together. HDB performed statistical analyses with input from ÅV and BNB. HDB drafted the manuscript. All authors read and approved the final manuscript.

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Disease patterns and incidence of immune-mediated disease in insured Swedish Nova Scotia Duck Tolling Retrievers

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