Childhood pet ownership and multiple sclerosis: a systematic review and meta-analysis

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Abstract:

Background: Many studies have been conducted investigating a range of environmental factors which have been implicated in the pathogenesis of multiple sclerosis (MS). We collated available data about exposure to domestic animals before symptom onset in MS to perform a systematic review and meta-analysis.

Methods: Medline, Embase and Cinahl were searched for relevant articles, based on pre-defined inclusion and exclusion criteria and reference lists were hand-searched. Data were extracted and critical analysis was conducted using the Newcastle-Ottawa criteria. Meta-analysis used random effects.

Results: Study heterogeneity was high and study quality was variable. Random effects meta-analysis showed no associations with any pet ownership and development of MS.

Conclusion: It is not possible to draw definitive conclusions from this work. The studies included had a high level of heterogeneity. There are many variables involved in pet ownership and exposure and the nature of the way these have been studied makes the analysis challenging.

Keywords: multiple sclerosis – pet ownership – cat – dog – meta-analysis

Highlights:

- **Childhood environmental exposure may influence later development of MS**
- **Childhood pet ownership is one such potential factor**
- **This meta-analysis did not draw any definitive conclusions**
- **The field of study is challenging and suggestions are made for future work**

Introduction

Multiple sclerosis (MS) is one of the most common chronic neurological diseases affecting young adults (Browne, Chandraratna et al. 2014). It is thought to be caused by combination of environmental and genetic factors (Olsson, Barcellos et al. 2017). Genetic influences have primarily focussed on HLA alleles but there is also evidence for non-HLA alleles having predisposing and protecting influences (International Multiple Sclerosis Genetics, Hafler et al. 2007). Environmental factors suggested include sunlight (and vitamin D) exposure, Epstein-Barr Virus infection, cigarette smoking and obesity, and exposure to these at or around the time of adolescence is thought to be particularly important (Olsson, Barcellos et al. 2017).

The role of pet ownership and animal exposure has been explored in several previous studies. Initially, there were concerns that MS might be due to transmission of canine viruses, and researchers sought to investigate the link between dog ownership and MS (Cook and Dowling 1977, Cook, Natelson et al. 1978). More recently, the hygiene hypothesis has gained traction and popularity, suggesting that over-sanitisation of our living and working environments has led to our immune systems being predisposed to harmless "other" (e.g. grass pollen in hayfever) or "self" (e.g. myelin in MS) antigens, as there is more restricted exposure to pathogens in today's industrialised society (Bach 2002). Studies have shown that growing up on a farm is associated with reduced risk of asthma and allergy (Riedler, Braun-Fahrlander et al. 2001), as is exposure to dogs at a young age (Cullinan, Harris et al. 2003, Fall, Lundholm et al. 2015). Growing up in a small family is associated with increased rates of atopic disease, particularly related to number of brothers (Cullinan, Harris et al. 2003). Another study showed that exposure to pets in the first year of life was associated with reduced risks of atopic diseases (Ownby, Johnson et al. 2002). Rather less work has been carried out looking at pet ownership and autoimmune disease.

Pet ownership is common in the developed world, with nearly half of UK households (PFMA 2018) and two-thirds of USA households (Association 2020) owning pets, most commonly cats and dogs (PFMA 2018). Many advantages have been described in owning a pet, with research demonstrating increased levels of physical activity (mainly with pets which need to be exercised regularly e.g. dogs), emotional wellbeing and even better health outcomes in some populations (Allen, Blascovich et al. 2002, Baun and McCabe 2003, Irani, Mahler et al. 2006, Wells 2009). However, pet ownership is not without risks or adverse effects – it can be expensive, animals can cause illness or injury, and the loss of a pet can be distressing (Stallones 1994).

Several epidemiological studies have investigated environmental factors preceding MS onset, including exposure to animals. To the best of our knowledge, these data have not previously been gathered together in a systematic review or meta-analysis.

The aim of this piece of work was to review the available literature assessing childhood exposure to pets and the subsequent development of multiple sclerosis.

Methods

Search Strategy

Databases were searched as outlined in Table 1.

Table 1: Database search

Database and Dates covered	Date searched	Concept search strategy	Hits
Ovid (medline) all 1946 – 11 September 2020	11/9/2020	1. Multiple sclerosis/ 2. Pets/ 3. cat*.ti,ab 4. dog*.ti,ab 5. 2 or 3 or 4 6. 1 and 5 7. Case-control studies/ 8. 6 and 7	82
Ovid Embase 1974 to 2020 week 36	11/9/2020	1. Multiple sclerosis/ 2. Pet animal/ 3. cat*.ti,ab 4. dog*.ti,ab 5. 2 or 3 or 4 6. 1 and 5 7. Case control study/ 8. 6 and 7	83
Cinahl 2001-2017	11/9/2020	1. (MH “Multiple Sclerosis”) 2. (MM=”Pets”) 3. “cat*” 4. “dog*” 5. S2 or S3 or S4 6. (MH “Case Control Studies”) 7. S1 and S5 and S6	23

Reference lists of relevant articles were reviewed for further studies.

Study Selection

Retrieved studies were exported from the databases and imported into EndNote X9. Duplicate studies were removed.

All titles were screened. Where titles did not provide sufficient information, abstracts and then full text articles were screened for inclusion / exclusion.

Eligibility Criteria

Included studies were:

- case control studies
- examining the associations between exposure to domestic / companion animals and subsequent development of MS
- companion animals were those living in the same household as the participants, or defined as being owned by the participants
- companion animals included cats / dogs / rabbits / guinea pigs / birds / horses
- providing numerical data
- comparing against non-MS controls

Excluded studies were:

- studies not published in English
- review articles, abstracts, meta-analyses
- articles giving statements about conclusions drawn without providing data (authors were contacted to clarify wherever possible)
- twin studies
- studies looking at current pet ownership and presence / absence of MS (where this was not clear, the studies' authors were contacted to clarify details if possible)
- studies looking at occupational exposure only
- studies where it was unclear whether participants were sharing a home / owning pets (e.g. some studies refer to "contact" or "exposure" with animals, but do not clarify)
- animals not clearly companion animals / pets (i.e. cows / goats / poultry / sheep)

For studies where raw data were not provided or where it was unclear whether exposure preceded symptom onset, if overall animal contact rather than types of animals were specified, contact details for the corresponding, first and/or last authors were sought and emails sent asking for clarification.

Data extraction

A database was developed and the following information was extracted from each selected study:

- Title, first author, year of publication
- Sample country of origin

- Numbers of cases and controls included; definition of cases and controls; non-participation / refusal rates of cases and controls where documented
- Definitions and ascertainments of exposure
- Types of animal
- Numbers of cases / controls exposed / not exposed to each animal

Quality assessment

Newcastle-Ottawa Scale for case control studies (Wells, Shea et al. 2013) was used to assess the risk of bias for each study. The studies were rated in 3 domains – selection, comparability and exposure, for a total maximum score of 9.

Meta-analysis

Heterogeneity of studies was assessed using Higgins I^2(Higgins and Thompson 2002). In view of the expected heterogeneity, a random-effects meta-analysis was performed using RevMan 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Odds ratios (Mantel-Haenszel) and 95% confidence intervals were calculated for each exposure.

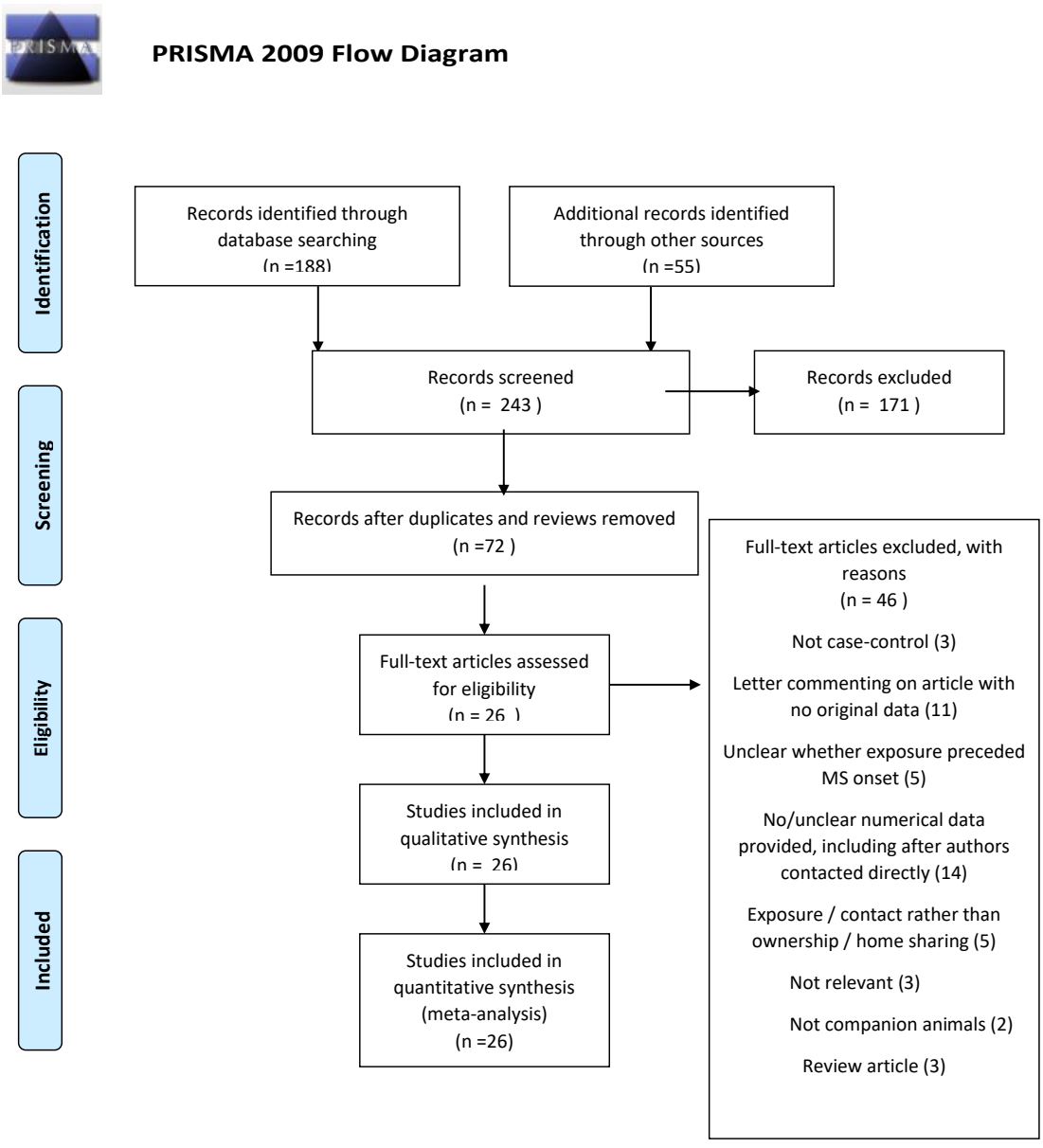
Separate analyses were conducted for each individual animal type, as well as for overall pet ownership.

Results

Search results

The process of sorting articles is illustrated in the PRISMA diagram.

Figure 1: PRISMA flow diagram



After removal of duplicates and articles that did not meet the inclusion criteria, a total of 26 studies were included in the meta-analysis. These are shown in table 2.

All of the information presented in table 2 is taken directly from the papers referenced with the exception of:

- Odds ratios and 95% confidence intervals calculated using RevMan
- Newcastle-Ottawa scores assessed by the authors independently; any disagreements resolved through discussion
- Some studies provided exposure in percentages rather than raw numbers. In those cases (Antonovsky, Leibowitz et al. 1965, Antonovsky, Leibowitz et al. 1968, Anderson, Kibler et al.

1984), percentages are given in the table; the raw numbers were calculated from the percentage and the number of cases/controls provided and follows the percentage in brackets.

There were 6 articles from 3 groups of authors where overlap in the included populations could not be excluded (Antonovsky, Leibowitz et al. 1965) and (Antonovsky, Leibowitz et al. 1968); (Cook and Dowling 1977) and (Cook, Natelson et al. 1978); (Mititelu and Bourceanu 1985) and (Mititelu, Cernescu et al. 1986). These articles have been included in the quality assessment but only one from each of these was included in each meta-analysis

Study characteristics

In total, included in the systematic review were 26 studies involving 4612 people with multiple sclerosis (PwMS) and 6428 controls (although this cannot exclude some duplication in the patients and controls). Mean number of cases and controls per study was 177 and 247; median 100 and 140 with a minimum and maximum of 12-1008 and 20-1008 respectively.

Details of included studies are given in Table 2.

Author, Year	Country	Cases / Controls (n)	Cases definition	Diagnostic criteria used	Control definition	Refusal /non-participation rate cases / controls	Exposure ascertainment	Exposure definition	Animal	Cases exposed (n)	Control exposed (n)	OR M-H, 95% CI	Quality assessment (Newcastle-Ottawa)
Alonso, 2011(Alonso, Cook et al. 2011)*	Iran	394 / 394	Recruited "*from multiple MS clinics across different cities*"	McDonald 2001(McDonald, Compston et al. 2001)	Referred by patient, *"childhood friend or relative, free of MS, of similar age (and sex, where possible*"	533 cases	Physician charts, telephone interviews	Pet ownership in period before onset of disease (cases) and time of interview (controls) *	dog	24	39	0.59 (0.35-1.00)	S 3 C 2 E 1 Total 6
									cat	22	25	0.87 (0.48-1.58)	
									bird	78	77	1.02 (0.72-1.44)	
Alter, 1968(Alter and Speer 1968)	USA	36/72	From MS clinic at University of Minnesota hospitals with "*history of remissions and exacerbations of neurological deficit…. [with clinical] signs of scattered deficit of CNS….., had had studies to rule out mimics of MS*"	History and examination	From outpatient medical clinic at University of Minnesota hospitals with no neurologic or psychiatric problems, age and sex matched to cases	Not stated	Questionnaire	Pet ownership in period before symptom onset (cases) and matched "*age of onset*" (controls, matched to case)	dog	83% = 30	89% = 64	0.63 (0.2-1.96)	S 3 C 1 E 1 Total 5
									cat	60% = 22	82% = 59	0.35 (0.14-0.85)	
									bird	33% = 12	40% = 29	0.74 (0.32-1.71)	
									rabbit	41% = 15	38% = 27	1.19 (0.53-2.69)	
									horse	34% = 12	40% = 29	0.40 (0.17-0.92)	
									other pet	28%	39%		
Anderson, 1984(Anderson, Kibler et al. 1984)	USA	70/70 (neighbours)	*"The medical records of 175 patients, seen in the Emory University Clinic since 1960 and diagnosed as*	McDonald, 1977 (McDonald and Halliday 1977)	*"Neighborhood controls were selected from households randomly identified*	0/23	Interview using questionnaires, information verified by a friend or relative of	Living in same household as dog between ages 0-4 years	Dog	41%	46%		S 3 C 2 E 1 Total 6

			having MS were reviewed by two neurologists to determine whether they 1. Met the published criteria for definite or probable MS(McDonald and Halliday 1977), 2. Did not have dementia, 3. Were aged 50 years or younger and 4. Resided in metropolitan Atlanta"		*from an address directory as being in the neighborhood of a case…" reached by telephone, matched by age (+/-6 years) and sex.*		subject who knew the subject in childhood and adolescence, interviewed by telephone using standard questionnaire	Living in same household as dog between 0-9y	Dog	79%	79%		
								Living in same household as dog between 0-14y	Dog	90%	90%		
								Living in same household as dog between 0-19y	**Dog**	**91%**	**91%**	1.00 (0.31-3.27)	
								Living in same household as dog 0-4y before MS onset	Dog	63%	61%		
								Living in same household as dog 0-9y before MS onset	Dog	73%	80%		
								Living in same household as dog 0-14y before MS onset	Dog	83%	84%		
								Living in same household as dog 0-19y before MS onset	Dog	87%	89%		
		70/57 (clinic)			*"156 age (+/-6y) and sex matched*	0/7		Living in same household	Dog	41%	39%		

					potential control subjects were randomly selected from patients seen from January 1977-December 1978 at the medical and surgical clinics of Emory University Medical Center"			as dog between ages 0-4 years					
								Living in same household as dog between 0-9y	Dog	79%	75%		
								Living in same household as dog between 0-14y	Dog	90%	86%		
								Living in same household as dog between 0-19y	Dog	91%	88%		
								Living in same household as dog 0-4y before MS onset	Dog	63%	61%		
								Living in same household as dog 0-9y before MS onset	Dog	73%	82%		
								Living in same household as dog 0-14y before MS onset	Dog	83%	89%		
								Living in same household as dog 0-	Dog	87%	93%		

								19y before MS onset					
Antonovsky, 1965(Antonovsky, Leibowitz et al. 1965)**	Israel	241/964 (but duplicated 47 controls)	From a nationwide survey of multiple sclerosis	clinical notes review +/- examination	Planned 4:1 from 1961 census, selected at random and matched by age, sex, region of birth. NB "*material available for analysis fell short of the planned four to one ratio by 47 controls. In order to correct for the deficiency of controls and to utilize all available patient data, it was decided to duplicate existing control data*"	20 / not stated	Questionnaire via interview	"*Dog as pet at some time before age of onset*"… "*an age at onset was assigned to each control which was the same as the patient's with whom the control was matched*"	Dog	28%	21%		S 3 C 1 E 0 Total 4
Antonovsky, 1968(Antonovsky, Leibowitz et al. 1968)**	Israel	221/442	From a nationwide survey of people living with MS in 1961 plus those diagnosed since	clinical notes review +/- examination	2:1 from national census stratified by sex, age, region of birth to correspond to groupings of patients	Not stated / 222		*"questions about the childhood home referred arbitrarily to about age ten years"* *"age at onset was assigned to each control which was the same*	Dog	16%	10%	1.70 (1.06-2.74)	S 2 C 2 E 1 Total 5

								as the patient's with whom the control was matched"					
Bauer, 1977(Bauer and Wikstrom 1977)	German y	184/111	"*Patients with MS*" (42 inpatients; remainder outpatients)	Not stated	Other neurologic diseases	Not stated	Questionnaire	Dog during childhood	Dog	61	33	1.17 (0.70-1.95)	S 1 C 0 E 1 Total 2
								Dog at onset of MS or 1-2y before	Dog	39	27		
Bunnell, 1979(Bunnell, Visscher et al. 1979)	USA	60/60	*"White, non-California born, …diagnosis of definite or probable MS made by UCLA neurologists"*	Not stated	*"Non-California born…. matched for age, sex, race and neighbourhood of present residence"*	Not stated	Questionnaire administered in person	Housepet owned for more than 6 months, before age 19	Dog between birth and 19 years	37	33	1.32 (0.64-2.72)	S 0 C 2 E 1 Total 3
Cendrowski, 1969(Cendrowski, Wender et al. 1969)	Poland	300/300	*"In the district [of Poznan] all accessible medical records of patients with multiple sclerosis from Neurological In- and Out-Patients' Departments were included into this study. In addition, patients from Sanatorial Centres and Care Homes for Chronic Disabled were registered in a similar way…Patients who…did not have evident and convincing signs of*	Probable MS – "*unequivocally satisfied clinical criteria of the progressive disease with dissemination of lesions in time and space, and left only little doubt about the diagnosis";* possible multiple sclerosis – "*alternative diagnoses had been excluded as far as practicable, and when the clinical picture was more suggestive for*	*"patients with sciatica who were residing in the district of Poznan and did have similar demographic pattern"*	Not stated	*"Interviewed by a specially formulated questionnaire which comprised 10 basic subjects relevant to the period both for patients and controls prior to the age of onset"*	Period prior to age of onset… "*arbitrarily to age of about 15"* – animals in the household	dogs	207	191	1.27 (0.9-1.78)	S 3 C 0 E 1 Total 4
									Cats	177	155	1.35 (0.97-1.86)	
									Birds	173	132	1.73 (1.25-2.40)	
									Horses	130	104	1.44 (1.04-2.00)	
									Total contact	842	696		

			multiple sclerosis were discarded from the study"… "from the list of definitively accepted over 1,500 patients with multiple sclerosis, a smaller group of 300 cases was randomly selected"	*multiple sclerosis than of other neurological disorders"*									
Cook, 1977(Cook and Dowling 1977)***	USA	29/29	diagnosed as *"definite MS by highly competent neurologists in the area"*	Not stated	*Friend who grew up in same environment*	9/not stated	Questionnaire via telephone interview	pet ownership before onset of symptoms	Small indoor pet	25	13		S 1 C 2 E 1 Total 4
Cook, 1978(Cook, Natelson et al. 1978)***	USA	61/61	From neurologists, from a "*hospital caring for patients with chronic MS, and from local MS society chapters"*	Schumacher, 1965(Schumacher, Beebe et al. 1965)	*"Longstanding friend who had lived in the same general neighbourhood prior to onset of first symptoms in MS subject… same sex and race…generally of same socioeconomic background"*	Not stated	Questionnaire in person or over the telephone	Pet ownership up to the age of symptom onset ("same time epoch was used for matched control")	Dog	40	34	1.5 (0.73-3.14)	S 1 C 2 E 1 Total 4
									Cat	18	27	0.53 (0.25-1.11)	
									Indoor dog	39	29		
									Indoor dog 5y before symptom onset	26	14		
									Small indoor dog 5y before symptom onset	22	12		
De Jong, 2019(de Jong, Tremlett et al. 2019)	USA	151/235	Female nurses with MS from US Nurses' Health Study, medical records reviewed by neurologist	Not stated	"*Matched by age at cohort entry and study cohort*"	10% overall	Questionnaire	Animals kept as pets prior to MS onset	Any	136	200	1.59 (0.83-3.02)	S 3 C 2 E 2 Total 7
									Dog	120	170	1.48 (0.91-2.41)	

									Cat	86	124	1.18 (0.78-1.79)	
									Rabbit	22	41	0.81 (0.46-1.42)	
									Guinea pig	18	24	1.19 (0.62-2.28)	
									Birds	23	29	1.28 (0.71-2.30)	
									Other animal	25	46		
De Keyser, 1997(De Keyser and Zwanikken 1997)	Belgium	100/100	Database of MS patients from previous study, clinically or laboratory supported definite MS, less than 50y old, symptom onset after 20y	Poser, 1983 (Poser, Paty et al. 1983)	Selected from employee list of industrial complex, matched by gender and age, lack of MS	6/0	Questionnaire	E to household animal age 0-10 years	Dog	47	31		S 3 C 2 E 1 Total 6
									Cat	29	30		
									Bird	23	21		
								Exposure to household animal age 0-15 years	Dog	50	44		
									Cat	31	40		
									Bird	34	36		
								Exposure to household animal age 0-20 years	Dog	55	49	1.27 (0.73-2.22)	
									Cat	34	42	0.71 (0.40-1.26)	
									Bird	38	38	1.00 (0.56-1.77)	
Ghadirian, 2001(Ghadirian, Dadgostar et al. 2001)	Canada	197/202	"*Incident MS cases, resident in greater Montreal and diagnosed between January 1991 and December 1994*"	Not stated	"drawn at random from the general population…. matched… by age, sex, residential phone number…., selected from	69/not stated	Questionnaire via interview	Domestic animals	Cats	127	156	0.53 (0.34-0.83)	S 2 C 2 E 1 Total 5
									cats for less than 5 years	32	36		
									cats for 5-10y	23	32		
									cats for 10y or more	34	83		

					telephone directory"				Birds	84	54	2.04 (1.34-3.10)	
									birds for less than 5y	41	29		
									birds for 5-10y	16	12		
									birds for more than 10y	20	7		
Gustavsen, 2014(Gustavsen, Page et al. 2014)	Norway	530/918	Oslo MS registry	Poser 1983(Poser, Paty et al. 1983), and / orMcDonald 2010(Polman, Reingold et al. 2011)	Randomly selected from Norwegian bone marrow donor registry	160/172	Postal questionnaire	Animals in household before age of 18	Dog	192	427	0.62 (0.50-0.78)	S 2 C 2 E 1 Total 5
									Cat	207	463	0.65 (0.52-0.81)	
									Horse	32	63	0.87 (0.56-1.35)	
									Other animal	138	240		
Hughes, 1980(Hughes, Russell et al. 1980)	England	64/103	"*definite or probable MS attending Neurology Department of Guys Hospital*"	McDonald, 1977(McDonald and Halliday 1977)	"*next in or outpatient attending the department with some condition other than MS who was of the same sex and within 5 y of the same age*" AND 39 age and sex matched friend known for 5y before illness onset	Not stated	Cases and neurological controls were "*questioned*"; friend was "*asked to answer a postal questionnaire*"	Pet ownership at any time before onset date	Any	55	94		S 2 C 2 E 0 Total 4
									Dog	40	60	1.19 (0.63-2.26)	
									Cat	40	69	0.82 (0.43-1.58)	
								Dog ownership 5y before onset date	Dog	24	43		
								Dog ownership 1y before onset date	Dog	19	30		
Jotkowitz, 1977(Jotkowitz 1977)	Not stated	50/50	"*Multiple sclerosis patients*"	Not stated	"*patients with migraine, epilepsy or low back pain and about the*	Not stated	"were questioned"	"*close contact with a house pet, usually within 5 or*	House pet	46	24	12.46 (3.90-39.85)	S 0 C 0 E 0 Total 0

					same age and sex"			*10 years prior to disease onset*"					
Koch-Henriksen, 1989(Koch-Henriksen 1989)	Denmark	295/295	<75y, ascertained through Danish MS registry or diagnostic registers of hospitals or neurologists who met criteria for probable or possible MS. Clinical examination performed.	Allison and Millar, 1954(Allison and Millar 1954) (modified)	age and sex matched drawn at random from central population registry	312/59	Questionnaire and telephone interview	*"…animal exposure… . From birth up to the age of 15 years " – "lived, stayed or worked in near physical contact with animal in question"*	Dog	195	188	1.11 (0.79-1.56)	S 2 C 2 E 1 Total 5
									Cat	189	189	1.00 (0.71-1.40)	
									Caged bird	57	67	0.82 (0.55-1.21)	
									Fish	41	49		
									Guinea pig, rabbits	114	107		
								Animal exposure between age 15y and age at onset The age at "onset" for a control-person was determined by the matched case"	Dog	180	174		
									Cat	154	133		
									Caged bird	64	65		
									Fish	38	29		
									Guinea pig, rabbits	45	44		
Landtblom, 1993(Landtblom	Sweden	67/176	*"Cases of MS were collected from the patient files of the*	Schumacher 1965(Schumacher, Beebe et al.	*"Randomly drawn from the*	6/52	Questionnaire *"without revealing the*	Exposed for minimum	Pet Dog	29	67	1.24 (0.70-2.20)	S 3 C 0 E 1

, Flodin et al. 1993)			*neurological departments of the hospitals in Jonkoping and Kalmar…..diagnosed in 1983 through 1989….labelled as definite multiple sclerosis or as probable or possible multiple sclerosis"*	1965) (definite MS), Rose 1976(Rose, Ellison et al. 1976) (probable or possible MS)	*population registers of …Jonkoping and Kalmar…20 to 65 years of age"*		*purpose of the study with respect to multiple sclerosis". "All exposure data of a priori interest were critically checked for credibility in telephone interviews with both cases and referents"*	of 1 year with 5y latency period to pet. Mean year of diagnosis for cases was taken as "*anchor point in time for referents*".	Pet Cat	25	65	1.02 (0.57-1.82)	Total 4
									Pet Caged bird	13	27	1.33 (0.64-2.76)	
Mititelu, 1985(Mititelu and Bourceanu 1985)****	Romania	12/20	*"Patients with MS on the record of the neurological polyclinical service."*	Schumacher, 1965(Schumacher, Beebe et al. 1965)	*"Hospitalized patients with neurologic disease, matched for age, sex, residence, social and economic background"*	13 / not stated	Questionnaire at interview	Possession in childhood	Dogs	10	9		S 1 C 2 E 1 Total 4
								Possession 5y before illness onset	Dogs	9	7		
								Possession 10y before illness onset	Dogs	10	4		
Mititelu, 1986(Mititelu, Cernescu et al. 1986)****	Romania	67/67	*"..fulfilled McDonald-Halliday criteria of clinically definite MS and were in the evidence the outpatient clinics [sic]"*	McDonald, 1977(McDonald and Halliday 1977)	*"Without demyelinative or infectious diseases of CNS, were of the same socioeconomic background, being of similar age and sex with MS cases"*	Not stated	Postal questionnaire	Exposure to own pet dogs in childhood	Dogs	53	35	3.46 (1.62-7.40)	S 2 C 0 E 1 Total 3
Mowry, 2018(Mowry, Hedstrom et al. 2018)	USA	1008/1008	White non Hispanic people with MS identified through medical records, aged 18-69, diagnosis made	McDonald 2001 and 2005 (McDonald, Compston et al. 2001, Polman,	Randomly selected from same healthcare plan medical records	Not stated	Computer assisted telephone interview	Exposure to pets prior to MS onset	Not stated	558	376	2.08 (1.74-2.49)	S 4 C 2 E 1 Total 7

			by neurologist, validated by chart review	Reingold et al. 2005)	without MS or related condition, matched by sex, age, ethnicity, residence								
Norman, 1983(Norman, Cook et al. 1983)	USA	22/55	"*white men under age 35 years, admitted to VA hospitals between 1971-1977 with diagnosis of MS*"	Not stated	18 white men matched by year of birth with Hodgkin's lymphoma; 37 white men hospitalized with other conditions chosen at random from VA hospitalizatio n list, but not psychiatric, neurologic disorders or alcoholism	3/ 20	Postal questionnaire	Owned dogs within 10y prior to MS onset (or matched age in controls)	Dog	13	45	0.32 (0.11-0.96)	S 1 C 2 E 1 Total 4
								Owned dogs within 5y prior to MS onset	Dog	10	30		
Operskalski, 1989(Operskalsk i, Visscher et al. 1989)	USA	145/145	*"persons who were white, born in the United States and had onset of disease during the 10 year period 1960-1969" (population identified as definite or probable MS from a previous prevalence study)*	*Not stated*	*"Friend named by each MS patient….who had no neurologic disorder and was of the same sex, age (within 5 years) and race. Each control was also matched for birthplace and for residence in the same geographic area…."*	Not stated	Self-administered postal questionnaire	Events before age of onset of MS "*and the same age was used as a point of reference for the matched control*". Defined as "*regular contact*" with household pet	Dogs	126	123	1.19 (0.61-2.30)	S 3 C 2 E 1 Total 6
									Cats	94	81	1.46 (0.91-2.34)	
									Birds	42	46	0.28 (0.17-0.46)	
									Horses	62	49	1.46 (0.91-2.36)	

Read, 1982(Read, Nassim et al. 1982)	England	72/144	"*born in 1942 or later… had been admitted to neurological wards or had attended OPD at University Department of Neurology in Oxford…. between 1976 and 1980*", with CDMS	McDonald, 1977(McDonald and Halliday 1977)	selected at random using computer generated diagnostic index, one neurological and one non neurological. Similar date of birth, sex, place of residence, admitted to hospital in same year that case developed MS	12/94	Questionnaire via interview	Dog living in same household as subject at any time between birth and onset of MS	56	118		3.74 (2.03-6.88)	S 2 C 2 E 1 Total 5
Siejka, 2016(Siejka, Taylor et al. 2016)	Australia	136/272	*"People with MS under the age of 60 were recruited in the state of Tasmania through the use of advertising, information evening and letters from neurologists…. Case respondents were interviewed and examined by one of the participating neurologists. MRI were assessed for 134/136 and for the other two cases MRI reports from previously conducted scans were obtained."*	Paty 1988(Paty, Oger et al. 1988), Poser 1983(Poser, Paty et al. 1983)	*"Controls were selected from the roll of registered electors…. For each verified case, two control subjects were randomly selected and matched to the index case on sex and birth year"*	Not stated/76%	*"Partly self-completed life and lifetime calendar and a face-to-face interview"*	*"whether they had any pets at home that were owned by members of the household, including the type and number of pets….prior to the age of first symptom (and the same age for each matched control)"*	Dogs	123	243	1.13 (0.57-2.25)	S 2 C 2 E 1 Total 5
									Pet cats	114	201	1.83 (1.08-3.11)	
									Pet birds	64	115	1.21 (0.80-1.84)	
									Pet guinea pigs	11	23	0.95 (0.45-2.02)	
									Pet rabbits	22	42	1.06 (0.60-1.85)	
Sylwester, 1979(Sylwester and Poser 1979)	USA	100/135	"*Definite MS*"	Not stated	medical students, secretaries,	Not stated	"*postcard questionnaire*"	"*frequent and close exposure*	Cats	65	57	2.54 (1.49-.34)	S 0 C 0 E 1

					laboratory personnel			*between the ages of 8 and 16 years*"	Dogs	69	70	2.07 (1.20-3.55)	Total 1
									Rabbits	22	15	2.26 (1.10-4.61)	
									Horses	32	22	2.42 (1.30-4.50)	

- *Alonso – exposure implies that controls will have had a longer time period to own pets as time before interview versus time before onset (which by definition will have been earlier as had to be diagnosed to be eligible for study)
- **Antonovsky – cannot exclude duplication of participants. Also note duplication of control data in 1965 study
- *** Cook – cannot exclude duplication of participants
- **** Mititelu – cannot exclude duplication of participants

Table 2: Included studies. Abbreviations used in table: CDMS = clinically definite multiple sclerosis; OPD = outpatient department; for Newcastle-Ottawa Scale – S = selection; C = comparability; E = exposure. Italics indicate direct quotations from sources.

Dates of publication: ranged from 1965-2019. The majority of articles were published in the 20th century.

Case definition varied significantly between studies, perhaps unsurprisingly considering the evolution of diagnostic criteria for MS over the past decades (Przybek, Gniatkowska et al. 2015). Earlier studies focussed primarily on neurological history and examination; later studies used a range of diagnostic criteria, including those suggested by McDonald (with various revisions) (McDonald and Halliday 1977, McDonald, Compston et al. 2001, Polman, Reingold et al. 2005, Polman, Reingold et al. 2011), Poser (Poser, Paty et al. 1983), Schumacher (Schumacher, Beebe et al. 1965), Rose (Rose, Ellison et al. 1976), Paty (Paty, Oger et al. 1988) and Allison and Miller (Allison and Millar 1954).

Control selection: there was a large variation in control selection between studies, including hospital (even some neurological clinics / departments) and community controls; those referred by cases, those selected at random from population or other records. In one case (Antonovsky, Leibowitz et al. 1965), inability to recruit sufficient controls led to the authors duplicating existing control data. Matching was carried out in most studies to a greater or lesser extent; frequently by age and sex and sometimes including area of birth / residence, socio-economic status and race. For the purpose of the meta-analysis, when there was a study which included both hospital and community controls which were described separately (Anderson, Kibler et al. 1984), we used the data for community controls, as these score more highly for the Newcastle-Ottawa rating (Wells, Shea et al. 2013).

Non-participation rates: were not consistently stated through the studies. In some studies, neither case nor control refusal / non-participation rates were stated; in some only one or the other were stated.

Animal types: Dogs were by far the most common animal type studied. Some studies further subdivided this by size of dog, or whether the dog lived primarily inside or outside. A wide range of animals were included in the papers; in order of descending frequency, with the number of studies looking specifically at that animal type: dog (22) / cat (14) / bird (10) / horse (6) / rabbit (4) / guinea pig (2). Other studies did not specify animal type but made overall comparisons of exposure.

Definition of exposure: there was wide variation in definition of periods and nature of exposure, not only between studies but also in some cases within studies, when looking at cases and controls. While one of the exclusion criteria was for studies that included current pet ownership for cases, some studies compared prior pet ownership for cases with pet ownership at any time (i.e. up to and including the study period) for controls (Flodin, Soderfeldt et al. 1988, Alonso, Cook et al. 2011), while others deliberately matched controls to cases and took the case age of onset as a “cut-off” for the control exposure (Antonovsky, Leibowitz et al. 1965, Alter and Speer 1968, Antonovsky, Leibowitz et al. 1968, Cook, Dowling et al. 1978, Koch-Henriksen 1989, Operskalski, Visscher et al. 1989, Landtblom, Flodin et al. 1993, Siejka, Taylor et al. 2016). Furthermore, there was little consistency between ages of exposure to the animals, with studies ranging from at any time before disease onset, to specific narrow age ranges, to “childhood” / before age 15, age 19; specifically in the 1 year period prior to symptom onset.

When selecting which exposure to use, in the face of these varying time periods and sub-classification of animals, for the purpose of the meta-analysis, we were keen to keep things as

comparable as possible, by using whichever set was closest to our definition of "childhood exposure":

- Anderson *et al.* (Anderson, Kibler et al. 1984), there was a choice of living in the same household as dogs between the ages of 0-4, 0-9, 0-14 or 0-19 years of age as well as between 0-4, 0-9, 0-14 or 0-19 years before onset of MS; the period of 0-19 years of age was selected;
- Bauer (Bauer and Wikstrom 1977) included dog ownership in childhood and dog ownership at the onset of MS or 1-2 years before; the former was used for analysis;
- de Keyser et al. (de Keyser and Zwanikken 1997) included data for ages 0-10 years, 0-15 years and 0-20 years; the period of 0-20 years was used;
- Ghadirian et al. (Ghadirian, Dadgostar et al. 2001) included pet ownership for less than 5y, 5-10 years, 10y or more, or overall; overall ownership was used
- Hughes (Hughes, Russell et al. 1980) looked at time periods of 1 year before MS onset; 5y before onset, or any time before onset – the period of any time before onset was used
- Koch-Henriksen (Koch-Henriksen 1989) assessed time periods from birth to 15 years, and from 15 years to age of onset – the former was used
- Norman (Norman, Cook et al. 1983) had the option of dog ownership either 10 or 5 years before disease onset; the longer time period was selected for the meta-analysis

and was broadest in terms of animal exposure

- Cook (Cook, Natelson et al. 1978) investigated ownership of "dogs", "indoor dogs" and "small indoor dogs" – the group of "dogs" was selected)

Table 2 shows the range of exposures and time periods; the data used for the meta-analysis are demonstrated by having odds ratios and 95% confidence intervals calculated and inserted into the table for these.

Ascertainment of exposure: the majority of studies used questionnaires or interviews (usually structured with a questionnaire), either postal, telephone or in person. Verification of pet exposure was sought in only two studies, when childhood friends or family were contacted to confirm the subjects' answers.

Quality assessment:

The Newcastle-Ottawa scale showed a range of scores for these studies of 0-7; median 5. We used an algorithm based on that from McPheeters *et al* to divide studies into "good", "fair" and "poor" (McPheeters, Kripalani et al. 2012), with a cut-off score of 7 to indicate good and 5 to indicate fair. Only 2 studies scored a total of 7 (Mowry, Hedstrom et al. 2018, de Jong, Tremlett et al. 2019) and only one of these (de Jong, Tremlett et al. 2019) scored sufficient points using the subcategories NOS as outlined by McPheeters to be scored as "good" or "fair" due mainly to the recording of exposures. We had considered performng a "second round" of analysis using cut-off overall scores of 5 or 6, but recognised that this would have artificially dichotomised our data without valid arguments for doing so, and so chose to only perform a single "round" of data analysis.

Meta-analysis results

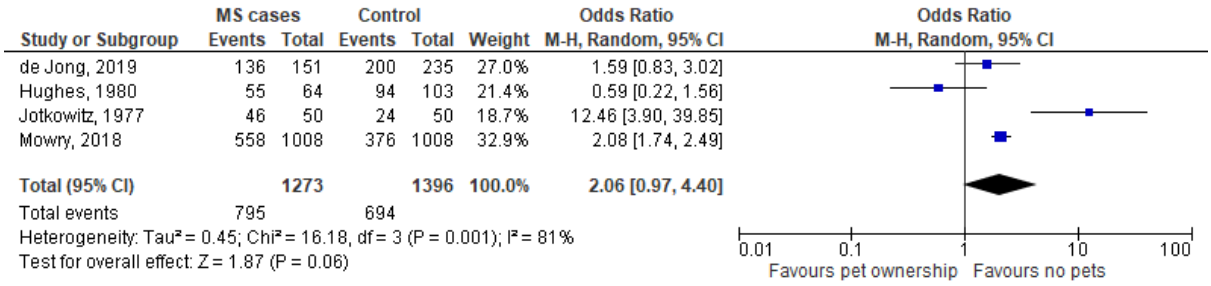
Calculated odds ratios with 95% confidence intervals are shown in table 3:

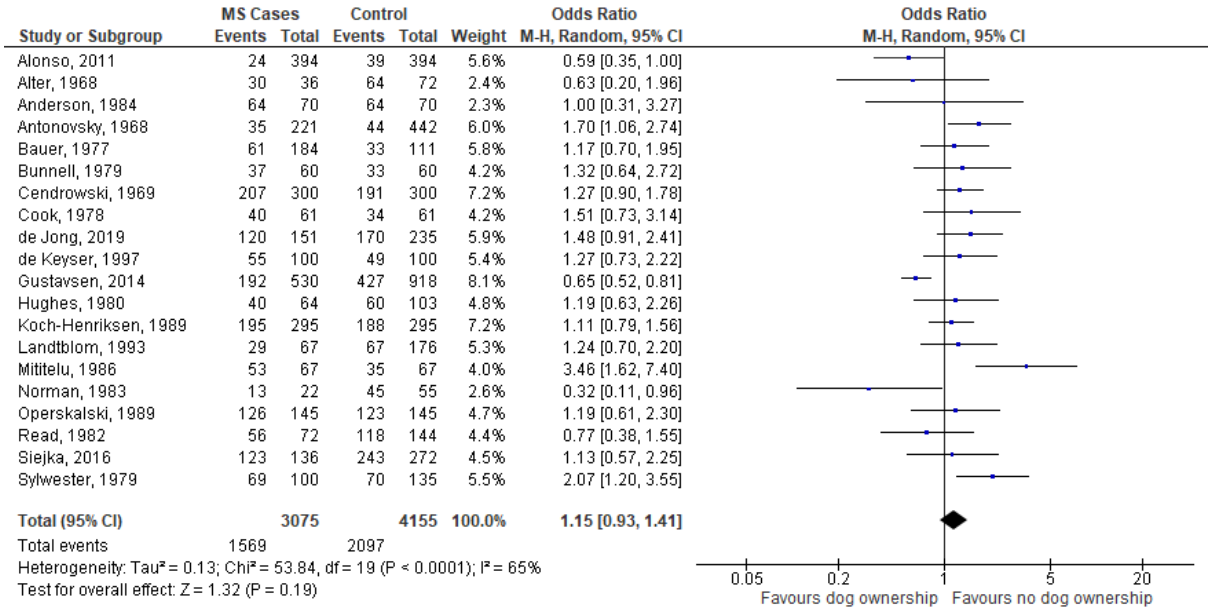
Table 3: Odds ratios, 95% confidence intervals, study heterogeneity and random effects Mantel-Haenszel analysis by type of pet:

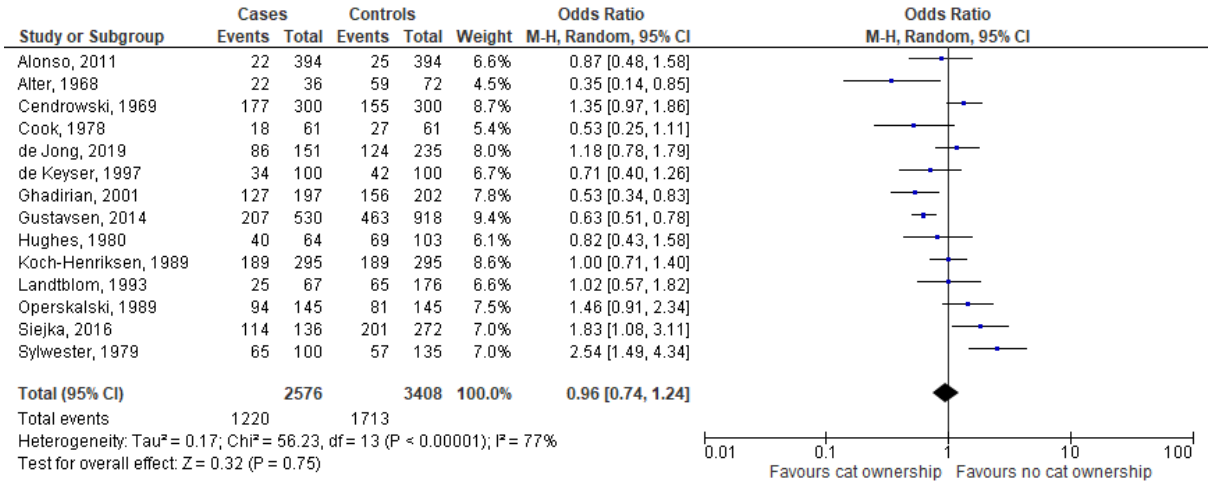
Pet type	Odds ratio	95% confidence interval	Higgins I^2(%)	Number of studies	Total no. MS cases	Total no. controls	Median NOS of studies (range)
Any pets	2.06	0.97-4.40	81	4	1273	1396	6 (0-7)
Dogs	1.15	0.93-1.41	65	20	3075	4155	5 (1-6)
Cats	0.96	0.74-1.24	77	14	2576	3408	5 (1-7)
Birds	1.18	0.95-1.47	52	10	1821	2191	5 (4-7)
Rabbits	1.18	0.78-1.80	40	4	423	714	6 (1-7)
Horses	1.19	0.77-1.84	74	5	1111	1570	5 (1-6)
Guinea pigs	1.08	0.66-1.77	0	2	287	507	6 (5-7)

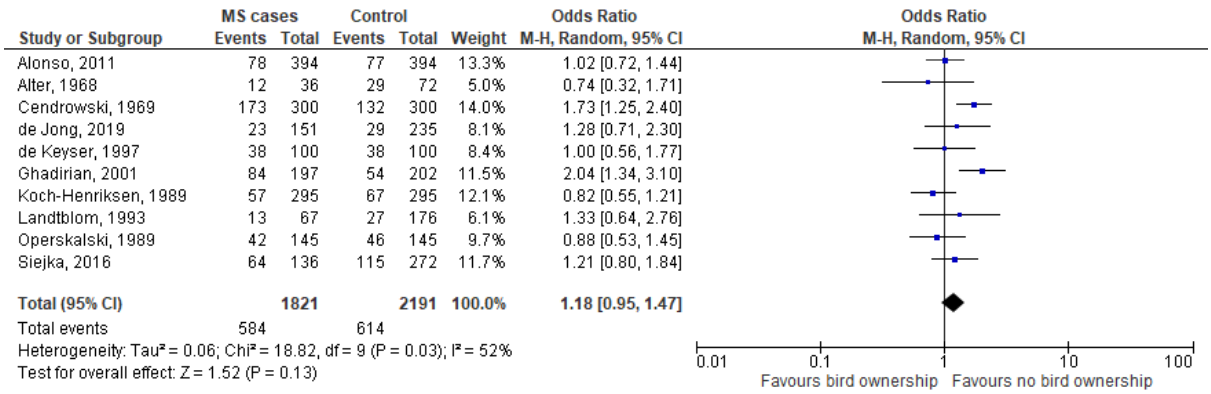
Forest plots are shown in figure 2.

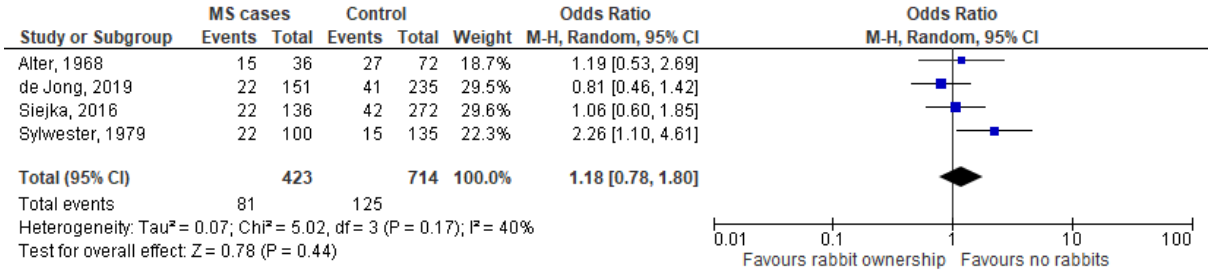
Figure 2: Forest plots from meta-analysis showing (top to bottom): overall pet ownership, dog ownership, cat ownership, bird ownership, rabbit ownership, horse ownership and guinea pig ownership.

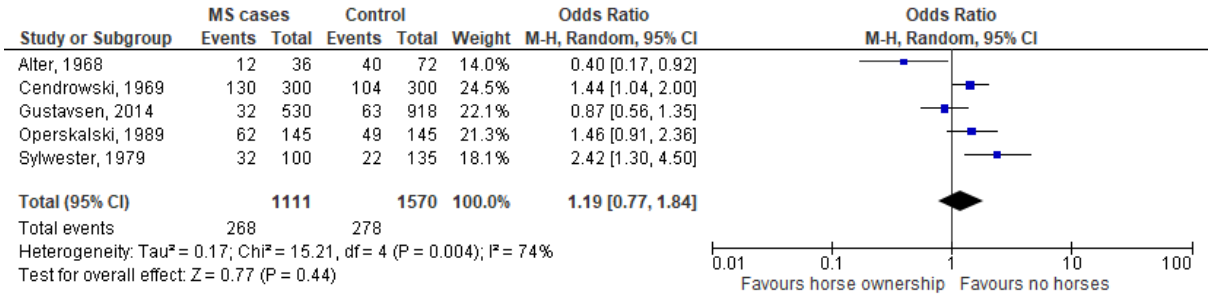


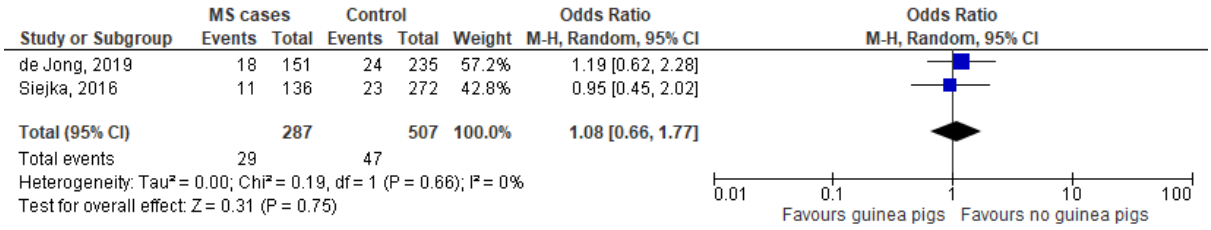

MS Cases
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Alonso, 2011 24 394 39 394 5.6% 0.59 [0.35, 1.00]
Alter, 1968 30 36 64 72 2.4% 0.63 [0.20, 1.96]
Anderson, 1984 64 70 64 70 2.3% 1.00 [0.31, 3.27]
Antonovsky, 1968 35 221 44 442 6.0% 1.70 [1.06, 2.74]
Bauer, 1977 61 184 33 111 5.8% 1.17 [0.70, 1.95]
Bunnell, 1979 37 60 33 60 4.2% 1.32 [0.64, 2.72]
Cendrowski, 1969 207 300 191 300 7.2% 1.27 [0.90, 1.78]
Cook, 1978 40 61 34 61 4.2% 1.51 [0.73, 3.14]
de Jong, 2019 120 151 170 235 5.9% 1.48 [0.91, 2.41]
de Keyser, 1997 55 100 49 100 5.4% 1.27 [0.73, 2.22]
Gustavsen, 2014 192 530 427 918 8.1% 0.65 [0.52, 0.81]
Hughes, 1980 40 64 60 103 4.8% 1.19 [0.63, 2.26]
Koch-Henriksen, 1989 195 295 188 295 7.2% 1.11 [0.79, 1.56]
Landtblom, 1993 29 67 67 176 5.3% 1.24 [0.70, 2.20]
Mititelu, 1986 53 67 35 67 4.0% 3.46 [1.62, 7.40]
Norman, 1983 13 22 45 55 2.6% 0.32 [0.11, 0.96]
Operskalski, 1989 126 145 123 145 4.7% 1.19 [0.61, 2.30]
Read, 1982 56 72 118 144 4.4% 0.77 [0.38, 1.55]
Siejka, 2016 123 136 243 272 4.5% 1.13 [0.57, 2.25]
Sylwester, 1979 69 100 70 135 5.5% 2.07 [1.20, 3.55]
Total (95% CI) 3075 4155 100.0% 1.15 [0.93, 1.41]
Total events 1569 2097
Heterogeneity: Tau² = 0.13; Chi² = 53.84, df = 19 (P < 0.0001); I² = 65%
Test for overall effect: Z = 1.32 (P = 0.19)
0.05 0.2 1 5 20
Favours dog ownership Favours no dog ownership


Cases
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Alonso, 2011 22 394 25 394 6.6% 0.87 [0.48, 1.58]
Alter, 1968 22 36 59 72 4.5% 0.35 [0.14, 0.85]
Cendrowski, 1969 177 300 155 300 8.7% 1.35 [0.97, 1.86]
Cook, 1978 18 61 27 61 5.4% 0.53 [0.25, 1.11]
de Jong, 2019 86 151 124 235 8.0% 1.18 [0.78, 1.79]
de Keyser, 1997 34 100 42 100 6.7% 0.71 [0.40, 1.26]
Ghadirian, 2001 127 197 156 202 7.8% 0.53 [0.34, 0.83]
Gustavsen, 2014 207 530 463 918 9.4% 0.63 [0.51, 0.78]
Hughes, 1980 40 64 69 103 6.1% 0.82 [0.43, 1.58]
Koch-Henriksen, 1989 189 295 189 295 8.6% 1.00 [0.71, 1.40]
Landtblom, 1993 25 67 65 176 6.6% 1.02 [0.57, 1.82]
Operskalski, 1989 94 145 81 145 7.5% 1.46 [0.91, 2.34]
Siejka, 2016 114 136 201 272 7.0% 1.83 [1.08, 3.11]
Sylwester, 1979 65 100 57 135 7.0% 2.54 [1.49, 4.34]
Total (95% CI) 2576 3408 100.0% 0.96 [0.74, 1.24]
Total events 1220 1713
Heterogeneity: Tau² = 0.17; Chi² = 56.23, df = 13 (P < 0.00001); I² = 77%
Test for overall effect: Z = 0.32 (P = 0.75)
0.01 0.1 1 10 100
Favours cat ownership Favours no cat ownership


MS cases
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Alonso, 2011 78 394 77 394 13.3% 1.02 [0.72, 1.44]
Alter, 1968 12 36 29 72 5.0% 0.74 [0.32, 1.71]
Cendrowski, 1969 173 300 132 300 14.0% 1.73 [1.25, 2.40]
de Jong, 2019 23 151 29 235 8.1% 1.28 [0.71, 2.30]
de Keyser, 1997 38 100 38 100 8.4% 1.00 [0.56, 1.77]
Ghadirian, 2001 84 197 54 202 11.5% 2.04 [1.34, 3.10]
Koch-Henriksen, 1989 57 295 67 295 12.1% 0.82 [0.55, 1.21]
Landtblom, 1993 13 67 27 176 6.1% 1.33 [0.64, 2.76]
Operskalski, 1989 42 145 46 145 9.7% 0.88 [0.53, 1.45]
Siejka, 2016 64 136 115 272 11.7% 1.21 [0.80, 1.84]
Total (95% CI) 1821 2191 100.0% 1.18 [0.95, 1.47]
Total events 584 614
Heterogeneity: Tau² = 0.06; Chi² = 18.82, df = 9 (P = 0.03); I² = 52%
Test for overall effect: Z = 1.52 (P = 0.13)
0.01 0.1 1 10 100
Favours bird ownership Favours no bird ownership







As can be seen from table 3 and figure 2, there was significant heterogeneity between studies and no associations were seen between ownership of any pets, dogs, cats, birds, rabbits, horses and guinea pigs prior to symptom onset and development of MS.

Publication bias

In view of the selection of random effects analysis and the significant heterogeneity between studies, no assessment of publication bias was performed; the commonly used funnel plot may be may not be appropriate, for example(Terrin, Schmid et al. 2003).

Discussion

We believe this study is the first systematic review and meta-analysis of published observational studies assessing the association between pet ownership before symptom onset and development of MS.

These studies do not show any association between childhood pet ownership or exposure and development of MS. This is out of keeping with our hypothesis, which was that pet ownership could act as a protective factor against the development of MS.

Dogs are the most common types of pets to own globally (GFK 2016), so any associations with pet ownership are most heavily weighted by dog ownership. Our initial hypothesis was that dog owners would be more likely to have increased levels of physical activity (through walking the dog), with reduced risk of obesity; increased exposure to sunlight and subsequently higher levels of serum vitamin D, thought to be a protective factor in the development of MS (Ascherio 2013). Indeed, dog ownership in adulthood is associated with higher rates of physical activity, particularly walking (Christian, Westgarth et al. 2013), and time spent outdoors does correlate with serum vitamin D levels (Fayet-Moore, Brock et al. 2019). However, adolescent and childhood dog ownership is not associated with an increase in physical activity or physical fitness, or a decrease in obesity (Westgarth, Boddy et al. 2017, Westgarth, Ness et al. 2017) reminding us, as discussed in more detail below, that each child-pet dyad is unique and cannot be generalised.

Furthermore, pet ownership may impact exposure to micro-organisms (Fujimura, Johnson et al. 2010, Nermes, Niinivirta et al. 2013) which has been suggested to be relevant to MS (i.e. the hygiene hypothesis) (Wendel-Haga and Celius 2017, Kira and Isobe 2019).

It is important to recognise that pet ownership or exposure is complex and multifactorial. One might argue that defining it as a “yes / no” exposure is over-simplifying this, a problem that has also been identified in previous work looking at associations between pet exposure and allergies (Apfelbacher, Frew et al. 2016). A young baby whose parents own an elderly sedentary cat that spends most of its time in one room of the house is likely to have less interaction with the animal than a teenager who takes responsibility for feeding, walking, grooming and playing with a dog, for instance. Similarly, being a member of a household which owns horses may encompass individuals who have nothing to do with the horse, and those who spend several hours on a daily basis in direct contact with the horse. The duration and nature of the human-animal interaction will be dictated by many things, including the age, character and preferences of the child – and their parents – the species of animal, its care requirements, character and preferences. So it is possible that dichotomising animal exposure is artificial or even meaningless. It is certainly an area that needs consideration for future approaches, whether through assessing amount of time spent with the animal, the nature of the interaction and the physical proximity required, or even through identifying some sort of biomarker which may be elevated in those spending more time in closer contact with animals.

Pet ownership may also be a confounder for other variables of significance in MS risk. Overall pet ownership within the US population has been shown to be associated with being Caucasian, female and asthmatic (Saunders, Parast et al. 2017) – which factors are also associated with higher risk of MS (Hill, Abboud et al. 2019, Roberts and Erdei 2020). Associations have also been demonstrated between living in a single-child household and pet ownership (Christian, Mitrou et al. 2020), and MS has been suggested to be higher in people without siblings (Ponsonby, van der Mei et al. 2005).

The need for multivariate analysis is demonstrated most strongly in the article by Mowry and colleagues - the largest and highest scoring in our critical appraisal. Our odds ratio calculation shows

that data from this paper indicates greater risk of MS development following any pet exposure. However, the authors performed much higher level statistical analysis than is included in our article (LASSO regression and multivariate analysis), following which no statistical association was shown between pet ownership and MS development (Mowry, Hedstrom et al. 2018).

Strength and limitations of the research

Each paper included was studied closely to reduce the risk of covert duplication, and when there was a chance of this, the paper was excluded. We made reasonable effort to clarify any areas of concern with corresponding authors. We gathered data from a wide range of studies from diverse geographical areas and carried out over long time periods, with different aims and objectives and areas of study.

The broad nature of the included studies may also be perceived as a weakness, however. The majority of these studies were looking at a wide range of potential environmental factors in MS development, of which pet ownership / exposure was only one. Styles in reporting and research approaches have varied as, of course, have sample sizes and study designs. The time period of exposure varied a great deal between studies. It is generally agreed that there is a key point for exposure to risk of protective factors for MS around the time of adolescence (Olsson, Barcellos et al. 2017), while the studies included herein generally included much wider time frames.

Our quality assessment scores were consistently low, which at least partly is due to the nature of the research. As outlined above, there was a high reliance on recall of childhood events. Childhood pet ownership has been shown to be frequently under-reported (Nicholas, Wegienka et al. 2009) and recall bias can be a major concern with case control studies (Tenny, Kerndt et al. 2020). There was also inconsistency between the studies regarding selection of both cases and controls. Looking more specifically at the Newcastle Ottawa scale, while this is a highly-rated tool for quality assessment, it also has some drawbacks which may be particularly pertinent to this sort of study, including the focus on hospital controls, validity of scoring for matching, the requirement for participants to be blinded to outcome, and the requirement for a validated measure of exposure (Stang 2010).

Future work

While our study of disease grows ever more in depth and complicated, there remains a key problem in epidemiology of studying retrospective exposures where recall may not be reliable and exposure cannot be validated. It is difficult to conceptualise a solution for this with our current resources, without enormous, costly, long-duration and extensive cohort studies which are not necessarily feasible to conduct. While it has been feasible to study some potential MS contributors in this way (including traumatic brain injury (Pfleger, Koch-Henriksen et al. 2009), childhood body mass index(Munger, Bentzen et al. 2013) and type 2 diabetes mellitus (Hou, Li et al. 2017)), these have relied on pre-existing health databases or national registries, which do not exist for pet ownership.

Any case control study attempting to look at this issue in the future would ideally control for potential confounding factors including rural or urban residence, socioeconomic status, gender, race, co-morbidities, sunlight exposure, obesity and other factors associated with MS. In addition, it would be important to specify age periods, duration and intensity of animal exposure for cases and controls which, as outlined above, may be challenging. Based on the estimates of risk from the existing work reported here, a sample size can be estimated. Considering the dog ownership studies

only, this report finds that the meta-estimate of odds ratio is (from table 3) 1.15 (95% confidence interval 0.93-1.41). Considering an odds ratio of 1.15 suggests a sample size of 3300 per group for 80% power. However, considering the upper interval of odds ratio 1.41 (which could be compared to the increased risk of developing MS among smokers (Hedstrom, Baarnhielm et al. 2009)), the sample size is reduced to a more manageable 510 per group.

Conclusions:

- There is significant variation between the findings of previous epidemiological studies looking at pet ownership in the period before development of MS.
- The nature and timing of the exposure may be difficult to ascertain with confidence, leading to methodological challenges for future work
- We would caution against making any decisions around recommendations for or against pet ownership based on these findings.

Authorship contribution statement:

Laura Edwards: conceptualisation, data curation, formal analysis, methodology, writing

Christopher Tench: data curation, formal analysis, methodology, writing

Declaration of competing interest:

Nil financial. Dr Edwards has an interest in human-animal interaction and pet ownership as a source of wellbeing and has previously published an article on this topic ("Human animal interaction, animal assisted therapy and pet ownership in neurorehabilitation" – Advances in Clinical Neuroscience and Rehabilitation, February 2020).

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Nottingham Systematic Review Course

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