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Review

The role of cats and dogs in asthma and allergy – a systematic review

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ABSTRACT

Studies have reported contradictory effects of cat and dog exposure on allergy, resulting in inconsistent recommendations on animal avoidance. We conducted a systematic review of observational studies published in English from 2000 to January 2009. It shows in this review that the reported exposure-response relationships are contradictory. A total of 17 and 13 birth cohort studies on cat and dog exposure, respectively, are included in the review. Most of the birth cohort studies found that cat or dog exposure in early life had no effect on the development of asthma or wheezing symptoms and dog exposure during infancy was found to protect children from developing sensitization against aeroallergens. A total of 7 and 6 prospective studies in school-age children or adults on cat and dog exposure, respectively, are included in this review and most of these studies suggested an inverse association between cat exposure and asthma and wheezing symptoms. As for cross-sectional studies, 26 and 21 studies on cat and dog exposure, respectively, are included in this review, which cover a broad range of age groups and geographical areas, and reported inconsistent results. The evidence summarised in this systematic review needs to be interpreted with caution, the inconsistent study results may be due to study design, exposure assessment, and avoidance measure. The exposure-response relationships may also alter in geographical areas where the community prevalence of cats and dogs are significantly different. However, as the evidence of the effects of pet keeping on subsequent development of asthma or allergic diseases presented in this review are not overwhelmingly strong, the decision of whether to keep a cat or a dog in the family should be based on arguments other than the concern of developing asthma and allergy.

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Introduction

Allergen exposure is a known environmental risk factor for allergic symptom severity. Avoiding allergens that worsen symptoms for those with allergy is highly recommended for disease management (Custovic et al., 1996). However, whether allergen avoidance prevents or delays the onset of allergy development is still debated. Several randomised control trials on mite allergen avoidance were conducted and the preventive effects were not conclusive (Custovic et al., 2001; Marks et al., 2006; Peat et al., 2004). For pet allergen avoidance, it is difficult to conduct randomized controlled trials. Therefore, the influence of pet allergen exposure on the subsequent development of sensitization and allergic symptoms and diseases relies on the results of observational studies.

The effect of early life cat allergen exposure or cat ownership on the onset of cat sensitization or allergic symptoms and diseases is complex. Conflicting study results with various proposed mechanisms were published in the past ten years (Almqvist et al., 2003; Celedon et al., 2002; Lau et al., 2005; Platts-Mills et al., 2001). Some studies suggest that cat allergen, like mite allergen, is positively associated with the development of cat sensitization defined as having increased specific IgE antibody reaction to cat allergen when in contact (Chen et al., 2007; Heissenhuber et al., 2003). Other studies suggested that exposure to high level of cat allergen may induce immune tolerance (Custovic et al., 2001; Platts-Mills et al., 2001). This is suggested to involve a modified Th2 response by increasing the expression of IgG4 isotype, which is regulated by IL-4 cytokine, like IgE, but does not trigger clinical immune reactions, and does not increase the serum IgE level (Aalberse and Schuurman, 2002; Platts-Mills et al., 2001). However, this observation has not yet been replicated in other studies (Jarvis et al., 2007; Perzanowski et al., 2008). The interaction between gene and environmental exposure was proposed to be a major cause of the inconsistent observations. A recent study showed that cat ownership during infancy substantially increases the risk of eczema within the first year of life in children with the loss-of-function variants in the gene encoding filaggrin (FLG), which was shown as a major determinant of eczema development, but not amongst those without the variants (Bisgaard et al., 2008).

The effect of childhood dog or dog allergen contact has received less attention. However, some studies have observed a negative association between childhood dog exposure and sensitization to aeroallergens, predominantly outdoor aeroallergens, and respiratory symptoms such as wheezing (Almqvist et al., 2003; Litonjua et al., 2002; Remes et al., 2001). It was proposed that pet keeping, especially dog, may increase the exposure to bacterial components such as endotoxin, which may enhance children's type 1 lymphocyte (T-helper 1) development and therefore protect them from the development of allergy (Campo et al., 2006; Gern et al., 2004; Lau et al., 2005). However, this speculation could not be verified by studies which attempted to untangle the protective effect from the simultaneous exposure of dog and endotoxin (Bufford et al., 2008; Chen et al., 2008). Gene-environment interaction between the genetic variant of CD14, which encodes the LPS receptor, and dog ownership on the

development of atopic dermatitis has also been reported (Gern et al., 2004); dog ownership protected children with TT genotype from developing atopic dermatitis.

Recently, Takkouche et al attempted a meta-analysis of the effect of exposures to furry pets on the risk of asthma and allergic rhinitis (Takkouche et al., 2008). However, this work had several flaws and mislead the readers to draw inadequate conclusions (Chen and Heinrich, 2009). As the debate on the appropriateness of pet avoidance goes on, we find that there is a need for a comprehensive systematic review on the association between cat and dog exposure and allergy. In this article, we sought to systematically summarize the scientific evidence that assess these associations.

Method

Data source and extraction

This review was conducted following the MOOSE guidelines for meta-analyses of observational studies (Stroup et al., 2000). The literature was searched using a computerised bibliographic database, PubMed, with the following free text search terms:

1. Cat
2. Dog
3. Cat allergen
4. Dog allergen
5. Cat ownership
6. Dog ownership
7. Feld
8. Canf
9. Sensitization
10. Asthma
11. Rhinitis
12. Wheezing
13. Hay fever
14. Allergy
15. Respiratory
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
17. 9 or 10 or 11 or 12 or 13 or 14 or 15
18. 18 16 and 17

Inclusion criteria were: observational studies, human study population, English, from 2000 to January 2009, study population recruited from community. Publications which assess exposure to cat or dog based on cat or dog ownership and measured domestic allergen level are included in this review. Publications which assess exposure through frequent contact with cats or dogs, or assess exposures outside domestic areas were excluded. Studies that did not evaluate asthma or allergic health outcomes were also excluded in this review. Further hand searches were conducted using citations from the previous systematic review (Langan et al., 2007) and personal files. Both longitudinal study design and cross-sectional study design were included. We have restricted the health outcome to allergic sensitization, asthma, allergic rhinitis, hay fever, and respiratory symptoms such as

wheezing, which is an indication of asthma. Eczema was not considered in this review because a systematic review on the association between furry pet exposure and eczema has been conducted recently (Langan et al., 2007). Each relevant article underwent standardised data extraction by one of the authors and all data were assessed again by all the authors.

Results

Search results

The literature search identified 1341 peer reviewed scientific publications, of which 63 articles which reported relevant exposures and health outcomes in suitable study populations, and are included in this review (Fig. 1). Results of the effect of exposure to cat and dog grouped by study design are summarized below.

Cat – birth cohort studies

There were 21 publications of 17 birth cohorts that investigated the influence of cat exposure on allergy related health outcomes (Table 1A). Sixteen studies of these evaluated the effect of exposure to domestic cat allergen or cat ownership prenatally or during early infancy (before or at the age of one year) on allergy later in life.

The most commonly reported clinical health outcomes were questionnaire based wheezing symptom and asthma. Of the 15 studies which evaluated the exposure-response relationships between cat exposure in early life and wheezing symptom and asthma (12 and 6 studies respectively), 10 studies did not observe any associations. Only one study reported that cat allergen exposure during infancy increases the risk of ever physician diagnosed asthma up to the age of 6 years (Torrent et al., 2007). In addition, this study also reported an increased risk of early wheezing symptoms. Only one other study reported a similar finding with early wheezing symptoms up to the age of two years, however, the positive association disappeared as children were followed beyond this age (Chen et al., 2007; Heissenhuber et al., 2003). On the contrary, two studies from the U.S. reported a protective effect of cat allergen exposure during infancy on wheezing (Celedon et al., 2002; Remes et al., 2001). One study reported a negative association between cat ownership and rhinitis; however, this association was assessed using cross-sectional data (Perzanowski et al., 2008).

There are nine studies reported the effect of exposure to cats on the development of cat sensitization, assessed by either serum IgE antibody or skin prick test. Three out of these studies found an increased risk (Chen et al., 2007; Heissenhuber et al., 2003; Perzanowski et al., 2008; Torrent et al., 2007, 2006). Two of these studies had a sample size of more than 1000 children. Although the biggest birth cohort (n=3596) did not observe a significant association between direct exposure to cat (defined as cat ownership) and cat sensitization developed later in life, a positive link was found between direct and indirect exposure to cat (defined as cat ownership and regular contact with relatives who are cat owners) and cat sensitization (OR=1.44(1.03-2.01)) (Almqvist et al., 2003). Only one study reported a negative association between cat ownership and cat sensitization, however, this association was evaluated using cross-sectional information (Sandin et al., 2004). When the association was assessed longitudinally, no significant link between cat exposure and the development of cat sensitization was found.

Cat – cohort studies which are not recruited at birth

A total of 7 prospective studies in school-age children and adults were included (Table 1B). Three studies reported negative association between previous and current cat ownership and current asthma and wheezing symptoms. The only positive association was reported by a Danish study examining a wide age range of adults (Linneberg et al., 2003). It was observed in this study that previous cat owners were more likely to develop allergic rhinitis to animals and there was higher prevalence of allergic asthma to animals in current cat owners. Two out of four studies suggested that previous and current cat ownership was negatively associated with cat specific IgE reaction (Linneberg et al., 2003; Perzanowski et al., 2002; Ronmark et al., 2003) and one study suggested a positive association (Linneberg et al., 2003).

Cat – cross-sectional studies

A total of 26 cross-sectional studies are included and 6 of these studies are case-control studies (Tables 2 and 3). These studies cover a broad range of age groups and geographical areas and environmental exposures were assessed at different time points, however, factors other than those mentioned above also contribute to the conflicting observations. Thirteen studies reported the observed association between exposure to cat and asthma. Four studies, conducted in Brazil, Russia, Turkey and Australia with study populations ranging from 6 year old school children to 56 year old adults (Dharmage et al., 2001; Hugg et al., 2008; Kuschner and Alves da Cunha, 2007; Tamay et al., 2007), found a positive association and one German study reported a negative association (Oberle et al., 2003). Regarding wheeze, 3 out of 11 studies observed a positive link with exposure to cat (El-Sharif et al., 2003; Lewis et al., 2002; Oberle et al., 2003; Salo et al., 2004). These three studies were conducted in China, the U.S., and Palestine with study populations ranging from 6 year old school children to 64 year old adults, however, all of these studies investigated the effect of previous cat ownership. There was no negative association between exposure to cat and wheezing symptom reported.

The reported associations between cat exposure and the prevalence of cat sensitization in cross-sectional studies are very inconsistent: two studies observed a positive link (Al-Mousawi et al., 2004; Custovic et al., 2003), three studies reported a negative association (Braback et al., 2001; Clausen et al., 2008; Henriksen et al., 2001), and four studies did not observe any

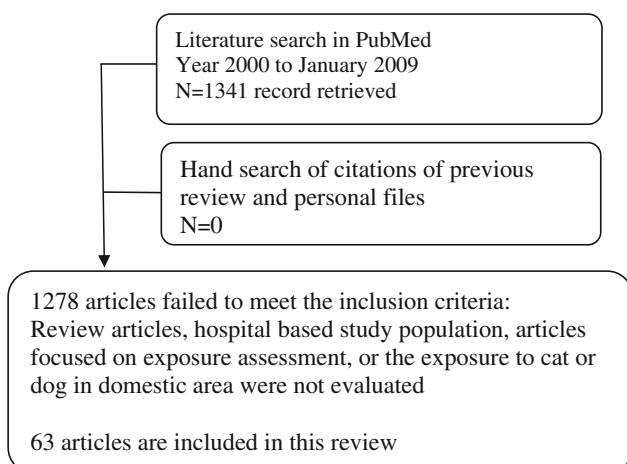


Fig. 1. Flow chart for study selection process

Table 1

Data from cohort studies arranged by sample size – cat (retrieved from 2000 to Jan 2009)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Stratified analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Table 1.A BIRTH COHORT STUDIES								
Almqvist et al., 2003, Sweden (BAMSE)	Population based	3596	Cat ownership (1y)	(Q)asthma (2y): 0.87(0.58–1.30) (Q)asthma (4y): 0.88(0.56–1.38) Cat sensitization (IgE) (4y): 1.46(0.84–2.54) Aeroallergens sensitization except cat (IgE) (4y): 0.63(0.37–1.07)	sex, parental allergy, maternal smoking, maternal age, SES	Aeroallergens sensitization, stratified by parental allergy – no effect	n.s. n.s.	n.s. n.s.
Nafstad et al., 2001, Norway	Population based	2531	Cat ownership (birth)	(Q) asthma (4y): 0.7(0.4–1.5)	Parental allergy, gender, birth weight, birth order, maternal age at delivery, maternal education, family income, ETS, breast feeding, ≥ 1 episode of lower respiratory tract infections during first year of life		n.s.	
Heissenhuber et al., 2003, Germany (LISA)	Population based	2098	Measured Fel d 1 ^s from mother's mattress (3 mon.) ≥ 1 µg/g	Cat sensitization (IgE) (2y): 10.91(3.40–34.98) (Q)wheezing (0–2y): 2.03(1.05–3.91)	sex, study centre, parental allergy, and parental education		n.s. +	+
Chen et al., 2007, Germany (LISA)	Population based	1603	Measured Fel d 1 ^s from mother's mattress (at 3 mon.) (unit: inter-quartile range)	(Q)doctor diagnosed asthma (4–6y): 1.2(0.7–2.0) (Q)doctor diagnosed hay fever(4–6y): 0.9(0.5–1.5) (Q)doctor diagnosed wheezing(4–6y): 1.2(0.9–1.6) Cat sensitization (IgE) (2y): 6.2(2.6–14.8) Cat sensitization (IgE) (6y): 1.3(0.2–9.4)	sex, study centre, parental educational, moving, and parental allergy		n.s. n.s. n.s.	+
Polk et al., 2004, U.K. and Spain (AMICS)	Population based	1289	Cat ownership (0–6y)	Cat sensitization (IgE) (2–6): 2.4(1.2–4.7)	sex, study centre, parental allergy, and parental educational	Stratified by parental allergy – no effect		+
			Measured Fel d 1 ^s from living room floor/sofa and baby's bed) (1y) (Fel d 1 ^s > median)	(Q)wheezing (1y): 0.86(0.69–1.08) (Q)wheezing (2y): 1.02(0.79–1.31) (Q)wheezing (3y): 1.41(1.08–1.83) Not reported			n.s. n.s. +	
Arshad et al., 2001, U.K (Isle of Wight Study)	Population based,	1218	Cat ownership (4y) Yes: No:	Cat sensitisation (SPT) (4y): 5.1% 6.2%		(Q)Wheezing at age 4, stratified by maternal asthma: No: 1.16(0.80–1.67) Yes: 2.77(1.19–6.46)		n.s. n.s.

Torrent et al., 2006, U.K. & Spain (AMICS)	Population based	937	Measured Fel d 1 ^s from living room floor/child's mattress (3 mon.)	Cat sensitization (IgE) (4y): 2 nd tertile: 4.78(1.06–21.67) RR 3 rd tertile: 5.69(1.24–26.07) RR	Study centre, home crowding, maternal asthma, maternal smoking		+
							+
Torrent et al., 2007, U.K. & Spain (AMICS)	Population based	1059	Measured Fel d 1 ^s from living room floor (3 mon.)	Cat sensitization (SPT) (6y): 2 nd tertile: 4.09(1.14–14.67) 3 rd tertile: 4.43(1.22–16.07) (Q) persistent wheezing (3–4y or 5–6y): 2 nd tertile: 0.73(0.34–1.54) 3 rd tertile: 1.56(0.79–3.08) (Q) doctor diagnosed asthma (0–6y): 2 nd tertile: 1.59(0.75–5.34) 3 rd tertile: 2.60(1.27–5.34)	Sex, firstborn child, high home crowding, Maternal SES, Maternal atopy, Maternal asthma, paternal asthma, LRTI in the first year, NO ₂ exposure, smoking during pregnancy, breast feeding, study centre (additionally adjusted for atopy at 6 years for wheezing and asthma model)	Stratified by maternal atopy – no effect for cat sensitization and persistent wheezing: (Q) doctor diagnosed asthma (0–6y): n.s. Yes: n.s. 2 nd tertile: 2.76 (0.66–50.68) 3 rd tertile: 18.43 (2.20–154.0) n.s. No: + 2 nd tertile: 1.32 (0.60–2.88) 3 rd tertile: 1.55 (0.71–3.41)	+
							+
Remes et al., 2001, USA	Population based	1076	Cat ownership (birth)	(Q) wheezing (0–12y): not reported		Stratified by number of dogs (1 and ≥ 2): No effect Stratified by parental asthma: Yes: 0.19 (not sig) HR No: 0.53 (sig) HR Stratified by children with atopy: Yes: 0.47(0.24–0.91) HR No: 0.56(0.32–0.98) HR	–
Sandin et al., 2004, Sweden	Population based	1043	Cat ownership (1y)	Cat sensitisation (SPT) (1y): 2.2(0.9–5.6) Cat sensitisation (SPT) (4y): 1.6(0.8–3.5) Sensitisation to pollen (SPT) (4y): 1.2(0.5–2.9) (Q) wheezing (1–4y): 0.4(0.1–1.3) (Q) wheezing (3–4y): 0.7(0.3–1.6)	Parental allergy, maternal smoking, older siblings, sex, dog and cat keeping	All analyses exclude children who reported avoidance of pet keeping due to allergy in the family.	n.s.
							n.s.
							n.s.
			Cat ownership (2–4y)	Cat sensitisation (SPT) (4y): 0.3(0.0–2.1) Sensitisation to pollen (SPT) (4y): 0.6(0.1–2.6)	See above		n.s.
			Cat ownership (4y)	Cat sensitization (SPT) (4y): 0.4(0.1–1.0)			–
Brussee et al., 2005, Netherlands (PIAMA)	Population based (enriched*)	365	Measured Fel d 1 ^s from mattress (3 mon.) (ref.: not detectable)	Cat sensitization (IgE) (4y): 1 st tertile: 1.00 2 nd tertile: 1.13(0.37–3.43) 3rd tertile: 2.60(0.97–6.95) (Q) wheezing (0–4y): 1 st tertile: 1.97(0.85–4.55) 2 nd tertile: 1.35(0.56–3.26) 3 rd tertile: 2.31(0.98–5.46) (Q) doctor diagnosed asthma (4y): 1 st tertile: 1.48(0.46–4.72) 2 nd tertile: 0.75(0.21–2.67) 3 rd tertile: 1.92(0.60–6.14)	Sex, study region, maternal education, older siblings, contact with children other than siblings, ETS, parental allergy.	Stratified by maternal allergy (3 rd tertile): Yes: 1.98(0.43–9.06) No: 5.76(1.23–26.93)	n.s.
		881				Stratified by maternal allergy – no effect	n.s.
							n.s.
						Stratified by maternal allergy – no effect	n.s.
							n.s.

Table 1 (continued)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Stratified analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Belanger et al., 2003, USA	Population based (enriched*)	849	Measured Fel d 1 ^s from main living area (2–4 mon.) ($\geq 2 \mu\text{g/g}$)	(Q) wheezing (1y) not reported	Dust mite, cockroach, cat, dog, gas stove, mold/mildew, wood stove, respiratory illness, maternal education, ethnicity, sex, smoking in the home	Stratified by maternal asthma: Yes: 0.64(0.36–1.2) No: 0.84(0.57–1.24)		
Marinho et al., 2007, U.K (MAAS)	Population based	815	Cat ownership (1y) Sum of the measured Fel d 1 ^s at 0y, 3y, and 5 y from mother's , child's mattress bedroom and living room floor	(Q) rhino conjunctivitis (5y): 1.14(0.71,–1.83) (Q) rhino conjunctivitis (5y): 1.02 (0.91–1.13)			n.s. n.s.	
Hagendorens et al., 2005, Belgium (PIPO)	Population based	810	Cat ownership (prenatal/postnatal)	Cat sensitization (IgE) (1y): Not significant (the estimated value not reported) (Q) wheezing (1y): Not significant	Sex, mode of delivery, birth weight, breastfeeding, siblings, day care attendance, pre-and postnatal contact with cats, dogs and smoking, parental education, carpeting in the child's bedroom and parental atopy.	Stratified by sex: No effect	n.s.	n.s.
Lau et al., 2000, Germany (MAS)	Population based (enriched*)	648	Measured cat allergen from carpet (6 mon.)	Interviewed by doctor, wheezing (7y): 2 nd quartile: 0.95(0.45,2.88) 3 rd quartile: 1.42(0.70,2.99) 4 th quartile: 1.47(0.73,1.27) Interviewed by doctor, ever wheezing (0–7y): 2 nd quartile: 0.94(0.54,1.68) 3 rd quartile: 1.15(0.66,2.02) 4 th quartile: 1.41(0.81,2.43) Interviewed by doctor, asthma (7y): 2 nd quartile: 1.15(0.46,2.87) 3 rd quartile: 0.93(0.36,2.42) 4 th quartile: 1.52(0.64,3.62)			n.s. n.s. n.s. n.s. n.s. n.s. n.s.	
Lau et al., 2005, Germany	Population based (enriched*)	115	Cat allergen from carpets and mattresses (6 mon.)	Early cat allergen exposure during the first 2 years of life correlated with IgE responses to cat at age 5 and 7 years, but not at age 10. Cat allergen exposure at later ages did not correlate with serum IgE responses.				n.s.
Cullinan et al., 2004, U.K	Population based	552	Measured cat allergen from living room floor (8 weeks)	Cat sensitisation (SPT) (5y): 2 nd quintile:0.93(0.27,3.27) 3 rd quintile:1.70(0.54,5.33) 4 th quintile:1.77(0.57,5.50) 5 th quintile:1.00(0.30,3.35) (Q) wheezing (5y):	First born child, SES, sex, parental atopy (stepwise selection)			n.s. n.s. n.s. n.s.

		604		2 nd quintile:1.14(0.36,3.65) 3 rd quintile:0.73(0.21,2.47) 4 th quintile:0.88(0.27,2.86) 5 th quintile:0.51(0.14,1.81)	First born child, parental asthma, maternal age, crowding, ETS at age 1, paternal atopy (stepwise selection)	n.s. n.s. n.s. n.s.
Mitchell et al., 2007, New Zealand (ABC study)	Population based	591	Cat ownership (1y)	(Q) wheezing (3.5 or 7y): 25.9% v.s.25.1% of wheezing with v.s. without cats, respectively P=0.73		n.s.
Perzanowski et al., 2008, USA	Children from African American or Dominican mothers	257	Cat ownership (up to age of health outcomes)	Cat sensitization (IgE) (2y): 6.4 (1.9-2.2) RR Cat sensitization (IgE) (2-5y): 0.88(0.24-2.3) RR (Q) wheezing (1y): 1.1(0.64-1.9) (Q) wheezing (2y): 1.3(0.71-2.4) (Q) wheezing (3y): 1.7(0.80-3.4) (Q) wheezing (5y): 0.48(0.21-1.1)	Maternal asthma, sex, race/ethnicity, and ETS.	+ n.s.
				(Q) rhinitis (1y): 1.0(0.63-1.7) (Q) rhinitis (2y): 0.80(0.45-1.9) (Q) rhinitis (3y): 1.0(0.54-1.9) (Q) rhinitis (5y): 0.41(0.19-0.89)	Maternal asthma, sex, race/ethnicity, and ETS.	n.s. n.s. n.s. -
Campo et al., 2006, USA	Population based (enriched*)	532	Cat ownership, 1 cat (0y)	(Q) recurrent wheeze (1y): 1.2(0.6-2.4) (Q) wheezing with an event (1y): 1.2(0.6-2.6) (Q) wheezing (1y): 1.1(0.6-2.0)		n.s. n.s. n.s.
			Cat ownership, ≥ 2 cats (0y)	(Q) recurrent wheeze (1y): 0.8(0.4-1.8) (Q) wheezing with an event (1y): 1.0(0.5-2.2) (Q) wheezing (1y): 0.9(0.4-1.7)		n.s. n.s. n.s.

Table 1 (continued)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Stratified analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Celedón et al., 2002, USA	Population based (enriched*)	448	Cat exposure (2 mon.) Cat allergen (2-3 mon.) ($\geq 8\mu\text{g/g}$)	(Q) wheezing (1-5y): 0.7(0.5-1.0) RR Not reported	Maternal asthma	Stratified by maternal asthma: (Q) wheezing (1-5y): Yes: 2.4(1.3-5.4) RR No: 0.6(0.4-0.9) RR	-	
Table 1.B NON BIRTH COHORT STUDIES								
McConnell et al., 2002, USA (SCCH study)	5y follow-up of a cross-sectional study population (9-16y)	3535	Cat ownership (9-16y)/ history of wheeze (9-16y)	(Q) asthma (12-21y): 0.7(0.5-1.1) RR		Stratified by history of wheeze: No: 0.9(0.6-1.3) RR	n.s.	
Perzanowski et al., 2002, Sweden	Follow-up of a cross-sectional study population (7-8y, 10-11y school children)	3431	Cat ownership (ever)	(Q) ever asthma (7-8y): 0.50(0.35-0.70) RR (Q) dd asthma (7-8y): 0.54(0.38-0.76) RR (Q) current wheezing (7-8y): 0.71(0.57-0.88) RR		Stratified by parental allergy: Yes: 0.50(0.28-0.89) – ever asthma RR Yes: 0.58(0.32-1.0) – dd asthma RR Yes: 0.72(0.46-1.1) – current wheezing RR	-	
			Cat ownership (ever)	(Q) dd asthma (7-11y): 0.55(0.25-1.21) RR Cat sensitization (SPT) (7-8y): 0.62(0.47-0.83) RR	Allergy, parental asthma, low birth weight, respiratory infection, ever cat, ever dog, damp house, gender		n.s.	-
			Cat ownership (ever)	(Q) cumulative incidence of asthma (7-11y)		Stratified by parental allergy: Yes: 0.52(0.32-0.84) RR No: 0.77(0.53-1.1) RR Children without sensitization: Yes: 0.56(0.31-0.99) RR Stratified by parental allergy: Yes: 0.52(0.24-1.1) – ever asthma RR Yes: 0.26(0.08-0.88) – dd asthma RR Yes: 0.33(0.41-1.3) – current wheezing RR		
Bjerg-Backlund et al., 2006, Sweden	Follow-up of a cross-sectional study population (7-8y, 11-12y)	1870	Cat ownership (ever)	(Q) asthma (7-8y): 0.71(0.43-1.17) (Q) asthma (11-12y): 0.54(0.34-0.86) (Q) dd asthma (7-8y): 0.70(0.44-1.14) (Q) dd asthma (11-12y): 0.67(0.46-0.99) (Q) Wheeze (last 12 months) (7-8y): 0.86(0.62-1.19) (Q) Wheeze (last 12 months) (11-12y): 0.70(0.49-1.00)	Gender, parental asthma, breastfeeding ≤ 3 months, birth weight $< 2500\text{g}$, respiratory infections, maternal smoking, cat at home, dog at home, living in damp area, living in an apartment, allergic sensitization, citrus fruit/ week	Stratified by parental asthma: effects remained significant, even more pronounced among children with a family history of the disease (cat ownership)	n.s.	
Ronmark et al., 2003, Sweden	School cohort (11-12y)	1870	Cat ownership (earlier)	Cat-dog sensitization (SPT) (11-12y): 0.77(0.51-1.14) 4y-incidence of any positive SPT response: 0.73(0.42-1.27)	Cat/Dog ownership, sex, parental allergy, rural living, area of domicile			n.s.
								n.s.

Linneberg et al., 2003, Denmark	Adult cohort (15-69y, follow up 7y later)	734	Cat ownership (later)	Cat-dog sensitization (SPT) (11-12y): 0.65(0.41-1.04) 4y-incidence of any positive SPT response: 0.88(0.48-1.61)	See above		n.s.
							n.s.
			Cat ownership (7, 8 to 11,12y)	Cat-dog sensitization (SPT) (11-12y): 0.39(0.26-0.60) 4y-incidence of any positive SPT response: 0.72(0.45-1.14)	See above		-
							n.s.
			Cat ownership (previously)	Cat sensitization (IgE) (baseline): 1.65(1.03-2.64) Cat sensitization (IgE) (incidence): 3.16(0.60-16.65)	Gender, age, cat/dog at home Gender, age, cat/dog at home, IgE at baseline Gender, age, cat/dog at home	+ n.s.	n.s.
				(Q/IgE) allergic rhinitis to animals (incidence): 5.22(1.45-18.75) (Q/IgE) allergic asthma to animals (incidence): 2.28(0.31-16.51)			
Litonjua et al., 2002, USA	5y follow-up of a cross-sectional study population (< 5 y)	226	Cat ownership (currently)	Cat sensitization (IgE) (baseline): 1.22(0.65-2.30) Cat sensitization (IgE) (incidence): 8.43(1.66-42.71) (Q/IgE) allergic rhinitis to animals (incidence): 3.34(0.71-15.80) (Q/IgE) allergic asthma to animals (incidence): 7.80(1.37-44.34)	See above		n.s.
							+
							n.s.
							+
de Meer et al., 2004, Australia	20y follow-up of a cross-sectional study population (8-10y)	224	Measured Fel d 1 ^s from living-room and bedroom floor (< 5y) (< 1µg/g, ≥ 1µg/g)	(Q) wheezing (longitudinal model): 0.61(0.37-1.01)	Maternal asthma, maternal age, sex, prematurity, area of residence, clustering of outcomes.		n.s.
			Measured Fel d 1 ^s from living-room and bedroom floor (< 5y) (< 1µg/g, ≥ 1µg/g)	(Q) wheezing (2x within 4y follow-up): 0.61(0.27-1.35)	Maternal asthma, maternal age, sex, prematurity, area of residence.		n.s.
de Meer et al., 2004, Australia	20y follow-up of a cross-sectional study population (8-10y)	224	Cat ownership (< 18y only)	Indoor allergen sensitization (28y): 0.68(0.13-2.18) Outdoor allergen sensitization (28y): 0.38(0.10-1.44) Cat sensitization (28y): 0.57(0.15-2.17) (Q) wheezing (28y): 0.15(0.03-0.63) (Q) asthma (28y): 0.08(0.01- 0.46)	Gender, parental allergy, atopic siblings, number of siblings, ETS, parental smoking (past & current), childhood other pet ownership, ever occupational dust exposure, wheeze at job	Stratified by childhood asthma – no childhood asthma: Indoor allergen sensitization (28y): 0.85(0.21-3.39) Outdoor allergen sensitization (28y): 0.23(0.05-0.74) Cat sensitization (28y): 0.66(0.16-2.80) (Q) wheezing (28y): 0.10(0.02-0.49) (Q) asthma (28y): 0.03 (0.00-0.32) Stratified by parental allergy – no parental allergy: similar results Stratified by cat sensitization – not sensitized: no change of results	n.s. n.s. n.s. - -

Table 1 (continued)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Stratified analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
			Cat ownership (< 18y and ≥ 18y)	Indoor allergen sensitization (28y): 0.49(0.14–1.69) Outdoor allergen sensitization (28y): 0.34(0.10–1.18) Cat sensitization (28y): 0.31(0.08–1.19) (Q) wheezing (28y): 0.50(0.15–1.73) (Q) asthma (28y): 0.17(0.04–0.77)	See above	Stratified by childhood asthma – no childhood asthma: Indoor allergen sensitization (28y): 0.69(0.18–2.58) Outdoor allergen sensitization (28y): 0.18(0.05–0.98) Cat sensitization (28y): 0.32(0.08–1.40) (Q) wheezing (28y): 0.43(0.11–1.67) (Q) asthma (28y): 0.14(0.02–0.76) Stratified by parental allergy – no parental allergy: similar results Stratified by cat sensitization – not sensitized: no change of results Subgroup who were not sensitized to any inhalant allergen before 18y: 0.19(0.04–1.06) Stratified by parental allergy – no parental allergy: similar results Stratified by cat sensitization – not sensitized: no change of results	n.s. n.s. n.s. n.s. – n.s. n.s. n.s. n.s. n.s.	n.s. n.s. n.s.
			Cat ownership (> 18y only)	Indoor allergen sensitization (28y): 0.74(0.13–4.05) Outdoor allergen sensitization (28y): 0.31(0.04–2.15) Cat sensitization (28y): 2.43(0.44–13.32) (Q) wheezing (28y): 1.34(0.24–7.50) (Q) asthma (28y): 2.62(0.34–19.97)	See above		n.s. n.s. n.s.	n.s. n.s. n.s.

Q = Questionnaire based

dd = Doctor diagnosed

HR = Hazard Ratio

RR = Relative risks

§ Fel d 1 is major cat allergen *Felis domesticus* allergen I

* Enriched stands for studies which has over selected subjects who are at risk of developing allergic diseases for their study population.

Table 2

Data from cross-sectional studies arranged by sample size and grouped by children and adult study population – cat (retrieved from 2000 to Jan 2009)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
<i>Children study population</i> Kurosaka et al., 2006, Japan	Cross-sectional (6y school children)	35401	Cat ownership (current)	(Q) current asthma: 0.90(0.68–1.19) RR (Q) current rhinitis: 0.71(0.57–0.89) RR	Asthma: gender, cat, dog, and cat and dog. Rhinitis: gender, passive smoking, cat, dog, and cat and dog;		n.s.	
Oberle et al., 2003, Germany	Cross-sectional (5–7y school children)	8216	Cat ownership (1y)	(Q) dd asthma : Not reported	Gender, parental education, allergy in family, number of older siblings, ETS See above	stratified by cat allowed to be is child's room (asthma): Yes: 0.28(0.10,0.62) No: 0.84 (0.48,1.38) stratified by cat allowed to be is child's room (hey fever): Yes: 0.58(0.26,1.13) No: 0.54 (0.24,1.04) stratified by cat allowed to be is child's room (wheezing): Yes: 0.68(0.37,1.14) No: 1.25 (0.81,1.85) stratified by cat allowed to be is child's room (asthma): Yes: 0.86(0.52,1.34) No: 1.07 (0.71,1.55) stratified by cat allowed to be is child's room (hey fever): Yes: 0.86(0.49,1.41) No: 0.72 (0.42,1.16) stratified by cat allowed to be is child's room (wheezing): Yes: 0.93(0.60,1.39) No: 1.04 (0.71,1.48) (Q)doctor diagnosed atopic asthma: 0.33(0.12–0.56)	-	-
Salo et al., 2004, China	Cross-sectional (6y school children)	4185	Cat ownership (current)	(Q) current wheezing: 1.48(0.99–2.23) (Q) dd asthma: 1.11(0.67–1.84)	Gender, living area		n.s.	
			Cat ownership (before age of 6)	(Q) current wheezing: 2.00(1.38–2.89) (Q) dd asthma: 1.38(0.86–2.22)	See above		n.s.	+

Table 2 (continued)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Kuschnir and Alves da Cunha, 2007, Brazil (ISAAC IV)	Cross-sectional (13-14y school children)	3033	Cat ownership (current)	(Q) current asthma: 1.32(1.04-1.69)	Gender, maternal smoking, cat at home, firstborn, use of paracetamol, allergic rhinitis, atopic eczema.		+	
Tamay et al., 2007, Turkey	Cross-sectional (6-12y school children)	2387	Cat ownership (1y)	(Q) current allergic rhinitis: 2.21(1.36-3.61)	parental allergy, dd eczema or food allergy, upper airway infections, sinusitis, adenoidectomy, antibiotic/paracetamol use (1y), cat or dog exposure (1y), home dampness, exposure to diesel trucks, perianal redness Parental asthma, whooping cough, breast feeding > 2 months, sensitization to <i>A alternate</i> , and <i>P juliflora</i>	Stratified by parental asthma or allergic rhinitis: Yes: 0.4(0.3-0.6) No: 0.7(0.4-1.2)	+	
				(Q) dd asthma, asthma medication, symptoms in the past 12 (months): 5.29(1.15-18.55)			+	
Braback et al., 2001, Sweden	Cross-sectional (10-11y school children)	2108 / 1848	Cat ownership (past)	(Q) allergic rhinitis: 0.9(0.7-1.1) Cat sensitization (SPT): 0.6(0.4-1.0)			n.s.	
			Cat ownership (current)	(Q) allergic rhinitis: 0.6(0.5-0.8) Cat sensitization (SPT): 0.4(0.2-0.6)			-	-
Hugg et al., 2008. Finland/ Russia	Cross-sectional. (7-16y school children)	1093	Current cat ownership	(Q) Current asthma in Finnish children: 0.47(0.14-1.58)	Age, gender, parental smoking, any dampness or visible mould		n.s.	
			Cat ownership (1y)	1.90(0.23-16.07)			n.s.	
			Current cat ownership	(Q) Current asthma in Russian children: 1.65(0.67-4.05)	Age, gender, any dampness or visible mould		n.s.	
			Cat ownership (1y)	Not analyzed Not analyzed				
Clausen et al., 2008, Iceland	Cross-sectional (10-11y school children)	946	Cat ownership (1y)	1.28(0.49-3.34)			n.s.	
				4.56(1.10-18.91)			+	
				1.46(0.60-3.59)			n.s.	
Clausen et al., 2008, Iceland	Cross-sectional (10-11y school children)	946	Cat ownership (1y)	Cat sensitization (SPT): 0.27(0.08-0.88)				-
Demir et al., 2004, Turkey	Cross-sectional (school children, mean age 9.2 (SD: 1.5))	621	Current cat ownership	No children have any of the disease	Age, gender			

Henriksen et al., 2001, Norway	Cross-sectional (13-19y)	431	Cat ownership (ever)	Cat sensitization (IgE): 0.5(0.3-0.9)				-
Wickens et al., 2002, New Zealand	Cross-sectional (7-10y school children)	293	Cat ownership (1y)	(Q) hay fever (past 12 months): 0.4(0.1-1.0) (Q) allergic rhinitis (current): 1.4(0.6-3.1) (Q) asthma (ever): 0.7(0.3-1.5) (Q) wheezing (current): 1.0(0.4-2.4)	Pets (1y), pets (currently), Diet at < 2y, gender, ethnicity, maternal education, parental allergy, family size, antibiotic use (1y), maternal smoking (1y) and currently, coal and wood fires (1y and currently), measles, whooping cough infection, dairy food consumption See above		-	
				(Q) hay fever (past 12 months): 0.7(0.3-1.9) (Q) allergic rhinitis (current): 1.0(0.5-2.2) (Q) asthma (ever): 1.5(0.7-3.3) (Q) wheezing (current): 0.9(0.4-2.1)		n.s.		
			Cat ownership (current)			n.s.		
						n.s.		
						n.s.		
						n.s.		
Platts-Mills et al., 2001, USA	Cross-sectional (12-13y school children)	226	Measured Fel d 1 [§] from 4 different areas at home	Cat sensitization (RAST or SPT): p-value: n.s. Asthma (defined as symptomatic BHR): 0.8(0.3-1.9)			n.s.	
Erwin et al., 2005, New Zealand	Cross-sectional (10-11y)	224	Cat ownership (ever)	(Q) wheezing: no effect			n.s.	
			Cat ownership (current)	(Q) wheezing: no effect			n.s.	
Adults study population								
Svanes et al., 2003, Europe (ECRHS I)	Survey (20-44y)	18530	Cat ownership (childhood)	(Q) current wheezing: 1.08(0.99-1.17) (Q) current hay fever: 1.01 (0.93-1.09)	parental allergy, siblings allergy, parental smoking, number of siblings, age, sex, current smoking, current occupation, and study centre	Wheezing stratified by atopy: Yes: 1.43(1.22-1.67) No: 1.06(0.92-1.21) Hay fever stratified by atopy: No effect Wheezing stratified by atopy: No effect Hay fever stratified by atopy: No effect	n.s.	
							n.s.	
			Cat ownership (adult)	(Q) current wheezing: 0.97(0.88-1.06) (Q) current hay fever: 0.98 (0.90-1.07)	See above		n.s.	
							n.s.	
Simpson et al., 2001, U.K (Parents of the MAAS cohort)	Cross-sectional (18-58y adults)	5687	Cat ownership (current)	(Q) dd asthma: 0.86(0.72-1.02) (Q) current asthma: 0.84(0.68-1.0) (Q) hay fever: 0.86(0.74-1.0)			n.s.	
							n.s.	
							n.s.	
Jarvis et al., 2007, Europe (ECRHS I)	Cross-sectional (27-56y adults)	2704	Cat ownership (childhood) Yes Don't know	Cat sensitization (IgE): 0.79(0.59-1.05) 0.65(0.20-2.27)	Gender, Age, smoking, siblings, current cat exposure, parental allergy, BMI, SES, centre, selection group		n.s.	
			Current cat ownership	Cat sensitization (IgE):	Gender, Age, smoking, siblings, current cat		n.s.	

Table 2 (continued)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Skorge et al., 2005, Norway (HCCS II)	Cross-sectional (26-81y adults)	2401	Not in bedroom	1.26(0.73-2.19)	exposure, parental allergy, BMI, SES, centre, selection group Gender, Age, smoking, siblings, parental allergy, BMI, SES, centre, selection group			n.s.
			In Bedroom	1.12(0.75-1.66)				n.s.
			Measured Fel d 1 [§] from mattress (ug/g)	Cat sensitization (IgE): 1.00				
			< 0.69	0.97(0.56-1.66)				n.s.
			0.70-1.69	1.02(0.56-1.87)				n.s.
			1.70-4.39	1.08(0.59-1.97)				n.s.
			4.40-22.90	1.29(0.67-2.49)				n.s.
			23.00-106.00	1.05(0.65-1.69)				n.s.
			> 106.00					
			Cat ownership (childhood)	(Q) Current wheezing: 1.1(0.87-1.33) (Q) dd asthma: 1.2(0.81-1.69)	Age, smoking, education, pack years, exposure to occupational dust or fume		n.s.	
Custovic et al., 2003, U.K (Parents of the MAAS cohort)	Cross-sectional (18-58y adults)	2254	Cat ownership (adulthood)	(Q) Current wheezing: 1.0(0.77-1.28) (Q) dd asthma: 0.8(0.46-1.24)				
			Measured Fel d 1 [§] from mattress and living room floor	Cat sensitization (IgE):	SES, age, gender, smoking			
			2 nd quartile	1.41(1.05-1.89)				n.s.
			3 rd quartile	1.51(1.12-2.01)				+
			4 th quartile	0.97(0.71-1.33)				n.s.
			Cat ownership	Grass sensitization (IgE):				
				1.35(1.07-1.70)				+
				1.15(0.91-1.45)				n.s.
				1.14(0.91-1.45)				n.s.
			Cat ownership	Cat sensitization (IgE): 0.65(0.50-0.85)				-
				Dog sensitization (IgE): 0.54(0.35-0.81)				-
				Grass sensitization (IgE): 0.98(0.81-1.18)				n.s.
				Cat sensitization (IgE): 0.66(0.49-0.89)				-
Custovic et al., 2001			Measured Fel d 1 [§] from mattress and living room floor	Dog sensitization (IgE): 0.60(0.38-0.94)				-
				Grass sensitization: not reported				
				Cat sensitization (SPT):	See above			
				2.3(1.2-4.4)				+
				2.1(1.1-4.0)				+
				2.2(1.2-4.3)				+
				2.5(1.3-4.9)				+
			Cat ownership	Cat sensitization (SPT): 0.66(0.50-0.89)	See above			-

Vargas et al., 2008, Chile	Cross-sectional (median age 25, IQR: 24–26)	1232	Cat ownership (1y)	(Q) rhinitis: 1.82(1.06–3.14)	SES, birth weight, BMI, current smoking	+
				(Q) wheezing: 0.87(0.49–1.57)		n.s.
				(Q) asthma attacks: 1.29(0.36–4.61)		n.s.
			Cat ownership (1–5y)	(Q) rhinitis: 0.85(0.50–1.43)	See above	n.s.
				(Q) wheezing: 1.27(0.72–2.23)		n.s.
				(Q) asthma attacks: 0.75(0.21–2.64)		n.s.
			Cat ownership (adulthood)	(Q) rhinitis: 1.05(0.80–1.37)	See above	n.s.
				(Q) wheezing: 1.22(0.91–1.62)		n.s.
				(Q) asthma attacks: 1.80(0.98–3.32)		n.s.
Dharmage et al., 2001, Australia (follow-up of ECHRS)	Cross-sectional (follow-up of ECHRS, 24–48y)	485	Measured Fel d 1 [§] from mattress and bedroom floor (current)	Cat sensitisation (SPT): 3-fold increased risk, but not significant	SES, current smoking, parental asthma/allergy, medication use, season of dust sampling, and mattress Fel d 1 exposure	n.s.
			Fel d 1 [§] from mattress	(Q) current asthma: 6.29 (sign.)	SES, current smoking, parental asthma/allergy, medication use, season of dust sampling, and floor Fel d 1 exposure	+
				(Q) current wheezing: not reported – not significant	SES, current smoking, parental asthma/allergy, medication use, season of dust sampling, and floor and bed Fel d 1 exposure are simultaneously adjusted	n.s.
Lewis et al., 2002, USA (part of the Epidemiology of Home Allergens and Asthma study)	Cross-sectional (18–64y, mothers)	458	Measured Fel d 1 [§] from bed and bedroom floor High ownership and sensitized	(Q) wheezing: 6.8(3.3–14.0)	Race/ethnicity, area poverty	+

Q = Questionnaire based

dd = Doctor diagnosed

RR = Relative risks

[§] Fel d 1 is major cat allergen *Felis domesticus* allergen I

Table 3

Data from cross-sectional case-control studies arranged by sample size – cat (retrieved from 2000 to Jan 2009)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Al-Mousawi et al., 2004, Kuwait	Case-Control (8–15y, matched by age and sex)	461	Current cat ownership	Cat sensitization (SPT): 3.32(1.19–9.25)	Parental allergy, maternal smoking, SES, older siblings			+
Gehring et al., 2001, Germany (INGA)	Cross-sectional enriched (25–50y)	405	Measured Fel d 1 [§] from mattress (current)	(Q) asthma attacks (past 12 months): 1.59(0.35–7.08) (Q) wheezing (past 12 months): 1.77(0.86–3.64)	Case-controls, season of dust sampling, region, gender, age, education, and active smoking	Stratified by subjects who were sensitized to common allergens – no effect	n.s. n.s.	
El-Sharif et al., 2003, Palestine	Case-control (6–12y, matched by school location, class and gender)	375	Cat ownership (1y)	(Q) wheezing (past 12 months): 3.10(1.22–7.86) (Q) dd asthma: not reported	Family factors, environmental factors, specific IgE and SPT		+	
Nicolaou et al., 2006, Cyprus	Case-control (15–16y) Case: self-reported asthma	128	Measured Fel d 1 [§] from child's mattress	Aeroallergens sensitization (SPT): not analyzed Cat sensitization (SPT): 1.10(0.83–1.45)	Gender, area of residence, parental allergy		n.s.	
El-Sharif et al., 2006, Palestine	Case-control (6–12y, matched by school location, class and gender)	110	Measured Fel d 1 [§] from child's mattress Medium (0.22–0.41 µg/g) High (> 41 µg/g)	(Q) wheezing (past 12 months): 1.52(0.45–5.08) 2.64(0.73–9.46)	adjusted for all other measured exposure, atopic sensitization, gender, and place of residence		n.s. n.s.	
			Measured Fel d 1 [§] from living-room floor Medium (0.22–0.41 µg/g) High (> 41 µg/g)	(Q) wheezing (past 12 months): 1.09(0.32–3.71) 0.73(0.20–2.55)	See above		n.s. n.s.	
Surdu et al., 2006, USA	Case-control (2–14y) Case: doctor diagnosed asthma (Native American population)	50	Measured Fel d 1 [§] from living room and bedroom floor and air samples ≥ 8 µg/g dust: ≥ 1 µg/g dust:	(Q) dd asthma 3.45 (PAR 9.3%) 1.06 (PAR 1.8%)				

Q = Questionnaire based

dd = Doctor diagnosed

[§] Fel d 1 is major cat allergen *Felis domesticus* allergen I

associations (Dharmage et al., 2001; Erwin et al., 2005; Jarvis et al., 2007; Platts-Mills et al., 2001).

Dog – birth cohort studies

A total of 13 birth cohort studies investigated the influence of exposure to dogs on allergy related health outcomes (Table 4A). There was a consistent indication that dog exposure during infancy and early childhood does not effect the development of specific IgE reaction to dog allergens. One study suggested a negative association, however, this association was assessed using cross-sectional information (Sandin et al., 2004). On the other hand, dog ownership seems to have a protective effect on the development of sensitization to mixed aeroallergens, especially mixed outdoor aeroallergens. All four studies, in which this association was assessed, reported a protective effect (Almqvist et al., 2003; Chen et al., 2008; Ownby et al., 2002; Sandin et al., 2004). However, the influence of exposure to dog on the development of allergic rhinitis was only reported in two cohorts, and the results are not consistent (Chen et al., 2008; Nafstad et al., 2001).

Ten studies reported wheezing as one of the health outcomes. Three studies observed that dog exposure in early life was associated with a reduced risk of wheezing symptoms during childhood (Bufford et al., 2008; Remes et al., 2001; Sandin et al., 2004) and one reported an association with increased risk (Mitchell et al., 2007). None of the 4 studies which assessed the association between dog ownership/exposure to dog allergen and asthma observed any significant link (Almqvist et al., 2003; Brussee et al., 2005; Chen et al., 2008; Nafstad et al., 2001).

Dog – cohort studies which are not recruited at birth

Six prospective studies in school-age children or in adults were included (Table 4B). These studies supported the hypothesis that dog ownership has no association with asthma. One study in the U.S. reported a negative association between dog ownership and wheezing symptom (Litonjua et al., 2002), however, two other studies in Sweden, with significantly larger sample sizes ($n=3431$ and 1870 respectively) did not observe any association (Bjerg-Backlund et al., 2006; Perzanowski et al., 2002).

Dog – cross-sectional studies

A total of 21 peer reviewed scientific publications from 20 cross-sectional studies are included here and 5 of these studies are case-control studies (Tables 5 and 6). Ten studies investigated the association between dog ownership and asthma. Using current dog ownership as an exposure, two studies observed a positive association with asthma (El-Sharif et al., 2003; Simpson et al., 2001), one study observed a negative association (Addo-Yobo et al., 2001), and six studies did not observe any significant link. Four studies observed a positive association between past or current dog ownership and the wheezing symptom (Clausen et al., 2008; Demir et al., 2004; Salo et al., 2004; Svanes et al., 2003); however, another four studies did not observe any significant link (El-Sharif et al., 2006; Skorge et al., 2005; Vargas et al., 2008; Wickens et al., 2002). One study in Kuwait observed that current dog exposure was associated with a higher prevalence of sensitization to dog (Al-Mousawi et al., 2004), while two European studies did not observe any association (Custovic et al., 2003; Nicolaou et al., 2006). Previous dog ownership, on the other hand, was also not associated with sensitization to dog.

Cats and/or dogs

Some studies did not distinguish between cat and dog exposure, these studies are listed in Table 7. One birth cohort study suggested that having more than 2 cats and/or dogs during infancy was associated with a lower risk of developing sensitization against aeroallergens at school age (Ownby et al., 2002) and one cross-sectional study indicated that cat or dog ownership during the first 2 years of life was associated with a reduced risk of developing sensitization against outdoor allergens (Anyo et al., 2002). One study observed that current cat or dog ownership was associated with a higher prevalence of wheezing symptom (Hong et al., 2004), while the other two studies suggested that previous cat or dog ownership was not associated with the development of wheezing symptoms (Anyo et al., 2002; de Meer et al., 2005).

Discussion

This review systematically documented peer reviewed scientific publications that investigated the associations between exposures to cat or dog and allergy related health outcomes in observational studies over the past nine years. This review shows that the reported exposure-response relationships are contradictory. A total number of 17 and 13 birth cohort studies on cat and dog exposure, respectively, are included in the review. Most of the birth cohort studies observed that cat or dog exposure in early life does not have an effect on the development of asthma or wheezing symptom and dog exposure during infancy protect children from developing sensitization against outdoor aeroallergens. A total number of 7 and 6 prospective studies in school-age children or adults on cat and dog exposure respectively are included in this review and most of these studies suggested an inverse association between cat exposure and asthma and wheezing symptoms. As for cross-sectional studies, 26 and 21 studies on cat and dog exposure respectively are included in this review. These studies cover a broad range of age groups and geographical areas, and reported inconsistent results.

Study design

This review shows that different study designs partly contribute to the conflicting results. While no apparent link between cat or dog exposure and asthma and wheezing symptom were observed in birth cohort studies, prospective studies recruited school-age children and adults showed a protective effect from cat exposure and cross-sectional studies showed an increased risk of having wheezing symptom in dog owners. In observational studies, more weight needs to be given to studies with longitudinal design as they can better assign the direction of causality. The negative exposure-response relationships observed in some of the cross-sectional studies may be due to reverse causation and the retrospective pet ownership used as exposure in some of prospective studies in school-age children or adults may also contain recall bias. On the other hand, assessing health outcomes at different time points of life may also contribute to the contradictory observations. It is known that the prevalence of respiratory allergic diseases increases in older populations. Furthermore, several papers have reported a gender-age interaction for the incidence of asthma (de Marco et al., 2000) and the prevalence of allergic rhinitis (Olivieri et al., 2002). In this review, birth cohort studies assessed health outcomes up to the age of 11 years and prospective studies in school-age children or adults reported health outcomes which were assessed in more advanced

Table 4

Data from cohort studies arranged by sample size - dog (retrieved from 2000 to Jan 2009)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Table 4.A BIRTH COHORT STUDIES								
Chen et al., 2008, Germany (LISA and GINI)	Population based	8163	Dog ownership (0-1y)	(Q)doctor diagnosed asthma (4-6 y): 0.9(0.4-2.2) (Q)allergic rhinitis (4-6 y): 0.8(0.4-1.6) (Q)wheezing (4-6 y): 0.9(0.6-1.3)	sex, study centre, parental educational level, parental allergy, and studies As above		n.s.	
			Dog ownership (0-4y)	(Q)doctor diagnosed asthma (4-6 y): 1.2(0.5-3.0) (Q)allergic rhinitis (4-6 y): 0.5(0.2-1.0) (Q)wheezing (4-6 y): 1.0(0.7-1.4)			n.s. n.s.	
		3155	Dog ownership (1y)	Dog sensitization (IgE): 1.1(0.5-1.9) Mixed pollen sensitization (IgE): 0.6(0.4-0.8) Aeroallergens sensitisation (IgE): 0.5(0.4-0.7)			n.s.	n.s.
			Dog ownership (6y)	Dog sensitization (IgE): 1.4(0.8-2.3) Mixed pollen sensitization (IgE): 0.8(0.6-1.1) Aeroallergens sensitisation (IgE): 0.7(0.5-1.0)				n.s.
			Dog ownership (up to 6 y)	Dog sensitisation (IgE): 1.1(0.7-1.8) Mixed pollen sensitization (IgE): 0.7(0.5-0.9) Aeroallergens sensitisation (IgE): 0.6(0.5-0.8)				n.s.
Almqvist et al., 2003, Sweden (BAMSE)	Population based	3596	Dog ownership (1y)	(Q)asthma (2y): 0.87(0.51-1.49) (Q)asthma (4y): 0.50(0.24-1.03) Dog sensitization (IgE) (4y): 0.62(0.22-1.76) Aeroallergens sensitization except dog (IgE) (4y): 0.36(0.51-0.83)	Gender, parental allergy, maternal smoking, maternal age, SES	Aeroallergens sensitization, stratified by parental allergy No: 0.43(0.18-1.00) Yes: 0.40(0.14-1.15)	n.s. n.s.	n.s.
Nafstad et al., 2001, Norway	Population based	2531	Dog ownership (birth)	(Q) asthma (4y): 1.1(0.6-1.9) (Q) allergic rhinitis (4y): 0.8(0.4-1.6)	Parental allergy, gender, birth weight, birth order, maternal age at delivery, maternal education, family income, ETS, breast feeding, ≥ 1 episode of lower respiratory tract infections during first year of life		n.s. n.s.	

Remes et al., 2001, USA	Population based	1076	Dog ownership (birth)	(Q) wheezing (0–12y): inverse association		Stratified by number of dogs (1 and $\geq$ 2): No effect Stratified by parental asthma: Yes: 0.19 (not sig) HR No: 0.53 (sig) HR Stratified by children with atopy: Yes: 0.47(0.24–0.91) HR No: 0.56(0.32–0.98) HR	-
			Dog ownership (6y)	(Q) wheezing (6y): 0.54			n.s.
			Dog ownership (8y)	(Q) wheezing (8y): 0.55			n.s.
Sandin et al., 2004, Sweden	Population based	1043	Dog ownership (11y)	(Q) wheezing (11y): 0.46			-
			Dog ownership (1y)	Dog sensitisation (SPT) (1y): 1.2(0.5–2.9) Dog sensitisation (SPT) (4y): 0.9(0.4–1.8) Sensitisation to pollen (SPT) (4y): 0.3(0.1–0.9) (Q) wheezing (1–4y): 1.5(0.7–3.2) (Q) wheezing (3–4y): 0.5(0.2–1.0)	Parental allergy, maternal smoking, older siblings, sex, dog and cat keeping		n.s.
				Dog sensitisation (SPT) (4y): 0.3(0.0–2.4) Sensitisation to pollen (SPT) (4y): 0.7(0.2–3.1)			n.s.
			Dog ownership (2–4y)	Dog sensitization (SPT) (4y): 0.4(0.1–0.8)	See above		n.s.
							n.s.
			Dog ownership (4y)		See above		-
Brussee et al., 2005, Netherlands (PIAMA)	Population based (enriched*)	365	Measured Can f 1 ^s from mattress (3 mon.) (ref.: not detectable)	Dog sensitization (IgE) (4y): 1 st tertile: 1.38(0.12–16.32) 2 nd tertile: 0.34(0.03–3.49) 3 rd tertile: 0.52(0.06–4.86)	Gender, study region, maternal education, older siblings, contact with children other than siblings, ETS, parental allergy.	Stratified by maternal allergy: 1 st tertile: Yes: 23.63(1.28–435) No: 1.38(0.12–16.32)	n.s.
		881		(Q) wheezing (0–4y): 1 st tertile: 1.69(0.86–3.31) 2 nd tertile: 1.40(0.65–3.02) 3 rd tertile: 1.72(0.82–3.63) (Q) doctor diagnosed asthma (4y): 1 st tertile: 1.10(0.36–3.33) 2 nd tertile: 1.02(0.33–3.10) 3 rd tertile: 1.20(0.39–3.71)		2 nd tertile: Yes: 7.03(0.43–147) No: - 3 rd tertile: Yes: - No: 0.52(0.04–6.67)	n.s. n.s. n.s. n.s. n.s. n.s.
							n.s.
							n.s.
							n.s.
							n.s.
Belanger et al., 2003, USA	Population based (enriched*)	849	Measured Can f 1 ^s from main living area (2–4 mon.)	(Q) wheezing (1y): not reported	Dust mite, cockroach, cat, dog, gas stove, mold/mildew, wood stove, respiratory illness, maternal education, ethnicity, gender, smoking in the home	Stratified by maternal asthma: Yes: 0.69(0.39–1.21) No: 1.03(0.71–1.49)	
Hagendorens et al., 2005, Belgium (PIPO)	Population based	810	Dog ownership (prenatal/postnatal)	Dog sensitization (IgE) (1y): not significant (the estimated value not reported) (Q) wheezing (1y): not significant	Gender, mode of delivery, birth weight, breastfeeding, siblings, day care attendance, pre-and postnatal contact with cats, dogs and smoking, parental	Stratified by sex: No effect	n.s.
							n.a.

Table 4 (continued)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Mitchell et al., 2007, New Zealand (ABC study)	Population based	591	Dog ownership (1y)	(Q) wheezing (3.5 and 7y): 2.1(1.1–3.8)	education, carpeting in the child's bedroom and parental atopy. Parental asthma, child having eczema, rhinitis or, sleeping on a used cot mattress in the first year of life, use of pillows, use of quilts, antibiotic use, day care attendance in the first year, current maternal smoking and during pregnancy, and hospitalized in the first year.		+	
Campo et al., 2006, USA	Population based (enriched*)	532	Dog ownership, 1 dog (0y)	(Q) recurrent wheeze (1y): 0.9(0.6–1.5) (Q) wheezing with an event (1y): 1.0(0.6–1.7) (Q) wheezing (1y): 0.8(0.5–1.3) (Q) recurrent wheeze (1y): 1.0(0.5–2.3)			n.s. n.s. n.s. n.s.	
			Dog ownership, ≥ 2 dogs (0y)	(Q) wheezing with an event (1y): 1.1(0.5–2.6) (Q) wheezing (1y): 0.9(0.5–1.9)			n.s. n.s.	
Ownby et al., 2002, USA (Childhood Allergy Study)	Population based	474	Dog ownership (1y) (ref.: no cat or dog exposure)	Dog sensitisation (SPT) (6–7y): p-value: 0.06 Outdoor inhalant sensitisation (SPT) (6–7y): p-value: 0.01 Indoor inhalant sensitisation (SPT) (6–7y): p-value: 0.02 Interviewed by doctor, asthma (6–7y): p-value: 0.81	Chi-Squared Test			n.s. - - n.s.
Celedon et al., 2002, USA	Population based (enriched*)	448	Dog exposure or dog ownership	(Q) wheezing: not reported			n.s.	
Bufford et al., 2008, USA (COAST)	Population based (enriched*)	275	Dog ownership (birth)	Dog sensitisation (IgE) (3y): 0.92(0.33–2.56) (Q) doctor diagnosed wheezing or wheezing medication (3y): 0.49(0.25, 0.95)	RSV infection (1y), day-care (6m), older siblings, paternal asthma, paternal allergy		-	n.s.
			Dog ownership (3y)	Dog sensitisation (IgE) (3y): 0.99(0.36, 2.76) (Q) doctor diagnosed wheezing or wheezing medication (3y): 0.75 (0.38, 1.47)	See above		n.s.	n.s.

Table 4.B NON BIRTH COHORT STUDIES

McConnell et al., 2002, USA (SCCH study)	5y follow-up of a cross-sectional study population (9–16y)	3535	Dog ownership (9–16y)/ history of wheeze (9–16y)	(Q) asthma-(12–21y): 1.4(0.9–2.2) RR		Stratified by wheezing: No: 1.4(1.0–2.0) RR	n.s. +
Perzanowski et al., 2002, Sweden	Follow-up of a cross-sectional study population (7–8y, 10–11y school children)	3431	Dog ownership (ever)	(Q) ever asthma (7–8y): 0.69(0.51–0.92) RR (Q) dd asthma (7–8y): 0.75(0.55–1.01) RR (Q) current wheezing (7–8y): 0.82(0.67–1.01) RR	Allergy, parental asthma, low birth weight, respiratory infection, ever cat, ever dog, damp house, gender		– n.s. n.s.
			Dog ownership (ever)	(Q) dd asthma (7–11y): 1.2(0.60–1.80) RR Dog sensitization (SPT) (7–8y): 0.79(0.58–1.1) RR	See above	Stratified by parental allergy: Yes: 0.58(0.37–0.91) RR No: 1.2(0.75–1.8) RR Children without sensitization: Yes: 0.79(0.47–1.3) RR	n.s. n.s.
Bjerg-Backlund et al., 2006, Sweden	Follow-up of a cross-sectional study population (7–8y, 11–12y)	1870	Dog ownership (ever)	(Q) asthma (7–8y): 0.99(0.65–1.51) (Q) asthma (11–12y): 0.78(0.54–1.13) (Q) dd asthma (7–8y): 0.91(0.61–1.37) (Q) dd asthma (11–12y): 0.95(0.69–1.31) (Q) Wheeze (last 12 months) (7–8y): 0.96(0.71–1.28) (Q) Wheeze (last 12 months) (11–12y): 0.91(0.67–1.23)	Gender, parental asthma, breastfeeding $\leq$ 3 months, birth weight < 2500g, respiratory infections, maternal smoking, cat at home, dog at home, living in damp area, living in an apartment, allergic sensitization, citrus fruit/week		n.s. n.s. n.s. n.s. n.s. n.s.
Ronmark et al., 2003, Sweden	School cohort (11–12y)	1870	Dog ownership earlier	Cat-dog sensitization (SPT) (11–12y): 0.70(0.46–1.08) 4y-incidence of any positive SPT response: 0.94(0.53–1.66)	Cat/Dog ownership, sex, parental allergy, rural living, area of domicile		n.s.
			Dog ownership later	Cat-dog sensitization (SPT) (11–12y): 0.58(0.35–0.97) 4y-incidence of any positive SPT response: 0.74(0.44–1.23)	See above		n.s. –
			Dog ownership (7,8 – 11–12y)	Cat-dog sensitization (SPT) (11–12y): 0.37(0.23–0.59) 4y-incidence of any positive SPT response: 0.91(0.63–1.31)	See above		– n.s.
Linneberg et al., 2003, Denmark	Adult cohort (15–69y, follow up 7y later)	734	Dog ownership (previously)	Dog sensitization (IgE) (baseline): 0.89(0.44–1.80) Dog sensitization (IgE) (incidence): 0.20(0.02–1.86) (Q/IgE) allergic rhinitis to animals (incidence): 0.15(0.03–0.73) (Q/IgE) allergic asthma to animals (incidence): 0.75(0.18–3.13)	Gender, age, cat/dog at home Gender, age, cat/dog at home, IgE at baseline Gender, age, cat/dog at home		n.s. n.s. – n.s.

Table 4 (continued)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Litonjua et al., 2002, USA	5y follow-up of a cross-sectional study population (< 5 y)	226	Dog ownership (currently)	Dog sensitization (IgE) (baseline): 1.19(0.58–2.46) Dog sensitization (IgE) (incidence): 1.78(0.42–7.55) (Q/IgE) allergic rhinitis to animals (incidence): 0.27(0.06–1.27) (Q/IgE) allergic asthma to animals (incidence): Not analyzed	See above			n.s.
			Dog ownership (< 5y)	(Q) wheezing (longitudinal model): 0.34(0.12–0.98)	Maternal asthma, maternal age, sex, prematurity, area of residence, clustering of outcomes.		-	n.s.
			Dog ownership (< 5y)	(Q) wheezing (2x within 4y follow-up): 0.12(0.01–0.97)	Maternal asthma, maternal age, sex, prematurity, area of residence.		-	n.s.

Q = Questionnaire based

dd = Doctor diagnosed

HR = Hazard Ratio

RR = Relative risks

§ Can f 1 is dog allergen *Canis familiaris* allergen I

* Enriched stands for studies which has over selected subjects who are at risk of developing allergic diseases for their study population.

Table 5

Data from cross-sectional studies arranged by sample size and grouped by children and adult study population – dog (retrieved from 2000 to Jan 2009)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
<i>Children study population</i>								
Kurosaka et al., 2006, Japan	Cross-sectional (6y school children)	35401	Dog ownership (current)	(Q) current rhinitis: 1.06(0.83-1.36) RR	Asthma: gender, cat, dog, and cat and dog. Rhinitis: gender, passive smoking, cat, dog, and cat and dog;		n.s.	
Oberle et al., 2003, Germany	Cross-sectional (5-7y school children)	8216	Dog ownership (1y and current)	(Q) dd asthma: not reported (Q) dd hay fever: not reported	Gender, parental education, allergy in family, number of older siblings, ETS		n.s. n.s.	
Salo et al., 2004, China	Cross-sectional (6y school children)	4185	Dog ownership (current)	(Q) current wheezing: 1.70(1.18-2.46) (Q) dd asthma: 0.85(0.51-1.40)	Gender, living area		+ n.s.	
			Dog ownership (before 6y)	(Q) current wheezing: 2.10(1.46-3.01) (Q) dd asthma: 1.54(0.97-2.44)	See above		+ n.s.	
Kuschnir et al., 2006, Brazil (ISAAC IV)	Cross-sectional (13-14y school children)	3033	Dog ownership (current)	(Q) current asthma: Not reported	Gender, maternal smoking, cat at home, firstborn, use of paracetamol, allergic rhinitis, atopic eczema.		n.s.	
Tamay et al., 2007, Turkey	Cross-sectional (6-12y school children)	2387	Dog ownership (1y)	(Q) current allergic rhinitis: not reported	parental allergy, dd eczema or food allergy, upper airway infections, sinusitis, adenoidectomy, antibiotic/paracetamol use (1y), cat or dog ownership (1y), home dampness, exposure to diesel trucks, perianal redness		n.s.	
Braback et al., 2001, Sweden	Cross-sectional (10-11y school children)	2108 / 1848	Dog ownership (past & current)	(Q) allergic rhinitis: Not reported Dog sensitization (SPT): Not reported				
Hugg et al., 2008. Finland/Russia	Cross-sectional. (7-16y school children)	1093		(Q) Current asthma in Finnish children: 0.37(0.13-1.10)	Age, gender, parental smoking, any dampness or visible mould		n.s.	
			Dog ownership (current)	0.37(0.04-3.18)			n.s.	
			Dogs indoors: 1y+, currently-1y-, currently+1y+, currently+ Any	0.36(0.05-2.77) 0.37(0.11-1.26) 0.31(0.04-2.43) 0.35(0.13-0.95)			n.s. n.s. n.s. -	
				(Q) Current asthma in Russian children: Not analyzed	Age, gender, any dampness or visible mould			
			Dog ownership (current)	Not analyzed				
			Dog ownership (1y)	Not analyzed				

Table 5 (continued)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Clausen et al., 2008, Iceland	Cross-sectional (10–11y school children)	946	Dog ownership (1y)	Dog sensitisation: (SPT): Not reported (Q) Wheezing: 2.3(1.02–5.26)			+	n.s.
Demir et al., 2004, Turkey	Cross-sectional (school children, mean age 9.2 (SD: 1.5))	621	Dog ownership (current)	(Q) current wheezing: 6.1(1.6–23.4)	Age, gender		+	
Henriksen et al., 2001, Norway	Cross-sectional (13–19y)	431	Dog ownership (ever)	Dog sensitization (IgE): 1.0(0.5–1.6)				n.s.
Wickens et al., 2002, New Zealand	Cross-sectional (7–10y school children)	293	Dog ownership (1y)	(Q) hay fever (past 12 months): 0.5(0.2–1.3) (Q) allergic rhinitis (current): 0.7(0.4–1.4) (Q) asthma (ever): 0.4(0.2–0.8) (Q) wheezing (current): 0.6(0.3–1.2)	Pets (1y), pets (currently), Diet at < 2y, gender, ethnicity, maternal education, parental allergy, family size, antibiotic use (1y), maternal smoking (1y) and currently, coal and wood fires (1y and currently), measles, whooping cough infection, dairy food consumption		n.s.	
			Dog ownership (current)	(Q) hay fever (past 12 months): 1.5(0.5–4.0) (Q) allergic rhinitis (current): 1.0(0.5–2.2) (Q) asthma (ever): 1.6(0.8–3.5) (Q) wheezing (current): 1.5(0.7–3.4)	See above		n.s.	
							n.s.	
							n.s.	
<i>Adults study population</i>								
Svanes et al., 2003, Europe (ECRHS I)	Survey (20–44y)	18530	Dog ownership (childhood)	(Q) current wheezing: 1.10(1.01–1.20) (Q) current hay fever: 0.90(0.83–0.98)	parental allergy, siblings allergy, parental smoking, number of siblings, age, sex, current smoking, current occupation, and study centre	Wheezing stratified by atopy: Yes: 1.00(0.85–1.17) No: 1.26(1.10–1.44) Hay fever stratified by atopy: Yes: 0.84(0.72–0.98) No: 0.98(0.85–1.14)	+	
			Dog ownership (adult)	(Q) current wheezing: 1.12(1.02–1.23) (Q) current hay fever: 1.04(0.95–1.15)	See above	Wheezing stratified by atopy: No effect Hay fever stratified by atopy: No effect	+	n.s.
Simpson et al., 2001, U.K (Parents of the MAAS cohort)	Cross-sectional (18–58y adults)	5687	Dog ownership (current)	(Q) dd asthma: 1.31(1.1–1.57) (Q) current asthma: 1.37(1.1–1.69) (Q) fever: not reported (n.s.)	Sensitization (SPT) to mite, cat, dog, pollen, sex, and smoking status		+	n.s.
Custovic et al., 2003, U.K (Parents of the MAAS cohort)	Cross-sectional (18–58y adults)	2254	Measured Can f 1 ^s from mattress and living room floor					n.s.

Skorge et al., 2005, Norway (HCCS II)	Cross-sectional (26–81y adults)	2401	2nd quartile	Dog sensitization (IgE): 0.88(0.58–1.33)			n.s.
			3rd quartile	0.88(0.57–1.33)			n.s.
			4th quartile	0.86(0.56–1.30)			n.s.
			2nd quartile	Grass sensitization (IgE): 1.02(0.81–1.29)			n.s.
			3rd quartile	0.86(0.68–1.08)			n.s.
			4th quartile	1.07(0.85–1.35)			n.s.
			Dog ownership	Dog sensitization (IgE): 0.68(0.45–1.03)			n.s.
				Grass sensitization (IgE): 1.11(0.91–1.34)			n.s.
			Dog ownership	Not reported	SES, age, gender, smoking		
			Dog ownership (childhood)	(Q) Current wheezing: 1.0(0.82–1.25)	Age, smoking, education, pack years, exposure to occupational dust or fume		n.s.
				(Q) dd asthma: 0.8(0.52–1.13)			n.s.
			Dog ownership (adulthood)	(Q) Current wheezing: 1.0(0.78–1.38)			n.s.
Vargas et al., 2008, Chile	Cross-sectional (median age 25, IQR: 24–26)	1232		(Q) dd asthma: 0.9(0.55–1.61)			n.s.
			Dog ownership (1y)	(Q) rhinitis: 0.47(0.28–0.80)	SES, birth weight, BMI, current smoking		-
				(Q) wheezing: 1.03(0.57– 1.85)			n.s.
				(Q) asthma attacks: 1.14(0.38–3.47)			n.s.
			Dog ownership (1– 5y)	(Q) rhinitis: 1.52(0.48–2.62)	See above		n.s.
				(Q) wheezing: 1.07(0.58– 1.96)			n.s.
				(Q) asthma attacks: 0.79(0.26–2.44)			n.s.
			Dog ownership (adulthood)	(Q) rhinitis: 1.02(0.77–1.35)	See above		n.s.
				(Q) wheezing: 1.03(0.76– 1.40)			n.s.
				(Q) asthma attacks: 0.55(0.30–1.02)			n.s.

Q = Questionnaire based

dd = Doctor diagnosed

RR = Relative risks

§ Can f 1 is dog allergen *Canis familiaris* allergen I

Table 6

Data from cross-sectional case-control studies arranged by sample size – dog (retrieved from 2000 to Jan 2009)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Al-Mousawi et al., 2004, Kuwait	Case-Control (8-15y, matched by age and sex)	461	Dog ownership (current)	Dog sensitization (SPT): 6.02(1.30-27.96) Dog sensitization (IgE): 6.76(1.44-31.64) Dog sensitization (IgE): 2.56(1.17-5.58)	Parental allergy, maternal smoking, SES, older siblings			+
El-Sharif et al., 2003, Palestine	Case-control (6-12y, matched by school location, class and gender)	375	Dog ownership (recently)	(Q) wheezing (past 12 months): not reported (Q) dd asthma: 3.24(1.09-9.56)	Family factors, environmental factors, specific IgE and SPT		+	
Nicolaou et al., 2006, Cyprus	Case-control (15-16y) Case: self-reported asthma	128	Measured Can f 1 from child's mattress	Aeroallergen sensitization (SPT): not reported Dog sensitization (SPT): 1.36(0.67-2.75)	Gender, area of residence, parental allergy			n.s.
El-Sharif et al., 2006, Palestine	Case-control (6-12y, matched by school location, class and gender)	110	Measured Can f 1 from child's mattress Medium (0.25-0.52 µg/g) High (> 52 µg/g) Measured Can f 1 from living-room floor Medium (0.25-0.52 µg/g) High (> 52 µg/g)	(Q) wheezing (past 12 months) 0.48(0.12-1.92) 0.27(0.05-1.40) (Q) wheezing (past 12 months) 1.08(0.31-3.74) 0.40(0.08-1.91)	adjusted for all other measured exposure, atopic sensitization, gender, and place of residence See above		n.s. n.s.	
Addo-Yobo et al., 2001, Ghana	Case-Control (8-17y, matched by age and sex)	100	Dog ownership (current)	Cases (dd asthma, asthma medication, symptoms in the past 12 months): 0.37 (0.16-0.87)			-	

Q = Questionnaire based

dd = Doctor diagnosed

s Can f 1 is dog allergen *Canis familiaris* allergen I

Table 7
Data from cohort and cross-sectional studies -pets (retrieved from 2000 to Jan 2009)

Author, Year, Country (Study Acronym)	Study type	N	Exposure & time (age)	Outcome & time (age) (in odds ratios unless indicated otherwise)	Confounders adjusted/ Other factors in the multivariate model	Sensitivity analysis	Significance level for respiratory symptoms & diseases	Significance level for sensitization
Almqvist et al., 2003, Sweden (BAMSE)	Population based	3596	Cat or dog ownership (at 1y)	Not reported		Aeroallergens sensitization, stratified by parental allergy No: 0.64(0.41-0.99) Yes: 0.84(0.45-1.57)		
Ownby et al., 2002, USA (Childhood Allergy Study)	Population based	474	One cat or dog ownership (1y)	Sensitization against aeroallergens (6-7y): IgE: 0.93(0.51-1.68) SPT: 0.85(0.48-1.52)	CB IgE, levels of HDM in child's bedroom (2y), sex, older sibling, ETS, parental asthma, current dog and cat exposure	Stratified by sex – no effect		n.s.
			≥ 2 cats or dogs ownership (1y)	Sensitization against aeroallergens (6-7y): IgE: 0.33(0.13-0.83) SPT: 0.23(0.09-0.60)			n.s.	
			≥ 2 cats or dogs ownership (6-7y)	Sensitization against aeroallergens (6-7y): IgE: 0.81(0.43-1.95) SPT: 0.79(0.44-1.85)	CB IgE, levels of HDM in child's bedroom (2y), sex, older sibling, ETS, parental asthma.		- - n.s. n.s.	
			CROSS-SECTIONAL STUDIES Pet					
Hong et al., 2004, Korea (ISSAC)	Survey (12-15y school children)	1995: 14964 2000: 15214	Cat or dog ownership (current)	(Q) current wheezing (1995): 1.087(0.910-1.300) (Q) current wheezing (2000): 1.220(1.047-1.422)	Age, sex, centre, BMI, monthly electricity bill, passive smoking, living with dog or cat, and living environments		n.s. +	
Anyo et al., 2002, Netherlands	Cross-sectional (7-12y school children)	2729	Cat/dog ownership in the first 2 years	(Q) Current wheezing: 0.87 (0.63-1.20)	Age, gender, foreign descent, parental asthma, parental hay fever, parental education, older siblings, smoking in the home, having visited a day care centre, area or residence	Stratified by parental allergy and symptoms: No major changes or the odds ration. For pollen , the negative association was somewhat stronger for the “no parental symptoms and allergy ”group	n.s.	
				(Q) Current rhinitis: 0.88 (0.72-1.08)			n.s.	
				(Q) Current asthma: 1.13 (0.80-1.60)			n.s.	
				(Q) Current hay fever: 0.82 (0.58-1.15)			n.s.	
				Sensitization outdoor allergens (SPT and/or IgE): 0.73(0.57-0.92)				-
				Sensitization to indoor allergens (SPT and/or IgE): 0.93(0.74-1.15)				n.s.
Cat sensitization (SPT and/or IgE): 0.94(0.68-1.30)		n.s.						
Dog sensitization (SPT and/or IgE): 0.89(0.66-1.21)		n.s.						
De Meer et al., 2005	Cross-sectional (8-13y school children)	1553	Cat or dog ownership (0-2y)	(Q) current wheezing: 1.27 (0.93-1.73)	Age, gender, parental asthma, foreign descent, maternal education, breast feeding > 3 months, passive smoking, smooth floor child's bedroom, cat or dog after 2 y, airway disease < 2y, day care, older siblings		n.s.	
				(Q) current asthma: 1.09 (0.66-1.81)			n.s.	
				(Q) current rhinitis: 0.83 (0.65-1.07)			n.s.	

Q = Questionnaire based

ages. The exposure-response relationship may alter with ageing as exposures from public environment such as schools or workplace may be also important for the development of allergic diseases and symptoms in adolescents or adults. Furthermore, it is known that wheezing symptoms during the first three years of life may be transient and unrelated to the risk of later development of asthma (Stern et al., 2008). Some birth cohorts included in this review are too young to classify their wheezing symptom into transient, persistent, and late onset wheezing. Some birth cohort studies have simply defined the wheezing symptom as “ever having wheezing symptom during childhood” and the children not at risk of developing asthma are misclassified in these studies.

Exposure

In this review, exposure to cat or dog was restricted to cat or dog ownership and measured domestic allergen level. Publications with the information on exposure through frequent contact to cats or dogs are not included in this review as we found it difficult to assess whether the intensity of cat or dog exposure from owning a cat or dog is the same as having frequent contact with the animal from different sources and the definition of the word “frequent” is rather subjective. Studies with exposure assessments conducted only in a public setting were also not included. We also excluded a study which assesses the allergen exposure solely in classrooms and assigns non-cat owners to have the same amount of allergen exposure as the cat owners from the same class and the ignores domestic exposures (Smedje and Norback, 2001). It is known that cat allergen is ubiquitous, measurable cat allergens can be found in non-cat owner's home and the level may differ based on the allergen level in the community (Chen et al., 2007; Heinrich et al., 2006). Passive transfer of dog allergen has also been demonstrated (Custovic et al., 1998; Liccardi et al., 2000). The domestic only exposure is only a component of overall exposure. It is demonstrated in this review that none of the common methods of assessing pet allergen exposure in observational studies is optimal, especially for adults and adolescents who spend significantly less time at home compared to young children.

Allergen or microbe exposure at different ages may also cause significantly different effect on the health outcomes. It was proposed that exposure to allergen or microbes during perinatal phase may have the most crucial effect as infants' immune system are vulnerable and the development of the immune response was still ongoing, and a shift from Th2 cells dominate immune response to Th1-dominated immune response happens during early childhood (Holt and Jones, 2000; Holt et al., 1999). Exposure during this crucial time window was best captured by birth-cohort studies. The results summarised in this review strongly suggest that dog exposure protects children from developing sensitization against mixed aeroallergens, regardless of allergic symptoms, up to school age. Unfortunately only two birth cohort studies reported the effect of exposure to dog on allergic rhinitis and one showed no significant association while the other showed a borderline protective effect. The effect of early childhood exposure to cat, on the other hand, was less clear. Although half of the studies showed a positive link between exposure and the development of cat sensitization, all but one of these studies have significantly bigger sample size ($n > 1000$). As the population of these studies are not pre-selected based on family history of allergic disease, this observation of positive link was not likely due to the predisposition of the children. The hypothesis that exposure to high cat allergen may induce immune tolerance and reduce the risk of developing elevated IgE against cat allergen is not supported by the birth cohort studies included in this review.

This may be due to the fact that the doses of exposure in these birth cohort studies are not sufficient for the induction of the immune tolerance. However, because all but one of these studies were conducted in western European countries, it could be assumed that the allergen level in these population-based studies are representative to the domestic cat allergen exposure in the western European population and no protective effect was observed.

Community effect

Community exposure to dog or cat allergen is highly influenced by the prevalence of dog or cat owners. It was well demonstrated in the earlier publications that the prevalence of pet ownership are different between European countries (Eller et al., 2008) and the level of cat allergen measured from domestic settled house dust of non-cat owners' homes is influenced by the community prevalence of cat ownership (Heinrich et al., 2006). The discrepancies between study results may be due to different levels of exposure in the community. Svanes et al. (2003) reported results from a European survey suggesting that the effect of domestic cat allergen exposure during childhood on allergic disease in adulthood may be modulated by the community prevalence of cats. Low community prevalence of cats may increase the risk of having asthma in sensitised adults who were exposed to cats during childhood (Svanes et al., 2003). Another example was the study conducted in Kuwait, where the prevalence of dog ownership was 1.5% (Al-Mousawi et al., 2004). It was the only study included in this review which reported a positive link between exposure to dog and the risk of sensitization to dog allergen. The high diversity of pet ownership between the communities may be one of the major causes for the conflicting exposure-response relationship observed.

Avoidance effect

Genetically pre-disposed children were more likely to develop allergic disorders and their parents or siblings were more likely to perform allergen avoidance due to their own allergic symptoms. A strong negative association between maternal pet allergy and cat ownership was observed by a Swedish birth cohort study (Almqvist et al., 2003). Similar observation of cat avoidance or cat acquisition subsequent to asthma or allergy was observed in the European Community Respiratory Health Survey in adults (Svanes et al., 2006). Avoidance of dog keeping, on the other hand, was less observed (Almqvist et al., 2003). Most of the studies try to address this possible bias by stratifying the analysis was based on the history of parental allergic diseases. However, only those families with parents or siblings who have developed symptoms when in contact with cats or dogs would have a strong need to avoid pets. On the other hand, in some families, there was a strong emotional bond between the pets and family members would rather suffer from the symptoms than remove the pets. Unfortunately only two studies have collected information on pet avoidance and taken it into account when performing the statistical analysis (Sandin et al., 2004, 2006); therefore, one cannot rule out the bias due to avoidance in observational studies.

Gene-environmental interaction

Children who have a certain gene mutation may react differently when exposed to allergens (Bisgaard et al., 2008). However, these interactions may only have moderate effects and cannot be observed by simple stratification of the study population based on their family history of allergic diseases.

Some of the conflicting observations may be resolved in the future with the continued search for gene associated with allergic diseases.

Action on avoidance?

Given that all the studies included in this review were peer reviewed and published in scientific journals, all have a similar structure and we were able to extract information regarding the study population, sample size, definition and assessment of outcomes and exposures, study results, confounders considered in the analytical model, and additional analysis such as stratified analysis. As such, all of the included studies contain the components of the STROBE checklist, the checklist for the reporting of observational studies in epidemiology (von Elm et al., 2008). Considering the quality of the study based on the study design, birth cohort studies were less biased since the exposure and health outcome information were assessed prospectively and less effected by potential avoidance. Adjustment or stratification of parental atopy or allergic diseases were not performed only in three birth cohort studies assessing the effect of cat exposure and three birth cohort studies assessing the effect of dog exposure, allowing the possibility of reverse causation caused by parental avoidance to pets. Cohort studies that recruit cohorts at an older age and assessed early life exposure retrospectively, allowing for recall bias.

Based on this review; It can be concluded that early childhood exposure to cat or dog do not have an impact on the development of asthma and wheezing symptoms up to school age. Exposure to cat allergen leads to a higher risk of developing cat sensitization in children. Conversely, dog exposure protects children from developing sensitization against aeroallergens with indication that it was associated with wheezing symptom later in life. However, based on the available evidence only the tendency of the exposure-response association can be summarised, we were not able perform meta-analysis to calculate the magnitude of the effects because of differences among studies in the definition of exposure and health outcomes. This review cannot be used for the recommendation of actions for pet owning or avoidance but to disentangle the apparent contradictory observations. On the other hand, as the evidence of the effects of pet keeping on subsequent development of asthma or allergic diseases presented in this review were not overwhelmingly strong, the decision of whether to keep a cat or a dog in the family should be based on arguments other than the concern of developing asthma and allergy. To complete our knowledge on the association between exposures to pets and asthma and atopy, efforts from scientific consortiums in different geographical areas attempting to conduct pooled or meta-analysis on studies conducted in these areas were needed.

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