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Dog Ownership and Contact during Childhood and Later Allergy Development

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Abstract

The effect of dog ownership during childhood on the development of allergy has been investigated in few studies with conflicting results. We investigated the association between dog contact and indoor endotoxin exposure during infancy and the development of allergic sensitization and atopic disease up to age 6.

Two ongoing birth cohorts GINI (n=1962) and LISA (n=1193) were analysed. In both studies, information on children's contact with dogs and their allergic symptoms and doctor diagnosed allergic disease were collected during follow-up using questionnaires. Specific IgE to common aeroallergens were measured at age 6. House dust samples were collected at age of 3 months and the amount of endotoxin in house dust was determined.

Dog ownership in early childhood was associated with a significant lower rate of mixed pollen and inhalant sensitization but not with dog sensitization and allergic symptoms and diseases up to age 6. Regular contact with dog during childhood without ownership was not associated with the health outcomes. No associations were found between house dust endotoxin exposure during infancy and sensitization outcomes.

In conclusion, dog ownership in early childhood protects against the development of inhalant sensitization and this effect cannot be attributed to the simultaneous exposure to endotoxin.

Key Words

Allergy, Cohort Study, Dog Ownership, Endotoxin, Sensitization

Introduction

The effect of pet ownership and pet contact on the development of allergic sensitization and disease is disputed. Previous studies have mainly focused on cat allergen exposure and cat ownership while not many prospective studies have specifically discussed the effect of childhood dog contact. Cohort studies have associated early childhood dog ownership with reduced risk of wheezing(1-3) and one has reported that dog ownership in infancy seems to reduce the risk of asthma(4) while the Dutch PIAMA cohort has reported that infancy dog allergen exposure has no effect on the development of wheezing nor asthma(5). Some cross-sectional studies have collected retrospective information on dog ownership in early childhood. In the European Community Respiratory Health Survey, Svanes et al has reported that childhood dog ownership is associated with decreased risk of hay fever but promote non-allergic asthma(6). Associations between childhood dog ownership and allergic sensitization have also been reported(4;7-9). While most of the studies have observed a negative association between childhood dog ownership and sensitization to aeroallergens, particularly outdoor aeroallergens, the Tucson birth cohort reported that no such protective effect was found(3). The observed protective effect of dog ownership, however, may be partly due to selective dog avoidance by atopic parents(10-12). On the other hand, the simultaneous exposure to higher level of indoor endotoxin may be the biological mechanism behind the observed protective effect(13;14).

Higher level of endotoxin exposure in early childhood has been inversely associated with the development of allergic sensitization and disease(15-17). Studies have shown that endotoxin can stimulate the production of cytokine IL-12 which may consequently enhance young children's type 1 lymphocyte (T-helper 1) development and decrease their susceptibility for sensitization to allergens(18-20). Dog ownership has been directly associated with higher endotoxin level measured in the settled house dust(1;13;14;21;22). It has been speculated that dog ownership during early childhood may therefore protect young children from developing allergic sensitization and disease.

The aim of this study is to investigate the association between dog ownership and contact with dogs outside the domestic area and the development of inhalant sensitization and allergic diseases up to 6 years of age using two cohort studies conducted in Germany. We also investigated whether endotoxin exposure during infancy, which has previously been associated with dog ownership, contribute to the protective effect on allergy.

Method

Study population

The study population was composed of two ongoing birth cohorts conducted in Germany. The Influences of lifestyle-related factors on the immune system and the development of allergies in childhood study (LISA) and the German Infant Nutritional Intervention Program (GINI). Detailed description of screening and recruitment has been provided elsewhere(23;24).

Briefly, in the GINI study, 5991 newborns from the 16 maternity wards in Munich and Wesel, Germany fulfilled the inclusion criteria were recruited in the study between September 1995 and June 1998. There are two subgroups in the GINI study: interventional study arm and non-interventional study arm (observational cohort group). 2252 infants with at least one parent or sibling having a history of allergic disease agreed to participate in the randomized trial which aimed to compare the effect of hydrolyzed formulas and conventional cow's milk formula on the prevention of the development of allergic disease in high risk children. The infants with no family history of allergic disease and those whose parents denied participating in the trial were allocated in the non-interventional study arm. Children from both groups were followed-up at the age of 1, 2, 3, 4, and 6 years.

In the LISA study, parents of neonates admitted to maternity hospitals in Munich, Leipzig, Wesel, and Bad Honnef, Germany were contacted. 3097 neonates were recruited in the study between December 1997 and January 1999. LISA is designed as a population based study and the participants were not pre-selected based on family history of allergic disease. In the Munich and the Leipzig subgroup, the house dust samples were collected. The cohort was followed up at the age of six months, twelve months, eighteen months, two years, four years, and six years. Both studies were approved by the local ethics committees.

Questionnaire data

In both studies, information on parental educational level, and parental history of allergic disease were collected using self-administered questionnaires at birth. Information on children's allergic symptoms, doctor diagnosed asthma, eczema, and allergic rhinitis, dog ownership, contact with dogs outside home, and environmental tobacco smoking at home were collected at each follow up using self-administered questionnaires. The question "(In the past 6/12 months /2 years,) did your child had regular contact with any of the following animals outside the house – dog?" was used to assess any regular contact with dog in the non-domestic settings at each follow-up until the children were 4 years old.

Collection and analysis of blood samples

Blood samples were collected from 1962 (51%) and 1193(50%) children from the GINI and LISA study respectively at age 6(Figure 1). Specific IgE antibodies to aeroallergens were measured using RAST FEIA CAP system (Pharmacia, Freiburg, Germany). A screening test for sensitization was used to detect specific IgE antibodies against inhalant allergens (SX1: timothy grass, rye, birch, mugwort, house-dust mite, cat, dog, and moulds) in the serum. The children who were tested positive for SX1 were tested for single specific allergens including dog allergen Can f1. Sensitisation to mixed pollen allergens included timothy grass, rye, birch, and mugwort. Sensitisation was defined as having a specific serum IgE titer >0.35 kU/L to specific allergens.

Collection of settled house dust samples and analysis of endotoxin

The house dust samples were collected from 2166 families in the LISA study, Munich and Leipzig group when the children were 3 months old. Trained field workers carried out dust sampling based on a standardized operating procedure(21;22). Independent dust samples from parents' and child's mattresses were taken by vacuuming 1 m^2 of each mattress surface for two minutes using vacuum cleaners equipped with special nozzles (ALK-Abelló allergen mouthpiece, Hørsholm, Denmark). The samples were stored at -20°C until extraction to prevent bacteria growth. The dust samples plus filter paper were extracted with 0.125 M NH4HCO3 plus 0.05% Tween20 for 2h at room temperature under constant shaking, with an extraction ratio of 1:10 to 1:100 (w/v), depending on the amount of sampled dust. House dust endotoxin levels were quantified using the kinetic Limulus Amebocyte Lysate assay (Bio Whittaker, Walkerville, MD) with 50 EU/g dust detection limit. The endotoxin levels were expressed as endotoxin load, the amount of endotoxin per m^2 of sample surface and endotoxin concentration, the amount of endotoxin in per gram of sampled dust.

Information on household density in living area

Information on household density (i.e. number of households per unit area of land) were available in the Munich subgroups from the GINI and LISA cohort(25). Demographic information including the number of households in every postcode area in Bavaria, Germany was collected from the company INFAS GEOdaten (Bonn, Germany). The data was updated in December 2003. The household density of a 2500 meter buffer was calculated for each residential address of the Munich subgroups from both cohorts. The proportions of the postcode area and the proportion of household counts were calculated for each buffer and the area weighted averages of the household numbers were used as household density.

Statistical Analysis

The correlation between endotoxin loads and concentrations from parents' and children's mattress were calculated using Spearman correlation coefficient. Adjusted logistic regression

models were fitted to describe the associations between dog ownership and regular dog contact outside the domestic area during childhood and the development of dog ,and mixed pollen ,and inhalant sensitization at age 6. To describe the association between dog ownership and dog contact and the development of allergic symptoms and diseases between age 4 and 6, longitudinal analysis with marginal logistic regression model (GEE) were used. The longitudinal analysis approach takes the dependence of repeated outcome measures within each subject into account. In the statistical models, parental history of allergic diseases, parental educational level, sex, and study centre were adjusted. In the sensitivity analyses which assess the association between dog ownership and contact with dogs and the development of allergy taking cat ownership and contact with cats into account, cat ownership and contact with cats outside the domestic area were additionally adjusted. The endotoxin loads and concentrations in mattresses were normalised using log-transformation. T-test was used to test if log-transformed endotoxin loads and concentrations in mattresses were different between families with and without dog ownership. Adjusted logistic regression models were fitted to estimate the association between health outcomes and domestic endotoxin level. The results were presented as odds ratios with 95% confidence intervals. Wilcoxon Rank-Sum Test was used to assess whether the household density is different between the dog owner and non dog owner's living area. The analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Information of children's health outcomes and demographic characteristics is listed in table 1. Due to the study design, there were only 26% of the parents with a history of allergic disease in the GINI non-interventional study arm but 90% in the GINI interventional study arm. The remaining 10% of the children in the GINI intervention study group have at least one sibling with a history of allergic disease. The high genetic risk of the children from the GINI intervention study group explains the higher sensitization rates to dog, mixed pollen, and inhalant allergens and the higher prevalence of diagnosed asthma, eczema, and allergic rhinitis. The prevalence of dog ownership between birth and age one were 10% in the LISA cohort, 10% in the GINI non-interventional study arm and 8.5% in the GINI interventional study arm. At age 6, the prevalence of dog ownership was significantly different between the three study groups ($p=0.02$). Ten percent of the families in the LISA study had a dog, while 12% of the families in the GINI non-interventional study arm owned a dog and 11% of the families in the GINI interventional study arm are dog owners.

We investigated the associations between dog ownership and contact with dogs outside the domestic area and the allergic sensitization rate at age 6. Dog ownership in infancy, during early childhood, and at age 6 was not associated with dog sensitization (table 2). However, dog ownership was associated with a significant lower rate of mixed pollen and inhalant allergen sensitization, particularly if the child's family had a dog in the child's first year of life. On the other hand, contact with dogs outside the domestic area without ownership was not associated with any of the sensitization outcomes. Further investigation showed that dog ownership and contact with dogs outside the domestic area during childhood had no effect on the development of doctor diagnosed allergic disease or reported allergic symptoms up to age 6 (table 3a).

We further investigated whether having contact with cats is an important confounder in the association between dog ownership and contact and the development of allergic sensitization and diseases in young children. Additional analyses were carried out with cat ownership and frequent cat contact outside domestic area during childhood as two added confounders. The results showed that adding the variables cat ownership and frequent cat contact outside domestic area during childhood as the two additional confounders in the original models did not affect the estimated associations between dog ownership and contact during childhood and the development of allergic sensitization in young children in general as well as in the sensitivity analysis, in which the children were stratified by parental history of allergic diseases (data not shown). The associations between dog ownership and contact during childhood and the development of allergic diseases in young children were not strongly affected by the additionally added confounders of cat ownership and cat contact. Except for those children

who had frequent contact with dog in their first year of life in the GINI non-intervention study arm, it is now shown that these children have a statistically significantly higher chance of being diagnosed of having asthma at school age. The chances of developing eczema symptoms in those children who have ever had a dog up to age 4 in the GINI non- interventional arm are also shown to be higher (table 3b).

The amounts of the endotoxin were available from 2108 mother's mattress dust samples and 2093 children's mattress dust samples from 2166 families. All of the analysed dust samples contained endotoxin above the detection limit. The median (25th, 75th percentile) of the load and concentration of endotoxin from mother's mattress dust were 2071 (595, 6919) EU/m^2 and 3008 (1046, 7913) EU/g respectively. In children's mattress dust sample, the median (25th, 75th percentile) of the load and concentration of endotoxin were 1015 (330, 3022) EU/m^2 and 5866 (2336, 14669) EU/g respectively. The correlation between the amount of endotoxin in mother's and children's mattress dust samples were 0.4 for both concentration and surface load. The amount of endotoxin in mother's and children's mattress dust samples were significantly different between families with and without a dog in the household within the first year of child's life ($p<0.01$). The median (25th, 75th percentile) of endotoxin load from mother's mattress dust were 4739 (996, 15934) EU/m^2 and 1941 (562, 6494) EU/ m^2 for families with and without dogs respectively. For children's mattress, the endotoxin load were 1724 (539, 6372) EU/m^2 and 949 (324, 2871) EU/ m^2 for families with and without dogs respectively. However, further analysis showed that there were no associations between early childhood endotoxin exposure from mattress and sensitization to dog (OR (95% C.I.)= 1.01 (0.80, 1.26)), mixed pollen (OR (95% C.I.)= 1.07 (0.95, 1.19)), and inhalant allergens (OR (95% C.I.)= 1.08 (0.97, 1.19)) (when using the endotoxin loads sampled from children's mattresses as exposure, similar results were observed with the amount of endotoxin sampled from parents' mattresses). The associations between endotoxin exposure and sensitization outcome in homes with and without dog ownership in their child's first year of life were also assessed by including an interaction term of dog ownership in the first year and mattress endotoxin level in the model. The results showed that in homes with and without dog ownership, early childhood endotoxin exposure had no effect on the sensitization outcomes at age 6 (data not shown).

In a further subgroup analysis, we investigated whether the household density where the dog owners live confounds the observed protective effect of dog ownership. In the Munich subgroups of both GINI and LISA cohorts, information on household density of their home address were available. We found that dog owners are more likely to live in areas with lower household density ($p<0.01$). Further adjusting for household density in the model, however, did not modify the negative effect of dog ownership on sensitization outcomes (OR (95%

C.I.)= 0.53(0.24, 1.05) for pollen sensitization and OR (95% C.I.)= 0.51(0.26, 0.92) for inhalant sensitization).

To overcome possible bias from selective avoidance of dog due to parental history of allergic disease, a stratified analysis was performed. We stratified the cohort by whether the parents ever had asthma, eczema, or hay fever and re-analyzed the association between dog ownership and contact and the sensitization rate at age 6. The results confirmed that the negative association between dog ownership during childhood and sensitization to mixed pollen and inhalant allergens at age 6. The negative associations were slightly stronger in families with a history of allergic disease (table 4).

To overcome possible confounding effect from exposure to environmental tobacco smoking, we performed sensitivity analysis restricted to those children who have not been exposed to environmental tobacco smoke at home up to age 6 (n=1752). The negative association between dog ownership during childhood and sensitization to mixed pollen (OR (95%C.I.)=0.7(0.5, 1.0)) and inhalant allergens (OR (95%C.I) = 0.7(0.5, 1.0) at age 6 remained.

Furthermore, in both GINI and LISA study, not all children agreed to participate in the blood examination. We therefore compared the demographic characteristics between children with and without IgE measurements (table 5). We found that parents with higher educational level were more likely to agree to participate in the IgE measurement, while parental history of allergic disease was negatively associated with the participation of the IgE measurement. However, all children in the GINI interventional study arm are with at least one parent or sibling having a history of allergic disease.

Discussion

Dog ownership in early childhood was associated with a significant lower rate of mixed pollen and inhalant sensitization but not dog specific allergic sensitization. The negative associations remained when the data are stratified by parental history of allergic disease or restricted the analysis to those children who have never been exposed to ETS at home. Dog contact outside domestic area solely had no effect on the development of allergic sensitization. No consistent association between dog ownership and dog contact and the development allergic symptoms and diseases were found. In homes with and without dog ownership, early childhood endotoxin exposure had no effect on the sensitization outcomes at age 6.

Protective effects of dog ownership in childhood on the development of inhalant allergen sensitization in both low- and high-risk children have been reported(4;6;7;26). Cumulative evidence suggests that dog ownership in early childhood prevents the development of allergy. There is, however, a recent cross-sectional study in Kuwait which has reported positive associations between dog ownership in school age children and the prevalence of dog sensitization(27). The author of the study pointed out that the prevalence of dog ownership is extremely low in this study population (1.5%), so is the dog allergen levels in the children's home. Therefore, this study result may not be suitable to be generalised to the communities where the prevalence of dog ownership is 7 times higher. Simultaneous exposure to endotoxin has been speculated as the explanation behind the apparent protective effect. Particularly due to a large number of studies which reported that children raised on farms where high level of endotoxin have been measured have a lower prevalence of hay fever and allergic sensitization(11;16;28;29). Laboratory experiments on mice have provided further evidence that endotoxin exposure induces cytokines which may shift the infants' developing immune system to a predominantly T_H1 type responses that protect children from developing allergy(19;20). Gern et al have also observed the association between dog ownership and higher IL-10 and IL-13 cytokine secretion in 1 year old children(30). However, the results from our study and the cohort study in Boston (2)showed that the negative association between dog ownership and allergic sensitization and symptoms are independent of the effect of endotoxin exposure.

It has also been speculated that the observed protective effect of dog ownership may be partly due to selective dog avoidance by atopic parents. It has been reported by the Swedish BAMSE study that dogs are less common in families with than in families without parental atopic eczema/dermatitis syndrome. However, the study has also reported that less dog avoidance behaviour were observed comparing to cat avoidance(12). The recent publication from the European Community Respiratory Health Survey reported that selective avoidance subsequent to asthma or allergy was not observed for childhood dog keeping and adult dog

acquisition(31). In our study, the negative association between dog ownership during childhood and sensitization to mixed pollen and inhalant allergens at age 6 was found in families with and without parental history of allergic disease. However, a stronger protective effect was observed in subjects with parental allergy. Since not all parents with a history of allergy also have pet especially dog allergy, we cannot rule out the possibility that dog avoidance may partly contributed to the observed protective effect.

In our study, no associations between dog ownership and dog contact during childhood and the prevalence of allergic disease and symptoms between age 4 and 6 were found. In the previous publication of the GINI study, however, a negative association between keeping a dog in the 1st year of life and the development of eczema in the 1st and the 2nd years of life was observed (23). When children grow older, they are more likely to have frequent contact with multiple triggers for allergic disease and symptoms, the observed protective effect in infancy may therefore disappear when the children are in school age. In addition, one might conclude that dog ownership during the first year of life is associated with a lower risk of early onset eczema, but this association disappeared beyond age of 2 years. Additional adjustment for cat ownership and cat contact did not strongly affect the estimated associations but with two exceptions. Within the GINI non-interventional study arm, children with frequent contact with dogs outside the domestic area are associated with a higher risk of being diagnosed of asthma and those children who ever had a dog up to 4 years of age seem to be more likely to have eczema symptoms. However, there are only 14, 27, 26 children who have had frequent contact with dog at age 1 and were diagnosed of having asthma at age 4, 5 and 6 respectively. Furthermore, this estimated association was not echoed by the estimated associations in the LISA and GINI intervention study arm nor was it echoed by the observed associations between dog ownership at age one and the development of asthma in all three study populations. We therefore argue that this estimation may reach the statistical significance level by chance and a conclusion need to be made cautiously. Similar argument can also be used for the estimated association between dog ownership up to age 4 and the prevalence of reported symptoms of eczema in the GINI non-interventional arm. Further investigation for the associations between dog ownership and dog contact and the development of allergic diseases at older age may provide more robust estimation. Finally, it is crucial to compare the effect of cat ownership and frequent contact with cats on the development of childhood allergy with the effect of dog ownership and frequent contact with dogs. The association between exposure to cat allergen and the development of allergy in children has been previously investigated in the Munich and Leipzig study population of the LISA study (32). It was observed that cumulative allergen exposure from cat ownership and regular cat contact during childhood increased the risk of cat sensitization up to age 6 years. Exposure to cat allergen during infancy, however, was only associated with cat sensitization at age 2 years. It was not associated with cat

sensitization at age 6 years or with allergic symptoms and diseases up to age 6 years. These two attempts to investigate the effect of exposure to pets on the development of allergy show substantial different effects from the two most popular family pets. Exposure to cat allergen during childhood directly increases the risk of developing cat sensitization in children while dog ownership during childhood is not associated with the development of dog sensitization in children and it negatively associates with the development of inhalant sensitization in children.

In the current study, we were not able establish how dog ownership leads to a lower atopy, especially the observation that dog ownership was associated with a lower prevalence of mix pollen and inhalant sensitization but not with sensitization to specific dog allergen. As we did not quantify the dog allergen Can f 1 level in the collected house dust samples, we could only use the information on dog ownership as a surrogate of dog allergen exposure. However, the observed protective effect is more likely due to other unknown factors associated with dog ownership. Dogs require more outdoor activities than most of the other pets. Dog fur is likely to carry wide range of microbes other than endotoxin from outdoor environment such as soil. Close contact with dogs at very young age may increase the exposure to variety of microbes and stimulate the maturation of the immune system. Keeping dogs also means a different life style that involves more outdoor activities, which may explain why such protective effect was not observed in children who only had regular contact with dogs outside the domestic area but were not dog owners. Furthermore, some families may have had their dog before the birth of the child. It has been observed in laboratory experiment on mice that prenatal plus postnatal exposure to endotoxin is associated with a robust shift toward predominantly T_H1 Immune response(33). This result corresponds to the finding that exposure to farm environment during pregnancy and the first year of life leads to a lower prevalence of allergy(34). It has also been observed in the LISA study that exposure to high levels of endotoxin is negatively associated with cord blood IgE level(35). Finally, Ownby et al have reported that exposure to only one dog is not sufficient to stimulate children's immune system. Exposure to 2 or more dogs or cats in the first year of life is associated with a lower risk of inhalant sensitization at age 7. Unfortunately, we do not have information on the number of pets in each household of our cohorts. Therefore, we are unable to replicate the analysis. The fact that more indoor pets is associated with higher level of endotoxin may indicate that the amount of endotoxin exposure in most of the homes with only one dog is not sufficient to cause a modification in the development of children's immune system. The household density where the dog owners live, on the other hand, had no effect on the negative associations between dog ownership and sensitization outcomes.

One difficulty in the interpretation of our results is that as every longitudinal cohort study, we have lost participants during the follow-up and some did not participate in the IgE test at age 6. Although parental history of allergic disease was negatively associated with the participation of the IgE measurement, the GINI non-interventional study arm, LISA study population, and GINI interventional study arm represented low, normal and high-risk children respectively. Furthermore, there was no difference between the dog ownership of the participants and non-participants. However, the results should be interpreted with caution.

In conclusion, our cohort studies provided evidence that dog ownership in early childhood protects against the development of inhalant sensitization but not allergic symptoms and diseases up to age 6. We also found that this protective effect could not be attributed to the simultaneous exposure to endotoxin or the avoidance measures. Further study on the effect of wider range of microbial exposure through dog ownership and prenatal exposure are in need.

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Table captions:

Table 1. Children's health outcomes and demographic characteristics

Table 2. Dog ownership and dog contact during childhood and sensitization to dog, mixed pollen, and inhalant allergens at age 6

Table 3a. Dog ownership and dog contact during childhood and the development of allergic symptoms and diseases

Table 3b. Dog ownership and dog contact during childhood and the development of allergic symptoms and diseases, additionally adjust for cat ownership and frequent contact with cats

Table 4. Dog ownership and dog contact childhood and sensitization to dog, mixed pollen, and inhalant allergens at age 6 by parental history of allergic disease

Table 5. Demographic characteristics between children with and without IgE measurements by study group

Figure 1. Consort Diagram of the GINI and LISA study

Table 1. Children's health outcomes and demographic characteristics

	LISA Study	GINI Non-Intervention	GINI Intervention	Total
	n/N(%)	n/N(%)	n/N(%)	n/N(%)
Sensitization to dog allergen at age 6	49/1193(4.1%)	43/945(4.6%)	64/1017(6.3%)	156/3155(4.9%)
Sensitization to mixed pollen at age 6	221/1193(18.5%)	182/945(19.3%)	238/1017(23.4%)	641/3155(20.3%)
Sensitization to inhalant allergens at age 6	318/1193(26.7%)	257/945(27.2%)	335/1017(32.9%)	910/3155(28.8%)
Doctor diagnosed allergic disease				
Eczema at age 4	229/2362(9.7%)	181/2379(7.6%)	193/1598(12.1%)	603/6339(9.5%)
at age 5	212/2179(9.7%)	177/2175(8.1%)	196/1663(11.8%)	585/6017(9.7%)
at age 6	187/2171(8.6%)	156/2083(7.5%)	171/1632(10.5%)	514/5886(8.7%)
Allergic Rhinitis at age 4	56/2353(2.4%)	50/2378(2.1%)	66/1601(4.1%)	172/6332(2.7%)
at age 5	90/2174(4.1%)	66/2179(3%)	120/1659(7.2%)	276/6012(4.6%)
at age 6	126/2165(5.8%)	77/2085(3.7%)	137/1632(8.4%)	340/5882(5.8%)
Asthma at age 4	23/2349(1.0%)	20/2383(0.8%)	32/1597(2%)	75/6329(1.2%)
at age 5	48/2173(2.2%)	34/2176(1.6%)	49/1664(2.9%)	131/6013(2.2%)
at age 6	45/2169(2.1%)	34/2088(1.6%)	53/1634(3.2%)	132/5891(2.2%)
Study Centre Munich	1467/3097(47.4%)	1784/3739(47.7%)	1165/2252(51.7%)	4416/9088(48.6%)
Leipzig	976/3097(31.5%)	n.a.	n.a.	976/9088(10.7%)
Wesel	348/3097(11.2%)	1955/3739(52.3%)	1087/2252(48.3%)	3390/9088(37.3%)
Bad Honnef	306/3097(9.9%)	n.a.	n.a.	306/9088(3.4%)
Parents had asthma, eczema, or hay fever	1585/2857(55.5%)	940/3656(25.7%)	2006/2241(89.5%)	4531/8754(51.8%)
Parental Education level[1] High	1966/3060(64.3%)	1984/3706(53.5%)	1432/2241(63.9%)	5382/9007(59.8%)
Medium	906/3060(29.6%)	1136/3706(30.7%)	614/2241(27.4%)	2656/9007(29.5%)
Low	188/3060(6.1%)	586/3706(15.8%)	195/2241(8.7%)	969/9007(10.8%)

Environmental Tobacco Smoke at home up to age 6	1049/2427(43.2%)	1265/2425(52.2%)	845/1657(51%)	3070/6498(47.3%)
Sex Male	1586/3097(51.2%)	1441/2814(51.2%)	1173/2252(52.1%)	4200/8163(51.5%)
Female	1511/3097(48.8%)	1373/2814(48.8%)	1079/2252(47.9%)	3963/8163(48.6%)

[1] The parental educational level was categorised based on the German educational system, less, equal, and more than grade 10. The higher education level from either parent was taken.

Table 2. Dog ownership and dog contact during childhood and sensitization to dog, mixed pollen, and inhalant allergens at age 6

		Adjusted model (OR (C.I.))[1] Sensitization outcome at age 6[2]		
		dog	**mixed pollen**	**inhalant allergen**
LISA	Dog ownership at age 1	0.9(0.4,2.6)	0.6(0.1,1.2)	0.6(0.3,1.0)
	Dog ownership at age 6	1.0(0.2,2.8)	0.7(0.3,1.3)	0.8(0.4,1.3)
	Dog ownership up to age 6	0.5(0.2,1.4)	0.6(0.4, 1.0)	0.6(0.3,0.9)
GINI OB	Dog ownership at age 1	1.7(0,4.2)	0.5(0.8,1.1)	0.5(0.2,0.9)
	Dog ownership at age 6	1.9(0.6,4.1)	1.1(0.2,1.8)	0.8(0.5,1.3)
	Dog ownership up to age 6	1.9(0.8,3.9)	0.8(0.7,1.3)	0.8(0.5,1.2)
GINI IN	Dog ownership at age 1	0.7(0,1.9)	0.5(0.4, 1.0)	0.5(0.3,0.9)
	Dog ownership at age 6	1.2(0.2,2.7)	0.6(0.2,1.0)	0.6(0.3,0.9)
	Dog ownership up to age 6	1.0 (0.4,2.1)	0.5(0.3,0.9)	0.5(0.3,0.8)
Total[4]	Dog ownership at age 1	1.1(0.5,1.9)	0.6(0.4,0.8)	0.5(0.4,0.7)
	Dog ownership at age 6	1.4(0.8,2.3)	0.8(0.6,1.1)	0.7(0.5, 1.0)
	Dog ownership up to age 6	1.1(0.7,1.8)	0.7(0.5,0.9)	0.6(0.5,0.8)
LISA	Dog Contact only at age 1[3]	1.4(0.4,2.9)	1.0(0.4,1.5)	0.9(0.6,1.2)
	Dog Contact only up to age 4[3]	0.8(0.7,1.7)	0.9(0.7,1.3)	0.8(0.6,1.1)
GINI OB	Dog Contact only at age 1[3]	0.9(0.4,1.9)	0.8(0.3,1.3)	1.0 (0.7,1.4)
	Dog Contact only up to age 4[3]	0.7(0.4,1.8)	0.8(0.55,1.3)	1.2(0.8,1.8)
GINI IN	Dog Contact only at age 1[3]	0.9(0.4,1.7)	1.0 (0.6,1.5)	0.9(0.6,1.3)
	Dog Contact only up to age 4[3]	1.2(0.4,2.2)	0.9(0.7,1.3)	0.9(0.6,1.3)
Total[4]	Dog Contact only at age 1[3]	1.0(0.7,1.6)	1.0 (0.76,1.2)	0.9(0.7,1.1)
	Dog Contact only up to age 4[3]	0.9(0.6,1.4)	0.9(0.7,1.1)	0.9(0.8,1.1)

[1] Adjusted for sex, study centre, parental educational level, and parental allergy

[2] Specific IgE titer >0.35kU/L to tested allergen

[3] Dog owners were excluded

[4] Additionally adjusted for studies

Table 3a. Dog ownership and dog contact during childhood and development of allergic diseases and symptoms between age 4 and 6

			Adjusted GEE model (OR (C.I.))[1]					
			LISA Study		GINI Observation		GINI Intervention	
			Dog Ownership	Dog Contact only[5]	Dog Ownership	Dog Contact only[5]	Dog Ownership	Dog Contact only[5]
Dog ownership and dog contact in the first year of life	Doctor diagnosed allergic disease	Asthma (4, 5, and 6 years)	1.5(0.6,3.9)	1(0.5,2.2)	2.1(0.9,5.0)	2.1(1.0,4.3)	0.9(0.4,2.2)	1.1(0.5,2.1)
		Allergic Rhinitis (4, 5, and 6 years)	0.5(0.2,1.2)	1.4(0.9,2.3)	0.9(0.4,2.0)	0.5(0.3,0.9)	0.8(0.4,1.6)	1.3(0.8,1.9)
		Eczema(4, 5,and 6 years)	0.6(0.4,1.1)	1.1(0.8,1.6)	1.2(0.8,1.9)	0.8(0.6,1.2)	1.0(0.6,1.6)	1.0(0.7,1.4)
	Symptoms of allergic disease	Asthma (4, 5, and 6 years)[2]	0.9(0.6,1.3)	1.3(1.0,1.8)	1.0(0.6,1.5)	0.9(0.7,1.3)	0.8(0.5,1.4)	1.0(0.7,1.5)
		Allergic Rhinitis (4, 5, and 6 years)[3]	1.1(0.8,1.6)	1.0(0.8,1.4)	1.4(0.9,2.0)	0.8(0.6,1.1)	0.7(0.4,1.1)	1.3(1.0,1.9)
		Eczema(4, 5,and 6 years)[4]	0.7(0.5,1.0)	1.1(0.8,1.4)	1.4(1.0,2)	0.8(0.6,1.1)	1.1(0.7,1.6)	1.0(0.7,1.3)
Dog ownership and dog contact in the first 4 years of life	Doctor diagnosed allergic disease	Asthma (4, 5, and 6 years)	1.2(0.5,3-0)	0.8(0.4,1.5)	1.5(0.7,3.4)	1.3(0.5,3.2)	0.8(0.3,1.8)	1(0.5,2)
		Allergic Rhinitis (4, 5, and 6 years)	0.5(0.2,1.0)	1.3(0.9,2.1)	0.8(0.4,1.6)	1.2(0.7,2.0)	0.8(0.4,1.5)	1.1(0.7,1.7)
		Eczema(4, 5,and 6 years)	0.7(0.4,1.0)	1.0(0.8,1.4)	1.2(0.8,1.8)	1(0.7,1.5)	0.7(0.5,1.2)	1.0(0.7,1.4)
	Symptoms of allergic disease	Asthma (4, 5, and 6 years)[2]	1.0(0.7,1.4)	1.0(0.8,1.4)	1.1(0.8,1.5)	1.1(0.8,1.6)	1.2(0.8,1.8)	1.2(0.8,1.8)
		Allergic Rhinitis (4, 5, and 6 years)[3]	0.9(0.6,1.3)	1.1(0.8,1.4)	1.1(0.8,1.6)	1.1(0.8,1.49)	0.8(0.6,1.2)	1.2(0.8,1.6)
		Eczema(4, 5,and 6 years)[4]	0.7(0.5,1.0)	1.0(0.8,1.2)	1.4(1.0,1.9)	1.0(0.8,1.4)	0.9(0.6,1.3)	0.9(0.7,1.2)

[1] Adjusted for sex, study centre, parental educational level, and parental allergy

[2] Defined as wheezing sound in the chest

[3] Defined as sneezing, running nose, or nasal congestion without cold

[4] Defined as itchy rash that effected skin crease, face, neck, extremities, hands, or feet.

[5] Dog owners were excluded

Table 3b. Dog ownership and dog contact during childhood and development of allergic diseases and symptoms between age 4 and 6, additionally adjust for cat ownership and frequent contact with cats

			Adjusted GEE model (OR (C.I.))					
			LISA Study		GINI Observation		GINI Intervention	
			Dog Ownership	Dog Contact only[6]	Dog Ownership	Dog Contact only[6]	Dog Ownership	Dog Contact only[6]
Dog ownership and dog contact in the first year of life[1]	Doctor diagnosed allergic disease	Asthma (4, 5, and 6 years)	1.6(0.6,4.0)	1(0.4,2.3)	2.1(0.9,5.0)	2.5(1.2,5.4)	0.7(0.3,1.9)	1(0.5,1.9)
		Allergic Rhinitis (4, 5, and 6 years)	0.5(0.2,1.3)	1.5(0.9,2.4)	0.9(0.4,2.0)	0.5(0.3,0.9)	0.7(0.3,1.4)	1.3(0.8,2)
		Eczema(4, 5,and 6 years)	0.7(0.4,1.2)	1.1(0.8,1.6)	1.2(0.8,2.0)	0.8(0.5,1.2)	1.0(0.6,1.6)	0.9(0.6,1.3)
	Symptoms of allergic disease	Asthma (4, 5, and 6 years)[3]	0.9(0.6,1.39)	1.3(0.9,1.8)	0.9(0.6,1.4)	1(0.7,1.4)	0.9(0.5,1.4)	1(0.7,1.4)
		Allergic Rhinitis (4, 5, and 6 years)[4]	1.1(0.8,1.7)	1.1(0.8,1.5)	1.4(0.9,2.0)	0.9(0.6,1.2)	0.6(0.4,1.0)	1.4(1.0,1.9)
		Eczema(4, 5,and 6 years)[5]	0.7(0.5,1.0)	1(0.8,1.3)	1.4(1.0,2.07)	0.8(0.6,1.1)	1.0(0.7,1.6)	0.9(0.7,1.3)
Dog ownership and dog contact in the first 4 years of life[2]	Doctor diagnosed allergic disease	Asthma (4, 5, and 6 years)	1.1(0.4,2.8)	0.7(0.4,1.5)	1.9(0.8,4.3)	1.5(0.5,4)	0.8(0.3,2)	1(0.5,1.9)
		Allergic Rhinitis (4, 5, and 6 years)	0.5(0.2,1.2)	1.2(0.8,2)	0.8(0.4,1.6)	0.9(0.5,1.7)	0.7(0.3,1.4)	0.9(0.6,1.5)
		Eczema(4, 5,and 6 years)	0.7(0.4,1.1)	1(0.7,1.4)	1.4(0.9,2.1)	1(0.6,1.5)	0.6(0.4,1.1)	0.9(0.6,1.4)
	Symptoms of allergic disease	Asthma (4, 5, and 6 years)[3]	0.9(0.6,1.3)	1(0.7,1.3)	1(0.7,1.5)	1.1(0.8,1.6)	1.2(0.8,2)	1.3(0.9,2)
		Allergic Rhinitis (4, 5, and 6 years)[4]	0.8(0.6,1.2)	1.1(0.8,1.4)	1.2(0.8,1.7)	1(0.7,1.4)	0.9(0.6,1.3)	1.1(0.8,1.5)

		Eczema(4, 5,and 6 years)[5]	0.7(0.5,1)	1.1(0.8,1.3)	1.5(1.1,2.1)	1.1(0.8,1.5)	0.8(0.5,1.2)	0.9(0.6,1.2)

1. Adjusted for sex, study centre, parental educational level, parental allergy, cat ownership at age 1, and frequent contact with cat outside the domestic area at age 1

2. Adjusted for sex, study centre, parental educational level, parental allergy, cat ownership up to age 4, and frequent contact with cat outside the domestic area up to age 4

3 Defined as wheezing sound in the chest

4 Defined as sneezing, running nose, or nasal congestion without cold

5 Defined as itchy rash that effected skin crease, face, neck, extremities, hands, or feet.

6 Dog owners were excluded

Table 4. Dog ownership and dog contact during childhood and sensitization to dog, mixed pollen, and inhalant allergens at age 6 stratified by parental history of allergic disease

	Adjusted model (OR (C.I.))[1]					
	Sensitization to dog at age 6[2]		**Sensitization to mixed pollen at age 6[2]**		**Sensitization to inhalant allergen at age 6[2]**	
	Parental allergy[4]		Parental allergy[4]		Parental allergy[4]	
	Yes	No	Yes	No	Yes	No
Dog ownership at age 1	0.7(0.2,1.5)	1.7(0.6,4.0)	0.5(0.3,0.8)	0.6(0.3,1.1)	0.4(0.3,0.7)	0.6(0.3,1.0)
Dog ownership at age 6	1.3(0.6,2.4)	1.7(0.7,3.8)	0.6(0.4,1)	1.0(0.6,1.6)	0.6(0.4,0.9)	0.8(0.5,1.2)
Dog ownership up to age 6	0.9(0.4,1.6)	1.6(0.7,3.5)	0.5(0.3,0.8)	0.8(0.5,1.2)	0.5(0.4,0.8)	0.7(0.5,1.0)
Dog Contact only at age 1[3]	1.1(0.6,1.7)	0.9(0.4,2.3)	1.0(0.7,1.3)	0.9(0.6,1.3)	1.0(0.7,1.3)	0.8(0.6,1.2)
Dog Contact only up to age 4[3]	1.0(0.6,1.6)	0.7(0.3,1.7)	0.9(0.7,1.2)	0.9(0.6,1.4)	0.9(0.7,1.2)	0.9(0.7,1.4)

[1] Adjusted for sex, study centre, parental educational level, and studies.

[2] Specific IgE titer >0.35kU/L to tested allergen

[3] Dog owners were excluded

[4] Defined as parent has asthma, eczema, or hay fever

Table 5. Demographic characteristics between children with and without IgE measurements at age 6 by study

		Proportion of children who had IgE measurement at age 6 by demographic characteristics	
		LISA n^1/N^2(%)	**GINI n^1/N^2(%)**
Dog ownership at age 6	yes	105/211(50%)	216/446(48%)
	No	1083/1977(55%)	1739/3411(51%)
Parents had asthma, eczema, or hay fever	Yes	460/1272(36%)*	766/2951(26%)*
	No	655/1585(41%)	1179/2946(40%)
Parental Education level[1]	High	554/1263(44%)*	757/1957(39%)*
	Medium	446/1191(37%)	686/1930(36%)
	Low	1827606(30%)	517/2060(35%)
ETS at home up to age 6	Yes	396/1049(38%)*	780/2021(39%)*
	No	762/1378(55%)	1080/2050(53%)

[1] Number of children who had IgE measurement at age 6

[2] Number of children who had IgE measurement at age 6 + number of children who did not have IgE measurement at age 6

* Chi-square test, p-value<0.05.
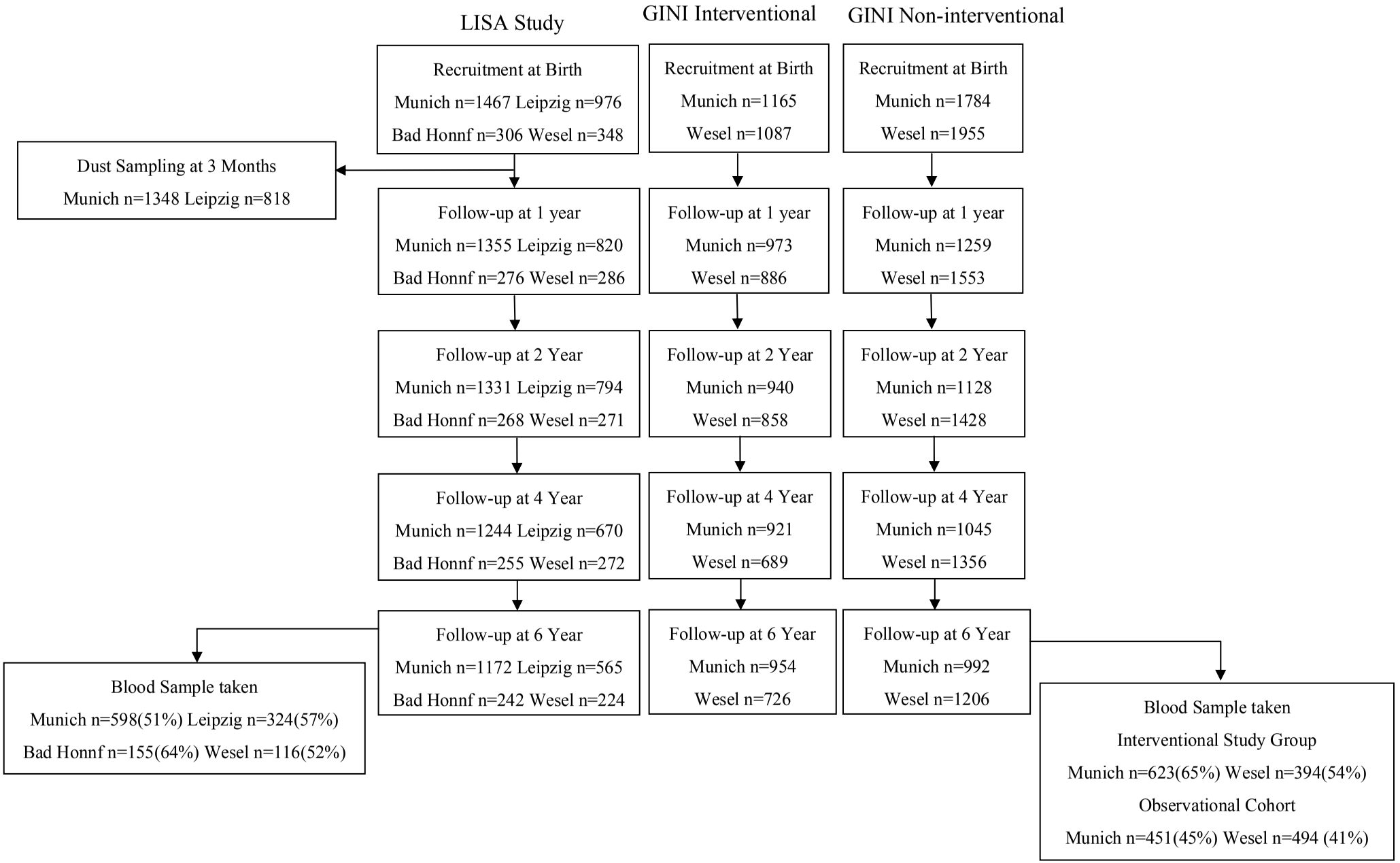
Figure 1. Consort Diagram of the GINI and LISA study