Molds, Parental Atopy and Pediatric Incident Asthma

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A POINT-BY-POINT RESPONSE

Re: ID INA-11-03-066 entitled "Molds, Family History of Atopy and Pediatric Incident Asthma,"

Reviewer: 1
Comments to the Author
Major concern: The two interacting factors (parental allergy and environmental dampness) are not independent factors. In a country where house dust mite is the most important allergen (>95% of asthmatic children), parents, who share the household environment with their children, are expected to be exposed to the same allergenic stimulation and hence have or have not allergy due to the shared dampness. The parental allergy hence cannot be considered as an independent factor from environmental dampness. The results of this paper hence may simply show that environmental dampness increases the allergic presentation in both parents and children. The possibility needs to be addressed in the result section and in the discussion section.

We address this issue of two interaction factors (parental atopy and home dampness) are not independent factors in the results section and discussion section on page 7, and 10 respectively.

Minor points: Professional English edition may be still helpful.

We have asked English native speaker for proofreading.

Reviewer: 2
Comments to the Author
Comments have been addressed by the authors.

Reviewer: 3
Comments to the Author
Major concern 1: The method for random sampling is not addressed. It is not enough to just state "—we approached a random sample of---."

We have addressed the method for random sampling in the method section (page 3).

Major concern 2: The outcome (cumulative incidence) cannot justify the method used. The control group in a matched case-control study is a biased sample of the source population.

We agreed the matched case-control study may be biased sample of the source population. To avoid bias effect estimation, we deleted the cumulative incidence and estimated matched pair odds ratio applying conditional logistic regression in tables 2-5.

Major concern 3: Again, the control group in a matched case-control study is a biased sample of the source population. The authors need to explain why crude cumulative incidence rate ratio is quite different from the crude estimate by conditional logistic regression.

As mention above, we estimated matched odds ratio applying conditional logistic regression. We also added Rothman synergy index and it's 95% confidence interval to assess the interaction between parental atopy and home dampness in addictive scale on pages 5-7.

ABSTRACT

To assess the independent and joint effects of parental atopy and exposure to molds on the development of asthma in childhood, the authors conducted a cohort based, incident case-control study in 2008. The case group consisted of 188 children with new asthma and the control group (n=376) was matched one to two for age and sex. The outcome of interest was the development of asthma during the study period. The studied determinants were parental atopy and three indicators of exposure including histories of water damage, presence of visible molds, and perceived mold odor in the home at baseline in 2002. In conditional logistic regression adjusting for confounding, parental atopy (adjusted odds ratio [aOR] 3.29, 95% CI 2.19-4.94) and the presence of mold odor (aOR 2.09, 95 % CI 1.30-3.37) and visible mold (aOR 1.76, 95 % CI 1.18-2.62) were independent determinants of incident asthma, and apparent interaction in additive scale was observed. Our finding suggests the interaction between parental atopy and molds may play a role in the development of asthma in children.

Practical Implication

Our study strengthens the evidence for the roles of indoor dampness problem and parental atopy as determinants of asthma in children. Furthermore, the interaction between parental atopy and exposure to molds suggests a role for the development of childhood asthma i.e. the children whose parents had atopic disease and molds exposure are more susceptible to develop asthma.

Key words: molds, childhood asthma, interaction, effect modification, incidence, cohort

Abstract: 173 words

Introduction

Since the late of 1980s, there is a series of epidemiological studies from Scotland (Strachan and Sanders 1989), the Netherlands (Brunekreef 1992), Sweden (Andrae et al., 1998), Finland (Jaakkola et al., 1993), Italy (Pirastu et al., 2009), USA (Brunekeef et al., 1989), Canada (Dales et al., 1991), and Taiwan (Yang et al., 1997). These studies consistently reported the association between dampness and mold problems in the home and the risk of asthma in children. A recent review of 22 studies in children suggested that home dampness and molds are associated with approximately increases of 30% in asthma (Fisk et al., 2007).

The previous evidences were mainly based on cross-sectional or case-control studies with prevalent rather that incident cases, where establishment of causal relationship between exposure and outcome is problematic. Sahakian et al. (2008) suggest that the effect of asthma development on the home dampness and mold should be studied through additional prospective studies. In our systematic Medline search, we identified only three previous longitudinal studies (Belanger et al., 2003; Jaakkola et al., 2005; Wickman et al., 2003) and a population-based incident case-control study (Pekkanen et al., 2007) which investigated exposure prior to the onset of asthma or asthma-related outcomes in children, and a cohort-based matched case-control study (Nafstad et al., 1998) where the exposure assessment was carried out within two weeks from the diagnosis. All the five studies reported that early exposure to dampness and molds problems increase the incidence of asthma (Jaakkola et al., 2005; Pekkanen et al., 2007; Wickman et al., 2003) and asthma-related symptoms and signs, such as cough and wheezing (Belanger et al., 2003), and bronchial obstruction during the first two years of life (Nafstad et al., 1998). However, potential modification or interaction between exposure to molds and development of asthma by genetic propensity to asthma (i.e. gene-environment interaction) remains inconclusive. One of these studies provided evidence that the effect of mold exposure is stronger on children whose mother has asthma for cough and wheezing (Belanger et al., 2003). The other study reported that no apparent interaction between

mold odor and parental atopy was observed for asthma in children (Jaakkola et al., 2005). We assumed that parents with asthma, allergic rhinitis or atopic eczema give their children a large set of genes that increase the child's susceptibility to the effects of environmental factors on asthma. We used parental atopy as a measure of genetic propensity to asthma.

We conducted a cohort based, incident case-control study to investigate the relationship between indicator of exposure to molds and the development of asthma. This design enabled to establish an appropriate temporality between the hypothesized exposure and outcome. Furthermore, we tested the hypothesis that the joint effect of parental atopy and environmental exposure on the risk of childhood asthma is more than expected on the basis of their independent effects.

Methods

Data collection and study design

The source population comprised all 44,385 children aged 1-7 years in Taoyuan, born between January 1, 1995 and December 31, 2002. Taoyuan is an urban-suburban municipality, with a population of 397,056 in 2008, located across the north-western border of Taiwan. In the October 2002 baseline survey, a modified Chinese version of The International Study of Asthma and Allergies in Childhood (ISAAC-C) questionnaire was used to collect information on children's health, environmental exposures, and other relevant factors (Asher et al., 1995). The parents or other guardians were asked about children's personal characteristics, health, details of the environment, and other relevant factors (Table 1). We applied proportionate stratified sampling from source population focusing on 1-7 years children (approximately 10% in each age category) and approached a random sample of 2,253 children. The response rate was 85.3%. We excluded 331 children with asthma (n=220) and incomplete questionnaire (n=111). The study population included 1,922 children free of asthma at baseline.

In October 2008, we conducted a cohort-based incidence case-control study. We identified 188 newly diagnosed asthma cases during the study period between October 15, 2002

and October 31, 2008. Children who did not develop doctor- diagnosed asthma were selected as controls applying one-to-two matching for age and sex since 2002 from 1,922 children. The final study population consisted of 188 cases and 376 controls. The study protocol was approved by the Institutional Review Board of China Medical University, and it complied with the principles outlined in the Helsinki Declaration.

Parental atopy and environmental determinants of interest

Parental atopy was a measure of genetic predisposition to asthma and it was defined as the father or mother of the index child ever having been diagnosed as having asthma, allergic rhinitis, or atopic eczema at baseline. We used three indicators of exposure defined from the answers to following structured questions at the baseline in 2002:

Mold odor. "Have you perceived mold odor in your dwelling during the past 12 months?" (No; Yes, almost daily; Yes, 1-3 days a week; Yes, 1-3 days a month; Yes, less often.)

Visible mold. "Have your ever had visible mold in your dwelling?"(No; Yes, during the past 12 months; Yes, only earlier.)

Water damage. "Have you ever had water damage in your dwelling?" (No; Yes, during the past 12 months; Yes, only earlier.)

Any exposure indicator. Presence of any of the three exposure indicators.

We decided to focus on exposures documented prior to the study period to ensure a plausible temporal sequence between exposure and the studied outcome for the causal inference.

Covariates

Information on potential confounders was obtained from the baseline questionnaire. The covariates in the present analyses included parental atopy, parental education, duration of breastfeeding, daily time spent in outdoors, furry/feathery pets and environmental tobacco smoke (ETS) (Table 1). The duration of breastfeeding was categorized into i) less than 1 months, ii) 2 to 3 months and iii) 4 months or longer. Other covariates were dichotomous.

Statistical methods

First, we estimated the incidence rate of asthma during the 6-year study period according to parental atopy and indicators exposure to dampness and molds. We also assessed how parental atopy, including parental asthma, allergic rhinitis and atopic eczema, alone predicted asthma incidence. In the crude analysis, odds ratios of the relationship between exposure and outcome relations were estimated. We estimated adjusted odds ratios applying conditional logistic regression analysis. The odds ratios were adjusted for the covariates as described above.

Second, we studied the joint effects of parental atopy and the two most relevant exposure indicators, namely 'mold odor' and 'visible mold' on the risk of asthma on an additive scale (Greeland and Rothman 1998). We compared the risk (OR) of asthma in four exposure categories: 1) no parental atopy and no exposure ($OR_{00,}$ reference category); 2) parental atopy and no exposure (OR_{10}); 3) no parental atopy and exposure (OR_{01}); and 4) parental atopy and exposure (OR_{11}). On an additive scale, the interaction of two factors was quantified by calculating the Rothman synergy index (Rothman 1976) and its 95% CI was calculated to investigate the joint effect of the two factors. The synergy index (S) is equal to the calculation of $[OR_{11}-1] / [(OR_{10}-1)+(OR_{01}-1)]$. An observed synergy index value that departs substantially from the expected additive null, i.e., synergy index not equal to 1, suggests an additive interaction effect. The OR values and their variance covariance matrix were then used to calculate values for synergy index and 95% CIs (Hosmer and Lemeshow 1992).

Then we used the odds ratio as a measure of effect and estimated adjusted odds ratios as above adjusting for the covariates as described above. To assess the joint effect of parental atopy and exposure, we calculated odds ratios contrasting each of the three exposure categories to the reference category. Estimates for the independent effects of parental atopy and exposure and their joint effect were derived from the same conditional logistic regression model adjusting for the covariates.

Results

Characteristics of case and control subjects

Table 1 compared the demographic and environmental characteristics between cases and controls at baseline. Comparing with the controls, the cases who had lower duration of breastfeeding and spent more time outdoors were more commonly exposed to cockroaches (94.7 vs. 90.2%) and furry or feathery pets (30.3 vs. 27.1%) in the home.

Effects of parental atopy and exposure to dampness and mold problems

Parental atopy was a significant determinant of asthma with an adjusted odds ratio of 3.29 (95% CI 2.19-4.94). Table 2 also showed parental asthma (adjusted OR 5.31, 95% CI 2.72-10.4) and allergic rhinitis (adjusted OR 3.14, 95% CI 2.07-4.79) as predictors of asthma in children.

Table 3 presented the odds ratios according to the three exposure indicators at baseline compared to the reference category of no exposure. The risk of asthma was associated with any indicator of exposure (adjusted OR 1.69, 95% CI 1.67-2.45), presence of mold odor (adjusted OR 2.09, 95% CI 1.30-3.39) and visible mold (adjusted OR 1.76, 95% CI 1.18-2.62). The risk of asthma during the study period was not related to water damage.

Joint effect of parental atopy and exposure to mold odor and visible mold

Table 4 showed the effects of parental atopy and exposure to mold odor, and their joint effect on the risk of asthma. In children without exposure to mold odor, parental atopy alone significantly increased the risk of asthma with an adjusted odds ratio of 2.53 (95% CI 1.22 – 5.24) (Table 4). The effect of mold odor exposure in children with no parental atopy also increased with an OR of 1.60 (95% CI 0.84-3.05). In children with both parental atopy and exposure to mold odor, the adjusted OR of asthma was 4.11 (95% CI 2.22-7.64). The Rothman synergy index [(4.11-1)/((2.53-1)+(1.60)-1))] was 1.46 (95% CI 1.13-1.88) substantially greater than 1. Thus, the interaction on an additive scale was observed.

Table 5 indicated that joint excess risk from parental atopy and exposure to visible mold (4.10=5.10-1) was of larger magnitude as the sum (3.09) of the independent excess risks for

parental atopy (2.54=3.54-1) and exposure to visible mold (0.55=1.55-1). The Rothman synergy index was 1.33 (95% CI 1.09-1.61) departs substantially from the expected additive null. Thus, there was evidence of interaction between parental atopy and visible mold.

Our results showed that there existed an additive interaction between parental atopy and home dampness. Since parents might share the household environment with their children, who are expected to get exposed to the same home dampness, we were not be able to consider the two interacting factors are independent factors. Thus, it implied that exposure to mold odor or visible mold may increase the allergic presentation in both parents and children.

Discussion

The current study found there existed approximately 100% and 70% increased risk of development of asthma for children living in homes with mold odor or visible mold respectively. The history of water damage did not predict asthma. Parental atopy increased asthma risk over 200%. The results indicated that the joint effect of parental atopy, representing indirectly genetic constitution, and exposure to mold odor or visible was stronger than expected on the basis of their independent effects in additive scale.

Validity of results

A cohort-based incident case-control study, offered an appropriate approach to assess the role of mold problems on the development of asthma. The prospective study design eliminated selection bias, if the parents of children with asthma are more likely to change housing conditions after the first symptoms and signs of asthma compared with parents of healthy children.

The limitation of the present study is the exposure assessment was based on parental reporting rather than objective measurements. Objective measurements were not yet used in any of the epidemiologic studies conducted at the time of the data collection. Visual observation by a trained person would also have improved the exposure assessment (Pekkanen et al., 2007). However, our exposure information was collected at baseline before the onset of

the asthma and therefore any bias due to awareness of the disease or exposure to molds will be minimized.

Our outcome assessment was based on reported doctor-diagnosed asthma rather than clinical examination for the purposes of the study. This is a possible source of misclassification of outcome, which is likely to be random, that is, not related to the exposure of interest at baseline, and thus it could lead to underestimation of the effect. Important features in the Taiwan national health care system limit the amount of outcome misclassification. Taiwanese children are almost all covered by health insurance (>99%) and have easy and free access to medical consultation. The diagnoses are approved centrally by the Bureau of National Health Insurance when applying for subsidizes, which reduces heterogeneity in diagnostic practice.

We were able to take into account most of the known potential confounders related to individual characteristics and other environmental exposure in the condition logistic regression analysis, where most of the known determinants were included. However, dampness problems may also be related to other indoor environmental factors than molds, such as house dust mite. Dampness problems may also imply low ventilation rate and consequently increase the levels of indoor pollutants such as diisononyl phthalate (DiNP), diisodecyl phthalate (DiDP), and di-2-ethyl-hexyl phthalate (DEHP) from interior surface and food wrappers (Jaakkola et al., 2008) Any known or unknown factors such as lipopolysaccharide (LPS) and its bioactive moiety endotoxin exposure (Simpson and Martinez 2009), diet (Allan and Devereux 2011), physical activity, occupational status, air exchange, penetration, deposition, as well as emission strengths for outdoor pollutants could be responsible for the observed association. We cannot rule out these unmeasured factors that likely influence our results.

Synthesis with the previous knowledge

We identified only three previous prospective cohort or incident case-control studies with incident asthma in children as the outcome of interest (Jaakkola et al., 2005; Pekkanen et al., 2007; Wickman et al., 2003). First, Wickman and colleagues conducted a population-based

birth cohort study of 4089 children in Stockholm, where they reported an increased risk of asthma among children in damp home environment during the first two years of life compared with unexposed with an adjusted odds ratio of 1.75 (95% CI 1.26-2.43). The exposure was defined as smell and visible signs of mold, water damage inside construction, and persistent windowpane condensation in dwellings with double-glazing (Wickman et al., 2003). Jaakkola and colleagues conducted a 6-year cohort study of 1916 children in Finland using self-reported exposure. The results indicated an association between the risk of asthma and mold odor with an adjusted incidence rate ratio of 2.44 (95% CI 1.07-5.60), but not visible mold, and water damage (Jaakkola et al., 2005).The incident case-control study conducted by Pekkanen and colleagues in Finland found the presence of visible mold and moisture damage in main living parts increase the risk of asthma (Pekkanen et al., 2007). The current study strengths the evidence that home dampness due to mold odor or visible mold increase the risk of the development of asthma in childhood.

The specific causal agents of asthma related to indoor dampness and mold problems are not well known, and several possible causes have been suggested including molds, bacteria, house dust mites, and enhanced emission of chemicals from surface materials. Our results suggest that mold odor and visible mold are important indicators of relevant exposure rather than water damage per se. Several biological mechanisms by which indoor molds, particular concerning Penicillium, Aspergillus, Cladosporium and Alternaria could induce asthma have been suggested including immunoglobulin E (IgE) or immunoglobulin G (IgG)-mediated hypersensitivity reactions, toxic reactions caused by mycotoxins, and non-specific inflammatory reactions caused by irrigative volatile organic compounds produced by microbes (MVOCs) or cell wall components, such as 1, 3-ß-D-glucan and ergosterol (Etzel 2003; Johanning et al., 1999; Husman 1996; Norbäck et al., 1999; Thorn and Rylander 1998). It is possible that different species of molds induce asthma by different mechanisms or that several mechanisms are involved.

There is previous evidence that parental atopic diseases are important risk factors of asthma (Jaakkola et al., 1991; Laitinen et al., 1998; von Mutius et al., 1994). We found parental asthma and allergic rhinitis to be the strong determinants of developing asthma in childhood. The results also show that the joint effect of hereditary atopy representing indirectly genetic constitution and exposure to molds is stronger than expected on the basis on the basis of their independent effects in additive scale. This phenomenon- effect modification of home dampness and exposure to molds (environment) by genetic constitution, or gene by environment- suggests that some genetic markers could indicate susceptibility to environmental factors. Identification of these markers and exposure to molds derived components is an interesting challenge for future studies.

There has a long-standing debate on whether the scale should be determined by the statistical model that fits best or whether interaction should be assessed on an additive scale irrespectively of the underling statistical model. It has been suggested that the additive scale is more appropriate to assess "biologic interaction" which is implied by terms such as synergism or antagonism (Knol et al., 2009). An important rationale for presenting the interaction in the additive scale is that it fits with the sufficient-component concept of causality (VanderWeele and Robins 2007). Also, the additive scale which uses absolute risks may also be more appropriate for public health and clinical decision making (Kaufiman 2009).

In Taiwan, house dust mite is common allergens (>52% of asthmatic children) (Tang et al. 1990). Parents may share the household environment with their children, who are expected to be exposed to the same allergenic stimulation and hence have or have not allergy due to the shared dampness. The parental atopy may not be considered as an independent factor from home dampness. Our finding may simply show that environmental dampness increases the allergic presentation in both parents and children.

Conclusions

Our results are consistent with the hypothesis that parental atopy and molds play an important role in childhood asthma. Our finding indicates a role of interaction between parental atopy and molds exposure on the development of childhood asthma. The results provide further evidence that children whose parents had atopic disease are more susceptible to exposure to molds and more likely to develop asthma. Preventive intervention against dampness and molds in homes should be implemented without any delay, particularly those children whose parents have atopic disease.

Acknowledgements

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Table 1. Comparisons of both demographic and environmental characteristics of cases and controls at baseline.

Categories	Cases n=188 (%)	Controls n=376 (%)	OR (95%CI)
Highest level of parental education (years)			
≤9	13 (6.9)	23 (6.2)	Reference
10-12	76 (40.4)	173 (46.4)	0.88 (0.43-1.80)
13-16	87 (46.3)	158 (42.4)	1.10 (0.54-2.25)
≥l7	12 (6.4)	19 (5.1)	1.26 (0.47-3.37)
Daily time spent in outdoor (hours)			
≥5	21 (11.2)	34 (9.0)	Reference
2-4	107 (56.9)	202 (53.7)	0.86 (0.47-1.55)
≤ 1	60 (31.9)	140 (37.2)	0.69 (0.37-1.29)
Duration of Breastfeeding (months)			
< 1	147 (78.2)	264 (70.2)	Reference
1-5	29 (15.4)	81 (21.5)	0.66 (0.41-1.04)
≥ 6	12 (6.4)	31 (8.3)	0.69 (0.34-1.40)
Cockroaches			
No	10(5.3)	37(9.8)	Reference
Yes	178(94.7)	339(90.2)	1.94(0.94-4.00)
Furry/feathery pets			
No	131(69.7)	274(72.9)	Reference
Yes	57(30.3)	102(27.1)	1.17(0.80-1.72)
Environmental Tobacco Smoke			
No	76(40.4)	152(40.4)	Reference
Yes	112(59.6)	224(59.6)	1.00 (0.70-1.43)

Table 2. Parental atopy, asthma, allergic rhinitis, and atopic eczema in the relation to asthma incidence.

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Determinant	Size of the group	No of new asthma cases	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
Parental atopy				
No	352	84	1.00	1.00
Yes	212	104	3.30 (2.22-4.90)	3.29 (2.19-4.94)
Parental asthma				
No	513	154	1.00	1.00
Yes	51	34	4.57 (2.44-8.54)	5.31 (2.72-10.4)
Parental allergic rhinitis				
No	391	100	1.00	1.00
Yes	173	88	3.22 (2.15-4.83)	3.14 (2.07-4.79)
Parental atopic eczema				
No	529	174	1.00	1.00
Yes	35	14	1.36 (0.68-2.73)	1.41 (0.69-2.89)

*Conditional logistic regression controlling for parents' highest education, duration of breastfeeding, daily time spent in outdoor , presence of hairy or feathery pets at home and exposure to environmental tobacco smoke (ETS).

Table 3. Incidence rates of asthma in the different exposure categories and incidence rate ratios calculated contrasting the reference category and adjusted for confounding in conditional logistic regression analysis.

Exposure at baseline	Size of the group	No of new asthma cases	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
No exposure (reference)	244	63	1.00	1.00
Any exposure indicator	320	125	1.80 (1.25-2.57)	1.69 (1.67-2.45)
Mold odor	200	83	2.20 (1.41-3.43)	2.09 (1.30-3.37)
Visible mold	263	107	1.82 (1.25-2.64)	1.76 (1.18-2.62)
Water damage	20	10	2.57 (0.65-10.1)	2.80 (0.59-13.3)

*Conditional logistic regression controlling for parents' highest education, duration of breastfeeding, daily time spent in outdoor , presence of hairy or feathery pets at home and exposure to environmental tobacco smoke (ETS).

Table 4. Independent and joint effects of hereditary atopy and exposure to mold odor on the development of asthma.

Exposure category	Size of the group	No of new asthma cases	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
No parental atopy, No exposure	171	34	1.00	1.00
Parental atopy, No exposure	73	29	2.48 (1.24-4.96)	2.53 (1.22-5.24)
No parental atopy, Mold odor	108	32	1.63 (0.89-2.99)	1.60 (0.84-3.05)
Parental atopy, Mold odor	92	51	4.29 (2.39-7.70)	4.11 (2.22-7.64)

* Conditional logistic regression controlling for parents' highest education, duration of breastfeeding, daily time spent in outdoor , presence of hairy or feathery pets at home and exposure to environmental tobacco smoke (ETS).

Table 5. Independent and joint effects of hereditary atopy and exposure to visible mold on the development of asthma.

Exposure category	Size of the group	No of new asthma cases	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
No parental atopy, No exposure	137	34	1.00	1.00
Parental atopy, No exposure	73	29	3.15 (1.64-6.04)	3.54 (1.76-7.11)
No parental atopy, Visible mold	145	42	1.45 (0.85-2.47)	1.55 (0.87-2.77)
Parental atopy, Visible mold	118	65	5.08 (2.88-8.94)	5.10 (2.80-9.31)

* Conditional logistic regression controlling for parents' highest education, duration of breastfeeding, daily time spent in outdoor , presence of hairy or feathery pets at home and exposure to environmental tobacco smoke (ETS).