Comorbidity of ADHD and allergic diseases in early adolescence: the role of parental smoking at home

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Abstract

A growing body of research suggests an association between attention deficit hyperactivity disorder (ADHD) and allergic disorders, but little work has been done to explore the role of external factors such as parental smoking at home in the development of comorbid ADHD and allergic disorders. This study aimed to examine the association between allergic diseases and ADHD in early adolescents after adjusting for exposure to parental smoking at home. We recruited 250 male (41.7%) and 350 female (58.3%) adolescents (mean [SD] age, 13.29 [0.52] years) via chain-referral sampling. Their ADHD symptoms were assessed by the parent proxy-report version of the Chinese Strengths and Weaknesses of Attention-Deficit/Hyperactivity-symptoms and Normal-behaviours (SWAN) rating scale. Data on the participants' history of clinician-diagnosed allergic diseases, family socio-demographics, and parental smoking habit were collected using a parent-completed questionnaire. Regression analyses were performed to examine the associations of interest. The levels of ADHD symptoms were comparable between allergic and non-allergic participants after controlling for child and family demographics and parental smoking at home. Notably, the risk of probable ADHD was particularly high in participants with food allergies (odd ratio=4.51, p=0.011) but not in those with allergic rhinitis after adjusting for parental smoking at home. Our findings suggest that second-hand smoke exposure at home is a potential risk factor underlying the link between ADHD and allergic diseases. Current management guidelines should encourage the practice of early identification and cessation of tobacco smoke exposure for prevention of comorbidity of ADHD and allergic disorders.

Keywords: allergic disease; attention deficit hyperactivity disorder; comorbidity; second-hand smoke exposure; environmental allergen

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of childhood and adolescence. Individuals high in symptoms of ADHD encounter more challenging academic and social situations that could have lifelong effects on health and well-being (Faraone et al., 2003; Gillberg et al., 2004). While the exact aetiology of ADHD is not entirely clear, emerging research reveals a complex underlying mechanism involving the interplay of genetic (e.g., dopaminergic and noradrenergic neurotransmitter deficiencies) and environmental factors (e.g., physical and emotional trauma during birth and early childhood) (Biederman & Faraone, 2005; Faraone et al., 2014; Faraone et al., 2005; Yüksel et al., 2021). Currently, 7.2% of children worldwide are living with ADHD (Thomas et al., 2015). A previous study found that Chinese schoolboys from Grades 7, 8 and 9 of mainstream high schools in Hong Kong exhibited an above-average prevalence of 8.9%, with a prevalence of 3.9% observed among early adolescents (Leung et al., 2008; Leung et al., 1996).

The comorbidity of ADHD and allergies

Numerous studies, including meta-analyses (Miyazaki et al., 2017; Schans et al., 2017), have shown an association between ADHD and allergies. These diseases are clinical syndromes relating to immunological dysregulation, including hypersecretion of Ig-E, increased eosinophilic activity, and a predominantly T helper type 2 (Th2) cytokine over-secretion (Chen et al., 2013; Pelsser et al., 2009). A study of 8,201 participants from the Taiwan National Health Insurance Research Database showed an increased prevalence of allergic diseases including asthma (odds ratio [OR] = 1.53), allergic rhinitis (AR) (OR = 1.59), and atopic dermatitis (AD) (OR = 1.53) among ADHD patients when compared to the healthy controls (Chen et al., 2013).

However, there is a high degree of heterogeneity across the studies about the association between symptoms of allergies and ADHD in children, which has been found to differ in both direction and strength (van der Schans et al., 2020).

Parental smoking at home as a potential cause of the comorbidity

The frequent co-occurrence of ADHD and allergic diseases suggests that these two distinct diseases may share some common casual pathways. In addition to genetic predisposition, for some individuals, the presentation of allergic and ADHD symptoms could be resulted from exposure to environmental allergens. Despite mounting evidence showing the link between ADHD and allergic diseases (Miyazaki et al., 2017; Schans et al., 2017), much less is known about the co-occurrence of these diseases in relation to environmental allergens. It is possible that the relationship between ADHD and allergic diseases may not be causal but arise due to exposure to the shared environmental allergen. For example, second-hand smoke is a known risk factor for ADHD (Huang et al., 2021). Evidence from meta-analysis also support the association between environmental tobacco smoke exposure in childhood and the increased risk for allergic diseases such as allergic rhinitis (Saulyte et al., 2014), asthma (Wang et al., 2015), and eczema (Kantor et al., 2016). An observation of note is that parental smoking at home is not uncommon. A previous survey study of Hong Kong primary 2–4 students found that 34% of the students reported parental smoking and 19% reported second-home smoke exposure at home (Wang et al., 2011). This social phenomenon presents a new research question as to whether repeated exposure to the shared environmental allergen (tobacco smoke) at home may potentially increase children's susceptibility to the comorbidity of ADHD and allergic diseases, which deserves further investigations.

The present study

Based on current evidence and knowledge gap, we identified second-hand smoke at home as a potential environmental allergen underlying the link of ADHD and allergic diseases. Specifically, we used a cross-sectional study design to investigate the differences in the strength of this comorbid association before and after adjusting for exposure to parental smoking at home. We hypothesized that the adjustment of exposure to parental smoking at home would change the estimate of the comorbid association between ADHD and allergic diseases.

Method

Study design and participants

This study adopted a survey approach for characterizing exposure to parental smoking at home and history of allergic diseases and ADHD symptoms. Data were from parents of Grade 7 or Grade 8 students who either participated in the Healthy Kids cohort study (Ip et al., 2016; Tso et al., 2019) or were enrolled in the schools where the cohort participants were attending. For Healthy Kids cohort participants, research assistants retrieved their contact information from the database and invited each family unit by phone. If they expressed interest to join, the survey materials including questionnaires and information sheet and consent were mailed to them, and they were instructed to return the completed questionnaires to the research team by mail using the prepaid envelop. This approach was found to collect more valid responses than online survey approach (Al-Salom & Miller, 2019). For participants recruited through schools, survey hardcopies were sent to those schools consenting to join. Teachers would then distribute the questionnaires to the interested students and return the completed questionnaires to the research

team afterwards. All parents of eligible students were invited to review the survey information and provide informed consent. Upon obtaining informed consent, parents of participating students completed questionnaires concerning home environment and their child's history of allergic diseases and ADHD symptoms and would receive an incentive of HKD 100 (USD 12.8) upon survey completion. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 18-057).

Measures

Parents rated their child's ADHD symptoms using the Chinese Strengths and Weaknesses of Attention-Deficit/Hyperactivity-symptoms and Normal-behaviours Questionnaire (SWAN) (Lai et al., 2013). The Chinese SWAN consists of 18 items on a 7-point scale ranging from -3 (far better than normal) to +3 (far worse than normal) (Lakes et al., 2012), the average of which is the ADHD-combined (ADHD-C) score. The items can be further grouped with nine items each for ADHD-inattentive type (ADHD-I) and ADHD-hyperactive/impulsive type (ADHD-HI), respectively. The average of these subset items is the subscale score. The Chinese SWAN has been validated and demonstrated good psychometric properties in Hong Kong (Lai et al., 2013). In the present study, Hong Kong locally relevant Chinese SWAN cut-offs (0.33 for boys and 0.39 for girls) were used to identify participants with probable ADHD (i.e., displaying symptoms with sufficient frequency, duration, and characteristics that pre-clinically fulfil the DSM-IV criteria for ADHD diagnosis). Furthermore, as the number of cases with physician-diagnosed ADHD was not large enough to adequately answer the research question of interest, we computed the raw Chinese SWAN score as a proxy for ADHD symptom severity.

In addition, parents were also asked to indicate whether their child had been physician-diagnosed with asthma, AR, AD, and food allergies, as well as to provide child and family characteristics such as child age and gender, monthly family income, maternal education, and parental smoking habits at home.

Data analysis

Descriptive statistics were used to describe demographic characteristics, ADHD symptoms, and responses to parental smoking at home and allergic diagnosis questions. We used linear regression analysis to examine four models of ADHD symptoms in relation to diagnosis of allergic diseases. In the first model, we examined the association between ADHD symptoms and allergic disease overall and by disease type. In the second model, the association of interest was controlled for other allergic diagnoses. The third model was further adjusted for demographic factors (i.e., child age and gender, monthly family income, and maternal education level). Monthly family income and maternal education level were included as covariates because of their strong associations with child health (Cooper & Stewart, 2021; Cuartas, 2021). The fourth model was built upon the third model with further adjustment for exposure to parental smoking at home. We also used logistic regression analysis to study the association of dichotomous probable ADHD status to individual and any allergic disease type with adjustment for parental smoking at home and demographic factors. As the parental smoking at home variable had missing data on 35% of the cases, regressions were based on full information maximum likelihood estimation to maximize the analytical sample size. All the analyses were performed using SPSS 25.0 software, with $p < 0.05$ indicating statistical significance. As this is an exploratory study, analyses were not corrected for multiple testing (Bender & Lange, 2001).

Results

The participant sample (n=600) consisted of 250 males (41.7%) and 350 females (58.3%) (mean age: 13.3 years; range: 13-16 years). All of them were living with parents at the time of survey. Their sociodemographic characteristics were shown in Table 1. 48 participants (12.3%) had ever been exposed to parental smoking at home. 76 (12.7%) were SWAN-screened positive of probable ADHD. Regarding history of allergic diseases, 279 participants (46.5%) were reported to have at least one allergic diagnosis of interest. Specifically, there were 35 participants with asthma, 225 with AR, 86 with AD, and 41 with food allergy.

Table 2 shows the association between allergic diagnosis and continuous ADHD symptoms. The association of having at least one allergic diagnosis with ADHD symptoms was positive and significant in both unadjusted (β=0.18, p=0.027) and adjusted (β=0.19, p=0.023) models. The results of crude regression analysis showed no association between individual allergic diagnosis and ADHD symptoms. After adjusting for other allergic diseases and demographics, the association between the diagnosis of asthma and ADHD symptoms became significant (β=-0.41, p=0.019). On the other hand, the association of AR with ADHD symptoms was significant only in the mutually adjusted model (β=0.18, p=0.037). With the addition of exposure to parental smoking at home as a covariate in the model, the association of ADHD symptoms with allergic diagnosis became weaker for both overall and individual allergic disease groups, whereas parental smoking at home showed a significant and positive association with ADHD symptoms (β=0.12, p=0.015).

Table 3 shows the logistic association of dichotomous probable ADHD status with overall and specific allergic disease type. The association between probable ADHD status and having at least one allergic diagnosis was statistically insignificant in the adjusted models. On the other hand, the mutually adjusted models showed significantly higher likelihood of having probable ADHD among participants with AR (OR=1.95, p=0.010) and food allergy (OR=4.37, p=0.001) when compared to those without the disease of interest. These associations remained significant after further adjusting for child and family demographics. However, when the effect of exposure to parental smoking at home was controlled, the association remained significant only with food allergy (OR=4.51, p=0.011) but not with AR (OR=1.83, p=0.072).

Discussion

This study examined the association between allergic diseases and ADHD in early adolescents by means of evaluating ADHD as both continuous symptom and dichotomous positive SWAN-screen status variables in the analyses. In addition, we explored the change in the strength of association between allergic diseases and ADHD before and after adjusting for exposure to parental smoking at home. Results showed differential patterns of ADHD symptoms among allergic disease groups, with asthmatic participants showing fewer ADHD symptoms than those non-asthmatic participants even after adjusting for other allergic diseases and child and family demographics. However, with the addition of parental smoking at home as a covariate in the model, all allergic diseases showed no association with ADHD symptoms, suggesting that further studies using longitudinal data are needed to confirm whether exposure to parental smoking at home could contribute to the development of ADHD and allergic symptoms. Another finding of note is that the diagnosis of food allergy remained to have a strong association with

probable ADHD even after further adjusting for parental smoking at home, yet this pattern of association was not observed in participants with AR. Our findings highlight the critical role of second-hand smoke exposure at home which has a potential to exacerbate the progression of comorbidity of allergic disease and ADHD.

This study reveals a mixed pattern of presentation of ADHD among allergic patients. Previous studies have shown that allergic inflammation could induce production of IgE at sites distal from the original location of allergic irritation, giving rise to inflammatory reactions via mast cell high-affinity IgE receptor (FcεRI) in various tissues including neuroinflammation in the brain (Galli et al., 2008; Gould & Sutton, 2008). Although the role of immunoglobulin E (IgE) in the pathogenesis and pathophysiology of allergic diseases is well established (Owen, 2007), some studies found that IgE levels differed between allergic diseases (Stone et al., 2010; Wittig et al., 1980). Furthermore, the expression of mast cell FcεRI itself and its effector inflammatory function could be IgE dependent (Gould & Sutton, 2008), suggesting that differences in IgE levels, among other factors, could potentially explain the manifestation of ADHD symptoms in allergic patients. Hence, quantification of IgE levels would be helpful to elucidate the IgE-FcεRI mediated link between allergies and ADHD.

Another finding of note is the negative association between the diagnosis of asthma and ADHD symptoms in this study, although much evidence in the literature points to a positive link (Miyazaki et al., 2017; Schans et al., 2017; Yang et al., 2014). Methodological limitations such as small sample size may have biased the findings of this study. However, a recent meta-analysis of the relationship between ADHD and asthma has highlighted the potential of publication bias

in the literature, as negative findings could have been underreported (Cortese et al., 2018). In addition, it is known that cytokines are released during allergic reactions and can pass through the blood-brain barrier to activate neuro-immunological mechanisms, resulting in unregulated neuro-inflammation and autoimmune brain destruction (Banks & Erickson, 2010). To prevent ADHD symptoms, adequate control of cytokines is needed, although the process partly depends on the nature and frequency of allergic treatment. For example, the use of inhalers can quickly relieve asthma and breathlessness in 10-20 minutes, but AR treatments such as intranasal corticosteroids may take a day to achieve adequate symptom control (deShazo & Kemp, 2020; Sawicki & Haver, 2020). However, a previous study found that early antihistamine use was associated with increased ADHD symptoms (Schmitt et al., 2018). Further studies would be needed to clarify the direction and strength of effect of allergic treatment on ADHD symptoms in the affected patients.

Our findings also support the notion that second-hand smoke exposure is one of the risk factors for ADHD (Max et al., 2013) and adds to the current literature that the strength of association between symptoms of ADHD and allergic disease could be reduced in the absence of exposure to second-hand smoke. This is consistent with evidence from human and animal studies that found an association between second-hand smoke exposure and ADHD (Huang et al., 2021). Previous studies have reported a graded association between exposure to second-hand smoke and behavioural problems in children (Zhou et al., 2014). Likewise, the links between second-hand smoke exposure and allergies are also well established (Braun et al., 2020). Indeed, mechanisms such as elevated cytokines, neurotransmitter alteration, and brain structure changes that underlie

the development of ADHD and allergies could be activated through exposure to tobacco smoke (Braun et al., 2020; Huang et al., 2021; Lambrecht et al., 2019; Strzelak et al., 2018).

In addition to the findings based on continuous ADHD symptoms, we also investigated the relationship between allergic diseases and dichotomous probable ADHD status. Given that participants who had probable ADHD were those with the highest levels of ADHD symptoms, the examination of probable ADHD status would help increase our understanding of whether allergic diseases could predispose children and adolescents to the clinical diagnosis of ADHD. We found that food allergy and AR were most strongly associated with probable ADHD status. Specifically, participants with AR were 1.91 more likely to have probable ADHD than those without AR, and participants with food allergy were 3.18 more likely to have probable ADHD than those without food allergy. Nevertheless, when the effect of exposure to parental smoking at home was controlled, there were smaller differences in the likelihood of probable ADHD between participants with AR and those without, although the association between food allergy and probable ADHD remained strong. These results align with the notion that repeated exposure to environmental allergens such as second-hand smoke could exacerbate AR symptoms (Lin et al., 2011) and increase susceptibility for the development of neurobehavioral diseases such as ADHD (Huang et al., 2021). In addition, this study revealed a strong association between food allergy and probable ADHD which was independent of exposure to parental smoking at home. It has been posited that the manifestation of ADHD symptoms in individuals with food allergy could be a hypersensitivity reaction towards food-derived allergens (de Theije et al., 2014). The resulting upregulation of proinflammatory cytokines may cause damages to multiple systems such as respiratory, immune, and nervous system, and thus provide a possible explanation for

increased ADHD symptoms in individuals with food allergy (Ferro et al., 2016; Jiang et al., 2018).

Limitations

In the present study, we used a validated measure to assess ADHD symptoms in a relatively large sample of early adolescents. We also proposed a new perspective that accounts for the influence of exposure to second-hand smoke exposure at home on the interpretation of association between ADHD and allergies. However, there were several limitations. First, this is a cross-sectional study, and thus we cannot determine whether there is a causal link between ADHD and allergic diseases. Furthermore, parent-proxy reports of second-hand smoke exposure at home, allergic diagnoses, and ADHD symptom severity may involve recall bias. Second, participants were recruited via chain-referral sampling, which could limit the generalizability of the present findings to other populations. In particular, the small number of participants with allergic diagnoses or screened positive of probable ADHD may have influenced the reliability of the results. More longitudinal studies with robust features such as large sample size and use of electronic health records are needed to ascertain the effect of second-hand smoke exposure on the development of comorbidity between ADHD and allergic diseases and its underlying mechanism.

Implications

Future research

This study provides evidence on the role of exposure to parental smoking at home as a risk factor for ADHD symptoms in allergic patients. Future research could consider examining the

psychological impact of exposure to parental smoking at home on the child through qualitative approaches such as using photovoice which is an innovative way to reflect, talk, learn, and share affective experiences through a specific photographic technique (Tanhan & Strack, 2020).

Child and public health professionals

The providers should perform a detailed assessment of home environment and parental smoking behavior to inform their decision on whether the ADHD symptoms require therapeutic and pharmacological treatments or can be alleviated by eliminating the environmental allergens such as tobacco smoke. This is particularly pertinent during the COVID-19 pandemic when children spend more time at home or other indoor environments and thus could have a higher risk of inhaling contaminated air by second-hand smoke.

Educators

Child health and public health educators should train future providers to be cautious and conscious when interpreting symptoms, which could have consequences for diagnostic classification (Rosendal et al., 2013). Moreover, information on the impact of environmental allergens on ADHD symptoms among allergic patients can be integrated into the teaching process to prepare future practitioners. This can be done through providing academic reading and case studies, inviting affected parents to share their experiences, promoting research collaboration, and public seminars.

Conclusion

In this cross-sectional study, the levels of ADHD symptoms in early adolescents were found to vary by allergic diagnosis. Exposure to parental smoking at home appears to predispose individuals with allergies to ADHD symptoms particularly for those with AR. Our findings suggest that environmental factors such as exposure to second-hand smoke could create a favorable condition for the development of allergic and ADHD symptoms, thereby causing a spurious association between these two conditions. It is important for parents and clinicians to assess the impact of environmental allergens on the manifestation of ADHD symptoms in allergic children, particularly during the COVID-19 pandemic period when infection control measures such as home confinement are implemented. Avoidance of allergens such as tobacco smoke and timely administration of medications to relieve allergic reactions in early life are among the promising strategies to prevent the onset and progression of ADHD.

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Table 1. Subject characteristics

Gender, n(%), *n=600*	
Female	350 (58.3)
Male	250 (41.7)
Age, mean(SD), *n=600*	13.29 (0.52)
Monthly family income, mean(SD), HKD'000, *n=588*	54.5 (38.4)
Maternal education level, n(%), *n=596*	
Bachelor degree or above	207 (34.7)
Grade 10 to diploma	273 (45.8)
Grade ≤9	116 (19.5)
Parent smoking at home, n(%), *n=392*	
Never	344 (87.8)
Seldom	18 (4.6)
Sometimes	20 (5.1)
Always	10 (2.6)
Diagnosis of allergic diseases, n(%)	
Asthma, *n=596*	35 (5.9)
Allergic rhinitis, *n=599*	225 (37.6)
Eczema, *n=596*	86 (14.4)
Food allergy, *n=597*	41 (6.9)
Any one of the above, *n=600*	279 (46.5)
ADHD symptoms, *n=600*	
Positive SWAN ADHD-Combined screen, n(%)	76 (12.7)
Positive SWAN ADHD-Inattention screen, n(%)	87 (14.5)
Positive SWAN ADHD-Hyperactivity screen, n(%)	48 (8.0)
Combined score, mean(SD)	-0.71 (0.91)
Inattention score, mean(SD)	-0.46 (0.95)
Hyperactivity score, mean(SD)	-0.95 (1.01)

Table 2. Association between ADHD symptoms and diagnosis of allergic diseases

	Model A	Model B	Model C	Model D
	β (95%CI, p-value)	β [a] (95%CI, p-value)	β[b] (95%CI, p-value)	β[c] (95%CI, p-value)
Asthma	-0.26 (-0.60 to 0.08, p=0.140)	-0.37 (-0.72 to -0.02, p=0.040)	-0.41 (-0.75 to -0.07, p=0.019)	-0.41 (-0.88 to 0.05, p=0.082)
Allergic rhinitis	0.15 (-0.02 to 0.31, p=0.076)	0.18 (0.01 to 0.35, p=0.037)	0.16 (-0.01 to 0.33, p=0.061)	0.20 (-0.01 to 0.41, p=0.062)
Atopic dermatitis	0.03 (-0.20 to 0.26, p=0.786)	-0.01 (-0.26 to 0.24, p=0.943)	0.04 (-0.20 to 0.29, p=0.725)	-0.03 (-0.34 to 0.27, p=0.828)
Food allergy	0.12 (-0.20 to 0.44, p=0.466)	0.10 (-0.25 to 0.44, p=0.590)	0.14 (-0.20 to 0.48, p=0.425)	-0.07 (-0.50 to 0.36, p=0.753)

[a] Mutually adjusted for allergic disease.

[b] Model B further adjusted for child age and gender, monthly family income, and maternal education level

[c] Model C further adjusted for parental smoking at home

Table 3. Association between probable ADHD status and diagnosis of allergic diseases

	Model A	Model B	Model C	Model D
	OR (95%CI, p-value)	OR [a] (95%CI, p-value)	OR[b] (95%CI, p-value)	OR[c] (95%CI, p-value)
Asthma[+]	0.81 (0.30 to 2.56, p=0.809)	0.68(0.22 to 2.10, p=0.506)	0.61(0.19 to 1.92, p=0.398)	0.53(0.11 to 2.62, p=0.434)
Allergic rhinitis[+]	1.91(1.18 to 3.10, p=0.009)	1.95(1.18 to 3.23, p=0.010)	1.82(1.07 to 3.07, p=0.026)	1.83(0.95 to 3.53, p=0.072)
Atopic dermatitis [+]	1.02(0.52 t0 2.03, p=0.950)	0.51(0.22 to 1.17, p=0.511)	0.59(0.25 to 1.37, p=0.220)	0.60(0.20 to 1.81, p=0.362)
Food allergy[+]	3.18(1.55 to 6.54, p=0.002)	4.37(1.86 to 10.29, p=0.001)	4.88(2.00 to 11.87, p<0.001)	4.51(1.41 to 14.43, p=0.011)

[+] Compared to those without the disease (reference group)

[a] Mutually adjusted for allergic disease.

[b] Model B further adjusted for child age and gender, monthly family income, and maternal education level

[c] Model C further adjusted for parental smoking at home