

令和 2 年 7 月 6 日現在

機関番号：10101

研究種目：若手研究(B)

研究期間：2017～2019

課題番号：17K15843

研究課題名(和文) Identification of non-invasive novel biomarkers predicting future asthma exacerbations in adults and early-onset wheeze in children

研究課題名(英文) Identification of non-invasive novel biomarkers predicting future asthma exacerbations in adults and early-onset wheeze in children

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交付決定額(研究期間全体)：(直接経費) 3,300,000円

研究成果の概要(和文)：9-11歳の児では、41%の児が喘息/喘鳴、鼻結膜炎、湿疹のうち、少なくとも一つ以上のアレルギーを有していた。高Th2バイオマーカー値の児の割合は、FeNO (>20 parts per billion)が45.2%、好酸球数 (>300/μl) が37.3%であった。また、吸入アレルギーと食物アレルギー抗原を有する児は、それぞれ70.8%、30.0%であった。日本人の児と他のアジア諸国の児は、欧米諸国の児より高いTh2バイオマーカーの値を有し、特にFeNOでその傾向が顕著であることがみとめられた。

研究成果の学術的意義や社会的意義

We found that early-life asthma may increase the risk of overweight/obesity. Thus, the prevention of overweight/obesity could be possible with early detection and treatment of asthma. We identified biomarkers associated with allergies and applicable as predictors of wheeze/asthma among children.

研究成果の概要(英文)：We assessed association of early life allergic diseases with overweight/obesity risk in children at age 7. Also, we assessed the association of 3 urinary biomarkers including 8-hydroxy-2 deoxyguanosine (8-OHdG), hexanoyl-lysine (HEL), and 4-hydroxynonenal (4-HNE) with the risk of allergic diseases at age 7 (n=568) and 10 years (n=428). We found the prevalence of rhinitis (3.3 to 21.2%) and eczema (11.3% to 22.4%) increased from early life to age 10. Prevalence of wheeze peaked at 4 years of age (21.6%) with a decline at age 7 (13.3%) and 10 (9.2%). Among children aged 10, 41.5% had at least of the allergic diseases, 46.0% had FeNO >20 p.p.b, and 38.5% had blood eosinophil number >300/μl. At age 10, 70.5% and 22.3% of children were sensitized to inhaled and food allergens, respectively. Wheeze, but not other allergies, at age 0-2, 4 and 7 years of age was associated with risk of overweight/obesity at age 7. Also, HEL had higher levels among children with wheeze at age 7.

研究分野：Respiratory Medicine

キーワード：Birth cohort childhood allergies Overweight and obesity Biomarkers Early life wheeze

様式 C-19、F-19-1、Z-19 (共通)

1. 研究開始当初の背景

Worldwide obesity has nearly tripled since 1975 and over 340 million children and adolescents aged 5-19 were overweight or obese in 2016 (WHO report). Asthma and obesity are among the most common chronic childhood disorders, both having had a parallel dramatic increase in prevalence worldwide in recent decades (Eder et al. *N EJM* 2006). Although recent longitudinal studies suggested obesity as a risk factor for asthma incidence, little is known regarding the impact of asthma and other allergic diseases on the risk of obesity incidence. Two previous studies examined the potential impact of asthma on obesity development in school-aged children (Chen et al. *AJRCCM* 2017; Contreas et al. *ERJ* 2018) which need to be replicated across different, population-based prospective studies, examining not only asthma but other allergic conditions after controlling for extensive confounders.

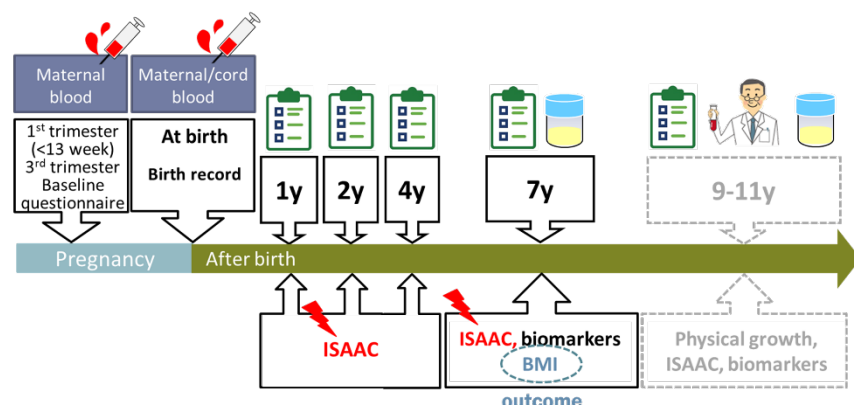
2. 研究の目的

In a large-scale prospective birth cohort in Japan, we investigated the association of early life allergic conditions (including wheeze, rhinoconjunctivitis, and eczema) with overweight/obesity risk in children at age 7.

3. 研究の方法

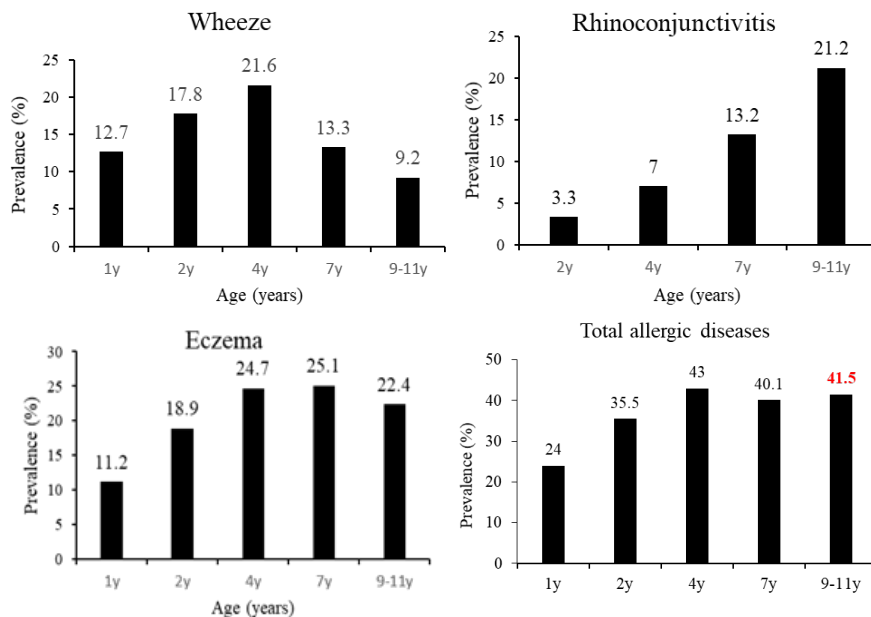
Hokkaido study was initiated in February 2003 with native Japanese mother-child pairs (> 20,000 pairs). Pregnant women who attended prenatal visits in early pregnancy at any of the 37 participating hospitals in the Hokkaido prefecture were eligible for this study (Kishi et al. *EHPM* 2017; Goudarzi et al. *Env. Int.* 2017). In the current study, 7,288 mother-child pairs are included in data analysis. Parents completed the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires about symptoms of allergic diseases (wheeze, rhinoconjunctivitis, and eczema) at age 1, 2, 4, and 7 years (Asher et al. *Lancet* 2006). Overweight/Obese status was defined according to the 2012 International Obesity Task Force age and sex-specific cut-offs (Cole et al. *Pediatr Obes* 2012). We also examined three inflammatory urine biomarkers at age 7 including 8-hydroxy-2 deoxyguanosine (8-OHdG), hexanoyl-lysine (HEL), 4-Hydroxynonenal (HNE), and urinary creatinine. We estimated adjusted hazard ratios (HRs) and 95% CI for the associations of early-onset allergic diseases with overweight/obesity risk during follow-up using Cox proportional hazards models. The confounders included in the adjusted models were child's sex, maternal education, pre-pregnancy maternal BMI, birth weight, maternal smoking during pregnancy, duration of breastfeeding, second-hand tobacco smoke exposure at age 7.

Fig 1. Study flowchart.



4. 研究成果

Fig 2. Prevalence of total allergic diseases in Hokkaido.



Total allergic diseases indicate cases with at least one of the allergic diseases.

Fig 3. Childhood BMI and urinary HEL levels at age 7 according to allergic conditions.

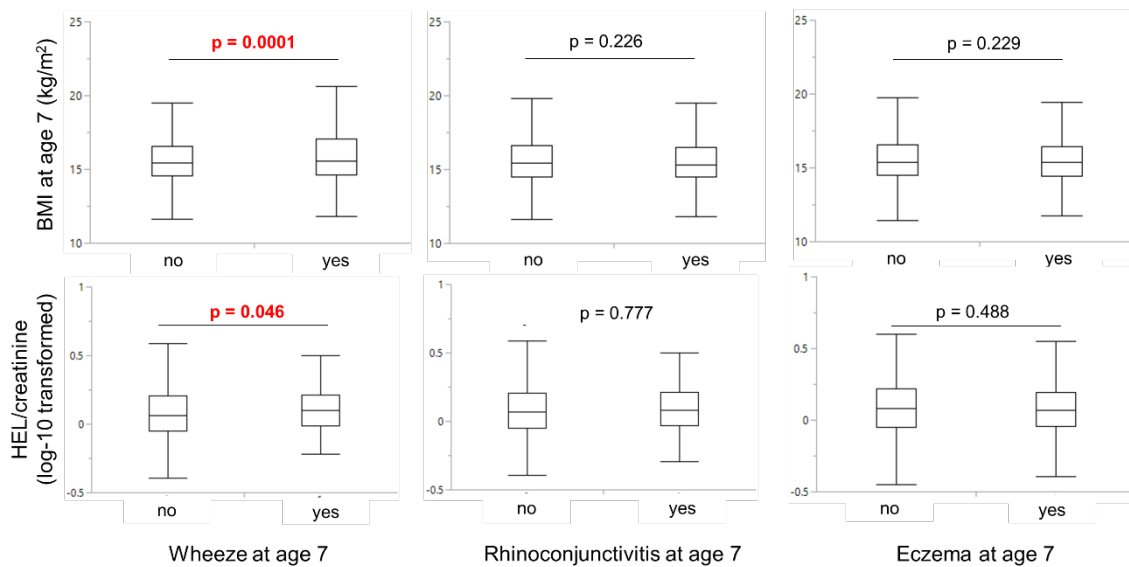


Table. Association of early-onset wheeze and asthma with incident overweight/obesity at age 7.

Allergic conditions/diseases	Adjusted HR (95% CI)	p-value
Wheeze at 0-2 years of age	reference	
No		
Yes	1.33 (0.97-1.82)	0.072
Wheeze at 4 years of age	reference	
No		
Yes	1.36 (1.03-1.79)	0.027
Wheeze at 7 years of age	reference	
No		
Yes	1.49 (1.21-1.82)	< 0.001
History of doctor-diagnosed asthma	reference	
No		
Yes	1.30 (1.09-1.54)	0.003

Adjusted by child's sex, maternal education, pre-pregnancy maternal BMI, birth weight, maternal smoking during pregnancy, duration of breastfeeding, second-hand tobacco smoke exposure at age 7.

Note: We did not find any association of rhinoconjunctivitis or eczema with the risk of overweight/obesity at age 7.

With a collaborative study in two prospective ongoing cohorts in adults and children with enough sample size, we could identify a new profile of biomarkers to predict asthma exacerbation in adults and early-onset wheezing/asthma in children. We focused on novel non-invasive biomarkers in blood and urine available in our cohorts. This could eventually lead to predict and prevent asthma attacks, better asthma monitoring/management, and reduction of economic burden in childhood and adulthood asthma. In detail, we assessed the association of early life allergic diseases with overweight/obesity risk in children at age 7. Also, we assessed the association of 3 urinary inflammatory biomarkers including 8-hydroxy-2 deoxyguanosine (8-OHdG), hexanoyl-lysine (HEL), and 4-hydroxynonenal (4-HNE) with the risk of allergic diseases at age 7 (n=568) and 10 years (n=428). We found the prevalence of rhinitis (3.3 to 21.2%) and eczema (11.3% to 22.4%) increased from early life to age 10. Prevalence of wheeze peaked at 4 years of age (21.6%) with a decline at age 7 (13.3%) and 10 (9.2%). Among children aged 10, 41.5% had at least of the allergic diseases, 46.0% had FeNO >20 p.p.b, and 38.5% had blood eosinophil number >300/ μ l. At age 10, 70.5% and 22.3% of children were sensitized to inhaled and food allergens, respectively. Wheeze, but not other allergies, at age 0-2, 4, and 7 years of age was associated with the risk of overweight/obesity at age 7. HEL, as one of omega 6 fatty acid oxidation biomarkers, had higher levels among children with wheeze at age 7. Among adult asthma patients, we examined HEL and HNE and found the association of abdominal visceral fat with examined urinary biomarkers (data not shown here).

Conclusion: Early life wheeze and asthma, but not rhinoconjunctivitis and eczema, are associated with a higher risk of childhood overweight/obesity independent of pre-pregnancy maternal BMI and birth weight.

Clinical implication: Early interventions for children with wheeze or asthma could play an important role in preventing obesity and related metabolic diseases in later life.

Ongoing data analysis: Currently, I am examining the association of urinary and blood biomarkers with the development of allergic diseases and overweight/obesity at age 9-11.

Future studies: More studies are warranted to explore the mechanistic relationship of asthma and allergic diseases with obesity in children. Therefore, we are now following up on children at age 9-11 years collecting information on allergic diseases, anthropometric measures, and measuring systemic biomarkers.

5. 主な発表論文等

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〔産業財産権〕

〔その他〕

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6. 研究組織

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