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Asthma and the risk of type 2 diabetes in the Singapore Chinese Health Study

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Abstract

Aim—Asthma is believed to increase the risk for several proinflammatory diseases, yet epidemiologic studies on asthma in relation to risk of developing type 2 diabetes are sparse and have reported inconsistent results. In the present study, we investigated the hypothesis that asthma is associated with an increased risk of incident type 2 diabetes in Chinese adults.

Methods—We used data from the Singapore Chinese Health Study, including Chinese men and women aged 45–74 years, free of cancer, heart disease, stroke, and diabetes at baseline (1993–1998) and followed through 2004 for incident physician-diagnosed diabetes. Cox regression models were used to examine the associations between self-reported history of physician-diagnosed asthma and risk of diabetes.

Results—During an average follow-up of 5.7 years per person, 2,234 of the 42,842 participants included in the current analyses reported diagnoses of type 2 diabetes. After adjustment for potential confounders, not including body mass index (BMI), asthma was associated with a 31% increased risk of incident diabetes (HR = 1.31; 95% CI: 1.00–1.72). The association was attenuated after adjustment for adult BMI (HR = 1.25 95% CI: 0.95–1.64). The asthma-diabetes association appeared stronger for adult- versus child-diagnosed asthma cases, and for participants who were obese compared to non-obese.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contribution

NTM: Conceptualized, designed and carried out analysis, interpreted data, wrote manuscript, edited manuscript; WPK: Contributed to discussion, reviewed and edited the manuscript, contributed to design and data interpretation; AOO: Contributed to discussion, reviewed and edited the manuscript, contributed to design and data interpretation; MDG: Reviewed and edited the manuscript; JMY: Reviewed and edited manuscript; MAP: Contributed to design and data interpretation, reviewed and edited manuscript.

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Conclusions—In Singaporean Chinese adults we observed a positive association between self-reported, physician-diagnosed asthma and risk of developing type 2 diabetes that was modestly attenuated upon adjustment for BMI.

Keywords

Asthma; Type 2 diabetes; Obesity

INTRODUCTION

Asthma is a chronic inflammatory lung disease affecting nearly 300 million people globally, and its prevalence is on the rise in many parts of the world [1, 2]. In addition to being a major cause of morbidity in-and-of itself, asthma may be a potential risk factor for the development of proinflammatory conditions such as type 2 diabetes (T2D) [3–5]. Possible mechanisms for the hypothesized link between asthma and increased risk for T2D include genetic pleiotropy [6], lung-related inflammatory cytokines and their effects on insulin sensitivity [6–8], direct effects of hypoxia on glucose metabolism [9–11], and adverse early-life exposures and their effects on organ development [12, 13].

One retrospective [3] and two prospective [4, 5] studies have reported findings on the association between asthma and T2D in adults. In the Nurses' Health Study, asthma was not associated with increased risk of T2D [3]. However, the Women's Health Study reported a 1.5-fold increased T2D risk for women with asthma, after adjusting for baseline BMI and other potential confounders [4]. A recent population-based retrospective matched case-control study found a greater than twofold increased risk of diabetes in asthmatics compared to those without asthma. However, this study did not adjust for important confounding factors including adiposity, smoking, and other lifestyle factors.

There have been no prospective studies to date that have examined whether the asthma-diabetes association exists in both males and females or is specific to women, as has been reported in studies of asthma and cardiovascular disease [14–18], or if the association is present in non-Western populations. Furthermore, whether the asthma-diabetes association differs by asthma age-at-onset was not assessed in previous studies. Asthma is a heterogeneous disease presenting with various immunologic, physiologic, and pathologic phenotypes [19, 20]. Child- and adult-onset asthma differ with respect to asthma triggers [20], sex [20], and patterns of inflammation [21].

We therefore prospectively examined the association of physician diagnosed child- and adult-diagnosed asthma with incidence of T2D in a large cohort of Chinese men and women. We hypothesized that asthma would be positively associated with incident T2D. A secondary aim of the study was to explore potential effect modifiers for the asthma-diabetes association, including age at asthma diagnosis and adult obesity.

METHODS

Study population

The Singapore Chinese Health Study (SCHS) is a prospective investigation of diet and cancer risk [22]. The Institutional Review Boards of the National University of Singapore and the University of Minnesota approved the study, and all subjects who were enrolled gave informed consent. The cohort was drawn from permanent residents of government-built housing estates, where 86% of the Singapore population resided during the enrollment period. Study subjects were restricted to the two major dialect groups of Chinese in Singapore, the Hokkiens and Cantonese, who originated from the contiguous provinces of

Fujian and Guangdong, respectively, in the southern part of China. Recruitment was initiated with a letter informing potential participants of the study and inviting them to take part. Five to seven days later, study staff went door-to-door to invite subjects to participate. Approximately 85% of eligible subjects who were invited agreed to participate [22].

Ascertainment of asthma and other covariates

At recruitment each subject was interviewed face-to-face in their home by a trained interviewer using a structured, scanner-readable questionnaire which requested information on demographics, height, weight, use of tobacco, usual physical activity, reproductive history (women only), medical history, familial history of cancer and dietary intake. Between April 1993 and December 1998, 63,257 Chinese women and men ages 45–74 years (mean age 56.5) were enrolled in the study [22]. A follow-up interview was completed between 1999 and 2004 for 52,325 cohort members. The follow-up interview included detailed information on environmental tobacco smoke exposures and items on cough and phlegm from the American Thoracic Society questionnaire (ATS-DLD-78-A) [23]. We defined never smokers as those participants who reported “no” the question at baseline about ever having smoked at least one cigarette a day for 1 year or longer. Ever smokers (current and former) were then asked, “At what age did you start smoking cigarettes on a regular basis?” The age at which women started smoking and the number of cigarettes they smoked per day were used to categorize smoking status into three levels (never smokers, started smoking at age ≥ 15 years or <15 years and smoke ≤ 13 cigarettes per day, or started smoking at age <15 years and smoke >13 cigarettes per day).

Ascertainment of asthma diagnosis

At baseline participants were asked whether they had asthma, hay fever, skin allergy, food allergy, or any other allergy in a single question. At follow-up exam, the same participants were asked whether or not a doctor had told them that they had asthma and, if yes, the age at which they were diagnosed with asthma and the age at which they last had an asthma attack. A participant was considered to have a history of asthma if they indicated “yes” to the non-specific allergy- and asthma-related question at baseline and “yes” to the specific physician-diagnosed asthma question at the follow-up exam. Seventeen percent of participants (873 of 5,115) who said, “yes” to the baseline question also said “yes” to the follow-up question specific to asthma. We defined child-onset asthma cases as persons with a history of physician-diagnosed asthma at age ≤ 18 years, and adult-onset at age >18 years, and we stratified duration of symptoms at 20 years. Participants who reported having an asthma attack in the 12 months prior to baseline exam were considered current asthmatics; those who did not were considered former asthmatics.

Ascertainment of diabetes

Self-reported diabetes as diagnosed by a physician was evaluated at baseline and follow-up by the question “Have you been told by a doctor that you have diabetes (high blood sugar)?” If yes: “Please also tell me the age at which you were first diagnosed?” Participants with diagnosed diabetes reported at baseline were excluded from the analysis. Participants were classified as having incident diabetes if they reported developing diabetes anytime between the initial enrollment interview and the follow-up 1 telephone interview that occurred between July 1999 and October 2004.

A validation study of the incident diabetes mellitus cases used two different methods and is reported in detail by Odegaard *et al* [24, 25]. First, cases were ascertained through linkage with a nationwide, hospital-based discharge summary database—an administrative database in the Singapore Ministry of Health. If subjects were admitted to hospitals for diabetes-related *International Classification of Diseases*, Ninth Revision, codes 250.00–250.92 after

recruitment into the cohort they were considered a valid case. Cases that did not have hospitalization records were contacted to answer a supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy during a telephone interview. A valid case had the following 3 criteria: 1) confirmed diagnosis later than the baseline interview date, 2) diabetes still present at the time of interview, and 3) use of oral medications or insulin injections to treat diabetes. On the basis of these criteria, we observed a positive predictive value of 99% [24].

Alternatively, 2,625 randomly selected participants who answered “no” to the question of diabetes diagnosis at baseline and follow up, and provided blood samples at their follow up interview were analyzed for HbA1c % (glycated hemoglobin). One hundred forty eight subjects (5.6% of the sample) had an HbA1c $\geq 6.5\%$, meeting the most recent diagnostic guidelines for the presence of diabetes [26]. Thus, 94.4% of persons who reported being free of diabetes at baseline and follow up were below the HbA1c threshold for diabetes, as previously reported [24].

Statistical analysis

We excluded from the analysis participants who died before the follow up interview ($n = 7,722$), reported baseline diabetes ($n = 5,469$), cancer, heart disease or stroke ($n = 5975$), reported extreme sex-specific energy intakes (<600 or $>3,000$ kcal women) (<700 or $>3,700$ kcal men), had missing information on respiratory illnesses ($n = 334$), or subjects from the initial cohort that migrated out of Singapore ($<0.5\%$) were not included in these analyses. These, along with further exclusion of 20 participants whose diabetes status was not clear after the validation effort, left 42,842 participants in the present analysis.

For descriptive purposes, baseline participant characteristics were compared across asthma categories. Person-years for each participant were calculated from the year of recruitment to year of reported diabetes diagnosis, or year of follow up telephone interview for those who did not report a diabetes diagnosis. Cox regression was applied to calculate hazard ratios (HRs) and 95% confidence intervals (CI). HRs were calculated separately among those with ever asthma, current and former asthma, child- and adult-onset asthma, and asthma symptoms ≥ 20 and >20 years versus those who never had asthma.

Two main models were constructed including risk factors associated with T2D in this population, with the final model including body mass index (BMI; kg/m^2), which may be a potential confounder or on the causal pathway between asthma and diabetes risk. Model 1 included age (<50 , 50–54, 55–59, 60–64, 65), year of baseline interview (1993–1995 and 1996–1998), sex, dialect (Hokkiens and Cantonese), height (continuous), education level (none, primary, secondary, A level +), living in a household with a tobacco smoker (never, at age 0–18 years, at age 18 years +, or at both ages 0–18 years and 18 years +), physical activity (<2 hours/week of moderate and no strenuous vs. ≥ 2 hours/week moderate and any strenuous), alcohol intake (none or >7 drinks/week vs. monthly to 7 drinks/week), smoking (never, light, heavy), vegetable-fruit-soy dietary pattern (continuous), coffee (nondaily, once per day, 2–3 times/day, 4 times/day), tea (none, monthly, weekly, daily), and total energy intake (kcal). We furthered adjusted Model 2 for baseline BMI (quadratic) to evaluate potential mediation by adult adiposity.

In sensitivity analyses we excluded diabetes cases that occurred within the first 2 years of follow-up after the baseline interview. To determine if detection bias was at play, we used the same multivariate models as for the asthma analyses to evaluate association between self-reported physician-diagnosed allergic rhinitis and diabetes.

We assessed effect modification by age (<55 vs. ≥55), sex (male vs. female), smoking status (ever vs. never), and BMI (<27.5 kg/m² vs. ≥27.5 kg/m²), which were all specified *a priori*. Ethnic-specific cutoffs for overweight and obesity by BMI (kg/m²) were applied, 23 and 27.5 kg/m², respectively, for Southeast Asians [26]. The log-likelihood ratio test was used to evaluate the interaction terms. All analyses were performed using SAS (version 9.2; SAS Institute Inc, Chicago, IL) and all tests of statistical significance were based on 2-sided $p < 0.05$.

RESULTS

Two percent ($n = 873$) of the participants in the final analytic sample said “yes” to both the baseline and follow-up questions related to asthma diagnosis. Approximately 56% ($n = 487$) of those asthmatics reported symptoms within the year prior to the baseline exam, and 34% ($n = 295$) reported experiencing asthma attacks for 20 or more years. Roughly 44% ($n = 384$) of asthma cases were diagnosed as adults.

The distributions of selected participant characteristics by asthma subtype are presented in Table 1. Participants diagnosed with asthma during childhood were younger, more likely to be female with a high school education, and consumed more soft drinks and total calories than non- and adult-diagnosed asthmatics. Childhood asthmatics were also less likely to smoke cigarettes than their counterparts. BMI and alcohol consumption were not materially different across asthma categories. Adult-diagnosed asthmatics were older, more likely to smoke cigarettes and drink coffee, and less likely to have a high-school education than their non- and child-diagnosed asthmatic counterparts.

A total of 2,234 participants reported developing incident diabetes during a mean follow up of 5.7 years. Participants reporting a history of asthma diagnosis had a 31% (95% CI: 0%–72%) increased risk of T2D relative to those with no history of asthma after adjustment for multiple potential confounders excluding BMI. Compared to individuals with no asthma at all, subjects with asthma at baseline had a higher diabetes risk (HR = 1.41, 95% CI: 1.00–1.99) than those with asthma in the past (HR = 1.18, 95% CI: 0.77–1.81). The risk of developing diabetes for subjects with child-diagnosed asthma (HR = 1.11, 95% CI: 0.71–1.75) was lower than for those with adult-diagnosed asthma (HR = 1.45, 95% CI: 1.04–2.03). The risks of incident diabetes for participants having asthma for more than 20 years versus less than or equal to 20 years were comparable (Table 2). The positive association between asthma and diabetes risk was attenuated after further adjustment for BMI (HR = 1.25 95% CI: 0.95–1.64).

The positive association between asthma and diabetes was stronger in obese than non-obese participants (P for interaction = 0.09). Although the associations appeared to be stronger in women than men (P for interaction = 0.38) and in those who were less than 55 versus greater than or equal to 55 years (P for interaction = 0.43), these interaction terms were not close to statistical significance. Cigarette smoking status did not significantly modify the asthma-diabetes risk association (Table 3).

To examine the temporal robustness of the observed associations, we performed sensitivity analyses excluding diabetes cases diagnosed within the first 2 years of follow-up. The results from these analyses were not materially different from those reported from the entire dataset. After excluding the first 2 years of follow-up, the HR of developing diabetes among those with a history of asthma was 1.33 (95% CI: 0.99–1.78) compared to those without a history of asthma.

DISCUSSION

In this large cohort study of Chinese men and women, we observed an elevated risk of developing T2D among participants with self-reported, physician-diagnosed asthma; however this association was partly explained by BMI. This asthma-diabetes association appeared to be stronger in adult- compared to child-diagnosed asthmatics, and in obese than non-obese participants with asthma.

This was the first prospective cohort study to test the association of asthma in relation to T2D risk in both men and women. Onset of asthma has been shown to vary greatly between sexes, with males at higher risk prior to puberty and females after puberty [19, 20]. Our findings provide evidence that female asthmatics may be at modestly higher risk of developing diabetes than male asthmatics. Our study is also the first to differentiate between asthma age-at-diagnosis subtypes. Adult-onset asthma differs from child-onset asthma in several aspects, including its distribution in men and women and its immunologic and inflammatory pathophysiologic characteristics [19–21]. Our findings provide suggestive evidence that the asthma-T2D association may differ by asthma age-at-onset.

Glucose metabolism has not been studied extensively in individuals diagnosed with asthma. Some studies have suggested that reduced lung function increases risk for insulin resistance and diabetes [8, 28, 29]. However, these studies only focused on impaired lung function [28, 39] or forced vital capacity [8] and did not look into the association between physician-diagnosed asthma and incident diabetes. One retrospective study in men and women [3] and two large prospective cohort studies in women [4, 5] have examined the asthma-diabetes association. It is difficult to directly compare our results to those from the retrospective case-cohort study, which found a twofold increased risk of diabetes among patients with asthma compared to those without, because results were not adjusted for lifestyle or BMI—factors that may confound the asthma-diabetes association [3]. Our results are consistent with findings from the Women's Health Study, in which women with a history of asthma were at a 50% increased risk of incident diabetes [5]. They differ, however, from the findings from the Nurses' Health Study, which found a null association between asthma and diabetes [4]. The lack of association in the Nurses' Health Study may reflect mixing of the heterogeneous effects of adult- and child-onset subtypes. In addition, demographic and lifestyle differences in study population, as well as duration of follow-up, may partially explain the differences between our findings and those from the Nurses' Health Study. The discrepant findings may also be due to differences in the sensitivity and specificity of asthma case definitions. Using information from a supplementary questionnaire sent to participants who reported a respiratory illness, the Nurses' Health Study investigators defined asthmatics as those who 1) reiterated that a physician had diagnosed the subject as having asthma and 2) reported using an asthma medication since diagnosis. On the contrary, our study and the Women's Health Study relied on self-report of physician diagnosed respiratory illnesses both at baseline and follow-up exam.

There are several plausible mechanisms for an increased risk of diabetes among asthmatic subjects, which may be nuanced by asthma phenotype (e.g. child- vs. adult-onset and obese vs. non-obese asthma). Asthma is associated with unregulated expression of myriad proinflammatory cytokine pathways, including nuclear factor interleukin-6 (IL6), tumor necrosis factor- α (TNF α), and adhesion molecules, likely through its activation of nuclear factor- κ B [7, 30, 31]. Circulating levels of these inflammatory cytokines have been shown to be positively associated with T2D risk [32, 33]. Hypoxia and intermittent hypoxia, as commonly occurs in obese-adult asthmatics [34, 35], results in worsening of glucose metabolism *via* insulin-dependent and insulin-independent mediated glucose disposal [9–11]. Such altered glucose metabolism may be mediated by oxygen-regulated expression of

inflammatory cytokines [7, 31] or formation of reactive oxygen species, which can suppress insulin secretion and worsen insulin sensitivity [36]. Chronic airflow limitation, as opposed to intermittent hypoxia, may also affect insulin resistance, as evidenced by the inverse association found between forced expiratory volume in one second and incidence of T2D [29]. While the above candidate mechanisms may act in a synergistic manner to alter glucose metabolism in asthmatics, our understanding of intermediate pathways is still evolving, and future research using animal and human studies are warranted.

Future investigation into this topic must carefully examine the role of adiposity in the pathogenic pathways linking asthma and diabetes. Our study found that the association between asthma diagnosis and incident diabetes was stronger in obese participants than non-obese participants, suggesting that excess body fat and airway inflammation may interact to promote the future development of diabetes. Epidemiologic studies have shown obesity is a risk factor for, and involved in the exacerbation of asthma [6, 31]. Several hypotheses have been proposed to explain the physiologic mechanisms underlying this association, including genetic pleiotropy, dietary intake of antioxidants, and alterations in immune or inflammatory responses [6, 31]. Asthma may interact synergistically with obesity to increase circulating levels of proinflammatory cytokines (e.g. leptin, resistin, TNF α , and IL6) and thereby increase risk of insulin resistance and T2D [6, 31]. Thus, the preeminent etiology driving the development of both asthma and obesity may be a hyperinflammatory state whereby the two disorders perpetuate each other through pernicious reinforcing proinflammatory mechanisms that ultimately disrupt glucose metabolism. Others have even suggested a distinct obese-asthma phenotype with unique inflammatory patterns [37]. Future studies on this topic are needed examine varying subtypes of asthma and potential biologic interaction between asthma and body fat on the risk of T2D.

Our study has limitations, one being the validity of self-reported, physician-diagnosed of asthma in a middle-aged and older population. Although there is evidence to suggest that self-report of asthma yields high specificity [38], there are also reports suggesting the misdiagnosis of chronic obstructive pulmonary disease (COPD) as asthma occurs frequently [39]. The Nurses' Health Study asthma case definition (described above) may be more sensitive than ours and that of the Women's Health Study. If COPD were related to an increased risk of diabetes, then misdiagnosis of asthma as COPD in our study would bias the asthma-diabetes measure of association away from the null. However, considering a large proportion of patients with COPD have a history of smoking and, in our study, the strength of the asthma-diabetes association was similar in ever and never smokers suggests that our findings were not explained by asthma misdiagnosed as COPD. Moreover, using age at asthma diagnosis increases reliability of self-reported asthma diagnosis in our study [40]. Nonetheless, future research should classify asthma objectively through clinical guidelines. Other limitations to our study include lack of data on asthma medication use or immunoglobulin E levels to further differentiate asthma subtypes, as well as lack of direct measures of adiposity or inflammatory markers, which may help shed etiological insight on the observed associations. Our study also did not collect information on inhaled corticosteroids (e.g. prednisolone) or other asthma medications. However, a recent study found a null association between inhaled corticosteroids and incident diabetes [41]. Finally, because our study was observational, we cannot exclude the influence of unmeasured or residual confounding.

Our study also has several strengths. It is first study to examine the asthma-diabetes association in a non-Western population of men and women with high rates of diabetes. The SCHS is a large prospective study with rich and high-quality participant data, allowing us to assess effect modification and control for potential confounding. Another strength of our study is the prospective analytic approach, which allowed us to reduce the potential for

incidence-prevalence bias [42]. By excluding baseline diabetes cases in the main analyses, and only assessing the prospective association between history of asthma diagnosis and incident T2D, we were able to eliminate differences between lead-in duration of diabetes and reduce the potential influence of differential diagnosis of diabetes across exposure categories prior to entering into the study.

Our sensitivity analyses also attempt to discover and resolve detection/selection bias—whereby individuals who are diagnosed with asthma are more likely to be diagnosed with diabetes because of greater availability and use of medical care (medical surveillance) [42]. To examine if the detection bias might explain the observed associations, we performed the Cox regression analysis on self-reported history of allergic rhinitis and T2D risk, controlling for the same confounding variables that were included in the asthma analyses. After multivariate adjustment, individuals with self-reported allergic rhinitis were not at greater risk of diabetes (HR = 0.78; 95% CI: 0.54–1.13), suggesting better medical surveillance itself does not explain the higher incidence of diabetes in asthmatics. Nevertheless, it is possible that such biases remain.

In conclusion, this study provides evidence for a positive association between self-reported asthma and type 2 diabetes that is partly attenuated after adjustment for BMI. If this association is causal, and not due to residual confounding or other biases, it indicates additional health burdens imposed by asthma, an increasingly prevalent condition in the general population [1, 2]. The biologic mechanism by which asthma may increase adult diabetes risk merits further investigation.

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The mean (SD) or n (%)^a of selected characteristics in study participants at baseline by age at diagnosis of asthma: the Singapore Chinese Health Study

Table 1

<i>Variable</i>	Never asthma (N=41,969)	Asthma diagnosis age 18 (N=386)	Asthma diagnosis > age 18 (N=487)
Age (years)	55.2 (7.6)	52.6 (6.5)	56.7 (8.1)
Sex (% female)	24,136 (58)	241 (63)	529 (56)
BMI (kg/m ²)	23.0 (3.2)	23.2 (3.3)	23.2 (3.7)
Height (cm)	159.4 (7.9)	159.1 (7.4)	159.6 (7.8)
High school education + ^a	12,811 (31)	174 (45)	140 (29)
Vigorous physical activity ^a	4,029 (10)	42 (11)	49 (10)
Ever smoked ^a	11,516 (27)	93 (24)	150 (31)
Lived with smoker			
Before 18 years ^a	2,955 (7)	36 (9)	30 (6)
After 18 years ^a	4780 (11)	38 (10)	69 (14)
Before and after 18 years ^a	26,644 (63)	251 (65)	329 (67)
Any alcohol ^a	8,416 (20)	64 (17)	76 (16)
Soft drinks, 1/week	6,689 (16)	69 (18)	63 (13)
Coffee, 2/day	14,759 (35)	139 (36)	185 (38)
Tea, 1/day	9,352 (22)	68 (18)	77 (16)
Energy (kcal)	1,566.0 (521.9)	1,596.1 (494.1)	1,571.2 (492.1)

BMI, body mass index; Kcal, kilocalories

Hazard ratios (HRs) and 95% confidence intervals for type 2 diabetes according to asthma diagnosis in the Singapore Chinese Health Study.

Table 2

Asthma definition	No. of diabetes cases	Incidence Rate ^a	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Never asthma (N=42 842)	2180	9.07	1 (referent)	1 (referent)
Ever asthma (N=873)	54	11.56	1.31 (1.00, 1.72)	1.25 (0.95, 1.64)
Former (N=386)	21	9.41	1.18 (0.77, 1.81)	1.17 (0.76, 1.80)
Current (N=487)	33	13.19	1.41 (1.00, 1.99)	1.30 (0.92, 1.84)
Asthma diagnosis				
Childhood (N=489)	35	10.18	1.11 (0.71, 1.75)	1.05 (0.67, 1.65)
Adulthood (N=384)	19	12.63	1.45 (1.04, 2.03)	1.39 (0.99, 1.94)
Asthma duration				
20 years (N=578)	37	13.01	1.36 (0.98, 1.88)	1.30 (0.94, 1.79)
>20 years (N=295)	17	11.49	1.22 (0.76, 1.97)	1.15 (0.72, 1.86)

^aCrude (per 1000 person-years)

Model 1 is adjusted for year of interview, sex, age (5 categories), ethnicity (Hokkien/Cantonese), educational level (none, primary, secondary plus), height (continuous), exposure to second-hand cigarette smoke (none, age 18, > age 18, both), smoking (never, former, current), alcohol intake (never or >7/day vs. monthly-7/day), monthly, weekly, daily), physical activity (<2 hr/wk of any moderate and no strenuous activity vs. 2 hr/wk of any moderate or any strenuous activity), soft drinks (never, 1–3/month, 1/week, 2/week), coffee (nondaily, 1/day, 2–3/day, 4/day), tea (never, monthly, weekly, daily), vegetable-fruit-soy dietary pattern (continuous), and total kcal (continuous).

Model 2 is additionally adjusted for baseline BMI (quadratic).

Table 3

Hazard ratios (HRs) and 95% confidence intervals for type 2 diabetes with childhood and adulthood asthma in subgroups stratified by age, sex, BMI, active smoking and physical activity in the Singapore Chinese Health Study.

Never asthma (referent)		Ever asthma (vs. referent)		Childhood asthma (vs. referent)		Adulthood asthma (vs. referent)		<i>P</i> for interaction
Diabetes cases/ <i>n</i>		Diabetes cases/ <i>n</i>	HR (95% CI)	Diabetes cases/ <i>n</i>	HR (95% CI)	Diabetes cases/ <i>n</i>	HR (95% CI)	
Age (years)								
								0.43
<55	1,106/23 490	32/508	1.37 (0.96, 1.95)	13/269	1.12 (0.65, 1.93)	19/239	1.62 (1.03, 2.55)	
55	1074/18 479	22/365	1.10 (0.72, 1.68)	6/115	0.96 (0.43, 2.15)	16/250	1.16 (0.71, 1.91)	
Sex								
								0.42
Male	936/17 833	19/358	1.08 (0.68, 1.70)	6/143	0.82 (0.37, 1.84)	13/215	1.25 (0.72, 2.17)	
Female	1244/24 136	35/515	1.40 (1.00, 1.96)	13/241	1.23 (0.71, 2.13)	22/274	1.52 (0.99, 2.31)	
BMI (kg/m ²)								
								0.09
<27.5	1,783/38 636	36/780	1.10 (0.79, 1.53)	14/353	0.99 (0.58, 1.67)	22/427	1.19 (0.78, 1.81)	
27.5	397/3333	18/93	1.69 (1.05, 2.73)	5/31	1.26 (0.52, 3.06)	13/62	1.95 (1.12, 3.41)	
Smoking								
								0.94
Never	1,521/30 453	37/630	1.33 (0.63, 2.85)	13/291	0.92 (0.23, 3.71)	24/339	1.63 (0.67, 4.00)	0.98
Ever	659/11 516	17/243	1.21 (0.64, 2.27)	6/93	1.11 (0.41, 2.99)	11/150	1.28 (0.57, 2.87)	

All analyses adjusted for year of interview, sex, age (5 categories), ethnicity (Hokkien/Cantonese), educational level (none, primary, secondary plus), height (continuous), exposure to second-hand cigarette smoke (none, age 18, > age 18, both), smoking (never, former, current), alcohol intake (never or >7/day vs. monthly-7/day), monthly, weekly, daily), physical activity (<2 hours/week of any moderate and no strenuous activity vs. 2 hours/week of any moderate or any strenuous activity), soft drinks (never, 1-3/month, 1/week, 2/week), coffee (nondaily, 1/day, 2-3/day, 4/day), tea (never, monthly, weekly, daily), vegetable-fruit-soy dietary pattern (continuous), total kcal (continuous), and BMI (quadratic).