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Asthma and cardiovascular disease mortality: a cohort study of 446 346 Taiwanese adults

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ABSTRACT

Objectives: A significant proportion of cardiovascular disease (CVD) cannot be explained by well-known risk factors such as high cholesterol, hypertension and diabetes. One potential novel risk factor for CVD is asthma. We aimed to investigate the association between asthma and mortality due to cardiovascular disease.

Design: Prospective cohort study.

Setting: A large health check-up program from 1994 to 2011 in Taipei, Taiwan.

Participants: 446 346 Taiwanese adults. Each participant answered questions regarding asthma history (yes/no) and current daily use of asthma medications (yes/no). Active asthma was defined as those using current daily medication for asthma.

Outcomes: The participants were followed for mortality from CVD, coronary heart disease (CHD), and stroke obtained through linkage to the cause-of-death register until 31st December 2011.

Results: We found an increased risk of dying from CVD in individuals with active asthma (adjusted hazard ratio 1.32, 95 % confidence interval 1.08-1.62). The risk of death from CHD or stroke was increased in a similar manner. For deaths from CVD, CHD and stroke we found stronger associations with active asthma than non-active asthma, and for CVD and stroke stronger associations in men than women.

Conclusion: Our study suggests that asthma, particularly active asthma, may have adverse cardiovascular consequences.

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Strengths and limitations of this study

- To our best knowledge this is the largest study to date on asthma and CVD mortality.
- We had objective measures of lung function that allowed us to exclude possible misclassification of asthma with COPD.
- However there is no gold standard for asthma diagnosis and asthma was confirmed based on self-report from a questionnaire.
- Finally, Taiwan has some of the lowest mortality rates from CVD in the world; our sample was young and this led to a relatively small number of CVD deaths.

INTRODUCTION

An estimated 17 million people die of cardiovascular diseases (CVDs) every year(1). Among the main forms of CVD are coronary heart disease (CHD) and stroke(1). Some well-known factors that increase the risk of developing CVD are unfavorable cholesterol levels, high blood pressure, diabetes and cigarette smoking. A significant proportion of CVD cannot be explained by these known risk factors, and a high incidence of the diseases makes it important to detect other potentially modifiable risk factors. One novel potential risk factor is asthma. As much as 330 million adults worldwide are estimated to have asthma,(2) emphasizing the potential public health importance of any effect of asthma on the occurrence of CVD. Such an association is plausible as it is suggested that asthma is associated with low-grade systemic inflammation and decline in pulmonary function,(3) which has been linked to an increase in CVD later in life(4, 5). Despite the plausibility of such an association, only few studies have investigated the association between asthma and risk of CVD(5, 6). For example, Iribarren et al(6) recently reported a risk ratio (RR) of 1.22 (95% confidence interval [CI] 1.14 to 1.31) for CVD related death or hospitalization in women with asthma compared with women without asthma after adjusting for demographic and established CVD risk factors; there was no association in men. To considerably strengthen the existing evidence for a causative association, there is a need for large prospective studies on asthma and the risk of CVD which can additionally investigate the influence of sex.

Approximately 5.5 million people die from stroke every year(1). Among the survivors, the consequences on physical, cognitive and emotional functioning are potentially devastating. Despite the devastating consequences of stroke, asthma as a novel risk factor has not been thoroughly investigated and only a few studies have examined this association(5, 7). Our aim was to examine whether asthma at baseline was associated with an increased risk of

deaths from CVD, and more specifically, CHD and stroke utilizing a large cohort of more than 400,000 Taiwanese adults participating in a health check-up program.

METHODS

Study population

The original study cohort consisted of 593,225 Taiwanese adults aged 20 years or older who participated in a large health check-up program from 1994 to 2011, run by MJ Health Management Institution, Taipei, Taiwan (https://www.mjclinic.com.tw). The baseline questionnaire included questions about history of asthma and current use of asthma medications. The participants went through a number of biochemical tests and physical examinations as described previously(8). The study was based on 446,346 (75%) participants who attended check-ups between 1998 and 2011 and who had full information on asthma, asthma medications, and potential confounding variables including sociodemographic and life style factors.

Asthma

Participants answered questions related to asthma history (yes/no) and current daily use of asthma medications (yes/no). We first defined 'ever asthma' as those reporting a history of asthma or current daily use of asthma drugs, and then grouped these individuals into two subgroups: 1) non-active asthma (those who only reported a history of asthma but not current use of asthma medications) and; 2) active asthma (those who reported current daily use of asthma medications). Self-reported asthma is commonly used in population based studies; this approach has been rigorously evaluated and displays reasonable sensitivity and specificity(9, 10).

CVD mortality

From baseline, the participants were followed for mortality until the end of follow-up, 31st December 2011, through linkage to the Taiwanese cause-of-death register using the national identification numbers. The International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10), codes were used to identify mortality from CVD (ICD-9 390-459; ICD-10 I00-I99), CHD (ICD-9 codes 410-414; ICD-10 I20-I25), and stroke (ICD-9 430-438; ICD-10 I60-I69).

Covariates

At the baseline health check-up participants were wearing light-weight clothes and were measured barefoot. Their weight (to the nearest 0.1 kg) and height (to the nearest mm) were measured using an auto-anthropometer, Nakamura KN-5000A (Nakamura, Tokyo, Japan) and their body mass index (BMI) was calculated (kg/m^2). After 5 minutes seated rest, blood pressure was measured twice at 10-minute intervals using a computerized auto-mercury sphygmomanometer (CH-5000, Citizen, Tokyo, Japan). We used the mean of the two measurements in our analysis. Glucose, total cholesterol, and triglyceride levels were measured in blood collected after overnight fasting using the Hitachi 7150 auto-analyzer (Hitachi Ltd., Tokyo, Japan). Respiratory functions were measured using an electronic spirometer (HI-501, HI-701, or HI-801; Chest M.I. Inc., Tokyo, Japan).

The participants reported their education (middle school or below, high school, junior college, college or higher), marital status (single, married, divorced or separated, widowed), smoking (never, former, current), alcohol consumption (no or occasional use, former drinking, regular drinking), and physical activity (inactive, low, moderate or high). They also reported whether they had a history of hypertension, diabetes, heart disease, heart surgery, stroke, or whether they were taking medications for hypertension, diabetes, or heart diseases. In the study hypertension was defined as the presence of any of the following: reporting a history of hypertension, taking any hypertensive drugs, a systemic blood pressure >= 140

mmHg, or a diastolic blood pressure >= 90 mmHg. Diabetes was defined as the presence of any of the following: reporting a history of diabetes, taking diabetes medications, or a fasting blood sugar >= 126 mmol/L.

Statistical methods

We used Cox proportional hazards models to investigate the associations of self-reported asthma with CVD, CHD and stroke mortality respectively. Time at entry was date of recruitment and time of exit was 31st December 2011, or death if earlier.

For ever asthma (those answering "yes" to asthma history or use of asthma medications), we estimated the association with CVD, CHD and stroke mortality controlling for age and sex. In a second model we controlled for age, sex, education and marital status, smoking, alcohol consumption, physical activity, hypertension, diabetes, BMI, total cholesterol, triglycerides, and history of heart disease/heart surgery/use of heart drug, and history of stroke. We also investigated the associations of CVD, CHD and stroke mortality with active and non-active asthma separately, compared to those without asthma.

We investigated whether the associations differed in men and women, between age groups (above and below 60 years) and by smoking status (non-current smoker vs. current smokers) by including appropriate interaction terms in the models and conducting subgroup analyses. We then reported the p value for interaction by comparing models with and without the interaction terms using a likelihood ratio test.

We conducted a series of sensitivity analyses to test the robustness of findings. First, we excluded deaths due to CVD, CHD, or stroke occurring in the first two years of follow-up and repeated the analyses, as these deaths may be due to pre-existing cardiovascular diseases but not asthma. We excluded participants with a history of heart disease, heart surgery, use of heart medications and a history of stroke at baseline in a second sensitivity analysis. Lastly,

we excluded participants with possible chronic obstructive pulmonary disease (COPD) at baseline. In this analysis we excluded those who had an FEV_1/FVC ratio (forced expiratory volume in 1 second divided by forced vital capacity) < 0.7.

The proportional hazards assumption was examined by plotting Schoenfeld residuals with time and by examining their correlation.

Ethics approval

Our study complies with the Declaration of Helsinki; the China Medical University Hospital ethics committee has approved the research protocol and informed consent has been obtained from the subjects. The study was approved by the National Health Research Institutes, Taiwan, and the MJ Health Management Institution.

RESULTS

Among the 446,346 participants there were 2,945 deaths from cardiovascular disease, 780 deaths from coronary heart disease and 1,146 deaths from stroke over the follow-up period. At baseline, 3.34% (n=14,917) of the participants reported to have ever asthma; 2.60% (n=11,603) reported to have a history of asthma only and 0.74% (n=3,314) reported to have active asthma. The characteristics of the participants according to baseline asthma status are presented in Table 1.

Table 1. Characteristics of the Participants in the MJ Health Check-up Programme, Taiwan (N=446346).

	Asthma (N= 14917)		No asthma (N= 431429)	
Characteristic	*n*	*(%)*	*n*	*%*
Female	6,893	(46.2)	220,253	(51.1)
College or higher education	5,726	(38.4)	143,649	(33.3)
Married	8,659	(58.0)	281,011	(65.1)
Current smoker	3,461	(23.2)	98,730	(22.9)
Regular alcohol use	1,210	(8.1)	29,884	(6.9)
Physically inactive	7,462	(50.0)	220,976	(51.2)

Hypertension (history of hypertension + hypertensive drug use + systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg)	3,121	(20.9)	77,972	(18.1)
Diabetes (history of diabetes + diabetes drug use + fasting blood glucose >=126) mmol/L)	841	(5.6)	21,274	(4.9)
History of heart disease/heart surgery/use of heart drug	1,045	(7.0)	15,044	(3.5)
History of stroke	129	(0.9)	2,050	(0.5)
	Mean	*(SD)*	*Mean*	*(SD)*
Age (years)	41.0	(15.6)	40.0	(13.4)
Body mass index (kg/m2)	23.4	(3.8)	23.0	(3.6)
Total cholesterol (mmol/L)	5.0	(1.0)	5.0	(1.0)
Triglycerides (mmol/L)	3.0	(2.4)	3.0	(2.6)

In the age- and sex-adjusted model (Model 1), those with ever asthma had a 27% (Hazard Ratio (HR) 1.27, 95% Confidence Interval [CI]: 1.09, 1.48) increased risk of CVD (Table 2). In the multi-adjusted model (Model 2) the association attenuated (HR 1.13, 95% CI: 0.97, 1.31). Using a stricter definition of asthma (active asthma) we found that those that reported any current use of asthma medications had a 32% (HR 1.32, 95% CI: 1.08, 1.62) increased risk of dying from CVD in Model 2. In contrast there was no association of non-active asthma with CVD mortality (HR 0.96, 95% CI: 0.77, 1.62).

Table 2. Hazard Ratios (HRs) for the Association of Asthma with Cardiovascular Disease, Coronary Heart Disease, and Stroke Mortality in the MJ Health Check-up Programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	431,429	2,763	1.00		1.00		730	1.00		1.00		1078	1.00		1.00	
Asthma	14,917	182	1.27	(1.09 ,1.48)	1.13	(0.97 ,1.31)	50	1.29	(0.97 ,1.72)	1.09	(0.82 ,1.45)	68	1.23	(0.96 ,1.57)	1.14	(0.89 ,1.46)
Non-active asthma (history only)	11,603	84	1.04	(0.84 ,1.29)	0.96	(0.77 ,1.19)	25	1.16	(0.78 ,1.73)	1.03	(0.69 ,1.53)	35	1.11	(0.80 ,1.56)	1.08	(0.77 ,1.51)
Active asthma (current drug use)	3,314	98	1.57	(1.29 ,1.93)	1.32	(1.08 ,1.62)	25	1.46	(0.98 ,2.17)	1.16	(0.78 ,1.73)	33	1.37	(0.97 ,1.94)	1.23	(0.86 ,1.74)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

There was evidence that the association of asthma (grouped as non-active and active asthma) with the risk of dying from CVD was stronger in males than in females (*P* for interaction = 0.005 in Model 2) (Table 3). Men who reported ever asthma had a 25% increased risk (HR1.25, 95% CI: 1.04, 1.49) of dying from CVD over the duration of the follow-up in Model 2; among men with ever asthma those with active asthma had a 63% higher risk (HR 1.63, 95% CI: 1.30, 2.04) compared to men without asthma, while men with non-active asthma showed no increased risk (HR 0.90, 95% CI: 0.68, 1.19). These associations were not found in women. When stratifying by age we found no appreciable differences (Supplementary table 1).

Table 3. Hazard ratios (HRs) for the Association of Asthma with Cardiovascular Disease, Coronary Heart Disease, and Stroke Mortality by Sex in the MJ Health Check-up Programme, Taiwan

	N	CVD mortality				CHD mortality				Stroke mortality			
		Cases (n)	Model 1		Model 2	Cases (n)	Model 1		Model 2	Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR 95% CI		HR	95% CI	HR 95% CI		HR	95% CI	HR	95% CI
Males														
No asthma	211,176	1,730	1.00		1.00	494	1.00		1.00	657	1.00		1.00	
Asthma	8,024	132	1.39	(1.16 ,1.66)	1.25 (1.04 ,1.49)	39	1.42	(1.02 ,1.97)	1.21 (0.87 ,1.67)	49	1.36	(1.02 ,1.82)	1.29	(0.96 ,1.72)
Non-active asthma (history only)	6,130	50	0.96	(0.73 ,1.28)	0.90 (0.68 ,1.19)	18	1.21	(0.75 ,1.93)	1.08 (0.67 ,1.73)	20	1.02	(0.65 ,1.59)	1.00	(0.64 ,1.56)
Active asthma (current drug use)	1,894	82	1.91	(1.53 ,2.38)	1.63 (1.30 ,2.04)	21	1.67	(1.08 ,2.59)	1.34 (0.86 ,2.08)	29	1.77	(1.22 ,2.57)	1.62	(1.11 ,2.35)
Females														
No asthma	220,253	1,033	1.00		1.00	236	1.00		1.00	421	1.00		1.00	
Asthma	6,893	50	1.04	(0.78 ,1.38)	0.88 (0.66 ,1.17)	11	0.97	(0.53 ,1.78)	0.82 (0.44 ,1.51)	19	0.98	(0.62 ,1.56)	0.89	(0.56 ,1.42)
Non-active asthma (history only)	5,473	34	1.17	(0.83 ,1.65)	1.05 (0.74 ,1.48)	7	1.05	(0.49 ,2.22)	0.93 (0.44 ,1.99)	15	1.28	(0.77 ,2.14)	1.21	(0.72 ,2.03)
Active asthma (current drug use)	1,420	16	0.83	(0.51 ,1.36)	0.65 (0.40 ,1.07)	4	0.86	(0.32 ,2.32)	0.67 (0.25 ,1.81)	4	0.52	(0.20 ,1.40)	0.45	(0.17 ,1.20)
Sex interaction p														
Asthma (yes/no)			0.19		0.10		0.40		0.27		0.33		0.29	
Asthma (no, history only, history and drug)			0.012		0.005		0.62		0.42		0.043		0.032	

Model 1: adjust for age

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

When only looking at CHD mortality in the total sample, we found consistent associations with those of CVD mortality, although the associations of asthma and CHD mortality were somewhat weaker with limited statistical evidence given the smaller number of deaths and thus reduced power (Table 3). When stratifying by sex, we found a 67% increased risk (HR 1.67, 95% CI: 1.08, 2.59) for active asthma in men in the age adjusted model (Model 1) but the association was largely attenuated when additionally adjusting for potential confounders (Model 2). We did not find any association in women (Table 3). Similarly, we found a more than doubled risk in those below 60 years (HR 2.57, 95% CI: 1.06, 6.26) in Model 1 but the confidence interval was wide and the association was attenuated when adjusting for potential confounders (Supplementary Table 1).

When restricting our analyses to only stroke, we found similar but slightly weaker associations between asthma and stroke mortality (Table 1). We found a 77% increased risk in men with active asthma (HR 1.77, 95% CI: 1.22, 2.57) in Model 1, that persisted after adjusting for potential confounders in Model 2 (HR 1.62, 95% CI: 1.11, 2.35) (Table 2). This risk was not seen in women (*P* for interaction = 0.032). We found no differences in risk of having a stroke death associated with asthma between the age groups (i.e. below and above 60 years old) (Supplementary Table 1).

When excluding deaths occurring during the two first years of follow-up, the results did not change considerably for any of the cardiovascular outcomes (Supplementary table 2). When excluding participants with a history of heart disease, heart surgery, use of heart medications and a history of stroke at baseline, the results were generally similar to those of the main analysis except that the association between asthma and CHD was largely attenuated, although the number of CHD deaths was small (n=13 and 10 in the non-active and active asthma groups respectively) in this analysis (Supplementary table 3). When excluding individuals with FEV1/FVC ratio <0.7 at baseline, the analysis based on the remaining

sample showed that the effect estimate remained the same although the confidence interval widened slightly because of lower power in this analysis (Supplementary table 4).

Overall there was no strong statistical evidence for a difference in the association of asthma with CVD/CHD/Stroke mortality between current smokers and non-current smokers (all p for interaction > 0.05), although there was a tendency towards stronger associations in current smokers than in non- or ex-smokers (Supplementary table 5).

DISCUSSION

To our best knowledge this is the largest study to date on asthma and CVD mortality. In this sample of more than 400,000 Taiwanese adults we found an increased risk of dying from CVD in individuals with active, but not non-active, asthma. The risk of death from CHD or stroke was increased in a similar manner, however in sensitivity analysis excluding those with previous heart disease, only the associations with CVD and stroke mortality remained. For deaths from CVD and stroke we found a stronger association with active asthma in men than in women.

A few previous studies have investigated the association of asthma with risk of cardiovascular disease. One very large recent study including almost one million Italian adults agreed with our findings and reported asthma to be moderately associated with different cardiovascular diseases(11). Additionally, this study did not find any differences in the association between men and women, while our study observed a stronger association in men. This Italian study was cross-sectional however, and there is no way of knowing whether the CVD diagnosis preceded the asthma diagnosis. Additionally, this study did not have access to spirometry measurements such as FEV_1 and FVC and thus was not able to exclude those with a FEV_1/FVC ratio of less than 0.7 to minimise the possibility of misclassification between asthma and COPD.

A smaller study was undertaken in Australia including approximately 4000 people amongst whom 500 were classified as having asthma(12). Individuals with asthma were not only identified by self-report, but also through identification of significant reversibility of airway obstruction. The result were in accordance with our findings and when subjects with COPD were excluded from the analysis ($FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ of predicted), the association of asthma with CVD remained.

Coronary heart disease contributes to a large part of the burden of cardiovascular disease(13) and the risk of complications or even death is high, thus detecting novel risk factors is essential. A few studies have found an increased risk of CHD in patients with asthma(14, 15). However, the results are inconsistent, and a recent study including almost 16 000 participants from the Atherosclerosis Risk in Communities (ARIC) Study failed to confirm this increase in risk of CHD in patients with current asthma (HR 0.69, 95% CI: 0.46, 1.05) (5).

In the current study, we did not find any differences in the association of asthma with CHD between men and women. Other studies have previously found sex differences. A large prospective study by Iribarren and colleagues(16) found that the increased risk of CHD was higher in women with asthma (RR 1.49, 95% CI: 1.43, 1.56) than in men (RR 1.28, 95% CI: 1.21, 1.34) (*P* for interaction <0.001). The authors speculate that the increased risk of CHD among people with asthma may be due to chronic inflammation in people with asthma. Supporting this is the fact that women with asthma tend to have more severe disease than men with asthma,(17) and likely more systemic inflammation. By contrast, we generally observed stronger results in men than in women in this adult Taiwanese population.

In spite of the devastating consequences of stroke, asthma as a novel risk factor has not been thoroughly investigated and only a few studies have examined this association. The

previously mentioned study using data from the ARIC Study,(5) found similar results to ours, with a 55% increased risk of stroke (HR 1.55, 95% CI: 0.95, 2.52) in patients with current asthma compared with those without asthma. A recent meta-analysis of five studies on asthma and stroke found a pooled HR of 1.32 (95% CI: 1.13, 1.54)(18). In contrast to our findings, this meta-analysis found that the associations between asthma and stroke were stronger in women (HR 1.42, 95% CI: 1.15, 1.76) than in men (HR 1.19, 95% CI: 0.90, 1.43). The authors speculate that sex hormones could play a crucial role in modulating immunological inflammation in asthma. However, our results showed an increased risk in men, but not in women. The underlying reasons driving these differences between studies is not clear and further investigations from countries with different ethnicities may help to shed light on this observation.

The biological mechanisms by which asthma may influence CVD are not known, but several mechanisms have been suggested. Asthma is associated with low-grade systemic inflammation,(19) which could influence later risk of CVD(20). Previous studies also suggest that C-reactive protein is associated with both asthma(21) and CVD(22, 23). Lung function impairment is also associated with CVD risk(24, 25). Patients with impaired lung function have increased inflammatory markers (including C-reactive protein, interleukin-1β, and interleukin-6) (26), which are associated with atherosclerosis and cardiovascular events(20, 27). The long-term airway remodelling from the inflammatory response in asthma can produce irreversible airway obstruction and cause a decline in lung function(28). In addition, severe asthma exacerbations are associated with a more rapid decline in lung function(29). Another hypothesis is that asthma is associated with risk of CVD through asthma medication use, in particular the cardiotoxic effects of beta-2 (β_2) agonists(30, 31). Finally, asthma may be associated with CVD due to other factors such as obesity,(32) smoking,(33) or physical inactivity(34). It is also possible that the association between asthma and CVD is due to

comorbidities such as diabetes which has a strong link to CVD(35) and also to asthma(36). In our study, we adjusted for these potential confounders however and it is unlikely that any confounding by these factors would be behind the observed associations.

To the best of our knowledge, our study is the largest to date, investigating the link between asthma and risk of death from cardiovascular disease. Despite the large study size, the objective measures of lung function that allowed us to exclude possible misclassification of asthma with COPD, and the wide range of potential confounders included in our models, the limitations of this study must be considered.

There is no gold standard for asthma diagnosis and despite using spirometry measures to exclude possible COPD, asthma in this study was confirmed based on self-report from a questionnaire. Additionally, we cannot rule out the potential misdiagnosis of heart disease as asthma. Among those diagnosed with asthma, we were unable to separate asthma patients by disease onset (i.e., childhood vs. adulthood), and it is possible that childhood asthma and adult onset asthma differs in regard to asthma triggers,(37) gender distribution(37) and systemic inflammation(38). Thus our observations may not be representative of these subgroups.

Taiwan and some other East Asian countries such as Japan and Hong Kong have some of the lowest mortality rates from CVD in the world(39, 40). Furthermore, our sample was fairly young (mean age 40.4 years), and these may have contributed to the relatively small number of CVD deaths in our study. This may have reduced our power to detect any small effects of asthma on risk of CVD death.

Observational studies inherently limit causal inference. Although we adjusted for a number of potential confounders in our analyses, there is a possibility of uncontrolled confounding contributing to the observed associations. However, any residual confounding would need to be strongly associated with both asthma and CVD mortality and be unrelated to the covariates included in our models.

Finally, the sample was from a health check-up programme run by a private company and the participants may have come from a somewhat more advantaged socioeconomic position than Taiwan's general population and therefore our findings may not be representative of the general population. However, the cohort was similar to the general population reported in a national survey(41) in terms of certain characteristics including the prevalence of smoking.

CONCLUSION

Our study suggests that asthma, particularly active asthma, may have adverse cardiovascular consequences. For deaths from CVD and stroke, the association was stronger in men than in women. The associations persisted even after adjustment for established CVD risk factors. Further studies are needed to elucidate better the mechanisms underlying this association and to explain sex difference in the association.

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COMPETING INTERESTS

None declared.

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CONTRIBUTIONS

LBS wrote the analysis plan and wrote the first draft of the manuscript. MKT did the data analysis. CPW supervised the work and reviewed the manuscript. SSC helped supervise the work, reviewed the manuscript and coordinated the collaboration between the researchers. BMB designed the study, helped write the analysis plan, wrote the methods section of the manuscript and reviewed the manuscript. All authors confirm that they have reviewed and approved the final version of the manuscript.

DATA SHARING STATEMENT

No additional data are available.

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Supplementary Table 1. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality by age in the MJ health check-up programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Rate per 100,000 py	Model 1		Model 2	Cases (n)	Rate per 100,000 py	Model 1		Model 2	Cases (n)	Rate per 100,000 py	Model 1		Model 2
				HR	(95% CI)	HR 95% CI			HR	95% CI	HR 95% CI			HR	95% CI	HR 95% CI
<60 years																
No asthma	384,436	802	22	1.00		1.00	186	5	1.00		1.00	319	9	1.00		1.00
Asthma	12,392	34	32	1.30	(0.92 ,1.84)	1.18 (0.84 ,1.66)	11	10	1.76	(0.96 ,3.24)	1.54 (0.84 ,2.85)	12	11	1.16	(0.65 ,2.06)	1.10 (0.62 ,1.97)
Non-active asthma (history only)	10,237	18	21	0.99	(0.62 ,1.58)	0.97 (0.61 ,1.54)	6	7	1.40	(0.62 ,3.15)	1.32 (0.58 ,2.97)	6	7	0.83	(0.37 ,1.87)	0.86 (0.39 ,1.94)
Active asthma (current drug use)	2,155	16	76	2.02	(1.23 ,3.31)	1.57 (0.96 ,2.58)	5	24	2.57	(1.06 ,6.26)	1.95 (0.80 ,4.78)	6	29	1.89	(0.84 ,4.24)	1.53 (0.68 ,3.44)
>=60 years																
No asthma	46,993	1,961	421	1.00		1.00	544	117	1.00		1.00	759	163	1.00		1.00
Asthma	2,525	148	599	1.27	(1.07 ,1.50)	1.13 (0.95 ,1.33)	39	158	1.20	(0.87 ,1.66)	1.02 (0.73 ,1.41)	56	227	1.25	(0.95 ,1.64)	1.16 (0.88 ,1.52)
Non-active asthma (history only)	1,366	66	479	1.05	(0.82 ,1.34)	0.97 (0.76 ,1.24)	19	138	1.09	(0.69 ,1.71)	0.96 (0.61 ,1.53)	29	211	1.19	(0.82 ,1.73)	1.14 (0.79 ,1.65)
Active asthma (current drug use)	1,159	82	749	1.52	(1.22 ,1.90)	1.30 (1.04 ,1.63)	20	183	1.33	(0.85 ,2.08)	1.07 (0.68 ,1.68)	27	247	1.31	(0.89 ,1.92)	1.18 (0.80 ,1.74)
Age interaction p																
Asthma (yes/no)				0.85		0.50			0.25		0.15			0.85		1.00
Asthma (no, history only, history and drug)				0.079		0.32			0.15		0.22			0.18		0.49

PY: person-years

Model 1: adjust for sex

Model 2: adjust for sex education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

Supplementary table 2. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding deaths[a] occurring during the two first years of follow-up, in the MJ health check-up programme, Taiwan

		CVD mortality					CHD mortality					Stroke mortality				
	N[a]	Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	431,200	2,534	1.00		1.00		661	1.00		1.00		988	1.00		1.00	
Asthma	14,896	161	1.23	(1.05 ,1.44)	1.10	(0.94 ,1.29)	44	1.26	(0.93 ,1.71)	1.07	(0.79 ,1.46)	60	1.18	(0.91 ,1.53)	1.10	(0.85 ,1.44)
Non-active asthma (history only)	11,597	78	1.05	(0.84 ,1.32)	0.98	(0.78 ,1.23)	22	1.13	(0.74 ,1.72)	1.01	(0.66 ,1.54)	33	1.14	(0.81 ,1.61)	1.11	(0.78 ,1.57)
Active asthma (current drug use)	3,299	83	1.47	(1.18 ,1.83)	1.24	(1.00 ,1.55)	22	1.46	(0.98 ,2.17)	1.15	(0.75 ,1.76)	27	1.23	(0.84 ,1.80)	1.10	(0.75 ,1.62)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

[a] The number of deaths due to CVD, CHD, and stroke varied and thus the total number of participants after excluding deaths due to each of three causes differed.

Supplementary Table 3. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding individuals with history of heart disease / heart surgery / use of heart drug, and history of stroke at baseline, in the MJ health check-up programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	414,859	1,992	1.00		1.00		514	1.00		1.00		823	1.00		1.00	
Asthma	13,802	108	1.16	(0.96 ,1.41)	1.15	(0.95 ,1.39)	23	0.94	(0.62 ,1.43)	0.92	(0.60 ,1.40)	42	1.10	(0.81 ,1.50)	1.09	(0.80 ,1.49)
Non-active asthma (history only)	10,935	51	0.94	(0.71 ,1.25)	0.95	(0.72 ,1.26)	13	0.92	(0.53 ,1.60)	0.91	(0.52 ,1.58)	21	0.94	(0.61 ,1.45)	0.97	(0.63 ,1.50)
Active asthma (current drug use)	2,867	57	1.47	(1.13 ,1.92)	1.41	(1.08 ,1.84)	10	0.96	(0.52 ,1.80)	0.93	(0.50 ,1.75)	21	1.32	(0.85 ,2.03)	1.25	(0.81 ,1.93)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol and triglycerides.

Supplementary table 4. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding individuals with FEV1/FCV < 0.7 at baseline, in the MJ health check-up programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	352,774	2,319	1.00		1.00		617	1.00		1.00		902	1.00		1.00	
Asthma	11,074	117	1.27	(1.06 ,1.53)	1.12	(0.93 ,1.36)	32	1.29	(0.90 ,1.84)	1.08	(0.76 ,1.55)	46	1.29	(0.96 ,1.73)	1.21	(0.90 ,1.63)
Non-active asthma (history only)	8,835	60	1.05	(0.81 ,1.36)	0.98	(0.76 ,1.27)	19	1.25	(0.79 ,1.97)	1.11	(0.70 ,1.76)	25	1.13	(0.76 ,1.68)	1.11	(0.75 ,1.66)
Active asthma (current drug use)	2,239	57	1.62	(1.25 ,2.11)	1.33	(1.02 ,1.73)	13	1.36	(0.78 ,2.35)	1.05	(0.60 ,1.82)	21	1.55	(1.01 ,2.39)	1.36	(0.88 ,2.10)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

Supplementary Table 5. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality by smoking status in the MJ health check-up programme, Taiwan

		CVD mortality					CHD mortality					Stroke mortality				
	N	Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Non or ex-smoker																
No asthma	332,699	1,898	1.00		1.00		470	1.00		1.00		754	1.00		1.00	
Asthma	11,456	113	1.15	(0.95 ,1.39)	1.04	(0.86 ,1.25)	30	1.20	(0.83 ,1.73)	1.03	(0.71 ,1.50)	40	1.03	(0.75 ,1.42)	0.98	(0.71 ,1.35)
Non-active asthma (history only)	9,018	56	1.00	(0.77 ,1.31)	0.94	(0.72 ,1.23)	16	1.15	(0.70 ,1.89)	1.04	(0.63 ,1.72)	24	1.09	(0.72 ,1.63)	1.07	(0.71 ,1.61)
Active asthma (current drug use)	2,438	57	1.33	(1.02 ,1.74)	1.14	(0.88 ,1.49)	14	1.26	(0.74 ,2.14)	1.02	(0.60 ,1.75)	16	0.96	(0.59 ,1.58)	0.87	(0.53 ,1.43)
Current smoker																
No asthma	98,730	865	1.00		1.00		260	1.00		1.00		324	1.00		1.00	
Asthma	3,461	69	1.55	(1.21 ,1.98)	1.34	(1.04 ,1.71)	20	1.45	(0.92 ,2.29)	1.20	(0.75 ,1.90)	28	1.67	(1.13 ,2.45)	1.51	(1.02 ,2.23)
Non-active asthma (history only)	2,585	28	1.13	(0.78 ,1.65)	1.01	(0.69 ,1.48)	9	1.18	(0.61 ,2.30)	1.01	(0.52 ,1.97)	11	1.19	(0.65 ,2.17)	1.11	(0.61 ,2.04)
Active asthma (current drug use)	876	41	2.07	(1.51 ,2.84)	1.72	(1.25 ,2.36)	11	1.78	(0.97 ,3.25)	1.41	(0.77 ,2.60)	17	2.26	(1.38 ,3.69)	1.97	(1.20 ,3.23)
Smoking status interaction p																
Asthma (yes/no)					0.18					0.74					0.12	
Asthma (no, history only, history and drug)					0.27					0.82					0.088	

Model 1: adjust for age

Model 2: adjust for age, education, marital status, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	8,9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	8,9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Asthma and cardiovascular disease mortality: a cohort study of 446 346 Taiwanese adults

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Asthma and cardiovascular disease mortality: a cohort study of 446 346 Taiwanese adults

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ABSTRACT

Objectives: A significant proportion of cardiovascular disease (CVD) cannot be explained by well-known risk factors such as high cholesterol, hypertension and diabetes. One potential novel risk factor for CVD is asthma. We aimed to investigate the association between asthma and mortality due to cardiovascular disease.

Design: Prospective cohort study.

Setting: A large health check-up program from 1994 to 2011 in Taipei, Taiwan.

Participants: 446 346 Taiwanese adults. Each participant answered questions regarding asthma history (yes/no) and current daily use of asthma medications (yes/no). Active asthma was defined as those using current daily medication for asthma.

Outcomes: The participants were followed for mortality from CVD, coronary heart disease (CHD), and stroke obtained through linkage to the cause-of-death register until 31st December 2011.

Results: We found an increased risk of dying from CVD in individuals with active asthma (adjusted hazard ratio 1.32, 95 % confidence interval 1.08-1.62). The risk of death from CHD or stroke was increased in a similar manner. For deaths from CVD, CHD and stroke we found stronger associations with active asthma than non-active asthma, and for CVD and stroke stronger associations in men than women.

Conclusion: Our study suggests that asthma, particularly active asthma, may have adverse cardiovascular consequences.

Word count: 202

Strengths and limitations of this study

- To our best knowledge this is the largest study to date on asthma and CVD mortality.
- We had objective measures of lung function that allowed us to exclude possible misclassification of asthma with COPD.
- However there is no gold standard for asthma diagnosis and asthma was confirmed based on self-report from a questionnaire.
- Finally, Taiwan has some of the lowest mortality rates from CVD in the world; our sample was young and this led to a relatively small number of CVD deaths.

INTRODUCTION

An estimated 17 million people die of cardiovascular diseases (CVDs) every year(1). Among the main forms of CVD are coronary heart disease (CHD) and stroke(1). Some well-known factors that increase the risk of developing CVD are unfavorable cholesterol levels, high blood pressure, diabetes and cigarette smoking. A significant proportion of CVD cannot be explained by these known risk factors, and a high incidence of the diseases makes it important to detect other potentially modifiable risk factors. One novel potential risk factor is asthma. As much as 330 million adults worldwide are estimated to have asthma,(2) emphasizing the potential public health importance of any effect of asthma on the occurrence of CVD. Such an association is plausible as it is suggested that asthma is associated with low-grade systemic inflammation and decline in pulmonary function,(3) which has been linked to an increase in CVD later in life(4, 5). Despite the plausibility of such an association, only few studies have investigated the association between asthma and risk of CVD(5, 6). For example, Iribarren et al(6) recently reported a hazard ratio of 1.22 (95% confidence interval 1.14 to 1.31) for CHD related death or hospitalization in women with asthma compared with women without asthma after adjusting for demographic and established CHD risk factors; there was no association in men. To considerably strengthen the existing evidence for a causative association, there is a need for large prospective studies on asthma and the risk of CVD which can additionally investigate the influence of sex.

Approximately 5.5 million people die from stroke every year(1). Among the survivors, the consequences on physical, cognitive and emotional functioning are potentially devastating. Despite the devastating consequences of stroke, asthma as a novel risk factor has not been thoroughly investigated and only a few studies have examined this association(5, 7). Our aim was to examine whether asthma at baseline was associated with an increased risk of

deaths from CVD, and more specifically, CHD and stroke utilizing a large cohort of more than 400,000 Taiwanese adults participating in a health check-up program.

METHODS

Study population

The original study cohort consisted of 593,225 Taiwanese adults aged 20 years or older who participated in a large health check-up program from 1994 to 2011, run by MJ Health Management Institution, Taipei, Taiwan (https://www.mjclinic.com.tw). The baseline questionnaire included questions about history of asthma and current use of asthma medications. The participants went through a number of biochemical tests and physical examinations as described previously(8). The study was based on 446,346 (75%) participants who attended check-ups between 1998 and 2011 and who had full information on asthma, asthma medications, and potential confounding variables including sociodemographic and life style factors.

Asthma

Participants answered questions related to asthma history (yes/no) and current daily use of asthma medications (yes/no). We first defined 'ever asthma' as those reporting a history of asthma or current daily use of asthma drugs, and then grouped these individuals into two subgroups: 1) non-active asthma (those who only reported a history of asthma but not current use of asthma medications) and; 2) active asthma (those who reported current daily use of asthma medications). Self-reported asthma is commonly used in population based studies; this approach has been rigorously evaluated and displays reasonable sensitivity and specificity(9, 10).

CVD mortality

From baseline, the participants were followed for mortality until the end of follow-up, 31st December 2011, through linkage to the Taiwanese cause-of-death register using the national identification numbers. The International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10), codes were used to identify mortality from CVD (ICD-9 390-459; ICD-10 I00-I99), CHD (ICD-9 codes 410-414; ICD-10 I20-I25), and stroke (ICD-9 430-438; ICD-10 I60-I69). A previous study showed good accuracy of cause-of-death coding for both heart diseases and stroke in Taiwan(11).

Covariates

At the baseline health check-up participants were wearing light-weight clothes and were measured barefoot. Their weight (to the nearest 0.1 kg) and height (to the nearest mm) were measured using an auto-anthropometer, Nakamura KN-5000A (Nakamura, Tokyo, Japan) and their body mass index (BMI) was calculated (kg/m^2). After 5 minutes seated rest, blood pressure was measured twice at 10-minute intervals using a computerized auto-mercury sphygmomanometer (CH-5000, Citizen, Tokyo, Japan). We used the mean of the two measurements in our analysis. Glucose, total cholesterol, and triglyceride levels were measured in blood collected after overnight fasting using the Hitachi 7150 auto-analyzer (Hitachi Ltd., Tokyo, Japan). Respiratory functions were measured using an electronic spirometer (HI-501, HI-701, or HI-801; Chest M.I. Inc., Tokyo, Japan).

The participants reported their education (middle school or below, high school, junior college, college or higher), marital status (single, married, divorced or separated, widowed), smoking (never, former, current), alcohol consumption (no or occasional use, former drinking, regular drinking), and physical activity (inactive, low, moderate or high). They also reported whether they had a history of hypertension, diabetes, heart disease, heart surgery, stroke, or whether they were taking medications for hypertension, diabetes, or heart diseases. In the study hypertension was defined as the presence of any of the following: reporting a

history of hypertension, taking any hypertensive drugs, a systemic blood pressure >= 140 mmHg, or a diastolic blood pressure >= 90 mmHg. Diabetes was defined as the presence of any of the following: reporting a history of diabetes, taking diabetes medications, or a fasting blood sugar >= 126 mmol/L.

Statistical methods

We used Cox proportional hazards models to investigate the associations of self-reported asthma with CVD, CHD and stroke mortality respectively. Time at entry was date of recruitment and time of exit was 31st December 2011, or death if earlier.

For ever asthma (those answering "yes" to asthma history or use of asthma medications), we estimated the association with CVD, CHD and stroke mortality controlling for age and sex. In a second model we controlled for age, sex, education and marital status, smoking, alcohol consumption, physical activity, hypertension, diabetes, BMI, total cholesterol, triglycerides, and history of heart disease/heart surgery/use of heart drug, and history of stroke. We also investigated the associations of CVD, CHD and stroke mortality with active and non-active asthma separately, compared to those without asthma.

We investigated whether the associations differed in men and women, between age groups (above and below 60 years) and by smoking status (non-current smoker vs. current smokers) by including appropriate interaction terms in the models and conducting subgroup analyses. We then reported the p value for interaction by comparing models with and without the interaction terms using a likelihood ratio test.

We conducted a series of sensitivity analyses to test the robustness of findings. First, we excluded deaths due to CVD, CHD, or stroke occurring in the first two years of follow-up and repeated the analyses, as these deaths may be due to pre-existing cardiovascular diseases but not asthma. We excluded participants with a history of heart disease, heart surgery, use of

heart medications and a history of stroke at baseline in a second sensitivity analysis. Lastly, we excluded participants with possible chronic obstructive pulmonary disease (COPD) at baseline. In this analysis we excluded those who had an FEV_1/FVC ratio (forced expiratory volume in 1 second divided by forced vital capacity) < 0.7.

The proportional hazards assumption was examined by plotting Schoenfeld residuals with time and by examining their correlation.

Ethics approval

Our study complies with the Declaration of Helsinki; the China Medical University Hospital ethics committee has approved the research protocol and informed consent has been obtained from the subjects. The study was approved by the National Health Research Institutes, Taiwan, and the MJ Health Management Institution.

RESULTS

Among the 446,346 participants there were 2,945 deaths from cardiovascular disease, 780 deaths from coronary heart disease and 1,146 deaths from stroke over the follow-up period. At baseline, 3.34% (n=14,917) of the participants reported to have ever asthma; 2.60% (n=11,603) reported to have a history of asthma only and 0.74% (n=3,314) reported to have active asthma. The characteristics of the participants according to baseline asthma status are presented in Table 1.

Table 1. Characteristics of the Participants in the MJ Health Check-up Programme, Taiwan (N=446346).

	Asthma (N= 14917)		No asthma (N= 431429)	
Characteristic	*n*	*(%)*	*n*	*%*
Female	6,893	(46.2)	220,253	(51.1)
College or higher education	5,726	(38.4)	143,649	(33.3)
Married	8,659	(58.0)	281,011	(65.1)
Current smoker	3,461	(23.2)	98,730	(22.9)
Regular alcohol use	1,210	(8.1)	29,884	(6.9)
Physically inactive	7,462	(50.0)	220,976	(51.2)

Hypertension (history of hypertension + hypertensive drug use + systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg)	3,121	(20.9)	77,972	(18.1)
Diabetes (history of diabetes + diabetes drug use + fasting blood glucose >=126) mmol/L)	841	(5.6)	21,274	(4.9)
History of heart disease/heart surgery/use of heart drug	1,045	(7.0)	15,044	(3.5)
History of stroke	129	(0.9)	2,050	(0.5)
	Mean	*(SD)*	*Mean*	*(SD)*
Age (years)	41.0	(15.6)	40.0	(13.4)
Body mass index (kg/m2)	23.4	(3.8)	23.0	(3.6)
Total cholesterol (mmol/L)	5.0	(1.0)	5.0	(1.0)
Triglycerides (mmol/L)	3.0	(2.4)	3.0	(2.6)

In the age- and sex-adjusted model (Model 1), those with ever asthma had a 27% (Hazard Ratio [HR] 1.27, 95% Confidence Interval [CI]: 1.09, 1.48) increased risk of CVD (Table 2). In the multi-adjusted model (Model 2) the association attenuated (HR 1.13, 95% CI: 0.97, 1.31). Using a stricter definition of asthma (active asthma) we found that those that reported any current use of asthma medications had a 32% (HR 1.32, 95% CI: 1.08, 1.62) increased risk of dying from CVD in Model 2. In contrast there was no association of non-active asthma with CVD mortality (HR 0.96, 95% CI: 0.77, 1.62).

Table 2. Hazard Ratios (HRs) for the Association of Asthma with Cardiovascular Disease (CVD), Coronary Heart Disease (CHD), and Stroke Mortality in the MJ Health Check-up Programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	431,429	2,763	1.00		1.00		730	1.00		1.00		1078	1.00		1.00	
Asthma	14,917	182	1.27	(1.09 ,1.48)	1.13	(0.97 ,1.31)	50	1.29	(0.97 ,1.72)	1.09	(0.82 ,1.45)	68	1.23	(0.96 ,1.57)	1.14	(0.89 ,1.46)
Non-active asthma (history only)	11,603	84	1.04	(0.84 ,1.29)	0.96	(0.77 ,1.19)	25	1.16	(0.78 ,1.73)	1.03	(0.69 ,1.53)	35	1.11	(0.80 ,1.56)	1.08	(0.77 ,1.51)
Active asthma (current drug use)	3,314	98	1.57	(1.29 ,1.93)	1.32	(1.08 ,1.62)	25	1.46	(0.98 ,2.17)	1.16	(0.78 ,1.73)	33	1.37	(0.97 ,1.94)	1.23	(0.86 ,1.74)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

There was evidence that the association of asthma (grouped as non-active and active asthma) with the risk of dying from CVD was stronger in males than in females (*P* for interaction = 0.005 in Model 2) (Table 3). Men who reported ever asthma had a 25% increased risk (HR1.25, 95% CI: 1.04, 1.49) of dying from CVD over the duration of the follow-up in Model 2; among men with ever asthma those with active asthma had a 63% higher risk (HR 1.63, 95% CI: 1.30, 2.04) compared to men without asthma, while men with non-active asthma showed no increased risk (HR 0.90, 95% CI: 0.68, 1.19). These associations were not found in women. When stratifying by age we found no appreciable differences (Supplementary table 1).

Table 3. Hazard ratios (HRs) for the Association of Asthma with Cardiovascular Disease (CVD), Coronary Heart Disease (CHD), and Stroke Mortality by Sex in the MJ Health Check-up Programme, Taiwan

	N	CVD mortality				CHD mortality				Stroke mortality			
		Cases (n)	Model 1		Model 2	Cases (n)	Model 1		Model 2	Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR 95% CI		HR	95% CI	HR 95% CI		HR	95% CI	HR	95% CI
Males														
No asthma	211,176	1,730	1.00		1.00	494	1.00		1.00	657	1.00		1.00	
Asthma	8,024	132	1.39	(1.16 ,1.66)	1.25 (1.04 ,1.49)	39	1.42	(1.02 ,1.97)	1.21 (0.87 ,1.67)	49	1.36	(1.02 ,1.82)	1.29	(0.96 ,1.72)
Non-active asthma (history only)	6,130	50	0.96	(0.73 ,1.28)	0.90 (0.68 ,1.19)	18	1.21	(0.75 ,1.93)	1.08 (0.67 ,1.73)	20	1.02	(0.65 ,1.59)	1.00	(0.64 ,1.56)
Active asthma (current drug use)	1,894	82	1.91	(1.53 ,2.38)	1.63 (1.30 ,2.04)	21	1.67	(1.08 ,2.59)	1.34 (0.86 ,2.08)	29	1.77	(1.22 ,2.57)	1.62	(1.11 ,2.35)
Females														
No asthma	220,253	1,033	1.00		1.00	236	1.00		1.00	421	1.00		1.00	
Asthma	6,893	50	1.04	(0.78 ,1.38)	0.88 (0.66 ,1.17)	11	0.97	(0.53 ,1.78)	0.82 (0.44 ,1.51)	19	0.98	(0.62 ,1.56)	0.89	(0.56 ,1.42)
Non-active asthma (history only)	5,473	34	1.17	(0.83 ,1.65)	1.05 (0.74 ,1.48)	7	1.05	(0.49 ,2.22)	0.93 (0.44 ,1.99)	15	1.28	(0.77 ,2.14)	1.21	(0.72 ,2.03)
Active asthma (current drug use)	1,420	16	0.83	(0.51 ,1.36)	0.65 (0.40 ,1.07)	4	0.86	(0.32 ,2.32)	0.67 (0.25 ,1.81)	4	0.52	(0.20 ,1.40)	0.45	(0.17 ,1.20)
Sex interaction p														
Asthma (yes/no)			0.19		0.10		0.40		0.27		0.33		0.29	
Asthma (no, history only, history and drug)			0.012		0.005		0.62		0.42		0.043		0.032	

Model 1: adjust for age

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

When only looking at CHD mortality in the total sample, we found consistent associations with those of CVD mortality, although the associations of asthma with CHD mortality were somewhat weaker with limited statistical evidence given the smaller number of deaths and thus reduced power (Table 3). When stratifying by sex, we found a 67% increased risk (HR 1.67, 95% CI: 1.08, 2.59) for active asthma in men in the age-adjusted model (Model 1) but the association was largely attenuated when additionally adjusting for potential confounders (Model 2). We did not find any association in women (Table 3). Similarly, we found a more than doubled risk in those below 60 years (HR 2.57, 95% CI: 1.06, 6.26) in Model 1 but the confidence interval was wide and the association was attenuated when adjusting for potential confounders (Supplementary Table 1).

When restricting our analyses to only stroke, we found similar but slightly weaker associations between asthma and stroke mortality (Table 1). We found a 77% increased risk in men with active asthma (HR 1.77, 95% CI: 1.22, 2.57) in Model 1, that persisted after adjusting for potential confounders in Model 2 (HR 1.62, 95% CI: 1.11, 2.35) (Table 2). This risk was not seen in women (*P* for interaction = 0.032). We found no differences in risk of having a stroke death associated with asthma between the age groups (i.e. below and above 60 years old) (Supplementary Table 1).

When excluding deaths occurring during the two first years of follow-up, the results did not change considerably for any of the cardiovascular outcomes (Supplementary table 2). When excluding participants with a history of heart disease, heart surgery, use of heart medications and a history of stroke at baseline, the results were generally similar to those of the main analysis except that the association between asthma and CHD was largely attenuated, although the number of CHD deaths was small (n=13 and 10 in the non-active and active asthma groups respectively) in this analysis (Supplementary table 3). When excluding individuals with FEV1/FVC ratio <0.7 at baseline, the analysis based on the remaining

sample showed that the effect estimate remained the same although the confidence interval widened slightly because of lower power in this analysis (Supplementary table 4).

Overall there was no strong statistical evidence for a difference in the association of asthma with CVD/CHD/Stroke mortality between current smokers and non-current smokers (all p for interaction > 0.05), although there was a tendency towards stronger associations in current smokers than in non- or ex-smokers (Supplementary table 5).

DISCUSSION

To our best knowledge this is the largest study to date on asthma and CVD mortality. In this sample of more than 400,000 Taiwanese adults we found an increased risk of dying from CVD in individuals with active, but not non-active, asthma. The risk of death from CHD or stroke was increased in a similar manner, however in sensitivity analysis excluding those with previous heart disease, only the associations with CVD and stroke mortality remained. For deaths from CVD and stroke we found a stronger association with active asthma in men than in women.

A few previous studies have investigated the association of asthma with risk of cardiovascular disease. One very large recent study including almost one million Italian adults agreed with our findings and reported asthma to be moderately associated with different cardiovascular diseases(12). Additionally, this study did not find any differences in the association between men and women, while our study observed a stronger association in men. This Italian study was cross-sectional however, and there is no way of knowing whether the CVD diagnosis preceded the asthma diagnosis. Additionally, this study did not have access to spirometry measurements such as FEV_1 and FVC and thus was not able to exclude those with a FEV_1/FVC ratio of less than 0.7 to minimise the possibility of misclassification between asthma and COPD.

A smaller study was undertaken in Australia including approximately 4000 people amongst whom 500 were classified as having asthma(13). Individuals with asthma were not only identified by self-report, but also through identification of significant reversibility of airway obstruction. The result were in accordance with our findings and when subjects with COPD were excluded from the analysis ($FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ of predicted), the association of asthma with CVD remained.

Coronary heart disease contributes to a large part of the burden of cardiovascular disease(14) and the risk of complications or even death is high, thus detecting novel risk factors is essential. A few studies have found an increased risk of CHD in patients with asthma(15, 16). However, the results are inconsistent, and a recent study including almost 16 000 participants from the Atherosclerosis Risk in Communities (ARIC) Study failed to confirm this increase in risk of CHD in patients with current asthma (HR 0.69, 95% CI: 0.46, 1.05) (5).

In the current study, we generally observed stronger results in men than in women in this adult Taiwanese population. By contrast, other studies have previously found stronger associations in women than in men. A large prospective study by Iribarren and colleagues(17) found that the increased risk of CHD was higher in women with asthma (HR 1.49, 95% CI: 1.43, 1.56) than in men (HR 1.28, 95% CI: 1.21, 1.34) (*P* for interaction <0.001). The authors speculate that the increased risk of CHD among people with asthma may be due to chronic inflammation in people with asthma. Supporting this is the fact that women with asthma tend to have more severe disease than men with asthma,(18) and likely more systemic inflammation.

In spite of the devastating consequences of stroke, asthma as a novel risk factor has not been thoroughly investigated and only a few studies have examined this association. The

previously mentioned study using data from the ARIC Study,(5) found similar results to ours, with a 55% increased risk of stroke (HR 1.55, 95% CI: 0.95, 2.52) in patients with current asthma compared with those without asthma. A recent meta-analysis of five studies on asthma and stroke found a pooled HR of 1.32 (95% CI: 1.13, 1.54)(19). In contrast to our findings, this meta-analysis found that the associations between asthma and stroke were stronger in women (HR 1.42, 95% CI: 1.15, 1.76) than in men (HR 1.19, 95% CI: 0.90, 1.43). The authors speculate that sex hormones could play a crucial role in modulating immunological inflammation in asthma. However, our results showed an increased risk in men, but not in women. The underlying reasons driving these differences between studies are not clear and further investigations from countries with different ethnicities may help to shed light on this observation.

The biological mechanisms by which asthma may influence CVD are not known, but several mechanisms have been suggested. Asthma is associated with low-grade systemic inflammation,(20) which could influence later risk of CVD(21). Previous studies also suggest that C-reactive protein is associated with both asthma(22) and CVD(23, 24). Lung function impairment is also associated with CVD risk(25, 26). Patients with impaired lung function have increased inflammatory markers (including C-reactive protein, interleukin-1β, and interleukin-6) (27), which are associated with atherosclerosis and cardiovascular events(21, 28). The long-term airway remodelling from the inflammatory response in asthma can produce irreversible airway obstruction and cause a decline in lung function(29). In addition, severe asthma exacerbations are associated with a more rapid decline in lung function(30). Another hypothesis is that asthma is associated with risk of CVD through asthma medication use, in particular the cardiotoxic effects of beta-2 (β_2) agonists(31, 32). Finally, asthma may be associated with CVD due to other factors such as obesity,(33) smoking,(34) or physical inactivity(35). It is also possible that the association between asthma and CVD is due to

comorbidities such as diabetes which has a strong link to CVD(36) and also to asthma(37). In our study, we adjusted for these potential confounders however and it is unlikely that any confounding by these factors would be behind the observed associations.

To the best of our knowledge, our study is the largest to date, investigating the link between asthma and risk of death from cardiovascular disease. Despite the large study size, the objective measures of lung function that allowed us to exclude possible misclassification of asthma with COPD, and the wide range of potential confounders included in our models, the limitations of this study must be considered.

There is no gold standard for asthma diagnosis and despite using spirometry measures to exclude possible COPD, asthma in this study was confirmed based on self-report from a questionnaire. Additionally, we cannot rule out the potential misdiagnosis of heart disease as asthma. Among those diagnosed with asthma, we were unable to separate asthma patients by disease onset (i.e., childhood vs. adulthood) or any other phenotype such as obesity-related, exercise-induced and neutrophilic asthma(38), and it is possible that these phenotypes differ in regard to asthma triggers(39), gender distribution(39) and systemic inflammation(40). For example, obesity-related asthma which usually develops in adulthood might be of particular importance to the development of cardiovascular disease. However, we were unable to differentiate between these subgroups and therefore our observations may not be representative of each. Finally, patients who used asthma medication less frequently than daily were grouped together with other patients with only a history of asthma, defining a very heterogeneous group which might be a limitation of this study.

Taiwan and some other East Asian countries such as Japan and Hong Kong have some of the lowest mortality rates from CVD in the world(41, 42). Furthermore, our sample was fairly young (mean age 40.4 years), and these may have contributed to the relatively small

number of CVD deaths in our study. This may have reduced our power to detect any small effects of asthma on risk of CVD death.

Observational studies inherently limit causal inference. Although we adjusted for a number of potential confounders in our analyses, there is a possibility of uncontrolled confounding contributing to the observed associations. Specifically, we did not have information on pack years of cigarette smoking which could be a potential confounder. However, any residual confounding would need to be strongly associated with both asthma and CVD mortality and be unrelated to the covariates included in our models. Additionally, bias due to the exclusion of participants with missing information might have limited our study.

Finally, the sample was from a health check-up programme run by a private company and the participants may have come from a somewhat more advantaged socioeconomic position than Taiwan's general population and therefore our findings may not be representative of the general population. However, the cohort was similar to the general population reported in a national survey(43) in terms of certain characteristics including the prevalence of smoking.

CONCLUSION

Our study suggests that asthma, particularly active asthma, may have adverse cardiovascular consequences. For deaths from CVD and stroke, the association was stronger in men than in women. The associations persisted even after adjustment for established CVD risk factors. Further studies are needed to elucidate better the mechanisms underlying this association and to clarify any sex difference in the association.

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COMPETING INTERESTS

None declared.

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CONTRIBUTIONS

LBS wrote the analysis plan and wrote the first draft of the manuscript. MKT did the data analysis. CPW supervised the work and reviewed the manuscript. SSC helped supervise the work, reviewed the manuscript and coordinated the collaboration between the researchers. BMB designed the study, helped write the analysis plan, wrote the methods section of the manuscript and reviewed the manuscript. All authors confirm that they have reviewed and approved the final version of the manuscript.

DATA SHARING STATEMENT

No additional data are available.

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Supplementary Table 1. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality by age in the MJ health check-up programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Rate per 100,000 py	Model 1		Model 2	Cases (n)	Rate per 100,000 py	Model 1		Model 2	Cases (n)	Rate per 100,000 py	Model 1		Model 2
				HR	(95% CI)	HR (95% CI)			HR	(95% CI)	HR (95% CI)			HR	(95% CI)	HR (95% CI)
<60 years																
No asthma	384,436	802	22	1.00		1.00	186	5	1.00		1.00	319	9	1.00		1.00
Asthma	12,392	34	32	1.30	(0.92 ,1.84)	1.18 (0.84 ,1.66)	11	10	1.76	(0.96 ,3.24)	1.54 (0.84 ,2.85)	12	11	1.16	(0.65 ,2.06)	1.10 (0.62 ,1.97)
Non-active asthma (history only)	10,237	18	21	0.99	(0.62 ,1.58)	0.97 (0.61 ,1.54)	6	7	1.40	(0.62 ,3.15)	1.32 (0.58 ,2.97)	6	7	0.83	(0.37 ,1.87)	0.86 (0.39 ,1.94)
Active asthma (current drug use)	2,155	16	76	2.02	(1.23 ,3.31)	1.57 (0.96 ,2.58)	5	24	2.57	(1.06 ,6.26)	1.95 (0.80 ,4.78)	6	29	1.89	(0.84 ,4.24)	1.53 (0.68 ,3.44)
>=60 years																
No asthma	46,993	1,961	421	1.00		1.00	544	117	1.00		1.00	759	163	1.00		1.00
Asthma	2,525	148	599	1.27	(1.07 ,1.50)	1.13 (0.95 ,1.33)	39	158	1.20	(0.87 ,1.66)	1.02 (0.73 ,1.41)	56	227	1.25	(0.95 ,1.64)	1.16 (0.88 ,1.52)
Non-active asthma (history only)	1,366	66	479	1.05	(0.82 ,1.34)	0.97 (0.76 ,1.24)	19	138	1.09	(0.69 ,1.71)	0.96 (0.61 ,1.53)	29	211	1.19	(0.82 ,1.73)	1.14 (0.79 ,1.65)
Active asthma (current drug use)	1,159	82	749	1.52	(1.22 ,1.90)	1.30 (1.04 ,1.63)	20	183	1.33	(0.85 ,2.08)	1.07 (0.68 ,1.68)	27	247	1.31	(0.89 ,1.92)	1.18 (0.80 ,1.74)
Age interaction p																
Asthma (yes/no)				0.85		0.50			0.25		0.15			0.85		1.00
Asthma (no, history only, history and drug)				0.079		0.32			0.15		0.22			0.18		0.49

PY: person-years
Model 1: adjust for sex
Model 2: adjust for sex education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

Supplementary table 2. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding deaths[a] occurring during the two first years of follow-up, in the MJ health check-up programme, Taiwan

	CVD mortality						CHD mortality					Stroke mortality				
	N[a]	Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	431,200	2,534	1.00		1.00		661	1.00		1.00		988	1.00		1.00	
Asthma	14,896	161	1.23	(1.05 ,1.44)	1.10	(0.94 ,1.29)	44	1.26	(0.93 ,1.71)	1.07	(0.79 ,1.46)	60	1.18	(0.91 ,1.53)	1.10	(0.85 ,1.44)
Non-active asthma (history only)	11,597	78	1.05	(0.84 ,1.32)	0.98	(0.78 ,1.23)	22	1.13	(0.74 ,1.72)	1.01	(0.66 ,1.54)	33	1.14	(0.81 ,1.61)	1.11	(0.78 ,1.57)
Active asthma (current drug use)	3,299	83	1.47	(1.18 ,1.83)	1.24	(1.00 ,1.55)	22	1.46	(0.98 ,2.17)	1.15	(0.75 ,1.76)	27	1.23	(0.84 ,1.80)	1.10	(0.75 ,1.62)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

[a] The number of deaths due to CVD, CHD, and stroke varied and thus the total number of participants after excluding deaths due to each of three causes differed.

Supplementary Table 3. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding individuals with history of heart disease / heart surgery / use of heart drug, and history of stroke at baseline, in the MJ health check-up programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	414,859	1,992	1.00		1.00		514	1.00		1.00		823	1.00		1.00	
Asthma	13,802	108	1.16	(0.96 ,1.41)	1.15	(0.95 ,1.39)	23	0.94	(0.62 ,1.43)	0.92	(0.60 ,1.40)	42	1.10	(0.81 ,1.50)	1.09	(0.80 ,1.49)
Non-active asthma (history only)	10,935	51	0.94	(0.71 ,1.25)	0.95	(0.72 ,1.26)	13	0.92	(0.53 ,1.60)	0.91	(0.52 ,1.58)	21	0.94	(0.61 ,1.45)	0.97	(0.63 ,1.50)
Active asthma (current drug use)	2,867	57	1.47	(1.13 ,1.92)	1.41	(1.08 ,1.84)	10	0.96	(0.52 ,1.80)	0.93	(0.50 ,1.75)	21	1.32	(0.85 ,2.03)	1.25	(0.81 ,1.93)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol and triglycerides.

Supplementary table 4. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding individuals with FEV1/FCV < 0.7 at baseline, in the MJ health check-up programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	352,774	2,319	1.00		1.00		617	1.00		1.00		902	1.00		1.00	
Asthma	11,074	117	1.27	(1.06 ,1.53)	1.12	(0.93 ,1.36)	32	1.29	(0.90 ,1.84)	1.08	(0.76 ,1.55)	46	1.29	(0.96 ,1.73)	1.21	(0.90 ,1.63)
Non-active asthma (history only)	8,835	60	1.05	(0.81 ,1.36)	0.98	(0.76 ,1.27)	19	1.25	(0.79 ,1.97)	1.11	(0.70 ,1.76)	25	1.13	(0.76 ,1.68)	1.11	(0.75 ,1.66)
Active asthma (current drug use)	2,239	57	1.62	(1.25 ,2.11)	1.33	(1.02 ,1.73)	13	1.36	(0.78 ,2.35)	1.05	(0.60 ,1.82)	21	1.55	(1.01 ,2.39)	1.36	(0.88 ,2.10)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

Supplementary Table 5. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality by smoking status in the MJ health check-up programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Non or ex-smoker																
No asthma	332,699	1,898	1.00		1.00		470	1.00		1.00		754	1.00		1.00	
Asthma	11,456	113	1.15	(0.95 ,1.39)	1.04	(0.86 ,1.25)	30	1.20	(0.83 ,1.73)	1.03	(0.71 ,1.50)	40	1.03	(0.75 ,1.42)	0.98	(0.71 ,1.35)
Non-active asthma (history only)	9,018	56	1.00	(0.77 ,1.31)	0.94	(0.72 ,1.23)	16	1.15	(0.70 ,1.89)	1.04	(0.63 ,1.72)	24	1.09	(0.72 ,1.63)	1.07	(0.71 ,1.61)
Active asthma (current drug use)	2,438	57	1.33	(1.02 ,1.74)	1.14	(0.88 ,1.49)	14	1.26	(0.74 ,2.14)	1.02	(0.60 ,1.75)	16	0.96	(0.59 ,1.58)	0.87	(0.53 ,1.43)
Current smoker																
No asthma	98,730	865	1.00		1.00		260	1.00		1.00		324	1.00		1.00	
Asthma	3,461	69	1.55	(1.21 ,1.98)	1.34	(1.04 ,1.71)	20	1.45	(0.92 ,2.29)	1.20	(0.75 ,1.90)	28	1.67	(1.13 ,2.45)	1.51	(1.02 ,2.23)
Non-active asthma (history only)	2,585	28	1.13	(0.78 ,1.65)	1.01	(0.69 ,1.48)	9	1.18	(0.61 ,2.30)	1.01	(0.52 ,1.97)	11	1.19	(0.65 ,2.17)	1.11	(0.61 ,2.04)
Active asthma (current drug use)	876	41	2.07	(1.51 ,2.84)	1.72	(1.25 ,2.36)	11	1.78	(0.97 ,3.25)	1.41	(0.77 ,2.60)	17	2.26	(1.38 ,3.69)	1.97	(1.20 ,3.23)
Smoking status interaction p																
Asthma (yes/no)					0.18					0.74					0.12	
Asthma (no, history only, history and drug)					0.27					0.82					0.088	

Model 1: adjust for age

Model 2: adjust for age, education, marital status, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	8,9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	8,9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Is having asthma associated with an increased risk of dying from cardiovascular disease? A prospective cohort study of 446 346 Taiwanese adults

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Is having asthma associated with an increased risk of dying from cardiovascular disease? A prospective cohort study of 446 346 Taiwanese adults

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ABSTRACT

Objectives: A significant proportion of cardiovascular disease (CVD) cannot be explained by well-known risk factors such as high cholesterol, hypertension and diabetes. One potential novel risk factor for CVD is asthma. We aimed to investigate the association between asthma and mortality due to cardiovascular disease.

Design: Prospective cohort study.

Setting: A large health check-up program from 1994 to 2011 in Taipei, Taiwan.

Participants: 446 346 Taiwanese adults. Each participant answered questions regarding asthma history (yes/no) and current daily use of asthma medications (yes/no). Active asthma was defined as those using current daily medication for asthma.

Outcomes: The participants were followed for mortality from CVD, coronary heart disease (CHD), and stroke obtained through linkage to the cause-of-death register until 31st December 2011.

Results: We found an increased risk of dying from CVD in individuals with active asthma (adjusted hazard ratio [aHR] = 1.32, 95 % confidence interval [CI] 1.08-1.62). The risk of death from CHD or stroke was increased in a similar manner (aHR=1.16, 95% CI 0.78-1.73 and aHR=1.23, 95% CI 0.86-1.74, respectively) although the hazard ratio estimates were less precise than that of CVD. For deaths from CVD, CHD and stroke we found stronger associations with active asthma than non-active asthma, and for CVD and stroke stronger associations in men than women.

Conclusion: Our study suggests that asthma, particularly active asthma, may be associated with adverse cardiovascular consequences

Word count: 202

Strengths and limitations of this study

- We had objective measures of lung function that allowed us to exclude possible misclassification of asthma with COPD.
- However there is no gold standard for asthma diagnosis and asthma was confirmed based on self-report from a questionnaire.
- Taiwan has some of the lowest mortality rates from CVD in the world; our sample was young and this led to a relatively small number of CVD deaths.

INTRODUCTION

An estimated 17 million people die of cardiovascular diseases (CVDs) every year(1). Among the main forms of CVD are coronary heart disease (CHD) and stroke(1). Some well-known factors that increase the risk of developing CVD are unfavorable cholesterol levels, high blood pressure, diabetes and cigarette smoking. A significant proportion of CVD cannot be explained by these known risk factors, and a high incidence of the diseases makes it important to detect other potentially modifiable risk factors. One novel potential risk factor is asthma. As much as 330 million adults worldwide are estimated to have asthma,(2) emphasizing the potential public health importance of any effect of asthma on the occurrence of CVD. Such an association is plausible as it is suggested that asthma is associated with low-grade systemic inflammation and decline in pulmonary function,(3) which has been linked to an increase in CVD later in life(4, 5). Despite the plausibility of such an association, only a few studies have investigated the association between asthma and risk of CVD(5, 6). For example, Iribarren et al(6) recently reported a hazard ratio of 1.22 (95% confidence interval 1.14 to 1.31) for CHD related death or hospitalization in women with asthma compared with women without asthma after adjusting for demographic and established CHD risk factors; there was no association in men. To strengthen the existing evidence for a causative association, there is a need for large prospective studies on asthma and the risk of CVD, which can additionally investigate the influence of sex.

Approximately 5.5 million people die from stroke every year(1). Among the survivors, the consequences on physical, cognitive and emotional functioning are potentially devastating. Despite the devastating consequences of stroke, asthma as a novel risk factor has not been thoroughly investigated (5, 7). Our aim was to examine whether asthma at baseline was associated with an increased risk of deaths from CVD, and more specifically, CHD and

stroke utilizing a large cohort of more than 400,000 Taiwanese adults participating in a health check-up program.

METHODS

Study population

The study cohort consisted of 593,225 Taiwanese adults aged 20 years or older who participated in a large health check-up program from 1994 to 2011, run by MJ Health Management Institution, Taipei, Taiwan (https://www.mjclinic.com.tw). The baseline questionnaire included questions about history of asthma and current use of asthma medications. The participants went through a number of biochemical tests and physical examinations as described previously (8). In the present study, 67,682 (11.4%) of 593,225 adults were excluded due to missing information on asthma or asthma medications, and a further 79,197 (13.4%) were excluded as information was missing on potential confounding variables including sociodemographic and life style factors. The analysis included 446,346 (75%) participants who attended check-ups between 1998 and 2011 and who had full information on asthma, asthma medications, and potential confounding variables.

Asthma

Participants answered questions related to asthma history (yes/no) and current daily use of asthma medications (yes/no). We first defined asthma as those reporting a history of asthma or current daily use of asthma drugs, and then grouped these individuals into two subgroups: 1) non-active asthma (those who only reported a history of asthma but not current use of asthma medications) and; 2) active asthma (those who reported current daily use of asthma medications). Self-reported asthma is commonly used in population-based studies; this approach has been evaluated and displays reasonable sensitivity and specificity(9, 10).

CVD mortality

From baseline, the participants were followed for mortality until the end of follow-up, 31st December 2011, through linkage to the Taiwanese cause-of-death register using the national identification numbers. The International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10), codes were used to identify mortality from CVD (ICD-9 390-459; ICD-10 I00-I99), CHD (ICD-9 codes 410-414; ICD-10 I20-I25), and stroke (ICD-9 430-438; ICD-10 I60-I69). A previous study showed good accuracy of cause-of-death coding for both heart diseases and stroke in Taiwan(11).

Covariates

At the baseline health check-up participants were wearing light-weight clothes and were measured barefoot. Their weight (to the nearest 0.1 kg) and height (to the nearest mm) were measured using an auto-anthropometer, Nakamura KN-5000A (Nakamura, Tokyo, Japan) and their body mass index (BMI) was calculated (kg/m^2). After 5 minutes seated rest, blood pressure was measured twice, at 10-minute intervals, using a computerized auto-mercury sphygmomanometer (CH-5000, Citizen, Tokyo, Japan). We used the mean of the two measurements in our analysis. Glucose, total cholesterol, and triglyceride levels were measured in blood collected after overnight fasting using the Hitachi 7150 auto-analyzer (Hitachi Ltd., Tokyo, Japan). Respiratory functions were measured using an electronic spirometer (HI-501, HI-701, or HI-801; Chest M.I. Inc., Tokyo, Japan).

The participants reported their education (middle school or below, high school, junior college, college or higher), marital status (single, married, divorced or separated, widowed), smoking status (never, former, current), alcohol consumption (no or occasional use, former drinking, regular drinking), and physical activity (inactive, low, moderate or high). They also reported whether they had a history of hypertension, diabetes, heart disease, heart surgery, stroke, or whether they were taking medications for hypertension, diabetes, or heart diseases.

Hypertension was defined as the presence of any of the following: reporting a history of hypertension, taking any hypertensive drugs, a systemic blood pressure >= 140 mmHg, or a diastolic blood pressure >= 90 mmHg. Diabetes was defined as the presence of any of the following: reporting a history of diabetes, taking diabetes medications, or a fasting blood sugar >= 126 mmol/L.

Statistical methods

We used Cox proportional hazards models to investigate the associations of self-reported asthma with CVD, CHD and stroke mortality respectively. Time at entry was date of recruitment and time of exit was 31st December 2011, or death if earlier.

We estimated the association between asthma (those answering "yes" to asthma history or use of asthma medications), and CVD, CHD and stroke mortality adjusting for age and sex (Model 1). In a second model we adjusted for age, sex, education and marital status, smoking status, alcohol consumption, physical activity, hypertension, diabetes, BMI, total cholesterol, triglycerides, and history of heart disease/heart surgery/use of heart drug, and history of stroke (Model 2). We also investigated the associations between active and non-active asthma and CVD, CHD and stroke mortality

We investigated whether the associations differed in men and women, between age groups (above and below 60 years) and by smoking status (non-current smoker vs. current smokers) by including interaction terms in the models and conducting subgroup analyses. We reported the p value for interaction by comparing models with and without the interaction terms using a likelihood ratio test.

We conducted a series of sensitivity analyses to test the robustness of our findings. First, we excluded deaths due to CVD, CHD, or stroke occurring in the first two years of follow-up, as these deaths may be due to pre-existing cardiovascular diseases and not asthma.

We excluded participants with a history of heart disease, heart surgery, use of heart medications and a history of stroke at baseline in a second sensitivity analysis. Lastly, we excluded participants with possible chronic obstructive pulmonary disease (COPD) at baseline. In this analysis we excluded those who had an FEV_1/FVC ratio (forced expiratory volume in 1 second divided by forced vital capacity) < 0.7.

The proportional hazards assumption was examined by plotting Schoenfeld residuals with time and by examining their correlation.

Ethics approval

Our study complies with the Declaration of Helsinki; the China Medical University Hospital ethics committee has approved the research protocol and informed consent has been obtained from the subjects. The study was approved by the National Health Research Institutes, Taiwan, and the MJ Health Management Institution.

Patient and Public Involvement

This study utilized data from the MJ Health Management Institution, Taipei, Taiwan and patients were not involved in the design, recruitment, or conduct of this study. The outcome measures were not informed by patients' priorities, experience, and preferences. The MJ Health Management Institution will disseminate all key findings from this study on its website. Participants were thanked in the acknowledgment section.

RESULTS

Among the 446,346 participants there were 2,945 deaths from cardiovascular disease, 780 deaths from coronary heart disease and 1,146 deaths from stroke over the follow-up period. At baseline, 3.34% (n=14,917) of the participants reported to have asthma; 2.60% (n=11,603)

reported to have a history of asthma and 0.74% (n=3,314) reported to have active asthma. The characteristics of the participants according to baseline asthma status are presented in Table 1.

Table 1. Characteristics of the Participants in the MJ Health Check-up Programme, Taiwan (N=446346).

	Asthma (N= 14917)		No asthma (N= 431429)	
Characteristic	*n*	*(%)*	*n*	*%*
Female	6,893	(46.2)	220,253	(51.1)
College or higher education	5,726	(38.4)	143,649	(33.3)
Married	8,659	(58.0)	281,011	(65.1)
Current smoker	3,461	(23.2)	98,730	(22.9)
Regular alcohol use	1,210	(8.1)	29,884	(6.9)
Physically inactive	7,462	(50.0)	220,976	(51.2)
Hypertension (history of hypertension + hypertensive drug use + systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg)	3,121	(20.9)	77,972	(18.1)
Diabetes (history of diabetes + diabetes drug use + fasting blood glucose >=126) mmol/L)	841	(5.6)	21,274	(4.9)
History of heart disease/heart surgery/use of heart drug	1,045	(7.0)	15,044	(3.5)
History of stroke	129	(0.9)	2,050	(0.5)
	Mean	*(SD)*	*Mean*	*(SD)*
Age (years)	41.0	(15.6)	40.0	(13.4)
Body mass index (kg/m2)	23.4	(3.8)	23.0	(3.6)
Total cholesterol (mmol/L)	5.0	(1.0)	5.0	(1.0)
Triglycerides (mmol/L)	3.0	(2.4)	3.0	(2.6)

In the age- and sex-adjusted model (Model 1), those with asthma had a 27% (Hazard Ratio [HR] 1.27, 95% Confidence Interval [CI]: 1.09, 1.48) increased risk of CVD (Table 2). In the multi-adjusted model (Model 2) the association attenuated (HR 1.13, 95% CI: 0.97, 1.31). Using a stricter definition of asthma (active asthma) we found that those that reported any current use of asthma medications had a 32% (HR 1.32, 95% CI: 1.08, 1.62) increased risk of dying from CVD in Model 2. In contrast there was no association between non-active asthma and CVD mortality (HR 0.96, 95% CI: 0.77, 1.62).

Table 2. Hazard Ratios (HRs) for the Association between Asthma and Cardiovascular Disease (CVD), Coronary Heart Disease (CHD), and Stroke Mortality in the MJ Health Check-up Programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	431,429	2,763	1.00		1.00		730	1.00		1.00		1078	1.00		1.00	
Asthma	14,917	182	1.27	(1.09 ,1.48)	1.13	(0.97 ,1.31)	50	1.29	(0.97 ,1.72)	1.09	(0.82 ,1.45)	68	1.23	(0.96 ,1.57)	1.14	(0.89 ,1.46)
Non-active asthma (history only)	11,603	84	1.04	(0.84 ,1.29)	0.96	(0.77 ,1.19)	25	1.16	(0.78 ,1.73)	1.03	(0.69 ,1.53)	35	1.11	(0.80 ,1.56)	1.08	(0.77 ,1.51)
Active asthma (current drug use)	3,314	98	1.57	(1.29 ,1.93)	1.32	(1.08 ,1.62)	25	1.46	(0.98 ,2.17)	1.16	(0.78 ,1.73)	33	1.37	(0.97 ,1.94)	1.23	(0.86 ,1.74)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

There was evidence that the association between asthma (grouped as non-active and active asthma) and CVD was stronger in males than in females (*P* for interaction = 0.005 in Model 2) (Table 3). Men who reported asthma had a 25% increased risk (HR1.25, 95% CI: 1.04, 1.49) of dying from CVD in Model 2, those with active asthma had a 63% increased risk (HR 1.63, 95% CI: 1.30, 2.04) compared to men without asthma, while men with non-active asthma showed no increased risk (HR 0.90, 95% CI: 0.68, 1.19). No associations were found in women. When stratifying by age we found no appreciable differences (Supplementary table 1).

Table 3. Hazard ratios (HRs) for the Association between Asthma and Cardiovascular Disease (CVD), Coronary Heart Disease (CHD), and Stroke Mortality by Sex in the MJ Health Check-up Programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Males																
No asthma	211,176	1,730	1.00		1.00		494	1.00		1.00		657	1.00		1.00	
Asthma	8,024	132	1.39	(1.16 ,1.66)	1.25	(1.04 ,1.49)	39	1.42	(1.02 ,1.97)	1.21	(0.87 ,1.67)	49	1.36	(1.02 ,1.82)	1.29	(0.96 ,1.72)
Non-active asthma (history only)	6,130	50	0.96	(0.73 ,1.28)	0.90	(0.68 ,1.19)	18	1.21	(0.75 ,1.93)	1.08	(0.67 ,1.73)	20	1.02	(0.65 ,1.59)	1.00	(0.64 ,1.56)
Active asthma (current drug use)	1,894	82	1.91	(1.53 ,2.38)	1.63	(1.30 ,2.04)	21	1.67	(1.08 ,2.59)	1.34	(0.86 ,2.08)	29	1.77	(1.22 ,2.57)	1.62	(1.11 ,2.35)
Females																
No asthma	220,253	1,033	1.00		1.00		236	1.00		1.00		421	1.00		1.00	
Asthma	6,893	50	1.04	(0.78 ,1.38)	0.88	(0.66 ,1.17)	11	0.97	(0.53 ,1.78)	0.82	(0.44 ,1.51)	19	0.98	(0.62 ,1.56)	0.89	(0.56 ,1.42)
Non-active asthma (history only)	5,473	34	1.17	(0.83 ,1.65)	1.05	(0.74 ,1.48)	7	1.05	(0.49 ,2.22)	0.93	(0.44 ,1.99)	15	1.28	(0.77 ,2.14)	1.21	(0.72 ,2.03)
Active asthma (current drug use)	1,420	16	0.83	(0.51 ,1.36)	0.65	(0.40 ,1.07)	4	0.86	(0.32 ,2.32)	0.67	(0.25 ,1.81)	4	0.52	(0.20 ,1.40)	0.45	(0.17 ,1.20)
Sex interaction p																
Asthma (yes/no)			0.19		0.10			0.40		0.27			0.33		0.29	
Asthma (no, history only, history and drug)			0.012		0.005			0.62		0.42			0.043		0.032	

Model 1: adjust for age

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

The associations between asthma and CHD mortality, were consistent with those of CVD mortality, although less precise due to the smaller number of deaths (Table 2). When stratifying by sex, we found a 67% increased risk (HR 1.67, 95% CI: 1.08, 2.59) for CHD among men with active asthma in the age-adjusted model (Model 1) but the association was largely attenuated when adjusting for additional potential confounders (Model 2). We did not find any association among women (Table 3). We found more than double the risk in those below 60 years (HR 2.57, 95% CI: 1.06, 6.26) in Model 1 but the confidence interval was wide and the association was attenuated when adjusting for additional potential confounders (Supplementary Table 1).

When investigating mortality due to stroke, we found similar but slightly weaker associations between asthma and stroke mortality than asthma and CVD mortality (Table 2?). We found a 77% increased risk in men with active asthma (HR 1.77, 95% CI: 1.22, 2.57) in Model 1, that persisted after adjusting for potential confounders in Model 2 (HR 1.62, 95% CI: 1.11, 2.35) (Table 3). This risk was not seen in women (*P* for interaction = 0.032). We found no differences in the association between asthma and stroke mortality between age groups (i.e. below and above 60 years old) (Supplementary Table 1).

When excluding deaths occurring during the two first years of follow-up, the results did not change considerably for any of the cardiovascular outcomes (Supplementary table 2). When excluding participants with a history of heart disease, heart surgery, use of heart medications and a history of stroke at baseline, the results were generally similar to those of the main analysis except that the association between asthma and CHD was largely attenuated, although the number of CHD deaths was small (n=13 and 10 in the non-active and active asthma groups respectively) in this analysis (Supplementary table 3). When excluding individuals with FEV1/FVC ratio <0.7 at baseline, the analysis based on the remaining

sample showed that the effect estimate remained the same although the confidence interval widened slightly because of lower power in this analysis (Supplementary table 4).

Overall there was no statistical evidence for a difference in the association between asthma and CVD/CHD/Stroke mortality between current smokers and non-current smokers (all p for interaction > 0.05), although there was a tendency towards stronger associations in current smokers than in non- or ex-smokers (Supplementary table 5).

DISCUSSION

To the best of our knowledge this is the largest study to date on asthma and CVD mortality. In this sample of more than 400,000 Taiwanese adults we found an increased risk of dying from CVD in individuals with active, but not non-active, asthma. The risk of death from CHD or stroke was increased in a similar manner, however in sensitivity analysis excluding those with previous heart disease, only the associations with CVD and stroke mortality remained. For deaths from CVD and stroke we found a stronger association with active asthma in men than in women.

A few previous studies have investigated the association between asthma and risk of cardiovascular disease. One very large recent study including almost one million Italian adults agreed with our findings and reported asthma to be moderately associated with different cardiovascular diseases(12). Additionally, this study did not find any differences in the association between men and women, while our study observed a stronger association in men. This Italian study was cross-sectional however, and there is no way of knowing whether the CVD diagnosis preceded the asthma diagnosis. Additionally, this study did not have access to spirometry measurements such as FEV_1 and FVC and thus was not able to exclude those with a FEV_1/FVC ratio of less than 0.7 to minimise the possibility of misclassification between asthma and COPD.

A smaller study was undertaken in Australia including approximately 4000 people amongst whom 500 were classified as having asthma(13). Individuals with asthma were not only identified by self-report, but also through identification of significant reversibility of airway obstruction. The result were in accordance with our findings and when subjects with COPD were excluded from the analysis ($FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ of predicted), the association between asthma and CVD remained.

Coronary heart disease contributes to a large part of the burden of cardiovascular disease(14) and the risk of complications or even death is high, thus detecting novel risk factors is essential. A few studies have found an increased risk of CHD in patients with asthma(15, 16). However, the results are inconsistent, and a recent study including almost 16 000 participants from the Atherosclerosis Risk in Communities (ARIC) Study failed to confirm this increase in risk of CHD in patients with current asthma (HR 0.69, 95% CI: 0.46, 1.05) (5).

In the current study, we generally observed stronger results in men than in women in this adult Taiwanese population. By contrast, other studies have previously found stronger associations in women than men. A large prospective study by Iribarren and colleagues(17) found that the increased risk of CHD was higher in women with asthma (HR 1.49, 95% CI: 1.43, 1.56) than in men (HR 1.28, 95% CI: 1.21, 1.34) (*P* for interaction <0.001). The authors speculate that the increased risk of CHD among people with asthma may be due to chronic inflammation in people with asthma. Supporting this is the fact that women with asthma tend to have more severe disease than men with asthma,(18) and likely more systemic inflammation.

In spite of the devastating consequences of stroke, asthma as a novel risk factor has not been thoroughly investigated and only a few studies have examined this association. The

previously mentioned study using data from the ARIC Study,(5) found similar results to ours, with a 55% increased risk of stroke (HR 1.55, 95% CI: 0.95, 2.52) in patients with current asthma compared with those without asthma. A recent meta-analysis of five studies on asthma and stroke found a pooled HR of 1.32 (95% CI: 1.13, 1.54)(19). In contrast to our findings, this meta-analysis found that the associations between asthma and stroke were stronger in women (HR 1.42, 95% CI: 1.15, 1.76) than in men (HR 1.19, 95% CI: 0.90, 1.43). The authors speculate that sex hormones could play a crucial role in modulating immunological inflammation in asthma. However, our results showed an increased risk in men, but not in women. The underlying reasons driving these differences between studies are not clear and further investigations from countries with different ethnicities may help to shed light on this observation.

The biological mechanisms by which asthma may influence CVD are not known, but several mechanisms have been suggested. Asthma is associated with low-grade systemic inflammation,(20) which could influence later risk of CVD(21). Previous studies also suggest that C-reactive protein is associated with both asthma(22) and CVD(23, 24). Lung function impairment is also associated with CVD risk(25, 26). Patients with impaired lung function have increased inflammatory markers (including C-reactive protein, interleukin-1β, and interleukin-6) (27), which are associated with atherosclerosis and cardiovascular events(21, 28). The long-term airway remodelling from the inflammatory response in asthma can produce irreversible airway obstruction and cause a decline in lung function(29). In addition, severe asthma exacerbations are associated with a more rapid decline in lung function(30). Another hypothesis is that asthma is associated with risk of CVD through asthma medication use, in particular the cardiotoxic effects of beta-2 (β_2) agonists(31, 32). Finally, asthma may be associated with CVD due to other factors such as obesity,(33) smoking,(34) or physical inactivity(35). It is also possible that the association between asthma and CVD is due to

comorbidities such as diabetes which has a strong link to CVD(36) and also to asthma(37). In our study, we adjusted for these potential confounders however and it is unlikely that any confounding by these factors would be behind the observed associations.

To the best of our knowledge, our study is the largest to date, investigating the association between asthma and risk of death from cardiovascular disease. Despite the large study size, the objective measures of lung function that allowed us to exclude possible misclassification of asthma with COPD, and the wide range of potential confounders included in our models, the limitations of this study must be considered.

There is no gold standard for asthma diagnosis and despite using spirometry measures to exclude possible COPD, asthma in this study was indicated by self-report from a questionnaire. Additionally, we cannot rule out the potential misdiagnosis of heart disease as asthma. Among those diagnosed with asthma, we were unable to separate asthma patients by disease onset (i.e., childhood vs. adulthood) or any other phenotype such as obesity-related, exercise-induced and neutrophilic asthma(38), and it is possible that these phenotypes differ in regard to asthma triggers(39), gender distribution(39) and systemic inflammation(40). For example, obesity-related asthma which usually develops in adulthood might be of particular importance to the development of cardiovascular disease. However, we were unable to differentiate between these subgroups and therefore our observations may not be representative of each. Finally, patients who used asthma medication less frequently than daily were grouped together with other patients with only a history of asthma, defining a very heterogeneous group which might be a limitation of this study.

Taiwan and some other East Asian countries such as Japan and Hong Kong have some of the lowest mortality rates from CVD in the world(41, 42). Furthermore, our sample was fairly young (mean age 40.4 years), and these may have contributed to the relatively small

number of CVD deaths in our study. This may have reduced our power to detect any small effects of asthma on risk of CVD death.

Observational studies inherently limit causal inference. Although we adjusted for a number of potential confounders in our analyses, there is a possibility of uncontrolled confounding contributing to the observed associations. Specifically, we did not have information on pack years of cigarette smoking which could be a potential confounder. However, any residual confounding would need to be strongly associated with both asthma and CVD mortality and be unrelated to the covariates included in our models. Additionally, bias due to the exclusion of participants with missing information might have limited our study.

Finally, the sample was from a health check-up programme run by a private company and the participants may have come from a somewhat more advantaged socioeconomic position than Taiwan's general population and therefore our findings may not be representative of the general population. However, the cohort was similar to the general population reported in a national survey(43) in terms of certain characteristics including the prevalence of smoking.

CONCLUSION

Our study suggests that asthma, particularly active asthma, may be associated with adverse cardiovascular consequences. For deaths from CVD and stroke, the association was stronger in men than in women. The associations persisted even after adjustment for established CVD risk factors. Further studies are needed to elucidate better the mechanisms underlying this association and to clarify any sex difference in the association.

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COMPETING INTERESTS

None declared.

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CONTRIBUTIONS

LBS wrote the analysis plan and wrote the first draft of the manuscript. MKT did the data analysis. CPW supervised the work and reviewed the manuscript. SSC helped supervise the work, reviewed the manuscript and coordinated the collaboration between the researchers. BMB designed the study, helped write the analysis plan, wrote the methods section of the manuscript and reviewed the manuscript. All authors confirm that they have reviewed and approved the final version of the manuscript.

DATA SHARING STATEMENT

No additional data are available.

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Supplementary Table 1. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality by age in the MJ health check-up programme, Taiwan

		CVD mortality						CHD mortality						Stroke mortality					
	N	Cases (n)	Rate per 100,000 py	Model 1		Model 2		Cases (n)	Rate per 100,000 py	Model 1		Model 2		Cases (n)	Rate per 100,000 py	Model 1		Model 2	
				HR	(95% CI)	HR	95% CI			HR	95% CI	HR	95% CI			HR	95% CI	HR	95% CI
<60 years																			
No asthma	384,436	802	22	1.00		1.00		186	5	1.00		1.00		319	9	1.00		1.00	
Asthma	12,392	34	32	1.30	(0.92 ,1.84)	1.18	(0.84 ,1.66)	11	10	1.76	(0.96 ,3.24)	1.54	(0.84 ,2.85)	12	11	1.16	(0.65 ,2.06)	1.10	(0.62 ,1.97)
Non-active asthma (history only)	10,237	18	21	0.99	(0.62 ,1.58)	0.97	(0.61 ,1.54)	6	7	1.40	(0.62 ,3.15)	1.32	(0.58 ,2.97)	6	7	0.83	(0.37 ,1.87)	0.86	(0.39 ,1.94)
Active asthma (current drug use)	2,155	16	76	2.02	(1.23 ,3.31)	1.57	(0.96 ,2.58)	5	24	2.57	(1.06 ,6.26)	1.95	(0.80 ,4.78)	6	29	1.89	(0.84 ,4.24)	1.53	(0.68 ,3.44)
>=60 years																			
No asthma	46,993	1,961	421	1.00		1.00		544	117	1.00		1.00		759	163	1.00		1.00	
Asthma	2,525	148	599	1.27	(1.07 ,1.50)	1.13	(0.95 ,1.33)	39	158	1.20	(0.87 ,1.66)	1.02	(0.73 ,1.41)	56	227	1.25	(0.95 ,1.64)	1.16	(0.88 ,1.52)
Non-active asthma (history only)	1,366	66	479	1.05	(0.82 ,1.34)	0.97	(0.76 ,1.24)	19	138	1.09	(0.69 ,1.71)	0.96	(0.61 ,1.53)	29	211	1.19	(0.82 ,1.73)	1.14	(0.79 ,1.65)
Active asthma (current drug use)	1,159	82	749	1.52	(1.22 ,1.90)	1.30	(1.04 ,1.63)	20	183	1.33	(0.85 ,2.08)	1.07	(0.68 ,1.68)	27	247	1.31	(0.89 ,1.92)	1.18	(0.80 ,1.74)
Age interaction p																			
Asthma (yes/no)				0.85		0.50				0.25		0.15				0.85		1.00	
Asthma (no, history only, history and drug)				0.079		0.32				0.15		0.22				0.18		0.49	

PY: person-years

Model 1: adjust for sex

Model 2: adjust for sex education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

Supplementary table 2. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding deaths[a] occurring during the two first years of follow-up, in the MJ health check-up programme, Taiwan

	CVD mortality						CHD mortality					Stroke mortality				
	N[a]	Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	431,200	2,534	1.00		1.00		661	1.00		1.00		988	1.00		1.00	
Asthma	14,896	161	1.23	(1.05 ,1.44)	1.10	(0.94 ,1.29)	44	1.26	(0.93 ,1.71)	1.07	(0.79 ,1.46)	60	1.18	(0.91 ,1.53)	1.10	(0.85 ,1.44)
Non-active asthma (history only)	11,597	78	1.05	(0.84 ,1.32)	0.98	(0.78 ,1.23)	22	1.13	(0.74 ,1.72)	1.01	(0.66 ,1.54)	33	1.14	(0.81 ,1.61)	1.11	(0.78 ,1.57)
Active asthma (current drug use)	3,299	83	1.47	(1.18 ,1.83)	1.24	(1.00 ,1.55)	22	1.46	(0.98 ,2.17)	1.15	(0.75 ,1.76)	27	1.23	(0.84 ,1.80)	1.10	(0.75 ,1.62)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

[a] The number of deaths due to CVD, CHD, and stroke varied and thus the total number of participants after excluding deaths due to each of three causes differed.

Supplementary Table 3. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding individuals with history of heart disease / heart surgery / use of heart drug, and history of stroke at baseline, in the MJ health check-up programme, Taiwan

		CVD mortality					CHD mortality					Stroke mortality				
	N	Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	414,859	1,992	1.00		1.00		514	1.00		1.00		823	1.00		1.00	
Asthma	13,802	108	1.16	(0.96 ,1.41)	1.15	(0.95 ,1.39)	23	0.94	(0.62 ,1.43)	0.92	(0.60 ,1.40)	42	1.10	(0.81 ,1.50)	1.09	(0.80 ,1.49)
Non-active asthma (history only)	10,935	51	0.94	(0.71 ,1.25)	0.95	(0.72 ,1.26)	13	0.92	(0.53 ,1.60)	0.91	(0.52 ,1.58)	21	0.94	(0.61 ,1.45)	0.97	(0.63 ,1.50)
Active asthma (current drug use)	2,867	57	1.47	(1.13 ,1.92)	1.41	(1.08 ,1.84)	10	0.96	(0.52 ,1.80)	0.93	(0.50 ,1.75)	21	1.32	(0.85 ,2.03)	1.25	(0.81 ,1.93)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol and triglycerides.

Supplementary table 4. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality, excluding individuals with FEV1/FCV < 0.7 at baseline, in the MJ health check-up programme, Taiwan

	N	CVD mortality					CHD mortality					Stroke mortality				
		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
No asthma	352,774	2,319	1.00		1.00		617	1.00		1.00		902	1.00		1.00	
Asthma	11,074	117	1.27	(1.06 ,1.53)	1.12	(0.93 ,1.36)	32	1.29	(0.90 ,1.84)	1.08	(0.76 ,1.55)	46	1.29	(0.96 ,1.73)	1.21	(0.90 ,1.63)
Non-active asthma (history only)	8,835	60	1.05	(0.81 ,1.36)	0.98	(0.76 ,1.27)	19	1.25	(0.79 ,1.97)	1.11	(0.70 ,1.76)	25	1.13	(0.76 ,1.68)	1.11	(0.75 ,1.66)
Active asthma (current drug use)	2,239	57	1.62	(1.25 ,2.11)	1.33	(1.02 ,1.73)	13	1.36	(0.78 ,2.35)	1.05	(0.60 ,1.82)	21	1.55	(1.01 ,2.39)	1.36	(0.88 ,2.10)

Model 1: adjust for age and sex

Model 2: adjust for age, education, marital status, smoking, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

Supplementary Table 5. Hazard ratios (HRs) for the association of asthma with cardiovascular disease (CVD), coronary heart disease (CHD), and stroke mortality by smoking status in the MJ health check-up programme, Taiwan

		CVD mortality					CHD mortality					Stroke mortality				
	N	Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2		Cases (n)	Model 1		Model 2	
			HR	(95% CI)	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Non or ex-smoker																
No asthma	332,699	1,898	1.00		1.00		470	1.00		1.00		754	1.00		1.00	
Asthma	11,456	113	1.15	(0.95 ,1.39)	1.04	(0.86 ,1.25)	30	1.20	(0.83 ,1.73)	1.03	(0.71 ,1.50)	40	1.03	(0.75 ,1.42)	0.98	(0.71 ,1.35)
Non-active asthma (history only)	9,018	56	1.00	(0.77 ,1.31)	0.94	(0.72 ,1.23)	16	1.15	(0.70 ,1.89)	1.04	(0.63 ,1.72)	24	1.09	(0.72 ,1.63)	1.07	(0.71 ,1.61)
Active asthma (current drug use)	2,438	57	1.33	(1.02 ,1.74)	1.14	(0.88 ,1.49)	14	1.26	(0.74 ,2.14)	1.02	(0.60 ,1.75)	16	0.96	(0.59 ,1.58)	0.87	(0.53 ,1.43)
Current smoker																
No asthma	98,730	865	1.00		1.00		260	1.00		1.00		324	1.00		1.00	
Asthma	3,461	69	1.55	(1.21 ,1.98)	1.34	(1.04 ,1.71)	20	1.45	(0.92 ,2.29)	1.20	(0.75 ,1.90)	28	1.67	(1.13 ,2.45)	1.51	(1.02 ,2.23)
Non-active asthma (history only)	2,585	28	1.13	(0.78 ,1.65)	1.01	(0.69 ,1.48)	9	1.18	(0.61 ,2.30)	1.01	(0.52 ,1.97)	11	1.19	(0.65 ,2.17)	1.11	(0.61 ,2.04)
Active asthma (current drug use)	876	41	2.07	(1.51 ,2.84)	1.72	(1.25 ,2.36)	11	1.78	(0.97 ,3.25)	1.41	(0.77 ,2.60)	17	2.26	(1.38 ,3.69)	1.97	(1.20 ,3.23)
Smoking status interaction p																
Asthma (yes/no)					0.18					0.74					0.12	
Asthma (no, history only, history and drug)					0.27					0.82					0.088	

Model 1: adjust for age

Model 2: adjust for age, education, marital status, alcohol consumption, physical activity, diabetes, hypertension, body mass index, total cholesterol, triglyceride, history of heart disease/heart surgery/use of heart drug, and history of stroke

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	8,9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8,9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	8,9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.