Original Article

Nonrespiratory Diseases in Adults Without and With Asthma by Age at Asthma Diagnosis

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What is already known about this topic? Asthma seems to differ by age of onset in many ways. Subjects with asthma have also been previously found to suffer from more nonrespiratory common chronic diseases than subjects without asthma.

What does this article add to our knowledge? This study finds that with older age at asthma diagnosis, the number of nonrespiratory diseases associated with asthma increase. In addition, the asthma-associated nonrespiratory diseases are different by age at asthma diagnosis.

How does this study impact current management guidelines? Multimorbidity in asthma diagnosed at older age should be better noticed in clinical practice and scientific studies. Different associations between nonrespiratory diseases and asthma diagnosed at different ages could be explained by common pathogenic processes.

BACKGROUND: Chronic nonrespiratory diseases are seemingly more prevalent in subjects with than without asthma, and asthma seems to differentiate by age of onset. However, studies with comparison of nonrespiratory diseases in subjects with and without asthma, considering asthma age of onset, are scarce.

OBJECTIVE: To compare the quantity and type of chronic nonrespiratory diseases in adults with and without asthma considering age at asthma diagnosis.

METHODS: In 2016, a FinEsS questionnaire was sent to 16,000 20- to 69-year-old adults randomly selected in Helsinki and

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Abbreviations used
BMI- body mass index
COPD- chronic obstructive pulmonary disease
GERD- gastroesophageal reflux disease
OR- odds ratio
TIA- transient ischemic attack

Western Finland populations. Physician-diagnosed asthma was categorized to early (0-11), intermediate (12-39), and late-diagnosed (40-69 years).
RESULTS: A total of 8199 (51.5%) responded, and 842 (10.3%) reported asthma and age at diagnosis. In age and sex-adjusted binary logistic regression model, the most represented non-respiratory disease was treated gastroesophageal reflux disease in early-diagnosed (odds ratio, 1.93; 95% CI, 1.17-3.19; $P = .011$) and osteoporosis in both intermediate-diagnosed (odds ratio, 3.45; 95% CI, 2.01-5.91; $P < .001$) and late-diagnosed asthma (odds ratio, 2.91; 95% CI, 1.77-4.79; $P < .001$), compared with subjects without asthma. In addition, gastroesophageal reflux disease, depression, sleep apnea, painful condition, and obesity were significantly more common in intermediate- and late-diagnosed asthma compared with without asthma, and similarly anxiety or panic disorder in intermediate-diagnosed and hypertension, severe cardiovascular disease, arrhythmia, and diabetes in late-diagnosed asthma. In age-adjusted analyses, having 3 or more nonrespiratory diseases was more common in intermediate (12.1%) and late-diagnosed asthma (36.2%) versus without asthma (10.4%) (both $P < .001$).
CONCLUSIONS: Nonrespiratory diseases were more common in adults with asthma than in adults without asthma. The type of nonrespiratory diseases differed, and their frequency increased by increasing age at asthma diagnosis. **(J Allergy Clin Immunol Pract 2023;11:555-63)**

Key words: *Asthma; Age of onset; Comorbidity; Hypertension; Diabetes; Sleep apnea; Osteoporosis; Obesity; Chronic diseases; Population Study*

INTRODUCTION

During the past decade, asthma heterogeneity has become well recognized, and phenotyping and endotyping of asthma have had promising results in dealing with it.[1] Age of asthma onset has been identified as an important influencer of asthma phenotypes[1,2]; however, phenotyping studies have rarely considered asthma comorbidities.

The burden of comorbidities especially in adult patients with asthma is marked: more than 50% suffer from a nonrespiratory comorbid condition.[3,4] In addition, comorbidities most probably act as confounding factors in asthma studies.[5] Better identification of comorbidities related to asthma could also play an important role in unraveling molecular mechanisms especially in less understood adult-onset asthma[2]— indeed, a recent review[6] summarized several shared mechanisms between asthma and other common chronic diseases.

In recent register and population samples, some nonrespiratory comorbidities are suggested to be more prevalent in subjects suffering from asthma.[7-10] Evidence of this coexistence has been published at least on dyspepsia,[8,9] cardiovascular diseases,[11-13] obesity,[10,14] mental disorders,[15] depression,[6,8,10] osteoporosis,[8] diabetes,[8] and sleep apnea.[16] Nevertheless, evidence is limited to few or no studies regarding some common chronic diseases and their relationship with asthma.[17]

Furthermore, although age of asthma onset is a key modifier of asthma,[1,2,18,19] few studies have investigated the influence of age of asthma onset on coexistence of nonrespiratory diseases in patients with asthma, or simultaneously made comparisons between subjects with and without asthma. In the few studies, age of asthma onset is also limited to dichotomous categorization to childhood- and adult-onset asthma,[11,13,20,21] although more differences are presumed to be found if adult-onset asthma is further divided into earlier and later adult-onset asthma.[18,22,23]

Therefore, we aimed to investigate nonrespiratory diseases in subjects with and without asthma, considering age at asthma diagnosis. We hypothesized that subjects with asthma would suffer more often from nonrespiratory diseases than subjects without asthma, and that increasing age at asthma diagnosis would increase the quantity of the nonrespiratory diseases coexistent with asthma.

METHODS

Study subjects

In 2016, a FinEsS questionnaire was sent to 16,000 subjects aged 20 to 69 years. Subjects were randomly selected by Statistics Finland from Helsinki and Western Finland areas conforming the age and sex distribution in the population. Power analyses were made to define the sufficient study size, and an approval of the Ethics Committee of Helsinki University Hospital was received before the initiation of the study.

Study design

Detailed description of the study methods and the FinEsS questionnaire is reported elsewhere.[24,25]

The common variables were defined as follows.

Physician-diagnosed asthma by a positive and *without asthma* by a negative answer to "Have you been diagnosed by a doctor as having asthma?"

Age at asthma diagnosis "What age were you when asthma was diagnosed?"

Age at asthma diagnosis in those aged 0 to 11 years was defined as *early-diagnosed*, 12 to 39 years as *intermediate-diagnosed*, and 40 to 69 years as *late-diagnosed asthma.* The cutoff points were chosen on the basis of asthma incidence shifts.[19,21] Age 12 years is also most often used to delineate child- and adult-onset asthma,[23] and age 40 years suggested to be a cutoff point needing more research.[19,22]

COPD "Have you been diagnosed by a physician as having chronic bronchitis, chronic obstructive pulmonary disease (COPD), or emphysema?"

Allergic rhinitis "Have you been diagnosed by a doctor as having allergic rhinitis caused by pollen?" or "Have you been diagnosed by a doctor as having other allergic rhinitis?"

Obesity Self-reported body mass index (BMI) greater than or equal to 30.

Other nonrespiratory diseases with the question "Has a physician diagnosed you with any of the following diseases" and an affirmative positive answer to following:

Coronary artery disease "Coronary disease."

Heart failure "Heart insufficiency."

Stroke or TIA "Cerebral infarction or TIA (transient ischemic attack)."

Hypertension "Hypertension."

Arrhythmia "Atrial fibrillation or other arrhythmia."

Depression "Depression."

Anxiety or panic disorder "Panic disorder or anxiety disorder."

Gastroesophageal reflux disease (GERD) "Treatment or medication to esophageal reflux disease (dyspepsia or GERD)."

Sleep apnea "Sleep apnea."

Diabetes "Diabetes."

Chronic kidney failure "Chronic renal insufficiency."

Osteoporosis "Osteoporosis."

Painful condition "Pain, that requires daily usage of pain killers."

Severe cardiovascular disease "Heart failure," "Coronary disease," or "Stroke or TIA."

Number of nonrespiratory diseases included the following 14 diseases: hypertension, arrhythmia, heart failure, coronary artery disease, stroke or TIA, depression, anxiety or panic disorder, diabetes, GERD, chronic kidney failure, sleep apnea, osteoporosis, painful condition, and obesity.

Asthma medication use "Do you currently use asthma medication (permanently or as needed)?"

Statistical analyses

Analyses were conducted with SPSS Statistics version 26 (IBM). Associations between categorical variables were analyzed by χ^2 or Fisher exact test. Associations between dichotomous categorical and normally distributed continuous variables were analyzed by *t* test, and nonnormally distributed continuous variables by Mann-Whitney test. In case of 3 or more strata to compare, 1-way ANOVA for normally distributed and Kruskal-Wallis test for nonnormally distributed continuous variables were used. Normality was assessed by Kolmogorov-Smirnov analysis.

Both multivariable and univariate binary logistic regression analyses were used to estimate odds ratios (ORs). The outcome variables in the analyses were nonrespiratory diseases. The covariates were chosen by clinical experience of the most important confounding factors before the analyses, and age and sex were used in all the analyses as covariates. Sensitivity analyses were conducted by excluding COPD and including more covariates, smoking, COPD, and BMI, to the regression models. Age was used as a continuous variable and other covariates as categorical. A *P* value of less than .05 was considered statistically significant, and CIs with 95% accuracy were reported. Bonferroni correction was applied to 3 strata comparisons in categorical variables, for which the corresponding level of statistical significance was less than .017. Subjects lacking full smoking data were excluded from the analyses.

RESULTS

Basic characteristics of the study subjects and nonresponders

Altogether, 8199 (51.5%) responded. Detailed demographic characteristics of the responders are published elsewhere.[23-25] Briefly, median age of the responders was 50 years, and males consisted a minority (44.9%) of the responders, whereas median age of the nonresponders was 36 years in Helsinki and 40 years in Western Finland data, and the nonresponders were more often males (53.1%).

Physician-diagnosed asthma was reported by 879, and age at asthma diagnosis by 842 subjects: early-diagnosed asthma by 245 (29.1%), intermediate-diagnosed by 358 (42.5%), and late-diagnosed by 239 (28.4%) subjects. In total, 7051 subjects did not have asthma. BMI was highest and current smoking the least prevalent in late-diagnosed asthma, whereas allergic rhinitis and family history of asthma the most common in early-diagnosed asthma (Table I).

Different nonrespiratory diseases

The most common diseases were hypertension in subjects without asthma (18.9%) and with late-diagnosed asthma (42.3%), and obesity in early- (17.5%) and intermediate-diagnosed asthma (21.1%) (Table II). Prevalence of some of the most common studied diseases in subjects 40 years or older is illustrated in Figure 1. In addition, demographic characteristics and nonrespiratory diseases in subjects 40 years or older are reported in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

In subjects with physician-diagnosed asthma versus without asthma, the median age was lower (47 vs 50 years; $P = .006$), but most of the analyzed diseases were significantly more prevalent in those with physician-diagnosed asthma (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). When subjects with COPD were excluded, most of the statistically significant differences remained (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Number of nonrespiratory diseases

One or more nonrespiratory diseases were reported by 3260 (47.0%) subjects without asthma and 508 (58.7%) subjects with physician-diagnosed asthma ($P < .001$). Number of nonrespiratory diseases more than 1 was significantly higher in all age groups at asthma diagnosis strata compared with without asthma, and highest in late-diagnosed asthma compared with early- and intermediate-diagnosed asthma.

The number of nonrespiratory diseases is visualized in Figure 2. In both all and subjects 40 years or older, 3 and 4 diseases and 5 or more diseases, respectively, were most commonly present in subjects with late-diagnosed asthma.

Nonrespiratory diseases in multivariable logistic regression model

To compare the risk of individual diseases between subjects with and without asthma by age at asthma diagnosis, we conducted multivariable binary logistic regression analysis. In age- and sex-adjusted analysis, the variables significantly more common in subjects with asthma despite of diagnosis age compared with without asthma were GERD, COPD, and 1 or more nonrespiratory disease (Table III). The most overrepresented disease in subjects with physician-diagnosed asthma compared with those without asthma was GERD in early-diagnosed (OR, 1.93; 1.17-3.19; $P = .011$) and osteoporosis in both intermediate-diagnosed (OR, 3.45; 2.01-5.91; $P < .001$) and late-diagnosed asthma (OR, 2.91; 1.77-4.79; $P < .001$). The univariate analyses can be found in Table E4 in this article's Online Repository at www.jaci-inpractice.org.

Interestingly, as COPD was excluded, intermediate-diagnosed asthma became a significant risk factor of stroke or TIA (OR, 2.33; 1.15-4.71; $P = .019$) and late-diagnosed asthma lost significant association with severe cardiovascular disease (see

TABLE I. Demographic characteristics of subjects without and with asthma by age at asthma diagnosis strata

	Without asthma (N = 7051)		Early-diagnosed asthma (0-11 y; N = 245)		Intermediate-diagnosed asthma (12-39 y; N = 358)		Late-diagnosed asthma (40-69 y; N = 239)	
Variable	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**
Age (y)	50	35-61	32	26-44	42	32-54	62	57-66
Years since diagnosis	ND	ND	27	20-39	19	10-28	10	4-17
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
BMI*	26.0	6.4	25.6	4.8	26.5	5.2	28.1	5.4
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Sex: female	3855	54.7	98	40.0	223	62.3	152	63.6
Allergic rhinitis	1275	18.1	174	71.0	228	63.7	85	35.6
Family history of asthma	1523	21.6	112	45.7	159	44.4	104	43.5
Smoking								
Never	3838	54.4	124	50.6	172	48.0	98	41.0
Current	1508	21.4	68	27.8	80	22.3	49	20.5
Ex	1705	24.2	53	21.6	106	29.6	92	38.5
Asthma medication use	282	4.0	148	60.4	256	71.5	212	88.7

ND, Not defined; Q_1-Q_3, quartiles.
*Missing =126.

TABLE II. Nonrespiratory diseases and COPD in subjects without and with asthma by age at asthma diagnosis strata and statistical comparison between age at asthma diagnosis strata adjusted by age and sex

	Without asthma (N = 7051)		Early-diagnosed asthma (0-11 y; N = 245)		Intermediate-diagnosed asthma (12-39 y; N = 358)		Late-diagnosed asthma (40-69 y; N = 239)		
Variable	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	***P***
Hypertension	1333	18.9	27	11.0	58	16.2	101	42.3	.23
Severe cardiovascular disease	344	4.9	6	2.4	11	3.1	30	12.6	.65
Coronary artery disease	165	2.3	1	0.4	1	0.3	15	6.3	.14
Arrhythmia	419	5.9	11	4.5	21	5.9	38	15.9	.65
Heart failure	87	1.2	1	0.4	2	0.6	8	3.3	.56
Stroke or TIA	140	2.0	4	1.6	9	2.5	14	5.9	.87
Diabetes	404	5.7	6	2.4	18	5.0	35	14.6	.30
Depression	733	10.4	29	11.8	59	16.5	42	17.6	.38
Anxiety or panic disorder	427	6.1	17	6.9	43	12.0	18	7.5	.04
GERD	399	5.7	18	7.3	37	10.3	44	18.4	.92
Chronic kidney failure	51	0.7	1	0.4	3	0.8	3	1.3	.79
Sleep apnea	247	3.5	7	2.9	19	5.3	26	10.9	.32
Osteoporosis	122	1.7	1	0.4	17	4.7	21	8.8	.22
Painful condition	460	6.5	12	4.9	36	10.1	51	21.3	.31
Obesity*	1152	16.6	42	17.5	75	21.1	73	31.1	.34
COPD	97	1.4	8	3.3	28	7.8	44	18.4	.05

$P < .017$ was the threshold for statistical significance due to Bonferroni correction for multiple comparisons.
*Missing = 126.

Table E5 in this article's Online Repository at www.jaci-inpractice.org).

When regression analysis was adjusted by COPD, smoking, and BMI in addition to age and sex, we saw hypertension, severe cardiovascular disease, and diabetes lose their significant associations with late-diagnosed asthma compared with without asthma. Otherwise, significant associations remained similar (Table IV). To point out, after these adjustments, sleep apnea and depression remained significant in both intermediate- and late-diagnosed asthma as opposed to without asthma.

DISCUSSION

In this population-based study, we found that adults with asthma suffer from nonrespiratory diseases and multimorbidity more often than adults without asthma. In adjusted analyses, the number of nonrespiratory diseases was greater at older age at asthma diagnosis than when asthma was diagnosed at younger ages.

Some associations between asthma and nonrespiratory diseases have been previously described.[7-10] However, different age of asthma onset has been considered only in a few previous studies

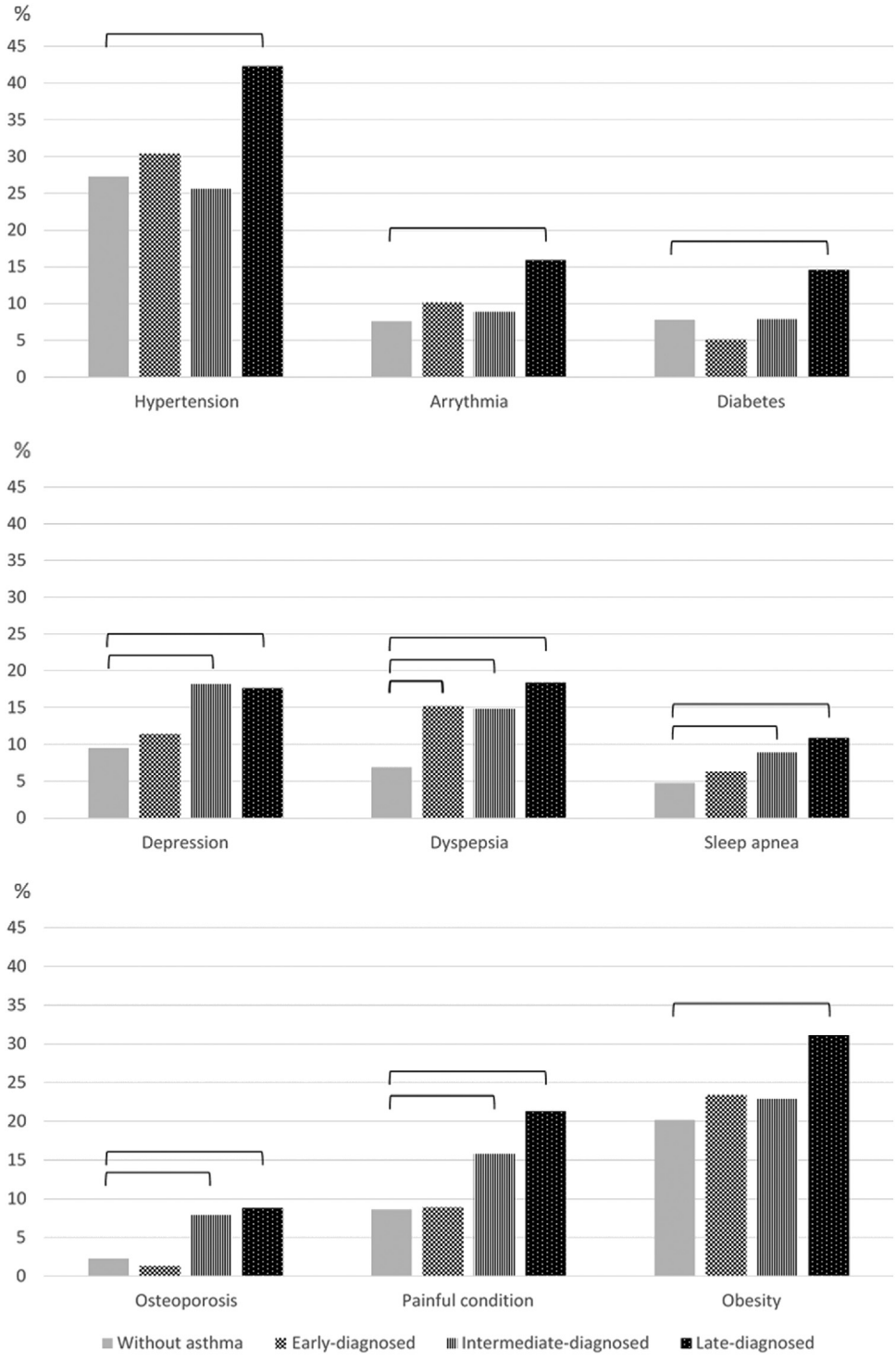

FIGURE 1. Prevalence (%) of different nonrespiratory diseases in subjects with and without asthma by age at asthma diagnosis. Only subjects 40 years or older are included. *P* less than .05 between without asthma and different asthma strata are marked with connector lines. Analyses were done with logistic regression and adjusted by age and sex.

investigating asthma and its nonrespiratory comorbidities[11,13,20,21] but otherwise than in this study, they have usually not included controls without asthma,[11,20,21] analyses have been concentrated to a limited group of diseases,[11,13,15,21] or study subjects have represented only, for example, severe asthma and not asthma in the general population.[20,21] Neither have they categorized asthma to more than 2 strata by age of onset,[11,13,15,21] although more age of onset strata would be

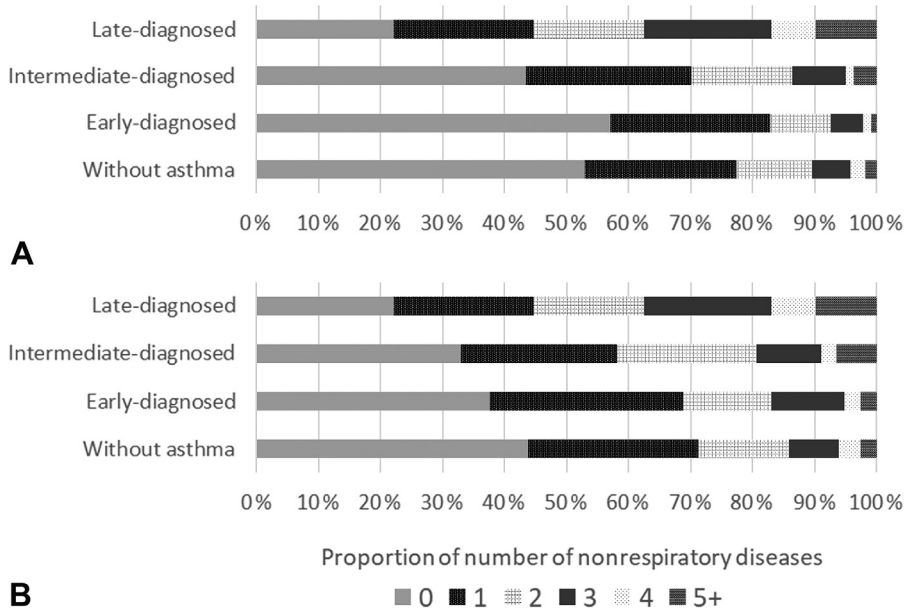

FIGURE 2. Number of nonrespiratory diseases in subjects with and without asthma by age at asthma diagnosis in (**A**) all subjects and (**B**) subjects 40 years or older.

TABLE III. The risk of nonrespiratory diseases and COPD in subjects with early-, intermediate-, and late-diagnosed asthma vs subjects without asthma in multivariable binary logistic regression analysis adjusted by age and sex

	Early-diagnosed asthma (0-11 y)		Intermediate-diagnosed asthma (12-39 y)		Late-diagnosed asthma (40-69 y)	
Variable	**OR (95 % CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Hypertension	1.49 (0.94-2.37)	.09	1.31 (0.95-1.80)	.10	1.54 (1.17-2.03)	**.002**
Severe cardiovascular disease	1.07 (0.46-2.51)	.88	1.00 (0.54-1.88)	.99	1.61 (1.07-2.41)	**.02**
Arrhythmia	1.29 (0.69-2.43)	.42	1.29 (0.81-2.04)	.28	1.94 (1.34-2.79)	**<.001**
Stroke or TIA	1.9 (0.69-5.42)	.21	1.92 (0.95-3.86)	.068	1.75 (0.99-3.11)	.06
Diabetes	0.76 (0.33-1.75)	.52	1.25 (0.76-2.10)	.38	1.75 (1.19-2.56)	**.004**
Depression	1.13 (0.76-1.69)	.55	1.60 (1.20-2.14)	**.002**	2.00 (1.41-2.84)	**<.001**
Anxiety or panic disorder	1.09 (0.65-1.81)	.75	1.96 (1.40-2.74)	**<.001**	1.43 (0.87-2.37)	.16
GERD	1.93 (1.17-3.19)	**.011**	2.17 (1.52-3.12)	**<.001**	2.77 (1.95-3.93)	**<.001**
Sleep apnea	1.17 (0.53-2.56)	.70	2.38 (1.45-3.91)	**.001**	2.57 (1.65-4.00)	**<.001**
Osteoporosis	0.63 (0.086-4.60)	.65	3.45 (2.01-5.91)	**<.001**	2.91 (1.77-4.79)	**<.001**
Painful condition	1.28 (0.70-2.33)	.43	1.91 (1.33-2.75)	**.001**	2.54 (1.83-3.54)	**<.001**
Obesity	1.41 (1.0-2.0)	.051	1.52 (1.16-1.98)	**.002**	1.72 (1.29-2.30)	**<.001**
COPD	4.38 (1.03-9.43)	**<.001**	8.40 (5.33-13.22)	**<.001**	10.74 (7.20-16.01)	**<.001**
No. of nonrespiratory diseases ≥1	1.48 (1.13-1.95)	**.005**	1.88 (1.50-2.36)	**<.001**	2.27 (1.65-3.12)	**<.001**
No. of nonrespiratory diseases ≥2	1.30 (0.91-1.86)	.16	1.94 (1.52-2.49)	**<.001**	2.59 (1.98-3.40)	**<.001**
No. of nonrespiratory diseases ≥3	1.36 (0.82-2.27)	.23	1.86 (1.34-2.59)	**<.001**	3.14 (2.36-4.17)	**<.001**

Without asthma was coded as 0 and in each regression analysis, diagnosis-age stratum as 1. Bolded text indicates statistical significance ($P < .05$).

justified.[19,22,23] Therefore, only very limited information exists previously on the association between asthma categorized by age of onset and other chronic nonrespiratory diseases.

We found several nonrespiratory diseases to be more common not in early-diagnosed but in intermediate- and late-diagnosed asthma compared with subjects without asthma in age- and

TABLE IV. The risk of nonrespiratory diseases in subjects with early-, intermediate-, and late-diagnosed asthma vs subjects without asthma in multivariable binary logistic regression analysis adjusted by age, sex, COPD, smoking, and BMI

	Early-diagnosed asthma (0-11 y)		Intermediate-diagnosed asthma (12-39 y)		Late-diagnosed asthma (40-69 y)	
Variable	OR (95 % CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Hypertension	1.37 (0.84-2.23)	.20	1.12 (0.80-1.58)	.51	1.30 (0.96-1.75)	.09
Severe cardiovascular disease	1.02 (0.43-2.41)	.97	0.91 (0.48-1.71)	.76	1.28 (0.83-1.98)	.26
Arrhythmia	1.27 (0.67-2.39)	.47	1.09 (0.68-1.76)	.72	1.64 (1.11-2.41)	**.01**
Stroke or TIA	1.81 (0.64-5.12)	.27	1.74 (0.85-3.55)	.13	1.43 (0.78-2.64)	.25
Diabetes	0.73 (0.31-1.70)	.46	1.05 (0.63-1.75)	.85	1.41 (0.94-2.11)	.10
Depression	1.00 (0.66-1.53)	.98	1.45 (1.08-1.95)	**.015**	1.74 (1.20-2.52)	**.003**
Anxiety or panic disorder	1.01 (0.59-1.71)	.98	1.85 (1.31-2.61)	**<.001**	1.32 (0.78-2.21)	.30
GERD	1.95 (1.18-3.24)	**.009**	2.14 (1.48-3.08)	**<.001**	2.80 (1.94-4.03)	**<.001**
Sleep apnea	1.10 (0.50-2.43)	.82	2.06 (1.23-3.43)	**.006**	1.99 (1.23-3.20)	**.005**
Osteoporosis	0.58 (0.078-4.24)	.59	2.97 (1.69-5.22)	**<.001**	2.41 (1.41-4.16)	**.001**
Painful condition	1.23 (0.67-2.27)	.50	1.64 (1.12-2.39)	**.011**	2.05 (1.44-2.92)	**<.001**
No. of nonrespiratory diseases ≥1	1.44 (1.07-1.96)	**.018**	1.63 (1.27-2.10)	**<.001**	1.75 (1.23-2.48)	**.002**
No. of nonrespiratory diseases ≥2	1.22 (0.83-1.80)	.32	1.64 (1.24-2.17)	**<.001**	2.01 (1.48-2.72)	**<.001**
No. of nonrespiratory diseases ≥3	1.28 (0.73-2.23)	.39	1.48 (1.02-2.15)	**.038**	2.52 (1.82-3.49)	**<.001**

Without asthma was coded as 0 and in each regression analysis, diagnosis-age stratum as 1. Bolded text indicates statistical significance ($P < .05$).

sex-adjusted analyses. Additionally adjusting for smoking, BMI, and COPD generally diminished these associations, most of which remained significant. As asthma diagnosis-age strata were compared with each other, none of the analyzed diseases differed between them. Another recent study that included quite a versatile set of chronic diseases neither found any of the analyzed diseases to differ between age of onset—defined difficult asthma.[20] In that study, asthma was divided only to 2 strata by age of onset, and subjects without asthma were not included.

In our results, we demonstrated that not only was asthma associated with more comorbid diseases, as has been reported before,[3] but also that later age at asthma diagnosis was associated with a higher number of nonrespiratory diseases. To our knowledge, this was the first study to describe age-independent association with age at asthma diagnosis and number of nonrespiratory comorbid diseases.

The prevalence of obese responders with asthma increased with age at diagnosis in our study. Obesity is previously found to impact child-onset asthma severity more than adult-onset asthma.[26] However, only adult-onset asthma is found to have a genetic association with obesity,[27] and many studies have found obesity to associate especially with adult-onset female asthma.[1,14,20] Therefore, obesity seems to play a different role in asthma depending on asthma diagnosis age.

GERD is commonly found to associate with asthma,[8,9] but as a novel finding, it also had an increasing association with asthma by increasing asthma diagnosis age in our results. Variable results on proton pump inhibitor treatment influencing asthma outcome are reported.[5] However, long-term acid-suppressive medication has been shown to increase asthma risk.[28]

In our data, depression was more prevalent in subjects with intermediate- or late-diagnosed asthma than in subjects without asthma. Anxiety or panic disorder, however, was more prevalent in those with intermediate-diagnosed asthma than in those without asthma, being a novel finding. Of mental disorders, especially depression has been reported previously to have a significant association with asthma.[8,10] It is linked to asthma in a genetic manner[29] and is also associated with poorer control of asthma[30] and has common molecular pathways with asthma.[6] Common molecular pathways and genetics may explain the association mostly, but also the burden of asthma could play a role in development of depression.

Osteoporosis was associated with intermediate- and late-diagnosed asthma, and it had the most marked association with asthma in these age at diagnosis strata of the analyzed diseases. It was not significantly associated with early-diagnosed asthma. This could indirectly indicate a more difficult disease if asthma is diagnosed in adulthood and by implication, an emphasized corticosteroid use, which predisposes to osteoporosis.[31,32] However, other factors may also have an impact, and indeed, the pathogenetic processes have similarities between osteoporosis and asthma.[31] Corticosteroid use may also play an important role in other associations between asthma and other chronic diseases investigated in this study.

In this study, late-diagnosed asthma was associated with hypertension, cardiac arrhythmia, and severe cardiovascular diseases, but we demonstrated that the associations mostly disappeared after further adjusting for smoking, COPD, and BMI. Of cardiovascular diseases, especially hypertension has been associated with asthma earlier.[8,11,12] Another study

described association of cardiovascular diseases with adult-onset, but not with child-onset, asthma.[11] Consistently with our results, almost all significant associations disappeared as the model was further adjusted with lifestyle-associated variables in that study. Yet another study considering age of onset did not find differences between child- and adult-onset asthma[13] but adult-onset asthma was limited to onset at 54 years of age maximum. Subjects with asthma may suffer from both hypertension and arrhythmias more often due to harmful effects of asthma medication, community in inflammation status or metabolic condition, or even mechanisms related to subjective burden of asthma, stress, or lack of sleep.[6,12]

Subjects with intermediate- and late-diagnosed asthma had more sleep apnea than subjects without asthma in this study. Asthma and sleep apnea have been associated before also.[16] Furthermore, controlling for obese subjects in this study diminished but did not abolish the associations. Thus, our study indicates that other factors than obesity must also play a role in this association.

Subjects with intermediate- and late-diagnosed asthma had more painful condition than those without asthma, with a prominent effect size even after adjusting for lifestyle factors in this study. The etiology of painful condition was not defined and could result from either individual or multifactorial cause. Perhaps of its ambiguity, it is a condition and a variable mainly overlooked in previous studies investigating comorbidities of asthma. Regarding cause of this association, regular paracetamol use has been previously connected with asthma prevalence.[33]

Because COPD is shown to associate with more comorbidities than asthma,[34] and misdiagnoses between asthma and COPD is a frequent concern, we did sensitivity analyses by excluding coexisting COPD. This did not generally change the results markedly. COPD was most common in late-diagnosed asthma compared with other diagnosis-age strata, and it is also one of the few comorbidities previously identified to differ between age of asthma onset phenotypes: it was more common in adult-onset than in child-onset asthma in a recent study that was, however, limited to severe asthma.[20]

Generally, various potential explanations for associations between asthma and nonrespiratory diseases exist. Many of them have common genetic or molecular mechanisms with asthma,[6,14] whereas others share environmental risk factors with asthma.[6] Some diseases are also influenced by asthma medication, such as osteoporosis and diabetes.[6] In addition, genetic differences seem to be associated more with child-onset disease[1,35] and environmental factors with later-onset asthma.[2] They seem also to differ in asthma pathogenesis.[2,17]

Strengths of this study include a large, multicenter general population sample with no marked exclusions, and therefore the result generalizability should finely extend to the general population. We included subjects with a broad age range (20-69 years), which is quite rarely seen in asthma studies. Furthermore, the study is a part of a larger consortium, and the questionnaire and other study procedures have been previously validated empirically, as dozens of original articles have followed since the initial FinEsS study in 1995. Finally, the data are collected from areas in which asthma diagnoses are generally very reliable due to good availability of spirometry and peak expiratory flow, high standard physician and nurse training, and disciplinarily followed, uniform national protocols.[36] There is also a requirement of objective asthma diagnosis to obtain asthma medication reimbursement in Finland.

The main weaknesses of this study are as follows. Concern of recall bias related to preciseness of asthma diagnosis age is a major consideration. However, it is demonstrated that retrospective assessment of self-reported age at diagnosis of asthma is specific and widely used.[24,37] Furthermore, in Finland, patients with newly diagnosed asthma are granted an asthma medication reimbursement and a new governmental insurance card holding the issue date that corresponds roughly to time at diagnosis, enhancing the memory trace. The reimbursement system and issue card have been used since 1970, covering most of the study period. When assessing reliability of self-report of the diagnoses of diseases, they are found to be relatively reliable, but mostly underreported,[38] which applies also to asthma.[37] However, overdiagnosis of asthma is also common, and diagnosing asthma is particularly challenging.[39] However, in Finland, the common practice is to objectively measure lung function in asthma diagnosis.[36] It is also notable that cohort effect affects the current results because diagnostic tools and practice have changed over time, and asthma diagnoses reflect a long period as the study was cross-sectional asking for asthma diagnosis age.

Furthermore, the study could have been done by using register data, and therefore the validity of presence of the different chronic diseases could have been better. Finally, our response rate of 52% is a level that has been quite common in questionnaire studies recently, which should not deviate the result markedly in asthma studies, as we have discussed previously with detail.[24] In addition, the responders were more often older subjects, in which diseases were also more prevalent.

Comorbidities supposedly confound results of asthma phenotyping studies,[3] and other studies of asthma control. Higher number of comorbidities is previously associated with lower Asthma Control Test score,[4] and obesity and mental diseases have also been found to independently influence asthma control negatively.[6,30,40] The potential of comorbidities acting as confounding factors in many ways is therefore quite significant, which also the current results support—not only age but also age at asthma diagnosis influences diseases associated with asthma. Furthermore, better identification of asthma multimorbidity would benefit by unraveling possibilities in more holistic and personalized treatment approach. In addition, concentration on asthma comorbidities could promote finding common molecular pathways between asthma and other diseases to target future treatment methods and better understanding of pathogenesis especially regarding adult-onset asthma, in which specific mechanisms are mostly unknown, contributing to worse outcomes.[2]

CONCLUSIONS

Adults with asthma suffer overall from many more diseases than adults without asthma. Age at asthma diagnosis modified frequency of diseases, so that the number of nonrespiratory diseases increased by increasing age at asthma diagnosis. The results could indicate not only that higher corticosteroid usage, especially in adult-onset asthma, predisposes to other chronic diseases but also that asthma shares several molecular mechanisms with other chronic diseases. Better understanding of comorbid diseases could help us in obtaining enhanced asthma

control, and for the first thing, they should be more readily noted in studies of adult asthma.

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TABLE E1. Demographic characteristics, nonrespiratory diseases, and COPD in subjects without and with asthma by age at asthma diagnosis strata and statistical comparison between age at asthma diagnosis strata adjusted by age and sex in subjects aged ≥40 y

	Without asthma (N = 4699)		Early-diagnosed asthma (N = 79)		Intermediate-diagnosed asthma (N = 203)		Late-diagnosed asthma (N = 239)		
Variable	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	***P****
Age (y)	58	50-64	51	45-59	52	45-61	62	57-66	
Years since diagnosis	ND	ND	44	39-56	26	19-34	10	4-17	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
BMI†	26.7	6.6	26.6	4.4	27.1	5.2	28.1	5.4	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Sex: female	2503	53.3	27	34.2	130	64.0	152	63.6	
Allergic rhinitis	720	15.3	52	65.8	134	66.0	85	35.6	
Family history of asthma	985	21.0	34	43.0	95	46.8	104	43.5	
Smoking									
Never	2467	52.5	38	48.1	89	43.8	98	41.0	
Current	918	19.5	21	26.6	41	20.2	49	20.5	
Ex	1314	28.0	20	25.3	73	36.0	92	38.5	
Hypertension	1285	27.3	24	30.4	52	25.6	101	42.3	.12
Severe cardiovascular disease	327	7.0	6	7.6	11	5.4	30	12.6	.61
Coronary disease	163	3.5	1	1.3	1	0.5	15	6.3	.14
Heart failure	74	1.6	1	1.3	2	1.0	8	3.3	.55
Arrhythmia	359	7.6	8	10.1	18	8.9	38	15.9	.59
Stroke or TIA	135	2.9	4	5.1	9	4.4	14	5.9	.88
Diabetes	368	7.8	4	5.1	16	7.9	35	14.6	.26
Depression	447	9.5	9	11.4	37	18.2	42	17.6	.32
Anxiety or panic disorder	252	5.4	1	1.3	21	10.3	18	7.5	.10
GERD	323	6.9	12	15.2	30	14.8	44	18.4	.87
Chronic kidney failure	44	0.9	1	1.3	3	1.5	3	1.3	.89
Sleep apnea	227	4.8	5	6.3	18	8.9	26	10.9	.30
Osteoporosis	109	2.3	1	1.3	16	7.9	21	8.8	.34
Painful condition	405	8.6	7	8.9	32	15.8	51	21.3	.18
COPD	89	1.9	4	5.1	23	11.3	44	18.4	.06
Obesity†	930	20.2	18	23.4	46	22.9	73	31.1	.38
Nonrespiratory diseases ≥1†	2589	56.1	48	62.3	135	67.2	183	77.9	.28
Nonrespiratory diseases ≥2†	1327	28.8	24	31.2	84	41.8	130	55.3	.07
Nonrespiratory diseases ≥3†	653	14.2	13	16.9	39	19.4	88	37.4	**.01**

ND, Not defined; Q_1-Q_3, quartiles.
*Three diagnosis-age strata compared. Bolded text indicates statistical significance ($P < .017$).
†Missing= 85.

TABLE E2. Demographic characteristics, nonrespiratory diseases, and COPD, and statistical comparison between subjects with and without physician-diagnosed asthma

	Without asthma (N = 7051)		Physician-diagnosed asthma (N = 879)		
Variable	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	***P***
Age (y)	50	35-61	47	32-61	**.01**
Years since diagnosis	ND	ND	19	10-28	ND
Variable	**Mean**	**SD**	**Mean**	**SD**	
BMI*	26.0	6.4	26.7	5.3	**.001**
	N	**%**	**N**	**%**	
Sex: female	3855	54.7	498	56.7	.27
Allergic rhinitis	1275	18.1	508	57.8	**<.001**
Family history of asthma	1523	21.6	392	44.6	**<.001**
Smoking					**<.001**
Never	3838	54.4	409	46.5	
Current	1508	21.4	208	23.7	
Ex	1705	24.2	262	29.8	
Hypertension	1333	18.9	195	22.2	**.02**
Severe cardiovascular disease	344	4.9	50	5.7	.30
Coronary artery disease	165	2.3	18	2.0	.59
Arrhythmia	419	5.9	72	8.2	**.01**
Heart failure	87	1.2	13	1.5	.54
Stroke or TIA	140	2.0	27	3.1	**.03**
Diabetes	404	5.7	63	7.2	.09
Depression	733	10.4	133	15.1	**<.001**
Anxiety or panic disorder	427	6.1	81	9.2	**<.001**
GERD	399	5.7	103	11.7	**<.001**
Chronic kidney failure	51	0.7	7	0.8	.81
Sleep apnea	247	3.5	56	6.4	**<.001**
Osteoporosis	122	1.7	41	4.7	**<.001**
Painful condition	460	6.5	102	11.6	**<.001**
COPD	97	1.4	81	9.2	**<.001**
Obesity*	1152	16.6	302	23.2	**<.001**
No. of nonrespiratory diseases ≥1*	3260	47.0	508	58.7	**<.001**
No. of nonrespiratory diseases ≥2*	1558	22.5	288	33.3	**<.001**
No. of nonrespiratory diseases ≥3*	721	10.4	162	18.7	**<.001**

ND, Not defined; Q_1-Q_3, quartiles.
Bolded text indicates statistical significance ($P < .05$).
*Missing =126.

TABLE E3. Demographic characteristics, nonrespiratory diseases, and statistical comparison between subjects with and without physician-diagnosed asthma when subjects with COPD were excluded

	Without asthma (N = 6954)		Physician-diagnosed asthma (N = 798)		
Variable	**Median**	**Q_1-Q_3**	**Median**	**Q_1-Q_3**	***P***
Age (y)	49	35-61	45	32-60	**<.001**
Years since diagnosis	ND	ND	19	10-28	ND
Variable	**Mean**	**SD**	**Mean**	**SD**	
BMI*	26.0	6.4	26.6	5.2	**.001**
	N	**%**	**N**	**%**	
Sex: female	3808	54.8	459	57.5	.14
Allergic rhinitis	1248	17.9	466	58.4	**<.001**
Family history of asthma	1487	21.4	350	43.9	**<.001**
Smoking					**.003**
Never	3817	54.9	394	49.4	
Current	1469	21.1	171	21.4	
Ex	1668	24.0	233	29.2	
Hypertension	1295	18.6	163	20.4	.22
Severe cardiovascular disease	327	4.7	38	4.8	.94
Coronary artery disease	158	2.3	12	1.5	.16
Arrhythmia	80	1.2	58	7.3	.09
Heart failure	401	5.8	9	1.1	.96
Stroke or TIA	132	1.9	22	2.8	.10
Diabetes	389	5.6	48	6.0	.63
Depression	713	10.3	114	14.3	**<.001**
Anxiety or panic disorder	418	6.0	74	9.3	**<.001**
GERD	390	5.6	94	11.8	**<.001**
Chronic kidney failure	49	0.7	4	0.5	.51
Sleep apnea	233	3.4	47	5.9	**<.001**
Osteoporosis	113	1.6	34	4.3	**<.001**
Painful condition	440	6.3	82	10.3	**<.001**
Obesity*	1124	16.4	176	22.4	**<.001**
No. of nonrespiratory diseases ≥1*	3186	46.6	447	56.9	**<.001**
No. of nonrespiratory diseases ≥2*	1506	22.0	243	30.9	**<.001**
No. of nonrespiratory diseases ≥3*	691	10.1	133	16.9	**<.001**

ND, Not defined; Q_1-Q_3, quartiles.
Bolded text indicates statistical significance ($P < .05$).
*Missing = 126.

TABLE E4. The risk of nonrespiratory diseases in subjects with early-, intermediate-, and late-diagnosed asthma vs subjects without asthma in univariate binary logistic regression analysis

	Early-diagnosed asthma (0-11 y)		Intermediate-diagnosed asthma (12-39 y)		Late-diagnosed asthma (40-69 y)	
Variable	**OR (95 % CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Hypertension	0.53 (0.36-0.80)	**.002**	0.83 (0.62-1.11)	.20	3.14 (2.41-4.09)	**<.001**
Severe cardiovascular disease	0.49 (0.22-1.11)	.087	0.62 (0.34-1.14)	.12	2.80 (1.88-4.17)	**<.001**
Arrhythmia	0.74 (0.40-1.37)	.34	0.99 (0.63-1.55)	.95	2.99 (2.09-4.29)	**<.001**
Stroke or TIA	0.82 (0.30-2.23)	.70	1.27 (0.64-2.52)	.49	3.07 (1.75-5.41)	**<.001**
Diabetes	0.41 (0.18-0.93)	**.034**	0.87 (0.54-1.41)	.58	2.82 (1.95-4.10)	**<.001**
Depression	1.16 (0.78-1.72)	.47	1.70 (1.27-2.27)	**<.001**	1.84 (1.31-2.59)	**<.001**
Anxiety or panic disorder	1.16 (0.70-1.91)	.57	2.12 (1.52-2.96)	**<.001**	1.26 (0.77-2.06)	.35
GERD	1.32 (0.81-2.16)	.27	1.92 (1.35-2.74)	**<.001**	3.76 (2.67-5.30)	**<.001**
Sleep apnea	0.81 (0.38-1.74)	.59	1.54 (0.96-2.49)	.076	3.36 (2.20-5.15)	**<.001**
Osteoporosis	0.23 (0.032-1.67)	.15	2.83 (1.69-4.76)	**<.001**	5.47 (3.38-8.86)	**<.001**
Painful condition	0.74 (0.41-1.33)	.31	1.60 (1.12-2.29)	**.010**	3.89 (2.81-5.37)	**<.001**
Obesity	1.07 (0.76-1.49)	.72	1.34 (1.03-1.75)	**.027**	2.26 (1.70-3.00)	**<.001**
COPD	2.42 (1.16-5.03)	**.018**	6.08 (3.94-9.40)	**<.001**	16.2 (11.0-23.7)	**<.001**
No. of nonrespiratory diseases ≥1	0.85 (0.65-1.10)	.21	1.47 (1.19-1.82)	**<.001**	3.97 (2.90-5.42)	**<.001**
No. of nonrespiratory diseases ≥2	0.71 (0.51-1.00)	**.050**	1.47 (1.16-1.86)	**.001**	4.27 (3.28-5.56)	**<.001**
No. of nonrespiratory diseases ≥3	0.70 (0.43-1.14)	.15	1.35 (0.98-1.84)	.063	5.16 (3.92-6.79)	**<.001**

Without asthma was coded as 0 and in each regression analysis, diagnosis-age stratum as 1. Bolded text indicates statistical significance ($P < .05$).

TABLE E5. The risk of nonrespiratory diseases in subjects with early-, intermediate-, and late-diagnosed asthma vs subjects without asthma in multivariable binary logistic regression analysis adjusted by age and sex, when subjects with COPD were excluded

	Early-diagnosed asthma (0-11 y)		Intermediate-diagnosed asthma (12-39 y)		Late-diagnosed asthma (40-69 y)	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Hypertension	1.55 (0.97-2.48)	.068	1.32 (0.94-1.86)	.11	1.46 (1.07-1.98)	**.017**
Severe cardiovascular disease	0.97 (0.39-2.46)	.95	1.20 (0.64-2.25)	.58	1.31 (0.80-2.15)	.29
Arrhythmia	1.25 (0.65-2.41)	.51	1.26 (0.77-2.07)	.36	1.82 (1.19-2.76)	**.005**
Stroke or TIA	1.61 (0.49-5.25)	.43	2.33 (1.15-4.71)	**.019**	1.61 (0.83-3.15)	.16
Diabetes	0.53 (0.19-1.45)	.22	1.10 (0.63-1.91)	.74	1.75 (1.14-2.68)	**.011**
Depression	1.04 (0.68-1.58)	.87	1.49 (1.09-2.04)	**.012**	2.00 (1.36-2.94)	**<.001**
Anxiety or panic disorder	1.12 (0.67-1.87)	.67	1.91 (1.34-2.71)	**<.001**	1.50 (0.85-2.54)	.17
GERD	1.88 (1.12-3.16)	**.016**	2.15 (1.47-3.14)	**<.001**	3.20 (2.21-4.63)	**<.001**
Sleep apnea	1.09 (0.47-2.53)	.84	2.47 (1.46-4.16)	**.001**	2.70 (1.64-4.46)	**<.001**
Osteoporosis	0.69 (0.09-5.01)	.71	3.44 (1.91-6.19)	**<.001**	3.00 (1.74-5.17)	**<.001**
Painful condition	1.23 (0.66-2.30)	.52	1.86 (1.26-2.75)	**.002**	2.27 (1.56-3.31)	**<.001**
Obesity	1.35 (0.95-1.94)	.10	1.55 (1.18-2.05)	**.002**	1.69 (1.23-2.33)	**.001**
No. of nonrespiratory diseases ≥1	1.46 (1.10-1.93)	**.008**	1.88 (1.49-2.38)	**<.001**	2.17 (1.54-3.05)	**<.001**
No. of nonrespiratory diseases ≥2	1.26 (0.87-1.82)	.23	1.90 (1.47-2.47)	**<.001**	2.47 (1.84-3.32)	**<.001**
No. of nonrespiratory diseases ≥3	1.28 (0.75-2.19)	.37	1.76 (1.23-2.50)	**.002**	3.17 (2.32-4.33)	**<.001**

Without asthma was coded as 0 and in each regression analysis, diagnosis-age stratum as 1. Bolded text indicates statistical significance ($P < .05$).