

## RESEARCH PAPER

# Chronic disease co-morbidity of asthma and unscheduled asthma care among adults: results of the national telephone health interview survey German Health Update (GEDA) 2009 and 2010

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### Abstract

**Background:** Co-morbidities may complicate the clinical management of chronic conditions such as asthma.

**Aims:** To quantify the strength of the relationship between asthma and other chronic diseases and to analyse whether co-morbidities contribute to unscheduled asthma care.

**Methods:** Data from two consecutive national telephone health interview surveys (GEDA 2009 and 2010) including a total of 43,312 adults ( $\geq 18$  years of age) were analysed. Persons with and without a current diagnosis of asthma were compared with respect to concurrent diagnoses (diabetes mellitus, hypertension, chronic heart failure, depression, osteoarthritis, stroke, coronary heart disease, and cancer). Logistic regression models were applied to assess the strength of the association between asthma and co-morbidities in the total study population and, among persons with asthma, between the number of co-morbidities and unscheduled inpatient (hospital admissions and/or emergency department admissions) or outpatient asthma care in the past 12 months.

**Results:** Overall, 5.3% (95% CI 5.0% to 5.6%) of adults reported current physician-diagnosed asthma. Asthma was significantly associated with most of the conditions considered and 18% of persons with asthma had three or more co-morbidities. Adjusted odds ratios (AOR) of unscheduled asthma care increased with numbers of conditions, with AOR 3.40 (95% CI 1.39 to 8.31) for unscheduled inpatient care and AOR 2.32 (95% CI 1.30 to 4.14) for unscheduled outpatient care comparing those with three or more co-morbidities versus those with none.

**Conclusions:** The magnitude of chronic disease co-morbidity is substantial in asthma, is related to unscheduled asthma care, and implies a significant number of adults with asthma facing complex healthcare needs.

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## Background

Co-morbidity – the presence of concomitant health conditions in individuals with an index disease – may complicate the clinical

course and treatment of patients with the index disease.<sup>1</sup> Previous studies have demonstrated that co-morbidity can have an adverse impact on patients' health-related quality of life (HRQoL) and can increase the socio-economic burden of chronic conditions on the healthcare system.<sup>1,2</sup>

Although asthma is a chronic disease that is highly relevant both to the individual and with regard to public health, published data covering a range of co-morbidities in the general population of

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adults with and without asthma are few. The data available suggest associations between asthma and major chronic conditions such as hypertension, diabetes, coronary heart disease, chronic heart failure, or malignancies that are not commonly recognised as co-morbidities typical of patients with asthma.<sup>3</sup> Previous reports, however, have mainly been based on administrative data,<sup>4,7</sup> which do not permit adjustment for potential confounders such as socio-demographic factors or health-related behaviours.

Moreover, few studies have so far addressed the consequences of co-morbidities for health outcomes and healthcare among adults with asthma. Two previous analyses of population-based data suggested an adverse effect of major chronic conditions on usual activity levels as well as on general and disease-specific HRQoL.<sup>8,9</sup> When comparing adults with and without asthma, co-morbidity was found to be associated with a significant proportion of overall hospitalisations, emergency room visits, and ambulatory care visits based on administrative health data.<sup>5</sup> In an analysis of data from a large national health survey, Zhang *et al.* reported that persons with asthma who had at least one concurrent major chronic condition had a significantly higher chance to have experienced asthma symptoms and/or acute asthma attacks in the past year than those with no concurrent major chronic conditions.<sup>10</sup> These authors also addressed the relevance of further research on the influence of major chronic conditions on asthma-related hospitalisations, emergency department (ED) visits, and physician visits.

Against this background, we used nationally representative health survey data of adults in Germany to quantify the strength of the association between asthma and eight other chronic conditions selected for their high prevalence and/or high impact on the healthcare system.<sup>11,12</sup> We further analysed the influence of co-morbidity on unscheduled inpatient and outpatient asthma care among adults with asthma.

## Methods

### Study design and study population

German Health Update (GEDA) is a periodically repeated national telephone health interview survey of adults ( $\geq 18$  years of age).<sup>13</sup> The target population of these cross-sectional studies consists of all adults who live in private households with a landline telephone and who can fluently speak and understand German. A two-stage sampling procedure was used.<sup>14,15</sup> For sampling at the household level, the Gabler-Häder method<sup>16</sup> was applied to randomly generate a pool of about 220,000 telephone numbers from complete listings of landline telephone extensions<sup>14,15</sup> while, for random sampling at the individual level, the 'last birthday method' was used.<sup>17</sup> The study was approved by the Federal Commissioner for Data Protection and Freedom of Information and verbal informed consent had been received from all participants prior to the interview.

Between July 2008 and June 2009 and between September 2009 and July 2010, respectively, 21,262 persons and 22,050 persons completed the telephone interview. The cooperation rate at the individual level, which represents the cooperation rate at the respondent level,<sup>18</sup> was 51.2% for GEDA 2009 and 55.8% for GEDA 2010.<sup>14,15</sup>

**Table 1. Main characteristics of survey participants in the pooled sample of the German Health Update (GEDA) 2009 and 2010 surveys, the total sample of the GEDA 2010 survey, and among participants of the GEDA 2010 survey with current self-reported physician-diagnosed asthma**

Characteristics	Pooled sample of GEDA 2009 and 2010 (N=43,312)	Total sample of GEDA 2010 (N=22,050)	Current asthma population in GEDA 2010 (N=1,136)
Gender			
Women, % (n)	51.5 (24,597)	51.5 (12,483)	61.1 (737)
Age, in years			
Mean (SD)	49.0 (17.9)	49.0 (17.9)	52.1 (18.2)
Range	18–100	18–99	18–95
Age groups, % (n)			
18–29 years	17.1 (7,620)	16.9 (3,831)	13.4 (171)
30–44 years	25.7 (12,072)	25.9 (6,096)	21.5 (276)
45–64 years	32.7 (15,441)	32.7 (7,980)	35.3 (440)
$\geq 65$ years	24.5 (8,179)	24.4 (4,143)	29.8 (249)
BMI status, % (n)			
<25 kg/m <sup>2</sup>	47.9 (22,324)	47.8 (11,322)	39.3 (488)
25–<30 kg/m <sup>2</sup>	36.2 (14,383)	36.3 (7,338)	36.7 (387)
$\geq 30$ kg/m <sup>2</sup>	15.9 (5,722)	15.8 (2,931)	24.0 (237)
Educational attainment, % (n)			
Primary	22.1 (4,210)	22.1 (2,082)	27.1 (126)
Middle	55.6 (21,976)	55.5 (11,076)	55.7 (625)
High	22.3 (17,063)	22.3 (8,865)	17.3 (384)
Smoking status, % (n)			
Current	29.8 (12,514)	30.0 (6,291)	29.7 (322)
Former	26.3 (11,409)	26.6 (5,881)	31.0 (338)
Never	43.9 (19,373)	43.4 (9,873)	39.3 (476)
Health condition, % (n)			
Diabetes mellitus	7.4 (2,477)	7.4 (1,262)	10.7 (92)
Hypertension	26.5 (9,999)	26.7 (5,136)	37.7 (368)
Coronary heart disease	8.1 (2,602)	8.2 (1,327)	15.8 (136)
Chronic heart failure	3.0 (1,034)	3.0 (531)	8.8 (81)
Stroke	2.5 (835)	2.6 (427)	5.1 (34)
Cancer (any)	7.1 (2,910)	7.1 (1,464)	10.9 (107)
Osteoarthritis	19.0 (7,527)	19.2 (3,878)	28.2 (300)
Depression	6.7 (3,084)	7.1 (1,618)	13.6 (158)
Number of chronic conditions, % (n)			
0	56.0 (24,783)	55.5 (12,577)	38.6 (475)
1	23.5 (9,816)	23.7 (5,046)	26.7 (293)
2	12.0 (4,559)	12.1 (2,338)	18.1 (164)
$\geq 3$	8.5 (2,875)	8.7 (1,479)	16.7 (155)

The results are weighted and refer to participants providing information for the variable of interest. Numbers of observations per variable (n) are unweighted. Weighted percentage of missing values may vary for each variable and population sample (<sup>1</sup>pooled sample of GEDA 2009 and 2010, <sup>2</sup>total sample of GEDA 2010, and <sup>3</sup>subsample of participants with current asthma in GEDA 2010) for BMI status (n<sup>1</sup>=2.1, n<sup>2</sup>=2.3, n<sup>3</sup>=1.9), educational attainment (n<sup>1</sup>=0.2, n<sup>2</sup>=0.2, n<sup>3</sup>=0.2), smoking status (n<sup>1</sup>=0.0, n<sup>2</sup>=0.0, n<sup>3</sup>=0.0), diabetes mellitus (n<sup>1</sup>=0.2, n<sup>2</sup>=0.2, n<sup>3</sup>=0.5), hypertension (n<sup>1</sup>=0.4, n<sup>2</sup>=0.4, n<sup>3</sup>=0.4), coronary heart disease (n<sup>1</sup>=0.6, n<sup>2</sup>=0.7, n<sup>3</sup>=1.1), chronic heart failure (n<sup>1</sup>=0.9, n<sup>2</sup>=0.9, n<sup>3</sup>=1.5), stroke (n<sup>1</sup>=0.1, n<sup>2</sup>=0.2, n<sup>3</sup>=0.2), cancer (any) (n<sup>1</sup>=0.2, n<sup>2</sup>=0.1, n<sup>3</sup>=0.2), osteoarthritis (n<sup>1</sup>=1.0, n<sup>2</sup>=1.0, n<sup>3</sup>=1.0), depression (n<sup>1</sup>=0.3, n<sup>2</sup>=0.3, n<sup>3</sup>=0.8), number of chronic conditions (n<sup>1</sup>=3.5, n<sup>2</sup>=3.3, n<sup>3</sup>=5.3).

BMI=body mass index.

## Data collection and study variables

Information on health status, medical history, health-related behaviours, socio-demographic, and anthropometric variables was collected based on computer-assisted telephone interviews. Based on a highly standardised protocol, interviewers who were trained and closely supervised according to the guidelines of the Behavioural Risk Factor Surveillance System of the Centers for Disease Control and Prevention (BRFSS) carried out the interviews.<sup>19</sup> Participants were defined as having current asthma if they answered affirmatively to both of the consecutive questions about whether they had ever been told by a physician that they had asthma and whether asthma had been present within the last 12 months.

For the present analysis, data from the two consecutive national telephone health interview surveys (GEDA 2009 and 2010) were analysed. Persons with and without physician-diagnosed asthma in the past 12 months were compared with regard to eight concurrent high impact and/or high prevalence physician-diagnosed chronic conditions<sup>11,12</sup>: diabetes mellitus, hypertension, chronic heart failure, depression, osteoarthritis, and a lifetime diagnosis of stroke, coronary heart disease (with or without myocardial infarction), and cancer based on definitions that have previously been described in detail.<sup>20,21</sup> An additive co-morbidity index was calculated as a four-level categorical variable (0, 1, 2,  $\geq 3$ ) adapted from Broemeling *et al.* and Prosser *et al.*<sup>4,12</sup>

In the subset of 1,136 individuals who participated in the 2010 GEDA survey and who reported a history of current asthma, information on the age of asthma onset and asthma-specific healthcare utilisation was obtained.<sup>22</sup> The duration of asthma in years was calculated based on information on the current age and reported age of asthma onset. Asthma-related unscheduled care during the past 12 months was assessed using questions adapted from the BRFSS Asthma Call-back Survey section on healthcare utilisation, Adult Questionnaire.<sup>23</sup> Unscheduled asthma care was differentiated into unscheduled inpatient care (any vs. no asthma-related hospital or ED admission) and unscheduled outpatient care (any vs. no unscheduled doctor's office visit for urgent treatment of worsening asthma symptoms or an asthma attack).

Self-reported weight in kilograms was divided by height in metres squared in order to obtain the body mass index (BMI) of each survey participant. BMI level categories were classified according to criteria of the World Health Organization<sup>24,25</sup> and defined as obese ( $\geq 30$  kg/m<sup>2</sup>), overweight ( $\geq 25$ – $< 30$  kg/m<sup>2</sup>) and non-overweight/non-obese ( $< 25$  kg/m<sup>2</sup>). Educational attainment was defined according to the three-level International Standard Classification of Education (ISCED) and classified as primary, middle, or low.<sup>26</sup> Smoking status was defined as 'current' (for reported daily or occasional smoking), 'former', and 'never', and chronological age groups were classified as 18–29, 30–44, 45–64, and  $\geq 65$  years. Analyses of co-morbidity patterns were performed between younger and older adults using a cut-off level of 55 years of age ( $< 55$  vs.  $\geq 55$  years) according to previous research.<sup>4,9</sup>

## Statistical analyses

All results were weighted to adjust for sampling probabilities and selective participation in order to represent the adult residential

**Table 2. Main characteristics of the study population with respect to self-reported physician-diagnosed asthma: German telephone health interview survey German Health Update (GEDA) 2009 and 2010**

Characteristics	Current asthma (N=2,242)	No current asthma (N=40,947)	p value*
Gender			<0.001
Women, % (n)	58.6 (1,429)	51.0 (23,092)	
Age, in years			
Mean (SD)	52.5 (18.2)	48.8 (17.9)	
Range	18–95	18–100	
Age groups, % (n)			<0.001
18–29 years	13.5 (335)	17.3 (7,265)	
30–44 years	21.7 (566)	25.9 (11,477)	
45–64 years	33.5 (825)	32.7 (14,576)	
$\geq 65$ years	31.3 (516)	24.1 (7,629)	
BMI status, % (n)			<0.001
<25 kg/m <sup>2</sup>	39.1 (958)	48.4 (21,304)	
25– $< 30$ kg/m <sup>2</sup>	35.3 (762)	36.3 (13,585)	
$\geq 30$ kg/m <sup>2</sup>	25.7 (480)	15.3 (5,222)	
Educational attainment, % (n)			<0.001
Primary	26.5 (259)	21.8 (3,932)	
Middle	55.4 (1,212)	55.6 (20,703)	
High	18.1 (765)	22.6 (16,255)	
Smoking status, % (n)			0.013
Current	28.5 (616)	29.9 (11,866)	
Former	29.8 (659)	26.1 (10,722)	
Never	41.7 (967)	44.0 (18,343)	
Health condition, % (n)			
Diabetes mellitus	12.0 (210)	7.1 (2,255)	<0.001
Hypertension	37.9 (734)	25.8 (9,219)	<0.001
Coronary heart disease	16.7 (269)	7.5 (2,318)	<0.001
Chronic heart failure	8.2 (146)	2.7 (885)	<0.001
Stroke	5.5 (81)	2.3 (751)	<0.001
Cancer (any)	10.1 (199)	6.9 (2,701)	<0.001
Osteoarthritis	29.4 (619)	18.4 (6,884)	<0.001
Depression	13.3 (304)	6.3 (2,769)	<0.001
Number of chronic conditions, % (n)			<0.001
0	38.9 (938)	57.0 (23,796)	
1	26.2 (579)	23.4 (9,214)	
2	17.1 (317)	11.7 (4,224)	
$\geq 3$	17.8 (318)	8.0 (2,542)	

The results are weighted and refer to participants providing information for the variable of interest. Numbers of observations per variable (n) are unweighted. Weighted percentage of missing values may vary for each variable and strata of current asthma<sup>1</sup> vs. no current asthma<sup>2</sup> for BMI status (n<sup>1</sup>=2.0, n<sup>2</sup>=2.1), educational attainment (n<sup>1</sup>=0.4, n<sup>2</sup>=0.2), smoking status (n<sup>1</sup>=0.0, n<sup>2</sup>=0.0), diabetes mellitus (n<sup>1</sup>=0.3, n<sup>2</sup>=0.2), hypertension (n<sup>1</sup>=0.4, n<sup>2</sup>=0.4), coronary heart disease (n<sup>1</sup>=0.8, n<sup>2</sup>=0.6), chronic heart failure (n<sup>1</sup>=1.7, n<sup>2</sup>=0.8), stroke (n<sup>1</sup>=0.2, n<sup>2</sup>=0.1), cancer (any) (n<sup>1</sup>=0.2, n<sup>2</sup>=0.2), depression (n<sup>1</sup>=0.4, n<sup>2</sup>=0.3), osteoarthritis (n<sup>1</sup>=1.1, n<sup>2</sup>=1.0), number of chronic conditions (n<sup>1</sup>=4.7, n<sup>2</sup>=3.4).

\*p values obtained from Rao-Scott  $\chi^2$  test of independence with second-order adjustment. BMI=body mass index.

population of Germany, as previously described in detail.<sup>14,15</sup> Data were analysed using IBM SPSS Statistics for Windows (version 20, Released 2011, Armonk, NY: IBM Corp.) with the complex sample module to ensure correct variance estimation in the presence of weights. For each variable, weighted proportions and unweighted n

refer to the number of participants who gave the information. The Rao-Scott  $\chi^2$  test of independence with second-order adjustment was used to test globally for differences in the distribution of proportions.<sup>27</sup> Besides age and gender, BMI categories, educational attainment, and smoking status as well as years of asthma duration were considered for adjustment as co-variables in multivariable logistic regression models. Missing values were excluded from the analyses and complete case analyses were performed. Based on two-sided tests, a significance level set at  $p < 0.05$  was regarded statistically significant.

## Results

### Sample characteristics

The characteristics of the whole sample of the pooled GEDA 2009 and 2010 surveys are summarised in Table 1. From the available pooled sample of 43,312 persons interviewed between 2008 and 2010, 2,242 people reported current physician-diagnosed asthma (5.3%; 95% confidence interval (CI) 5.0% to 5.6%). The distribution of the main characteristics among those with and without asthma is shown in Table 2. Persons with current asthma were significantly more likely also to report other chronic conditions (Table 2). More than 60% of adults with current asthma reported at least one of the eight selected chronic conditions compared with less than half of those without current asthma.

### Relationship between asthma and co-morbidities

A statistically independent association between asthma and selected co-morbidities generally persisted after controlling for possible confounders in multivariable analyses (Table 3). Independent associations with asthma were strongest for cardiovascular end-organ diseases and depression and least pronounced for a lifetime history of any cancer. Age-stratified analyses demonstrated that the independent pairwise associations were of similar direction and strength in both older and younger age groups (<55 vs.  $\geq 55$  years of age), while the prevalence of co-morbidities strongly increased among older adults independent of current asthma (see Table S1 in Appendix available online at [www.thepcrj.org](http://www.thepcrj.org)).

### Relationship between the number of co-morbidities and asthma outcomes

A total of 1,136 (5.3%) study participants (737 women, 399 men) of

the total GEDA 2010 survey sample of 22,050 persons aged  $\geq 18$  years were included in the subset analysis. Among these, nearly every second person reported at least one asthma-related urgent care visit in the past 12 months (46.4%; 95% CI 42.6% to 50.3%). Overall, 9.0% (95% CI 7.1% to 11.5%) reported at least one asthma-related hospitalisation and/or ED admission,<sup>22</sup> and 45.3% (95% CI 41.5% to 49.2%) reported at least one unscheduled outpatient care visit for asthma.

The distribution of the main characteristics according to the number of co-morbidities (0, 1, 2,  $\geq 3$ ) is shown in Table 4. Statistically significant differences were found according to age, educational attainment, and BMI status using the second-order adjusted Rao-Scott  $\chi^2$  test of independence. Both outcome measures were associated with the number of co-morbidities and odds ratios (OR) rose with increasing number of chronic conditions irrespective of age, gender, BMI status, educational attainment, smoking status, and asthma duration (Table 5). In particular, a threefold higher chance of an asthma-related unscheduled inpatient care visit and a twofold higher chance of an unscheduled asthma-related outpatient care visit were estimated among individuals with  $\geq 3$  chronic conditions compared with those without co-morbid conditions.

## Discussion

### Main findings

In this large national health interview study, a range of chronic conditions with high healthcare relevance was over-represented among adults with physician-diagnosed asthma compared with those without asthma. In particular, asthma was significantly associated with cardiovascular conditions and depression, irrespective of age. Among persons with asthma, the odds of any unscheduled asthma care visits (inpatient and outpatient) during the 12 months preceding the survey increased with increasing numbers of co-morbidities. Compared with persons without co-morbidities, those with multiple chronic conditions ( $\geq 3$ ) had a more than threefold higher chance of any asthma-related hospital/ED admission and a more than twofold higher chance of an unscheduled outpatient visit for urgent treatment of worsening asthma symptoms or an asthma attack.

### Strengths and limitations of this study

We used data from a large national health survey covering a range

**Table 3. Association between current asthma and selected chronic conditions (yes vs. no) among German adults aged  $\geq 18$  years: German telephone health interview survey German Health Update (GEDA) 2009 and 2010**

Health condition	OR (95% CI)*	OR (95% CI)†	OR (95% CI)‡
Diabetes mellitus	1.80 (1.48 to 2.18)	1.58 (1.29 to 1.94)	1.31 (1.06 to 1.63)
Hypertension	1.76 (1.56 to 1.98)	1.63 (1.42 to 1.86)	1.47 (1.28 to 1.69)
Coronary heart disease	2.46 (2.06 to 2.94)	2.34 (1.93 to 2.83)	2.14 (1.76 to 2.60)
Chronic heart failure	3.22 (2.54 to 4.09)	2.84 (2.22 to 3.64)	2.74 (2.13 to 3.52)
Stroke	2.48 (1.82 to 3.39)	2.16 (1.57 to 2.97)	2.12 (1.54 to 2.91)
Cancer (any)	1.50 (1.22 to 1.84)	1.28 (1.04 to 1.58)	1.21 (0.98 to 1.50)
Osteoarthritis	1.85 (1.63 to 2.10)	1.63 (1.42 to 1.87)	1.55 (1.35 to 1.79)
Depression	2.27 (1.93 to 2.68)	2.18 (1.85 to 2.58)	2.06 (1.74 to 2.45)

Odds ratio (OR) and 95% confidence interval (CI) obtained from multivariable logistic regression analyses: \*Crude OR. †OR adjusted for age group and gender. ‡OR adjusted for age group, gender, body mass index categories, educational attainment, and smoking status.

**Table 4. Distribution of characteristics of the study population by number of chronic conditions among 1,136 adults with current asthma: German telephone health interview survey German Health Update (GEDA) 2010**

Characteristic	Number of chronic conditions				p value*
	0 (N=475)	1 (N=293)	2 (N=164)	≥3 (N=155)	
Gender					0.608
Women, % (n)	57.7 (295)	64.1 (191)	62.3 (109)	62.3 (105)	
Age (years)					
Mean (SD)	40.2 (15.3)	51.9 (16.4)	60.3 (13.3)	68.2 (11.8)	
Age groups, % (n)					<0.001
18–29 years	27.2 (128)	10.8 (34)	0.8 (3)	0.4 (1)	
30–44 years	37.4 (176)	19.7 (64)	12.1 (25)	1.8 (4)	
45–64 years	26.7 (134)	45.5 (146)	43.7 (83)	31.1 (56)	
≥65 years	8.8 (37)	23.9 (49)	43.4 (53)	66.8 (94)	
BMI status, % (n)					<0.001
<25 kg/m <sup>2</sup>	52.6 (256)	34.2 (113)	25.6 (45)	29.5 (51)	
25–<30 kg/m <sup>2</sup>	35.2 (148)	41.7 (109)	40.5 (66)	28.9 (48)	
≥30 kg/m <sup>2</sup>	12.2 (56)	24.1 (69)	33.9 (51)	41.6 (53)	
Educational attainment, % (n)					0.006
Primary	20.9 (48)	24.5 (27)	34.3 (21)	34.1 (22)	
Middle	54.6 (239)	59.7 (174)	55.7 (101)	52.1 (81)	
High	24.5 (187)	15.8 (92)	9.9 (42)	13.9 (52)	
Smoking status, % (n)					0.089
Current	32.7 (141)	30.2 (84)	24.8 (44)	24.3 (36)	
Former	23.9 (116)	36.4 (105)	33.8 (54)	35.0 (47)	
Never	43.4 (218)	33.4 (104)	41.5 (66)	40.7 (72)	
Asthma duration, years	(N=450)	(N=281)	(N=159)	(N=145)	
Mean (SD)	16.9 (13.4)	21.5 (18.1)	20.7 (18.8)	19.6 (18.4)	

Results are weighted and refer to participants providing information for the variable of interest. Numbers of observations per variable (n) are unweighted and may vary due to the number of missing values.

\*p values obtained from Rao-Scott  $\chi^2$  test of independence with second-order adjustment. BMI=body mass index.

**Table 5. Association of the number of co-morbidities (1, 2, ≥3 vs. 0) with asthma outcome measures among 1,136 adults with current asthma: German telephone health interview survey German Health Update (GEDA) 2010**

Number of chronic conditions	% (n/N)	OR (95% CI)*	OR (95% CI)†	OR (95% CI)‡
<b>Any asthma-related unscheduled inpatient care visit</b>				
0	9.5 (33/474)	Reference	Reference	Reference
1	6.8 (24/293)	0.70 (0.34 to 1.42)	0.96 (0.43 to 2.11)	1.09 (0.53 to 2.24)
2	8.5 (18/163)	0.88 (0.42 to 1.85)	1.49 (0.62 to 3.57)	1.50 (0.63 to 3.55)
≥3	14.0 (19/155)	1.54 (0.73 to 3.25)	2.90 (1.17 to 7.22)	3.40 (1.39 to 8.31)
<b>Any asthma-related unscheduled outpatient care visit</b>				
0	42.0 (177/471)	Reference	Reference	Reference
1	39.3 (127/290)	0.89 (0.61 to 1.30)	0.95 (0.64 to 1.41)	1.07 (0.72 to 1.59)
2	51.6 (82/160)	1.47 (0.91 to 2.37)	1.65 (0.98 to 2.79)	1.86 (1.09 to 3.16)
≥3	54.3 (76/149)	1.64 (1.00 to 2.69)	1.95 (1.10 to 3.45)	2.32 (1.30 to 4.14)

%, weighted prevalence of asthma outcomes refers to participants providing information for the variable of interest. Numbers of observations per variable (n) are unweighted and may vary due to the number of missing values.

Odds ratio (OR) and 95% confidence interval (95% CI) obtained from multivariable logistic regression analyses: \*Crude OR. †OR adjusted for age group and gender. ‡OR adjusted for age group, gender, body mass index categories, educational attainment, smoking status, and asthma duration.

of chronic health conditions. Our analyses were based on individual level data that do not only comprise information on the utilisation of asthma-related healthcare services, but also on individual characteristics such as anthropometric, socio-demographic and behavioural factors, and the age of asthma onset. By assessing the association of major chronic disease co-morbidity with unscheduled

asthma care outcomes, our findings extend previous research addressing the effects of co-morbidity on the utilisation of non-specific inpatient and outpatient healthcare services,<sup>5</sup> on asthma-specific HRQoL,<sup>8</sup> and on asthma symptoms and/or attacks.<sup>10</sup>

We assessed self-reported medical diagnoses cross-sectionally. Although this is considered an established method for assessing

morbidity in large epidemiological studies,<sup>20</sup> some methodological limitations need to be discussed. First, misclassification bias is an issue. A questionnaire-based definition of physician-diagnosed asthma in epidemiological studies is considered to have a high specificity and positive predictive value,<sup>28</sup> and adult patients were found to report physician-diagnosed asthma accurately.<sup>29</sup> Nevertheless, underdiagnosis of asthma cannot be excluded, particularly among elderly persons.<sup>30-32</sup> Moreover, it is conceivable that confounding of asthma and chronic obstructive pulmonary disease (COPD) might occur, especially with respect to older age.<sup>33,34</sup> However, current evidence indicates that diagnostic confusion of both conditions in primary care has decreased in recent years, which might be due to better guideline implementation in clinical practice.<sup>35</sup> On the other hand, COPD might develop and overlap, particularly among older individuals with asthma.<sup>36,37</sup> COPD was not assessed in the present study and, hence, we could not disentangle the relationship between the two conditions. Still, the relationships between asthma and the co-morbidities were consistent in older and younger adults and the associations with asthma outcomes were also independent of years of asthma duration.

Second, it is conceivable that non-respiratory co-morbidities causing respiratory symptoms such as chronic heart failure might be missed among individuals with asthma.<sup>32</sup> Detection bias might therefore have resulted in an underestimation of the actual effect size in our results. On the other hand, detection bias might have led to an overestimation of the effect of the association with asthma and health conditions comprising relevant proportions of asymptomatic cases such as diabetes. However, a positive association between asthma and diabetes has also been reported from longitudinal assessments.<sup>38,39</sup>

Finally, we could not perform non-response analyses based on information collected for non-responders and responders. However, all results were weighted to adjust for sampling probabilities and selective participation in order to assure representativeness at the population level and increase the generalisability of the present findings to the adult population of Germany.<sup>14,15</sup>

## Interpretation of findings in relation to previously published research

### a) Association of co-morbidities with asthma

The patterns and strengths of the relationships between asthma and co-morbidities observed in our study are essentially in line with reports from two large population-based surveys and a large health administrative data analysis.<sup>4,9,10</sup> Specifically, our observation that more than 60% of adults with asthma reported at least one concurrent disorder and 18% reported at least three concurrent disorders of high public health impact agrees very well with previous estimates obtained from an analysis of a large population-based administrative health database.<sup>4</sup> Our findings on cross-sectional relationships between asthma and co-morbidities are supported by results from previous longitudinal studies.<sup>38-41</sup>

In the present study, asthma was particularly related to cardiovascular diseases and depression, with ORs increased more than twofold. Moderate associations were found for other conditions, and were least pronounced for a lifetime history of any

cancer. Adams *et al.* also reported approximately twofold higher ORs of self-reported stroke or heart disease in association with asthma. In this previous study, asthma was moderately and significantly associated with arthritis and cancer<sup>9</sup> while a positive relation between asthma and diabetes was not statistically significant. Zhang *et al.* previously showed considerable associations of asthma with mental health conditions with more than twofold higher ORs, and demonstrated moderately increased ORs for self-reported stroke, heart disease, high blood pressure, diabetes, and arthritis/ rheumatism.<sup>10</sup> In agreement with our results, no significant association between asthma and cancer was observed in this previous study. Findings on the relationships between asthma and co-morbidities based on administrative health service data are also consistent with our results.<sup>4</sup> Moreover, longitudinal associations of asthma with depression, cardiovascular diseases, and diabetes have also been observed in studies of the relationship between asthma and a single co-morbidity.<sup>38-41</sup> These associations may be due to the fact that asthma and other chronic conditions share common risk factors such as obesity or smoking. As has been discussed for COPD, there may be an early interaction between disease processes on the basis of chronic inflammation.<sup>42-44</sup> Our observation that the strength of the association between asthma and chronic co-morbidities was of similar direction and strength in both older and younger individuals, while the prevalence of co-morbidities strongly increased among older adults independent of current asthma is supported by results from a previous large study of asthma co-morbidity including age-stratified analyses. Similar to the results of the present study, this previous study showed an age-related increase in the prevalence of cardiovascular and hypertensive disease, depression and diabetes, while the strength of the associations between asthma and these conditions remained stable across age groups.<sup>3,6</sup>

### b) Association of co-morbidities with asthma outcomes

In the present study the chance of asthma-related hospital/ED admissions and of unscheduled outpatient visits for urgent treatment of worsening asthma symptoms or an asthma attack increased with the number of co-morbidities. In particular, persons with asthma and  $\geq 3$  co-morbid conditions had a significantly two- to threefold higher chance of adverse outcomes compared to persons with asthma who had no concurrent chronic health condition, independent of age, gender, BMI status, educational attainment, smoking status, and asthma duration. This is in line with previous analyses based on an administrative health database which showed that among adults with asthma compared to those without co-morbidity was associated with a significant proportion of overall non-specific hospitalisations, emergency room visits, and ambulatory care visits.<sup>5</sup> Similarly, in two other population-based surveys, a negative effect of the presence of major chronic conditions on asthma-specific HRQOL<sup>8</sup> as well as on asthma symptoms and/or attacks<sup>10</sup> was observed.

There are several possible explanations for the association between asthma co-morbidity and adverse asthma outcomes observed here and previously. First, the association could be due to interactive disease processes. Systemic inflammation has not only

been related to several chronic diseases such as cardiovascular end-organ disease and diabetes, but might also be common among adults with asthma.<sup>42,45</sup> Interactive inflammatory processes have recently been suggested to contribute to a higher risk of asthma exacerbations in individuals with higher levels of non-asthma-related visits to the general practitioner.<sup>46</sup> However, the relationship between systemic inflammation and co-morbidity in asthma remains to be elucidated.<sup>42</sup>

Second, the presence of multiple chronic conditions could also influence patient self-management.<sup>47</sup> In particular, several perceived barriers to self-care have been identified by authors of a qualitative study among adults aged  $\geq 31$  years who had two or more of the following chronic conditions: osteoarthritis, coronary artery disease, COPD, asthma, diabetes, hypertension, or congestive heart failure.<sup>47</sup> In this previous study, participants were facing competing demands between self-management tasks for one condition and self-care of another (e.g. difficulties in adhering to exercise for the management of diabetes in the presence of respiratory conditions). Moreover, in this previous study, drug treatment for one condition was found to increase the morbidity of another due to therapeutic or adverse effects.<sup>47</sup> Thus, thirdly, an additive effect of co-morbidity on asthma outcomes might also reflect drug effects including drug-drug interactions. Several drugs that are commonly used for the treatment of hypertension, cardiovascular conditions or osteoarthritis (e.g. non-steroidal anti-inflammatory drugs or beta-adrenergic blockers) can influence asthma control.<sup>48,49</sup> As the number of drugs increases and the medication regimen becomes more complex, barriers to adherence and the risk of drug interactions and adverse drug effects can also increase.<sup>50,51</sup>

### Implications for future research, policy and practice

Based on data from a large national health survey, we observed that chronic conditions that are highly prevalent in the general population and that have a substantial impact on the healthcare system commonly co-exist with asthma, irrespective of age. To date, this has been largely disregarded among adults with asthma and raises the question whether there is an early interaction between disease processes. Longitudinal epidemiological and experimental research needs to further clarify the mechanisms of more than chance co-occurrence in order to identify potential preventive strategies. One possibility that might be particularly relevant to clinical practice is the role of common risk factors in asthma co-morbidity. In order to reduce the burden of co-morbidity in later life, early interventions targeting common risk factors might be particularly relevant for young persons with asthma. In addition, the findings of our population-based study also highlight the need for considering co-morbidities in secondary and tertiary preventive care of patients with asthma.

The results of our population-based study provide evidence that multiple co-morbid conditions are common among adults with asthma. It can therefore be assumed that a significant number of individuals in the general asthma population face complex healthcare needs. So far, this reality has received little attention in clinical guidelines. As demonstrated in the present analysis, multiple co-morbid conditions relate to an adverse asthma outcome. Thus, future research needs to investigate the mechanisms by which specific

patterns of co-morbidity influence the clinical course and the outcome of asthma patients. Our findings further underline the need for interventions tailored to specific disease combinations in clinical practice. With a lack of sufficient evidence it has proved difficult to adapt evidence-based clinical guideline recommendations accordingly.<sup>52</sup> Apart from additive effects resulting from the interaction between disease processes or drug interactions, the effects of multiple co-morbidities on patient self-management as well as other aspects of patient complexity such as depression and social factors need to be considered.<sup>53,54</sup>

### Conclusions

National health survey data indicate that asthma co-morbidity has a high public health impact and needs to be adequately considered in clinical guidelines for the management of older as well as younger adults with asthma. Further research is needed to gain insight into the mechanisms underlying the observed independent association between asthma and various other chronic diseases – in particular cardiovascular conditions and depression – and to identify the specific healthcare needs of patients with asthma in the presence of specific co-morbidities.

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**Appendix: Table S1 Association between current asthma and selected chronic conditions among German adults by age category (<55 vs. ≥55 years): German telephone health interview surveys (GEDA) 2009 and 2010**

Health condition	<55 years of age			≥55 years of age		
	Asthma bronchiale		OR	Asthma bronchiale		OR
	Yes	No	(95% CI)	Yes	No	(95% CI)
Diabetes mellitus	5.1	2.3	1.70 (1.16 to 2.50)	19.7	14.9	1.18 (0.92 to 1.53)
Hypertension	19.3	11.5	1.55 (1.26 to 1.91)	58.4	49.0	1.38 (1.15 to 1.66)
Coronary heart disease	4.5	1.9	2.13 (1.44 to 3.14)	30.4	16.9	2.09 (1.68 to 2.60)
Chronic heart failure	2.3	0.7	2.77 (1.54 to 4.98)	14.9	6.0	2.67 (2.01 to 3.54)
Stroke	1.8	0.6	2.23 (1.11 to 4.47)	9.6	5.1	2.02 (1.41 to 2.91)
Cancer (any)	4.8	2.9	1.58 (1.13 to 2.20)	15.8	13.6	1.08 (0.83 to 1.41)
Osteoarthritis	13.8	8.1	1.60 (1.29 to 1.99)	46.7	35.2	1.52 (1.26 to 1.82)
Depression	13.9	6.1	2.21 (1.78 to 2.75)	12.6	6.6	1.94 (1.48 to 2.56)

%, weighted proportions refer to participants providing information for the variable of interest.

Odds ratios (OR) and 95% confidence intervals (95% CI) obtained from multivariable logistic regression analyses adjusted for age (metric scale), gender, body mass index categories, educational attainment, and smoking status.