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Factors associated with well-controlled asthma—A cross-sectional study

To the Editor,

The present Global Initiative of Asthma (GINA) guidelines define asthma control as a combination of symptom control and risk-minimizing future adverse outcomes such as exacerbations.[1] Asthma symptom control can be assessed using the Asthma Control Test (ACT). ACT includes five items on a 6-point score from 0 to 6 referring to the previous four weeks, the lower total score the worse.[2] Few studies have investigated factors associated with asthma control using the present GINA definition. We performed a study with the aims of investigating levels of asthma control as measured by ACT and exacerbation frequency and to identify factors associated with well-controlled asthma.

The study population included 1199 primary and secondary care patients from 14 hospitals and 54 primary healthcare centres (PHCCs) in central Sweden.[3] All centres established lists of patients with a doctor's diagnosis of asthma (ICD-10 code J45), from which 2794 patients were randomly selected. Data were obtained by mail from patient questionnaires. The questionnaires included the Swedish version of ACT and data on sex, age, educational level, tobacco smoking habits, self-rated severity of asthma, height and body weight, comorbid conditions, visits to an asthma/COPD-nurse, written action plans, access to a specific responsible physician, knowledge on self-management of exacerbations, exercise habits, pharmacological treatment and compliance, emergency visits and oral steroid courses due to deterioration in their asthma. The response rate was 46%, and 1199 patients had data on both exacerbation frequency and all ACT items.

Well-controlled asthma symptoms were defined as ACT score ≥ 20. An exacerbation was defined as an episode of worsened asthma symptoms during the previous 6 months, resulting in an unscheduled healthcare visit in primary or secondary care and/or a course of oral corticosteroids. Well-controlled asthma was defined as both well-controlled asthma symptoms (ACT score ≥ 20) and absence of exacerbations previous 6 months.

Logistic regression analyses were performed, using well-controlled asthma, ACT score ≥ 20, and no exacerbations previous 6 months and as dependent variables. Univariable analyses used patient characteristics and measures as independent variables. Multivariable logistic regression analyses included sex, age groups and all statistically significant independent variables from any of the univariable logistic regression analyses.

The proportion of patients with well-controlled asthma was 49%. (Figure 1A). Well-controlled asthma was, most importantly, inversely associated with moderate/severe self-rated disease, underweight, obesity, rhinitis and heart disease (Table 1).

Well-controlled asthma symptoms as measured by ACT were associated with high education (OR [95% CI] 1.56 [1.11-2.19]), moderate/severe disease (0.14 [0.10-0.19]), overweight (0.64 [0.44-0.92]), obesity (0.43 [0.29-0.65]), rhinitis (0.55 [0.36-0.85]), heart disease (0.52 [0.27-0.99]) and self-rated self-management knowledge (1.80 [1.19-2.72]). Absence of exacerbations previous 6 months was associated with self-assessed moderate/severe disease (OR [95% CI] 0.23 [0.16-0.32]). Multivariable regression with the main model stratified by sex showed associations between high education and well-controlled asthma, ACT ≥ 20 and absence of exacerbations in men but not in women, *P* for interactions .009, .041 and .021, respectively. All the results from logistic regression analyses were substantially unchanged after further adjustment for maintenance pharmacological treatment (data not shown).

Self- rated asthma disease severity was the only patient-related variable that was associated with both high ACT score and absence of exacerbations, and with well-controlled asthma in both sexes. Figure 1B shows the proportions of patients with self-rated mild and moderate/severe asthma distributed over asthma symptom control and exacarbation frequency. Even though self-rated mild disease was strongly associated with well-controlled asthma, a considerable proportion of patients with poor asthma control estimated their disease as mild, and conversely, some patients with well-controlled asthma considered their disease as moderate/severe (Figure 1B). We believe that the greatest challenge is to detect the patients with self-rated mild disease but with poor symptom control, as exacerbations often lead to contact with the health care. This indicates the importance of using ACT as a structured way of assessing asthma symptom control.

To the best of our knowledge, the associations of underweight and mild self-assessed asthma severity with well-controlled asthma, and of self-reported self-management knowledge and rhinitis with high ACT score, are novel findings. Our study also confirms the previous reported associations of higher BMI[3,4] and heart disease with uncontrolled asthma symptoms.[5] Interestingly, our finding of underweight is consistent with the well-known association of underweight with low-health related quality of life in COPD.[6,7] Our association of rhinitis with poor asthma control included both allergic and nonallergic rhinitis. Some 61% reported to have allergic rhino-conjunctivitis but there was no association of allergic rhino-conjunctivitis alone with asthma control. Previous research suggests that allergic rhinitis impairs the asthma control level and increases the risk for adverse outcomes [8,9] and that any type of rhinitis influences Asthma Control Questionnaire scores and exacerbation risk.[10,11] Thus, our study

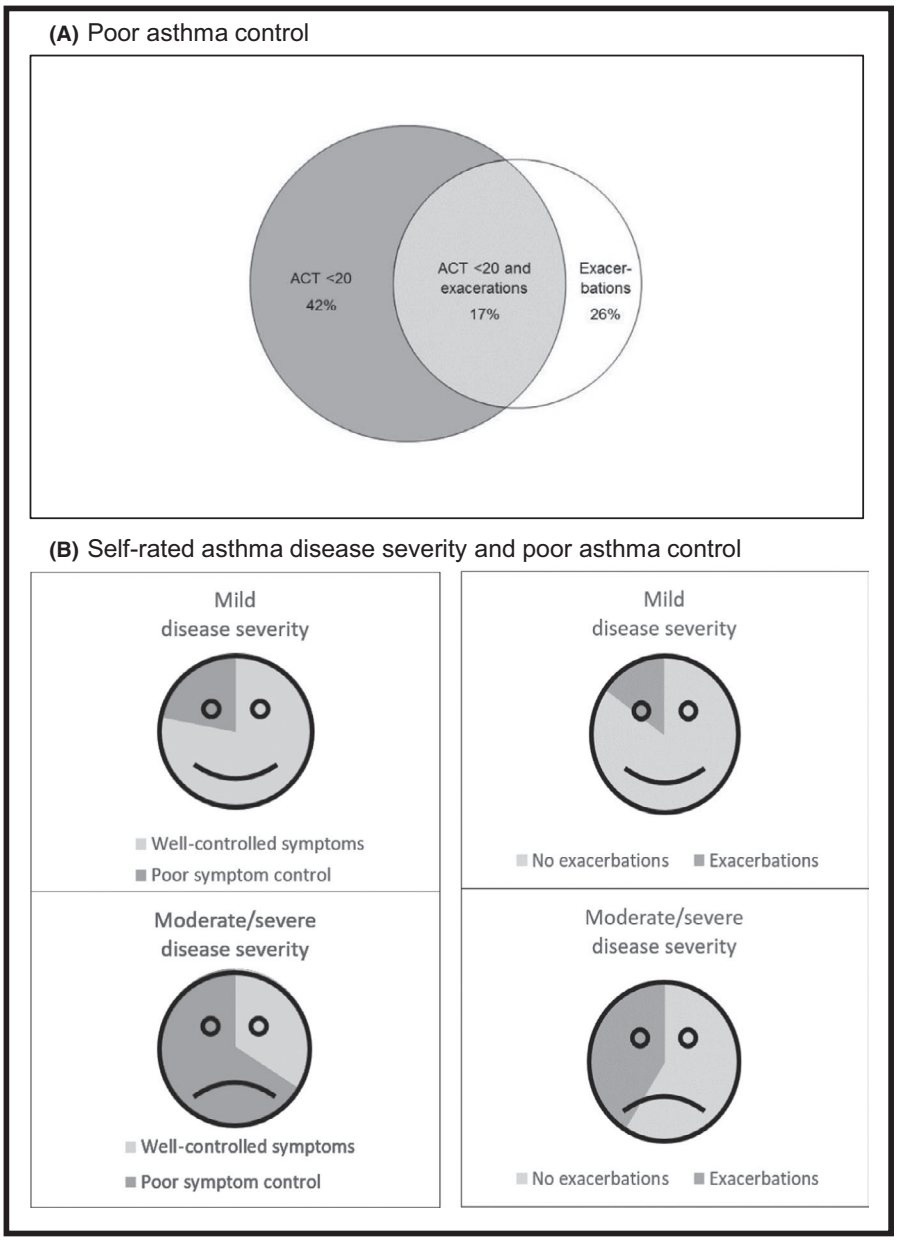

FIGURE 1 A, Venn diagram showing proportions of study population with different kinds of poor asthma control. Exacerbations were defined as at least one unscheduled healthcare visit or an oral steroid course due to asthma symptoms previous 6 mo. ACT, Asthma Control Test. B, Proportions of patients with self-rated mild and moderate/severe asthma distributed over asthma symptom control according to ACT, and respectively over absence or presence of exacerbations previous six months. Well-controlled asthma symptoms was defined as ACT score ≥ 20, and poor asthma symptom control as ACT < 20. Exacerbations were defined as at least one unscheduled healthcare visit or an oral steroid course due to asthma symptoms previous six months. Abbreviations: ACT, Asthma Control Test

adds the association of rhinitis with poor asthma symptom control as measured by ACT.

Main strengths of the present study is that it is a real world study, describing an unselected population of patients with asthma from both primary care and hospital care settings, and that we chose to use two different measures of asthma control according to GINA. Major potential limitations are in the cross-sectional study design which cannot investigate causal associations and that all data are self-reported. Asthma was defined as a doctor's diagnosis, without the confirmation by objective measurements in lung function, and reported exacerbations were not confirmed by medical records. Thus, we cannot exclude reporting bias.

We conclude that only half of the patients have well-controlled asthma and that well-controlled asthma is inversely associated with self-assessed moderate/severe asthma disease severity, obesity, underweight, rhinitis and heart disease. In addition, self-reported self-management knowledge is associated with well-controlled asthma symptoms as measured by ACT. Important clinical implications are that assessment of asthma control always should include both symptoms and exacerbations as in the present GINA recommendations and that comorbid conditions, weight and low self-management skills are important addressable risk factors for poor asthma control.

CONFLICT OF INTEREST

The authors have no conflicts of interest related to this study to declare.

TABLE 1 Factors associated with well-controlled asthma

Patient characteristics	ACT ≥ 20 and no exacerbations Univariate regression OR (95% CI)	*P*-value	ACT ≥ 20 and no exacerbations Multivariate regression OR (95% CI)	*P*-value
Female sex	0.80 (0.63-1.00)	.054	0.86 (0.62-1.18)	.337
Age				
<40	Ref		Ref	
40-59	0.85 (0.62-1.18)	.334	0.77 (0.49-1.20)	.251
≥60	0.56 (0.41-0.76)	<.0001	0.70 (0.44-1.12)	.138
High education	1.77 (1.40-2.23)	<.0001	1.69 (1.21-2.36)	.002
Current daily smoking	0.46 (0.27-0.77)	.003	0.62 (0.31-1.24)	.180
Moderate/severe disease	0.15 (0.11-0.19)	<.0001	0.15 (0.11-0.21)	<.0001
BMI				
Underweight	0.58 (0.31-1.11)	.098	0.35 (0.15-0.83)	.018
Normal weight	Ref			
Overweight	0.78 (0.59-1.03)	.078	0.93 (0.65-1.34)	.696
Obesity	0.56 (0.41-0.75)	<.0001	0.60 (0.40-0.90)	.013
Rhinitis	0.47 (0.36-0.62)	<.0001	0.62 (0.41-0.94)	.023
Allergic rhino-conjunctivitis	0.50 (0.45-0.72)	<.0001	0.78 (0.54-1.15)	.207
Anxiety/depression	0.56 (0.41-0.76)	.001	0.74 (0.47-1.16)	.185
Heart disease	0.41 (0.25-0.65)	<.0001	0.48 (0.24-0.93)	.030
Asthma/COPD-nurse visit	0.38 (0.28-0.50)	<.0001	0.51 (0.35-0.74)	<.0001
Specific responsible physician	0.70 (0.55-0.89)	.003	1.14 (0.81-1.59)	.453
Written action plan	0.61 (0.45-0.83)	.002	0.76 (0.51-1.11)	.168
Self-management knowledge	0.95 (0.72-1.26)	.716	1.46 (0.96-2.21)	.074

Note: Logistic regression analysis of well-controlled asthma, defined as ACT ≥ 20 and no exacerbations previous 6 mo. The multivariate regression model included all variables in the table.
Abbreviations: ACT, Asthma Control Test; BMI, Body Mass Index (kg/m^2); CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; OR, Odds Ratio.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the manuscript.

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REFERENCES

1. Asthma GIf.2017 GINA Report, Global Strategy for Asthma Management and Prevention.
2. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113(1):59-65.
3. Kämpe M, Lisspers K, Ställberg B, Sundh J, Montgomery S, Janson C. Determinants of uncontrolled asthma in a Swedish asthma population: cross-sectional observational study. *Eur Clin Respir J* 2014;1(1):24109.
4. Stanford RH, Gilsenan AW, Ziemiecki R, Zhou X, Lincourt WR, Ortega H. Predictors of uncontrolled asthma in adult and pediatric patients: analysis of the asthma control characteristics and prevalence survey studies (ACCESS). *J Asthma* 2010;47(3):257-262.
5. Panek M, Mokros Ł, Pietras T, Kuna P. The epidemiology of asthma and its comorbidities in Poland-health problems of patients with severe asthma as evidenced in the province of Lodz. *Respir Med* 2016;112:31-38.
6. Katsura H, Yamada K, Kida K. Both generic and disease specific health-related quality of life are deteriorated in patients with underweight COPD. *Respir Med* 2005;99(5):624-630.
7. Sundh J, Ställberg B, Lisspers K, Montgomery SM, Janson C. Comorbidity, body mass index and quality of life in COPD using the clinical COPD questionnaire. *COPD* 2011;8(3):173-181.
8. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the world health organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(Suppl 86):8-160.
9. Gaugris S, Sazonov-Kocevar V, Thomas M. Burden of concomitant allergic rhinitis in adults with asthma. *J Asthma* 2006;43(1):1-7.
10. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Respir J* 2009;18(4):300-305.
11. Lisspers K, Janson C, Larsson K, et al. Comorbidity, disease burden and mortality across age groups in a Swedish primary care asthma population: An epidemiological register study (PACEHR). *Respir Med* 2018;136:15-20.

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CD203c distinguishes the erythroid and mast cell-basophil differentiation trajectories among human FcεRI$^+$ bone marrow progenitors

To the Editor,

IgE molecules that bind their specific antigen crosslink FcεRI receptors present on mast cells and basophils. Downstream signaling results in cell activation and subsequent release of diverse compounds that exhibit potential to trigger allergic symptoms. Although mature FcεRI$^+$ cells have been extensively studied, less is known about the FcεRI$^+$ progenitors and their differentiation capacity.[1] Here, we analyzed the FcεRI$^+$ progenitor population from human bone marrow with multicolor flow cytometry and fate assays. The results revealed distinct subpopulations of FcεRI$^+$ progenitors, all showing capacity to form mast cells and basophil-like cells but not granulocytes or monocytes. The CD203c$^-$ subsets displayed erythroid potential, whereas the CD203c$^+$ subset did not, altogether providing early evidence for a common mast cell-basophil-erythroid differentiation trajectory in human, distinct from the granulocyte-monocyte axis.

The CD34$^+$ CD117$^+$ FcεRI$^+$ phenotype identifies the human mast cell progenitor population in blood.[2] Other characteristics include expression of the IL-3 receptor and the absence of CD45RA, positioning the cells among common myeloid progenitors (CMPs) when analyzing the progenitors with flow cytometry.[2,3] In contrast to blood, we recently demonstrated that CMPs$^{FcεRI+}$ in bone marrow do not exclusively form CD117^{hi} mast cells.[4] This observation warranted further characterization of the bone marrow CMPs$^{FcεRI+}$ phenotype and cell-forming potential.

Morphologic assessment following cell sorting and May-Grünwald Giemsa stain revealed that the CMP$^{FcεRI+}$ population was heterogenous (Figure 1A,C; see Methods S1 for materials and methods). Some cells exhibited a blast-like phenotype with little cytoplasm, whereas other displayed numerous metachromatic granules (Figure 1C). The cell heterogeneity prompted us to design a multicolor flow cytometry panel that further characterizes the progenitors. Analyzing the CD203c and integrin β7 expression patterns revealed subpopulations of CMP$^{FcεRI+}$ cells (Figure S1). Three CMP$^{FcεRI+}$ subpopulations—CD203c$^+$, integrin β7$^+$ CD203c$^-$, and integrin β7$^-$ CD203c$^-$ cells—exhibited distinct protein expression profiles and were studied further (Figure 1B,D). These three populations, along with CMPs$^{FcεRI-}$ and granulocyte/monocyte progenitors (GMPs), were sorted and cultured to investigate their cell-forming potential (Figure 2A). The five bone marrow progenitor populations were first cultured with IL-3 and IL-6. These conditions support mast cell progenitors from peripheral blood to form CD117^{hi} FcεRI$^+$ mast cells.[3] We analyzed the cultured bone marrow cells with a flow cytometry panel that distinguished three subsets of FcεRI$^+$ cells separated based on the CD117 expression, CD235a$^+$ erythroid cells, and