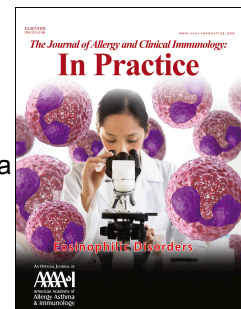


# Journal Pre-proof

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Wen Wen Wu, MD, Xin Zhang, PhD, MD, Min Li, MD, Ying Liu, MD, PhD, Zhi Hong Chen, MD, Min Xie, MD, Shu Zhen Zhao, RN, Gang Wang, MD, Hong Ping Zhang, PhD, MD, Ting Wang, MD, Ling Qin, MD, Lei Wang, MD, Brian G. Oliver, PhD, Hua Jing Wan, PhD, Jie Zhang, MD, Vanessa M. Donald, PhD, Guy B. Marks, MD, PhD, Wei Min Li, MD, PhD, Surinder S. Birring, MD, Gang Wang, PhD, MD, Peter G. Gibson, MBBS



PII: S2213-2198(21)00387-1

DOI: <https://doi.org/10.1016/j.jaip.2021.03.042>

Reference: JAIP 3531

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 13 November 2020

Revised Date: 26 February 2021

Accepted Date: 22 March 2021

Please cite this article as: Wu WW, Zhang X, Li M, Liu Y, Chen ZH, Xie M, Zhao SZ, Wang G, Zhang HP, Wang T, Qin L, Wang L, Oliver BG, Wan HJ, Zhang J, Donald VM, Marks GB, Li WM, Birring SS, Wang G, Gibson PG, Treatable traits in elderly asthmatics from the Australasian Severe Asthma Network: a prospective cohort study, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.03.042>.

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# TITLE PAGE

## Treatable traits in elderly asthmatics from the Australasian Severe Asthma Network: a prospective cohort study

Wen Wen Wu, MD<sup>1, 2, 3\*</sup>, Xin Zhang, PhD, MD<sup>1, 2, 3\*</sup>, Min Li, MD<sup>2, 3</sup>, Ying Liu, MD, PhD<sup>1, 2, 3</sup>, Zhi Hong Chen, MD<sup>4</sup>, Min Xie, MD<sup>5</sup>, Shu Zhen Zhao, RN<sup>6</sup>, Gang Wang, MD<sup>1, 2, 3, 7, 8, 9</sup> Hong Ping Zhang, PhD, MD<sup>1, 3</sup>, Ting Wang, MD<sup>2</sup>, Ling Qin, MD<sup>10</sup>, Lei Wang, MD<sup>1, 3</sup>, Brian G. Oliver, PhD<sup>11, 12</sup>, Hua Jing Wan, PhD<sup>2, 3</sup>, Jie Zhang, MD<sup>13</sup>, Vanessa M. Donald, PhD<sup>14</sup>, Guy B. Marks, MD, PhD<sup>12</sup>, Wei Min Li, MD, PhD<sup>2, 15</sup>, Surinder S. Birring, MD<sup>16</sup>, Gang Wang, PhD, MD<sup>2, 3</sup>, Peter G. Gibson, MBBS<sup>14</sup>

\* These authors contributed equally to this work.

<sup>1</sup>Pneumology Group, Department of Integrated Traditional Chinese and Western Medicine, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China.

<sup>2</sup>Department of Respiratory and Critical Care Medicine, Clinical Research Center for Respiratory Disease, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China.

<sup>3</sup>Laboratory of Pulmonary Immunology and Inflammation, Frontiers Science Center for Disease-related Molecular Network, Sichuan University, Chengdu, Sichuan 610041, China.

<sup>4</sup>Shanghai Institute of Respiratory Disease, Respiratory Division of Zhongshan Hospital, Fudan University, Shanghai 200032, PR. China.

<sup>5</sup>Department of Respiratory and Critical Care Medicine, Tongji Hospital, Huazhong University of Science & Technology, Wuhan 430030, PR. China.

<sup>6</sup>Outpatient Department, West China Hospital, Sichuan University, Chengdu, Sichuan 610041,

China.

<sup>7</sup>West China School of Medicine, Sichuan University, Chengdu, PR China.

<sup>8</sup>Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

<sup>9</sup>Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden.

<sup>10</sup>Department of Respiratory and Critical Care Medicine, Xiangya Hospital, Central South University, Changsha China.

<sup>11</sup>School of Life Sciences, University of Technology Sydney, Ultimo, NSW, 2007, Australia.

<sup>12</sup>Woolcock Institute of Medical Research, The University of Sydney, NSW 2017, Australia.

<sup>13</sup>Department of Respiratory and Critical Care Medicine, The Second Hospital of Jilin University, Changchun 130041, China.

<sup>14</sup>Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, The University of Newcastle, Newcastle, NSW, Australia.

<sup>15</sup>Respiratory Microbiome Laboratory, Frontiers Science Center for Disease-related Molecular Network, Sichuan University, Chengdu, Sichuan 610041, China.

<sup>16</sup>Centre for Human & Applied Physiological Sciences, School of Basic & Medical Biosciences, Faculty of Life Sciences & Medicine, King's College London, London, United Kingdom.

**Corresponding author:** Dr. Gang Wang, PhD. & MD., Department of Respiratory and Critical Care Medicine, Clinical Research Center for Respiratory Disease, West China Hospital, Sichuan University, Chengdu 610041, P. R. China. Tel: +86 28 85422376. Fax: +86 28 85423373. ORCID: 0000-0002-5048-6606; E-mail: [wcums-respiration@hotmail.com](mailto:wcums-respiration@hotmail.com)

**Authors Contribution:** GW, PGG, WWW, VM, XZ: designed the framework for the study. WWW, XZ, ML, YL, GW, HPZ, SZZ: contributed to acquisition of data. WWW, XZ, ML:

contributed to data analysis. WWW, XZ, GW, PGG, ZHC, MX, BGO, JZ, GBM, VM, WML, SSB, TW, LQ, LW, HJW: contributed to interpretation of results. WWW, XZ, GW: contributed to draft the manuscript. GW, PGG, VM, ZHC, MX, HJW, JZ, BGO, GBM, SSB: contributed to revise the manuscript critically for important intellectual content.

**Funding:** This study was supported by the National Key Development Plan for Precision Medicine Research (2017YFC091004), National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (No. Z2018A09), the National Natural Science Foundation of China (81900026, 81920108002, 81870027, 31701011 and 81670023), Science and Technology Foundation of Sichuan Province (No. 2018SZ0167), 1.3.5 project for disciplines of excellence-Clinical Research Incubation Project, West China Hospital, Sichuan University (2018HXFH016), China Postdoctoral Science Foundation (2019M653437) and Post-Doctor Research Project, West China Hospital, Sichuan University (2019HXBH066).

**Conflict of interest:** The authors declare no conflicts of interest.

**Abstract word count:** 250

**Text word count:** 4142

**ABSTRACT**

**Background:** Data on treatable traits (TTs) in different populations are limited.

**Objective:** To assess TTs in elderly patients with asthma and compare them to younger patients, to evaluate the association of TTs with future exacerbations, and develop an exacerbation prediction model.

**Methods:** We consecutively recruited 521 participants at West China Hospital, Sichuan University based on the Australasian Severe Asthma Network, classified as elderly (n = 62) and non-elderly (n = 459). Participants underwent a multidimensional assessment to characterize the TTs and were then followed up for 12 months. TTs and their relationship with future exacerbations were described. Based on the TTs and asthma control levels, an exacerbation prediction model was developed, and the overall performance was externally validated in an independent cohort.

**Results:** A total of 38 TTs were assessed. Elderly asthmatics had more chronic metabolic diseases, fixed airflow limitation, emphysema and neutrophilic inflammation, while non-elderly asthmatics exhibited more allergic characteristics and psychiatric diseases. Nine traits were associated with increased future exacerbations, of which exacerbation prone, upper respiratory infection-induced asthma attack (URI), cardiovascular disease, diabetes and depression were the strongest. A model including exacerbation prone, psychiatric disease, cardiovascular disease, URI, non-eosinophilic inflammation, cachexia, food allergy and asthma control was developed to predict exacerbation risk and showed good performance.

**Conclusions:** TTs can be systematically assessed in elderly patients with asthma, some of which are associated with future exacerbations, proving their clinical utility of evaluating them. A model based on TTs can be used to predict exacerbation risk in people with asthma.

**Highlights box:****What is already known about this topic?**

The treatable traits (TTs) approach has been increasingly recommended and applied effectively in patients with severe asthma. However, data on the prevalence of TTs in different subgroups of asthmatics are limited, especially for elderly individuals.

**What does this article add to our knowledge?**

TTs can be systematically assessed in elderly patients with asthma. Some TTs were found to be strongly associated with future exacerbations, demonstrating their crucial clinical utility. A prediction model based on TTs can be used to predict exacerbation risk in people with asthma.

**How does this study impact current management guidelines?**

Assessing TTs in elderly patients with asthma is of great necessity, and future exacerbation can be predicted by identifying risk factors of TTs, thus allowing targeted intervention for its prevention.

**Key Words:** asthma; elderly; treatable traits; exacerbation; prediction model; the Australasian Severe Asthma Network

**Abbreviations list**

ACT: asthma control test

AQLQ: asthma quality of life questionnaire

ASAN: Australasian Severe Asthma Network

ATS: American Thoracic Society

AUC: area under the curve

BMI: body mass index

- 122 CI: confidence interval
- 123 CT: computed tomography
- 124 FeNO: fractional exhaled nitric oxide
- 125 FBC: full blood count
- 126 FEV<sub>1</sub>: forced expiratory volume in 1 s
- 127 FFM: fat-free mass
- 128 FFMI: fat-free mass index
- 129 FPG: fasting plasma glucose
- 130 ERS: European Respiratory Society
- 131 FVC: forced vital capacity
- 132 HADS: hospital anxiety and depression scale
- 133 Hb: hemoglobin
- 134 HDL-C: high-density lipoprotein cholesterol
- 135 ICS: inhaled corticosteroid
- 136 IFG: impaired fasting glucose
- 137 IgE: immunoglobulin E
- 138 IRR: incidence rate ratio
- 139 GERD, gastroesophageal reflux disease
- 140 GINA: Global Initiative for Asthma
- 141 LABA: long-acting  $\beta$ 2 agonist
- 142 LAMA: long-acting muscarinic antagonist
- 143 LASSO: least absolute shrinkage and selection operator
- 144 LDL-C: low-density lipoprotein cholesterol
- 145 LLN: lower limit of normal
- 146 LTRA: leukotriene receptor

- 147 MMEF: maximum mid-expiratory flow
- 148 OCS: oral corticosteroid
- 149 OGTT: oral glucose tolerance test
- 150 PSG: polysomnography
- 151 Q1: first quartile
- 152 Q3: third quartile
- 153 ROC curve: receiver operating characteristic curve
- 154 RPG: random plasma glucose
- 155 SABA: short-acting  $\beta_2$  agonist
- 156 SD: standard deviation
- 157 SE: standard error
- 158 SPT: skin prick test
- 159 TC: total cholesterol
- 160 TG: triglyceride
- 161 TTs: treatable traits
- 162 URI: upper respiratory infection-induced asthma attack

## INTRODUCTION

Asthma in the elderly is extraordinarily complex and is an increasingly serious health issue, with a prevalence ranging from 4% to 13%<sup>1</sup>. For the worldwide trend of increased average life expectancy, the number of people aged over 64 years is expected to reach approximately 1.5 billion by 2050<sup>2</sup>. Thus, the number of elderly patients with asthma will also increase<sup>3</sup>. Unfortunately, the rates of hospitalization and mortality of elderly patients with asthma are higher than those of younger asthmatics<sup>4</sup>, which may be explained by underdiagnosis and undertreatment in elderly people<sup>5</sup>. The management of asthma in the elderly is complicated by comorbidities and polypharmacotherapy. Given these complexities, comprehensive multidimensional assessment approaches have been advocated<sup>6</sup>.

To optimize disease control in the context of advanced modern medicine<sup>7</sup>, ‘treatable traits (TTs)’ have been proposed as a new paradigm for the 21st-century management of chronic airway diseases<sup>8-11</sup>. TTs involve the application of personalized medicine based on a multidimensional assessment, then the identification of pulmonary, extrapulmonary, and behavioral/risk factors that are identifiable, clinically relevant, and modifiable<sup>11</sup>. The implementation of a TTs approach can form the basis of a precision medicine strategy in which specific investigations and treatments are tailored<sup>10</sup>. This label-free approach could be useful for patients with airway diseases, particularly those with complex conditions such as severe asthma, and provide individualized care and improve outcomes<sup>11</sup>.

In this study, we first characterized TTs in elderly asthmatics and compared them to younger patients from the Australasian Severe Asthma Network (ASAN). Second, we assessed the relationship between TTs and future exacerbations. Third, an exacerbation prediction model based on the asthma control level and critical risk factors among TTs was developed, and the overall performance was externally validated in an independent cohort.

## METHODS

### *Study design and participants*

The ASAN (<https://www.severeasthma.org.au>) is a multicenter clinical research network (Australia, Singapore, China, and New Zealand) in a real-world setting. This prospective observational cohort study was conducted from March 2014 to December 2019 at West China Hospital, Sichuan University, China's ASAN center. Participants aged  $\geq 18$  years with stable asthma (no respiratory tract infection and no exacerbation in the previous four weeks) were consecutively recruited and followed up for 12 months. The recruitment period of our study was from March 2014 to December 2018, and the follow-up period was from March 2014 to December 2019 (Figure 1). Asthma in the elderly was defined as asthma in people aged  $> 64$  years<sup>1</sup>. Ethics approval was received from the Clinical Trial and Biomedicine Ethics Committee of West China Hospital of Sichuan University (No. 2014-244). Written and oral informed consent was obtained from all the participants. The detailed inclusion and exclusion criteria of the participants are described in the Online Repository Text.

### *Socio-demographic information and clinical data collection*

At baseline, all participants underwent a multidimensional assessment to identify TTs present within the pulmonary, extrapulmonary, and behavioral/psychosocial domains. Socio-demographic information and data including height, weight, asthma history, medications and adherence, asthma triggers, comorbidities, smoking history, asthma-related exacerbation (in the past 12 months), asthma control test (ACT)<sup>12</sup> score, the asthma quality of life questionnaire (AQLQ)<sup>13</sup> score were collected. Other medical investigations performed within the last six months, including high-resolution computed tomography of the chest (HRCT), chest X-ray, sinus CT, esophagoscopy, polysomnography, rhinoscopy and 24 h esophageal pH, were included. During the follow-up period, patients underwent face-to-face

visits (or telephone if unable to attend) to collect detailed information about exacerbation. Early-onset asthma was defined as < 12 years old at the onset of asthma<sup>14</sup>. More details are provided in the Online Repository Text.

#### *Depression and anxiety assessment*

Depression or anxiety was assessed using the 14-item hospital anxiety and depression scale (HADS) and defined as a score  $\geq 8$  on the respective HADS-D or HADS-A domains<sup>15</sup>.

#### *Lung function and bronchodilator test*

Spirometry was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines<sup>16</sup>. Forced expiratory volume in 1 s (FEV<sub>1</sub>) and forced vital capacity (FVC) were measured before and 15 min after 400 µg of salbutamol was delivered by a metered-dose inhaler and spacer.

#### *Sputum induction and processing*

Sputum was induced and processed based on a standardized operating procedure as previously described<sup>17-18</sup>.

#### *Fractional exhaled nitric oxide, fat-free mass and peripheral blood*

Fractional exhaled nitric oxide (FeNO) levels were measured according to the ATS<sup>19</sup> guidelines. Fat-free mass was measured through body composition measurements using a bioimpedance analyzer. Fasting blood samples were collected for complete blood counts, total immunoglobulin E (IgE), triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and fasting plasma glucose. Biomarkers, including the blood eosinophil count and serum IgE and FeNO levels, were used to define T2 inflammation if two or more of the following were present: eosinophil count  $\geq 0.14 \times 10^9$  cells/L, IgE level

234  $\geq 100$  IU/mL, or FeNO  $\geq 30$  ppb<sup>20-21</sup>. Eosinophilic inflammation was defined as a sputum  
 235 eosinophil count  $\geq 3\%$  and/or FeNO  $\geq 30$  ppb and/or blood eosinophil count  $\geq 0.3$   
 236  $\times 10^9/L$ <sup>22</sup>.

#### 237 *Skin prick tests*

238 Skin prick tests were performed on 11 common allergens, including dog hair, cat hair,  
 239 cockroach, pollen (ragweed, birch, maize, and London plane), mold (*Alternaria tenuis* and  
 240 *Aspergillus fumigatus*), and house dust mites (*Dermatophagoides pteronyssinus* and  
 241 *Dermatophagoides farinae*). Allergen sensitization was confirmed if the participant exhibited a  
 242 positive skin response to one or more of the tested allergens of skin prick tests<sup>22</sup>.

#### 243 *TTs identification*

244 The TTs assessed in this study were based on published recommendations relevant to this  
 245 concept<sup>8-11, 22-26</sup>. A total of 38 TTs were assessed, and the traits identified within the  
 246 pulmonary (n = 12), extrapulmonary (n = 18), and behavioral/psychosocial domains (n = 8)  
 247 are presented in Table 1.

#### 248 *Outcomes*

249 The outcomes of the study were moderate to severe asthma exacerbations during the 12  
 250 months after enrollment. Severe asthma exacerbation<sup>27-28</sup> was defined as worsening of asthma  
 251 symptoms that led to one of the following: temporary use of systemic corticosteroids or an  
 252 increase in use from a stable maintenance dose for at least three days, an asthma-specific  
 253 hospitalization, an emergency room visit or an intensive care unit visit requiring systemic  
 254 corticosteroids. Moderate asthma exacerbation<sup>27-28</sup> was defined as any increase in rescue  
 255 bronchodilator use for at least two days or any temporary increase in inhaled corticosteroids,  
 256 an emergency department visit, or an unscheduled visit while not requiring systemic  
 257 corticosteroids due to worsening asthma symptoms.

## Statistical analysis

Normally distributed data are expressed as the mean  $\pm$  standard deviation and non-normally distributed data as the median (quartiles [Q] 1, 3). Categorical variables are summarized as numbers and percentages. A student's t-test, Chi-square test, Fisher's exact test, or Wilcoxon rank-sum test were used to assess the differences in TTs from the cross-sectional assessment between the elderly asthma and non-elderly asthma groups, as appropriate. Correlations between the TTs were expressed using Spearman's correlation coefficients. Negative binomial regression was used to assess the association between TTs and exacerbations during follow-up. The association between each of trait and exacerbation was measured as the ratio of the rate of exacerbations in the trait-positive group to the rate in the trait-negative, group and summarized as incidence rate ratio (IRR). These analyses were conducted using SPSS version 25.0 (IBM Corp, Armonk, NY, USA). In all statistical analyses, a P-value of  $< 0.05$  was considered statistically significant.

## Clinical prediction model derivation

An exacerbation prediction model was developed based on the TTs and the asthma control level (ACT)<sup>29</sup>. Variables with missing data were imputed using multiple imputation<sup>30</sup>, as described to reduce bias and increase statistical power. Before imputation we diagnosed the mechanism of missingness, and variables with missing data thought to be missing not at random were not considered in the multiple imputation process. We used the least absolute shrinkage and selection operator (LASSO) method, which is appropriate for high-dimensional and multicollinear data, to select the most useful predictors of future exacerbation. A multivariate logistic regression analysis was used to build a prediction model by incorporating all the features selected from the LASSO regression analysis. The final prediction model's relationships among predictors were visualized using a nomogram. Detailed information about the handling of missing values, nomogram and LASSO are described in the Online

Repository Text.

*Clinical prediction model performance and validation*

The concordance index (C-index) and the area under the receiver operating characteristics curve with the calculation of the area under curve (AUC) replies were used to quantify the discrimination performance of the clinical model. The Hosmer-Lemeshow goodness-of-fit test and calibration curves were used to assess the model calibration. A P-value  $> 0.05$  for the Hosmer-Lemeshow test suggests no evidence of poor goodness-of-fit, which is the desired outcome for a predictive model<sup>31</sup>. The internal and external validity of the model were determined. Internal validation was performed using both 1000 bootstrap sampling and 10-fold cross-validation to produce bias-corrected estimates of the model's performance. External validation (temporal validation) was evaluated by studying participants who were recently recruited from a completely different cohort of asthma participants. These participants were prospectively and consecutively recruited from January 2019 to December 2019 at West China Hospital, Sichuan University, based on the ASAN (Figure E3). The follow-up period for the temporal validation cohort was from January 2019 to December 2020. In addition, a sensitivity analysis was conducted to test the influence of age on the model. The model performance and validation were performed using R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Detailed information about the model performance and validation are described in the Online Repository Text.

## RESULTS

### *Socio-demographic and clinical characteristics*

Of the 521 eligible participants screened, 62 were classified into the elderly group ( $> 64$  years old), and 459 were classified into the non-elderly group ( $\leq 64$  years old; Table 2). The median ages of the elderly and non-elderly groups were 70.0 (Q1, Q3: 67.0, 72.3) years and 43.0 (Q1, Q3: 34.0, 52.0) years, respectively. The proportion of female participants in the elderly group was lower than that in the non-elderly group (46.8% vs. 65.6%,  $P = 0.004$ ). Among the smokers, the pack-years was higher in the elderly group (median [Q1, Q3]: 25.5 [14.7, 44.5]) than in the non-elderly group (median [Q1, Q3]: 12.0 [3.0, 27.0]) ( $P = 0.002$ ). The elderly asthma group showed a lower proportion of early-onset asthma than the non-elderly asthma group (4.8% vs. 17.6%,  $P = 0.010$ ). Of the 62 elderly participants, 11 (17.7%) had severe asthma, 21 (33.9%) had moderate asthma and 30 (48.4%) had mild asthma as defined by GINA. Furthermore, the elderly group participants had worse airway obstruction ( $FEV_1\%$  predicted: 63.03 [21.29] vs. 70.51 [21.25];  $FEV_1/FVC$ : 57.60 [12.27] vs. 67.55 [13.21], all  $P < 0.001$ ). Compared with the non-elderly group, the elderly group included a greater proportion of patients with  $FEV_1/FVC < LLN$  (82.0%) ( $P = 0.035$ ) and a lower  $\Delta FEV_1/FVC$ , % (median [Q1, Q3]: -14.76 [-45.22, -1.75] %) ( $P = 0.010$ ). Regarding exacerbation history, the elderly group included a higher proportion of patients who had experienced at least one severe exacerbation in the past year compared to the non-elderly group (46.8% vs. 32.5%,  $P = 0.027$ ). A greater proportion of patients in the elderly asthma group than in the non-elderly asthma group had been admitted to hospital (41.9% vs. 22.7%,  $P = 0.001$ ). The socio-demographic and clinical characteristics of the 521 participants are presented in Table E1. The socio-demographic and clinical characteristics of the temporal validation cohort are presented in Table E7.

### *TTs and prevalence*

We assessed 38 TTs in total, including 12 pulmonary traits, 18 extrapulmonary traits, and eight behavioral/psychosocial traits. The median (Q1, Q3) number of traits assessed in the elderly and non-elderly groups were 8 (Q1, Q3: 7, 10) and 8 (Q1, Q3: 6, 10,  $P = 0.51$ ) respectively. The proportion of the possible traits present in the three domains between the two groups were similar (Figure E1).

The prevalence of TTs in participants classified as elderly or non-elderly is shown in Table 3. The prevalence of TTs of all participants is shown in Table E2. In the pulmonary domain, the prevalence of fixed airflow limitation (73.3% vs. 41.0%,  $P < 0.001$ ), neutrophilic inflammation (40.0% vs. 23.0%,  $P = 0.028$ ) and emphysema (8.1% vs. 1.3%,  $P < 0.001$ ) were significantly higher in the elderly group than the non-elderly group. However, eosinophilic inflammation (48.4% vs. 70.0%,  $P = 0.001$ ) and T2 inflammation (32.3% vs. 67.5%,  $P < 0.001$ ) were less common in the elderly group than in the non-elderly group. Compared with asthmatic patients in the non-elderly group, those with asthma in the elderly group had a higher prevalence of cardiovascular disease (17.7% vs. 5.2%,  $P < 0.001$ ), osteoporosis (12.9% vs. 4.1%,  $P = 0.009$ ), anemia (4.8% vs. 0.7%,  $P = 0.025$ ), impaired fasting glucose (15.4% vs. 2.0%,  $P < 0.001$ ), diabetes (8.1% vs. 2.4%,  $P = 0.043$ ) and dyslipidemia (72.5% vs. 41.5%,  $P < 0.001$ ) in the context of extrapulmonary traits. However, the prevalence of eczema (6.5% vs. 20.7%,  $P = 0.007$ ) and allergen sensitization (36.8% vs. 60.0%,  $P = 0.001$ ) were lower in the elderly group than in the non-elderly group. As for TTs in the behavioral/psychosocial domain, low socioeconomic status showed a higher prevalence in the elderly asthma group than in the non-elderly asthma group (55.0% vs. 31.0%,  $P < 0.001$ ). Elderly asthmatics had a lower prevalence of depression (1.6% vs. 10.0%,  $P = 0.030$ ) and anxiety (0.0% vs. 8.7%,  $P = 0.030$ ) than non-elderly patients with asthma. The associations between TTs are shown in Table E3.

#### *TTs and moderate-severe exacerbations*

Of the 521 participants, 86.6% ( $n = 451$ ) completed the one-year follow-up. Among them,

33.5% ( $n = 151$ ) experienced at least one moderate-severe asthma exacerbation during the follow-up period, 15.1% ( $n = 68$ ) experienced at least one severe exacerbation, and 24.2% ( $n = 109$ ) experienced at least one moderate exacerbation. The relationship between TTs and exacerbations are presented in Table 4. For each additional trait present, there was a 13.6% increase in exacerbation risk ( $P < 0.001$ ). The magnitude of risk was similar within the pulmonary (IRR: 1.143,  $P = 0.002$ ) and behavioral/psychosocial domains (IRR: 1.149,  $P = 0.012$ ). In the pulmonary traits, exacerbation prone (IRR: 3.263,  $P < 0.001$ ) and upper respiratory infection-induced asthma attack (URI) (IRR: 2.073,  $P < 0.001$ ) were associated with increased future exacerbations. Eosinophilic inflammation (IRR: 0.689,  $P = 0.007$ ) and T2 inflammation (IRR: 0.730,  $P = 0.024$ ) were associated with decreased risk of future exacerbations. Among the extrapulmonary traits, the presence of cardiovascular disease (IRR: 2.623,  $P < 0.001$ ), cachexia (IRR: 1.839,  $P = 0.001$ ) and diabetes (IRR: 2.484,  $P = 0.006$ ) could increase the risk of future exacerbations. In the behavioral/psychosocial domain, anxiety (IRR: 1.668,  $P = 0.035$ ), depression (IRR: 2.368,  $P < 0.001$ ), inhaler device polypharmacy (IRR: 1.588,  $P = 0.035$ ) and food allergy (IRR: 1.579,  $P = 0.003$ ) were all predictive of future exacerbations.

#### *Clinical prediction model*

Eight variables with nonzero coefficients in the LASSO regression model remained and were then included in the final multivariate logistic regression model (Figure E2). These risk factors were exacerbation prone, depression, cardiovascular disease, URI, non-eosinophilic inflammation, cachexia, food allergy and ACT control. Among them, URI, ACT control, psychiatric disease, and cardiovascular disease were the main contributing factors (Table 5). A model that incorporated the above eight predictors were developed and visualized as a nomogram (Figure 2).

This model showed excellent discrimination in distinguishing between patients who did

and did not experience exacerbation (C-index: 0.743, 95% CI: 0.629-0.857; AUC: 0.729, 95% CI: 0.615-0.843, Figure 3). The goodness-of-fit of the model was evaluated using the Hosmer-Lemeshow test and bias-corrected calibration curves. The Hosmer-Lemeshow test yielded a non-significant statistic ( $P = 0.456$ ), which suggested that the model fit was acceptable. Evaluating the bias-corrected calibration curves for the prediction model of our study indicated good agreement (Figure E4, Figure E5). On internal validation, both bootstrapping (bias-corrected C-index = 0.727) and 10-fold cross-validation (bias-corrected C-index = 0.719) suggested that the model discrimination was good. The temporal validation cohort included 154 participants, of which 131 (85.1%) completed 12 months of follow-up. The temporal validation of the AUC was 0.715 (95% CI: 0.602-0.828; Figure E6), indicating the model discrimination was good and did not differ significantly from the AUC in our primary dataset ( $P = 0.346$ ). The model fit was acceptable (Hosmer-Lemeshow test,  $P = 0.478$ ; calibration curve, Figure E7).

In addition, to assess the impact of age on the exacerbation prediction model, a sensitivity analysis was conducted. The final prediction model's relationship among the predictors with and without adjustment for age was investigated (Table 5, Table E8) and visualized using nomograms (Figure 2, Figure E8). The results showed that age had a negligible impact on the clinical prediction model.

## DISCUSSION

In a cohort study based on the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes project, 23 TTs were identified in white European adults with asthma. TTs were found to be more common in severe asthma than non-severe asthma<sup>23</sup>. By analyzing the Australasian Severe Asthma Web-Based Database, the Australian group we cooperated with reported the prevalence and exacerbation risk of 24 TTs and found several traits were associated with future asthma exacerbation risk<sup>22</sup>. Additionally, they recently published a randomized controlled trial that applied a multidimensional assessment to define the number and type of traits present and demonstrated that a TT intervention could significantly improve the health status of people with severe asthma<sup>26</sup>. Although the TT approach has been increasingly recommended by the scientific community to optimize the management of asthma<sup>11</sup>, available data on the prevalence of TTs in different populations, particularly elderly asthmatics, are limited<sup>11</sup>.

To the best of our knowledge, our study is the first to describe TTs of asthma in the elderly. It is certainly the first to assess TTs in Chinese adults with asthma and compare the burden in elderly and non-elderly patients. We assessed the prevalence of 38 potential TTs, including 12 pulmonary traits, 18 extrapulmonary, and eight behavioral/psychosocial traits. Although there was no statistically significant difference in the number of present TTs between the elderly and non-elderly groups, elderly patients with asthma had more chronic metabolic diseases, fixed airflow limitation, emphysema and neutrophilic inflammation. In contrast, non-elderly asthmatics exhibited more allergic diseases or characteristics and psychiatric diseases. Nine traits were related to increased future exacerbations. The strongest of these were exacerbation prone, upper respiratory infection-induced asthma attack (URI), cardiovascular disease, diabetes and depression. In addition, we developed a model that showed good discrimination and calibration allowing for personalized future exacerbation risk prediction.

TTs as therapeutic targets can provide more precise and inclusive individualized treatment, which could result in greater improvement of health status and fewer hospital admissions and exacerbations<sup>26, 32-33</sup>. In our study, 35 of 38 traits have been proposed as asthma TTs in previously published studies<sup>8-11, 22-26</sup>. Three of 38 traits including small airway dysfunction, food allergy, and impaired fasting glucose, were first presented as TTs, which were described as asthma comorbidities, causes of asthma or co-morbid features in prior studies<sup>34-36</sup>. It is necessary to stress that these new potentially TTs may be useful for the expansion of the candidate list of asthma TTs. In the pulmonary domain, we found that elderly adults with asthma had more fixed airflow limitation, neutrophilic inflammation and emphysema than non-elderly asthmatics, which is in agreement with previous studies<sup>4, 37</sup>. In accordance with previous studies, this study demonstrated that eosinophilic inflammation and T2 inflammation were more common in non-elderly people with asthma<sup>4, 38</sup>. For metabolic diseases of extrapulmonary traits, cardiovascular disease, osteoporosis, impaired fasting glucose, diabetes, and dyslipidemia were more common in older participants, consistent with previous studies<sup>39, 40</sup>. Additionally, we found a larger proportion of elderly patients had anemia, which was in agreement with the conclusion that anemia is most frequent in older people<sup>41</sup>. Conversely, non-elderly people with asthma were more likely to have rhinitis, eczema and allergen sensitization which is in agreement with previous studies<sup>42, 43</sup>. Our study found that the elderly were more likely to be in a lower socioeconomic status than the non-elderly in China. However, the generalization of this finding may be limited due to differences in the definitions of socioeconomic status between countries<sup>44</sup>. In contrast to a previous finding<sup>45</sup>, anxiety and depression were found to be less common in elderly patients with asthma than in non-elderly in our study.

Asthma exacerbation has always been an intractable problem because of its close association with morbidity, mortality and health care costs. Its prevention is a vital metric for

measuring the success of asthma treatments<sup>46</sup>. We intended to determine whether TTs can be predictors of future exacerbations to inform key targets for future research. Therefore, we used negative binomial regression to evaluate the associations between TTs and future exacerbations. Just as the relationship between respiratory infection and asthma exacerbation has been recognized for centuries<sup>47</sup>, our data also revealed that respiratory infection is strongly correlated with exacerbation. We also confirmed the findings of previous study<sup>22</sup>, that previous exacerbation was the strongest predictor of future exacerbations. In addition, cardiovascular disease, diabetes, anxiety, depression, inhaler device polypharmacy, and food allergy were also found to be risk factors for future exacerbations, as has been previously reported in asthma<sup>22, 25, 35, 47</sup>. Cachexia was significantly associated with future exacerbations of asthma in our study. Although it has not been clearly documented that components of metabolic diseases are significantly related to asthma exacerbations, cachexia is an independent risk factor for mortality in chronic obstructive pulmonary disease<sup>48</sup>. These findings highlight important TTs that could be targeted in an effort to reduce exacerbation and inform future clinical trials. However, eosinophilic inflammation and T2 inflammation seemed to be protective factors in our study, which was inconsistent with a previous study<sup>22</sup>. A possible explanation may be that patients with eosinophilic inflammation and/or T2 inflammation have a better response to ICS<sup>49</sup>. A prior study confirmed that personalized management of asthma based on eosinophilia results in significant benefits<sup>50</sup>.

Using multivariable logistic regression, we developed a clinical prediction model with eight factors to predict future exacerbation risk, and visualized it as a nomogram. Our model had good calibration and predictive performance, demonstrating that it can accurately predict future exacerbation. This nomogram can be conveniently used by clinicians.

We need to emphasize that this is a real-world pragmatic study. Randomized controlled trials designed to implement and test the TTs approach are complex but necessary. Prospective,

longitudinal, interventional studies designed to explore whether modifying TTs makes a difference are still urgently needed. As such, our analyses are important for the progress of research in this area.

This study had several limitations. First, the sample size of elderly asthma patients was relatively small. However, this was because our study was conducted in a real-world setting where the prevalence of asthma in the elderly was 11.9%, consistent with previous studies<sup>1</sup>. In addition, the sample size of elderly patients with asthma experiencing exacerbation (n= 19, 37.3%) was not sufficient to establish a predictive model for future asthma exacerbation. To explore the effects of the identified TTs as predictors of future asthma exacerbation, we assessed predictors of future exacerbation in all patients in the cohort (the elderly and non-elderly) using a regression analysis and nomogram. However, to assess the impact of age on the exacerbation prediction model, a sensitivity analysis was conducted. The results showed that age had a negligible impact on the clinical prediction model. Second, some TTs on our list are controversial. For example, fixed airflow obstruction, emphysema, bronchiectasis, and small airway dysfunction may not be treatable. However, this is because there is no international consensus on the criteria for the establishment of TTs. The classification criteria for our TTs were determined by using published recommendations relevant to this concept. Third, although the identification of some TTs in our study was based on a doctor's diagnosis, all diagnoses were made by clinicians according to the specific combination of signs, symptoms, and laboratory testing recommended by guidelines. Fourth, as a hypothesis-generating (exploratory analysis) study, we used multiple testing on TTs to ensure that we did not miss out on something potentially interesting. We used a standard alpha level of 0.05, with a P-value of less than 0.05, without adjusting  $\alpha$  (Type I errors), which may produce false-positive results. Thus, future studies are needed to validate the generalizability of our findings from the exploratory analyses. Finally, participants in our study were from a

single center. Therefore, the generalizability of our results may be limited as no validation was conducted in another population from other countries or regions. However, to some extent, our findings from a real-world setting are generally characterized by relatively good external validity and generalizability<sup>51</sup>.

## CONCLUSION

In conclusion, TTs can be systematically assessed in elderly patients with asthma. Some TTs were identified as associated with future exacerbations. Among the strongest of these were exacerbation prone, upper respiratory infection-induced asthma attack, cardiovascular disease, diabetes, and depression. In addition, we presented a nomogram based on specific TTs that can be conveniently used to allow personalized future exacerbation prediction in patients with asthma. Although many questions remain in relation to the TTs approach particularly concerning practical implementation, these data add new knowledge and a practical tool to aid implementation.

## ACKNOWLEDGEMENTS

We are grateful to Ms. Michelle Gleeson (Hunter Medical Research Institute, the University of Newcastle, Australia), Mr. Xiao Fei Liu (West China Hospital, Sichuan University, China), Ms. Dan Wang (West China Hospital, Sichuan University, China) and Ms. Zhi Lin (West China Hospital, Sichuan University, China) for their sputum processing and thanks to all participants volunteered in this study. We also appreciate the advice of statistic analysis from Prof. De Ying Kang (West China Hospital, Sichuan University, China), and appreciate the suggestions for revision from Prof. Hua Hao Shen (Second Affiliated Hospital of Zhejiang University, China), Prof. Shao Xi Cai (Nanfang Hospital, Southern Medical University, China), Prof. Ping Chen (General Hospital of Northern Theater Command, China),

Prof. Jun Tao Feng (Xiangya Hospital, Central South University, China), Prof. Xue Jun Guo (Xinhua Hospital, Shanghai Jiao Tong University, China), Prof. Ji Tao Guan (the Second Affiliated Hospital of Hebei Medical University, China.), Prof. Qian Li Ma (North-Kuanren General Hospital, China), Prof. Xue Yi Tang (People's Hospital Affiliated to Zhengzhou University, China), Prof. Ling Wei Wang (Shenzhen People's Hospital, Jinan University, China) and Prof. Min Zhang (Shanghai General Hospital, Shanghai Jiao Tong University, China).

#### **CONFLICT OF INTEREST STATEMENT**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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676 **Tables**

| Table 1. A full description of the definitions of treatable traits, including the assessment method and guide for identification |                                         |                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Exposure/Treatable traits                                                                                                        | Assessment method                       | Guide for identification                                                                                                         |
| <b>Pulmonary traits</b>                                                                                                          |                                         |                                                                                                                                  |
| Fixed airflow limitation                                                                                                         | Spirometry                              | Post-bronchodilator $FEV_1/FVC < 0.7$                                                                                            |
| Bronchodilator reversibility                                                                                                     | Spirometry                              | Post-bronchodilator increases in $FEV_1 > 12\%$ and $> 200$ mL                                                                   |
| Small airway dysfunction                                                                                                         | Spirometry                              | $MMEF < LLN$                                                                                                                     |
| Eosinophilic inflammation                                                                                                        | Induced sputum; FeNO;<br>Fasting blood  | Sputum eosinophils $\geq 3\%$ and/or FeNO $\geq 30$ ppb and/or blood eosinophils $\geq 0.3 \times 10^9/L$                        |
| T2 inflammation                                                                                                                  | Blood eosinophil count;<br>FeNO; IgE    | Meet two or more of the following: eosinophil count $\geq 0.14 \times 10^9$ cells/L, IgE $\geq 100$ IU/mL, or FeNO $\geq 30$ ppb |
| Neutrophilic inflammation                                                                                                        | Induced sputum                          | Sputum neutrophil count $\geq 61\%$ and eosinophil count $< 3\%$                                                                 |
| Bronchial hyperresponsiveness                                                                                                    | Bronchial provocation<br>challenge test | Decrease in $FEV_1 \geq 20\%$ with methacholine provocative concentration $< 8$ mg/mL                                            |
| Emphysema                                                                                                                        | Chest CT                                | Doctor and/or radiologist diagnosis                                                                                              |
| Bronchiectasis                                                                                                                   | Chest CT                                | Doctor and/or radiologist diagnosis                                                                                              |
| Exacerbation prone                                                                                                               | Questionnaire                           | $\geq 3$ courses of systemic corticosteroids in the last 12 months                                                               |
| Cough*                                                                                                                           | AQLQ                                    | AQLQ: Question 12 score $\leq 4$                                                                                                 |
| Upper respiratory infection-induced<br>asthma attack                                                                             | Questionnaire                           | Self-report of upper respiratory infection as a trigger of asthma attack                                                         |
| <b>Extrapulmonary traits</b>                                                                                                     |                                         |                                                                                                                                  |
| Rhinitis                                                                                                                         | Questionnaire                           | Doctor diagnosis                                                                                                                 |
| Rhinosinusitis                                                                                                                   | Questionnaire; Sinus CT                 | Doctor diagnosis                                                                                                                 |
| Nasal polyps                                                                                                                     | Questionnaire; Rhinoscopy               | Doctor diagnosis                                                                                                                 |
| Vocal cord dysfunction                                                                                                           | Questionnaire                           | Doctor diagnosis                                                                                                                 |
| Obstructive sleep apnea                                                                                                          | Questionnaire;<br>Polysomnography       | Doctor diagnosis                                                                                                                 |
| Gastroesophageal reflux disease                                                                                                  | Questionnaire;<br>24 h esophageal pH    | Doctor diagnosis                                                                                                                 |
| Cardiovascular disease                                                                                                           | Questionnaire                           | Doctor diagnosis                                                                                                                 |

|                                         |                                        |                                                                                                                                    |
|-----------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Systemic inflammation                   | Leukocyte                              | Leukocyte count $> 9 \times 10^9/L$                                                                                                |
| Osteoporosis                            | Questionnaire;<br>Bone mineral density | Doctor diagnosis                                                                                                                   |
| Eczema                                  | Questionnaire                          | Doctor diagnosis                                                                                                                   |
| Allergen sensitization                  | Skin prick test                        | $\geq$ one positive skin response to tested allergens                                                                              |
| Underweight                             | BMI                                    | $BMI < 18.5 \text{ kg/m}^2$                                                                                                        |
| Obesity                                 | BMI                                    | $BMI \geq 30 \text{ kg/m}^2$                                                                                                       |
| Anemia                                  | Hemoglobin                             | $Hb < 120 \text{ g/L}$ in males and $< 110 \text{ g/L}$ in females                                                                 |
| Cachexia <sup>52</sup>                  | $FFMI = FFM/Height^2$                  | $FFMI$ of $< 15 \text{ kg/m}^2$ for females and $16 \text{ kg/m}^2$ for males                                                      |
| Impaired fasting glucose                | FPG                                    | IFG was defined as an FPG of 6.1-7.0 mmol/L.                                                                                       |
| Diabetes                                | Plasma glucose                         | $RPG \geq 11.1 \text{ mmol/L}$ or $FPG \geq 7.0 \text{ mmol/L}$ or $OGTT \text{ 2hPG} \geq 11.1 \text{ mmol/L}$                    |
| Dyslipidemia <sup>53</sup>              | TG, TC, HDL-C, LDL-C                   | $TC \geq 5.2 \text{ mmol/L}$ or $LDL-C \geq 3.4 \text{ mmol/L}$ or $TG \geq 1.7 \text{ mmol/L}$ or $HDL-C \leq 1.0 \text{ mmol/L}$ |
| Behavioral/psychosocial traits          |                                        |                                                                                                                                    |
| Smoking                                 | Questionnaire                          | Report current smoking                                                                                                             |
| Psychiatric disease                     |                                        |                                                                                                                                    |
| Anxiety                                 | HADS or doctor diagnosis               | HADS: anxiety domain score $\geq 8$ or doctor diagnosis                                                                            |
| Depression                              | HADS or doctor diagnosis               | HADS: depression domain score $\geq 8$ or doctor diagnosis                                                                         |
| Inhaler device polypharmacy             | Questionnaire                          | Prescription of three or more different inhalers                                                                                   |
| Poor medication adherence <sup>54</sup> | Questionnaire                          | Participants who used less than 70% of their prescribed dose of inhaled corticosteroid                                             |
| Low socioeconomic status*               | Questionnaire                          | Education, vocation and income                                                                                                     |
| Aspirin sensitivity                     | Questionnaire                          | Self-report of aspirin as an asthma trigger                                                                                        |
| Food allergy                            | Questionnaire                          | Self-report of certain food as an asthma trigger                                                                                   |

AQLQ, asthma quality of life questionnaire; BMI, body mass index; CT, computed tomography;  $FEV_1$ , forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide; FFM, fat-free mass; FFMI, fat-free mass index; FVC, forced vital capacity; FPG, fasting plasma glucose; Hb, hemoglobin; HADS, hospital anxiety and depression scale; GERD, gastroesophageal reflux disease; HDM, house dust mites; HDL-C, high-density lipoprotein cholesterol; IgE, immunoglobulin E; IFG, impaired fasting glucose; LLN, lower limit of normal; LDL-C, low-density lipoprotein cholesterol; MMEF, maximum mid-expiratory flow; OGTT, oral glucose tolerance test; PG, plasma glucose; PSG, polysomnography; RPG, random plasma glucose; SPT, skin prick test; TG, triglyceride; TC, total cholesterol; URI, upper respiratory infection-induced asthma attack.

Psychiatric disease includes anxiety and/or depression.

Inhaler device types: Pressurized Metered-Dose Inhaler; Turbuhaler; Autohaler; Nebulizer; Accuhaler; Aerolizer; Handihaler; Intranasal Spray.

\*the detailed definitions of socioeconomic status and cough are listed in the Online Repository Text.

Journal Pre-proof

| Characteristics                                        | n1‡ | Elderly<br>(n=62)      | n2‡ | Non-elderly<br>(n=459) | $t/\chi^2/Z$ | P-value |
|--------------------------------------------------------|-----|------------------------|-----|------------------------|--------------|---------|
| Age, years, median (Q1, Q3)                            | 62  | 70.0 (67.0, 72.3)      | 459 | 43.0 (34.0, 52.0)      | -12.792      | <0.001  |
| Female, n (%)                                          | 62  | 29 (46.8)              | 459 | 301 (65.6)             | 8.317        | 0.004   |
| BMI, kg/m <sup>2</sup> , mean (SD)                     | 62  | 23.71 (3.49)           | 459 | 23.18 (3.70)           | -1.303       | 0.193§  |
| Smoking, Never/Former/Current, n                       | 61  | 45/11/5                | 459 | 336/80/43              | 0.094        | 0.954   |
| Pack-years, median (Q1, Q3)                            | 25  | 25.5 (14.7, 44.5)      | 111 | 12.0 (3.0, 27.0)       | -3.082       | 0.002   |
| Age of asthma onset, years, mean (SD)                  | 62  | 53.8 (19.5)            | 459 | 30.7 (16.0)            | -8.277       | <0.001  |
| Early-onset asthma, n (%)                              | 62  | 3 (4.8)                | 459 | 81 (17.6)              | 6.626        | 0.010   |
| Asthma family history, n (%)                           | 61  | 24 (38.7)‡‡            | 459 | 150 (32.7)             | 0.222        | 0.638   |
| ICS (BDP equivalent) dose, ug/day, median (Q1, Q3)     | 62  | 200 (0, 400)           | 459 | 200 (0, 400)           | -0.251       | 0.801   |
| Additional medications, n (%)                          |     |                        |     |                        |              |         |
| LABA                                                   | 62  | 32 (51.6)              | 459 | 266 (58.0)             | 0.897        | 0.344   |
| LTRA                                                   | 62  | 17 (27.4)              | 459 | 152 (33.1)             | 0.809        | 0.369   |
| LAMA                                                   | 62  | 5 (8.1)                | 459 | 11 (2.4)               | 4.145        | 0.042   |
| OCS                                                    | 62  | 5 (8.1)                | 459 | 14 (3.1)               | 2.612        | 0.106   |
| SABA                                                   | 62  | 9 (14.5)               | 459 | 77 (16.8)              | 0.202        | 0.653   |
| Theophylline                                           | 62  | 14 (22.6)              | 459 | 80 (17.4)              | 0.980        | 0.322   |
| Asthma severity (mild/moderate/severe), n#             | 62  | 30/21/11               | 459 | 204/198/57             | 0.540        | 0.734   |
| Spirometry,                                            |     |                        |     |                        |              |         |
| Pre-bronchodilator FEV <sub>1</sub> %                  | 61  | 63.03 (21.29)          | 453 | 74.91 (19.91)          | -4.302       | <0.001  |
| Pre- bronchodilator FEV <sub>1</sub> /FVC%             | 61  | 57.60 (12.27)          | 453 | 67.55 (13.21)          | -5.380       | <0.001  |
| Pre- bronchodilator FEV <sub>1</sub> /FVC < LLN, n (%) | 61  | 50 (82.0)‡‡            | 453 | 312 (68.9)‡‡           | 4.425        | 0.035   |
| ΔFEV <sub>1</sub> /FVC, %, median (Q1, Q3)*            | 61  | -14.76 (-45.22, -1.75) | 453 | -8.30 (-25.82, 2.34)   | -2.562       | 0.010   |
| AQLQ scores, median (Q1, Q3)                           | 62  | 6.03 (5.41, 6.50)      | 451 | 5.88 (5.22, 6.38)      | -1.181       | 0.238   |
| ACT scores, median (Q1, Q3)                            | 62  | 20 (17, 23)            | 459 | 20 (16, 23)            | -1.129       | 0.259   |
| Asthma control levels assessed by ACT, n (%)※          |     |                        |     |                        |              |         |
| Controlled                                             | 62  | 35 (56.5)              | 459 | 233 (50.8)             | 1.691        | 0.429   |

|                               |    |           |     |            |        |        |
|-------------------------------|----|-----------|-----|------------|--------|--------|
| Somewhat controlled           | 62 | 18 (29.0) | 459 | 127 (27.7) |        |        |
| Poorly controlled             | 62 | 9 (14.5)  | 459 | 99 (21.6)  |        |        |
| Exacerbation in the past year |    |           |     |            |        |        |
| Moderate exacerbation         |    |           |     |            |        |        |
| n (%)                         | 62 | 19 (30.6) | 459 | 192 (41.8) | 2.836  | 0.092  |
| median (Q1, Q3)               | 62 | 0 (0, 1)  | 459 | 0 (0, 1)   | -1.369 | 0.171  |
| Severe exacerbation           |    |           |     |            |        |        |
| n (%)                         | 62 | 29 (46.8) | 459 | 149 (32.5) | 4.920  | 0.027  |
| median (Q1, Q3)               | 62 | 0 (0, 1)  | 459 | 0 (0, 1)   | -2.359 | 0.018  |
| Unscheduled visit             |    |           |     |            |        |        |
| n (%)                         | 62 | 16 (25.8) | 459 | 156 (34.0) | 1.653  | 0.199  |
| median (Q1, Q3)               | 62 | 1 (0, 3)  | 459 | 1 (0, 3)   | -0.957 | 0.339  |
| Emergency room visit          |    |           |     |            |        |        |
| n (%)                         | 62 | 8 (12.9)  | 459 | 65 (14.2)  | 0.061  | 0.805  |
| median (Q1, Q3)               | 62 | 0 (0, 1)  | 459 | 0 (0, 1)   | -0.468 | 0.640  |
| Hospitalization               |    |           |     |            |        |        |
| n (%)                         | 62 | 26 (41.9) | 459 | 104 (22.7) | 10.840 | 0.001  |
| median (Q1, Q3)               | 62 | 1 (0, 2)  | 459 | 1 (0, 1)   | -2.405 | 0.016  |
| Intensive care admission      |    |           |     |            |        |        |
| n (%)                         | 62 | 2 (3.2)   | 459 | 2 (0.4)    | NA**   | 0.070† |
| median (Q1, Q3)               | 62 | 0 (0, 0)  | 459 | 0 (0, 0)   | -2.385 | 0.017  |

AQLQ, asthma quality of life questionnaire; ACT, asthma control test; BDP, beclomethasone dipropionate; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting  $\beta$  agonist; LAMA, long-acting muscarinic antagonist; LLN, lower limit of normal; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; Pre, pre-bronchodilator; SABA, short-acting  $\beta$  agonist; SD, standard deviation; Q1, first quartile; Q3, third quartile.

‡n1 and n2 represent the total number of people actually assessed for each characteristic in the elderly and non-elderly groups, respectively.

§Data are transformed to normal distribution.

‡‡Percentages calculated on non-missing data.

# The severity of asthma classified as mild, moderate and severe was defined based on the GINA guidelines.

\* $\Delta\text{FEV}_1/\text{FVC}, \% = (\text{Pre-FEV}_1/\text{FVC} - \text{FEV}_1/\text{FVC}_{\text{LLN}}) / \text{Pre-FEV}_1/\text{FVC} \times 100\%$

※ACT levels were graded using the ACT total score: ‘poorly controlled’ (score < 16), ‘somewhat controlled’ (score 16-19), and ‘controlled’ (score  $\geq$  20).

\*\*NA: not available.

†Fisher’s exact probabilities.

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| Treatable traits                                  | Elderly<br>(n=62)   |      | Non-elderly<br>(n=459) |      |              |         |
|---------------------------------------------------|---------------------|------|------------------------|------|--------------|---------|
|                                                   | Expressed/Assessed* | %    | Expressed/Assessed*    | %    | $t/\chi^2/Z$ | P-value |
| Pulmonary traits                                  |                     |      |                        |      |              |         |
| Fixed airflow limitation                          | 44/60               | 73.3 | 173/422                | 41.0 | 22.194       | < 0.001 |
| Bronchodilator reversibility                      | 28/61               | 45.9 | 193/421                | 45.8 | 0.000        | 0.993   |
| Small airway dysfunction                          | 41/62               | 67.2 | 292/459                | 64.9 | 0.128        | 0.721   |
| Eosinophilic inflammation                         | 30/62               | 48.4 | 321/459                | 70.0 | 11.537       | 0.001   |
| T2 inflammation                                   | 20/62               | 32.3 | 306/453                | 67.5 | 29.239       | < 0.001 |
| Neutrophilic inflammation                         | 14/35               | 40.0 | 62/270                 | 23.0 | 4.807        | 0.028   |
| Bronchial hyperresponsiveness                     | 23/26               | 88.5 | 234/248                | 94.4 | 0.574        | 0.449   |
| Emphysema                                         | 5/62                | 8.1  | 6/459                  | 1.3  | 9.020        | 0.003   |
| Bronchiectasis                                    | 0/62                | 0.0  | 25/460                 | 5.4  | 2.455        | 0.117   |
| Exacerbation prone                                | 6/62                | 9.7  | 23/459                 | 5.0  | 1.462        | 0.227   |
| Cough                                             | 18/61               | 29.5 | 143/444                | 32.2 | 0.180        | 0.671   |
| Upper respiratory infection induced asthma attack | 47/62               | 75.8 | 339/458                | 74.0 | 0.091        | 0.762   |
| Extrapulmonary traits                             |                     |      |                        |      |              |         |
| Rhinitis                                          | 19/62               | 30.6 | 258/458                | 56.3 | 14.474       | < 0.001 |
| Rhinosinusitis                                    | 1/62                | 1.6  | 18/459                 | 3.9  | 0.302        | 0.583   |
| Nasal polyps                                      | 2/62                | 3.2  | 40/458                 | 8.7  | 2.231        | 0.135   |
| Vocal cord dysfunction                            | 0/62                | 0.0  | 1/457                  | 0.2  | NA**         | 1.000†  |
| Obstructive sleep apnea                           | 0/62                | 0.0  | 5/458                  | 1.1  | NA**         | 1.000†  |
| Gastroesophageal reflux disease                   | 2/62                | 3.2  | 32/457                 | 7.0  | 0.730        | 0.393   |
| Cardiovascular disease                            | 11/62               | 17.7 | 24/459                 | 5.2  | 11.724       | 0.001   |

|                                                                                                                                                                                                     |       |      |         |      |        |         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|------|---------|------|--------|---------|
| Systemic inflammation                                                                                                                                                                               | 8/62  | 12.9 | 43/451  | 9.5  | 0.691  | 0.406   |
| Osteoporosis                                                                                                                                                                                        | 8/62  | 12.9 | 19/458  | 4.1  | 6.817  | 0.009   |
| Eczema                                                                                                                                                                                              | 4/62  | 6.5  | 95/458  | 20.7 | 7.235  | 0.007   |
| Allergen sensitization                                                                                                                                                                              | 21/57 | 36.8 | 240/400 | 60.0 | 10.923 | 0.001   |
| Obesity                                                                                                                                                                                             | 8/62  | 12.9 | 50/459  | 10.9 | 0.223  | 0.637   |
| Underweight                                                                                                                                                                                         | 2/62  | 3.2  | 35/459  | 7.6  | 1.005  | 0.316   |
| Anemia                                                                                                                                                                                              | 3/62  | 4.8  | 3/452   | 0.7  | 5.000  | 0.025   |
| Cachexia                                                                                                                                                                                            | 9/43  | 20.9 | 116/395 | 29.3 | 1.301  | 0.254   |
| Impaired fasting glucose                                                                                                                                                                            | 6/39  | 15.4 | 6/298   | 2.0  | 14.272 | < 0.001 |
| Diabetes                                                                                                                                                                                            | 5/62  | 8.1  | 11/457  | 2.4  | 4.108  | 0.043   |
| Dyslipidemia                                                                                                                                                                                        | 29/40 | 72.5 | 124/299 | 41.5 | 13.717 | < 0.001 |
| Behavioral/psychosocial traits                                                                                                                                                                      |       |      |         |      |        |         |
| Smoking                                                                                                                                                                                             | 8/61  | 12.9 | 41/458  | 9.0  | 0.999  | 0.318   |
| Psychiatric disease                                                                                                                                                                                 | 1/62  | 1.6  | 68/459  | 14.8 | 8.286  | 0.004   |
| Anxiety                                                                                                                                                                                             | 0/62  | 0.0  | 40/459  | 8.7  | 4.687  | 0.030   |
| Depression                                                                                                                                                                                          | 1/62  | 1.6  | 48/459  | 10.0 | 4.706  | 0.030   |
| Inhaler device polypharmacy                                                                                                                                                                         | 5/62  | 8.1  | 40/459  | 8.7  | 0.029  | 0.864   |
| Poor medication adherence                                                                                                                                                                           | 14/50 | 28.0 | 125/390 | 32.1 | 0.337  | 0.562   |
| Low socioeconomic status                                                                                                                                                                            | 33/60 | 55.0 | 126/406 | 31.0 | -3.651 | < 0.001 |
| Aspirin sensitivity                                                                                                                                                                                 | 2/62  | 3.2  | 7/458   | 1.5  | 0.196  | 0.658   |
| Food allergy                                                                                                                                                                                        | 9/62  | 14.5 | 114/458 | 24.9 | 3.255  | 0.071   |
| * Expressed/Assessed represent the ratio of the number of people who expressed each treatable trait by age group (elderly and non-elderly) to the number of people actually assessed in that group. |       |      |         |      |        |         |
| **NA: not available                                                                                                                                                                                 |       |      |         |      |        |         |
| †Fisher's exact probability.                                                                                                                                                                        |       |      |         |      |        |         |

| Table 4. Predicting exacerbations over the follow-up period in participants with asthma (elderly and non-elderly, combined) |                  |       |       |         |                |       |       |         |
|-----------------------------------------------------------------------------------------------------------------------------|------------------|-------|-------|---------|----------------|-------|-------|---------|
|                                                                                                                             | Unadjusted model |       |       |         | Adjusted model |       |       |         |
| Treatable traits                                                                                                            | IRR              | 95%CI |       | P-value | IRR            | 95%CI |       | P-value |
| Total number of traits present                                                                                              | 1.136            | 1.076 | 1.200 | < 0.001 | -              | -     | -     | -       |
| Pulmonary traits                                                                                                            |                  |       |       |         |                |       |       |         |
| Fixed airflow limitation                                                                                                    | 1.024            | 0.784 | 1.337 | 0.863   | 1.010          | 0.743 | 1.372 | 0.949   |
| Bronchodilator variability                                                                                                  | 0.796            | 0.607 | 1.043 | 0.098   | 0.792          | 0.604 | 1.038 | 0.091   |
| Small airway dysfunction                                                                                                    | 0.979            | 0.746 | 1.285 | 0.879   | 0.973          | 0.740 | 1.280 | 0.844   |
| Eosinophilic inflammation                                                                                                   | 0.688            | 0.526 | 0.901 | 0.007   | 0.689          | 0.526 | 0.903 | 0.007   |
| T2 inflammation                                                                                                             | 0.736            | 0.563 | 0.962 | 0.025   | 0.730          | 0.555 | 0.959 | 0.024   |
| Neutrophilic inflammation                                                                                                   | 1.385            | 0.952 | 2.015 | 0.089   | 1.399          | 0.958 | 2.045 | 0.083   |
| Bronchial hyperresponsiveness                                                                                               | 0.704            | 0.360 | 1.377 | 0.306   | 0.813          | 0.412 | 1.602 | 0.549   |
| Emphysema                                                                                                                   | 0.588            | 0.212 | 1.632 | 0.308   | 0.553          | 0.197 | 1.551 | 0.260   |
| Bronchiectasis                                                                                                              | 1.397            | 0.784 | 2.489 | 0.256   | 1.341          | 0.749 | 2.399 | 0.324   |
| Exacerbation prone                                                                                                          | 3.251            | 2.026 | 5.217 | < 0.001 | 3.263          | 2.031 | 5.240 | < 0.001 |
| Cough                                                                                                                       | 1.146            | 0.866 | 1.517 | 0.341   | 1.120          | 0.847 | 1.482 | 0.426   |
| Upper respiratory infection-induced asthma attack                                                                           | 2.066            | 1.482 | 2.880 | < 0.001 | 2.073          | 1.484 | 2.897 | < 0.001 |
| Total number of pulmonary traits present                                                                                    | 1.143            | 1.049 | 1.247 | 0.002   | -              | -     | -     | -       |
| Extrapulmonary traits                                                                                                       |                  |       |       |         |                |       |       |         |
| Rhinitis                                                                                                                    | 0.955            | 0.735 | 1.241 | 0.731   | 1.011          | 0.777 | 1.317 | 0.933   |
| Rhinosinusitis                                                                                                              | 1.161            | 0.610 | 2.210 | 0.649   | 1.158          | 0.604 | 2.223 | 0.659   |
| Nasal polyps                                                                                                                | 1.411            | 0.925 | 2.154 | 0.110   | 1.427          | 0.933 | 2.182 | 0.101   |
| Vocal cord dysfunction                                                                                                      | -                | -     | -     | -       | -              | -     | -     | -       |
| Obstructive sleep apnea                                                                                                     | 0.592            | 0.141 | 2.492 | 0.475   | 0.576          | 0.136 | 2.435 | 0.454   |
| Gastroesophageal reflux disease                                                                                             | 0.961            | 0.562 | 1.643 | 0.884   | 0.929          | 0.543 | 1.590 | 0.787   |
| Cardiovascular disease                                                                                                      | 2.347            | 1.484 | 3.712 | < 0.001 | 2.623          | 1.599 | 4.302 | < 0.001 |
| Systemic inflammation                                                                                                       | 0.816            | 0.516 | 1.291 | 0.386   | 0.791          | 0.496 | 1.261 | 0.323   |
| Osteoporosis                                                                                                                | 0.991            | 0.533 | 1.841 | 0.977   | 0.931          | 0.493 | 1.756 | 0.824   |
| Eczema                                                                                                                      | 0.934            | 0.670 | 1.302 | 0.687   | 0.908          | 0.648 | 1.272 | 0.575   |
| Allergen sensitization                                                                                                      | 0.93             | 0.70  | 1.24  | 0.658   | 0.87           | 0.65  | 1.17  | 0.378   |

|                                                                                                                    |           |           |           |            |           |           |           |            |
|--------------------------------------------------------------------------------------------------------------------|-----------|-----------|-----------|------------|-----------|-----------|-----------|------------|
|                                                                                                                    | 8         | 5         | 7         |            | 8         | 8         | 2         |            |
| Obesity                                                                                                            | 1.23<br>0 | 0.82<br>4 | 1.83<br>5 | 0.312      | 1.22<br>3 | 0.81<br>7 | 1.83<br>1 | 0.329      |
| Underweight                                                                                                        | 1.51<br>2 | 0.94<br>6 | 2.41<br>8 | 0.084      | 1.53<br>7 | 0.94<br>6 | 2.49<br>9 | 0.083      |
| Anemia                                                                                                             | 1.47<br>5 | 0.98<br>8 | 2.20<br>1 | 0.057      | 1.51<br>0 | 0.99<br>9 | 2.28<br>3 | 0.051      |
| Cachexia                                                                                                           | 1.93<br>4 | 1.38<br>8 | 2.69<br>6 | <<br>0.001 | 1.83<br>9 | 1.29<br>5 | 2.61<br>1 | 0.001      |
| Impaired fasting glucose                                                                                           | 0.35<br>6 | 0.09<br>7 | 1.30<br>7 | 0.120      | 0.34<br>7 | 0.09<br>3 | 1.29<br>7 | 0.115      |
| Diabetes                                                                                                           | 2.43<br>4 | 1.28<br>8 | 4.60<br>0 | 0.006      | 2.48<br>4 | 1.29<br>4 | 4.76<br>9 | 0.006      |
| Dyslipidemia                                                                                                       | 1.02<br>4 | 0.73<br>0 | 1.43<br>7 | 0.889      | 0.96<br>3 | 0.66<br>3 | 1.39<br>9 | 0.843      |
| Total number of extrapulmonary traits present                                                                      | 1.09<br>2 | 0.99<br>5 | 1.20<br>0 | 0.064      | -         | -         | -         | -          |
| Behavioral/psychosocial traits                                                                                     |           |           |           |            |           |           |           |            |
| Smoking                                                                                                            | 0.67<br>3 | 0.41<br>6 | 1.08<br>9 | 0.107      | 0.64<br>9 | 0.39<br>0 | 1.08<br>1 | 0.096      |
| Psychiatric disease                                                                                                | 2.23<br>2 | 1.56<br>3 | 3.18<br>6 | <<br>0.001 | 2.28<br>5 | 1.59<br>5 | 3.27<br>3 | <<br>0.001 |
| Anxiety                                                                                                            | 1.64<br>1 | 1.02<br>2 | 2.63<br>6 | 0.041      | 1.66<br>8 | 1.03<br>6 | 2.68<br>8 | 0.035      |
| Depression                                                                                                         | 2.34<br>3 | 1.55<br>8 | 3.52<br>4 | <<br>0.001 | 2.36<br>8 | 1.57<br>2 | 3.56<br>7 | <<br>0.001 |
| Inhaler device polypharmacy                                                                                        | 1.52<br>7 | 1.00<br>6 | 2.31<br>9 | 0.047      | 1.58<br>8 | 1.03<br>4 | 2.43<br>9 | 0.035      |
| Poor medication adherence                                                                                          | 0.82<br>9 | 0.61<br>4 | 1.11<br>9 | 0.221      | 0.81<br>7 | 0.60<br>4 | 1.10<br>5 | 0.190      |
| Low socioeconomic status                                                                                           | 1.29<br>8 | 0.97<br>4 | 1.72<br>9 | 0.075      | 1.30<br>5 | 0.96<br>8 | 1.76<br>0 | 0.080      |
| Aspirin sensitivity                                                                                                | 1.12<br>1 | 0.37<br>4 | 3.36<br>2 | 0.838      | 1.11<br>6 | 0.37<br>0 | 3.36<br>1 | 0.846      |
| Food allergy                                                                                                       | 1.54<br>4 | 1.14<br>7 | 2.07<br>9 | 0.004      | 1.57<br>9 | 1.16<br>5 | 2.14<br>0 | 0.003      |
| Total number of behavioral/psychosocial traits present                                                             | 1.14<br>9 | 1.03<br>2 | 1.28<br>0 | 0.012      | -         | -         | -         | -          |
| The “adjusted” model included adjustment only for age and sex. CI, confidence interval; IRR, incidence rate ratio. |           |           |           |            |           |           |           |            |

Table 5. Independent predictors of future exacerbation risk in participants with asthma (elderly and non-elderly, combined)

| Variable                                          | Prediction model      |                      |                  |
|---------------------------------------------------|-----------------------|----------------------|------------------|
|                                                   | Odds ratio (95% CI)   | $\beta$ coefficients | <i>P</i> -value* |
| Exacerbation prone                                | 5.497 (2.008, 17.006) | 1.7041               | 0.002            |
| Psychiatric disease#                              | 2.613 (1.211, 5.704)  | 0.9605               | 0.014            |
| Cardiovascular disease                            | 2.494 (0.976, 6.440)  | 0.9139               | 0.050            |
| Upper respiratory infection-induced asthma attack | 2.880 (1.549, 5.649)  | 1.0579               | 0.001            |
| Non-eosinophilic inflammation                     | 1.482 (0.869, 2.522)  | 0.3934               | 0.140            |
| Cachexia                                          | 1.882 (1.086, 3.260)  | 0.6323               | 0.024            |
| Food allergy                                      | 1.589 (0.879, 3.263)  | 0.4630               | 0.122            |
| ACT poorly controlled##                           | 2.039 (1.064, 3.910)  | 0.7125               | 0.032            |

\*The least absolute shrinkage and selection operator (LASSO) method was used to evaluate and screen the most important independent predictors of future asthma exacerbation. These independent predictors were then included in a final multivariate logistic regression.

#Psychiatric disease includes anxiety and/or depression.

##The 'ACT' variables are dummy variables, with the controlled level group serving as the reference category.

ACT, asthma control test; CI, confidence interval.

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**FIGURE LEGENDS**

**Figure 1.** Flowchart of the cohort included in this study.

**Figure 2.** Asthma future exacerbation nomogram. The asthma future exacerbation nomogram was developed based on the established multivariable regression models in the whole cohort population (elderly and non-elderly, combined). Using the nomogram, the probability of future asthma exacerbation in the following year can be estimated as follows. First, the judgment on predictor variables (e.g., yes or no, somewhat controlled or poorly controlled) can be obtained from patients. Second, if a predictor is judged as “Yes,” the value of the predictor can be designated by drawing an upward straight line from “Yes” up to the ‘Points’ line. Third, add up the points of all the predictors assessed as “Yes” to get the total points. Finally, the probability of future asthma exacerbation in the following year can be obtained by drawing a straight line from the “Total Points line” down to the “Risk of exacerbation in the following year” line. ACT, asthma control test; URI, upper respiratory infection-induced asthma attack; Non-eos, non-eosinophilic inflammation.

**Figure 3.** Receiver operating characteristic (ROC) curve of the prediction model. The x-axis specificity represents the true negative rate. The y-axis sensitivity represents the true positive rate. The area under the curve (AUC) and the 95% confidence interval (CI) are shown in the graph.

