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Asthma is associated with frailty among community-dwelling adults: the GAZEL cohort

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ABSTRACT

Introduction Early management of chronic respiratory diseases (CRDs) and frailty have been identified as key targets towards healthy ageing, but the association between CRDs and frailty has been poorly investigated. We studied the association between asthma and frailty in adults of the GAZEL cohort using different definitions of asthma over the 26 years of follow-up.

Methods Current asthma definitions are based on yearly self-reports of symptoms or medication (in 2015, constant reports or at least one report between 1990 and 2015), or on a detailed respiratory symptoms questionnaire in 2002. Frailty definition is based on weakness, fatigue, unintentional weight loss, low physical activity and mobility in 2015. Frail participants had three criteria or more, pre-frail 1 or 2, and robust 0. Multinomial regression models adjusted for age, sex, body mass index, smoking, education, marital status and comorbidities were performed.

Results In 2015, 12 345 adults (73% men, 61 to 77 years old) were included: 3% of them reported current asthma, 1.6% had constant reports during the follow-up and 9% reported current asthma at least once. In 2015, 6% were frail, 34% pre-frail and 13% of current asthmatics and 6% of non-asthmatics were frail (adjusted OR (aOR) 2.19 (1.44 to 3.34)). Significant associations were also found with the 2002 definition (aOR 2.24 (1.73 to 2.90)), constant reports (aOR 3.67 (1.70 to 7.93)) or at least once (aOR 1.50 (1.15 to 1.98)). Current asthma was also associated with pre-frailty with the 2002 definition (aOR 1.46 (1.26 to 1.68)).

Discussion Participants with asthma had increased risk of frailty. A better understanding of their relationship could help to define and evaluate strategies for a better ageing of asthmatics.

Key messages

- The link between chronic respiratory diseases and frailty had not been extensively studied yet; this study assessed for the first time the association between frailty and asthma among community-dwelling participants.
- Among 12 345 community-dwelling adults of the GAZEL cohort, current asthmatics had increased risk of frailty, regardless of the questions used to assess current asthma.
- The present study adds new knowledge on the determinants of frailty and highlights that, as the population is ageing worldwide, early asthma management might be key for healthy ageing.

INTRODUCTION

As the population is ageing worldwide,[1] the efforts to support an older population in Western countries have become a real societal challenge and will be a central topic for emerging countries in a few decades.[2] To address this challenge, WHO's work on ageing focuses on a multidimensional approach, 'healthy ageing',[3] which aims to promote active and independent life while ageing.

Frailty can be viewed as an indicator of biological ageing.[4 5] It identifies individuals with decreased physiological resources and resistance to stressors, who may be prone to adverse health situations[6]: falls, hospitalisation, institutionalisation, increased cost of cares, lower quality of life and increased risk of death. The understanding of frailty determinants may allow a better insight into healthy ageing, and non-communicable diseases such as cardiovascular, kidney diseases and depression have already been linked to frailty.[7–9] The simultaneous presence of several of these chronic diseases, that is, multimorbidity, is a clinical situation that increases with age[10] and is associated with frailty.[11] The prevention and early management of non-communicable diseases have been identified as key targets towards healthy longevity and chronic respiratory diseases (CRDs) as good pilot to assess this action plan.[12] However, links between CRDs and frailty had not been extensively studied yet.

Chronic obstructive pulmonary disease (COPD) is one of the two major preventable CRDs along with asthma; together they affect 572 million persons worldwide in 2017.[13] Regarding frailty, COPD is the most frequently studied CRDs. In a recent

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meta-analysis, Marengoni *et al* pointed out that individuals with COPD had a twofold increased risk of frailty.[14] Moreover, old people with COPD and frailty had a poorer survival than any other combination of frailty and COPD.[15] Frail patients with COPD also reported a poorer quality of life suggesting that their health situation considerably impairs their everyday life.[16] To the best of our knowledge, only one study has reported a positive and significant association between asthma and frailty among other self-reported long-term conditions in middle-aged people.[17] Overall, it is likely that older age, asthma and frailty are intertwined.

We hypothesised that asthmatic individuals may be more prone to develop frailty while ageing. In a generalist cohort of 12 345 participants followed for 26 years, we aimed to assess the relationship between asthma and frailty, and test the robustness of the association using different definitions of asthma.

METHOD

Study design

Data used for the analyses were collected in the framework of the GAZEL cohort (Electricité de France—Gaz de France, EDF-GDF, http://www.gazel.inserm.fr/en), a French cohort of community-dwelling adults. The protocol and descriptive characteristics have been described previously[18] and in online supplementary appendix. Every year, since 1989, participants have been invited to complete a postal questionnaire.

Participants included in the analyses were those with available data on asthma and frailty in 2015 (see online supplementary appendix).

Definitions of asthma

From 1990 to 2015, participants were asked to indicate the diseases they had suffered during the past 12 months, including asthma: "*Here is a list of health problems. Indicate here those of which you suffer or have suffered during the last 12 months", "Among the health problems you have indicated here, what are the 'new' problems?*", "*What are the health problems, new or not, for which you are currently receiving a treatment?*". Participants who indicated asthma were defined as having current asthma. Those who did not indicate asthma were considered as not having current asthma. Based on this information, we defined "current asthma in 2015" and "at least one current asthma report" from 1990 to 2015.

We also defined current asthma in 2002 using respiratory health questions from the standardised and validated questionnaire of the Epidemiological Study on the Genetics and Environment of Asthma.[19] Participants were considered as having 'current asthma' if they answered positively to one of the following questions: '"*Have you had an asthma attack in the last 12 months?*", "*Have you had wheezing in the chest, at any moment, in the last 12 months?*", "*Have you been woken up with difficulty breathing in the last 12 months?*", "*Have you been woken up with a breathlessness in the last 12 months?*" or "*Are you currently taking any asthma medications? (including inhaled medicine, aerosol, pills…)*". Participants who answered negatively to all of these questions were considered as not having current asthma in 2002.

We defined participants with or without 'constant current asthma reports' as follows: participants who constantly reported current asthma during the follow-up, and those who never reported current asthma from 1990 to 2015 nor reported asthma symptoms or medication in 2002. Participants with inconsistent current asthma reports or participants without report of current asthma during the follow-up but reporting asthma symptoms or medication in 2002 were excluded from the definition.

Definition of frailty

Frailty was assessed in 2015 as closely as possible to the definition proposed by Fried and colleagues in 2001.[20] The five criteria, namely weakness, slowness, low physical activity, exhaustion, and unintentional weight loss, were assessed by questionnaire. The unintentional weight loss and exhaustion criteria were assessed according to the original definition, whereas the three other criteria were adapted to be assessed by questionnaire as previously done and validated in other epidemiological studies.[21]

Unintentional weight loss was assessed as a declaration of unintentional loss of at least 4.5 kg ("*Have you unintentionally lost weight in the last 12 months, outside of a diet? If yes, how many kilograms?*") or a variation of more than 5% of actual weight. Fatigue was assessed using self-reported exhaustion identified by two questions from the Center for Epidemiological Studies Depression scale ("*How often in the last week did you feel this way?: (1) I felt that everything I did was an effort and (2) I could not get going*"). Weakness was assessed as self-reported difficulty in carrying 5 kg or lifting a grocery bag ("*Do you find it difficult to carry a 5 kg bag like a large shopping bag without help?*") and/or difficulty in kneeling and standing up ("*Do you have difficulty kneeling and standing up without help?*"). Slowness was assessed as self-reported difficulty in walking 500 m ("*Can you walk 500 metres alone, without stopping (with or without sticks, crutches, etc)?*") and/or difficulties in climbing stairs without help ("*Are you able to climb up or down a flight of stairs alone?*"). Low physical activity level was assessed using self-reported weekly activity. Participants were considered as having low level of physical activity if they did not report walking at least 10 min 5 days a week ("*In a usual week, how many days do you walk at least 10 min?*") and did not practise more intense activities such as bike ("*In a usual week, how many days are you cycling for at least 10 min?*") or sport at least once a week ("*In a usual week, how many days do you exercise (jogging, fitness, swimming, mountain biking, etc.) for at least 10 min continuously?*"). Frailty status was defined based on the total number of impaired criteria. Frail participants had three impaired criteria or more, pre-frail 1 or 2, and robust 0.

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Statistical methods

Population characteristics were described by number and percentage for categorical variables and by mean and SD for continuous variables. We used t-test for continuous variables and χ^2 test for categorical variables. We performed multinomial regression models to investigate the associations between asthma and frailty by using the R-VGAM package (V.1.0-6). Robust participants were considered as the reference group.

As body mass index (BMI) may modify the association between asthma and frailty, we formally tested the interaction between BMI expressed as categories (normal: 18.5–25 kg/m², overweight: 25 kg/m² to 30 kg/m² and obese: ≥30 kg/m²) and asthma. The 128 participants (1.0%) with a BMI <18.5 kg/m² in 2015 were not included in this analysis. The interaction between BMI and asthma was not significant (p>0.10) (see online supplementary appendix table A1). Age (continuous), sex, BMI (continuous), education, marital status and tobacco consumption were considered as confounders in the regression models. Models were then further adjusted for the presence of comorbidities: diabetes, joint pain, cancer, cardiac diseases and mental status. Cancer and cardiovascular diseases were assessed using validated registers.[22 23] Joint pain, diabetes and psychological problems were assessed using self-reported information in the 2013, 2014 and 2015 questionnaires (at least one occurrence over the 3 years).

To further test the robustness of the association between current asthma and frailty, we performed sensitivity analyses. First, for 2015 current asthmatics, we assessed the use of asthma-related drug among drugs for obstructive airway disease (code R03 of the Anatomical Therapeutic Chemical classification). R03 medication reimbursements were collected over a period of 1 year prior to the response to the 2015 questionnaire, from the French National Health Insurance database. We excluded current asthmatics who did not appear in the claim database (n=83) or took a treatment that may be related to COPD (n=8). We then tested the association between frailty and 'current asthma in 2015 confirmed by drug database'. Second, we modified the definition of the non-asthmatic category in the 'constant current asthma reports' definition by including participants with inconsistent current asthma reports in the non-asthmatic category.

All the statistical analyses were performed using R statistical software (V.3.4.4).

RESULTS

Our study population consisted of 12 345 participants with a mean follow-up of 24±4.1 years. They were younger and more likely to be men than those not included in the analyses (see online supplementary appendix). The two groups did not differ for any other characteristics.

Table 1 shows the characteristics of the 12 345 participants. They were more often men and living in couple. Their mean age and BMI were 69.8±3.5 years and 26.1±3.9 kg/m², and 49% of them were former smokers. The most commonly reported condition was joint pain. In 2015, 372 (3%) participants reported current asthma. They were more likely to have obesity or mood disorder compared with non-asthmatic individuals (p<0.0001). Differences in the prevalence of obesity and mood disorders between asthmatics and non-asthmatics were also observed after stratification according to frailty status (see online supplementary appendix table A3).

In 2002, information on respiratory symptoms was available for 8 016 participants (65%); 18% were asthmatics (see online supplementary appendix table A2). Constant current asthma reports definition was available for 6 309 participants (51%), and 1.6% of them had constant reports of current asthma. During the 26-year follow-up, 1 165 (9.4%) participants reported asthma at least once. Among them, the median number of asthma reports was 3, and 240 (21%) reported current asthma more than 10 times during the follow-up.

Among all participants, 6% (n=706) were considered as frail, 34% (n=4 258) were pre-fail and 60% (n=7 381) were robust. Frailty prevalence was 4% for men and 10% for women, and pre-frailty prevalence was 33% for men and 37% for women. The prevalence of frailty was higher in the asthmatic group compared with the non-asthmatic group, whatever the definition of current asthma (see figure 1). In 2015, 13% of participants with current asthma were frail versus 5.5% of non-asthmatics. These proportions were similar with current asthma symptoms in 2002 (11% vs 5%), and when considering the 'constant current asthma reports' definition (16% vs 4.4%), or the 'at least one report of current asthma' definition (10% vs 5.3%). The prevalence of pre-frailty was also higher in the asthmatic group compared with the non-asthmatic group whatever the asthma definition (38% vs 34% for current asthma in 2015, 42% vs 33% for current asthma symptoms in 2002, 38% vs 33% for constant current asthma reports, and 37% vs 34% for 'at least one report of current asthma' definition, all p<0.05).

Associations between current asthma and frailty

Positive and significant associations between asthma and frailty were observed (table 2). Participants who reported current asthma in 2015 had increased risk of being frail (adjusted OR (aOR) 2.19 (1.44 to 3.34)) as those who reported asthma symptoms or medication in 2002 (aOR 2.24 (1.73 to 2.90)).

The aOR was the strongest when the definition of 'constant current asthma reports' was used and the weakest when the 'at least one current asthma report' definition was used. All models showed significant positive association between asthma and pre-frailty before adjustment. After adjustment, the strength of the association decreased and remained significant only with the 'current asthma in 2002' definition (aOR 1.46 (1.26 to 1.68)).

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Table 1 Characteristics of the participants in 2015

	All participants (n=12 345)	Participants without current asthma in 2015 (n=11 973)	Participants with current asthma in 2015 (n=372)	P value*
Age, years, mean±SD	69.8 (±3.5)	69.8 (±3.5)	69.8 (±3.5)	0.93
Sex, n (%)				
Female	3 238 (26)	3 116 (26)	122 (33)	<0.01
Marital status, n (%)				
Living alone	2 186 (18)	2 114 (18)	72 (20)	0.42
Education, n (%)				
<High school	2 412 (20)	2 344 (20)	68 (19)	0.85
High school	7 156 (59)	6 940 (59)	216 (60)	
University and other	2 564 (21)	2 485 (21)	79 (22)	
Body mass index (BMI), kg/m², mean±SD	26.1±3.9	26.1±3.8	26.9±4.9	<0.01
Obese (BMI ≥30 kg/m²), N (%)	1 702 (14)	1 616 (14)	86 (23)	<0.001
Current tobacco consumption, n (%)				
Non-smoker	4 617 (44)	4 475 (44)	142 (46)	0.84
Current smoker	778 (7)	755 (7)	23 (7)	
Former smoker	5 113 (49)	4 966 (49)	147 (47)	
Frailty, n (%)				
Robust	7 381 (60)	7 198 (60)	183 (49)	<0.001
Pre-frail	4 258 (34)	4 116 (34)	142 (38)	
Frail	706 (6)	659 (6)	47 (13)	
Asthma, n (%)				
Current asthma in 2015	372 (3)	–	–	
Current asthma in 2002	1 456 (18)	1 241	215	
Constant reports	103 (1.6)	0	103	
At least one	1 165 (9)	793	372	
Confirmed by drug database	281 (2.3)	0	281	
Sensibility	154 (1.3)	0	154	
Mood, n (%)				
Depressed, stressed or anxious	2 400 (19)	2 293 (19)	107 (29)	<0.001
Other chronic diseases, N (%)				
Heart diseases	853 (7)	832 (7)	21 (6)	0.35
Diabetes	1 385 (11)	1 329 (11)	56 (15)	0.02
Joint pain	5 305 (43)	5 113 (43)	192 (52)	<0.001
Cancer	1 530 (13)	1 477 (13)	53 (15)	0.36

Sensibility definition: participants who constantly reported current asthma, or only once, in 2015, were considered as having current asthma; otherwise they were considered as not having current asthma.
*P value of t-test for continuous variables and χ^2 test for categorical variables.

Performing the analyses among those with 'current asthma in 2015 confirmed by drug database' or using another definition of non-asthmatics in the 'constant current asthma reports' definition did not change the conclusions (table 2).

Among those with current asthma in 2015, a trend between duration since first asthma declaration and risk of frailty was observed independently of age and sex (aOR 2.44 (1.37 to 4.34), aOR 2.54 (1.29 to 5.02) and aOR 2.79 (1.69 to 4.63) for participants with less than 10 years, 10 to 19 years and 20 years or more since the first declaration of asthma (terciles), compared with non-asthmatics).

Slowness was the frailty criterion the most associated with frailty (see online supplementary appendix table A4).

DISCUSSION

Main findings

In the present study, we assessed the association between asthma and frailty using four definitions of current

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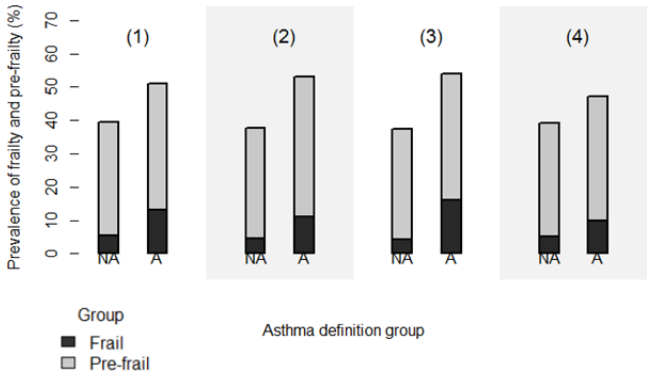

Figure 1 Prevalence of frailty and pre-frailty among non-asthmatics (NA) and asthmatics (A) according to asthma definition legend. 1, current asthma in 2015 (A: n=372; NA: n=11 973); 2, current asthma symptoms in 2002 (A: n=1 456; NA: n=6 560); 3, constant current asthma reports (A: n=103; NA: n=6 206); 4, at least one asthma report (A: n=1 165; NA: n=11 180).

asthma among 12 345 community-dwelling adults of the GAZEL cohort. Participants with current asthma had increased risk of frailty compared with those without current asthma, regardless of the definition of asthma. Pre-frailty was also observed more frequently among participants with current asthma.

Strengths, limitations and comparison with the literature

The present study analyses benefited from the large amount of data carried by the GAZEL cohort. The long follow-up allowed tracing asthma history of participants during a large part of their adulthood, although we did not have information about asthma in childhood. The prevalence of current asthma reported in our study is close to the ones previously reported in the literature.[24]

We acknowledge that the definition of current asthma was not based on a set of standardised questions, probably leading to declaration and misclassification bias[25] and under-evaluation[26] of the true prevalence of current asthma. But it is interesting to note that 98% of the participants who reported having current asthma in 2002 also reported having symptoms of asthma or medication the same year, suggesting the reliability of annual asthma reports. Furthermore, several definitions of asthma were used to ascertain and challenge the association with frailty. Performing analyses with different definitions and therefore on samples of different size raises the question of selection bias. However, all analyses consistently led to the same conclusion, showing the robustness of the results whatever the definition used.

The associations we found were close to that of the only other study, to our knowledge, reporting an association

Table 2 Associations between current asthma and pre-frailty/frailty

Asthma definition		N	OR of pre-frailty (95% CI)	N	OR of frailty (95% CI)
Current asthma in 2015	Crude	11 639	1.36 (1.09 to 1.70)	8 087	2.81 (2.02 to 3.90)
	M2	9 406	1.33 (1.03 to 1.72)	6 561	2.47 (1.66 to 3.68)
	M3	9 303	1.26 (0.97 to 1.64)	6 493	2.19 (1.44 to 3.34)
Current asthma in 2002	Crude	7 552	1.74 (1.54 to 1.96)	5 262	3.21 (2.61 to 3.95)
	M2	6 204	1.62 (1.41 to 1.86)	4 335	2.81 (2.20 to 3.59)
	M3	6 139	1.46 (1.26 to 1.68)	4 293	2.24 (1.73 to 2.90)
Constant report of current asthma between 1990 and 2015	Crude	6 018	1.56 (1.02 to 2.39)	4 239	4.73 (2.65 to 8.43)
	M2	4 971	1.55 (0.94 to 2.55)	3 511	3.98 (1.92 to 8.25)
	M3	4 924	1.47 (0.89 to 2.44)	3 481	3.67 (1.70 to 7.93)
At least one report between 1990 and 2005	Crude	11 639	1.26 (1.10 to 1.43)	8 087	2.19 (1.77 to 2.72)
	M2	9 406	1.17 (1.01 to 1.36)	6 561	1.78 (1.37 to 2.31)
	M3	9 303	1.09 (0.93 to 1.27)	6 493	1.50 (1.15 to 1.98)
Confirmed by drugs database	Crude	11 558	1.32 (1.02 to 1.71)	8 033	2.91 (2.01 to 4.22)
	M2	9 343	1.26 (0.94 to 1.70)	6 520	2.45 (1.56 to 3.85)
	M3	9 240	1.15 (0.85 to 1.55)	6 452	2.00 (1.24 to 3.22)
Sensibility	Crude	11 639	1.30 (0.92 to 1.84)	8 087	2.95 (1.81 to 4.81)
	M2	9 406	1.37 (0.92 to 2.04)	6 561	2.54 (1.38 to 4.67)
	M3	9 303	1.31 (0.87 to 1.97)	6 493	2.37 (1.24 to 4.51)

Results are expressed as OR (95% CI).
Model 2 (M2): adjusted for sex, age (continuous), body mass index (continuous), education, marital status, tobacco consumption.
Model 3 (M3): further adjustment on diabetes, joint pain, cancer, cardiac diseases and mental status.
Sensibility: participants who constantly reported current asthma, or only once, in 2015, were considered as having current asthma; otherwise they were considered as not having current asthma.

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between asthma and frailty in a younger population,[17] and in the range of associations previously found between COPD and frailty.[14] We found the strongest association with 'constant current asthma reports', a more restrictive definition, probably reflecting highly contrasted groups including participants with more active or severe asthma. Moreover, this definition excluded participants for whom constant current asthma cannot be undoubtedly confirmed. Interestingly, even if the association was weaker, it remained significant in the sensitivity analysis in which the non-asthmatic category also included participants who had inconsistent current asthma reports during the follow-up. By using this definition, we classified as 'non-asthmatics' participants who were in fact more likely to be asthmatics.[25] The lowest association with frailty was found with the simplest definition ('at least one'), which considered participants as asthmatics if they reported current asthma at least once at any time during the follow-up. Apart from possible classification errors between asthmatics and non-asthmatics, this broad definition probably encompassed participants with heterogeneous clinical and physiological features of asthma than for other definitions.

In the current study, we assessed frailty phenotype using questionnaire, as previously done and validated in other epidemiological settings.[21] The prevalence we found is consistent with the review by Collard *et al*[27] which reported frailty among 5.2% of men and 9.6% of women, and pre-frailty among 37% of men and 39% of women.

Interpretation

The mechanisms linking frailty and asthma remain to be determined. Several inflammatory markers have been identified among frail individuals,[28] many of which may also be found in individuals with asthma or COPD.[29] Inflammation is one of the biological pathways suggested in the association between COPD and frailty,[14] and to date the most studied in the literature.

Asthma may also interplay with other chronic diseases associated with frailty,[30] the most frequent in the general population being obesity,[31] although its exact mechanism remains uncertain.[32] To ensure that the association between frailty and asthma was not modified by obesity status, the modifying effect of the BMI on the association between asthma and frailty was investigated in the present study. No significant interaction was observed but the small sample size of the subgroups did not allow us to perform stratified analyses.

We acknowledge that no strict conclusion can be made on the exact temporal relationship between asthma and the onset of frailty as only one assessment of frailty was available in 2015.

Future directions

The associations between asthma and frailty may increase the risk of death or negative health outcome including poor quality of life or increased number of symptoms and exacerbations. Interventions aiming to reduce frailty level or to delay its complications have been proposed. Those with the highest level of evidence involve exercises and nutrition in multicomponent interventions and holistic diseases management.[33] Overall, further research is needed to highlight the potential interest of measuring frailty among patients with asthma in clinical practice. The temporal relationship between asthma and frailty should be clarified, and the added value of studying the clinical evolution of frail asthmatics compared with non-frail asthmatics and of the screening frailty among asthmatics elderly should be determined.

CONCLUSION

In conclusion, the present study showed that participants with current asthma had increased risk of frailty whatever the definition of asthma. This result adds new knowledge on the intertwining between chronic respiratory diseases and frailty and calls for further research to reduce the burden of asthma and frailty among ageing populations.

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