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CONFLICTS OF INTERESTS

The authors report no conflicts of interest.

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Abstract

Objectives: People at risk of chronic obstructive pulmonary disease (COPD) can benefit from appropriate medical management before severe symptoms appear. This study assesses the value of the COPD Assessment Test (CAT) questionnaire for screening dairy farmers, who tend to be slow or reluctant to seek health care.

Methods: During the time period 2012-2017, 2089 randomly selected dairy farmers in Brittany (France) were invited to complete self-administered questionnaires (including the CAT) and to undergo an occupational health check-up using an electronic mini-spirometer and conventional spirometry. Those showing symptoms suggestive of COPD and/or a ratio $FEV_1/FEV_6 < 80\%$ were sent to a pulmonologist for further check-up, including spirometry with a reversibility test. Multivariate logistic models based on CAT scores and socio-demographic or work-related factors were developed to predict COPD.

Results: The 1231 farmers who underwent the occupational health check-up included 1203 who met the inclusion/exclusion criteria. Pulmonologist identified 16 (1.3%) cases of COPD. A multivariate logistic regression model (covariates: CAT sum score, on-farm time, BMI, smoking status, free-stall mulching) provided an area under the receiver-operating characteristic curve (AUC) of 0.87 (95% CI: 0.75-0.98). Using a cut-off of 0.007 gave a sensitivity of 93.8%, and a specificity of 62.4%. Another model that included CAT breathlessness and the same covariates performed marginally better (AUC = 0.88, 95% CI: 0.77-0.98).

Conclusion: Our predictive models can both benefit dairy farmers by providing early diagnosis and management of their COPD and avoid unnecessary, costly spirometry during screening process.

KEYWORDS

Chronic obstructive pulmonary disease; CAT questionnaire; screening; dairy farmers

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major public health concern that could become the fourth leading cause of death world-wide by 2030.[1] The onset of symptoms is insidious so that COPD is frequently under-diagnosed and, when diagnosed, this is often late with severe respiratory disorders.[2] Overwhelming interest in smoking as the major risk factor has overshadowed the importance of non-smoking causes,[3] such as occupational exposure (including farming activities).[4-6]

Although spirometry is the reference test for diagnosing COPD, it is not a cost-effective way to screen the general population.[7] A promising alternative is low-cost electronic mini-spirometry (EMS) measuring the FEV_1/FEV_6 ratio but its diagnostic performance depends very much on how well practitioners are trained.[8] Previous studies have suggested using self-administered questionnaires to screen for COPD.[9-11] The COPD Assessment Test (CAT) was initially developed and validated for routinely assessing and monitoring COPD patients.[12-13] It was later used to help screen for COPD in both smokers,[14-15] and the general population.[16-17] Subjects who the CAT questionnaire indicated were at risk then underwent diagnostic spirometry and appropriate medical management, if necessary, before any severe symptoms developed. However, the CAT questionnaire has not yet been used to screen farmers for COPD, who are often slow or reluctant to seek health care.

We therefore assessed the value of the CAT questionnaire for screening a large population of dairy farmers for COPD and for developing a predictive model that combines CAT scores with other COPD predictors.

2. MATERIALS AND METHODS

2.1 Study population

The AIRBAg cross-sectional study was conducted between March 2012 and February 2017 in the French region of Brittany to determine the prevalence and to identify the risk factors of COPD in dairy farmers.[18] It was carried out on 2089 dairy farmers randomly selected from the 3831 registered in the "Mutualité Sociale Agricole" (MSA, French Health Insurance for farmers) regional database. The inclusion criteria were: dairy farming for more than ten years and agreeing to participate in the study. The exclusion criteria were: pig, poultry or agricultural farming as the main activity, having a legal guardian, having had a respiratory infection in the two months immediately preceding sampling, having been treated with oral corticosteroids or immunosuppressive drugs, having been pregnant or not having had any dairy activity for more than five years (e.g. retired).

2.2 Data collection

Each randomly selected dairy farmer was invited to complete a standardized self-administered questionnaire and to undergo a health check-up with his/her local MSA occupational physician. During this check-up, the questionnaire was reviewed and a clinical examination, followed by an EMS and conventional spirometry, was performed. The first part of the questionnaire contained items pertaining to health outcomes including: chronic cough (cough > 2 months), chronic bronchitis (cough and sputum > 3 months/year for over two consecutive years) and wheezing when handling hay or during any other activity. The second part of the questionnaire collected farm and occupational characteristics such as farm size, numbers of cattle and milking cows, crops grown and daily activities (milking, production and distribution of feed concentrate, free stall mulching, etc.). CAT and the modified Medical Research Council (mMRC) scores were also assessed during this check-up. The CAT questionnaire consists of 8 items (cough, phlegm, chest tightness, breathlessness, activity limitation, confidence leaving home, sleep, energy) with scores of 0–5 for the severity of each item. These were then summed to give an overall score ranging from 0 (excellent perceived health) to 40 (worst case).

2.3 Respiratory tests performed by occupational physicians

The occupational physicians had been trained to use the EMS (Neo-6®, model 4000, Vitalograph, Ennis, Ireland) and the spirometer (SpiroWin®, FIM medical, Spl10 USB S/N:01824, Villeurbanne, France), which was followed by annual updating. Spirometry testing (without bronchodilator challenge) was performed in accordance with standard American Thoracic Society/European Respiratory Society protocol.[19] A minimum of three blows that met test quality criteria (including an expiration maintained for more than 6 s) were performed by each participant. Spirometry results were reviewed by two pulmonologists from Rennes University Hospital.

2.4 Definition of COPD and absence of bronchial obstruction

Those subjects whose health check-up revealed at least one evocative symptom (chronic cough, chronic bronchitis, wheezing, dyspnea [mMRC $\geq$ 1]) and/or a ratio $FEV_1/FEV_6 < 80\%$ with the EMS were considered to be "at-risk of bronchial obstruction". A higher cut-off was chosen for FEV_1/FEV_6 because mild forms of limited airflow can be missed using a 70% cut-off.[20] "At-risk" farmers were referred to the nearest pulmonologist for further examination, including spirometry with a reversibility test. COPD was diagnosed if the post-bronchodilator FEV_1/ forced vital capacity (FVC) ratio was < 70% (GOLD criterion).[21] The control population was farmers not "at-risk" and those "at-risk" at screening who were subsequently not found to be suffering from a chronic obstructive disease and

were assumed to be free of bronchial obstruction. Any control subject diagnosed with asthma was excluded from the current study. Asthma was ascertained after a thorough medical record review by the same trained pulmonologist by means of history of allergic disposition, episodes of paroxysmal wheezing, asthma medication use, spirometry, and/or methacholine challenge test.

2.5 Statistical analyses

A logistic regression model containing only the CAT sum score as predictor was first prepared (univariate model). Other independent COPD predictors were then selected according to a two-step strategy: i) the candidate covariates collected during the occupational health check-up (questionnaire, mMRC) were selected at $p < 0.20$ on the basis of relevant univariate tests, ii) a bootstrap method was then used to identify the best subset of independent predictors of COPD. This was done by repeated sampling with replacement from the original entire dataset, followed by stepwise logistic regression based on Akaike's Information Criterion in each of 1000 subsamples. The decision rule for selecting the predictors included in the final model is based on the frequency at which they appeared in the multiple bootstrap models (> 60 % in our study, as recommended[22]). Continuous variables were not transformed if they were found to be linear. Subjects were divided into two groups according to their body mass index (BMI): above or below 21 kg/m², as in the BODE mortality index.[23-24] The diagnostic performance of the univariate and multivariate models was assessed by measuring the area under the receiver operating characteristic curve (AUC). However, a predictive model may be too optimistic if it is tested on the same dataset as that used to develop it. We used a 1000-fold bootstrap resampling including the previously selected predictors to obtain optimism-corrected AUCs. An optimal cut-off point was determined to obtain the best sensitivity by minimizing the number of false negatives.

The second step involved building a decision tree with the predictors from the previous multivariate model using the Classification And Regression Tree (CART) method.[25] Briefly, CART uses successive iterations to divide the study sample into smaller binary subgroups. Each step investigates all possible splits among the variables to create two subgroups. The variable with the optimal threshold leading to the most homogeneous partitioning with respect to the dependent variable (COPD in the current study) is selected. The same variable can be chosen several times, based on different thresholds because all predictors are considered at each step. Decision trees are sensitive to the imbalance in the numbers of events and non-events. A weighting of misclassified subjects (false positives and negatives) was thus used to improve sensitivity. False negatives and false positives were each weighted by the inverse of the frequencies of events and non-events in the sample.

The predictive model and CART analyses were first prepared with the CAT sum score and then with each of the CAT items most strongly linked to COPD ($P < 0.05$). All statistical analyses were

performed with R software, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria, URL https://www.R-project.org/).

3. RESULTS

3.1 Population

The 1231 farmers who underwent the occupational health check-up included 28 who met an exclusion criterion (poultry farmer (5); pig farmer (5); arable farmer (1); recent treatment with antibiotics or corticosteroids (7); immunosuppressive treatment (4); no signed consent (1); incomplete questionnaire (5)), leaving 1203 for analyses (Figure 1). The occupational health check-up showed that 525 farmers were "at-risk of bronchial obstruction", of these 432 were seen by the pulmonologist. The 93 farmers who did not go to the pulmonologist included a greater proportion of smokers (23.7%), a lower FEV_1/FVC ratio (0.76) and had spent more time on-farm (47.4 years) than the 432 who were seen by the pulmonologist (13.7%, $P = 0.01$; 0.78, $P < 0.01$; 44.3 years, $P < 0.01$).

Pulmonologist identified 16 cases of COPD (1.3%), eight of whom (50%) were non-smokers. None of these subjects were known to be ill prior to the study. The mean standard spirometry test data were: FEV_1/FVC ratio = 0.66 (± 0.09), FEV_1 = 2.52 (± 1.02) L and 83.6 (± 2.9) % of predicted values. The distribution of the disease severity according to GOLD classification was: GOLD I = 11 subjects, GOLD II = 4, GOLD III = 1.

The final bronchial obstruction-free group consisted of 996 (673+323) farmers: 107 were excluded because they were asthmatic (9+93 in the "at-risk" group and 5 in the not "at-risk" group) (Figure 1). None of the 107 asthma cases had obstruction on spirometry.

The farmers with COPD were significantly older (54.6 years), had spent more time on-farm (51.4 years) and in dairying (33.8 years, and more were current smokers (37.5%) than the controls (50.8 years, $P = 0.02$; 44.3 years, $P < 0.01$; 27.8 years, $P = 0.01$; 10.2%, $P = 0.02$) (Table 1). The COPD farmers had a higher CAT sum score (9.6 ± 6.2) than the controls (6.2 ± 4.5) and higher scores for the four main items (cough, phlegm, chest tightness, breathlessness) (Table 2).

3.2 COPD predictive models

The univariate logistic regression model constructed with the CAT sum score provided an AUC of 0.68 (95% confidence interval [CI]: 0.53-0.83). The independent predictors of COPD introduced into the multivariate model were: time spent on-farm (continuous variable, in years), BMI (≤ or > 21 kg/m²), smoking status (non-smoker, former smoker, current smoker), free-stall mulching (yes/no). The corresponding risk estimates are shown in Table 3. The AUC of this multivariate model was 0.87

(95% CI: 0.75-0.98). Bootstrap resampling optimised the AUC to 0.83. Using a cut-off of 0.007 gave a sensitivity of 93.8%, and a specificity of 62.4%. The ROC curves of the univariate and multivariate predictive models are shown in Figure 2. One COPD farmer was misclassified with the multivariate model: his CAT sum score was 3, he was a non-smoking 44-year-old farmer, had spent 33 years on-farm, had a BMI of 23.9 kg/m² and reported performing free-stall mulching.

The predictive performances of the models including each of the four CAT items most strongly associated with COPD (cough, phlegm, chest tightness, breathlessness) are shown in Table 4. Independent COPD predictors were the same as those identified for the CAT sum score model whatever the single CAT item model. The only multivariate regression model which performed marginally better than the CAT sum score model involved breathlessness (AUC = 0.88 (95% CI: 0.77-0.98), cAUC = 0.84, sensitivity = 93.8% and specificity = 76.1%, for a cut-off of 0.013).

3.3 Decision trees

The root node of the decision tree constructed with the CAT sum score was the CAT sum score itself with a cut-off value of 11 (Figure 3). Two COPD cases were misclassified traversing the tree (CAT sum score < 11, BMI > 21 kg/m² and time spent on-farm < 57 years, sensitivity = 87.5% (14/16)). The CART model relying on breathlessness was simpler (3 splits instead of 5 splits) and misclassified only one case (sensitivity = 93.8% (1/16)) (Figure 4). The three main splits in the "breathlessness" model were current smoker: yes / no; years spent on-farm: < 60 / ≥ 60; breathlessness: <2 / ≥ 2).

4. DISCUSSION

Our model that combines the CAT sum score and four independent predictors (time spent on-farm, BMI, smoking status, free-stall mulching) is a highly sensitive and reasonably specific tool for screening dairy farmers for COPD.

The main strength of the AIRBAg study is its robust methodology based on a large randomly-selected sample of dairy farmers. The comprehensive questionnaire completed during the occupational health visit contained many variables, some specific to dairy farming, which make it possible to test many potential predictors of COPD. COPD was diagnosed using a spirometry reference test rather than the mini-spirometry employed in most similar studies.[14-15] No COPD-asthma overlap was to be feared because asthma cases had no evidence of obstructive spirometry. Finally, we used a sound statistical methodology based on bootstrap resampling to select the best subset of independent covariates and to adjust for overfitting.

But this study has some limitations. First, over one-fifth (21.6%; 451/2089) of the farmers refused to undergo the occupational health check-up and 17.7% (93/525) of those who were "at risk of bronchial obstruction" did not visit the pulmonologist. Cases of COPD may thus have been missed. In addition, the 93 subjects who did not visit the pulmonologist included a greater proportion of smokers (23.7%) than the 432 who did (13.7%). Finally, the relatively few cases (16) may not have provided the statistical power needed to identify other predictive factors of COPD. However, this study also identified the basic predictors highlighted in other similar studies (age and smoking). As the number of subjects was too small for the sample to be divided into learning and validation datasets we used an internal bootstrap validation rather than a cross validation approach.

Early detection of COPD is essential because cases of even mild COPD are at increased risk of death.[26] While the diagnostic performance of EMS, developed as a screening solution, is good in a primary care setting, its use requires physician training for it to be reliable.[8] In contrast, the CAT questionnaire can be completed by the subject him/her self before the medical examination. Various questionnaires that screen for COPD in the general population have been developed,[9-11] but the advantage of the CAT questionnaire is its dual screening and monitoring function, which enables patients to be followed-up.

Previous studies on other populations have assessed the performance of the CAT questionnaire for COPD screening. A Japanese study on 3062 smokers over 40 years old who consulted for repeated respiratory infections or to monitor their cardiovascular disease found that the CAT sum score was significantly higher in those with airflow limitation.[14] A study in Turkey of 648 smokers over 40 years old who went to a university hospital for a check-up or visit found that the variables associated with COPD were age, smoking (number of pack-years) and the CAT sum score.[15] The first four CAT items were also significantly associated with COPD. The AUC obtained with the CAT sum score alone was similar to that reported here (0.61). A Canadian population-based study of 532 subjects over 40 confirmed the value of the CAT scores for defining "at-risk" subjects.[16] The CAT sum score performed well and the breathlessness score performed even better (although not as well as in the present study). The AUC with the predictive model including breathlessness, age and smoking status was 0.77; sensitivity was 77.6% and specificity was 64.9% with a cut-off of 0.096.

The present model contains five variables, making it slightly more complex than the three-variable one constructed by Raghavan *et al.*.[16] However, the predictive performance of our model for dairy farmers is better (cAUC = 0.83, sensitivity = 93.8%, specificity = 62.4%), with only one subject misclassified. Logically, it includes the smoking status of the subjects, an influential risk factor. Consistent with many previous studies,[27-32] we found a negative association between BMI and COPD (while adjusting for other confounding factors). However, the observed relationship may not be causal as COPD prevalence (and not incidence) was recorded in this cross-sectional study.

Age was not included in the multivariate selection, but the on-farm time was, suggesting that agricultural exposure plays a role in COPD occurrence. Many farming tasks, such as handling hay

(during feeding), straw and animal feed, expose farmers to airborne contaminants and dust.[33-34] This exposure could trigger inflammatory reactions leading to the development of COPD. Finally, and somewhat paradoxically, the absence of free stall mulching was predictive of COPD. Further analyses showed that farmers who did not do this mulching generally performed fewer other agricultural activities (results not shown). This negative association could then be also explained by a reverse causal effect, as the disease at its preclinical phase may limit or hinder the execution of burdensome tasks. Finally, in-depth item analyses highlighted how "breathlessness" improved the screening for COPD in dairy farmers (as evidenced by a marginally increased AUC, due to a better specificity), in agreement with the growing evidence showing that even subjects in the early stages of COPD experience dyspnea with exertion.[35-38]

A CART analysis provides simple decision rules that are easy for physicians to use. The "breathlessness" based decision tree has the double advantage of being simpler and more sensitive than the "CAT sum score" tree. However, it would avoid less diagnostic spirometries (those non-performed in farmers predicted not at risk of COPD) than the "CAT sum score" tree, as assessed by the denominators of solid line ovals in Figures 3 and 4 (589 and 697+42+43=782, respectively).

In conclusion, the predictive performance of a model that includes the CAT sum score (or even only the breathlessness score), obtained from an easy-to-use questionnaire in current practice, plus four other predictors that are also readily collected during an interview (smoking status, on-farm time, type of farming activity) or an elementary clinical examination (BMI) was good when used to assess a population of dairy farmers. We therefore believe that this combination provides a simple, low-cost on-site tool for screening them for COPD. It would both benefit farmers by providing early diagnosis and management of their disease and avoid unnecessary, costly spirometry.

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ETHICS

The AIRBAg study was approved by the Rennes Ouest V Ethics Committee (11/28–817) and was registered on ClinicalTrials.gov (NCT03654469). Written informed consent was provided by all participants.

REFERENCES

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLOS Med. 2006;3: e442.
2. Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374:721–32.
3. Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, Studnicka M, Bateman E, Anto JM, Burney P, Mannino DM, Buist SA. COPD in Never Smokers, Results from the population-based burden of obstructive lung disease study. Chest. 2011;139:752–63.
4. Lamprecht B, Schirnhofer L, Kaiser B, Studnicka M, Buist AS. Farming and the prevalence of non-reversible airways obstruction: results from a population-based study. Am J Ind Med. 2007;50:421–6.
5. Blanc PD, Menezes AMB, Plana E, Mannino DM, Hallal PC, Toren K, Eisner MD, Zock JP. Occupational exposures and COPD: an ecological analysis of international data. Eur Respir J. 2009;33:298–304.
6. Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. Chest. 2009;136:716–25.
7. U.S. Preventive Services Task Force. Screening for chronic obstructive pulmonary disease using spirometry: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;148:529–34.
8. Perez T, Bizon C. Mini-spirometry: A relevant tool for the screening of COPD in general practice? [in French] Rev Mal Respir. 2012;29: 853–5.
9. Martinez FM, Raczek AE, Seifer FD, Conoscenti CS, Curtice TG, D'Eletto T, Cote C, Hawkins C, Phillips AL. COPD-PS Clinician Working Group, Development and initial validation of a self-scored COPD population screener questionnaire (COPD-PS). COPD. 2008;5:85–95.
10. Yawn BP, Mapel DW, Mannino DM, Martinez FJ, Donohue JF, Hanania NA, Kosinski M, Rendas-Baum R, Mintz M, Samuels S, Dalal AA. Lung Function Questionnaire Working Group, Development of the Lung Function Questionnaire (LFQ) to identify airflow obstruction. Int J Chron ObstrucT Pulmon Dis. 2010;5:1–10.
11. Weiss G, Steinacher I, Lamprecht B, Kaiser B, Mikes R, Sator L, Hartl S, Wagner H, Studnicka M. Development and validation of the Salzburg COPD-screening questionnaire (SCSQ): a questionnaire development and validation study. NPJ Prim Care Respir Med. 2017;27:4.
12. Jones P, Harding G, Wiklund I, Berry P, Leidy N. Improving the process and outcome of care in COPD: development of a standardised assessment tool. Prim Care Respir J. 2009;18:208–15.
13. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Leidy NK. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34:648–54.

14. Yoshimoto D, Nakano Y, Onishi K, Hagan G, Jones P. The relationship between the COPD Assessment Test score and airflow limitation in Japan in patients aged over 40 years with a smoking history. Int J Chron Obstruct Pulmon Dis. 2014;9:1357–63.
15. Kart L, Akkoyunlu ME, Bayram M, Yakar F, Özçelik HK, Karaköse F, Sezer M. COPD: an underdiagnosed disease at hospital environment. Wien Klin Wochenschr. 2014;126:73–8.
16. Raghavan N, Lam YM, Webb KA, Guenette JA, Amornputtisathaporn N, Raghavan R, Tan WC, Bourbeau J, O'Donnell DE. Components of the COPD Assessment Test (CAT) associated with a diagnosis of COPD in a random population sample. COPD. 2012;9:175–83.
17. Jones PW, Shahrour N, Nejjari C, Lahlou A, Doble A, Rashid N, El Hasnaoui A. BREATHE Study Group, Psychometric evaluation of the COPD assessment test: data from the BREATHE study in the Middle East and North Africa region. Respir Med. 2012.106 Suppl 2:S86-99.
18. Jouneau S, Marette S, Robert AM, Gouyet T, Guillot S, Chapron A, Mailloux C, Desrues B, Viel JF. Prevalence and risk factors of chronic obstructive pulmonary disease in dairy farmers: AIRBAg study. Environ Res. 2019;169:1–6.
19. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
20. Vandevoorde J, Verbanck S, Schuermans D, Kartounian J, Wincken W. Obstructive and restrictive spirometric patterns: fixed cut-offs for FEV1/FEV6 and FEV6. Eur Respir J. 2006;27: 378–83.
21. Vollmer WM, Gíslason T, Burney P, Enright PL, Gulsvik A, Kocabas A, Buist AS. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. Eur Respir J. 2009;34:588–97.
22. Austin PC, Tu JV. Bootstrap methods for developing predictive models. Am Stat. 2004;58:131–7.
23. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005–12.
24. Roberts MH, Mapel DW, Bruse S, Petersen H, Nyunoya T. Development of a modified BODE index as a mortality risk measure among older adults with and without chronic obstructive pulmonary disease. Am J Epidemiol. 2013;178:1150–60.
25. Breiman L, Friedman J, Olshen RA, Stone CJ. Classification and regression trees. Wadsworth, Belmont: Chapman and Hall/CRC; 1984.
26. Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? Thorax. 2007;62:237–41.

27. Harik Khan RI, Fleg JL, Wise RA. Body mass index and the risk of COPD. Chest. 2002;121:370 -6.

28. Zhou Y, Wang D, Liu S, Lu J, Zheng J, Zhong N, Ran P. The association between BMI and COPD: the results of two population-based studies in Guangzhou, China. COPD J Chronic Obstr Pulm Dis. 2013;10:567–72.

29. Smith M, Li L, Augustyn M, Kurmi O, Chen J, Collins R, Guo Y, Han Y, Qin J, Xu G, Wang J, Bian Z, Zhou G, Peto R, Chen Z. Prevalence and correlates of airflow obstruction in 317 000 never-smokers in China. Eur Respir J. 2014;44:66–77.

30. Lee SJ, Chang JH, Kim SW, Kong KA, Ryu YJ, Lee JH. Risk factors for chronic obstructive pulmonary disease among never-smokers in Korea. Int J Chron Obstruct Pulmon Dis. 2015;497-506.

31. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, Kang J, Ran P, Shen H, Wen F, Huang K, Yao W, Sun T, Shan G, Yang T, Lin Y, Wu S, Zhu J, Wang R, Shi Z, Zhao J, Ye X, Song Y, Wang Q, Zhou Y, Ding L, Yang T, Chen Y, Guo Y, Xiao F, Lu Y, Peng X, Zhang B, Xiao D, Chen CS, Wang Z, Zhang H, Bu X, Zhang X, An L, Zhang S, Cao Z, Zhan Q, Yang Y, Cao B, Dai H, Liang L, He J. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. The Lancet. 2018;391:1706–17.

32. Li J, Zhu L, Wei Y, Lv J, Guo Y, Bian Z, Du H, Yang L, Chen Y, Zhou Y, Gao R, Chen J, Chen Z, Cao W, Yu 1, Li L. Association between adiposity measures and COPD risk in Chinese adults. Eur Respir J. 2020; in press.

33. von Essen SG, Banks DE. Life-long exposures on the farm, respiratory symptoms, and lung function decline. Chest. 2009;136:662–3.

34. Thaon I, Thiebaut A, Jochault L, Lefebvre A, Laplante JJ, Dalphin JC. Influence of hay and animal feed exposure on respiratory status: a longitudinal study. Eur Respir J. 2011;37:767–74.

35. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177:622–9.

36. O'Donnell DE, Laveneziana P, Ora J, Webb KA, Lam YM, Ofir D. Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I COPD. Thorax. 2009;64:216–23.

37. Guenette JA, Jensen D, Webb KA, Ofir D, Raghavan N, O'Donnell DE. Sex differences in exertional dyspnea in patients with mild COPD: physiological mechanisms. Respir Physiol Neurobiol. 2011;177:218–27.
38. Neder JA, Berton DC, Müller PT, Elbehairy AF, Rocha A, Palange P, O'Donnell DE. Canadian Respiratory Research Network; Ventilatory inefficiency and exertional dyspnea in early chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2017;14:S22–9.

TABLE 1 Characteristics of farmers with COPD and farmers free of bronchial obstruction

	COPD (n=16)		Bronchial obstruction free (n=996)	
Qualitative variable	n	%	n	%
Quantitative variable	m	± SD	m	± SD
Age (years)	54.6	± 7.7	50.8	± 6.5
On-farm time (years)	51.4	± 10.3	44.3	± 11.7
Gender				
Male	10	62.5	717	72.0
Female	6	37.5	279	28.0
BMI (kg/m²)				
≤ 21	5	31.3	71	7.1
> 21	11	68.7	925	92.9
Smoking status				
Never	8	50.0	701	70.4
Former	2	12.5	193	19.4
Current	6	37.5	102	10.2
Farm characteristics				
Area (Ha)	83.5	± 47.7	82.7	± 42.9
Dairy farming activities (years)	33.8	± 9.6	27.8	± 9.1
Milking cows (number)	49.8	± 24.6	51.7	± 23.7

TABLE 2 COPD assessment test (CAT) scores in dairy farmers with COPD and bronchial obstruction-free controls (Brittany, France, 2012-2017)

	COPD (n=16)	Bronchial obstruction free (n=996)	*P* value
	m ± SD	m ± SD	
Item 1: Cough	1.8 ± 0.8	1.2 ± 0.9	0.02
Item 2: Phlegm	1.4 ± 1.2	0.7 ± 0.9	< 0.01
Item 3: Chest tightness	1.0 ± 1.1	0.5 ± 0.7	0.02
Item 4: Breathlessness	1.8 ± 1.3	1.1 ± 1.0	0.03
Item 5: Activity limitation	0.8 ± 0.9	0.5 ± 0.8	0.29
Item 6: Confidence leaving home	0.4 ± 0.8	0.2 ± 0.6	0.22
Item 7: Sleep	0.8 ± 1.2	0.7 ± 0.9	0.51
Item 8: Energy	1.6 ± 1.2	1.2 ± 1.0	0.14
Sum score	9.6 ± 6.2	6.2 ± 4.5	< 0.01

Abbreviations: COPD: chronic obstructive pulmonary disease; m: mean; SD: standard deviation.

TABLE 3 Odds ratio estimates for COPD in dairy farmers (n=993, multivariate model, Brittany, France, 2012-2017)

	Odds ratio	95% CI			*P* value
CAT sum score (unitless)	1.12	1.02	-	1.21	0.02
On-farm time (years)	1.11	1.05	-	1.19	< 0.001
BMI ≤ 21 kg/m²	12.93	3.43	-	46.51	< 0.001
Smoking status					< 0.01
never	1.00		-		-
former	1.36	0.19	-	6.15	
current	12.12	3.35	-	45.26	
No free-stall mulching activity	3.35	1.01	-	10.50	0.05

Abbreviations: BMI: body mass index; CAT: COPD assessment test: CI, confidence interval; COPD: chronic obstructive pulmonary disease.

TABLE 4 Predictive performance of multivariate models including either the CAT sum score or one of four CAT items (dairy farmers, Brittany, France, 2012-2017)

	AUC (95% CI)	cAUC	Sensitivity	Specificity	Cut-off
CAT sum score	0.87 (0.75-0.98)	0.83	93.8%	62.4%	0.007
Item 1: Cough	0.86 (0.75-0.97)	0.82	93.8%	63.4%	0.008
Item 2: Phlegm	0.86 (0.74-0.97)	0.82	93.8%	70.9%	0.011
Item 3: Chest tightness	0.86 (0.75-0.98)	0.82	93.8%	74.3%	0.012
Item 4: Breathlessness	0.88 (0.77-0.98)	0.84	93.8%	76.1%	0.013

Abbreviations: CAT: chronic obstructive pulmonary disease assessment test; AUC: area under the receiver operating characteristic curve; cAUC: corrected AUC; CI: Confidence Interval.

FIGURE 1 AIRBAg study flow chart (Brittany, France, 2012-2017)

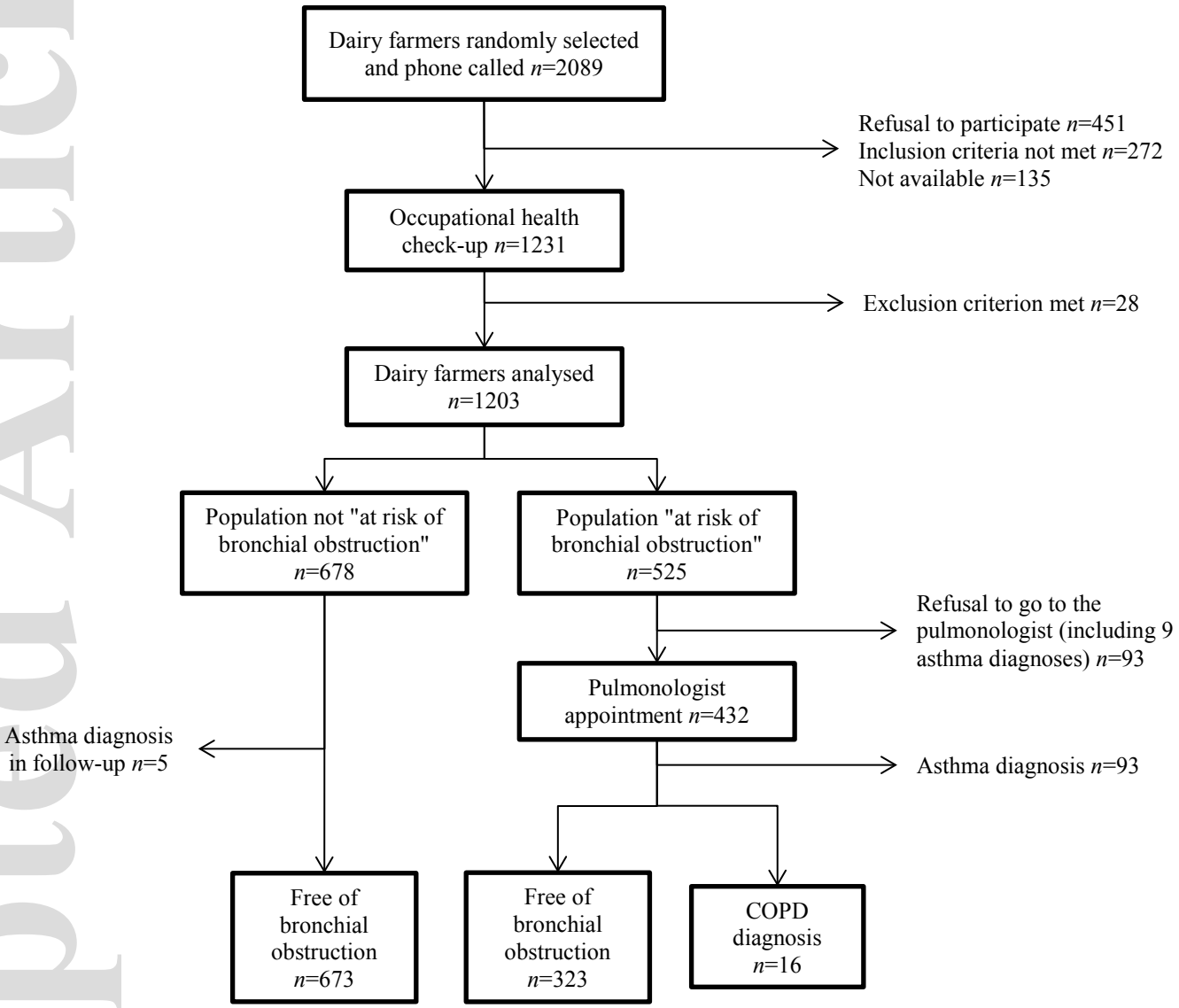

FIGURE 2 Receiver operating characteristic curves of predictive models for COPD (dairy farmers, Brittany, France, 2012-2017)

Solid line: multivariate model, AUC = 0.87, 95% CI: 0.75-0.98; dotted line: univariate model, AUC = 0.68, 95% CI: 0.53-0.83.

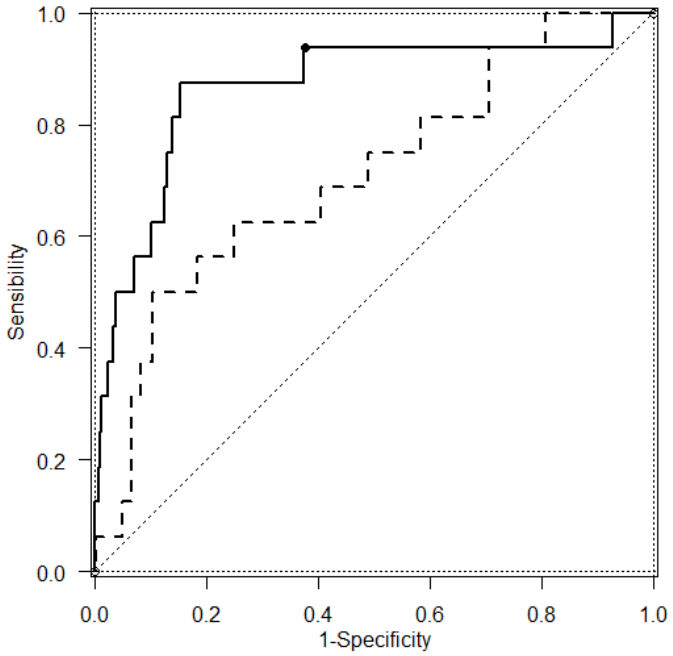

FIGURE 3 CART decision tree using the CAT sum score for predicting COPD in dairy farmers (n=993, Brittany, France, 2012-2017)

Solid line oval: farmers predicted not at-risk of COPD; dotted line oval: farmers predicted at-risk of COPD; COPD cases/group size.

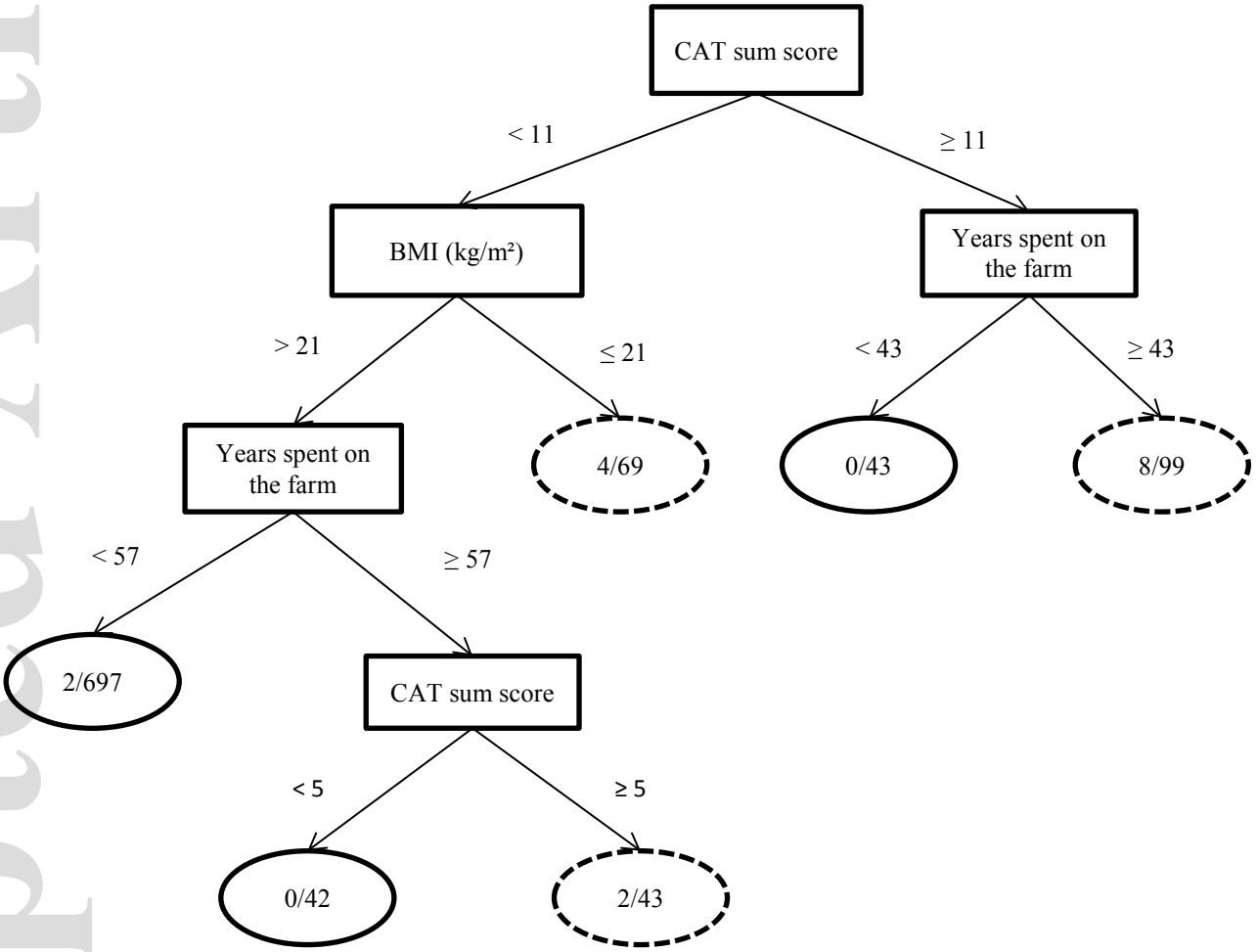

FIGURE 4 CART decision tree using the CAT breathlessness score for predicting COPD in dairy farmers (n=1004, Brittany, France, 2012-2017)

Solid line oval: farmers predicted not at-risk of COPD; dotted line oval: farmers predicted at-risk of COPD; COPD cases/group size.