

Bronchial Hyperresponsiveness in Farmers: Severity and Work-Relatedness

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Abstract

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Key words: work-related respiratory symptoms; farming; questionnaire; cow breeders; spirometry; airway responsiveness.

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OBJECTIVE: To evaluate the prevalence of respiratory symptoms, lung function and bronchial hyperresponsiveness in farmers, with emphasize to their severity and work-relatedness due occupational risk factors and farming characteristics.

METHODS: A cross-sectional survey was performed including 60 cow breeders aged 21 to 65 years, compared to an equal number of agricultural farmers matched by age, job exposure duration, and smoking status. We have used a questionnaire to record the chronic respiratory symptoms, detailed work history, specific farming activities and tasks performed, and smoking history. Evaluation of examined subjects also included lung function spirometry tests, and bronchial hyperresponsiveness testing.

RESULTS: We found higher prevalence of work related respiratory symptoms in the last 12 months in cow breeders with significant difference for phlegm ($P = 0.039$), and wheezing ($P = 0.026$). Mean values of all spirometric parameters were lower in cow breeders, reaching significance for MEF50 ($P = 0.001$) and MEF75 ($P = 0.000$). Significant difference was found for mild bronchial hyperresponsiveness among cow breeders with job exposure of more than 15 years. The risk of developing work-related respiratory symptoms increased significantly with full-time farming, exposure to gases and vapors, and keeping more than 10 cows.

CONCLUSION: Our data suggest that workplace exposure in farmers may cause respiratory impairment which is closely related to its duration, characteristics, and intensity. The results suggest that cow breeders in general have higher rates of work-related respiratory symptoms and bronchial hyperresponsiveness than agricultural farmers, whereas their severity increases with an increase in frequency and duration of animal contact.

Introduction

The social and economical transition process in Republic of Macedonia led to significant decrease in the number of large agricultural complexes and development of smaller agricultural enterprises and individual farmers working on relatively small agricultural holdings. Farming and animal husbandry are most frequent occupational activities and relevant financial sources among Macedonian rural population [1].

According to the latest Census of Agriculture in Republic of Macedonia in 2007, conducted by the State Statistical Office, number of individual farms is 192.378, with 471.069 employed persons, while total available agricultural land is estimated to 321.813.7

ha [2].

The family farm is an enterprise and a homestead, combining family relationships with the production of food and other raw materials. Farms range from small, subsistence or part-time operations worked with draught animals and hand tools to very large, family-held corporations with numerous full-time employees and large amount of mechanization. The size and type of operations determine the demand for labor from family members and the need for hired full- or part-time workers. A typical farm operation may combine the tasks of livestock handling, manure disposal, grain storage, heavy equipment operation, pesticide application, machinery maintenance, construction and many other jobs [3].

Farming has been known as a high-risk occupation for the development of work-related symptoms since 1555, when Olaus Magnus recognized farming health hazards with respect to grain dust [4]. Farmers involved in animal production have a higher prevalence of respiratory symptoms than other farmers and other rural residents. An increase in respiratory symptoms has been noted among animal farmers in North America, Europe and New Zealand [5, 6]. Although the prevalence of smoking is lower in farming than in other occupations [7], farmers have a greater risk of respiratory disorders than people in non-farming occupations [8]. While at work, animal farmers are exposed to inorganic dust, and organic dust containing microorganisms, mycotoxins, endotoxins, animal feed particles, allergens and chemical agents [9]. Organic dust exposure is known to cause allergic and nonallergic rhinitis [10], or organic dust toxic syndrome [11], and can induce chronic bronchitis, asthma or an asthma-like syndrome [12]. In addition, many farmers start working in childhood and frequently continue to work well beyond the age of 65 years. Due to the fact that farmers often live at the farm, their daily exposure to occupational agents is usually longer than in other occupations [4].

Farmers are exposed to dusts and several types of gases in their working environment [13, 14]. Dust is mainly composed of organic material from straw, hay, grain, animals, mites, and microorganisms. Of gases normally found in animal buildings ammonia occurs most frequently in harmful concentrations [15, 14]. In confinement buildings, the two major constituents in total and respirable aerosol are grain particles and dried faecal material [16]. Especially in cow farms, levels of airborne gases [13] and concentrations of total dust and endotoxins of gram negative bacteria [17] are higher than in other farms.

The aim of this study was to evaluate the prevalence of respiratory symptoms, lung function and bronchial hyperresponsiveness in farmers, with special emphasize to their severity and work-relatedness due to some occupational risk factors and job characteristics of farm work.

Subjects and Methods

Study design and setting

Our team carried out a cross-sectional study within the Center for Respiratory Functional Diagnostics at the Institute for Occupational Health of R. Macedonia, Skopje - WHO Collaborating Center for Occupational Health and GA²LEN Collaborating Center between April 2013 and February 2014.

Subjects

We have examined 120 agricultural workers divided in two groups. The Group I was composed of 60 cow breeders, 46 males and 12 females, aged 21 to 65 years with duration of exposure 4 to 45 years (mean duration 22.7 ± 5.6).

Subjects in this Group were defined as "cow breeders" because they kept at least 5 cows. Among them, 49 were full-time cow breeders who worked indoors and/or outdoors among cows each working day of the week, having animal contact for at least 8 hours per day. The remainder of the participants in this Group (11 subjects) worked less than 8 hours per day with animal contact inside or outside cow stall and, thus, was defined as part-time cow breeders.

The farm activities of the participating subjects included: feed production and feed planning, management of weeds and pests to maintain pasture and crops, milking and milking process, plant hygiene, maintenance of standards, effluent farm system and good animal health, management of repairs and scheduling for plants, machinery and infrastructure, practicing farm work within environmental guidelines, and ensuring health and safety policies and procedures in farming.

In addition, the Group II included 60 agricultural farmers, 43 males and 17 females, aged 19 to 65 years with duration of exposure 2 to 46 years (mean duration 23.1 ± 5.8), matched to cow breeders by age, gender, duration of exposure, and daily smoking. Agricultural farmers were defined as farmers who did not keep cows within the year preceding the survey.

For the study purposes concerning airway responsiveness the examinees were divided in two subgroups by duration of exposure: exposed less or more than 15 years.

The subjects with chronic respiratory disease diagnosed by physician were excluded from the study. All study subjects were informed about the study and signed the written consent for participation.

Questionnaire

All subjects were interviewed by a physician who filled the questionnaire. The questionnaire included questions on work history, respiratory symptoms in the last 12 months, and overall nasal symptoms in the last 12 months, and smoking status of the study subjects.

The work histories of the study subjects were assessed through questions on previous and current job, daily working time, job description, working conditions, specific job activities and farming characteristics, as well as protective measures used.

Chronic respiratory symptoms in the last 12 months (cough, phlegm, dyspnea, wheezing, chest tightness, and nasal symptoms) were documented

using the European Community for Coal and Steel questionnaire (ECCS-87), and the European Community Respiratory Health Survey (ECRHS) questionnaire [18, 19].

Detailed smoking history was also evaluated, using the classification of smoking status according to the World Health Organization (WHO) guidelines [20].

Namely, daily smoker was defined as a subject who smoked at the time of the survey at least once a day, except on days of religious fasting. Ex-smoker was defined as a formerly daily smoker, no longer smokes. Passive smoking or exposure to environmental tobacco smoke (ETS) was defined as the exposure of a person to tobacco combustion products from smoking by others [21].

Spirometry

Spirometry, with measures of forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), FEV₁/FVC ratio, and maximal expiratory flow at 50%, 75%, and 25-75% of FVC (MEF₅₀, MEF₇₅, and MEF₂₅₋₇₅, respectively), was performed in all subjects using spirometer Ganshorn SanoScope LF8 (Ganshorn Medizin Electronic GmbH, Germany) with recording the best result out of three subsequent measurements of the values of FEV1 within 5% of each other. The results of spirometry were given as percentages of the predicted values according to the European Community for Coal and Steel (ECCS) norms [22].

Histamine challenge

The histamine challenge test was performed according to the actual European Respiratory Society (ERS)/American Thoracic Society (ATS) recommendations [23, 24]. Concentrations of 0.5, 1, 2, 4, and 8 mg/ml histamine (Torlak, Serbia) were prepared by dilution with buffered saline. Afterwards, the doses of aerosol generated by Pari LC nebulizer with output rate 0.17 ml/min were inhaled by mouthpiece. Subjects inhaled increasing concentrations of histamine using a tidal breathing method until FEV1 fell by more than 20 % of its base value (provocative concentration 20 - PC20) or until the highest concentration was reached.

According to the ATS recommendations, bronchial hyperresponsiveness (BHR) was categorized as moderate to severe BHR (PC20 < 1.0 mg/ml), mild BHR (PC20 = 1.0 - 4.0 mg/ml) and borderline BHR (PC20 = 4.0 - 8.0 mg/ml) [24].

Statistical analysis

Statistica for Windows version 7 and Epi info 6 were used for data description and analysis. Continuous variables were expressed as mean values

with standard deviation, while categorical variables as numbers and percentages. The differences in the prevalence of respiratory symptoms were tested by chi-square test (or Fisher's exact test where appropriate), whereas the comparison of spirometric measurements was performed by independent-samples *T*-test. A *P*-value of less than 0.05 was considered statistically significant. Logistic regression was used to analyze the influence of specific occupational risk factors and farming characteristics on the prevalence of respiratory symptoms, taking into account for some confounding factors (age, gender, and smoking habit). The results are given in terms of odds ratios (ORs) with 95% confidence intervals (95% CIs).

Results

Demographic characteristics of the study subjects were similar in both examined groups (Table 1).

Table 1: Demographics of the study subjects.

Variable	Cow breeders (n = 60)	Agricultural farmers (n = 60)
M/F ratio	1.3	1.4
Age range (years)	21 - 65	19 - 65
Age (years)	54.7 ± 7.1	54.2 ± 6.9
BMI (kg/m ²)	25.2 ± 3.4	24.8 ± 3.2
Job exposure (years)	22.7 ± 5.6	23.1 ± 5.8
Daily smokers	16 (26.7%)	17 (28.3%)
Life-time smoking (years)	17.8 ± 6.1	18.3 ± 5.9
Cigarettes / day	14.2 ± 7.6	15.9 ± 7.2
Job status		
Full-time	49 (81.7%)	46 (76.7%)
Part-time	11 (18.3%)	14 (23.3%)

Numerical data are expressed as mean value with standard deviation; frequencies as number and percentage of study subjects with certain variable. BMI: body mass index; kg: kilogram; m: meter.

Prevalence of respiratory symptoms in the last 12 months was higher in cow breeders than in agricultural farmers with statistical significant difference for phlegm, wheezing, and nasal symptoms (Table 2).

Table 2: Prevalence of respiratory symptoms in the last 12 months in examined groups.

Respiratory symptoms in the last 12 months	Cow breeders (n = 60)	Agricultural farmers (n = 60)	<i>P</i> -value*
Any respiratory symptom	19 (31.7%)	14 (23.3%)	0.306
Cough	14 (23.3%)	7 (11.7%)	0.092
Phlegm	13 (21.7%)	5 (8.3%)	0.040
Dyspnea	8 (13.3%)	4 (6.7%)	0.223
Wheezing	12 (20%)	4 (6.7%)	0.031
Chest tightness	5 (8.3%)	4 (6.7%)	0.729
Nasal symptoms	23 (38.3%)	13 (21.7%)	0.046

Data are expressed as number and percentage of study subjects with certain variable. * Tested by chi-square test or Fisher's exact test where appropriate.

Mean values of spirometric parameters were lower in agricultural workers with statistical difference for MEF₅₀ and MEF₇₅, whereas difference in the mean values of MEF₂₅₋₇₅ just missed statistical significance (Table 3).

Table 3: Mean values of spirometric parameters in examined groups.

Spirometric parameter	Cow breeders (n = 60)	Agricultural farmers (n = 60)	P-value*
FVC (% pred.)	85.4 ± 8.6	87.3 ± 8.8	0.092
FEV ₁ (% pred.)	82.4 ± 9.1	84.1 ± 7.4	0.113
FEV ₁ /FVC%	73.6 ± 4.6	74.7 ± 4.8	0.071
MEF ₅₀ (% pred.)	57.3 ± 7.5	60.9 ± 6.8	0.001
MEF ₇₅ (% pred.)	53.7 ± 6.1	60.3 ± 7.2	0.000
MEF ₂₅₋₇₅ (%pred.)	62.9 ± 8.2	63.4 ± 8.1	0.061

Data are expressed as mean value with standard deviation. FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 second; MEF₅₀, MEF₇₅, MEF₂₅₋₇₅: maximal expiratory flow at 50%, 75%, and 25-75% of FVC, respectively; % pred: % of predicted value. Tested by independent-sample T-test.

Prevalence of BHR was higher in cow breeders than in agricultural farmers, but statistical significance was not reached (Figure 1).

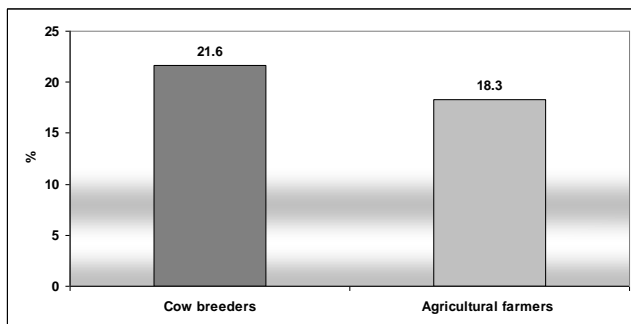


Figure 1: Prevalence of BHR in examined groups: (21.6% vs. 18.3%, $P = 0.648$; chi-square test). BHR: bronchial hyperresponsiveness.

In both examined groups there was no subject with moderate to severe BHR. Prevalence of borderline BHR was similar in both examined groups, whereas prevalence of mild BHR was higher in cow breeders, but still without statistical significance (Table 4).

Table 4: Prevalence of BHR categories in examined groups.

BHR category	Cow breeders (n = 60)	Agricultural farmers (n = 60)	P-value*
Moderate to severe BHR	/	/	/
Mild BHR	5 (8.3%)	2 (3.3%)	0.219
Borderline BHR	8 (13.3%)	9 (15%)	0.793

Data are expressed as number and percentage of study subjects with certain variable. *Tested by chi-square test or Fisher's exact test where appropriate.

Prevalence of borderline BHR was similar in both cow breeders and agricultural farmers with workplace exposure more than 15 years, while prevalence of mild BHR was significantly higher in cow breeders than in agricultural farmers with workplace exposure more than 15 years (Table 5).

Table 5: Prevalence of BHR categories in cow breeders and agricultural farmers with workplace exposure more than 15 years.

BHR category	Cow breeders exposed more than 15 years (n = 35)	Agricultural farmers exposed more than 15 years (n = 37)	P-value*
Moderate to severe BHR	/	/	/
Mild BHR	6 (17.1%)	1 (2.7%)	0.045
Borderline BHR	4 (11.4%)	5 (13.5%)	0.536

Data are expressed as number and percentage of study subjects with certain variable. *Tested by chi-square test or Fisher's exact test where appropriate.

Prevalence of work-related respiratory symptoms in the last 12 months was higher in cow breeders than in agricultural farmers with statistical significant difference for phlegm, and wheezing (Table 6).

Table 6: Prevalence of work-related respiratory symptoms among cow breeders and agricultural farmers.

Respiratory symptoms in the last 12 months	Cow breeders (n = 60)	Agricultural farmers (n = 60)	P-value*	OR (95% CI)
Any work-related respiratory symptoms	14 (23.3%)	10 (16.7%)	0.361	1.52 (0.56-4.14)
Cough	11 (18.3%)	5 (8.3%)	0.107	2.47 (0.72-8.86)
Phlegm	10 (16.7%)	3 (5%)	0.039	3.80 (0.89-18.55)
Dyspnea	6 (10%)	3 (5%)	0.298	2.11 (0.44-11.30)
Wheezing	9 (15%)	2 (3.33%)	0.026	5.12 (0.96-36.08)
Chest tightness	4 (6.7%)	3 (5%)	0.696	1.36 (0.24-8.08)
Nasal symptoms	16 (26.7%)	9 (15%)	0.115	2.06 (0.76-5.66)

* Tested using multivariate logistic regression adjusted for age, gender and smoking habit.

Distribution of work-related respiratory symptoms and farming characteristics in cow breeders, expressed as prevalence ORs (95% CI) after adjusting for age, gender and smoking habit is given in Table 6. The risk of developing work-related wheezing increased significantly with full-time farming (OR=7.4 [95% CI 2.3 to 24.6]), exposure to gases and vapors (OR=11.2 [95% CI 3.8 to 26.3]) and keeping more than 10 cows (OR=8.7 [95% CI 2.1 to 28.3]). A similar relationship was found for dyspnea (full-time farming (OR=8.2 [95% CI 2.9 to 22.4]), exposure to gases and vapors (OR=6.1 [95% CI 1.7 to 15.3]) and keeping more than 10 cows (OR=5.9 [95% CI 2.1 to 17.4])).

Table 7: Distribution of work-related respiratory symptoms and farming characteristics in cow breeders (Prevalence ORs (95% CI)*).

Farming characteristics	Cough	Phlegm	Dyspnea	Wheezing	Chest tightness
Full-time vs. part-time	1.4 (0.7-3.5)	3.1 (0.8-9.4)	8.2 (2.9-22.4)	7.4 (2.3-24.6)	4.5 (1.3-12.8)
Kept cows and other animals	1.02 (0.3-2.6)	1.04 (0.4-2.9)	1.7 (0.6-4.7)	2.6 (0.5-10.3)	1.3 (0.5-3.6)
Use of pesticide	1.03 (0.3-1.9)	1.2 (0.5-2.3)	1.3 (0.5-3.3)	1.07 (0.4-3.9)	1.04 (0.3-2.0)
Exposure to gases and vapors	3.7 (1.2-9.6)	5.8 (1.3-14.9)	6.1 (1.7-15.3)	11.2 (3.8-26.3)	4.7 (1.4-13.6)
Dust exposure	2.34 (0.9-4.8)	1.23 (0.5-3.0)	1.8 (0.7-4.2)	2.9 (0.6-7.2)	1.2 (0.4-3.2)
Number of cows					
> 10 vs. 5-10	3.1 (1.2-6.3)	4.7 (1.04-17.1)	5.9 (2.1-17.4)	8.7 (2.1-28.3)	6.4 (2.2-18.3)
> 50 vs. 5-10	1.3 (0.2-3.7)	17.3 (3.9-58.6)	23.4 (4.1-67.8)	11.5 (2.1-21.8)	7.3 (1.7-19.8)

* Tested using multivariate logistic regression adjusted for age, gender and smoking habit.

Exposure to gases and vapors and keeping a large number of cows were shown to be associated with around fivefold increase in the risk of incidence of phlegm (OR=5.8 [95% CI 1.3 to 14.9], OR=4.7 [95% CI 1.04 to 17.1], respectively). A similar association was found for incidence of cough and chest tightness. The actual study did not confirm a positive relationship between pesticide use and keeping animals other than cows and development of work-related respiratory symptoms among exposed subjects. Also, there was only a weak association between dust exposure and work-related respiratory symptoms among exposed subjects.

Discussion

Chronic respiratory and nasal symptoms and chronic lung diseases remain nowadays important clinical and public health problems for agricultural workers. Many surveys performed during last few decades, have shown an increased risk of respiratory morbidity and mortality among farm workers, as a result of the relationship between exposure to respiratory hazards with development of chronic respiratory symptoms, as well as of chronic lung diseases [4].

Our present study evaluated the prevalence of respiratory symptoms, lung function and airway responsiveness among Macedonian farmers, having a special emphasize to their severity and work-relatedness due to some occupational risk factors and job characteristics of the farm work, adjusted for age, gender, and smoking habit.

Data obtained from our previous and current research linked to farmers showed that their most common activities were: feed production and planning, cattle breeding, management of weeds and pests, milking process, plant hygiene, maintenance of standards, farm systems and good animal health, management of repairs, machinery and infrastructure, and ensuring health and safety policies in farming. Over the farm working process, workers were exposed to inappropriate indoor and outdoor climate, dust, chemical agents and pesticides, extensive animal and plant contact, heavy manual work, lifting and loading, inappropriate body postures, repetitive hand movements, and working with sharp tools (25).

Working with animals has been associated with development of work-related respiratory symptoms among farmers [4, 6, 12, 26, 27], especially those with direct animal contact, working in confinement areas. This usually results with exposure to a wide array of hazardous airborne agents [4]. Farmers can be exposed to many different potential respiratory hazards despite generally being healthier compared to the general population, considering the fact that they have a tendency to smoke less than others [5]. Selecting an appropriate referent comparison group is always a great concern for researchers involved in evaluation of work-related respiratory as well as other symptoms and diseases among farmers. A large number of studies focused on animal farming have used non-farming rural or working populations as their controls, while very few studies focused on respiratory symptoms and lung function in farmers were able to make comparisons across agricultural workers and farmers to explore the impact of animal exposures more profoundly [4, 28].

Our present study assessed the prevalence of general and work-related chronic respiratory symptoms, accompanied with evaluation of the potential risk factors for their development and aggravation among Macedonian farmers within the

last year preceding the field survey. The European Community Respiratory Health Survey [29] contains standardized questions, tools, and items validated for the assessment of chronic respiratory symptoms including evaluation of the lung disease status. On the other hand, farming process and practices, especially cattle breeding remain stable for some time, so questionnaires assessing farming methods represent relevant exposure predictors [27].

The prevalence of overall chronic respiratory symptoms in our actual study among cow breeders was 31.6%, being similar with research conducted in Europe whose frequencies in farmers ranged between 25% and 35% [30]. We have registered lower values of spirometric parameters among cow breeders compared to agricultural farmers with statistical significance for mean values of MEF50 and MEF75, whereas statistical significance was just missed for the difference in the mean values of MEF25-75. The most frequent among all examined cow breeders was mixed type of respiratory functional impairment, while in general ventilatory impairment was associated with age over 55 years, duration of job exposure over 25 years, smoking habit, and exposure to gases, vapors dust and pesticides.

Dosman et al. [31], exploring the effect of specific workplace exposure on the frequency of chronic respiratory symptoms and lung functional parameters in cereal grain workers in Denmark registered significantly lower values of both basic spirometric and MEF parameters compared to the control group, and confirmed that it was associated with age and pesticide exposure. Dalphin et al., exploring the specific occupational exposure in France reported significantly lower values of VC and FEV1 among cattle breeders compared to controls [32]. Danish study, concerning exposure-response relationship in pig farmers showed annual decrease in FEV1 of about 12 mL in exposed workers [33], while Canadian study exploring the effect of occupational exposure on lung function in cattle breeders reported significant association between the decrease in FVC, and number of working hours [34].

The results obtained in study in Ukraine focused on the impact of specific occupational exposure over the lung functional parameters in cow breeders, showed significant correlation between the decrease of FVC and FEV1, and the duration of job exposure [35]. The longitudinal study of Dalphin et al. among cow farmers in France discovered significant difference in lung function parameters compared to controls, showing also correlation between the decrease in value of FEV1 and FVC and both age and length of job exposure [26]. Sigsgaard et al. in the Danish study of young farmers, registered significant difference between male farmers and male controls, whereas in female farmers the basic spirometry parameters were significantly lower compared to controls [36].

Scheefeldt in a German study dedicated to bronchial hyperreactivity of employees in swine and cattle breeding found a significant higher rate of bronchial hyperreactivity in pig farmers (16.2%) versus 7.8% in cattle breeders and 4.3% in control persons [37]. Vogelzang et al. reported that long-term average exposure to dust and ammonia in pig farms contributes to chronic inflammation of the airways and was associated with increases in responsiveness expressed as steps for provocative concentration causing a 20% fall in FEV1 [38]. Our results confirmed significantly higher prevalence of mild BHR in cow breeders compared to agricultural farmers with workplace exposure more than 15 years.

Exposure to animal proteins can aggravate the existing or cause new occupational asthma in farmers. Irritant induced occupational asthma can be developed after extensive inhalation of gases and vapors among cattle breeders, such as anhydride ammonia and nitrogen oxides. Studies in agricultural workers have reported prevalence of chronic bronchitis of 7.5% among Finnish up to 23% among farmers in Manitoba, Canada [39]. Higher frequency of chronic bronchitis was registered among cattle breeders in former Yugoslavia [40], while its prevalence was 30% in smokers and 16% in non-smokers among workers engaged in dairy and milk production in Wermont, USA [41]. The research in this area have shown higher prevalence of chronic bronchitis among farmers and cattle breeders in confinement areas compared to other agricultural farmers [42].

The present study showed increased odds ratio for work related respiratory symptoms among cow breeders. Comparing farmers engaged as cow breeders with agricultural farmers, we have observed a higher prevalence of work-related symptoms among cow breeders involved with animal handling. The prevalence of work-related respiratory symptoms, especially wheezing and phlegm (OR=5.12 [95% CI 0.96 to 36.08], and OR=3.80 [95% CI 0.89 to 18.55], respectively), was significantly higher among cow breeders. Having in mind the fact that the majority of the cow breeders lived in rural areas, and mainly followed traditional farming methods, our results cannot be fully generalized to all farmers in the country.

In the present study, an increased frequency of animal contact was associated with an increased risk of work-related symptoms. The results have shown a significant association between the number of daily hours working indoors and/or outdoors with animals and the development of work-related respiratory symptoms. Our study included cow breeders who maintained contact with their animals throughout the working hours that encompassed almost all day. In this group, the prevalence of asthma symptoms was up to fivefold more frequent than in agricultural farmers, while respiratory symptoms concerning chronic bronchitis were about threefold

more common. Obtained results have confirmed the association between full-time farming and a greater risk of wheezing, which is similar with the findings of a European animal farming study (OR=7.4 [95% CI 2.3 to 24.6] vs. OR=1.57 [95% CI 0.77 to 3.2], respectively) [43]. On the other hand, full-time farming was not shown to be a risk factor for breathlessness in the European study [43], unlike it was in our study (OR=0.44 [95% CI 0.16 to 1.25] vs. OR=8.2 [95% CI 2.9 to 22.4], respectively). An increase in the number of animals that were kept by farmers was strongly associated with a higher risk of work-related respiratory symptoms. In the same line with German farmers' study, our study reported positive dose-response pattern of work-related frequency of phlegm [44]. Our results together with many other studies [4] found an increased risk for development of wheezing followed by an increased number of animals kept on the farm, whereas a study of Ohio grain farmers [45] showed an inverse dose-response trend with rising of the number of animals kept. At this point, it is very important to understand whether it is a case of multiple hazardous agents creating a synergistic exposure effect in farming. Studying the increased adverse exposure quantity effect on workers and its significance especially in cow and sheep breeders, Radon and Winter [44] discovered a significant amount of endotoxin units/mg in sheep wool, particularly within the process of animal shearing. In addition, an association between the use of a formaldehyde dip and breathing problems at work was described by Kimbell-Dunn et al [6]. After adjusting for some potential confounding variables, our present study did not confirmed that the use of pesticides was associated with an increased risk of individual work-related respiratory symptoms, as it was reported for the risk of overall work-related respiratory symptoms in the study about the Iranian farmers (OR=2.3 [95% CI 1.01 to 5.3]) [46].

In general, our results confirmed significantly higher prevalence of work-related respiratory symptoms among Macedonian farmers, compared to those found in the studies performed in New Zealand, Spain, Germany and some other countries [6, 44, 47]. These differences could be due to regional climate, differences in exposure patterns or probably due to the use of different agricultural and farming methods worldwide.

Our present study has some limitations. Namely, relatively small number of the subjects in the study groups may be a limitation, with possible implications on the data obtained and its interpretation. Also, there is a lack of ambient monitoring and exposure measurement (endotoxin, dust, gases, vapors, and chemicals) in this survey. As a conclusion, within the actual study focused on assessment of adverse respiratory effects in farmers, their severity and work-relatedness, we found higher prevalence of work-related chronic respiratory symptoms in the last 12 months with significant

difference for phlegm, wheezing, and nasal symptoms as well as significantly lower values of two parameters of forced expiratory flow (MEF50 and MEF75), in cow breeders compared to controls. Respiratory impairment and bronchial hyperresponsiveness were closely related to the duration of workplace exposure, but also with occupational risk factors, work intensity, and farming characteristics. Our data suggest that workplace exposure in cow breeders farmers may cause respiratory impairment which is closely related to its duration, characteristics, and intensity, while its severity increases with the frequency and duration of animal contact.

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