RESEARCH ARTICLE

COPD, metabolic syndrome, respiratory symptoms, and functional incapacity in smokers, ex-smokers, and never-smokers aged 40-59 in Almaty, Kazakhstan: a cross-sectional study [version 1; peer review: 1 not approved]

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Abstract

Background: No study has reported the relationship between smoking status with chronic obstructive pulmonary diseases (COPD) and metabolic syndrome (MetS) in Kazakhstan. The aim of this study was to assess the associations between health outcomes, including COPD, MetS, respiratory symptoms, and functional incapacity, with the cigarette smoking status.

Methods: The cross-sectional study recruited 500 smokers, 200 ex-smokers, and 200 never-smokers aged 40-59 in Almaty, Kazakhstan. Questions assessed socio-demographic, clinical characteristics, and smoking behavior. Blood glucose and lipid profiles were determined after overnight fasting. COPD was defined according to the GOLD 2017 statement. Respiratory symptoms and functional incapacity were assessed by the COPD Assessment Test (CAT) and 6-min walk test (6MWT), respectively. Logistic regression models were used to assess the associations.

Results: The prevalence of COPD among smokers, ex-smokers and never-smokers were 5.5%, 3.0% and 3.0%, respectively. Respiratory symptoms based on CAT were more prevalent among smokers (42.8%) as compared to ex-smokers (42.8% vs 17.0%; aOR 3.43, 95% CI 2.25–5.23) and never-smokers (42.8% vs 12.5%; aOR 5.44, 95% CI 3.42–8.65). Current smokers were more likely to walk less than 450 meters during 6MWT as compared to never-smokers (16.5% vs 5.0%; aOR 3.72, 95% CI 1.86–7.44). No significant association was found between the smoking status with COPD and MetS.

Conclusions: Respiratory symptoms are common among the current smokers, even if most of them had preserved pulmonary function defined by spirometry.

Keywords
COPD, respiratory symptoms, smoking, 6-min walk test
**Introduction**

Tobacco smoking is the greatest preventable cause of death and illness in the world that attributed to more than 7 million deaths in 2015. Smoking is associated with elevated risk of mortality from lung and other cancers, heart disease, stroke, chronic obstructive pulmonary disease (COPD) and other respiratory diseases, and other conditions. The Global Adult Tobacco Survey (GATS) conducted in Kazakhstan in 2014 found that 19.1% of the study population were daily smokers (36.9% of males and 3.2% of females) (http://apps.who.int/tobacco/surveillance/survey/gats/kaz_countryreport_en.pdf?ua=1). COPD accounted for 3.2 million deaths worldwide in 2015 and is the fourth leading cause of death globally. In Kazakhstan, an expected 1.4 million people might have COPD based on estimations from neighboring countries.

Metabolic syndrome (MetS), or the set of specific cardiovascular risk factors, is also identified as a significant public health challenge that increases risk of developing type 2 diabetes, cardiovascular disease and several cancers. MetS is prevalent among patients with COPD. It was shown that cardiovascular disease, hypertension and diabetes in patients with COPD are associated with higher hospitalization and mortality rates.

The presence of respiratory symptoms prompts to recognize and diagnose respiratory disease including COPD and is often used to evaluate a severity of disease.

Smoking cessation has proven to have significant health benefits, including reduction in cardiovascular and COPD morbidity and mortality, and decrease in onset of respiratory symptoms. Some studies demonstrated that smoking is associated with metabolic syndrome and quitting smoking is recommended for the prevention and management of metabolic syndrome.

Assessment of the associations between several health outcomes, including COPD, respiratory symptoms, MetS and functional incapacity, and cigarette smoking status has not been done in Kazakhstan.

This study investigated these associations by comparing prevalence of these outcomes in smokers, ex-smokers, and never-smokers aged 40–59 in Almaty City, Kazakhstan.

**Methods**

**Study design**

The design of the study was described in detail in the study protocol published earlier.

The study included three groups of male and female residents of City of Almaty between the ages of 40 and 59 (inclusive), those who: 1) currently smoke cigarettes (current smokers); 2) quitted smoking between 1 and 5 years ago (ex-smokers); 3) have never smoked regularly (never-smokers). Smokers and ex-smokers were individuals with a minimum of 10 pack-year smoking history. Pack-years were calculated by taking the average number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked. The actual sample size was 900 including 500 smokers, 200 ex-smokers, and 200 never-smokers. The data was collected from September 2017 to April 2018.

**Outcome measures**

**COPD.** COPD is defined according to the Global strategy for the diagnosis, management, and prevention of COPD (COPD Gold) as a post-bronchodilator ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) less than 70% detecting by spirometry testing.

**Respiratory symptoms.** The COPD Assessment Test (CAT) is a quick and useful tool to weigh impact of COPD symptoms on health-related quality of life. Participants with a CAT score of 10 and more are considered having more severe respiratory symptoms.

**MetS.** We used the International Diabetes Federation definition (https://www.idf.org/our-activities/advocacy-awareness/resources-and-tools/60:idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html). Specifically, subjects were considered to have MetS if they had had central obesity (waist circumference (WC) > 94 cm in males and >80 cm in females) plus two and more of the following criteria: (1) hypertriglyceridemia, ≥150 mg/dL; (2) reduced HDL cholesterol, <40 mg/dL in males and <50 mg/dL in females; (3) high blood pressure, ≥130/85 mm Hg; high fasting plasma glucose (FPG), ≥100 mg/dL.

**Functional incapacity.** The six-minute walk test (6MWT) determines functional exercise capacity in patients with moderate-to-severe heart or lung disease. There are several reference systems predicting distance of 6MWT in healthy subjects. They take into account subject’s gender, age, height and weight. However, no study has been conducted so far to develop such a system for the Kazakh population. Therefore, we consider the distance of 450 meters as a cut-off level to define functional incapacity because distances less than this value is highly correlated with maximal oxygen capacity.

**Statistical analysis**

Data were analyzed using R, a language and environment for statistical computing, version 3.3.1 (https://www.R-project.org/). Logistic regression analyses were utilized to measure the crude and adjusted associations between the smoking status and the four health outcomes. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. For adjustment, logistic regression models included gender (categorical), age (continuous), ethnicity (categorical), level of education (categorical), secondary smoking (for the ‘ex-smokers vs never-smokers’ comparison, categorical), pack-year (for the ‘smokers vs ex-smokers’ comparison, continuous). An alpha-level of 0.05 was chosen to test statistical significance. The Bonferroni Correction of the significance level was applied to account that three associations (smokers vs ex-smokers, smokers vs never-smokers, and ex-smokers vs never-smokers) were studied for each health outcome. Therefore, a P-value<0.017 (0.05/3) was considered significant.
Results
Basic characteristics and smoking patterns of study participants by study group are summarized in Table 1. The study participants were approximately equally distributed as those who were younger than 50 years and older than 50 years of age. There were about twice as many participants of Kazakh ethnicity (Asian origin) compared to Russians (European origin). Most of the participants had higher education. Majority of those who were smoking had more than 20 pack-years of smoking (61%).

Data on COPD prevalence, CAT-test, functional capacity based on 6MWT and prevalence of MetS are shown in Table 2. The prevalence of COPD among smokers, ex-smokers and never-smokers were 5.5%, 3.0% and 3.0%, respectively. Respiratory symptoms based on CAT were more prevalent among smokers (42.8%) as compared to ex-smokers (17.0%) and never-smokers (12.5%). Proportion of participants with MetS varied across the study groups from 28.6% among never-smokers to 37.5% among current smokers. Current smokers were more likely (16.7%) to walk less than 450 meters during the 6MWT as compared to never-smokers (5.0%).

Mean scores of CAT components are show in Figure 1. Smokers had significantly worse mean scores in all CAT components.

| Smokers (N=500) | Ex-smokers (N=200) | Never-smokers (N=200) |
|----------------|-------------------|-----------------------|
| **Female**     |                   |                       |
| n (%)          | n (%)             | n (%)                 |
| 245 (49.0)*    | 100 (50.0)        | 102 (51.0)            |
| **Age group**  |                   |                       |
| ≤50            |                   |                       |
| 256 (51.2)     | 92 (46.0)         | 99 (49.5)             |
| 50+            |                   |                       |
| 244 (48.8)     | 108 (54.0)        | 101 (50.5)            |
| **Ethnicity**  |                   |                       |
| Kazakh         |                   |                       |
| 274 (54.8)     | 123 (61.5)        | 133 (66.5)            |
| Russian        |                   |                       |
| 147 (29.4)     | 42 (21.0)         | 44 (22.0)             |
| Other          |                   |                       |
| 79 (15.8)      | 35 (17.5)         | 23 (11.5)             |
| **Education**  |                   |                       |
| Secondary ed, and less | 77 (15.4) | 24 (12.0) | 13 (6.5) |
| Vocational school | 128 (25.6) | 41 (20.5) | 35 (17.5) |
| Some college   | 205 (59.0)        | 135 (67.5)            | 152 (76.0) |
| **Number of pack-year** |                   |                       |
| 0              |                   |                       |
| 200 (100.0)    | 200 (100.0)       | 200 (100.0)           |
| 10–19          |                   |                       |
| 197 (39.4)     | 110 (55.0)        | 90 (45.0)             |
| 20+            |                   |                       |
| 303 (60.6)     | 90 (45.0)         | 100 (50.0)            |
| **Regular secondary smoking in past 12 months** | 57 (28.5) | 38 (19.0) | 56 (28.0) |

* The number of cases (percentage).

Table 2. Health outcomes by study group.

| COPD | Ex-smokers (N=200) | Never-smokers (N=200) |
|------|--------------------|-----------------------|
| n (%)| n (%)              | n (%)                 |
| 27 (5.5)* | 6 (3.0) | 6 (3.0) |
| CAT≥10 | 214 (42.8) | 34 (17.0) | 25 (12.5) |
| CAT score, mean [SD] | 9.6 [6.1] | 5.9 [4.9] | 4.7 [4.3] |
| MetS  | 183 (37.4) | 70 (35.2) | 56 (28.6) |
| 6MWT<450 | 82 (16.5) | 22 (11.0) | 10 (5.0) |
| 6MWT, mean [SD] | 511 [63] | 530 [64] | 544 [60] |

Notes. COPD = chronic obstructive pulmonary disease; CAT = COPD Assessment Test; MetS = metabolic syndrome; SD=standard deviation; 6MWT=6-minute walk test.

* The number of cases (percentage).
than ex-smokers and never-smokers except in the sleeping category. There were statistically significant (p<0.017) differences between mean scores of ex-smokers and never-smokers for cough, phlegm, and chest tightness.

The relationship between the smoking status and the prevalence of metabolic syndrome components is presented in Table 3. The prevalence of reduced levels of high-density lipoproteins was significantly higher for the group of current smokers than for ex-smokers and never smokers. No significant relationship was found between the prevalence of other components and the smoking status (P>0.017).

Crude and adjusted odds ratios (aOR) between COPD, respiratory symptoms, MetS, functional incapacity and the smoking status are presented in Table 4. Current smokers were significantly associated with increased prevalence of functional incapacity (6MWT<450 meters) while comparing with never-smokers (aOR 3.72, 95% CI 1.86–7.44). Current smokers had more prevalent respiratory symptoms than ex-smokers (aOR 3.43, 95% CI 2.25–5.23) and never-smokers (aOR 5.44, 95% CI 3.42–8.65). No significant association was found between the smoking status and prevalence of COPD and MetS in all three pairwise comparisons.

Dataset 1. Raw data behind the results of this study

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The main data are provided for 900 subjects who completed the study (500 smokers, 200 ex-smokers, and 200 never-smokers). Missing data were not replaced.

Subject ID (ID), study group, gender, age, ethnicity, education, cigarette consumption (expressed as a number of pack-year), regular secondary smoking in past 12 months (for ex- and never-smokers), airflow obstruction by spirometry (FEV1/FVC < 70%), Six minute walk test, CAT total score, CAT components: - cough; - phlegm; - tightness of chest; - shortness of breath (SOB); - limited doing activities at home; - not confident leaving home; - not sleeping soundly; - no energy, metabolic syndrome (1 – yes, 0 – no), central obesity (1 – yes, 0 – no), raised triglyceride (≥ 150 mg/dL: 1 – yes, 0 – no), reduced high-density lipoprotein (< 40 mg/dL for males and < 50 mg/dL for females: 1 – yes, 0 – no), raised blood pressure (≥130/85 mm Hg: 1 – yes, 0 – no), raised fasting plasma glucose (≥100 mg/dL: 1 – yes, 0 – no).

Discussion

This study was the first in Kazakhstan to assess prevalence of COPD, respiratory symptoms, MetS, functional exercise incapacity in adults aged 40–59, those who smoked cigarettes, quit smoking and never smoked. The study demonstrated that at least 3% of the study population were affected by
Table 3. Prevalence of metabolic syndrome and is components by study group.

|                  | Smokers (N=485) | Ex-smokers (N=197) | Never-smokers (N=195) | Significant between-group difference* |
|------------------|----------------|--------------------|-----------------------|--------------------------------------|
|                  | n (%)          | n (%)              | n (%)                 |                                      |
| MetS             | 183 (37.7)†    | 70 (35.5)          | 56 (28.7)             |                                      |
| Central Obesity  | 368 (75.9)     | 152 (77.2)         | 137 (70.3)            |                                      |
| Serum TG ≥ 150 mg/dL | 144 (29.7)   | 47 (23.9)          | 41 (21.0)             |                                      |
| Reduced HDL cholesterol | 166 (34.2) | 45 (22.8)          | 40 (20.5)             | SE, SN                               |
| FPG ≥ 100 mg/dL  | 180 (37.1)     | 77 (39.1)          | 63 (32.3)             |                                      |
| BP ≥ 130/85 mmHg | 183 (37.7)     | 72 (36.5)          | 72 (36.9)             |                                      |

Notes. MetS = metabolic syndrome; TG= triglyceride; HDL= high-density lipoprotein; FPG= fasting plasma glucose; BP=blood pressure.
* p<0.017 for each pairwise comparison (SE – smokers vs ex-smokers; SN – smokers vs never-smokers; EN – ex-smokers vs never-smokers) by the chi-square test.
† The number of cases (percentage).

Table 4. Crude and adjusted odds ratios of COPD, respiratory symptoms, MetS, functional incapacity in adults according to cigarette smoking status.

| Comparison          | COPD       | CAT≥10     | MetS       | 6MWT<450 m |
|---------------------|------------|------------|------------|------------|
| Smokers vs Ex-smokers |           |            |            |            |
| Crude OR (95% CI)   | 1.85 (0.75-4.54) | 3.65 (2.43-5.50)* | 1.10 (0.78-1.55) | 1.60 (0.97-2.64) |
| Adjusted OR (95% CI)| 1.88 (0.75-4.70) | 3.43 (2.25-5.23)* | 1.04 (0.73-1.48) | 1.56 (0.92-2.63) |
| Smokers vs Never-smokers |           |            |            |            |
| Crude OR (95% CI)   | 1.86 (0.75-4.57) | 5.24 (3.23-8.26)* | 1.50 (1.05-2.16) | 3.73 (1.89-7.36)* |
| Adjusted OR (95% CI)| 2.01 (0.80-5.03) | 5.44 (3.42-8.65)* | 1.46 (1.01-2.12) | 3.72 (1.86-7.44)* |
| Ex-smokers vs Never-smokers |           |            |            |            |
| Crude OR (95% CI)   | 1.00 (0.32-3.17) | 1.43 (0.82-2.51) | 1.37 (0.89-2.09) | 2.34 (1.08-5.07) |
| Adjusted OR (95% CI)| 0.96 (0.30-3.11) | 1.37 (0.75-2.49) | 1.31 (0.84-2.04) | 1.95 (0.87-4.36) |

Notes. COPD = chronic obstructive pulmonary disease; CAT = COPD Assessment Test; MetS = metabolic syndrome; 6MWT=6-minute walk test; OR=odds ratio.
* p<0.017

COPD. This value is much higher than the rate of previously reported COPD cases of 340.5 per 100,000 population (http://www.mz.gov.kz/en/pages/statistical-symposium-health-republic-kazakhstans-population-and-activity-health-service).

Two of four health outcomes assessed in the study, respiratory symptoms and functional exercise incapacity, were significantly worse among current smokers than among those participants who never smoked cigarettes. Two other study outcomes, COPD and MetS, were more prevalent in current smokers, but the study couldn’t demonstrate statistically significant association with the smoking status.

The presence of all symptoms and signs of respiratory disease that are used as CAT components were significantly lower among ex-smokers compared to those who continued smoking. This study is in line with other studies, suggesting that respiratory symptoms improve after smoking cessation, however remain worse or at least similar to those found in never-smokers. One may assume that respiratory symptoms may be a significant reason for smoking cessation in a number of cases.

It is important to notice that a substantial proportion of the current smokers or 42.8% had respiratory symptoms, even if most of them had preserved pulmonary function defined by spirometry. It was shown that high CAT scores in current or ex-smokers are associated with exacerbation-like events, i.e. that symptomatic smokers with preserved pulmonary function have evidence of airway disease even when they do not meet the current definition for COPD. Exacerbation-like
events in individuals without COPD raise the burden of respiratory disease and are associated with considerable health outcomes. Thus, even proper diagnosis of COPD based on the spirometric criterion substantially underestimates the effect of smoking on the individual with smoking history.

The study has several limitations. This was cross-sectional study that was not designed to determine causal relationship. Second, although we adjusted for the known potential confounders, residual bias attributable to uncontrolled confounding variables may exist and cannot be estimated. Third, we used a quota sample which may have affected the generalizability of the study results to the study population. Fourth, our study participants were adults aged 40–59 from Almaty city, and further assessment is needed to determine whether the results are applicable to the other population groups.

Data availability

Dataset 1: Raw data behind the results of this study.

The main data are provided for 900 subjects who completed the study (500 smokers, 200 ex-smokers, and 200 never-smokers). Missing data were not replaced.

Subject ID (ID), study group, gender, age, ethnicity, education, cigarette consumption (expressed as a number of pack-year), regular secondary smoking in past 12 months (for ex- and never-smokers), airflow obstruction by spirometry (FEV1/FVC < 70%), Six minute walk test, CAT total score, CAT components: cough; phlegm; tightness of chest; shortness of breath (SOB); limited doing activities at home; not confident leaving home; not sleeping soundly; no energy, metabolic syndrome (1 – yes, 0 – no), central obesity (1 – yes, 0 – no), raised triglyceride (≥ 150 mg/dL: 1 – yes, 0 – no), reduced high-density lipoprotein (< 40 mg/dL for males and < 50 mg/dL for females: 1 – yes, 0 – no), raised blood pressure (≥ 130/85 mm Hg: 1 – yes, 0 – no), raised fasting plasma glucose (≥ 100 mg/dL: 1 – yes, 0 – no).

Ethics and consent

The National Central Ethic Committee under Ministry of Health and Social Development of the Republic of Kazakhstan approved this study on August 19, 2016. Written informed consent was obtained from all participants. The study has been registered in ClinicalTrial.gov (the release date: October 3, 2016; Identification No. NCT02926534).

Competing interests

No competing interests were declared.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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- The aim of this study is not quite clear, yet the topic is very interesting.
- The abstract is irrelevant and incomplete, and the conclusion is not fully corresponding to the aim of the study.
- Citations are correctly referenced at the end, but please check for the two internet links that were mentioned in our specific comments.
- Appropriate key studies were included.
- It is clear what is already known about the topic, but it is not clear what research question is outlined.
- The relationship between COPD and metabolic syndrome needs more justification in the introduction.
- Process of the subject selection is clear, and the method is valid.
- Please add more details regarding the software used.
- Tables and Figures are clearly presented. Please add statistical significance for Tables 1, 2 and 3. Titles, columns, and rows are labelled correctly. Still not quite sure about what is statistically significant and practically meaningful. Results may be over-interpreted.
- The discussion is very uncertain and repetitive. Limitations are not fatal and there should be another opportunity to inform future research. Discussion section is low quality.
- The article is not consistent within itself:
  - Conclusions of the study reflecting only one aspect of the aim, and it is only respiratory symptoms.
  - There is no data presented on spirometry of patients from 3 groups. It is not clear if it was performed in all groups.
- In the protocol of this study published earlier, it was mentioned that there was laboratory testing of serum: its not clear if alfa1antitripsin was tested.
- The same for chest computed tomography: any data from the smoking group?
- There is surprisingly low prevalence of COPD in the smoker group!
- In the discussion, the data from the current study must be compared with the data from other studies.
  o Conclusions are not corresponding to the aim of the study.

Questions to the author(s):
1. How reliable is the COPD Assessment Test (CAT) for this study?
2. What was the cause for COPD among never-smoker subjects?
3. In your introduction, first paragraph: You used 2015 statistic numbers. Why not 2017 or 2018?
4. Why is metabolic syndrome associated with COPD? Please consider adding a paragraph regarding the pathophysiology between those entities.
5. What impact you did consider having with this paper?
6. Regarding the statistical computing “R”: Where was it designed? Is it reliable and accurate?
7. What was the etiology for the metabolic syndrome of those patients?
8. Is it possible that patients with metabolic syndrome had respiratory symptoms due to their obesity?

Specific comments from reviewer to author(s):
1. Introduction, 3rd paragraph: Please use the correct internet citation for this paragraph (Vancouver style if possible) and place it as #3. Then move all the numbers according to their new assigned number citation. (for example: ...“20153” now is “20154”.)
2. Outcome measures: MetS – Correct internet citation for the definition and also assigned a number as well. Then correct the reference list and check that all the numbers are according to their citation in the article.
3. Please add more information about the statistical computing “R”.

Is the work clearly and accurately presented and does it cite the current literature?  Yes

Is the study design appropriate and is the work technically sound? No

Are sufficient details of methods and analysis provided to allow replication by others? No

If applicable, is the statistical analysis and its interpretation appropriate? Yes

Are all the source data underlying the results available to ensure full reproducibility? Yes

Are the conclusions drawn adequately supported by the results? No

Competing Interests: No competing interests were disclosed.
We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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