High COPD prevalence at high altitude

Brakema, Evelyn A; Tabyshova, Aizhamal; Kasteleyn, Marise J; Molendijk, Eveline; van der Kleij, Rianne M J J; van Boven, Job F M; Emilov, Berik; Akmatalieva, Meerim; Mademilov, Maamed; Numans, Mattijs E

Published in:
European Respiratory Journal

DOI:
10.1183/13993003.01193-2018

Publication date:
2019

ERJ Express. Published on November 21, 2018 as doi: 10.1183/13993003.01193-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

High COPD prevalence at high altitude: does household air pollution play a role?

Evelyn A. Brakema, Aizhamal Tabyshova, Marise J. Kasteleyn, Eveline Molendijk, Rianne M.J.J. van der Kleij, Job F.M. van Boven, Berik Emilov, Meerim Akmatalieva, Maamed Mademilov, Mattijs E. Numans, Sian Williams, Talant Sooronbaev, Niels H Chavannes

Please cite this article as: Brakema EA, Tabyshova A, Kasteleyn MJ, *et al*. High COPD prevalence at high altitude: does household air pollution play a role?. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01193-2018).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

High COPD prevalence at high altitude: does household air pollution play a role?

Authors:

Evelyn A Brakema[1], Aizhamal Tabyshova[2,3], Marise J Kasteleyn[1], Eveline Molendijk[1], Rianne MJJ van der Kleij[1], Job FM van Boven[3], Berik Emilov[2], Meerim Akmatalieva[2], Maamed Mademilov[2], Mattijs E Numans[1], Sian Williams[4], Talant Sooronbaev[2], Niels H Chavannes[1]

Affiliations:

[1] Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

[2] Pulmonary Department, National Center of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan

[3] Department of General Practice & Elderly Care Medicine, Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[4] International Primary Care Respiratory Group (IPCRG), London, United Kingdom

Correspondence: Evelyn A. Brakema, Department of Public Health and Primary Care, Leiden University Medical Center, Postzone V0-P, Postbus 9600, 2300 RC , Leiden, The Netherlands. Email: e.a.brakema@lumc.nl

Key words: COPD, altitude, household air pollution, FRESH AIR (epidemiology, solid fuel, low-resource setting), Kyrgyzstan

Take home message:

High indoor PM2.5 levels could explain elevated COPD prevalence in rural, high altitude settings: prevention is key!

Abstract

Studies comparing COPD prevalence across altitudes report conflicting results. Yet, household air pollution, a major COPD risk factor, was mostly not accounted for in previous analyses and never objectively measured. We aimed to compare the prevalence of COPD and its risk factors between low-resource highlands and lowlands, with a particular focus on objectively-measured household air pollution.

We conducted a population-based, observational study in a highland (~2050m) and lowland (~750m) setting in rural Kyrgyzstan. We performed spirometry in randomly selected households, measured indoor particulate matter <2.5μm ($PM_{2.5}$), and administered a questionnaire on other COPD risk factors. Descriptive statistics and multivariable logistic regressions were used for analyses.

We included 392 participants: 199 highlanders and 193 lowlanders. COPD was more prevalent among highlanders (36.7% vs. 10.4%,$p<0.001$). Also, their average $PM_{2.5}$-exposure was higher (290.0 vs. 72.0 μg/m^3,$p<0.001$). Besides high $PM_{2.5}$-exposure (OR 3.174;95%CI 1.061–9.493), the altitude setting (3.406;1.483–7.825), pack years (1.037;1.005–1.070), and age (1.058;1.037–1.079) also contributed to a higher COPD prevalence among highlanders.

COPD prevalence and household air pollution were highest in the highlands and were independently associated. Preventive interventions seem warranted in these low-resource, highland settings. With this study being one of the first spirometry-based prevalence studies in Central-Asia, generalisability needs to be assessed.

Introduction

Chronic obstructive pulmonary disease (COPD) is the world's third leading cause of death, accounting for 5.7% of all deaths globally[1, 2]. Over 90% of COPD-related deaths occur in low- and middle-income countries, leading to a substantial clinical, economic and societal burden[3, 4]. Gaining insight into risk factors and places where the burden of disease is highest is key to a tailored approach to COPD.

Globally, around 400 million people live at high altitude (>1500 meters above sea-level)[5], yet it remains equivocal whether COPD prevalence is higher in these settings. Five observational studies in diverse settings reported contradicting findings[6-10]. Additionally, two studies pooled data from various prevalence studies, and while one described a lower COPD prevalence at higher altitude[11], the other observed no difference when adjusting for several risk factors[12]. However, household air pollution (HAP) was not adjusted for in either of these pooled studies. Of note, especially in low-resource settings, HAP is increasingly reported as a major risk factor for COPD[2, 3, 13-18].

HAP is caused by the indoor use of coal and biomass (e.g. animal dung, wood, crop residues), also known as solid fuels. Cooking and heating with solid fuels – as is common in 90% of rural households worldwide – leads to variably high levels of lung-damaging pollutants. Most exposed are women and their children, as women often prepare the meals above the fire in poorly ventilated houses for several hours daily, keeping their children close to them[13-15]. In 2015, HAP was estimated to be responsible for 4.2 million deaths and 103.1 million lost years of healthy life[19].

Some of the previous studies did report HAP-exposure across altitudes, but used self-reported proxies (such as 'solid fuel use')[7, 8, 10]. None objectively measured personal particulate matter (PM) exposure in vivo, which is needed for accurate pollution assessment[20]. Also, earlier studies focused almost exclusively on urban settings, yet rural settings have more limited access to clean fuels and are consequently more severely affected by HAP[14].

Therefore, in this study we aimed to compare the prevalence of COPD and its risk factors between rural, low-resource highlands and lowlands, with a special focus on HAP. We expected that the more extreme climate conditions at high altitude increase the need for (solid fuel-based) heating and for limiting ventilation, thereby increasing the risk of COPD. We therefore hypothesised HAP-exposure to be higher at high altitude and, consequently COPD prevalence to be higher as well.

Methods

Study design and setting

We conducted an observational, cross-sectional, population-based study in a lowland and highland setting in rural Kyrgyzstan. This lower-middle income country in Central-Asia has a population of 5.96 million, with an average life expectancy of 71 years[21]. It has the highest respiratory mortality of all countries in the European Respiratory Society 'White Book'[22]. Kyrgyzstan offers a large contrast in altitude. Its lowest region (Chui, ~750 meters above sea level) and one of its highest regions (Naryn, ~2050 meters) were selected as low- and highland setting[23]. Chui has 756,000 rural inhabitants (total 922,000) and hosts the country's capital Bishkek. It's neighbouring region, Naryn, counts 245,000 rural inhabitants (total 284,000)[24]. We collected data in the lowlands between 3 February and 7 May 2015, and in the highlands between 16 July and 13 September 2014. The colder measurement period in the year in the lowlands compared to the highlands was considered to involve relatively more (solid fuel-based) heating and less ventilation in the lowlands. Hence, seasonal influences would lead to an underestimation of differences in exposure to HAP and in respiratory symptoms.

This study preceded the Free Respiratory Evaluation and Smoke- exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR) project (NTR5759), an implementation science project targeting chronic lung diseases in low-resource settings[25].

Participants

Given at the time of protocol development no previous studies of COPD prevalence in Kyrgyzstan or neighbouring countries existed, we aimed for 600 participants based on a previous FRESH AIR study in Uganda[26] and on the BOLD study[27]. To this end, fifty households per setting were selected randomly through a multi-stage sampling approach. All permanent residents ≥18 years who provided informed consent were included, because people highly exposed to HAP may develop COPD even before the age of 30[26]. Persons with a current respiratory infection or a contraindication for spirometry[28] were excluded. We obtained written, informed consent from all participants. All field-researchers were trained on ethics and the informed consent procedure. The Research Ethics Committee of the National Centre for Cardiology and Internal Medicine (Bishkek) approved the study (protocol 9;2014/3/1).

Demographics, COPD risk factors, and respiratory symptoms

A standardised questionnaire, composed of validated questionnaires and used in the FRESH AIR study in Uganda[26], was tailored to Kyrgyzstan (Appendix 1). It was researcher-administered in the local language (Kyrgyz or Russian). It included questions on demographics, cooking- and heating circumstances, COPD risk factors, and respiratory symptoms (Table 1&2).

Household air pollution

HAP was measured by the time-weighted average concentration of particulate matter with an aerodynamic diameter <2.5µm ($PM_{2.5}$), using the TSI SidePak AM510 Personal Aerosol Monitor (TSI Inc., Minneapolis, US). Households' cooks were instructed to wear the device continuously on their body throughout the measurements. Measurements mostly started in the morning (median time 11:41 vs. 11:48 respectively) and hence involved preparation of at least one warm meal. The median time of continuous measurement was 269 minutes in the lowlands and 284 in the highlands (Appendix 2). Of note, we initially aimed to measure 24-hour indoor concentrations but this was not feasible due to the limited possibility to charge the battery of the device in the rural areas.

COPD diagnosis

A local team of medical doctors, trained by teachers from Imperial College London, assessed lung function using spirometry (EasyOne^{TM}; Medizintechnik AG, Zürich, Switzerland) following joint American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines[29]. We determined forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) before and after bronchodilation with 400µg salbutamol using a spacer. COPD was defined as having a post-bronchodilator FEV_1/ FVC ratio of <70%[30], and classified severity according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages[31]. Subjects with complete reversibility were included as non-COPD in the analyses (an asthma diagnosis was suspected.) Oxygen saturation (SpO_2) was measured with pulse-oximetry (YX302 Fingertip Pulse-Oximeter; Timago International Group**,** Bielsko-Biała, Poland).

Data analysis

SPSS version 23 (IBM, Armonk, US) was used for the analysis. Baseline characteristics, COPD prevalence and HAP exposure across altitudes were compared with independent T-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed variables and Chi-square or Fisher's exact tests for categorical variables. Univariable and forced-entry multivariable logistic regression models, adjusting for clustering within households by Generalised Estimating Equation analyses[32] were used to assess the independent association between risk factors and COPD. HAP and other known COPD predictors (age, sex, education level, pack years)[12] and altitude were included as predictors. Tuberculosis (ever-diagnosed) was not included in the model due to the limited number of cases. Working in the primary or secondary sector was included as a predictor due to the assumed higher occupational exposure compared to the tertiary/quaternary sector[33]. HAP was categorised into tertiles (Appendix 4, Table E1), given the non-normal distribution with high values (in this high range we did not assume linearity of HAP with the logit of the outcome). Multicollinearity was not evident in the model. *P*-values <0.05 and odds ratios with a 95% confidence interval excluding 1 were considered statistically significant.

Handling of missing data

Inadequate registration of several households and residents resulted in various duplications and uncertainty about these residents' $PM_{2.5}$ measurements. To guarantee data quality and enable adjustment for a clustering effect within households, we discarded both these original and duplicate measurements from the analysis. Also, participants with missing $PM_{2.5}$- and/or spirometry values were excluded.

Results

Study population

All 599 invited individuals consented to participate in the study. After exclusion, 193 lowlanders and 199 highlanders from 41 households per setting remained for analysis (Figure 1).

Demographics and distribution of risk factors for COPD

Highlanders were significantly older, and had a lower height and weight (Table 1). They had a lower level of education, worked more often in the primary sector, and less frequently in the secondary sector. The highland population consisted of significantly fewer smokers, although their pack years were significantly higher. Highlanders were (non-significantly) more frequently ever-diagnosed with tuberculosis.

Household air pollution across altitudes

The time-weighted average $PM_{2.5}$ concentration per household in the highlands was significantly higher than in the lowlands (median [IQR] 290.0 µg/m^3 [123.5; 703.5] vs. 72.0 µg/m^3 [31.0; 167.0]; $p<0.001$) (Figure 2). Furthermore, higher maximum $PM_{2.5}$ concentrations were measured in the highlands (5822.0 µg/m^3 [2308.0; 9152.5] vs. 272.0 µg/m^3 [140.0; 901.5]; $p<0.001$). In both areas these maxima were mostly reached at the beginning of the afternoon (median 13:42:04 vs. 13:05:40). Measurement duration is specified in Appendix 2. Highlanders' cooking- and heating circumstances were also more at risk of generating HAP. For example, highlanders significantly more often had higher risk types of fuel use (e.g. dung vs. gas), stoves (e.g. open fire vs. improved cookstove), ventilation (e.g. eaves spaces vs open door), and cooking- locations and durations. Details on these factors across the settings are provided in Appendix 3.

COPD prevalence across altitudes

COPD was more prevalent in the highlands (36.7% vs. 10.4%; $p<0.001$), although severity was lower (GOLD≥ 2 of 24.7% vs. 70.0%; $p<0.001$) (Table 2, Figure 3). COPD was equally distributed over men and women in the highlands, while in the lowlands the vast majority of patients were male (49.3% vs. 80.0%; $p<0.001$). COPD patients in the highlands were significantly less frequently smokers and were exposed to significantly higher $PM_{2.5}$ levels compared to lowlanders (Figure 4 and Appendix 4, Figure E1). Additionally, oxygen saturation was significantly lower among highlanders (SpO_2% 93.0 vs 95.0; $p<0.001$).

Predictors for COPD

Across the two altitudes, a total of 93 participants met COPD criteria. In the univariable logistic regression model, age, sex, pack years, altitude, and HAP were positively associated with COPD (Figure 5 and Appendix 4). In the multivariable logistic regression model, age, pack years, altitude, and the highest HAP-exposure remained significantly positively associated with COPD. The decline in lung function along with an increase in $PM_{2.5}$ exposure is depicted in Appendix 4 Figure E2.

Discussion

In this study, we have compared the prevalence of COPD and its risk factors between highlands and lowlands in rural, low-resource settings in Kyrgyzstan, with a special focus on objectively-measured HAP. Both COPD prevalence and HAP-exposure (peak- and average $PM_{2.5}$-concentrations) were significantly higher among highlanders. Besides living at high altitude and being exposed to high HAP-concentrations, more pack years and a higher age were also independently associated with COPD (and more common in the highlands). Our results highlight the particular vulnerability of rural highlanders to COPD, and confirm the increasingly acknowledged impact of HAP on respiratory health.

Overall COPD prevalence in both Kyrgyz settings was high considering our relatively low age inclusion criterion (≥18 years). Our lowlands prevalence was similar to the global ~10%, yet the prevalence observed in the highlands was more than threefold higher[27]. Our definition of COPD might have contributed to this high prevalence, especially among highlanders who were slightly older (a fixed FEV_1/FVC ratio is known to overdiagnose COPD in elderly[35]). Also, we used Caucasian reference values (rural, high-altitude, Central-Asian values do not exist), while a Kyrgyz study at middle-altitude (~1000-2000m) reported larger FVC values among their population[36]. Larger physiological FVC values may result in smaller FEV_1/FVC ratios and hence to overdiagnosis. A recent Kazakh population-based study found a prevalence of 6.7%[37]. The authors only studied a lowland, adult (≥18 years) population, used the same definition of COPD, but studied an urban rather than a rural setting. Given the lesser use of solid fuels in urban settings, the latter factor may explain the lower COPD prevalence they observed.

In accordance with our hypothesis, along with a higher COPD prevalence in the highlands we observed significantly higher HAP-exposures. It seems plausible to observe more HAP at higher altitude in rural areas, because more extreme climate conditions increase the need for (solid fuel-based) heating and for limiting ventilation. Furthermore, highlanders more commonly worked in the primary sector where dung is both cheaper and more easily available than clean fuels. Hence, particularly in the highlands our HAP-measurements dramatically exceeded the average 25 $\mu g/m^3$ as stated in the WHO 24-hour $PM_{2.5}$ air quality guideline[34]. These measurements are consistent with $PM_{2.5}$-concentrations in other households using predominantly biomass fuels[13]. Our findings support the assumption that HAP plays a substantial role in explaining a high COPD prevalence at high altitude. This assumption is furthermore consistent with the relatively more (non-smoking) female patients in our highland population, like in other settings where women are highly exposed to biomass fuel smoke[13-15, 17, 26, 38]. Although the pathogenic mechanisms of the harm of HAP are not yet fully uncovered, HAP is considered to alter the innate immune response, enhance pulmonary and systemic inflammation and promote an oxidative stress state. This may cause macromolecular cell damage, including DNA changes[39]. Nevertheless, BOLD results remind us to remain alert for causes other than HAP for airflow obstruction[40].

Besides the strong and significant relation between COPD and $PM_{2.5}$-concentrations, altitude itself was another independent predictor in the multivariable analysis, also after adjusting for age and pack years. Altitude might either directly impact COPD prevalence as it is associated with an increase in both airways and total lung capacities. Yet evidence remains inconclusive if this increase is proportional (hence, if and how FEV_1/FVC ratios are affected[41-43]). Alternatively, altitude could relate to COPD prevalence indirectly via (unmeasured) factors. These could be a more frequent history of pneumonia/tuberculosis, lower level of physical activity[44, 45], higher occupational exposure[33], or more (childhood) poverty/lower sociodemographic development (as again a mediator for other factors)[2, 46].
Remarkably, prevalence of moderate/severe COPD (GOLD ≥ 2) appeared to be lower in the highlands. This could be due to down-migration of the severely ill for higher ambient oxygen levels[47], for better access to advanced healthcare in the Kyrgyz capital, or to a potential relation between severity and solid fuel smoke versus tobacco smoke[38]. The lower highland oxygen saturation levels we observed seem plausible due to lower ambient oxygen levels in the highlands. Furthermore, a double exposure of tobacco- and biomass fuel smoke among COPD patients is associated with lower oxygen saturation levels.[48] Yet, although the

number of COPD patients with a double exposure was significantly higher in the highlands, the total number of participants with a double exposure was equal.

As mentioned earlier, the seven other studies covering COPD prevalence across altitudes reported conflicting findings[6-12]. We argue that these conflicting results can be partly explained by differences in HAP-exposure, which these studies either did not measure, or measured by proxy, or did not adjust for in the analyses. HAP-exposure, associated COPD prevalence, and the difference across altitudes may have differed substantially between the study settings. The settings were almost exclusively urban, sometimes in a high-income country, meaning more extreme high altitude climates could be less influential on HAP-exposure due to better access to clean fuels[14]. Furthermore, ethnicity often differed between the high- and low altitude settings within a study, hampering proper comparison of lung functions.

We corrected for objectively-measured HAP in our analyses, compared consistently between rural, low-resource settings and between people of the same ethnicity. Altitude remained an independent predictor for COPD. The conflicting results between all present studies, performed in different settings, may indicate COPD prevalence might not be attributable to altitude itself. Instead, it could be mainly mediated through (unmeasured) factors expressed by altitude, with HAP being one of them.

A major strength of this study is the objective, personally monitored $PM_{2.5}$-exposure combined with spirometry according to ATS/ERS guidelines[29], other than self-reported presence of risk factors or symptoms. This method precisely answers a recent call for objective measurements on the association between HAP and COPD[20]. Also, this study benefited from a high participation rate. Participants indicated they were eager to receive extra medical attention as access to healthcare is generally limited in these rural areas. This high rate impedes selection bias, and enhances generalisability to other settings. Lastly, we present one of the first spirometry-based COPD prevalence studies in Central-Asia[2]. Some limitations must also be noted. Due to organisational difficulties during data collection, we had to exclude various participant- and household measurements in both settings. Differences between the two settings however were still statistically significant, and we were not able to identify any differences between excluded and included participants. Also, due to the limited battery- and charging capacity in the rural areas we could not perform 24-hour $PM_{2.5}$ measurements. We therefore measured each household for approximately four hours and at the same hour during the day, including the preparation of at least one warm meal. Hence, 24-hour $PM_{2.5}$-concentrations are likely to be lower as those contain a longer period without meal preparations. Lastly, given that the data in the lowlands were collected in a relatively colder period of the year, with a relatively higher need for (solid fuel-based) heating and limiting ventilation, differences in HAP and respiratory symptoms might be underestimated.

In conclusion, we observed a substantially higher COPD prevalence in high altitude areas compared to low altitude areas in rural Kyrgyzstan. HAP-exposure was high in both settings, but particularly in the highlands. There was a strong, significant relation between COPD and HAP that remained significant when adjusted for other risk factors. Although generalisability to other rural, low-resource highlands remains to be assessed, our results call for an increased focus on COPD awareness, diagnosis, and treatment. Policy makers, healthcare workers and highlanders in these settings should moreover focus on prevention by increasing awareness on HAP and by reducing it (e.g. by the implementation of clean cooking stoves). This could not only benefit chronic lung health, but also target other $PM_{2.5}$-related diseases such as ischemic heart disease, cerebrovascular disease, lung cancer, low birth weight and preterm birth, type 2 diabetes, and lower respiratory infections[16].

Declaration of interest: We declare no competing interests.

Financial support: This study was funded by Healthy Lungs for Life from the European Lung Foundation. The funders had no role in study design, data collection, analysis, interpretation, or writing of the report.

Acknowledgements: This study was based on a pre-FRESH AIR study in Uganda. We thank Frederik van Gemert University Medical Center Groningen, Groningen, Netherlands, and co-authors for sharing their protocol and questionnaire. We thank Beraki Ghezai, Lunger i Praksis, Oslo, Norway, for his important role in introducing the program in Kyrgyzstan, educating the researchers, and translating the protocol to Russian. Also, we thank Ron Wolterbeek and Nan van Geloven, (retired) statisticians at the Leiden University Medical Center (LUMC), Leiden, the Netherlands, for his statistical input. We thank Charlotte Poot, LUMC, for her assistance in designing the figures. We thank International Primary Care Respiratory Group (IPCRG) for securing the grant from European Lung Foundation. Lastly, we thank all participants.

This paper was presented as an oral presentation during the ERS congress 2018 (OA288).

Author's contributions: TS and AT adapted the FRESH AIR study to the Kyrgyz settings and coordinated data collection. EB, AT, MK, and EM analysed and interpreted data. EB wrote the first draft of this report. All authors provided comments and EB revised the report. Again, all authors gave input to the final version. All authors had full access to all the data and EB and NC had the final responsibility for the decision to submit the study for publication.

References

1. Institute for Health Metrics and Evaluation. GBD Compare Data Visualization. 2016 [cited 2018 Apr 4]; Available from: http://vizhub.healthdata.org/gbd-compare
2. GBD Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017: 5(9): 691-706.
3. World Health Organization. Chronic obstructive pulmonary disease (COPD). 2016 Nov [cited 2018 Apr 4]; Available from: http://www.who.int/mediacentre/factsheets/fs315/en/
4. Khakban A, Sin DD, FitzGerald JM, Ng R, Zafari Z, McManus B, Hollander Z, Marra CA, Sadatsafavi M. Ten-Year Trends in Direct Costs of COPD: A Population-Based Study. *Chest* 2015: 148(3): 640-646.
5. Cohen JE, Small C. Hypsographic demography: the distribution of human population by altitude. *Proc Natl Acad Sci U S A* 1998: 95(24): 14009-14014.
6. Caballero A, Torres-Duque CA, Jaramillo C, Bolivar F, Sanabria F, Osorio P, Orduz C, Guevara DP, Maldonado D. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). *Chest* 2008: 133(2): 343-349.
7. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, Montes de Oca M, Talamo C, Hallal PC, Victora CG, Team P. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005: 366(9500): 1875-1881.
8. Laniado-Laborin R, Rendon A, Batiz F, Alcantar-Schramm JM, Bauerle O. High altitude and chronic obstructive pulmonary disease prevalence: a casual or causal correlation? *Arch Bronconeumol* 2012: 48(5): 156-160.
9. McDaniel JT. Prevalence of chronic obstructive pulmonary disease: county-level risk factors based on the Social Ecological Model. *Perspect Public Health* 2018: 1757913918772598.
10. Miele CH, Grigsby MR, Siddharthan T, Gilman RH, Miranda JJ, Bernabe-Ortiz A, Wise RA, Checkley W, Group CCS. Environmental exposures and systemic hypertension are risk factors for decline in lung function. *Thorax* 2018.
11. Aaron SD, Gershon AS, Gao Y, Yang J, Whitmore GA. Influence of country-level differences on COPD prevalence. *Int J Chron Obstruct Pulmon Dis* 2016: 11: 2305-2313.
12. Horner A, Soriano JB, Puhan MA, Studnicka M, Kaiser B, Vanfleteren L, Gnatiuc L, Burney P, Miravitlles M, Garcia-Rio F, Ancochea J, Menezes AM, Perez-Padilla R, Montes de Oca M, Torres-Duque CA, Caballero A, Gonzalez-Garcia M, Buist S, Flamm M, Lamprecht B, Group BCR, Team E-S, Team P, Group PS. Altitude and COPD prevalence: analysis of the PREPOCOL-PLATINO-BOLD-EPI-SCAN study. *Respir Res* 2017: 18(1): 162.
13. Gordon SB, Bruce NG, Grigg J, Hibberd PL, Kurmi OP, Lam KB, Mortimer K, Asante KP, Balakrishnan K, Balmes J, Bar-Zeev N, Bates MN, Breysse PN, Buist S, Chen Z, Havens D, Jack D, Jindal S, Kan H, Mehta S, Moschovis P, Naeher L, Patel A, Perez-Padilla R, Pope D, Rylance J, Semple S, Martin WJ, 2nd. Respiratory risks from household air pollution in low and middle income countries. *Lancet Respir Med* 2014: 2(10): 823-860.
14. World Health Organization. Fuel for life: household energy and health. 2006 [cited 2018 Apr 4]; Available from: http://www.who.int/indoorair/publications/fuelforlife/en/index.html
15. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009: 374(9691): 733-743.
16. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, Feigin V, Freedman G, Hubbell B, Jobling A, Kan H, Knibbs L, Liu Y, Martin R, Morawska L, Pope CA, 3rd, Shin H, Straif K, Shaddick G, Thomas M, van Dingenen R, van Donkelaar A, Vos T, Murray CJL, Forouzanfar MH. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017: 389(10082): 1907-1918.
17. Siddharthan T, Grigsby MR, Goodman D, Chowdhury M, Rubinstein A, Irazola V, Gutierrez L, Miranda JJ, Bernabe-Ortiz A, Alam D, Kirenga B, Jones R, van Gemert F, Wise RA, Checkley W.

Association between Household Air Pollution Exposure and Chronic Obstructive Pulmonary Disease Outcomes in 13 Low- and Middle-Income Country Settings. *Am J Respir Crit Care Med* 2018: 197(5): 611-620.
18. Magitta NF, Walker RW, Apte KK, Shimwela MD, Mwaiselage JD, Sanga AA, Namdeo AK, Madas SJ, Salvi SS. Prevalence, risk factors and clinical correlates of COPD in a rural setting in Tanzania. *Eur Respir J* 2018: 51(2).
19. GBD Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016: 388(10053): 1659-1724.
20. Balmes JR, Eisen EA. Household Air Pollution and Chronic Obstructive Pulmonary Disease. "A Riddle, Wrapped in a Mystery, Inside an Enigma". *Am J Respir Crit Care Med* 2018: 197(5): 547-549.
21. World Bank. Country Profile Kyrgyz Republic. 2016 [cited 2018 Jun 16]; Available from: http://databank.worldbank.org/data/Views/Reports/ReportWidgetCustom.aspx?Report_Name=CountryProfile&Id=b450fd57&tbar=y&dd=y&inf=n&zm=n&country=KGZ
22. European Respiratory Society. European Lung White Book - The burden of lung disease. 2011 [cited 2018 Jun 26]; Available from: https://www.erswhitebook.org/chapters/the-burden-of-lung-disease/
23. Elevation Map. Chui and Naryn, Kyrgyzstan: Google Map data; 2017.
24. National Statistical Committee of the Kyrgyz Republic. Population - 2018-жылдын 1-январына карата Кыргыз Республикасынын калкынын саны. 2018.
25. Cragg L, Williams S, Chavannes NH. FRESH AIR: an implementation research project funded through Horizon 2020 exploring the prevention, diagnosis and treatment of chronic respiratory diseases in low-resource settings. *NPJ Prim Care Respir Med* 2016: 26: 16035.
26. van Gemert F, Kirenga B, Chavannes N, Kamya M, Luzige S, Musinguzi P, Turyagaruka J, Jones R, Tsiligianni I, Williams S, de Jong C, van der Molen T. Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (FRESH AIR Uganda): a prospective cross-sectional observational study. *Lancet Glob Health* 2015: 3(1): e44-51.
27. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, Nizankowska-Mogilnicka E, Group BCR. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007: 370(9589): 741-750.
28. Cooper BG. An update on contraindications for lung function testing. *Thorax* 2011: 66(8): 714-723.
29. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. *Eur Respir J* 2005: 26(2): 319-338.
30. Fabbri LM, Hurd SS. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. *Eur Respir J* 2003: 22(1): 1-2.
31. (GOLD); GIfCOLD. From the Global Strategy for the Diagnosis, Management and Prevention of COPD; 2017.
32. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986: 42(1): 121-130.
33. World Health Organization. Preventing noncommunicable diseases (NCDs) by reducing environmental risk factors 2017.
34. World Health Organization. WHO Indoor Air Quality Guidelines: Household Fuel Combustion. Geneva, 2014.
35. Hnizdo E, Glindmeyer HW, Petsonk EL, Enright P, Buist AS. Case definitions for chronic obstructive pulmonary disease. *COPD* 2006: 3(2): 95-100.
36. Vinnikov D, Blanc PD, Brimkulov N. Spirometry reference values for a Kyrgyz population. *Clin Respir J* 2018: 12(2): 826-828.

37. Nugmanova D, Feshchenko Y, Iashyna L, Gyrina O, Malynovska K, Mammadbayov E, Akhundova I, Nurkina N, Tariq L, Makarova J, Vasylyev A. The prevalence, burden and risk factors associated with chronic obstructive pulmonary disease in Commonwealth of Independent States (Ukraine, Kazakhstan and Azerbaijan): results of the CORE study. *BMC Pulm Med* 2018: 18(1): 26.
38. Ramirez-Venegas A, Sansores RH, Perez-Padilla R, Regalado J, Velazquez A, Sanchez C, Mayar ME. Survival of patients with chronic obstructive pulmonary disease due to biomass smoke and tobacco. *Am J Respir Crit Care Med* 2006: 173(4): 393-397.
39. Olloquequi J, Silva OR. Biomass smoke as a risk factor for chronic obstructive pulmonary disease: effects on innate immunity. *Innate Immun* 2016: 22(5): 373-381.
40. Amaral AFS, Patel J, Kato BS, Obaseki DO, Lawin H, Tan WC, Juvekar SK, Harrabi I, Studnicka M, Wouters EFM, Loh LC, Bateman ED, Mortimer K, Buist AS, Burney PGJ, Group BCR. Airflow Obstruction and Use of Solid Fuels for Cooking or Heating: BOLD Results. *Am J Respir Crit Care Med* 2017.
41. Havryk AP, Gilbert M, Burgess KR. Spirometry values in Himalayan high altitude residents (Sherpas). *Respir Physiol Neurobiol* 2002: 132(2): 223-232.
42. Wood S, Norboo T, Lilly M, Yoneda K, Eldridge M. Cardiopulmonary function in high altitude residents of Ladakh. *High Alt Med Biol* 2003: 4(4): 445-454.
43. Rupert JL, Hochachka PW. The evidence for hereditary factors contributing to high altitude adaptation in Andean natives: a review. *High Alt Med Biol* 2001: 2(2): 235-256.
44. Lee CH, Lee MC, Lin HH, Shu CC, Wang JY, Lee LN, Chao KM. Pulmonary tuberculosis and delay in anti-tuberculous treatment are important risk factors for chronic obstructive pulmonary disease. *PLoS One* 2012: 7(5): e37978.
45. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. *Am J Respir Crit Care Med* 2007: 175(5): 458-463.
46. Townend J, Minelli C, Mortimer K, Obaseki DO, Al Ghobain M, Cherkaski H, Denguezli M, Gunesekera K, Hafizi H, Koul PA, Loh LC, Nejjari C, Patel J, Sooronbayev T, Buist SA, Burney PGJ. The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study. *Eur Respir J* 2017: 49(6).
47. Regensteiner JG, Moore LG. Migration of the elderly from high altitudes in Colorado. *JAMA* 1985: 253(21): 3124-3128.
48. Olloquequi J, Jaime S, Parra V, Cornejo-Cordova E, Valdivia G, Agusti A, Silva OR. Comparative analysis of COPD associated with tobacco smoking, biomass smoke exposure or both. *Respir Res* 2018: 19(1): 13.

Table 1. Demographics and distribution of risk factors for COPD

	Lowlands n = 193	**Highlands** n = 199	**P-value**
Male, n (%)	100 (51.8)	87 (43.7)	0.109
Age (years), mean (SD)	44.4 (13.6)	50.0 (16.3)	<0.001
Height (cm), mean (SD)	166.3 (8.9)	161.1 (9.6)	<0.001
Weight (kg), mean (SD)	71.7 (14.7)	67.4 (13.7)	0.002
BMI (kg/m^2), mean (SD)	25.9 (4.7)	26.0 (5.6)	0.793
Higher education*, n (%)	54 (28.0)	10 (5.0)	<0.001
Profession, n (%)			<0.001
- Primary sector	4 (2.1)	92 (46.2)	
- Secondary sector	23 (11.9)	8 (4.0)	
- Tertiary/quaternary sector	90 (46.6)	13 (6.5)	
- Housewife/man	31 (16.1)	37 (18.6)	
- Other	45 (23.3.)	49 (24.6)	
Smoking status, n (%)			<0.001
- Never smoker	110 (57.0)	140 (74.1)	
- Former smoker	12 (6.2)	14 (7.4)	
- Current smoker	71 (36.8)	35 (18.5)	
➢ *Male*	*58 (81.7)*	*30 (85.7)*	*0.604*
Pack years, median [IQR]	4.0 [1.6-11.5]	11.0 [2.0-24.5]	0.009
Tuberculosis (ever diagnosed), n (%)	0 (0.0)	3 (2.0)	0.086
Solid fuel, n (%)			
- Solid fuel use	145 (75.1)	199 (100.0)	<0.001
- Non-solid fuel use	193 (100.0)	82 (41.2)	<0.001

SD = standard deviation; BMI = body mass index; IQR = interquartile range. *The highest level of completed education above secondary education. For ‘former smoker’, two values were missing in the lowlands and 14 in the highlands. For ‘pack years’, two values were missing in the lowlands and six in the highlands. Tuberculosis (ever diagnosed) had 46 missing values, all in the highlands.

Table 2. Prevalence of COPD and respiratory symptoms

	Lowlands **n = 193**	**Highlands** **n = 199**	**p-value**
Post-BD FVC (% predicted), median [IQR]	92.0 [84.0; 104.0]	100.0 [92.0; 110.0]	<0.001
Post-BD FEV_1 (% predicted), median [IQR]	90.0 [83.0; 101.5]	92.0 [85.0; 104.0]	0.091
Post-BD FEV_1/FVC (%), median [IQR]	82.0 [75.0; 96.0]	76.0 [65.0; 97.0]	0.003
COPD, n (%)	20 (10.4)	73 (36.7)	<0.001
➢ *Male*	*16 (80.0)*	*36 (49.3)*	*<0.001*
➢ *Moderate/severe (GOLD ≥2)*	*14 (70.0)*	*18 (24.7)*	*<0.001*
SpO_2 (%), median [IQR]	95.0 [95.0; 96.0]	93.0 [92.0; 95.0]	<0.001
Chronic cough/sputum*, n (%)	15 (7.8)	47 (23.6)	<0.001
Severe breathlessness (MRC ≥*4*)	6 (3.1)	22 (11.1)	0.003

BD = bronchodilation; FVC = forced vital capacity; FEV_1 = forced expiratory volume < 1 second; IQR = interquartile range; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease. SpO_2 = oxygen saturation; MRC = Medical Research Council Breathlessness scale; *Chronic is defined as having symptoms for ≥ 2 months. Missing outcomes for lung function were excluded from the study (Figure 2). There were no other missing values.

Figure 1. Flowchart of participants

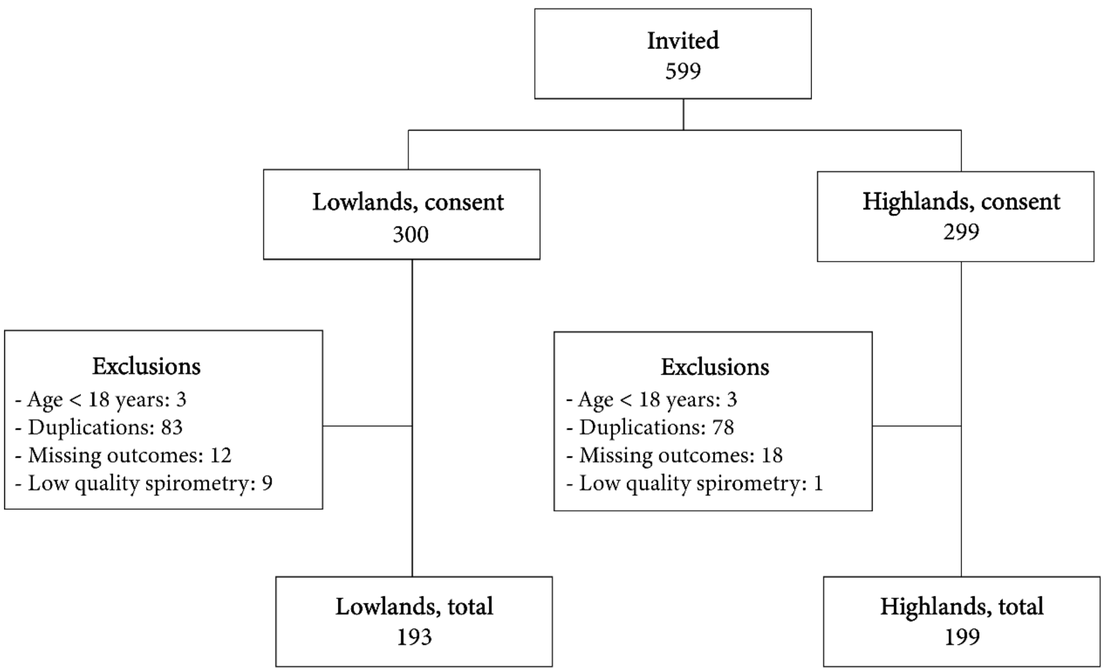
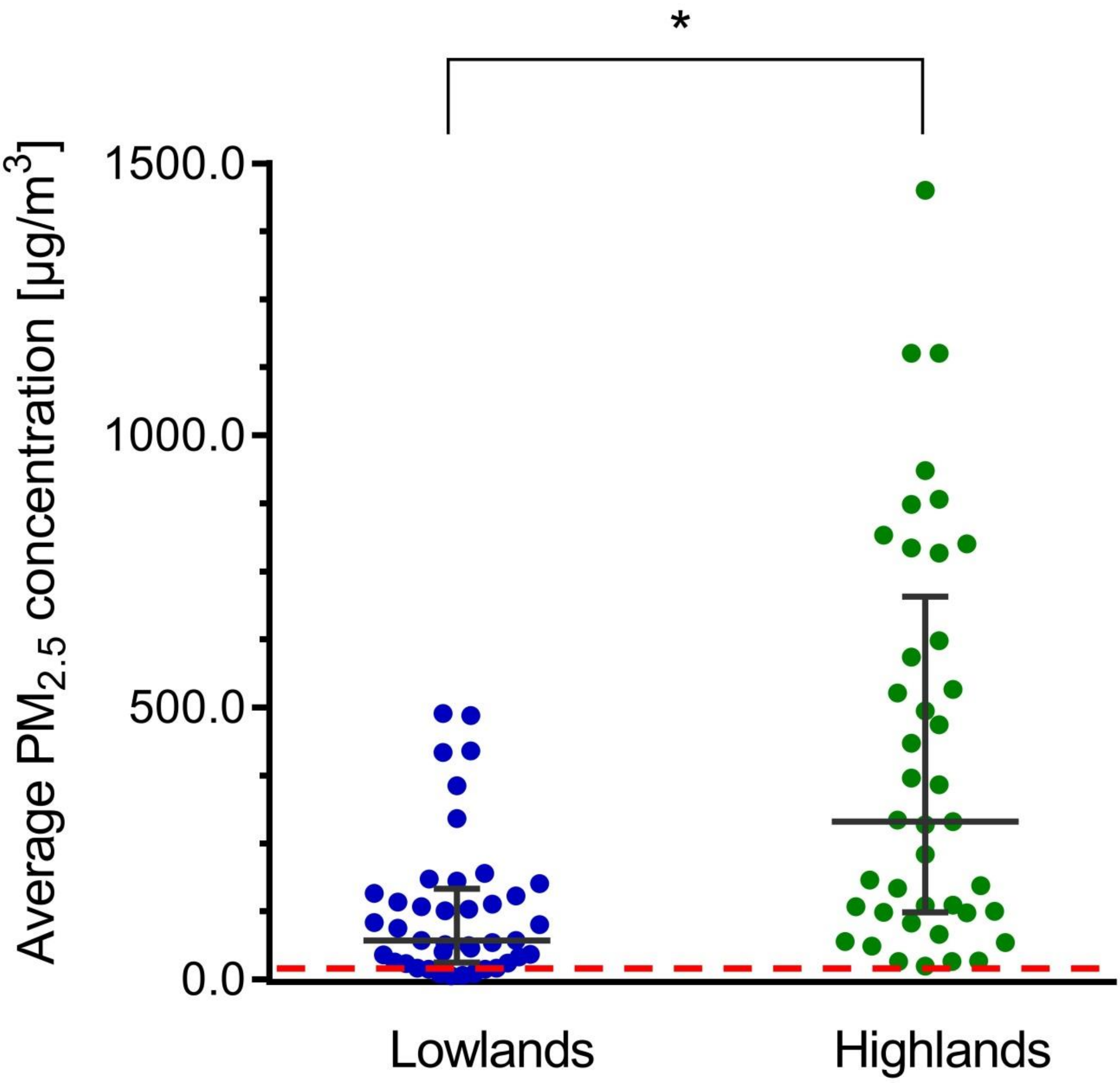


Figure 2. $PM_{2.5}$ levels in lowlands versus highlands



PM = particulate matter, measured as time-weighted average concentration per household. *Difference is statistically significant (p<0.001). Dashed line is the maximum average 24-hour $PM_{2.5}$ concentration of 25 µg/m^3 as stated in the WHO indoor air quality guideline [34]. Missing values were excluded from the study (Figure 1).

Figure 3. COPD prevalence in lowlands versus highlands

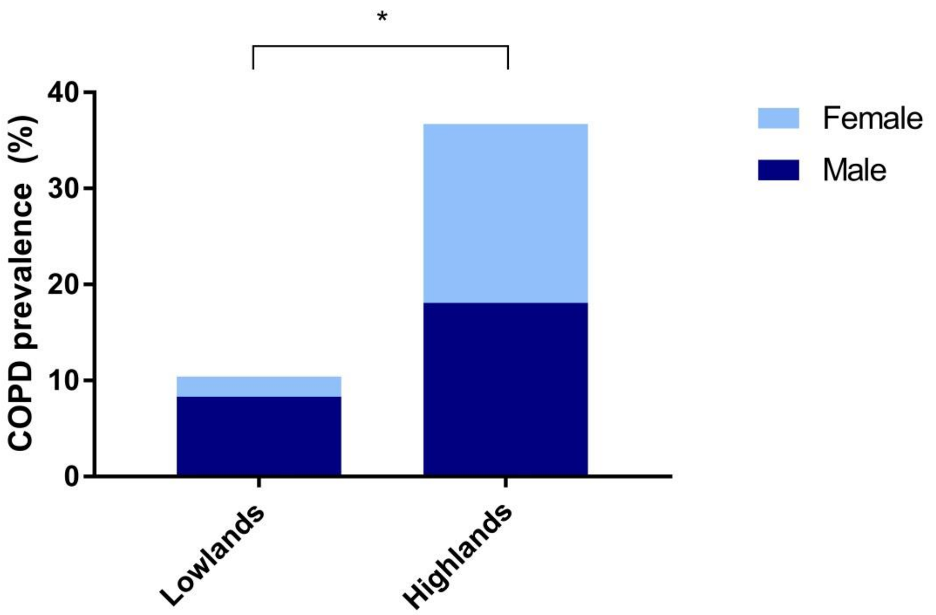


Figure 4 COPD prevalence in lowlands and highlands by sex and HAP-exposure

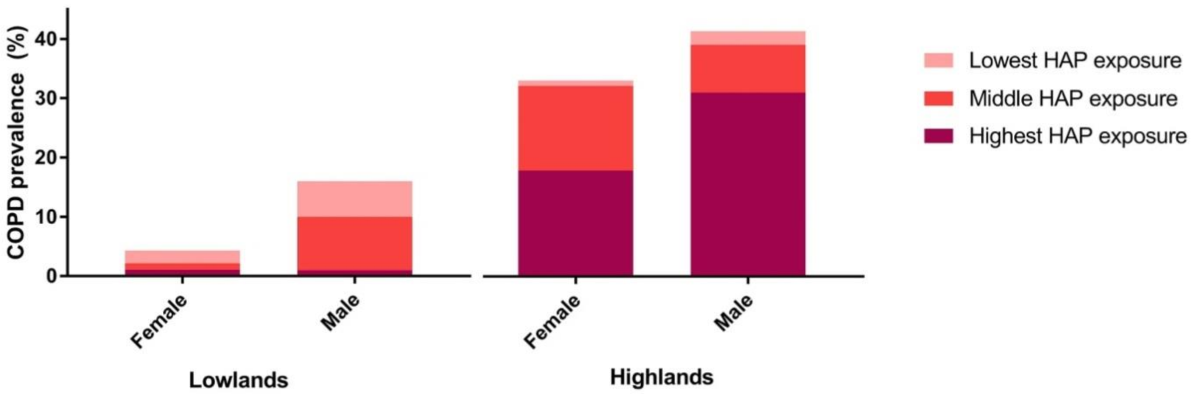
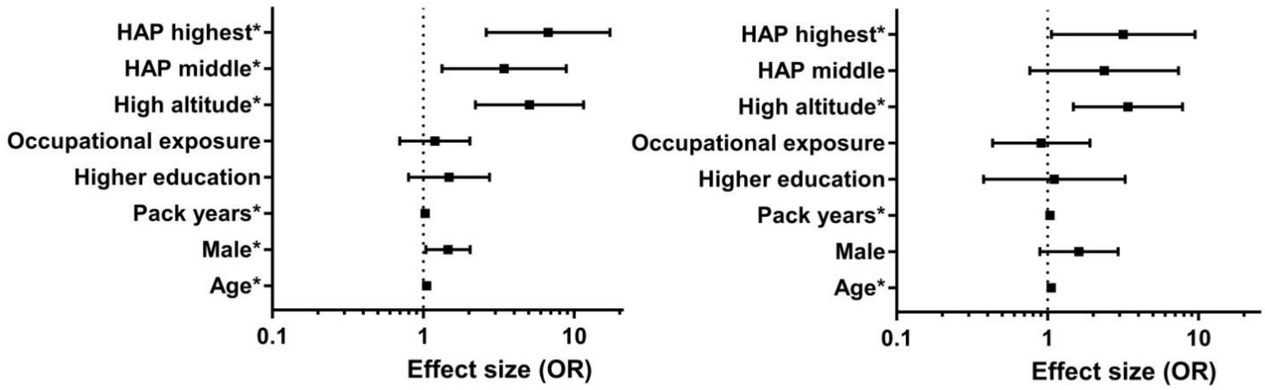


Figure 5. Potential predictors for COPD

A Univariable analysis B Multivariable analysis



Appendix1. English version of the questionnaire (FRESH AIR Uganda)

Please note: This is the English version used in Uganda. In Kyrgyzstan, a Russian translation was used.

Screening Questionnaire FRESH AIR Uganda

Interviewer: Date of screening:

Name patient:	ID number:
Date of birth:	Age:

Married: ☐ yes ☐ no Number of children alive……………deceased……….

Gender: ☐ male ☐ female

Weight:……………………….kg Length:………………………….cm BMI:…………

Highest education level: ……………………………………………………………………………………………………….

Occupation:…………………………………………………………………Tribal origin:…………………………………….

Village name:…………………………………………..Parish…………………………….County………………………….

Residence: ☐ rural ☐ urban ☐ sub urban

Respiratory symptoms:

Cough

1a .Do you cough several times most day? ☐ yes ☐ no

1b. If 'yes', when do you cough?
- ☐ I wake up with cough
- ☐ in the morning
- ☐ during the day
- ☐ during the night

2. Is it a chronic cough? ☐ yes ☐ no

3. Do you cough with exertion? ☐ yes ☐ no

4. For how long have you been coughing? ………………………years

Sputum

5a. Do you bring up phlegm or mucus on most days? ☐ yes ☐ no

5b. If 'yes', when do you bring up phlegm or mucus: ☐ first thing in the morning

☐ during the day

6. Do you have chronic phlegm? ☐ yes ☐ no

7. Do you have phlegm of mucus when you don't have a cold? ☐ yes ☐ no

---

Wheezing

8a. Do you wheeze or have any whistling on the chest? ☐ yes ☐ no

8b. For how long do you wheeze or have any whistling on the chest? …………… years

9. Do you wake up with wheezing? ☐ yes ☐ no

10. Have you been at all breathless when wheezing was present? ☐ yes ☐ no

---

Shortness of breath:

11. Do you get out of breath more easily than others your age? ☐ yes ☐ no

MRC breathlessness Scale

12. Which of the following statements best describes your situation?

☐ *1* *Not troubled by breathlessness except on strenuous exercise*

☐ *2* *Short of breath when hurrying on the level or walking up a slight hill*

☐ *3* *Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace*

☐ *4* *Stops for breath after walking about 100 yards or after walking a few minutes in level ground*

☐ *5* *Too breathless to leave house, or breathless when undressing*

Exacerbation(s)

13a. Did you have periods of increased breathing difficulty with increased cough with or without sputum during the last 12 months? ☐ yes ☐ no

13b. If 'yes', how many times did you have such a period during the last 12 months?

………times

Tobacco use:

14a. Do you smoke? ☐ current smoker how many per day……………..
☐ former smoker how many per day……………..
☐ passive smoker ☐ never smoker

14b. If you currently smoke or have smoked, how many years?…………….years

14c. Which products: ☐ cigarettes ☐ cigars
☐ pipes ☐ snuff
☐ chewing tobacco ☐ water pipe
☐ cannabis ☐ leaves
☐ local tobacco products, name: ……………………….

Biomass fuel use

15. ☐ indoor biomass fuel smoke: years of exposure ……….

16. ☐ outdoor biomass fuel smoke: years of exposure ……….

17. Do you have a chimney in your kitchen? ☐ yes ☐ no

18a. Do you burn wood? ☐ yes ☐ no
18b. Do you burn dung? ☐ yes ☐ no
18c. Do you burn LPG? ☐ yes ☐ no
18d. Do you burn grass? ☐ yes ☐ no
18e. Do you burn crop residues? ☐ yes ☐ no
18f. Do you burn natural gas? ☐ yes ☐ no
18g. Do you burn charcoal? ☐ yes ☐ no
18h. Do you burn kerosene? ☐ yes ☐ no
18i. Do you use electricity? ☐ yes ☐ no

19. Time spent cooking <u>indoor</u> ………..hours/day

20. Time spent cooking <u>outdoor</u> ………..hours/day

21. Do you use biomass fuel for heating? ☐ yes ☐ no

22. Where do you sleep?
☐ same room as kitchen
☐ separate room but in the same house as the kitchen
☐ separate house from the kitchen

Tuberculosis

23. Did you ever have tuberculosis?

☐ Yes, I have active TB now.

☐ Yes, I had TB in the past but was treated and I am cured now.

☐ No, I never had TB

☐ I don't know

24a. Is documentation about your TB present? ☐ yes ☐ no 24b. if 'yes', the documentation is a

☐ a TB card

☐ a TB discharge card

☐ lab reports

☐ others…………………………………

<u>Disease history:</u>

26. Did you (recently?) have a cold gone to the chest: ☐ yes ☐ no

27a. Do you have allergies: ☐ yes ☐ no

27b. Which allergies do you have?

………

28. How often do you have a chest infection:

- ☐ more than 2 per year
- ☐ 1 or 2 per year
- ☐ less than 1 per year

29. Do you receive treatment for breathing?

- ☐ yes
- ☐ no

30. Did you have pulmonary problems in childhood?

- ☐ yes
- ☐ no

31. What respiratory diagnosis did you receive in the past?

……

Comorbidity

32. Do you have heart failure?

- ☐ yes
- ☐ no

33. Do you have AIDS/HIV?

- ☐ yes
- ☐ no

34 a. Do you have other comorbidities?

- ☐ yes
- ☐ no

34 b. Please describe any other comorbidities

………

Medication:

35a. Do you use medication? ☐ yes ☐ no

35b. What is de name of the medication that you use?……………………………………………….

………

…….

36a. Were you admitted to hospital during the last 2 years? ☐ yes ☐ no

36b. If you were admitted, please describe for what reason(s)

………

………

36c. If you were admitted, please describe how often this happened during the last 2 years:

....

37a. Did you visit healthcenters during the last 2 years? ☐ yes ☐ no

37b. If you did, please describe for what reason(s)

………
……….

37c. If you did, please describe how often this happened during the last 2 years:

....

---

38. CCQ score: Total score ………………………

Symptom score (number 1, 2, 5 and 6) …………

Mental state score (number 3 and 4) ………….

Functional state score (number 7, 8, 9 and 10) ………….

Spirometry

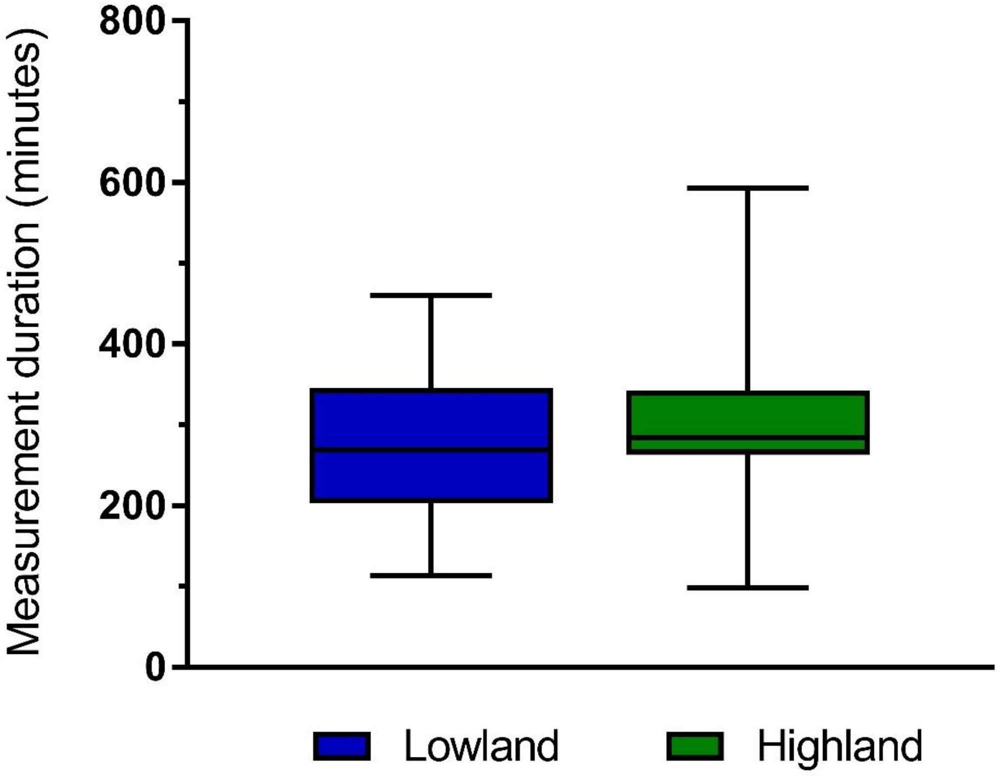
preBD: *FVC…………Lt (…………%)* *FEV$_1$………………Lt (…………%) FEV$_1$/FVC ratio………………..*

postBD: *FVC…………Lt (…………%)* *FEV$_1$………………Lt (…………%) FEV$_1$/FVC ratio………………..*

Reversibility……………………………….

Diagnosis	☐ *COPD, GOLD stage……….*	*without reversible component*
	☐ *COPD, GOLD stage……….*	*with reversible component*
	☐ *asthma* ☐ *no objective evidence of obstructive lung disease*	
	☐ *restrictive*	

Appendix 2. Figure E1. Duration of $PM_{2.5}$**-measurements per setting**



Appendix 3. Cooking- and heating circumstances

Cooking and heating circumstances relating to household air pollution, across altitudes

Highlanders more commonly used solid fuels for cooking and heating than lowlanders (100% vs. 75.1%; $p<0.001$), particularly dung and wood, and their gas and electricity use was significantly lower (Table E1). Almost all highlanders cooked exclusively on open fires (95.0% vs. 0.0%; $p<0.001$) or griddle stoves (100% vs. 66.3%; $p<0.001$), and less on improved single pot stoves (34.2% vs. 74.1%; $p<0.001$). In both areas, almost all participants cooked indoors (100% in the highlands and 99.0% in the lowlands; $p=0.242$). Highlanders more commonly cooked in the same room used for living and sleeping (62.8% vs. 4.1%; $p<0.001$). Most of the participants had some type of ventilation in the room where the stove was used; in the highlands this was significantly less often an open door or window (46.7% vs. 93.3%; $p<0.001$), while a room with eaves spaces was more popular (54.8% vs. 1.6%; $p<0.001$).

Table E1: Risk factors for household air pollution

	Lowlands n = 193 (%)	Highlands n = 199 (%)	p-Value
Solid fuel use	145 (75.1)	199 (100.0)	<0.001
Heating*	133 (68.9)	199 (100.0)	*<0.001*
- *Dung*	*28 (14.5)*	*199 (100.0)*	*<0.001*
- *Grass*	*0*	*0*	-
- *Crop residues*	*0*	*11 (5.5)*	*0.001*
- *Wood*	*124 (64.2)*	*177 (88.9)*	*<0.001*
- *Coal*	*133 (68.9)*	*109 (54.8)*	*0.004*
Cooking*	46 (23.8)	196 (98.5)	*<0.001*
- *Dung*	*25 (13.0)*	191 (96.0)	*<0.001*
- *Grass*	*0*	*6 (3.0)*	*0.030*
- *Crop residues*	*0*	*3 (1.5)*	*0.248*
- *Wood*	*26 (13.5)*	*100 (50.3)*	*<0.001*
- *Coal*	*24 (12.4)*	*70 (35.2)*	*<0.001*
Non-solid fuel use*	193 (100.0)	82 (41.2)	<0.001
- *Kerosene*	*0*	*7 (3.5)*	*0.015*
- *Gas (LPG)*	*64 (33.2)*	*7 (3.5)*	*<0.001*
- *Electricity*	*193 (100.0)*	*75 (37.7)*	*<0.001*
Stove used for cooking*			
- Open fire	0 (0.0)	189 (95.0)	<0.001
- Surrounded fire	0 (0.0)	19 (9.5)	<0.001
- Improved single pot stove	143 (74.1)	68 (34.2)	<0.001
- Improved multiple pot stove	37 (19.2)	20 (10.1)	0.010
- Griddle stove	128 (66.3)	199 (100.0)	<0.001
Cooking location*			
- Outdoors	4 (2.1)	32 (16.1)	<0.001
- Indoors	191 (99.0)	199 (100.0)	0.242
➢ *Time cooking indoors (hours/day), median [IQR]*	*2.0 [1.0; 2.0]*	*2.0 [0.0; 4.0]*	*0.563*
➢ *In same room as living/sleeping room*	*8 (4.1)*	*125 (62.8)*	*<0.001*
Presence of hood/chimney	157 (81.3)	164 (82.4)	0.784
Ventilation*			
- Closed room	5 (2.6)	3 (1.5)	0.497
- Room with open door/window	180 (93.3)	93 (46.7)	<0.001
- Room with ≤3 walls	5 (2.6)	16 (8.0)	0.017
- Room with eaves spaces	3 (1.6)	109 (54.8)	<0.001

LPG = liquefied petroleum gas; IQR = interquartile range. Values are n (%) unless stated otherwise. *Multiple answers could be given to this question. Sub-questions are shown in italics. There were no missing values.

Appendix 4. COPD and its risk factors

Figure E1: COPD prevalence in lowlands and highlands by sex and smoking status

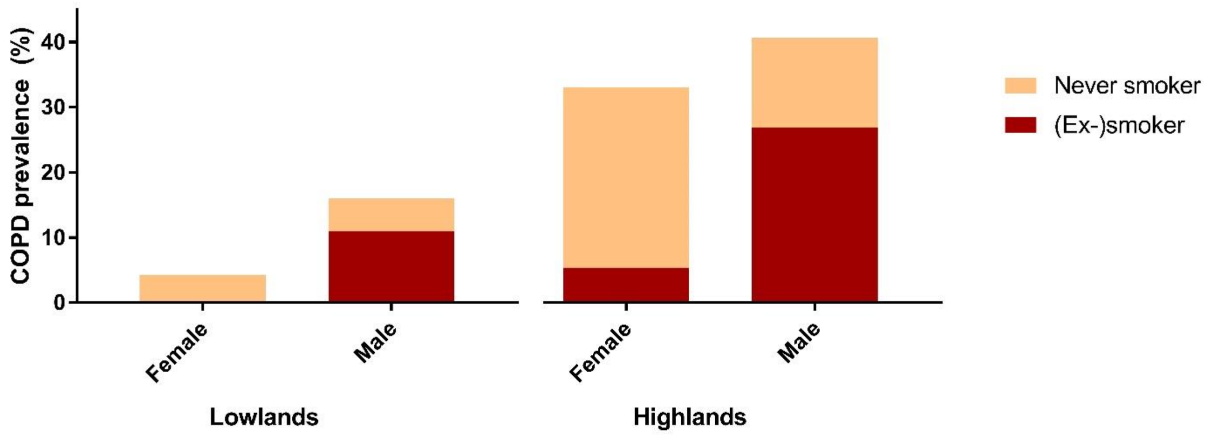


Table E1: Univariable and multivariable predictors for COPD

	Univariable OR (95% CI)	**P-Value**	**Multivariable** OR (95% CI)	**P-Value**
Age (per year increase)	1.055 (1.036-1.073)	<0.001	1.058 (1.037-1.079)	<0.001
Male	1.460 (1.041-2.047)	0.028	1.614 (0.889-2.930)	0.116
Pack years	1.031 (1.011-1.052)	0.002	1.037 (1.005-1.070)	0.024
Higher education*	1.483 (0.800-2.752)	0.211	1.107 (0.376-3.264)	0.853
Working in primary/secondary sector	1.194 (0.699-2.039)	0.516	0.908 (0.432-1.908)	0.798
High altitude	5.064 (2.217-11.568)	<0.001	3.406 (1.483-7.825)	0.004
HAP – middle exposure group (reference = lowest exposure group)	3.433 (1.329-8.866)	0.011	2.372 (0.763-7.377)	0.136
HAP – highest exposure group (reference = lowest exposure group)	6.714 (2.614-17.249)	<0.001	3.174 (1.061-9.493)	0.039

COPD (n = 91) vs. no COPD (n = 293). Generalised Estimating Equation analyses adjusted for a clustering effect within households. *The highest level of completed education above secondary education. Household air pollution (HAP) was categorised into a lowest, middle and highest tertiles of exposure, respectively with time-weighted average concentrations of particulate matter$_{2.5}$ of ≤72, >72-293 and >293 μg/m^3.

Figure E2: Lung function and particulate matter exposure