Positive association between moderate altitude and chronic lower respiratory disease mortality in United States counties

Jeongeun Hwang¹, Miso Jang², Namkug Kim³,⁴*, Seunghyun Choi⁴, Yeon-Mok Oh⁴,⁵, Joon Beom Seo³

¹ Asan Institute for Life Sciences, Asan Medical Center, Seoul, Republic of Korea, ² Department of Family Medicine and Center for Cancer Prevention and Detection, Hospital, National Cancer Center, Goyang, Republic of Korea, ³ Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, ⁴ Department of Convergence Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, ⁵ Department of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

☯ These authors contributed equally to this work.

* namkugkim@gmail.com

Abstract

For patients with chronic lower respiratory disease, hypobaric hypoxia at a high altitude is considered a risk factor for mortality. However, the effects of residing at moderately high altitudes remain unclear. We investigated the association between moderate altitude and chronic lower respiratory disease mortality. In particular, we examined the lower 48 United States counties for age-adjusted chronic lower respiratory disease mortality rates, altitude, and socioeconomic factors, including tobacco use, per capita income, population density, sex ratio, unemployment, poverty, and education between 1979 and 1998. The socioeconomic factors were incorporated into the correlation analysis as potential covariates. Considerable positive (R = 0.235; P < 0.001) and partial (R = 0.260; P < 0.001) correlations were observed between altitude and chronic lower respiratory disease mortality rate. In the subgroup with high COPD prevalence subgroup, even stronger positive (R = 0.346; P < 0.001) and partial (R = 0.423, P < 0.001) correlations were observed. Multivariate regression analysis of all available socioeconomic factors revealed that additional knowledge on altitude improved the adjusted R² values from 0.128 to 0.186 for all counties and from 0.301 to 0.421 for counties with high COPD prevalence. We concluded that in the lower 48 United States counties, even a moderate altitude may pose considerable risks in patients with chronic lower respiratory disease.

Introduction

Chronic obstructive pulmonary disease (COPD) and lower respiratory infections are ranked by the World Health Organization as the third and fourth most common causes of death in the world, respectively.[1] In 2020, the number of deaths due to respiratory disease is expected...
to increase and account for 11.9 of the 68 million total deaths worldwide.[2] However, the causes, potential risk factors, and mechanisms of progression of chronic lower respiratory disease are not completely understood. A number of epidemiologic studies have assessed the prevalence, comorbidities, and risk factors for chronic lower respiratory disease.[3–6] For example, Lewis et al investigated a representative population of the United States (US) and found that low education and low family income were associated with lung cancer and COPD.[4]

Altitude is one of the most fundamental environmental factors that has been reported to have association with diseases, such as cardiovascular disease cancer, COPD, pneumonia, and renal disease.[7–12] The association between altitude and diseases of the respiratory system is pleiotropic. In Mexico, high altitude was shown to have a beneficial association with tuberculosis mortality but had a harmful association with pneumonia and influenza mortality.[11] In Peru, the seemingly protective effect of altitude in tuberculosis was overwhelmed by the population density.[13] Among the studies that investigated the effect of altitude on mortality rates due to chronic lower respiratory disease, a national study on US counties that was conducted by Ezzati et al between 2001 and 2005 found a harmful dose-response association between COPD mortality and altitude,[8] but that study did not include other chronic lower respiratory diseases or pneumonia. Many of the studies concerning altitude and respiratory disease mortality rates were focused on a limited region [14, 15] or on acute reactions to high altitudes, such as acute mountain sickness [16] and high-altitude pulmonary edema.[17–19]

In the present study, we collected the United States mortality statistics for 20 years between 1979 and 1998. We analyzed the association between respiratory disease mortality rates and altitude in the 3,089 counties of lower 48 US, while controlling for potential covariates, such as per capita income, population density, unemployment rate, poverty, education, and sex ratio.

**Materials and methods**

**Ethics approval**

Ethics approval was not required because this study was performed using a publicly accessible national epidemiology database.

**Mortality statistics**

The Centers for Disease Control and Prevention WONDER database was used to extract the US mortality data from 1979 to 1998 by disease, which was classified by the International Classification of Disease (ICD)-9. Diseases of the respiratory system (460–519), pneumonia (480–486), and chronic lower respiratory disease (490–496) were investigated. Chronic lower respiratory diseases included bronchitis, emphysema, asthma, and COPD. Mortality rates were age-adjusted for deaths per 100,000 by standard populations in 2000, and subjects aged <5 years were excluded. County was used as the residential unit, and mortality rates were extracted for every lower 48 US continental county that had available data on altitude. Counties with <20 deaths for a specific mortality code were excluded.

**Altitude**

The Shuttle Radar Topography Mission (SRTM) elevation data, which were created by the National Geospatial-Intelligence Agency and the National Aeronautics and Space Administration, were used to determine the average altitudes of the counties, as previously described.[20] SRTM is a global dataset developed in February 2000, with a spatial resolution of approximately 0.1 km. In brief, the average altitude of each county was calculated using zonal statistics.
in the ArcGIS/ArcInfo 9.3 environment (ESRI, Redlands, CA), which is a geographical information system software that is used to calculate related data on mapping and for querying geographical databases. The data from the SRTM provided the mean altitude calculations for each square kilometer in each county. County boundaries, which were provided by the National Atlas of the United States Geological Survey, were overlaid on the mean spatial data to obtain the mean altitude for each US county. The data inputs for this analysis used a 1:2,000,000 scale for US county vector dataset and a mosaic digital elevation model with approximately 0.5-km spatial resolution, which was derived from the SRTM dataset.

Socioeconomic factors

Socioeconomic factors, such as per capita income, population density, sex ratio, unemployment, poverty, education, and tobacco use, were considered as potential covariates for mortality. The Area Health Resources Files system was accessed to obtain the unemployment rates for 1990–1998, sex ratio in 2000, percentage of persons in poverty in 2000, and percentage of individuals aged >25 years with <9 years of education in 2000 for every county. Unfortunately, county-specific smoking rates were not available. Instead, the Behavioral Risk Factor Surveillance System was accessed to obtain the current smoking rate per state in 1996. Counties that lacked one or more census data were excluded from the analysis; therefore, 2,678 counties were included in the final analysis.

COPD prevalence

The data on the COPD prevalence of each county were not available during the study period (1979–1998). Alternatively, we consulted a COPD prevalence study that used the census 2010 data. [21] The exact prevalence rate was not shown, but the COPD prevalence was shown in a five-grade color code on the published figure. From this, 114 counties with the highest (>13%) COPD prevalence were identified and underwent the same analysis as that for all the counties combined.

Correlation analysis

Pearson’s correlation and partial correlation coefficients between altitude and the mortality rates of the three respiratory disease categories were calculated using normality tests. Partial correlation coefficients were measured while controlling for all of the socioeconomic factors. A multivariate linear regression model was used to assess the contribution of altitude to the explanation power of the models for mortality rates. The adjusted R² values of the multivariate linear regression models were measured while accounting for all the socioeconomic factors without altitude. Next, altitude was added to the multivariate linear regression analysis, and new adjusted R² values were calculated; significance and multicollinearity statistics were measured accordingly. Statistical analyzes were performed using the R statistical software version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) and the following R packages: dplyr,[22] ggplot2,[23] maps,[24] and ppcor.[25]

Results and discussion

Table 1 shows the demographics of all studied counties and those with high COPD prevalence. The geographical patterns of altitude and chronic lower respiratory disease mortality rate are depicted in Fig 1. A considerable positive association was found between the counties’ altitude and chronic lower respiratory disease mortality rate. In Table 2, a simple correlation coefficient of 0.235 and a partial correlation coefficient of 0.260 were observed after controlling for
the other covariates, with P values of <0.001. Altitude remained a significant factor in the multivariate regression analysis that incorporated all the socioeconomic factors. The adjusted R² value of the multivariate regression model that included all covariates, except altitude, was 0.128; addition of altitude in the model enhanced the R² value to 0.186. The mortality rates by disease of the respiratory system had a similar correlation with altitude. Pneumonia mortality correlated with altitude, but the intensity of this association and the explanation power were less obvious than those of chronic lower respiratory disease mortality.

We hypothesized that the correlation between mortality rate and altitude would be more intense in counties where the underlying chronic lower respiratory disease was more prevalent. Considering that the prevalence of COPD reflected that of chronic lower respiratory disease, Fig 2 shows how the association patterns of altitude with mortality differed between COPD-prevalent counties and all counties combined. In the subgroup analysis (Table 3), altitude and chronic lower respiratory disease mortality rate had a simple correlation coefficient of 0.346 and a partial correlation coefficient of 0.423, with p values of <0.001. In the multivariate linear regression analysis, the adjusted R² value was 0.301 for socioeconomic factors alone and improved to 0.421 after adding altitude to the model. The associations between altitude and mortality rate were similar for diseases of the respiratory system and chronic lower respiratory disease but were less significant for pneumonia. The distributions of the socioeconomic factors in COPD-prevalent counties and those in all counties did not significantly differ (S1 Fig).

In this study that encompassed almost all US counties during a 20-year period between 1979 and 1998, significant positive associations between altitude and respiratory disease mortality were observed among COPD-prevalent counties.

### Table 1. Demographics in all counties and in counties with high COPD prevalence (>13%).

| Category                              | All counties | Counties with high COPD prevalence |
|---------------------------------------|--------------|-----------------------------------|
| Number of counties                    | 2678         | 114                               |
| Mortality rate: chronic lower respiratory disease | 45.1 ± 9.8 (17.8–98.8) | 54.9 ± 13.9 (24.5–98.8) |
| Mortality rate: pneumonia             | 30.9 ± 7.8 (11.6–75.3) | 36.4 ± 8.0 (16.0–56.0) |
| Mortality rate: disease of the respiratory system | 91.2 ± 16.0 (51.6–179.8) | 109.6 ± 22.0 (64.5–177.3) |
| Altitude (m)                          | 375.2 ± 431.5 (0.8–3,041.5) | 312.0 ± 304.2 (25.3–2080.5) |
| Per capita income ($F)                | 18,083 ± 3,973 (7,271–60,297) | 14,826 ± 22,26 (10,328–19,637) |
| Population density                   | 235.1 ± 1535.5 (0.9–53,180.9) | 48.0 ± 37.4 (1.1–191.1) |
| Sex ratio (male/total)                | 0.980 ± 0.078 (0.742–1.909) | 0.964 ± 0.055 (0.866–1.299) |
| Poverty rate                         | 16.5 ± 7.8 (2.2–63.1) | 24.6 ± 8.8 (10.6–52.1) |
| Under-education rate (percentage)     | 14.5 ± 7.2 (1.1–56.3) | 24.7 ± 9.2 (7.4–49.1) |
| Smoking rate (percentage)            | 24.3 ± 2.9 (15.9–31.7) | 26.9 ± 3.9 (20.3–31.7) |

Data are shown as mean ± standard deviation (range).

*Counts that lacked one or more census data were excluded, therefore, 2,678 counties were included in the final analysis.

*bCOPD prevalence of >13% based on the 2010 census [21]

*cage-adjusted mortality rate per 100,000 in 1979–1998, ICD9 code J40–J47

dage-adjusted mortality rate per 100,000 in 1979–1998, ICD9 code J12–J18

eage-adjusted mortality rate per 100,000 in 1979–1998, ICD9 code J00–J98

f2000

g2000

ipercentage of persons in poverty in 2000

jpercentage of individuals aged >25 years with <9 years of education in 2000

k1996

https://doi.org/10.1371/journal.pone.0200557.t001
mortality rates were observed. The results were qualitatively consistent with those of previous studies.[8, 11, 14–19, 26, 27] Moreover, this study showed new findings that chronic lower respiratory disease mortality was positively correlated with both extremely high and moderate altitudes. This implied that a moderate altitude, even in ordinary US counties, should not be neglected when dealing with respiratory diseases.

Although the mechanisms by which high altitude affects respiratory disease are not completely understood, several processes were proposed. First, lower oxygen partial pressure [28] and increased solar radiation at high altitudes are generally detrimental [8] for COPD and other respiratory diseases. In addition, climatic factors, such as low temperature, low humidity, and high wind velocity, which are found at high altitudes, worsened asthma by increasing
bronchial hyperresponsiveness and inflammation.\[28, 29\] Latitude is another geographical factor that is closely related with temperature; however, it did not have significant associations with any of the three respiratory disease categories in our study. Considering that the counties investigated in this study had latitudes that ranged from 25 to 45 degrees from the subtropical to the subpolar regions, the association of altitude with mortality could not be discounted as a mere result of temperature variations. Low absolute and partial pressures of oxygen can inhibit lung fluid absorption and lead to acute pulmonary edema.\[17–19\] Residents of places with relatively high altitudes might undergo chronic, progressive inhibition of lung fluid absorption and become more susceptible to respiratory infections. A simulation study showed that patients with chronic airway obstruction exhibited pulmonary dysfunction and worse hypoxemia in atmospheric conditions that mimicked altitudes of \( \geq 1,524 \) meters.\[30\] Furthermore, chronic hypoxemia induced leukocyte-mediated tissue damage.\[31\] Therefore, the pathophysiological response of lung tissue to hypoxia, might be mediated by hypoxia inducible factor-1 \[32–35\] or nitric oxide \[36, 37\], could be detrimental to a diseased lung.

### Table 2. Correlation coefficients between altitude and mortality rates for diseases of the respiratory system, pneumonia, and chronic lower respiratory disease and adjusted R\(^2\) values for multivariate linear regression models with or without altitude for all counties.

|                                | Chronic lower respiratory disease | Pneumonia | Disease of the respiratory system |
|--------------------------------|----------------------------------|-----------|-----------------------------------|
| Correlation coefficient        | 0.235                            | 0.074     | 0.171                             |
| Partial correlation coefficient | 0.260                            | 0.148     | 0.238                             |
| Adjusted R\(^2\) of the regression models that included all covariates\(^a\) except altitude | 0.128                             | 0.090     | 0.133                             |
| Adjusted R\(^2\) of the regression models that included all covariates and altitude | 0.186                             | 0.110     | 0.182                             |

\(^a\)per capita income, population density, sex ratio, unemployment rate, percentage of persons in poverty, percentage of individuals aged \( \geq 25 \) years with \(< 9 \) years of education. All correlation coefficients and R\(^2\) values had statistical significance (\( P < 0.001 \)).

https://doi.org/10.1371/journal.pone.0200557.t002

**Fig 2.** Correlation between altitude and chronic lower respiratory disease mortality rate. A positive correlation was found and was stronger in counties with higher COPD prevalence (\( > 13\% \); red dots) than in all counties combined (black circles). COPD, chronic obstructive pulmonary disease.

https://doi.org/10.1371/journal.pone.0200557.g002
In the present observational study, determination of a causal association between mortality rate and altitude and of the exact aspect of low altitude that was harmful for respiratory diseases was difficult. This limitation raises the need for further studies.

**COPD prevalence**

The stronger correlation between altitude and mortality rate in counties with high COPD prevalence (Fig 2 and Table 2) can lead us to speculate that a diseased lung is susceptible to further destruction at moderate altitudes. If the prevalence data for chronic lower respiratory disease in each county were available at the time of this study, this speculation could have been more thoroughly investigated.

**Air quality**

Air pollution is a significant risk factor for respiratory disease [38–40], and the public tends to believe that high-altitude ranges have cleaner air, compared with low-altitude areas. We investigated the covariates that represented the extent of air pollution, daily fine particulate matter, and days with an eight-hour average ozone over National Ambient Air Quality Standards, but we could not determine significant associations between air pollution and mortality rates (data not shown). There were reports that the associations among altitude, air quality, and respiratory disease were equivocal or not simply proportional [41–43]; however, we did not observe these in our current study. Further studies are warranted to resolve the cause-and-effect associations among these factors.

**Limitations**

Other potential confounding factors, such as county-wise wind chill temperature, background radiation, ethnicity, medical care system, utilization of preventive measures, and industrial background of the counties, were not included in the analysis. Considerable variations in mortality rate, altitude, prevalence, and socioeconomic status within a county were also not accounted for in the present study. Another limitation of the present study was a study period mismatch among mortality statistics (1979–1998), unemployment rate (1990–1998), sex ratio (2000), poverty (2000), education (2000), smoking rate (1996), and COPD prevalence (2010). Although this mismatch was inevitable, it may add some complexity in the interpretation of the results, because there could have been considerable changes in between the time gaps. To clarify the mechanism underlying the association between altitude and chronic lower respiratory disease mortality rate, further studies are required. Nevertheless, this investigation across the entire US over 20 years should partially compensate for the limitations of these confounding factors.

### Table 3. Correlation coefficients between altitude and mortality rates for diseases of the respiratory system, pneumonia, and chronic lower respiratory disease and adjusted $R^2$ values for multivariate linear regression models with or without altitude for counties with high COPD prevalence (>13%).

| Covariates                                   | Chronic lower respiratory disease | Pneumonia | Disease of the respiratory system |
|----------------------------------------------|----------------------------------|-----------|----------------------------------|
| Correlation coefficient                      | 0.346*                           | 0.214*    | 0.335**                          |
| Partial correlation coefficient              | 0.423**                          | 0.275**   | 0.453**                          |
| Adjusted $R^2$ of the regression models that included all covariates except altitude | 0.301**                          | 0.168**   | 0.374**                          |
| Adjusted $R^2$ of the regression models that included all covariates and altitude       | 0.421**                          | 0.224**   | 0.497**                          |

* $P < 0.05$  
** $P < 0.001$; COPD: chronic obstructive pulmonary disease.

https://doi.org/10.1371/journal.pone.0200557.t003
Conclusions

In the US, there was a positive association between altitude and mortality rate from respiratory diseases, especially for chronic lower respiratory disease. In counties with high COPD prevalence, the harmful association was even stronger than that in the other counties. There is a need for further studies on the underlying mechanism of this association.

Supporting information

S1 Fig. Histogram of the socioeconomic factors in all counties (dark gray) and in COPD-prevalent counties (light gray). The distribution patterns did not differ significantly. COPD, chronic obstructive pulmonary disease.

S1 Table. Correlation coefficients between all variables and the mortality rates for chronic lower respiratory disease, according to county and state.

Author Contributions

Conceptualization: Jeongeun Hwang, Miso Jang, Namkug Kim, Joon Beom Seo.
Data curation: Jeongeun Hwang, Miso Jang, Yeon-Mok Oh.
Formal analysis: Jeongeun Hwang, Miso Jang, Seunghyun Choi.
Funding acquisition: Jeongeun Hwang, Namkug Kim, Yeon-Mok Oh, Joon Beom Seo.
Investigation: Jeongeun Hwang, Miso Jang, Seunghyun Choi, Yeon-Mok Oh, Joon Beom Seo.
Methodology: Jeongeun Hwang, Miso Jang, Namkug Kim, Seunghyun Choi.
Project administration: Namkug Kim, Yeon-Mok Oh, Joon Beom Seo.
Resources: Namkug Kim, Yeon-Mok Oh, Joon Beom Seo.
Software: Jeongeun Hwang, Miso Jang, Namkug Kim.
Supervision: Namkug Kim, Yeon-Mok Oh, Joon Beom Seo.
Validation: Namkug Kim, Seunghyun Choi, Yeon-Mok Oh, Joon Beom Seo.
Visualization: Jeongeun Hwang, Miso Jang, Namkug Kim, Seunghyun Choi.
Writing – original draft: Jeongeun Hwang, Miso Jang.
Writing – review & editing: Namkug Kim, Seunghyun Choi, Yeon-Mok Oh, Joon Beom Seo.

References

1. World Health Organization. Chronic respiratory disease [Web page on the Internet] [2017 Oct 11]. Available from: http://www.who.int/respiratory/en/.
2. World Health Organization. Fact sheet: The top 10 causes of death [Web page on the Internet]. 2017 [updated Jan 2017; cited 2017 Oct 12]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.
3. Burney P, Kato B, Janson C, Mannino D, Studnicka M, Tan W, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty: a BOLD analysis-authors’ reply. Thorax. 2014; 69(6). doi: 10.1136/thoraxjnl-2014-205474. WOS:000340239900020. PMID: 24789424
4. Lewis DR, Clegg LX, Johnson NJ. Lung disease mortality in the United States: the Nationa Longitudinal Mortality Study. Int J Tuberc Lung D. 2009; 13(6):1008–14. WOS:000268516300014.
5. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007; 370(9589):765–73. doi: 10.1016/S0140-6736(07)61380-4. WOS:000249209300031. PMID: 17765526

6. Rosenberg SR, Kalhan R, Mannino DM. Epidemiology of Chronic Obstructive Pulmonary Disease: Prevalence, Morbidity, Mortality, and Risk Factors. Semin Resp Crit Care. 2015; 36(4):457–69. doi: 10.1056/s-0035-1555607. WOS:000358817300002. PMID: 26238634

7. Winkelmayr WC, Liu J, Brookhart MA. Altitude and All-Cause Mortality in Incident Dialysis Patients. Jama J Am Med Assoc. 2009; 301(5):508–12. WOS:000262992400020.

8. Ezzati M, Howitz MEM, Thomas DSK, Friedman AB, Roach R, Clark T, et al. Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of US counties. J Epidemiol Commun H. 2012; 66(7). ARTN e17 doi: 10.1136/jech.2010.112938. WOS:000304922600005. PMID: 21406589

9. Hurtado A, Escudero E, Pando J, Sharma S, Johnson RJ. Cardiovascular and renal effects of chronic exposure to high altitude. Nephrol Dial Transpl. 2012; 27:iv11–iv6. doi: 10.1093/ndt/gfs427. WOS:000312895000004. PMID: 23258804

10. Mortimer EA Jr., Monson RR, MacMahon B. Reduction in mortality from coronary heart disease in men residing at high altitude. N Engl J Med. 1977; 296(11):581–58. Epub 1977/03/17. https://doi.org/10.1056/NEJM197703172961101. PMID: 840241.

11. Perez-Padilla R, Franco-Marina F. The impact of altitude on mortality from tuberculosis and pneumonia. Int J Tuberc Lung D. 2004; 8(11):1315–20. WOS:000225229000007.

12. Youk AO, Buchanich JM, Fryzek J, Cunningham M, Marsh GM. An Ecological Study of Cancer Mortality Rates in High Altitude Counties of the United States. High Alt Med Biol. 2012; 13(2):98–104. doi: 10.1089/ham.2011.1051. WOS:000305764400005. PMID: 22724612

13. Saito M, Pan WK, Gilman RH, Bautista CT, Bamrah S, Martin CA, et al. Comparison of altitude effect on Mycobacterium tuberculosis infection between rural and urban communities in Peru. Am J Trop Med Hyg. 2006; 75(1):49–54. WOS:000238902600011. PMID: 16837708

14. Firth PG, Zheng H, Windsor JS, Sutherland AI, Imray CH, Moore GWK, et al. CHRISTMAS 2008: SPORT Mortality on Mount Everest, 1921–2006: descriptive study. Brit Med J. 2008; 337. ARTN a2654 doi: 10.1136/bmj.a2654. WOS:000262776900004. PMID: 19074222

15. Virues-Ortega J, Hogan AM, Baya-Botti A, Kirkham FJ, Baldeweg T, Mahillo-Fernandez I, et al. Survival and Mortality in Older Adults Living at High Altitude in Bolivia: A Preliminary Report. J Am Geriatr Soc. 2009; 57(10):1955–6. WOS:000270551300046. https://doi.org/10.1111/j.1532-5415.2009.02468.x PMID: 19807809

16. Nespoulet H, Wuyam B, Tamisier R, Saunier C, Monneret D, Remy J, et al. Altitude illness is related to low hypoxic chemoresponses and low oxygenation during sleep. Eur Respir J. 2012; 40(3):673–80. doi: 10.1183/09031936.00073111. WOS:000303903400022. PMID: 22523356

17. Gabry AL, Martin C. High-altitude pulmonary edema. Chest. 2003; 124(4):1620–1. WOS:000186002500063. PMID: 14555602

18. Kaminsky DA, Jones K, Schoene RB, Voelkel NF. Urinary leukotriene E(4) levels in high-altitude pulmonary edema— A possible role for inflammation. Chest. 1996; 110(4):393–45. doi: 10.1378/chest.110.4.939. WOS:A1996VN26900018. PMID: 874249

19. Kubo K, Hanaoka M, Yamauchi S, Hayano T, Hayasaka M, Koizumi T, et al. Cytokines in bronchoalveolar lavage fluid in patients with high altitude pulmonary oedema at moderate altitude in Japan. Thorax. 1996; 51(7):739–42. doi: 10.1136/thx.51.7.739. WOS:A1996UY36300016. PMID: 8882083

20. Kim N, Mickelson JB, Brenner BE, Haws CA, Yurgelun-Todd DA, Renshaw PF. Altitude, Gun Ownership, Rural Areas, and Suicide. Am J Psychiat. 2011; 168(1):49–54. doi: 10.1176/appi.ajp.2010.10020289. WOS:000285868100009. PMID: 20843869

21. Zhang XY, Holt JB, Lu H, Wheaton AG, Ford ES, Greenlund KJ, et al. Multilevel Regression and Poststratification for Small-Area Estimation of Population Health Outcomes: A Case Study of Chronic Obstructive Pulmonary Disease Prevalence Using the Behavioral Risk Factor Surveillance System. Am J Epidemiol. 2014; 179(8):1025–33. doi: 10.1093/aje/kwu18. WOS:000340757000011. PMID: 24598867

22. Hadley Wickham RF, Lionel Henry and Kirill Muller. dplyr: A Grammar of Data Manipulation. R package version 0.7.3. 2017. Available from: https://CRAN.R-project.org/package=dplyr.

23. Wickham H. ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag; 2009.

24. Richard A. Becker ARW, Ray Brownrigg. Thomas P Minka, Alex Deckmyn. maps: Draw Geographical Maps 2017. Available from: https://CRAN.R-project.org/package=maps.

25. Kim S. ppcor: An R Package for a Fast Calculation to Semi-partial Correlation Coefficients. Commun Stat Appl Methods. 2015; 22(6):665–74. Epub 2015/12/22. https://doi.org/10.5351/CSAM.2015.22.6.665 PMID: 26688802; PubMed Central PMCID: PMC4681537.
26. Caballero A, Torres-Duque CA, Jaramillo C, Bolivar F, Sanabria F, Osorio P, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). Chest. 2008; 133(2):343–9. doi: 10.1378/chest.07-1361. WOS:000253178400006. PMID: 17951621

27. Menezes AM, Jardim JR, Perez-Padilla R, Camelier A, Rosa F, Nascimento O, et al. Prevalence of chronic obstructive pulmonary disease and associated factors: the PLATINO Study in Sao Paulo, Brazil. Cad Saude Publica. 2005; 21(5):1565–73. Epub 2005/09/15. S0102-311X2005000500030. PMID: 16158163.

28. Schoene RB. Lung disease at high altitude. Adv Exp Med Biol. 1999; 474:47–56. WOS:000084730500003. PMID: 10634992

29. Cogo A, Basnyat B, Legnani D, Allegra L. Bronchial asthma and airway hyperresponsiveness at high altitude. Respir. 1997; 64(6):444–9. WOS:A1997YD43500008. https://doi.org/10.1159/000196721 PMID: 9383820

30. Gong H, Tashkin DP, Lee EY, Simmons MS. Hypoxia-Altitude Simulation Test—Evaluation of Patients with Chronic Airway-Obstruction. Am Rev Respir Dis. 1984; 130(6):980–6. WOS:A1984TW55400006. doi: 10.1164/arrd.1984.130.6.980 PMID: 6508019

31. Karakurum M, Shreeniwas R, Chen J, Pinsky D, Yan SD, Anderson M, et al. Hypoxic Induction of Interleukin-8 Gene-Expression in Human Endothelial-Cells. J Clin Invest. 1994; 93(4):1564–70. doi: 10.1172/JCI117135. WOS:A1994NF56200028. PMID: 8163658

32. Clerici C, Matthay MA. Hypoxia regulates gene expression of alveolar epithelial transport proteins. J Appl Physiol. 2000; 88(5):1890–6. WOS:000086985000050. https://doi.org/10.1152/jappl.2000.88.5.1890 PMID: 10797154

33. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. J Appl Physiol. 2000; 88(4):1474–80. WOS:000086312900043. https://doi.org/10.1152/jappl.2000.88.4.1474 PMID: 10749844

34. Semenza GL. Hypoxia-inducible factor 1: oxygen homeostasis and disease pathophysiology. Trends Mol Med. 2001; 7(8):345–50. doi: 10.1016/S1471-4914(01)02090-1. WOS:000170534000003. PMID: 11516994

35. Yu AY, Frid MG, Shimoda LA, Wiener CM, Stenmark K, Semenza GL. Temporal, spatial, and oxygen-regulated expression of hypoxia-inducible factor-1 in the lung. Am J Physiol-Lung C. 1998; 275(4):L818–L26. WOS:000076268200021.

36. Stenmark KR, Fagan KA, Frid MG. Hypoxia-induced pulmonary vascular remodeling—Cellular and molecular mechanisms. Circ Res. 2006; 99(7):675–91. doi: 10.1161/01.RES.0000243584.45145.3f. WOS:000204846800005. PMID: 17008597

37. Tuder RM, Flook BE, Voelkel NF. Increased Gene-Expression for Vegf and the Vegf Receptors Kdr/Flk and Flt in Lungs Exposed to Acute or to Chronic Hypoxia—Modulation of Gene-Expression by Nitric-Oxide. J Clin Invest. 1995; 95(4):1798–807. doi: 10.1172/JCI117858. WOS:A1995Q059600049. PMID: 7706486

38. Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet. 1997; 349(9063):1436–42. doi: 10.1016/S0140-6736(96)07495-8. WOS:A1997WZ76500011. PMID: 9164317

39. Pope CA, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, et al. Particulate Air-Pollution as a Predictor of Mortality in a Prospective-Study of Us Adults. Am J Resp Crit Care. 1995; 151(3):669–74. WOS:A1995QL391000016.

40. Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. Fine particulate air pollution and mortality in 20 US Cities, 1987–1994. New Engl J Med. 2000; 343(24):1742–9. doi: 10.1056/NEJM200012143432401. WOS:000016581200001. PMID: 11114312

41. Bishop GA, Morris JA, Stedman DH, Cohen LH, Countess RJ, Countess SJ, et al. The effects of altitude on heavy-duty diesel truck on-road emissions. Environ Sci Technol. 2001; 35(8):1574–8. doi: 10.1021/es010353a. WOS:000086990000003. PMID: 11329704

42. Grissom CK, Jones BE. Respiratory Health Benefits and Risks of Living at Moderate Altitude. High Alt Med Biol. 2017. Epub 2017/04/05. https://doi.org/10.1089/ham.2016.0142 PMID: 28375663.

43. Luks AM, Swenson ER. Travel to high altitude with pre-existing lung disease. Eur Respir J. 2007; 29(4):770–72. doi: 10.1183/09031936.00052606. WOS:000245663100023. PMID: 17400877