Online Supplement for:

Influence of Country-Level Differences on COPD Prevalence

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Section 1 of this online supplement describes the PubMed literature search and data sources. Section 2 presents a table of summary statistics for the data. Section 3 provides information about data analysis and statistical computation. It includes a fragment of data for one qualified study to illustrate the formatting used for data records. Section 4 gives the reference list for the 80 qualified articles of our study. The Appendix contains a fragment of Stata computer code for the stepwise binomial regression analysis used in this study.

1. PubMed Literature Search and Data Sources

PubMed literature search

Table S1 presents a list of our initial keyword searches in PubMed for qualified articles. The table shows both the keyword combinations and the number of cited articles obtained in each search. Observe that the searches, by design, are not overlapping.

| Search | Key Words | Combination | Citations |
|--------|----------------------------------------------------------|-------------|-----------|
| 1 | COPD prevalence spirometry GOLD population | (11111) | 85 |
| 2 | ((COPD prevalence spirometry population) NOT GOLD) | (11101) | 288 |
| 3 | ((COPD prevalence GOLD population) NOT spirometry) | (11011) | 83 |
| 4 | ((COPD prevalence spirometry GOLD) NOT population) | (11110) | 98 |
| 5 | (((COPD prevalence GOLD) NOT spirometry) NOT population) | (11010) | 167 |
| Total | | | 721 |

Table S1. List of initial keyword searches in PubMed for qualified articles.

Study-level data

Table S2 shows the number of countries and reference numbers for the 80 qualified articles, classified by world region. Literature citations for the articles are presented alphabetically at the end of this online supplement because they are too numerous to be listed in the main report.

| World Region | Number of Countries | Number of Articles | Reference Numbers for Qualified Articles |
|-----------------|------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------|
| Australasia | 2 | 6 | 6, 12, 45, 62, 67, 74 |
| Latin America | 5 | 3 | 47, 48, 56 |
| Mediterranean | 10 | 18 | 2, 3, 6, 7, 10, 12, 13, 18, 44, 50, 51, 52, 63, 64, 65, 68, 73, 77 |
| North America | 2 | 11 | 6, 8, 9, 12, 22, 27, 41, 42, 49, 66, 70 |
| Northern Europe | 14 | 30 | 4, 5, 6, 11, 12, 14, 15, 19, 20, 21, 23, 26, 29, 30, 31, 32, 36, 37, 38, 40, 46, 53, 54, 57, 58, 59, 60, 69, 71, 72 |
| Southeast Asia | 5 | 17 | 6, 16, 17, 24, 25, 28, 33, 34, 35, 39, 55, 61, 75, 76, 78, 79, 80 |
| Other | 3 | 3 | 1, 6, 43 |
| Total | 41 | 88 | |

Table S2. Numbers of countries and articles, and reference numbers for qualified articles, classified by world region.

Note: Some countries were covered by several articles so the number of articles exceeds the number of countries. The total number of articles exceeds 80 because some qualified articles studied multiple countries.

Prevalence data were extracted from tables, figures and texts of the qualified articles. Some articles did not provide sample sizes for prevalence percentages reported in risk classes but did provide standard errors or 95% confidence intervals. The latter were then used to estimate sample sizes, assuming simple random sampling. In all cases, sums of imputed sample sizes were adjusted to match reported subtotals. Some studies adjusted sample estimates of prevalence for differences between sample and population distributions, resulting in the reporting of population-adjusted estimates. Adjusted prevalence estimates were used only when unadjusted estimates were not reported. The statistical analysis required imputation of representative values for closed- and open-end classes for age groups and smoking amounts. Mid-points were uniformly used for closed-end classes. Judgment was used to choose representative values for open-end classes.

Country-level data

The following public databases provided country-level statistics on demographic, socioeconomic, environmental, and geographic factors that might be associated with COPD.

- 1. Smoking prevalence was assessed using the WHO tobacco surveillance database which provides country-level prevalence rates of tobacco and cigarette smoking by men and women in 2012. <u>http://www.who.int/tobacco/surveillance/policy/country_profile/en/</u>.
- 2. A percentage breakdown of population by age and sex was obtained from the CIA World Fact Book for 2013. <u>https://www.cia.gov/library/publications/the-world-factbook/geos/xx.html</u>.
- 3. Education was assessed using UNESCO data. We focused on a single statistic, namely, the percent of the population that is literate, defined as having more than primary education (ISCED level 2 or higher). <u>http://data.uis.unesco.org/</u>.
- 4. Income was assessed by per-capita gross national income (GNI) by country in current international dollars for 2013. <u>http://data.worldbank.org/country</u>.
- 5. Overall health system performance levels were assessed using system ranks for 191 member states presented in the World Health Report 2000:

http://www.who.int/whr/2000/en/whr00_en.pdf?ua=1.

- 6. CO2 emissions in 2010 were assessed using World Bank data <u>http://data.worldbank.org/country</u>.
- 7. Motor vehicles per capita in 2011 were assessed using World Bank statistics <u>http://data.worldbank.org/indicator/IS.VEH.NVEH.P3</u>.
- 8. Elevation and latitude for major cities were obtained from http://dateandtime.info/citycoordinates.php.

2. Data Summary Statistics

Table S3 lists variables and their definitions, variable names (used in later computer codes), and descriptive statistics for the master data set, classified by (a) study-level variables and (b) country-level variables.

Study-level variables in Table S3 have 1583 records, except for risk factors sex, age, smoking status and smoking amount which do not appear in every study record. Country-level variables have records for 41 countries and, in the case of latitude and elevation, 112 districts (subnational regions) and countries. For studies that involved a representative national sample over a wide geographical area, we computed population weighted averages for elevation and latitude using the readings for the five largest cities in each country. If multiple sites were chosen, but were not nationally representative, sample weighted averages for sites were used. Preliminary analysis revealed that districts having elevations above a threshold tended to have lower COPD prevalence and that the protective effect increased with elevation above this threshold. The threshold, estimated as a tuning parameter by minimizing model deviance, was found to be 6.16 on the log-elevation scale (about 470 meters above sea level). Therefore, a covariate highelev was created which equals 0 when log-elevation is 6.16 or less and which increases linearly with log-elevation above 6.16. The Stata coding for the variable follows:

gen highelev=0; replace highelev=lnelev-6.16 if lnelev>6.16;

Because the country-level socioeconomic variables are in disparate units, we standardized each variable (mean 0, standard deviation 1) to achieve comparable odds ratios in our regression analyses. In the case of the overall health system performance variable, the WHO health system performance ranks for countries were converted into standard normal percentiles or z-scores. Standardized variables have prefix z_{i} in the Stata code in the Appendix.

3. Data Analysis and Statistical Computation

Data record format

Table S4 presents a fragment of the data for one illustrative article.

| | | | Mean or | Std. | | |
|--------------------------------------|---------------|---------|------------|--------|------|-------|
| Variable | Variable Name | Records | percent | Dev. | Min. | Max. |
| (a) Study-level variables | | | | | | |
| Prevalence (percent points) | prev | 1583 | 12.4 | 10.6 | 0 | 74.2 |
| COPD GOLD I-IV severity | defn | 1583 | 60.0% | | | |
| Post-bronchodilation used | pbd | 1583 | 68.9% | | | |
| Respondents in the study | ntotal | 1583 | 2793.2 | 4091.9 | 106 | 20245 |
| Respondents in the record | n | 1583 | 1583 749.8 | | 2 | 15440 |
| COPD cases in the record | r | 1583 | 81.1 | 205.8 | 0 | 3434 |
| Sex (male) | male | 1008 | 49.7% | | | |
| Age (years) | age | 796 | 57.0 | 14.1 | 12.5 | 90.0 |
| Smoking status – Never | smkstatus | 454 | 43.4% | | | |
| Ever (former) | | 454 | 23.6% | | | |
| Current | | 454 | 33.0% | | | |
| Smoking amount (pack-years) | smk | 422 | 16.9 | 16.9 | 0 | 80.1 |
| | | | | | | |
| (b) Country-level variables | | | | | | |
| Smoking prevalence (men, %) | smkpc_m | 41 | 32.6 | 10.0 | 13.0 | 52.9 |
| Smoking prevalence (women, %) | smkpc_f | 41 | 17.8 | 9.3 | 1.2 | 38.0 |
| Children (male, under 15, %) | under15pc_m | 41 | 10.3 | 2.9 | 6.7 | 17.2 |
| Children (female, under 15, %) | under15pc_f | 41 | 9.8 | 2.9 | 6.3 | 16.5 |
| Working-age men (15-64, %) | age15_64pc_m | 41 | 33.5 | 1.8 | 30.5 | 38.7 |
| Working-age women (15-64, %) | age15_64pc_f | 41 | 33.0 | 1.4 | 30.5 | 35.8 |
| Seniors (men, over 64, %) | over64pc_m | 41 | 5.8 | 2.6 | 1.6 | 11.2 |
| Seniors (women, over 64, %) | over64pc_f | 41 | 7.5 | 3.4 | 1.5 | 14.6 |
| Literacy level (percent points) | literacy | 41 | 77.6 | 19.0 | 34.1 | 100.0 |
| Gross national income (000s/ capita) | gni | 41 | 30.9 | 15.2 | 5.0 | 66.5 |
| Health system performance | WHOrank | 41 | | | | |
| CO2 emissions (metric tons/ capita) | co2 | 41 | 7.43 | 4.22 | .7 | 17.6 |
| Motor vehicles per capita | vehicles | 41 | .423 | .227 | .014 | .786 |
| Latitude (North or South, degrees) | latitude | 112 | 40.6 | 12.6 | 10 | 66 |
| Elevation above sea level (meters) | elevation | 112 | 188.1 | 325.8 | 1 | 2240 |

Table S3. Variables and definitions, variable names, and descriptive statistics for the master data set: (a) Studylevel variables; (b) Country-level variables.

Table S4. A fragment of the data record for one qualified article. Many record lines and some variables for this study have been removed in order to fit this page. The fragment is for illustrative purposes only.

| Country | district | Table | prev | defn | ntotal | n | r | agegrp | male | smkstatus | elevation | latitude | pbd |
|---------|----------|--------|------|--------|--------|-----|----|--------|------|-----------|-----------|----------|-----|
| Swe | umea | t3t2t1 | 3.4 | g1plus | 1237 | 89 | 3 | 46-47 | 1 | never | 22.7 | 64.2 | 1 |
| Swe | umea | t3t2t1 | 6.3 | g1plus | 1237 | 63 | 4 | 61-62 | 1 | never | 22.7 | 64.2 | 1 |
| Swe | umea | t3t2t1 | 28 | g1plus | 1237 | 25 | 7 | 76-77 | 1 | never | 22.7 | 64.2 | 1 |
| Swe | umea | t3t2t1 | 3.7 | g1plus | 1237 | 107 | 4 | 46-47 | 1 | ever | 22.7 | 64.2 | 1 |
| Swe | umea | t3t2t1 | 15.8 | g1plus | 1237 | 101 | 16 | 61-62 | 1 | ever | 22.7 | 64.2 | 1 |
| Swe | umea | t3t2t1 | 27.6 | g1plus | 1237 | 76 | 21 | 76-77 | 1 | ever | 22.7 | 64.2 | 1 |
| Swe | umea | t3t2t1 | 13 | g1plus | 1237 | 77 | 10 | 46-47 | 1 | current | 22.7 | 64.2 | 1 |
| Swe | umea | t3t2t1 | 38.9 | g1plus | 1237 | 54 | 21 | 61-62 | 1 | current | 22.7 | 64.2 | 1 |
| Swe | umea | t3t2t1 | 66.7 | g1plus | 1237 | 12 | 8 | 76-77 | 1 | current | 22.7 | 64.2 | 1 |

Stata Computational Procedures

In each step of the step-wise binomial regression, the effects of variables that entered the regression model in preceding steps were included as a fixed offset in the binomial regression function, that is, the regression function estimated in the preceding step was forced into the regression function at the current step with a regression coefficient of 1. Thus, the explanatory contribution of each new group of variables was evaluated as an increment to the contribution of groups that preceded it. A fragment of the Stata computer program for the step-wise binomial regression analysis reported in the article appears in the Appendix to this document. Comment lines are inserted to explain analytical steps as the computation progresses.

| profile | agegrp | male | smkstatus | smkexp | frequency |
|---------|--------|------|-----------|--------|-----------|
| 1 | 1 | 1 | 1 | 1 | 52 |
| 2 | 1 | 1 | 1 | 0 | 74 |
| 3 | 1 | 1 | 0 | 1 | 43 |
| 4 | 1 | 1 | 0 | 0 | 370 |
| 5 | 1 | 0 | 1 | 1 | 0 |
| 6 | 1 | 0 | 1 | 0 | 93 |
| 7 | 1 | 0 | 0 | 1 | 0 |
| 8 | 1 | 0 | 0 | 0 | 164 |
| 9 | 0 | 1 | 1 | 1 | 10 |
| 10 | 0 | 1 | 1 | 0 | 69 |
| 11 | 0 | 1 | 0 | 1 | 214 |
| 12 | 0 | 1 | 0 | 0 | 176 |
| 13 | 0 | 0 | 1 | 1 | 9 |
| 14 | 0 | 0 | 1 | 0 | 147 |
| 15 | 0 | 0 | 0 | 1 | 94 |
| 16 | 0 | 0 | 0 | 0 | 68 |
| Total | | | | | 1583 |

Table S5. Frequency of records for each combination (profile) of the established risk factors of sex, age, smoking status and smoking amount, represented by indicator variables agegrp, male, smkstatus, and smkexp.

Step 2 of the stepwise binomial regression requires explanation. This step takes account of the studylevel established risk factors for sex, age, smoking status (current, ever, never) and smoking amount (in total pack years). Studies differed in their reporting formats for these risk factors. Frequently one or more of the four risk factors were omitted. Thus, these risk factors appeared singly or jointly in various combinations across the 80 studies. The Stata routine for this second step creates a categorical variable **profile** that represents every possible combination of the four variables representing age, sex, smoking status and smoking amount. There are 16 possible combinations of the four variables but combinations **profile==5** and **profile==7** do not occur and, hence, only 14 combinations enter the regression analysis. Table S5 shows the number of prevalence records for each profile. The most common reporting profile for prevalence was a cross-classification by sex and age group (370 among the 1583 records). A separate binomial regression was run for each of the 14 profiles with the reported established risk factors for that profile included in the regression function. Each of the 14 regression functions also included the fitted regression function for the COPD outcome measure from step 1 as a fixed offset.

4. References For Qualified Articles

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Appendix

The following is a fragment of the Stata computer program for the step-wise binomial regression analysis reported in the article. The Stata procedure **binreg** offers an option **offset(varname)** that includes *varname* in the regression model with a coefficient constrained to 1. The generic command **predict** *varname*, **xb** is used to generate the fitted values from the current step in the regression analysis that can be carried forward to the next regression step as an offset with name *varname*.

```
***
*Remove the effects of the COPD diagnostic definition,
*the post-bronchodilation indicator, and their interaction
***
char defn[omit] "g2plus"
char smkstatus[omit] "never"
#delimit ;
xi: binreg r
i.defn*i.pbd,
or n(n);
predict offset0, xb;
#delimit cr
***
*Variable 'profile' represents all 16 possible
*combinations of risk factors for sex, age, smoking
*status and smoking amount reported in the article
***
***
*Fit binomial regression models for all risk factor
*profiles (profiles 5 and 7 have no cases)
***
#delimit ;
quietly xi: binreg r
age agesq male i.smkstatus smk offset0 if profile==1,
or n(n);
predict off1 if profile==1, xb;
gen offset1=off1 if off1!=.;
quietly xi: binreg r
age agesq male i.smkstatus offset0 if profile==2,
or n(n);
predict off2 if profile==2, xb;
replace offset1=off2 if off2!=.;
quietly xi: binreg r
age agesq male smk offset0 if profile==3,
or n(n);
```

```
predict off3 if profile==3, xb;
replace offset1=off3 if off3!=.;
quietly xi: binreg r
age agesq male offset0 if profile==4,
or n(n);
predict off4 if profile==4, xb;
replace offset1=off4 if off4!=.;
*xi: binreg r
*age agesq i.smkstatus smk offset0 if profile==5,
*or n(n);
*predict off5 if profile==5, xb;
*replace offset1=off5 if off5!=.;
quietly xi: binreg r
age agesq i.smkstatus offset0 if profile==6,
or n(n);
predict off6 if profile==6, xb;
replace offset1=off6 if off6!=.;
*xi: binreg r
*age agesq smk offset0 if profile==7,
*or n(n);
*predict off7 if profile==7, xb;
*replace offset1=off7 if off7!=.;
quietly xi: binreg r
age agesq offset0 if profile==8,
or n(n);
predict off8 if profile==8, xb;
replace offset1=off8 if off8!=.;
#delimit ;
quietly xi: binreg r
male i.smkstatus smk offset0 if profile==9,
or n(n);
predict off9 if profile==9, xb;
replace offset1=off9 if off9!=.;
quietly xi: binreg r
male i.smkstatus offset0 if profile==10,
or n(n);
predict off10 if profile==10, xb;
replace offset1=off10 if off10!=.;
quietly xi: binreg r
male smk offset0 if profile==11,
or n(n);
predict off11 if profile==11, xb;
replace offset1=off11 if off11!=.;
quietly xi: binreg r
male offset0 if profile==12,
or n(n);
predict off12 if profile==12, xb;
replace offset1=off12 if off12!=.;
quietly xi: binreg r
i.smkstatus smk offset0 if profile==13,
or n(n);
predict off13 if profile==13, xb;
replace offset1=off13 if off13!=.;
```

```
quietly xi: binreg r
i.smkstatus offset0 if profile==14,
or n(n);
predict off14 if profile==14, xb;
replace offset1=off14 if off14!=.;
quietly xi: binreg r
smk offset0 if profile==15,
or n(n);
predict off15 if profile==15, xb;
replace offset1=off15 if off15!=.;
quietly xi: binreg r
offset0 if profile==16,
or n(n);
predict off16 if profile==16, xb;
replace offset1=off16 if off16!=.;
#delimit cr
***
*Remove effects of study-level risk factors for
*sex, age, smoking status and smoking amount
***
xi: binreg r, or n(n) offset(offset1)
***
*Sequentially fit binomial regression models for
*groups of country-level effects
***
char defn[omit] "g2plus"
char smkstatus[omit] "never"
char worldregion[omit] "NEurope"
#delimit ;
xi: binreg r
smkpc_m smkpc_f a15_64pc_m a15_64pc_f over64pc_m over64pc_f,
or n(n) offset(offset1) ;
predict offset2, xb;
xi: binreg r
z_literacy z_gni z_hsys,
or n(n) offset(offset2) ;
predict offset3, xb;
xi: binreg r
z_co2 z_vehicles,
or n(n) offset(offset3) ;
predict offset4, xb;
xi: binreg r
latitude highelev,
or n(n) offset(offset4);
predict offset5, xb;
xi: binreg r
i.worldregion,
or n(n) offset(offset5) ;
```

```
14
```

predict lgtfit, xb;

#delimit cr