Online Supplement
COPD With Lung Cancer Among Older United States Adults: Prevalence, Diagnostic Timeliness, and Association With Earlier Stage Tumors

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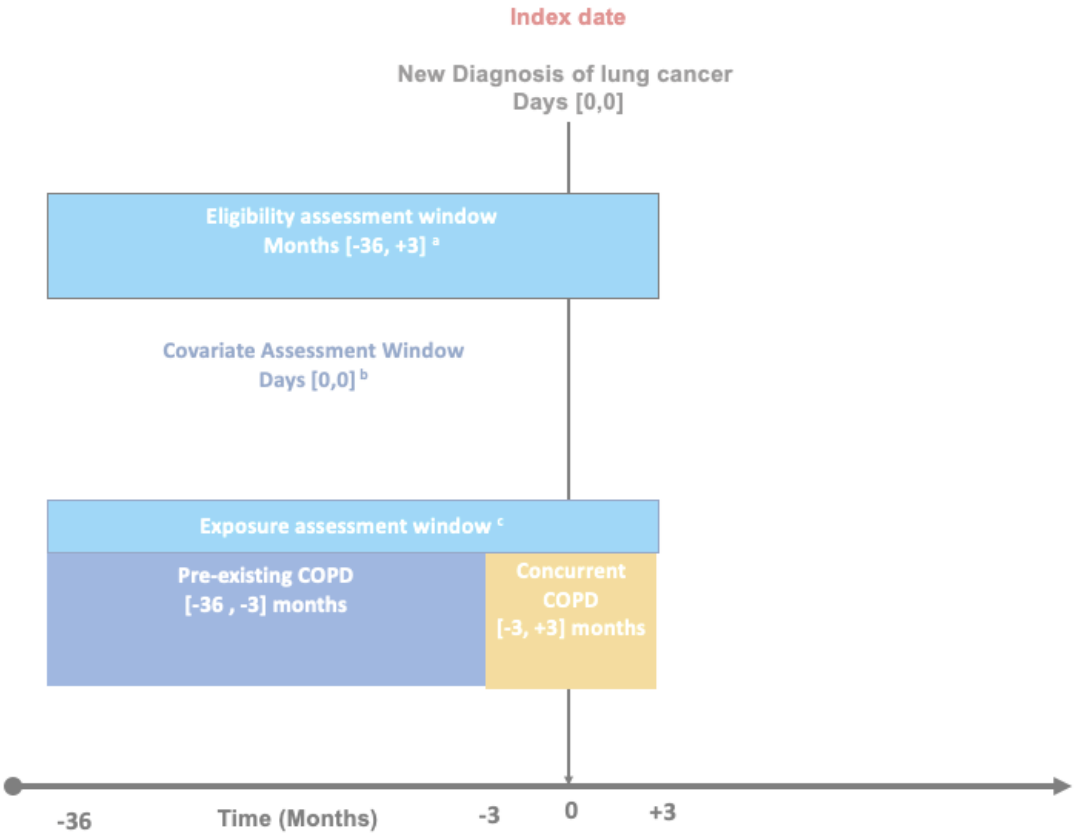
Supplement Table1. Subgroup analyses for the association between timing of COPD diagnosis and stage of lung cancer at diagnosis by sex, race and ethnicity, and census tract measure of socioeconomic status.

Subgroup	**Ratio of prevalence ratios (RPR) (95% CI); P-value ***	**Difference in prevalence differences (DID) (95% CI); P-value ***
SEX (ref= "female")		
Females	PR= 1.21 (1.16 to 1.26)	PD= 0.045 (0.035 to 0.055)
Males	PR= 1.33 (1.28 to 1.39)	PD= 0.049 (0.040 to 0.058)
Contrast between males and females estimates	RPR [b]= 1.09 (1.04 to 1.16); **<0.001**	DID [c]= 0.004 (-0.009 to 0.018); 0.50
RACE (ref= NHWs)		
NHWs	PR= 1.26 (1.22 to 1.30)	PD= 0.048 (0.040 to 0.057)
NHBs	PR= 1.37 (1.22 to 1.54)	PD= 0.049 (0.024 to 0.074)
Contrast between NHWs and NHBs estimates	RPR= 1.09 (0.97 to 1.22); **0.16**	DID=0.001 (-0.025 to 0.027); 0.9
Hispanic	PR= 1.39 (1.19 to 1.63)	PD= 0.084 (0.049 to 0.120)
Contrast between Hispanic and NHWs estimates	RPR= 1.11 (0.94 to 1.30); **0.22**	DID= 0.036 (-0.0002 to 0.072); **0.05**
Asian	PR= 1.11 (0.95 to 1.30)	PD= 0.034 (-0.008 to 0.077)
Contrast between Asian and NHWs estimates	RPR= 0.88 (0.75 to 1.04); **0.20**	DID= -0.014 (-0.057 to 0.029); 0.52
AIAN	PR= 1.54 (0.92 to 2.59)	PD= 0.094 (-0.109 to 0.297)

Contrast between AIAN and NHWs estimates	RPR= 1.22 (0.72 to 2.06); 0.45	DID= 0.079 (-0.066 to 0.224); **0.29**
NHPI	PR= 0.98 (0.54 to 1.76)	PD= -0.030 (-0.175 to 0.115)
Contrast between NHPI and NHWs estimates	RPR= 0.78 (0.43 to 1.40); **0.05**	DID= -0.078 (-0.224 to 0.067); **0.29**
Mixed	PR= 0.87 (0.49 to 1.57)	PD= -0.036 (-0.287 to 0.216)
Contrast between Mixed and NHWs estimates	RPR= 0.69 (0.39 to 1.25); **0.22**	DID= -0.084 (-0.336 to 0.168); 0.51
SES (ref=Highest SES)		
Highest SES	PR= 1.23 (1.16 to 1.29)	PD= 0.047 (0.032 to 0.062)
Lowest SES	PR= 1.27 (1.18 to 1.36)	PD= 0.037 (0.023 to 0.051)
Contrast between Lowest and Highest SES estimates	RPR= 1.03 (0.94 to 1.13); 0.50	DID= -0.010 (-0.030 to 0.010); **0.30**
Lower Middle SES	PR= 1.29 (1.21 to 1.38)	PD= 0.047 (0.032 to 0.062)
Contrast between Lower Middle and Highest SES estimates	RPR= 1.05 (0.97 to 1.15); **0.26**	DID= 0.000 (-0.020 to 0.021); 1
Middle SES	PR= 1.26 (1.18 to 1.35)	PD= 0.047 (0.033 to 0.062)
Contrast between Middle and Highest SES estimates	RPR= 1.03 (0.95 to 1.12); 0.50	DID= -0.000 (-0.021 to 0.021); 1
Upper Middle SES	PR= 1.29 (1.22 to 1.37)	PD= 0.049 (0.027 to 0.071)
Contrast between Upper Middle and Highest SES estimates	RPR= 1.05 (0.97 to 1.14); **0.20**	DID= 0.008 (-0.012 to 0.029); 0.43

*Subgroup /effect measure modification (EMM) analysis adjusted for age at cancer diagnosis, sex, socioeconomic status (SES), year of diagnosis, SEER Registry Region, Charlson Comorbidity Score Index (CCI) and all healthcare utilization during the one year before lung cancer diagnosis. P-value < 0.3 threshold is considered statistically significant to reject the Null hypothesis and is presented in bold.

RPR= Ratio of prevalence ratios, **DID**= Difference in prevalence differences.



Supplement Figure E1. Patient assessment windows and study timeline

a. Exclusion criteria include age <68years, previous diagnosis of cancer, lung cancer diagnosed before 2008 or after 2017, in situ tumor, patient was diagnosed at autopsy or only on death certificate, any enrollment in Health Maintenance Organization (HMO) Medicare plan or any gaps in Medicare fee for service (FFS) parts A, B enrollment from 36 months prior to 3 months after lung cancer diagnosis.

b. Covariates assessment window includes assessing sociodemographic, clinical, and tumor characteristics.

c. Exposure includes evidence of claim-based diagnosis of chronic obstructive pulmonary disease (COPD) during the 36 months prior to 3 months after lung cancer diagnosis using the international classification of disease diagnosis codes versions 9 and 10 (ICD9, ICD10).

Simplified Bias analyses using the Rothman Epi Sheets Available at:
https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=http://krothman.hostbyet2.com/episheet.xls&ved=2ahUKEwiQxcu_y72FAxXoD1kFHRIYDCoQFnoECA0QAQ&usg=AOvVaw0cealnxt2WCri6B9YnQ9_n

- **Direction of the bias** for both COPD severity and smoking is expected to be upward bias (overestimated observed association estimate) because both confounders have positive association with the exposure (COPD diagnosis timing) and outcome (early-stage lung cancer diagnosis).

- **Bias parameters:**

1- **Unmeasured COPD severity:**

Bias parameters based on reviewing literature are:

Prevalence of severe COPD among those with pre-existing COPD diagnosis= 0.3

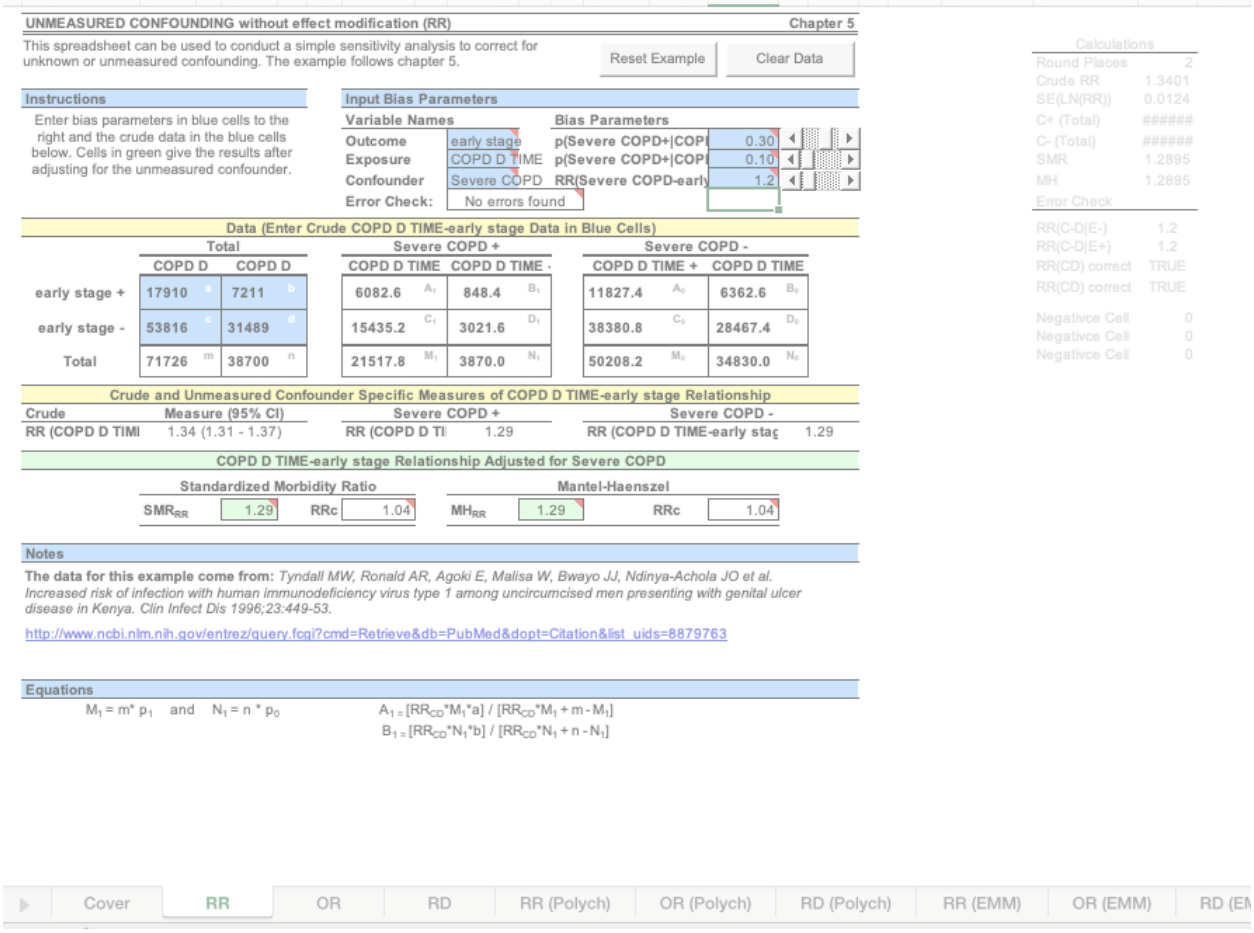
Prevalence of severe COPD among those with concurrent COPD diagnosis= 0.1

Possible association between severe COPD and early-stage lung cancer was set to 2 scenarios:

RR= 1.2, RR=1.5

Observed PR between COPD diagnosis timing and early-stage lung cancer "unadjusted for severe COPD"	Assumed RR between severe COPD and early stage of lung cancer	**Corrected PR**
1.34	1.2	1.29
1.34	1.5	1.22

Scenario 1: RR between severe COPD and early stage of lung cancer =1.2



UNMEASURED CONFOUNDING without effect modification (RR) — Chapter 5

This spreadsheet can be used to conduct a simple sensitivity analysis to correct for unknown or unmeasured confounding. The example follows chapter 5.

Reset Example | Clear Data

Instructions

Enter bias parameters in blue cells to the right and the crude data in the blue cells below. Cells in green give the results after adjusting for the unmeasured confounder.

Input Bias Parameters

Variable Names		Bias Parameters	
Outcome	early stage	p(Severe COPD+|COPD	0.30
Exposure	COPD D TIME	p(Severe COPD+|COPD	0.10
Confounder	Severe COPD	RR(Severe COPD-early	1.2
Error Check:	No errors found		

Data (Enter Crude COPD D TIME-early stage Data in Blue Cells)

	Total		Severe COPD +		Severe COPD -	
	COPD D	COPD D	COPD D TIME	COPD D TIME -	COPD D TIME +	COPD D TIME
early stage +	17910 a	7211 b	6082.6 A_1	848.4 B_1	11827.4 A_0	6362.6 B_0
early stage -	53816 c	31489 d	15435.2 C_1	3021.6 D_1	38380.8 C_0	28467.4 D_0
Total	71726 m	38700 n	21517.8 M_1	3870.0 N_1	50208.2 M_0	34830.0 N_0

Crude and Unmeasured Confounder Specific Measures of COPD D TIME-early stage Relationship

Crude	Measure (95% CI)	Severe COPD +		Severe COPD -	
RR (COPD D TIMI	1.34 (1.31 - 1.37)	RR (COPD D TI	1.29	RR (COPD D TIME-early stag	1.29

COPD D TIME-early stage Relationship Adjusted for Severe COPD

Standardized Morbidity Ratio			Mantel-Haenszel		
SMR_{RR}	1.29	RRc 1.04	MH_{RR}	1.29	RRc 1.04

Notes

The data for this example come from: *Tyndall MW, Ronald AR, Agoki E, Malisa W, Bwayo JJ, Ndinya-Achola JO et al. Increased risk of infection with human immunodeficiency virus type 1 among uncircumcised men presenting with genital ulcer disease in Kenya. Clin Infect Dis 1996;23:449-53.*

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8879763

Equations

$M_1 = m^* p_1$ and $N_1 = n * p_0$

$A_1 = [RR_{CD}*M_1*a] / [RR_{CD}*M_1 + m - M_1]$

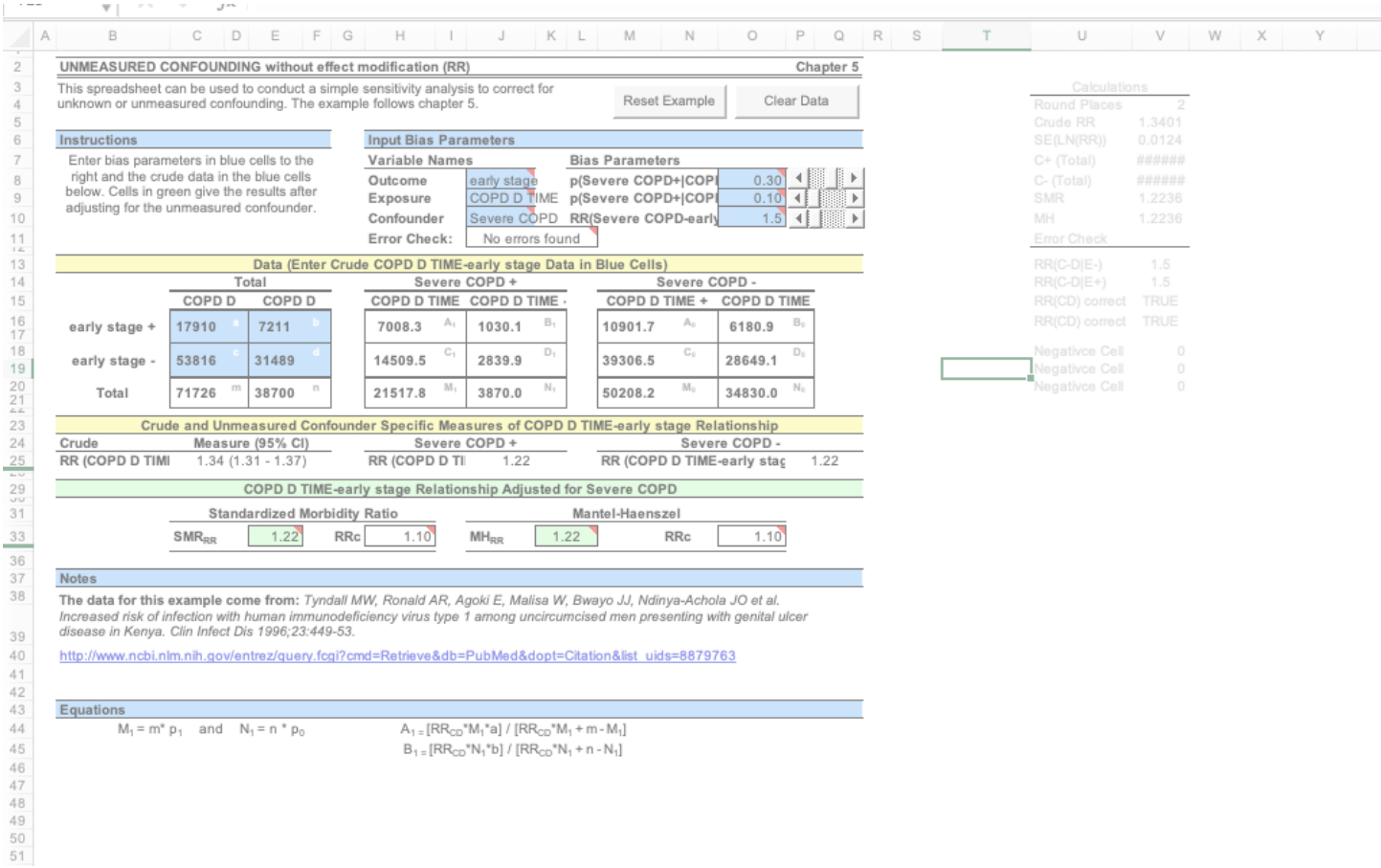
$B_1 = [RR_{CD}*N_1*b] / [RR_{CD}*N_1 + n - N_1]$

Calculations

Round Places	2
Crude RR	1.3401
SE(LN(RR))	0.0124
C+ (Total)	######
C- (Total)	######
SMR	1.2895
MH	1.2895
Error Check	
RR(C-D|E-)	1.2
RR(C-D|E+)	1.2
RR(CD) correct	TRUE
RR(CD) correct	TRUE
Negativce Cell	0
Negativce Cell	0
Negativce Cell	0

Cover | RR | OR | RD | RR (Polych) | OR (Polych) | RD (Polych) | RR (EMM) | OR (EMM) | RD (EM

Scenario 2: RR between severe COPD and early stage of lung cancer =1.5



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Instructions

Enter bias parameters in blue cells to the right and the crude data in the blue cells below. Cells in green give the results after adjusting for the unmeasured confounder.

Input Bias Parameters

Variable Names		Bias Parameters	
Outcome	early stage	p(Severe COPD+|COPI	0.30
Exposure	COPD D TIME	p(Severe COPD+|COPI	0.10
Confounder	Severe COPD	RR(Severe COPD-early	1.5
Error Check:	No errors found		

Data (Enter Crude COPD D TIME-early stage Data in Blue Cells)

	Total		Severe COPD +		Severe COPD -	
	COPD D	COPD D	COPD D TIME	COPD D TIME -	COPD D TIME +	COPD D TIME
early stage +	17910 a	7211 b	7008.3 A_1	1030.1 B_1	10901.7 A_0	6180.9 B_0
early stage -	53816 c	31489 d	14509.5 C_1	2839.9 D_1	39306.5 C_0	28649.1 D_0
Total	71726 m	38700 n	21517.8 M_1	3870.0 N_1	50208.2 M_0	34830.0 N_0

Crude and Unmeasured Confounder Specific Measures of COPD D TIME-early stage Relationship

Crude	Measure (95% CI)	Severe COPD +		Severe COPD -	
RR (COPD D TIMI	1.34 (1.31 - 1.37)	RR (COPD D TI	1.22	RR (COPD D TIME-early stag	1.22

COPD D TIME-early stage Relationship Adjusted for Severe COPD

Standardized Morbidity Ratio			Mantel-Haenszel		
SMR_{RR}	1.22	RRc 1.10	MH_{RR}	1.22	RRc 1.10

Notes

The data for this example come from: *Tyndall MW, Ronald AR, Agoki E, Malisa W, Bwayo JJ, Ndinya-Achola JO et al. Increased risk of infection with human immunodeficiency virus type 1 among uncircumcised men presenting with genital ulcer disease in Kenya. Clin Infect Dis 1996;23:449-53.*

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8879763

Equations

$M_1 = m^* p_1$ and $N_1 = n * p_0$

$A_1 = [RR_{CD}{}^*M_1{}^*a] / [RR_{CD}{}^*M_1 + m - M_1]$

$B_1 = [RR_{CD}{}^*N_1{}^*b] / [RR_{CD}{}^*N_1 + n - N_1]$

Calculations

Round Places	2
Crude RR	1.3401
SE(LN(RR))	0.0124
C+ (Total)	######
C- (Total)	######
SMR	1.2236
MH	1.2236
Error Check	
RR(C-D|E-)	1.5
RR(C-D|E+)	1.5
RR(CD) correct	TRUE
RR(CD) correct	TRUE
Negativce Cell	0
Negativce Cell	0
Negativce Cell	0

2- Unmeasured smoking:

Bias parameters are:

Prevalence of ever smoking among those with known (pre-existing) COPD diagnosis= 0.9

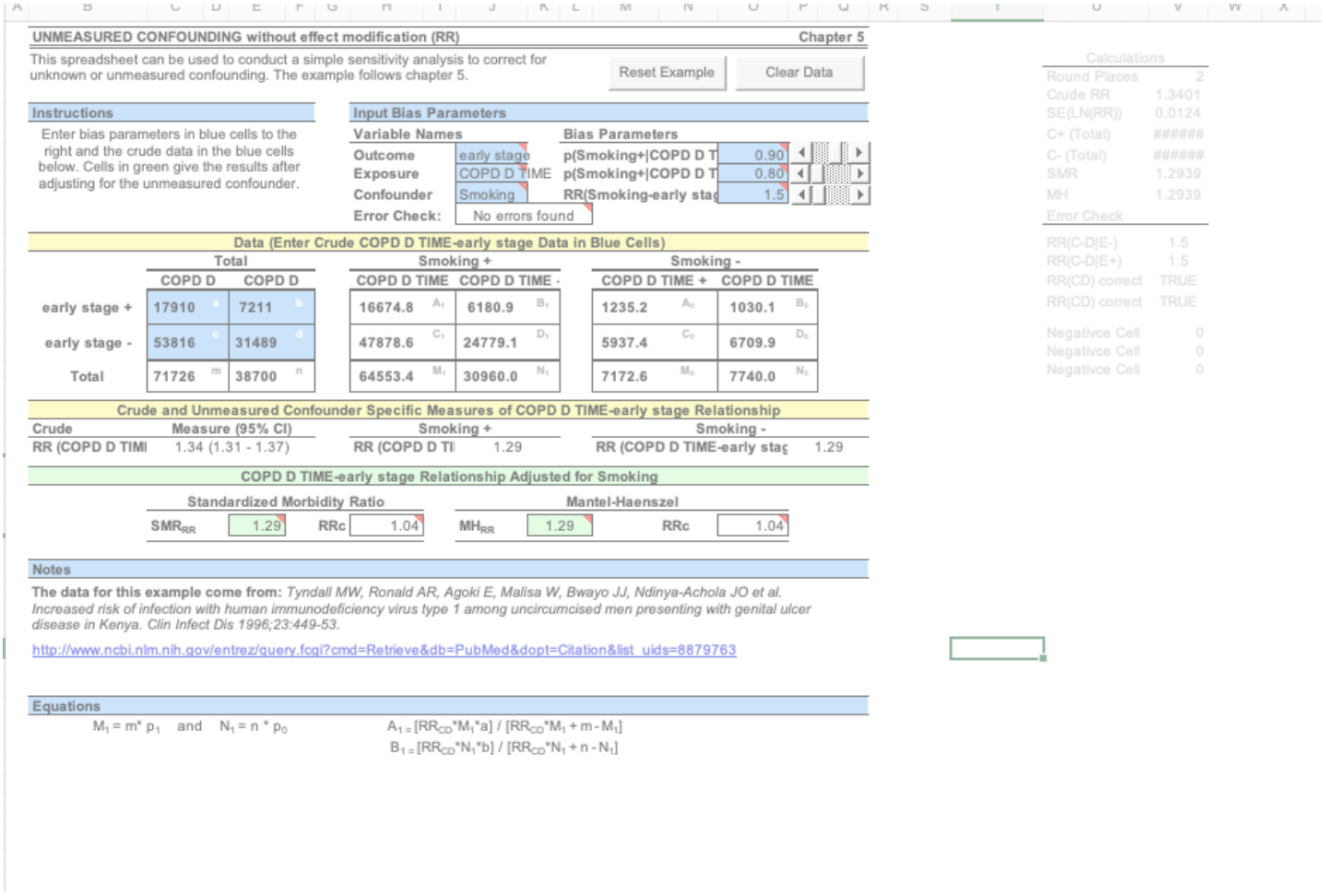
Prevalence of ever smoking among those with Unknown (concurrent) COPD diagnosis= 0.8

Possible association between ever smoking and early-stage lung cancer was set to 2 scenarios.

RR= 1.3, RR=1.5

Observed PR between COPD diagnosis timing and early-stage lung cancer "unadjusted for severe COPD"	Assumed RR between smoking and early stage of lung cancer	**Corrected PR**
1.34	1.3	1.29
1.34	1.5	1.31

Scenario 1: RR between smoking and early diagnosis of lung cancer= 1.5



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Instructions

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Input Bias Parameters

Variable Names		Bias Parameters	
Outcome	early stage	p(Smoking+|COPD D T	0.90
Exposure	COPD D TIME	p(Smoking+|COPD D T	0.80
Confounder	Smoking	RR(Smoking-early stag	1.5
Error Check:	No errors found		

Data (Enter Crude COPD D TIME-early stage Data in Blue Cells)

	Total		Smoking +		Smoking -	
	COPD D	COPD D	COPD D TIME	COPD D TIME -	COPD D TIME +	COPD D TIME
early stage +	17910 a	7211 b	16674.8 A_1	6180.9 B_1	1235.2 A_0	1030.1 B_0
early stage -	53816 c	31489 d	47878.6 C_1	24779.1 D_1	5937.4 C_0	6709.9 D_0
Total	71726 m	38700 n	64553.4 M_1	30960.0 N_1	7172.6 M_0	7740.0 N_0

Crude and Unmeasured Confounder Specific Measures of COPD D TIME-early stage Relationship

Crude	Measure (95% CI)	Smoking +		Smoking -	
RR (COPD D TIMI	1.34 (1.31 - 1.37)	RR (COPD D TI	1.29	RR (COPD D TIME-early stag	1.29

COPD D TIME-early stage Relationship Adjusted for Smoking

Standardized Morbidity Ratio			Mantel-Haenszel		
SMR_{RR}	1.29	RRc 1.04	MH_{RR}	1.29	RRc 1.04

Notes

The data for this example come from: *Tyndall MW, Ronald AR, Agoki E, Malisa W, Bwayo JJ, Ndinya-Achola JO et al. Increased risk of infection with human immunodeficiency virus type 1 among uncircumcised men presenting with genital ulcer disease in Kenya. Clin Infect Dis 1996;23:449-53.*

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Equations

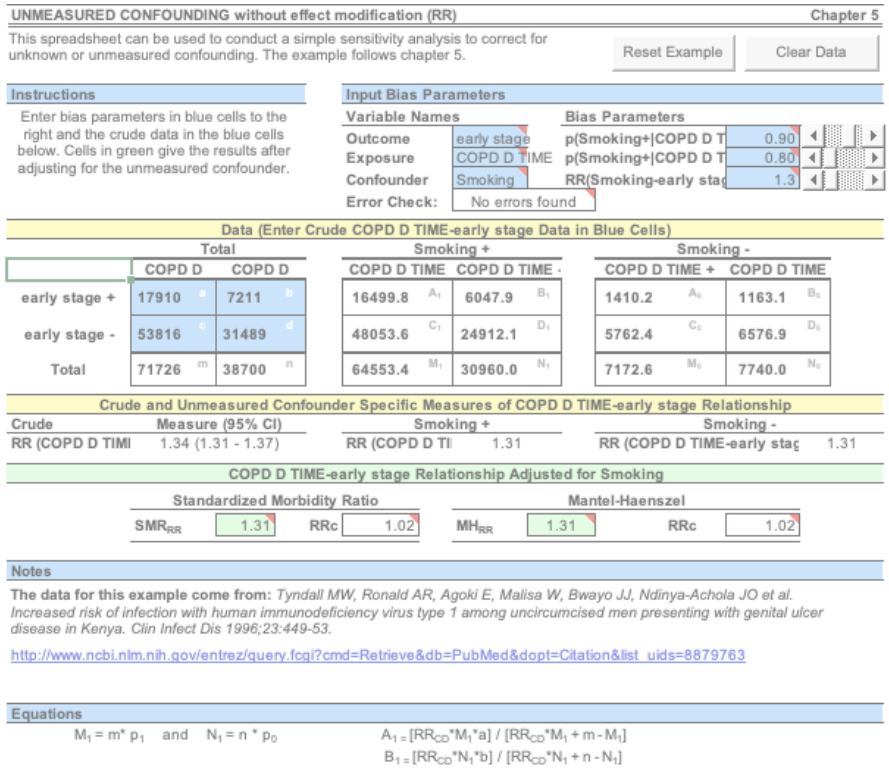
$M_1 = m^* p_1$ and $N_1 = n * p_0$

$A_1 = [RR_{CD}{}^*M_1{}^*a] / [RR_{CD}{}^*M_1 + m - M_1]$

$B_1 = [RR_{CD}{}^*N_1{}^*b] / [RR_{CD}{}^*N_1 + n - N_1]$

Calculations	
Round Places	2
Crude RR	1.3401
SE(LN(RR))	0.0124
C+ (Total)	######
C- (Total)	######
SMR	1.2939
MH	1.2939
Error Check	
RR(C-D|E-)	1.5
RR(C-D|E+)	1.5
RR(CD) correct	TRUE
RR(CD) correct	TRUE
Negativce Cell	0
Negativce Cell	0
Negativce Cell	0

Scenario 2: RR between smoking and early diagnosis of lung cancer= 1.3



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Input Bias Parameters

Variable Names		Bias Parameters	
Outcome	early stage	p(Smoking+|COPD D T	0.90
Exposure	COPD D TIME	p(Smoking+|COPD D T	0.80
Confounder	Smoking	RR(Smoking-early stag	1.3
Error Check:	No errors found		

Data (Enter Crude COPD D TIME-early stage Data in Blue Cells)

	Total		Smoking +		Smoking -	
	COPD D	COPD D	COPD D TIME	COPD D TIME -	COPD D TIME +	COPD D TIME
early stage +	17910 a	7211 b	16499.8 A_1	6047.9 B_1	1410.2 A_0	1163.1 B_0
early stage -	53816 c	31489 d	48053.6 C_1	24912.1 D_1	5762.4 C_0	6576.9 D_0
Total	71726 m	38700 n	64553.4 M_1	30960.0 N_1	7172.6 M_0	7740.0 N_0

Crude and Unmeasured Confounder Specific Measures of COPD D TIME-early stage Relationship

Crude	Measure (95% CI)	Smoking +		Smoking -	
RR (COPD D TIMI	1.34 (1.31 - 1.37)	RR (COPD D TI	1.31	RR (COPD D TIME-early stag	1.31

COPD D TIME-early stage Relationship Adjusted for Smoking

Standardized Morbidity Ratio			Mantel-Haenszel		
SMR_{RR}	1.31	RRc 1.02	MH_{RR}	1.31	RRc 1.02

Notes

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Equations

$M_1 = m^* p_1$ and $N_1 = n * p_0$

$A_1 = [RR_{CD}*M_1*a] / [RR_{CD}*M_1 + m - M_1]$

$B_1 = [RR_{CD}*N_1*b] / [RR_{CD}*N_1 + n - N_1]$

Calculations

Round Places	2
Crude RR	1.3401
SE(LN(RR))	0.0124
C+ (Total)	######
C- (Total)	######
SMR	1.3084
MH	1.3084
Error Check	
RR(C-D|E-)	1.3
RR(C-D|E+)	1.3
RR(CD) correct	TRUE
RR(CD) correct	TRUE
Negativce Cell	0
Negativce Cell	0
Negativce Cell	0