Preoperative Atelectasis

Part 7: Posthoc Analyses

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Rationale

We observed that SpO2 starts decreasing at BMIs above 40-45. Thus, by having used the WHO obesity class categories, detail on differences above BMI 40 for the extent of atelectasis percentage may have been lost. The WHO obesity class categories do not reflect the extent of variation in BMI observed in this sample of patients:

- Class 1, **BMI [30,35)**: ~25% participants

- Class 2, **BMI [35,40)**: ~25% participants

- Class 3, **BMI >40**: ~50% of participants, with a median BMI above a 5 units range.

Thus, creating subcategories within the class 3 obesity may allow to assess the impact of BMI increases above 40 on atelectasis percentage with more detail.

Thus, I will extend the categories of BMI with the following categories:

- **BMI [30,35)** kg/m²
- **BMI [35,40)** kg/m²
- **BMI [40,45)** kg/m²
- **BMI [44,50)** kg/m²
- **BMI >50** kg/m²

Setup

Packages used

```r
if (!require("pacman", quietly = TRUE)) {
  install.packages("pacman")
}


pacman::p_load(
  tidyverse, # Used for basic data handling and visualization.
  table1, #Used to add lables to variables.
  RColorBrewer, #Color palettes for data visualization.
  gridExtra, #Used to arrange multiple ggplots in a grid.
  grid, #Used to arrange multiple ggplots in a grid.
  mgcv, #Used to model non-linear relationships with a general additive model.
  ggmosaic, #Used to create mosaic plots.
  car, #Used assess distribution of continuous variables (stacked Q-Q plots).
  simpleboot, boot, # Used to calculate mean atelectasis coverage and
                    # 95%CI through bootstrapping.
  broom, #Used to exponentiate coefficients of regression models.
  sandwich, #Used to calculate robust standard errors for prevalence ratios.
  flextable, #Used to export tables.
  rms, #Used to model ordinal outcome (atelectasis percent) and
       #test proportional odds assumptions.
```

```
  VGAM, #Used to model partial proportional odds model.
  gt #Used to present a summary of the results of regression models.
)
```

Session and package dependencies

```
R version 4.3.2 (2023-10-31 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 11 x64 (build 22621)

Matrix products: default


locale:
[1] LC_COLLATE=Spanish_Mexico.utf8  LC_CTYPE=Spanish_Mexico.utf8
[3] LC_MONETARY=Spanish_Mexico.utf8 LC_NUMERIC=C
[5] LC_TIME=Spanish_Mexico.utf8

time zone: Europe/Berlin
tzcode source: internal

attached base packages:
 [1] splines   stats4    grid      stats     graphics  grDevices utils
 [8] datasets  methods   base

other attached packages:
 [1] gt_0.10.0          VGAM_1.1-9          rms_6.7-1           Hmisc_5.1-1
 [5] flextable_0.9.4    sandwich_3.0-2      broom_1.0.5         boot_1.3-28.1
 [9] simpleboot_1.1-7   car_3.1-2           carData_3.0-5       ggmosaic_0.3.3
[13] mgcv_1.9-0         nlme_3.1-164        gridExtra_2.3       RColorBrewer_1.1-3
[17] table1_1.4.3       lubridate_1.9.3     forcats_1.0.0       stringr_1.5.1
[21] dplyr_1.1.4        purrr_1.0.2         readr_2.1.4         tidyr_1.3.0
[25] tibble_3.2.1       ggplot2_3.4.4       tidyverse_2.0.0     pacman_0.5.1
```

Set seed (for reproducibility of bootstrapping) as the current year 2023:

```
seed <- 2023
```

Outcome variable

Corroborate that the new BMI breaks category was created successfully:

```
type_obesity
30-35 35-40 40-45 45-50    50
   63    53    57    31    32
```

Percentages:

```
type_obesity
30-35 35-40 40-45 45-50    50
 26.7  22.5  24.2  13.1  13.6
```

Prevalence of atelectasis

```
            Yes    No
frequencies 77.0 159.0
percent     32.6  67.4
```

Prevalence of atelectasis with 95% confidence interval

```
    1-sample proportions test without continuity correction

data:  frequencies, null probability 0.5
X-squared = 28.492, df = 1, p-value = 9.411e-08
alternative hypothesis: true p is not equal to 0.5
95 percent confidence interval:
 0.2696526 0.3884549
sample estimates:
        p
0.3262712
```

The prevalence of atelectasis was **32.6 (95%CI: 26.97, 38.85)**.

Atelectasis - obesity class

Mean expected frequency:

```
  mean_expected_freq
1               23.6
```

Frequencies:

```
          atelectasis
type_obesity Yes No
      30-35   8 55
      35-40  15 38
      40-45   7 50
      45-50  15 16
         50  32  0
```

Percentage:

```
          atelectasis
type_obesity    Yes      No
      30-35  12.70   87.30
      35-40  28.30   71.70
      40-45  12.28   87.72
      45-50  48.39   51.61
         50 100.00    0.00
```

Mosaic Plot
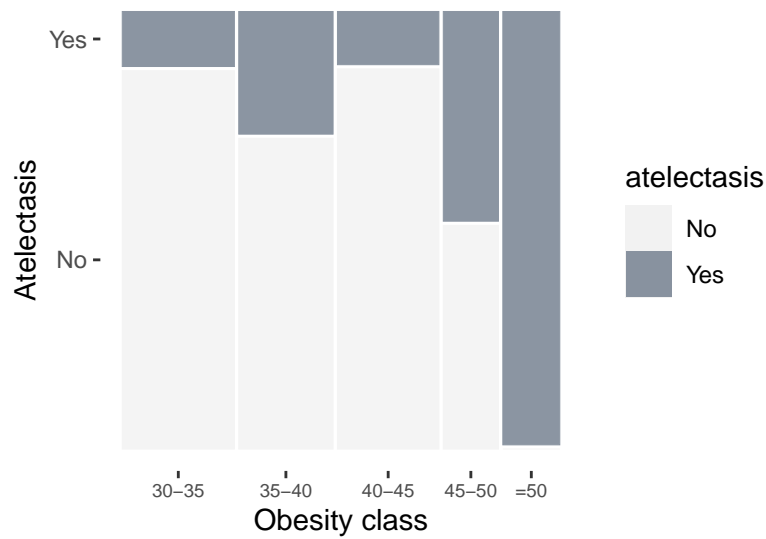
```
    Pearson's Chi-squared test

data:  frequencies
X-squared = 92.149, df = 4, p-value < 2.2e-16
```

Atelectasis location by obesity class

Mean expected frequency:

```
  mean_expected_freq
1                7.7
```

Mean expected frequency is greater than 5.0, so chi-squared without continuity correction is adequate.

Frequencies:

```
              atelectasis_location
type_obesity Bilateral Unilateral
       30-35         1          7
       35-40         5         10
       40-45         4          3
       45-50         4         11
        50          10         22
```

Percentage:

```
              atelectasis_location
type_obesity Bilateral Unilateral
       30-35     12.50      87.50
       35-40     33.33      66.67
       40-45     57.14      42.86
       45-50     26.67      73.33
          50     31.25      68.75
```

Mosaic Plot
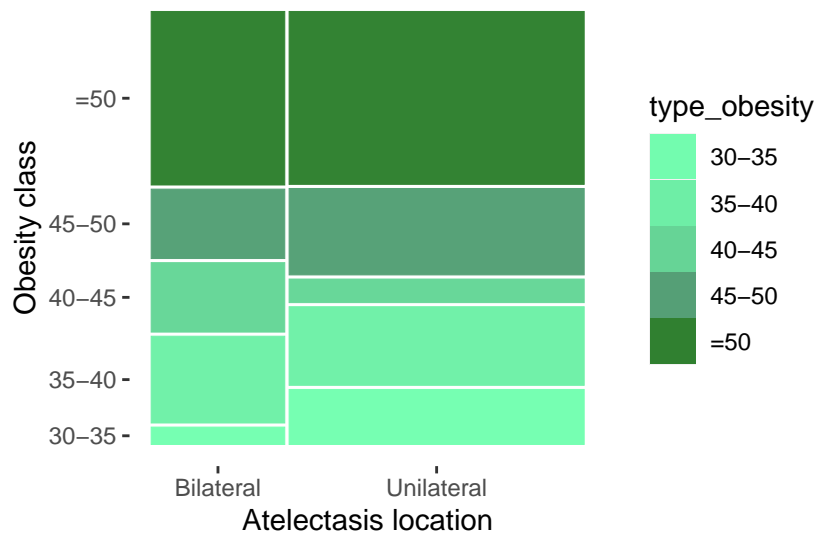

```
    Pearson's Chi-squared test

data:  frequencies
X-squared = 3.6755, df = 4, p-value = 0.4517
```

Prevalence of atelectasis with 95% confidence intervals calculated with sourced script **Prevalence_atelectasis.R**

atelectasis	type_obesity	n	prev	confint	Bilateral	Unilateral
Yes	Total	77	32.63	26.77 - 39.06	24 (31.17%)	53 (68.83%)
No	Total	159	67.37			
Yes	30-35	8	12.70	6.03 - 24.04	1 (12.5%)	7 (87.5%)

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No	30-35	55	87.30			
Yes	35-40	15	28.30	17.2 - 42.56	5 (33.33%)	10 (66.67%)
No	35-40	38	71.70			
Yes	40-45	7	12.28	5.49 - 24.29	4 (57.14%)	3 (42.86%)
No	40-45	50	87.72			
Yes	45-50	15	48.39	30.56 - 66.6	4 (26.67%)	11 (73.33%)
No	45-50	16	51.61			
Yes	50	32	100.00	86.66 - 100	10 (31.25%)	22 (68.75%)

Atelectasis Percent

Mean atelectasis percentage

The following would be the mean atelectasis percentage coverage if a normal distribution were assumed, which is what has been done in some prior studies:

```
      mean       sd
1 2.658898 4.687145
```

And by obesity class:

```
# A tibble: 5 x 3
  type_obesity   mean    sd
  <fct>         <dbl> <dbl>
1 30-35         0.913  2.89
2 35-40         1.56   3.15
3 40-45         0.702  2.05
4 45-50         3.63   4.22
5 50           10.5    5.40
```

As is evident from these numbers, assuming normality causes standard deviation to capture negative values, which is impossible in reality for this variable.

Thus, bootstrapping the mean and 95%CI is expected to lead to more appropriate estimates.

I will calculate this for class 3 subgroups:

Subgroup 1

Mean:

```
[1] 0.7022018
```

95% CI:

```
BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
Based on 10000 bootstrap replicates

CALL :
boot.ci(boot.out = boot_sub1)

Intervals :
Level      Normal              Basic
95%   ( 0.1772,  1.2254 )   ( 0.1316,  1.1842 )

Level      Percentile          BCa
95%   ( 0.2193,  1.2719 )   ( 0.2193,  1.2719 )
Calculations and Intervals on Original Scale
```

Subgroup 2

Mean:

```
[1] 3.62979
```

95% CI:

```
BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
Based on 10000 bootstrap replicates

CALL :
boot.ci(boot.out = boot_sub2)

Intervals :
Level      Normal              Basic
95%   ( 2.169,  5.087 )   ( 2.177,  5.000 )

Level      Percentile          BCa
95%   ( 2.258,  5.081 )   ( 2.177,  5.000 )
Calculations and Intervals on Original Scale
```

Subgroup 3

Mean:

```
[1] 10.44323
```

95% CI:

```
BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
Based on 10000 bootstrap replicates

CALL :
boot.ci(boot.out = boot_sub3)

Intervals :
Level      Normal              Basic
95%   ( 8.66, 12.33 )   ( 8.52, 12.19 )

Level     Percentile           BCa
95%   ( 8.75, 12.42 )   ( 8.83, 12.50 )
Calculations and Intervals on Original Scale
```

> The mean atelectasis percentage coverage in class 3 obesity subcategories was: subgroup 1 (0.7%, 95%CI:0.22-1.27), subgroup 2 (3.63%, 95%CI:2.18-5), and subgroup 3 (10.44%, 95%CI:8.83-12.5).

Atelectasis percentage by obesity subgroups

Now, I will continue assessing atelectasis percentage if assumed to be categorical ordinal:

Mean expected frequency:

```
  mean_expected_freq
1        5.244444
```

Mean expected frequency is very close to 5.0, so I will use chi-squared with continuity correction.

Frequencies:

```
                type_obesity
atelectasis_percent 30-35 35-40 40-45 45-50 50
               0       55    38    50    16    0
              2.5       2     7     2     0    0
              5         1     2     1     5    5
              7.5       4     4     4     7   14
             10         0     1     0     2    3
             12.5       0     0     0     0    1
             15         0     1     0     1    2
             17.5       1     0     0     0    6
             27.5       0     0     0     0    1


    Pearson's Chi-squared test

data:  frequencies
X-squared = 145.94, df = 32, p-value < 2.2e-16
```

Figure 2

Figure 2 created with sourced script ***Figure2.R***

Prevalence Ratio

This paper and accompanying code were used to calculate prevalence ratios.

A modified Poisson regression model with robust errors will be applied to obtain prevalence ratios.

Prevalence ratios were calculated with the accompanying sourced script ***Prevalence_Ratio_subgroups.R***

Table 2 appendage

Category	PR	SE	95%CI	aPR	aSE	a95%CI
35-40	2.23	0.40	1.03-4.84	2.17	0.38	1.04-4.53
40-45	0.97	0.48	0.37-2.5	0.91	0.45	0.38-2.18
45-50	3.81	0.38	1.81-8.01	3.35	0.37	1.63-6.87
50	7.87	0.33	4.12-15.05	7.01	0.32	3.72-13.22

Note that in this model the PR for class 2 obesity changed slightly. Nonetheless, the direction of the results did not change and there are only slight changes in estimates and confidence
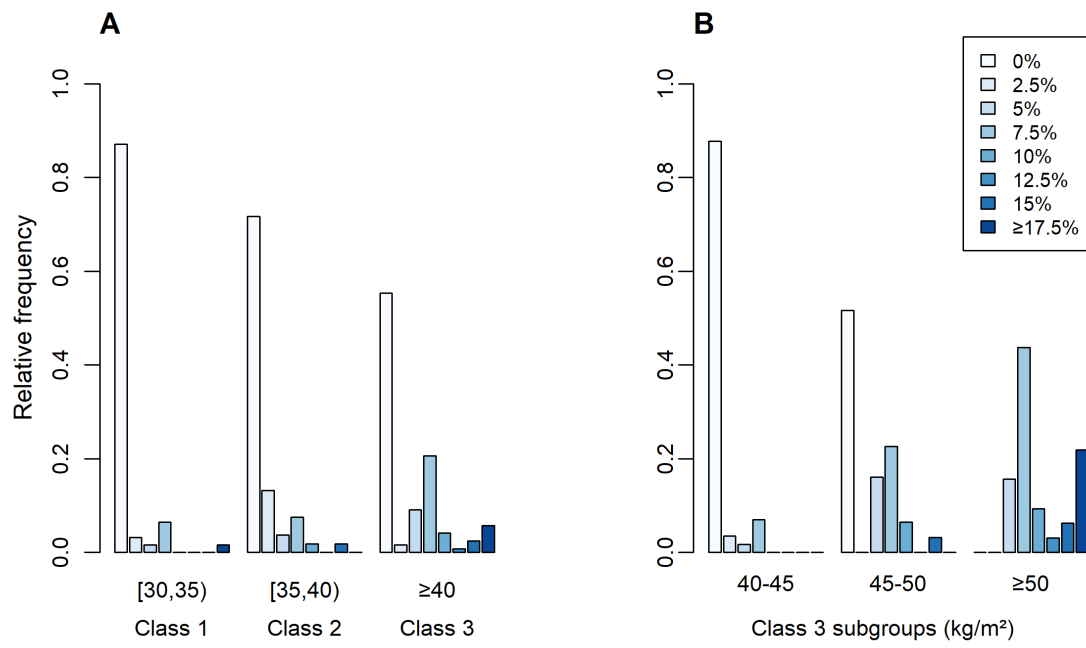
Figure 1: Figure 2. Atelectasis percentage on chest CT by obesity categories.

intervals by a few decimals. Thus, I will keep the results of the original model for class 2 obesity as they are more conservative.

Ordinal Logistic Regression Model

This modelling strategy was performed according to:
- Harrel, Frank. March, 2022. "Assessing the Proportional Odds Assumption and its Impact". Statistical Thinking. March 9, 2022.

Atelectasis percent increase by obesity subgroups
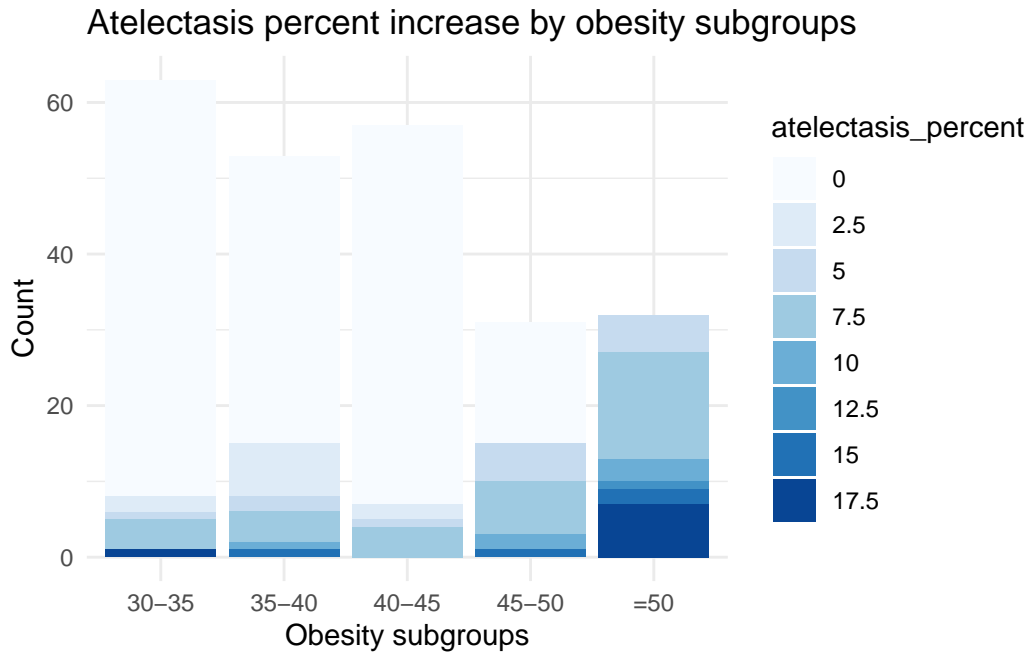
Check proportional odds assumption for main variable of interest:

	Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes
Obs 236	LR χ^2 110.61		R^2 0.416		0.556
Distinct Y 8	d.f. 4		$R^2_{4,236}$ 0.363		
$Y_{0.5}$ 1	$\mathrm{Pr}(>\chi^2)$ <0.0001		$R^2_{4,163.1}$ 0.480		
max $\mid$ log	Score χ^2 130.41		$\mid\mathrm{Pr}(Y$		
$L/\partial\mid$ 3×10^{-7}			median)-½$\mid$ 0.303		
	$\mathrm{Pr}(>\chi^2)$ <0.0001				

		S.E.	Wald Z	Pr($>|Z|$)
y 2.5	-1.9013	0.3782	-5.03	<0.0001
y 5	-2.2844	0.3922	-5.82	<0.0001
y 7.5	-2.8457	0.4148	-6.86	<0.0001
y 10	-4.6674	0.5112	-9.13	<0.0001
y 12.5	-5.1894	0.5434	-9.55	<0.0001
y 15	-5.2932	0.5508	-9.61	<0.0001
y 17.5	-5.7973	0.5934	-9.77	<0.0001
type_obesity=35-40	0.9189	0.4822	1.91	0.0567
type_obesity=40-45	-0.0551	0.5524	-0.10	0.9205
type_obesity=45-50	2.0158	0.5164	3.90	<0.0001
type_obesity= 50	4.4561	0.5591	7.97	<0.0001

Odds ratio for type obesity in an univariable model:

Effects
    Response:
`atelectasis_percent`

	Low	High	Δ	Effect	S.E.	Lower 0.95	Upper 0.95
type_obesity --- 35---40:30---35	1	2		0.91890	0.4822	-0.02626	1.864
Odds Ratio	1	2		2.50600		0.97410	6.449
type_obesity --- 40---45:30---35	1	3		-0.05514	0.5524	-1.13800	1.028
Odds Ratio	1	3		0.94640		0.32050	2.794
type_obesity --- 45---50:30---35	1	4		2.01600	0.5164	1.00400	3.028
Odds Ratio	1	4		7.50700		2.72900	20.650
type_obesity --- 50:30---35	1	5		4.45600	0.5591	3.36000	5.552
Odds Ratio	1	5		86.15000		28.80000	257.800

Proportional odds assumption:

Wald Statistics for `atelectasis_percent`			
	^{2}	d.f.	P
type_obesity	85.40	4	<0.0001
TOTAL	85.40	4	<0.0001

This shows that the proportional odds assumption is not met since p<0.05 in the ANOVA test.

Will repeat the process described in Part 5:

```
  0    5   10   15
170   47    7   12
```

Are subgroups better represented now?

```
   30-35 35-40 40-45 45-50 50
0     57    45    52    16  0
5      5     6     5    12 19
10     0     1     0     2  4
15     1     1     0     1  9
```

Some improvement.

Will now test the impact of not meeting the proportional odds assumption in a model adjusted for covariates:

```
impact_PO <- impactPO(
  atelectasis_percent ~ type_obesity + sleep_apnea + age + sex,
  nonpo = ~ type_obesity,
  data = data,
  newdata = data_prop,
  relax = "multinomial"
  )
```

I was not able to compare against the partial proportional odds (PPO). This can be corroborated by changing `relax = "multinomial"` to `relax = "both"` or `relax = "ppo"` in the above code. This was likely due to a problem in convergence of models with such small subgroups. Previously, I tried comparing models for posthoc analyses in the `VGAM` package and had problems in convergence. Thus, I am presenting the results for the comparison against a multinomial model only:

	PO	Multinomial
Deviance	322.9848	303.0841
d.f.	10	24
AIC	342.9848	351.0841
p	7	21
LR chi^2	140.4303	160.3310
LR - p	133.4303	139.3310
LR chi^2 test for PO		19.90066

		14
d.f.		14
Pr(>chi^2)		0.1333047
MCS R2	0.4484616	0.4930630
MCS R2 adj	0.4318574	0.4458864
McFadden R2	0.3030336	0.3459770
McFadden R2 adj	0.2728231	0.2553456
Mean |difference| from PO		0.03241786

A multinomial model seems to be a better model. Nonetheless, note that such small subgroups would lead to not having estimates for several subgroups:

```
                    type_obesity
atelectasis_percent 30-35 35-40 40-45 45-50 50
                0      55    38    50    16   0
              2.5       2     7     2     0   0
                5       1     2     1     5   5
              7.5       4     4     4     7  14
               10       0     1     0     2   3
             12.5       0     0     0     0   1
               15       0     1     0     1   2
             17.5       1     0     0     0   7
```

As I mentioned, I previously tried fitting a PPO model with `VGAM` and I couldn't obtain estimates for several subgroups. Despite being potentially better, since this study is not powered to fit a multinomial model with such numerous comparisons, I will proceed to fit ordinal models as the intention of these posthoc analyses is to gain greater insight into the main findings.

Univariate models for covariates:

	Model Likelihood Ratio Test	Discrimination Indexes	Rank Discrim. Indexes
Obs 236	LR χ^2 26.05	R^2 0.116	0.377
Distinct Y 8	d.f. 1	$R^2_{1,236}$ 0.101	
$Y_{0.5}$ 1	Pr(>χ^2) <0.0001	$R^2_{1,163.1}$ 0.142	
max | $\partial \log$	Score χ^2 32.43	|Pr($Y \geq$	
$L/\partial\beta$ | 8×10^{-7}		median)-½| 0.224	
	Pr(>χ^2) <0.0001		

		S.E.	Wald Z	Pr$(>|Z|)$
y 2.5	-0.9434	0.1518	-6.21	<0.0001
y 5	-1.1940	0.1611	-7.41	<0.0001
y 7.5	-1.5483	0.1768	-8.76	<0.0001
y 10	-2.8408	0.2697	-10.53	<0.0001
y 12.5	-3.2688	0.3145	-10.39	<0.0001
y 15	-3.3563	0.3250	-10.33	<0.0001
y 17.5	-3.7933	0.3856	-9.84	<0.0001
sleep_apnea=Yes	2.1919	0.4287	5.11	<0.0001

Effects

    Response:

`atelectasis_percent`

	Low	High	Δ	Effect	S.E.	Lower 0.95	Upper 0.95
sleep_apnea --- Yes:No	1	2		2.192	0.4287	1.352	3.032
Odds Ratio	1	2		8.952		3.864	20.740

	Model Likelihood Ratio Test	Discrimination Indexes	Rank Discrim. Indexes
Obs 236	LR χ^2 2.08	R^2 0.010	0.096
Distinct Y 8	d.f. 1	$R^2_{1,236}$ 0.005	
$Y_{0.5}$ 1	Pr$(>\chi^2)$ 0.1490	$R^2_{1,163.1}$ 0.007	
max $|$ log	Score χ^2 2.24	$|$Pr$(Y$	
$L/\partial\beta|$ 2×10^{-7}		median)-½$|$ 0.173	
	Pr$(>\chi^2)$ 0.1347		

		S.E.	Wald Z	Pr$(>|Z|)$
y 2.5	-0.1503	0.4093	-0.37	0.7134
y 5	-0.3731	0.4100	-0.91	0.3628
y 7.5	-0.6938	0.4119	-1.68	0.0921
y 10	-1.8759	0.4418	-4.25	<0.0001
y 12.5	-2.2836	0.4676	-4.88	<0.0001
y 15	-2.3679	0.4745	-4.99	<0.0001
y 17.5	-2.7909	0.5164	-5.40	<0.0001
sex=Woman	-0.6380	0.4315	-1.48	0.1392

Effects

Response:

`atelectasis_percent`

	Low	High	Δ	Effect	S.E.	Lower 0.95	Upper 0.95
sex --- Woman:Man	1	2		-0.6380	0.4315	-1.4840	0.2076
Odds Ratio	1	2		0.5284		0.2268	1.2310

	Model Likelihood Ratio Test	Discrimination Indexes	Rank Discrim. Indexes
Obs 236	LR χ^2 0.63	R^2 0.003	0.049
Distinct Y 8	d.f. 1	$R^2_{1,236}$ 0.000	
$Y_{0.5}$ 1	Pr($> \chi^2$) 0.4273	$R^2_{1,163.1}$ 0.000	
max $\mid$ log	Score χ^2 0.63	$\mid$Pr(Y	
$L/$ $\mid$ 0.003		median)-½$\mid$ 0.173	
	Pr($> \chi^2$) 0.4274		

		S.E.	Wald Z	Pr($>\mid Z\mid$)
y 2.5	-0.2840	0.5705	-0.50	0.6186
y 5	-0.5054	0.5715	-0.88	0.3765
y 7.5	-0.8240	0.5733	-1.44	0.1506
y 10	-1.9975	0.5986	-3.34	0.0008
y 12.5	-2.4040	0.6188	-3.89	0.0001
y 15	-2.4885	0.6239	-3.99	<0.0001
y 17.5	-2.9121	0.6559	-4.44	<0.0001
age	-0.0110	0.0138	-0.79	0.4278

Effects

Response:

`atelectasis_percent`

	Low	High	Δ	Effect	S.E.	Lower 0.95	Upper 0.95
age	32.75	48.25	15.5	-0.1702	0.2146	-0.5908	0.2504
Odds Ratio	32.75	48.25	15.5	0.8435		0.5539	1.2850

Multivariable model

	Model Likelihood Ratio Test	Discrimination Indexes	Rank Discrim. Indexes
Obs 236	LR χ^2 144.21	R^2 0.508	0.640
Distinct Y 8	d.f. 7	$R^2_{7,236}$ 0.441	
$Y_{0.5}$ 1	Pr($>\chi^2$) <0.0001	$R^2_{7,163.1}$ 0.569	
max $\mid$ log	Score χ^2 166.82	$\mid$Pr(Y	
$L/\partial\beta\mid$ 8×10⁻⁶		median)-½$\mid$ 0.331	
	Pr($>\chi^2$) <0.0001		

		S.E.	Wald Z	Pr($>\mid Z\mid$)
y≥2.5	-2.3218	0.9571	-2.43	0.0153
y≥5	-2.7784	0.9675	-2.87	0.0041
y≥7.5	-3.4214	0.9797	-3.49	0.0005
y≥10	-5.4693	1.0363	-5.28	<0.0001
y≥12.5	-6.0661	1.0641	-5.70	<0.0001
y≥15	-6.1879	1.0710	-5.78	<0.0001
y≥17.5	-6.7727	1.1036	-6.14	<0.0001
type_obesity=35-40	0.8155	0.4967	1.64	0.1006
type_obesity=40-45	-0.4684	0.5972	-0.78	0.4328
type_obesity=45-50	1.7911	0.5299	3.38	0.0007
type_obesity= 50	4.6513	0.5807	8.01	<0.0001
sleep_apnea=Yes	2.7551	0.5180	5.32	<0.0001
sex=Woman	-0.0889	0.5398	-0.16	0.8691
age	0.0091	0.0162	0.56	0.5747

Effects
  Response:
`atelectasis_percent`

	Low	High	Δ	Effect	S.E.	Lower 0.95	Upper 0.95
age	32.75	48.25	15.5	0.14050	0.2504	-0.3502	0.6313
Odds Ratio	32.75	48.25	15.5	1.15100		0.7045	1.8800
type_obesity --- 35---40:30---35	1.00	2.00		0.81550	0.4967	-0.1580	1.7890
Odds Ratio	1.00	2.00		2.26000		0.8538	5.9840
type_obesity --- 40---45:30---35	1.00	3.00		-0.46840	0.5972	-1.6390	0.7020
Odds Ratio	1.00	3.00		0.62600		0.1942	2.0180
type_obesity --- 45---50:30---35	1.00	4.00		1.79100	0.5299	0.7525	2.8300
Odds Ratio	1.00	4.00		5.99600		2.1220	16.9400
type_obesity --- 50:30---35	1.00	5.00		4.65100	0.5807	3.5130	5.7890
Odds Ratio	1.00	5.00		104.70000		33.5500	326.8000

Effects
    Response:
`atelectasis_percent`

	Low	High	Δ	Effect	S.E.	Lower 0.95	Upper 0.95
sleep_apnea --- Yes:No	1.00	2.00		2.75500	0.5180	1.7400	3.7700
Odds Ratio	1.00	2.00		15.72000		5.6960	43.4000
sex --- Woman:Man	1.00	2.00		-0.08894	0.5398	-1.1470	0.9690
Odds Ratio	1.00	2.00		0.91490		0.3176	2.6350