Underweight and Obesity are Associated with an Increased Risk of Death after Lung Transplantation

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Online Data Supplement

Supplemental Methods

Statistical Analysis

We used both Cox proportional hazards models and generalized additive models (GAMs) to examine the association between BMI and survival. GAMs incorporate smoothing functions to allow non-linear associations between each continuous dependent variable and the independent variable (E1). Our GAMs were logistic regression models (binary regression with a logit link) with the outcomes of death at 1 year (early mortality) and death at 5 years conditional on 1 year survival (late mortality). These models incorporated local regression (loess) smoothing functions for all continuous variables, including BMI as shown in Figure 3.
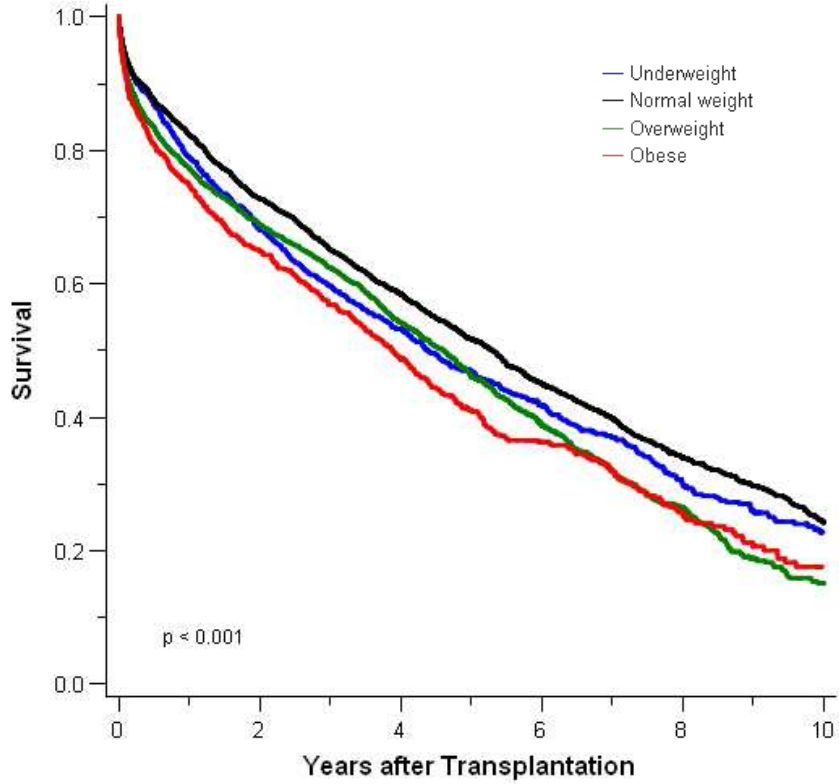
Multiple imputation

Missing data and the approach to handling missing data can lead to biased effect estimates and incorrectly estimated standard errors. In our study, we used multiple imputation to handle missing covariate data, an approach that accounts for the uncertainty of the "right" value to impute for missing data (E2, E3). This method has been shown to minimize bias compared to alternative methods (E4). We used a Markov Chain Monte Carlo method to impute five plausible values for each missing value in all of our survival models (E5), as previously implemented in analyses of UNOS/OPTN data (E6, E7).

Supplemental References

E1. Hastie TJ, Tibshirani RJ. Generalized Additive Models. London: Chapman & Hall; 1990.

E2. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med 1991;10:585-598.

E3. Rubin DB. Inference and missing data. Biometrika 1976;63:581-592.

E4. van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol 2006;59:1102-1109.

E5. Schafer JL. Analysis of Incomplete Multivariate Data. New York: Chapman and Hall; 1997.

E6. Lederer DJ, Benn EK, Barr RG, Wilt JS, Reilly G, Sonett JR, Arcasoy SM, Kawut SM. Racial differences in waiting list outcomes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;177:450-454.

E7. Thabut G, Ravaud P, Christie JD, Castier Y, Fournier M, Mal H, Leseche G, Porcher R. Determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2008;177:1156-1163.

Figure E1: Unadjusted Survival after lung transplantation

Underweight	862	583	445	272	136	49
Normal weight	2864	2056	1586	906	451	181
Overweight	1644	1117	840	412	173	50
Obese	608	393	280	151	66	23

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Figure E2: Continuous relationships of body mass index and the risks of death at 1 year (A) and at 5 years conditional on 1 year survival (B) after lung transplantation for <u>cystic fibrosis</u>. Both curves are adjusted for the covariates listed in the footnote to Table 2 (Model 4)
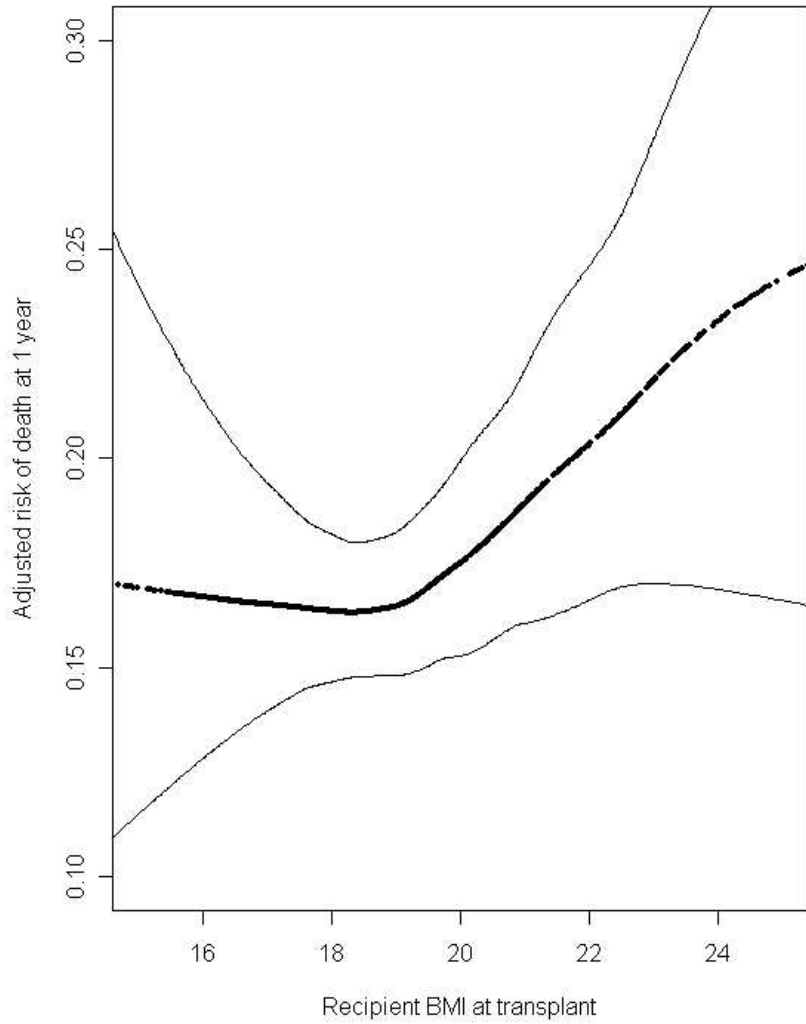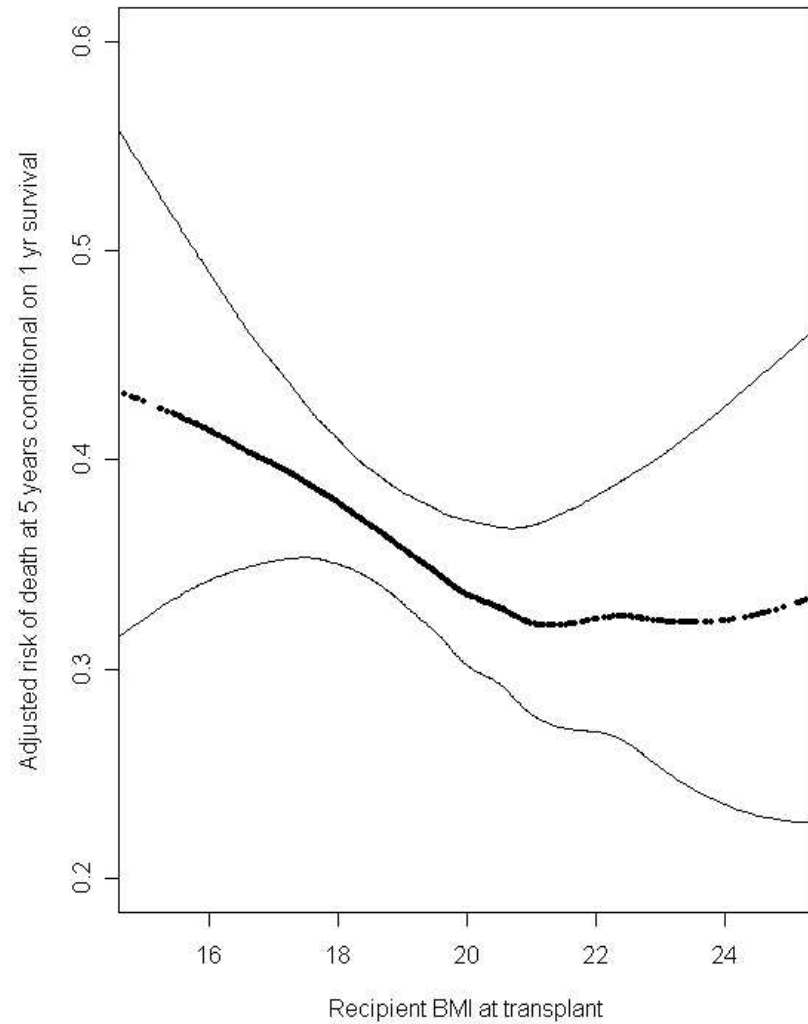

A

B

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Figure E3: Continuous relationships of body mass index and the risks of death at 1 year (A) and at 5 years conditional on 1 year survival (B) after lung transplantation for <u>chronic obstructive pulmonary disease</u>. Both curves are adjusted for the covariates listed in the footnote to Table 2 (Model 4)

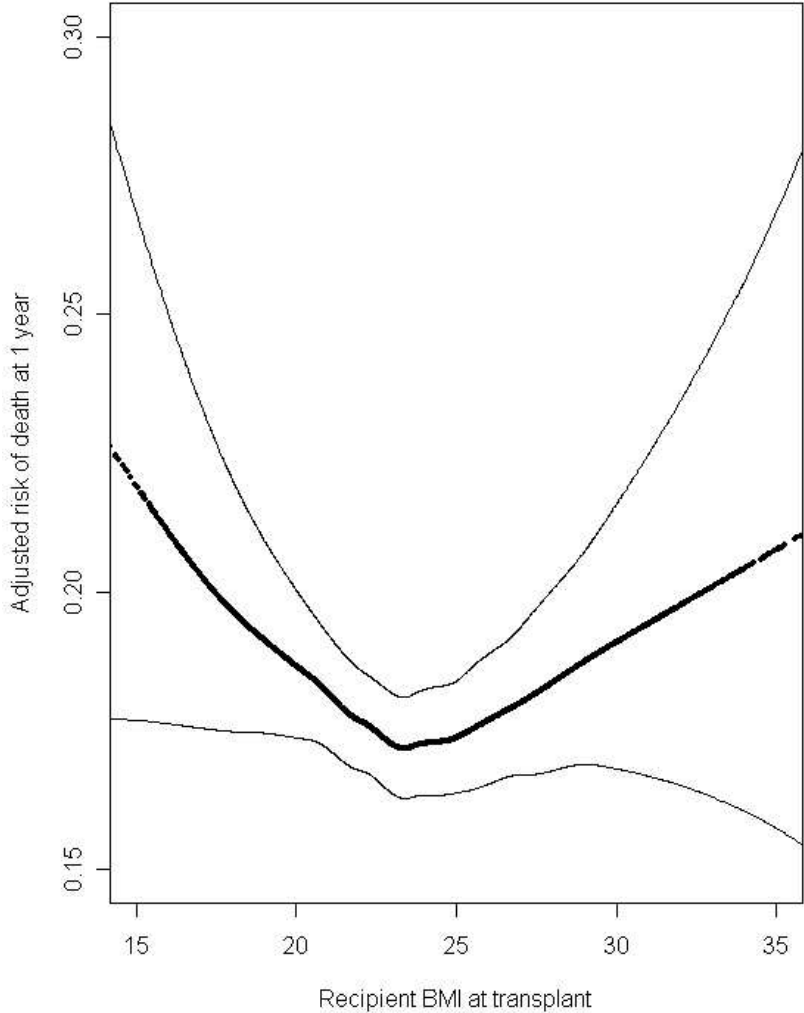
A   B

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Figure E4: Continuous relationships of body mass index and the risks of death at 1 year (A) and at 5 years conditional on 1 year survival (B) after lung transplantation for <u>diffuse parenchymal lung disease</u>. Both curves are adjusted for the covariates listed in the footnote to Table 2 (Model 4)
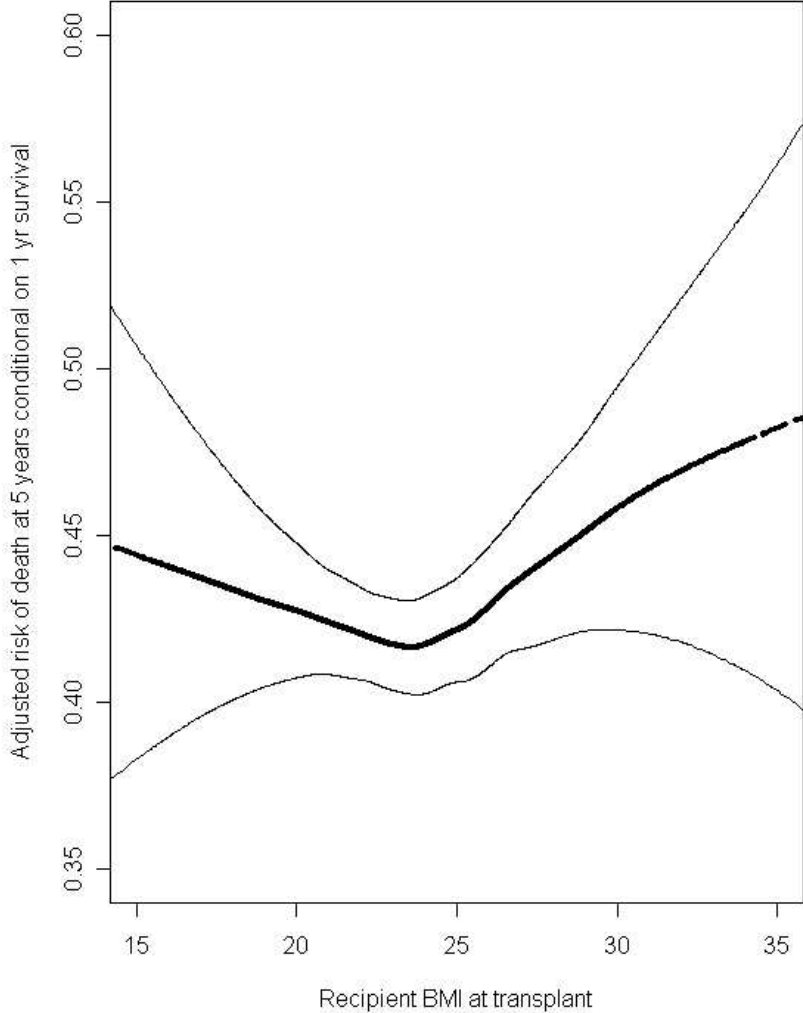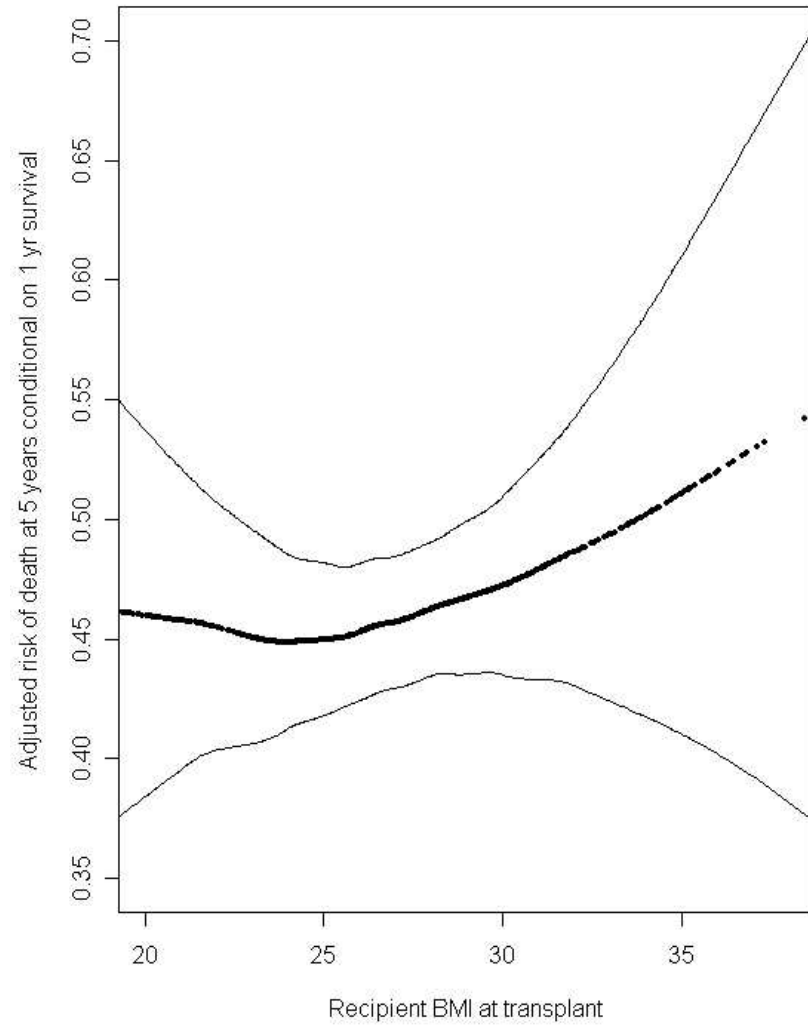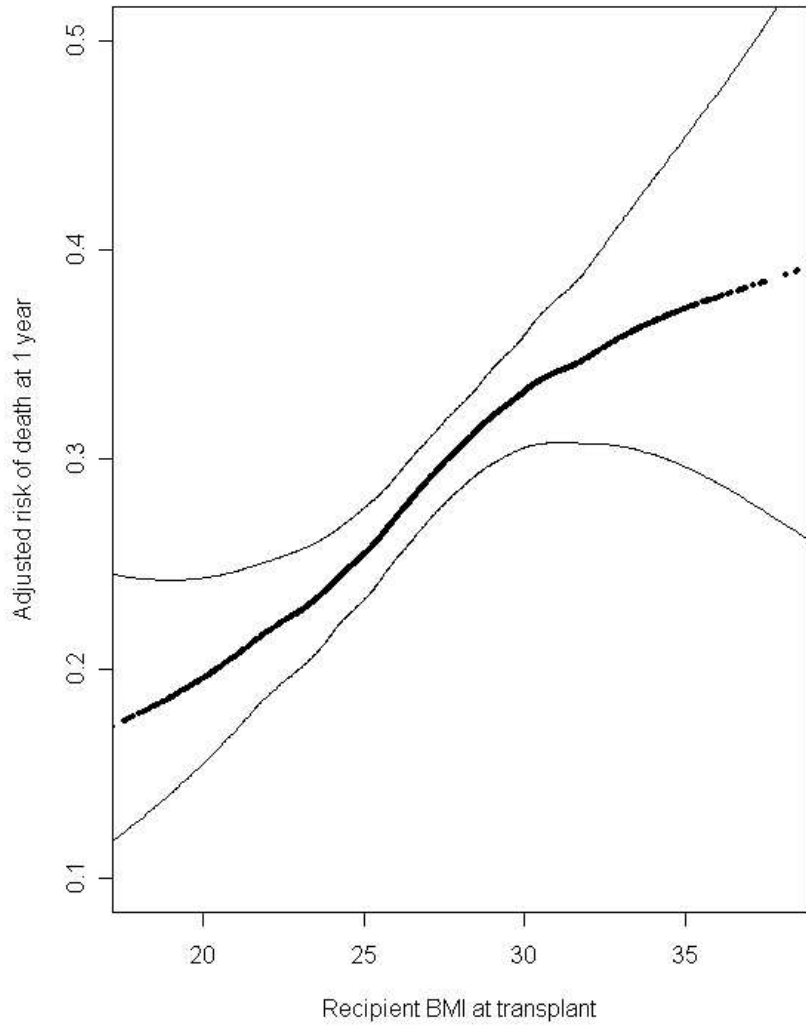

A   B

Table E1: Unadjusted cause-specific mortality rate ratios after lung transplantation

Cause of Death	Normal Weight	Underweight			Overweight			Obese		
	No.	No.	RR (95% CI)	p value	No.	RR (95% CI)	p value	No.	RR (95% CI)	p value
Alive	1038	274			507			178		
Primary graft failure	79	15	0.66 (0.37 – 1.12)	0.13	62	1.54 (1.10 – 2.15)	0.01	17	1.21 (0.69 – 1.99)	0.49
Respiratory failure	367	123	1.16 (0.95 – 1.42)	0.15	196	1.05 (0.88 – 1.25)	0.57	102	1.55 (1.24 – 1.93)	<0.001
Chronic allograft dysfunction	216	84	1.35 (1.04 – 1.73)	0.02	131	1.19 (0.96 – 1.48)	0.12	44	1.15 (0.81 – 1.56)	0.43
Infection	427	161	1.31 (1.09 – 1.57)	0.003	255	1.17 (1.00 – 1.37)	0.045	109	1.43 (1.15 – 1.74)	0.001
Cardiac	85	11	0.45 (0.23 – 0.82)	0.007	62	1.43 (1.03 – 1.99)	0.03	24	1.58 (0.98 – 2.45)	0.06
Cerebrovascular	47	14	1.04 (0.55 – 1.84)	0.89	29	1.21 (0.76 – 1.92)	0.42	8	0.97 (0.42 – 1.94)	0.93
Cancer	130	33	0.88 (0.59 – 1.28)	0.52	101	1.53 (1.17 – 1.98)	0.002	40	1.72 (1.19 – 2.43)	0.004
Other	475	147	1.07 (0.89 – 1.29)	0.45	301	1.24 (1.07 – 1.44)	0.003	86	1.01 (0.80 – 1.27)	0.92
Cystic fibrosis										
Alive	252	153								
Primary graft failure	10	6	0.85 (0.28 – 2.33)	0.76						
Respiratory failure	52	61	1.65 (1.14 – 2.40)	0.008						
Chronic allograft dysfunction	36	43	1.68 (1.08 – 2.63)	0.02						
Infection	67	72	1.51 (1.08 – 2.11)	0.02						
Cardiac	5	4	1.13 (0.27 – 4.44)	0.86						
Cerebrovascular	10	6	0.85 (0.28 – 2.33)	0.76						
Cancer	14	6	0.61 (0.21 – 1.54)	0.31						
Other	73	59	1.14 (0.80 – 1.60)	0.46						

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Table E1 – continued

COPD

Alive	650	111			340			84		
Primary graft failure	61	9	0.76 (0.35 – 1.46)	0.44	36	1.14 (0.75 – 1.72)	0.53	11	1.30 (0.65 – 2.37)	0.44
Respiratory failure	276	55	1.02 (0.75 – 1.35)	0.91	117	0.82 (0.66 – 1.02)	0.07	52	1.35 (0.99 – 1.79)	0.06
Chronic allograft dysfunction	153	35	1.17 (0.80 – 1.67)	0.41	102	1.29 (1.00 – 1.66)	0.048	28	1.31 (0.86 – 1.83)	0.20
Infection	304	80	1.34 (1.04 – 1.71)	0.02	158	1.01 (0.83 – 1.22)	0.95	56	1.31 (0.98 – 1.73)	0.07
Cardiac	69	7	0.53 (0.22 – 1.07)	0.08	43	1.21 (0.82 – 1.76)	0.34	9	0.94 (0.44 – 1.79)	0.87
Cerebrovascular	28	7	1.30 (0.52 – 2.82)	0.55	19	1.32 (0.72 – 2.35)	0.36	3	0.80 (0.18 – 2.26)	0.71
Cancer	94	24	1.31 (0.82 – 2.01)	0.26	55	1.13 (0.81 – 1.58)	0.46	19	1.45 (0.86 – 2.32)	0.16
Other	341	83	1.24 (0.97 – 1.57)	0.08	208	1.18 (0.99 – 1.40)	0.06	39	0.82 (0.58 – 1.12)	0.22

DPLD

Alive	136				157			93		
Primary graft failure	8				26	2.58 (1.21 – 6.15)	0.01	6	1.07 (0.34 – 3.13)	0.90
Respiratory failure	39				75	1.54 (1.05 – 2.30)	0.03	49	1.78 (1.17 – 2.72)	0.007
Chronic allograft dysfunction	27				25	0.93 (0.74 – 1.17)	0.53	93	0.97 (0.74 – 1.26)	0.81
Infection	56				89	1.28 (0.92 – 1.79)	0.15	53	1.34 (0.92 – 1.95)	0.13
Cardiac	27				25	0.75 (0.42 – 1.29)	0.29	16	0.84 (0.44 – 1.55)	0.59
Cerebrovascular	9				9	0.80 (0.31 – 2.09)	0.65	5	0.80 (0.24 – 2.35)	0.69
Cancer	22				45	1.64 (0.99 – 2.78)	0.053	21	1.35 (0.74 – 2.47)	0.33
Other	61				87	1.15 (0.83 – 1.60)	0.41	47	1.09 (0.74 – 1.60)	0.65

RR = unadjusted rate ratio for death after lung transplantation, CI = confidence interval

Normal weight group is the referent group for all effect estimates.

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Table E2: Sensitivity Analyses: Multivariate adjusted hazard ratios for death after lung transplantation

| | No. | Body mass index category | | | | p value |
		Underweight	Normal weight	Overweight	Obese	
All diagnoses	7143	1.12*	1.0	1.15†	1.20†	<0.001
PTSS instead of LAS	5978	1.15†	1.0	1.14†	1.18†	<0.001
Including pediatric donors	6037	1.13*	1.0	1.16†	1.22†	<0.001
All heights and weights	6238	1.15†	1.0	1.15†	1.20†	<0.001
Adjustment for recipient:donor gender interaction	5978	1.15*	1.0	1.16†	1.22†	<0.001

Effect estimates are hazards ratios from stratified Cox models adjusted for age, gender, height, donor characteristics (age, gender, height, body mass index, and smoking history > 20 packyears), lung allocation score, cardiovascular risk factors (hypertension, smoking status, diabetes), hospitalized at transplant, CMV mismatch, donor cause of death, HLA mismatch, use of steroids prior to transplant, and ischemic time. Cox models are stratified by diagnosis, transplant procedure and transplant year. P values are from likelihood ratio tests comparing a model containing variables for BMI categories to the model without BMI categories.

* Wald test $p < 0.05$

† Wald test $p < 0.01$