

Impact of Recipients' Obesity on the Outcome of Kidney Transplantation

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Financial Disclosure Statement

- None

Q1: The pre-transplant obesity/higher weight is associated with worse post-transplant mortality.

- A) True
- B) False

How strong the data is?

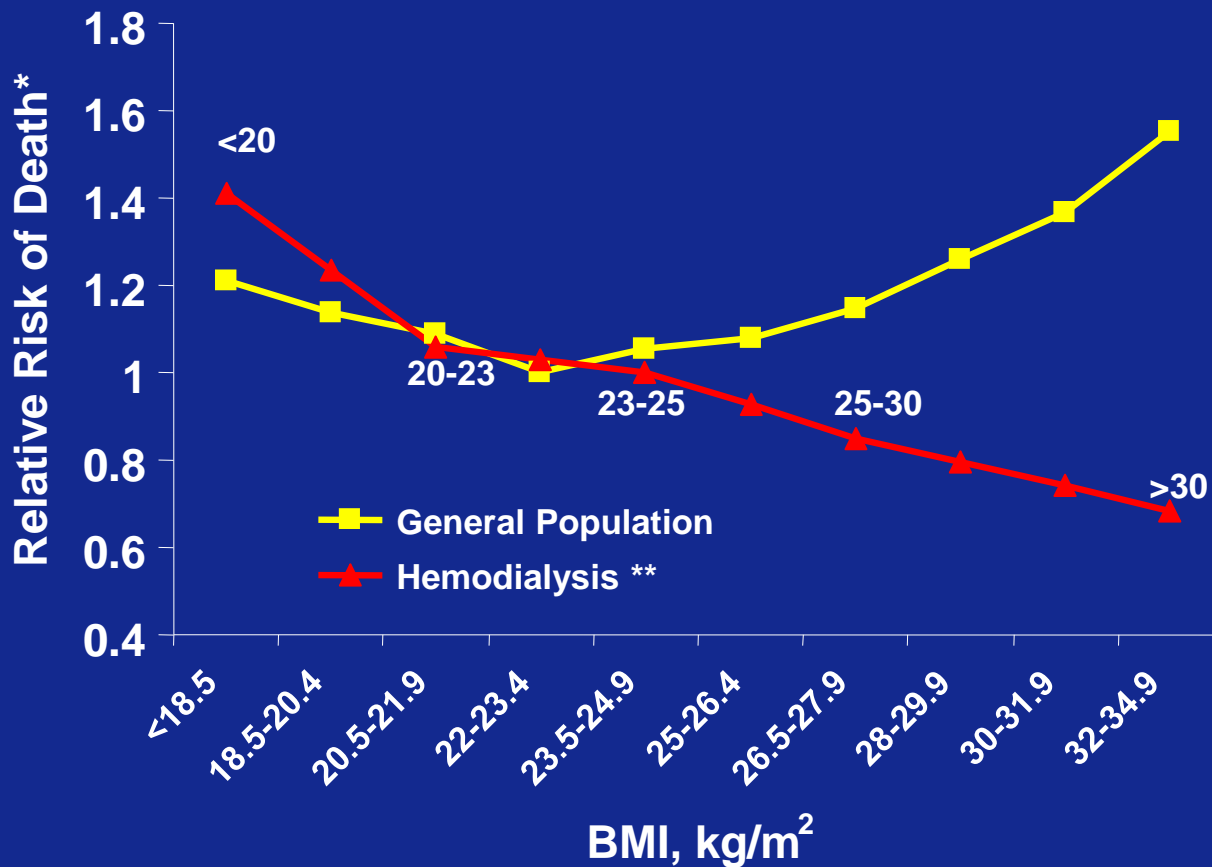
Q2: Waitlisted hemodialysis patient with BMI=32 kg/m² should lose weight while he/she is on hemodialysis to get transplanted.

- A) True
- B) False

How strong the data is?

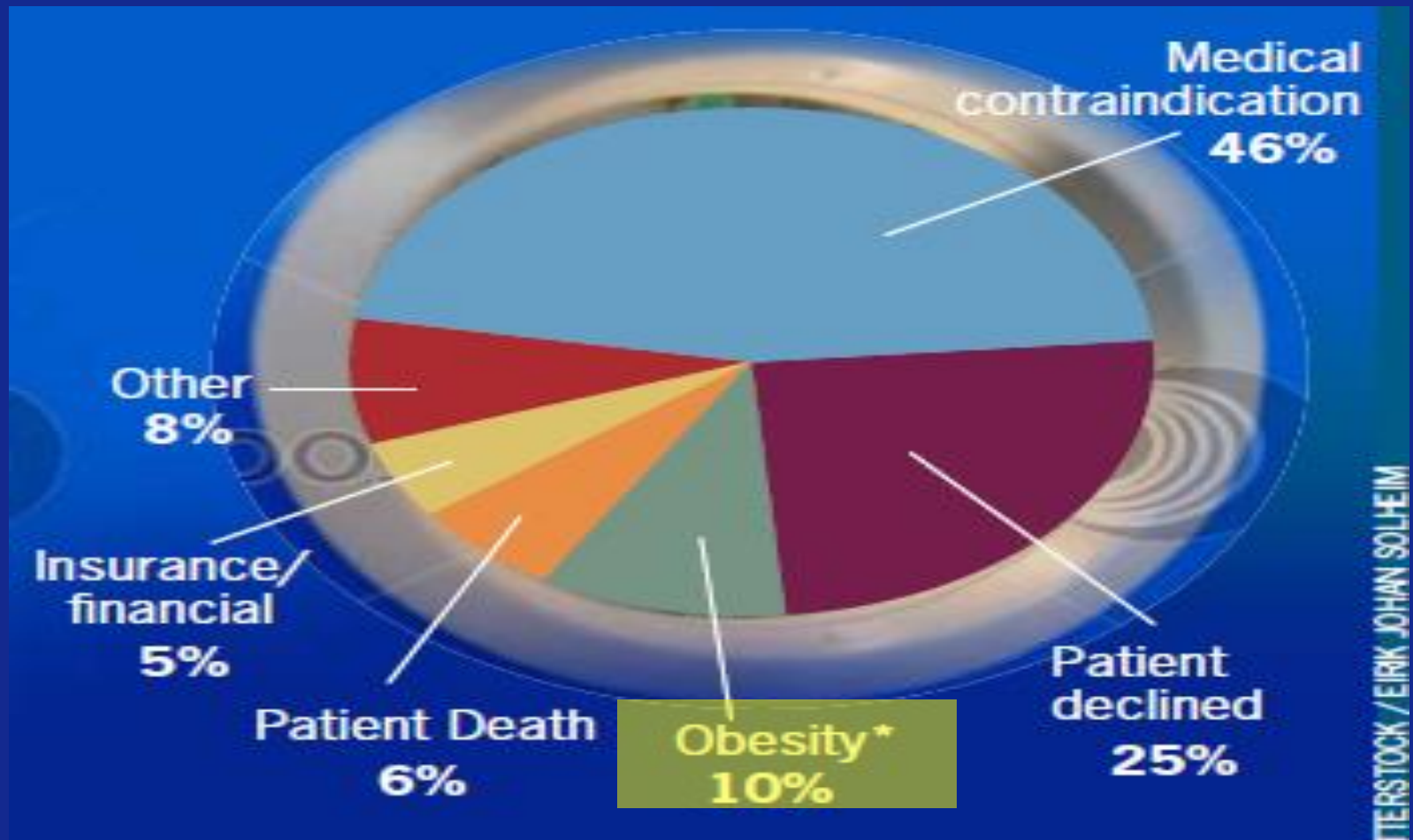
Obesity Paradox or Reverse Epidemiology in Dialysis Patients

BMI Associated Death Risk:
General Population versus Hemodialysis Patients



Kalantar-Zadeh et al. *Kidney Int.* 2003;63:793-808.

Obesity (BMI>35 kg/m²): A major cause of kidney transplant denial in dialysis patients

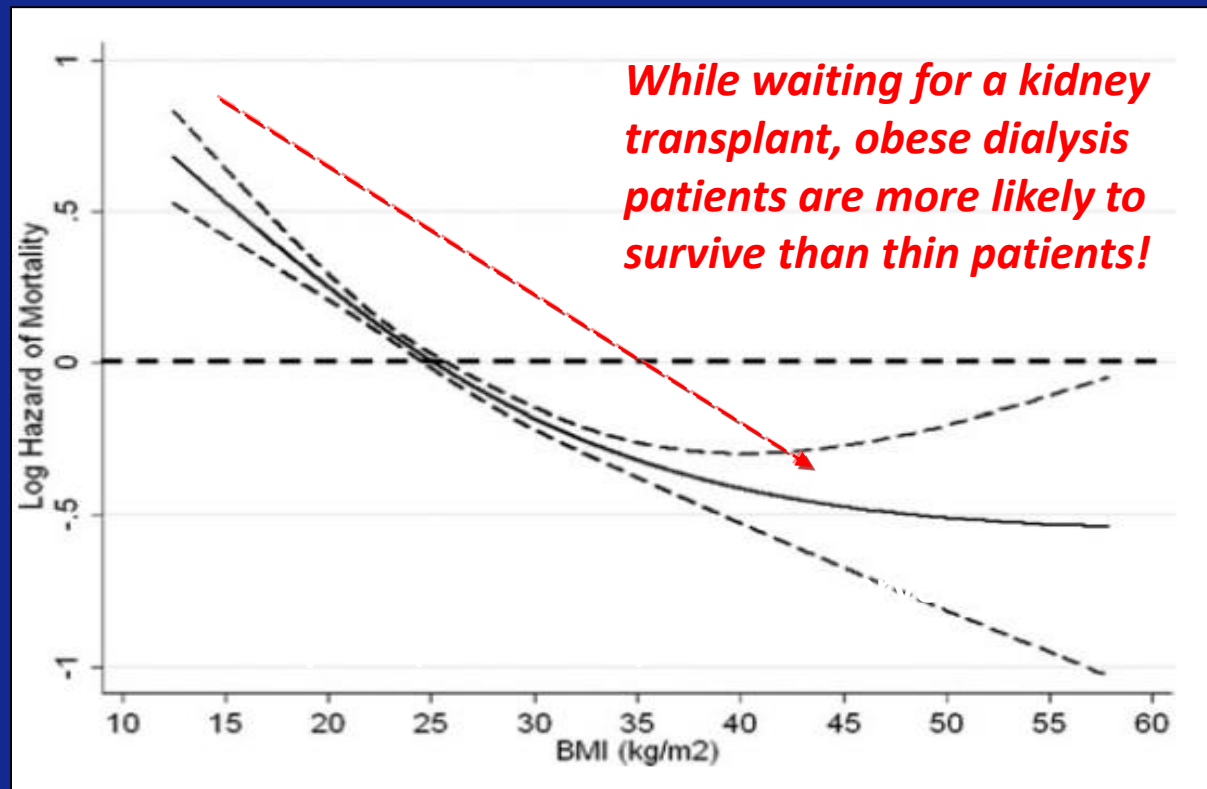


Holley ... Bronsther. An examination of the renal transplant evaluation process focusing on cost and the reasons for patient exclusion. *Am J Kidney Dis.* 1998; 32:567-574

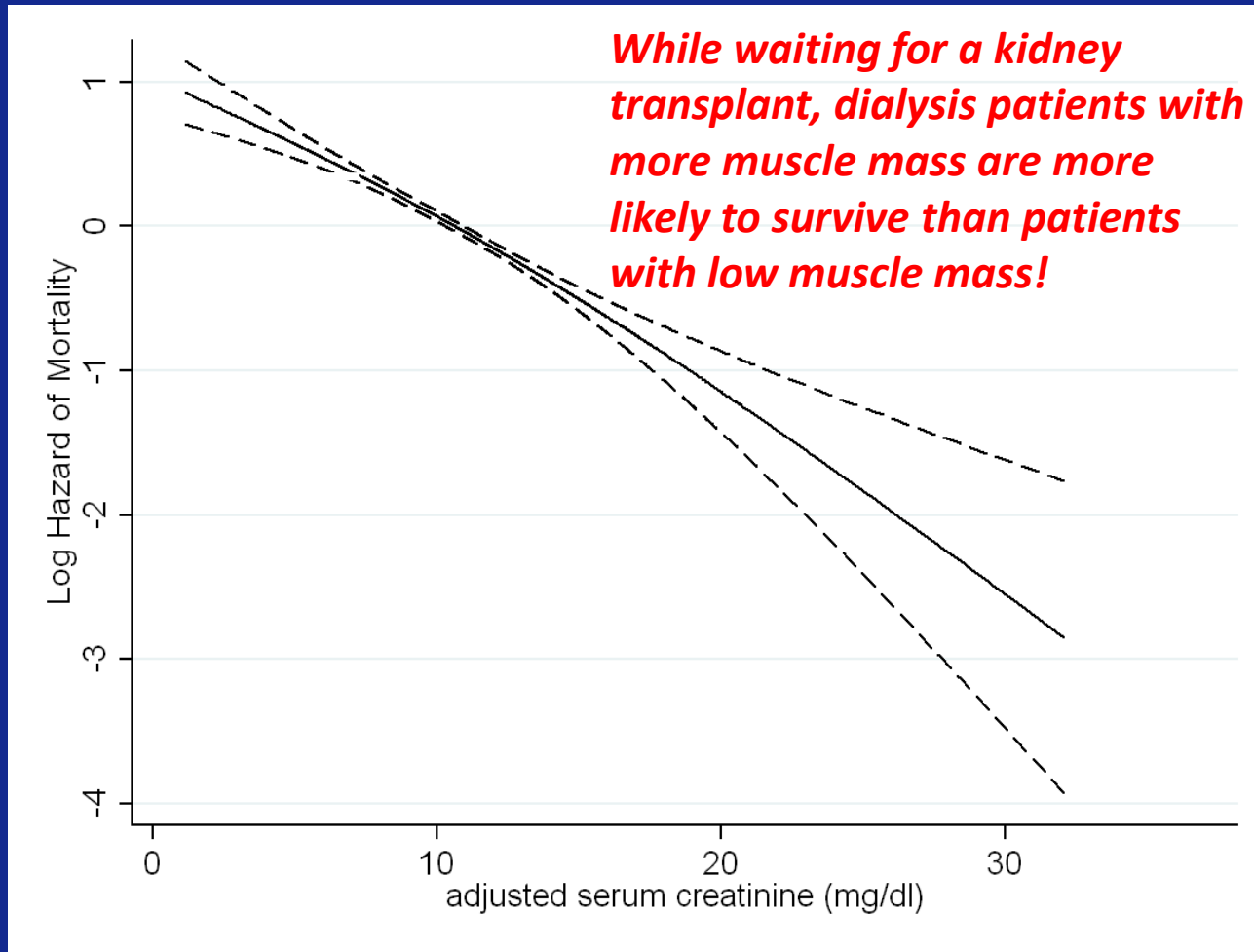
Am J Transplant 2011

Associations of Body Mass Index and Weight Loss with Mortality in Transplant-Waitlisted Maintenance Hemodialysis Patients

M. Z. Molnar^{a,b}, E. Streja^{a,c}, C. P. Kovesdy^{d,e},
S. Bunnapradist^f, M. S. Sampaio^f, J. Jing^a,
M. Krishnan^g, A. R. Nissenson^g,
G. M. Danovitch^{g,h} and K. Kalantar-Zadeh^{a,b,f,*}



Serum Creatinine (Surrogate of MUSCLE) in Dialysis Patients: → Outcomes



Molnar ... Kalantar-Zadeh, *Am J Transplant.* 2011

M. Z. Molnar^{a,b}, E. Streja^{a,c}, C. P. Kovesdy^{d,e},
S. Bunnapradist^f, M. S. Sampaio^f, J. Jing^a,
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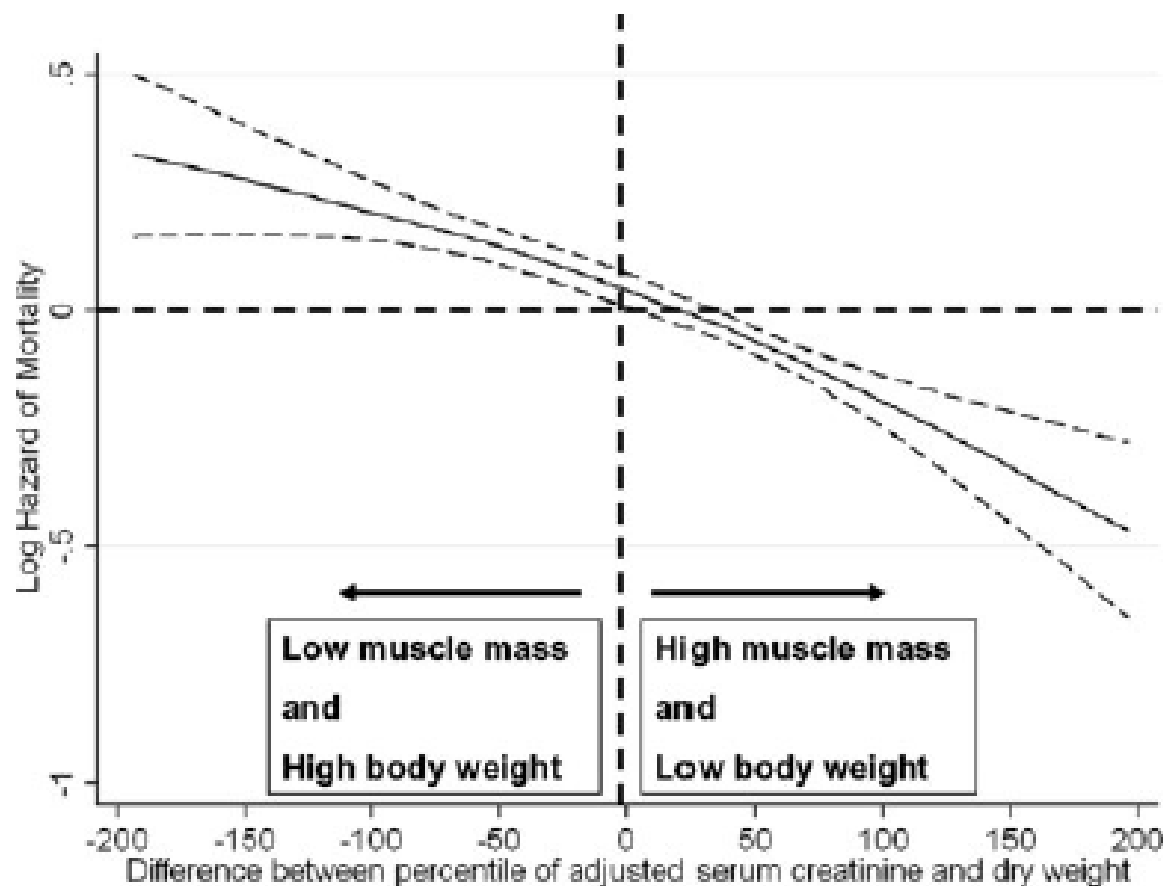
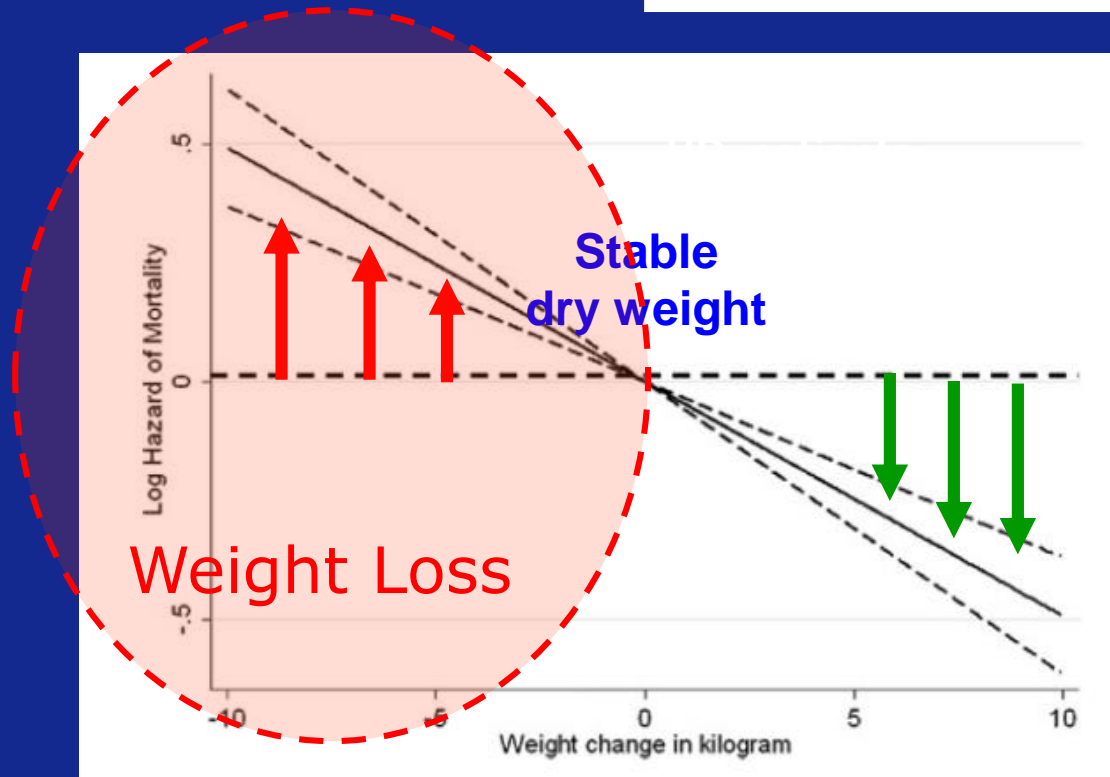


Figure 7: Cubic splines models of Cox proportional regression to examine the mortality predictability of the combinations of the dry weight and in adjusted serum creatinine levels over a 6-year observation period (7/2001–6/2007). The Y-axis shows the logarithm of the risk ratio of all-cause mortality over 6 years based on a multivariable Cox regression spline model, adjusted for case-mix. Dashed lines are 95% point wise confidence levels. Each patient received a percentile score between –100 and +100 according to the percentile rank of the change in dry weight or adjusted serum creatinine. The *difference* between adjusted serum creatinine concentration and dry weight in each patient also resulted in a number between –200 and +200.

Associations of Body Mass Index and Weight Loss with Mortality in Transplant-Waitlisted Maintenance Hemodialysis Patients

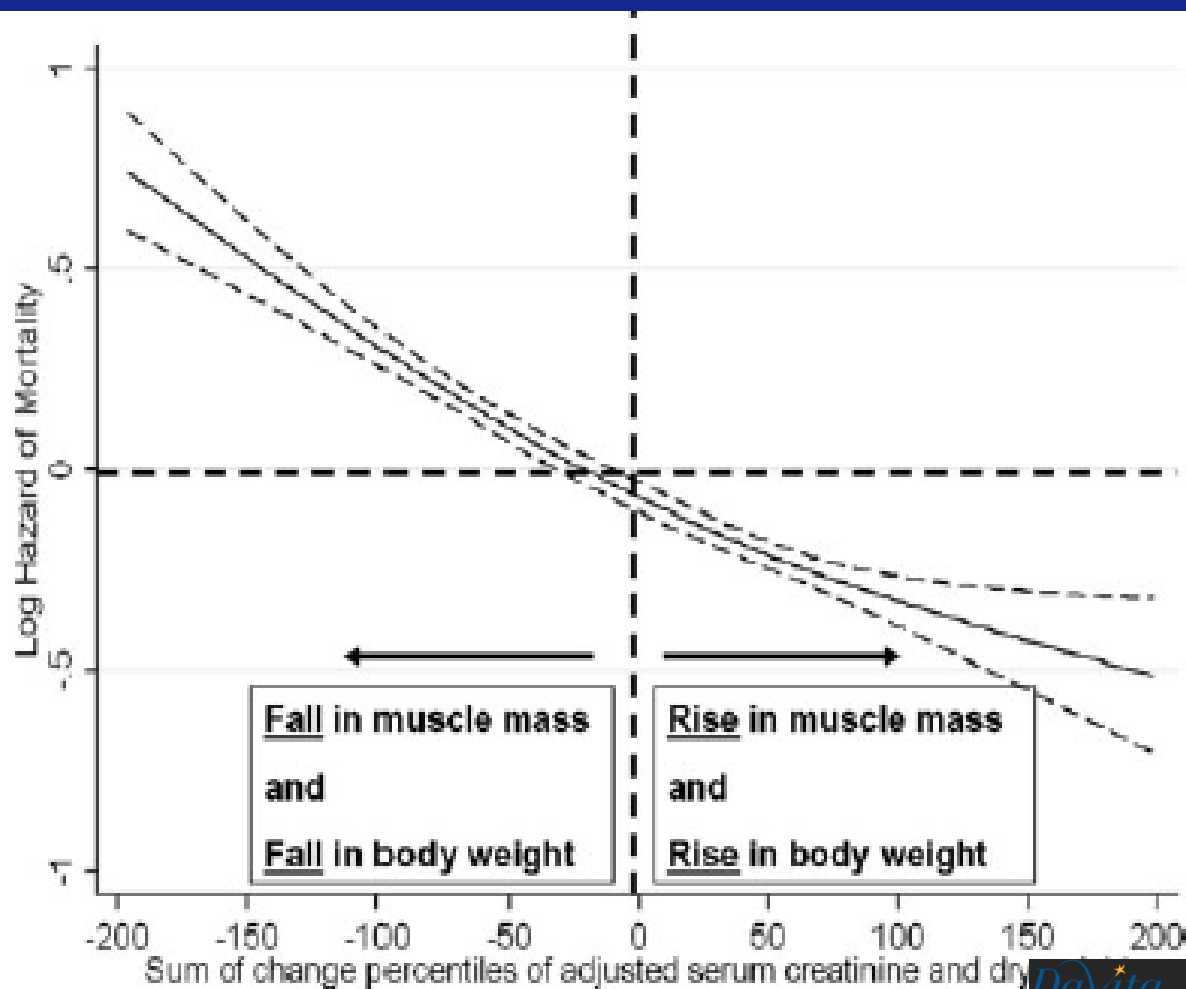
M. Z. Molnar^{a,b}, E. Streja^{a,c}, C. P. Kovesdy^{d,e},
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M. Z. Molnar^{a,b}, E. Streja^{a,c}, C. P. Kovesdy^{d,e},
S. Bunnapradist^f, M. S. Sampaio^f, J. Jing^a,
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G. M. Danovitch^{g,h} and K. Kalantar-Zadeh^{a,b,f,*}

Associations of Body Mass Index and Weight Loss with Mortality in Transplant-Waitlisted Maintenance Hemodialysis Patients

Figure 8: Cubic splines models of Cox proportional regression to examine the mortality predictability of the combinations of the changes in dry weight and in adjusted serum creatinine levels over a 6-year observation period (7/2001–6/2007). The Y-axis shows the logarithm of the risk ratio of all-cause mortality over 6 years based on a multivariable Cox regression spline model, adjusted for case-mix. Dashed lines are 95% point wise confidence levels. Each patient received a percentile score between -100 and +100 according to the percentile rank of the change in dry weight or adjusted serum creatinine. The sum of the two percentile scores for each patient resulted in a number between -200 and +200.



The Survival Benefit of Kidney Transplantation in Obese Patients

J. S. Gill^{1,2,3}, J. Lan¹, J. Dong¹, C. Rose¹,
E. Hendren¹, O. Johnston¹ and J. Gill^{1,2,*}

American Journal of Transplantation 2013; 13: 2083–2090

- Comparing 208,498 waitlisted dialysis patients with 118,662 kidney transplant recipients from the same period (1995-2007)
- Source of data: USRDS
- Stratified by BMI and race

Table 3: Risk of death in transplant recipients compared to wait-listed patients with the same body mass index 1 year after transplantation

	SCD recipients	ECD recipients	LD recipient
BMI < 18.5	0.33 (0.26, 0.41)	0.30 (0.21, 0.42)	0.35 (0.24, 0.52)
BMI 18.5–24.9	0.34 (0.30, 0.39)	0.37 (0.32, 0.42)	0.20 (0.15, 0.26)
BMI 25.0–29.9	0.32 (0.28, 0.37)	0.43 (0.38, 0.50)	0.30 (0.22, 0.47)
BMI 30.0–34.9	0.32 (0.26, 0.39)	0.42 (0.35, 0.51)	0.23 (0.17, 0.32)
BMI 35.0–39.0	0.34 (0.26, 0.46)	0.39 (0.24, 0.52)	0.28 (0.14, 0.50)
BMI ≥ 40.0	0.52 (0.37, 0.72)	0.54 (0.33, 0.78)	0.34 (0.19, 0.59)

Separate multivariate nonproportional hazards analyses with transplantation treated as a time-dependent covariate to account for the fact that patients switched treatment from dialysis to transplantation at different times. Models adjusted for differences in patients characteristics including age, gender, cause of ESRD, history of comorbid conditions (ischemic heart disease, cerebrovascular disease, congestive heart failure, peripheral vascular disease, cancer), year of wait-listing and propensity score for transplantation.

The Survival Benefit of Kidney Transplantation in Obese Patients

J. S. Gill^{1,2,3}, J. Lan¹, J. Dong¹, C. Rose¹, *American Journal of Transplantation* 2013; 13: 2083–2090

Table 4: Risk of death in Black and White transplant recipients compared to wait-listed patients with the same body mass index 1 year after transplantation

	SCD recipients	ECD recipients	LD recipient
BMI < 18.5			
Black	0.40 (0.30, 0.60)	0.23 (0.11, 0.46)	0.43 (0.18, 1.00)
White	0.29 (0.21, 0.39)	0.29 (0.21, 0.42)	0.26 (0.21, 0.54)
BMI 18.5–24.9			
Black	0.35 (0.27, 0.59)	0.42 (0.31, 0.57)	0.26 (0.15, 0.35)
White	0.29 (0.25, 0.35)	0.35 (0.29, 0.41)	0.22 (0.17, 0.25)
BMI 25.0–29.9			
Black	0.30 (0.22, 0.41)	0.47 (0.35, 0.62)	0.28 (0.23, 0.76)
White	0.33 (0.28, 0.39)	0.35 (0.26, 0.40)	0.30 (0.20, 0.42)
BMI 30.0–34.9			
Black	0.34 (0.24, 0.49)	0.53 (0.37, 0.75)	0.30 (0.16, 0.32)
White	0.33 (0.24, 0.41)	0.36 (0.28, 0.41)	0.23 (0.16, 0.33)
BMI 35.0–39.9			
Black ¹	0.41 (0.24, 0.78)	0.77 (0.50, 1.22)	0.40 (0.27, 0.66)
White	0.35 (0.24, 0.49)	0.42 (0.29, 0.62)	0.32 (0.20, 0.52)
BMI ≥ 40.0			
Black ²	0.56 (0.33, 1.08)	0.76 (0.08, 1.12)	0.75 (0.31, 1.80)
White	0.54 (0.33, 0.82)	0.44 (0.25, 0.76)	0.22 (0.07, 0.67)

Separate multivariate nonproportional hazards analyses with transplantation treated as a time-dependent covariate to account for the fact that patients switched treatment from dialysis to transplantation at different times. Models adjusted for differences in patients characteristics including age, gender, cause of ESRD, history of comorbid conditions (ischemic heart disease, cerebrovascular disease, congestive heart failure, peripheral vascular disease, cancer), year of wait-listing.

¹There were n = 5785 Black patients with BMI 35.0–39.9 including n = 671 who received and ECD transplant during follow-up.

²There were n = 3832 Black patients with BMI ≥ 40 including n = 763, n = 335 and n = 350 who received and SCD, ECD and LD transplant during follow-up.

The Survival Benefit of Kidney Transplantation in Obese Patients

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American Journal of Transplantation 2013; 13: 2083–2090

Table 5: Time (days) to equal risk of death and equal survival* in transplant recipients compared to wait-listed patients with the same body mass index

	<18.5 (n = 13 714)	18.5–24.9 (n = 67 260)	25–29.9 (n = 64 655)	30–34.9 (n = 37 453)	35–39.9 (n = 16 070)	≥40 (n = 9 346)
Death rate on waiting list per 100 patient years	5	5	6	6	6	6
Days to equal risk of death						
SCD	68	50	70	80	85	145
ECD	135	95	90	160	150	200
LD	55	Immediate	33	57	60	65
Days to equal survival						
SCD	118	100	137	210	179	245
ECD	216	226	210	331	257	387
LD	116	Immediate	75	121	135	157

*Calculated from separate multivariate nonproportional hazards regression models.

A 'Weight-Listing' Paradox for Candidates of Renal Transplantation?

American Journal of Transplantation 2007; 7: 550-559

J.D. Schold^{a,c,*}, T.R. Srinivas^a, G. Guerra^a,
A.I. Reed^b, R.J. Johnson^a, I.D. Weiner^{a,d},
R. Oberbauer^e, J.S. Harman^c, A.W. Hemming^b
and H.U. Meier-Kriesche^a

USRDS (1990-2003)
18-70 years old
124,713 patients received transplant

Table 5: Adjusted cox proportional hazard for overall graft loss associated with rate of BMI change during waitlisted period

Rate of Change	Waitlisted BMI								
	Underweight or normal weight (<25 kg/m ²)			Overweight (25-30 kg/m ²)			Obese (>30 kg/m ²)		
	n	Hazard ratio	95% CI	n	Hazard ratio	95% CI	n	Hazard ratio	95% CI
> 12%	9153	1.13	1.09-1.18	4128	1.15	1.08-1.21	1945	1.07	0.96-1.16
+8 to 12%	2613	1.06	0.99-1.14	1405	1.06	0.97-1.16	702	1.04	0.92-1.19
+4 to 8%	4479	0.93	0.88-0.98	2515	1.02	0.95-1.10	1321	1.03	0.93-1.13
-4 to +4%	24 377	Ref	-	16 901	Ref	-	10 691	Ref	-
-8 to -4%	2523	1.07	1.00-1.14	2204	1.02	0.95-1.10	1858	1.04	0.95-1.13
-12 to -8%	1339	1.05	0.96-1.15	1222	1.04	0.95-1.15	985	1.01	0.90-1.13
< -12%	4707	1.07	1.02-1.13	3748	1.10	1.04-1.17	3167	1.00	0.93-1.08

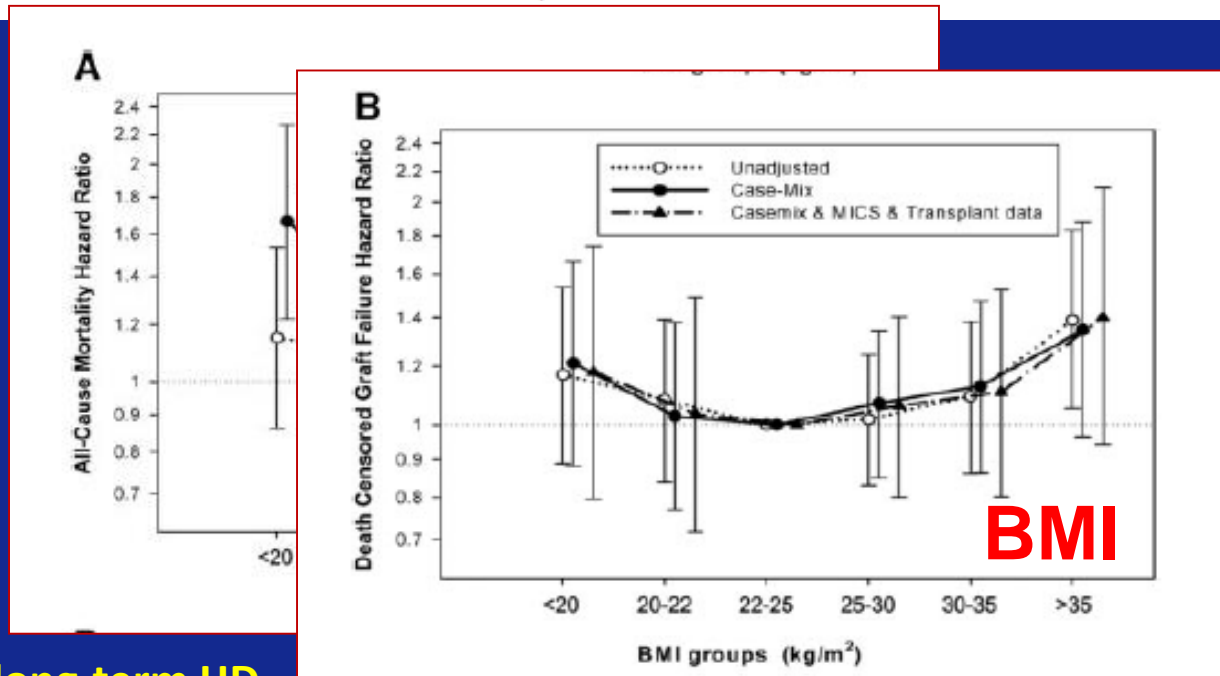
Rate of change calculated as percentage change divided by time to transplant (in years). Models adjusted for recipient primary diagnosis, gender, age, race, time of pretransplant dialysis, donor age, donor race and number of HLA-mismatches. Reference group is patients with -4 to +4% rate of change during listing.

BMI = body mass index.

Associations of Pretransplant Weight and Muscle Mass with Mortality in Renal Transplant Recipients

CJASN 2011

Elani Streja,^{*†} Miklos Z. Molnar,^{*‡} Csaba P. Kovesdy,^{§||} Suphamai Bunnapradist,[¶] Jennie Jing,^{*†} Allen R. Nissenson,^{¶**} Istvan Mucsi,^{††} Gabriel M. Danovitch,[¶] and Kamyar Kalantar-Zadeh^{*†¶}



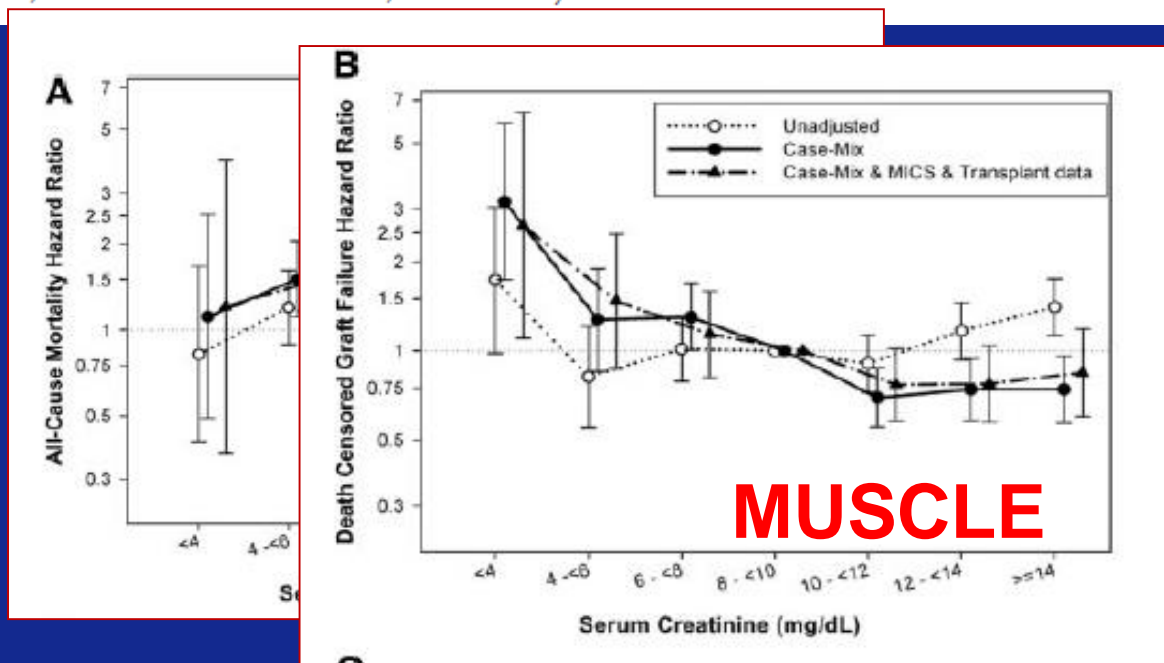
N= 10,090 long-term HD patients who underwent renal transplantation and were observed over a 6-year observation period (July 2001 to June 2007).

Streja, Molnar ... Kalantar-Zadeh, *CJASN*. 2011

Associations of Pretransplant Weight and Muscle Mass with Mortality in Renal Transplant Recipients

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Associations of Pretransplant Weight and Muscle Mass with Mortality in Renal Transplant Recipients

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Istvan Mucsi,^{††} Gabriel M. Danovitch,[¶] and Kamyar Kalantar-Zadeh^{*†¶}

CJASN 2011

Conclusions: *Pre-transplant obesity does not appear to be associated with poor post-transplant outcomes.*

Clin J Am Soc Nephrol 6: 1463–1473, 2011.

1,151 kidney transplant recipients from Toronto

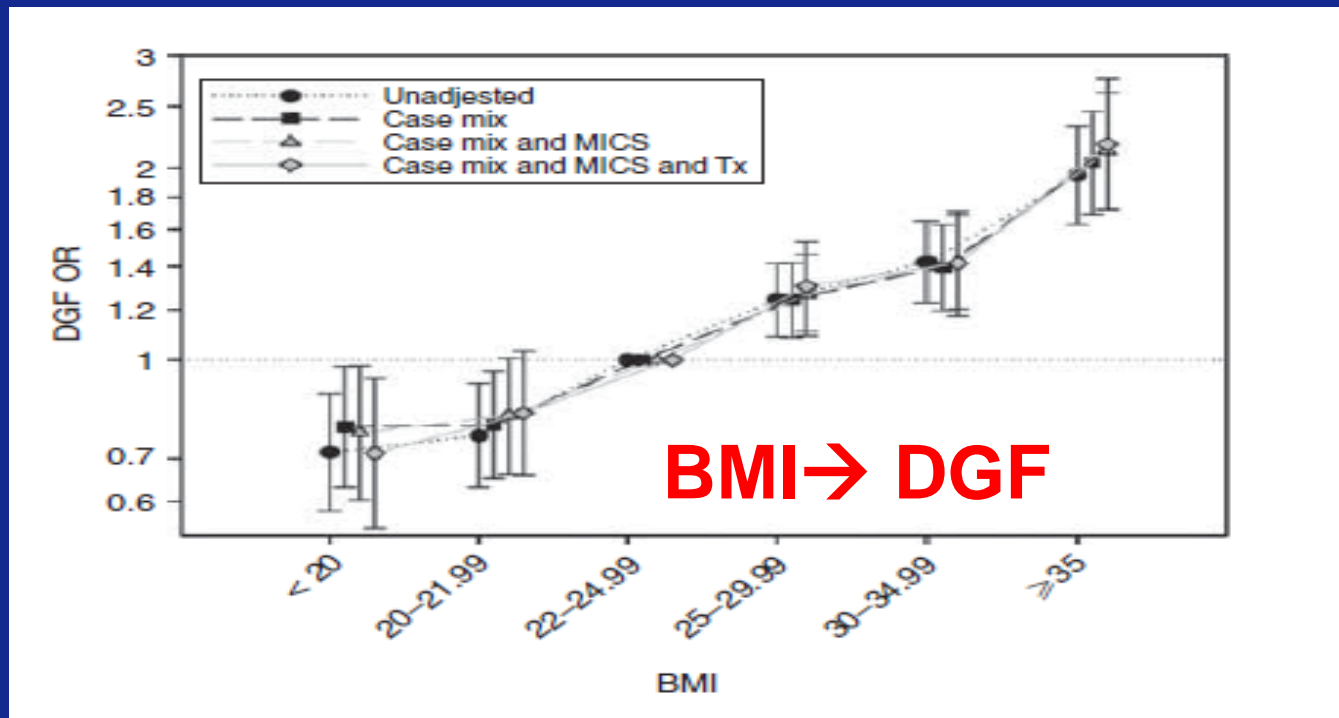
TABLE 4. Hazard Ratios (95% Confidence Intervals) for the Risk of Graft Loss or Death by Body Mass Index Categories

Outcome	BMI < 20 kg/m ²	BMI 20-24.9 kg/m ²	BMI 25-29.9 kg/m ²	BMI 30-34.9 kg/m ²	BMI ≥ 35 kg/m ²
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
No Adjustment for Biopsy-Proven Acute Rejection as a Time-Varying Covariate					
All-Cause Graft Failure	1.09 (0.61, 1.94)	Reference	1.07 (0.73, 1.58)	0.80 (0.47, 1.36)	1.97 (1.09, 3.56)
Death-Censored Graft Failure	0.95 (0.45, 1.98)	Reference	1.10 (0.65, 1.87)	0.90 (0.42, 1.94)	2.43 (1.07, 5.51)
Death with Graft Function	1.11 (0.43, 2.86)	Reference	1.08 (0.62, 1.90)	0.65 (0.31, 1.37)	1.56 (0.64, 3.80)
Adjustment for Biopsy-Proven Acute Rejection as a Time-Varying Covariate					
All-Cause Graft Failure	1.24 (0.69, 2.20)	Reference	1.11 (0.76, 1.64)	0.84 (0.50, 1.43)	1.38 (0.74, 2.54)
Death-Censored Graft Failure	1.41 (0.67, 3.00)	Reference	1.30 (0.76, 2.23)	1.14 (0.53, 2.45)	1.48 (0.62, 3.52)
Death with Graft Function	1.15 (0.44, 2.96)	Reference	1.10 (0.62, 1.92)	0.66 (0.32, 1.40)	1.57 (0.63, 3.89)

All models include BMI categories and recipient, donor, and transplant characteristics shown in Table 1

Higher recipient body mass index is associated with post-transplant delayed kidney graft function

Miklos Z. Molnar^{1,2}, Csaba P. Kovesdy^{3,4}, Istvan Mucsi^{2,5,6}, Suphamai Bunnapradist⁷, Elani Streja¹, Mahesh Krishnan⁸ and Kamyar Kalantar-Zadeh^{1,7,9}



Molnar ... Kalantar-Zadeh, *Kidney Int.* 2011

1,151 kidney transplant recipients from Toronto

TABLE 2. Odds Ratios (95% Confidence Intervals) for the Risk of Delayed Graft Function by Body Mass Index Categories

Logistic Regression Models	BMI < 20 kg/m ² OR (95% CI)	BMI 20-24.9 kg/m ² OR (95% CI)	BMI 25-29.9 kg/m ² OR (95% CI)	BMI 30-34.9 kg/m ² OR (95% CI)	BMI ≥ 35 kg/m ² OR (95% CI)
Model 1	0.83 (0.46, 1.52)	Reference	1.12 (0.78, 1.61)	1.62 (1.07, 2.45)	3.04 (1.79, 5.16)
Model 2	0.76 (0.38, 1.52)	Reference	1.19 (0.81, 1.76)	1.74 (1.10, 2.74)	4.02 (2.24, 7.24)
Model 3	1.07 (0.53, 2.16)	Reference	1.11 (0.73, 1.68)	1.80 (1.10, 2.96)	4.13 (2.11, 8.07)
Model 4	0.93 (0.45, 1.92)	Reference	1.08 (0.71, 1.65)	1.92 (1.16, 3.19)	4.49 (2.24, 9.00)

Increased risk of DGF

Model 1: BMI categories only

Model 2: Model 1 plus recipient characteristics in Table 1

Model 3: Model 2 plus donor characteristics in Table 1

Model 4: Model 3 plus transplant characteristics in Table 1

TABLE 3. Hazard Ratios (95% Confidence Intervals) for the Risk of Acute Rejection by Body Mass Index Categories

Cox Proportional Hazards Models	BMI < 20 kg/m ² HR (95% CI)	BMI 20-24.9 kg/m ² HR (95% CI)	BMI 25-29.9 kg/m ² HR (95% CI)	BMI 30-34.9 kg/m ² HR (95% CI)	BMI ≥ 35 kg/m ² HR (95% CI)
Model 1	1.35 (0.84, 2.19)	Reference	0.87 (0.61, 1.25)	1.10 (0.73, 1.68)	2.19 (1.37, 3.49)
Model 2	1.16 (0.71, 1.91)	Reference	0.95 (0.66, 1.36)	1.19 (0.78, 1.82)	2.25 (1.39, 3.64)
Model 3	1.14 (0.69, 1.87)	Reference	0.99 (0.69, 1.43)	1.25 (0.81, 1.92)	2.26 (1.39, 3.67)
Model 4	1.06 (0.64, 1.75)	Reference	0.96 (0.67, 1.38)	1.28 (0.83, 1.98)	2.43 (1.48, 3.99)

Increased risk of BPAR

Model 1: BMI categories only

Model 2: Model 1 plus recipient characteristics in Table 1

Model 3: Model 2 plus donor characteristics in Table 1

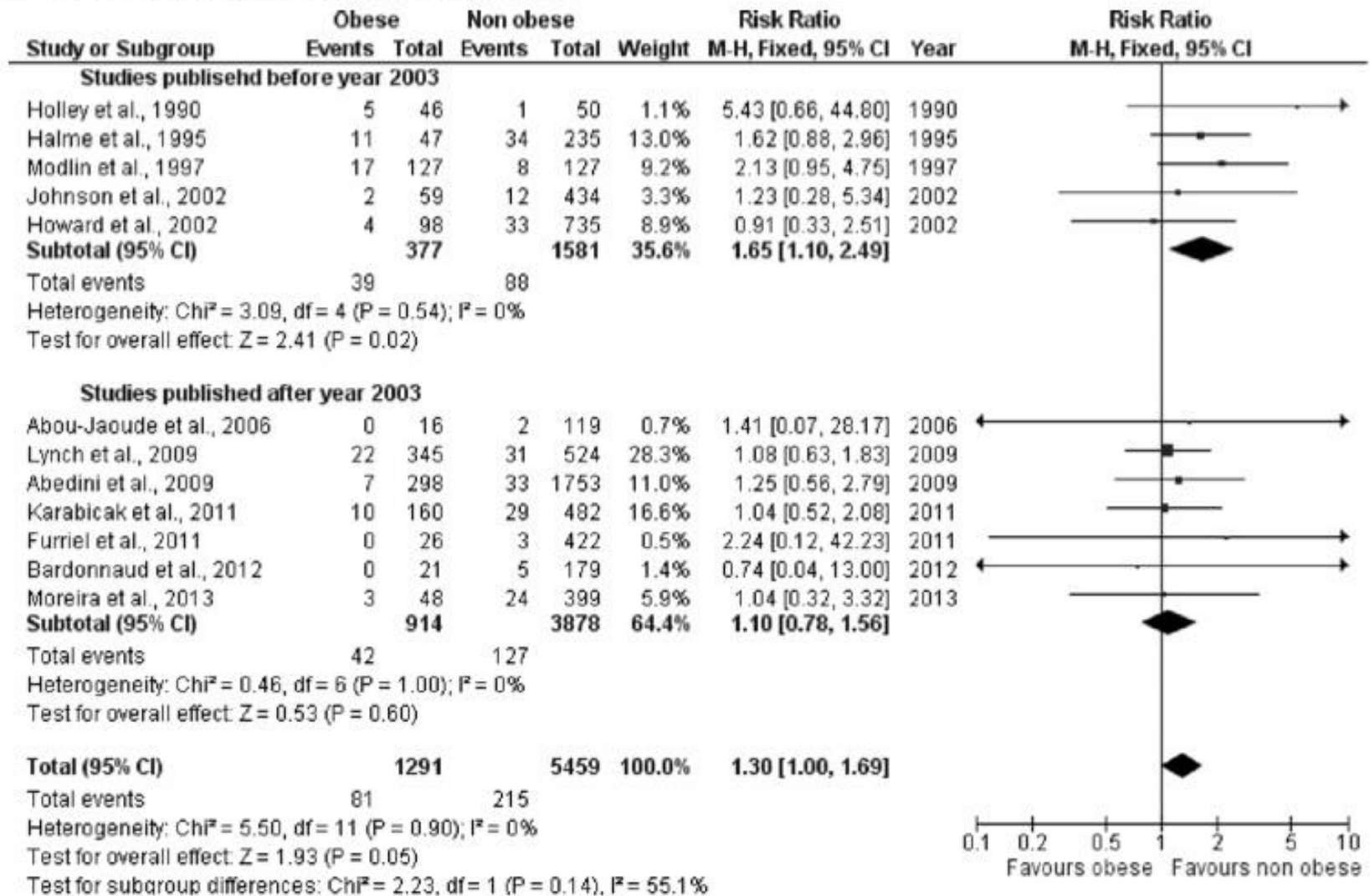
Model 4: Model 3 plus transplant characteristics in Table 1

Recent Systematic Review and Meta-analysis

- MEDLINE, EMBASE, Cochrane Library, and gray literature were searched up to August 6, 2013
- Two independent reviewers extracted the data and assessed the quality of the studies
- Published between 1990-August of 2013
- 1,973 articles were reviewed
- 21 studies (9,296 patients) were included

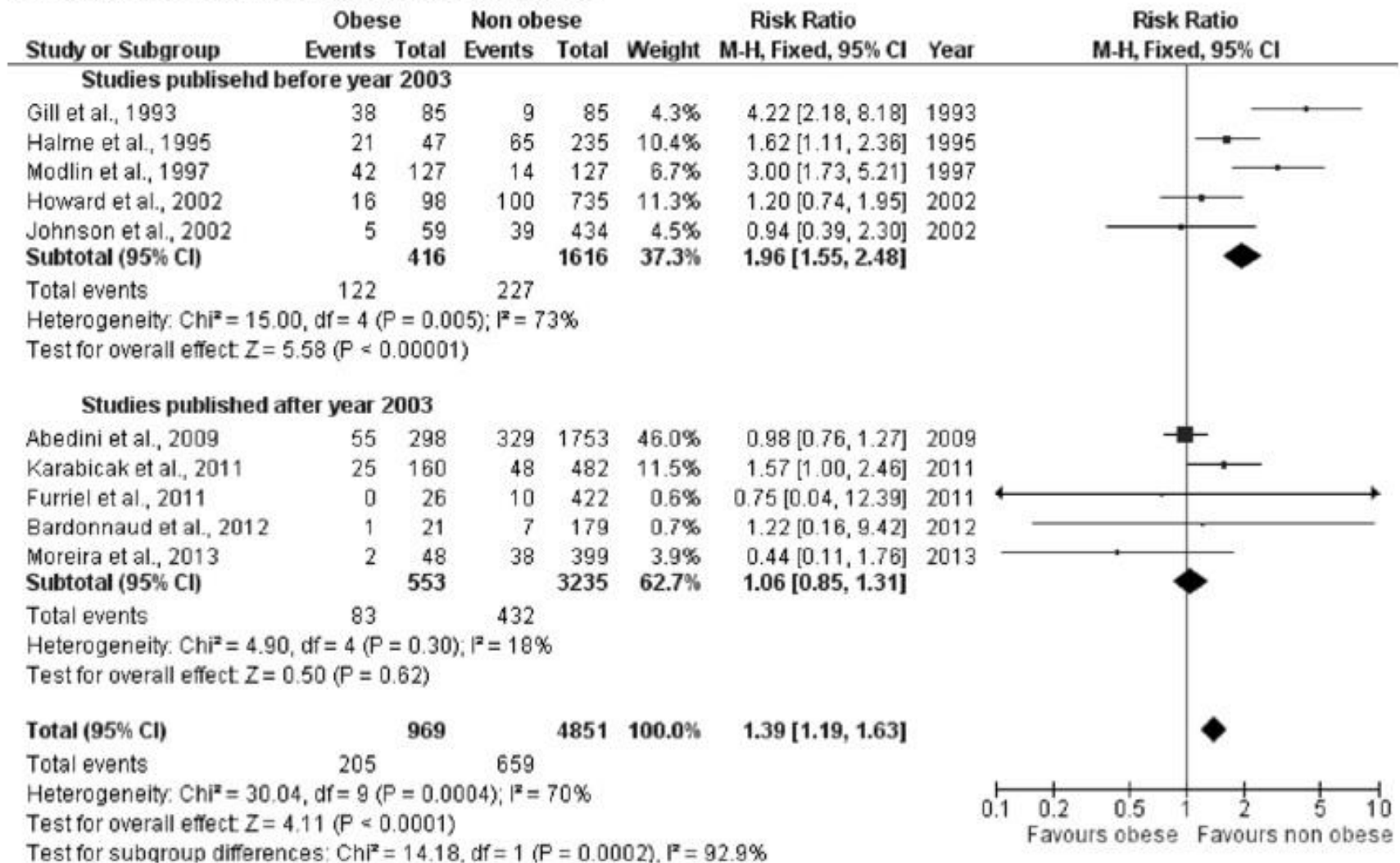
Mortality after 1-year

A Death at one year after transplantation



Mortality after 5-years

B Death at five years after transplantation



Cardiovascular mortality

Death by CVD

Study or Subgroup	Obese		Non obese		Weight	Risk Ratio	Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI	
Gill et al., 1993	2	85	1	85	6.2%	2.00 [0.18, 21.64]	1993
Modlin et al., 1997	18	127	5	127	31.0%	3.60 [1.38, 9.40]	1997
Howard et al., 2002	5	98	32	735	46.8%	1.17 [0.47, 2.94]	2002
Johnson et al., 2002	2	59	8	434	11.9%	1.84 [0.40, 8.45]	2002
Furriel et al., 2011	0	26	5	422	4.1%	1.42 [0.08, 25.09]	2011
Total (95% CI)		395		1803	100.0%	2.07 [1.17, 3.64]	

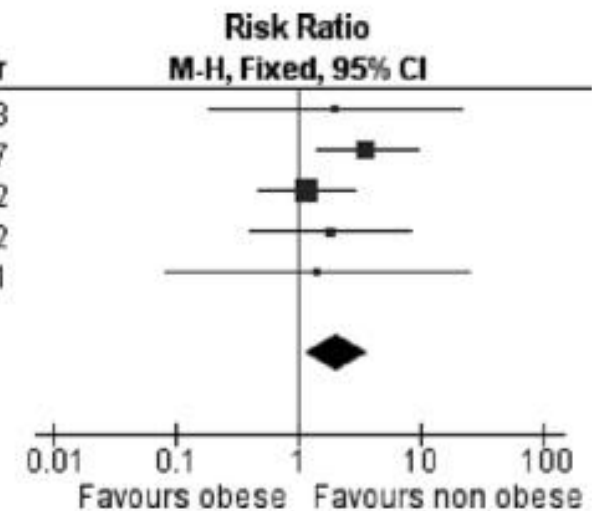
Total events

27

51

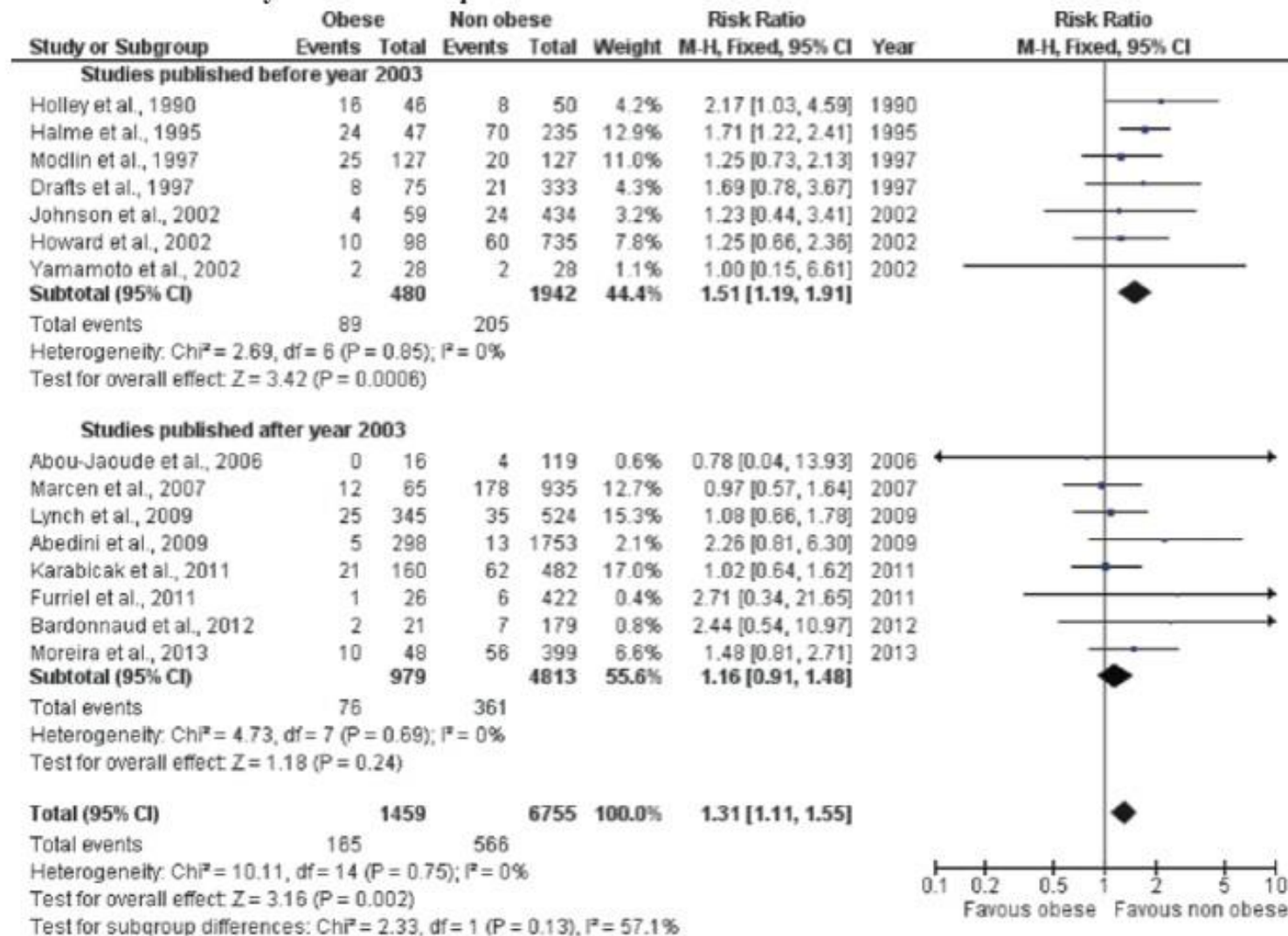
Heterogeneity: $\text{Chi}^2 = 2.84$, $\text{df} = 4$ ($P = 0.59$); $I^2 = 0\%$

Test for overall effect: $Z = 2.52$ ($P = 0.01$)



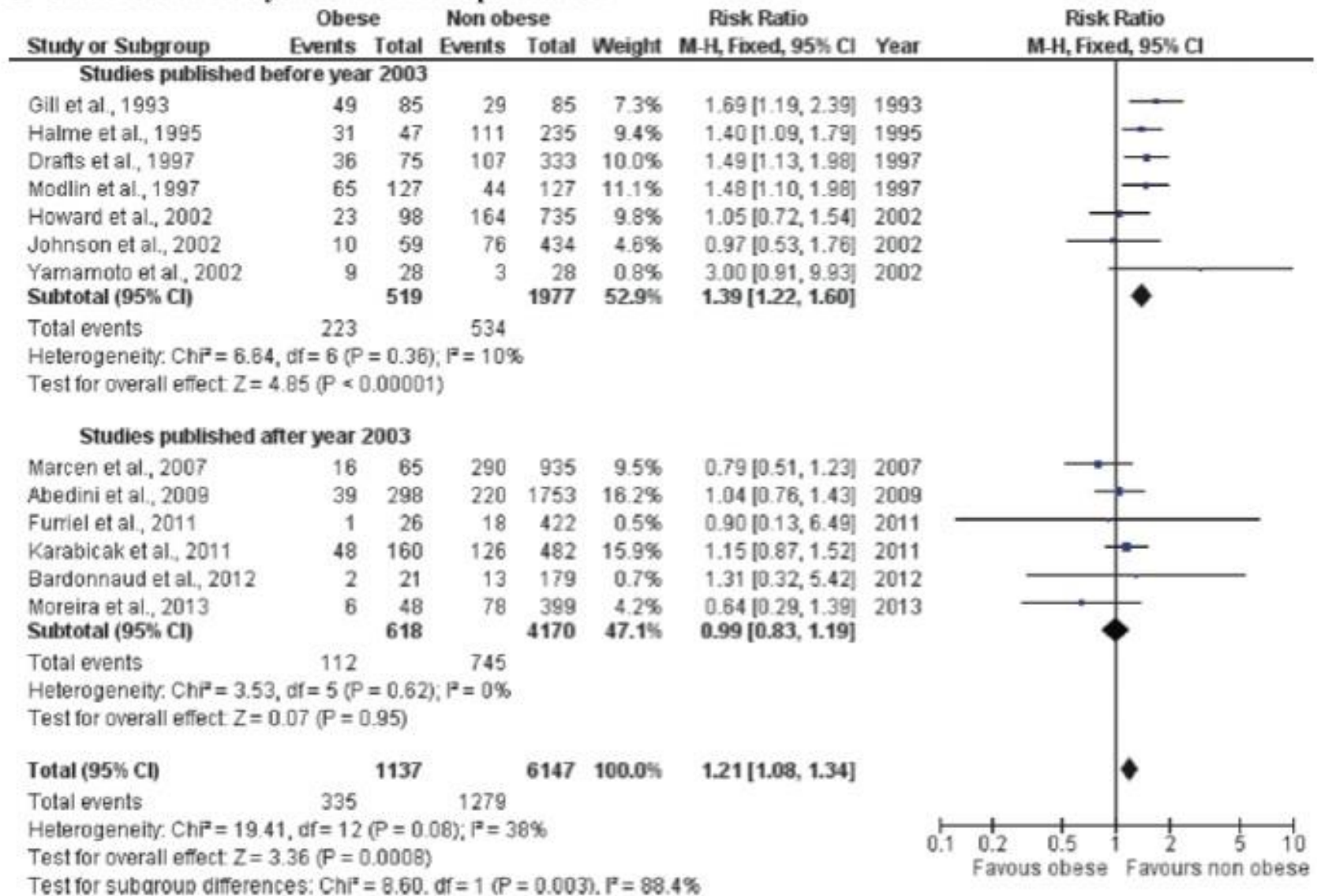
Graft Loss after 1-year

A Graft loss at one year after transplantation



Graft Loss after 5-years

B Graft loss at five years after transplantation



Acute Rejection

B Acute rejection

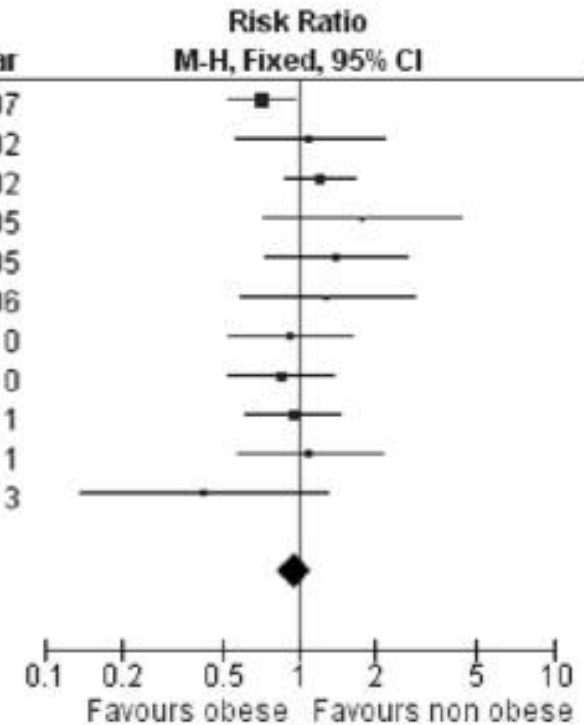
Study or Subgroup	Obese		Non obese		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Fixed, 95% CI		
Modlin et al., 1997	44	127	62	127	25.5%	0.71 [0.53, 0.96]	1997	
Yamamoto et al., 2002	11	28	10	28	4.1%	1.10 [0.56, 2.17]	2002	
Johnson et al., 2002	25	59	152	434	15.0%	1.21 [0.88, 1.67]	2002	
Singh et al., 2005	10	33	6	35	2.4%	1.77 [0.72, 4.32]	2005	
Massarweh et al., 2005	12	56	21	137	5.0%	1.40 [0.74, 2.64]	2005	
Abou-Jaoude et al., 2006	5	16	29	119	2.8%	1.28 [0.58, 2.83]	2006	
Walczak et al., 2010	14	46	20	61	7.1%	0.93 [0.53, 1.63]	2010	
Zaydfudim et al., 2010	18	118	62	346	13.0%	0.85 [0.53, 1.38]	2010	
Karabicak et al., 2011	23	160	73	482	15.0%	0.95 [0.62, 1.46]	2011	
Furriel et al., 2011	7	26	103	422	4.9%	1.10 [0.57, 2.12]	2011	
Moreira et al., 2013	3	48	59	399	5.2%	0.42 [0.14, 1.30]	2013	

Total (95% CI) 717 2590 100.0% 0.95 [0.82, 1.11]

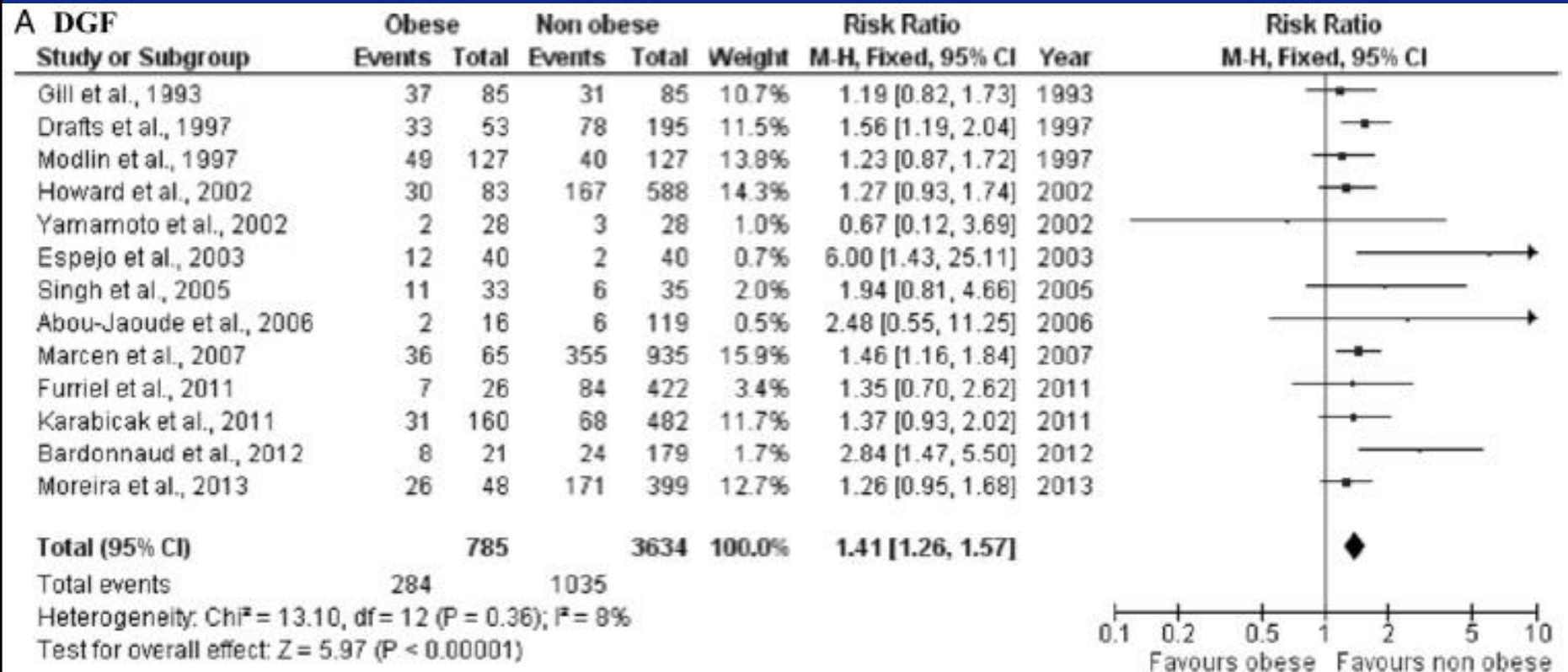
Total events 172 597

Heterogeneity: $\text{Chi}^2 = 12.22$, $\text{df} = 10$ ($P = 0.27$); $I^2 = 18\%$

Test for overall effect: $Z = 0.65$ ($P = 0.52$)



Delayed Graft Function



7,123 "Records were identified through searching electronic databases"

2,205	Medline	2,328	Web of Science
2,165	Embase	356	CINAHL
69	Cochrane Central Register of Controlled Trials		

2,554 Duplicates were removed

4,569 Records were screened based on title/abstract

4,127 "Records were excluded" Due to being obviously irrelevant to the aim of the systematic review

442 "Full-text articles" were assessed for eligibility

381 "Full-text articles were excluded" Due to:

- 52 unavailability of full-text article
- 24 presenting duplicated results
- 67 insufficient sample size (<1000)
- 38 no report of longitudinal comparative study
- 31 no recruitment of chronic kidney disease participants
- 125 no measurement of BMI and/or mortality/survival
- 44 insufficient information to decide upon inclusion

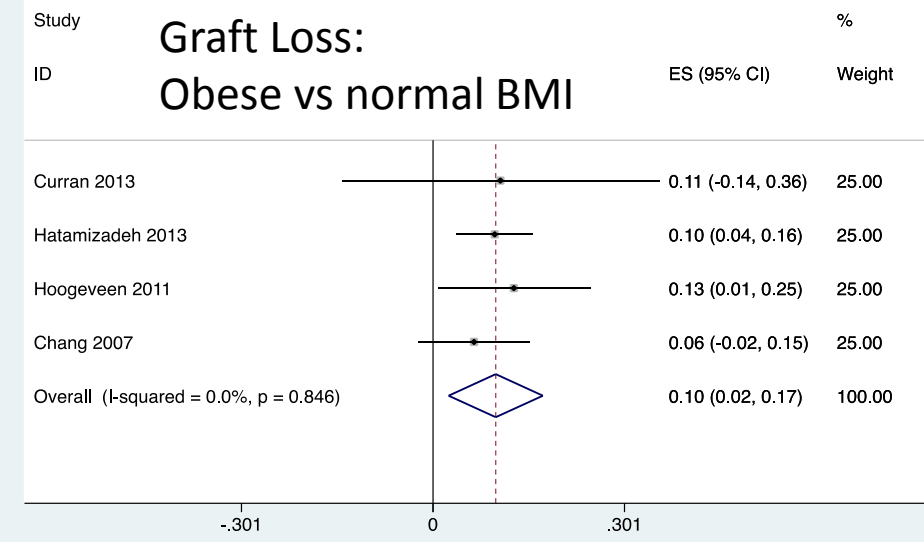
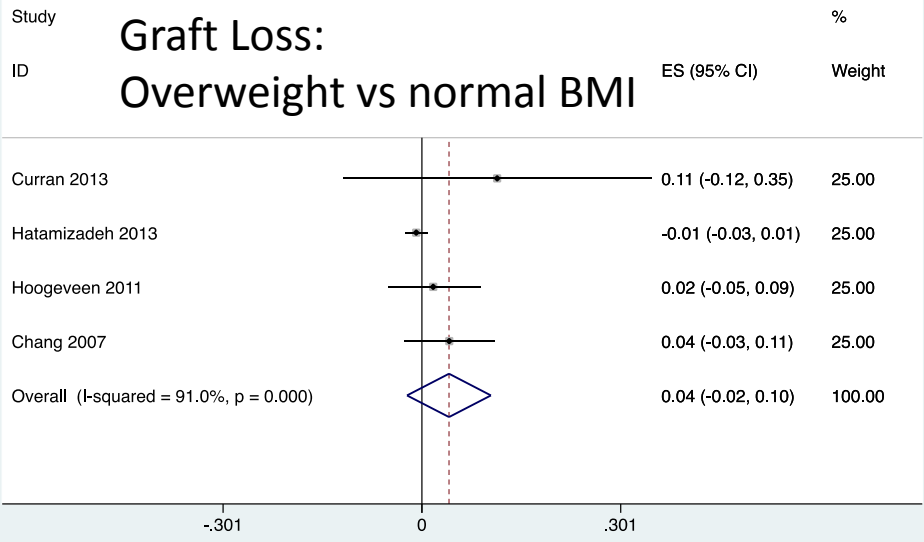
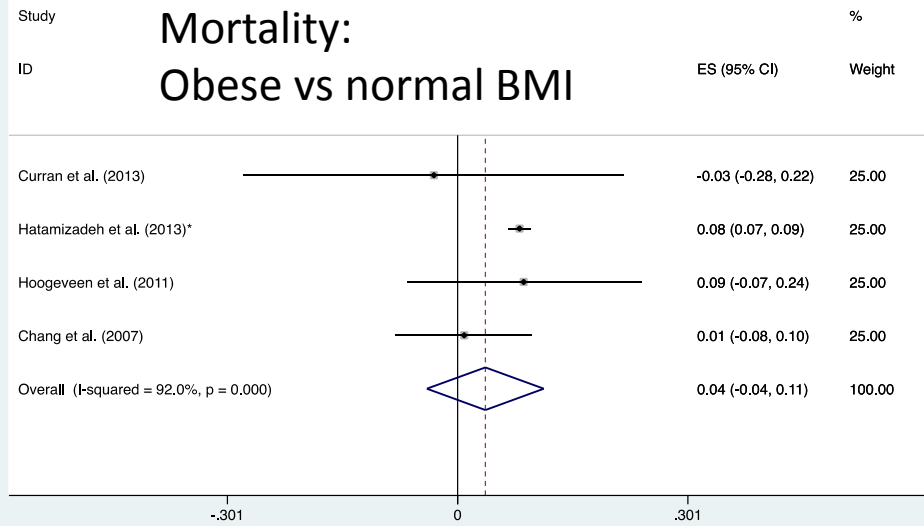
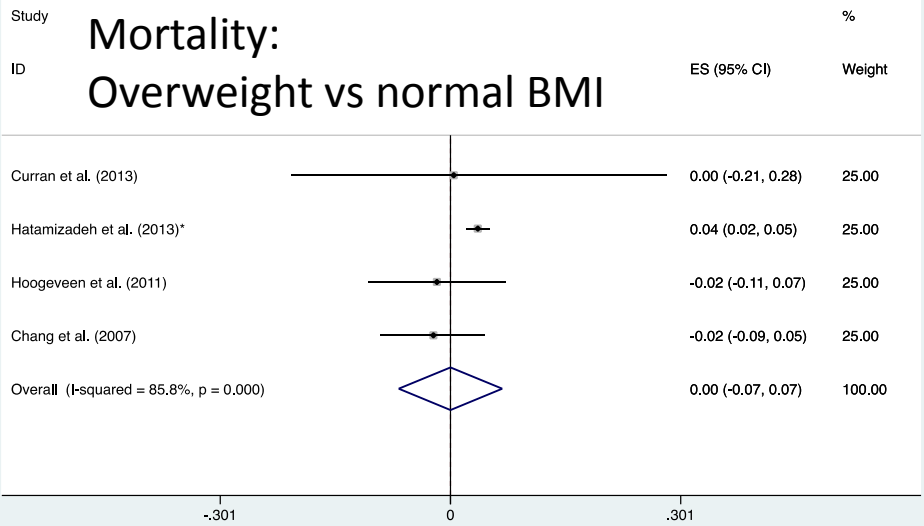
61 "Studies were included" in our systematic review series (10 on kidney transplantation)

1 "Unpublished study identified by consulting field experts"

11 "Studies on kidney transplantation were included" in this systematic review

4 "Studies on kidney transplantation were included" in meta-analyses

Ahmadi SF et al., 2014, Am J Nephrol, in press



Interpreting Body Composition in Kidney Transplantation: Weighing Candidate Selection, Prognostication, and Interventional Strategies to Optimize Health

Krista L. Lentine,^{*†} David Axelrod,[‡] and Kevin C. Abbott[§]

Clin J Am Soc Nephrol 6: 1238–1240, 2011. doi: 10.2215/CJN.02510311

Although current data have not defined limits of body composition that preclude clinical benefit from transplantation ..., work such as the study by Streja *et al.* should be pursued to help **define accurate, practical measures of body composition** that predict clinical outcomes.

Take Home Message

- Losing weight during dialysis is associated higher risk of mortality
- Higher BMI, especially higher muscle mass is associated with better survival in patients on hemodialysis
- Higher pre-transplant BMI is NOT associated with higher post-transplant mortality
- Obesity is associated with increased risk of DGF, graft loss?
- BMI itself, should not be a contraindication for kidney transplantation
- Clinical trials with intervention are urgently needed

Thank you for your attention!