Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Early High Dose Vitamin D_3 for Critically Ill Patients with Vitamin D Deficiency

Supplementary Materials

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Supplementary Tables

Table S1. Baseline characteristics for all randomized participants (screened deficient)

Characteristic	Vitamin D (N=690)	Placebo (N=668)
Demographic		
Age in years – mean ± SD	57.3 ± 15.6 (n=690)	55.3 ± 16.5 (n=668)
Women – no. (%)	300 (43.5)	304 (45.5)
Race/ethnicity		
Non-Hispanic white – no. (%)	375 (54.3)	354 (53.0)
Black – no. (%)	155 (22.5)	148 (22.2)
Nonblack Hispanic – no. (%)	35 (5.1)	35 (5.2)
Other – no. (%)	19 (2.8)	20 (3.0)
Not available – no. (%)	106 (15.4)	111 (16.6)
Facility residence prior to hospitalization – no. (%)	53 (7.7)	48 (7.2)
EQ-5D-5L – mean ± SD	0.7 ± 0.3 (n=644)	0.7 ± 0.3 (n=622)
Clinical		
Charlson co-morbidity index – mean ± SD	4.1 ± 2.9 (n=670)	3.6 ± 2.9 (n=644)
Body mass index, kg/m^2 – mean ± SD	30.1 ± 10.1 (n=669)	31 ± 11.5 (n=657)
Acute risk factors for mortality – no. (%)*		
Pneumonia	256 (37.1)	232 (34.7)
Shock	237 (34.3)	227 (34.0)
Sepsis	235 (34.1)	220 (32.9)
Mechanical ventilation for acute respiratory failure	150 (21.7)	148 (22.2)
Aspiration	42 (6.1)	39 (5.8)
Lung contusion	21 (3.0)	22 (3.3)
Pancreatitis	20 (2.9)	23 (3.4)
Smoke inhalation	1 (0.1)	3 (0.4)
Medical intensive care unit admission – no. (%)	577 (83.6)	569 (85.2)
Illness severity		
Total SOFA – mean ± SD	5.5 ± 3.6 (n=690)	5.3 ± 3.7 (n=668)
LIPS – mean ± SD	5.2 ± 3.0 (n=690)	5.2 ± 3.0 (n=668)
Mechanical ventilation – no. (%)	220 (31.9)	222 (33.2)
ARDS – no. (%)	54 (7.8)	49 (7.3)
Vasopressor use at baseline – no. (%)	215 (31.2)	211 (31.6)
Vitamin D-related		
Vitamin D supplement use in past week – no. (%)	60 (8.7)	48 (7.2)
Multivitamin use in past week – no. (%)	57 (8.3)	52 (7.8)
Estimated average daily vitamin D dose, IU – mean ± SD	3386 ± 11317 (n=95)	4278 ± 13337 (n=83)
25-hydroxyvitamin D, ng/mL – mean ± SD	13.9 ± 7.7 (n=661)	13.5 ± 7.9 (n=644)
Total serum calcium, mg/dL – mean ± SD	8.3 ± 0.9 (n=678)	8.3 ± 1.0 (n=649)
Ionized calcium, mg/dL – mean ± SD	4.3 ± 1.3 (n=264)	4.3 ± 0.9 (n=259)
Creatinine, mg/dL – mean ± SD	2.3 ± 2.4 (n=687)	2.0 ± 2.1 (n=667)
eGFR, ml/min/1.73m^2 – mean ± SD	57.8 ± 39.1 (n=687)	60.6 ± 37.9 (n=667)

* may have more than one risk factor

Abbreviations: LC/MS/MS, liquid chromatography tandem mass spectrometry; EQ-5D-5L, EuroQol-5 dimension-5 level quality of life assessment; SOFA, sequential organ failure assessment; LIPS, lung injury prediction score; ARDS, acute respiratory distress syndrome; eGFR, estimated glomerular filtration rate

Table S2. Study initiation and dosing

Characteristic	Confirmed Deficient		Screened Deficient (All Randomized)	
	Vitamin D (N=538)	Placebo (N=540)	Vitamin D (N=690)	Placebo (N=668)
Met inclusion in emergency department – no. (%)	453 (84)	460 (85)	579 (84)	566 (85)
Inclusion to randomization, hrs – mean ± SD	6.6±3.4 (n=538)	6.8±3.5 (n=540)	6.7±3.5 (n=690)	6.8±3.5 (n=668)
Randomization to study drug administration, hrs – mean ± SD	1.2±1.1 (n=538)	1.1±1.0 (n=540)	1.2±1.1 (n=677)	1.1±1.0 (n=655)
Study drug administered – no. (%)	532 (99)	532 (99)	677 (98)	655 (98)
Study drug tolerated – no. (%)	521 (98)	524 (99)	662 (98)	644 (98)

Confirmed deficient was the primary analysis population and included all patients who underwent randomization and had vitamin D deficiency confirmed by liquid chromatography–tandem mass spectrometry.

Table S3. Patient outcomes for all randomized participants (screened deficient)

Characteristic	Vitamin D (N=690)	Placebo (N=668)	P-Value or Diff (95% CI)
Primary Endpoint: All-cause, all-location mortality to day 90–no. (%)	159 (23.3) (n=681)	137 (20.9) (n=656)	0.28
Secondary Endpoints			
Clinical			
All-cause, all-location mortality to day 28 – no. (%)	112 (16.4) (n=681)	89 (13.6) (n=656)	2.9 (-0.9, 6.7)
Hospital mortality to day 90 – no. (%)	115 (16.7) (n=690)	96 (14.4) (n=667)	2.3 (-1.6, 6.1)
Alive and home (prior level of care) at day 90 – no. (%)	438 (64.7) (n=677)	432 (66.1) (n=654)	-1.4 (-6.5, 3.8)
Hospital length of stay to day 90, days – mean ± SD	8.9±9.0 (n=522)	10.1±10.7 (n=517)	-1.2(-2.4, -0.0)
Hospital length of stay to day 90, days – mean ± SE*	8.8±0.32 (n=522)	9.7±0.35 (n=517)	-0.8 (-1.8, 0.1)
Discharged to other healthcare facility – no. (%)	94 (18.0) (n=522)	109 (21.0) (n=519)	-3.0 (-7.8, 1.8)
Healthcare facility length of stay, days – mean ± SD	6.8±19.1 (n=518)	8.3±20.6 (n=515)	-1.5 (-4.0, 0.9)
Healthcare facility length of stay, days – mean ± SE*	6.1±0.60 (n=518)	7.8±0.67 (n=515)	-1.6 (-3.4,0.1)
Ventilator-free days to day 28 – mean ± SD	21.7±11.1 (n=671)	22.1±10.5 (n=659)	-0.5 (-1.6, 0.7)
EQ-5D-5L (Δ day 90 minus baseline) – mean ± SD	0.0±0.2 (n=432)	0.0±0.2 (n=429)	0.0 (-0.0, 0.0)
EQ-5D-5L (Δ day 90 minus baseline) – mean ± SE*	0.0±0.0 (n=432)	0.0±0.0 (n=429)	0.0 (-0.0, 0.0)
Physiological			
New (post-randomization) mechanical ventilation – no. (%)	49 (10.4) (n=470)	38 (8.6) (n=443)	1.8 (-2.0, 5.6)
Lowest P/F to day 7 – mean ± SD	187.8±103.0 (n=155)	185.7±107.1 (n=170)	2.0 (-20.9, 25.0)
New ARDS to day 7 – no. (%)	22 (4.1) (n=531)	23 (4.5) (n=515)	-0.3 (-2.8, 2.1)
ARDS severity to day 7	(n=22)	(n=23)	
Mild – no. (%)	8 (36.4)	5 (21.7)	14.6 (-11.6, 40.9)
Moderate – no. (%)	9 (40.9)	15 (65.2)	-24.3 (-52.6, 4.0)
Severe – no. (%)	5 (22.7)	3 (13.0)	9.7 (-12.6, 32.0)
Worst AKI severity to day 7	(n=615)	(n=607)	
None – no. (%)	350 (56.9)	366 (60.3)	-3.4 (-8.9, 2.1)
Mild – no. (%)	99 (16.1)	94 (15.5)	0.6 (-3.5, 4.7)
Moderate – no. (%)	67 (10.9)	62 (10.2)	0.7 (-2.8, 4.1)
Severe – no. (%)	99 (16.1)	85 (14.0)	2.1 (-1.9, 6.1)
New RRT to day 7 – no. (%)	25 (4.0) (n=620)	25 (4.1) (n=614)	-0.0 (-2.2, 2.2)
Highest creatinine, mg/dl to day 7 – mean ± SE†	2.2±0.1 (n=666)	2.2±0.1 (n=653)	-0.0 (-0.2, 0.1)
New vasopressor use to day 7 – no. (%)	56 (12.2) (n=460)	55 (12.1) (n=454)	0.1 (-4.2, 4.3)
Highest cardiovascular SOFA to day 7 – mean ± SE†	1.4±0.1 (n=671)	1.4±0.1 (n=661)	-0.0 (-0.2, 0.1)
25-hydroxyvitamin D, ng/mL at day 3 – mean ± SD	49.0±23.9 (n=170)	13.7±7.7 (n=163)	35.3 (31.4, 39.2)
<20 – no. (%)	19 (11.2)	134 (82.2)	-71.0 (-78.6, -63.5)
20 to <30 – no. (%)	21 (12.4)	25 (15.3)	-3.0 (-10.4, 4.4)
30 to <120 – no. (%)	129 (75.9)	4 (2.5)	73.4 (66.6, 80.3)
≥120 – no. (%)	1 (0.6)	0 (0.0)	0.6 (-0.6, 1.7)
IL-6, pg/ml at day 3 – mean ± SD	190±1456 (n=165)	252±2000 (n=154)	-63 (-446, 378)
Safety			
Serious adverse events – no.	18	19	0.87
Hypercalcemia to day 14 – no. (%)	19 (2.9) (n=659)	12 (1.9) (n=648)	0.22
Highest total calcium to day 14, mg/dL – mean ± SD	8.9±0.8 (n=652)	8.8±0.7 (n=637)	<0.001
Highest ionized calcium to day 14, mg/dL – mean ± SD	4.7±0.8 (n=190)	4.6±0.7 (n=216)	0.26
Kidney stones to day 90 – no. (%)	1 (0.2) (n=652)	4 (0.6) (n=631)	0.21
Falls to day 90 – no. (%)	46 (7.1) (n=652)	35 (5.5) (n=631)	0.27
Fall-related fractures to day 90 – no. (%)	6 (0.9) (n=652)	4 (0.6) (n=631)	0.75

* Survivor average causal effect

† Controlled for baseline value using repeated measures ANOVA with a treatment by time interaction and shared intercept at baseline.

Abbreviations: LC/MS/MS, liquid chromatography tandem mass spectrometry; EQ-5D-5L, EuroQol-5 dimension-5 level quality of life assessment; P/F, PaO2/FiO2; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; IL-6, interleukin-6

Table S4. Mortality estimates by baseline 25-hydroxyvitamin D level

Baseline 25-hydroxyvitamin D by LC/MS/MS (ng/mL)	Vitamin D (N=653) Mortality (% ± SE)	Placebo (N=632) Mortality (% ± SE)	Difference (95% CI)
5	27.1 ± 3.3	24.0 ± 3.7	3.1 (-5.4, 13.2)
10	24.7 ± 2.5	20.4 ± 2.4	4.4 (-3.6, 10.0)
15	22.3 ± 2.3	18.9 ± 2.5	3.4 (-3.7, 9.7)
20	19.9 ± 2.7	19.4 ± 3.4	0.5 (-9.5, 7.4)
25	17.5 ± 3.6	20.8 ± 4.4	-3.3 (-11.4, 10.9)
30	16.0 ± 4.9	22.0 ± 5.9	-6.0 (-18.4, 11.6)

Estimates and SEs were obtained from the quadratic smoothing spline in each treatment group

Corresponds with estimates displayed in Figure 3

Table S5. Total calcium by study day

Study Day	Confirmed Deficient			Screened Deficient		
Mean ± SD (n)	Vitamin D	Placebo	P-value	Vitamin D	Placebo	P-value
Day 1	8.1±0.9 (483)	8.1±0.8 (487)	0.530	8.2±0.9 (626)	8.1±0.8 (605)	0.31
Day 2	8.4±0.8 (440)	8.2±0.7 (438)	0.005	8.4±0.8 (570)	8.2±0.7 (540)	<.001
Day 3	8.5±0.9 (392)	8.3±0.8 (411)	0.001	8.5±0.9 (504)	8.3±0.8 (506)	<.001
Day 4	8.5±0.9 (340)	8.4±0.7 (350)	0.006	8.6±0.9 (440)	8.4±0.7 (434)	0.003
Day 5	8.5±0.8 (287)	8.4±0.7 (303)	0.02	8.6±0.8 (369)	8.4±0.8 (371)	0.002
Day 6	8.6±0.8 (251)	8.4±0.8 (254)	0.006	8.6±0.8 (327)	8.4±0.7 (318)	0.001
Day 7	8.5±0.8 (215)	8.4±0.8 (231)	0.11	8.6±0.8 (276)	8.4±0.7 (282)	0.02
Day 8	8.4±1.2 (182)	8.3±1.0 (203)	0.35	8.5±1.2 (227)	8.4±0.9 (250)	0.23
Day 9	8.6±1.0 (146)	8.3±1.2 (167)	0.03	8.6±1.0 (185)	8.3±1.1 (199)	0.03
Day 10	8.6±1.0 (126)	8.3±1.0 (148)	0.05	8.6±0.9 (158)	8.4±0.9 (179)	0.03
Day 11	8.6±0.8 (118)	8.2±1.4 (132)	0.01	8.6±0.8 (148)	8.2±1.3 (160)	0.008
Day 12	8.5±0.8 (94)	8.4±0.9 (118)	0.21	8.5±0.8 (121)	8.4±0.9 (142)	0.15
Day 13	8.6±0.9 (82)	8.4±1.0 (98)	0.22	8.6±0.8 (103)	8.4±0.9 (123)	0.15
Day 14	8.5±0.7 (72)	8.4±0.7 (92)	0.51	8.5±0.8 (90)	8.4±0.7 (112)	0.38

Table S6. Ionized calcium by study day

Study Day	Confirmed Deficient			Screened Deficient		
Mean ± SD (n)	Vitamin D	Placebo	P-value	Vitamin D	Placebo	P-value
Day 1	4.4±0.8 (96)	4.4±0.7 (122)	0.86	4.4±0.7 (121)	4.4±0.7 (143)	1.00
Day 2	4.4±0.4 (75)	4.5±0.6 (73)	0.24	4.5±0.7 (93)	4.5±0.6 (97)	0.74
Day 3	4.4±0.4 (66)	4.5±0.7 (49)	0.45	4.4±0.4 (80)	4.5±0.6 (63)	0.39
Day 4	4.4±0.4 (47)	4.6±0.8 (47)	0.40	4.4±0.4 (57)	4.6±0.7 (60)	0.21
Day 5	4.5±0.5 (35)	4.5±0.4 (41)	0.88	4.6±0.5 (46)	4.5±0.4 (48)	0.62
Day 6	4.8±1.0 (29)	4.5±0.5 (26)	0.22	4.7±0.9 (38)	4.6±0.5 (30)	0.32
Day 7	4.5±0.4 (23)	4.5±0.5 (30)	0.67	4.6±0.5 (30)	4.5±0.4 (34)	0.60
Day 8	4.7±0.8 (19)	4.4±0.4 (30)	0.04	4.8±0.8 (23)	4.4±0.4 (35)	0.01
Day 9	4.7±0.9 (13)	4.6±0.8 (22)	0.69	4.7±0.7 (18)	4.6±0.7 (27)	0.56
Day 10	4.6±0.5 (12)	4.7±0.8 (23)	0.64	4.6±0.5 (15)	4.7±0.7 (27)	0.65
Day 11	4.4±0.5 (11)	4.4±0.4 (17)	0.80	4.5±0.5 (15)	4.5±0.4 (20)	0.86
Day 12	4.4±0.5 (12)	4.6±0.4 (14)	0.26	4.4±0.5 (15)	4.6±0.4 (16)	0.16
Day 13	4.4±0.4 (12)	4.6±0.5 (16)	0.48	4.4±0.4 (15)	4.6±0.5 (19)	0.22
Day 14	4.4±0.2 (10)	4.7±0.6 (10)	0.07	4.4±0.3 (13)	4.7±0.6 (13)	0.08

Table S7. **Adverse events**

		Confirmed Deficient		Confirmed Not Deficient		Screened Deficient	
Organ System	**Type**	**Vitamin D**	**Placebo**	**Vitamin D**	**Placebo**	**Vitamin D**	**Placebo**
Blood and lymphatic disorders	Severe	2	0	0	0	2	0
	Non-severe	1	0	0	0	1	0
Cardiac disorders	Severe	0	2	0	0	0	2
	Non-severe	2	6	1	0	3	6
Ear and labyrinth disorders	Severe	0	0	0	0	0	0
	Non-severe	0	1	0	0	0	1
Endocrine disorders	Severe	2	0	0	0	2	0
	Non-severe	0	0	0	0	0	0
Gastrointestinal disorders	Severe	2	1	1	1	3	2
	Non-severe	1	0	0	0	1	0
General disorders and administration	Severe	0	1	0	0	0	1
	Non-severe	2	2	0	0	2	2
Infections ad infestations	Severe	1	0	0	0	1	0
	Non-severe	0	1	1	0	1	1
Injury, poisoning, and procedural complications	Severe	0	0	0	0	0	0
	Non-severe	1	0	0	0	1	0
Investigations	Severe	1	0	0	0	1	0
	Non-severe	0	0	0	0	0	0
Nervous system disorders	Severe	0	0	0	0	0	0
	Non-severe	1	1	2	2	3	3
Renal and urinary disorders	Severe	1	1	0	0	1	1
	Non-severe	2	1	0	0	2	1
Respiratory, thoracic, and mediastinal disorders	Severe	0	0	1	0	1	0
	Non-severe	2	3	0	0	2	3
Skin and subcutaneous tissue disorders	Severe	1	0	0	0	1	0
	Non-severe	0	0	0	0	0	0
Vascular disorders	Severe	0	0	0	0	0	0
	Non-severe	0	2	1	0	1	2

Supplementary Figures

Figure S1. Flow of participants through trial

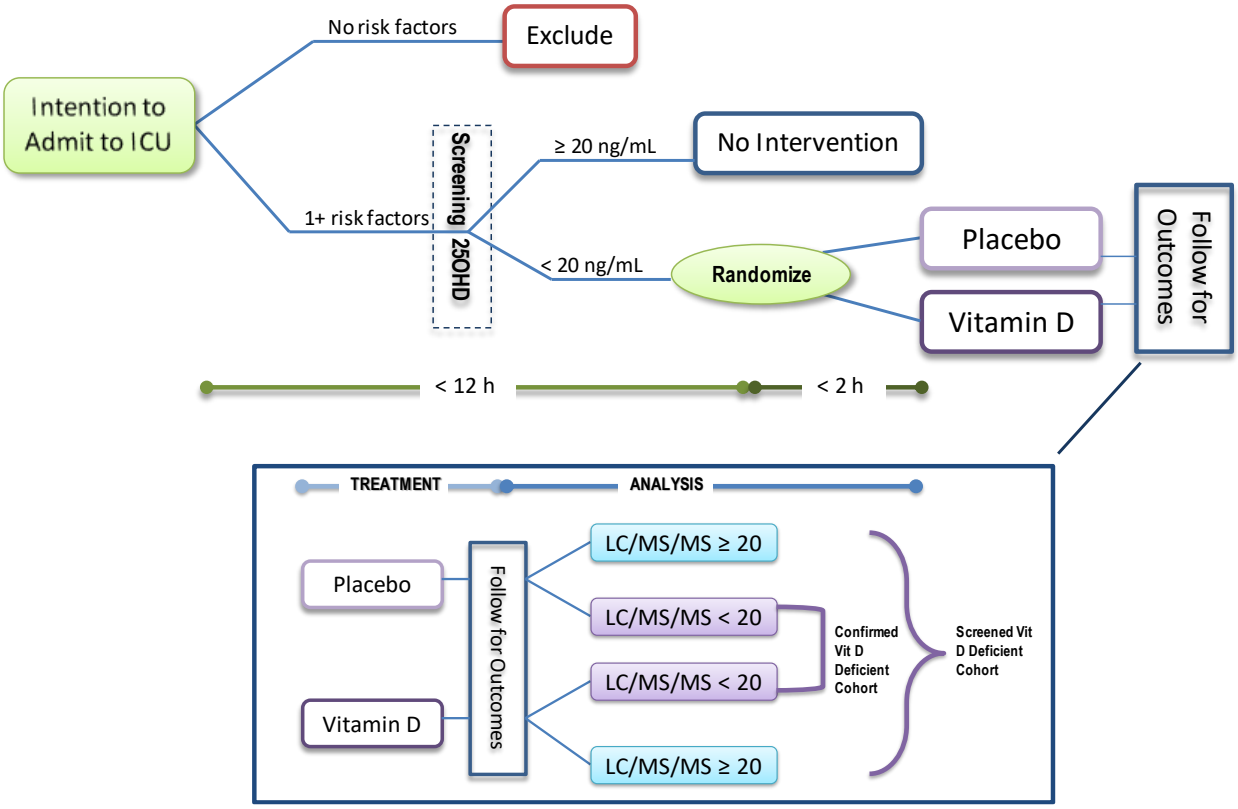
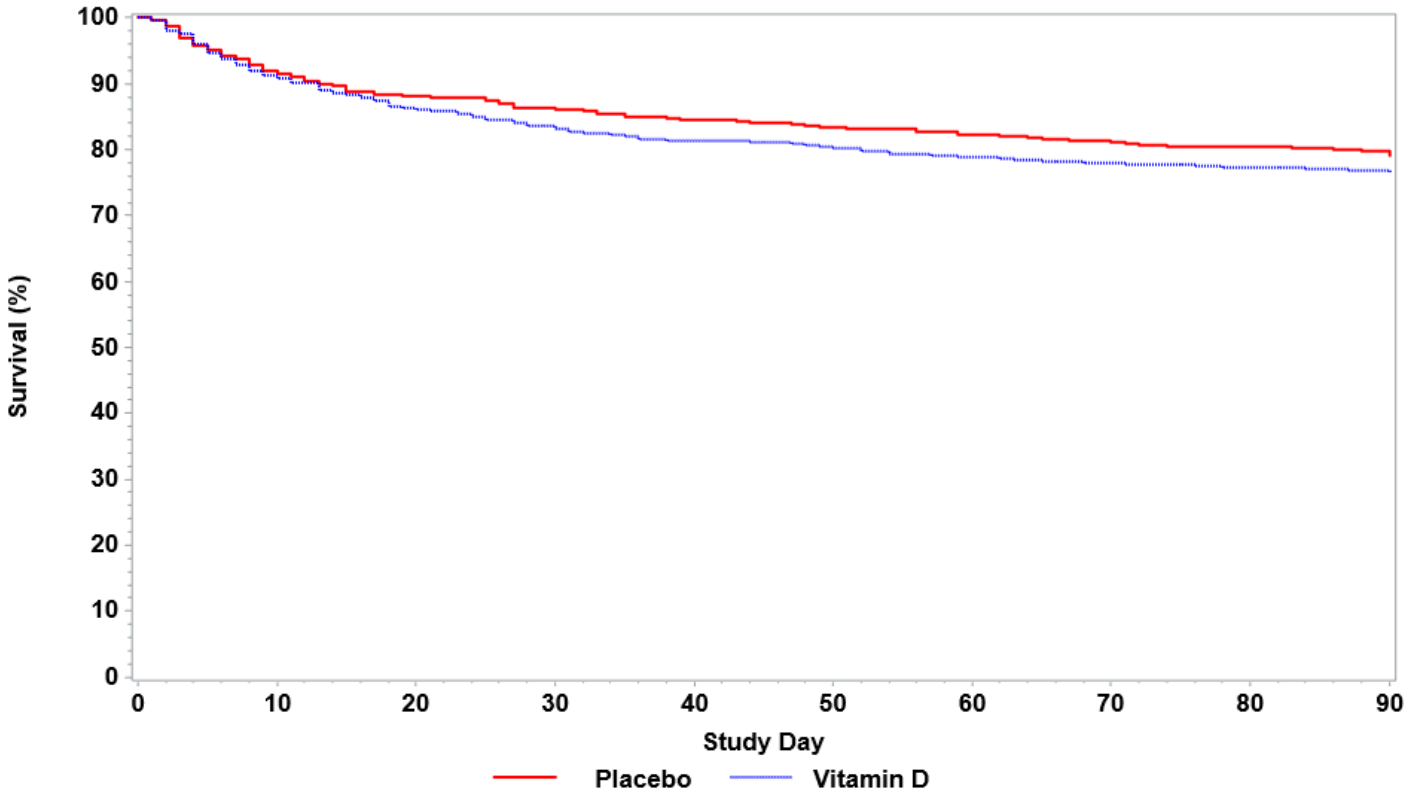
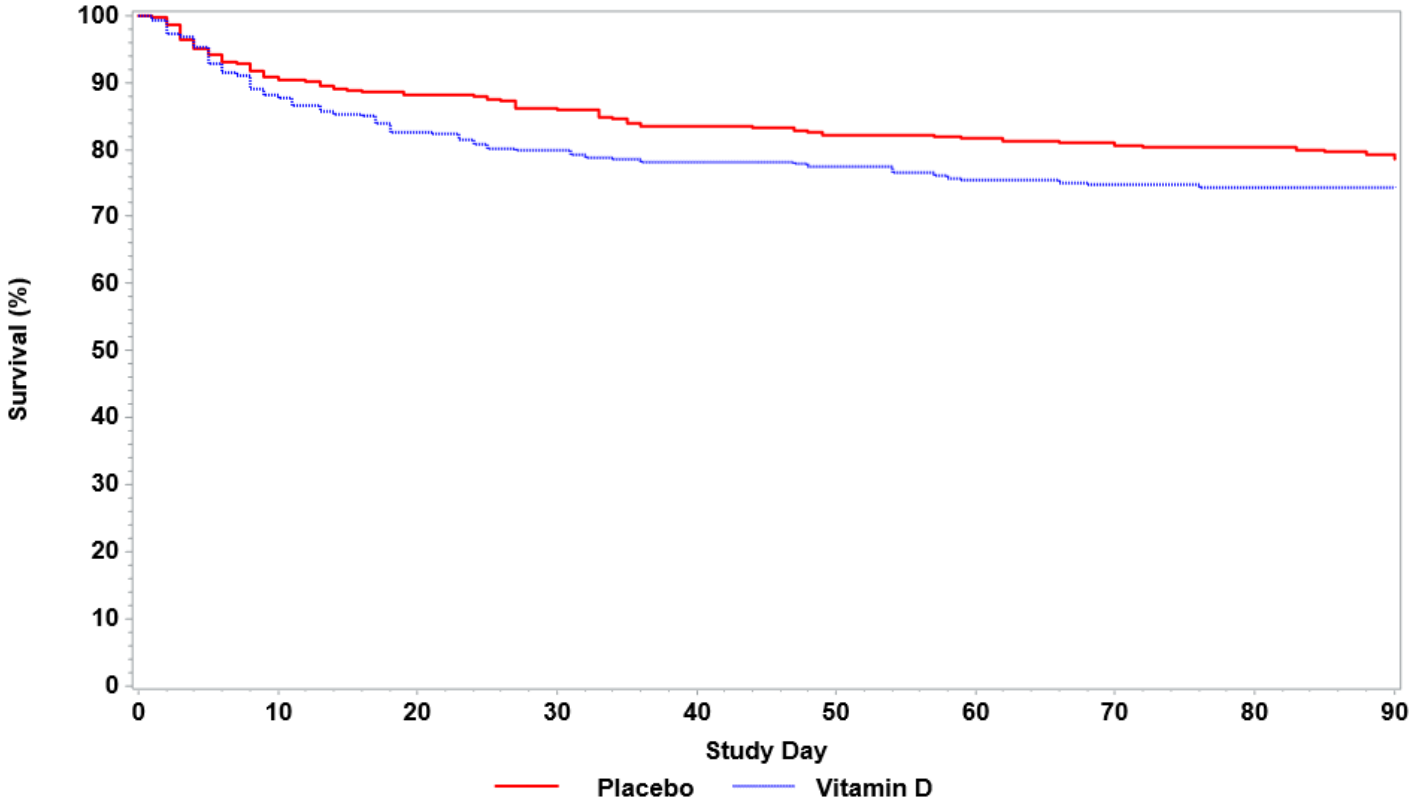


Figure S2. **Survival to day 90 by vitamin D or placebo group for all randomized participants (screened deficient)**

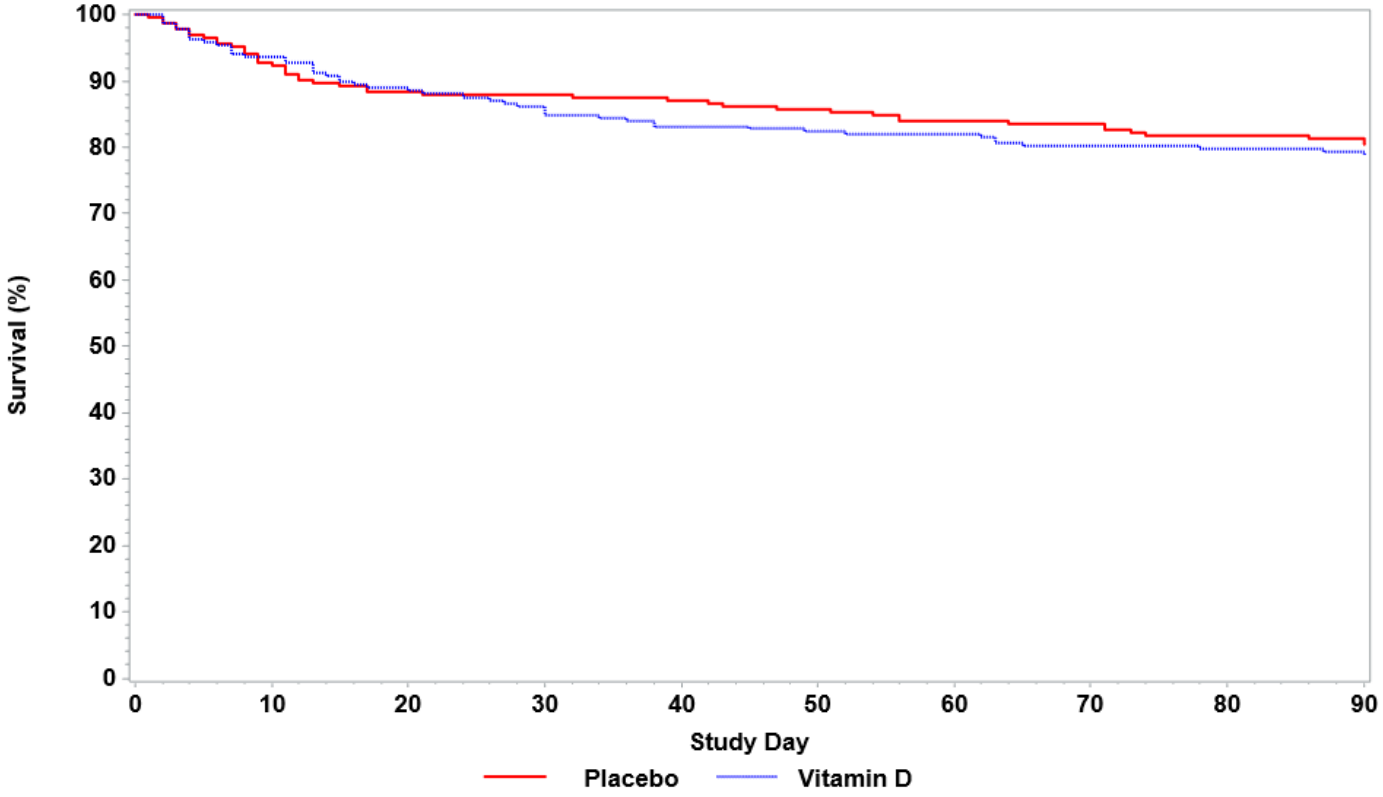
A) All randomized



B) Baseline 25-hydroxyvitamin D <12 ng/mL



C) Baseline 25-hydroxyvitamin D 12-19 ng/mL



D) Baseline 25-hydroxyvitamin D ≥20 ng/mL

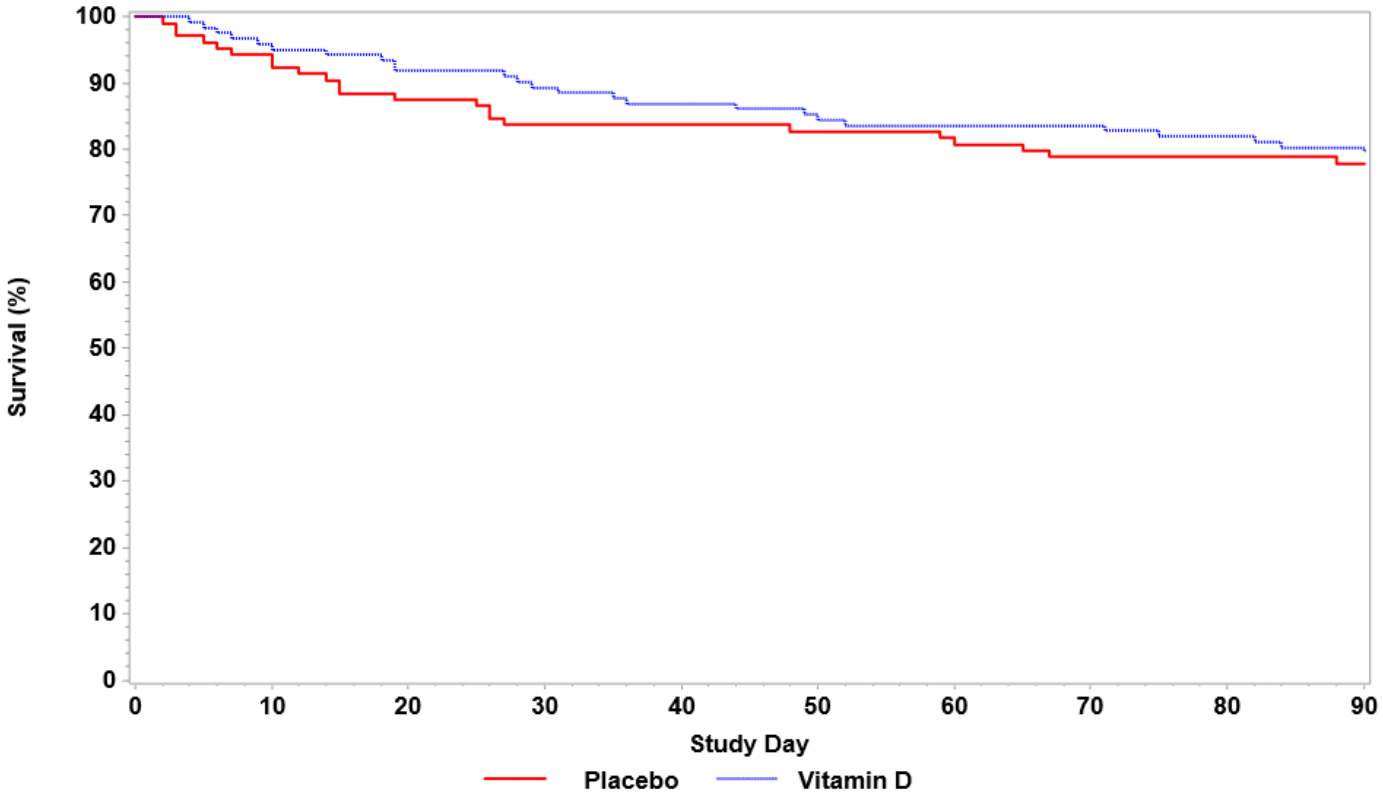
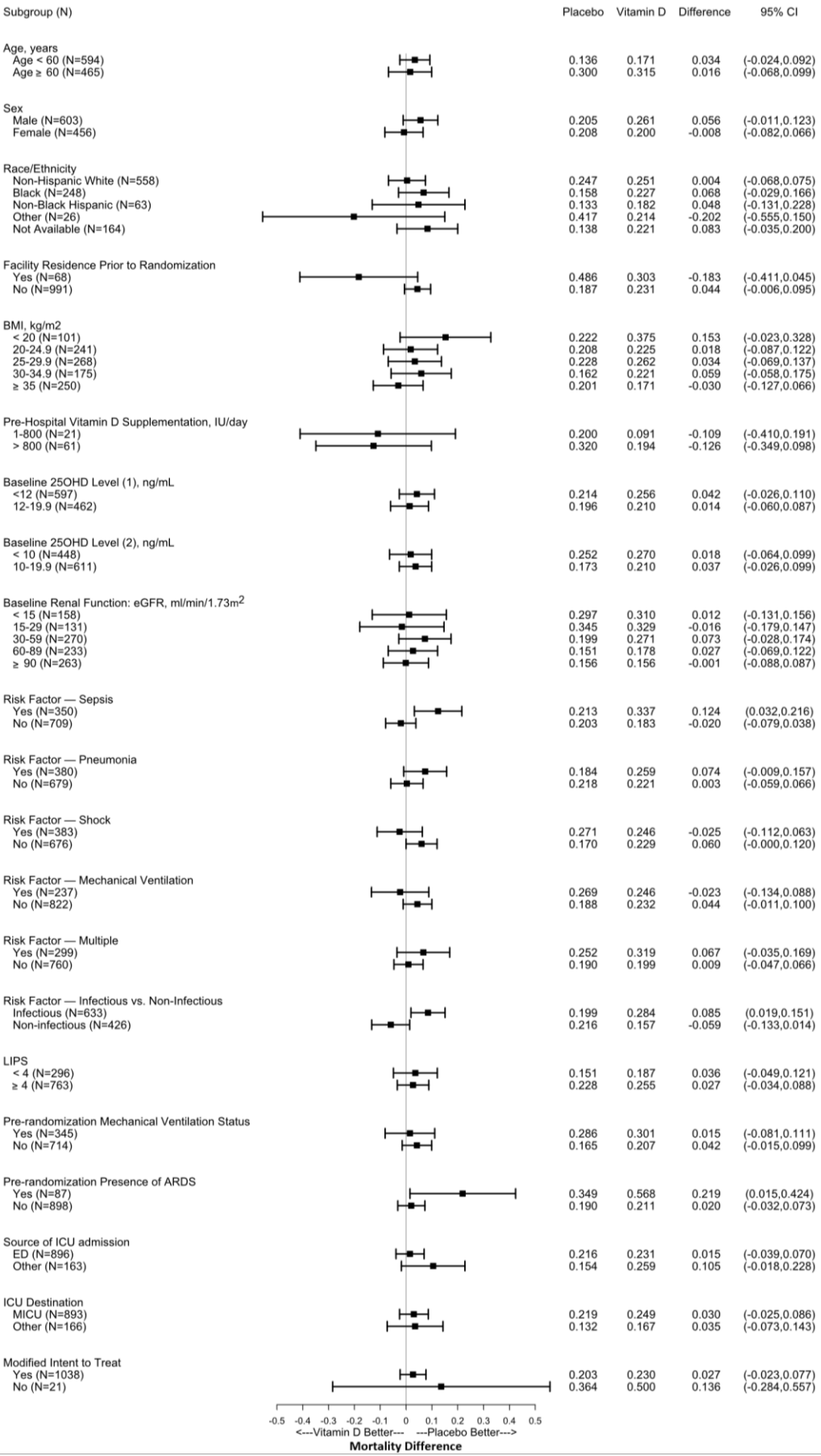
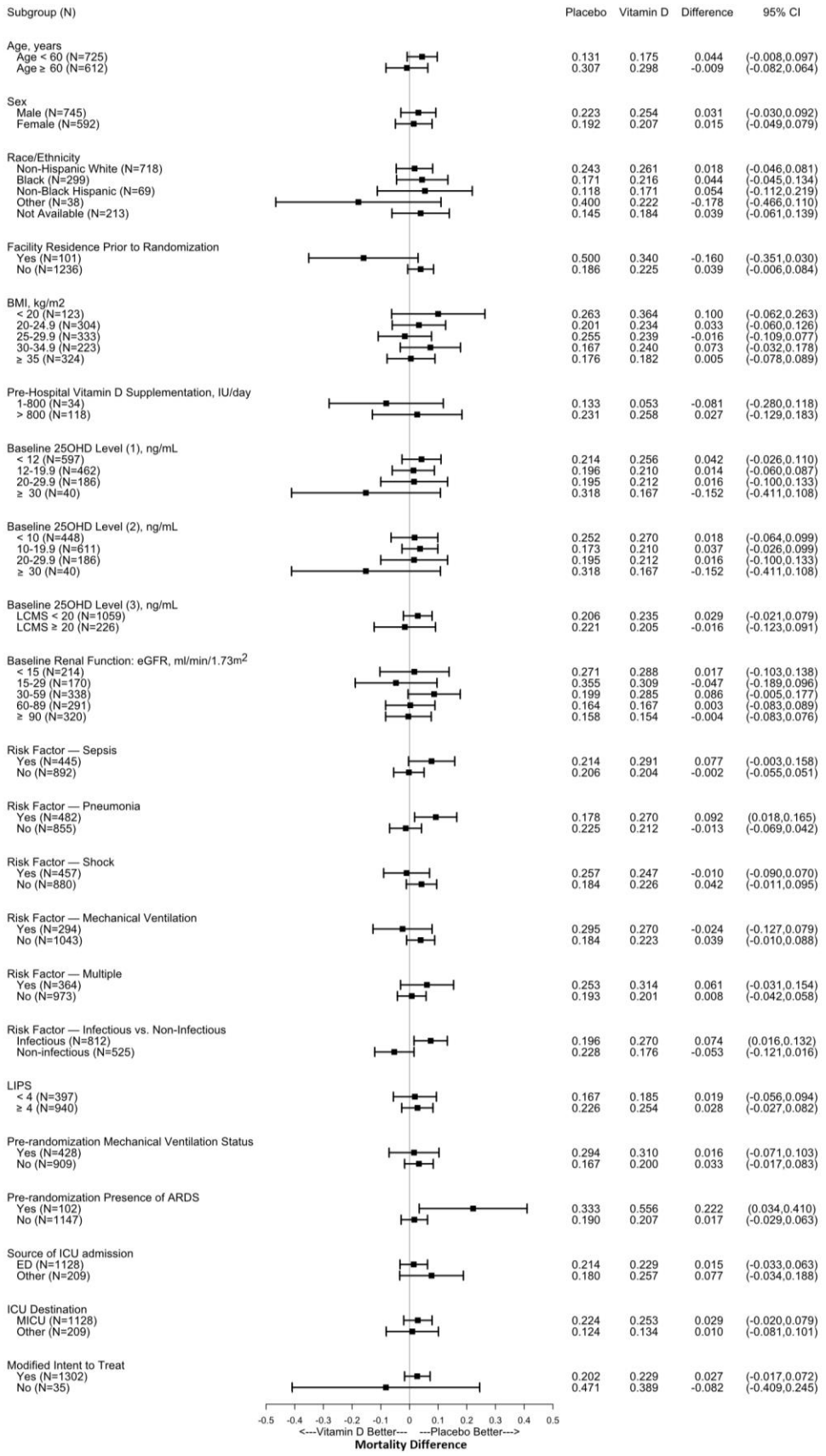


Figure S3. Subgroup analysis for all-cause, all-location mortality to day 90 (primary endpoint)

A) Confirmed vitamin D deficient



B) All randomized



Error bars represent 95% confidence intervals. Plasma 25-hydroxyvitamin D concentrations measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS). **Abbreviations:** BMI, body mass index; 25OHD, 25-hydroxyvitamin D; IU, international units; eGFR, estimated glomerular filtration rate; LIPS, lung injury prediction score; ARDS, acute respiratory distress syndrome; ICU, intensive care unit