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Effect of Early High-Dose Vitamin D3 Repletion on Cognitive Outcomes in Critically Ill Adults

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CHEST 2021; 160(3):909-918

 DOI: 10.1016/j.chest.2021.03.046

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e-Appendix 1.

Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) Investigators

The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network:

ALIGNE Clinical Center: Baystate Medical Center –Jay S Steingrub*, Mark Tidswell, Lori-Ann Kozikowski, Lesley DeSouza, Cynthia Kardos; Tufts Medical Center –Nicholas S Hill, Veronica Bacong, Omar Shweish, Haval Chweich, Erik Garpestad; Brigham and Women's Hospital –Peter Hou*, Rebecca Baron, Anthony Massaro, Laura Fredenburgh, Imoigele Aisiku, Raghu Seethala, Jeffrey Skubic, Arman Isrealyan, Lauren Precopio , Meghan Fawcett, Sarah Pajak; Maine Medical Center – Richard Riker, Adelene MacLeod, Theresa May, Thomas Van der Kloot, David Seder

BOSTON Clinical Center: Beth Israel Deaconess Medical Center –Daniel Talmor*, Nathan Shapiro*, Valerie Banner-Goodspeed, Sharon Hayes, Ted Raddell; Massachusetts General Hospital –Kathryn A Hibbert, Michael Filbin, Kelsey Brait, Melissa Stathas, Caroline Rizzo; St. Vincent Hospital –Nathan Shapiro*, Patricia A Arsenault, Pam Sigel, David Miru; University of Mississippi Medical Center – Alan E Jones, John R Spurzem, Michael A Puskarich, Jasmine McDonald, Maggie Kirby

CALIFORNIA Clinical Center: UCSF San Francisco – Michael Matthay*, Kathleen Liu, Carolyn S Calfee, Jeff Gotts, Amy Ni, Kathryn Vessel, Annika Belzer; UCSF Fresno – Eyad Almarsi, Janna Blaauw, Alyssa Hughes, Kyndra Sousa, Patil Armenian; UC Davis –Timothy E Albertson, Brian Morrissey, Skyler J Pearson, Maya Juarez, James Chenoweth; Stanford University Hospital – Joe Levitt, Jenny Wilson, Angela Rogers, Rosemary Vojnik, Jonasel Roque; UCLA– Gregory W Hendey*, Steven Y Chang, Nida Qadir, Bryan Garber, Christopher Phan

COLORADO Clinical Center: University of Colorado Hospital –Adit Ginde*, Marc Moss*, Lani Finck, Sarah Perman, Jean Hoffman, Katherine Mayer; Denver Health Medical Center –Ivor Douglas, Jason Haukoos, Terra Hiller, Carolynn Lyle, Judy Oakes, Emily Caruso, Meggan Schmidt, Stephanie Gravitz; Medical Center of Aurora – David Van Pelt, Jeff McKeehan, Carrie Higgins; National Jewish Health I Saint Joseph's Hospital–James Finigan, Ryan Paterson, Kenneth Lyn-Kew, Michelle Howell

MICHIGAN Clinical Center: University of Michigan Medical Center –Robert C Hyzy*, Pauline K Park*, Kristine Nelson, Ivan N Co, Jake I McSparron, Kyle J Gunnerson, Tina Chen, Sinan Hanna, Norman Olbrich; Henry Ford Medical Center— Emmanuel P Rivers, Jayna Gardner Gray, Bruno DiGiovine, Jasreen Kaur Gill, Aaron Cook, Kaleem Chaudry, Jacqueline Day, Sarah Rubino, Anja Kathrina Jaehne, Jacqueline Pflaum, Gina Hurst, Jennifer Swiderek, Namita Jayaprakesh

MONTEFIORE-SINAI Clinical Center: Montefiore Moses—Michelle Ng Gong*, Aluko Hope, Swarna Gummadi; Mount Sinai Hospital— Lynne D. Richardson*, Samuel Acquah, Mark Andreae, Kusum Mathews, Neha Goel, Cindy Clesca, Natalie S Massenburg; Montefiore Weiler –Jen-Ting (Tina) Chen, Brenda Lopez, Michael Aboodi

OHIO Clinical Center: Cleveland Clinic Foundation –R. Duncan Hite*, Abhijit Duggal, Sharon Mace, Andrei Hastings, Omar Mehkri, Stephanie Stoianoff; Ohio State University Wexner Medical Center–Thomas E Terndrup*; Matthew C Exline, Joshua A Englert, Sarah C Karow, Joshua Garmatter; University of Cincinnati Medical Center – Kristin Hudock, Ope Adeoye, David Norton, Autumn Studer, Kari Gorder; Northwestern Memorial Hospital –D. Mark Courtney, Megan Rowland

PACIFIC NORTHWEST Clinical Center: Harborview Medical Center –Catherine L Hough*, Bryce R.H Robinson*, Nicholas J Johnson, Stephanie Gundel, Sarah Katsandres; University of Washington Medical Center– Daniel Henning, Tzevan Poon, Sarah Dean, Jennifer Cardey, Anna Ungar; Swedish Medical Center –D. Shane O'Mahony, Julie Wallick; Oregon Health and Science University –Akram Khan, Martin Schreiber, Bory Kea, Ebaad Haq, Olivia Krol

PITTSBURGH Clinical Center: UPMC Presbyterian—Derek C Angus*, Donald M Yealy*, David T Huang, Bryan J McVerry, Caroline Gacka; UPMC Mercy –Donald M Yealy*, Derek C Angus*, Joseph Yanta, Michael Abesamis, Sarah L McGarry; Penn State Hershey Medical Center –Jordan Schooler, Margaret Wojnar, Elizabeth Sinz, Christopher Zacko, Nancy Campbell

SOUTHEAST Clinical Center: Wake Forest Baptist Health –D. Clark Files*, Chadwick Miller*, Kevin Gibbs, Lori Flores, Lauren Koehler; U. Virginia Medical Center –Kyle Enfield, Mark Sochor, Mary Marshall, Ashley Simpson, Desmarie Sherwood; Virginia Commonwealth University Medical Center–Marjolein de Wit, Stephen Miller, Aamer Syed, Jessica Mason, Stella Hamman; U. Kentucky–Peter Morris, Roger Humphries, Jamie Sturgill, Ashley Montgomery-Yates, Evan P Cassity

UTAH: Intermountain Medical Center –Samuel M Brown*, Joseph Bledsoe*, Ithan Peltan, Michael Lanspa, Katie Brown, Brent Armbruster, Quinn Montgomery, Valerie Aston, Eliotte Hirshberg; Utah Valley Regional Medical Center – Dixie Harris, Wayne Woodard, Naresh Kumar, Mardee Merrill, David Nielson, Austin Daw; University of Utah Hospital – Estelle Harris, Robert Paine, Amber Plante, Elizabeth Middleton;

VANDERBILT Clinical Center: Vanderbilt University Medical Center –Wesley H Self*, Todd W Rice*, Matthew W Semler, Adrienne Baughman, Margaret Hays, Karen Miller, Susan Mogan; Louisiana State University Health Sciences Center—David R Janz, Paula Lauto, Margaret M Moore, Bennett P deBoisblanc, John P Hunt; UNC Medical Center— Shannon S Carson, Timothy F Platts-Mills, Eugenia B Quackenbush, Kevin J Chronowski, Colleen Rice; Duke University Medical Center—Alexander T Limkakeng, Jr., S. Michelle Griffin, J. Clancy Leahy, Christopher Cox, John Eppensteiner

Clinical Coordinating Center: Massachusetts General Hospital Biostatistics Center (CCC): David A Schoenfeld*, B Taylor Thompson*, Kathleen Tiffany Lee, Christine Ulysse, Cathryn F Oldmixon, Nancy J Ringwood, Jenna R Pedrin, Richard E Morse, Douglas Hayden

Steering Committee Chair: Johns Hopkins University School of Medicine: Roy G Brower

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Protocol Review Committee: Laurie J Morrison, Charles B Cairns, D. Mark Courtney, Mark N Gillespie, Richard J Kryscio, Damon Scales

Data and Safety Monitoring Board: Polly Parsons, Jason D Christie, Jesse R Hall, Nicholas J. Horton, Jeffrey A Kline, Mitchell Levy, Mark Siegel, Ian Stiell, Laurie S Zoloth
**Clinical Center or CCC Principal Investigator*

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Vitamin D to Improve Outcomes by Leveraging Early Treatment Brain Outcomes in Vitamin D Deficient Patients (VIOLET-BUD) Investigators and Study Personnel

Beth Israel Deaconess Medical Center: Nathan Shapiro*, Valerie Banner-Goodspeed, Sharon Hayes, Ted Raddell.

Massachusetts General Hospital: Peter Hou*, Rebecca Baron, Anthony Massaro, Laura Fredenburgh, Imoigele Aisiku, Raghu Seethala, Lauren Precopio, Ellen Muldoon

University of Colorado Hospital: Adit Ginde*, Lani Finck, Michelle Howell
Montefiore Medical Center: Montefiore Moses - Michelle Ng Gong*, Aluko Hope*, Swarna Gummadi. Montefiore Weiler –Jen-Ting (Tina) Chen, Brenda Lopez, Michael Aboodi

Oregon Health and Science University: Akram Khan, Ramanpreet Kaur Randhawa, Ebaad Haq, Vincent Pinker, Olivia Krol, Kelly Nguyen

Intermountain Medical Center: Samuel M Brown*, Ithan Peltan, Michael Lanspa, Katie Brown, Brent Armbruster, Quinn Montgomery, Valerie Aston, Eliotte Hirshberg, Sarah Beesley, Mardee Merrill, Austin Daw, Carlos Barbagelata

Vanderbilt University Medical Center: Wesley H Self*, Todd W Rice*, Matthew W Semler, Adrienne Baughman, Margaret Hays, Karen Miller, Susan Mogan, James C. Jackson, Erin Collar, Mayur Patel, E. Wesley Ely, Rameela Raman, Onur M. Orun

*Site principal investigators for VIOLET-BUD

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Supplemental Methods

Participants

Inclusion criteria for VIOLET included: age ≥ 18 years old; ICU admission or intention for ICU admission from the emergency department; ≥ 1 risk factor for acute respiratory disease syndrome and mortality (pneumonia, aspiration, smoke inhalation, lung contusion, mechanical ventilation for acute respiratory failure expected to last > 24 hours, shock, sepsis, or pancreatitis); and vitamin D deficiency, defined as a serum 25-hydroxyvitamin D levels < 20 mg/dL. Key exclusion criteria for VIOLET included: inability to be randomized within 12 hours of ICU admission decision; unable to take study medication by mouth or enteral tube; serum calcium >10.2 mg/dL or ionized calcium >5.2 mg/dL; kidney stone in past year or history of multiple prior kidney stone episodes; life-sustaining treatment being withheld; expected survival < 48 hours; pregnancy. VIOLET-BUD additionally excluded those who were non-English speaking, deaf, or blind because the neuropsychological raters only spoke English and the tests had visual and aural components.

Patients were enrolled based on plasma 25-hydroxyvitamin D concentrations measured locally at enrolling sites, which was largely completed with immunoassays or a point-of-care test (FastPack IP, Sekisui Diagnostics). As part of the VIOLET parent trial, plasma 25-hydroxyvitamin D concentrations were also measured from banked plasma samples collected at baseline (pre-randomization) using liquid chromatography-tandem mass spectrometry (LC-MS/MS), which is considered a more accurate method of measuring 25-hydroxyvitamin D concentrations than immunoassays. LC-MS/MS measurement of 25-hydroxyvitamin D was completed at the University of Washington reference laboratory. All enrolled patients in VIOLET with a local measurement of serum 25-hydroxyvitamin D <20 mg/dl were included in this VIOLET-BUD study; that is, inclusion in VIOLET-BUD was not limited to patients with 25-hydroxyvitamin D concentration <20 mg/dl confirmed by LC-MS/MS.

Outcomes	Placebo	Vitamin D	Adjusted OR
Adjusted for Time to			
Adjusted median (95%CI) RBANS	82.0 (74.6,	79.5 (72.9, 84.0)	0.83 (0.50 – 1.38)
Adjusted median (95%CI) Executive	8.1 (6.1,	7.5 (5.7, 9.0)	0.77 (0.42 – 1.42)
Adjusted for enrollment vitamin D			
Adjusted median (95%CI) RBANS	81.9 (72.2,	78.8 (70.0, 84.5)	0.75 (0.37 – 1.51)
Median 95%CI) Executive Function	8.2 (6.2,	7.6 (5.8, 9.1)	0.74 (0.38 – 1.44)

e-Table 1. Sensitivity Analyses for Primary Outcomes. RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

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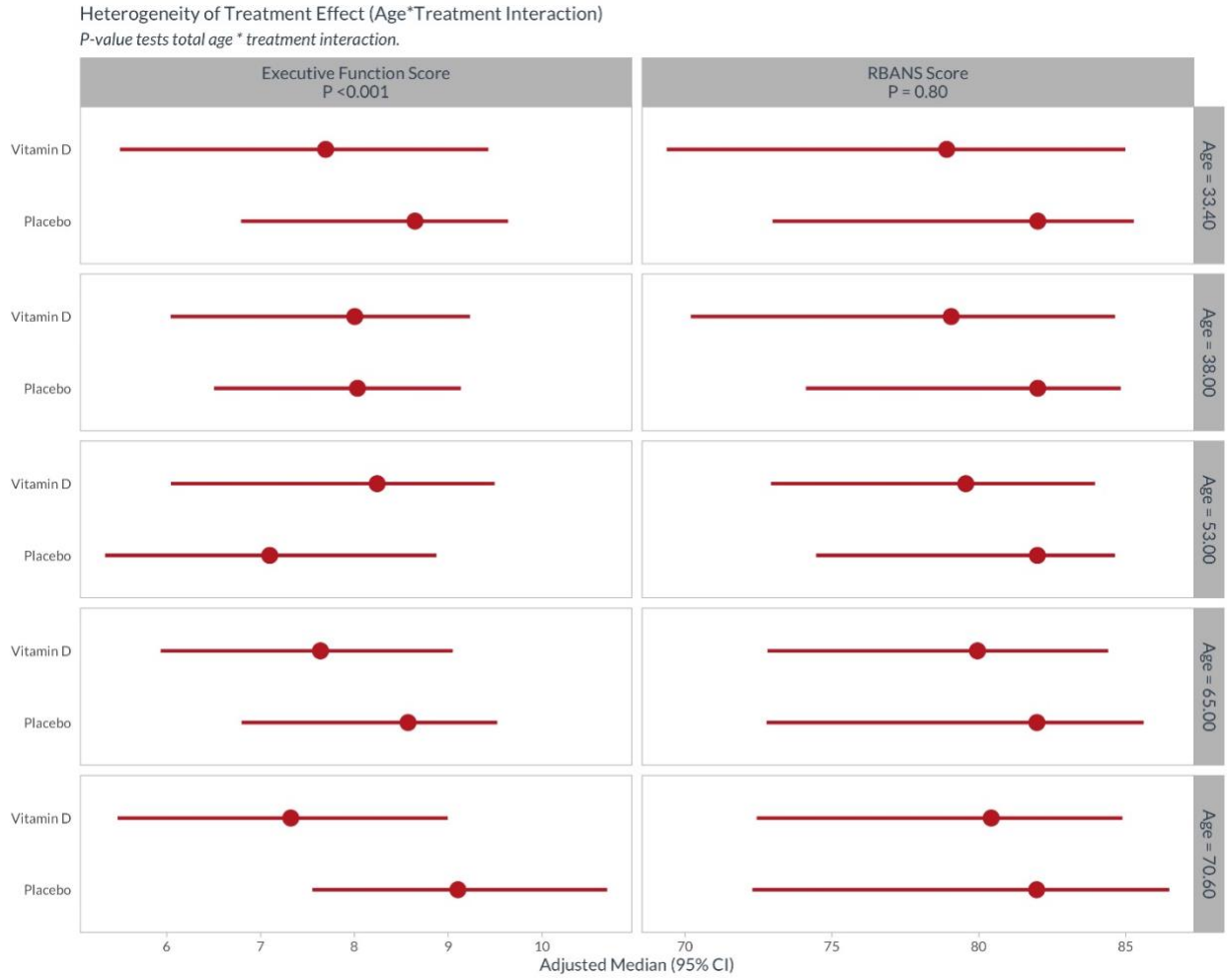
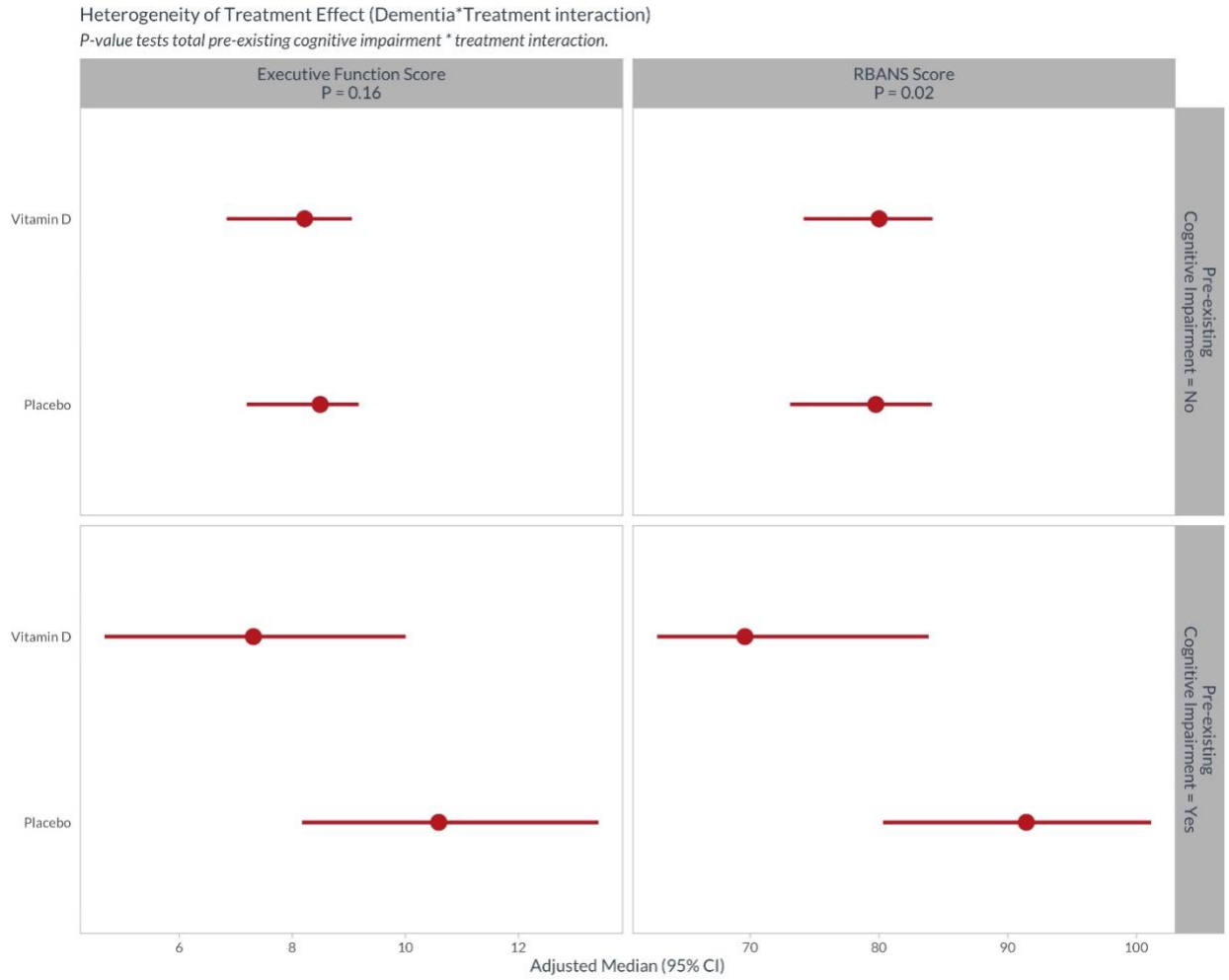
Supplemental e-Figures. Heterogeneity of Treatment Effect

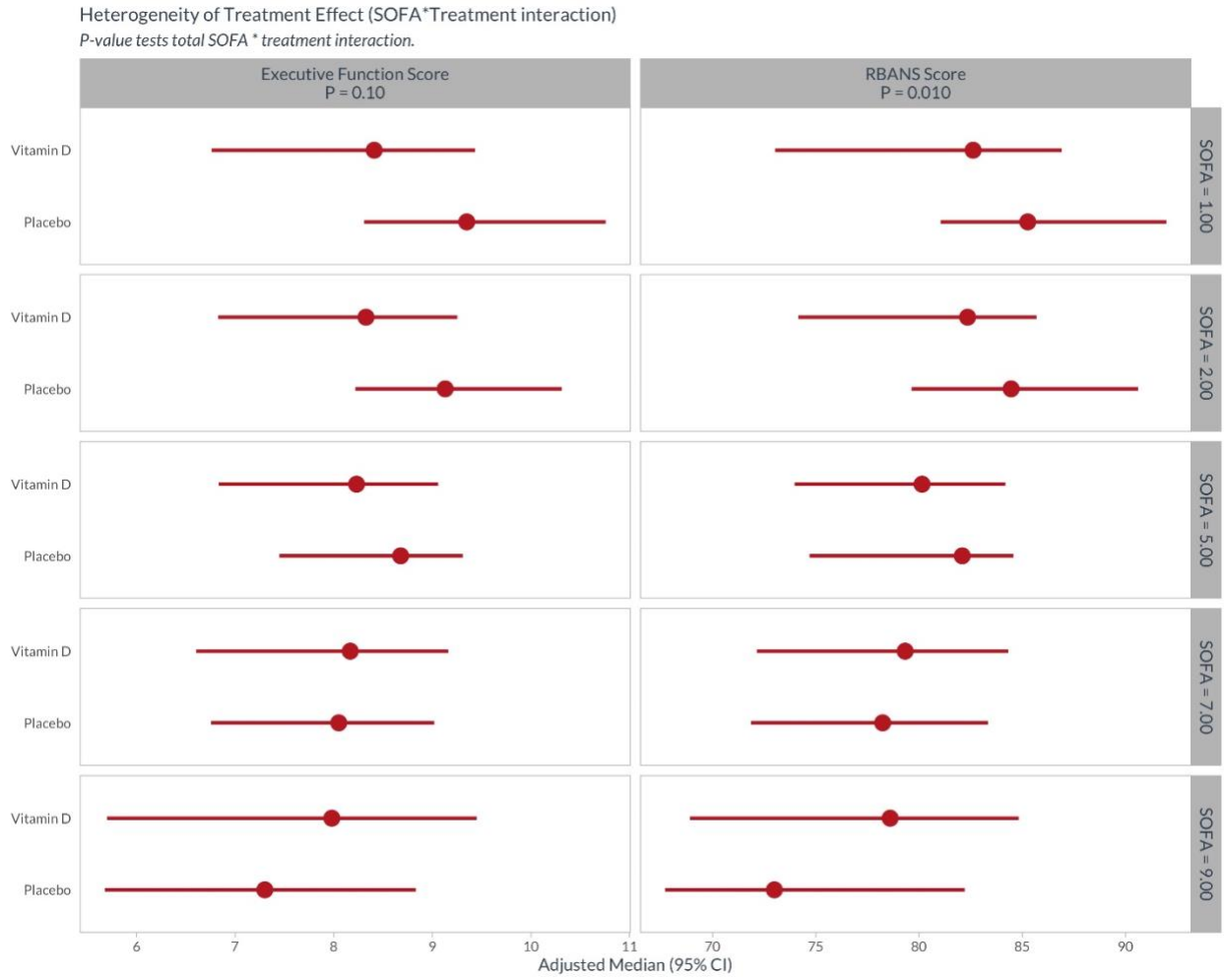
The overall results for this trial were negative, and our heterogeneity of treatment effect (HTE) analyses were limited by the small sample size. Thus, all HTE results are exploratory only. While some of the treatment interaction p-values were < 0.20, there were marked overlap in the 95% confidence intervals between the vitamin D3 and placebo groups.



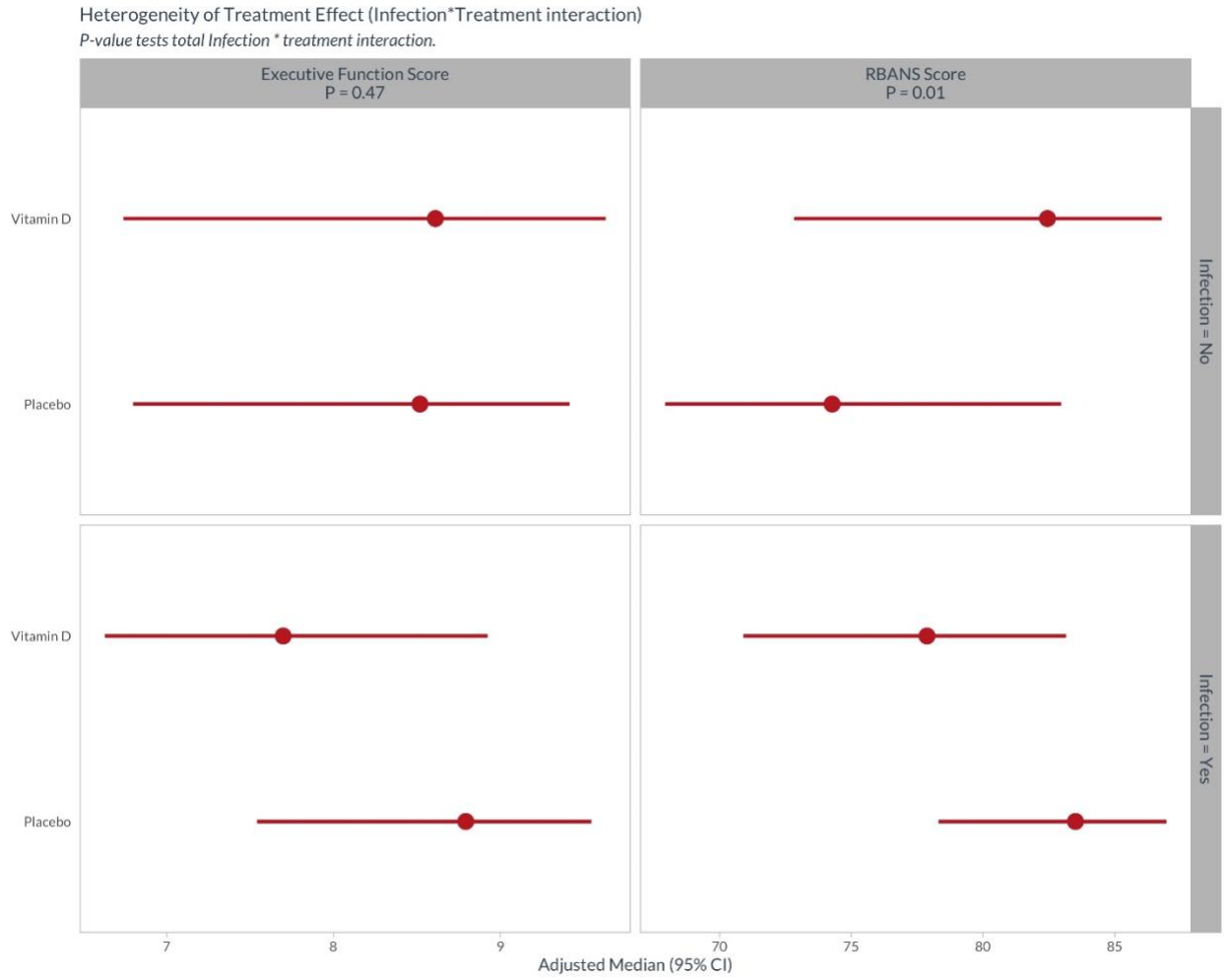
e-Figure 1. Age*treatment interaction. The adjusted medians at the 10th, 25th, 50th, 75th, and 90th percentile of age are reported. The age*treatment p-value for the executive function score was <0.001. In evaluating the pattern of HTE results, we did not identify a clinically plausible subgroup defined by age that would benefit from vitamin D3 treatment. In younger and older age groups, placebo had better scores than the vitamin D3 group. Vitamin D3 tended to have higher scores than placebo in subjects who were approximately 50 years old. However, there were considerable overlap in the 95% confidence intervals between the vitamin D3 and placebo groups.



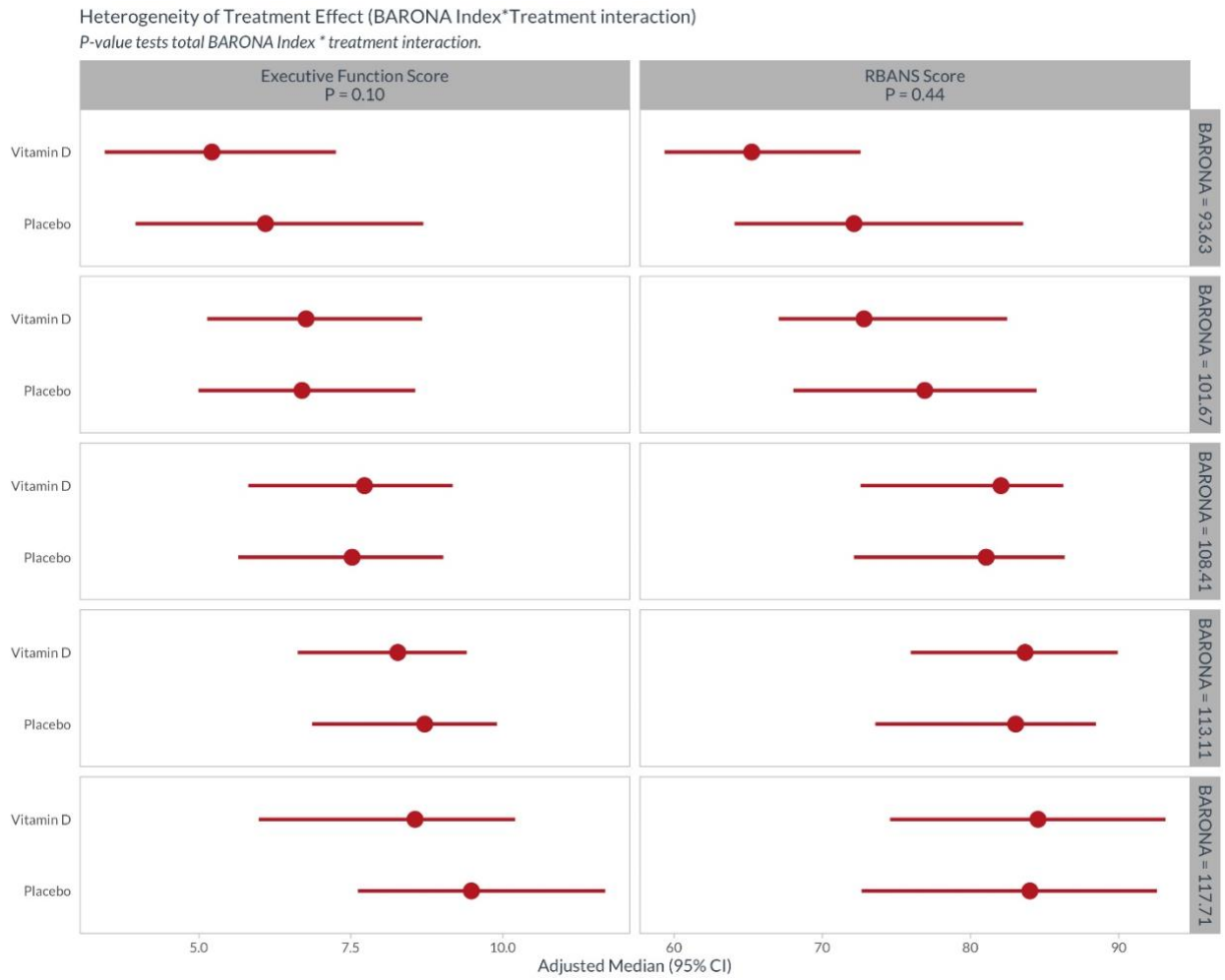
e-Figure 2. Pre-existing dementia*treatment interaction. The pre-existing dementia*treatment interaction p-values for the executive function and RBANS scores were 0.16 and 0.02, respectively. In patients with pre-existing dementia, placebo appeared to result in better executive function and RBANS scores than vitamin D3 treatment. However, there were some overlap in the 95% confidence intervals between the vitamin D3 and placebo groups.



e-Figure 3. Sequential Organ Failure Assessment (SOFA)*treatment interaction. The adjusted medians at the 10th, 25th, 50th, 75th, and 90th percentile of SOFA scores are reported. The SOFA*treatment p-values were 0.10 for both the executive function and RBANS scores. In evaluating the pattern of HTE results, we did not identify a clinically plausible subgroup defined by SOFA score that would benefit from vitamin D3 treatment. Placebo tended to result in higher executive function and RBANS scores than vitamin D3 treatment in patients with a SOFA score of 5 or less. Executive function and RBANS scores tended to be higher with vitamin D3 treatment compared to placebo only for the patients with the highest SOFA scores (scores of at least 9, representing the 90th percentile of SOFA scores in the population). However, there were considerable overlap in the 95% confidence intervals between the vitamin D3 and placebo groups.



e-Figure 4. Infection (pneumonia and sepsis)*treatment interaction. The infection*treatment p-value was 0.01 for the RBANS scores. Vitamin D3 tended to result in higher RBANS scores than placebo in patients without infection but tended to have lower scores in patients with infection. However, there were considerable overlap in the 95% confidence intervals between the vitamin D3 and placebo groups.



e-Figure 5. Barona Index*treatment interaction. The adjusted medians at the 10th, 25th, 50th, 75th, and 90th percentile of Barona Index scores are reported. The Barona Index*treatment p-value was 0.10 for the executive function scores. In evaluating the pattern of HTE results, we did not identify a clinically plausible subgroup defined by Barona Index that would benefit from vitamin D3 treatment. Placebo tended to result in higher executive function scores than vitamin D3 treatment in patients with higher Barona Indices. However, there was considerable overlap in the 95% confidence intervals between the vitamin D3 and placebo groups.