CBMRT Null Hypothesis Paper Round Up: December 2020

Welcome to the first compilation of high-quality negative and inconclusive results published over the last few months through CBMRT's Null Hypothesis collaborations with AAN/Neurology, the American Heart Association Journals, and Cohen Veterans' Bioscience/Neurotrauma Reports. These highly successful partnerships use existing journal/society/research funder infrastructure to create dedicated journal space for negative studies that are too often precluded due to publication bias.

So far, we've helped over 400 researchers get published, and these papers have yielded altmetrics at least as high as those of 'positive' results in the same journal. We will be expanding into new therapeutic areas in 2021 so please get in touch if you want to be part of our Null Hypothesis movement.

Best wishes,
Sandy
Sandra J. Petty, MBBS, FRACP, PhD
CEO, Center for Biomedical Research Transparency

Neurology Null Hypothesis

Estimated age of first exposure to American football and outcome from concussion
Jaclyn B. Caccese, Zac Houck, Thomas W. Kaminski, et al.
Neurology September 09, 2020

There has been much debate over the potential negative consequences from repeated head impacts associated with American football, focusing in particular on the later-in-life effects observed in individuals with multiple sport-related concussions. This study examined the association between estimated age at first exposure (eAFE) to American football and clinical recovery following a concussion. Earlier eAFE to American football was not associated with longer symptom recovery, worse balance, worse cognitive performance, or greater psychological distress following concussion. In these NCAA football players, longer duration of exposure to football during childhood and adolescence appears to be unrelated to clinical recovery following concussion.

In vivo distribution of α-synuclein in multiple tissues and biofluids in Parkinson disease
Lana M. Chahine, Thomas G. Beach, Michael C. Brumm, et al.
Neurology August 03, 2020

Parkinson disease (PD) accounts for a large proportion of the global burden of disease. Many clinical trials in PD have failed to identify disease-modifying therapies. To have a meaningful impact, intervention likely must occur in the earliest stages of pathology and accurate PD biomarkers are needed to enable early diagnosis, test for target engagement, and serve as surrogate measures of disease in clinical trials.

α-Synuclein – a protein that is abundant in the brain - is a lead candidate PD biomarker based on its key role in PD pathophysiology, yet studies to date are somewhat conflicting. This study assessed key gaps in knowledge by comparing inter-individual and intra-individual total α-synuclein in spinal cord and peripheral (blood, saliva) fluid compartments, and the occurrence of the protein in the colon, skin, and submandibular gland at different PD stages compared to health controls.

The study concluded that spinal cord fluid α-synuclein does not accurately distinguish patients with PD from healthy controls, and that monoclonal antibody staining for submandibular gland and skin α-synuclein is specific but not sensitive for PD diagnosis. Importantly, this study also provides the research community with samples of fluids and tissues, with which to assess promising new assays and stains. Ultimately, understanding the distribution of α-synuclein in biofluids and tissues will help advance development of PD biomarkers and our understanding of PD pathology including its progression.

Neurology Null Hypothesis

The Heart Failure Readmission Intervention by Variable Early Follow-up (THRIVE) Study: A Pragmatic Randomized Trial
Keane K. Lee, Rachel C. Thomas, Thida C. Tan, et al.
Circulation: Cardiovascular Quality and Outcomes Volume 13, Issue 101 October 2020

Readmission rates within 30 days after hospitalization for heart failure remain high (more than 20%) despite intensive efforts. In-person clinic follow-up within 7 days after discharge from a heart failure hospitalization is associated with lower 30-day readmission. However, such follow-up is resource intensive and difficult to achieve due to patient-level and health system obstacles, especially during the current coronavirus disease 2019 (COVID-19) pandemic. This study evaluated the effectiveness of an alternative 7 day follow up strategy, specifically a structured telephone visit with a nonphysician who followed protocol-driven next steps under physician supervision. It evaluated for differences in 30-day risks of readmission and death (along with overall clinic and telephone appointment utilization in the first 7 days after discharge). Among the 2,091 participants it found that early follow-up after hospitalization for HF guided by an initial nonphysician, structured telephone visit reduces the number of early in-person clinic visits required without any significant difference in 30-day readmission or mortality compared with follow-up guided by an initial physician clinic visit. It also found that completed 7-day follow-up was higher in the 1,027 patients randomized to telephone follow-up (92%) compared with the 1,064 patients assigned to physician clinic follow-up (79%). The findings suggest that there may be an opportunity to improve the efficiency of HF transitional care by using adequately trained and resourced nonphysician telephone providers supported within an integrated health care framework.

YKL-40 (Chitinase-3-Like Protein 1) Serum Levels in Aortic Stenosis
Fizza Arain, Aurelija Abraityte, Mariia Bogdanova, et al.
Circulation: Heart Failure Volume 13, Issue 101 October 2020

Aortic valve stenosis (narrowing of the aortic valve) is the most common cause of left ventricular outflow obstruction and aortic valve replacement surgery. It is the third most common cardiovascular disease after coronary artery disease and hypertension. Due to changing demographics with an increasing elderly population, the burden of aortic stenosis (AS) is predicted to increase.

Biomarkers that can monitor progression, severity, and prognosis of aortic stenosis (narrowing of the aortic valve) are needed improve risk stratification and decision-making regarding timing of aortic valve area and follow-up. This study explored whether the protein YKL-40, which has been shown to be markedly upregulated in narrowed aortic valves, is correlated with AS severity.

The study found no association between circulating levels of YKL-40 and the degree of AS severity, indicating that YKL-40 has low clinical utility as a biomarker in patients with AS. It found however that circulating YKL-40 is associated with poor prognosis generally (the protein is increased in multiple disorders and seems universally associated with adverse outcome).

[No Evidence for Erythro-Myeloid Progenitor-Derived Vascular Endothelial Cells in Multiple Organs]
Teng Feng, Zibei Gao, Shan Kou, et al.
Circulation Research Volume 127, Issue 1023 October 2020

Endothelial cells (cell layer that lines all blood vessels and regulates exchanges between the bloodstream and the surrounding tissues – see image below) are thought to emerge de novo from the mesoderm (middle layer of cells or tissues of an embryo) to form the entire circulatory system. Recently, erythro-myeloid progenitors (EMPs) have been proposed to be another possible developmental origin for blood vessels in multiple organs, including the hindbrain, liver, lung, and heart. These observations challenge the current consensus that intraembryonic vessels are thought to expand solely by the proliferation of preexisting endothelial cells. Resolution of this controversy over the developmental origin of endothelial cells is crucial for developing future therapeutics for vessel-dependent organ repair and regeneration. This study suggested that EMPs are not the origin of intraembryonic endothelial cells.