Heterogeneous Treatment Effects of an Intensive Lifestyle Intervention: Evidence from the Look AHEAD Study

Ian Davis, MA[1,2]; Peter J Huckfeldt, PhD[3]; Ann Harada, PhD[2,4]; Neeraj Sood, PhD[2,4]; Mark A Espeland, PhD[5]; Dana P Goldman, PhD[2,4]

[1]Department of Pharmaceutical and Health Economics, School of Pharmacy, University of Southern California, Los Angeles, CA, United States; [2]Leonard D. Schaeffer Center for Health Policy and Economics, School of Pharmacy, University of Southern California, Los Angeles, CA, United States; [3]Division of Health Policy and Management, University of Minnesota School of Public Health, Minneapolis, MN, United States; [4]Price School of Public Policy, University of Southern California, Los Angeles, CA, United States; [5]Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, United States.

Background

Look AHEAD (Action for Health in Diabetes) was a multi-site randomized clinical trial designed to assess the effect of an intensive lifestyle intervention (ILI) on participants aged 45-76 with type 2 diabetes and overweight or obesity compared to diabetes support and education (DSE). The trial showed positive results in reducing body mass index (**BMI**), hemoglobin A_{1c} (**HbA_{1c}**), disability, healthcare use/costs but was stopped early (median follow-up of 9.6 years) based on a futility analysis of the primary outcome of cardiovascular morbidity and mortality[1]. Cost-effectiveness of ILI over the initial 9 years was uncertain as different utility measured produced different conclusions[2]. A better understanding of whether certain participant characteristics could be used to identify those expected to be high/low responders could lead to more targeted, cost-effective interventions.

Objective

Use machine learning methods to produce flexible, data-driven identification of subgroups more affected by treatment.

1. Assess the presence of heterogeneity in treatment effects of ILI on HbA_{1c} and BMI reduction in Year 1
2. Determine whether heterogeneity persists to Year 4;
3. Assess if being a high responder for BMI reduction is predictive of being a high responder for HBA_{1c} reduction.

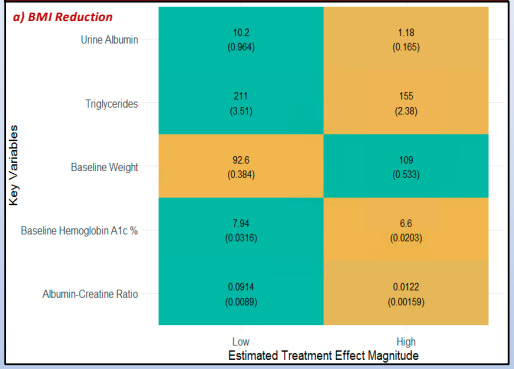
Methods

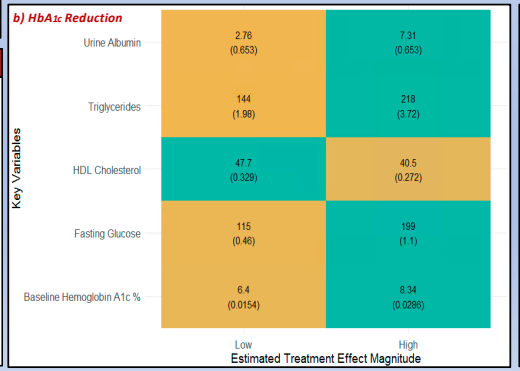
Data: We use 84 baseline covariates including medical history, physical/laboratory/psychosocial measures, quality of life, sociodemographic characteristics, and health behavior risk factors to predict Year 1, 2, and 4 HBA_{1c} and BMI reductions.

Causal forest analysis: Causal forests are built by aggregating numerous causal trees, which are an extension of regression trees. Causal trees behave similarly to regression trees but maximize variation in average treatment effect across partitions and estimate the conditional average treatment effect (CATE) For this analysis, we aggregate 4000 causal trees with minimum node sizes of 5 to create the causal forest.

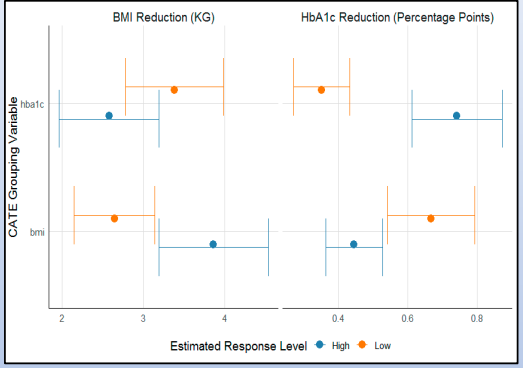
Data-driven subgroup analysis: Samples were categorized into two groups (high and low responders) based on estimated CATE terciles for each outcome. Means and standard errors for the most important variables within each group are reported along with CATES between variables and across groups.

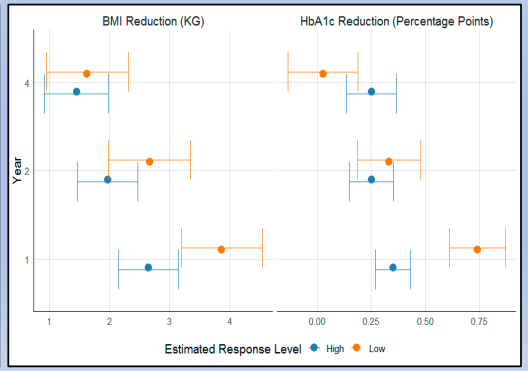
Kidney functioning and adiposity are associated with heterogeneity in Year 1 outcomes





Causal forests predict significant heterogeneity in Year-1 outcomes, but heterogeneity does not persist to later years





Results

- The sample includes 4,350 (2,143 DSE and 2,207 ILI) participants.
- There was significant heterogeneity in Years 1 and 2 for BMI reduction as well as Years 1 and 4 for HBA_{1c} reduction.
- Covariate make up between high short term HBA_{1c} responders and high BMI responders differed dramatically with low adiposity and high kidney function being a positive predictor of high HBA_{1c} but low BMI response.
- All individuals regressed with respect to BMI reduction after the first year with the high responders regressing further than the low responders. High HBA_{1c} responders were unlikely to have any measurable reduction after 4 years while the low responders were able to sustain their HBA_{1c} reduction into Year 4. (could colors be reversed in Year1-4 plot?)

Conclusion

- The causal forest method can uncover variable interactions obscured in pre-specified sub-group analyses.
- We find short-term heterogeneity in secondary outcomes of the Look AHEAD trial but analysis of short-term heterogeneity is not sufficient to determine the impact of heterogeneity on cost-effectiveness of ILIs.
- Future research should assess the likelihood of patient subpopulations having larger expected treatment effects from lifestyle interventions, weight loss pharmaceutical treatments such as GLP-1 inhibitors, or combinations of the two.

Conflicts of Interest

Mr. Davis receives funding from the National Institute on Aging (NIA) and Edwards Lifesciences. Dr Huckfeldt reported receiving grant funding from the National Institute on Aging (NIA) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), the Agency for Healthcare Research and Quality, and the Robert Wood Johnson Foundation and contract funding from the Centers for Medicare & Medicaid Services during the conduct of the study. Dr Harada reported receiving grant funding from the NIH during the conduct of the study and being a prior employee of UnitedHealth Group, receiving stock as partial compensation. Dr Sood reports receiving grants from NIH, PCORI, and Petersen Foundation and personal fees from Amazon outside the submitted work. Dr Espeland reported receiving grant funding from the NIH during the conduct of the study, receiving research funding from the Alzheimer's Association, and is compensated for service on a Steering Committee for a study conducted by Nestle. Dr Goldman reported receiving grant funding from the NIDDK during the conduct of the study and receiving grant funding from Amgen Inc, Blue Cross Blue Shield of Arizona, Bristol Myers Squibb, Cedars-Sinai Health System, Edwards Lifesciences, Gates Ventures, Genentech Inc, Gilead Sciences Inc, Johnson & Johnson, the Kaiser Family Foundation, Novartis AG, Pfizer Inc, F. Hoffmann–La Roche AG, and Walgreens Boots Alliance Inc; receiving personal fees from the National Railway Labor Conference and Biogen Inc; being a cofounder of EntityRisk with equity; and receiving travel support from The Aspen Institute outside the submitted work.

Contact

Ian Davis, MA, ijdavis@usc.edu

Funding

This study was funded by NIDDK grant R01DK107552 and NIA U01AG073697. Look AHEAD was funded by U01DK57136.

Citations

[1]Wing et al., 2013 *NEJM*. [2]Zhang et al., 2021 *Diabetes Care*.