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The relation between hyperlipidemia, hypertension, and downstream cognitive and neuroanatomical function

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THE RELATION BETWEEN HYPERLIPIDEMIA, HYPERTENSION, AND DOWNSTREAM COGNITIVE AND NEUROANATOMICAL FUNCTION

by

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Dedications

To my sister, my parents, and my wife; for caring, caring too much, and feigning indifference about this project.

Acknowledgments

Data for this project was collected by the Framingham Heart Study (FHS). Hundreds of partitioned datasets were received from FHS, with related datapoints separated across many data tables according to exam cycle, criteria of interest, or previously constructed in order to address a specific research question from a previous internal or outside data request. The process of data preparation, including dataset construction and the creation of regression-based norms, took approximately 1 year and the full-time effort of a talented research assistant, in addition to the persistent contributions of the Dr. David J. Libon, the lab director, and participating graduate students.

Dr. Libon has been a constant source of support, instruction, and wisdom in the completion of my graduate training. This study would simply not have taken place without his mentorship and patience. His manifest competence and dedication to neuropsychology set the goal markers for what I seek from my own education.

Abstract

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THE RELATION BETWEEN HYPERLIPIDEMIA, HYPERTENSION, AND DOWNSTREAM COGNITIVE NEURAL ANATOMICAL FUNCTION
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Doctor of Philosophy

Objective: Cardiovascular risks (CVR) such as hypertension and hyperlipidemia play a critical role in the emergence of dementia syndromes. Medication to treat CVR may not obviate downstream risk for cognitive change. Methods: To examine the relation between history of treatment with medications to treat CVR and cognitive outcomes, participants were seen at time points ~7 years apart, completed neuropsychological evaluations, assessed for history of treatment with medication associated with hypertension and hyperlipidemia as indicators of CVR, and classified into 3 groups: Not Treated, Inconsistently Treated, and Consistently Treated. Regression models associating neuropsychological outcome measures of cognition and CVR were explored and refined within a "test dataset," and analyses were replicated using an independent "validation dataset." Result: Most outcome measures were not significant, including episodic memory and executive tests. A main effect was found for hypertension for the Similarities subtest and the Digit Symbol Test; participants with no hypertension treatment history obtained better scores compared to other groups. While some measures were sensitive to impairment, MRI parameters were not associated with CVR indicators. Conclusion: Between group differences on outcome measures of cognition were detectable in the presence of well-controlled blood pressure, indicating that downstream cognitive consequences persist in the presence of intervention for hypertension.

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Chapter 1

Introduction

Cognitive decline associated with dementia such as Alzheimer's disease (AD) is a leading concern among older and aging populations, with projections indicating that as many as 14 million Americans may be affected by AD by the year 2050 (Alzheimer's Association, 2019). It is now well-known that vascular disease, including alterations in the blood-brain barrier (Emrani et al., 2020; Nation et al., 2019) and cardiovascular (CV) risks such as hypertension and elevated lipids, plays a role in the emergence of AD. Indeed, these CV risks, well-known to be associated with stroke, have emerged as significant risk factors for AD (Iulita & Girouard, 2017; Poels, Ikram et al., 2012). It is therefore increasingly important that CV risk factors be closely observed within the context of dementia risk and as a possible avenue for prevention and intervention of dementia onset (Knopman et al., 2018).

Longitudinal research has demonstrated that the incidence of dementia declines when CV and cerebrovascular disease are controlled (Satizabal, Beiser, & Seshadri, 2016; Schrijvers et al., 2012; Wu et al., 2017). It is increasingly evident that dementia arising from mixed aetiologies involving proteins such as amyloid and tau, in addition to vascular disease, is the most common pathway for insidious onset dementia (Emrani et al., 2020; Sweeney et al., 2019). Common CV risk factors include hypertension, hyperlipidemia, diabetes, smoking status and history, obesity, alcohol consumption, arterial stiffness and pulse pressure, atrial fibrillation, diet, and body mass index (BMI) score; as well as genetic vulnerabilities, including apolipoprotein epsilon 4 (APOE4) status (Institute of Medicine, 2015).

Community-Based Longitudinal Studies

The Framingham Heart Study (FHS) is a multigenerational, longitudinal community study of CV health and cognition in a primarily white population recruited from the Massachusetts town of Framingham. The original FHS cohort consisted of 5,209 participants first recruited in 1948. At the time of enrollment, the mean age was 44 years (range 28–62 years), 55% were female, the majority were white and of middle socioeconomic class. Participants returned for regular exam cycles roughly three to five years apart.

Research from the FHS has linked cognitive impairment with CV risk factors such as hypertension (M. F. Elias, Wolf, D'Agostino, Cobb, & White, 1993; Farmer et al., 1987, 1990). Studies employing the Framingham Stroke Risk Profile (Wolf, D'Agostino, Belanger, & Kannel, 1991), a composite measure of stroke risk, have established and supported that CV risk factors contribute not just to stroke risk, but also insidious onset dementia. CV risk factors are also associated with smaller cerebral brain volume and poorer performance on tests measuring executive function, visuospatial processing, attention, planning and psychomotor performance (Seshadri et al., 2004). P. K. Elias, Elias, D'Agostino, Sullivan, & Wolf (2005) also found that elevated total cholesterol was associated with declining performance on measures of attention/concentration, abstract reasoning, and verbal fluency. In another study, M. F. Elias, Elias, Sullivan, Wolf, & D'Agostino (2003) showed the negative association of hypertension on immediate and delayed visual and auditory episodic memory in men, but not women. For male participants, the relation was compounded by obesity.

Research from the Rotterdam study, a similarly designed, community-based longitudinal epidemiological study, likewise pointed to an association between CV health and cognition, finding reduced cortical gray matter thickness on magnetic resonance imaging (MRI) to be positively associated with elevated diastolic blood pressure and higher HDL cholesterol levels (van Velsen et al., 2013). The Rotterdam study has also been a source of support for the connection between blood-brain barrier integrity and CV health, as demonstrated in a study by Wieberdink and colleagues (2011) that found hypotriglyceridemia increased the risk for intracerebral hemorrhage and infratentorial cerebral microbleeds. White matter lesions have also been reported to be more common among participants with uncontrolled hypertension (Poels, Zaccai, et al., 2012).

What is interesting about past research is the nonlinear relation between CV risk factors like blood pressure, triglycerides and cholesterol, and cognitive and neuroanatomical outcomes, as negative outcomes are associated with falling above or below an ideal range for risk factor measures. In addition, the age of the population being considered is important when interpreting CV risk and outcomes, with some research indicating that age modifies the relation of CV risk on cognition and mortality risk (Beckett et al., 2008; Blom et al., 2013). Comorbidity involving multiple CV risk factors increases risk for emergent dementia. In addition to diabetes (van Velsen et al., 2013), other CV factors including homocysteine levels (Lu et al., 2019), sex assigned at birth (Matthews et al., 2016; Satizabal et al., 2016), smoking status, and BMI (Dregan, Stewart, & Gulliford, 2013) can compound the extent to which cognitive abilities are negatively impacted. To better reflect the relations among risk factors, composite

measures such as the Framingham Stroke Risk Profile (Wolf et al., 1991) have been developed.

Keeping these factors in mind, it should not be neglected that hypertension and hyperlipidemia are generally closely monitored and controlled. Thus, the chosen method for intervention may further complicate the picture when trying to understand the extent these leading CV risks may signal vulnerability to cognitive decline. As such, the mere fact of being treated for a condition is often considered synonymous with having the condition (Institute of Medicine, 2015).

Hypertension and Treatment

For most studies, a participant is considered to be hypertensive when average systolic blood pressure is at or above 140 mmHg, diastolic blood pressure is 90 mmHg or above, or if an individual is receiving antihypertensive medications (Institute of Medicine, 2015). Six commonly prescribed drug classes of medication for antihypertensive treatment are thiazides, beta-blockers, alpha-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin-II receptor blockers (Wright, Musini, & Gill, 2018).

Reduction of stroke risk is the most obvious cognitive benefit of well-managed blood pressure, and is well-associated with antihypertensive drug use (Wright et al., 2018). Additionally, robust longitudinal data supports a relation between blood pressure and cognitive decline (M. F. Elias, Goodell, & Dore, 2012; Etgen, Sander, Bickel, & Förstl, 2011; Unverzagt et al., 2011), with more consistent associations observed for midlife hypertension than later-life. Lamar and colleagues (2020) reported a negative association between decision making and blood pressure among older individuals.

A systemic review by Walker, Power, & Gottesman (2017) strongly supports the relation between age, duration/chronicity of hypertension, and cognitive decline, emphasizing in particular that late-life cognitive decline and dementia was consistently related to elevated hypertension measures during mid-life. The collective research of early- and mid-life indicators of hypertension corroborates the evidence from longitudinal studies that the downstream consequences of hypertension on brain anatomy and cognitive functioning are cumulative. Some have gone so far as to argue that studies of interventions in later life may underestimate the protective ability of antihypertensive medications to affect cognition (Institute of Medicine, 2015; Qiu, Winblad, & Fratiglioni, 2005). Nonetheless, the ability for antihypertensive drugs to curb cognitive consequences of hypertension remains uncertain. Antihypertensive medications may have some cognitive protective effects (Rouch et al., 2015; Streit, Poortvliet, Den Elzen, Blom, & Gussekloo, 2019), but studies frequently return inconclusive findings (Chang-Quan et al., 2011; Ligthart & Press, 2010; van Dalen, Moll van Charante, van Gool, & Richard, 2019).

Inconsistent findings, as reported in Rouch et al., (2015) and Staessen et al., (2011), are likely indicative of differences among antihypertensive drug classes with respect to cognition. For example, Peters (2019) found that treatment with calcium-channel blockers may have no benefits for preventing cognitive decline. Adherence, duration of treatment, and dosage level are other likely causes of varying findings for hypertension and cognitive outcomes.

Hyperlipidemia and Treatment

Hyperlipidemia is characterized by a high level of blood lipids, including triglycerides and cholesterol (Crawford et al., 2010), and has been implicated in cognitive decline (Etgen et al., 2011). Fifty percent of older Americans are estimated to have hyperlipidemia (Crawford et al., 2010). Hyperlipidemia may be a stronger risk factor for midlife cognitive decline than later life (Reynolds, Gatz, Prince, Berg, & Pedersen, 2010; Van Vliet, 2012). Consequently, as with hypertension, early life interventions may demonstrate greater protective effects than mid- and late-life interventions. For example, interventions with B vitamins, including niacin, in young adulthood was associated with better cognitive function outcomes, particularly psychomotor speed as measured with the Digit Symbol Substitution test and executive function measured with the Stroop Test (Qin et al., 2017).

Intervention with medication may involve a variety of medication types with differing mechanisms of action, including statins; non-statin drugs such as B-vitamins, omega-3 supplements, and anti-triglycerides; or a combination of all. Statin and non-statin drugs are often handled separately in literature when discussing cognitive consequences of treating hyperlipidemia with medication. Statins are the preferred treatment unless patients are poor responders to statin therapy, though non-statins may also be combined with statins if indicated (Catapano et al., 2016).

There is inconclusive evidence that hyperlipidemia treatments have a significant impact on cognitive aging (Catapano et al., 2016; Gauthier & Massicotte, 2015; Institute of Medicine, 2015). Although statins have previously been associated with potential

memory loss (FDA, 2012), these results have not been consistently upheld (McGuinness, Todd, Passmore, & Bullock, 2009; Ong et al., 2018; Richardson et al., 2013).

Differences in methodology and design may be partly to blame for the lack of consensus over the past two decades of research. In a recent review, Tan and colleagues (2019) suggest that randomized, double-blind, placebo-controlled studies that returned negative findings related to statins and cognition were generally underpowered, differed in participant demographics, and used a variety of cognitive measures differing from measures used in studies reporting significant associations between statins and cognition.

Another explanation that may underlie the inconsistent findings associating cognition and hyperlipidemia treatment is the differences in the mechanisms of action among statin-type drugs. Highly lipophilic statins (atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin, and pitavastatin) more easily cross the blood-brain barrier than hydrophilic statins (pravastatin and rosuvastatin; Schachter, 2005). In most cases of statin-related cognitive impairment, the association has been with the more lipophilic statins (Rojas-Fernandez & Cameron, 2012; Wagstaff, Mitton, Arvik, & Doraiswamy, 2003).

Previous studies from the FHS have been mixed. Tan and colleagues (2003) found no relation between cholesterol measures and AD among first generation study participants. Examining the same cohort, Silverman and Schmeidler (2018) observed that non-use of statins was associated with greater risk for cognitive decline as measured by performance below 25 on the Mini-Mental States Exam (MMSE). However, the relation between mid-life hyperlipidemia indicators and later life cognition was attenuated by age at follow up, with an inflection point for individuals older than 85. In

these oldest participants, hyperlipidemia risk factors were inversely related with risk for dementia. This may reflect a survivorship bias, with the oldest of participants reflecting a subset of "protected" individuals who remain cognitively intact despite the presence of risk factors. The reversal of the risk association may also be a consequence of having too few time points to model a quadratic relation between cholesterol and cognition.

Treatment of hyperlipidemia with statins is considered safe and beneficial for those who respond to them (Adhyaru & Jacobson, 2018; Catapano et al., 2016); however, there remains no consensus on cognition. Fibrate use, a non-statin alternative, is associated with poor visual memory as assessed with the Benton Visual Retention Test for women, but not for men, over a 7-year period (Ancelin et al., 2012). Other domains of cognition that were tested, including processing speed as measured by the Trail Making Tests, overall cognition as measured by the MMSE, and verbal fluency/semantic access as measured by Isaacs Set test, were not significant.

Combined treatment with statins and non-statins is common, but no more associated with consistent cognitive findings than either treatment type individually. For example, lipid-modifying treatment combining statins and ezetimibe can reduce the loss of cerebral volume related to atrial fibrillation, particularly in the medial temporal lobe (Lappegård et al., 2013; Tendolkar et al., 2012). This is hypothesized to be related to the reduction in the effects of inflammation on cognition.

The Current Study

In summary, the relation between hyperlipidemia, hypertension, and downstream decline in cognitive abilities and neural anatomical function is strongly indicated in the literature, but not well understood. In particular, whether interventions that are beneficial

for CV risk are associated with any measurable benefits on cognitive performances remains an open question. The near-universal availability of treatment for individuals with CV risk is an important consideration when attempting to understand cognitive vulnerability.

The current study was designed to address these questions through an analysis of data available from the FHS utilizing a Cumulative Analytic Strategy (Fife & Rodgers, 2019) involving Rough Confirmatory Data Analysis (CDA) into a Strict CDA approach using a holdout sample. This approach was intended to articulate the relation between treatment history for CV risk factors and cognitive outcomes. In particular, the current research intended to answer the following question - Is there a negative outcome for cognition and brain anatomy associated with whether one is identified as treated for CV risk; despite the fact that treated indicators for CV risks are generally within an acceptable range? Put another way, does generally successful treatment of CV risks obviate downstream neuropsychological impairment and putative neuroanatomic compromise as measured with MRI regions of interest?

Study Aims

This central question was addressed through four aims: 1.) Do adults who endorse a history of treatment for hypertension or hyperlipidemia show worse neuropsychological (NP) outcomes than participants who do not? 2.) As well, do adults who endorse a comorbidity of treatment for hypertension and hyperlipidemia show worse neuropsychological outcomes than those participants without comorbidity? 3.) Recent research suggests that visual episodic memory measures, as compared to verbal episodic memory tests, may be more sensitive to emergent decline (Wasserman et al., 2019).

Thus, the current research assessed for modality-associated sensitivity within episodic memory testing relating to treatment history/combination of treatment histories. 4.) Are relations among treatment history and neuroanatomy measured using MRI scans consistent with findings from neuropsychology in Aim 1?

Hypotheses

Hypothesis 1 was constructed to address Study Aims 1, 2 and 3. Hypothesis 2 addresses Study Aim 4.

Hypothesis 1a. Poorer NP outcomes were expected for individuals with treatment history than individuals with less or without treatment history across NP domains known to be susceptible to controlled, but nonetheless chronic, CV illness. Those with a consistent history of treatment (Consistent Treatment Group) for hypertension were expected to perform more poorly on these tasks than participants with inconsistent history (Inconsistent Treatment Group) of treatment or no history (No Treatment Group). Having some history (i.e., Inconsistent Treatment Group) was expected to be associated with worse performance on measures than having no history (No Treatment Group). The same pattern was expected for treatment history for hyperlipidemia.

Hypothesis 1b. CV risk factors were expected to have a compounding impact when multiple CV risks are present. If an interaction were present, it was expected that NP measure performance would decline inversely with greater degree of treatment history for each CV risk factor. Because of the uncertainty in the existing literature surrounding these relations, observed effect sizes related to Hypotheses 1a and 1b were reported; however, interpretation of the results of analysis was hedged to consider the

clinical value of small effect sizes and the provisional nature of results obtained through a Rough CDA paradigm (Fife & Rodgers, 2019).

Hypothesis 1c. In the presence of significant findings for episodic memory, delayed recall on a visual episodic memory test (WMS-Visual Reproduction) was expected to be more sensitive to cognitive impairment, and therefore would yield a larger effect size, than performance obtained from a verbal episodic memory test (WMS-Logical Memory). A meaningfully larger effect size would explain at least 1% additional variance.

Hypothesis 2. It was expected that there would be more gray matter volume in the never treated groups for both lipids and hypertension compared to the consistently treated groups. The inconsistently treated group was expected to fall between the mean values of the other two groups.

Chapter 2

Methods

Sample & Demographics

Data for the present study, including participant medication history, CV measures, and NP test performance, were obtained from the FHS through a research contract with Rowan University School of Osteopathic Medicine (Rowan SOM; IRB protocol number: 2016001189). The so-called "offspring cohort" was recruited in 1971, consisting of 5,124 offspring of the original cohort and their spouses. At enrollment, the mean age was 36 years (range 5–70 years), 52% were women. As with the original cohort, follow-up exams were completed in cycles held approximately 5 years apart, with most variance in scheduling related to participant availability. In addition to a "core exam" focused on CV factors, FHS participants were invited to participate in ancillary study exams. Recruitment for an on-going study of cognition, dementia, and NP performance for the Offspring Cohort began in the 7th core exam cycle. More information on the FHS cohorts and exam cycles can be found in Ang, Joshi, & Au (2020).

Data received from FHS included medical, CV, cerebrovascular, NP, psychological, and mortality data for all Framingham cohorts, as well as on-going and concluded sub-studies for other heart health-related topics such as stroke risk, pregnancy, bone density, diabetes, and radiological imaging. For data security, all datasets were received without identifying information such as names and birthdays. Measures of CV health and NP performance were collated and organized to create a sample of 1,160 participants who had consistently participated in the three most recent exam cycles

(Exams 7, 8 and 9) of the FHS Offspring Cohort; and who also attended separate, corresponding NP evaluations.

Of the 1,160 participants identified for the current research, 44 participants were determined to have evidence of stroke history or dementia and were excluded. Of the 1,116 remaining participants, 56 participants did not have medication use data at both exam 8 and exam 9, and were also excluded. The remaining 1,060 participants formed the final study sample. Of those who met criteria for study inclusion, a subsample (n = 823) had also contributed MRI data concurrent with their NP evaluation. Demographic information for the overall and MRI samples are available in Table 1.

Table 1

Demographics for Total Sample and MRI Subsample

	Total Sample (n=1060)			MRI Subsample (n=823)		
Age (years) Mean (sd)	71.45 (8.03)			70.89 (7.77)		
Years of Education						
	<12 years	28	2.6%	<12 years	19	2.3%
	High School Graduate	212	20%	High School Graduate	158	19.2%
	Some College	307	29%	Some College	228	27.7%
	College Graduate	513	48.4%	College Graduate	418	50.8%
Female Sex at Birth (%Female)		616	58.1%		468	56.9%
Body Mass Index (BMI; kg/m^2)		28.35 (5.37)			28.00 (5.08)	

Cardiovascular Risk and Measurement of Treatment History

The CV features of interest were whether a patient was treated for 1.) hypertension, and 2.) lipids, at exams 8 and 9. This information was expressed as two categorical variables with three levels each: 1.) Never Treated, did not endorse treatment

at exam 8 or exam 9; 2.) Inconsistently Treated, endorsed treatment at only 1 time point; and 3.) Consistently Treated, endorsed treatment at both exam 8 and 9. To determine for which level of treatment participants met criteria, two approaches were considered: whether participants reported treatment history for hypertension and lipids as part of a self-report interview during the cycle core exam, and whether participants endorsed taking medication at core exam cycle 8 and 9 that treats hypertension and/or hyperlipidemia.

While both approaches rely on self-report, cross tabulation of both grouping criteria indicated that participant knowledge of medication purpose was a limiting factor on the reliability of reported treatment history (see Table 2 & 3). Participants occasionally endorsed no treatment when being treated with medication, as well as treatment when not being treated with medication, although this was less frequent and may reflect the heterogeneity of treatment approaches for CV risk factors in addition to medication, such as diet and exercise.

Table 2

Comparison of Self-Report and Medication-Endorsed Hypertension Treatment History

		Self-Report History of Hypertension			Total
		Never Treated	Inconsistently Treated	Consistently Treated	
History of Hypertension Medication	Never Treated	372	1	1	374
	Inconsistently Treated	38	124	7	169
	Consistently Treated	28	38	450	516
Total		438	163	458	1059

Table 3

Comparison of Self-Report and Medication-Endorsed Hyperlipidemia Treatment History

		Self-Report History of Hyperlipidemia			Total
		Never Treated	Inconsistently Treated	Consistently Treated	
History of Hyperlipidemia Medication	Never Treated	320	0	0	320
	Inconsistently Treated	126	126	2	254
	Consistently Treated	30	38	417	485
Total		476	164	419	1059

Early designs of the study relied on the self-report approach; however, preliminary analysis indicated that study participants might have anywhere between a well-developed understanding of their medical treatment or a poor grasp on it. While interesting within the context of treatment and adherence, FHS is a community study of CV health and cognition, and these self-report items are informed by the individual's understanding of their medical history. As a consequence, the self-report method for grouping participants is less reliable than the approach based on endorsed medication history. Groups were therefore based on whether an individual endorsed using an antihypertensive or lipid-modifying agent at exam 8 and/or exam 9.

For the total sample, groups for both treatment history for hypertension (TxHxHypertension) and treatment history for hyperlipidemia (TxHxLipids) significantly differed in age (TxHxHypertension: $F[2,1057] = 60.459$, $p < .001$; TxHxLipids: $F[2,1057] = 24.136$ $p < .001$), education (TxHxHypertension: $F[2,1057] = 5.010$, $p < .01$; TxHxLipids: $F[2,1057] = 3.576$, $p < .05$), and sex at birth (TxHxHypertension: $F[2,1057] = 14.919$, $p < .001$; TxHxLipids: $F[2,1057] = 6.139$, $p < .002$). For the MRI subsample, groups differed for age (TxHxHypertension: $F[2,820] = 51.303$, $p < .001$; TxHxLipids:

F[2,820] = 18.742, $p < 0.001$), education (TxHxHypertension: F[2,820] = 3.815 , $p < .05$; TxHxLipids: F[2,820] = 3.421, $p < .05$), and sex at birth (TxHxHypertension: F[2,820] = 9.667, $p < .001$; TxHxLipids: F[2,820] = 4.143, $p < .05$). Group distributions and demographics are displayed in Tables 4 and 5.

Table 4

Demographics for Hypertension Treatment Groups in the Total Sample and MRI Subsample

		Total Sample (n=1060)				MRI Subsample (n=823)		
		Never Treated	Inconsistently Treated	Consistently Treated		Never Treated	Inconsistently Treated	Consistently Treated
Group Size		374	170	516		308	129	386
Age (years) Mean (sd)		68.42 (7.70)	70.41 (7.33)	74.01 (7.64)		67.86 (7.41)	70.28 (7.26)	73.52 (7.31)
Education		3.34 (0.85)	3.23 (0.86)	3.15 (0.86)		3.37 (0.82)	3.26 (0.85)	3.19 (0.86)
	<12 years	6	4	16	<12 years	3	2	12
	High School Graduate	78	38	126	High School Graduate	64	29	88
	Some College	76	41	87	Some College	61	29	100
	College Graduate	214	87	230	College Graduate	180	69	186
Female Sex at Birth		256 (68.4%)	100 (58.8%)	260 (50.3%)		202 (65.6%)	76 (58.9%)	190 (49.2%)
Body Mass Index (BMI; kg/m^2)		26.70 (4.46)	28.31 (5.42)	29.58 (5.67)		26.76 (4.50)	28.41 (5.22)	29.34 (5.41)

Table 5

Demographics for Hyperlipidemia Treatment Groups in the Total Sample and MRI Subsample

		Total Sample (n=1060)				MRI Subsample (n=823)		
		Never Treated	Inconsistently Treated	Consistently Treated		Never Treated	Inconsistently Treated	Consistently Treated
Group Size		320	255	485		262	197	364
Age (years) Mean (sd)		69.37 (8.47)	70.76 (7.64)	73.20 (7.53)		69.02 (8.24)	70.13 (7.43)	72.66 (7.22)
Education		3.25 (0.83)	3.34 (0.84)	3.16 (0.88)		3.26(0.83)	3.40 (0.81)	3.21 (0.87)
	<12 years	4	3	19	<12 years	3	3	11
	High School Graduate	72	53	117	High School Graduate	59	37	85
	Some College	78	60	123	Some College	63	41	86
	College Graduate	166	139	226	College Graduate	137	116	182
Female Sex at Birth (% Female)		200 (62.5%)	162 (63.5%)	254 (52.4%)		158 (60.3%)	123 (62.4%)	187 (51.4%)
Body Mass Index (BMI; kg/m^2)		27.31 (5.24)	28.52 (5.63)	28.95 (5.23)		27.23 (5.00)	28.60 (5.74)	28.75 (4.91)

The following antihypertensive drug classes were considered indicative of antihypertensive treatment for the purposes of this study (Wright et al., 2018): thiazides, beta-blockers, alpha-blockers, calcium channel blockers, ACE inhibitors, and angiotensin II receptor blockers. Medications considered lipid-modifying agents included statin and non-statin drugs (Catapano et al., 2016). The following were considered non-statins: Bile Acid Sequestrants, a medication that reduces the volume of bile acid in the blood stream and contributes to the synthesis of cholesterol by the liver; Fibrates, which interact with lipoprotein metabolism; Omega-3 fatty acids, mainly taken to lower triglyceride levels and indirectly reduce LDL concentration; Ezetimibe, a medication that targets lipid absorption in the intestines and is typically paired with a statin; Niacin, a B vitamin

influencing the production of blood fat and derived from nicotinic acid; and PCSK9 Inhibitors, a newer statin-alternative prescribed as a preventative for CV disease through inhibiting the PCSK9 protein involved in plasma LDL concentration. Of these interventions, only use of PCSK9 Inhibitors was not endorsed by any participants.

While the use of medication history was expected to be a more reliable indicator of group membership than participant-endorsed treatment history, this approach was not without limitations. Firstly, it did not control for any instances of polypharmacy; that is, the use of multiple medications to treat a particular medical issue or set of issues, and the possibility of drug interactions that may affect efficacy. In this same vein, changes in medication class/specific medication between exams was not monitored with this approach. Given that changes in a treatment regimen are likely to be reactive and based on how well the individual responds to treatment, adjustments to intervention with medication may obscure some of the relation between CV risk and cognitive performance. Secondly, being prescribed a medication does not guarantee adherence. Participants may discontinue medication without consulting a physician due to undesired side-effects, or present with low adherence due physical and/or cognitive limitations, or psychological conditions such as depression (Hennein et al., 2018). Individuals taking a combination of statins and non-statins are more likely to discontinue due to adverse events compared to statins alone (Chaiyasothi et al., 2019). Also, a participant endorsing treatment with a medication does not guarantee that the medication is being taking according to instruction. Lastly, other health and CV factors, such as type 2 diabetes status, may modify responding to antihypertensives and lipid modifying agents (Institute of Medicine, 2015).

Neuropsychological Measures of Cognition

The FHS neuropsychological protocol of tests was a comprehensive, 1-hour to 1.5-hour evaluation of multiple domains of cognition and had been updated at several times since its initial administration (Ang et al., 2020; Au, Piers, & Devine, 2017). The full protocol of tests, as of the 9th exam cycle of the Offspring Cohort, consisted of 23 distinct tasks adapted in part or in whole from widely-used published tests and protocols. Due to the high number of available NP measures within the FHS dataset, *a priori* considerations were used to select an exemplar set of six NP tests that could each be related to particular domains of cognition; either Executive Control/ Processing Speed, Naming/Lexical Access, or Episodic Memory. These considerations included how well-associated the selected task was with the intended domain and the relative sensitivity of these tasks to CV aetiologies of cognitive impairment (Frances, Sandra, & Lucy, 2016).

Selected Neuropsychological Tasks and Domains

Processing speed. This domain was assessed with the Verbal Fluency test (Spreen & Strauss, 1990) and the Digit-Symbol Coding subtest from the Wechsler Adult Intelligence Scales-Revised (WAIS-R; Wechsler, 1981).

Naming/ lexical access. Language and lexical access were assessed with a 30-item version of the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) and the Similarities subtest from the WAIS-R (Wechsler, 1981).

Episodic memory. Because of previous research indicating differences in the relative sensitivity of visual and auditory episodic memory to cognitive change (Wasserman et al., 2019), both a visual and an auditory task of episodic memory were included. The Visual Reproduction task – delayed free recall from the Weschler Memory

Scale (WMS; Wechsler, 1945) was used to assess visual episodic memory and the WMS Logical Memory task – delayed free recall (Wechsler, 1945) was selected to assess auditory episodic memory.

Considerations for Memory Measures

Recognition memory tasks were considered in place of delayed free recall tasks, but were discarded due to the truncated range of the recognition measure used for Visual Reproduction, which had a maximum possible score of four and a minimum possible score of zero. This would have negatively affected the ability to make relative comparisons to verbal memory recognition, which had twelve response items.

Regression-Based Normative Approach

Generally speaking, normed, standardized scores are preferable to raw performance measures when interpreting NP data. Raw data do not allow for direct comparisons between different measurement scales. For example, some tasks were based on accuracy, while others were based on performance speed. Some allowed for "partial" accuracy or a correct response after a cue, while others did not. Critically, correlated factors such as age, sex at birth, race, and years of education are well-known to affect performance on NP measures apart from differences related to the theorized associated domains of cognition (Marchant et al., 2013; Matthews et al., 2016; Ritchie, Artero, & Touchon, 2001; Satizabal et al., 2016; Schmand, Jonker, Hooijer, & Lindeboom, 1996).

Traditional norms were not available for any NP measures used in this study due to FHS using older versions of tests that were normed in a different generation and due to the participant cohort being older than the upper limits of the original norms. Regression-based norms (RBN) were employed to address this limitation. RBN is a

method in which demographic covariates are regressed against the centralized mean performance of a cognitively healthy subsample in order to yield beta weights for the covariates (Duff & Ramezani, 2015; Shirk et al., 2011). These beta weights allowed for calculating an individual's predicted performance on a measure given their age, education, and sex at birth. These predicted scores provided a normative basis from which standardized scores for the entire sample could be calculated.

While valuable when employed appropriately, RBNs are not a panacea for obtaining norms in understudied populations or populations who otherwise lack published norms. Fastenau (1998) demonstrated that RBNs are biased towards false negatives when the reference sample is overly small; however, RBNs may be more practical to obtain for an appropriately-sized sample than comparative observation-based norms (Oosterhuis, van der Ark, & Sijtsma, 2016). Several studies have demonstrated the utility of RBN approaches in NP research (Beeri et al., 2006; Cavaco et al., 2013; Cysique et al., 2012; Heaton, Avitable, Grant, & Matthews, 1999; Shirk et al., 2011). RBNs also have the added benefit of modeling demographic information continuously, as opposed to traditional normed scores that frequently convert continuous data to discrete scaled scores (Lenhard, Lenhard, Suggate, & Segerer, 2018).

For the present study, RBNs were constructed by identifying a subsample of cognitively healthy participants within the general purpose sample of n = 1,116 without likely dementia concern or cognitive impairment from stroke. This healthy subsample consisted of n = 619 participants who consistently scored greater than 27 out of 30 on the Mini Mental Status Examination (MMSE) across five exam cycles. This criterion was

employed to optimize the sensitivity of the MMSE to detect cognitive impairment (O'Bryant et al., 2008; Spering et al., 2012).

Step 1. While MMSE performance was used to increase the likelihood of identifying a cognitively healthy subsample, each NP task for this group was screened for outliers, defined as scores falling outside the range of $-3.29 \leq z \leq +3.29$ (Tabachnick & Fidell, 2013), in order to ensure both 1.) a normal distribution of scores and 2.) that all individuals included reflected the intended cognitively healthy subsample. Of the NP measures of interest for this study, outliers were found for only the BNT ($n = 1$). Extreme values were treated as missing, consistent with Tabachnick & Fidell (2013), because the extreme standardized score ($z = -6.91$) indicated that the individual's performance was not consistent with other individuals believed to be cognitively healthy.

Step 2. Polynomial relations for age and education were tested to see if effect size from regression suggested important curvilinear relations for cubic and quadratic terms. Quadratic relations were found for education and BNT, education and Similarities, age and BNT, and age and Logical Memory delayed free recall. A cubic association was found for age and the Digit Symbol Coding subtest. Associations without significant polynomial relations were treated as linear.

Step 3. Regression analyses were run adjusting for age, education and sex at birth, and including polynomial terms where indicated by assumption testing, to obtain coefficients and standard error of the estimate. Predicted scores were calculated using coefficients from these regressions. Z-scores were computed from the difference between actual and predicted scores divided by the standard error of the estimate. Of the 619 subjects from the cognitively healthy subsample of the original 1,116 participants in

NP exams 7, 8 and 9, there were 584 "normal" participants who were included in the current study sample after study-specific exclusion criteria previously described (i.e., without stroke or dementia, with medication history data available).

Step 4. The remaining participants from the current study sample (n = 476 "non-normal" participants) were processed separately. In contrast to the methods in Step 1, outliers were not removed for this group. Removal of outliers was previously necessary to ensure a normal distribution and that all included participants were cognitively normal, as they would serve as the healthy comparison group for constructing norms. For the "non-normal" sample, cognitively healthy performance was not a necessary assumption for inclusion; therefore, outliers were not screened out. Age, education, and polynomial terms were recalculated to center values around the mean of the non-normal subjects. Then Step 3 was repeated to generate predicted scores and converted into z scores using the same coefficients and standard error of the estimate as the normal group. Normal (n = 584) and Non-normal (n = 476) groups datasets were then merged (n = 1060).

Limitations of RBN approach. Education history for FHS participants was only available in a categorical format (less than 12 years, High School Graduate, Some College, College Graduate), thus the RBNs could have been strengthened if continuous education history was available.

Measures of Gray and White Matter Volume

Those participants with imaging data (n = 823) were seen for MRI on the same day as their exam 9 neuropsychological evaluation. Reasons individuals might not have undergone an MRI include refusal due to scheduling, claustrophobia, or personal reasons; positive pregnancy test; and medical contraindication such as a recent tattoo, permanent

dentistry, and metallic or electronic implant. Those who participated in MRI at exam 9 were significantly younger (Mean Age: participants without MRI = 73.42 years, participants with MRI = 70.89) and better educated at Exam 9; however, true between group differences for education were very small (Education, No: *M* = 3.09, Yes: *M* = 3.27). See Figures 1 and 2.

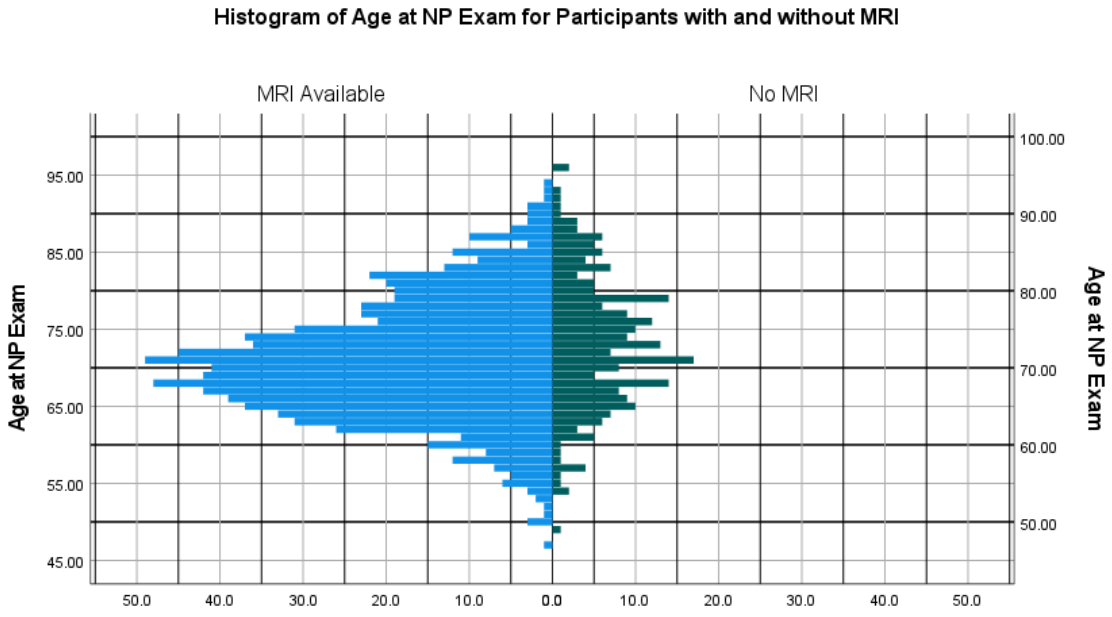

Figure 1. Histogram of Age at NP Exam for Participants with and without MRI.

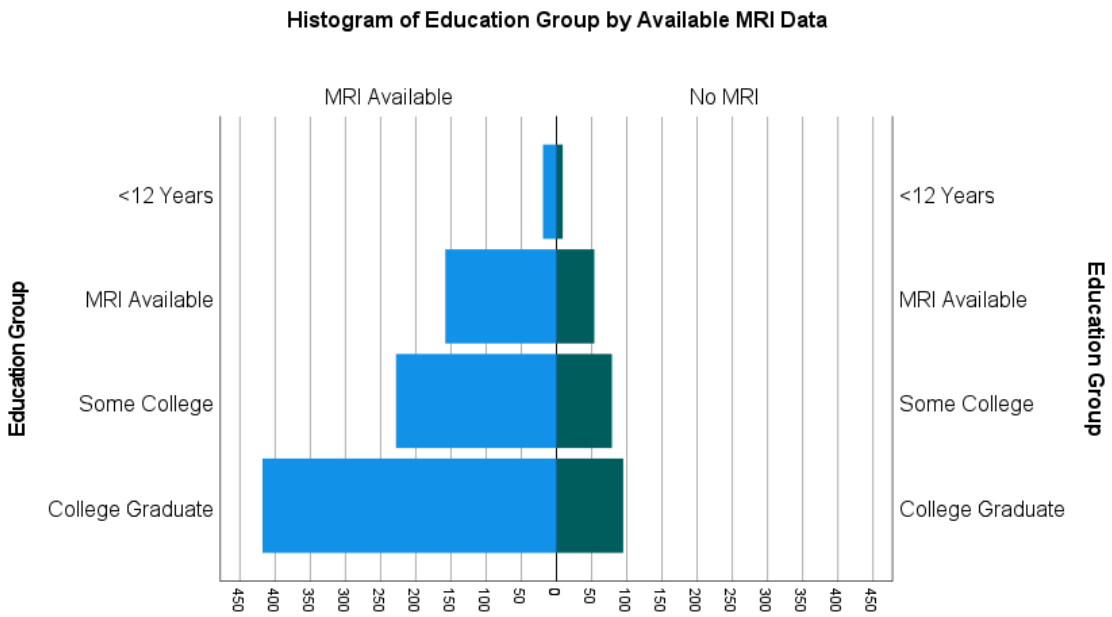

Figure 2. Histogram of Education Group by Available MRI Data.

Participants were imaged on a Siemens Magnetom 1 T field strength magnetic resonance machine using a T2-weighted double spin-echo coronal imaging sequence of 4 mm contiguous slices from nasion to occiput with a repetition time (TR) of 2420 ms, echo time (TE) of TE1 20/TE2 90 ms; echo train length 8 ms; field of view (FOV) 22 cm and an acquisition matrix of 182 × 256 interpolated to a 256 × 256 with one excitation.

Methods for the measurement of region and overall brain matter volumes from structural MRI within the Framingham cohorts have been described in detail elsewhere (DeCarli et al., 2005). Briefly, quantification of regional brain volumes required a multi-step process. First, removal of the skull and other non-brain tissue from the image. Structural MRI brain images are then nonlinearly registered to a minimal deformation template synthetic brain image, which provides a reference for computer-directed image separation and is adapted for ages 60 and above. For segmentation of brain from

cerebrospinal fluid (CSF), a difference image was created by subtracting the second echo image from the first echo image. Image intensity non-uniformities were then removed from the difference image. Gray and white matter segmentation was accomplished using an expectation-maximization algorithm that iteratively refines the segmentation estimates to produce outputs that were the most consistent with the input intensities from the native-space T1 images, along with a model of image smoothness. At each iteration, the algorithm used a Gaussian model of T1-weighted image intensity for each tissue class in order to produce a segmentation. This methodology yielded values for total gray and white matter volumes in cubic centimeters for regions above the tentorium and excluding brain matter in the cerebellum and brain stem.

Differences in head size accounts for some of the interindividual differences on MRI variables and measures are typically adjusted to account for this (Mathalon, Sullivan, Rawles, & Pfefferbaum, 1993). To control for the effect of head size, three methods were considered: a proportional method, a residualized method, and a regression-based method (Barnes et al., 2010; O'Brien et al., 2006; Sanfilipo, Benedict, Zivadinov, & Bakshi, 2004). In the regression-based method, a measure of head size is included as a covariate along with any independent variables, such that any associations between the region of interest (ROI) and the independent variable take into account any baseline variation in head size that may contribute to true score variance. The residualized method is similar to the regression-based method, but only the head size measure is used in the regression equation in order to produce a residualized value of the ROI after removing the influence of head size. The residuals of this first regression are then used in place of the original variable for any further analyses.

In the proportional method, the ROI is expressed as a percentage of a highly correlated region indicative of head size in order to normalize the size of the ROI in terms of its relative ratio to the designated region. The head size measure needs to be highly correlated in order to reduce the likelihood of introducing unexplained error into the ROI. For this study, Total Cranial Volume (TCV) for the region above the tentorium served as the measure of head size, consistent with previous FHS studies (Aparicio et al., 2017; DeCarli et al., 2005; Seshadri et al., 2004); Gray matter, Pearson $r = .877$; White matter, Pearson $r = .865$; see Figures 3 and 4).

Formula: $$\text{ROI volume\%} = (\text{ROI}/\text{TCV}) * 100 \quad (1)$$

The resulting variables of interest are thus Total Percentage Gray Matter and Total Percentage White Matter.

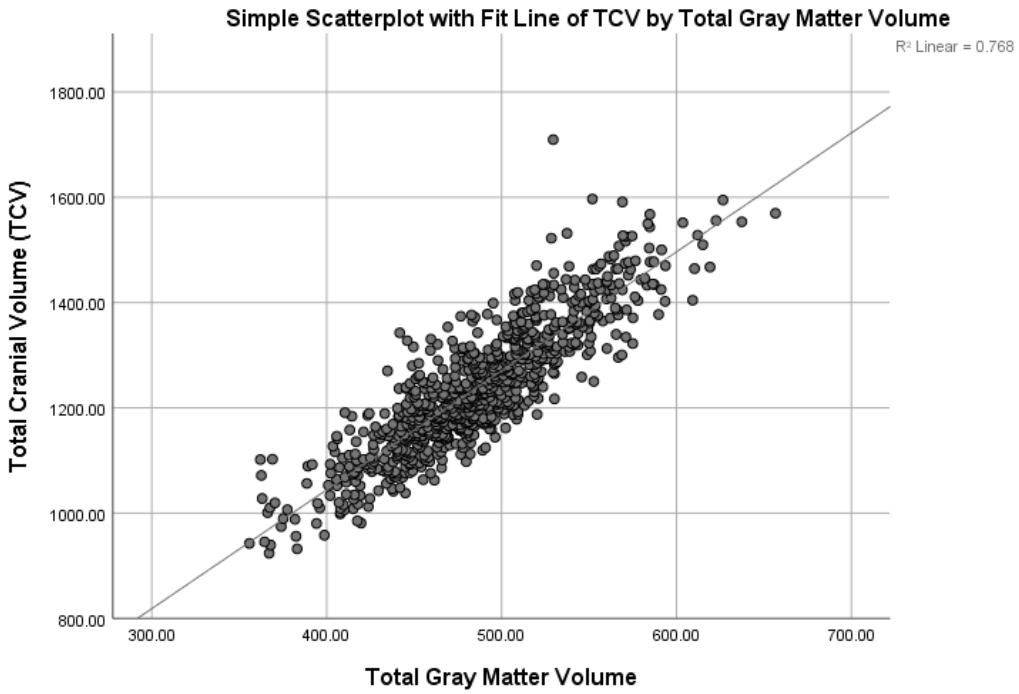

Figure 3. Simple Scatterplot of Fit Line of TCV by Total Gray Matter Volume.

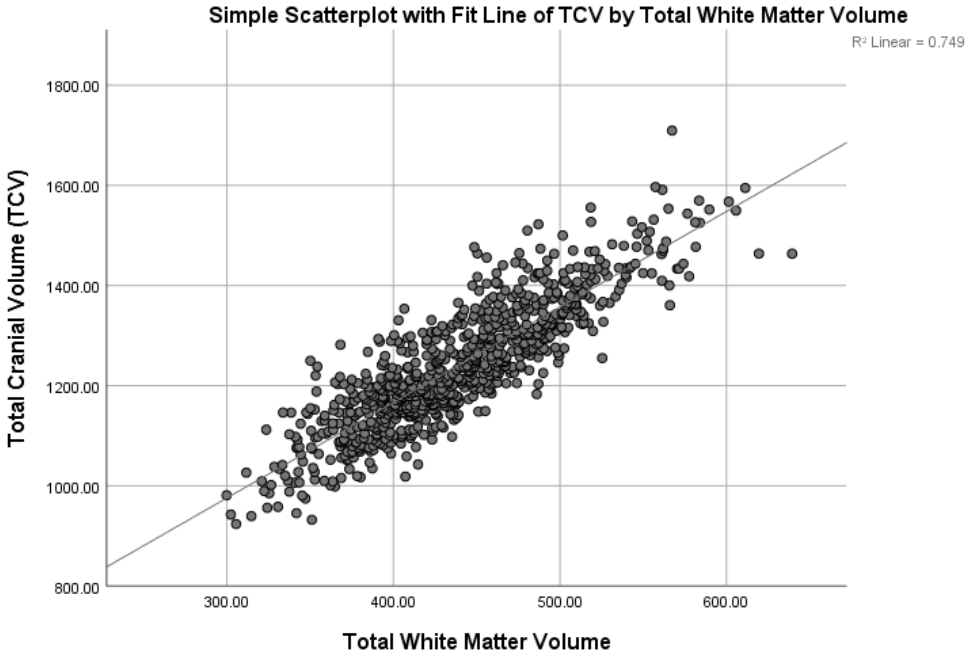

Figure 4. Simple Scatterplot of Fit Line of TCV by Total White Matter Volume.

Several factors for this study contributed to selecting the proportional method. First, it had the advantage of being intuitive, and preserved the same units of measure as the ROI and head size reference region. Second, because there was no literature to suggest that CV risk may affect head size (Aparicio et al., 2017; Seshadri et al., 2004), there was no concern that TCV might also be impacted by the independent variables in the study, which would have the effect of obscuring neuroanatomical differences attributable to CV risk factors. Lastly, the regression-based methods were intended for situations in which there is a control group or when operating within a question without classifications (O'Brien et al., 2006). This was inconsistent with the methods in the present design, because the study had two sets of classifiers and no true control group.

Analysis Plan

The hypotheses for the present study were tested using a two-step approach with a hold-out sample. Other methods, such as k-fold cross-validation, a more computationally expensive approach common in machine learning studies, were also considered. K-fold cross-validation approximates the separation of a hold-out group through repeated tests in which the data is split into k roughly equal proportions, and one proportion of the total sample is held out as a test set during each validation, and incorporated into the training set during all other validations, with the process repeated k times. True hold out samples have the benefit of being entirely uninvolved in the initial testing of the analysis, and are considered ideal when the data size allows for it (Hastie, Tibshirani, & Friedman, 2009).

For this approach, approximately two-thirds (n = 729) of the initially identified sample (n = 1060) was randomly assigned to the Test analysis, and the remaining third (n

= 331) were assigned to the Validation analysis. This process was repeated for the subsample of participants who contributed MRI data (total sub-sample: n = 823; Test: n = 538; Validation: n = 285). Selection of sample proportions to dedicate to the Test and Validation groups was based on recommendations in Schorfheide & Wolpin (2016).

Step 1. For the Test step, in which the analysis followed a Rough CDA plan (Fife & Rodgers, 2019), eight linear regressions were performed. For each regression, one neuropsychological test (Digit Symbol, Verbal Fluency, Similarities, BNT, Logical Memory, and Visual Reproduction) or MRI variable (Total Percentage Gray Matter and Total Percentage White Matter) served as the dependent variable, with treatment history for hypertension and treatment history for lipids entered as IVs, along with an interaction variable for comorbidity of the IVs (TxHxHypertension*TxHxLipids).

To assess the comparative value of analyzing the relations of NP variables with RBNs, regression of NP measures were performed with raw NP scores as the dependent variables and again with RBN NP scores as the dependent variable. The independent variables and interaction variable remained the same across all analyses. The analyses of raw score NP variables and MRI variables also included demographics covariates, i.e., age, education, and sex at birth, consistent with previous studies (DeCarli et al., 2005). The effects of age, education and sex at birth on NP measures were already accounted for through the RBN procedures. In total, 14 regressions were performed using the Test subsample (6 raw NP measure score, 6 RBN NP measure score, 2 MRI measures).

Given that these data were drawn from a community sample of otherwise healthy individuals, any impairment observed was expected to be relatively minor and not of clinical concern. As a baseline, effect sizes were considered not meaningful when the

partial eta^2 value accounted for less than one percent of variance. In the process of refining the analytical model used to assess the Test data set, interaction terms and covariates that were not both statically significant (meeting or exceeding an alpha level of 0.05) and with a meaningful effect size were excluded from the model. In addition to effect sizes, visual inspection of added variable plots guided decisions about meaningful findings, consistent with a Rough CDA strategy. These effect sizes and graphics informed the expected association strength to be seen when the analyses were repeated in the separate Validation group.

Step 2. For the Validation step, the 14 regressions previously described were repeated using the Validation hold-out group in order to identify consistently supported relations between treatment history variables and NP & MRI outcomes, within a strict CDA paradigm. Meaningful findings were informed by analyses meeting or exceeding an alpha level of 0.05 or by yielding an effect size consistent with Step 1 analyses.

Interpretation of findings. For each of the six NP outcome measures assessed, four regression analyses were planned. To reduce potential of type 1 errors, individual NP measures were only considered to be meaningfully associated with CV risk when all four analyses supported that conclusion.

Chapter 3

Results

Between Group Differences for Demographics

Tables 4 and 5 summarize group means and standard deviations for age and BMI, as well as group frequencies for education and gender distribution, for treatment history for hypertension (TxHxHypertension) and treatment history for hyperlipidemia (TxHxLipids).

Age significantly differed among all three groups for TxHxHypertension (all *p*-values < .05), with the Inconsistently Treated group presenting with older age than Never Treated, and Consistently Treated presenting with older age than Inconsistently Treated. This pattern was also observed when considering only participants who contributed MRI data (all *p*-values < .01). For the TxHxLipids groups, age did not significantly differ between the Never Treated and Inconsistently Treated groups (Mean difference = 1.38, Std Error = 0.66, $p > .05$). All other 2-group comparisons were significantly different (all *p*-values < .001), with greater degree of treatment history presenting with older age. As before, this pattern was also seen when considering only those participants with MRI data (Never Treated vs Inconsistently Treated: $p > .05$; all other *p*-values < .001).

BMI among TxHxHypertension groups significantly differed between all groups (*p*s < .05) and among all but one of the TxHxLipids groups (all *p*s < .05). Inconsistently Treated and Consistently Treated groups for TxHxLipids did not differ (Mean difference = 0.43, Std Error = 0.41, $p > .05$). For the participants who contributed MRI data, Inconsistently Treated and Consistently Treated groups for both TxHxHypertension and TxHxLipids did not differ (TxHxHypertension: Mean difference = 0.94, Std Error = 0.51,

$p > .05$; TxHxLipids: Mean difference = 1.52, Std Error = 0.42, $p > .05$). All other group comparisons were significant ($p < .05$).

Considering education, the College Graduate group was the largest education group for TxHxHypertension and TxHxLipids for both the full sample and for only the participants with MRI data. The Never Treated group from the full sample for TxHxHypertension was the only instance in which the next largest education group was not participants with Some College. For the Never Treated TxHxHypertension group, the second largest education group was High School Graduate. Less than 1 percent of any group had fewer than 12 years of education. Education group representation only significantly differed among TxHxHypertension groups for the Never Treated and Consistently Treated groups ($p < .05$). Among TxHxLipid groups, the education group representation differed for the Inconsistently Treated and Consistently Treated groups ($p < .05$).

With the exception of the MRI sample, more than 50% of all groups were Female and the Consistently Treated group accounted for more than half of all participants with respect to TxHxHypertension. For the MRI sample, the Consistently Treated groups for TxHxHypertension had a greater representation of Male Sex at Birth compared to lower levels of treatment history.

Test Set

Consistent with a Rough CDA approach to data analysis (Fife & Rodgers, 2019; Tukey, 1977), the relation between CV treatment group and NP test performance was first examined through the analyses of a Test dataset consisting of approximately 69% of the original total sample of 1060 participants (Test sample $n = 729$). The remaining

participants (n = 331) served as a hold-out group used to validate results obtained in the Test set.

To demonstrate the utility of regression-based norms (RBN), both raw score NP measures and RBN NP scores were evaluated. Effect sizes obtained in the Test Set analyses informed decisions for refining the model. In instances where the interaction term had a non-significant p-value and a small effect size (i.e.: partial eta^2 < 1%), the interaction term was dropped from the model and the analysis was repeated. Levene's Test of Equality of Error Variance indicated that assumptions of homoscedasticity were met for all analyses. This was in agreement with visual inspections of residual plots. ANOVA and ANCOVA summary tables for finalized models using NP raw scores, RBN scores, and MRI measures from the Test data set are available in Appendix B.

Naming/ lexical access. Relations between CV risk and Lexical Access were examined with the Boston naming Test (BNT) and the Similarities subtest.

Boston naming test (RBN score). When considering this relation in the context of RBNs for the BNT, the interaction term for TxHxHypertension and TxHxLipids was non-significant (p > .05) and evidenced a less-than-meaningful effect size (partial eta^2 = .009). Therefore, the decision was made to remove the interaction term from the model and re-run the analysis with only the treatment history independent variables. Table 6 shows the ANOVA table for this analysis, which found no evidence of a meaningful relation between TxHxHypertension or TxHxLipids and returned very small effect sizes explaining less than 1 percent of variance (TxHxHypertension partial eta^2 = .001; TxHxLipids partial eta^2 = .003). Visual inspection of added variable plots for

TxHxHypertension and TxHxLipids also indicated no meaningful relation between independent variables and measure performance.

Table 6

RBN Boston Naming Test Model

ANOVA – RBN BNT Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	1.147	2	0.573	0.358	0.699	0.001	0.001
TxHxLipids	3.209	2	1.605	1.003	0.367	0.003	0.003
Residuals	1102.344	689	1.600				

Note. Type III Sum of Squares
Interaction term excluded

Boston naming test (Raw score). Considering the relation for BNT raw score performance and CV risk factors when controlling for demographic variables, the interaction term for TxHxHypertension and TxHxLipids was again found to be non-significant ($p > .05$) with a similar effect size (partial $eta^2 = .011$). The interaction effect size was large enough to be considered meaningful (partial $eta^2 > .01$), but was not supported by a significant *p*-value, reducing confidence for including the term in the model. Age and education, but not sex at birth, were significantly associated with BNT performance. The interaction term and sex at birth were excluded and the model was re-analyzed. Table 7 shows the results of the ANCOVA table for this analysis. Consistent with the RBN BNT analysis, effect sizes of much less than 1 percent were observed for TxHxHypertension or TxHxLipids (TxHxHypertension partial $eta^2 > .001$; TxHxLipids partial $eta^2 = .001$). Visual inspection of added variable plots for TxHxHypertension and

TxHxLipids did not support a meaningful association between the CV risk variables and BNT performance.

Table 7

Raw Score Boston Naming Test Model

ANCOVA – Raw Scores BNT Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	10.312	2	5.156	1.863	0.157	0.009	0.010
TxHxLipids	2.843	2	1.422	0.514	0.599	0.003	0.003
Age	42.317	1	42.317	15.292	< .001	0.038	0.041
Education	56.200	1	56.200	20.310	< .001	0.051	0.054
Residuals	993.417	359	2.767				

Note. Type III Sum of Squares
Interaction term and sex at birth excluded

The results of both the RBN and raw score analyses suggested that repeating the analysis with the Validation data set would not find a relation between either CV risk factor and BNT performance.

Similarities (RBN score). The interaction term for TxHxHypertension and TxHxLipids was non-significant with a very small effect size (partial eta^2 = .006) when examining the RBN performance on the Similarities subtest. This informed the decision to remove the interaction term from the model and re-run the analysis with only the treatment history independent variables. Table 8 shows the resulting ANOVA table for this analysis, which found a small but meaningful relation between TxHxHypertension and this measure of verbal reasoning (partial eta^2 = .016). In particular, a small between-group effect size was found between the highest and lowest levels of TxHxHypertension (Cohen's *d* = .29). TxHxLipids was not significantly associated with Similarities

performance (partial eta^2 = .001). Meeting expectations for the small effect size observed, visual inspection of the added variable plots for TxHxHypertension and TxHxLipids showed only minor differences between groups.

Table 8

RBN Similarities Model

ANOVA – RBN Similarities Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	15.430	2	7.715	5.958	0.003	0.016	0.016
TxHxLipids	0.948	2	0.474	0.366	0.694	0.001	0.001
Residuals	925.847	715	1.295				

Note. Type III Sum of Squares
Interaction term excluded

Similarities (raw score). In analysis of Similarities raw score performance and CV risk factors when controlling for demographic variables, the interaction term for TxHxHypertension and TxHxLipids was again found to be non-significant ($p > .05$) with a small effect size (partial eta^2 = .005). Age and education, but not sex at birth, were significantly associated with Similarities performance. The interaction term and sex at birth were excluded and the model was re-analyzed. Table 9 shows the results of ANCOVA table for this analysis. Compared with the RBN Similarities analysis, TxHxHypertension demonstrated a significant ($p < .05$) but smaller than meaningful association with raw score Similarities performance when covarying for age and education (partial eta^2 = .009). TxHxLipids was not significantly associated with Similarities performance (partial eta^2 < .001). Visual inspection of added variable plots

for TxHxHypertension and TxHxLipids was consistent with the results of the RBN Similarities analysis.

Table 9

Raw Score Similarities Model

ANCOVA – Raw Score Similarities Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	67.162	2	33.581	3.281	0.038	0.007	0.009
TxHxLipids	2.004	2	1.002	0.098	0.907	< .001	< .001
Age	117.570	1	117.570	11.489	< .001	0.013	0.016
Education	1832.576	1	1832.576	179.075	< .001	0.196	0.200
Residuals	7317.008	715	10.234				

Note. Type III Sum of Squares
Interaction term and sex at birth excluded

The results of both the RBN and raw score analyses suggested that repeating the analysis with the Validation data set would show a relation between TxHxHypertension and Similarities performance.

Processing speed. Relations between CV risk and Processing Speed were examined with the Digit Symbol Coding subtest and the Verbal Fluency test.

Digit symbol coding (RBN score). For the relation between RBN performance on Digit Symbol Coding and CV risk factors, the interaction term for TxHxHypertension and TxHxLipids was non-significant ($p > .05$) with a very small effect size (partial eta^2 = .002). The decision was made to remove the interaction term from the model and re-run the analysis with only the treatment history independent variables. Table 10 shows the ANOVA table for this analysis, which found a meaningful relation between

TxHxHypertension and this task of graphomotor function and processing speed (partial eta^2 = .014). A small between-group effect size was found between the highest and lowest levels of TxHxHypertension (Cohen's *d* = .26). TxHxLipids returned a small effect size explaining less than 1 percent of variance (partial eta^2 = .002). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids was consistent with statistical findings.

Table 10

RBN Digit Symbol Coding Model

ANOVA – RBN Digit Symbol Coding Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	9.669	2	4.835	4.683	0.010	0.014	0.014
TxHxLipids	1.356	2	0.678	0.657	0.519	0.002	0.002
Residuals	665.871	645	1.032				

Note. Type III Sum of Squares
Interaction term excluded

Digit symbol coding (raw score). For raw score Digit Symbol Coding, the effect size for the interaction term for TxHxHypertension and TxHxLipids was large enough to be considered meaningful (partial eta^2 = .011), but was not supported by a significant *p*-value ($p > .05$), reducing confidence for including the term in the model. Age, education and sex at birth were significantly associated with Digit Symbol Coding performance. The interaction term was excluded and the model was re-analyzed. Table 11 shows the results of the ANCOVA table for this analysis. Consistent with the RBN Digit Symbol Coding analysis, TxHxHypertension demonstrated a small but meaningful association with raw score Digit Symbol Coding performance when controlling for age, education,

and sex at birth (TxHxHypertension: partial eta^2 = .015; TxHxLipids: partial eta^2 = .002). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids agreed with these findings, showing a small group distribution difference for TxHxHypertension groups.

Table 11

Raw Score Digit Symbol Coding Model

ANCOVA – Raw Score Digit Symbol Coding Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	1219.650	2	609.825	4.797	0.009	0.012	0.015
TxHxLipids	191.115	2	95.558	0.752	0.472	0.002	0.002
Age	14354.168	1	14354.168	112.901	< .001	0.136	0.150
Education	3513.599	1	3513.599	27.636	< .001	0.033	0.041
Sex at Birth	4425.942	1	4425.942	34.812	< .001	0.042	0.051
Residuals	81623.590	642	127.140				

Note. Type III Sum of Squares
Interaction term excluded

The results of both the RBN and raw score analyses suggested that repeating the analysis with the Validation data set would show a relation between TxHxHypertension and Digit Symbol Coding performance.

Verbal fluency (RBN score). The interaction term for TxHxHypertension and TxHxLipids was non-significantly associated with RBN Verbal Fluency performance (p > .05) and evidenced a smaller than meaningful effect size (partial eta^2 = .008). Therefore, the decision was made to remove the interaction term from the model and re-run the analysis with only the treatment history independent variables. Table 12 shows the ANOVA table for this analysis, which found evidence of a meaningful relation with

TxHxHypertension, but not TxHxLipids (TxHxHypertension partial eta^2 = .016; TxHxLipids partial eta^2 = .005). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids also indicated lower performance on RBN Verbal Fluency among the Consistently Treated group for TxHxHypertension compared to other groups. No meaningful relation with TxHxLipids was observed for this measure of performance.

Table 12

RBN Verbal Fluency Model

ANOVA – RBN Verbal Fluency Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	0.842	2	0.421	5.637	0.004	0.016	0.016
TxHxLipids	0.281	2	0.141	1.884	0.153	0.005	0.005
Residuals	51.876	695	0.075				

Note. Type III Sum of Squares
Interaction term excluded

Verbal fluency (raw score). For raw score performance on the Verbal Fluency task, the interaction term for TxHxHypertension and TxHxLipids was not significant (p > .05) with a similar effect size (partial eta^2 = .008). Age and education, but not sex at birth, were significantly associated with BNT performance. The interaction term and sex at birth were excluded and the model was re-analyzed. Table 13 shows the ANCOVA table for this analysis. In contrast to the RBN analysis, no meaningful relation with TxHxHypertension or TxHxLipids was observed (TxHxHypertension: partial eta^2 = .007; TxHxLipids: partial eta^2 = .002). Visual inspection of added variable plots for

TxHxHypertension and TxHxLipids also indicates no meaningful relation between independent variables and measure performance.

Table 13

Raw Score Verbal Fluency Model

ANCOVA – Raw Score Verbal Fluency Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	667.126	2	333.563	2.409	0.091	0.006	0.007
TxHxLipids	196.718	2	98.359	0.710	0.492	0.002	0.002
Age	2503.217	1	2503.217	18.078	< .001	0.023	0.025
Education	7119.014	1	7119.014	51.411	< .001	0.067	0.069
Residuals	96099.105	694	138.471				

Note. Type III Sum of Squares
Interaction term and sex at birth excluded

The results of the RBN and raw score analyses did not align and suggested that repeating the analysis with the Validation data set would find a relation between TxHxHypetension and verbal fluency performance, but only in the context of RBNs.

Episodic memory. Relations between CV risk and Episodic Memory were examined with the Logical Memory subtest and the Visual Reproduction subtest.

Logical memory (RBN score). For the relation between RBN performance on Logical Memory delayed free recall and CV risk factors, the interaction term for TxHxHypertension and TxHxLipids was non-significant ($p > .05$) with a very small effect size (partial $eta^2 = .004$). The decision was made to remove the interaction term from the model and re-run the analysis with only the treatment history independent variables. Table 14 shows the ANOVA table for this analysis, which found no evidence of a meaningful relation between TxHxHypertension or TxHxLipids and returned very

small effect sizes explaining less than 1 percent of variance (TxHxHypertension partial eta^2 = .004; TxHxLipids partial eta^2 = .002). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids also indicated no meaningful relation between independent variables and measure performance.

Table 14

RNB Logical Memory Delayed Free Recall Model

ANOVA – RNB Logical Memory Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	2.782	2	1.391	1.366	0.256	0.004	0.004
TxHxLipids	1.319	2	0.659	0.648	0.523	0.002	0.002
Residuals	719.632	707	1.018				

Note. Type III Sum of Squares
Interaction term excluded

Logical memory (raw score). For raw score Logical Memory delayed free recall, the interaction term for TxHxHypertension and TxHxLipids was again found to be non-significant ($p > .05$) with a similar effect size (partial eta^2 = .005). Age, education, and sex at birth were significantly associated with verbal episodic memory performance on this task. The interaction term was excluded and the model was re-analyzed. Table 15 shows the results of the ANCOVA table for this analysis. Consistent with the RBN analysis, no evidence of a meaningful relation between TxHxHypertension or TxHxLipids was found when controlling for age, education and sex (TxHxHypertension: partial eta^2 = .006; TxHxLipids: partial eta^2 < .001). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids agreed with these findings.

Table 15

Raw Score Logical Memory Delayed Free Recall Model

ANCOVA – Raw Score Logical Memory Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	51.066	2	25.533	1.993	0.137	0.005	0.006
TxHxLipids	13.226	2	6.613	0.516	0.597	0.001	0.001
Age	269.078	1	269.078	20.999	< .001	0.027	0.029
Education	549.517	1	549.517	42.884	< .001	0.055	0.057
Sex at Birth	166.099	1	166.099	12.962	< .001	0.016	0.018
Residuals	9021.086	704	12.814				

Note. Type III Sum of Squares
Interaction term excluded

The results of both the RBN and raw score analyses suggested that repeating the analysis with the Validation data set would not find a relation between either CV risk factor and Logical Memory performance.

Visual reproduction (RBN score). The interaction term for TxHxHypertension and TxHxLipids was non-significantly associated with RBN Visual Reproduction delayed free recall performance ($p > .05$) and evidenced a less-than-meaningful small effect size (partial $eta^2 = .009$). Therefore, the decision was made to remove the interaction term from the model and re-run the analysis with only the treatment history independent variables. Table 16 shows the ANOVA table for this analysis, which found no evidence of a meaningful relation between TxHxHypertension or TxHxLipids and returned very small effect sizes explaining less than 1 percent of variance (TxHxHypertension partial $eta^2 = .006$; TxHxLipids partial $eta^2 = .003$). Visual

inspection of added variable plots for TxHxHypertension and TxHxLipids also indicates no meaningful relation between independent variables and measure performance.

Table 16

RBN Visual Reproduction Delayed Free Recall Model

ANOVA – RBN Visual Reproduction Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	4.671	2	2.335	2.206	0.111	0.006	0.006
TxHxLipids	2.252	2	1.126	1.064	0.346	0.003	0.003
Residuals	754.869	713	1.059				

Note. Type III Sum of Squares
Interaction term excluded

Visual reproduction (raw score). For raw score performance on the Visual Reproduction delayed free recall task, the interaction term for TxHxHypertension and TxHxLipids was not significant ($p > .05$) with an effect size (partial eta^2 = .010) similar to the RBN analysis. Age and education, but not sex at birth, were significantly associated with visual episodic memory performance. The interaction term and sex at birth were excluded and the model was re-analyzed. Table 17 shows the ANCOVA table for this analysis. Consistent with the RBN analysis, no meaningful relation with TxHxHypertension or TxHxLipids was observed (TxHxHypertension: partial eta^2 = .007; TxHxLipids: partial eta^2 = .003). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids also indicated no meaningful relation between independent variables and measure performance.

Table 17

Raw Score Visual Reproduction Delayed Free Recall Model

ANCOVA – Raw Score Visual Reproduction Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	36.130	2	18.065	2.511	0.082	0.006	0.007
TxHxLipids	13.533	2	6.767	0.941	0.391	0.002	0.003
Age	549.893	1	549.893	76.441	< .001	0.092	0.097
Education	252.441	1	252.441	35.092	< .001	0.042	0.047
Residuals	5114.680	711	7.194				

Note. Type III Sum of Squares
Interaction term and Sex at Birth excluded

The results of both the RBN and raw score analyses suggested that repeating the analysis with the Validation data set would not find a relation between either CV risk factor and Visual Reproduction performance.

Volumetric measures of whole brain gray and white matter. Relations between CV risk and brain matter volumes were examined to determine if group-based differences in gray and white matter volume corresponded with observed neuropsychological performance.

Gray matter volume. The proportional measure of total brain gray matter volume after correcting for head size was initially entered into a model with TxHxHypertension, TxHxLipids, and the interaction term of these two independent variables, and with age, education and sex at birth as covariates. In this first model, the interaction term for TxHxHypertension and TxHxLipids was non-significant ($p > .05$) with a very small effect size (partial $eta^2 = .006$). Age and sex at birth, but not education, were significantly associated with gray matter volume. The decision was made to remove the interaction term and education from the model and re-run the analysis. Table 18 shows

the ANCOVA table for this analysis, which found no evidence of a meaningful relation between TxHxHypertension or TxHxLipids and returned very small effect sizes explaining less than 1 percent of variance (TxHxHypertension partial eta^2 = .004; TxHxLipids partial eta^2 = .004). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids also indicated no meaningful relation between independent variables and proportional gray matter volume.

Table 18

Total Percentage Gray Matter Volume Model

ANCOVA – Total Percentage Gray Matter Volume Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	5.696	2	2.848	1.158	0.315	0.003	0.004
TxHxLipids	4.663	2	2.331	0.948	0.388	0.003	0.004
Age	343.040	1	343.040	139.504	< .001	0.192	0.208
Sex at Birth	131.263	1	131.263	53.381	< .001	0.073	0.091
Residuals	1305.730	531	2.459				

Note. Type III Sum of Squares
Interaction term and Education excluded

White matter volume. Consistent with the model for Gray Matter, the proportional measure of total brain white matter volume after correcting for head size was initially entered into a model with TxHxHypertension, TxHxLipids, and the interaction term of these two independent variables, and with age, education and sex at birth as covariates. As with the gray matter model, the interaction term for TxHxHypertension and TxHxLipids was found to be non-significant ($p > .05$). Notably, the effect size was larger than in the gray matter model (partial eta^2 = .014), but remained small in comparison to other terms in the model. Age and sex at birth, but not education,

were significantly associated with the model. The interaction term and education were excluded and the model was re-analyzed. Table 19 shows the results of the ANCOVA table for this analysis. Consistent with the gray matter analysis, no evidence of a meaningful relation with TxHxHypertension or TxHxLipids was found when controlling for age and education (TxHxHypertension: partial $eta^2 = .002$; TxHxLipids: partial $eta^2 < .001$). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids agreed with these findings.

Table 19

Total Percentage White Matter Volume Model

ANCOVA – Total Percentage White Matter Volume Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	3.273	2	1.637	0.403	0.668	0.001	0.002
TxHxLipids	1.052	2	0.526	0.130	0.878	< .001	< .001
Age	381.432	1	381.432	93.958	< .001	0.148	0.150
Sex at Birth	41.956	1	41.956	10.335	0.001	0.016	0.019
Residuals	2155.645	531	4.060				

Note. Type III Sum of Squares
Interaction term and Education excluded

The results of these analyses suggested that repeating the analysis with the Validation data set would not find a relation between either CV risk factor and proportional measures of total gray and white matter volume.

Test set summary. Table 6 summarizes the results of Test set analyses. No final model for any of the analyses included an interaction term for TxHxHypertension and TxHxLipids. TxHxHypertension was associated with performance on RBN Verbal

Fluency, raw score Digit Symbol Coding, RBN Digit Symbol Coding, raw score Similarities and RBN Similarities; however effect sizes remained small across all analyses, with partial eta^2 values falling between .010 and .020.

Verbal Fluency task performance was the only Test set measure to show inconsistent findings between raw score and RBN analyses. Any measure of verbal production is highly related to demographic covariates, in particular education for letter fluency tasks. Thus, this may be related to the exclusion of the covariate sex at birth when refining the raw score model, as sex at birth was a covariate included in the creation of the RBN performance scores. The RBN Verbal Fluency analysis reports an effect size of TxHxHypertension more than twice the size of the non-significant raw score partial eta^2 (RBN partial eta^2 = .016; Raw partial eta^2 = .007). The effect size of sex at birth in the initial model was small (partial eta^2 = .004), so the decision to exclude remains supported.

Among raw score covariates, age and education were consistently associated with raw score neuropsychological performance, although sex at birth was inconsistently included in final models and was associated with Digit Symbol Coding and Logical Memory delayed free recall only. Age and sex at birth, but not education, were associated with MRI measures.

Validation Set

Following analysis with the Test data in which the final model for each analysis was determined, ANOVA and ANCOVA analyses using the final models were repeated using the Validation data set, a hold-out sample of one-third of the original study sample

whose data had not been used in the earlier analyses. Analysis with this group represents a replication of the Test data set results in an independent sample of 331 participants randomly withheld from the Test set analyses.

As with the Test set, both raw score NP measures and RBN NP scores were evaluated for evidence of significant relations between CV risk factors and NP performance. Final models and effect sizes obtained through evaluation of the Test data set informed expectations for analyses in the Validation sample. ANOVA and ANCOVA summary tables for finalized models using NP raw scores, RBN scores, and MRI measures from the Test data set are available in Appendix D.

Naming/ lexical access. Relations between CV risk and Lexical Access were examined with the Boston naming Test (BNT) and the Similarities subtest.

Boston naming test (RBN score). Table 20 shows the ANOVA table for this analysis. Consistent with the Test set analysis, no evidence of a meaningful relation was observed between RBN BNT performance and TxHxHypertension or TxHxLipids ($p >$ .05). Both independent variables produced noticeably larger effect sizes compared to the Test set analysis, indicating poor consistency of findings upon replication (TxHxHypertension partial $eta^2 = .009$; TxHxLipids partial $eta^2 = .012$). This supports the conclusion that RBN BNT is not meaningfully associated with CV risk factors. Visual inspection of added variable plots for TxHxHypertension and TxHxLipids also indicated no meaningful relation between independent variables and measure performance.

Table 20

RBN Boston Naming Test Model

ANOVA – RBN BNT Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	3.730	2	1.865	1.375	0.254	0.009	0.009
TxHxLipids	5.132	2	2.566	1.892	0.152	0.012	0.012
Residuals	425.776	314	1.356				

Note. Type III Sum of Squares

Boston naming test (raw score). As with the other analyses of BNT, the relation for BNT raw score performance and CV risk factors when controlling for demographic variables was not meaningful. Table 21 shows the results of the ANCOVA table for this analysis. Effect sizes of less than 1 percent were observed for TxHxHypertension and TxHxLipids (TxHxHypertension partial $eta^2 = .003$; TxHxLipids partial $eta^2 = .001$). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids did not support a meaningful relation between the CV risk variables and BNT performance.

Table 21

Raw Score Boston Naming Test Model

ANCOVA – Raw Score BNT Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	3.964	2	1.982	0.414	0.661	0.002	0.003
TxHxLipids	2.048	2	1.024	0.214	0.808	0.001	0.001
Age	142.268	1	142.268	29.702	< .001	0.079	0.086
Education	145.533	1	145.533	30.383	< .001	0.081	0.088
Residuals	1508.816	315	4.790				

Note. Type III Sum of Squares

Considering the four analyses of BNT performance across the Test and Validation sets, the results of both the RBN and raw score analyses indicate that a meaningful relation was not observed between either CV risk factor and BNT performance.

Similarities (RBN score). Table 22 shows the resulting ANOVA table for this analysis, which replicated the finding of a meaningful relation between TxHxHypertension and this measure of verbal reasoning (partial eta^2 = .031). The effect size for this relation was twice as large as what was observed in the Test set analysis, indicating that there remains some uncertainty as to the degree of impact of CV risk factors on verbal reasoning. As in the Test analysis, a moderate between-group effect size was found between the highest and lowest levels of TxHxHypertension (Cohen's *d* = .41) and TxHxLipids was not significantly associated with Similarities performance (partial eta^2 = .001). Visual inspection of the added variable plots for TxHxHypertension and TxHxLipids was consistent with these observations.

Table 22

RBN Similarities Model

ANOVA – RBN Similarities Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	12.970	2	6.485	5.225	0.006	0.031	0.031
TxHxLipids	0.452	2	0.226	0.182	0.834	0.001	0.001
Residuals	400.920	323	1.241				

Note. Type III Sum of Squares

Similarities (raw score). Table 23 shows the ANCOVA table for this analysis. Consistent with the RBN Similarities analysis, TxHxHypertension, but not TxHxLipids,

demonstrated meaningful association with raw score Similarities performance when covarying for age and education (TxHxHypertension: partial eta^2 = .031; TxHxLipids: partial eta^2 < .003). A moderate between-group effect size was found between the highest and lowest levels of TxHxHypertension (Cohen's *d* = .43). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids was consistent with the results of the RBN Similarities analysis.

Table 23

Raw Score Similarities Model

ANCOVA – Raw Score Similarities Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	92.726	2	46.363	5.076	0.007	0.025	0.031
TxHxLipids	9.263	2	4.632	0.507	0.603	0.002	0.003
Age	91.906	1	91.906	10.062	0.002	0.025	0.030
Education	611.270	1	611.270	66.923	< .001	0.164	0.173
Residuals	2931.994	321	9.134				

Note. Type III Sum of Squares

The four analyses of Similarities performance across the Test and Validation sets indicate that a meaningful relation exists between TxHxHypertension and Similarities performance, with greater treatment history relating to poorer measure performance.

Processing speed. Relations between CV risk and Processing Speed were examined with the Digit Symbol Coding subtest and the Verbal Fluency test.

Digit symbol coding (RBN score). For the relation between RBN performance on Digit Symbol Coding and CV risk factors, Table 24 shows the ANOVA table for this analysis, which found a meaningful relation between TxHxHypertension and this task of

graphomotor function and processing speed (partial eta^2 = .042). A moderate between-group effect size was found between the highest and lowest levels of TxHxHypertension (Cohen's *d* = .48). TxHxLipids returned a small effect size explaining less than 1 percent of variance (partial eta^2 = .004). These findings support the results of the Test set analysis of RBN Digit Symbol Coding, and visual inspection of added variable plots for TxHxHypertension and TxHxLipids was consistent with statistical findings.

Table 24

RBN Digit Symbol Coding Model

ANOVA – RBN Digit Symbol Coding Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	14.203	2	7.102	6.564	0.002	0.042	0.042
TxHxLipids	1.226	2	0.613	0.566	0.568	0.004	0.004
Residuals	321.320	297	1.082				

Note. Type III Sum of Squares

Digit symbol coding (Raw score). Table 25 shows the results of the ANCOVA table for raw score Digit Symbol Coding. Consistent with the RBN Digit Symbol Coding analysis, TxHxHypertension demonstrated a meaningful association with raw score Digit Symbol Coding performance when controlling for age, education and sex at birth (TxHxHypertension: partial eta^2 = .042; TxHxLipids: partial eta^2 < .007). A large between-group effect size was found between the highest and lowest levels of TxHxHypertension (Cohen's *d* = .63). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids agreed with these findings, showing noticeably lower performance for individuals at higher levels of TxHxHypertension.

Table 25

Raw Score Digit Symbol Coding Model

ANCOVA – Raw Score Digit Symbol Coding Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	1676.518	2	838.259	6.490	0.002	0.032	0.042
TxHxLipids	285.888	2	142.944	1.107	0.332	0.005	0.007
Age	3913.683	1	3913.683	30.299	< .001	0.075	0.093
Education	5597.953	1	5597.953	43.338	< .001	0.107	0.128
Sex at Birth	2645.028	1	2645.028	20.477	< .001	0.051	0.065
Residuals	37975.769	294	129.169				

Note. Type III Sum of Squares

Across the four analyses of Digit Symbol Coding performance for the Test and Validation sets, a consistent meaningful relation existed between TxHxHypertension and both raw score and RBN performance.

Verbal fluency (RBN score). Table 26 shows the ANOVA table for this analysis, which found evidence of a meaningful relation for RBN Verbal Fluency with TxHxHypertension, but not with TxHxLipids (TxHxHypertension partial eta^2 = .031; TxHxLipids partial eta^2 = .004). A moderate between-group effect size was found between the highest and lowest levels of TxHxHypertension (Cohen's *d* = .41). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids indicated lower performance on RBN Verbal Fluency among the Consistently Treated group for TxHxHypertension compared to other groups. No meaningful relation with TxHxLpids was observed for this measure of performance.

Table 26

RBN Verbal Fluency Model

ANOVA – RBN Verbal Fluency Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	0.801	2	0.401	5.008	0.007	0.031	0.031
TxHxLipids	0.094	2	0.047	0.589	0.556	0.004	0.004
Residuals	25.126	314	0.080				

Note. Type III Sum of Squares

Verbal fluency (raw score). In contrast to the analysis conducted for raw score Verbal Fluency in the Test set, the validation analysis for raw scores concurred with the RBN analysis and showed a meaningful relation between the NP measure and TxHxHypertension, and no relation with TxHxLipids (TxHxHypertension: partial eta^2 = .020; TxHxLipids: partial eta^2 = .002). Table 27 shows the ANCOVA table for this analysis. A moderate between-group effect size was found between the highest and lowest levels of TxHxHypertension (Cohen's *d* = .34). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids was consistent with these findings.

Table 27

Raw Score Verbal Fluency Model

ANCOVA – Raw Score Verbal Fluency Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	890.845	2	445.423	3.180	0.043	0.018	0.020
TxHxLipids	96.593	2	48.296	0.345	0.709	0.002	0.002
Age	633.808	1	633.808	4.525	0.034	0.013	0.014
Education	4575.913	1	4575.913	32.669	< .001	0.092	0.095
Residuals	43701.509	312	140.069				

Note. Type III Sum of Squares

Between the Test set and Validation set analyses, RBN Verbal Fluency consistently demonstrated a meaningful association with TxHxHypertension, showing poorer performance at higher levels of treatment history. The replication of the raw score analysis with the validation set showed agreement between RBN and raw score measures, but failed to replicate the findings of the Test set raw score analysis, which, in contrast, found no relation between the NP measure and CV risk factors. The existence of this relation appears likely, but would require further replication with additional datasets to verify the degree of impact that CV risk may impart to assessments of Verbal Fluency.

Episodic memory. Relations between CV risk and Episodic Memory were examined with the Logical Memory subtest and the Visual Reproduction subtest.

Logical memory (RBN score). For the relation between RBN performance on Logical Memory delayed free recall and CV risk factors, no evidence of a meaningful relation with TxHxHypertension or TxHxLipids was observed (TxHxHypertension partial $eta^2 = .003$; TxHxLipids partial $eta^2 < .001$). Table 28 shows the ANOVA table for this analysis. Visual inspection of added variable plots for TxHxHypertension and TxHxLipids also indicates no meaningful relation between independent variables and measure performance.

Table 28

RNB Logical Memory Delayed Free Recall Model

ANOVA – RNB Logical Memory Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	1.001	2	0.500	0.511	0.600	0.003	0.003
TxHxLipids	0.151	2	0.076	0.077	0.926	< .001	< .001
Residuals	313.219	320	0.979				

Note. Type III Sum of Squares

Logical memory (raw score). For raw score Logical Memory delayed free recall, Table 29 shows the results of the ANCOVA table for this analysis. Consistent with the RBN analysis, no evidence of a meaningful relation between TxHxHypertension or TxHxLipids was found when controlling for age, education, and sex at birth (TxHxHypertension: partial eta^2 < .001; TxHxLipids: partial eta^2 < .001). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids agreed with these findings.

Table 29

Raw Score Logical Memory Delayed Free Recall Model

ANCOVA – Raw Score Logical Memory Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	2.428	2	1.214	0.098	0.906	< .001	< .001
TxHxLipids	0.071	2	0.036	0.003	0.997	< .001	< .001
Age	222.862	1	222.862	18.074	< .001	0.049	0.054
Education	341.642	1	341.642	27.708	< .001	0.075	0.080
Sex at Birth	72.145	1	72.145	5.851	0.016	0.016	0.018
Residuals	3908.673	317	12.330				

Note. Type III Sum of Squares

The four analyses of Logical Memory performance across the Test and Validation sets indicated that no meaningful relation exists between TxHxHypertension or TxHxLipids and Logical Memory performance.

Visual reproduction (RBN score). Table 30 shows the ANOVA table for this analysis, which found no evidence of a meaningful relation between TxHxHypertension or TxHxLipids and, consistent with the Test set analysis, returned very small effect sizes explaining less than 1 percent of variance (TxHxHypertension partial eta^2 = .003; TxHxLipids partial eta^2 = .006). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids also indicated no meaningful relation between independent variables and measure performance.

Table 30

RBN Visual Reproduction Delayed Free Recall Model

ANOVA – RBN Visual Reproduction Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	0.954	2	0.477	0.452	0.637	0.003	0.003
TxHxLipids	2.160	2	1.080	1.022	0.361	0.006	0.006
Residuals	338.021	320	1.056				

Note. Type III Sum of Squares

Visual reproduction (raw score). Table 31 shows the ANCOVA table for raw score performance on the Visual Reproduction delayed free recall task this analysis. Consistent with other analyses, no meaningful relation with TxHxHypertension or TxHxLipids was observed (TxHxHypertension: partial eta^2 = .002; TxHxLipids: partial

eta^2 = .008). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids indicated no meaningful relation between independent variables and measure performance.

Table 31

Raw Score Visual Reproduction Delayed Free Recall Model

ANCOVA – Raw Score Visual Reproduction Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	4.806	2	2.403	0.337	0.714	0.002	0.002
TxHxLipids	17.196	2	8.598	1.205	0.301	0.006	0.008
Age	282.130	1	282.130	39.532	< .001	0.100	0.111
Education	234.479	1	234.479	32.855	< .001	0.084	0.094
Residuals	2269.510	318	7.137				

Note. Type III Sum of Squares

Considering the four analyses of Visual Reproduction performance across the Test and Validation sets, the results of both the RBN and raw score analyses indicated that a meaningful relation was not observed for Visual Reproduction performance and either CV risk factor.

Volumetric measures of whole brain gray and white matter. Relations between CV risk and brain matter volumes were examined to determine if group-based differences in gray and white matter volume corresponded with observed neuropsychological performance.

Gray matter volume. Table 32 shows the ANCOVA table for this analysis for the proportional measure of total brain gray matter volume after correcting for head size. As with the Test set, there was no evidence of a significant association between

TxHxHypertension or TxHxLipids and the analysis returned relatively small effect sizes when compared to covariates (TxHxHypertension partial eta^2 = .013; TxHxLipids partial eta^2 = .001). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids also indicates no meaningful relation between independent variables and proportional gray matter volume.

Table 32

Total Percentage Gray Matter Volume Model

ANCOVA – Total Percentage Gray Matter Volume Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	10.525	2	5.262	1.818	0.164	0.010	0.013
TxHxLipids	1.075	2	0.537	0.186	0.831	< .001	0.001
Age	185.736	1	185.736	64.182	< .001	0.170	0.188
Sex at Birth	88.790	1	88.790	30.682	< .001	0.081	0.099
Residuals	804.502	278	2.894				

Note. Type III Sum of Squares

White matter volume. As with the gray matter model, Table 33 shows the results of the ANCOVA table for the analysis of CV risk factors, age, sex at birth, and the proportional measure of total brain white matter volume. This analysis found no evidence of a significant association with TxHxHypertension or TxHxLipids when controlling for age and sex at birth (TxHxHypertension: partial eta^2 = .013; TxHxLipids: partial eta^2 = .006). Visual inspection of added variable plots for TxHxHypertension and TxHxLipids agreed with these findings.

Table 33

Total Percentage White Matter Volume Model

ANCOVA – Total Percentage White Matter Volume Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	17.159	2	8.579	1.845	0.160	0.011	0.013
TxHxLipids	7.675	2	3.838	0.825	0.439	0.005	0.006
Age	236.204	1	236.204	50.794	< .001	0.146	0.154
Sex at Birth	65.714	1	65.714	14.131	< .001	0.041	0.048
Residuals	1292.761	278	4.650				

Note. Type III Sum of Squares

Combined with the results from the Test set analyses, the results of these analyses suggested that an association does not exist between either CV risk factor and proportional measures of total gray and white matter volume.

Validation set summary. Table 6 summarizes the results of Validation set analyses. TxHxHypertension was associated with performance on Verbal Fluency, Digit Symbol Coding, and Similarities across models using raw scores and RBN. No NP measures were associated with TxHxLipids and no volumetric measures of brain matter volume were associated with CV risk factors. These results were broadly consistent with the results of the Test set analyses; however, of the four analyses of Verbal Fluency performance, only the Test set raw score analysis found no evidence of a meaningful association between TxHxHypertension and NP performance. Because of inconsistent support, it cannot be concluded that Verbal Fluency is associated with TxHxHypertension based on these analyses. Effect sizes within meaningful associations remained small across all analyses, with partial eta^2 values falling between .010 and .040.

Table 34

Summary of Test and Validation Dataset Analyses

		Regression Based Norms Measures			Raw Score and Volumetric Measures					
NP and MRI Measures		TxHx Hypertension	TxHx Lipids	Interaction	TxHx Hypertension	TxHx Lipids	Interaction	Age	Education	Sex at Birth
Boston Naming Task	Test	Not Associated	Not Associated	Not Included in Final Model	Not Associated	Not Associated	Not Included in Final Model	**Associated**	**Associated**	Not Included in Final Model
	Validation	Not Associated	Not Associated	Not Included in Final Model	Not Associated	Not Associated	Not Included in Final Model	**Associated**	**Associated**	Not Included in Final Model
Similarities	Test	**Associated**	Not Associated	Not Included in Final Model	**Associated**	Not Associated	Not Included in Final Model	**Associated**	**Associated**	Not Included in Final Model
	Validation	**Associated**	Not Associated	Not Included in Final Model	**Associated**	Not Associated	Not Included in Final Model	**Associated**	**Associated**	Not Included in Final Model
Digit Symbol Coding	Test	**Associated**	Not Associated	Not Included in Final Model	**Associated**	Not Associated	Not Included in Final Model	**Associated**	**Associated**	**Associated**
	Validation	**Associated**	Not Associated	Not Included in Final Model	**Associated**	Not Associated	Not Included in Final Model	**Associated**	**Associated**	**Associated**
Verbal Fluency	Test	**Associated**	Not Associated	Not Included in Final Model	Not Associated	Not Associated	Not Included in Final Model	**Associated**	**Associated**	Not Included in Final Model
	Validation	**Associated**	Not Associated	Not Included in Final Model	**Associated**	Not Associated	Not Included in Final Model	**Associated**	**Associated**	Not Included in Final Model
Logical Memory	Test	Not Associated	Not Associated	Not Included in Final Model	Not Associated	Not Associated	Not Included in Final Model	**Associated**	**Associated**	**Associated**
	Validation	Not Associated	Not Associated	Not Included in Final Model	Not Associated	Not Associated	Not Included in Final Model	**Associated**	**Associated**	**Associated**
Visual Reproduction	Test	Not Associated	Not Associated	Not Included in Final Model	Not Associated	Not Associated	Not Included in Final Model	**Associated**	**Associated**	Not Included in Final Model
	Validation	Not Associated	Not Associated	Not Included in Final Model	Not Associated	Not Associated	Not Included in Final Model	**Associated**	**Associated**	Not Included in Final Model
Gray Matter Volume	Test	--	--	--	Not Associated	Not Associated	Not Included in Final Model	**Associated**	Not Included in Final Model	**Associated**
	Validation	--	--	--	Not Associated	Not Associated	Not Included in Final Model	**Associated**	Not Included in Final Model	**Associated**
White Matter Volume	Test	--	--	--	Not Associated	Not Associated	Not Included in Final Model	**Associated**	Not Included in Final Model	**Associated**
	Validation	--	--	--	Not Associated	Not Associated	Not Included in Final Model	**Associated**	Not Included in Final Model	**Associated**

Chapter 4

Discussion

The primary aim of this study was to examine the relation between key domains of cognition and indirect markers of CV risk in a community sample where individuals were grouped according to medication treatment history. Memory is both a highly circumscribed cognitive operation located within the temporal lobes, and generally considered to be the earliest cognitive sign of dysfunction (Jack et al., 2013). As such, a potential finding was that only memory would be associated with CV risk. Other cognitive functions, such as executive functioning and lexical access, are couched within neural networks that are more broadly distributed throughout the brain. Because of the diffuse impact of CV factors on whole brain functionality, findings of impairment in one or both of these domains was also a possibility, and may have occurred without or without corresponding impairment on measures of memory. As such, all, some, or none of these domains may have been impacted by CV influences on neuronal function, and that pattern is informative about how CV risk can factor into risk for cognitive decline.

Of the six NP measures tested for associations, only two measures evidenced an association with medication treatment history. Associations between measures of processing speed/graphomotor functioning and of naming/lexical access were observed with participants who were treated for hypertension across both an initial Test study sample and within a secondary Validation study sample. Participants who were treated for hypertension scored lower on both tests compared to participants without treatment history. Effect sizes for these associations were small, explaining less than 5% of variance in the outcome measure, with partial eta^2 values between .010 and .040;

however, the conclusion that these associations are meaningful is supported both by the *a priori* assumption that participants drawn from a community sample are without clinically significant impairment, and by the broadly consistent findings between the independently analyzed Test and Validation sample groups.

Meaningful relations were restricted to treatment history for hypertension and no meaningful associations were found between domains of cognition and treatment history for hyperlipidemia. Additionally, no meaningful interactions between studied CV risk factors were observed, counter to expectations stated in Hypothesis 1b. Further, no measure of episodic memory was observed to be associated with CV risk factors. This preempted the assumptions of Hypothesis 1c, which indicated that visual episodic memory would produce a larger effect size compared to verbal episodic memory testing. This larger effect size would have supported the hypothesis that a visual measure of episodic memory would be more sensitive to impairment related to CV risk factors than similar verbal measures. In all analyses, episodic memory measures were related to effect sizes much smaller than 1 percent and were not determined to be meaningfully associated with CV risk factors.

The secondary aim of this study was to identify any concurrent differences in whole brain gray and white matter concomitant with performance differences observed on neuropsychological testing. While neuropsychological testing detected differences among participant groups with different degrees of history for treatment of hypertension, no neuroanatomical differences were observed for these groups.

Neuropsychological Performance in the Context of CV Risk

In the present study, evidence was found supporting an association between an established history of intervention with medication typically prescribed to address hypertension and cognitive performance on NP tests sensitive to deficits affecting relatively non-localizing neurocognitive networks. Within these associations, individuals who were consistently treated for hypertension scored lower.

The Digit Symbol subtest is well-known to be a sensitive measure to neuropsychological impairment (González-Blanch et al., 2011; Joy, Kaplan, & Fein, 2004). Successful performance requires a range of cognitive operations including motor control, visual scanning, and incidental learning. In this research, we were not able to disambiguate between all three of these domains; nonetheless, one or some combination of these cognitive operations likely negatively impacted test performance. Between-group performance differed across all levels of treatment history for hypertension. Reduced output on this task in the context of CV risk suggests these cognitive operations may be among the earliest cognitive signs of a potentially pernicious cognitive consequence related to CV risk.

The Similarities test is a measure of verbal concept formation requiring participants to provide the superordinate concept for word pairs. There are a variety of cognitive operations that underlie performance, including problem solving and word finding/lexical access. A reduced score on this test indicates a greater occurrence of concrete (and therefore less superordinate) responses, reflecting some incapacity to find an optimal abstract response. It is possible that subtle to mild word finding difficulty could explain these between-group differences. Modification to test administration could

help to disambiguate the nature of the underlying impairment observed. For test items that yielded less than an optimal response, participants could be queried with a multiple choice. The extent to which participants benefit from multiple choice cuing can clarify the involvement of word finding issues in yielding reduced Similarities performance, compared to a true reduction in ability to extrapolate to a superordinate connection (see WAIS-R NI; Kaplan, Fein, Morris, & Delis, 1991 for an example of this administration).

As noted above, word finding and graphomotor processing do not necessarily localize to a single brain region. By contrast, episodic memory is well-known to be mediated and localized to medial temporal lobe brain regions. In dementia syndromes such as AD, episodic memory is often viewed as the earliest and most prominent area of cognitive disability. To the extent that CV disease contributes to dementia syndromes, these data suggest that word finding and graphomotor processing may be early signs of cognitive impairment. As well, tests of episodic memory and measures that access cognitive functions rooted in more circumscribed brain regions did not demonstrate sensitivity to potential impairment.

The nature of cognitive impairment assessment is one of sensitivity to impairment in general vs specificity that implicates a particular neurocognitive network. Results significant for episodic memory would have indicated a specific neurocognitive network involving the temporal lobe and the hippocampus, which has been linked to memory and AD (Den Heijer et al., 2012). However, the results of the present study identified impairment only on tests of lexical access and processing speed, which can occur in the context of any kind of cognitive impairment, regardless of cause. While detectable with NP measures sensitive to nonspecific impairment, these findings suggest that the early

signs of cognitive deficits are both mild and diverse, appearing most clearly on measures that access multiple domains of cognitive function.

Downstream Cognition in the Context of CV Intervention

Among individuals taking medication commonly prescribed to address hypertension, and without significant differences in measures of blood pressure, small but identifiable differences in performance on NP measures were observed. Consequently, this study indicates that interventions designed to address risk factors for CV disease, while generally successful at managing CV risk, do not prevent downstream neurocognitive dysfunction.

The absence of meaningful findings with respect to lipid modifying agents offers valuable insight into the value of assessing CV treatment history as a potential marker for cognitive decline and the possible subsequent emergence of a dementia illness. The independent variables employed in this study were constructed from the participant's demonstrated history of treatment with medication typically prescribed for hypertension and hyperlipidemia. Importantly, hypertension and hyperlipidemia, while frequently comorbid, are distinct conditions with diverse treatment plans and considerations. In particular, hypertensive medication is typically prescribed in the presence of elevated blood pressure levels or when a family history indicates an increased risk for elevated pressure (Jarraya, 2017). Conversely, lipid-modifying medication, in particular statin drugs, are often a valuable, proactive treatment begun on the basis of a patient's age (Silverman & Schmeidler, 2018), rather than in the context of specific risk indications.

As such, as a marker of underlying CV risk, treatment with lipid modifying agents may attempt to sort into groups individuals whose principal difference lay, not in their

underlying condition, but in how aggressive their primary care physician chooses to be with respect to cholesterol management. In contrast, while antihypertensive medications have some off-label usages, which may contribute to their use by individuals without concern for high blood pressure, it is highly unlikely to encounter an individual with untreated hypertension (Ang et al., 2020). The presence of observed group-based differences with respect to neuropsychological performance among hypertension treatment history groups supports the theoretical value of this indirect marker of CV risk.

Neuroanatomical Substrates of Impairment

While the present study reports associations between NP testing and treatment history for hypertension, no corresponding associations were found for treatment history and same-day volumetric measures of gray and white matter on MRI. The absence of meaningful findings associating MRI and hypertension treatment is surprising in the context of the pervading model of biomarkers of AD.

A prevailing model proposed by Jack and colleagues (2013) attempts to describe the chronology in which markers of AD present and thereafter become detectable. The presence of amyloid beta peptides (Aβ) in cerebrospinal fluid or positron emission tomography imaging is hypothesized to be among the earliest biomarkers signaling the emergence of dementia such as Alzheimer's disease; followed, perhaps by other pathophysiological and anatomical alterations. Thus the predominant model of AD biomarkers suggests that volumetric changes should precede cognitive changes. More intuitively, cognitive deficits likely either co-occur or precede detectable organic changes to the brain. The results of the current study align with this alternative expectation.

Although the model proposed by Jack and colleagues has been revised since the original publication (Jack et al., 2010) to de-emphasize the temporal relations between biomarkers, the updated model maintains that cognitive impairment does not emerged before biological signs of pathology. In part, this emphasis on concrete signs of physiological alterations reflects the underutilization of measures that may be particularly sensitive to neuropsychological impairment.

Wider adoption of digital assessment technology might provide a means to reliably measure behaviors that are difficult to quantify, including linguistic and acoustic markers that may be extracted for speech and verbal test responses and highly nuanced graphomotor output. Emerging research in digital technologies and process-based NP testing (Binaco et al., 2020; Emrani et al., 2018, 2019; Piers et al., 2017; Wasserman et al., 2019, 2020) continue to indicate that subtle cognitive performance markers may soon move the cognitive marker curve further to the left of the AD pathology cascade model.

CV Risk and Insidious Dementia

CV risk is associated with the emergence of insidious onset dementia. Hyperlipidemia and hypertension act upon blood vessels in the brain and heart, such that having one condition or the other would indicate a vasculopathy, in which the vessel may be narrowed by plaque or a disturbance in the hemodynamics of blood flow due to pressure. Regardless of the phenotype, these conditions within the blood vessels may result in reduction in brain profusion such that blood may not necessarily consistently flow through the brain, causing micro-disruptions in oxygenation (M. F. Elias et al., 2012).

Concomitant with fluctuating conditions with the vessel, deterioration of the blood-brain barrier can contribute to a greater accumulation of molecules in the brain that are damaging to neuronal function, as well as reducing the ability to regulate and clear these substances. The blood-brain barrier is composed of endothelial cells, pericytes, vascular smooth muscle cells, glia and neurons, that together act to control blood-brain barrier permeability and blood flow. Microstructural changes found in pericytes (e.g. intracellular inclusions, large lipid granules) correlate with capillary reduction, dilation of vessels, and the appearance of tortuous vessels (Hughes & Craft, 2016; Nelson, Sweeney, Sagare, & Zlokovic, 2016; Sweeney, Sagare, & Zlokovic, 2015), indicating a pathway by which CV risk factors result in reduced cerebral perfusion.

This two-hit vascular hypothesis (Zlokovic, 2011) asserts that vascular risk factors and cerebrovascular damage (hit 1) is the primary insult that has a causal sequence promoting blood-brain barrier dysfunction and reduction in cerebral blood flow, ultimately leading to accumulation of Aβ and other neuropathology in the brain associated with AD (hit 2). This model describes two pathways: 1.) a nonamyloid-β pathway, in which circulating neurotoxic molecules (e.g. thrombin, plasminogen, fibrinogen) and hypoperfusion induce early neuronal dysfunction; and 2.) an amyloidogenic Aβ pathway, in which Aβ clearance is derailed by blood-brain barrier dysfunction. This results in overexpression and enhanced processing of amyloid precursor protein, which can promote Aβ accumulation. The increase in Aβ (hit 2) amplifies neuronal dysfunction and accelerates the neurodegenerative processes of AD. Furthermore, Aβ is known to be a potent vasoconstrictor, thus impairing the mechanisms

regulating cerebral circulation, and perpetuating vascular dysfunction and neuropathology.

The current study can only hypothesize about the involvement of blood-brain barrier breach in explaining the observed associations between NP measures of processing speed and lexical access and CV risk in the absence of anatomical differences in structural brain MRI. Further study involving clinical samples and use of serum-based markers of blood-brain barrier deterioration will expand on the available evidence that explains the aetiology of cognitive changes relating to CV risk factors.

Regression-Based Norms

Use of RBN methods enables the cross-comparison of measure performance with differing qualities and characteristics, as well as allowing an individual's performance to be viewed within the context of the demographic factors that are known to, in part, impact performance. However, NP measures are not immune to cultural or functional biases (Fastenau, 1998; Strauss, Sherman, & Spreen, 2006), and normative scores allow for the ready evaluation of performance within the accepted paradigm that these biases have yet to be fully expunged (Duff & Ramezani, 2015; Oosterhuis et al., 2016; Shirk et al., 2011).

For the present study, RBNs were constructed based on accounting for the normative impact of age, education, and sex at birth on NP performance. Each analysis of RBN-based performance measures employing the Test and Validation data sets was repeated in an ANCOVA model using the raw score performance measure and for which the covariates of age, education and sex at birth were directly controlled. All but one set

of repeated analyses across the 12 analysis pairs (6 Test set pairs, 6 Validation set pairs) consistently yielded equivalent measures of statistical significance and effect size.

In the case of Test set analyses of raw score and RBN Verbal Fluency, only the RBN analysis returned a meaningful effect size. While this was not the case for the Validation set, in which both analyses supported the presence of a relation between treatment history for hypertension and Verbal Fluency performance, several factors may explain the contrasting outcomes of analysis with these two methods.

Firstly, the Test data set analyses involved the refinement of the model through the exclusion of non-meaningful interaction and covariate terms. For the Verbal Fluency analysis, sex at birth was excluded from the final model due to low effect size and non-significant *p*-value at an alpha level of .05. This differed from the design of the RBN performance score, in which sex at birth was retained in the model. Given that the effect sizes for NP performance was small across most analyses, never rising about 4%, it is possible that the exclusion of sex at birth resulted in other covariates absorbing variance that would otherwise have been attributed to the independent variables, particularly treatment history for hypertension.

Secondly, although one benefit of an RBN approach is that performance on NP measures is articulated as a continuous scale, rather than a discrete partition such as scaled scores (Lenhard et al., 2018), education as a covariate is typically recorded in non-continuous terms, often either as a grade-year equivalence scale or a rank-order diploma scale. The education variable available for these data was based on a rank-order diploma scale, compressing all possible education outcomes into only four potential categories: 1. “less than 12 years,” 2. “high school graduate, 3. “some college,” and 4. “graduate

college." As a consequence, the treatment of this important demographic factor as an ordinal variable may have obscured important, subtle contributions of education, which may have impacted both the raw score and RBN performance analyses, contributing to inconsistent findings.

Lastly, although the intention of this analytic approach was to reduce the potential of an erroneous finding through minimizing the total number of independent analyses performed, the final design resulted in 24 general linear models being tested for six NP dependent variables (6 Test set raw score, 6 Test set RBN, 6 Validation set raw score, 6 Validation set RBN). It is not unexpected that some analyses would return conflicting findings. In the case of Verbal Fluency, three of the four analyses performed with this dependent variable yielded meaningful associations with treatment history for hypertension. Nonetheless, the decision was made to not conclude a relation between CV risk and Verbal Fluency on the basis of these data. It was anticipated at the outset of the study that meaningful relations would withstand repeated analyses with two independent datasets (Test and Validation). While other measures meaningfully met this standard (Digit Symbol Coding and Similarities), inconsistent findings for Verbal Fluency indicate that further validation with a unrelated sample is necessary before further conclusions can be drawn.

Strengths and Limitations

The strengths of the present study include the use of a prestigious and trusted data set drawing on a healthy, community dwelling, independently functioning population without cognitive impairment. These analyses employ commonly administered tests of neuropsychological function and draw on pharmaceutical data as an indirect indicator of

CV risk. The methodology is structured to include several self-validation procedures, including repeat analyses of dependent variables based upon raw score performance and RBN performance, as well as replication in a hold-out sample. Decisions about meaningful findings were based on both a standard statistical decision criteria (alpha = .05) as well as a theoretically informed judgment considering the relative effect sizes of variables and between-group differences. In all cases in which a meaningful relation was concluded to exist, these indicators were in agreement.

The present study is not without limitations, many of which have already been discussed in detail, including the non-continuous nature of the education history variable used in these analyses and the limited ability to account for potential instances of polypharmacy. The homogeneity of the FHS sample limits the ability to generalize these results to demographically distinct groups. These results are best understood to describe the relation between medication usage for CV risk factors and cognitive performance among white individuals of middle age and older originating in the northeastern region of the United States. Efforts to expand on the current study would benefit from exploring a more racially and regionally diverse sample, as well as employing a less-restricted measure of educational attainment.

Conclusion

Medication history shows promise as an indirect measure of cardiovascular risk when assessing for cognitive impairment related to insidious onset dementia. Neuropsychological measures sensitive to diffuse cognitive change can detect small but present differences in performance among individuals with a consistent history of cardiovascular medication use for hypertension in independently functioning middle-aged

and older adults in a community sample. Crucially, these differences are detectable in the presence of monitored and well-controlled blood pressure, indicating that downstream cognitive consequences persist in the presence of intervention for hypertension.

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Appendix A

Tables and Figures of Additional Demographics

Table A1

Mean Blood Pressure Values for Hypertension Treatment History Groups

Mean Blood Pressure Values for Hypertension Treatment History Groups		N	Mean	Std. Deviation
Average systolic blood pressure (mmHg), Exam 9	Never Treated	374	123.12	14.755
	Partially Treated	170	125.80	15.515
	Fully Treated	516	128.83	16.633
	Total	1060	126.33	16.011
Average diastolic blood pressure (mmHg), Exam 9	Never Treated	374	72.95	8.644
	Partially Treated	170	72.42	9.149
	Fully Treated	516	69.65	9.781
	Total	1060	71.26	9.418

Table A2

Mean Cholesterol Values for Lipid Treatment History Groups

Mean Cholesterol Values for Lipid Treatment History Groups		N	Mean	Std. Deviation
HDL cholesterol (mg/dL), Exam 9	Never Treated	319	67.12	18.758
	Partially Treated	251	64.28	19.059
	Fully Treated	480	58.75	17.112
	Total	1050	62.62	18.456
Calculated LDL cholesterol (mg/dL), Exam 9	Never Treated	318	110.30	25.224
	Partially Treated	251	102.83	33.076
	Fully Treated	479	88.26	27.010
	Total	1048	98.44	29.694

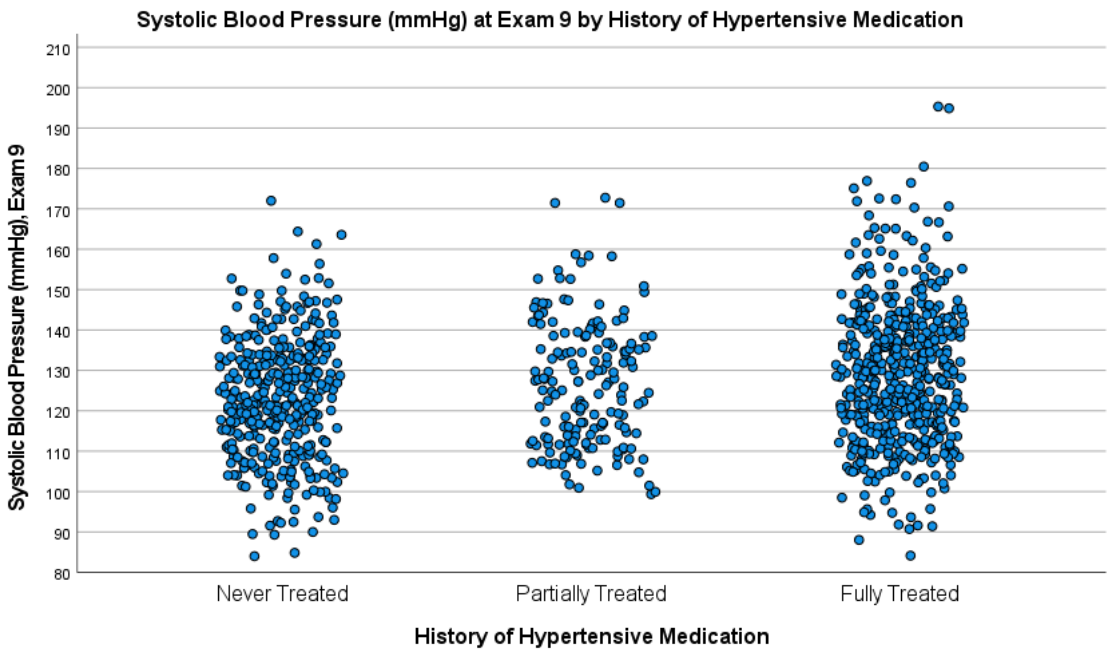

Figure A1. Systolic Blood Pressure (mmHg) at Exam 9 by History of Hypertensive Medication.

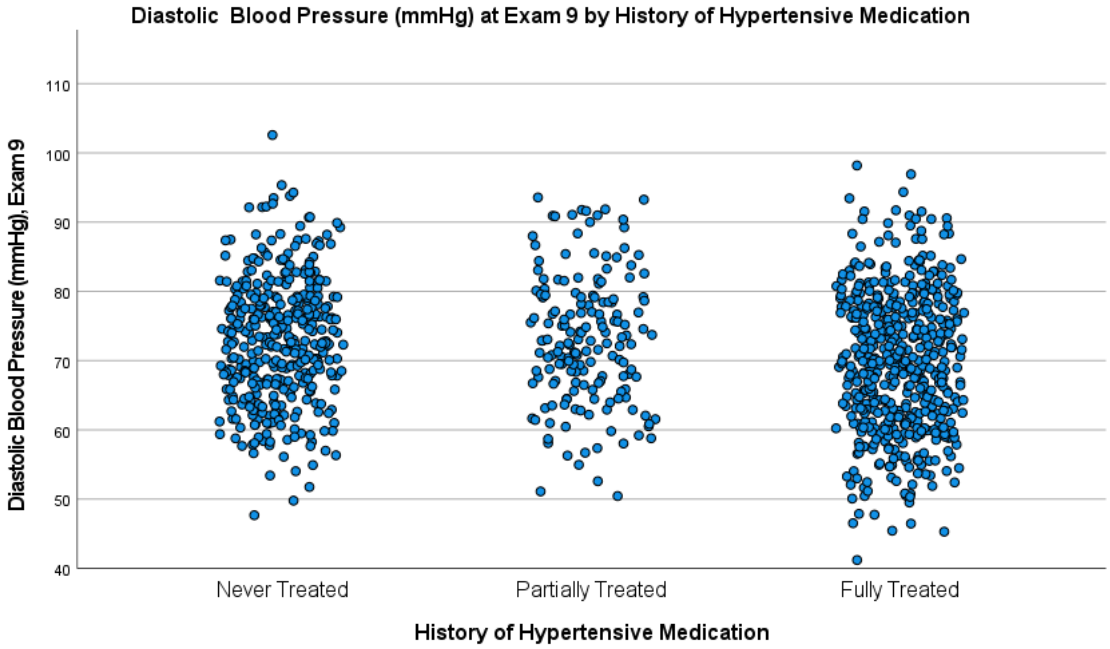

Figure A2. Diastolic Blood Pressure (mmHg) at Exam 9 by History of Hypertensive Medication.

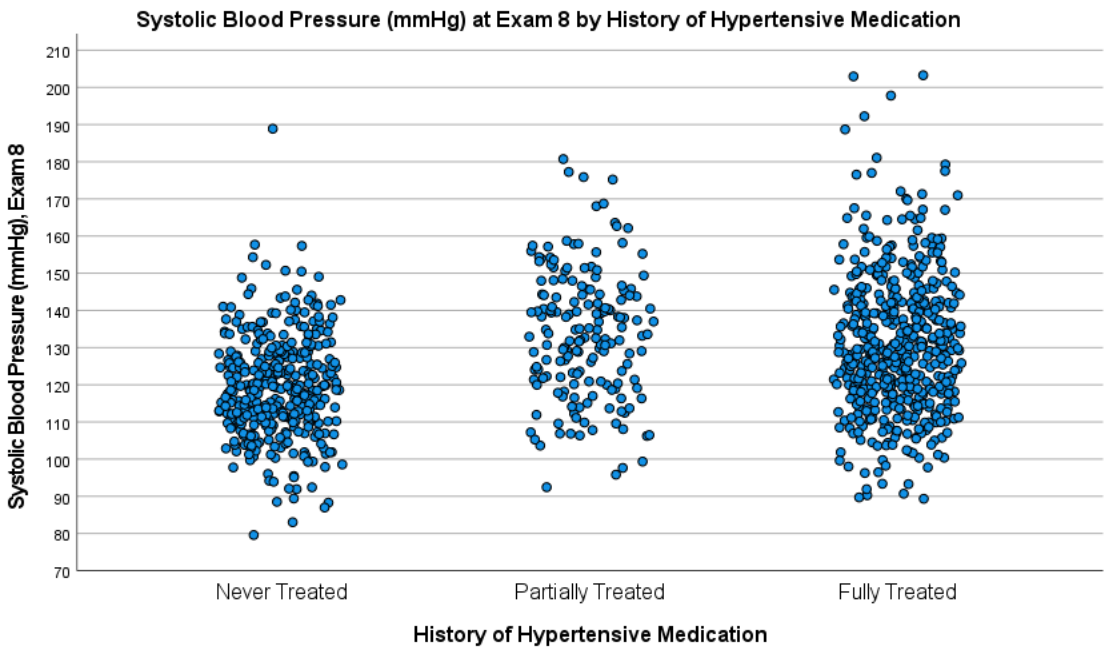

Figure A3. Systolic Blood Pressure (mmHg) at Exam 8 by History of Hypertensive Medication.

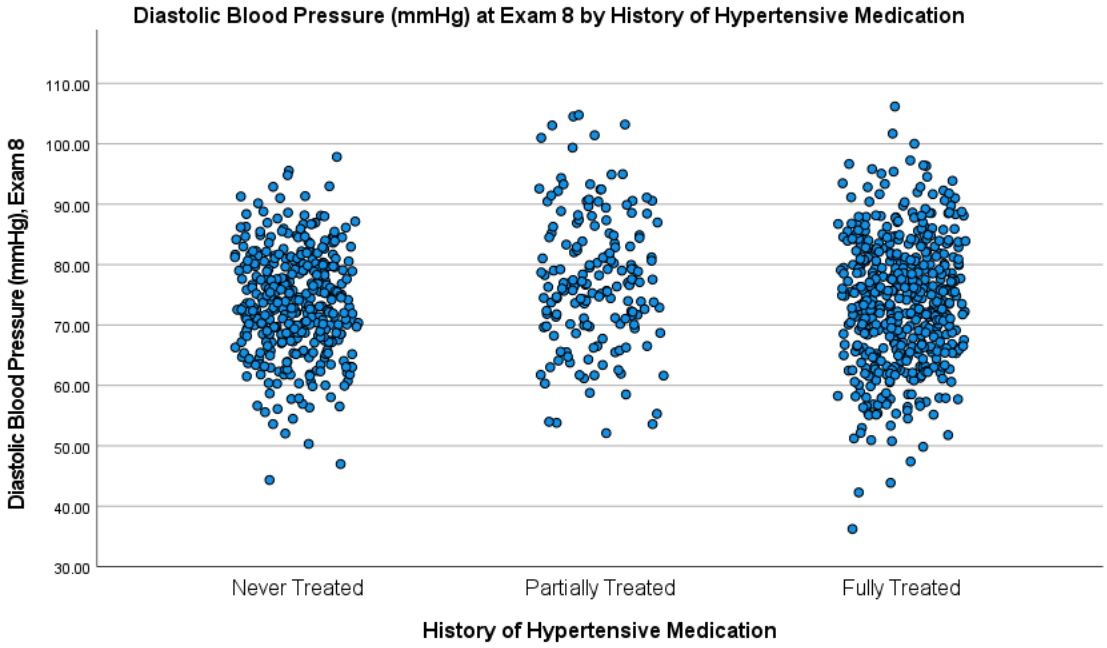

Figure A4. Diastolic Blood Pressure (mmHg) at Exam 8 by History of Hypertensive Medication.

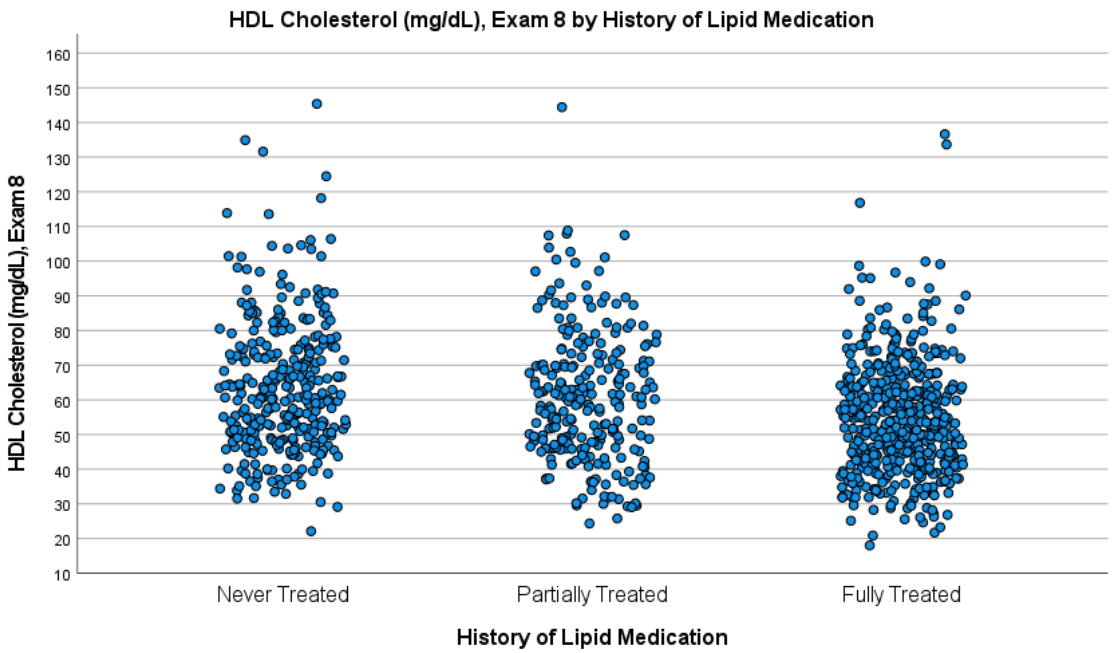

Figure A5. HDL Cholesterol (mg/dL), Exam 8 by History of Lipid Medication.

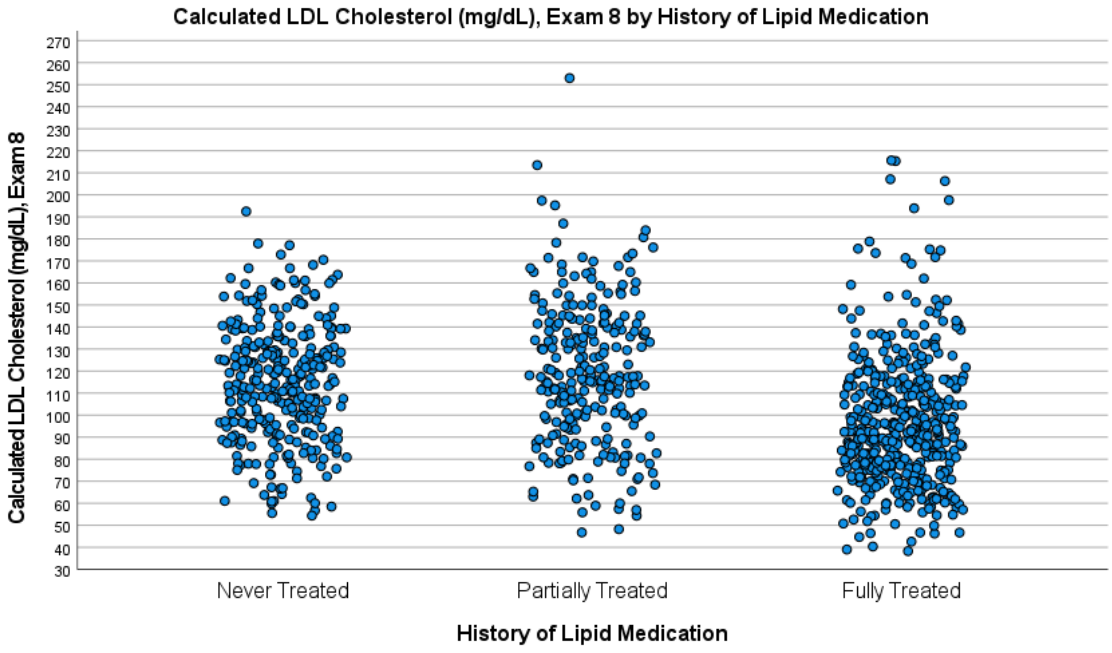

Figure A6. Calculated LDL Cholesterol (mg/dL), Exam 8 by History of Lipid Medication.

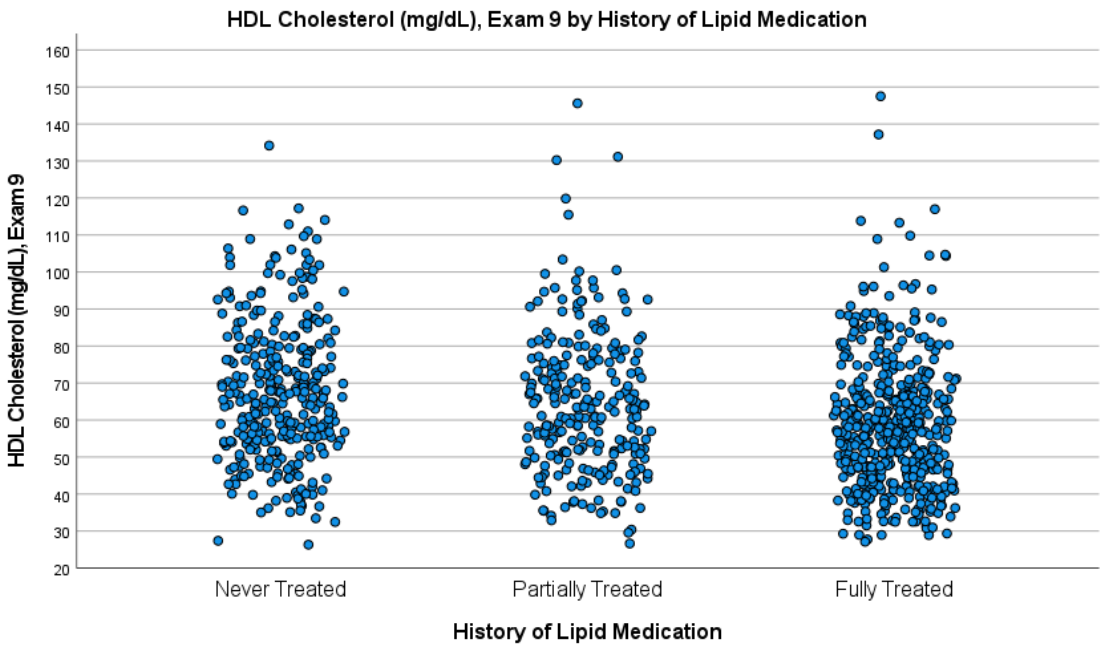

Figure A7. HDL Cholesterol (mg/dL), Exam 9 by History of Lipid Medication.

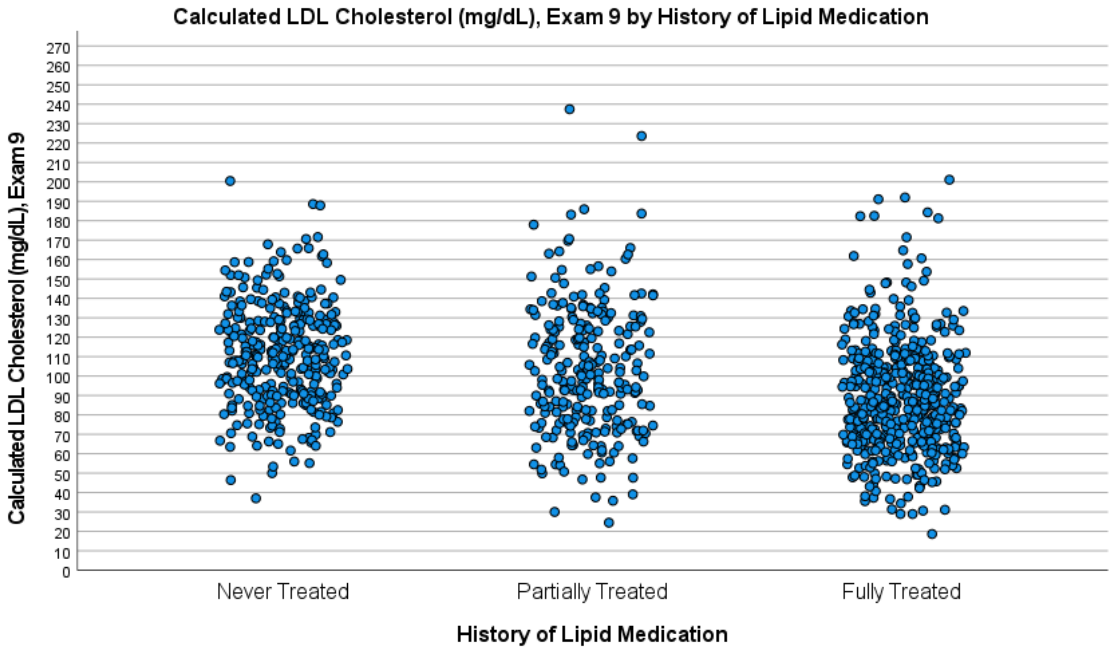

Figure A8. Calculated LDL Cholesterol (mg/dL), Exam 9 by History of Lipid Medication.

Appendix B

Analysis of Variance Tables of Test Dataset Final Models

Table B1

RBN Boston Naming Test Model

ANOVA – RBN BNT Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	1.147	2	0.573	0.358	0.699	0.001	0.001
TxHxLipids	3.209	2	1.605	1.003	0.367	0.003	0.003
Residuals	1102.344	689	1.600				

Note. Type III Sum of Squares
Interaction term excluded

Mean Differences Between Groups – RBN BNT Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Consistently Treated	0.082	-0.412	0.575	0.064
	Inconsistently Treated-Consistently Treated	0.095	-0.257	0.447	0.075
	Inconsistently Treated-Never Treated	0.013	-0.456	0.483	0.011
TxHxLipids	Never Treated-Consistently Treated	0.147	-0.290	0.583	0.116
	Inconsistently Treated-Consistently Treated	0.142	-0.232	0.516	0.112
	Inconsistently Treated-Never Treated	-0.005	-0.406	0.397	-0.004

Table B2

Raw Score Boston Naming Test Model

ANCOVA – Raw Scores BNT Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	10.312	2	5.156	1.863	0.157	0.009	0.010
TxHxLipids	2.843	2	1.422	0.514	0.599	0.003	0.003
Age	42.317	1	42.317	15.292	< .001	0.038	0.041
Education	56.200	1	56.200	20.310	< .001	0.051	0.054
Residuals	993.417	359	2.767				

Note. Type III Sum of Squares
Interaction term and sex at birth excluded

Mean Differences Between Groups

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Consistently Treated	-0.050	-0.889	0.789	-0.023
	Inconsistently Treated-Consistently Treated	0.070	-0.529	0.669	0.033
	Inconsistently Treated-Never Treated	0.120	-0.678	0.918	0.056
TxHxLipids	Never Treated-Consistently Treated	0.056	-0.685	0.798	0.026
	Inconsistently Treated-Consistently Treated	0.130	-0.506	0.766	0.060
	Inconsistently Treated-Never Treated	0.073	-0.609	0.756	0.034

Table B3

RBN Similarities Model

ANOVA – RBN Similarities Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	15.430	2	7.715	5.958	0.003	0.016	0.016
TxHxLipids	0.948	2	0.474	0.366	0.694	0.001	0.001
Residuals	925.847	715	1.295				

Note. Type III Sum of Squares
Interaction term excluded

Mean Differences Between Groups – RBN Similarities Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Consistently Treated	0.330	-0.107	0.768	0.290
	Inconsistently Treated-Consistently Treated	0.253	-0.057	0.563	0.222
	Inconsistently Treated-Never Treated	-0.077	-0.495	0.340	-0.068
TxHxLipids	Never Treated-Consistently Treated	-0.017	-0.400	0.366	-0.015
	Inconsistently Treated-Consistently Treated	0.076	-0.254	0.407	0.067
	Inconsistently Treated-Never Treated	0.093	-0.261	0.447	0.082

Table B4

Raw Score Similarities Model

ANCOVA – Raw Score Similarities Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	67.162	2	33.581	3.281	0.038	0.007	0.009
TxHxLipids	2.004	2	1.002	0.098	0.907	2.146e -4	2.738e -4
Age	117.570	1	117.570	11.489	< .001	0.013	0.016
Education	1832.576	1	1832.576	179.075	< .001	0.196	0.200
Residuals	7317.008	715	10.234				

Note. Type III Sum of Squares
Interaction term and sex at birth excluded

Mean Differences Between Groups – Raw Scores Similarities Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Consistently Treated	0.710	-0.515	1.935	0.223
	Inconsistently Treated-Consistently Treated	0.609	-0.258	1.476	0.191
	Inconsistently Treated-Never Treated	-0.101	-1.271	1.069	-0.032
TxHxLipids	Never Treated-Consistently Treated	-0.121	-1.191	0.950	-0.038
	Inconsistently Treated-Consistently Treated	-0.004	-0.929	0.922	-0.001
	Inconsistently Treated-Never Treated	0.117	-0.872	1.106	0.037

Table B5

RBN Digit Symbol Coding Model

ANOVA – RBN Digit Symbol Coding Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	9.669	2	4.835	4.683	0.010	0.014	0.014
TxHxLipids	1.356	2	0.678	0.657	0.519	0.002	0.002
Residuals	665.871	645	1.032				

Note. Type III Sum of Squares
Interaction term excluded

Mean Differences Between Groups – RBN Digit Symbol Coding Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Consistently Treated	0.267	-0.137	0.671	0.263
	Inconsistently Treated-Consistently Treated	0.237	-0.054	0.527	0.233
	Inconsistently Treated-Never Treated	-0.030	-0.419	0.359	-0.030
TxHxLipids	Never Treated-Consistently Treated	0.113	-0.248	0.473	0.111
	Inconsistently Treated-Consistently Treated	0.035	-0.275	0.345	0.035
	Inconsistently Treated-Never Treated	-0.078	-0.411	0.256	-0.076

Table B6

Raw Score Digit Symbol Coding Model

ANCOVA – Raw Score Digit Symbol Coding Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	1219.650	2	609.825	4.797	0.009	0.012	0.015
TxHxLipids	191.115	2	95.558	0.752	0.472	0.002	0.002
Age	14354.168	1	14354.168	112.901	< .001	0.136	0.150
Education	3513.599	1	3513.599	27.636	< .001	0.033	0.041
Sex at Birth	4425.942	1	4425.942	34.812	< .001	0.042	0.051
Residuals	81623.590	642	127.140				

Note. Type III Sum of Squares
Interaction term excluded

Mean Differences Between Groups – Raw Score Digit Symbol Coding Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Consistently Treated	3.138	-1.346	7.622	0.278
	Inconsistently Treated-Consistently Treated	2.791	-0.434	6.015	0.247
	Inconsistently Treated-Never Treated	-0.347	-4.667	3.972	-0.031
TxHxLipids	Never Treated-Consistently Treated	1.372	-2.629	5.372	0.122
	Inconsistently Treated-Consistently Treated	0.446	-2.994	3.886	0.040
	Inconsistently Treated-Never Treated	-0.926	-4.630	2.778	-0.082

Table B7

RBN Verbal Fluency Model

ANOVA – RBN Verbal Fluency Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	0.842	2	0.421	5.637	0.004	0.016	0.016
TxHxLipids	0.281	2	0.141	1.884	0.153	0.005	0.005
Residuals	51.876	695	0.075				

Note. Type III Sum of Squares
Interaction term excluded

Mean Differences Between Groups – RBN Verbal Fluency Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Inconsistently Treated	-0.033	-0.138	0.073	-0.119
	Consistently Treated-Inconsistently Treated	-0.092	-0.167	-0.017	-0.337
	Consistently Treated-Never Treated	-0.059	-0.160	0.041	-0.218
TxHxLipids	Never Treated-Consistently Treated	0.028	-0.065	0.121	0.103
	Inconsistently Treated-Consistently Treated	0.051	-0.030	0.131	0.185
	Inconsistently Treated-Never Treated	0.022	-0.064	0.109	0.082

Table B8

Raw Score Verbal Fluency Model

ANCOVA – Raw Score Verbal Fluency Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	667.126	2	333.563	2.409	0.091	0.006	0.007
TxHxLipids	196.718	2	98.359	0.710	0.492	0.002	0.002
Age	2503.217	1	2503.217	18.078	< .001	0.023	0.025
Education	7119.014	1	7119.014	51.411	< .001	0.067	0.069
Residuals	96099.105	694	138.471				

Note. Type III Sum of Squares
Interaction term and sex at birth excluded

Mean Differences Between Groups – Raw Score Verbal Fluency Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Inconsistently Treated	-2.219	-6.748	2.310	-0.188
	Consistently Treated-Inconsistently Treated	-2.980	-6.226	0.266	-0.253
	Consistently Treated-Never Treated	-0.761	-5.105	3.582	-0.065
TxHxLipids	Never Treated-Consistently Treated	0.258	-3.752	4.268	0.022
	Inconsistently Treated-Consistently Treated	1.306	-2.156	4.767	0.111
	Inconsistently Treated-Never Treated	1.048	-2.664	4.759	0.089

Table B9

RNB Logical Memory Delayed Free Recall Model

ANOVA – RNB Logical Memory Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	2.782	2	1.391	1.366	0.256	0.004	0.004
TxHxLipids	1.319	2	0.659	0.648	0.523	0.002	0.002
Residuals	719.632	707	1.018				

Note. Type III Sum of Squares
Interaction term excluded

Mean Differences Between Groups – RNB Logical Memory Delayed Free Recall Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Inconsistently Treated	-0.114	-0.506	0.278	-0.113
	Consistently Treated-Inconsistently Treated	0.030	-0.245	0.306	0.030
	Consistently Treated-Never Treated	0.144	-0.231	0.519	0.143
TxHxLipids	Never Treated-Consistently Treated	0.043	-0.298	0.384	0.043
	Inconsistently Treated-Consistently Treated	0.110	-0.184	0.405	0.109
	Inconsistently Treated-Never Treated	0.067	-0.248	0.383	0.067

Table B10

Raw Score Logical Memory Delayed Free Recall Model

ANCOVA – Raw Score Logical Memory Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	51.066	2	25.533	1.993	0.137	0.005	0.006
TxHxLipids	13.226	2	6.613	0.516	0.597	0.001	0.001
Age	269.078	1	269.078	20.999	< .001	0.027	0.029
Education	549.517	1	549.517	42.884	< .001	0.055	0.057
Sex at Birth	166.099	1	166.099	12.962	< .001	0.016	0.018
Residuals	9021.086	704	12.814				

Note. Type III Sum of Squares
Interaction term excluded

Mean Differences Between Groups – Raw Score Logical Memory Delayed Free Recall Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Inconsistently Treated	-0.495	-1.885	0.896	-0.138
	Consistently Treated-Inconsistently Treated	0.131	-0.848	1.109	0.037
	Consistently Treated-Never Treated	0.626	-0.704	1.955	0.175
TxHxLipids	Never Treated-Consistently Treated	0.013	-1.197	1.223	0.004
	Inconsistently Treated-Consistently Treated	0.352	-0.693	1.397	0.098
	Inconsistently Treated-Never Treated	0.339	-0.780	1.459	0.095

Table B11

RBN Visual Reproduction Delayed Free Recall Model

ANOVA – RBN Visual Reproduction Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	4.671	2	2.335	2.206	0.111	0.006	0.006
TxHxLipids	2.252	2	1.126	1.064	0.346	0.003	0.003
Residuals	754.869	713	1.059				

Note. Type III Sum of Squares
Interaction term excluded

Mean Differences Between Groups – RBN Visual Reproduction Delayed Free Recall Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Inconsistently Treated	-0.149	-0.543	0.245	-0.145
	Consistently Treated-Inconsistently Treated	-0.239	-0.519	0.042	-0.232
	Consistently Treated-Never Treated	-0.090	-0.466	0.287	-0.087
TxHxLipids	Never Treated-Consistently Treated	-0.090	-0.438	0.257	-0.088
	Inconsistently Treated-Consistently Treated	0.063	-0.236	0.362	0.061
	Inconsistently Treated-Never Treated	0.153	-0.168	0.474	0.148

Table B12

Raw Score Visual Reproduction Delayed Free Recall Model

ANCOVA – Raw Score Visual Reproduction Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	36.130	2	18.065	2.511	0.082	0.006	0.007
TxHxLipids	13.533	2	6.767	0.941	0.391	0.002	0.003
Age	549.893	1	549.893	76.441	< .001	0.092	0.097
Education	252.441	1	252.441	35.092	< .001	0.042	0.047
Residuals	5114.680	711	7.194				

Note. Type III Sum of Squares
Interaction term and Sex at Birth excluded

Mean Differences Between Groups – Raw Score Visual Reproduction Delayed Free Recall Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Inconsistently Treated	-0.401	-1.427	0.624	-0.150
	Consistently Treated-Inconsistently Treated	-0.692	-1.423	0.038	-0.258
	Consistently Treated-Never Treated	-0.291	-1.271	0.689	-0.109
TxHxLipids	Never Treated-Consistently Treated	-0.202	-1.106	0.702	-0.075
	Inconsistently Treated-Consistently Treated	0.160	-0.619	0.938	0.060
	Inconsistently Treated-Never Treated	0.361	-0.474	1.197	0.135

Table B13

Total Percentage Gray Matter Volume Model

ANCOVA – Total Percentage Gray Matter Volume Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	5.696	2	2.848	1.158	0.315	0.003	0.004
TxHxLipids	4.663	2	2.331	0.948	0.388	0.003	0.004
Age	343.040	1	343.040	139.504	< .001	0.192	0.208
Sex at Birth	131.263	1	131.263	53.381	< .001	0.073	0.091
Residuals	1305.730	531	2.459				

Note. Type III Sum of Squares
Interaction term and Education excluded

Mean Differences Between Groups – Total Percentage Gray Matter Volume Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Consistently Treated	0.241	-0.439	0.922	0.154
	Inconsistently Treated-Consistently Treated	0.046	-0.446	0.538	0.029
	Inconsistently Treated-Never Treated	-0.195	-0.854	0.463	-0.125
TxHxLipids	Never Treated-Consistently Treated	-0.206	-0.815	0.402	-0.132
	Inconsistently Treated-Consistently Treated	0.011	-0.516	0.538	0.007
	Inconsistently Treated-Never Treated	0.217	-0.347	0.782	0.138

Table B14

Total Percentage White Matter Volume Model

ANCOVA – Total Percentage White Matter Volume Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	3.273	2	1.637	0.403	0.668	0.001	0.002
TxHxLipids	1.052	2	0.526	0.130	0.878	< .001	< .001
Age	381.432	1	381.432	93.958	< .001	0.148	0.150
Sex at Birth	41.956	1	41.956	10.335	0.001	0.016	0.019
Residuals	2155.645	531	4.060				

Note. Type III Sum of Squares
Interaction term and Education excluded

Mean Differences Between Groups – Total Percentage White Matter Volume Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Never Treated-Consistently Treated	0.111	-0.763	0.986	0.055
	Inconsistently Treated-Consistently Treated	0.227	-0.406	0.859	0.113
	Inconsistently Treated-Never Treated	0.115	-0.731	0.962	0.057
TxHxLipids	Never Treated-Consistently Treated	0.094	-0.688	0.876	0.047
	Inconsistently Treated-Consistently Treated	0.093	-0.584	0.770	0.046
	Inconsistently Treated-Never Treated	-0.001	-0.726	0.724	-0.001

Appendix C

Added Variable Plots of Test Dataset Final Models

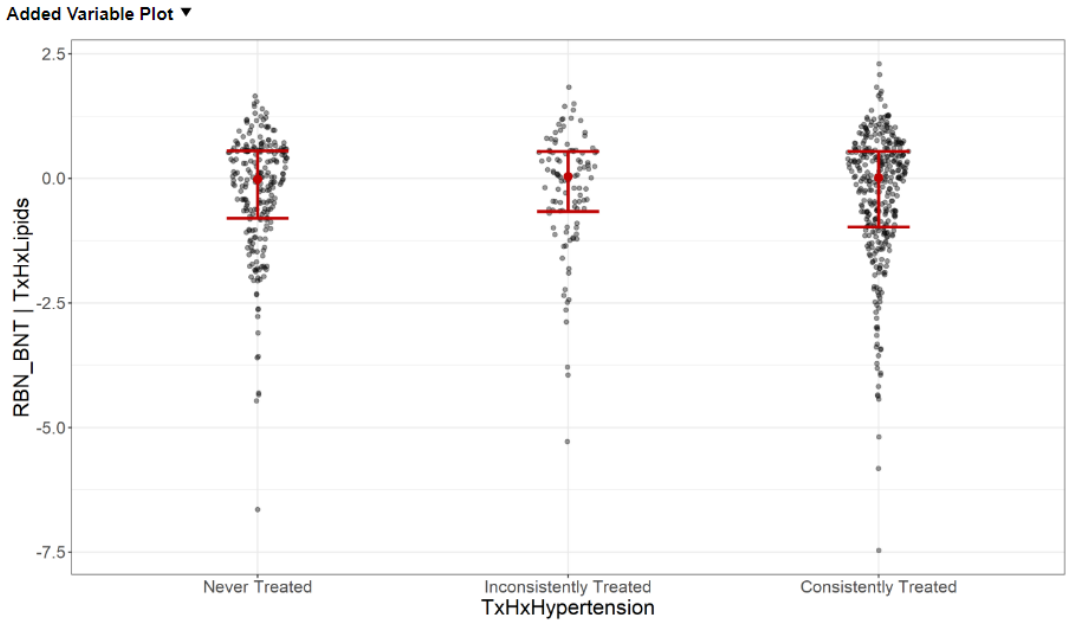

Figure C1. RBN BNT Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

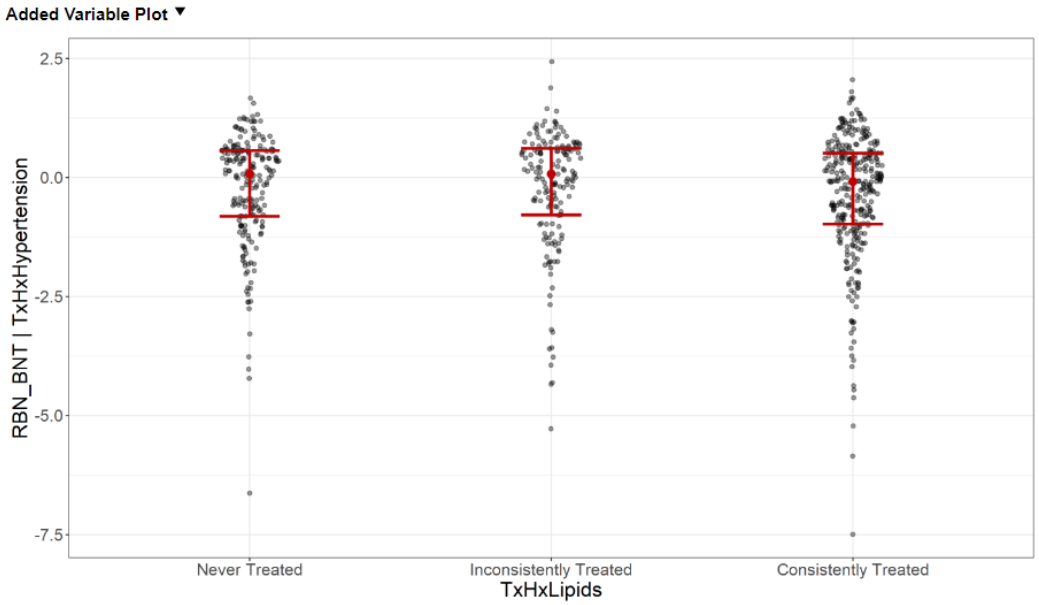

Figure C2. RBN BNT Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

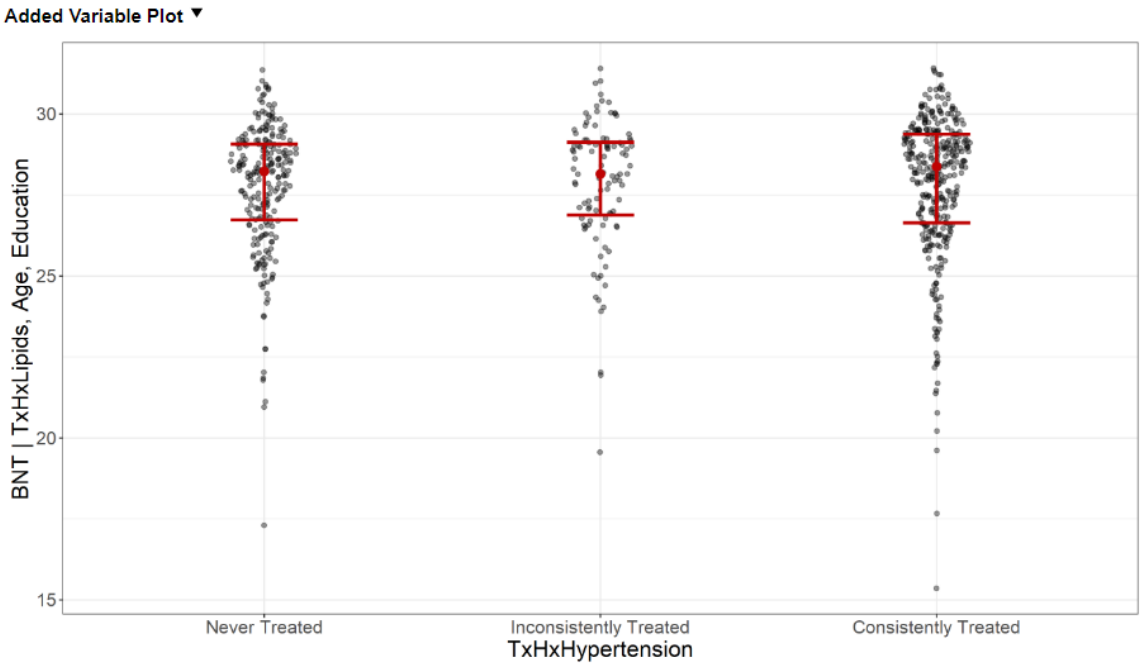

Figure C3. Raw Score BNT Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

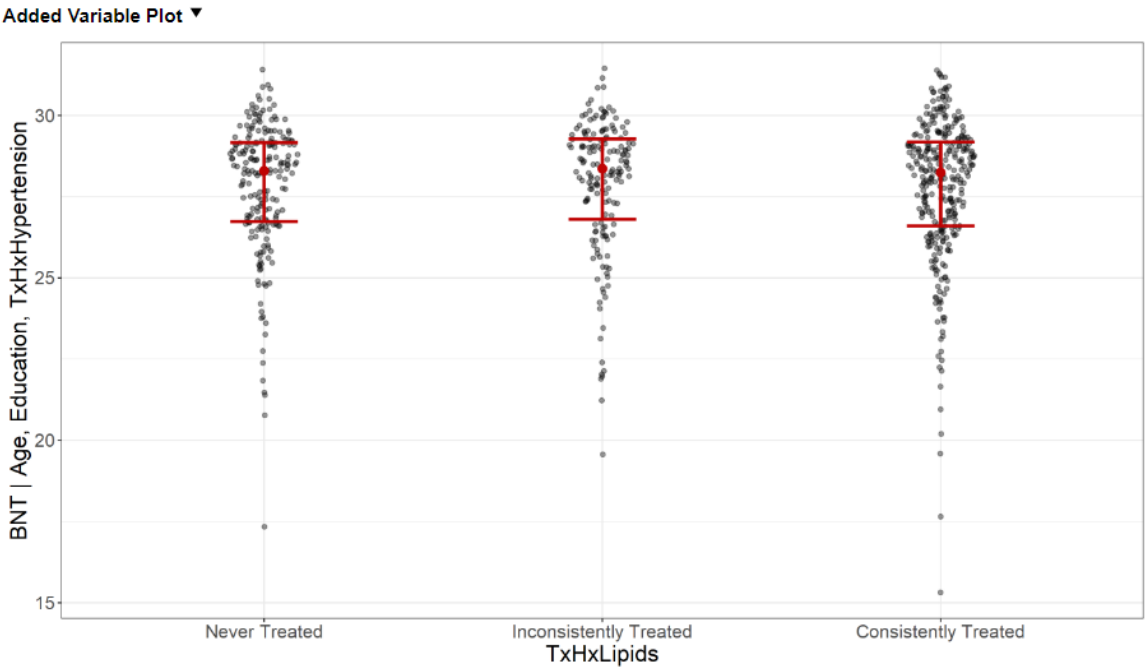

Figure C4. Raw Score BNT Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

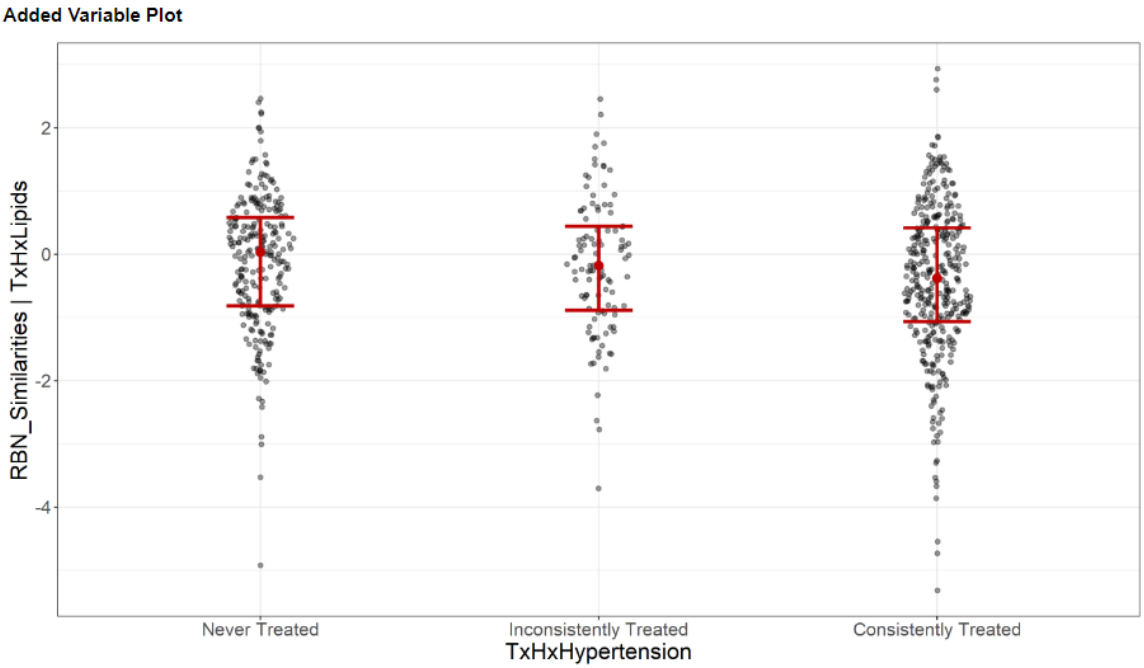

Figure C5. RBN Similarities Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

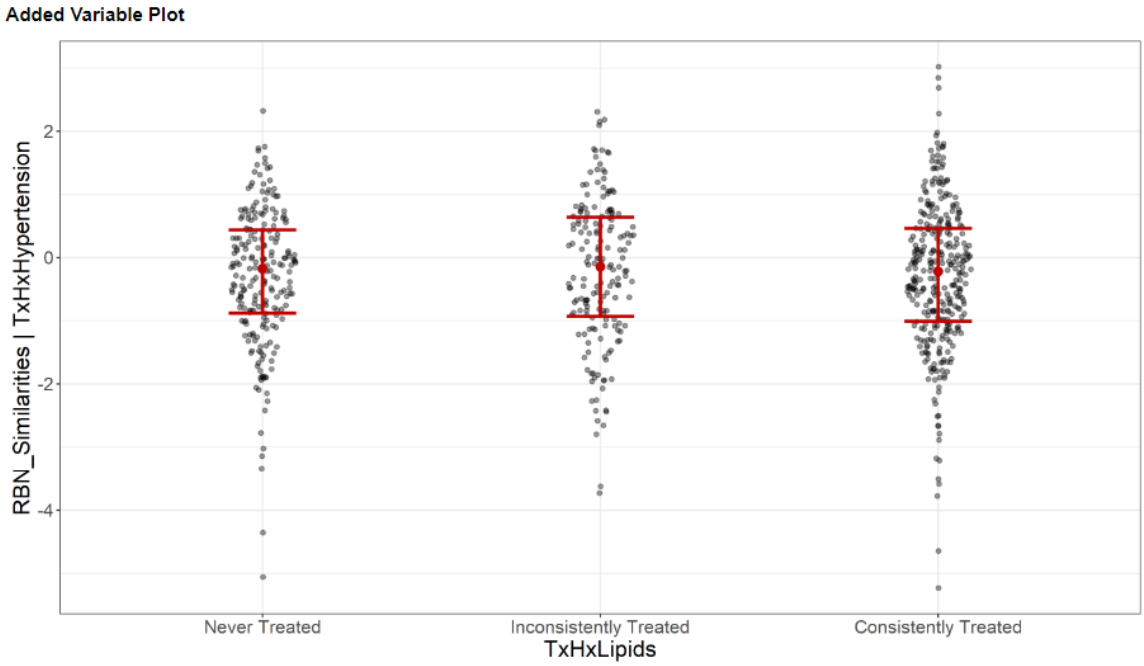

Figure C6. RBN Similarities Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

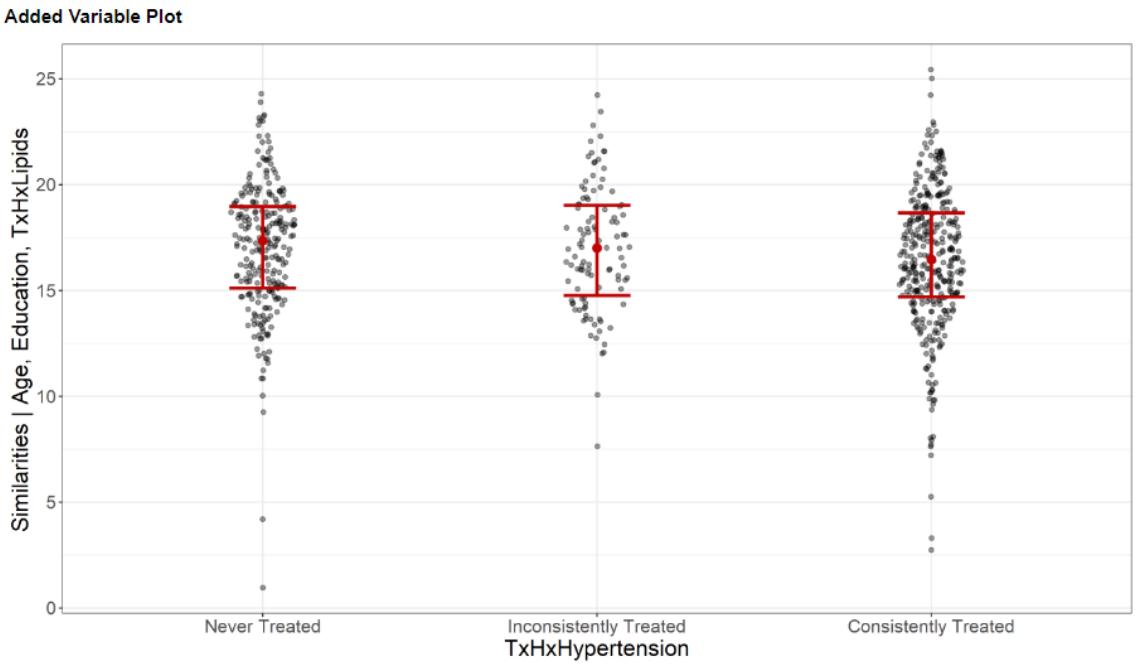

Figure C7. Raw Score Similarities Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

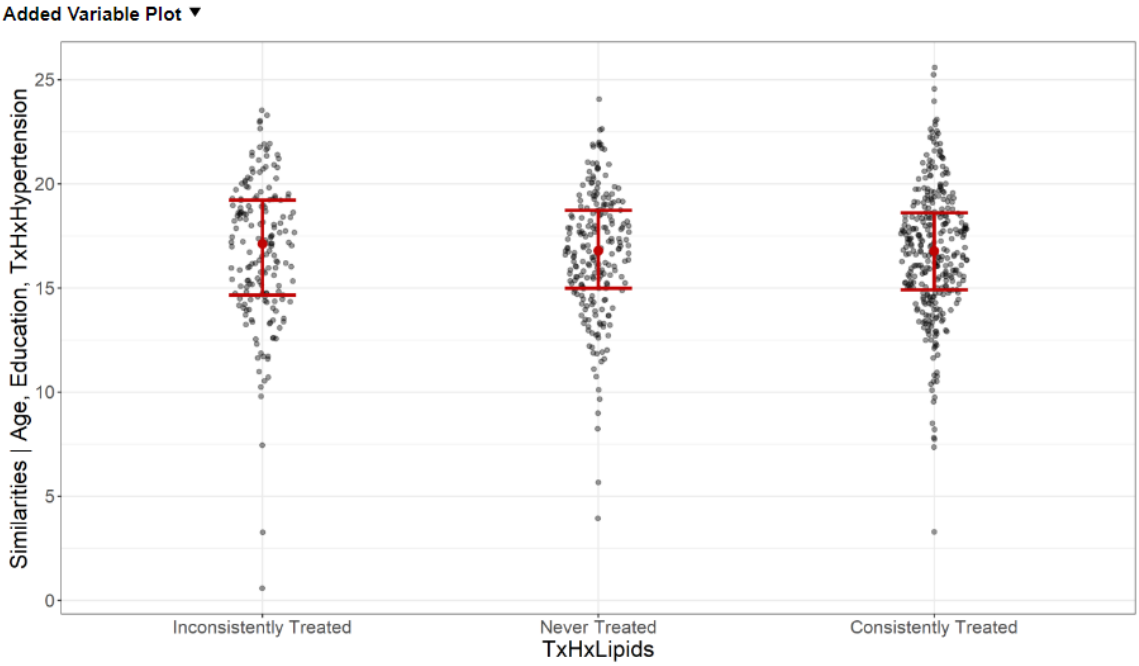

Figure C8. Raw Score Similarities Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

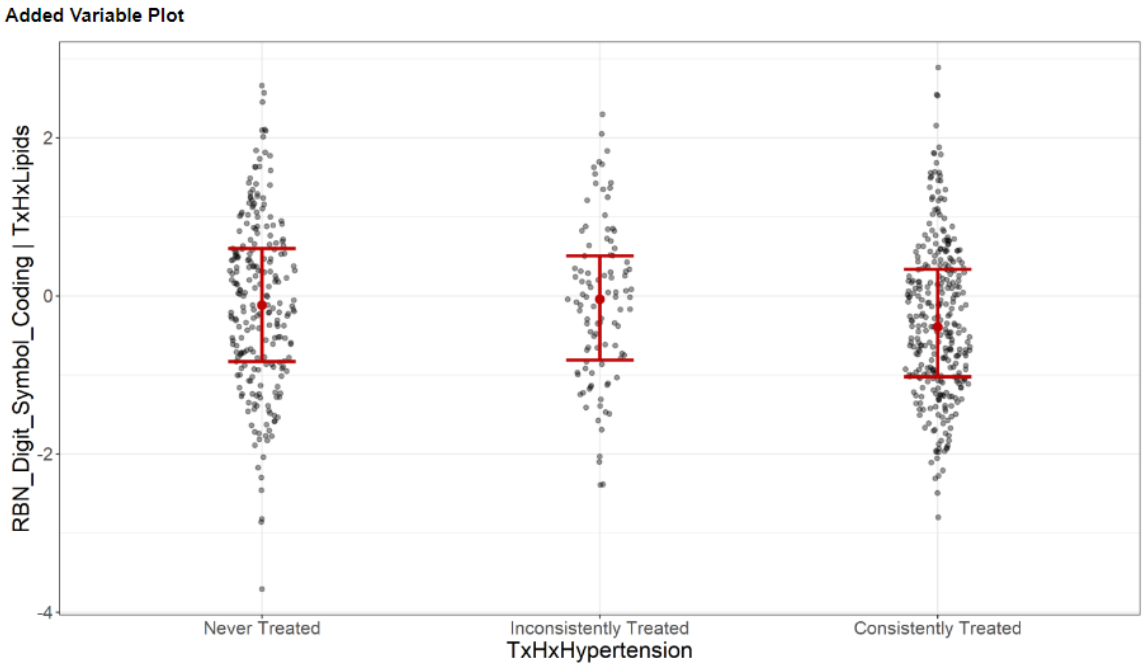

Figure C9. RBN Digit Symbol Coding Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

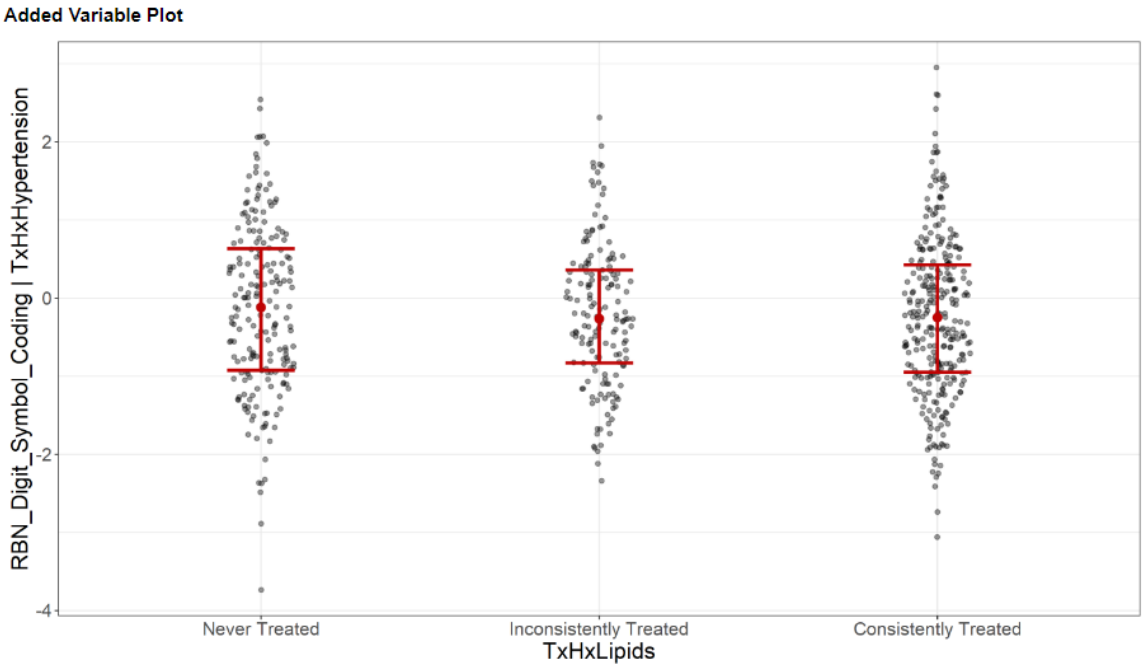

Figure C10. RBN Digit Symbol Coding Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

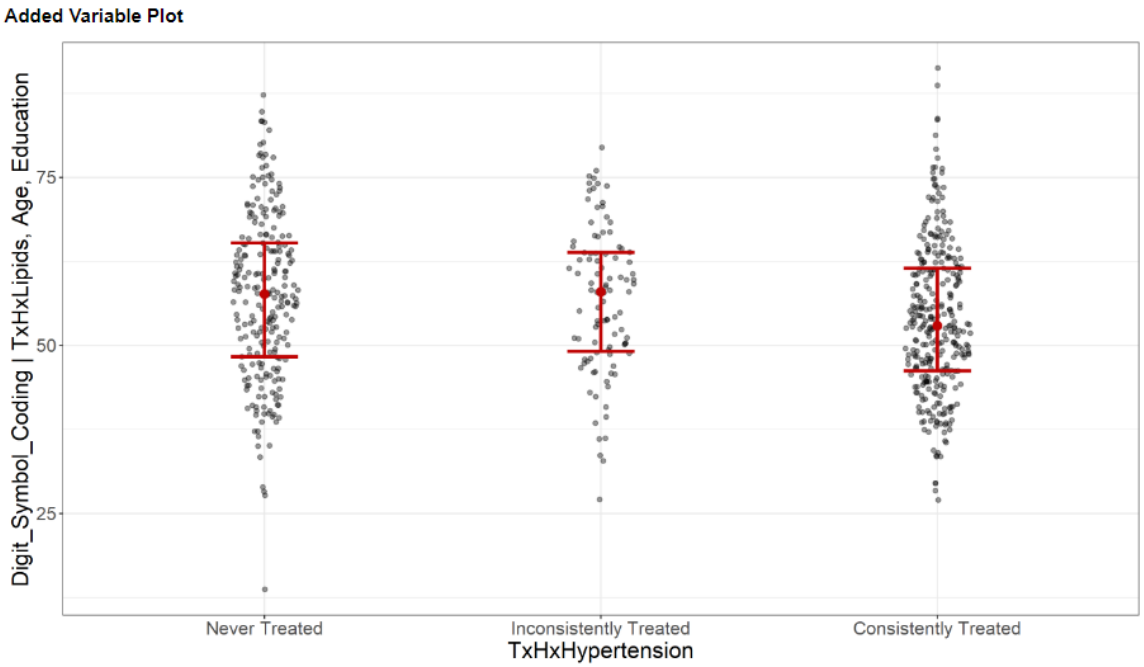

Figure C11. Raw Score Digit Symbol Coding Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

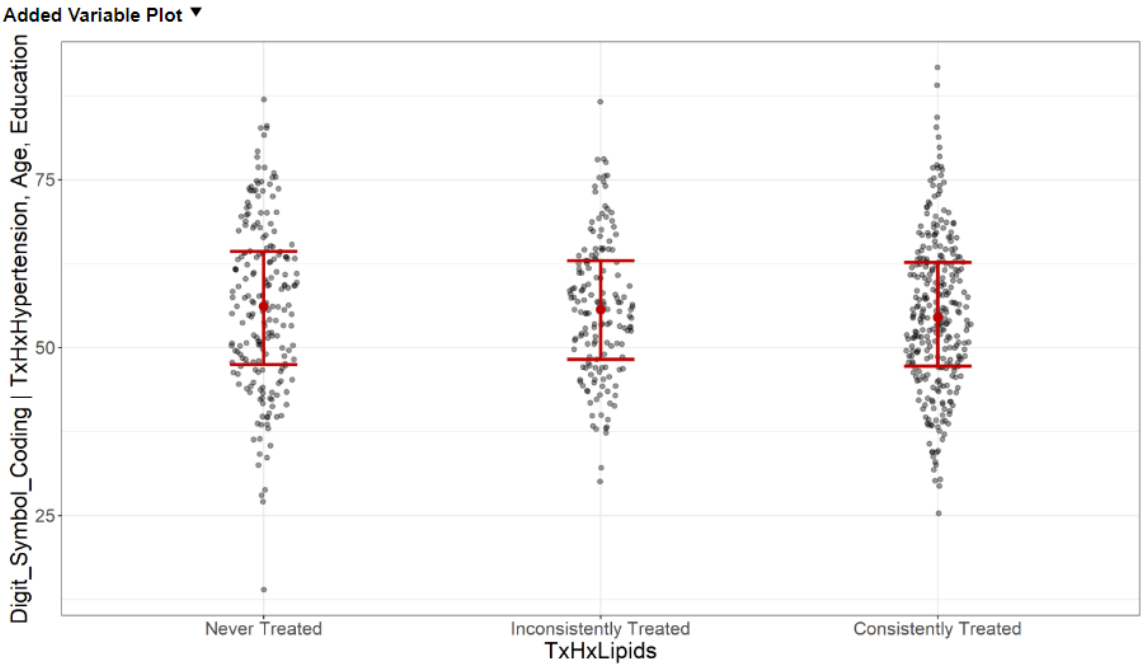

Figure C12. Raw Score Digit Symbol Coding Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

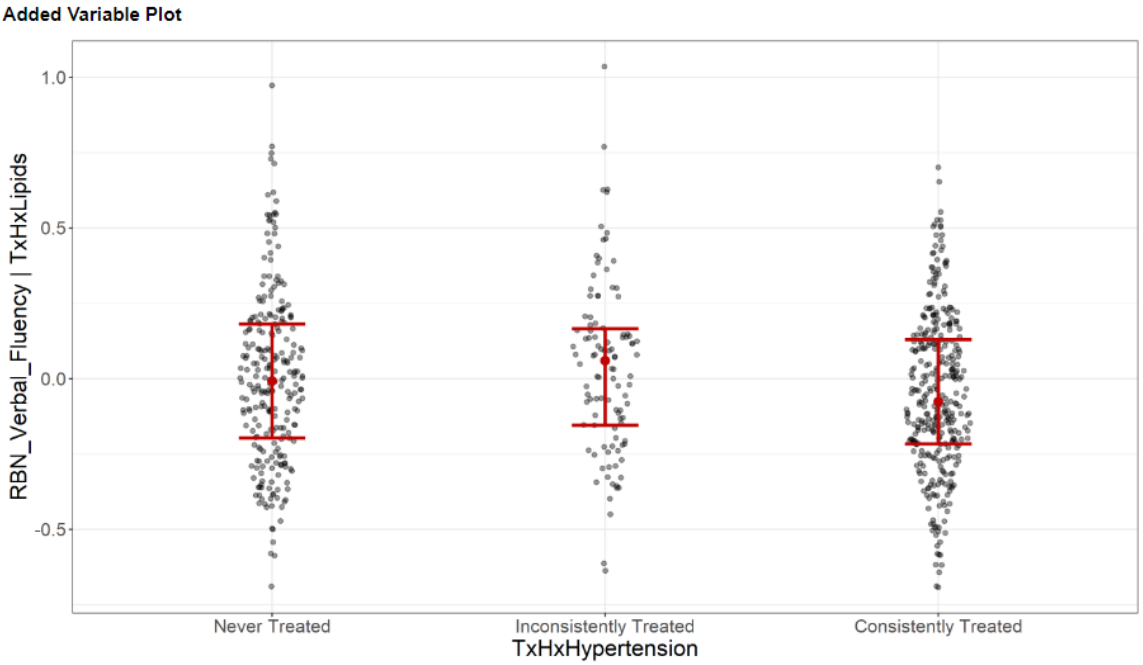

Figure C13. RBN Verbal Fluency Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

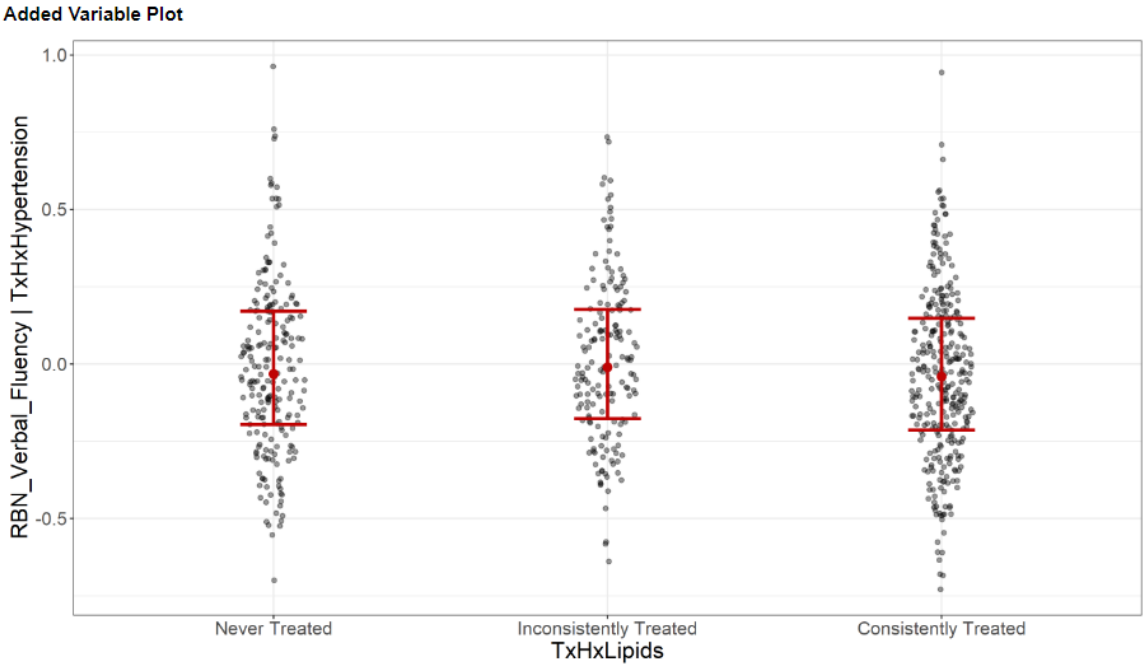

Figure C14. RBN Verbal Fluency Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

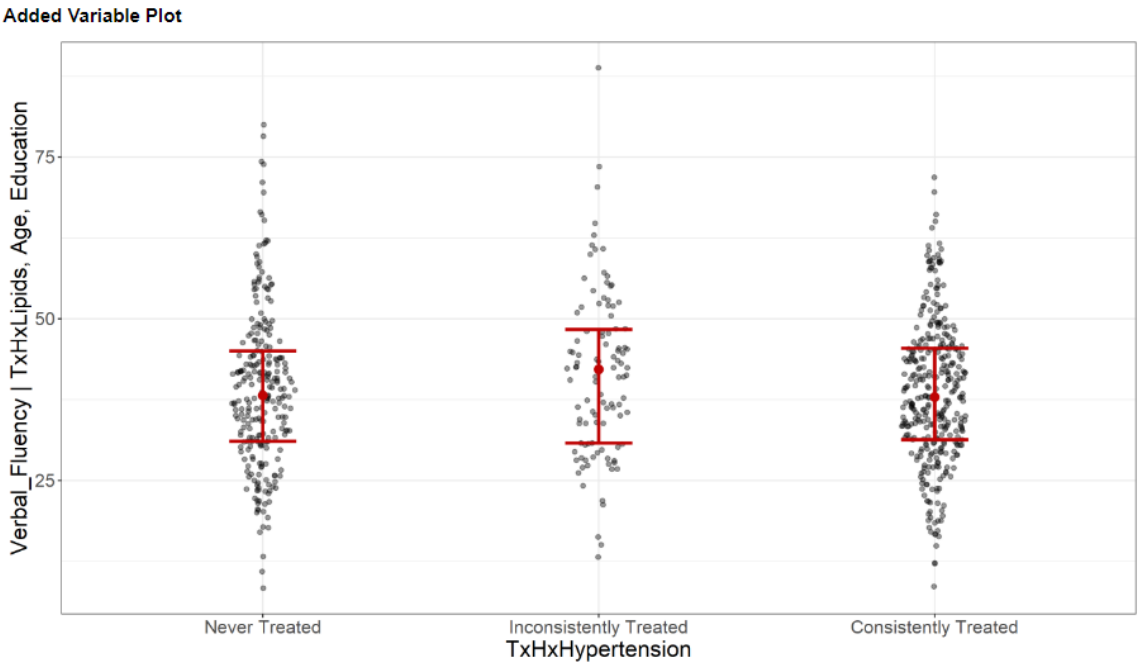

Figure C15. Raw Score Verbal Fluency Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

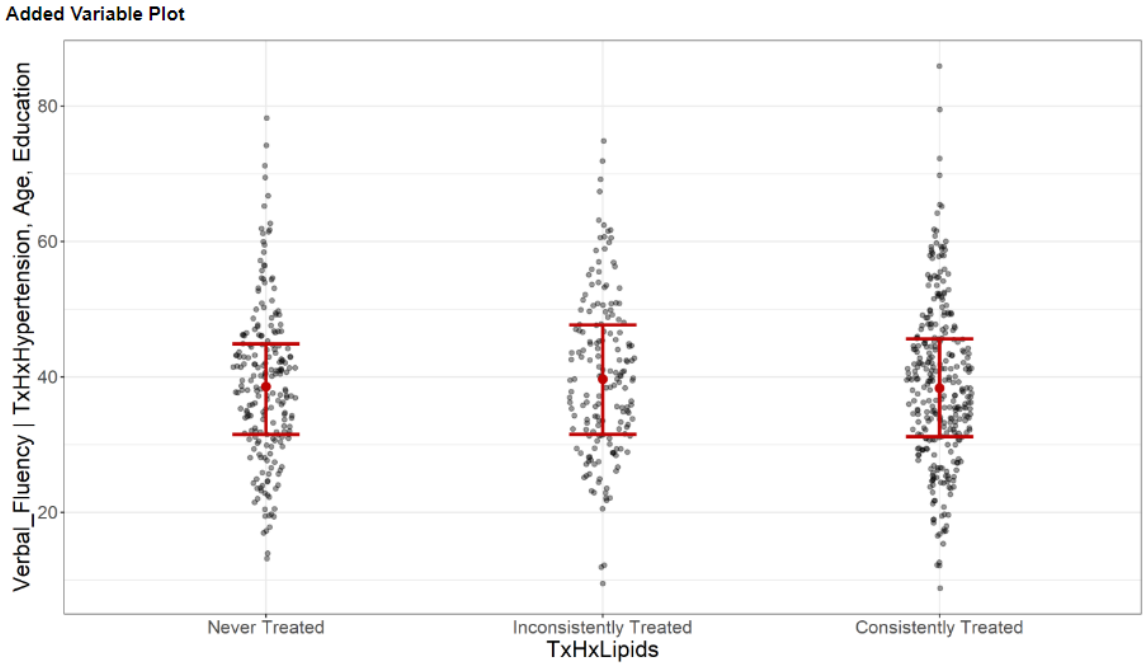

Figure C16. Raw Score Verbal Fluency Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

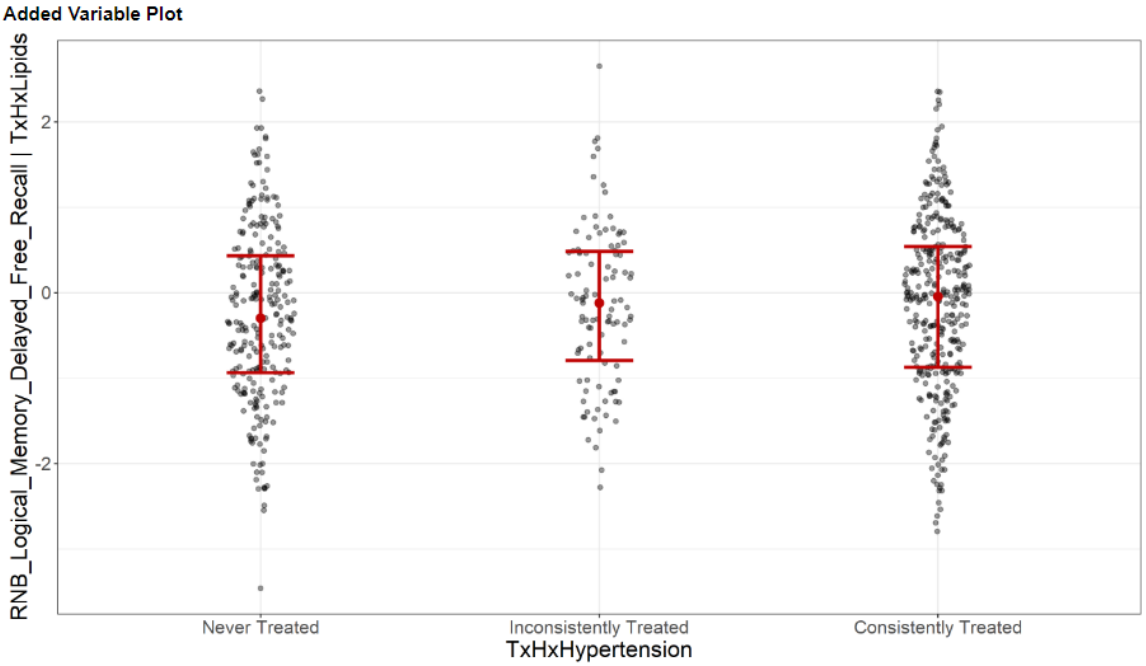

Figure C17. RBN Logical Memory Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

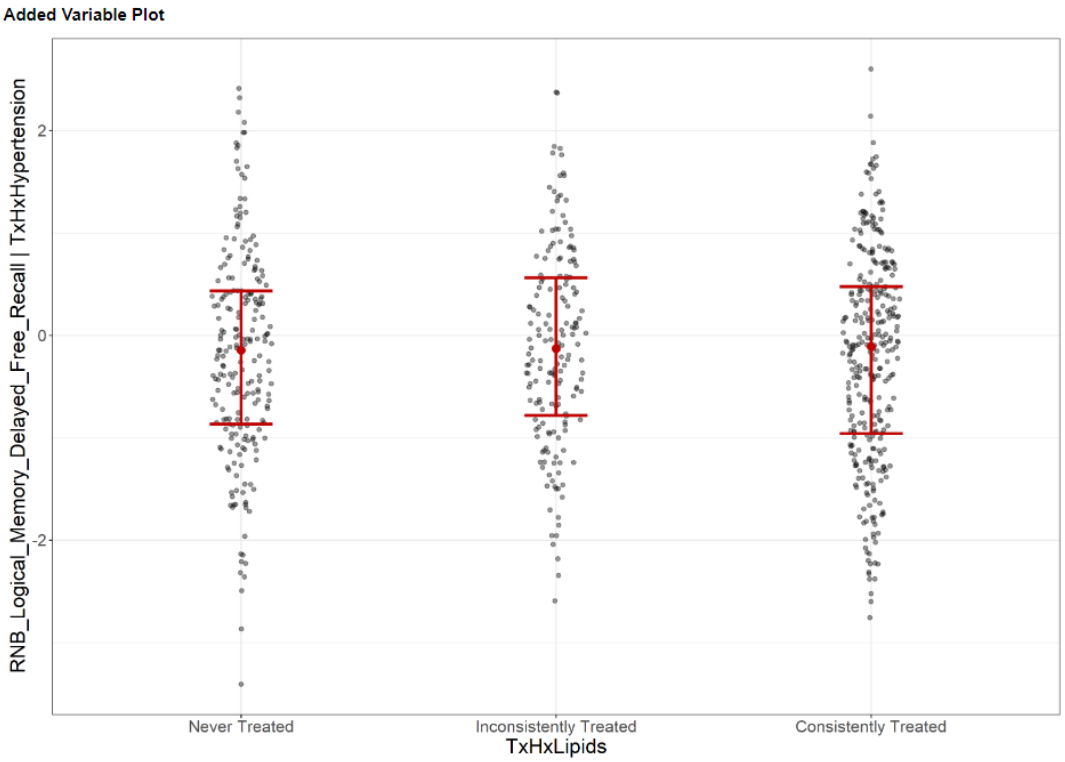

Figure C18. RBN Logical Memory Delayed Free Recall Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

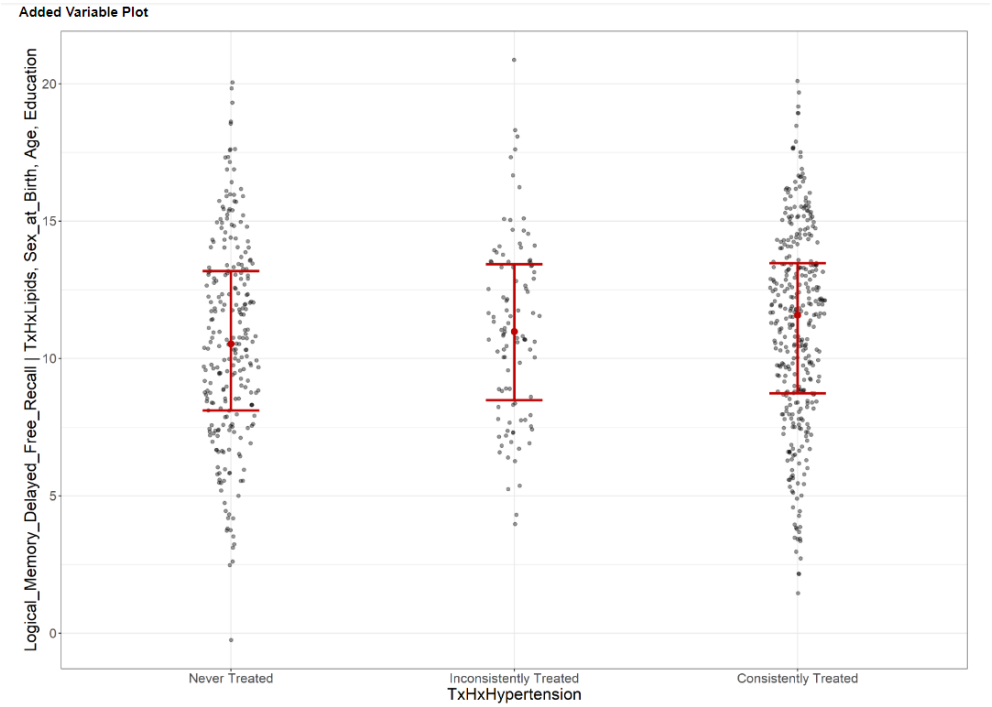

Figure C19. Raw Score Logical Memory Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

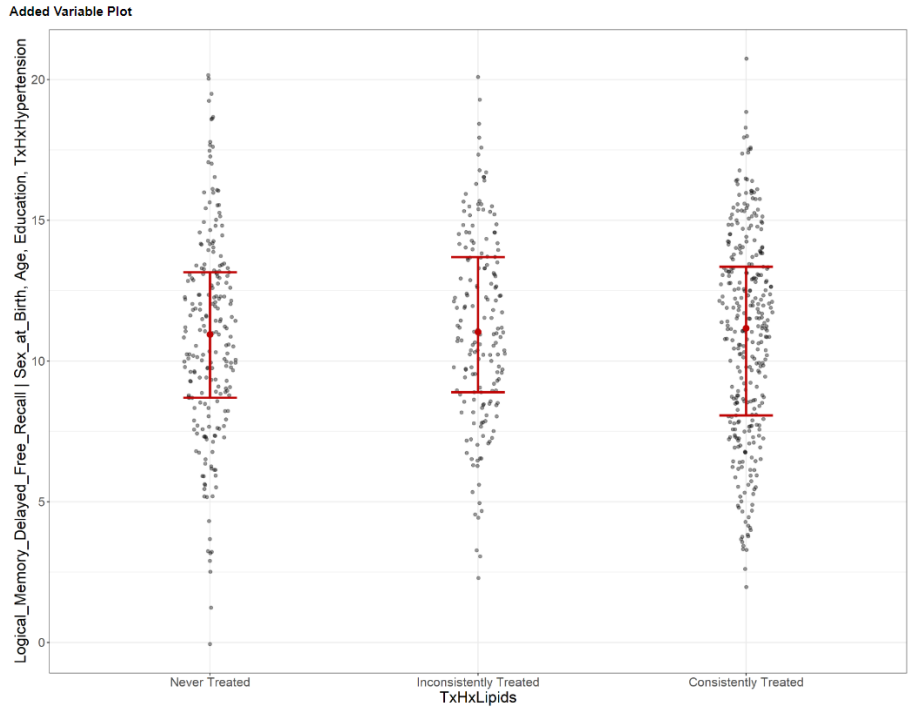

Figure C20. Raw Score Logical Memory Delayed Free Recall Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

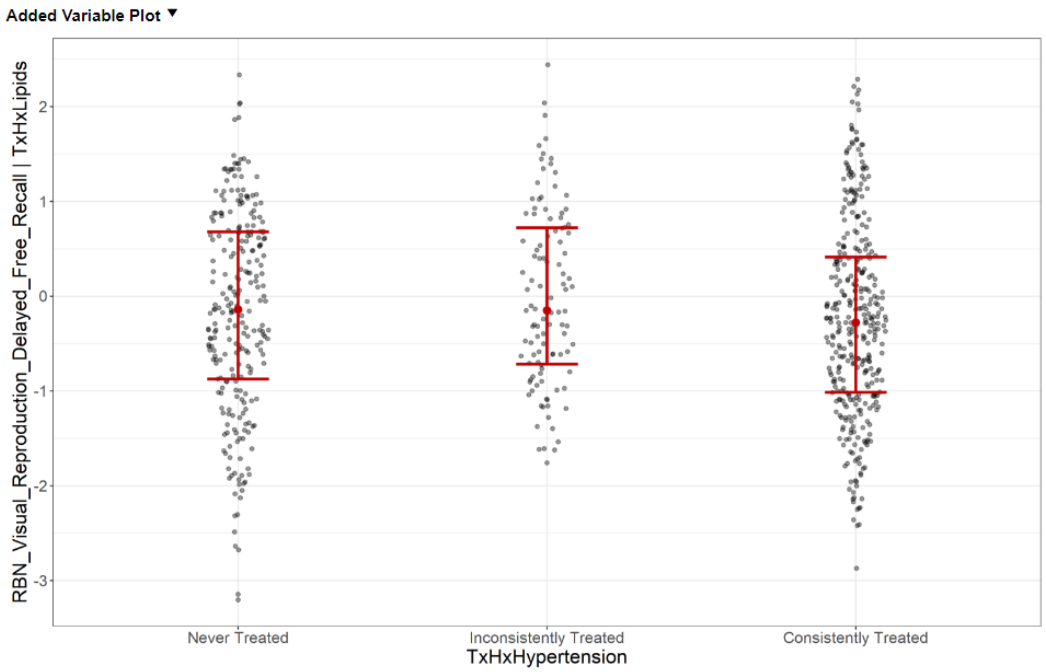

Figure C21. RBN Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

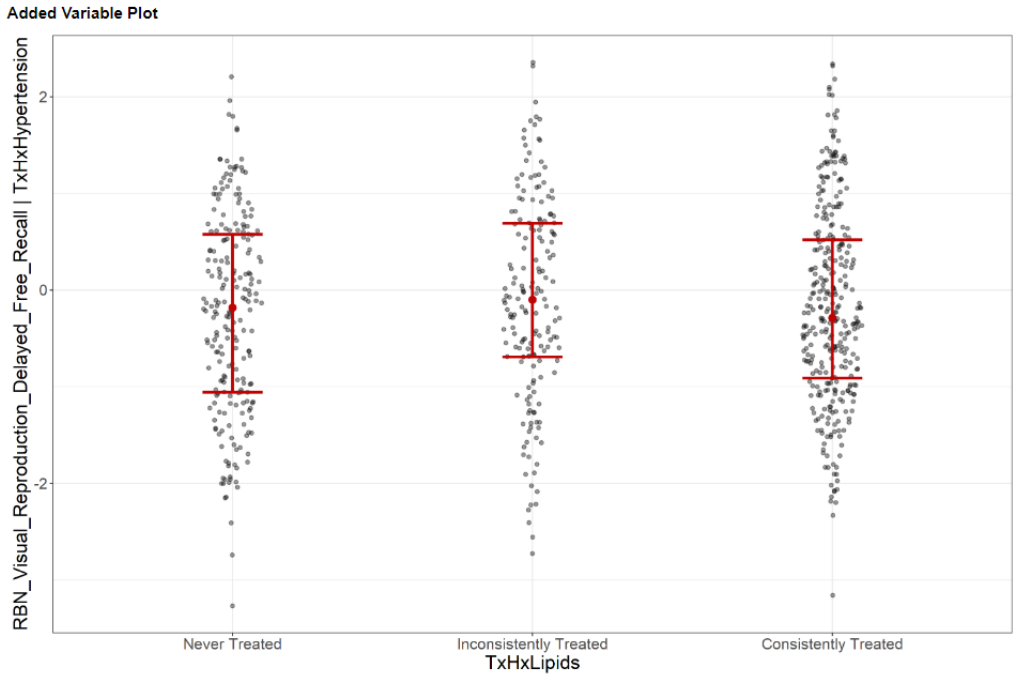

Figure C22. RBN Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

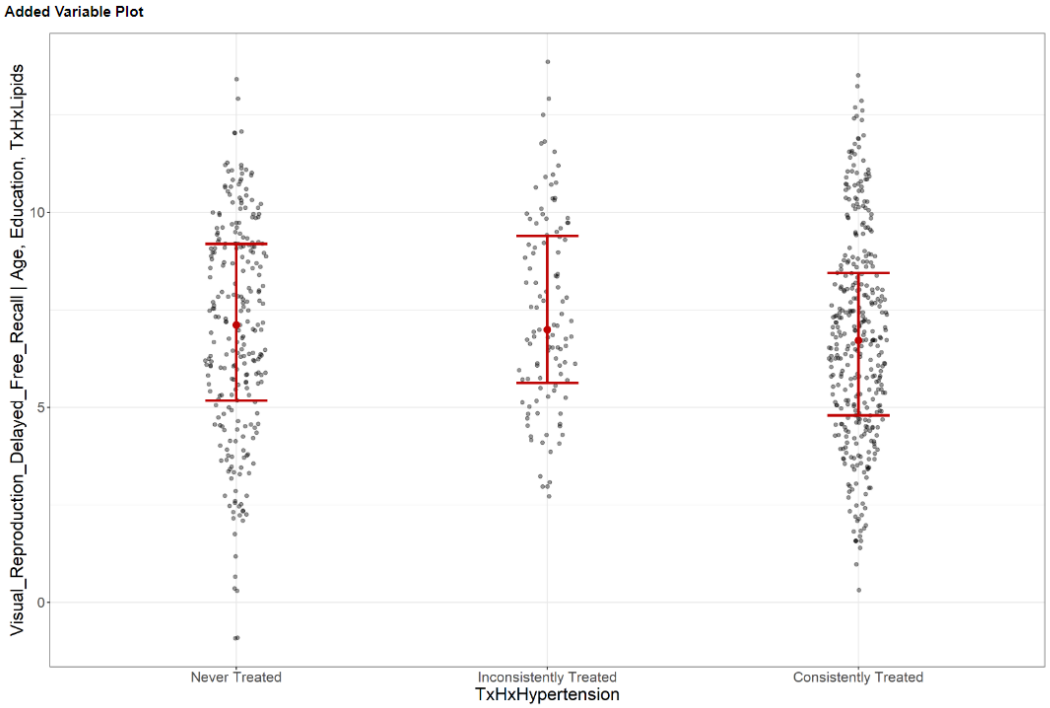

Figure C23. Raw Score Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

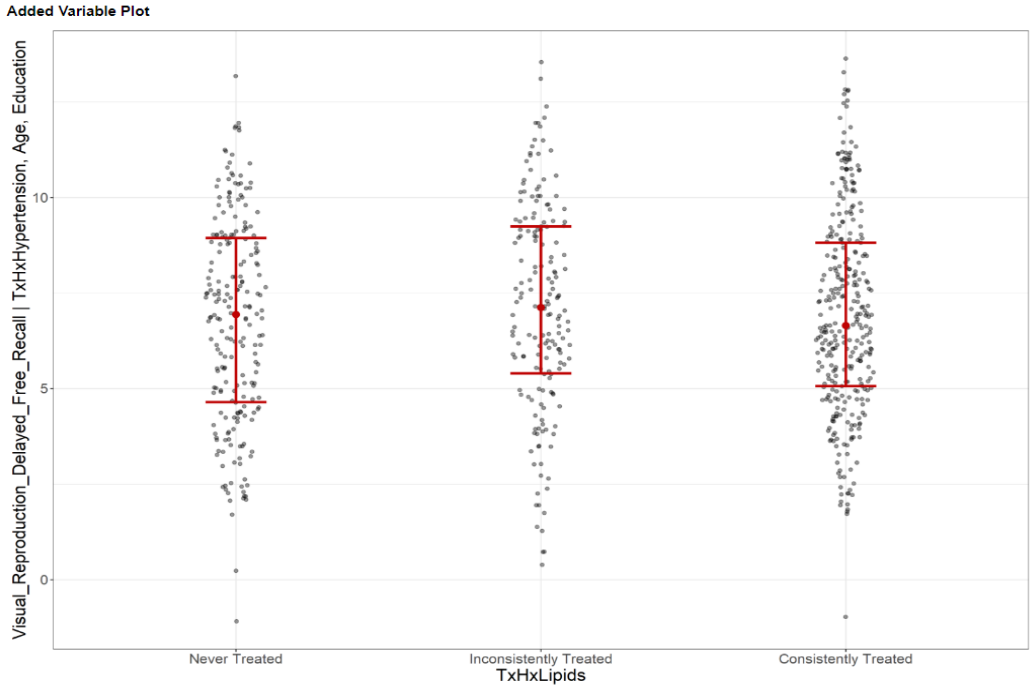

Figure C24. Raw Score Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

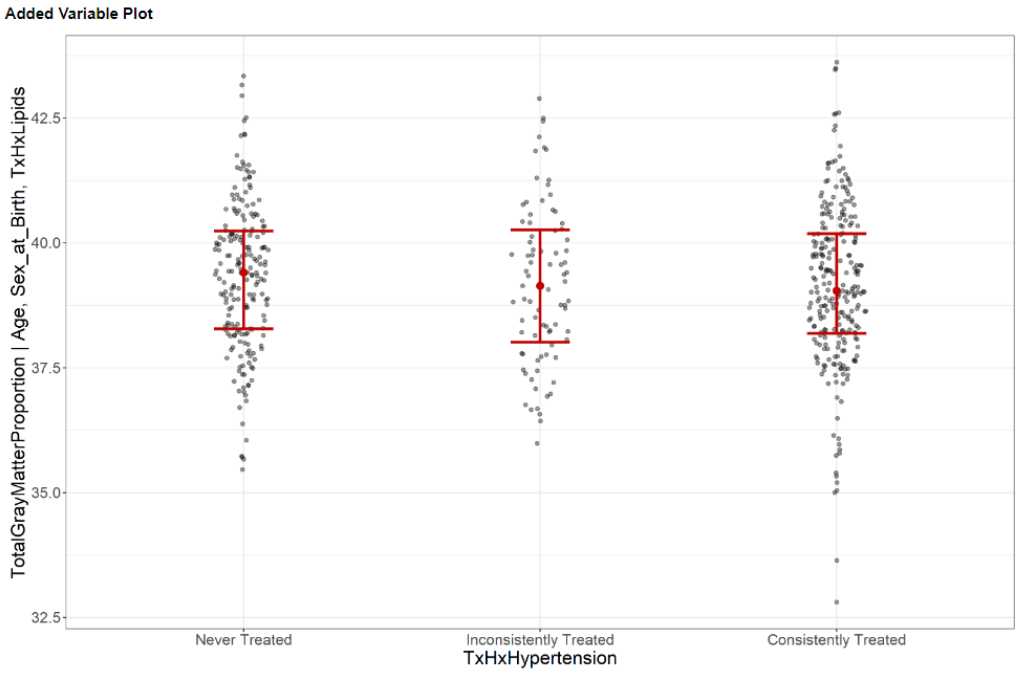

Figure C25. Total Percentage Gray Matter Volume Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

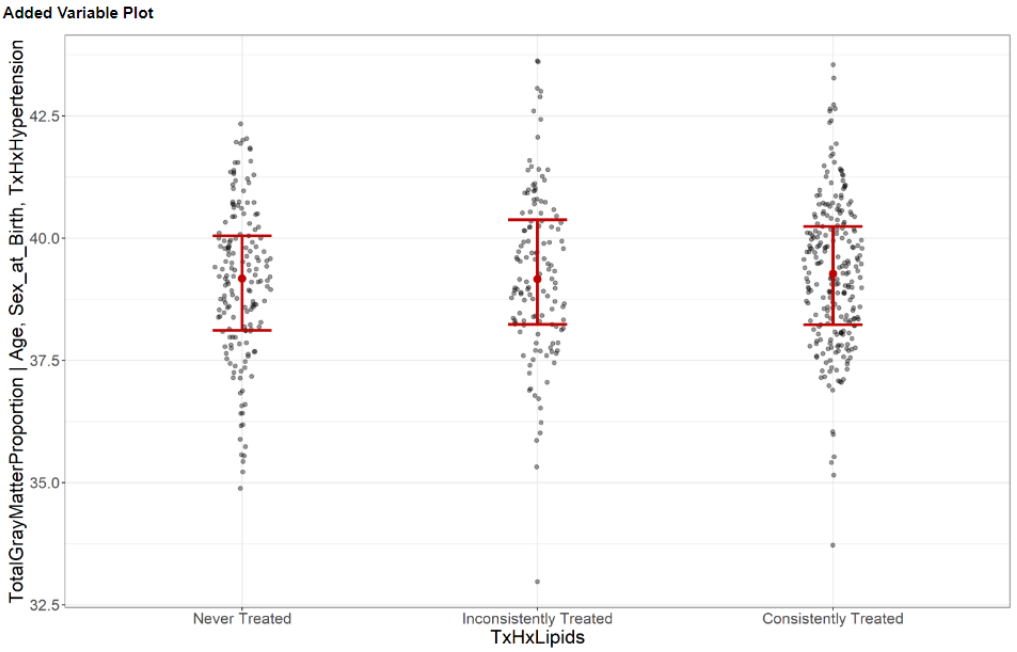

Figure C26. Total Percentage Gray Matter Volume Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

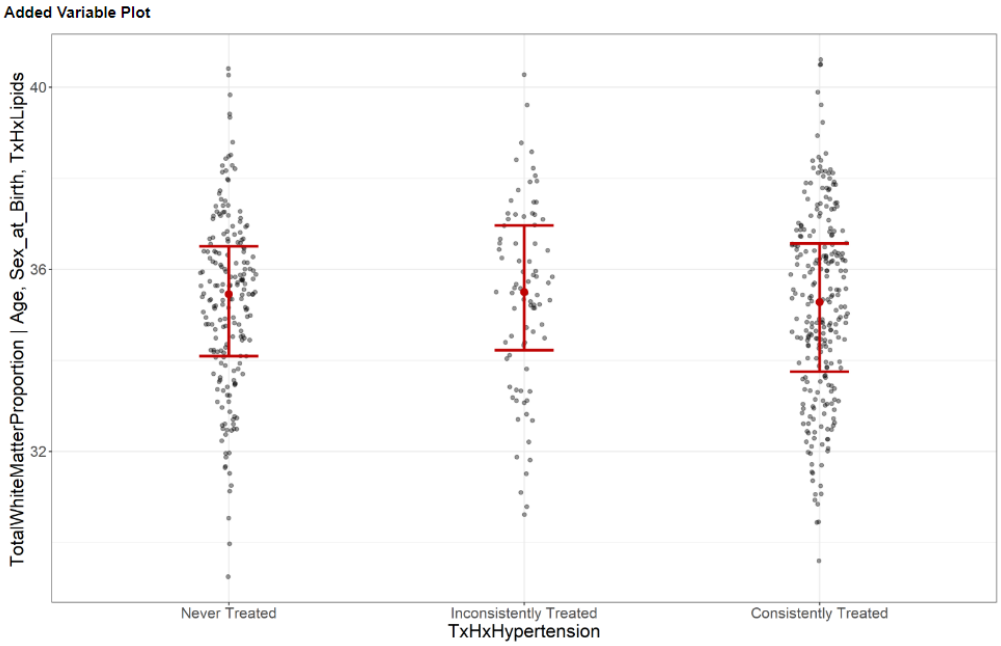

Figure C27. Total Percentage White Matter Volume Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

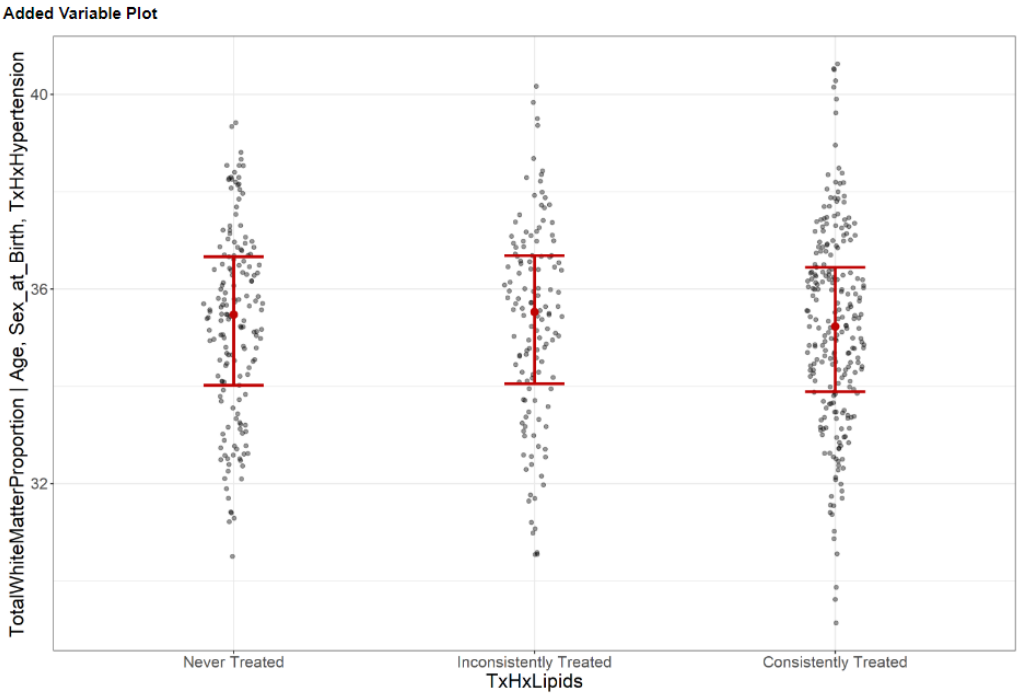

Figure C28. Total Percentage White Matter Volume Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

Appendix D

Analysis of Variance Tables of Validation Dataset Models

Table D1

RBN Boston Naming Test Model

ANOVA – RBN BNT Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	3.730	2	1.865	1.375	0.254	0.009	0.009
TxHxLipids	5.132	2	2.566	1.892	0.152	0.012	0.012
Residuals	425.776	314	1.356				

Note. Type III Sum of Squares

Mean Differences Between Groups – RBN BNT Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	0.148	-0.473	0.769	0.127
	Consistently Treated-Never Treated	-0.151	-0.635	0.333	-0.130
	Consistently Treated-Inconsistently Treated	-0.299	-0.898	0.300	-0.257
TxHxLipids	Inconsistently Treated-Never Treated	-0.020	-0.626	0.587	-0.017
	Consistently Treated-Never Treated	-0.279	-0.789	0.230	-0.240
	Consistently Treated-Inconsistently Treated	-0.260	-0.812	0.292	-0.223

Table D2

Raw Score Boston Naming Test Model

ANCOVA – Raw Score BNT Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	3.964	2	1.982	0.414	0.661	0.002	0.003
TxHxLipids	2.048	2	1.024	0.214	0.808	0.001	0.001
Age	142.268	1	142.268	29.702	< .001	0.079	0.086
Education	145.533	1	145.533	30.383	< .001	0.081	0.088
Residuals	1508.816	315	4.790				

Note. Type III Sum of Squares

Mean Differences Between Groups – Raw Score BNT Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	0.195	-0.964	1.353	0.089
	Consistently Treated-Never Treated	-0.049	-0.955	0.857	-0.022
	Consistently Treated-Inconsistently Treated	-0.244	-1.361	0.873	-0.111
TxHxLipids	Inconsistently Treated-Never Treated	0.046	-1.086	1.178	0.021
	Consistently Treated-Never Treated	-0.193	-1.147	0.760	-0.088
	Consistently Treated-Inconsistently Treated	-0.239	-1.270	0.791	-0.109

Table D3

RBN Similarities Model

ANOVA – RBN Similarities Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	12.970	2	6.485	5.225	0.006	0.031	0.031
TxHxLipids	0.452	2	0.226	0.182	0.834	0.001	0.001
Residuals	400.920	323	1.241				

Note. Type III Sum of Squares

Mean Differences Between Groups – RBN Similarities Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-0.143	-0.728	0.442	-0.128
	Consistently Treated-Never Treated	-0.461	-0.918	-0.004	-0.414
	Consistently Treated-Inconsistently Treated	-0.318	-0.882	0.246	-0.285
TxHxLipids	Inconsistently Treated-Never Treated	0.101	-0.465	0.667	0.091
	Consistently Treated-Never Treated	0.061	-0.420	0.542	0.055
	Consistently Treated-Inconsistently Treated	-0.040	-0.558	0.478	-0.036

Table D4

Raw Score Similarities Model

ANCOVA – Raw Score Similarities Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	92.726	2	46.363	5.076	0.007	0.025	0.031
TxHxLipids	9.263	2	4.632	0.507	0.603	0.002	0.003
Age	91.906	1	91.906	10.062	0.002	0.025	0.030
Education	611.270	1	611.270	66.923	< .001	0.164	0.173
Residuals	2931.994	321	9.134				

Note. Type III Sum of Squares

Mean Differences Between Groups – Raw Score Similarities Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-0.316	-1.905	1.274	-0.104
	Consistently Treated-Never Treated	-1.305	-2.547	-0.063	-0.431
	Consistently Treated-Inconsistently Treated	-0.989	-2.521	0.543	-0.327
TxHxLipids	Inconsistently Treated-Never Treated	0.336	-1.203	1.874	0.111
	Consistently Treated-Never Treated	0.467	-0.840	1.773	0.154
	Consistently Treated-Inconsistently Treated	0.131	-1.276	1.538	0.043

Table D5

RBN Digit Symbol Coding Model

ANOVA – RBN Digit Symbol Coding Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	14.203	2	7.102	6.564	0.002	0.042	0.042
TxHxLipids	1.226	2	0.613	0.566	0.568	0.004	0.004
Residuals	321.320	297	1.082				

Note. Type III Sum of Squares

Mean Differences Between Groups – RBN Digit Symbol Coding Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-0.296	-0.870	0.278	-0.284
	Consistently Treated-Never Treated	-0.503	-0.945	-0.061	-0.484
	Consistently Treated-Inconsistently Treated	-0.207	-0.765	0.350	-0.199
TxHxLipids	Inconsistently Treated-Never Treated	-0.131	-0.678	0.416	-0.126
	Consistently Treated-Never Treated	0.028	-0.441	0.498	0.027
	Consistently Treated-Inconsistently Treated	0.160	-0.341	0.660	0.153

Table D6

Raw Score Digit Symbol Coding Model

ANCOVA – Raw Score Digit Symbol Coding Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	1676.518	2	838.259	6.490	0.002	0.032	0.042
TxHxLipids	285.888	2	142.944	1.107	0.332	0.005	0.007
Age	3913.683	1	3913.683	30.299	< .001	0.075	0.093
Education	5597.953	1	5597.953	43.338	< .001	0.107	0.128
Sex at Birth	2645.028	1	2645.028	20.477	< .001	0.051	0.065
Residuals	37975.769	294	129.169				

Note. Type III Sum of Squares

Mean Differences Between Groups – Raw Score Digit Symbol Coding Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated- Never Treated	-4.044	-10.530	2.441	-0.344
	Consistently Treated- Never Treated	-7.354	-12.349	-2.359	-0.626
	Consistently Treated- Inconsistently Treated	-3.310	-9.606	2.987	-0.282
TxHxLipids	Inconsistently Treated- Never Treated	-2.129	-8.310	4.053	-0.181
	Consistently Treated- Never Treated	-0.714	-6.021	4.593	-0.061
	Consistently Treated- Inconsistently Treated	1.415	-4.236	7.067	0.120

Table D7

RBN Verbal Fluency Model

ANOVA – RBN Verbal Fluency Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	0.801	2	0.401	5.008	0.007	0.031	0.031
TxHxLipids	0.094	2	0.047	0.589	0.556	0.004	0.004
Residuals	25.126	314	0.080				

Note. Type III Sum of Squares

Mean Differences Between Groups – RBN Verbal Fluency Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-0.079	-0.229	0.071	-0.279
	Consistently Treated-Never Treated	-0.117	-0.234	0.001	-0.412
	Consistently Treated-Inconsistently Treated	-0.038	-0.184	0.108	-0.133
TxHxLipids	Inconsistently Treated-Never Treated	0.048	-0.099	0.194	0.168
	Consistently Treated-Never Treated	0.020	-0.105	0.144	0.070
	Consistently Treated-Inconsistently Treated	-0.028	-0.161	0.105	-0.099

Table D8

Raw Score Verbal Fluency Model

ANCOVA – Raw Score Verbal Fluency Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	890.845	2	445.423	3.180	0.043	0.018	0.020
TxHxLipids	96.593	2	48.296	0.345	0.709	0.002	0.002
Age	633.808	1	633.808	4.525	0.034	0.013	0.014
Education	4575.913	1	4575.913	32.669	< .001	0.092	0.095
Residuals	43701.509	312	140.069				

Note. Type III Sum of Squares

Mean Differences Between Groups – Raw Score Verbal Fluency Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-3.105	-9.362	3.152	-0.264
	Consistently Treated-Never Treated	-3.976	-8.864	0.912	-0.337
	Consistently Treated-Inconsistently Treated	-0.870	-6.948	5.208	-0.074
TxHxLipids	Inconsistently Treated-Never Treated	1.134	-4.956	7.224	0.096
	Consistently Treated-Never Treated	1.410	-3.762	6.583	0.120
	Consistently Treated-Inconsistently Treated	0.277	-5.267	5.820	0.023

Table D9

RNB Logical Memory Delayed Free Recall Model

ANOVA – RNB Logical Memory Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	1.001	2	0.500	0.511	0.600	0.003	0.003
TxHxLipids	0.151	2	0.076	0.077	0.926	4.807e -4	4.822e -4
Residuals	313.219	320	0.979				

Note. Type III Sum of Squares

Mean Differences Between Groups – RNB Logical Memory Delayed Free Recall Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-0.029	-0.548	0.490	-0.029
	Consistently Treated-Never Treated	-0.126	-0.534	0.281	-0.128
	Consistently Treated-Inconsistently Treated	-0.097	-0.600	0.406	-0.098
TxHxLipids	Inconsistently Treated-Never Treated	0.003	-0.501	0.508	0.003
	Consistently Treated-Never Treated	-0.044	-0.472	0.384	-0.045
	Consistently Treated-Inconsistently Treated	-0.047	-0.510	0.415	-0.048

Table D10

Raw Score Logical Memory Delayed Free Recall Model

ANCOVA – Raw Score Logical Memory Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	2.428	2	1.214	0.098	0.906	5.338e -4	6.207e -4
TxHxLipids	0.071	2	0.036	0.003	0.997	1.565e -5	1.821e -5
Age	222.862	1	222.862	18.074	< .001	0.049	0.054
Education	341.642	1	341.642	27.708	< .001	0.075	0.080
Sex at Birth	72.145	1	72.145	5.851	0.016	0.016	0.018
Residuals	3908.673	317	12.330				

Note. Type III Sum of Squares

Mean Differences Between Groups – Raw Score Logical Memory Delayed Free Recall Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-0.010	-1.846	1.826	-0.003
	Consistently Treated-Never Treated	-0.009	-1.451	1.434	-0.002
	Consistently Treated-Inconsistently Treated	0.001	-1.778	1.781	0.000
TxHxLipids	Inconsistently Treated-Never Treated	-0.060	-1.847	1.726	-0.017
	Consistently Treated-Never Treated	-0.069	-1.585	1.446	-0.020
	Consistently Treated-Inconsistently Treated	-0.009	-1.647	1.629	-0.003

Table D11

RBN Visual Reproduction Delayed Free Recall Model

ANOVA – RBN Visual Reproduction Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	0.954	2	0.477	0.452	0.637	0.003	0.003
TxHxLipids	2.160	2	1.080	1.022	0.361	0.006	0.006
Residuals	338.021	320	1.056				

Note. Type III Sum of Squares

Mean Differences Between Groups – RBN Visual Reproduction Delayed Free Recall Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-0.146	-0.689	0.397	-0.142
	Consistently Treated-Never Treated	-0.089	-0.512	0.334	-0.087
	Consistently Treated-Inconsistently Treated	0.057	-0.468	0.581	0.055
TxHxLipids	Inconsistently Treated-Never Treated	-0.161	-0.688	0.365	-0.157
	Consistently Treated-Never Treated	-0.194	-0.638	0.250	-0.189
	Consistently Treated-Inconsistently Treated	-0.033	-0.515	0.450	-0.032

Table D12

Raw Score Visual Reproduction Delayed Free Recall Model

ANCOVA – Raw Score Visual Reproduction Delayed Free Recall Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	4.806	2	2.403	0.337	0.714	0.002	0.002
TxHxLipids	17.196	2	8.598	1.205	0.301	0.006	0.008
Age	282.130	1	282.130	39.532	< .001	0.100	0.111
Education	234.479	1	234.479	32.855	< .001	0.084	0.094
Residuals	2269.510	318	7.137				

Note. Type III Sum of Squares

Mean Differences Between Groups – Raw Score Visual Reproduction Delayed Free Recall Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Inconsistently Treated-Never Treated	-0.146	-1.997	1.705	-0.041
	Consistently Treated-Never Treated	-0.213	-1.667	1.241	-0.060
	Consistently Treated-Inconsistently Treated	-0.067	-1.861	1.727	-0.019
TxHxLipids	Inconsistently Treated-Never Treated	-0.039	-1.840	1.762	-0.011
	Consistently Treated-Never Treated	-0.140	-1.667	1.388	-0.040
	Consistently Treated-Inconsistently Treated	-0.101	-1.752	1.551	-0.029

Table D13

Total Percentage Gray Matter Volume Model

ANCOVA – Total Percentage Gray Matter Volume Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	10.525	2	5.262	1.818	0.164	0.010	0.013
TxHxLipids	1.075	2	0.537	0.186	0.831	9.855e -4	0.001
Age	185.736	1	185.736	64.182	< .001	0.170	0.188
Sex at Birth	88.790	1	88.790	30.682	< .001	0.081	0.099
Residuals	804.502	278	2.894				

Note. Type III Sum of Squares

Mean Differences Between Groups – Total Percentage Gray Matter Volume Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Consistently Treated-Never Treated	-0.430	-1.428	0.568	-0.253
	Inconsistently Treated-Never Treated	-0.454	-1.191	0.282	-0.267
	Inconsistently Treated-Consistently Treated	-0.025	-0.996	0.947	-0.014
TxHxLipids	Consistently Treated-Never Treated	-0.084	-0.993	0.825	-0.049
	Inconsistently Treated-Never Treated	-0.166	-0.935	0.604	-0.097
	Inconsistently Treated-Consistently Treated	-0.082	-0.951	0.788	-0.048

Table D14

Total Percentage White Matter Volume Model

ANCOVA – Total Percentage White Matter Volume Model

Cases	Sum of Squares	df	Mean Square	F	p	η^2	η^2_p
TxHxHypertension	17.159	2	8.579	1.845	0.160	0.011	0.013
TxHxLipids	7.675	2	3.838	0.825	0.439	0.005	0.006
Age	236.204	1	236.204	50.794	< .001	0.146	0.154
Sex at Birth	65.714	1	65.714	14.131	< .001	0.041	0.048
Residuals	1292.761	278	4.650				

Note. Type III Sum of Squares

Mean Differences Between Groups – Total Percentage White Matter Volume Model

Variable	Comparison	Difference	95% Confidence Interval		Cohen's d
			Lower	Upper	
TxHxHypertension	Consistently Treated-Never Treated	-0.547	-1.812	0.718	-0.254
	Inconsistently Treated-Never Treated	0.014	-0.920	0.948	0.007
	Inconsistently Treated-Consistently Treated	0.561	-0.670	1.793	0.260
TxHxLipids	Consistently Treated-Never Treated	0.400	-0.752	1.552	0.186
	Inconsistently Treated-Never Treated	0.198	-0.777	1.174	0.092
	Inconsistently Treated-Consistently Treated	-0.202	-1.304	0.900	-0.093

Appendix E

Added Variable Plots of Validation Dataset Models

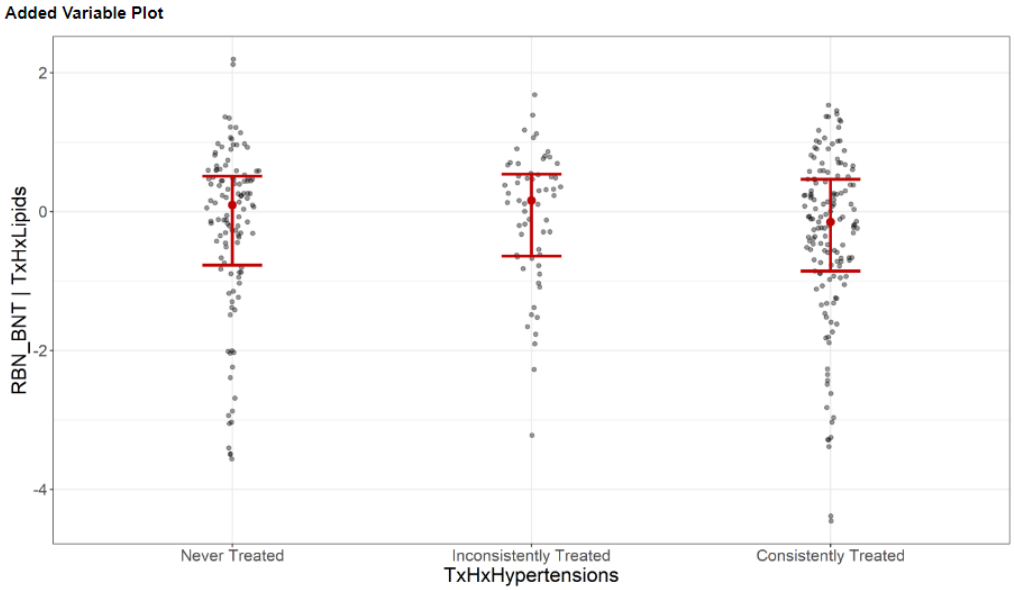

Figure E1. RBN BNT Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

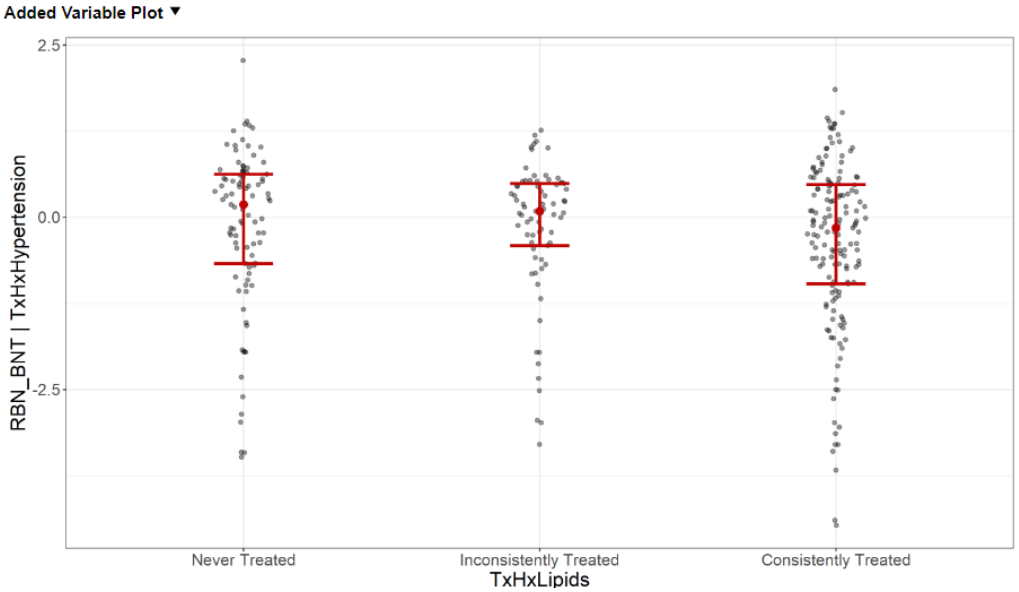

Figure E2. RBN BNT Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

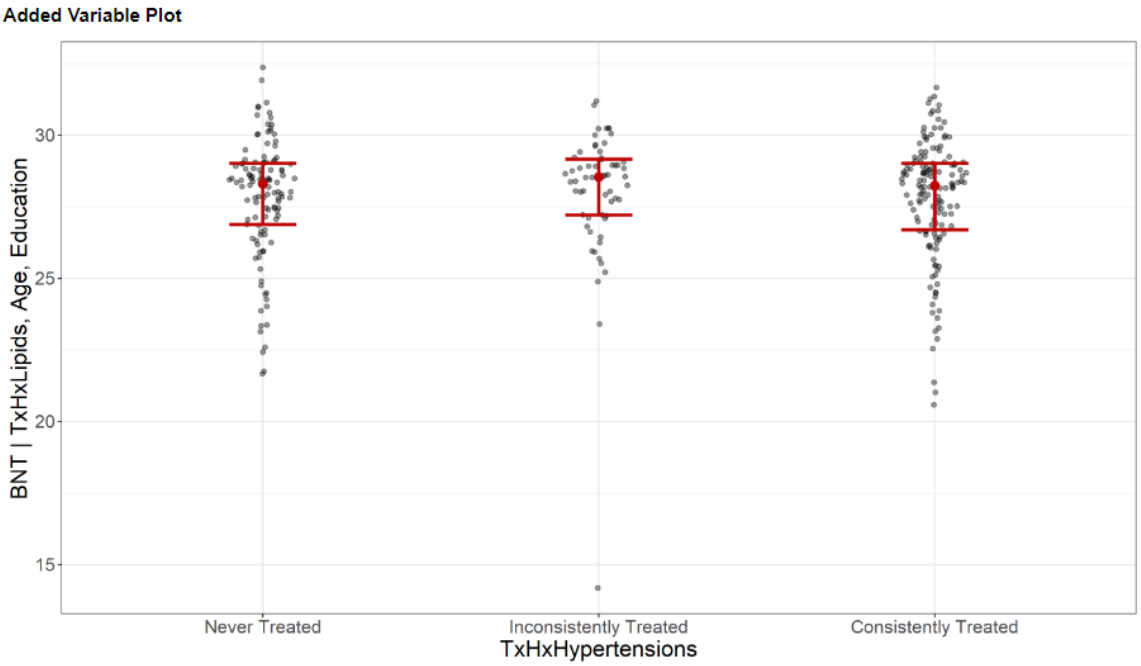

Figure E3. Raw Score Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

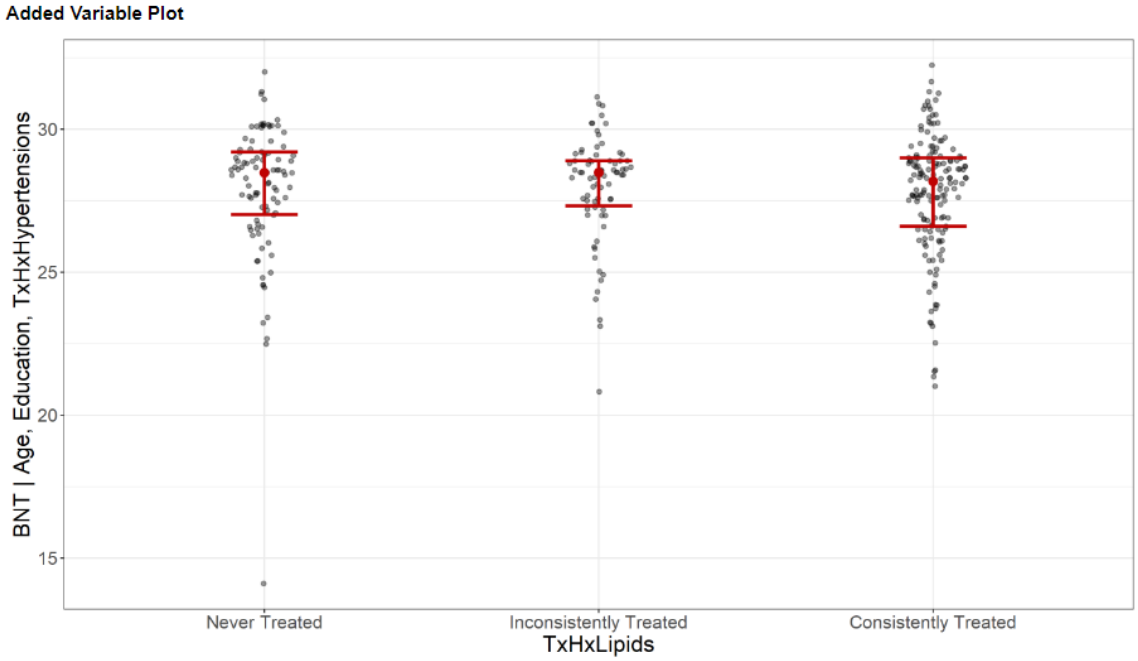

Figure E4. Raw Score BNT Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

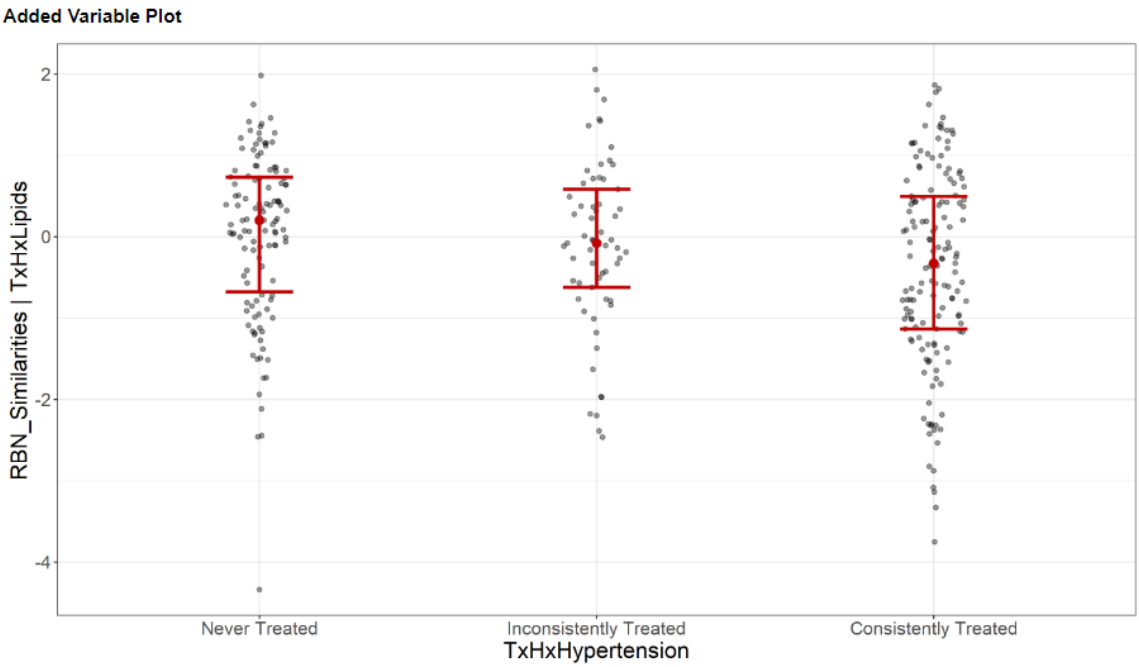

Figure E5. RBN Similarities Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

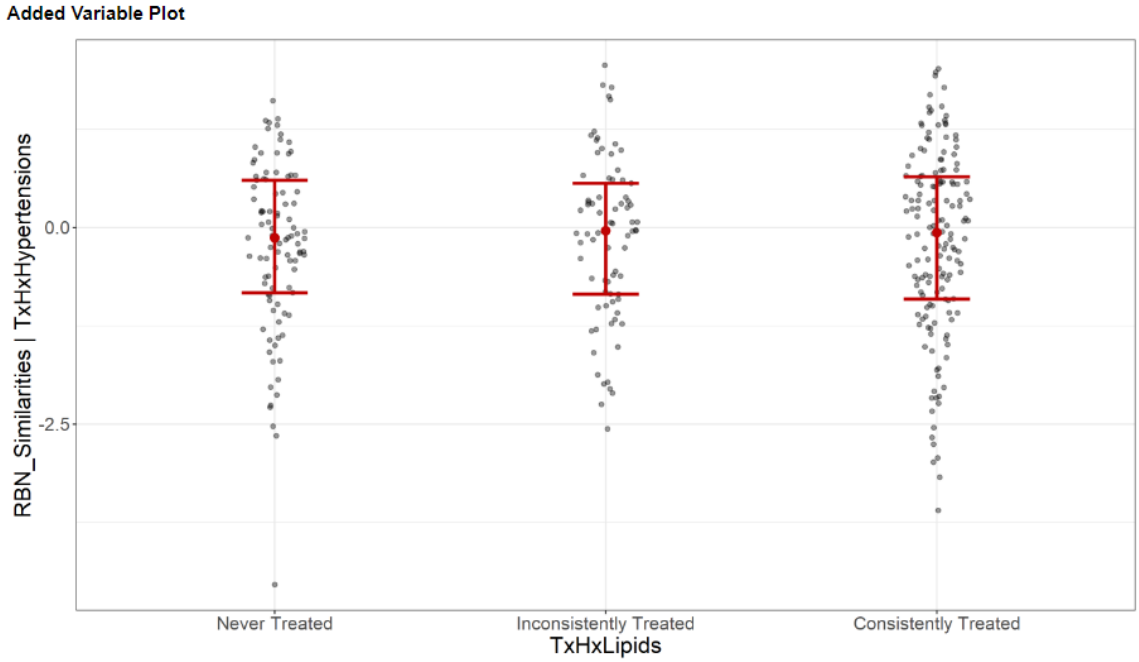

Figure E6. RBN Similarities Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

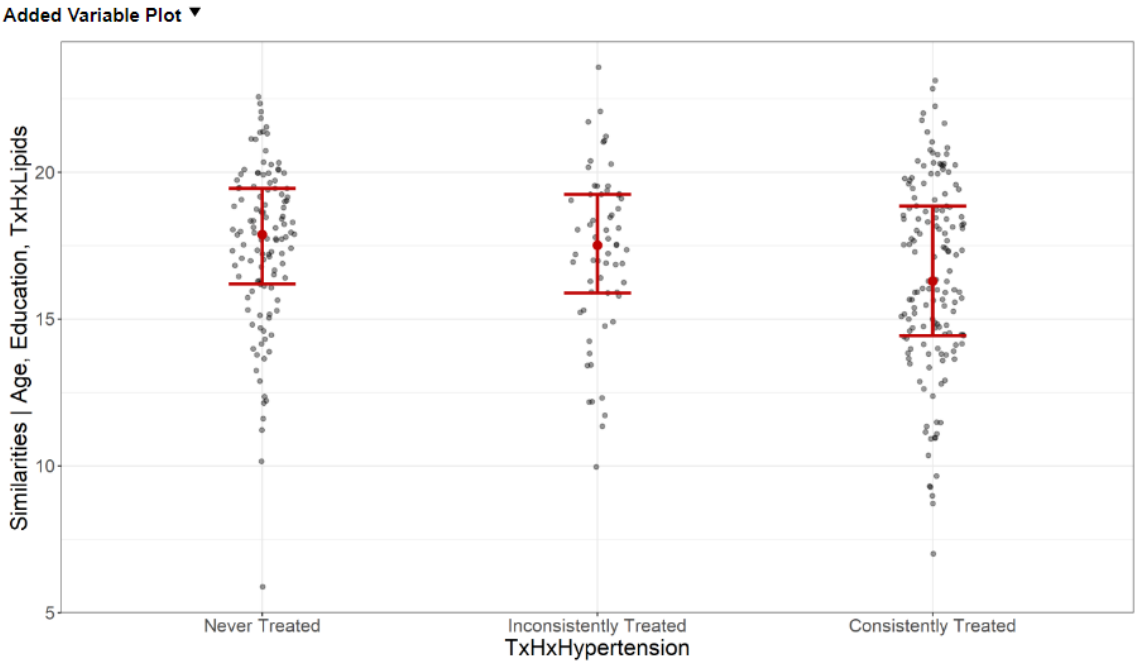

Figure E7. Raw Score Similarities Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

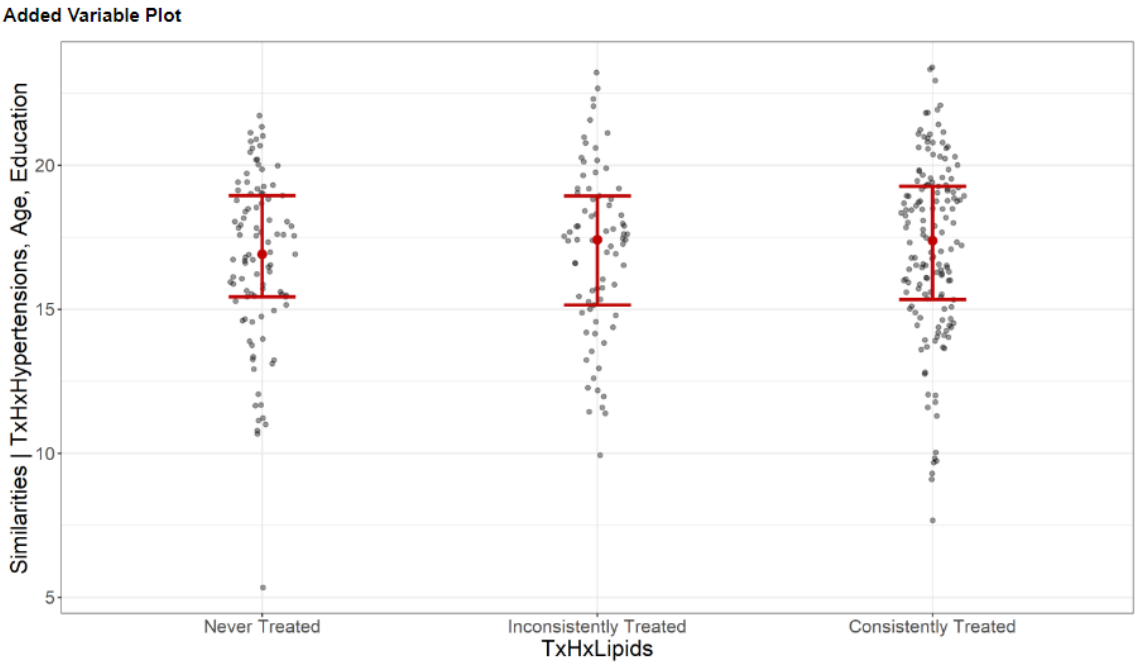

Figure E8. Raw Score Similarities Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

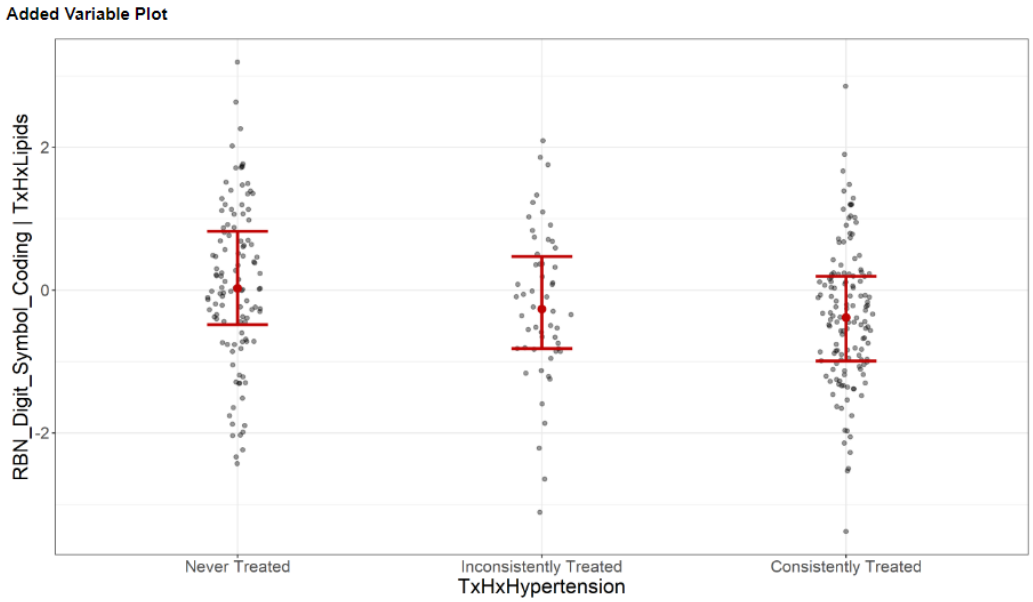

Figure E9. RBN Digit Symbol Coding Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

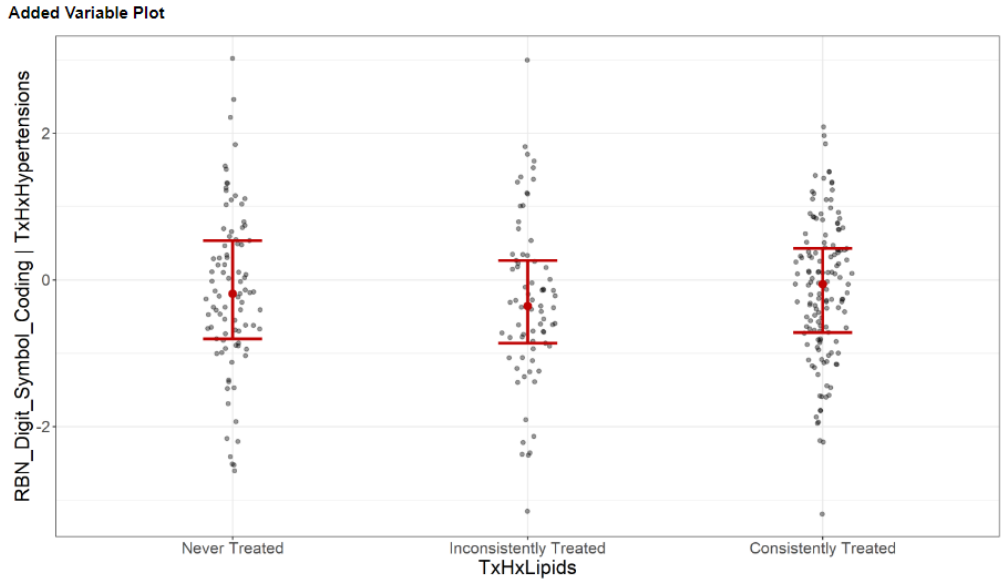

Figure E10. RBN Digit Symbol Coding Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

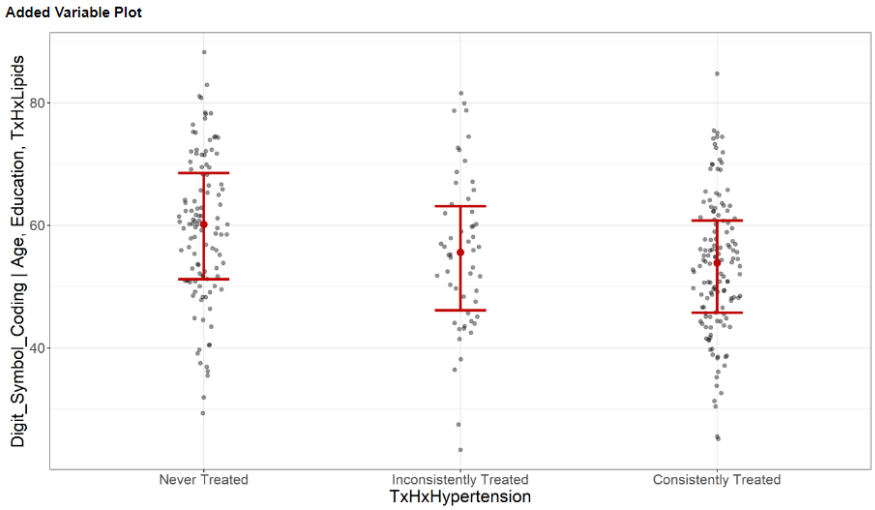

Figure E11. Raw Score Digit Symbol Coding Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

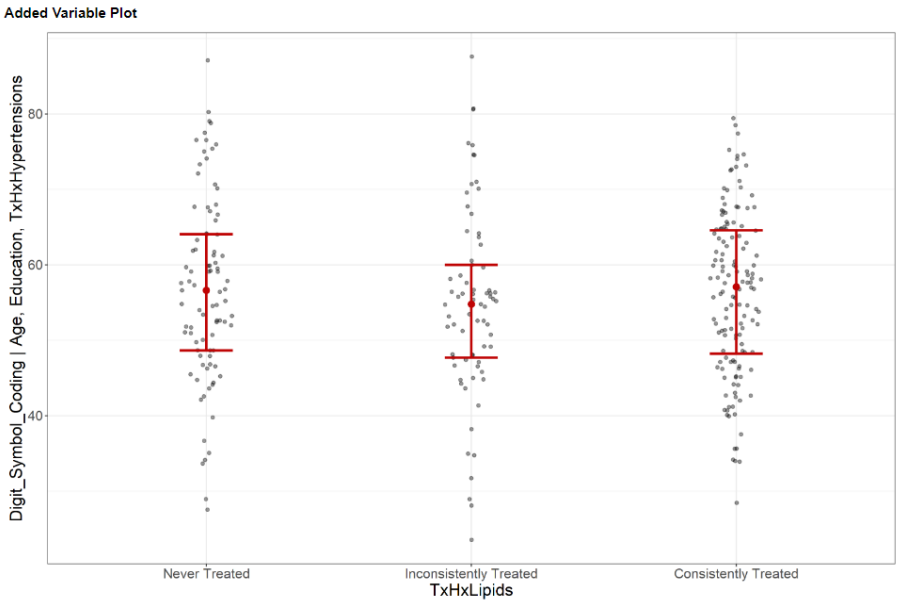

Figure E12. Raw Score Digit Symbol Coding Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

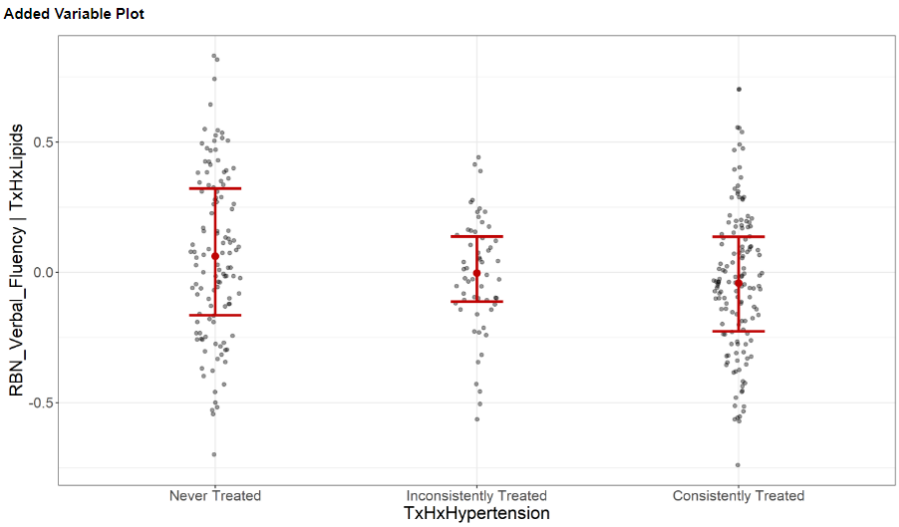

Figure E13. RBN Verbal Fluency Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

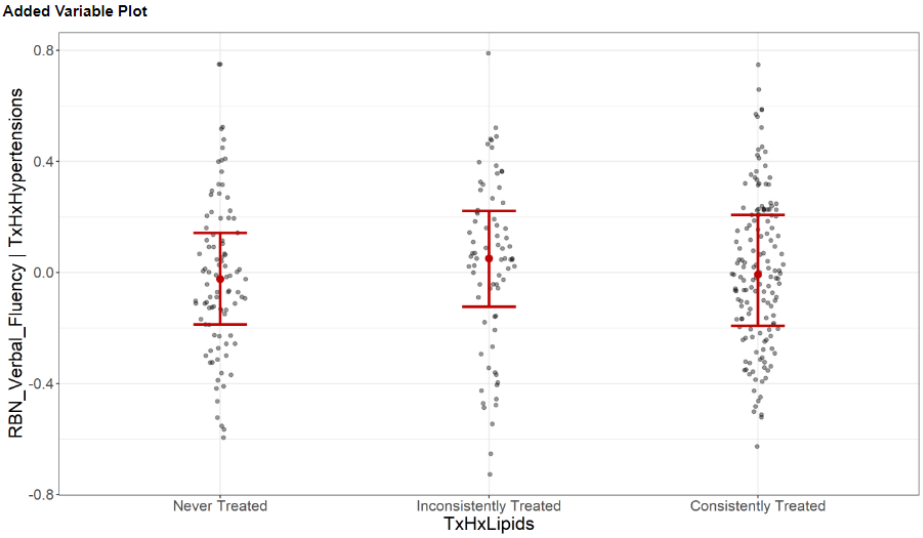

Figure E14. RBN Verbal Fluency Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

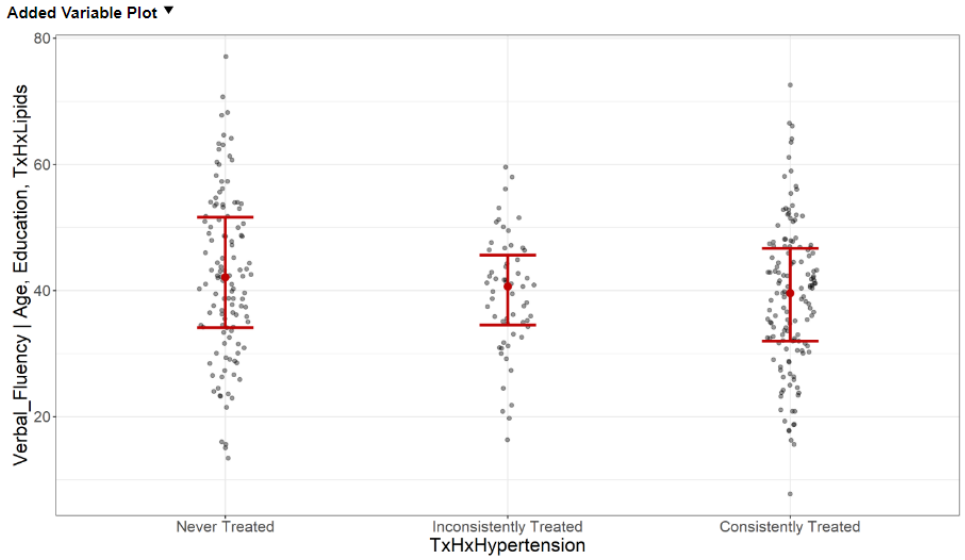

Figure E15. Raw Score Verbal Fluency Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

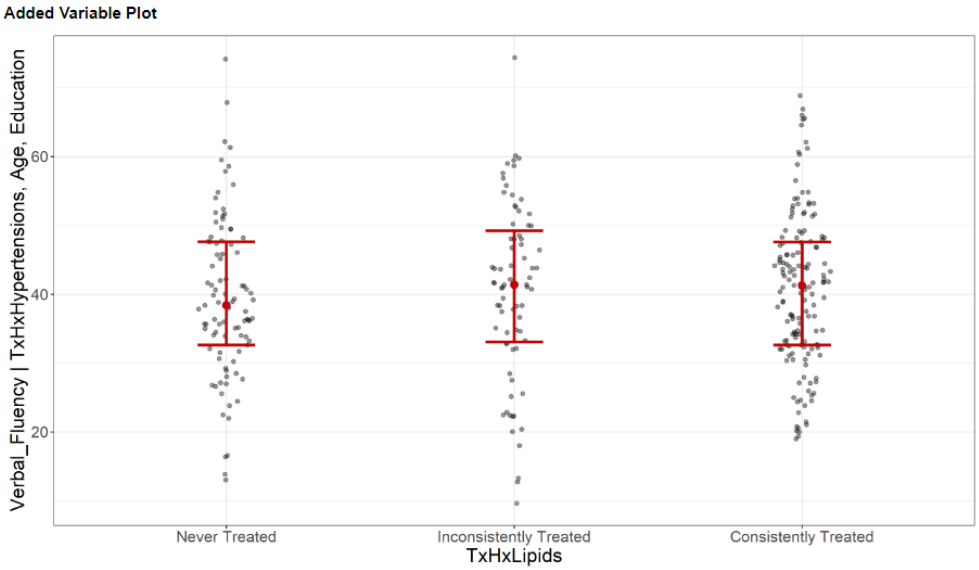

Figure E16. Raw Score Verbal Fluency Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

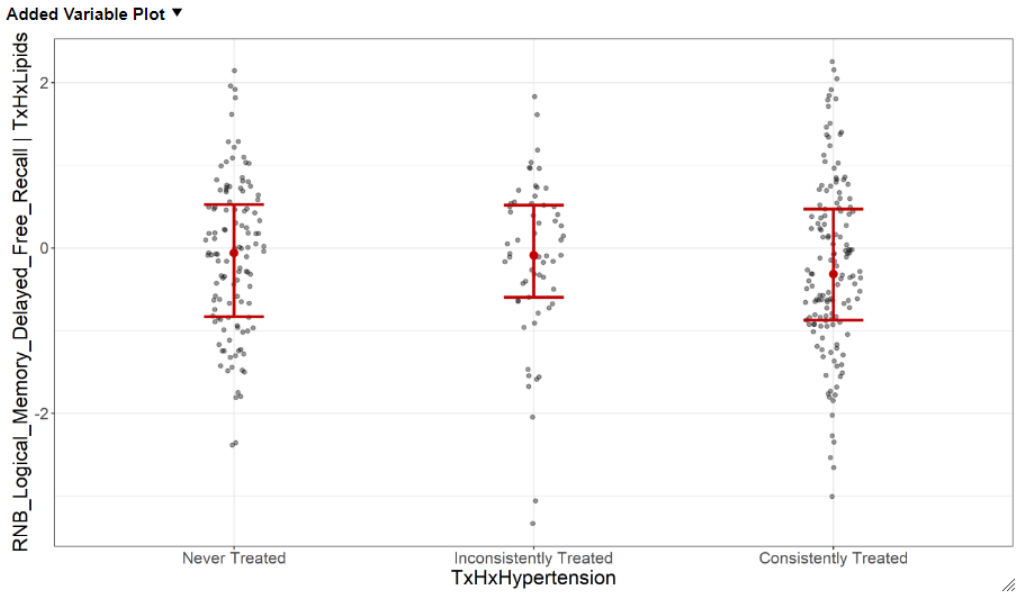

Figure E17. RBN Logical Memory Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

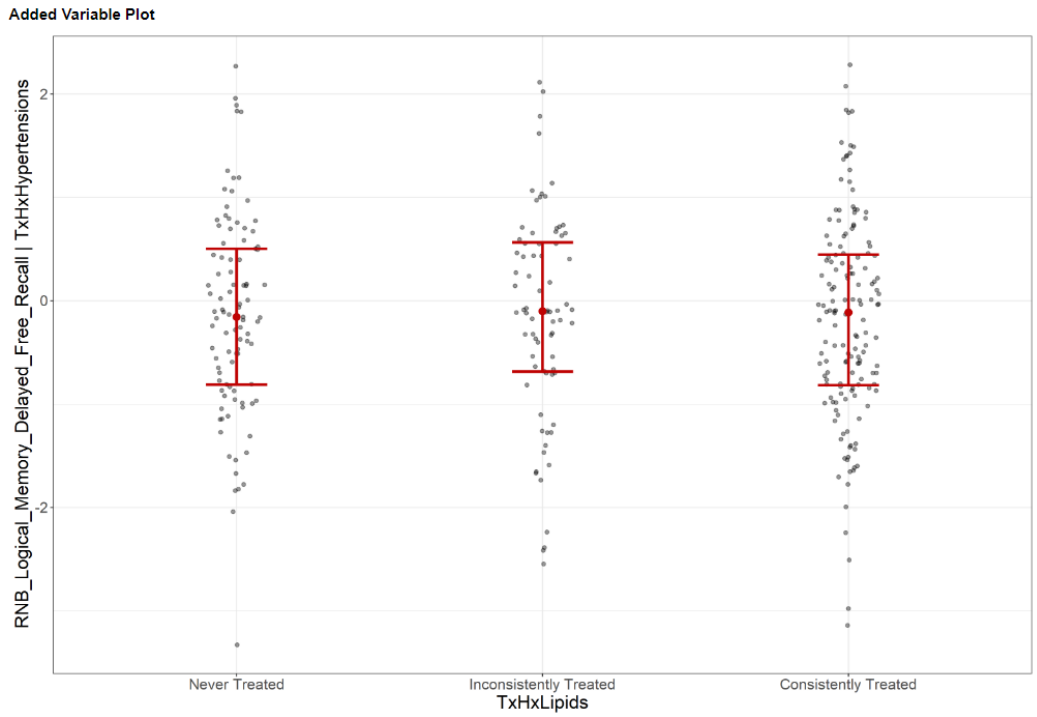

Figure E18. RBN Logical Memory Delayed Free Recall Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

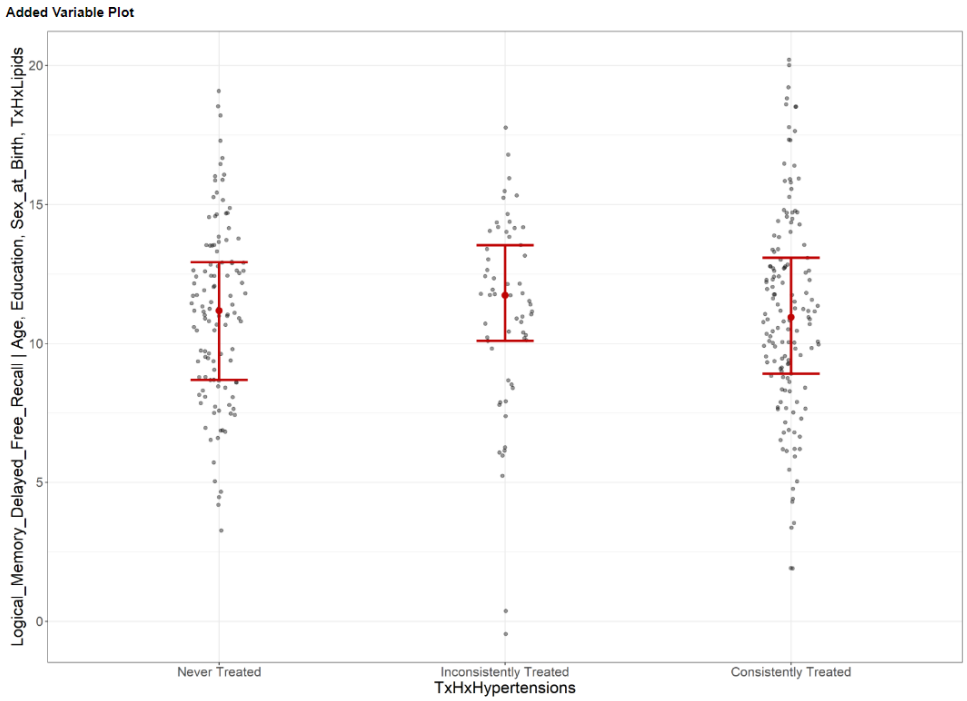

Figure E19. Raw Score Logical Memory Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

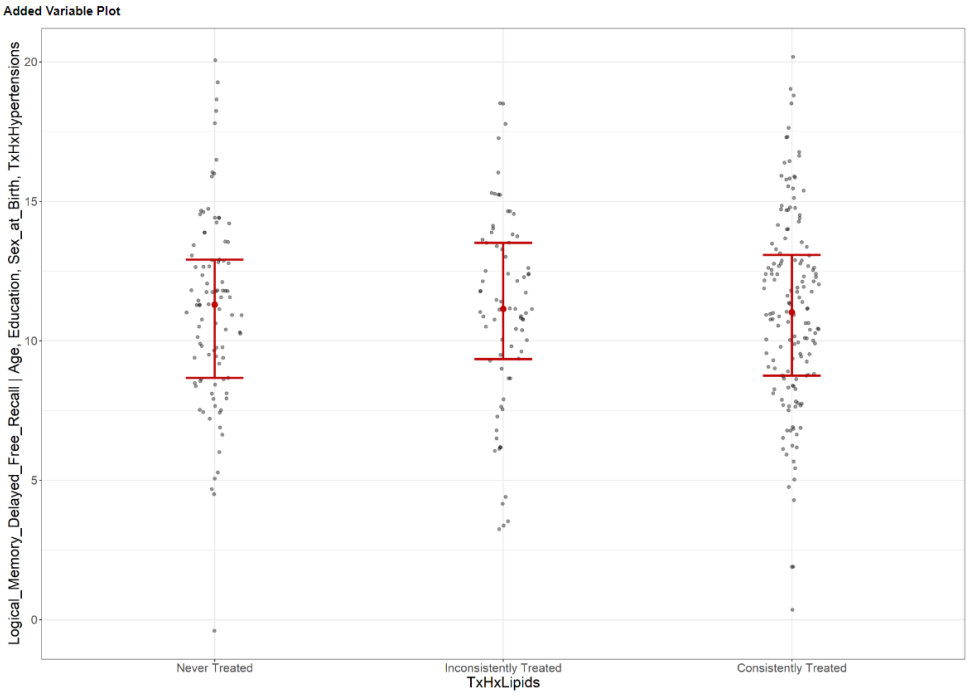

Figure E20. Raw Score Logical Memory Delayed Free Recall Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

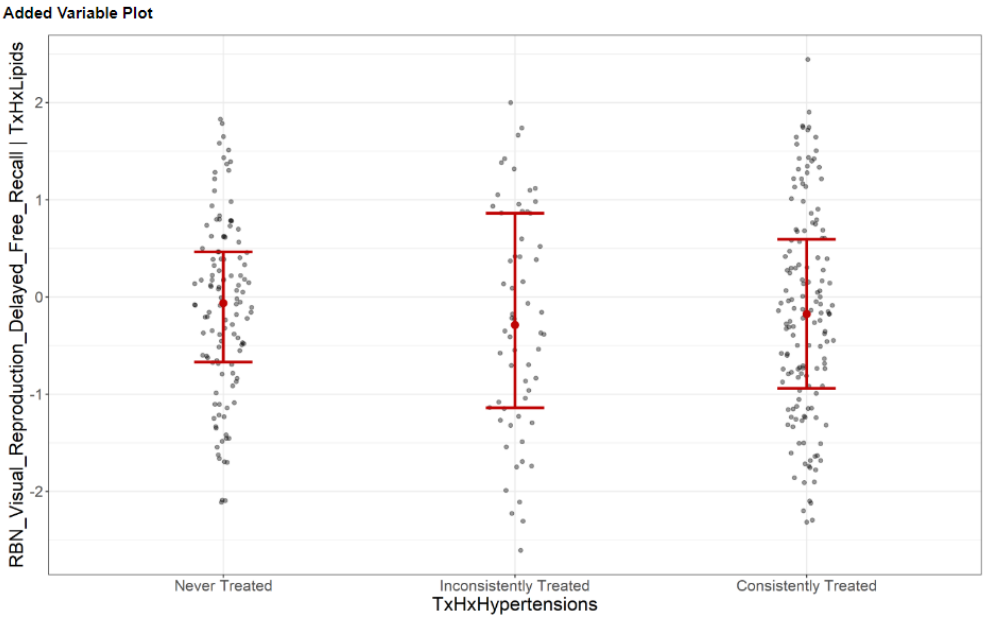

Figure E21. RBN Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids.

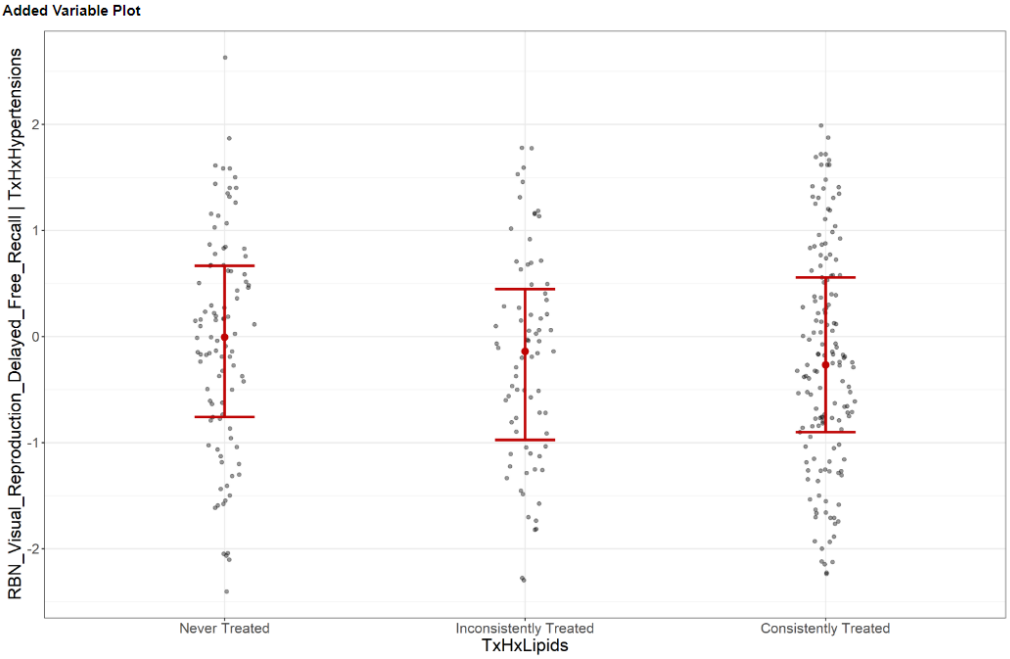

Figure E22. RBN Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension.

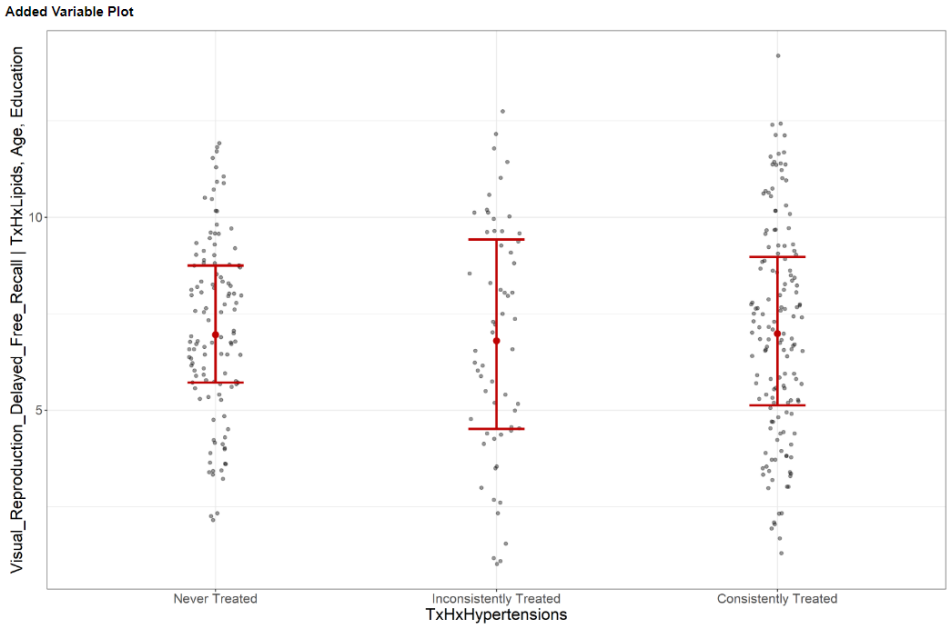

Figure E23. Raw Score Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

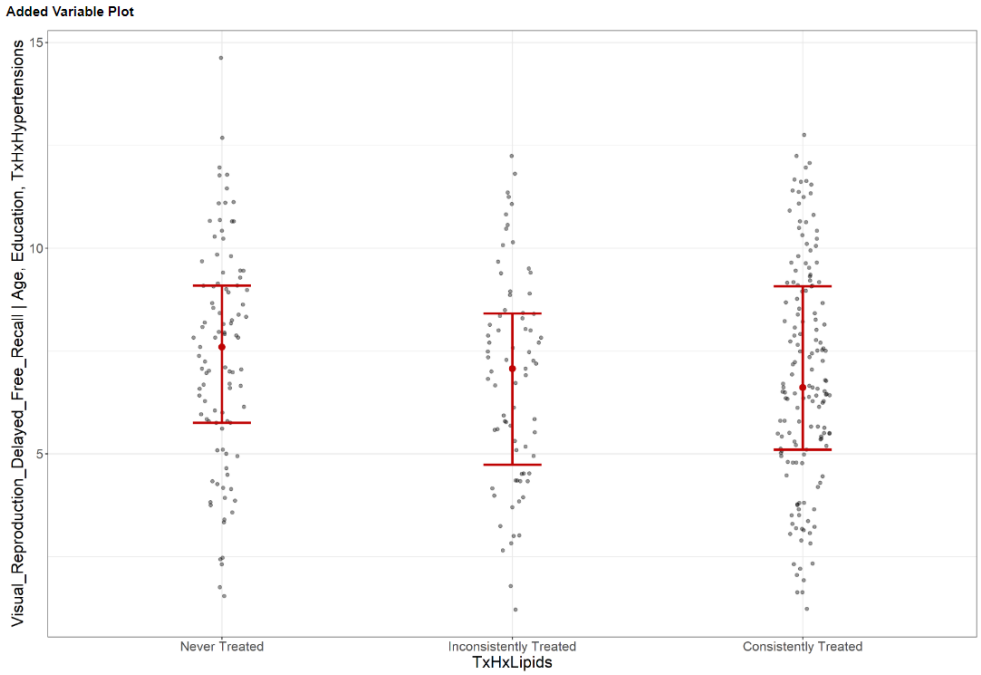

Figure E24. Raw Score Visual Reproduction Delayed Free Recall Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

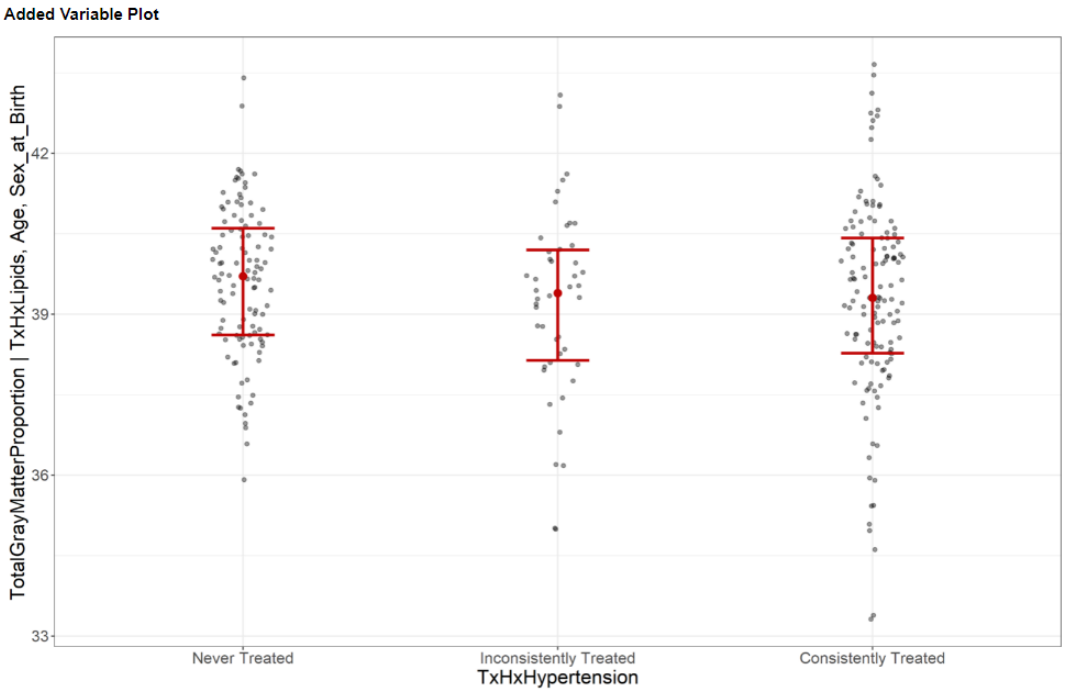

Figure E25. Total Percentage Gray Matter Volume Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

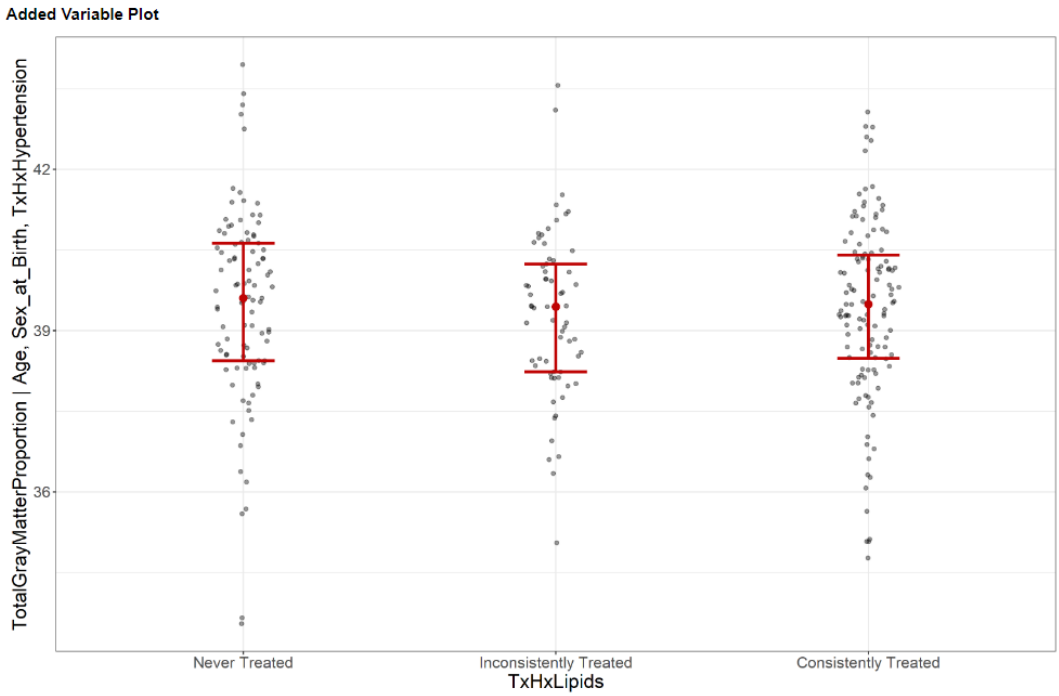

Figure E26. Total Percentage Gray Matter Volume Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.

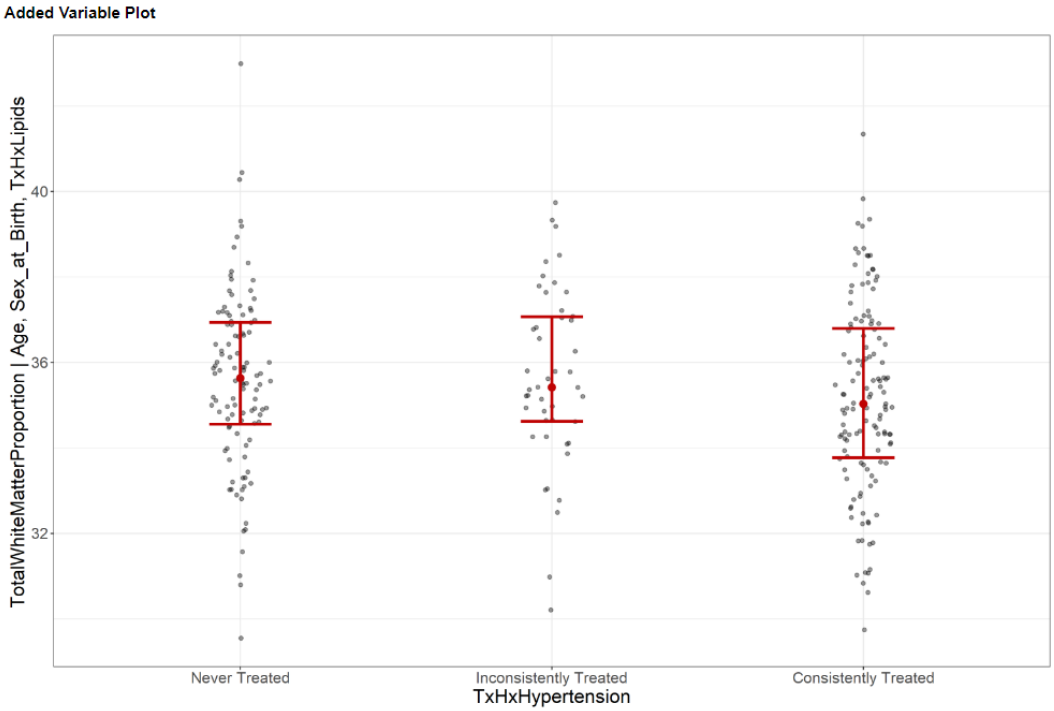

Figure E27. Total Percentage White Matter Volume Added Variable Plot of TxHxHypertension after Accounting for TxHxLipids and Covariates.

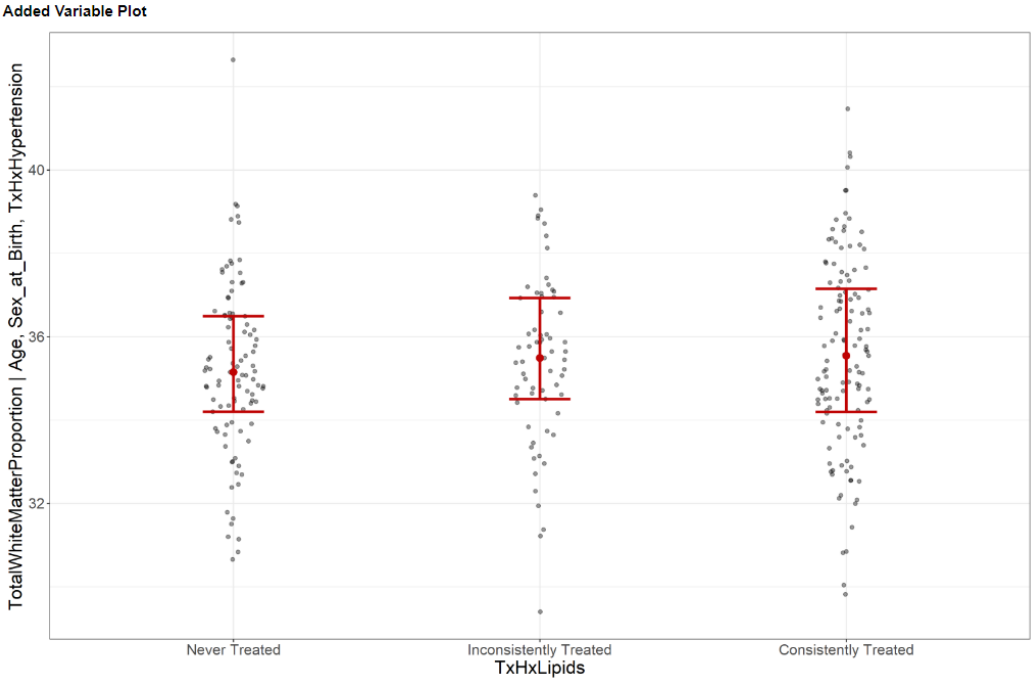

Figure E28. Total Percentage White Matter Volume Added Variable Plot of TxHxLipids after Accounting for TxHxHypertension and Covariates.