ORIGINAL RESEARCH

Midlife and Late-Life Vascular Risk Factors and White Matter Microstructural Integrity: The Atherosclerosis Risk in Communities Neurocognitive Study

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***Background*—**Diffusion tensor imaging measures of white matter (WM) microstructural integrity appear to provide earlier indication of WM injury than WM hyperintensities; however, risk factors for poor WM microstructural integrity have not been established. Our study quantifies the association between vascular risk factors in midlife and late life with measures of late-life WM microstructural integrity.

***Methods and Results*—**We used data from 1851 participants in ARIC (Atherosclerosis Risk in Communities Study) who completed 3-T magnetic resonance imaging, including diffusion tensor imaging, as part of the ARIC Neurocognitive Study (ARIC-NCS). We quantified the association among lipids, glucose, and blood pressure from the baseline ARIC visit (1987–1989, ages 44–65, midlife) and visit 5 of ARIC (2011–2013, ages 67–90, late life, concurrent with ARIC-NCS) with regional and overall WM mean diffusivity and fractional anisotropy obtained at ARIC visit 5 for ARIC participants. We also considered whether these associations were independent of or modified by WM hyperintensity volumes. We found that elevated blood pressure in midlife and late life and elevated glucose in midlife, but not late life, were associated with worse late-life WM microstructural integrity. These associations were independent of the degree of WM hyperintensity, and the association between glucose and WM microstructural integrity appeared stronger for those with the least WM hyperintensity. There was little support for an adverse association between lipids and WM microstructural integrity.

***Conclusions*—**Hypertension in both midlife and late life and elevated glucose in midlife are related to worse WM microstructural integrity in late life. **(*J Am Heart Assoc*. 2017;6:e005608. DOI: 10.1161/JAHA.117.005608.)**

Key Words: blood pressure • epidemiology • leukoencephalopathy • risk factor • type 2 diabetes mellitus

Vascular risk factors may increase the risk of subsequent cognitive decline and dementia, with the strongest evidence supporting a link between midlife vascular risk-factor levels and late life cognition.[1–3] In the absence of stroke, subclinical brain injury likely mediates these associations. Diffusion tensor imaging (DTI) quantifies the microstructural integrity of white matter (WM),[4] which almost certainly plays a role in later life cognitive impairment,[5,6] and so can be used to assess subclinical brain injury. DTI also complements other neuroimaging measures, namely measures of WM hyperintensities (WMHs) or WM volumes, because it provides an assessment of pathologic changes that precede and predict the development of WMH or WM loss.[7–12] Consequently, changes to WM microstructural integrity provide an early

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Accompanying Data S1, Tables S1 through S5 and Figures S1 through S32 are available at http://jaha.ahajournals.org/content/6/5/e005608/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Diffusion tensor imaging quantifies the microstructural integrity of white matter in the brain.
- Changes to brain white matter microstructural integrity provide an early indication of who is at risk of cerebral white matter injury and subsequent cognitive impairment.
- We found elevated glucose in midlife and elevated blood pressure at both midlife and late life were associated with worse brain white matter microstructural integrity. These associations were largely independent of the severity of white matter hyperintensities, a marker of cerebral white matter injury.
- Lipid levels at midlife or late life were not associated with brain white matter microstructural integrity.

What Are the Clinical Implications?

- Avoiding elevated glucose in midlife and hypertension at any point may prevent later damage to brain white matter microstructural integrity and its downstream effects.
- Diffusion tensor imaging–based measures may be appropriate risk-stratification tools or surrogate outcomes in clinical trials intervening with regard to vascular risk factors.
- Additional work is required to confirm these findings and to better establish the utility of these markers.

indication of who is at risk of cerebral WM injury, including both WMH and WM loss, and subsequent cognitive impairment. Identifying risk factors for poor WM microstructural integrity will help us understand the extent to which DTI-based measures are appropriate risk-stratification tools or surrogate outcomes in clinical trials. As such, understanding risk factors for poor WM microstructural integrity will be critical in efforts to prevent or mitigate these adverse outcomes.

Given the link between measures of WM microstructural integrity and subsequent development of WMHs, we hypothesized that risk factors for poor WM microstructural integrity and WMHs would be similar. Elevated blood pressure is consistently associated with the presence, severity, and progression of WMH, regardless of the timing of measurement.[13–18] Although diabetes mellitus and fasting glucose are not typically associated with WMH in cross-sectional analyses,[19,20] previous diabetes mellitus and fasting glucose are related to WMH progression and later WMH severity in longitudinal analyses.[16,18] Conversely, lipids do not appear to be associated with severity or progression of WMH.[16,19] In comparison, existing studies evaluating the association between these risk factors and WM microstructural integrity are typically small and cross-sectional, and despite evidence of a link between WM microstructural integrity and WMH, most have not investigated whether the association is independent of or modified by WMH. The goal of this study was to quantify the association of midlife and late-life measures of vascular risk factors with late-life WM microstructural integrity in a relatively large sample of persons drawn from ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study) and to consider whether the association is independent of or modified by WMH.

Methods

Study Population

The ARIC study is a longitudinal cohort study of 15 792 persons recruited between 1987 and 1989 (visit 1) from 4 US communities: suburbs of Minneapolis, Minnesota; Forsyth County, North Carolina; Washington County, Maryland; and Jackson, Mississippi. In 2011–2013 (visit 5), all persons with evidence of cognitive impairment and a stratified random sample of other participants were invited to complete brain magnetic resonance imaging (MRI) as part of ARIC-NCS.[21] As such, although the MRI subsample is enriched with persons with cognitive impairment, use of derived sampling weights allows estimation of what the effects would be had we obtained MRI on all ARIC visit 5 participants. Our eligible sample included those ARIC-NCS participants with valid DTI data, excluding nonblack and nonwhite persons (n=6), black participants from Maryland or Minnesota (n=9), persons disallowing the use of genetic data (n=10), and persons with prior stroke (n=66). Primary analyses also excluded persons missing exposure or covariate data; we considered associations in the full eligible sample after multiply imputing missing data in sensitivity analyses. The institutional review boards of all participating institutions approved this study, and participants provided written informed consent before participation.

Brain Imaging

At ARIC-NCS, each study site followed identical protocols for 3-T brain MRI. All scans included sagittal T1-weighted MPRAGE (magnetization-prepared rapid gradient-echo imaging), axial T2 FLAIR (fluid attenuation inversion recovery), and axial DTI pulse sequences. Data were processed by the ARIC MRI Reading Center at the Mayo Clinic (Rochester, MN). We provide an overview below (see Supplementary Methods for details).

Fractional anisotropy (FA) measures the directional constraint of water diffusion and ranges from 0 to 1 (unitless). Mean diffusivity (MD) is a scalar measure of how quickly water molecules diffuse overall (mm^2/s). Lower FA and higher MD indicate worse WM microstructural integrity. WM FA and MD were calculated for brain regions defined by an in-house atlas of lobar and deep WM regions based on the STAND400 template.[22] The WM regions were intersected with tissue segmentations from each participant's T1-weighted and FLAIR

images; WM FA and MD were calculated using voxels with a >50% probability of being WM. The segmentation takes care to include WMHs as WM. To account for imperfect registration between the DTI and T1-weighted images, an upper cutoff of MD <0.002 mm^2/s was applied to exclude edge voxels that were primarily cerebrospinal fluid. We averaged left and right WM FA and MD across atlas regions and then took a weighted average, with weights based on the number of voxels in each WM region, to create WM FA and MD measures for 7 regions of interest (ROIs): frontal, temporal, occipital, and parietal lobes; anterior and posterior corpus callosum; and an overall measure—the weighted average of these 6 ROIs (capsular WM was not included). WMH and intracranial volumes were quantified via in-house algorithms.[23,24]

Vascular Risk Factors

We considered vascular risk factors at ARIC visit 1 (1987–1989, midlife, ages 44–65) and ARIC visit 5 (2011–2013, late life, ages 67–90). Plasma total cholesterol and triglycerides were measured using enzymatic methods,[25,26] high-density lipoprotein cholesterol (HDL-C) concentrations were determined after precipitation of non-HDL lipoproteins,[27,28] and low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation.[29] Serum glucose was measured using the hexokinase method.[30] Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured 3 times according to a standard protocol; we consider the mean of the 2 final measurements.

Covariates

All covariates are based on data collected at ARIC visit 1 or at ARIC visit 5 and include age (years), sex (male, female), race and center (black–Mississippi, black–North Carolina, white–North Carolina, white–Maryland, white–Minnesota), education (less than high school/high school, General Educational Development test, vocational school, some college/college, graduate or professional school), *APOE*E4* allele status (present, absent), body mass index (kg/m^2), smoking status (current, former, never), antihypertensive medication use (yes, no), lipid-lowering medication use (yes, no), and diabetes mellitus medication use (yes, no). Medication use was determined through direct visual inspection and linkage to Medi-Span therapeutic classification codes.

Statistical Methods

We standardized ROI WM FA and MD by subtracting the sample mean and dividing by the sample standard deviation. For our primary analyses, we used separate weighted linear regression models to quantify the association between each vascular risk factor and WM FA and MD in each ROI. The weights account for the approach used to select ARIC participants for MRI. Given slight deviations from a linear dose-response pattern for some exposures in exploratory analyses, we considered associations with both categorical and linear exposure parameterizations. All analyses were adjusted for the covariates described above and the other vascular risk factors (eg, SBP, DBP, and glucose in models estimating associations with lipids). Time-varying covariates were updated to reflect the status at the time of exposure assessment (eg, visit 1 age when considering visit 1 SBP, visit 5 age for visit 5 SBP). We then adjusted these primary models for total WMH volumes and intracranial volume to determine whether our associations were independent of WMH severity.

We conducted several sensitivity analyses. We repeated analyses considering glucose and lipids after restricting those who were fasting ≥8 hours at blood draw (98% at visit 1, 96% at visit 5). We repeated analyses for glucose and blood pressure adjusting for total cholesterol, HDL-C, and triglycerides rather than LDL-C. We restricted analyses of triglycerides to those with <500 mg/dL triglycerides to exclude potentially influential outliers. We considered analyses after multiply imputing missing exposure and covariate data[31] to understand the influence and missing data. Finally, we considered unweighted analyses to understand the influence of the selection process by which we selected visit 5 participants for MRI and analyses additionally weighted with inverse probability of attrition weights[32,33] to better understand the potential influence of potentially informative attrition from visit 1 to visit 5 on our results.

We used multiplicative interaction terms to evaluate effect modification by age (<75 or ≥75 years), race (black or white), sex (male or female), *APOE*E4* (present or absent), cognitive status (normal/mild cognitive impairment or dementia), and WMH severity (deciles of intracranial volume-standardized WMH volumes). We considered $P<0.05$ to be statistically significant and reported 95% confidence intervals. We did not adjust for multiple comparisons, given that the association between a vascular risk factor at a given time point and 1 measure of WM microstructural integrity is likely correlated with associations considering other time points or ROIs. All analyses were completed using SAS version 9.4, STATA version 14.0, or R version 3.1.2.

Results

Weighted characteristics of the 1851 eligible persons are provided in Table. Mean SBP and glucose were higher at visit 5 than at visit 1, whereas mean DBP, total cholesterol, and LDL-C were lower. Tables S1 and S2 provide unweighted summary statistics and information on missingness.

Table. Weighted Characteristics of Eligible ARIC-NCS Participants at Visits 1 and 5 (n=1851)

	Visit 1 (1987–1989)	Visit 5 (2011–2013)	
	Mean (25th, 75th Percentile) or %*		*P* Value†
Time to MRI, y	23.6 (23.0, 24.2)	0 (0, 0)	…
Age, y	51.7 (46.8, 55.1)	75.3 (70.4, 78.7)	<0.0001
Cognitively normal	…	74.1%	…
*APOE*E4* allele	27.4%		…
Male	38.5%		…
Race-center			…
White-Minnesota	29.9%		
White-Maryland	27.6%		
White-North Carolina	21.2%		
Black-North Carolina	1.7%		
Black-Mississippi	19.6%		
Education			…
<12 y	11.8%		
12–16 y	40.3%		
>16 y	47.9%		
Smoking status			<0.0001
Current	16.6%	5.2%	
Former	33.2%	51.6%	
Never	50.2%	43.1%	
Body mass index, kg/m^2	26.8 (23.3, 29.3)	28.4 (24.7, 31.2)	<0.0001
Systolic blood pressure, mm Hg	114.8 (103.7, 122.9)	129.8 (117.1, 140.1)	<0.0001
Diastolic blood pressure, mm Hg	72.2 (64.7, 78.0)	66.0 (58.6, 72.3)	<0.0001
Fasting glucose, mg/dL	99.4 (90.9, 102.8)	112.0 (96.9, 117.2)	<0.0001
Total cholesterol, mg/dL	209.6 (182.0, 231.2)	185.9 (155.2, 212.4)	<0.0001
HDL-C, mg/dL	54.2 (42.0, 63.1)	53.4 (43.0, 61.6)	0.007
LDL-C, mg/dL	132.2 (107.5, 154.5)	107.4 (81.3, 128.3)	<0.0001
Triglycerides, mg/dL	117.3 (71.3, 139.8)	125.7 (85.2, 147.9)	<0.0001
Antihypertensive medication use	20.2%	72.6%	<0.0001
Medication use for diabetes mellitus	1.7%	18.5%	<0.0001
Lipid-lowering medication use	1.6%	51.9%	<0.0001
Hypercholesterolemia	57.3%	34.9%	<0.0001
Fractional anisotropy, by region			
Frontal	…	0.28 (0.27, 0.30)	…
Temporal	…	0.28 (0.27, 0.30)	…
Parietal	…	0.30 (0.29, 0.31)	…
Occipital	…	0.22 (0.20, 0.24)	…
Anterior corpus callosum	…	0.43 (0.39, 0.47)	…
Posterior corpus callosum	…	0.58 (0.54, 0.62)	…
Overall	…	0.28 (0.27, 0.30)	…

Continued

Table. Continued

	Visit 1 (1987–1989)	Visit 5 (2011–2013)	
	Mean (25th, 75th Percentile) or %*		*P* Value†
Mean diffusivity, by region, 10^{-4} mm^2/s			
Frontal	…	8.5 (8.2, 8.9)	…
Temporal	…	8.8 (8.4, 9.2)	…
Parietal	…	8.8 (8.3, 9.1)	…
Occipital	…	8.7 (8.2, 9.1)	…
Anterior corpus callosum	…	11.5 (10.7, 12.2)	…
Posterior corpus callosum	…	11.2 (10.4, 11.8)	…
Overall	…	8.7 (8.3, 9.1)	…

ARIC-NCS indicates Atherosclerosis Risk in Communities Neurocognitive Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging.
*Summary measures among those with data for a given variable.
†Comparing visits 1 and 5 using a weighted paired *t* test or McNemar test, as appropriate.

Findings were generally consistent across ROIs, sensitivity analyses, and categorical and linear versions of the exposures (Figures S1 through S28; Tables S3 through S5). We reported the linear association between our vascular risk factors and overall WM MD or FA in the next sections and discussed other analyses only when they differed substantially from these analyses. Likewise, we discussed effect measure modification by age, sex, or race only when there was evidence supporting its presence.

Plasma Lipids

Although there was little support for an adverse association between elevated lipids at visit 1 and overall WM FA, elevated total cholesterol, LDL-C, and HDL-C at visit 5 appeared to be associated with better overall WM FA (Figure 1). However, these protective associations were limited to those who remained cognitively normal at visit 5 (interaction $P<0.05$, with the exception of $P=0.08$ for visit 5 HDL-C) and were attenuated in sensitivity analyses omitting sampling weights or weighting for attrition, which upweight persons with cognitive impairment (Figures S6, S10, and S14). Findings were materially unchanged after adjustment for WMH (Figure 1), and there was little support for effect modification by WMH volumes (Figures S29 through S32). Analyses considering effect modification suggested an association between higher visit 5 triglycerides and worse overall FA in women but not men (interaction $P=0.004$).

Visit 1 and 5 plasma lipids were not associated with overall WM MD, with the exception of an adverse association with

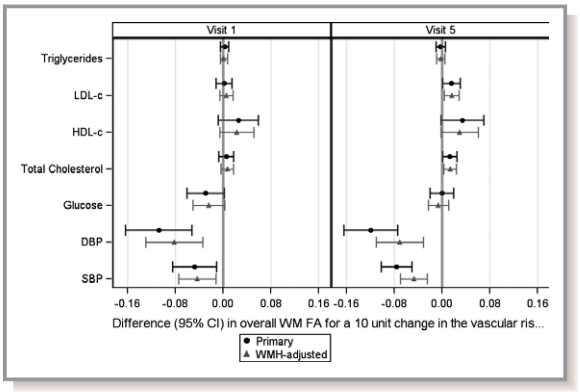

Figure 1. Comparison of primary and WMH-adjusted analyses of the association of mid- or late-life cardiovascular risk factors with overall WM FA. CI indicates confidence interval; DBP, diastolic blood pressure; FA, fractional anisotropy; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; WM, white matter; WMH, white matter hyperintensity.

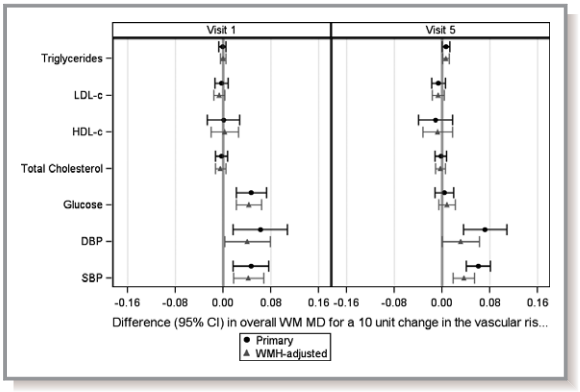

Figure 2. Comparison of primary and WMH-adjusted analyses of the association of mid- or late-life cardiovascular risk factors with overall WM MD. CI indicates confidence interval; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MD, mean diffusivity; SBP, systolic blood pressure; WM, white matter; WMH, white matter hyperintensity.

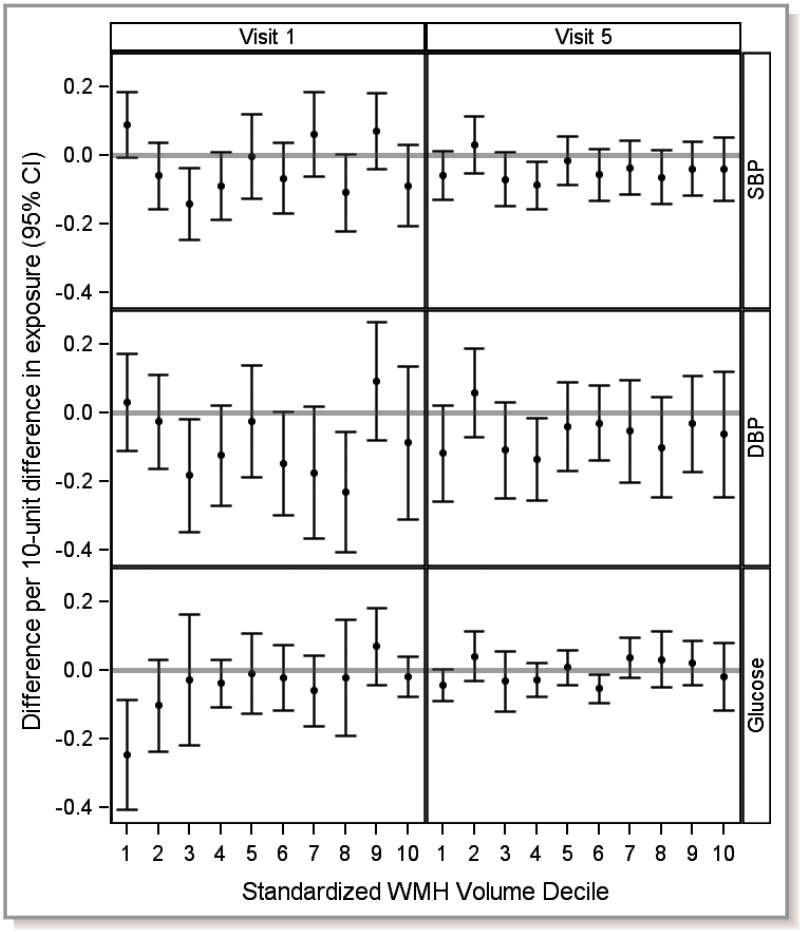

Figure 3. The adjusted association between cardiovascular risk factors at visit 1 or 5 and measures of overall white matter fractional anisotropy by decile of intracranial-volume standardized WMH volumes. CI indicates confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; WMH, white matter hyperintensity.

elevated triglycerides at visit 5 (Figure 2); however, this result was not robust to sensitivity analyses omitting sampling weights or imputing missing data (Figure S4). Adjustment for WMH did not alter these findings (Figure 2). Some evidence suggested an association between elevated LDL-C and worse overall WM FA and MD only in those in the highest decile of standardized WMH volumes (Figure S30). Analyses considering effect modification also suggested a protective association between visit 1 HDL-C and overall WM MD in black but not white participants (interaction P=0.01).

Serum Glucose

Elevated serum glucose at visit 1 was strongly associated with worse overall WM MD (Figure 2). Although elevated glucose at visit 1 was marginally associated with worse overall WM FA (Figure 1), analyses considering categories of glucose did not support an association (Table S4). Visit 5 glucose was not associated with overall WM FA or MD, except in sensitivity analyses implementing inverse probability of attrition weighting, where higher visit 5 glucose was associated with worse overall WM MD. Results were similar after additional adjustment for WMH (Figures 1 and 2), and the adverse association between elevated visit 1 glucose and worse MD or FA was stronger in those with the least WMH (Figures 3 and 4).

Blood Pressure

Elevated SBP and DBP at either visit were strongly associated with worse overall WM FA and MD. Additional adjustment for WMH slightly attenuated, but did not eliminate, these associations (Figures 1 and 2). There was little support for effect modification by WMH volumes (Figures 3 and 4). Of note, in ROI-specific analyses, associations with MD or FA in the anterior or posterior corpus callosum were often weaker or null, and the association between visit 1 DBP and MD was attenuated slightly in inverse probability of attrition weighting sensitivity analyses (Figures S21 through S28).

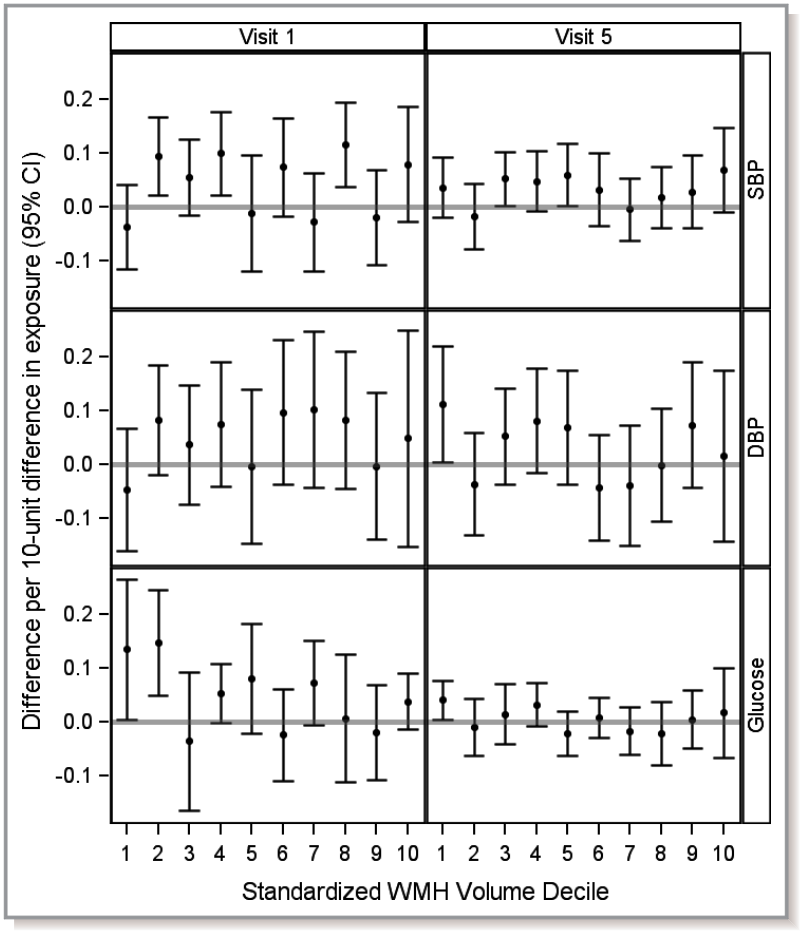

Figure 4. The adjusted association between cardiovascular risk factors at visit 1 or 5 and measures of overall white matter mean diffusivity by decile of intracranial-volume standardized WMH volumes. CI indicates confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; WMH, white matter hyperintensity.

Discussion

To our knowledge, this study of the relation of vascular risk factors and WM microstructural integrity is the largest and most comprehensive to date. Consistent with our own findings that elevated blood pressure at both midlife and late life was associated with worse WM microstructural integrity, several small cross-sectional studies also previously reported an association between elevated blood pressure and worse WM microstructural integrity.[7,34–42] Our finding of an association between midlife glucose and late-life WM microstructural integrity is also consistent with 1 prior report of stronger associations between diabetes mellitus and WM microstructural integrity with increasing duration of diabetes mellitus.[43] Although we did not observe a cross-sectional association between glucose and WM microstructural integrity, prior cross-sectional studies generally reported worse microstructural integrity in participants with diabetes mellitus compared with controls.[43–48] Given that these studies were modest in size (n<250), focused on diabetes mellitus rather than glucose, and often reported effects only in localized brain regions, further work will be needed to reconcile these findings with our own. Finally, although we found little support for an adverse association between elevated lipids and late-life WM microstructural integrity, prior reports are mixed, with studies reporting both null and adverse associations between lipids and WM microstructural integrity.[47,49–51] As with the literature on diabetes mellitus and WM microstructural integrity, however, these studies frequently report localized effects, which may not be reflected in our analyses, given our focus on large ROIs, and are limited by their size (n<250). Our finding that associations between vascular risk factors and WM microstructural integrity were largely independent of WMH volumes is also consistent with some prior reports,[43,45,47] reinforcing the notion that WM microstructural integrity damage likely precedes WMH.

Our findings underscore the importance of moving to longitudinal designs that can answer questions about when exposures are relevant. Strengths of this study include the large number participants, the use of data on midlife and

late-life vascular risk factors, and a community-based sample. Compared with a voxelwise comparison-based approach, our ROI-based approach has a reduced chance of type I error and greater reproducibility but is unlikely to identify localized effects. Because we based our study on an MRI subsample, selection bias is a potential concern; however, we do not believe that this is a significant source of bias in this study because our sensitivity analyses designed to address and quantify this source of bias were generally consistent with our primary analyses. Other limitations include the lack of serial MRIs, precluding assessment change in FA or MD, and the potential for chance findings or residual bias.

Changes to WM microstructural integrity provide an early indication of who is at risk of cerebral WM injury, including both WMH and WM loss, and subsequent cognitive impairment. Our study confirmed that the risk factors for WM microstructural integrity and WMH are similar, and that, perhaps most important, these associations were independent of WMH presence and severity. Although our study provides early evidence to suggest that DTI-based measures may be appropriate outcomes risk-stratification tools or surrogate outcomes in clinical trials intervening with regard to vascular risk factors, additional work is required to confirm these findings and to better establish the utility of these markers. Regardless, our study suggests that avoiding elevated glucose in midlife and hypertension at any point may prevent later damage to WM microstructural integrity and its downstream effects.

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Disclosures

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SUPPLEMENTARY MATERIAL

Midlife and late life vascular risk factors and white matter integrity on diffusion tensor imaging: the ARIC-NCS study

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Supplementary Methods: MRI Scan Parameters and Processing

At Visit 5/ARIC-NCS, each study site followed similar protocols for 3T brain MRI. The North Carolina and Mississippi sites used Skyras, the Maryland site used a Verio, and the Minnesota site used a Trio Tim, all manufactured by Siemens. The T1-weighted volumetric scans used a sagittal magnetization prepared gradient echo (MPRAGE) sequence with 1.2mm x 1.0mm x 1.0 mm resolution in the x (~LR), y (~AP), and z (~SI) directions. The resulting images were unwarped in post-processing to account for gradient nonlinearity, using coefficients provided by the manufacturer. The FLAIR scans, primarily used to detect WMH, had a resolution of 0.9mm x 0.9mm x 5.0mm in x, y, and z. The DTI scans used the Siemens product echo planar imaging (EPI) pulse sequence and diffusion gradient set, namely a single b = 0 volume followed by 64 b = 1000 s/mm^2 diffusion directions uniformly spread over the whole sphere. An isotropic 2.7mm voxel resolution was used, and DTI echo time (TE) was 87 ms for all scanners.

In post-processing the DTI images were simultaneously corrected for volume-to-volume head motion and eddy current distortion by affinely registering each of the diffusion weighted volumes to the b=0 volume. EPI sequences are also affected by distortions at changes in magnetic susceptibility, such as air/tissue/bone interfaces around the sinuses and ear canals. These distortions were corrected by nonlinearly registering the DTI images to the T1-weighted anatomical reference scan using the BrainSuite (Bhushan, Haldar, Choi, Joshi, Shattuck, & Leahy, 2015) program, which also produced FA and MD images in each subject's T1-weighted space after fitting diffusion tensors to the data with a weighted least-squares scheme. Each FLAIR-to-T1 and DTI-to-T1 registration was manually examined to catch and correct or remove gross registration failures.

Image analysis for all four sites was completed by the ARIC MRI Reading Center (Mayo Clinic, MN; PI: Dr. Cliff Jack, Jr.) using the same protocols, ensuring consistency of measurement across sites. Finally, we also adjusted for site in our regression models, as part of the race-center variable.

Reference:

Bhushan, C., Haldar, J., Choi, S., Joshi, A., Shattuck, D., & Leahy, R. (2015). Co-registration and distortion correction of diffusion and anatomical images based on inverse contrast normalization. *Neuroimage , 115*, 269-80.

Table I. Unweighted characteristics eligible ARIC-NCS sample participants at Visit 1 and Visit 5 (n=1851)		
	Visit 1 (1987-89)	Visit 5 (2011-2013)
	Mean (25th, 75th percentile) or %*	
Time to MRI (years)	23.7 (23.0, 24.2)	0 (0, 0)
Age (years)	52.7 (47.7, 56.1)	76.4 (71.3, 79.9)
Cognitively Normal	N/A	59.4%
APOE e4 allele (CT or CC)	29.2%	
Male	39.9%	
Race-center		
MN whites	22.5%	
MD whites	26.5%	
NC whites	23.4%	
NC blacks	1.8%	
MS blacks	25.8%	
Education		
<12 years	14.1%	
12-16 years	40.9%	
>16 years	44.9%	
Smoking status		
Current	16.6%	5.4%
Former	32.4%	50.9%
Never	51.0%	43.7%
BMI (kg2/m)	27.0 (23.6, 29.5)	28.4 (24.7, 31.1)
Systolic BP (mm Hg)	116.2 (104.4, 124.5)	131.0 (118.0, 141.5)
Diastolic BP (mm Hg)	72.8 (65.1, 79.5)	66.2 (58.7, 72.6)
Fasting glucose (mg/dL)	100.0 (91.3, 103.2)	112.7 (96.9, 118.5)
Total cholesterol (mg/dL)	212.7 (184.8, 234.3)	183.7 (153.3, 210.2)
HDL cholesterol (mg/dL)	54.7 (41.4, 63.7)	53.0 (42.9, 61.0)
LDL cholesterol (mg/dL)	134.7 (109.2, 156.9)	105.8 (80.2, 126.6)
Triglycerides (mg/dL)	118.5 (72.5, 139.3)	125.2 (83.9, 146.6)
Antihypertensive medication use	22.2%	74.9%
Medication use for diabetes	1.9%	21.2%
Lipid lowering medication use	1.7%	54.0%
Hypercholesterolemia	61.2%	33.0%
Fractional anisotropy, by region		
Frontal	--	0.28 (0.27, 0.30)
Temporal	--	0.28 (0.27, 0.30)
Parietal	--	0.30 (0.28, 0.31)
Occipital	--	0.22 (0.20, 0.23)
Anterior corpus callosum	--	0.42 (0.38, 0.46)
Posterior corpus callosum	--	0.57 (0.54, 0.62)
Overall	--	0.28 (0.27, 0.30)
Mean diffusivity, by region (10^{-4} mm^2/s)		
Frontal	--	8.6 (8.2, 8.9)
Temporal	--	8.9 (8.5, 9.3)
Parietal	--	8.8 (8.3, 9.2)
Occipital	--	8.7 (8.3, 9.1)
Anterior corpus callosum	--	11.6 (10.8, 12.4)
Posterior corpus callosum	--	11.2 (10.4, 11.9)
Overall	--	8.8 (8.4, 9.1)
Abbreviations: ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; MRI, magnetic resonance imaging		
*All summary measures among those with data for a given variable. Number missing each variable is provided in Appendix Table 2.		

Table II. Number of eligible ARIC-NCS sample participants missing covariate or exposure data at Visit 1 or Visit 5

	Visit 1 (1987-89)	Visit 5 (2011-2013)
	N missing	
Time to MRI (years)	0	0
Age (years)	0	0
Cognitively Normal	N/A	13
APOE e4 allele (CT or CC)	55	
Male	0	
Race-center	0	
Education	2	
Smoking status	0	117
BMI (kg2/m)	1	8
Systolic BP (mm Hg)	2	6
Diastolic BP (mm Hg)	2	6
Fasting glucose (mg/dL)	56	106
Total cholesterol (mg/dL)	25	13
HDL cholesterol (mg/dL)	24	13
LDL cholesterol (mg/dL)	43	36
Triglycerides (mg/dL)	24	13
Antihypertensive medication use	0	0
Medication use for diabetes	332	5
Lipid lowering medication use	20	5
Hypercholesterolemia	25	13

Abbreviations: MRI, Magnetic resonance imaging
*All summary measures among those with data for a given variable. Number missing each variable is provided in Appendix Table 2.

Table III. Adjusted associations between a 10-unit increase in the level of each vascular risk factor approximately 24 years prior to or concurrent with MRI and standardized measures of overall WM microstructural integrity on diffusion MRI in ARIC-NCS

		Visit 1 (~24 years prior to MRI)			Visit 5 (Concurrent with MRI)		
		N	beta (95%CI)*	p-value	N	beta (95%CI)*	p-value
WM FA							
	Triglycerides (mg/dL)	1425	0.0024 (-0.0046, 0.0094)	0.50	1574	-0.0026 (-0.0104, 0.0052)	0.51
	LDL-c (mg/dL)	1410	0.0017 (-0.0117, 0.0151)	0.81	1564	0.0156 (0.0011, 0.0302)	0.04
	HDL-c (mg/dL)	1425	0.0255 (-0.0081, 0.0591)	0.14	1574	0.0340 (-0.0019, 0.0698)	0.06
	Total Cholesterol (mg/dL)	1425	0.0053 (-0.0071, 0.0177)	0.40	1574	0.0129 (0.0009, 0.0249)	0.04
	Glucose (mg/dL)	1425	-0.0292 (-0.0604, 0.0020)	0.07	1574	-0.0003 (-0.0199, 0.0193)	0.97
	DBP (mmHg)	1425	-0.1077 (-0.1634, -0.0519)	0.0002	1574	-0.1195 (-0.1648, -0.0743)	<0.0001
	SBP (mmHg)	1425	-0.0481 (-0.0849, -0.0114)	0.01	1574	-0.0762 (-0.1019, -0.0506)	<0.0001
WM MD							
	Triglycerides (mg/dL)	1425	-0.0013 (-0.0069, 0.0044)	0.66	1574	0.0065 (0.0002, 0.0127)	0.04
	LDL-c (mg/dL)	1410	-0.0028 (-0.0136, 0.0080)	0.61	1564	-0.0061 (-0.0178, 0.0056)	0.31
	HDL-c (mg/dL)	1425	0.0005 (-0.0267, 0.0277)	0.97	1574	-0.0111 (-0.0399, 0.0176)	0.45
	Total Cholesterol (mg/dL)	1425	-0.0028 (-0.0128, 0.0072)	0.59	1574	-0.0020 (-0.0117, 0.0076)	0.68
	Glucose (mg/dL)	1425	0.0473 (0.0221, 0.0726)	0.0002	1574	0.0034 (-0.0124, 0.0191)	0.67
	DBP (mmHg)	1425	0.0621 (0.0170, 0.1073)	0.007	1574	0.0720 (0.0356, 0.1084)	0.0001
	SBP (mmHg)	1425	0.0465 (0.0168, 0.0761)	0.002	1574	0.0606 (0.0401, 0.0811)	<0.0001

Abbreviations: ARIC-NCS, Atherosclerosis Risk in Communities Study Neurocognitive Study; DBP, diastolic blood pressure; FA, fractional anisotrophy; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; MD, mean diffusivity; SBP, systolic blood pressure; WM, white matter

*Fully adjusted model including age, gender, education, race/center, BMI, the square of BMI, smoking status, APOE E4, the other vascular risk factors, antihypertensive medication use, antidiabetic medication use, and lipid-lowering medications.

Table IV. Adjusted difference in total FA by category of vascular risk factors measured at Visit 1 or Visit 5				
	Visit 1 (~24 years prior to MRI)		Visit 5 (Concurrent with MRI)	
	beta (95%CI)	p-value	beta (95%CI)	p-value
Triglycerides				
500+ mg/dL	0.3206 (-0.3586, 0.9998)	0.35	-0.2905 (-1.5258, 0.9449)	0.64
200-500 mg/dL	-0.0767 (-0.2471, 0.0937)	0.38	-0.07 (-0.219, 0.0791)	0.36
150-200 mg/dL	0.113 (-0.0355, 0.2615)		-0.1156 (-0.2472, 0.016)	
<150 mg/dL	0 (ref)	0.14	0 (ref)	0.09
LDL-c				
190+ mg/dL	-0.0186 (-0.2393, 0.2021)	0.87	0.1672 (-0.1831, 0.5174)	0.35
160-190 mg/dL	0.0026 (-0.166, 0.1712)	0.98	0.1947 (-0.0048, 0.3943)	0.06
130-160 mg/dL	0.0437 (-0.0986, 0.1861)	0.55	0.0635 (-0.0777, 0.2046)	0.38
100-130 mg/dL	0.0337 (-0.1022, 0.1696)	0.63	0.0526 (-0.0549, 0.1601)	0.34
<100 mg/dL	0 (ref)		0 (ref)	
HDL-c				
60+ mg/dL	0.0931 (-0.0666, 0.2528)	0.25	0.0992 (-0.0514, 0.2498)	0.20
40-60 mg/dL	0.0133 (-0.1217, 0.1483)	0.85	0.0527 (-0.0749, 0.1803)	0.42
<40 mg/dL	0 (ref)		0 (ref)	
Total Cholesterol				
240+ mg/dL	0.0422 (-0.0877, 0.172)	0.52	0.0827 (-0.0694, 0.2348)	0.29
200-240 mg/dL	0.0517 (-0.0577, 0.161)	0.35	0.0613 (-0.049, 0.1716)	0.28
<200 mg/dL	0 (ref)		0 (ref)	
Glucose				
126+ mg/dL	-0.0359 (-0.3913, 0.3195)	0.84	0.0092 (-0.1383, 0.1567)	0.90
100-126 mg/dL	-0.036 (-0.1416, 0.0696)	0.50	0.0022 (-0.0975, 0.1019)	0.97
<100 mg/dL	0 (ref)		0 (ref)	
DBP				
80+ mm Hg	-0.3137 (-0.5235, -0.1039)	0.003	-0.3487 (-0.5238, -0.1737)	0.0001
60-80 mm Hg	-0.2161 (-0.3901, -0.0422)	0.01	-0.1415 (-0.2439, -0.0392)	0.01
<60 mm Hg	0 (ref)		0 (ref)	
SBP				
140+ mm Hg	-0.1686 (-0.3852, 0.048)	0.13	-0.3448 (-0.4639, -0.2257)	<0.0001
120-140 mm Hg	-0.1305 (-0.2449, -0.016)	0.03	-0.1863 (-0.2886, -0.084)	0.0004
<120 mm Hg	0 (ref)		0 (ref)	
Abbreviations: ARIC-NCS, Atherosclerosis Risk in Communities Study Neurocognitive Study; DBP, diastolic blood pressure; FA, fractional anisotrophy; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure.				
*Fully adjusted model including age, gender, education, race/center, BMI, the square of BMI, smoking status, APOE E4, the other vascular risk factors, antihypertensive medication use, antidiabetic medication use, and lipid-lowering medications.				

Table V. Adjusted difference in total MD by category of vascular risk factors measured at Visit 1 or Visit 5				
	Visit 1 (~24 years prior to MRI)		Visit 5 (Concurrent with MRI)	
	beta (95%CI)	p-value	beta (95%CI)	p-value
Triglycerides				
500+ mg/dL	-0.1893 (-0.7397, 0.3611)	0.50	0.635 (-0.3551, 1.6252)	0.21
200-500 mg/dL	0.0462 (-0.0919, 0.1842)	0.51	0.0585 (-0.0609, 0.178)	0.34
150-200 mg/dL	-0.0388 (-0.1592, 0.0815)		0.0663 (-0.0392, 0.1718)	
<150 mg/dL	0 (ref)	0.53	0 (ref)	0.22
LDL-c				
190+ mg/dL	0.0247 (-0.154, 0.2034)	0.79	-0.0277 (-0.3086, 0.2533)	0.85
160-190 mg/dL	-0.0192 (-0.1558, 0.1173)	0.78	-0.0452 (-0.2053, 0.1149)	0.58
130-160 mg/dL	-0.0388 (-0.1541, 0.0765)	0.51	-0.0035 (-0.1168, 0.1097)	0.95
100-130 mg/dL	-0.0452 (-0.1553, 0.0648)	0.42	0.0113 (-0.0749, 0.0975)	0.80
<100 mg/dL	0 (ref)		0 (ref)	
HDL-c				
60+ mg/dL	-0.0405 (-0.1698, 0.0888)	0.54	-0.0357 (-0.1564, 0.085)	0.56
40-60 mg/dL	-0.0472 (-0.1565, 0.0621)	0.40	-0.0487 (-0.151, 0.0537)	0.35
<40 mg/dL	0 (ref)		0 (ref)	
Total Cholesterol				
240+ mg/dL	0.0025 (-0.1027, 0.1076)	0.96	0.0383 (-0.0837, 0.1603)	0.54
200-240 mg/dL	0.0203 (-0.0683, 0.1088)	0.65	-0.018 (-0.1064, 0.0704)	0.69
<200 mg/dL	0 (ref)		0 (ref)	
Glucose				
126+ mg/dL	0.3066 (0.0184, 0.5949)	0.04	0.0184 (-0.0997, 0.1365)	0.76
100-126 mg/dL	0.0672 (-0.0184, 0.1529)	0.12	0.0898 (0.01, 0.1696)	0.03
<100 mg/dL	0 (ref)		0 (ref)	
DBP				
80+ mm Hg	0.1713 (0.0014, 0.3412)	0.05	0.2062 (0.0656, 0.3468)	0.004
60-80 mm Hg	0.1459 (0.0051, 0.2868)	0.04	0.0921 (0.0099, 0.1743)	0.03
<60 mm Hg	0 (ref)		0 (ref)	
SBP				
140+ mm Hg	0.0961 (-0.079, 0.2712)	0.28	0.2691 (0.1736, 0.3646)	<0.0001
120-140 mm Hg	0.1216 (0.0291, 0.2141)	0.01	0.1216 (0.0396, 0.2036)	0.004
<120 mm Hg	0 (ref)		0 (ref)	Visit 5
Abbreviations: ARIC-NCS, Atherosclerosis Risk in Communities Study Neurocognitive Study; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; MD, mean diffusivity; SBP, systolic blood pressure.				
*Fully adjusted model including age, gender, education, race/center, BMI, the square of BMI, smoking status, APOE E4, the other vascular risk factors, antihypertensive medication use, antidiabetic medication use, and lipid-lowering medications.				

Figure I. Comparison of the primary analyses of the association of triglycerides with regional and total FA with sensitivity analyses considering different adjustment sets

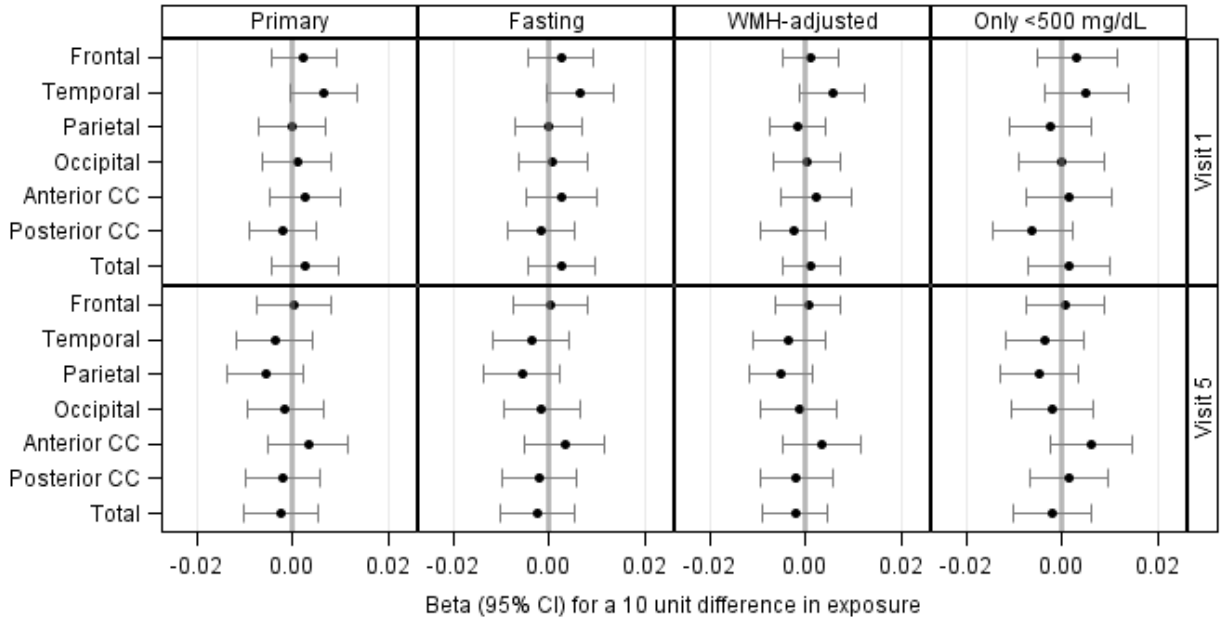

Figure II. Comparison of the primary analyses of the association of triglycerides with regional and total FA with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

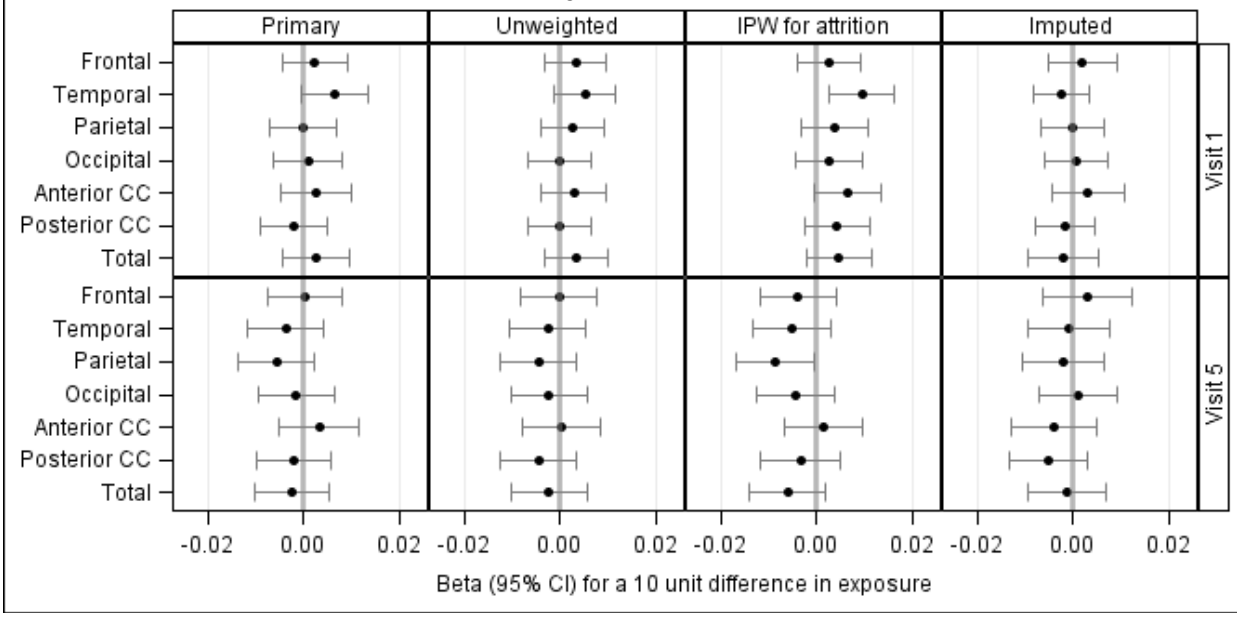

Figure III. Comparison of the primary analyses of the association of triglycerides with regional and total MD with sensitivity analyses considering different adjustment sets

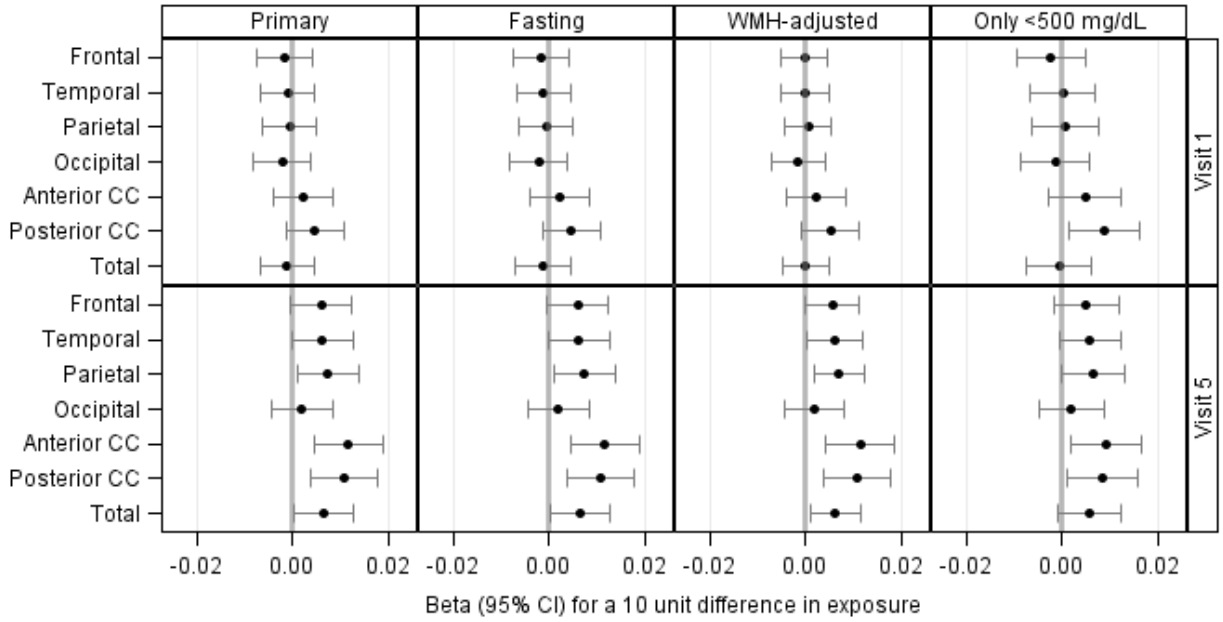

Figure IV. Comparison of the primary analyses of the association of triglycerides with regional and total MD with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

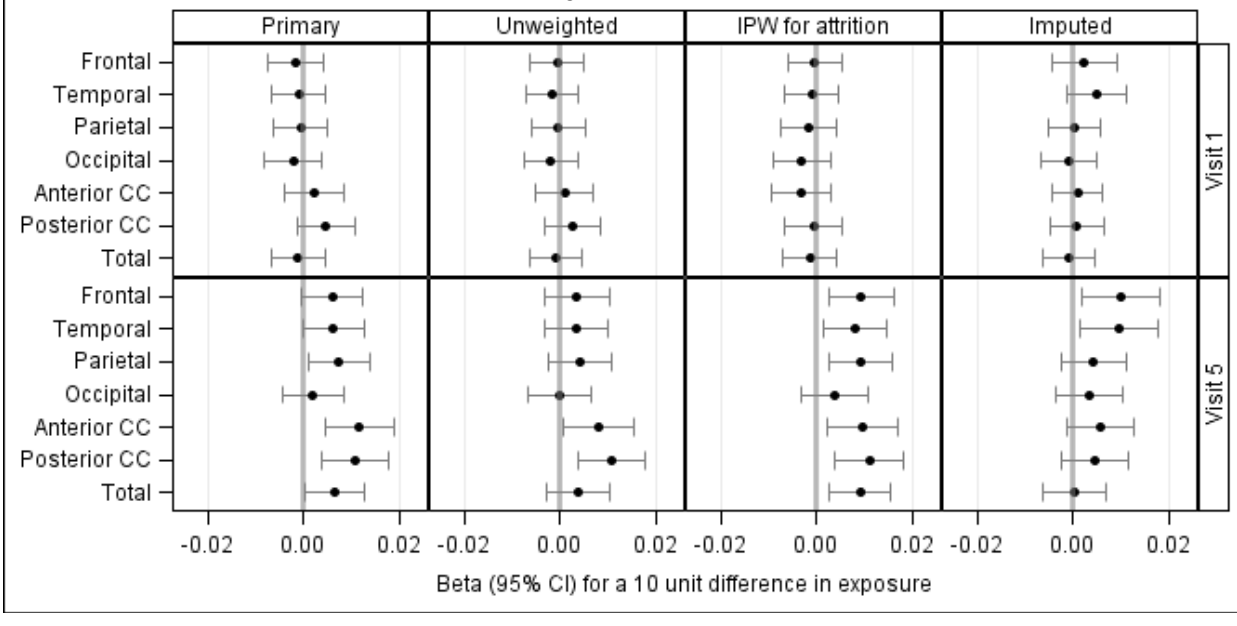

Figure V. Comparison of the primary analyses of the association of LDL-c with regional and total FA with sensitivity analyses considering different adjustment sets

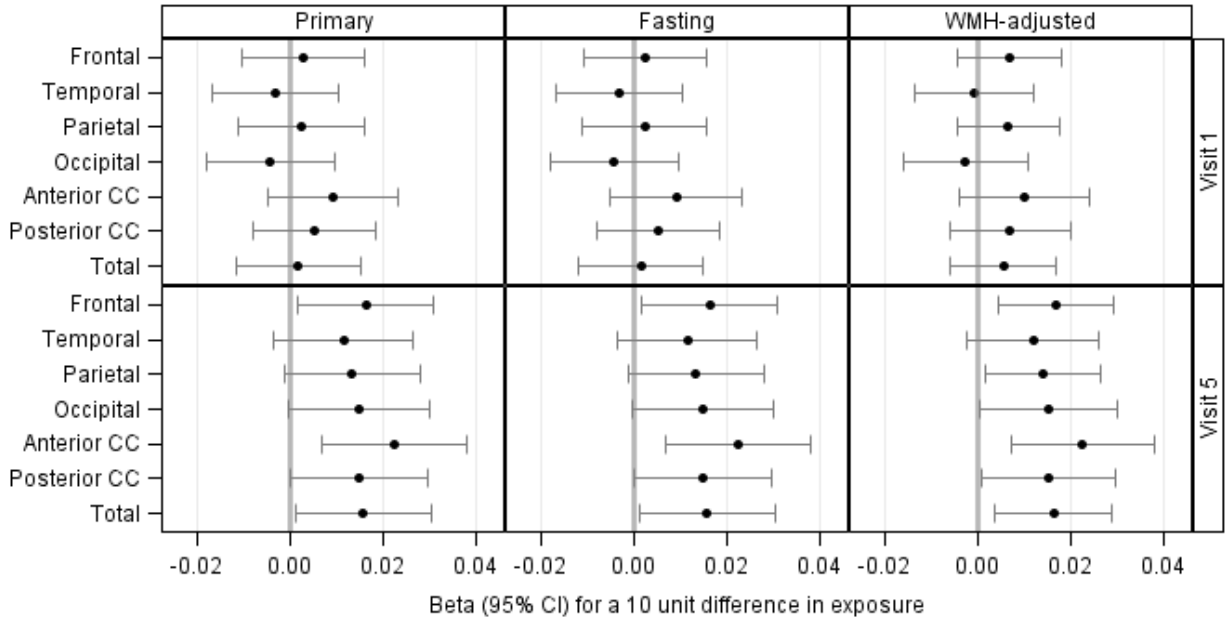

Figure VI. Comparison of the primary analyses of the association of LDL-c with regional and total FA with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

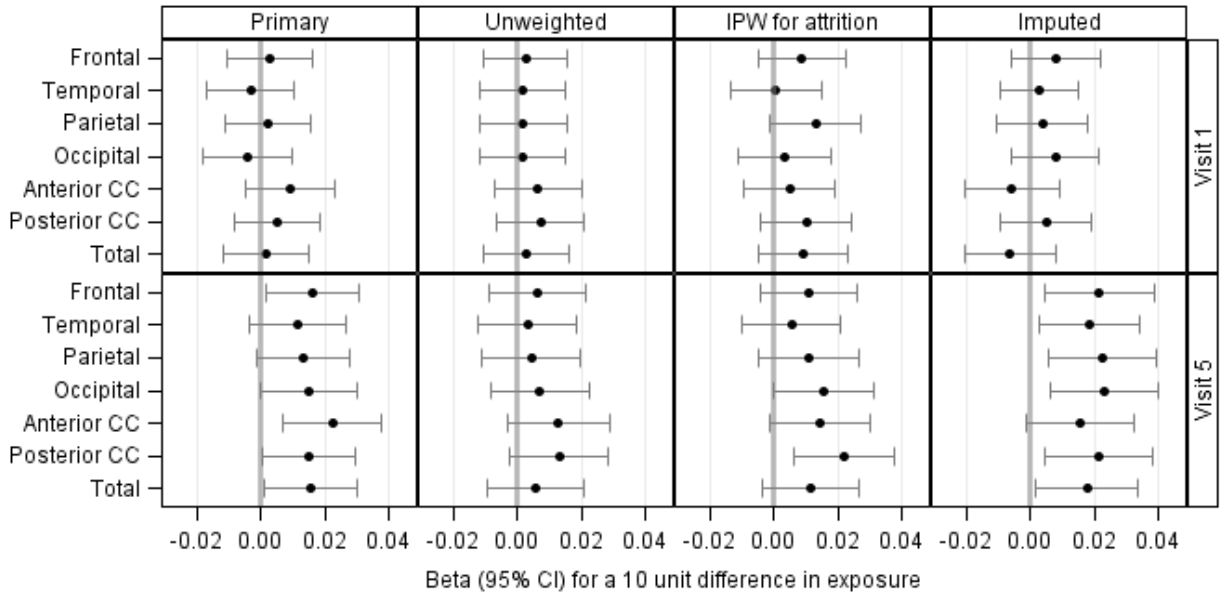

Figure VII. Comparison of the primary analyses of the association of LDL-c with regional and total MD with sensitivity analyses considering different adjustment sets

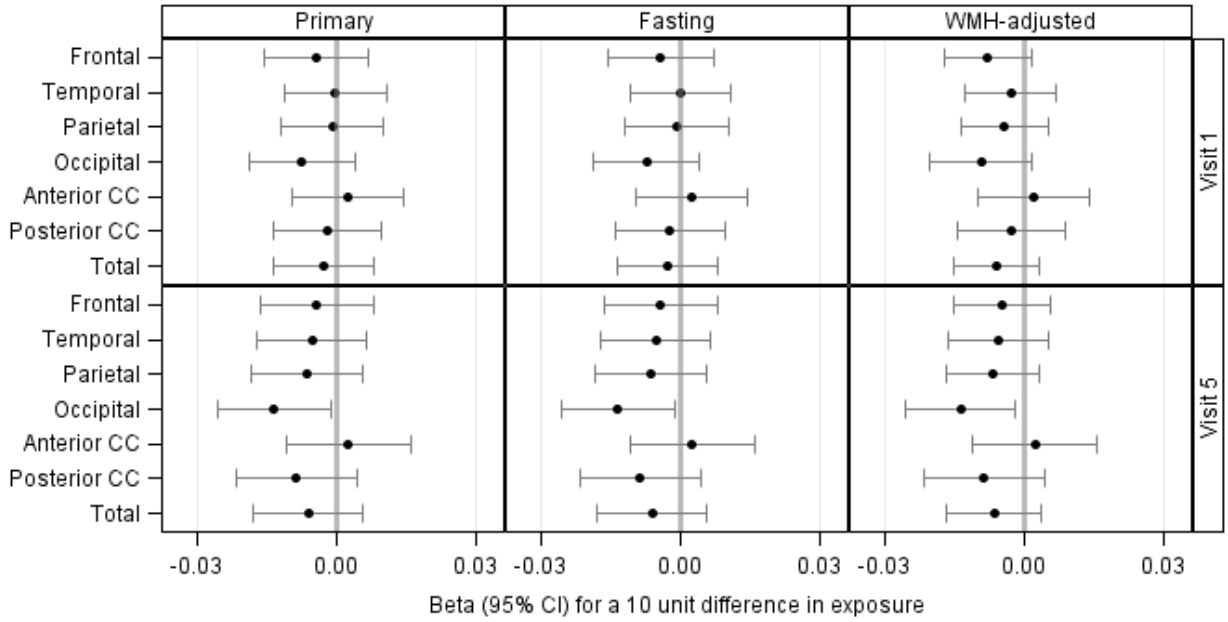

Figure VIII. Comparison of the primary analyses of the association of LDL-c with regional and total MD with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

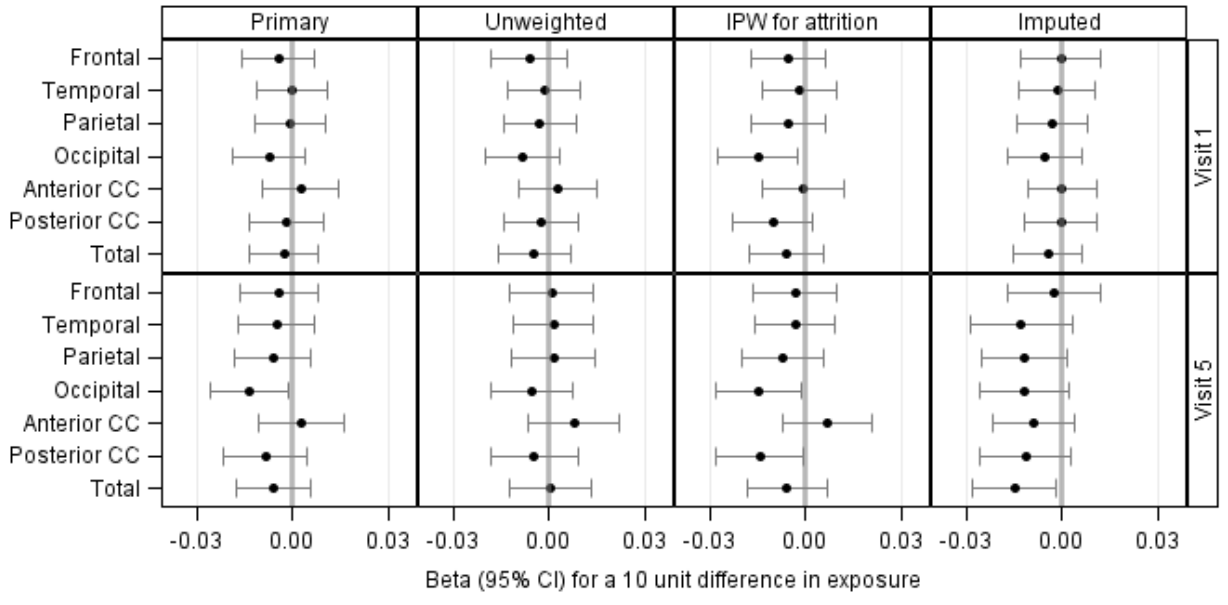

Figure IX. Comparison of the primary analyses of the association of HDL-c with regional and total FA with sensitivity analyses considering different adjustment sets

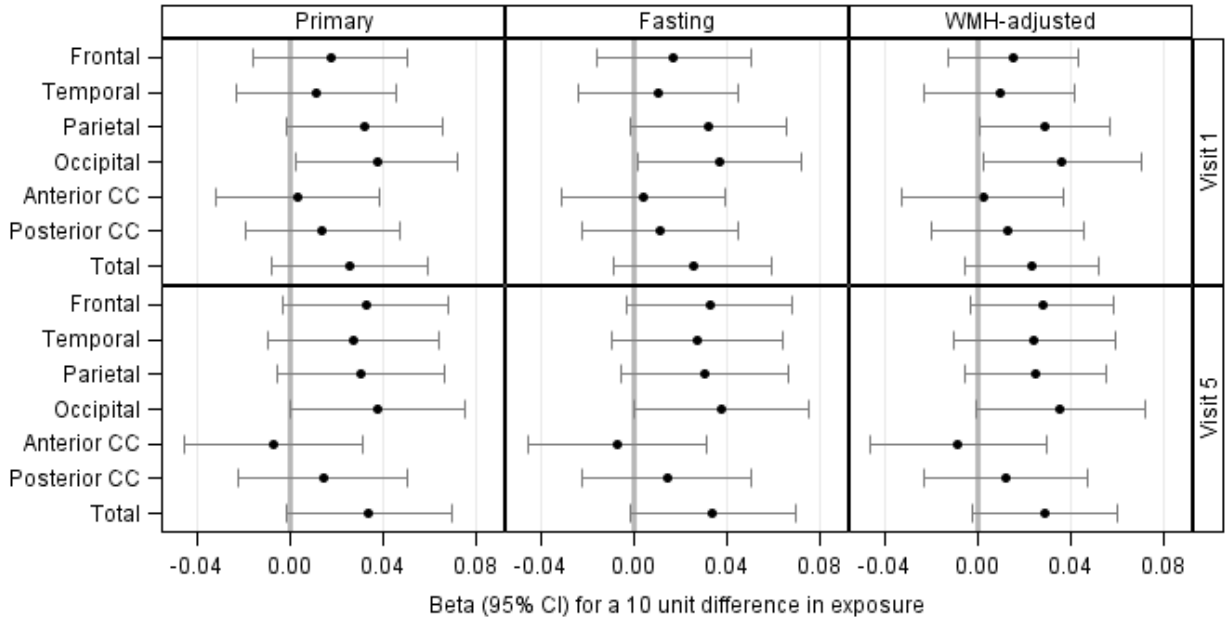

Figure X. Comparison of the primary analyses of the association of HDL-c with regional and total FA with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

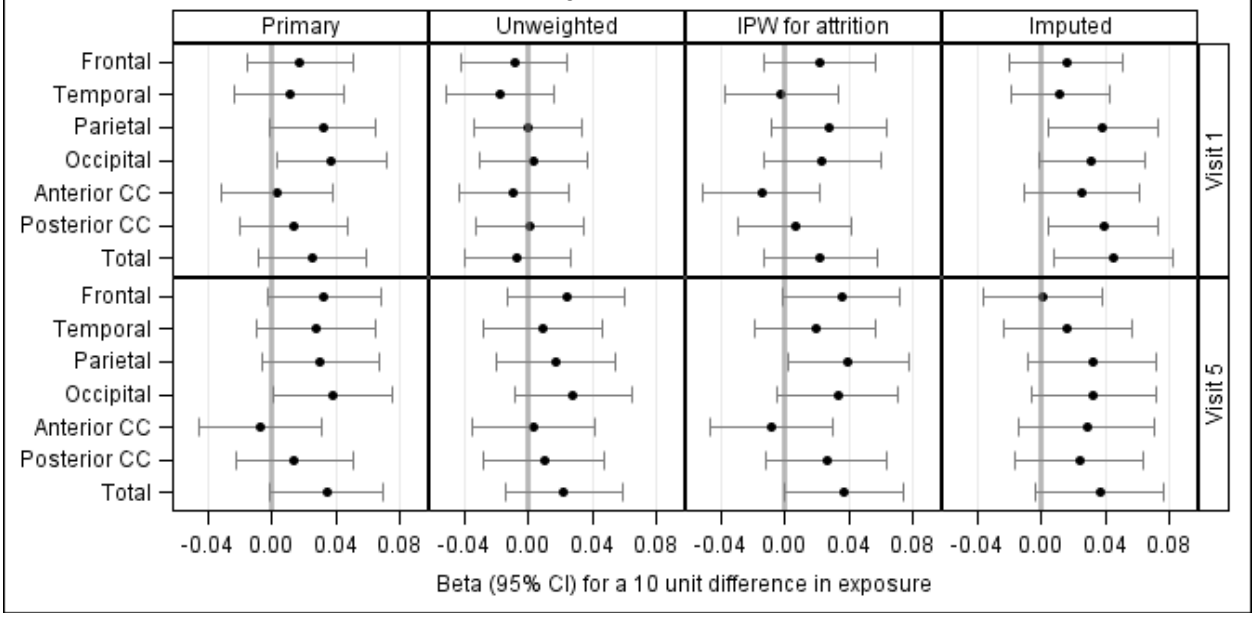

Figure XI. Comparison of the primary analyses of the association of HDL-c with regional and total MD with sensitivity analyses considering different adjustment sets

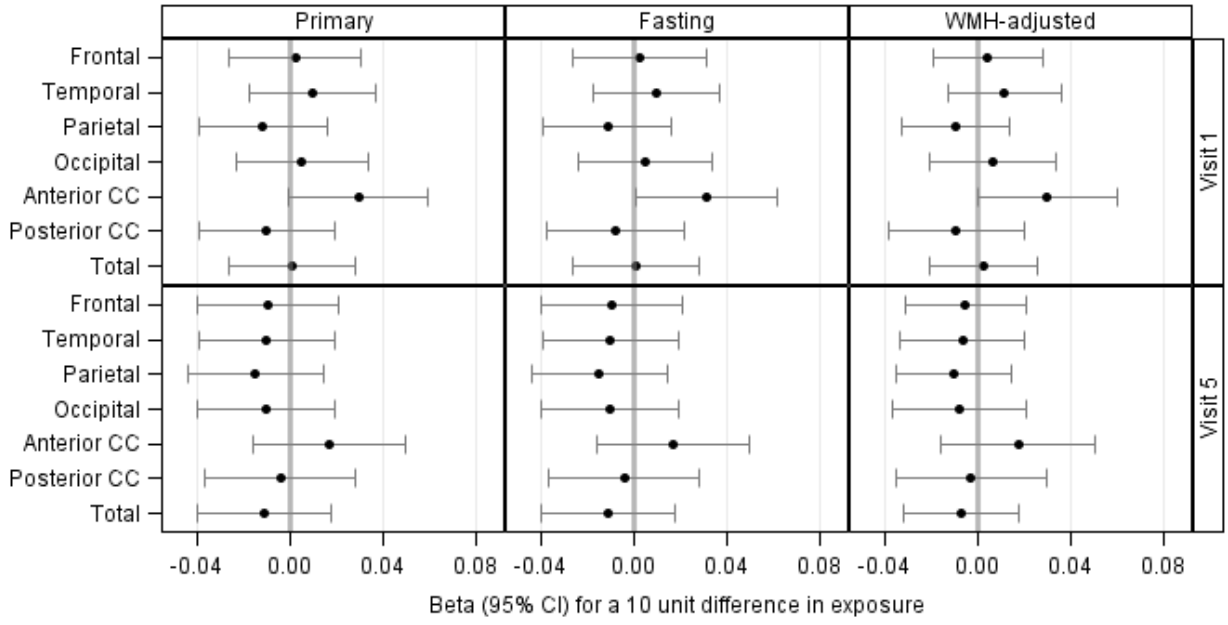

Figure XII. Comparison of the primary analyses of the association of HDL-c with regional and total MD with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

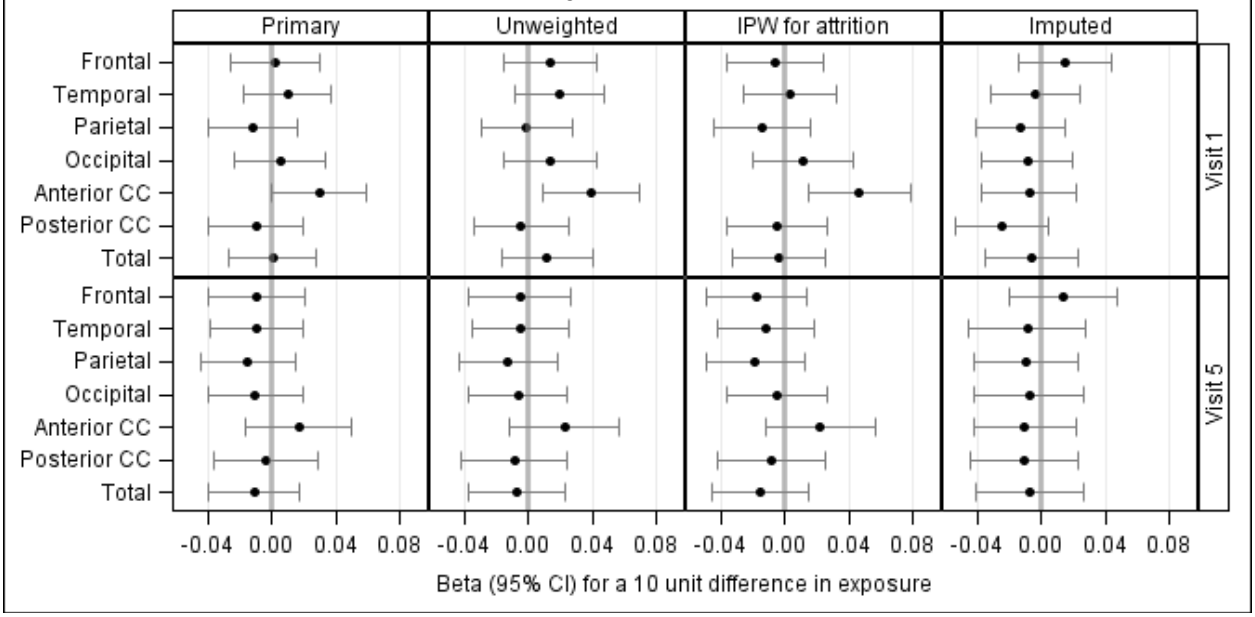

Figure XIII. Comparison of the primary analyses of the association of total cholesterol with regional and total FA with sensitivity analyses considering different adjustment sets

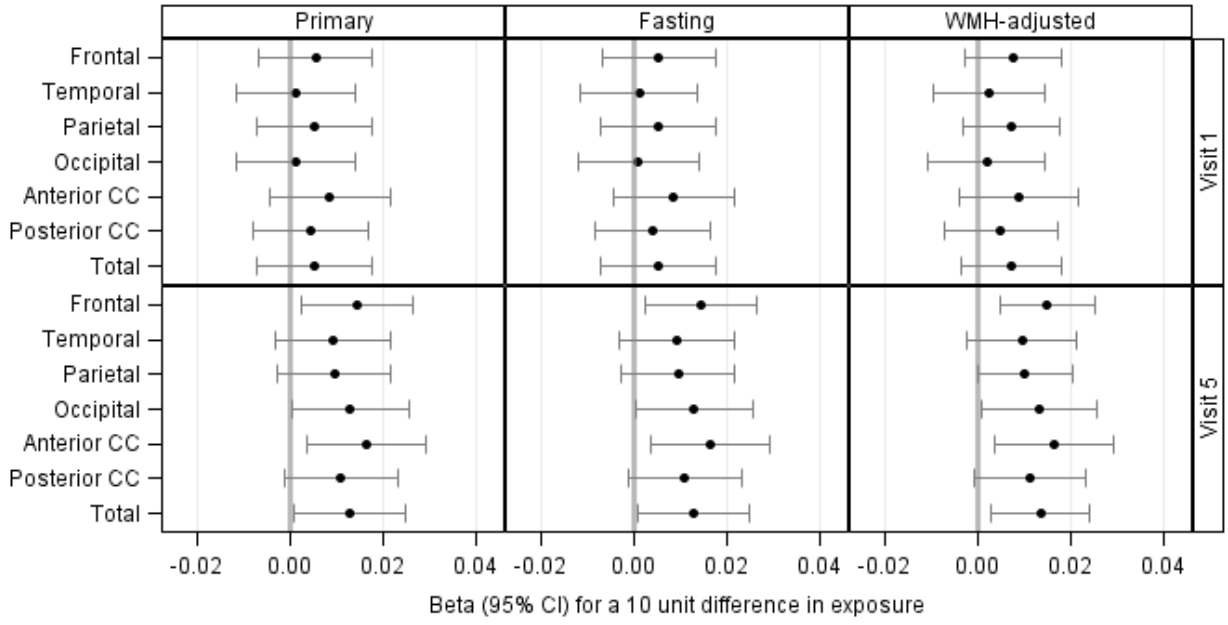

Figure XIV. Comparison of the primary analyses of the association of total cholesterol with regional and total FA with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

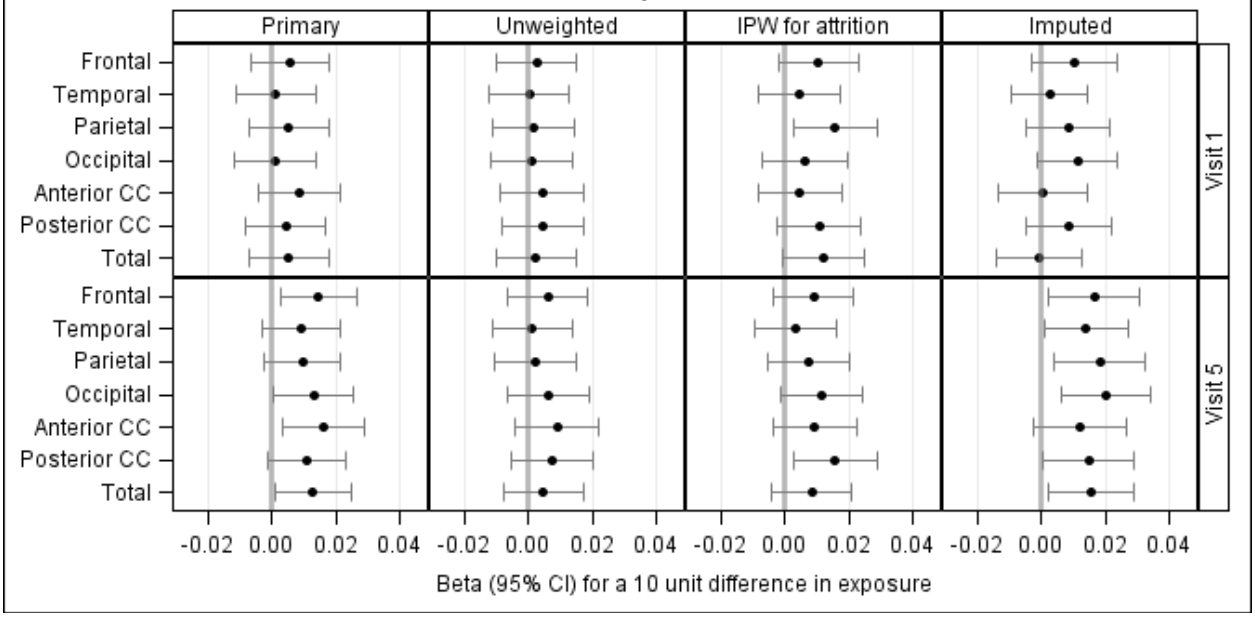

Figure XV. Comparison of the primary analyses of the association of total cholesterol with regional and total MD with sensitivity analyses considering different adjustment sets

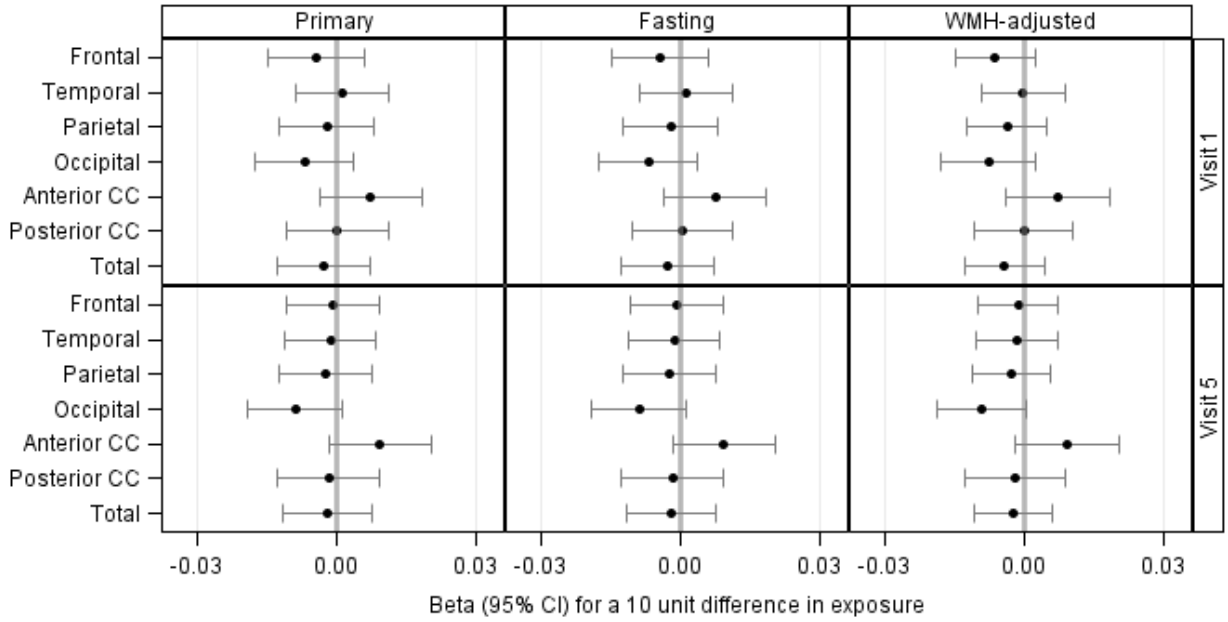

Figure XVI. Comparison of the primary analyses of the association of total cholesterol with regional and total MD with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

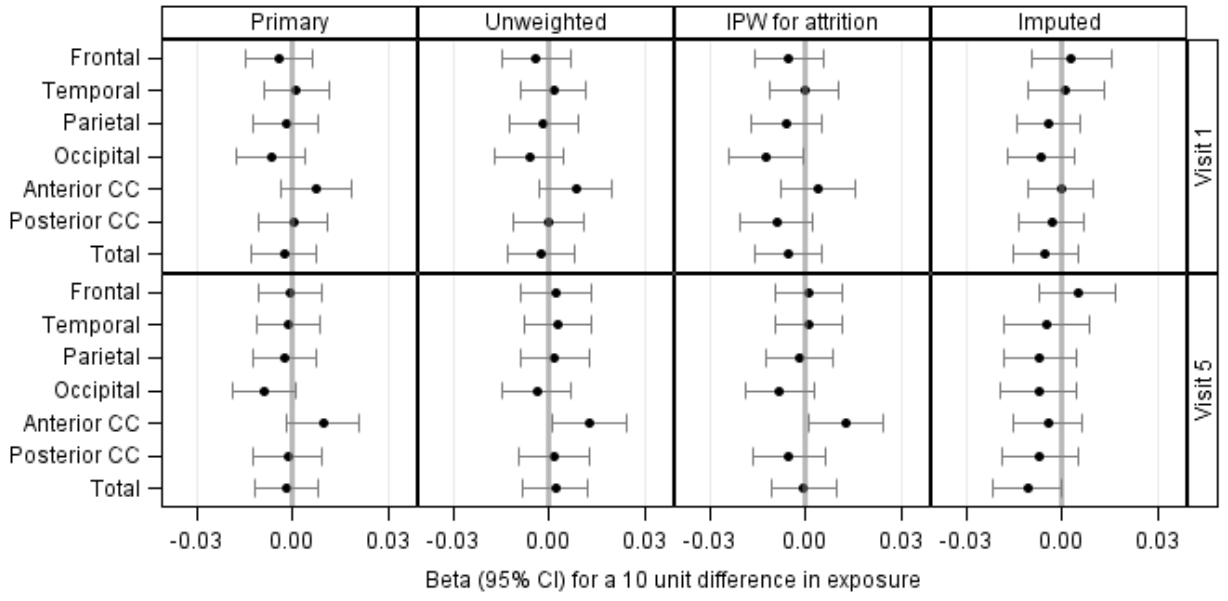

Figure XVII. Comparison of the primary analyses of the association of glucose with regional and total FA with sensitivity analyses considering different adjustment sets

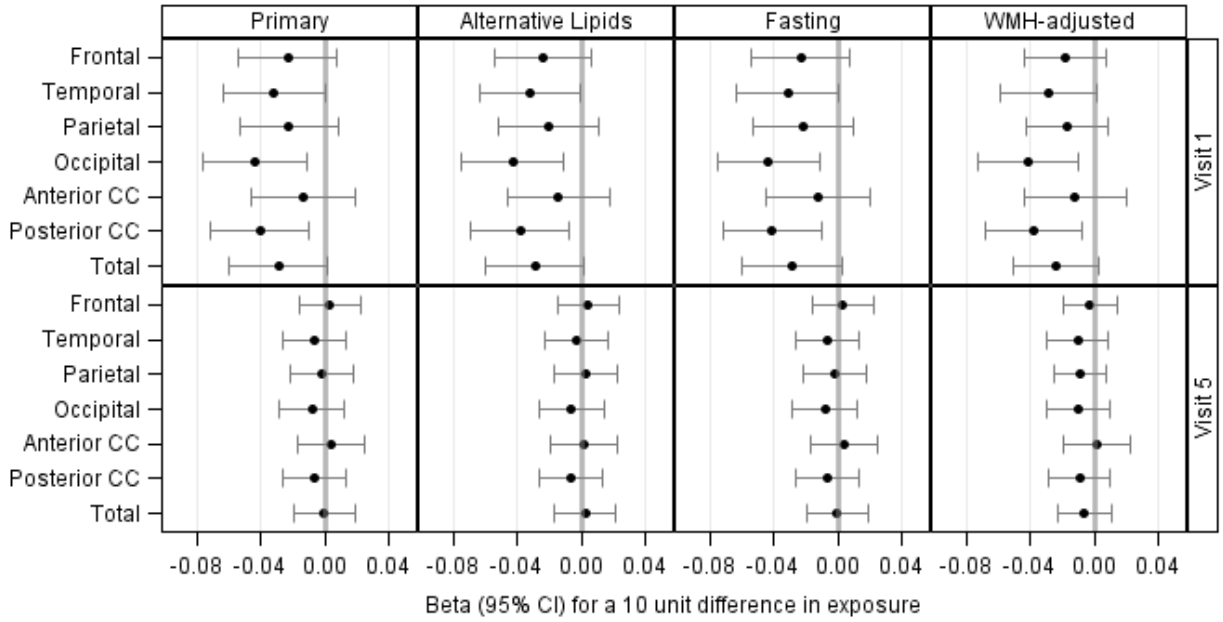

Figure XVIII. Comparison of the primary analyses of the association of glucose with regional and total FA with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

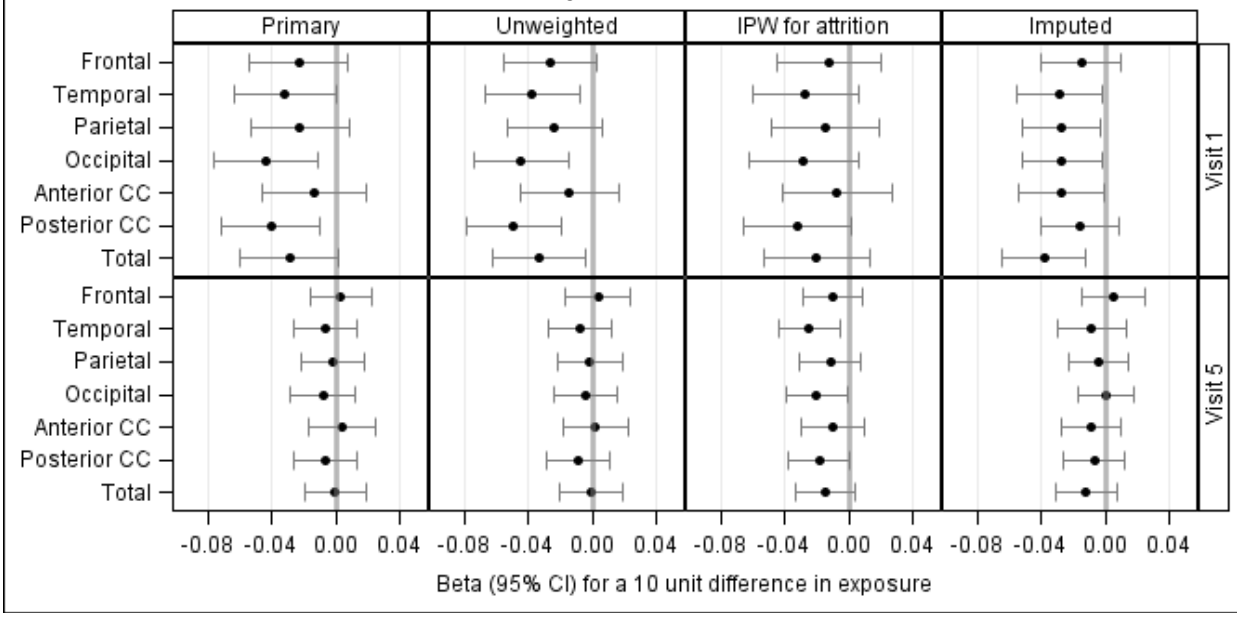

Figure XIX. Comparison of the primary analyses of the association of glucose with regional and total MD with sensitivity analyses considering different adjustment sets

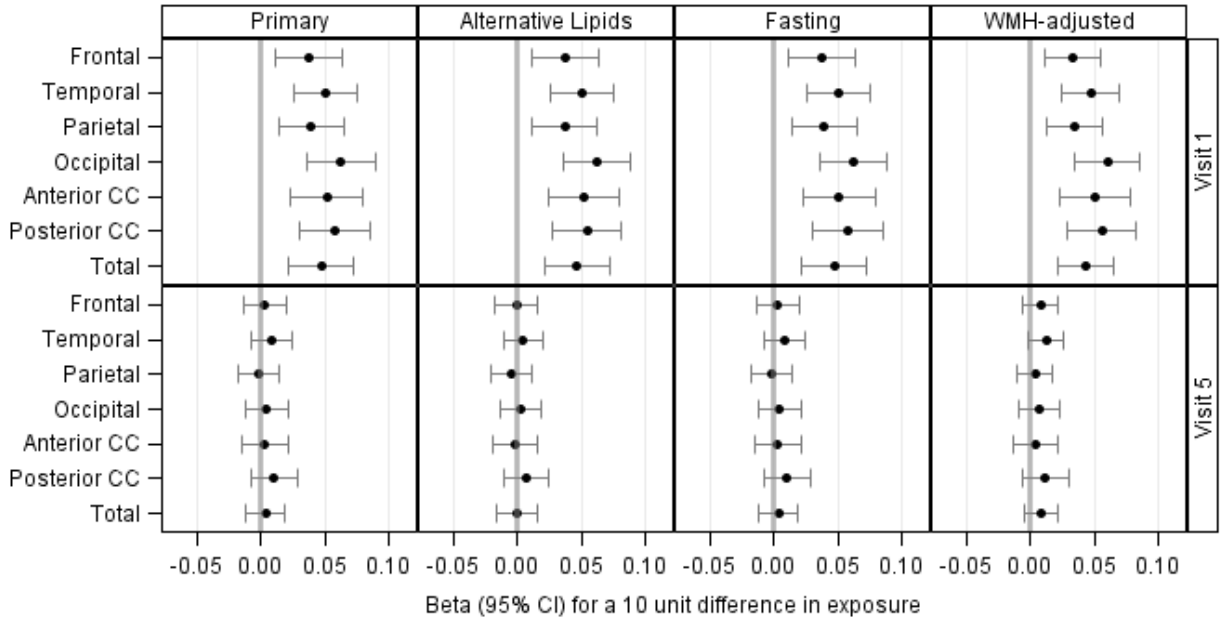

Figure XX. Comparison of the primary analyses of the association of glucose with regional and total MD with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

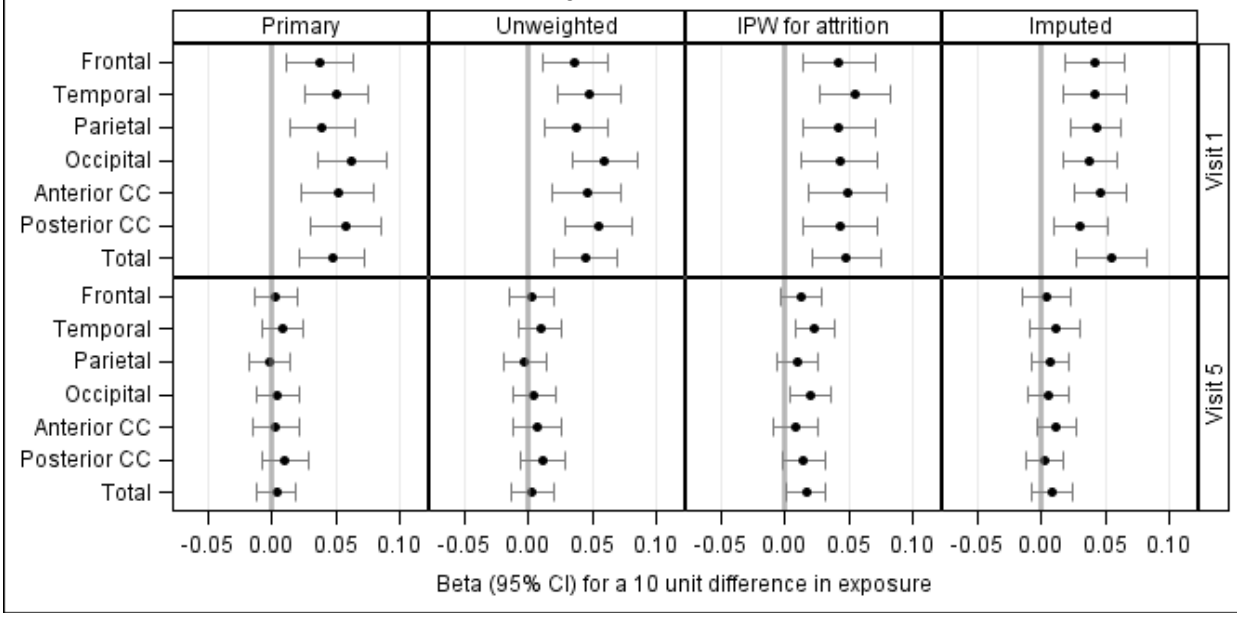

Figure XXI. Comparison of the primary analyses of the association of diastolic blood pressure with regional and total FA with sensitivity analyses considering different adjustment sets

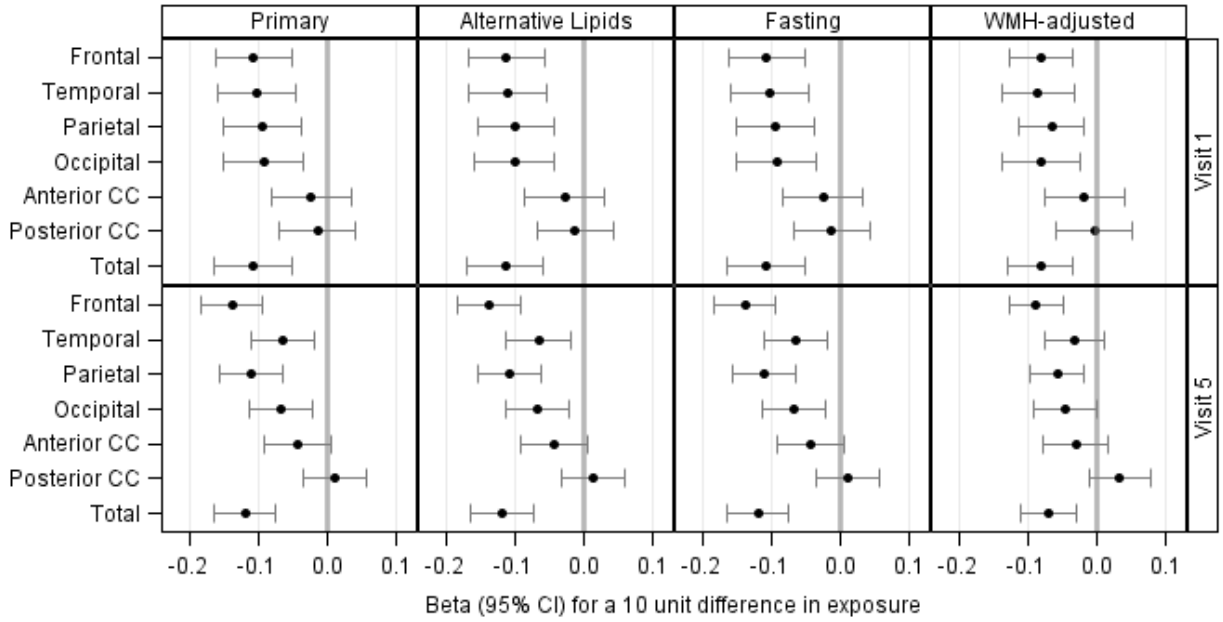

Figure XXII. Comparison of the primary analyses of the association of diastolic blood pressure with regional and total FA with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

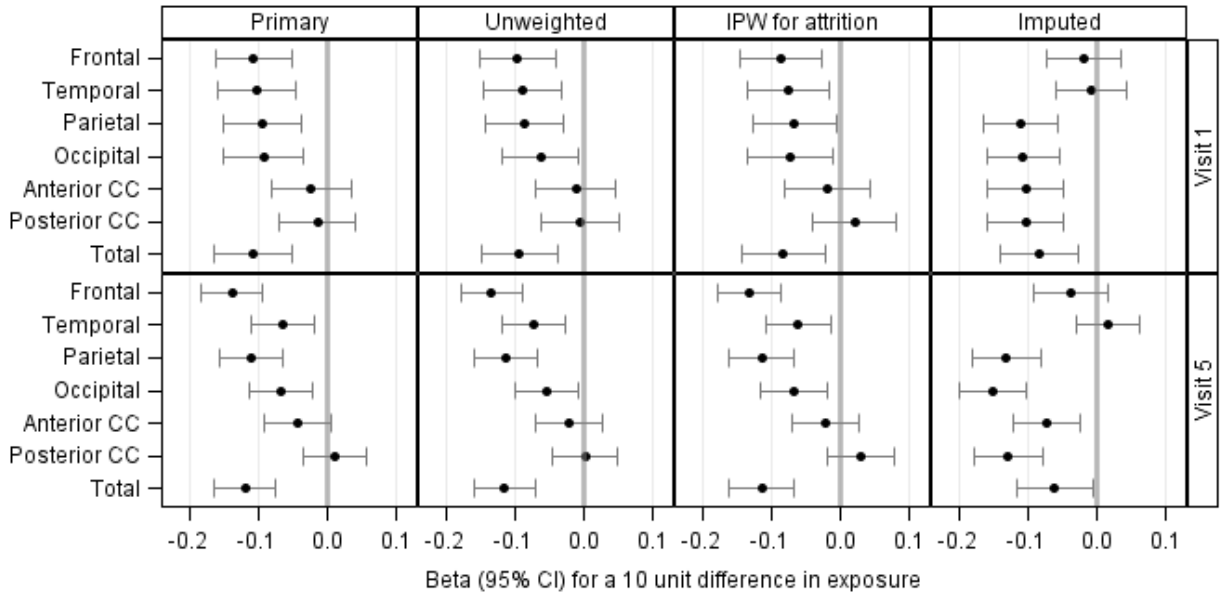

Figure XXIII. Comparison of the primary analyses of the association of diastolic blood pressure with regional and total MD with sensitivity analyses considering different adjustment sets

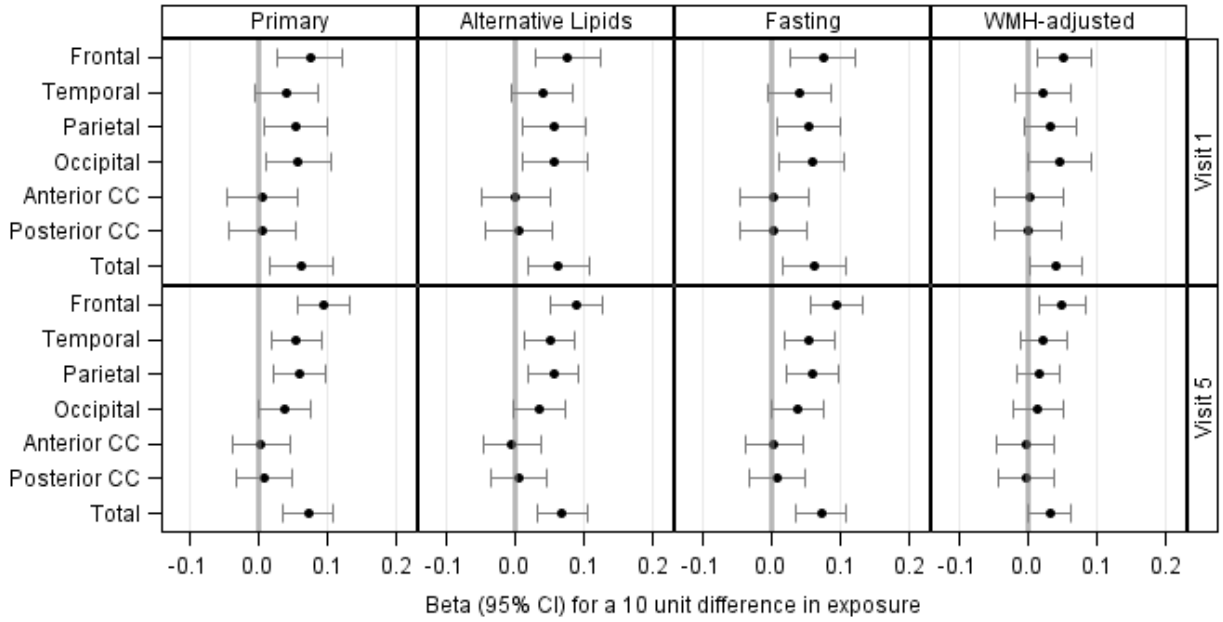

Figure XXIV. Comparison of the primary analyses of the association of diastolic blood pressure with regional and total MD with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

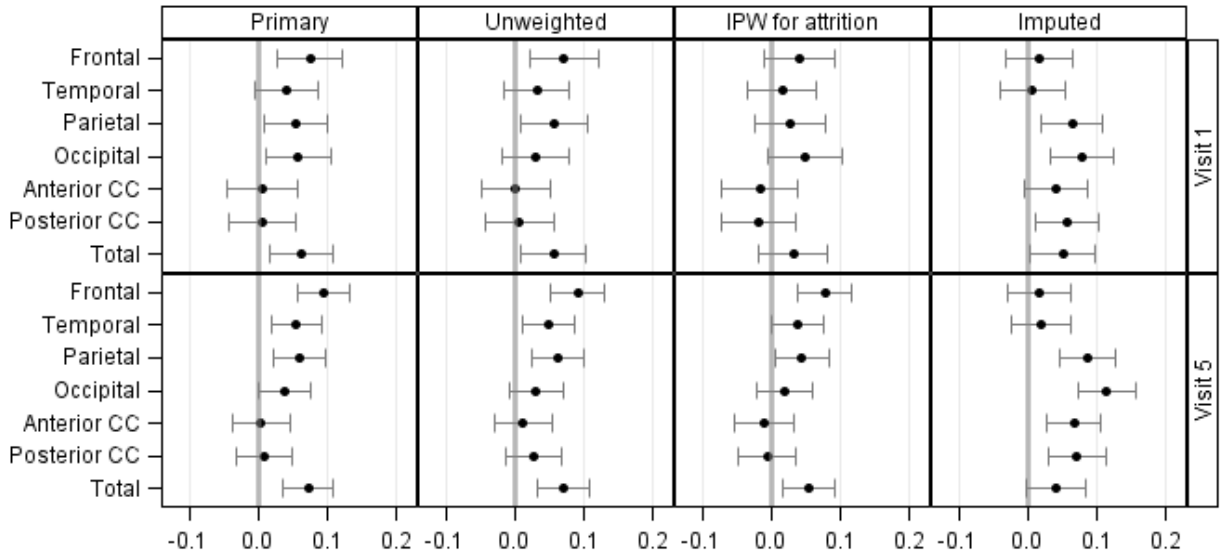

Figure XXV. Comparison of the primary analyses of the association of systolic blood pressure with regional and total FA with sensitivity analyses considering different adjustment sets

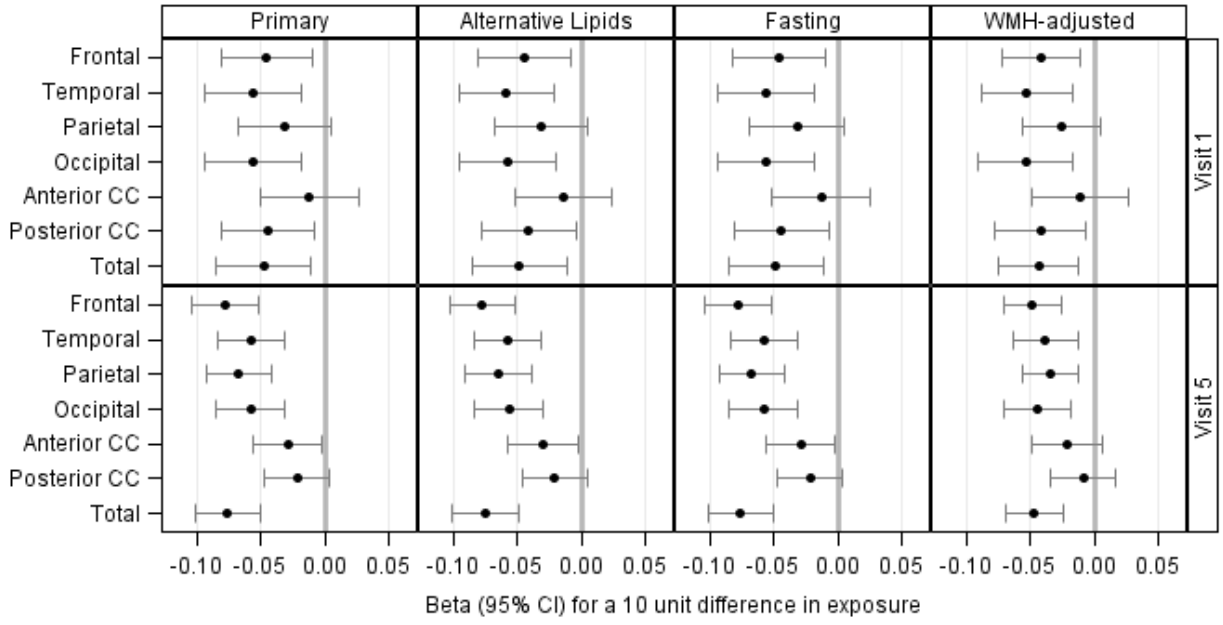

Figure XXVI. Comparison of the primary analyses of the association of systolic blood pressure with regional and total FA with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

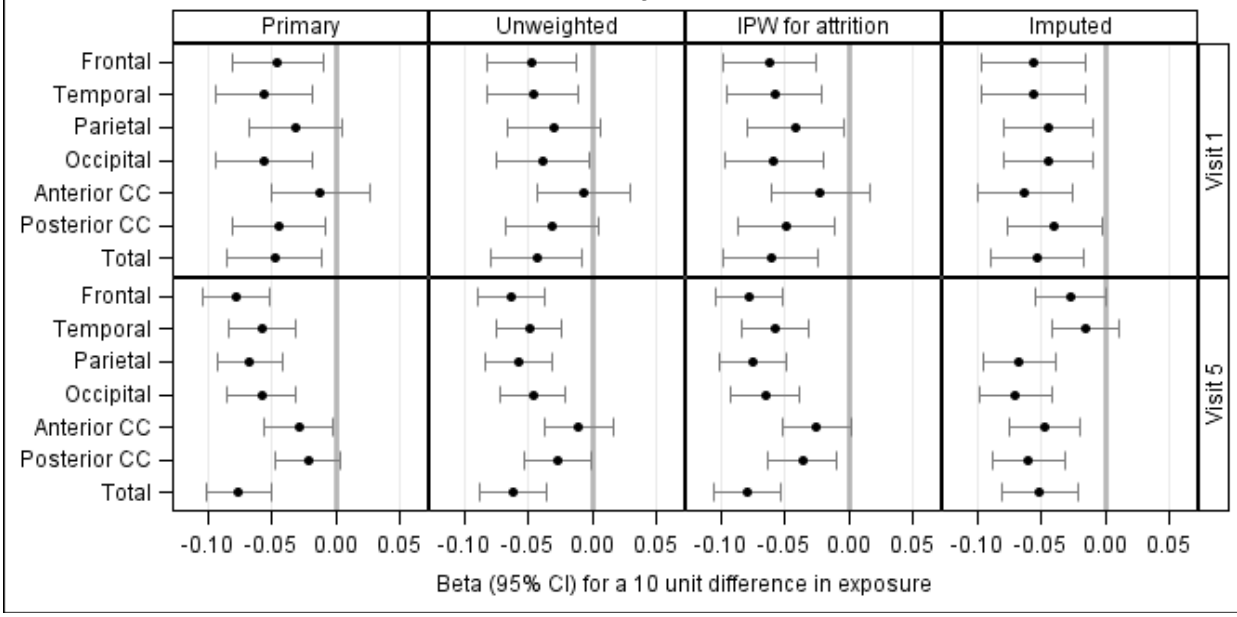

Figure XXVII. Comparison of the primary analyses of the association of systolic blood pressure with regional and total MD with sensitivity analyses considering different adjustment sets

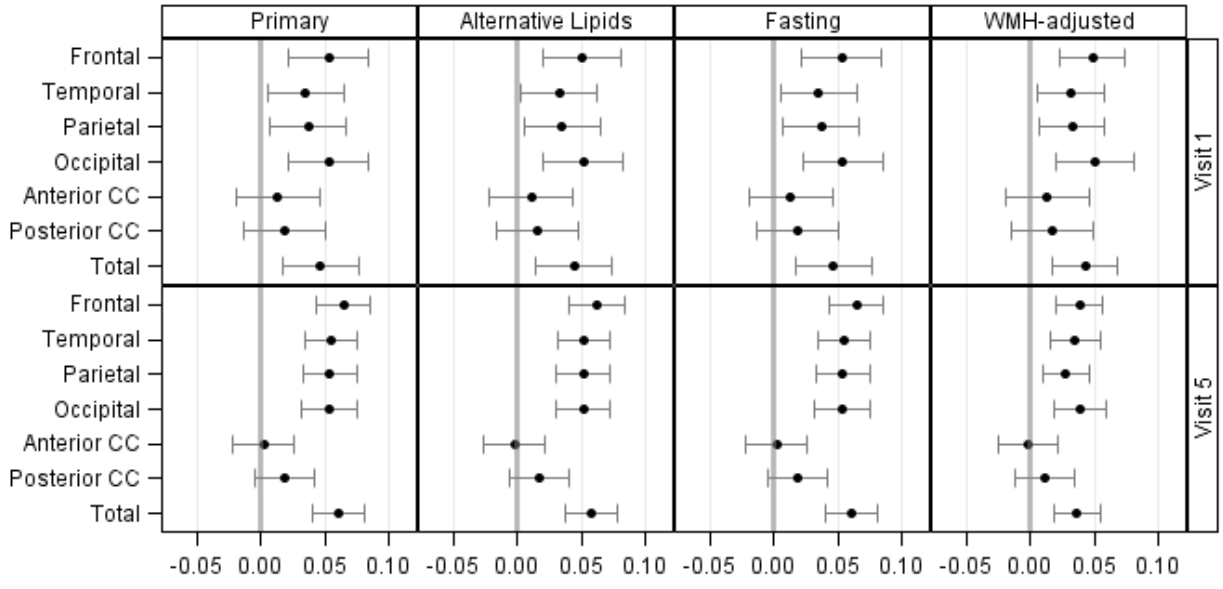

Figure XXVIII. Comparison of the primary analyses of the association of systolic blood pressure with regional and total MD with sensitivity analyses considering the influence of weighting/attrition/missing covariate or exposure data

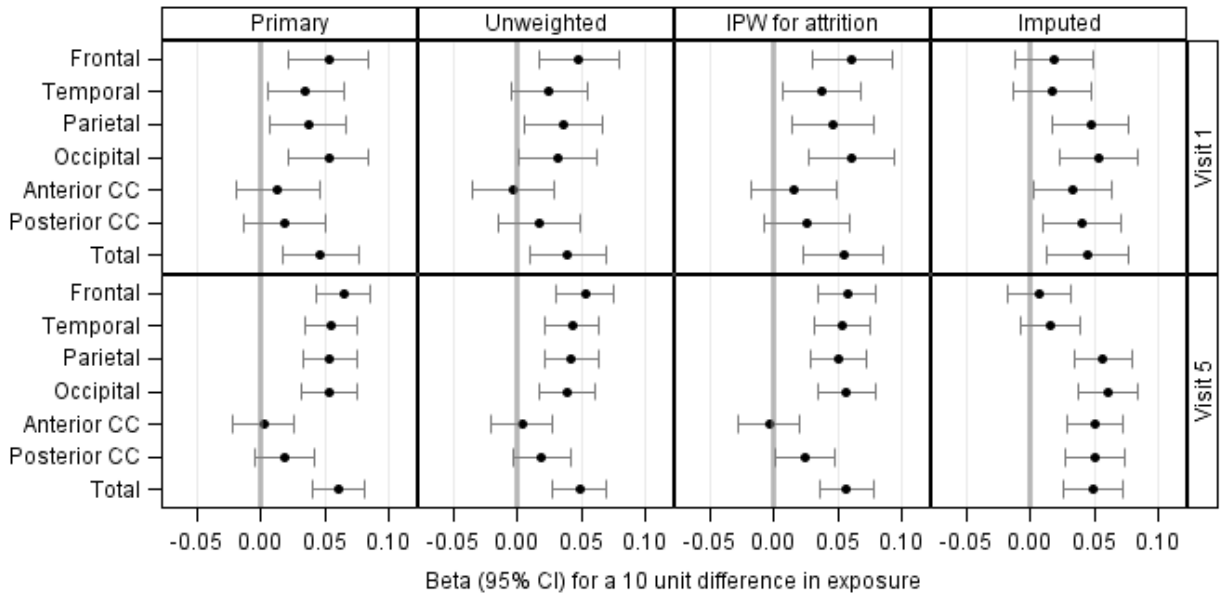

Figure XXIX. The adjusted association between triglycerides at Visit 1 or Visit 5 and measures of total white matter integrity by decile of intracranial-volume standardized WMH volumes

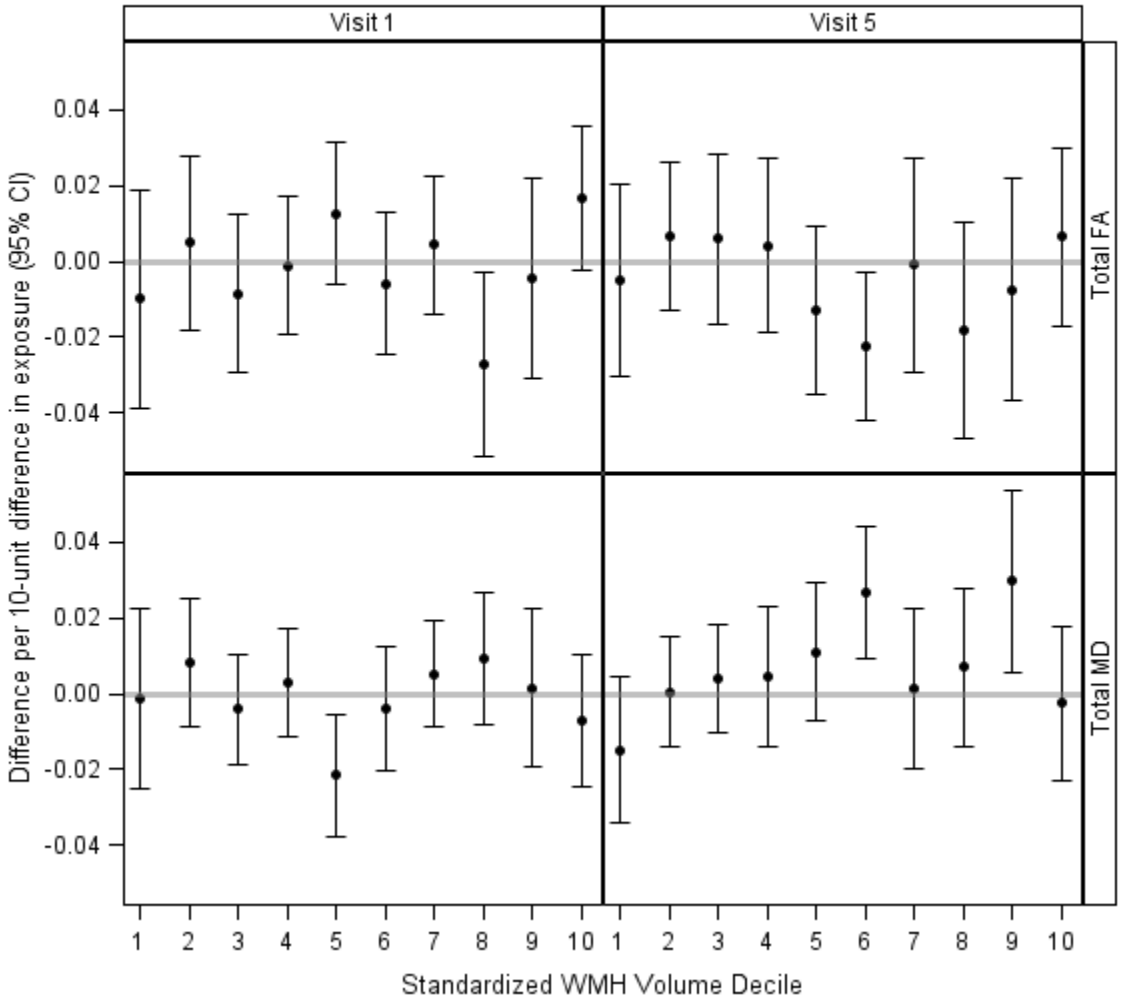

Figure XXX. The adjusted association between LDL-c at Visit 1 or Visit 5 and measures of white matter integrity by decile of intracranial-volume standardized WMH volumes

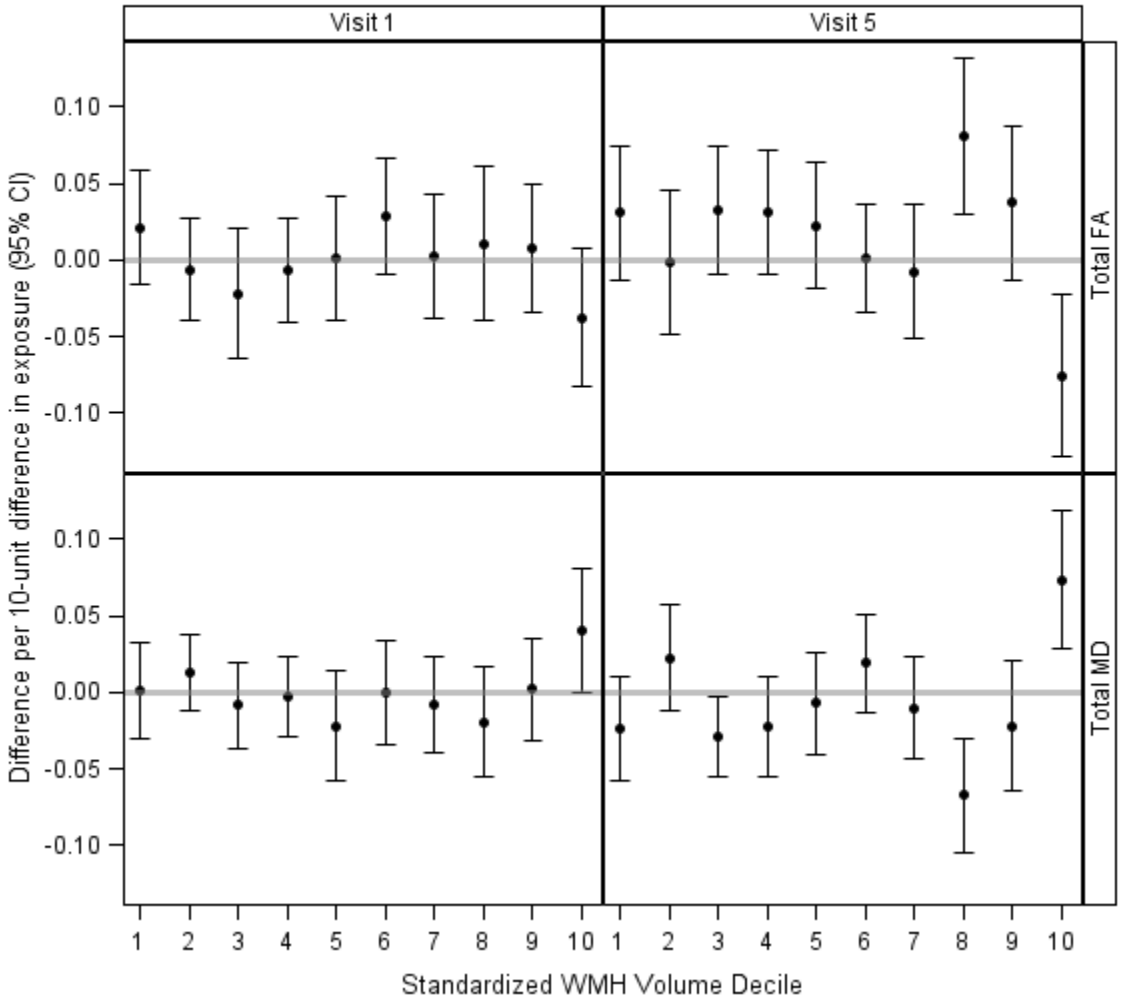

Figure XXXI. The adjusted association between HDL-c at Visit 1 or Visit 5 and measures of white matter integrity by decile of intracranial-volume standardized WMH volumes

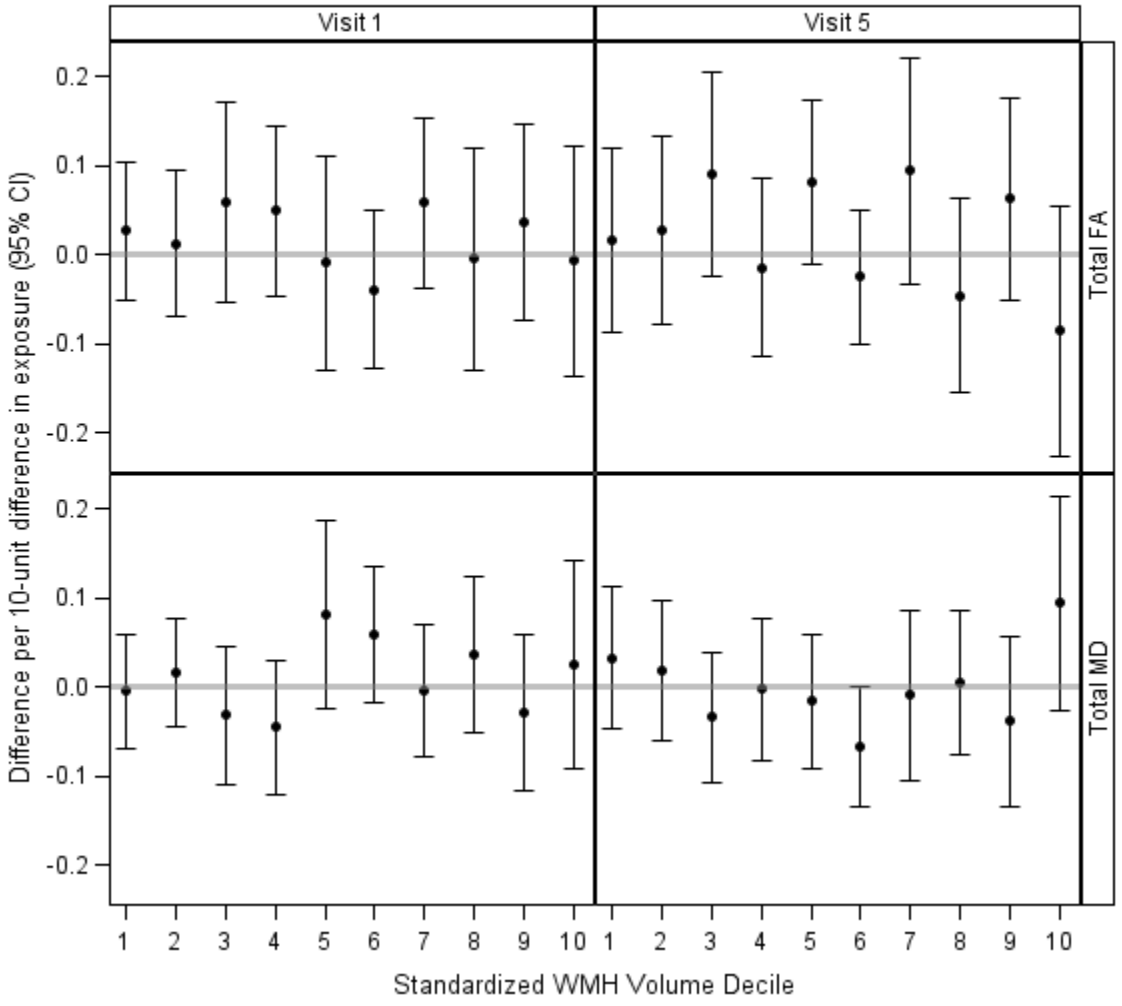

Figure XXXII. The adjusted association between total cholesterol at Visit 1 or Visit 5 and measures of white matter integrity by decile of intracranial-volume standardized WMH volumes