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Red cell distribution width, anemia and their associations with white matter integrity among middle-aged urban adults

Beydoun et. al.

ONLINE SUPPLEMENTARY MATERIAL

Supplemental Method 1. Brain structural (s) and diffusion (d) MRI detailed description:

sMRI

T1-weighted MP-RAGE images at a thickness of 1.2 mm for 160 sagital slices (TR/TE/TI=2300/2.9/900 ms; FOV 25.6cm) were completed for the entire brain. Then, in order to allow for comparison, these images were converted to axial sections.

The Artificial Intelligence in Biomedical Imaging Lab, Center for Biomedical Image Computing and Analytics (CBICA), Department of Radiology at the University of Pennsylvania, preprocessed structural MRI scans with techniques developed in-house. A multi-atlas registration method(Doshi et al., 2013) was used to remove the extra-cranial material on the T1-weighted images. A multiplicative intrinsic component optimization (MICO) method(Li et al., 2014) was used to correct for bias. Multi-atlas region Segmentation utilizing Ensembles (MUSE) grouped the pre-processed images into a set of anatomical regions of interest (ROIs) (Doshi et al., 2016). MUSE integrates a broad ensemble of labeled templates by using a number of warping algorithms, regularization atlases and parameters (Doshi et al., 2016).

dMRI

Isotropic resolution images were obtained with an in-plane resolution of 2x2 mm and 2 mm slice thickness over a 22.4 cm FOV. A total of 66 slices at a TE = 122ms, TR = 3300ms, and flip angle = 90° were used. Eddy current effects were reduced by using bipolar diffusion. Diffusion-weighting scheme was a 2-shell (b = 1000, 2500), optimized for uniform sampling of each shell and non-overlapping diffusion directions of 60 and 120, respectively, and 6 b0 volumes. Image acquisition time was ten minutes.

Joint Linear Minimum Mean Squared Error software, (jLMMSE; Tristan-Vega and Aja-Fernandez, 2010) was used to de-noise the raw DWI data. The DT images were reconstructed by fitting the de-noised DWI data using multivariate linear fitting. Motion correction was conducted with FSL' s "eddycorrect" tool (Andersson and Sotiropoulos, 2016).

Fractional Anisotropy (FA) is a widely established method for quantifying WMI that is sensitive to the degree of myelination, density, and organization of WM. FA was used to determine directionality of water diffusion in the brain. FA measures the degree of anisotropy of the diffusion at the voxel level. This is derived from the variance of the average of the three eigenvalues of the diffusion tensor that are used to compute FA values (0 - 1; 0 = completely unrestricted diffusion, 1 = completely restricted diffusion). Computing the sum of the eigenvalues of the diffusion tensor yields the TR or mean diffusivity (MD), with a higher value indicative of poorer WMI. (Jones, 2008).

Quality assurance

The Core for Translational Research in Imaging @ Maryland (C-TRIM), managed by the Department of Diagnostic Radiology at UMB's School of Medicine, has several quality control measures in place to ensure the highest level of quality and safety. For example, as mandated by the American College of Radiology(Mulkern et al., 2008), the scanner routine undergoes quality data assurance. In addition, the AD Neuroimaging Initiative phantom assesses weekly signal-to-noise ratio and monthly structural distortions(Gunter et al., 2009). Finally, the reliability of diffusion data is periodically checked with the National Institutes of Standards and Technology diffusion phantom. This ensures that the measurements from diffusion MRI are stable(phantom)

Table S1: Regions of Interest (ROI) used for dMRI measures: Fractional anisotropy (FA) and trace (TR)[1]

LEFT BRAIN			GM vs. WM	REGION
1	SPG_L	Superior Parietal Gyrus Left	GM	
2	CingG_L	Cingulate Gyrus Left	GM	
3	SFG_L	Superior Frontal Gyrus Left	GM	
4	MFG_L	Middle Frontal Gyrus Left	GM	
5	IFG_L	Inferior Frontal Gyrus Left	GM	
6	PrCG_L	Precentral Gyrus Left	GM	
7	PoCG_L	Postcentral Gyrus Left	GM	
8	AG_L	Angular Gyrus Left	GM	
9	PrCu_L	Pre-Cuneus Left	GM	
10	Cu_L	Cuneus Left	GM	
11	LG_L	Lingual Gyrus Left	GM	
12	Fu_L	Fusiform Gyrus Left	GM	
13	PHG_L	Parahippocampal Gyrus Left	GM	
14	SOG_L	Superior Occipital Gyrus Left	GM	
15	IOG_L	Inferior Occipital Gyrus	GM	
16	MOG_L	Middle Occipital Gyrus	GM	
17	ENT_L	Entorhinal Area	GM	
18	STG_L	Superior Temporal Gyrus	GM	
19	ITG_L	Inferior Temporal Gyrus	GM	
20	MTG_L	Middle Temporal Gyrus	GM	
21	LFOG_L	Lateral Fronto-Orbital Gyrus	GM	
22	MFOG_L	Middle Fronto-Orbital Gyrus	GM	
23	SMG_L	Supramarginal Gyrus	GM	
24	RG_L	Gyrus Rectus	GM	
25	Ins_L	Insular	GM	
26	Amyg_L	Amygdala	GM	
27	Hippo_L	Hippocampus	GM	
28	Cerebrellum_L	Cerebellum	GM	
29	CST_L	Corticospinal Tract Left	WM	
30	ICP_L	Inferior Cerebellar Peduncle Left	WM	
31	ML_L	Medial Lemniscus Left	WM/GM	
32	SCP_L	Superior Cerebellar Peduncle Left	WM	
33	CP_L	Cerebellar Peduncle Left	WM	
34	ALIC_L	Anterior Limb of Internal Capsule Left	WM	
35	PLIC_L	Posterior Limb of Internal Capsule Left	WM	
36	PTR_L	Posterior Thalamic Radiation (Include Optic Radiation) Left	WM	
37	ACR_L	Anterior Corona Radiata Left	WM	

38	SCR_L	Superior Corona Radiata Left	WM	
39	PCR_L	Posterior Corona Radiata Left	WM	
40	CGC_L	Cingulum (Cingulate Gyrus) Left	WM	
41	CGH_L	Cingulum (Hippocampus) Left	WM	
42	Fx/ST_L	Fornix (Cres) / Stria Terminalis (Can Not Be Resolved With Current Resolution) Left	WM	
43	SLF_L	Superior Longitudinal Fasciculus Left	WM	
44	SFO_L	Superior Fronto-Occipital Fasciculus (Could Be A Part of Anterior Internal Capsule) Left	WM	
45	IFO_L	Inferior Fronto-Occipital Fasciculus Left	WM	
46	SS_L	Sagittal Stratum (Include Inferior Longitidinal Fasciculus And Inferior Fronto-Occipital Fasciculus) Left	WM	
47	EC_L	External Capsule Left	WM	
48	UNC_L	Uncinate Fasciculus Left	WM	
49	PCT_L	Pontine Crossing Tract (A Part of Mcp) Left	WM	
50	MCP_L	Middle Cerebellar Peduncle Left	WM	
51	FX_L	Fornix (Column And Body of Fornix) Left	WM	
52	GCC_L	Genu of Corpus Callosum Left	WM	
53	BCC_L	Body of Corpus Callosum Left	WM	
54	SCC_L	Splenium of Corpus Callosum Left	WM	
55	RLIC_L	Retrolenticular Part of Internal Capsule Left	WM	
56	REDNC_L	Red Nucleus Left	GM	
57	SNIGRA_L	Substancia Nigra Left	GM	
58	TAP_L	Tapatum Left	GM	
59	Caud_L	Caudate Nucleus Left	GM	
60	Put_L	Putamen Left	GM	
61	Thal_L	Thalamus Left	GM	
62	GP_L	Globus Pallidus Left	GM	
63	Midbrain_L	Midbrain Left	GM	
64	Pons_L	Pons Left	WM	
65	Medulla_L	Medulla Left	WM/GM	
66	SPWM_L	Superior Parietal WM Left	WM	Parietal
67	Cingwm	Cingulum WM Left	WM	Cingulum
68	SFWM_L	Superior Frontal WM Left	WM	Frontal
69	MFWM_L	Middle Frontal WM Left	WM	Frontal
70	IFWM_L	Inferior Frontal WM Left	WM	Frontal
71	PrCWM_L	Precentral WM Left	WM	Frontal
72	PoCWM_L	Postcentral WM Left	WM	Parietal
73	AWM_L	Angular WM Left	WM	Parietal
74	PrCuWM_L	Pre-Cuneus WM Left	WM	Parietal
75	CuWM_L	Cuneus WM Left	WM	Occipital
76	LWM_L	Lingual WM Left	WM	Occipital

77	Fu_WM_L	Fusiform WM Left	WM	Occipital
78	SOWM_L	Superior Occipital WM Left	WM	Occipital
79	IOWM_L	Inferior Occipital WM Left	WM	Occipital
80	MOWM_L	Middle Occipital WM Left	WM	Occipital
81	STwm_L	Superior Temporal WM Left	WM	Temporal
82	ITWM_L	Inferior Temporal WM Left	WM	Temporal
83	MTWM_L	Middle Temporal WM Left	WM	Temporal
84	LFOWM_L	Lateral Fronto-Orbital WM Left	WM	Frontal
85	MFOWM_L	Middle Fronto-Orbital WM Left	WM	Frontal
86	SMWM_L	Supramarginal WM Left	WM	Parietal
87	RGWM_L	Rectus WM Left	WM	Frontal
88	Cerebrellumwm_L	Cerebellum WM Left	WM	
RIGHT BRAIN				
89	SPG_R	Superior Parietal Gyrus Right	GM	
90	CingG_R	Cingulate Gyrus Right	GM	
91	SFG_R	Superior Frontal Gyrus Right	GM	
92	MFG_R	Middle Frontal Gyrus Right	GM	
93	IFG_R	Inferior Frontal Gyrus Right	GM	
94	PrCG_R	Precentral Gyrus Right	GM	
95	PoCG_R	Postcentral Gyrus Right	GM	
96	AG_R	Angular Gyrus Right	GM	
97	PrCu_R	Pre-Cuneus Right	GM	
98	Cu_R	Cuneus Right	GM	
99	LG_R	Lingual Gyrus Right	GM	
100	FuG_R	Fusiform Gyrus Right	GM	
101	PHG_R	Parahippocampal Gyrus Right	GM	
102	SOG_R	Superior Occipital Gyrus Right	GM	
103	IOG_R	Inferior Occipital Gyrus Right	GM	
104	MOG_R	Middle Occipital Gyrus Right	GM	
105	ENT_R	Entorhinal Area Right	GM	
106	STG_R	Superior Temporal Gyrus Right	GM	
107	ITG_R	Inferior Temporal Gyrus Right	GM	
108	MTG_R	Middle Temporal Gyrus Right	GM	
109	LFOG_R	Lateral Fronto-Orbital Gyrus Right	GM	
110	MFOG_R	Middle Fronto-Orbital Gyrus Right	GM	
111	SMG_R	Supramarginal Gyrus Right	GM	
112	RG_R	Gyrus Rectus Right	GM	
113	Ins_R	Insular Right	GM	
114	Amyg_R	Amygdala Right	GM	
115	Hippo_R	Hippocampus Right	GM	
116	Cerebellum_R	Cerebellum Right	GM	

117	CST_R	Corticospinal Tract Right	WM	
118	ICP_R	Inferior Cerebellar Peduncle Right	WM	
119	ML_R	Medial Lemniscus Right	WM/GM	
120	SCP_R	Superior Cerebellar Peduncle Right	WM	
121	CP_R	Cerebellar peduncle, Right		
122	ALIC_R	Anterior Limb of Internal Capsule Right	WM	
123	PLIC_R	Posterior Limb of Internal Capsule Right	WM	
124	PTR_R	Posterior Thalamic Radiation (Include Optic Radiation) Right	WM	
125	ACR_R	Anterior Corona Radiata Right	WM	
126	SCR_R	Superior Corona Radiata Right	WM	
127	PCR_R	Posterior Corona Radiata Right	WM	
128	CGC_R	Cingulum (Cingulate Gyrus) Right	WM	
129	CGH_R	Cingulum (Hippocampus) Right	WM	
130	Fx/ST_R	Fornix (Cres) / Stria Terminalis (Can Not Be Resolved With Current Resolution) Right	WM	
131	SLF_R	Superior Longitudinal Fasciculus Right	WM	
132	SFO_R	Superior Fronto-Occipital Fasciculus (Could Be A Part of Anterior Internal Capsule) Right	WM	
133	IFO_R	Inferior Fronto-Occipital Fasciculus Right	WM	
134	SS_R	Sagittal Stratum (Include Inferior Longitidinal Fasciculus And Inferior Fronto-Occipital Fasciculus) Right	WM	
135	EC_R	External Capsule Right	WM	
136	UNC_R	Uncinate Fasciculus Right	WM	
137	PCT_R	Pontine Crossing Tract (A Part of MCP) Right	WM	
138	MCP_R	Middle Cerebellar Peduncle Right	WM	
139	FX_R	Fornix (Column And Body of Fornix) Right	WM	
140	GCC_R	Genu of Corpus Callosum Right	WM	
141	BCC_R	Body of Corpus Callosum Right	WM	
142	SCC_R	Splenium of Corpus Callosum Right	WM	
143	RLIC_R	Retrolenticular Part of Internal Capsule Right	WM	
144	REDNC_R	Red Nucleus Right	GM	
145	SNIGRA_R	Substancia Nigra Right	GM	
146	TAP_R	Tapatum Right	GM	
147	Caud_R	Caudate Nucleus Right	GM	
148	Put_R	Putamen Right	GM	
149	Thal_R	Thalamus Right	GM	
150	GP_R	Globus Pallidus Right	GM	
151	Midbrain_R	Midbrain Right	GM	
152	Pons_R	Pons Right	WM	
153	Medulla_R	Medulla Right	WM/GM	
154	SPwm_R	Superior Parietal WM Right	WM	Parietal
155	Cingwm_R	Cingulum WM Right	WM	Cingulum
156	SFWM_R	Superior Frontal WM Right	WM	Frontal

157	**MFWM_R**	**Middle Frontal WM Right**	**WM**	**Frontal**
158	**IFWM_R**	**Inferior Frontal WM Right**	**WM**	**Frontal**
159	**PrCWM_R**	**Precentral WM Right**	**WM**	**Frontal**
160	**PoCWM_R**	**Postcentral WM Right**	**WM**	**Parietal**
161	**AWM_R**	**Angular WM Right**	**WM**	**Parietal**
162	**PrCuWM_R**	**Pre-Cuneus WM Right**	**WM**	**Parietal**
163	**CuWM_R**	**Cuneus WM Right**	**WM**	**Occipital**
164	**LWM_R**	**Lingual WM Right**	**WM**	**Occipital**
165	**Fuwm_R**	**Fusiform WM Right**	**WM**	**Occipital**
166	**SOWM_R**	**Superior Occipital WM Right**	**WM**	**Occipital**
167	**IOWM_R**	**Inferior Occipital WM Right**	**WM**	**Occipital**
168	**MOWM_R**	**Middle Occipital WM Right**	**WM**	**Occipital**
169	**STWM_R**	**Superior Temporal WM Right**	**WM**	**Temporal**
170	**ITWM_R**	**Inferior Temporal WM Right**	**WM**	**Temporal**
171	**MTWM_R**	**Middle Temporal WM Right**	**WM**	**Temporal**
172	**LFOWM_R**	**Lateral Fronto-Orbital WM Right**	**WM**	**Frontal**
173	**MFOWM_R**	**Middle Fronto-Orbital WM Right**	**WM**	**Frontal**
174	**SMWM_R**	**Supramarginal WM Right**	**WM**	**Parietal**
175	**RGWM_R**	**Rectus WM Right**	**WM**	**Frontal**
176	**Cerebrellumwm_R**	**Cerebellum WM Right**	**WM**	

[1]Right and Left measures of FA and TR were averaged out before analyses C and D was carried out. This resulted in 100 measures in total, 50 for FA and 50 for TR, when excluding measures with missing data. Measures included in the analysis are bolded and in red font. All others are excluded. In addition, cerebellum wm TR (Right and Left) were only available for 85 subjects, as was the case for SNIGRA FA/TR (Right and Left). TR is also known as mean diffusivity or MD.

Supplemental Method 2: Mixed-effects linear regression models and empirical Bayes estimation

The main multiple mixed-effects regression models can be summarized as follows:

	Multi-level models vs. **Composite models**	
Eq.	$\pi_{0i} = \gamma_{00} + \gamma_{0a}X_{aij} + \sum_{k=1}^{l}\gamma_{0k}Z_{ik} + \zeta_{0i}$	$Y_{ij} = \gamma_{00} + \gamma_{0a}X_{aij} + \sum_{k=1}^{l}\gamma_{0k}Z_{ik}$
1.1-1.4 $Y_{ij} = \pi_{0i} + \pi_{1i}Time_{ij} + \varepsilon_{ij}$		$+ \gamma_{10}Time_{ij} + \gamma_{1a}X_{aij}Time_{ij}$
	$\pi_{1i} = \gamma_{10} + \gamma_{1a}X_{aij} + \sum_{m=1}^{n}\gamma_{1m}Z_{im} + \zeta_{1i}$	$+ \sum_{m=1}^{n}\gamma_{1m}Z_{im}Time_{ij}$
		$+ (\zeta_{0i} + \zeta_{1i}Time_{ij} + \varepsilon_{ij})$

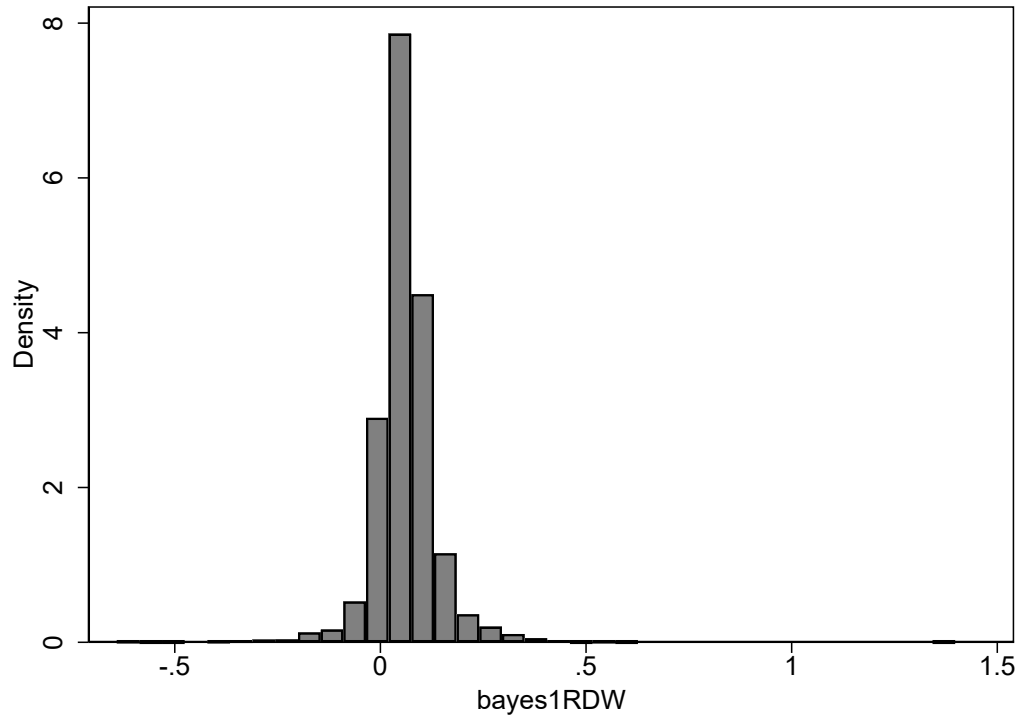
Where Y_{ij} is the outcome (RDW) for each individual "i" and visit "j"; π_{0i} is the level-1 intercept for individual i; π_{1i} is the level-1 slope for individual i; γ_{00} is the level-2 intercept of the random intercept π_{0i}; γ_{10} is the level-2 intercept of the slope π_{1i}; Z_{ik} is a vector of fixed covariates for each individual *i* that are used to predict level-1 intercepts and slopes and included baseline age (Age_{base}) among other covariates. $X_{ija,}$ represents the main predictor variables. In this case, all predictor variables were socio-demographic and used for prediction. ζ_{0i} and ζ_{1i} are level-2 disturbances; ε_{ij} is the within-person level-1 disturbance. Main effect of *TIME* (γ_{1a}) and interactions with socio-demographic factors (γ_{1a}) along with random effects ζ_{1i} were used to estimate each individual slope π_{1i}, also known as the empirical bayes estimator. The time interval model is described in details in this methodological paper.(Blackwell et al., 2006) Since time is measured as year elapsed since visit 1 up till visit 2, the interpretation of π_{1i} is the predicted individual-level annual rate of change in the outcome Y_{ij}, between visits 1 and 2. This empirical bayes estimator of slope was used to examine association between annual rates of change in each of RDW vs. brain MRI markers. Below are the results of the mixed effects regression models for each of the RDW exposure:

	RDW (n=3,017, k=1.7)
Intercept (γ_{00} ±SE)	14.09±0.18***
Time (γ_{10} ±SE)	+0.02±0.04
Age(v_1) γ_{01}±SE	-0.000±0.003
Age(v_1)×Time, γ_{11}±SE	0.001±0.001
Sex (0=Female, 1=Male), γ_{02}±SE	-0.48±0.06***
Sex×Time, γ_{12}±SE	+0.013±0.014
Race (0=Whites, 1=AA), γ_{03}±SE	+0.658±0.064***
Race×Time, γ_{13}±SE	+0.004±0.014
Poverty (0=Below, 1=Above), γ_{04}±SE	-0.13±0.06*
Poverty×Time, γ_{14}±SE	-0.025±0.014
Var (ζ_{0i})	1.97±0.11
Var (ζ_{1i})	0.03±0.01
Var (ε_{ij})	0.80±0.09

***p<0.001; **P<0.010; *p<0.05

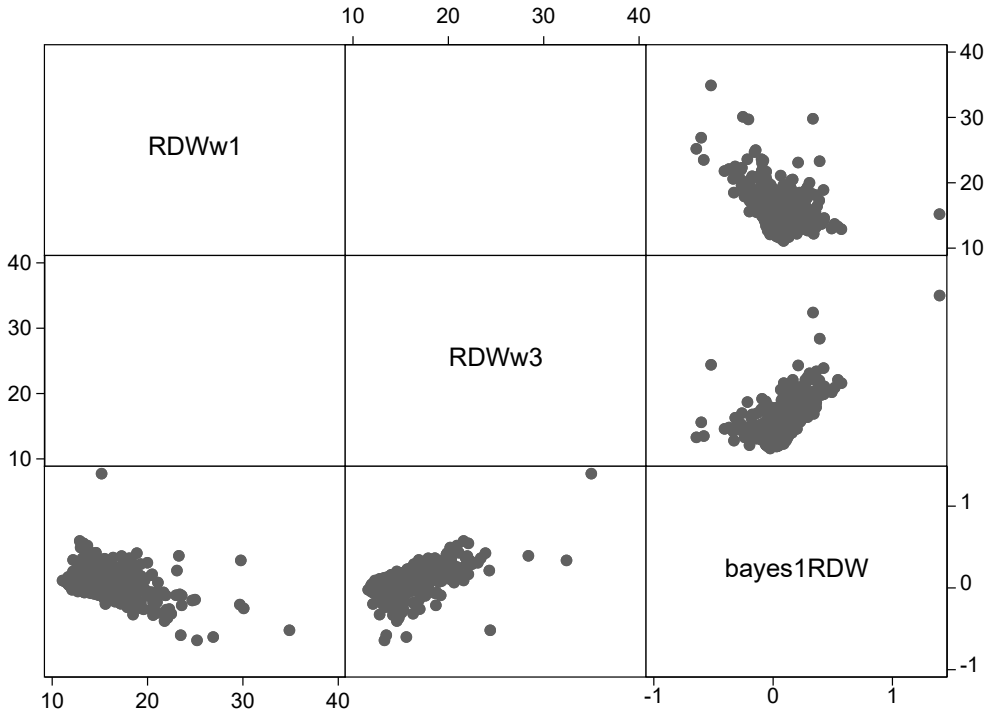
Below are distributional graphs for each of the 3 empirical Bayes estimators of the slope, which are estimated as follows: $\gamma_{10} + \gamma_{11}\times$ Age + $\gamma_{12}\times$ Sex + $\gamma_{13}\times$ Race + $\gamma_{14}\times$ Poverty + ζ_{1i}

RDW annual rate of change



Below is a scatter plot of the empirical Bayes estimators against visits 1 and 2 values.

Baseline and annual rates of change in RDW



Abbreviations: RDWw1=RDW at visit 1 (HANDLS wave 1); RDWw3= RDW at visit 2 (HANDLS wave 3); bayes1RDW=Empirical bayes estimator of annual rate of change in RDW or δRDW.

Supplemental Method 3: Additional covariates, LASSO regression and multiple imputations

A. Additional covariates:

A.1. Socio-demographic

Additional socio-demographic confounders included educational attainment (0 ≤ High School (HS); 1 = HS and 2 ≥ HS), the Wide Range Achievement Test (WRAT) letter and word reading subtotal scores to measure literacy, and marital status (1=married, 0=not married) (Beydoun et al., 2018b).

A.2. Lifestyle

Smoking and drug use
Current use of opiates, marijuana or cocaine ("current" *vs*. "never or former") and smoking status ("current" vs. "never or former") were considered.

Adiposity measures
Measured body mass index (BMI, kg/m^2), waist circumference, and waist-hip-ratio were considered among potential confounders.

Healthy Eating Index 2010-
The Healthy Eating Index (HEI-2010) total score, based on two 24-hr recalls administered at baseline, was used as a measure of overall dietary quality. See steps for calculating HEI-2010 at http://appliedresearch.cancer.gov/tools/hei/tools.html and http://handls.nih.gov/06Coll-dataDoc.html.

Dietary Approaches to Stop Hypertension (DASH)

DASH diet adherence score, based on eight nutrients, was determined for each participant using the formula reported by Mellen *et al*.(Mellen et al.). The nine target nutrients were: total fat, saturated fat, protein, fiber, cholesterol, sodium, calcium, magnesium, and potassium. Micronutrient goals were expressed per 1000 kcal. The total DASH score was generated by the sum of all nutrient targets met. If the participant achieved the DASH target for a nutrient, a value of one was assigned, and if an intermediate target for a nutrient was achieved, a value of 0.5 was assigned. A value of zero was assigned if neither target was met. The maximum DASH score was nine; individuals meeting approximately half of the DASH targets (DASH score = 4.5) were considered DASH adherent (Mellen et al.).

Mean Adequacy Ratio (MAR)
Diet quality was also assessed using Nutrient Adequacy Ratio (NAR) and Mean Adequacy Ratio (MAR) scores(Fanelli Kuczmarski et al., 2013; Murphy et al., 2006). NAR score was determined by taking each participant's daily intake of a nutrient divided by the Recommended Dietary Allowance (RDA) for that nutrient. NAR scores were determined for 17 micronutrients: vitamins A, C, D, E, B_6, B_{12}, folate, iron, thiamin, riboflavin, niacin, copper, zinc, calcium, magnesium, phosphorus, and selenium. The RDA was adjusted for participants' ages and sexes and vitamin C was adjusted for smokers(Murakami et al., 2019). The NAR score was converted into a percent with values exceeding 100 truncated to 100. MAR scores were calculated by averaging the NAR scores: MAR= (∑NAR scores)/17(Fanelli Kuczmarski et al., 2018). NAR and MAR were calculated separately for each daily-intake and then averaged. MAR scores, based on food intakes only, were used as the nutrient-based diet quality variable.

Supplemental use

The HANDLS dietary supplement questionnaire was adapted from the 2007 NHANES instrument.(Centers for Disease Control and Prevention, 2007) Information on Over-The-Counter (OTC) vitamin and mineral supplements, antacids, prescription supplements, and botanicals were reported, and supplement users were asked about dose strength, dose amount consumed, length of supplement use (converted to days), frequency of use (daily, monthly, seasonally, annually), and if each supplement was taken the day prior to interview(Beydoun et al., 2018b). Participants had to provide supplement bottles during their dietary interview at the follow-up visit (i.e. visit 2).

A HANDLS dietary supplement database was developed by trained nutritionists and registered dietitians. This database consisted of four files integrated to generate daily intake of each nutrient consumed by a dietary supplement user. [See detailed description at the HANDLS study website: https://handls.nih.gov/].

Depressive symptoms

Depressive symptoms were operationalized using the CES-D at baseline and follow-up. The 20-item CES-D is a self-reported symptom rating scale assessing affective and depressed mood.(Radloff, 1977) A score of ≥16 on the CES-D is reflective of elevated depressive symptoms (EDS), (Ramos et al., 2004) and predicts clinical depression based on the Diagnostic and Statistical Manual, fourth edition (DSM-IV) criteria.(Myers and Weissman, 1980) Four CES-D sub-domains exhibiting an invariant factor structure between The National Health and Nutrition Examination Survey I and pilot HANDLS data (Nguyen et al., 2004) were computed. We tested our hypotheses using total and domain-specific CES-D scores: **(1)** Somatic complaints; **(2)** Depressive affect; **(3)** Positive affect and **(4)** Interpersonal problems.(Nguyen et al., 2004)

A.3. Health-related

Baseline chronic conditions included self-reported history measurement, biomarker-based measurement, and medication-based measurement, of type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, and inflammatory disease. Dyslipidemia was based on a combination of self-report, HDL, total cholesterol, triglyceride criteria, and statin use. Similarly, type 2 diabetes was determined using a combination of self-report, serum glucose criteria and medication. The same was conducted for hypertension. Additionally, a composite of cardiovascular disease history was added in which self-reported stroke, congestive heart failure, non-fatal myocardial infarction or atrial fibrillation combined into a yes/no variable. Similarly, inflammatory disease was a binary composite of multiple sclerosis, systemic lupus, gout, rheumatoid arthritis, psoriasis, Thyroid disorder and Crohn's disease. The use of NSAIDs (prescription and over-the-counter) and statins over the past two weeks were considered separately as potential covariates.

A.4. Other biomarkers

All laboratory tests selected for this study were done at Quest Diagnostics, Chantilly, VA.

Serum cholesterol and atherogenic indices

Total cholesterol (TC), High density lipoprotein-cholesterol (HDL-C) and Triacylglycerols (TA) were assessed using a spectrophotometer (Olympus 5400). Low density lipoprotein-cholesterol (LDL-C) was calculated as TC-(HDL-C+TA/5) and directly measured in a sub-sample (N=236) using a spectrophotometer (Olympus 5400). The correlation between those with baseline calculated LDL-C and those with measured LDL-C was r~0.95. From these calculations, two relative measures were obtained, namely TC:HDL-C and LDL-C:HDL-C ratios. These were termed "atherogenic indices" and have been previously studied in relation to various cardiovascular outcomes that found them to be positively associated with measures of atherosclerosis and coronary heart disease. (Hisamatsu et al., 2014; Manickam et al., 2011; Nair et al., 2009)

Serum uric acid (SUA)

SUA measurements are useful in the diagnosis and treatment of renal and metabolic disorders, including renal failure, gout, leukemia, psoriasis, starvation or other wasting conditions, as well as in patients receiving cytotoxic drugs. Using 1 ml of fasting blood serum, uric acid was measured using a standard spectrophotometry method. The reference range for adult men is 4.0-8.0 mg/dL, whereas for

women the range is 2.5-7.0 mg/dL. (http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=905) Other reference ranges were also recently suggested and depend on the menopausal status of women. Those reference ranges are based on predictive value for gout outcomes among healthy individuals and do not necessarily predict other pathologies. Thus, based on recent research evidence, a "normal" SUA value is suggested to be <6.0 mg/dL for all healthy adult individuals.

Serum albumin

Using 0.5-1 mL samples of plasma prepared with heparin and refrigerated for up to 30 days, albumin was measured with spectrophotometry, with an expected reference range of 3.6-5.1 g/dL(Beydoun et al., 2016b; Beydoun et al., 2019).

High sensitivity C-reactive protein (CRP)

High sensitivity CRP (hs-CRP) was analyzed with an immunoturbidimeter (Siemens/Behring Nephelometer II), using 0.5-1 mL of plasma. A range of 1-10 mg/dL indicates average to high cardiovascular risk and >10 mg/dL suggests an infection or a chronic inflammation.

Serum creatinine

Using participant fasting blood specimens, baseline serum creatinine was measured at the National Institute on Aging, Clinical Research Branch Core Laboratory, using a modified kinetic Jaffe method (CREA method, Dade Dimension X-Pand Clinical Chemistry System, Siemens Healthcare Diagnostics Inc., Newark, DE) for a small group of participants (n=88). However, a majority of participants (n=1,528) had baseline serum creatinine analyzed at Quest Diagnostics, Inc. by isotope dilution mass spectrometry (IDMS) (Olympus America Inc., Melville, NY) and standardized to the reference laboratory, Cleveland Clinic. While inter-assay coefficients of variation (CV) for this sample could not be calculated due to the use of only one or the other measurement of creatinine at baseline, only intra-assay CVs (mean/SD) could be estimated. These were 0.192 and 0.187 for the CREA and the IDMS methods, respectively.

HbA1c

Glycated hemoglobin is derived from the nonenzymatic addition of glucose to amino groups of hemoglobin. HbA1c is a specific glycated hemoglobin that results from the attachment of glucose to the N-terminal valine of the hemoglobin b-chain. Numerous assays were subsequently developed to measure glycated hemoglobins. The principle of all methods is to separate the glycated and nonglycated forms of hemoglobin(Beydoun et al., 2016a). This can be accomplished based on differences in charge (usually by HPLC) or structure (usually immunoassays or boronate affinity chromatography). In this study, HPLC was used (Quest diagnostics).

White blood cell inflammatory markers

Fasting blood samples were collected from participants at baseline and follow-up to determine total white blood cell count (K/mm^3), using electronic Cell Sizing, counting, cytometry, and microscopy. (http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=7064).

Serum 25-hydroxyvitamin D, folate and cobalamin

Participants were asked to fast for ≥8 hours prior to the MRV visits, and serum specimens in volumes of 2 mL were collected and frozen at −80°C. Similar procedures were adopted for serum folate and cobalamin, both measured using chemiluminescence immunoassay (Siemens Centaur) by Quest Diagnostics, Chantilly, VA (Beydoun et al., 2018a; Diagnostics), and previously validated against other automated methods with coefficient of variation (CV) < 10% (Ispir et al., 2015; Owen and Roberts, 2003).

25(OH)D were measured using slightly revised methodologies between v_1 and v_2. In this study, only the v_1 measure was used. At v_1, total levels of serum 25(OH)D (in ng/ml; D_2 and D_3) were measured using tandem mass spectrometry (interassay CV, 8.6%) at Massachusetts General Hospital for less than 60 days later, as recommended for frozen samples (Powe et al., 2013). Blood samples drawn at examination were stored at −80°C.

Dietary and supplemental intakes of vitamin D, folate and cobalamin were shown to moderately correlate with their corresponding serum biomarkers in HANDLS and national surveys (Beydoun et al., 2010a; Beydoun et al., 2018b; Beydoun et al., 2010b).

Hemoglobin and other hematological measures

Hemoglobin (Hb)

Similarly, using electronic cell sizing/cytometry/microscopy, Hb was assayed from a sample of 1 ml of blood drawn from participants after an overnight fast, and refrigerated up to 6 days (Quest diagnostics).

Other hematological markers

Ferritin: Ferritin is decreased in iron deficiency anemia and increases with iron overload. It is measured with immunoassay with reference ranges of 20-380 ng/mL among men and 10-232 ng/mL among women.(Diagnostics)

Erythrocyte Sedimentation Rate (ESR): Using 5 mL of refrigerated whole blood stored in lavender-top EDTA tubes, the ESR was tested within 24 hr of blood draw. This test used automated modified Westergren photochemical capillary-stopped flow kinetic analysis.(Diagnostics; Larsson and Hansson, 2004) The Mayo Clinic reports a reference of 0-22 mm/hr for men and 0-29 mm/hr for women(Mayo Clinic, 2017) and is considered a proxy measure for serum fibrinogen.(Yin et al., 2017)

Serum iron: 0.5-1 mL of fasting serum was collected, transported at room temperature (with heparin added) and refrigerated or frozen subsequently. Serum iron was measured with spectrophotometry,

(Diagnostics; Samarina and Proskurnin, 2015) with reference ranges for men aged ≥30y set at 50-180 μg/dL, and for women: 20-49y (40-190 μg /dL) and 50+y(45-160 μg /dL). (Diagnostics)

MCV: Also known as erythrocyte mean corpuscular volume, MCV is measured using standard electronic cell sizing/counting/cytometry/microscopy. Similar to other hemogram measures (e.g. ESR), a microtainer 1 mL whole blood in an EDTA (lavender-top) tube was transported at room temperature to the laboratory facility.(Diagnostics)

MCH: The hematologic index MCH was calculated as follows: MCH = Hb/RBC.

B. Least absolute shrinkage and selection operator (LASSO) regression procedure

In order to select the appropriate set of predictive model for RDW, we used a statistical learning method for variable selection known as adaptive LASSO, and compared it to cross-validation LASSO (cvLASSO) and lowest BIC LASSO. Socio-demographic variables, (age, sex, race/ethnicity, poverty status) were force entered as fixed terms into all models. The LASSO then selected among the other covariates listed above as variables that should be retained. Covariates were imputed using chained equations (5 imputations, 10 iterations), accounting for their level of measurement. Socio-demographic factors were entered into all the chained equations. Continuous covariates were entered as outcomes in a series of linear regression models, while binary and categorical variables were entered into a series of multinomial logit regression models.

LASSO is a covariate selection methodology that is superior to both generalized linear models without covariate selection as well as the usually applied stepwise or backward elimination process.(Zou, 2006) In fact, stepwise selection is often trapped into a local optimal solution rather than the global optimal solution and backward elimination can be time-consuming given the large number of variables in the full model.(Zou, 2006) These methods often ignore stochastic errors or uncertainty incurred during variable selection, with the LASSO estimate being defined as:

$\beta(\text{lasso}) = \arg min_{\beta} || \, y - \sum_{j=1}^{p} x_j \beta_j \, ||^2 + \lambda \sum_{j=1}^{p} |\beta_j \, |$

with λ being a nonnegative regularization parameter.(Zou, 2006) The second term of the equation termed the "l1 penalty" is a key portion of this equation that ensures the success of the lasso method of covariate selection. This method was shown to discover the right sparse representation of the model, given certain conditions. Nevertheless, this method can produce biased estimates for larger coefficients. Thus, there a number of scenarios whereby the LASSO can yield inconsistent results. Recent methods have shown that an adaptive version of the LASSO gave more consistent findings, particularly when compared with the nonnegative garotte, another popular variable selection technique.

In our modeling approach, we used this convex optimization technique with l_1 constraint known as adaptive LASSO as one of three methods to select the final linear regression models. The model is trained on a random half sample of the total population (first imputation out of 5) and validated against the other half sample to check robustness of findings, by comparing R^2 between samples. One model was selected among the cvLASSO, adaptive LASSO or minBIC LASSO, depending on how close the R^2 are between half-samples. This parsimonious model selected for RDW (measured at v_1 and empirical Bayes slope

estimator measured between v_1 and v_2) as 2 potential outcomes is then run on the entire population and a backward elimination process is carried out to keep only significant covariates at type I error = 0.10. Thus, the selected model through LASSO was used as a starting point for further backward elimination. Backward elimination was conducted on the imputed data for the entire sample, rather than the half sample for the first imputation.

In our analysis, the following LASSO models were selected and the final model included is shown also in this Table.

	Selected covariates[1]			
	cvLASSO	**Min BIC LASSO**	**Adaptive LASSO**	**Reduced model**
RDW (v_1)	MCH, Hb, Creatinine, smoking, CES-D, age, Cholesterol:HDL ratio, HEI-2010 total score, CVD, sex, WHR, CRP, B-12, WBC, Triglycerides, Poverty status, race, WRAT total score, albumin, cholesterol, Hypertension medication, Iron, education, current drugs, HbA1C	MCH, Hb, Creatinine, smoking, CES-D, age, Cholesterol:HDL ratio, HEI-2010 total score, CVD, sex, WHR, CRP, B-12, WBC, poverty status, race, albumin cholesterol	**MCH, Hb, Creatinine, smoking, CES-D, age, Cholesterol:HDL ratio, HEI-2010 total score, CVD, sex, WHR, CRP, B-12, WBC, Triglycerides, poverty status, race, WRAT total score, NSAIDS, albumin.**	**MCH, Hb, Creatinine, smoking, age, Cholesterol:HDL ratio, HEI-2010 total score, sex, CRP, B-12, WBC, Triglycerides, poverty status, race, WRAT total score.**
RDW (v_2-v_1, annual)	**Poverty status, Hb, race, age, WBC, MCV, WHR, CVD and sex.**	**Poverty status, Hb, race, age, WBC, MCV, WHR, CVD and sex.**	**Poverty status, Hb, race, age, WBC, MCV, WHR, CVD and sex.**	**Poverty status, Hb, race, age, WBC, MCV**
Anemia (v_1)	ESR, RDW, MCH, Albumin, Serum iron, race, WBC, age, WRAT total score, Cholesterol, Folate, B12,	ESR, RDW, MCH, Albumin, Serum iron, race, WBC, age, poverty status.	**ESR, RDW, MCH, Albumin, Serum iron, race, WBC, age, WRAT total score, Cholesterol, Folate, B12, Inflammatory**	**ESR, RDW, MCH, Albumin, Serum iron, race, WBC, age, Cholesterol, Folate,**

	Inflammatory conditions, education, WC, married, diagnosed hypertension, vitamin supplements, current drugs, WHR, Triglycerides, 25(OH)D, poverty status, sex.	**conditions, education, WC, poverty status, sex.**	**B12, education, WC, poverty status, sex.**

Abbreviations: B-12=vitamin B-12 (cobalamin); BIC=Bayesian information criterion; BMI=Body Mass Index; CES-D=Center for Epidemiologic Studies-Depression; CRP=C-reactive Protein; cv=cross-validation; CVD=Self-reported cardiovascular disease; DASH=Dietary Approaches to Stop Hypertension; ESR=Erythrocyte Sedimentation Rate; HbA1c=Glycated hemoglobin; HDL=High Density Lipoprotein Cholesterol; LASSO= Least absolute shrinkage and selection operator; HEI-2010=Healthy Eating Index, 2010 revision; MAR=Mean Adequacy Ratio; MCH=Mean cell hemoglobin; MCV=Mean Cell Volume; NSAIDS=Non-Steroidal Anti-inflammatory Drugs; RDW=Red cell distribution Width; WBC=White Blood Cells; WC=Waist circumference, WHR=Waist-Hip-Ratio

[1]Bolded sets of covariates are the ones that are selected at each step of the model selection process. A full row of bolded sets of covariates indicates that the selection process is equivalent and that backward elimination did not reduce the model further.

The final common set of covariates that were chosen using the reduced model for each exposure was:

Anemia(v_1): RDW(v_1), age, sex, race, poverty status, ESR, MCH, Serum iron, Creatinine, albumin, cholesterol, Cholesterol:HDL ratio, HEI-2010 total score, CRP, B-12, folate, WBC, Triglycerides, smoking, WC, WRAT total score, education.

RDW(v_1) and RDW (v_2-v_1, annual): Hb(v_1), age, sex, race, poverty status, ESR, MCH, MCV, Serum iron, Creatinine, albumin, cholesterol, Cholesterol:HDL ratio, HEI-2010 total score, CRP, B-12, folate, WBC, Triglycerides, smoking, WC, WRAT total score, education.

From these, six models were constructed:

Model 1: Only socio-demographic

Model 2: Socio-demographic + hematological measures [i.e Hb for RDW (or δRDW) and RDW for anemia + other iron status measures (MCH, Serum iron, ESR).

Model 3: Socio-demographic +hematological measures + other nutritional/dietary (HEI-2010 total score, B-12, folate).

Model 4: Socio-demographic +hematological measures +inflammatory (CRP, albumin, WBC).

Model 5: Socio-demographic +hematological measrues+ adiposity and metabolic factors (WC, cholesterol, Cholesterol:HDL ratio, Triglycerides, Creatinine)

Model 6: Socio-demographic + hematological measures + other (education, WRAT, smoking).

C. Full description of the modeling approach:

Using multiple imputed data (k=5 imputations), a sensitivity analysis (SA) adjusted for additional covariates, selected with a multi-step process detailed in **supplemental method 3**, that included machine learning, followed by backward elimination and finally selection of a common pool of covariates that were independent predictors of at least one of 3 exposures. The pool of covariates initially selected had exhibited associations with either hematological measures and/or cognitive outcomes in previous studies. Thus, the final modeling approach consisted of a minimally adjusted basic model i.e. **Model 1** conducted on the unimputed data. Subsequently, the SA was carried out on multiple imputed data, with the following modeling approach:

Model 2: Model 1 +hematological measures [i.e Hb for RDW (or δRDW) and RDW for anemia + other hematological measures (MCH, Serum iron, ESR).

Model 3: Model 2 + other nutritional/dietary (Healthy Eating Index-2010 total score, B-12, folate); Model 4: Model 2+inflammatory (high sensitivity C-reactive protein, albumin, White blood cells); Model 5: Model 2+ adiposity and metabolic factors (WC, cholesterol, Cholesterol:HDL ratio, Triglycerides, Creatinine); Model 6: Model 2 + other covariates (education, WRAT, smoking). For this SA, formal effect modification testing was conducted by including 2-way interaction terms between exposure and sex in

the non-stratified model, with a type I error of 0.10 used for 2-way interaction terms due to reduced statistical power (Selvin, 2004).

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Table S2. Descriptive analyses by anemia status and RDW tertiles: Study sample characteristics of eligible study sample by Anemia (v_1 and v_1/v_2) status and by RDW(v_1) tertiles, overall, among males and among females ; HANDLS 2004-2009 and HANDLS-SCAN 2011-2015[a]

	Anemia status at v_1		*Anemia status at v_1/v_2*		*RDW at v_1, tertiles*		
	Non-anemic	*Anemic*	*Non-anemic (v1 or v2)*	*Anemic (v1 and v2)*	*T1*	*T2*	*T3*
Total sample	*(N=190)*	*(N=24)*	*(N=182)*	*(N=14)*	*(N=74)*	*(N=70)*	*(N=70)*
Demographic factors							
Sex, % males	47.8[b]	25[b]	47.3	21.4	46	52.9	37.1
Age_{v1}	48±8.8	45±11.2	48.3±8.6[b]	44.1±13.1[b]	47.4±9.4	48.3±8.4	47.2±9.5
Race, % AA	36.3[b]	75[b]	39	64.2	29.7[c]	37.1[c]	55.7[c]
% above poverty	68.42	58.3	70.3	57.1	67.6	71.4	62.9
RDW (v_1)							
CV (%)	13.7±1.1[b]	16.2±2.7[b]	13.7±1.2[b]	15.69±2.9[b]	12.8±.36[c]	13.7±.22[c]	15.5±1.8[c]
Median	13.5	16.1	13.5	14.1	12.9	13.7	14.9
IQR	13;14.1	13.8;18	13;14.2	13.7;18.3	12.6;13.1	13.5;13.9	14.3;15.8
dMRI measures	*(N=190)*	*(N=24)*	*(N=182)*	*(N=14)*	*(N=74)*	*(N=70)*	*(N=70)*
dMRI, Analysis A							
Mean FA	+0.30±0.02	+0.29±0.02	+0.30±0.02	+0.30±.01	+0.3±0.01	+0.3±0.02	+0.30±0.02
Mean MD	2.546E-03±1.563E-04	2.545E-03±1.918E-04	2.546E-03±1.586E-04	2.476E-03±1.280E-04	2.541E-03±1.669E-04	2.557E-03±1.604E-04	2.540E-03±1.542E-04
dMRI, Analysis B							

Left Brain							
Frontal FA	+0.23±0.02	+0.23±0.02	+0.23±0.01	+0.24±0.02	+0.24±0.02 [c]	+0.23±0.02 [c]	+0.23±0.01 [c]
Frontal MD	2.394E-03±1.421E-04	2.397E-03±1.902E-04	2.393E-03±1.445E-04	2.341E-03±1.619E-04	2.382E-03±1.235E-04	2.408E-03±1.724E-04	2.392E-03±1.453E-04
Temporal FA	+0.24±0.02	+0.24±0.02	+0.24±0.02	+0.24±0.01	+0.24±0.01	+0.24±0.02	+0.24±0.01
Temporal MD	2.432E-03±1.468E-04	2.435E-03±1.379E-04	2.431E-03±1.470E-04	2.413E-03±1.253E-04	2.440E-03±1.662E-04	2.429E-03±1.442E-04	2.428E-03±1.237E-04
Parietal FA	+0.23±0.02	+0.23±0.02	+0.23±0.02	+0.24±0.01	+0.23±0.01	+0.23±0.02	+0.23±0.02
Parietal MD	2.665E-03±1.922E-04	2.637E-03±2.433E-04	2.664E-03±1.963E-04	2.583E-03±1.762E-04	2.663E-03±1.957E-04	2.663E-03±1.810E-04	2.659E-03±2.188E-04
Occipital FA	+0.2±0.01	+0.2±0.01	+0.2±0.01	+0.21±0.01	+0.21±0.01	+0.2±0.02	+0.2±0.02
Occipital MD	2.475E-03±1.532E-04	2.509E-03±1.965E-04	2.478E-03±1.561E-04	2.422E-03±1.182E-04	2.484E-03±1.593E-04	2.462E-03±1.424E-04	2.491E-03±1.730E-04
Right Brain							
Frontal FA	+0.23±0.01	+0.23±0.02	+0.23±0.01	+0.24±0.01	+0.24±0.01	+0.23±0.02	+0.23±0.02
Frontal MD	2.366E-03±1.326E-04	2.372E-03±1.850E-04	2.366E-03±1.348E-04	2.308E-03±1.422E-04	2.367E-03±1.283E-04	2.376E-03±1.486E-04	2.357E-03±1.410E-04
Temporal FA	+0.25±0.02	+0.25±0.02	+0.25±0.02	+0.25±0.01	+0.25±0.01	+0.25±0.02	+0.25±0.02
Temporal MD	2.344E-03±1.401E-04	2.344E-03±1.341E-04	2.341E-03±1.383E-04	2.321E-03±1.171E-04	2.344E-03±1.628E-04	2.353E-03±1.330E-04	2.335E-03±1.178E-04
Parietal FA	+0.23±0.02	+0.22±0.02	+0.23±0.02	+0.23±0.02	+0.23±0.01 [c]	+0.22±0.02 [c]	+0.22±0.02 [c]
Parietal MD	2.720E-03±2.129E-04	2.671E-03±2.439E-04	2.717E-03±2.160E-04	2.608E-03±1.934E-04	2.722E-03±2.110E-04	2.709E-03±2.074E-04	2.714E-03±2.336E-04
Occipital FA	+0.2±0.01	+0.2±0.02	+0.2±0.01	+0.21±0.01	+0.21±0.01	+0.2±0.02	+0.2±0.02
Occipital MD	2.554E-03±1.718E-04	2.569E-03±2.028E-04	2.553E-03±1.713E-04	2.522E-03±1.409E-04	2.554E-03±1.900E-04	2.556E-03±1.623E-04	2.556E-03±1.734E-04
Males	*(N=91)*	*(N=6)*	*(N=86)*	*(N=3)*	*(N=34)*	*(N=37)*	*(N=26)*
Demographic factors							
Age_{v1}	47.7±8.8	49.3±8.8	48.5±8.5	47.6±12.9	47.2±9.6	47.4±8	49.1±9
Race, % AA	35.2 [b]	50.0	36.0 [b]	100.0 [b]	26.4	40.5	53.9
% above poverty	75.8	66.7	77.9	66.7	76.5	78.4	69.2

RDW (v_1)							
CV (%)	13.6±.77 [b]	15.3±1.3	13.5±0.77 [b]	14.3±0.72 [b]	12.8±0.34 [c]	13.6±0.21 [c]	14.8±0.74 [c]
Median	13.5	15.4	13.5	14.1	12.9	13.6	14.7
IQR	13;14	14.1;16.6	13;14	13.7;15.1	12.6;13.1	13.5;13.9	14.2;15.2
dMRI measures	*(N=91)*	*(N=6)*	*(N=86)*	*(N=3)*	*(N=34)*	*(N=37)*	*(N=26)*
dMRI, Analysis A							
Mean FA	+0.30±0.02 [b]	+0.28±0.04 [b]	+0.30±0.02	+0.31±0.02	+0.30±0.01 [c]	+0.30±0.02 [c]	+0.29±0.02 [c]
Mean MD	2.576E-03±1.463E-04 [b]	2.696E-03±3.072E-04 [b]	2.579E-03±1.494E-04	2.451E-03±1.937E-04	2.549E-03±1.007E-04	2.597E-03±1.866E-04	2.609E-03±1.817E-04
dMRI, Analysis B							
Left Brain							
Frontal FA	+0.23±0.02 [b]	+0.22±0.03 [b]	+0.23±0.02	+0.24±0.01	+0.24±0.01 [c]	+0.23±0.02 [c]	+0.23±0.02 [c]
Frontal MD	2.434E-03±1.556E-04	2.529E-03±2.675E-04	2.438E-03±1.593E-04	2.320E-03±1.801E-04	2.405E-03±1.276E-04	2.453E-03±1.904E-04	2.466E-03±1.647E-04
Temporal FA	+0.24±0.02	+0.23±0.03	+0.24±0.01	+0.25±0.01	+0.25±0.01	+0.24±0.02	+0.23±0.02
Temporal MD	2.462E-03±1.349E-04	2.523E-03±2.137E-04	2.464E-03±1.364E-04	2.381E-03±2.266E-04	2.453E-03±1.027E-04	2.460E-03±1.733E-04	2.490E-03±1.319E-04
Parietal FA	+0.23±0.01 [b]	+0.22±0.03 [b]	+0.23±0.01 [b]	+0.24±0.01 [b]	+0.23±0.01 [c]	+0.23±0.02 [c]	+0.22±0.02 [c]
Parietal MD	2.731E-03±1.775E-04	2.804E-03±3.935E-04	2.739E-03±1.803E-04	2.519E-03±2.542E-04	2.717E-03±1.565E-04	2.734E-03±1.806E-04	2.762E-03±2.552E-04
Occipital FA	+0.2±0.01 [b]	+0.19±0.02 [b]	+0.20±0.01	+0.20±0.01	+0.2±0.01 [c]	+0.2±0.01 [c]	+0.16±0.02 [c]
Occipital MD	2.502E-03±1.434E-04 [b]	2.662E-03±3.361E-04 [b]	2.507E-03±1.486E-04	2.410E-03±2.432E-04	2.487E-03±1.101E-04	2.498E-03±1.607E-04	2.563E-03±2.129E-04
Right Brain							
Frontal FA	+0.23±0.01 [b]	+0.21±0.03 [b]	+0.23±0.01	+0.24±0.01	+0.24±0.01 [c]	+0.23±0.02 [c]	+0.23±0.02 [c]
Frontal MD	2.398E-03±1.323E-04 [b]	2.521E-03±2.798E-04 [b]	2.404E-03±1.356E-04	2.310E-03±2.218E-04	2.380E-03±9.660E-05	2.417E-03±1.695E-04	2.425E-03±1.640E-04

Temporal FA	+0.25±0.02 [b]	+0.23±0.03 [b]	+0.25±0.01	+0.26±0.01	+0.25±0.01	+0.24±0.02	+0.24±0.02
Temporal MD	2.365E-03±1.210E-04	2.425E-03±1.994E-04	2.364E-03±1.221E-04	2.294E-03±1.761E-04	2.347E-03±9.870E-05	2.380E-03±1.440E-04	2.380E-03±1.332E-04
Parietal FA	+0.22±0.02	+0.21±0.04	+0.22±0.02 [b]	+0.24±0.02 [b]	+0.23±0.01 [c]	+0.23±0.02 [c]	+0.22±0.02 [c]
Parietal MD	2.799E-03±2.021E-04	2.833E-03±4.089E-04	2.807E-03±2.055E-04	2.550E-03±3.464E-04	2.782E-03±1.861E-04	2.796E-03±2.125E-04	2.831E-03±2.619E-04
Occipital FA	+0.2±0.02 [b]	+0.19±0.03 [b]	+0.2±0.02	+0.21±0.02	+0.21±0.01 [c]	+0.2±0.02 [c]	+0.2±0.02 [c]
Occipital MD	2.584E-03±1.483E-04	2.699E-03±3.660E-04	2.588E-03±1.512E-04	2.464E-03±2.689E-04	2.552E-03±1.054E-04	2.608E-03±1.820E-04	2.620E-03±2.078E-04
Females	*(N=99)*	*(N=18)*	*(N=96)*	*(N=11)*	*(N=40)*	*(N=33)*	*(N=44)*
Demographic factors							
Age_{v1}	48.3±8.7 [b]	43.5±11.8 [b]	48.1±8.81 [b]	43.2±13.6 [b]	47.7±9.3	49.4±8.8	46.07±9.8
Race, % AA	37.4 [b]	66.7 [b]	41.2	54.6	32.5 [c]	33.3 [c]	56.8 [c]
% above poverty	61.6	55.6	63.5	54.6	60.0	63.6	59.1
RDW (v_1)							
CV (%)	13.8±1.3 [b]	16.5±3 [b]	14±1.5 [b]	16.1±3.2 [b]	12.8±.38 [c]	13.7±.22 [c]	16±2 [c]
Median	-13.7	17.1	13.7	14	12.8	13.7	15.2
IQR	13;14.3	13.7;18.3	13;14.5	13.6;19.7	12.6;13.1	13.5;13.9	14.4;17.5
dMRI measures	*(N=99)*	*(N=18)*	*(N=96)*	*(N=11)*	*(N=40)*	*(N=33)*	*(N=44)*
dMRI, Analysis A							
Mean FA	+0.3±0.02	+0.3±0.01	+0.3±0.02	+0.3±0.01	+0.3±0.01	+0.3±0.02	+0.3±0.01
Mean MD	2.519E-03±1.609E-04	2.495E-03±1.067E-04	2.517E-03±1.615E-04	2.482E-03±1.171E-04	2.534E-03±2.085E-04	2.513E-03±1.117E-04	2.499E-03±1.200E-04
dMRI, Analysis B							

Left Brain							
Frontal FA	+0.24±0.02	+0.24±0.01	+0.24±0.02	+0.24±0.01	+0.24±0.02	+0.23±0.02	+0.23±0.01
Frontal MD	2.357E-03±1.176E-04	2.353E-03±1.403E-04	2.352E-03±1.166E-04	2.347E-03±1.655E-04	2.363E-03±1.182E-04	2.358E-03±1.357E-04	2.348E-03±1.131E-04
Temporal FA	+0.24±0.02	+0.24±0.01	+0.24±0.02	+0.24±0.01	+0.24±0.02	+0.24±0.02	+0.24±0.01
Temporal MD	2.406E-03±1.528E-04	2.406E-03±9.290E-05	2.402E-03±1.508E-04	2.421E-03±9.880E-05	2.430E-03±2.062E-04	2.396E-03±9.390E-05	2.391E-03±1.034E-04
Parietal FA	+0.23±0.02	+0.23±0.01	+0.23±0.02	+0.23±0.01	+0.23±0.02	+0.23±0.02	+0.23±0.01
Parietal MD	2.604E-03±1.859E-04	2.581E-03±1.462E-04	2.598E-03±1.868E-04	2.601E-03±1.608E-04	2.617E-03±2.151E-04	2.583E-03±1.468E-04	2.599E-03±1.701E-04
Occipital FA	+0.2±0.01	+0.21±0.02	+0.2±0.02	+0.21±0.01	+0.21±0.02	+0.2±0.02	+0.21±0.01
Occipital MD	2.451E-03±1.586E-04	2.458E-03±8.890E-05	2.453E-03±1.590E-04	2.425E-03±7.940E-05	2.481E-03±1.930E-04	2.422E-03±1.075E-04	2.448E-03±1.288E-04
Right Brain							
Frontal FA	+0.24±0.02	+0.24±0.01	+0.24±0.01	+0.24±0.01	+0.24±0.01	+0.23±0.02	+0.24±0.01
Frontal MD	2.336E-03±1.263E-04	2.322E-03±1.130E-04	2.333E-03±1.254E-04	2.308E-03±1.283E-04	2.357E-03±1.505E-04	2.329E-03±1.050E-04	2.317E-03±1.091E-04
Temporal FA	+0.25±0.02	+0.25±0.01	+0.25±0.02	+0.25±0.01	+0.25±0.02	+0.25±0.02	+0.25±0.01
Temporal MD	2.325E-03±1.538E-04	2.318E-03±9.790E-05	2.319E-03±1.489E-04	2.328E-03±1.065E-04	2.341E-03±2.033E-04	2.324E-03±1.141E-04	2.309E-03±9.990E-05
Parietal FA	+0.23±0.02	+0.23±0.02	+0.23±0.02	+0.23±0.02	+0.23±0.01	+0.23±0.02	+0.23±0.02
Parietal MD	2.649E-03±1.976E-04	2.618E-03±1.379E-04	2.637E-03±1.931E-04	2.623E-03±1.529E-04	2.671E-03±2.195E-04	2.611E-03±1.524E-04	2.644E-03±1.854E-04
Occipital FA	+0.21±0.01	+0.21±0.01	+0.21±0.01	+0.21±0.01	+0.21±0.02	+0.2±0.01	+0.21±0.01
Occipital MD	2.526E-03±1.872E-04	2.526E-03±9.090E-05	2.522E-03±1.827E-04	2.538E-03±1.003E-04	2.556E-03±2.411E-04	2.498E-03±1.137E-04	2.519E-03±1.389E-04

Abbreviations: Age_{v1}=age measured at HANDLS visit 1 (2004-2009); CV=Coefficient of Variation; dMRI=Diffusion Magnetic Resonance Imaging; δRDW=Red Cell Distribution Width annualized change between visits 1 and 2; FA=Fractional Anisotropy; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; HANDLS-SCAN=Brain magnetic resonance imaging scan ancillary study of HANDLS; IQR=Interquartile range (25^{th}-75^{th} percentile); MD=Mean Diffusivity; RDW=Red Cell Distribution Width; T1-T3=tertiles; v_1=visit 1 of HANDLS (2004-2009); v_2=visit 2 of HANDLS (2009-2013); v_{scan}=HANDLS-SCAN visit (2011-2015).

[a] Values are Mean±SD, or %. For RDW, medians and inter-quartile ranges (IQR) were also provided. Volumes are expressed in mm^3 for hippocampal volumes and white matter lesion volume and cm^3 otherwise. MD is measured in mm^2/sec.

[b] P<0.05 for null hypothesis of no difference between anemic or non-anemic, t-test; [c] P<0.05 for null hypothesis of no trend across tertiles of RDW.

Table S3. RDW analyses (Cont'd): Hematological measures and other covariate-adjusted associations from analyses A (global FA/MD), B (regional FA/MD) vs. visit 1 RDW (overall and stratified by sex): ordinary least square analyses; HANDLS 2004-2009 and HANDLS-SCAN 2011-2015: Sensitivity analyses[a]

	Model 3		*Model 4*		*Model 5*		*Model 6*	
Total sample (N=214)	*β*	*(SE)*	*β*	*(SE)*	*β*	*(SE)*	*β*	*(SE)*
dMRI, Analysis A								
Mean FA	-0.0013072	(0.0010711)	-0.0011523	(0.0010678)	-0.001326	(0.001088)	-0.0010872	(0.0010995)
Mean MD	+1.27e-06	(9.57e-06)	+2.55e-06	(9.69e-06)	+4.00e-06	(9.58e-06)	+2.53e-06	(9.75e-06)
Males (N=97)								
dMRI, Analysis A								
Mean FA	-0.0061189	(0.0024086)[d,f]	-0.0068095	(0.0024779)[e,f]	-0.0064143	(0.0025614)[d,f]	-0.0053811	(0.0025583)[d,f]
Mean MD	+0.0000417	(0.0000211)[c,f]	+0.0000498	(0.0000217)[d,f]	+0.0000367	(0.0000222)	+0.0000389	(0.0000224)[c,f]
dMRI, Analysis B								
Left Brain								
Frontal FA	-0.0064265	(0.0022481)[e,f]	-0.007076	(0.0022551)[e,f]	-0.0066959	(0.0023443)[e,f]	-0.0059463	(0.0023719)[d,f]
Frontal MD	+0.000031	(0.0000207)[f]	+0.0000393	(0.0000215)[c,f]	+0.0000326	(0.0000225)[f]	+0.0000289	(0.0000222)[f]
Temporal FA	-0.0039687	(0.002306)[c,f]	-0.0043248	(0.0023592)[c,f]	-0.003822	(0.0024024)[f]	-0.0026346	(0.0023733)
Temporal MD	+0.0000186	(0.0000202)	+0.0000229	(0.0000204)	8.13e-06	(0.0000206)	9.98e-06	(0.0000209)
Parietal FA	-0.0069908	(0.0021851)[e,f]	-0.0078526	(0.002206)[e,f]	-0.0072938	(0.0023132)[e,f]	-0.0060713	(0.0022953)[d,f]
Parietal MD	+0.0000576	(0.0000258)[d]	+0.0000657	(0.0000265)[d]	+0.0000524	(0.0000269)[c]	+0.0000549	(0.0000269)[d]
Occipital FA	-0.0054071	(0.0019033)[e,f]	-0.0059088	(0.002073)[e,f]	-0.0050007	(0.0020933)[d,f]	-0.0045708	(0.0021247)[d,f]
Occipital MD	+0.0000602	(0.0000213)[e,f]	+0.0000642	(0.000022)[e,f]	+0.0000478	(0.0000212)[d]	+0.0000584	(0.0000226)[d,f]
Right Brain								
Frontal FA	-0.0059632	(0.0021011)[e,f]	-0.0068167	(0.0021735)[e,f]	-0.0067503	(0.0022576)[e,f]	-0.0054727	(0.0022344)[d,f]
Frontal MD	+0.000026	(0.0000181)[f]	+0.0000345	(0.0000191)[c,f]	0.0000314	(0.0000197)[f]	+0.0000249	(0.0000199)[f]
Temporal FA	-0.0051441	(0.0023779)[d,f]	-0.0057939	(0.0024318)[e,f]	-0.0051369	(0.0024906)[d,f]	-0.0047414	(0.0025071)[c,f]
Temporal MD	+0.0000305	(0.0000173)	+0.0000368	(0.0000174)[d]	+0.0000333	(0.0000185)[c]	+0.0000302	(0.000018)
Parietal FA	-0.0082193	(0.0024504)[e,f]	-0.0089263	(0.0025193)[e,f]	-0.0082897	(0.0026023)[e,f]	-0.0080125	(0.0026049)[e,f]

Parietal MD	+0.0000658	(0.0000282)[d]	+0.0000736	(0.0000294)[d]	+0.0000602	(0.0000298)[d]	+0.0000697	(0.0000296)d
Occipital FA	-0.0073574	(0.0022346)[e,f]	-0.0079766	(0.0023243)[e,f]	-0.0073366	(0.0023859)[e,f]	-0.0070161	(0.0024197)[e,f]
Occipital MD	+0.0000595	(0.0000221)[e]	+0.0000671	(0.000023)[e,f]	+0.0000524	(0.0000226)[d]	+0.000057	(0.0000236)[d,f]
Females (N=117)								
dMRI, Analysis A								
Mean FA	-0.0007666	(0.0012518)	-0.0001301	(0.0012146)	-0.0001499	(0.0012589)	-0.0004769	(0.0012667)
Mean MD	-7.83e-06	(0.0000115)	-9.25e-06	(0.0000114)	-5.93e-06	(0.0000115)	-4.92e-06	(0.0000113)

Abbreviations: Age_{v1}=age measured at HANDLS visit 1 (2004-2009); B-12=serum cobalamin; CV=Coefficient of Variation; dMRI=Diffusion Magnetic Resonance Imaging; ESR=Erythrocyte Sedimentation Rate; FA=Fractional Anisotropy; FDR=False Discovery Rate; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; HANDLS-SCAN=Brain magnetic resonance imaging scan ancillary study of HANDLS; HDL=High Density Lipoprotein; MCH=Mean Cell Hemoglobin; MD=Mean Diffusivity; RDW=Red Cell Distribution Width; SA=Sensitivity Analysis; SE=Standard Error; v_1=visit 1 of HANDLS (2004-2009); v_2=visit 2 of HANDLS (2009-2013); v_{scan}=HANDLS-SCAN visit (2011-2015); WRAT=Wide Range Achievement Test.

a Values are adjusted linear regression coefficients β with associated SE. (N) is the sample size in each analysis. Model 2 in Table 3 was adjusted for age, sex, race, poverty status and time of follow-up between visit 1 and v_{scan} and selected hematological measures [i.e Hb + other hematological measures (MCH, Serum iron, ESR)]. MD is measured in mm^2/sec.

[b] Model 3 is a sensitivity analysis further adjusting Model 2 (Table 3) for selected nutritional/dietary factors (Healthy Eating Index-2010 total score, B-12, folate); Model 4 is a sensitivity analysis further adjusting Model 2 (Table 3) for selected inflammatory markers (high sensitivity C-reactive protein, albumin, White blood cells); Model 5 is a sensitivity analysis further adjusting Model 2 (Table 3) for selected adiposity and metabolic disturbance factors (Waist circumference, cholesterol, Cholesterol:HDL ratio, Triglycerides, Creatinine); Model 6 is a sensitivity analysis further adjusting Model 2 (Table 3) for other selected covariates (education, WRAT, smoking).

[c] P<0.10 [d] P<0.05 [e] P<0.010 for null hypothesis that exposure main effect is =0 in each model, stratified or unstratified.

[f] P<0.10 for null hypothesis that exposure×sex 2-way interaction term is =0 in the unstratified model with exposure and sex included as main effects.

Table S4. δRDW analyses: Minimally and hematological measure adjusted associations from analyses A (global FA/MD), B (Regional cortical FA/MD, Left/Right) vs. δRDW (overall and stratified by sex; and among non-anemic participants): ordinary least square analyses; HANDLS 2004-2009 and HANDLS-SCAN 2011-2015[a]

	***Model 1**: Minimally adjusted*					***Model 2**: Hematological measure-adjusted, sensitivity analysis (SA)[b]*			
Total sample (N=214)	*β*	*(SE)*	*b*	*P*	*q-value*	*β*	*(SE)*	*P*	*Interaction of* δRDW *by sex*
dMRI, Analysis A									
Mean FA	+0.0021	(0.016)	+0.088	0.18	__	+0.020	(0.016)	0.21	__
Mean MD	-0.000011	(0.0014)	+0.004	0.94	__	7.87e-06	(0.00014)	0.96	__
Males (N=97)									
dMRI, Analysis A									
Mean FA	+0.027	(0.036)	+0.08	0.45	__	+0.009	(0.038)	0.81	0.79
Mean MD	-0.00007	(0.00031)	-0.02	0.83	__	+0.0001	(0.0003)	0.75	0.67
Females (N=117)									
dMRI, Analysis A									
Mean FA	+0.021	(0.018)	+0.11	0.23	__	+0.023	(0.017)	0.19	__
Mean MD	+4.12e-06	(0.0002)	+0.002	0.97	__	-3.83E-06	(0.00016)	0.98	__
Non-Anemic (N=182)									
dMRI, Analysis A									
Mean FA	+0.018	(0.016)	+0.078	0.28	__	+0.012	(0.0017)	0.51	__
Mean MD	+0.00002	(0.0002)	+0.009	0.89	__	+0.0001	(0.0002)	0.68	__

Abbreviations: Age_{v1}=age measured at HANDLS visit 1 (2004-2009); CV=Coefficient of Variation; dMRI=Diffusion Magnetic Resonance Imaging; ESR=Erythrocyte Sedimentation Rate; FA=Fractional Anisotropy; FDR=False Discovery Rate; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; HANDLS-SCAN=Brain magnetic resonance imaging scan ancillary study of HANDLS; MCH=Mean Cell Hemoglobin; MD=Mean Diffusivity; RDW=Red Cell Distribution Width; SA=Sensitivity Analysis; SE=Standard Error; v_1=visit 1 of HANDLS (2004-2009); v_2=visit 2 of HANDLS (2009-2013); v_{scan}=HANDLS-SCAN visit (2011-2015).

a Values are adjusted linear regression coefficients β with associated SE, standardized beta, uncorrected p-values, corrected q-values (false discovery rate) and results of sensitivity analysis. (N) is the sample size in each analysis. Standardized betas for δRDW are computed as SD in outcome per SD in δRDW. Q-values presented only for uncorrected P-values<0.05 for model 1. Model 1 was adjusted for age, sex, race, poverty status and time of follow-up between visit 1 and v_{scan}.

[b] Model 2 is a sensitivity analysis further adjusting Model 1 for selected hematological measures [i.e Hb + other hematological measures (MCH, Serum iron, ESR)] after screening using machine learning techniques (See Supplemental methods 3). MD is measured in mm^2/sec.

[c] P<0.10 for null hypothesis that exposure×sex 2-way interaction term is =0 in the unstratified model with exposure and sex included as main effects.