Insulin resistance among obese middle-aged is associated with decreased cerebrovascular reactivity

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ABSTRACT

Objective: To evaluate differences in cerebrovascular reactivity (CVR) to mild hypercapnia in obese/overweight individuals with and without insulin resistance (IR) compared to comparable lean controls.

Methods: A total of 60 cognitively normal participants (20 lean controls and 24 obese/overweight individuals with and 16 without IR) were evaluated using a high spatial resolution arterial spin labeling MRI technique at rest and during mild hypercapnia. We analyzed group differences in CVR in cerebral cortex and ascertained the relationships between CVR, IR, and body mass index (BMI).

Results: Obese/overweight participants with and without IR had significantly lower CVR to hypercapnia than lean controls after controlling for age, sex, and the presence of hypertension ($F_{2,53}$ = 5.578, p = 0.006 η_p^2 = 0.174). In the obese/overweight participants with IR, there was a significant correlation between higher CVR and a measure of insulin sensitivity, even after accounting for BMI (r_p = 0.575, p = 0.004). In contrast, there was no relationship between CVR and BMI when controlling for IR. No such relationships existed for the other 2 groups.

Conclusions: IR is associated with impaired CVR; the relationship appears to be driven by the degree of IR and not by obesity. These rarely reported results suggest that early forms of cerebrovascular dysfunction exist among obese middle-aged individuals with significant IR but without type 2 diabetes mellitus. These functional vascular abnormalities may help explain the associations among IR, diabetes, and dementia, and suggest that interventions aiming to improve IR or CVR may help prevent cognitive decline later in life. ***Neurology*® 2017;89:249–255**

GLOSSARY

AD = Alzheimer disease; **ASL** = arterial spin labeling; **BMI** = body mass index; **bSSFP** = balanced steady-state free precession; **CVR** = cerebrovascular reactivity; **FAIR** = flow-sensitive alternating inversion recovery; **GM** = gray matter; **HbA1c** = hemoglobin A1c; **IR** = insulin resistance; **LC** = lean controls without insulin resistance; **MetS** = metabolic syndrome; **ObIR** = individuals with overweight/obesity and insulin resistance; **ObNIR** = individuals with overweight/obesity but no insulin resistance; **T2DM** = type 2 diabetes mellitus; **WM** = white matter.

Endothelial dysfunction has been well-described in type 2 diabetes mellitus (T2DM) and insulin resistance (IR).[1–6] The effect of IR or T2DM on cerebrovascular reactivity (CVR) is important but less studied. Although cognitive and other brain abnormalities are associated with the metabolic syndrome (MetS) and T2DM,[7–9] there are limited data on the mechanisms for those associations. We have proposed that these associations are partly due to impairments in CVR, which may impair the ability to maintain an optimal neuronal environment during periods of neuronal activation, potentially leading to damage to vulnerable brain regions over time.[10–12] Such mechanisms may be important and help explain some of the associations between metabolic disease and dementia.[13,14]

Impaired CVR has been reported in adults with T2DM by measuring blood velocity in the middle cerebral artery using transcranial Doppler, as well as with direct measures of tissue perfusion such as arterial spin labeling (ASL) MRI.[6,15–17] The literature on CVR in adults with IR without diabetes is much less consistent. Studies have found reduced CVR[18,19] or no differences

Supplemental data at Neurology.org

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Table Participant characteristics and arterial spin labeling hemodynamic measures

	Lean control (n = 20), mean ± SD	Overweight/obese, non-IR (n = 16), mean ± SD	Overweight/obese, IR (n = 24), mean ± SD	p Value
Demographics and glycemic measures				
Age, y	53.27 ± 4.27	50.69 ± 3.15	51.83 ± 4.87	0.20
Education, y	16.08 ± 2.49	15.75 ± 2.35	15.63 ± 2.12	0.81
Sex, F/M	14/6	8/8	9/15	0.10
Black/white/Asian/Hispanic/others	5/11/1/3/0	7/6/1/2/0	8/11/0/2/3	0.45
Hypertension[a]	2	2	8	0.11
Systolic BP, mm Hg[b,c]	113.38 ± 9.74	116.09 ± 10.93	124.42 ± 9.50	0.001[e]
Fasting glucose, mg/dL[b]	86.70 ± 9.65	89.06 ± 5.62	92.00 ± 6.78	0.08
Fasting insulin, μIU/mL[b,c]	29.98 ± 8.82	38.45 ± 11.56	92.53 ± 35.08	<0.001[e]
HbA1c, %	5.54 ± 0.28	5.58 ± 0.30	5.70 ± 0.46	0.33
BMI, kg/m^2[b,d]	21.99 ± 1.91	30.21 ± 4.45	34.87 ± 6.41	<0.001[e]
QUICKI[b,d]	0.393 ± 0.024	0.376 ± 0.025	0.328 ± 0.016	<0.001[e]
ASL hemodynamic parameters				
CVR, % change per mm Hg CO_2[b,d]	3.31 ± 1.64	1.80 ± 1.47	2.37 ± 1.98	<0.01[e]
Respiratory rate, breaths/min				
Baseline[b]	11.50 ± 3.05	12.47 ± 3.27	13.88 ± 3.66	0.07
Rebreathing	12.20 ± 3.16	13.93 ± 4.03	14.13 ± 4.04	0.21
Heart rate, beats/min				
Baseline	66.55 ± 8.91	67.81 ± 11.65	72.67 ± 11.03	0.14
Rebreathing	69.20 ± 7.97	68.50 ± 9.79	74.00 ± 12.24	0.18
O_2 saturation, %				
Baseline	96.85 ± 1.50	96.56 ± 1.46	96.25 ± 1.65	0.45
Rebreathing	96.10 ± 1.80	95.44 ± 1.93	95.13 ± 1.70	0.20
End-tidal PCO_2, mm Hg				
Baseline	42.10 ± 3.70	41.87 ± 2.75	42.83 ± 3.96	0.67
Rebreathing	47.40 ± 3.65	47.40 ± 3.18	48.04 ± 3.38	0.78
Delta, baseline to rebreathing	5.30 ± 1.30	5.53 ± 2.26	5.21 ± 1.86	0.86

Abbreviations: ASL = arterial spin labeling; BMI = body mass index; BP = blood pressure; CVR = cerebrovascular reactivity; HbA1c = hemoglobin A1c; IR = insulin resistance; LC = lean controls without insulin resistance.
[a] Number of participants with a diagnosis of hypertension.
[b] Significant difference between LC and IR groups.
[c] Significant difference between non-IR and IR groups.
[d] Significant difference between LC and non-IR groups.
[e] Statistically significant at $p < 0.05$.

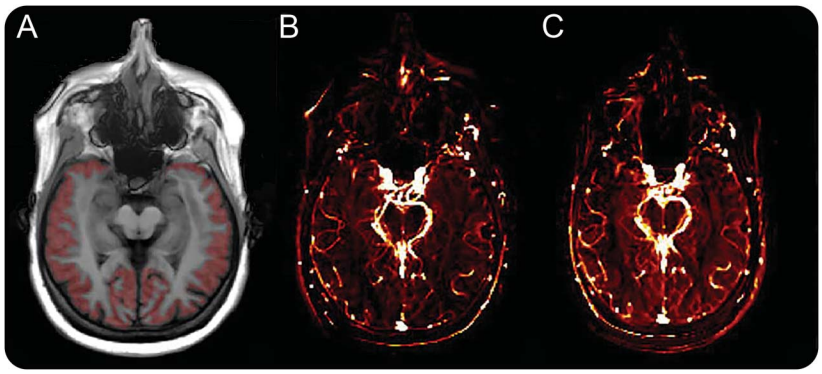
between control individuals and those with MetS.[20] Although several studies have reported reduced resting cortical blood flow using ASL-MRI[21,22] or SPECT[23] methods, no studies have looked at CVR in obese insulin-resistant individuals without MetS or T2DM.

We hypothesized that individuals with IR, but not MetS or T2DM, would have compromised cerebrovascular reactivity in response to a mild hypercapnic stimulus when compared to lean control individuals without insulin resistance. Further, we also sought to ascertain the association between cortical CVR and insulin function, after accounting for potential confounds.

METHODS

Participants. As part of an NIH-sponsored study of the effects of T2DM, IR, and obesity on the brain, we evaluated 3 groups of individuals. Forty individuals with obesity and T2DM, 40 with obesity but not T2DM, and 40 lean control individuals were evaluated. In this report, we include only those in the 2 groups without T2DM, since the effect of T2DM on CVR is well-described in the literature. There was no access to the CVR evaluation during a period of time and 11 participants did not receive it, resulting in 69 participants reported here. Sixty-nine middle-aged adults (40–60 years of age) without T2DM were evaluated. Individuals studied were respondents to web

Figure 1 Tissue perfusion images for one participant



(A) Gray matter region of interest (red) used to calculate blood flow, (B) tissue perfusion map generated in the baseline condition, (C) tissue perfusion map generated in the challenge condition.

advertisements ("job" ads on Craigslist) or were referred by people familiar with the project. All participants had at minimum a high school education. Exclusion criteria included history of head trauma, a family history of early-onset Alzheimer disease (AD), extensive cardiovascular disease, history of alcohol, drug abuse, or other significant psychiatric condition, history or signs of neurologic disease on physical examination, poorly controlled hypertension, pulmonary or hematologic conditions, or any other condition that would interfere with MRI acquisition. Participants were defined as obese if their body mass index (BMI) was greater than 30 kg/m^2, overweight if their BMI was between 25 and 30 kg/m^2, and lean if their BMI was less than 25 kg/m^2. IR was estimated from the quantitative insulin sensitivity check index (QUICKI = 1/[Log10 (fasting insulin) + Log10 (fasting glucose)])[24]; participants were considered to be insulin-resistant if they had a QUICKI less than or equal to 0.35.

Of the 69 participants evaluated, 9 were excluded from this study because they could not tolerate the MRI procedure (1), had unusable images due to movement (6), or had IR despite being lean (2). Participants were divided into 3 groups: 20 lean controls without IR (LC), 16 individuals with overweight/obesity but no IR (ObNIR), and 24 individuals with overweight/obesity and IR (ObIR).

Due to the narrow age range for study inclusion (45–60 years), and careful attention to balancing sex and racial distribution of participants during initial recruitment, the final groups after the exclusions mentioned above did not differ significantly on age, sex, race, or years of education. However, given that age, sex, and presence of hypertension are associated with measures of CVR, we controlled for those variables in all analyses. The table includes detailed group demographics.

Standard protocol approvals, registrations, and patient consents. This study was approved by the NYU Langone Medical Center Institutional Review Board. All participants were recruited from the community and gave informed written consent to participate.

Evaluations. Evaluations collected medical data and acquired MRI scans of the brain. All participants underwent a full physical examination and complete bloodwork, including fasting insulin and glucose levels, lipid panel, and hemoglobin A1c (HbA1c).

MRI and procedure for increasing end-tidal CO_2. We used an ASL-MRI technique that measures regional blood flow in brain parenchyma with high spatial resolution and high tissue contrast to ascertain CVR in response to a mild (5–7 mm Hg) hypercapnic challenge. The advantage of this method is that the measure of cortical tissue CVR is less contaminated by the contribution of large blood vessels, white matter (WM), or CSF spaces.

All MRI data were acquired on the same 3T Siemens (Erlangen, Germany) Tim Trio MRI system, using a 12-element head coil for signal reception. ASL measurements utilized a flow-sensitive alternating inversion recovery (FAIR) technique with a balanced steady-state free precession (bSSFP) readout and spatial resolution sufficient to resolve small blood vessels (1.2 × 1.2 mm^2 in-plane and 8 mm slice thickness). FAIR, a type of pulsed ASL, acquires 2 inversion recovery images, one with a slice-selective inversion pulse (generates "labeled image") and one with a nonselective inversion pulse (generates the "control image"). The slice-selective inversion pulse is applied in a thin slab encompassing the imaging slice, and the inversion time is chosen so that blood proximal to the inversion slab will have time to flow into the imaging slice and perfuse the tissue. When the control image is subtracted from the labeled image, signal from static spins in the tissue will cancel out, leaving only signal from water in the blood that has flowed into the imaging slice and perfused the tissue. The difference image generates a map of tissue perfusion. In our implementation, an inversion time of 1,200 ms was allowed for blood to flow into the imaging slice and perfuse the tissue, and a repetition time of 3 seconds between successive inversion pulses was allowed for partial recovery of the magnetization towards equilibrium. Forty-eight repetitions were run, alternating between nonselective and slice-selective inversions, with the first 4 excluded from the analysis to eliminate transient effects. The flip angle was 50° for the bSSFP readout and the acquisition time was 2.24 minutes per slice. Imaging was performed in a baseline condition and after increased end-tidal CO_2 (challenge condition), utilizing the rebreathing technique described below.

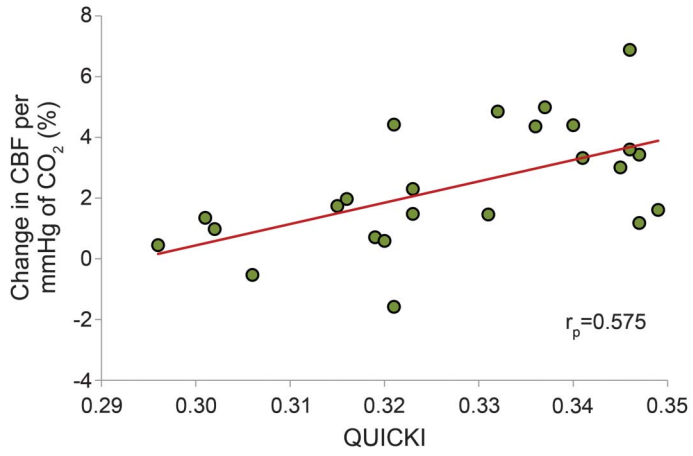
In order to increase end-tidal CO_2 5–7 mm Hg above baseline, participants breathed room air through an open-end tube with an internal diameter of 1.5 in (3.81 cm) attached to a snorkel-like mouthpiece, with the nose clipped to prevent nasal breathing. The length of the hose was individually adjusted to have a volume equivalent to 50% of the forced expiratory volume in the first second of expiration and based on the age, height, and sex of the participant. Individuals were trained on the apparatus outside of the MRI machine. Heart rate, respiratory rate, oxygen saturation, and end-tidal CO_2 were monitored throughout by means of a capnometer monitor (Novametrix Capnogard, Wallingford, CT). The CO_2 monitor was calibrated at each session.

Evaluation of cerebral vascular reactivity. To compute CO_2-based CVR, baseline and challenge ASL images were converted to quantitative perfusion images. WM method was used to correct for imperfect inversion profile, as previously described.[22,25] Sample tissue perfusion maps can be seen in figure 1, B and C.

Blood flow within the gray matter (GM) mask was then calculated for each condition, excluding voxels with blood flow values less than 10 mL/100 g/min, so as to remove nonparenchymal GM brain regions, and greater than 125 mL/100 g/min to eliminate blood vessels. CVR was then calculated as the percent change in average GM blood flow from baseline to challenge condition divided by the change in end-tidal CO_2 from baseline to challenge.

Statistical analyses. SPSS version 20 (IBM Corporation, Armonk, NY) was used for all analyses. Group differences for continuous variables were evaluated using univariate analysis of

Figure 2 Partial correlation between QUICKI (insulin sensitivity) and cerebrovascular reactivity (residualized to age, sex, and hypertension) and controlling for body mass index for obese/overweight participants with insulin resistance



Raw values are shown on the axes and the correlation coefficient (*r*) value presented is for the partial correlation. CBF = cerebral blood flow.

variance and followed up by Fisher least significant difference test. Chi-square tests were used for categorical variables. To control for influences of age, sex, and presence of hypertension (0 for no and 1 for yes), all of which have been shown to affect cerebral blood flow,[22,26] analysis of covariance was performed adjusting for age, sex, and hypertension to evaluate differences in CVR between the LC, obese/overweight without IR and obese/overweight with IR groups. Partial correlations were performed to assess the relationship between CVR, BMI, and QUICKI. All correlational analyses were performed using CVR residualized for age, sex, and presence of hypertension, in order to control for those variables and their effect on CVR without having to have multiple covariates in the analyses. Effect sizes were estimated using partial η^2 (η_p^2), utilizing cutoffs for small, medium, and large effect sizes as defined by Cohen.[27] Effect size was considered large if the η_p^2 was greater than 0.14, medium if the η_p^2 was 0.06, and small if the η_p^2 was less than 0.01.

RESULTS **Group differences on medical/endocrine data.** Demographic and laboratory characteristics are shown in the table. Groups were well-matched on age and did not differ on ethnicity distributions. There was a nonsignificant difference in sex distribution among the 3 groups ($p = 0.098$), therefore sex was controlled for in all analyses. Blood pressures were significantly higher in the IR participants relative to the 2 non-IR groups, but did not differ between the LC and ObNIR groups. Of the 24 IR participants, 8 carried a diagnosis of hypertension and 2 of the 8 were receiving antihypertensive medications. Two LC participants and 2 non-IR overweight/obese participants had diagnoses of hypertension; both of these 2 lean participants and neither overweight/obese non-IR with hypertension participants were taking antihypertensive medications. However, all 4 were coded as hypertensive when the presence of hypertension was controlled for in the analyses.

Hemodynamic parameters, including respiratory rate, pulse, O_2 saturation, and end-tidal CO_2, were monitored throughout the imaging protocol (see the bottom of the table). Groups did not differ in their pulse rate, O_2 saturation, or end-tidal CO_2 in either condition. Importantly, the 3 groups showed the same level of change in end-tidal CO_2 from baseline to challenge conditions.

Relationship of CVR to obesity and IR. Across all participants, and after controlling for age, sex, and the presence of hypertension, higher CVR was associated with QUICKI score ($r_p[57] = 0.279$, $p = 0.032$). That is, lower QUICKI scores (higher IR) were associated with reduced CVR. Also, across all participants and after controlling for age, sex, and the presence of hypertension, lower CVR was associated with higher BMI ($r_p[57] = -0.334$, $p = 0.01$). That is, increasing BMI was associated with reduced CVR. However, when we controlled for QUICKI score, this relationship was no longer significant. This pattern was different for the ObIR participants. After controlling for age, sex, and presence of hypertension, the ObIR group still had a very strong relationship between QUICK and CVR ($r_p[22] = 0.619$, $p = 0.001$). Furthermore, when we also adjusted for BMI in ascertaining the relationship between QUICKI and CVR, the relationship remained significant ($r_p[22] = 0.575$, $p = 0.004$; figure 2). The LC and ObNIR groups did not show any relationships between QUICKI and CVR.

Figure e-1 at Neurology.org shows the relationships between QUICKI and CVR for all 3 groups (lean, obese IR, and obese non-IR).

Group differences in CVR. There was a significant group effect on CVR with a large effect size after controlling for age, sex, and hypertension ($F_{2,53} = 5.578$, $p = 0.006$, $\eta_p^2 = 0.174$). This group effect was unchanged controlling for systolic blood pressure (instead of hypertension), for smoking or medications (antihypertensives or statins), for reported degree of physical activity, and for glucose or HbA1c levels. Post hoc least significant difference testing revealed that CVR in the LC group was significantly higher than in overweight/obese non-IR participants ($p = 0.003$) and overweight/obese IR participants ($p = 0.030$). However, there were no significant differences in reactivity between the 2 overweight/obese groups ($p = 0.262$).

Due to a routine software upgrade to the operating system of our Tim Trio (Siemens) scanner, we needed to slightly modify our ASL sequence and 9 participants were scanned under the modified sequence. In order to ensure that this did not influence our results, the analyses were repeated excluding those participants and they yielded the same statistical

conclusion; therefore the results presented here include all participants.

DISCUSSION It is becoming clear that the 2-fold increase in all-cause dementia among individuals with T2DM is not mediated by the classic neuritic plaques and neurofibrillary tangles that are characteristic of AD.[28–30] Discrepancies between a clinical diagnosis of AD and amyloid burden have also been found in the oldest-old.[31] Both findings suggest that a clinical diagnosis of dementia cannot be equated with presence of typical AD neuropathology, and that multiple underlying etiologies may be contributing to the clinical AD phenotype.[32] Therefore, our data demonstrating the effect of IR on cerebrovascular function among cognitively normal individuals carrying excess weight and having significant IR may shed light on the understanding of the association between metabolic disease, brain impairment, and risk for dementia, particularly taking into account how common IR is among the elderly.

Controlling for age, sex, and the presence of hypertension, we found that CVR was significantly lower (impaired) in obese individuals with and without IR when compared to insulin-sensitive lean individuals. Moreover, decreased insulin sensitivity was strongly associated with CVR among the ObIR (figure 2).

The well-characterized endothelial dysfunction that is seen systemically in T2DM has also been shown among individuals with MetS but without diabetes, in both microvascular and macrovascular beds.[33] The presence of endothelial dysfunction in the prediabetic state, combined with our and other groups' findings of cognitive and structural brain impairments in insulin resistance, obesity, and MetS,[34,35] raises the question as to whether these endothelial abnormalities may be involved in the mechanisms behind those brain impairments. The results suggest that IR is a key component of the MetS that is likely driving the impairments and may help explain the later associations with dementia.

In support of our proposed model linking endothelial dysfunction to cerebral damage over time in T2DM and IR, we found impairment in hypercapnia-induced CVR in overweight/obese individuals with IR. Our high-resolution ASL method allows for accurate separation of GM and WM and exclusion of large blood vessels in favor of tissue-based perfusion.[22] In order to evaluate whether obesity or IR may be driving the impairments in CVR, we performed correlations between CVR and QUICKI and BMI, while controlling for age, sex, and hypertension. We found that BMI was significantly associated with CVR when the entire study group was considered; however, this relationship was not significant when we controlled for IR in the analysis. Importantly and supporting our hypotheses, we found a significant relationship between CVR and IR among the overweight/obese IR group, which remained significant when controlling for BMI, suggesting that IR has a contribution to CVR above and beyond obesity. However, we found no relationship between QUICKI and CVR for the LC or ObNIR groups (figure e-1), leading us to speculate that given the physiologic importance of CVR it is conserved, and only with high degrees of IR is CVR reduced.

These results are in overall agreement with the findings using transcranial Doppler previously reported in obese individuals,[18] which also found significant relationships between vasomotor reactivity and insulin resistance. That study, however, was not able to show independence from BMI, likely due to major methodologic differences between the studies as well as differing analytical approaches.[18]

Limitations in the current study include the relatively small sample size, particularly of overweight/obese individuals without IR. IR is very common among 40- to 60-year-old individuals carrying excess weight; thus overweight/obese middle-aged individuals without IR are somewhat rare. However, even our relatively small numbers yielded significant results with large effect sizes. The nature of our high-resolution ASL technique, with an acquisition time of approximately 2.5 minutes per slice, makes it impractical to cover the entire brain. With that said, the findings of decreased CVR among obese individuals with IR are unlikely to be regional as there is no report that hypercapnia-based CVR varies from one cortical area to another. A strength of our approach is that unlike global ASL measures, which use a typical voxel size 3×3 mm, our spatial resolution of 1.2×1.2 mm provides superior separation of GM and WM. Avoidance of partial-volume WM is important because both perfusion and CVR are several times larger in GM than WM.

This study represents one of the few to investigate the relationship of IR and CVR in the presence of BMI. This suggests that the metabolic consequences of obesity (IR), and not obesity itself, are driving these relationships. In addition, in this report we evaluated cerebrovascular reactivity at the tissue level, using a method with excellent spatial resolution that allows exclusion of blood vessels and WM and minimizes partial volume effects. These data indicate that impairments in CVR, classically associated with T2DM, precede the onset of diabetes and are associated with the degree of IR. These rarely previously reported findings, albeit somewhat preliminary given our relatively modest numbers of participants, will inform future animal studies necessary to understand the underlying mechanisms. Further, given the clear

links between physical fitness and insulin sensitivity, these findings could also be used to counsel individuals carrying excess weight on the importance of improving their insulin function via lifestyle modifications. It may be helpful to assess if insulin-sensitizing interventions, lifestyle modifications, or treatment are effective in improving CVR and whether they lead to maintaining brain integrity and preventing age-associated cognitive decline.

AUTHOR CONTRIBUTIONS

Olivia Frosch processed imaging data, conducted statistical analyses, and drafted the manuscript. Po Lai Yau processed imaging data, conducted statistical analyses, and drafted the manuscript. Ricardo Osorio interpreted data and edited the manuscript. Henry Rusinek developed the CVR method utilized, interpreted data, and edited the manuscript. Pippa Storey developed the imaging sequence utilized for the CVR measurement and edited the manuscript. Antonio Convit designed the study and obtained funding, supervised acquisition of the data and the statistical analyses, interpreted the data, and edited the manuscript. All authors had final approval of the manuscript.

STUDY FUNDING

Study funded by DK064087, DK 083537, and HL 118624, and supported in part by grant 1UL1RR029893 from the National Center for Research Resources.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received July 12, 2016. Accepted in final form April 14, 2017.

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This Week's *Neurology*® Podcast

Diagnosis of DWI-negative acute ischemic stroke: A meta-analysis **(see p. 256)**

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the July 18, 2017, issue of *Neurology*. In the first segment, Dr. Kevin Barrett talks with Dr. Brian Edlow about his paper on the diagnosis of DWI-negative acute ischemic stroke. In the second part of the podcast, Dr. Stacey Clardy focuses her interview with Dr. Emmanuelle Waubant on MS therapeutics and pediatric MS patients.

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