Alzheimer disease (AD) is characterized by progressive hypometabolism on [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scans. Peripheral insulin resistance (IR) increases AD risk. No studies have examined associations between FDG metabolism and IR in mild cognitive impairment (MCI) and AD, as well as MCI conversion to AD. We studied 26 cognitively normal (CN), 194 MCI (39 MCI-progressors, 148 MCI-stable, 2 years after baseline), and 60 AD subjects with baseline FDG-PET from the Alzheimer’s Disease Neuroimaging Initiative. Mean FDG metabolism was derived for AD-vulnerable regions of interest (ROIs), including lateral parietal and posteromedial cortices, medial temporal lobe (MTL), hippocampus, and ventral prefrontal cortices (vPFC), as well as postcentral gyrus and global cerebrum control regions. The homeostasis model assessment of IR (HOMA-IR) was used to measure IR. For AD, higher HOMA-IR predicted lower FDG in all ROIs. For MCI-progressors, higher HOMA-IR predicted higher FDG in the MTL and hippocampus. Control regions showed no associations. Higher HOMA-IR predicted hypometabolism in MCI-progressors and hypermetabolism in AD in medial temporal regions. Future longitudinal studies should examine the pathophysiologic significance of the shift from MTL hyper- to hypometabolism associated with IR.

Type 2 diabetes is a risk factor for Alzheimer disease (AD) (1,2). Peripheral insulin resistance (IR), broadly defined as reduced cellular response to insulin (3), also increases AD risk even without hyperglycemia (4). In certain brain regions with a high density of insulin receptors, insulin normally facilitates glucose metabolism (5). Interestingly, AD-related pathology and atrophy preferentially target these same temporal, prefrontal, and posteromedial parietal areas (6). In AD, these regions show disruption of insulin signaling (7), and the degree of disruption in at least the hippocampus is related to worse antemortem cognition (8). Furthermore, peripheral IR is associated with atrophy in these regions in aged rhesus macaques (9) and humans (10,11). The pathogenic significance of IR in AD is further highlighted by a recent study that showed brain IR preceding development of clinical AD (12).

Progressive brain hypometabolism is a hallmark of AD (13). Glucose metabolism is often assessed using [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET). Lower FDG metabolism corresponds to declines in memory, executive function, and global cognition in mild cognitive impairment (MCI) and AD (14–16). There is preliminary evidence that IR inhibits glucose metabolism in AD-sensitive brain regions. For example, in euglycemic, healthy men with somatostatin-suppressed insulin secretion, insulin infusion stimulates regional metabolism in the prefrontal cortex (PFC), an effect that is diminished in men with IR (17). Among cognitively normal (CN), aged participants with hyperglycemia, higher peripheral IR corresponds to lower resting FDG metabolism in parietal, ventral PFC, and medial temporal lobe (MTL) areas, which
are particularly vulnerable to AD pathology (18). In addition, intranasal insulin treatment in patients with MCI and early AD improves memory performance and maintains glucose metabolism in similar frontal, posteromedial, and temporal areas (14).

To date, no systematic study has been conducted of the association between peripheral IR and FDG metabolism in AD-vulnerable regions across the spectrum of CN older adults, patients with MCI who later progressed to AD or remained stable, or in those with early AD. To this end, we used Alzheimer’s Disease Neuroimaging Initiative (ADNI) data to calculate the homeostatic model assessment of IR (HOMA-IR), an index of peripheral IR. We also derived FDG metabolism in AD-sensitive regions of interest (ROIs), including ventral PFC (vPFC), MTL, hippocampus, lateral parietal cortex, postcentral gyrus and global cerebrum control regions, and studied their associations with HOMA-IR. Finally, we investigated if HOMA-IR and FDG associations remained stable when enriching MCI and AD cohorts for amyloid-positivity.

**RESEARCH DESIGN AND METHODS**

**Participants**

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the U.S. Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neurological assessment can be combined to measure the progression of MCI and early AD. The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco.

The following baseline data were available for 26 CN, 194 MCI, and 60 AD participants:

1. demographic/anthropometric measures including age, sex, education, and BMI;
2. FDG-PET scans;
3. regional gray matter (GM) volumes;
4. fasting insulin and glucose;
5. apolipoprotein E (ApoE) ε4 genotype;
6. neuropsychological performance measures; and
7. clinical diagnosis at baseline and at month 24, as well as confirmation of MCI conversion by the ADNI Conversion Committee.

Data for cerebrospinal fluid or amyloid PET scans on 227 of 280 participants were also downloaded for a supplementary analysis (Supplementary Data). Participants were clinically diagnosed at the screening and each subsequent visit based on standardized criteria (19).

Participants with MCI at baseline who remained stable by 24 months were categorized as MCI-S (n = 148) versus participants who progressed to AD and were categorized as MCI-P (n = 39). To determine MCI conversion, MCI participants were seen at 0, 6, 12, 24, and 36 months and assessed for cognitive and general function. Briefly, for an MCI participant who met criteria for probable AD on a given visit, the site physician provided diagnostic data to the ADNI Conversion Committee, which reached a consensus regarding conversion. Probable AD was in part defined as 1) a Clinical Dementia Rating of 0.5 or 1.0; 2) abnormal, education-adjusted memory function on the Logical Memory II subscale; 3) Mini-Mental State Examination (MMSE) inclusive of 20–26; and 4) having met probable AD criteria defined by National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association. We refer readers to the ADNI1 procedural manual for further details (http://adni.loni.usc.edu/).

**Standard Protocol Approvals, Registrations, and Patient Consents**

Written informed consent was obtained from all ADNI participants at their respective ADNI sites. The ADNI protocol was approved by site-specific institutional review boards.

**Insulin, Glucose, and HOMA-IR**

As described in the ADNI1 protocol manual (http://adni.loni.usc.edu/), baseline blood samples were collected from subjects after overnight fasting. Insulin was assayed from plasma using a multiplex array (Human Discovery Map; Rules-Based Medicine, Austin, TX). The least detectable dose was 0.6 μU/mL. Glucose was assayed as part of routine blood work. HOMA-IR (20) and the quantitative insulin sensitivity check index (QUICKI) (21) were calculated from insulin and glucose values from the baseline visit. Baseline samples were collected within 14 days from baseline FDG-PET. Willette et al. (22) found that HOMA-IR is stable across at least 4 years in overweight, late middle-aged humans; therefore, our index of HOMA-IR very likely reflects IR at the time of the scan. Morris et al. (23) also used baseline glucose and insulin data in ADNI to compute QUICKI and determine glycemic groups for use in cognitive and imaging analyses. Participants were defined as hyperglycemic rather than euglycemic if their fasting blood glucose levels were 100 mg/dL or greater (American Diabetes Association criterion) or were taking medication or insulin to control type 2 diabetes.

**Cognition and Clinical Stage Measures**

Table 1 indicates values for the MMSE, AD assessment scale-cognitive subscale, the clinical dementia rating-sum of boxes, and previously derived ADNI factor scores for executive function (24) and memory (25).

**MRI**

Regional GM volumes were used to account for the potential effects of regional atrophy in FDG analyses, because expanding sulci in MCI and AD brains may lead to
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underestimation of FDG values (26). Mean regional GM corresponding to each ROI was downloaded from a hierarchical parcellation MRI data set made available in ADNI from Davatzikos and colleagues (27,28). This data set consisted of 264 volumetric regions derived from preprocessed T1 images using techniques previously described (27,28).

FDG-PET

FDG-PET acquisition and preprocessing details have been described elsewhere (29). Briefly, $^{[18}F$-FDG (185 MBq) was injected intravenously. After approximately 30 min, six 5-min frames were acquired. Each frame of a given baseline image series was coregistered to the first acquired frame. The image series was aggregated into a dynamic image set. The image set was then averaged, reoriented to a standard $160 \times 160 \times 96$ voxel spatial matrix of resliced 1.5 mm$^3$ voxels, intensity normalized, and smoothed with an 8-mm full width at half maximum kernel. We then normalized FDG-PET pixel intensity to the pons, due to its preserved glucose metabolism in AD (30), to derive the standardized uptake value ratio. This step removes interindividual variability in tracer metabolism. Images were spatially normalized to Montreal Neurological Institute space using an existing template in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/).

Five bilateral ROIs (Supplementary Fig. 1) were defined using the Wake Forest PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas). ROIs were selected based on previous studies examining progressive hypometabolism across the temporal progression of AD (31,32) or areas where glucose metabolism has been associated with IR (18). These ROIs included hippocampus, MTL, lateral parietal, posteromedial (precuneus and posterior cingulate cortex), and vPFC. Two control regions were also examined: 1) global cerebrum, to assess the possibility of IR affecting glucose metabolism in a diffuse and regionally nonspecific manner; and 2) postcentral gyrus, because it is not vulnerable to AD pathology and its glucose metabolism does not appear to be affected by IR (18).

ApoE ε4 Genotype

The ADNI Biomarker Core at the University of Pennsylvania conducted ApoE genotyping. We characterized participants as being “non-ApoE ε4” (i.e., zero ApoE ε4 alleles) or “ApoE ε4” (i.e., one to two ApoE ε4 alleles).

| Table 1—Sample demographic, cognitive, and metabolic indices |
|-----------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Index                       | CN   n=26      | MCI* n=194     | AD n=60        | P value      | MCI-S n=148    | MCI-P n=39     | P value      |
| Age (years)                 | 75.69±5.68 | 75.17±7.29     | 75.25±7.26     | 0.943        | 75.26±7.10     | 75.83±7.22     | 0.671        |
| Education (years)           | 15.34±3.15 | 15.77±2.90     | 14.80±3.45     | 0.096        | 15.69±2.96     | 15.92±2.75     | 0.678        |
| Sex                         | Male 11 | Female 15      |                |              | 132           |                |              |
| ApoE ε4 genotype            | ε4+   | 23             |                | <0.001       | 73            |                | 0.039        |
|                            | ε4*   | 3              |                |              | 103           |                |              |
| CDR-sob                     | 0.06±0.16 | 1.53±0.80     | 4.32±1.54      | <0.001       | 1.55±0.82     | 1.61±0.92      | 0.712        |
| MMSE                        | 28.73±1.43 | 27.18±1.69     | 23.90±1.92     | <0.001       | 27.26±1.68     | 26.64±1.57     | 0.047        |
| ADAS-cog (11-item)          | 7.11±3.01 | 10.75±4.08     | 18.32±6.12     | <0.001       | 10.55±3.81     | 12.94±4.16     | 0.001        |
| Memory factor               | 0.53±0.53 | 0.02±0.70      | -1.00±0.72     | <0.001       | 0.04±0.66     | -0.32±0.69    | 0.004        |
| Executive function factor   | 0.77±0.44 | -0.03±0.57     | -0.85±0.49     | <0.001       | -0.02±0.53     | -0.33±0.45    | 0.001        |
| BMI (kg/m²)                 | 26.76±3.48 | 26.30±3.93     | 26.08±3.38     | 0.761        | 26.33±3.91     | 25.79±3.56     | 0.454        |
| Insulin (μU/mL)             | 2.98±3.10 | 2.78±3.08      | 2.41±1.46      | 0.589        | 2.66±2.68     | 3.34±4.49     | 0.245        |
| Glucose (mg/dL)             | 104.68±30.17 | 101.18±20.36   | 100.59±20.88   | 0.718        | 100.44±19.15   | 98.56±18.11   | 0.593        |
| QUICKI                      | 0.45±0.09 | 0.44±0.06      | 0.45±0.08      | 0.387        | 0.44±0.06     | 0.44±0.07     | 0.705        |
| HOMA-IR                     | 0.87±1.10 | 0.71±0.84      | 0.60±0.40      | 0.270        | -0.30±0.31     | -0.26±0.37    | 0.538        |

Data are shown as n or as mean ± SD. Boldface values indicate statistical significance. ADAS-cog, Alzheimer Disease Assessment Scale–cognitive subscale; CDR-sob, Clinical Dementia Rating–sum of boxes. *The 194 MCI participants were classified as MCI-S (n = 148), MCI-P (n = 39), or CN (n = 7) according to the 24-month visit.
standardized uptake value ratio for a given ROI. All models included the following covariates: age at baseline, sex, education, hyperglycemia status, ApoE ε4 genotype, and mean regional GM within the ROI examined. Exploratory analyses that also included BMI did not influence results (data not shown). We examined the main effect of baseline diagnosis or MCI conversion, anticipating a step-wise decrease in FDG-PET from CN to MCI to AD, and from MCI-S to MCI-P (33). We also examined the fixed effects of HOMA-IR and the interaction of HOMA-IR × baseline diagnosis or HOMA-IR × MCI conversion to assess whether HOMA-IR was differentially associated with glucose metabolism in CN versus MCI versus AD, or MCI-S versus MCI-P. Similar analyses were done with QUICKI and yielded nearly identical results (data not shown). We addressed type 1 error by using Holm-Bonferroni correction (34) for all analyses. This closed test procedure maintains a family-wise α = 0.05 by requiring unadjusted P values of 0.05 divided by x, x being the number of null hypotheses tested. For example, when testing five ROIs, a P value of 0.010 is needed among one of the tested ROIs for the test to achieve significance, followed by 0.013, 0.017, 0.025, and 0.050. For significant interactions, we performed follow-up analyses for each baseline diagnosis or MCI conversion group (35) to assess whether a significant linear association existed between HOMA-IR and FDG metabolism in one or more groups.

RESULTS

Demographics, Cognition, and IR Biomarkers
Diagnostic groups did not differ by age, sex, or education (Table 1). As expected, cognitive scores were lower and the proportion of non-ApoE ε4 versus ApoE ε4 increased from CN to MCI to AD participants as well as from MCI-S to MCI-P in a step-wise manner (data not shown). No significant differences were found for insulin, glucose, BMI, HOMA-IR, or QUICKI.

ROI Analysis: Differences in FDG Metabolism by Clinical Diagnosis and MCI Conversion
For each of the five ROIs and two control regions, separate mixed models were used to test effects of baseline diagnosis (CN, MCI, AD) or MCI conversion (MCI-S, MCI-P). Supplementary Table 1 reports lower FDG metabolism in a step-wise manner from CN to MCI to AD for global cerebrum, lateral parietal, posteromedial parietal, and hippocampus ROIs. Ventral PFC and MTL showed lower FDG metabolism for MCI versus CN and AD versus CN, but not AD versus MCI. No differences in FDG-PET metabolism were found for MCI-P versus MCI-S. No differences were noted for postcentral gyrus. Supplementary Fig. 2 illustrates the step-wise differences for MTL as an example. These results suggest that this ADNI subcohort shows the typical progressive hypometabolism from CN, to MCI, to AD (31–33).

ROI Analysis: HOMA-IR and FDG Metabolism Associations
The following analyses were conducted in the cohort (n = 280). Supplementary Text 1 describes a supplemental analysis among 227 participants, where MCI and AD groups were enriched for amyloid-positive status. All results for the amyloid-positive analysis are similar to findings described below.

MTL and Hippocampus
For hippocampus but not MTL, the HOMA-IR main effect surpassed Holm-Bonferroni correction (Supplementary Table 1). Significant HOMA-IR × baseline diagnosis interactions were seen for both hippocampus and MTL (Table 2). Figure 1 illustrates that higher HOMA-IR corresponded to less MTL FDG metabolism for AD, whereas no significant relationships were seen for CN or MCI. Among MCI participants, the main effect of HOMA-IR was nonsignificant (Supplementary Table 1), but there was a significant HOMA-IR × MCI conversion interaction (Table 2). Follow-up analyses indicated that higher HOMA-IR predicted more FDG metabolism in MCI-P and had no significant association with MCI-S (Fig. 2 depicts MTL results). Therefore, higher HOMA-IR predicted less FDG metabolism in the MTL and hippocampus among AD participants but higher FDG for MCI participants who progressed to AD by 24 months.

vPFC
Among all participants, the main effect of HOMA-IR was not significant (Supplementary Table 1), but there was a significant HOMA-IR × baseline diagnosis interaction (Table 2). As shown in Supplementary Fig. 3, higher IR predicted less PFC FDG metabolism only in AD patients, whereas no significant associations were seen for CN or MCI. Among MCI participants, the main effect of HOMA-IR was nonsignificant (Supplementary Table 1), but there was a significant HOMA-IR × MCI conversion interaction (Table 2). Follow-up analyses indicated that higher HOMA-IR was associated with lower FDG metabolism for MCI-S but had no significant association for MCI-P (Supplementary Fig. 4). Importantly, this pattern differed from temporal regions, where higher HOMA-IR predicted hypermetabolism for MCI-P and had no significant relationship for MCI-S. Among AD participants, by contrast, higher HOMA-IR predicted lower FDG metabolism in the prefrontal and temporal areas.

Lateral Parietal and Posteromedial Cortices
Results were similar for lateral parietal and posteromedial ROIs. Among all participants, the main effects of HOMA-IR were nonsignificant (Supplementary Table 1), but the HOMA-IR × baseline diagnosis interactions were significant (Table 2). Higher IR again predicted lower FDG metabolism in the lateral and posteromedial parietal regions for AD, whereas associations for CN or MCI were nonsignificant. Among MCI participants, the main effects of HOMA-IR (Supplementary Table 1) and the
HOMA-IR baseline diagnosis interactions (Table 2) were nonsignificant.

Control Regions: Global Cerebrum and Postcentral Gyrus

No significant main effects or interactions were noted for HOMA-IR or HOMA-IR baseline diagnosis for either control area (Table 2 and Supplementary Table 1). Among MCI conversion interactions (Table 2) were nonsignificant.

MCI conversion groups (Table 2) were nonsignificant.

Table 2—Interaction effects of diagnosis and HOMA-IR on ROI FDG metabolism

| Region                  | F-value | P-value | F-value | P-value | F-value | P-value | F-value | P-value |
|------------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| Postcentral gyrus      | 2.545   | 0.112   | 0.308   | 0.580   | 0.202   |         |         |         |
| Global cerebrum        | 2.572   | 0.110   | 2.984   | 0.086   |         |         |         |         |
| Lateral parietal       | 6.351   | 0.012   | 0.795   | 0.374   | 0.148   |         |         |         |
| Precuneus + PCC        | 6.846   | 0.009   | 0.660   | 0.418   | 0.094   |         |         |         |
| Hippocampus            | 5.857   | 0.016   | 6.419   | 0.012   | 0.073   |         |         |         |
| MTL                     | 4.834   | 0.029   | 8.087   | 0.005   | 0.052   |         |         |         |
| VPFC                    | 5.052   | 0.025   | 5.856   | 0.017   | 0.135   |         |         |         |

HOMA-IR baseline diagnosis interactions (Table 2) were nonsignificant.
participants, the HOMA-IR main effects and HOMA-IR × MCI conversion interactions were also nonsignificant.

**DISCUSSION**

In this study, we examined the relationships among peripheral IR, baseline diagnosis or MCI conversion, and mean FDG metabolism within several ROIs targeted by AD and two control regions.

Our ADNI subsample was typical in showing progressive hypometabolism from CN to MCI to AD (31–33). Clinical groups did not show differences in HOMA-IR. However, significant interactions were found between the baseline diagnosis and HOMA-IR in all ROIs as well as interactions between MCI conversion and HOMA-IR for temporal and frontal areas. These results suggest that IR may be differentially associated with FDG metabolism depending on disease status. No HOMA-IR associations were found for the global cerebrum or postcentral gyrus control regions. Higher HOMA-IR predicted less FDG metabolism in all temporal, parietal, and frontal areas for AD participants, whereas associations were nonsignificant for CN or MCI participants. Baker et al. (18) similarly found that higher HOMA-IR predicts less FDG metabolism in these areas in hyperglycemic, CN elderly individuals. Intranasal insulin therapy maintains FDG metabolism over time in these regions in MCI and early AD patients (14). The association of IR with glucose metabolism in these ROIs is further validated by findings that postprandial hyperglycemia (36) or somatostatin-suppressed subphysiologic insulin infusion (17) also modulate FDG metabolism in these regions.

Three findings were of particular interest: First, in MCI-P participants, higher HOMA-IR predicted hypermetabolism in the hippocampus and MTL. Second, in MCI-S participants, higher HOMA-IR predicted vPFC hypometabolism. Third, in AD participants, higher HOMA-IR was associated with hypometabolism in hippocampus and MTL as well as the other ROIs. Collectively, these findings suggest that during the MCI stage, HOMA-IR is differentially associated with either hypo- or hypermetabolism in different brain areas, depending on whether participants progress to develop clinical AD. We depict these differential associations in Fig. 3. Regionally specific patterns of hypo- and hypermetabolism or hypo- and hyperactivation (with FDG-PET and functional MRI, respectively) have been seen in populations at risk for AD and have been implicated in the transition to clinical AD. Hyperactivation and increased functional connectivity of the hippocampus and MTL has been proposed as an early compensatory response to the presence of amyloid in default mode network regions (37–39). Middle-aged, predated individuals with Down syndrome, who are at high risk for AD, also show relative MTL hypermetabolism (40), as do aged individuals with subjective memory impairment (41). In addition, higher mean amyloid deposition in the precuneus corresponds to hypermetabolism in MCI and hypometabolism in AD in frontal and parietocipital areas (42), suggesting that this hyperactivation is transient and gives way to hypoactivation in AD.

Previous studies have also shown positive associations between measures related to IR and brain indices, such as volume, in MCI/early AD and aged monkeys. Higher insulin area under the curve from a glucose tolerance test, which reflects higher IR, predicts better cognitive performance and more hippocampal volume cross-sectionally (43) and longitudinally (44) in MCI/early AD. Similarly, in aged rhesus macaques not on long-term calorie restriction, less insulin sensitivity is related to higher hippocampal volume (9). The underlying mechanism behind these IR associations with volume and FDG metabolism in the MTL in MCI/early AD is currently unclear. Hyperinsulinemia, a feature of IR, is related to higher insulin concentrations in the brain (45). Higher brain insulin concentrations may reduce amyloid oligomerization and toxicity (46), increase synaptogenesis (47), or modulate long-term potentiation and depression in the hippocampus to improve learning and memory (45). These phenomena may be the basis of a compensatory effect of IR at some transient stage during AD pathogenesis. Also unclear is whether IR directly affects FDG through changes in glucose metabolism or indirectly. Talbot et al. (8) found that physiologic and supraphysiologic insulin administration in CN and AD postmortem hippocampal tissue did not affect glucose metabolism. Yet, insulin infusion in somatostatin-suppressed men (17) or intranasal insulin in MCI and AD both affected MTL FDG metabolism (14). Alternatively, a potential indirect mechanism underlying IR and FDG associations may be differences in regional amyloid deposition. Higher amyloid in the precuneus, as
measured by Pittsburgh Compound B, corresponds to hypermetabolism in MCI and hypometabolism in AD (42).

As a limitation, our sample size for CN was small, and thus, the lack of associations for this group should be interpreted with caution. Our most intriguing finding was the positive relationship of HOMA-IR with MTL and hippocampus FDG in MCI-P, in line with the findings of higher resting state activity or FDG metabolism in MTL (37–42) as well as higher IR and higher hippocampal volume in MCI/early AD participants and aged rhesus monkeys (9,43,44). Our findings further motivate ongoing therapeutic efforts for treating AD by targeting peripheral and/or central IR, including the on-going clinical trials of exenatide (NCT01255163) and intranasal insulin (NCT01767909), and support their rationale of recruiting subjects at the stage of MCI when IR may be exercising different effects from those seen in AD. Completion of these and future trials will ultimately test whether targeting IR is a viable strategy for AD therapeutics.

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The data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report.

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Author Contributions. A.A.W. conceptualized and designed the study, analyzed and interpreted the data, and wrote and revised the manuscript for intellectual content. N.M. collected and interpreted the data and revised the manuscript for intellectual content. D.K. conceptualized and designed the study, analyzed and interpreted the data, and revised the manuscript for intellectual content. D.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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