Obesity and Oxidative Stress in Older Adults At Risk for Dementia

A Magnetic Resonance Spectroscopy Study

Ashlee Turner, MBMSc,*†‡ Camilla Hoyos, PhD,*†‡ § Loren Mowszowski, DPsych,*† Haley La Monica, PhD,*||
Jim Lagopoulos, PhD,¶ Marilena M. DeMayo, PhD,*##
Catriona Ireland, FRACP,* Ian B. Hickie, FRANZCP,*||
Sharon L. Naismith, DPsych,*† and Shantel L. Duffy, PhD*‡

Objective: This study aimed to investigate the relationship between obesity and oxidative stress in older adults at risk for dementia. It also aimed to explore the influence of physical activity on the relationship between obesity and oxidative stress in this at risk cohort.

Methods: Older adults at risk for dementia underwent comprehensive medical, neuropsychological, and psychiatric assessment. At risk was defined as participants with subjective or mild cognitive impairment. Glutathione was assessed by magnetic resonance spectroscopy in the left hippocampus and the anterior and posterior cingulate cortex. Body mass index (BMI) was calculated and classified as healthy (BMI <25 kg/m²) or overweight/obese (BMI ≥25 kg/m²).

Results: Sixty-five older adults (mean age = 66.2 y) were included for analysis. The overweight/obese group had significantly greater glutathione in the hippocampus compared with the healthy weight group (t = −2.76, P = 0.008). No significant difference in glutathione was observed between groups in the anterior or posterior cingulate. In the overweight/obese group, a higher BMI was associated with a diabetes diagnosis and lower total time engaging in physical activity (r = −0.36, P = 0.025), however, glutathione did not correlate with activity levels across groups.

Conclusion: This study demonstrates that changes in in vivo markers of oxidative stress are present in overweight/obese older adults at risk for dementia. Future research should explore the relationship with diabetes and the longitudinal relationship between BMI and oxidative stress, and response to therapeutic interventions.

Key Words: cognitive decline, dementia, glutathione, proton magnetic resonance spectroscopy, obesity, BMI

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Dementia affects an estimated 47 million people worldwide.1 The lack of effective disease-modifying therapies has shifted the research focus in recent years to early identification and modification of risk factors early in the disease course to prevent or slow cognitive decline. Increasing evidence suggests that the neuropathological changes underpinning neurodegenerative disorders may be evident 10 to 20 years before symptom onset.2 In this regard, the cognitive decline associated with dementia occurs on a continuum, such that individuals presenting with both subjective [subjective cognitive impairment (SCI)] and objective cognitive deficits [mild cognitive impairment (MCI)] are considered at risk for dementia over time. Indeed, studies suggest that up to 50% of those with MCI will progress to dementia within 5 years.3 Importantly, epidemiological research has now firmly established that key modifiable risk factors, including physical inactivity, midlife hypertension, obesity, diabetes, and smoking, account for up to 35% of dementia cases worldwide, with other risk factors such as depression, hearing loss, and social isolation linked to dementia in later life.4 This research and its findings highlight the importance of identifying these at risk groups as a key target for developing and administering early interventions aimed at modifying dementia disease trajectory. Independent of other risk factors, obesity accounts for ~20% of the disease burden associated with dementia.5 Importantly, it is also associated with an increase in diseases that have been implicated in neurodegeneration, including insulin resistance, which is central in the development of type 2 diabetes, and cardiovascular disease.6 As a condition
characterized by a chronic state of low-grade inflammation, obesity is also associated with a perpetual state of oxidative stress.7 Oxidative stress occurs when the endogenous antioxidant system is overwhelmed by reactive oxygen species (ROS) production.8 In normal conditions, inflammation is a protective mechanism that facilitates the healing process by restoring cells to their normal state.9 Upon activation, immune cells secrete proinflammatory cytokines that activate the production of ROS. During this response, macrophages play a crucial role in generating ROS to continue the inflammatory response until pathogens that have caused the inflammatory activation are eliminated and the cells are repaired. However, chronic inflammation can lead to overproduction of ROS, which causes damage and death to cells through oxidative stress.10 Oxidative stress and inflammation are thought to have a synergistic effect on one another, where increased release of proinflammatory cytokines increases ROS production through the activation of microglia, and ROS production promotes the release of proinflammatory cytokines by dysregulating the production of adipocytokines.7 Importantly, oxidative stress has been implicated in the pathophysiology of various types of dementia including Alzheimer’s disease (AD) and vascular dementia.11 In AD specifically, it has been linked to the accumulation of both beta-amyloid and hyperphosphorylated tau in the brain, both of which are neuropathological features of AD, and also occur as a result of the activation of these proteins.12 The link between oxidative stress and dementia is unsurprising because of the highly vulnerable nature of the brain to excessive ROS production and oxidative damage owing to the high rate of oxygen consumption, high energy demands, and the relatively limited endogenous antioxidant capacity.13

The majority of research to date has measured oxidative stress using peripheral markers, however, proton magnetic resonance spectroscopy (1H-MRS) allows for the measurement of oxidative stress, specifically glutathione (GSH), in biologically active brain tissue.14 GSH is the brain’s primary antioxidant, and is responsible for the detoxification of ROS.8 Studies have shown that people with AD have reduced concentrations of GSH in the brain, supporting the hypothesis that oxidative stress is implicated in neurodegenerative processes.15 Altered GSH states have also been observed in individuals at risk for full threshold disorders, including first-episode psychosis,16 MCI,17 and older adults at risk for depression.18 Our team has previously demonstrated increased GSH in individuals with MCI and older adults at risk for depression, with GSH associated with cognitive functioning and depressive symptoms.17,18 Of particular significance, we have also shown that GSH can be directly modulated through omega-3 supplementation, suggesting that the oxidative stress response may be a therapeutic target.19 Together, these findings suggest that changes in the oxidative system are evident even in the early stages of disease progression, and may represent an important target for early intervention strategies.17

In this regard, physical activity may be a potent intervention to optimize antioxidant capacity in older adults. A plethora of epidemiological and clinical evidence suggests that physical activity and exercise promote brain health and reduce dementia risk.20 Importantly, this benefit may be intimately linked to the role of exercise in increasing energy utilization efficiency and improving the body’s capacity to manage ROS overproduction. Although acute, and in particular high intensity, bouts of physical activity are associated with an increase in ROS production and oxidative stress, regular physical activity is associated with improved antioxidant capacity and lower markers of lipid peroxidation across the lifespan.21 Indeed, evidence indicates that similar total antioxidant capacity and lipid peroxidation levels are evident in elderly individuals and sedentary young adults, suggesting that physical activity may modulate age-associated changes in oxidative stress.22

The aim of this study was to investigate the relationship between obesity and oxidative stress in older adults at risk for dementia. The secondary aim of this study was to investigate whether physical activity mediated the relationship between obesity and oxidative stress in this at risk group.

METHOD

Participants

Participants at risk for dementia were recruited between October 2010 and August 2016 from the Healthy Brain Ageing Clinic at the Brain and Mind Centre, Sydney, Australia. The clinic is a specialized early diagnosis and intervention research clinic for older adults with new-onset (ie, within the last 5 y) subjective mood or cognitive complaints. For the present study, at risk was defined as those seeking help for assessment or intervention for cognitive decline, including those with SCI or MCI. Exclusion criteria included age younger than 50 years at the time of testing, a diagnosis of dementia, history of neurological disease or nonaffective psychiatric illness (eg, psychosis), head injury (including loss of consciousness > 30 min), other medical conditions known to affect cognition (eg, cancer, stroke), or medical contraindications to magnetic resonance imaging. This study was approved by the University of Sydney Human Research Ethics Committee (Approval #2012/1873). All participants provided written informed consent before participation.

Clinical and Neuropsychological Assessment

All participants underwent a comprehensive neuropsychological, mood, and medical assessment. As detailed elsewhere,17 a clinical neuropsychologist administered a comprehensive standardized battery of tests chosen for their sensitivity to detect the cognitive deficits typical of MCI and dementia. MCI was diagnosed using Winblad’s criteria that requires evidence of at least 1.5 SD decline on ≥1 neuropsychological tests, relative to age- and education-adjusted normative data.23 All MCI diagnoses were consensus rated by 2 clinical neuropsychologists and a medical specialist (geriatrician and/or neurologist). Participants with subjective concerns but no evidence of objective cognitive impairment were characterized as SCI.

The medical assessment included a detailed medical and clinical history. BMI was calculated using height and weight measurements [weight in kg/height in m²] and was categorized as falling within the healthy (BMI <25) or overweight/obese (BMI ≥25) range. Medical burden was measured using the Cumulative Illness Rating Scale24 and the Mini-Mental Status Examination (MMSE)25 was administered for descriptive purposes to broadly characterize global cognition for this sample. Premorbid intellect was estimated using the Wechsler Test of Adult Reading.26 A semistructured clinical interview was administered to determine lifetime and any current depression diagnoses, and current use of antidepressant medication was recorded. Participants also completed the 15-item Geriatric Depression Scale (GDS-15) to measure subjective depressive symptomology.
Physical Activity Assessment

Subjective reports of physical activity were obtained using the Active Australia Survey, an 8-question survey used to assess participation in various types of activity in the past 7 days. Responses to these questions are used to calculate the total time spent doing physical activity (time spent walking + time spent doing moderate intensity + [2*time spent doing vigorous intensity]) and the total number of physical activity bouts (walking bouts + moderate intensity bouts + vigorous intensity bouts).

Proton Magnetic Resonance Spectroscopy

Imaging was conducted within 4 weeks of clinical assessment and took place at the Brain and Mind Centre on a 3-Tesla GE Discovery 750 scanner (GE Medical Systems, Milwaukee, WI) using an 8-channel phased array head coil. The following images were acquired in order: (i) 3-dimensional sagittal whole-brain scout for orientation and positioning of subsequent scans, (ii) T1-weighted magnetization-prepared rapid gradient echo sequence producing 196 sagittal slices (repetition time 7.2 ms; echo time 2.8 ms; flip angle, 10 degrees; matrix, 256×256; isotropic voxels, 0.9 mm) to aid in the anatomic localization of sampled voxels, and (iii) single-voxel 1H-MRS using point-resolved spectroscopy (PRESS) acquisition, with 2 chemical shift-selective imaging pulses for water suppression. Spectra were shimmed to achieve full-width at half maximum of <13 Hz.

Spectra were acquired separately from voxels placed over the left hippocampus, and midline in the anterior and posterior cingulate cortex (Fig. 1). A voxel measuring 10×15×30 mm was used for the left hippocampus and 20×20×20 mm for the anterior and posterior cingulate, using identical imaging parameters (repetition time, 2000 ms; echo time, 35 ms; and 128 averages). Anatomic localization of voxel placement was based on the Talairach brain atlas, and positioning was guided by the T1-weighted image. Because of time and funding constraints, not all regions of interest were acquired for all participants during their magnetic resonance imaging scan (anterior cingulate = 49, posterior cingulate = 22). In alignment with the key outcome data for the Healthy Brain Ageing Program, priority was given to the acquisition of structural and hippocampal spectroscopy data. As total scan session time was capped, in cases where it was deemed necessary to repeat a sequence (eg, because of excessive movement), or if the participant arrived late to their allotted scan time, the anterior and posterior cingulate spectroscopy sequences were omitted.

After 1H-MRS acquisition, data were transferred offline for postprocessing using the LCModel software package (Version 6.3-1M). All spectra were quantified using a PRESS echo time 35 ms basis set of 15 metabolites (including L-alanine, aspartate, creatine, phosphocreatine, y-aminobutyric acid, glucose, glutamine, glutamate, glycerophosphocholine, phosphocholine, GSH, myo-inositol, L-lactate, N-acetyl aspartate (NAA), N-acetylaspartylglutamate, scyllo-inositol, taurine) and incorporated macromolecule and baseline fitting routines. GSH and full-width half maximum outcomes were used for further analyses. For comparison with previous literature, NAA was also reported as a relative ratio to creatine (NAA/Cr). The spectra were visually inspected by 2 independent raters to ensure consistent spectra, and poorly fitted metabolite peaks, as reflected by a Cramer-Rao lower bounds exceeding 20%, were excluded from further analysis. From an imaging perspective, GSH is often resolved using edited pulse sequences such as MEGAPRESS (MEshcher-Garwood Point-RESolved Spectroscopy). However, GSH is also able to
be reliably resolved using an optimized PRESS sequence with higher order shimming.16,20 As described in detail elsewhere,17 to obtain the reference spectra used to determine GSH quantification, 6 phantom solutions containing varying concentrations of GSH were mixed with physiological brain concentrations of creatine, glutamate, glutamine, and phosphate. Absolute GSH concentration was determined using the ensuing reference spectral calibration curve (for additional detail, see our prior work30 32). The linear dependence of GSH was calculated as $R^2 = 0.994$.

For each MRS voxel, tissue segmentation was conducted using the Gannet toolbox CoRegStandAlone feature (version 3.1.5).33 This uses SPM1234 to segment the individual T1 anatomic images used for voxel placement, providing a proportion of gray matter, white matter, and cerebrospinal fluid (CSF) in each voxel. GSH and NAA values were corrected for CSF fraction (given no GSH is contained in CSF) within the voxel of interest (ie, observed value in the sample for absolute hippocampus GSH (n = 3) and anterior cingulate GSH concentrations (n = 5).

RESULTS

Participants
Sixty-five participants at risk for dementia were included in the analyses. Demographic characteristics are presented in Table 1. There were no significant differences between the healthy and overweight/obese BMI groups with regards to age, premorbid IQ, MMSE scores, type of presenting memory complaint (objective vs. subjective), GDS-15 score, medical burden, or smoking status. There were, however, more male individuals, a lower level of education overall, and a greater proportion of those reporting a diagnosis of type 2 diabetes in the overweight/obese group compared with the healthy weight group. In addition, those

| TABLE 1. Demographic, Clinical and Neuropsychological Characteristics of Participants and Mean Glutathione Levels in the Hippocampus, Anterior Cingulate, and Posterior Cingulate Cortex |
|----------------|----------------|----------------|----------------|
|                 | BMI <25 (N = 22) | BMI ≥ 25 (N = 43) | t Value | P       |
| Sex, % female  | 77.27 (17)       | 46.51 (22)       | 5.62†   | 0.018*  |
| Age, y          | 66.50 ± 8.93     | 65.91 ± 9.14     | 0.25    | 0.804   |
| Education, y    | 14.59 ± 3.19     | 13.02 ± 2.89     | 2.00    | 0.050*  |
| Cognitive diagnosis, % MCI | 81.81 (18)        | 88.37 (38)       | 0.52†   | 0.469   |
| MMSE score      | 28.55 ± 1.44     | 28.68 ± 1.62     | −0.33   | 0.740   |
| GDS-15 score    | 3.76 ± 3.24      | 4.35 ± 3.96      | −0.59   | 0.561   |
| WTAR, predicted IQ | 106.64 ± 9.59   | 104.41 ± 8.88    | 0.92    | 0.361   |
| CIRS score      | 3.71 ± 2.83      | 5.11 ± 3.06      | −1.72   | 0.091   |
| Type 2 diabetes, % positive | 0.00 (0)         | 22.50 (9)        | 5.79†   | 0.016*  |
| Hypertension, % positive | 36.36 (8)        | 55.00 (22)       | 1.97†   | 0.160   |
| Smoking status, % history | 50.00 (11)       | 62.50 (25)       | 0.91†   | 0.340   |
| Glutathione concentration‡ | | | | |
| Left hippocampus  | 1.12 ± 0.18     | 1.34 ± 0.54      | −2.76   | 0.010*  |
| Anterior cingulate cortex | 1.73 ± 0.36    | 1.86 ± 0.82      | −0.79   | 0.433   |
| Posterior cingulate cortex | 1.26 ± 0.27    | 1.25 ± 0.15      | 0.16    | 0.874   |
| N-acetyl aspartate/creatine ratio||| | |
| Left hippocampus  | 1.26 ± 0.13     | 1.28 ± 0.28      | −0.47   | 0.635   |
| Anterior cingulate cortex | 1.09 ± 0.46    | 0.94 ± 0.66      | 1.12    | 0.266   |
| Posterior cingulate cortex | 0.64 ± 0.79    | 0.52 ± 0.77      | 0.56    | 0.579   |
| Active Australia Survey||| | |
| Physical activity total time¶ | 772.10 ± 363.77 | 522.82 ± 444.42 | 2.16    | 0.036*  |
| Physical activity, total sessions¶ | 15.26 ± 8.18 | 9.58 ± 7.26 | 2.70    | 0.009*  |

Data are mean ± SD or percent (n).
†χ² statistic.
‡Glutathione is expressed as an absolute concentration.
§Statistics conducted on values corrected for CSF fraction. Because of missing data, the sample size for anterior cingulate with BMI <25 kg/m² is n = 19 and n = 30 with BMI >25 kg/m². For the posterior cingulate, the sample size with BMI <25 kg/m² is n = 8 and n = 14 with BMI >25 kg/m².
∥Total physical activity time was calculated as (time spent walking) + (2*time spent doing vigorous activity) + (time spent doing moderate activity) in a 7-day period.
¶Total physical activity sessions were calculated as (number of walking sessions) + (number of vigorous activity sessions) + (number of moderate activity sessions) in a 7-day period.
BMI indicates body mass index; CIRS, Cumulative Illness Rating Scale; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; WTAR, Wechsler Test of Adult Reading.
*P < 0.05.
TABLE 2. Correlations Between BMI and Demographic Data for Participants with a BMI $\geq 25$ kg/m$^2$

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Correlation Coefficient</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.043</td>
<td>0.785</td>
</tr>
<tr>
<td>Education, y</td>
<td>$-0.247$</td>
<td>0.115</td>
</tr>
<tr>
<td>MMSE</td>
<td>$-0.012$</td>
<td>0.940</td>
</tr>
<tr>
<td>GDS-15</td>
<td>0.139</td>
<td>0.392</td>
</tr>
<tr>
<td>Hippocampus glutathione</td>
<td>$-0.016$</td>
<td>0.918</td>
</tr>
<tr>
<td>Physical activity, total time</td>
<td>$-0.364$</td>
<td>0.025$^*$</td>
</tr>
<tr>
<td>Physical activity, total sessions</td>
<td>$-0.265$</td>
<td>0.099</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

$^*$p < 0.05. Statistics represent Pearson correlations.

with a BMI $\geq 25$ spent significantly less time engaging in and did fewer total sessions of physical activity compared with those with a BMI <25. Further, in those with a BMI $\geq 25$, a higher BMI was associated with a lower total time engaging in physical activity (Table 2).

Proton Magnetic Resonance Spectroscopy

There were no significant differences in age, years of education, MMSE, GDS, or BMI of those with anterior and posterior cingulate spectra versus those without. For the included MRS acquisitions the mean full-width half maximum calculated by LCModel was 0.066, 0.067, and 0.048 ppm for the hippocampal, anterior cingulate, and posterior cingulate voxels, respectively.

As shown in Table 1, participants with a BMI $\geq 25$ had elevated GSH levels in the hippocampus compared with participants with a BMI <25 (Fig. 2). There were also no between-group differences in gray ($t = -0.25, P = 0.804$) and white matter ($t = 1.46, P = 0.150$) tissue volume within the hippocampal voxel ($t = 0.396, P = 0.342$). Mean GSH Cramer-Rao lower bounds did not differ between normal BMI ($M = 14.9, SD = 3.3$) and overweight/obese ($M = 16.4, SD = 2.6$) groups ($t = -2.04, P = 0.068$). There were no significant differences in the ratio of hippocampus NAA/Cr.

To examine whether differences in GSH concentration between groups was because of the presence of type 2 diabetes, an analysis of covariance controlling for diabetes diagnosis was conducted. Between-group differences in GSH did not remain significant after controlling for the presence of diabetes ($F = 2.74, P = 0.103$). No significant differences in anterior or posterior cingulate GSH levels or NAA/Cr ratios were observed between the groups (Table 1). In those with a BMI $\geq 25$, there were no significant correlations between left hippocampus GSH and demographic variables or physical activity ($r < 0.080, P > 0.081$ for all analyses).

DISCUSSION

To our knowledge, this is the first study to investigate the relationships between obesity and in vivo markers of brain oxidative stress in a sample of older adults at risk for dementia. Despite no differences in markers of neuronal integrity (NAA/Cr) between groups, individuals with overweight or obesity had elevated levels of GSH in the left hippocampus, suggesting greater oxidative stress in this critical brain region. Elevated levels of GSH have been reported in previous studies of individuals with prodromal disorders, including individuals at risk for dementia and late-life depression,17,18 and individuals with first-episode psychosis who are at risk for schizophrenia.19 However, in contrast to previous work looking at prodromal groups,22,23 we found no significant differences in anterior and posterior cingulate GSH. Unsurprisingly, we found significant negative associations between obesity and frequency/engagement in physical activity, and obesity and education.

There was also a positive association between obesity and type 2 diabetes. These data are consistent with existing evidence suggesting that those with obesity engage in less physical activity.35 tend to live in lower socioeconomic status areas with lower levels of educational attainment,36 and are more likely to have multiple comorbid vascular risk factors including diabetes.37

Our finding of increased hippocampal GSH in the overweight/obese group is consistent with the early involvement of the hippocampus in cognitive decline. It is well established that the medial temporal lobe, particularly the hippocampus, is affected by accumulating AD pathology early in the disease course.38 In addition, neuroinflammation in the hippocampus because of hypoperfusion or hypoxia is evident in individuals with cerebrovascular disease.39 Interestingly, we observed no difference in GSH between groups in the anterior or posterior cingulate cortex, which seems to be in contrast to previous studies showing elevated GSH in these regions in other at risk cohorts.17,23 This discrepancy may be explained by the inclusion of a broader range of at risk participants, encompassing those with both subjective and objective cognitive impairments, without comparison with a control sample of healthy older adults. Thus, future work should investigate the associations between GSH, obesity, and physical activity in cognitively intact older adults.

There are a number of plausible mechanisms that may be driving the changes in GSH observed in this study. Consistent with previous research in at risk populations, increases in GSH in overweight/obese participants may be reflective of compensatory upregulation of GSH to counter increased oxidative stress in tissue. It is posited that after an initial compensatory response, there may be a decline in antioxidant availability, with lower concentrations of endogenous antioxidant markers seen in full threshold disorders.40 This highlights the potential for changes in the oxidative stress system having a predictive capacity for cognitive decline, further emphasizing the importance of identifying such at risk
groups for early intervention. Changes in GSH between groups may also represent a protective adaptation to physical activity where there is an increased ability to manage oxidative stress long term, despite increases in oxidative stress following acute bouts of physical activity.21 Alternatively, the differences observed in the present study may be reflective of differential responses from reduced and oxidized (GSSG) forms of GSH. Although previous research has shown that changes in the redox balance of GSH and increases in GSH/GSSG overall are apparent in those with obesity or diabetes, it is unclear whether these effects translate to changes in brain tissue because of the inability of GSH to cross the blood-brain barrier. Future research would benefit from delineating between changes in reduced GSH versus oxidized GSSG, and how these changes relate to oxidative stress and cognitive decline in at risk populations.

Given the increasing incidence of obesity in the population, it is essential to identify and implement appropriate lifestyle interventions to assist in controlling obesity and other inflammatory-related conditions. Although our findings revealed a significant association between BMI and physical activity, we did not show a direct correlation between physical activity and oxidative stress markers. However, physical activity is a key modifiable risk factor for dementia and an important contributor to the maintenance of a healthy weight, indicating its clinical importance. Regular physical activity reduces the risk of a number of diseases associated with inflammation, including obesity, type 2 diabetes, and cardiovascular disease. Importantly, this is consistent with our finding of an association between diabetes and oxidative stress in overweight/obese participants. Given the role of physical activity in type 2 diabetes prevention and management, it is possible that our observations in relation to physical activity are proxy markers for indicators of diabetes risk reduction or management, for example, improved insulin sensitivity or blood glucose control. Although beyond the scope of this study, diabetes is also an independent risk factor for dementia. This relationship warrants further investigation in future research. Moreover, maintaining a healthy lifestyle, by being physically active and consuming a diet rich in antioxidants, is associated with reduced cellular damage because of oxidative stress. The antioxidant effects of physical activity are apparent because of its ability to suppress leading sources of ROS and to upregulate the endogenous antioxidant system. Similarly, being active has also been shown to play a role in moderating inflammation by reducing the secretion of proinflammatory cytokines and increasing the secretion of adiponectin, even in the absence of effects on overall weight and adiposity levels.

This study has a number of limitations that need to be considered. First, both SCI and MCI as diagnostic entities are inherently heterogenous. It is possible that different pathologies underpin the cognitive profiles in this cohort, which may influence disease trajectory, and oxidative stress processes. Although heterogeneity increases representiveness and therefore generalizability of the present results to the broader population, future research should explore differences by clinical subtype. In addition, the cross-sectional nature of the analyses limits our capacity for making inferences about causal relationships between oxidative stress, obesity, and cognitive decline. As such, longitudinal investigations are needed to explore the causal links between these factors. We also acknowledge evidence suggesting that BMI has limited diagnostic accuracy for correctly identifying obesity. Although unfortunately unavailable in this study, future research should consider using objective measures of adiposity, such as waist circumference or DEXA body composition scanning, to increase the accuracy of obesity characterization. Given the association between obesity and incidence of type 2 diabetes, it is unsurprising that there was a greater proportion of participants with type 2 diabetes in the overweight/obese group. It is possible that the oxidative stress response is being driven by a combination of vascular risk factors; however, the current analyses did not allow for delineation of these risk factors and so further investigation is needed to unpack the relationship between oxidative stress and comorbid vascular risk factors. We also acknowledge that the LCModel metabolite fit for GSH contains both the reduced and oxidized forms of GSH. Although GSSG levels are usually below detectable limits using 1H-MRS, we are unable to differentiate between GSH and GSSG and therefore are unable to comment on how individual changes in reduced and oxidized GSH may be driving the results. Our sample included a larger proportion of male individuals in the overweight/obese group. Evidence has suggested that fat distribution varies with sex, thus it is possible that sex-based differences may account for the increased oxidative stress in the overweight/obese group. Finally, it is important to acknowledge that the majority of research to date has explored oxidative stress markers collected from peripheral blood samples or from brain tissue postmortem. However, the concordance between peripheral and central measures is contentious. Although this study is novel and has explored this relationship in vivo, in biologically active brain tissue, future research would benefit from the inclusion of both central and peripheral markers to explore the concordance between these outcomes.

In summary, this is the first known study to investigate the relationship between obesity and in vivo markers of oxidative stress in biologically active brain tissue in a cohort of older adults at risk for dementia. The results indicate that, in comparison with those in a healthy weight range, those with overweight or obesity had increased hippocampal GSH. Future research should now seek to explore the mechanisms underpinning the relationship identified in this study and examine the link between oxidative stress, cognitive function, and cardiovascular health in this cohort. This area would also benefit from longitudinal studies looking at changes in the oxidative stress response over time and rates of cognitive decline in those with obesity and deemed at risk for dementia, particularly in relation to lifestyle interventions that may significantly influence the oxidative stress system.

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