Evidence of association between obesity and lower cerebral myelin content in cognitively unimpaired adults

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Abstract

Background: Myelin loss is a central feature of several neurodegenerative diseases, including Alzheimer’s disease (AD). In animal studies, a link has been established between obesity and impairment of oligodendrocyte maturation, the cells that produce and maintain myelin. Although clinical magnetic resonance imaging (MRI) studies have revealed microstructural alterations of cerebral white matter tissue in subjects with obesity, no specific myelin vs. obesity correlation studies have been performed in humans using a direct myelin content metric.

Objectives: To assess the association between obesity and myelin integrity in cerebral white matter using advanced MRI methodology for myelin content imaging.

Methods: Studies were performed in the clinical unit of the National Institute on Aging on a cohort of 119 cognitively unimpaired adults. Using advanced MRI methodology, we measured whole-brain myelin water fraction (MWF), a marker of myelin content. Automated brain mapping algorithms and statistical models were used to evaluate the relationships between MWF and obesity, measured using the body mass index (BMI) or waist circumference (WC), in various white matter brain regions.

Results: MWF was negatively associated with BMI or WC in all brain regions evaluated. These associations, adjusted for sex, ethnicity, and age, were statistically significant in most brain regions examined (p < 0.05), with higher BMI or WC corresponding to lower myelin content. Finally, in agreement with previous work, MWF exhibited a quadratic, inverted U-shaped, association with...
This is attributed to the process of myelination from youth through middle age, followed by demyelination afterward.

**Conclusions:** These findings suggest that obesity was significantly associated with white matter integrity, and in particular myelin content. We expect that this work will lay the foundation for further investigations to clarify the nature of myelin damage in neurodegeneration, including AD, and the effect of lifestyle factors such as diet and physical activity on myelination.

1. **INTRODUCTION**

People suffering from obesity are at higher risk for a myriad of diseases and health conditions, including hypertension, type 2 diabetes, stroke, elevated cholesterol, and sleep apnea. Furthermore, epidemiological evidence has established a link between obesity and central nervous system (CNS) degeneration (1–3). This may reflect neuronal and synaptic degeneration secondary to obesity-induced metabolic disturbances; in turn, these may be contributors to the onset and progression of neurodegenerative diseases including Alzheimer’s and Parkinson’s diseases (1, 4–7). Moreover, growing evidence indicates that lifestyle factors such as diet and physical activity improve brain structure and function, suggesting novel therapeutic strategies against neurodegenerative disorders (8–10).

Microstructural changes in the gray and white matter of the brain secondary to obesity have been documented by conventional quantitative magnetic resonance imaging (MRI) (11–14). Using diffusion tensor imaging (DTI), magnetization transfer (MT), MR relaxation time mapping, and morphometry, it has been shown that body mass index (BMI) is negatively correlated with tissue integrity in several brain structures (11–13, 15, 16). However, as recognized by these authors, it is very difficult to interpret these findings in terms of underlying histopathologic changes. Indeed, while sensitive to changes in brain tissue microstructure, conventional MRI techniques are not specific; in addition to axonal degeneration and demyelination, these parameters may also reflect other tissue properties such as macromolecular content, flow, and fiber architecture. Similar comments apply to the non-specificity of MR spectroscopy studies of the correlation between obesity and myelination (17). Thus, to the best of our knowledge, the specific association between obesity and myelination remains to be established. Furthermore, these previous MRI investigations were conducted on cohorts of limited size and limited age range, both limiting the statistical power of the analysis and providing results that may not be reflective of a wide adult age range.

Several multicomponent MRI relaxometry methods have been introduced for myelin content mapping through measurement of the myelin water fraction (MWF) (18), including BMC-mcDESPOT (19–21) which provides rapid whole-brain MWF maps (19–22). BMC-mcDESPOT has been extensively used in several MWF-based studies to provide quantitative evidence of myelin loss in mild cognitive impairment and dementia (23), to investigate myelination patterns with normative aging (24–26), and to demonstrate an association between myelin content and cerebral blood flow (27).

Production and maintenance of myelin through oligodendrocyte metabolism is critical for saltatory conduction and normal axonal function. Growing evidence is establishing a direct
relationship between myelin loss and a number of functional neurological disorders (18, 23, 28), suggesting that the breakdown of the myelin sheath could represent an important feature of early neurodegeneration, including mild cognitive impairment and Alzheimer’s disease (AD) (23, 29, 30). This notion is further supported by animal studies showing that a high fat diet can trigger myelin damage while obesity inhibits the maturation of the oligodendrocyte cells (9, 31, 32).

In this work, we examined the association between myelin content and obesity in 119 cognitively unimpaired subjects with healthy weight, overweight, or obesity spanning a wide age-range (22 to 94 years). Our main goal was to characterize the association between regional MWF, as a measure of myelin content, and BMI and waist circumference (WC), as measures of obesity, and to develop new insights into the specific effect of obesity on regional myelin integrity.

2. MATERIALS AND METHODS

2.1. Participants

One hundred thirty-one participants were recruited from the Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing (GESTALT) study and the Baltimore Longitudinal Study of Aging (BLSA). Conducted by the National Institute on Aging, the goal of these studies is to evaluate multiple aging biomarkers. The criteria for exclusion and inclusion are identical for the GESTALT and BLSA studies. Participants were excluded if they had significant medical or neurologic conditions. Participants had undergone the Mini Mental State Examination (MMSE). Nine participants with cognitive impairment and three participants with MRI data corrupted by motion artifacts were excluded. The final cohort therefore consisted of 119 cognitively unimpaired volunteers (mean ± standard deviation MMSE = 28.7 ± 1.5) ranging in age from 22 to 94 years (56.3 ± 20.9 years) of whom 63 were men (58.1 ± 22 years) and 56 were women (54.4 ± 19.7 years). The number of participants per age-decade was: 13 (6 males) in the range of 20-29 years, 16 (10 males) within 30-39 years, 31 (13 males ) within 40-49 years, 8 (5 males) within 50-59 years, 9 (3 males) within 60-69 years, 17 (10 males) within 70-79 years, 22 (13 males) within 80-89 years, and 3 (3 males) within 90-99 years. Age did not differ significantly between men and women. Following established BMI cutoff points (33), the cohort consisted of 51 lean participants (BMI < 25), 52 overweight participants (25 ≤ BMI < 30), and 16 participants with obesity (BMI ≥ 30), while following the National Institutes of Health cutoff points for WC, the cohort consisted of 67 lean participants (WC < 94 cm for men and WC < 80 cm for women), 33 overweight participants (94 ≤ WC < 102 for men and 80 ≤ WC < 88 for women), and 19 participants with obesity (WC ≥102 for men and WC ≥88 for women). The cohort included 85 Caucasians participants, 26 African American participants, and 8 Asians or Pacific Islanders. Participants provided written informed consent and all experimental procedures were performed in compliance with our local Institutional Review Board.
2.2. Data acquisition

All MRI images were acquired on a 3T Philips MRI system (Achieva, Best, The Netherlands). We used the quadrature body coil for radiofrequency (RF) signal transmission and an eight-channel phased-array head coil for signal reception. Each participant was studied using the following BMC-mcDESPOT imaging protocol for MWF mapping:

- Ten 3D spoiled gradient recalled echo (SPGR) images were obtained with flip angles (FAs) incremented linearly from 2° to 20°, with echo time (TE)/repetition time (TR) = 1.37/5 ms. The acquisition matrix for all images was 150 × 130 × 94, while the acquisition voxel size was 1.6 mm × 1.6 mm × 1.6 mm. The total acquisition time was ~5 min.

- Ten 3D balanced steady state free precession (bSSFP) images were obtained with FAs of 2°, 7°, 11°, 16°, 24°, 32°, 40°, and 60°, with TE/TR = 2.8/5.8 ms. To account for the off-resonance effects, all bSSFP images were acquired with RF excitation phase increments of 0° or 180°. The acquisition matrix for all images was 150 × 130 × 94, while the acquisition voxel size was 1.6 mm × 1.6 mm × 1.6 mm. The total acquisition time was ~12 min.

- To correct for excitation RF inhomogeneity, we used the double-angle method (DAM). For this, two fast spin-echo images were acquired with FAs of 45° and 90°, TE = 102 ms, TR= 3000 ms, and acquisition voxel size of 2.6 mm × 2.6 mm × 4 mm. The total acquisition time was ~4 min.

- All SPGR, bSSFP, and DAM images were acquired with field-of-view of 240 mm × 208 mm × 150 mm, and reconstructed to a voxel size of 1 mm × 1 mm × 1 mm.

2.3. Data processing

The scalp tissue was discarded using the FMRIB Software Library (FSL) with the SPGR image averaged over all 10 FAs used as the input image. Then, the SPGR, bSSFP, and DAM images were linearly registered to the averaged SPGR image. Next, a whole-brain MWF map was generated for the parenchymal regions using BMC-mcDESPOT from the registered SPGR, bSSFP, and DAM images. Finally, the derived MWF map was nonlinearly registered to the Montreal Neurological Institute (MNI) standard space.

Twenty-one white matter regions of interest (ROIs) were defined from the MNI structural atlas corresponding to the whole brain (WB) white matter, frontal lobes (FL), parietal lobes (PL), temporal lobes (TL), occipital lobes (OL), cerebellum (CRB), body of corpus callosum (BCC), genu of corpus callosum (GCC), splenium of corpus callosum (SCC), internal capsules (IC), cerebral peduncle (CP), anterior corona radiata (ACR), posterior corona radiata (PCR), anterior thalamic radiation (ATR), posterior thalamic radiation (PTR), inferior fronto-occipital fasciculus (IFOF), superior fronto-occipital fasciculus (SFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), forceps minor (Fm), and forceps major (FM) (Fig. 1). ROIs were eroded to avoid partial volume contamination from adjacent structures. Within each ROI, the mean MWF was calculated.
2.4. Statistical analysis

For each ROI, the correlation between BMI or WC and MWF was investigated using multiple linear regression with the mean MWF within the ROI as the dependent variable and BMI or WC, sex, ethnicity, age, and age$^2$ as independent variables, after mean age centering. The inclusion of age$^2$ as an independent variable is based on our and others’ recent observations that myelination follows a quadratic relationship with age (25, 36).

To investigate the associations between BMI or WC and MWF between the groups of subjects with healthy weight (lean), overweight, and obesity, we performed between-group ANCOVA analyses for each ROI. These included i) obese vs. lean groups, ii) overweight vs. lean groups, and iii) obese vs. overweight groups. All between-group comparisons controlled for sex, ethnicity, age and age$^2$.

The threshold for statistical significance was set to $p < 0.05$ after correction for multiple ROI comparisons using the false discovery rate (FDR) method for all statistical analyses. Calculations were performed with MATLAB (MathWorks, Natick, MA, USA). All MATLAB codes are available upon request from the corresponding author.

3. RESULTS

Figure 2 shows regression relationships between MWF and BMI, after adjusting for sex, ethnicity, age, and age$^2$, for the indicated 21 cerebral white matter regions. Visual inspection indicates that larger BMI corresponds to lower MWF in all examined ROIs, with the best-fit lines displaying regional variation in this relationship. Further, the multiple regression analysis indicates that this negative correlation between MWF and BMI was statistically significant ($p_{BMI} < 0.05$) or close to significance ($p_{BMI} < 0.1$) in most brain regions investigated (Table 1). In addition, our results indicate that the steepest negative slopes in MWF versus BMI were found in the corona radiata and thalamic radiation regions, while the smallest slopes were found in the forceps minor and cerebral peduncle regions. Comparison of each of the steepest and smallest slopes indicated statistically significantly different slopes between the posterior corona radiata and the forceps minor or cerebral peduncle ($p < 0.05$; Z-test computed as the difference between the two slopes divided by the square root of the sum of the squared standard error of the slopes (37)). Furthermore, as expected, significant age effects were found for all brain regions evaluated (Table 1). Similarly, the quadratic effect of age, age$^2$, was statistically significant or close to significance in most brain regions (Table 1).

Figure 3 shows regression relationships between MWF and WC, after adjusting for sex, ethnicity, age, and age$^2$, for the indicated 21 cerebral white matter regions. Visual inspection indicates that larger WC corresponds to lower MWF in all examined ROIs, with the best-fit lines displaying regional variation. Further, the multiple regression analysis indicates that this negative correlation between MWF and WC was statistically significant ($p_{WC} < 0.05$) or close to significance ($p_{WC} < 0.1$) in most brain regions investigated (Table 2). In addition, our results indicate that the steepest negative slopes in MWF with WC were found in the corona radiata, longitudinal fasciculus, and thalamic radiation regions, while the smallest slopes were found in the forceps minor and cerebral peduncle regions. Comparison
of each of the steepest and smallest slopes indicated statistically significantly different slopes between the posterior corona radiata or posterior longitudinal fasciculus and the forceps minor or cerebral peduncle. Furthermore, as expected, significant age effects were found for all brain regions evaluated (Table 2). Similarly, the quadratic effect of age, age², was statistically significant in most brain regions (Table 2).

We further note that with a null hypothesis of no relationship between MWF and BMI or WC, the probability of a given regression relationship exhibiting a slope greater than zero, \( Pr = 0.5 \), equals the probability of it exhibiting a slope less than zero. The probability then of all these 21 regional relationships exhibiting a negative slope, as we found (Fig. 2), is \( Pr = 0.5^{21} < 10^{-6} \). Though not regionally specific, this provides further strong statistical support to the hypothesized inverse relationship between BMI or WC and myelin content.

Table 3 summarizes the results of the between-group ANCOVA analyses of the associations between BMI or WC and MWF. In comparing subjects with obesity to lean subjects, we found significantly lower MWF in the group of subjects with obesity in all ROIs despite controlling for age, age², sex, and ethnicity. Moreover, controlling for these same covariates, while comparison of overweight to lean subjects as defined by BMI did not show statistically significant differences in MWF, we found significantly lower MWF in the overweight group as compared to the lean group as defined by WC, in various ROIs before or after FDR correction. Further, in comparing subjects with obesity to overweight subjects as defined by BMI, we found significantly lower MWF in the group of subjects with obesity in most ROI; however, this finding as restricted to only a few ROIs, before FDR correction, when the groups were defined by WC.

4. DISCUSSION

Using advanced MR methodology for myelin content quantification, in this study, we provided the first demonstration of associations between obesity and MWF. We found a strong quantitative relationship between obesity, measured either by BMI or WC, and lower myelin content. These associations were observed in a large cohort of cognitively unimpaired subjects spanning a wide age range and were statistically significant in several critical brain regions, even after adjusting for age, ethnicity, and sex. These results do not prove, but strongly suggest, a causal link between obesity and white matter integrity, especially myelin content, also consistent with basic science and animal data (9, 11–13, 15–17, 31, 32).

We found that the brain regions investigated exhibit similar trends but different slopes for obesity, as measured by WC or BMI, vs. myelination (Fig. 2). Interestingly, these negative slopes were the largest in magnitude for the corona radiata, longitudinal fasciculus, and thalamic radiation structures (Tables 1–2). These fiber pathways carry most of the neural traffic to and from the cerebral cortex and have been shown to be susceptible to a number of pathologies, including leukoencephalopathy and multiple sclerosis (38, 39); these conditions are associated with deficits in intellectual, social, and emotional functioning (40, 41). Furthermore, epidemiological studies have showed that these regions are particularly prone to atrophy and microstructural changes with obesity (42–46); these structural changes could
be partially explained by the lower myelin content observed here. Moreover, our results indicated that the anterior lobes, including the frontal and temporal lobes, exhibited more rapid decrease in MWF with age, BMI, or WC as compared to the other lobes (Tables 1–2). This pattern is consistent with the retrogenesis hypothesis, in which posterior brain regions are spared from degeneration as compared to anterior brain regions (47–50). However, longitudinal and histological investigations are required to elucidate the mechanisms underlying this vulnerability and concomitant rapid decline in structural integrity.

Our results indicated that overweight subjects have lower myelin content than lean subjects in various cerebral white matter structures (Table 3). The difference was generally lower in magnitude compared to the obese vs. normal results. Our results agree with Raji and colleagues’ observations of association between higher BMI and lower brain WM volumes in subjects with obesity and, to a lesser extent, in overweight subjects (42). Accelerated demyelination in WM structures observed here, and subsequent axonal loss, could explain these consistent observations of WM atrophy with obesity (42, 51–53). Interestingly, unlike BMI, WC was sensitive enough to capture differences in myelin content between overweight and lean subjects. Besides differences in the number of subjects per group due to the BMI or WC stratifications, the BMI is not a robust surrogate for body fat mass, while high BMI does not necessarily result in a higher mortality (54, 55). In contrast, WC provides higher predictive power of disease risk than does BMI (56, 57). Indeed, increased WC indicates increased susceptibility to insulin resistance, cancer, and dyslipidemia due to its strong association with visceral fat (33, 58, 59).

Our results indicate a quadratic association between myelin content and age in all white matter regions investigated (Tables 1–2), in agreement with previous studies (25, 36). This association is attributed to the process of myelination from young adulthood through middle age, followed by demyelination afterward (36, 60); this agrees with postmortem studies and with MRI studies based on myelin-sensitive methods such as relaxation times and diffusion tensor imaging.

Obesity may represent a modifiable risk factor for disruption of white matter integrity, and therefore an important therapeutic target. Our results indicate the possibility of a direct link between obesity and myelin breakdown, and therefore provides a foundation for further investigation of, for example, the effect of diet and physical activity on myelination and cognitive function.

Our work, while conducted on a large cohort, has several limitations. Our dataset is cross-sectional, and longitudinal and intervention studies will be required to establish a causal relationship between MWF and BMI or WC. Such work is underway. Moreover, errors may have arisen from imperfect registration and segmentation. Finally, MWF estimation could be biased by several experimental and physiological parameters that are not incorporated into the BMC-mcDESPOT formalism. These include, but not limited to, differential water diffusion in the underlying compartments, exchange between water pools, and iron content.

In conclusion, in this first study examining the association between obesity and cerebral myelin content in a large cohort and across a wide age range of cognitively normal subjects,
we showed that lower myelin content is associated with obesity in most cerebral white matter structures.

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Figure 1.
Visualization of the white matter ROIs investigated. 1) Frontal lobes, 2) Parietal lobes, 3) Occipital lobes, 4) Cerebellum, 5) Splenium of corpus callosum, 6) Body of corpus callosum, 7) Genu of corpus callosum, 8) Internal capsule, 9) Temporal lobes, 10) Forceps major, 11) Forceps minor, 12) Anterior corona radiata, 13) Inferior longitudinal fasciculus, 14) Cerebral peduncles, 15) Anterior thalamic radiation, 16) Posterior corona radiata, 17) Superior longitudinal fasciculus, 18) Posterior thalamic radiation, 19) Inferior fronto-occipital fasciculus, and 20) Superior fronto-occipital fasciculus.
Regression results for the relationship between MWF and BMI adjusted for age, age$^2$, sex, and ethnicity (N = 119). Results are shown for 21 brain structures/ROIs. For each ROI, the coefficient of determination, $R^2$, of the multiple linear regression model is reported with the symbol * indicating significance at $p < 0.01$. All ROIs exhibited significant negative correlations between MWF and BMI. WB: whole brain white matter, FL: frontal lobes, PL: parietal lobes, TL: temporal lobes, OL: occipital lobes, CRB: cerebellum, BCC: body of corpus callosum, GCC: genu of corpus callosum, SCC: splenium of corpus callosum, IC:
internal capsules, CP: cerebral peduncle, ACR: anterior corona radiata, PCR: posterior corona radiata, ATR: anterior thalamic radiation, PTR: posterior thalamic radiation, IFOF: inferior fronto-occipital fasciculus, SFOF: superior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, Fm: forceps minor, FM: forceps major.
Figure 3.
Regression results for the relationship between MWF and WC adjusted for age, age$^2$, sex, and ethnicity (N = 119). Results are shown for 21 brain structures/ROIs. For each ROI, the coefficient of determination, $R^2$, of the multiple linear regression model is reported with the symbol * indicating significance at $p < 0.01$. All ROIs exhibited significant negative correlations between MWF and WC. WB: whole brain white matter, FL: frontal lobes, PL: parietal lobes, TL: temporal lobes, OL: occipital lobes, CRB: cerebellum, BCC: body of corpus callosum, GCC: genu of corpus callosum, SCC: splenium of corpus callosum, IC:...
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Table 1. Slope, $\beta$, and significance, $p$, of the regression terms incorporated in the multiple linear regression given by: \[ \text{MWF} \sim \beta_0 + \beta_{\text{BMI}} \times \text{BMI} + \beta_{\text{age}} \times \text{age} + \beta_{\text{age}^2} \times \text{age}^2 + \beta_{\text{sex}} \times \text{sex} + \beta_{\text{ethnicity}} \times \text{ethnicity}. \] Sex and ethnicity results are not shown as they exhibited non-significant associations with MWF in all ROIs. All $p$-values presented are obtained after FDR correction.

|        | MWF |      |      |      |      |      |
|--------|-----|------|------|------|------|------|
|        | BMI |      | Age  |      |      |      |
|        | $\beta_{\text{BMI}} \times 10^3$ | $p_{\text{BMI}}$ | $\beta_{\text{age}} \times 10^4$ | $p_{\text{age}}$ | $\beta_{\text{age}^2} \times 10^5$ | $p_{\text{age}^2}$ |
| WB     | -1.46 | 0.053 | -7.19 | 0.000 | -2.06 | 0.012 |
| FL     | -1.68 | 0.049 | -8.56 | 0.000 | -2.29 | 0.012 |
| OL     | -1.37 | 0.099 | -5.73 | 0.000 | -2.29 | 0.019 |
| PL     | -1.45 | 0.036 | -6.34 | 0.000 | -2.08 | 0.013 |
| TL     | -1.75 | 0.029 | -8.68 | 0.000 | -2.16 | 0.012 |
| CRB    | -1.06 | 0.108 | -4.52 | 0.000 | -1.11 | 0.104 |
| BCC    | -1.36 | 0.100 | -7.53 | 0.000 | -1.79 | 0.038 |
| GCC    | -1.90 | 0.019 | -9.51 | 0.000 | -1.55 | 0.034 |
| SCC    | -1.58 | 0.036 | -6.92 | 0.000 | -2.51 | 0.012 |
| IC     | -1.53 | 0.053 | -7.17 | 0.000 | -1.74 | 0.026 |
| CP     | -0.93 | 0.137 | -3.15 | 0.000 | -0.91 | 0.156 |
| ACR    | -2.38 | 0.017 | -10.30 | 0.000 | -1.93 | 0.030 |
| PCR    | -3.09 | 0.005 | -11.15 | 0.000 | -2.59 | 0.012 |
| ATR    | -2.18 | 0.017 | -8.82 | 0.000 | -1.49 | 0.056 |
| PTR    | -1.76 | 0.050 | -9.60 | 0.000 | -2.10 | 0.021 |
| SFOF   | -1.90 | 0.036 | -10.42 | 0.000 | -2.30 | 0.012 |
| IFOF   | -1.76 | 0.053 | -9.10 | 0.000 | -2.10 | 0.024 |
| SLF    | -2.54 | 0.005 | -8.55 | 0.000 | -2.11 | 0.012 |
| ILF    | -1.68 | 0.005 | -7.57 | 0.000 | -2.17 | 0.023 |
| Fm     | -1.70 | 0.055 | -7.25 | 0.000 | -2.39 | 0.012 |
| FM     | -0.50 | 0.508 | -3.81 | 0.001 | -1.65 | 0.044 |

MWF: myelin water fraction, BMI: body mass index, WB: whole brain, FL: frontal lobes, PL: parietal lobes, TL: temporal lobes, OL: occipital lobes, CRB: cerebellum, BCC: body of corpus callosum, GCC: genu of corpus callosum, SCC: splenium of corpus callosum, IC: internal capsules, CP: cerebral peduncle, ACR: anterior corona radiata, PCR: posterior corona radiata, ATR: anterior thalamic radiation, PTR: posterior thalamic radiation, IFOF: inferior fronto-occipital fasciculus, SFOF: superior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, Fm: forceps minor, FM: forceps major.
Table 2.

Slope, β, and significance, p, of the regression terms incorporated in the multiple linear regression given by: MWF ~ \(\beta_0 + \beta_{WC} \times WC + \beta_{age} \times age + \beta_{age^2} \times age^2 + \beta_{sex} \times sex + \beta_{ethnicity} \times ethnicity\). The results of sex and ethnicity are not shown as they exhibited non-significant associations with MWF in all ROIs. All p-values presented are obtained after FDR correction.

|        | \(\beta_{WC} (\times 10^4)\) | \(p_{WC}\) | \(\beta_{age} (\times 10^4)\) | \(p_{age}\) | \(\beta_{age^2} (\times 10^5)\) | \(p_{age^2}\) |
|--------|-----------------------------|------------|-----------------------------|------------|-----------------------------|------------|
| WB     | -8.28                       | 0.005      | -6.23                       | 0.000      | -2.30                       | 0.003      |
| FL     | -9.02                       | 0.005      | -7.52                       | 0.000      | -2.56                       | 0.003      |
| OL     | -8.83                       | 0.008      | -4.67                       | 0.000      | -2.56                       | 0.008      |
| PL     | -9.08                       | 0.005      | -5.30                       | 0.000      | -2.34                       | 0.003      |
| TL     | -9.36                       | 0.005      | -7.57                       | 0.000      | -2.44                       | 0.008      |
| CRB    | -5.98                       | 0.026      | -3.83                       | 0.000      | -1.29                       | 0.058      |
| BCC    | -8.51                       | 0.011      | -6.52                       | 0.000      | -2.05                       | 0.016      |
| GCC    | -8.69                       | 0.005      | -8.55                       | 0.000      | -1.79                       | 0.014      |
| SCC    | -8.57                       | 0.007      | -5.93                       | 0.000      | -2.76                       | 0.003      |
| IC     | -7.61                       | 0.011      | -6.31                       | 0.000      | -1.95                       | 0.011      |
| CP     | -5.89                       | 0.023      | -2.45                       | 0.000      | -1.10                       | 0.089      |
| ACR    | -10.90                      | 0.005      | -9.10                       | 0.000      | -2.23                       | 0.011      |
| PCR    | -13.66                      | 0.002      | -9.65                       | 0.000      | -2.96                       | 0.003      |
| ATR    | -10.35                      | 0.005      | -7.67                       | 0.000      | -1.78                       | 0.023      |
| PTR    | -10.16                      | 0.005      | -8.41                       | 0.000      | -2.40                       | 0.006      |
| SFOF   | -8.59                       | 0.008      | -9.48                       | 0.000      | -2.54                       | 0.003      |
| IFOF   | -9.34                       | 0.008      | -8.02                       | 0.000      | -2.38                       | 0.009      |
| SLF    | -12.08                      | 0.000      | -7.20                       | 0.000      | -2.44                       | 0.003      |
| ILF    | -9.71                       | 0.007      | -6.43                       | 0.000      | -2.30                       | 0.008      |
| Fm     | -10.01                      | 0.005      | -6.072                      | 0.000      | -2.56                       | 0.003      |
| FM     | -3.95                       | 0.210      | -3.32                       | 0.003      | -2.56                       | 0.029      |

MWF: myelin water fraction, WC: waist circumference, WB: whole brain, FL: frontal lobes, PL: parietal lobes, TL: temporal lobes, OL: occipital lobes, CRB: cerebellum, BCC: body of corpus callosum, GCC: genu of corpus callosum, SCC: splenium of corpus callosum, IC: internal capsules, CP: cerebral peduncle, ACR: anterior corona radiata, PCR: posterior corona radiata, ATR: anterior thalamic radiation, PTR: posterior thalamic radiation, IFOF: inferior fronto-occipital fasciculus, SFOF: superior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, Fm: forceps minor, FM: forceps major.
Table 3.
Significance, p-value, of the between-group ANCOVA analyses of the effect of BMI or WC on MWF in all ROIs. All between-group comparisons were controlled for age, age\(^2\), sex, and ethnicity. All p-values presented are obtained after FDR correction.

|                  | Obese vs. Lean | Overweight vs. Lean | Obese vs. Overweight |
|------------------|----------------|--------------------|----------------------|
|                  | BMI  WC        | BMI  WC            | BMI  WC              |
| WB               | 0.033 0.002   | 0.865 0.165\(^*\) | 0.0156 0.045         |
| FL               | 0.033 0.002   | 0.967 0.165\(^*\) | 0.0150 0.040         |
| OL               | 0.046 0.003   | 0.936 0.165        | 0.038 0.528          |
| PL               | 0.030 0.000   | 0.927 0.100        | 0.0156 0.040         |
| TL               | 0.033 0.002   | 0.754 0.166\(^*\) | 0.145 0.043          |
| CRB              | 0.045 0.002   | 0.979 0.180\(^*\) | 0.086 0.528          |
| GCC              | 0.030 0.006   | 0.795 0.165        | 0.038 0.400          |
| SCC              | 0.030 0.002   | 0.763 0.147        | 0.015 0.528          |
| IC               | 0.054 0.011   | 0.984 0.294        | 0.034 0.400\(^*\)    |
| CP               | 0.126 0.016   | 0.722 0.180        | 0.213 0.522          |
| ACR              | 0.030 0.003   | 0.706 0.215        | 0.038 0.528\(^*\)    |
| PCR              | 0.003 0.000   | 0.288 0.012        | 0.015 0.528          |
| ATR              | 0.046 0.008   | 0.538 0.165\(^*\) | 0.102\(^*\) 0.462    |
| PTR              | 0.030 0.002   | 0.712 0.037        | 0.038 0.528          |
| SFOF             | 0.037 0.003   | 0.281 0.215        | 0.086 0.405          |
| IFOF             | 0.064 0.007   | 0.735 0.355        | 0.039 0.400\(^*\)    |
| SLF              | 0.003 0.000   | 0.312 0.091        | 0.015 0.401\(^*\)    |
| ILF              | 0.050 0.004   | 0.722 0.309        | 0.015 0.401\(^*\)    |
| Fm               | 0.033 0.002   | 0.827 0.031        | 0.038 0.533          |
| FM               | 0.096 0.256   | 0.584\(^*\) 0.674 | 0.010 0.528          |

MWF: myelin water fraction, BMI: body mass index, WB: whole brain, FL: frontal lobes, PL: parietal lobes, TL: temporal lobes, OL: occipital lobes, CRB: cerebellum, BCC: body of corpus callosum, GCC: genu of corpus callosum, SCC: splenium of corpus callosum, IC: internal capsules, CP: cerebral peduncle, ACR: anterior corona radiata, PCR: posterior corona radiata, ATR: anterior thalamic radiation, PTR: posterior thalamic radiation, IFOF: inferior fronto-occipital fasciculus, SFOF: superior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, Fm: forceps minor, FM: forceps major.

\(^*\) indicates significance or close to significance before FDR correction (but lost significance after FDR correction).