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Lipid Metabolism, Abdominal Adiposity and Cerebral Health in the Amish

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Abstract

Objective—To assess the association between peripheral lipid/fat profiles and cerebral grey matter (GM) and white matter (WM) in healthy, Old Order Amish (OOA).

Methods—Blood lipids, abdominal adiposity, liver lipid contents and cerebral microstructure were assessed in OOA (N=64, 31 Males/33 Females, ages 18–77). Orthogonal factors were extracted from lipid and imaging adiposity measures. GM assessment used the Human Connectome Project protocol to measure whole-brain average cortical thickness. Diffusion weighted imaging derived WM fractional anisotropy and kurtosis anisotropy measurements.

Results—Lipid/fat measures were captured by three orthogonal factors explaining 80% of the variance. Factor 1 loaded on cholesterol/LDL-C; Factor 2 on triglyceride/liver measurements; Factor 3 on abdominal fat measurements. A two-stage regression including age/sex (1^{st} stage) and the three factors (2^{nd} stage) examined the peripheral lipid/fat effects. Factors 2 and 3 significantly contributed to WM measures after Bonferroni corrections ($p<0.007$). No factor significantly contributed to GM. Blood pressure inclusion did not meaningfully alter the lipid/fat-WM relationship.

Conclusions—Peripheral lipid/fat indicators significantly and negatively associated with cerebral WM rather than GM, independent of age and blood pressure. Dissecting the fat/lipid

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components contributing to different brain imaging parameters may open a new understanding of the body-brain connection through lipid metabolism.

Keywords

Lipids; adiposity; white matter; diffusion weighted imaging; Old Order Amish

Introduction

Adiposity underlies energy storage, hormone regulation and other important functions[1]. Excessive adiposity is a risk factor for reduced cerebral integrity[2]. We systematically evaluated body adiposity/blood lipids as potential risk factors for brain microstructure in a sample of healthy, largely normotensive Old Order Amish (OAA). Compared to the general population, OAA have uniform farm-dwelling lifestyles and relative genetic/environmental homogeneity (see supplement)[3]. This cohort also has relatively uniform diet and greatly reduces potential confounds due to alcohol, tobacco and illicit substance use[3]; thus constituting a good sample for studying body-brain relationships.

We combined advanced body imaging and liver spectroscopy with standard clinical lipid assessment to derive lipid/adiposity profiles. We utilized high-resolution structural and diffusion kurtosis imaging (DKI) to assess cerebral integrity. DKI is a model-independent extension of diffusion tensor imaging (DTI) that accounts for non-Gaussian diffusivity behavior observed in cerebral white matter (WM) and gray matter (GM)[4]. DKI calculates DTI's fractional anisotropy and axial/radial diffusivity parameters, and axial/radial kurtosis and kurtosis anisotropy, to capture non-Gaussian diffusion behavior of slowly diffusing water molecules. These measures show higher sensitivity to tissue integrity impairment in stroke and schizophrenia[5,6](see supplement).

We hypothesized cerebral WM may be particularly sensitive to increased adiposity/lipids, even under healthy conditions, due to high lipid content in myelinated WM and previously established susceptibility to cardiovascular/metabolic factors[7,8] and adiposity[9].

Methods

Subjects

N=64 (31 Male/33 Female) participants from the Amish Connectome Project (18–77, average=46.3±17.5 years). Subjects underwent a medical assessment and lipid panel analysis (Table 1, see supplement). Every subject signed a written informed consent form approved by the University of Maryland IRB.

Fat and Brain Imaging

MRI examination consisted of high-resolution abdominal fat imaging, magnetic resonance spectroscopy measurement of hepatic fat concentration, and diffusion weighted brain imaging using a 3T Siemens Trio scanner with a 32-channel head coil and an 8-channel body coil at the Maryland Psychiatric Research Center (see supplement). DKI analysis

extracted whole-brain averaged Fractional Anisotropy (FA), Kurtosis Anisotropy (KA), Axial/Radial Diffusivity (AD/RD) and Axial/Radial Kurtosis (AK/RK).

Statistical Analyses

We identified peripheral lipid/adiposity profile factors by entering blood and imaging-based data into a principle component analysis to uncover related measures, reduce the number of dependent variables, and minimize co-linearity. A varimax rotation orthogonized the individual eigenvectors.

A general linear mixed effect (GLME) model used the lipid/fat factors as predictors for averaged whole-brain GM cortical thickness and WM metrics in separate GLME models (see supplement). Bonferroni correction set significance to $p \leq 0.007$.

Results

Factor Analysis

Three orthogonal factors captured 80% of the total variance (Table S1). Factor 1 loaded with total cholesterol and LDL-C; Factor 2 with blood triglyceride, liver fat concentration, and HDL-C; and Factor 3 with abdominal and perirenal fat volumes. The factors were relabeled as “Cholesterol Factor (CF)”"Triglyceride Factor (TF)” and “Abdominal Fat Factor (AFF)” for Factors 1, 2 and 3, respectively.

WM Microstructure

The model was significant for whole-brain WM average FA (χ^2=25.9,p=9.3·10^{-5}), KA (χ^2=50.3, p=1·10^{-10}), RD (χ^2=18.7, p=0.003), AK (χ^2=37.7 p=4·10^{-10}), and RK (χ^2=31.4; p=8·10^{-6})(Table 2).

After considering age, sex, and household covariates, the Cholesterol Factor showed no significant WM associations. The Triglyceride Factor showed significantly positive associations with RD (β_{TF}=6.4 ± 2.1·10^{-5}, p=0.002) and AK (β_{TF}=1.2 ± 0.4·10^{-2}, p=0.001). The Abdominal Fat Factor showed a significantly negative KA association (β_{AFF}=-4.7 ± 1.7·10^{-10}, p=0.004) and significantly positive AK association (β_{AFF}=2.5 ± 0.6·10^{-2}, p=2·10^{-5})(Table 2).

Repeat analysis included BMI, which proved an insignificant predictor (Table S2).

GM Microstructure

The model was significant for whole-brain average cortical GM thickness (χ^2=55.3,p=1·10^{-12}). After considering age, sex, and household covariates, average GM thickness showed no significant association with any factor (Table 2). Experimental DKI showed no significant factor associations (Table S3).

Potential Blood Pressure Effects

BP showed no significant association with whole-brain measurements, Triglyceride Factor, or Cholesterol Factor (p>0.3). BP was significantly and positive correlated with the

Abdominal Fat Factor ($p<0.001$). Lipid/fat-WM associations were repeated to include systolic and diastolic BP, which rendered the Triglyceride Factor-RD relationship insignificant (Table 3). The Triglyceride Factor-AK, Abdominal Fat Factor-KA, and Abdominal Fat Factor-AK relationships remained statistically significant. Lipid/fat and whole-brain GM cortical thickness relationships remained insignificant (Table 3).

Discussion

We report lipid/fat profiles and cerebral WM associations in healthy, mainly normotensive, Old Order Amish. We show that increases in abdominal fat, liver adiposity and circulating triglycerides levels negatively impact cerebral WM integrity beyond hypertension. This suggests abdominal adiposity/high blood lipids may present cerebral risk, even in physically active normotensive individuals, but whether the WM specific relationship is causal or secondary remains unclear. The associations were not significant for cerebral GM, potentially due to differences in cerebrovascular architecture between cortical GM and WM where perfusion rate in cerebral WM is lower[10]. Additionally, WM is particularly sensitivity to systemic inflammation and obesity-associated metabolic disorders[5–8].

Adiposity imaging and spectroscopy formed three orthogonal factors. Total cholesterol and LDL-C formed the Cholesterol Factor, which is consistent with clinical implications of elevated total cholesterol and LDL-C as risk factors for ischemic heart disease[11]. Triglycerides, liver fat fractions and HDL-C formed the Triglyceride Factor. Triglycerides are primarily synthesized/stored in the liver, and triglyceridemia is a risk factor for non-alcoholic fatty liver disease[12]. The Abdominal Fat Factor was based on abdominal and perirenal fat volumes. Abdominal obesity is directly associated with atherosclerosis progression[13] and perirenal fat may have specific cardiovascular risks[14]. Overall, there is confidence in the biological validity of the factors.

Previous imaging studies in aging or hypertensive populations reported negative associations between abdominal obesity and cerebral WM FA[15,16]. The obesity-WM relationship in hypertensive subjects was interpreted as driven by BP, secondary to obesity[15]. Although not statistically significant after Bonferroni correction, our normotensive sample replicated the negative FA-abdominal obesity association ($r=-0.45$, $p=0.04$)[15,16], and became marginally stronger with BP as covariates ($p=0.02$, Tables 3/4). Therefore, abdominal adiposity may impact FA beyond a BP mechanism. The Abdominal Fat Factor was significantly and negatively associated with KA, driven by axial kurtosis (AK) (see supplement). Elevation in AK is observed in stroke and brain trauma, reflecting inflammation-related changes in the intra-axonal space[6]. Higher AK values are also observed in neuropsychiatric conditions, reflecting neuroinflammation[5].

The underlying mechanisms of the Abdominal Fat Factor-WM associations are complex. Obesity is a risk factor for hypertension that directly affects cerebral integrity[7,8,17] due to the stenosis of long-penetrating cerebral blood vessels that perfuse cerebral WM[7]. Post-hoc analysis showed a negative correlation between systolic BP and FA ($r=-0.34$, $p=0.004$) (Figure S1). However, including BP did not meaningfully alter the lipid/fat factor-WM relationships (Tables 3/4) suggesting that in normotensive individuals, abdominal adiposity

may impact WM through a yet-to-be-determined mechanism. A recent study formed a similar conclusion, stating adiposity-WM associations partially result from mechanisms other than BP[18].

Triglyceride Factor scores associated with WM AK ($p=0.001$) even after inclusion of BP (see supplement). The Triglyceride Factor-Radial Diffusivity (RD) relationship was rendered insignificant after BP inclusion, partly because RD was significantly associated with systolic ($r=0.33$) and diastolic ($r=0.25$) BP. Therefore, BP may drive the Triglyceride Factor-RD relationship. A study in normotensive and prehypertensive adults associated BP with RD, concluding that increased adiposity affects WM directly and indirectly through BP mediated pathways[18].

We replicated the significant age-associated reduction in cortical GM thickness. However, DWI parameters showed no significant factor associations. These results are considered experimental (Table S3), but suggest increased body lipid/fat has less impact on GM, potentially due to higher lipid content in myelinated WM and cerebrovascular architectural differences[7,8]. Therefore, WM may be more sensitive to fat/lipid factors than GM.

The Cholesterol Factor was not significantly correlated with GM or WM. Williams and colleagues[19], observed a negative FA-LDL-C association in older adults, which they postulated as a risk for Alzheimer's and vascular dementias caused by elevated BP and atherosclerosis. Directly comparing results is difficult because the sample used by Williams was older, with 30% of the subjects using cholesterol-controlling medications[19]. Moreover, total cholesterol and LDL-C in OOA were not significantly correlated with their suggested BP mediation mechanism ($r<0.05$, $p>0.5$)[19]. Instead, our study showed BP might present more subtly in a healthy population. Both studies reported significantly negative triglyceride-WM associations.

Specific biological interpretations are limited as diffusion metrics are mathematically derived and underlying neurobiological correlates not fully understood[20]. This study also used a small number of subjects ($N=64$), which prevented detailed causal exploration of WM-adiposity relationships. Further statistical analysis did not show significant gender contrasts for WM-adiposity relationships. Males/females were not different on BMI, WM, or GM measurements (all $p>0.4$) after age correction. The OOA may be considered an advantage and study limitation. The clear advantage is the environmental uniformity and minimal confounds. However, the generalizability to the US population may be limited. OOA were primarily normotensive (<10% hypertensive) compared to the US population (~30%), but comparable in BMI. If the primary goal is to understand peripheral lipid/fat-brain integrity relationships, OOA offers an excellent cohort to examine this question under healthy conditions. Therefore, we believe the advantages outweigh potential generalizability limitations.

Conclusion

We performed a comprehensive analysis on the impact lipids/adiposity have on cerebral integrity in healthy, Old Order Amish. The multifactorial analysis demonstrated increases in

abdominal fat, liver adiposity and circulating triglycerides significantly impact cerebral WM microstructure. The impact on cerebral GM was much less obvious.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject?

- Elevated blood lipids and abdominal adiposity are risk factors of developing cerebral vascular disorders

What does this study add?

- In this study of normotensive Old Order Amish, peripheral lipid/fat profiles significantly and negatively associated with cerebral White Matter, but not Gray Matter, microstructural measurements
- The associations between increased adiposity and changes in white matter microstructure were independent of age and blood pressure
- The connection between fat/lipid components and brain imaging parameters may allow for a new understanding of the body-brain connection through lipid metabolism.

Table 1
Demographic information for study participants

The BMI classification was the following: Underweight: <18.5, Normal: 18.5 to 24.9, Overweight: 25–29.9, Obese: > 30. Blood cholesterol level was classified based on the following: high > 240 mg/dL borderline: 200–239 mg/dL. Blood LDL-C levels were classified as: 130–159 mg/dL – borderline high, 160–189 mg/dL - high, 190 g/dL or higher – very high. Blood triglycerides levels were classified as borderline: 150–199 mg/dL, high – 200–499 mg/dL.

	Average	Range
Age (years)	46.3 ± 17.5	18–77
Height (cm)	168.27 ± 9.39	149.4–184.8
Weight (kg)	83.19 ± 12.85	51.2–109.6
BMI [% Sample under, normal, over-weight, obese]	28.16 ± 5.20 [1.6%, 37.5%, 23.4%, 37.5%]	17.66 – 39.01
Systolic Blood Pressure (mm Hg) [% Sample > 140mm Hg]	120.79 ± 15.25 [9.5%]	94–169
Diastolic Blood Pressure (mm Hg) [% Sample > 90mm Hg]	71.23 ± 7.99 [4.8%]	56–91
Cholesterol (mg/dL) [% Sample borderline, high]	209.8 ± 43.6 [39.06%, 25.00%]	108–315
HDL-C (mg/dL) [% Sample < 40 mg/dL]	61.02 ± 18.95 [7.81%]	29–128
LDL-C (mg/dL) [% Sample borderline, high, very high]	131.5 ± 38.4 [35.95%, 12.50%, 7.94%]	51–246
Triglycerides (mg/dL) [% Sample borderline, high]	86.5 ± 45.66 [12.50%, 1.56%]	34–264

Table 2

Regression results (beta and p-values for fixed factors) for the for the subcortical white matter (WM) microstructural and cortical gray matter (GM) thickness measurements. Bolded values indicate statistical significance after correction for seven regression analyses ($p<0.05/7=0.007$). CF = Cholesterol Factor; TF = Triglyceride Factor; AFF = Abdominal Fat Factor

Cerebral WM	**β_{Age} (p-value)**	**β_{Sex} (p-value)**	**β_{CF}**	**β_{TF}**	**β_{AFF}**	**Model, χ^2 (p-value)**
Fractional Anisotropy (FA)	**−3.46E-04 ± 1.29E-04 (p = 0.006)**	−6.39E-05 ± 4.30E-03 (p = 0.9)	−5.50E-04 ± 1.94E-03 (p = 0.7)	1.68E-03 ± 1.65E-03 (p = 0.3)	*−4.38E-03 ± 2.33E-03 (p = 0.04)*	**25.9 (p = 9.32E-05)**
Kurtosis Anisotropy (KA)	**−3.85E-04 ± 9.26E-05 (p = 4E-05)**	1.68E-03 ± 3.10E-03 (p = 0.6)	−1.36E-03 ± 1.30E-03 (p = 0.2)	−8.55E-04 ± 1.20E-03 (p = 0.454)	**−4.72E-03 ± 1.70E-03 (p = 0.004)**	**50.3 (p = 1E-10)**
Axial Diffusivity (AD)	−3.68E-07 ± 1.39E-06 (p = 0.5)	8.73E-05 ± 4.72E-05 (p = 0.05)	7.17E-06 ± 2.26E-5 (p = 0.7)	2.09E-05 ± 2.28E-05 (p = 0.4)	1.31E-05 ± 2.51E-05 (p = 0.6)	6.6 (p = 0.3)
Radial Diffusivity (RD)	2.03E-06 ± 1.51E-06 (p = 0.06)	−7.36E-06 ± 5.24E-05 (p = 0.9)	6.95E-05 ± 2.14E-05 (p = 0.01)	**6.40E-05 ± 2.05E-05 (p = 0.002)**	2.64E-05 ± 2.81E-05 (p = 0.3)	**18.7 (p = 0.003)**
Axial Kurtosis (AK)	−6.96E-05 ± 3.02E-04 (p = 0.8)	1.30E-04 ± 1.01E-02 (p = 0.9)	7.87E-03 ± 4.23E-03 (p = 0.06)	**1.20E-02 ± 3.91E-03 (p = 0.001)**	**2.49E-02 ± 5.53E-03 (p = 1.7E-05)**	**37.7 (p = 4E-07)**
Radial Kurtosis (RK)	**−2.75E-03 ± 5.92E-04 (p = 9E-06)**	3.63E-03 ± 1.98E-02 (p = 0.8)	1.32E-02 ± 8.30E-03 (p = 0.09)	6.41E-04 ± 7.67E-03 (p = 0.9)	−2.98E-03 ± 1.08E-02 (p = 0.8)	**31.4 (p = 8E-06)**
Cortical GM						
GM Thickness	**-6.90E-03 ± 9.08E-04 (p = 1E-12)**	−2.54E-02 ± 3.14E-02 (p = 0.4)	1.26E-03 ± 1.28E-02 (p = 0.8)	−5.31E-03 ± 1.29E-02 (p = 0.6)	3.49E-03 ± 1.75E-02 (p = 0.8)	**55.3 (p = 1E-12)**

Table 3

Regression results (beta and p-values for fixed factors) for the for the subcortical white matter (WM) microstructural and cortical gray matter (GM) thickness measurements. This model (Eq 9) included systolic and diastolic blood pressure (SBP and DBP) measurements. Bolded values indicate statistical significance after correction for seven regression analyses ($p<0.05/7=0.007$). CF = Cholesterol Factor; TF = Triglyceride Factor; AFF = Abdominal Fat Factor

Subcortical WM	**β_{Age} (p-value)**	**β_{Sex} (p-value)**	**$\beta_{CF\text{-}Factor}$ (p-value)**	**$\beta_{TF\text{-}Factor}$ (p-value)**	**$\beta_{AFF\text{-}Factor}$ (p-value)**	**β_{SBP} (p-value)**	**β_{DBP} (p-value)**	**Model, χ^2 (p-value)**
Fractional Anisotropy (FA)	−3.27E-04 ±1.37E-04 (p = 0.01)	−1.45E-03 ±4.36E-03 (p = 0.72)	−8.12E-04 ±1.95E-03 (p = 0.66)	1.58E-03 ±1.64E-03 (p = 0.30)	*−5.75E-03 ±2.56E-03 (p = 0.02)*	−1.60E-04 ±1.36E-04 (p = 0.21)	−4.55E-04 ±2.83E-04 (p = 0.09)	**29.14 (p = 1.4E-04)**
Kurtosis Anisotropy (KA)	**−4.39E-04 ±9.73E-05 (p = 8.40E-06)**	8.73E-04 ±3.10E-03 (p = 0.76)	−1.30E-03 ±1.29E-03 (p = 0.28)	−1.09E-03 ±1.18E-03 (p = 0.32)	**−6.16E-03 ±1.84E-03 (p = 6.31E-04)**	7.20E-05 ±9.81E-05 (p = 0.43)	−2.90E-04 ±2.03E-04 (p = 0.13)	**54.91 (p = 1.6E-09)**
Axial Diffusivity (AD)	−8.69E-06 ±5.32E-06 (p = 0.11)	−4.72E-05 ±1.53E-04 (p = 0.76)	1.33E-04 ±6.75E-05 (p = 0.06)	1.32E-04 ±6.35E-05 (p = 0.04)	2.36E-05 ±9.45E-05 (p = 0.81)	−3.21E-08 ±4.98E-06 (p = 0.99)	−4.96E-06 ±9.97E-06 (p = 0.63)	9.56 (p = 0.21)
Radial Diffusivity (RD)	−2.52E-06 ±1.84E-06 (p = 0.21)	−9.31E-06 ±5.60E-05 (p = 0.83)	5.30E-05 ±2.39E-05 (p = 0.02)	4.08E-05 ±2.23E-05 (p = 0.04)	1.88E-05 ±3.39E-05 (p = 0.53)	2.86E-07 ±1.80E-06 (p = 0.89)	1.04E-06 ±3.67E-06 (p = 0.82)	9.32 (p = 0.23)
Axial Kurtosis (AK)	1.81E-04 ±3.23E-04 (p = 0.60)	1.70E-03 ±1.00E-02 (p = 0.86)	6.84E-03 ±4.22E-03 (p = 0.09)	**1.27E-02 ±3.92E-03 (p = 8.83E-04)**	**2.79E-02 ±6.02E-03 (p = 5.66E-06)**	−4.39E-04 ±3.21E-04 (p = 0.17)	−5.23E-04 ±6.57E-04 (p = 0.39)	**41.98 (p = 5.2E-07)**
Radial Kurtosis (RK)	**−2.69E-03 ±6.20E-04 (p = 1.82E-05)**	−4.25E-03 ±1.97E-02 (p = 0.82)	1.14E-02 ±8.19E-03 (p = 0.14)	−2.11E-04 ±7.53E-03 (p = 0.98)	−1.23E-02 ±1.17E-02 (p = 0.26)	−7.80E-04 ±6.26E-04 (p = 0.18)	***−2.73E-03 ±1.29E-03 (p = 0.03)***	**36.46 (p = 5.9E-06)**
Cortical GM								
GM Thickness	**−9.13E-03 ±1.85E-03 (p = 4.03E-06)**	4.56E-02 ±5.75E-02 (p = 0.37)	−2.83E-02 ±2.49E-02 (p = 0.24)	1.69E-02 ±2.51E-02 (p = 0.48)	2.22E-02 ±3.37E-02 (p = 0.45)	−3.06E-03 ±1.87E-03 (p = 0.09)	1.10E-04 ±4.00E-03 (p = 0.99)	**44.49 (p = 1.7E-07)**