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ARTICLE

Alterations in cerebral perfusion and substrate metabolism in type 2 diabetes: interactions with *APOE-ε4*

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Abstract

Aims/hypothesis Epidemiological studies indicate that type 2 diabetes increases the risk for Alzheimer's disease. Alterations in cerebral metabolism have been proposed as a potential mechanism underlying this association. A better understanding of these metabolic changes may elucidate potential pathways linking type 2 diabetes to Alzheimer's disease. The aim of the current exploratory study was to investigate whether cerebral metabolism, including glucose and fatty acid uptake as well as cerebral blood flow, is altered in individuals with type 2 diabetes compared with both overweight individuals and lean control individuals.

Methods This exploratory study included 38 participants (ten with type 2 diabetes, 13 overweight individuals and 15 lean control individuals). Brain metabolism was assessed using multiple imaging techniques: [^{18}F]fluorodeoxyglucose and [^{18}F]fluoro-6-thiaheptadecanoic acid positron emission tomography for glucose and fatty acid uptake; arterial spin-labelling MRI for cerebral perfusion; and ^{1}H-magnetic resonance spectroscopy for specific metabolites. Neurodegeneration markers were evaluated from lumbar puncture samples. Group comparisons were assessed using one-way ANOVA and unpaired *t* tests, and correlations were assessed with linear regression.

Results Individuals with type 2 diabetes exhibited lower cerebral glucose uptake compared with both lean and overweight groups ($p<0.01$). Cerebral perfusion was reduced in both participants with type 2 diabetes and overweight participants relative to lean control participants ($p<0.01$). Both glucose uptake and perfusion correlated negatively with HOMA-IR, insulin and HbA_{1c} levels ($p<0.001$–$p<0.05$). White matter fatty acid uptake was elevated in the diabetes group compared with the lean group ($p<0.05$). Post hoc analyses revealed that lean *APOE-ε4* carriers had increased fatty acid uptake in the entire brain relative to lean non-carriers. Among non-carriers of *APOE-ε4*, those with type 2 diabetes showed higher fatty acid uptake than lean control individuals ($p<0.01$–$p<0.05$), and this uptake correlated positively with HOMA-IR, insulin and HbA_{1c} levels ($p<0.05$).

Conclusions/interpretation Type 2 diabetes was associated with decreased cerebral perfusion and glucose uptake but increased fatty acid uptake in white matter. The elevated fatty acid uptake observed both in individuals with type 2 diabetes and in *APOE-ε4* carriers suggests a common metabolic dysfunction for these Alzheimer's disease risk factors and suggests that targeting cerebral metabolic dysfunction, particularly fatty acid metabolism, could be a potential strategy for reducing the risk for neurodegeneration in individuals with type 2 diabetes.

Keywords Alzheimer's disease · Brain metabolism · Fatty acid metabolism · Glucose metabolism · Neuroimaging · Perfusion · Positron emission tomography · Type 2 diabetes

Abbreviations

Aβ	Amyloid-β
AIF	Arterial input function
ASL	Arterial spin labelling
CSF	Cerebrospinal fluid
DPP4	Dipeptidyl peptidase-4
FDG	Fluorodeoxyglucose
FTHA	Fluoro-6-thiaheptadecanoic acid
GLP1	Glucagon-like peptide 1
MRGlu	Metabolic rate of glucose
MRS	Magnetic resonance spectroscopy
NAA	*N*-acetylaspartate
PET	Positron emission tomography
ROIs	Regions of interest
SGLT2	Sodium–glucose cotransporter 2

Extended author information available on the last page of the article

Research in context

What is already known about this subject?

- Type 2 diabetes increases the risk for Alzheimer's disease
- Cerebral metabolic changes may link type 2 diabetes to Alzheimer's disease
- *APOE-ε4* is a known risk factor for Alzheimer's disease

What is the key question?

- How does cerebral metabolism differ in individuals with type 2 diabetes compared with overweight and lean control individuals?

What are the new findings?

- Type 2 diabetes was associated with decreased cerebral glucose uptake, whereas perfusion was reduced in overweight individuals regardless of diabetes status
- Both lean *APOE-ε4* carriers and individuals with type 2 diabetes without this genetic variant showed increased fatty acid uptake in the brain, relative to corresponding control individuals
- HOMA-IR, HbA_{1c} and insulin levels were negatively correlated with cerebral glucose uptake and perfusion and positively correlated with fatty acid uptake

How might this impact on clinical practice in the foreseeable future?

- These findings suggest that targeting cerebral metabolic dysfunction, particularly fatty acid metabolism, could be a potential strategy for reducing the risk for neurodegeneration in individuals with type 2 diabetes

Introduction

Epidemiological studies show that type 2 diabetes and diabetic complications increase the risk of Alzheimer's disease [1]. Conditions that are associated with type 2 diabetes, such as obesity and insulin resistance, are also identified as risk factors for Alzheimer's disease [1, 2]. In addition, individuals with Alzheimer's disease and type 2 diabetes both display similar structural changes in the brain, including reduced volumes of whole brain, grey matter and hippocampus [3].

The growing elderly population in developed countries is expected to significantly increase dementia prevalence [4]. This demographic shift is further compounded by the age-related increase in type 2 diabetes, as well as the rising prevalence of obesity, which also contributes to higher type 2 diabetes rates. This underscores the need to better understand how metabolic disorders contribute to dementia, and to develop interventions that can prevent or delay cognitive decline.

Evidence is accumulating that glucose-lowering therapies (e.g. sodium–glucose cotransporter 2 [SGLT2] inhibitors and glucagon-like peptide 1 [GLP1] receptor agonists) may decrease the risk for Alzheimer's disease [5–7], yet these therapies seem to affect the risk reduction differently [7–9]. The effect of glucose-lowering therapies on Alzheimer's disease risk is interesting, considering that cerebral glucose hypometabolism is a shared feature of type 2 diabetes and Alzheimer's disease [10] and may contribute to the comorbidity. Still, considering the complex nature of cerebral substrate metabolism, glucose hypometabolism is unlikely to be the sole link between Alzheimer's disease and type 2 diabetes. For instance, the strongest genetic risk factor for late-onset Alzheimer's disease (i.e. carrying the *APOE-ε4* isoform) has been shown to be associated with both fatty acid and glucose abnormalities in the brain in vitro [11]. Although studies have investigated fatty acid uptake in people with the metabolic syndrome and obesity [12, 13], cerebral fatty acid uptake has, to the best of our knowledge, not been investigated in vivo in either type 2 diabetes or Alzheimer's disease.

N-acetylaspartate (NAA) and choline are abundant neuronal metabolites that have been used as magnetic resonance spectroscopy (MRS) biomarkers. The NAA brain level is believed to reflect neuronal energy metabolism, especially mitochondrial density and health, and NAA is a source of acetate for fatty acid and sterol synthesis [14]. Levels of NAA have been shown to be reduced in the brain in both Alzheimer's disease and type 2 diabetes [14, 15] and to correlate with age, BMI, HbA_{1c} and fasting glucose levels [15, 16]. Cerebral choline is involved in lipid metabolism and membrane turnover. It also functions as a precursor for acetylcholine, a neurotransmitter hypothesised to be involved

in the association between type 2 diabetes and Alzheimer's disease [17].

Brain metabolism is also dependent on blood-flow regulation. Cerebral blood flow has been shown to be reduced in both Alzheimer's disease [18] and type 2 diabetes as compared with healthy individuals [19]. However, studies of brain perfusion in type 2 diabetes have shown variable results, including reports of no differences between people with and without type 2 diabetes [20].

The aim of the current exploratory study was to assess cerebral metabolism alterations in the fasted state in individuals with type 2 diabetes compared with overweight control individuals and lean, physically active control individuals. Specifically, the primary objective was to investigate whether brain glucose utilisation differs between lean, physically active individuals and people with type 2 diabetes. Secondary objectives were to test whether glucose and fatty acid uptake and cerebral perfusion differ between overweight individuals with type 2 diabetes, overweight individuals without type 2 diabetes and lean physically active individuals. Exploratory objectives included correlational analysis between imaging markers for brain metabolism and blood-based biomarkers for deranged metabolism, cerebrospinal fluid (CSF)-based markers for neurodegeneration and MRS-based markers for mitochondrial function and lipid turnover in the brain, as well as effects of carrying the *APOE-ε4* genetic variant. Glucose and fatty acid uptake were assessed using positron emission tomography (PET) imaging with [^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]fluoro-6-thiaheptadecanoic acid (FTHA). Cerebral perfusion was measured with arterial spin labelling (ASL) and NAA and choline levels were measured with MRS. By comparing the results with those from both overweight and lean control individuals, we aimed to clarify the specific changes in brain metabolism associated with type 2 diabetes.

Methods

Study design

This was a non-interventional single-site trial. Each enrolled participant undertook a total of four visits, including a screening visit, two imaging visits ([^{18}F]FDG PET and MRS on visit 2 and [^{18}F]FTHA and ASL on visit 3), and lumbar puncture on visit 4. See electronic supplementary material section 1 (ESM 1) for details. Recruitment of participants occurred between December 2019 and June 2022 (delayed during the COVID-19 pandemic). Recruitment aimed at a balanced distribution across age and gender, but no assessment of how representative the study sample was of the larger population in terms of gender, ethnicity, age, regional and socioeconomic factors was performed. Written informed consent was obtained from all participants. The study was approved by the Swedish Ethical Review Authority and performed in accordance with the principles of the Declaration of Helsinki and applicable regulatory requirements. All imaging procedures and blood analyses were performed at Akademiska University Hospital, Uppsala, Sweden, unless otherwise stated in the methods.

Participants

A total of 38 participants were included (Table 1). Inclusion criteria for the diabetes group included a type 2 diabetes diagnosis according to the WHO/ADA standards, 27.0 kg/m^2 ≤ BMI ≤ 38.0 kg/m^2, and less than 30 min of self-reported physical activity per day. Inclusion criteria for the overweight group included no history of diabetes, 27 kg/m^2 ≤ BMI ≤ 38.0 kg/m^2, and less than 30 min of self-reported physical activity per day. For the lean group, inclusion criteria included no history of diabetes, 18.5 kg/m^2 ≤ BMI ≤ 25.0 kg/m^2, and more than 45 min of self-reported physical activity per day. General exclusion criteria included cognitive dysfunction as defined by a Mini Mental State Examination (MMSE) score of <27 or diagnosed Alzheimers' disease. Participants' genders were self-reported. A complete list of inclusion/exclusion criteria is provided in ESM 2.

Imaging procedures

All imaging acquisitions were performed on an integrated 3T PET/MR system (Signa PET/MR; GE Healthcare, Waukesha, WI, USA). PET images were reconstructed using the manufacturer's standard methods (time-of-flight ordered subset iteration maximisation with three iterations and 16 subsets and a 3 mm gaussian post filter, including point spread function recovery), including all recommended corrections. All imaging was performed in the morning, after participants had fasted for at least 6 h.

[^{18}F]FDG imaging Participants received a controlled bolus injection of approximately 2 MBq/kg [^{18}F]FDG (5 ml tracer at 1 ml/min followed by 35 ml saline [NaCl 154 mmol/l] at 2 ml/min). The scan started with 10 min acquisition of the thorax, followed by a 20 min dynamic scan of the brain with 4 × 5 min time frames. Brain acquisitions started 27.4 (SD 2.6) min after injection. The thorax scan was used to measure tracer concentration in the blood during the first 10 min, which was used in subsequent analyses. In addition, two manual arterialised plasma samples were acquired at 20 min and 60 min post radioligand injection.

[^{18}F]FTHA imaging [^{18}F]FTHA scans were initiated with a controlled bolus injection (as above) of approximately 3 MBq/kg, followed by a dynamic 45 min acquisition.

Table 1 Participant characteristics

Characteristic	Lean	Overweight	Type 2 diabetes	*p* value
N	15	13	10	—
Age, years	56.9 ± 4.6	56.3 ± 4.9	60.5 ± 5.9	0.18
BMI, kg/m^2	22.6 ± 1.8	33.1 ± 2.8	33.6 ± 2.3	<0.00001
WHR	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	<0.05
Gender (*n* male/*n* female)	4/11	3/10	7/3	—
APOE-ε4 (*n* homo/*n* hetero/*n* non-carrier)	0/9/6	1/4/8	0/1/9	—
HbA_{1c}, mmol/mol	33.6 ± 2.8	37.2 ± 3.4	51.5 ± 6.9	<0.00001
HbA_{1c}, %	5.2 ± 2.4	5.6 ± 2.5	6.9 ± 2.8	<0.00001
Glucose, mmol/l	5.4 ± 0.3	5.9 ± 0.6	7.9 ± 1.1	<0.00001
Insulin, pmol/l	37.5 ± 16.7	104.2 ± 41.0	159.0 ± 84.0	<0.00001
HOMA-IR	1.3 ± 0.6	4.0 ± 1.7	8.3 ± 5.2	<0.00001
Cholesterol, mmol/l	5.8 ± 1.2	5.6 ± 1.3	4.5 ± 1.1	<0.05
HDL-cholesterol, mmol/l	2.0 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	<0.0001
LDL-cholesterol, mmol/l	3.5 ± 1.2	3.9 ± 1.3	2.7 ± 1.0	<0.05
Triglycerides, mmol/l	0.9 ± 0.4	1.5 ± 0.6	1.9 ± 0.9	<0.01
C-reactive protein, mg/l	1.1 ± 1.4	4.5 ± 6.7	4.5 ± 5.4	<0.01
Haemoglobin, g/l	137.3 ± 15.6	149.3 ± 12.2	146.4 ± 12.7	0.07
Lymphocytes, 10^9/l	1.3 ± 0.5	1.7 ± 0.4	2.1 ± 0.5	<0.01
Monocytes, 10^9/l	0.4 ± 0.1	0.5 ± 0.1	0.6 ± 0.2	<0.01
Neutrophils, 10^9/l	2.6 ± 0.8	3.8 ± 1.1	3.8 ± 1.2	<0.01
Platelets, 10^9/l	227.5 ± 38.8	273.7 ± 51	271.1 ± 56.3	<0.05
Erythrocytes, 10^{12}/l	4.6 ± 0.5	4.9 ± 0.4	5.0 ± 0.4	<0.05
Leucocytes, 10^9/l	4.5 ± 0.9	6.2 ± 1.4	6.8 ± 1.2	<0.001
Aβ 1–40, ng/l	12,696.9 ± 2343.8	12,059 ± 2393.5	12,709.3 ± 3082.8	0.75
Aβ 1–42, ng/l	1134.3 ± 327.5	1158.9 ± 281.4	1293.3 ± 316.2	0.47
Amyloid positive, *n* yes/*n* no	3/12	0/13	0/10	—
Plasma tau, ng/l	35.5 ± 9.9	32.7 ± 9.1	32.8 ± 8.3	0.59
Total tau, ng/l	252.1 ± 62.6	293.6 ± 107.0	304.4 ± 118.2	0.55
Metformin	0 (0)	0 (0)	9 (90)	—
DPP4 inhibitors	0 (0)	0 (0)	2 (20)	—
Thiazolidinediones	0 (0)	0 (0)	0 (0)	—
Statins	0 (0)	2 (15)	5 (50)	—

Data are presented as mean ± SD or *n* (%) unless otherwise stated

Radioligand concentration in arterial blood was measured with an automated blood sampling system (Twilite two; Swisstrace, Zurich, Switzerland) to obtain high frequency measurements for the first 10 min post radioligand injection. In addition, eight manual plasma samples distributed between 5 min and 45 min after radioligand injection were collected and used to measure the radioactivity concentration in whole blood and plasma. The samples taken at 5, 15 and 25 min post injection were also used to measure the parent fraction [21] using HPLC.

ASL

Whole brain perfusion maps were acquired using a 3D pseudo-continuous ASL imaging sequence with transit delay correction, provided by the scanner manufacturer (eASL – Enhanced Arterial Spin Labelling).

MRS

MRS was used to assess NAA and choline/creatine signal ratios in hippocampus, anterior cingulate cortex, precuneus and centrum semiovale via a single-voxel point-resolved spectroscopy (PRESS) sequence. The respective number of excitations and voxels placements are provided in ESM 3.

CSF and plasma samples

All participants (except one in the diabetes group) underwent lumbar puncture. The procedure was performed by a trained

physician according to standard clinical routine. Samples were immediately frozen and subsequently shipped to Gothenburg University Hospital for analysis. CSF concentrations of selected biomarkers for neurodegeneration (amyloid-β [Aβ] 1–40, Aβ 1–42, plasma tau 181 and total tau) were measured using the LUMIPULSE G assay (Fujirebio, Ghent, Belgium). Individuals with an Aβ 1–42/Aβ 1–40 ratio <0.072 were assigned amyloid positive [22].

Blood samples were acquired for *APOE* genotyping and for analysis of fasting plasma insulin and glucose levels to calculate HOMA-IR. During imaging sessions, blood samples were taken to measure plasma glucose and serum NEFA levels before and after the [^{18}F]FDG and [^{18}F]FTHA PET measurements, respectively. Samples were stored at −70°C and shipped to clinical chemistry laboratory TYKSLAB (Laboratory of Turku University Hospital), where NEFA measurements were performed.

Data analyses

Brain regions of interest Anatomical brain regions of interest (ROIs) were derived from the Automated Anatomical Labelling atlas, via processing of the T1-weighted MR image using SPM12 (https://www.fil.ion.ucl.ac.uk/spm). ROIs were derived for the following brain structures: parietal lobe; temporal lobe; occipital lobe; frontal cortex; anterior cingulate cortex; precuneus; hippocampus; and cerebellar cortex. ROIs covering the entire grey and white matter were also included.

PET data quantification Arterial input functions (AIFs) were created for both [^{18}F]FDG and [^{18}F]FTHA data. For [^{18}F]FDG, the AIFs were derived by concatenating the radioactivity signal measured in descending aorta in the thorax scan with plasma samples obtained at 20 min and 60 min post radioligand injection. For [^{18}F]FTHA, a plasma/blood ratio was calculated from the manual blood samples and used to convert the automated measurements to a plasma curve. This curve was then concatenated with the plasma samples. A parent fraction curve, obtained by fitting a single exponential function to the measured parent fractions, was then multiplied by the plasma curve, resulting in a metabolite-corrected [^{18}F]FTHA AIF. Whole-blood and plasma samples were also used to estimate the haematocrit.

For both [^{18}F]FDG and [^{18}F]FTHA, the Patlak Graphical Analysis approach was used to calculate net radioligand influx rate, K_i [23]. For [^{18}F]FDG, all four PET frames (i.e. approximately 27–47 min post injection) were included in the analysis. The metabolic rate of glucose (MRGlu) was calculated by multiplying the [^{18}F]FDG K_i value by the mean glucose level measured before and after the scan. For [^{18}F]FTHA, only PET data acquired until 15 min post radioligand injection were included ($t^* = 5$ min) as the Patlak plot did not display a linear behaviour for the reminder of the acquisition time. This approximate time window has also been used in previous reports using [^{18}F]FTHA [12]; see ESM 4 for additional details. No correction for circulating NEFA was performed (see Discussion). Instead we interpreted the [^{18}F]FTHA K_i values as an indicator of fatty acid uptake. Parametric maps of K_i and MRGlu were created with in-house software, and spatially normalised to MNI-space using SPM12 for visualisation.

Statistical procedures

Group differences in imaging outcomes were assessed using a one-way ANOVA, followed by post hoc pairwise comparisons. Where parameter distribution was not normal, the parameters were log-transformed prior to analysis. Imaging outcomes were correlated to each other, as well to other measurements (e.g. HOMA-IR, insulin levels and HbA_{1c}) using linear regression. Unpaired *t* tests were performed to investigate differences between carriers and non-carriers of the *APOE-ε4* isoform. As there was only one *APOE-ε4* homozygote, the carrier group included both homozygotes and heterozygotes. Due to the exploratory nature of the current study, no corrections for multiple comparisons were performed.

Results

Table 1 displays the demographics of the included cohort. Notably, participants with type 2 diabetes were slightly older with a different gender distribution than the other groups. Three individuals (all lean control participants) were assigned amyloid positive from the CSF samples. These individuals had similar imaging outcome measures as the other lean control participants and were therefore included in all subsequent analyses. Aβ and tau levels were similar between the groups. Most participants with type 2 diabetes were treated with metformin (9/10) and a few with dipeptidyl peptidase-4 (DPP4) inhibitors (2/10).

Glucose uptake

Results from the [^{18}F]FDG examinations are shown in Fig. 1. [^{18}F]FDG uptake was consistently lower among participants with diabetes compared with the control groups, both when given as the net influx rate of [^{18}F]FDG (K_i), and as MRGlu. This group difference was consistent in all investigated brain regions except for cerebellum, where there was no difference in MRGlu between participants with diabetes and lean control participants.

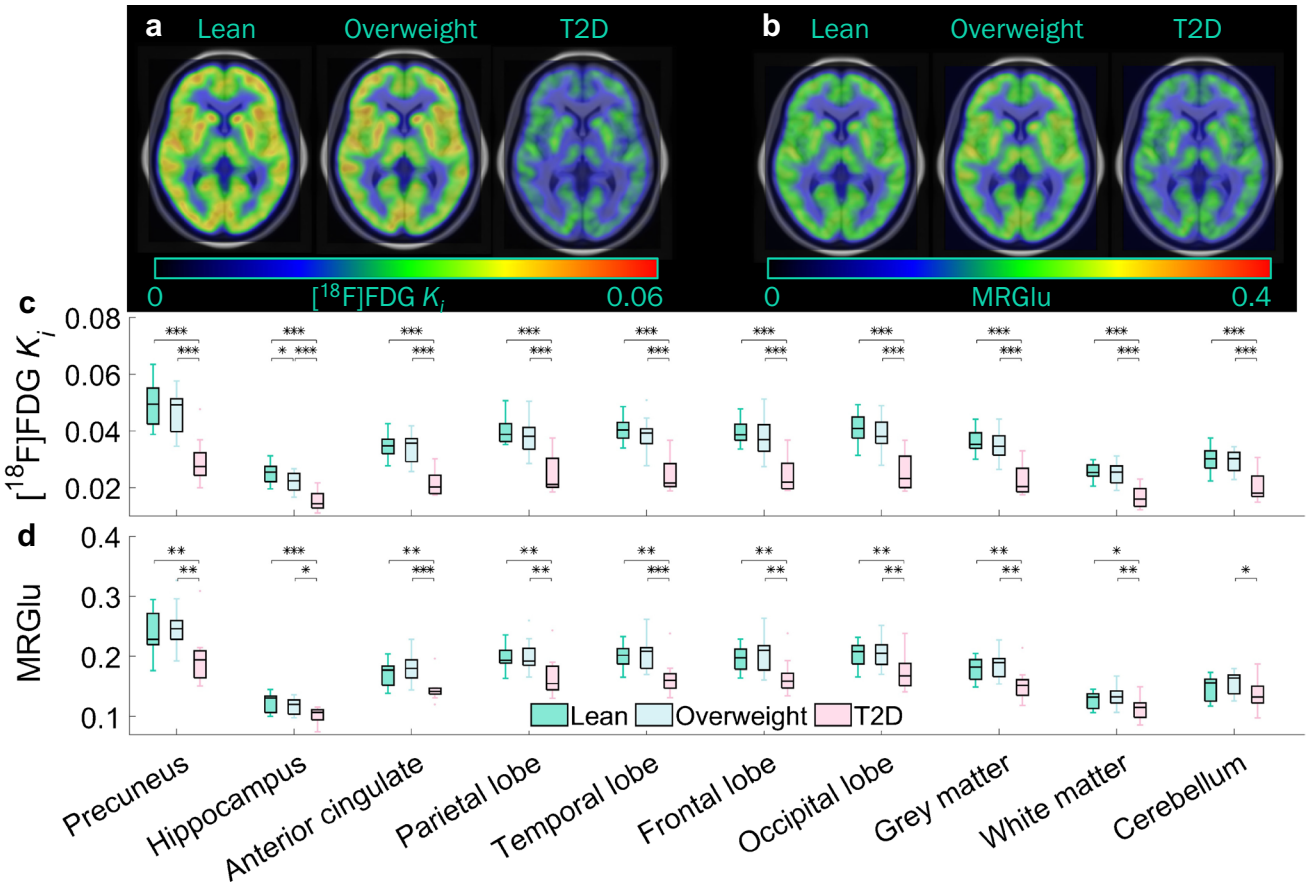

Fig. 1 Results from [^{18}F]FDG PET measurements. (**a**, **b**) Group average parametric maps (across participants within each group) of [^{18}F]FDG K_i (**a**) and MRGlu (**b**). (**c**, **d**) [^{18}F]FDG K_i (**c**) and MRGlu (**d**) PET data quantified in selected brain regions. [^{18}F]FDG K_i and MRGlu were both consistently lower among participants with diabetes compared with other groups across all regions except cerebellum. n=15 lean, 13 overweight and 10 participants with diabetes. The box extends from the first to the third quartile, and the horizontal line indicates the median. Whiskers extend to the data range, excluding outliers, which are shown as individual points. *p<0.05, **p<0.01, ***p<0.001. T2D, type 2 diabetes

Fatty acid uptake

Results from the [^{18}F]FTHA examinations are displayed in Fig. 2. Increased K_i values were observed among participants with type 2 diabetes in the whole white matter but this difference did not reach statistical significance in other brain regions. In addition, an unexpected large variance was observed among the lean control participants.

Perfusion

Participants with type 2 diabetes and overweight control participants had lower brain perfusion than lean controls (Fig. 3). This effect was consistent across all brain regions investigated. No group differences were detected in the arterial transit delay times (i.e. the duration for the labelled spins to reach the brain region of interest) (ESM 5).

As highlighted in previous reports, differences in haematocrit may cause biased estimates of brain perfusion [24]. Our data showed a strong association between the haematocrit and the perfusion measurements (ESM 6). Yet, there was no group difference in haematocrit (p=0.27). Including haematocrit as a covariate did not change the group difference observed in the ASL data (ESM 6).

Effect of *APOE-ε4*

To better understand the variance in the [^{18}F]FTHA data, a post hoc analysis was performed between carriers and non-carriers of *APOE-ε4*. Results from this stratification is shown in Fig. 4. Among lean controls, *APOE-ε4* carriers had higher [^{18}F]FTHA K_i in several brain regions compared with non-carriers. A similar effect was not observed among overweight controls. When considering only the non-carriers of the *APOE-ε4* allele, increased [^{18}F]FTHA K_i was observed in participants with diabetes relative to the lean control group in all brain regions and an intermediate uptake rate was observed in the overweight group. The corresponding

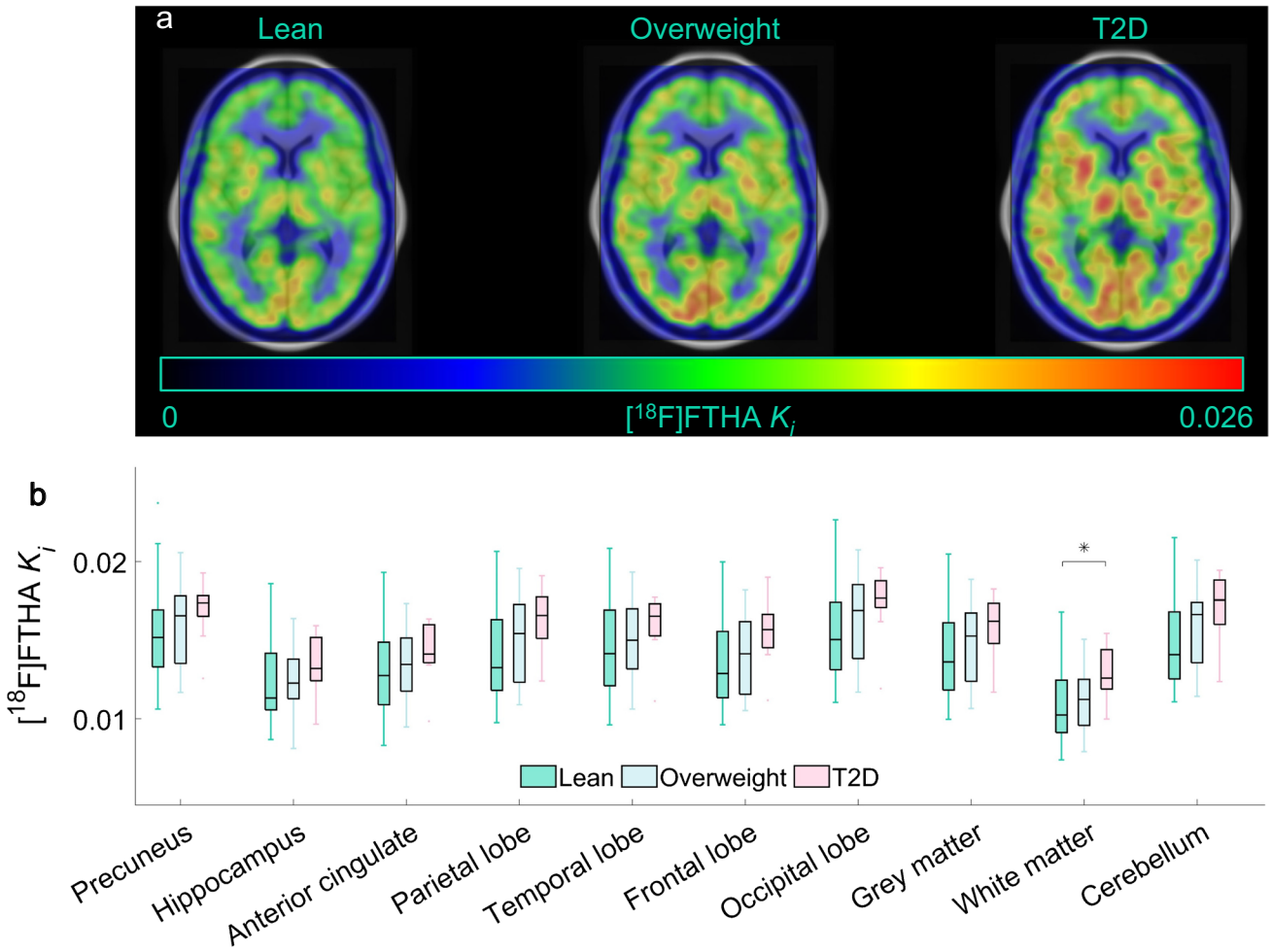

Fig. 2 Results from [^{18}F]FTHA PET measurements. Group average parametric maps of [^{18}F]FTHA K_i values are shown (**a**), with corresponding data quantified in selected brain regions (**b**). There were no group differences in [^{18}F]FTHA K_i values except in white matter, where participants with diabetes had higher [^{18}F]FTHA K_i than lean control participants. n=15 lean, 13 overweight and 10 participants with diabetes. The box extends from the first to the third quartile, and the horizontal line indicates the median. Whiskers extend to the data range, excluding outliers, which are shown as individual points. *p<0.05. T2D, type 2 diabetes

comparison could not be performed for the type 2 diabetes group due to the sample size being too small. In addition, stratifying the cohort based on *APOE* genotype revealed that ε4-carrying lean control participants had both higher perfusion and higher MRGlu in several brain regions compared with non-carriers (see ESM 7).

Correlation between imaging outcomes, markers of metabolic derangement and CSF biomarkers

Cerebral perfusion, MRGlu and [^{18}F]FTHA K_i values were all correlated with markers of deranged metabolism (HOMA-IR, HbA_{1c} and plasma insulin levels) (Fig. 5). Perfusion and MRGlu were negatively correlated with these markers, whereas among non-carriers of *APOE-ε4*, a positive association was observed for [^{18}F]FTHA K_i.

Perfusion in whole grey and white matter was negatively associated with levels of total tau in CSF (r=0.47, p=0.0043 and r=0.48, p=0.0034 for grey and white matter, respectively). No significant association was observed between perfusion and either MRGlu or [^{18}F]FTHA K_i, or between [^{18}F]FDG and [^{18}F]FTHA uptake (ESM 8).

In the anterior cingulate cortex, [^{18}F]FTHA K_i was negatively correlated to both the NAA/creatine ratio (r=0.43, p=0.01) and the choline/creatine ratio (r=0.38, p=0.03). Similar associations were not observed in other brain regions. No group differences were observed for any of the metabolites (ESM 9).

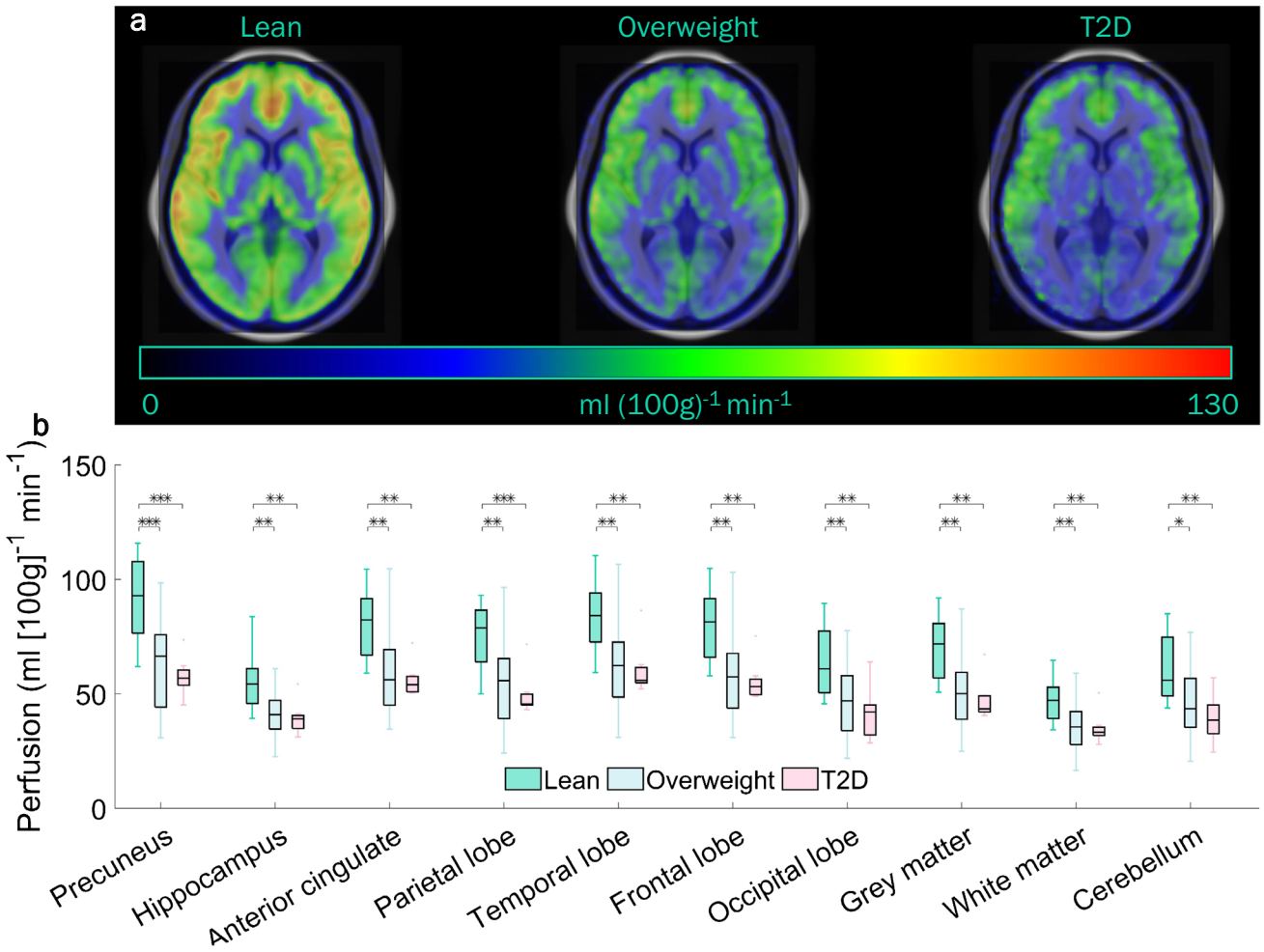

Fig. 3 Lower perfusion as measured with ASL was observed among participants with type 2 diabetes and overweight individuals across all considered brain regions. Average parametric maps of perfusion are shown (**a**), with results quantified in selected brain regions (**b**). n=15 lean, 13 overweight and 10 participants with diabetes. The box extends from the first to the third quartile, and the horizontal line indicates the median. Whiskers extend to the data range, excluding outliers, which are shown as individual points. *p<0.05, **p<0.01, ***p<0.001. T2D, type 2 diabetes

Discussion

In this exploratory study, the reduced cerebral glucose uptake in type 2 diabetes is corroborated and increased fatty acid uptake (estimated as [^{18}F]FTHA K_i values) in white matter is observed. Another important novel observation is the dependence on *APOE-ε4* for fatty acid uptake. Carrying *APOE-ε4* results in higher fatty acid uptake in lean controls. Among non-carriers of *APOE-ε4*, participants with type 2 diabetes had higher [^{18}F]FTHA K_i than lean participants in all investigated brain regions. We also demonstrate lower cerebral perfusion among overweight participants and participants with type 2 diabetes compared with lean participants, and a negative correlation between total tau in CSF and cerebral perfusion. Finally, we report negative correlations between biomarkers of deranged metabolism (HOMA-IR, fasting plasma insulin, HbA_{1c}) and both cerebral perfusion and glucose uptake, and positive correlation between these biomarkers and [^{18}F]FTHA K_i in white matter.

While reduced cerebral perfusion is an established finding in Alzheimer's disease [25], previous perfusion studies in type 2 diabetes have reported mixed results [19, 20, 26]. Since lower perfusion was also observed in overweight individuals, our findings suggest that alterations in cerebral perfusion may occur before the onset of type 2 diabetes or are related to overweight rather than diabetes itself. The finding that HOMA-IR, fasting insulin levels and HbA_{1c} are inversely associated with cerebral perfusion indicates that the common factor explaining low cerebral perfusion in diabetes and overweight is likely insulin resistance, which is a documented risk factor for Alzheimer's disease. That cerebral perfusion correlated negatively with total tau levels

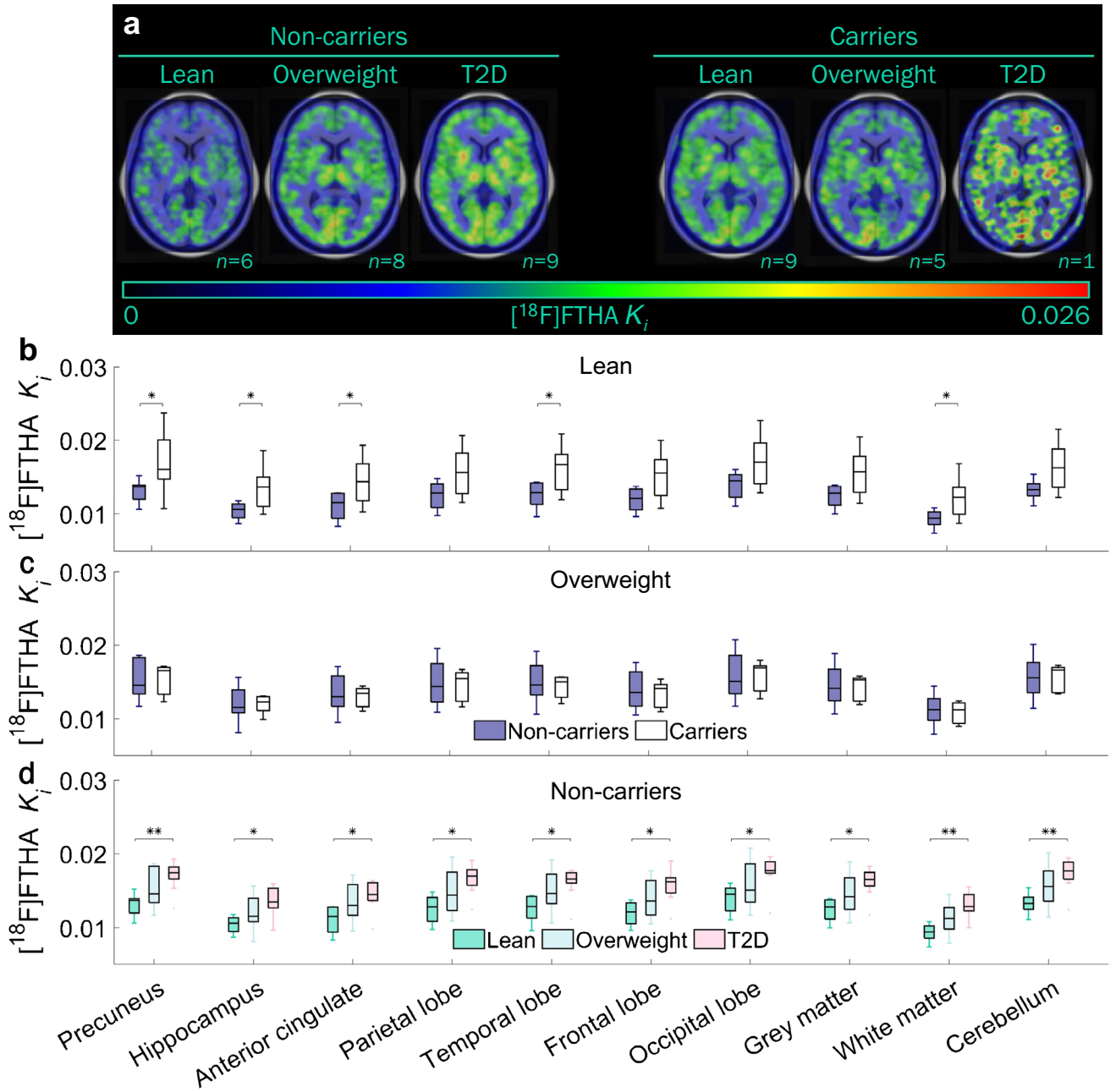

Fig. 4 Results from [^{18}F]FTHA PET measurements in carriers and non-carriers of the *APOE-ε4* isoform. Average parametric maps of [^{18}F]FTHA K_i values for each group are shown (**a**), with corresponding PET data quantified in selected brain regions of lean control participants (**b**), overweight participants (**c**) and non-carriers of the *APOE*-ε4 isoform (**d**). Among the lean control participants, *APOE-ε4* carriers had higher [^{18}F]FTHA K_i values than non-carriers, whereas no difference between genotypes were observed in the overweight control group. Among non-carriers of the *APOE*-ε4 isoform, participants with diabetes had higher [^{18}F]FTHA K_i than lean control participants. The box extends from the first to the third quartile, and the horizontal line indicates the median. Whiskers extend to the data range, excluding outliers, which are shown as individual points. *p<0.05, **p<0.01. T2D, type 2 diabetes

in the CSF is also of interest, as CSF tau levels are associated with Alzheimer's disease pathology [27]. Because we did not see any group differences in arterial transit delay times (see ESM 5), we speculate that the altered perfusion primarily reflects changes in microcirculation rather than obstruction of large vessels. We also observe that lean control individuals who carry *APOE-ε4* had higher perfusion than those without this variant (ESM 7). This finding is consistent with observations from previous studies [28].

This study also reports lower cerebral glucose uptake among participants with diabetes compared with control participants across all brain regions investigated, except for

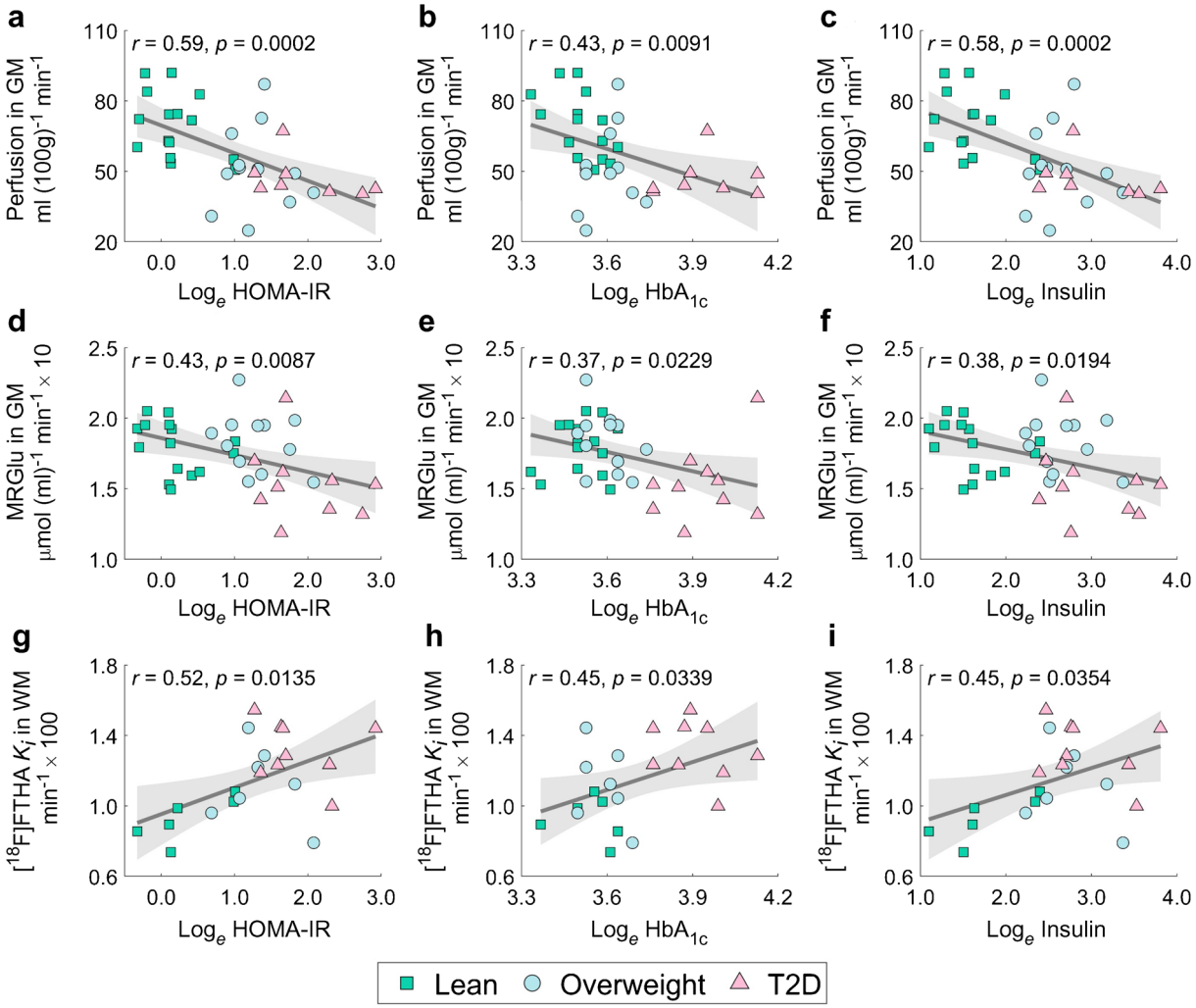

Fig. 5 Cerebral perfusion (**a**–**c**) and MRGlu (**d**–**f**) in whole grey matter (GM) were both negatively correlated with HOMA-IR, HbA_{1c} and plasma insulin levels, and fatty acid uptake (**g**–**i**) in white matter (WM) was positively correlated with these markers of deranged metabolism

cerebellum. In addition to being a robust finding in Alzheimer's disease [29], impaired [^{18}F]FDG uptake in the fasted state has been reported for individuals with obesity, impaired glucose tolerance and type 2 diabetes with cognitive impairment [30–32]. That cerebellum is less affected than other brain regions aligns with this structure having been identified as a 'pathologically preserved' region in several neurodegenerative disorders (including Alzheimer's disease) and often serves as a reference region for imaging of amyloid, tau and translocator protein (TSPO) [33–35].

A lower rate of cerebral glucose metabolism in participants with diabetes raises the question of to what extent systemic insulin resistance affects cerebral glucose uptake. In the current study, insulin resistance, as measured with HOMA-IR, correlated negatively with MRGlu. Although cerebral insulin signalling is associated with many brain functions, it is not currently considered to be a significant regulator of cerebral glucose metabolism [36], yet its role in Alzheimer's disease pathology is receiving increased interest [37]. Lastly, it has been reported that individuals with impaired glucose tolerance and obesity show an elevated cerebral glucose uptake during hyperinsulinaemia [30, 31].

We demonstrate that among non-carriers of *APOE-ε4*, participants with type 2 diabetes had elevated influx rate of the fatty acid PET tracer in several brain regions. This finding aligns with previous studies in obesity and the metabolic syndrome [12, 13]. There are several metabolic pathways for fatty acids in the brain, including biosynthesis pathways (e.g. formation of phospholipids, sphingolipids and triacylglycerols), and fatty acid oxidation for ATP production [38]. Importantly, β-oxidation of fatty acids comes with a higher oxygen demand than oxidation of glucose, and mitochondrial β-oxidation of fatty acids is associated with generation of reactive oxygen species, oxidative stress and

mitochondrial dysfunction [39, 40]. It could be speculated that the increased uptake of fatty acids is a compensatory mechanism to account for diminished ATP production following decreased glucose uptake and may eventually result in harmful effects to brain cells.

Among the lean control participants, *APOE-ε4* carriers had a higher [^{18}F]FTHA influx rate than non-carriers. This aligns with previous reports showing increased brain uptake of docosahexaenoic acid [41], and increased formation of lipid droplets in astrocytes [42] in *APOE-ε4* carriers. Carrying the *APOE-ε4* allele has been identified as the single most important genetic risk factor for developing late-onset Alzheimer's disease [43] and corroborates the idea of altered lipid metabolism in the brain as part of the Alzheimer's disease pathogenesis. In our data, lean physically active control participants who carried the *APOE-ε4* allele displayed similar fatty acid influx rates as overweight participants and participants with diabetes without the allele. This finding indicates that carrying the ε4 isoform and having type 2 diabetes could be two independent risk factors that both contribute to increased cerebral fatty acid uptake, which in turn may provoke negative effects on brain metabolism and contribute to neurodegeneration. Carrying the ε4 isoform has also been observed as a risk factor for neurodegenerative disorders beyond Alzheimer's disease [44].

An important consideration in this study is the potential impact of perfusion changes on PET tracer delivery to the brain. The lower MRGlu in participants with type 2 diabetes compared with both overweight and lean control individuals is unlikely to be only due to perfusion changes, as type 2 diabetes and overweight groups had similar perfusion. Higher [^{18}F]FTHA in white matter in type 2 diabetes or type 2 diabetes *APOE-ε4* non-carriers was observed despite reduced perfusion in participants with type 2 diabetes. Moreover, there was no correlation between [^{18}F]FTHA K_i values and perfusion (r=0.06, p=0.72 in white matter, ESM 8). Therefore, it is likely that the increased influx of [^{18}F]FTHA is mainly explained at the cellular level. However, the higher [^{18}F]FTHA influx in lean *APOE-ε4* carriers might be perfusion-related, as they also showed increased perfusion. We acknowledge that the full impact of perfusion on PET tracer uptake is not completely assessed in our analyses.

Our study used lean, physically active participants as a control group, contrasting with sedentary lifestyles in the other groups. This choice aimed to represent an 'optimal' metabolic state that could be targeted in potential intervention trials, and to maximise the difference in insulin resistance between groups, emphasising its potential connection to brain metabolism. However, this design introduces a limitation: by including physical activity as an additional variable, it does not allow for isolating obesity effects independent of activity levels. This constraint should be considered when interpreting the results.

Further, the potential influence of glucose-lowering medications on our results warrants consideration. While SGLT2 inhibitors, insulin and GLP1 receptor antagonists were excluded, participants with type 2 diabetes were treated with DPP4 inhibitors, statins and metformin. Few participants (2/10) were on DPP4 inhibitors, while a majority were on metformin (9/10) and therefore we cannot exclude the possibility that metformin impacted the results. However, previous studies suggest that the effect of metformin on [^{18}F]FDG uptake is small and localised [45, 46]. With regards to statins, a subgroup analysis (not shown) revealed no significant differences in [^{18}F]FDG uptake, [^{18}F]FTHA uptake or perfusion between statin users (5/10 participants) and non-users. Therefore, we believe that the included medications have not substantially impacted the interpretation of our data, though this limitation should be noted.

For [^{18}F]FTHA, we only report the rate constant, K_i, which represents the net influx rate of the tracer into brain tissue [23]. We interpret this parameter to be indicative of cerebral fatty acid uptake, although the outcome measure technically only reflects the influx of the tracer itself. Some studies have reported 'fatty acid uptake' [12, 13] analogous to MRGlu for [^{18}F]FDG. Fatty acid uptake is calculated by multiplying tracer influx rate by plasma substrate concentration and correcting for transport and phosphorylation rate differences. This conversion is relevant for [^{18}F]FDG due to glucose-tracer competition at blood–brain barrier transporters. However, such competition between [^{18}F]FTHA and circulating NEFA has not been demonstrated to be rate-limiting for brain fatty acid uptake. In our study, circulating NEFA measurements were unreliable due to unexpected variance between pre- and post-PET scans, attributed to methodological issues rather than true NEFA variability. Consequently, we omitted fatty acid uptake estimation. Notably, obese individuals and those with type 2 diabetes typically have, if anything, elevated serum NEFA [47]. Therefore, we can conclude the following: (1) that if fatty acid–[^{18}F]FTHA competition is rate-limiting for brain fatty acid exposure, the elevated K_i values among participants with type 2 diabetes may be underestimated; and (2) that with higher K_i values and serum NEFA, the difference in cerebral fatty acid uptake between control participants and participants with type 2 diabetes is likely larger than reported here.

We acknowledge that the current study includes a small and slightly unbalanced sample size, where participants with diabetes were marginally older and had a different gender distribution compared with other groups. This is particularly important to consider when interpreting the [^{18}F]FTHA results, as, in contrast to both perfusion and glucose uptake, this is the first study to report an *APOE-ε4*-dependent increase in fatty acid uptake. Due to the small sample size, correlational analyses were performed on the entire cohort, possibly resulting in inflated associations, Additionally, the

sample size prevented a meaningful gender analysis, limiting the generalisability of our findings across genders. Finally, because correction for multiple comparisons has not been performed, the findings should be considered exploratory and need to be replicated in larger trials.

Conclusion

In summary, the results from this study show that lower cerebral perfusion, reduced brain glucose and increased fatty acid uptake occur in individuals with type 2 diabetes. They further demonstrate that *APOE-ε4* carriers, who have increased risk for developing late-onset Alzheimer's disease, also have increased fatty acid uptake in the brain. We propose that these metabolic changes are key to understanding the mechanisms that link together type 2 diabetes and neurodegenerative disorders.

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Data availability The datasets generated and analysed in the current study are available from the corresponding author upon reasonable request.

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Authors' relationships and activities MS, EJ, IL, AFL, LJ and KH are employed by Antaros Medical. JO and RE are employed by AstraZeneca. The authors declare that there are no other relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement MS and IL were involved in conduct, analysis and interpretation. EJ, ML, AG, TD, PN, RE, LJ, JO and KH were involved in the conception, design and conduct of the study and the analysis and interpretation of the results. AFL was involved in conception, design and conduct of the study. MS wrote the first draft of the manuscript and all authors edited, reviewed and approved the final version. MS 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 analyses.

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