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Regional gray matter changes in steatotic liver disease provide a neurobiological link to depression: A cross-sectional UK Biobank cohort study

Dominic Arold [a], Stefan R. Bornstein [b,c,d], Nikolaos Perakakis [b,c,d,1], Stefan Ehrlich [a,1], Fabio Bernardoni [a,*,1]

[a] Translational Developmental Neuroscience Section, Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Dresden, Germany
[b] Department of Internal Medicine III, University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany
[c] Paul Langerhans Institute Dresden (PLID), Helmholtz Center Munich, University Hospital and Faculty of Medicine, TU Dresden, Dresden, Germany
[d] German Center for Diabetes Research (DZD e.V.), Neuherberg, Germany

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ABSTRACT

Background: Steatotic liver disease (SLD) is characterized by excessive accumulation of lipids in the liver. It is associated with elevated risk of hepatic and cardiometabolic diseases, as well as mental disorders such as depression. Previous studies revealed global gray matter reduction in SLD. To investigate a possible shared neurobiology with depression, we examined liver fat-related regional gray matter alterations in SLD and its most significant clinical subgroup metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: We analyzed regional cortical thickness and area obtained from brain MRI in 29,051 participants in UK Biobank. Liver fat amount was computed as proton density fat fraction (PDFF) from liver MRI scans. We examined the relationship between brain structure and PDFF, adjusting for sociodemographic, physical, lifestyle, and environmental factors, as well as alcohol intake and a spectrum of cardiometabolic covariates. Finally, we compared patterns of brain alterations in SLD/MASLD and major depressive disorder (MDD) using previously published results.

Results: PDFF-related gray matter alterations were region-specific, involving both increases and decreases in cortical thickness, and increased cortical area. In several regions, PDFF effects on gray matter could also be attributed to cardiometabolic covariates. However, PDFF was consistently associated with lower cortical thickness in middle and superior temporal regions and higher cortical thickness in pericalcarine and right frontal pole regions. PDFF-related alterations for the SLD and the MASLD group correlated with those observed in MDD (Pearson $r = 0.45–0.54$, $p < 0.01$).

Conclusion: These findings suggest the presence of shared biological mechanisms linking MDD to SLD and MASLD. They might explain the well-known elevated risk of depression in these groups and support early lifestyle interventions and treatment of metabolic risk factors for the successful management of the interconnected diseases depression and SLD/MASLD.

Abbreviations: BMI, body mass index; CT, cortical thickness; FDR, false discovery rate; IDEAL, iterative decomposition of water and fat with echo asymmetry and least-squares estimation; IDP, imaging derived phenotype; IPAQ, International Physical Activity Questionnaire; lh, left hemisphere; MASLD, metabolic dysfunction-associated steatotic liver disease; MDD, major depressive disorder; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; PDFF, proton density fat fraction; rh, right hemisphere; SBP, systolic blood pressure; SLD, steatotic liver disease.

* Corresponding author at: Translational Developmental Neuroscience Section, Division of Psychological and Social Medicine and Developmental Neurosciences, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, Fetscherstraße 74, Dresden 01307, Germany.
E-mail address: fabio.bernardoni@ukdd.de (F. Bernardoni).

[1] These Authors contributed equally to this work

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1. Introduction

Excessive accumulation of lipids in the liver ("liver fat") is primarily the result of overnutrition and/or increased alcohol intake [1]. This condition is known as hepatic steatosis, or steatotic liver disease (SLD), as recently named by a multi-society Delphi consensus statement [1]. SLD can be identified by imaging (e.g. ultrasound, MRI) or by biopsy and can progress to steatohepatitis, liver fibrosis, cirrhosis and/or hepatocellular carcinoma [1–3]. SLD is very common in the general population, particularly among individuals with obesity, diabetes, and hyperlipidemia, even in the absence of significant alcohol intake. Previously, clinicians used the term non-alcoholic fatty liver disease (NAFLD) to denote SLD in the absence of (excessive) alcohol consumption and other known liver diseases [4,5]. To provide an affirmative, non-stigmatizing name and diagnosis the condition of "metabolic dysfunction–associated steatotic liver disease" (MASLD) has been introduced recently in the nomenclature [1]. MASLD can be considered the hepatic manifestation of metabolic syndrome [5]. It refers to individuals with SLD in combination with at least one cardiometabolic risk factor, but no excessive alcohol consumption and no other known liver disease [1]. 98 % of individuals previously diagnosed with NAFLD would fall within the MASLD category [6]. Therefore, most previous findings associated with NAFLD should be applicable to MASLD as well. In our manuscript, we will still use the term NAFLD to correctly refer to knowledge which was generated using the old nomenclature. Epidemiological studies suggested that not only the presence of SLD (or specifically of NAFLD), but also the amount of liver fat is associated with an increased risk of development and progression of hepatic and cardiometabolic diseases [2]. This association might be causal, as the liver releases various signals, such as hormones, damage-associated molecular patterns, cytokines, metabolites, and neural signals that can regulate the function of various organs involved in energy and glucose homeostasis [3,7–10].

The brain is also an important organ for the homeostatic regulation of energy and glucose metabolism [11]. Conversely, obesity, diabetes, and NAFLD have been associated with an increased risk of brain and mental disorders, including dementia and depression [12,13]. Depression accounts for a substantial proportion of the years lived with disability worldwide [14,15]. Primary treatments such as antidepressant medication and cognitive behavioral therapy [16] address less than half of the impact of the disorder [17], indicating the need for more comprehensive prevention and treatment strategies. In adults and older adults depression also frequently co-occurs with metabolic conditions such as metabolic syndrome [18], which not only creates complex and multifaceted health challenges, but also spurs hypotheses about shared underlying biological mechanisms [19]. Depression has been associated with altered connectivity and network function, as well as with structural changes in the brain [20,21]. Interestingly, the presence of NAFLD and the amount of liver fat have also been suggested to correlate with alterations in brain volume and structure. This might provide a pathophysiological link between hepatic steatosis and brain or mental disorders [22–25]. Specifically, NAFLD has been associated with smaller total brain volume and lower gray matter cerebral blood flow [24,25]. Liver fat amount as assessed by MRI has also been shown to be linked to smaller total and gray matter brain volumes, increased white matter hyperintensities and altered white matter characteristics [23]. Although these studies provide some insight into the liver-brain axis, which might be perturbated in SLD, they have several important limitations. First, they focused on whole-brain structural changes rather than regional differences. Moreover, they did not compare the reported brain alterations related to SLD or MASLD to alterations observed in specific neurological or psychiatric conditions. Finally, in many cases, due to small sample sizes, it may not have been possible to account for all potentially confounding factors. Therefore, it was unclear whether the observed associations were truly related to liver fat accumulation or to the presence of relevant confounding factors.

Therefore, the first aim of our study was to evaluate whether and how liver fat measured by MRI was associated with regional characteristics of brain structure. Because the possible associations might be mediated by confounding factors, we used two models to control for a wide spectrum of covariates. The Base model controlled for a wide set of covariates, including sociodemographic, physical, lifestyle, environmental, and imaging factors. The Full model additionally controlled for potentially confounding cardiometabolic covariates and alcohol intake. Brain structural alterations linked to elevated liver fat (defined as liver fat amount $>$ 5.5 %), commonly referred to as SLD, and its subset MASLD were calculated using these models. To this end, we used a large population-based dataset collected by the UK Biobank. Participants underwent a liver MRI scan, from which proton density fat fraction (PDFF) was derived, and a structural MRI of the brain, taken on the same day. The second aim of our study was to evaluate the correspondence in structural brain changes between SLD, especially MASLD, and depression. Given our hypothesis of (partially) shared underlying mechanisms linking SLD and MASLD with depression, we tested for spatial alignment between SLD-related and MASLD-related brain changes with alterations in brain structure previously observed in the largest existing multi-site cohort of patients with depression from the ENIGMA Consortium [26,27]. Additionally, we compared our findings with alterations in brain structure previously observed in obsessive-compulsive disorder [28] as a negative control.

2. Methods

2.1. Study population

This research was conducted using the UK Biobank Resource under Application Number 43880. UK Biobank is a large prospective research cohort of approximately 500,000 population-based participants in the UK (baseline visit), aged 40–69 years, and recruited between 2006 and 2010. To date, brain and liver MRI images, acquired on the same day for each participant, were available for a large subset of over 60,000 participants. Of these, 29,051 had MRI-derived variables available for both, structural brain measures and liver fat PDFF (see below), which constituted our main sample. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. Ethical approval was granted from the North West Multicenter Research Ethics Committee. All participants gave written informed consent at recruitment. We considered all study participants whose data were available as of March 22, 2023.

2.2. MRI acquisition and processing

Brain and liver MRI images were obtained at the same imaging visit. Brain images were acquired using a Siemens Skyra 3 T scanner and an MPRAGE sequence (Supplementary Methods 1.1) and processed by the UK Biobank team [29,30]. We selected 138 imaging-derived phenotypes (IDPs) as primary outcomes: Six typically studied global measures comprised whole-brain gray matter volume, cerebrospinal fluid (CSF) volume, and hemispheric average cortical thickness (CT) and total surface area, while regional outcomes comprised all available 66 regional CT and 66 surface area IDPs derived using the Desikan-Killiany parcellation [31]. All brain measures and regression results for each are listed in the accompanying The Open Science Framework (OSF) repository.

Liver MRI images were acquired using a Siemens 1.5 T scanner as part of the UK Biobank abdominal imaging protocol. A single transverse slice was acquired through the center of the liver above the porta hepatis and image analysis was performed as previously described [32,33]. Scanning sequences included an iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) T1 acquisition ($N = 31{,}842$) [34]. Three 15 mm circular regions of interest were identified as representative of parenchymal tissue, from which PDFF was calculated. PDFF is a reliable measure of liver fat based using water-fat separation masks, with PDFF $>$ 5.5 % indicating steatotic liver

disease [33,35].

2.3. Control variables

Sociodemographic covariates included sex, age at imaging visit, and highest educational qualification. Lifestyle and environmental covariates included self-reported smoking status, alcohol intake, physical activity, and Townsend deprivation index. Alcohol intake was calculated as average daily pure ethanol intake based on self-reported consumption of several beverage categories (Supplementary Methods 1.2). Physical activity was quantified from responses to the simplified International Physical Activity Questionnaire (IPAQ) [36] into activity groups as suggested by UK Biobank [37]. Physical measure covariates included standing height, body mass index (BMI) calculated from height and weight, and systolic blood pressure. Lifetime clinical diagnoses were ascertained based on self-report data and linked data from hospital inpatient, death registry, and primary care records. UK Biobank mapped these heterogeneous data sources to summary variables represented as three-digit ICD-10 codes (data category 1712) which we used to define diagnostic categories (Supplementary Methods 1.3). As in previous work, this aggregation of data sources was considered necessary to increase the detection rate [38].

Of note, the above control variables were assessed at the imaging visit, except for the Townsend deprivation index, which was assessed at the earlier baseline visit. For clarity, we reported all variables used in the study, the corresponding UK Biobank fields, and, for derived variables, the formulas in terms of the primary variables (Table 1).

2.4. Statistical analysis

In our primary analysis, we employed General Linear Models to assess the effect of PDFF on global and regional brain structural IDPs. The whole sample ($N = 29,051$) consisted of all UK Biobank participants with values for both PDFF (measured using the IDEAL MRI protocol) and all primary outcomes, i.e. 138 brain structural IDPs as computed from MRI scans by UK Biobank. Within this sample we defined the following groups:

- SLD ($N = 6931$): Participants with steatotic liver disease, defined in our study as having a PDFF > 5.5 %.
- MASLD ($N = 4974$): Subgroup of the SLD cohort where participants had at least one cardiometabolic risk factor, but no other potential causes for steatosis, i.e. no excessive alcohol intake (< 30 g/day for men, < 20 g/day for women [39]) and no other liver disease (Supplementary Table S1). We adhered to the latest established official guidelines [1] for evaluating these criteria within the UK Biobank sample at the time of MRI imaging (Supplementary Methods 1.4).
- Control ($N = 22,120$): All participants not in the SLD group used as a normative comparison group (i.e. PDFF ≤ 5.5 %).

Additionally, we considered a SLD subgroup of participants with especially high liver fat (PDFF >15 %) which is associated with increased odds of fibrosis progression (Fibrosis Risk group; $N = 1492$). A conceptual overview of all groups defined in our sample can be found in Supplementary Table S2. Our main analysis comprised the following two models (Table 1):

Base model: This model assessed the direct effect of PDFF on brain structure. It accounted for sociodemographic, lifestyle, and environmental factors (except alcohol intake). Furthermore, we included as (imaging-related) confounds the main effects of intracranial volume, imaging site and scanner table coordinates (X, Y, Z and table position), as well as site by age/sex interactions, as recommended previously [40].

Full model: This model extended the Base model to control for alcohol intake and cardiometabolic covariates. The latter were incorporated as binary predictors for the presence of 1) any cerebrovascular disease, 2) any heart disease, 3) diabetes, and 4) hyperlipidemia (Supplementary Methods 1.3), along with a continuous (linear) predictor for systolic blood pressure. The aim of the Full model was to assess whether liver fat amount is associated with brain structure independent of these possible confounding factors that may also affect brain structure.

Sensitivity analyses: We also considered models extending the Base model to control only for alcohol intake (AC model) or only for cardiometabolic covariates (CM model) to compare their respective confounding effects on liver fat associations with brain structure (Supplementary Methods 1.5). The Full model corresponds to adding both sets of confounds to the Base model. In additional analyses, we examined whether the PDFF effects estimated in the whole sample were driven by participants with other known liver diseases or excessive alcohol intake. To this end, we replicated the main analyses in a subsample without known liver disease where these participants were excluded (Supplementary Methods 1.6, Fig. S1, Table S3).

Table 1
Overview of the variables used in the Base and Full model. A marked cell in the first two columns indicates that the variable in the corresponding row was used as a covariate in the model in the corresponding column. UK Biobank fields / categories refer to source data IDs. Missing values in the whole sample are summarized as count (percentage). IDPs refer to brain structural outcome measures (dependent variables) tested for liver fat associations in terms of PDFF (independent variable). Lifetime diagnoses were ascertained from self-report data and linked hospital inpatient, death registry, and primary care records (Supplementary Methods 1.3). SBP - systolic blood pressure; BMI - body mass index; PDFF - proton density fat fraction.

Base model	Full model		Variable	UK Biobank fields / categories	Missing values
X	X	Sociodemographic	Sex	31	0
X	X		Age	52, 34, 53	0
X	X		Highest qualification	6138	280 (1.0 %)
	X	Physical	SBP (mmHg)	4080, 93	4662 (16.0 %)
X	X		Height (cm)	50	1213 (4.2 %)
X	X		BMI (kg/m2)	21,001	1278 (4.4 %)
X	X	Imaging	Liver fat (PDFF, %)	40,061	0
X	X		Imaging derived phenotypes (IDP)	Category 192	0
X	X		Intracranial volume (cm3)	26,521	0
X	X		Imaging site	54	0
X	X		Scanner table coordinates	25,756, 25,757, 25,758, 25,759	11 (0.0 %)
X	X	Lifestyle & environment	Smoking status	20,116	182 (0.6 %)
X	X		Physical activity	874, 864, 894, 884, 914, 904	1783 (6.1 %)
X	X		Townsend deprivation index	189	30 (0.1 %)
	X		Alcohol intake (g/day)	Category 100,051	195 (0.7 %)
	X	Diagnoses	Diabetes	Category 1712	N/A
	X		Heart diseases	Category 1712	
	X		Cerebrovascular diseases	Category 1712	
	X		Hyperlipidemia	Category 41,270	

Details about the covariates used in the regression models are provided in Table 1. We also tested for group differences in covariates. For categorical variables Chi2 contingency tests were employed and for continuous normally/non-normally distributed variables *t*-tests/Mann-Whitney *U* tests for independent samples were used. Given the right-skewed distribution of PDFF (Supplementary Fig. S2), we always used log-transformed PDFF values as the main predictor. To account for potential nonlinear relationships of age and BMI with brain structural IDPs [41,42], we also included polynomial terms up to order three for age and up to order two for BMI. These terms were determined by a forward search (Supplementary Methods 1.7). Before model fitting, we performed missing value imputation of covariates (Table 1, Supplementary Methods 1.8) and standard scaling of all included continuous variables. We applied a false discovery rate (FDR) correction [43] ($q < 0.05$) to control for multiple comparisons across all outcome variables (138 brain structural IDPs). Effects on brain structure estimated from the continuous variable PDFF reflect the full range of liver fat percentages. Corresponding cortical surface plots with regression coefficients reflecting this continuous relationship are shown in Supplementary Figs. S3-S10. Based on this, we extracted group-specific, PDFF-related brain structure alterations for the clinically relevant groups SLD, MASLD, and Fibrosis Risk. Specifically, we regressed out all estimated model covariate effects (except PDFF) from the IDPs to obtain de-confounded brain structure measures. From these, we computed Cohen's d effect size maps of PDFF-related brain structure alterations for the SLD (Fig. 1) and MASLD (Fig. 2) group relative to the control group. Statistical analyses were conducted using Python v3.8.10, primarily with the statsmodels v0.13.5 [44] and ENIGMA Toolbox v2.0.3 [27] libraries.

2.5. Neuroanatomical association of steatosis and major depressive disorder

In a subsequent analysis, we sought to determine whether there was an association between PDFF-related brain structure alterations in SLD and MASLD and brain structure alterations implicated in major depressive disorder (MDD), which may indicate a potential pathophysiological link. To this end, we used the regional CT effect size map of regional CT alterations in adult patients with MDD compared to controls, previously obtained in a meta-analysis by the MDD working group within the ENIGMA Consortium. We accessed this map via the ENIGMA Toolbox [27] (Supplementary Fig. S11). This multi-site study was previously conducted in a cohort of patients diagnosed with MDD ($N = 2148$) based on at least one highly validated (semi-)structured interview (CIDI, M-CIDI, SCID, SCID-1, SCAN, MINI, depending on site; see Supplementary Methods 1.4) and healthy control individuals ($N = 7957$). Importantly, Schmaal et al. accounted for site effects (e.g. inclusion criteria, differences in scanners and protocols) using random effects modeling to improve the generalizability of the results obtained. Using the standardized contextualization method in the ENIGMA Toolbox, we correlated effect size maps of CT alterations in SLD and MASLD obtained here with corresponding map for MDD obtained by Schmaal et al. [26] Statistical significance was determined using spin-permutation testing, which accounts for regional homogeneity of cortical brain maps [45]. To probe the specificity of this association, we also tested for correlations with the effect size map of regional CT alterations in adult patients with obsessive-compulsive disorder ($N = 1905$) compared to healthy controls ($N = 1760$), previously obtained by the ENIGMA Consortium [28]. Also this map was accessed through the ENIGMA Toolbox [27].

3. Results

3.1. Sample characteristics

Table 2 summarizes the characteristics of the whole sample ($N = 29,051$). More than 20 % of participants had SLD (defined here as PDFF > 5.5 %). Relative to the control group, participants with SLD did not differ in age, were more frequently male, had lower education, smoked more, were less physically active, consumed more alcohol, lived in more deprived areas, had higher blood pressure and BMI, and had a higher prevalence of lifetime diabetes, cardiovascular disease, hyperlipidemia, and depressive disorders (21.2 % in SLD vs. 18.7 % in control; for inclusion criteria for depressive disorders, see Supplementary Methods 1.4). The same was observed for the MASLD group, except that this group was on average slightly younger than the control group and had a similar percentage of smokers. Conversely, participants with a diagnosis of depressive disorder were more likely to have SLD or MASLD than those without (Supplementary Table S4). Among all continuous predictors in the Full model, PDFF had the highest correlation with BMI (Spearman $r_s = 0.61$) and systolic blood pressure ($r_s = 0.25$).

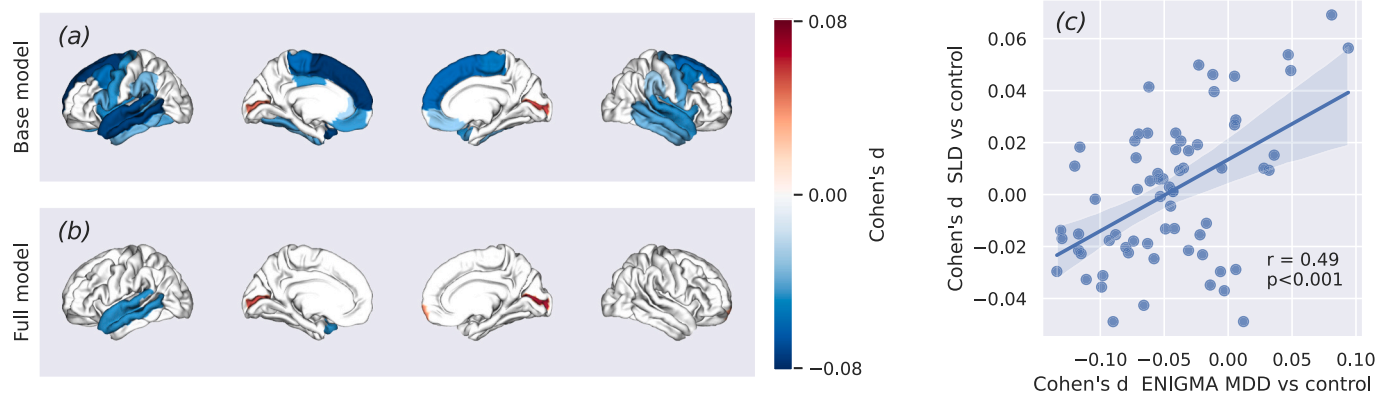

Fig. 1. Liver fat-related cortical thickness alterations in SLD and neuroanatomical association with MDD. Cohen's d effect sizes for the group difference SLD vs. control (PDFF≤5.5 %) explained by liver fat content according to the (a) Base and (b) Full regression models. The Base model accounted for a large set of covariates potentially confounding PDFF effects on brain structure. The Full model additionally accounted for alcohol intake and various cardiometabolic covariates to isolate the PDFF effect unrelated also to these confounds. All covariate factors estimated with the model, except the continuous PDFF effect, were regressed out of the cortical thicknesses to isolate the effect of liver fat on de-confounded cortical thickness. For these measures, Cohen's d between the SLD and control group was calculated. Only regions with significant PDFF effects after FDR correction for multiple comparisons (across all 138 brain structural outcome measures considered in this study) are shown. (c) In all models tested, these cortical thickness effect size maps correlated significantly with the ENIGMA effect size map for MDD. The scatterplot illustrates this for the Full model with a Pearson correlation $r = 0.48$ ($p < 0.001$) between effect size maps. PDFF - proton density fat fraction; SLD - steatotic liver disease; MDD - major depressive disorder.

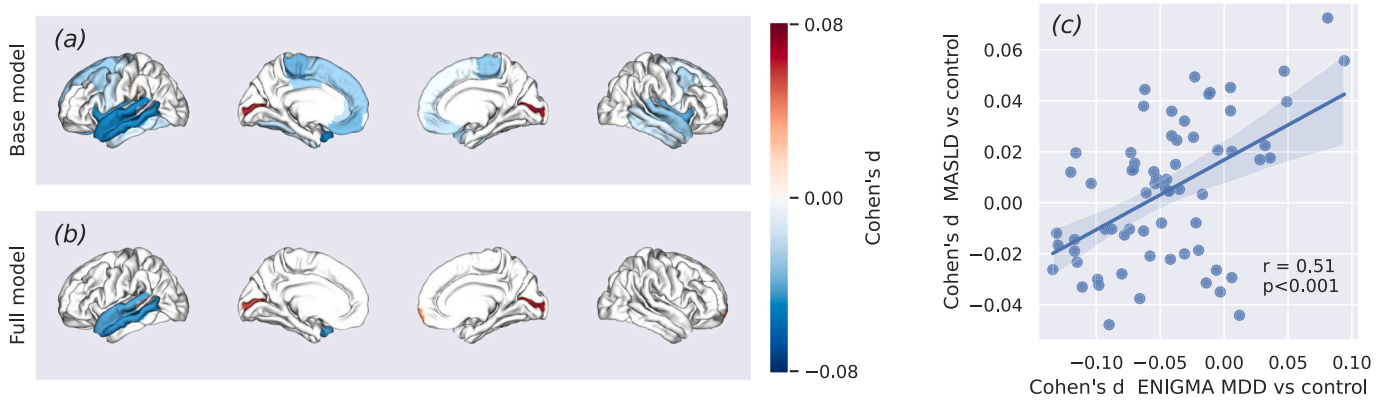

Fig. 2. Liver fat-related cortical thickness alterations in MASLD and neuroanatomical association with MDD. Cohen's d effect sizes for the group difference MASLD vs. control (PDFF ≤ 5.5 %) explained by liver fat content according to the (a) Base and (b) Full regression models. The Base model accounted for a large set of covariates potentially confounding PDFF effects on brain structure. The Full model additionally accounted for alcohol intake and various cardiometabolic covariates to isolate the PDFF effect unrelated also to these confounds. All covariate factors estimated with the model, except the continuous PDFF effect, were regressed out of the cortical thicknesses to isolate the effect of liver fat on de-confounded cortical thickness. For these measures, Cohen's d between the MASLD and control group was calculated. Only regions with significant PDFF effects after FDR correction for multiple comparisons (across all 138 brain structural outcome measures considered in this study) are shown. (c) In all models tested, these cortical thickness effect size maps correlated significantly with the ENIGMA effect size map for MDD. The scatterplot illustrates this for the Full model with a Pearson correlation $r = 0.51$ ($p < 0.001$) between effect size maps. PDFF - proton density fat fraction; MASLD - metabolic dysfunction-associated steatotic liver disease; MDD - major depressive disorder.

Table 2

Sample characteristics. Our whole sample (N = 29,051) consisted of the control group showing no signs of hepatic steatosis (PDFF ≤ 5.5 %) and the SLD group (PDFF > 5.5 %). Also shown are characteristics for the SLD subgroup MASLD, defined according to the latest nomenclature (Supplementary Methods 1.4). The broad definition of depressive disorders was based on several data sources that capture different diagnoses of depressive disorders, as described in Supplementary Methods 1.4. Categorical variables were summarized as count (percentage) and continuous variables as either mean (± standard deviation) or median [25 th percentile, 75 th percentile], if their distribution showed significant deviations from a Gaussian distribution. For each variable, we tested for group differences between control and SLD (pa) or MASLD (pb). For categorical variables, Chi2 contingency tests were applied, and for continuous normally/non-normally distributed variables Welch's t-tests/ Mann-Whitney U tests for independent samples were used. GCSE - General Certificate of Secondary Education; SBP - systolic blood pressure; BMI - body mass index; PDFF - proton density fat fraction; SLD - steatotic liver disease; MASLD - metabolic dysfunction-associated steatotic liver disease.

	Variable		Control (N = 22,120)	SLD (N = 6931)	MASLD (N = 4974)	pa	pb
Sociodemographic	Sex	Female	12,673 (57.3 %)	2792 (40.3 %)	2155 (43.3 %)	<0.001	<0.001
		Male	9447 (42.7 %)	4139 (59.7 %)	2819 (56.7 %)		
	Age at imaging (years)		64.9 (± 7.6)	64.9 (± 7.3)	65.2 (± 7.4)	0.933	0.012
	Highest qualification	Degree	11,555 (52.2 %)	2966 (42.8 %)	2117 (42.6 %)	<0.001	<0.001
		GCSE	5523 (25.0 %)	2125 (30.7 %)	1510 (30.4 %)		
		A Levels	2604 (11.8 %)	870 (12.6 %)	603 (12.1 %)		
		Other	1078 (4.9 %)	382 (5.5 %)	295 (5.9 %)		
		Not listed	1142 (5.2 %)	526 (7.6 %)	394 (7.9 %)		
Physical	SBP (mmHg)		137.7 (± 18.7)	145.1 (± 17.7)	145.0 (± 17.3)	<0.001	<0.001
	Height (cm)		168.6 (± 9.2)	170.3 (± 9.3)	169.7 (± 9.4)	<0.001	<0.001
	BMI (kg/m2)		24.9 [22.8, 27.2]	29.1 [26.6, 32.0]	29.3 [26.8, 32.2]	<0.001	<0.001
Lifestyle and environment	Smoking status	Never	14,206 (64.2 %)	4045 (58.4 %)	3119 (62.7 %)	<0.001	0.057
		Previous	7038 (31.8 %)	2590 (37.4 %)	1667 (33.5 %)		
		Current	661 (3.0 %)	230 (3.3 %)	130 (2.6 %)		
		No answer	75 (0.3 %)	24 (0.3 %)	20 (0.4 %)		
	Physical activity	Low	1498 (6.8 %)	825 (11.9 %)	605 (12.2 %)	<0.001	<0.001
		Moderate	9050 (40.9 %)	3073 (44.3 %)	2189 (44.0 %)		
		High	10,330 (46.7 %)	2492 (36.0 %)	1745 (35.1 %)		
	Alcohol intake (g/day)		12.1 [3.4, 23.1]	14.3 [3.3, 31.2]	8.6 [1.8, 18.6]	<0.001	<0.001
	Townsend deprivation index		−1.9 (± 2.7)	−1.8 (± 2.8)	−1.8 (± 2.8)	<0.001	0.004
Diagnoses	Diabetes		776 (3.5 %)	918 (13.2 %)	723 (14.5 %)	<0.001	<0.001
	Heart diseases		6709 (30.3 %)	3316 (47.8 %)	2399 (48.2 %)	<0.001	<0.001
	Cerebrovascular diseases		823 (3.7 %)	296 (4.3 %)	224 (4.5 %)	0.041	0.011
	Hyperlipidemia		330 (1.5 %)	192 (2.8 %)	141 (2.8 %)	<0.001	<0.001
	Depressive disorders		4143 (18.7 %)	1469 (21.2 %)	1047 (21.0 %)	<0.001	<0.001
Imaging	Liver fat (PDFF, %)		2.6 [2.1, 3.5]	9.3 [7.0, 14.1]	9.4 [7.0, 14.0]	<0.001	<0.001
	Intracranial volume (cm3)		1545.4 (± 152.7)	1562.9 (± 152.6)	1556.6 (± 153.5)	<0.001	<0.001

3.2. Global brain structure measures

We found that higher PDFF was associated with lower global gray matter volume, lower average hemispheric CT, and higher CSF volume in our Base model. However, after controlling for additional factors such as alcohol intake and cardiometabolic covariates in the Full model, the significant PDFF effect persisted only for CSF volume, but no longer for global gray matter measures. PDFF had no significant effect on total cortical surface area in either the Base or Full model. The difference between models was driven mostly by cardiometabolic covariates added in the Full model (Supplementary Results 2.1). These findings of altered global brain structure in the Base and Full model were mirrored when comparing SLD and its subgroup MASLD to the control group, but Cohen's effect sizes were larger in SLD compared to MASLD (Table 3).

Table 3
Regression results. Effects of PDFF on selected brain structural measures estimated with the Base model and the Full model. Standardized regression coefficients for PDFF (PDFF beta) are reported with significance level and 95 % confidence interval. Cohen's d effect sizes of PDFF-related brain structure alterations for the SLD and the MASLD group were derived from group comparisons with the control group. Effect sizes were computed on de-confounded measures of brain structure, i.e. measures from which all model effects of covariates (except PDFF) have been regressed out. PDFF effects on whole-brain global gray matter volume and hemispheric CT averages were significant in the Base model, but not in the Full model where we additionally controlled for alcohol intake and cardiometabolic covariates. Effects on regional CT in the left middle temporal and pericalcarine regions were significant in all models, illustrating regional heterogeneity of PDFF effects on brain structure. PDFF - proton density fat fraction; SLD - steatotic liver disease; MASLD - metabolic dysfunction-associated steatotic liver disease; CT - cortical thickness; lh/rh - left/right hemisphere; ns - not significant.

	Base model			Full model		
	PDFF beta	Cohen's d (SLD vs. control)	Cohen's d (MASLD vs. control)	PDFF beta	Cohen's d (SLD vs. control)	Cohen's d (MASLD vs. control)
Global gray matter volume	−0.01 * [−0.02, −0.00]	−0.06	−0.04	−0.00 ns [−0.01, 0.00]	−0.02	−0.01
Average CT (lh)	−0.02 ** [−0.04, −0.01]	−0.04	−0.01	−0.01 ns [−0.02, 0.00]	−0.01	−0.01
Average CT (rh)	−0.02 * [−0.03, −0.01]	−0.03	0.00	−0.00 ns [−0.02, 0.01]	0.00	0.01
Middle temporal CT (lh)	−0.05 *** [−0.06, −0.03]	−0.08	−0.05	−0.03 ** [−0.05, −0.02]	−0.05	−0.05
Pericalcarine CT (lh)	0.02 * [0.01, 0.04]	0.05	0.06	0.02 * [0.01, 0.04]	0.06	0.06

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

3.3. Regional cortical thickness

The effect of PDFF on CT varied across regions, but the observed pattern was similar when comparing the Base and Full model (Supplementary Fig. S3, S4) and when comparing the main analysis and sensitivity analyses in the subsample without known liver disease (Supplementary Results 2.2; Fig. S3-S10). PDFF associations with CT were mostly symmetric across hemispheres, but more pronounced in the left hemisphere. Negative associations were found in the left temporal and frontal regions, while positive associations were evident in the occipital lobe. In both models, the strongest effects of PDFF on CT were observed in the left middle temporal, superior temporal, and bilateral pericalcarine regions. However, compared to the Base model, the Full model no longer showed significant associations between PDFF and CT in frontal regions (Supplementary Fig. S3, S4).

Statistical maps showing group differences in CT explained by PDFF are shown in Fig. 1 (SLD vs. control) and Fig. 2 (MASLD vs. control). Overall, the effect size maps of the two groups were very similar (Pearson $r = 0.90$ for the Base model, $r = 0.98$ for the Full model). Underscoring the regional specificity of these effects, Cohen's d effect sizes of CT alterations in specific regions were considerably larger than those for mean CT or other global measures of gray matter (Table 3). In the Base model, negative effect sizes were more pronounced in the SLD group than in the MASLD group (Fig. 1a, 2a). Covarying additionally for alcohol intake (AC model) resulted in comparable magnitudes of PDFF-related effect sizes in SLD and MASLD (see also Full model in Fig. 1b, 2b). Therefore, increased effect sizes in the SLD group seemed to be due to participants with high alcohol intake (alcohol-associated liver disease), leading to additional reductions in CT relative to the control group. The effect size map for the Fibrosis Risk group showed larger PDFF-related effect sizes (Supplementary Fig. S13), with a pattern very similar to the ones observed for SLD and MASLD (Pearson $r = 0.85$ and $r = 0.84$ for the Full model).

3.4. Regional cortical area

Many of the associations between PDFF and cortical surface area were found in different regions than those in which an association with CT was found. PDFF was linked with increased cortical surface area in bilateral precuneus and paracentral cortex in both the Base and in the Full model (Supplementary Fig. S3, S4).

3.5. Neuroanatomical association of steatosis and major depressive disorder

The profile of PDFF-related alterations in SLD and MASLD correlated with previously found alterations in MDD (Pearson $r = 0.45$–0.54, $p < 0.01$; Supplementary Table S5). This means that CT reductions in specific brain regions characteristic for MDD were also observed in SLD and MASLD. These included temporal and frontal regions such as left medial orbitofrontal, middle temporal, and right insula in the Base model and left middle temporal in the Full model. In contrast, supporting the specificity of these associations with MDD, no significant correlations were found between MASLD or SLD and obsessive-compulsive disorder (Supplementary Table S5). In the Fibrosis Risk group, we found very similar results (Full Model: $r = 0.47$, $p < 0.001$ for MDD and $r = 0.20$, $p = 0.057$ for obsessive-compulsive disorder). The main findings on neuroanatomical associations with MDD were similar in the sensitivity analysis in the subsample without known liver disease (Supplementary Results 2.3).

4. Discussion

In a large population-based sample of UK Biobank participants, we observed that liver fat amount was strongly associated with a regionally specific pattern of predominantly reduced CT alterations in the brain. This association remained significant even after controlling for extensive sets of confounding factors, including technical, socioeconomic, demographic, cardiometabolic variables, and alcohol intake. Importantly, patterns of regional CT alterations in SLD and MASLD correlated with CT alterations characteristic of MDD. This suggests the possible presence of shared underlying neurobiological mechanisms between hepatic steatosis and MDD.

The brain regions where liver fat most significantly affected CT were the left middle and superior temporal regions (negative association) and bilateral pericalcarine and right frontal pole regions (positive associations). Only in these regions, CT associations remained significant after adjustment for the full list of confounding factors. Notably, these included BMI, which is used to diagnose obesity and has been documented to be associated with CT reductions in temporal, frontal, and cingulate cortical regions [46–48]. While obesity has been recognized as a modifying factor in the development of brain atrophy preceding cognitive impairment [49], we uncovered liver fat related brain

alterations beyond BMI that might constitute a distinct biomarker of neurodegeneration [22]. Specifically, the observed patterns of CT alterations related to liver fat in SLD and MASLD both exhibited a correlation with CT alterations documented in MDD by the ENIGMA collaboration (which comprises the largest sample of patients with MDD from around the world) [26]. In contrast, we found no correlation with the map of CT alterations implicated in obsessive-compulsive disorder, which served as a "negative control" disorder. This finding provides a mechanistic explanation for why individuals with SLD and MASLD might be at increased risk for depression [50]. Speculatively, liver fat induced metabolic abnormalities in SLD and MASLD (e.g. through inflammatory processes; see below) might have a detrimental effect on brain health, which can be measured via alterations in brain structure and expressed behaviorally in terms of depressive symptoms. Liver fat related CT alterations in SLD and MASLD were comparable after accounting for all confounding factors. Effects of liver fat identified in our study and effects of MDD in the ENIGMA study both indicated significantly reduced left middle temporal CT. We also confirmed previous findings of a negative association of liver fat with global gray matter volume and hemispheric CT averages, and a positive association with cerebrospinal fluid volume [23–25]. Importantly, however, the effects on global gray matter measures vanished when additionally controlling for cardiometabolic covariates or alcohol intake. This highlights the importance of focusing on regional gray matter effects in our analysis.

Another finding of our study was a positive association between cortical surface area and liver fat amount in various regions of the parietal lobe, in the superior temporal and in the rostral middle frontal cortex. These alterations could not be explained by cardiometabolic covariates, alcohol intake or any other known liver disease. Consequently, the small (or absent) effect on global gray matter observed here may be due to region-specific changes. Increases in surface area or cortical thickness in some regions were offset by reductions in cortical thickness in other regions, resulting in a vanishing net effect on global gray matter volume.

As with MASLD and SLD in our UK Biobank sample, an increased prevalence of depression has previously been observed in most chronic liver diseases, including NAFLD, alcoholic liver disease [50], viral hepatitis and autoimmune liver disease [51]. Socioeconomic factors (e.g. education level, employment, income) have been associated with both depression and chronic liver disease [51] and were accounted for in all of our models. Furthermore, alcohol intake was a relatively minor confounding factor of the associations between liver fat and CT, but explained quantitative differences between liver fat related CT alterations in SLD and MASLD. Excluding participants with other liver diseases or high alcohol intake did not substantially change the above results. This supports the hypothesis that biologic mechanisms exist that link chronic liver diseases of different etiologies with an increased risk for depression [50].

It has been suggested that inflammatory processes due to hepatic steatosis may contribute to neuroinflammation, which is considered an emerging factor in the pathogenesis of depression [51,52]. Specifically, excessive fat accumulation in the liver results in hepatocellular stress, which can lead to cell death and release of hepatokines (e.g. fetuin A), cytokines (tumor necrosis factor-alpha, TNF-α; interleukin-6, IL-6; interleukin-1β, IL-1β), or damage-associated molecular patterns that promote both local and systemic inflammation as well as oxidative stress [3]. Alterations in the gut microbiome may contribute to these proinflammatory events, which often aggravate a pre-existing chronic subclinical inflammatory state due to obesity and insulin resistance [53]. Interestingly, insulin resistance itself also appears to be associated with CT reductions in the cingulate cortex and temporal lobe regions consistent with those found in our study [54]. Two previous studies have shown that hepatic and systemic inflammation can induce neuroinflammation and depressive symptoms in mice [55,56]. Both microglial cells and cerebrovascular endothelial cells can get activated by peripheral inflammatory cytokines, which might recruit more immune cells to the brain [51]. Finally, neuroinflammation can affect neurotransmitter signaling and regulate pathways involved in mood and cognition [51]. Neuroinflammation and increased proinflammatory cytokines have also been associated with reduced cortical thickness in different brain regions during aging, as well as in neurodegenerative and psychiatric disorders such as bipolar depression and MDD [57–61].

We observed a slightly increased occurrence of depressive disorders in participants with SLD and MASLD and found similarities in structural brain alterations to the ones previously found in MDD. This suggests that brain regions affected in SLD and MASLD may play a significant role in the psychopathology of MDD. In our study, the regions with the strongest association between liver fat and CT are known for sensory and semantic processing as well as social cognition [62,63] (superior and middle temporal lobes) and visual perception [64] (pericalcarine). The superior temporal gyrus is crucial for processing auditory information and understanding language [65]. Biases in the processing and interpretation of spoken emotional cues are typical for depression. For instance, people with depression may interpret neutral or ambiguous vocal tones as negative, contributing to the cognitive biases seen in the disorder [66–68]. Similarly, the temporal lobes play a role in social cognition, i.e. understanding and processing social information [62]. Changes or dysfunctions in these regions may contribute to social withdrawal and difficulties in social interactions often seen in individuals with MDD [69]. The middle temporal lobe, along with other temporal lobe structures such as the amygdala and hippocampus, is involved in the formation and retrieval of memories, particularly emotional memories [70]. Depression may be associated with a bias toward recalling negative memories [71]. Therefore, future studies should examine whether the structural alterations revealed here are related to these symptoms and cognitive biases. Further, the neuroanatomical association with MDD was even more pronounced in people at high risk of fibrosis. Resmetirom was recently approved as the first medication against liver fibrosis, and phase II studies of other medications (e.g. the GLP-1 receptor agonists semaglutide and liraglutide and the GLP-1/Glucagon co-agonist survodutide) reported positive results regarding resolution of steatohepatitis [72]. Thus, an intriguing question that should be addressed in future studies is whether treatment of MASLD and liver fibrosis with the above-mentioned medications might be able to restore MASLD-related structural changes in the brain and disrupt the detrimental association of MASLD with depression.

The current study has several strengths. We used the recently updated nomenclature and assessed alterations of regional brain structure not only in SLD but also in MASLD. We leveraged a large population-based sample from the UK Biobank, which allowed us to rigorously account for extensive sets of confounding variables and thereby isolate the unique effects of liver fat on regional brain structure. While the found effect sizes may not represent large-scale alterations, they revealed a meaningful neuroanatomical association with MDD that may have implications for understanding and potentially treating comorbid depression in patients with MASLD or general SLD.

There are several limitations to consider. We have assessed liver fat and not liver inflammation or directly liver fibrosis. This was not possible because we did not have histologic data from liver biopsies [73]. Blood-based indices (e.g. FIB-4) could not be calculated due to the lack of relevant biochemical parameters at time of MRI imaging, and lifetime nonalcoholic steatohepatitis (NASH) diagnoses from hospital records as a proxy would have detected too few cases ($N = 10$, 0.1 % of the SLD group). Due to the lack of blood-based markers, we were also unable to calculate cardiometabolic risk factors based on these markers. Thus, we may have missed some participants with MASLD who would fulfill this inclusion criterion. However, since the prevalence of MASLD in NAFLD in our sample (96 %) was close to the only slightly higher prevalence (98 %) reported in a dedicated study [6], this effect did not appear to be substantial (NAFLD in our sample means participants with SLD who met MASLD exclusion criteria but not necessarily MASLD inclusion criteria; Supplementary Methods 1.4). The broadly defined

depressive disorder category in our UK Biobank sample relied on multiple data sources, such as hospital records and self-reports. This approach may not capture the nuances of different depression subtypes. The reference map for MDD-related brain alterations was previously derived from the ENIGMA-MDD multi-site sample. In this sample, the diagnosis of MDD was confirmed using at least one of several widely accepted (semi-)structured diagnostic interviews depending on site. Although the authors accounted for site effects through meta-analytic random effect modeling, variability in the diagnostic interviews used may have affected the consistency of the results. While we have focused on liver fat related brain structure alterations in SLD and MASLD, the relationship with MDD might well be bidirectional. Individuals with MDD might take certain antidepressant medications, potentially leading to obesity and liver fat accumulation [74]. Brain regions associated with both, liver fat and MDD, do not provide a complete picture of depression related brain structure alterations. E.g. cortical thickness of the medial orbitofrontal cortex was implicated in MDD [26], but not related to liver fat in our study. Additional depression-related phenotypic factors, like dietary habits and sleep patterns, not accounted for in this study, could influence brain structure significantly. Future research using advanced neuroimaging, like diffusion tensor imaging, may further clarify how hepatic steatosis affects brain structure beyond the measures used in this study.

5. Conclusion

We uncovered regionally specific brain structural alterations related to liver fat in SLD and in the most relevant subgroup, MASLD. MASLD remains an unmet clinical need (e.g. increased mortality due to increased cardiovascular and hepatic risk) with only one recently-approved medication available for the treatment of liver fibrosis. The similarity of brain structural changes in SLD and MASLD to those observed in MDD suggests a possible shared neurobiological mechanism that may explain the increased prevalence of depression in individuals with SLD observed in epidemiological studies. Whether reversal of hepatic steatosis in SLD and MASLD (e.g. by using new weight-loss medications, which reduce liver fat) restores structural changes in the brain and diminishes the elevated risk of depression remains unknown and should be addressed in future studies. Nevertheless, our study underscores the likely importance of early lifestyle interventions and treatment of risk factors, such as metabolic syndrome, as potential preventive measures against depression.

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CRediT authorship contribution statement

Dominic Arold: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stefan R. Bornstein:** Writing – review & editing, Supervision, Conceptualization. **Nikolaos Perakakis:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Stefan Ehrlich:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Fabio Bernardoni:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

SB reports participation in the advisory board of Boehringer Ingelheim and speaker honoraria from Novo Nordisk, Boehringer Ingelheim. NP reports consulting fees and participation in the advisory board from Bayer Vital GmbH, speaker honoraria from Novo Nordisk and GWT-Dresden, support for attending meetings/travel from Lilly and Novo Nordisk, and a patent application (WO 2021/092265A1). FB reports owning stocks in Johnsons & Johnsons, Merck, and Fresenius SE.

Data and code availability

Data and materials are available from UK Biobank at http://www.ukbiobank.ac.uk/. The analysis code used in this study is publicly available with the Open Science Framework (https://osf.io/2hvj8/).

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Appendix A. Supplementary data

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