Supplementary materials

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

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1. Methods

1.1. MRI acquisition and processing

Brain MRI data were acquired using a Siemens Skyra 3T scanner (Siemens Healthcare, Erlangen, Germany) using a standard 32-channel head coil, according to a freely available protocol (http://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf). High-resolution T1-weighted images were obtained using an MPRAGE sequence with the following parameters: TR=2,000ms; TE=2.01ms; 208 sagittal slices; flip angle, 8°; FOV=256mm; matrix=256 × 256; slice thickness=1.0mm (voxel size 1 × 1 × 1mm); total scan time=4min 54s.

1.2. Estimation of alcohol intake

Initially, participants were asked about the frequency of their alcohol consumption. Based on their response, if they reported drinking more than 1-2 times per week, they were subsequently inquired about the amount they consumed from various beverage categories including red wine, white wine/champagne, beer/cider, spirits, fortified wine, and "other" on a weekly basis. Conversely, those who consumed alcohol less frequently were asked about their monthly intake.

Each unit of alcohol is equivalent to 10ml or 8g of pure ethanol. Therefore, the volume of each type of beverage consumed was converted into its corresponding number of alcohol units for either a week or a month, as applicable[1,2]: a pint or can of beer/lager/cider equals 2.5 units (average of lower and higher strength beverage), a single shot of spirits (30ml) equals 1.2 units, a glass of fortified wine (62.5ml) equals 1.1 units, a small glass of wine (125ml) equals 1.5 units, and an alcopop beverage (275ml) equals 1.5 units.

The total regular alcohol intake was calculated by aggregating the units from all beverage categories. For those who reported their consumption on a monthly basis, we translated this into a weekly figure by dividing the monthly units by 4.3. To determine daily alcohol intake, we further divided the weekly units by 7.

1.3. Definition of diagnostic categories

Lifetime diagnoses were obtained based on self-report data (data field 20002) and linked data from hospital inpatient records (data category 2000), death registry records (data fields 40001, 40002), and primary care records (data category 3000). UK Biobank mapped these heterogeneous data sources to summary variables represented as three-digit ICD-10 codes[3] (data category 1712, https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=1712).

Wherever possible, we used these summary variables to define diagnosis categories by specifying the included three-digit ICD-10 summary codes. In some other cases, a to-be-defined diagnostic category would be too specific and thus map to the same three-digit ICD-10 summary code as other diagnoses. In this case, we restricted to hospital inpatient data (data field 41270) with the more specific ICD-10 codes to avoid false positive inclusions.

This procedure applies to the comorbid diagnoses that we used as binary covariates in our Full model: any cerebrovascular disease (ICD10: I60-I69, G45), any heart disease (ICD10: I10-I28), diabetes (ICD10: E10, E11, E13, E14), and hyperlipidemia (ICD10: E78.5). Thus, for hyperlipidemia, we had to limit ourselves to hospital inpatient data. This approach was also used for MASLD exclusion diagnoses (Table S1), type 2 diabetes for MASLD inclusion criteria (Supplementary Methods 1.4), and depressive disorders (Supplementary Methods 1.4).

1.4. Details on group definitions

MASLD

Following the recently published multi-society Delphi consensus statement, we included participants with SLD in the metabolic dysfunction-associated steatotic liver disease (MASLD) subgroup if they met two sets of criteria. First, participants with MASLD had to have no other underlying cause of steatosis, i.e. excessive alcohol intake or a co-occurring liver disease (MASLD exclusion criteria). Excessive alcohol intake was defined as alcohol intake exceeding 30g/day for men and 20g/day for women. For a complete list of exclusion conditions, see Table S3. Second, participants with MASLD had any of the following cardiometabolic risk factors (MASLD inclusion criteria) as defined from UK Biobank data:

- BMI > 25 kg/m2 OR waist circumference > 94 cm (male) 80 cm (female).
- Type 2 diabetes (category 1712, ICD-10 summary code E11; see Supplementary Methods 1.3) OR antidiabetic drug medication (field 6177 and 6153; field 20003 entries “metformin”, “rosiglitazone 1mg / metformin 500mg tablet”, “glimepiride”, “gliclazide”, “pioglitazone”, “rosiglitazone”).
- Blood pressure > 130/85 mmHg OR antihypertensive drug treatment (field 6177 and 6153).
- Lipid lowering treatment (field 6177 and 6153).

Additional plasma based cardiometabolic risk factors were not considered, as blood sampling took place on average 10 years before the data used in this study was collected (imaging visit).

Depressive disorders

To establish which participants in our sample had a depressive disorder, we used the Fields 130895 and 130897, which map to ICD-10 summary codes F32 and F33, and were created by the UK Biobank team based on hospital records (ICD-9 and ICD-10), primary care records, death registry records (ICD-10), and self-report at the on-site interview[3] (Supplementary Methods 1.3). Additionally, we included participants who self-reported at the online follow-up questionnaire to have been diagnosed with a depressive disorder by a professional (answer ‘Depression’ in the Field 20544). Not all sources distinguished between different depressive disorders which is why we broadly refer to “depressive disorders”. On the other hand, the ENIGMA multisite study, whose reference map we used in our research, specifically selected patients clinically diagnosed with MDD. The (semi-)structured interview used varied across sites (CIDI, M-CIDI, SCID, SCID-1, SCAN, MINI), as detailed in supplementary Table S3 of Schmaal et al.[4] which is available online[5].

1.5. Sensitivity analysis

When, relative to the Base model, additionally adjusting for alcohol intake and cardiometabolic comorbidities in the Full model, some effects of PDFF on brain structure no longer were significant. To assess whether these effects unspecific to liver fat were primarily related to the confounding effect of alcohol intake or cardiometabolic comorbidities, we examined two more models. The AC model extends the Base model by additionally covarying only for alcohol intake, while the CM model extends the Base model by additionally covarying only for cardiometabolic covariates (Table S1). The Full model corresponds to adding both confound sets to the Base model.

1.6. Secondary analyses

We tested whether our results were sensitive to the inclusion of participants in SLD subgroups other than MASLD which had other comorbid conditions potentially leading to hepatic steatosis. To this end, we repeated our main analyses in a subsample without known liver disease (N=23447), obtained from the whole sample by excluding any participant with liver-related comorbidities or excessive alcohol intake (MASLD exclusion criteria; Supplementary Methods 1.4, Table S3). In this subsample, the MASLD group makes up 96% of the participants with SLD. We note that because only those participants with SLD who did not have liver-related comorbidities or excessive alcohol intake were included in this subsample, they effectively represent the NAFLD group as defined in the nomenclature prior to the introduction of MASLD.

1.7. Forward search

In order to select higher-order polynomial terms for age and BMI that would explain variability in brain IDPs while ensuring model parsimony, we performed a stepwise regression[6] on the whole sample for each IDP. We started with a reference model containing all main effects of the Base model (i.e. the Base model without non-linear age and BMI terms) and iteratively added higher order age and BMI terms in a forward search. After the addition of each polynomial term, the Bayesian information criterion (BIC) for the model was computed. The BIC helps in model selection by penalizing models for the number of predictors, thus guarding against overfitting. A lower BIC suggests a better balance between the fit of the model and the number of parameters used. The stepwise regression proceeded iteratively, adding polynomial terms and calculating the corresponding BIC until a model was reached where the addition of another term resulted in an increase in BIC. At this point, the forward selection process was halted, and the previous model (with the lowest BIC) was considered optimal. The highest polynomial order found across all IDPs in this way, respectively for age and BMI, was then used in all models and all IDPs. This resulted in including polynomial terms up to order three for age and up to order two for BMI in each model.

1.8. Missing value imputation

Missing covariate values (at the imaging assessment; COV) were imputed using regression imputation based on covariate values available from the earlier baseline assessment (COV_base). Specifically, for each continuous/categorical covariate, we fitted a linear/logistic regression model

$$COV \sim COV_{base} + dt\_img + age + sex + age * sex$$

on all available participants with necessary data values (N>56,000 for each covariate). *dt_img* indicates the time difference between the baseline and imaging assessments. The fitted model was then applied to participants in our whole sample to impute as many missing covariate values as possible. Remaining missing values (i.e. in case COV_base was also unavailable) were imputed with the mean/mode value.

2. Results

2.1. Global measures

While average hemispheric CT was associated with PDFF in the Base model applied to the whole sample, this was not the case neither when adjusting for alcohol intake (i.e. in the AC model) nor when adjusting for cardiometabolic comorbidities (i.e. in the CM model). Furthermore, while the effect of PDFF on global gray matter volume remained significant in the AC model, this was not the case in the CM model (or in the Full model).

2.2. Regional measures

Relative to the Base model applied to the whole sample (Figure S2), neither adjustment for alcohol intake (AC model, Figure S4) nor for cardiometabolic comorbidities (CM model, Figure S5) did considerably affect the implicated cortical regions. Notably, while the effect of PDFF on regional CT in the right temporal lobe remained significant in the AC model, this was not the case in the CM model. The color range was kept constant across Figures S3-10 to allow visual comparability. It was determined from the maximum absolute regression coefficient displayed.

2.3. Secondary analysis

Global measures

When restricting to the subsample without known liver disease, only CSF had a significant PDFF effect in Base and Full model. Relative to the whole sample, PDFF effects on global gray matter volume or average CT were no longer significant in the Base model. Additionally, in the Full model, PDFF was significantly associated with increased total hemispheric surface area after adjustment for cardiometabolic comorbidities.

Regional cortical thickness

Compared to the whole sample, similar results were found in the subsample without known liver disease: The Base model again showed significant PDFF effects on CT in temporal and frontal lobes, however in fewer regions (Figure S6) and the Full model indicated significant association between PDFF and decreased left temporal an increased left occipital CT (Figure S7). While the effect of PDFF on regional CT in the right temporal lobe and left frontal lobe remained significant when additionally adjusting for alcohol intake (AC model; Figure S8), this was not the case when instead additionally adjusting for cardiometabolic comorbidities (CM model; Figure S9).

Regional cortical area

In the subsample without known liver disease, as for the whole sample, 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 Figure S6, S7). Different to the whole sample results, additional enlarged cortical surface areas were found across the occipital lobe (Supplementary Figure S7, S8, S9), when adjusting for cardiometabolic comorbidities (CM model).

Neuroanatomical association of steatosis and major depressive disorder

In the subsample without known liver disease, findings were very similar to the whole sample. We observed a significant correlation between the ENIGMA case-control effect size map for MDD and the Cohen's d effect size map of PDFF-related CT alterations for SLD (Base model r=0.52, p=0.002; Full model r=0.51, p=0.001) as well as for MASLD (Base model r=0.51, p=0.001; Full model r=0.50, p=0.002). And, supporting the specificity of these associations with MDD, no significant correlations were found between the ENIGMA effect size map for the control condition obsessive-compulsive disorder and the Cohen's d effect size maps of PDFF-related CT alterations for SLD (Base model r=0.06, p=0.359; Full model r=0.03, p=0.451) as well as for MASLD (Base model r=0.07, p=0.302; Full model r=0.05, p=0.400).

Tables

Table S1. *MASLD exclusion criteria. Count and percentage of participants in the whole sample that exhibited conditions used as MASLD exclusion criteria. These participants were dropped from the subsample without known liver disease. The measures were assessed through self-report (alcohol consumption; UK Biobank category 100051) and ICD-10 coded lifetime diagnoses ascertained based on self-report data and linked data from hospital inpatient, death registry, and primary care records (UK Biobank category 1712 if available, else category 41270; see Supplementary Methods 1.3).*

Condition	**N**	**ICD-10**
Excessive alcohol intake	4916 (16.9%)	N/A
Alcohol abuse	384 (1.3%)	F10
Drug_induced_liver_disease	6 (0.0%)	K71
Viral_hepatitis_B_or_C_infection	285 (1.0%)	B16.2, B16.9, B17.0-B17.9, B18.0-B18.9, B19.0-B19.9, B00.8; B25.1
Budd_Chiari	39 (0.1%)	I82
Liver_abscess	17 (0.1%)	K75.0, A06.4
HIV	30 (0.1%)	B20-B24
Hemochromatosis	62 (0.2%)	E83.1
Wilsons_disease	0 (0.0%)	E83.0
Autoimmune_hepatitis	16 (0.1%)	K75.4
Primary_biliary_cholangitis	14 (0.0%)	K74.3, K74.4

Table S2. *Conceptual description of groups defined in this study's main sample.*

Acronym	Full Name	Description
-	Control	Normative comparison group of all participants without steatotic liver disease, assessed as PDFF<5.5%.
SLD	Steatotic liver disease	Overarching category characterized by fat accumulation in the liver, assessed as PDFF>5.5%.
MASLD	Metabolic dysfunction associated fatty liver disease	A subtype of SLD characterized by the absence of (excessive) alcohol consumption and other known liver diseases and by the presence of at least one cardiometabolic risk factor such as obesity, type 2 diabetes, dyslipidemia, or hypertension.
-	Fibrosis risk	A subtype of SLD characterized by especially high liver fat (PDFF>15%) which is associated with increased odds of fibrosis progression.
-	Depressive disorder	Overarching category of lifetime depressive disorders.

Table S3. *Sample characteristics for the subsample without known liver disease (N=23447). The sample consists of all participants from the whole sample with no excessive alcohol intake and no liver comorbidities (MASLD exclusion criteria; Supplementary Methods 1.4). This includes the corresponding portions of the control and SLD group. The SLD group mostly consists of the MASLD subgroup. Categorical variables are 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 relative to the control group for MASLD (pa) and SLD (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; MASLD – metabolic dysfunction–associated steatotic liver disease.*

	Variable		**Control (N=18260)**	**MASLD (N=4974)**	**SLD (N=5187)**	**pa**	**pb**
Sociodemographic	Sex	Female	10709 (58.6%)	2155 (43.3%)	2246 (43.3%)	<0.001	<0.001
		Male	7551 (41.4%)	2819 (56.7%)	2941 (56.7%)		
	Age at imaging (years)		65.0 (± 7.7)	65.2 (± 7.4)	65.1 (± 7.4)	0.115	0.312
	Highest qualification	Degree	9594 (52.5%)	2117 (42.6%)	2226 (42.9%)	<0.001	<0.001
		GCSE	4493 (24.6%)	1510 (30.4%)	1564 (30.2%)		
		A Levels	2129 (11.7%)	603 (12.1%)	630 (12.1%)		
		Other	885 (4.8%)	295 (5.9%)	303 (5.8%)		
		Not listed	957 (5.2%)	394 (7.9%)	405 (7.8%)		
Physical	SBP (mmHg)		137.3 (± 18.7)	145.0 (± 17.3)	144.4 (± 17.5)	<0.001	<0.001
	Height (cm)		168.3 (± 9.2)	169.7 (± 9.4)	169.8 (± 9.4)	<0.001	<0.001
	BMI (kg/m2)		24.8 [22.7, 27.1]	29.3 [26.8, 32.2]	29.2 [26.7, 32.1]	<0.001	<0.001
Lifestyle and environment	Smoking status	Never	12339 (67.6%)	3119 (62.7%)	3261 (62.9%)	<0.001	<0.001
		Previous	5292 (29.0%)	1667 (33.5%)	1727 (33.3%)		
		Current	437 (2.4%)	130 (2.6%)	136 (2.6%)		
		No answer	59 (0.3%)	20 (0.4%)	21 (0.4%)		
	Physical activity	Low	1260 (6.9%)	605 (12.2%)	624 (12.0%)	<0.001	<0.001
		Moderate	7443 (40.8%)	2189 (44.0%)	2275 (43.9%)		
		High	8480 (46.4%)	1745 (35.1%)	1837 (35.4%)		
	Alcohol intake (g/day)		9.3 [2.2, 17.1]	8.6 [1.8, 18.6]	8.6 [1.8, 18.6]	0.506	0.450
	Townsend deprivation index		-2.0 (± 2.7)	-1.8 (± 2.8)	-1.8 (± 2.8)	<0.001	<0.001
Diagnoses	Diabetes		657 (3.6%)	723 (14.5%)	727 (14.0%)	<0.001	<0.001
	Heart diseases		5398 (29.6%)	2399 (48.2%)	2429 (46.8%)	<0.001	<0.001
	Cerebrovascular diseases		659 (3.6%)	224 (4.5%)	227 (4.4%)	0.004	0.012
	Hyperlipidemia		259 (1.4%)	141 (2.8%)	143 (2.8%)	<0.001	<0.001
	Depressive disorders		3361 (18.4%)	1047 (21.0%)	1083 (20.9%)	<0.001	<0.001
Imaging	Liver fat (PDFF, %)		2.6 [2.1, 3.4]	9.4 [7.0, 14.0]	9.3 [7.0, 13.9]	<0.001	<0.001
	Intracranial volume (cm3)		1542.6 (± 153.3)	1556.6 (± 153.5)	1556.9 (± 153.6)	<0.001	<0.001

Table S4. *Sample characteristics for participants with and without depressive disorder diagnosis. The whole sample is divided into groups of participants with and without a lifetime depressive disorder diagnosis. Categorical variables are 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 within both samples. 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		**Depressive disorder**	**No depressive disorder**	**p**
Sociodemographic	Sex	Female	3661 (65.2%)	11804 (50.4%)	<0.001
		Male	1951 (34.8%)	11635 (49.6%)	
	Age at imaging (years)		63.8 (± 7.4)	65.1 (± 7.6)	<0.001
	Highest qualification	Degree	2800 (49.9%)	11721 (50.0%)	0.399
		GCSE	1452 (25.9%)	6196 (26.4%)	
		A Levels	714 (12.7%)	2760 (11.8%)	
		Other	287 (5.1%)	1173 (5.0%)	
		Not listed	319 (5.7%)	1349 (5.8%)	
Physical	SBP (mmHg)		137.4 (± 18.8)	140.0 (± 18.7)	<0.001
	Height (cm)		167.4 (± 9.0)	169.4 (± 9.3)	<0.001
	BMI (kg/m2)		26.2 [23.6, 29.4]	25.7 [23.3, 28.4]	<0.001
Lifestyle & environment	Smoking status	Never	3265 (58.2%)	14986 (63.9%)	<0.001
		Previous	2037 (36.3%)	7591 (32.4%)	
		Current	261 (4.7%)	630 (2.7%)	
		No answer	19 (0.3%)	80 (0.3%)	
	Physical activity	Low	557 (9.9%)	1766 (7.5%)	<0.001
		Moderate	2425 (43.2%)	9698 (41.4%)	
		High	2191 (39.0%)	10631 (45.4%)	
	Alcohol intake (g/day)		10.7 [2.0, 23.3]	12.9 [3.7, 25.6]	<0.001
	Townsend deprivation index		-1.6 (± 2.9)	-2.0 (± 2.7)	<0.001
Diagnoses	Diabetes		393 (7.0%)	1301 (5.6%)	<0.001
	Heart diseases		2029 (36.2%)	7996 (34.1%)	0.004
	Cerebrovascular diseases		270 (4.8%)	849 (3.6%)	<0.001
	Hyperlipidemia		126 (2.2%)	396 (1.7%)	0.006
	SLD (PDFF > 5.5%)		1469 (26.2%)	5462 (23.3%)	<0.001
	MASLD		1083 (19.3%)	4104 (17.5%)	0.002
Imaging	Liver fat (PDFF, %)		3.1 [2.2, 5.8]	3.1 [2.3, 5.3]	0.094
	Intracranial volume (cm3)		1532.2 (± 148.1)	1553.7 (± 153.7)	<0.001

Table S5. *Neuroanatomical associations in the whole sample. Correlations of Cohen's d effect size maps of liver fat related CT alterations in SLD and MASLD with effect size maps of MDD and OCD. Significance of Pearson correlation coefficients was assessed via spin-permutation testing. SLD - steatotic liver disease; MASLD – metabolic dysfunction–associated steatotic liver disease; MDD – Major depressive disorder; OCD – Obsessive-compulsive disorder. n.s. – not significant; p > 0.05; * - p < 0.05; ** - p < 0.01; *** - p < 0.001.*

	SLD		**MASLD**	
Model	**r (MDD)**	**r (OCD)**	**r (MDD)**	**r (OCD)**
Base	0.45 **	0.17 n.s.	0.54 **	0.00 n.s.
Full	0.49 ***	0.10 n.s.	0.51 ***	0.02 n.s.
AC	0.50 **	012 n.s.	0.52 **	0.05 n.s.
CM	0.45 **	0.16 n.s.	0.53 ***	-0.04 n.s.

Figures

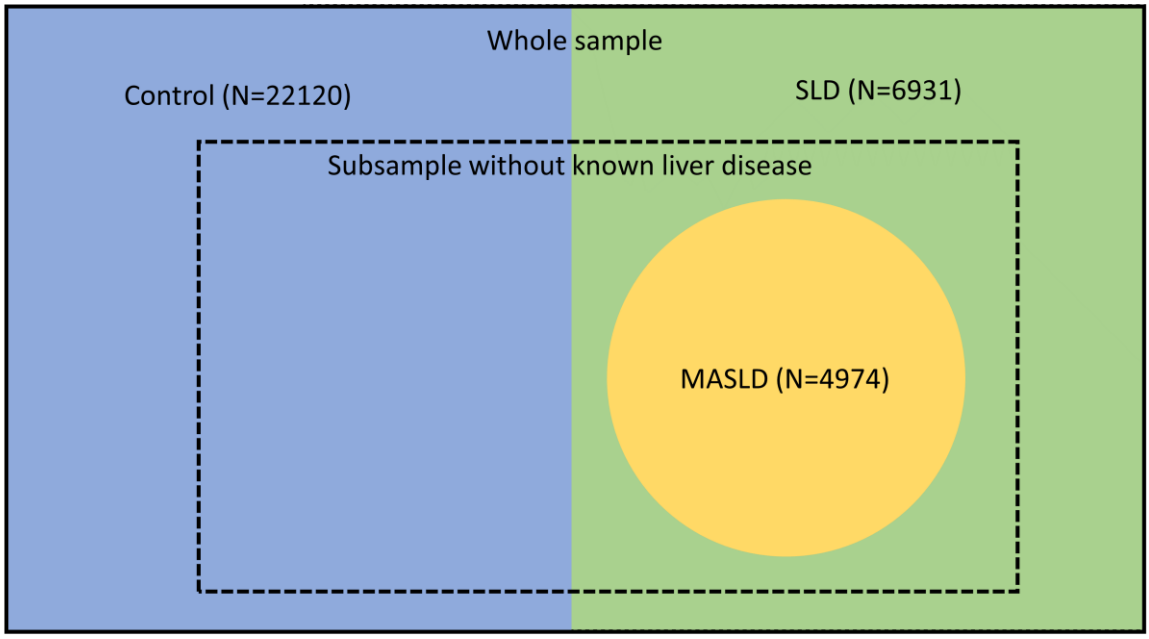

Figure S1. *Samples composition in terms of study groups. The whole sample (N=29051) used in the main analyses consisted of all UK Biobank participants with liver and brain MRI imaging derived variables of interest available. The sample is divided into the SLD group of all participants with hepatic steatosis (PDFF>5.5%) and the control group of participants without hepatic steatosis (PDFF≤5.5%). The subsample without known liver disease used in the secondary analyses (Supplementary Methods 1.6) consisted of all participants from the whole sample who did not report excessive alcohol intake and had no other liver diseases (which were the MASLD exclusion criteria, see Supplementary Methods 1.4). It is divided into the corresponding SLD and control subgroups who fulfill these criteria.*

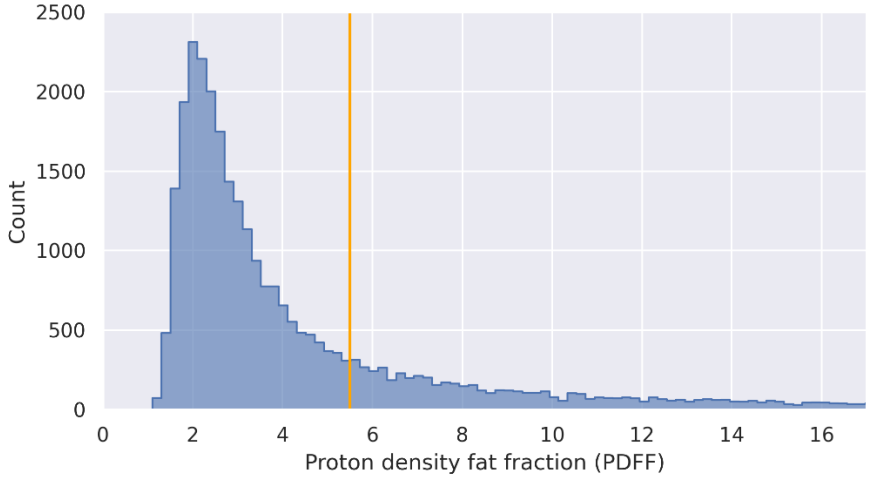

Figure S2. *Histogram of PDFF values in the whole sample. The vertical line indicates the threshold for SLD (PDFF>5.5%).*

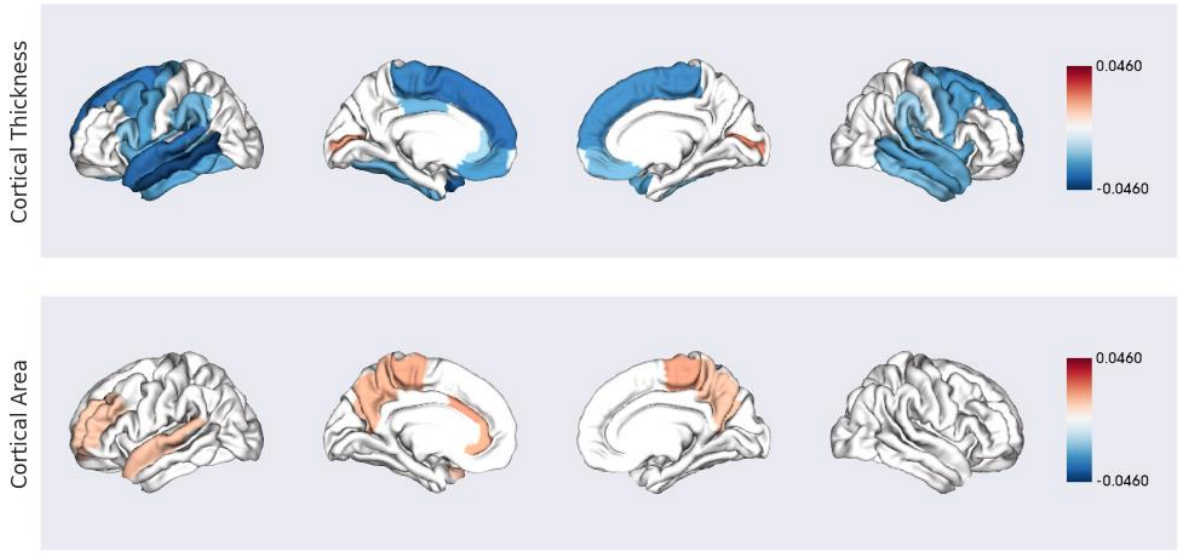

Figure S3. *Base model applied to the whole sample. Cortical surfaces show standardized regression coefficients of continuous variable effects of liver fat PDFF on cortical thickness (top) and area (bottom). Only regions with significant liver fat associations after FDR correction for multiple comparison (q<0.05) are shown. Blue color indicates a negative association of liver fat with gray matter, while red color indicates the opposite. Significant effects of liver fat on global gray matter measures not visualized here: Total gray matter volume (-0.01), average cortical thickness left/right hemisphere (-0.02/-0.02), cerebrospinal fluid volume (0.05).*

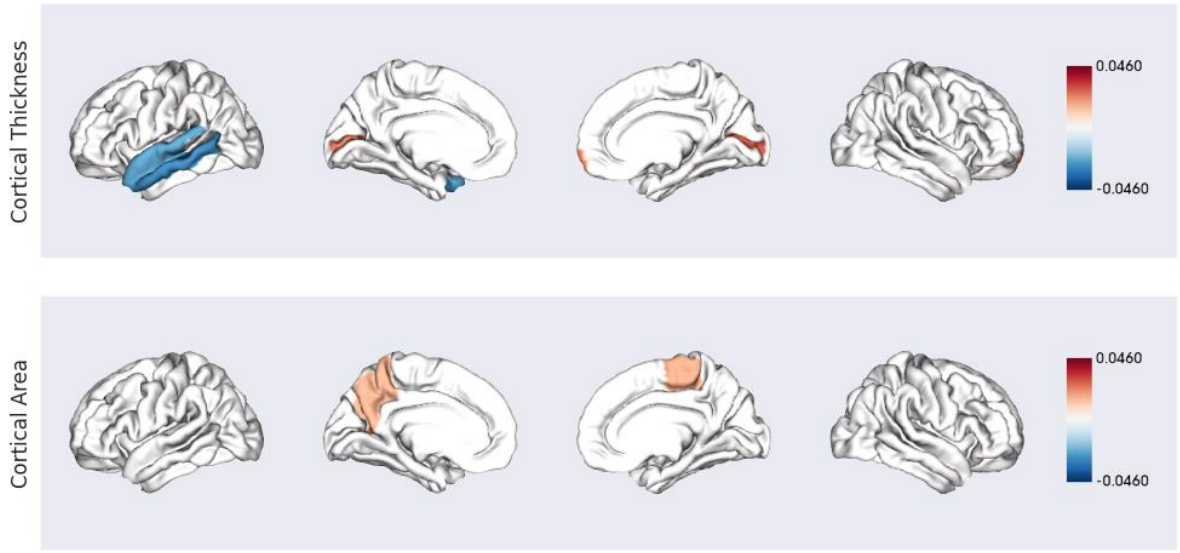

Figure S4. *Full model applied to the whole sample. Cortical surfaces show standardized regression coefficients of continuous variable effects of liver fat PDFF on cortical thickness (top) and area (bottom). Only regions with significant liver fat associations after FDR correction for multiple comparison (q<0.05) are shown. Blue color indicates a negative association of liver fat with gray matter, while red color indicates the opposite. Significant effects of liver fat on global gray matter measures not visualized here: Cerebrospinal fluid volume (0.05).*

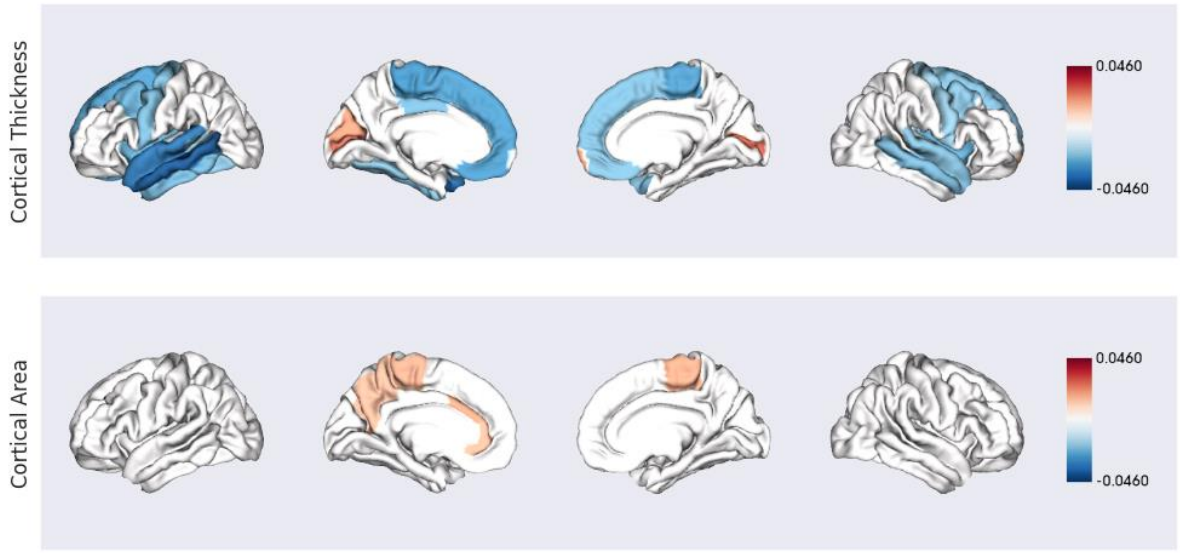

Figure S5. *AC model applied to the whole sample. Cortical surfaces show standardized regression coefficients of continuous variable effects of liver fat PDFF on cortical thickness (top) and area (bottom). Only regions with significant liver fat associations after FDR correction for multiple comparison (q<0.05) are shown. Blue color indicates a negative association of liver fat with gray matter, while red color indicates the opposite. Significant effects of liver fat on global gray matter measures not visualized here: Total gray matter volume (-0.01), cerebrospinal fluid volume (0.05).*

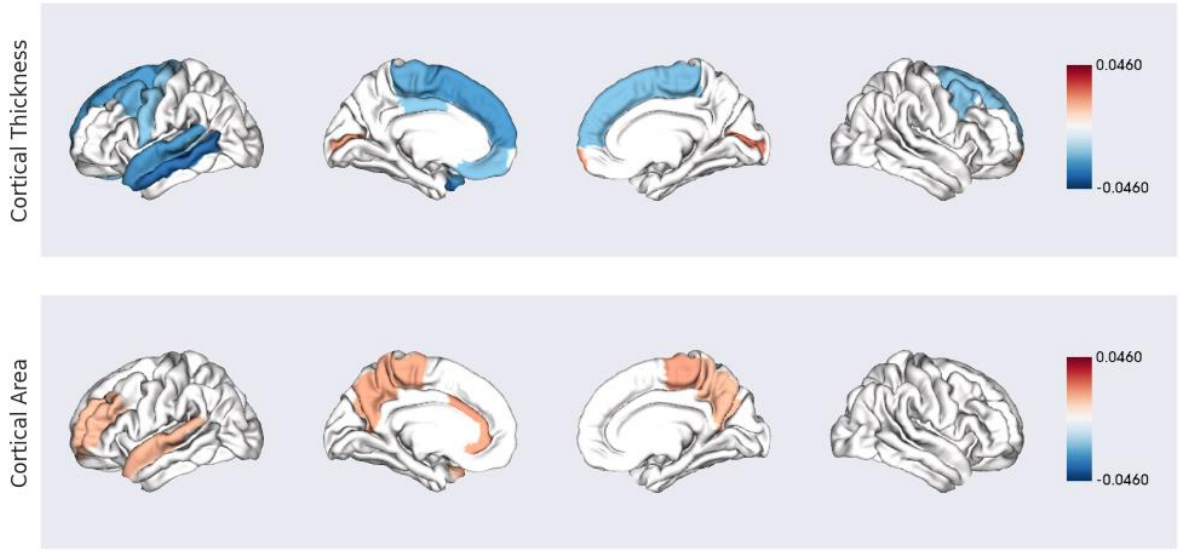

Figure S6. *CM model applied to the whole sample. Cortical surfaces show standardized regression coefficients of continuous variable effects of liver fat PDFF on cortical thickness (top) and area (bottom). Only regions with significant liver fat associations after FDR correction for multiple comparison (q<0.05) are shown. Blue color indicates a negative association of liver fat with gray matter, while red color indicates the opposite. Significant effects of liver fat on global gray matter measures not visualized here: Cerebrospinal fluid volume (0.05).*

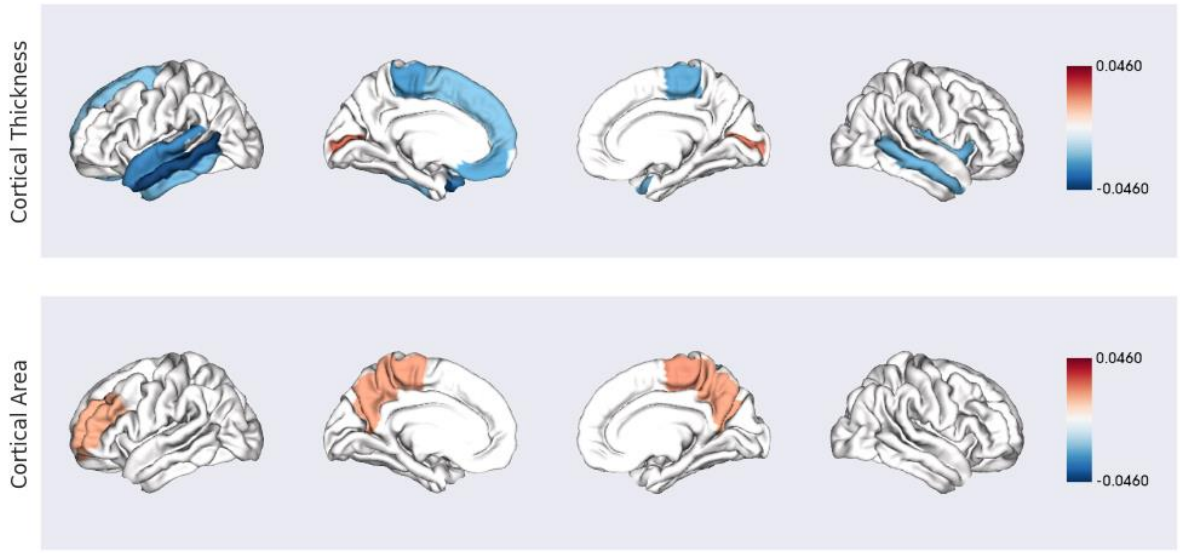

Figure S7. *Base model applied to the subsample without known liver disease. Cortical surfaces show standardized regression coefficients of continuous variable effects of liver fat PDFF on cortical thickness (top) and area (bottom). Only regions with significant liver fat associations after FDR correction for multiple comparison (q<0.05) are shown. Blue color indicates a negative association of liver fat with gray matter, while red color indicates the opposite. Significant effects of liver fat on global gray matter measures not visualized here: Cerebrospinal fluid volume (0.04).*

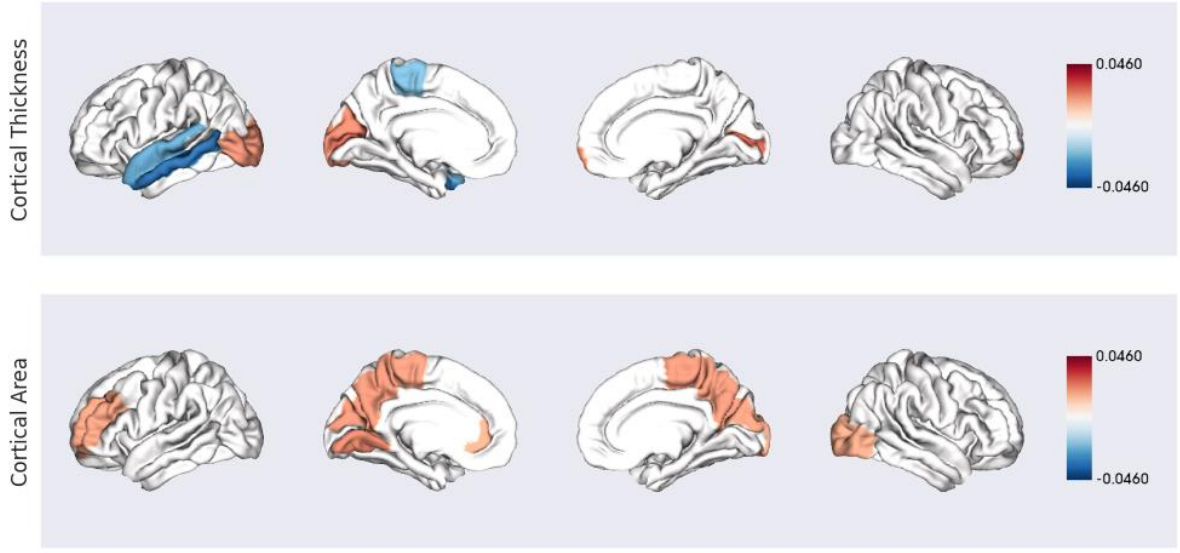

Figure S8. *Full model applied to the subsample without known liver disease. Cortical surfaces show standardized regression coefficients of continuous variable effects of liver fat PDFF on cortical thickness (top) and area (bottom). Only regions with significant liver fat associations after FDR correction for multiple comparison (q<0.05) are shown. Blue color indicates a negative association of liver fat with gray matter, while red color indicates the opposite. Significant effects of liver fat on global gray matter measures not visualized here: Cerebrospinal fluid volume (0.04), total surface area left/right hemisphere (0.01/0.01).*

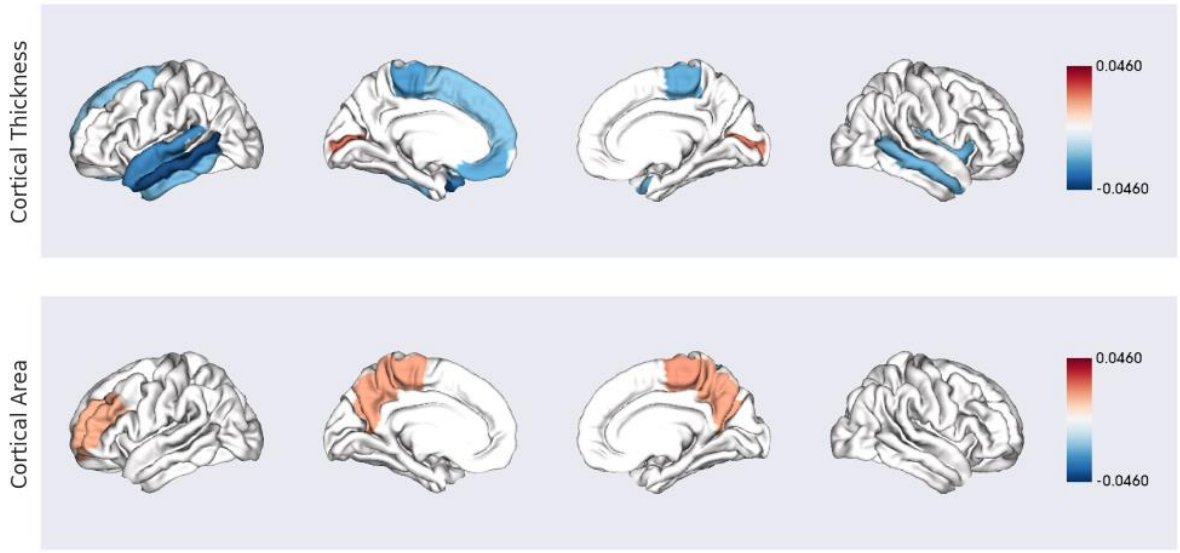

Figure S9. *AC model applied to the subsample without known liver disease. Cortical surfaces show standardized regression coefficients of continuous variable effects of liver fat PDFF on cortical thickness (top) and area (bottom). Only regions with significant liver fat associations after FDR correction for multiple comparison (q<0.05) are shown. Blue color indicates a negative association of liver fat with gray matter, while red color indicates the opposite. Significant effects of liver fat on global gray matter measures not visualized here: Cerebrospinal fluid volume (0.04).*

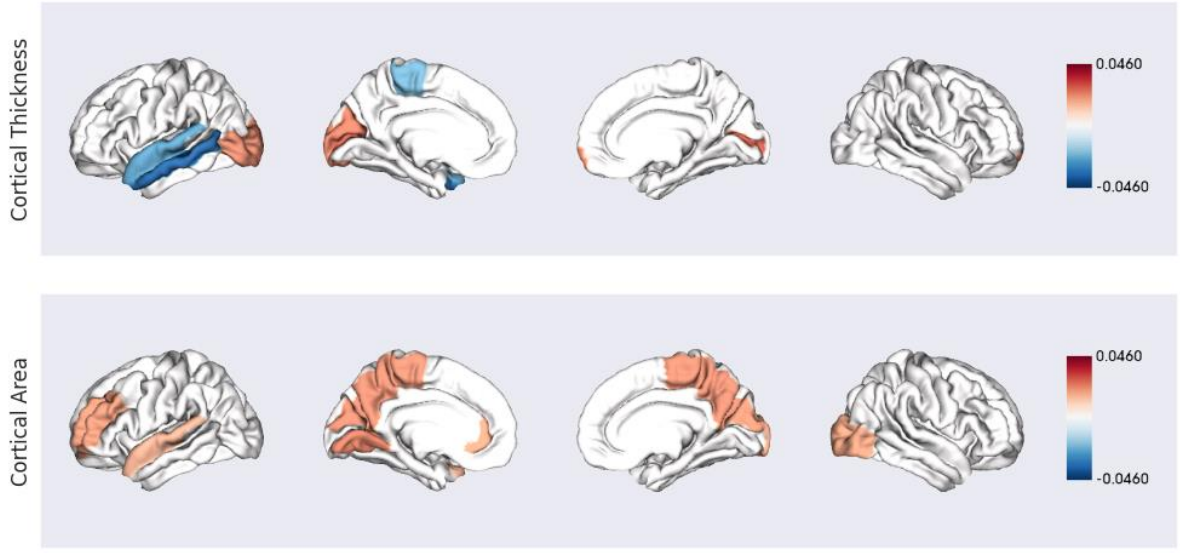

Figure S10. *CM model applied to the subsample without known liver disease. Cortical surfaces show standardized regression coefficients of continuous variable effects of liver fat PDFF on cortical thickness (top) and area (bottom). Only regions with significant liver fat associations after FDR correction for multiple comparison (q<0.05) are shown. Blue color indicates a negative association of liver fat with gray matter, while red color indicates the opposite. Significant effects of liver fat on global gray matter measures not visualized here: Cerebrospinal fluid volume (0.04), total surface area left/right hemisphere (0.01/0.01).*

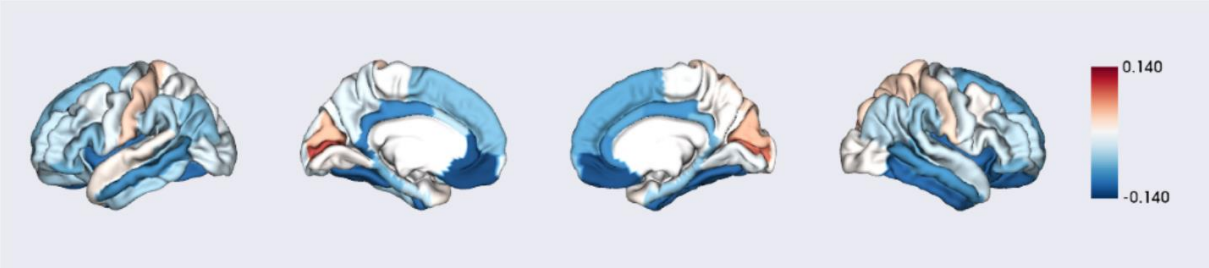

Figure S11. *Cortical thickness case-control effect size map for MDD in adults[4] as provided by the enigma toolbox[7]. Effects were controlled for site, age, and sex. False-discovery rate correction was applied to identify regions with significant effects (while all effects are visualized): Bilateral fusiform, insula, medial orbitofrontal, rostral anterior cingulate, and posterior cingulate, left middle temporal, and right caudal anterior cingulate, and inferior temporal.*

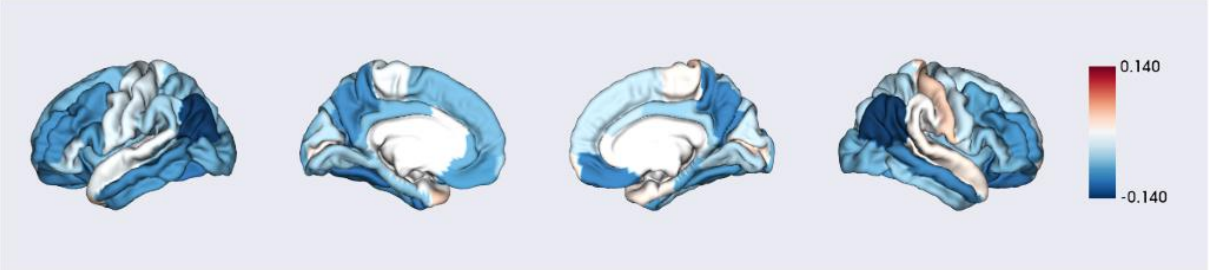

Figure S12. *Cortical thickness case-control effect size map for obsessive-compulsive disorder in adults[8] as provided by the enigma toolbox [7]. Effects were controlled for scan site, age, and sex. False-discovery rate correction was applied to identify regions with significant effects (while all effects are visualized): Bilateral inferior parietal.*

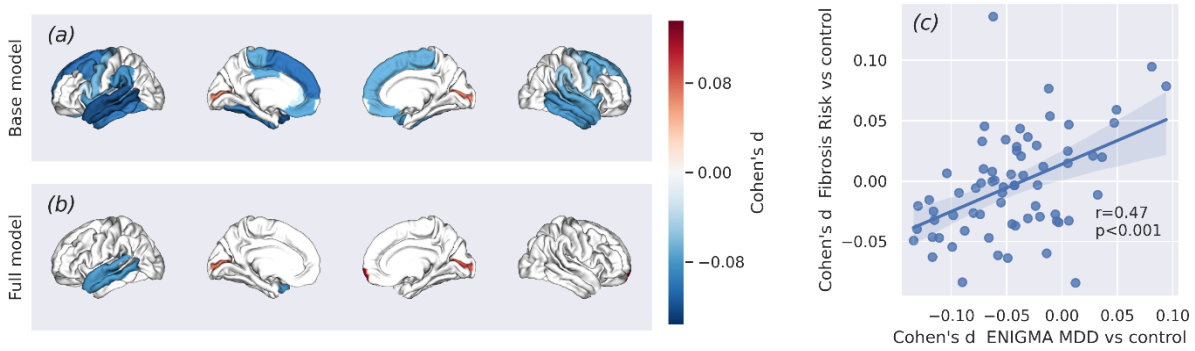

Figure S13. *Liver fat related cortical thickness alterations in the Fibrosis Risk group and neuroanatomical association with MDD. Cohen's d effect sizes for the group difference Fibrosis Risk vs. control (PDFF≤5.5%) explained by liver fat content according to the (a) Base and (b) Full regression models. 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 Fibrosis Risk 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=0.47 (p<0.001) between effect size maps. PDFF - proton density fat fraction, MDD - major depressive disorder.*

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