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The association of chronic pain, painkiller use, and potential mediators with liver fat content

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Excessive accumulation of liver fat content (LFC) is a pathological manifestation of steatotic liver diseases. This study aims to investigate the relationship between chronic pain and LFC development. In the UK Biobank, chronic pain sites were collected via questionnaire, while LFC was measured by magnetic resonance imaging and quantified by Proton Density Fat Fraction (PDFF). During the median follow-up of 10.5 (4.0-17.8) years, in 39,437 individuals, neck/shoulder, back, stomach/abdominal, knee, and general pain achieved significant arithmetic means difference of 0.02, 0.02, 0.04, 0.02, and 0.15 in PDFF ($P < 0.05$) using multivariable linear regression models. There was a significant dose-effect for number of pain sites and PDFF ($P < 0.001$). Additionally, the link between pain sites and PDFF was much stronger in aspirin users than non-users, while steroids had the reverse effect (P for interaction < 0.05). C-reactive protein, sleep, diet, and depression were proved to mediated 8.41%, 13.3%, 6.6%, and 23.0% of the relationship, respectively. In conclusion, there were quantified differences in the relationship between chronic pain and LFC. For chronic pain patients with potential liver health issues, aspirin may be prioritized as an analgesic option due to its potential protective benefits, whereas steroid medications should be avoided.

Keywords Chronic pain, Liver fat content, Liver proton density fat fraction, Metabolic dysfunction-associated steatotic liver disease, Aspirin

Background

Metabolic Associated Fatty Liver Disease (MAFLD) or Metabolic dysfunction-associated steatotic liver disease (MASLD) is an increasingly severe global public health problem, affecting one thirds of the population worldwide[1,2]. Its key pathological hallmark is liver fat content (LFC) accumulation exceeding 5%, which is classified as steatotic liver disease[1,2]. Given the strong association of MAFLD/MASLD with multi-system diseases and increased mortality, coupled with the lack of effective treatments to reverse LFC progression[3,4], identifying the risk factors for LFC and developing targeted prevention and management strategies have become critical priorities[5].

Chronic pain is a widespread condition, impacting more than 30% of the global population[6]. The reported prevalence of chronic non-cancer pain varies significantly, ranging from 8.7 to 64.4%, due to varying criteria[7]. Previous studies have demonstrated associations between chronic pain, cardiometabolic diseases and cardiometabolic multimorbidity[8,9]. Chronic pain may lead to metabolic disorders through multiple mechanisms. For instance, it is linked to systemic inflammation, changed lifestyle, and stress-induced mechanisms such as the hypothalamic-pituitary-adrenal axis and gut-liver axis dysregulation, all of which can influence liver metabolic pathways and alter metabolite levels[10–15]. Conversely, metabolic diseases, such as diabetes-related neuropathy, can also result in chronic pain[16]. Given the established pathological relationship between metabolic disorders and

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MAFLD/MASLD, chronic pain may potentially act as a risk factor for LFC. However, to our knowledge, there is currently no research that has specifically investigated this relationship. Chronic pain is typically managed with pain-relief medications, often without addressing the underlying causes[17]. Moreover, long-term or unreasonable use of painkillers may cause liver damage[18]. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) may cause liver enzyme abnormalities, while morphine-based drugs may lead to chronic liver injury[18]. Therefore, it is of great significance to clarify the relationship and potential mechanisms underlying chronic pain-mediated LFC progression. Additionally, such insights could guide the development of safer and more effective pain management strategies, minimizing the risk of liver damage.

Therefore, this study aims to investigate the relationship between the location and number of chronic pain sites and LFC development, illustrate potential mediators, and analyze the impact of pain-killer (NSAIDs, opioids, and steroids) on these associations.

Materials and methods

Study design and Population

UK Biobank is a prospective cohort study enrolled about half a million participants aged 37 to 63 years. Demographic data and lifestyle behaviors were collected using standardized questionnaires, while laboratory data were obtained through standardized blood sample analyses. The UK Biobank study, adhering to rigorous ethical guidelines, has obtained approval from the Northwest Multicenter Research Ethics Committee. Additionally, the Human Ethics Committee at West China Hospital, Sichuan University, has authorized the use of the UK Biobank dataset for this research.

UK Biobank included 502,357 participants. 39,437 individuals were ultimately analyzed according to the following exclusion criteria. To meet ethical requirements, we excluded participants who withdrew from the study during the follow-up period ($n = 241$). To ensure the integrity of exposure variable, we excluded those who lacked pain data ($n = 2{,}190$). To ensure the temporal relationship between exposure and outcome variables, participants with a history of liver disease were excluded ($n = 3{,}698$). To avoid incomplete outcome variable, we excluded participants who missed magnetic resonance imaging (MRI) examinations during the follow-up period ($n = 455{,}842$). Finally, to maximize the utility of the available data, we excluded participants with missing covariates exceeding 10% ($n = 950$).

Chronic pain sites

Pain assessments were conducted at each visit using a touchscreen questionnaire, which inquired about any pain that affected daily activities in the past month. Participants could select from eight specific pain sites, including headache, facial, neck/shoulder, back, stomach/abdominal, hip, and knee, with an additional 'all over the body' choice (general pain). Selection of the general pain option excluded the identification of specific sites. For those reporting pain at one or more specific sites, additional questions determined whether the pain had persisted for over three months. Chronic pain was defined as pain lasting more than 3 months at any specific site, while individuals reporting no chronic pain were categorized as pain-free. Based on previous study, participants were classified into four groups according to the number of chronic pain sites: 0, 1, 2–3, and ≥ 4[19]. General pain was categorized under the chronic pain site group of ≥ 4.

Painkilling medications

Data on routine medication usage, both at baseline and during the imaging study, was collected via two primary methods. First, participants completed a touchscreen questionnaire, reporting whether they had consistently used medications from a predefined list on most days of the week over the past month. Second, a nurse-led verbal interview was conducted to assess the regular use of prescribed medications, including treatments administered weekly, monthly, or quarterly, excluding short-term medications such as analgesics taken within the last 48 h. Self-reported medication use was considered reliable, as it showed high correlation with pharmaceutical claims data, especially for analgesics, with a kappa statistic ranging from 0.66 to 0.78. The use of any pain-relief medications, such as NSAIDs, opioids, and steroids, was specifically recorded. Common NSAIDs documented included aspirin, paracetamol, and ibuprofen, in accordance with the study's data recording protocols. Non-routine analgesic drugs, such as local anesthetics and antidepressants, were excluded from the analysis.

Assessment of liver fat content

The MRI research phase was conducted from 2014 to 2020. As of the latest count, MRI scans have been performed on 40,532 participants, accounting for 9.1% of the total UK Biobank cohort. MRI technology enables the precise measurement of the Proton Density Fat Fraction (PDFF), which represents the proportion of fat protons relative to the total protons in the liver. This non-invasive technique provides a direct assessment of LFC, accurately quantifying liver fat levels without requiring a liver biopsy. Moreover, MRI-based PDFF measurements are recognized for their exceptional precision, with an accuracy rate approaching 100%[20].

Covariate assessment

In the study, a multitude of covariates were taken into account for a comprehensive analysis, including sex (female vs. male), age, BMI (categorized into normal weight, overweight, and obese with thresholds at < 25.0, 25.0 to < 30, and ≥ 30 kg/m^2, respectively), abdominal obesity (identified with waist circumferences of ≥ 102 cm for males and ≥ 88 cm for females), the Townsend Deprivation Index (indicating socioeconomic status and based on the residential postcode), educational attainment, daily alcohol intake (measured in grams), smoking status (classified as never, current, or former smokers), hypertension (determined by medical history and medication use), diabetes (same as hypertension), physical activity levels (quantified by the metabolic equivalents task hours per day), psychological problems (determined by outpatient and medication), and blood measures including

C-reaction protein, glucose, triglycerides, and cholesterol. As referenced in previous studies, sleep quality was evaluated using measures such as chronotype, sleep duration, insomnia, snoring, and daytime sleepiness[21]. Depression and anxiety were evaluated by 4-item Patient Health Questionnaire[22]. Healthy diet score was calculated based on the consumption of fruit, vegetables, whole grains, fish consumption, red meat, processed meat, and refined grains intake[23].

Statistical analysis

Nonparametric data are expressed as median values with interquartile ranges (25th to 75th percentiles) and analyzed using the Kruskal–Wallis H test. In contrast, parametric data were presented as means with standard deviations and assessed using independent samples t tests or one-way analysis of variance for group comparisons. Categorical variables were described as frequencies and proportions, with comparisons performed using the chi-square test.

In our longitudinal study, multivariate linear regression was employed to evaluate the association between changes in PDFF and chronic pain sites. Due to the skewed PDFF distribution, we utilized the natural logarithm transformation to calculate geometric means. The beta coefficients derived from this analysis were interpreted as arithmetic mean differences (AMD), which, when exponentiated, yielded the ratio of arithmetic means. Additionally, percentage changes in the geometric mean were computed to quantify the magnitude of the effect. We adjusted for confounding factors based on their linear relationship with PDFF in univariate linear regression models, where these variables showed statistically significant associations. Consequently, we adjusted for the following potential confounders: age, sex, deprivation index, education level, physical activity, alcohol intake, smoking status, body mass index, abdominal obesity, hypertension, diabetes, glucose levels, triglycerides, and cholesterol levels.

To explore subgroup differences in the association between PDFF and chronic pain, we conducted analyses for populations with and without painkiller use. Specifically, six subgroup analyses were performed based on the use of NSAIDs, opioids, steroids, aspirin, paracetamol, and ibuprofen. Additional subgroup analyses were carried out based on age, sex, and BMI. To analyze the potential mechanisms by which chronic pain may lead to the development of PDFF, inflammation, physical activity, sleep quality, depression, and anxiety were examined as potential mediating factors[10,11,24,25]. Path analysis was utilized to assess direct and indirect effects of chronic pain on PDFF, with standardized regression coefficients (β) employed to evaluate the strength of these effects. The proportion of mediated effects was calculated as the ratio of the regression coefficient for the indirect pathway to the total effect's regression coefficient, providing a quantitative measure of the mediators' contribution.

Moderation analysis was conducted to identify whether adjusted factors moderated the effect of chronic pain on PDFF. To reinforce our findings, several sensitivity analyses were conducted: (1) adjusting for additional covariates such as C-reactive protein, healthy diet score, and sleep quality; (2) excluding non-white race individuals.

Statistical significance was set at a two-tailed p-value of <0.05. All analyses were conducted using SPSS (version 27.0; IBM Corp., Armonk, NY, USA) and R software (version 3.5.0; Vienna, Austria).

Results

Baseline characteristics

A total of 39,437 participants were included in this study, with a median age of 56 (49 to 61), of whom 18,889 (47.90%) were male. Among these participants, 17,805 (41.15%), 11,123 (28.20%), 8,587 (21.77%), and 1,922 (4.87%) individuals reported 0, 1, 2–3, and ≥4 chronic pain sites, respectively. Baseline characteristics are summarized in Table 1. Participants reporting pain at a greater number of sites were more likely to be female, younger, current cigarette smokers, and had psychological problems and obesity. They also tended to have lower levels of education, a higher Townsend Deprivation Index, and lower blood glucose levels (P for all <0.05).

Linear association between chronic pain and PDFF

During the median follow-up of 10.5 (4.0–17.8) years, the median of PDFF of all individuals was 3.0 (2.2, 5.4). Compared to individuals without pain, those experiencing chronic pain in 7 out of 8 body regions exhibited significantly elevated PDFF levels (Wilcoxon test, $P<0.05$, Fig. 1), including facial, neck/shoulder, back, stomach/abdominal, hip, knee, and general pain. In the fully adjusted linear regression model, association between chronic pain and PDFF persisted for specific sites: neck/shoulder (AMD: 0.02, 95%CI: 0.01, 0.04), back (AMD: 0.02, 95%CI: 0.00, 0.03), stomach/abdominal (AMD: 0.04, 95%CI: 0.02, 0.06), knee (AMD: 0.02, 95%CI: 0.00, 0.04), and general pain (AMD: 0.15, 95%CI: 0.08, 0.21). Similar results were found in percentage change of PDFF (**Table S1** and **S2**).

Moreover, the association between the number of chronic pain sites and PDFF remain significant after adjusting for a range of confounders (Table 2). In the fully adjusted linear regression model, there was dose-response relationship between the number of pain sites and PDFF (AMD for per one site increase: 0.05, 95%CI: 0.03, 0.07). Compared to those without pain, participants experiencing pain ≥4 sites achieved the highest AMD of 0.07 (95%CI: 0.04, 0.10). Similar results were observed in percentage change of PDFF (Table 2).

Effect of painkiller on the association between chronic pain and PDFF

In the sub-cohort of participants with ≥4 vs. 0 chronic pain sites (Fig. 2), the association between the number of pain sites and PDFF was significantly stronger in participants with aspirin intake compared with those not taking aspirin (AMD: −0.03 vs. 0.08, P for interaction: 0.045). Conversely, the effect of steroids was the opposite, as steroids markedly strengthened the association between chronic pain and PDFF than that of non-steroids intake (AMD: 0.84 vs. 0.07, P for interaction: 0.003). Moreover, this relationship was consistent across other medications (**Table S3** and **S4**).

Characteristics	Number of chronic pain sites				*P*
	0	1	2–3	≥4	
Sample size, n (%)	17,805 (45.15%)	11,123 (28.20%)	8587 (21.77%)	1922 (4.87%)	
Male, n (%)	8829 (49.59%)	5434 (48.85%)	3903 (45.45%)	723 (37.62%)	**< 0.001**
White, n (%)	17,468 (98.11%)	10,845 (97.5%)	8353 (97.27%)	1855 (96.51%)	**< 0.001**
Age (years)	56 (50, 61)	55 (49, 61)	55 (48, 60)	54 (48, 60)	**< 0.001**
Townsend Deprivation Index	−2.67 (−3.93, −0.59)	−2.68 (−3.89, −0.65)	−2.55 (−3.88, −0.28)	−2.17 (−3.64, 0.52)	**< 0.001**
Highest education qualification, n (%)					**< 0.001**
College or University degree	8920 (50.1%)	5255 (47.24%)	3680 (42.86%)	701 (36.47%)	
A levels/AS levels or equivalent	2342 (13.15%)	1416 (12.73%)	1121 (13.05%)	248 (12.9%)	
O levels/GCSEs or equivalent	3827 (21.49%)	2554 (22.96%)	2233 (26%)	536 (27.89%)	
Other (e.g. NVO, nursing, missing)	2716 (15.25%)	1898 (17.06%)	1553 (18.09%)	437 (22.74%)	
Smoking status, n (%)					**< 0.001**
Never	11,121 (62.46%)	6793 (61.07%)	5029 (58.57%)	1074 (55.88%)	
Current	977 (5.49%)	664 (5.97%)	615 (7.16%)	156 (8.12%)	
Previous	5707 (32.05%)	3666 (32.96%)	2943 (34.27%)	692 (36%)	
Alcohol consumption (g/d)	8 (2.29, 14.86)	8 (2.29, 13.71)	6.86 (1.14, 13.71)	5.71 (0, 11.43)	**< 0.001**
Physical activity (MET hour/week)	29.42 (14.32, 54.2)	28.4 (13.97, 54.2)	28.29 (12.95, 53.57)	26.52 (11.5, 54.2)	0.197
Psychological problems, n (%)	4767 (26.77%)	3444 (30.96%)	3440 (40.06%)	1065 (55.41%)	**< 0.001**
Systolic blood pressure (mmHg)	134 (123.5, 147)	133 (122.5, 146)	133 (121.5, 145)	132.5 (121.5, 144)	**< 0.001**
Diastolic blood pressure (mmHg)	81 (74.5, 87.5)	81 (74.5, 87.5)	81 (74.5, 88)	81.5 (74.5, 88)	0.534
Glucose (mmol/L)	4.89 (4.57, 5.23)	4.87 (4.55, 5.21)	4.87 (4.55, 5.21)	4.86 (4.53, 5.22)	**0.043**
Triglycerides (mmol/L)	1.35 (0.97, 1.96)	1.38 (0.99, 2)	1.43 (1.01, 2.08)	1.52 (1.06, 2.24)	**< 0.001**
Cholesterol (mmol/L)	5.69 (5, 6.42)	5.66 (4.98, 6.41)	5.67 (4.97, 6.43)	5.72 (5.02, 6.43)	0.932
Antihypertensive medication, n (%)	1485 (8.34%)	899 (8.08%)	655 (7.63%)	171 (8.9%)	0.139
Cholesterol lowering medication, n (%)	1461 (8.21%)	863 (7.76%)	699 (8.14%)	169 (8.79%)	0.352
Medication for diabetes, n (%)	48 (0.27%)	27 (0.24%)	20 (0.23%)	3 (0.16%)	0.782
Painkilling medication, n (%)	3652 (20.51%)	3597 (32.34%)	3930 (45.77%)	1160 (60.35%)	**< 0.001**
Diabetes, n (%)	451 (2.53%)	277 (2.49%)	221 (2.57%)	71 (3.69%)	**0.019**
Hypertension, n (%)	7230 (40.61%)	4314 (38.78%)	3276 (38.15%)	705 (36.68%)	**< 0.001**
Body mass index (kg/m^2)	25.59 (23.39, 28.24)	25.93 (23.6, 28.73)	26.47 (23.93, 29.35)	27.4 (24.6, 30.61)	**< 0.001**
Abdominal obesity, n (%)	3746 (21.04%)	2665 (23.96%)	2421 (28.19%)	741 (38.55%)	**< 0.001**
C-reactive protein (mg/L)	0.98 (0.51, 1.93)	1.07 (0.55, 2.15)	1.16 (0.59, 2.39)	1.43 (0.7, 2.92)	**< 0.001**

Table 1. Baseline characteristics of participants included. Data are expressed as n (%) and median (25th-75th). Abbreviations: MET, metabolic equivalent task.

Mediation effect analyses

To analyze the potential mechanisms by which chronic pain may lead to the development of PDFF, we examined the mediating roles of inflammation, physical activity, diet, sleep quality, depression, and anxiety. In structural equation modeling (Table 3), mediating effect was particularly significant in the sub-cohort of participants with 2–3 vs. 0 chronic pain sites. For example, C-reactive protein levels (8.97%), sleep score (22.18%), depression score (28.60%), anxiety score (10.93%), and healthy diet score (6.63%) significantly mediated the relationship between chronic pain and PDFF (P for all < 0.05).

Subgroup, moderating, and sensitivity analysis

In the subgroup analysis based on age, sex and body mass index (**Table S5** and **6**), associations between chronic pain and the development of PDFF were consistent across different sex subgroups (P for interaction > 0.05). However, younger age and obesity amplified the associations compared with older age and normal weight (P for interaction < 0.05). Moderation analysis further revealed that lower educational attainment and the presence of psychological problems enhanced the associations (P for interaction < 0.05, **Table S8**). Follow-up duration did not significantly interact with these associations (P for interaction: 0.623).

After additional adjustment for the healthy diet index, C-reactive protein, and sleep, respectively, the association between chronic pain and PDFF remained statistically significant (**Table S9**). The dose-response relationship between the number of pain sites and PDFF changes was still consistent after excluding participants of non-white ethnicity ($n = 916$, **Table S10**).

Discussion

To the best of our knowledge, this study represents the first large-scale, prospective cohort investigation of the association between chronic pain and LFC (summarized in Fig. 3). Our analysis revealed a positive correlation between specific location and number of chronic pain sites with LFC progression. Pain in the neck or shoulder

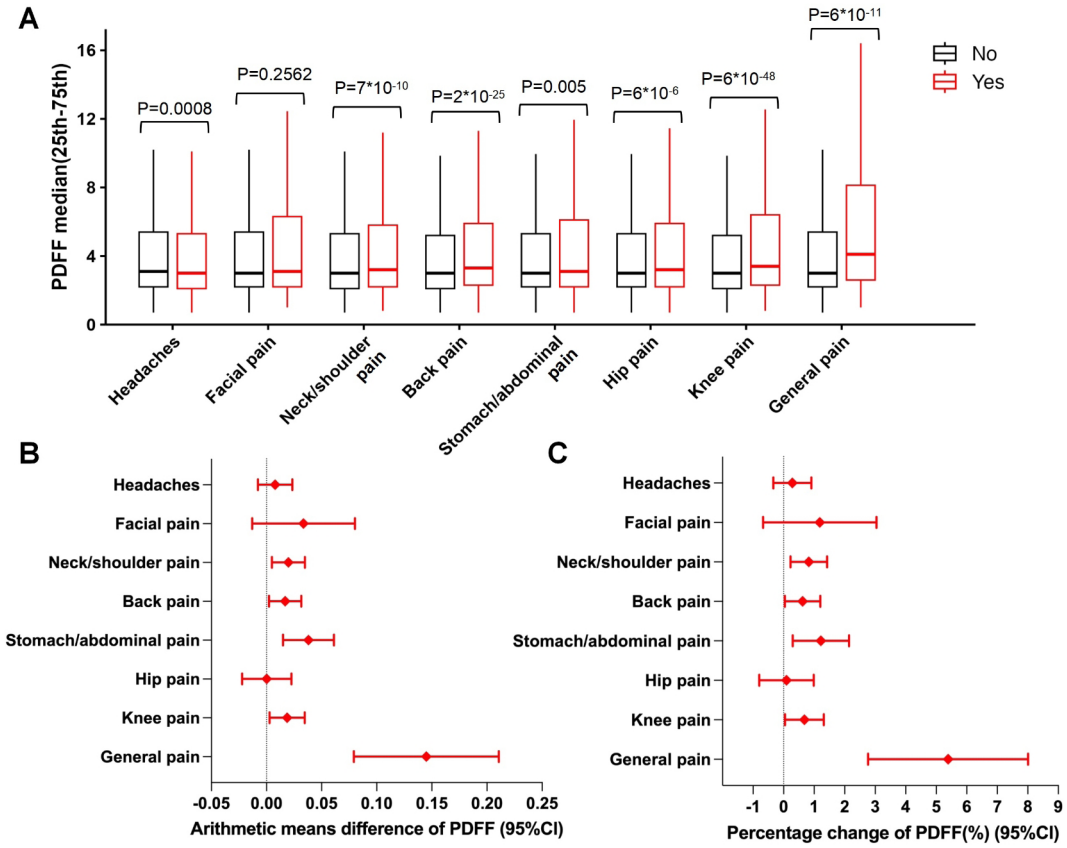

Fig. 1. The association between chronic sites and PDFF. (**A**) Compare the PDFF values of patients with or without pain in 8 specific areas (Mann–Whitney U test). Boxplot elements were defined as follows: the center line is the median value; box limits are the upper and lower quartiles; whiskers are 1.5× the interquartile range. Multivariable linear regression models were conducted to analyzing the association between chronic sites and absolute (**B**) and relative (**C**) changes of PDFF. Models were adjusted by Model 4 as Table 2.

Number of chronic pain sites	Difference (95%CI)			
	Model 1	Model 2	Model 3	Model 4
Arithmetic means difference of PDFF				
0	reference	reference	reference	reference
1	0.13 (0.07, 0.19)	0.09 (0.05, 0.13)	0.02 (0.00, 0.03)	0.01 (−0.01, 0.02)
2–3	0.33 (0.26, 0.40)	0.25 (0.20, 0.30)	0.05 (0.04, 0.07)	0.03 (0.01, 0.04)
≥4	0.78 (0.64, 0.92)	0.61 (0.51, 0.71)	0.13 (0.10, 0.16)	0.07 (0.04, 0.10)
Per 1 site increase	0.19 (0.16, 0.21)	0.20 (0.17, 0.22)	0.12 (0.10, 0.15)	0.05 (0.03, 0.07)
Percentage change of PDFF (%)				
0	reference	reference	reference	reference
1	1.30 (0.62, 1.98)	1.33 (0.68, 1.98)	0.71 (0.10, 1.32)	0.18 (−0.40, 0.75)
2–3	3.55 (2.81, 4.29)	3.85 (3.14, 4.56)	2.42 (1.74, 3.10)	1.23 (0.58, 1.87)
≥4	7.49 (6.14, 8.85)	8.44 (7.15, 9.74)	5.35 (4.11, 6.59)	2.70 (1.53, 3.87)
Per 1 site increase	1.50 (1.28, 1.72)	1.67 (1.45, 1.87)	1.04 (0.84, 1.25)	0.40 (0.20, 0.59)

Table 2. Linear regression models to analyse association between number of chronic pain sites and arithmetic means difference of PDFF or percentage change of PDFF (%). Model 1: Unadjusted. Model 2: Adjusted by age, sex, ethnicity, highest education qualification, townsend deprivation index, smoking status, alcohol consumption and physical activity. Model 3: Model 2 plus psychological problems, glucose, triglycerides, cholesterol, antihypertensive medication use, cholesterol lowering medication use, medication for diabetes and painkilling medication use. Model 4: Model 3 plus body mass index.

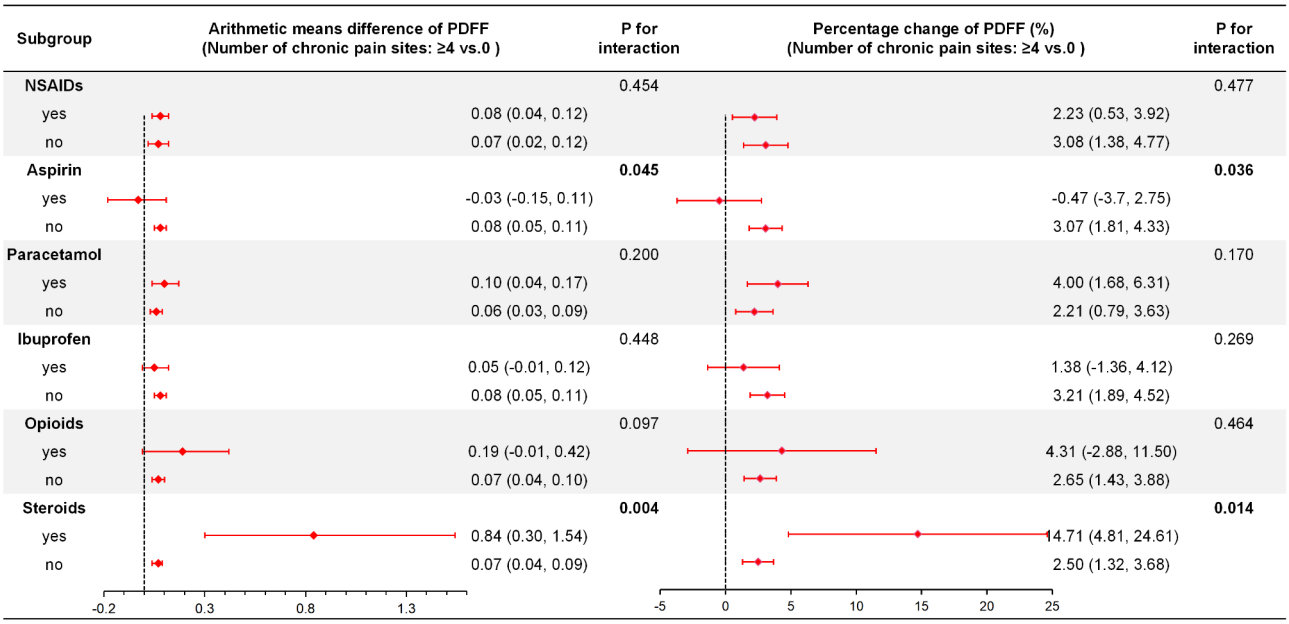

Fig. 2. In the sub-cohort of participants with ≥4 vs. 0 pain sites, the effects of 6 painkiller on the relationship between chronic pain and PDFF were analyzed. Models were adjusted by Model 4 as Table 2.

Mediator	Number of chronic pain sites	Arithmetic means difference of PDFF (95%Cl)			Mediated, (%)
		Total effect	Direct	Indirect	
C-reactive protein	0	reference	reference	reference	reference
	1	0.05 (−0.04, 0.16)	0.04 (−0.05, 0.15)	0.01 (0.00, 0.01)	7.27
	2–3	0.17 (0.07, 0.28)	0.15 (0.06, 0.26)	0.02 (0.01, 0.02)	**8.97**
	≥4	0.60 (0.42, 0.79)	0.55 (0.38, 0.75)	0.05 (0.03, 0.07)	**8.41**
Physical activity	0	reference	reference	reference	reference
	1	0.06 (−0.05, 0.15)	0.06 (−0.04, 0.15)	0.00 (−0.00, 0.00)	−0.28
	2–3	0.16 (0.06, 0.26)	0.16 (0.06, 0.26)	0.00 (−0.00, 0.00)	0.00
	≥4	0.59 (0.39, 0.78)	0.59 (0.39, 0.78)	0.00 (−0.00, 0.01)	0.00
Sleep score	0	reference	reference	reference	reference
	1	0.06 (−0.05, 0.16)	0.05 (−0.06, 0.15)	0.01 (0.00, 0.01)	10.85
	2–3	0.17 (0.05, 0.28)	0.13 (0.02, 0.24)	0.04 (0.03, 0.05)	**22.18**
	≥4	0.59 (0.41, 0.80)	0.51 (0.33, 0.72)	0.08 (0.05, 0.11)	**13.26**
Depression score	0	reference	reference	reference	reference
	1	0.07 (−0.04, 0.17)	0.04 (−0.07, 0.14)	0.03 (0.02, 0.03)	31.04
	2–3	0.16 (0.03, 0.27)	0.11 (−0.02, 0.23)	0.05 (0.03, 0.06)	**28.60**
	≥4	0.59 (0.40, 0.76)	0.46 (0.26, 0.64)	0.13 (0.08, 0.18)	**23.00**
Anxiety score	0	reference	reference	reference	reference
	1	0.06 (−0.03, 0.15)	0.05 (−0.03, 0.14)	0.01 (0.00, 0.01)	12.52
	2–3	0.16 (0.05, 0.27)	0.14 (0.03, 0.26)	0.02 (0.00, 0.03)	**10.93**
	≥4	0.63 (0.45, 0.81)	0.61 (0.42, 0.79)	0.02 (−0.02, 0.05)	3.18
Health diet score	0	reference	reference	reference	reference
	1	0.07 (−0.02, 0.15)	0.06 (−0.03, 0.14)	0.00 (0.00, 0.01)	5.82
	2–3	0.15 (0.02, 0.31)	0.14 (0.01, 0.30)	0.01 (0.01, 0.02)	**6.63**
	≥4	0.59 (0.38, 0.79)	0.57 (0.37, 0.78)	0.01 (0.01, 0.02)	**2.39**

Table 3. Estimated indirect effect of different mediators on association between number of chronic pain sites and PDFF. Models were adjusted by Model 4 as Table 2. Statistical significance is indicated in bold.

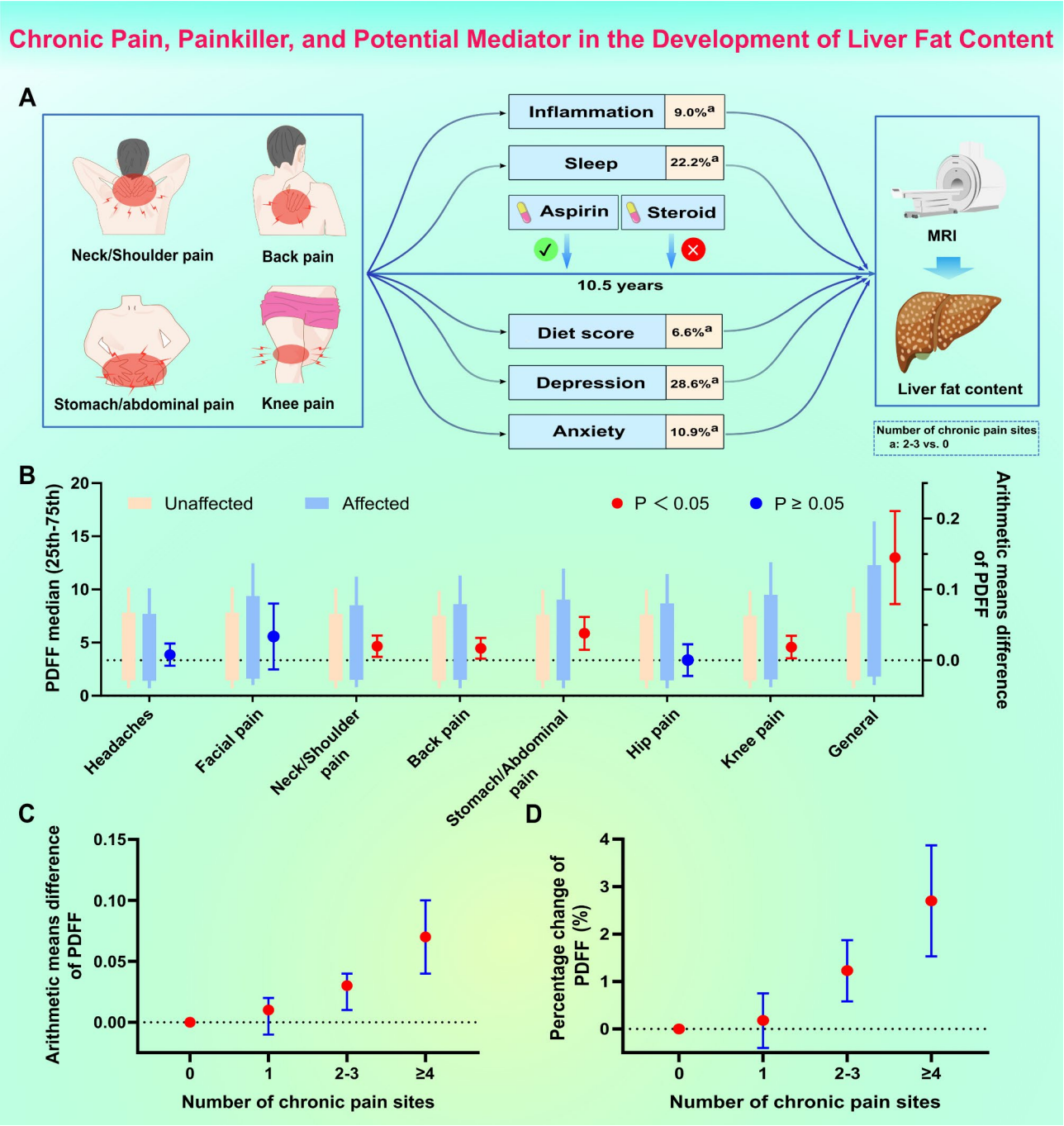

Fig. 3. Summary of findings. There is a positive dose-response relationship between the number of chronic pain sites and liver fat content, identifying the neck/shoulder, back, stomach/abdomen, and knee as significant risk factors. Additionally, inflammation, sleep quality, diet, depression, and anxiety medicated those association. Aspirin is suggested for its potential protective effect on LFC, while the use of steroids is advised against.

(0.020), back (0.017), stomach or abdominal area (0.038), knee (0.019), and general pain (0.145) contribute to significant changes in PDFF. Notably, individuals experiencing four or more pain sites achieved a 0.07 increase in PDFF. These associations remained consistent across different age, sex, and BMI subgroups, as well as in sensitivity analyses, underscoring the crucial role of chronic pain in the progression of LFC. These findings suggest the importance of early interventions targeting pain symptoms to mitigate LFC progression and the occurrence of MAFLD/MASLD.

Chronic pain is increasingly recognized as a distinct condition that often requires pain-relief interventions rather than solely focusing on treating the root causes[17]. Therefore, we further explored the role of analgesics in the association between chronic pain and LFC. Among the pain medications assessed, aspirin demonstrated a

protective effect against LFC progression during long-term follow-up. Several evidence suggests that daily aspirin use may offer benefits for patients with MAFLD/MASLD[26–28]. A prospective cohort study involving 361 patients with biopsy-proven MAFLD/MASLD demonstrated that daily aspirin users had a significantly lower likelihood of having non-alcoholic steatohepatitis and fibrosis compared with nonusers. This relationship demonstrated a duration-dependent trend, with the greatest benefit observed in individuals using aspirin more than 4 years[26]. A recent randomized clinical trial proved that daily low-dose aspirin over a 6-month period achieved a significant reduction in LFC in patients with MAFLD/MASLD[29]. Mechanically, aspirin demonstrated its anti-inflammatory and antiplatelet properties by suppressing the activity of proinflammatory cyclooxygenase-2 (COX-2) and signaling pathways related to platelet-derived growth factor[30,31]. Additionally, it influenced the balance of bioactive lipids[32]. Thus, these factors may explain the benefits of aspirin in both pain relief and inhibiting LFC progression. However, despite its promising effects, aspirin is not currently recommended in clinical guidelines for MAFLD/MASLD management, warranting further investigation into its broader clinical applications[5].

In contrast, steroids exhibited a significant exacerbating effect on the chronic pain–LFC relationship, likely due to their potential to induce hepatic fat deposition and toxicity[33]. While opioid use demonstrated a near-significant interaction effect ($P = 0.097$), further research is needed to clarify its role. For chronic pain patients with potential liver health issues, aspirin may be prioritized as an analgesic option due to its potential protective benefits, whereas steroid medications should be avoided.

Aspirin may represent a relatively convenient strategy in clinical practice. However, avoiding steroid use solely to minimize the risk of adverse effects on liver health should be tailored to the patient's specific circumstances. If alternative options for pain management are available, we recommend reducing steroid use to safeguard long-term liver health. Conversely, if the patient's pain management options are limited and other strategies prove less effective, the use of steroids remains necessary. It is important to note that some steroids are essential for treating the underlying disease, such as pain caused by rheumatic conditions[34], and should still be prioritized when clinically indicated. For patients with chronic pain and coexisting cardiovascular disease[35]or elevated liver fat content, Aspirin may offer dual benefits. However, it is contraindicated in individuals at high risk of gastrointestinal bleeding[36] or with specific contraindications for antiplatelet therapy. The use must be individualized, taking into account the patient's overall health profile and specific contraindications. This nuanced approach ensures optimal outcomes while minimizing risks.

In this study, the association of specific chronic pain sites with LFC development may be explained by several conditions. For example, chronic diarrhea, dysbiosis of gut microbiota, and rheumatoid arthritis are involved in the occurrence and development of MAFLD/MASLD[37]. However, most pain is nonspecific; for example, nonspecific back pain accounts for 85%[38]. Therefore, we conducted mediation analysis to uncover potential mediators worthy of research. In this study, inflammation, sleep quality, depression, and anxiety were proven to significantly mediate the association between chronic pain and LFC. Unexpectedly, depression served as the most significant mediator, indicating the complex role of pain at biological, psychological, and social levels in LFC development. Furthermore, factors such as sociodemographics, psychological state, and lifestyle choices might exert a two-way influence on the link between chronic pain and LFC to a certain degree. Previous studies have also reached similar conclusion[12,13,39,40]. A study involving 4,688 Korean adults reported that depression was a significant predictor of MAFLD/MASLD, with insulin resistance identified as a key factor mediating the relationship between depression and the risk of MAFLD/MASLD[12]. Based on these findings and our study's results, it is evident that mental health and sleep quality are essential considerations in managing patients with chronic pain, not only for improving their quality of life but also for ensuring better long-term liver health. By addressing these factors, we can potentially mitigate the risk of liver fat accumulation in this population.

Our research offers several notable strengths, including its expansive participant base, a well-structured longitudinal approach, and the utilization of MRI for assessing cardiac structure and function with precision. We have also taken into account an extensive array of potential confounding variables, ensuring a more robust analysis. Additionally, by conceptualizing chronic pain as an independent disease entity, the research provides novel insights into the temporal dynamics between pain multiplicity and LFC progression. The analysis from multiple perspectives, including painkillers and mediating factors, provides suggestions for intervention and mechanism exploration.

Our study, while robust in its approach, has several limitations. First, the UK Biobank cohort, characterized by a selective response rate of 5.5%, may be subject to the healthy volunteer effect, which could skew the study's generalizability due to its association with painful symptoms. Second, the reliance on self-reported pain assessments could lead to recall bias. Nonetheless, self-reports are a valuable and prevalent method for capturing pain experiences in research and clinical settings, given the inherently subjective nature of pain. The absence of data on pain severity, patterns, and additional chronic pain outcomes limits our capacity to explore their relationships with LFC. Third, considering the complexity of pain at the biological, psychological, and social levels, confounding factors may not have been fully corrected. Fourth, the absence of a PDFF baseline in the database precludes the analysis of PDFF's temporal dynamics. The lack of baseline PDFF data limited our ability to quantify the differences in hepatic fat accumulation over time. If such data were available, it would strengthen the causal inference of our findings by providing more robust evidence for temporal relationships.

Conclusion

In conclusion, as summarized in Fig. 3, our study revealed a positive dose-response relationship between the number of chronic pain sites and LFC, identifying the neck/shoulder, back, stomach/abdomen, and knee as significant contributing factors. For chronic pain patients with potential liver health issues, aspirin may be prioritized as an analgesic option due to its potential protective benefits, whereas steroid medications should be avoided. Additionally, inflammation, sleep quality, diet, depression, and anxiety are not only mediators but also

may potential protection targets of MASLD in individuals with chronic pain. Further high-quality research is warranted to deeply elucidate the underlying mechanisms.

Data availability

Data is provided within the manuscript or supplementary information files.

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Author contributions

Dr. YC, RY and XL designed the research. Dr. YJ and YC analyzed the data under the supervision of Dr. XL and QZ. Dr. YC and YJ wrote the first draft of the manuscript. Dr. JY, YZ, YY, CS, RY, RZ, ZW, DL, QZ LJ, and XL reviewed the manuscript and provided critical scientific input. Dr. LJ and XL had the main responsibility for the final content of the manuscript. All the authors approved the final draft of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

of the UK Biobank study was approved by the NHS National Research Ethics Service (16/NW/0274). The experimental protocols were established according to the ethical guidelines of the Helsinki Declaration. Written informed consent was obtained from individual or guardian participants. All methods were carried out in accordance with guidelines and regulations developed by the UK Biobank. Data usage was approved by the Human Ethical Committee of the West China Hospital of Sichuan University (2023 – 1207).

Additional information

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