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A cross-sectional study

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ORIGINAL ARTICLE

Steatotic liver disease is the most important somatic determinant of quality of life in patients with obesity: A cross-sectional study

Charlotte Wilhelmina Wernberg[1,2] | Mads Fallesen Kjer[1,3] | Lea Ladegaard Grønkjær[1,3] | Birgitte Gade Jacobsen[1,3] | Mette Munk Lauridsen[1,2]

[1]Liver Research Group, Department of Gastroenterology and Hepatology, University Hospital of South Denmark, Esbjerg, Denmark

[2]ATLAS Center for Functional Genomics and Tissue Plasticity, University of Southern Denmark, Odense, Denmark

[3]OPEN Open Patient Data Explorative Network, Odense, Denmark

Correspondence
Mette Munk Lauridsen, Liver Research Group, Department of Gastroenterology and Hepatology, University Hospital of South Denmark, Esbjerg, Denmark.
Email: mette.enok.munk.lauridsen@rsyd.dk

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Abstract

Background and Aims: Patients with metabolic dysfunction-associated steatotic liver disease (MASLD) are often comorbid and stigmatized. This can negatively affect quality of life (QOL). Other studies have primarily used the Chronic Liver Disease Questionnaire (CLDQ), which focuses on liver-related symptoms, to characterize QOL, but most MASLD patients have only mild liver disease, and CLDQ might overlook QOL issues pertaining to them. We aimed to determine the impact of metabolic dysfunction-associated steatohepatitis (MASH) on QOL in obese patients using a 136-item generic QOL questionnaire.

Methods: We included participants with BMI ≥ 35 kg/m^2 who all fully answered the sickness impact profile (SIP, range 0–100, normal = 3.4, 100 = worst) and had a liver biopsy to diagnose MASLD. Sociodemographics, comorbidity and biometric data were obtained from all participants.

Results: Of 176 (mean age 45.9 years, 70% female, 12.6 years of education), 132 had no-MASH and 44 MASH. On stepwise multivariable regression analysis, divorce ($p = .011$), unemployment ($p < .003$) and hepatic steatosis ($p = .01$) were associated with poor overall QOL. No other somatic comorbidity was associated. MASH patients more frequently than no-MASH reported physical discomfort (48% vs. 30%, $p = .04$), inability to do daily activities (29% vs. 54%, $p = .006$) and attention problems (32% vs. 57%, $p = .003$).

Conclusion: MASLD severity was the only somatic determinant of QOL in patients with obesity in this cohort, and a large fraction reported debilitating symptoms. Patients and caregivers should consider the limitations this poses when planning interventions.

Abbreviations: HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; KFS, Kleiner Fibrosis Score; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MDI, Major Depression Inventory; MetS, metabolic syndrome; MHE, minimal hepatic encephalopathy; NAS, NAFLD activity score; QOL, quality of life; SIP, sickness impact profile.

Charlotte Wilhelmina Wernberg and Mads Fallesen Kjer contributed equally.

KEYWORDS
fatty liver, non-alcoholic fatty liver disease, obesity, quality of life, sickness impact profile

1 | INTRODUCTION

Hepatic steatosis is common in obesity[1–3] and represents the initial, least severe manifestation of metabolic dysfunction-associated steatotic liver disease (MASLD),[4] previously known as non-alcoholic fatty liver disease (NAFLD). In some cases, MASLD progresses to metabolic dysfunction-associated steatohepatitis (MASH), histologically characterized by lobular inflammation. MASH significantly elevates the risk of hepatic fibrosis formation that, in severe cases, can lead to liver cirrhosis.[5–8] The global prevalence of adult MASLD has surged, reaching 33%, with a 50.4% increase observed between 1990–2006 and 2016–2019.[9] This development is primarily attributed to a steep rise in obesity and type 2 diabetes mellitus prevalence,[10,11] and necessitates comprehensive clinical attention across various medical sectors and specialties.

The rise in MASLD prevalence implies that the clinical and pharmaceutical focus is shifting towards MASLD management and treatment. This new scenario requires a fundamental understanding of how MASLD across various severities affects the patients' quality of life (QOL).[5,12] Existing evidence from studies that have made QOL a primary endpoint in MASLD patients suggests that both MASLD and MASH detrimentally affect QOL.[13–17] Prior studies have primarily used the Chronis Liver Disease Questionnaire (CLDQ), which was designed explicitly for use in chronic liver diseases and covers 29 items in the following domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worry, or the Short Form 36 (SF-36), which is a generic questionnaire reflecting eight domains of overall health (physical functioning, physical role, pain, general health, vitality, social function, emotional role and mental health). A review from 2018 indicated that MASH had adverse effects on health-related quality of life (HRQOL) as measured by the SF-36 ($n = 1031$) and CLDQ ($n = 230$). Subsequently, a comprehensive review in 2022 reaffirmed these findings.[18] Notably, physical functioning appeared particularly impaired, potentially attributable to frequent fatigue reported within these patient cohorts. An extensive study on this subject, a US survey (NHANES, $n = 3333$), identified reduced HRQOL using the HRQOL-4 questionnaire among patients with a fatty liver index (FLI) score >60 (the score is based on BMI, waist circumference, gamma-glutamyl transferase and triglycerides).[17] However, this study did not encompass biopsy-confirmed MASLD or MASH patients, and the QOL questionnaire included only four questions.

The use of CLDQ, which assumes the patients have liver-specific symptoms, introduces the risk of overlooking QOL domains outside the CLDQ questions, including domains that may be specific to MASLD/MASH. Thus, the primary objective of our study is to employ a comprehensive generic questionnaire, the sickness impact profile (SIP), to adopt a more expansive perspective on the determinants of QOL in a group of well-characterized individuals with obesity. We aim to investigate the correlation between QOL indices and the severity of biopsy-proven MASLD. Furthermore, we intend to provide an in-depth understanding of the patient's daily challenges based on their responses to each of the 136 SIP items.

Key points

In this study, we investigated the quality of life in a group of 176 people with obesity. All had a BMI above 35 kg/m^2, had a liver biopsy as part of the study and answered a 136-item questionnaire about their quality of life and daily functioning. We found that quality of life was worst in people who were divorced, outside the workforce and those with fat accumulation in the liver. Fatty liver was the only physical factor associated with poor quality of life. More than 40% of patients with fatty liver reported that they experience physical discomfort, do less housework, have decreased sexual activity and have problems with attention. These findings and symptoms should be taken into account in care plans for patients with obesity and fatty liver disease.

2 | PATIENTS

2.1 | Patients with obesity—at risk of MASLD

The data for this cross-sectional analysis were collected in the PROMETHEUS study (NCT03535142) at the University Hospital of Southern Denmark, which is an ongoing, prospective case–control study including persons with BMI ≥ 35 kg/m^2 (where half undergo bariatric surgery) and are 18 years of age or older. Data were collected between 2018 and 2022. All study participants had a liver biopsy at inclusion and extensive clinical phenotyping and history taking. The baseline characteristics are shown in Table 1. Data from a subset of the cohort have previously been previously published.[19] In this sub-study, we analysed data from 176 participants with a complete SIP questionnaire and a liver biopsy. Some of the patients were recruited from the bariatric clinic and were on the waiting list for surgery, the rest were recruited from different outpatient clinics or through social media recruitment specifically for the PROMETHEUS study; others were referred to the hepatology unit with elevated liver enzymes or hepatic steatosis on ultrasound for further assessment.

TABLE 1 Characteristics and liver status of the 176 participants with a complete sickness impact profile questionnaire and a liver biopsy, stratified into no-MASH (metabolic-associated dysfunction steatosis liver disease) or MASH. MASH was defined as ≥1 steatosis, ≥1 inflammation and ≥1 ballooning according to the NAFLD Activity Score.

	All ($n=176$)	No-MASH ($n=132$)	MASH ($n=44$)
Demographics			
Female (%)	123 (70)	87 (66)	36 (82)
Age, years mean (SD)	45.9 (12.2)	45.5 (12.4)	47.4 (11.6)
Formal education, years mean (SD)	12.6 (2.9)	12.5 (2.7)	12.9 (3.4)
Marital status*, *n* (%)			
Single	41 (24)	29 (22)	12 (27)
Living with partner (Married or not)	114 (66)	89 (68)	25 (57)
Divorced	19 (11)	12 (9)	7 (16)
Employment status*, *n* (%)			
Full time (>35 h/week)	66 (38)	51 (39)	15 (34)
Reduced hours	36 (21)	26 (20)	10 (23)
Long-term sick leave	41 (23)	28 (21)	13 (30)
Other (e.g. Retiree/student)	32 (18)	26 (20)	6 (14)
Metabolic comorbidity			
BMI, kg/m^2	41.7 (7.4)	41.9 (7.6)	40.8 (7.7)
Type-2 Diabetes mellitus, *n* (%)	45 (26)	26 (20)	19 (43)
Hypertension, *n* (%)	80 (45)	58 (45)	22 (50)
Sleep apnoea, *n* (%)	40 (23)	29 (22)	11 (26)
Hypercholesterolemia, *n* (%)	50 (28)	32 (24)	18 (41)
MetS points, mean (SD)	3.7 (1.2)	3.5 (1.2)	4.0 (1.2)
Mental health			
Major depression inventory Score, mean (SD)	10.8 (9.0)	10.0 (9.2)	11.8 (8.6)
Antidepressants use, *n* (%)	35 (20)	23 (17)	12 (27)
Benzodiazepines or Antipsychotics use, *n* (%)	15 (9)	11 (8)	4 (9)
Liver status			
NAS, mean (SD)	2.6 (1.9)	1.9 (1.4)	4.8 (1.3)
Fibrosis Grade: F0-1/F2/F3-4, *n*	127/41/8	105/25/2	22/16/6
Steatosis grade: S0/S1/S2/S3, *n*	35/68/48/25	35/56/29/12	0/12/19/13
Liver stiffness, kPa	7.8 (6.8)	7.5 (6.4)	9.1 (8.6)
Controlled attenuation parameter (CAP), dB/m	345 (92)	334 (94)	367 (49)
Fatty liver index (FLI)^	92 (17)	90 (22)	94 (11)
FIB-4	0.75 (0.63)	0.71 (0.60)	0.99 (0.76)

Note: Categoric data are represented as frequency (%), and continuous data are represented as mean (±SD) if normally distributed (noted) otherwise as median (IQR) (not noted).

Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; FIB-4; fibrosis-4 * available in $n=174$; FLI; fatty liver index ^ available in $n=160$; MASLD; metabolic dysfunction-associated steatotic liver disease; MetS, metabolic syndrome severity score; NAS, NAFLD activity score.

Exclusion criteria were other aetiology to liver disease than MASLD alone, hepatotoxic medications, weekly alcohol consumption above 240 g/daily and 30 g/daily for women and men, respectively, inability to give consent, contraindications for doing a liver biopsy, cancer or other comorbidities with life expectancy <12 months.

2.2 | Reference group with liver cirrhosis

As a reference group, we post hoc added SIP information from a group of patients with liver cirrhosis ($n=111$) who had completed the SIP questionnaire in a different project.[20] This group included 68% white Danish males, with a mean age of 60 years (SD: 8.7), a median

Child-Pugh score of 6 (IQR: 6–8), and an average of 10.8 years of formal education (SD: 2.4). The aetiology of cirrhosis was ALD (82%), MASLD (6%), viral hepatitis B or C (5%) and other cases involving a mix or combination of autoimmune diseases. All had a BMI below 30 kg/m^2.

Both studies were conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of good clinical practice. All subjects gave written informed consent for study participation.

3 | METHODS

3.1 | Clinical phenotyping

All patients had fasting venous blood tests the morning of the biopsy visit, including HOMA-IR, HBA1c, blood lipids, and liver enzymes. Medical charts were reviewed, and the patients enquired about comorbidities and the use of medications. Metabolic Syndrome Score (MetS) was calculated based on the Danish definition (two or more: waist circumference >94/80 cm, BMI > 30 kg/m^2, triglycerides >2 mmol/L and/or HDL-cholesterol <1.0 mol/L—or treatment for hypercholesterolemia, blood pressure >140/90 mm Hg or treatment, fasting glucose >6 mmol/L).[21,22] Furthermore, patients had bioimpedance measurement (Tanita) and hand dynamometric measurement before but on the day of liver biopsy.

3.2 | Histological assessment of liver biopsies

Liver biopsies were obtained percutaneously with a 16-18G suction needle. Liver histology was assessed by a single experienced MASLD pathologist (T.C.) using the NAFLD activity score (NAS) and NAS-CRN criteria: steatosis (0–3), lobular Inflammation (0–3), ballooning (0–2). We define MASH as at least 1 grade of each feature and report the total score NAFLD Activity Score (0–8). Fibrosis was assessed using Kleiner fibrosis core (F0-F4).

3.3 | Non-invasive liver status

All patients underwent liver stiffness measurement (LSM) using FibroScan® (Echosens). The Fibroscan also measures hepatic steatosis with controlled attenuated parameter (CAP). Patients were examined in a fasting state during the morning hours by trained study staff using probe as indicated by the Fibroscan software (M or XL). The fatty liver index score was also calculated to provide another diagnostic threshold for steatosis presence used in other studies.[17]

3.4 | Sickness impact profile

Participants in the study completed online questionnaires to assess their QOL and daily functioning. The sickness impact profile questionnaire (SIP) comprises physical, psychosocial and independent categories. It includes a total of 12 subdomains: three physical; body care and movement, ambulation, mobility, and four psychosocial; emotional behaviour, alertness behaviour, social interactions, communication and five independent; sleep and rest, home management, eating, recreation and pastimes and work. The questionnaire totals 136 statements where the patients mark 'yes' if the statement is true to them on the day of answering. These subdomains are differently weighted and sum into the total SIP score, which ranges from 0 to 100, where a higher score indicates lower QoL. The SIP was developed by Bergner et al and John Hopkins University holds the copyright. A healthy Dutch background population had a mean SIP total of 3.4 for reference [23]. The SIP is widely used, well-validated and translated into numerous languages. It has previously been used in liver disease but not as extensively as the disease-specific CLDQ and shorter generic QOL questionnaires.[20,24–27]

3.5 | Depression questionnaire

The Major Depression Inventory (MDI) questionnaire consists of 10 questions assessing depressive symptoms experienced over the preceding 2 weeks. Respondents select from six response options, ranging from 'at no time' to 'all of the time'. MDI scores are categorized as follows: <20 suggests the absence of depression, between 20 and 24 indicates mild depression; from 25 to 29 suggests moderate depression, and above 29, with a maximum possible score of 50, are indicative of severe depression.[28]

4 | DATA ANALYSES AND STATISTICS

We categorized the cohort based on liver biopsy results, with 132 patients assigned to the no-MASH category. This category included individuals with no MASLD and those with MASLD, while 44 patients had MASH. For specific analyses, we further subdivided these two groups based on fibrosis severity, classifying them into mild (F0-1), moderate (F2) and advanced (F3-4) fibrosis categories.

The study power was calculated using STATA and comparing the means of total SIP score between the No-MASH/MASH groups yielded a power of 1.

Descriptive statistics for continuous data are presented as means (±SD) or medians (IQR) as appropriate, and categorical variables are expressed as absolute frequencies/percentages unless otherwise noted. We used a two-tailed Student's *t* test for normally distributed data and the Wilcox Mann–Whitney test or Kruskal–Wallis as appropriate for comparison.

The appropriate weighting of each SIP domain was applied in accordance with the copyright holders of the original SIP questionnaire at Johns Hopkins University.[29] The SIP sum scores (the 12 sub-domain scores, the three category scores, physical, psychosocial and independent, and total SIP score) are continuous numerical

variables and were heavily right-skewed. To address this in the regression analysis, the total SIP score was log-transformed to achieve an equal distribution of residuals. Log-transformed total SIP score (range from min: −0.99 to max: 3.97).

Multivariable and univariable linear regression assessed the association between a higher total SIP score and different covariates. We used a stepwise, backward selection for the multivariable model, removing terms with $p \geq .2$ and adding those with $p < .1$ in all with complete data ($n = 173$). Covariates multivariable model: sex, age, education (years), marital status (single, living with a partner, divorced), employment status (full time OR reduced hours <20 h OR long-term sick leave OR others), body

TABLE 2 Univariable and stepwise multivariable linear regression analysis of the association with a higher total SIP score (logarithmic; min: −0.99 max: 3.97) and different covariates. In univariable model, all covariables were analysed.

	Univariable analysis		Multivariable analysis	
	Coefficient (95% CI)	***p*-value**	**Coefficient (95% CI)**	***p*-value**
Demographics				
Gender (male)	−0.066 (−0.42–0.28)	.708		
Age, years	0.009 (−0.005–0.022)	.170	0.011 (0.001–0.02)	.061
Formal education (years)	−0.018 (−0.07–0.047)	.516		
Marital status ¤				
Living with partner (married or not)	0.14 (−0.24–0.52)	.481	0.26 (−0.06–0.59)	.050
Divorced	0.77 (0.19–1.36)	**.009**	0.65 (0.15–1.15)	**.009**
Employment status*				
Reduced hours	0.66 (0.24–1.07)	**.002**	0.60 (0.24–0.97)	**.001**
Long-term sick leave or disability leave	0.89 (0.50–1.30)	**<.001**	0.55 (0.19–0.90)	**.003**
Other (e.g. retiree/student)	0.49 (0.05–0.92)	**.028**	0.40 (0.02–0.78)	**.040**
Metabolic comorbidity				
BMI	0.004 (−0.02–0.03)	.754	0.016 (−0.007–0.04)	.173
Metabolic syndrome severity (MetS) score	0.126 (−0.006–0.26)	**.062**		
Mental health				
Major depression inventory (MDI) score	0.057 (0.042–0.07)	**<.001**	0.06 (0.04–0.07)	**<.001**
Use of antidepressants^	0.49 (0.0937464 .886	**.016**		
Use of antipsychotics (or benzodiazepines)^	0.66 (0.097–1.23)	**.022**		
Non-invasive liver status				
Liver stiffness, kPa	−0.002 (−0.019–0.016)	.847		
CAP, dB/m	0.002 (−.0009701 .00452)	.203		
Fatty liver index (FLI)	0.007 (−0.004–0.018)	.187		
Liver biopsy				
NAFLD Activity score (NAS)	0.13 (0.045–0.21)	**.003**		
MASH (yes)	0.40 (0.034–0.76)	**.032**		
Steatosis	0.23 (0.07–0.39)	**.006**	0.20 (0.04–0.32)	**.010**
Inflammation	0.27 (0.06–0.48)	**.014**		
Ballooning	0.35 (0.03–0.67)	**.030**		
Moderate fibrosis§ (F2)	−0.018 (−0.40–0.36)	.927		
Advanced fibrosis§ (F3-4)	−0.23 (−1.00–0.55)	.563		

Note: For the multivariable model, we used a stepwise, backward selection, removing terms with $p \geq .2$ and adding those with $p < .1$ in all with complete data ($n = 173$). Covariates multivariable model: sex, age, education (years), marital status (single, living with partner, divorced), employment status (full time, reduced hours <20 h, long-term sick leave, others), body mass index (BMI), MetS score, Major depression inventory score, psychoactive medication (no use, antidepressants, benzodiazepines or antipsychotics), liver stiffness by Fibroscan, NAFLD activity score (NAS), MASH or not, steatosis grade, fibrosis grade-groups (F0-1: mild, F2: moderate, F3-4: advanced). ^No individual was using medications from both categories. Reference variable: ¤ Being single, * Working full time, ^ No use of these medications, § Mild fibrosis (F0-1).

mass index, metabolic syndrome severity score (MetS), major depression inventory score (MDI), psychoactive medication (no use OR antidepressants OR benzodiazepines or antipsychotics), liver stiffness by Fibroscan, NAFLD activity score (NAS), MASH or not, steatosis grade, fibrosis grade groups (F0-1: mild, F2: moderate, F3-4: advanced).

As a secondary outcome, a review of the 136 statements within the sickness impact profile was conducted, and statements for which at least 40% of participants in either the No-MASH or MASH group selected 'true' were subjected to comparative analysis between these two groups using Fisher's exact test or the χ^2 test. Statistical significance was set at $p = .05$. Statistical analyses were conducted using STATA version 18.0. Graphs were made using either STATA version 18.0 or Microsoft PowerPoint.

4.1 | Post hoc reference group

We added a post hoc reference group of patients with liver cirrhosis ($n = 111$). The purpose was to compare the 136 QOL statements in the SIP reported by patients with no-MASH or MASH to that of a group diagnosed with liver cirrhosis. This group was not included in the statistical analyses so as not to introduce additional multiple-testing problems but was solely used as a comparison reference group.

5 | DATA MANAGEMENT

Study data were entered into and managed via a secured REDCap[30] (Research Electronic Data Capture) database hosted by Open Patient data Explorative Network (https://www.sdu.dk/en/forskning/open). All writers had access to the study data and reviewed the final manuscript.

6 | RESULTS

The baseline characteristics of the study cohort are summarized in Table 1. The mean age of participants was 45.9 years (SD: ±12.23), and the majority were female (70%). On average, participants had 12.6 years of education (SD: ±2.9), with no difference between no-MASH and MASH groups. In our cohort, only 38% were working full time (>35 h/week), and the majority were married or living with a partner (57%).

The mean BMI was 41.3 kg/m^2 (IQR: 7.4), and eight patients had lost weight between inclusion and biopsy visit, all had a BMI above 32 kg/m^2 at the time of biopsy. Obesity-related metabolic comorbidities were prevalent, with 45% hypertension affecting, 26% type-2 diabetes mellitus and 28% hypercholesterolemia. Patients with no-MASH were less affected compared to MASH: type-2 diabetes (20% vs. 43%) and hypercholesterolemia (24% vs. 41%) (Table 1).

7 | DETERMINANTS OF TOTAL SICKNESS IMPACT PROFILE SCORE

7.1 | Demographics

A higher SIP score indicates a lower QOL, and the multivariable regression analysis showed a slight positive correlation between age and total SIP (0.013, $p = .035$), indicating a decrease in QOL with increasing age (Table 2). Being divorced was one of the factors most strongly associated with having a higher total SIP (coefficient 0.65, $p = .011$). Working reduced hours or being on long-term sick leave or disability leave (compared to working full time) also showed similar associations with a higher total SIP and, hence, a worse QOL (Table 2). Disability leave refers to persons who are on early retirement due to health problems.

7.2 | Liver health

Forty-four had MASH, while 132 were in the no-MASH group (Table 1). No-MASH patients had a median total SIP score of 10.5 (IQR 14), while this was 15.3 (IQR 16.3) in MASH patients, indicating a lower QOL in MASH ($p = .02$, Figure 1). There were no significant differences among fibrosis stages mild (F0-1), moderate (F2) or severe (F3-4) in the two subgroups, no-MASH ($p = .705$) and MASH ($p = .061$).

On univariable regression analysis, total SIP score increased with increasing NAFLD activity score (coefficient: 0.13; $p < .01$),

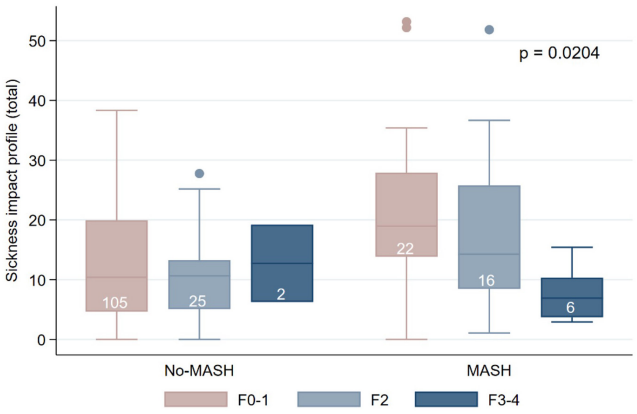

FIGURE 1 Total SIP score by liver biopsy. All participants ($n = 176$) with a complete SIP questionnaire were divided based on biopsy into a no-MASH ($n = 132$) or a MASH ($n = 44$) cluster. The graph shows the median sickness impact profile (SIP) score for each cluster, further stratified according to fibrosis stage groups mild (F0-1), moderate (F2) and significant (F3-F4) (number of patients written in white in each box). There was a difference in median SIP total score ($p = .0204$) between groups no-MASH and MASH, but no difference between fibrosis groups in each separate group, respectively ($p = .7045$) and ($p = .0608$). Boxplots with median SIP and 25th–75th (interquartile range) percentile. p-values obtained performing the Kruskal–Wallis rank test.

steatosis-, inflammation- and hepatocellular ballooning grade (coefficient: 0.23; $p < .01$ vs. coefficient: 0.27; $p < .05$ vs. coefficient: 0.35; $p < .05$), and was positively associated with having MASH (coefficient: 0.40; $p < .05$) (Table 2). On multivariable analysis, only steatosis remained significant (coefficient: 0.18, $p = .010$). Fibrosis severity, moderate (F2) or advanced (F3-4) compared with mild (F0-1), was not associated with a higher total SIP.

None of the non-invasive liver measurements, liver stiffness, controlled attenuation parameter or fatty liver index (FLI) were associated with a higher total SIP score.

7.3 | Metabolic comorbidities

A higher metabolic syndrome severity (MetS) score was correlated to a higher total SIP (coefficient: 0.126, $p = .062$) in the univariable analysis; however, it did not remain significant in the multivariable analysis (Table 2). None of the biometric factors, BMI, weight, waist/hip ratio and hand grip strength were significant in univariate linear regression (Table 2 and Table S1).

7.4 | Mental health

Depressive symptoms measured using the major depression inventory showed a slight positive correlation with a higher total SIP score (coefficient: 0.06, $p < .001$). Taking antidepressants or antipsychotics was, in the univariable regression, associated with a higher SIP score and a worse reported QOL (Table 2). However, this did not remain significant in the stepwise model. More females than males used antidepressants or psychoactive drugs (38.64% vs. 20.75%).

8 | DETERMINANTS OF SICKNESS IMPACT PROFILE CATEGORIES AND DOMAINS

8.1 | Physical and psychosocial categories

We saw differences between the two groups in the physical and psychosocial sum scores (Figure 2), with MASH patients reporting a worse QOL. No-MASH patients had a median physical sum score of 5.5 (IQR: 11.7), while this was 8.9 (IQR: 11.1) in MASH patients ($p = .013$). For the psychosocial score, no-MASH compared with MASH, respectively scored 9.6 (IQR: 19.6) vs. 15.4 (IQR: 20.4) ($p = .03$).

8.2 | The SIP domains

We saw a difference in median SIP domain scores between no-MASH and MASH patients in five out of the 12 domains: 'emotional behaviour' (13.2 vs. 19.2; $p \leq .05$), 'body care and movement' (4.1 vs. 7.5, $p \leq .05$) 'home management' (6.6 vs. 14.7, $p \leq .05$)), 'ambulation' (4.2 vs. 10.6, $p \leq .05$), 'alertness behaviour' (8.6 vs. 27.7, $p = .001$) (Figure 2). We stratified the no-MASH and MASH groups into fibrosis severity groups and found no difference between domain scores except for in 'alertness behaviour' in the MASH group (ns; $p = .004$) (Figure S1A,B). MASH patients with mild fibrosis had a higher SIP score than moderate and severe fibrosis in this domain, respectively, 37.7, 14.4 and 0.

8.3 | Individual SIP statements

We reviewed each of the 136 SIP statements individually, as described in the methods section (Table 3). The majority (59%) of the

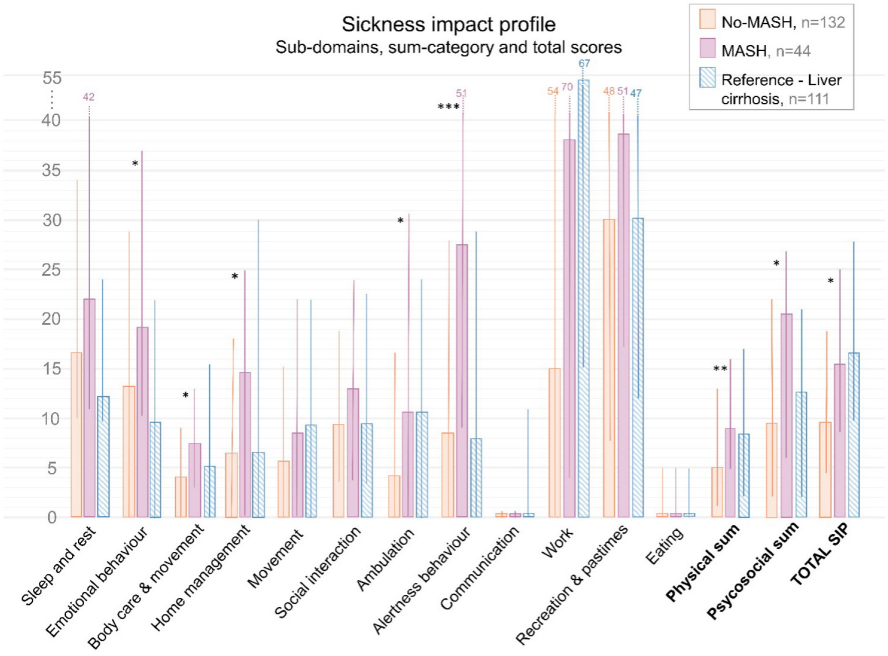

FIGURE 2 Twelve domains of the sickness impact profile (SIP), two sum-category scores and the total SIP in all participants ($n = 176$) were divided into no-MASH and MASH groups. A reference group of patients with liver cirrhosis ($n = 111$) is added for comparison, but these are not included in the statistical analysis. The graph shows the median sickness impact profile (SIP) score in each sub-category presented as the median; the vertical line represents IQR (p25-p75). Note, the scale is not continuous; a break after SIP 40, value noted on top of IQR line if value >40. ***$p \leq .001$; **$p \leq .01$; *$p \leq .05$.

TABLE 3 One hundred thirty-six sickness impact profile statements were reviewed individually, and statements that were frequently reported as a problem (at least 40% of the participants) in either the no-MASH or MASH group and were answered '*true*' (as opposed to '*not true*') are shown here.

The most frequently reported problems	All full SIP responders ($n=176$)	No-MASH patients ($n=132$)	MASH patients ($n=44$)	Controls liver cirrhosis ($n=111$)
Sleep and rest				
I sit during much of the day	46%	45%	48%	36%
I sleep less at night, for example wake up too early, do not fall asleep for a long time, awaken frequently	46%	46%	45%	49%
Emotional behaviour				
I often moan and groan in pain or discomfort	35%	30%	48%* $p=.044$	32%
I keep rubbing or holding areas of my body that hurt or are uncomfortable	35%	30%	48%*; $p=.044$	20%
Body care and movement				
I change position frequently	41%	39%	47%	19%
Home management				
I do work around the house only for short periods of time or rest often	36%	29%	54%**; $p=.006$	43%
I am doing less of the regular daily work around the house than I would usually do	48%	42%	66%**; $p=.003$	30%
Social interaction				
I am doing fewer social activities with groups of people	38%	36%	43%	58%
My sexual activity is decreased	47%	42%	59%	37%
I often express concern over what might be happening to my health	59%	57%	64%	44%
Ambulation				
I walk shorter distances or stop to rest often	38%	35%	48%	51%
I go up and down stairs more slowly, for example, one step at a time, stop often	40%	35%	57%**; $p=.013$	20%
I walk more slowly	49%	48%	52%	59%
Alertness behaviour				
I forget a lot, for example, things that happened recently, where I put things, appointments	29%	23%	48% **; $p=.002$	23%
I do not keep my attention on any activity for long	38%	32%	57%**; $p=.003$	23%
Work				
Reply 'yes' to having at permanent paid- or association work	68%	67%	72%	11%
Recreation and pastimes				
I am going out for entertainment less often	51%	52%	50%	48%
I am doing more inactive pastimes in place of my other usual activities	51%	50%	55%	56%
I am doing fewer community activities	42%	40%	48%	39%
I am cutting down on some of my usual physical recreation or activities	55%	54%	57%	51%

Note: We report data using these groups in all participants ($n=176$) and have added a control group with liver cirrhosis as reference. Statements with significant differences using Fisher's exact test/χ^2 test are marked with *$p \le .05$; or **$p \le .01$.

cohort shared concerns for what might happen to their health; 55% were cutting down on usual physical recreation or activities, and 51% were less often out for entertainment or had inactive pastimes compared to usual (Table 3). Problems with decreased sexual activity were also frequent in the cohort as a whole (47%), without differences between the two groups. Patients in the MASH group, compared to no-MASH, more frequently experienced discomfort (48% vs. 30%, $p \le .05$), did less work around the house than usual (66% vs. 42%, $p \le .01$) and had problems keeping attention on any activity for long periods (57% vs. 32%; $p \le 0.01$).

8.4 | Comparison to the reference group with liver cirrhosis

MASH patients in this cohort report statements on QOL that are on par with patients with liver cirrhosis and sometimes slightly worse (Figure 2 and Table 3).

9 | DISCUSSION

The aim of this study was to explore what determines QOL as measured by the SIP in patients with obesity at risk of having MASLD, with a focus on the effect of MAFLD severity. This risk group is growing, and attention to this specific phenotype with MASLD is needed. The major strengths of this study are that we use biopsy-proven staging of MASLD, have a response rate of 100% in 176 persons and thorough phenotyping.

We here present data from a relatively young cohort where many should be at the height of their lives, busy with jobs and family. This cohort had a poor quality of life as compared to Dutch reference values (mean SIP all 11.8 vs. 3.4). In some domains, the quality of life was even impacted to the same extent as we, and others, have previously observed in lean, somewhat older patients with mainly alcoholic cirrhosis.[23–25] QOL, as measured by SIP, was not impacted by obesity in itself (BMI, waist–hip ratio) or obesity-related metabolic morbidities. Instead, the determinants of poor quality of life in our cohort were being divorced, working reduced hours, being on long-term sick leave, or disability benefits. Liver metabolic dysfunction, represented by hepatic steatosis, remained the only somatic determinant of QOL on multivariate analysis.

Our findings are in line with other studies that found worsening QOL with increasing NAFLD severity.[13–15,17,18] The fact that QOL is impacted by MASLD, and not to the same extent by other obesity-related diseases, may be explained by the fact that MASLD, in particular, reflects a disturbed metabolism, and our regression analysis implies that steatosis carries the association—not lobular inflammation and hepatocellular ballooning, using multivariate analysis. It would be an oversimplification to state that hepatic steatosis is the driver of poor QOL because, as our data show, socio-demographic factors are more important, but the finding is nevertheless interesting and calls for further characterization of factors driving hepatic steatosis, such as diet, gut microbiome and recent weight fluctuations.

Patients with MASLD seem to be characterized by problems with 'body care and movement', 'home management', 'ambulation', and 'alertness behaviour'. In the analysis of each SIP statement, it is evident that physical discomfort, reduced activity levels, especially in the sphere of sexuality, and challenges related to attention are the prevailing issues that significantly impact the daily lives of our study participants—and more so in patients with MASH. The reason for these problems is likely multifactorial, but others have proposed that a mild hepatic encephalopathy or a 'new' composite metabolic encephalopathy might exist in metabolically dysfunctional patients with or without obesity.[31–35] If present, this could adversely impact QOL, particularly attention span and low activity level, which are well-known problems in HE. However, more studies are needed to explore this hypothesis. Others suggest a link between obesity and ADHD that could partly explain the attention problems we observe.[36–38] A central unanswered question remains if the observed QOL issues were present before the obesity, or if they are a consequence of obesity. Longitudinal studies are needed to assess this.

Many of the QOL issues detected in MASLD by the SIP are also part of the CLDQ. The CLDQ also inquired about irritability, attention, pain, general energy level, depressive feelings and worries about the future. The SIP adds information on sexual activity and tells us in which domains of daily life the various symptoms are most pronounced. Our notion is that the use of CLDQ is appropriate for coarse QOL measurements in MASLD.

Our study has some limitations. There could be bias regarding the online questionnaires, where the participants have been unable to consult on questions they did not understand and thus could have answered wrongfully, that is response bias. Also, a Hawthorne effect might be present, meaning that the respondents change their response to QOL questions due to the disease awareness introduced by the questionnaire itself. Furthermore, since these data come from an ongoing cohort study, which requires multiple meetings and biopsies, chances are that less resourceful individuals fitting within the inclusion criteria have chosen not to participate. This would result in sampling bias with an overrepresentation of resourceful individuals and, as such, likely overestimation of QOL.

The knowledge gained from this and other similar studies can be used to inform patients that a low activity level is a frequently reported symptom in MASLD and especially MASH. Such knowledge might alleviate self-stigmatization. Also, the lifestyle interventions we plan for MASLD patients with obesity should take the low physical activity level into consideration. Likewise, the prevalent QOL issues could serve as surrogate markers in intervention studies.

10 | CONCLUSION

In this cohort, the determinants of poor QOL were working reduced hours, being on long-term sick leave or disability benefits, and hepatic steatosis, which remained the only somatic determinant of QOL on multivariate analysis. Physical discomfort, low activity level—also sexually—and problems with attention are reported by more than 40% of participants, and more often in MASLD. Therefore, in the management of patients at risk of MASLD, healthcare professionals need to address and consider the limitations these symptoms pose.

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CONFLICT OF INTEREST STATEMENT

We have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The full data set is available on request.

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ORCID

Charlotte Wilhelmina Wernberg https://orcid.org/0000-0001-8964-0650
Lea Ladegaard Grønkjær https://orcid.org/0000-0001-5754-8235
Mette Munk Lauridsen https://orcid.org/0000-0003-0586-8549

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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