# **Research Article**

# The burden of non-alcoholic steatohepatitis (NASH) among patients from Europe: A real-world patientreported outcomes study

# Authors

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# Graphical abstract



# Highlights

- Non-alcoholic steatohepatitis (NASH) is a progressive form of non-alcoholic fatty liver disease.
- NASH imposes a significant humanistic and economic burden on individuals and society.
- NASH impairs health-related quality of life, work productivity and activity, while increasing healthcare resource use.
- This study highlights the unmet need of patients with NASH in the absence of any approved treatment.

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## Lay summary

These findings show that patients with non-alcoholic steatohepatitis (NASH) experience a significant burden of illness, in terms of health-related quality of life, work productivity and activity impairment, and healthcare resource use. As there is currently no approved treatment for NASH, these findings highlight the unmet medical need of patients with NASH.

# The burden of non-alcoholic steatohepatitis (NASH) among patients from Europe: A real-world patient-reported outcomes study



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**Background & Aims:** Data on the economic and humanistic burden of non-alcoholic steatohepatitis (NASH) are scarce. This study assessed the comparative burden of NASH, relative to a representative sample from the general population and a type 2 diabetes mellitus (T2DM) cohort, in terms of health-related quality of life, work productivity and activity impairment (WPAI), and healthcare resource use.

**Methods:** Data across 5 European countries came from the 2016 National Health and Wellness Survey, a nationally representative patient-reported outcomes survey. Outcomes included mental (MCS) and physical (PCS) component scores from the Short-Form (SF)-36v2, WPAI scores, self-reported physician diagnosis of sleep difficulties, anxiety, and depression, and health-care resource use: healthcare professional visits, hospital visits, and emergency room visits in the previous 6 months. Bivariate and multivariable analyses were conducted for each outcome and comparative group.

**Results:** After adjusting for matching criteria and covariates, patients with NASH (n = 184) reported significantly worse health-related quality of life, worse WPAI scores, and more healthcare resource use than the general population (n = 736) (MCS 39.22 vs. 45.16, PCS 42.84 vs. 47.76; overall work impairment 49.15% vs. 30.77%, healthcare professional visits 10.73 vs. 6.01, emergency room visits 0.57 vs. 0.22, hospitalizations 0.47 vs. 0.17, p < 0.05 for all). Patients with NASH did not differ from patients with T2DM (n = 368) on PCS and WPAI scores, suggesting a similar impairment on work and daily activities, but did report significantly worse mental status (MCS 39.64 vs. 43.64, p < 0.05) and more healthcare resource use than those with T2DM (healthcare professional visits 10.85 vs. 7.86, emergency room visits 0.65 vs. 0.23, hospitalizations 0.39 vs. 0.19, p < 0.05 for all).

**Conclusions:** These findings suggest that the burden of NASH may be underestimated, highlighting the unmet needs of patients with NASH.

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### Introduction

Non-alcoholic steatohepatitis (NASH) is a progressive form of nonalcoholic fatty liver disease (NAFLD) that can progress to cirrhosis and associated complications.<sup>1</sup> NASH is considered a "silent" disease, as many patients might not have specific symptoms until later stages. In many cases, symptoms are attributed to comorbidities commonly associated with NASH, rather than NASH itself.<sup>2</sup> Confirmatory diagnosis of NASH is done via liver biopsy, which is not performed routinely in the absence of approved therapies.

Given the low rate of liver biopsy, the lack of targeted therapies, and an asymptomatic presentation, current estimates of the true prevalence of NASH may be inaccurate.<sup>3–6</sup> In addition, there is no published evidence on the prevalence of NASH in

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the general population, *per se*. Instead, NASH prevalence is commonly reported as a proportion among NAFLD populations.

An increasing number of studies have described the humanistic and economic burden of NASH. NASH may be associated with increased healthcare resource use (HRU),<sup>7</sup> impairment of work and non-work activities,<sup>8</sup> and diminished health-related quality of life (HRQoL).<sup>9</sup> Yet, further research is needed to comprehensively examine the humanistic and economic burden of NASH.

The main objective of this study was to quantify the humanistic and economic burden of NASH, relative to the general population and relative to type 2 diabetes mellitus (T2DM), in terms of HRQoL, impairment of work and non-work activities, and HRU.

## Patients and methods Data source

Data were collected between February and May 2016 in the National Health and Wellness Survey (NHWS, N = 80,600), a multinational internet-based patient-reported outcomes survey designed to reflect health in the general adult population with stratified random sampling to ensure representativeness in terms of



Keywords: non-alcoholic steatohepatitis; non-alcoholic fatty liver disease; type 2 diabetes; burden of illness.

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age and gender. Over 90% of NHWS participants were sourced through opt-in online panels (*e.g.*, MySurvey.com) and the remainder of participants were recruited offline. Data from 5 European (EU5) countries were used: Germany, France, Spain, Italy, and the United Kingdom.<sup>10</sup> The NHWS was reviewed and granted exemption by the Pearl Institutional Review Board. All respondents provided informed consent.

### Study sample

Three study cohorts were defined based on self-reported physician diagnosis: a) NASH; b) general population (representative sample of general population with varying health status); c) T2DM. The latter 2 cohorts were also used to create a matched general population cohort and a matched T2DM cohort, respectively. Respondents with a self-reported physician diagnosis of hepatitis B, hepatitis C, or cirrhosis were excluded from all analyses, except for analyses used to estimate the diagnosed prevalence of NASH.

Demographics and patient characteristics were collected at the time of survey administration (see supplementary information). Two versions of the Charlson comorbidity index (CCI) were used in the analysis, including a standard CCI<sup>11</sup> and an adjusted CCI. The adjusted CCI omitted the following conditions: diabetes, diabetes with end organ damage, mild liver disease, peripheral vascular disease, myocardial infarction (heart attack), and congestive heart failure (for explanation, see Statistical Analysis).

#### **Outcome measures**

#### Health-related quality of life

HRQoL was assessed with the Medical Outcomes Study 36-Item Short Form Survey Instrument Version 2 (SF-36v2). Two summary scores were calculated: physical component summary (PCS) score and mental component summary (MCS) score. PCS and MCS scores were utilized as normed scores. This was achieved by transforming the raw scores for the items to a mean of 50 and a standard deviation of 10, such that scores could be interpreted relative to a population average of 50. The minimal important difference (MID) for PCS and MCS is 3.0.<sup>12–14</sup>

Two utility scores were calculated: SF-6D utility score (MID= 0.041), using PCS and MCS scores, and EQ-5D utility score (MID=0.074), using responses from the EQ-5D-5L question-naire.<sup>15</sup> SF-6D and EQ-5D utility scores range from 0 (death) to 1 (perfect health). Higher scores indicate better quality of life for all scores described above.<sup>14,16,17</sup>

#### Psychological conditions

Self-reported physician diagnoses of anxiety, depression, and sleep difficulties (other than insomnia, narcolepsy, or sleep apnea) in the past 12 months were collected and the proportion of respondents reporting each of these diagnoses was calculated.

#### Work productivity and activity impairment

Respondents completed the Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH) with a recall period of 7 days. The items related to work were answered only by employed respondents and items about daily activities were answered by all respondents. Four scores were calculated on a scale from 0 to 100%: absenteeism (the percentage of work time missed because of one's health), presenteeism (the percentage of impairment experienced while at work because of one's health), overall work impairment (a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health). Higher scores indicate more impairment.<sup>18</sup>

#### Healthcare resource use

HRU was assessed based on self-reported total number of visits within the past 6 months and was categorized as follows: health-care professional (HCP) visits (*e.g.*, general practitioner/family practitioner, internist, allergist, cardiologist, *etc.*), non-traditional HCP visits (*e.g.*, acupuncturist, herbalist, nutritionist, massage therapist, *etc.*), emergency room (ER) visits, and hospitalizations. The full list of HCP visit types and non-traditional HCP visit types is presented in the supplementary information.

HCP visits were assessed in 2 ways: a) number of visits to any HCP; b) number of visits to specific specialty HCPs. Non-traditional HCP visits were assessed in 2 ways: a) number of different types of non-traditional HCPs visited; b) number of non-traditional HCP visits ( $\geq 1$  vs. none).

## Statistical analysis

## Descriptive statistics

Descriptive statistics were used to characterize unmatched cohorts, in terms of demographics and patient characteristics. The diagnosed prevalence of NASH in the EU5 adult population was estimated using weighted frequencies on self-reported physician diagnosis of NASH. Weights were based on age, gender, and country. 2016 NHWS post-stratification sampling weights were used, which were calculated using data collected from an official national census source.<sup>19</sup>

#### Matched bivariate comparisons

Matched bivariate comparisons were assessed for the NASH cohort versus a matched general population cohort and a matched T2DM cohort. Matched general population and matched T2DM cohorts were created via a standard matching procedure (see supplementary information). This resulted in the following matching criteria: age, gender, education, income, smoking behavior, current alcohol use, current exercise behavior, and adjusted CCI. Note that several CCI conditions were already controlled in other ways in the analyses (*e.g.*, as cohort inclusion/exclusion criteria or covariates) and were, therefore, not included in the adjusted CCI, described earlier.

Matched bivariate comparisons for categorical variables included chi-square tests; matched bivariate comparisons for continuous variables included one-way ANOVAs. Outcomes assessed included HRQoL outcomes, WPAI scores, and HRU metrics. Any two-sided *p* value <0.05 was considered statistically significant.

#### Multivariable analysis

These same matched group comparisons were assessed by modeling each outcome individually, using multivariable analysis. Matching criteria that remained unbalanced between matched cohorts were used as covariates. This resulted in the following covariates for NASH versus matched general population comparisons: income and smoking behavior.

In addition, a proportion of patients with NASH in this sample had comorbid T2DM. For this reason, T2DM-related variables were used as covariates in NASH versus matched T2DM comparisons, to control for T2DM severity and to more precisely examine the burden of NASH, as opposed to the burden of comorbid T2DM in patients with NASH. Three covariates were used to control for the severity of T2DM: type of prescription currently taken to treat T2DM, self-reported physician diagnosis of at least 1 relevant heart or blood condition, and self-reported physician diagnosis of at least 1 T2DM-related comorbidity (for further details, see supplementary information).

Regression model type varied according to the distribution of data for a given outcome variable and included linear models, binary logistic models, and generalized linear models with negative binomial distribution and log-link. Any two-sided *p*-value <0.05 was considered statistically significant.

For further details regarding the methods used, please refer to the supplementary information.

### Results

### Characteristics of the NASH cohort

Demographics and patient characteristics of the NASH cohort (n = 184), the unmatched general population cohort (n = 79,267), and the unmatched T2DM cohort (n = 4,783) are presented in Table 1. The prevalence of self-reported diagnosed NASH was calculated to be 0.29% in the EU5 adult population. The mean (SD) age of NASH respondents was 54.5 (13.1) years. The majority of NASH respondents were male (57.1%), 46.7% of NASH respondents were obese, and 46.7% had not exercised in the previous month. NASH respondents self-reported physician diagnoses of various comorbidities: 52.7% had a CCI  $\geq$ 1, 49.5% had hypertension, 69.0% had 1 or more relevant heart or blood condition (*e.g.*, congestive heart failure), 22.8% had T2DM, and 8.2% had 1 or more T2DM-related complication (*e.g.*, foot or leg ulcer).

#### The burden of NASH

#### NASH vs. matched general population

In matched bivariate comparisons, patients with NASH reported a greater burden than the matched general population (n = 736) on all outcomes assessed, including HRQoL outcomes, WPAI scores, and HRU (Table S1A). Results of multivariable analysis, comparing NASH versus the matched general population, align with all bivariate results and are described below as adjusted means.

HRQoL results show that the NASH cohort, relative to the matched general population cohort, had significantly lower PCS (42.8 vs. 47.8, p < 0.001), MCS (39.2 vs. 45.2, p < 0.001), SF-6D utility (0.59 vs. 0.68, p < 0.001), and EQ-5D utility scores (0.67 vs. 0.78, p < 0.001) (Fig. 1 and Fig. 2). Differences on all 4 scores exceeded known MIDs.

A greater proportion of respondents in the NASH cohort, compared to the matched general population, reported diagnoses of anxiety (32.0% vs. 17.5%, p <0.001), depression (31.2% vs. 19.6%, p = 0.001), and sleep difficulties (14.5% vs. 8.9%, p = 0.025) (Fig. 3).

WPAI results show that the NASH cohort, relative to the matched general population cohort, reported more absenteeism (28.5% vs. 12.4%, p = 0.003), presenteeism (33.7% vs. 23.0%, p = 0.006), overall work impairment (49.2% vs. 30.8%, p < 0.001), and activity impairment (48.0% vs. 32.6%, p < 0.001) (Fig. 4).

The NASH cohort, relative to the matched general population, reported more HCP visits (10.7 *vs.* 6.0, *p* <0.001), ER visits (0.57 *vs.* 0.22, *p* <0.001), and hospitalizations (0.47 *vs.* 0.17, *p* <0.001) in the past 6 months (Fig. 5). For all specialty HCP visits, the NASH cohort reported more visits than the matched general population (for all *p* <0.05) (Table 2). For example, the NASH cohort, relative to the matched general population, reported more general practitioner/family practitioner visits (3.80 *vs.* 2.23, *p* <0.001), hepatologist visits (0.07 *vs.* 0.01, *p* <0.001), gastroenterologist visits (0.28 *vs.* 0.07 *p* <0.001), and cardiologist visits (0.32 *vs.* 0.19, *p* = 0.013).

In addition, the NASH cohort reported visiting more types of non-traditional HCPs than the matched general population (1.2 vs. 0.8, p < 0.001) and a greater proportion of respondents with NASH reported at least 1 non-traditional HCP visit in the past 6 months (76.0% vs. 57.0%, p < 0.001).

#### NASH vs. matched T2DM

In matched bivariate comparisons, patients with NASH reported a greater burden than matched T2DM (n = 368), in terms of MCS score, SF-6D utility score, anxiety diagnosis, absenteeism, activity impairment, HCP visits, ER visits, and hospitalizations (for all p < 0.05). Patients with NASH did not differ from matched T2DM on any other measures assessed in matched bivariate comparisons (Table S2A). Results of multivariable analysis align with the majority of bivariate results and are described below as adjusted means.

HRQoL results show that the NASH cohort, relative to the matched T2DM cohort, had a significantly lower MCS (39.6 vs. 43.6, p = 0.003) and SF-6D utility score (0.60 vs. 0.64, p = 0.002), whereas no significant difference was found for PCS or EQ-5D utility score, nor diagnoses of anxiety, depression, or sleep difficulties (Figs. 1-3). The difference for MCS score exceeded the known MID.

The NASH cohort did not differ from the matched T2DM cohort on any WPAI scores (Fig. 4), suggesting a similar impairment on work and daily activities.

HRU results show that the NASH cohort, relative to the matched T2DM cohort, reported more HCP visits (10.9 vs. 7.9, p = 0.006), ER visits (0.65 vs. 0.23, p = 0.009), and hospitalizations (0.39 vs. 0.19, p = 0.033) in the past 6 months (Fig. 5). For the majority of specialty HCP visits assessed, the NASH cohort reported more visits than the matched T2DM cohort (for all *p* <0.05) (Table 3). For example, patients with NASH, relative to the matched T2DM cohort, reported more general practitioner/ family practitioner visits (3.68 vs. 2.81, p = 0.033), hepatologist visits (0.09 vs. 0.00, p <0.001), gastroenterologist visits (0.28 vs. 0.08, p = 0.001), and endocrinologist visits (0.27 vs. 0.09, p =0.004). In addition, a greater proportion of the NASH cohort, relative to the matched T2DM cohort, reported at least 1 nontraditional HCP visit in the past 6 months (77.0% vs. 64.0%, p =0.016). The NASH cohort did not differ from the matched T2DM cohort on any other HRU outcomes.

### Discussion

This is the first study to assess the comparative burden of NASH in a nationally representative database. We compared patients with NASH to a representative sample of the general population with varying health status and to patients with T2DM. Comparison of patients with NASH to patients with T2DM was of particular interest, as T2DM is a condition with a substantial, well-characterized, and well-known burden.<sup>20–23</sup> Our results extend our knowledge of the burden of NASH in multiple important ways.

First, we show that, although patients with NASH tend to be obese with many comorbidities, including diabetes with complications (1 in 10), NASH is independently associated with a significant humanistic and economic burden. After adjusting for matching criteria and covariates, patients with NASH still reported worse HRQoL (exceeding MIDs), more WPAI, and more HRU than the general population across all measures assessed.

Second, after adjusting for matching criteria and covariates, patients with NASH reported a similar and, in some instances, greater burden than patients with T2DM, as shown by their significantly and clinically relevant worse mental status (lower MCS score, exceeding MID) and lower SF-6D utility score. Patients

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Table 1. Demographics and health characteristics for NASH, unmatched general population, and unmatched T2DM cohorts.

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n(%)     n(%)     n(%)       Demographics     Cender		NASH n = 184	General Population n = 79,267	T2DM n = 4,783	
Demographic       Center       Female     79 (42.92)     43.937 (55.43)     1.655 (34.22)       Male     105 (57.14)     35.330 (44.65)     3.148 (65.85)       Klean (SD) age (yean)     554 (31.1)     48.1 (16.5)     62.82 (10.9)       Education     101 (54.93)     39.840 (50.33)     2.2799 (55.53)       University degree of higher     81 (44.05)     39.843 (45.33)     1.294 (40.25)       Decline to answer     2 (1.15)     39.647 (46.13)     2.422 (50.63)       At or above region median income     95 (51.63)     34.6247 (46.13)     2.422 (50.63)       At or above region median income     95 (51.63)     34.6247 (46.13)     2.422 (50.63)       Decline to answer     63.33     34.624 (0.63)     34.528 (43.3)       Decline to answer     105 (75.83)     4.068 (65.08)       Decline to answer     17 (2.24)     34.07 (75.83)     2.63 (53.0)       Current yengle     5 (2.77)     2.67 (0.35)     2.63 (0.83)       Obley     71 (2.25)     3.400 (75.56)     2.63 (0.83)       Outer weight     5 (2.77)     2.67 (0.35)     2.63 (0.83)		n (%)	n (%)	n (%)	
Gender     97 (0.298)     343.937 (55.48)     1.435 (142.16)       Male     105 (57.18)     35.330 (14.68)     3.148 (65.83)       Main (30) ger (years)     545 (13.1)     48.41 (16.5)     62.81 (0.9)       Education       39.840 (90.33)     2.799 (95.33)     10.99 (12.8)     0.90 (13.8)       Decline to answer     21.113     939 (12.8)     0.90 (3.8)     0.	Demographics				
Fendle     79 (4.29%)     44.397 (35/43)     1.635 (34.23)       Male     105 (57.13)     35.30 (44.68)     3.148 (65.83)       Mona (20) age (years)     545 (13.1)     48.11 (16.5)     62.8 (10.3)       Education      79.10 (54.93)     39.840 (50.33)     2.2790 (58.33)     1.924 (40.23)       Decime to answer     2 (1.53)     38.617 (46.13)     2.2422 (50.63)     36.547 (46.13)     2.422 (50.63)       At or above region median income     55 (51.63)     36.547 (46.13)     2.422 (50.63)     34.642 (10.63)     3.57 (78.3)       Decline to answer     63.33     8.422 (10.68)     3.57 (78.3)     Decline to answer     10.15 (21.28)     45.06 (38.67 (55.3)     1.424 (25.08)       Decline to answer     17 (02.3)     8.467 (10.73)     2.63 (53.3)     Carrent yee (10.12)     4.66 (70.3)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8)     2.65 (78.8) <td>Gender</td> <td></td> <td></td> <td></td>	Gender				
Male     105 (57.13)     15.30 (44.68)     3.148 (6.58.5)       Mean (SD) age (years)     54.5 (13.1)     48.1 (16.5)     62.8 (10.9)       Extoration     39.0 (15.9)     2.799 (82.8.5)     10.1 (54.9)     39.481 (46.53.5)     2.799 (82.8.5)       Lust han university degree     2 (1.13)     39.9 (1.25)     60 (1.33)       Decline to answer     2 (1.13)     39.9 (1.25)     60 (1.33)       Relow region median income     35 (51.68)     36.547 (46.13)     2.422 (20.60)       Ar above region median income     35 (51.68)     36.547 (46.13)     2.422 (20.68)       Decline to answer     36 (51.78)     36.547 (46.13)     2.422 (20.68)       Protex     21 (20.98)     36.547 (46.13)     2.422 (20.83)       Decline to answer     21 (20.98)     36.547 (46.13)     2.422 (20.83)       Protex     17 (9.22)     8.467 (10.72)     2.67 (35.9)     2.33 (53.5)       Decline to answer     17 (9.22)     8.467 (10.72)     2.67 (10.72)     2.67 (10.73)     2.63 (63.73)       Orecoveright     5 (20.73)     7.58 (24.83)     1.136 (26.83)     1.136 (26.83)     1.36 (26.83) <td>Female</td> <td>79 (42.9%)</td> <td>43,937 (55.4%)</td> <td>1,635 (34.2%)</td>	Female	79 (42.9%)	43,937 (55.4%)	1,635 (34.2%)	
Mean (50) age (years)     545 (13.1)     48.1 (16.5)     62.8 (10.9)       Education     Education     Education     10.1 (54.93)     39.840 (50.33)     2.799 (58.53)       University degree of higher     81 (44.043)     39.8413 (48.55)     11.224 (40.23)       Decline to answer     2 (1.13)     989 (1.23)     60 (1.33)       Income     95 (51.63)     36.547 (46.13)     2.2422 (50.63)       Ac or above region median income     36 (36.13)     34.238 (43.33)     1.989 (41.53)       Decline to answer     6 (3.33)     8.422 (10.63)     375 (7.83)       Paivate     22 (12.03)     11.162 (12.83)     4.426 (9.53)       Paivate     22 (12.03)     10.162 (12.83)     4.426 (9.53)       Decline to answer     17 (9.23)     8.467 (10.78)     2.263 (5.53)       Decrine to answer     17 (9.23)     8.467 (10.78)     2.30 (5.53)       Decrine to answer     17 (9.23)     8.467 (10.78)     2.30 (5.53)       Decrine to answer     17 (9.23)     8.467 (10.78)     2.30 (5.53)       Decrine to answer     17 (9.23)     8.467 (10.78)     2.30 (5.53) <t< td=""><td>Male</td><td>105 (57.1%)</td><td>35,330 (44.6%)</td><td>3,148 (65.8%)</td></t<>	Male	105 (57.1%)	35,330 (44.6%)	3,148 (65.8%)	
Education     101 (5493)     39,840 (535)     2,799 (58.5)       Inversity degree of higher     101 (5493)     39,840 (35.5)     1,224 (40.23)       Decline to answer     2 (1.13)     989 (1.26)     60 (1.33)       Income     2     30,6547 (46.11)     2,422 (50.68)       At on above region median income     83 (45.13)     34,288 (43.33)     1,386 (41.53)       Decline to answer     63 (33.3)     8,422 (10.53)     1,386 (41.53)       Decline to answer     22 (12.03)     10,162 (12.83)     456 (85.33)       Private     22 (12.03)     10,162 (12.83)     450 (85.83)       Decline to answer     121 (52.8)     440 (87.55.6)     1,342 (28.13)       Decline to answer     171 (52.3)     2,670 (35.8)     2,31 (53.8)       Outernet sinter     7     84.433     1,342 (83.13)     1,342 (83.13)       Decline to answer     5 (27.3)     2,670 (35.8)     2,30 (45.8)     1,50 (35.8)     2,31 (45.8)     2,31 (45.8)     2,31 (45.8)     2,31 (45.8)     2,31 (45.8)     2,31 (45.8)     2,31 (45.8)     2,31 (45.8)     2,31 (45.8)     2,31 (45.8)     1,31 (45.8) <td>Mean (SD) age (years)</td> <td>54.5 (13.1)</td> <td>48.1 (16.5)</td> <td>62.8 (10.9)</td>	Mean (SD) age (years)	54.5 (13.1)	48.1 (16.5)	62.8 (10.9)	
Less han university degree     101 (5493)     38,489 (50,38)     2.299 (58.53)       University degree of higher     81 (4403)     38,488 (48.53)     1.924 (4023)       Decline to answer     2 (1,13)     989 (122)     60 (1,38)       Ar or above region median income     95 (51,65)     34,623 (323)     1.986 (41,53)       Decline to answer     63 (3,33)     84,221 (0,63)     3.75 (7,83)       Health insurance type     7     7     7     7       Private     22 (1203)     10,162 (12,84)     452 (9,53)       Public/Other     144 (7,833)     60,638 (76,55)     4,466 (5,50)       Decline to answer     17 (9,22)     8,467 (10,78)     2.263 (5,85)       Currently employed     78 (24,23)     44,067 (55,85)     1.244 (28,18)       Patier     10     10     1.248 (28,18)     1.248 (28,18)       Overweight     5 (27,3)     2.670 (3,5%)     2.30 (5,8)       Overweight     5 (6,04,37)     1.313 (16,81)     2.113 (6,83)       Overweight     5 (6,04,37)     1.333 (16,81)     2.136 (6,853)       Overweight     5 (6,04,37)	Education				
University degree of higher     81 (44,02)     38,438 (48,53)     1,924 (40,23)       Decline to answer     2 (1,13)     989 (1,23)     60 (1,33)       Income     38 (45,13)     346,547 (46,13)     2,422 (50,63)       At or above region median income     83 (45,13)     34,288 (43,33)     1,936 (41,58)       Decline to answer     63 (33)     8,422 (10,03)     457 (58,5)       Health insurance type     7     145 (78,83)     60,63 (55,5)     4,068 (85,06)       Decline to answer     17 (9,23)     8,467 (10,73)     263 (55,5)       Decline to answer     17 (9,23)     8,467 (10,73)     263 (55,5)       Decline to answer     17 (9,23)     8,467 (10,73)     263 (55,5)       Outer to answer     17 (9,23)     8,467 (10,73)     263 (55,5)       Outer to answer     17 (9,23)     8,467 (10,73)     263 (55,8)       Outer to answer     17 (9,23)     8,467 (10,73)     23 (0,58)       Outer to answer     17 (9,23)     8,467 (10,73)     23 (0,58)       Outer to answer     5 (3,04)     1,570 (3,58)     2,050 (3,58)       Outer to answer	Less than university degree	101 (54.9%)	39,840 (50.3%)	2,799 (58.5%)	
Decline to answer     2 (1.18)     989 (1.28)     60 (1.38)       Income     B6low region median income     95 (51.68)     36547 (46.13)     2,422 (50.68)       At or above region median income     83 (45.13)     34,298 (43.33)     1,986 (41.58)       Decline to answer     6 (3.33)     8,422 (10.63)     757 (78.8)       Private     22 (12.03)     10,162 (12.83)     4505 (85.08)       Decline to answer     22 (12.03)     10,162 (12.83)     4505 (85.08)       Decline to answer     71 (92.28)     8,467 (10.23)     263 (5.53)       Currently employed     78 (42.44)     44.607 (55.8)     1.342 (28.18)       Patient characteristics     Underweight     5 (27.78)     2.670 (3.58)     23 (0.58)       Normal weight     5 (27.78)     2.670 (3.58)     2.31 (94.53)     1.766 (3.59.8)       Obese     6 (3.03.4)     34.221 (43.23)     688 (14.43)       Obese     2.6 (16.28)     1.877 (23.73)     9.89 (20.58)       Normal weight     5 (13.8)     2.10 (45.8)     1.766 (3.89.8)       Obese     2.8 (15.28)     1.8.774 (23.73)     9.89 (20.58)	University degree of higher	81 (44.0%)	38,438 (48.5%)	1,924 (40.2%)	
Income     95 (51.6)     36.67 (46.13.2)     2.422 (50.65.2)       At or above region median income     95 (51.63.2)     34.228 (43.33.2)     1.986 (41.53.2)       Decline to answer     6 (3.33.2)     8.422 (10.68.2)     3.75 (7.88.2)       Private     22 (12.08.2)     10.162 (12.88.2)     4.4068 (85.08.2)       Decline to answer     7.17 (92.27.2)     8.467 (10.7.3)     2.63 (5.5.8.2)       Dublic/Other     145 (78.88.2)     64.063 (76.58.2)     4.068 (85.08.2)       Decline to answer     7.19 (92.21.8)     8.467 (10.7.3)     2.63 (5.5.8.2)       Currently employed     7.87 (42.43.2)     4.4067 (55.68.2)     1.342 (28.18.3)       Patent characteristics     Underweight     5 (2.7.8)     2.670 (3.5.8)     1.342 (28.18.3)       Normal weight     5 (13.04.3)     3.4221 (43.28.3)     6.688 (14.48.3)     0.988 (14.68.3)     0.923 (15.8)     1.766 (38.98.3)     0.213 (13.8)     1.76 (38.98.3)     0.213 (14.68.3)     2.230 (45.68.3)     1.263 (13.68.3)     2.230 (45.68.3)     1.263 (13.68.3)     2.230 (45.68.3)     1.263 (13.8)     1.263 (13.8)     2.230 (45.68.3)     1.57 (32.98.3)     1.57 (32.98.3)     1.563 (13.68.	Decline to answer	2 (1.1%)	989 (1.2%)	60 (1.3%)	
Below region median income     95 (51.6%)     36,547 (46.1%)     24,242 (50.6%)       At or above region median income     83 (45.13)     34,298 (43.33)     1,966 (41.5X)       Decline to answer     6 (33.3)     84,222 (10.6%)     375 (7.8%)       Health insurance type     22 (12.0%)     10,162 (12.8%)     450 (56.6%)     420 (55.6%)       Public/Other     126 (7.8%)     66.638 (7.65.3%)     4.068 (65.0%)     1.342 (28.1%)       Decline to answer     17 (19.2.3)     8,467 (10.7%)     626 (55.6%)     1.342 (28.1%)       Patient Characteristies     342.291 (43.2%)     44.067 (55.6%)     1.342 (28.1%)       Multion directristies     5     2,670 (3.5%)     2.36 (0.5%)       BMI     0uderweight     5 (2.7%)     2,670 (3.5%)     2.30 (0.5%)       Overweight     5 (3.04%)     2.503 (31.6%)     1.76 (3.3%)       Overweight     5 (6.33)     4.033 (5.1%)     1.76 (3.7%)       Owerweight     6 (3.33)     4.033 (5.1%)     1.290 (46.5%)       Owerweight     6 (3.33)     4.033 (5.1%)     1.290 (46.5%)       Owerweight     26 (15.2%)     1.3,313 (	Income				
Ar or above region median income     83 (45.1x)     34.298 (43.3x)     1.986 (41.5x)       Decline to answer     6 (3.33)     8.422 (10.68)     375 (7.88)       Health insurance type     22 (12.03)     10.162 (12.83)     452 (9.58)       Public/Other     145 (78.83)     60.633 (75.53)     40.68 (85.07)       Decline to answer     17 (9.23)     8.467 (10.73)     263 (5.53)       Currently employed     78 (42.48)     44.067 (15.58)     1.342 (28.18)       Patient characteristics     34.22 (40.28)     6.86 (45.73)     1.342 (28.18)       Morreal weight     5 (2.73)     2.2670 (3.58)     2.3 (0.58)       Normal weight     34.23 (3.14)     34.23 (4.33)     1.766 (36.693)       Overweight     56 (30.44)     2.670 (3.58)     2.130 (63.693)       Obese     66 (46.73)     1.313 (16.83)     2.430 (45.8)       Overweight     56 (30.44)     3.4238 (43.3)     1.766 (36.693)       Obese     86 (46.73)     1.331 (16.83)     2.430 (46.63)       Normal weight     51 (30.43)     2.430 (45.8)     1.573 (2.89)       Current smoker     28 (15.23) <td>Below region median income</td> <td>95 (51.6%)</td> <td>36,547 (46.1%)</td> <td>2,422 (50.6%)</td>	Below region median income	95 (51.6%)	36,547 (46.1%)	2,422 (50.6%)	
Deckine to answer     6 (3.3x)     8.422 (10.6x)     3.75 (7.8x)       Hadhi isurance type	At or above region median income	83 (45.1%)	34,298 (43.3%)	1,986 (41.5%)	
Health insurance type   22 (12.0%)   10.162 (12.8%)   452 (0.5%)     Public/Other   12 (52.0%)   60.638 (76.5%)   42.068 (85.0%)     Decline to answer   17 (92.3%)   8.467 (10.7%)   62.83 (5.5%)     Currently employed   78 (42.4%)   44.067 (55.6%)   1.342 (28.1%) <b>Prior BI</b> Underweight   5 (2.7%)   2.670 (3.5%)   23 (0.5%)     Normal weight   5 (2.7%)   2.670 (3.5%)   23 (0.5%)     Normal weight   5 (6.30.48)   24.021 (43.2%)   688 (14.4%)     Overweight   6 (3.3.4)   24.031 (16.8%)   24.21 (43.2%)   688 (14.4%)     Overweight   6 (3.3.4)   24.033 (15.1%)   1.766 (3.69.4%)     Obese   86 (6.67.3%)   13.313 (16.8%)   24.30 (44.5%)     Outnown   6 (3.3.4)   4.033 (5.1%)   1.766 (3.69.4%)     Smoking behavior   2   8 (15.2%)   13.313 (16.8%)   24.30 (4.8%)     Outnown   6 (3.3.4)   4.033 (5.1%)   176 (3.5%)     Smoking behavior   2   8 (4.0.3%)   3.593 (3.6%)   1.573 (3.69.2%) <td andi<="" cows="" td=""><td>Decline to answer</td><td>6 (3.3%)</td><td>8,422 (10.6%)</td><td>375 (7.8%)</td></td>	<td>Decline to answer</td> <td>6 (3.3%)</td> <td>8,422 (10.6%)</td> <td>375 (7.8%)</td>	Decline to answer	6 (3.3%)	8,422 (10.6%)	375 (7.8%)
Private     22 (12.0%)     10.162 (12.8%)     452 (9.5%)       Public/Other     145 (78.8%)     66.038 (75.5%)     44.068 (85.0%)       Decline to answer     71 (9.2%)     84.67 (10.7%)     263 (5.5%)       Currendy employed     78 (42.4%)     44.067 (55.5%)     1,342 (28.1%)       Patient characteristics      5     2,770 (3.5%)     23 (0.5%)       Normal weight     31 (16.8%)     34,221 (43.2%)     6688 (14.4%)       Overweight     56 (30.4%)     25,030 (31.6%)     1,766 (36.9%)       Obese     86 (46.7%)     13,313 (16.8%)     2,130 (44.5%)       Unknown     68 (46.7%)     35,943 (51.9%)     17,66 (36.9%)       Obese     86 (46.7%)     13,313 (16.8%)     2,130 (44.5%)       Unknown     68 (46.7%)     2,550 (31.0%)     2,230 (46.6%)       Noreit smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     88 (26.1%)     13,230 (23.0%)     1,315 (36.6%)       Vers smoker     28 (15.2%)     35,943 (45.3%)     1,359 (23.6%)       Vers smoker     88 (26.1%)     18,203 (23.0%)	Health insurance type				
Public/Other     145 (78.8%)     60.638 (76.5%)     4.068 (85.0%)       Decline to answer     17 (9.2%)     8.467 (10.7%)     263 (5.5%)       Currently employed     78 (42.4%)     40.67 (55.6%)     1.342 (28.1%)       Pattent characteristics     2     2     2     0.05%)     2     0.05%)     2     0.05%)     2     0.05%)     2     0.05%)     2     0.05%)     2     0.05%)     0.05%)     0.05%     2     0.05%)     0.05%)     0.05%     2     0.05%)     0.05%     0.05%)     0.05%     0.05%)     0.05%     0.05%)     0.05%     0.05%)     0.05%     0.05%)     0.05%     0.05%)     0.05%     0.05%)     0.05%     0.05%)     0.05%     0.05%)     0.05%)     0.05%)     0.05%)     0.05%)     0.05%     0.05%)	Private	22 (12.0%)	10,162 (12.8%)	452 (9.5%)	
Decline to answer     17 (9.2%)     8.467 (10.7%)     263 (5.5%)       Currently employed     78 (42.4%)     44.067 (55.6%)     1,342 (28.1%)       Patient characteristics          BM       3.13 (16.8%)     3.4221 (43.2%)     6688 (14.4%)       Overweight     5 (2.7%)     2.670 (3.5%)     2.30 (44.5%)       Overweight     5 (5.0.4%)     2.500 (31.6%)     1.766 (36.9%)       Obese     66 (46.7%)     13.313 (16.8%)     2.130 (44.5%)       Ownown     63 (33)     4.003 (5.1%)     17.67 (3.7%)       Smoking behavior      2     18,774 (23.7%)     980 (20.5%)       Current smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Never smoker     75 (40.8%)     25,593 (1.0%)     2.230 (46.6%)       Never smoker     75 (40.8%)     18,203 (23.0%)     13.392 (28.6%)       Yes, daily     124 (67.4%)     18,203 (23.0%)     13.69 (28.6%)       Yes, daily     124 (67.4%)     13.203 (23.0%)     13.69 (28.6%)       Yes, daily     124 (67.4%)     13.203 (23.0%)	Public/Other	145 (78.8%)	60,638 (76.5%)	4,068 (85.0%)	
Currently employed     78 (42.4%)     44.067 (55.6%)     1,342 (28.1%)       Patient characteristics        BMI         Underweight     5 (2.7%)     2,670 (3.5%)     23 (0.5%)       Normal weight     5 (3.04%)     34,221 (43.2%)     668 (14.4%)       Overweight     56 (30.4%)     25,030 (31.6%)     1,766 (36.9%)       Obese     86 (46.7%)     13,313 (16.8%)     2,130 (44.5%)       Unknown     63 (33.2%)     44,037 (23.7%)     980 (20.5%)       Smoking behavior     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Current smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Nome     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Norme smoker     75 (40.8%)     35,943 (45.3%)     1.573 (32.9%)       Current alcohol use           None     48 (26.13)     18,203 (23.0%)     1,369 (28.6%)       Yes, daily     12 (65.7%)     29,592 (37.4%)     22,59 (47.2%)       Current alcohol use       31,102 (16.8%)	Decline to answer	17 (9.2%)	8,467 (10.7%)	263 (5.5%)	
Patient characteristics       BM       M     \$5(27)     2,670(35)     22(05)       Normal weight     31(168)     34221(432)     688(144)       Overweight     56(304)     2503(30)     1,766 (38-9)       Obse     86(467)     13,31 (168)     2,130 (458)       Obse     86(467)     13,31 (168)     2,130 (458)       Obse     86 (467)     13,31 (168)     2,130 (458)       Obse     86 (467)     13,31 (168)     2,130 (458)       Obse     86 (467)     18,714 (23.7)     980 (20.5)       Former smoker     81 (440)     24,550 (31.0)     2,20 (466.0)       Former smoker     75 (408)     35,943 (453)     1,573 (28.0)       Never smoker     75 (408)     2,593 (318)     1,392 (46.8)       Yes, ladily     2,20 (46.61)     1,203 (23.00)     1,209 (28.0)       Yes, ladily     1,216 (53)     5,892 (34.0)     1,209 (48.0)       Yes, ladily     1,216 (54)     5,892 (34.0)     2,299 (47.2)       Nove crise: 0 days in past month     56 (46.73)     2,592 (37.	Currently employed	78 (42.4%)	44,067 (55.6%)	1,342 (28.1%)	
BMI       Underweight     5 (2.7%)     2.670 (3.5%)     32 (0.5%)       Normal weight     31 (16.8%)     34.221 (43.2%)     668 (14.4%)       Overweight     56 (0.4%)     25,030 (31.6%)     1.766 (36.9%)       Obese     86 (46.7%)     13,313 (16.8%)     2.130 (44.5%)       Unknown     6 (3.3%)     4.033 (5.1%)     1.76 (36.9%)       Smoking behavior     28 (15.2%)     18,774 (23.7%)     9.80 (20.5%)       Former smoker     28 (15.2%)     18,774 (23.7%)     9.80 (20.5%)       Current skohol use     75 (0.4%)     35,933 (15.3%)     1.730 (32.6%)       None     48 (26.1%)     18,203 (23.0%)     1.369 (28.6%)       Yes, less than daily     12 (67.4%)     55,172 (69.6%)     2.934 (61.3%)       Ves, exercise: 0 days in past month	Patient characteristics				
Underweight     5 (2.7%)     2.670 (3.5%)     23 (0.5%)       Normal weight     31 (16.8%)     34,221 (43.2%)     668 (14.4%)       Overweight     56 (30.4%)     25,030 (31.6%)     1.766 (36.9%)       Obese     86 (46.7%)     13,313 (16.8%)     2.130 (44.5%)       Obese     86 (46.7%)     13,313 (16.8%)     2.130 (44.5%)       Obese     6 (3.3%)     4033 (5.1%)     1.766 (36.9%)       Smoking behavior     6 (3.3%)     4033 (5.1%)     1.766 (36.9%)       Current smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Never smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Never smoker     75 (40.8%)     35,943 (45.3%)     1.757 (32.9%)       Current alcohol use     7     71.08%     2.739 (46.6%)       None     48 (26.1%)     18,203 (23.0%)     1.399 (28.6%)       Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2.934 (61.3%)       Yes, daily     124 (67.4%)     51,910.6%)     7.717 (15.0%)	BMI				
Normal weight     31 (16.8%)     34,221 (43.2%)     668 (14.4%)       Overweight     56 (30.4%)     25,030 (31.6%)     1,766 (36.9%)       Obese     86 (46.7%)     13,313 (16.8%)     2,130 (44.5%)       Unknown     6 (3.3%)     4.033 (5.1%)     176 (3.7%)       Smoking behavior     2     2     30 (45.3%)     176 (3.7%)       Current smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     81 (44.0%)     24,550 (31.0%)     2,230 (46.6%)       Never smoker     75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use      124 (67.4%)     55,172 (69.6%)     2,934 (61.3%)       Yes, daily     12 (65.%)     5,892 (7.4%)     480 (10.0%)       Current exercise behavior      No exercise: 1-5 days in past month     37 (20.1%)     17,130 (21.6%)     717 (15.0%)       Moderate exercise: 6-11 days in past month     26 (41.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 12+ days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       CCI - higher scores indicate greater comorbid burden on patient </td <td>Underweight</td> <td>5 (2.7%)</td> <td>2,670 (3.5%)</td> <td>23 (0.5%)</td>	Underweight	5 (2.7%)	2,670 (3.5%)	23 (0.5%)	
Overweight     56 (30.4%)     25,030 (31.6%)     1,766 (36.9%)       Obese     86 (46.7%)     13,313 (16.8%)     2,130 (44.5%)       Unknown     6 (3.3%)     4.033 (5.1%)     176 (37.8%)       Smoking behavior     2     15,23%)     18,774 (23.7%)     980 (20.5%)       Current smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Pormer smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Never smoker     28 (14.0%)     24,550 (31.0%)     2,230 (46.6%)       Never smoker     81 (44.0%)     24,550 (31.0%)     2,230 (46.6%)       Verrent alcohol use     75 (40.8%)     18,203 (23.0%)     1,369 (28.6%)       Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2,934 (61.3%)       Yes, daily     12 (65.7%)     29,592 (37.4%)     2,259 (47.2%)       Low exercise: 0 days in past month     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Moderate exercise: 6-11 days in past month     37 (20.1%)     17,130 (21.6%)     717 (15.0%)       Moderate exercise: 6-11 days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%) <	Normal weight	31 (16.8%)	34,221 (43.2%)	688 (14.4%)	
Obese     86 (46.7%)     13,313 (16.8%)     2,130 (44.5%)       Unknown     6 (3.3%)     4.033 (5.1%)     176 (3.7%)       Smoking behavior     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Current smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     28 (14.0%)     24,550 (31.0%)     2,230 (46.6%)       Never smoker     75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use	Overweight	56 (30.4%)	25,030 (31.6%)	1,766 (36.9%)	
Unknown     6 (3.3%)     4.03 (5.1%)     176 (3.7%)       Smoking behavior     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Never smoker     75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use     75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use     80 (26.1%)     18,203 (23.0%)     1,369 (28.6%)       Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2,934 (61.3%)       Yes, daily     12 (65.%)     5.892 (7.4%)     480 (10.0%)       Current exercise behavior     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       No exercise: 1-5 days in past month     26 (14.1%)     13,102 (1.6%)     628 (13.1%)       High exercise: 12+ days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 12+ days in past month     26 (14.1%)     13,102 (16.5%)     0 (0.0%) <t< td=""><td>Obese</td><td>86 (46.7%)</td><td>13,313 (16.8%)</td><td>2,130 (44.5%)</td></t<>	Obese	86 (46.7%)	13,313 (16.8%)	2,130 (44.5%)	
Smoking behavior     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     81 (44.0%)     24,550 (31.0%)     2,230 (46.6%)       Never smoker     75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use      75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use      48 (26.1%)     18,203 (23.0%)     1,369 (28.6%)       Yes, less than daily     124 (67.4%)     55.172 (69.6%)     2,934 (61.3%)       Yes, daily     12 (6.5%)     5.892 (7.4%)     480 (10.0%)       Current exercise behavior      86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Low exercise: 1-5 days in past month     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Moderate exercise: 6-11 days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 1-2* days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       CCI - higher scores indicate greater comorbid burden on patient     CCI - 0     87 (47.3%)     63,913 (80.6%)     0 (0.0%)	Unknown	6 (3.3%)	4,033 (5.1%)	176 (3.7%)	
Current smoker     28 (15.2%)     18,774 (23.7%)     980 (20.5%)       Former smoker     81 (44.0%)     24,550 (31.0%)     2,230 (46.6%)       Never smoker     75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use     48 (26.1%)     18,203 (23.0%)     1,369 (28.6%)       Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2,934 (61.3%)       Yes, daily     124 (65.7%)     5,892 (7.4%)     480 (10.0%)       Current exercise behavior     5     5,892 (7.4%)     480 (10.0%)       Current exercise: 1-5 days in past month     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Low exercise: 1-5 days in past month     37 (20.1%)     17,130 (21.6%)     717 (15.0%)       Moderate exercise: 6-11 days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 12+ days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 12+ days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       CCI - higher scores indicate greater comorbid burden on patient     20 (1 - 4.1%)     13,102 (16.5%)     0 (0.0%)       CC1 - 1	Smoking behavior				
Former smoker     81 (44.0%)     24,550 (31.0%)     2,230 (46.6%)       Never smoker     75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use     48 (26.1%)     18,203 (23.0%)     1,369 (28.6%)       Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2,934 (61.3%)       Yes, daily     122 (65.%)     5,892 (7.4%)     480 (10.0%)       Current exercise behavior     12 (65.%)     5,892 (7.4%)     480 (10.0%)       Current exercise: 0 days in past month     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Low exercise: 1-5 days in past month     37 (20.1%)     17,130 (21.6%)     717 (15.0%)       Moderate exercise: 6-11 days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 12+ days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       CCI - higher scores indicate greater comorbid burden on patient     20 (14.1%)     13,102 (16.5%)     628 (13.1%)       CCI: 0     87 (47.3%)     63,913 (80.6%)     0 (0.0%)     0 (0.0%)     0 (0.0%)     0 (0.0%)     0 (0.0%)     0 (0.0%)     0 (0.0%)     0 (0.0%)     0 (0.0%) <t< td=""><td>Current smoker</td><td>28 (15.2%)</td><td>18,774 (23.7%)</td><td>980 (20.5%)</td></t<>	Current smoker	28 (15.2%)	18,774 (23.7%)	980 (20.5%)	
Never smoker     75 (40.8%)     35,943 (45.3%)     1,573 (32.9%)       Current alcohol use           None     48 (26.1%)     18,203 (23.0%)     1,369 (28.6%)        Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2,934 (61.3%)       Yes, daily     12 (65.%)     5,892 (7.4%)     480 (10.0%)       Current exercise behavior      37 (20.1%)     17,130 (21.6%)     2,259 (47.2%)       Low exercise: 1-5 days in past month     36 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Moderate exercise: 6-11 days in past month     37 (20.1%)     17,130 (21.6%)     628 (13.1%)       High exercise: 12+ days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       Coll - higher scores indicate greater comorbid burden on patient     57 (47.3%)     63,913 (80.6%)     0 (0.0%)       CCI: 0     87 (47.3%)     63,913 (80.6%)     0 (0.0%)     3 (0.16.4%)       CCI: 1     23 (12.5%)     3,401 (4.3%)     852 (17.8%)     3 (0.16.4%)       CCI: 2     3,401 (4.3%)     852 (17.8%)     3 (0.17.4%)     3 (2.17.4%)     3 (2.17.8%)<	Former smoker	81 (44.0%)	24,550 (31.0%)	2,230 (46.6%)	
Current alcohol use     48 (26.1%)     18.203 (23.0%)     1,369 (28.6%)       Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2,934 (61.3%)       Yes, daily     12 (65.%)     5,892 (7.4%)     480 (10.0%)       Current exercise behavior     12 (65.%)     29,592 (37.4%)     2,259 (47.2%)       No exercise: 0 days in past month     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Low exercise: 1-5 days in past month     37 (20.1%)     17,130 (21.6%)     717 (15.0%)       Moderate exercise: 6-11 days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 12+ days in past month     35 (19.0%)     19,443 (24.5%)     1,179 (24.6%)       CCI - higher scores indicate greater comorbid burden on patient     27 (47.3%)     63,913 (80.6%)     0 (0.0%)       CCI: 1     62 (12.2%)     9,852 (12.4%)     3,101 (64.8%)     0 (0.0%)       CCI: 2     23 (12.5%)     3,401 (4.3%)     852 (17.8%)     0 (17.4%)     0,2101 (2.7%)     830 (17.4%)     0,2101 (2.7%)     830 (17.4%)     0,2101 (2.7%)     830 (17.4%)     0,2101 (2.7%)     0,266 (56.2%)     0,100 (57.9%)     0,266 (56.2%) <td< td=""><td>Never smoker</td><td>75 (40.8%)</td><td>35,943 (45.3%)</td><td>1,573 (32.9%)</td></td<>	Never smoker	75 (40.8%)	35,943 (45.3%)	1,573 (32.9%)	
None     48 (26.1%)     18,203 (23.0%)     1,369 (28.6%)       Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2,934 (61.3%)       Yes, daily     12 (6.5%)     5,892 (7.4%)     480 (10.0%)       Current exercise behavior     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       No exercise: 0 days in past month     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Low exercise: 1-5 days in past month     37 (20.1%)     17,130 (21.6%)     717 (15.0%)       Moderate exercise: 6-11 days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 12+ days in past month     26 (14.1%)     19,443 (24.5%)     1,179 (24.6%)       CCI - higher scores indicate greater comorbid burden on patient     50 (10.0%)     0 (0.0%)     0 (0.0%)       CCI: 0     87 (47.3%)     63,913 (80.6%)     0 (0.0%)	Current alcohol use				
Yes, less than daily     124 (67.4%)     55,172 (69.6%)     2.934 (61.3%)       Yes, daily     12 (65.%)     5,892 (7.4%)     480 (10.0%)       Current exercise behavior        480 (10.0%)       No exercise: 0 days in past month     86 (46.7%)     29,592 (37.4%)     2,259 (47.2%)       Low exercise: 1-5 days in past month     37 (20.1%)     17,130 (21.6%)     717 (15.0%)       Moderate exercise: 6-11 days in past month     26 (14.1%)     13,102 (16.5%)     628 (13.1%)       High exercise: 12+ days in past month     35 (19.0%)     19,443 (24.5%)     1,179 (24.6%)       Comorbidities       35 (19.0%)     19,443 (24.5%)     1,179 (24.6%)       CCI - higher scores indicate greater comorbid burden on patient <t< td=""><td>None</td><td>48 (26.1%)</td><td>18,203 (23.0%)</td><td>1,369 (28.6%)</td></t<>	None	48 (26.1%)	18,203 (23.0%)	1,369 (28.6%)	
Yes, daily     12 (6.5%)     5,892 (7.4%)     480 (10.0%)       Current exercise behavior	Yes, less than daily	124 (67.4%)	55,172 (69.6%)	2,934 (61.3%)	
Current exercise behavior     No exercise: 0 days in past month   86 (46.7%)   29,592 (37.4%)   2,259 (47.2%)     Low exercise: 1-5 days in past month   37 (20.1%)   17,130 (21.6%)   717 (15.0%)     Moderate exercise: 6-11 days in past month   26 (14.1%)   13,102 (16.5%)   628 (13.1%)     High exercise: 12+ days in past month   35 (19.0%)   19,443 (24.5%)   1,179 (24.6%)     Comorbidities     CCI - higher scores indicate greater comorbid burden on patient     CCI: 0   87 (47.3%)   63,913 (80.6%)   0 (0.0%)     CCI: 1   42 (22.8%)   9,852 (12.4%)   3,101 (64.8%)     CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	Yes, daily	12 (6.5%)	5,892 (7.4%)	480 (10.0%)	
No exercise: 0 days in past month   86 (46.7%)   29,592 (37.4%)   2,259 (47.2%)     Low exercise: 1-5 days in past month   37 (20.1%)   17,130 (21.6%)   717 (15.0%)     Moderate exercise: 6-11 days in past month   26 (14.1%)   13,102 (16.5%)   628 (13.1%)     High exercise: 12+ days in past month   35 (19.0%)   19,443 (24.5%)   1,179 (24.6%)     Comorbidities     CCI - higher scores indicate greater comorbid burden on patient     CCI - higher scores indicate greater comorbid burden on patient   87 (47.3%)   63,913 (80.6%)   0 (0.0%)     CCI: 1   42 (22.8%)   9,852 (12.4%)   3,101 (64.8%)     CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	Current exercise behavior				
Low exercise: 1-5 days in past month   37 (20.1%)   17,130 (21.6%)   717 (15.0%)     Moderate exercise: 6-11 days in past month   26 (14.1%)   13,102 (16.5%)   628 (13.1%)     High exercise: 12+ days in past month   35 (19.0%)   19,443 (24.5%)   1,179 (24.6%)     Comorbidities     CCI - higher scores indicate greater comorbid burden on patient     CCI - 0   87 (47.3%)   63,913 (80.6%)   0 (0.0%)     CCI: 1   42 (22.8%)   9,852 (12.4%)   3,101 (64.8%)     CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	No exercise: 0 days in past month	86 (46.7%)	29,592 (37.4%)	2,259 (47.2%)	
Moderate exercise: 6-11 days in past month   26 (14.1%)   13,102 (16.5%)   628 (13.1%)     High exercise: 12+ days in past month   35 (19.0%)   19,443 (24.5%)   1,179 (24.6%)     Comorbidities     CCI - higher scores indicate greater comorbid burden on patient     CCI: 0   87 (47.3%)   63,913 (80.6%)   0 (0.0%)     CCI: 1   42 (22.8%)   9,852 (12.4%)   3,101 (64.8%)     CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	Low exercise: 1-5 days in past month	37 (20.1%)	17,130 (21.6%)	717 (15.0%)	
High exercise: 12+ days in past month   35 (19.0%)   19,443 (24.5%)   1,179 (24.6%)     Comorbidities   CCI - higher scores indicate greater comorbid burden on patient   Set (47.3%)   63,913 (80.6%)   0 (0.0%)     CCI: 0   87 (47.3%)   63,913 (80.6%)   0 (0.0%)     CCI: 1   42 (22.8%)   9,852 (12.4%)   3,101 (64.8%)     CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	Moderate exercise: 6-11 days in past month	26 (14.1%)	13,102 (16.5%)	628 (13.1%)	
Comorbidities       CCI - higher scores indicate greater comorbid burden on patient       CCI: 0     87 (47.3%)     63,913 (80.6%)     0 (0.0%)       CCI: 1     42 (22.8%)     9,852 (12.4%)     3,101 (64.8%)       CCI: 2     23 (12.5%)     3,401 (4.3%)     852 (17.8%)       CCI: 3+     32 (17.4%)     2,101 (2.7%)     830 (17.4%)       Self-reported physician diagnosis of high blood pressure (hypertension)     91 (49.5%)     14,217 (17.9%)     2,686 (56.2%)	High exercise: 12+ days in past month	35 (19.0%)	19,443 (24.5%)	1,179 (24.6%)	
CCI - higher scores indicate greater comorbid burden on patient     CCI: 0   87 (47.3%)   63,913 (80.6%)   0 (0.0%)     CCI: 1   42 (22.8%)   9,852 (12.4%)   3,101 (64.8%)     CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	Comorbidities		, , , ,	,	
CCI: 0   87 (47.3%)   63,913 (80.6%)   0 (0.0%)     CCI: 1   42 (22.8%)   9,852 (12.4%)   3,101 (64.8%)     CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	CCI - higher scores indicate greater comorbid burden on patient				
CCI: 1   42 (22.8%)   9,852 (12.4%)   3,101 (64.8%)     CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	CCI: 0	87 (47.3%)	63,913 (80.6%)	0 (0.0%)	
CCI: 2   23 (12.5%)   3,401 (4.3%)   852 (17.8%)     CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	CCI: 1	42 (22.8%)	9,852 (12.4%)	3,101 (64.8%)	
CCI: 3+   32 (17.4%)   2,101 (2.7%)   830 (17.4%)     Self-reported physician diagnosis of high blood pressure (hypertension)   91 (49.5%)   14,217 (17.9%)   2,686 (56.2%)	CCI: 2	23 (12.5%)	3,401 (4.3%)	852 (17.8%)	
Self-reported physician diagnosis of high blood pressure (hypertension)91 (49.5%)14,217 (17.9%)2,686 (56.2%)OutputOutputOutputOutputOutputOutputOutputOutput	CCI: 3+	32 (17.4%)	2,101 (2.7%)	830 (17.4%)	
	Self-reported physician diagnosis of high blood pressure (hypertension)	91 (49.5%)	14,217 (17.9%)	2,686 (56.2%)	
Self-reported physician diagnosis of $\frac{\text{one or more}}{\text{mere}}$ relevant heart or blood conditions 127 (69.0%) 25,763 (32.5%) 3,444 (72.0%)	Self-reported physician diagnosis of one or more relevant heart or blood conditions	127 (69.0%)	25,763 (32.5%)	3,444 (72.0%)	

(continued on next page)

	Unmatched Cohorts		
	NASH n = 184	General Population n = 79,267	T2DM n = 4,783
	n (%)	n (%)	n (%)
T2DM			
Self-reported physician diagnosis of T2DM	42 (22.8%)	4,783 (6.0%)	4,783 (100.0%)
Self-reported physician diagnosis of one or more relevant T2DM-related complications	15 (8.2%)	1,001 (1.3%)	1,001 (20.9%)
Use of insulin prescription to treat T2DM	10 (5.4%)	1,101 (1.4%)	1,101 (23.0%)
Use of non-insulin prescription to treat T2DM	36 (19.6%)	3,592 (4.5%)	3,592 (75.1%)
Use of a prescription to treat T2DM	37 (20.1%)	3,952 (5.0%)	3,952 (82.6%)

BMI, body mass index; CCI, Charlson comorbidity index; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

with NASH and those with T2DM also reported similar impairment on physical status (PCS) and EQ-5D utility scores. Psychological comorbidities, such as anxiety, depression, and sleep difficulties were reported equally among patients with NASH or T2DM, and the impact on work and non-work activities was similarly high. With respect to HRU, patients with NASH reported more HCP visits (traditional and non-traditional visits), ER visits, and hospitalizations than patients with T2DM. Patients with NASH also reported more visits to general practitioners, gastroenterologists, endocrinologists, psychiatrists, and hepatologists than those with T2DM and a similar number of visits to cardiologists, internists, and diabetologists.

Findings from the current study differ from those reported in previous research in many ways. To our knowledge, no prior work has examined the comparative burden of NASH in a nationally representative sample. Available data up to this point have been limited by the biases intrinsic to referral for liver biopsy.<sup>8,24,25</sup> In addition, the current study excluded patients with cirrhosis who are traditionally thought to have the worst patient-reported outcomes, further substantiating the burden of NASH before the cirrhosis stage. Only a handful of studies have examined European populations and those that have typically do not differentiate NASH from NAFLD, making comparisons between results from prior European studies and the current study difficult to interpret.<sup>7,26</sup> Perhaps most importantly, no prior study has performed comparative analysis to patients with T2DM or to well-matched controls from the general population, making the comparative burden of NASH difficult to define. Instead, prior work has examined the burden of NASH in the context of other chronic liver diseases,<sup>7,26,27</sup> or in comparison to pre-existing standardized population norms, without sufficiently controlling for confounding patient demographics and characteristics.<sup>8,27,28</sup>

Previous research on the humanistic burden of NASH suggests that the physical burden of NASH, as opposed to the mental/emotional burden of NASH, is most prominent, with fatigue being a major aspect of reduced HRQoL.<sup>9</sup> Chawla *et al.*<sup>28</sup> found that patients with NASH in the US, who were referred for evaluation of histology-proven NASH, exhibited reduced PCS scores, relative to pre-existing standardized general population norms. Similarly, Younossi *et al.*<sup>8</sup> found that patients with NASH in the US and Canada, enrolled in a phase II open label study, exhibited reduced PCS scores (but not reduced MCS scores), relative to the standardized general population norms. In contrast, results from this study indicate that patients with NASH report a greater physical and mental/emotional burden than the general population.

Prior studies on the economic burden of NASH indicate impairment of work and non-work activities and medical resource use in patients with NASH.<sup>7,8,24,29</sup> Younossi *et al.*<sup>8</sup> found that WPAI scores of patients with NASH in the US and Canada were greater than a





**Fig. 1. Mental and physical component scores on SF-36v2: NASH vs. matched general population and NASH vs. matched T2DM – multivariable results.** Note: For each comparison, *p* values represent significance of the regression coefficient in the regression model with matched general population and matched T2DM population as reference groups. Adjusted means and 95% CIs are displayed. Linear models were used for all outcomes reported in this figure. MCS, mental component summary; NASH, non-alcoholic steatohepatitis; PCS, physical component summary; T2DM, type 2 diabetes mellitus.

**Fig. 2. SF-6D and EQ-5D utility scores: NASH vs. matched general population and NASH vs. matched T2DM – multivariable results.** Note: For each comparison, *p* values represent significance of the regression coefficient in the regression model with matched general population and matched T2DM population as reference groups. Adjusted means and 95% CIs are displayed. Linear models were used for all outcomes reported in this figure. NASH, non-alcoholic steatohepatitis; SF-6D, Short Form-6D; T2DM, type 2 diabetes mellitus.

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**Fig. 3. Percentage of patients reporting a physician diagnosis of anxiety, depression, or sleep difficulties: NASH vs. matched general population and NASH vs. matched T2DM – multivariable results.** Note: For each comparison, *p* values represent significance of the regression coefficient in the regression model with matched general population and matched T2DM population as reference groups. Adjusted means and 95% Cls are displayed. Binary logistic models were used for all outcomes reported in this figure. NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

pseudo-comparison group with zero impairment of work and nonwork activities. Findings from the current study corroborate these results using a more robust comparison group (general population). Patton *et al.*<sup>24</sup> reported that NAFLD patients in the US exhibited increased hospitalizations and HCP visits (office visits) as NAFLD progressed to more severe forms, such as NASH. However, comparison cohorts in that study were mainly defined in terms of cirrhosis status and not in terms of the presence of NASH, *per se*. Similarly, Sayiner *et al.*<sup>29</sup> found that NAFLD Medicare beneficiaries in the US had more HRU, as assessed by total provider payments, if NAFLD involved cirrhosis. Younossi *et al.*<sup>7</sup> reported similar findings in patients with NAFLD in the US and the EU. Results from the current study clearly indicate that patients with NASH, specifically, report more HRU than the general population or those with T2DM.

These results confirm previous research and provide more clarity on the burden of NASH from the patient perspective. However, NASH is often regarded as an asymptomatic "silent" disease and the mechanisms that produce this burden remain



**Fig. 4. Work productivity and activity impairment: NASH vs. matched general population and NASH vs. matched T2DM – multivariable results.** Note: For each comparison, *p* values represent significance of the regression coefficient in the regression model with matched general population and matched T2DM population as reference groups. Adjusted means and 95% CIs are displayed. Absenteeism, presenteeism, and overall work impairment includes only employed respondents. Generalized linear models with negative binomial distribution and log-link were used for all outcomes reported in this figure. NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.



**Fig. 5. Healthcare resource use in past 6 months: NASH vs. matched general population and NASH vs. matched T2DM – multivariable results.** Note: For each comparison, *p* values represent significance of the regression coefficient in the regression model with matched general population and matched T2DM population as reference groups. Adjusted means and 95% Cls are displayed. Generalized linear models with negative binomial distribution and log-link were used for all outcomes reported in this figure. ER, emergency room; HCP, healthcare professional; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

poorly defined.<sup>2</sup> Future research is needed to further examine the connection between the biological mechanisms of NASH (*i.e.*, accumulation of fat, inflammation, and fibrosis), the psychology of an incurable disease, associated health outcomes, and HRU.

In addition to the burden of disease, this study reports the prevalence of self-reported physician diagnosed NASH in the EU5 adult population. Though the sample size of patients with NASH in this study was relatively small, this is the first study to assess NASH prevalence using a representative sample from the adult EU5 general population. Previous studies have offered highly variable prevalence estimates, likely resulting from the variety of diagnostic tools assessed (*e.g.*, liver biopsy, diagnosis code, lab values), the preponderance of center-specific studies with relatively small samples, and assessments of NASH solely within pre-identified selective NAFLD populations.<sup>3–6</sup>

These data must be interpreted in the context of the particularities of a real-world study. All respondents self-reported their respective conditions (*i.e.*, NASH) based on their recall of physician diagnosis. Therefore, this study design assumes that there was an accurate diagnosis and an accurate recall of that diagnosis. This is a noteworthy limitation, given difficulties physicians currently have with accurately diagnosing NASH. There was no confirmation of NASH diagnosis via liver biopsy in these data. Specifically, these results do not account for those who have NASH, but do not report a NASH diagnosis (*i.e.*, are unaware they have NASH because it has not been diagnosed or do not accurately recall their NASH diagnosis). Nor do these results account for those who erroneously report a NASH diagnosis, as may very well be the case for some patients with NAFLD who confuse their NAFLD for NASH.

All measures and outcomes assessed were patient-reported data and these results are susceptible to the potential for inaccurate self-reports related to variable health literacy, errors in memory, or respondent fatigue. Finally, this was a cross-sectional study. As such, this study cannot establish causal nor longitudinal relationships between variables of interest (*e.g.*, NASH diagnosis and subsequent health outcomes).

### Conclusion

These findings suggest that patients with NASH experience a significant burden of illness, which highlights the unmet needs

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Table 2. Healthcare resource use in past 6 months (specific specialty visits): NASH vs. matched general population – multivariable results.

	Matched Cohorts		
	NASH n = 184	Matched general population n = 736	
	Adjusted mean (SE)	Adjusted mean (SE)	p value
General practitioner/Family practitioner visits	3.80 (0.33)	2.23 (0.10)	<0.001
Specialists (any type) visits	6.94 (0.69)	3.77 (0.19)	<0.001
Cardiologist visits	0.32 (0.05)	0.19 (0.02)	0.013
Gastroenterologist visits	0.28 (0.06)	0.07 (0.01)	<0.001
Endocrinologist visits	0.27 (0.05)	0.04 (0.01)	<0.001
Internist visits	0.28 (0.06)	0.12 (0.02)	0.002
Diabetologist visits	0.22 (0.06)	0.09 (0.02)	0.007
Psychiatrist visits	0.37 (0.12)	0.16 (0.04)	0.034
Hepatologist visits	0.07 (0.02)	0.01 (0.00)	0.000

Note: *p* values represent significance of the regression coefficient in the regression model with matched general population as reference group. Generalized linear models with negative binomial distribution and log-link were used for all outcomes reported in this table.

NASH, non-alcoholic steatohepatitis.

#### Table 3. Healthcare resource use in past 6 months (specific specialty visits): NASH vs. matched T2DM - multivariable results.

	Matcl		
	NASH n = 184	Matched T2DM n = 368	
	Adjusted mean (SE)	Adjusted mean (SE)	p value
General practitioner/Family practitioner visits	3.68 (0.36)	2.81 (0.19)	0.033
Specialists (any type) visits	7.13 (0.73)	5.01 (0.35)	0.008
Cardiologist visits	0.31 (0.07)	0.23 (0.04)	0.333
Gastroenterologist visits	0.28 (0.07)	0.08 (0.02)	0.001
Endocrinologist visits	0.27 (0.07)	0.09 (0.02)	0.004
Internist visits	0.26 (0.09)	0.23 (0.05)	0.740
Diabetologist visits	0.26 (0.05)	0.27 (0.04)	0.964
Psychiatrist visits	0.38 (0.11)	0.16 (0.04)	0.041
Hepatologist visits	0.09 (0.03)	0.00 (0.00)	<0.001

Note: *p* values represent significance of the regression coefficient in the regression model with matched T2DM population as reference group. Generalized linear models with negative binomial distribution and log-link were used for all outcomes reported in this table.

NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

of this patient population. There are currently no approved treatments for NASH other than lifestyle modification with diet and exercise, which is often ineffective.<sup>30–33</sup> As awareness about this disease grows and as treatment options continue to develop, it is impera-

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### **Conflict of interest**

Relevant conflicts of interest are outlined in 'Financial support'. Please refer to the accompanying ICMJE disclosure forms for further details.

#### **Authors' contributions**

Concept: All authors. Design: All authors. Data analysis: Nate Way, PhD. Data interpretation: All authors. Manuscript drafting: All authors. Manuscript edition and final approval: All authors.

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#### Supplementary data

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