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Symptom severity and health-related quality of life in patients with irritable bowel syndrome: The role of body mass index

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8 **Symptom severity and health-related quality of life in patients with irritable bowel**
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Abstract

Objective

The aim of this study was to explore the association between body mass index (BMI), symptom severity and health-related quality of life (QoL) in different subtypes of patients with irritable bowel syndrome (IBS).

Methods

A cross-sectional study was carried out in patients visiting our outpatient Functional Gastrointestinal Disorders specialty clinic. IBS diagnosis was made based on ROME III criteria. Abdominal pain and IBS symptom severity were investigated using the IBS severity score system (IBS-SSS). QoL was assessed using the Short-Form-36-Health-Survey (SF-36). This study was approved by the Ethics Committee of Heidelberg University (S-041/2014) and carried out in accordance with the Declaration of Helsinki.

Results

Excluding 113 patients who had missing Rome III data and 38 patients who had missing BMI data, a total of 325 patients with IBS were included. The most frequent IBS subtype was mixed IBS (IBS-M, 45.5%), followed by diarrhoea predominant IBS (IBS-D, 41.2%) and constipation predominant IBS (IBS-C, 10.8%). Overall, 54.2% of patients with IBS were in the normal weight range, 33.8% were overweight or obese, and 12.0% were underweight. The percentage of obese patients was highest in the IBS-D subgroup (20.1%, $p < 0.01$). With regard to the different BMI groups, there was no difference in IBS-SSS or abdominal pain. In the subgroup of obese patients, we found a correlation between BMI and impaired physical,

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3 but not mental, QoL. Interestingly, different pain distribution patterns were found for the
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5
6 different BMI groups.
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8 **Conclusion**

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10 Our findings add to the evidence that nutritional balance is disturbed in patients with IBS.
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12 Our findings emphasize that patients with IBS that are overweight or obese may have reduced
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14 physical quality of life.
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21 **Keywords:**

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23 Irritable bowel syndrome; Body mass index; Abdominal pain; Obesity; Symptom score or
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25 index
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31 **Strengths and limitations of this study:**

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34 **Strengths:** 1) Using a large patient cohort with a validated diagnosis of IBS based on the
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36 Rome III criteria;
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39 2) The findings add to the evidence that nutritional balance is disturbed in patients with IBS.
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42 **Limitations:** 1) The study was cross-sectional, therefore, it is impossible to infer causation;
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44 2) BMI was based on the self-reported height and weight of patients and computed without
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46 objective measurement, therefore bias may have been introduced.
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1 Introduction

Irritable bowel syndrome (IBS) is a chronic and common functional bowel disorder that is characterized by recurrent abdominal pain or discomfort associated with altered bowel habits [1]. According to the Rome criteria, IBS is classified into four subtypes [IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), mixed IBS (IBS-M) and un-subtyped IBS (IBS-U)] based on the predominant bowel habits [1]. The distribution of IBS subtypes differs in different studies and probably depends on the population investigated, geographic location and definition used for each subtype [2, 3]. Each of the subtypes of IBS are associated with different eating habits and IBS symptoms that have far-reaching consequences on patients' nutritional status as well as on their quality of life. However, nutritional status may also independently modulate IBS symptoms and patient quality of life. So far, however, very little attention has been paid to the role of nutritional status on health-related quality of life and symptom severity in patients with IBS.

Epidemiologic studies have shown that as many as 10-25% of adults in European countries are obese [body mass index (BMI) > 30 kg/m²] and that the incidence of obesity is increasing [4]. Additionally, a cross-sectional multicentre study found that more than 63% of outpatients and 80% of inpatients in gastroenterological centres suffered from significant changes in body composition [5]. However, although extensive research has been carried out on the prevalence of overweight and obesity in the general population and in connection with numerous diseases, to date, there is little published data on the prevalence and clinical relevance of nutritional status in patients with IBS. Locke *et al.* [6] found no association

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3 between IBS status and BMI. Thus far, there have been very few studies with a large enough
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5 sample size that compare differences between different IBS subtypes. In particular, little is
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7 known about the influence of BMI on quality of life in patients with IBS.
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11 It has been frequently reported that IBS leads to impaired quality of life [7-9]. An
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13 underweight (BMI < 18.5 kg/m²) or obese body condition (BMI > 30 kg/m²) have both been
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15 found to be associated with multiple abdominal symptoms leading to reduced quality of life
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17 [10, 11]. Abdominal pain, the major symptom of IBS, is considered to be the most important
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19 factor affecting patients' quality of life [12, 13]. In the latest Rome IV criteria, the outstanding
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21 role of pain in IBS has been fully emphasized [14], and experts highlight the significance of
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23 pain in IBS for diagnosis as well as therapy [15]. Researchers have found that pain sensitivity
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25 is an independent factor contributing to IBS symptoms [16]. However, data on differences
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27 between different IBS subtypes are sparse, and thus far, relatively little attention has been paid
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29 to the association of nutritional status with differences in pain location in different IBS
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31 subtypes.
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39 IBS is a heterogeneous disease and is often differentiated into different IBS subtypes in
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41 studies because of the different expected aetiologies, severity levels and levels of impairment
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43 [17]. Therefore, the aim of this study is to determine the effect of BMI on IBS symptom
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45 severity and quality of life for each subtype of IBS based on the Rome III criteria.
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52 **2 Methods**

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54 This cross-sectional survey included patients evaluated at the Functional Gastrointestinal
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3 Disorders (FGIDs) specialty clinic of the Department of General Internal Medicine and
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5 Psychosomatics of Heidelberg University Hospital, which is a tertiary care facility. All
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7 patients who completed our routine baseline documentation were enrolled. The routine data
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9 from individual health records was transferred into the database and pseudonymized. This
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11 study was approved by the Ethics Committee of Heidelberg University (S-041/2014) and
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13 carried out in accordance with the Declaration of Helsinki.
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21 **2.1 Patients recruitment**

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23 From 01/2011 to 12/2016, patients' clinical data were consecutively collected from our
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25 outpatient FGIDs clinic at Heidelberg University Hospital for this explorative and descriptive
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27 study. All patients ≥ 18 years of age were included, if they fulfilled the Rome III criteria for
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29 the diagnosis of IBS [1]. The subtype criteria for IBS were based on stool consistency as
30
31 the diagnosis of IBS [1]. The subtype criteria for IBS were based on stool consistency as
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33 assessed by the Bristol Stool Scale (BSS) and Rome III criteria [18]. Demographic data
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35 including gender, age, family status, level of education and residence, was also collected at
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37 baseline using the Psychosomatic Basis Documentation Questionnaire (Psy-BaDo) [19].
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44 **2.2 Measurement of IBS symptom severity and pain**

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46 Patients rated the severity of their IBS symptoms by completing the IBS severity score
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48 system (IBS-SSS) [20]. The IBS-SSS has a maximum score of 500 and comprises five items:
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50 frequency and intensity of abdominal pain, severity of abdominal distension, dissatisfaction
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52 with bowel habits, and interference of IBS with daily life. Based on validated cut-off values,
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3 three IBS severity subgroups can be distinguished: Mild (IBS-SSS: 75-175), Moderate
4 (IBS-SSS: 175-300) and Severe (IBS-SSS: > 300). This questionnaire can also be used to
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6 assess the intensity of abdominal pain, with scores ranging from 0 (“no pain”) to 100 (“worst
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8 pain”). The pain location (right upper abdomen, middle upper abdomen, left upper abdomen,
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10 middle navel, right lower abdomen, middle lower abdomen and left lower abdomen) and
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12 number of painful areas (ranging from 0 to 7) are also recorded. The German version of this
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14 questionnaire was validated by Betz et al. [21] and the total score was computed in
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16 accordance with the manual.
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26 **2.3 Measurement of BMI**

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28 In the context of self-reporting, BMI was calculated as the individual's body weight (kg)
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30 divided by the square of their height (m). BMI was categorized according to the World Health
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32 Organization (WHO) classification of physical status [22]: underweight (BMI < 18.5 kg/m²),
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34 normal weight (BMI 18.5–25 kg/m²), overweight (25–30 kg/m²), or obese (BMI > 30 kg/m²).
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42 **2.4 Measurement of quality of life**

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44 Quality of life was measured using the Short Form 36 Health Survey (SF-36) [23]. SF-36
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46 is a 36 item, patient-reported survey of patient health-related quality of life, which consists of
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48 a physical health index and mental health index. Each scale is directly transformed into a
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50 0-100 scale. Lower scores represent a higher degree of disability. The SF-36 is widely used
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52 and well validated for assessing generic health outcomes. Validation of the German version
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3 was performed by Morfeld *et al.* [24].
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8 **2.5 Statistical analysis**

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11 Routine data were transformed into an SPSS file and evaluated using the statistical
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13 program SPSS (IBM, version 22.0). Descriptive statistics are presented as the means and
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15 standard deviation for continuous variables and as absolute numbers and percentages for
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17 categorical variables. All analyses were explorative and not of a confirmatory nature. All
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19 primary and secondary variables were first tested for normal distribution. For normally
20
21 distributed variables, the mean and standard deviation (SD) were calculated. Variables that
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23 lacked a normal distribution were reported using the median and interquartile range. The
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25 Mann-Whitney U Test was used to assess the level of significance because not all the data
26
27 were normally distributed and a number of participants differed between the groups.
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34 Comparison of socio-demographical and anthropometric data according to BMI was
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36 performed using analysis of variance (ANOVA) and nonparametric tests in the first instance.
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38 Where significant group differences were detected based on ANOVA, post-hoc least significant
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40 difference tests were conducted to compare the study groups in a pairwise fashion. Associations
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42 with BMI were investigated using the WHO categories (normal weight as the reference group)
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44 and the continuous BMI variable. We also used the Pearson and Spearman correlation
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46 coefficients to investigate the linear association between demographics, clinical and
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48 psychological features.
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54 Because of the explorative nature of the study, we abstained from adjustment for
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multiple testing and interpreted *p* values cautiously as descriptive measures of effect. For dichotomous data the odds ratio (OR) was calculated and reported with a 95% confidence interval (CI). All tests were two-sided and statistical significance was accepted if $p < 0.05$.

3 Results

3.1 Characteristics of study sample

A total of 576 patients completed the questionnaire from 01/2011-12/2016. Excluding 113 patients who were missing Rome III data and 38 patients who were missing BMI data, eventually 325 patients with IBS were enrolled in this study (98 males, 227 females; mean BMI 23.91 ± 5.54 kg/m²). The demographic and baseline symptom profile of the patients with IBS among the different subtypes are summarized in Table 1. Of the included subjects, the most frequent IBS subtype was IBS-M (45.5%), followed by IBS-D (41.2%), and IBS-C (10.8%). Only 54.2% of patients with IBS were within the normal weight range, whereas 33.8% were overweight or obese, and only a minority were underweight (12.0%). Taking gender into account, 6.1% of males and 14.5% of females were underweight. Additionally, 8.2% of males and 14.5% of females were obese and 29.6% of males and 17.6% of females were overweight. Interestingly, this distribution pattern was similar between the different IBS groups. In particular there was no difference between the IBS-C and IBS-M groups. In the IBS-D group the percentage of obese patients reached 20.1%. There were no significant differences between the BMI groups with regard to pain symptoms, symptom severity or mental health, but the groups were significantly different with regard to physical health.

3.2 BMI and health-related quality of life in IBS subtypes

Two-way ANOVA analysis between subjects was conducted to compare the effect of BMI level on physical health in underweight, normal weight, overweight and obese conditions in each IBS subtype. There was a significant effect of BMI ($F = 4.38, p < 0.01$). However, there was no significant effect of IBS subtype ($F = 0.06, p = 0.945$). Post-hoc comparisons using the LSD test indicated that the mean score for obese patients ($M = 35.08, SD = 10.02$) was significantly different from patient with other BMIs ($p < 0.01$) with regard to physical health. However, the underweight patients ($M = 41.97, SD = 9.02$) did not significantly differ from the normal weight ($M = 40.97, SD = 8.86$) or overweight ($M = 42.05, SD = 9.17$) patients with regard physical health. As seen in Figure 1, obese patients with IBS had worse physical health than patients with other BMIs ($p < 0.05$). With regard to mental health, there was no significant relationship.

3.3 Correlations between demographics, clinical and psychological features

Pearson product-moment correlations (Table 2) indicated that BMI was negatively correlated with physical health (SF-36) ($r = -0.198, p < 0.01$). Abdominal pain (IBS-SSS item 1b) was positively correlated with symptom severity (IBS-SSS) ($r = 0.666, p < 0.01$) and number of pain locations with a range from 0 to 7 ($r = 0.117, p < 0.05$). Additionally, abdominal pain was negatively correlated with physical health ($r = -0.388, p < 0.01$) and mental health ($r = -0.252, p < 0.01$).

3.4 Characteristics of IBS subtypes pain location separated by BMI

As shown in Table 3 and Figure 2, compared with normal the BMI group, underweight patients with IBS-D had significantly worse pain in the right lower abdomen (OR 3.44; 95% CI, 1.19 to 9.94) and middle lower abdomen (OR 3.99; 95% CI, 1.28 to 12.43). Similarly, underweight patients with IBS-M had significantly worse pain in the middle lower abdomen (OR 3.33; 95% CI 1.05 to 10.60). Similar analyses were also conducted to compare the overweight BMI group and obese BMI group to the normal BMI group. Of note, there was a significant association between IBS-M and middle upper abdominal pain (OR 0.35; 95% CI, 0.13 to 0.94).

4 Discussion

The aim of this study was to determine the effect of BMI on the relationship between symptom severity and quality of life for each subtype of IBS based on the Rome III criteria. For this purpose, we used standardized questionnaires to confirm the diagnosis and to assess patient symptoms and quality of life.

The most important findings were that 54.2% of patients with were in the range of normal weight, while 33.8% were overweight or obese and while there was no difference in symptom severity or abdominal pain between the different BMI groups, obesity was associated with reduced quality of life and a significant negative correlation between BMI and physical health was found.

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4 Our data show that being overweight is a phenomenon in patients with IBS regardless of
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6 IBS subtype. These findings are in agreement with the results of a previous study based on
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8 obese patients in France, which found that 30.0% of obese patients had IBS [25]. We found
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10 that 54.2% of patients with IBS were in the normal weight range, which is consistent with
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12 previous results [26]. What is worth noting is that the overweight and obesity rate in the
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14 general adult population in Germany [27] is higher. According to the German Health Update
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16 (GEDA) [27], in 2012 the overweight rate of adults was 36.2% and the obese rate was 16.5%.
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18 The causal relationship between IBS and abnormal body weight are hard to elucidate.
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20 However, abnormal body weight has an undeniable influence in both patients with IBS and in
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22 the general population. Interestingly, the distribution of weight was similar between the
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24 different IBS groups. In particular, there was no difference between the IBS-C and IBS-M
25
26 groups. Notably, in the IBS-D group the percentage of obese patients reached 20.1%. Lee et al.
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28 [28] evaluated the relationship between visceral adipose tissue and the risk of IBS and
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30 suggested that IBS-D may be more common in obese patients. This study, however, was
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32 confined to patients from South Korea. Therefore, further research is needed to confirm high
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34 obesity rates in patients with IBS-D with metabolic disturbances of visceral fat.
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45 Though there was no significant difference in symptom severity or abdominal pain
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47 between the different BMI groups, these groups differed significantly with regard to quality of
48
49 life. The obese groups were characterized by reduced physical quality of life. This is an
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51 interesting but not completely new result which gives rise to the question of what mechanisms
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53 are responsible for this association. Obesity may lead to more physiological stress on organs.
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3 Richards et al. [29] found that obese patients, when compared to normal weight participants,
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Richards et al. [29] found that obese patients, when compared to normal weight participants, have more severe pain and their daily functions, such as work, study and social communications, are to a larger extent restricted. This suggests that differences in abdominal symptoms affect the quality of life of patients with IBD less than differences in BMI [30, 31].

Our data show an association between BMI and quality of life with regard to physical health. This similar to findings of previous studies [11], in that increasing BMI is associated with increased upper gastrointestinal symptoms, bloating, and diarrhoea. Our results suggest that higher BMI adversely affects patients' physical health in IBS. Of note, however, BMI has to exceed a certain threshold so that an effect can be seen. A BMI up to the limit of < 30 kg/m² did not significantly decrease the quality of life with regard to physical health in patients with IBS. An additional finding was that BMI had no effect on the quality of life with regard to mental health in patients with IBS, which requires further research. This finding is in agreement with a study by Mykletun [32], which suggested that BMI has no significant association with IBS with regard to anxiety and mood disorders. However, their study only evaluated female patients. Further study is needed in this area.

According to the Rome committee "pain" is one of the most critical diagnostic symptoms of IBS [33, 34]. Occasionally, we found that the pain location differed among IBS subtypes based on different BMI levels. To our knowledge, this finding has never been described previously. Previous studies have explored the association between obesity and IBS pain symptoms [12]. An additional finding of this study is that patients who are underweight also have specific pain characteristics. Compared with the normal BMI group, underweight

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3 patients in the IBS-D subgroup had significantly more pain in the right upper abdomen, right
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5 lower abdomen and middle lower abdomen. Similarly, underweight patients in the IBS-M
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7 subgroup had significantly worse pain in the left lower abdomen and middle lower abdomen.
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9 Severe pain in these areas may be associated with increased pressure in the colon and rectum
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11 [35] and visceral hypersensitivity [36]. Underweight patients may suffer a more severe degree
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13 of pain. Stanghellini et al. [37] reported delayed gastric emptying and functional dyspepsia
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15 women with lower body weight. Delays in gastric emptying may lead to longer small intestine
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17 and colon transit [38], causing more severe gastrointestinal pain in related areas. However, no
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19 final conclusion has been drawn with regard to this matter and more research is needed.
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26 There are two main limitations of this study. The study was cross-sectional, therefore, it
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28 is impossible to infer causation. BMI was based on the self-reported height and weight of
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30 patients and computed without objective measurement, therefore bias may have been
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32 introduced. Patients may occasionally underreport or overreport their weight and height
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34 leading to an underestimation of underweight or obese patients. However, in the
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36 Nutrinet-Santé study, researchers reported that deviations in self-reported BMIs from
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38 questionnaires can be ignored because their results confirmed the validity and agreement of
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40 self-reported data with measured data [39, 40].
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47 The strengths of this study are the use of a large patient cohort with a validated diagnosis
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49 of IBS based on the Rome III criteria. The findings from this study suggest that clinical
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51 doctors should pay special attention to abnormal weight in patients with IBS because this may
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53 be an indicator of a poorer quality of life with regard to physical health. Our findings add to
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3 the evidence that nutritional balance is disturbed in patients with IBS. They emphasize that
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6 overweight and obesity are relevant factors in IBS, which may have a more selective
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8 influence on quality of life with regard to physical health.
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18 from any funding agency in the public, commercial or not-for-profit sectors.
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25
26 The authors have indicated no financial conflicts of interest.
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29 Yuanjun Dong, Jonas Tesarz, Rainer Schäefert and Wolfgang Eich designed the study and
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31 wrote the protocol.
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34 Yuanjun Dong, Sabrina Berens and Jonas Tesarz performed the literature searches and
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36 analyses.
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39 Yuanjun Dong wrote the first draft of the manuscript.
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42 All of the authors contributed to and have approved the final manuscript.
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Table and Figure Legends

Table 1. Distribution of demographic variables by BMI categories in IBS patients

a Comparison by two-tailed Fisher's exact test;

b Comparison among the four groups of BMI by one-way ANOVA.

* $p < 0.05$,

** $p < 0.05$ for post-hoc comparison between BMI < 18.5, BMI 25-30 or BMI > 30 and BMI 18.5-25.

$p < 0.05$ for post-hoc comparison between BMI < 18.5 and BMI > 30.

§ $p < 0.01$ for post-hoc comparison between BMI < 18.5, BMI 18.5-25 or BMI 25-30 and BMI > 30.

△ IBS-SSS: Mild (IBS-SSS: 75-175), Moderate (IBS-SSS: 175-300) and Severe (IBS-SSS: > 300).

☆ IBS-SSS: range from 0 ("no pain") to 100 ("worst pain").

† SF-36: range from 0 ("highest disability") to 100 ("no disability").

IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass index;

Table 2. Correlation Matrix for the Study Variables in IBS patients

BMI, Body mass index;

* $p < 0.05$; ** $p < 0.01$

Table 3. Association of pain locations with being underweight, overweight and obese based on BMI versus those of normal weight (Effective N=325)

IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass index; OR, odds ratio; 95%CI, 95% confidence interval

Figure 1. Estimated marginal means of physical health and mental health in each IBS subtype.

Figure 2. Significantly different pain locations in IBS subtypes separated by BMI compared with normal weight

IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass index

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Tables

Table 1. Distribution of demographic variables by BMI categories in IBS patients

	Total	BMI								<i>p</i> value ^a
		< 18.5 kg/m ²		18.5-25 kg/m ²		25-30 kg/m ²		> 30 kg/m ²		
	Effective N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]		
N	325 (100.0)	39 (12.0)**	176 (54.2)	69 (21.2)**	41 (12.6)**				< 0.01	
Gender										
Male	98 (30.2)	6 (6.1)	55 (56.1)	29 (29.6)	8 (8.2)				0.012	
Female	227 (69.8)	33 (14.5)	121 (53.3)	40 (17.6)	33 (14.5)					
Age	38.87 [15.68]	34.92 [15.57] [#]	37.25 [15.41]	43.55 [15.67]**	41.88 [15.15]				0.007 ^b	
Family status										
Single	149 (46.3)	23 (15.4)	89 (59.7)	27 (18.1)	10 (6.7)				0.011	
Married or unmarried cohabitation	140 (43.5)	10 (7.1)	68 (48.6)	37 (26.4)	25 (17.9)					
Divorced or widowed	33 (10.2)	5 (15.2)	18 (54.5)	5 (15.2)	5 (15.2)					
Education status										
Below highschool	91 (30.7)	9 (9.9)	50 (54.9)	16 (17.6)	16 (17.6)				0.35	
Above highschool	205 (69.3)	25 (12.2)	111 (54.1)	47 (22.9)	22 (10.7)					
IBS subtypes										
IBS-C	35 (10.8)	5 (14.3)	19 (54.3)	9 (25.7)	2 (5.7)				0.057	
IBS-D	134 (41.2)	19 (14.2)	63 (47.0)	25 (18.7)	27 (20.1)					
IBS-M	148 (45.5)	15 (10.1)	88 (59.5)	34 (23.0)	11 (7.4)					
IBS-U	8 (2.5)	0 (0.0)	6 (75.0)	1 (12.5)	1 (12.5)					
Symptom severity [△]	291.99 [84.79]	277.76 [72.53]	292.96 [86.45]	291.46 [85.82]	299.21 [84.71]				0.739 ^b	
Abdomen pain [*]	40.57 [9.30]	44.51 [23.26]	46.74 [25.66]	47.56 [30.19]	50.49 [26.54]				0.814 ^b	

Quality of life [†]							
Physical health	40.57 [9.30]	41.97 [9.02] [§]	40.97 [8.86] [§]	42.05 [9.17] [§]	35.08 [10.02]	0.001 ^b	
Mental health	39.22 [12.69]	36.66 [12.35]	39.63 [13.00]	39.92 [11.96]	38.79 [13.05]	0.613 ^b	

Table 2. Correlation Matrix for the Study Variables in IBS patients

		BMI	Gender	Education	Number of Pain Symptom location	Pain Symptom severity	Abdominal pain	Physical Health	Mental health
Pearson Correlation	BMI	1.000							
	Gender	-0.050	1.000						
	Education	-0.080	-0.108	1.000					
	Number of Pain location	-0.083	0.087	0.121*	1.000				
	Symptom severity	0.065	0.059	-0.048	0.094	1.000			
	Abdominal pain	0.034	0.046	-0.011	0.117*	0.666**	1.000		
	Physical Health	-0.198**	-0.070	0.204**	-0.044	-0.394**	-0.388**	1.000	
	Mental health	0.037	-0.022	-0.040	-0.045	-0.303**	-0.252**	0.046	1.000

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Table 3. Association of pain locations with being underweight, overweight and obese based on BMI versus those of normal weight (Effective N=325)

IBS subtypes	Pain location	BMI < 18.5 kg/m ²				BMI 25-30 kg/m ²				BMI > 30 kg/m ²			
		OR value	95% CI		P value	OR value	95% CI		P value	OR value	95% CI		P value
			Lower	Upper			Lower	Upper			Lower	Upper	
IBS-C	right upper abdomen	2.50	0.306	20.453	0.393	0.469	0.045	4.931	0.528	No cases			
	middle upper abdomen	0.429	0.04	4.637	0.486	0.49	0.079	3.045	0.444	No cases			
	left upper abdomen	0.700	0.062	7.853	0.772	2.240	0.424	11.837	0.342	No cases			
	middle navel	No cases				5.143	0.4	66.148	0.209	18.00	0.585	553.586	0.098
	right lower abdomen	0.225	0.021	2.405	0.217	0.450	0.086	2.350	0.344	0.900	0.049	16.594	0.944
	middle lower abdomen	No cases				1.4	0.25	7.83	0.702	2.800	0.146	53.706	0.495
	left lower abdomen	0.225	0.021	2.405	0.217	0.720	0.146	3.544	0.686	0.900	0.049	16.594	0.944
IBS-D	right upper abdomen	2.479	0.805	7.632	0.114	1.653	0.564	4.847	0.360	0.739	0.215	2.539	0.631
	middle upper abdomen	1.167	0.4	3.399	0.778	1.333	0.512	3.47	0.555	0.571	0.2	1.629	0.295
	left upper abdomen	1.518	0.458	5.036	0.495	1.342	0.441	4.083	0.604	1.214	0.403	3.662	0.730
	middle navel	1.049	0.326	3.374	0.936	1.382	0.502	3.81	0.531	1.028	0.367	2.882	0.958
	right lower abdomen	3.437	1.188	9.943	0.023	0.972	0.347	2.723	0.957	0.875	0.316	2.426	0.797
	middle lower abdomen	3.985	1.277	12.43	0.017	0.67	0.252	1.782	0.422	0.837	0.331	2.118	0.707
	left lower abdomen	0.984	0.328	2.741	0.921	0.914	0.349	2.392	0.855	0.813	0.315	2.097	0.668
IBS-M	right upper abdomen	1.500	0.462	4.867	0.500	0.633	0.232	1.731	0.373	0.657	0.132	3.274	0.608
	middle upper abdomen	1.905	0.633	5.736	0.252	0.351	0.131	0.936	0.037	1.964	0.555	6.946	0.295
	left upper abdomen	1.778	0.572	5.528	0.320	1.432	0.614	3.337	0.406	1.500	0.403	5.589	0.546
	middle navel	1.590	0.514	4.921	0.421	1.535	0.667	3.532	0.313	1.417	0.381	5.27	0.603
	right lower abdomen	1.731	0.576	5.202	0.329	0.619	0.264	1.453	0.271	0.849	0.231	3.118	0.805
	middle lower abdomen	3.333	1.048	10.601	0.041	0.589	0.245	1.415	0.237	0.935	0.254	3.44	0.92
	left lower abdomen	2.167	0.709	6.621	0.175	1.118	0.502	2.490	0.784	1.181	0.334	4.167	0.796

Figures:

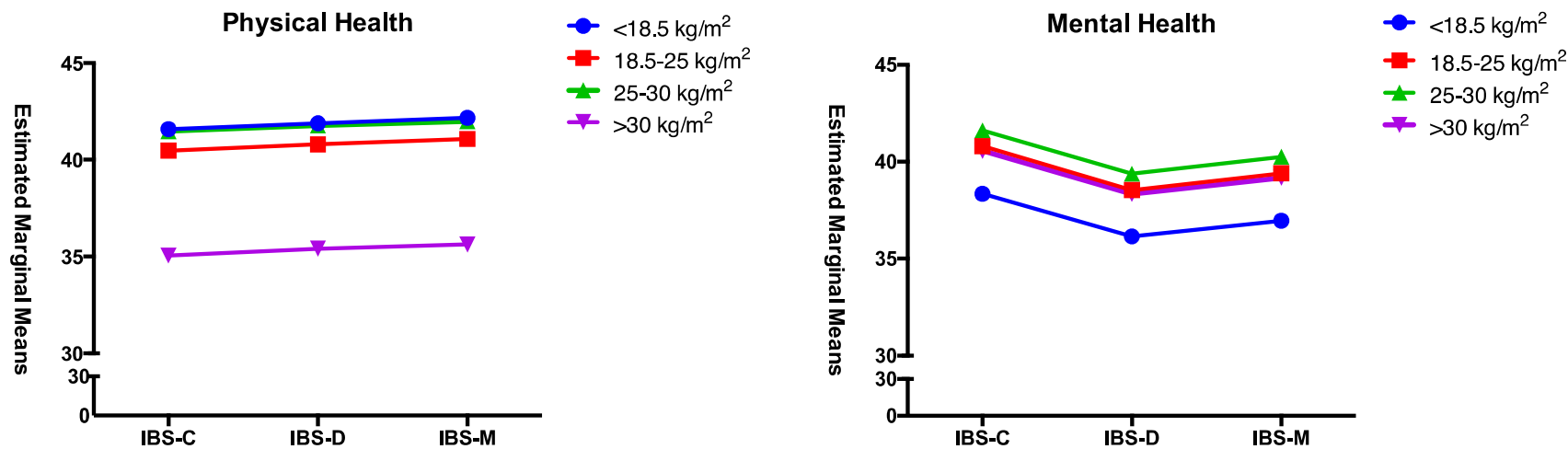


Figure 1. Estimated marginal means of physical health and mental health in each IBS subtype.

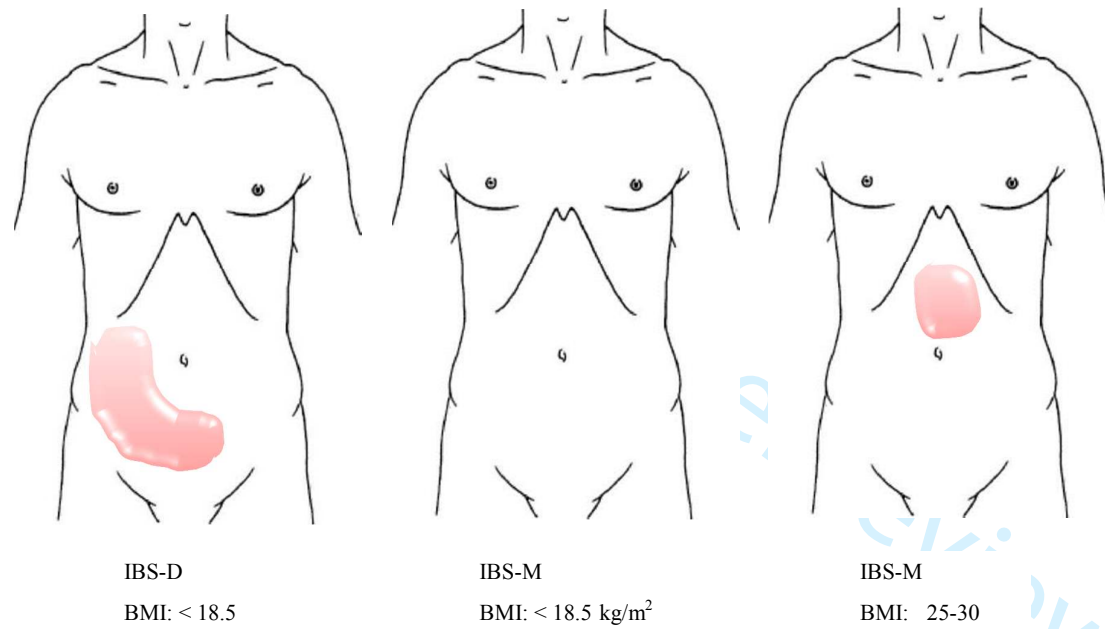


Figure 2. Significantly different pain locations in IBS subtypes separated by BMI compared with normal

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract 【Page 1】 (b) Provide in the abstract an informative and balanced summary of what was done and what was found 【Pages 2 - 3】
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 【Pages 4 - 5】
Objectives	3	State specific objectives, including any prespecified hypotheses 【Pages 4 - 5】
Methods		
Study design	4	Present key elements of study design early in the paper 【Pages 5 - 6】
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 【Page 6 - 7】
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants 【Page 6】
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 【Pages 6 - 7】
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 【Pages 6 - 7】
Bias	9	Describe any efforts to address potential sources of bias 【Page 6】
Study size	10	Explain how the study size was arrived at 【Page 6】
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 【Pages 6 - 7】
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding 【Pages 8 - 9】 (b) Describe any methods used to examine subgroups and interactions 【Page 8】 (c) Explain how missing data were addressed 【Page 8】 (d) If applicable, describe analytical methods taking account of sampling strategy 【N/A】 (e) Describe any sensitivity analyses 【N/A】
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 【Page 9; table 1】 (b) Give reasons for non-participation at each stage 【N/A】 (c) Consider use of a flow diagram 【Page 9】
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 【Pages 9 - 11】 (b) Indicate number of participants with missing data for each variable of interest 【Page 9; table 1】
Outcome data	15*	Report numbers of outcome events or summary measures 【Pages 9 - 11】
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 【Pages 9 - 11; table 3】

		(b) Report category boundaries when continuous variables were categorized 【N/A】
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period 【N/A】
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 【Pages 9 – 11; figures 1 -2; tables 2 - 3】
Discussion		
Key results	18	Summarise key results with reference to study objectives 【Page 11】
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 【Page 14】
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 【Pages 11 - 15】
Generalisability	21	Discuss the generalisability (external validity) of the study results 【Pages 12 - 15】
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 【Page 1 and Page 15】

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Symptom severity and health-related quality of life in patients with irritable bowel syndrome: The role of body mass index

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Secondary Subject Heading:	Nutrition and metabolism, Mental health
Keywords:	Irritable bowel syndrome, Abdominal pain, Obesity, Symptom score or index, Body mass index

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43
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Abstract

Objective

The aim of this study was to explore the association between body mass index (BMI), symptom severity and health-related quality of life (QoL) in different subtypes of patients with irritable bowel syndrome (IBS).

Methods

A cross-sectional study was carried out in patients visiting our outpatient Functional Gastrointestinal Disorders specialty clinic. IBS diagnosis was made based on ROME III criteria. Abdominal pain and IBS symptom severity were investigated using the IBS severity score system (IBS-SSS). QoL was assessed using the Short-Form-36-Health-Survey (SF-36).

Results

325 patients (227 females) who fulfilled ROME III criteria and provided complete BMI data ($23.91 \pm 5.54 \text{ kg/m}^2$) were included. The most frequent IBS subtype was mixed IBS (IBS-M, 45.5%), followed by diarrhoea predominant IBS (IBS-D, 41.2%) and constipation predominant IBS (IBS-C, 10.8%). Overall, 54.2% of patients with IBS were in the normal weight range, 33.8% were overweight or obese, and 12.0% were underweight. The percentage of obese patients was highest in the IBS-D subgroup (20.1%, $p < 0.01$). Both physical and mental health decreased significantly with the severity of symptom (all $p < 0.01$). However, the relationship between symptom severity and mental health was affected by age, family status, IBS subtypes and BMI. The significantly negative dose response between symptom severity and physical health in each BMI group was found ($p < 0.05$ or $p < 0.01$). There were

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3 no significant correlations between symptom severity and mental health in the <18.5, 25-30
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6 and > 30 BMI groups (all $p > 0.05$).
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8 **Conclusion**

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11 Being overweight is a phenomenon in patients with IBS regardless of IBS subtype. The
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13 association between physical health and symptom severity followed a dose response pattern.
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15 The relationship between mental health and symptom severity seems to be affected by age,
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17 family status, IBS subtypes and BMI.
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24 **Keywords:**

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26 Irritable bowel syndrome; Abdominal pain; Obesity; Symptom score or index
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4 **Strengths and limitations of this study:**
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6 **Strengths:** 1) Using a large patient cohort with a validated diagnosis of IBS based on the
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8 Rome III criteria;
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11 2) Compared with physical health, mental health was more susceptible to age, family status,
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13 IBS subtypes and BMI;
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16 3) Mental health was consistently poor in non-normal BMI groups, regardless of the
17
18 respective symptom severity.
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21 **Limitations:** 1) The study was cross-sectional, therefore it is not possible to infer causation;
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24 2) BMI assessment was based on patient self-reported and computed without objective
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26 measurement;
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29 3) BMI cannot fully reflect the impact of the factors of fatty mass, dietary habit, other lifestyle
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31 factors such as physical exercise on IBS.
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1 Introduction

Irritable bowel syndrome (IBS) is a chronic and common functional bowel disorder that is characterized by recurrent abdominal pain or discomfort associated with altered bowel habits [1]. According to the Rome criteria, IBS is classified into four subtypes [IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), mixed IBS (IBS-M) and un-subtyped IBS (IBS-U)] based on the predominant abdominal symptomatology [1]. The distribution of IBS subtypes differs in different studies and depends on the population investigated, geographic location and definitions used for subtype classification [2, 3]. The symptom severities of IBS are associated with different eating habits [4, 5] and IBS symptoms that have far-reaching consequences on patients' nutritional status as well as on their quality of life [6]. This has far-reaching consequences on patients' nutritional status and on their quality of life (QoL).

It has been frequently reported that IBS leads to impaired QoL [7-9]. However, nutritional status may also independently modulate IBS symptoms and patients' quality of life. So far, however, very little attention has been paid to the role of nutritional status on health-related quality of life and symptom severity in patients with IBS.

Epidemiologic studies have shown that as many as 16.5% of adults in European countries are obese [body mass index (BMI) > 30 kg/m²] [10] and that the incidence of obesity is increasing [11]. Additionally, a cross-sectional multicentre study found that more than 63% of outpatients and 80% of inpatients in gastroenterological centres suffered from significant changes in body composition [12]. And also the other way round: Underweight (BMI < 18.5 kg/m²) or obese body condition (BMI > 30 kg/m²) are both associated with

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3 multiple abdominal symptoms leading to reduced QoL [13, 14]. However, although extensive
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6 research has been carried out on the prevalence of obesity in the general population and in
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9 connection with numerous diseases, there is only little published data on the prevalence and
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12 clinical relevance of nutritional status in patients with IBS. Locke *et al.* [15] found no
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15 association between IBS status and BMI. Although extensive research has been carried out on
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18 the prevalence of obesity in the general population and in connection with numerous diseases,
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21 data on the prevalence and clinical relevance of nutritional status in patients with IBS are
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24 sparse. Studies with a large enough sample size and specifying between the different IBS
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27 subtypes are missing so far. In particular, little is known about the influence of BMI on
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30 quality of life in patients with IBS.

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33 Taken together, IBS is a heterogeneous disease and can be differentiated into different
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36 IBS subtypes because of the different expected aetiologies, severity levels and levels of
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39 impairment [16]. Therefore, the aim of this study is to determine the effect of BMI on IBS
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42 symptom severity and quality of life for each subtype of IBS based on the Rome III criteria.
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2 Methods

This cross-sectional survey included patients evaluated at the Functional Gastrointestinal Disorders (FGIDs) specialty clinic of the Department of General Internal Medicine and Psychosomatics of Heidelberg University Hospital, which is a tertiary care facility. All patients who completed our routine baseline documentation were enrolled. The routine data

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3 from individual health records was transferred into the database and pseudonymized. This
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6 study was approved by the Ethics Committee of Heidelberg University (S-041/2014) and
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8 carried out in accordance with the Declaration of Helsinki.
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10 11 12 13 **2.1 Patients recruitment**

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16 From 01/2011 to 12/2016, patients' clinical data were consecutively collected from our
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18 outpatient FGIDs clinic at Heidelberg University Hospital for this explorative and descriptive
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20 study. All patients ≥ 18 years of age were included, if they fulfilled the Rome III criteria for
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22 the diagnosis of IBS [1]. The subtype criteria for IBS were based on stool consistency as
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24 assessed by the Bristol Stool Scale (BSS) and Rome III criteria [17]. Demographic data
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26 including gender, age, family status, level of education and residence, was also collected at
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28 baseline using the Psychosomatic Basis Documentation Questionnaire (Psy-BaDo) [18].
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37 **2.2 Measurement of IBS symptom severity and pain**

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39 Patients rated the severity of their IBS symptoms by completing the IBS severity score
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41 system (IBS-SSS) [19]. The IBS-SSS has a maximum score of 500 and comprises five items:
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43 frequency and intensity of abdominal pain, severity of abdominal distension, dissatisfaction
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45 with bowel habits, and interference of IBS with daily life. Based on validated cut-off values,
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47 three IBS severity subgroups can be distinguished: Mild (IBS-SSS: 75-175), Moderate
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49 (IBS-SSS: 175-300) and Severe (IBS-SSS: > 300). The German version of this questionnaire
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3 was validated by Betz et al. [20] and the total score was computed in accordance with the
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6 manual.
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10 11 **2.3 Measurement of BMI**

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13 In the context of self-reporting, BMI was calculated as the individual's body weight (kg)
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15 divided by the square of their height (m). BMI was categorized according to the World Health
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17 Organization (WHO) classification of physical status [21]: underweight (BMI < 18.5 kg/m²),
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19 normal weight (BMI 18.5–25 kg/m²), overweight (25–30 kg/m²), or obese (BMI > 30 kg/m²).
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26 27 **2.4 Measurement of quality of life**

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29 Quality of life was measured using the Short Form 36 Health Survey (SF-36) [22]. SF-36
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31 is a 36-item, patient-reported survey of patient health-related quality of life, which consists of
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33 a physical health index and mental health index. Each scale is directly transformed into a
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35 0-100 scale. Lower scores represent a higher degree of disability. The SF-36 is widely used
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37 and well validated for assessing generic health outcomes. Validation of the German version
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39 was performed by Morfeld *et al.* [23].
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47 48 **2.5 Statistical analysis**

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50 Routine data were transformed into an SPSS file and evaluated using the statistical
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52 program SPSS (IBM, version 22.0). Descriptive statistics are presented as the means and
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54 standard deviation (*SD*) for continuous variables and as absolute numbers and percentages for
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3 categorical variables. All analyses were explorative and not of a confirmatory nature. All
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5 primary and secondary variables were first tested for normal distribution. For normally
6
7 distributed variables, the mean and standard deviation were calculated. Variables that lacked a
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9 normal distribution were reported using the median and interquartile range. The
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11 Mann-Whitney U Test was used to assess the level of significance because a number of
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13 participants differed between the groups. Comparison of socio-demographical and
14
15 anthropometric data according to BMI was performed using analysis of variance (ANOVA)
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17 and nonparametric tests in the first instance. Where significant group differences were detected
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19 based on ANOVA, post-hoc least significant difference tests were conducted to compare the
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21 study groups in a pairwise fashion. Associations with BMI were investigated using the WHO
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23 categories (normal weight as the reference group) and the continuous BMI variable. We also
24
25 used the Pearson and Spearman correlation coefficients to investigate the linear association
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27 between demographics, clinical and psychological features. Hierarchical multiple regression
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29 analysis was used to help understand the impact of potential confounders. All tests were
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31 two-sided and statistical significance was accepted if $p < 0.05$.
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47 **3 Results**

48 **3.1 Characteristics of study sample**

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50 A total of 576 patients completed the questionnaire. Excluding 113 patients whose Rome
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52 III criteria data were partly missing and 38 patients whose BMI data were missing, eventually
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3 325 patients with IBS were enrolled in this study (98 males, 227 females; mean BMI $23.91 \pm$
4 5.54 kg/m^2). The demographic and baseline characteristics of the patients with IBS among the
5
6 different subtypes are summarized in Table 1. Of the included subjects, the most frequent IBS
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8 subtype was IBS-M (45.5%), followed by IBS-D (41.2%), and IBS-C (10.8%). Only 54.2%
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10 of patients with IBS were within the normal weight range, whereas 33.8% were overweight or
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12 obese, and only a minority were underweight (12.0%). Taking gender into account, 6.1% of
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14 males and 14.5% of females were underweight. Additionally, 8.2% of males and 14.5% of
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16 females were obese and 29.6% of males and 17.6% of females were overweight. Interestingly,
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18 this distribution pattern was similar between the different IBS groups. In particular, there was
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20 no difference between the IBS-C and IBS-M groups. In the IBS-D group the percentage of
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22 obese patients reached 20.1%. There were no significant differences between the BMI groups
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24 with regard to symptom severity or mental health, but the groups were significantly different
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26 with regard to physical health.
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39 **3.2 BMI and health-related quality of life in IBS subtypes**

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41 Two-way ANOVA analysis between subjects was conducted to compare the effect of
42
43 BMI level on physical health in underweight, normal weight, overweight and obese
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45 conditions in each IBS subtype. There was a significant effect of BMI ($F = 4.38, p < 0.01$).
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47 However, there was no significant effect of IBS subtype ($F = 0.06, p = 0.945$). Post-hoc
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49 comparisons using the LSD test indicated that the mean score for obese patients ($M = 35.08,$
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51 $SD = 10.02$) was significantly different from patient with other BMIs ($p < 0.01$) with regard to
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3 physical health. However, the underweight patients ($M = 41.97$, $SD = 9.02$) did not
4 significantly differ from the normal weight ($M = 40.97$, $SD = 8.86$) or overweight ($M = 42.05$,
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6 $SD = 9.17$) patients with regard physical health. As seen in Figure 1, obese patients with IBS
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8 had worse physical health than patients with other BMIs ($p < 0.05$). With regard to mental
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10 health, there was no significant relationship.
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16 17 18 19 **3.3 Correlations between demographics, clinical and psychological features**

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21 Pearson product-moment correlations (Table 2) indicated that BMI was negatively
22 correlated with physical health (SF-36) ($r = -0.198$, $p < 0.01$). Education was positively
23 correlated with physical health (SF-36) ($r = 0.204$, $p < 0.01$). Additionally, symptom severity
24 correlated with physical health (SF-36) ($r = 0.204$, $p < 0.01$). Additionally, symptom severity
25 (IBS-SSS) was negatively correlated with physical health ($r = -0.394$, $p < 0.01$) and mental
26 health ($r = -0.303$, $p < 0.01$).
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34 35 36 37 **3.4 Hierarchical multiple regression analysis of physical and mental health across** 38 39 **categories of symptom severity**

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41 We divided the severity of symptom into three groups (mild, moderate and severe). As
42 shown in Table 3 and Table 4, significantly positive correlations between symptom severity
43 and physical and mental health (all $p < 0.01$) were found. Hierarchical multiple regression
44 analysis was used to stratify gender, age, family status, education status, IBS subtypes, and
45 BMI. We found that as the symptom severity increased, physical health was observed in each
46 hierarchy to be significantly different (all $p < 0.05$). However, mental health only had
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3 significant difference in the analysis by gender and education status (both $p < 0.05$). There
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6 were no significant differences of mental health in the hierarchical multiple regression
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8 analysis by age, family status, IBS subtypes and BMI.
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10 11 12 13 **3.5 The influence of symptom severity on physical and mental health in each BMI group**

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16 As shown in Table 1, the physical health of IBS patients in different BMI groups had
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18 significant difference ($p = 0.001$). However, there was no significant difference in mental
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20 health ($p = 0.613$). As shown in Figure 2, the significantly negative dose response between
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22 symptom severity and physical health in each BMI group was found ($p < 0.05$ or $p < 0.01$).
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24 The influence of symptom severity on mental health had significant difference ($p < 0.01$) only
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26 within the normal BMI group (BMI 18.5-25). In the other three BMI groups (BMI <18.5,
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28 25-30 and > 30), there were no significant correlations between symptom severity and mental
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30 health.
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42 **4 Discussion**

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44 The aim of this study was to determine the effect of BMI on the relationship between
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46 symptom severity and quality of life for IBS based on the Rome III criteria. For this purpose,
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48 we used standardized questionnaires and medical records to confirm the diagnosis and to
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50 assess patient symptoms and quality of life.
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4 Our data show that being overweight is a common phenomenon in patients with IBS
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6 regardless of IBS subtype. These findings are in agreement with the results of a previous
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8 study based on obese patients in France, which found that 30.0% of obese patients had IBS
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10 [24]. We found that 54.2% of patients with IBS were in the normal weight range, which is
11
12 consistent with previous results [25]. What is worth noting is that, the overweight and obesity
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14 rates in the general adult population in Germany [10] are higher than those found in our IBS
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16 cohort. According to the German Health Update (GEDA) [10], in 2012 the overweight rate of
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18 adults was 36.2% and the obese rate was 16.5%. The causal relationship between IBS and
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20 abnormal body weight are hard to elucidate. However, abnormal body weight has an
21
22 undeniable influence in both patients with IBS and in the general population. Interestingly,
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24 the distribution of weight was similar between the different IBS groups. In particular, there
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26 was no difference between the IBS-C and IBS-M groups. Notably, in the IBS-D group the
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28 percentage of obese patients reached 20.1%. Lee et al. [26] evaluated the relationship between
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30 visceral adipose tissue and the risk of IBS and suggested that disturbances of visceral fat may
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32 be more common in IBS-D patients. In addition, another Korean study found increased
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34 intestinal permeability in IBS-D patients [27]. One possible explanation is that the increase in
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36 visceral fat leads to an increase in intestinal osmolality [28] and then leads to the chronic
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38 diarrhea. These studies, however, were confined to patients from South Korea. Therefore,
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40 further research is needed to these findings.
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52 Our data show an association between symptom severity and QoL with regard to
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54 physical and mental health. By the hierarchical multiple regression analysis, we found that in
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3 each hierarchy (gender, age, family status, education status, IBS subtypes and BMI), the
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6 significantly negative correlations between symptom severity and physical health were found.
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9 However, significant difference only existed by the hierarchy of gender and education status
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11 in mental health. The relationship between physical health and symptom severity was not
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13 affected by the confounders above. What's more, the relationship between mental health and
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15 symptom severity seems to be more likely affected by age, family status, IBS subtypes and
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17 BMI. This finding is in agreement with a study by Mykletun [29], which suggested that BMI
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19 had significant association with IBS with regard to anxiety and mood disorders. However,
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21 their study evaluated only female patients.
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27 Though there was no significant difference in symptom severity between the different
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29 BMI groups, these groups differed significantly with regard to QoL. Whereas our data suggest
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31 that there is a kind of dose response relationship of symptom severity with physical health in
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33 all BMI groups and with mental health in the normal BMI group. In non-normal BMI groups
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35 (BMI <18.5, 25-30 and > 30), the impact of the symptom severity on mental health was not
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37 significantly different, i.e. mental health was always poor in non-normal BMI groups,
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39 regardless of the severity of the symptom. IBS has a significant impact on patients' QoL [30].
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42 We partly agree with the study of Amouretti et al. [31], which found that the IBS patients who
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44 reported their symptoms as severe or very severe had a very poor QoL compared with those
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46 who reported their symptoms as moderate. Their study did not distinguish between physical
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48 and mental health and did not consider the effects of confounding factors such as BMI. This is
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3 an interesting but not completely new result which gives rise to the question of what
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5 mechanisms are responsible for this association.
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8 Our results suggest that higher BMI adversely affects patients' physical health in IBS.
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10 The obese groups were characterized by reduced physical quality of life. This is in line with
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12 previous studies [14], in that increasing BMI is associated with increased upper
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14 gastrointestinal symptoms, bloating, and diarrhoea. Obesity may lead to more physiological
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16 stress on organs. Richards et al. [32] reported that obese patients have more severe pain and
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18 are to a larger extent restricted in their daily functioning compared to patients of normal
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20 weight. An additional finding of our study was that a low level of BMI (BMI < 18.5) also had
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22 negative effect on the QoL in patients with IBS indicating an U-shaped relationship between
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24 BMI and quality of life. This might suggest that differences in symptom severity affect the
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26 quality of life of patients with IBS less than differences in BMI [33, 34].
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34 Several limitations of this study must be taken into account. Firstly, the study was
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36 cross-sectional, therefore, it is impossible to infer causation. Secondly, BMI was based on the
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38 self-reported height and weight of patients and computed without objective measurement,
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40 therefore bias may have been introduced. Patients may occasionally underreport or overreport
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42 their weight and height leading to an underestimation of underweight or obese patients.
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44 However, in the Nutrinet-Santé study, researchers reported that deviations in self-reported
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46 BMIs from questionnaires can be ignored because their results confirmed the validity and
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48 agreement of self-reported data with measured data [35, 36]. The choice of SF-36 as the only
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50 QoL tool may partly miss the relationship between symptom severity and QoL. Moreover,
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3 BMI is associated with a multitude of different factors, such as genetics, fatty mass, dietary
4 habit or physical exercise. Thus, BMI cannot fully reflect the impact of those factors on IBS
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6 in more details and more research is needed. The strengths of this study, however are the use
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8 of a large patient cohort with a validated diagnosis of IBS based on the Rome III criteria.
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13 To conclude, being overweight is a common phenomenon in IBS patients regardless of
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15 IBS subtypes. Our data further suggest that overweight and obesity may have a relevant
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17 influence on quality of life. The findings of this study have some implications for future
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19 practice. If there is a crucial relationship between physical health and BMI in IBS patients,
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21 clinical doctors should pay special attention to abnormal weight in IBS patients as this may be
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23 an indicator of a poorer quality of life, especially with regard to the physical health.
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44 **Conflict of interest:**

45
46 The authors have indicated no financial conflicts of interest.

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48
49 Yuanjun Dong, Jonas Tesarz, Rainer Schaefer and Wolfgang Eich designed the study and
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51 wrote the protocol.
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3 Yuanjun Dong, Sabrina Berens and Jonas Tesarz performed the literature searches and
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6 analyses.

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8 Yuanjun Dong wrote the first draft of the manuscript.

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11 All of the authors contributed to and have approved the final manuscript.
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19 **Data sharing statements:** No additional data are available.
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Table and Figure Legends

Table 1. Distribution of demographic variables by BMI categories in IBS patients

a Comparison by two-tailed Fisher's exact test;

b Comparison among the four groups of BMI by one-way ANOVA.

* $p < 0.05$,

** $p < 0.05$ for post-hoc comparison between BMI<18.5, BMI 25-30 or BMI >30 and BMI 18.5-25.

$p < 0.05$ for post-hoc comparison between BMI<18.5 and BMI >30.

§ $p < 0.01$ for post-hoc comparison between BMI<18.5, BMI 18.5-25 or BMI 25-30 and BMI >30.

△ IBS-SSS: Mild (IBS-SSS: 75-175), Moderate (IBS-SSS: 175-300) and Severe (IBS-SSS: > 300).

† SF-36: range from 0 ("highest disability") to 100 ("no disability").

IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass index;

Table 2. Correlation Matrix for the Study Variables in IBS patients

* $p < 0.01$; BMI, Body mass index;

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6 **Table 3. Geometric mean values for physical health across categories of IBS-SSS level, by**
7
8 **gender, age, family and education status, IBS subtypes and BMI**
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10 * IBS-U was not included in the analysis because the sample size is too small.

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12
13 IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass
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16 index; 95%CI, 95% confidence interval
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21 **Table 4. Geometric mean values for mental health across categories of IBS-SSS level, by**
22
23 **gender, age, family and education status, IBS subtypes and BMI**
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26 * IBS-U was not included in the analysis because the sample size is too small.

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29 IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass
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32 index; 95%CI, 95% confidence interval
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37 **Figure 1. Estimated marginal means of physical health and mental health stratified**
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39 **according to IBS subtype**
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41 IBS: irritable bowel syndrome, IBS-C, IBS with constipation; IBS-D, IBS with diarrhea;
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44 IBS-M, mixed IBS
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49 **Figure 2. The influence of IBS-SSS on physical health and mental health stratified**
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51 **according to BMI level**
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54 * $p < 0.05$; # $p < 0.01$;
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3 BMI, body mass index;
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6 IBS symptom severity (IBS-SSS) subgroups: Mild (IBS-SSS: 75-175), Moderate (IBS-SSS:
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8 175-300) and Severe (IBS-SSS: > 300).
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Table 1. Distribution of demographic variables by BMI categories in IBS patients

	BMI											
	Total	< 18.5 kg/m ²				18.5-25 kg/m ²				> 30 kg/m ²		<i>p</i> value ^a
		Effective N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]	N (%) or Mean [SD]		
N	325	(100.0)	39	(12.0)**	176	(54.2)	69	(21.2)**	41	(12.6)**	< 0.01	
Gender												
Male	98	(30.2)	6	(6.1)	55	(56.1)	29	(29.6)	8	(8.2)	0.012	
Female	227	(69.8)	33	(14.5)	121	(53.3)	40	(17.6)	33	(14.5)		
Age	38.87	[15.68]	34.92	[15.57] [#]	37.25	[15.41]	43.55	[15.67]**	41.88	[15.15]	0.007 ^b	
Family status												
Single	149	(46.3)	23	(15.4)	89	(59.7)	27	(18.1)	10	(6.7)	0.011	
Married or unmarried cohabitation	140	(43.5)	10	(7.1)	68	(48.6)	37	(26.4)	25	(17.9)		
Divorced or widowed	33	(10.2)	5	(15.2)	18	(54.5)	5	(15.2)	5	(15.2)		
Education status												

1												
2												
3	Below highschool	91	(30.7)	9	(9.9)	50	(54.9)	16	(17.6)	16	(17.6)	0.35
4												
5	Above highschool	205	(69.3)	25	(12.2)	111	(54.1)	47	(22.9)	22	(10.7)	
6												
7												
8	IBS subtypes											
9												
10	IBS-C	35	(10.8)	5	(14.3)	19	(54.3)	9	(25.7)	2	(5.7)	0.057
11												
12	IBS-D	134	(41.2)	19	(14.2)	63	(47.0)	25	(18.7)	27	(20.1)	
13												
14	IBS-M	148	(45.5)	15	(10.1)	88	(59.5)	34	(23.0)	11	(7.4)	
15												
16	IBS-U	8	(2.5)	0	(0.0)	6	(75.0)	1	(12.5)	1	(12.5)	
17												
18												
19												
20												
21	Symptom severity [△]	291.99	[84.79]	277.76	[72.53]	292.96	[86.45]	291.46	[85.82]	299.21	[84.71]	0.739 ^b
22												
23	Quality of life [†]											
24												
25												
26	Physical health	40.57	[9.30]	41.97	[9.02] [§]	40.97	[8.86] [§]	42.05	[9.17] [§]	35.08	[10.02]	0.001 ^b
27												
28	Mental health	39.22	[12.69]	36.66	[12.35]	39.63	[13.00]	39.92	[11.96]	38.79	[13.05]	0.613 ^b
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Table 2. Correlation Matrix for the Study Variables in IBS patients

		BMI	Gender	Education	Symptom severity	Physical Health	Mental health
Pearson	BMI	1.000					
Correlation	Gender	-0.050	1.000				
	Education	-0.080	-0.108	1.000			
	Symptom severity	0.065	0.059	-0.048	1.000		
	Physical Health	-0.198*	-0.070	0.204*	-0.394*	1.000	
	Mental health	0.037	-0.022	-0.040	-0.303*	0.046	1.000

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Table 3. Geometric mean values for physical health across categories of IBS-SSS level, by gender, age, family and education status, IBS subtypes and BMI

Variable	Total			IBS -SSS			F value	p value
	N	Mean	95% CI	Mild	Moderate	Severe		
Total sample	283	40.85	39.75, 41.96	45.64	43.77	36.98	23.63	0.000
Gender								
Male	84	41.83	39.96, 43.73	44.18	45.00	37.41	8.88	0.000
Female	199	40.44	39.07, 41.80	46.36	43.19	36.82	15.18	0.000
Age								
18-25	66	41.91	39.83, 43.99	46.89	45.56	38.36	7.44	0.001
26-49	145	41.02	39.55, 42.50	47.38	43.61	37.45	13.79	0.000
≥ 50	71	39.61	36.99, 42.24	42.31	42.67	33.77	5.72	0.005
Family status								
Single	124	41.59	40.08, 43.10	45.95	44.88	38.58	10.21	0.000
Married or unmarried cohabitation	127	40.23	38.43, 42.02	45.52	42.60	35.68	10.76	0.000
Divorced or widowed	28	40.47	36.48, 44.45	-	44.98	33.50	11.62	0.002

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Education status

Below highschool

74 38.45 36.15, 40.75 48.34 42.41 33.52 11.05 0.000

Above highschool

189 42.12 40.84, 43.41 46.20 44.59 38.60 13.70 0.000

IBS subtypes *

IBS-C

26 41.10 36.79, 45.41 48.85 46.62 35.06 5.84 0.009

IBS-D

118 40.96 39.22, 42.70 44.34 43.95 37.22 8.30 0.000

IBS-M

135 40.87 39.32, 42.42 45.96 43.41 37.24 10.61 0.000

BMI

< 18.5 kg/m²

31 42.37 39.05, 45.70 54.73 42.66 39.44 4.30 0.024

18.5-25 kg/m²

139 40.83 39.32, 42.34 46.33 43.60 37.41 11.65 0.000

25-30 kg/m²

53 42.39 39.92, 44.86 42.87 46.71 38.48 5.87 0.005

> 30 kg/m²

31 35.33 31.43, 39.23 38.35 42.54 29.35 7.92 0.002

Table 4. Geometric mean values for mental health across categories of IBS-SSS level, by gender, age, family and education status, IBS subtypes and BMI

Variable	Total			IBS -SSS			<i>F</i> value	<i>p</i> value
	N	Mean	95% CI	Mild	Moderate	Severe		
Total sample	283	39.27	37.77, 40.78	45.92	41.44	35.75	11.02	0.000
Gender								
Male	84	39.30	36.29, 42.31	40.10	43.40	34.14	4.51	0.014
Female	199	39.26	37.53, 41.00	48.83	40.51	36.32	9.13	0.000
Age								
18-25	66	39.30	36.25, 42.36	40.03	40.39	38.32	0.22	0.806
26-49	145	37.83	35.74, 39.93	45.02	41.04	33.55	9.17	0.000
≥ 50	71	42.46	39.45, 45.52	49.39	42.89	39.19	2.16	0.124
Family status								
Single	124	37.62	35.37, 39.86	38.70	39.95	35.70	1.68	0.191
Married or unmarried cohabitation	127	40.42	38.14, 42.71	48.45	42.44	35.21	9.83	0.000

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2									
3	Divorced or widowed	28	41.88	37.34, 46.42	-	44.01	38.59	1.45	0.239
4									
5	Education status								
6									
7									
8	Below highschool	74	40.68	37.60, 43.75	53.80	45.51	34.58	9.22	0.000
9									
10	Above highschool	189	38.56	36.77, 40.36	45.26	39.82	35.50	6.60	0.002
11									
12									
13	IBS subtypes *								
14									
15	IBS-C	26	39.95	34.25, 45.65	57.68	43.76	32.92	6.13	0.007
16									
17	IBS-D	118	39.02	36.60, 41.45	45.41	41.43	35.32	4.34	0.015
18									
19	IBS-M	135	38.96	36.89, 41.03	42.41	40.87	36.31	2.80	0.064
20									
21									
22									
23	BMI								
24									
25									
26	< 18.5 kg/m ²	31	37.95	33.47, 42.43	49.71	37.78	35.60	1.73	0.196
27									
28	18.5-25 kg/m ²	139	39.39	37.18, 41.61	47.74	43.14	34.60	10.74	0.000
29									
30	25-30 kg/m ²	53	39.86	36.42, 43.30	45.34	40.38	38.09	0.84	0.437
31									
32									
33	> 30 kg/m ²	31	39.47	43.69, 44.24	41.01	40.86	38.14	0.16	0.851
34									
35									

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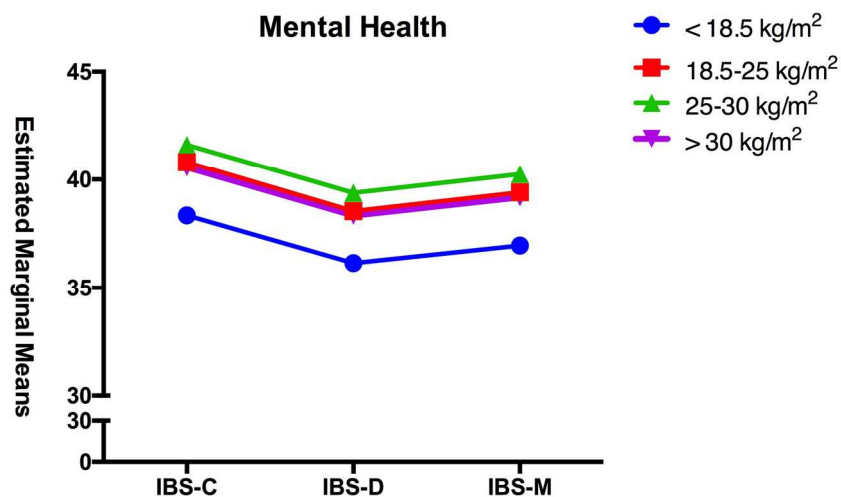
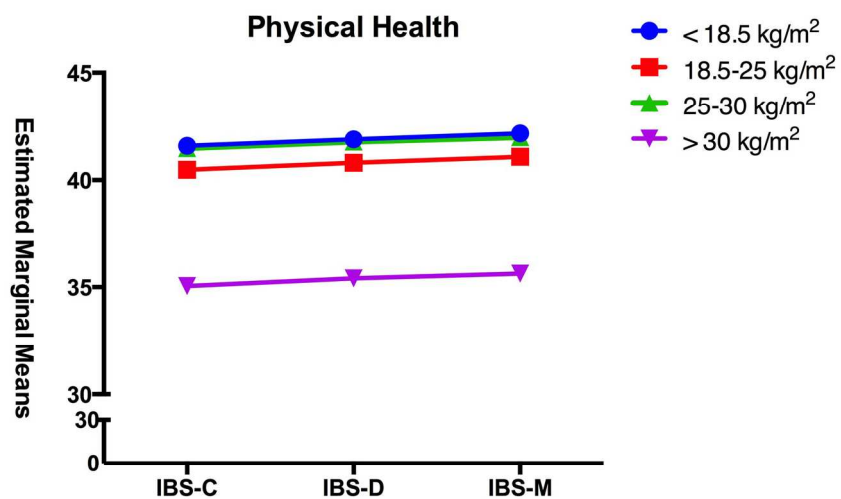


Figure 1

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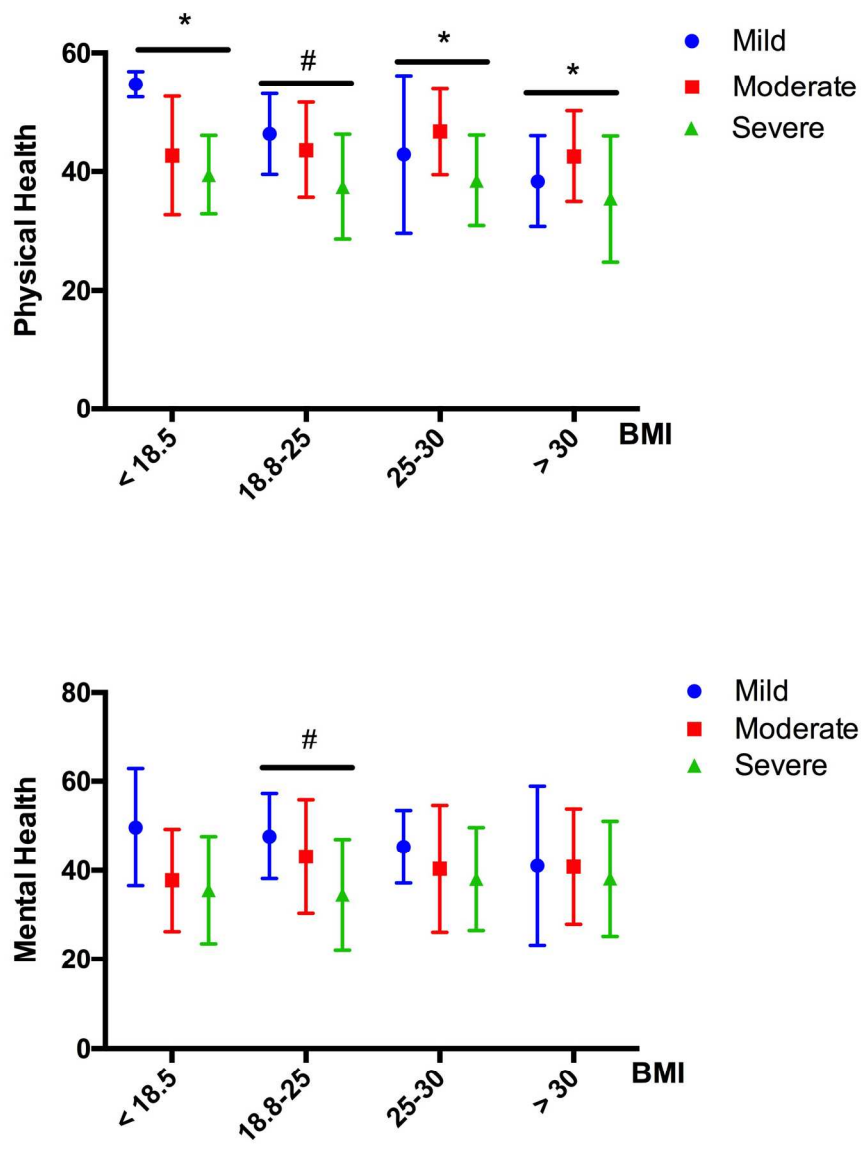


Figure 2

225x297mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract 【Page 1】 (b) Provide in the abstract an informative and balanced summary of what was done and what was found 【Pages 2 - 3】
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 【Pages 4 - 5】
Objectives	3	State specific objectives, including any prespecified hypotheses 【Pages 4 - 5】
Methods		
Study design	4	Present key elements of study design early in the paper 【Pages 5 - 6】
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 【Page 6 - 7】
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants 【Page 6】
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 【Pages 6 - 7】
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 【Pages 6 - 7】
Bias	9	Describe any efforts to address potential sources of bias 【Page 6】
Study size	10	Explain how the study size was arrived at 【Page 6】
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 【Pages 6 - 7】
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding 【Pages 8 - 9】 (b) Describe any methods used to examine subgroups and interactions 【Page 8】 (c) Explain how missing data were addressed 【Page 8】 (d) If applicable, describe analytical methods taking account of sampling strategy 【N/A】 (e) Describe any sensitivity analyses 【N/A】
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 【Page 9; table 1】 (b) Give reasons for non-participation at each stage 【N/A】 (c) Consider use of a flow diagram 【Page 9】
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 【Pages 9 - 11】 (b) Indicate number of participants with missing data for each variable of interest 【Page 9; table 1】
Outcome data	15*	Report numbers of outcome events or summary measures 【Pages 9 - 11】
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 【Pages 9 - 11; table 3】

		(b) Report category boundaries when continuous variables were categorized 【N/A】
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period 【N/A】
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 【Pages 9 – 11; figures 1 -2; tables 2 - 3】
Discussion		
Key results	18	Summarise key results with reference to study objectives 【Page 11】
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 【Page 14】
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 【Pages 11 - 15】
Generalisability	21	Discuss the generalisability (external validity) of the study results 【Pages 12 - 15】
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 【Page 1 and Page 15】

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Symptom severity and health-related quality of life in patients with irritable bowel syndrome: The role of body mass index

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Nutrition and metabolism, Mental health
Keywords:	Irritable bowel syndrome, Body mass index, Symptom severity, Quality of life

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1 **Original Article**

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6 **Symptom severity and health-related quality of life in patients with irritable bowel syndrome: The role**
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8 **of body mass index**
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Abstract

Objective

The aim of this study was to describe the body mass index (BMI) distribution in patients with irritable bowel syndrome (IBS) based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and quality of life (QOL).

Methods

A cross-sectional study was carried out in patients visiting our outpatient Functional Gastrointestinal Disorders specialty clinic. IBS diagnosis was made based on ROME III criteria. IBS symptom severity was investigated using the IBS severity score system (IBS-SSS). QOL was assessed using the Short-Form-36-Health-Survey (SF-36), which consists of physical health and mental health.

Results

366 patients (252 females) who fulfilled ROME III criteria and provided complete BMI data (23.90 ± 5.22 kg/m²) were included. Overall, 59.0% of patients with IBS were in the normal weight range, 30.3% were overweight or obese, and 10.7% were underweight. Both physical and mental health decreased significantly with the severity of symptom (all $p < 0.01$). We adjusted all the confounders (age, gender, family status, education status and IBS subtypes). Taking physical health into consideration, BMI and symptom severity significantly predicted the physical health of QOL ($\beta = -0.376$, $\Delta R^2 = 0.137$, $p < 0.01$; $\beta = -0.135$, $\Delta R^2 = 0.017$, $p < 0.05$). Taking mental health into consideration, symptom severity ($\beta = -0.280$, $\Delta R^2 = 0.076$, $p < 0.01$) was significant predictor of mental health. However, BMI didn't account for an additional significant amount of variance in mental health of QOL ($p > 0.05$).

Conclusion

Being overweight is a phenomenon in patients with IBS regardless of IBS subtype. The association between QOL and symptom severity followed a negative dose response pattern. Patients with higher BMI

1 were more frequently in poor physical health. However, this kind of relationship was not found in BMI and
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3 mental health of QOL.
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6 **Keywords:**

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8 Irritable bowel syndrome; Body mass index; Symptom severity; Quality of life
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16 **Strengths and limitations of this study:**

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18 1) This study uses a large and well described patient cohort with a validated diagnosis of IBS based on the
19 Rome III criteria;
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21 2) The association between QOL and symptom severity followed a negative dose response pattern;
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23 3) Patients with higher BMI were more frequently in poor physical health. However, this kind of relationship
24 was not found in BMI and mental health of QOL.
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26 4) The study was cross-sectional, therefore it is not possible to infer causation;
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28 5) BMI cannot fully reflect the impact of the factors of fatty mass, dietary habit, other lifestyle factors such as
29 physical exercise on IBS.
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1 Introduction

Irritable bowel syndrome (IBS) is a chronic and common functional bowel disorder that is characterized by recurrent abdominal pain or discomfort associated with altered bowel habits [1]. According to the Rome criteria, IBS is classified into four subtypes [IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), mixed IBS (IBS-M) and un-subtyped IBS (IBS-U)] based on the predominant abdominal symptomatology [1]. It has been frequently reported that IBS leads to impaired quality of life (QOL) [2-4]. The symptoms of IBS are associated with different eating habits [5]. In a randomized controlled trial, a diet low in FODMAPs can improve the IBS-D patients' QOL, anxiety, and activity impairment [6].

Epidemiologic studies have shown that as many as 16.5% of adults in European countries are obese [body mass index (BMI) > 30 kg/m²] [7] and that the incidence of obesity is increasing [8]. Additionally, a cross-sectional multicentre study found that more than 63% of outpatients and 80% of inpatients in gastroenterological centres suffered from significant changes in body composition [9]. In addition, Underweight (BMI < 18.5 kg/m²) or obese body condition (BMI > 30 kg/m²) are both associated with multiple abdominal symptoms leading to reduced QOL [10, 11]. However, although extensive research has been carried out on the prevalence of obesity in the general population and in connection with numerous diseases, there is only little published data on the prevalence and clinical relevance of nutritional status in patients with IBS. Locke *et al.* [12] found no association between IBS status and BMI. However, this study was a population-based study. Studies with large enough sample size based on clinic patients are missing so far.

Therefore, the aim of this study was to describe the BMI distribution in patients with IBS based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and the physical health and mental health of QOL.

2 Methods

1 This cross-sectional survey included patients evaluated at the Functional Gastrointestinal Disorders
2 (FGIDs) specialty clinic of the Department of General Internal Medicine and Psychosomatics of Heidelberg
3 University Hospital, which is a tertiary care facility. All patients who completed our routine baseline
4 documentation were enrolled. The routine data from individual health records was transferred into the
5 database and pseudonymized. This study was approved by the Ethics Committee of Heidelberg University
6 (S-041/2014) and carried out in accordance with the Declaration of Helsinki.

18 **2.1 Patients recruitment**

21 From 01/2011 to 12/2016, patients' clinical data were consecutively collected from our outpatient FGIDs
22 clinic at Heidelberg University Hospital for this explorative and descriptive study. All patients ≥ 18 years of
23 age were included, if they fulfilled the Rome III criteria for the diagnosis of IBS [1]. The subtype criteria for
24 IBS were based on stool consistency as assessed by the Bristol Stool Scale (BSS) and Rome III criteria [13].
25 Demographic data including gender, age, family status, level of education and residence, was also collected at
26 baseline using the Psychosomatic Basis Documentation Questionnaire (Psy-BaDo) [14].

39 **2.2 Patient Involvement**

41 There is no patient involved in the conduct of the study. However, in order to increase the clinical
42 relevance of the study, we established an advisory group to answer the related questions.

49 **2.3 Measurement of IBS symptom severity**

51 Patients rated the severity of their IBS symptoms by completing the IBS severity score system (IBS-SSS)
52 [15]. The IBS-SSS has a maximum score of 500 and comprises five items: frequency and intensity of
53 abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference of IBS

1 with daily life. Based on validated cut-off values, three IBS severity subgroups can be distinguished: Mild
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3 (IBS-SSS: 75-175), Moderate (IBS-SSS: 175-300) and Severe (IBS-SSS: > 300). The German version of this
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5 questionnaire was validated by Betz et al. [16] and the total score was computed in accordance with the
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7 manual.
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10 11 12 13 **2.4 Measurement of BMI**

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16 In the context of self-reporting, BMI was calculated as the individual's body weight (kg) divided by the
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18 square of their height (m). BMI was categorized according to the World Health Organization (WHO)
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20 classification of physical status [17]: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–25 kg/m²),
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22 overweight (25–30 kg/m²), or obese (BMI > 30 kg/m²).
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29 **2.5 Measurement of quality of life**

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31 Quality of life was measured using the Short Form 36 Health Survey (SF-36) [18]. SF-36 is a 36-item,
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33 patient-reported survey of patient quality of life, which consists of a physical health index and mental health
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35 index. The SF-36 is widely used and well validated for assessing generic health outcomes. Each scale is
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37 directly transformed into a 0-100 scale. Lower scores represent a higher degree of disability. Validation of the
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39 German version was performed by Morfeld *et al.* [19].
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47 **2.6 Statistical analysis**

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49 Routine data were transformed into an SPSS file and evaluated using the statistical program SPSS (IBM,
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51 version 22.0). Descriptive statistics are presented as the means and standard deviation (*SD*) for continuous
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53 variables and as absolute numbers and percentages for categorical variables. All analyses were explorative
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55 and not of a confirmatory nature. All primary and secondary variables were first tested for normal distribution.
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1 For normally distributed variables, the mean and standard deviation were calculated. Variables that lacked a
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3 normal distribution were reported using the median and interquartile range. The Mann-Whitney U Test was
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5 used to assess the level of significance because a number of participants differed between the groups.
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7 Comparison of socio-demographical and anthropometric data according to BMI was performed using analysis
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9 of variance (ANOVA) and nonparametric tests in the first instance. Where significant group differences were
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11 detected based on ANOVA, post-hoc least significant difference tests were conducted to compare the study
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13 groups in a pairwise fashion. We also used the Pearson correlation coefficients to investigate the linear
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15 association between demographics, BMI, clinical and psychological features. Hierarchical multiple regression
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17 was used to help understand the impact of potential confounders as well as the predictive role of BMI in
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19 physical health and mental health of QOL. We tested the impact of the confounders (gender, age, family
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21 status, education status & IBS subtypes) in Model 1. In model 2, we added the symptom severity. BMI was
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23 added in model 3. All tests were two-sided and statistical significance was accepted if $p < 0.05$.
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34 **3 Results**

35 **3.1 Characteristics of study sample**

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39 A total of 576 patients completed the questionnaire. Excluding 113 patients whose Rome III criteria data
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41 were partly missing, eventually 366 patients with IBS were enrolled in this study (114 males, 252 females;
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43 mean BMI 23.90 ± 5.22 kg/m²). The demographic and baseline characteristics of the patients with IBS among
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45 the different subtypes are summarized in Table 1. Of the included subjects, the most frequent IBS subtype was
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47 IBS-M (45.9%), followed by IBS-D (41.3%), and IBS-C (10.1%). Only 59.0% of patients with IBS were
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49 within the normal weight range, whereas 30.3% were overweight or obese, and only a minority were
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51 underweight (10.7%). The percentage of obese patients was highest in IBS-D (17.9%, $p < 0.01$). Taking
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53 gender into account, 5.3% of males and 13.1% of females were underweight. Additionally, 7.0% of males and
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13.1% of females were obese and 26.3% of males and 15.9% of females were overweight. Overall, patients reported moderate to severe IBS symptom severity (IBS-SSS range: 125 - 484) and lower QOL (physical health range of SF-36: 15.19 – 64.00, mental health range of SF-36: 7.89 – 65.85).

3.2 Correlations between BMI, symptom severity and QOL

Pearson product-moment correlations (Table 2) indicated that BMI was negatively correlated with physical health ($r = -0.177, p < 0.01$). Age was negatively correlated with symptom severity ($r = -0.129, p < 0.05$) and positively correlated with physical health ($r = 0.167, p < 0.01$). Additionally, symptom severity was negatively correlated with physical health ($r = -0.394, p < 0.01$) and mental health ($r = -0.268, p < 0.01$).

3.3 Characteristics of BMI, symptom severity and QOL Across Demographic and IBS subtypes

As shown in Table 1, male reported significantly higher physical health problems than female ($t = 2.141, p < 0.05$). Compare with older patients (age > 50), the younger patients (age 18 - 49) reported significantly lower BMI level ($t = -3.20, p < 0.01$), worse symptom severity ($t = 2.039, p < 0.05$) and worse mental health ($t = -2.528, p < 0.05$). Married or unmarried cohabitation patients were significantly higher in BMI level than single patients ($p < 0.01$). The patients with below high school education reported significantly higher physical health problems than those who with above high school education ($t = -3.376, p < 0.01$). Compared with IBS-M patients, the IBS-D patients reported significantly higher BMI level ($p < 0.05$).

3.4 the predictive role of BMI in physical health and mental health of QOL

As shown in Table 3, the hierarchical multiple regression examined the relationship between dependent variable (physical health) and independent variables (symptom severity and BMI). Model 1 was significant ($F = 2.448, p < 0.05$) and predicted 5.1% of the variance in physical health. Education status ($\beta = 0.177, p <$

0.01) was significant predictor of physical health. In model 2, symptom severity significantly added to the amount of variance in the dependent accounted for in the model ($\Delta R^2 = 0.137$, $\Delta F = 53.283$, $p < 0.01$). In model 3, BMI also significantly added to the amount of variance in the dependent accounted for in the model ($\Delta R^2 = 0.017$, $\Delta F = 6.581$, $p < 0.01$). Similarly, when mental health was used as the dependent variable, Model 1 was insignificant ($F = 1.309$, $p > 0.05$). In model 2, symptom severity significantly increased the amount of variance in the dependent accounted for in the model ($\Delta R^2 = 0.076$, $\Delta F = 26.671$, $p < 0.01$). Taking both model 1 and model 2 into consideration, it predicted 10.4% of the variance in mental health. In model 3, BMI didn't account for an additional significant amount of variance in mental health ($\Delta R^2 = 0.000$, $\Delta F = 0.057$, $p > 0.05$).

4 Discussion

This study sought to describe the BMI distribution in patients with IBS based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and the physical health and mental health of QOL. Therefore, we used standardized questionnaires and medical records to confirm the diagnosis and to assess patient symptoms and quality of life.

Our data show that being overweight is a common phenomenon in patients with IBS regardless of IBS subtype. These findings are in agreement with the results of a previous study based on obese patients in France, which found that 30.0% of obese patients had IBS [20]. We found that almost 40% of patients with IBS were not in the normal weight range, which is consistent with previous results [21]. What is worth noting is that, the overweight and obesity rates in the general adult population in Germany [7] are higher than those found in our IBS cohort. According to the German Health Update (GEDA) [7], in 2012 the overweight rate of adults was 36.2% and the obese rate was 16.5%. The causal relationship between IBS and abnormal body weight are hard to elucidate. However, abnormal body weight has an undeniable influence in both patients

1 with IBS and in the general population. Interestingly, the distribution of weight was similar between the
2
3 different IBS groups. In particular, there was no difference between IBS-C and IBS-M. Notably, in IBS-D the
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5 percentage of obese patients reached 17.9%. Lee et al. [22] evaluated the relationship between visceral
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7 adipose tissue and the risk of IBS and suggested that disturbances of visceral fat may be more common in
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9 IBS-D patients. In addition, another Korean study found increased intestinal permeability in IBS-D patients
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11 [23]. One possible explanation is that the increase in visceral fat leads to an increase in intestinal osmolality
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13 [24] and then leads to the chronic diarrhea. These studies, however, were confined to patients from South
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15 Korea. Therefore, further research is needed to these findings.
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21 IBS has a significant impact on patients' QOL [25]. Our data show an association between symptom
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23 severity and QOL with regard to physical and mental health. The patients in our study reported moderate to
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25 severe IBS symptom severity and lower QOL. What's more, this association followed a negative dose
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27 response pattern. We partly agree with the study of Amouretti et al. [26], which found that the IBS patients
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29 who reported their symptoms as severe or very severe had a very poor QoL compared with those who reported
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31 their symptoms as moderate. Their study did not distinguish between physical and mental health and did not
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33 consider the effects of confounding factors such as BMI. This is an interesting but not completely new result
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35 which gives rise to the question of what mechanisms are responsible for this association.
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41 Through the hierarchical multiple regression, we tested the relationship between dependent variable
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43 (QOL) and independent variables (symptom severity & BMI). We excluded the impact of the confounders
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45 (gender, age, family status, education status & IBS subtypes). The correlation between symptom severity and
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47 QOL was significantly negative no matter which BMI level was. Our findings show that BMI was significant
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49 predictor of physical health of QOL. Patients with higher BMI were more frequently in poor physical health.
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51 This is in line with previous studies [11], in that increasing BMI is associated with increased upper
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53 gastrointestinal symptoms, bloating, and diarrhoea. Obesity may lead to more physiological stress on organs.
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1 Richards *et al.* [27] reported that obese patients have more severe pain and are to a larger extent restricted in
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3 their daily functioning compared to patients of normal weight. An additional finding of our study was that
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5 BMI didn't account for an additional significant amount of variance in mental health of QOL. This was
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7 inconsistent with findings by Mykletun [28], which found that BMI had significant association with IBS with
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9 regard to anxiety and mood disorders. However, their study evaluated only female patients. The findings of
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11 genome-wide association studies, from the genetic perspective, suggest the presence of many genetic loci each
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13 with a small effect influencing susceptibility to mental health symptoms (depression and anxiety) [29]. We
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15 can therefore hypothesise that, the unpredictable association between risk of mental health and BMI in our
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17 study may be due to non-modifiable genetic influences which predispose individuals to bad mental health.
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24 Several limitations of this study must be taken into account. Firstly, the study was cross-sectional,
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26 therefore, it is impossible to infer causation. Secondly, BMI was based on the self-reported height and weight
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28 of patients and computed without objective measurement, therefore bias may have been introduced. Patients
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30 may occasionally underreport or overreport their weight and height leading to an underestimation of
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32 underweight or obese patients. However, in the Nutrinet-Santé study, researchers reported that deviations in
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34 self-reported BMIs from questionnaires can be ignored because their results confirmed the validity and
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36 agreement of self-reported data with measured data [30, 31]. The choice of SF-36 as the only QOL tool may
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38 partly miss the relationship between symptom severity and QOL. Moreover, BMI is associated with a
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40 multitude of different factors, such as genetics, fatty mass, dietary habit or physical exercise. Thus, BMI
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42 cannot fully reflect the impact of those factors on IBS in more details and more research is needed. The
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44 strengths of this study, however are the use of a large patient cohort with a validated diagnosis of IBS based on
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46 the Rome III criteria.
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54 To conclude, being overweight is a common phenomenon in IBS patients regardless of IBS subtypes.
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56 Our data further suggest that overweight and obesity may have a relevant influence on QOL. Patients with
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1 higher BMI were more frequently in poor physical health. The findings have some implications for future
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3 practice. Clinical doctors should pay special attention to abnormal weight in IBS patients as this may be an
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5 indicator of a poorer QOL, especially with regard to the physical health.
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11 2016;22:670-676.

22 23 24 **Footnotes**

25
26 **CONTRIBUTORS:** Yuanjun Dong, Jonas Tesarz, Rainer Schaefer and Wolfgang Eich designed the study
27 and wrote the protocol. Yuanjun Dong, Sabrina Berens and Jonas Tesarz performed the literature searches and
28 analyses. Yuanjun Dong wrote the first draft of the manuscript. All of the authors contributed to and have
29 approved the final manuscript.

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36 **COMPETING INTERESTS:** The authors have indicated no financial conflicts of interest.

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39 **PATIENT CONSENT:** Obtained.

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42 **ETHICS APPROVAL:** This study was approved by the Ethics Committee of Heidelberg University
43 (S-041/2014) and carried out in accordance with the Declaration of Helsinki.

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46 **PROVENANCE AND PEER REVIEW:** Not commissioned; externally peer reviewed.

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49 **DATA SHARING STATEMENT:** There is no additional unpublished data from this study.

Tables:

Table 1. Distribution of BMI at symptom severity and QOL based on several demographic and clinical features (n = 366)

	N	BMI mean (SD)	Symptom severity mean (SD)	Quality of life	
				Physical health mean (SD)	Mental health mean (SD)
Gender					
Male	114	24.30 (3.48)	280.27 (78.23)	42.21 (7.87) *	39.41 (12.76)
Female	252	23.71 (5.84)	292.10 (76.14)	40.21 (9.16)	39.23 (11.84)
Age					
18-49	264	23.36 (5.14) *	293.39 (77.52) *	41.28 (8.21)	38.32 (12.17) *
> 50	102	25.29 (5.12)	275.55 (74.04)	39.69 (10.19)	41.80 (11.67)
Family status					
Single	160	22.69 (4.13) #	298.15 (71.90)	41.42 (7.69)	37.96 (12.09)
Marr [§]	164	25.19 (5.07)	281.94 (82.67)	40.58 (9.59)	40.32 (12.18)
Divo [§]	37	23.50 (5.11)	283.11 (69.13)	39.45 (10.12)	40.87 (11.20)
Education status					
Below Hs [§]	97	24.62 (6.19)	296.31 (71.99)	38.40 (9.33) *	40.51 (12.35)
Above Hs [§]	232	23.68 (4.87)	286.54 (81.60)	42.10 (8.47)	38.60 (12.02)
IBS subtypes					
IBS-C	37	23.38 (5.34)	293.13 (82.41)	40.76 (9.33)	40.43 (12.30)
IBS-D	151	24.69 (5.93) [△]	293.96 (78.00)	40.57 (9.17)	38.74 (12.88)
IBS-M	168	23.22 (4.01)	283.53 (73.19)	41.09 (8.40)	38.98 (11.39)

* $p < 0.05$ # $p < 0.05$ for post-hoc comparison between single and Married or unmarried cohabitation

1 $\Delta p < 0.05$ for post-hoc comparison between IBS-D and IBS-M

2 § Marr means “Married or unmarried cohabitation”, Divo means “Divorced or widowed”, Hs means “High
3 school”
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5 IBS-U was not included in the analysis because the sample size is too small.
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7 Symptom severity based on IBS-SSS: Mild (IBS-SSS: 75-175), Moderate (IBS-SSS: 175-300) and Severe
8 (IBS-SSS: > 300).
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10 QOL based on SF-36: range from 0 (“highest disability”) to 100 (“no disability”).
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12 IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass index;
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Table 2. Correlation Matrix for the Study Variables in IBS patients

	BMI	Age	Symptom severity	Physical Health	Mental health
BMI	1.00				
Age	0.173**	1.00			
Symptom severity	0.055	-0.129*	1.00		
Physical Health	-0.177**	-0.085	-0.349**	1.00	
Mental health	0.033	0.167**	-0.268**	0.029	1.00

* $p < 0.05$

** $p < 0.01$

BMI, Body mass index;

Table 3. Results of hierarchical multiple regression relating physical health and mental health to symptom severity and BMI

	Model 1		Model 2		Model 3		Model summary			
	β	t	β	t	β	t	F	R^2	ΔF	ΔR^2
physical health										
Age	-0.048	-0.679	-0.092	-1.392	-0.081	-1.224	2.448*	0.051*	-	-
Gender	-0.100	-1.820	-0.080	-1.574	-0.091	-1.781				
Single & Marr [§]	0.008	0.105	0.026	0.394	0.000	0.006				
Divo [§] & Marr [§]	0.000	-0.002	0.005	0.084	-0.010	-0.190				
Education	0.177	3.152**	0.152	2.918**	0.144	2.784**				
IBS-C & IBS-D	0.026	0.453	-0.010	-0.185	-0.022	-0.416				
IBS-M & IBS-D	0.026	0.460	0.023	0.425	0.017	0.323				
symptom severity	-	-	-0.376	-7.300**	-0.365	-7.124**	9.156**	0.188**	53.283**	0.137**
BMI	-	-	-	-	-0.135	-2.565*	9.013**	0.205**	6.581*	0.017*
mental health										
Age	0.173	2.393*	0.140	2.009*	0.139	1.985*	1.309	0.028	-	-
Gender	-0.018	-0.323	-0.003	-0.061	-0.002	-0.042				
Single & Marr [§]	0.026	0.356	0.040	0.569	0.042	0.598				
Divo [§] & Marr [§]	-0.031	-0.523	-0.028	-0.483	-0.026	-0.454				
Education	-0.060	-1.053	-0.078	-1.429	-0.077	-1.410				
IBS-C & IBS-D	0.008	0.129	-0.019	-0.341	-0.018	-0.318				
IBS-M & IBS-D	0.011	0.191	0.008	0.147	0.009	0.157				
symptom severity	-	-	-0.280	-5.164**	-0.281	-5.159**	4.572**	0.104**	26.671**	0.076**
BMI	-	-	-	-	0.013	0.239	4.058**	0.104**	0.057	0.000

* $p < 0.05$

** $p < 0.01$

Model 1 predictors: age, gender, family status, education status, IBS subtypes;

Model 2 predictors: age, gender, family status, education status, IBS subtypes, symptom severity;

Model 3 predictors: age, gender, family status, education status, IBS subtypes, symptom severity, BMI.

§ Marr means “Married or unmarried cohabitation”, Divo means “Divorced or widowed

IBS-U was not included in the analysis because the sample size is too small.

IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass index

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract 【Page 1】 (b) Provide in the abstract an informative and balanced summary of what was done and what was found 【Pages 2 - 3】
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 【Pages 4】
Objectives	3	State specific objectives, including any prespecified hypotheses 【Pages 4】
Methods		
Study design	4	Present key elements of study design early in the paper 【Pages 5 - 7】
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 【Page 5 - 7】
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants 【Page 5】
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 【Pages 6 - 7】
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 【Pages 6 - 7】
Bias	9	Describe any efforts to address potential sources of bias 【Page 5】
Study size	10	Explain how the study size was arrived at 【Page 5】
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 【Pages 6 - 7】
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding 【Pages 6 - 7】 (b) Describe any methods used to examine subgroups and interactions 【Page 6 - 7】 (c) Explain how missing data were addressed 【Page 6 - 7】 (d) If applicable, describe analytical methods taking account of sampling strategy 【N/A】 (e) Describe any sensitivity analyses 【N/A】
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 【Page 7 - 8; table 1】 (b) Give reasons for non-participation at each stage 【N/A】 (c) Consider use of a flow diagram 【N/A】
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 【Pages 7 - 9】 (b) Indicate number of participants with missing data for each variable of interest 【Page 7; table 1】
Outcome data	15*	Report numbers of outcome events or summary measures 【Pages 7 - 9, table 1-3】
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 【Pages 7 - 9; table 1 - 3】

		(b) Report category boundaries when continuous variables were categorized 【N/A】
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period 【N/A】
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 【N/A】
Discussion		
Key results	18	Summarise key results with reference to study objectives 【Page 9 - 11】
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 【Page 11】
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 【Pages 9 - 12】
Generalisability	21	Discuss the generalisability (external validity) of the study results 【Pages 9 - 12】
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 【Page 15】

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Symptom severity and health-related quality of life in patients with irritable bowel syndrome: The role of body mass index

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Original Article**Symptom severity and health-related quality of life in patients with irritable bowel syndrome: The role of body mass index**

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Abstract

Objective

The aim of this study was to describe the body mass index (BMI) distribution in patients with irritable bowel syndrome (IBS) based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and quality of life (QOL).

Methods

A cross-sectional study was carried out in patients visiting our outpatient Functional Gastrointestinal Disorders specialty clinic. IBS diagnosis was made based on Rome III criteria. IBS symptom severity was investigated using the IBS severity score system (IBS-SSS). QOL was assessed using the Short-Form-36-Health-Survey (SF-36), which consists of physical health and mental health.

Results

366 patients (252 females) who fulfilled Rome III criteria and provided complete BMI data (23.90 ± 5.22 kg/m²) were included. Overall, 59.0% of patients with IBS were in the normal weight range, 30.3% were overweight or obese, and 10.7% were underweight. Both physical and mental health decreased significantly with the severity of symptoms (all $p < 0.01$), whilst controlling for several covariates (age, gender, family status, education status and IBS subtypes). Obesity and symptom severity ($\beta = -0.177$, $\Delta R^2 = 0.037$, $p < 0.01$; $\beta = -0.387$, $\Delta R^2 = 0.147$, $p < 0.01$) were significant negative factors that influencing physical health. Symptom severity ($\beta = -0.301$, $\Delta R^2 = 0.084$, $p < 0.01$) was significant negative factor that influencing mental health. However, BMI didn't account for additional variance in mental health ($p > 0.05$).

Conclusion

Being overweight is a common phenomenon in patients with IBS regardless of IBS subtype. The association between QOL and symptom severity followed a negative dose response pattern. Patients with

1 higher BMI, especially obese patients, were more frequently in poor physical health. However, this kind of
2
3 relationship was not found in BMI and mental health.
4

5
6 **Keywords:**

7
8 Irritable bowel syndrome; Body mass index; Symptom severity; Quality of life
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16 **Strengths and limitations of this study:**

- 17
18 1) This study uses a large and well described patient cohort with a validated diagnosis of IBS based on the
19 Rome III criteria;
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21 2) The association between QOL and symptom severity followed a negative dose response pattern;
22
23 3) Patients with higher BMI were more frequently in poor physical health. However, this kind of relationship
24 was not found in BMI and mental health of QOL.
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26 4) The study was cross-sectional, therefore it is not possible to infer causation;
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28 5) BMI cannot fully reflect the impact of the factors of fatty mass, dietary habit, other lifestyle factors such as
29 physical exercise on IBS.
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1 Introduction

Irritable bowel syndrome (IBS) is a chronic and common functional bowel disorder that is characterized by recurrent abdominal pain or discomfort associated with altered bowel habits [1]. According to the Rome III criteria, IBS is classified into four subtypes [IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), mixed IBS (IBS-M) and un-subtyped IBS (IBS-U)] based on the predominant abdominal symptomatology [1]. It has been frequently reported that IBS leads to impaired quality of life (QOL) [2-4]. The symptoms of IBS are associated with different eating habits [5]. In a recent randomized controlled trial, a diet low in Fermentable Oligo-, Di-, Mono-saccharides And Polyols (FODMAPs) was shown to improve the IBS-D patients' QOL, anxiety, and activity impairment [6].

Epidemiologic studies have shown that as many as 16.5% of adults in European countries are obese [body mass index (BMI) > 30 kg/m²] [7] and that the incidence of obesity is increasing [8]. Additionally, a cross-sectional multicentre study found that more than 63% of outpatients and 80% of inpatients in gastroenterological centres suffered from significant changes in body composition [9]. In addition, underweight (BMI < 18.5 kg/m²) or obese body condition (BMI > 30 kg/m²) are both associated with multiple abdominal symptoms leading to reduced QOL [10, 11]. Although extensive research has been carried out on the prevalence of obesity in the general population and in connection with numerous diseases, there is only little published data on the prevalence and clinical relevance of nutritional status and body mass in patients with IBS. Locke *et al.* [12] found no association between IBS status and BMI. However, this study was a population-based study. Studies with large enough sample size based on clinic patients are missing so far.

Therefore, the aim of this study was to describe the BMI distribution in patients with IBS based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and the physical health and mental health of QOL.

2 Methods

This cross-sectional survey included patients evaluated at the Functional Gastrointestinal Disorders (FGIDs) specialty clinic of the Department of General Internal Medicine and Psychosomatics of Heidelberg University Hospital, which is a tertiary care facility. All patients who completed our routine baseline documentation were enrolled. The routine data from individual health records was transferred into the database and pseudonymized. This study was approved by the Ethics Committee of Heidelberg University (S-041/2014) and carried out in accordance with the Declaration of Helsinki.

2.1 Patients recruitment

From 01/2011 to 12/2016, patients' clinical data were consecutively collected from our outpatient FGIDs clinic at Heidelberg University Hospital for this explorative and descriptive study. All patients ≥ 18 years of age were included, if they fulfilled the Rome III criteria for the diagnosis of IBS [1]. The subtype criteria for IBS were based on stool consistency as assessed by the Bristol Stool Scale (BSS) and Rome III criteria [13]. Demographic data including gender, age, family status, level of education and residence, was also collected at baseline using the Psychosomatic Basis Documentation Questionnaire (Psy-BaDo) [14].

2.2 Patient Involvement

No patients were involved in conducting the study. However, in order to increase the clinical relevance of the study, we established an advisory group to advise the research project.

2.3 Measurement of IBS symptom severity

Patients rated the severity of their IBS symptoms by completing the IBS severity score system (IBS-SSS) [15]. The IBS-SSS has a maximum score of 500 and comprises five items: frequency and intensity of

1 abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference of IBS
2
3 with daily life. Based on validated cut-off values, three IBS severity subgroups can be distinguished: Mild
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5 (IBS-SSS: 75-175), Moderate (IBS-SSS: 175-300) and Severe (IBS-SSS: > 300). The German version of this
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7 questionnaire was validated by Betz *et al.* [16] and the total score was computed in accordance with the
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9 manual.
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16 **2.4 Measurement of BMI**

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18 BMI was calculated as the individual's self-reported body weight (kg) divided by the square of their
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20 height (m). BMI was categorized according to the World Health Organization (WHO) classification of
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22 physical status [17]: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–25 kg/m²), overweight (25–
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24 30 kg/m²), or obese body condition (BMI > 30 kg/m²).
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31 **2.5 Measurement of quality of life**

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34 Quality of life was measured using the Short Form 36 Health Survey (SF-36) [18]. SF-36 is a 36-item,
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36 patient-reported survey of patient quality of life, which consists of a physical health index and mental health
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38 index. The SF-36 is widely used and well validated for assessing generic health outcomes. Each scale is
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40 directly transformed into a 0-100 scale. Lower scores represent a higher degree of disability. Validation of the
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42 German version was performed by Morfeld *et al.* [19].
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49 **2.6 Statistical analysis**

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52 Routine data were transformed into an SPSS file and evaluated using the statistical program SPSS (IBM,
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54 version 22.0). Descriptive statistics are presented as the means and standard deviation (*SD*) for continuous
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56 variables and as absolute numbers and percentages for categorical variables. All analyses were explorative
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1 and not of a confirmatory nature. All primary and secondary variables were first tested for normal distribution.
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3 For normally distributed variables, the mean and standard deviation were calculated. Variables that lacked a
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5 normal distribution were reported using the median and interquartile range. The Mann-Whitney U Test was
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7 used to assess the level of significance because a number of participants differed between the groups.
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10 Comparison of socio-demographical and anthropometric data according to BMI was performed using analysis
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12 of variance (ANOVA) and nonparametric tests in the first instance. Where significant group differences were
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14 detected based on ANOVA, post-hoc least significant difference tests were conducted to compare the study
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16 groups in a pairwise fashion. We also used the Pearson correlation coefficients to investigate the linear
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18 association between demographics, BMI, clinical and psychological features. Hierarchical multiple regression
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20 was used to help understand the impact of potential confounders as well as the predictive role of BMI in
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22 physical health and mental health of QOL. We tested the impact of the confounders (gender, age, family
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24 status, education status and IBS subtypes) in Model 1. In model 2, we added the symptom severity. BMI
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26 categories (underweight, normal weight, overweight and obesity) were added in model 3. All tests were
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28 two-sided and statistical significance was accepted if $p < 0.05$.
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39 **3 Results**

40 **3.1 Characteristics of study sample**

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42 A total of 576 patients completed the questionnaire. Excluding 113 patients whose Rome III criteria data
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44 were partly missing, 366 patients with IBS were enrolled in this study (114 males, 252 females; mean BMI
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46 23.90 ± 5.22 kg/m²). The demographic and baseline characteristics of the patients with IBS among the
47
48 different subtypes are summarized in Table 1. Of the included subjects, the most frequent IBS subtype was
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50 IBS-M (45.9%), followed by IBS-D (41.3%), and IBS-C (10.1%). Only 59.0% of patients with IBS were
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52 within the normal weight range, whereas 30.3% were overweight or obese, and only a minority were
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1 underweight (10.7%). The percentage of obese patients was highest in IBS-D (17.9%, $p < 0.01$). Taking
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3 gender into account, 5.3% of males and 13.1% of females were underweight. Additionally, 7.0% of males and
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5 13.1% of females were obese and 26.3% of males and 15.9% of females were overweight. Overall, patients
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7 reported moderate to severe IBS symptom severity (IBS-SSS range: 125 - 484) and lower QOL (physical
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9 health range of SF-36: 15.19 – 64.00, mental health range of SF-36: 7.89 – 65.85).
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16 **3.2 Correlations between BMI, symptom severity and QOL**

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18 Pearson product-moment correlations indicated that high BMI values and elevated symptom severity
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20 were associated with poorer QOL. As shown in Table 2, BMI was negatively correlated with physical health (r
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22 = -0.177, $p < 0.01$). Symptom severity was negatively correlated with physical health ($r = -0.394$, $p < 0.01$)
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24 and mental health ($r = -0.268$, $p < 0.01$). Additionally, age was negatively correlated with symptom severity (r
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26 = -0.129, $p < 0.05$) and positively correlated with physical health ($r = 0.167$, $p < 0.01$).
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34 **3.3 Characteristics of BMI, symptom severity and QOL Across Demographic and IBS subtypes**

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36 As shown in Table 1, male reported significantly higher physical health problems than female ($t = 2.141$,
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38 $p < 0.05$). Compared to older patients (age > 50), the younger patients (age 18 - 49) reported significantly
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40 lower BMI level ($t = -3.20$, $p < 0.01$), greater symptom severity ($t = 2.039$, $p < 0.05$) and worse mental health
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42 ($t = -2.528$, $p < 0.05$). Patients living with a stable partner (married or unmarried cohabitation) had higher BMI
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44 compared to single participants ($t = -4.397$, $p < 0.01$). The patients with below high school education reported
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46 significantly higher physical health problems than those who with above high school education ($t = -3.376$, $p <$
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48 0.01). Compared with IBS-M patients, the IBS-D patients reported significantly higher BMI level ($t = -2.572$,
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50 $p < 0.05$).
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3.4 the influences of BMI in physical health and mental health of QOL

As shown in Table 3, the hierarchical multiple regression examined the relationship between dependent variable (physical health) and independent variables (symptom severity and BMI). Model 1 was significant ($F = 2.252, p < 0.05$) and explained 5.2% of the variance in physical health. Education status ($\beta = 0.174, p < 0.01$) was a significant positive factor that influencing physical health. In model 2, symptom severity significantly added to the amount of explained variance ($\Delta R^2 = 0.147, \Delta F = 52.498, p < 0.01$). In model 3, BMI also significantly added to the amount of explained variance ($\Delta R^2 = 0.037, \Delta F = 4.605, p < 0.01$). Obesity ($\beta = -0.177, p < 0.01$) was a significant negative factor that influencing physical health. Similarly, when mental health was used as the dependent variable, Model 1 was insignificant ($F = 0.854, p > 0.05$). In model 2, symptom severity significantly increased the amount of explained variance ($\Delta R^2 = 0.084, \Delta F = 26.824, p < 0.01$). In model 3, BMI didn't account for an additional significant amount of variance in mental health ($\Delta R^2 = 0.007, \Delta F = 0.772, p > 0.05$).

4 Discussion

This study sought to describe the BMI distribution in patients with IBS based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and the physical health and mental health of QOL. Therefore, we used standardized questionnaires and medical records to confirm the diagnosis and to assess patient symptoms and quality of life.

Our data show that being overweight is a common phenomenon in patients with IBS regardless of IBS subtype. These findings are in agreement with the results of a previous study based on obese patients in France, which found that 30.0% of obese patients had IBS [20]. We found that almost 40% of patients with IBS were not in the normal weight range, which is consistent with previous results [21]. Notably, the overweight and obesity rates in the general adult population in Germany [7] are higher than those found in our

1 IBS cohort. According to the German Health Update (GEDA) [7], in 2012 the overweight rate of adults was
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3 36.2% and the obesity rate was 16.5%. Interestingly, the distribution of weight was similar between the
4
5 different IBS groups. In particular, there was no difference between IBS-C and IBS-M. Notably, in IBS-D the
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7 percentage of obese patients reached 17.9%. Lee *et al.* [22] evaluated the relationship between visceral
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9 adipose tissue and the risk of IBS and suggested that disturbances of visceral fat may be more common in
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11 IBS-D patients. In addition, another Korean study found increased intestinal permeability in IBS-D patients
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13 [23]. One possible explanation is that the increase in visceral fat leads to an increase in intestinal osmolality
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15 [24] and then leads to the chronic diarrhea. These studies, however, were confined to patients from South
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21 Korea.

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24 IBS has a significant impact on patients' QOL [25]. Our data show an association between symptom
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26 severity and QOL with regard to physical and mental health. The patients in our study reported moderate to
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28 severe IBS symptom severity and lower QOL. Further, this association followed a negative dose response
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30 pattern. Our findings partially match those of Amouretti *et al.* [26], who found that IBS patients who reported
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32 their symptoms as severe or very severe had a very poor QoL compared with those who reported their
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34 symptoms as moderate. However, their study did not distinguish between physical and mental health and did
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36 not consider the effects of confounding factors such as BMI. This is an interesting but not completely new
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38 result which gives rise to the question of what mechanisms are responsible for this association.
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44 Through the hierarchical multiple regression, we tested the relationship between dependent variable
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46 (QOL) and independent variables (symptom severity and BMI). We controlled for the impact of the
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48 confounders (gender, age, family status, education status and IBS subtypes). The correlation between
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50 symptom severity and QOL was significantly negative, no matter which BMI category was. Our findings
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52 show that obesity was significant negative predictor of physical health. Patients with higher BMI were more
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54 frequently in poor physical health. This is in line with previous studies [11], in that increasing BMI is
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1 associated with increased upper gastrointestinal symptoms, bloating, and diarrhoea. Obesity may lead to more
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3 physiological stress on organs. Richards *et al.* [27] reported that obese patients have more severe pain and are
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5 to a larger extent restricted in their daily functioning compared to patients of normal weight. An additional
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7 finding of our study was that BMI didn't account for an additional significant amount of variance in mental
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9 health. This was inconsistent with findings by Mykletun [28], who found that BMI had significant association
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11 with IBS with regard to anxiety and mood disorders. However, their study evaluated only female patients. The
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13 findings of genome-wide association studies, from the genetic perspective, suggest the presence of many
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15 genetic loci each with a small effect influencing susceptibility to mental health symptoms (depression and
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17 anxiety) [29]. We can therefore hypothesise that, the unpredictable association between risk of mental health
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19 and BMI in our study may be due to non-modifiable genetic influences which predispose individuals to bad
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21 mental health.
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29 Several limitations of this study must be taken into account. First, the study was cross-sectional,
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31 therefore, it is impossible to infer causation. Second, BMI was based on the self-reported height and weight of
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33 patients and computed without objective measurement, therefore bias may have been introduced. Patients may
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35 occasionally underreport or overreport their weight and height leading to an underestimation of underweight
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37 or obese patients. However, in the Nutrinet-Santé study, researchers reported that deviations in self-reported
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39 BMIs from questionnaires can be ignored because their results confirmed the validity and agreement of
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41 self-reported data with measured data [30, 31]. The choice of SF-36 as the only QOL tool may partly miss the
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43 relationship between symptom severity and QOL. Moreover, BMI is associated with a multitude of different
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45 factors, such as genetics, fatty mass, dietary habit or physical exercise. Thus, BMI cannot fully reflect the
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47 impact of those factors on IBS in more details and more research is needed. The strengths of this study,
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49 however are the use of a large patient cohort with a validated diagnosis of IBS based on the Rome III criteria.
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1 To conclude, being overweight is a common phenomenon in IBS patients regardless of IBS subtypes.
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3 Our data further suggest that overweight and obesity may have a relevant influence on QOL. Patients with
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5 higher BMI were more frequently in poor physical health. The findings have some implications for future
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7 practice. Clinical doctors should pay special attention to abnormal weight in IBS patients as this maybe an
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9 indicator of a poorer QOL, especially with regard to the physical health.
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31 **Footnotes**

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34 **CONTRIBUTORS:** Yuanjun Dong, Jonas Tesarz, Rainer Schaefer and Wolfgang Eich designed the study
35
36 and wrote the protocol. Yuanjun Dong, Sabrina Berens and Jonas Tesarz performed the literature searches and
37
38 analyses. Yuanjun Dong wrote the first draft of the manuscript. All of the authors contributed to and have
39
40 approved the final manuscript.
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43

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45
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47
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49 **COMPETING INTERESTS:** The authors have indicated no financial conflicts of interest.
50

51 **PATIENT CONSENT:** Obtained.
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54 **ETHICS APPROVAL:** This study was approved by the Ethics Committee of Heidelberg University
55
56 (S-041/2014) and carried out in accordance with the Declaration of Helsinki.
57
58

PROVENANCE AND PEER REVIEW: Not commissioned; externally peer reviewed.

DATA SHARING STATEMENT: There is no additional unpublished data from this study.

Tables:

Table 1. Distribution of BMI at symptom severity and QOL based on several demographic and clinical features (n = 366)

	N	BMI mean (SD)	Symptom severity mean (SD)	Quality of life	
				Physical health mean (SD)	Mental health mean (SD)
Gender					
Male	114	24.30 (3.48)	280.27 (78.23)	42.21 (7.87) *	39.41 (12.76)
Female	252	23.71 (5.84)	292.10 (76.14)	40.21 (9.16)	39.23 (11.84)
Age					
18-49	264	23.36 (5.14) *	293.39 (77.52) *	41.28 (8.21)	38.32 (12.17) *
> 50	102	25.29 (5.12)	275.55 (74.04)	39.69 (10.19)	41.80 (11.67)
Family status					
Single	160	22.69 (4.13) #	298.15 (71.90)	41.42 (7.69)	37.96 (12.09)
Marr [§]	164	25.19 (5.07)	281.94 (82.67)	40.58 (9.59)	40.32 (12.18)
Divo [§]	37	23.50 (5.11)	283.11 (69.13)	39.45 (10.12)	40.87 (11.20)
Education status					
Below Hs [§]	97	24.62 (6.19)	296.31 (71.99)	38.40 (9.33) *	40.51 (12.35)
Above Hs [§]	232	23.68 (4.87)	286.54 (81.60)	42.10 (8.47)	38.60 (12.02)
IBS subtypes					
IBS-C	37	23.38 (5.34)	293.13 (82.41)	40.76 (9.33)	40.43 (12.30)

1	IBS-D	151	24.69 (5.93) [△]	293.96 (78.00)	40.57 (9.17)	38.74 (12.88)
2						
3	IBS-M	168	23.22 (4.01)	283.53 (73.19)	41.09 (8.40)	38.98 (11.39)
4						

5 * $p < 0.05$

6
7 # $p < 0.05$ for post-hoc comparison between single and Married or unmarried cohabitation

8
9 $\Delta p < 0.05$ for post-hoc comparison between IBS-D and IBS-M

10
11 § Marr means “Married or unmarried cohabitation”, Divo means “Divorced or widowed”, Hs means “High
12 school”

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14 IBS-U was not included in the analysis because the sample size is too small.

15
16 Symptom severity based on IBS-SSS: Mild (IBS-SSS: 75-175), Moderate (IBS-SSS: 175-300) and Severe
17 (IBS-SSS: > 300).

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19 QOL based on SF-36: range from 0 (“highest disability”) to 100 (“no disability”).

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21 IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass index;
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Table 2. Correlation Matrix for the Study Variables in IBS patients

	BMI	Age	Symptom severity	Physical Health	Mental health
BMI	1.00				
Age	0.173**	1.00			
Symptom severity	0.055	-0.129*	1.00		
Physical Health	-0.177**	-0.085	-0.349**	1.00	
Mental health	0.033	0.167**	-0.268**	0.029	1.00

* $p < 0.05$

** $p < 0.01$

BMI, Body mass index;

Table 3. Results of hierarchical multiple regression relating physical health and mental health to symptom severity and BMI

	Model 1		Model 2		Model 3		Model summary			
	β	t	β	t	β	t	F	R^2	ΔF	ΔR^2
Physical health										
Age	-0.081	-1.093	-0.116	-1.688	-0.141	-2.063*	2.252*	0.052*	-	-
Gender	-0.061	-1.052	-0.050	-0.937	-0.033	-0.611				
Single & Marr [§]	-0.020	-0.263	0.003	0.048	-0.030	-0.439				
Divo [§] & Marr [§]	-0.043	-0.697	-0.035	-0.609	-0.035	-0.621				
Education	0.174	2.913**	0.150	2.725**	0.130	2.404*				
IBS-C & IBS-D	0.032	0.529	0.024	0.438	-0.004	-0.081				
IBS-M & IBS-D	0.048	0.775	0.003	0.049	-0.030	-0.529				
Symptom severity	-	-	-0.389	-7.246**	-0.387	-7.295**	8.007**	0.200**	52.498**	0.147**
Under [§] & Normal	-	-	-	-	-0.003	-0.060	7.965**	0.237**	4.605**	0.037**
Over [§] & Normal	-	-	-	-	0.067	1.193				
Obesity & Normal	-	-	-	-	-0.177	-3.170**				
Mental health										
Age	0.159	2.106*	0.133	1.834	0.119	1.611	0.854	0.020	-	-
Gender	-0.029	-0.499	-0.021	-0.375	-0.006	-0.110				
Single & Marr [§]	0.052	0.690	0.070	0.958	0.068	0.922				
Divo [§] & Marr [§]	-0.020	-0.316	-0.014	-0.224	-0.007	-0.117				
Education	-0.045	-0.750	-0.064	-1.092	-0.066	-1.133				
IBS-C & IBS-D	0.024	0.381	0.018	0.300	0.009	0.144				
IBS-M & IBS-D	0.022	0.356	-0.012	-0.194	-0.025	-0.408				
Symptom severity	-	-	-0.294	-5.179**	-0.301	-5.263**	4.168**	0.105**	26.824**	0.084**
Under [§] & Normal	-	-	-	-	-0.077	-1.307	3.234**	0.112**	0.772	0.007
Over [§] & Normal	-	-	-	-	0.017	0.280				
Obesity & Normal	-	-	-	-	-0.041	-0.684				

* $p < 0.05$

** $p < 0.01$

Model 1 factors: age, gender, family status, education status, IBS subtypes;

1 Model 2 factors: age, gender, family status, education status, IBS subtypes, symptom severity;

2 Model 3 factors: age, gender, family status, education status, IBS subtypes, symptom severity, BMI
3 categories.

4 § Marr means “Married or unmarried cohabitation”, Divo means “Divorced or widowed, Under means
5 “underweight”, Over means “overweight”.

6 IBS-U was not included in the analysis because the sample size is too small.

7 Underweight, BMI < 18.5 kg/m²; normal weight, BMI 18.5–25 kg/m²; overweight, 25–30 kg/m²; obesity,
8 BMI > 30 kg/m²; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body
9 mass index

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For peer review only

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract 【Page 1】 (b) Provide in the abstract an informative and balanced summary of what was done and what was found 【Pages 2 - 3】
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 【Pages 4】
Objectives	3	State specific objectives, including any prespecified hypotheses 【Pages 4】
Methods		
Study design	4	Present key elements of study design early in the paper 【Pages 5 - 7】
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 【Page 5 - 7】
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants 【Page 5】
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 【Pages 6 - 7】
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 【Pages 6 - 7】
Bias	9	Describe any efforts to address potential sources of bias 【Page 5】
Study size	10	Explain how the study size was arrived at 【Page 5】
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 【Pages 6 - 7】
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding 【Pages 6 - 7】 (b) Describe any methods used to examine subgroups and interactions 【Page 6 - 7】 (c) Explain how missing data were addressed 【Page 6 - 7】 (d) If applicable, describe analytical methods taking account of sampling strategy 【N/A】 (e) Describe any sensitivity analyses 【N/A】
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 【Page 7 - 8; table 1】 (b) Give reasons for non-participation at each stage 【N/A】 (c) Consider use of a flow diagram 【N/A】
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 【Pages 7 - 9】 (b) Indicate number of participants with missing data for each variable of interest 【Page 7; table 1】
Outcome data	15*	Report numbers of outcome events or summary measures 【Pages 7 - 9, table 1-3】
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 【Pages 7 - 9; table 1 - 3】

		(b) Report category boundaries when continuous variables were categorized 【N/A】
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period 【N/A】
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 【N/A】
Discussion		
Key results	18	Summarise key results with reference to study objectives 【Page 9 - 12】
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 【Page 11】
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 【Pages 9 - 12】
Generalisability	21	Discuss the generalisability (external validity) of the study results 【Pages 9 - 12】
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 【Page 15】

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Is body mass index associated with symptom severity and health-related quality of life in irritable bowel syndrome? A cross-sectional study

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Secondary Subject Heading:	Nutrition and metabolism, Mental health
Keywords:	Irritable bowel syndrome, Body mass index, Symptom severity, Quality of life

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Original Article**Is body mass index associated with symptom severity and health-related quality of life in irritable bowel syndrome? A cross-sectional study**

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Abstract

Objective

The aim of this study was to describe the body mass index (BMI) distribution in patients with irritable bowel syndrome (IBS) based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and quality of life (QOL).

Methods

A cross-sectional study was carried out in patients visiting our outpatient Functional Gastrointestinal Disorders specialty clinic. IBS diagnosis was made based on Rome III criteria. IBS symptom severity was investigated using the IBS severity score system (IBS-SSS). QOL was assessed using the Short-Form-36-Health-Survey (SF-36), which consists of physical health and mental health.

Results

366 patients (252 females) who fulfilled Rome III criteria and provided complete BMI data (23.90 ± 5.22 kg/m²) were included. Overall, 59.0% of patients with IBS were in the normal weight range, 30.3% were overweight or obese, and 10.7% were underweight. Both physical and mental health decreased significantly with the severity of symptoms (all $p < 0.01$), whilst controlling for several covariates (age, gender, family status, education status and IBS subtypes). Obesity and symptom severity ($\beta = -0.177$, $\Delta R^2 = 0.037$, $p < 0.01$; $\beta = -0.387$, $\Delta R^2 = 0.147$, $p < 0.01$) were significant negative factors that influencing physical health. Symptom severity ($\beta = -0.301$, $\Delta R^2 = 0.084$, $p < 0.01$) was significant negative factor that influencing mental health. However, BMI didn't account for additional variance in mental health ($p > 0.05$).

Conclusion

Being overweight is a common phenomenon in patients with IBS regardless of IBS subtype. The association between QOL and symptom severity followed a negative dose response pattern. Patients with

1 higher BMI, especially obese patients, were more frequently in poor physical health. However, this kind of
2
3 relationship was not found in BMI and mental health.
4

5
6 **Keywords:**

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8 Irritable bowel syndrome; Body mass index; Symptom severity; Quality of life
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16 **Strengths and limitations of this study:**

- 17
18 1) This study uses a large and well described patient cohort with a validated diagnosis of IBS based on the
19 Rome III criteria;
20
21 2) The association between QOL and symptom severity followed a negative dose response pattern;
22
23 3) Patients with higher BMI were more frequently in poor physical health. However, this kind of relationship
24 was not found in BMI and mental health of QOL.
25
26 4) The study was cross-sectional, therefore it is not possible to infer causation;
27
28 5) BMI cannot fully reflect the impact of the factors of fatty mass, dietary habit, other lifestyle factors such as
29 physical exercise on IBS.
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1 Introduction

Irritable bowel syndrome (IBS) is a chronic and common functional bowel disorder that is characterized by recurrent abdominal pain or discomfort associated with altered bowel habits [1]. According to the Rome III criteria, IBS is classified into four subtypes [IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), mixed IBS (IBS-M) and un-subtyped IBS (IBS-U)] based on the predominant abdominal symptomatology [1]. It has been frequently reported that IBS leads to impaired quality of life (QOL) [2-4]. The symptoms of IBS are associated with different eating habits [5]. In a recent randomized controlled trial, a diet low in Fermentable Oligo-, Di-, Mono-saccharides And Polyols (FODMAPs) was shown to improve the IBS-D patients' QOL, anxiety, and activity impairment [6].

Epidemiologic studies have shown that as many as 16.5% of adults in European countries are obese [body mass index (BMI) > 30 kg/m²] [7] and that the incidence of obesity is increasing [8]. Additionally, a cross-sectional multicentre study found that more than 63% of outpatients and 80% of inpatients in gastroenterological centres suffered from significant changes in body composition [9]. In addition, underweight (BMI < 18.5 kg/m²) or obese body condition (BMI > 30 kg/m²) are both associated with multiple abdominal symptoms leading to reduced QOL [10, 11]. Although extensive research has been carried out on the prevalence of obesity in the general population and in connection with numerous diseases, there is only little published data on the prevalence and clinical relevance of nutritional status and body mass in patients with IBS. Locke *et al.* [12] found no association between IBS status and BMI. However, this study was a population-based study. Studies with large enough sample size based on clinic patients are missing so far.

Therefore, the aim of this study was to describe the BMI distribution in patients with IBS based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and the physical health and mental health of QOL.

2 Methods

This cross-sectional survey included patients evaluated at the Functional Gastrointestinal Disorders (FGIDs) specialty clinic of the Department of General Internal Medicine and Psychosomatics of Heidelberg University Hospital, which is a tertiary care facility. All patients who completed our routine baseline documentation were enrolled. The routine data from individual health records was transferred into the database and pseudonymized. This study was approved by the Ethics Committee of Heidelberg University (S-041/2014) and carried out in accordance with the Declaration of Helsinki.

2.1 Patients recruitment

From 01/2011 to 12/2016, patients' clinical data were consecutively collected from our outpatient FGIDs clinic at Heidelberg University Hospital for this explorative and descriptive study. All patients ≥ 18 years of age, who voluntarily signed an informed consent, were included, if they fulfilled the Rome III criteria for the diagnosis of IBS [1]. There was no exclusion criteria. The subtype criteria for IBS were based on stool consistency as assessed by the Bristol Stool Scale (BSS) and Rome III criteria [13]. Demographic data including gender, age, family status, level of education and residence, was also collected at baseline using the Psychosomatic Basis Documentation Questionnaire (Psy-BaDo) [14].

2.2 Patient Involvement

No patients were involved in conducting the study. However, in order to increase the clinical relevance of the study, we established an advisory group to advise the research project.

2.3 Measurement of IBS symptom severity

Patients rated the severity of their IBS symptoms by completing the IBS severity score system (IBS-SSS) [15]. The IBS-SSS has a maximum score of 500 and comprises five items: frequency and intensity of abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference of IBS with daily life. Based on validated cut-off values, three IBS severity subgroups can be distinguished: Mild (IBS-SSS: 75-175), Moderate (IBS-SSS: 175-300) and Severe (IBS-SSS: > 300). The German version of this questionnaire was validated by Betz *et al.* [16] and the total score was computed in accordance with the manual.

2.4 Measurement of BMI

BMI was calculated as the individual's self-reported body weight (kg) divided by the square of their height (m). BMI was categorized according to the World Health Organization (WHO) classification of physical status [17]: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–25 kg/m²), overweight (25–30 kg/m²), or obese body condition (BMI > 30 kg/m²).

2.5 Measurement of quality of life

Quality of life was measured using the Short Form 36 Health Survey (SF-36) [18]. SF-36 is a 36-item, patient-reported survey of patient quality of life, which consists of a physical health index and mental health index. The SF-36 is widely used and well validated for assessing generic health outcomes. Each scale is directly transformed into a 0-100 scale. Lower scores represent a higher degree of disability. Validation of the German version was performed by Morfeld *et al.* [19].

2.6 Statistical analysis

Routine data were transformed into an SPSS file and evaluated using the statistical program SPSS (IBM, version 22.0). Descriptive statistics are presented as the means and standard deviation (*SD*) for continuous variables and as absolute numbers and percentages for categorical variables. All analyses were explorative and not of a confirmatory nature. All primary and secondary variables were first tested for normal distribution. For normally distributed variables, the mean and standard deviation were calculated. Variables that lacked a normal distribution were reported using the median and interquartile range. The Mann-Whitney U Test was used to assess the level of significance because a number of participants differed between the groups. Comparison of socio-demographical and anthropometric data according to BMI was performed using analysis of variance (ANOVA) and nonparametric tests in the first instance. Where significant group differences were detected based on ANOVA, post-hoc least significant difference tests were conducted to compare the study groups in a pairwise fashion. We also used the Pearson correlation coefficients to investigate the linear association between demographics, BMI, clinical and psychological features. Hierarchical multiple regression was used to help understand the impact of potential confounders as well as the predictive role of BMI in physical health and mental health of QOL. We tested the impact of the confounders (gender, age, family status, education status and IBS subtypes) in Model 1. In model 2, we added the symptom severity. BMI categories (underweight, normal weight, overweight and obesity) were added in model 3. All tests were two-sided and statistical significance was accepted if $p < 0.05$.

3 Results

3.1 Characteristics of study sample

A total of 576 patients completed the questionnaire. Excluding 113 patients whose Rome III criteria data were partly missing, 366 patients with IBS were enrolled in this study (114 males, 252 females; mean BMI 23.90 ± 5.22 kg/m²). The demographic and baseline characteristics of the patients with IBS among the different subtypes are summarized in Table 1. Of the included subjects, the most frequent IBS subtype was IBS-M (45.9%), followed by IBS-D (41.3%), and IBS-C (10.1%). Only 59.0% of patients with IBS were within the normal weight range, whereas 30.3% were overweight or obese, and only a minority were underweight (10.7%). The percentage of obese patients was highest in IBS-D (17.9%, $p < 0.01$). Taking gender into account, 5.3% of males and 13.1% of females were underweight. Additionally, 7.0% of males and 13.1% of females were obese and 26.3% of males and 15.9% of females were overweight. Overall, patients reported moderate to severe IBS symptom severity (IBS-SSS range: 125 - 484) and lower QOL (physical health range of SF-36: 15.19 – 64.00, mental health range of SF-36: 7.89 – 65.85).

3.2 Correlations between BMI, symptom severity and QOL

Pearson product-moment correlations indicated that high BMI values and elevated symptom severity were associated with poorer QOL. As shown in Table 2, BMI was negatively correlated with physical health ($r = -0.177$, $p < 0.01$). Symptom severity was negatively correlated with physical health ($r = -0.394$, $p < 0.01$) and mental health ($r = -0.268$, $p < 0.01$). Additionally, age was negatively correlated with symptom severity ($r = -0.129$, $p < 0.05$) and positively correlated with physical health ($r = 0.167$, $p < 0.01$).

3.3 Characteristics of BMI, symptom severity and QOL Across Demographic and IBS subtypes

As shown in Table 1, male reported significantly higher physical health problems than female ($t = 2.141$, $p < 0.05$). Compared to older patients (age > 50), the younger patients (age 18 - 49) reported significantly lower BMI level ($t = -3.20$, $p < 0.01$), greater symptom severity ($t = 2.039$, $p < 0.05$) and worse mental health ($t = -2.528$, $p < 0.05$). Patients living with a stable partner (married or unmarried cohabitation) had higher BMI compared to single participants ($t = -4.397$, $p < 0.01$). The patients with below high school education reported significantly higher physical health problems than those who with above high school education ($t = -3.376$, $p < 0.01$). Compared with IBS-M patients, the IBS-D patients reported significantly higher BMI level ($t = -2.572$, $p < 0.05$).

3.4 the influences of BMI in physical health and mental health of QOL

As shown in Table 3, the hierarchical multiple regression examined the relationship between dependent variable (physical health) and independent variables (symptom severity and BMI). Model 1 was significant ($F = 2.252$, $p < 0.05$) and explained 5.2% of the variance in physical health. Education status ($\beta = 0.174$, $p < 0.01$) was a significant positive factor that influencing physical health. In model 2, symptom severity significantly added to the amount of explained variance ($\Delta R^2 = 0.147$, $\Delta F = 52.498$, $p < 0.01$). In model 3, BMI also significantly added to the amount of explained variance ($\Delta R^2 = 0.037$, $\Delta F = 4.605$, $p < 0.01$). Obesity ($\beta = -0.177$, $p < 0.01$) was a significant negative factor that influencing physical health. Similarly, when mental health was used as the dependent variable, Model 1 was insignificant ($F = 0.854$, $p > 0.05$). In model 2, symptom severity significantly increased the amount of explained variance ($\Delta R^2 = 0.084$, $\Delta F = 26.824$, $p < 0.01$). In model 3, BMI didn't account for an additional significant amount of variance in mental health ($\Delta R^2 = 0.007$, $\Delta F = 0.772$, $p > 0.05$).

4 Discussion

This study sought to describe the BMI distribution in patients with IBS based on the Rome III criteria, and to evaluate the association of BMI with symptom severity and the physical health and mental health of QOL. Therefore, we used standardized questionnaires and medical records to confirm the diagnosis and to assess patient symptoms and quality of life.

Our data show that being overweight is a common phenomenon in patients with IBS regardless of IBS subtype. These findings are in agreement with the results of a previous study based on obese patients in France, which found that 30.0% of obese patients had IBS [20]. We found that almost 40% of patients with IBS were not in the normal weight range, which is consistent with previous results [21]. Notably, the overweight and obesity rates in the general adult population in Germany [7] are higher than those found in our IBS cohort. According to the German Health Update (GEDA) [7], in 2012 the overweight rate of adults was 36.2% and the obesity rate was 16.5%. Interestingly, the distribution of weight was similar between the different IBS groups. In particular, there was no difference between IBS-C and IBS-M. Notably, in IBS-D the percentage of obese patients reached 17.9%. Lee *et al.* [22] evaluated the relationship between visceral adipose tissue and the risk of IBS and suggested that disturbances of visceral fat may be more common in IBS-D patients. In addition, another Korean study found increased intestinal permeability in IBS-D patients [23]. One possible explanation is that the increase in visceral fat leads to an increase in intestinal osmolality [24] and then leads to the chronic diarrhea. These studies, however, were confined to patients from South Korea.

IBS has a significant impact on patients' QOL [25]. Our data show an association between symptom severity and QOL with regard to physical and mental health. The patients in our study reported moderate to severe IBS symptom severity and lower QOL. Further, this association followed a negative dose response

1 pattern. Our findings partially match those of Amouretti *et al.* [26], who found that IBS patients who reported
2 their symptoms as severe or very severe had a very poor QoL compared with those who reported their
3 symptoms as moderate. However, their study did not distinguish between physical and mental health and did
4 not consider the effects of confounding factors such as BMI. This is an interesting but not completely new
5 result which gives rise to the question of what mechanisms are responsible for this association.
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13 Through the hierarchical multiple regression, we tested the relationship between dependent variable
14 (QOL) and independent variables (symptom severity and BMI). We controlled for the impact of the
15 confounders (gender, age, family status, education status and IBS subtypes). The correlation between
16 symptom severity and QOL was significantly negative, no matter which BMI category was. Our findings
17 show that obesity was significant negative predictor of physical health. Patients with higher BMI were more
18 frequently in poor physical health. This is in line with previous studies [11], in that increasing BMI is
19 associated with increased upper gastrointestinal symptoms, bloating, and diarrhoea. Obesity may lead to more
20 physiological stress on organs. Richards *et al.* [27] reported that obese patients have more severe pain and are
21 to a larger extent restricted in their daily functioning compared to patients of normal weight. An additional
22 finding of our study was that BMI didn't account for an additional significant amount of variance in mental
23 health. This was inconsistent with findings by Mykletun [28], who found that BMI had significant association
24 with IBS with regard to anxiety and mood disorders. However, their study evaluated only female patients. The
25 findings of genome-wide association studies, from the genetic perspective, suggest the presence of many
26 genetic loci each with a small effect influencing susceptibility to mental health symptoms (depression and
27 anxiety) [29]. We can therefore hypothesise that, the unpredictable association between risk of mental health
28 and BMI in our study may be due to non-modifiable genetic influences which predispose individuals to bad
29 mental health.
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1 Several limitations of this study must be taken into account. First, the study was cross-sectional,
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3 therefore, it is impossible to infer causation. Second, BMI was based on the self-reported height and weight of
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5 patients and computed without objective measurement, therefore bias may have been introduced. Patients may
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7 occasionally underreport or overreport their weight and height leading to an underestimation of underweight
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9 or obese patients. However, in the Nutrinet-Santé study, researchers reported that deviations in self-reported
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11 BMIs from questionnaires can be ignored because their results confirmed the validity and agreement of
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13 self-reported data with measured data [30, 31]. The choice of SF-36 as the only QOL tool may partly miss the
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15 relationship between symptom severity and QOL. Moreover, BMI is associated with a multitude of different
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17 factors, such as genetics, fatty mass, dietary habit or physical exercise. Thus, BMI cannot fully reflect the
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19 impact of those factors on IBS in more details and more research is needed. The strengths of this study,
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21 however are the use of a large patient cohort with a validated diagnosis of IBS based on the Rome III criteria.
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28 To conclude, being overweight is a common phenomenon in IBS patients regardless of IBS subtypes.
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30 Our data further suggest that overweight and obesity may have a relevant influence on QOL. Patients with
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32 higher BMI were more frequently in poor physical health. The findings have some implications for future
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34 practice. Clinical doctors should pay special attention to abnormal weight in IBS patients as this maybe an
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36 indicator of a poorer QOL, especially with regard to the physical health.
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Footnotes

CONTRIBUTORS: Yuanjun Dong, Jonas Tesarz, Rainer Schaefer and Wolfgang Eich designed the study and wrote the protocol. Yuanjun Dong, Sabrina Berens and Jonas Tesarz performed the literature searches and analyses. Yuanjun Dong wrote the first draft of the manuscript. All of the authors contributed to and have approved the final manuscript.

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Tables:

Table 1. Distribution of BMI at symptom severity and QOL based on several demographic and clinical features (n = 366)

	N	BMI mean (SD)	Symptom severity mean (SD)	Quality of life	
				Physical health mean (SD)	Mental health mean (SD)
Gender					
Male	114	24.30 (3.48)	280.27 (78.23)	42.21 (7.87) *	39.41 (12.76)
Female	252	23.71 (5.84)	292.10 (76.14)	40.21 (9.16)	39.23 (11.84)
Age					
18-49	264	23.36 (5.14) *	293.39 (77.52) *	41.28 (8.21)	38.32 (12.17) *
> 50	102	25.29 (5.12)	275.55 (74.04)	39.69 (10.19)	41.80 (11.67)
Family status					
Single	160	22.69 (4.13) #	298.15 (71.90)	41.42 (7.69)	37.96 (12.09)
Marr [§]	164	25.19 (5.07)	281.94 (82.67)	40.58 (9.59)	40.32 (12.18)
Divo [§]	37	23.50 (5.11)	283.11 (69.13)	39.45 (10.12)	40.87 (11.20)
Education status					
Below Hs [§]	97	24.62 (6.19)	296.31 (71.99)	38.40 (9.33) *	40.51 (12.35)
Above Hs [§]	232	23.68 (4.87)	286.54 (81.60)	42.10 (8.47)	38.60 (12.02)
IBS subtypes					
IBS-C	37	23.38 (5.34)	293.13 (82.41)	40.76 (9.33)	40.43 (12.30)
IBS-D	151	24.69 (5.93) ^Δ	293.96 (78.00)	40.57 (9.17)	38.74 (12.88)
IBS-M	168	23.22 (4.01)	283.53 (73.19)	41.09 (8.40)	38.98 (11.39)

* $p < 0.05$ # $p < 0.05$ for post-hoc comparison between single and Married or unmarried cohabitation $\Delta p < 0.05$ for post-hoc comparison between IBS-D and IBS-M

1 § Marr means “Married or unmarried cohabitation”, Divo means “Divorced or widowed”, Hs means “High
2 school”
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4 IBS-U was not included in the analysis because the sample size is too small.
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6 Symptom severity based on IBS-SSS: Mild (IBS-SSS: 75-175), Moderate (IBS-SSS: 175-300) and Severe
7 (IBS-SSS: > 300).
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9 QOL based on SF-36: range from 0 (“highest disability”) to 100 (“no disability”).
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11 IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body mass index;
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Table 2. Correlation Matrix for the Study Variables in IBS patients

	BMI	Age	Symptom severity	Physical Health	Mental health
BMI	1.00				
Age	0.173**	1.00			
Symptom severity	0.055	-0.129*	1.00		
Physical Health	-0.177**	-0.085	-0.349**	1.00	
Mental health	0.033	0.167**	-0.268**	0.029	1.00

* $p < 0.05$

** $p < 0.01$

BMI, Body mass index;

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Table 3. Results of hierarchical multiple regression relating physical health and mental health to symptom severity and BMI

	Model 1		Model 2		Model 3		Model summary			
	β	t	β	t	β	t	F	R^2	ΔF	ΔR^2
Physical health										
Age	-0.081	-1.093	-0.116	-1.688	-0.141	-2.063*	2.252*	0.052*	-	-
Gender	-0.061	-1.052	-0.050	-0.937	-0.033	-0.611				
Single & Marr [§]	-0.020	-0.263	0.003	0.048	-0.030	-0.439				
Divo [§] & Marr [§]	-0.043	-0.697	-0.035	-0.609	-0.035	-0.621				
Education	0.174	2.913**	0.150	2.725**	0.130	2.404*				
IBS-C & IBS-D	0.032	0.529	0.024	0.438	-0.004	-0.081				
IBS-M & IBS-D	0.048	0.775	0.003	0.049	-0.030	-0.529				
Symptom severity	-	-	-0.389	-7.246**	-0.387	-7.295**	8.007**	0.200**	52.498**	0.147**
Under [§] & Normal	-	-	-	-	-0.003	-0.060	7.965**	0.237**	4.605**	0.037**
Over [§] & Normal	-	-	-	-	0.067	1.193				
Obesity & Normal	-	-	-	-	-0.177	-3.170**				
Mental health										
Age	0.159	2.106*	0.133	1.834	0.119	1.611	0.854	0.020	-	-
Gender	-0.029	-0.499	-0.021	-0.375	-0.006	-0.110				
Single & Marr [§]	0.052	0.690	0.070	0.958	0.068	0.922				
Divo [§] & Marr [§]	-0.020	-0.316	-0.014	-0.224	-0.007	-0.117				
Education	-0.045	-0.750	-0.064	-1.092	-0.066	-1.133				
IBS-C & IBS-D	0.024	0.381	0.018	0.300	0.009	0.144				
IBS-M & IBS-D	0.022	0.356	-0.012	-0.194	-0.025	-0.408				
Symptom severity	-	-	-0.294	-5.179**	-0.301	-5.263**	4.168**	0.105**	26.824**	0.084**
Under [§] & Normal	-	-	-	-	-0.077	-1.307	3.234**	0.112**	0.772	0.007
Over [§] & Normal	-	-	-	-	0.017	0.280				
Obesity & Normal	-	-	-	-	-0.041	-0.684				

* $p < 0.05$ ** $p < 0.01$

Model 1 factors: age, gender, family status, education status, IBS subtypes;

Model 2 factors: age, gender, family status, education status, IBS subtypes, symptom severity;

1 Model 3 factors: age, gender, family status, education status, IBS subtypes, symptom severity, BMI
2 categories.
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4 § Marr means “Married or unmarried cohabitation”, Divo means “Divorced or widowed, Under means
5 “underweight”, Over means “overweight”.
6
7

8 IBS-U was not included in the analysis because the sample size is too small.
9

10 Underweight, BMI < 18.5 kg/m²; normal weight, BMI 18.5–25 kg/m²; overweight, 25–30 kg/m²; obesity,
11 BMI > 30 kg/m²; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; BMI, body
12 mass index
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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract 【Page 1】 (b) Provide in the abstract an informative and balanced summary of what was done and what was found 【Pages 2 - 3】
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 【Pages 4】
Objectives	3	State specific objectives, including any prespecified hypotheses 【Pages 4】
Methods		
Study design	4	Present key elements of study design early in the paper 【Pages 5 - 7】
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection 【Page 5 - 7】
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants 【Page 5】
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 【Pages 6 - 7】
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 【Pages 6 - 7】
Bias	9	Describe any efforts to address potential sources of bias 【Page 5】
Study size	10	Explain how the study size was arrived at 【Page 5】
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why 【Pages 6 - 7】
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding 【Pages 6 - 7】 (b) Describe any methods used to examine subgroups and interactions 【Page 6 - 7】 (c) Explain how missing data were addressed 【Page 6 - 7】 (d) If applicable, describe analytical methods taking account of sampling strategy 【N/A】 (e) Describe any sensitivity analyses 【N/A】
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 【Page 8; table 1】 (b) Give reasons for non-participation at each stage 【N/A】 (c) Consider use of a flow diagram 【N/A】
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 【Pages 8-9】 (b) Indicate number of participants with missing data for each variable of interest 【Page 8; table 1】
Outcome data	15*	Report numbers of outcome events or summary measures 【Pages 8-9, table 1-3】
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 【Pages 8-9; table 1-3】

		(b) Report category boundaries when continuous variables were categorized 【N/A】
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period 【N/A】
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 【N/A】
Discussion		
Key results	18	Summarise key results with reference to study objectives 【Page 10-12】
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 【Page 11】
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 【Pages 10-12】
Generalisability	21	Discuss the generalisability (external validity) of the study results 【Pages 10-12】
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 【Page 17】

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.