Prevalence of severe irritable bowel syndrome among Italian adults. A meta-analysis

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Abstract. – **OBJECTIVE:** To provide a summary estimate of the prevalence of irritable bowel syndrome (IBS) and IBS with severe symptomatology, stratified by gender and subtype, among Italian adults.

MATERIALS AND METHODS: We searched MedLine and Scopus databases to identify surveys on IBS prevalence among Italian samples, and/or severe IBS prevalence among Caucasian populations, up to June 2017. Random-effect proportion meta-analyses were used to obtain summary estimates of IBS prevalence. Raw numbers of adults with IBS or severe IBS were computed multiplying pooled prevalence estimates by the current Italian adult population. For both IBS and severe IBS, several estimates were provided according to different scenarios, using the pooled estimates from meta-analyses, their highest and lowest 95% confidence intervals (CI), and the lowest prevalence among all individual studies.

RESULTS: The pooled prevalence of IBS among Italian adults, resulting from a meta-analysis of 5 studies including 40,654 subjects, was 7.7% (95% CI: 6.0%-9.7%). The lowest published estimate was 5.4%. The overall number of Italian adults with IBS may thus range between a minimum of 2,736,700 (1,797,800 females; 65.7%) and 4,915,800. From a meta-analysis of 17 studies including 16,873 subjects, the pooled proportion of severe IBS was 23.5% (95% CI: 18.7%-28.7%), with a lowest published estimate of 8.4%. The overall number of Italian adults with severe IBS may thus range between 229,900 (86,600 with constipation-predominant subtype; 70,600 diarrhea-predominant; 72,600 mixed/alternating) and 1,410,800. In a standard, still conservative scenario, based upon the lowest 95% CIs from meta-analyses, the Italians with severe IBS would be 511,800.

CONCLUSIONS: Using an extremely conservative, lowest plausible estimate, no less than 230,000 Italian adults are suffering from severe IBS, requiring appropriate treatment and recognition by healthcare providers. A standardized instrument to measure IBS severity is urgently required to support diagnostic and therapeutic processes, and improve the precision of epidemiological estimates.

Key Words:
Irritable bowel syndrome, Clinical severity, Prevalence, Italy.

Introduction

Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract, characterized by abdominal pain and altered bowel habit, with either predominant diarrhea, constipation, or both[1,2]. The clinical severity largely varies, ranging from episodic mild pain up to severe daily symptoms, associated with psychological distress and a drop of quality of life[3].

As no definitive biomarker has been found, IBS is diagnosed clinically, using a set of criteria that has been refined over time, up to the current set, the Roma IV Diagnostic Criteria for IBS[3]. Despite formally established criteria, estimating IBS epidemiology remains a complex issue[4,5]. On one side, few IBS patients are admitted to the hospital[6], and there is no standardized therapy[7,8]. Thus, both hospital discharge abstracts and prescription data have limited utility, and surveys have to use expensive and suboptimal approaches such as postal questionnaires of phone interviews to collect self-reported symptoms, or ask whether participants received a diagnosis of IBS[2,9]. On the other side, diagnostic criteria have changed over time and still have some margin of error in

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their application, especially among primary care physicians dealing with less severe patients[7,10]. As a consequence, the estimates of IBS prevalence show wide variations depending on the adopted diagnostic criteria[2,9].

Worldwide, the overall prevalence of IBS has been estimated by one meta-analysis published in 2012 as 11.2% (95% CI: 9.8%-12.8%)[9], and by another meta-analysis published in 2016 as 8.8% (8.7%-8.9%)[5]. The prevalence, however, varied largely by country, study, and gender[2,5,9,11]. Table I shows some of the most recent estimates in selected countries: in Southern European studies, the pooled prevalence is estimated as 15.0% (95% IC: 11.0%-20.0%).

In spite of the public health relevance of IBS, in several countries including Italy uncertainty remains on the prevalence of IBS, and especially on the prevalence of patients with severe symptoms. These estimates are required to estimate the overall disease burden and guide public health policies[12].

We aimed at providing an overall estimate of the IBS prevalence in Italy through a systematic literature search and a proportion meta-analysis of individual study results. We also aimed at providing an estimate of the overall Italian prevalence of IBS patients with severe symptoms, stratified by gender and IBS subtype (IBS-C: Constipation-predominant IBS; IBS-D: diarrhea-predominant IBS; or IBS-M: mixed stool pattern or alternating stool pattern IBS[13]).

Materials and Methods

Bibliographic Search

We first searched MedLine and Scopus databases to identify cross-sectional surveys evaluating the prevalence of IBS in the general population of Italian adults. Those that reported the prevalence of IBS in convenience samples such as university students, employees at an institution, or those attending screening clinic health check-ups were not eligible for inclusion. As the number of retrieved Italian studies evaluating the severity of IBS patients was scarce, we then searched for all studies that evaluated the prevalence of IBS patients with severe symptoms performed in countries where the majority of the population is Caucasian. Both searches were done by two independent investigators (LM, MEF), up to June 1, 2017, using various combinations of search terms. First search: (irritable bowel syndrome OR IBS) AND (prevalence) AND (Italy OR Italian) [ALL FIELDS][9]; Second search: (irritable bowel syndrome OR IBS) AND (severe OR severity OR FBDSI OR IBS-SSS) [Title/Abstract][14]. We also screened the reference lists of reviews and retrieved articles, for additional pertinent papers. No language restrictions were used.

Data Extraction and Analysis

We used random-effect meta-analyses of proportions to combine data and obtain summary estimates of the prevalence of IBS, overall and by gender[15]. We also used proportion meta-analyses to estimate the percentage of patients with severe symptoms in the population of subjects with IBS, overall and by IBS subtype. We extracted data on IBS and IBS severe symptoms or disease as defined by the authors. When more than a definition of IBS or IBS severe symptomatology was used, we conservatively included in the analyses the lowest estimate. Data on the overall prevalence of IBS severity were extracted only when the proportion of severe subjects could be extracted.

The number of retrieved studies reporting data on IBS severity by IBS subtype was very scarce, and two studies only reported the overall mean and standard deviation of each IBS subtype[16,17]. To avoid any loss of information, in these two stud-

Table I. Estimates of the prevalence of IBS in selected countries[2,9,19].

Country	Lowest estimate, % (95% CI)	Highest estimate, % (95% CI)
Southern Europe	–	15.0 (11.0-20.0)
France	1.1	4.7 (4.4-5.0)
Spain	3.3 (2.1-4.9)	14.1 (10.0-18.0)
Greece	–	21.4
Italy	5.4	11.5
UK	6.1	21.6
USA	3.0	20.4 (16.7-24.2)

ies, we derived the proportion of subjects with severe symptoms from existing means, standard deviations and totals, simulating a normal distribution (Stata command "drawnorm").

Procedures Used to Derive the Overall Number of Italian IBS Patients

The overall number of Italian adults with IBS was computed multiplying the pooled estimate of the prevalence of IBS subjects by the current Italian adult population, using the Italian National Institute of Statistics official 2017 estimate of 50,678,735 adult inhabitants (http://dati.istat.it). Four different prevalence rates were used to provide four possible scenario: (1) the pooled point estimate of the prevalence resulting from the proportion meta-analysis; (2) the higher 95% confidence interval (CI) of the pooled prevalence; (3) the lower 95% CI of the pooled prevalence; (4) the lowest prevalence reported in all of the individual studies.

Procedures Used to Derive the Overall Number of Italian IBS Patients with Severe Symptoms

A similar approach was used to estimate the overall proportion of subjects with severe symptoms among the total population of subjects with IBS: four different estimated were provided: (1) the pooled point estimate of the prevalence resulting from the proportion meta-analysis; (2) the higher 95% CI of the pooled prevalence; (3) the lower 95% CI of the pooled prevalence; (4) the lowest prevalence reported in all of the individual studies.

To estimate the overall number of Italian adults with severe IBS symptoms, we thus multiplied each of the four estimates of the total number of IBS patients by each of the four estimates of the proportion of IBS subjects with severe symptoms, obtaining 16 different results (ranging from the lowest to the highest conservative scenarios). To avoid redundancy, we only showed eight different results, those corresponding to the lowest and highest estimates according to each of the four estimated proportion of IBS subjects with severe symptoms.

Procedures Used to Derive the Overall Number of Italian IBS Patients with Severe Symptoms, by IBS Subtype

The overall pooled estimates of the prevalence of each IBS subtype are available from a meta-analysis[9]. According to this analysis, based

upon 14 studies, the pooled prevalence of IBS-C, IBS-D and IBS-M are 35% (95% CI: 29%-41%), 40% (95% CI: 31%-48%), 23% (95% CI: 15%-31%). To estimate the overall number of IBS patients with severe symptoms, however, we could not simply multiply such percentages to the raw numbers, because the proportion of severe subjects varies by IBS subtype. We thus estimated the proportion of any of the IBS subtype among the overall sample of IBS severe subjects: once the raw numbers of severe IBS-C, IBS-D, and IBS-M subjects were extracted, we performed three proportion meta-analyses to estimate the percentage of IBS-C, IBS-D, and IBS-M patients among the total population of IBS patients with severe symptoms. Due to the expected unbalanced weighting of proportion meta-analyses, the three proportions did not sum up exactly to 100%, and we thus recomputed each of them to achieve 100%.

Once the relative distribution of each IBS subtype among severe subjects was computed, the overall number of patients with severe symptoms was computed multiplying the pooled proportions of each of the three IBS subtypes by the eight overall numbers of severe subjects, estimated as described above.

All proportion meta-analyses were carried out using StatsDirect 2.7.9 (StatsDirect Ltd, Altrincham, UK, 2012) and confirmed using Stata 13.1 (Stata Corp. College Station, TX, USA, 2014).

Results

Overall IBS Prevalence

With the initial online search, we identified 329 abstracts of studies on IBS prevalence in Italy. After a careful revision, which included also existing reviews and meta-analyses, five studies fulfilled inclusion criteria[18-22] (Table II). All have been performed in the general population, with a combined overall sample of 40,654. Although the criteria used to define IBS varied, the results were similar in 4 out of 5 studies, reporting an IBS prevalence ranging between 7% and 8%. The lowest estimate, based upon Rome II criteria, was 5.4%, the highest 11.5%. When the results of these studies were combined using a proportion meta-analysis (Figure 1), the pooled prevalence of IBS among Italian adults was 7.7% (95% CI: 6.0%-9.7%).

Using the meta-analysis pooled estimate as a basis (standard scenario), considering a current

Table II. Characteristics of the Italian surveys on IBS prevalence[18-22].

First author	Year	Sample	Setting	Methods	Criteria	Prevalence, %	Prevalence, M-F	% severe cases
Neri[20]	2001	3500	General population	Questionnaire	Manning, Rome I, Rome II	7.7 (Manning) 6.9 (Rome I) 5.4 (Rome II)	3.6-7.1	24.0
Hungin[19]	2003	5082	General population	Questionnaire	Manning, Rome I, Rome II	11.5	7.1-12.0*	17.0*
Corazziari[18]	2008	29,139	General population	Questionnaire, visit, ultrasonography	NR	7.9	5.5-10.7	NR
Usai[21]	2010	1900	General population	Questionnaire	Rome II	7.2	5.0-9.2	NR
Zagari[22]	2010	1033	General population	Questionnaire, endoscopy	Rome I	7.1	NR	NR

NR: Not reported. *Overall value of 8 European countries including Italy.
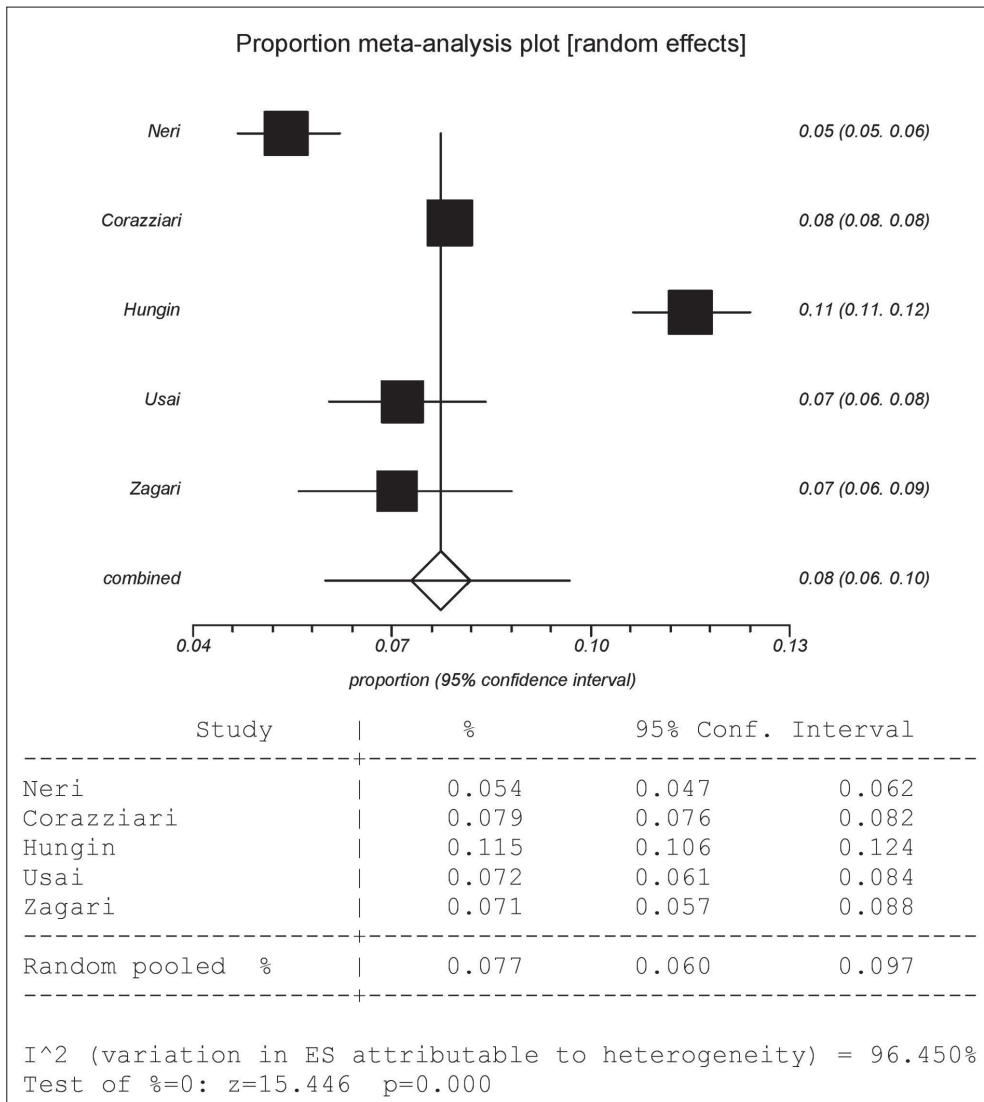

Figure 1. Proportion meta-analysis of IBS prevalence in Italy.

Italian adult population of 50,678,735 citizens, the overall number of IBS patients would be approximately 3,902,300 (Table III).

In the worst possible, least conservative scenario, where the higher 95% CI of the pooled estimate is used as the basis of the calculation, the overall number of persons with IBS would be 4,915,800.

In a conservative scenario, where the lower 95% CI of the pooled estimate is used as the basis of the calculation, the overall number of persons with IBS would be 3,040,700.

In the best, most conservative, and logically plausible scenario, where the lowest estimate reported in the available studies (5.4%) is used as the basis of the calculation, the overall number of persons with IBS would be 2,736,700.

IBS Prevalence by Gender

As reported in Table II, and similar to the rest of the World[9,11], the IBS prevalence estimated by the Italian surveys was higher among females. The pooled estimate was 4.7% among males (95% CI: 3.6%-6.0%; Figure 2) and 9.0% among females (95% CI: 6.7-11.5%; Figure 3). Considering 2017 Italian estimated male and females adult populations (24,344,264 and 26,334,471, respectively), conservatively using the lowest CI for both genders, the above prevalence translates into an overall number of Italian males and females with IBS of 1,144,200 and 2,370,100, respectively. These values sum to a total of 3,514,300, which is higher than the previously computed overall estimate (2,736,700), due to the use of different datasets (and different CIs). If the total estimate of 2,736,700 adults with IBS is assumed, and the male/female ratio (4.7/9.0) is applied, the overall number of males and females would be 938,900 and 1,797,800, respectively (Table III).

Prevalence of Severe IBS

IBS severity is multi-dimensional, being influenced by the intensity of gastrointestinal and extra-intestinal symptoms, quality of life, co-morbidities, psychosocial factors, degree of disability, and illness behaviors[23,24]. Although the concept of severity is clinically recognized and operative in diagnostic decision making and treatment planning, the methodology and approaches used to measure IBS severity largely varied[14], with few studies adopting standardized scales such as FBDSI[25] or IBS-SSS[26]. We were able to retrieve 17 surveys with data on the proportion of IBS subjects with severe symptoms[13,16,19,20,25-37].

Overall, in the 17 investigaions available, which included a total of 16,873 subjects, the proportion of subjects with severe IBS widely varied, ranging from 8.4% to 55.3% (Table IV), and reflecting the various approaches adopted to define IBS severity (Table V). As shown in Figure 4, the pooled proportion of severe IBS patients was 23.5% (95% CI: 18.7%-28.7%).

In the standard scenario, using meta-analysis pooled estimate as a basis, the overall number of IBS patients with severe symptoms in Italy would range between 643,100 (if the most conservative, lowest estimate of the Italian total IBS population is used – n = 2,736,700) and 1,155,200 (if the least conservative, highest estimate of the Italian total IBS population is used – n = 4,915,800, Table VI).

In the worst possible, least conservative scenario, where the higher 95% CI of the pooled estimate is used as the basis of the calculation, the overall number of IBS patients with severe symptoms would range between 785,400 and 1,410,800.

Table III. Estimated numbers of IBS adult patients in Italy according to four different scenarios.

Scenario	Prevalence	Overall number*
Prevalence of IBS in Italy		
Highest 95% CI of the pooled estimate[A]	9.7%	4,915,800
Pooled estimate[A]	7.7%	3,902,300
Lowest 95% CI of the pooled estimate[A]	6.0%	3,040,700
Lowest estimate reported in individual studies	5.4%	2,736,700
Total number of males according to the lowest estimate[B]	3.9%	938,900
Total number of females according to the lowest estimate[B]	6.8%	1,797,800

*Computed from the current overall adult population of Italy (n = 50,678,735; source: Italian Institute of Statistics). [A]Pooled estimates have been extracted from the proportion meta-analysis showed in Figure 1. [B]Derived from the male/female ratio obtained from proportion meta-analyses showed in Figures 2 and 3.
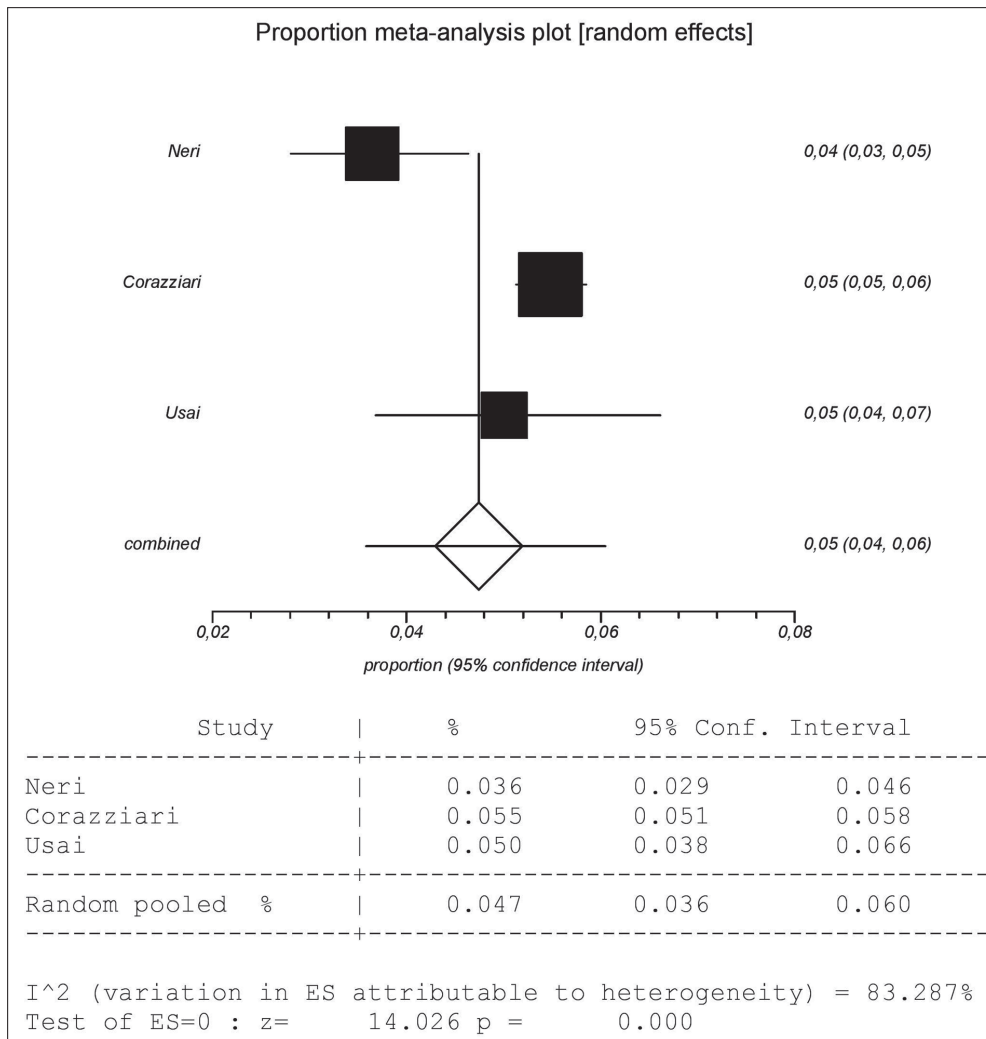
Figure 2. Proportion meta-analysis of IBS prevalence among Italian males.

In a conservative scenario, where the lower 95% CI of the pooled estimate is used as the basis of the calculation, the overall number of IBS patients with severe symptoms would range between 511,800 and 919,300.

In the best, most conservative, and logically plausible scenario, where the lowest estimate reported in the available studies (8.4%) is used as the basis of the calculation, the overall number of IBS patients with severe symptoms would range between 229,900 and 412,900.

Prevalence of Severe IBS by IBS Subtype

As reported in Table VII, data on the number of subjects with severe symptoms stratified by IBS subtype were available from a few studies[13,16,17,27,30]. One study only included IBS-C and IBS-D patients. Thus, it could not be used to estimate the relative distribution of each IBS subtype among severe subjects[17].

Three proportion meta-analyses were made to estimate the proportion of subjects with IBS-C, IBS-D, and IBS-M among the total population of IBS patients with severe symptoms (Figures 5A, 5B, and 5C). Overall, of the IBS severe patients, 35.6% were diagnosed with IBS-C, 29.5% with IBS-D, and 30.4% with IBS-M (Figure 5). As these proportion did not perfectly totaled 100% due to weights unbalance in proportion meta-analyses, these were re-computed as 37.7%, 30.7% and 31.6%, respectively (Table VII).

In the standard scenario, using meta-analysis pooled estimate of the total prevalence of IBS severe subjects as a basis (23.5%, Table VI), the overall numbers of IBS-C, IBS-D, and IBS-M patients with severe symptoms in Italy would lie in the following ranges: 242,400/435,500 (IBS-C), 197,400/354,700 (IBS-D), and 203,200/365,100 (IBS-M; Table VII).

Figure 3. Proportion meta-analysis of IBS prevalence among Italian females.

Proportion meta-analysis plot [random effects]

Study		%	95% Conf. Interval

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              Study     |      %         95% Conf. Interval
   ---------------------+------------------------------------------
   Neri                 |    0.071      0.060        0.084
   Corazziari           |    0.107      0.102        0.112
   Usai                 |    0.092      0.075        0.112
   ---------------------+------------------------------------------
   Random pooled   %    |    0.090      0.067        0.115
   ---------------------+------------------------------------------

   I^2 (variation in ES attributable to heterogeneity) =    92.118%
   Test of ES=0 : z=       13.798 p =       0.000
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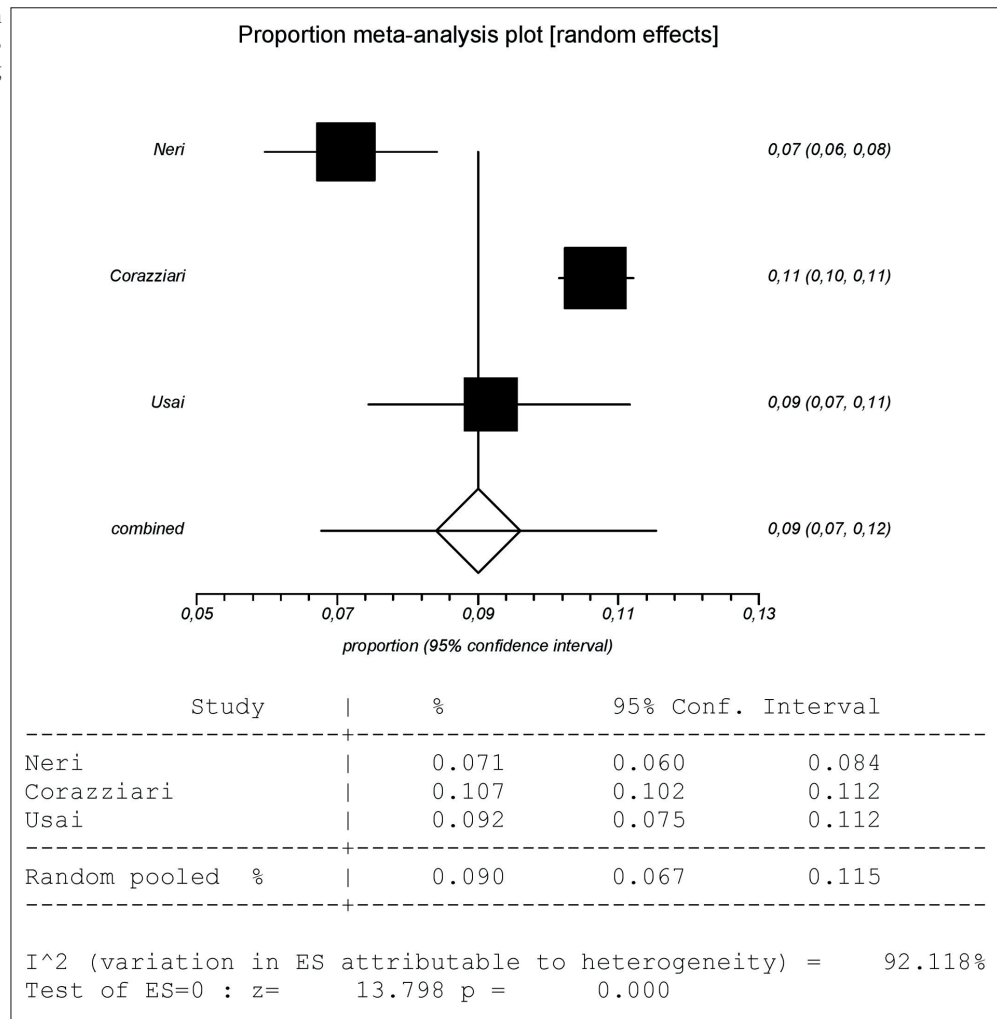
Table IV. Characteristics of the surveys evaluating the proportion of IBS patients with severe symptoms.

First author	Year	Sample	Criteria	% Severe cases
Drossman[A,25]	1995	270	Rated by physicians	18.9
Francis[26]	1997	61	IBS-SSS	40.9
Hahn[29]	1997	112	Self-reported IBS severity	23.2[A]
Longstreth[A,33]	2001	245	Self-reported IBS severity	12.2
Neri[20]	2001	3500	NR	24.0
Ricci[35]	2001	1426	Rated by physicians	15.0
Sach[36]	2002	256	Self-reported IBS severity	15.0[A]
Hungin[19]	2003	5082	Hospitalized	17.0[B]
Longstreth[B,34]	2003	578	Self-reported IBS severity	23.9
Coffin[16]	2004	858	IBS-SSS	50.4
Hillila[31]	2004	587	Self-reported pain or discomfort	27.0[C]
Spiegel[37]	2005	1410	Self-reported annoying symptoms	8.4
Drossman[B,28]	2009	1966	FBDSI or IBS-SSS	20.0[D]
Drossman[C,27]	2009	16	FBDSI	31.3
Heitkemper[30]	2011	161	Self-reported pain	55.3
Lackner[32]	2011	98	IBS-SSS	11.2
Su[13]	2014	247	Self-reported IBS severity	31.6

FBDSI: Functional Bowel Disorder Severity Index. IBS-SSS: IBS Symptom Severity Score. [A]Very severe patients only. [B]Overall value of 8 European countries including Italy. [C]According to Manning 2 criteria. Severe subjects were 44% according to Rome II criteria. [D]According to FBDSI. Severe subjects were 55.0% according to IBS-SSS

Table V. Criteria used by the authors to identify IBS patients with severe symptoms, and proportion of severe subjects by IBS subtype.

First author	Year	Criteria	IBS-C	IBS-D	IBS-M
Drossman[A,25]	1995	Physician's global rating of severity, used to develop the FBDSI. Patients scoring ≥ 111 have been classified as severe.	NR	NR	NR
Francis[26]	1997	Self-reported questionnaire, with 5 items pertaining: pain intensity, pain frequency, abdominal distention/tightness severity, satisfaction with bowel habit, and quality of life. Each item was measured with a VAS scale, weighting 100 point. A severe case scored > 300. The questionnaire was then defined as IBS-SSS.	NR	NR	NR
Hahn[29]	1997	Patient-perceived severity was defined using the following question from the Bowel Symptom Checklist: "How bad is the discomfort usually?" Discomfort referred to pain and associated IBS symptoms. Responses were rated as follows: mild (can be ignored if you don't think about it); moderate (cannot be ignored, but does not affect your lifestyle); severe (affects your lifestyle); and very severe (markedly affects your lifestyle). Only the latter were extracted. Severe subjects were 46%.	NR	NR	NR
Longstreth[A,33]	2001	The symptom severity during the previous 7 days was rated as moderate (sufficient to interfere with normal activities) or severe (incapacitating with inability to perform normal activities).	NR	NR	NR
Neri[20]	2001	No details available	NR	NR	NR
Ricci[35]	2001	No details available	NR	NR	NR
Sach[36]	2002	Only very severe patients were extracted. Severe subjects were 41%.	NR	NR	NR
Hungin[19]	2003	Has been seen in a hospital.	NR	NR	NR
Longstreth[B,34]	2003	The severity of abdominal pain/discomfort was assessed with the question: "How much of a problem was your abdominal pain and discomfort over the last 3 months?". Respondents answered with a 6-point Likert scale: absent, very mild, mild, moderate, severe, and very severe. We extracted severe and very severe subjects, no other data were available.	NR	NR	NR
Coffin[16]	2004	Self-reported questionnaire (French version of the IBS-SSS), composed of: two items on the presence of abdominal pain and bloating (yes or no); four visual analogue scales measuring intensity of pain, bloating, relief after defecation, and impact of symptoms on general quality of life (0-100 scale); an item on the number of days of suffering in the preceding 10 days. It is a modified version of the Francis et al. questionnaire 26. A severe case scored > 300.	59.6% (190/ 319)*	37.5% (120/ 320)*	56.2% (123/ 219)*
Hillila[31]	2004	Self-reported questionnaire, assessing abdominal pain and discomfort (using a 4-grade Likert scale: mild, moderate, severe, very severe) and frequency of abdominal pain/discomfort (through a 5-grade Likert scale: seldom or never, sometimes, often, very often, constantly). The proportion of severe subjects was 27% according fo Manning 2 criteria, 44% according to Rome II criteria.	NR	NR	NR
Spiegel[37]	2005	Self-reported questionnaire assessing disease severity through a 0-20 VAS scale, with 20 = most severe.	NR	NR	NR

Table continued

Table V (Continued). Criteria used by the authors to identify IBS patients with severe symptoms, and proportion of severe subjects by IBS subtype.

Drossman[B,28]	2009	Patient-perceived severity was defined using: (1) FBDSI questionnaire; (2) IBS-SSS questionnaire; (3) the question: "Rate how severe your IBS is on a 5-point Likert scale (not at all, somewhat, moderately, very, extremely)". A severe case scored > 110 on the FBDSI questionnaire. No other details were provided. Severe subjects were 20.0 according to FBDSI, 55.0 according to IBS-SSS, and 35.0 according to the 5-point Likert scale.	NR	NR	NR
Drossman[C,27]	2009	Patient-perceived severity was defined using: (1) FBDSI questionnaire; (2) IBS-SSS questionnaire. No details are provided on which of the two instruments was used to classify patients as severe.	100% (2/2)	0% (0/5)	33.3% (3/9)
Heitkemper[30]	2011	Rome II Diagnostic Questionnaire for Functional Gastrointestinal Disorders was used to assess abdominal pain and IBS symptoms severity over the previous 1 year.	63.4% (26/41)	52.8% (47/89)	51.6% (16/31)
Lackner[32]	2011	Patient-perceived severity was defined using: (1) IBS-SSS; (2) a single item 21-point rating UCLA symptom severity scale (20: most intense symptoms imaginable). The proportion of severe subjects was similar using both scales.	NR	NR	NR
Colucci[17]	2013	IBS symptom severity was evaluated by means of IBS-SSS questionnaire.	66.0% (70/ 106)*	51.0% (50/ 98)*	NR
Su[13]	2014	Patients were administered a bowel symptom questionnaire (BSQ), which included the Rome III diagnostic questions for IBS and was declared to also characterize the severity of symptoms. The available data on severe patients, however, were referred only to self-reported abdominal pain.	36.2% (25/69)	29.2% (19/65)	31.2% (34/109)

IBS-C: Constipation-predominant IBS; IBS-D: diarrhea-predominant IBS; IBS-M: mixed stool pattern or alternating stool pattern IBS. NR: Not reported. FBDSI: Functional Bowel Disorder Severity Index. IBS-SSS: IBS Symptom Severity Score. *Derived from existing means, standard deviations and totals, simulating a normal distribution (Stata command "drawnorm").

In the best, most conservative, and logically plausible scenario, where the lowest estimate of the total prevalence of IBS severe subjects available (8.4%) is used as the basis for the calculation, the overall numbers of IBS-C, IBS-D, and IBS-M patients with severe symptoms in Italy would lie in the following ranges: 86,600/155,700 (IBS-C), 70,600/126,800 (IBS-D), and 72,600/130,500 (IBS-M).

Discussion

Although a number of studies have focused on IBS pathophysiology, diagnosis, and treatment, its epidemiological impact is still controversial and the estimates of the prevalence for Southern European Countries largely vary[9]. Because of the complexity of its definition, this is particularly true for severe IBS, which has large impact on quality of life and social costs, directly influences treatment and targeted health policies, thus urgently requiring a precise estimation[38].

In several countries including Italy, the severity of IBS is likely to be substantially underestimated in the clinical setting, and such an underestimation directly affect patient care by preventing appropriate treatment[38]. To the best of our knowledge, this study provides the first estimates of the prevalence of severe IBS in Italy, stratifying by gender and IBS type. We computed the possible numbers of citizens with severe IBS symptoms according to a range of potential hypotheses, from extremely conservative approaches, up to the worst possible scenario. Although it was not possible to provide a definitive, reliable precise estimate of the prevalence of severe IBS, we were able to find the lowest and highest plausible num-
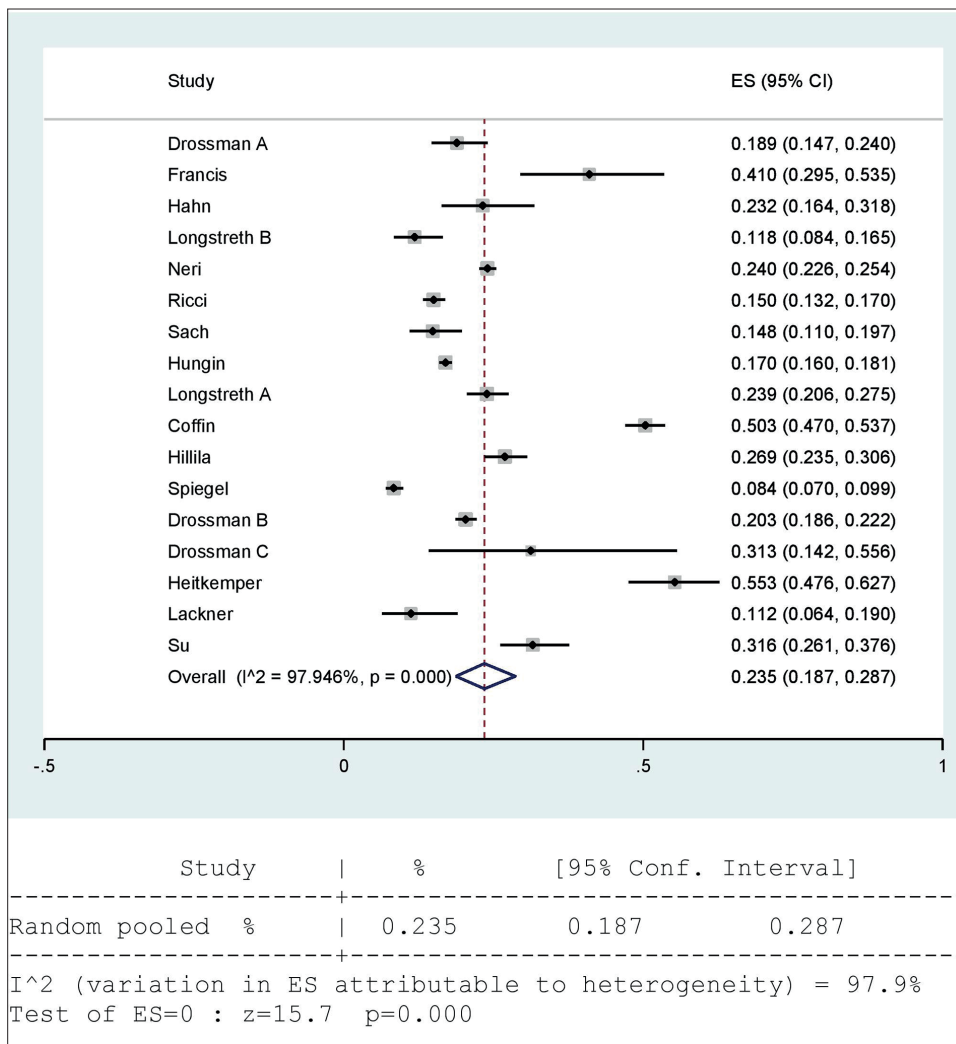
Figure 4. Proportion meta-analysis of the percentage of IBS patients with severe symptoms.

bers of patients affected by severe symptoms. These estimates may provide a solid base for the discussion among all the stakeholders, patients, and decision makers, on the strategies that are needed to improve the process of diagnosis and care of these subjects.

The key findings follow. Firstly, based upon a meta-analysis of five studies including a total of more than 40,000 subjects, depending on the adopted diagnostic criteria (and methodology to assess them) the overall number of Italian adults with IBS may range between an extremely con-

Table VI. Estimated numbers of Italian adult IBS patients with severe symptoms, according to eight different scenarios.

Scenario	Prevalence	Overall number
Prevalence of severe IBS in Italy		Min./Max.
Highest 95% CI of the pooled estimate[A]	28.7%	785,400/1,410,800
Pooled estimate[A]	23.5%	643,100/1,155,200
Lowest 95% CI of the pooled estimate[A]	18.7%	511,800/919,300
Lowest estimate reported in individual studies	8.4%	229,900/412,900

[A]Pooled estimates have been extracted from the proportion meta-analysis showed in Figure 4, and multiplied by the lowest and highest estimates of the overall numbers of Italian IBS adults reported in Table III.

Table VII. Estimated numbers of IBS adult patients in Italy with severe symptoms according to IBS subtype * and various estimates of overall IBS prevalence in Italy (extracted from Table IV).

Scenario	Prevalence	Overall number[A]
Highest 95% CI of the pooled estimate[B]	28.7%	
- Overall	(100%)	785,400/1,410,800
- IBS-C	(37.7%)	296,100/531,900
- IBS-D	(30.7%)	241,100/433,100
- IBS-M	(31.6%)	248,200/445,800
Pooled estimate[B]	23.5%	
- Overall	(100%)	643,100/1,155,200
- IBS-C	(37.7%)	242,400/435,500
- IBS-D	(30.7%)	197,400/354,700
- IBS-M	(31.6%)	203,200/365,100
Lowest 95% CI of the pooled estimate[B]	18.7%	
- Overall	(100%)	511,800/919,300
- IBS-C	(37.7%)	192,900/346,600
- IBS-D	(30.7%)	157,100/282,200
- IBS-M	(31.6%)	161,700/290,500
Lowest estimate reported in individual studies	8.4%	
- Overall	(100%)	229,900/412,900
- IBS-C	(37.7%)	86,600/155,700
- IBS-D	(30.7%)	70,600/126,800
- IBS-M	(31.6%)	72,600/130,500

IBS-C: Constipation-predominant IBS; IBS-D: diarrhea-predominant IBS; IBS-M: mixed stool pattern or alternating stool pattern IBS. *The relative distribution of IBS subtypes has been computed from the pooled estimates of the proportion meta-analyses showed in Figure 5. As the global sum was not totaling 100% (96.1%, due to unbalanced weights of the included studies), we multiplied each estimate for the ratio between 100 and 96.1. [A]Using the lowest and highest estimates of the overall prevalence of IBS in Italy. [B]Pooled estimates have been extracted from the proportion meta-analysis showed in Figure 4.

servative, lowest estimate of 2,736,700 (938,900 males; 1,797,800 females), up to a maximum of 4,915,800. Secondly, based upon these numbers, and a meta-analysis of 17 studies including ≈17,000 subjects, the overall number of Italian adults with severe IBS may range between an extremely conservative, lowest estimate of 229,900, up to 1,410,800. Thirdly, using the former estimate, which has to be interpreted however as the lowest logically plausible estimate, the overall numbers of IBS-C, IBS-D and IBS-M patients would be 86,600, 70,600, and 72,600, respectively. Fourthly, according to a still conservative approach, but based upon the lowest estimates that are commonly accepted in literature (those obtained from a meta-analysis), the overall number of Italian adults with severe IBS would be 511,800, which is probably the most reliable estimate. Fifthly, the present computations showed a female predominance in IBS prevalence, in line with the available meta-analyses, potentially reflecting microbiota/host genetic gender-related characteristics and/or a different psychological approach[2,11].

In addition to the above-mentioned impossibility of providing precise, univocal estimates of severe IBS prevalence, some limitations must be taken into account in interpreting the study findings, which are to be considered preliminary and require confirmation. First, despite an updated systematic search performed according to PRISMA guidelines, we might have missed some studies or data from the grey literature. Second, because of the scarcity of Italian studies on the prevalence of severe IBS, we were forced to perform a meta-analysis on all studies from countries with predominant Caucasian population. Third, the meta-analyses performed to estimate the relative distribution of each IBS type were based upon a scarce number of studies. Fourth, and most importantly, we had to extract the definitions of severe IBS provided by the authors, which were often different and which may relevantly impact the overall prevalence. The variation was wide, and we could not perform a meaningful assessment of the potential impact of the adopted instrument on prevalence estimates. Although most of the used scales were validated[14,25,26,39], and some multidimensional[25,26], a consensus conference would be definitively helpful to provide the clinicians and patients worldwide with a validated

A

```
         Study     |     ES    [95% Conf. Interval]
-------------------+----------------------------------------------
Coffin             |    0.440       0.394        0.487
Drossman C         |    0.400       0.118        0.769
Heitkemper         |    0.292       0.208        0.394
Su                 |    0.321       0.227        0.430
-------------------+----------------------------------------------
Random pooled  ES  |    0.356       0.261        0.457
-------------------+----------------------------------------------

  I^2 (variation in ES attributable to heterogeneity) =   67.703%
  Test of ES=0 : z=    10.698 p =       0.000
```

B

```
         Study     |     ES    [95% Conf. Interval]
-------------------+----------------------------------------------
Coffin             |    0.278       0.238        0.322
Drossman C         |    0.000       0.000        0.434
Heitkemper         |    0.528       0.425        0.628
Su                 |    0.244       0.162        0.349
-------------------+----------------------------------------------
Random pooled  ES  |    0.295       0.154        0.457
-------------------+----------------------------------------------

  I^2 (variation in ES attributable to heterogeneity) =   87.778%
  Test of ES=0 : z=     5.801 p =       0.000
```

C

```
         Study     |     ES    [95% Conf. Interval]
-------------------+----------------------------------------------
Coffin             |    0.285       0.244        0.329
Drossman C         |    0.600       0.231        0.882
Heitkemper         |    0.180       0.114        0.272
Su                 |    0.436       0.331        0.546
-------------------+----------------------------------------------
Random pooled  ES  |    0.304       0.189        0.431
-------------------+----------------------------------------------

  I^2 (variation in ES attributable to heterogeneity) =   80.174%
  Test of ES=0 : z=     7.501 p =       0.000
```

Figure 5. *A*, Proportion meta-analysis estimating the percentage of IBS-C among IBS patients with severe symptoms. ***B*,** Proportion meta-analysis estimating the percentage of IBS-D among IBS patients with severe symptoms. ***C*,** Proportion meta-analysis estimating the percentage of IBS-M among IBS patients with severe symptoms.

and universally accepted instrument to measure IBS severity. Indeed, establishing a clear, standardized definition of severe IBS could potentially help practitioners identify more appropriate and effective treatments and may, in turn, lessen patient suffering[38].

Conclusions

With these caveats, this work has clear implications for both future research and clinical practice. No less than 230,000 Italian citizens are currently suffering from severe IBS, requiring

appropriate treatment and recognition by healthcare providers. This estimate can be used as a minimum, most likely underestimated basis for targeted public health policies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) STANGHELLINI V. Perspectives on irritable bowel syndrome: where have we been? Where are we now? Expert Rev Gastroenterol Hepatol 2013; 7: 3-7.

2) CANAVAN C, WEST J, CARD T. The epidemiology of irritable bowel syndrome. Clin Epidemiol 2014; 6: 71-80.

3) DROSSMAN DA, HASLER WL. Rome IV-Functional GI Disorders: disorders of gut-brain interaction. Gastroenterology 2016; 150: 1257-1261.

4) CORAZZIARI E. Definition and epidemiology of functional gastrointestinal disorders. Best Pract Res Clin Gastroenterol 2004; 18: 613-631.

5) SPERBER AD, DUMITRASCU D, FUKUDO S, GERSON C, GHOSHAL UC, GWEE KA, HUNGIN APS, KANG JY, MINHU C, SCHMULSON M, BOLOTIN A, FRIGER M, FREUD T, WHITEHEAD W. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut 2017; 66: 1075-1082.

6) THOMPSON WG, HEATON KW, SMYTH GT, SMYTH C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut 2000; 46: 78-82.

7) FORD AC, TALLEY NJ. Irritable bowel syndrome. Br Med J 2012; 345: e5836.

8) SPAGNUOLO R, COSCO C, MANCINA RM, RUGGIERO G, GARIERI P, COSCO V, DOLDO P. Beta-glucan, inositol and digestive enzymes improve quality of life of patients with inflammatory bowel disease and irritable bowel syndrome. Eur Rev Med Pharmacol Sci 2017; 21(2 Suppl): 102-107.

9) LOVELL RM, FORD AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012; 10: 712-721 e714.

10) SPIEGEL BM, FARID M, ESRAILIAN E, TALLEY J, CHANG L. Is irritable bowel syndrome a diagnosis of exclusion?: a survey of primary care providers, gastroenterologists, and IBS experts. Am J Gastroenterol 2010; 105: 848-858.

11) LOVELL RM, FORD AC. Effect of gender on prevalence of irritable bowel syndrome in the community: systematic review and meta-analysis. Am J Gastroenterol 2012; 107: 991-1000.

12) FORTEA J, PRIOR M. Irritable bowel syndrome with constipation: a European-focused systematic literature review of disease burden. J Med Econ 2013; 16: 329-341.

13) SU AM, SHIH W, PRESSON AP, CHANG L. Characterization of symptoms in irritable bowel syndrome with mixed bowel habit pattern. Neurogastroenterol Motil 2014; 26: 36-45.

14) LEMBO A, AMEEN VZ, DROSSMAN DA. Irritable bowel syndrome: toward an understanding of severity. Clin Gastroenterol Hepatol 2005; 3: 717-725.

15) MANZOLI L, DE VITO C, SALANTI G, D'ADDARIO M, VILLARI P, IOANNIDIS JP. Meta-analysis of the immunogenicity and tolerability of pandemic influenza A 2009 (H1N1) vaccines. PLoS One 2011; 6: e24384.

16) COFFIN B, DAPOIGNY M, CLOAREC D, COMET D, DYARD F. Relationship between severity of symptoms and quality of life in 858 patients with irritable bowel syndrome. Gastroenterol Clin Biol 2004; 28: 11-15.

17) COLUCCI R, GAMBACCINI D, GHISU N, ROSSI G, COSTA F, TUCCORI M, DE BORTOLI N, FORNAI M, ANTONIOLI L, RICCHIUTI A, MUMOLO MG, MARCHI S, BLANDIZZI C, BELLINI M. Influence of the serotonin transporter 5HTTLPR polymorphism on symptom severity in irritable bowel syndrome. PLoS One 2013; 8: e54831.

18) CORAZZIARI E, ATTILI AF, ANGELETTI C, DE SANTIS A. Gallstones, cholecystectomy and irritable bowel syndrome (IBS) MICOL population-based study. Dig Liver Dis 2008; 40: 944-950.

19) HUNGIN AP, WHORWELL PJ, TACK J, MEARIN F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003; 17: 643-650.

20) NERI M, CAVAZZUTI, L, VISONA, G, BAMFI, F, BOZZANI, A, UBALDI, E, D'AMBROSIO, G, LATERZA, F, STANGHELLINI, V. Prevalence of irritable bowel syndrome in Italy: a population-based study. Gastroenterology 2001; 120: A230.

21) USAI P, MANCA R, LAI MA, RUSSO L, BOI MF, IBBA I, GIOLITTO G, CUOMO R. Prevalence of irritable bowel syndrome in Italian rural and urban areas. Eur J Intern Med 2010; 21: 324-326.

22) ZAGARI RM, LAW GR, FUCCIO L, CENNAMO V, GILTHORPE MS, FORMAN D, BAZZOLI F. Epidemiology of functional dyspepsia and subgroups in the Italian general population: an endoscopic study. Gastroenterology 2010; 138: 1302-1311.

23) DROSSMAN DA, CHANG L, BELLAMY N, GALLO-TORRES HE, LEMBO A, MEARIN F, NORTON NJ, WHORWELL P. Severity in irritable bowel syndrome: a Rome Foundation Working Team report. Am J Gastroenterol 2011; 106: 1749-1759; quiz 1760.

24) YILDIRIM AE, KORKMAZ M, ALTUN R, SANDIKCI SC, OCAL S, SELCUK H. Is there any association between irritable bowel syndrome subgroups and autonomous dysfunction. Eur Rev Med Pharmacol Sci 2016; 20: 1315-1322.

25) Drossman DA, Li Z, Toner BB, Diamant NE, Creed FH, Thompson D, Read NW, Babbs C, Barreiro M, Bank L, Whitehead WE, Schuster MM, Guthrie EA. Functional bowel disorders. A multicenter comparison of health status and development of illness severity index. Dig Dis Sci 1995; 40: 986-995.

26) Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997; 11: 395-402.

27) Drossman DA, Chang L, Schneck S, Blackman C, Norton WF, Norton NJ. A focus group assessment of patient perspectives on irritable bowel syndrome and illness severity. Dig Dis Sci 2009; 54: 1532-1541.

28) Drossman DA, Morris CB, Schneck S, Hu YJ, Norton NJ, Norton WF, Weinland SR, Dalton C, Leserman J, Bangdiwala SI. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. J Clin Gastroenterol 2009; 43: 541-550.

29) Hahn BA, Kirchdoerfer LJ, Fullerton S, Mayer E. Patient-perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilization and quality of life. Aliment Pharmacol Ther 1997; 11: 553-559.

30) Heitkemper M, Cain KC, Shulman R, Burr R, Poppe A, Jarrett M. Subtypes of irritable bowel syndrome based on abdominal pain/discomfort severity and bowel pattern. Dig Dis Sci 2011; 56: 2050-2058.

31) Hillila MT, Farkkila MA. Prevalence of irritable bowel syndrome according to different diagnostic criteria in a non-selected adult population. Aliment Pharmacol Ther 2004; 20: 339-345.

32) Lackner J, Jaccard J, Baum C, Smith A, Krasner S, Katz L, Firth R, Raby T, Powell C. Patient-reported outcomes for irritable bowel syndrome are associated with patients' severity ratings of gastrointestinal symptoms and psychological factors. Clin Gastroenterol Hepatol 2011; 9: 957-964 e951.

33) Longstreth GF, Hawkey CJ, Mayer EA, Jones RH, Naesdal J, Wilson IK, Peacock RA, Wiklund IK. Characteristics of patients with irritable bowel syndrome recruited from three sources: implications for clinical trials. Aliment Pharmacol Ther 2001; 15: 959-964.

34) Longstreth GF, Wilson A, Knight K, Wong J, Chiou CF, Barghout V, Frech F, Ofman JJ. Irritable bowel syndrome, health care use, and costs: a U.S. managed care perspective. Am J Gastroenterol 2003; 98: 600-607.

35) Ricci J, Jhingran, P, Harris W, Asgharian A, Markowitz M, Carter EG. Impact of differences in severity of irritable bowel syndrome (IBS) on patients' well being and resource use. Gastroenterology 2001; 120.

36) Sach J, Bolus R, Fitzgerald L, Naliboff BD, Chang L, Mayer EA. Is there a difference between abdominal pain and discomfort in moderate to severe IBS patients? Am J Gastroenterol 2002; 97: 3131-3138.

37) Spiegel BM, Kanwal F, Naliboff B, Mayer E. The impact of somatization on the use of gastrointestinal health-care resources in patients with irritable bowel syndrome. Am J Gastroenterol 2005; 100: 2262-2273.

38) Lacy BE. Irritable bowel syndrome and disease severity: are we undertreating our patients? Expert Rev Gastroenterol Hepatol 2010; 4: 1-3.

39) Camilleri M, Mangel AW, Fehnel SE, Drossman DA, Mayer EA, Talley NJ. Primary endpoints for irritable bowel syndrome trials: a review of performance of endpoints. Clin Gastroenterol Hepatol 2007; 5: 534-540.