

Quality of Life in Irritable Bowel Syndrome: A Narrative Overview

Andrew Ming Liang ONG,^{1,*} and Yu Tien WANG¹

¹Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore

*Corresponding author: Andrew Ming Liang, Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore. Tel: +65-63214684, Fax: +65-62273623, E-mail: Andrew.ong.m.l@sgh.com.sg

Received 2016 January 25; Revised 2016 February 11; Accepted 2016 February 11.

Abstract

Context: Health-related quality of life (HRQoL) is increasingly important in the assessment of chronic conditions, especially for irritable bowel syndrome (IBS), which has no associated mortality, but is prevalent and significantly impacts patient's lives. Disease-specific instruments such as the irritable bowel syndrome quality of life instrument (IBS-QOL), in addition to generic instruments such as the short form (SF)-36, are useful in measuring health-related quality of life, and have been shown to be reliable in assessing disease severity and as an endpoint to monitor treatment response. We reviewed the impact of IBS on patients' HRQoL, the factors causing HRQoL impairments, and the utility of HRQoL instruments in the assessment of IBS.

Evidence Acquisition: We performed electronic literature searches in Medline, the Cochrane library, and digestive disease week (DDW) meeting abstracts. Across all databases searched, common keywords included "Irritable bowel syndrome", "Quality of life" and "Health related quality of life". For databases that accommodated Boolean searches, terms specifically related to QOL and military were added.

Results: We summarized the data available in the literature to show that HRQoL is poorer in patients with IBS compared to healthy controls, and compared to most serious chronic conditions. There are several factors that contribute to HRQoL impairments in IBS, of which gastrointestinal symptoms, physical co-morbidities, psychosocial factors and demographics all play significant roles.

Conclusions: It is crucial for clinicians to be aware of the importance of measuring HRQoL. Understanding the factors causing impairment of HRQoL is also important for clinicians seeing these patients as it helps to individualise treatment and treat the patient more holistically, to achieve greater patient satisfaction.

Keywords: Irritable Bowel Syndrome, Health-Related Quality of Life

1. Context

Irritable bowel syndrome (IBS) is a chronic and prevalent condition defined by the presence of chronic and bothersome gastrointestinal (GI) symptoms such as abdominal pain and altered bowel movement, in patients with no physical or biochemical cause that explains the symptoms (1). While nonfatal, there is no effective standardized treatment for IBS. Current management relies on symptom management and efficacy is highly variable (1), therefore often dissatisfactory, resulting in psychological distress and disruption of work and sleep. Consequently, the evaluation of health-related quality of life (HRQoL) that provides a holistic assessment of patient's emotional, social and physical function is an important outcome measure for patients with IBS (2).

Military personnel are a unique population in that they are exposed to extreme levels of anxiety and stress and are also prone to development of infectious diarrhoea, which is a known association of IBS (3-5). The joint effect of these risk factors has recently been shown to result in an increased IBS risk compared to either of these expo-

sure alone (6). A study showed that around 48% of the US military personnel deployed to Turkey or Egypt developed a functional GI disorder (IBS or functional dyspepsia), of which 84% were preceded by at least one episode of infectious diarrhoea (7). The HRQoL burden of these post-deployment-related functional GI disorders was comparable to post-traumatic stress disorders (PTSD) (8) and IBS was found to be three times more likely to be present in those with PTSD than those without (9), thus highlighting the importance of awareness of managing IBS in this population.

We reviewed the impact of IBS on the patients' HRQoL, the factors causing HRQoL impairments, and the utility of HRQoL instruments in the assessment of IBS.

2. Evidence Acquisition

We performed electronic literature searches in Medline, the Cochrane library, and digestive disease week (DDW) meeting abstracts. There were no date restrictions. Across all the databases searched, common keywords in-

cluded “Irritable bowel syndrome”, “Quality of life” and “Health related quality of life”. For databases that accommodated Boolean searches, terms specifically related to QOL and military were added. The Medline search limited the results to English articles. All the searches were performed in December 2015. The studies were not evaluated for quality.

3. Results

3.1. Health-Related Quality of Life Definition

According to the classic world health organization (WHO) definition, health is a state of complete physical, mental and social well-being and not merely the absence of disease (10). Correspondingly, HRQoL is a multi-domain metric which incorporates patient’s perceptions, illness experience, and functional status (11) allowing the clinician to quantify each domain and derive a composite score that represents the patient’s health status. Healthcare administrators and policy makers have also utilized HRQoL as a tool to compare the impact of different chronic diseases for allocation of health resources (12).

HRQoL is also effective for the assessment of disease severity and treatment response. Even for organic diseases such as inflammatory bowel disease, where clinicians have the option to use tangible biological markers like laboratory, radiological and histological results to assess disease severity, it is increasingly recognized that such markers do not allow the clinician to appreciate the patients’ perceptions of their illness and thus underrepresent the true severity of the disease impact on patients. This concept is further magnified in IBS, where psychosocial factors have a strong effect on patient morbidity (13). As such, measuring only patient’s symptoms would present an incomplete measure of the patient’s overall disease severity, whereas HRQoL would reflect a more holistic measurement of disease severity. A systematic review has shown that therapy response in IBS-related pain had a corresponding HRQoL improvement (9), supporting its role in treatment outcome assessment. This has led the American college of Gastroenterology to recommend the routine screening of HRQoL in patients with IBS (14), to holistically assess the severity and impact of the disease, and to initiate treatment when such HRQoL is diminished.

3.2. Health-Related Quality of Life Measurement

In broad terms, a HRQoL instrument may be classified as generic or disease-specific. Examples of generic instruments available to measure HRQoL are short form (SF)-36 (15) and EuroQol (EQ)-5D (16) (Table 1). Such instruments

can be used across all health conditions and hence are often used to compare healthy controls and patients, or to compare patients across different diseases. However, there may be some facets of a patient’s life that may be uniquely affected by certain diseases, such as the need to be near washroom at all times in patients with IBS. These impairments in QOL will not be picked up by such generic instruments.

Table 1. Examples of Generic and Irritable Bowel Syndrome-Specific Instruments to Measure Quality of Life

Instrument	Number of Items/Domains	Domain	Scoring Method
SF-36 (generic)	36 items, 8 domains	Physical functioning (e.g. walking), Physical role limitations (e.g. inability to perform a usual activity); bodily pain, general health (e.g. perception of current health), vitality (e.g. energy level), social functioning; emotional role limitations (e.g. impact of emotional problems on usual activities), mental health	Each domain was scored 0 (poor) to 100 (best). Overall scores were either expressed as total value or percentage of maximum attainable score.
EQ-5D (generic)	5 items, 5 domains, 1 visual analogue scale for general health	Mobility, self-care, usual activities, pain, anxiety/depression	Each domain was graded 1-5 and the total score ranged from -60 to 100 with higher scores reflecting better QOL.
IBS-QOL (disease-specific)	34 items, 8 domains	Dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, relationships	Item responses were graded on a 5-point scale. Total scores ranged from 0-100 with higher scores reflecting poorer QOL

Disease-specific instruments are thus designed to target certain manifestations of specific conditions. An example for IBS includes the well-validated IBS-QOL (17, 18), which has been recommended by experts to be the instrument of choice when assessing IBS-related QOL, as it is the most extensively validated measure and has also shown both accurate psychometric and methodological properties (19). It was also validated for the assessment of IBS

treatment response where a change of 10 to 14 points from baseline was clinically meaningful (20).

3.3. Health-Related Quality of Life in Irritable Bowel Syndrome

Several studies have shown that patients with IBS have had poorer HRQoL than non-consulting patients with IBS, and both groups were significantly worse than healthy controls (9, 21). This suggests that patients with IBS overall have a worse HRQoL than healthy controls and that HRQoL is especially lower in patients seen in a referral setting as compared to non-consulting patients with IBS. HRQoL impairment in IBS is comparable and sometimes more severe than many other severe chronic organic diseases such as inflammatory bowel disease, gastro-esophageal reflux disease, end-stage renal failure, diabetes and hypertension (22-24), but has had higher scores than patients with depression (16) (Table 2). Qualitative studies evaluating IBS "Through the patients' eyes" have shown that IBS has caused multiple aspects of their life to be disrupted; hence, not surprisingly, these patients have had lower HRQoL. Many patients feel stigmatized and misunderstood for having a condition without an organic cause and their symptoms are often a big cause for embarrassment (25, 26).

However, it is worth noting that the literature on HRQoL in patients with IBS is limited by several factors, which may exaggerate its impact. First, most of the available data are collected from tertiary centers, hence do not reflect the bigger outpatient community. Second, the data often excludes IBS patients with mild symptoms. Third, many of these studies have not considered the fact that many patients with IBS may also have co-existing physical or psychological illnesses and these illnesses may further exacerbate the overall HRQoL status of the patient independent of IBS.

3.4. Factors Contributing to Health-Related Quality of Life Impairments

The etiology of reduced HRQoL is complex and may vary between disorders. Patients with inflammatory bowel disease cite pain severity as the most important factor for reduced HRQoL, while patients with IBS cite illness perception as the most important factor (29). GI symptoms, comorbidities, extra-intestinal functional disorders, psychiatric disorders and illness perceptions all affect HRQoL to different extents and will be discussed below (Box 1).

3.5. Gastrointestinal Symptoms

There has been conflicting evidence with regards to whether IBS subtypes differ in HRQoL impairments. Most studies have shown no differences in HRQoL scores between IBS subtypes (9, 20, 30-33), while others have suggested that diarrhea-predominant IBS (IBS-D) may have

lower QOL than constipation-predominant IBS (IBS-C) or mixed type IBS (IBS-M) (34), or that patients with IBS-C have lower QOL than those with IBS-D (35); however, such studies may be difficult to interpret, as patients with IBS commonly transit between the different subtypes if they are followed up for long periods (36).

It was also shown that mental and physical scores reduced in most patients with moderate to severe symptoms, while no reduction was found in patients with mild symptoms (9). These results suggest that increasing severity of bowel symptoms correspond to increasing impairments of HRQoL, with pain severity having a greater adverse impact than pain frequency (37). Different symptoms also appear to impair HRQoL to different extents, with pain and discomfort causing the most impairment, followed by alteration of bowel habits, bloating, and then nausea (38-41). The integrated severity of intestinal symptoms is more significantly associated with reduced HRQoL than individual symptom severity (35).

3.6. Co-Morbidities

There is prevailing assumption that GI symptoms reduce HRQoL in patients with IBS. However, organic comorbidities are not taken into account in many of the studies looking at HRQoL in patients with IBS, and these comorbidities may be more bothersome to the patient than the GI symptoms themselves (42). Co-morbidities are independent predictors of HRQoL regardless of the severity of GI complaints and are often significant drivers of reduced HRQoL rather than IBS itself (43). Increasing number of organic diseases present in an individual is also associated with reduced HRQoL (42).

In addition to bowel symptoms, it is well known that somatization and extra-intestinal functional disorders (EIFD) such as low energy and muscular pain are also prevalent in patients with IBS (44). EIFD and somatization lead to greater health care resource utilization (45), and patients with these disorders are less likely to respond and be compliant to pharmacotherapies (46). EIFD and mood disorders exert an effect on HRQoL independent of GI symptom severity, and may also impact the GI symptom severity and frequency itself, with anxiety causing the most dramatic influence. IBS patients without mood and EIFD comorbidities were comparable to healthy controls, suggesting that these psychiatric comorbidities drive the HRQoL impairments. Furthermore, the effects of mood and EIFD appear to be additive and associated with incremental decline of HRQoL (47, 48).

3.7. Psychiatric Disorders

Psychiatric disorders are common in patients with IBS, with reported incidence of 50 - 90% primary anxiety and

Table 2. Mean (Standard Deviation) of SF-36 Scores in Patients With Irritable Bowel Syndrome Compared to Healthy Controls as Well as Other Chronic Conditions^a

SF-36 Domain	US Population (27) (n = 2474)	IBS (27) (n = 877)	GERD (27) (n = 516)	Diabetes Mellitus (27) (n = 541)	Depression (27) (n = 502)	ESRD (27) (n = 165)	Asthma (28) (n = 246)	Migraine (28) (n = 303)	Rheumatoidarthritis (28) (n = 693)	Panic Disorder (28) (n = 73)	IBD (23) (n = 80)
Physical functioning	84 (9) ^b	79 (22)	80 (23)	68 (29) ^b	72 (27) ^b	52 (30) ^b	71 (23) ^b	89 (15) ^b	42 (24) ^b	70 (22) ^b	80 (22)
Role-physical	81 (9) ^b	50 (42)	72 (38) ^b	57 (42) ^b	44 (40)	33 (40) ^b	61 (41)	56 (43) ^b	28 (37) ^b	39 (43) ^b	53 (46)
Bodily pain	74 (5) ^b	54 (25)	58 (21) ^b	69 (27) ^b	59 (27) ^b	59 (30)	63 (27) ^b	50 (23) ^b	38 (18) ^b	61 (25) ^b	55 (28)
General health	72 (5) ^b	55 (23)	68 (21) ^b	56 (21)	53 (23)	44 (25) ^b	60 (22)	72 (18) ^b	55 (21)	63 (24)	44 (20)
Vitality	75 (2) ^b	65 (20)	71 (19) ^b	77 (18) ^b	46 (21) ^b	70 (20) ^b	51 (22)	57 (20) ^b	39 (22) ^b	41 (24) ^b	51 (21)
Social functioning	81 (3) ^b	65 (41)	78 (35) ^b	76 (37) ^b	39 (40) ^b	60 (44)	73 (21) ^b	74 (21) ^b	65 (27) ^b	55 (26) ^b	58 (26)
Role-emotional	61 (3) ^b	44 (23)	57 (20) ^b	56 (22) ^b	40 (21) ^c	46 (24)	75 (37) ^b	82 (33) ^b	57 (44) ^b	38 (43) ^b	52 (43)
Mental health	83 (3) ^b	63 (28)	79 (23) ^b	82 (25) ^b	57 (28) ^b	64 (30)	74 (18)	74 (16) ^b	71 (19) ^b	46 (20) ^b	57 (22)

Abbreviations: ESRD, end stage renal disease; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

^a Lower scores signify poorer QOL in that domain.

^b P < 0.003.

^c P values reflect comparisons with IBS patients in their respective studies.

Box 1. Factors Contributing to Health-Related Quality of Life Impairments

Gastrointestinal Symptoms
Type (pain > altered bowel habit > bloating > nausea)
Severity
Frequency
Co-Morbidities
Organic
Extra-intestinal functional disorders
Psychological factors
Affective disorders (e.g. depression, anxiety)
Somatization
Illness perceptions (e.g. GI-specific anxiety)
Demographics
Gender
Culture

Abbreviation: GI, gastrointestinal.

depression (13, 49, 50). It has also been shown that IBS patients with co-existing anxiety or depression, evaluated using the hospital anxiety and depression scale, showed lower HRQoL scores (50-52). However, most of these studies are cross-sectional and cannot establish a causal relationship (53).

Psychological factors may have a stronger direct effect on HRQoL than bowel symptoms (54). Furthermore, there is also suggestion that it may not be the bowel symptom severity that results in the HRQoL impairment, but rather

the patient's perception of the severity and the limitations imposed by the disease (37). These perceptions are important in determining those who perceive their illness as severe, suffer most from it, and present to health care centers. The relationship between HRQoL and health care seeking behavior has shown that patients with IBS seeking health care for colonic symptoms have lower QOL scores on SF-36 compared to people not seeking care (55). Likewise, patients who at baseline perceive their disease to be impacting their life and functioning significantly are more likely to have psychiatric disorders such as anxiety, and also have reduced HRQoL (56).

GI-specific anxiety (GSA), which is an anxiety about specific GI symptoms rather than general anxiety or depression, has been suggested to be more relevant in IBS and potentially mediate much of the effects of GI symptoms on HRQoL (57). GSA refers to a specific fear of GI symptoms such as abdominal pain and patients with GSA may become hypervigilant and fearful due to beliefs that GI symptoms may have aversive consequences. This results in increased frequency and severity of GI symptoms (58). Visceral sensitivity index (VSI) (59), a validated GSA assessment instrument, was found to be the strongest predictor for GI symptom severity in a group of patients with IBS and was independently associated with poorer HRQoL, likely due to excessive avoidance of activities or situations where they expected GI symptoms to occur (60). GSA also accounted for 14% of variation in patients' IBS-QoL, which was independent of symptom severity and mental illness, suggesting that impaired HRQoL was not due to their mental state alone, but rather their perception and fear of their illnesses (58).

Coping styles of patients with IBS have significant impacts on their HRQoL (61) and it is known that patients with IBS differ from healthy controls on the severity of irrational cognitions (62). Early adverse life events have been well established to be important in causing vulnerability in the development of IBS, and these likely contribute to maladaptive coping styles (63). A positive coping style (e.g. active coping and planning and use of support instruments) is associated with better psychological adjustment and better physical functioning, whereas an avoidant coping style (e.g. denial and self-blame) seems related to lower HRQoL. The perception that IBS symptoms were controllable was positively related to psychological, social functioning, and vitality domains of HRQoL, whereas the perceived adverse consequences of and negative identity associated with IBS were linked to impaired psychological domains of HRQoL (64).

In the evaluation of HRQoL in IBS treatment response, psychosocial improvement was found to be the most important contributing factor, as evidenced by the more responsive psychosocial domain scores (33, 54). In addition, the effects that bowel symptoms exerted on HRQoL were found to be mediated by psychological factors and illness perceptions (54, 64). This dominant effect that psychosocial factors exert on IBS patients' HRQoL highlights the importance of its diagnosis and IBS management. To this end, our group has recently shown that adopting a comprehensive psychological intervention approach has been effective to improve HRQoL and make it feasible in a high volume tertiary center (50).

3.8. Demographic Factors

Epidemiological studies in western populations have shown that IBS has been more prevalent in females than males, and it was also noted that females reported poorer IBS-QoL scores than males (32, 56, 65). However, in most Asian studies, IBS-QoL scores were similar in males and females, although food avoidance and social reaction scores were lower in females (66, 67).

Studies on the impact of age, occupation, education, marriage and socio-economic status have yielded differing results on QoL in patients with IBS (67-71). A study from Egypt revealed that patients with lower education and socio-economic status had lower QoLs (72), while others (33, 35) concluded that these factors did not affect QoL.

Since socio-cultural factors are likely to impact how individuals interpret health, investigators are often mindful to validate a questionnaire before applying it to a different population. Despite the prevalence and importance of IBS in many western communities, there is a perception that IBS is less of a problem and epidemiologically different in Asian communities (73). However, most features of

HRQoL impairments in Asian patients with IBS are similar to those of western studies, in that poorer HRQoL is seen in patients with IBS for both physical and mental domains (69, 74). Similarly, symptom severity and psychiatric morbidity were important determinants for poorer QoL in Asian studies (74).

Socio-cultural influences contribute to unique differences in HRQoL impairments in Asian societies, as compared to western societies. It was interesting to note that studies in Korean (67) and Chinese (75) patients with IBS showed that the score for social functioning domain in the SF-36 and that for the sexual and relationship domain of the IBQ-QoL were higher than those of western studies.

3.9. Clinical Utility of Health-Related Quality of Life Measurements

Appreciating the value of HRQoL has important clinical implications. Patient with IBS consultations are typically focused on addressing GI-specific issues (e.g. abdominal pain and bowel pattern); but what matters more to the patient is perhaps the overall well-being and ability to function in society, which is better addressed by improvement in their HRQoL.

By understanding the factors behind HRQoL impairments, the treatment may be individualized and directed against these "Culprit" factors. For example, identifying that maladaptive illness perception is the major factor of HRQoL impairment in a patient with IBS would direct the clinician towards psycho-behavioral management (e.g. cognitive behavioral therapy) to correct his maladaptive illness perception rather than isolated GI symptom management (76).

HRQoL may be used as a holistic research outcome assessment tool for IBS research. Many IBS HRQoL instruments have been validated and shown to correspond with symptom improvement (20). However, investigators should be cognizant of the factors that confound HRQoL such as co-morbidities and mood disorders.

A limitation of this review was that it was not performed as a systematic review, and hence abstracts may be excluded, resulting in the potential of missing relevant information. We attempted to overcome this by performing extensive searches for all relevant published papers. Another limitation was the nature of literature in patients with IBS, as most data are retrospective and compare patients to historical controls seen at different institutions. Future studies are needed to prospectively compare such patients to validate these data.

4. Conclusions

Patients with IBS experience significant HRQoL impairment of a magnitude comparable to other serious organic chronic diseases. These data, combined with the prevalence of IBS in the general population, emphasize the magnitude of humanistic and economic cost of IBS. Clinicians need to appreciate and address the different factors that cause HRQoL impairments to treat patients holistically. HRQoL measures such as IBS-QOL are important research outcomes in evaluating the severity of a patient's illness and their response to treatment.

References

- Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;**130**(5):1480-91. doi: [10.1053/j.gastro.2005.11.061](https://doi.org/10.1053/j.gastro.2005.11.061). [PubMed: [16678561](https://pubmed.ncbi.nlm.nih.gov/16678561/)].
- El-Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. *Aliment Pharmacol Ther*. 2002;**16**(6):1171-85. [PubMed: [12030961](https://pubmed.ncbi.nlm.nih.gov/12030961/)].
- Riddle MS, Sanders JW, Putnam SD, Tribble DR. Incidence, etiology, and impact of diarrhea among long-term travelers (US military and similar populations): a systematic review. *Am J Trop Med Hyg*. 2006;**74**(5):891-900. [PubMed: [16687698](https://pubmed.ncbi.nlm.nih.gov/16687698/)].
- Porter CK, Gloor K, Cash BD, Riddle MS. Risk of functional gastrointestinal disorders in U.S. military following self-reported diarrhea and vomiting during deployment. *Dig Dis Sci*. 2011;**56**(11):3262-9. doi: [10.1007/s10620-011-1762-3](https://doi.org/10.1007/s10620-011-1762-3). [PubMed: [21643738](https://pubmed.ncbi.nlm.nih.gov/21643738/)].
- Trivedi KH, Schlett CD, Tribble DR, Monteville MR, Sanders JW, Riddle MS. The impact of post-infectious functional gastrointestinal disorders and symptoms on the health-related quality of life of US military personnel returning from deployment to the Middle East. *Dig Dis Sci*. 2011;**56**(12):3602-9. doi: [10.1007/s10620-011-1766-z](https://doi.org/10.1007/s10620-011-1766-z). [PubMed: [21647652](https://pubmed.ncbi.nlm.nih.gov/21647652/)].
- Riddle MS, Welsh M, Porter CK, Nieh C, Boyko EJ, Gackstetter G, et al. The Epidemiology of Irritable Bowel Syndrome in the US Military: Findings from the Millennium Cohort Study. *Am J Gastroenterol*. 2016;**111**(1):93-104. doi: [10.1038/ajg.2015.386](https://doi.org/10.1038/ajg.2015.386). [PubMed: [26729548](https://pubmed.ncbi.nlm.nih.gov/26729548/)].
- Porter CK, Thura N, Schlett CD, Sanders JW, Tribble DR, Monteville MR, et al. Establishment of Health Utility Indices for Post-Infectious Functional Gastrointestinal Disorders in Active Duty US Military. *J Travel Med*. 2015;**22**(4):237-41. doi: [10.1111/jtm.12200](https://doi.org/10.1111/jtm.12200). [PubMed: [25827629](https://pubmed.ncbi.nlm.nih.gov/25827629/)].
- Porter CK, Thura N, Riddle MS. Quantifying the incidence and burden of postinfectious enteric sequelae. *Mil Med*. 2013;**178**(4):452-69. doi: [10.7205/MILMED-D-12-00510](https://doi.org/10.7205/MILMED-D-12-00510). [PubMed: [23707833](https://pubmed.ncbi.nlm.nih.gov/23707833/)].
- Maguen S, Madden E, Cohen B, Bertenthal D, Seal K. Association of mental health problems with gastrointestinal disorders in Iraq and Afghanistan veterans. *Depress Anxiety*. 2014;**31**(2):160-5. doi: [10.1002/da.22072](https://doi.org/10.1002/da.22072). [PubMed: [23494973](https://pubmed.ncbi.nlm.nih.gov/23494973/)].
- World Health Organization. Constitution of the World Health Organization. Handbook of Basic Documents. 5th ed. Geneva: WHO; 1948. p. 3-20.
- Wong RK, Drossman DA. Quality of life measures in irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol*. 2010;**4**(3):277-84. doi: [10.1586/egh.10.19](https://doi.org/10.1586/egh.10.19). [PubMed: [20528115](https://pubmed.ncbi.nlm.nih.gov/20528115/)].
- Patrick DL, Erickson P. Health Status and Health Policy: Quality of Life in Health Care Evaluation and Resource Allocation. NY, USA: Oxford University Press; 1993.
- Gros DF, Antony MM, McCabe RE, Swinson RP. Frequency and severity of the symptoms of irritable bowel syndrome across the anxiety disorders and depression. *J Anxiety Disord*. 2009;**23**(2):290-6. doi: [10.1016/j.janxdis.2008.08.004](https://doi.org/10.1016/j.janxdis.2008.08.004). [PubMed: [18819774](https://pubmed.ncbi.nlm.nih.gov/18819774/)].
- American College of Gastroenterology Task Force on Irritable Bowel S, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;**104** Suppl 1:S1-S5. doi: [10.1038/ajg.2008.122](https://doi.org/10.1038/ajg.2008.122). [PubMed: [19521341](https://pubmed.ncbi.nlm.nih.gov/19521341/)].
- Ware JE. In: Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Spilker B, editor. Philadelphia: Lippincott-Raven; 1996. p. 337-40. The sf-36 health survey.
- Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*. 2001;**33**(5):337-43. [PubMed: [11491192](https://pubmed.ncbi.nlm.nih.gov/11491192/)].
- Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci*. 1998;**43**(2):400-11. [PubMed: [9512138](https://pubmed.ncbi.nlm.nih.gov/9512138/)].
- Drossman DA, Patrick DL, Whitehead WE, Toner BB, Diamant NE, Hu Y, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. *Am J Gastroenterol*. 2000;**95**(4):999-1007. doi: [10.1111/j.1572-0241.2000.01941.x](https://doi.org/10.1111/j.1572-0241.2000.01941.x). [PubMed: [10763950](https://pubmed.ncbi.nlm.nih.gov/10763950/)].
- Bijkerk CJ, de Wit NJ, Muris JW, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics. *Am J Gastroenterol*. 2003;**98**(1):122-7. doi: [10.1111/j.1572-0241.2003.07158.x](https://doi.org/10.1111/j.1572-0241.2003.07158.x). [PubMed: [12526947](https://pubmed.ncbi.nlm.nih.gov/12526947/)].
- Drossman D, Morris CB, Hu Y, Toner BB, Diamant N, Whitehead WE, et al. Characterization of health related quality of life (HRQOL) for patients with functional bowel disorder (FBD) and its response to treatment. *Am J Gastroenterol*. 2007;**102**(7):1442-53. doi: [10.1111/j.1572-0241.2007.01283.x](https://doi.org/10.1111/j.1572-0241.2007.01283.x). [PubMed: [17509027](https://pubmed.ncbi.nlm.nih.gov/17509027/)].
- Creed F, Ratcliffe J, Fernandez L, Tomenson B, Palmer S, Rigby C, et al. Health-related quality of life and health care costs in severe, refractory irritable bowel syndrome. *Ann Intern Med*. 2001;**134**(9 Pt 2):860-8. [PubMed: [11346322](https://pubmed.ncbi.nlm.nih.gov/11346322/)].
- Wells NE, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. *Aliment Pharmacol Ther*. 1997;**11**(6):1019-30. [PubMed: [9663824](https://pubmed.ncbi.nlm.nih.gov/9663824/)].
- Pace F, Molteni P, Bollani S, Sarzi-Puttini P, Stockbrugger R, Bianchi Porro G, et al. Inflammatory bowel disease versus irritable bowel syndrome: a hospital-based, case-control study of disease impact on quality of life. *Scand J Gastroenterol*. 2003;**38**(10):1031-8. [PubMed: [14621276](https://pubmed.ncbi.nlm.nih.gov/14621276/)].
- Whitehead WE, Burnett CK, Cook E3, Taub E. Impact of irritable bowel syndrome on quality of life. *Dig Dis Sci*. 1996;**41**(11):2248-53. [PubMed: [8943980](https://pubmed.ncbi.nlm.nih.gov/8943980/)].
- Halpert A, Dalton CB, Palsson O, Morris C, Hu Y, Bangdiwala S, et al. What patients know about irritable bowel syndrome (IBS) and what they would like to know. National Survey on Patient Educational Needs in IBS and development and validation of the Patient Educational Needs Questionnaire (PEQ). *Am J Gastroenterol*. 2007;**102**(9):1972-82. doi: [10.1111/j.1572-0241.2007.01254.x](https://doi.org/10.1111/j.1572-0241.2007.01254.x). [PubMed: [17488254](https://pubmed.ncbi.nlm.nih.gov/17488254/)].
- Farndale R, Roberts L. Long-term impact of irritable bowel syndrome: a qualitative study. *Prim Health Care Res Dev*. 2011;**12**(1):52-67. doi: [10.1017/S1463423610000095](https://doi.org/10.1017/S1463423610000095). [PubMed: [21426615](https://pubmed.ncbi.nlm.nih.gov/21426615/)].
- Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology*. 2000;**119**(3):654-60. [PubMed: [10982758](https://pubmed.ncbi.nlm.nih.gov/10982758/)].
- Frank L, Kleinman L, Rentz A, Ciesla G, Kim JJ, Zacker C. Health-related quality of life associated with irritable bowel syndrome: comparison with other chronic diseases. *Clin Ther*. 2002;**24**(4):675-89. [PubMed: [12017411](https://pubmed.ncbi.nlm.nih.gov/12017411/)] discussion 674.
- Seres G, Kovacs Z, Kovacs A, Kerekgyarto O, Sardi K, Demeter P, et al.

- Different associations of health related quality of life with pain, psychological distress and coping strategies in patients with irritable bowel syndrome and inflammatory bowel disorder. *J Clin Psychol Med Settings*. 2008;**15**(4):287-95. doi: [10.1007/s10880-008-9132-9](https://doi.org/10.1007/s10880-008-9132-9). [PubMed: [19104985](https://pubmed.ncbi.nlm.nih.gov/19104985/)].
30. Schmulson M, Lee OY, Chang L, Naliboff B, Mayer EA. Symptom differences in moderate to severe IBS patients based on predominant bowel habit. *Am J Gastroenterol*. 1999;**94**(10):2929-35. doi: [10.1111/j.1572-0241.1999.01440.x](https://doi.org/10.1111/j.1572-0241.1999.01440.x). [PubMed: [10520847](https://pubmed.ncbi.nlm.nih.gov/10520847/)].
 31. Tillisch K, Labus JS, Naliboff BD, Bolus R, Shetzline M, Mayer EA, et al. Characterization of the alternating bowel habit subtype in patients with irritable bowel syndrome. *Am J Gastroenterol*. 2005;**100**(4):896-904. doi: [10.1111/j.1572-0241.2005.41211.x](https://doi.org/10.1111/j.1572-0241.2005.41211.x). [PubMed: [15784038](https://pubmed.ncbi.nlm.nih.gov/15784038/)].
 32. Simren M, Abrahamsson H, Svedlund J, Bjornsson ES. Quality of life in patients with irritable bowel syndrome seen in referral centers versus primary care: the impact of gender and predominant bowel pattern. *Scand J Gastroenterol*. 2001;**36**(5):545-52. [PubMed: [11346211](https://pubmed.ncbi.nlm.nih.gov/11346211/)].
 33. Jamali R, Jamali A, Poorrahnama M, Omidi A, Jamali B, Moslemi N, et al. Evaluation of health related quality of life in irritable bowel syndrome patients. *Health Qual Life Outcomes*. 2012;**10**:12. doi: [10.1186/1477-7525-10-12](https://doi.org/10.1186/1477-7525-10-12). [PubMed: [22284446](https://pubmed.ncbi.nlm.nih.gov/22284446/)].
 34. Muscatello MR, Bruno A, Pandolfo G, Mico U, Stilo S, Scaffidi M, et al. Depression, anxiety and anger in subtypes of irritable bowel syndrome patients. *J Clin Psychol Med Settings*. 2010;**17**(1):64-70. doi: [10.1007/s10880-009-9182-7](https://doi.org/10.1007/s10880-009-9182-7). [PubMed: [20094761](https://pubmed.ncbi.nlm.nih.gov/20094761/)].
 35. Si JM, Wang LJ, Chen SJ, Sun LM, Dai N. Irritable bowel syndrome consulters in Zhejiang province: the symptoms pattern, predominant bowel habit subgroups and quality of life. *World J Gastroenterol*. 2004;**10**(7):1059-64. [PubMed: [15052694](https://pubmed.ncbi.nlm.nih.gov/15052694/)].
 36. Amouretti M, Le Pen C, Gaudin AF, Bommelaer G, Frexinos J, Ruzsniowski P, et al. Impact of irritable bowel syndrome (IBS) on health-related quality of life (HRQOL). *Gastroenterol Clin Biol*. 2006;**30**(2):241-6. [PubMed: [16565657](https://pubmed.ncbi.nlm.nih.gov/16565657/)].
 37. Hahn BA, Kirchoefer 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**(3):553-9. [PubMed: [9218082](https://pubmed.ncbi.nlm.nih.gov/9218082/)].
 38. Monnikes H. Quality of life in patients with irritable bowel syndrome. *J Clin Gastroenterol*. 2011;**45** Suppl:S98-101. doi: [10.1097/MCG.0b013e31821bf44](https://doi.org/10.1097/MCG.0b013e31821bf44). [PubMed: [21666428](https://pubmed.ncbi.nlm.nih.gov/21666428/)].
 39. Cain KC, Headstrom P, Jarrett ME, Motzer SA, Park H, Burr RL, et al. Abdominal pain impacts quality of life in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006;**101**(1):124-32. doi: [10.1111/j.1572-0241.2006.00404.x](https://doi.org/10.1111/j.1572-0241.2006.00404.x). [PubMed: [16405544](https://pubmed.ncbi.nlm.nih.gov/16405544/)].
 40. Spiegel BM, Gralnek IM, Bolus R, Chang L, Dulai GS, Mayer EA, et al. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Arch Intern Med*. 2004;**164**(16):1773-80. doi: [10.1001/archinte.164.16.1773](https://doi.org/10.1001/archinte.164.16.1773). [PubMed: [15364671](https://pubmed.ncbi.nlm.nih.gov/15364671/)].
 41. Mearin F, Baro E, Roset M, Badia X, Zarate N, Perez I. Clinical patterns over time in irritable bowel syndrome: symptom instability and severity variability. *Am J Gastroenterol*. 2004;**99**(1):113-21. [PubMed: [14687152](https://pubmed.ncbi.nlm.nih.gov/14687152/)].
 42. Michalsen VL, Vandvik PO, Farup PG. Predictors of health-related quality of life in patients with irritable bowel syndrome. A cross-sectional study in Norway. *Health Qual Life Outcomes*. 2015;**13**:113. doi: [10.1186/s12955-015-0311-8](https://doi.org/10.1186/s12955-015-0311-8). [PubMed: [26223784](https://pubmed.ncbi.nlm.nih.gov/26223784/)].
 43. Lackner JM, Gudleski GD, Ma CX, Dewanwala A, Naliboff B. Representing the IOSRG. Fear of GI symptoms has an important impact on quality of life in patients with moderate-to-severe IBS. *Am J Gastroenterol*. 2014;**109**(11):1815-23. doi: [10.1038/ajg.2014.241](https://doi.org/10.1038/ajg.2014.241). [PubMed: [25223577](https://pubmed.ncbi.nlm.nih.gov/25223577/)].
 44. Riedl A, Schmidtman M, Stengel A, Goebel M, Wissner AS, Klapp BF, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res*. 2008;**64**(6):573-82. doi: [10.1016/j.jpsychores.2008.02.021](https://doi.org/10.1016/j.jpsychores.2008.02.021). [PubMed: [18501257](https://pubmed.ncbi.nlm.nih.gov/18501257/)].
 45. 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**(10):2262-73. doi: [10.1111/j.1572-0241.2005.00269.x](https://doi.org/10.1111/j.1572-0241.2005.00269.x). [PubMed: [16181379](https://pubmed.ncbi.nlm.nih.gov/16181379/)].
 46. Sayuk GS, Elwing JE, Lustman PJ, Clouse RE. Predictors of premarital antidepressant discontinuation in functional gastrointestinal disorders. *Psychosom Med*. 2007;**69**(2):173-81. doi: [10.1097/PSY.0b013e318031391d](https://doi.org/10.1097/PSY.0b013e318031391d). [PubMed: [17289822](https://pubmed.ncbi.nlm.nih.gov/17289822/)].
 47. Zhu L, Huang D, Shi L, Liang L, Xu T, Chang M, et al. Intestinal symptoms and psychological factors jointly affect quality of life of patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes*. 2015;**13**:49. doi: [10.1186/s12955-015-0243-3](https://doi.org/10.1186/s12955-015-0243-3). [PubMed: [25925746](https://pubmed.ncbi.nlm.nih.gov/25925746/)].
 48. Vu J, Kushnir V, Cassell B, Gyawali CP, Sayuk GS. The impact of psychiatric and extraintestinal comorbidity on quality of life and bowel symptom burden in functional GI disorders. *Neurogastroenterol Motil*. 2014;**26**(9):1323-32. doi: [10.1111/nmo.12396](https://doi.org/10.1111/nmo.12396). [PubMed: [25070610](https://pubmed.ncbi.nlm.nih.gov/25070610/)].
 49. Guthrie E, Barlow J, Fernandes L, Ratcliffe J, Read N, Thompson DG, et al. Changes in tolerance to rectal distension correlate with changes in psychological state in patients with severe irritable bowel syndrome. *Psychosom Med*. 2004;**66**(4):578-82. doi: [10.1097/01.psy.0000128899.22514.co](https://doi.org/10.1097/01.psy.0000128899.22514.co). [PubMed: [15272106](https://pubmed.ncbi.nlm.nih.gov/15272106/)].
 50. Wang YT, Kwok KF, Tan SM, Yek MH, Ong WC, Barbier S, et al. Comprehensive psychological intervention to improve outcome in functional gastrointestinal disorder: a cohort study. *Singapore Med J*. 2015;**56**(07):385-92. doi: [10.11662/smedj.2015109](https://doi.org/10.11662/smedj.2015109).
 51. Cho HS, Park JM, Lim CH, Cho YK, Lee IS, Kim SW, et al. Anxiety, depression and quality of life in patients with irritable bowel syndrome. *Gut Liver*. 2011;**5**(1):29-36. doi: [10.5009/gnl.2011.5.1.29](https://doi.org/10.5009/gnl.2011.5.1.29). [PubMed: [21461069](https://pubmed.ncbi.nlm.nih.gov/21461069/)].
 52. Thijsen AY, Jonkers DM, Leue C, van der Veek PP, Vidakovic-Vukic M, van Rood YR, et al. Dysfunctional cognitions, anxiety and depression in irritable bowel syndrome. *J Clin Gastroenterol*. 2010;**44**(10):e236-41. doi: [10.1097/MCG.0b013e3181eed5d8](https://doi.org/10.1097/MCG.0b013e3181eed5d8). [PubMed: [20733511](https://pubmed.ncbi.nlm.nih.gov/20733511/)].
 53. Gwee KA, Bak YT, Ghoshal UC, Gonlachanvit S, Lee OY, Fock KM, et al. Asian consensus on irritable bowel syndrome. *J Gastroenterol Hepatol*. 2010;**25**(7):1189-205. doi: [10.1111/j.1440-1746.2010.06353.x](https://doi.org/10.1111/j.1440-1746.2010.06353.x). [PubMed: [20594245](https://pubmed.ncbi.nlm.nih.gov/20594245/)].
 54. Naliboff BD, Kim SE, Bolus R, Bernstein CN, Mayer EA, Chang L. Gastrointestinal and psychological mediators of health-related quality of life in IBS and IBD: a structural equation modeling analysis. *Am J Gastroenterol*. 2012;**107**(3):451-9. doi: [10.1038/ajg.2011.377](https://doi.org/10.1038/ajg.2011.377). [PubMed: [22085819](https://pubmed.ncbi.nlm.nih.gov/22085819/)].
 55. O'Keefe EA, Talley NJ, Zinsmeister AR, Jacobsen SJ. Bowel disorders impair functional status and quality of life in the elderly: a population-based study. *J Gerontol A Biol Sci Med Sci*. 1995;**50**(4):M184-9. [PubMed: [7614239](https://pubmed.ncbi.nlm.nih.gov/7614239/)].
 56. Rutter CL, Rutter DR. Illness representation, coping and outcome in irritable bowel syndrome (IBS). *Br J Health Psychol*. 2002;**7**(Part 4):377-91. doi: [10.1348/135910702320645372](https://doi.org/10.1348/135910702320645372). [PubMed: [12614492](https://pubmed.ncbi.nlm.nih.gov/12614492/)].
 57. Labus JS, Mayer EA, Chang L, Bolus R, Naliboff BD. The Central Role of Gastrointestinal-Specific Anxiety in Irritable Bowel Syndrome: Further Validation of the Visceral Sensitivity Index. *Psychosom Med*. 2007;**69**(1):89-98. doi: [10.1097/PSY.0b013e31802e2f24](https://doi.org/10.1097/PSY.0b013e31802e2f24).
 58. Lackner JM, Ma CX, Keefer L, Brenner DM, Gudleski GD, Satchidanand N, et al. Type, rather than number, of mental and physical comorbidities increases the severity of symptoms in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2013;**11**(9):1147-57. doi: [10.1016/j.cgh.2013.03.011](https://doi.org/10.1016/j.cgh.2013.03.011). [PubMed: [23524278](https://pubmed.ncbi.nlm.nih.gov/23524278/)].
 59. Labus JS, Bolus R, Chang L, Wiklund I, Naesdal J, Mayer EA, et al. The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. *Aliment Pharmacol Ther*. 2004;**20**(1):89-97. doi: [10.1111/j.1365-2036.2004.02007.x](https://doi.org/10.1111/j.1365-2036.2004.02007.x). [PubMed: [15225175](https://pubmed.ncbi.nlm.nih.gov/15225175/)].
 60. Jerndal P, Ringstrom G, Agerforz P, Karpefors M, Akkermans LM, Bayati A, et al. Gastrointestinal-specific anxiety: an important factor for severity of GI symptoms and quality of life in IBS. *Neurogastroenterol Motil*. 2010;**22**(6):646-e179. doi: [10.1111/j.1365-2982.2010.01493.x](https://doi.org/10.1111/j.1365-2982.2010.01493.x).

- [PubMed: 20367800].
61. Stanculete MF, Matu S, Pojoga C, Dumitrascu DL. Coping strategies and irrational beliefs as mediators of the health-related quality of life impairments in irritable bowel syndrome. *J Gastrointest Liver Dis.* 2015;24(2):159-64. doi: 10.15403/jgld.2014.1121.242.strtt. [PubMed: 26114174].
 62. Kovacs Z, Kovacs F. Depressive and anxiety symptoms, dysfunctional attitudes and social aspects in irritable bowel syndrome and inflammatory bowel disease. *Int J Psychiatry Med.* 2007;37(3):245-55. [PubMed: 18314852].
 63. Fadgyas-Stanculete M, Buga AM, Popa-Wagner A, Dumitrascu DL. The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations. *J Mol Psychiatry.* 2014;2(1):4. doi: 10.1186/2049-9256-2-4. [PubMed: 25408914].
 64. De Gucht V. Illness perceptions mediate the relationship between bowel symptom severity and health-related quality of life in IBS patients. *Qual Life Res.* 2015;24(8):1845-56. doi: 10.1007/s11136-015-0932-8. [PubMed: 25663636].
 65. Voci SC, Cramer KM. Gender-related traits, quality of life, and psychological adjustment among women with irritable bowel syndrome. *Qual Life Res.* 2009;18(9):1169-76. doi: 10.1007/s11136-009-9532-9. [PubMed: 19728159].
 66. Tang YR, Yang WW, Liang ML, Xu XY, Wang MF, Lin L. Age-related symptom and life quality changes in women with irritable bowel syndrome. *World J Gastroenterol.* 2012;18(48):7175-83. doi: 10.3748/wjg.v18.i48.7175. [PubMed: 23326122].
 67. Park JM, Choi MG, Kim YS, Choi CH, Choi SC, Hong SJ, et al. Quality of life of patients with irritable bowel syndrome in Korea. *Qual Life Res.* 2009;18(4):435-46. doi: 10.1007/s11136-009-9461-7. [PubMed: 19247807].
 68. Koloski N. A. , Boyce P. M. , Jones M. P. , Talley N. J. . What level of IBS symptoms drives impairment in health-related quality of life in community subjects with irritable bowel syndrome?. *Qual Life Res.* 2012;21(5):829-36. doi: 10.1007/s11136-011-9985-5.
 69. Wang YT, Lim HY, Tai D, Krishnamoorthy TL, Tan T, Barbier S, et al. The impact of irritable bowel syndrome on health-related quality of life: a Singapore perspective. *BMC Gastroenterol.* 2012;12:104. doi: 10.1186/1471-230X-12-104. [PubMed: 22873839].
 70. Xiong LS, Chen MH, Chen HX, Xu AG, Wang WA, Hu PJ. [A population-based epidemiologic study of irritable bowel syndrome in Guangdong province]. *Zhonghua Yi Xue Za Zhi.* 2004;84(4):278-81. [PubMed: 15059507].
 71. Gwee KA, Wee S, Wong ML, Png DJ. The prevalence, symptom characteristics, and impact of irritable bowel syndrome in an Asian urban community. *Am J Gastroenterol.* 2004;99(5):924-31. doi: 10.1111/j.1572-0241.2004.04161.x. [PubMed: 15128362].
 72. Abdulmajeed A, Rabab MA, Sliem HA, Hebatallah NE. Pattern of irritable bowel syndrome and its impact on quality of life in primary health care center attendees, Suez governorate, Egypt. *Pan Afr Med J.* 2011;9:5. [PubMed: 22145053].
 73. Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees. Prevalence, demographics, and clinical correlates. *Dig Dis Sci.* 1993;38(9):1581-9. [PubMed: 8359067].
 74. Choi MG, Jung HK. Health related quality of life in functional gastrointestinal disorders in Asia. *J Neurogastroenterol Motil.* 2011;17(3):245-51. doi: 10.5056/jnm.2011.17.3.245. [PubMed: 21860816].
 75. Lau EM, Chan FK, Ziea ET, Chan CS, Wu JC, Sung JJ. Epidemiology of irritable bowel syndrome in Chinese. *Dig Dis Sci.* 2002;47(11):2621-4. [PubMed: 12452405].
 76. Tang QL, Lin GY, Zhang MQ. Cognitive-behavioral therapy for the management of irritable bowel syndrome. *World J Gastroenterol.* 2013;19(46):8605-10. doi: 10.3748/wjg.v19.i46.8605. [PubMed: 24379577].