Functional bowel symptoms in the general population (Review)

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Abstract. Several patients with irritable bowel syndrome (IBS) do not seek medical attention for their symptoms. When patients with IBS seek help, the majority of them are handled at primary healthcare centers, whereas research studies are performed at tertiary healthcare centers. The present study aimed to summarize findings from >4,000 participants of the general population included in the Malmö Offspring Study (inclusion rate 46.7%). The participants were clinically examined, their blood and fecal samples collected, and their questionnaires completed. The participants were divided into subjects with or without self-reported IBS and those having functional gastrointestinal (GI) symptoms in the past 2 weeks. The presence of IBS and GI symptoms in the participants were associated with each other. Zonulin levels did not differ between participants with or without GI diseases and were not associated with the degree of GI symptoms. The parameters low body weight at birth and small for gestational age were associated with the degree of the symptoms' influence on daily life. IBS and GI symptoms were positively associated with *Blautia* abundance. Beta-diversity differed between participants with or without these two conditions. Positive correlations were noted between the degree of diarrhea and the mean 24-h measurements of systolic blood pressure, diastolic blood pressure, and heart rate. Both IBS and GI symptoms were associated with female sex, smoking, stress, poor sleeping habits, unemployment, drug use, and a family history of GI diseases, whereas younger age was inversely associated with IBS and its associated symptoms. In conclusion, only a limited number of medical findings could be identified in participants with IBS and GI symptoms, whereas sociodemographic and environmental conditions were associated with these entities.

Contents

1. Introduction

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disorder, diagnosed by symptom questionnaires according to defined criteria (1). The worldwide prevalence of IBS according to the Rome IV criteria is 4.1% (range 1.3-7.6%) and varies depending on the country and definition used (2,3). The majority of the IBS patients are handled at primary healthcare centers; however, recruitment of these subjects in studies is performed at tertiary healthcare centers (4). Since only 21% of the patients who experienced IBS symptoms in the previous year will consult a physician, the number of unknown cases in the society may be considerably high (5).

Several research studies have been performed during the last decades to identify the etiology and pathophysiology of IBS. The most established risk factors for the development of IBS are female sex, smoking, and psychological stress (6). Although a low-grade inflammation has been suggested, this theory is difficult to be confirmed (7). Alterations in gut microbiota have also been widely discussed; however, different studies have shown varying results, and no definitive conclusions have been reached (8). Impaired intestinal barrier is one of the several hypotheses established to explain functional GI symptoms. Zonulin has been suggested to be a marker of increased intestinal permeability (9). Genetic studies have described associations between IBS and certain gene variants, such as *IKBKAP*; these variants are found in patients with familial dysautonomia and associated GI symptoms (10,11). Therefore, a hypothesis was established suggesting that certain forms of IBS may depend on autonomic dysfunction (12). Furthermore, the increased survival of premature children

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exerts a certain impact on the general health of the affected subjects. Infants born prior to the 37th completed week of pregnancy, those with low birth weight (LBW) (<2,500 g), low Apgar scores, or small for gestational age (SGA), have been associated with negative health consequences, such as IBS [13-16].

During the last years, a population-based cross-sectional study, termed the Malmö Offspring Study (MOS), was performed in the south of Sweden to include participants from the general population. Several studies have been performed to estimate risk factors for IBS/GI symptoms. The aim of the present minireview was to summarize the estimated associations between self-reported IBS and GI symptoms in the general population and intestinal permeability, early life factors, gut microbiota, autonomic homeostasis, sociodemographic characteristics, lifestyle habits, chronic stress, sleeping habits, concomitant disorders, and drug treatment.

2. MOS

The Malmö Diet and Cancer Study (n=28,098) is a population-based study, which was performed between 1991 and 1996 and invited all subjects born between 1923 and 1950 [17]. Subsequently, 6,103 of these individuals were randomly selected and re-examined for assessing cardiovascular risk factors. These subjects comprised the Malmö Diet and Cancer Cardiovascular Cohort (MDC-CC) [18]. MOS consists of children and grandchildren of the participants of the MDC-CC [19]. The participants were clinically examined, their blood and fecal samples were collected and the study questionnaires were completed. The participants were categorized to suffer from self-reported IBS if they answered 'yes' to the following question: 'Have you several times during a month suffered from abdominal pain related to irregular bowel habits, which is called IBS?' The formulation was considered to reflect the Rome III criteria for IBS [20]. They were categorized to suffer from GI symptoms if they answered 'yes' to the following question: 'Have you suffered from any GI symptoms within the past 2 weeks?' The two conditions were associated with each other throughout the study (P<0.001). The participants who experienced GI symptoms were encouraged to complete the visual analog scale (VAS) for IBS (VAS-IBS) to assess the degree of specific symptoms on a VAS scale [21].

Citations of three sets of MOS cohorts. Firstly, 363 of the 1,500 participants attended between March 2013 and November 2015, of whom 186 were women accounting for 51.2%. These patients were randomly selected for serum analysis of zonulin by a commercial ELISA kit. A total of 238 participants of the 363 selected had completed the study questions regarding GI symptoms (Fig. 1, Table I) [22]. Secondly, 2,644 participants were included between March 2013 and April 2017. The participants who reported organic GI diseases, did not answer the questions regarding GI symptoms, or did not have data regarding autonomic function tests, gut microbiota, or data from the Swedish Medical Birth Registry (started 1973) were excluded. In total, 1,013 participants were included in the study of early life factors [23], whereas 1,988 participants were included in the study of gut microbiota [24], and 2,094 participants were included in the studies of autonomic, hemodynamic

parameters [12] (Fig. 1, Table I). Thirdly, 1,577 participants of the 4,225 participants included between March 2013 and June 2020 (46.7% participation rate) were excluded due to the presence of any type of organic GI disease or due to their inability to provide an answer to the questions regarding GI symptoms. Therefore, 2,648 individuals were finally included in the study of sociodemographic factors [25], chronic stress and sleeping habits [26], concomitant diseases, drug use, and family history of any diseases [27] (Fig. 1; Table I).

3. Zonulin

The serum concentration of zonulin did not differ between sexes [21]. Zonulin levels correlated with weight, body mass index (BMI), waist- and hip-circumference, systolic blood pressure, diastolic blood pressure, and fasting plasma glucose levels, whereas sociodemographic factors and lifestyle habits did not influence zonulin levels. The presence or absence of GI symptoms during the past 2 weeks (n=44) did not affect zonulin levels. Accordingly, the degree of GI symptoms or psychological well-being did not correlate with the serum values of zonulin [22]. The participants with any type of history of organic GI diseases (n=54) exhibited the same zonulin levels as those without the presence of any disease. The same finding was also noted in the subjects with functional dyspepsia or self-reported IBS (n=61) [22].

4. Early life factors

Age and BMI did not differ between the subjects with or without IBS or GI symptoms [23]. A trend for an association between GI symptoms and preterm birth was noted compared with the term birth, which was also noted following estimation of the gestational age used as a continuous variable. Further calculations stratifying for the severity of the GI symptoms did not show significant associations between prematurity and GI symptoms. Lower body weight at birth, low Apgar score, or SGA did not show significant associations with the presence of functional GI symptoms or the degree of symptom severity. However, in contrast to a low Apgar score, both lower body weight measured as a continuous scale and SGA were associated with a high degree of symptom influence on daily life. No association of the early life factors was noted with self-reported IBS [23].

5. Gut microbiota

The subjects with IBS and/or GI symptoms were younger than those without these two conditions, whereas the parameter BMI did not differ between these groups [24].

Beta-diversity, assessed by the Bray-Curtis dissimilarity index, was significantly different between individuals reporting either IBS or GI symptoms compared with those who did not present with GI complaints. In contrast to these findings, alpha-diversity did not significantly differ between these conditions. Following calculations of the different genera with adjustments for confounders and false discovery rate (FDR), it was found that IBS was associated with an abundance of *Blautia*; GI symptoms were associated with *Blautia* and a genus in the order of SHA-98 bacteria. Diarrhea was
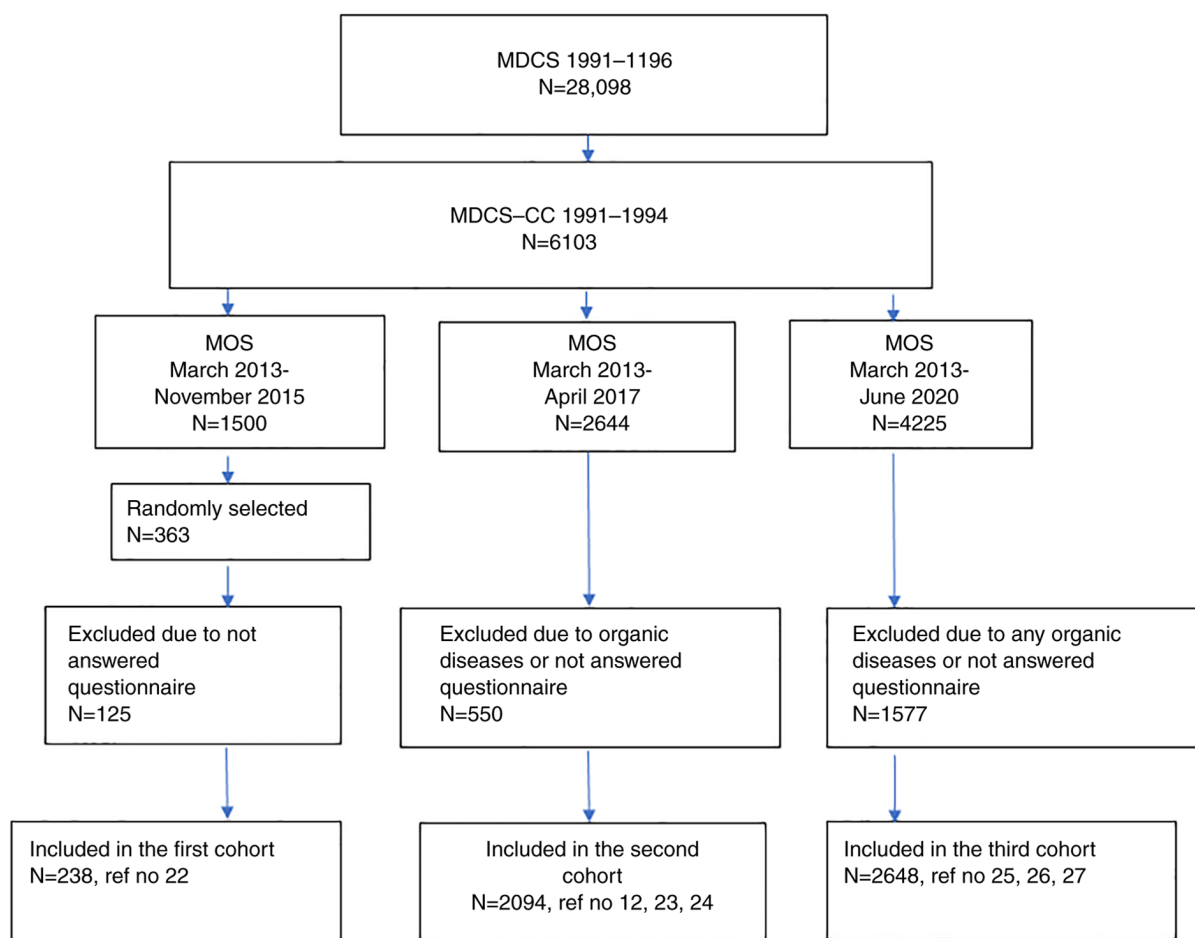
Figure 1. Flow chart of participants. MDCS invited the entire population living in Malmö. From this cohort, MDCS-CC was randomly extracted. The MOS consisted of children and grandchildren to the subjects included in the MDCS-CC. The final study cohorts included the MOS participants who had answered the questions regarding GI symptoms and did not suffer from organic GI diseases (celiac disease, Crohn's disease, ulcerative colitis, lactose intolerance, reflux and ulcer). References refer to the original publications. MDCS, Malmö Diet and Cancer Study; MDCS-CC, Malmö Offspring Study cardiovascular cohort; MOS, Malmö Offspring Study; GI, gastrointestinal.

associated with *Blautia*, *Prevotella*, and a genus in the order of SHA-98 bacteria and *Christensellaceae* family (24).

6. Hemodynamic parameters

BMI did not differ between groups, but the subjects with IBS or GI symptoms were younger than those without these conditions (12). No significant alterations were noted in hemodynamic parameters between IBS and non-IBS subjects following adjustment for confounders. In contrast to these findings, lower values of diastolic blood pressure in supine and standing positions, and mean systolic and diastolic blood pressures during ambulatory 24-h measurements, demonstrated significant differences in those with GI symptoms compared with those without any GI symptoms following adjustments for age, sex, current smoking, and chronic stress. A total of 142 subjects (27.9%) reported diarrhea being their most predominant symptom; this was the only specific symptom, which was associated with hemodynamic parameters following adjustment of confounders. For the 24-h measurements, concordant positive correlations were noted between systolic blood pressure, diastolic blood pressure, and heart rate, and the severity of diarrhea. In accordance with the correlation analyses, the adjusted linear regression indicated associations between the 24-h hemodynamic measurements of the systolic blood pressure, diastolic blood pressure, and heart rate. Significant associations were also noted for the diastolic blood pressure in the supine position following comparisons of the fourth quartile with quartiles 1-3 of diarrhea (12).

7. Sociodemographic and lifestyle factors

Strong associations were noted between all specific symptoms and self-reported IBS (P<0.001, except for constipation, P=0.008). The IBS participants had the same age as those without IBS, whereas those with GI symptoms were younger than those without these symptoms. BMI was lower in participants with IBS and GI symptoms than in those without these conditions (25).

Self-reported IBS was associated with female sex, former smoking, and present smoking, and inversely associated with drinking frequency of 2-3 times a week and drinking 3-4 standard glasses per occasion (25).

The GI symptoms in the past 2 weeks were associated with female sex, studying, unemployment, former smoking, and present smoking, whereas the symptoms were inversely associated with age 50-59 years and age ≥60 years (25).

Table I. Description of the different original manuscripts published from the Malmö Offspring Study cohorts and summarized in the minireview.

First author/s, year	Cohorts	No.	Age, years	BMI, kg/m²	Female sex, n (%)	GI symptoms, n (%)	IBS, n (%)	(Refs.)
Ohlsson et al, 2017	Serum zonulin	238	42.6±13.2	22.8±4.2	127 (53.4)	44 (18.5)	40 (16.8)	(22)
Wennerberg et al, 2021	Early life factors; excluded celiac disease, IBD and lactose intolerance	1013	29.0±6.8	24.9±4.5	546 (53.9)	253 (25.0)	179 (17.7)	(23)
Brunkwall et al, 2021	Gut microbiota; excluded celiac disease, IBD and lactose intolerance	1988	39.8±13.9	25.8±4.7	1055 (53.1)	396 (19.9)	305 (15.3)	(24)
Hamrefors et al, 2019	Hemodynamic parameters; excluded celiac disease and IBD	2094	40.1±13.6	25.9±4.9	1127 (53.8)	509 (24.3)	347 (16.6)	(12)
Nilsson and Ohlsson, 2021	Sociodemography and lifestyle; excluded any organic GI disease	2648	42.6±14.4	25.9±4.7	1391 (52.5)	459 (17.3)	316 (11.9)	(25)
Zejnelagic and Ohlsson, 2021	Stress and sleeping habits; excluded any organic GI disease	2648	42.6±14.4	25.9±4.7	1391 (52.5)	459 (17.3)	316 (11.9)	(26)
Ruderstam and Ohlsson, 2022	Concomitant diseases and drugs; excluded any organic GI disease	2648	42.6±14.4	25.9±4.7	1391 (52.5)	459 (17.3)	316 (11.9)	(27)

Participants with organic gastrointestinal diseases in the different cohorts were excluded before calculations. The types of excluded organic diseases varied between the cohorts and are shown for each study. Any organic GI disease included celiac disease, IBD, gastric ulcer, lactose intolerance and reflux. Values are presented as the mean ± standard deviation or n (%). BMI, body mass index; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome. References refer to the original publication.

The examination of specific GI symptoms, with the exception of diarrhea and vomiting and nausea indicated that worse symptoms were associated with female sex and worse psychological well-being. Present smoking was associated with more severe GI symptoms and worse psychological well-being. Studying was associated with a higher degree of abdominal pain, and bloating and flatulence, but improved psychological well-being. Sick leave and unemployment were, in comparison to working, associated with more symptoms and poorer psychological well-being (25).

Following stratification for sex, IBS in male sex was associated with an age range of 30-39, 40-49, and unemployment. The GI symptoms in the past 2 weeks were associated with unemployment. IBS in women was associated with present smoking and GI symptoms were associated with former smoking and were inversely associated with age ≥50 years and intermediate physical activity at work (25).

No significant associations were noted between IBS or GI symptoms in the past 2 weeks and BMI groups, education, marital status, snuff use, or physical activity during leisure time (25).

8. Chronic stress and sleeping habits

The experience of chronic stress during the past year was associated with self-reported IBS and GI symptoms, as was chronic stress during the past 5 years, following adjustment for sociodemographic factors (26).

Average, bad, or very bad sleeping quality, sleeping onset difficulties, and ≥3 wake-ups per week were associated with self-reported IBS, whereas a sleeping duration of 7 h was inversely associated with self-reported IBS. The only sleeping habit associated with GI symptoms was a wake-up frequency of 3-6 times per week.

Following the combined calculation of all the variables of stress and sleeping disturbances in the full model adjusted for all confounders, a marked association was noted between self-reported IBS and sleeping onset difficulties and chronic stress during the past 5 years, whereas GI symptoms were associated with chronic stress in the past year (26).

Stress, poor sleeping quality, sleeping onset difficulties, and IBS/GI symptoms were all associated with poor psychological well-being (26).

9. Self-reported IBS or GI symptoms and comorbidity, medication, and family history of diseases

When examining comorbidity, asthma was associated with self-reported IBS. The associations between asthma and GI symptoms in the past 2 weeks and chest pain >30 min and IBS disappeared following adjustment for FDR (27).

IBS was associated with prescription of drugs in the past week or the use of a non-prescription drug in the past week. When calculations were performed with specific medications, antihistamines, beta blockers, and hypnotics were the drugs associated with IBS (27).

GI symptoms in the past 2 weeks were associated with non-prescription drugs prior to FDR correction, as well as the prescribed drugs beta-blockers and proton pump inhibitors (27).

A family history of prostate cancer was associated with IBS, whereas a family history of joint diseases and myocardial infarction were associated with GI symptoms. In addition, there was an association between GI disease in the family and self-reported IBS and GI symptoms. Regarding the subgroups of GI diseases, IBS was associated with celiac disease, gastric ulcer, functional dyspepsia, IBS, and reflux; GI symptoms were associated with functional dyspepsia, IBS, and reflux (27).

10. Discussion

The main findings from the studies performed in the general population were that a limited number of objective findings could be identified in the group of participants with IBS and GI symptoms (12,22,24). In contrast to this observation, strong associations between IBS and GI symptoms were noted with female sex, younger age, smoking, unemployment, stress, poor psychological well-being, poor sleeping habits as well as drug use, and family history of GI diseases (25-27).

The findings are in accordance with previous studies, showing a high prevalence of IBS in the general population (28). Moreover, the data indicated that psychosocial and sensory factors contributed to self-reported pain in IBS (29). In addition, dietary and lifestyle habits are of importance for symptom development (30). Collectively, the included studies support the importance of performing scientific studies in subjects from the general population, and not only in subjects from tertiary healthcare centers (4), where selected patients are referred who may suffer from enteric dysmotility and not by IBS, which can obscure the results (31,32).

It has been previously shown that IBS and GI symptoms are strongly associated with female sex and smoking, whereas higher age is inversely associated with these conditions (25). Unemployment was associated with GI symptoms, notably in men. Sick leave and unemployment were associated with the presence of GI symptoms and with more severe symptoms and impaired psychological well-being (25). This is in accordance with prior studies that have shown a high degree of unemployment and absence from work in patients with self-reported IBS (5). Men have been found to have poorer mental health than women when they are unemployed, possibly due to traditional beliefs that they should be solely responsible for providing financial support to their families (33). The subjective social status relative to other individuals in the same community may mediate the association between occupational status, psychological well-being, and stress (34).

Most studies performed have a cross-sectional design and causality can therefore not be analyzed. Among the limited number of prospective studies performed regarding sleeping habits, the parameters poor self-reported sleeping quality, and frequent waking episodes could predict additional abdominal or other types of pain, anxiety, and fatigue the following day (35-37). The most important predictor of poor sleeping quality was pre-sleep cognitive arousal (35). Higher arousal and awakening index have been described in IBS patients, which can be associated with sleeping fragmentation (38). Collectively, low quality of life, depression, and arousal affect the quality and efficiency of sleeping as well as the experience of pain and IBS symptoms (35-37).

It has been previously reported that drug treatment may increase the prevalence of GI symptoms (39). However, this increase may be due to the disease *per se*, which requires drug treatment, leading to the development of GI symptoms. Furthermore, chronic illness behavior is a learned behavior found to be increased in IBS patients (40). Children of parents with IBS had a significantly higher number of ambulatory care visits; this trend was independent of the presence of GI symptoms (41). The model of social learning and behavior may thus explain the associations found in family history (27), although genetic components have been found as well, which may lead to disease development of several members within the same family (42,43). Perinatal factors were not associated with the significance of the development of IBS in the MOS cohort, although previous studies have found an increased risk to develop IBS when infants are born with LBW (14,42).

Intestinal permeability assessed by zonulin cannot alone explain the GI symptoms. By contrast, overweight and metabolic syndromes exhibited a higher association with zonulin levels (22). Despite these findings, in a larger population-based study within the same area, subjects with prevalent inflammatory bowel disease had higher zonulin levels compared with those without inflammatory bowel disease (44). The microbiota changes noted in IBS in the general population were modest and suggested that gut microbiota was not the major explanation to GI symptoms (23), which was in line with a study performed in the general population, indicating no significant differences in the microbiota from tissue biopsies or feces of IBS patients compared with those of healthy subjects (45). Furthermore, autonomic neuropathy cannot explain IBS in the general population (12) and the findings do not support the genetic associations with familial dysautonomia found in IBS (10,11).

The advantage of the performed studies of self-reported IBS and GI symptoms is the examination of the general population as opposed to the examination of the tertiary healthcare centers. The major limitation of the present study was that the dietary habits were not examined, since the symptom development in IBS is suggested to depend on the accumulation of unabsorbed carbohydrates in the bowel leading to gas production and osmotic diffusion of water (46). However, the present findings confirm the multifactorial etiology of IBS, suggesting that not only dietary factors are of importance in the development of this disease.

In conclusion, few objective medical findings could be identified in participants with IBS and GI symptoms from the general population. The etiology to IBS seems to be multifactorial. Strong associations were reported with younger age, female sex, smoking, unemployment, stress, poor psychological well-being, drugs, and a family history of GI disorders. Therefore, sociodemographic factors and lifestyle habits must be considered, and the treatment should be focused on the prevention and elimination of stressful life factors, and not only on medical reasons, drug treatment, and dietary advice.

Acknowledgements

Funding

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

BO wrote this minireview and drew the figure. Data authentication is not applicable. The author has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that she has no competing interests.

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