Predictive Factors for the Diagnosis of Irritable Bowel Syndrome in a Large Cohort of 440,822 Young Adults

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Background: The prevalence of irritable bowel syndrome (IBS) in the community has been reported in numerous cross-sectional surveys. However, little is known about the incidence and predictive factors for the clinical diagnosis of IBS.

Methods: We examined the association of socioeconomic, anthropometric, and occupational factors with the incidence of IBS in a cohort of 440,822 young Israeli adults aged 18 to 39 who served in active military service during the years 2005 to 2011.

Results: During the follow-up of 1,925,003 person-years, IBS was diagnosed de novo in 976 patients, giving an incidence rate of 221:100,000 (0.2%) person-years for the diagnosis of IBS. On multivariable Cox analysis, higher socioeconomic status [hazard ratio (HR) 1.629; 95% confidence interval (CI), 1.328-1.999; $P < 0.0001$], Israeli birth (HR 1.362; 95% CI, 1.084-1.712; $P = 0.008$), Jewish ethnicity (HR 2.089; 95% CI, 1.344-3.248; $P = 0.001$), education $\geq$than 11 years (HR 1.674; 95% CI, 1.019-2.751; $P = 0.042$), and a noncombat military position (HR 1.196; 95% CI, 1.024-1.397; $P = 0.024$) were found to be risk factors for the diagnosis or for the worsening of IBS. Overweight (HR 0.744; 95% CI, 0.589-0.941; $P = 0.014$), obesity (HR 0.698; 95% CI, 0.510-0.95; $P = 0.025$), living in a rural settlement (HR 0.705; 95% CI, 0.561-0.886; $P = 0.003$), and Middle Eastern (HR 0.739; 95% CI, 0.617-0.884; $P = 0.001$,) or North African and Ethiopian origin (HR 0.702; 95% CI, 0.585-0.842; $P < 0.001$) were found to be protective for the diagnosis or the worsening of IBS.

Conclusions: This study provides novel data on the socioeconomic, anthropometric, and occupational factors predictive for IBS development. The predictive factors for IBS diagnosis may point to the fact that stress had a lower impact on IBS incidence in our study cohort.

Key Words: irritable bowel syndrome, epidemiology, functional gastrointestinal syndromes

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Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder associated with chronic abdominal pain, constipation, diarrhea, or both.[1,2] IBS causes significant morbidity and decrease in the quality of life.[3,4] The reported prevalence of IBS depends on geographical and cultural factors, as well as on the criteria for IBS diagnosis,[5,6] and is reported to be between 5% and 15% in most western countries and between 1% and 22% in Asia.[7] The chronic nature of IBS represents a considerable economic burden[8] and causes considerable morbidity and absence from work.[9]

The exact etiology of IBS remains obscure. Proposed mechanisms include visceral hypersensitivity,[10] alerted central perception of pain,[11] low-grade intestinal inflammation,[12,13] intestinal motility disorders,[14] and intestinal flora dysbiosis.[15]

The prevalence of IBS in the community has been reported in numerous cross-sectional surveys. However, little is known about the incidence of IBS.[16,17] Furthermore, only 1 study has analyzed data concerning potential risk factors for the diagnosis of IBS.[18] We have examined the incidence of IBS in a large cohort of young adults and looked at the association of socioeconomic, anthropometric, and occupational factors with the incidence of IBS.

METHODS

Population

In this retrospective study, the population consisted of Israeli men and women aged 18 to 39 years who served in active military service (mandatory and career service) between the years 2005 and 2011. One year before their recruitment into military service, all eligible men and women of Jewish origin, and all eligible men of Druze and Circassian origin, undergo obligatory medical board examination for health status assessment that includes reviewing their medical file obtained from the primary care physician, taking a medical history and conducting a physical examination, and, if needed, providing referral for further evaluation. All potential recruits undergo baseline measurement of weight and height. The medical state of each individual is recorded and coded in a medical profile, defined as the standards of medical fitness for different jobs, and limitations to physical activity because of medical conditions. The medical profile is constructed accordingly by any major medical problem and its severity. Thus, the medical profile related to IBS includes mild, moderate, and severe sickness, giving different medical profile for each IBS severity. In the case of significant alteration in the state of health during military service, the medical profile is changed, thus defining the new medical status and its severity. Excluded from military service following the medical board examination are those with a low health status and psychiatric disorders, as well as ultraorthodox Jews and women claiming religious reasons. However, IBS in any severity does not disqualify from military service.

Definitions and Follow-up

At the medical checkup 1 year before recruitment, all recruits undergo thorough medical examination that is conducted by experienced military physicians. A formatted medical questionnaire, which encompasses questions

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The authors declare that they have nothing to disclose.

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regarding all systems, is filled by the physicians during the checkup. In addition, a structured medical questionnaire regarding the past medical history is filled before the checkup by the family physician of the recruits and by the recruits themselves. All recruits who reported any significant abdominal complaint during their medical inspection or who had had any prior history of significant abdominal symptoms reported by the family practitioner are referred for further examination by expert military gastroenterologists. Similarly, soldiers in active military service who report chronic abdominal complaints are sent for gastroenterological consult that is usually carried out by military gastroenterologist experts. Therefore, the diagnosis of IBS in recruits before their enlisting, as well as in soldiers who had been recruited and were in active military service, was made solely on the opinion of expert gastroenterologists using standard and uniform process, according to the Rome II Criteria.[19] It had to be based on clinical symptoms of long-standing abdominal pain or discomfort (at least 12 wk in the preceding 12 mo), relieved by defecation; and/or onset associated with a change in frequency of stool; and/or onset associated with a change in the form of stool. Other symptoms that could support the diagnosis of IBS included abnormal stool frequency, abnormal stool form, abnormal stool passage, passage of mucus, and bloating or a feeling of abdominal distension. Hemoglobin levels and C-reactive protein levels had to be in the normal range, and celiac serology had to be negative. Normal colonoscopy and small bowel imaging (small bowel follow-through, abdominal computed tomography, or magnetic resonance imaging) were required for the exclusion of organic gastrointestinal disease before the diagnosis of moderate and severe IBS.

The severity of IBS was divided into mild, moderate, and severe categories by the examining gastroenterologist at the time of examination, based on the impact of IBS symptoms on everyday activity, as formulated by the Rome Foundation Working Team report on severity of IBS.[20] To diagnose moderate to severe IBS, significant disability had to be confirmed, based on school or working day loss because of IBS symptoms, as well as the primary physician's opinion based on the severity and frequency of abdominal pain and other symptoms.

The IBS-diagnosed group consisted of all new cases of IBS (not diagnosed previously at the obligatory medical board examination before enlisting). A new diagnosis of IBS was thus defined as the presence of a new medical profile owing to the diagnosis of IBS in a person without a preceding diagnosis of IBS. We excluded from the IBS cohort every case in which the initial diagnosis of IBS was changed to that of celiac disease and inflammatory bowel disease during follow-up (n = 26). Follow-up was stopped at the diagnosis of IBS, discharge from military service, or on December 31, 2011.

Data Collection

We collected demographic, anthropometric, and medical data on our study cohort. Baseline data included country of origin (defined a priori by the central Israel Defense Force statistical branch as the father's place of birth or grandfather's place of birth if the father was Israeli-born). All individuals were then grouped into the following categories: Israeli, former Soviet Union, Middle Eastern (mainly originating from Iran, Iraq, Turkey, and Yemen), African (mainly originating from North Africa and Ethiopia), and Western origin (Europe/America/Australia). Other baseline data included gender, an immigrant to Israel (Yes/no), ethnicity (Jewish/non-Jewish), and education (< 11 y/≥ 11 y). Socioeconomic status was classified according to characteristics of the settlement or city of residence on a 1 to 10 scale by the Central Bureau of Statistics, which we divided into 3 groups (low, medium, and high). Other data collected included the type of settlement the individual originated from (classified as rural or urban by the Central Bureau of Statistics), the number of siblings in the household and position held in the military (combat/other). Height and weight were measured during the obligatory medical board examination at the initial medical checkup (at the age of 17) by trained medical personnel using a stadiometer and a beam balance (subjects were barefoot and wore only a shirt and underwear). Body mass index (BMI) at the time of examination was stratified into 4 groups: underweight (< 5 percentile), normal or healthy weight (5 to < 85 percentile), overweight (85 to < 95 percentile), and obese (≥ 95 percentile) according to definitions established by the 2000 United States CDC BMI-for-age growth charts.[21,22] The 85th percentile of Israeli adolescents was previously reported to be similar to the 85th percentile United states center of disease control threshold for men.[23]

The study was approved by the Israeli Defense Forces Medical Corps Ethical Committee.

Statistical Analysis

The socioeconomic, anthropometric, and occupational characteristics of the participants are presented as arithmetic means ($\pm$ SD) or as percentages. Cox proportional hazards regression models were used to assess the association between the baseline adolescent characteristics and time to diagnosis or worsening of IBS. Log minus log plots for each variable were inspected to verify the assumption of proportionality of the hazards, which was confirmed for all variables studied. The predictor variables were initially introduced in a "univariate" model adjusted for age at recruitment and year of recruitment. P-values < 0.05 were considered to be significant. All variables (except gender that was found not significantly associated with time to diagnosis or worsening of IBS) were included in a multivariable adjusted analysis. In the multivariable analysis, number of siblings < 5 was compared with ≥ 5. IBM SPSS Statistics for Windows (version 19.0.; IBM Corp. software, Armonk, NY) was used for statistical analyses.

RESULTS

The study cohort consisted of 440,822 young adults who served in the Israel Defense Force (58.8% men and 41.2% women), with a mean age at recruitment of 18.9 ± 1.0 years. The mean age at recruitment for participants with IBS was 18.7 ± 0.7, and for those without IBS was 18.3 ± 1.0 year. The mean follow-up period was 1.3 ± 1.1 and 4.4 ± 2 years, for IBS and non-IBS, respectively. The demographic and the anthropometric characteristics of the study cohort are summarized in Table 1.

During follow-up of 1,925,003 person-years, IBS was diagnosed de novo in 976 patients. This defined an incidence rate for IBS development of 221:100,000 (0.2%) person-years. The severity of IBS was classified as mild in 187 patients, moderate in 413 patients, and severe in 376 patients. "Univariate" Cox proportional hazard ratios for the diagnosis or worsening of IBS (adjusted for age at recruitment and

TABLE 1. Demographic, Anthropometric, and Occupational Characteristics of the Study Cohort

Parameters	
Age at recruitment (mean) (y)	18.9 ± 0.99
Gender [n (%)]	
Male/female	259,142/181,680 (58.8/41.2)
Origin* [n (%)]	
Israel	43,960 (10)
Former Soviet Union	80,625 (18.3)
Middle East	91,632 (20.8)
Africa	113,210 (25.7)
West	106,680 (24.2)
Immigration [n (%)]	
No	352,480 (80)
Yes	88,255 (20)
Ethnicity [n (%)]	
Jews	411,235 (93.3)
Non-Jews	29,585 (6.7)
Education (y) [n (%)]	
< 11	14,717 (3.3)
≥ 11	425,933 (96.6)
Settlement [n (%)]	
Rural	50,400 (11.4)
Urban	382,534 (89)
Socioeconomic status [n (%)]	
Low	113,117 (25.7)
Medium	233,115 (52.9)
High	92,107 (20.9)
No. siblings [n (%)]	
≤2	125,835 (28.5)
3 to 4	247,015 (56)
≥ 5	66,618 (15.1)
Weight status [n (%)]	
Underweight	29,140 (6.6)
Healthy weight	337,311 (76.5)
Overweight	46,195 (10.5)
Obese	27,072 (6.1)

*Origin—father's place of birth or grandfather's place of birth if the father was Israeli-born.

year of recruitment) are summarized in Table 2. We found that Israeli-born, Jewish ethnicity, higher socioeconomic status, and fewer siblings in the household were risk factors associated with a new diagnosis or worsening of IBS. Table 3 summarizes the results of the multivariable Cox regression analysis. Risk factors for the diagnosis of IBS included: higher socioeconomic status [hazard ratio (HR) 1.450; 95% confidence interval (CI), 1.211-1.735; $P < 0.001$ for medium state and HR 1.629; 95% CI, 1.328-1.999; $P < 0.001$ for high state, compared with low state], Israeli-born (HR 1.362; 95% CI, 1.084-1.712; $P = 0.008$), Jewish ethnicity (HR 2.089; 95% CI, 1.344-3.248; $P = 0.001$), and education ≥ 11 years (HR 1.674; 95% CI, 1.019-2.751; $P = 0.042$). Protective factors for the diagnosis or of worsening of IBS included: overweight (HR 0.744; 95% CI, 0.589-0.941; $P = 0.014$), obesity (HR 0.698; 95% CI, 0.510-0.956; $P = 0.025$, compared with healthy weight), living in a rural settlement (HR 0.705; 95% CI, 0.561-0.886; $P = 0.003$), and Middle Eastern (HR 0.739; 95% CI, 0.617-0.884; $P = 0.001$), or African origin (HR 0.702; 95% CI, 0.585-0.842; $P < 0.001$) compared with a western origin.

DISCUSSION

In this study, we examined the cumulative incidence of IBS development in a cohort of young adults during their obligatory military service, as well as the predictive socioeconomic, anthropometric, and combatant role for IBS development or deterioration.

The incidence rate of IBS was 221:100,000 people (0.2%) in our study cohort. Our results present a similar incidence rate to that reported previously in studies from Europe and USA (196 to 300 per 100,000),[16,17] although much lower than the 9% onset rate of IBS previously reported in a single study, based on 2 surveys sent to a random sample of the population about 1 year apart in the United States.[24] As the diagnosis of IBS in our study was based on gastroenterological expert opinions, we assume that the actual incidence of IBS was even higher than that established in our study population. Nevertheless, considering the stressful environment of military service, we find that the overall incidence of IBS in our study population was surprisingly low. A few possible explanations for our findings can be taken into account: lower incidence of IBS among Israeli than among other populations in the western world, underreporting of IBS symptoms in our study cohort, and a higher incidence of diagnosis of organic disease owing to the requirement for endoscopic and radiologic gastrointestinal evaluation before the diagnosis of moderate to severe IBS. If chronic stress is a trigger or a mediator of IBS symptoms, one might expect high rates in Israel as a result of the chronic stress that affects all Israelis because of geopolitical instability. The high availability and use of medical services makes the possibility of significant IBS symptom underreporting less likely. However, the possibility that mild cases of IBS with no disabling symptoms do not reach medical consultation cannot be excluded. Furthermore, the fact that 80% of cases with a new diagnosis of IBS in this study population were moderate to severe as compared with only 51% reported by Drossman et al[20] supports the possibility of underreporting of mild symptoms consistent with IBS. Whether the prerequisite of endoscopic and gastrointestinal imaging studies before the diagnosis of moderate to severe IBS in the study population actually decreased the incidence of IBS diagnosis owing to identification of organic causes for the symptoms (celiac or inflammatory bowel disease) is unknown. However, in a previous study on 575 patients diagnosed with IBS using symptom-based criteria, organic disease was identified only in 3%.[25]

Fortunately, we had access to extensive information regarding the socioeconomic, anthropometric, and occupational characteristics of our study population, enabling us to look for predictive factors for the development or deterioration of IBS.

Middle Eastern (mainly Turkish, Iraqi, Iranian, and Yemenite) and North African origins of individuals were found to be preventive factors for IBS development or deterioration. In previous epidemiologic studies from various Asian countries (mainly Turkey and China), the prevalence of IBS was found frequently to be lower than that in western countries.[26,27] Taking into account that the origin of our cohort was based on parenteral (father's or grandfather's) place of birth, it seems that the country of origin has a long-lasting effect on IBS incidence. As most of the study cohort was Jewish, we hypothesize that the impact of origin may be explained by cultural variances. Jewish ethnicity was also found to be a predictive factor for IBS diagnosis. The fact that most of the non-Jewish population in our study cohort were of Druze and Circassian origin (originating in Caucasus) seems to strengthen the idea that cultural differences, even within a small

TABLE 2. Univariate Cox Proportional Hazard Ratios (HRs) for the Diagnosis or for the Worsening of IBS in 440,822 Young Adults

Parameters	IBS	No IBS	Hazard Ratio	95% CI	*P*
Follow-up (y)	1.28	4.37	0.94	0.91-0.97	< 0.0001
Age at recruitment (y)	18.79	18.91	0.86	0.79-0.94	0.001
Gender					
Male	574	253,400	0.95	0.84-1.081	0.4
Female	402	181,278			
Origin*					
Israel	93	43,867	0.75	0.57-0.95	< 0.0001
Former Soviet Union	154	80,471	0.67	0.55-0.81	0.016
Middle East	204	91,428	0.77	0.64-0.92	< 0.0001
Africa	211	112,999	0.65	0.55-0.78	0.003
West	308	106,064	1		
Immigration					
No	834	351,646	1.45	1.2-1.73	< 0.0001
Yes	142	88,113	1		
Ethnicity					
Jews	954	410,281	2.77	1.81-4.23	0.005
Non-Jews	22	29,563	1		
Education (y)					
< 11	16	14,701	0.49	0.30-0.81	0.005
≥ 11	960	424,973	1		
Settlement					
Rural	86	50,314	0.76	0.61-0.95	0.016
Urban	889	381,645	1		
Socioeconomic status					
Low	163	112,954	1		
Medium	5415	227,700	1.57	1.32-1.87	< 0.0001
High	271	91,836	1.98	1.63-2.40	< 0.0001
No. siblings					
≤2	2925	122,910	1.36	1.09-1.70	0.007
3 to 4	575	246,530	1.35	1.10-1.66	0.005
≥ 5	108	66,402	1		
Weight status					
Underweight	80	29,060	1.28	0.96-1.52	0.107
Healthy weight	777	335,757	0.75	0.59-0.94	0.013
Overweight	78	46,117	0.68	0.50-0.93	0.016
Obese	41	27,031	1		

Model adjusted for age at recruitment and recruitment year.
In parameters that do not add to 976, data are lacking for some the included subjects.
*Origin—father's place of birth or grandfather's place of birth if the father was Israeli-born.
CI indicates confidence interval; IBS, irritable bowel syndrome.

country such as Israel, might have a major impact on the occurrence of IBS.

The prevalence of IBS was found to be moderately increased in women in most geographical locations,[28] including the Middle East.[29–34] However, we found that gender had no influence on IBS incidence in our study population. Higher socioeconomic status was a predictive factor for IBS diagnosis and deterioration in our study cohort. Furthermore, a higher level of education, lower number of siblings, and Israeli birth (vs. immigration) were also found to increase the incidence of IBS. The fact that all 4 factors were found to be correlated with the diagnosis of IBS supports the overall impression that IBS is associated with higher socioeconomic status. Unfortunately, previous data regarding the relation of economic status with IBS is limited,[35–37] and in general has not demonstrated any similar correlation.

Interestingly, the fact that higher socioeconomic status, higher educational levels, and noncombat military roles were predictive factors for IBS diagnosis may point to the fact that stress had a lower impact on IBS incidence in our study cohort.

Overweight was a preventive factor for an IBS diagnosis or worsening in our cohort. Moreover, in the overweight cohort, higher BMI scores reduced the incidence of IBS. In a recently published meta-analysis, no significant associations were found for general abdominal pain, lower abdominal pain, bloating, constipation/hard stools, fecal incontinence, nausea, and anal blockage with obesity.[38] Furthermore, IBS was not found to be associated with increased BMI in another study.[39]

The strength of this study includes its large size and the multiplicity of data. The period of observation was also reasonably long. The diagnosis of IBS was based on an expert gastroenterological opinion, and organic diseases mimicking IBS were excluded either by endoscopy or abdominal imaging at diagnosis or during follow-up. This study provides novel data on the socioeconomic, anthropometric, and occupational factors predictive for IBS.

Our study has several limitations. First, the results might not be applicable to practice settings that are different from ours. However, we believe that our data can be extrapolated to the general community. The incidence of IBS was not different from that reported in the general population in the west, and factors that can be associated with stress and may be exaggerated owing to military service did not seem to have crucial effect on IBS diagnosis

TABLE 3. Multivariable Cox Regression Analysis for Independent Predictors of IBS Diagnosis or Worsening

Parameters	Hazard Ratio	95% CI	*P*
Follow-up (y)	0.95	0.92-0.10	0.001
Age at recruitment (y)	0.93	0.85-1.01	0.097
Origin			
West	1		
Israel	0.85	0.67-1.08	0.171
Former Soviet Union	0.87	0.69-1.10	0.254
Middle East	0.74	0.62-0.88	0.001
Africa	0.70	059-0.84	< 0.0001
Immigration			
Yes	1		
No	1.36	1.08-1.71	0.008
Ethnicity			
Non-Jews	1		
Jewish	2.09	1.34-3.25	0.001
Education (y)			
< 11	1		
≥ 11	1.67	1.02-2.75	0.042
Settlement			
Urban	1		
Rural	0.71	0.56-0.89	0.003
Socioeconomic status			
Low	1		
Medium	1.45	1.21-1.74	< 0.0001
High	1.63	1.39-2.00	< 0.0001
No. siblings			
≥ 5	1		
< 5	1.20	0.91-1.39	0.274
Weight status			
Healthy weight	1		
Underweight	1.22	0.97-1.54	0.09
Overweight	0.74	0.59-0.94	0.014
Obese	0.70	0.51-0.96	0.025

CI indicates confidence interval; IBS, irritable bowel syndrome.

or deterioration in our cohort. Another limitation is the inability to assess the number of potentially missed cases of IBS. Owing to the retrospective nature of this study, we cannot estimate how many people who might have had IBS symptoms were not examined by an expert or were not diagnosed by their gastroenterology consultant.

In conclusion, this study reports the incidence and predictive factors for IBS diagnosis and its deterioration in a large cohort of young people. The incidence rate was 221:100,000 (0.2%). The factors found to be predictive for IBS development were a higher socioeconomic status, a higher level of education, lower number of children in the family, Israeli birth, living in urban areas, Jewish ethnicity, and western origin. Protective factors for a new IBS diagnosis or worsening of a previous existing IBS included overweight, obesity, and African (mainly North African and Ethiopian) or Middle Eastern origin.

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