Original Article

Emerging Epidemic of Inflammatory Bowel Disease in a Middle Income Country: A Nation-wide Study from Iran

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Abstract

Background: The burden of inflammatory bowel disease (IBD) hasn't been reported in Iran. We aimed to estimate the prevalence and incidence of IBD and its trend in Iran at national and subnational level from 1990 to 2012.

Methods: We conducted a systematic review of English and Persian databases about the epidemiology of IBD. We also collected outpatient data from 17 provinces of Iran using almost all public and private referral gastroenterology clinics. Prevalence and incidence rate was calculated at national and subnational levels. The Kriging method was used to extrapolate provinces with missing data and GPR model to calculate time trends of rates at subnational level.

Results: We found 16 case series, two population-based studies, and two review articles. We collected 11,000 IBD cases from outpatient databases. Among them, 9,269 (84.26%) had ulcerative colitis (UC), 1,646 (14.96%) had Crohn's disease (CD), and 85 had intermediate colitis (IC). A total of 5,452 (49.56%) patients were male. Mean age at diagnosis was 32.80 years (CI: 13 – 61) for UC and 29.98 years (CI: 11 – 58) for CD. Annual incidences of IBD, UC, and CD in 2012 were 3.11, 2.70, and 0.41 per 100,000 subjects respectively. Prevalence of IBD, UC, and CD in 2012 were 40.67, 35.52, and 5.03 per 100,000 subjects respectively. The incidence of UC and CD showed a significant increase during t he study period (*P* for trend < 0.05).

Conclusions: The incidence and prevalence of IBD are increasing in Iran. Establishing a national IBD registry seems necessary for comprehensive care of IBD patients in Iran.

Keywords: Crohn's disease Burden, inflammatory bowel disease, Iran, prevalence, ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD) is among costly gastrointestinal (GI) diseases, according to the reports on the burden of GI diseases in the United States (USA).[1] Although its mortality is low, its onset during early adulthood and its chronicity as a lifelong disease lead to a significant decline in quality of life for the patients and heavy burden on the health care system with huge cost. For example, the second most commonly prescribed drug by GI specialists in USA was Mesalazin after proton pump inhibitors and H2-blockers.[2] According to the Global burden of diseases (GBD) study, 10,576,000 people across the world were affected

by IBD that led to 3,729,100 disability-adjusted life years worldwide in 2013.[3,4] Furthermore, GBD study reported that 51,200 deaths were attributed to IBD in 2013.[5] A nationwide study in USA showed that the mean annual cost for each patient with Crohn's disease (CD) and ulcerative colitis (UC) were 8,265 $ and 5,066 $ respectively.[6] It was also estimated that work disability due to IBD in Europe cost about 4.6 – 5.6 billion Euros yearly.[7]

IBD was known to be more prevalent and incident in North America and North-West of Europe compared with Asia and Africa.[8] Incidence of IBD in Faroe Island is reported to be the highest (83.1 per 100,000) in the world.[9] Also the highest reported prevalence in the world was based on a national study in USA (908 per 100,000).[10] While in a comprehensive systematic review it was reported that the incidence and prevalence of IBD are increasing almost in all parts of the world,[11] some recent studies reported decreasing or stabilizing incidence of IBD in western countries,[12–14] in contrast to a considerable increase in IBD prevalence in Asia and Eastern Europe.[7,15–17]

IBD in Iran as a Middle-Eastern middle-income country with rapid socioeconomic changes seems to have similar trends. Previous epidemiologic studies of IBD in Iran did not report its incidence and prevalence nationally. Moreover, only two population-based studies reported their cases at provincial level.[18,19] Naghavi et al. estimated that the burden of GI diseases ranked 7th among all other diseases at national level in 2003,[20] but the burden of each GI disease has not been calculated yet. Therefore, calculating the national incidence and prevalence of IBD and its burden seems to be an essential step in facing the IBD epidemic in the country. In this study, we aimed to evaluate the prevalence and incidence of IBD and its trend in Iran at national and subnational level from 1990 up to 2012 as part of recent ongoing studies on the burden of GI disease in Iran,[21] which can help health policy makers for better health planning and providing an opportunity for further research on understanding the environmental risk factors of this disease in Iran.

Materials and Methods

Study population

Iran is one of the largest and most populated countries in Middle East (1.65 million sq. km area) with a substantially increased population during the 2nd half of the 20th century approaching 78.5 million in 2014. It is a country with diverse ethnicities, more than 10 ethnic backgrounds, cemented by the Persian language and culture, with Islam as the official religion. It has one of the highest urban growth rates in the world (from 27 to 71%). More than two thirds of the population is under the age of 30, with a life expectancy of 73 years for men and 76 years for women. The literacy rate is 86%. It has 31 provinces with the heterogeneous population distribution. There are 353 Gastroenterologists in clinical practice in the country. More than 60% of these gastroenterologists are living in Tehran and ten big provincial capital cities. The majority of IBD patients are treated in tertiary care centers in provincial capitals and many of them are referred to Tehran as the capital with higher skilled GI specialists and better medical services.

Case definition and diagnosis

Diagnosis of IBD was based on a combination of clinical, radiological, colonoscopic, and pathologic findings and was coded as K50 for UC, K51 for CD, and K52 for intermediate colitis (IC) according to international coding of diseases version 10. We categorized age in groups of 5-year intervals. For estimating incidence, we considered age at diagnosis equal to age at disease onset.

Data sources

Systematic review

We conducted a systematic review of English (PubMed, Web of Science, and Scopus) and Persian (IronDoc, Barakat knowledge network system, and SID) databases on incidence, prevalence, and epidemiology of IBD in Iran. Literature search was conducted up to 9/15/2015. The search terms were chosen according to the MeSH terms of the national library of medicine in the USA (supplementary Table 1). By evaluating the titles, abstracts, and full texts, we included all articles except those not related to IBD, not conducted in Iran, case reports or animal studies, done on age below 15, or conducted before 1990. Full texts were then collected and only those cases-series, reviews, or population-base studies, which reported the number of IBD patients with their demographic features, were included (Figure 1).

Outpatient data

For collecting outpatient data, a questionnaire including name, father's name, age, sex, place of living (at the provincial level), year of IBD diagnosis, and subtypes of IBD (UC, CD, IC) was used. We also managed to call most gastroenterologists in active clinical practice and invited them to participate and send us the data. All colleagues who shared their patients' data with us had used accurate and up to date criteria for diagnosis of IBD and most of their patients were under clinical care and follow up for more than 2 years. We finally received 12,635 patients' data from 17 provinces. Patients who were younger than 15 years old were excluded from our study as the study was designed for adults. Also, those patients who were diagnosed before 1990 were excluded. As we didn't have a unique identification code for each patient, duplicates were found and excluded by checking similarity in name, family name, father's name, and age. After excluding duplicates, only 11,000 cases remained in our database. To prevent false effect on our modeling, data of patients who referred to other provinces but lived in provinces with no local data were also omitted (Figures 2 and 3).

Statistical Analyses

We calculated the crude prevalence and incidence rate per 100,000 for outpatient data. The denominator was the national population at risk (adults older than 15 years old). The average annual incidence of IBD, UC, and CD were also calculated. We obtained national population data by sex, age group, and province up to 2012 from the Statistical Center of Iran and used it as the denominator for calculating incidence and prevalence.

The available dataset for analyses consisted of 543 crude incidence rates for two IBD types including UC and CD. We used attributed rates for all ages and both sex combinations from 1990 to 2012. The frequencies of incidence rates based on the number of provinces in each year are displayed in supplementary Table 2. For example, we had 13 provinces with incidence rates data for CD and 9 provinces for UC in 2000. Also, we had 44 prevalence rates at national level for two IBD types from 1990 to 2011.

Since prevalence rates were available at national level, we had to use a statistical method for adjusting prevalence rates at subnational level. Therefore, we applied a regression model for prevalence rates on existing national incidence rates in each year that

Supplementary Table 1. Search terms

Mesh Terms	Inflammatory Bowel Diseases
Entry Terms	Inflammatory bowel disease; Bowel Diseases, Inflammatory; Ulcerative Colitis; Crohn's Disease; Ileocolitis; Ileitis, Terminal; Ileitis, Regional; Colitis, Granulomatous; Enteritis, Granulomatous Enteritis, Regional
PubMed Search terms	"inflammatory bowel diseases"[MeSH Terms] AND (("iran"[MeSH Terms] OR "iran"[All Fields]) OR Iranian[All Fields] OR Iranians[All Fields] OR I.R.Iran[All Fields])
ISI, Scopus Search Terms	("iran" OR "Iranian" OR "Iranians" OR "I.R.Iran") AND (Inflammatory Bowel Disease OR Bowel Diseases, Inflammatory OR Ulcerative Colitis OR Crohn's Disease OR Ileocolitis OR Ileitis, Terminal OR Ileitis, Regional OR Colitis, Granulomatous OR Enteritis, Granulomatous OR Enteritis, Regional.

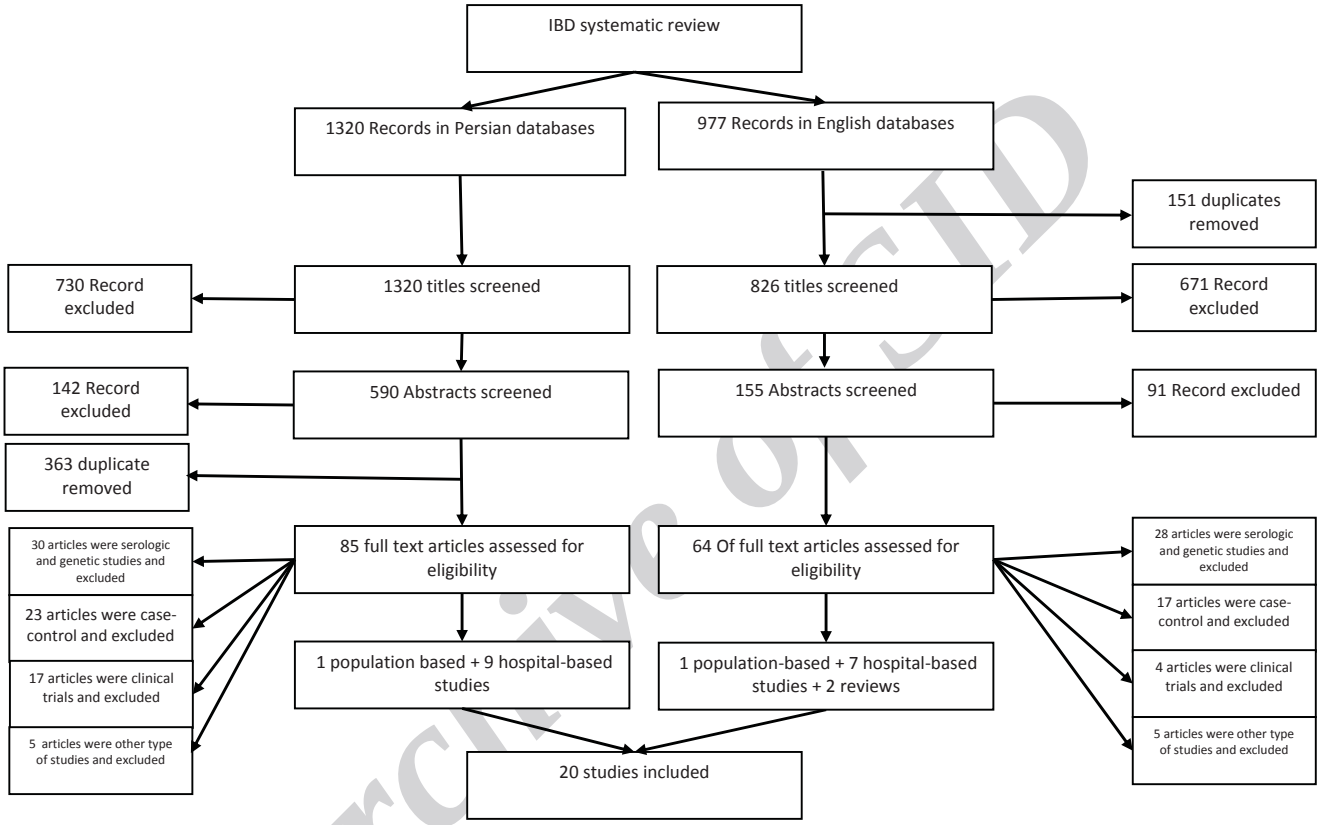

Figure 1. Systematic review of English and Persian databases.

Supplementary Table 2: The number of provinces with data on incidence rate in each year

Year	IBD subtype		Year	IBD subtype	
	UC	CD		UC	CD
1990	12	3	**2002**	14	8
1991	11	4	**2003**	12	8
1992	11	3	**2004**	15	8
1993	11	5	**2005**	15	6
1994	10	4	**2006**	15	12
1995	10	5	**2007**	14	9
1996	13	8	**2008**	15	12
1997	11	6	**2009**	16	16
1998	12	7	**2010**	16	13
1999	11	12	**2011**	16	13
2000	13	9	**2012**	16	14
2001	12	11			

IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease

demonstrated a good correlation between incidence and prevalence rates ($R^2 = 0.76$). Using the estimated coefficients of previous regression, prevalence rates at subnational level could be computed.

Our assumption was that IBD rates had spatial and temporal correlations between neighboring provinces and during the study period. As mentioned before, we had incomplete rates for some of the provinces and years. Thus, we needed prediction methods to compute these rates in the required time span and at subnational level. As demonstrated in supplementary Table 2, the available number of provinces for which we had data in each year is very few. If we wanted to use usual spatio-temporal models, we would face many limitations in defining neighborhood and model components. Therefore, we decided to use simpler models rather than modifying spatio-temporal model components for this study We also considered space and time modeling separately.

The spatial correlation was estimated by Kriging model to compute rates at provincial level. The result of Kriging is the expected value of the rates based on spatial interpolation methods for rates at subnational level for all 31 provinces and the variance is computed for every province in the country accordingly.[22,23]

The temporal correlation in IBD rates was considered using a Gaussian regression process method (GPR), a Bayesian method that is flexible with data and produces unique predictions with uncertainty intervals over time.[24] GPR needs mean function and covariance function that specifies all properties of the data. We used a generalized linear model as a mean function that captured the relationship between IBD rates and covariates including years of schooling, wealth index, urbanization rate, and gastrointestinal (GI) doctorate number. The first three covariates were derived from a household expenditure (HHS) survey for our desired time span at subnational level. The number of GI specialists was the cumulative number of graduated GI doctorates in each year. The covariance function was considered as a temporal correlation in IBD rates. The covariance function and standard errors of Kriging model for each data point were used to estimate the uncertainty interval over time.[25]

We repeated these methods for estimating the incidence and prevalence rates for each IBD subtype. Finally we made IBD rate estimates at subnational and national levels for 23 years (1990 – 2012). To produce total IBD rates, we conducted a simulation on UC and CD rates for each time province combination. This simulation was done based on a normal distribution with mean and standard error of IBD rates in each combination. Using simulations, we drew 2.5 and 97.5 percentile of total IBD rates and produced uncertainty interval over time.

Ethical Considerations

The final set of patients' data was de-identified for data analysis and report. The study was approved by the ethical committee of Digestive Diseases Research Institute in Tehran University of Medical Science.

Results

Systematic review

By searching English and Persian databases, we found 2,297 records of which, 514 were duplicates. A total of 1,401 irrelevant titles were excluded and 233 abstracts did not meet the inclusion criteria. A total of 149 full texts were chosen and after considering inclusion and exclusion criteria, we collected 16 case series, 2 population-based studies, and 2 review articles (Figure 1 and Table 1). We also checked the references of two review articles[26,27] to find missed papers. We attained most of the original data out of Iranian studies. Primary data of four studies were not available. The first one was a hospital-based study in Arak, which reported 188 IBD cases. Another one was a hospital-based study in Kermanshah reporting 85 IBD patients. The third one was a multicenter study in Ahwaz on 166 IBD cases and the last one was a hospital-based study in Hormozgan province. We extracted data from these papers considering year of the study, age groups, and sex, but we could not merge it with our outpatient data because we could not detect the duplicated cases. Two Iranian studies were population-based. The first one was conducted by Zahedi et al. It estimated the incidence of UC and CD in Kerman province to be 4.98 and 0.8 per 100,000, respectively and another one was an IBD registry in Shiraz, which only reported the number of IBD patients.[18,19] Also, two hospital-based studies reported incidence and prevalence rate for their provinces. The first report by Fani, et al. in center of Iran reported incidence and prevalence of 3.04 and 15.5 per 100,000 for UC in Markazi province.[28] The second by Masoodi, et al. reported incidence of 3.25 per 100,000 for UC in Hormozgan province in southern Iran.[29]

Outpatient data

There were 11,000 IBD patients. A total of 9,269 (84.26%) had UC, 1,646 (14.96%) had CD, and 85 had IC. A total of 5,452 patients (49.56%) were male. The female/male ratios were 1.01 and 1.06 for UC and CD, respectively. Mean age at diagnosis was 32.80 year (CI: 13 – 61) for UC and 29.98 year (CI: 11 – 58) for CD. There were no significant differences in incidence and prevalence between women and men. Peak age at diagnosis was in 20-30 year age group for CD and in 30-40 year age group for UC.

Incidence

The incidence of IBD increased from 0.62 to 3.11 per 100,000 from 1990 to 2012. CD and UC incidence increased from 0.19 to 0.41 and from 0.42 to 2.70 per 100,000 in the study period, respectively (Table 2 and Figure 4). UC and CD incidence had a significant increase (incidence rate ratios were 6.43 for UC and 2.16 for CD: 6.0, $P < 0.00$). There was no significant difference in incidence between men and women for UC and CD (P-value > 0.05). The incidence of IBD was most common in Guilan, Mazandaran, Qazvin, and Tehran with 6.19, 4.24, 4.24 and 3.88 per 100,000 respectively in 2012 (Table 2). Mean annual incidence was calculated for each province and demonstrated in Figure 5.

Prevalence

According to our estimation, the prevalence of IBD increased from 4.69 to 40.67 per 100,000 in 1990 to 2012. CD and UC prevalence increased from 1.06 to 5.03 and from 3.62 to 35.52 per 100,000 during the study period, respectively (Table 3 and Figure 6). There were no significant difference in prevalence between men and women for UC and CD. There were significant increases in UC and CD prevalence (prevalence rate ratio for UC: 9.81 and for CD: 4.74, $P < 0.001$). IBD was the most prevalent in Qazvin, Zanjan, Qom, Semnan, and Guilan with 72.56, 72.30, 67.32, 65.40, and 64.10 per 100,000, respectively in 2012 (Table 3 and Figure 7). UC/CD prevalence ratio was 3.41 in 1990, which increased significantly to 7.06 in 2012 ($P < 0.001$).

Table 1. Summary of papers about IBD epidemiology in Iran, results of systematic review in English and Persian databases.

Author	Publication date	Place	Method	Study period	Number of cases				Female /Male		Mean age at diagnosis		Access to data
					UC	CD	IC	IBD	UC	CD	UC	CD	
Fani A[28]	2000	Arak	Multi center	1999–2000	97	11		108	0.9	2.67			No
Malekzadeh R[33]	2000	Tehran	Multi center	1999		140		140		1.15		30	Yes
Daryani N[72]	2001	Tehran	Hospital-based	1995–2000	200			200	1.22				Yes
Aghazadeh R[73]	2005	Tehran	Multi center	1992–2002	401	47	9	457	1.25	0.77	31.9	30.5	Yes
Fakheri H[74]	2007	Sari	Office-based	2000–2007	265	35		300	1.15	1.19	34.5	28.4	Yes
Keshavarz AA[75]	2007	Kermanshah	Hospital-based	2002–2005	85			85	1.25		34.09		No
Masjedizadeh A[76]	2007	Ahwaz	Multi center	1999–2003	166	8	2	176	1.07	1.6			No
Darakhshan F[77]	2008	Tehran	Multicenter	2007	671	109	23	803	1.28	0.85	33.01	33.18	Yes
Vahedi H[78]	2009	Tehran	Hospital-based	2004–2007	293	207		500	1.43	1.11	37.1	33.8	Yes
Zahedi MJ[79]	2009	Kerman	Multicenter	2003–2007	85			85	1.24		33.31		Yes
Ghadir MR[80]	2010	Qom	Hospital-based	2007-2008				55	1.29	1.29			Yes
Yazdanbod A[81]	2010	Ardabil	Office-based	1998–2008	105			105	1.39		33.5		Yes
Abedian Sh[21]	2011	Tehran	Hospital-based	2000–2004	73	35		108					Yes
				2005–2009	90	62		152					
Taghavi S A[18]	2012	Shiraz	Population-based	2011	164	23		187					Yes
Masoodi M[29]	2012	Bandar Abbas	Multi center	2004–2005	37			37	1.25	1.25			No
				2005–2006	42			42	1.25	1.25			
Shirazi KM[82]	2013	Tabriz	Hospital-based	2005–2007	183	17		200	0.93	0.54			Yes
Taghavi SA[83]	2013	Shiraz	Hospital-based	1989–2009	620	120		740	1.09	1.03	34.68	32.97	Yes
Zahedi MJ [19]	2013	Kerman	Population-based	2011–2012	36	6		42	1.12	2	39.4	33.3	Yes

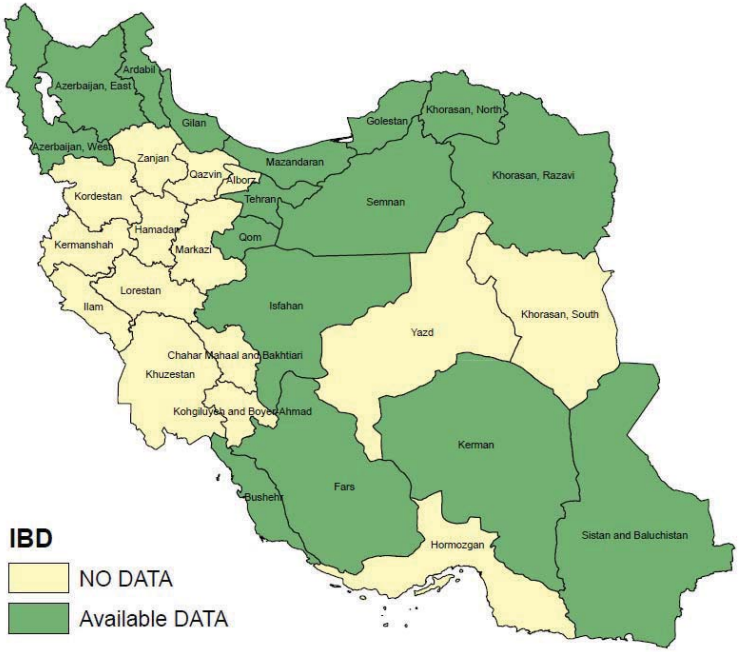

Figure 2. Pattern of data collection in out-patient data

Table 2. Estimated incidence based on statistical modeling for IBD rates at provincial level during the study period

Province	1990 (UI)	1995 (UI)	2000 (UI)	2005 (UI)	2010 (UI)	2012 (UI)
Markazi	0.69 (0.30–1.11)	0.79 (0.49–1.08)	1.01 (0.76–1.25)	1.44 (1.20–1.67)	2.40 (2.00–2.81)	3.08 (2.43–3.75)
Guilan	0.53 (0.24–0.84)	0.70 (0.47–0.93)	1.11 (0.91–1.29)	2.08 (1.86–2.30)	4.41 (3.96–4.85)	6.19 (5.29–7.06)
Mazandaran	0.62 (0.33–0.91)	0.76 (0.55–0.98)	1.06 (0.88–1.24)	1.69 (1.51–1.86)	3.12 (2.80–3.45)	4.24 (3.61–4.83)
Azerbaijan, East	0.57 (0.32–0.83)	0.66 (0.49–0.84)	0.87 (0.74–1.02)	1.27 (1.12–1.41)	2.06 (1.80–2.30)	2.62 (2.17–3.05)
Azarbeijan, West	0.63 (0.30–0.97)	0.72 (0.49–0.94)	0.90 (0.73–1.06)	1.25 (1.11–1.39)	1.97 (1.70–2.25)	2.48 (2.03–2.91)
Kermanshah	0.64 (0.29–1.00)	0.74 (0.50–1.00)	0.96 (0.76–1.16)	1.43 (1.24–1.62)	2.52 (2.18–2.88)	3.36 (2.72–4.01)
Khuzestan	0.66 (0.40–0.91)	0.77 (0.59–0.95)	0.98 (0.84–1.13)	1.39 (1.25–1.52)	2.25 (2.00–2.51)	2.86 (2.44–3.27)
Fars	0.68 (0.41–0.92)	0.77 (0.59–0.95)	0.96 (0.82–1.10)	1.25 (1.12–1.38)	1.85 (1.63–2.07)	2.28 (1.94–2.64)
Kerman	0.53 (0.23–0.82)	0.61 (0.41–0.82)	0.78 (0.62–0.95)	1.12 (0.97–1.28)	1.84 (1.57–2.10)	2.34 (1.89–2.78)
Khorasan, Razavi	0.45 (0.27–0.64)	0.56 (0.42–0.68)	0.75 (0.64–0.87)	1.13 (1.02–1.25)	1.88 (1.68–2.07)	2.38 (2.03–2.74)
Isfahan	0.53 (0.33–0.74)	0.63 (0.47–0.77)	0.82 (0.71–0.93)	1.19 (1.07–1.31)	1.95 (1.73–2.17)	2.50 (2.12–2.88)
Sistan	0.54 (0.18–0.90)	0.61 (0.36–0.86)	0.76 (0.57–0.94)	1.05 (0.89–1.21)	1.60 (1.31–1.86)	1.97 (1.54–2.39)
Kordestan	0.67 (0.22–1.11)	0.78 (0.49–1.09)	1.01 (0.80–1.23)	1.45 (1.23–1.67)	2.42 (1.99–2.83)	3.13 (2.47–3.79)
Hamedan	0.68 (0.30–1.02)	0.81 (0.54–1.08)	1.04 (0.83–1.24)	1.51 (1.30–1.72)	2.49 (2.11–2.88)	3.21 (2.60–3.80)
Chahar Mahaal	0.65 (0.10–1.18)	0.75 (0.38–1.10)	0.93 (0.65–1.22)	1.27 (0.99–1.53)	1.98 (1.49–2.45)	2.45 (1.75–3.15)
Lorestan	0.64 (0.25–1.03)	0.75 (0.50–1.02)	0.98 (0.76–1.16)	1.44 (1.24–1.65)	2.47 (2.07–2.83)	3.23 (2.55–3.86)
Ilam	0.70 (0.07–1.33)	0.79 (0.32–1.24)	1.00 (0.62–1.36)	1.40 (1.04–1.78)	2.37 (1.73–3.03)	3.14 (2.12–4.17)
Kohgiluyeh	0.73 (0.11–1.37)	0.82 (0.37–1.27)	0.99 (0.62–1.37)	1.36 (1.03–1.69)	2.13 (1.55–2.67)	2.70 (1.82–3.56)
Bushehr	0.77 (0.25–1.34)	0.85 (0.46–1.24)	1.02 (0.74–1.31)	1.36 (1.07–1.63)	2.09 (1.63–2.54)	2.60 (1.91–3.26)
Zanjan	0.69 (0.21–1.19)	0.82 (0.45–1.18)	1.10 (0.80–1.38)	1.65 (1.38–1.92)	2.89 (2.33–3.43)	3.80 (2.92–4.68)
Semnan	0.69 (0.09–1.30)	0.76 (0.30–1.20)	0.97 (0.64–1.32)	1.39 (1.05–1.71)	2.30 (1.73–2.87)	2.99 (2.04–3.89)
Yazd	0.63 (0.15–1.09)	0.69 (0.36–1.06)	0.87 (0.61–1.12)	1.21 (0.98–1.48)	1.97 (1.50–2.38)	2.56 (1.88–3.29)
Hormozgan	0.63 (0.19–1.05)	0.68 (0.38–0.98)	0.81 (0.58–1.04)	1.11 (0.89–1.32)	1.75 (1.39–2.10)	2.20 (1.66–2.75)
Tehran	0.65 (0.46–0.83)	0.79 (0.68–0.92)	1.05 (0.95–1.14)	1.53 (1.44–1.63)	2.81 (2.65–2.97)	3.88 (3.53–4.23)
Ardabil	0.65 (0.23–1.07)	0.77 (0.46–1.10)	0.97 (0.72–1.22)	1.36 (1.13–1.58)	2.22 (1.80–2.66)	2.84 (2.21–3.50)
Qom	0.68 (0.18–1.21)	0.79 (0.44–1.13)	1.03 (0.74–1.30)	1.53 (1.24–1.81)	2.81 (2.31–3.37)	3.82 (2.93–4.69)
Qazvin	0.70 (0.21–1.19)	0.86 (0.52–1.20)	1.17 (0.89–1.45)	1.82 (1.53–2.10)	3.23 (2.71–3.72)	4.24 (3.39–5.13)
Golestan	0.61 (0.24–0.99)	0.71 (0.43–0.98)	0.93 (0.71–1.15)	1.31 (1.10–1.51)	2.03 (1.68–2.39)	2.49 (1.95–3.04)
Khorasan, North	0.67 (0.11–1.22)	0.75 (0.37–1.15)	0.93 (0.63–1.24)	1.24 (0.98–1.51)	1.86 (1.36–2.33)	2.28 (1.57–2.96)
Khorasan, South	0.57 (–0.13–1.21)	0.63 (0.21–1.08)	0.80 (0.45–1.16)	1.11 (0.81–1.41)	1.79 (1.27–2.33)	2.29 (1.50–3.10)
Alborz	0.75 (0.34–1.21)	0.90 (0.60–1.21)	1.16 (0.94–1.39)	1.68 (1.47–1.89)	2.82 (2.44–3.19)	3.64 (3.01–4.27)
National	0.62 (0.31–0.91)	0.73 (0.52–0.95)	0.95 (0.78–1.12)	1.39 (1.23–1.56)	2.37 (2.07–2.67)	3.11 (2.55–3.61)

UI: Uncertainty Interval, Rate per 100,000

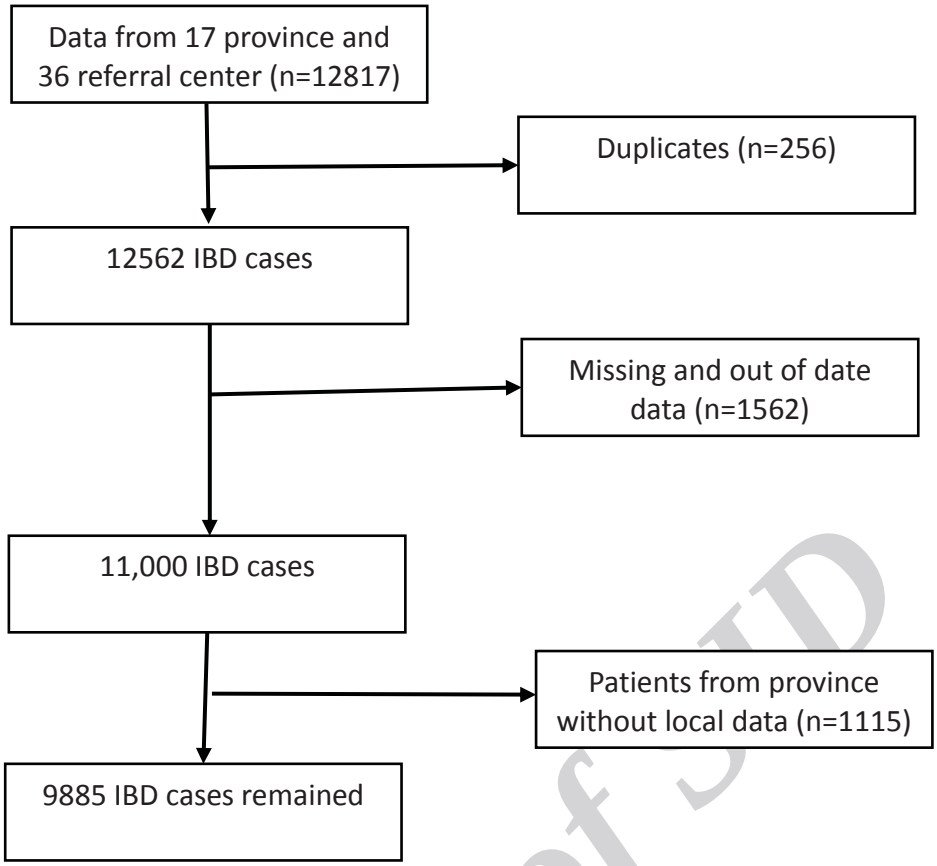

Figure 3. Data collection flow chart

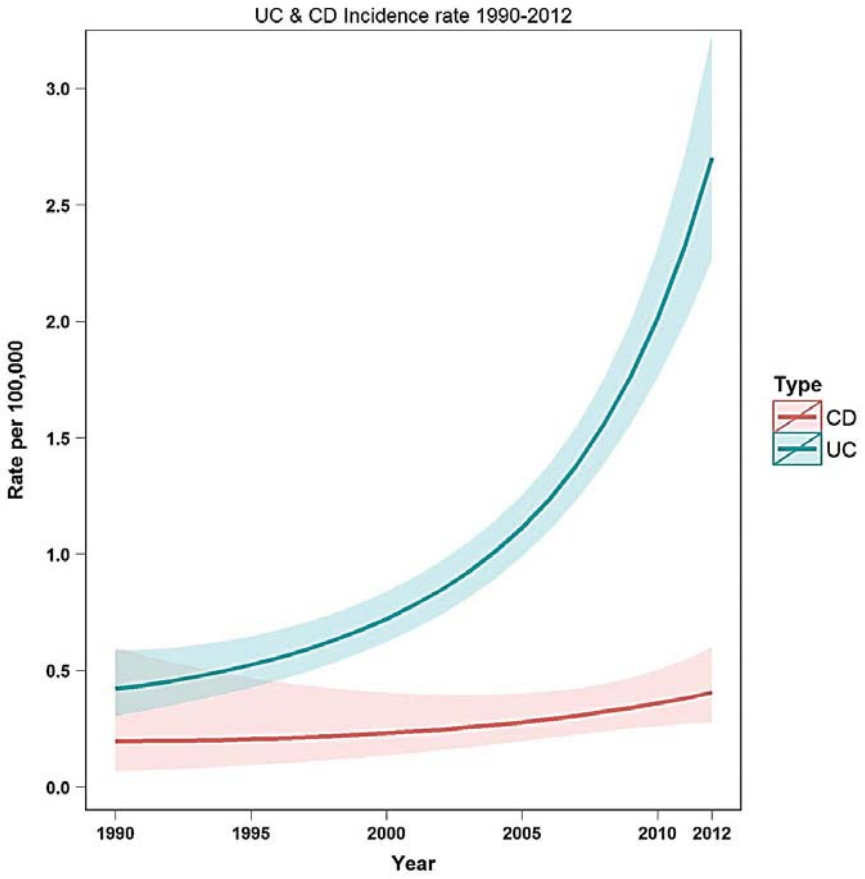

Figure 4. The trend of national incidence of UC and CD during study period.

Table 3. Estimated prevalence based on statistical modeling for IBD rates at provincial level during the study.

Province	1990 (UI)	1995 (UI)	2000 (UI)	2005 (UI)	2010 (UI)	2012 (UI)
Markazi	4.60 (1.85–7.26)	5.22 (3.55–6.94)	6.99 (5.21–8.62)	10.48 (8.53–12.42)	25.61 (20.59–30.39)	55.52 (36.28–74.28)
Guilan	3.68 (1.87–5.51)	4.61 (3.23–5.90)	7.95 (6.34–9.41)	20.83 (17.89–23.94)	41.83 (36.91–46.59)	64.10 (50.95–77.60)
Mazandaran	4.88 (2.70–7.03)	5.08 (3.92–6.22)	8.35 (6.85–9.83)	15.77 (13.79–17.67)	31.29 (27.49–34.65)	54.17 (43.27–66.49)
Azerbaijan, East	4.38 (2.20–6.53)	5.23 (3.84–6.58)	6.70 (5.49–7.90)	8.71 (7.55–9.85)	15.51 (13.36–17.72)	25.99 (18.97–32.64)
Azarbeijan, West	4.48 (2.49–6.39)	5.41 (3.98–6.87)	6.36 (5.04–7.59)	7.61 (6.56–8.73)	16.22 (13.77–18.79)	31.06 (22.68–39.85)
Kermanshah	4.29 (2.17–6.47)	5.17 (3.53–6.74)	7.21 (5.58–8.84)	10.74 (8.79–12.46)	20.33 (17.00–23.72)	36.78 (26.37–45.88)
Khuzestan	4.41 (2.52–6.26)	5.37 (4.12–6.52)	7.40 (6.28–8.53)	10.22 (9.00–11.48)	18.23 (16.16–20.23)	32.49 (25.04–39.79)
Fars	5.11 (2.61–7.68)	5.93 (4.33–7.44)	8.34 (6.90–9.70)	10.26 (8.90–11.73)	15.67 (13.57–17.61)	27.14 (19.82–34.38)
Kerman	3.83 (1.51–6.02)	4.78 (3.43–6.29)	6.30 (4.91–7.65)	7.59 (6.31–8.91)	15.96 (13.36–18.60)	31.31 (21.82–40.94)
Khorasan, Razavi	3.37 (1.88–4.83)	4.71 (3.70–5.79)	6.40 (5.40–7.37)	9.06 (7.99–10.14)	16.69 (14.74–18.59)	26.16 (20.27–32.01)
Isfahan	4.13 (2.32–5.84)	4.97 (3.85–6.07)	6.90 (5.80–8.04)	8.31 (7.23–9.36)	16.95 (14.86–18.96)	30.44 (23.00–38.10)
Sistan	4.26 (1.70–6.70)	4.87 (3.32–6.41)	5.72 (4.37–7.07)	7.13 (5.80–8.56)	16.25 (12.77–19.55)	31.56 (20.03–42.53)
Kordestan	4.27 (1.98–6.60)	5.20 (3.59–6.97)	7.21 (5.52–8.82)	10.20 (8.32–12.30)	21.44 (17.38–25.49)	41.04 (27.56–54.50)
Hamedan	4.27 (1.95–6.57)	5.28 (3.73–6.85)	7.31 (5.67–8.76)	11.91 (9.86–13.92)	24.78(20.45–29.17)	44.20 (31.30–58.36)
Chahar Mahaal	4.39 (0.64–7.84)	4.94 (3.00–7.00)	6.43 (4.33–8.50)	9.25 (6.97–11.54)	19.96 (14.79–25.59)	39.34 (21.11–57.12)
Lorestan	4.38 (1.86–7.01)	5.25 (3.65–6.97)	7.07 (5.47–8.55)	10.57 (8.67–12.35)	20.83 (17.40–23.97)	38.79 (27.01–49.84)
Ilam	5.10 (-0.51–10.90)	5.37 (2.69–8.23)	6.52 (3.98–8.95)	8.80 (6.11–11.38)	22.30 (15.24–28.93)	53.11 (27.49–80.60)
Kohgiluyeh	5.27 (-0.07–10.99)	5.30 (2.52–7.94)	6.16 (3.85–8.53)	9.21 (6.63–11.84)	20.88 (14.01–27.18)	41.86 (20.56–63.11)
Bushehr	5.46 (0.98–9.99)	5.85 (3.47–8.28)	7.31 (5.15–9.57)	9.71 (7.22–12.02)	19.88 (14.39–25.06)	39.87 (21.88–58.56)
Zanjan	3.80 (1.16–6.48)	5.35 (3.44–7.16)	7.85 (5.54–10.09)	13.37 (10.56–16.20)	34.63 (27.03–42.00)	72.30 (44.76–96.99)
Semnan	4.87 (0.10–9.55)	5.01 (2.73–7.42)	6.34 (4.11–8.65)	9.47 (6.63–12.25)	27.71 (19.48–35.77)	65.40 (33.23–95.91)
Yazd	4.24 (0.81–7.79)	5.01 (3.04–7.04)	6.17 (4.28–8.07)	7.65 (5.68–9.42)	19.11 (13.98–23.99)	46.11 (25.95–66.53)
Hormozgan	4.56 (1.24–7.84)	5.34 (3.30–7.47)	6.15 (4.52–7.76)	7.09 (5.36–8.74)	18.22 (13.69–22.47)	45.89 (28.32–63.39)
Tehran	6.68 (4.54–8.85)	5.60 (4.48–6.61)	8.71 (7.79–9.67)	14.82 (13.65–15.97)	25.36 (23.79–26.96)	46.10 (39.05–53.32)
Ardabil	3.78 (1.30–6.13)	5.06 (3.32–6.88)	7.05 (5.26–8.81)	9.80 (7.70–11.77)	20.18 (15.63–24.49)	37.52 (23.81–51.27)
Qom	4.88 (1.49–8.57)	5.54 (3.57–7.61)	6.78 (4.84–8.72)	8.95 (6.94–10.91)	26.81 (21.90–31.80)	67.32 (44.27–90.28)
Qazvin	4.10 (1.57–6.83)	5.17 (3.35–6.91)	8.20 (6.11–10.29)	16.19 (13.06–19.47)	38.15 (31.11–45.34)	72.57 (48.98–96.06)
Golestan	3.60 (1.35–5.74)	4.74 (3.21–6.25)	6.59 (5.02–8.25)	9.70 (7.85–11.51)	18.83 (15.35–22.67)	31.43 (20.23–42.29)
Khorasan, North	3.92 (1.04–6.95)	4.70 (2.73–6.63)	5.96 (4.02–7.80)	8.17 (6.05–10.25)	18.09 (12.62–23.63)	34.58 (17.90–51.04)
Khorasan, South	4.49 (0.07–8.95)	4.88 (2.44–7.24)	5.50 (3.48–7.72)	7.50 (5.22–9.90)	20.86 (13.70–28.00)	48.28 (21.17–73.49)
Alborz	4.75 (1.74–7.83)	5.23 (3.51–6.94)	8.16 (6.47–9.77)	15.38 (13.00–17.81)	30.86 (26.22–35.24)	57.71 (40.94–72.66)
National	4.69 (2.28–7.10)	5.22 (3.86–6.65)	7.33 (5.97–8.71)	11.21 (9.64–12.87)	22.04 (18.92–24.99)	40.67 (28.90–52.41)

UI: Uncertainty Interval, Rate per 100,000

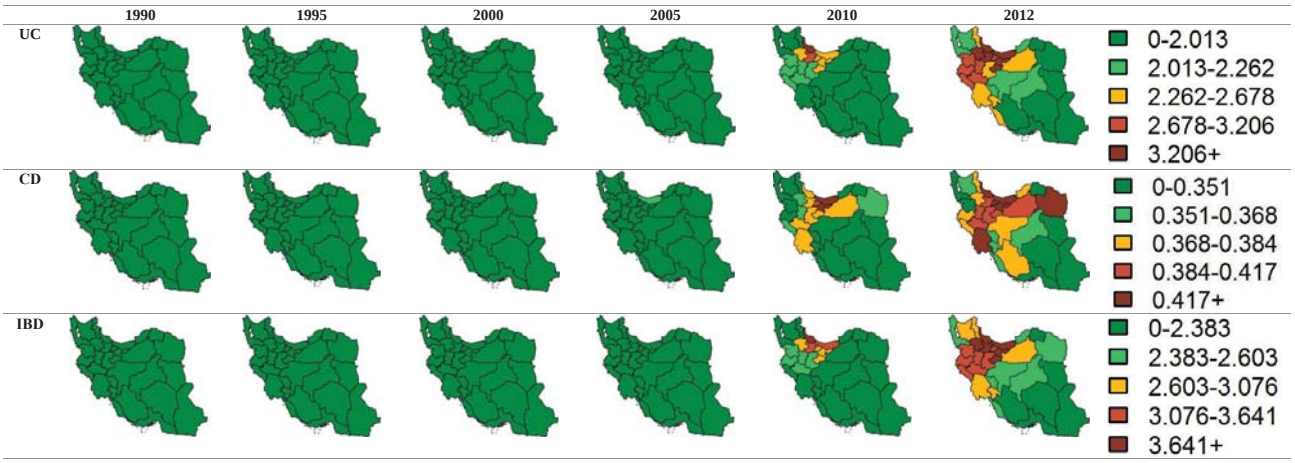

Figure 5. Mean annual incidence at provincial level (per 100,000).

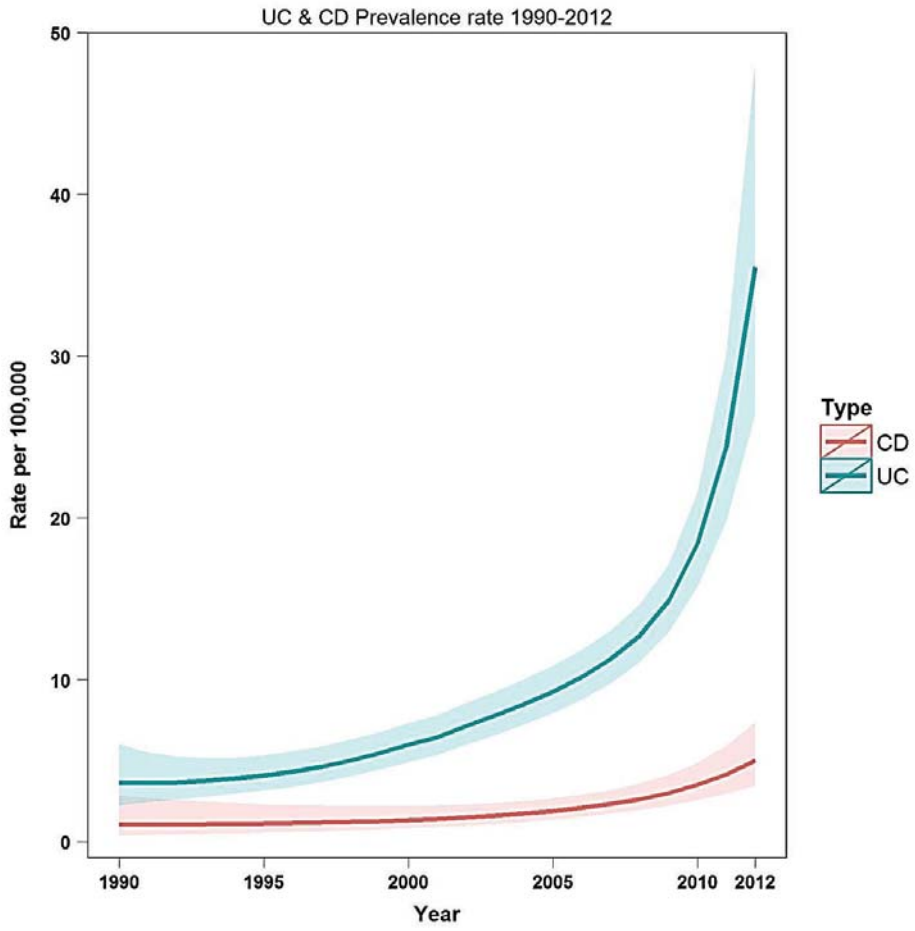

Figure 6. Prevalence of UC and CD during study period at national level.

Discussion

The first reports of UC in Iran appeared 30 years ago and the authors of the first two studies claimed that CD was not existent in Iran.[30,31] The first CD cases were reported 15 years ago.[32,33] Thereafter, as shown in Table 1, plenty of local studies were done, but this study is the first national and subnational report on the incidence and prevalence of IBD, as well as its trend in Iran. We found that the incidence of IBD, CD, and UC were 3.11, 0.41, and 2.70 per 100,000 respectively in 2012. Prevalence of IBD, CD, and UC were 40.67, 5.03, and 35.52 per 100,000 respectively in 2012.

Almost all studies in Middle Eastern countries were hospital-based or office-based (Table 4). Only a few studies reported incidence and prevalence rate. For instance, Abdul-Baki, et al.[34] reported a higher incidence rate in Lebanon than Iran (4.9, 1.4, and 5.5 per 100,000 for UC, CD, and IBD respectively). Also the estimated prevalence in Lebanon was much higher than our results (159.3 vs. 40.67). In contrary, studies from Oman (1.35/100,000) and Kuwait (2.8/100,000) reported incidence rates for UC simi-

Table 4. Summary of papers about IBD epidemiology in Middle East

Author	Publish date	Place	Study period	Method	# of IBD patients			Female/Male		Mean age at diagnosis		Peak age	Trend
					UC	CD	IBD	UC	CD	UC	CD		
Isbister WH[84]	1998	Riyadh, Saudi Arabia	1976–1994	Hospital–based	67	28	101	1.01		29.6	32.5	Unimodal	Increasing
Khawaja A[85]	2009	Jeddah, Saudi Arabia	2002–2007	Hospital–based	122	15	137	0.88	0.87			Unimodal	
Al–mofarreh MA[86]	2013	Riyadh, Saudi Arabia	1993–2009	Office–based	238	455	693	0.66	0.5	34	27	Unimodal	
Aljebreen AM[87]	2014	Riyadh, Saudi Arabia	2009–2013	Multi–center		497			0.69		25	Unimodal	
					# cases		Rate per 100000						
Radhakrishnan S[36]	1997	Oman	1987–1994	Hospital–based	108	Incidence	1.35		1.08		36		no increase
						Prevalence							
Al–Shamali MA[35]	2003	Kuwait	1985–1999	Hospital–based	346	Incidence	2.8		1.08		45	Unimodal	no increase
						Prevalence	41.7						
Al–Ghamdi AS[37]	2004	Riyadh, Saudi Arabia	1983–2002	Hospital–based	77	Incidence	0.94		1.33		25.3	Unimodal	Increasing
						Prevalence							
Abdul–Baki H[34]	2007	Lebanon	2000–2004	Multi–center	251	Incidence*	4.1	1.4	5.5	1.4	32	28.8	Unimodal	Increasing
						Prevalenc*	106.2	53.1	159.3				

*Rates were age–standardized

Table 5. Recent reports on incidence of IBD around the world.

Author	Publish date	Place	Year of study	Method	# of cases	Incidence per 100000		Female/ Male	Mean age at diagnosis			
						UC	CD	IBD	UC	CD	UC	CD
Hou J K*[39]	2013	USA	1998–2009	National veteran cohorts	58116	50	33					
Betteridge JD[88]	2013	USA	2008–2009	Tricare database (national military health service)	35404				1.26	1.54	53	50
Leddin D[12]	2014	Canada	1996	population–based (related to health insurance database)	7153	21.4	27.4					
			2009			16.7	17.7					
Burisch J*[9]	2014	Eastern Europe	2010–2011	Population–based	256	4.6	3.3	8.1	0.81	0.66	36^	32^
Burisch J*[9]	2014	Western Europe	2010–2011	Population–based	1259	9.8	6.3	18.5	0.79	0.96	39^	34^
Ng SC*[38]	2013	Eastern Asia & Australia	2011–2012	Population–based	419	0.76	0.54	1.37	0.73	0.63	42^	34^
Hong Yang*[89]	2014	Daqing, China		Population–based	27	1.64	0.13	1.77	1	0.5	48.9	39.5

*age adjusted rates; ^ median instead of mean

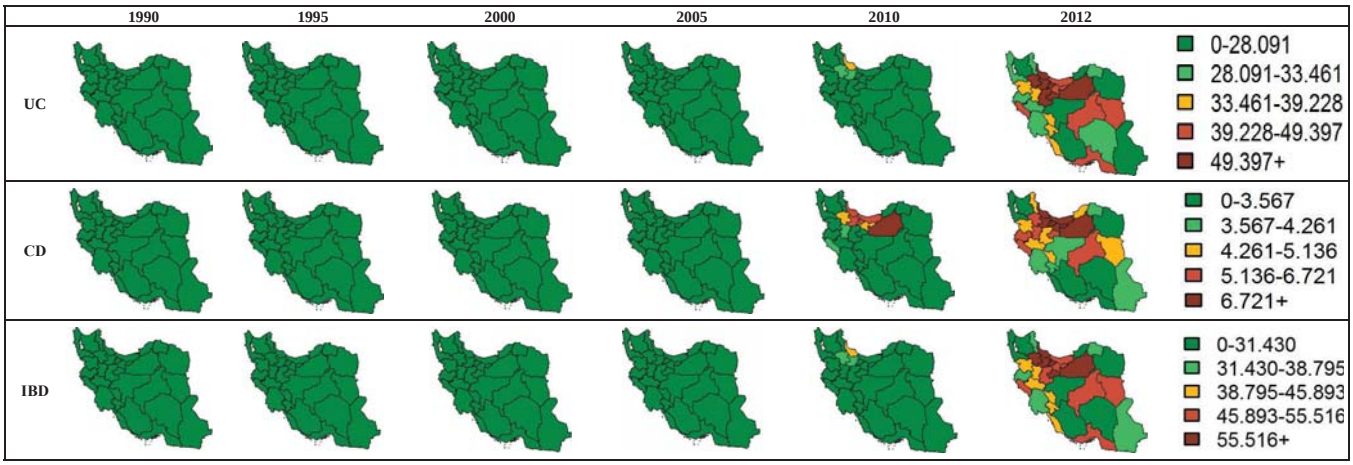

Figure 7. IBD prevalence at provincial level (per 100,000)

lar to ours.[35,36] One study from central Saudi Arabia reported incidence of CD as 0.94 per 100,000, which is higher than what we found in our country.[37] However, conducting multi-national population-based studies for a better estimate of incidence and prevalence of IBD and its geographical variation in Middle-East is necessary. Such studies have been conducted in Eastern Asia and Europe.[9,38]

The incidence and prevalence of UC and CD has a wide geographical variation across the world. Incidence of UC ranges from 0.24 per 100,000 in Thailand (Chiang Mai)[38] to 50 per 100,000 in the USA.[39] Incidence of CD ranges from zero in Greenland[9] to 33 per 100,000 in USA.[39] Prevalence of UC in ranges from 2.42 in Romania[40] to 413 per 100,000 in USA[39] and prevalence of CD ranges from 1.2 in Sri Lanka[41] to 287 per 100,000 in the USA.[39] Summary of recent reports on incidence of IBD across the world are demonstrated in Table 5. Our estimated UC prevalence (35.52 per 100,000) was higher than reported rates from China, Sri Lanka, and Taiwan.[41–43] Our estimated UC prevalence was also close to Korea and India,[44,45] but lower than Japan and New Zealand.[46,47] Our estimated CD prevalence (5.03 per 100,000) was similar to other Asian countries, but was less than some eastern countries such as Korea.[45] In spite of higher reported rates from Western Europe, our results were close to reports from Eastern Europe. Also, our rates were much lower than that of USA and Canada, but similar to central and southern American countries.

The prevalent cases of IBD in Iran based on the global burden of diseases (GBD) 2013 study were estimated to be 37,700 and 108,200 in 1990 and 2013 respectively, with a 9.6% increase in age-standardized prevalence rate. This estimation is much higher than the reported prevalence of IBD in this study, but the increasing trend is similar. As for IBD subtypes, the GBD study also showed a steady trend for UC prevalence and incidence, as well as the increasing trend for CD prevalence and incidence from 1990 to 2013. Due to the limitation in study methodology, we are reporting a minimum incidence of IBD in Iran. Therefore, the actual IBD incidence and prevalence is higher than what we have reported in this study. A very low UC/CD ratio and a more pronounced increasing trend of CD in GBD 2013 study is in fact what is expected based on the experience from other regions of the world. We will most likely observe CD incidence to approach that of UC in Iran in near future. Also quite a high number of CD cases may be diagnosed as UC at the onset of symptoms until the diagnosis of CD becomes established later during the follow-up. The rate of CD in Iran has been increasing rapidly during the first 2 decades of its emergence as shown in the previous reports.[32,33] Therefore, the possibility that we have underestimated the number of CDs in the onset of IBD epidemic in Iran is probably an explanation for higher UC/CD ratio in our study.[3,5,48,49]

This study confirmed a rapid increase in incidence of IBD (3.6 fold) in the last two decades corresponding with the experience observed in the Western countries more than 50 years ago due to the progressive adoption of modern lifestyle. Also, many studies in developing and developed Asian countries such as Korea, Japan, China, Hong Kong, Taiwan, and Lebanon, revealed a similar trend.[34,42,43,45,46,50] One of the most important aspects of western lifestyle that explains this increase is the western diet characterized by overconsumption of highly refined grains and saturated fats, over-refined sugars, animal protein, and a reduced intake of plant-based fibers. This type of diet which is increasingly consumed in Eastern Europe, Asia and Middle East can predispose people to IBD most likely by changing the gut microbiota.[51–53] Another important aspect of modern life is the widespread domestic food refrigeration, which was due to the fridge ownership during the second half of the 20th century.[54] Other proposed reasons were improvement in water supply, sewage, and optimal breast feeding.[46,51] In parallel, substantial improvement and availability of infrastructures such as healthy drinking water, healthy waste disposal, better access to electricity and gas has occurred in Iran. Urbanization, higher rate of literacy, and better communications have been substantial. Therefore, increasing incidence of IBD was expected in Iran due to these changes in lifestyle and improvement in socioeconomic indices.

Also, the possibility of uncontrolled case identification biases due to better availability of diagnostic facilities and improvement of physician knowledge may have contributed to this observation.[11] However, we adjusted our model for number of GI specialists across the country during the study period, which showed that this increase is not completely dependent on this issue. Moreover, the widely observed increasing trend in IBD incidence in other developing countries during recent decades highlights the effect of environmental factors rather than case identification bias.

By this increase in incidence, the increasing prevalence of both UC and CD is predictable. Additionally, early onset of IBD, better care, and reduced mortality of IBD patients will lead to further increase in prevalence.[7] This is in parallel with our findings indicating a 9.81 and 4.75 fold increase in UC and CD prevalence, respectively.

UC/CD prevalence rate ratio was 3.41 in 1990, which increased to 7.06 in 2012, showing that the prevalence of UC is more and has a higher pace. In Asia, it was shown that UC is more prevalent than CD[45,55,56] and one review estimated that the UC/CD ratio ranges from 1.2 to 6 in Asia.[57] Moreover, UC is more prevalent than CD in Scandinavian countries and some East European countries, but it was demonstrated that this ratio is diminishing in recent years.[8,45,57–62] However, in Canada, United States, Australia, and other European countries, the prevalence and incidence of CD is higher than UC.[13,63–69] In western countries, 60 years after the emergence of IBD, CD prevalence exceeded that of UC.[8,13,70,71] We expect that the prevalence of CD will increase more rapidly and will approach that of UC in the next 20 years.

The main limitation of this study was using non population-based data. This may lead to underestimation of the incidence and prevalence of IBD. Another problem is that we didn't take into account the dead or immigrants for calculating prevalence, which may lead to overestimation of the prevalence. The strength of our study was collecting the largest number of Iranian IBD patients in Iran and Middle East. Also, using GPR and spatial modeling, we made better estimations of IBD incidence and prevalence in provinces for which we did not have original data and this was another strength of our study.

In conclusion, the incidence and prevalence of IBD in Iran are growing rapidly in parallel with other developing countries, and it will become a major health challenge in near future. Its prevalence and incidence were similar with Middle Eastern, Central Asian, and East European countries and were less than Eastern Asian, Western European, and Northern American countries. The prevalence and incidence of both UC and CD were increasing and it is expected that CD will surpass UC in forthcoming years. Establishing a national population-based IBD registry seems to be necessary in Iran.

Authors' contribution

Masoud M. Malekzadeh: *Collecting the data, systematic review, data cleaning, writing the manuscript, confirming the final draft;* ***Homayoon Vahedi:*** *Designing the study, conducting the data collection, confirming the final draft;* ***Kimiya Gohari:*** *Statistical analysis, writing the manuscript, confirming the final draft;* ***Parinaz Mehdipour:*** *Statistical analysis, writing the manuscript, confirming the final draft;* ***Sadaf G. Sepanlou:*** *Drafting the manuscript, commenting on results and discussion;* ***Nasser Ebrahimi Daryani:*** *Share cases, commenting on the manuscript;* ***Mohammad R. Zali:*** *Share cases, commenting on the manuscript;* ***Fariborz Mansour-Ghanaei:*** *Share cases, commenting on the manuscript;* ***Alireza Safaripour:*** *Share cases, commenting on the manuscript;* ***Rahim Aghazadeh:*** *Share cases, commenting on the manuscript;* ***Hassan Vossoughinia:*** *Share cases, commenting on the manuscript;* ***Hafez Fakheri:*** *Share cases, commenting on the manuscript;* ***Mohammad H. Somi:*** *Share cases, commenting on the manuscript;* ***Iradj Maleki:*** *Share cases, commenting on the manuscript;* ***Vahid Hoseini:*** *Share cases, commenting on the manuscript;* ***Mohammad Reza Ghadir:*** *Share cases, commenting on the manuscript;* ***Hamed Daghaghzadeh:*** *Share cases, commenting on the manuscript;* ***Hamid Tavakoli:*** *Share cases, commenting on the manuscript;* ***Payman Adibi:*** *Share cases, commenting on the manuscript;* ***Alireza Taghavi:*** *Share cases, commenting on the manuscript;* ***Mohammad Javad Zahedi:*** *Share cases, commenting on the manuscript;* ***Taghi Amiriani:*** *Share cases, commenting on the manuscript;* ***Masoud Tabib:*** *Share cases, commenting on the manuscript;* ***Zainab Alipour:*** *Share cases, commenting on the manuscript;* ***Ahmad Arab:*** *Share cases, commenting on the manuscript;* ***Hossein Nobakht:*** *Share cases, commenting on the manuscript;* ***Abbas Yazdanbod:*** *Share cases, commenting on the manuscript;* ***Masoud Sadreddini:*** *Share cases, commenting on the manuscript;* ***Alireza Bakhshipour:*** *Share cases, commenting on the manuscript;* ***Ahmad Khosravi:*** *Share cases, commenting on the manuscript;* ***Pejman Khosravi:*** *Collecting the data, confirming the final draft;* ***Siavosh Naserimoghadam:*** *Share cases, commenting on the manuscript;* ***Shahin Merat:*** *Share cases, commenting on the manuscript;* ***Rasoul Sotoodehmanesh:*** *Share cases, commenting on the manuscript;* ***Farhad Barazandeh:*** *Share cases, commenting on the manuscript;* ***Peyman Arab:*** *Share cases, commenting on the manuscript;* ***Nadieh Baniasadi:*** *Share cases, commenting on the manuscript;* ***Seyyed Javad Pournaghi:*** *Share cases, commenting on the manuscript;* ***Mahboubeh Parsaeian:*** *Study design, statistical analysis, commenting on the manuscript;* ***Farshad Farzadfar:*** *Study design, statistical analysis, commenting on the manuscript;* ***Reza Malekzadeh:*** *Study design, collecting the data, writing the manuscript, confirming the final draft.*

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References

1. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. *Gastroenterology.* 2009; 136: 741 – 754.
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. *Gastroenterology.* 2009; 136: 376 – 386.
3. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990 – 2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015; 386: 743-800.
4. Global, regional, and national disability–adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990 – 2013: quantifying the epidemiological transition. *Lancet.* 2015; 386: 2145-2191.
5. Global, regional, and national age–sex specific all–cause and cause–specific mortality for 240 causes of death, 1990 – 2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015; 385: 117 – 171.
6. Kappelman MD, Rifas–Shiman SL, Porter CQ, Ollendorf DA, Sandler RS, Galanko JA, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology.* 2008; 135: 1907 – 1913.
7. Burisch J, Jess T, Martinato M, Lakatos PL. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis.* 2013; 7: 322 – 337.
8. Cosnes J, Gower–Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology.* 2011; 140: 1785 – 1794.
9. Burisch J, Pedersen N, Cukovic–Cavka S, Brinar M, Kaimakliotis I, Duricova D, et al. East–West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO–EpiCom inception cohort.

Gut. 2014; 63: 588 – 597.
10. Nguyen GC, Chong CA, Chong RY. National estimates of the burden of inflammatory bowel disease among racial and ethnic groups in the United States. *J Crohns Colitis.* 2014; 8: 288 – 295.
11. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012; 142: 46 – 54.e42; quiz e30.
12. Leddin D, Tamim H, Levy AR. Decreasing incidence of inflammatory bowel disease in eastern Canada: a population database study. *BMC Gastroenterol.* 2014; 14: 140.
13. Molinie F, Gower–Rousseau C, Yzet T, Merle V, Grandbastien B, Marti R, et al. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988 – 1999). *Gut.* 2004; 53: 843 – 848.
14. Loftus CG, Loftus EV, Jr., Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton LJ, 3rd, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940 – 2000. *Inflamm Bowel Dis.* 2007; 13: 254 – 261.
15. Prideaux L, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. *J Gastroenterol Hepatol.* 2012; 27: 1266 – 1280.
16. Ouyang Q, Tandon R, Goh KL, Ooi CJ, Ogata H, Fiocchi C. The emergence of inflammatory bowel disease in the Asian Pacific region. *Curr Opin Gastroenterol.* 2005; 21: 408 – 413.
17. Lakatos PL, Fischer S, Lakatos L. Is the epidemiology of inflammatory bowel disease changing in Eastern Europe? *Scand J Gastroenterol.* 2006; 41: 870 – 871; author reply 871 – 872.
18. Taghavi A Establishment of a population–based registry of inflammatory bowel diseases in Fars province, Iran. *Middle East Journal of Digestive Diseases.* 2012; 4: 97 – 101.
19. Zahedi MJ, Darvish Moghadam S, Hayat Bakhsh Abbasi M, Dehghani M, Shafiei Pour S, Zydabady Nejad H, et al. The incidence rate of inflammatory bowel disease in an urban area of iran: a developing country. *Middle East J Dig Dis.* 2014; 6: 32 – 36.
20. Naghavi M, Abolhassani F, Pourmalek F, Lakeh M, Jafari N, Vaseghi S, et al. The burden of disease and injury in Iran 2003. *Popul Health Metr.* 2009; 7: 9.
21. Salimzadeh H, Ardeshir Larijani F, Abedian S, Kalantar Motamedi SM, Malekzadeh MM, Mohaghegh H, et al. The trend of national and sub–national burden of gastrointestinal and liver diseases in Iran 1990 to 2013; study protocol. *Arch Iran Med.* 2014; 17: 33 – 53.
22. Le Riche R, *Introduction to kriging*. 2014.
23. Stein ML, *Interpolation of spatial data: some theory for kriging*. 1999, Springer–Verlag New York.
24. Rasmussen CE, *Gaussian Processes for Machine Learning*. 2006, the MIT Press: Massachusetts Institute of Technology.
25. Mehdipour P, Navidi I, Parsaeian M, Mohammadi Y, Moradi Lakeh M, Rezaei Darzi E, et al. Application of Gaussian Process Regression (GPR) in estimating under–five mortality levels and trends in Iran 1990 – 2013, study protocol. *Arch Iran Med.* 2014; 17: 189 – 192.
26. Safarpour AR, Hosseini SV, Mehrabani D. Epidemiology of inflammatory bowel diseases in Iran and Asia; A mini review. *Iranian Journal of Medical Sciences.* 2013; 38: 140 – 149.
27. Shayesteh AA, Saberifirozi M, Abedian S, Sebghatolahi V. Epidemiological, Demographic, and Colonic Extension ofUlcerative Colitis in Iran: A Systematic Review. *Middle East J Dig Dis.* 2013; 5: 29 – 36.
28. Fani A A study on the pattern of prevalence of inflammatory bowel disease and its clinical presentation in Arak. *Arak Medical University Journal (Rahavard Danesh)* 2002; 5: 23 – 28.
29. Masoodi M, Agah S, Kashani AHF, Eghbali H. Estimation of ulcerative colitis incidence in hormozgan province, Southern Iran. *Govaresh.* 2011; 16: 265 – 269.
30. Mir – Madjlessi SH, Forouzandeh B, Ghadimi R. Ulcerative colitis in Iran: a review of 112 cases. *Am J Gastroenterol.* 1985; 80: 862 – 866.
31. Malekzadeh R. Ulcerative colitis in southem Iran: A review of 64 cases. *Iranian journal od medicine.* 1986; 13: 54 – 59.
32. Malekzadeh R, Mirmadjlesi H, Varshoesaz J, Agah S, Tavakoli H. Rising the incidence of Crohn's disease in Iran during last decade(1989 – 1999). *Gastroenterology.* 2000; 118: A1356 – A1356.
33. Malekzadeh R VJ, Merat S, Hadidchi S, Mir Majlesi SH, Vahedi H, Radmehr A, Soroush Z, Tavakkoli H, Agah S, Kamalian N, Hormozdi M, Maghazei A, Vahid AA. Crohn's disease: A review of 140 cases from Iran. *Iranian Journal of Medical Sciences.* 2000; 25: 138 – 143.
34. Abdul–Baki H, ElHajj I, El–Zahabi LM, Azar C, Aoun E, Zantout H, et al. Clinical epidemiology of inflammatory bowel disease in Lebanon. *Inflamm Bowel Dis.* 2007; 13: 475 – 480.
35. Al–Shamali MA, Kalaoui M, Patty I, Hasan F, Khajah A, Al–Nakib B. Ulcerative colitis in Kuwait: a review of 90 cases. *Digestion.* 2003; 67: 218 – 224.
36. Radhakrishnan S, Zubaidi G, Daniel M, Sachdev GK, Mohan AN. Ulcerative colitis in Oman. A prospective study of the incidence and disease pattern from 1987 to 1994. *Digestion.* 1997; 58: 266 – 270.
37. Al–Ghamdi AS, Al–Mofleh IA, Al–Rashed RS, Al–Amri SM, Aljebreen AM, Isnani AC, et al. Epidemiology and outcome of Crohn's disease in a teaching hospital in Riyadh. *World J Gastroenterol.* 2004; 10: 1341 – 1344.
38. Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, et al. Incidence and Phenotype of Inflammatory Bowel Disease Based on Results From the Asia–Pacific Crohn's and Colitis Epidemiology Study. *Gastroenterology.* 2013; 145: 158 – 165.
39. Hou JK, Kramer JR, Richardson P, Mei M, El–Serag HB. The incidence and prevalence of inflammatory bowel disease among U.S. veterans: a national cohort study. *Inflamm Bowel Dis.* 2013; 19: 1059 – 1064.
40. Gheorghe C, Pascu O, Gheorghe L, Iacob R, Dumitru E, Tantau M, et al. Epidemiology of inflammatory bowel disease in adults who refer to gastroenterology care in Romania: A multicentre study. *Eur J Gastroenterol Hepatol.* 2004; 16: 1153 – 1159.
41. Niriella MA, De Silva AP, Dayaratne AH, Ariyasinghe MH, Navarathne MM, Peiris RS, et al. Prevalence of inflammatory bowel disease in two districts of Sri Lanka: a hospital based survey. *BMC Gastroenterol.* 2010; 10: 32.
42. Lok KH, Hung HG, Ng CH, Kwong KC, Yip WM, Lau SF, et al. Epidemiology and clinical characteristics of ulcerative colitis in Chinese population: experience from a single center in Hong Kong. *J Gastroenterol Hepatol.* 2008; 23: 406 – 410.
43. Wei SC, Lin MH, Tung CC, Weng MT, Kuo JS, Shieh MJ, et al. A nationwide population – based study of the inflammatory bowel diseases between 1998 and 2008 in Taiwan. *BMC Gastroenterol.* 2013; 13: 166.
44. Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. *Gut.* 2003; 52: 1587 – 1590.
45. Yang SK, Yun S, Kim JH, Park JY, Kim HY, Kim YH, et al. Epidemiology of inflammatory bowel disease in the Songpa – Kangdong district, Seoul, Korea, 1986 – 2005: a KASID study. *Inflamm Bowel Dis.* 2008; 14: 542 – 549.
46. Asakura K, Nishiwaki Y, Inoue N, Hibi T, Watanabe M, Takebayashi T. Prevalence of ulcerative colitis and Crohn's disease in Japan. *J Gastroenterol.* 2009; 44: 659 – 665.
47. Gearry RB, Richardson A, Frampton CM, Collett JA, Burt MJ, Chapman BA, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. *Inflamm Bowel Dis.* 2006; 12: 936 – 943.
48. Malekzadeh R Global Burden of Disease Study 2010: A real advance in global descriptive epidemiology: prospective for developing countries. *Arch Iran Med.* 2014; 17: 302 – 303.
49. *Epi Visualization.* 2015 [cited 2015 8/12/2015]; Available from: URL: http: //vizhub.healthdata.org/epi/.
50. Jiang L, Xia B, Li J, Ye M, Yan W, Deng C, et al. Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China. *Inflamm Bowel Dis.* 2006; 12: 212 – 217.
51. Leong RW, Kamm MA, Hu PJ, Sung JJ. Inflammatory bowel disease in Asia. *J Gastroenterol Hepatol.* 2010; 25: 436 – 8.
52. Hou JK, Abraham B, El–Serag H Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol.* 2011; 106: 563 – 573.
53. Sakamoto N, Kono S, Wakai K, Fukuda Y, Satomi M, Shimoyama T, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case–control study in Japan. *Inflamm Bowel Dis* 2005; 11: 154 – 163.
54. Malekzadeh F, Alberti C, Nouraei M, Vahedi H, Zaccaria I, Meinzer U, et al. Crohn's Disease and Early Exposure to Domestic Refrigeration. *PLoS One.* 2009; 4.
55. Thia KT, Loftus EV, Jr., Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol.* 2008; 103: 3167 – 3182.
56. Wang YF, Ouyang Q, Hu RW. Progression of inflammatory bowel disease in China. *J Dig Dis.* 2010; 11: 76 – 82.
57. Ng SC. Epidemiology of inflammatory bowel disease: focus on Asia. *Best Pract Res Clin Gastroenterol.* 2014; 28: 363 – 372.

58. Lakatos L, Kiss LS, David G, Pandur T, Erdelyi Z, Mester G, et al. Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002 – 2006. *Inflamm Bowel Dis.* 2011; 17: 2558 – 2565.
59. Jussila A, Virta LJ, Salomaa V, Maki J, Jula A, Farkkila MA. High and increasing prevalence of inflammatory bowel disease in Finland with a clear North–South difference. *J Crohns Colitis.* 2013; 7: e256 – e262.
60. Fonager K, Sorensen HT, Olsen J. Change in incidence of Crohn's disease and ulcerative colitis in Denmark. A study based on the National Registry of Patients, 1981 – 1992. *Int J Epidemiol.* 1997; 26: 1003 – 1008.
61. Tsianos EV, Masalas CN, Merkouropoulos M, Dalekos GN, Logan RF. Incidence of inflammatory bowel disease in north west Greece: rarity of Crohn's disease in an area where ulcerative colitis is common. *Gut.* 1994; 35: 369 – 372.
62. Wiercinska–Drapalo A, Jaroszewicz J, Flisiak R, Prokopowicz D. Epidemiological characteristics of inflammatory bowel disease in North – Eastern Poland. *World J Gastroenterol* 2005; 11: 2630 – 2633.
63. Montgomery SM, Morris DL, Pounder RE, Wakefield AJ. Asian ethnic origin and the risk of inflammatory bowel disease. *Eur J Gastroenterol Hepatol.* 1999; 11: 543 – 546.
64. Sincic BM, Vucelic B, Persic M, Brncic N, Erzen DJ, Radakovic B, et al. Incidence of inflammatory bowel disease in Primorsko–goranska County, Croatia, 2000 – 2004: A prospective population–based study. *Scand J Gastroenterol.* 2006; 41: 437 – 444.
65. Kappelman MD, Rifas–Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, Grand RJ, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol.* 2007; 5: 1424 – 1429.
66. Shivananda S, Lennard–Jones J, Logan R, Fear N, Price A, Carpenter L, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC–IBD). *Gut.* 1996; 39: 690 – 697.
67. Declercq C, Gower–Rousseau C, Vernier–Massouille G, Salleron J, Balde M, Poirier G, et al. Mapping of inflammatory bowel disease in northern France: spatial variations and relation to affluence. *Inflamm Bowel Dis.* 2010; 16: 807 – 812.
68. Wilson J, Hair C, Knight R, Catto–Smith A, Bell S, Kamm M, et al. High incidence of inflammatory bowel disease in Australia: a prospective population–based Australian incidence study. *Inflamm Bowel Dis.* 2010; 16: 1550 – 1556.
69. Cottone M, Renda MC, Mattaliano A, Oliva L, Fries W, Criscuoli V, et al. Incidence of Crohn's disease and CARD15 mutation in a small township in Sicily. *Eur J Epidemiol.* 2006; 21: 887 – 892.
70. Ekbom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population–based study in Sweden. *Gastroenterology.* 1991; 100: 350 – 358.
71. Makharia GK. Rising incidence and prevalence of Crohn's disease in Asia: is it apparent or real? *J Gastroenterol Hepatol.* 2006; 21: 929 – 931.
72. Ebrahimi Daeiani N MH, Airamloo M. Clinical and epidemiological characteristics in ulcerative colitis patients referred to Imam Hospital, 1995 – 2000. *The Journal of Tehran Faculty of Medicine.* 2001; 59(4): 80 – 85.
73. Aghazadeh R, Zali MR, Bahari A, Amin K, Ghahghaie F, Firouzi F. Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol.* 2005; 20: 1691 – 1695.
74. Fakheri H. Inflammatory Bowel Disease in Sari, Northern Iran: Review of 302 Patients. *Govaresh, Iranian Association of Gastroenterology And Hepatology.* 2007; 12: 155 – 160.
75. Keshavarz AAI. Frequency of Colonic Extension by Colonoscopy in Ulcerative Colitis Patients in Kermanshah Province in the Years 2002 – 200. *Behbood, The Scientific Quarterly.* 2008; 11: 441 – 449.
76. Masjedi zadeh RHE, Hashemi SJ, Azmi M, Shayesteh Ak. Epidemiological Features of Inflammatory Bowel Disease in Khozestan. *Scientific Medical Journal of Ahwaz University of Medical Sciences.* 2007; 6: 54 – 63.
77. Darakhshan F, Vali Khojeini E, Balaii H, Naderi N, Firouzi F, Farnood A, et al. Epidemiology of Inflammatory Bowel Disease in Iran: A review of 803 cases. *Gastroenterology and Hepatology from Bed to Bench.* 2008; 1: 19 – 24.
78. Vahedi H, Merat S, Momtahen S, Olfati G, Kazzazi AS, Tabrizian T, et al. Epidemiologic characteristics of 500 patients with inflammatory bowel disease in Iran studied from 2004 through 2007. *Arch Iran Med.* 2009; 12: 454 – 460.
79. Zahedi MJ, Darvish–moghadam S, Haiatbakhsh M, Dalirsani Z Demographic and Clinical Features of Ulcerative Colitis Patients in Kerman City during 2005 – 2007. *Journal of Kerman University of Medical Sciences.* 2009; 16: 45 – 53.
80. Ghadir MRSS. Colonoscopic Diagnostic Findings in Patients Undergoing Colonoscopy In Qom Hazrat–e–Masoome Hospital During 2007 – 2008. *Journal of Qom University of Medical Sciences.* 2011; 5(2): 64 – 69.
81. Yazdanbod A, Farzaneh E, Pourfarzi F, Azami A, Mostafazadeh B, Adiban V, et al. Epidemiologic profile and clinical characteristics of ulcerative colitis in northwest of Iran: a 10 – year review. *Trop Gastroenterol.* 2010; 31: 308 – 311.
82. Shirazi KM, Somi MH, Bafandeh Y, Saremi F, Mylanchy N, Rezaeifar P, et al. Epidemiological and clinical characteristics of inflammatory bowel disease in patients from northwestern iran. *Middle East J Dig Dis.* 2013; 5: 86 – 92.
83. Taghavi S, Sarfarpour A, Hosseini S, Noruzi H, Safarpour M, Rahimikazerooni S. Epidemiology of Inflammatory Bowel Disease (IBD) in Iran: A review of 740 patients in Fars province, southern Iran. *Annals of Colorectal Research.* 2013; 1: 17 – 22.
84. Isbister WH, Hubler M. Inflammatory bowel disease in Saudi Arabia: presentation and initial management. *J Gastroenterol Hepatol.* 1998; 13: 1119 – 1124.
85. Khawaja AQ, Sawan AS. Inflammatory bowel disease in the Western Saudi Arabia. *Saudi Med J.* 2009; 30: 537 – 540.
86. Al–Mofarreh MA, Al–Mofleh IA. Emerging inflammatory bowel disease in saudi outpatients: a report of 693 cases. *Saudi J Gastroenterol.* 2013; 19: 16 – 22.
87. Aljebreen AM, Alharbi OR, Azzam NA, Almalki AS, Alswat KA, Almadi MA. Clinical epidemiology and phenotypic characteristics of Crohn's disease in the central region of Saudi Arabia. *Saudi J Gastroenterol.* 2014; 20: 162 – 169.
88. Betteridge JD, Armbruster SP, Maydonovitch C, Veerappan GR. Inflammatory Bowel Disease Prevalence by Age, Gender, Race, and Geographic Location in the US Military Health Care Population. *Inflammatory Bowel Diseases.* 2013; 19: 1421 – 1427.
89. Yang H, Li Y, Wu W, Sun Q, Zhang Y, Zhao W, et al. The incidence of inflammatory bowel disease in Northern China: a prospective population–based study. *PLoS One.* 2014; 9: e101296.