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ORIGINAL ARTICLE

Gender differences in determinants of iron-deficiency anemia: a population-based study conducted in four European countries

Miriam Levi[1] · Monica Simonetti[2] · Ettore Marconi[2] · Ovidio Brignoli[3] · Maurizio Cancian[3] · Adriana Masotti[4] · Valeria Pegoraro[5] · Franca Heiman[5] · Claudio Cricelli[3] · Francesco Lapi[2]

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Abstract

Iron-deficiency anemia (IDA) was the main condition contributing to higher rates of years lived with disabilities in women in 2016. To date, few studies have investigated gender differences in determinants of IDA in Europe. The aim of the present study was to evaluate the determinants of IDA among females and males in four European countries. IDA determinants were estimated using multivariable Cox regression based on information gathered from national primary care databases, namely Italy (for years 2002–2013), Belgium, Germany, and Spain (for years 2007–2012). Adjusted hazard ratios (aHR) with 95% confidence intervals (CIs) were estimated. Age was significantly associated with IDA in females of childbearing age in all four countries, as well as pregnancy, for which the aHR ranged from 1.20 (95% CI 1.15–1.25) in Italy to 1.88 (95% CI 1.53–2.31) in Germany. In males, the aHR increased with age starting from the 65–69 age group. Menometrorrhagia was associated with IDA in Germany (aHR 2.71, 95% CI 1.96–3.73), Italy (aHR 1.80, 95% CI 1.60–2.03), and Spain (aHR 1.52, 95% CI 1.31–1.76). A greater risk for women with alopecia was also observed. Weakness and headache indicated a higher risk in both men and women. Patients with diseases characterized by blood loss or gastrointestinal malabsorption were also at significantly increased risk. Physicians should encourage women of childbearing age to adhere to dietary recommendations regarding iron intake and regularly prescribe screening of iron status. Upper and lower gastrointestinal investigations should be recommended for patients with a confirmed diagnosis of IDA.

Keywords Iron-deficiency anemia · Gender differences · Determinants · Europe

Introduction

In 2016, iron-deficiency anemia (IDA) was among the five leading causes of years lived with disability (YLDs) and among the ten causes with the greatest prevalence, with 1.24 billion cases (95% UI 1.21–1.28 billion) [1]. In particular, it was the main condition contributing to higher YLD rates in women, being IDA the leading cause among females in 35 countries [1]. While large decline in expected values is observed with increasing sociodemographic development, in developed countries, the main causes of IDA are age- and sex-related, with gastrointestinal diseases the main cause in men and in older patients, and excessive menstrual loss the most frequent aetiology in women of childbearing age [2–6]. In the USA, according to the findings of the National Health and Nutrition Examination Survey (NHANES), IDA prevalence is 5.0% ± 0.4% and 2.6% ± 0.7% in non-pregnant females (aged 15 to 49 years) and pregnant females (aged 12 to 49 years), respectively [7]. In Europe, a recent review found that the prevalence of IDA in apparently healthy women of reproductive age is comparable in Denmark (2.3–4.9%), Norway (4.7%), Belgium (3%), the Netherlands (4.0%), Finland (5.9%), France 4.4%), Spain (3.9%), and Sweden (6.9%) [8]. In a previous study, we calculated the prevalence rates of IDA in primary care obtaining data from four national databases.

✉ Francesco Lapi
lapi.francesco@simg.it

[1] Local Health Unit Tuscany Centre, Florence, Italy

[2] Health Search, Italian College of General Practitioners and Primary Care, Via Sestese, 61, 50141 Florence, Italy

[3] Italian College of General Practitioners and Primary Care, Florence, Italy

[4] Department of Transfusion Medicine, Pordenone, Italy

[5] IQVIA, Milan, Italy

Prevalence among women was 4.48% in Spain, 2.91% in Italy, 4.05% in Germany, and 2.23% in Belgium [9].

To date, few studies have been conducted to investigate gender differences in the determinants of IDA in Europe. Therefore, we built upon the foundation of our previous work to assess the determinants of IDA in females and males in four European countries, namely Italy, Belgium, Germany, and Spain.

Methods

Data sources

For Italy, data were obtained from the Health Search Database (HSD), a general practice database that comprises electronic healthcare records of a group of over 1000 general practitioners (GPs) distributed across Italy, who voluntarily agreed to collect patients' information and to attend training courses for data entry. The demographic details of patients in the HSD are linked by an encrypted code with clinical records, drug prescriptions, prevention records, hospital admissions, and date of death. Data are coded using ICD-9-CM codes for medical diagnoses and the ATC classification system for drugs. To be considered for participation in epidemiological studies, GPs have to meet "up-to-standard" quality criteria pertaining to the level of coding, prevalence of well-known diseases, mortality rates, and years of recording [10]. For the present study, 700 GPs homogeneously distributed throughout Italy, covering a patient population of 1,163,855 individuals and respecting the up-to-standard quality criteria, were selected. The validity of the HSD has been demonstrated by several publications [11–17].

For Belgium, Spain, and Germany, data based on representative doctors' samples were obtained from the IMS Health Longitudinal Patient Databases (LPD). Data are longitudinally collected during the GP's consultation via management software. In Germany, the database is composed of 4690 GPs who account for about 14,000,000 patients longitudinally monitored; in Spain, the database is composed of 900 GPs that account for about 1,000,000 patients; In Belgium, GPs are 300, accounting for about 300,000 patients. German, Spanish, and Belgium databases contain patients' demographic details that are linked by an encrypted code with clinical records (diagnoses, referrals, test prescriptions, and test results) and drug prescriptions (name of drug, date of prescription, and number of days' supply). Data are coded using internationally recognized systems, such as those of the 9th and 10th versions of the International Classification of Disease, Clinical Modification (ICD-9-CM and ICD-10) for medical diagnoses, and the Anatomical Therapeutic Chemical (ATC) classification system for drugs. In line with the Italian data, these databases also already have been used for epidemiological research [18, 19].

Study population

According to data availability, the study population was selected, for Italy, between the 1st of January 2000 and the 31st of December 2013, while the study populations of Germany, Spain, and Belgium were selected between the 1st of January 2006 and the 31st of December 2011.

For Italy, the determinants of IDA were evaluated for the cohort of patients with a first contact (index date) with their GP between the 1st of January 2002 and the 31st of December 2012, while for Germany, Spain, and Belgium, the same selection criteria were adopted between the 1st of January 2008 and the 31st of December 2010. Patients with a medical history of less than 1 year in the database and patients diagnosed with IDA during the 2 years preceding the index date were excluded.

Outcome definition

In order to maximize the discrimination between IDA and anemia of chronic diseases, [20] IDA was operationally defined by using the ICD-9-CM code 280* or ICD-10 code D50* or, in absence of codes, when hemoglobin was < 13 g/dL in men or < 12 g/dL in women, complemented by ferritin < 15 ng/mL or TfR > 29.5 nmol/L or TIBC > 3.15 mg/L (except for Belgium, whose database does not contain information on TfR or TIBC) which was captured within 6 months before or after the date of hemoglobin measurement. In the same time window, we also captured ferritin measurements whenever they were registered around ICD-9-CM/ICD-10 IDA coded diagnosis. By doing so, the event date was the earlier date of either the diagnosis of IDA or the registration of ferritin. This approach has been successfully adopted in our previous work [9].

We considered prodromal signs/symptoms such as weaknesses, irritability, headache, alopecia, xerostomia, and concurrent conditions/diseases as potential determinants, including menometrorrhagia and pregnancy for women, and the following for both sexes: obesity (BMI > 30 kg/m^2); polyposis of esophagus, stomach, small bowel, colon; cancer of esophagus, stomach, colon, small bowel; gastritis and peptic ulcer; esophagitis; ulcerative colitis; Crohn's disease; intestinal parasites; angiodysplasia; gastric antral vascular ectasia; Meckel's diverticulum; celiac disease; other intestinal malabsorption; Whipple's disease; lymphangiectasia; gastrectomy and gastric atrophy; gut resection or bypass; prosthetic valve; hemoglobinuria. In addition, concurrent medications were examined as well, namely, NSAIDs, aspirin, corticosteroids, antacids, and other drugs for ulcer and gastro-esophageal reflux diseases. The burden of comorbidities was also accounted for

by calculating the patient-specific Charlson comorbidity index (CCI) [21, 22]. All potential determinants of IDA were defined prior to or on the index date.

Data analysis

Descriptive statistics were reported for categorical variables by calculating proportional values (%). Determinants of IDA were estimated by using multivariable Cox regression. Each variable was retained in the final models according to a stepwise approach (p value < 0.15 and 0.10 for entering and exiting variable, respectively). Descriptive statistics and the calculation of adjusted hazard ratios (aHR) with 95% confidence intervals (CIs) were performed with STATA software, version 11 (STATA Cor, College Station, Tex).

Results

Tables 1 and 2 depict the predictors of IDA among females and males, respectively, across countries. Age was significantly associated with IDA in females of childbearing age (15–49 years) in all four countries, with aHR ranging from 2.09 (95% CI 1.04–4.21) in the 85–89 age group in Spain to 7.94 (95% CI 4.22–14.96) in the 30–34 age group in Belgium. In males, the aHR increased with age starting from the 65–69 age group, ranging from 1.90 (95% CI 1.25–2.90) in this age group in Germany to 14.96 (95% CI 1.97–113.42) among patients ≥ 95 years in Spain.

Regarding the signs and symptoms considered, in females, headache and alopecia were significantly associated with IDA all four countries (with aHR ranging, respectively, from 1.06, 95% CI 1.02–1.11, in Italy to 1.16, 95% CI 1.02–1.32, in Belgium and from 1.16, 95% CI 1.02–1.33, in Italy to 1.80, 95% CI 1.48–2.19, in Germany), and weaknesses significantly associated with IDA in all countries but Spain. In males, weaknesses were positively associated with IDA in Italy (aHR 1.17, 95% CI 1.02–1.34) and headache in Germany (aHR 1.44, 95% CI 1.23–1.67).

Among concurrent conditions/diseases, the following were positively associated with IDA: pregnancy in all four countries, the aHR ranging from 1.20 (95% CI 1.15–1.25) in Italy to 1.88 (95% CI 1.53–2.31) in Germany, menometrorrhagia in Germany (aHR 2.71, 95% CI 1.96–3.73), Italy (aHR 1.80, 95% CI 1.60–2.03), and Spain (aHR 1.52, 95% CI 1.31–1.76).

Obesity was positively associated with IDA in Germany (aHR 2.72, 95% CI 2.17–3.41), in Spain (aHR 1.46, 95% CI 1.24–1.72), and in Italy (aHR 1.09, 95% CI 1.04–1.14) among females and in Germany (aHR 3.26, 95% CI 2.23–4.76) and Spain (aHR 2.13, 95% CI 1.48–3.08) among males.

Gastric cancer was significantly associated with IDA in Italy (aHR 3.37, 95% CI 2.82–4.04) and in Germany (aHR 3.02, 95% CI 2.01–4.52) among women and in Spain (aHR 2.87, 95% CI 1.48–5.54) and in Italy (aHR 2.18, 95% CI 1.72–2.75) among men.

Gastritis and peptic ulcer were significantly associated with IDA in Belgium (aHR 1.34, 95% CI 1.19–1.52), Germany (aHR 1.21, 95% CI 1.12–1.31), and in Spain (aHR 1.11, 95% CI 1.01–1.22) among females and in Belgium (aHR 1.31, 95% CI 1.04–1.65), in Germany (aHR 1.28, 95% CI 1.15–1.43), and in Italy (aHR 1.18, 95% CI 1.10–1.26) among males; esophagitis in Belgium (aHR 1.41, 95% CI 1.22–1.62) and Germany (aHR 1.20, 95% CI 1.11–1.31) in females and in Germany among males (aHR 1.31, 95% CI 1.17–1.47); ulcerative colitis in Italy (aHR 2.01, 95% CI 1.57–2.59) and in Germany among females (aHR 1.50, 95% CI 1.13–2.00) and in Germany (aHR 1.81, 95% CI 1.25–2.64) and in Italy (aHR 1.80, 95% CI 1.19–2.70) among males; Crohn's disease in Belgium (aHR 2.32, 95% CI 1.50–3.61), Italy (aHR 2.01, 95% CI 1.28–3.16), and Germany (aHR 1.66, 95% CI 1.21–2.26) in females and in all four countries in males, with the aHR ranging from 1.98 (95% CI 1.15–3.42) in Spain to 4.01 (95% CI 2.77–5.79) in Germany; celiac disease in Italy among females (aHR 1.59, 95% CI 1.29–1.96) and in Spain among males (aHR 2.14, 95% CI 1.51–3.02), lymphangiectasia in Belgium in females (aHR 1.68, 95% CI 1.12–2.51) and in Italy (aHR 1.75, 95% CI 1.02–3.02) and in Germany (aHR 1.56, 95% CI 1.08–2.26) in males; gastrectomy and gastric atrophy in Belgium (aHR 2.13, 95% CI 1.06–4.29) and in Italy (aHR 1.22, 95% CI 1.05–1.42) in females; gut resection or bypass in Italy among females (aHR 15.99, 95% CI 5.16–49.59) and in Spain in males (aHR 1.88 95% CI 1.04–3.40), prosthetic valve in Germany in females (aHR 1.40, 95% CI 1.11–1.78).

Female aspirin users had a 13–44% higher risk of IDA than non-users, male aspirin users had a 16% increased risk in Spain and 10% in Italy. NSAIDs appeared to be negatively associated with IDA in Italy: the aHR being 0.93 (95% CI 0.91–0.96) in females and 0.94 (95% CI 0.90–0.98) in males, whereas they put patients at greater risk of IDA in females in Germany and Spain (31 and 15%, respectively, higher than non-users) and increased the risk by 44% with respect to non-users in Germany in males. Corticosteroids were positively associated with IDA in females in Germany (aHR 1.31, 95% CI 1.13–1.53) and in males in Belgium (aHR 1.74, 95% CI 1.16–2.62). Antacids and other drugs used for ulcer and gastroesophageal reflux disease increased the risk by 9–46% in females and by 28–44% in Belgium, Germany, and Spain in males.

A Charlson Index > 0 was almost always significantly associated to an increased risk of IDA in all countries: the aHR for a Charlson Index = 1 rose from 1.09 (95% CI 1.03–1.15) in Spain to 1.21 (95% CI 1.17–1.25) in Italy in females and from 1.10 (95% CI 1.01–1.21) in Germany to 1.70 (95% CI 1.44–2.02) in Belgium in males; the aHR for a Charlson index = 2 rose from 1.17 (95% CI 1.13–1.22) in females and 1.41 (95%

Table 1 Determinants of iron deficiency anemia occurrence in females across country

	Italy *N* = 38,340 Adjusted HR (95% CI)	Belgium *N* = 1593 Adjusted HR (95% CI)	Germany *N* = 8208 Adjusted HR (95% CI)	Spain *N* = 7858 Adjusted HR (95% CI)
Demographic				
Age				
< 5	1	1	1	–
5–9	*3.11 (1.69–5.71)*	*0.32 (0.11–0.93)*	1.52 (0.86–2.70)	–
10–14	*5 (2.76–9.05)*	*3.55 (1.82–6.95)*	*4.15 (2.44–7.03)*	1
15–19	*5.54 (3.07–10.03)*	*6.17 (3.25–11.72)*	*6.09 (3.63–10.19)*	*2.10 (1.04–4.24)*
20–24	*5.37 (2.97–9.71)*	*6.90 (3.65–13.05)*	*4.88 (2.91–8.17)*	1.68 (0.83–3.39)
25–29	*5.94 (3.28–10.73)*	*7.39 (3.92–13.95)*	*5.60 (3.34–9.38)*	1.88 (0.93–3.78)
30–34	*7.06 (3.91–12.76)*	*7.94 (4.22–14.96)*	*5.93 (3.55–9.93)*	*2.49 (1.24–4.99)*
35–39	*7.59 (4.2–13.71)*	*6.92 (3.67–13.03)*	*6.69 (4.01–11.17)*	*2.42 (1.21–4.87)*
40–44	*6.74 (3.73–12.18)*	*7.55 (4.02–14.19)*	*6.46 (3.88–10.78)*	*2.89 (1.44–5.80)*
45–49	*4.44 (2.46–8.03)*	*7.64 (4.07–14.34)*	*5.92 (3.55–9.88)*	*2.41 (1.20–4.84)*
50–54	*2.11 (1.17–3.82)*	*4.66 (2.47–8.80)*	*3.99 (2.39–6.67)*	1.12 (0.56–2.26)
55–59	1.72 (0.95–3.12)	*2.55 (1.33–4.89)*	*2.72 (1.62–4.55)*	0.72 (0.35–1.45)
60–64	*2.33 (1.29–4.21)*	*2.32 (1.21–4.47)*	*2.71 (1.62–4.55)*	0.75 (0.37–1.52)
65–69	*3.37 (1.86–6.09)*	*3.10 (1.62–5.94)*	*3.16 (1.89–5.28)*	0.79 (0.39–1.60)
70–74	*4.08 (2.25–7.37)*	*3.36 (1.76–6.41)*	*4.22 (2.53–7.05)*	1.17 (0.58–2.36)
75–79	*4.23 (2.34–7.65)*	*4.82 (2.54–9.13)*	*5.27 (3.15–8.80)*	1.67 (0.83–3.35)
80–84	*4.08 (2.25–7.38)*	*6.51 (3.43–12.35)*	*6.24 (3.73–10.42)*	1.91 (0.95–3.84)
85–89	*3.24 (1.79–5.88)*	*5.28 (2.73–10.23)*	*6.40 (3.82–10.73)*	*2.09 (1.04–4.21)*
90–94	*2.45 (1.34–4.49)*	*5.76 (2.71–12.25)*	*5.21 (3.02–8.97)*	2.04 (1.00–4.15)
≥ 95	1.81 (0.93–3.51)	*6.95 (2.95–16.38)*	1.78 (0.96–3.29)	1.62 (0.76–3.43)
Signs, symptoms				
Weaknesses	*1.14 (1.08–1.21)*	*1.33 (1.08–1.64)*	*1.46 (1.27–1.67)*	1.09 (0.98–1.22)
Irritability	–	–	–	–
Headache	*1.06 (1.02–1.11)*	*1.16 (1.02–1.32)*	*1.13 (1.05–1.22)*	*1.13 (1.04–1.23)*
Alopecia	*1.16 (1.02–1.33)*	*1.17 (1.02–1.33)*	*1.80 (1.48–2.19)*	*1.27 (1.06–1.52)*
Xerostomia	–	–	–	–
Menometrorrhagia	*1.8 (1.6–2.03)*	*1.42 (0.98–2.06)*	*2.71 (1.96–3.73)*	*1.52 (1.31–1.76)*
Pregnancy	*1.2 (1.15–1.25)*	*1.87 (1.40–2.51)*	*1.88 (1.53–2.31)*	*1.58 (1.41–1.77)*
Risk factors				
Obesity (BMI > 30 kg/m^2)*	*1.09 (1.04–1.14)*	–	*2.72 (2.17–3.41)*	*1.46 (1.24–1.72)*
Polyposis				
Esophagus	–	–	–	–
Stomach	–	–	–	–
Small bowel	–	–	–	–
Colon	–	–	–	–
Cancer				
Esophagus	–	–	–	–
Stomach	*3.37 (2.82–4.04)*	–	*3.02 (2.01–4.52)*	–
Colon	–	–	–	0.64 (0.40–1.02)
Small bowel	–	–	–	–
NSAIDs	*0.93 (0.91–0.96)*	–	*1.31 (1.22–1.41)*	*1.15 (1.09–1.20)*
Aspirin	*1.19 (1.14–1.24)*	*1.42 (1.15–1.75)*	1.13 (0.98–1.31)	*1.44 (1.33–1.56)*
Corticosteroids	–	1.34 (0.96–1.87)	*1.31 (1.13–1.53)*	–

Table 1 (continued)

	Italy $N = 38,340$ Adjusted HR (95% CI)	Belgium $N = 1593$ Adjusted HR (95% CI)	Germany $N = 8208$ Adjusted HR (95% CI)	Spain $N = 7858$ Adjusted HR (95% CI)
Antacids and other drugs for ulcer/gastroesophageal reflux diseases	*1.09 (1.06–1.12)*	*1.34 (1.15–1.57)*	*1.42 (1.30–1.54)*	*1.46 (1.37–1.55)*
Gastritis and peptic ulcer	1.05 (1–1.1)	*1.34 (1.19–1.52)*	*1.21 (1.12–1.31)*	*1.11 (1.01–1.22)*
Esophagitis	*1.26 (1.17–1.36)*	*1.41 (1.22–1.62)*	*1.20 (1.11–1.31)*	–
Ulcerative colitis	*2.01 (1.57–2.59)*	–	*1.50 (1.13–2.00)*	–
Crohn's disease	*2.01 (1.28–3.16)*	*2.32 (1.50–3.61)*	*1.66 (1.21–2.26)*	–
Intestinal parasites	*1.39 (1.11–1.74)*	–	–	–
Angiodysplasia	–	–	–	–
Gastric antral vascular ectasia (watermelon stomach)	–	–	–	–
Meckel's diverticulum	–	–	–	–
Celiac disease	*1.59 (1.29–1.96)*	–	–	–
Other intestinal malabsorption	–	–	–	–
Whipple's disease	–	–	–	–
Lymphangiectasia	1.25 (0.99–1.58)	*1.68 (1.12–2.51)*	–	–
Gastrectomy and gastric atrophy	*1.22 (1.05–1.42)*	*2.13 (1.06–4.29)*	–	–
Gut resection or bypass	*15.99 (5.16–49.59)*	–	–	–
Prosthetic valve	–	–	*1.40 (1.11–1.78)*	–
Hemoglobinuria	–	–	–	–
Charlson index				
= 0	1	*1*	1	1
= 1	*1.21 (1.17–1.25)*	*1.15 (1.02–1.30)*	1.07 (1.00–1.13)	*1.09 (1.03–1.15)*
= 2	*1.17 (1.13–1.22)*	*1.64 (1.31–2.04)*	*1.30 (1.19–1.42)*	*1.24 (1.14–1.35)*
> 2	*1.4 (1.33–1.47)*	*1.94 (1.39–2.71)*	*1.49 (1.35–1.64)*	*1.39 (1.27–1.52)*

Statistically significant adjusted hazard ratios are shown in italics

BMI, body mass index, CI confidence intervals, HR hazard ratio.

*Last measurement before the index date

CI 1.32–1.51) in males in Italy to 1.64 (95% CI 1.31–2.04) in females and 2.56 (95% CI 2.03–3.23) in males in Belgium; the aHR for a Charlson index > 2 rose from 1.39 (95% CI 1.27–1.52) in Spain to 1.94 (95% CI 1.39–2.71) in Belgium in females and from 1.56 (95% CI 1.45–1.67) in Italy to 2.28 (95% CI 1.63–3.19) in Belgium in males.

Discussion

To the best of our knowledge, this represents the first nationwide population-based study in which gender differences in the clinical determinants of IDA have been assessed in the primary care setting in Europe.

According to the World health Organization (WHO), globally, iron deficiency is the most common and widespread nutritional disorder [23]. Women who have particularly heavy or prolonged menstrual bleeding, as well as pregnant and lactating women are especially at risk of developing IDA. According to a recent systematic review, daily iron supplementation effectively reduces IDA among women of reproductive age, improves physical capacity, exercise and work performance, and decreases fatigue [24]. One cohort study and two cross-sectional studies conducted on nationally representative samples of pregnant women, respectively, conducted in Belgium [25], Switzerland [26], and Germany [27], showed that the prevalence of IDA was 16% in Belgium, 12% in Germany, and 3% in Switzerland, although 65–66% of the Belgian and Swiss women took iron supplements [8]. The prevalence is higher among pregnant women who do not take iron supplements: in controlled studies, IDA prevalence in this group ranged from 4% in Norway to 35% in Spain, increased gradually and peaked during the third trimester, whereas iron-supplemented pregnant women had lower prevalence than placebo-treated women [8]. The WHO therefore recommends for pregnant women daily oral iron supplementation with 30 mg of elemental iron; the dose recommended in settings where anemia in pregnant women is a severe

Table 2 Determinants of iron deficiency anaemia occurrence in males across country

	Italy *N* = 9725 Adjusted HR (95% CI)	Belgium *N* = 858 Adjusted HR (95% CI)	Germany *N* = 3543 Adjusted HR (95% CI)	Spain *N* = 2043 Adjusted HR (95% CI)
Demographic				
Age				
< 5	1	1	1	–
5–9	0.9 (0.57–1.44)	0.42 (0.19–0.93)	1.23 (0.77–1.98)	–
10–14	0.65 (0.41–1.01)	0.78 (0.39–1.55)	1.42 (0.90–2.25)	1
15–19	*0.32 (0.21–0.5)*	1.16 (0.63–2.13)	0.91 (0.57–1.44)	1.45 (0.19–10.83)
20–24	*0.3 (0.19–0.48)*	0.59 (0.29–1.20)	*0.59 (0.36–0.95)*	0.47 (0.06–3.73)
25–29	*0.28 (0.18–0.43)*	0.59 (0.29–1.18)	*0.56 (0.34–0.92)*	0.75 (0.10–5.60)
30–34	*0.28 (0.18–0.44)*	0.49 (0.24–1.00)	0.71 (0.44–1.14)	0.70 (0.10–5.18)
35–39	*0.31 (0.2–0.49)*	0.74 (0.40–1.37)	0.55 (0.34–0.88)	1.17 (0.16–8.49)
40–44	*0.39 (0.25–0.6)*	0.67 (0.36–1.24)	0.91 (0.59–1.41)	1.18 (0.16–8.59)
45–49	*0.4 (0.26–0.62)*	1.04 (0.59–1.82)	0.89 (0.57–1.37)	1.78 (0.25–12.85)
50–54	*0.51 (0.33–0.79)*	1.32 (0.76–2.28)	1.04 (0.67–1.60)	1.75 (0.24–12.64)
55–59	0.72 (0.47–1.12)	1.50 (0.88–2.57)	1.37 (0.89–2.09)	3.38 (0.47–24.23)
60–64	0.9 (0.58–1.39)	1.44 (0.83–2.47)	1.53 (1.00–2.34)	3.85 (0.54–27.50)
65–69	1.21 (0.79–1.87)	*2.02 (1.18–3.45)*	*1.90 (1.25–2.90)*	4.67 (0.65–33.36)
70–74	1.52 (0.99–2.34)	*2.07 (1.21–3.54)*	*2.64 (1.74–4.02)*	6.81 (0.95–48.55)
75–79	*1.73 (1.12–2.67)*	*3.10 (1.83–5.24)*	*3.35 (2.20–5.10)*	*8.95 (1.25–63.78)*
80–84	*1.67 (1.08–2.59)*	*3.15 (1.83–5.41)*	*3.60 (2.35–5.52)*	*11.23 (1.57–80.07)*
85–89	1.36 (0.87–2.12)	*3.25 (1.80–5.86)*	*3.82 (2.46–5.94)*	*12.98 (1.82–92.76)*
90–94	0.93 (0.57–1.52)	*3.47 (1.42–8.45)*	*4.71 (2.81–7.88)*	*13.90 (1.92–100.38)*
≥ 95	1.01 (0.51–2.02)	*3.51 (1.02–12.07)*	1.95 (0.87–4.35)	*14.96 (1.97–113.42)*
Signs, symptoms				
Weaknesses	*1.17 (1.02–1.34)*	–	–	–
Irritability	–	–	–	–
Headache	1.13 (0.98–1.29)	–	*1.44 (1.23–1.67)*	1.23 (0.96–1.58)
Alopecia	–	–	–	–
Xerostomia	–	–	–	–
Risk factors				
Obesity (BMI > 30 kg/m^2)*	–	–	*3.26 (2.23–4.76)*	*2.13 (1.48–3.08)*
Polyposis				
Esophagus	–	–	–	–
Stomach	–	*67.42 (9.33–487.35)*	–	–
Small bowel	–	–	*18.61 (2.64–131.17)*	–
Colon	–	6.88 (0.97–48.97)	–	–
Cancer				
Esophagus	–	–	–	–
Stomach	*2.18 (1.72–2.75)*	–	–	*2.87 (1.48–5.54)*
Colon	–	–	–	–
Small bowel	–	–	–	–
NSAIDs	*0.94 (0.9–0.98)*	–	*1.44 (1.30–1.60)*	–
Aspirin	*1.1 (1.03–1.16)*	–	–	*1.16 (1.04–1.28)*
Corticosteroids	*0.93 (0.88–0.99)*	*1.74 (1.16–2.62)*	–	–
Antacids and other drugs for ulcer/gastroesophageal reflux diseases	–	*1.30 (1.04–1.62)*	*1.28 (1.14–1.44)*	*1.44 (1.31–1.59)*
Gastritis and peptic ulcer	*1.18 (1.1–1.26)*	*1.31 (1.04–1.65)*	*1.28 (1.15–1.43)*	–
Esophagitis	1.13 (0.99–1.29)	–	*1.31 (1.17–1.47)*	–

Table 2 (continued)

	Italy $N = 9725$ Adjusted HR (95% CI)	Belgium $N = 858$ Adjusted HR (95% CI)	Germany $N = 3543$ Adjusted HR (95% CI)	Spain $N = 2043$ Adjusted HR (95% CI)
Ulcerative colitis	*1.8 (1.19–2.7)*	–	*1.81 (1.25–2.64)*	–
Crohn's disease	*2.3 (1.1–4.84)*	*3.73 (1.85–7.52)*	*4.01 (2.77–5.79)*	*1.98 (1.15–3.42)*
Intestinal parasites	–	–	–	–
Angiodysplasia	–	–	–	–
Gastric antral vascular ectasia (watermelon stomach)	–	–	–	–
Meckel's diverticulum	–	–	–	–
Celiac disease	2 (1–3.99)	–	–	*2.14 (1.51–3.02)*
Other intestinal malabsorption	–	–	–	–
Whipple's disease	–	–	–	–
Lymphangiectasia	*1.75 (1.02–3.02)*	2.11 (0.99–4.46)	*1.56 (1.08–2.26)*	–
Gastrectomy and gastric atrophy	1.21 (0.98–1.5)	–	–	–
Gut resection or bypass	–	–	–	*1.88 (1.04–3.40)*
Prosthetic valve	–	–	1.34 (0.97–1.84)	–
Hemoglobinuria	–	–	–	–
Charlson index				
= 0	1	1	1	1
= 1	*1.38 (1.31–1.46)*	*1.70 (1.44–2.02)*	*1.10 (1.01–1.21)*	*1.44 (1.28–1.63)*
= 2	*1.41 (1.32–1.51)*	*2.56 (2.03–3.23)*	*1.58 (1.41–1.77)*	*1.79 (1.56–2.06)*
> 2	*1.56 (1.45–1.67)*	*2.28 (1.63–3.19)*	*2.10 (1.89–2.34)*	*2.04 (1.79–2.32)*

Statistically significant adjusted hazard ratios are shown in italics

BMI, body mass index, CI confidence intervals, HR hazard ratio.

*Last measurement before the index date

public health problem (where ≥ 40% of pregnant women have a Hb concentration < 110 g/L) is 60 mg instead [28]. Our findings confirmed the role of menometrorrhagia and pregnancy as determinants of IDA. A greater risk for women with alopecia was also observed. This finding is in line with previous studies demonstrating that iron deficiency represents a risk factor for developing hair loss in premenopausal women [29, 30]. Among the other signs and symptoms taken into consideration, weaknesses and headache indicated a higher risk in both men and women.

The present study reaffirmed the greater risk of IDA for obese male and female patients. Obesity is notoriously associated with poor dietary iron intake, increased iron requirements, and/or impaired iron absorption, possibly secondary to antacids, often administered in order to control obesity-related acid peptic disorders [31–33]. Furthermore, obese patients are in a state of subclinical inflammation, which may play a central role in the development of IDA through an up-regulation of the peptide hormone hepcidin, produced by hepatocytes and key regulator of systemic iron homeostasis, which, in turn, enhances the degradation of the transmembrane iron transporter ferroportin, which exports iron to plasma from cells [34].

As expected, patients with diseases characterized by blood loss or gastrointestinal malabsorption such as gastric cancer, gastritis and peptic ulcer, esophagitis, ulcerative colitis, Crohn's disease, celiac disease, gastrectomy and gastric atrophy, gut resection or bypass, intestinal lymphangiectasia were at significantly increased risk of IDA.

A higher risk of IDA was observed in Germany also for female patients with prosthetic valve. This result is explained with the hemolysis which can occur as a major complication of mitral valve repair, either due to a prosthetic valve dysfunction causing a para-prosthetic leak, or to the collision of the regurgitant blood with the valvular apparatus [35]. The fact that the model did not retain prosthetic valve as covariate among males in any of the four countries is explained with the sample size of the within-country specific sub-category. Similarly, gastrectomy and gastric atrophy were retained only among Belgian and Italian women.

NSAID users showed a greater risk of IDA in Germany, and, as far as women are concerned, also in Spain, whereas NSAIDs appeared as "protective" in Italy. This finding might result from collinearity with the use of proton-pump inhibitors (PPIs), a drug class commonly used in Italy, and which artificially modified the predictive role of NSAIDs into a protective effect in the

multivariate model [9]. On the contrary, aspirin use maintained the same risk direction in all four countries. This might be explained with low-dose aspirin long-term use for the secondary prevention of cardiovascular diseases.

The production of gastric acid is pivotal for optimal intestinal absorption of iron. Long-term used of PPIs should be considered in the differential diagnosis of iron deficiency anemia in long-term PPI users [36]. In our study, antacids and other drugs for ulcer/gastro-esophageal reflux diseases posed patients at greater risk of IDA in all countries except Italy. The Italian finding is likely ascribable to the common prophylactic use of PPIs in combination with NSAIDs to reduce the risk of bleeding ulcers in at-risk patients.

We recognize that this study has a major limitation that needs to be commented. It is the lack of information regarding the frequency of consumption of foods with high iron bioavailability (i.e., meat, fish), which, if low, represents another important risk factor. As a matter of fact, iron intake in women of reproductive age appears to be below the recommended level in most countries [37, 38]. A strict vegan or vegetarian diet is a common cause of IDA in developed countries [34]. Furthermore, possible differences in dietary fiber intake by men and women could justify an increased risk of developing IDA and a reduced response to iron supplements in females [39, 40].

Conclusions

The findings of the present study may contribute to increase the awareness on the determinants of IDA in both men and women among primary care physicians. GPs should encourage women of childbearing age to adhere to dietary recommendations regarding iron intake and prescribe regular screening of iron status, particularly for those with heavy and prolonged menstrual bleeding. Furthermore, upper and lower gastrointestinal investigations should be recommended for patients with a confirmed diagnosis of IDA, in the absence of a clinically significant overt non-gastrointestinal bleeding.

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Compliance with ethical standards

Conflict of interest F. Lapi provided consultancies in protocol preparation for epidemiological studies and data analyses for Pierre Fabre.

A. Masotti is a scientific consultant and/or an Advisory Board member for Anemia Alliance. V. Pegoraro and F. Heiman are employed at IQVIA Italy.

O. Brignoli, M. Cancian, C. Cricelli provided clinical consultancies for Pierre Fabre. M. Levi, M. Simonetti and E. Marconi have no conflict of interest to disclose.

Ethics approval and consent to participate This was a retrospective observational study, for which the approval by the Ethics Committee is not required (GU n. 76 March 31, 2008). All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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