Prevalence of Celiac Disease in Patients with Iron Deficiency Anemia – a Systematic Review with Meta-analysis

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Abbreviations: CD, Celiac disease; GFD, Gluten-free diet; IDA, iron-deficiency anemia; VA, Villous atrophy

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ABSTRACT

Title: Prevalence of Celiac Disease in Patients with Iron Deficiency Anemia – a Systematic Review with Meta-analysis

Abstract:

Background & Aims: Anemia is common in patients with celiac disease and a frequent presentation. Guidelines recommend screening iron-deficient patients with anemia for celiac disease. However, the reported prevalence of celiac disease among patients with iron-deficiency anemia (IDA) varies. We performed a systematic review to determine the prevalence of biopsy-verified celiac disease in patients with IDA.

Methods: We performed a systematic review of manuscripts published in PubMed Medline or EMBASE through July 2017 for the term celiac disease combined with anemia or iron-deficiency. We used fixed-effects inverse variance-weighted models to measure the pooled prevalence of celiac disease. Meta-regression was used to assess subgroup heterogeneity.

Results: We identified 18 studies comprising 2998 patients with IDA for inclusion in our analysis. Studies originated from the United Kingdom, United States, Italy, Turkey, Iran, and Israel. The crude unweighted prevalence of celiac disease was 4.8% (n=143). Using a weighted pooled analysis, we demonstrated a prevalence of biopsy-confirmed celiac disease 3.2% (95% CI, 2.6%–3.9%) in patients with IDA. However, heterogeneity was high (I_2 = 67.7%). The prevalence of celiac disease was not significantly higher in studies with a mean participant age older or younger than years, nor in studies with a mixed-sex vs female-predominant (≥60%) population. On meta-regression, year of publication, the proportion of females, age at celiac disease testing, and the prevalence of in the general population were not associated with the prevalence of celiac disease in patients with IDA. In the 8 studies fulfilling all our quality criteria, the pooled prevalence of celiac disease was 5.5% (95% CI, 4.1%–6.9%).

Conclusions: In a systematic review and meta-analysis, we found that approximately 1 in 31 patients with IDA have histologic evidence of celiac disease. This prevalence value justifies the practice of testing patients with IDA for celiac disease.

KEY WORDS: celiac; coeliac; iron deficiency; meta-analysis

INTRODUCTION

Celiac disease (CD) occurs in about 1 in 100 patients in the Western world[1]. It is an immune-mediated disease triggered by the exposure to gluten. While environmental factors are important, recent data highlight the importance of genetic factors[2, 3]. Patients with CD are at increased risk of a number of disorders including lymphoma[4] and autoimmunity[5-7].

Typically, patients with CD demonstrate small intestinal inflammation and villous atrophy [8], and this may result in malabsorption of both calories and micronutrients including iron. Major guidelines for both management of CD [9-11] and iron-deficiency anemia (IDA)[12] point out the association between these two diseases and the need to test patients with unexplained IDA for CD. The highly-cited systematic review by Dube et al in 2005[13] reported a CD prevalence of between 2.9% and 6% in patients with asymptomatic IDA, increasing to 10-15% when patients with IDA and concomitant gastrointestinal symptoms were screened[13]. However, since the publication of the paper by Dube et al[13], a large number of publications on IDA and CD have appeared, with CD prevalence varying between 1.8%[14] and ≥20%[15, 16]. Despite this we are unaware of any up-to-date systematic review aiming to quantitatively combine prevalence data for CD in IDA.

The aim of this study was to investigate the prevalence of CD in patients with IDA, and to determine if CD prevalence differed by IDA subgroups.

METHODS

We used the PRISMA guidelines[17] when planning and executing this paper. We did not publish any pre-specified protocol prior to the study.

Search

The library of Karolinska Institutet searched PubMed and EMBASE for CD (celiac disease or coeliac disease or gluten or non-tropical sprue) combined with "anemia" or "anaemia" or "iron-deficiency", up until May 2016. We then updated our search in July 2017. The search was limited to English-language publications. SM and ML conducted the review of all search hits with assistance from JFL.

After initial review of abstracts and titles, 68 papers were read in detail. Eighteen papers were then included in the final analysis ((Table 1) and Appendix 1 (flowchart for study inclusion)) [14-16, 18-32]. For case-control studies we restricted the extracted information to those patients with IDA.

Celiac disease

Small intestinal biopsy was required for the CD diagnosis. Most biopsy-confirmed patients with available serology data had a positive CD serology but this was not a requirement for diagnosis in our study. Where authors did not report the prevalence of Marsh I-III, we assumed that "biopsy-verified CD" required at least Marsh II-III; where Marsh categories were presented, grade I was not accepted as CD. It is well-known from other studies that the prevalence of CD will increase when Marsh I is accepted as proof of CD or even when biopsy-negative patients are regarded as CD positive. In a sub-analysis, we examined the risk of CD in IDA where it was explicitly stated that Marsh III was required.

Anemia

The definition of anemia varied among the studies, with most studies requiring a hemoglobin (Hb) below 135 g/L in males and 120 in females, but both stricter[20, 27] and looser[22] inclusion criteria were applied (see Table 1 for details on anemia definition in individual studies). A "low Hb cut-off level" for anemia is sometimes relevant (eight of the studies included patients <18 years and some focused on younger children where Hb levels are generally lower than in an adult population and the mean/median ages in the different studies ranged from 5.3 years[15] to 63 years[18]). The majority of studies drew patients from tertiary referral hospitals, although one study looked at screening of blood donors[16], and another at blood specimens obtained from primary care providers[23]. Characteristics of the included studies are given in Table 1, with definitions of iron-deficiency anemia summarized in Appendix 2.

Upper and lower 95% confidence intervals (Cis) and standard errors based on the proportions reported in each paper were calculated.

Data items and risk of bias

Data on the following variables were extracted: (i) year of publication, (ii) age at screening (child<18 years, adult, mixed), (iii) country, and (iv) Marsh stage[33]. The prevalence of CD in the general population differs[34]. For this reason we examined the prevalence of CD in IDA in relationship to the underlying CD prevalence in each country (Italy[35]; US[36]; UK[35]; Iran[37]; Northern Ireland (we used UK data [35]); Israel[38], and Turkey[39]).

We used the Munn, et al critical appraisal tool to grade the quality of our prevalence studies [40] (Appendix 3). Since a funnel plot (eFigure 1) indicated that publication bias could not be ruled out, we carried out a separate analysis restricted to studies with a standard error ≤0.02. While random-effects models tend to

give greater relative weight to imprecise results,[41] especially where heterogeneity is present, we carried out such an analysis restricted also to studies with a standard error ≤0.02.

Summary measures, analysis method and heterogeneity

To calculate a weighted prevalence of CD among patients with IDA we used a fixed-effect model. This prevents smaller and imprecise studies from impacting the summary estimate unduly[42]. We report all estimates with 95% CIs. We also calculated the heterogeneity between studies as I^2. Given the high heterogeneity observed in this study (67.7%) we explored the prevalence of CD in subgroups based on geographic region, study size, age and gender. Studies were grouped according to country of origin, classified as North America, Europe, Turkey, or Asia (Iran and Israel). We defined subgroups of study size (≤199 vs. ≥200) and gender (<60 vs. ≥60% females; the average proportion of females in the 16 studies with available data was 64%). In addition, we carried out four meta-regression analyses to examine the association of CD prevalence in IDA with: (i) study size, (ii) publication year, (iii) proportion of females and (iv) underlying CD prevalence. All these factors can potentially explain the variance of CD prevalence.

Statistics software

Stata 13 was used for all analyses.

RESULTS

Titles and abstracts were read for 2057 papers published up until May 2016 (Flowchart). In July 2017 the search was updated. Since the Karolinska Institutet Library was only able to perform searches for full years, the second search started from Jan 2016 up until July 2017 (167 hits) and therefore overlapped with the first search but yielded no additional relevant papers.

Sixty-eight papers were identified as potentially relevant for our meta-analysis, and were read in detail. Any disagreement between SM and ML was solved through consensus, or through mediation with JFL. Reasons for exclusion of the 50 excluded papers were: unclear inclusion criteria (definition of CD or IDA, n=15[43-57]); looked at refractory IDA or anemia of obscure origin (n=10[58-67]); full-text unavailable or not available in English (n=7[68-74]); high risk of selection bias (n=6[32, 75-79]); looked at iron deficiency without anemia, or anemia not explicitly part of criteria (n=4[80-83]); looked at anemia in general, not IDA (n=3[84-86]); or other reason (small intestinal biopsy not performed (n=1[87]), case report (n=1[88]), examined prevalence of IDA in patients with CD (n=1[89]), not original research (n=1[90]), examined CD in general population not IDA (n=1[91])).

In the quantitative part of the analysis, we hence included 18 relevant studies with 2998 patients with IDA (Table 1) [14-16, 18-32]. Of these 2998 patients, 143 had CD, yielding an unweighted proportion of 4.8%. The median size of the 18 studies was 104 patients. Three studies contributed more than 400 patients each[14, 23, 31]. The median prevalence of CD was 5.0%. Eight studies had taken place in Europe.

Prevalence of CD in anemia

The pooled prevalence of CD in patients with IDA was 3.2% (95% CI=2.6-3.9%)(Figure 1). The heterogeneity was high ($p<0.001$; $I^2 = 67.7\%$). We therefore performed subgroup analyses and meta-regressions to examine this heterogeneity.

The pooled prevalence of CD in IDA was similar in studies that enrolled patients with an average age <18 years at publication (4.0%; 95%CI=2.1-5.8%)[15, 27, 32], as compared to those with a mean age ≥18 years (3.1%; 95%CI=2.5-3.8%)[14, 16, 18-26, 28-31]. Excluding two studies[14, 23] where the mean age was ≥18 but exact values were not possible to extract, we found no relationship between age at testing for CD and prevalence of CD in IDA (Figure 2a, p=0.461, see Figure legend for mean vs. median age).

The CD prevalence in IDA varied by continent (p=0.002 for subgroup analysis). The CD prevalence was 4.6% (95%CI=1.6-7.5%) in North America[25, 26]. The prevalence in Europe (without Turkey)[14, 16, 18, 19, 21-24] was 2.5% (95%=1.7-3.3%), with Turkey[15, 27-29, 32] (4.1%; 95%CI=2.5-5.7%) and other Asian countries [20, 30, 31] (6.4%; 95%CI=4.4-8.3%) showing the highest prevalence.

Two studies did not report the proportion of women[14, 23]. In IDA studies where at least 60% of participants were women[18-20, 22, 24, 25, 28-31] the CD prevalence was 5.5% (95%C=4.2-6.7%), as opposed to 4.2% (95%CI=2.6-5.7) in studies with a more mixed population or a majority of males[15, 16, 21, 26, 27, 32]. The CD prevalence in the two studies without data on sex distribution was 2.0% (95%CI=1.2-2.8%). In a meta-regression, we found no association between the proportion of women and the prevalence of CD in IDA (Figure 2b, p=0.726).

Several studies have reported an increase in the prevalence of CD over time[92, 93]; for this reason we

examined the association between CD prevalence in IDA according to year of publication. A meta-regression could not demonstrate any association with year of publication (Figure 2c, p=0.377). Fourteen studies had included consecutive patients with IDA for CD screening [14, 16, 19-26, 28-30]. Restricting the analysis to these studies, the CD prevalence was 2.9% (95%CI=2.2-3.6%). Seven studies explicitly reported that they required Marsh 3 for the CD diagnosis [15, 16, 21, 23, 28, 31, 32]. The prevalence of CD when requiring Marsh III (3.7%; 95%CI=2.1-3.8%) did not differ from that of other studies (p=0.267) where the prevalence was 2.9% (95%CI=2.3-3.9%). In eleven studies, all patients with positive antibodies had undergone biopsies [14-16, 20, 22, 25, 26, 28-31]. Smaller studies (≤199 participants) showed higher prevalence of CD in IDA (p=0.007)(4.8%; 95%CI=3.5-6.0%) compared to large studies (≥200 participants)(2.7%; 95%CI=2.0-3.5%). We also investigated if the underlying population prevalence of CD was associated with the CD prevalence in patients with IDA. We were unable to demonstrate any such association (Figure 2d; p=0.829). Restricting our dataset to studies with a standard error ≤0.02, the CD prevalence in IDA was 2.8% (95%CI=2.1-3.4%). Using a random-effects model applied to studies with a standard error ≤0.02, the CD prevalence in IDA was 3.3% (95%CI=2.2-4.3%).

Finally, we examined the prevalence of CD in IDA studies[20, 22, 24-26, 28, 30, 31] fulfilling all quality criteria (except the criterion concerning the identification of subpopulations, Appendix 3)[40]. In these eight studies, the CD prevalence was 5.5% (95%CI=4.1-6.9%).

DISCUSSION

In this systematic review with meta-analysis of 2998 individuals, we found that biopsy-proven CD is a relatively frequent finding in patients with IDA, with a prevalence of roughly 1 in 31. The CD prevalence in IDA was not influenced by the proportion of females, the average age, or the baseline prevalence of CD in the populations studied. This is notable given that IDA is more common in certain subgroups, such as premenopausal women. Our findings suggest that IDA is an important risk factor for CD irrespective of patient demographics, and that endoscopic small bowel biopsy should be a part of the diagnostic workup for the condition, even in persons in which other etiologies may be suspected.

To our knowledge, this is the first meta-analysis to report a pooled estimate for the overall prevalence of biopsy-proven CD in patients with IDA. Prior studies have shown highly varying prevalence data for CD in IDA. Only one prior systematic review has addressed the question specifically, examining the CD prevalence in iron-deficient individuals as a subgroup of Western European populations,[13] including 6 of the studies we also reviewed.[18, 20, 22, 24, 94, 95] A meta-analysis was not conducted in this prior review. The prevalence of biopsy-confirmed CD in IDA was reported to be between 2.9% and 6%, which is consistent but slightly higher than our pooled estimate of 3.2% (95% CI=2.6-3.9%). It is possible that restriction to Western European individuals in Dube et al. 2005 may have accounted for the slightly higher prevalence estimates, although we did not identify an association between the baseline risk of CD in the population studied and the prevalence of CD in IDA on meta-regression.

The prevalence of IDA in the overall population varies markedly by sex and age, being most prevalent in females of reproductive age and in infancy in both sexes, likely due to higher iron requirements and poor dietary intake.[96] As CD is a genetic disorder, it might be expected that the prevalence of CD might be lower in studies in which the population was more likely to have other acquired etiologies of IDA, such as in female-predominant cohorts. However, we found no relationship between the average participant age and the prevalence of CD in IDA in our meta-regression (p=0.461), or between the proportion of females in the sample and the prevalence of CD in IDA (p=0.726). We cannot, however rule out that CD may be more common in childhood IDA. The prevalence of CD in the latter population was 4.0% although only based on three studies (27 cases of CD in 446 children with IDA, non-weighted data)[15, 27, 32]. One reason for a higher prevalence of CD in children with IDA could be that other causes of IDA (including gastrointestinal bleeding and cancer) are less frequent in children. While IDA may occur in up to a third of CD patients, CD has also been associated with other causes of anemia such as folate and B12 deficiency as well as anemia of chronic disease[97, 98]. Both malnutrition and ongoing inflammation likely contribute to anemia in CD patients. In CD patients with IDA, a gluten-free diet alone has been shown to induce improvement in ferritin levels and reversal of anemia without iron supplementation, underscoring the link between the two conditions.[99] Our findings do suggest that testing for CD is warranted in all patients with IDA, without exclusion of groups that have a high prevalence of other IDA etiologies.

One explanation for the significant variation in reported CD prevalence may be publication bias. Smaller studies in our meta-analysis yielded higher prevalence figures (pooled weighted estimates of 4.8% as opposed to 2.7%). Considering that small studies are more difficult to publish, publication bias is likely on the basis of our funnel plot . In this analysis, 2 of the 3 smallest studies both reported that 1 in 5 tested patients with IDA had CD, compared to distinctively lower proportions in the largest studies (1 in 37 patients with IDA in studies of ≥200 participants had CD). In order to avoid giving undue weight to smaller studies we used a fixed-effect model. Data from other fields suggest that exclusion of unpublished data (as

in our study) may overestimate the pooled estimates[100]. We approached this potential limitation by restricting our dataset to studies with a standard error ≤0.02 in a subanalysis. This yielded a pooled prevalence of 2.8%, similar to the overall pooled prevalence of our study (3.2%) and in line with estimates from Dube et al[13].

Another kind of bias that may have pushed up the CD prevalence in some earlier screenings studies is if patients with concomitant gastrointestinal symptoms and IDA were more likely to undergo endoscopy as part of their assessment than asymptomatic IDA patients. We excluded studies where IDA patients with symptoms from the digestive tract were tested, and in another attempt to eliminate selection bias specifically examined studies where patients were (explicitly) included consecutively. This did not influence the results notably (2.9%).

Significant heterogeneity was observed which could not be explained by the examined characteristics. We performed meta-regressions to examine the interaction between the age, sex, and prevalence of CD in the general population and the prevalence of CD in IDA, none of which were explanatory. We also restricted our dataset to studies fulfilling all quality criteria, with a slight increase in the pooled CD prevalence (5.5%). We found no association between baseline CD prevalence and CD prevalence in IDA (p=0.829), but when merging data from different countries, the pooled CD prevalence in IDA patients from Asia (Israel and Iran) outside Turkey was 6.4%. We urge caution when interpreting these data, however, since they were based on only three studies[20, 30, 31]. Of note, most previous research on biopsy-verified CD in IDA is limited to few countries (mainly Italy and Turkey), and there are little data from elsewhere. For this meta-analysis we only identified two studies from the US[25, 26].

Strengths of the present study include a large pool of identified studies, drawn from two different databases (PubMed and EMBASE). This large number of studies allowed us to restrict the analysis to histologically-confirmed, rather than serologically-diagnosed CD which is frequently reported but which can overestimate the true prevalence of CD. It also afforded subgroup analysis and meta-regression with examination of important demographic variables as interacting factors.

The observed heterogeneity without explanatory factors is a significant limitation of our study, and impacts on interpretation of the pooled estimate. We had limited data on patients from many parts of the world, including Asia and Africa, and no information on the ethnicity of study participants. While our funnel plot indicated a degree of publication bias that may have overestimated CD prevalence, critical appraisal of study quality suggested that in high-quality studies, more than 1 in 20 IDA patients may have CD. We were unable to examine the linear relationship between hemoglobin levels and prevalence of CD. We also did not have complete antibody data, and were unable to examine the prevalence of biopsy-negative CD in IDA. Recently the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) developed a non-biopsy pathway to CD diagnosis in patients with repeatedly positive celiac-specific serology, positive HLA-DQ2/DQ8 and symptoms consistent with CD[101], however within these guidelines patients evaluated with anemia would require biopsy.

In conclusion, this meta-analysis found that approximately 1 in 31 patients with IDA had biopsy-verified CD, and that the prevalence of CD in IDA did not vary by the average age, proportion of females, or baseline CD

prevalence. While no major gastroenterology society advocates for screening the general population for CD, there is a consensus that testing should be performed in patients with IDA [9, 10, 12]. Our findings strongly support this recommendation, and further highlight the importance of endoscopy with histologic evaluation for CD in the diagnostic workup for patients with this condition, even in populations where other etiologies of IDA are common.

FIGURE LEGENDS

Figure 1. Prevalence of biopsy-verified celiac disease in iron-deficiency anemia

Figure 2a. Meta-regression: Relationship between age at CD investigation and CD prevalence in iron-deficiency anemia.

Legend: Y-axis: Percentage (%) of celiac disease among patients with iron-deficiency anemia among. X-axis: Age in years when tested for CD (p=0.461). Age represents median age for the following three studies[21, 22, 24] and otherwise mean age.

Figure 2b. Meta-regression: Relationship between proportion of women and CD prevalence in iron-deficiency anemia.

Legend: Y-axis: Percentage (%) of celiac disease among study participants with iron-deficiency anemia.X-axis: Percentage of females in each individual study (p=0.726).

Figure 2c. Meta-regression: Relationship between year of publication and CD prevalence in iron-deficiency anemia.

Legend: Y-axis: Percentage (%) of celiac disease among study participants with iron-deficiency anemia. X-axis: Year of study publication (p=0.377).

Figure 2d. Meta-regression: Relationship between CD prevalence in the general population and CD prevalence in iron-deficiency anemia.

Legend: Y-axis: Percentage (%) of celiac disease among study participants with iron-deficiency anemia. X-axis: Prevalence of CD in the general population (p=0.829).

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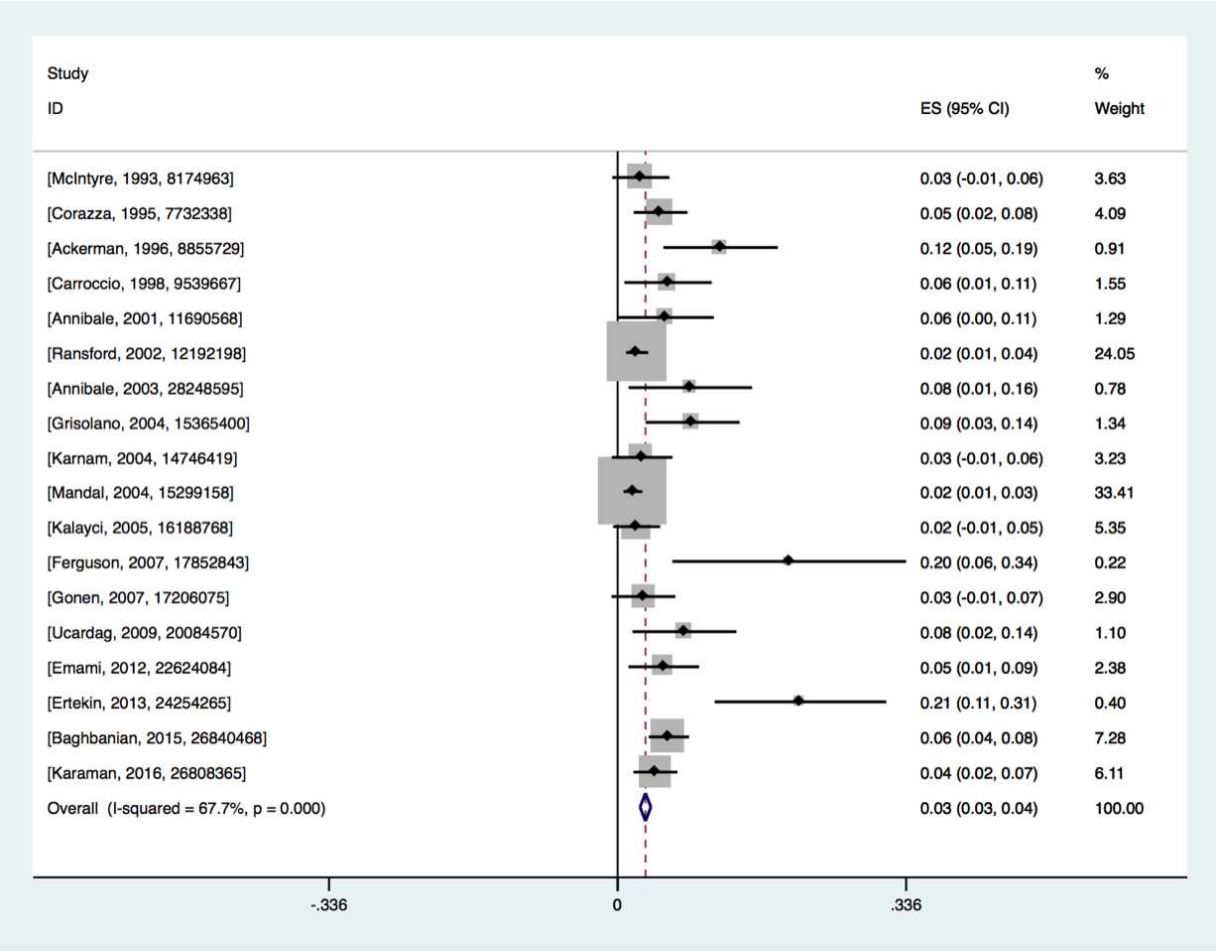
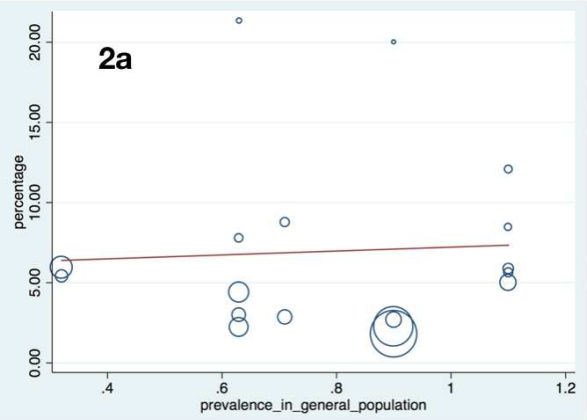
Table 1. Papers included in the systematic review on celiac disease prevalence in iron-deficiency anemia

Study and Year	Country	Percentage	Celiac patients, N	Patients with IDA, N
McIntyre, 1993 [18]	UK	2.7	3	111
Corazza, 1995 [19]	Italy	5.0	10	200
Ackerman, 1996 [20]	Israel	12.1	11	91
Carroccio, 1998 [21]	Italy	5.9	5	85
Annibale, 2001 [22]	Italy	5.6	4	71
Ransford, 2002 [23]	UK	2.3	11	484
Annibale, 2003 [24]	Italy	8.5	5	59
Mandal, 2004 [14]	UK	1.8	9	504
Karnam, 2004 [26]	USA	2.9	3	105
Grisolano, 2004 [25]	USA	8.7	9	103
Kalayci, 2005 [27]	Turkey	2.2	3	135
Ferguson, 2007 [16]	Northern Ireland	20.0	6	30
Gonen, 2007 [28]	Turkey	3.0	3	100
Ucardag, 2009 [29]	Turkey	7.8	6	77
Emami, 2012 [30]	Iran	5.4	7	130
Ertekin, 2013 [15]	Turkey	21.3	13	61
Baghbanian, 2015 [31]	Iran	6.0	24	402
Karaman, 2016 [32]	Turkey	4.4	11	250

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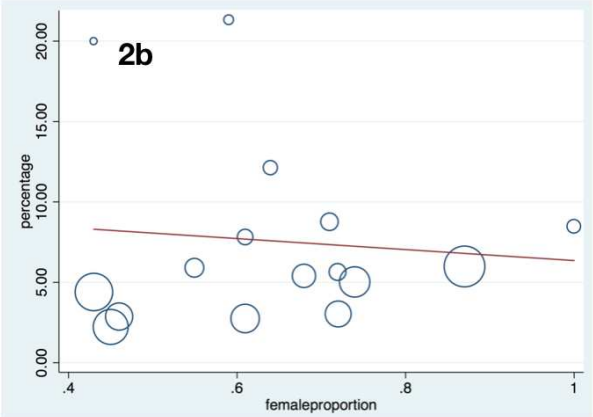
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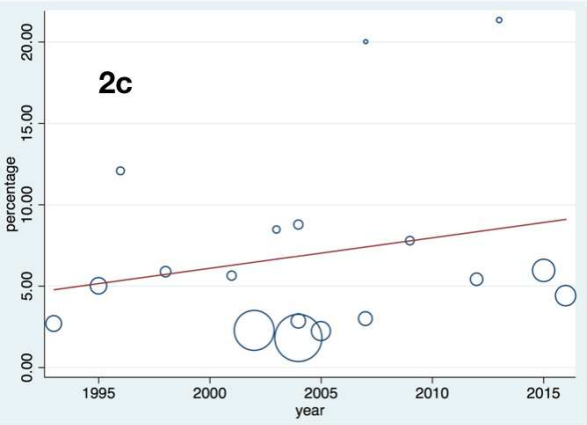
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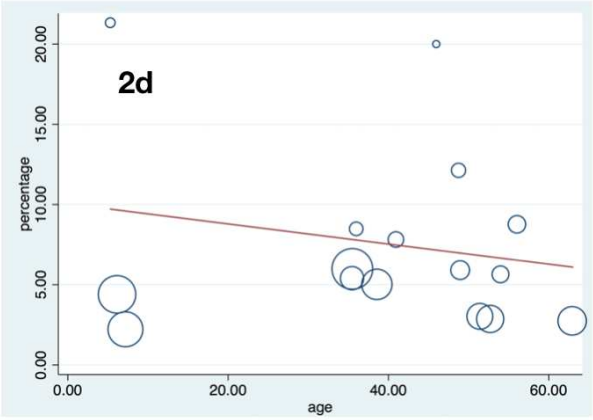
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Documentation of search strategies
University Library search consultation group

Date: maj 2016

Topic/research question: Bland patienter med järnbristanemi: hur vanligt är celiaki?

Name of researcher(s): Jonas Ludvigsson, MEB

Librarian(s): Carl Gornitzki & Susanne Gustafsson

Databases:

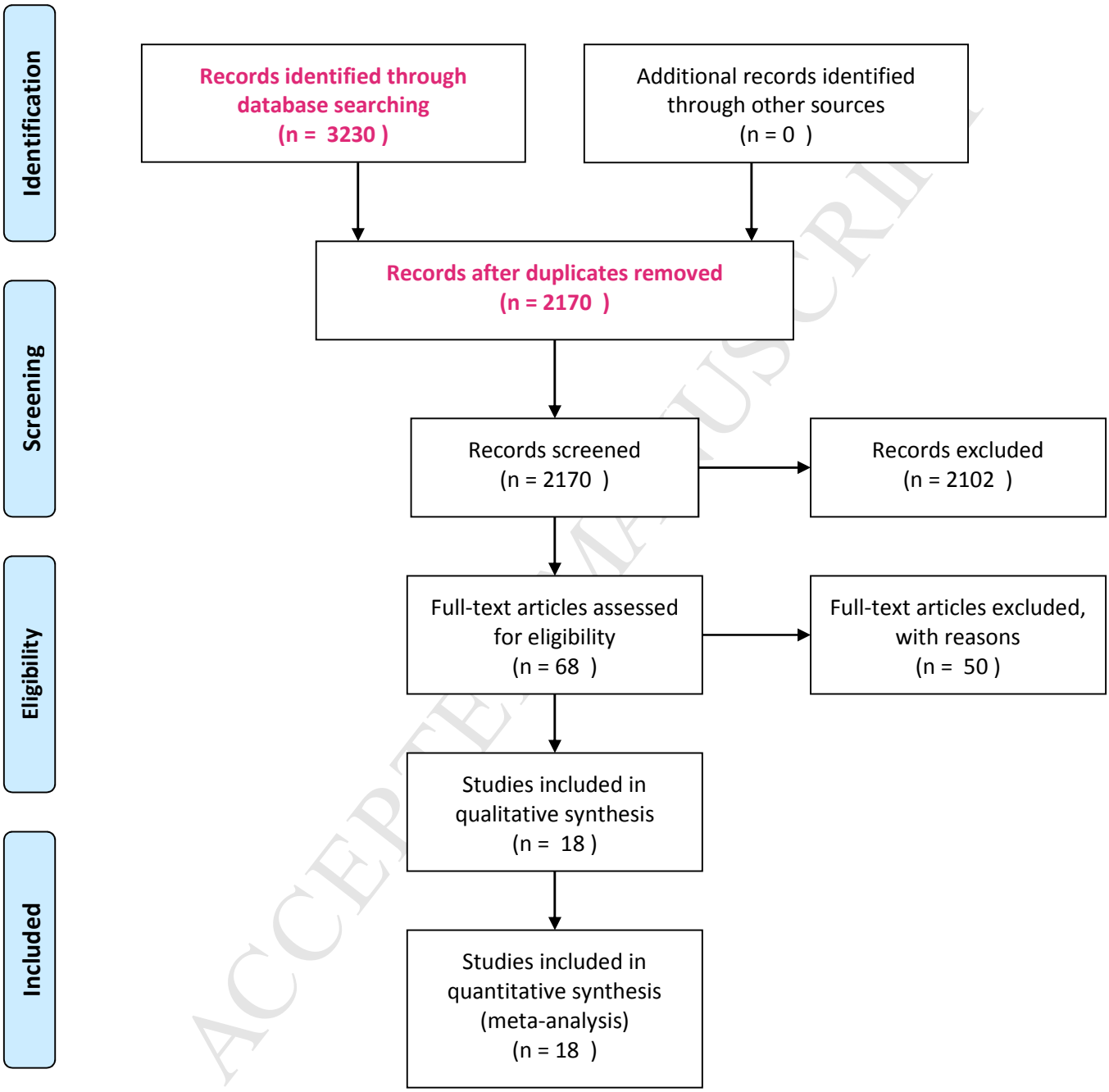
1. Medline (Ovid)
2. Embase (embase.com)

Total number of hits:

- Before deduplication: 3,230
- After deduplication: 2,170

Comments:

PRISMA 2009 Flow Diagram[1]



[1] From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

1. Medline (Ovid)

Date of Search: 2016-05-31 Number of hits: 1,393 Comments:	Field labels:

1. exp Celiac Disease/

2. exp Glutens/

3. (celiac* or celiak* or coeliac* or coeliak* or gluten or non-tropical sprue or nontropical sprue).ti,ab,kf.

4. 1 or 2 or 3

5. Anemia, Iron-Deficiency/

6. (anemi* or anaemi* or iron).ti,ab,kf.

7. 5 or 6

8. 4 and 7

9. remove duplicates from 8

2. Embase (embase.com)

Date of Search: 2016-05-31 Number of hits: 1,837 Comments:	Field labels:

No.	Query	Results
#11	#9 AND ('**article**'/it OR '**article in press**'/it OR '**editorial**'/it OR '**erratum**'/it OR '**letter**'/it OR '**note**'/it OR '**review**'/it OR '**short survey**'/it)	2,690
#9	#4 AND #8	324,467
#8	#5 OR #6 OR #7	317,600
#7	**anemi***:ab,ti OR **anaemi***:ab,ti OR **iron**:ab,ti	12,307
#6	'**iron deficiency**'/exp	22,607
#5	'**iron deficiency anemia**'/exp	42,347
#4	#1 OR #2 OR #3	35,206
#3	**celiac***:ab,ti OR **celiak***:ab,ti OR **coeliac***:ab,ti OR **coeliak***:ab,ti OR **gluten**:ab,ti OR '**non-tropical sprue**':ab,ti OR '**nontropical sprue**':ab,ti	7,117
#2	'**gluten**'/exp	26,266
#1	'**celiac disease**'/exp	

Supplementary Table 1. Criteria for Definition of Iron-Deficiency Anemia for Included Studies

Study and Year	Pts with IDA, N	Setting	IDA definition
McIntyre, 1993 [17]	111	Tertiary	Hb<13/11.5 & (ferritin<15 | iron<11 μmol/L & IBC>72)
Corazza, 1995 [18]	200	Tertiary	Hb<7.4/6.8 mmol/L & attending hematology clinic for IDA
Ackerman, 1996 [19]	91	Tertiary	Hb<12.5/10.6 & MCV≤70 | iron ≤ 65 + tsat ≤15 | BMBx
Carroccio, 1998 [20]	85	Tertiary	Hb<12.5/11.5 & iron<45 & ferritin<15
Annibale, 2001 [21]	71	Tertiary	Hb<14/12 & MCV<80 fL & ferritin<30 μg/L
Ransford, 2002 [22]	484	Primary	Hb<11.5/11 & hypochromia & microcytosis
Annibale, 2003 [23]	59	Tertiary	Hb<12 & ferritin <30 μg/L & MCV<80
Mandal, 2004 [13]	504	Tertiary	Hb<11.5/12.5 & microcytosis & low ferritin
Karnam, 2004 [25]	105	Tertiary	Hb<14/12 & (ferritin<25 | BMBx)
Grisolano, 2004 [24]	103	Tertiary	Hb<13.5/12 & (ferritin<15 | tsat < 8%)
Kalayci, 2005 [26]	135	Tertiary	Hb<10.5 & MCV<75 fL & RDW>14.2 & iron<6.9 μmol/L & tsat<10.9% & ferritin<14.7 μg/L
Ferguson, 2007 [15]	30	Screening	Hb<13.5/12.5 & low ferritin
Gonen, 2007 [27]	100	Tertiary	Hb<13.5/12 & (ferritin<12 | tsat<15%)
Ucardag, 2009 [28]	77	Tertiary	Hb<13.5/12 & ferritin<15 & tsat<15% & MCV<80
Emami, 2012 [29]	130	Tertiary	Hb<14/12 & ferritin<15
Ertekin, 2013 [14]	61	Tertiary	Hb & ferritin & iron & MCV low for age
Baghbanian, 2015 [30]	402	Tertiary	Hb<13.5/12 & ferritin<30 & tsat<20% & MCV<80
Karaman, 2016 [31]	250	Tertiary	Hb<11 & ferritin<12

Criteria are combined using AND (&), OR (|), or a combination thereof. Hemoglobin cutoffs for men and women, where specified individually, are noted for males / females. Abbreviations and units (unless otherwise specified): Hb, hemoglobin, mg/dL; serum ferritin μg/L; MCV, mean corpuscular volume, fL; serum iron, μg/dL; IBC, iron binding capacity, %; tsat, transferring saturation, %; BMBx, bone marrow biopsy demonstrating low iron stores.

Criterion	McIntyre, 1993	Corazza, 1995	Ackerman, 1996	Carroccio, 1998	Annibale, 2001	Ransford, 2002	Annibale, 2003	Mandal, 2004	Karnam, 2004	Grisolano, 20	Kalayci, 2005	Ferguson, 20	Gonen, 2007	Ucardag, 200	Emami, 2012	Ertekin, 2013	Baghbanian, 2	Karaman, 201
Was the sample representative of the target population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the study participants recruited in an appropriate way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the sample size adequate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Was the data analysis conducted with sufficient coverage of the identified sample	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were objective standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
Was the condition measured reliably?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was there appropriate statistical analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were all important confounding factors/subgroups/differences identified and acc	U	U	Y	N	Y	U	Y	Y	Y	Y	N	U	Y	U	Y	U	Y	U
Were subpopulations identified using objective criteria?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Apndx
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 & app.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	App
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	App
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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