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## Trends in celiac disease research

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## ABSTRACT

**Background:** To improve diagnosis and treatment of celiac disease (CD), research efforts are being made in many different areas. However, the focus, trend, and direction of such efforts require clarity, so that future efforts and directions can be appropriately planned.

**Method:** In this study, MEDLINE was used to search for trends in CD research. The keyword 'celiac disease' and its variants were searched in tandem with keywords commonly associated with CD. This search was done for each year from 1960 to 2013. Year of first instance of the associated keyword, linear regression coefficient, and trend in terms of the slope of the regression line were tabulated. For perspective, the same keywords were searched in tandem with 'inflammatory bowel disease' (IBD).

**Results:** CD appeared in the medical literature prior to 1960, and IBD first appeared in 1964. However, IBD overtook CD in terms of the number of research papers published per year, beginning in 1988. Keywords with strong positive trends ( $r^2 > 0.7$ ) in association with CD were: 'diagnosis', 'gluten', 'serology', 'autoimmune', 'treatment', 'gluten-free diet', 'endoscopy', 'villous atrophy', 'wasting', 'inflammation', and 'microbiome'. The keyword 'malabsorption' had the sole strong negative trend in association with CD. Keywords with strong positive trends ( $r^2 > 0.7$ ) in association with IBD also had strong positive association with CD: 'autoimmune', 'treatment', 'inflammation', and 'microbiome'.

**Conclusions:** The MEDLINE search approach is helpful to show first instance, association, and trend of keywords that are affiliated with CD in published biomedical research, and to compare CD research trends with those of other diseases.

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## 1. Introduction

The diagnosis and management of celiac disease (CD) is a subject of intense study, with recent guidelines appearing in the medical literature [1]. The research in CD is diverse, involving pathogenesis, epidemiology, clinical manifestations, diagnosis and therapy. Characterization of CD is potentially extensive, as clinically the manifestations are diverse [2]. The quantitation of CD research data is desirable, including the potential for validation of a clinical prediction score [3]. However, it is difficult to assess severity of disease status because there is no severity index [4]. Population-based studies are useful in determining the risk of disease complications [5,6]. Clinical aspects of CD in areas of the world where it has not received great attention previously, including the Asia-Pacific region, is increasing [7]. In previous work, it has been shown that CD studies are increasingly common in the medical research literature [8]. The sharpest increase was found to have occurred since 1995. In terms of the global research

effort for CD, countries including Italy, USA, and UK have the greatest volume of published studies [8]. Generally, the CD studies published in the medical research literature are of high quality and complexity [9]. Although CD research is gaining attention, research directions tend to be unfocused. Hence, it would be helpful to characterize trends in ongoing CD research so that areas of foci can be identified for future research.

To improve diagnosis and treatment of CD, research efforts are being made in many different areas. However, it is not entirely clear where efforts are being made and therefore, what further efforts and directions are needed for future work. In this study, we sought to determine the trends in CD research in terms of the prevalence of readily identifiable keywords in the CD literature. As a comparison, we determined the association of these same keywords with inflammatory bowel disease (IBD), since IBD is similar to CD in its clinical complexity and management difficulties.

## 2. Method

To search for trends in CD research, the MEDLINE database was used. The MEDLINE database indexes the instance of a searched

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word in the title, abstract, and list of keywords of a paper. The search tool can be used to search during single years, which is how it was utilized for this study. CD was searched using the terms shown in the top row in Table 1. The keyword 'celiac disease', and variants 'coeliac disease' and 'celiac sprue' were all included in the search. Also, 32 associated keywords and their similar terms (variants) were searched in association with CD (Table 1). The list was developed from a Google query of the 32 most common terms associated with celiac disease, and are listed in alphabetical order. The Google query was used for this purpose due to ease of procurement. Medical Subject Headings (MeSH) terms were not used, as this is a controlled vocabulary that may not reflect all of the terms affiliated with celiac disease. Although 'autism' and 'Down syndrome' are different disorders, they were grouped together, as they are often associated with CD.

To search for a keyword in association with CD, we used for example, the following syntax –

(*'celiac disease' or 'coeliac disease' or 'celiac sprue'*)  
and (*videocapsule or 'video capsule'*) (1)

When a keyword consisted of more than one word, it was bracketed by quotation marks in the MEDLINE form. The logical 'or' was used to combine the occurrence of several variants of a keyword. Thus for the example above,

(*'celiac disease' or 'coeliac disease' or 'celiac sprue'*) (2)

was used to determine any and all research papers containing one or more keywords 'celiac disease', 'coeliac disease', 'celiac sprue' which are three common ways to refer to CD.

Similarly, (*videocapsule or 'video capsule'*)

(*videocapsule or | video capsule|*) (3)

are two common ways to refer to this keyword. Query (1) is formed by adding a logical 'and' between queries (2) and (3), to identify research papers in which at least one of the three keywords referring to CD and at least one of the two keywords referring to 'videocapsule' appeared together.

The keywords for CD were searched using the logical 'and' function with each of the associated keywords, for each year from 1960 to 2013. The year 1960 was used as a starting point because at that time, it became widely promulgated that patients improved on a gluten-free diet, an important aspect in disease treatment [10]. Linear regression analysis was used to show trends in association. A trend was defined as a major upward or downward swing in the year-by-year query graph, excluding small deflections, with the endpoint being defined as 2013, the last year in which complete publishing information was available at the time of this study. The starting point of the regression line was defined to be the year that the upward or downward swing began. The starting point year, the slope of the regression line, and the correlation coefficient  $r^2$  were tabulated. The linear regression was constructed using SigmaPlot (Systat Software, Inc., San Jose, CA, 2005).

The keywords in association with CD were normalized with respect to the number of CD papers published in the medical literature during each year, i.e., for any given year,

*Normalized\_association*

$$= \frac{\text{Number of studies in which affiliated keyword appeared with CD}}{\text{Total number of studies in the literature with CD}}$$

which was calculated and then graphed. The above fraction ranges from 0 to 1, and can be expressed as a percentage by multiplying by 100%. Affiliated keywords were categorized using decade ranges according to whether their prevalence with CD in the

**Table 1**  
List of search terms.

Keyword	Variants
Celiac disease	Celiac sprue, celiac disease
Autism	Down syndrome
Autoimmune	Autoimmunity, immune
Biopsy	
Diagnosis	Diagnostic, diagnostics, screening
Dental	Enamel
Dermatitis	Dermatologic, herpetiformis, rash, skin
Diarrhea	
DQ2	DQ8, HLA
Endoscopy	
Fatigue	Apathy, inactivity, lethargy, tiredness, torpidity, torpor, weariness
Female	
Gluten	Barley, gliadin, wheat, rye
Gluten-free diet	Gluten free diet
Heart	Cardiac
Infertility	Fertile, fertility, infertile, pregnancy, pregnant
Inflammation	
Lymphocytic Colitis	
Malabsorption	
Male	
Malignancy	Cancer, lymphoma, neoplasia
Malnourishment	Malnutrition, nourishment, nutrient, nutrients, nutrition
microbiome	
Microscopic Colitis	
Motility	
Neurology	EEG, electroencephalogram, neurologic, neuropathy, seizure, seizures
Osteoporosis	Bone, fracture
Psychiatric	Depression, obsessive compulsive disorder
Serology	Antibodies, IgA, IgG, serological, transglutaminase
Treatment	Therapeutic, therapies, therapy
Videocapsule	Video capsule
Villous Atrophy	
Wasting	Growth, stature, stunted, weight loss

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