

# COELIAC DISEASE IN CENTRAL AND SOUTH AMERICA: time for a concerted approach to its epidemiology

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**ABSTRACT** - Central and South America offer an opportunity to resolve some of the current controversies that surround the epidemiology of celiac disease. Through a concerted action which brings together clinicians, researchers and patients there is an opportunity to establish robust data sets which will allow detailed analysis of environmental and genetic factors. In this review available data from the continent together with data from Spain and Italy are drawn together to give a current picture in the hope that it will stimulate further research.

**HEADINGS** - Celiac disease. Epidemiology. Transients and migrants. Religion and Medicine. Blood donors.

## INTRODUCTION

Traditionally coeliac disease has been said to be particularly common in Ireland. As a result it has been regarded as a disease associated with Celtic communities. This belief arose largely out of work published in the British Medical Journal almost 50 years ago<sup>(29)</sup>. At that time the prevalence of coeliac disease was almost 3 cases/1000 population. Such figures appeared extra-ordinary when most diagnoses were in children and required the use of Crosby capsules or similar unpredictable technology. There were no serological tests available and the concept of a specific and sensitive diagnostic test was 40 years in the future. However, by the 21st century comparable or greater prevalences were being reported from across the world, including Spain and Italy. The main differences between the two periods were the emergence of community screening and the easier investigation of patients with symptoms that could be linked to coeliac disease. At the beginning of the millennium Mandal and Mayberry suggested that based on a study from Brasilia which screened blood donors for potential coeliac disease the condition was likely to be significantly commoner in South America than had been thought previously<sup>(12, 22)</sup>. Similar subsequent studies in Brazil have given prevalences of between 2.4 and 4.7/1000 (Table 1). However, they are based on small numbers

of cases and blood donors are not truly representative of the populations from which they are drawn. However, such studies raise interesting questions as to how common coeliac disease really is in Central and South America. Are there variations between communities of different genetic backgrounds and perhaps, above all, is the region about to experience the explosion in incidence which is being described in other parts of the world?

Central and South America present a unique opportunity to investigate changes in the incidence of a number of conditions such as inflammatory bowel disease, coeliac disease and colorectal cancer. Wide area studies crossing national boundaries provide an opportunity to ensure uniform standards of diagnosis and common techniques for case detection. Such an approach was adopted in the European Union with its Concerted Actions in the late twentieth century. In addition to specific benefits in understanding of disease processes it also brought together clinicians and scientists from a wide range of backgrounds ensuring a critical mass of experienced researchers. These actions acted as a stimulus to original research and encouraged networks which have continued to the present day. If such an approach could be adopted in Central and South America its benefits for patients, clinicians and researchers are likely to be untold.

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TABLE 1. Incidence and prevalence of coeliac disease in South America and Certain European Communities

	Years	No. of cases	Incidence cases/10 <sup>3</sup> /year	Prevalence cases/10 <sup>3</sup>
<b>UK &amp; Ireland</b>				
Cardiff <sup>(18, 19)</sup>	1981 - 1995	137	3.1	
East Dorset <sup>(11)</sup>	1993 - 2002	159	8.7	
Leicester <sup>(40)</sup>	1975 - 1989			
i. Europeans		86	2.5	
ii. Punjabis		20	6.9	
West of Ireland <sup>(29)</sup>	1962 - 1973	110		3
<b>Italy</b>				
Naples <sup>(6)</sup>	2012	1453		2.6
Sardinia <sup>(39)</sup>	2009	124		1.2
Carcare <sup>(25)</sup>	2006	10		10
Brescia <sup>(20)</sup>	1984 - 2000	929	7	
	2000 - 2003	508	12	
Four areas study <sup>(9)</sup>	1990 - 1991	478	2.5	
North East Blood transfusion centres <sup>(42)</sup>	1999	10		2.5
Young people				
Trieste (children) <sup>(41)</sup>	1999 - 2000	35		11
Brescia <sup>(20)</sup>	1984 - 2000	?	4	
	2000 - 2003	?	5	
Padua <sup>(17)</sup>	1997	?		2.6
Lucca <sup>(26)</sup>	1996	2		1.8
Ancona <sup>(7)</sup>	1995	23		4.6
Turin <sup>(3)</sup>	1975 1989	494	3.4	11.3
South Tirol <sup>(34)</sup>	1973 - 1982			
German		45	10.5	105
Italian		5	3.3	33
<b>Spain</b>				
Madrid <sup>(13)</sup>	2007	10		6.3
Asturias <sup>(38)</sup>	2000	3		2.6
Young people				
Baracaldo <sup>(44)</sup>	1998 - 1999	7		8.5
Cáceres <sup>(21)</sup>	1981 - 1990		6.9	
<b>Portugal (young people)</b>				
Braga <sup>(4)</sup>	2006	3		7.5
<b>Brazil</b>				
Pernambuco <sup>(28)</sup>	2012	8		11.7
North east (African origins) <sup>(2)</sup>	2012	0		0
Mangueirinha (Kaingang & Guarani) <sup>(43)</sup>	2010	0		0
Sao Paulo <sup>(1, 30)</sup>	2012	14		3.5
	2007	14		4.7
Curitiba <sup>(33)</sup>	2006	5		2.4
Ribeirão Preto <sup>(24)</sup>	2006	11		3.7
Brasília <sup>(12)</sup>	2000	2		1.5
<b>Argentina</b>				
Buenos Aires <sup>(5)</sup>	1998 - 2006	283		2.2
La Plata <sup>(14)</sup>	1998 - 2000	11		6
Young people				
Five areas study <sup>(27)</sup>	2008 - 2009	21		12.7

### Case definition and case finding

Central to all robust epidemiological studies is the need for a standardised definition of what constitutes the condition under investigation and so to distinguish case from non-case. When different areas are being compared it is important that comparable methods of candidate case detection are used and preferably there is a system of capture and recapture of cases, which employs different sources. This will allow a more comprehensive study with fewer cases being omitted from the analysis.

In the case of coeliac disease this is complicated by the role of antibodies in case identification, the analysis of histology and the grading of villous atrophy together with the growing controversy surrounding the concept of wheat intolerance. However, as with inflammatory bowel disease, Central and South America could answer many of the questions that now surround the changing epidemiology of coeliac disease. Through a Concerted Action which employs uniform case definitions and modes of case detection it would be possible to produce an international database through which many of these issues could be addressed. In the case of coeliac disease there would be an argument for having centres in Spain, Portugal, Italy and Ireland. The choice of these states would include many with genetic links to the populations of the continent while Ireland would act as a marker country which traditionally had a high prevalence of the condition.

Screening communities with serological tests in Central and South America has happened in Mexico<sup>(36)</sup> and Brazil<sup>(1, 24, 30, 33)</sup>. However, it is only in Brazil that people with positive tests have been invited to have duodenal/jejunal biopsies to confirm the diagnosis through histology. This remains the gold standard of diagnosis and in any large scale epidemiological study histological confirmation will be essential for the data to be robust. The ideal community to be screened should be representative of society in general. However, to encourage the healthy population to participate in screening programs requires substantial funding and needs to confer specific and easily understood benefits on that community. In Argentina there is a wish to drive forward such an approach so that patients can be identified and appropriately counselled on their diet<sup>(8)</sup>. Where this is not possible other selected communities can be considered. One such group would be where there is a higher than normal prevalence of coeliac disease e.g. amongst diabetics. Here diagnosis will have a clear and readily recognised benefit for patients. In Mexico a high risk community of diabetic patients from the Mestizo community were chosen for a serological study<sup>(37)</sup>. Although a prevalence as high as 59/1000 was suggested, such data do not apply to the population in general and this is its major limitation. The significance of this limitation could be reduced through comparison of comparable patient groups across the continent. The screening of volunteers who come forward as blood donors would be more representative of the population in general. Forty four per cent of blood donors in Brazil donate for altruistic reasons and 42% in response to direct appeals<sup>(15, 16)</sup>. Although such motives are reassuring it does not mean that donors are a representative cross-section

of Brazilian society. However, it is likely that in many communities blood donors will have similarities and screening through blood tests may be more acceptable.

Other potential groups in whom serological screening could be considered are military recruits. Such an approach has been used in inflammatory bowel disease and can overcome some of the problems associated with case finding and the use of capture-recapture techniques<sup>(10)</sup>.

### Incidence versus prevalence

Screening of communities will give prevalence data which will include asymptomatic individuals who comprise the hidden part of the iceberg which makes up the totality of the disease. In Central and South America the magnitude of this hidden component is essential to our understanding as to whether there is any significant difference in the overall prevalence when compared with data from Europe. For this reason alone, it is important that screening of communities is paralleled by incidence studies which look at symptomatic patients in the same community.

### Ethnic groups

Within Spanish American society there are several interesting conjunctions with parent communities where the prevalence of celiac disease is high. These include:

Punjabi Mexicans who are predominantly to be found in Yuba City and Southern California's Imperial Valley. Migrant Punjabis have been shown to have a significantly higher incidence of the disease than the host community in Europe<sup>(40)</sup>.

Welsh people in Patagonia, Argentina. A study using the Welsh language periodical *Ninnau* was carried out amongst Welsh migrants in the USA<sup>(35)</sup>. Although the Welsh speaking population is small there is a place for what might be called a "boutique" study.

German Mennonites in Argentina, Brazil, Bolivia, Belize and Paraguay of whom some believe there may be as many as 1 million.

On a wider less defined scale there were significant Italian and Irish migrations to Brazil, Argentina and Colombia. However, these communities are now more diffuse than the above groups.

Attempts have been made to assess the prevalence of coeliac disease amongst the Kaingang & Guarani and those of African descent in Brazil and the Mestizo in Mexico<sup>(2, 43, 37)</sup>. However, no cases were identified in Brazil and the study in Mexico did not progress to small bowel biopsies. Although these communities may not be genetically predisposed to coeliac disease significantly larger studies are needed.

### Religious groups

Although not based on ethnicity a separate approach would be to seek help from other religious groups with well defined memberships and relatively centralised records<sup>(23)</sup>. The Church of Latter Day Saints or Mormons and Adventist churches have taken part in a number of studies of cancer risk as well as of the prevalence of inflammatory bowel

disease<sup>(31, 32)</sup>. Commitment from the churches' national leadership to epidemiology studies can ensure local co-operation and comprehensive coverage. Limitations again are similar to those seen when blood donors are studied. Adventist and Mormons are not representative of the communities from which they are drawn. However, such studies across national boundaries would allow comparisons between different states as it is likely that what draws someone to these denominations is generally similar throughout the continent. There are about 2 million Spanish speaking Mormons and 1.5 million Portuguese speakers. In the case of Adventists, the figures are approaching 1.5 million for both groups (Table 2). Such substantial communities could provide robust data on the disease's prevalence and allow direct comparisons between various regions.

**TABLE 2.** Estimates of Mormon and Adventist church membership in Central and South America

Country	Mormon membership	Adventist membership	Population
Venezuela	161,309	134,302	30,206,307
Uruguay	101,449	7,076	3,324,460
Peru	543,869	664,016	30,814,175
Paraguay	86,790	12,453	6,783,374
Ecuador	220,247	52,524	15,783,300
Colombia	185,891	221,927	47,681,000
Chile	583,359	117,730	17,773,000
Brazil	1,250,073	1,330,000	202,857,000
Bolivia	188,261	143,029	10,461,053
Argentina	421,971	88,956	42,610,981

These data are drawn from a number of sources on the internet

## CONCLUSION

The creation of a network of researchers across South and Central America is a real possibility. There already exist registers of patients with coeliac disease in a number of countries together with self-help groups. Argentina has committed itself to a national drive to identify patients throughout the country. For research studies registration on computer data bases and sharing of data can be restricted by legislation related to privacy and by concerns about the availability of such data outside national boundaries. However, such difficulties can be overcome and by pooling data the results become more robust and such studies will help clarify whether the apparent increase in incidence of coeliac disease is due to a reduction in the amount of undiagnosed cases rather than a genuine change in disease frequency. It will also clarify which environmental factors are converting antibody positive people into symptomatic patients.

Patient self help groups can provide useful support through political lobbying. Such groups already exist in Brazil, Argentina, Uruguay, Chile, Mexico and Panama. The development of research networks needs to include patient groups who can help identify barriers to case detection. In addition, the facilitation of meetings and support of a research program with common protocols and clearly defined endpoints will require funding. In the case of coeliac disease pharma companies have a limited role but may still provide seeding funds to, at least, initiate an international meeting of clinicians in Central and South America. From such a meeting a "concerted action" on coeliac disease can happen.

## Authors' contributions

Farrukh A and Mayberry J contributed equally to the concept of the review, identification of appropriate references and production of the final text.

Farrukh A, Mayberry JF. A doença celiaca na América Central e do Sul: tempo para uma abordagem conjunta sobre sua epidemiologia. *Arq Gastroenterol.* 2015,52(2):129-33.

**RESUMO** - A América Central e do Sul oferecem uma oportunidade de resolver algumas das atuais controvérsias que cercam a epidemiologia da doença celiaca. Através de uma ação conjunta reunindo médicos, pesquisadores e pacientes, há a oportunidade para estabelecer conjuntos de dados robustos que permitirão uma análise detalhada dos fatores ambientais e genéticos envolvidos. Nesta revisão, os dados disponíveis a partir do continente, juntamente os da Espanha e da Itália, são descritos em conjunto para dar uma imagem atual, na esperança de que se estimulem novas pesquisas.

**DESCRITORES** - Doença celiaca. Epidemiologia. Migrantes. Religião e Medicina. Doadores de sangue.

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