



# Global perspective of coeliac disease with a focus on Asia

**Coeliac disease: Past, Present, Future;  
50<sup>th</sup> years celebration  
Coeliac UK**

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# Coeliac disease: Then

- Initially thought to be limited to the Western Europe
- Seen only/mainly by pediatricians
- Making a diagnosis was TEDIOUS

While the curative treatment was known, but making the diagnosis was a challenge

# 1980 - 2000

- Change in the diagnostic criteria: three biopsies to one biopsy
- Advent of serology
- Wider recognition: Pediatrician to Adults

Recognised in countries having Caucasian population

# Coeliac disease: Now

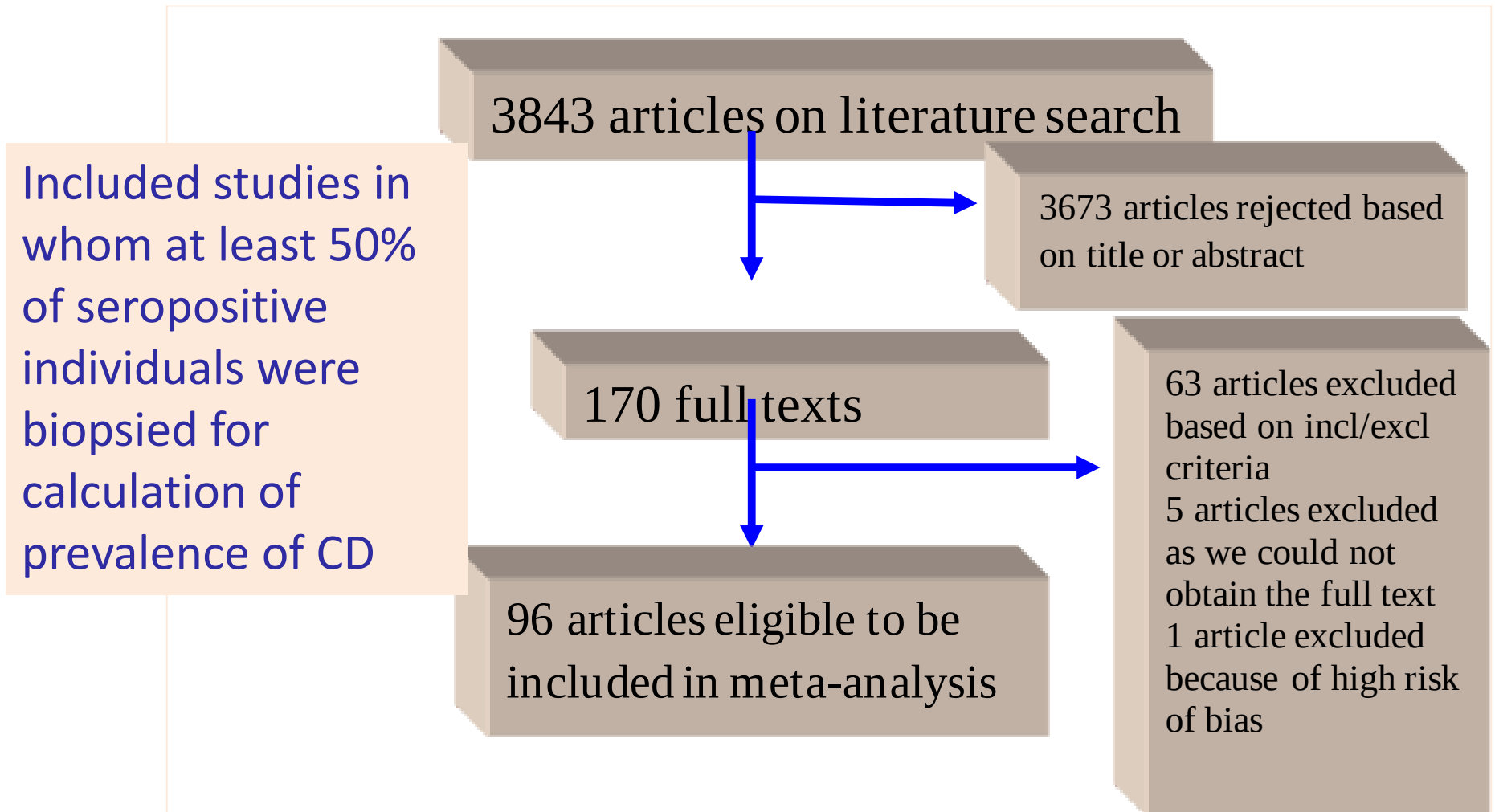
## Changing epidemiology globally

Clinical Gastroenterology and Hepatology 2017;■:■-■

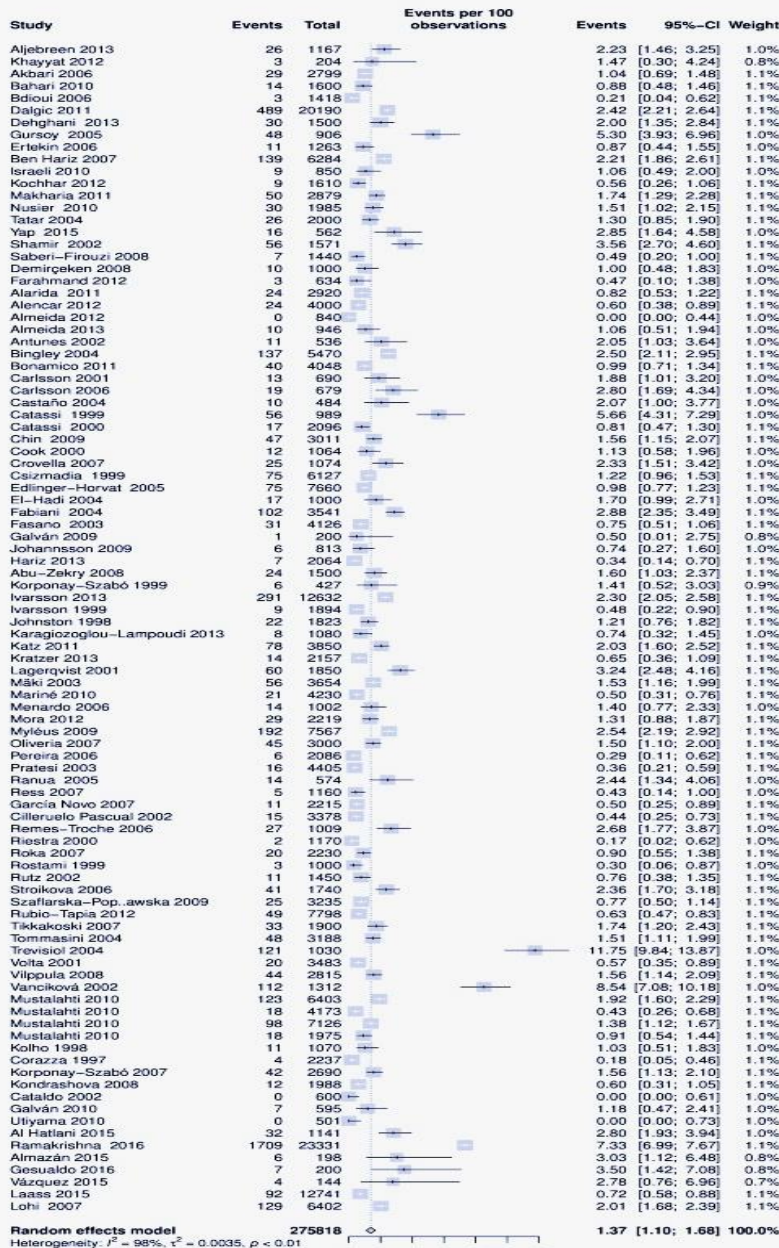
### Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis

Prashant Singh,<sup>\*</sup> Ananya Arora,<sup>‡</sup> Tor A. Strand,<sup>§,||</sup> Daniel A. Leffler,<sup>\*,¶</sup> Carlo Catassi,<sup>#</sup>  
Peter H. Green,<sup>\*\*,‡‡</sup> Ciaran P. Kelly,<sup>\*</sup> Vineet Ahuja,<sup>§§</sup> and Govind K. Makharia<sup>§§</sup>

# Global prevalence: systematic review and meta-analysis



# Global seroprevalence of CeD



96 studies: 275,818 subjects  
5,571 positive for TG2/EMA

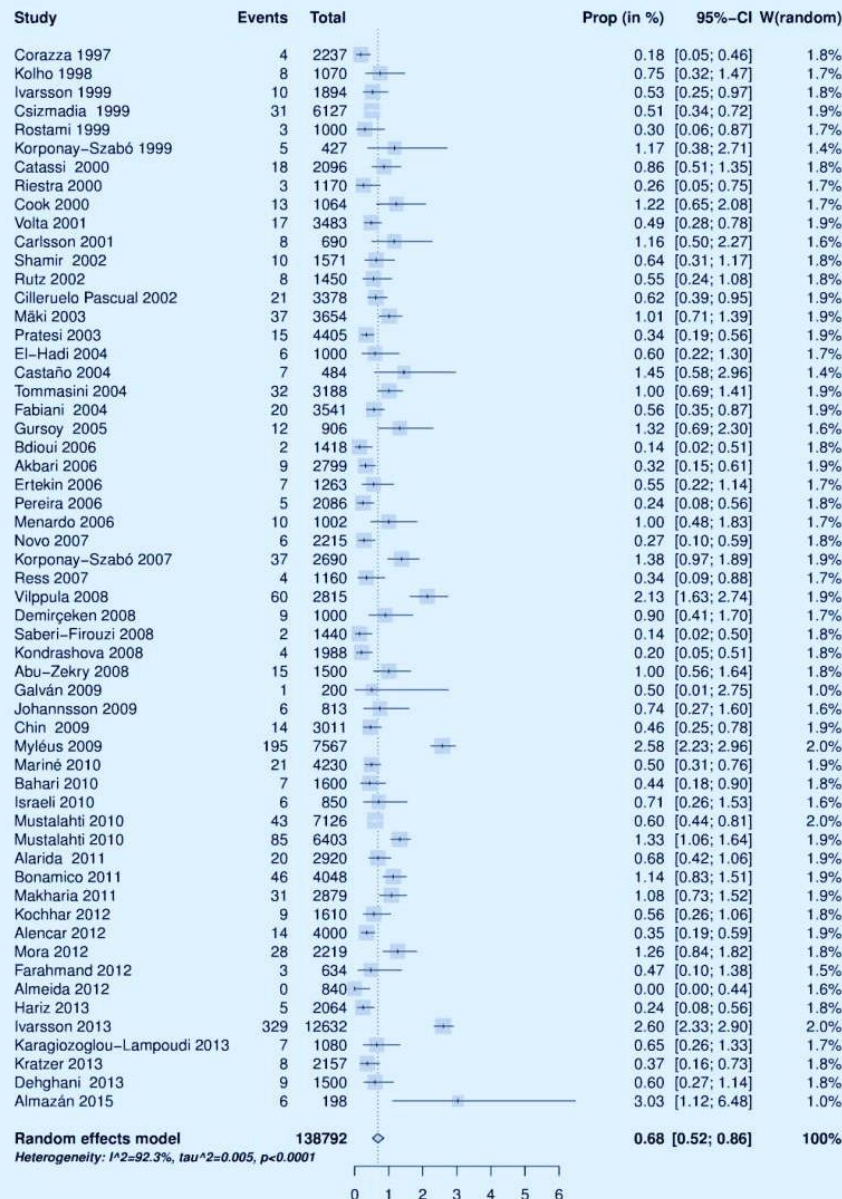
1.37% (95%CI 1.1%,  
1.68%)

0% to 11.7%

Heterogeneity: 98%

Singh P, Clin Gastroenterol Hepatol,  
In press

# Global prevalence of CeD



57 studies, 138, 792 patients

0.68%, 95% CI: 0.52-0.86



# Differences between pooled global sero-prevalence and prevalence of biopsy-confirmed CeD?

Sero-prevalence: 1.37%

Prevalence of CeD: 0.68%

Biopsy rate ranged from 51.2 to 100%

Under-estimation of actual CeD prevalence

Potential coeliac

False positive





# Estimated number of patients with CeD globally

- Pooled prevalence of biopsy confirmed CeD: 0.68% (95% CI 0.5%, 0.9%)
- Global population 7.4 billion,
  - 37 million to 59 million individuals are likely to have CeD around the world
- Globally, majority of patients (83%-95%)
- Still remain undiagnosed

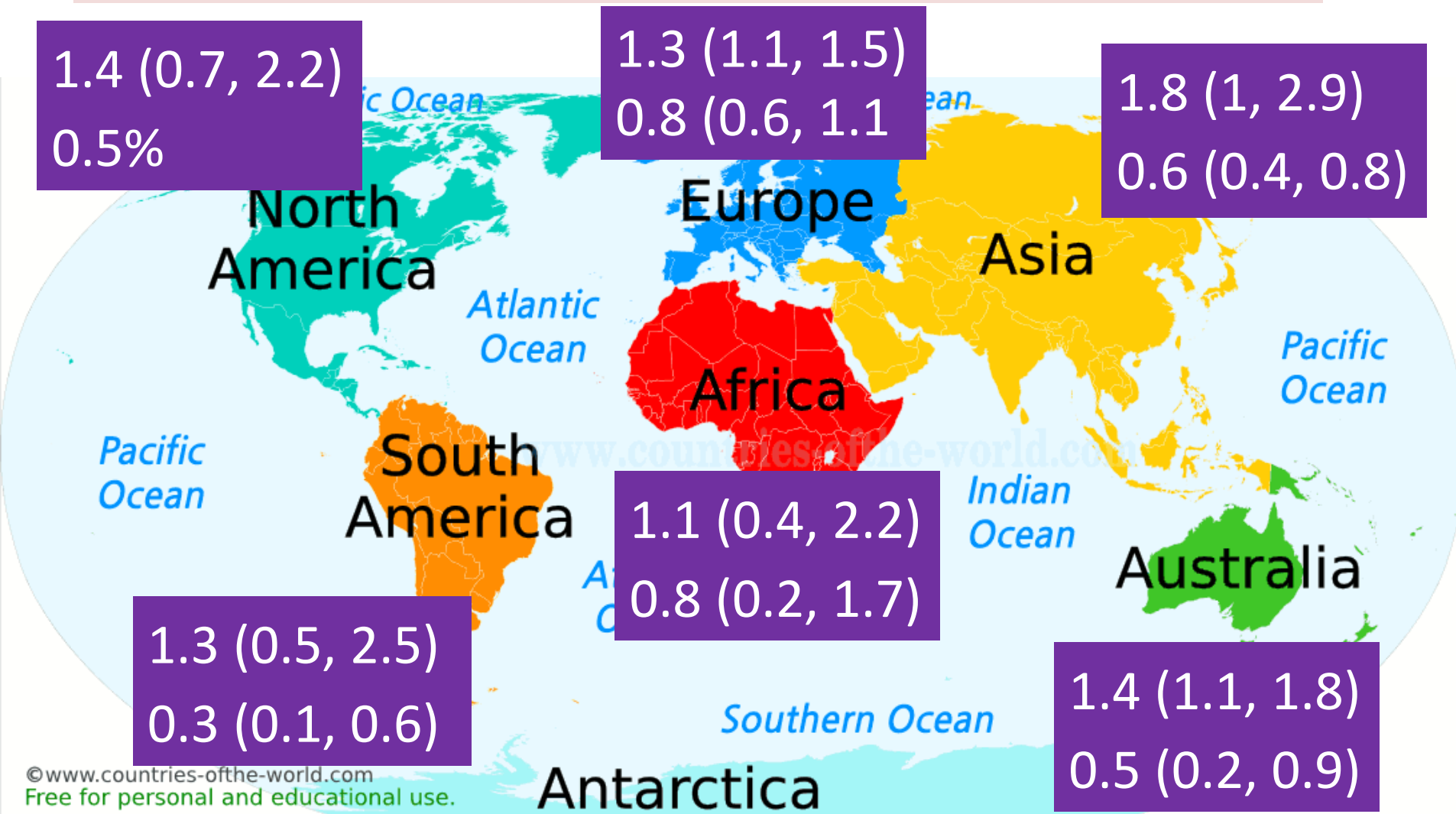
# Prevalence: Continent wise

# Continent wise prevalence



| Location          | No screened for sero-prevalence | sero + | Pooled sero-prevalence (95% CI) | No screened for biopsy proven CeD | Bx proven CeD | Pooled prevalence of CeD |
|-------------------|---------------------------------|--------|---------------------------------|-----------------------------------|---------------|--------------------------|
| <b>Continents</b> |                                 |        |                                 |                                   |               |                          |
| Europe            | 163,700                         | 2340   | 1.3 (1.1, 1.5)                  | 98, 391                           | 1119          | 0.8 (0.6, 1.1)           |
| N America         | 17,778                          | 200    | 1.4 (0.7, 2.2)                  | 200                               | 01            | 0.5                      |
| S America         | 20,245                          | 280    | 1.3 (0.5, 2.5)                  | 16,550                            | 69            | 0.3 (0.1, 0.6)           |
| Asia              | 68,632                          | 2607   | 1.8 (1, 2.9)                    | 18, 052                           | 114           | 0.6 (0.4, 0.8)           |
| Africa            | 15,775                          | 253    | 1.1 (0.4, 2.2)                  | 7902                              | 42            | 0.8 (0.2, 1.7)           |
| Oceania           | 4,075                           | 59     | 1.4 (1.1, 1.8)                  | 4075                              | 27            | 0.5 (0.2, 0.9)           |

# Prevalence: continent wise



# CeD in world's top ten most populous countries



- Population based prevalence available only from four top ten populous countries

- India
- USA
- Brazil
- Russia

## Lack of data from

- China
- Indonesia
- Pakistan
- Nigeria
- Bangladesh
- Japan

# Sero-prevalence: country wise

Highest Q  
Algeria  
Czech Rep  
India  
Israel  
Saudi-Arabia  
Sweden  
Portugal  
Turkey

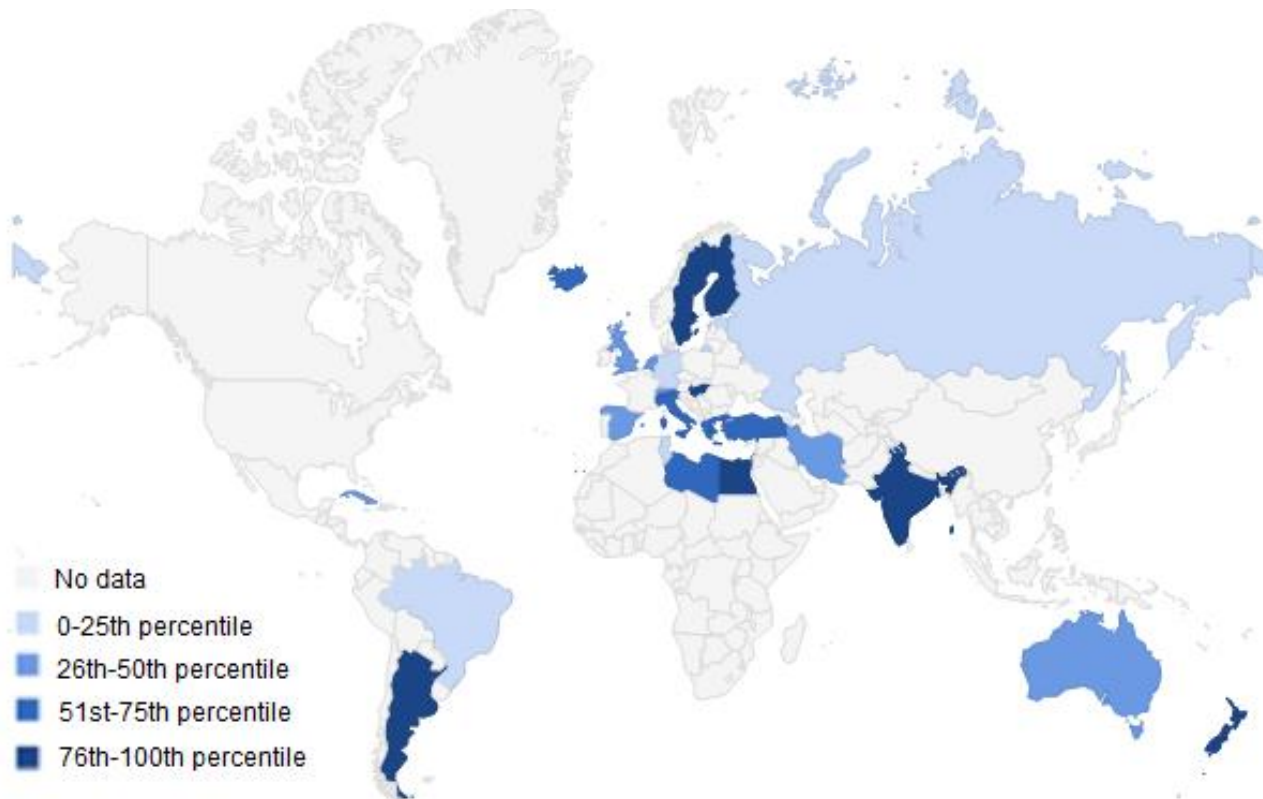


Lowest Q  
Estonia  
Germany  
Iceland  
Libya  
Poland  
Spain  
Switzerland

# Prevalence of CeD: country-wise



Highest Q  
Argentina  
Egypt  
Hungary  
Finland  
India  
NZ  
Sweden



Lowest Q  
Brazil  
Germany  
Russia  
Tunisia



# Children Vs Adults

## Difference in prevalence of biopsy confirmed CeD

- Of 57 studies, 43 reported separate pooled prevalence for pediatric pts and adult pts
- Pooled prevalence of CeD: ( $P < 0.001$ )
  - 276 of 40,076 adults: 0.5% (95% CI 0.3, 0.8)
  - 891 of 65,957 children: 0.9% (95% CI 0.6, 1.3)

# Summary: 1

- CeD is a global disease
- 1.37% of global population is seropositive
- 0.68% of the global population have biopsy confirmed CeD

## Underestimation of the disease

- Exclusion of studies in whom <50% were biopsied

# Trend of prevalence of CeD

## Two contexts

Has the prevalence of CeD  
plateaued, or still evolving

Emergence of CeD in new regions

# Increasing prevalence over time

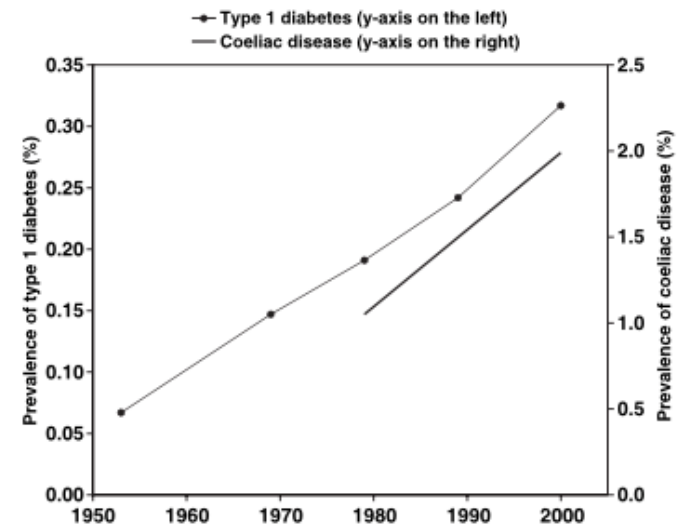
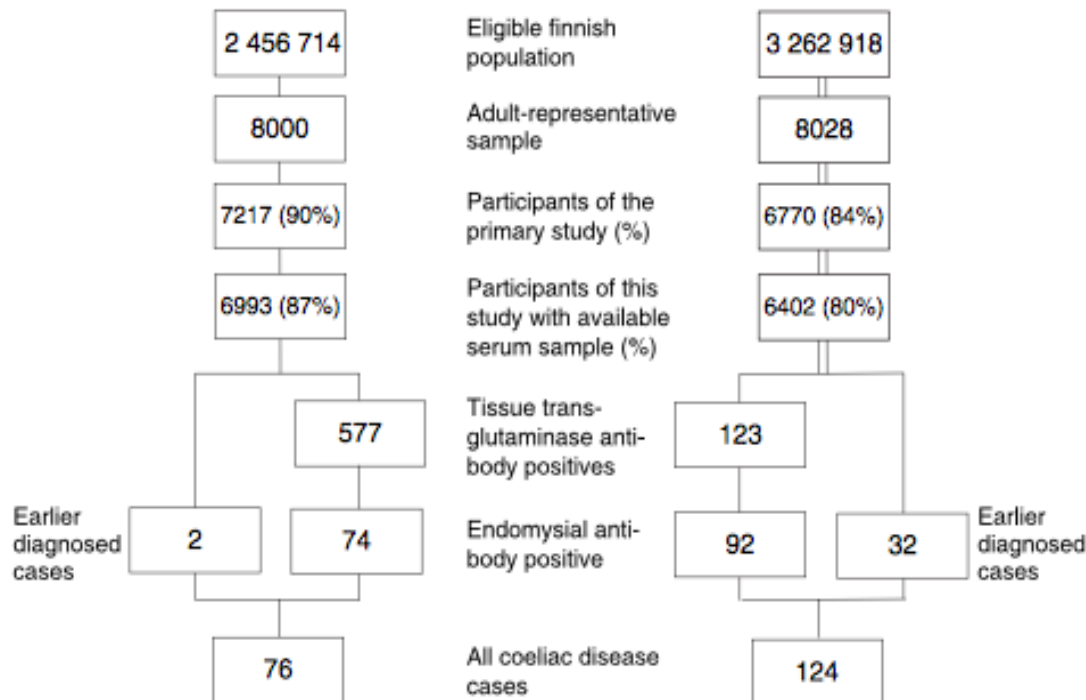
- Stratified the studies into 2 time periods:
  - January 1991 to December 2000
  - Jan 2001 onward (based on actual study period)
  - Studies overlapping 2 time periods: Deleted
- 1991 to 2000: 0.6% (95% CI, 0.5%–0.7%)
- 2011 to March 2016: 0.8% (95% CI, 0.5%– 1%)

# Prevalence almost doubled in Finland



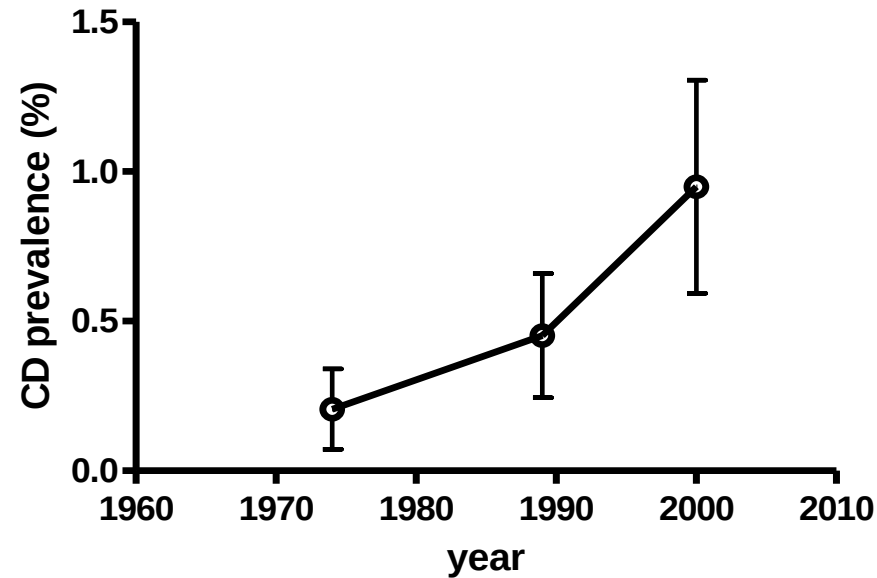
Mini-Finland survey in 1978–80

Health 2000 survey in 2000–01



Lohi S, Aliment Pharmacol Ther 2007;26: 1217–25

# CeD is increasing in USA



*Catassi C et al, Ann Med 2010*

# Rise in CeD: Why?

- Increase in awareness
- Advancement in the diagnostic tools
- Use of wheat in rice eating regions
- Increase in gluten content of infant feeding
  - Sweden epidemic (1985 to 1995)

Ivarsson A, Acta Paediatr 2000;89: 165–

## Summary: 2

In many countries, the prevalence has increased 2 to 4 fold over 20 - 30 yrs



# Europe



# Prevalence of CeD in children and adolescents in Germany.



- German Health Interview and Examination Survey for Children and Adolescents 2003-2006
- 12, 741 participants aged 1 to 17 years (6546 boys)
  - 9 (0.07%) had a reported history of CeD.
  - 98 anti-tTG positive on screening
- Prevalence of undiagnosed CeD (based on + serology): 0.8% (95% CI 0.6-1.0%),

Overall prevalence of the disease: 0.9%.

# Russia: still unexplored



Sparse reports on prevalence

Possibility of large burden of CeD in Russia, needs to be explored

# CeD in Russia



| Region           | Year      | Participants                 | Test                | screened | CD               |
|------------------|-----------|------------------------------|---------------------|----------|------------------|
| Karelia region   | 1997–2001 | School children              | Anti-tTG            | 1988     | 1 : 496 (0.20%)  |
| Ryazan region    | ND        | blood donors                 | Anti-tTG            | 1740     | 1 : 174 (0.57%)  |
| Irkutsk region   | 2011      | Specific risk <sup>*</sup>   | Anti-tTG            | 1441     | 1 : 18 (5.56%)   |
|                  |           |                              |                     | 1402     | 1 : 31 (3.32%)   |
|                  | 2014      | Specific risk <sup>*</sup>   |                     | 1775     | 1 : 40 (2.50%)   |
| Krasnodar region | 2010      | Specific risk <sup>*</sup>   | Anti-tTG and/or AEA | 742      | 1 : 36.6 (2.73%) |
| Moscow           | 2003–07   | Specific risk <sup>*</sup>   | Anti-tTG            | 363      | 1 : 6.2 (15.98%) |
|                  | 2012      | Specific risk <sup>**</sup>  |                     | 318      | 1 : 106 (0.94%)  |
| Nizhny Novgorod  | 2008      | Specific risk <sup>*</sup>   | Anti-tTG            | 1045     | 1 : 7.6 (13.16%) |
| Ryazan region    | 2002–2006 | Specific risk <sup>***</sup> | Anti-tTG            | 256      | 1 : 57 (1.75%)   |

[Lyudmila V. Savvateeva, J Immunol Res. 2017](#)

# CeD in Sub-Saharan



16 with positive AEA: All coeliac  
56/989 AEA+: 5.6%

5 fold higher  
High gluten consumption  
High HLA-DQ2/DQ8

Catassi, Lancet, 1999

Catassi, Tissue antigen, 2001

# Asia



# Map of CeD in Asian region



# India



# India: Population-based study



Two stage screening: Symptoms-based questionnaire and serology  
Seropositive: Biopsy

| Subgroup                | Corrected seroprevalence<br>(95% CI) | Corrected prevalence of CeD<br>(95% CI) |
|-------------------------|--------------------------------------|-----------------------------------------|
| Adults ( $n = 6845$ )   | 1.10% (0.86, 1.37)                   | 0.85% (0.64, 1.09)                      |
| Children ( $n = 3643$ ) | 2.06% (1.62, 2.57)                   | 1.41% (1.04, 1.84)                      |
| Males ( $n = 5305$ )    | 1.28% (1.00, 1.62)                   | 0.91% (0.67, 1.20)                      |
| Females ( $n = 5183$ )  | 1.60% (1.28, 1.98)                   | 1.20% (0.92, 1.53)                      |

1.04% (One in 96)

# Population prevalence of CeD in India



| Investigators             | Study                                       | No   | Prevalence       |
|---------------------------|---------------------------------------------|------|------------------|
| Sood et al, 2006          | Population based study in children (Punjab) | 4347 | 1 in 310 (0.3%)  |
| Makharia, 2010            | Population based study in adults (NCR)      | 2879 | 1 in 96 (1.04%)  |
| Kochhar, 2015             | Healthy blood donor                         | 1610 | 1 in 179 (0.56%) |
| <b>Singh P, JGH, 2016</b> | <b>Metaanalysis</b>                         |      | <b>0.6%</b>      |

# Regional differences



- Mostly in Northern part
- Few from Southern and North Eastern part of India.

- Is it dietary factor ?
- Genetic predisposition?

# Indian population: 1.2 Billion



Northern Indian  
(Aryans)



North Eastern  
(Indo Burman)

Southern India  
(Dravidians)

# Multi-site prevalence study

Total subjects contacted: 32,618

Agreed for screening for CeD: 23,331

Anti tTG ab +ve (Aeskulisa): 1,709 (7.3%)

Both positive

See

SA

Combined prevalence of CeD & potential  
CeD in India : 0.67%

Quodenal biopsy: 103/158

Abnormality (Marsh grade  $\geq 2$ ) S/o CeD: 38

Villous abnormality (Marsh grade 0-1) S/o potential CeD: 58

Inadequate biopsy: 7

Ramakrishna, AJG 2015

# India: Multi-site population based prevalence



## Northern part

|               |       |
|---------------|-------|
| Prevalence    | 1.2%  |
| CeD           | 0.85% |
| Potential CeD | 0.37% |

## Risk factors

## HLA haplotype

|               |       |
|---------------|-------|
| HLA -DQ2/-DQ8 | 38.1% |
|---------------|-------|

## Daily Dietary intake

|             |               |
|-------------|---------------|
| Wheat (gms) | 455.6 ± 114.5 |
|-------------|---------------|

|            |             |
|------------|-------------|
| Rice (gms) | 75.1 ± 39.2 |
|------------|-------------|

## North Eastern part

|               |       |
|---------------|-------|
| Prevalence    | 0.87% |
| CeD           | 0.46% |
| Potential CeD | 0.39% |

|               |       |
|---------------|-------|
| HLA -DQ2/-DQ8 | 31.4% |
|---------------|-------|

|            |             |
|------------|-------------|
| Wheat (gm) | 37.8 ± 11.5 |
|------------|-------------|

|           |               |
|-----------|---------------|
| Rice (gm) | 326.1 ± 130.6 |
|-----------|---------------|

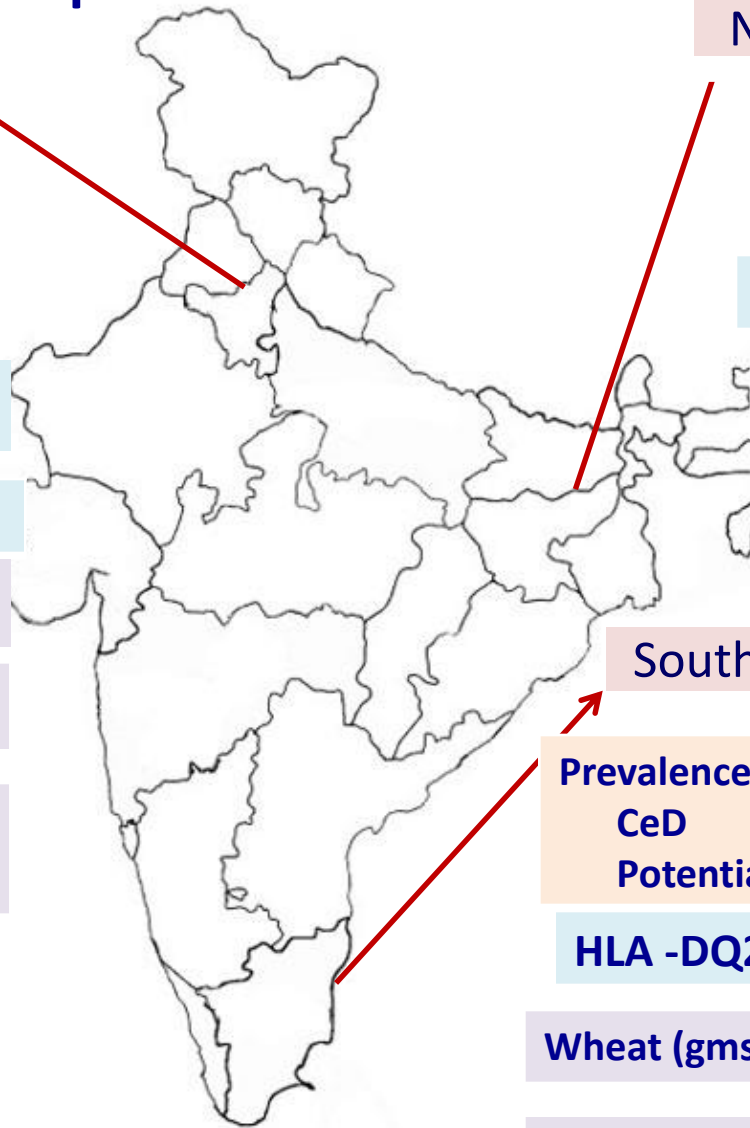
## Southern part

|               |       |
|---------------|-------|
| Prevalence    | 0.13% |
| CeD           | 0.01% |
| Potential CeD | 0.12% |

|               |       |
|---------------|-------|
| HLA -DQ2/-DQ8 | 36.4% |
|---------------|-------|

|             |             |
|-------------|-------------|
| Wheat (gms) | 25.7 ± 26.8 |
|-------------|-------------|

|            |              |
|------------|--------------|
| Rice (gms) | 167.5 ± 77.2 |
|------------|--------------|



# South Indians in USA: lowest prevalence

## Punjabis in USA: highest prevalence



National pathology laboratory 2008 and 2015.

Prevalence of villous atrophy

Algorithmic determination of ethnicity based on names

- Among all patients (n=454,885)
  - Overall prevalence: 1.74%.
  - Other Americans (n=380,163): 1.83%
- Lower prevalence in
  - Patients of South Indian (n=177, 0%; P=.08),
  - East Asian (n=4700, 0.15%; P=<.0001),
  - Hispanic (n=31,491, 1.06%; P=<.0001).
- Higher in pts from Punjab (n=617, 3.08%)
  - others North India (n=1195, 1.51%; P=.02).





# CeD in China: Unexplored

## Traditional belief: No CeD in China

| Study                                      | Province                                 | Patients                         | Criteria for diagnosis              | No.                        | Prevalence   |
|--------------------------------------------|------------------------------------------|----------------------------------|-------------------------------------|----------------------------|--------------|
| Wu J 2010, Rev Esp Enferm Dig.             | Nanjing                                  | IBS_D (72)<br>IDDM (6)           | IgA-AGA<br>IgA-TTG                  | 6/78 (AGA+)<br>2/78 (tTG+) | 7.7%<br>2.6% |
| Wang XQ, 2010<br>Zhonghua Er Ke<br>Za Zhi. | Shanghai                                 | Chronic<br>diarrhea              | Clinical<br>symptoms<br>Duodenal Bx | 14/118<br>suspected        | <b>12%</b>   |
| Xin-Qiong W,<br>JPGN, 2011                 | Shanghai,<br>Wuhan,<br>Jinan,<br>Chengdu | Children<br>with Chr<br>diarrhea |                                     | 14/118                     |              |

19,778 undiagnosed Chinese adolescents and young adults (age, 16-25 y): 2.19% coeliac disease Ab positive

Clin Gastroenterol Hepatol, 2017

# CeD in IBS-D patients

- 246 IBS patients (North China) and 246 healthy controls.
- Screened with anti-tTG: Positive test: probe-based confocal laser endomicroscopy (pCLE) and duod Bx
- Sero-prevalence: 12 IBS (4.8%) & 2 controls (0.81%)
- 5 underwent pCLE and targeted biopsy; all CeD
- With GFD: Seven serologically positive clinical improvement,
- **Minimum Prevalence of CeD: 2.85%.**

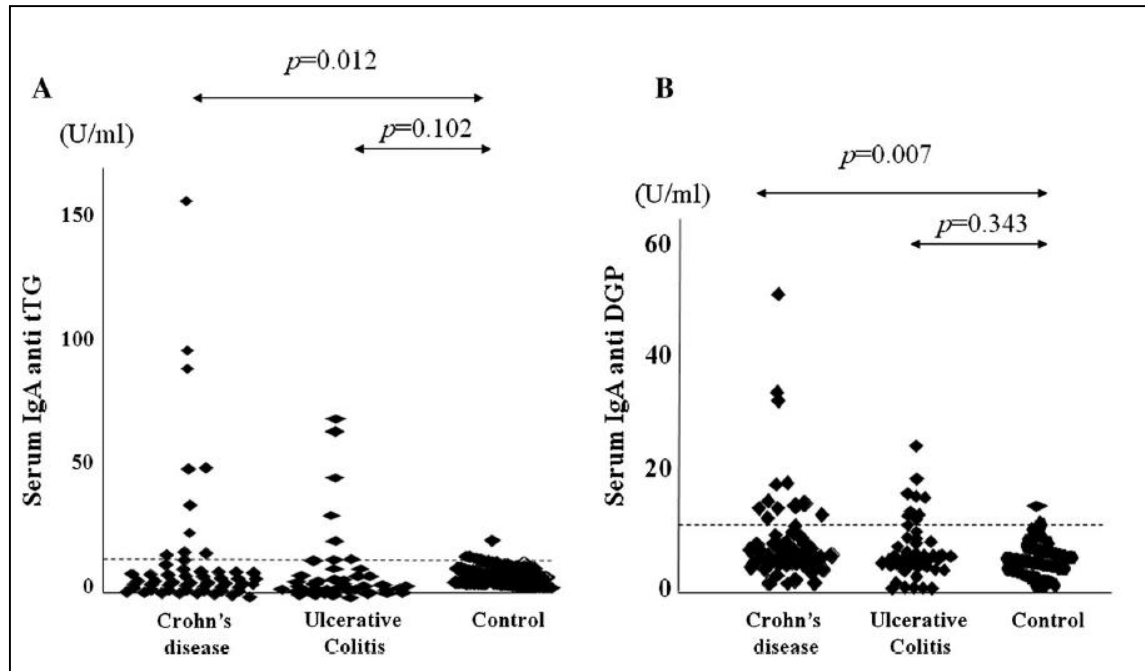
# CeD in Japan



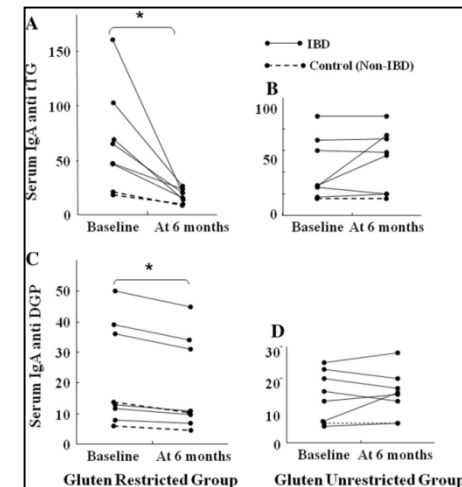
| Yr           | Diagnosis                                      | n | Gluten Challenge Test or GFD | Serological Test | Biopsy Confirmed     | HLA            |
|--------------|------------------------------------------------|---|------------------------------|------------------|----------------------|----------------|
| 1983         | Celiac sprue, Gluten induced enteropathy       | 1 | Yes(Gluten challenge, GFD)   | No               | Yes(villous atrophy) | No             |
| 1991         | Celiac sprue                                   | 4 | Yes (Gluten Challenge)       | No               | Yes(villous atrophy) | No             |
| 1988<br>1993 | Celiac disease                                 | 2 | Yes (GFD)                    | No               | Yes(villous atrophy) | No             |
| 2000         | Celiac sprue                                   | 1 | Yes (GFD)                    | No               |                      | No             |
| 2003         | Celiac disease                                 | 1 | No                           | No               | No                   | No             |
| 2006         | B-cell Lymphoma associated with celiac disease | 1 | No                           | positive for tTG | Yes(villous atrophy) | Yes (nonDQ2/8) |
| 2007         | T-cell Lymphoma associated with celiac disease | 1 | No                           | No               | Yes(villous atrophy) | No             |

Courtsey, Watanabe C

# Sero-prevalence of CeD in IBD: Japan



IBD: anti-tTG Ab and anti-DGP Ab: 22 (12.8%) and 23 (13.4 %)  
 Controls (n=172): 3 (1.6%) and 1(0.5%),



Watanabe; J Gastroenterol 2014

# CeD in Malaysia



- 562 Healthy young volunteers (mean age  $24 \pm 2.4$  yrs )
- Screening for CeD: Two stages
  - First step: IgG/IgA AGA and anti-tTG IgA/IgG.
  - Second step: Testing of positive samples by EmA.
- Definition of CeD: Both positive
- Seroprevalence of CeD: 1.25% (95% CI, 0.78-1.72) (7 of 562)
  - Median AGA: 38.2 U/ml (IQR, 28.3–60.4 U/ml)
  - IgA anti-tTG Ab: 49.2 U/ml (IQR, 41.1–65.9 U/ml)

Malay: 0.8% (2 of 236),  
Chinese: 1.7% (3 of 177)  
Indian: 1.3% (2 of 149)

Sero-prevalence of CeD: 1.25% (1 in 100)

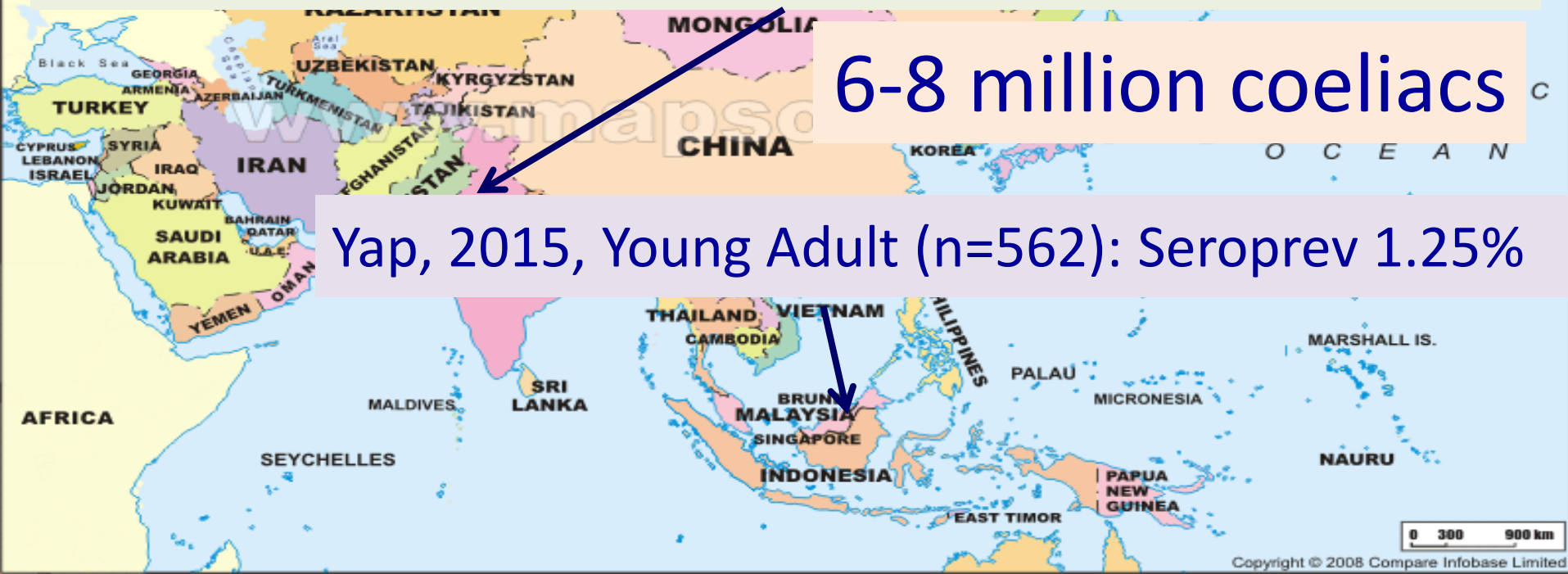
CD is underdiagnosed, Could be a much greater problem

# Population based studies: Eastern/Southern Asia

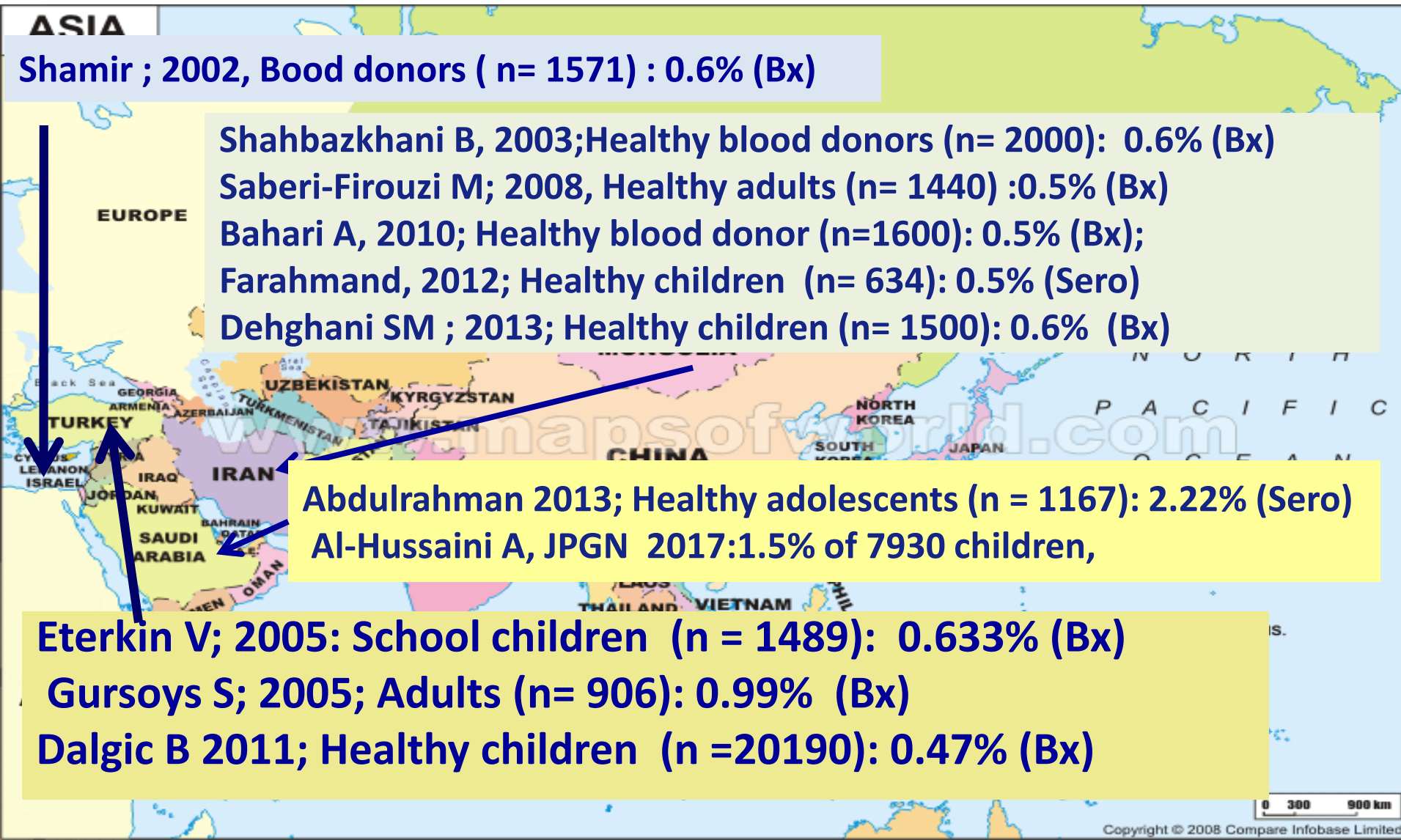
Sood A, Healthy school children (n=4347): 0.32%  
Makharia; 2011, General population (n=10488): 1.04%  
Ramakrishna, 2015 (n>23000): 0.67%  
Kochhar, 2012, Healthy blood donors : 0.56%

6-8 million coeliacs

Yap, 2015, Young Adult (n=562): Seroprev 1.25%

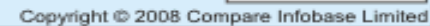


# Population based studies: Middle East/West Asia





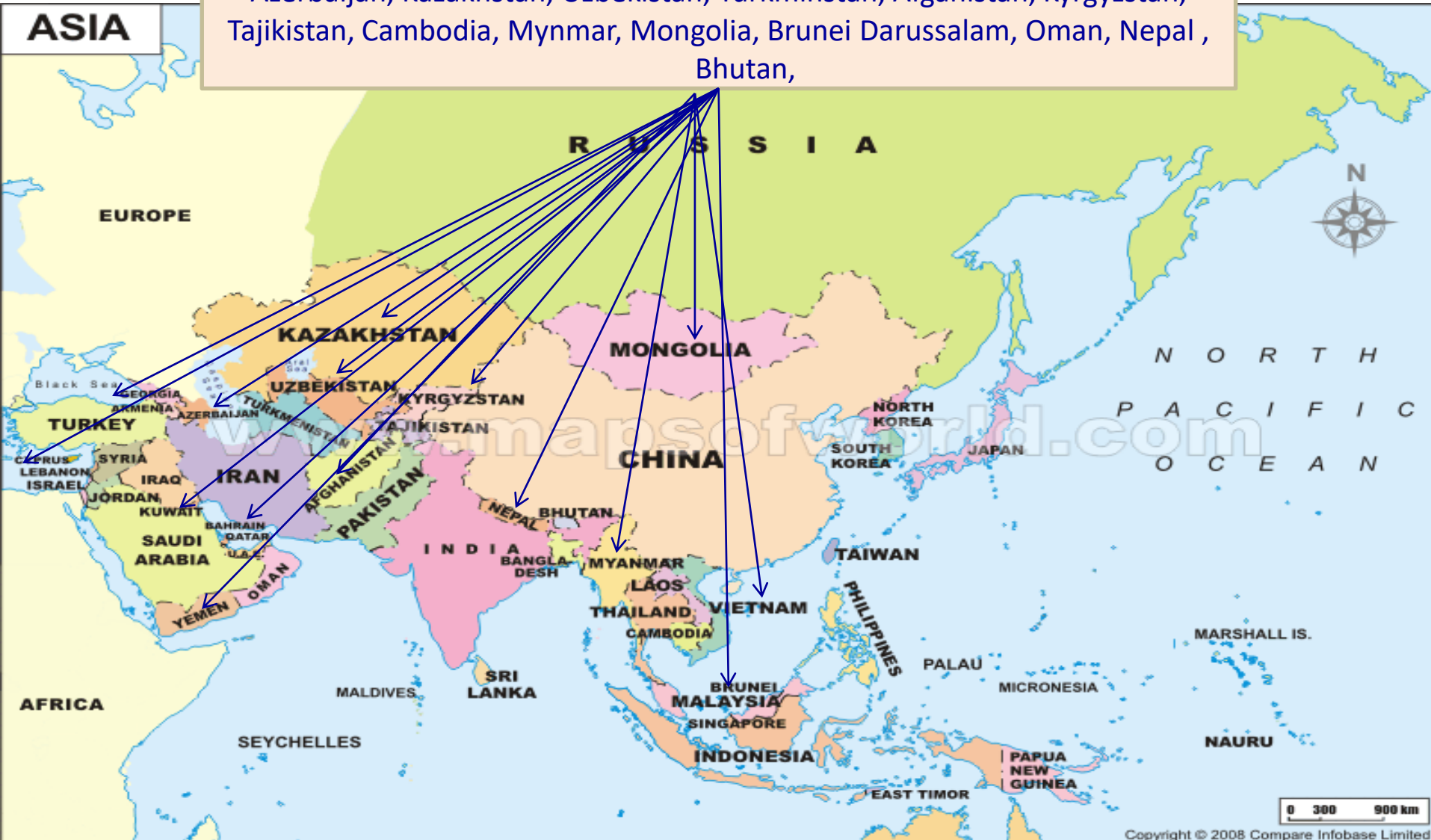
## ASIA



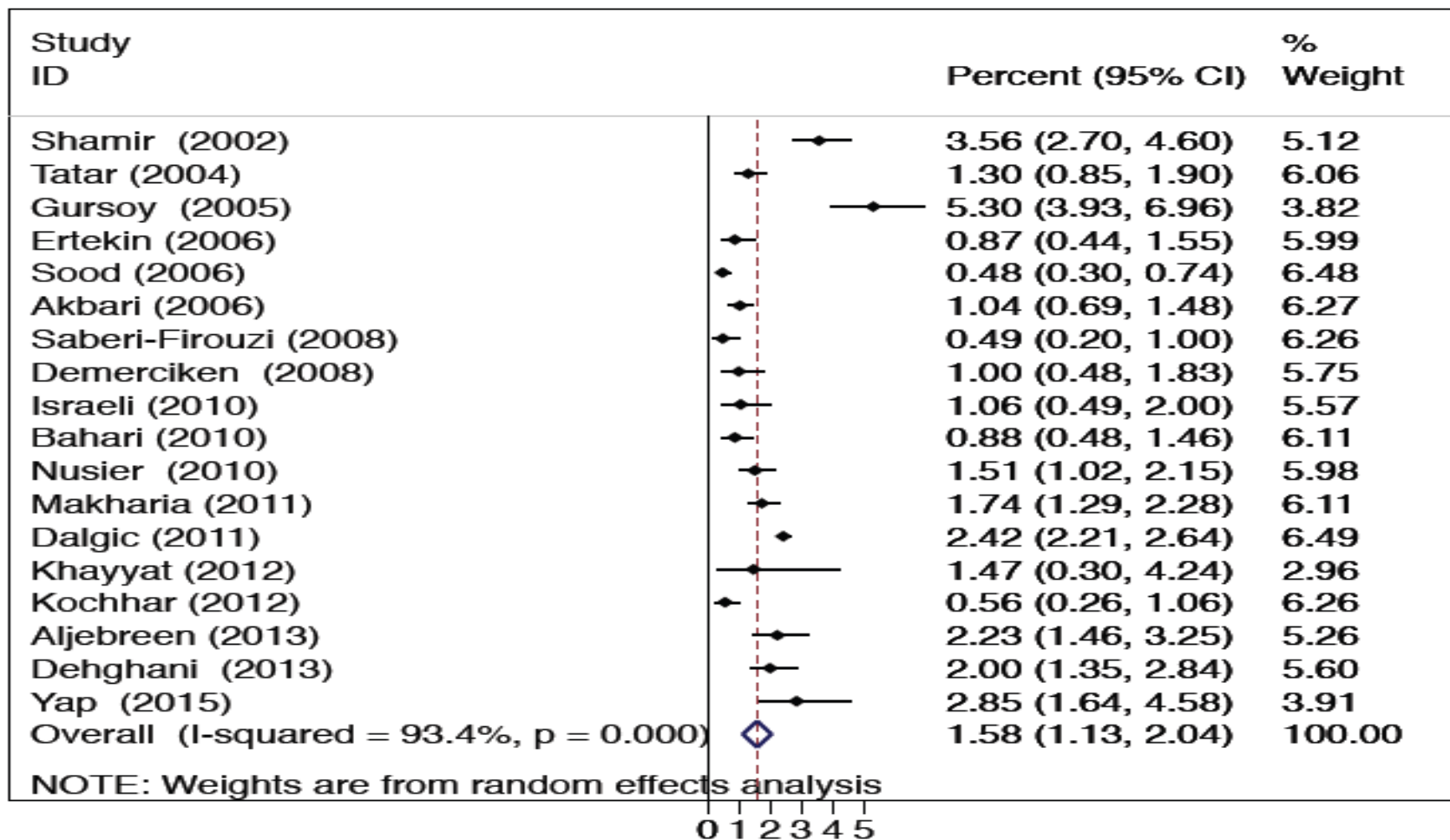


# No reports from

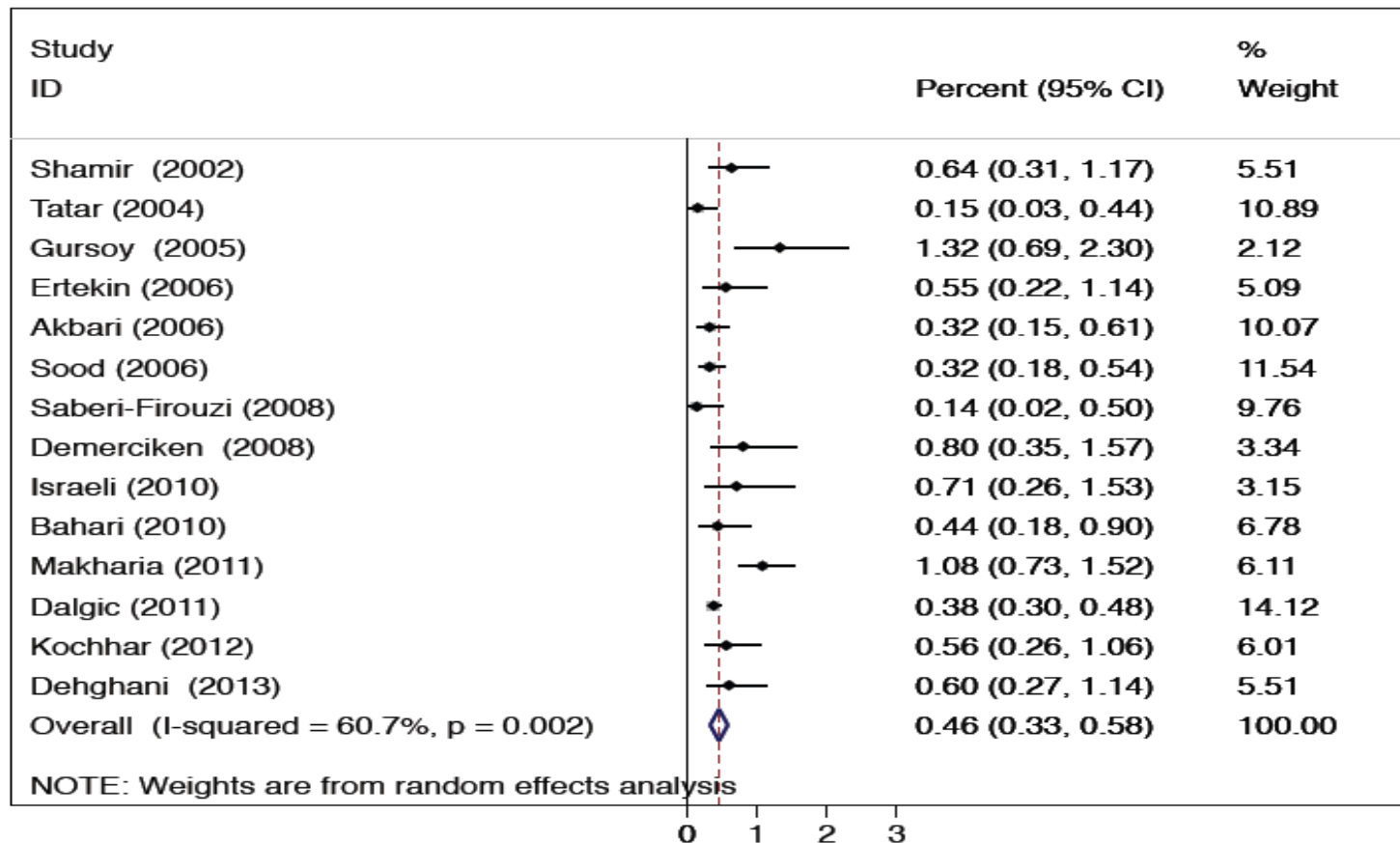
Azerbaijan, Kazakhstan, Uzbekistan, Turkminstan, Afganistan, Kyrgyzstan, Tajikistan, Cambodia, Mynmar, Mongolia, Brunei Darussalam, Oman, Nepal , Bhutan,



# Pooled seroprevalence of CeD in Asia: Systematic review



# Pooled prevalence of CeD in Asia: Systematic review



## Summary 3: CeD in Asia

- 50 countries
- 60% of the world's population 4.2 billion
- Two largest countries: China and India
  - China: 1.35 Billion
  - India: 1.22 Billion

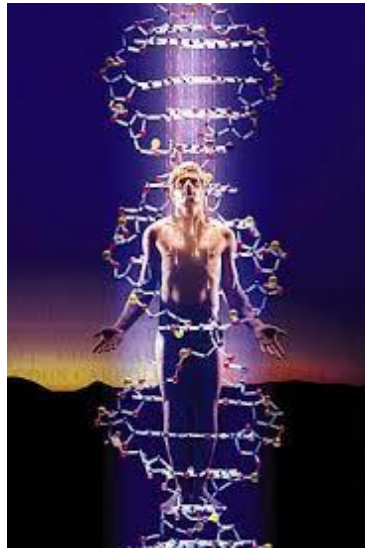
No of patients with CeD in Asia is likely to increase

There is a need to understand the epidemiology of coeliac disease in Asia

## CeD: In Future

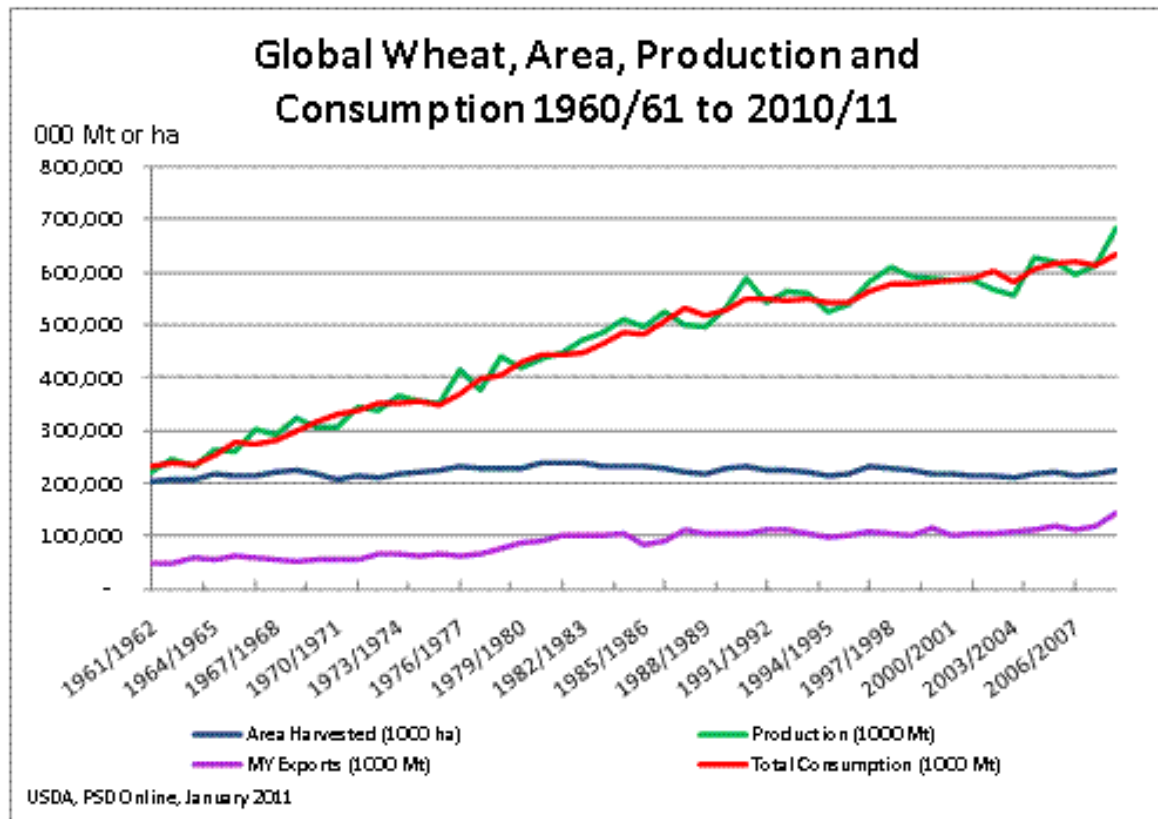
What are the predictions?

# CeD: Essential factors



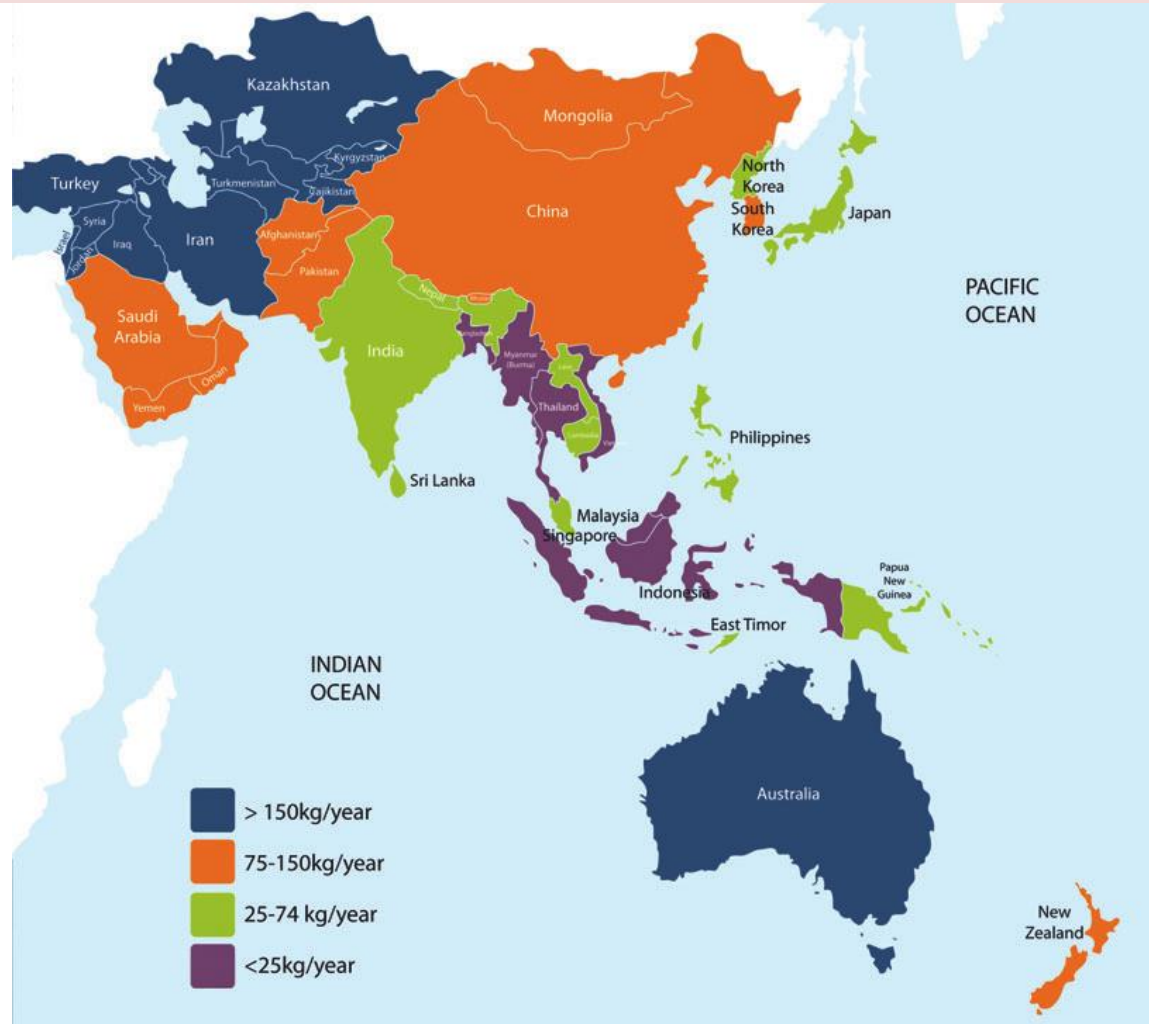
HLA-DQ2 and/or -DQ8)

# Wheat production has increased globally





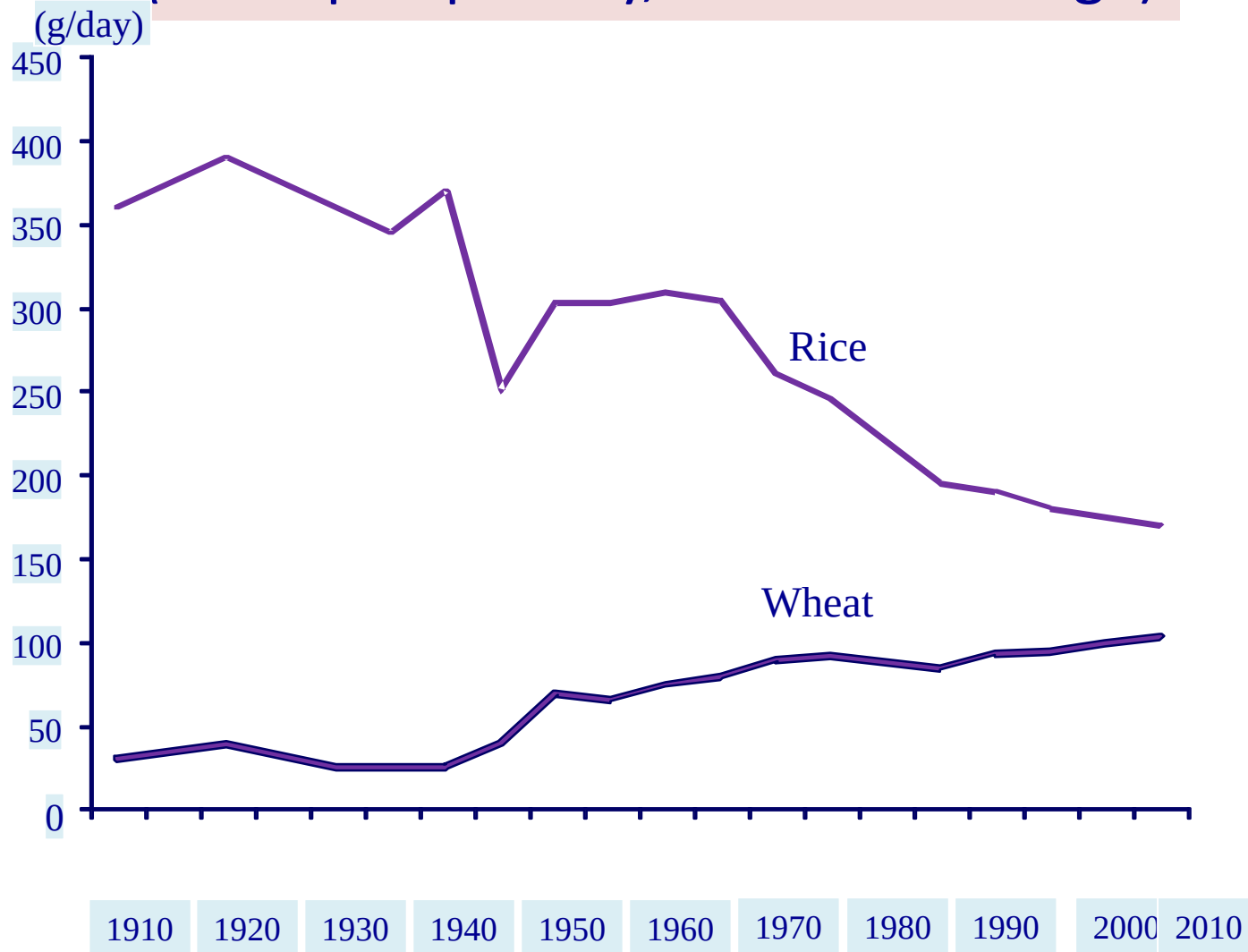
# Wheat consumption (kg) per person per year for countries in the Asia Pacific region



Aquino P, Carrión F, Calvo R. *Selected Wheat Statistics. 2001*  
Cummins AG, J Gastroenterol Hepatol. 2009



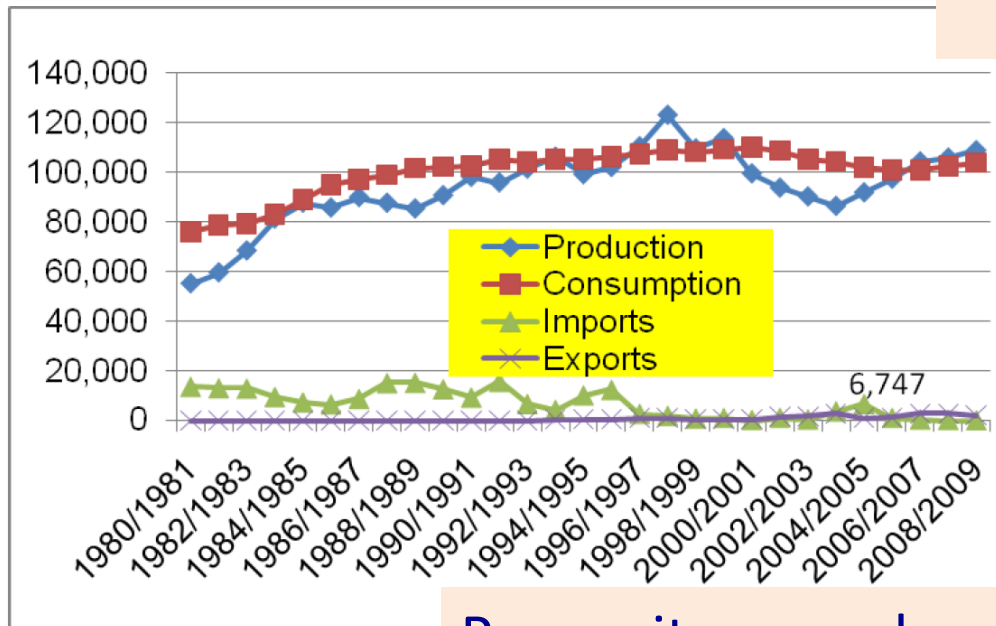
## Trends in Food Intake 1910 to 2011 (Per capita per day, National Average)



National Health and Nutrition Survey Japan, 2010

# Wheat statistics in China (1000mt)

Consumption of wheat is over 100 million metric tons for over 1,370 million people



Per capita annual consumption of wheat

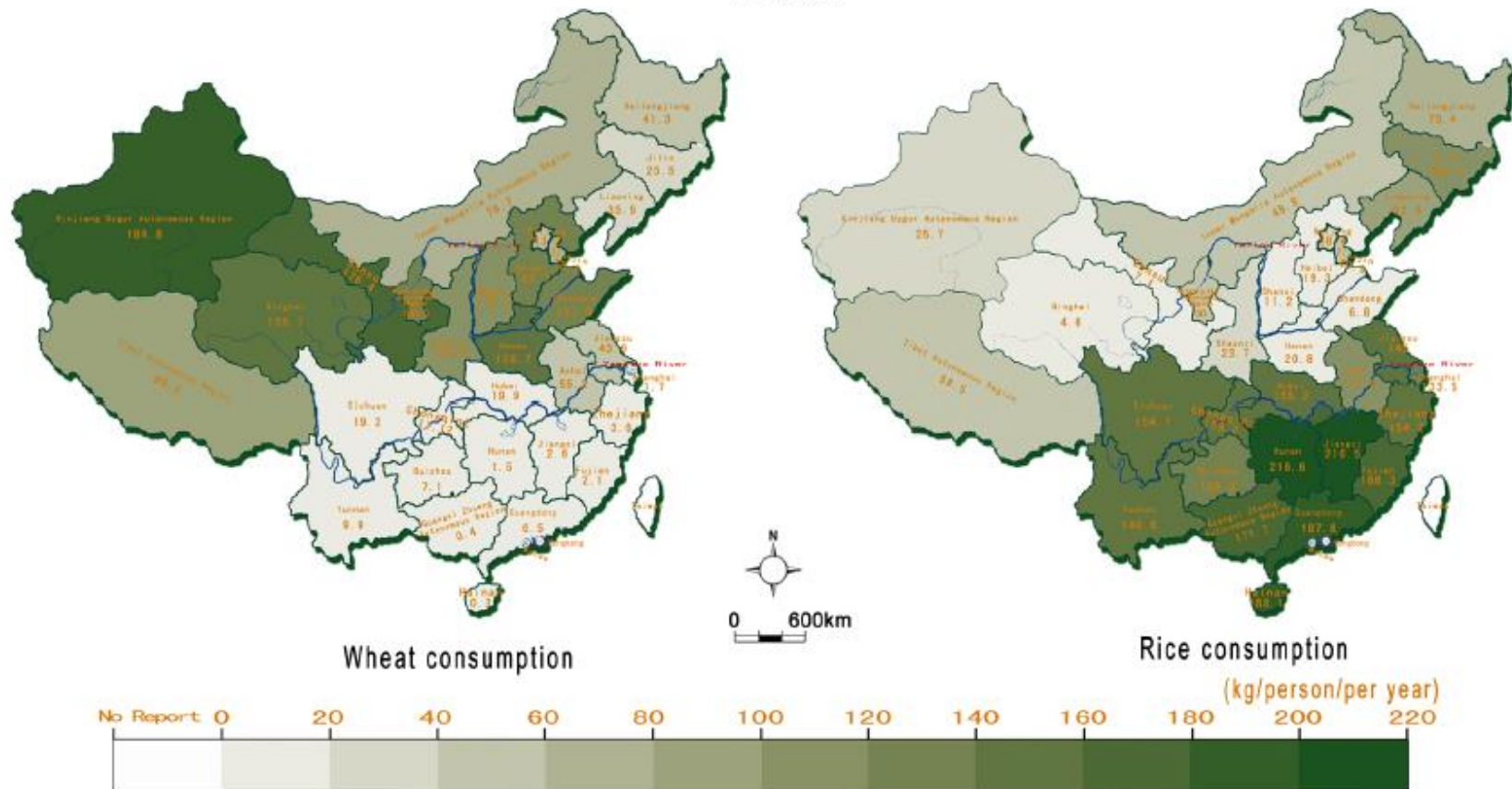
Rural households: 59.6kgs

Wheat flour in urban households: 12.5 kg

Yuan J, PLoS, 2013

# Wheat consumption pattern: China

Rural



Yuan J, PLoS, 2013

# Change in dietary pattern

- Increasing demand for convenience foods  
Urbanization
- Migration of people from rural to urban area
- Change in traditional eating practices to breads, pasta, pizza and burger

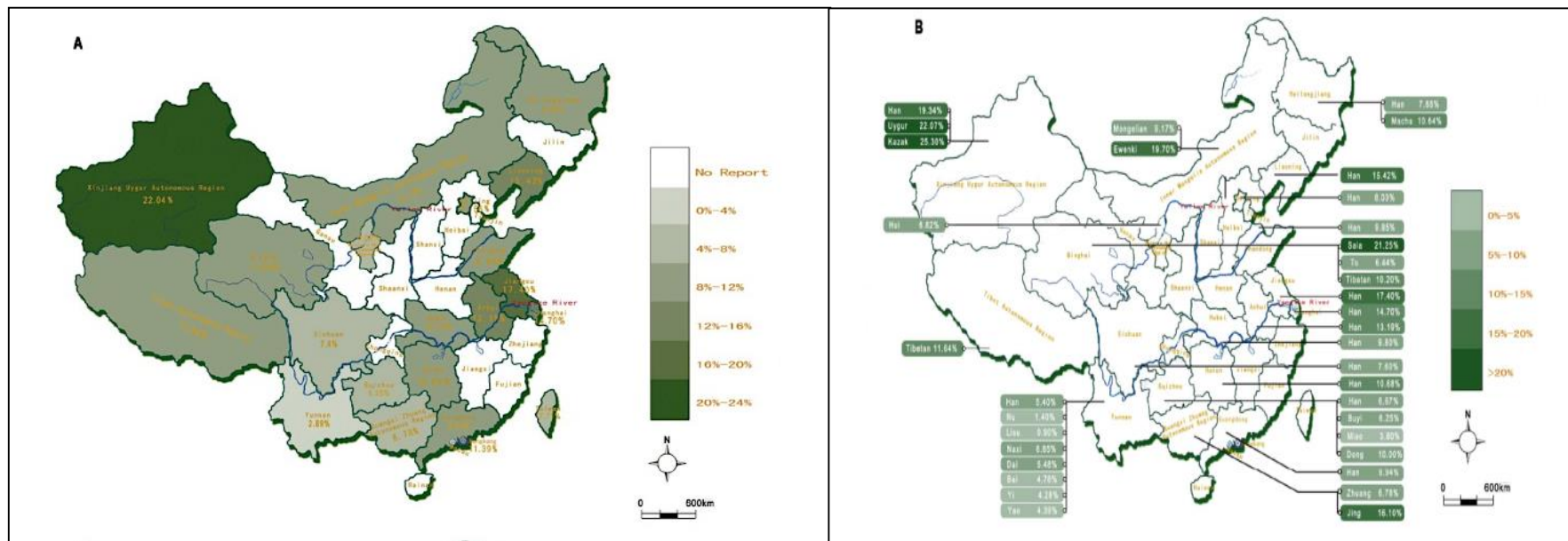
# Frequency of HLA-DQ2 in the population of various countries in the Asia–Pacific region

| < 5%             | 5-20%     | >20%         |
|------------------|-----------|--------------|
| Cook Islands     | China     | Australia    |
| Indonesia        | India     | Iran         |
| Japan            | Malaysia  | Israel       |
| Korea            | Mongolia  | New Zealand  |
| Nauru            | Singapore | Pakistan     |
| New Caledonia    | Sri Lanka | Saudi Arabia |
| Papua New Guinea | Taiwan    |              |
| Philippines      | Thailand  |              |
| Samoa            | Turkey    |              |
|                  | Vietnam   |              |

Middleton D. *Allele\*Frequencies in Worldwide Populations*.  
 Available from URL:<http://www.allelefrequencies.net/>  
 Cummins AG, J Gastroenterol Hepatol. 2009

# HLA DQB1\*0201/0202 allele in China

## Ethnic minorities



Yuan J, PLoS, 2013

## Summary 4

Both the initial reports and presence of predisposing factors highlight that coeliac disease exists in many Asian countries

# Barriers

- Believes
- Lack of diagnostic tests
- Very high threshold of suspicion





World Gastroenterology Organization



Asian Pacific Association



Awareness about CeD should be  
increased amongst medical  
clinicians and patients

# Final summary

- CeD is now a GLOBAL disease
  - It affects atleast 0.68% of global population (39-56 million globally)
- Prevalence of the disease has increased over past few decades
- Asia is now coming to the centerstage of CeD
- India presents a unique geographical region, with varying prevalence in North and South, to understand the factors

# Acknowledgement





# Artistic expression



Sankha Samatha