Genome-wide-association studies and polygenic risk scores in gastric cancer

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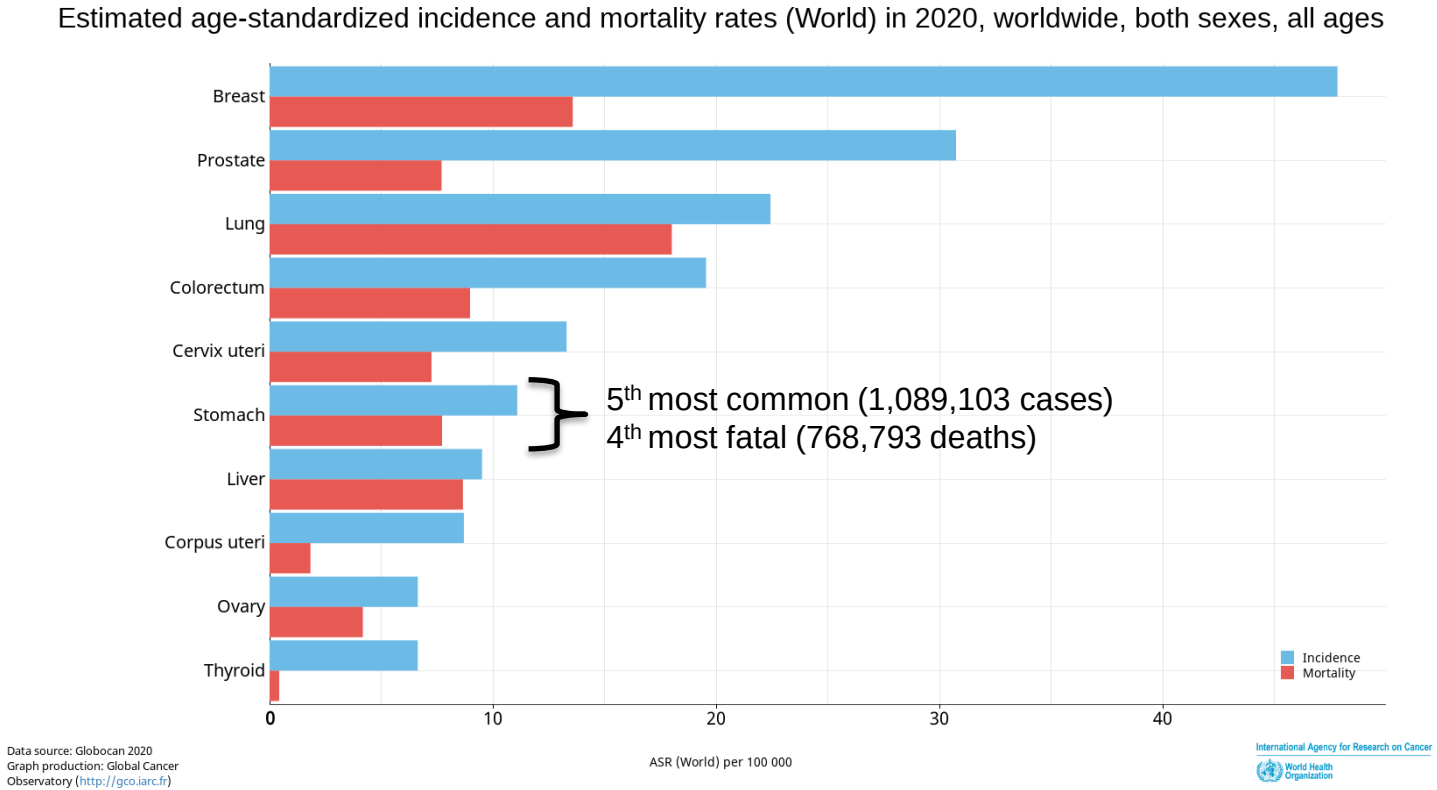
Outline

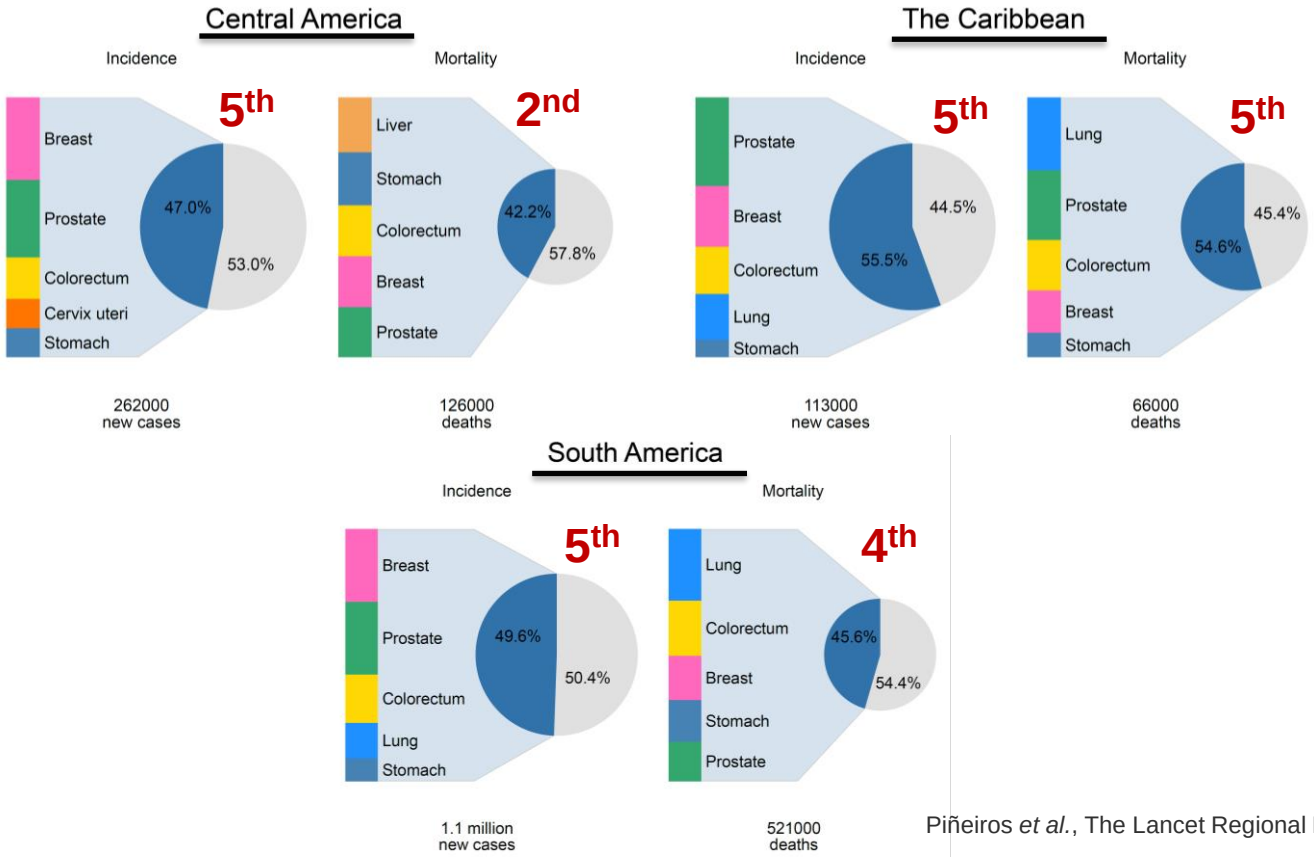
- Gastric cancer epidemiology
- Genome-wide-association studies
- Polygenic risk scores

Gastric Cancer Incidence and Mortality Worldwide



Sung *et al*., CA Cancer J Clin 2021

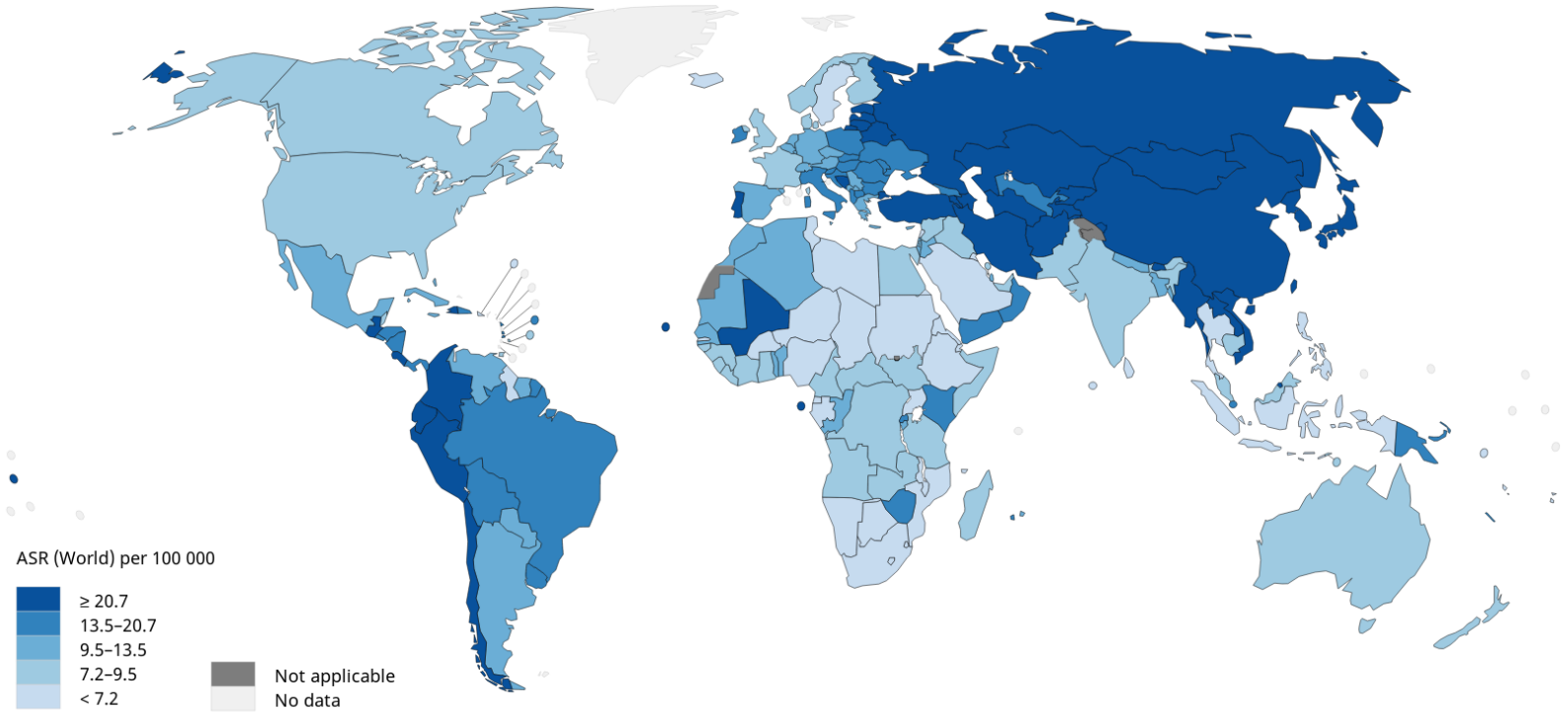
Five most frequent cancers in Latin America and the Caribbean by subregions, both sexes, incidence and mortality, 2020



Piñeiros *et al.*, The Lancet Regional Heath – Americas 2022

Gastric Cancer Incidence

Estimated age-standardized incidence rates (World) in 2020, stomach, both sexes, ages 25+



Data source: GLOBOCAN 2020
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

The proportion of the Latin-American population covered by the existing cancer registries in the region is ~20%, with high-quality information coverage estimated at 7.1%

Latin America Hub

IARC Hub Liaison

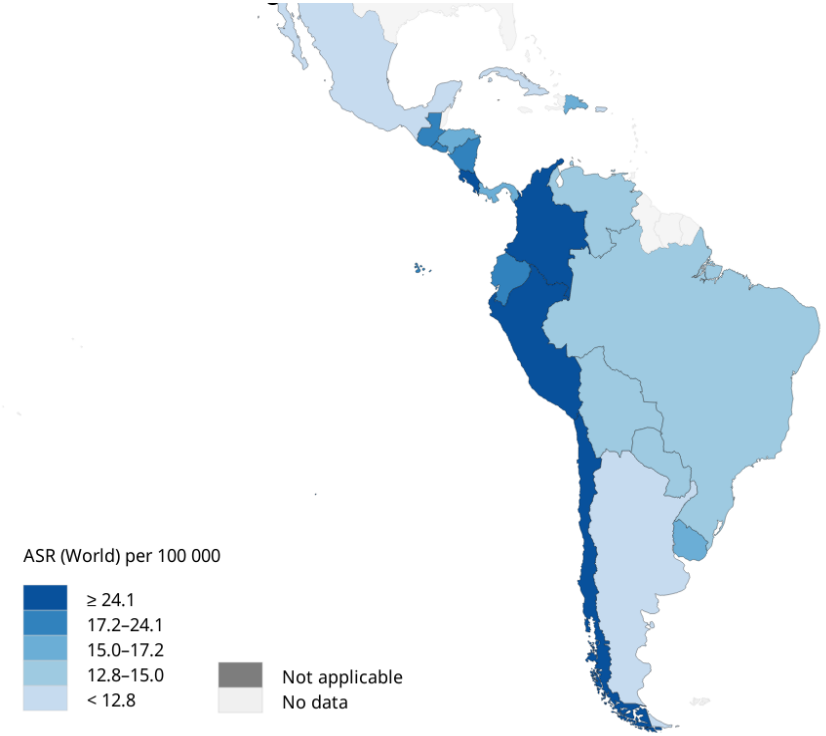
Dr Marion Piñeros

Hub officer, International Agency for Research on Cancer, Lyon, France

Buenos Aires, Argentina
Established in 2013

Piñeros *et al*., Rev Panam Salud Publica 2017

Estimated age-standardized incidence rates (World) of gastric cancer in 2020, both sexes, ages 25+

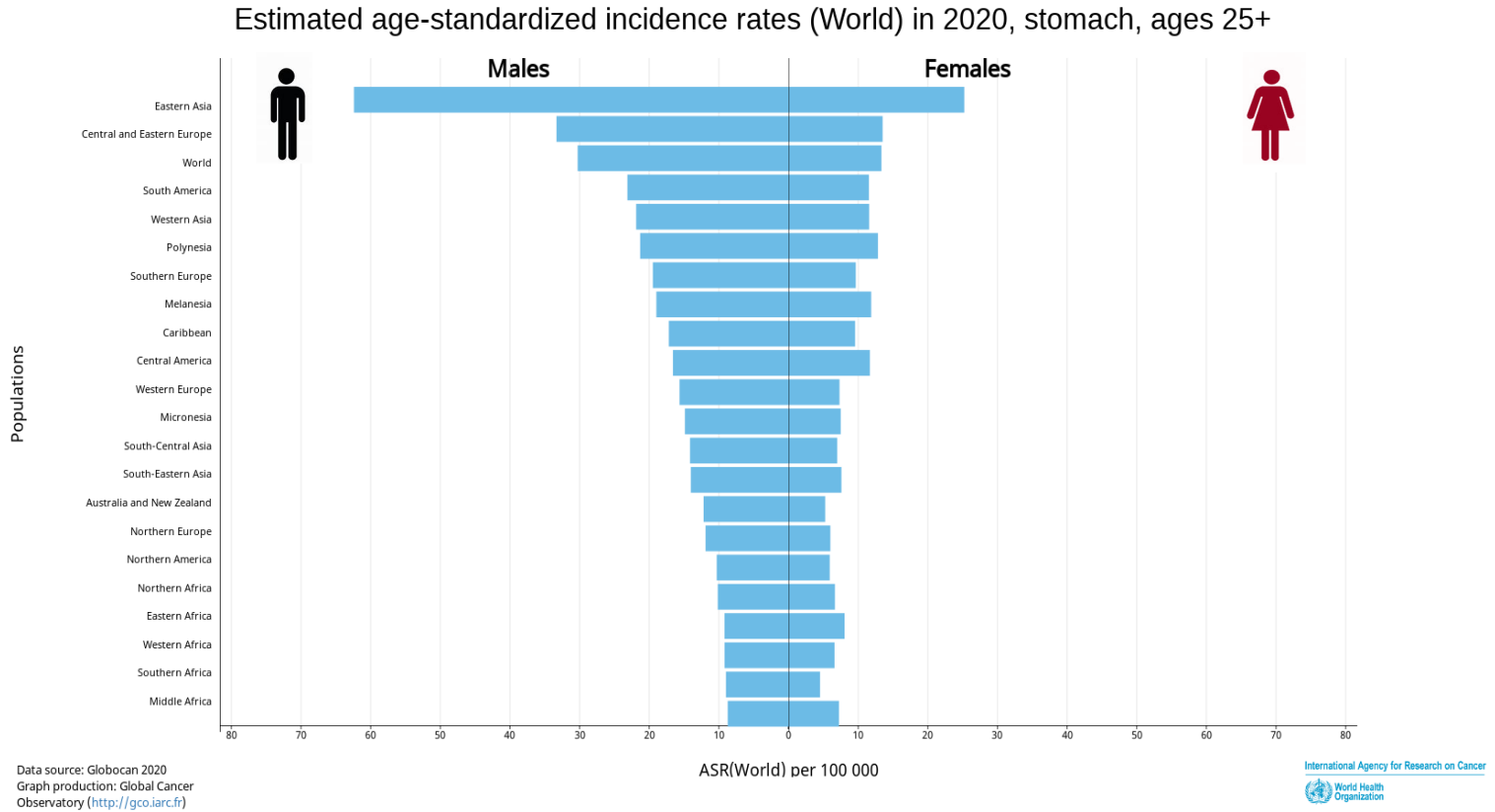


Population	ASR(W)
Peru	29.2
Chile	25.1
Colombia	24.6
Costa Rica	24.5
Ecuador	24.0
Guatemala	23.3
Nicaragua	19.8
El Salvador	17.5
Panama	17.0
Honduras	15.8
Uruguay	15.4
Dominican Republic	15.1
Bolivia, Plurinational State of	14.9
Brazil	13.6
Paraguay	13.2
Venezuela, Bolivarian Republic of	13.0
Argentina	12.1
Mexico	11.9
Cuba	10.0
Puerto Rico	4.8

Data source: GLOBOCAN 2020
Map production: IARC
(http://gco.iarc.fr/today)
World Health Organization

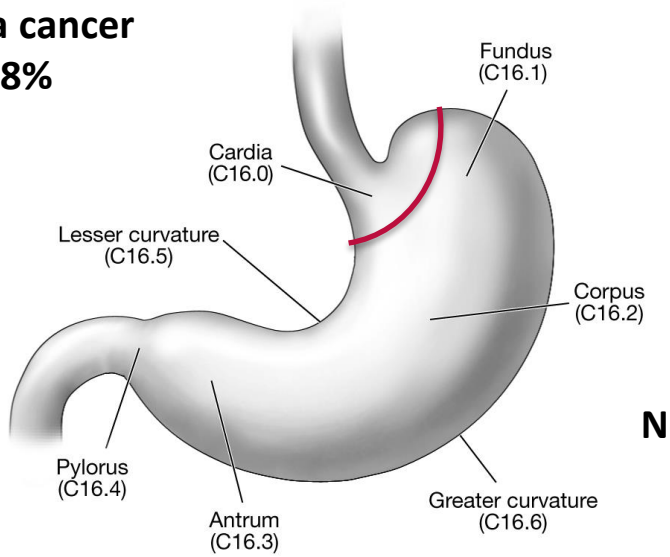
World Health Organization

Global Pattern of Male Predominance in Gastric Cancer, 2020



Anatomical subsites of gastric cancer

Cardia cancer
18%



Noncardia cancer
82%

Arnold *et al,* Gut 2020

Risk factors for gastric cancer by anatomical subsite

Level of evidence	Risk factor	Noncardia	Cardia
Convincing	Chronic *H. pylori* infection[1, 2]	↑	↓↑(E)
	Smoking[3]	↑	↑
Probable	High consumption of fruits and vegetables[4-6]	↓	↓
	Excessive salt/salty food consumption[7,8]	↑	↑
	High consumption of processed meat[9]	↑	↑
	Excess weight[6,10]	Null	↑
	Reflux[11]	?	↑
	Epstein-Barr virus infection[12]	↑	↑
	High consumption of alcohol[6,13]	↑	↑
	Autoimmunity[14]	↑	?
	Type II diabetes[15]	↑	↑
Suggestive	Estrogens[16]	↓	?
	Some genetic variants[17-20]	↑	↑

E= endemic areas

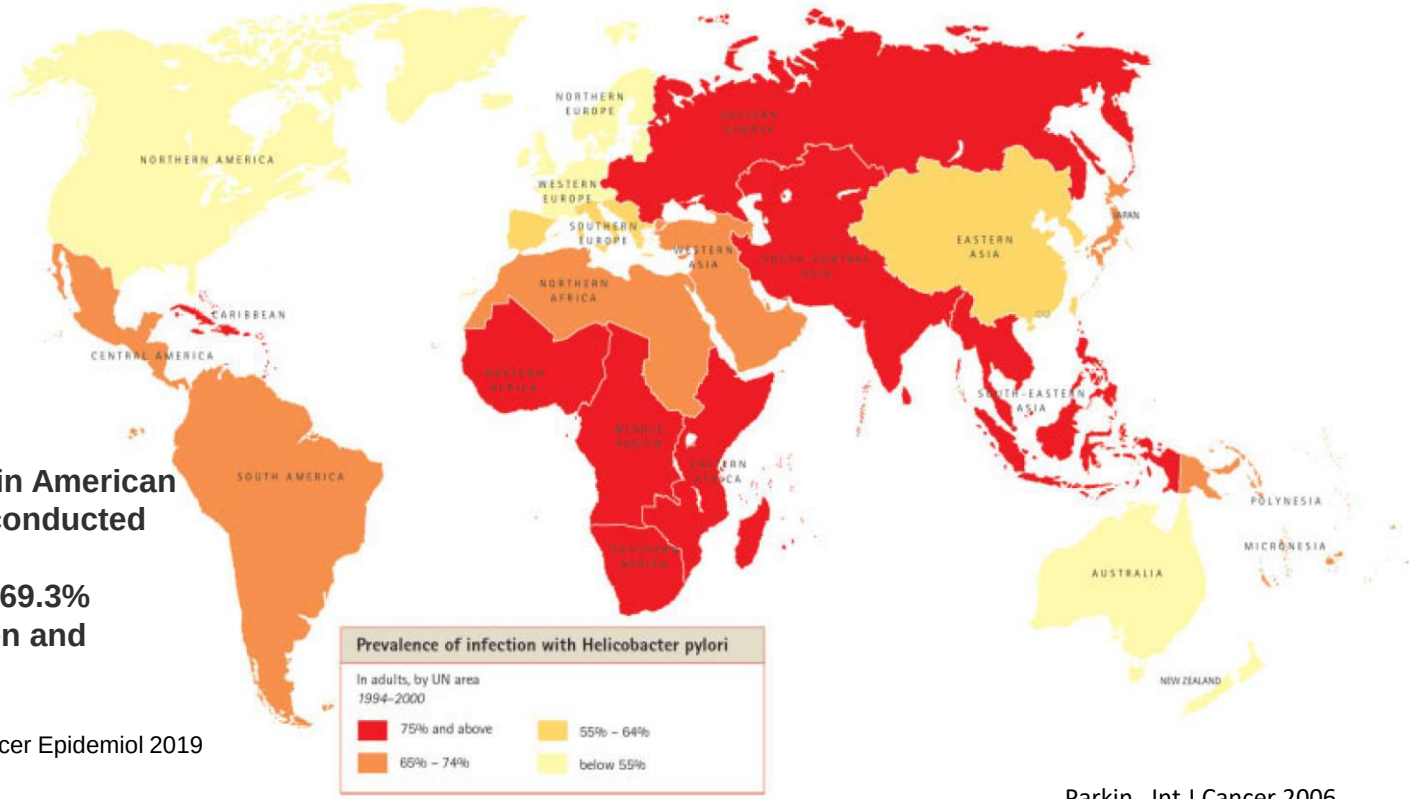
[1]Helicobacter and Cancer Collaborative Group, Gut 2001; [2]de Martel, Lancet Glob Health 2020; [3]Ladeiras-Lopez, Cancer Causes Control 2008; [4]Lunet, Eur J Cancer Prev 2007; [5]Lunet, Nutr Cancer 2005; [6]WCRF/AICR, 2016; [7]Tsugane, Gastric Cancer 2007; [8]D'Elia, Clin Nutr 2012; [9]Larsson, JNCI 2006; [10]Yang, Eur J Cancer 2009; [11]Forman, Aliment Pharmacol Ther 2004; [12]Murphy, Gastroenterol 2009; [13]Han, Oncotarget 2017; [14]Song, Cancer Res Treat 2019; [15]Ohkuma, Diabetologia 2018; [16]Camargo, CEBP 2012; [17]Gonzalez, Int J Cancer 2002; [18]Abnet, Nat Genet 2010; [19]Wang, Gut 2015; [20]Mocellin, Gut 2015.

H. pylori was responsible for ~800,000 new gastric cancer cases in 2018

	Total		
	New cases	New cases attributable to infectious pathogens	
Helicobacter pylori			
Non-cardia gastric cancer	850 000	760 000	**90%**
Cardia gastric cancer	180 000	36 000	**20%**
Non-Hodgkin lymphoma of gastric location	22 000	16 000	**72%**

de Martel *et al.*, Lancet Glob Health 2020

Prevalence of *H. pylori* infection in adults, 1994-2000



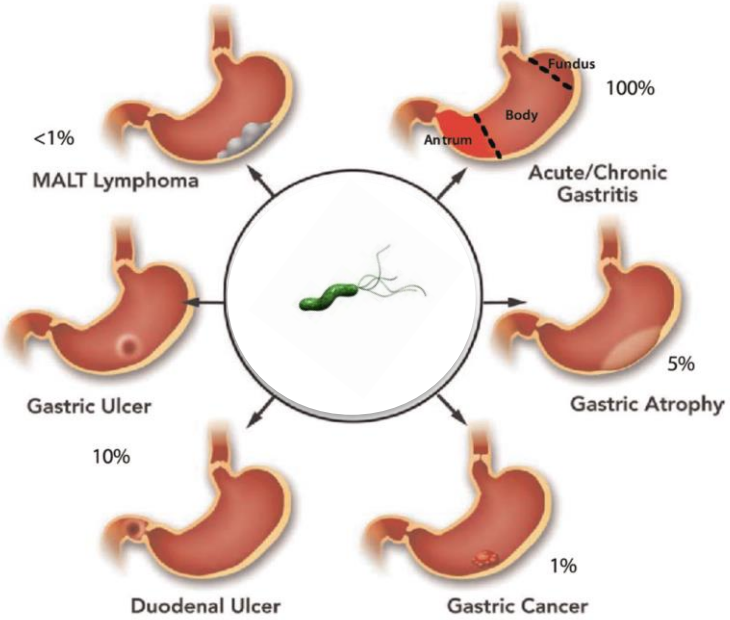
Meta-analysis of 22 Latin American studies (14 countries) conducted between 1987-2012:

- **Prevalence in adults 69.3%**
- **Prevalence in children and adolescents: 48.4%**

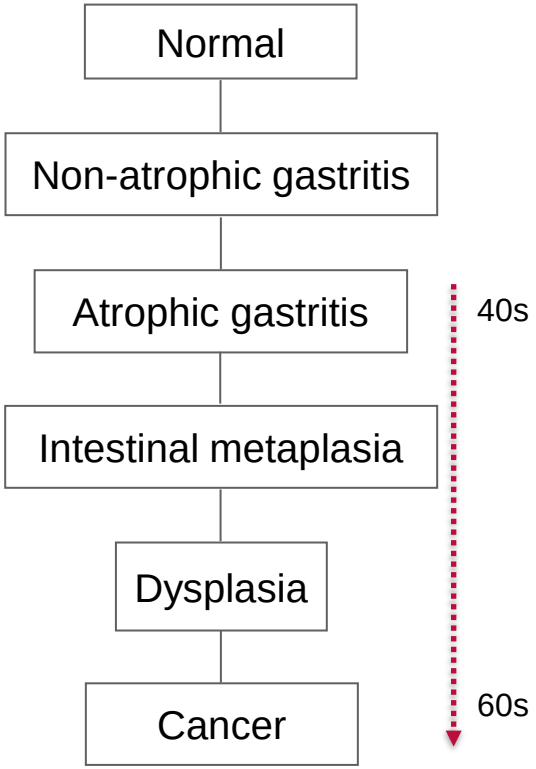
Curado *et al.*, Cancer Epidemiol 2019

Parkin, Int J Cancer 2006

Model of noncardia gastric carcinogenesis

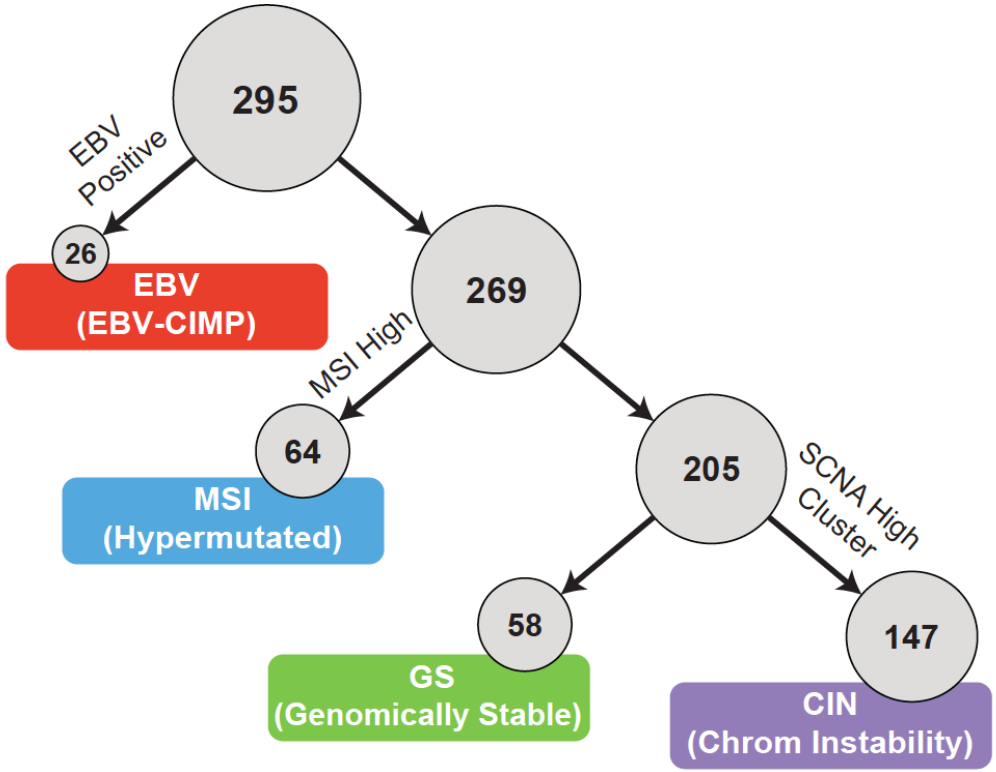


Adapted from Sachs *et al*., F1000 Reports 2012



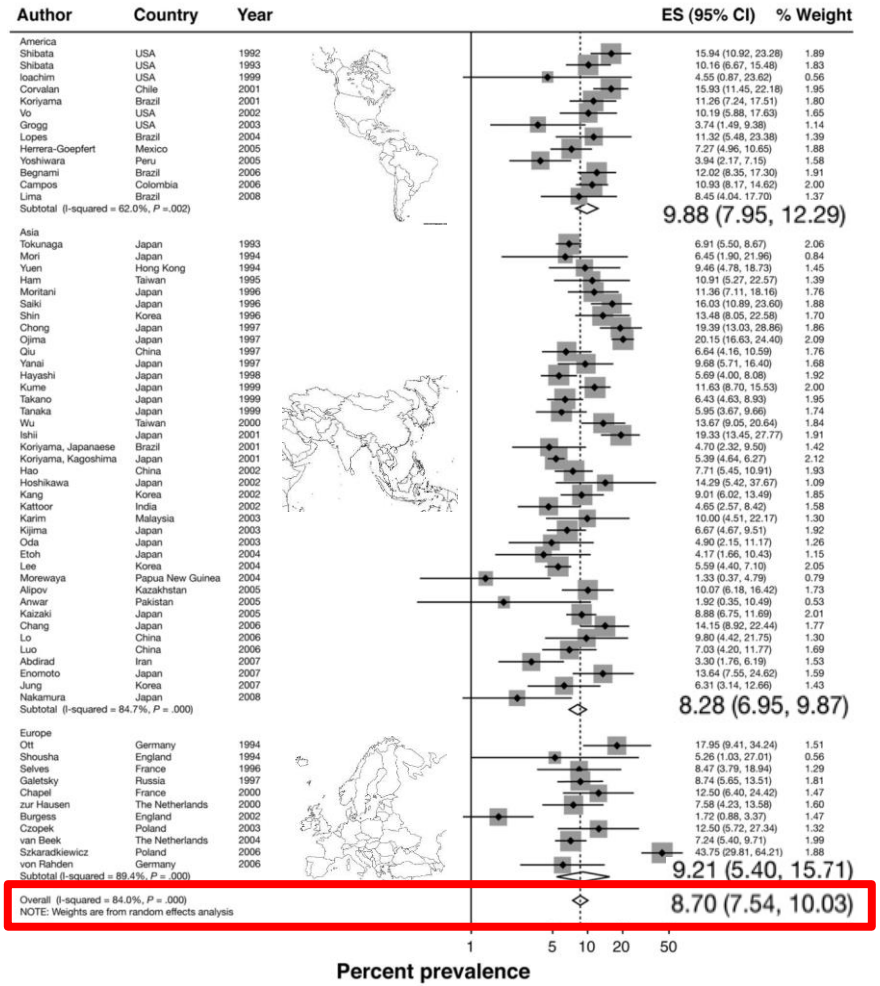
Correa *et al*. Lancet 1975

Molecular classification of gastric adenocarcinoma
The Cancer Genome Atlas



TCGA Analysis Working Group, Nature 2014

EBV prevalence in gastric tumors



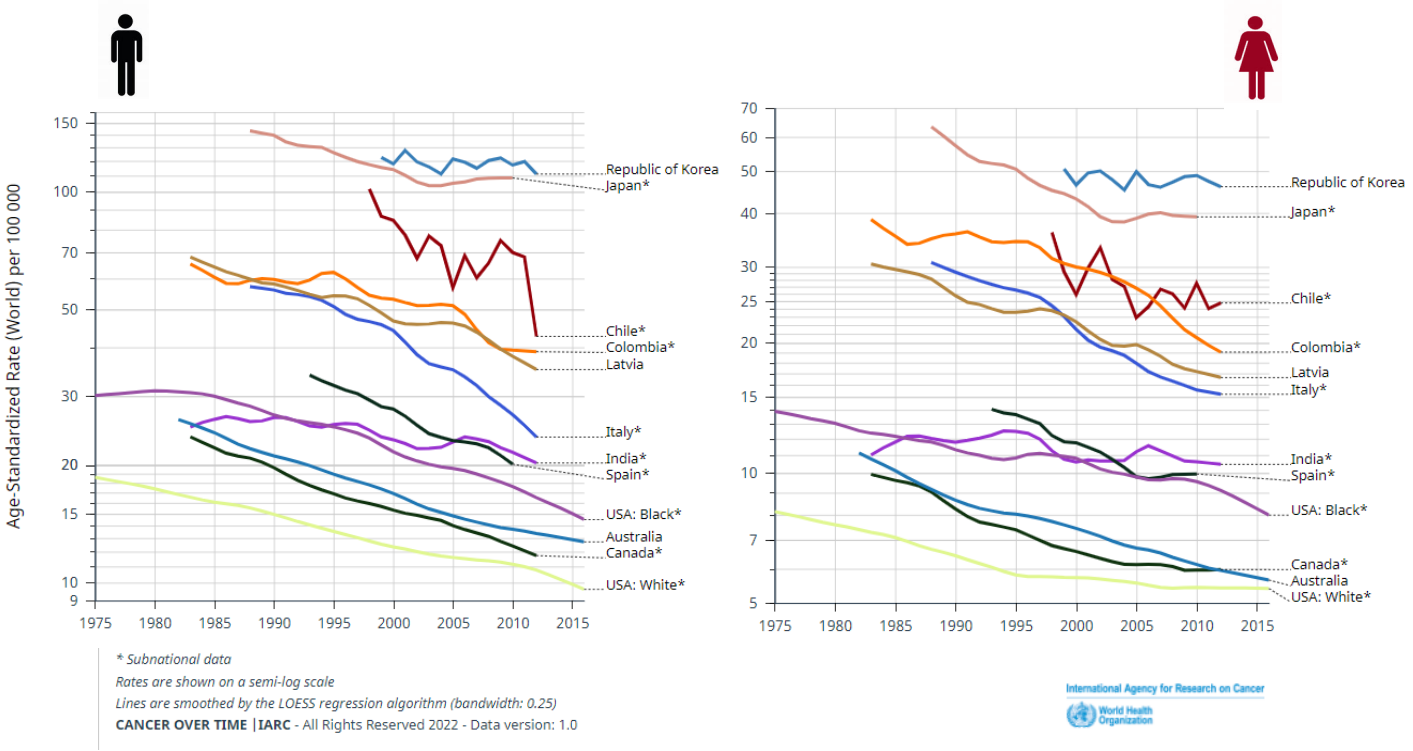
Murphy *et al.*, Gastroenterology 2009

Tumor EBV prevalence in Latin American populations

Country	Population	N	%
Brazil	Sao Paulo (non-Japanese-Brazilians)[1]	151	11
	Sao Paulo[2]	53	11
	Sao Paulo[3]	103	12
	Fortaleza[4]	100	8
Chile	Santiago[5]	185	17
Colombia	Cali[6]	178	13
	Cali y Bogota[7]	368	11
	Ibague (unpublished)	73	14
Costa Rica	Cartago (unpublished)	99	22
México	Ciudad de México[8]	330	7
	Ciudad de México y Merida[9]	75	11
Perú	Lima[10]	254	4

[1]Koriyama *et al.*, 2001; [2]Lopes *et al.*, 2004; [3]Begnami*et al.*, 2006; [4]Lima *et al.*,2008; [5]Corvalan *et al.*, 2001; [6]Carrascal *et al.*,2003 ; [7]Campos *et al.*, 2006; [8]Herrera-Goepfert *et al.*, 2005; [9]Martínez-López *et al.*, 2014; [10]Yoshiwara *et al.*, 2005

Trends in incidence of gastric cancer in selected countries



Impact of sanitation, refrigeration and widespread use of antibiotics

OXFORD

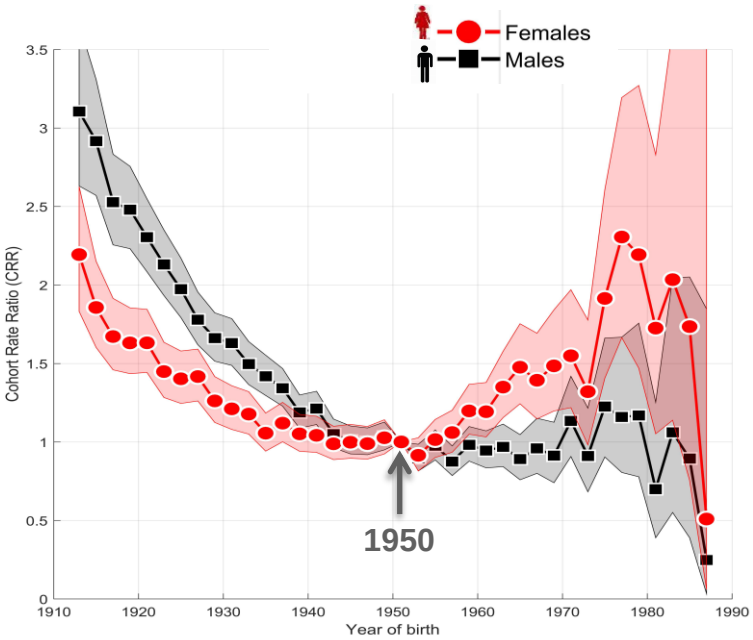
JNCI J Natl Cancer Inst (2018) 110(6): djx262

doi: 10.1093/jnci/djx262
Article

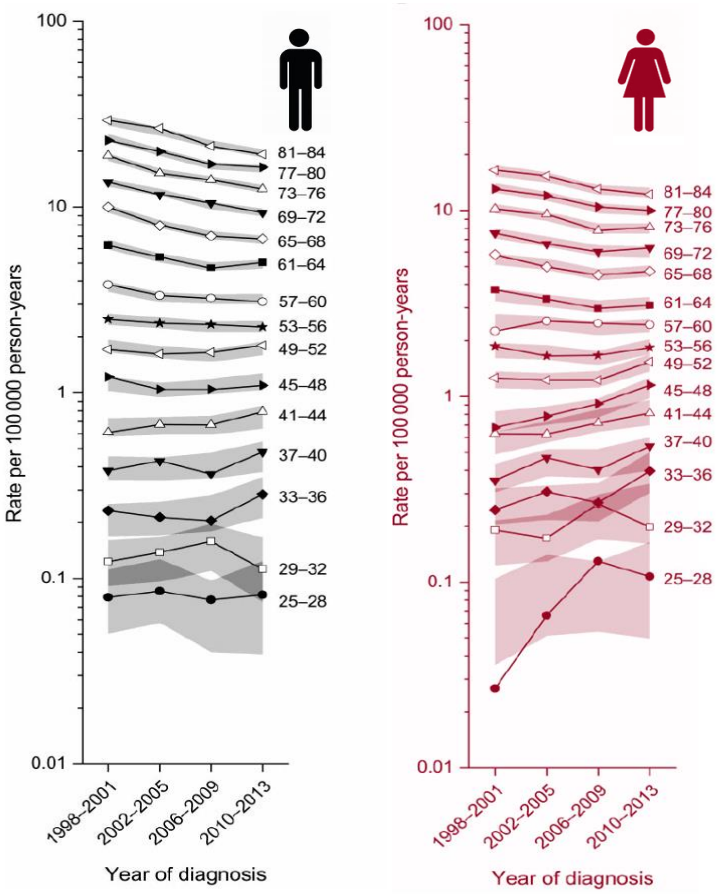
ARTICLE

The Changing Face of Noncardia Gastric Cancer Incidence Among US Non-Hispanic Whites

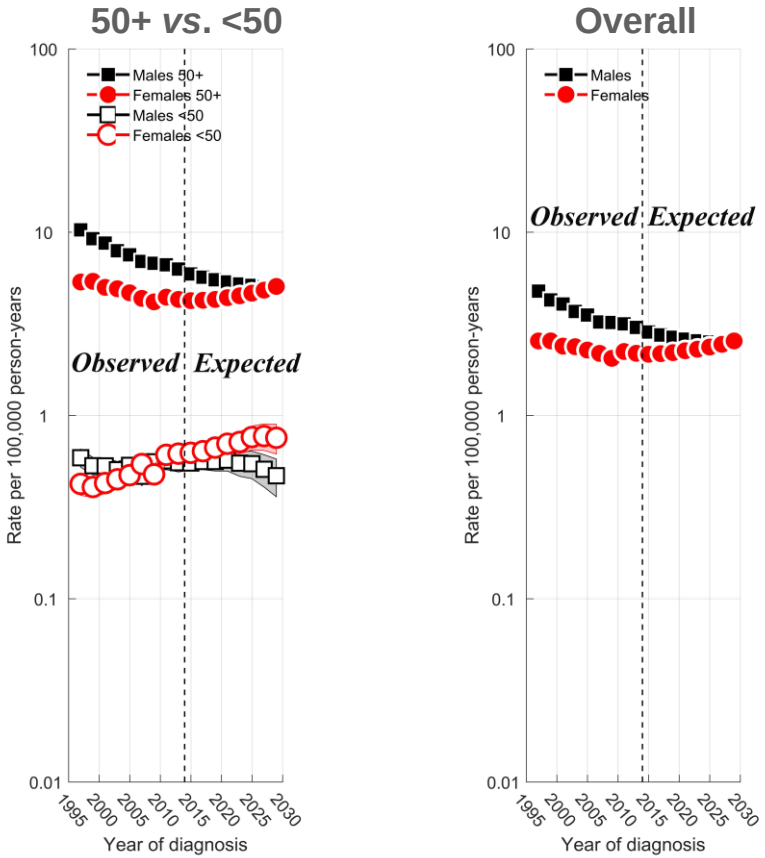
William F. Anderson, Charles S. Rabkin, Natalie Turner,
Joseph F. Fraumeni Jr., Philip S. Rosenberg, M. Constanza Camargo



NAACCR, 1995-2013



Observed and Expected Age-standardized Incidence of Noncardia Gastric Cancer among non-Hispanic Whites



Anderson *et al.*, JNCI 2018

Noncardia Gastric Cancer Increasing in Hispanic whites, but not in Blacks or Other Races (mainly Asians)

Hispanics all races		
	<50 years	50+ years
	EAPC	EAPC
Male	0.15	-2.58*
Female	**0.73***	-1.95*
non-Hispanic Blacks		
	<50 years	50+ years
Male	-2.36*	-1.88*
Female	0.51	-1.69*
non-Hispanic others		
	<50 years	50+ years
Male	-2.72*	-2.94*
Female	-0.41	-2.96*

*Statistically significant EAPC at the $p<0.05$ level

Anderson *et al.*, JNCI 2018

Rising noncardia gastric cancer rates mainly restricted to counties <20% prevalence of poverty

% Poverty		<50 years	50+ years
		EAPC	EAPC
<10	Male	0.56	-3.28*
	Female	**3.93***	-2.14*
10 - 19.9	Male	0.36	-3.12*
	Female	1.57*	-2.22*
20+	Male	-2.65	-3.16*
	Female	2.33	-1.74*

*Statistically significant EAPC at the $p<0.05$ level

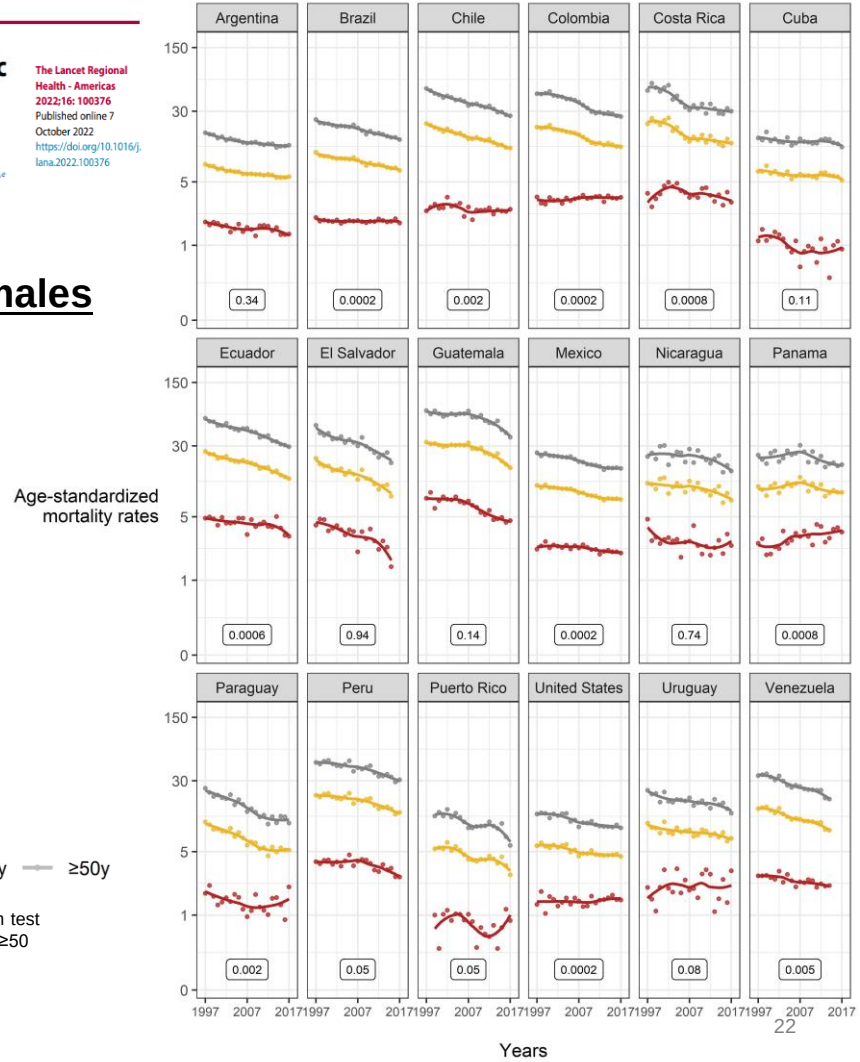
Anderson *et al.*, JNCI 2018

Sex and age differences in mortality trends of gastric cancer among Hispanic/Latino populations in the United States, Latin America, and the Caribbean

The Lancet Regional Health - Americas
2022;16: 100376
Published online 7 October 2022
https://doi.org/10.1016/j.lana.2022.100376

J. Smith Torres-Roman,[a,b,*] Christian S. Alvarez,[c] Pedro Guerra-Canchari,[b,d] Bryan Valcarcel,[b] José Fabián Martinez-Herrera,[b,e] Carlos A. Dávila-Hernández,[f] Camila Alves Santos,[b,g] Samara Carollyne Mafra Soares,[b,g] Dyego Leandro Bezerra de Souza,[b,g,h] and M. Constanza Camargo [c]

Mortality trends among females



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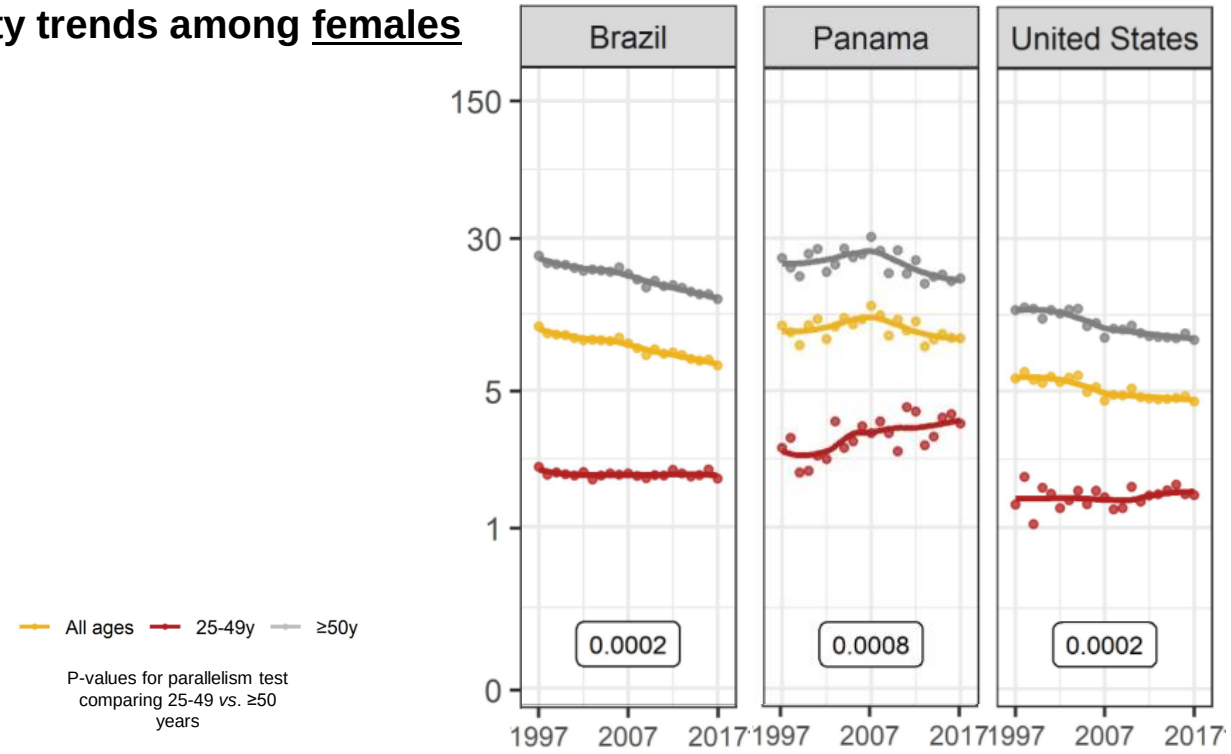
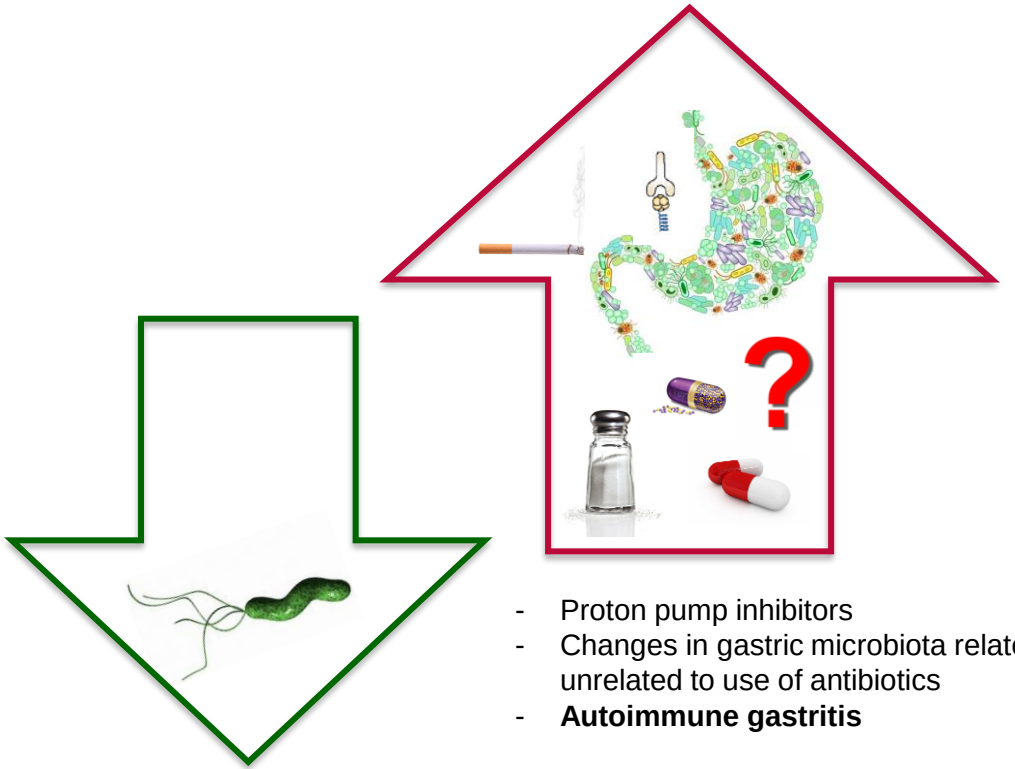


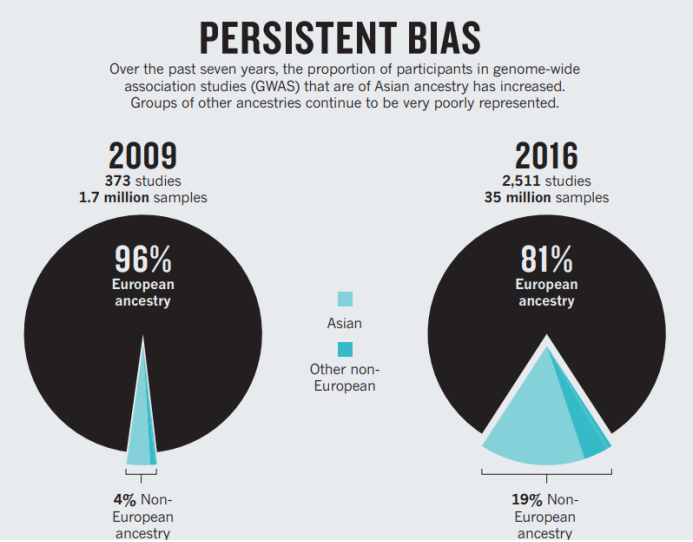
P-values for parallelism test comparing 25-49 *vs*. ≥50 years

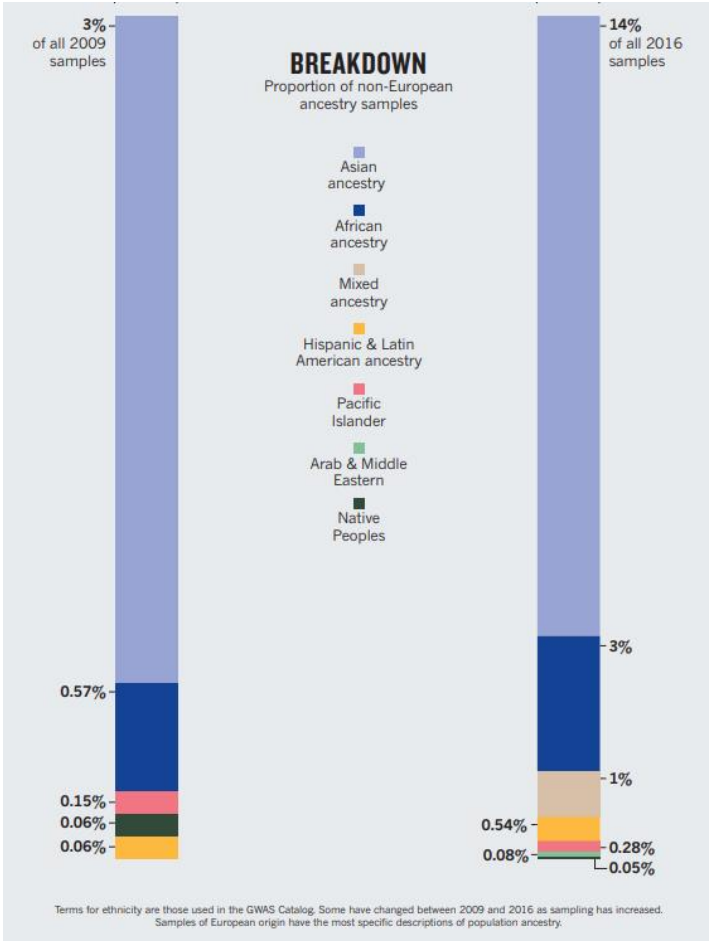
Potential Changes in the Etiologic Fractions of Major and Potential Risk Factors



- Proton pump inhibitors
- Changes in gastric microbiota related or unrelated to use of antibiotics
- **Autoimmune gastritis**

Genomics is failing on diversity

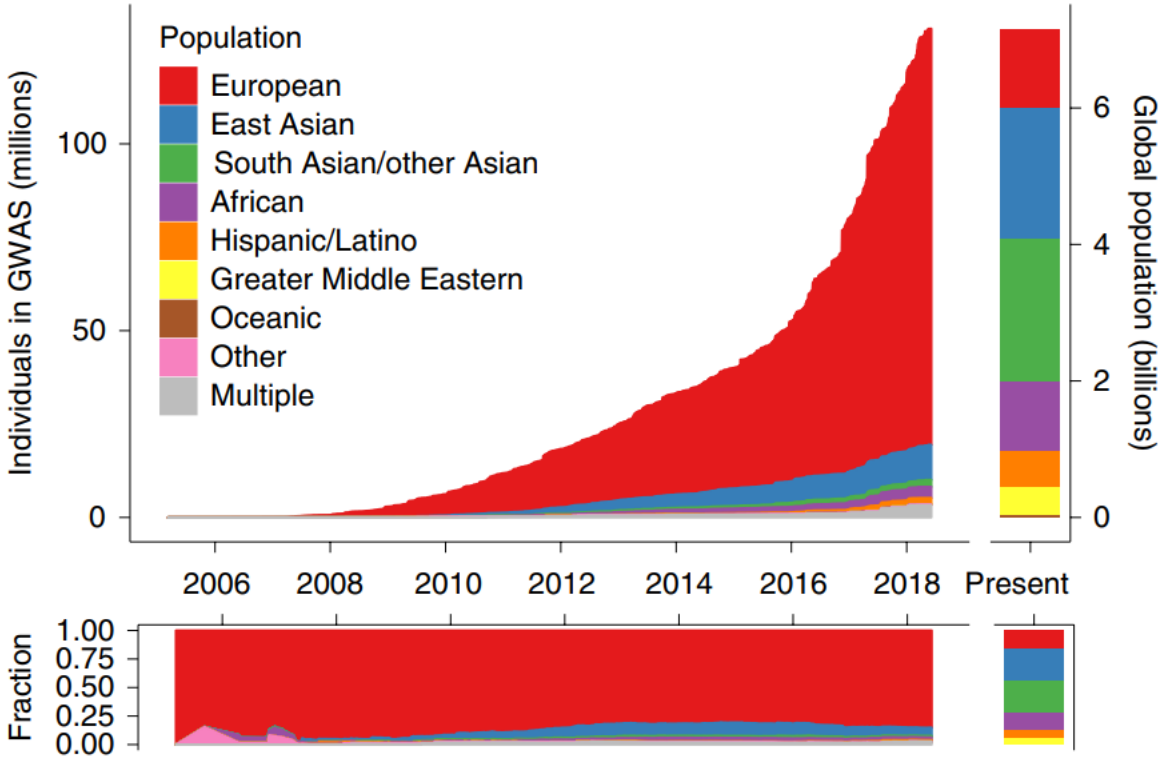




Hispanics/Latinos: 0.5%

Popejoy and Fullerton, Nature 2016

Ancestry of GWAS participants over time -- compared with the global population



Martin *et al.*, Nat Genet 2019

Heritability of Gastric Cancer

Proportion of variation among individuals that can be attributed to genes

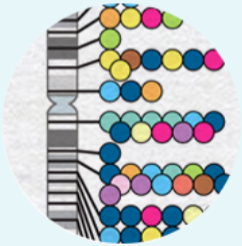
<u>Nordic populations</u>

- Lichtenstein *et al*.: 28%
- Mucci *et al.*: 22%

<u>East Asian populations</u>

- Dai *et al.*: 20%
- Sampson *et al.*: 25%

Lichtenstein *et al*., NEJM 2000; Sampson *et al*., JNCI 2015; Mucci *et al*., JAMA 2016; Dai *et al*., IJC 2017



GWAS Catalog

The NHGRI-EBI Catalog of human genome-wide association studies

GLOBAL CORE BIODATA RESOURCE

gastric cancer

Examples: breast carcinoma, rs7329174, Yao, 2q37.1, HBS1L, 6:16000000-25000000

feedback

Refine search results

- Publications 8
- Traits 11
- Genes 5

Search results for *gastric cancer*

gastric cancer MONDO_0001056

A primary or metastatic malignant neoplasm involving the stomach.

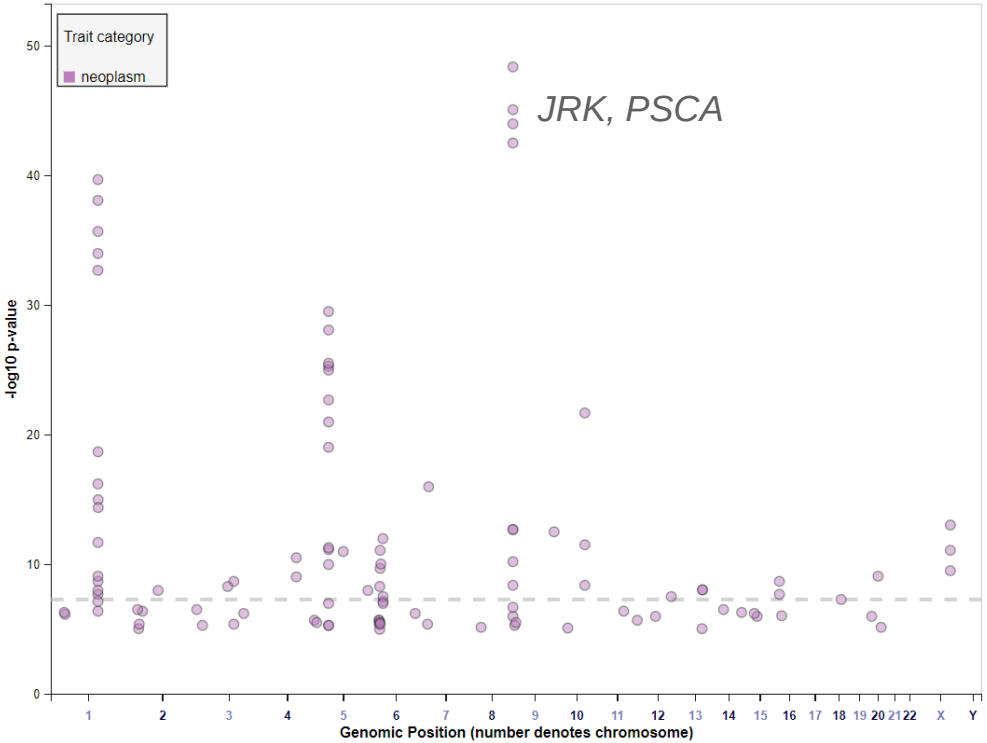
Associations 130 Studies 26

Gastric Cancer GWAS in the East Asian and European populations

First author	Population	Publication year
Abnet	East Asian	2010
Shi	East Asian	2011
Helgason	European	2015
Park	East Asian	2018
Tanikawa	East Asian	2018
Yan	East Asian	2019
Ishigaki	East Asian	2020
Rashkin	European	2020
Jin	East Asian	2020
Sakaue	European and East Asian	2021
Nam	East Asian	2022
Hess and Maj	European	2023

Total No. cases: ~48,000

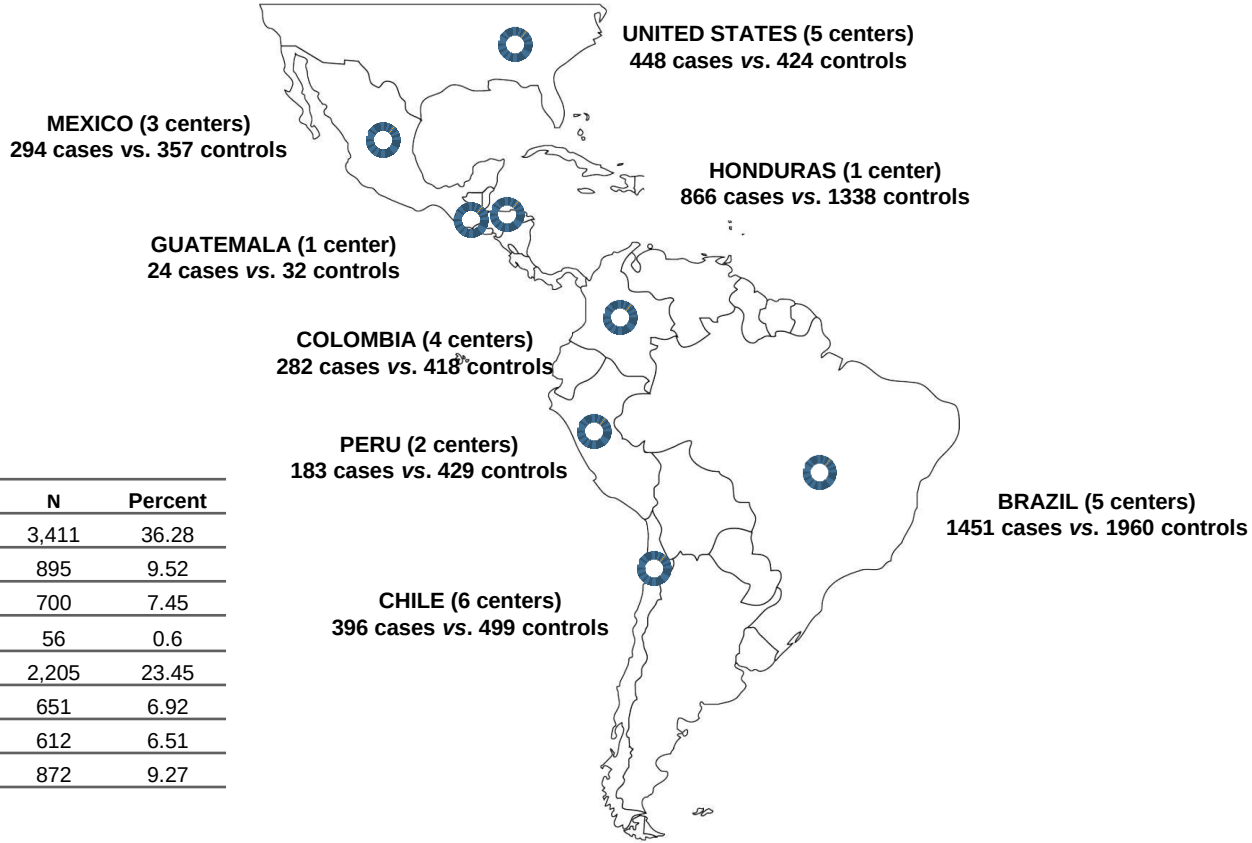
GWAS hits across all studies



ABO, ACYP2, ARC, MROH4P, ARL4C, ASH1L, BDKRB1, ATG2B, C7, CCDC32, CHST14, CHD6, CUX2, DEFB121, DNAH11, ECRG4, FAM183A, GAPDHP77, RNU6-309P, GBAP1, GON4L, HLA-C, HLA-F, HLA-U, HLA-A, ILF2P2, BRMS1L, JRK, KCNU1, KRTCAP2, LINC01068, LINC02161, LINC02363, MYL12BP2, LINC02516, LINC02580, LMNA, LRFN2, LRIG3, LINC02388, MAS1LP1, MAST2, MICA, HLA-S, MIR4457, TERT, MLN, LINC01016, MTX1; THBS3; MUC1, NPIPB2, NPM1P28, OARD1, UNC5CL, OPCML, PLCE1, PPP1R10, PRKAA1, PSCA, LY6K, PTGER4, TTC33, PTMAP5, HIGD1AP2, RANBP6, RMDN2, RNMTL1P2, PRPS1L1, RNU6-309P, GAPDHP77, RPL3P2, WASF5P, SIGLEC15, SMARCA2, SMIM15P2, PGBD1, SMIM23, FGF18, SNAP25-AS1, TACC1P1, TATDN2, THBS3, MTX1, THBS3-AS1, TRPM1, TTC33, U6, UNC5CL, VN1R10P, ZNF204P, VPS35L, ZBTB20, ZNF603P, ZNF192P1

GWAS Catalog – June 2023

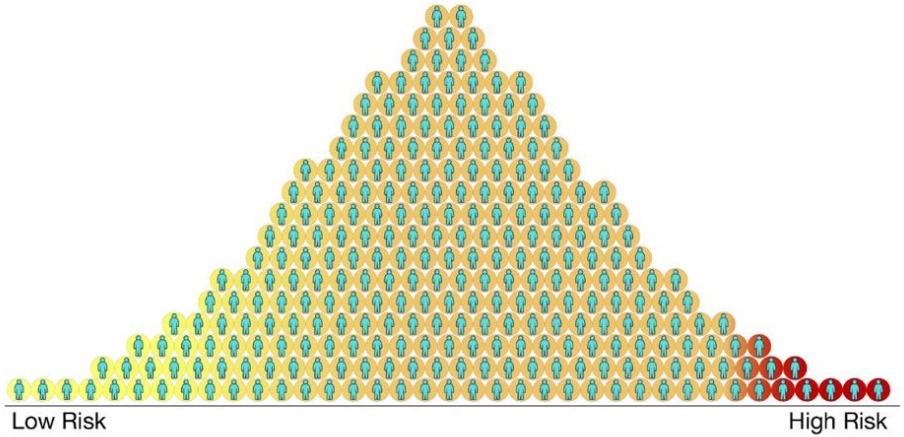
GWAS in Hispanic/Latino populations: 3,944 cases and 5,457 controls



Country	N	Percent
Brazil	3,411	36.28
Chile	895	9.52
Colombia	700	7.45
Guatemala	56	0.6
Honduras	2,205	23.45
Mexico	651	6.92
Peru	612	6.51
USA	872	9.27

Polygenic risk score (PRS)

- A PRS aggregates the effects of many genetic variants into a single number which predicts genetic predisposition for a phenotype
- PRS are typically composed of hundreds-to-millions of variants which are combined using a weighted sum of allele dosages multiplied by their corresponding effect sizes, as estimated from a relevant GWAS



https://www.cdc.gov/genomics/disease/polygenic.htm

Health Care and Public Health Implications

- PRS can provide a measure of disease risk due to your genes
- Combining PRS with other risk factors can give a better idea of how likely someone is to get a specific disease than considering either alone
- Knowing how likely someone is to get a disease can help you take steps to prevent a disease or find it earlier
- PRS can also be combined with other factors to help predict how a disease will progress and how well you will respond to a treatment

https://www.cdc.gov/genomics/disease/polygenic.htm

Latest release: **June 1, 2023**

The Polygenic Score (PGS) Catalog

An open database of polygenic scores and the relevant metadata required for accurate application and evaluation.

gastric cancer

Examples: breast cancer, glaucoma, BMI, EFO_0001645

Feedback

New tool!

We just released **pgsc_calc**: a reproducible workflow to calculate both PGS Catalog and custom polygenic scores. See more information

Explore the Data

In the current PGS Catalog you can **browse** the scores and metadata through the following categories:

Polygenic Scores	Traits	Publications
3,664	617	461

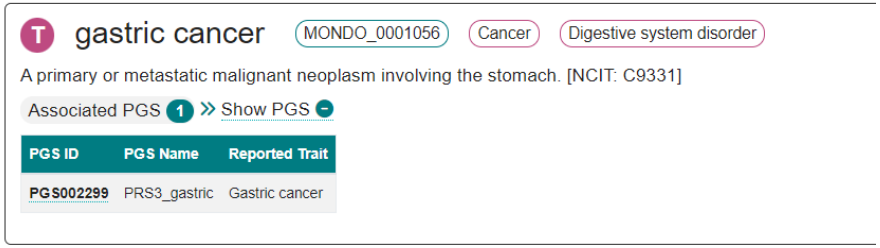
Development of the **PGS Catalog** is supported by:

University of Cambridge, Department of Public Health and Primary Care

EMBL-EBI

HDRUK Health Data Research UK

Baker Heart & Diabetes Institute



272 UK Biobank cases

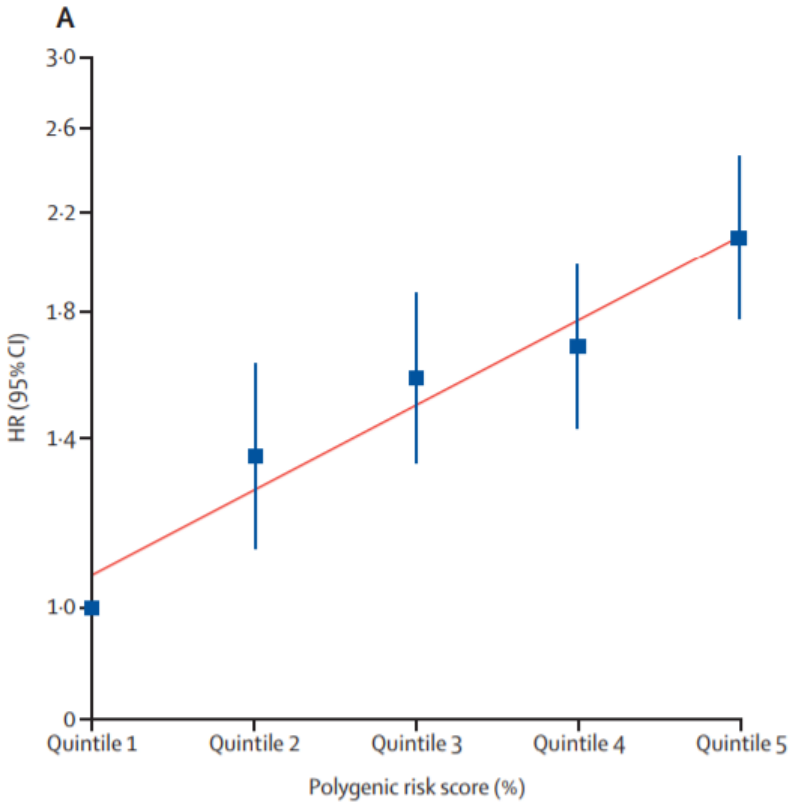
		PRS, Mean ± SD			
Number of SNPs	Number of loci	Cases	Noncases	*P* value	AUC (95% CIs)
3	3	0.82 ± 0.24	0.78 ± 0.24	.01	0.56 (0.53-0.60)

Cancer	Q1 (low)	Q2	Q3	Q4	Q5	*P* for trend
Gastric						
Number of cases	42	44	74	52	60	
HR (95% CI)	1.00 (Reference)	1.21 (0.79-1.84)	1.60 (1.10-2.34)	1.40 (0.93-2.10)	1.75 (1.18-2.59)	.005

PRS groups			
Top 5%	Top 1%	Bottom 5%	Bottom 1%
1.27 (0.75-2.15)[a]	1.27 (0.75-2.15)[b]	0.82 (0.47-1.43)[c]	0.53 (0.07-3.83)[d]

Choi et al., IJC 2020

Polygenic Risk Score in Chinese individuals (n=112 SNPs; $p<5\times10^{-5}$)



GWAS: 10,254 cancer and 10,914 controls

Effectiveness within Kadoorie Biobank (n=100,220)

- 692 gastric cancer cases during a median follow-up of 10·4 years

Jin *et al*., Lancet Oncology 2020

	Number of cases/ person-years	Hazard ratio (95% CI)	p value	p_{trend} value	Absolute risk over 10 years (95% CI)	Absolute risk reduction over 10 years (95% CI)	Number of participants who needed to adhere to a healthy lifestyle*
Low genetic risk	..	..	..	0·0051	..	..	..
Unfavourable lifestyle	33/34 206	1 (ref)	..	..	1·00% (0·65–1·34)	0 (ref)	..
Intermediate lifestyle	50/135 331	0·52 (0·31–0·88)	0·014	..	0·38% (0·27–0·49)	0·62% (0·26–0·97)	162
Favourable lifestyle	5/28 465	0·30 (0·11–0·84)	0·022	..	0·18% (0·02–0·34)	0·82% (0·45–1·19)	122
Intermediate genetic risk	..	..	..	0·00013	..	..	..
Unfavourable lifestyle	138/105 718	1 (ref)	..	..	1·33% (1·11–1·56)	0 (ref)	..
Intermediate lifestyle	243/403 912	0·64 (0·51–0·83)	0·00027	..	0·61% (0·53–0·69)	0·72% (0·50–0·97)	139
Favourable lifestyle	32/82 545	0·51 (0·33–0·78)	0·0019	..	0·39% (0·26–0·53)	0·94% (0·69–1·22)	106
High genetic risk	..	..	..	0·027	..	..	..
Unfavourable lifestyle	61/35 662	1 (ref)	..	..	1·62% (1·20–2·03)	0 (ref)	..
Intermediate lifestyle	115/133 277	0·73 (0·52–1·03)	0·076	..	0·81% (0·66–0·97)	0·81% (0·36–1·19)	124
Favourable lifestyle	15/28 468	0·53 (0·29–0·99)	0·048	..	0·49% (0·24–0·74)	1·12% (0·62–1·56)	89

ref=reference. *Refers to the number needed to adhere to a healthy lifestyle to prevent one gastric cancer case in 10 years.

Table 2: **Risk of incident gastric cancer according to lifestyle and level of genetic risk**

Defined as not smoking, never consuming alcohol, the low consumption of preserved foods, and the frequent intake of fresh fruits and vegetables. No significant interaction between genetic risk and lifestyle factors was observed (p=0·45).

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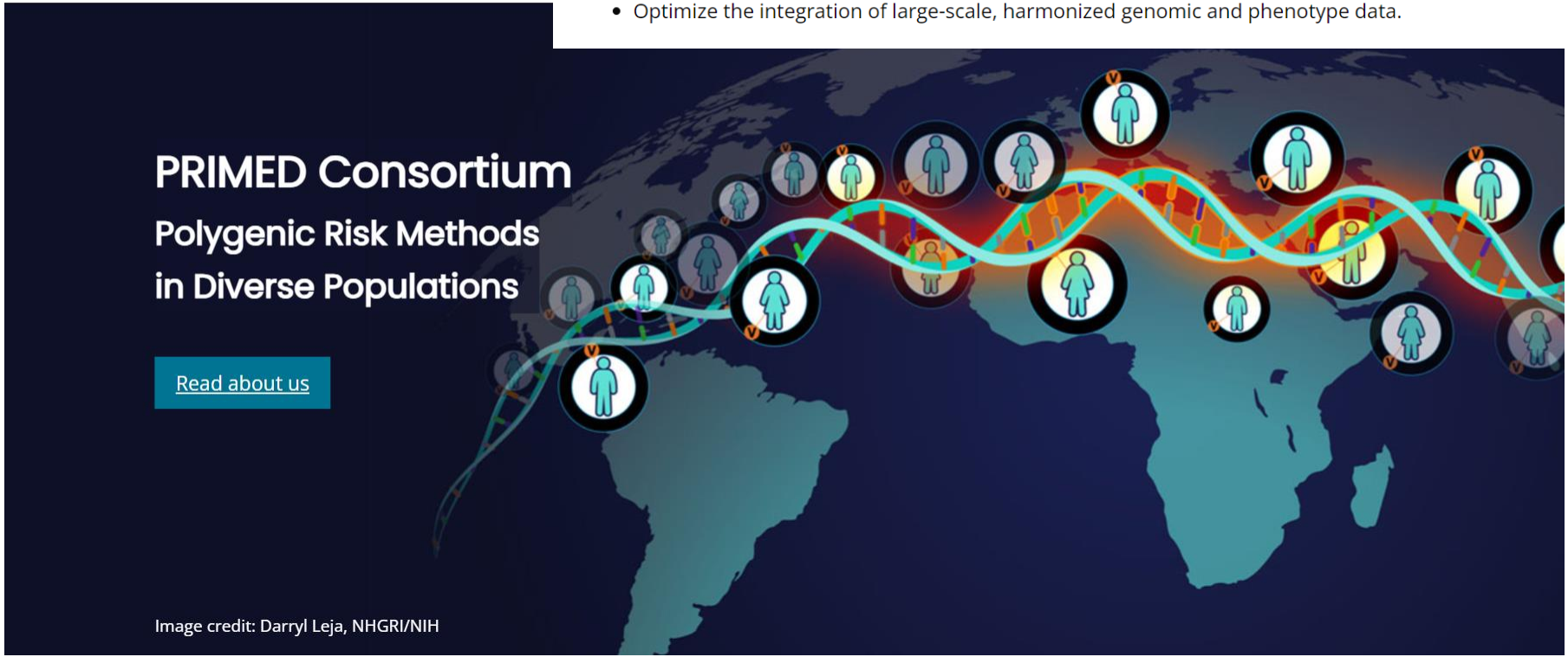
PRIMED consortium

The Polygenic RIsk MEthods in Diverse populations (PRIMED) Consortium is working to improve the methods and application of polygenic risk scores (PRS) in diverse populations. The consortium has two overarching goals:

- Improve the applicability of PRS in diverse populations.
- Optimize the integration of large-scale, harmonized genomic and phenotype data.



The PRIMED Consortium has the following goals:

1. Gather Diverse Datasets

Bring together large datasets with genomic and health measures from diverse ancestry populations

2. Develop New Methods

Develop new methods to improve genetic risk prediction across diverse populations for a broad range of health and disease outcomes

3. Enable Collaboration

Enable collaborative analysis by sharing PRS-related data, software, and other resources with the scientific community

4. Improve Health

Leverage existing precision medicine partner programs to develop, test, and refine PRS in diverse populations to improve health outcomes

Take home messages

- Additional GWAS are needed to identify risk variants to improve their PRS for risk prediction, especially by reflecting the ancestry and subtype (location, histology, molecular) of cancer

- Evaluation of the risk reduction benefit of *H. pylori* eradication in populations with different levels of genetic risk could be useful for an individualized primary gastric cancer prevention approach

- It is unknown whether individuals at a high genetic risk of gastric cancer would benefit more from endoscopic screening than those with a low genetic risk, which could ultimately improve secondary prevention

Key Collaborators

U.S. National Institutes of Health

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GWAS in Hispanic/Latino populations

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