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Big Data Approach in Gastrointestinal cancer research

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Outline

- Overview of Big Data approach
- Research on gastric cancer with Big Data approach (with examples)
- How to address common forms of biases in Big Data anlaysis
- Propensity score analysis

Where comes the Big Data ?

- Etymology of "Big Data" can be dated back to the 1990s
  - John Mashey, the then chief scientist at Silicon Graphics in California
- Datasets are exponentially expanding every day
  - Mobile communications, websites, social media/crowdsourcing, sensors, transaction process-generated data (e.g. sales queries, purchases), administrative, scientific experiments, science computing, industrial manufacturing
- Application of Big Data analysis
  - Technology giants (e.g. Amazon, Apple, Google) boost sales
  - Electoral strategies in political campaigns

Definition of Big Data

- No consensus
- Certain characteristics pertinent to the process of collection, storage, processing and analysis
- First described by Doug Laney in 2001 **(3 Vs)**
  - **V**olume (storage space for data recording & storage)
  - **V**elocity (speed of data generation & transformation)
  - **V**ariety (various data sources)
- Other proposed traits thereafter
  - Veracity, value, exhaustivity (n=all), fine-grained resolution, indexicality, relationality, extensionality, scalability, variability …

Big Data in Health

- Definition
  - Third Health Programme (2014-2020) from the Consumer, Health, Agriculture and Food Executive Agency (chafea) mandated by the European Commission
    - Large datasets collected routinely or automatically, and stored electronically
    - Merges existing databases and is reusable (i.e. multipurpose data not intended for a specific study)
    - Aim of improving health and health system performance
- Healthcare data volume projected to increased from 153 exabytes (10^{18}) in 2014 to 2,300 exabytes by 2020

Randomized controlled trials

- Advantages
  - no biases
  - no confounding

- Disadvantages
  - ethical issue
  - rare diseases, long term effect
  - rare exposures
  - resource intensive
  - not real-life situation (inclusion and exclusion criteria, differential level of care and follow-up)

Case-control study

- Advantages
  - multiple exposures
  - rare diseases
  - effects of harmful or beneficial exposures that are difficult/impossible to modify as in RCTs
  - cheap & quick

- Disadvantages:
  - rare exposures
  - multiple outcomes
  - Confounding
  - Biases

Prospective cohort study

- Advantages
  - multiple exposures and outcomes
  - rare exposures
  - effects of harmful or beneficial exposures that are difficult/impossible to modify as in RCTs

- Disadvantages
  - rare diseases, long term effect
  - Resource
  - Confounding
  - Biases

Large healthcare utilization databases

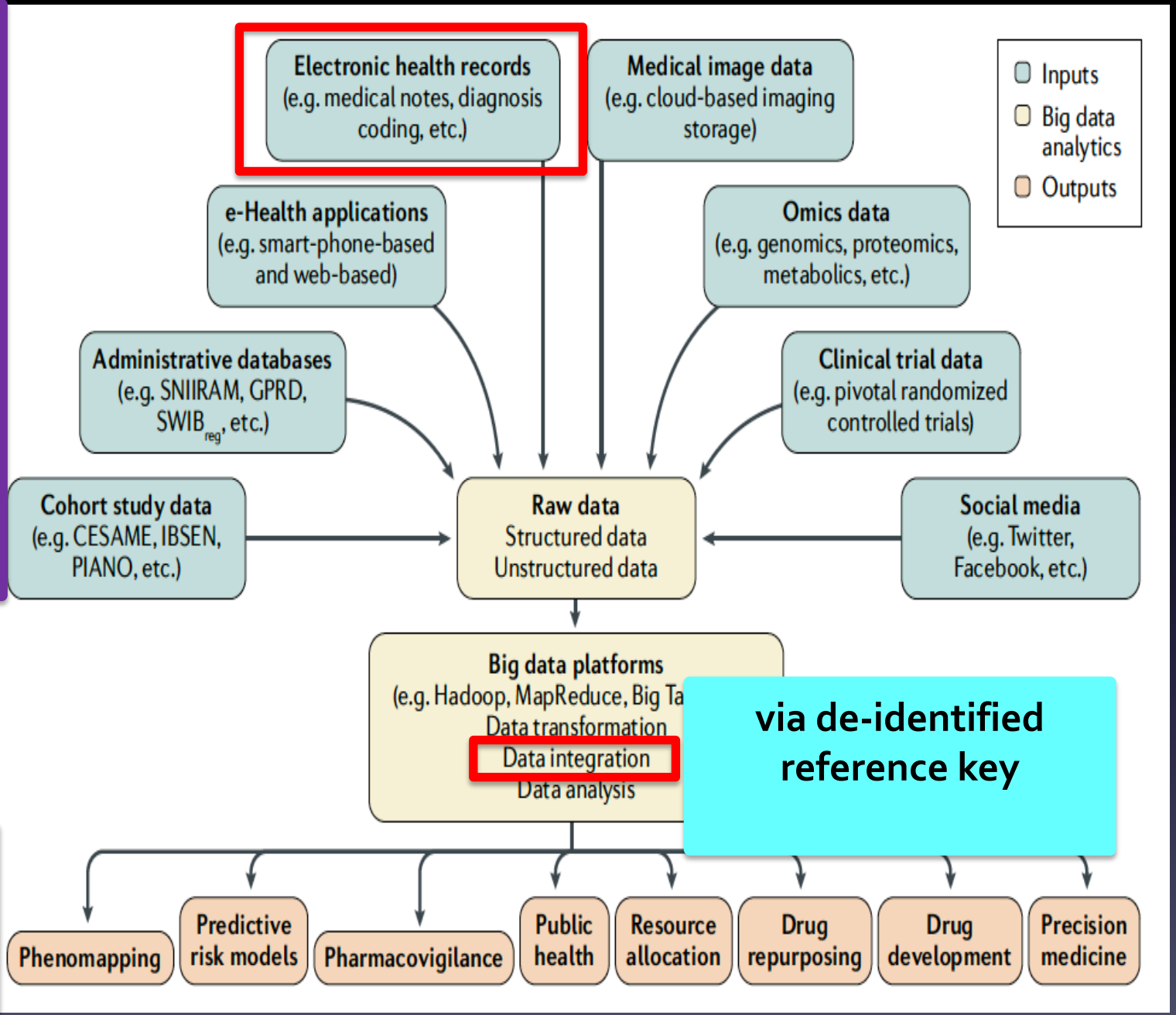
- Administrative or claims/insurance purpose
- Retrospective cohort study

  (non-concurrent / historical cohort study)
- Nested case-control study

Large healthcare utilization databases

Retains the advantages and corrects the disadvantages of both case-control and prospective cohort study design

Sources of Big Data



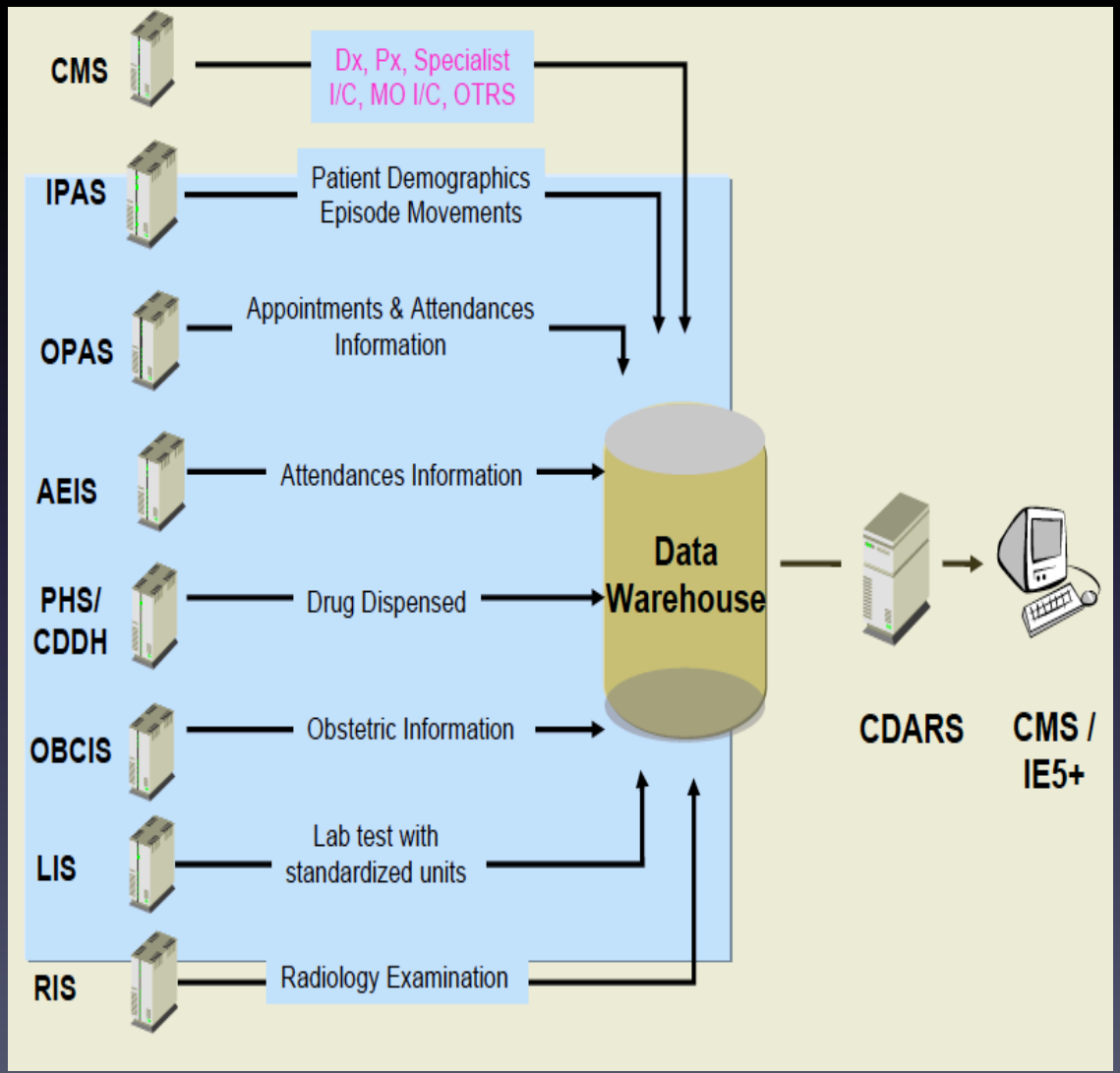
Application of Big Data analysis

Olivera P, et al. Nat Rev Gastroenterol Hepatol 2019

Population-based healthcare database

- US: Veterans Affairs, Kaiser Permanente
- Danish
- Swedish
- UK Twin Studies

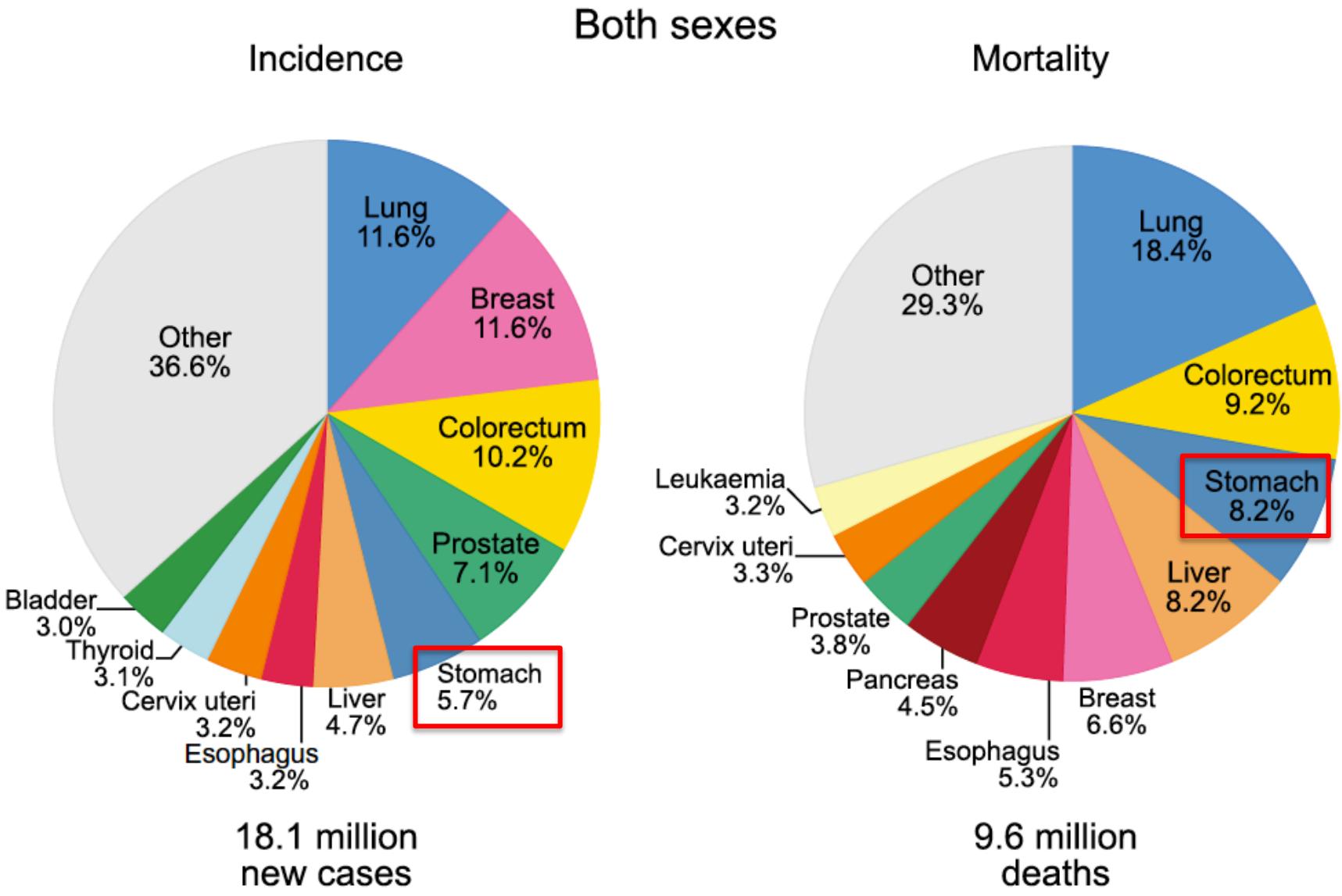
Clinical Data Analysis and Reporting System (CDARS)



Hong Kong Hospital Authority

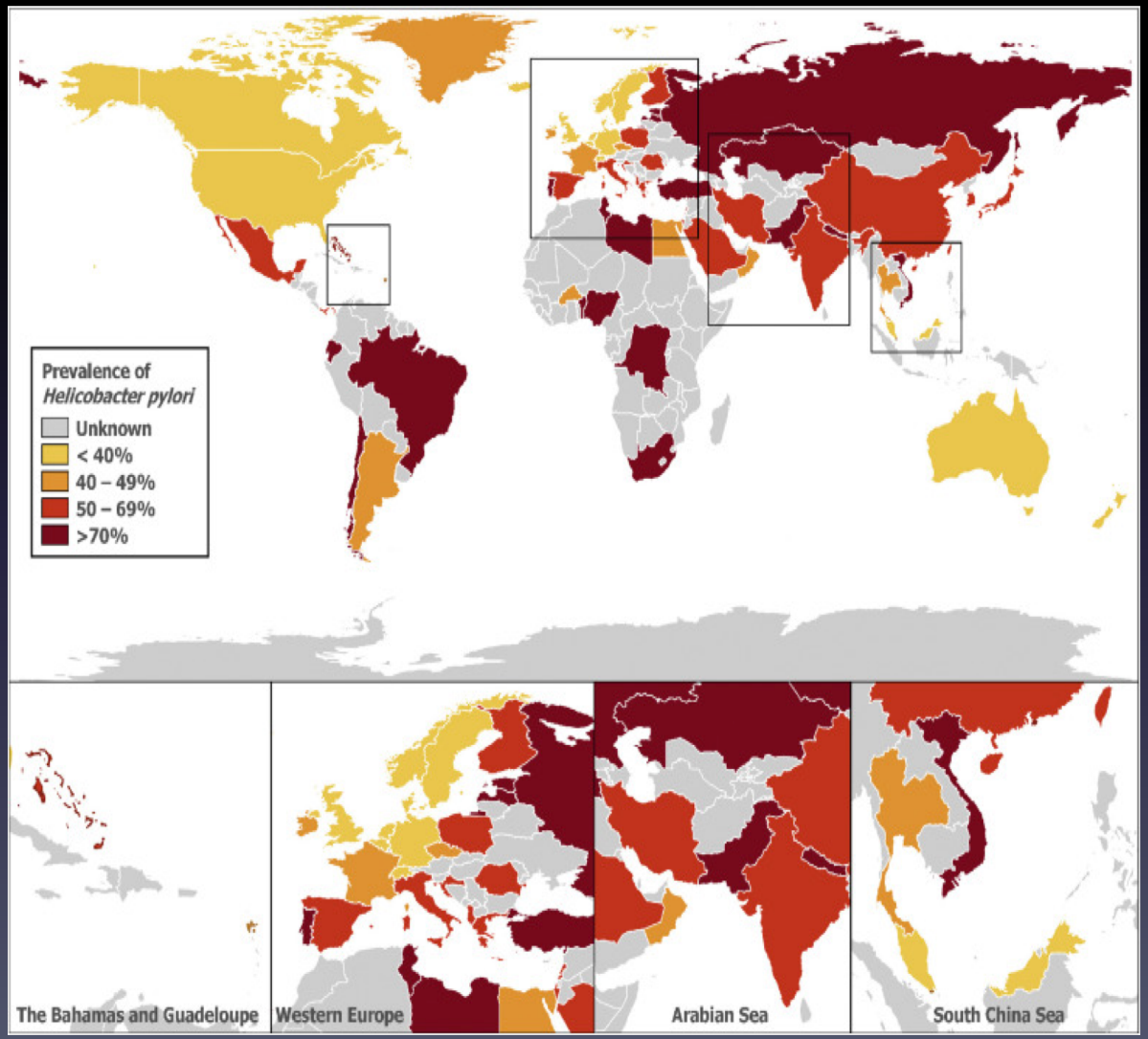
Gastric cancer (GC)

A



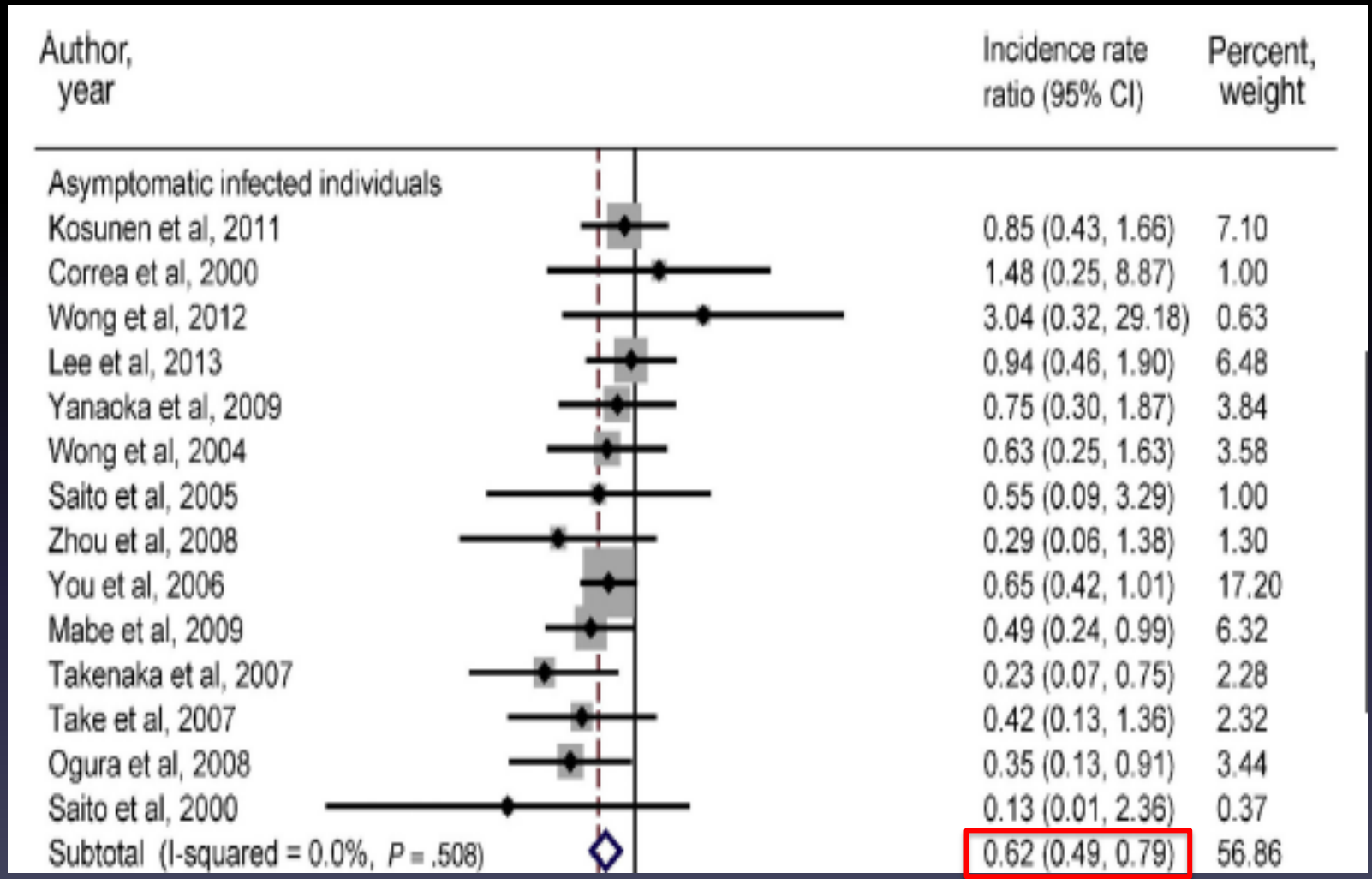
Bray F et al. Global Cancer Statistics. CA Cancer J Clin 2018

Global Prevalence of *Helicobacter pylori* (HP)



Hooi JLY et al.
Gastroenterology 2017

HP eradication and GC: asymptomatic Individuals



HP eradication can reduce GC development by 33-47%

Ford AC, et al. BMJ 2014
Lee TY, et al. Gastroenterology 2016

Do Proton pump inhibitors (PPIs) increase risk of GC?

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Drugs

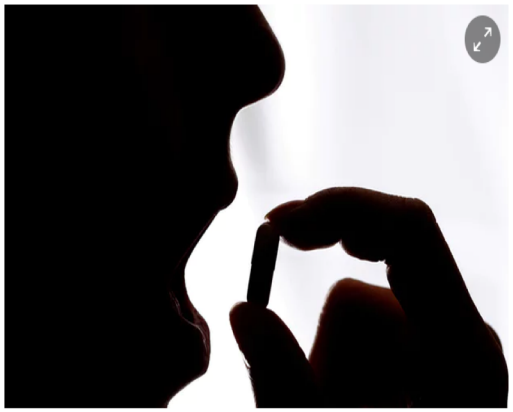
Acid reflux drug linked to more than doubled risk of stomach cancer - study

There are more than 50m prescriptions for proton pump inhibitors in the UK, though they have previously been linked to side-effects and increased risk of death

25,914

Press Association

Tuesday 31 October 2017 23.30 GMT



Long term use of the drugs was associated with the highest level of risk. Photograph: Jochen Tack/Getty Images/imageBROKER RM

A drug commonly used to treat acid reflux is linked to a more than doubled risk of developing stomach cancer, researchers have claimed.

Proton pump inhibitors (PPIs) reduce the amount of acid made by the stomach

Advertisement

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HOME SEARCH

The New York Times

Heartburn Drugs Tied to Stomach Cancer Risk

Heart Surgery May Be Safer in Afternoon Than in Morning

'Fat but Fit'? The Controversy Continues

PAID POST

Italian Gl

Avenue

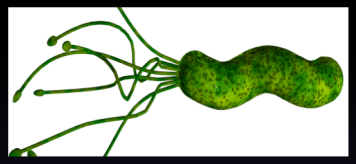
Heartburn Drugs Tied to Stomach Cancer Risk

By NICHOLAS BAKALAR OCT. 31, 2017

People who carry the stomach bacteria known as Helicobacter pylori are at increased risk for ulcers and stomach cancer. But even when antibiotic treatment has eliminated the bacterium, stomach cancer may still arise. A new study suggests that one reason may be the long-term use of proton pump inhibitors, or P.P.I.s, acid-reducing medicines sold under brand names such as Prilosec and Prevacid.

Researchers studied 63,397 people in Hong Kong successfully treated for H. pylori infection, of whom 3,271 used P.P.I.s and 21,179 took H2-receptor antagonists, another type of acid-controller (Tagamet, Pepcid and other brands). Over an average 7.6 years, 153 of them developed gastric cancer.

Correa's gastric carcinogenesis cascade
Proton pump inhibitors (PPIs) and GC



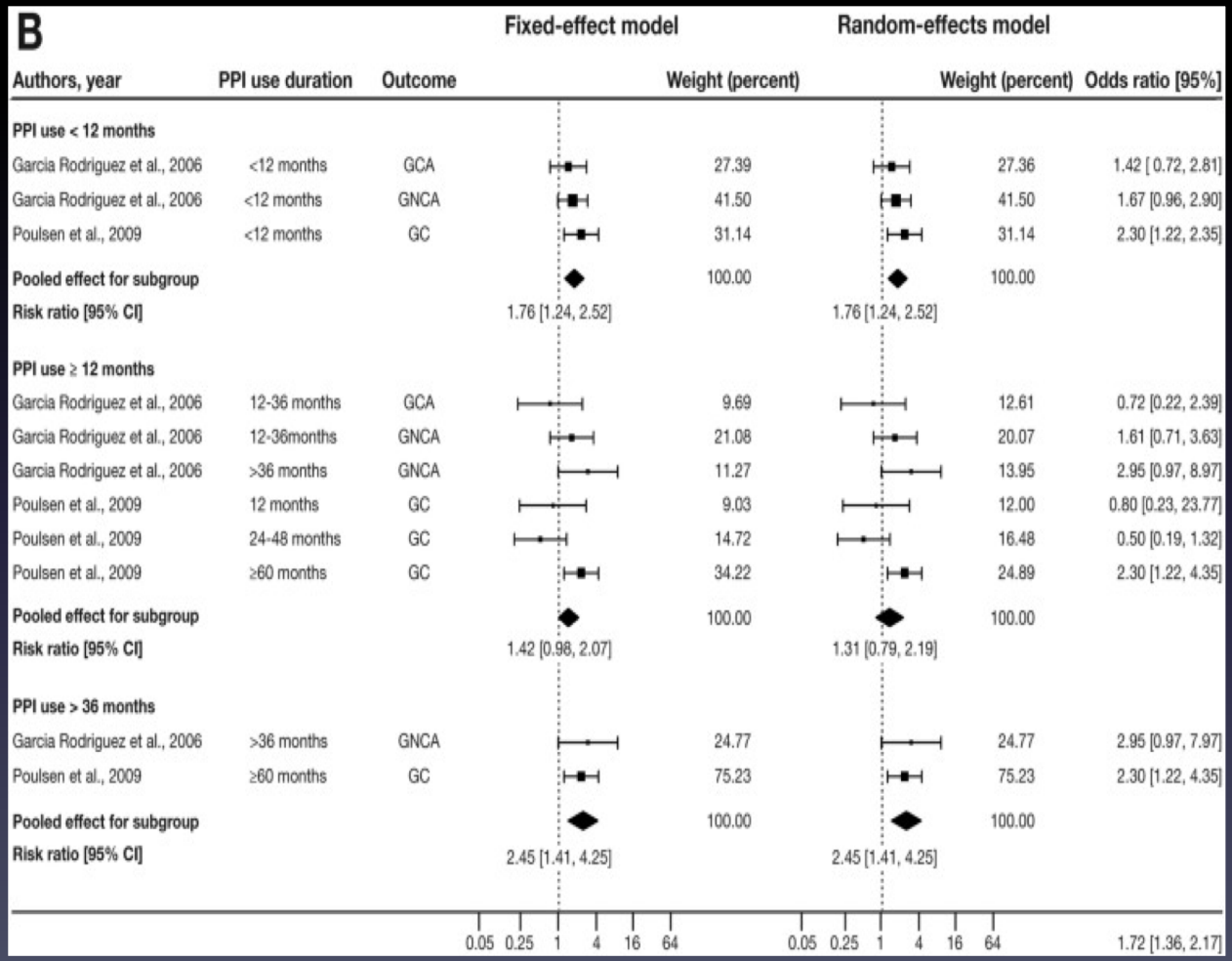
H. pylori

Host factors
(Cytokine gene polymorphism, low acid production)

Chronic gastritis → Glandular atrophy → Intestinal metaplasia → Dysplasia → Carcinoma

Proton pump inhibitors (PPIs):
- worsening of atrophic gastritis
- bacterial overgrowth

PPIs and risk of gastric cancer: Meta-analysis



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>12m

>36m

Tran-Duy A, et al Clin Gastroenterol Hepatol 2016

Limitations of previous studies

- Limited number of studies (n=3)
- Inclusion of both HP-infected and HP-negative subjects
- Concurrent medications that could modify GC risk (aspirin, NSAIDs, statins, metformin)
- Reverse causality/protopathic bias
- Confounding by indication (chronic gastritis per se)

Garcia Rodriguez LA, et al. Gut 2006
Tamim H, et al. Pharmacoepidemiol Drug Saf 2008
Poulsen AH, et al. Br J Cancer 2009

Aim

- To determine GC risk among individuals who have received anti-HP treatment with focus on the role of long-term PPIs

ORIGINAL ARTICLE

Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study

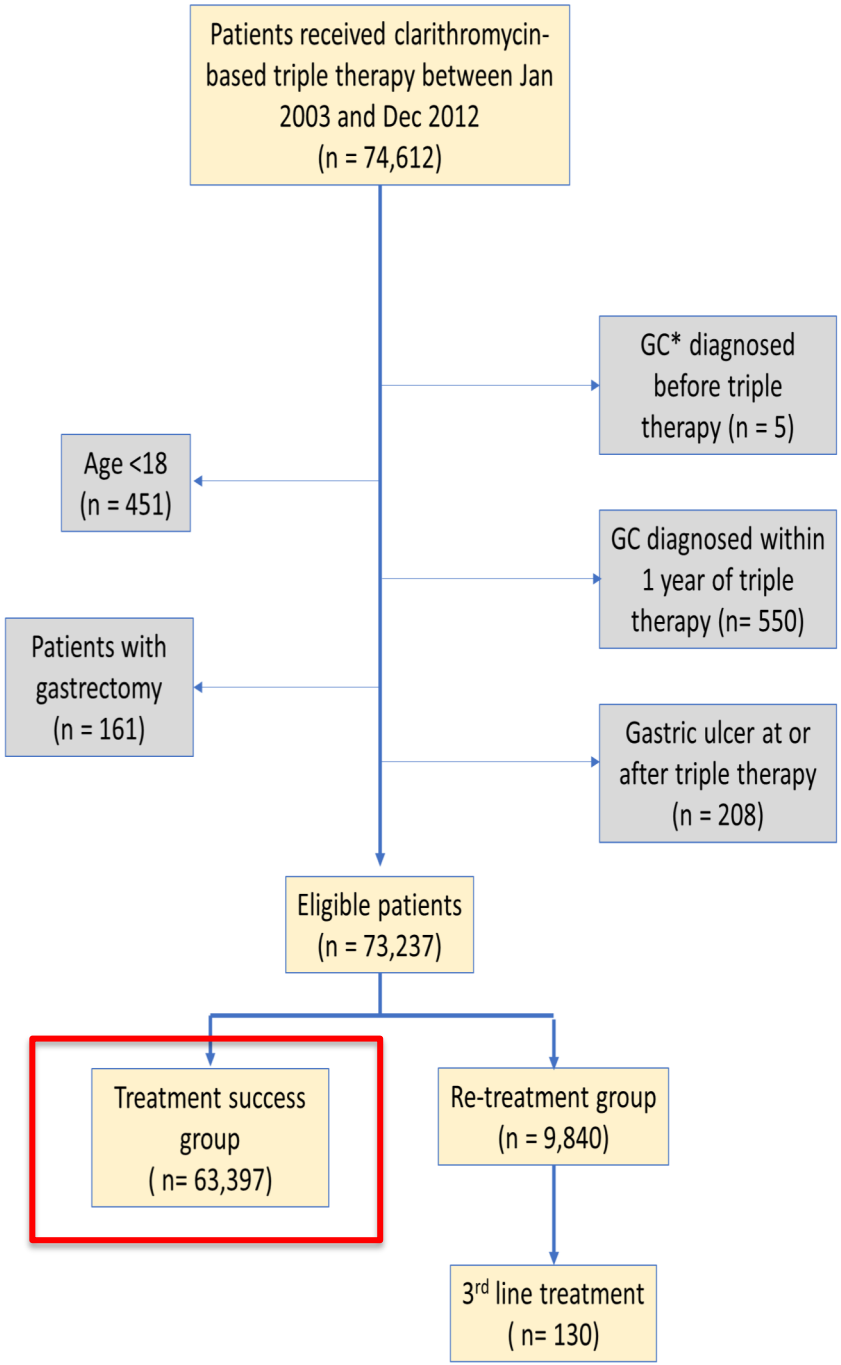
Ka Shing Cheung,[1] Esther W Chan,[2] Angel Y S Wong,[2] Lijia Chen,[1] Ian C K Wong,[3] Wai Keung Leung[1]

Cheung KS, et al. Gut 2018

HP+ Subjects

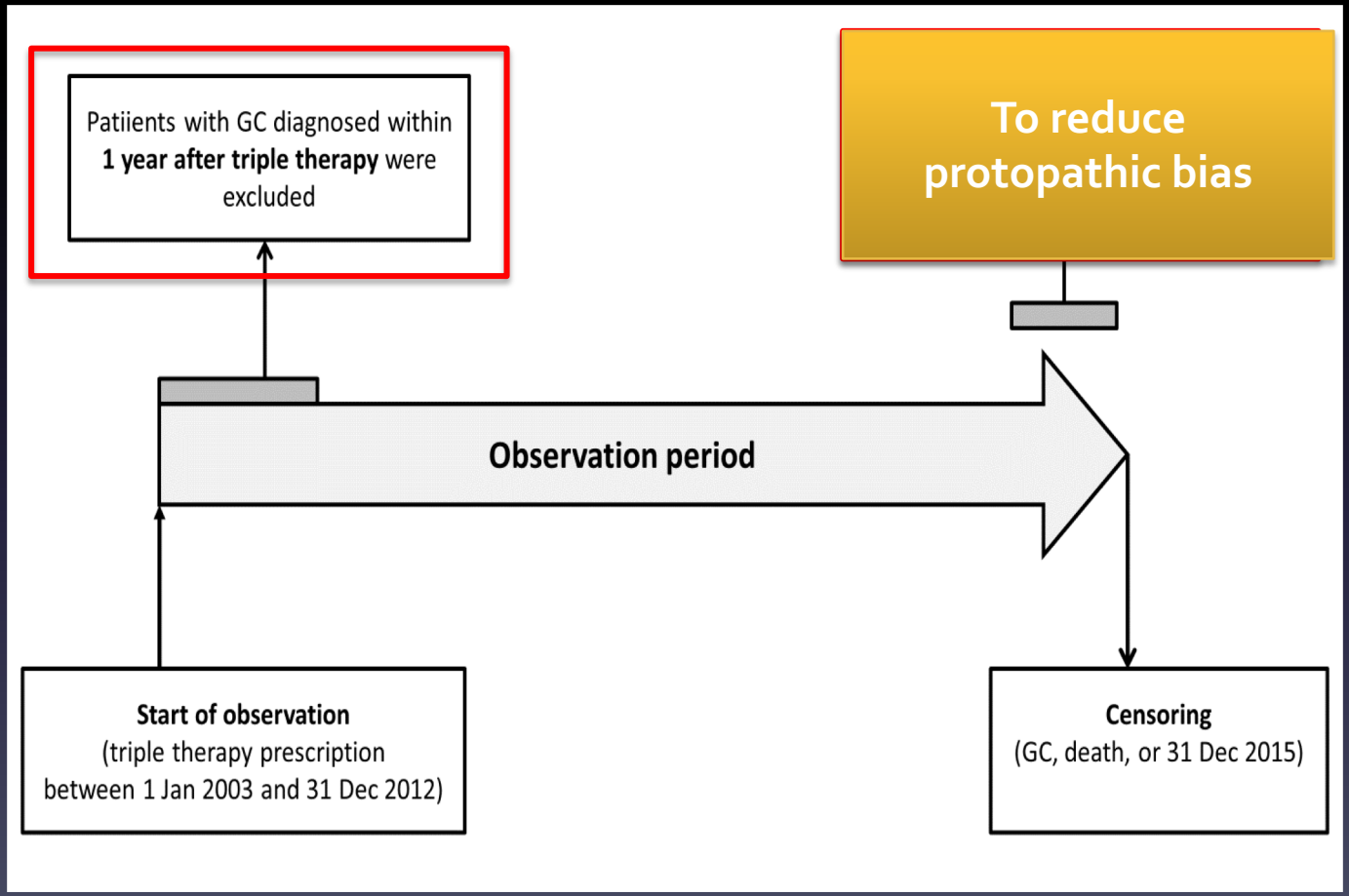
- Adults aged 18 or above
- Had received a course of clarithromycin-based triple therapy containing clarithromycin, amoxicillin or metronidazole and proton pump inhibitors for 7-14 days between Jan 2003 and Dec 2012
- Observation period:
  - From the date of HP therapy to diagnosis of GC, death or end of study (Dec 2015)
- Exclusion:
  - History of GC prior to or within 12 months of receiving HP eradication
  - Previous gastrectomy
  - Diagnosis of gastric ulcer after HP therapy

Cheung KS, et al. Gut 2018



Cheung KS, et al. Gut 2018

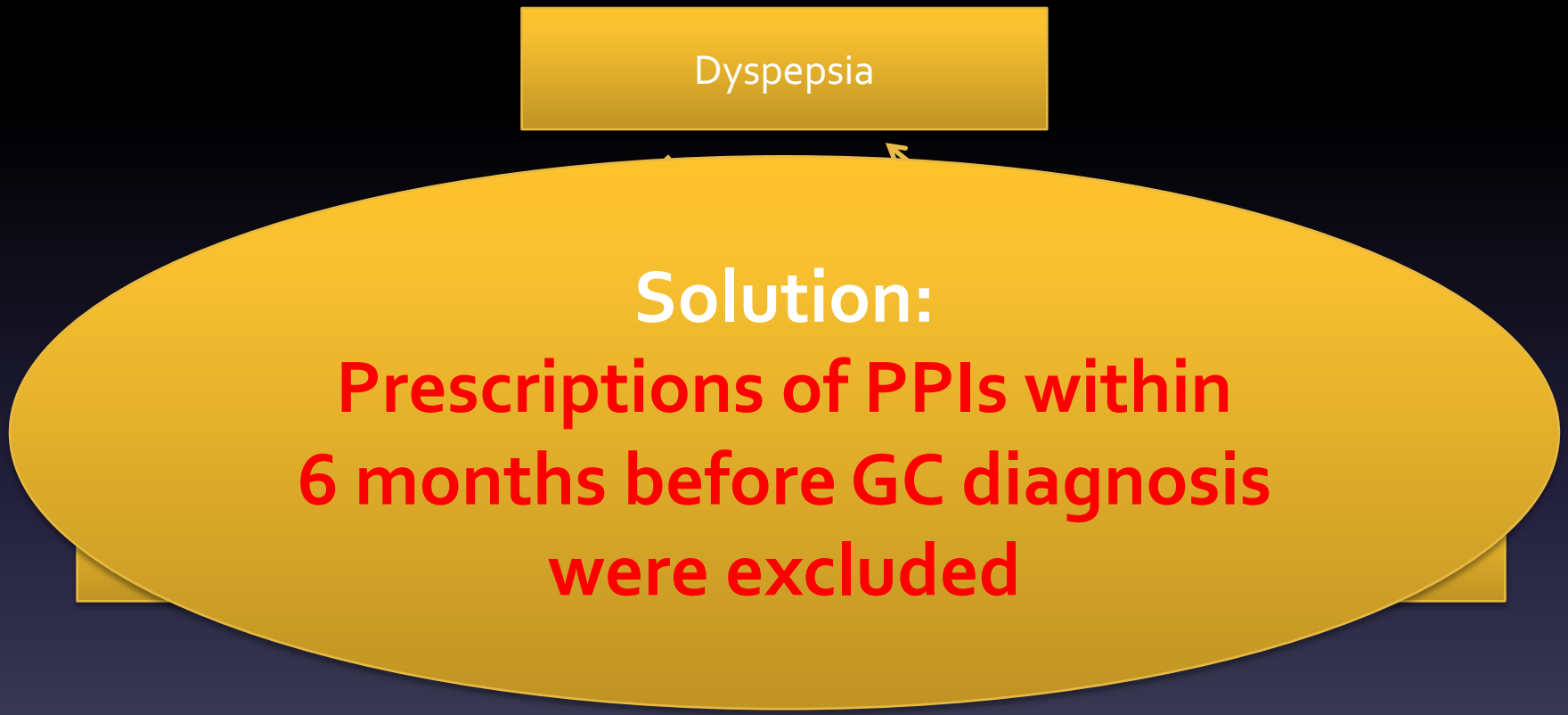
Study time frame



Cheung KS, et al. Gut 2018

Reverse causality / Protopathic bias

Reverse causality / Protopathic bias



Covariates

- 24 covariates in total
  - Age at receiving clarithromycin-based triple therapy
  - Sex
  - Smoking & alcohol use
  - History of gastric /duodenal ulcers
  - Other comorbidities (DM, HT, dyslipidemia, obesity, IHD, AF, CHF, stroke, CRF, cirrhosis)
  - Concurrent medications

Cheung KS, et al. Gut 2018

Medications

- Histamine 2 receptor antagonist (H2RA), statins, metformin, aspirin, NSAIDs/COX2-inhibitors
- Categorization of drug use
  - non-regular use (<weekly use; reference group)
  - regular use (at least weekly use)

Cheung KS, et al. Gut 2018

Statistical analysis

- Cox proportional hazards model → hazard ratio (HR)
- Primary analysis
  - Propensity score (PS) regression adjustment with trimming
    - PS was derived from logistic regression to represent the conditional probability of PPIs use given the covariates (age, sex, smoking/alcohol, PUD, DM, other comorbidities, concurrent medications)
    - Subjects with extreme scores in the upper and lower tails of the PS distribution were excluded (1st & 20th PS strata)
- Sensitivity analysis
  - Propensity score (PS) adjustment without trimming
  - Multivariable analysis from Cox model

Cheung KS, et al. Gut 2018

Characteristics of GC patients

- 169 (0.27%) of 63,397 patients developed GC (median follow-up of the whole cohort = 7.6 years)
  - Non-cardia GC: 98 (58.0%)
  - Cardia GC: 34 (20.1%)
  - Sites unspecified: 37 (21.9%)
- Overall incidence rate: 3.5 per 10,000 person-years
- Median age at GC diagnosis: 71.4 years (IQR 61.6 – 81.8 years)
- Median age of receiving HP therapy: 66.7 years (IQR 56.6 – 76.5)
- Median time from HP therapy to GC: 4.8 years (IQR 2.8 – 6.9)

Cheung KS, et al. Gut 2018

PPI use and GC

PPI frequency	Univariate analysis (n=63,397, GC=153)		Multivariable analysis (n=63,397, GC=153)		PS adjustment without trimming (n=63,397, GC=153)		PS adjustment with trimming (n=57,057, GC=139)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Non-user (<weekly use)	Ref	-	Ref	-	Ref	-	Ref	-
At least weekly	2.80	1.73 – 4.52	2.19	1.31 – 3.66	2.14	1.27 – 3.58	2.44	1.42 – 4.20

Cheung KS, et al. Gut 2018

Cardia vs Non-cardia GC (PS regression adjustment with trimming)

PPIs frequency	Non-cardia GC (n=57,028, GC=112)			Cardia GC (n=56,947, GC=27)		
	HR	95% CI	p	HR	95% CI	p
Non-PPI use (< weekly)	Ref	-	-	Ref	-	-
At least weekly	2.59	1.42 – 4.72	0.002	1.97	0.57 – 6.82	0.286

PPI Frequency and GC (PS adjustment with trimming)

PPI Frequency	Dose-response relationship (n=57,057, GC=139)		
	HR	95% CI	p-value
Non-PPI use (<weekly)	Ref	-	-
Weekly to <daily	2.43	1.37 – 4.31	0.002
Daily	4.55	1.12 – 18.52	0.034

PPI duration and GC (PS adjustment with trimming)

PPI frequency	PPI use ≥ 1 year (n=50,932, GC=112)			PPI use ≥ 2 years (n=49,462, GC=88)			PPI use ≥ 3 years (n=48,511, GC=69)		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Non-user (<weekly)	Ref	-	-	Ref	-	-	Ref	-	-
Weekly to <daily	1.81	0.90 – 3.64	0.098	0.98	0.31 – 3.17	0.979	0.58	0.08 – 4.23	0.590
Daily	5.04	1.23–20.61	0.024	6.65	1.62–27.26	0.009	8.34	2.02– 34.41	0.004

Cheung KS, et al. Gut 2018

Limitations

- Some risk factors (e.g. diet, family history) could not be obtained
- Underestimation of the prevalence of smoking, alcohol use by only using diagnosis code
- Generalizability (as mainly Chinese patients)
- Gastric histology not available
- Residual/Unmeasured confounding (inherent to all observational studies)
- Confounding by indication

LETTER

Proton pump inhibitors and gastric cancer: association is not causation

We read the article by Cheung *et al*[1] with interest. The research question whether there is a dose-related association between proton pump inhibitors (PPIs) and gastric cancer in a country where this malignancy is highly prevalent is an important one. They report that long-term PPI therapy is associated with an increased risk of gastric cancer in patients who have received *Helicobacter pylori* eradication therapy. The data suggest that patients taking PPI less than once per day had a lower risk of gastric cancer than did those taking PPIs at least daily, which would support there may be a dose-related response.

Moayyedi P, et al. Gut 2019

Limitations of RCTs

- Ethical issue (potential harmful effect)
- Relatively rare disease (3.2 per 10,000 person-years)
- Long time lag (median time interval of GC development: 4.9 years)
- Resource intensive (> 63,000 patients)

LETTER

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tion causal. Assessment of causality is best achieved in randomised controlled trials, and we are evaluating the harms of PPIs in a secondary analysis of the COMPASS trial that has randomised over 17 500 patients to PPI or placebo and followed them for 3 years.[5]

Moayyedi P, et al. Gut 2019

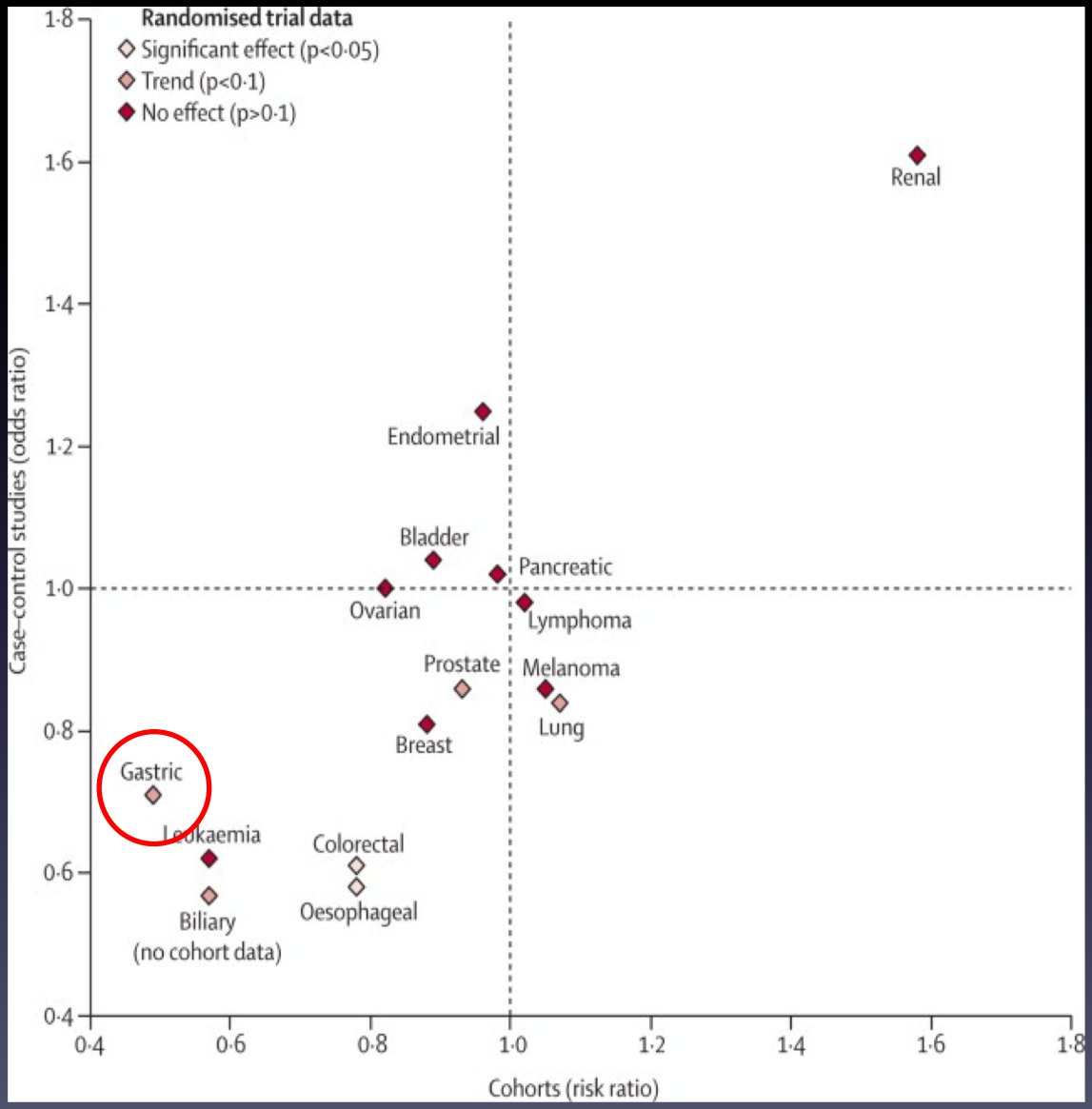
Gastroenterology 2019;■:1–10

Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

Paul Moayyedi,[1] John W. Eikelboom,[1] Jackie Bosch,[1] Stuart J. Connolly,[1] Leanne Dyal,[1] Olga Shestakovska,[1] Darryl Leong,[1] Sonia S. Anand,[1] Stefan Störk,[2] Kelley R. H. Branch,[3] Deepak L. Bhatt,[4] Peter B. Verhamme,[5] Martin O'Donnell,[6] Aldo P. Maggioni,[7] Eva M. Lonn,[1] Leopoldo S. Piegas,[8] Georg Ertl,[2] Matyas Keltai,[9] Nancy Cook Bruns,[10] Eva Muehlhofer,[10] Gilles R. Dagenais,[11] Jae-Hyung Kim,[12] Masatsugu Hori,[13] P. Gabriel Steg,[14] Robert G. Hart,[1] Rafael Diaz,[15] Marco Alings,[16] Petr Widimsky,[17] Alvaro Avezum,[18] Jeffrey Probstfield,[19] Jun Zhu,[20] Yan Liang,[20] Patricio Lopez-Jaramillo,[21] Ajay K. Kakkar,[22] Alexander N. Parkhomenko,[23] Lars Ryden,[24] Nana Pogosova,[25] Antonio L. Dans,[26] Fernando Lanas,[27] Patrick J. Commerford,[28] Christian Torp-Pedersen,[29] Tomek J. Guzik,[30,31] Dragos Vinereanu,[32] Andrew M. Tonkin,[33] Basil S. Lewis,[34] Camilo Felix,[35] Khalid Yusoff,[36] Kaj P. Metsarinne,[37] Keith A. A. Fox,[38] and Salim Yusuf,[1] for the COMPASS Investigators

- Major limitations for investigating outcome of GC
  - Median follow-up: 3 years
  - Post-hoc analysis of RCT; hence not specifically designed to investigate GC
    - 169 GI cancers (? number of gastric cancer not specified)
    - *H. pylori* infection status unknown
  - Aspirin is a chemopreventive agent against gastric cancer

Aspirin for Cancer Prevention



Algra AM, Rothwell PM. Lancet Oncol 2012

Chemoprevention of aspirin on GC

- Cyclooxygenase (COX)-2
- Phosphatidylinositol 3-kinase (PI3K)
- Nuclear factor (NF)- kB
- Wnt-ß-catenin
- Extracellular signal-regulated kinase (ERK)
- Activated protein1 (AP-1)

Shaheen NJ, et al. Cancer 2002
Cuzick J, et al. Lancet Oncol 2009
Yamamoto Y, et al. J Biol Chem 1999
Patrignani P, et al. J Am Coll Cardiol 2016

Limitations of previous studies

- Inclusion of both HP-infected and HP-negative subjects
- No studies on HP-eradicated subjects
- Dose- and duration-benefit unclear

OXFORD

JNCI J Natl Cancer Inst (2018) 110(7): djx267

doi: 10.1093/jnci/djx267
Article

ARTICLE

Aspirin and Risk of Gastric Cancer After *Helicobacter pylori* Eradication: A Territory-Wide Study

Ka Shing Cheung, Esther W. Chan, Angel Y. S. Wong, Lijia Chen, Wai Kay Seto, Ian C. K. Wong, Wai K. Leung

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Correspondence to: Wai K. Leung, MD, Department of Medicine, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong (e-mail: waikleung@hku.hk).

Cheung KS, et al. J Natl Cancer Inst 2018

Baseline characteristics of aspirin and non-aspirin users

Characteristic	All (n = 63 605)	Aspirin users (n = 9045)	Nonaspirin users (n = 54 560)
Age at triple therapy, median (IQR), y	54.8 (46.0–65.5)	67.5 (58.4–75.9)	52.9 (44.6–62.4)
Male sex, No. (%)	29 629 (46.6)	5184 (57.3)	24 445 (44.8)
Duration of follow-up, median (IQR), y	7.6 (5.1–10.3)	7.5 (5.0–10.1)	7.4 (5.0–10.1)
Smoking, No. (%)*	1647 (2.6)	549 (6.1)	1098 (2.0)
Alcohol, No. (%)†	556 (0.9)	84 (0.9)	472 (0.9)
History of GU, No. (%)	1463 (2.3)	388 (4.3)	1075 (2.0)
History of DU, No. (%)‡	1913 (3.0)	251 (2.8)	1662 (3.0)
DM, No. (%)	7436 (11.7)	2897 (32.0)	4539 (8.3)
Hypertension, No. (%)	13 173 (20.7)	5021 (55.5)	8152 (14.9)
Dyslipidemia, No. (%)	5082 (8.0)	2606 (28.8)	2476 (4.5)
Obesity, No. (%)	641 (1.0)	174 (1.9)	467 (0.9)
IHD, No. (%)	5756 (9.0)	4027 (44.5)	1729 (3.2)
AF, No. (%)	2439 (3.8)	1427 (15.8)	1012 (1.9)
CHF, No. (%)	2554 (4.0)	1502 (16.6)	1052 (1.9)
Stroke, No. (%)	4005 (6.3)	2488 (27.5)	1517 (2.8)
CRF, No. (%)	1416 (2.2)	689 (7.6)	727 (1.3)
Cirrhosis, No. (%)	1049 (1.6)	118 (1.3)	931 (1.7)
Statins, No. (%)	13 247 (20.8)	6130 (67.8)	7117 (13.0)
Metformin, No. (%)	7974 (12.5)	2599 (28.7)	5375 (9.9)
NSAIDs/COX-2 inhibitors, No. (%)	3565 (5.6)	580 (6.4)	2985 (5.5)
Clopidogrel, No. (%)	990 (1.6)	651 (7.2)	339 (0.6)
PPIs, No. (%)	3316 (5.2)	1380 (15.3)	1936 (3.5)

Cheung KS, et al. J Natl Cancer Inst 2018

Aspirin & GC Prevention after HP Eradication

	Univariate analysis		Multivariable analysis		PS adjustment without trimming		PS adjustment with trimming	
Aspirin frequency	HR (95% CI)	P*	HR (95% CI)	P*	HR (95% CI)	P*	HR (95% CI)	P*
Whole cohort†								
Nonuser (<weekly use)	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—
At least weekly	1.06 (0.69 to 1.62)	.79	0.41 (0.24 to 0.69)	<.001	0.36 (0.21 to 0.63)	<.001	0.30 (0.15 to 0.61)	<.001
Noncardia GC‡								
Nonuser (<weekly use)	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—
At least weekly	0.94 (0.57 to 1.55)	.81	0.41 (0.22 to 0.75)	.004	0.37 (0.19 to 0.70)	.003	0.28 (0.12 to 0.64)	.003
Cardia GC§								
Nonuser (<weekly use)	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—
At least weekly	1.58 (0.69 to 3.62)	.28	0.42 (0.16 to 1.15)	.09	0.34 (0.12 to 1.01)	.05	0.36 (0.10 to 1.33)	.13

Cheung KS, et al. J Natl Cancer Inst 2018

Aspirin & GC Prevention: Frequency, Duration and Dose Effects

Aspirin use	No. of patients (n = 57 243)	No. of GC (n = 151)	HR (95% CI)	P*	P_{trend}*
Frequency					
Never user	47 991	129	1.00 (ref)	–	<.001
<Monthly use	2204	9	0.90 (0.44 to 1.84)	.77	
Monthly to <weekly use	582	1	0.35 (0.05 to 2.53)	.30	
Weekly to <daily use	5125	10	0.30 (0.14 to 0.63)	.002	
Daily use	1341	2	0.21 (0.05 to 0.94)	.04	
Duration, y					
Never user	47 991	129	1.00 (ref)	–	<.001
<2	3900	16	0.92 (0.51 to 0.64)	.77	
2–<5	2464	4	0.27 (0.09 to 0.80)	.02	
≥5	2888	2	0.07 (0.02 to 0.31)	<.001	
Dose, mg					
Nonuser†	50 911	139	1.00 (ref)	–	<.001
<100	4607	10	0.38 (0.18 to 0.79)	.009	
≥100	1725	2	0.15 (0.03 to 0.65)	.01	

Cheung KS, et al. J Natl Cancer Inst 2018

EDITORIAL

The Value of Helicobacter Eradication in Long-term Aspirin Users

Jack Cuzick

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In this issue, Cheung et al. (1) report a surprisingly large preventive effect of aspirin on gastric cancer in individuals who have been successfully treated for *Helicobacter pylori*. Most of the more than 50 randomized trials and 100 epidemiologic studies examining the impact of aspirin use on gastric cancer reported a reduction of 30% to 35% in incidence and mortality among long-term users, with little impact in the first three to five years of use (2–5). However, most of these studies have not examined the effect of aspirin according to *H. pylori* status, and the ones that have (6–8) do not clearly separate those where the infection was successfully treated from those where it was not. The cur-

www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 97), pp: 36891-36893

Research Perspective

Modification of gastric cancer risk associated with proton pump inhibitors by aspirin after *Helicobacter pylori* eradication

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Keywords: aspirin; PPI; H. pylori; gastric adenocarcinoma; triple therapy

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Cheung KS, et al. Oncotarget 2018

Modification of PPI-associated GC risk by aspirin after HP eradication

Whole cohort									
	Multivariable analysis (n = 63397, GC = 153)			PS adjustment without trimming (n = 63397, GC = 153)			PS adjustment with trimming (n = 57057, GC = 139)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Non-PPI use	Ref	-	-	Ref	-	-	Ref	-	-
PPI use	2.19	1.31 – 3.66	0.003	2.14	1.27 – 3.58	0.004	2.44	1.42 – 4.20	0.002
Non-aspirin use									
	Multivariable analysis (n = 54432, GC = 133)			PS adjustment without trimming (n = 54432, GC = 133)			PS adjustment with trimming (n = 48988, GC = 115)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Non-PPI use	Ref	-	-	Ref	-	-	Ref	-	-
PPI use	3.27	1.93 – 5.53	<0.001	3.38	1.99 – 5.75	<0.001	3.73	2.11 – 6.60	<0.001
Aspirin use									
	Multivariable analysis (n = 8965, GC = 20)			PS adjustment without trimming (n = 8965, GC = 20)			PS adjustment with trimming (n = 8067, GC = 16)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Non-PPI use	Ref	-	-	Ref	-	-	Ref	-	-
PPI use	0.53	0.12 – 2.37	0.402	0.52	0.11 – 2.34	0.392	0.35	0.04 – 2.74	0.318

Conclusion of this study

- Clinical dilemma: should we still prescribe PPIs to aspirin users at risk of upper GI bleeding ?
- Aspirin probably negates the potential carcinogenic effects of PPIs
- Co-prescription of PPIs is indicated in aspirin users at high risk of upper GI bleeding

Gastroenterology 2019;■:1–10

Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

Paul Moayyedi,[1] John W. Eikelboom,[1] Jackie Bosch,[1] Stuart J. Connolly,[1] Leanne Dyal,[1] Olga Shestakovska,[1] Darryl Leong,[1] Sonia S. Anand,[1] Stefan Störk,[2] Kelley R. H. Branch,[3] Deepak L. Bhatt,[4] Peter B. Verhamme,[5] Martin O'Donnell,[6] Aldo P. Maggioni,[7] Eva M. Lonn,[1] Leopoldo S. Piegas,[8] Georg Ertl,[2] Matyas Keltai,[9] Nancy Cook Bruns,[10] Eva Muehlhofer,[10] Gilles R. Dagenais,[11] Jae-Hyung Kim,[12] Masatsugu Hori,[13] P. Gabriel Steg,[14] Robert G. Hart,[1] Rafael Diaz,[15] Marco Alings,[16] Petr Widimsky,[17] Alvaro Avezum,[18] Jeffrey Probstfield,[19] Jun Zhu,[20] Yan Liang,[20] Patricio Lopez-Jaramillo,[21] Ajay K. Kakkar,[22] Alexander N. Parkhomenko,[23] Lars Ryden,[24] Nana Pogosova,[25] Antonio L. Dans,[26] Fernando Lanas,[27] Patrick J. Commerford,[28] Christian Torp-Pedersen,[29] Tomek J. Guzik,[30,31] Dragos Vinereanu,[32] Andrew M. Tonkin,[33] Basil S. Lewis,[34] Camilo Felix,[35] Khalid Yusoff,[36] Kaj P. Metsarinne,[37] Keith A. A. Fox,[38] and Salim Yusuf,[1] for the COMPASS Investigators

- Testing PPI effect on GC in aspirin users is therefore not ideal

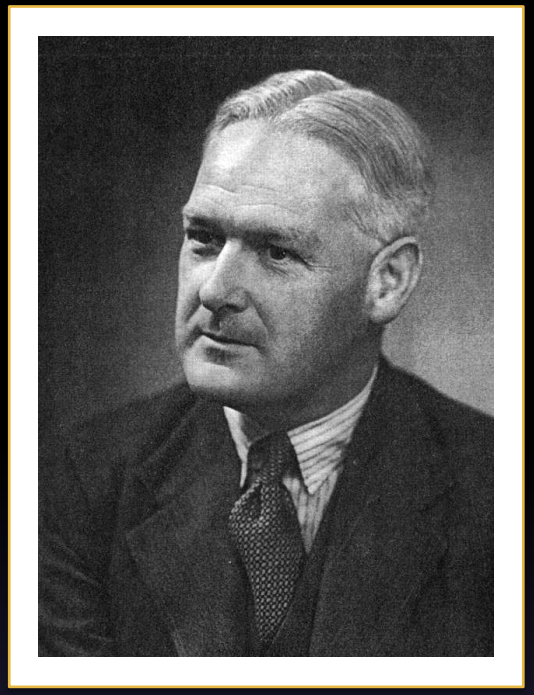
LETTER

Response to letter to the editor by Moayyedi *et al*

We thank Moayyedi *et al*[1] for their letter on our recent study investigating proton pump inhibitors (PPIs) on gastric cancer (GC) risk after *Helicobacter pylori* (HP) eradication.[2] Although the association detected by an observational study may not mean causation, the possibility of causality can be strengthened by fulfilling the Bradford Hill criteria. In our study, these include strength (HR: 2.43), specificity (stomach is the only organ that PPIs may impose a cancer risk), temporality (all GC cases developed after triple therapy), biological gradient (dose and duration response relationship shown), plausibility (worsening of preneoplastic gastric changes and bacterial overgrowth under profound acid suppression), experiment (as illustrated in animal model studies) and analogy (achlorhydria due to autoimmune gastritis causes GC).

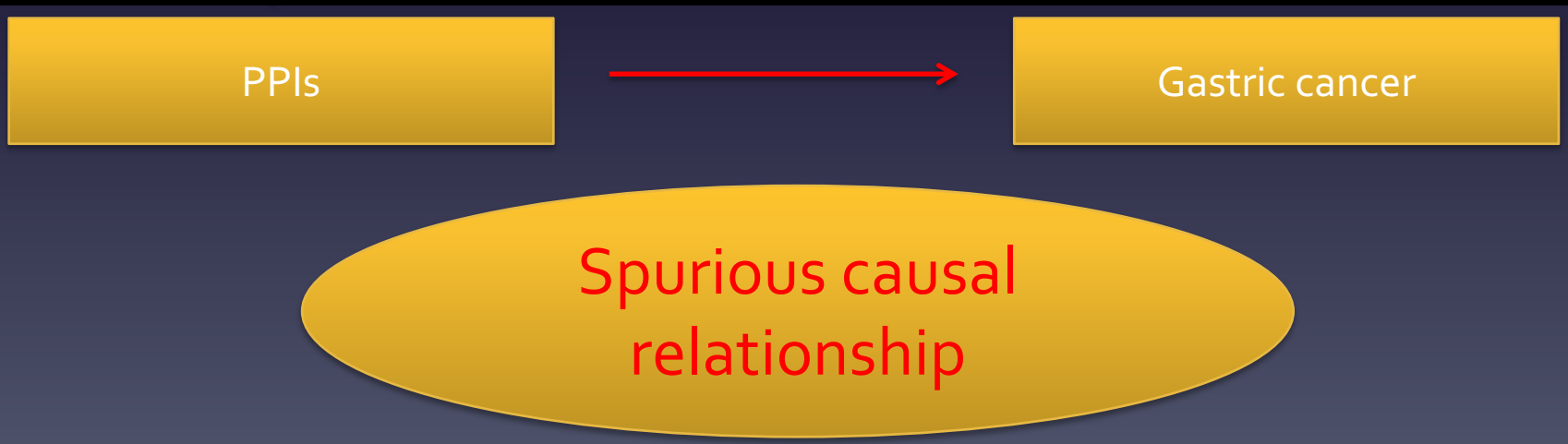
Cheung KS, et al. Gut 2019

Bradford Hill criteria for causality



- Strength (effect size of 2.44)
- Consistency (a nationwide Swedish study: SIR – 3.38)
- Temporality (patients with prior history of GC excluded)
- Biological gradient (duration & dose response relationship)
- Biological plausibility (worsening of atrophic gastritis, bacterial overgrowth)
- Coherence & Experimental (supported by animal models)
- Analogy (autoimmune gastritis → atrophic gastritis → GC)

Confounding by indication



How to address Confounding by indication ?

- Negative control exposure (H2RAs)
  - no causal effect on outcome (i.e. GC)
  - shares same unmeasured/measured confounders with exposure of interest (i.e. PPIs)
  - therefore, if a similar association with outcome is demonstrated, unmeasured confounding likely exist
- Histamine 2 receptor antagonist HR by PS adjustment with trimming: 0.72 (95% CI 0.48 – 1.07)

How to address Confounding by indication ? comparison of GC incidence rates

	Number of patients	Number of person-years	Number of GC cases	Incidence rate (per 10,000 person-years)	Incidence rate ratio with 95% CI
***H. Pylori*-eradicated cohort (n=63,397)**					
PPI use without prior HP therapy	142,460	705,094	59	0.8	0.29 (0.21 – 0.39)

How to address Confounding by indication ? comparison of GC incidence rates

	Number of patients	Number of person-years	Number of GC cases	Incidence rate (per 10,000 person-years)	Incidence rate ratio with 95% CI
Non-PPI use + prior HP therapy	60,126	459,864	134	2.9	Ref
PPI use without prior HP therapy	142,460	705,094	59	0.8	0.29 (0.21 – 0.39)

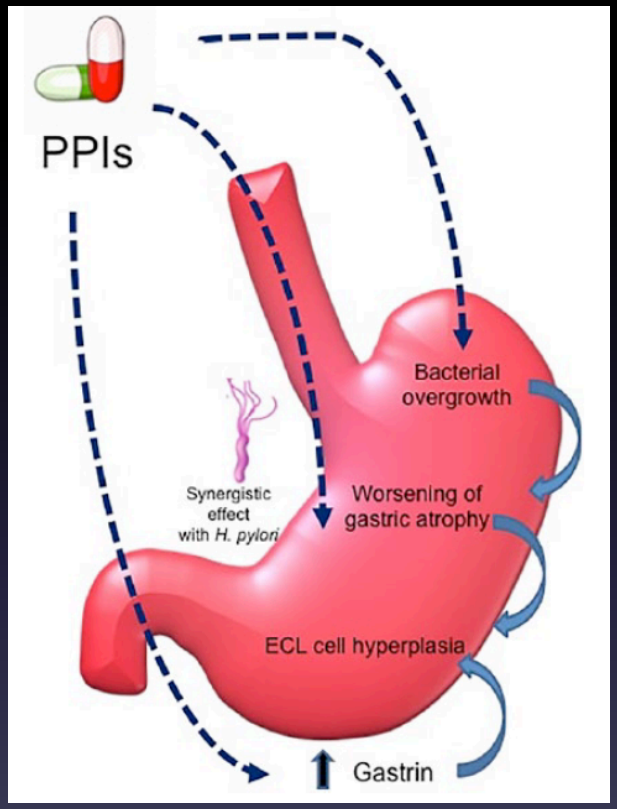
How to address Confounding by indication ? comparison of GC incidence rates

	Number of patients	Number of person-years	Number of GC cases	Incidence rate (per 10,000 person-years)	Incidence rate ratio with 95% CI
PPI use + prior HP therapy	3,271	23,395	19	8.1	2.81 (1.68 – 4.43)
PPI use without prior HP therapy	142,460	705,094	59	0.8	0.29 (0.21 – 0.39)

How to address Confounding by indication ? comparison of GC incidence rates

	Number of patients	Number of person-years	Number of GC cases	Incidence rate (per 10,000 person-years)	Incidence rate ratio with 95% CI
Non-PPI use + prior HP therapy	60,126	459,864	134	2.9	Ref
PPI use + prior HP therapy	3,271	23,395	19	8.1	2.81 (1.68 – 4.43)
PPI use without prior HP therapy	142,460	705,094	59	0.8	0.29 (0.21 – 0.39)

Postulation



- Pre-existing precancerous gastric lesions (e.g. induced by persistent or prior HP infection) is a more important risk factor than PPIs alone
- PPIs increase GC risk likely only in the context of pre-existing precancerous gastric lesions

Cheung KS, et al. Therap Adv Gastroenterol 2019

Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study

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Published in	Gut, October 2017
DOI	10.1136/gutjnl-2017-314605
Pubmed ID	29089382
Authors	Ka Shing Cheung, Esther W Chan, Angel Y S Wong, Lijia Chen, Ian C K Wong, Wai Keung Leung
Abstract	Proton pump inhibitors (PPIs) is associated with worsening of gastric atrophy, particularly in... [show]

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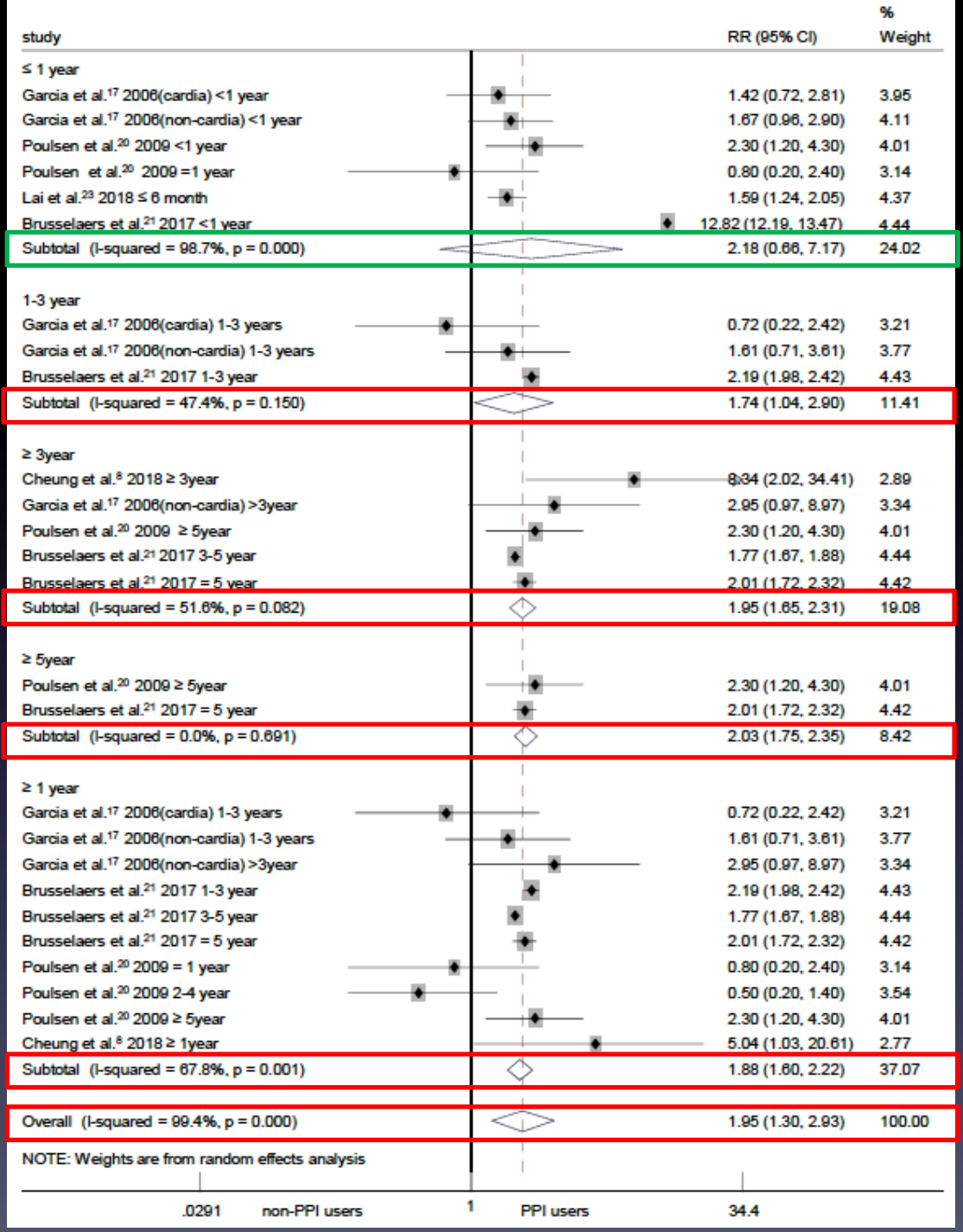
References	Study design	Sample size	Patient characteristics/ region	Factors considered (regression model or stratified analysis)	*Results
Garcia Rodriguez *et al.*[57]	Nested case-control study (matched with age, sex, and calendar year)	10,522	United Kingdom	1, 2, 4, 5, 13,14	OR 1.75 (95% CI 1.10–2.79)
Tamim *et al.*[80]	Nested case-control study (matched with age and sex)	8229	Canada	1,2, 17	OR 1.46 (95% CI: 1.22–1.74)
Poulsen *et al.*[56]	Population-based cohort study	280,872	Denmark	1, 3–5, 9, 10, 13, 17	IRR 2.3 (95% CI 1.2–4.3; patients with ⩾5years of follow up)
Cheung *et al.*[61]	Population-based cohort study	63,397	*H. pylori*-eradicated patients/Hong Kong	1–12, 16, 17	HR 2.44 (95% CI 1.42–4.20)
Brusselaers *et al.*[63]	Nationwide population-based cohort study	843,003 PPI or H2RA users (*versus* general population of 7.1–7.6 million)	Sweden	1–3, 6, 10, 13, 16, 17	SIR 3.38 (95% CI 3.25–3.53)
Peng *et al.*[64]	Case-control study (matched with age, sex, and calendar year)	2122 (1:1 ratio)	GERD patients/ Taiwan	1, 2, 10, 13, 14	OR 2.48 (95% CI 1.92–3.20)
Lai *et al.*[65]	Case-control study (matched with age, sex, and calendar year)	1298 (1:1 ratio)	Taiwan	1–8, 10, 13, 17	⩽6-month PPI: OR 1.59 (95% CI 1.24– 2.05) >6-month PPI: OR 2.00 (95% CI 1.36–2.95)
Niikura *et al.*[66]	Retrospective cohort study	571	*H. pylori*-eradicated patients/Japan	3, 10, 15	HR 3.61; 95% CI 1.49–8.77

Cheung KS, et al. Therap Adv Gastroenterol 2019



<1y

1-3y

≥3y

≥ 5y

≥ 1y

Overall

Lin JL, et al.
J Gastric Surg 2020

Conclusion of this study

- First study to demonstrate that long-term PPI use is associated with an increased GC risk even after HP eradication with comprehensive adjustment of various confounding factors (esp *H. pylori* infection status) and biases

– A dose-response trend, in terms of frequency and duration of PPI treatment

– Interaction of PPIs with baseline gastric histology should be further explored

Propensity score (PS) analysis

Propensity score analysis

- PS regression adjustment
- PS matching
- PS subclassification / stratification
- PS weighting
  - weighting by odds
  - Inverse probability of treatment weights

Multivariable logistic regression

- Outcome: binary or ordinal variable (e.g. gastric cancer)

$$g(E(Y)) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots$$

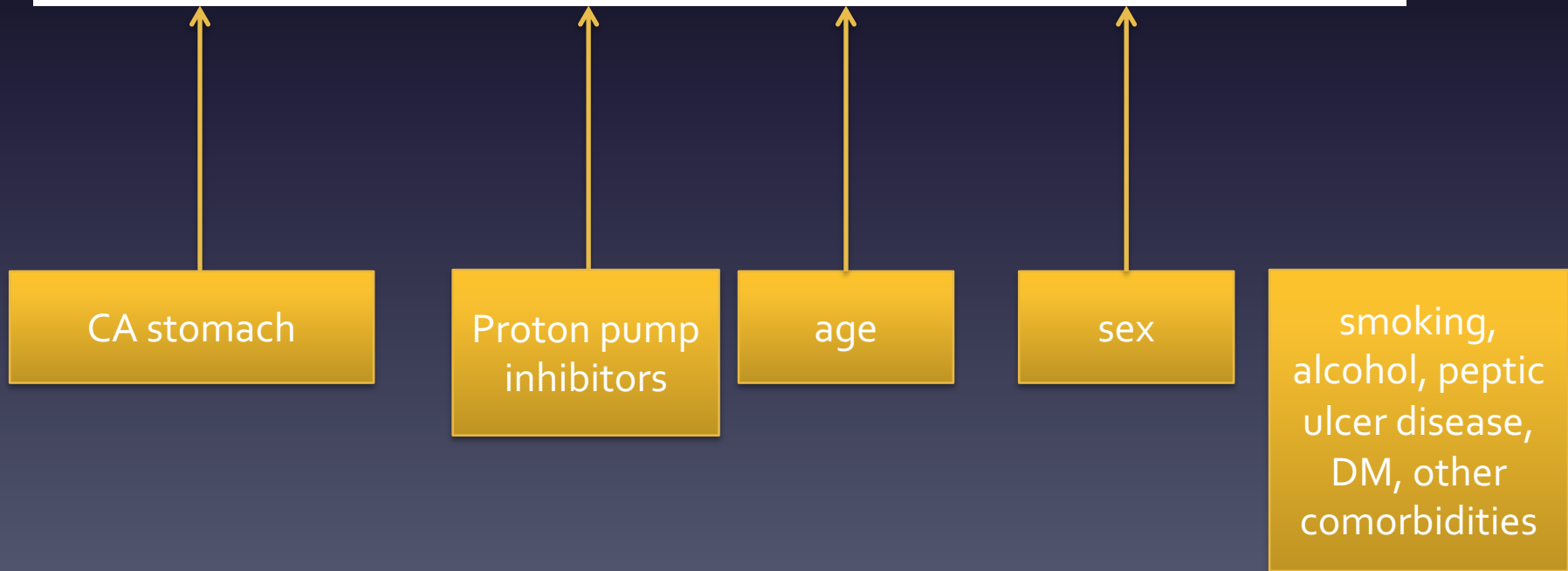


Table 1 Characteristics of PPIs and non-PPIs users

	All (n=63 397)	PPIs users (n=3271)	Non-PPIs users (n=60 126)
Age at triple therapy (years)*	54.7 (46.0–65.4)	64.1 (53.6–75.3)	54.3 (45.7–64.7)
Male sex (n, %)	29 499 (46.5%)	1641 (50.2%)	27 858 (46.3%)
Statins (n, %)	13 180 (20.8%)	1351 (41.3%)	11 829 (19.7%)
Metformin (n, %)	7935 (12.5%)	605 (18.5%)	7330 (12.2%)
Aspirin (n, %)	8965 (14.1%)	1358 (41.5%)	7607 (12.7%)
NSAIDs/COX-2 inhibitors (n, %)	3556 (5.6%)	391 (12.0%)	3165 (5.3%)
Clopidogrel (n, %)	980 (1.5%)	200 (6.1%)	780 (1.3%)
H2RA (n, %)	21 729 (34.3%)	1499 (45.8%)	20 230 (33.6%)

24 covariates

153 events (GC)

Curse of dimensionality

- The more dimensions (variables/covariates), the more difficult to predict certain quantities
- Sample size grow exponentially with increasing dimensions
- Pharmacoepidemiological research: relatively few outcomes, many potential covariates

"Rule of Ten" Logistic regression model

- Number of **events per variable (EPV) :** >= 10
- EPV <10:
  - **regression coefficients** biased in both positive and negative directions
  - **sample variance of the regression coefficients over- or under-estimated**
  - 90% confidence interval did not have proper coverage
  - paradoxical associations increased (significance in the wrong direction)

Peduzzi P, et al. J Clin Epidemiol 1996

What is Propensity score (PS) ?

- Propensity score (PS)
  - the conditional probability (propensity) of assigning a particular treatment to an individual
  - depends on the covariates
  - does not depend on the outcome

PS regression adjustment

- Outcome : binary or ordinal variable (e.g. GC)

$$g(E(Y)) = \alpha + \beta_1 X_1 + \beta_2 X_2$$

CA stomach

PPIs

PS

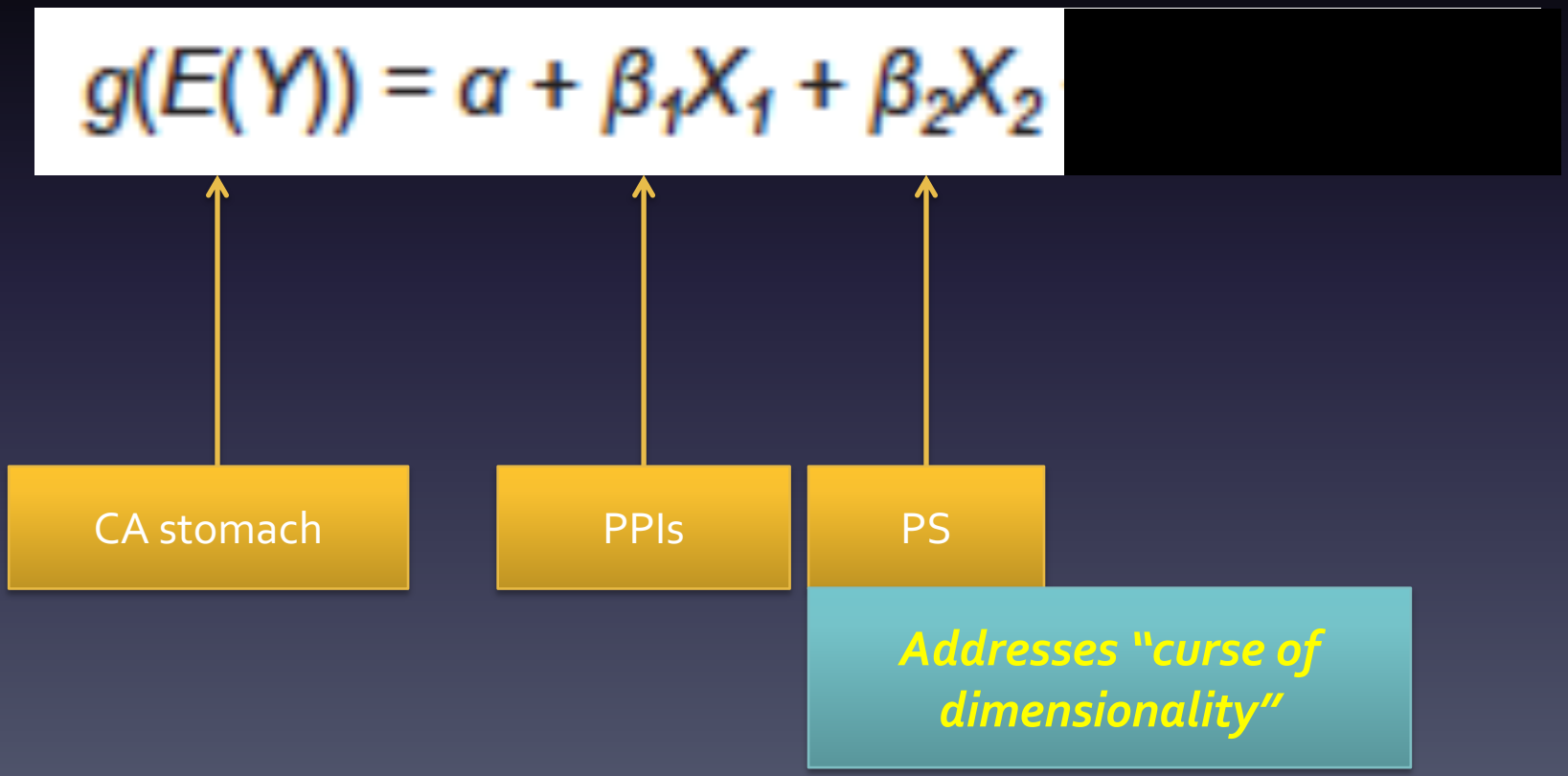
Derivation of PS in this study (Step 1)

$$g(E(Y)) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots$$

- Exposure of interest (i.e. PPI us)
- age
- sex
- other covariates in Table 1 (NOT gastric cancer)

PS regression adjustment (Step 2)

- Outcome of interest (i.e. gastric cancer)



Propensity score analysis

- PS regression adjustment
- PS matching
- PS subclassification / stratification
- PS weighting
  - weighting by odds
  - Inverse probability of treatment weights

PS matching with similar PS

- Greedy (nearest neighbor) matching
  - a priori "caliper" is defined: max distance in PS by which matches are allowed (usu 0.25 SD of logit of PS)
  - a treated subject is matched to the 1st case out of several comparison persons (even if it would better serve as match for a subsequent treated subject)

- Optimal matching
  - pairs of treated & untreated subjects are formed to minimize global distance in PS (i.e. sum of distances in PS in whole matched sample)
  - limited by high computational intensity

How do you know it is well matched ?

- Absolute standardized difference (ASD)
- absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation
- ASD > 0.1 – 0.2 indicates imbalance

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION | RESEARCH ARTICLE

Statins Were Associated with a Reduced Gastric Cancer Risk in Patients with Eradicated *Helicobacter Pylori* Infection: A Territory-Wide Propensity Score Matched Study

Ka Shing Cheung[1], Esther W. Chan[2], Angel Y.S. Wong[3], Lijia Chen[1], Wai-Kay Seto[1], Ian C.K. Wong[2,4], and Wai K. Leung[1]

ABSTRACT

Background: Individuals may still develop gastric cancer even after *Helicobacter pylori* eradication. We aimed to investigate statin effect on gastric cancer development in *H. pylori*–eradicated subjects.

Methods: All adult subjects who were prescribed clarithromycin-based triple therapy between 2003 and 2012 were identified in this retrospective cohort study utilizing a territory-wide electronic healthcare database. Patients were observed from index date of *H. pylori* therapy, and censored at gastric cancer diagnosis, death, or December 2015 (study end date). Statin use was defined as ≥180-day use after index date. Exclusion criteria included gastric cancer diagnosed within the first year after index date, previous gastric cancer or gastrectomy, and *H. pylori* treatment failure. Subdistribution hazard ratio (SHR) of gastric cancer with statins was calculated by competing risk regression with propensity score (PS) analysis matching 19 variables (age, sex, comorbidities, and other drug usage, including proton pump inhibitors, nonsteroidal anti-inflammatory drugs, aspirin, cyclooxygenase-2 inhibitors, and metformin).

Results: During a median follow-up of 7.6 years (interquartile range = 5.1–10.3), 169 (0.27%) of 63,605 patients developed gastric cancer at an incidence rate of 3.5 per 10,000 person-years. Among 22,870 PS-matched subjects, statins were associated with a lower gastric cancer risk (SHR = 0.34; 95% confidence interval, 0.19–0.61), in a duration– and dose–response manner ($P_{trend} < 0.05$).

Conclusions: Statins were associated with a lower gastric cancer risk in a duration– and dose–response manner among *H. pylori*–eradicated patients.

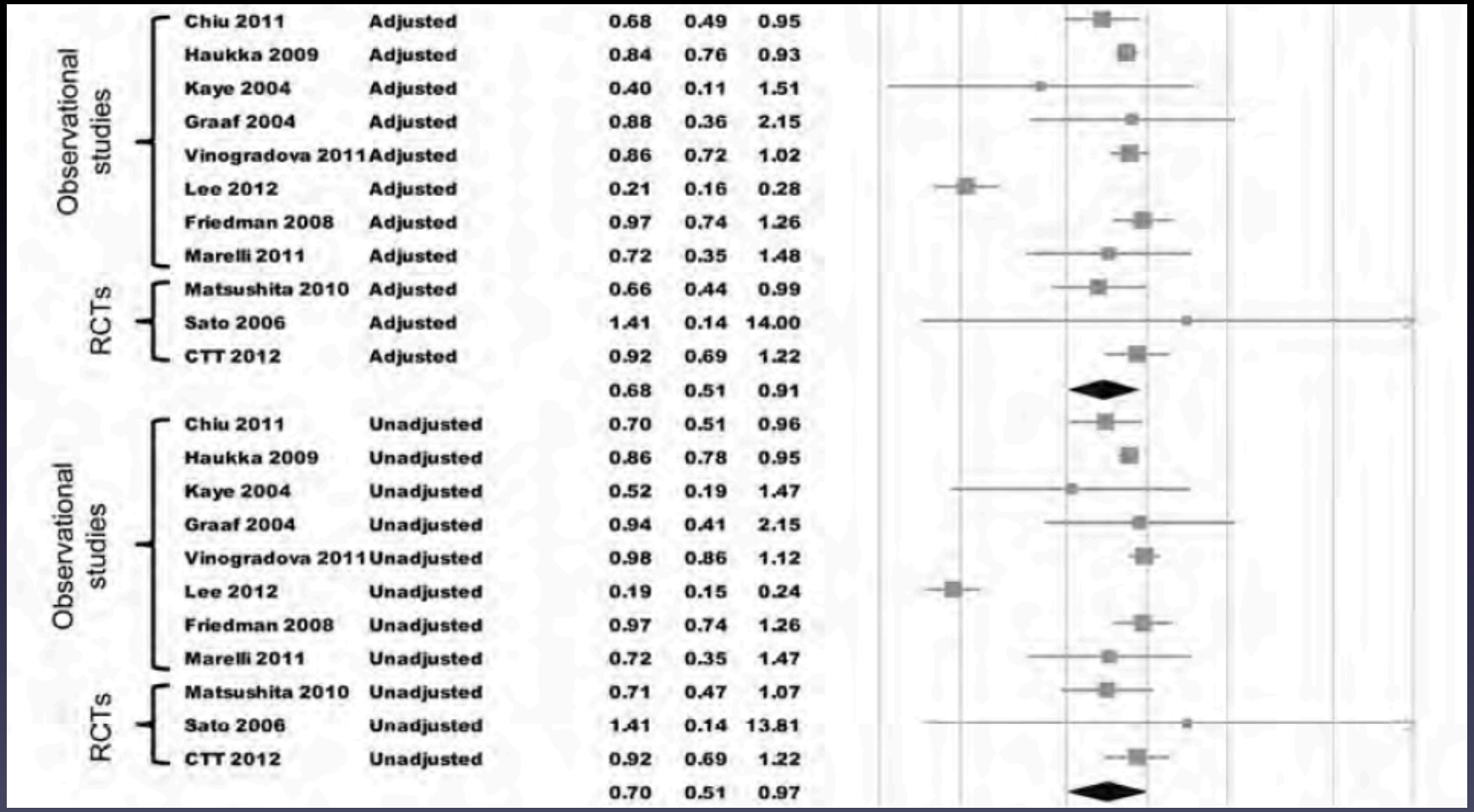
Impact: This study provides evidence on the additional benefits of statins as chemopreventive agents against gastric cancer among *H. pylori*–eradicated patients.

Cheung KS, et al. Cancer Epidemiol Biomarkers Prev 2020

Mechanisms of chemopreventive effects of statins

- Arrest of cell-cycle progression
- Induction of apoptosis
- Inhibition of angiogenesis
- Suppression of tumor growth

Statins and GC



Singh P.P et al. Ann Oncol 2013

	All (n=6,605)	Before PS Matching: Statin (n=15,990)	Before PS Matching: Non-statin (n=47,615)	Before PS Matching: ASD#	After PS Matching *: Statin (n=11,678)	After PS Matching *: Non-statin (n=11,192)	After PS Matching *: ASD#
Age at triple therapy (years)	55.6 (+/-14.6)	62.6 (+/-11.1)	53.5 (+/-14.9)	0.66	61.7 (+/-11.0)	63.6 (+/-13.8)	0.18
NSAIDs/ COX-2 inhibitors (n, %)	14692 (23.1%)	4435 (27.7%)	10257 (21.5%)	0.10	1418 (12.1%)	1383 (12.4%)	0.01
PPIs (n, %)	7715 (12.1%)	2955 (18.5%)	4760 (10.0%)	0.18	1224 (10.5%)	1020 (9.1%)	0.02

ASD for all covariates < 0.2 after PS matching

Cheung KS, et al. Cancer Epidemiol Biomarkers Prev 2020

Statins and GC (PS matching)

	PS matching (n=22,870, GC=62)			PS adjustment with trimming (n=63,605, GC=169)			PS adjustment (n=57,243, GC=150)		
	SHR	95% CI	p	SHR	95% CI	p	SHR	95% CI	p
Non-user (< 180 days)	Ref	-	-	Ref	-	-	Ref	-	-
Statin use (>= 180 days)	0.34	0.19 – 0.61	< 0.001	0.61	0.41 – 0.92	0.020	0.32	0.18 – 0.59	< 0.001

Cheung KS, et al. Cancer Epidemiol Biomarkers Prev 2020

Duration and dose of statins and GC (PS adjustment with trimming)

Statin use	Duration & Dose-response relationship (n=57,243, GC=150)		
	SHR	95% CI	p-value
Non-statin use	Ref	-	-
< 5 years	0.46	0.25 – 0.86	0.015
>= 5 years	0.43	0.29 – 0.66	<0.001
	SHR	95% CI	p-value
Non-statin use	Ref	-	-
Statin use (for every 100 increase in cDDD)	0.90	0.81 – 0.99	0.037

Cheung KS, et al. Cancer Epidemiol Biomarkers Prev 2020

Diabetes Mellitus Increases Risk of Gastric Cancer After *Helicobacter pylori* Eradication: A Territory-wide Study With Propensity Score Analysis

Ka Shing Cheung,[1] Esther W. Chan,[2] Lijia Chen,[1] Wai Kay Seto,[1] Ian C.K. Wong,[2,3] and Wai K. Leung[1]

https://doi.org/10.2337/dc19-0437

Cheung KS, et al. Diabetes Care 2019

OXFORD

JNCI J Natl Cancer Inst (2019) 111(5): djy144

doi: 10.1093/jnci/djy144
Article

ARTICLE

Metformin Use and Gastric Cancer Risk in Diabetic Patients After *Helicobacter pylori* Eradication

Ka Shing Cheung, Esther W. Chan, Angel Y. S. Wong, Lijia Chen, Wai Kay Seto, Ian C. K. Wong, Wai K. Leung

Cheung KS, et al. J Natl Cancer Inst 2019

Colorectal cancer

Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.14674

GASTROENTEROLOGY

Epidemiology, characteristics, and survival of post-colonoscopy colorectal cancer in Asia: A population-based study

Ka Shing Cheung, Lijia Chen, Wai Kay Seto and Wai K Leung

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Cheung KS, et al. J Gastroenterol Hepatol 2019

Statins reduce the progression of non-advanced adenomas to colorectal cancer: a postcolonoscopy study in 187 897 patients

Ka-Shing Cheung,[1] Lijia Chen,[1] Esther W Chan,[2] Wai-Kay Seto,[1] Ian C K Wong,[2,3] Wai K Leung[1]

ABSTRACT

Background and aims Postcolonoscopy colorectal cancer (PCCRC) accounts for up to 9% of all CRCs. Statins have been shown to be associated with a lower CRC risk. We aimed to investigate whether PCCRC risk was also lower among statin users.

Methods This is a retrospective cohort study using a territory-wide electronic healthcare database in Hong Kong including patients aged 40 years or above who had undergone colonoscopies between 2005 and 2013. Exclusion criteria included prior colorectal cancer (CRC), inflammatory bowel disease, prior colectomy and CRC detected within 6 months of index colonoscopy. We defined statin use as at least 90-day use before index colonoscopy. Medication use was traced up to 5 years before index colonoscopy. PCCRC-3y was defined as cancer diagnosed between 6 and 36 months after index colonoscopy. Sites of CRC were categorised as proximal (proximal to splenic flexure) and distal cancer. The subdistribution HR (SHR) of PCCRC-3y with statin use was derived by propensity score matching based on covariates (including patient factors, concurrent medication use and endoscopy centre's performance).

Results Of 187 897 eligible subjects, 854 (0.45%) were diagnosed with PCCRC-3y. Statin use was associated with a lower PCCRC-3y risk (SHR: 0.72; 95% CI 0.55 to 0.95; p=0.018). Subgroup analysis shows that SHRs were 0.50 (95% CI 0.28 to 0.91; p=0.022) for proximal and 0.80 (95% CI 0.59 to 1.09; p=0.160) for distal cancer. Older (>60 years) patients, women and those without diabetes mellitus or polyps appeared to benefit more from statins.

Conclusions Statins were associated with a lower PCCRC risk, particularly for proximal cancer.

Significance of this study

What is already known on this subject?

- Although the incidence and mortality of colorectal cancer (CRC) can be reduced by screening colonoscopy, CRC can still occur before the expected interval after an initial negative colonoscopy, which is named postcolonoscopy colorectal cancer (PCCRC).
- Meta-analyses of clinical studies report that statins are associated with a reduced CRC risk, but there are no studies that specifically explore its role in preventing PCCRC.

What are the new findings?

- Statin use was associated with a lower PCCRC risk.
- Older (>60 years) patients, women and those without diabetes mellitus or polyps appeared to benefit more from statins.

How might it impact on clinical practice in the foreseeable future?

- Our study results help in the decision-making process of commencing statins in patients at high risk for CRC with borderline indications for cardiovascular prevention.
- It prompts further studies on the potential role of statins in inhibiting the progression of colorectal adenoma to cancer.

programmes only.[7] PCCRC accounts for up to 9% of all diagnosed CRCs,[8] with proximal colon

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Nonsteroidal anti-inflammatory drugs but not aspirin are associated with a lower risk of post-colonoscopy colorectal cancer

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Summary

Background: Although nonsteroidal anti-inflammatory drugs (NSAIDs) reduce colorectal cancer (CRC) risk, their role in preventing post-colonoscopy CRC (PCCRC) remains undetermined.

Aims: To investigate whether NSAIDs reduce PCCRC risk after a negative baseline colonoscopy

Methods: This is a retrospective cohort study based on a territory-wide healthcare database of Hong Kong. All patients (aged 40 or above) who underwent colonoscopies between 2005 and 2013 were identified. Exclusion criteria included CRC detected within 6 months of index colonoscopy, prior CRC, inflammatory bowel disease and prior colectomy. The primary outcome was PCCRC-3y diagnosed between 6 and 36 months after index colonoscopy. Sites of CRC were categorised as proximal (proximal to splenic flexure) and distal. The adjusted hazards ratio (aHR) of PCCRC-3y with NSAID and aspirin use (defined as cumulative use for ≥90 days within 5 years before index colonoscopy) was derived by propensity score (PS) regression adjustment of 22 covariates (including patient factors, concurrent medication use and endoscopy centre's performance).

Results: Of 187 897 eligible patients, 21 757 (11.6%) were NSAID users. 854 (0.45%) developed PCCRC-3y (proximal cancer: 147 [17.2%]). NSAIDs were associated with a lower PCCRC-3y risk (aHR: 0.54, 95% CI: 0.41-0.70), but not CRC that developed >3 years (aHR: 0.78, 95% CI 0.56-1.09). The aHR was 0.48 (95% CI: 0.24-0.95) for proximal and 0.55 (95% CI: 0.40-0.74) for distal cancer. A duration- and frequency response relationship was observed (P_{trend} < 0.001). For aspirin, the aHR was 1.01 (95% CI: 0.80-1.28).

Conclusions: Non-aspirin NSAIDs were associated with lower PCCRC risk after a negative baseline colonoscopy.

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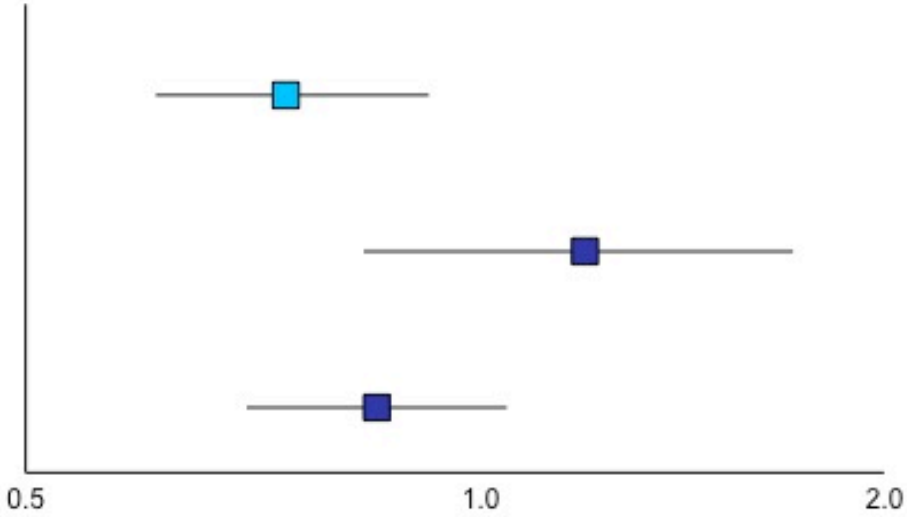
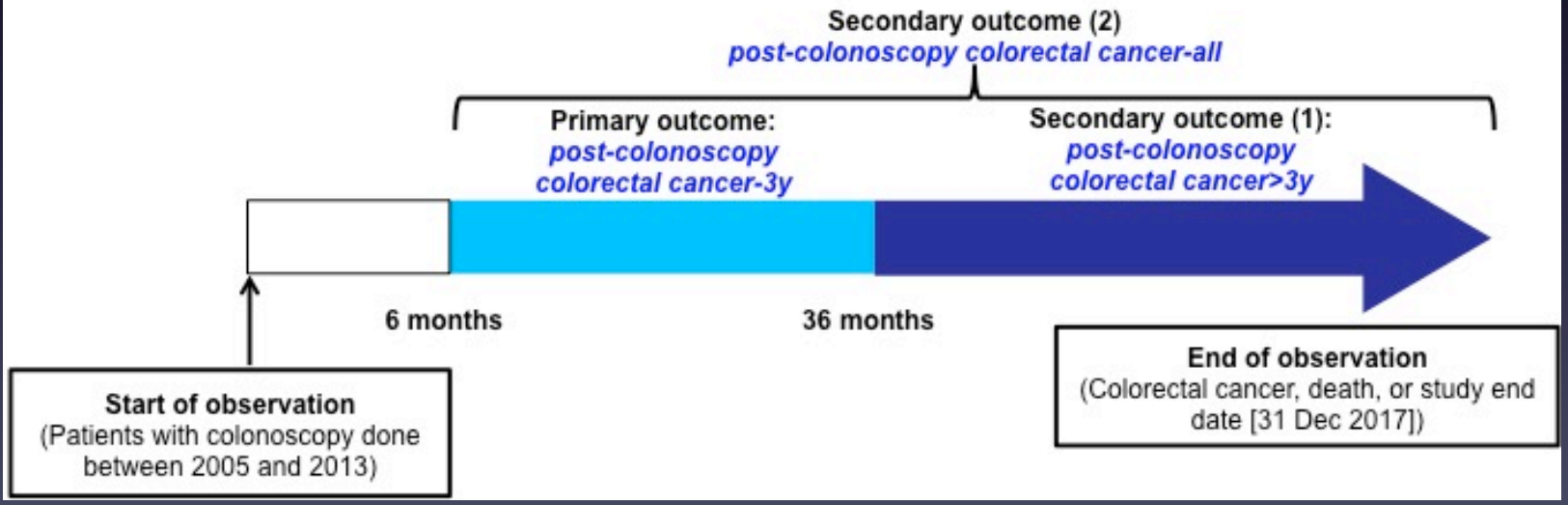
Outcomes	Adjusted HR	95 % CI
Primary outcome (6-36 months)	0.78	0.64 – 0.96
Secondary outcome (>36 months)	1.18	0.88 – 1.57
Secondary outcome (all)	0.89	0.75 – 1.06





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REVIEW

Application of Big Data analysis in gastrointestinal research

Ka-Shing Cheung, Wai K Leung, Wai-Kay Seto

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Shortcomings specific of Big Data analysis	Solutions
Data validity	Cross reference with medical records in a subset of the sample
Missing data	Statistical methods to deal with missing data, *e.g.* multiple imputation
	Text mining or natural language processing of unstructured data
Incomplete capture of variables or unavailability of certain diagnosis codes	Surrogate markers (*e.g.*, COPD for smoking, alcohol-related diseases for alcoholism)
	Inclusion of a large set of measured variables
	Text mining or natural language processing of unstructured data
Privacy	De-identification of individuals
	Review of study plan by local ethics committee
Hypothesis-free predictive models	Validation in prospective studies or randomized control trials

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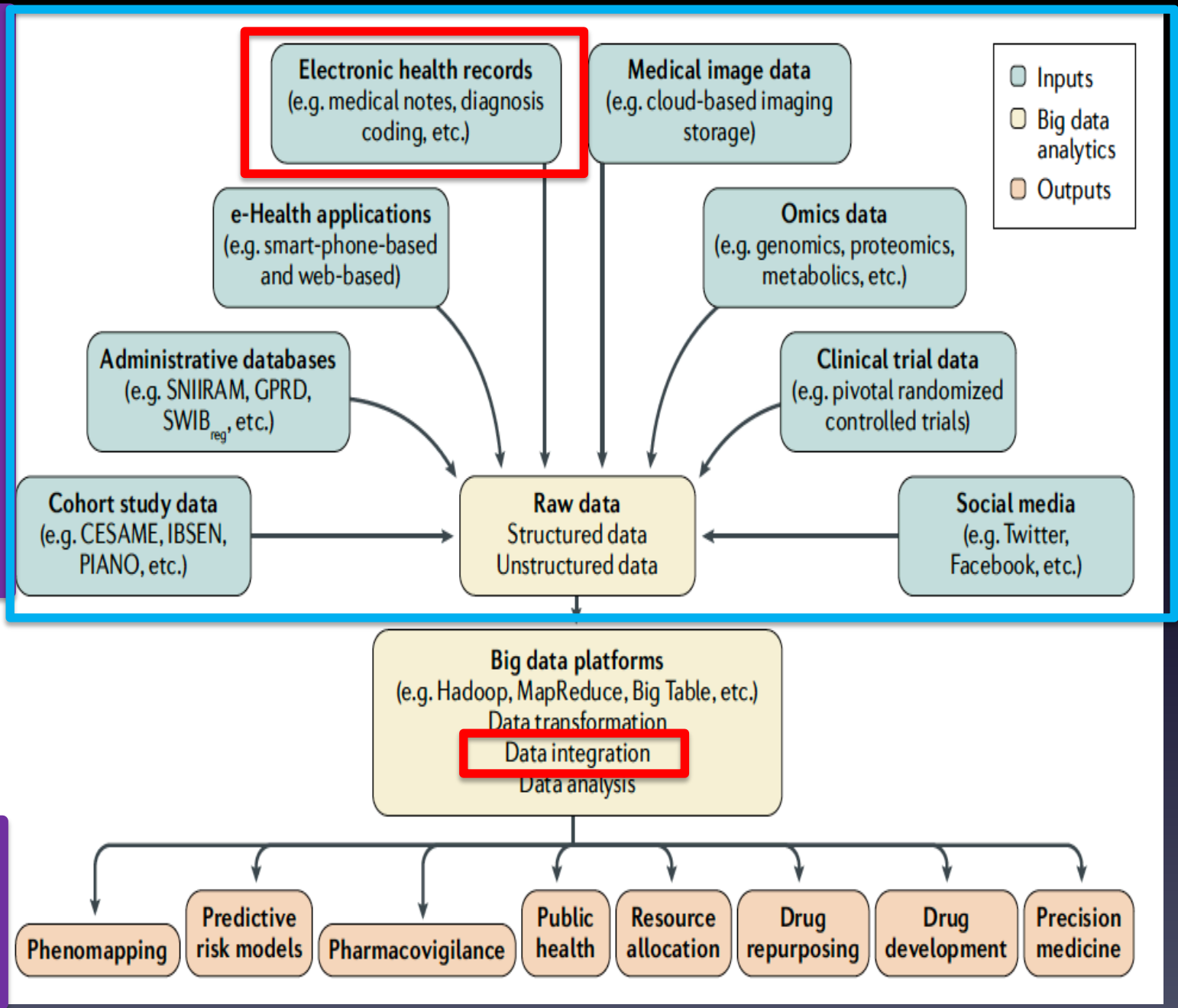
Shortcomings of all observational studies including Big Data analysis	Solutions
Residual and/or unmeasured confounding	Inclusion of a large set of measured variables
	Inclusion of RCT datasets with extensive collection of data and outcomes for trial participants or linkage with other data sources
	Fulfilment of Bradford Hill criteria
Reverse causality/protopathic bias (outcome of interest leads to exposure of interest)	Cohort study design instead of case-control study design
Example: Early symptoms of undiagnosed GC leads to PPI use, rather than PPIs cause GC	Excluding prescriptions of drugs of interest (*e.g.*, PPIs) within a certain period (*e.g.*, 6 mo) before development of the outcome of interest (*e.g.*, gastric cancer)
Selection bias	Encompassing entire study population (n = all)
Indication bias (or confounding by indication/disease severity)	Balance of patient characteristics, in particular comorbidities that are indications for a certain treatment (*e.g.*, PS matching of a large set of measured variables)
	Negative control exposure
Confounding by functional status and cognitive impairment	Balance of patient characteristics, in particular comorbidities that can affect functional and cognitive status (*e.g.*, PS matching)
Healthy user bias / adherer bias (individuals who are more health conscious tend to have better health outcomes)	Adjustment for other lifestyle factors – text mining or natural language processing of unstructured data
Immortal time bias (arises when the study outcome cannot occur during a period of follow-up due to study design)	Landmark analysis
	Analysis using time varying covariates
Ascertainment bias / surveillance bias / detection bias (differential degree of surveillance or screening for the outcome among exposed and unexposed individuals) Example: PPI users may undergo upper endoscopy more frequently than non-PPI users, and hence more GC detected in PPI users	Selection of an unexposed group with a similar likelihood of screening/testing
	Selection of an outcome that are likely to be diagnosed equally in exposed and control groups
	Adjustment for the surveillance rate
Access to healthcare	Stratified analysis according to patients' residential regions (*e.g.*, rural *vs* urban), socioeconomic status, immigration status, race/ethnicity, institutional factors (*e.g.*, restrictive formularies)
Selective prescription and treatment in frail and very sick patients	PS methodology (trimming of areas of non-overlap, PS matching, PS by treatment interaction)

Conclusions

- Population-based healthcare databases is one of the sources of Big Data (increasingly popular for clinical researches)
- Big data approach addresses some of the limitations of traditional observational study designs (case-control studies and cohort studies) and randomized controlled trials
- Causality may not be established via Big Data approach, though can be strengthened by good study design and control of biases / confounding
- Propensity score analysis is helpful in Big Data analysis

Sources of Big Data



Application of Big Data analysis

Olivera P, et al. Nat Rev Gastroenterol Hepatol 2019