DEPARTAMENTO DE SALUD PÚBLICA
FACULTAD DE MEDICINA

ACCDiS
ADVANCED CENTER FOR CHRONIC DISEASES

Study Designs in Epidemiology:
The Case of Arsenic exposure and health effects in northern Chile, 1958-2015

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Little history

1950´s Increase copper extraction & smelting 1976-78 Lung Cancer Death SMR 503 Antofagasta, SMR 449 Tocopilla (Haynes, 1983).

Ecological geographical and temporal association interpreted as causal (Rivara)

In favor:

- Inhaled arsenic implies lung cancer.
- Evidence of As carcinogenicity came from workers exposed to As in fumes.

Alternative explanations

- Drinking water, huge As exposure in coastal cities also high lung cancer death.
- In favor
  - **cancer distribution coastal**
  - **other As-associated cancers in excess same areas**
- In contra
  - Lung cancer: **inhalation not ingestion**
  - Healthy worker effect
- Real life implications: **modify the emission criteria vs Clean the water from arsenic.**

As concentration in Drinking water Variability in Northern Chile 1930-2015

Region	City or Town	Population[a]	Average Arsenic Concentration (µg/L) Years 1930-57	1958-70	1971-77	1978-79	1980-87	1988-2005	2005+
I	Arica	168,594	10	10	10	10	10	10	9
	Putre	1,799	1	1	1	1	1	1	1
	Iquique	196,941	60	60	60	60	60	60	10
	Huara	2,365	30	30	30	30	30	30	30
	Pica	5,622	10	10	10	10	10	10	10
	Pozo Almonte	9,855	40	40	40	40	40	40	40
II	Tocopilla	21,827	250	250	636	110	110	40	10
	Maria Elena	6,852	250	250	636	110	110	39	39
	Calama	125,946	150	150	287	110	110	40	38
	San Pedro	4,522	600	600	600	600	600	600	600
	Antofagasta	270,184	90	860	110	110	70	40	10
	Mejillones	7,660	90	860	110	110	70	37	10
	Taltal	10,101	60	60	60	60	60	60	60
	Recent migrants	82,312	<10	<10	<10	<10	<10	<10	<10

[a] Population data are based on the 2002 Chile census (41).

As average concentration in water (ug/L)

Case reports & prevalence surveys

Short term health effects: Case reports Systemic and dermatological manifestations

1960 : Bronchiectasis, Raynaud´s syndrome, peripheral vascular phenomena, ischemia, myocardial infarction and mesenteric thrombosis (Zaldivar, 1974).

1962 : Children with cutaneous lesions.

1968 : Over 100 cases of arsenicism in Antofagasta Hospital (Zaldivar, 1974).

1960-78: Cardiovascular & respiratory in children (Bruning 1968).

Anatomic-pathological findings in children

1973-74: 5 infants exposed to As in utero died myocardial infarction age circa 5 years, their pathology:

- Occlusive, diffuse, generalized lesions in medium and small size arteries (heart, skin, gastrointestinal tract, kidneys, pancreas, and liver)
- No inflammatory changes
- Arsenical skin lesions and
- Arsenic found in various organs

Rosenberg, HG. Systemic Arterial Disease with Myocardial Infarction Report on Two Infants (1973). Rosenberg, H.G. Systemic arterial disease and chronic arsenicism in infants (1974)

Prevalence surveys Antofagasta (Borgoño 1971-76)

- **Population Health Surveys schoolchildren Exposed & Non Exposed Areas:**

- Children‘ skin **lesions by years of exposure**:

  Exposure < 4 years =2%.

  Exposure 5-9 years = 50%.

- **Post-intervention Surveys** [1-3 years] Antofagasta children:

  Decrease skin arsenicism; dyspnea and cough from 38% to 7%.

Environmental Risk Assessment of As in Chile. Fondef 2-24

Various components

- Environmental assessment: As sources, concentration and distribution
- Health Risk evaluation: main sources of exposure and health effects in humans
- Environmental interventions: Options to control As in water and air

Background levels of As in the environment in Chile and health effects 1994 – 1996 Fondef 2-24

One year of National monitoring of As

- In PM10 in cities
- In PM 10 in industries
- In drinking waters
- In food
- In the urine of schoolchildren throughout Chile

As (%) Source Atribution Chile 1994 – 95 (Fondef 2-24)

Zone	City	Water	Air	Food
Northern	Arica	56.9	1.5	41.5
	Iquique	89.1	0.4	10.4
	Antofagasta	**81.7**	**1.4**	16.7
	Calama	82.9	2.7	14.3
	Copiapó	**33.2**	**12.2**	54.5
Central	Rancagua	69.3	2.0	28.7
	Talca	46.2	0.3	53.5
Southern	Concepción	19.2	1.3	79.5
	Rest	19.4	0.4	**80.2**

SMR lung cancer selected counties Chile 1985-2002(Fondef 2-24)

County [As ug/l 1958-1970]	SMR lung cancer 1985 – 92	SMR lung cancer 1993 – 02
Antofagasta [860 ug/l]	420.1	406.1
Tocopilla [250 ug/l]	479.1	397.2
Calama [150 ug/l]	140.7	112.5
Valparaiso [<10 ug/l]	136.6	131.8

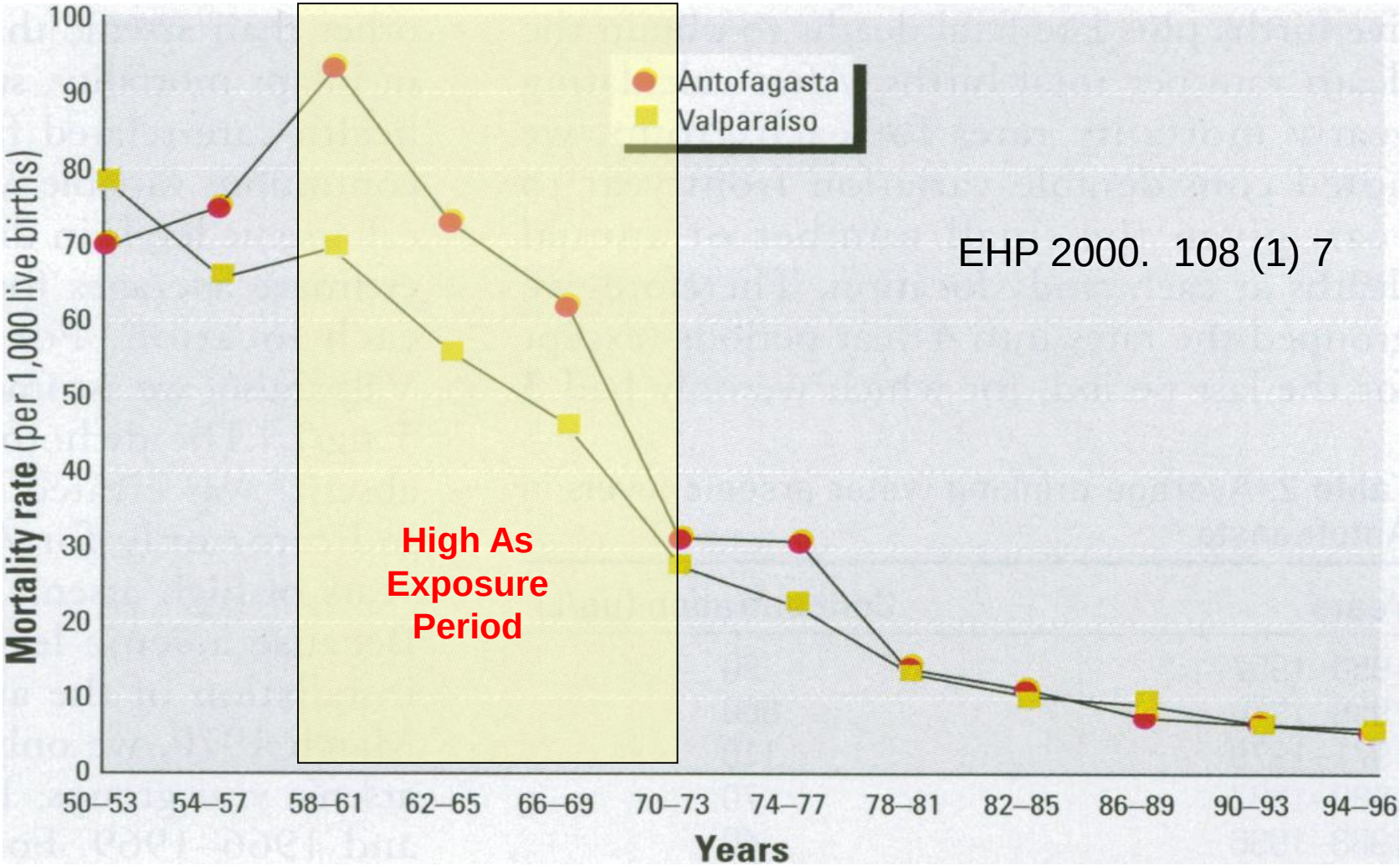
Ecologic Studies: Time series since 1950

Mortality trend by county

- Contrast cancer death in **exposed/unexposed** counties.
- Contrast specific causes of death **before/after exposure.**
- Contrast of **rates by age.**
- Exposed Antofagasta; unexposed Valparaiso

Post-Neonatal mortality Antofagasta/Valparaiso 1950-96.

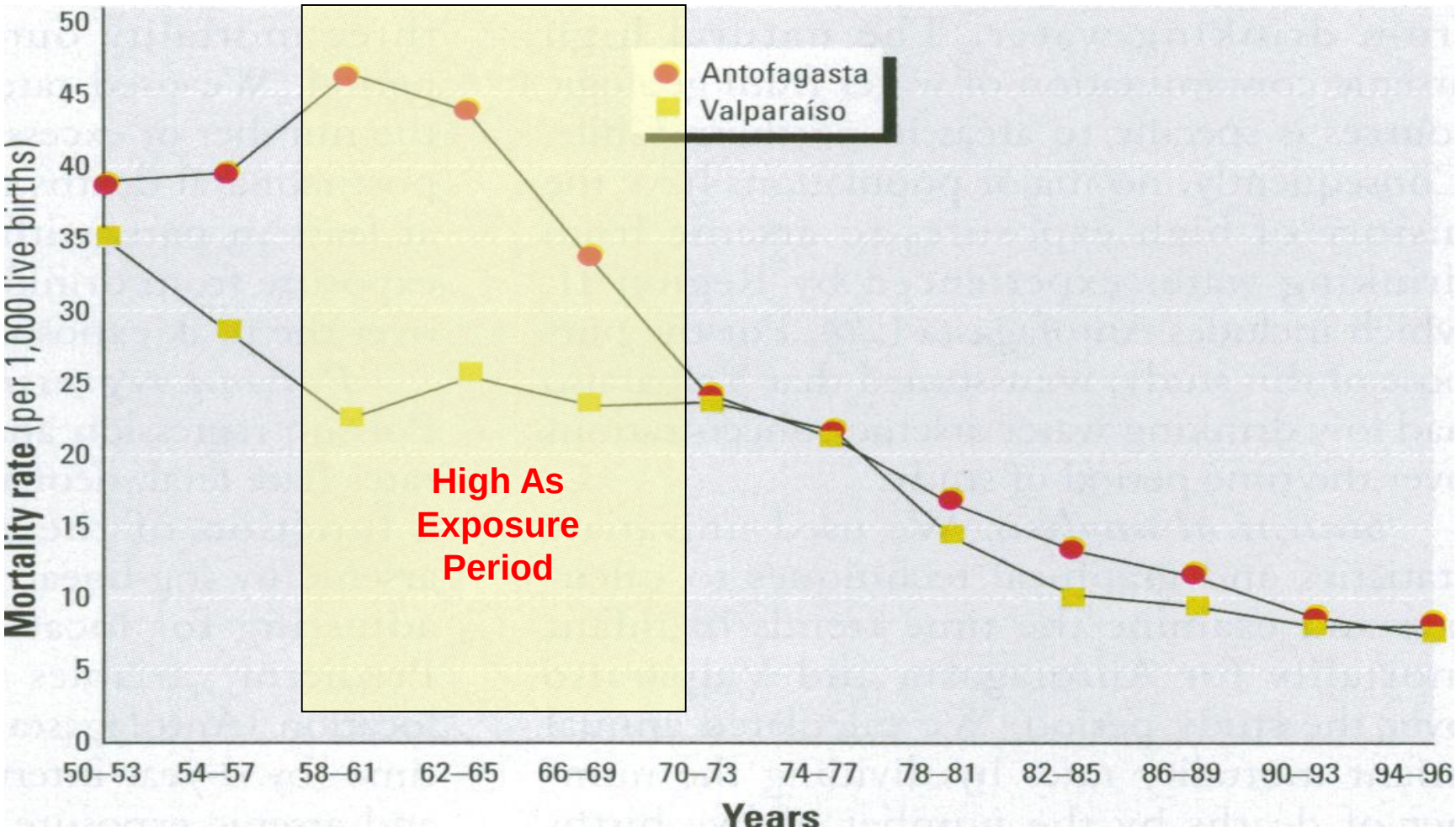
Rate Ratio = 1.26; (CI, 1.18-1.34)



EHP 2000. 108 (1) 7

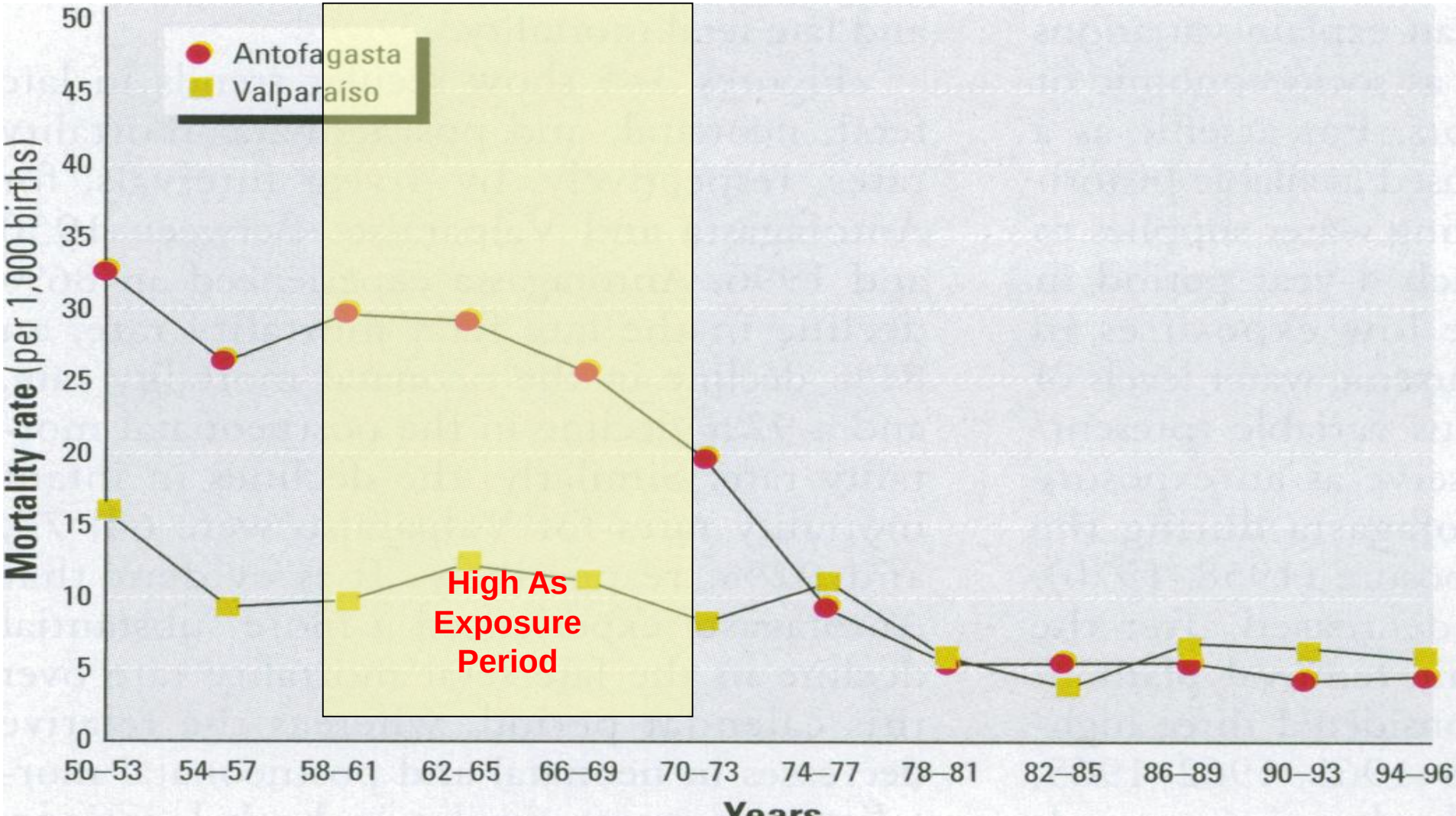
Neonatal mortality Antofagasta & Valparaiso, 1950-96.

Rate Ratio =1.53; (CI, 1.40-1.66)

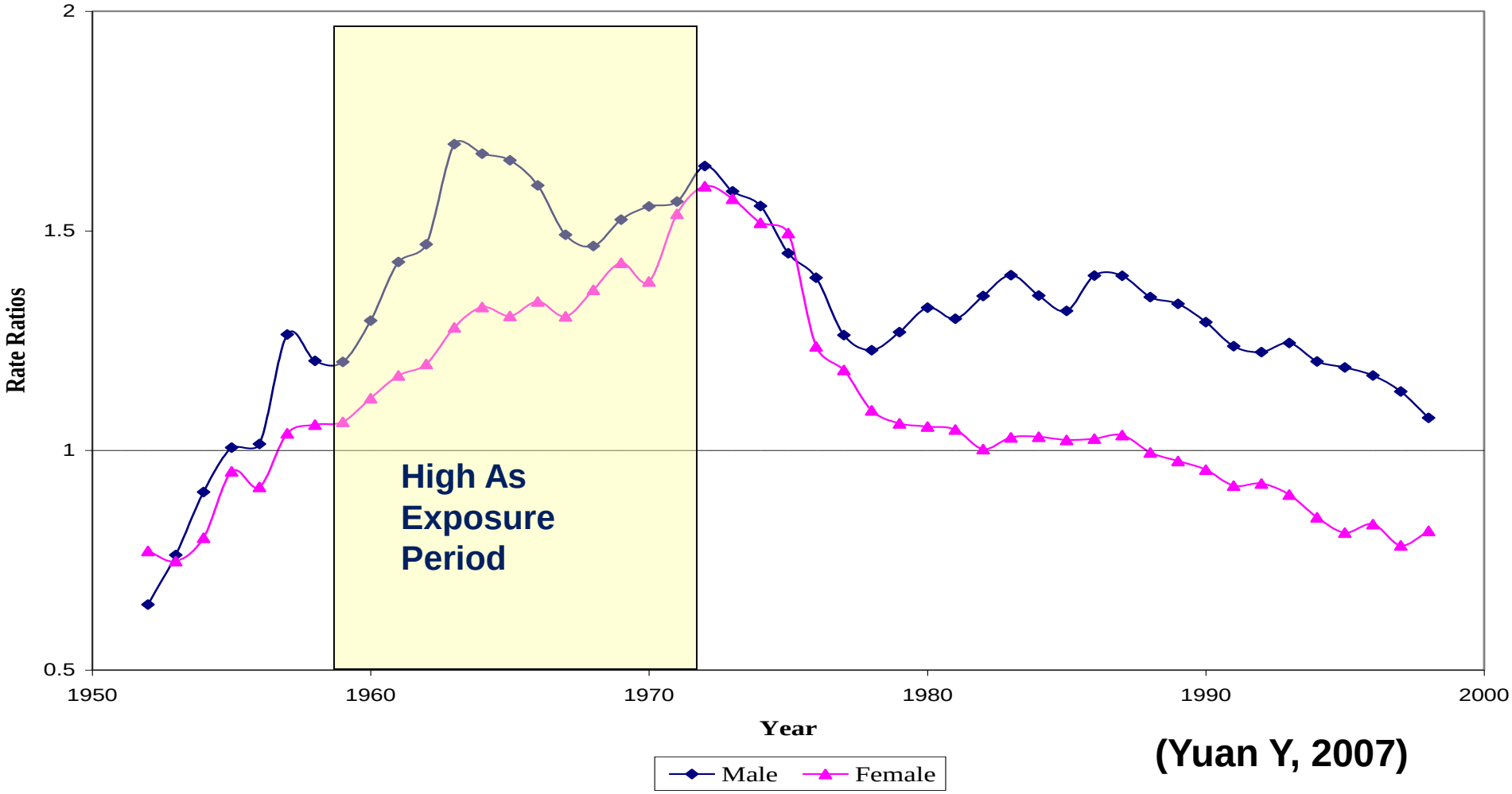


Late fetal mortality Antofagasta/Valparaiso, 1950-96.

RR = 1.72; (CI,1.54-1.93)



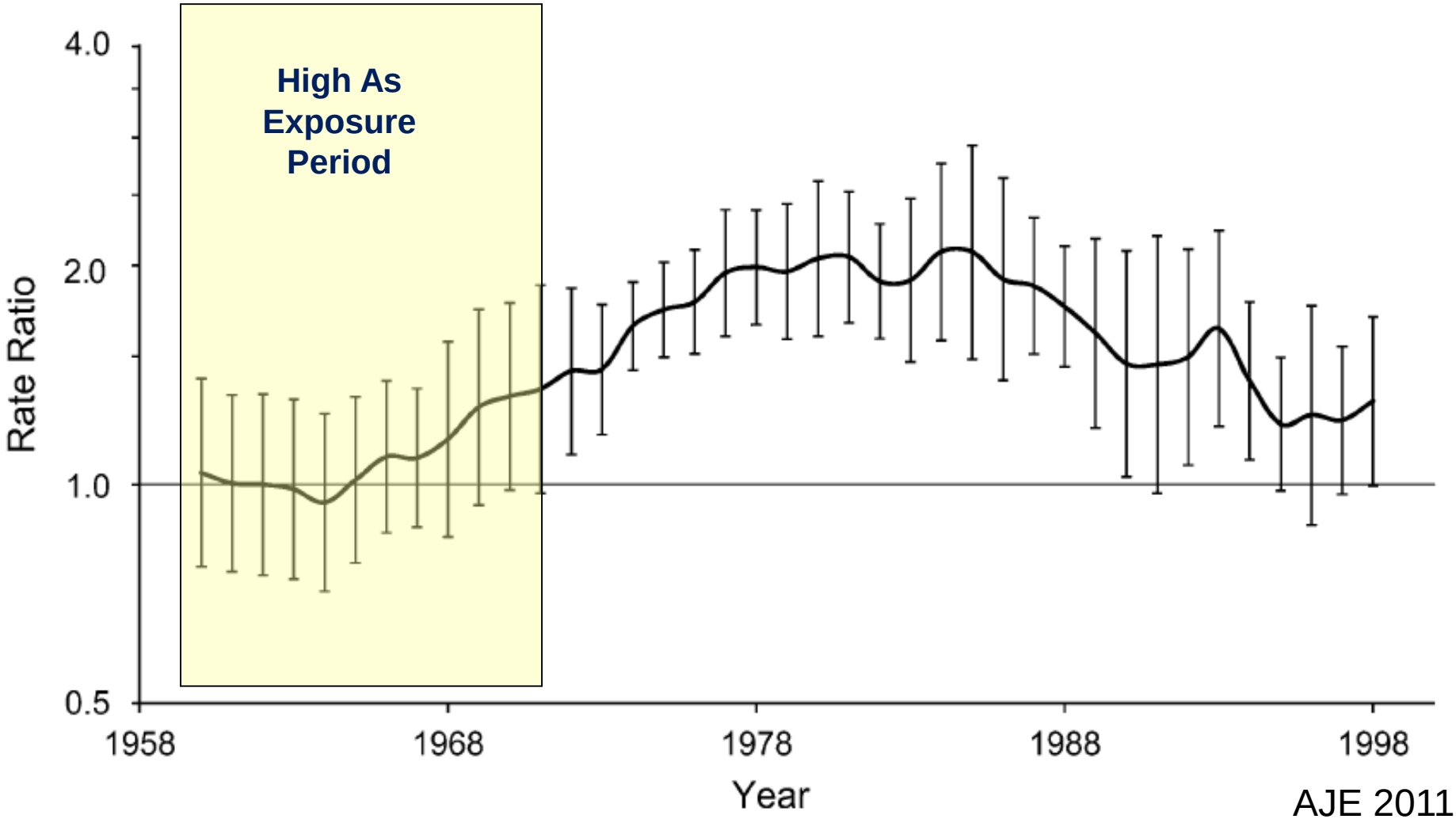
Mortality from Acute Myocardial Infarction related to high exposure to As, Region II vs V , Chile



(Yuan Y, 2007)

Mortality From Pulmonary Tuberculosis

Age-adjusted Rate Ratios for men, región II vs V



AJE 2011

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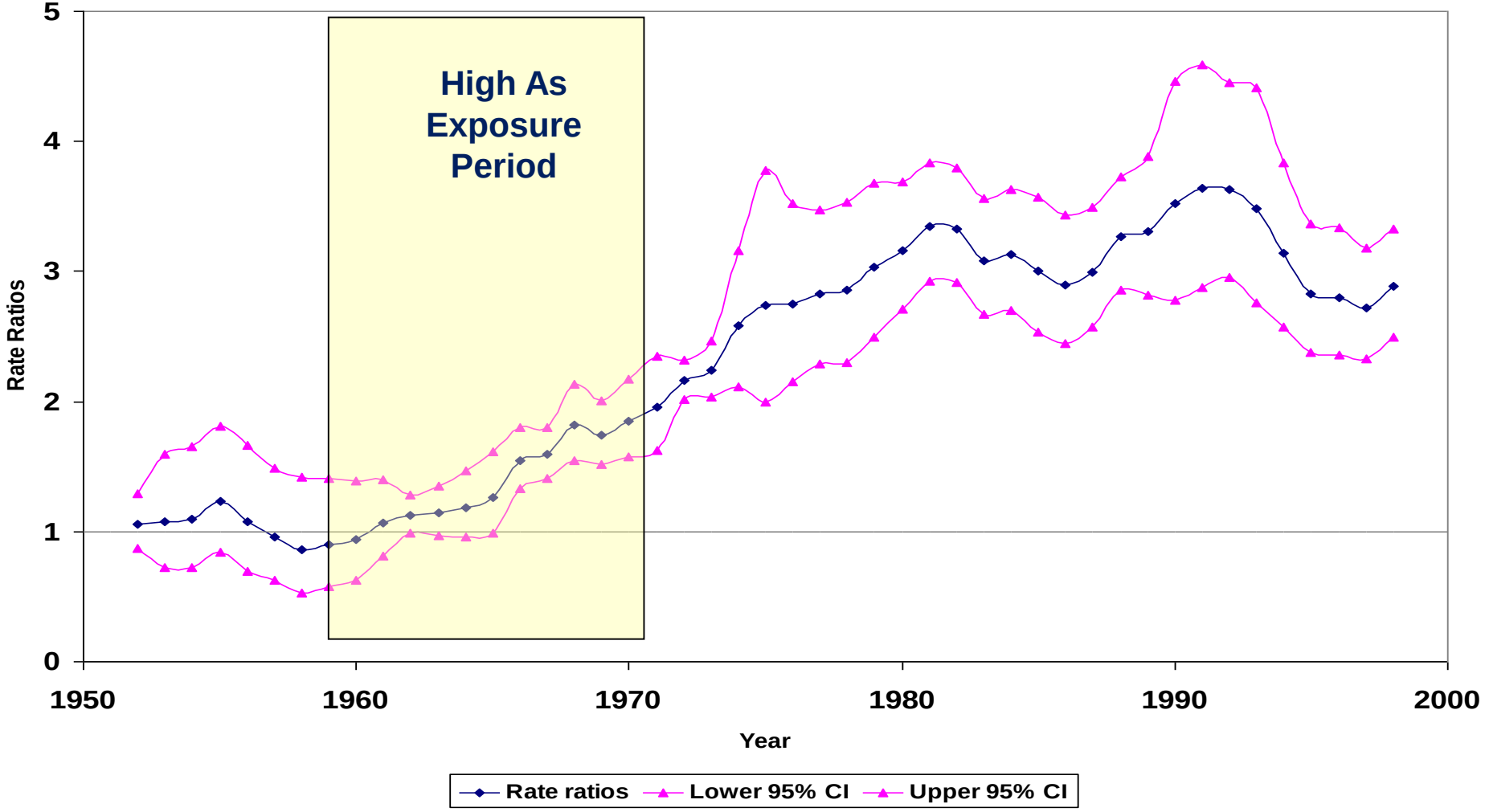
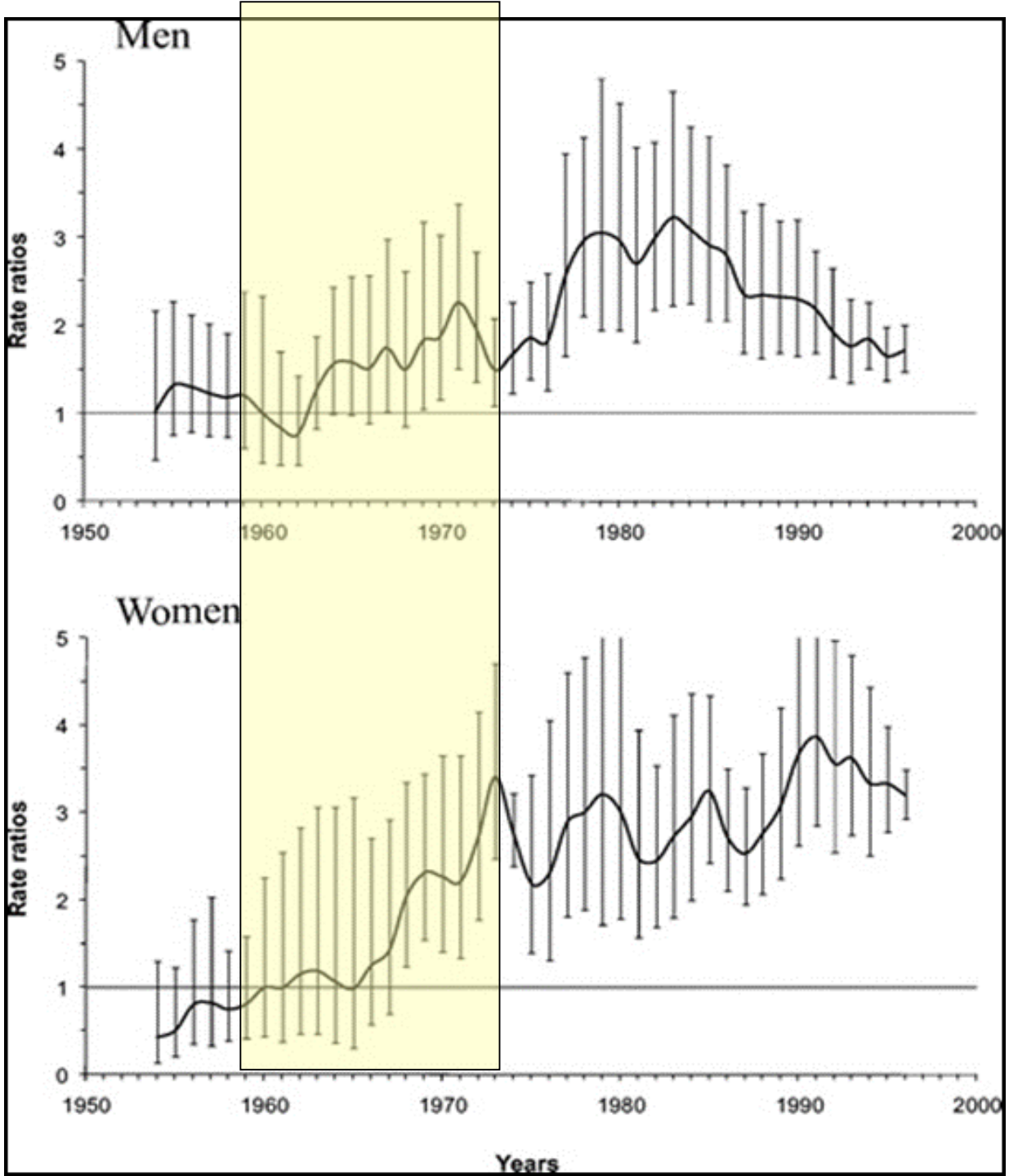
Latency Lung Cancer mortality, Región II, Chile





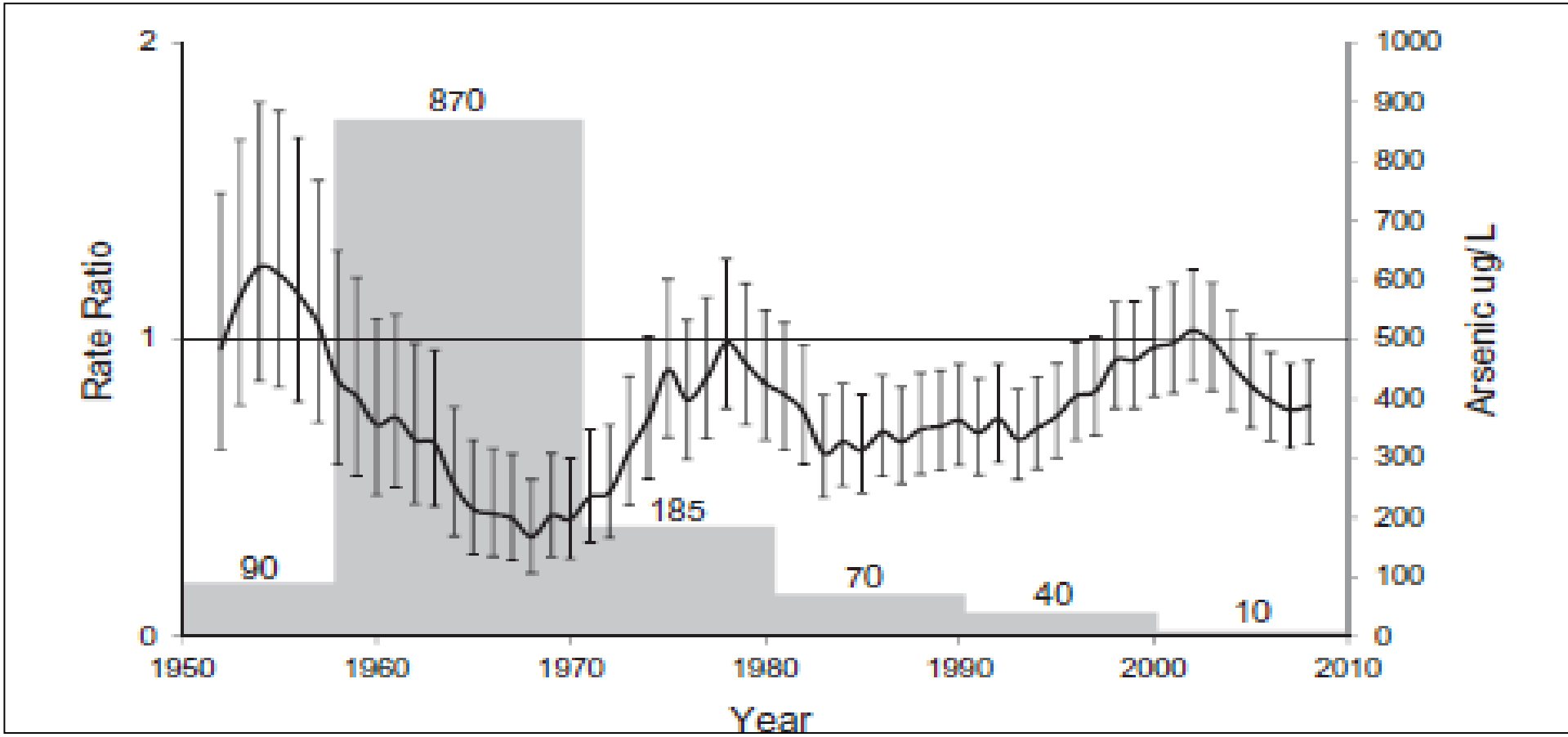
Kidney cancer mortality men and women aged ≥30 years.

Region II/Region V Chile, 1950–2000

Age-adjusted rate ratios and 95% CI.

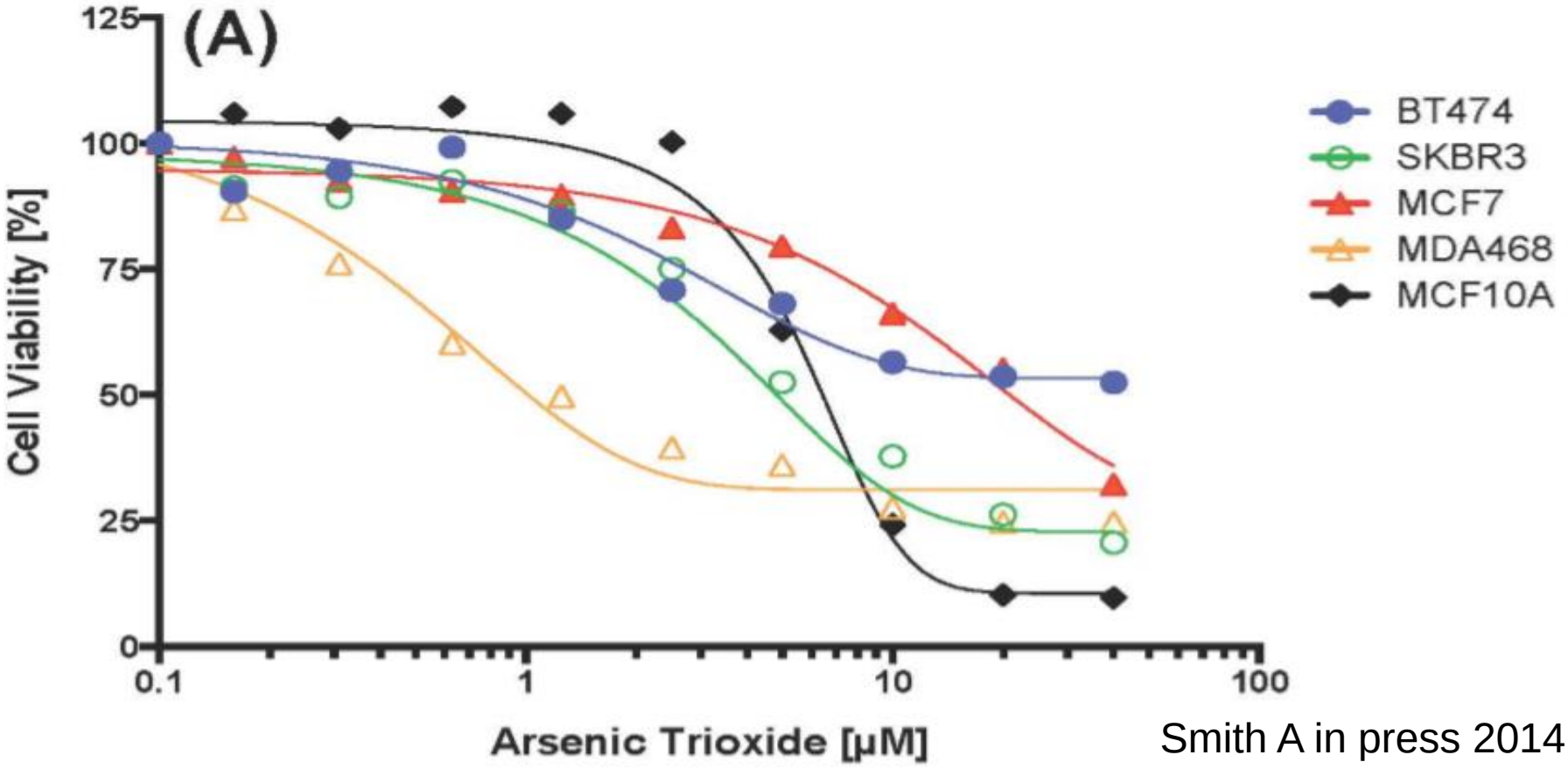
Yuan Y 2010

Breast Cancer and Arsenic exposure Antofagasta 1950-2010



Smith A 2015

Effects of A_2SO_3 in breast cancer cell lines vs normal breast cells



Smith A in press 2014

Retrospective Occupational Cohort

Health status of workers of Chuquicamata Mine Complex. Zamorano 1982.

- Prevalence of chronic bronchitis among the smelting workers was higher (29%) than the workers of administrative areas (12%).

- Prevalence among the non-smoker of the smelting was 12% compared to 1% among the administrative workers non-smokers (RR 10).

- Prevalence of chronic bronchitis among the smelter workers was 2,7 times higher for those employed more than five years.

Chronic bronchitis is probably reflecting the combined effect of the chemicals and particles in the smelter air, one of which is the arsenic.

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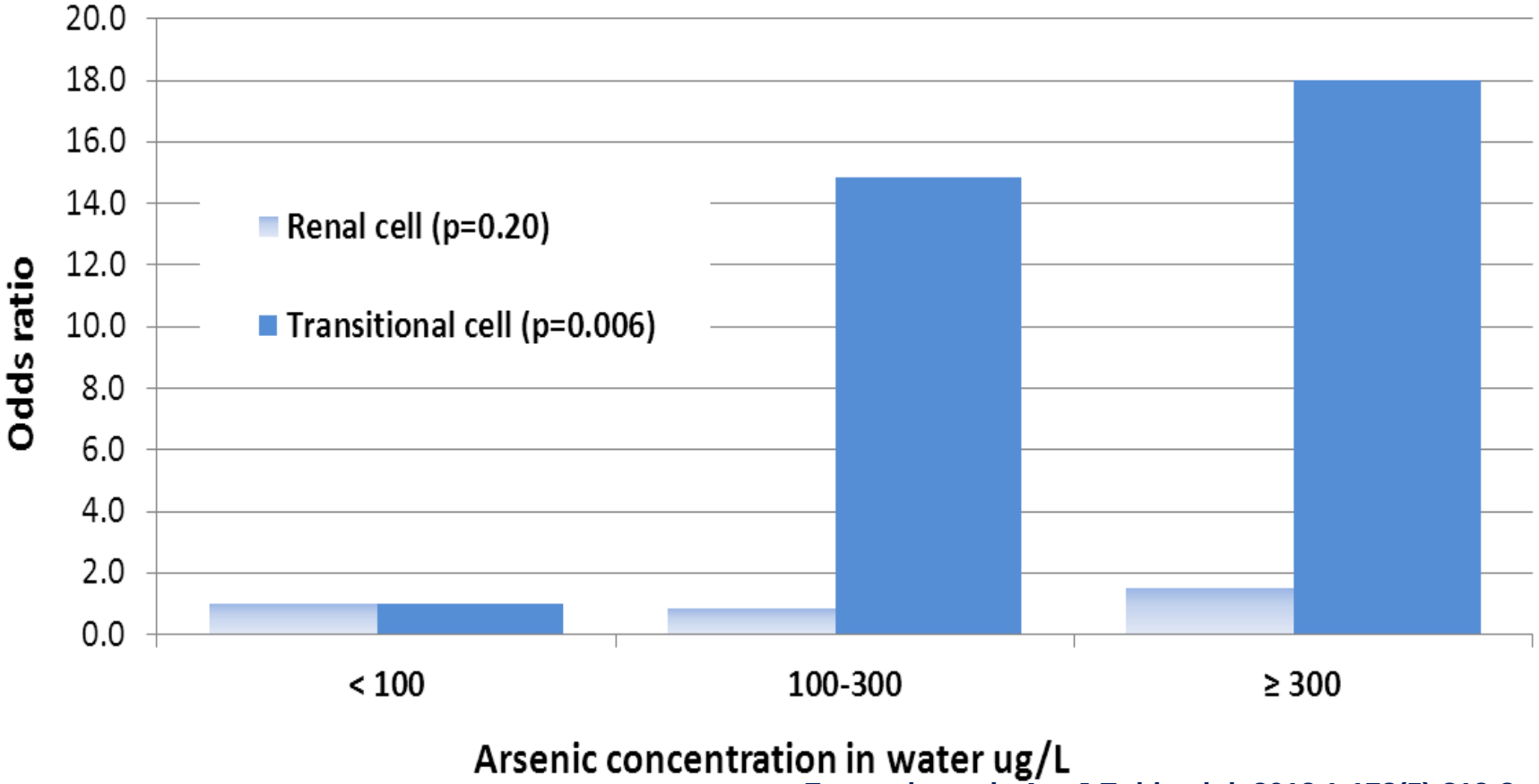
Delayed Health Effects of As exposure in Antofagasta: CASE-CONTROL STUDIES

Individual-Based case-control studies

Allows for:

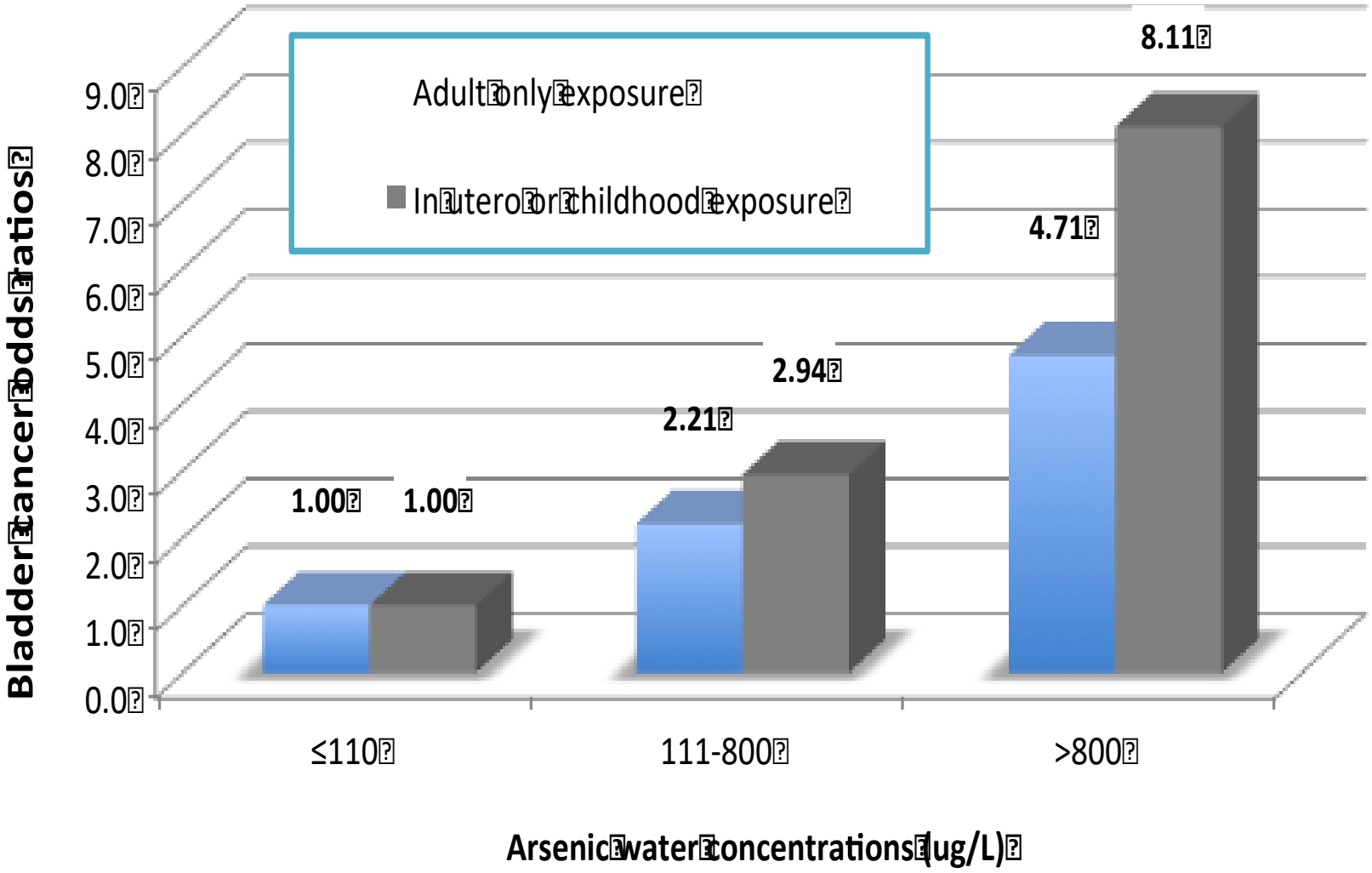
- Individual-based doses & age at exposure
- Cofactors and confounders
- Latency and duration of the excess risk
- Verify diagnoses and histology

Kidney cancer odds ratios by cell type, northern chile 2008-10



Ferreccio et al., Am J Epidemiol. 2013 1;178(5):813-8.

Age at exposure: Bladder Cancer

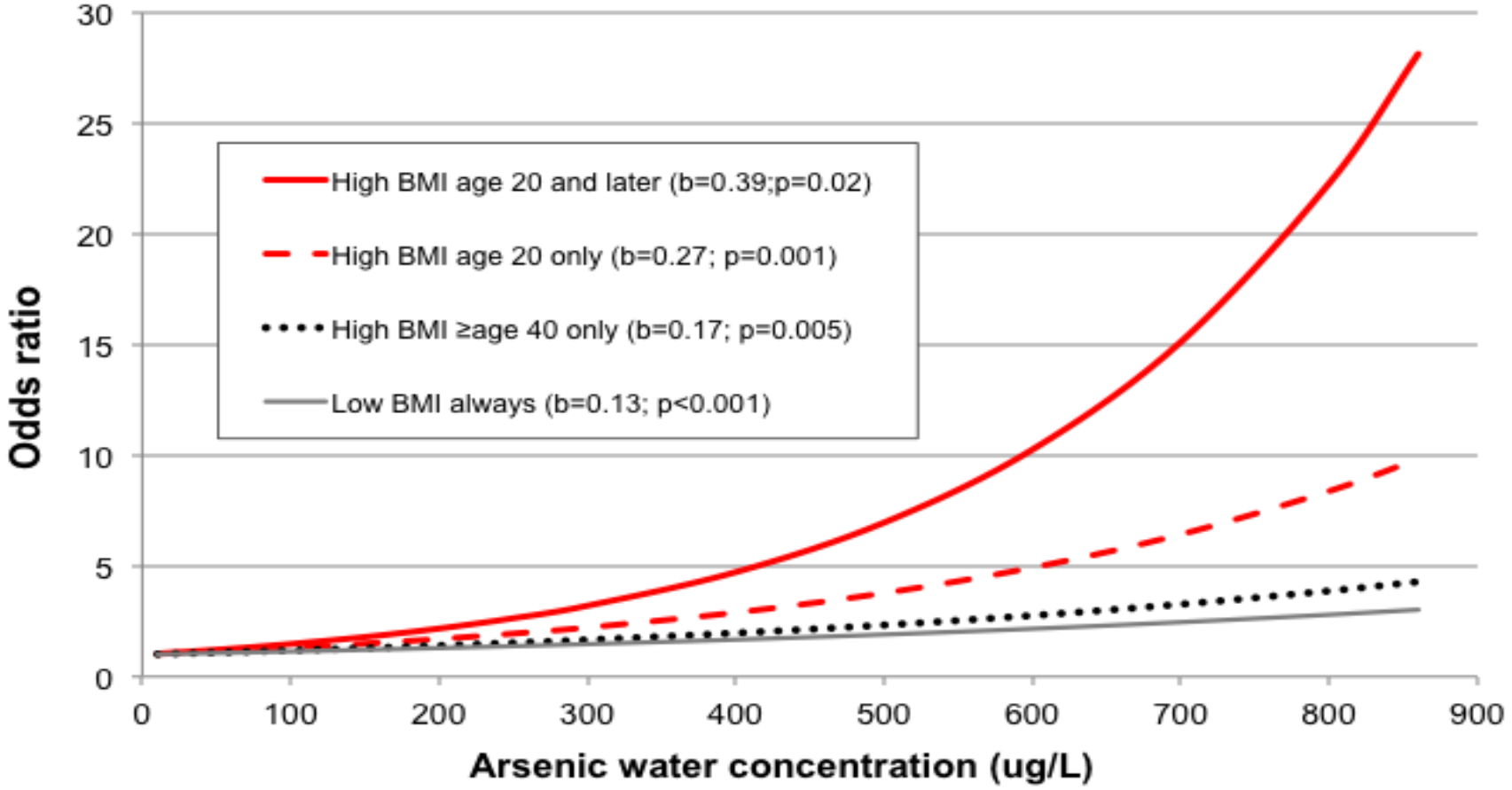


Steinmaus, C (2013). Adjusted for age, gender, and smoking

Bladder and Lung Risk, As & tobacco interaction_2007-2011

	Arsenic (µg/L)[a]	Bladder OR[b]	Lung OR[b]
Non smoker	<11	1.00	1.00
	11-91	2.66	0.68
	92-335	7.01	0.93
	>335	8.86	2.04
Smoker	<11	4.12	3.75
	11-91	4.72	4.39
	92-335	7.08	12.4
	>335	23.21	16.26

Odds ratios for arsenic and lung and bladder cancer combined: stratified by high BMI (>90th percentile)



Susceptibility factor: genetics

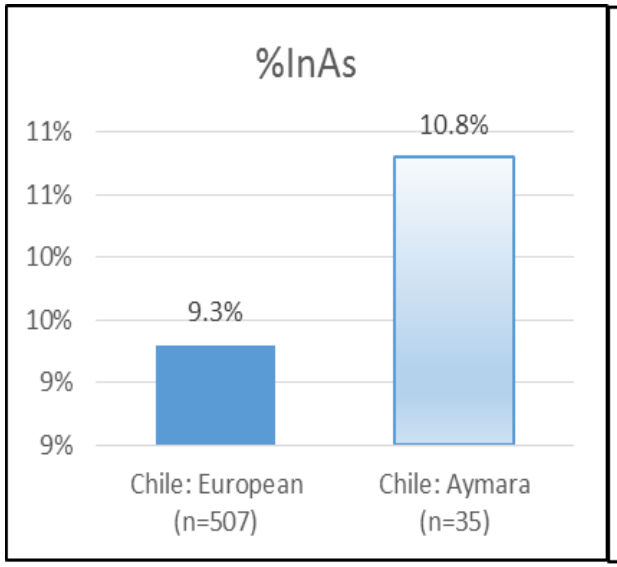
Urinary arsenic metabolite patterns and lung and bladder cancer odds ratios by AS3MT rs1046778 genotype

					Controls	Lung cancer		Bladder cancer	
Genotype	N	%InAs	%MMA	%DMA	N	N	OR (95% CI)	N	OR (95% CI)
TT	210	Ref	Ref	Ref	173	53	1.0 (ref)	71	1.0 (ref)
TC	206	1.1	-0.5	1.6*	200	51	0.8 (0.5-1.3)	60	0.7 (0.5-1.1)
CC	75	-2.2*	-2.1*	4.2*	82	14	0.6 (0.3-1.1)	15	0.5 (0.2-0.8)*

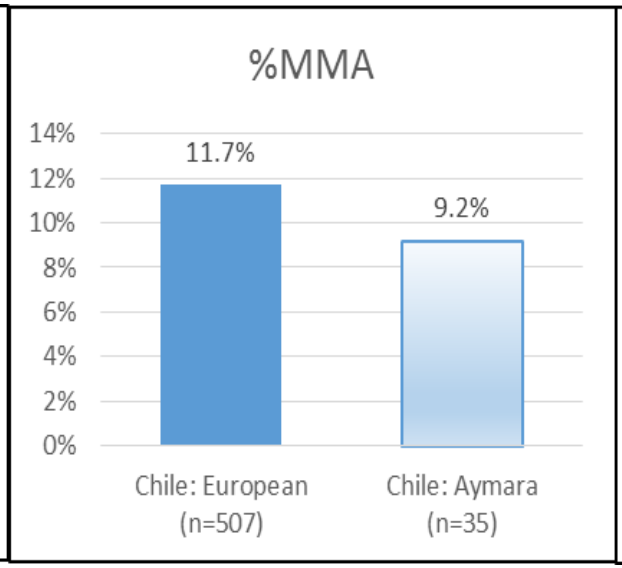
*p-value <0.05
Adjusted for age, sex, smoking
%InAs, %MMA, and %DMA values are the difference from the TT wildtype

- **AS3MT plays an important role in arsenic metabolism (see previous slide)**
- **Arsenic-exposed subjects with the CC allele have 40-50% lower cancer risks than arsenic-exposed subjects with the wildtype TT allele**

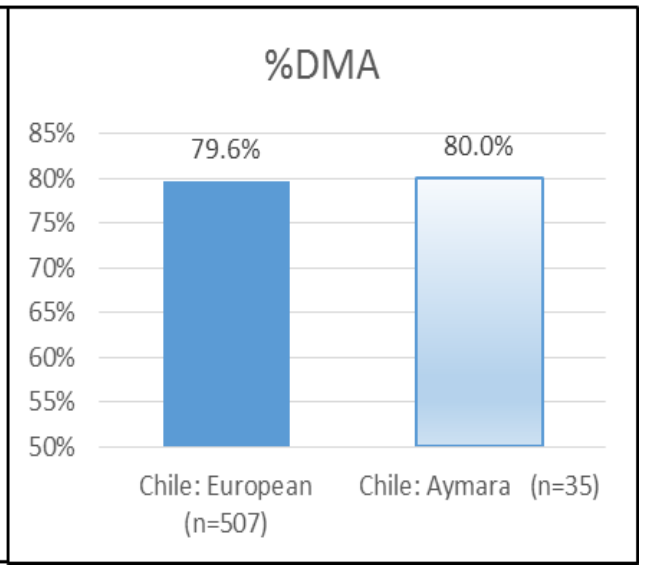
Arsenic metabolism by race/ethnicity



p=0.17



p=0.04



p=0.90

- Preliminary results from Regions I, II, 15
- Aymara produce less MMA (the primary toxic species) (p=0.04)
- Have centuries of exposure made them less susceptible (preliminary)? Further study is needed.

Conclusions

- Epidemiological research funded for decades: **unique exposure and ideal conditions**
- World problem that also **affected USA**: NIH funds
- Every design had a role in the play.
- The challenge is the intervention: the limit for epidemiology?

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Discussion

1. As exposure **at Antofagasta levels** is a risk factor for **various chronic diseases and cancers.**
2. **Suceptibility**: in utero, skin lesions, tobacco.
3. **Consistency:** through counties, genetic, environment.
4. Evidence suggests that government should:
   - Mantain As ≤10 ug/L (Lower?)
   - **Facilitate healthy lifestyle in the exposed population**
   - Keep the **doctors informed**
   - ¿Study Cost-benefit **lung cancer screening** low dose CT scan?

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