Alcohol and Mortality
A difficult problem for science

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International Conference
Demographic development of Russia in the global context
Higher School of Economics, 30 November – 1 December 2017

Outline

- Why is alcohol such a difficult scientific issue ?
- Russian mortality and alcohol – the most informative (and tragic) natural experiment
- Triangulating evidence
- A novel strategy for determining causality
- Alcohol and mortality in Russia today

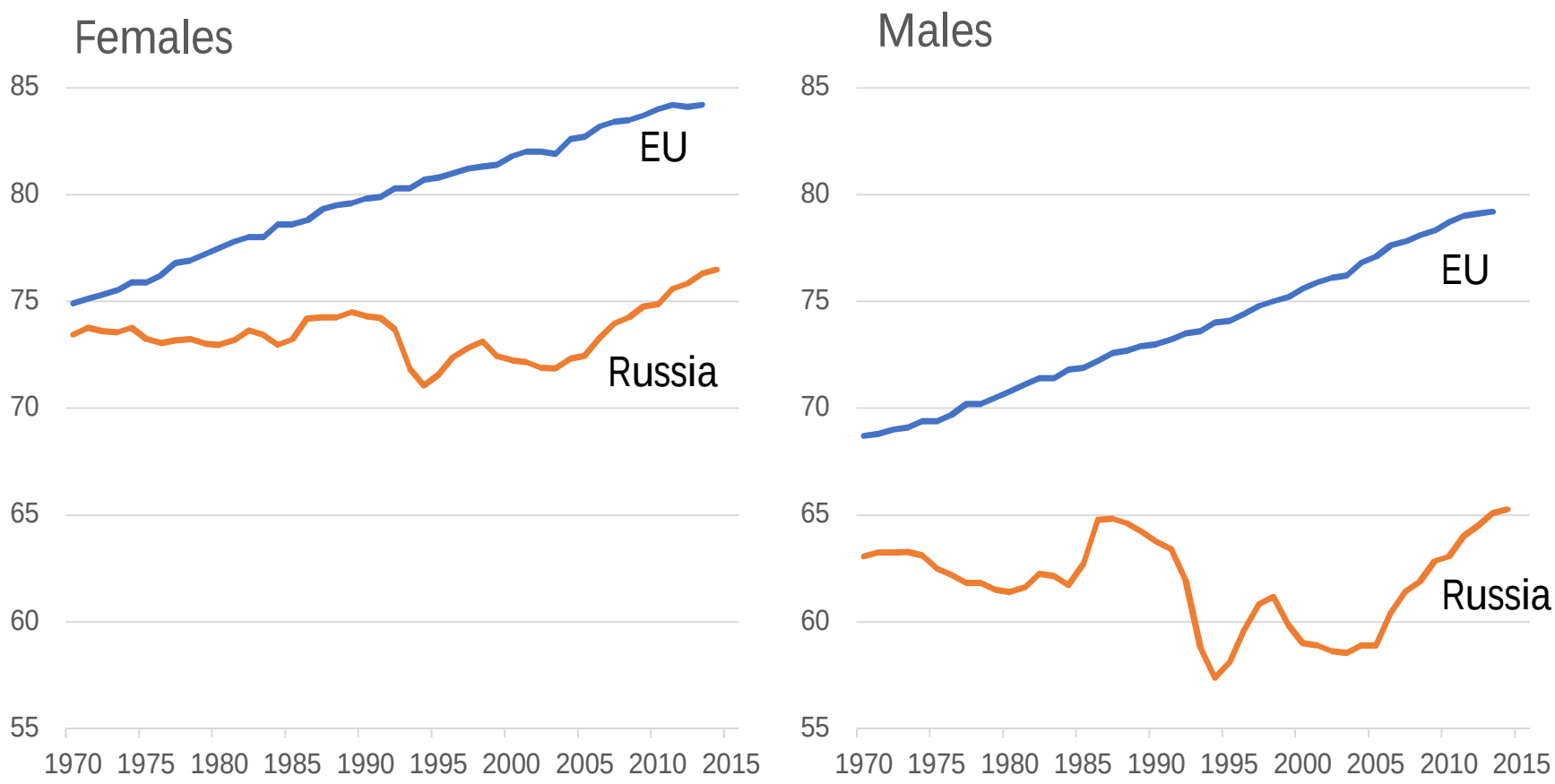
What are the problems (1) ?

- Measurement of exposure is challenging
  - Individual level (volume and pattern)
    - Accuracy of recall
    - Bias (social stigma)
  - Population level (per capita consumption only)
    - Unrecorded consumption
    - Cannot estimate by age, sex etc.
- Inference about associations
  - Problems of exposure measurement *as above*
  - Reverse causality (illness > decline consumption)
  - Selection bias (heavy drinkers tend not to participate)
  - Confounding

What are the problems (2) ?

- Estimating population impact or burden of alcohol-induced disease
  - Uncertainty about consumption estimates
  - Uncertainty about strength of associations with disease
  - Uncertainty about direction of associations (how far is alcohol ever “good” for your health ?)

Life expectancy at birth in Russia and the EU (pre-2005) 1970-2014



Source : WHO HFA and Human Mortality Database

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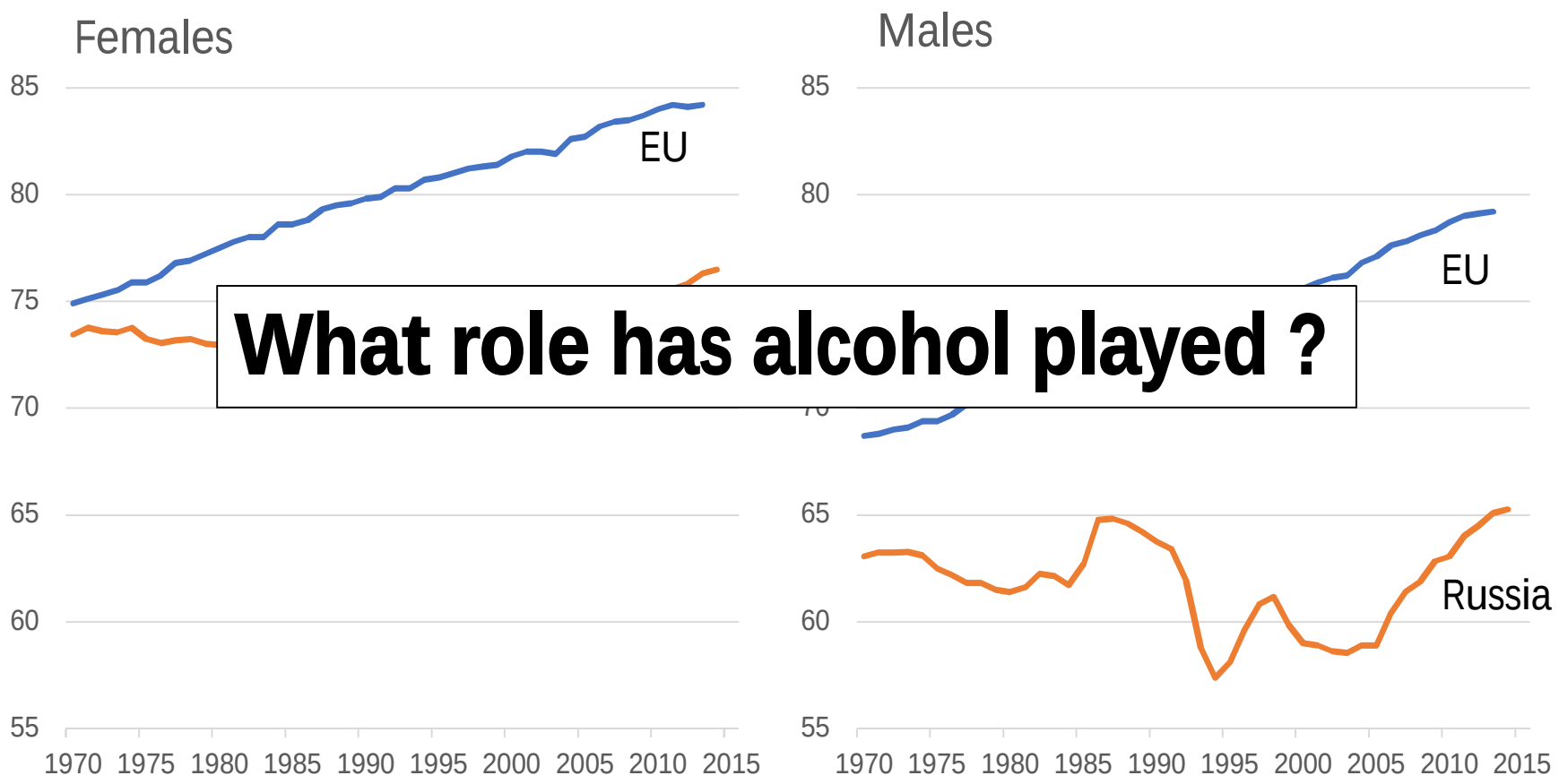


What role has alcohol played ?

Source : WHO HFA and Human Mortality Database

Measuring alcohol consumption

Two basic approaches

- Individual level
  - Self-reports of alcohol consumption from surveys
    - Frequency consumption (total and by type) X volume ethanol “usually” consumed per occasion = total volume ethanol in defined period

- Population level (per capita consumption)

Recorded consumption from excise data

+

Unrecorded consumption based on *expert* estimation

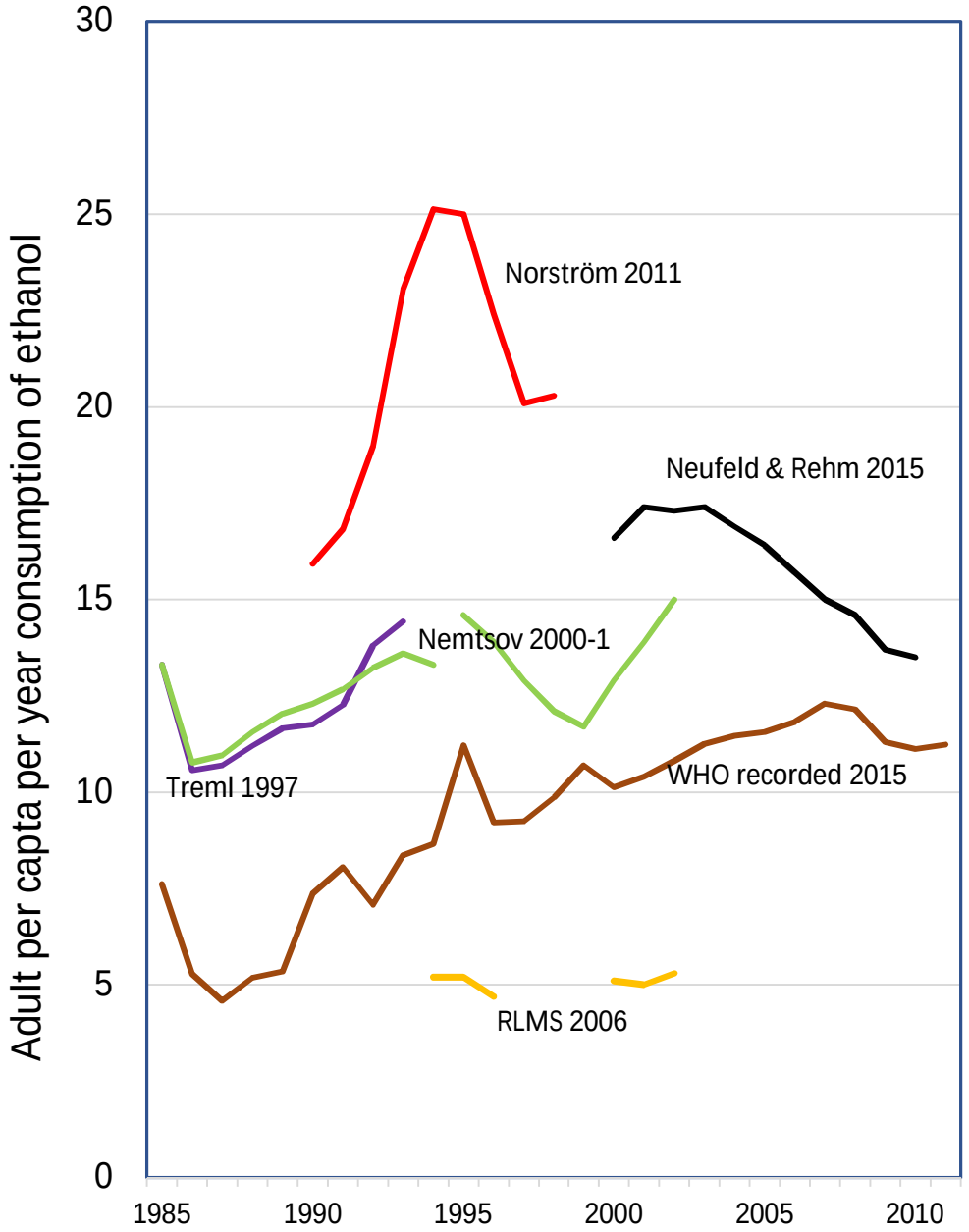
Unrecorded consumption

- In Europe WHO (Rehm et al) estimated unrecorded to be between 3% and 59% of total consumption. Particularly high for FSU and parts of CEE.
- In Russia varies over time between 25% - 40% of total consumption
  - home-made or informally produced alcohol (legal or illegal)
  - illegal “night-shift” alcohol
  - alcohol containing medicinal tinctures etc

How much do Russian’s drink ?

Various estimates

- Official recorded consumption data (WHO)
- Treml and Nemtsov and others have used a variety of indirect approaches including using information on acute alcohol-related health effects
- Back-casting based of injury mortality used by Norström
- RLMS survey data



Estimates of per total capita ethanol consumption in adults aged 15+, Russia, 1985-2011

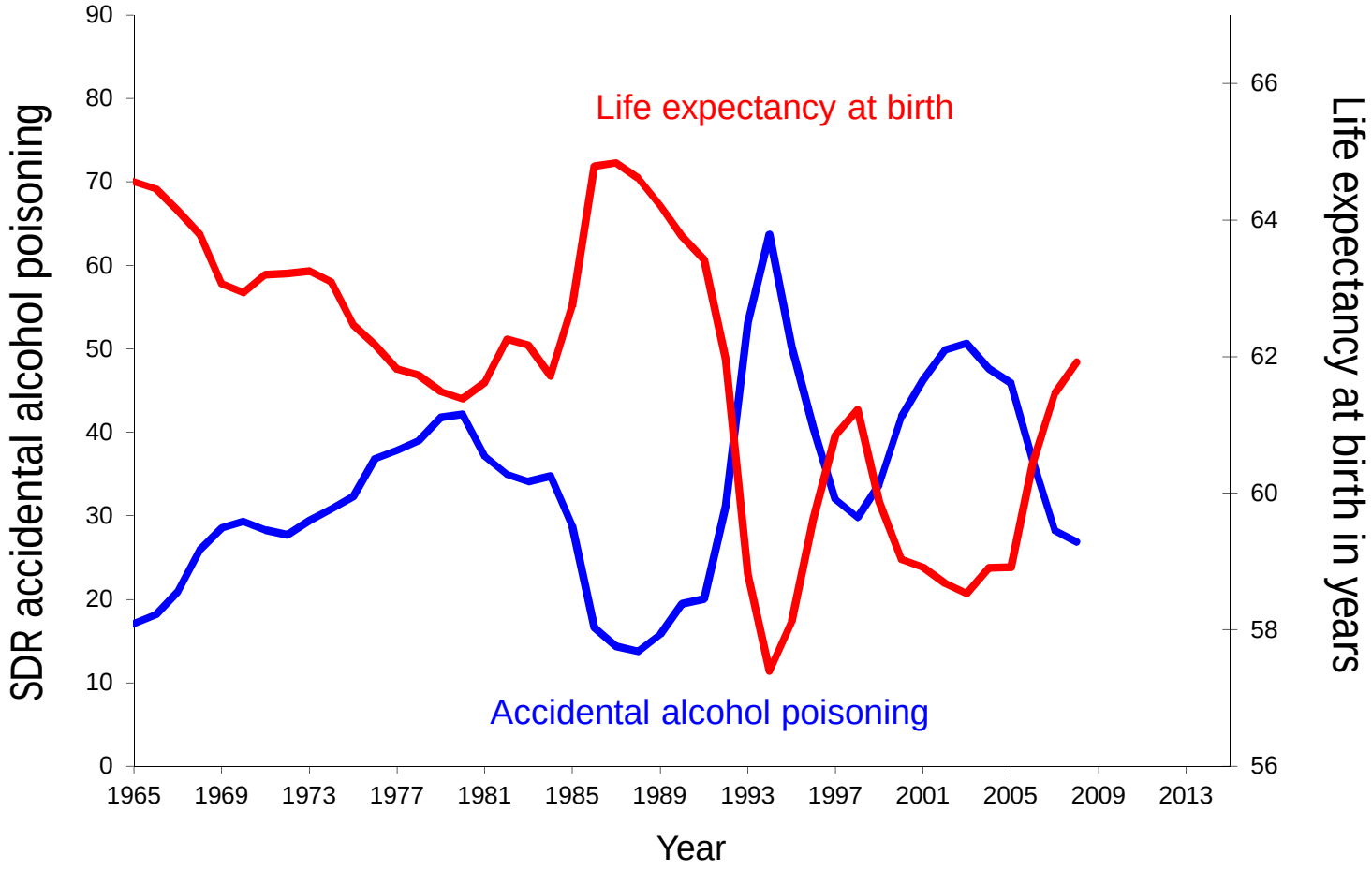
Source : Leon and Cook, unpublished

Alternative approaches to assessing alcohol effects on mortality

The beautiful informative butterfly

Using rates of mortality from acute alcohol poisoning as a marker of prevalence of heavy drinking in the population

Alcohol as a primary driver of fluctuations 1965-2008



Understanding fluctuations in accidental alcohol poisoning

- 1984-85 ⇩ Gorbachev anti-alcohol campaign
- 1986-88 Loss of momentum then end of campaign
- 1990-94 ⇧ Collapse USSR
  - relaxation price and other controls
  - flooding of market with cheap ethanol
- 1994-98 ⇩ Gradual return of regulation and control of alcohol market
- 1998-03 ⇧ Disturbance to market and availability from 1998 crisis
- 2005- ⇩ Increased regulation and control

Variation in cause-specific effects is informative

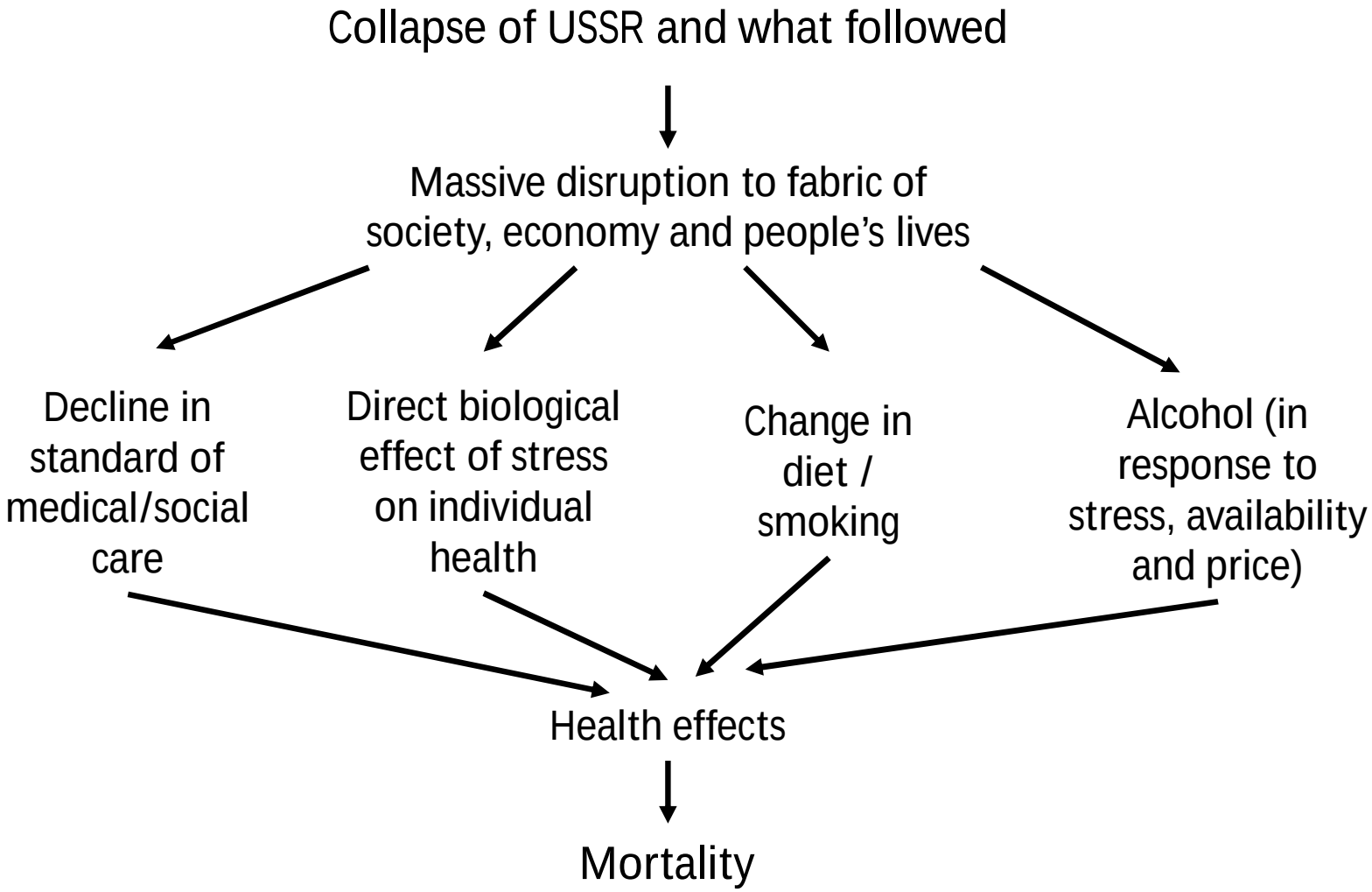
Cause-specific effects of anti-alcohol campaign mirror those around time of USSR collapse

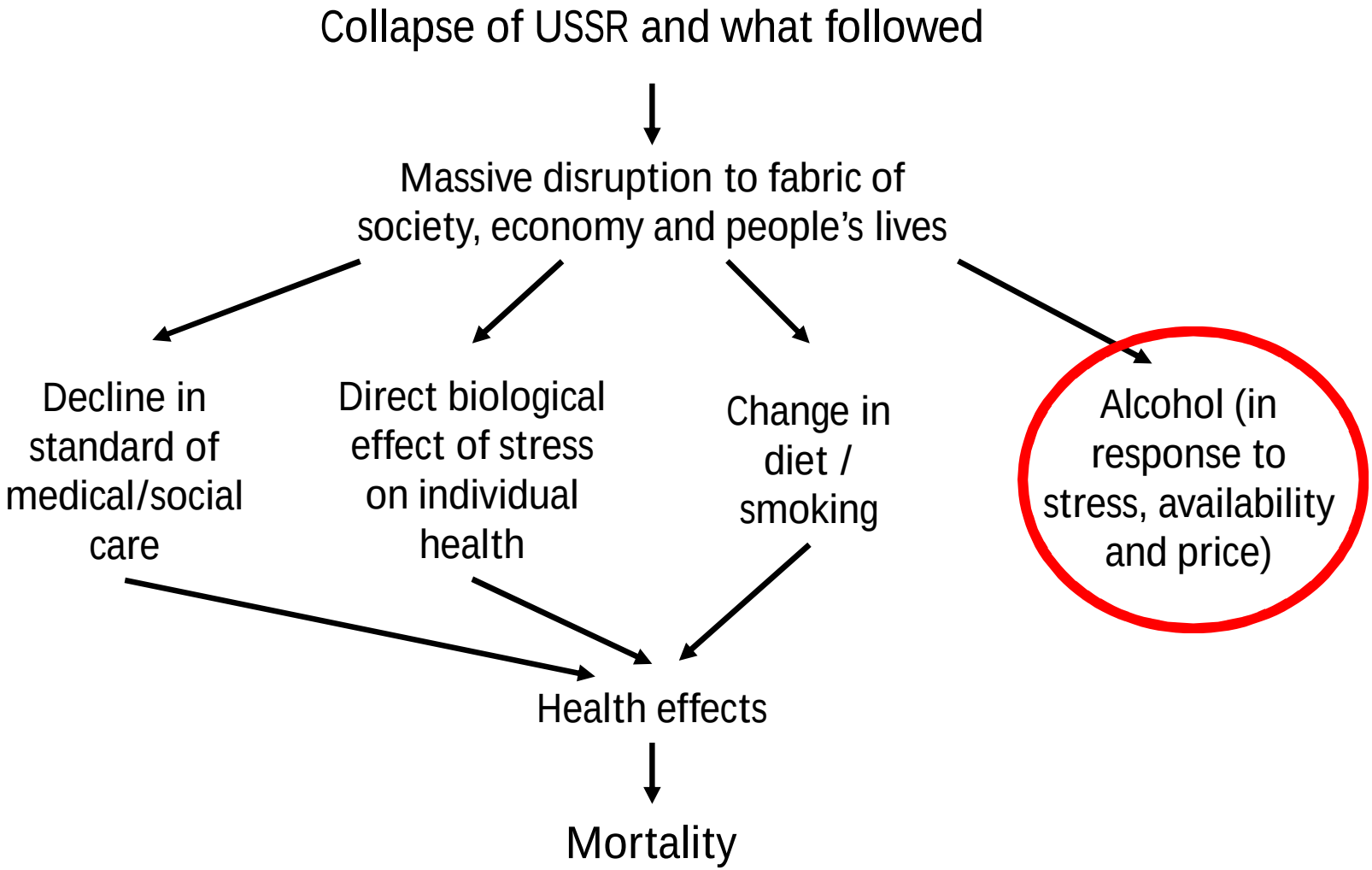
Cause of death	Rate in 1987 (per 10^6)		Ratio rate 1987/ rate 1984		Ratio rate 1994/ rate 1987	
	Male	Female	Male	Female	Male	Female
All causes	6326	2132	0·61	0·71	2·43	1·96
Infectious and parasitic diseases	258	38	0·64	0·78	2·40	2·24
All neoplasms	1041	768	0·88	0·92	1·05	1·10
Circulatory disease	1922	490	0·74	0·71	2·20	2·18
Pneumonia	64	20	0·28	0·50	7·50	4·35
Other respiratory disease	144	51	0·44	0·68	1·97	1·39
Alcohol-related disease	373	77	0·37	0·37	5·03	5·86
Accidents and violence*	2108	435	0·54	0·57	2·76	2·54

*Excluding accidental poisoning by alcohol. Mortality at age 40-44 years

Source : Leon DA et al *Lancet 1997;* ***350: 383-8***

Is alcohol really causal or simply a marker of social stress ?


Collapse of USSR and what followed
Massive disruption to fabric of society, economy and people's lives
Decline in standard of medical/social care
Direct biological effect of stress on individual health
Change in diet / smoking
Alcohol (in response to stress, availability and price)
Health effects
Mortality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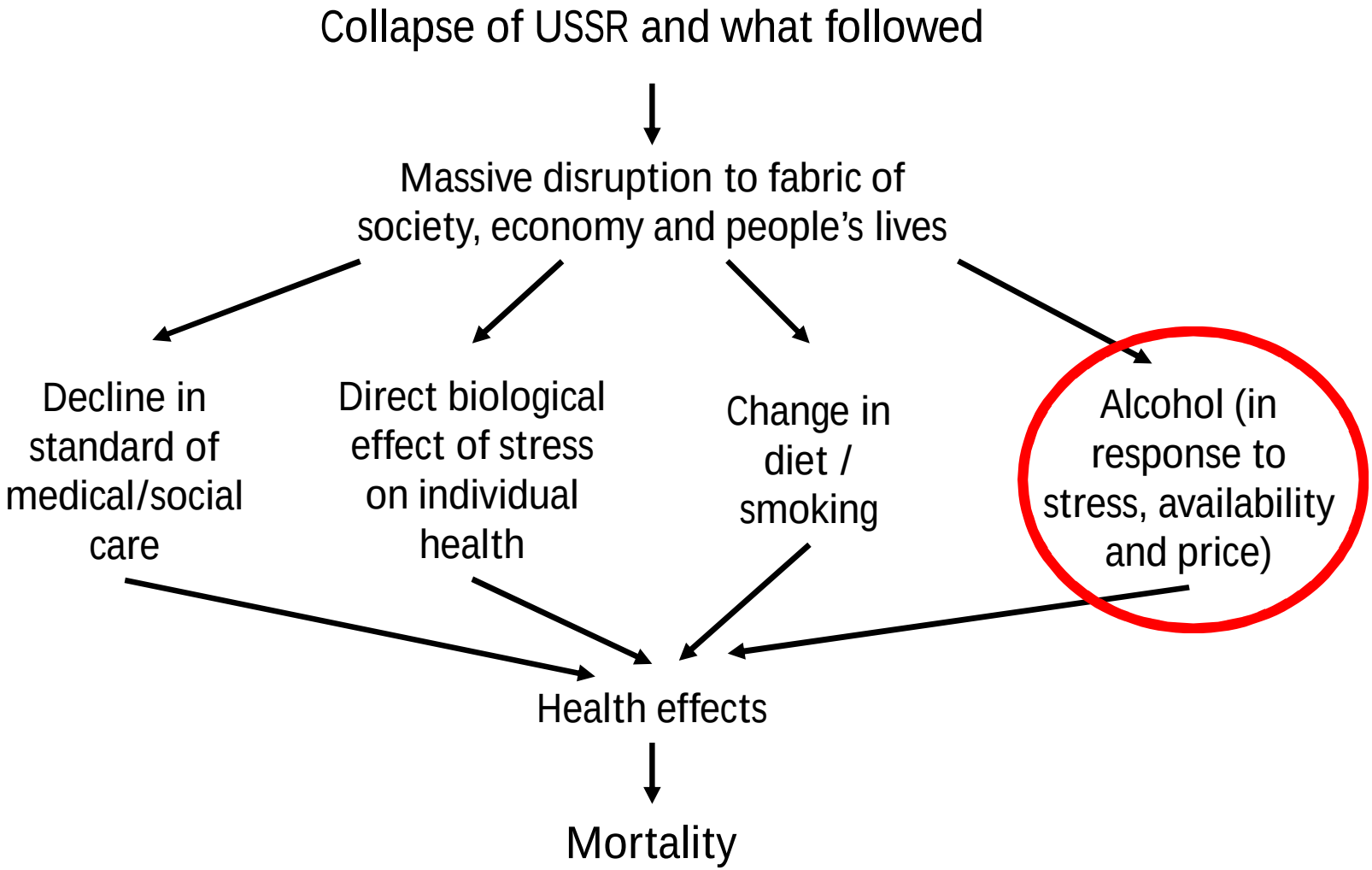
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Individual level evidence

Izhevsk Family Study 2003-5

(elaboration of initial studies by Shkolnikov & Cherykakov)

Aims

To investigate the causes of mortality among working age men (25-54 years) in a typical Russian city (Izhevsk) and in particular the role of alcohol as a factor in driving mortality

Funded by the Wellcome Trust

Design

- Case (dead men) – Control (live men)
- Proxy informants (living in same household)
- Interviewer administered questionnaire on alcohol drinking including indirect markers of heavy consumption in the previous year

Hazardous patterns of alcohol consumption

Prevalence of components of hazardous drinking in live men (25-54 years) in Izhevsk

Over past year	2003-5
Spirits daily or almost every day	3%
Hangover 2+ / week	4%
Excessively drunk* 2+ / week	4%
Non-beverage alcohol	6%
Zapoi	10%

* Specified in questionnaire as “Перепивает”

Alcohol and mortality in Izhevsk

Strong association of alcohol with mortality by various causes
Men aged 25-54 years, Izhevsk, 2003 - 5

Cause of death	Number of deaths	Hazardous drinking (proxy report)	
		OR*	(95% CI)
Circulatory disease	486	**4.1**	(3.2,5.3)
Acute alcohol poisoning	78	**18.9**	(10.7,33.3)
All causes	1446	**5.5**	(4.5,6.6)

* OR adjusted for age, smoking and education

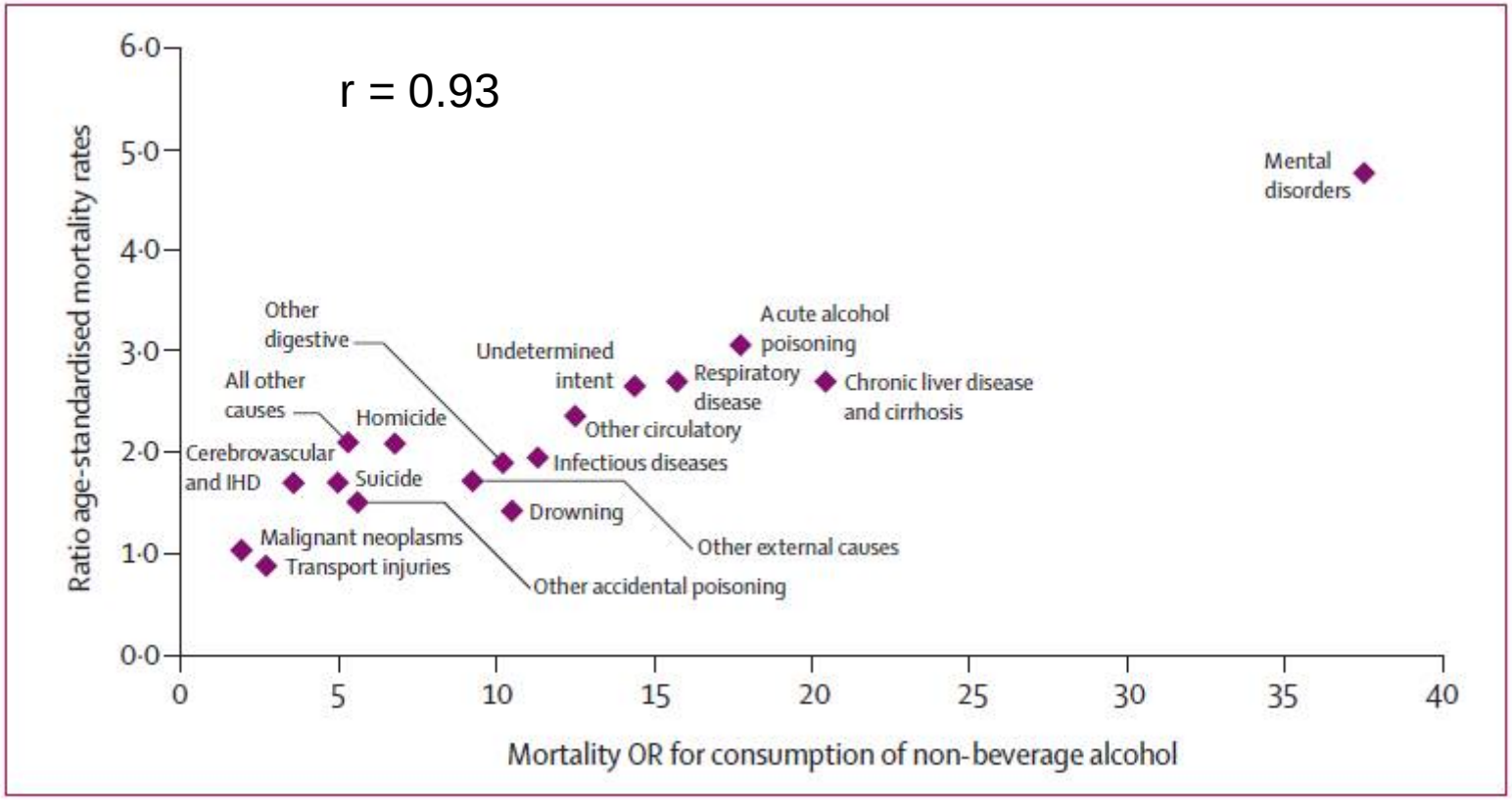
Source : Leon, Shkolnikov, McKee, Kiryanov, Andreev, IJE, 2010

What is relevance to understanding national mortality fluctuations ?

Triangulation

Inference from combining individual-level data with national mortality rates

Size of cause-specific mortality effects for hazardous drinking in Izhevsk (2003-5) match those for increase in Russian mortality 1991-94



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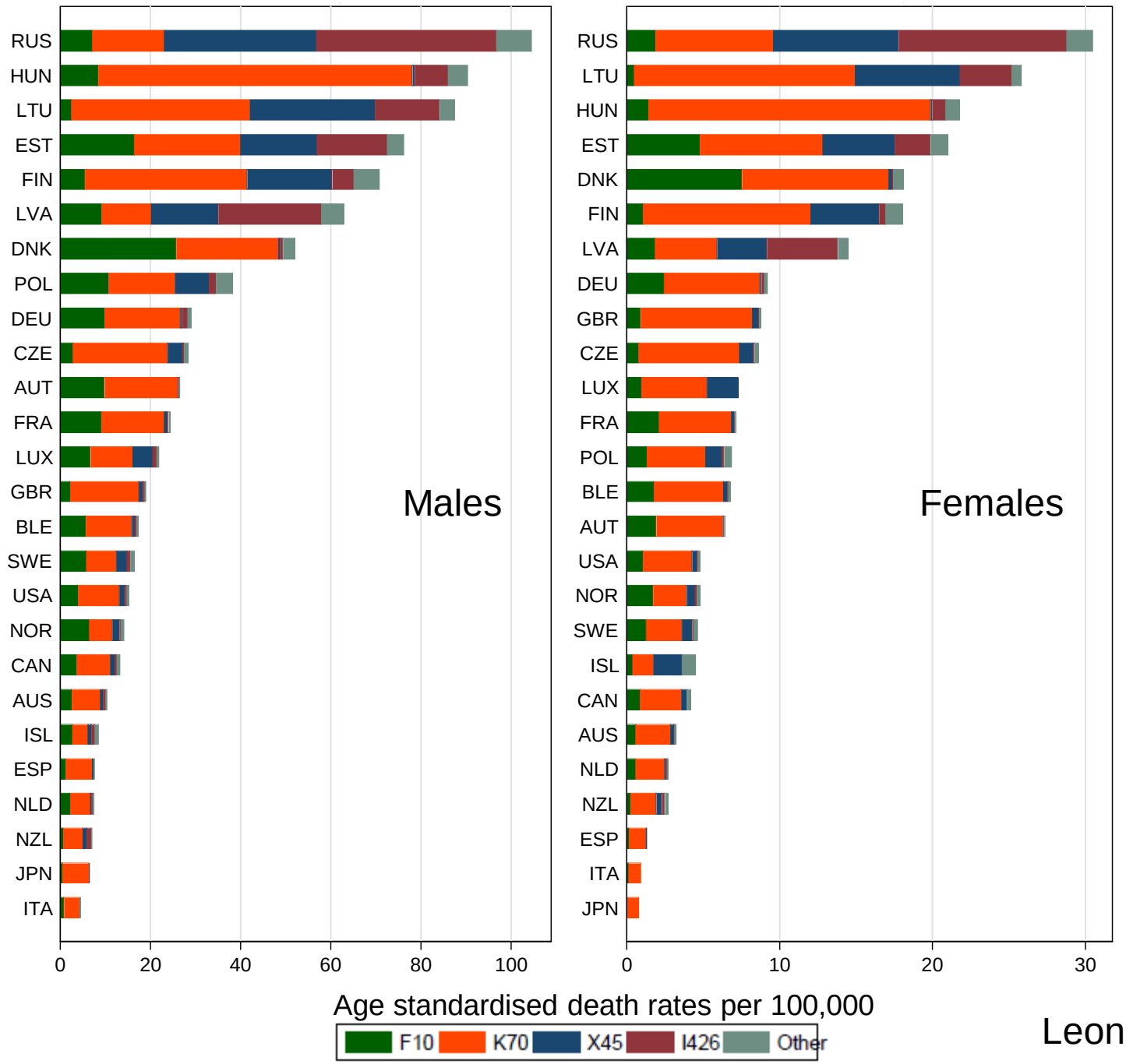
Conclusion

- This triangulation provides strong evidence that fluctuations in Russian mortality are indeed driven through alcohol per se
- Alcohol-related mortality in Russia is not simply an indirect (non-causal) marker of other factors or stress

Comparing impact of alcohol on mortality with other countries

Main ICD10 codes mentioning alcohol
(directly alcohol-related)

F10	Mental and behavioural disorders due to alcohol
I42.6	Alcoholic cardiomyopathy
K70	Alcoholic liver cirrhosis
X45	Accidental poisoning due to alcohol



Total directly alcohol-related death rates aged 15+ by sex and country 2007-9

Leon and Pechholodova

Total alcohol attributable mortality

Strategies for estimating attributable mortality

- Bottom-up : global
  - Estimate exposure profile and estimate cause-specific (causal) dose-response effects from systematic reviews
  - Generate total attributable fraction
- Top-down : study-specific
  - Estimate “unconfounded” effect measure for all cause mortality in relation to measures of exposure
  - Generate study-specific attributable fraction

Estimates for Russia

- Bottom-up : global (Rehm et al, 2007)
  - 29% M, 5% F aged 20-64 years
  - *33% M, 6% F aged 20-64 years corrected*
- Bottom-up : global (Shield & Rehm, 2015)
  - 29% M, **31% F** aged 0-64 years for 2012
- Top-down : study-specific (Leon et al, 2007)
  - 43% M aged 25-54 years for 2002-2005
- Top-down : study-specific (Zaridze et al, 2009)
  - 59% M, 33% F aged 15-54 years

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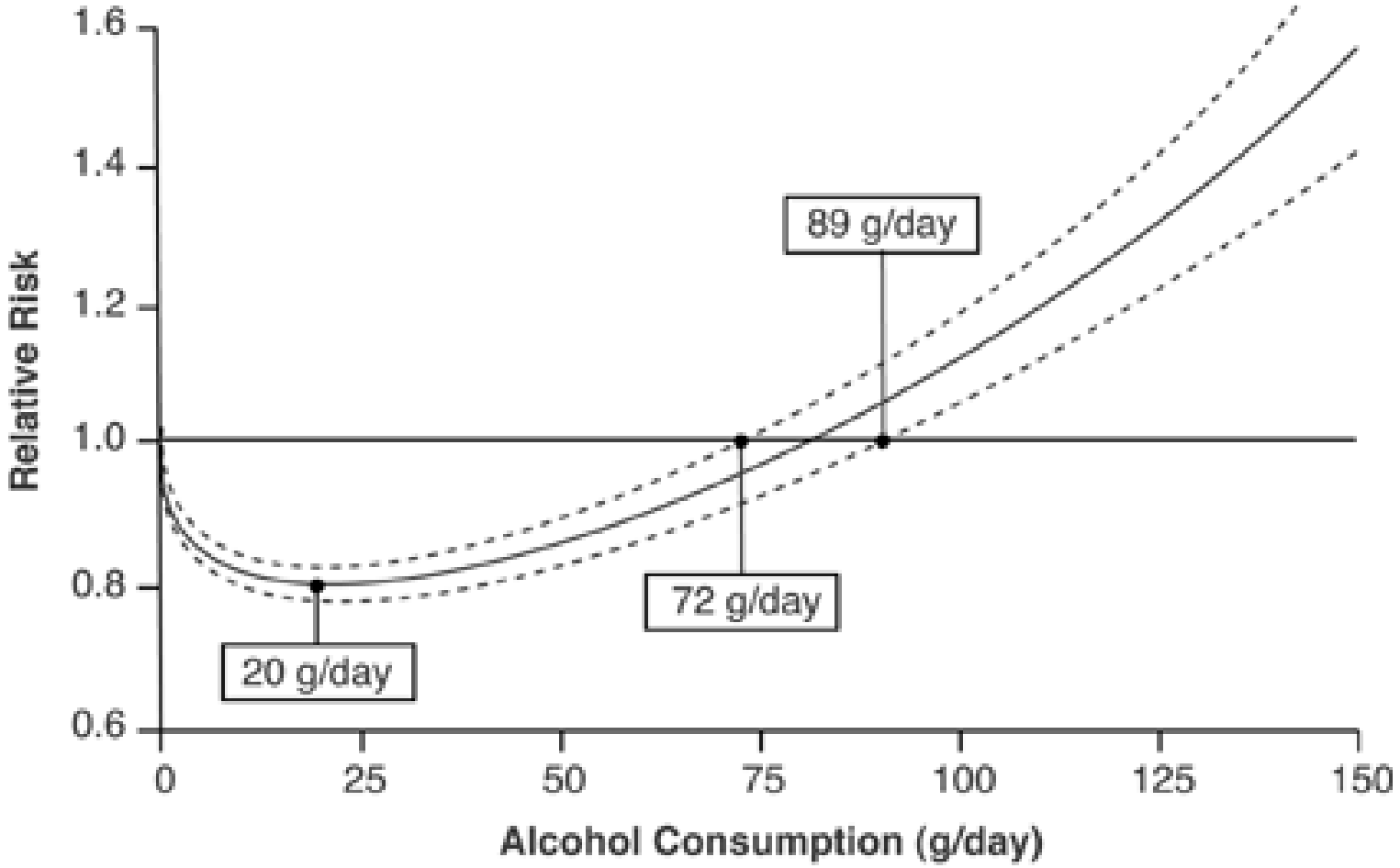
Bottom-up estimates dependent upon correct estimates of dose-response as well as consumption

Moderate drinking and ischaemic heart disease

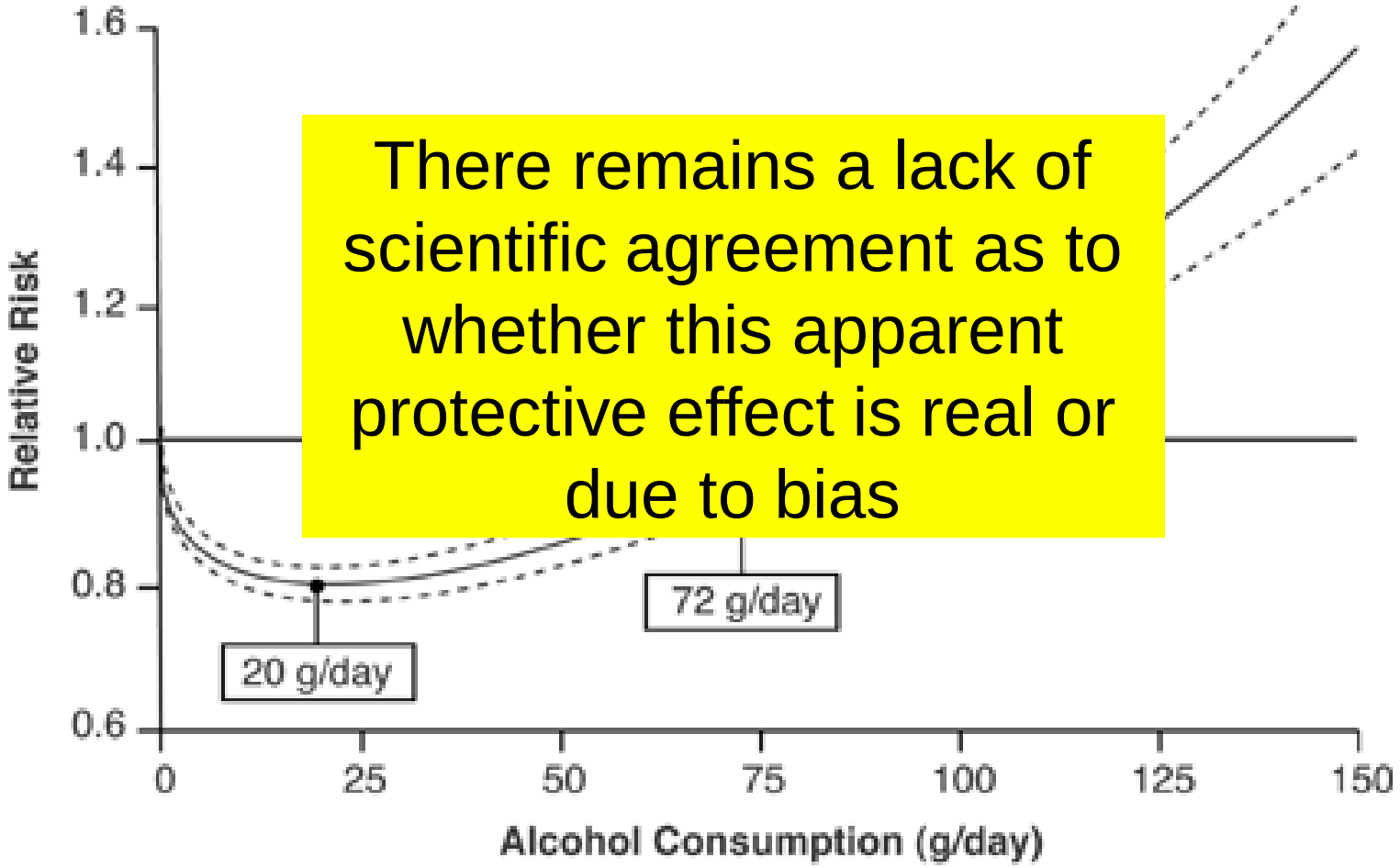
Is it cardio-protective ?

J-shaped curve of coronary heart disease risk with alcohol



Source : Corrao et al. Addiction 2000;95:1505-23.

J-shaped curve of coronary heart disease risk with alcohol

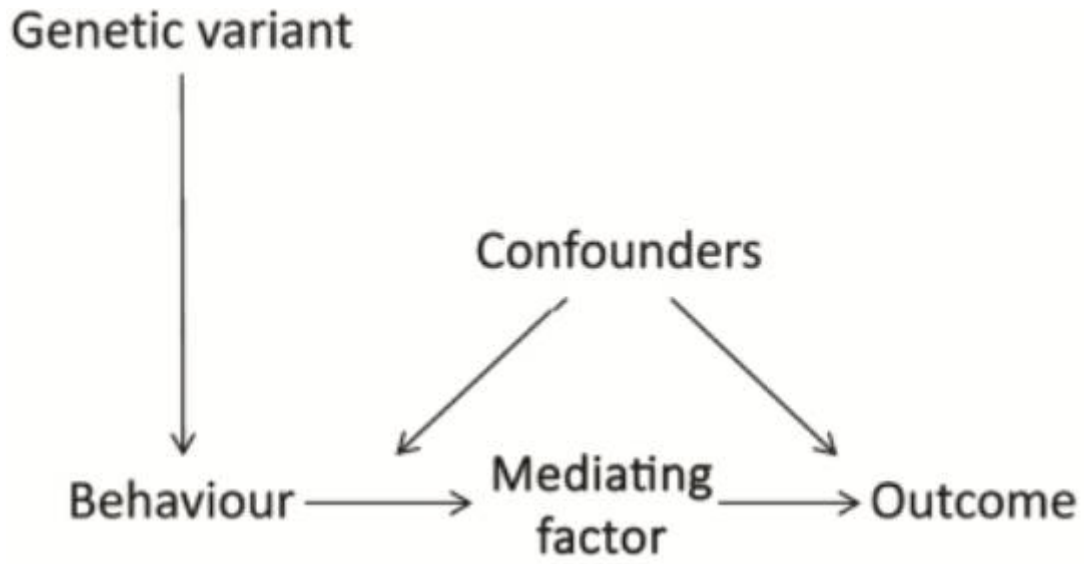


There remains a lack of scientific agreement as to whether this apparent protective effect is real or due to bias

Source : Corrao et al. Addiction 2000;95:1505-23.

How genes can help provide evidence of causality

Basic principles of mendelian randomization



Source : Katikireddi SV, Green M, Taylor AE, Smith GD, Munafò MR. Assessing causal relationships using genetic proxies for exposures: An introduction to Mendelian randomisation. Addiction 2017

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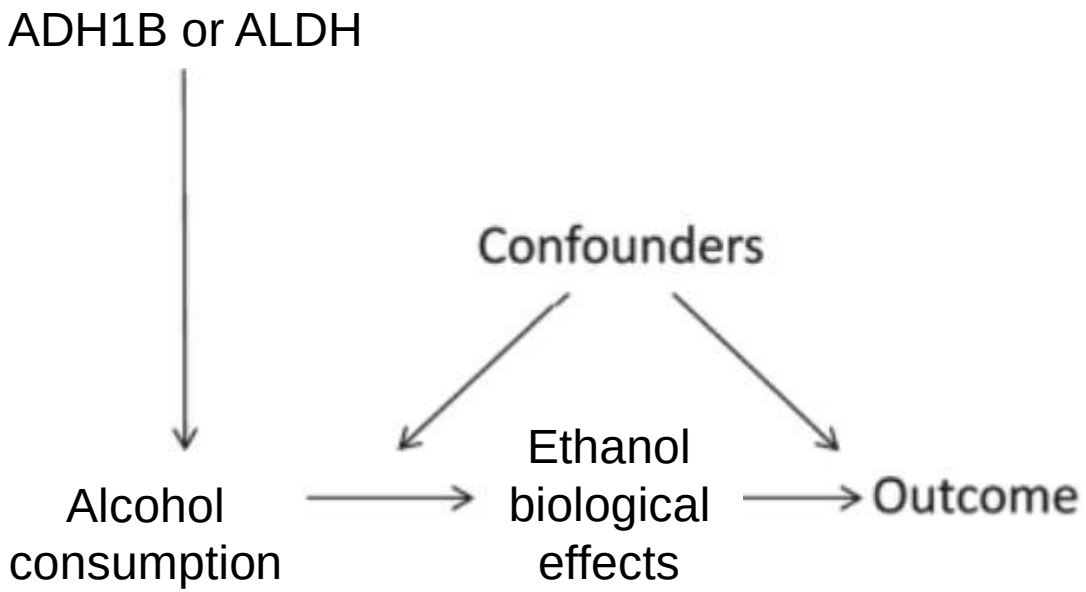

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BMJ 2014;349:g4164 doi: 10.1136/bmj.g4164 (Published 10 July 2014)

RESEARCH

Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data

Michael V Holmes *assistant professor (joint first author)*[1 2 3], Caroline E Dale *research fellow (joint*

Using gene ADH1B that codes for enzyme involved in alcohol metabolism

Pooled estimates of association between genetic variant ADH1B rs1229984 (A-allele carriers v non-carriers) and measures of alcohol consumption

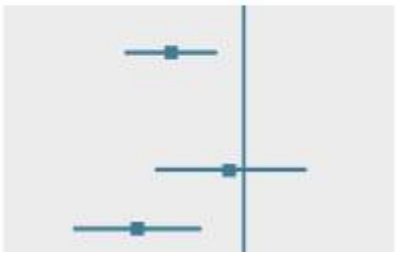
Alcohol consumption measure	Effect estimate (95% CI)	P value
Log transformed data*	**% difference**	
Intake volume (units/week†)	−17.22 (−18.86 to −15.55)	5.5×10^{-76}
γ-glutamyltransferase level (U/L)	−1.84 (−3.40 to −0.26)	0.028
Categorical data	**Odds ratio**	
Top tertile of alcohol intake	0.70 (0.68 to 0.73)	9.8×10^{-67}
Binge drinker‡	0.78 (0.73 to 0.84)	1.4×10^{-12}
Alcohol abstainer‡	1.27 (1.21 to 1.34)	2.6×10^{-19}

A-Allele carriers drink less

Source : Holmes MV et al. BMJ 2014; 349: g4164

Meta-analysis pooled estimates of the association between ADH1B rs1229984 (A-allele carriers v non-carriers) and coronary heart disease

Category for coronary heart disease outcome	No of studies	No of cases/ individuals	Odds ratio (95% CI)	Odds ratio (95% CI)	P value
Overall (all individuals)	46	20 259/168 731		0.90 (0.84 to 0.96)	0.001
Any or no alcohol intake					
Non-drinkers	31	5883/43 029		0.98 (0.88 to 1.10)	0.095*
Drinkers only	40	10 130/107 478		0.86 (0.78 to 0.94)	



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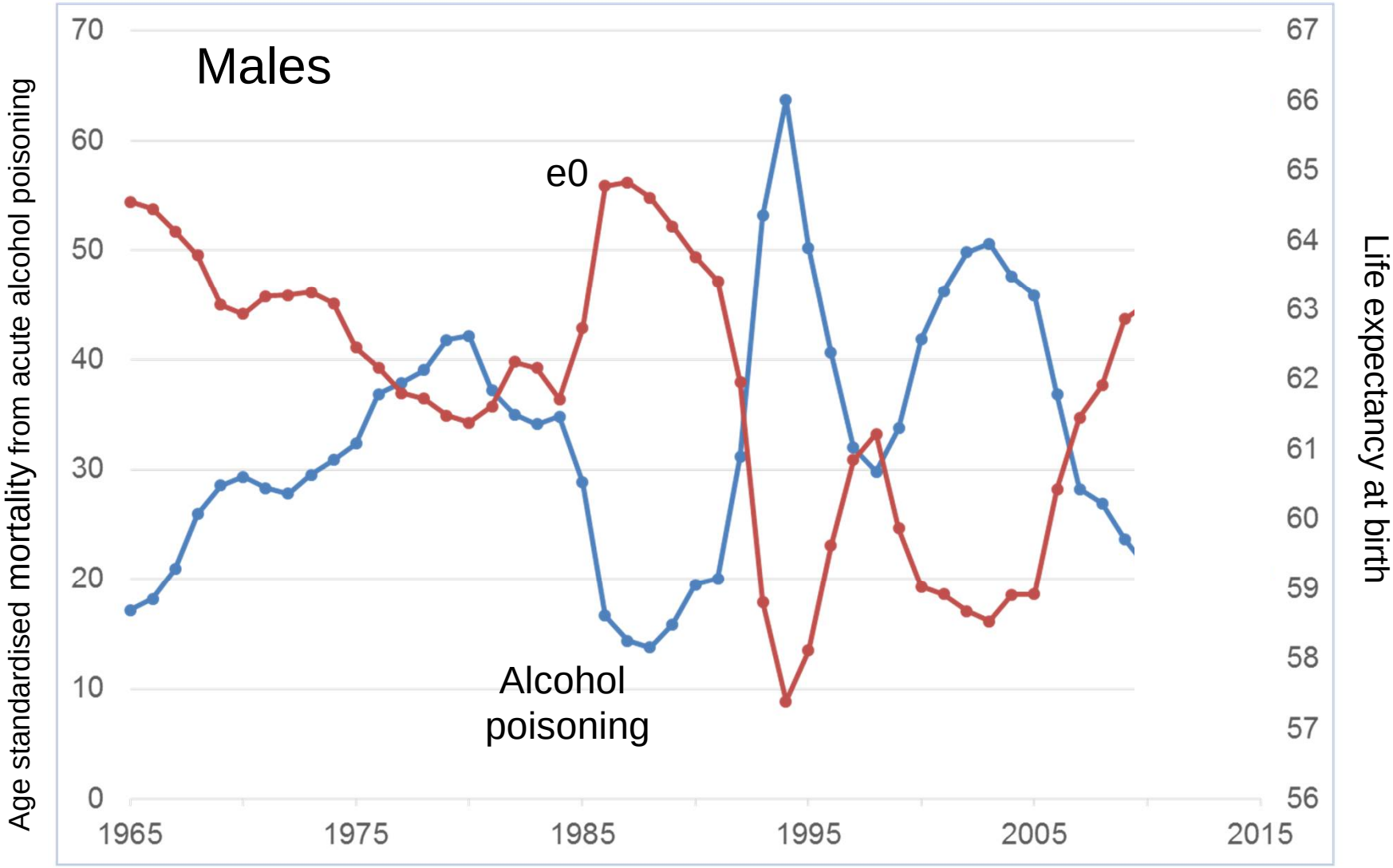
Conclusion

- Knowledge of functional genetic variation can be used to test “causal” hypotheses
- Approach known as “Mendelian Randomization”
- Adds to accumulating evidence that cardio-protective effects of alcohol do not exist or are over-stated

Russia today

Evidence that alcohol determines fluctuations in e0



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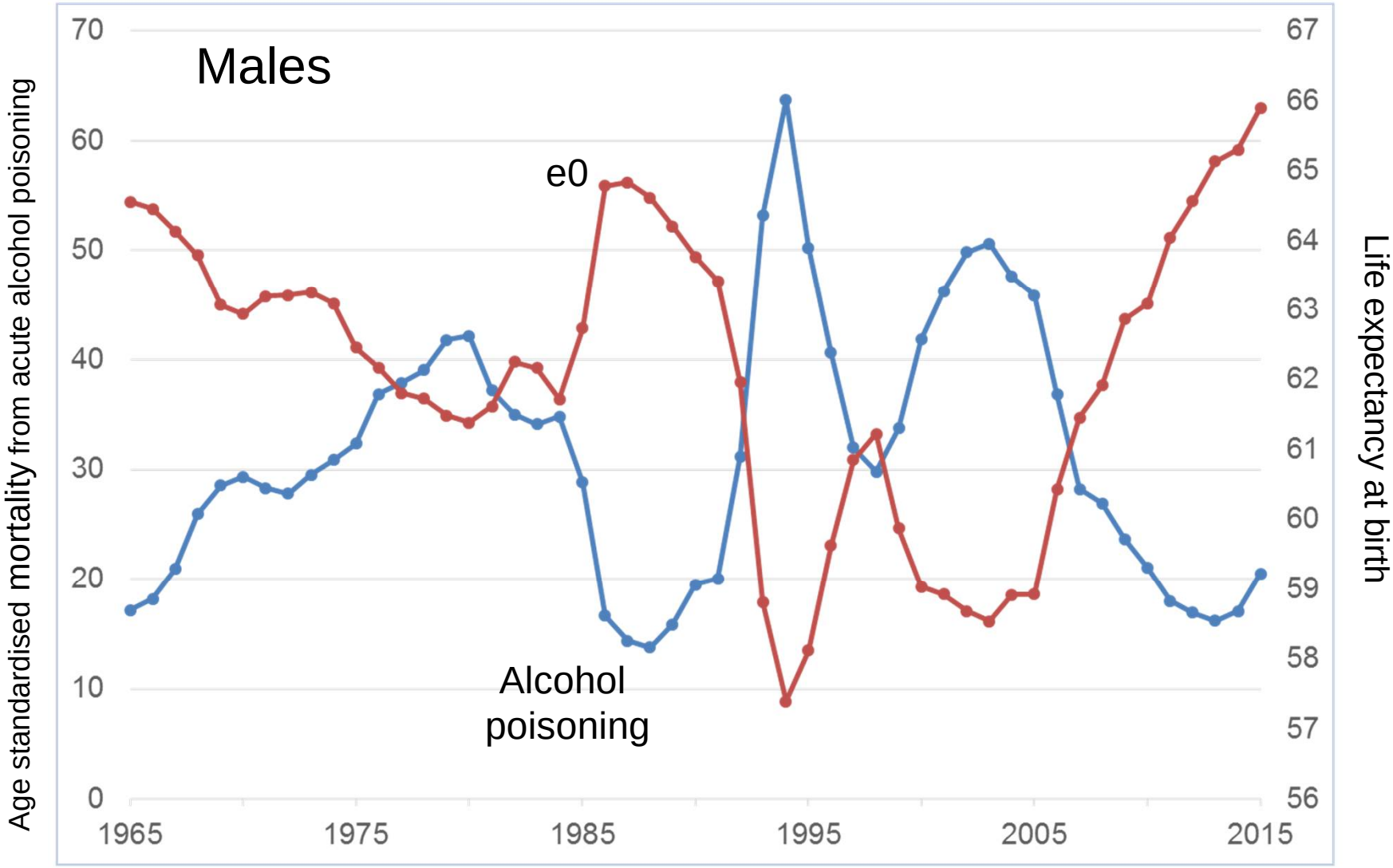

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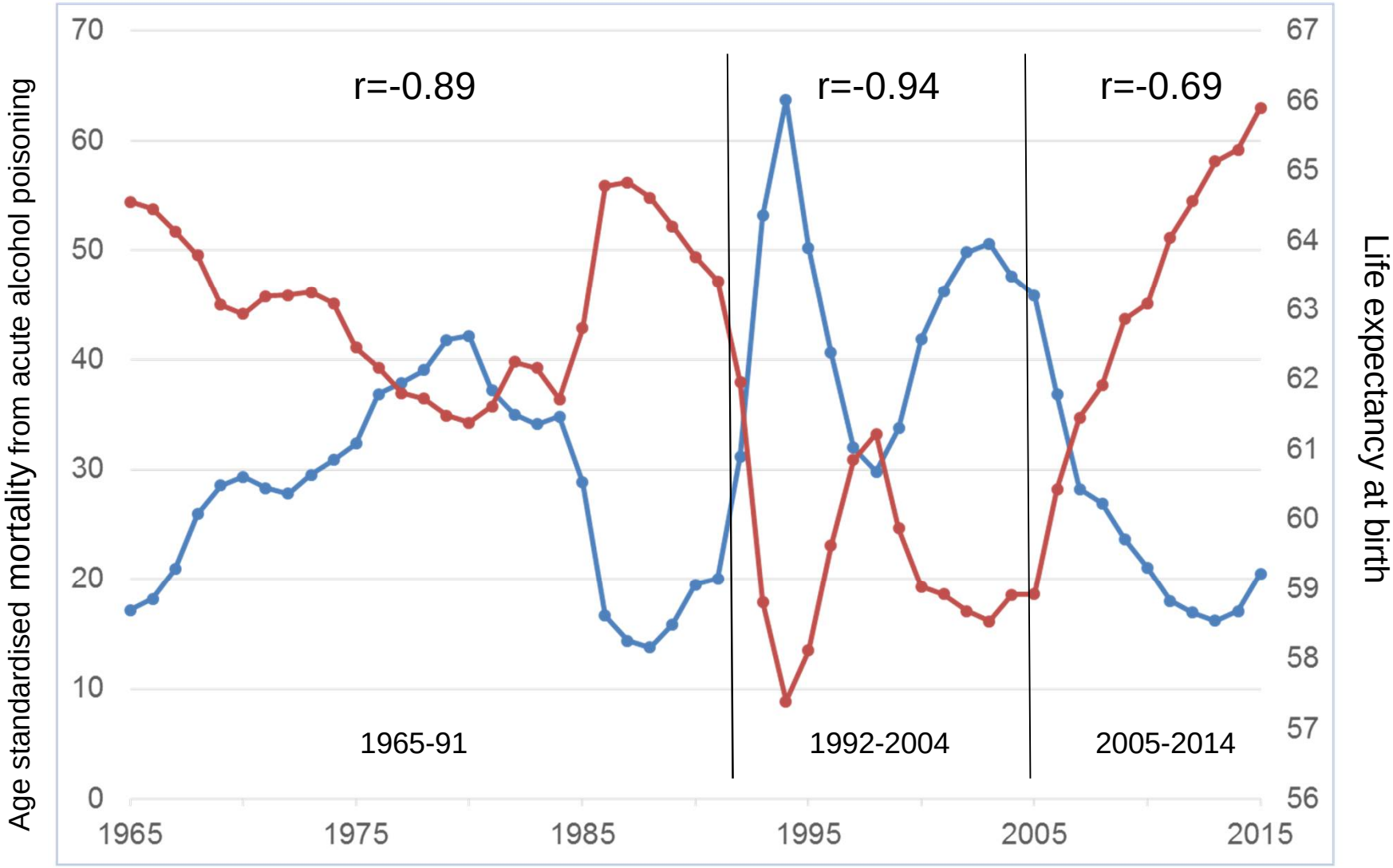

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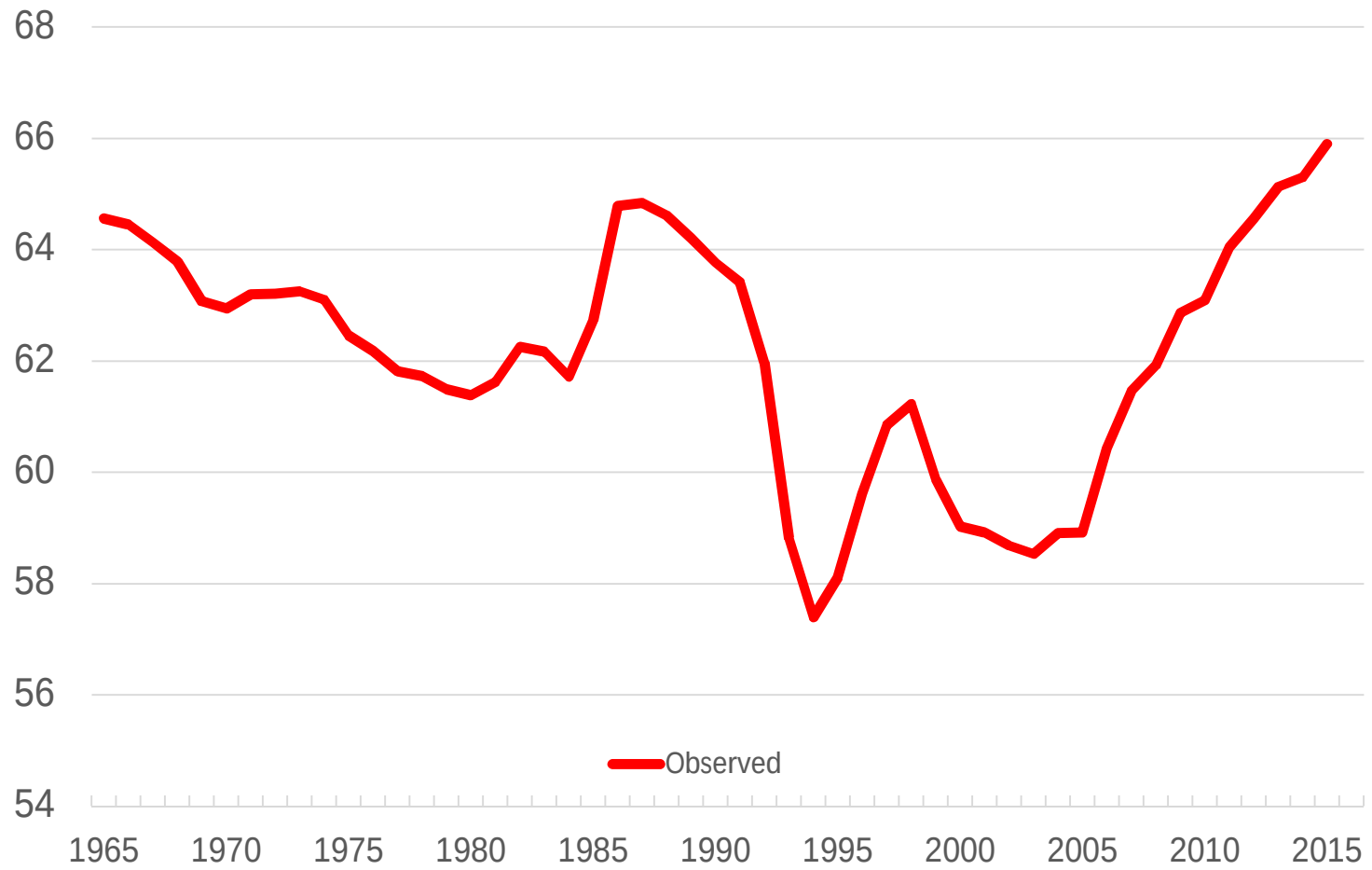
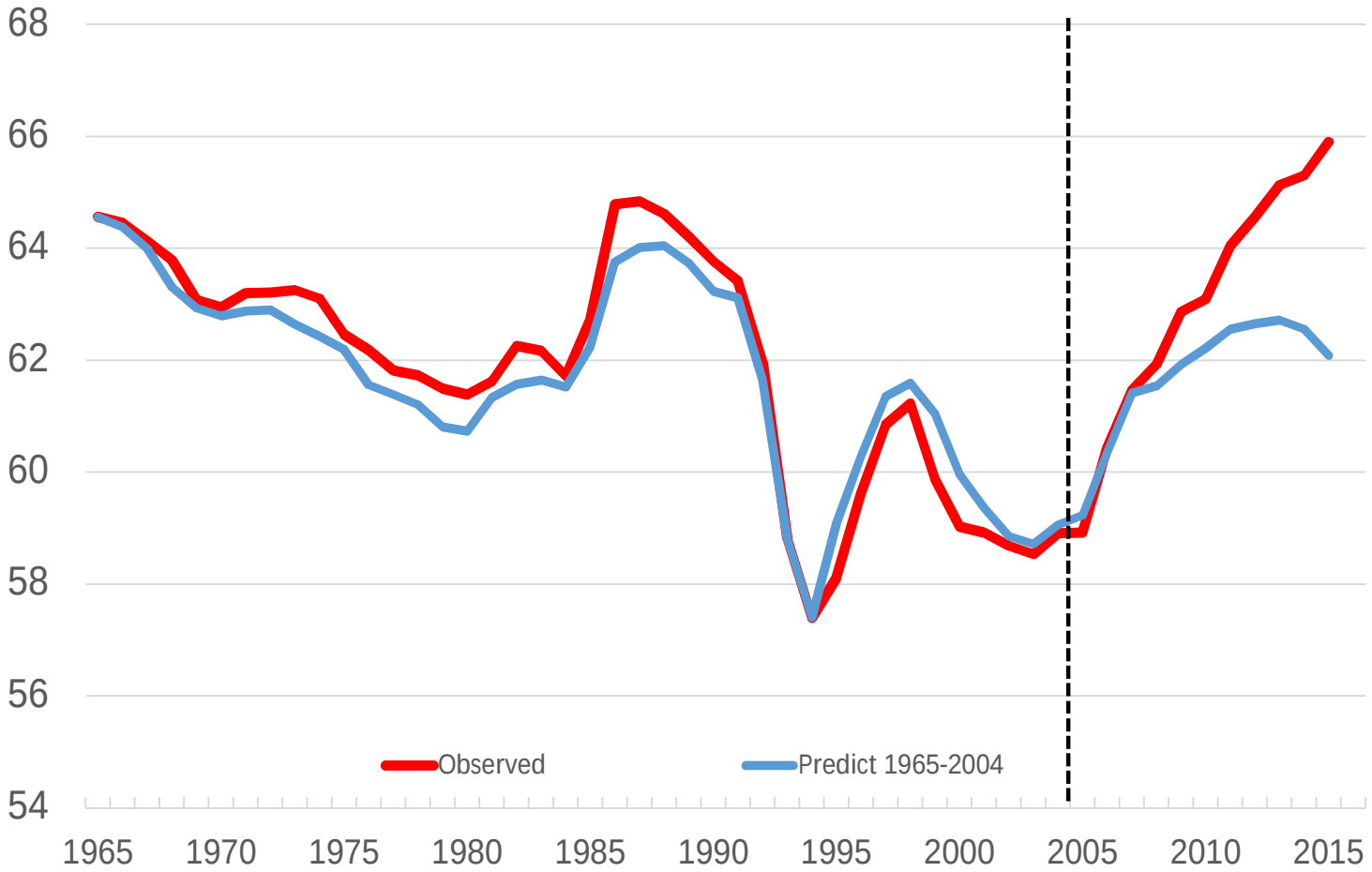
Predicting life expectancy regression against acute alcohol poisoning

Observed male Russian life expectancy based on acute alcohol mortality



Predicted male Russian life expectancy based on acute alcohol mortality



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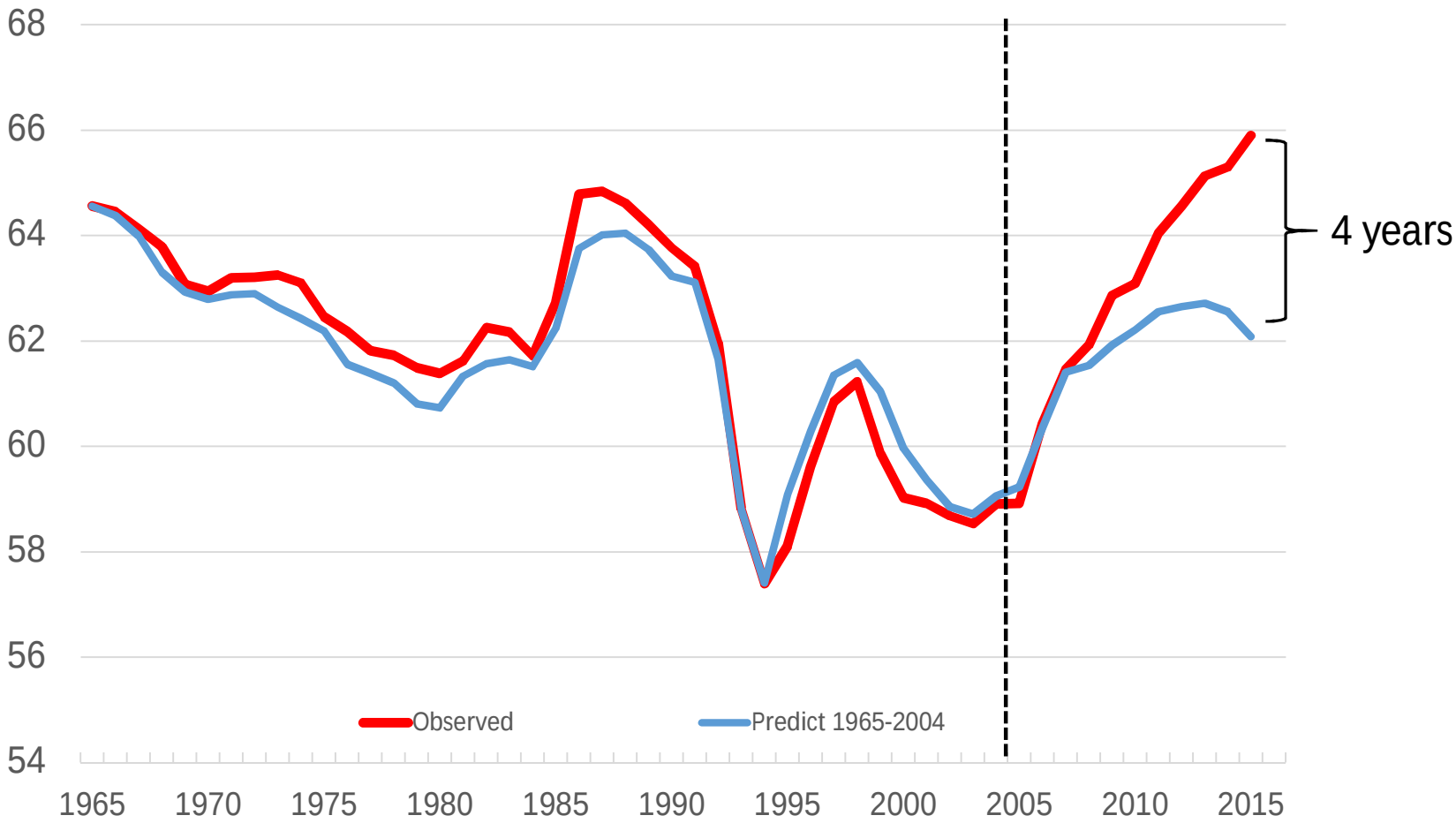

Recent improvements in life expectancy today only partly driven by alcohol

Thank you

Predicted male Russian life expectancy based on acute alcohol mortality