Trends over time in underlying causes of death in the D:A:D Study from 1999 to 2011

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for the D:A:D Study Group

Background

- In settings with access to ART, dramatic reductions in AIDS-related mortality have led to increased survival
- HIV positive individuals may therefore experience a wider range of complications (AIDS vs. non-AIDS) than in previous years
- It is increasingly important to accurately classify both AIDS-related and non-AIDS related causes of death, and to monitor trends over time

Methods – Study participants

- Participants included from the Data collection on Adverse events of anti-HIV Drugs (D:A:D) Study: a collaboration of 11 cohorts from Europe, USA and Australia
- Prospective follow-up for individuals began from 1999 onwards
- All clinical outcomes, including deaths, are reported in real time, and are centrally validated and categorised
- From 2004 onwards, deaths were reported using the CoDe form

Methods – Participant follow-up

- Individuals were followed from D:A:D entry to the first of:
  - Death
  - Six months after last clinic visit
  - 1st February 2011
- The primary (underlying) cause of death was considered
- Causes of death were grouped for analysis:
  A. AIDS-related
  B. Cardiovascular disease (CVD) related
  C. Liver disease related [a]
  D. Non-AIDS Malignancies (NADM) related [b]
  E. Other/Unknown

[a] Deaths related to chronic viral hepatitis / liver failure not related to viral hepatitis

[b] non-AIDS, non-HCV, non-HBV related malignancies

Methods – Statistical analysis

- Relative rates of the association of calendar time with all cause mortality and with each specific cause of death were calculated
- Relative rates were then calculated using Poisson regression, adjusting for factors that have potentially changed over time
- Factors included:
  - Fixed: Age, gender, ethnicity, mode of HIV acquisition
  - Time-updated: HBV status, HCV status, smoking status, diabetes, hypertension, HIV RNA, BMI, CD4 count

Baseline characteristics 1

		HIV positive individuals (%)
Number		49734 (100%)
Gender	*Male*	36701 (74%)
Age (years)	*Median (IQR)*	38 (32, 45)
Mode of HIV acquisition	*IDU*	7631 (15%)
	Heterosexual	16133 (32%)
	Other	4069 (8%)
	MSM	21901 (44%)
HCV positive[a]	*Yes*	6449 (13%)
HBV positive[b]	*Yes*	5425 (11%)
Smoking status	*Current*	17109 (34)
	Former	8521 (17)
	Never	12294 (25)
	Unknown	11810 (24)

[a] HCV antibody positive;

[b] HBsAg positive, HBeAg positive or HBV DNA positive/anti-Hbe positive

Baseline characteristics 2

		HIV positive individuals (%)
Number		49734 (100%)
BMI (kg/m^2)	*Median (IQR)*	23.0 (21.0, 25.3)
Hypertension[c]	*Yes*	7861 (16%)
Diabetes[d]	*Yes*	1260 (3%)
Total cholesterol (mmol/l)	*Median (IQR)*	4.7 (4.0, 5.7)
Previous AIDS diagnosis	*Yes*	10463 (21%)
CD4 (cells/mm^3)	*Median (IQR)*	400 (242, 590)
Exposure to ART (years)	*n; Median (IQR)*	30400 (61%); 2.9 (1.2, 4.8)
Exposure to PI (years)	*n; Median (IQR)*	20362 (41%); 2.2 (1.0, 3.2)
Exposure to NNRTI (years)	*n; Median (IQR)*	14447 (29%); 1.0 (0.4, 1.8)

[c] *Systolic BP >140 mmHg; Diastolic BP>90 Hg; or receiving anti-hypertensives*

[d] *Centrally validated endpoint: see www.cphiv.dk*

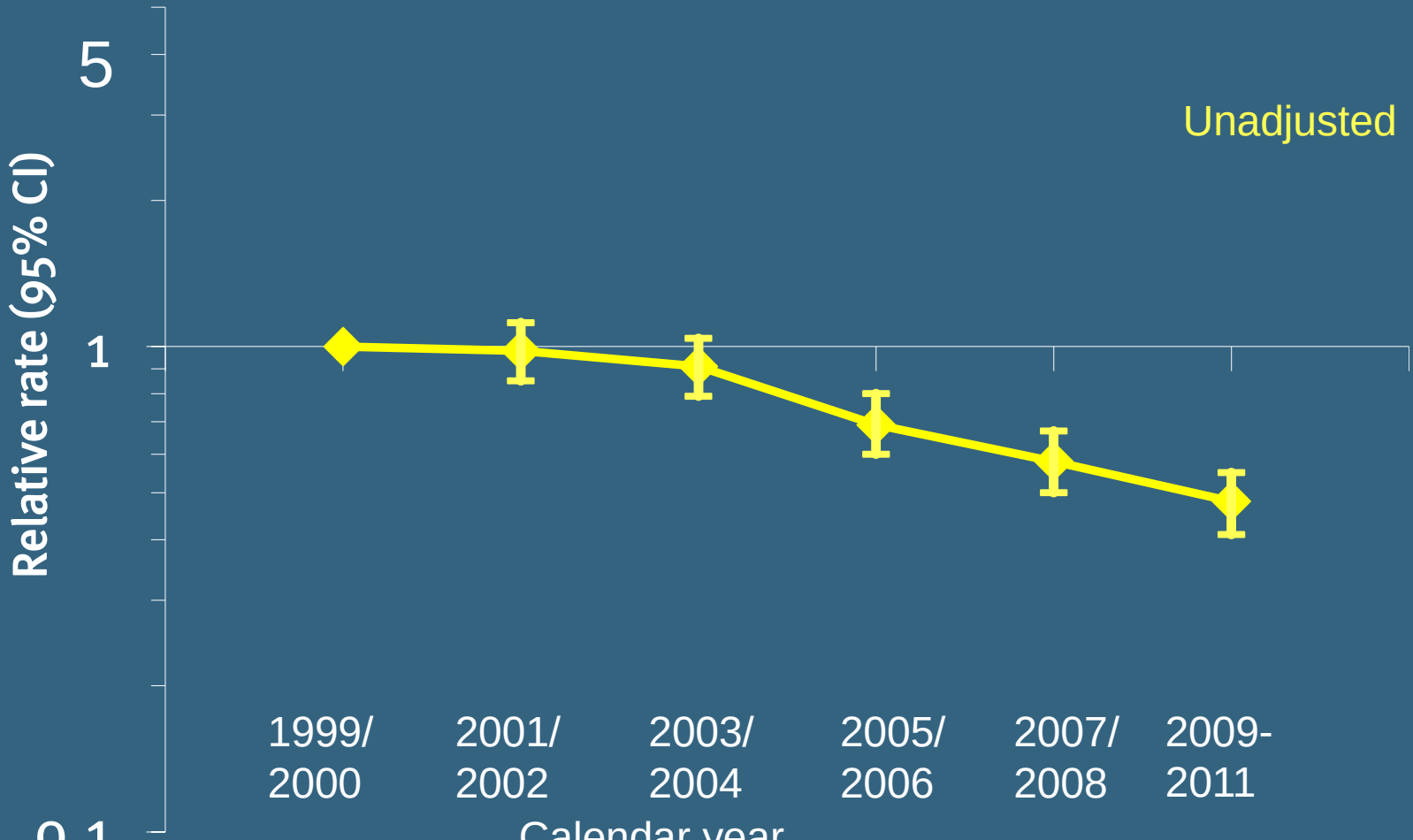
Overall death rate

There were 3,802 deaths in 49,734 HIV positive individuals followed for 304,695 person-years

Rate: 12.5 per 1,000 person-years

95% CI: 12.1 to 12.9

Association between calendar year and mortality: All causes



Incidence : (per 1000 pyrs)	17.4	17.0	15.8	12.0	10.0	8.3

D:A:D

Association between calendar year and mortality: All causes

* Adjusted for: age, gender, ethnicity, mode of HIV acquisition (fixed) and HBV, HCV, smoking, diabetes, hypertension, HIV RNA, BMI, CD4 count (time-updated)

D:A:D

Causes of death in the D:A:D Study

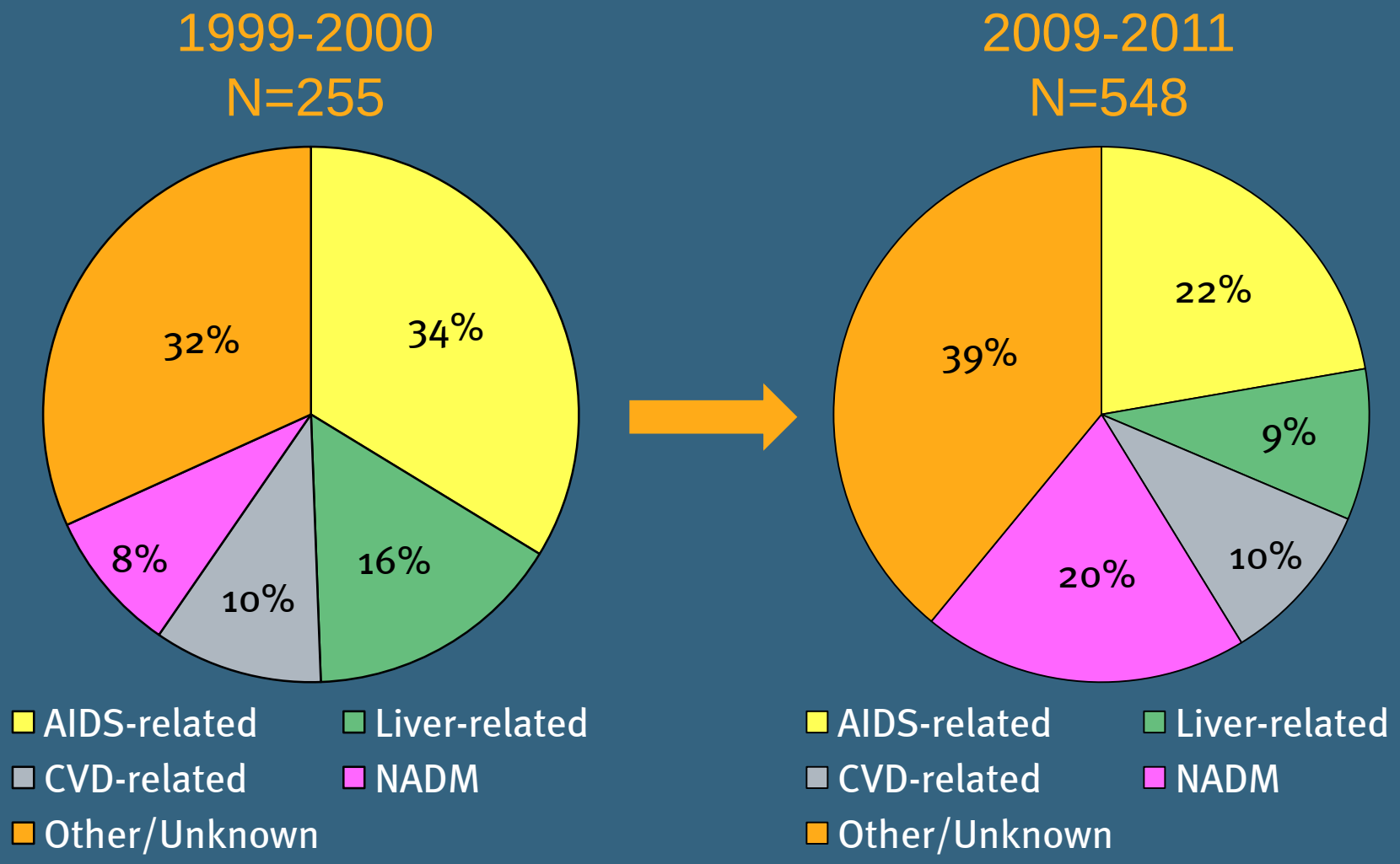
	N (%)
Total	**3802 (100)**
AIDS	**1094 (29)**
Liver-related	**499 (13)**
Chronic viral hepatitis	432 (11)
Liver failure	67 (2)
CVD-related	**421 (11)**
Myocardial Infarction	218 (6)
Stroke	55 (1.4)
Other CVD	55 (1.4)
Other heart disease	85 (2)
Diabetes mellitus complications	8 (0.2)
Non-AIDS cancer	**535 (14)**

	N (%)
Other/ Unknown	**1253 (33)**
Non-AIDS infections	277 (8)
COPD	27 (0.7)
Pancreatitis	20 (0.5)
Renal dysfunction/disease	50 (1.3)
Suicide	151 (4)
Drug overdose	106 (3)
Accident	72 (2)
Homicide	23 (0.6)
*Other known**	244 (4)
Unknown	283 (7)

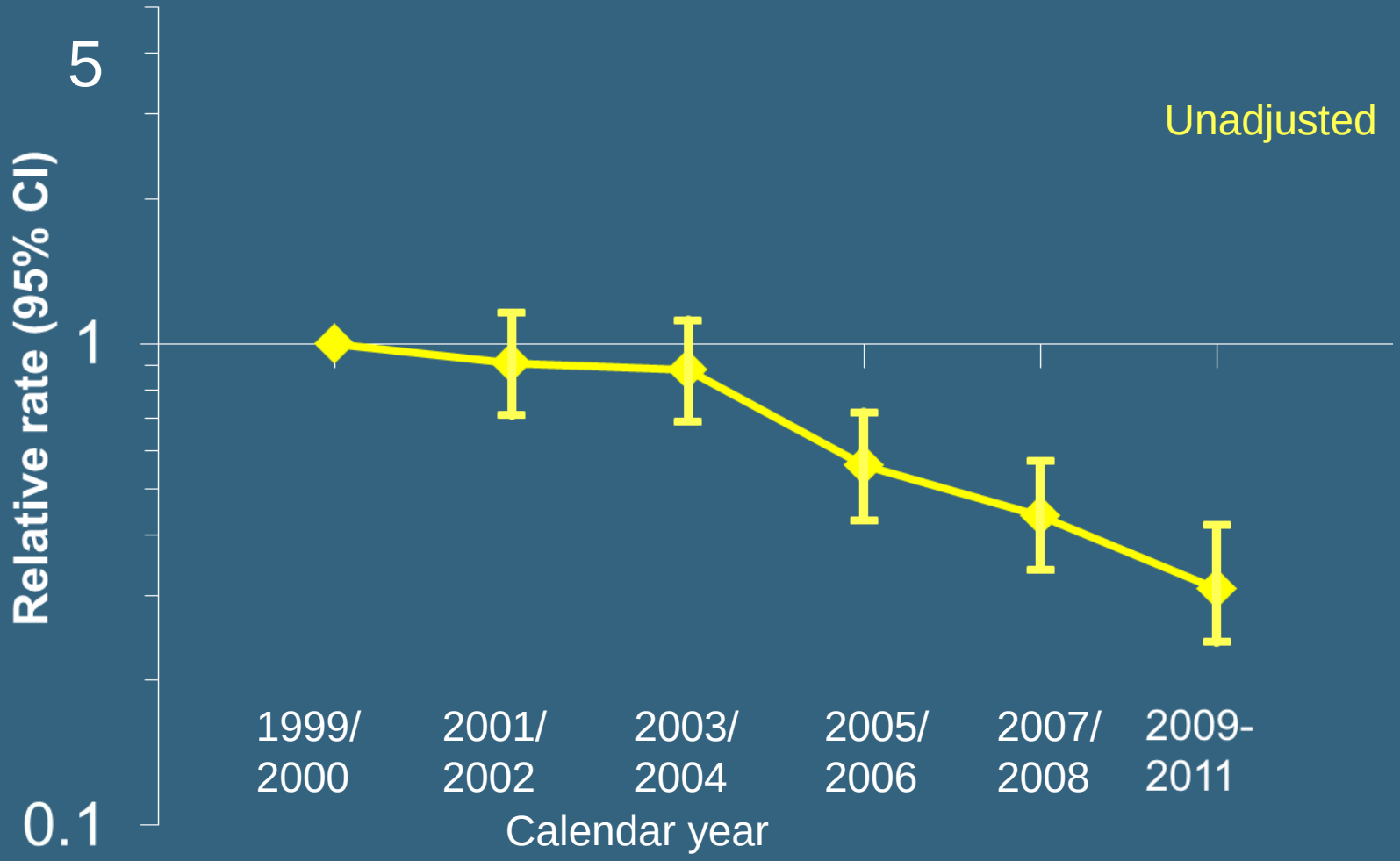
*fewer than 20 deaths per stated cause

D:A:D

Changes in causes of death over time



Association between calendar year and mortality: AIDS related



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D:A:D

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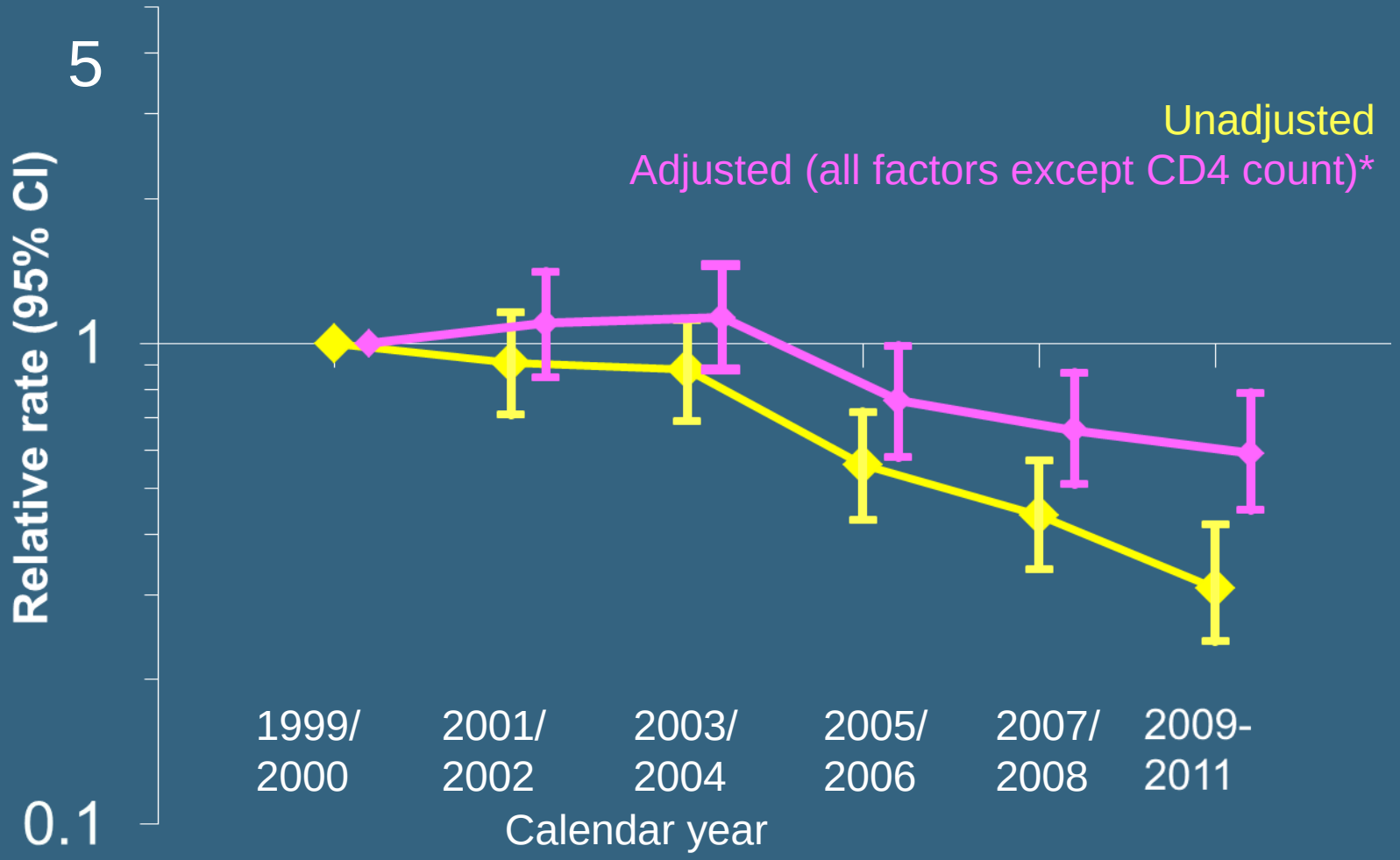

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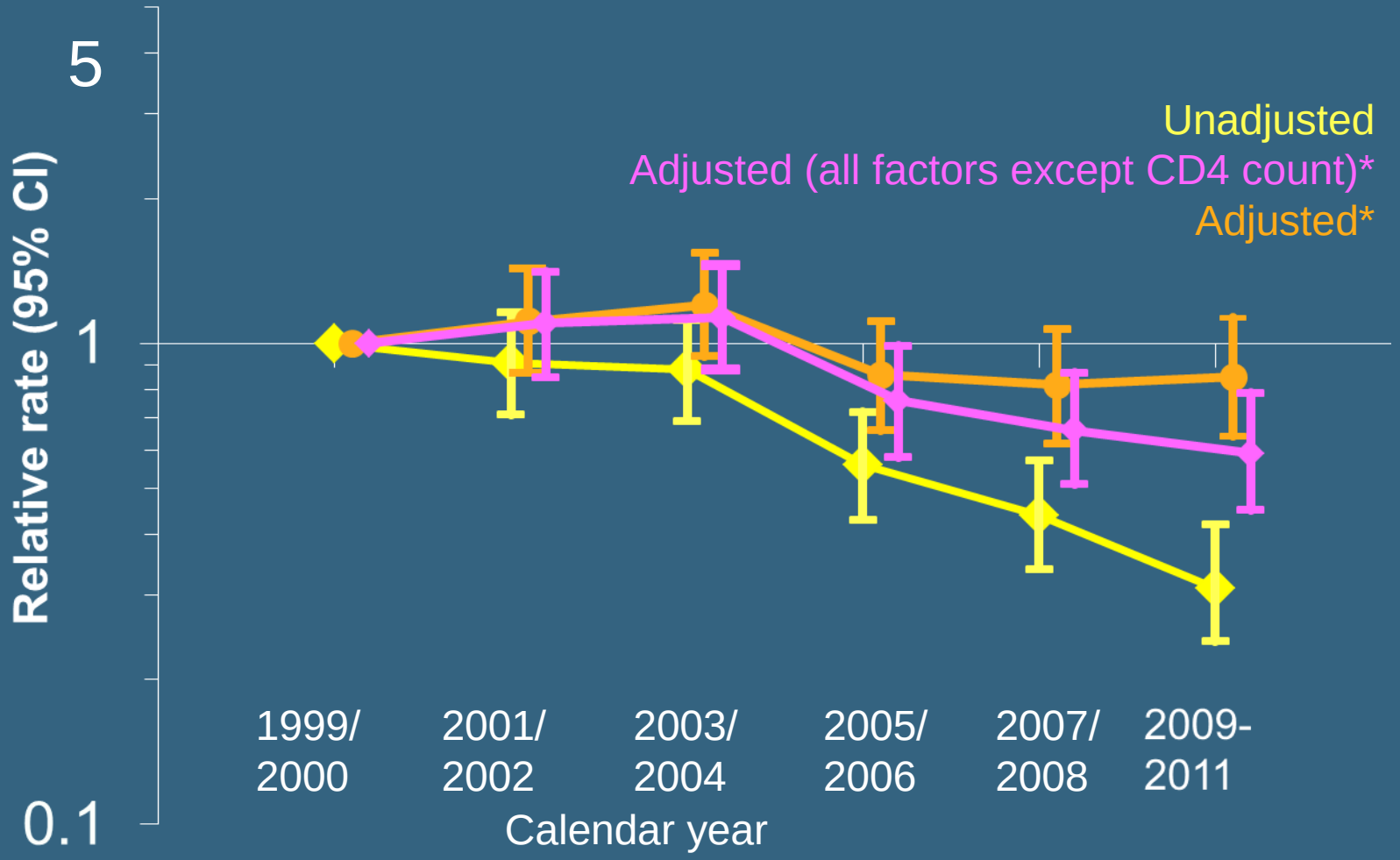

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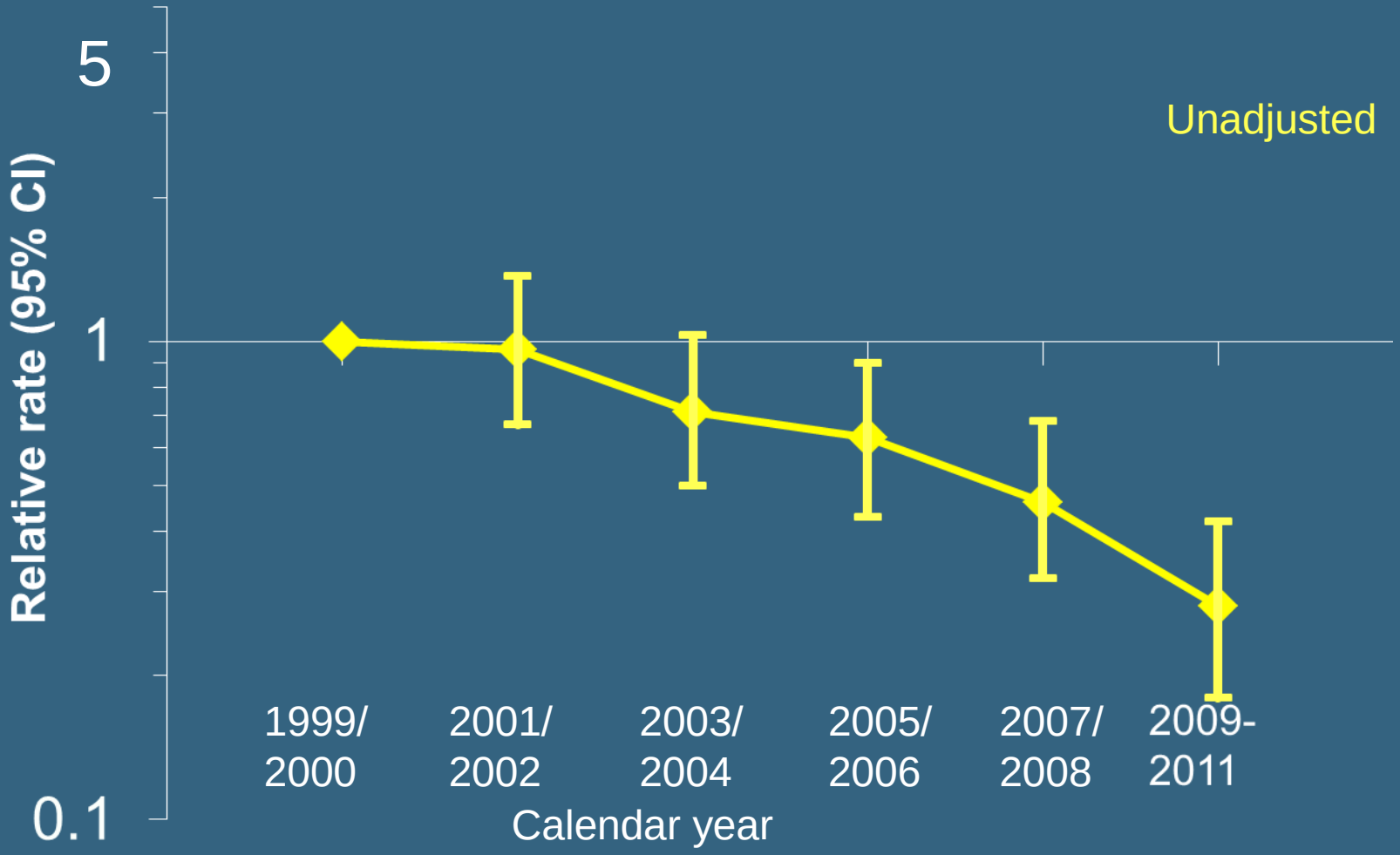
D:A:D

Association between calendar year and mortality: Liver-related



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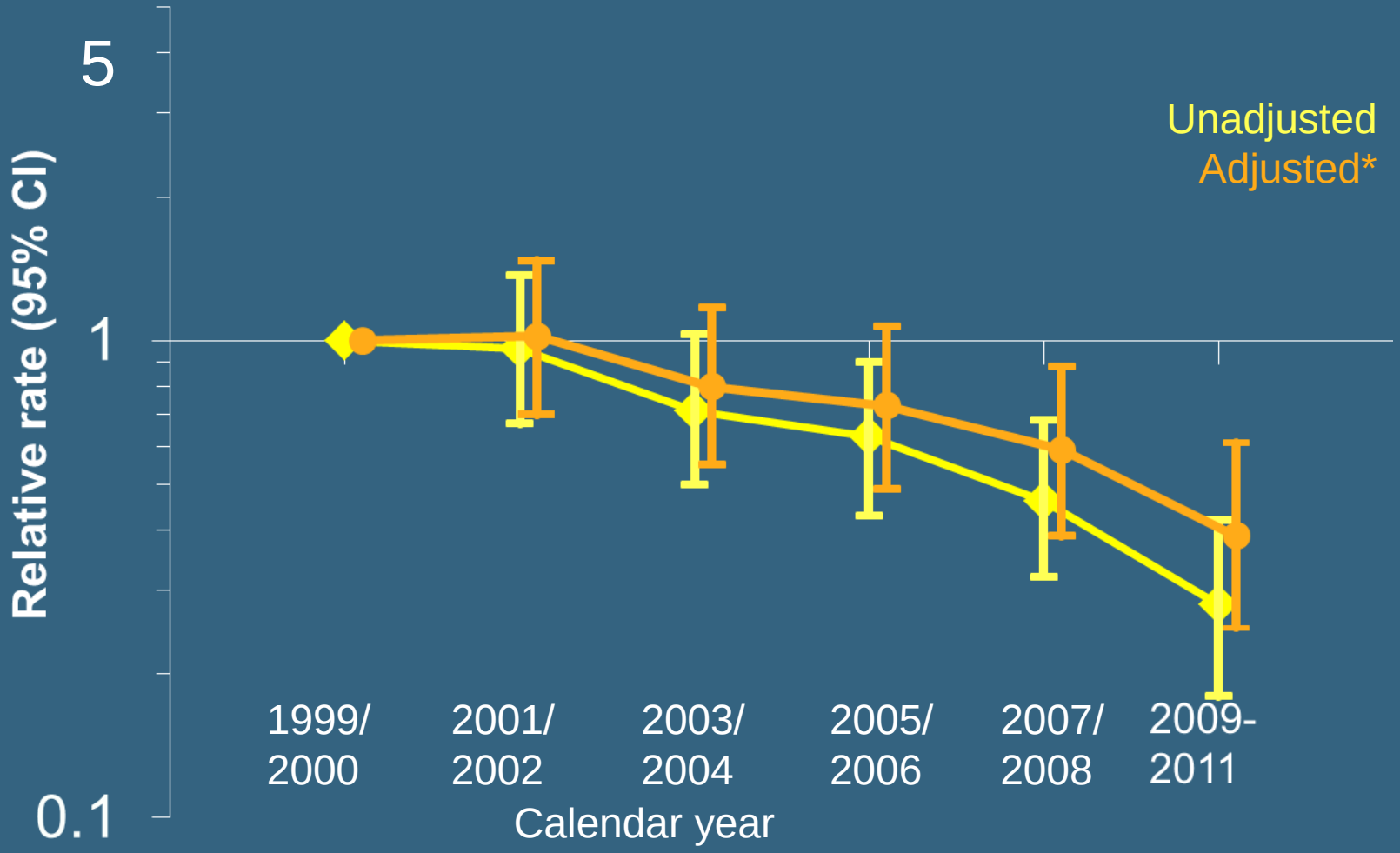

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D:A:D

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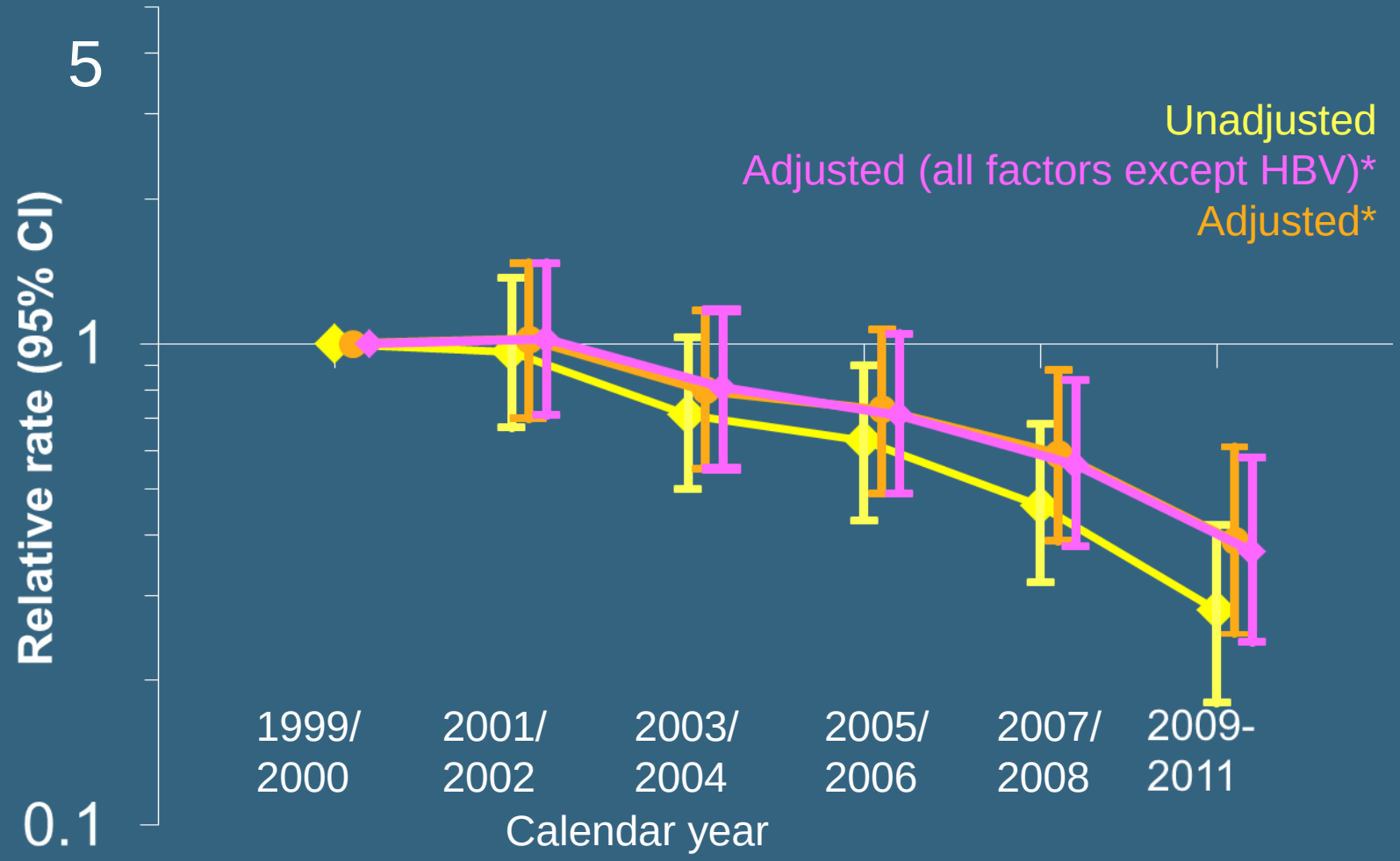

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D:A:D

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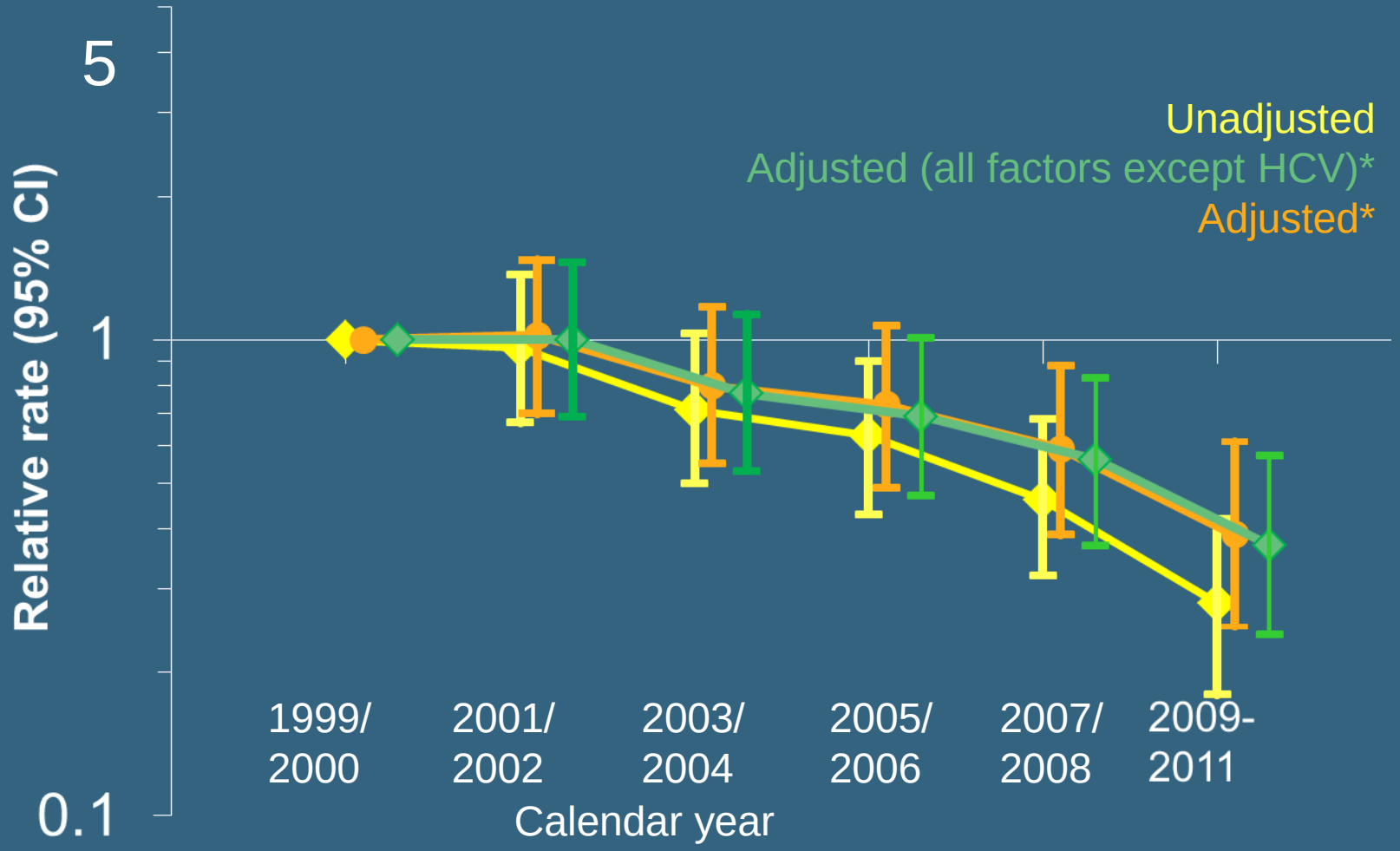

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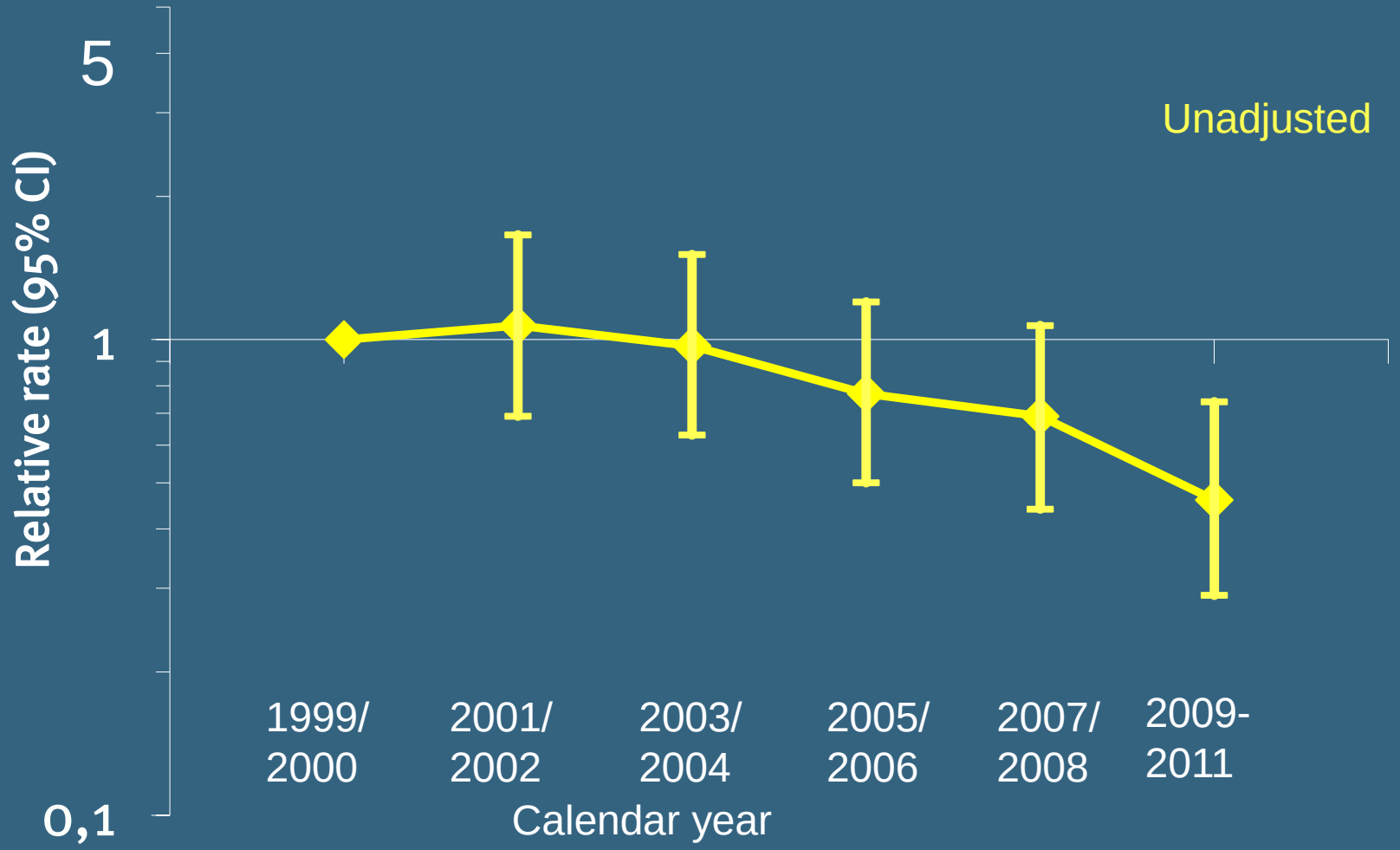
Association between calendar year and mortality: CVD-related



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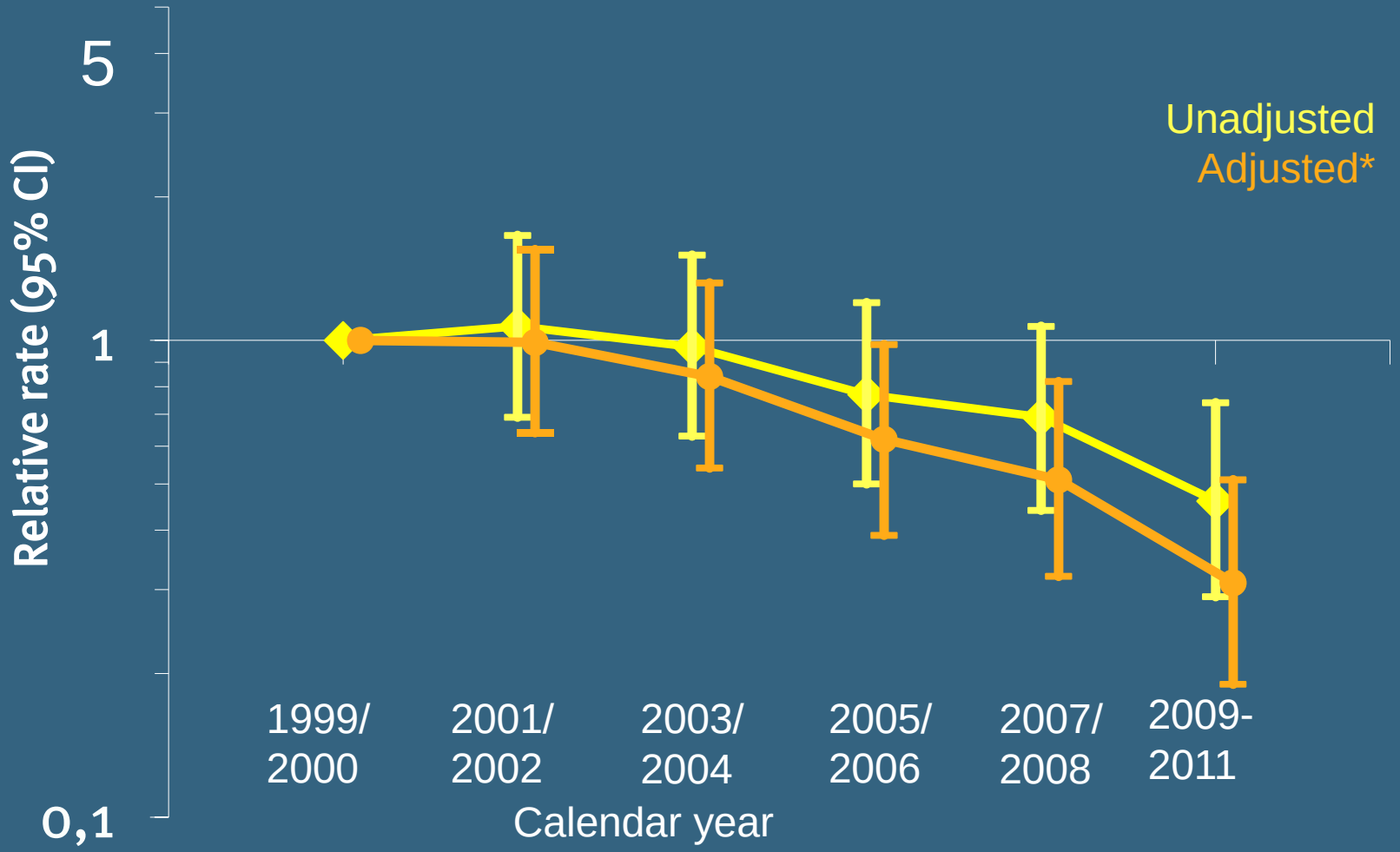

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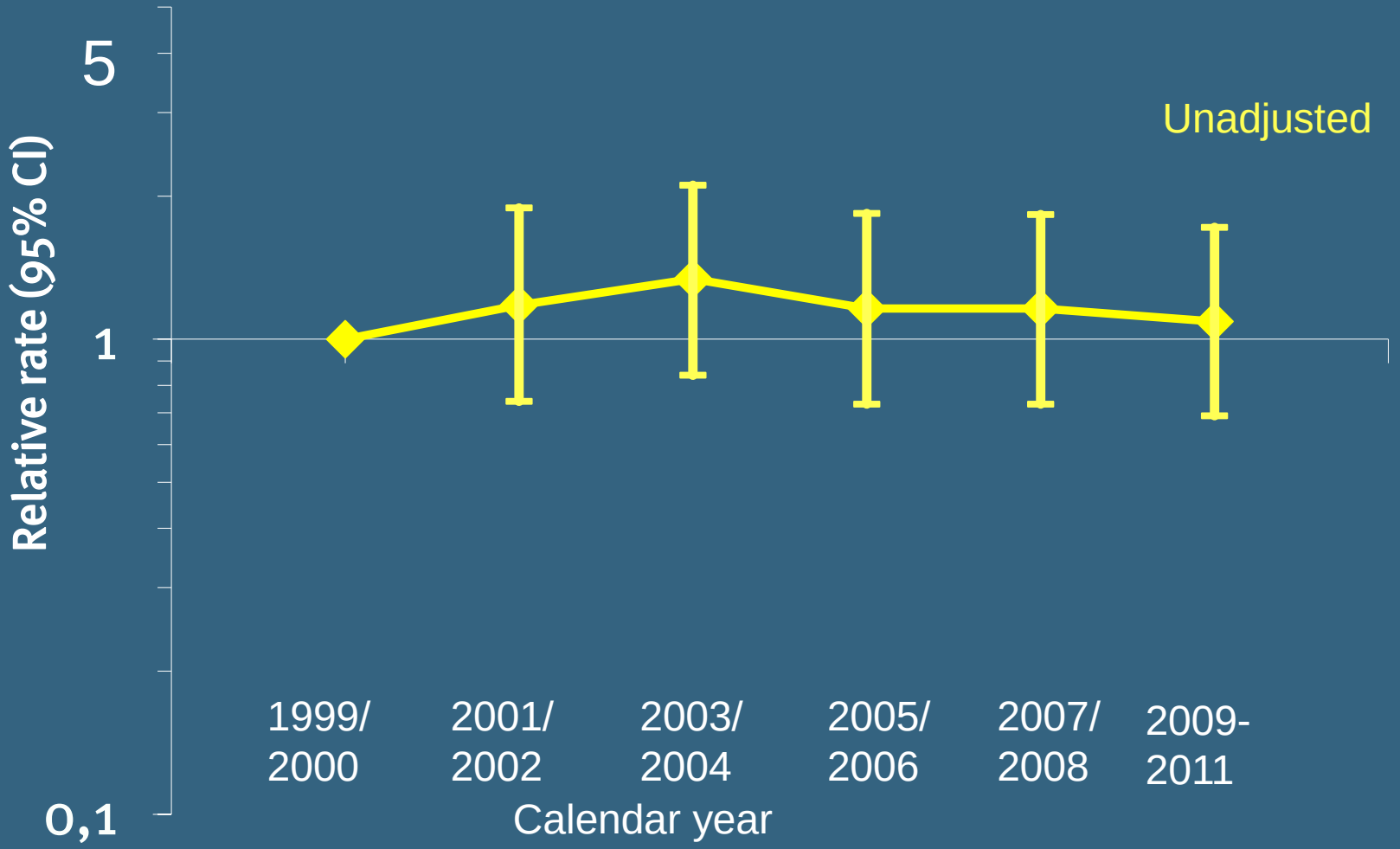
D:A:D

Association between calendar year and mortality: Non-AIDS malignancy*



* Includes lung cancers, prostate cancers, anal cancers, Hodgkin's lymphomas, primary liver cancers, gastrointestinal cancers, breast cancers, uterus cancers, testicular cancers, bladder cancers and leukemias

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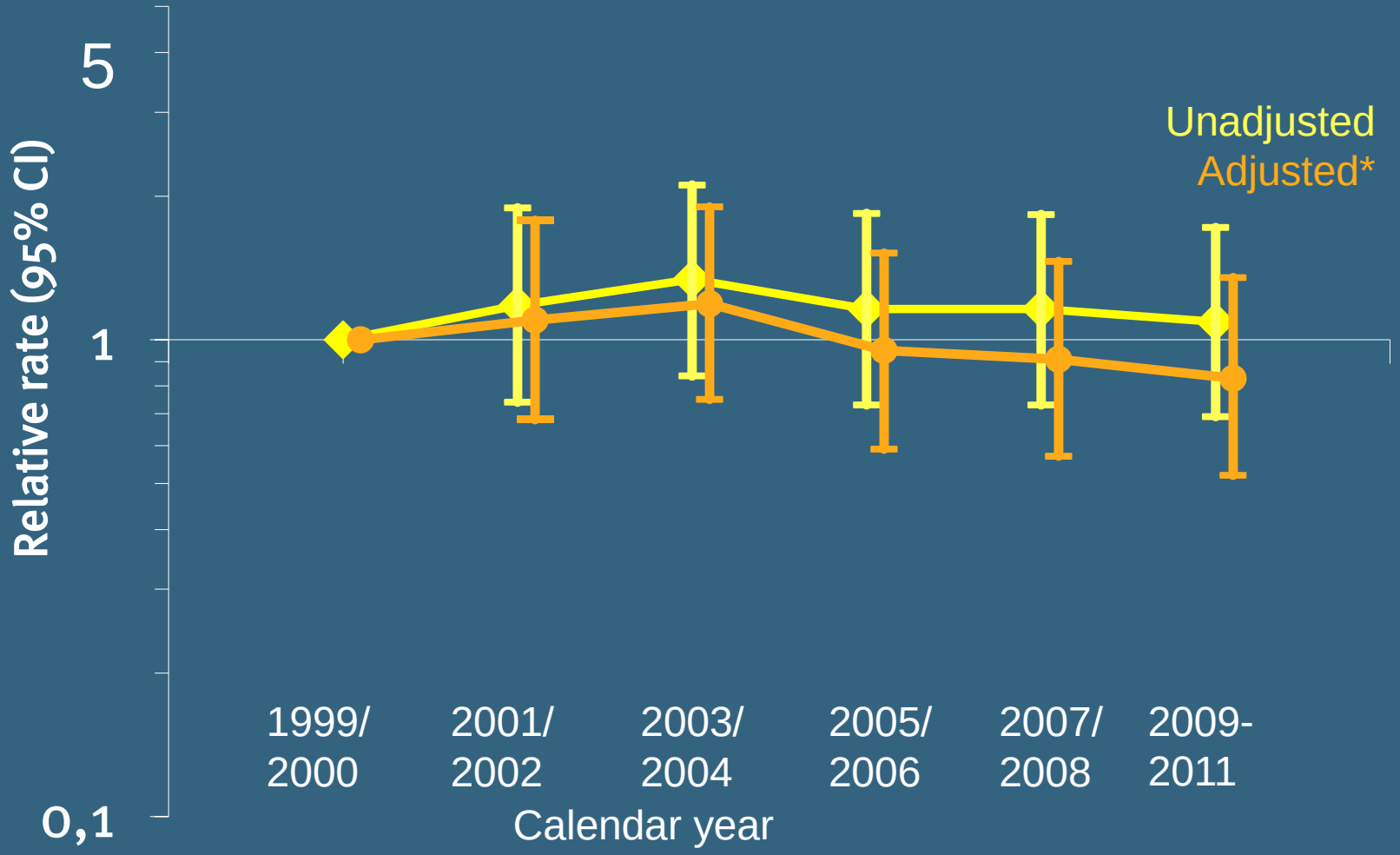
Association between calendar year and mortality: Non-AIDS malignancy



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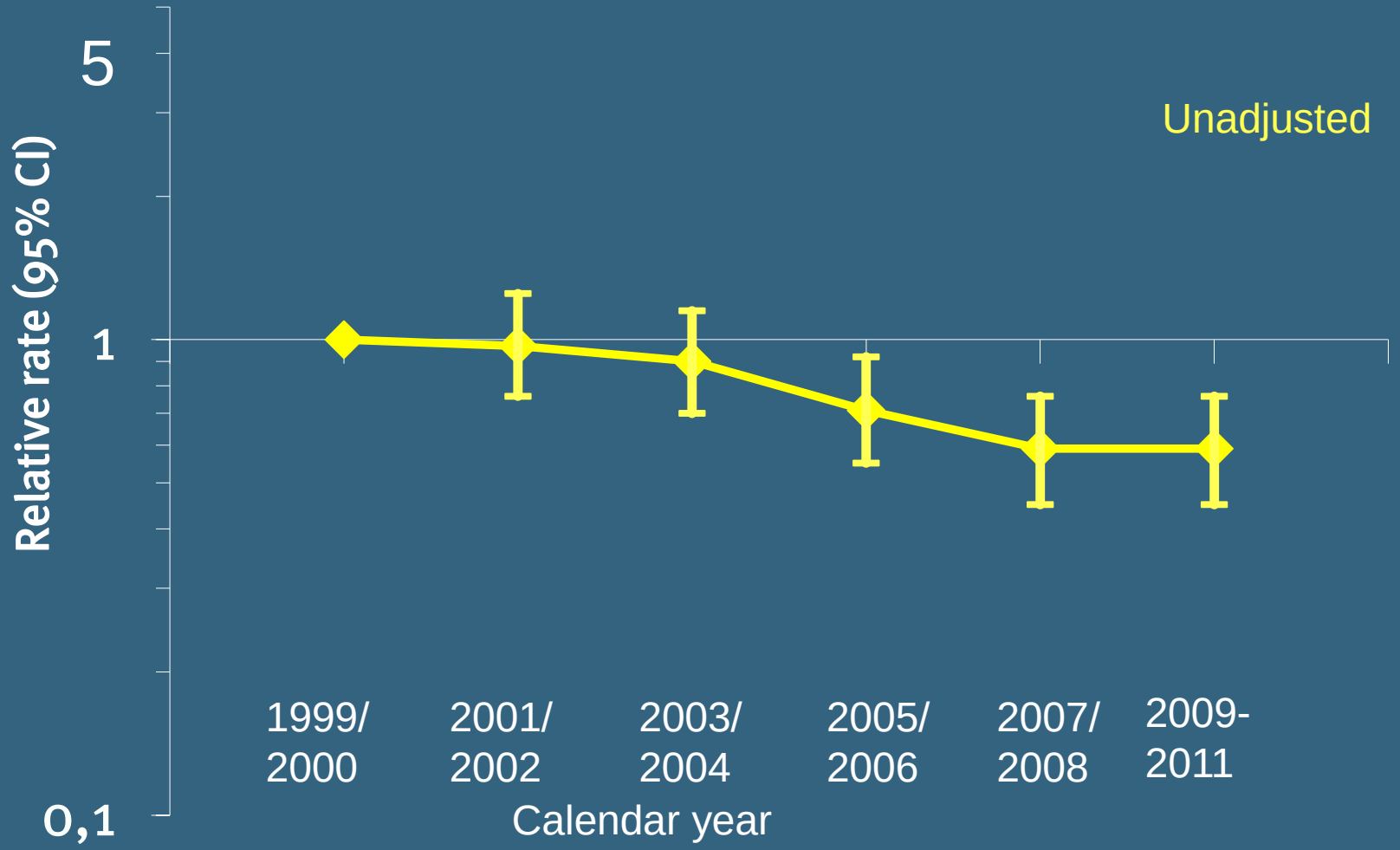
D:A:D

Association between calendar year and mortality: Other/Unknown



D:A:D

Association between calendar year and mortality: Other/Unknown

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Sensitivity analyses

- Adjustment for HIV RNA levels does not affect trends over time (once accounting for CD4 count)
- Results remain consistent when accounting for the presence of any competing risks (from the other causes of death)

Discussion

- Death rates amongst HIV-positive individuals with access to care has continued to decline, even after the initial dramatic decline when potent ART was first introduced
- Currently, there is no indication of any increase in risk of death from any specific cause as a potential result of long term adverse effects of ART
- This provides continued strong support for the substantial net benefits of ART
- AIDS remains the leading cause of death
- Decline in AIDS-related deaths is largely explained by improvements in CD4 count

Discussion

- Non-AIDS defining malignancy is now the leading non-AIDS cause of death. Rates have remained stable over time
- Liver and CVD-related deaths have decreased markedly, suggesting improvements in patient management over the study period
- Further work studying the impact of CVD-related interventions (e.g. statin use and revascularisation) is on-going
- Collection of specific causes of death in HIV is important to allow earlier interventions in HIV case management. Monitoring on causes and distributions of death remains on-going in the D:A:D study

D:A:D Study Group

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Funding: 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMEA and a consortium of "Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, ViiV Healtcare, Merck, Pfizer, F. Hoffmann-La Roche and Janssen Pharmaceuticals