

# Hydrochlorothiazide use and risk of non-melanoma skin cancer

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# Disclaimer

- This work was funded by the U.S. Food and Drug Administration through the Department of Health and Human Services contract number HHSF223200910006I.
- The views expressed in this presentation are mine and are not intended to convey official U.S. Food and Drug Administration policy or guidance.

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- Tancy Zhang

ORIGINAL ARTICLES

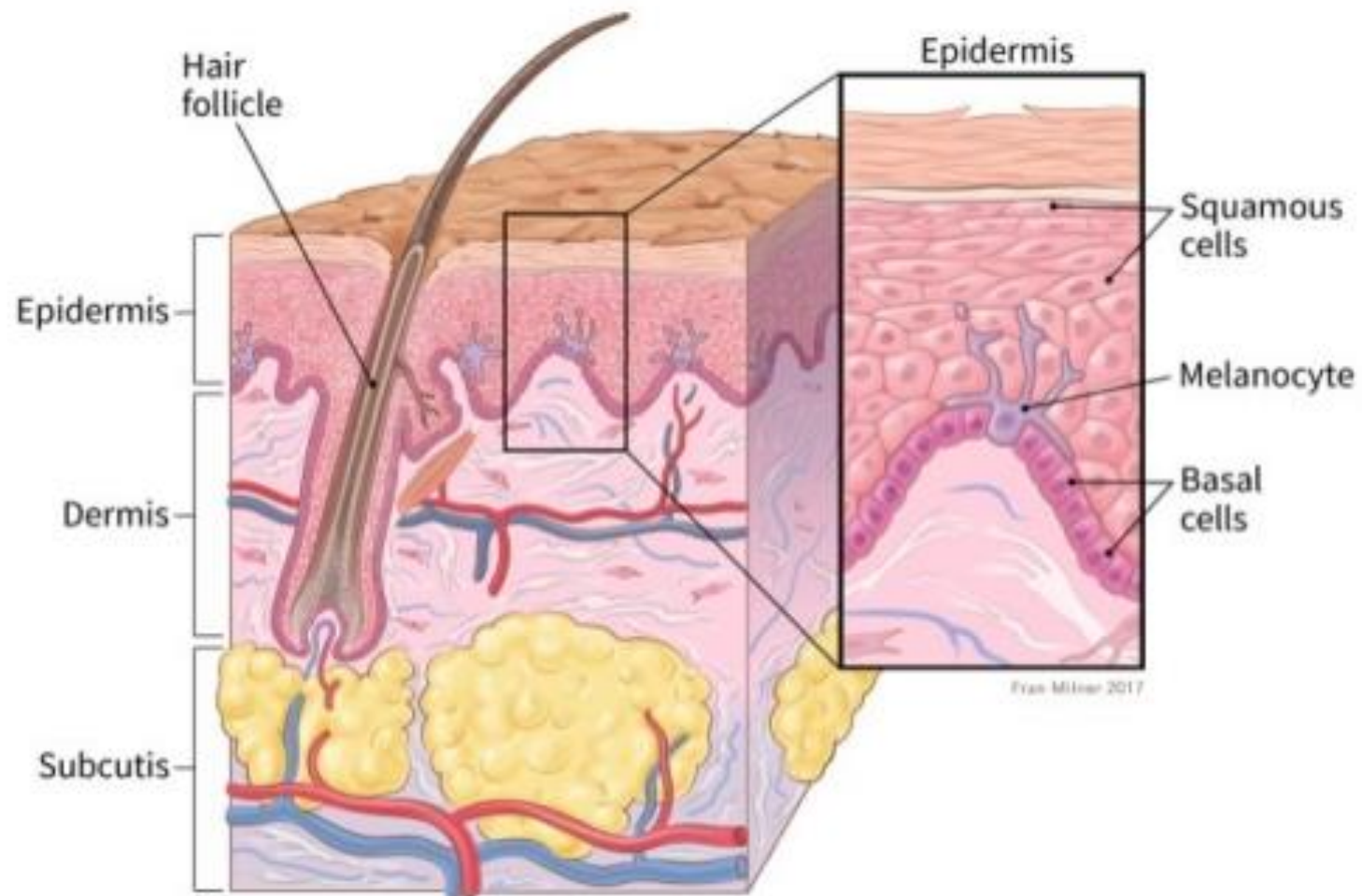
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**Hydrochlorothiazide use and risk of  
nonmelanoma skin cancer:  
A nationwide case-control study  
from Denmark**



Sidsel Arnsfang Pedersen, MD,<sup>a,b,c</sup> David Gaist, PhD,<sup>a,b</sup> Sigrun Alba Johannesdottir Schmidt, PhD,<sup>d</sup>  
Lisbet Rosenkrantz Hölmich, DMSc,<sup>e</sup> Søren Friis, MD,<sup>d,f,g</sup> and Anton Pottegård, PhD<sup>c</sup>  
*Odense, Aarhus, Herlev, and Copenhagen, Denmark*

J Am Acad Dermatol 2018;78:673-81



**Table II.** Association between exposure to hydrochlorothiazide and risk of NMSC according to cumulative hydrochlorothiazide use

Subgroup	Case patients	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI) <sup>†</sup>
Basal cell carcinoma				
Nonuse	63,653	1,281,894	1.0 (ref)	1.0 (ref)
Ever use	7900	148,989	1.07 (1.04-1.10)	1.08 (1.05-1.10)
High use (≥50,000 mg)	1897	30,075	1.28 (1.22-1.34)	1.29 (1.23-1.35)
Cumulative amount				
1-9999 mg	2907	57,782	1.02 (0.98-1.06)	1.02 (0.98-1.06)
10,000-24,999 mg	1815	36,003	1.02 (0.97-1.07)	1.03 (0.98-1.08)
25,000-49,999 mg	1281	25,129	1.03 (0.97-1.09)	1.03 (0.97-1.09)
50,000-74,999 mg	511	9148	1.13 (1.03-1.24)	1.14 (1.04-1.25)
75,000-99,999 mg	271	4700	1.17 (1.03-1.32)	1.18 (1.04-1.33)
100,000-149,999 mg	395	6134	1.29 (1.17-1.43)	1.30 (1.17-1.44)
150,000-199,999 mg	329	4863	1.38 (1.23-1.54)	1.39 (1.24-1.56)
≥200,000 mg	391	5230	1.50 (1.35-1.67)	1.54 (1.38-1.71)
Squamous cell carcinoma				
Nonuse	6817	149,944	1.0 (ref)	1.0 (ref)
Ever use	1812	22,518	1.80 (1.70-1.90)	1.75 (1.66-1.85)
High use	862	4802	4.05 (3.75-4.39)	3.98 (3.68-4.31)
Cumulative amount				
1-9999 mg	392	8369	1.04 (0.93-1.15)	1.01 (0.91-1.12)
10,000-24,999 mg	283	5476	1.14 (1.01-1.29)	1.12 (0.99-1.27)
25,000-49,999 mg	275	3871	1.57 (1.38-1.78)	1.54 (1.36-1.75)
50,000-74,999 mg	133	1432	2.08 (1.74-2.50)	2.05 (1.70-2.46)
75,000-99,999 mg	95	746	2.89 (2.32-3.60)	2.84 (2.28-3.54)
100,000-149,999 mg	180	1104	3.65 (3.10-4.30)	3.56 (3.02-4.20)
150,000-199,999 mg	206	768	5.87 (5.00-6.89)	5.82 (4.96-6.84)
≥200,000 mg	248	752	7.53 (6.46-8.77)	7.38 (6.32-8.60)

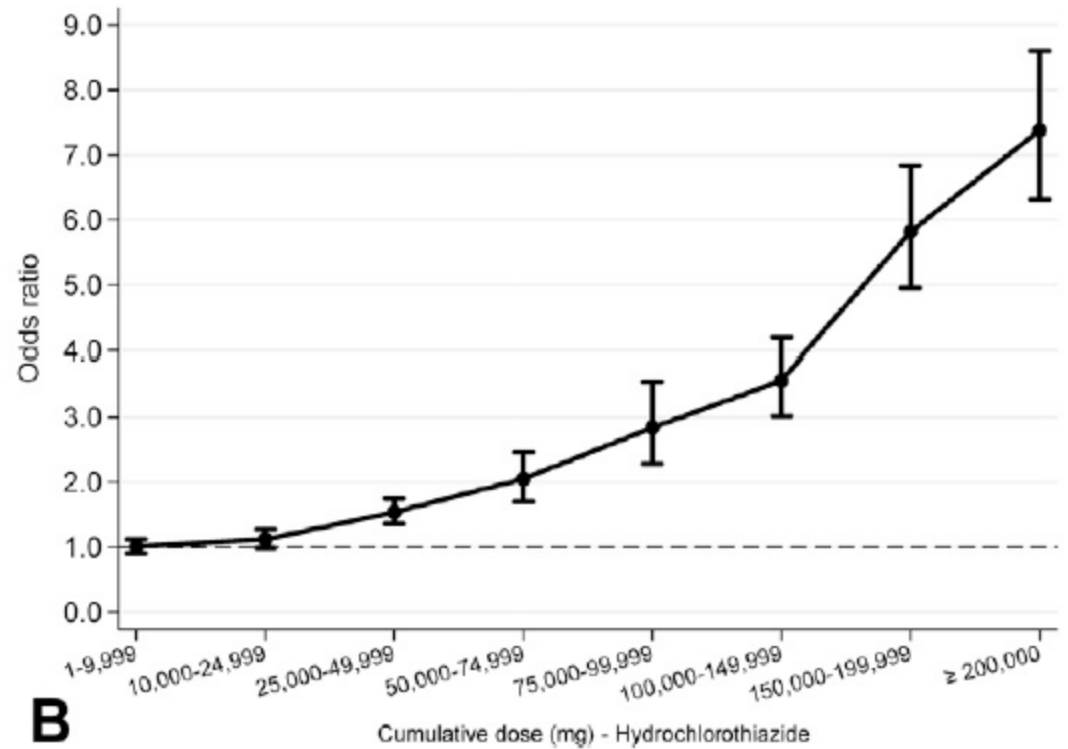
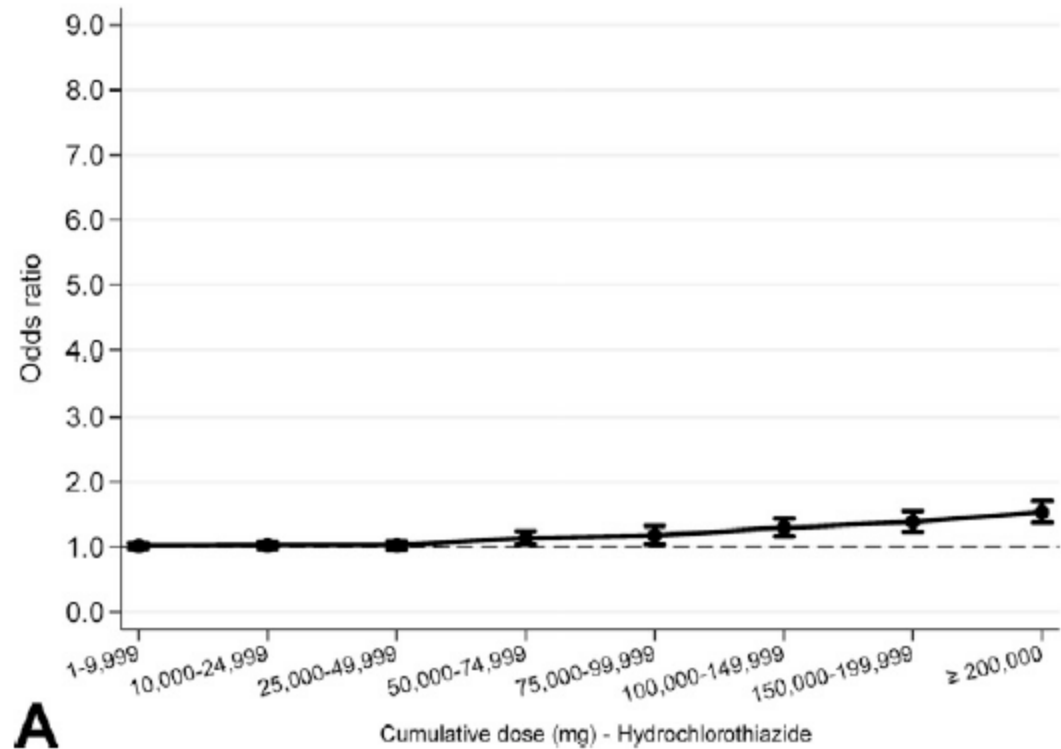
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**Fig 2.** Dose-response pattern between cumulative hydrochlorothiazide dose and risk of basal cell carcinoma (**A**) and squamous cell carcinoma (**B**). Error bars represent 95% confidence intervals.

# Question 1

Is the use of hydrochlorothiazide (HCTZ)-containing products associated with the risk of non-melanoma skin cancer?

## Question 2

Is there a *dose-response relation* between the use of HCTZ-containing products and the risk of non-melanoma skin cancer?

# Answering the questions

## Data source

- Option 1
- Option 2
- Option N

## Study design

- Option 1
- Option 2
- Option N

## Exposure

- Option 1
- Option 2
- Option N

## Comparator

- Option 1
- Option 2
- Option N

## Outcome

- Option 1
- Option 2
- Option N

## Potential confounders

- Option 1
- Option 2
- Option N

## Statistical analysis

- Option 1
- Option 2
- Option N

# Data source

- Administrative claims database(s) in the United States ✓
- Electronic health records
- Registries
- Others?

# Study design


- Self-control design (and its variants)
- Cohort design (and its variants)
  - Cohort design ✓
  - Case-control design



**FEATURED ARTICLE**

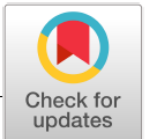
WILEY **Statistics**  
in *Medicine*

# A plea to stop using the case-control design in retrospective database studies

Martijn J. Schuemie<sup>1,2,3</sup>  | Patrick B. Ryan<sup>1,2,4</sup> | Kenneth K.C. Man<sup>5,6,7,8</sup> |  
Ian C.K. Wong<sup>5,6</sup> | Marc A. Suchard<sup>1,3,9,10</sup> | George Hripcsak<sup>1,4,11</sup>

Received: 19 June 2019 | Accepted: 21 June 2019


DOI: 10.1002/sim.8320



**COMMENTARY**

WILEY **Statistics**  
in *Medicine*

# Discussion of Schuemie et al: “A plea to stop using the case-control design in retrospective database studies”

Sebastian Schneeweiss<sup>1</sup>   
Samy Suissa<sup>2</sup>

# Exposure

Data source

Study design

Exposure

Comparator

Outcome

Potential  
confounders

Statistical  
analysis

- HCTZ-containing products
- Cumulative dose categories
  - <10,000mg
  - 10,000 – 24,999mg
  - 25,000 – 49,999mg
  - 50,000 – 74,999mg
  - 75,000 – 99,999mg
  - ≥100,000mg



# Comparator

Data source

Study design


Exposure

Comparator

Outcome

Potential  
confounders

Statistical  
analysis

- No use of HCTZ-containing products?
- Drugs used for similar indications? 
- Others?

Curr Epidemiol Rep (2015) 2:221–228  
DOI 10.1007/s40471-015-0053-5



PHARMACOEPIDEMIOLOGY (T STÜRMER, SECTION EDITOR)

# The Active Comparator, New User Study Design in Pharmacoepidemiology: Historical Foundations and Contemporary Application

Jennifer L. Lund<sup>1</sup> · David B. Richardson<sup>1</sup> · Til Stürmer<sup>1</sup>

**Supplemental Table IV.** Association between exposure to ACE inhibitors and risk of NMSC

Subgroup	Cases	Controls	Adjusted OR (95% CI)*	Adjusted OR (95% CI) <sup>†</sup>
Basal cell carcinoma				
Nonuse	58,669	1,167,222	1.0 (ref)	1.0 (ref)
Ever use	12,884	263,661	0.97 (0.95-0.99)	0.98 (0.96-1.00)
High use ( $\geq 2000$ DDD)	3889	79,623	0.97 (0.94-1.01)	0.99 (0.96-1.03)
Cumulative dose (DDD)				
1-399	4632	92,798	0.99 (0.96-1.03)	1.00 (0.96-1.03)
400-999	2317	47,961	0.96 (0.92-1.01)	0.97 (0.93-1.02)
1000-1999	2046	43,278	0.94 (0.90-0.99)	0.96 (0.91-1.01)
2000-2999	1235	25,624	0.95 (0.90-1.01)	0.97 (0.92-1.03)
3000-3999	796	16,561	0.96 (0.89-1.03)	0.97 (0.90-1.04)
$\geq 4000$	1858	37,439	1.00 (0.95-1.05)	1.02 (0.97-1.07)
Squamous cell carcinoma				
Nonuse	6331	130,503	1.0 (ref)	1.0 (ref)
Ever use	2298	41,959	1.14 (1.08-1.20)	1.00 (0.95-1.06)
High use ( $\geq 2000$ DDD)	735	13,034	1.18 (1.09-1.28)	1.00 (0.92-1.09)
Cumulative dose (DDD)				
1-399	742	14,421	1.05 (0.97-1.14)	0.96 (0.88-1.04)
400-999	416	7545	1.15 (1.04-1.28)	1.05 (0.95-1.18)
1000-1999	405	6959	1.20 (1.08-1.34)	1.09 (0.98-1.22)
2000-2999	198	4203	0.98 (0.85-1.13)	0.87 (0.74-1.01)
3000-3999	164	2757	1.25 (1.06-1.47)	1.07 (0.91-1.27)
$\geq 4000$	373	6074	1.28 (1.15-1.43)	1.08 (0.96-1.22)

# Outcome

Data source

Study design

Exposure

Comparator

Outcome

Potential  
confounders

Statistical  
analysis

- Non-melanoma skin cancer
  - Basal cell carcinoma
  - Squamous cell carcinoma

# Outcome

Data source

Study design

Exposure

Comparator

Outcome

Potential  
confounders

Statistical  
analysis

- ICD-9-CM codes (ICD-9-CM: 173.xx or ICD-10-CM: C44.xxx) **plus** a procedure code for excision, destruction, Mohs microscopic chemosurgery, or Mohs excision technique, or a NDC for a topical chemotherapy treatment on or within 30 days after the diagnosis date
- A previous study (in a large HMO health plan) showed a positive predictive value of 99% for the ICD-9-CM-based outcome algorithm
- The date of diagnosis was used to establish the date of the outcome

# Potential confounders

- Risk factors for BCC and SCC? ✓
- UV exposure? ✓
- Variables that are only predictive of exposure?

# Statistical analysis – Overall

Data source

Study design


Exposure

Comparator

Outcome

Potential  
confounders

Statistical  
analysis

- Multivariable-adjusted outcome regression?
- Propensity scores? 
- Disease risk scores?
- Instrumental variables?

# Statistical analysis – Overall

Data source

Study design

Exposure

Comparator

Outcome

Potential  
confounders

Statistical  
analysis

- Matching? ✓
- Stratification?
- Weighting?
- Restriction?
- Modeling?



# Statistical analysis – Overall

Data source

Study design


Exposure

Comparator

Outcome

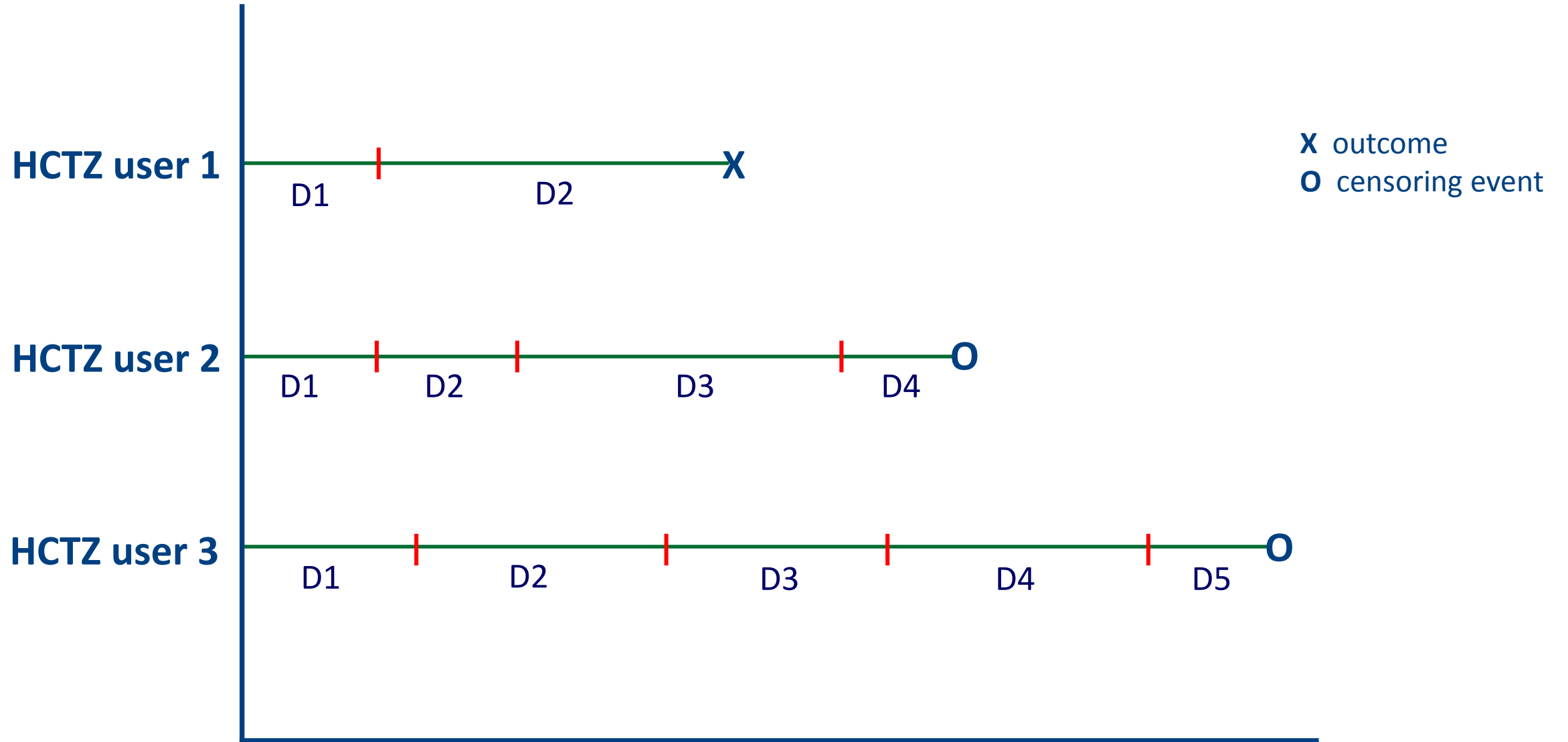
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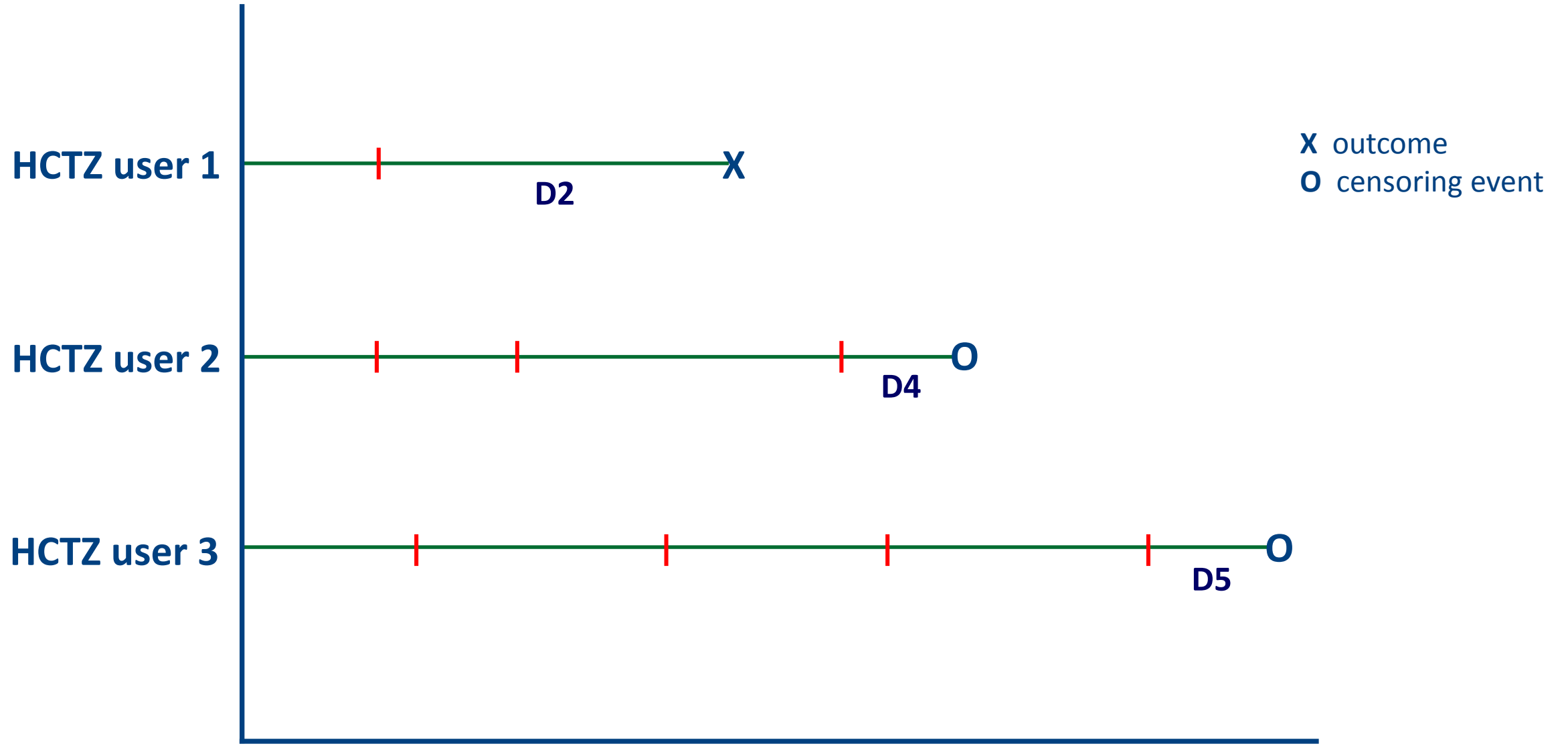
Statistical  
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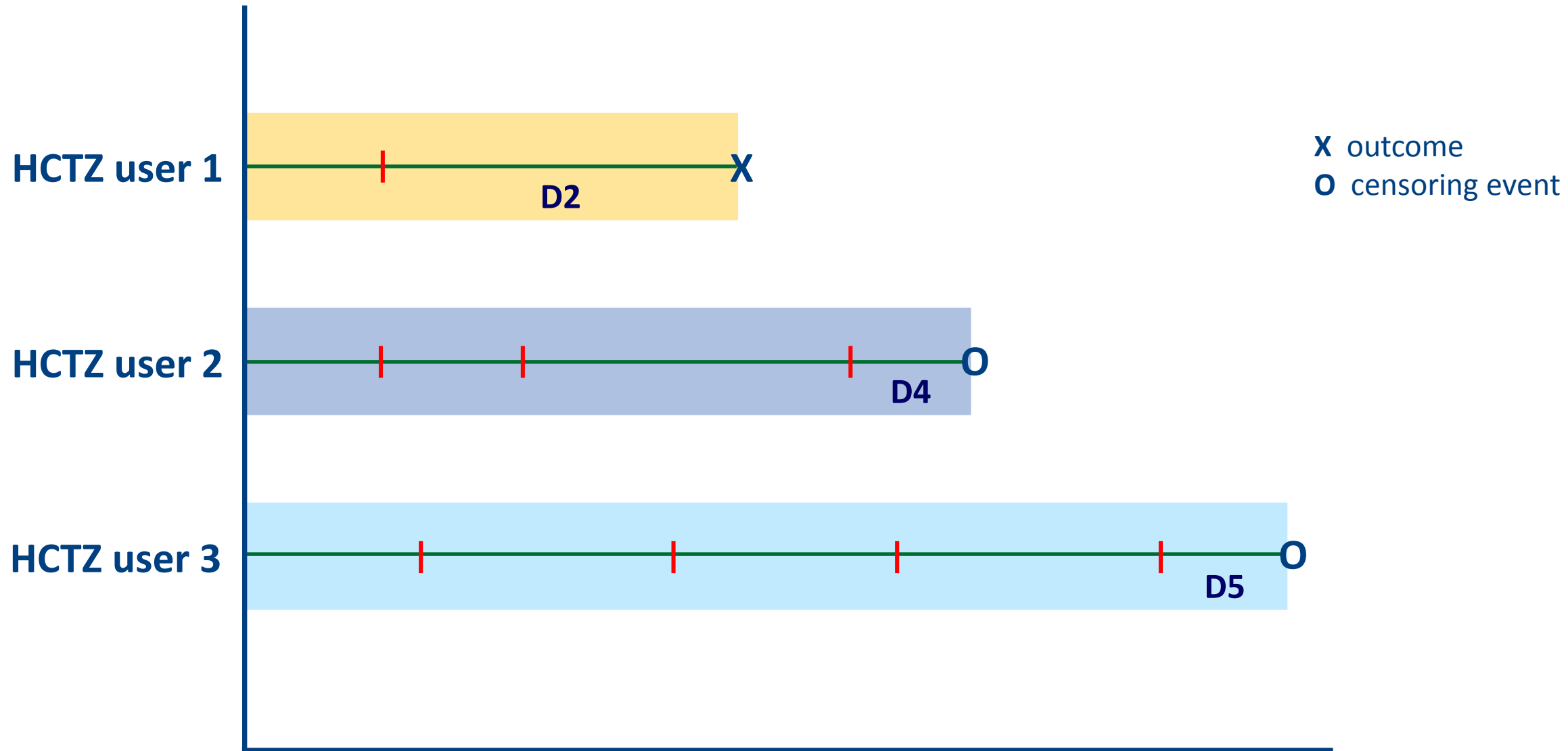
- “Intention-to-treat” analysis? 
- “On-treatment” or “as-treated” analysis?

# Dose-response relation

- Find the highest cumulative dose of each HCTZ user and assign the user's follow-up time to that dose category

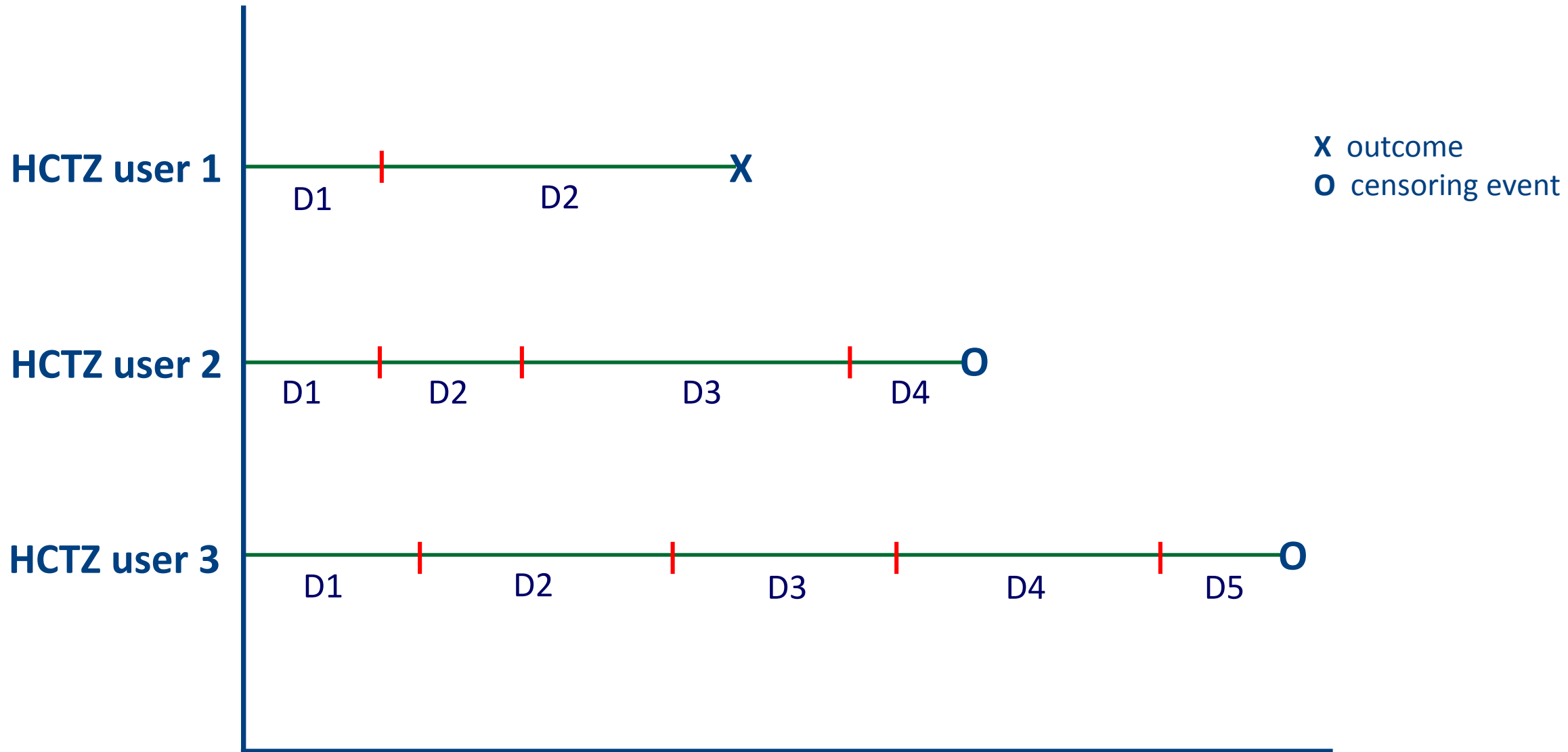






# Dose-response relation

- Update cumulative dose over time and assign person-time to a particular dose category



HCTZ user 1

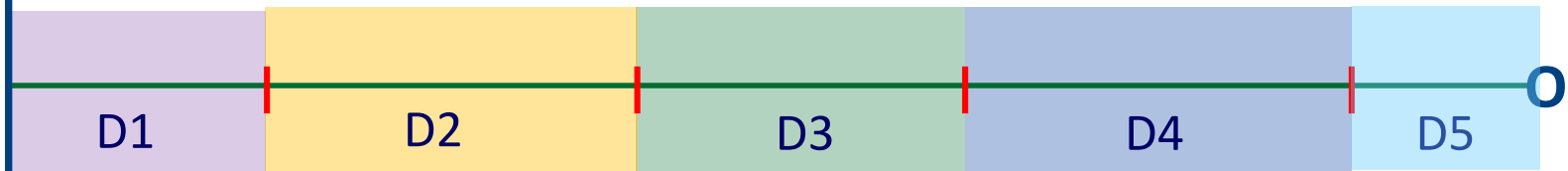


X outcome  
O censoring event

HCTZ user 2



HCTZ user 3





# Baseline patient characteristics

Characteristics	Before 1:1 PS matching			After 1:1 PS matching		
	HCTZ	ACEI	SMD	HCTZ	ACEI	SMD
<b>Number of Patients</b>	6,959,086	7,417,942		5,211,321	5,211,321	
<b>Demographics</b>						
Age, Mean	59.8	61.6	-0.14	60.7	60.7	0.001
Age, Categories (%)						
<50	27.7	23.7	0.09	25.6	25.4	0.005
50-59	22.1	21.3	0.02	21.2	21.8	-0.013
60-74	33.2	34.5	-0.03	34.8	34.1	0.013
≥75	17.1	20.6	-0.09	18.4	18.7	-0.008
<b>Female (%)</b>	61.5	46.8	0.30	52.5	53.1	-0.012

# Baseline patient characteristics (continued)

Characteristics	Before 1:1 PS matching			After 1:1 PS matching		
	HCTZ	ACEI	SMD	HCTZ	ACEI	SMD
<b>Recorded History of (%)</b>						
Actinic Keratosis	2.8	2.7	0.005	2.9	2.9	0.001
Arsenic Exposure	0.0	0.0	0.001	0.0	0.0	0.000
Diabetes	18.7	35.8	-0.391	24.3	24.3	0.001
Human Papillomavirus	0.2	0.1	0.022	0.2	0.2	0.000
<b>Immunosuppressive Conditions</b>						
Chronic Pulmonary Disease	11.8	15.7	-0.115	12.6	12.6	0.000
Connective Tissue Disease	1.7	1.8	-0.005	1.7	1.7	0.000
Cardiovascular Disease	11.2	26.0	-0.389	14.5	14.4	0.003
Moderate/severe Renal Disease	0.5	2.9	-0.184	0.7	0.9	-0.015
Transplant	0.2	0.7	-0.076	0.2	0.3	-0.005
Human Immunodeficiency Virus	0.3	0.4	-0.0147	0.4	0.4	0.000
Immune Disorders	0.1	0.1	-0.009	0.1	0.1	-0.000
Severe Skin Disease	0.1	0.3	-0.038	0.1	0.1	-0.002
White Blood Cell Disease	0.0	0.1	-0.015	0.1	0.1	-0.001
Mole Removal	0.9	0.8	0.011	0.8	0.8	0.000
Naevi	0.8	0.6	0.017	0.7	0.7	0.000
Xeroderma pigmentaosum	0.0	0.0	0.004	0.0	0.0	0.000

# Baseline patient characteristics (continued)

Characteristics	Before 1:1 PS matching			After 1:1 PS matching		
	HCTZ	ACEI	SMD	HCTZ	ACEI	SMD
<b>Medication or Behavioral History (%)</b>						
Alcohol Use or Abuse	0.9	1.5	-0.051	1.1	1.1	0.000
Drugs with Chemo-protective Effects	45.0	53.5	-0.169	48.3	48.2	0.004
Immunosuppressive Medications						
Glucocorticoids	28.6	27.4	0.025	27.7	27.8	0.000
Treatment for Immune Disorders	8.9	8.2	0.028	8.5	8.5	0.000
Photosensitizing Medications						
Aminoquinolines	0.5	0.5	0.005	0.5	0.5	0.000
Amiodarone	0.5	1.8	-0.118	0.7	0.7	-0.004
Macrolides	12.3	11.7	0.017	11.9	11.9	0.000
Methoxypsoralen	0.0	0.0	0.000	0.0	0.0	0.000
Retinoids	0.0	0.0	0.010	0.0	0.0	0.000
Tetracycline	0.2	0.2	0.008	0.2	0.2	0.000

# Baseline patient characteristics (continued)

Characteristics	Before 1:1 PS matching			After 1:1 PS matching		
	HCTZ	ACEI	SMD	HCTZ	ACEI	SMD
<b>UV Radiation Exposure (%)</b>						
Low	0.1	0.2	-0.012	0.1	0.1	0.000
Moderate	39.3	42.6	-0.069	41.5	41.4	0.001
High	43.1	39.1	0.082	40.1	40.1	0.000
Very High	16.0	16.7	-0.020	16.8	16.8	-0.001
Extreme	0.1	0.0	0.009	0.1	0.1	0.001
Unknown	1.4	1.4	0.008	1.4	1.4	0.000

# Baseline patient characteristics (continued)

Characteristics	Before 1:1 PS matching			After 1:1 PS matching		
	HCTZ	ACEI	SMD	HCTZ	ACEI	SMD
<b>Combined Comorbidity Score (mean)</b>	0.0	0.9	-0.435	0.2	0.2	-0.008
<b>Health Service Utilization Intensity (mean)</b>						
No. Ambulatory Encounters	6.7	7.4	-0.096	6.8	6.8	-0.002
No. Emergency Room Encounters	0.3	4.0	-0.113	0.3	0.3	-0.005
No. Inpatient Hospital Encounters	0.1	3.0	-0.326	0.1	0.1	-0.014
No. Non-acute Institutional Encounters	0.0	0.1	-0.144	0.0	0.0	-0.008
No. Other Ambulatory Encounters	1.6	3.2	-0.269	1.8	1.9	-0.013
No. Filled Prescriptions	13.6	16.0	-0.182	14.2	14.2	0.001

# Incidence rate (per 1,000 person-years) & hazard ratio

Population	Number of matched pair	Basal cell carcinoma			Squamous cell carcinoma		
		HCTZ	ACEI	HR (95% CI)	HCTZ	ACEI	HR (95% CI)
<b>Overall</b>	5,211,321	2.78	2.82	0.99 (0.97, 1.00)	1.66	1.60	1.04 (1.02, 1.06)
<b>Gender</b>							
Male	2,427,149	3.33	3.35	0.99 (0.97, 1.01)	1.89	1.78	1.06 (1.03, 1.09)
Female	2,716,796	2.30	2.37	0.98 (0.95, 1.00)	1.47	1.46	1.01 (0.98, 1.04)

# Incidence rate (per 1,000 person-years) & hazard ratio

Population	Number of matched pair	Basal cell carcinoma			Squamous cell carcinoma		
		HCTZ	ACEI	HR (95% CI)	HCTZ	ACEI	HR (95% CI)
<b>Age (years)</b>							
<50	1,268,629	0.50	0.57	0.88 (0.82, 0.94)	0.13	0.14	0.92 (0.80, 1.00)
50-59	1,095,379	1.52	1.67	0.91 (0.88, 0.95)	0.55	0.61	0.91 (0.85, 0.98)
60-74	1,753,457	3.78	3.84	0.99 (0.97, 1.01)	2.10	2.01	1.05 (1.02, 1.08)
≥75	942,684	6.04	6.02	1.01 (0.98, 1.03)	4.69	4.52	1.04 (1.01, 1.07)

# Incidence rate (per 1,000 person-years) & hazard ratio

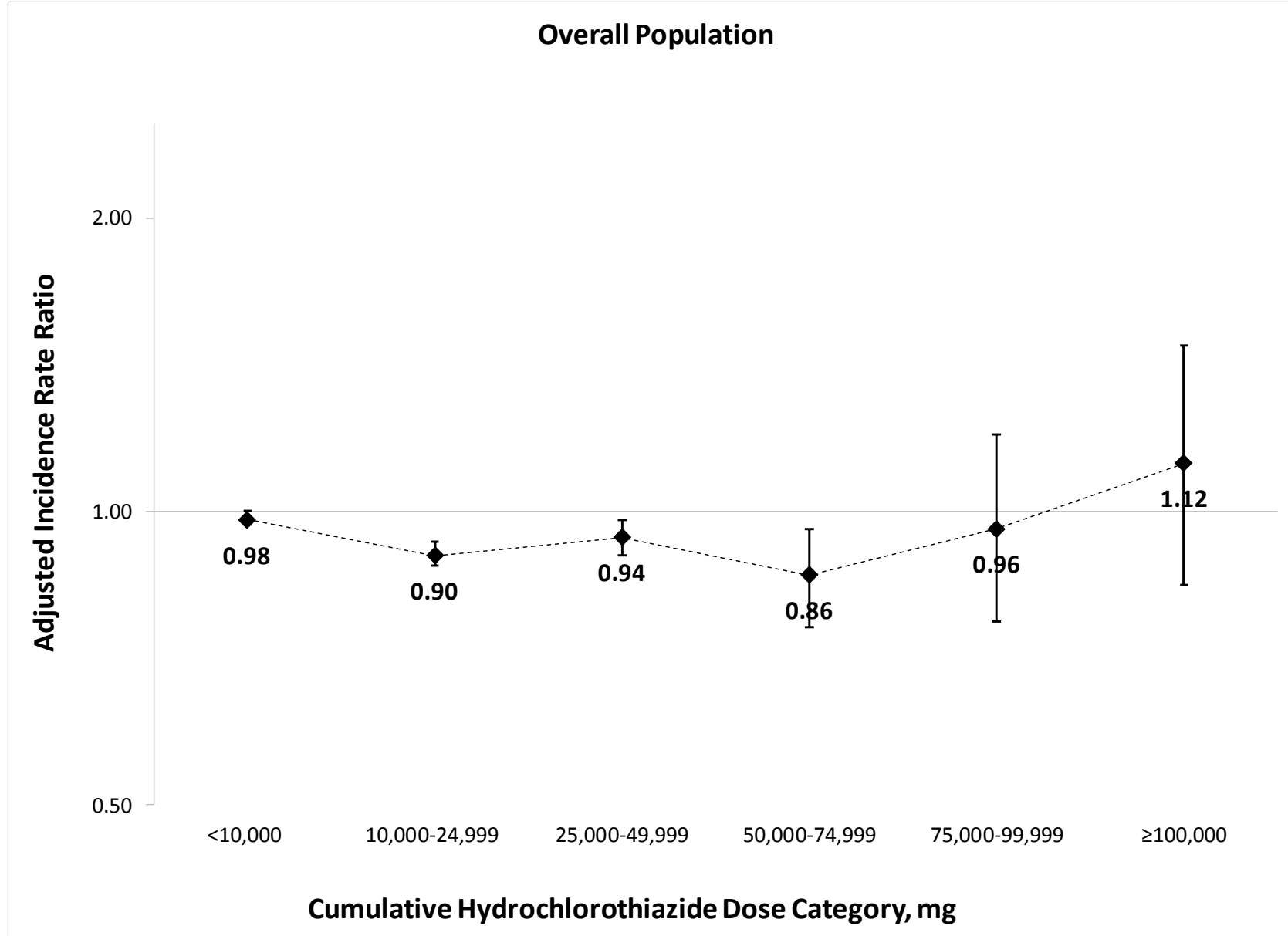
Population	Number of matched pair	Basal cell carcinoma			Squamous cell carcinoma		
		HCTZ	ACEI	HR (95% CI)	HCTZ	ACEI	HR (95% CI)
<b>Race</b>							
White	2,246,784	4.48	4.12	1.09 (1.07, 1.11)	2.92	2.55	1.15 (1.12, 1.17)
Black	336,205	0.04	0.05	0.83 (0.55, 1.27)	0.04	0.05	0.84 (0.54, 1.30)
Asian	103,864	0.14	0.08	1.72 (1.13, 2.61)	0.07	0.10	0.72 (0.44, 1.15)
Pac. Islander	13,377	0.27	0.25	1.09 (0.54, 2.21)	0.22	0.13	1.69 (0.70, 4.09)
Am. Indian	15,997	1.31	0.81	1.58 (1.06, 2.35)	0.44	0.48	0.95 (0.52, 1.72)
Unknown	2,260,367	1.91	1.99	0.96 (0.93, 0.99)	0.86	0.85	1.02 (0.98, 1.06)



# Dose-response relation for basal cell carcinoma

Cumulative HCTZ dose	No. patients	Mean follow-up (days)	No. events	Incidence rate ratio (95% CI)
<10,000mg	5,192,912	648	26,495	0.98 (0.97, 1.00)
10,000 – 24,999mg	1,329,225	618	6,157	0.90 (0.88, 0.93)
25,000 – 49,999mg	424,149	697	1,987	0.94 (0.90, 0.98)
50,000 – 74,999mg	95,738	706	281	0.86 (0.76, 0.96)
75,000 – 99,999mg	32,808	730	82	0.96 (0.77, 1.20)
≥100,000mg	13,842	1,173	49	1.12 (0.84, 1.48)
ACEI users	5,192,912	879	35,357	Reference

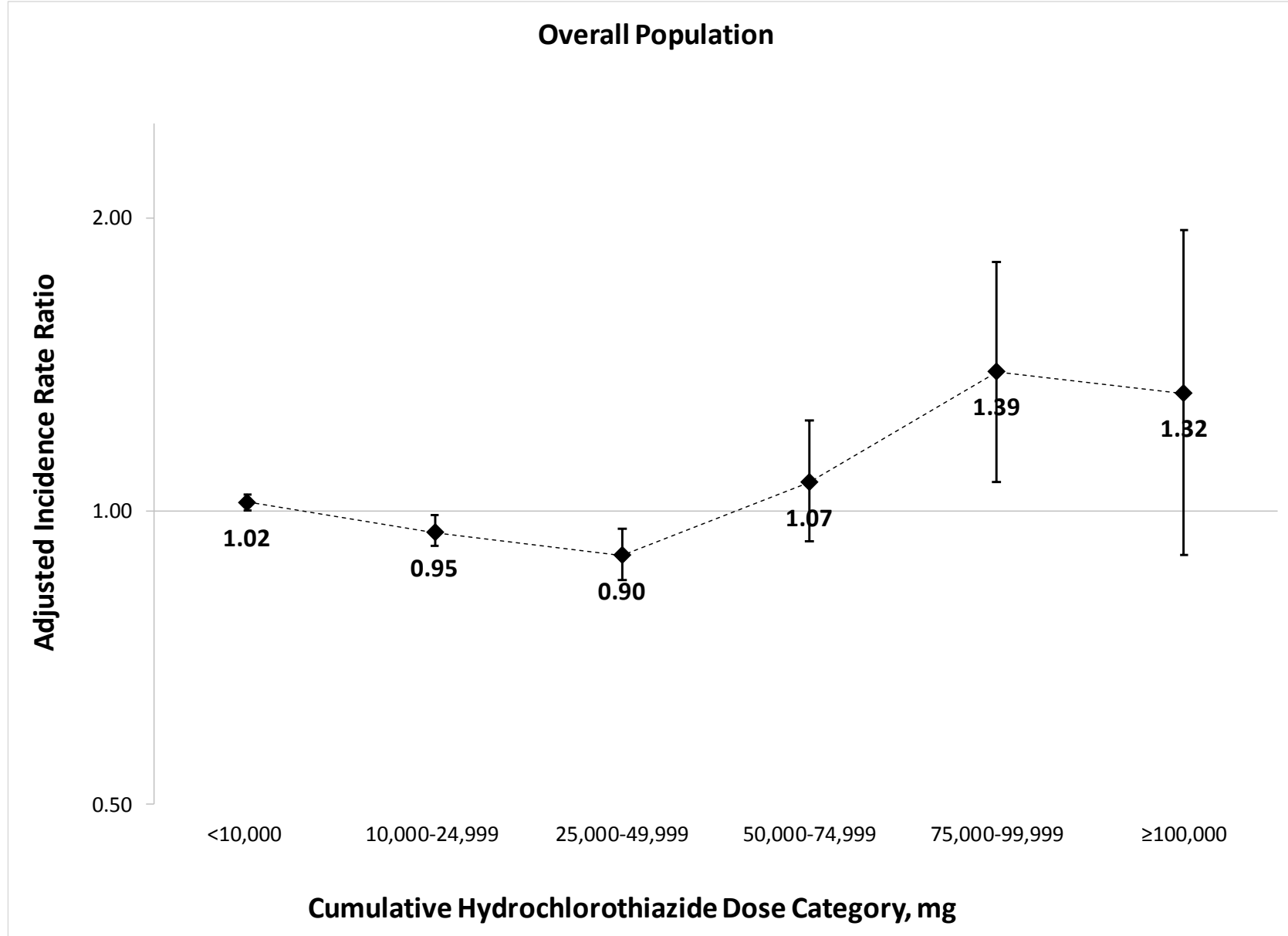
# Dose-response relation for basal cell carcinoma

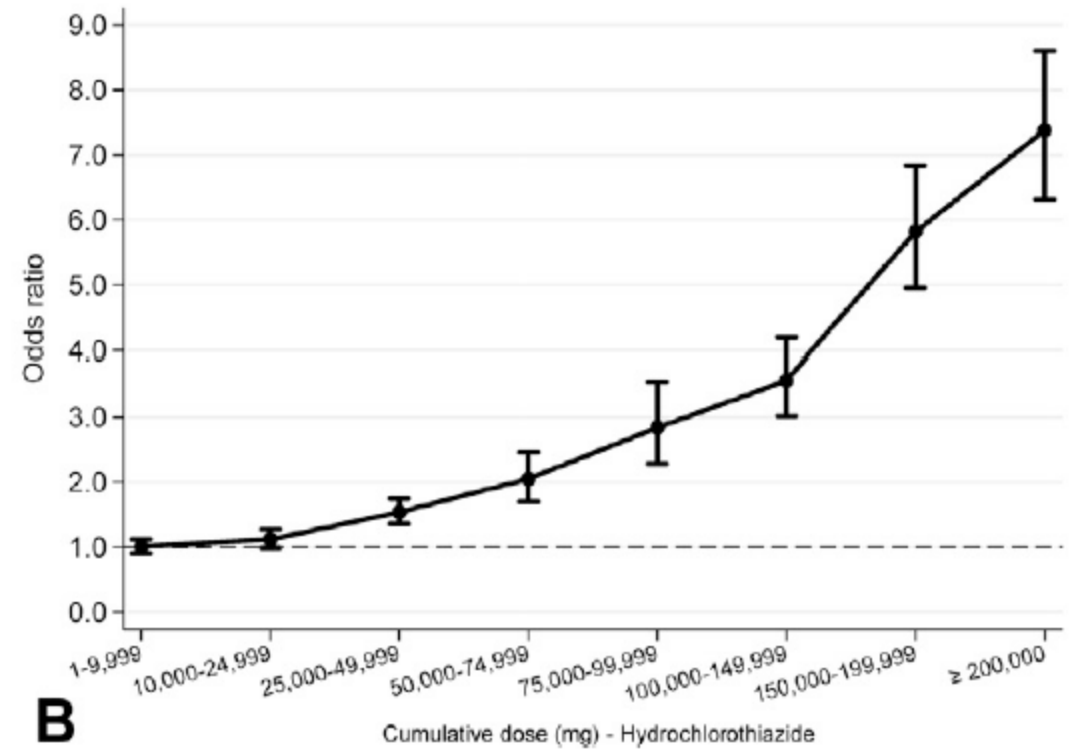
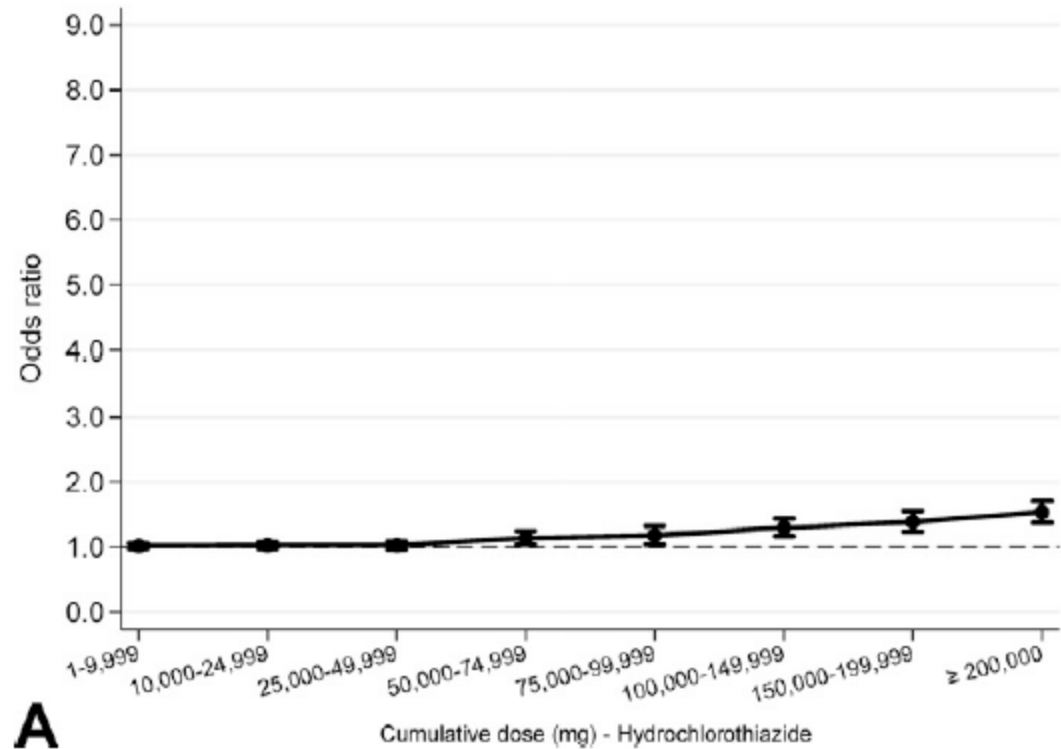


# Dose-response relation for BCC, adjusting for time-varying age

Cumulative HCTZ dose	No. patients	Mean follow-up (days)	No. events	Incidence rate ratio (95% CI)
<10,000mg	5,192,912	648	15,815	1.02 (1.00, 1.04)
10,000 – 24,999mg	1,328,085	618	3,765	0.95 (0.92, 0.99)
25,000 – 49,999mg	423,639	697	1,089	0.90 (0.85, 0.96)
50,000 – 74,999mg	95,648	706	186	1.07 (0.93, 1.24)
75,000 – 99,999mg	32,778	730	59	1.39 (1.07, 1.80)
≥100,000mg	13,830	1,173	27	1.32 (0.90, 1.94)
ACEI users	5,192,912	878	20,119	Reference

# Dose-response relation for squamous cell carcinoma





**Fig 2.** Dose-response pattern between cumulative hydrochlorothiazide dose and risk of basal cell carcinoma (**A**) and squamous cell carcinoma (**B**). Error bars represent 95% confidence intervals.

# Discussion

- Strengths of the study
- Limitation of the study

# Discussion

- What else would you like to see to determine if there is an association between HCTZ use and NMSC?

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**<https://www.distributedanalysis.org>**



# Sensitivity analysis

Population	Basal cell carcinoma			Squamous cell carcinoma		
	Excluding outcomes occurring in the first 2 years	Defining outcome over a 60-day period	Defining outcome over a 180-day period	Excluding outcomes occurring in the first 2 years	Defining outcome over a 60-day period	Defining outcome over a 180-day period
<b>Overall</b>	0.98 (0.95-1.00)	0.98 (0.97-0.99)	0.98 (0.97-0.99)	1.03 (1.00-1.06)	1.04 (1.02-1.05)	1.04 (1.02-1.06)
<b>Gender</b>						
Male	0.98 (0.95-1.02)	0.99 (0.97-1.00)	0.98 (0.97-1.00)	1.05 (1.01-1.10)	1.06 (1.03-1.08)	1.06 (1.04-1.09)
Female	0.96 (0.93-0.99)	0.97 (0.95-0.99)	0.97 (0.95-0.99)	1.01 (0.96-1.06)	1.01 (0.99-1.04)	1.01 (0.99-1.04)
<b>Age (years)</b>						
<50	0.90 (0.82-0.99)	0.87 (0.82-0.92)	0.87 (0.82-0.92)	0.90 (0.75-1.07)	0.94 (0.84-1.06)	0.95 (0.85-1.06)
50-59	0.90 (0.84-0.95)	0.91 (0.88-0.94)	0.90 (0.87-0.93)	0.91 (0.82-1.00)	0.93 (0.88-0.99)	0.94 (0.89-1.00)
60-74	0.97 (0.94-1.01)	0.98 (0.96-1.00)	0.97 (0.95-0.99)	1.06 (1.01-1.11)	1.05 (1.02-1.08)	1.05 (1.02-1.07)
≥75	1.02 (0.98-1.07)	1.01 (0.99-1.04)	1.02 (1.00-1.04)	1.05 (1.00-1.10)	1.04 (1.01-1.07)	1.04 (1.01-1.07)
<b>Race</b>						
White	1.08 (1.05-1.12)	1.09 (1.07-1.10)	1.09 (1.07-1.10)	1.13 (1.09-1.17)	1.14 (1.12-1.17)	1.14 (1.12-1.16)
Black	1.10 (0.49-2.50)	0.86 (0.59-1.26)	0.78 (0.54-1.13)	1.06 (0.54-2.05)	0.82 (0.55-1.24)	0.83 (0.57-1.21)
Asian	1.73 (1.01-2.96)	1.63 (1.12-2.35)	1.66 (1.16-2.36)	1.06 (0.58-1.92)	0.87 (0.57-1.34)	0.84 (0.55-1.28)
Pacific Islander	0.92 (0.36-2.40)	1.12 (0.62-2.03)	1.17 (0.66-2.08)	3.55 (0.98-12.89)	1.23 (0.55-2.75)	1.20 (0.57-2.53)
American Indian	1.63 (0.87-3.03)	1.75 (1.20-2.56)	1.90 (1.32-2.73)	1.47 (0.56-3.88)	0.95 (0.54-1.66)	0.92 (0.54-1.56)
Unknown	0.94 (0.90-0.98)	0.95 (0.93-0.98)	0.95 (0.93-0.97)	1.02 (0.96-1.09)	1.03 (0.99-1.07)	1.03 (0.99-1.07)