

Study Design

Christian Torp-Pedersen

December 10, 2022







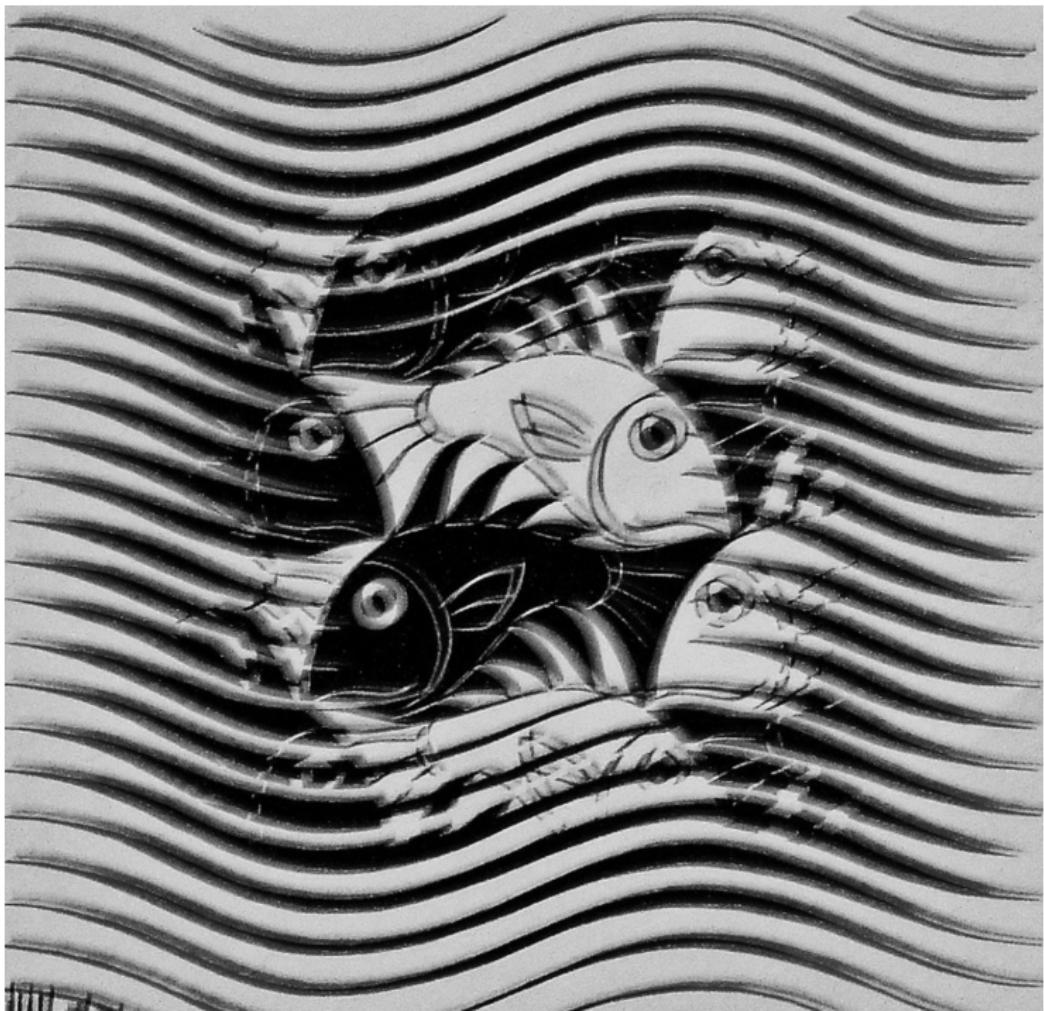
Modern Epidemiology

FOURTH EDITION

Timothy L. Lash

Population and Cohort

- ▶ A closed population does not add members over time and loses only by death. Another definition is population where there is no loss in relation to outcome
- ▶ An open population acquires members over time - and/or loses members
- ▶ A cohort is a population or subpopulation defined in a permanent manner
- ▶ A source population is a population from which a study population is selected
- ▶ A study population is a subset chosen
- ▶ A target population is one from which information is desired



Closed population

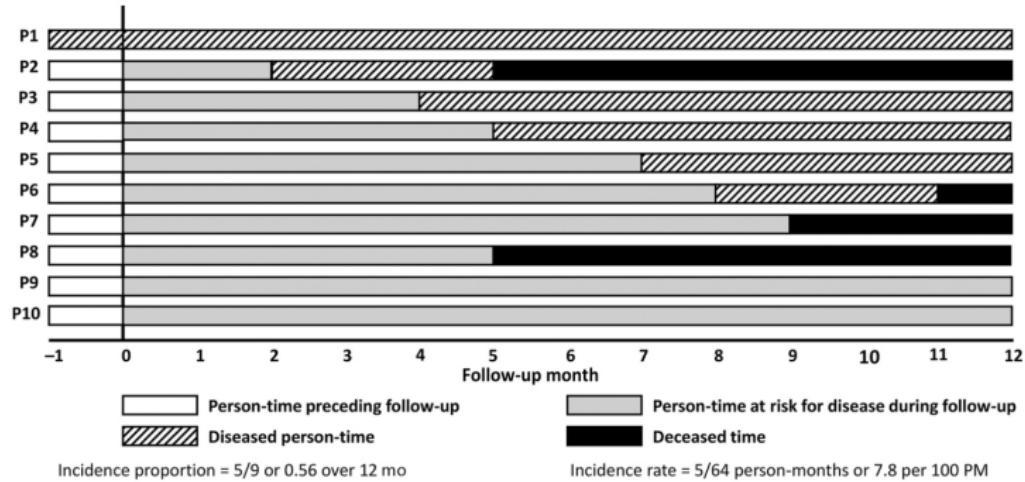


Figure 4.1 Illustration of four basic measures of disease frequency using a population of 10 persons (P1-P10) with person-time depicted 1 month before, and 12 months after, the start of follow-up for the occurrence of a disease.

Open population

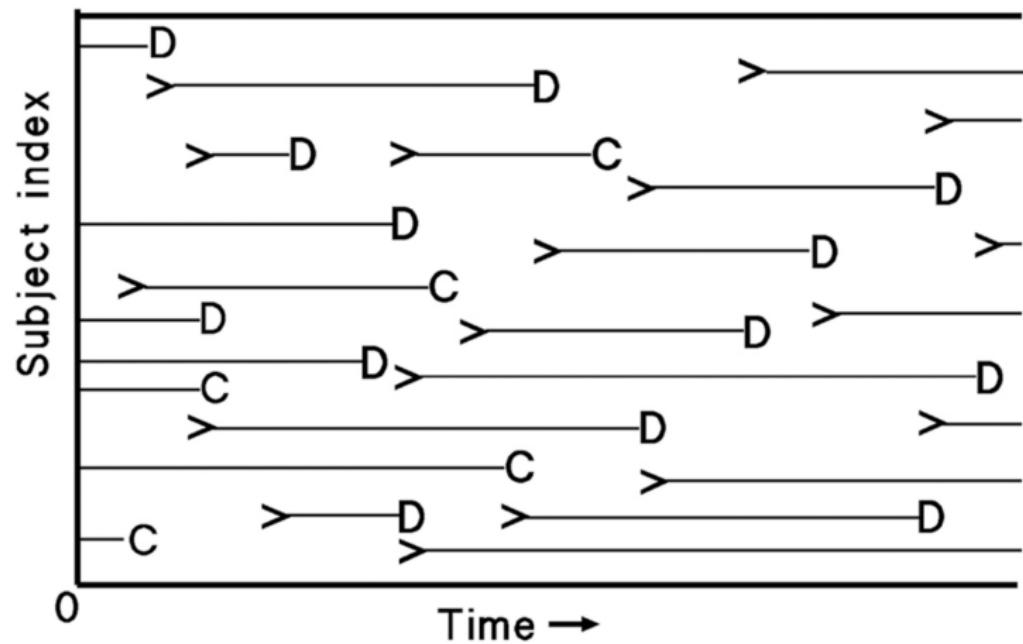
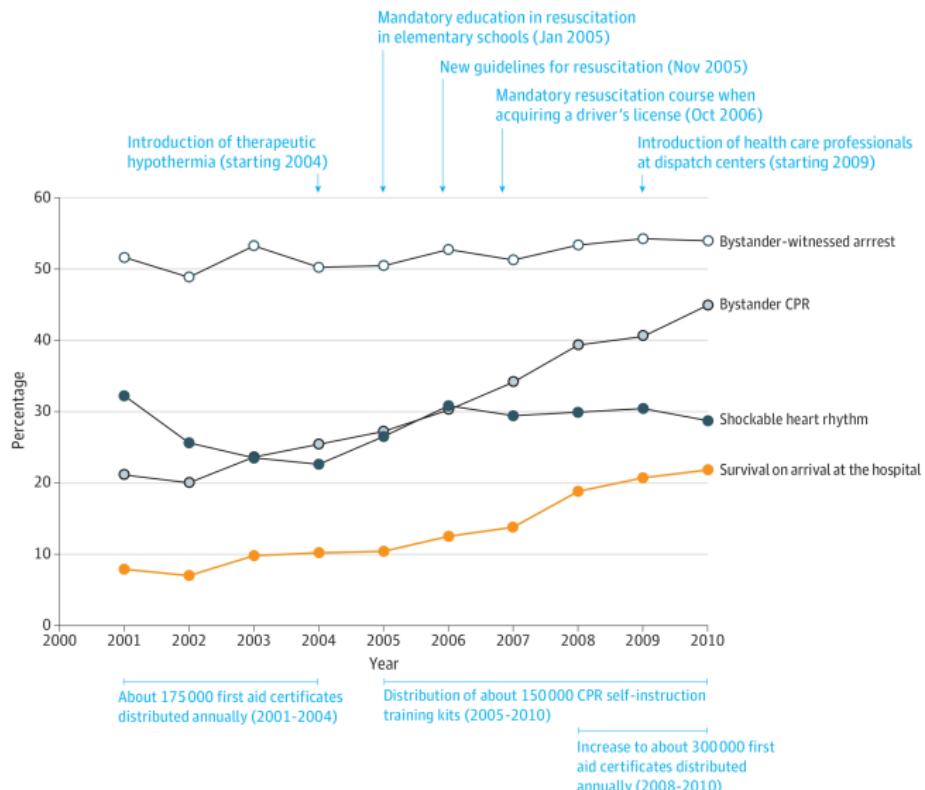
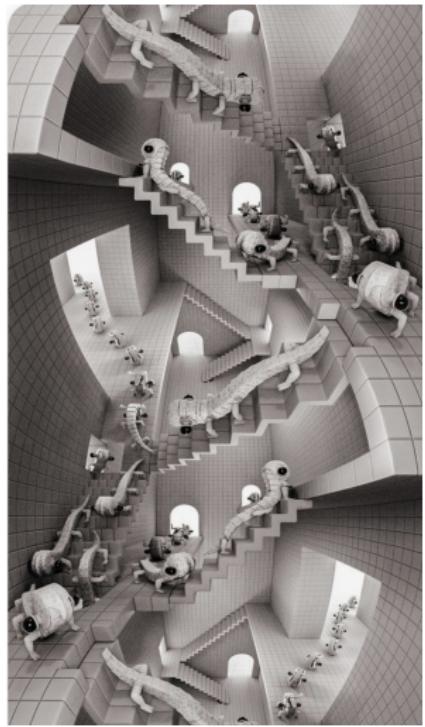


Figure 4.2 Composition of an open population in approximate steady state, by time; > indicates entry into the population, D indicates disease onset, and C indicates exit from the population without the disease.

Cardiac arrest

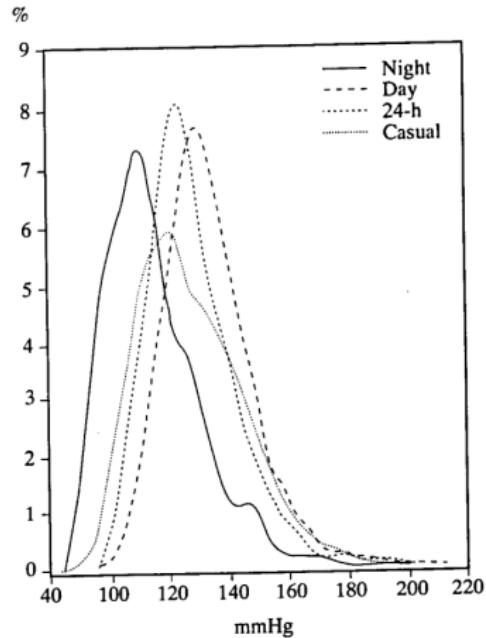
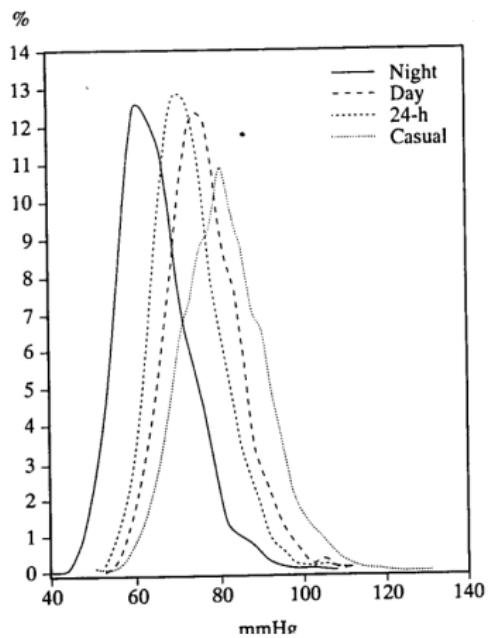




Study Designs

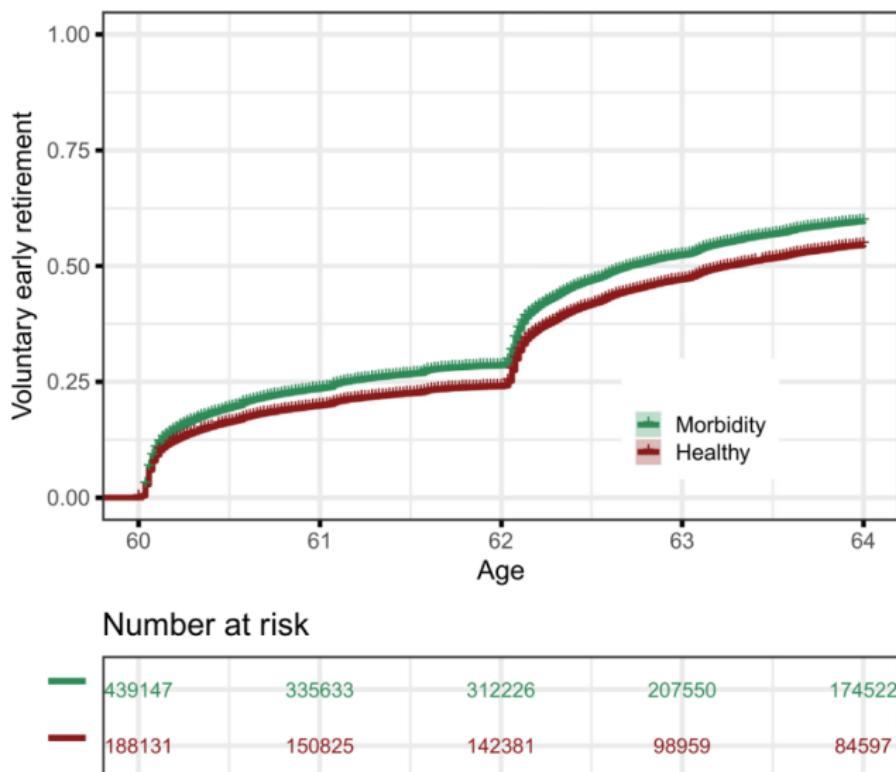
- ▶ Experimental studies
- ▶ Clinical trials
- ▶ Field trials
- ▶ Nonexperimental studies
 - ▶ Cross sectional studies
 - ▶ Cohort studies
 - ▶ Case-control studies
 - ▶ Prospective versus retrospective studies
 - ▶ Proportional mortality studies
 - ▶ Ecological studies

Cross Sectional Study



Rasmussen, Hypertension 1998

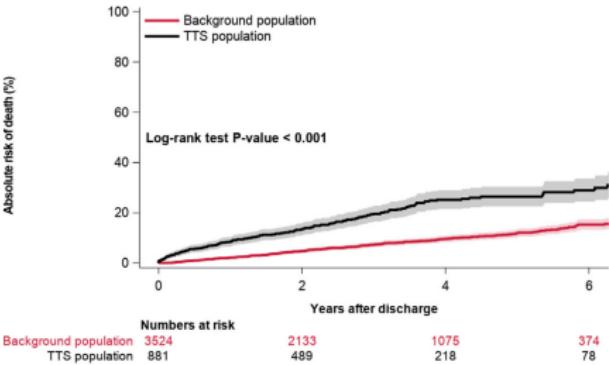
Voluntary retirement - Cohort study



Cohort study - matching

Table 1. Baseline characteristics of patients with takotsubo syndrome matched 1:4 for age, sex and year of diagnosis with individuals from the background population

	Background n = 3,524	TTS n = 881	P value
Demographics			
Age, median (25th–75th percentile)	70 (61–77)	70 (61–77)	N/A
Male, n (%)	372 (10.6)	93 (10.6)	N/A
Comorbidities, n (%)			
Ischemic heart disease*	371 (10.5)	160 (18.2)	<0.001
Mycardial infarction*	134 (3.8)	66 (7.5)	<0.001
Heart failure*	105 (3.0)	51 (5.8)	<0.001
Atrial fibrillation	243 (6.9)	114 (12.9)	<0.001
Ischemic stroke	150 (4.3)	72 (8.2)	<0.001
Cerebrovascular disease	221 (6.3)	104 (11.8)	<0.001
Hypertension	1,331 (37.8)	458 (52.0)	<0.001
Peripheral artery disease	75 (2.1)	36 (4.1)	<0.001
Diabetes	310 (8.8)	99 (11.2)	0.03
Thyroid disease	507 (14.4)	136 (15.4)	0.43
Malignancy	427 (12.1)	156 (17.7)	<0.001
Chronic kidney disease	89 (2.5)	42 (4.8)	<0.001
Chronic obstructive pulmonary disease	213 (6.0)	224 (25.4)	<0.001
Liver disease	71 (2.0)	35 (4.0)	<0.001
Epilepsy	56 (1.6)	37 (4.2)	<0.001
Concomitant medical treatment, N (%)*			
Beta-blockers	558 (15.8)	163 (18.5)	0.06
Calcium-blockers	625 (17.7)	127 (14.4)	0.02
ACEI or ARB	1,024 (29.1)	326 (37.0)	<0.001
Loop diuretics	256 (7.3)	112 (12.7)	<0.001
Lipid-lowering medication	899 (25.5)	271 (30.8)	0.002
Antiplatelets	612 (17.4)	221 (25.1)	<0.001
Oral anticoagulants	211 (6.0)	75 (8.5)	0.007
Antidepressants	463 (13.1)	180 (20.4)	<0.001
Antipsychotics	109 (3.1)	40 (4.5)	0.03
Benzodiazepines	165 (4.7)	67 (7.6)	<0.001



Butt, J. Cardiac Failure 2022

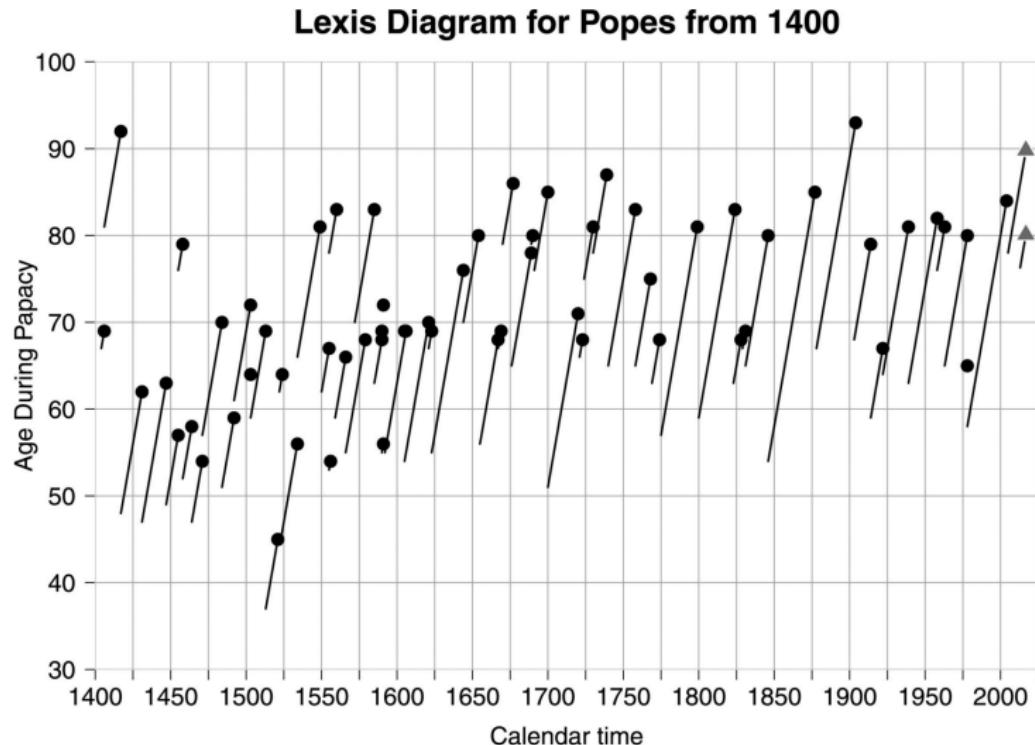
Cohort Study - Time varying exposure

Table 1 Characteristics of study population at baseline

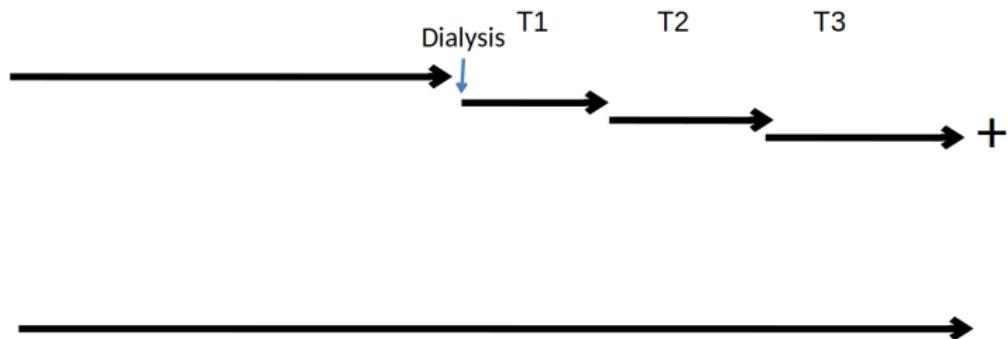
Characteristics	Hemodialysis	Peritoneal dialysis	Kidney transplant (preemptive)	Total (N%)
Total (N%)	6826 (68)	2882 (29)	289 (3)	9997 (100)
Age (years) ^a	65 ± 15	59 ± 15	41 ± 16	62.3 ± 16
	Preexisting heart valve disease			
Aortic valve	285 (4)	111 (3.6)	5 (2)	401 (4)
Mitral valve	172 (2.5)	56 (2)	6 (2)	234 (2.3)
	Comorbidity			
Myocardial infarction	621 (9)	185 (7)	4 (1.4)	810 (8)
Diabetes with complication	1924 (29)	759 (27)	47 (17)	2730 (28)
Diabetes	2133 (31)	818 (29)	48 (17)	2999 (31)
Chronic obstructive lung disease	518 (8)	120 (4)	<4	639 (7)
Peripheral vascular disease	791 (12)	189 (7)	<4	982 (10)
Liver disease	175 (2.5)	35 (1.2)	<4	212 (2.1)
Ischemic heart disease	1476 (22)	496 (18)	15 (5)	1987 (20)
Cardiac arrhythmia disorder	883 (13)	215 (8)	8 (3)	1106 (11)
Previous atrial fibrillation/flutter	746 (11)	174 (6)	5 (2)	925 (9)
Chronic heart failure	1185 (18)	316 (11)	<4	1503 (15)
	Etiology of kidney disease			
Diabetes mellitus	1663 (24)	713 (24)	44 (15)	2420 (24)
Chronic glomerulonephritis	523 (8)	383 (13)	66 (23)	1024 (10)
Vascular and hypertensive nephropathy	855 (13)	365 (13)	15 (5)	1235 (12)
Polycystic kidney disease	386 (6)	253 (9)	46 (16)	685 (7)
Chronic tubulointerstitial nephropathy	340 (5)	115 (4)	17 (6)	472 (5)
Other	1254 (18)	369 (13)	55 (19)	1678 (17)
Unknown	1805 (26)	684 (25)	46 (16)	2535 (25)

^aValues are given as mean, +/− SD or N (%)

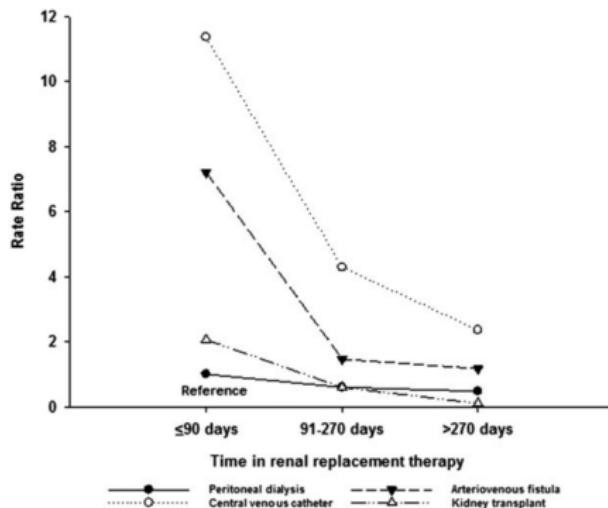
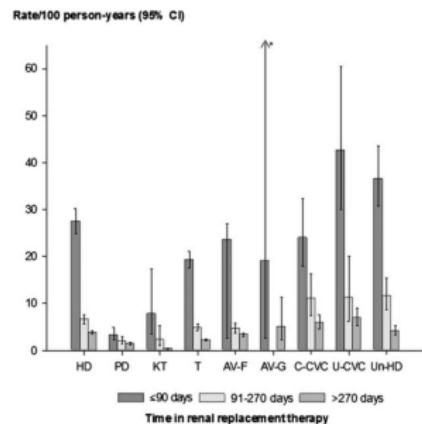
Lexis Diagram



Splitting



Cohort study - Time varying Exposure



Chaudry, Hemodialysis International 2019

Note with classical time dependent analysis

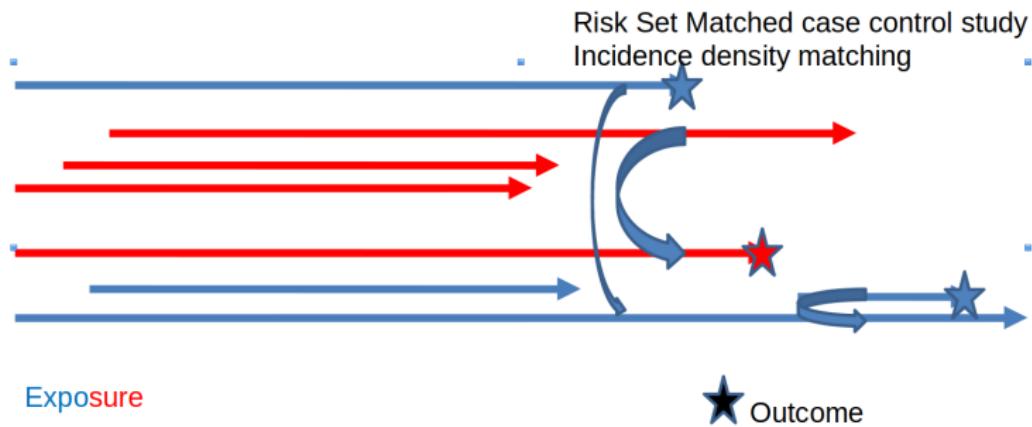
- ▶ What is estimated is the rate ratio at the time of event
- ▶ Exposure is treated as a switch which is immediately on during exposure and immediately off during a break
- ▶ Variables summing cumulative exposure can be calculated, but often erroneously
- ▶ Breaks in exposure can be difficult to summarize
- ▶ LTMLE is possibly the best way to examine future studies



Nested Case Control

Nestet case control study:

Cases and controls are selected from the same population



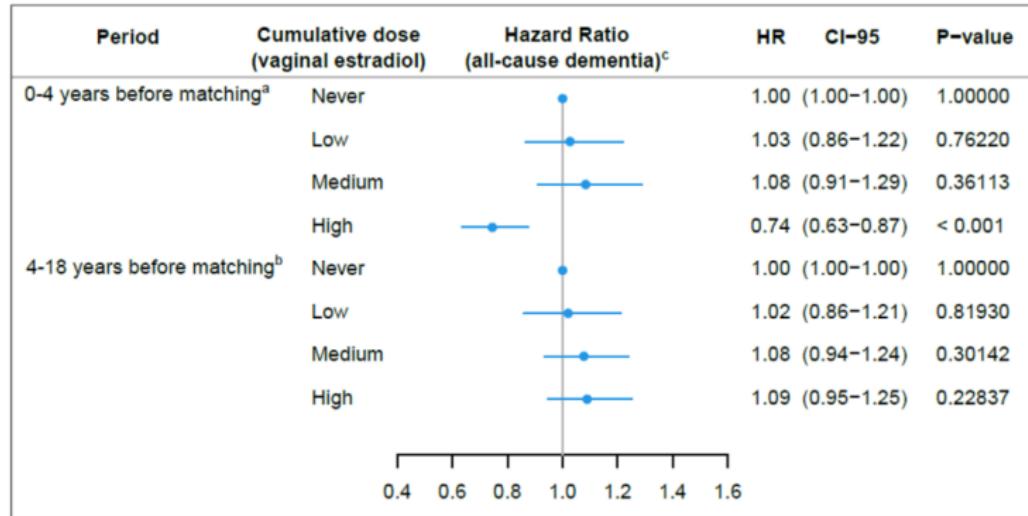
Analysis: Conditional logistic regression stratified by matching identification

Nested Case Control



Nestet case control makes it easy to evaluate time dependent Variable – cumulative exposure – time since exposuree etc.

Estrogen Dementia



Pourhadi, Alzheimer Dementia 2021

Note for Risk-Set-Matching

- ▶ Sampling at each time is independent
- ▶ Therefore, controls can be selected multiple times
- ▶ Controls may later appear as cases
- ▶ Check that multiple selection is not extreme

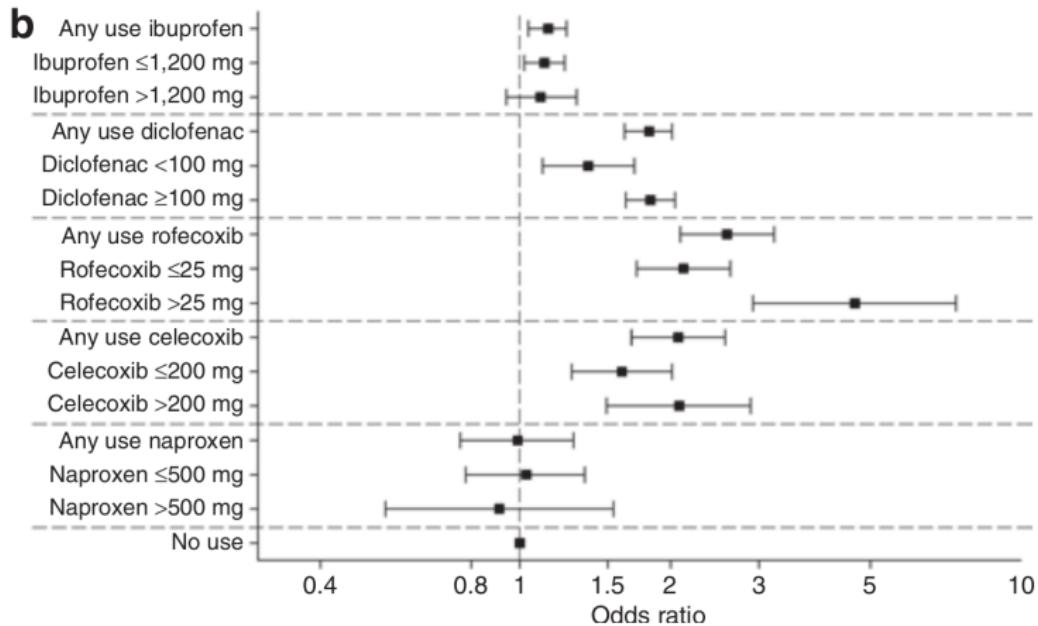
Case Only Design



Case Only Design

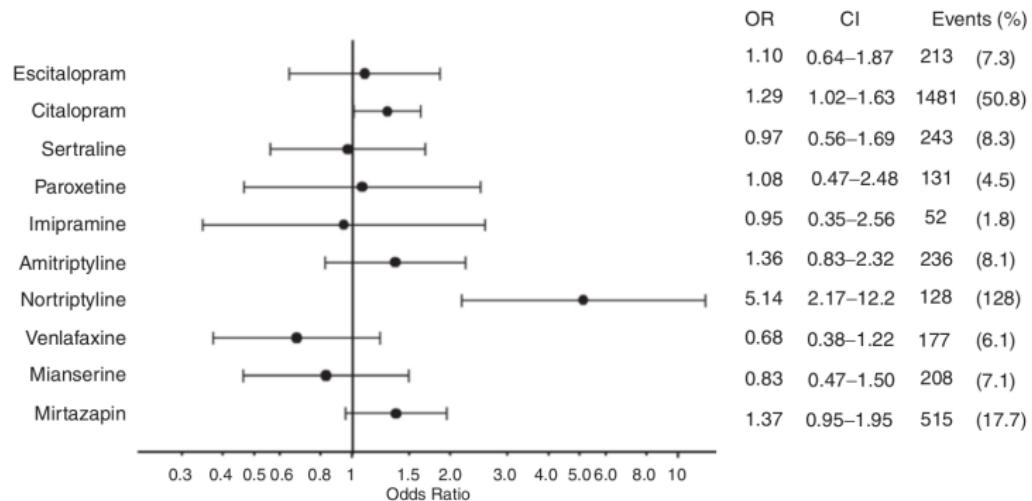
- ▶ Case Cross Over
- ▶ Case Time Control
- ▶ Self Controlled Case Series

Case Cross Over - NSAID Healthy People



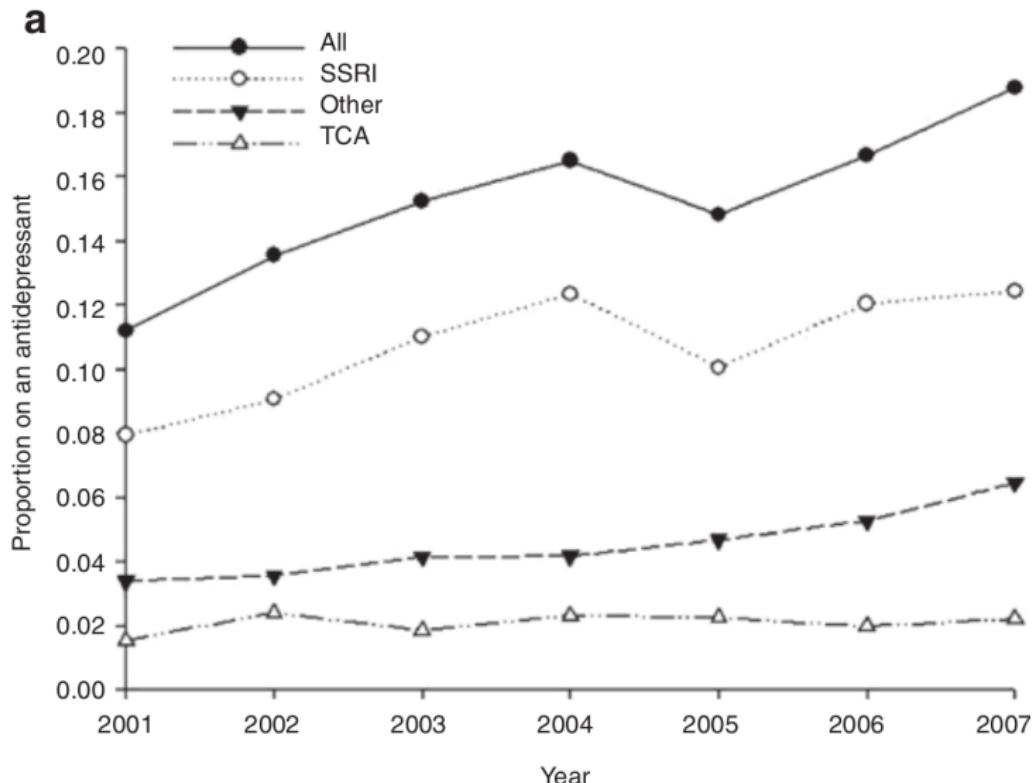
Fosbøll, Clinical Pharmacology and Therapeutics 2009

Case Time Control - SSRI Cardiac Arrest



Weeke, Clinical Pharmacology and Therapeutics 2012

Case Time Control



Persistent User Bias?

Practice of Epidemiology

Persistent User Bias in Case-Crossover Studies in Pharmacoepidemiology

Jesper Hallas*, Anton Pottegård, Shirley Wang, Sebastian Schneeweiss, and Joshua J. Gagne

* Correspondence to Dr. Jesper Hallas, Department of Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, JB Winsløwsvej 19,2, 5000 Odense C, Denmark (e-mail: jhallas@health.sdu.dk).

Initially submitted August 11, 2015; accepted for publication February 10, 2016.

Hallas, American Journal of Epidemiology 2016

Proportional Mortality Study

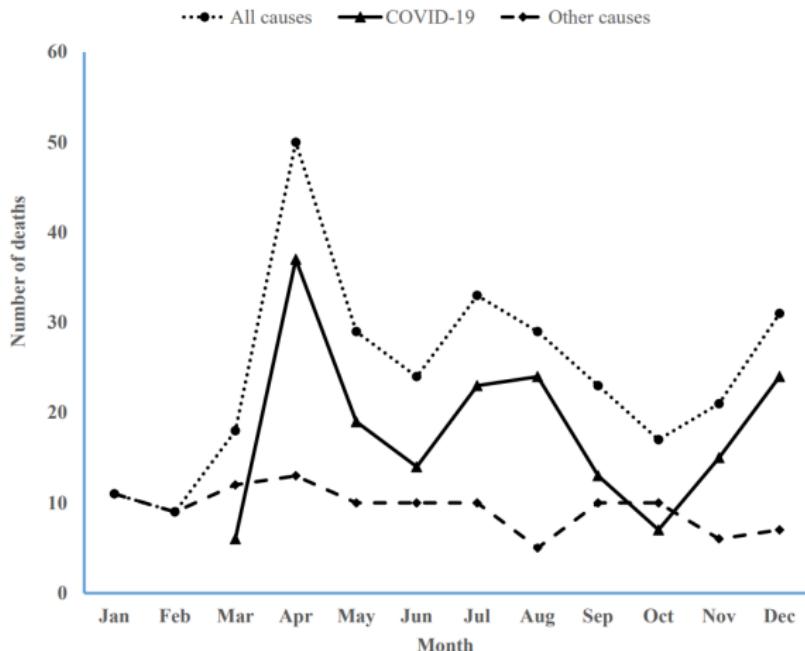
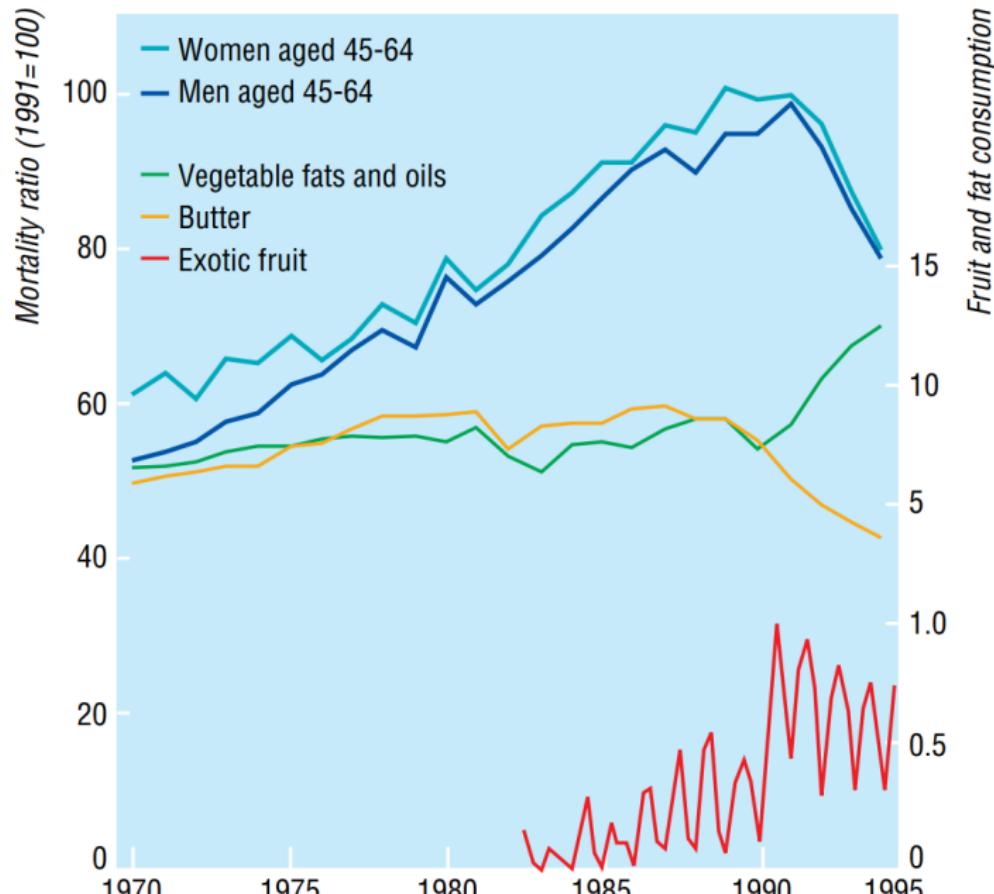


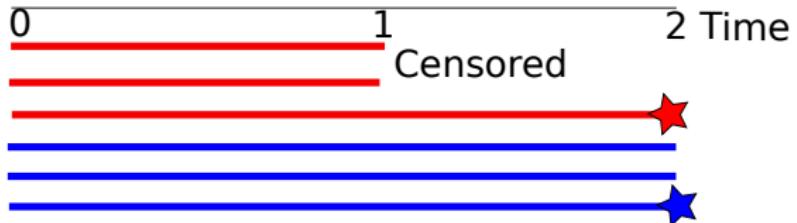
Figure 1.
Monthly frequency and
type of US law
enforcement officer
duty related
deaths, 2020

Ecological Study - Proportional Mortality





Rate and Risk



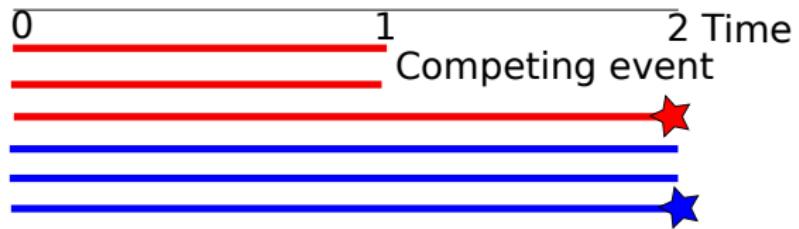
1-Kaplan meier: 0 2/3 Risk Ratio: $1/(1/3)=3$

Rate: $1/4$ $1/6$ Rate Ratio: $(1/4)/(1/6)=1.5$

Risk by Inverse Probability of Censoring Weighting:

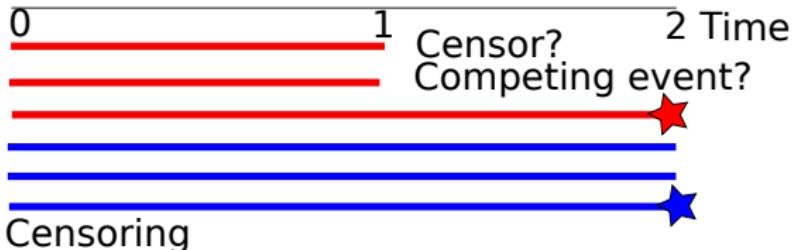
$(1/(1/3))*1/3=1$ $1*1/3=1/3$ Risk ratio: $(1)/(1/3)=3$

Rate and Risk



Cumulative risk: $1/3 * 1 = 1/3$ $1 * 1/3 = 1/3$ Risk ratio: 1

Rate and Risk



Censoring

1-Kaplan meier: 0 2/3 Risk Ratio: $1/(1/3)=3$

Rate: $1/4$ $1/6$ Rate Ratio: $(1/4)/(1/6)=1.5$

Risk by Inverse Probability of Censoring Weighting:

$(1/(1/3))*1/3=1$ $1*1/3=1/3$ Risk ratio: $(1)/(1/3)=3$

Competing risk

Cumulative risk: $1/3*1=1/3$ $1*1/3=1/3$ Risk ratio: 1

Rate and rate ratio: unchanged

CHADS VASC score derivation

Table 4—Univariate and Multivariate Predictive Power of Risk Factors for Thromboembolic Events

	Event Rate With Risk Factor	Event Rate Without Risk Factor	Univariate P Value	OR ^a	Multivariate P Value ^a
Age > 75	11 (3.6)	14 (1.8)	.083	1.46 (0.63-3.35)	.383
Female	16 (3.6)	9 (1.4)	.017	2.53 (1.08-5.92)	.029
Stroke/TIA/TE	5 (5.9)	20 (2.0)	.023	2.22 (0.78-6.35)	.163
Hypertension	19 (2.6)	6 (1.7)	.349	1.01 (0.38-2.66)	.992
Diabetes	8 (4.3)	17 (1.9)	.048	1.79 (0.73-4.40)	.220
Heart failure	6 (2.4)	19 (2.3)	.967	0.72 (0.27-1.88)	.493
LVEF < 40	1 (0.8)	12 (2.1)	.335	0.34 (0.04-2.73)	.243
Vascular disease ^b	16 (3.6)	9 (1.5)	.022	2.27 (0.94-5.46)	.063

OR = odds ratio. See Tables 1 and 2 for expansion of other abbreviations.

^aAll results other than LVEF from model without LVEF.

^bCoronary artery disease, peripheral vascular disease, or a previous thromboembolism other than stroke/TIA.

Lip, Chest 2010

