Kohorte studier

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Kursus i basal farmakoepidemiologi 2018

Maja Hellfritzsch Poulsen

Kohorte

En konkret persongruppe

Kohortedesign

Giver eksponering X og outcome Y?

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Tidspunkt for indtræden i kohorten

Kohortedesign

Giver eksponering X og outcome Y?

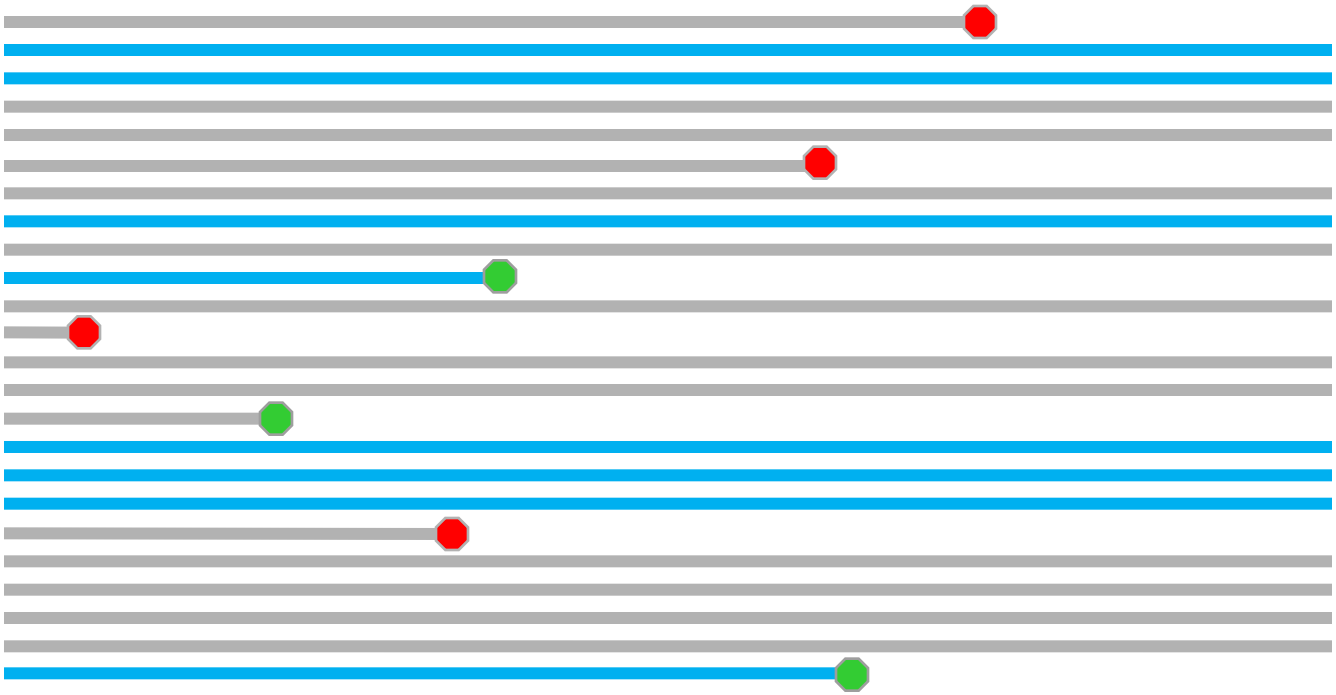
Tidspunkt for indtræden i kohorten

Kohortedesign

Giver eksponering X og outcome Y?

Outcome

Censurering



Start

Slut

Kohorte vs. kohortestudie

Kohorte

En konkret persongruppe

Kohortestudie

Undersøgelse af sammenhængen mellem en eksponering og et eller flere outcomes via et kohortedesign

= analytisk (/outcome) studie

Observationelt kohortestudie vs. RCT

Overordnet samme koncept: eksponerede og ikke-eksponerede følges over tid ift. udfald af outcome

Helt store forskel er allokering af eksponeringen: bevidst vs. tilfældigt
Og derved forskellig håndtering af confounding

<u>Andre hyppige forskelle</u>
Populationen: mindre selekteret i kohortestudiet
Outcome assessment

Øvelse: Design et kohortestudie

Brug af beta-blokere og risiko for depression?

Warfarin og NOAC i forhold til
risiko for hjerneblødning?

Brug af statiner og (nedsat) risiko for hoftefrakturer?

Design af kohortestudiet

Identifikation og definition af kohorten

Tid i kohorten (follow-up)

Inddeling af kohorten ift. eksponeringsstatus

Vurdering af sammenhæng mellem eksponering og outcome(s)

Identifikation af kohorten

Hele DK (evt. bestemt køn og/eller alder)

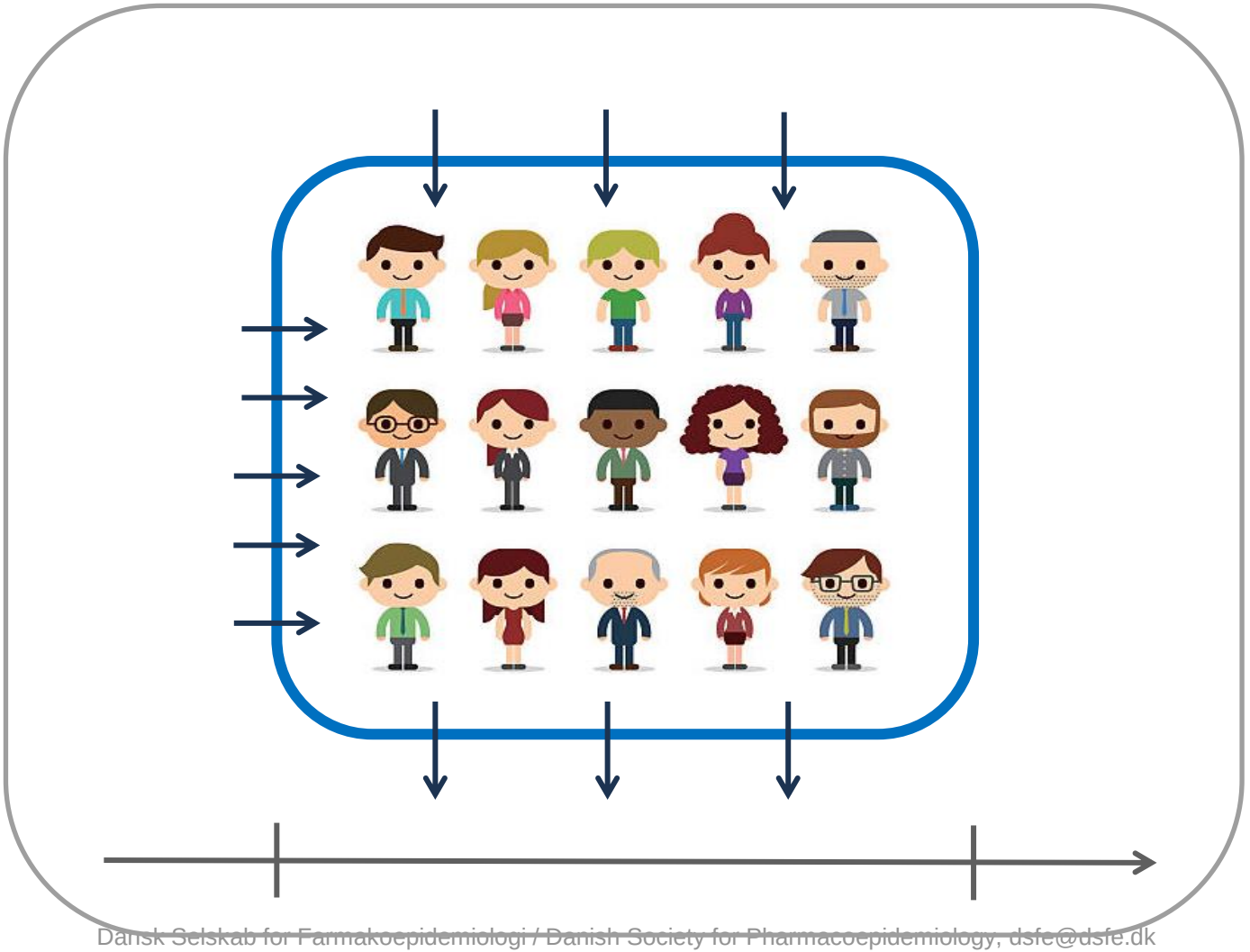
Patienter med en bestemt sygdom

Brugere af et bestemt lægemiddel

Osv.

Træder ind i kohorten når de opfylder inklusionskriterierne for studiet

Kohorten



Bidrag til kohorten

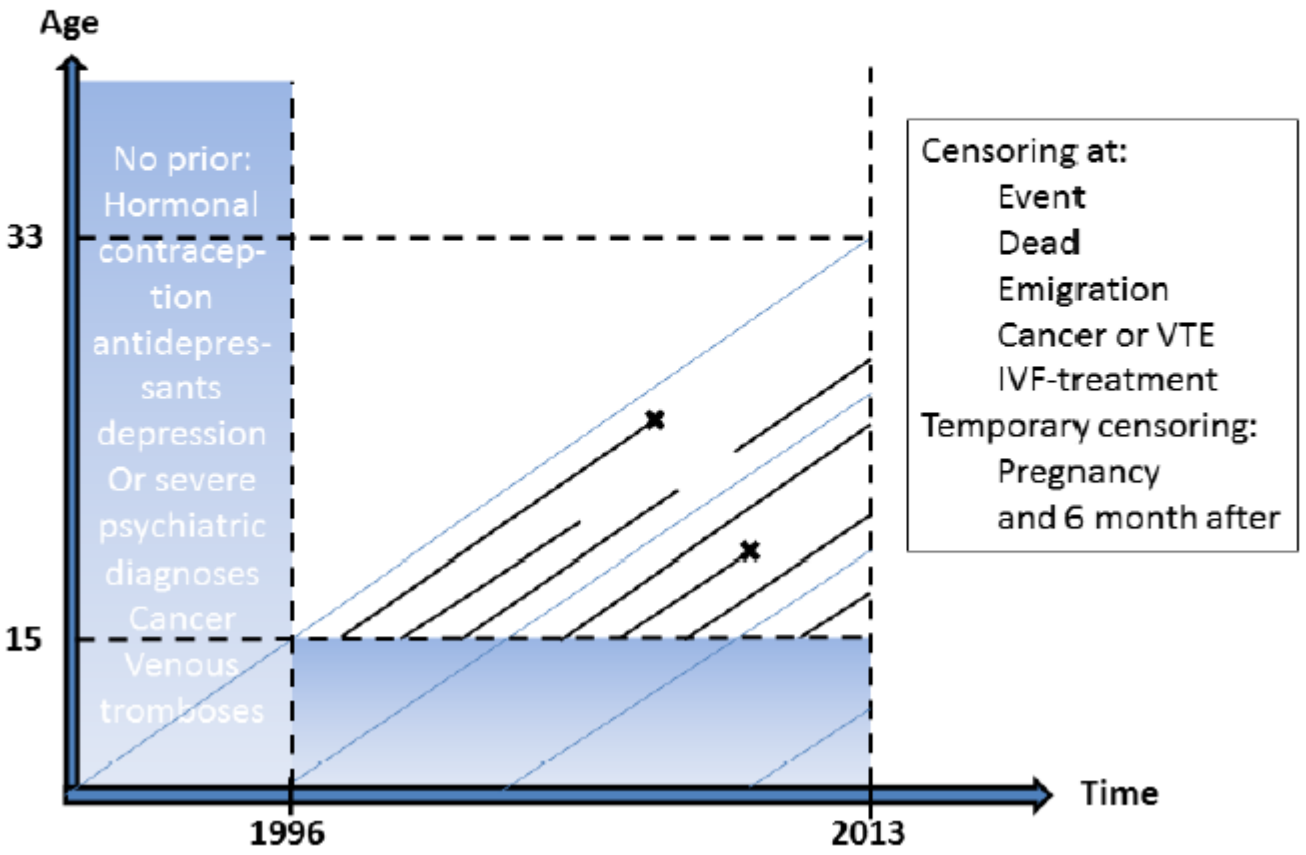
Personerne følges i kohorten for udfald af outcome fra indgang i studiet til:

De censureres (=død, migration, outcome, evt. behandlingsophør/skift, eksklusionskriterium)

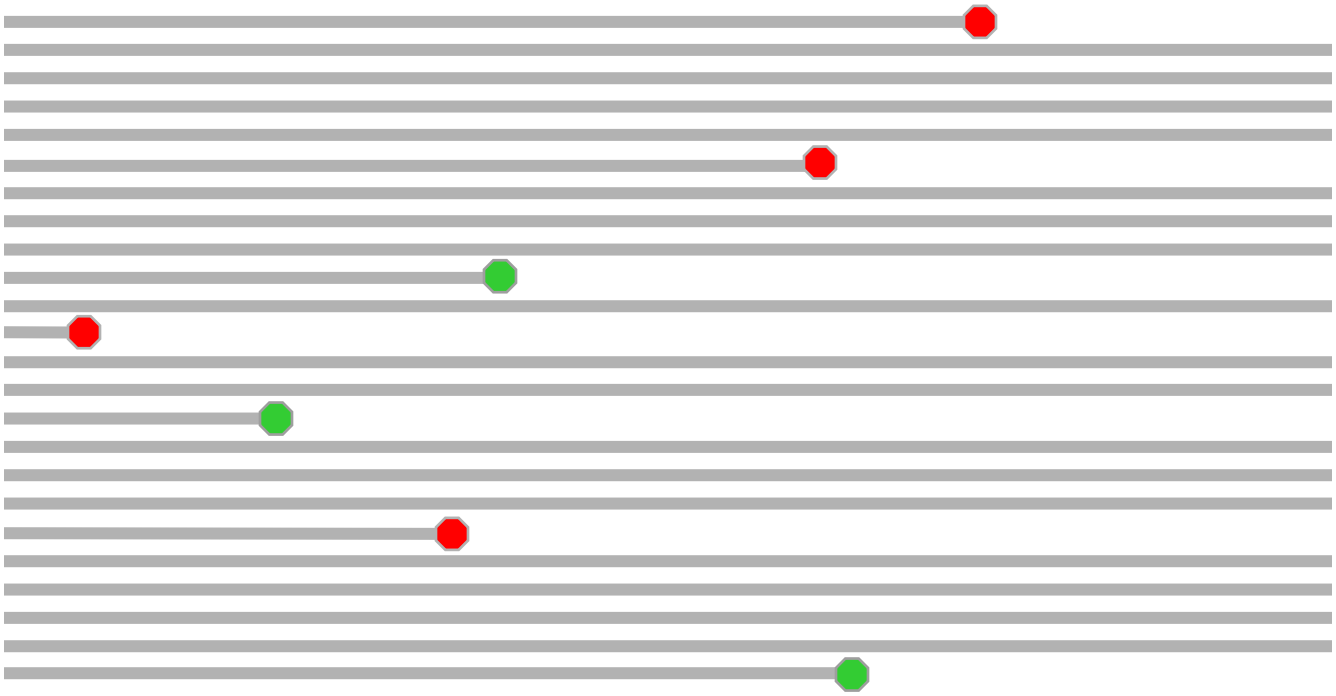
Studiets løbetid stopper (for den enkelte eller overall)

Den tid de følges kaldes "follow-up"

FIGURE S2. Lexis diagram: a cohort of women followed from age 15 through the period 1996–2013



Follow-up



Follow-up for den enkelte er (oftest) variende

Erfaring pr. person vs. erfaring pr. (person-)tid

Person-tid: mål for bidrag af "erfaring" til kohorten

Eksempel: 5 person-år kan være erfaringen fra:

1 person i 5 år

el.

2 personer i 2,5 år

el.

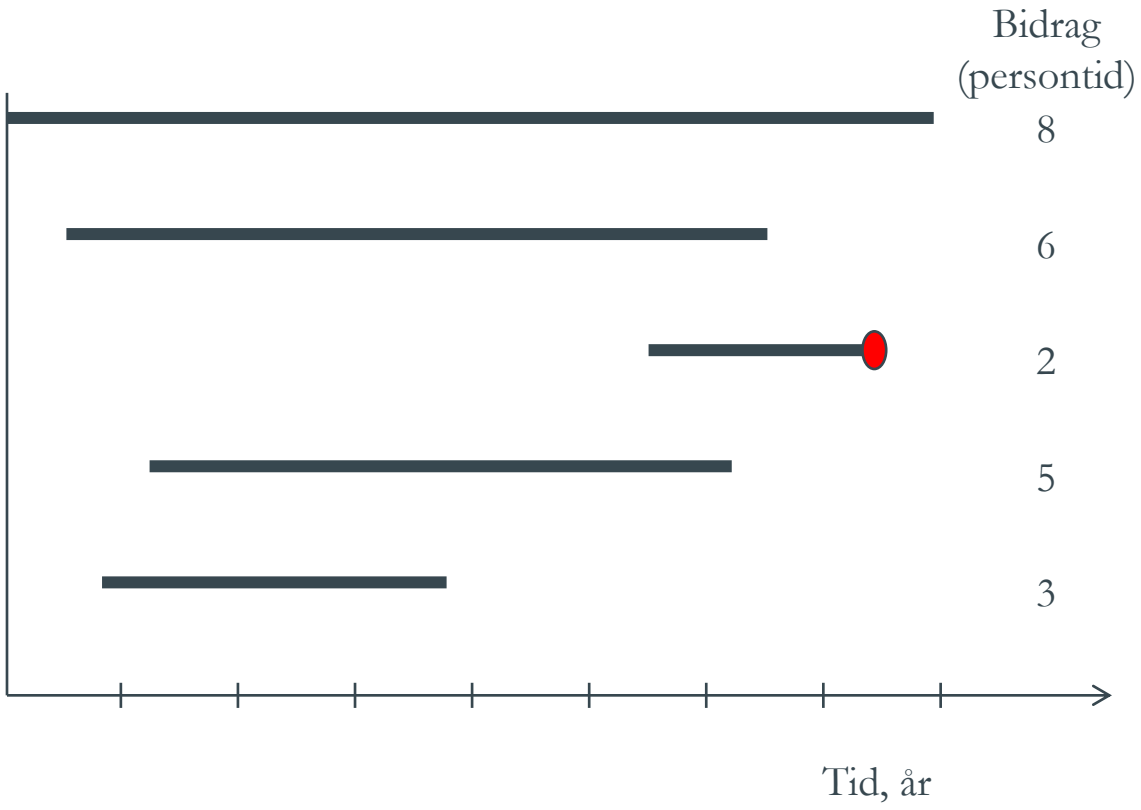
5 personer i 1 år

el.

10 personer i 6 mdr.

Osv…..

Incidensrate = events pr. persontid



Incidensrate

= 1 event /

24 person-år

= 0,0417/PY

= 4,17 / 100PY

Inddeling af kohorten ift. eksponering

Eksponeret vs. ikke eksponeret

IR i en ikke behandlet population

NB. Gavnlige effekter kan ikke studeres med en ikke-behandlet kohorte som sammenligning

Eksponering A vs. eksponering B

"Comparative effectiveness/safety"

"Active comparator"

Tager (til dels) højde for confounding by indication

Afhænger af forskningsspørgsmålet og risikoen for confounding by indication

Inddeling af kohorten ift. eksponering

Eksponeret på index dato = eksponeret resten af follow-up
(Ala "intention-to-treat")

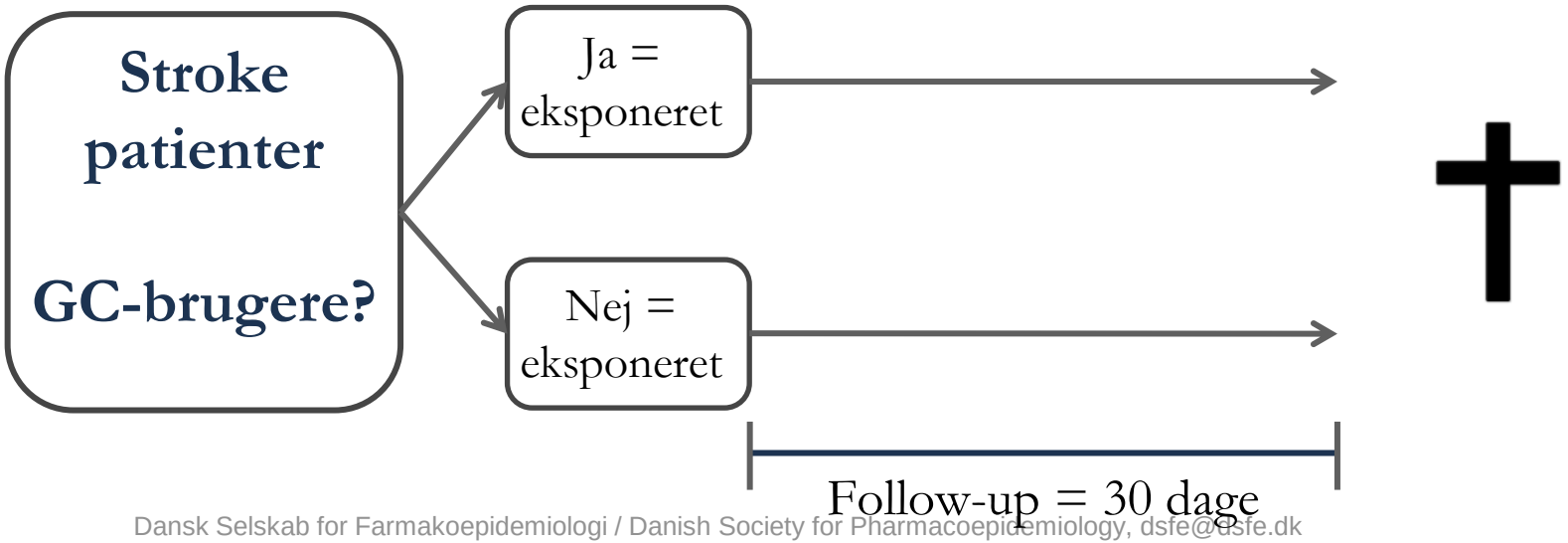
Hensynstagen til ændringer i eksponeringsstatus i løbet af follow-up
(Ala "per-protocol")

Valget kan være lige til højrebenet

Preadmission Use of Glucocorticoids and 30-Day Mortality After Stroke

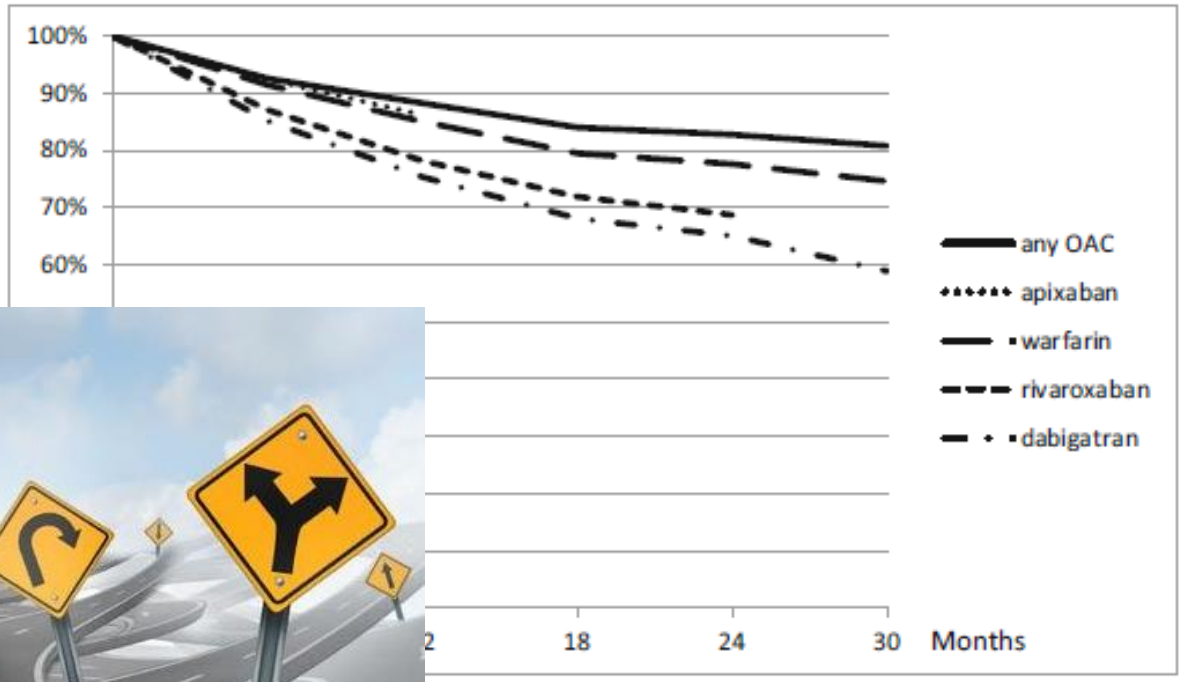
Jens Sundbøll, MD; Erzsébet Horváth-Puhó, PhD; Morten Schmidt, PhD; Olaf M. Dekkers, PhD; Christian F. Christiansen, PhD; Lars Pedersen, PhD; Hans Erik Bøtker, PhD; Henrik T. Sørensen, PhD

(*Stroke*. 2016;47:829-835. DOI: 10.1161/STROKEAHA.115.012231.)



Og så kan det være kompliceret…

Fig. 2 Unadjusted persistence with anticoagulant treatment in non-valvular atrial fibrillation patients with CHA_2DS_2VASc scores 2–9. The analysis comprises 16,096 OAC initiations in 14,426 individual patients



Forslund et al. EJCP 2015


ITT-like
PP-like

Fordele og ulemper ved metoderne

ITT-like	Per-protocol like
Analysemæssigt simpelt	Analysemæssigt mere komplekst
Studerer effekten af at blive sat i behandling/have været i behandling	Studerer effekten af at være i behandling
Mindre følsomt overfor tidsafhængig confounding	Mere følsomt overfor tidsafhængig confounding
Jo længere opfølgning jo højere risiko for betydelig misklassifikation af eksponeringen	Giver mulighed for at studere avancerede eksponeringer (behandlingslængde, kumulativt brug, tidligere brug)

Hvilken metode til hvilke studier?

ITT-like	Per-protocol like
Ingen/begrænset behov for at vurdere ændringer i eksponering i løbet af follow-up	Betydelige ændringer i eksponeringen i løbet af follow-up som der bør tages højde for
Ingen behov for forfinelse af eksponeringen	Kortvarige episoder med eksponering i løbet af follow-up
Stor risiko for tidsafhængig confounding	Lægemiddeleksponering med begrænset persistens i studier med lang follow-up
Hvis man ønsker at matche eksponerede og ikke-eksponerede	Behov for/ønske om forfinelse af eksponeringen

Hvilken metode til hvilke studier?

Det afhænger af forskningsspørgsmålet!

Hvis muligt (og hvis det giver mening) så lav begge!

Vurdering af associationen mellem eksponering og outcome

Sker outcomes hyppigere under eksponering end under ingen eksponering (/komperator)?

Person-tid

Outcome measure	Events	Follow-up (PY)	Rate (/1000 P	IRR	ade HR (95%CI)
Excessive anticoagulation‡					
Cont. use of branded	5665	224 282	25		1.0 (ref.)
Cont. use of generic	36	1349	27		1.1 (0.8–1.5)
Switch TO generic	53	1940	27		1.1 (0.8–1.5)
Switch FROM generic	11	375	29		1.2 (0.7–2.2)
Increased INR‡					
Cont. use of branded	1581	228 430	7		1.0 (ref.)
Cont. use of generic	12	1376	9		1.3 (0.7–2.2)
Switch TO generic	17	1995	9		1.2 (0.7–2.0)
Switch FROM generic	6	384	16		2.3 (1.0–5.0)*
Bleeding‡					
Cont. use of branded	4232	225 627	19		1.0 (ref.)
Cont. use of generic	26	1363	19		1.0 (0.7–1.5)
Switch TO generic	37	1958	19		1.0 (0.8–1.5)
Switch FROM generic	5	378	13		0.7 (0.3–1.7)
Excessive anticoagulation, fatal					
Cont. use of branded	773	229 615	3		1.0 (ref.)
Cont. use of generic	$n < 5$§	1390	2		0.6 (0.2–2.0)
Switch TO generic	7	2014	3		1.1 (0.5–2.3)
Switch FROM generic	$n < 5$§	388	3		0.8 (0.1–5.6)
Thromboembolism					
Cont. use of branded	2585	227 047	11		1.0 (ref.)
Cont. use of generic	39	1354	29		2.5 (1.8–3.5)*
Switch TO generic	20	1971	10		0.9 (0.6–1.5)
Switch FROM generic	$n < 5$§	379	8		0.7 (0.2–2.2)

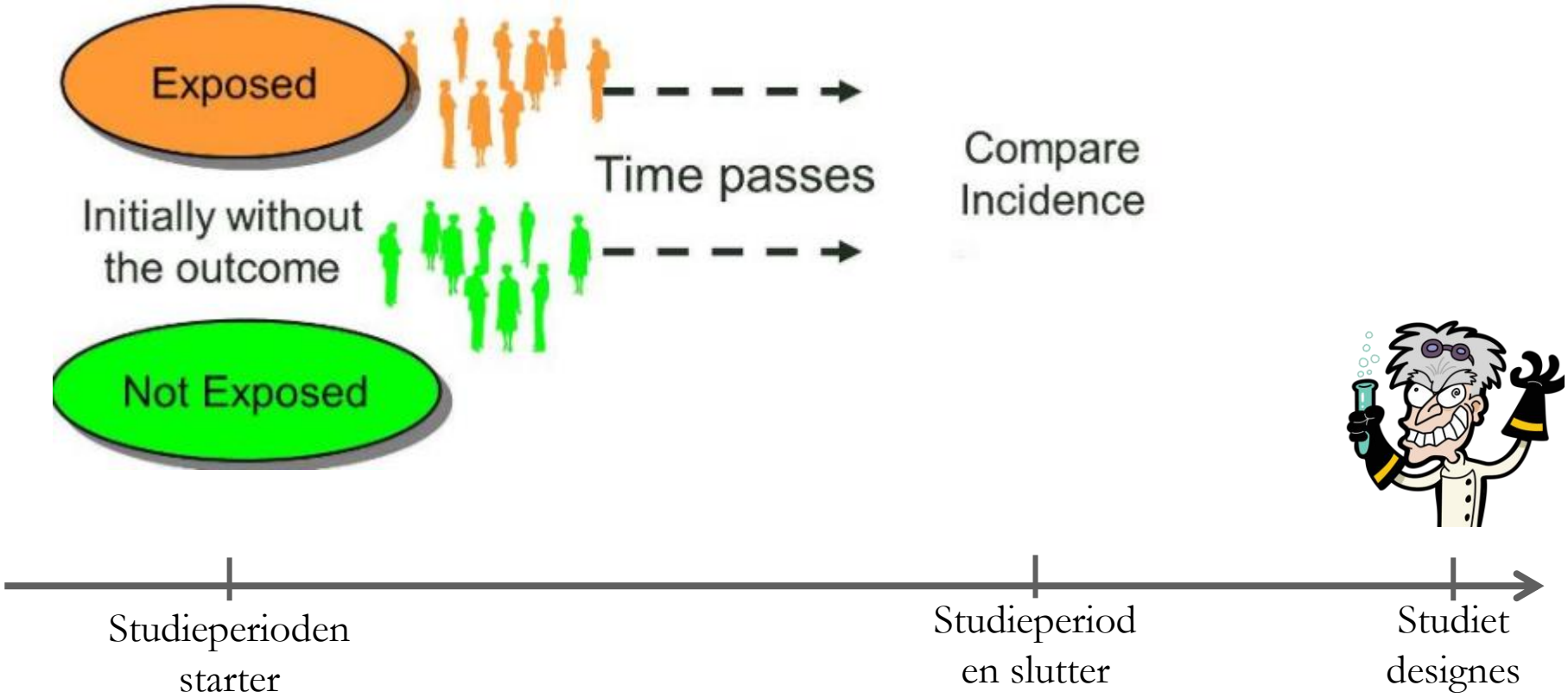
DSFE

Personer

Table 2. Preadmission Glucocorticoid Use and 30-Day Mortality Estimates Following Stroke

Glucocorticoid Use	Mo[KIP]k, % (95% CI)	Mortality Rate Ratio (95% CI)	
		Unadjusted	Adjusted*
Ischemic stroke			
Nonuse	10.2 (10.0–10.4)	1 (reference)	1 (reference)
Former use	13.6 (11.9–15.6)	1.36 (1.17–1.58)	1.17 (1.01–1.36)
Current use	19.5 (18.3–20.8)	2.01 (1.86–2.16)	1.58 (1.46–1.71)

*Adjusted for sex, age groups, and the individual comorbidities and comedications listed in Table 1.


Exposed
Initially without the outcome
Not Exposed
Time passes
Compare Incidence
Studieperioden starter
Studieperiod en slutter
Studiet designes

Eksempel på kohortestudie

Brug af inhalationssteroid efter indlæggelse for KOL og risiko for død/ny indlæggelse

Start follow-up: Udskrivelsesdagen

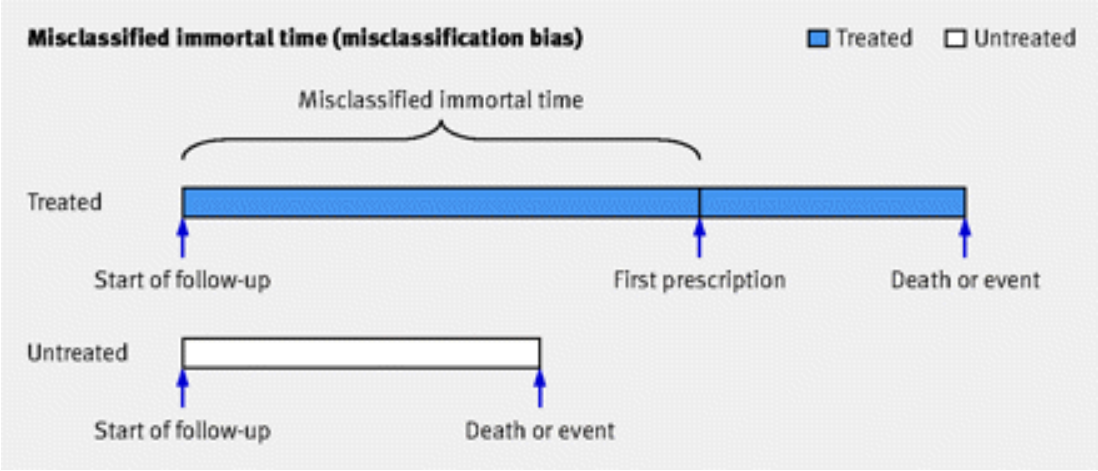
Allokering i eksponeringsgrupper (+/- steroid) baseret på om der indløses en recept indenfor 90 dage

Hvor er fejlen??

Immortal time bias

Allokering baseret på viden om hvad der kommer til at ske!

Event-fri follow-up inden eksponeringen (=immortal time) allokeres som eksponeret!



Suissa. PDS 2007

Resultat: får eksponeringen til at se bedre ud

Fristende…

Kohortestudie eksempel

Association of Hormonal Contraception With Suicide Attempts and Suicides

Charlotte Wessel Skovlund, Ph.D., Lina Steinrud Mørch, Ph.D., Lars Vedel Kessing, D.M.Sc., Theis Lange, Ph.D., Øjvind Lidegaard, D.M.Sc.

Objective: The purpose of this study was to assess the relative risk of suicide attempt and suicide in users of hormonal contraception.

Method: The authors assessed associations between hormonal contraceptive use and suicide attempt and suicide in a nationwide prospective cohort study of all women in Denmark who had no psychiatric diagnoses, antidepressant use, or hormonal contraceptive use before age 15 and who turned 15 during the study period, which extended from 1996 through 2013. Nationwide registers provided individually updated information about use of hormonal contraception, suicide attempt, suicide, and potential confounding variables. Psychiatric diagnoses or antidepressant use during the study period were considered potential mediators between hormonal contraceptive use and risk of suicide attempt. Adjusted hazard ratios for suicide attempt and suicide were estimated for users of hormonal contraception as compared with those who never used hormonal contraception.

Results: Among nearly half a million women followed on average for 8.3 years (3.9 million person-years) with a mean age of 21 years, 6,999 first suicide attempts and 71 suicides were identified. Compared with women who never used hormonal contraceptives, the relative risk among current and recent users was 1.97 (95% CI=1.85–2.10) for suicide attempt and 3.08 (95% CI=1.34–7.08) for suicide. Risk estimates for suicide attempt were 1.91 (95% CI=1.79–2.03) for oral combined products, 2.29 (95% CI=1.77–2.95) for oral progestin-only products, 2.58 (95% CI=2.06–3.22) for vaginal ring, and 3.28 (95% CI=2.08–5.16) for patch. The association between hormonal contraceptive use and a first suicide attempt peaked after 2 months of use.

Conclusions: Use of hormonal contraception was positively associated with subsequent suicide attempt and suicide. Adolescent women experienced the highest relative risk.

AJP in Advance (doi: 10.1176/appi.ajp.2017.17060616)

Hormonal contraception is used worldwide by more than 100 million women to avoid unintended pregnancies and to alleviate menstrual pain, heavy bleeding, premenstrual syndrome, and acne. Use of hormonal contraception has been associated with depression and adverse mood effects (1, 2). Apart from the daily burden depression imposes, it also in-

Because mood symptoms are a known reason for cessation of hormonal contraceptive use (9–11), the inclusion of women several years after they started using hormonal contraceptives is likely to cause a selection of those women who can tolerate hormonal contraception, resulting in an underestimation of any potential association between hormonal

Kohorten

Kildepopulation: Kvinder der i perioden 1995-2013 fyldte 15 år

Træder ind i kohorten når de fylder 15 år hvis de forud herfor:

Ikke tidligere har brugt hormonel antikonception

Ikke har et eksklusionskriterium

Tidl. selvmordsforsøg
Brug af antidepressiva
Psykiatriske diagnoser
Cancer diagnoner
Venøs trombose

Tid i kohorten (follow-up)

Statistical Analysis

The study population was followed from entry at their 15th birthday until emigration, death, a first diagnosis of cancer or venous thrombosis, time of event (suicide attempt or suicide), or end of follow-up on December 31, 2013, whichever came first.

Pregnant women were temporarily censored during pregnancy and for 6 months after delivery.

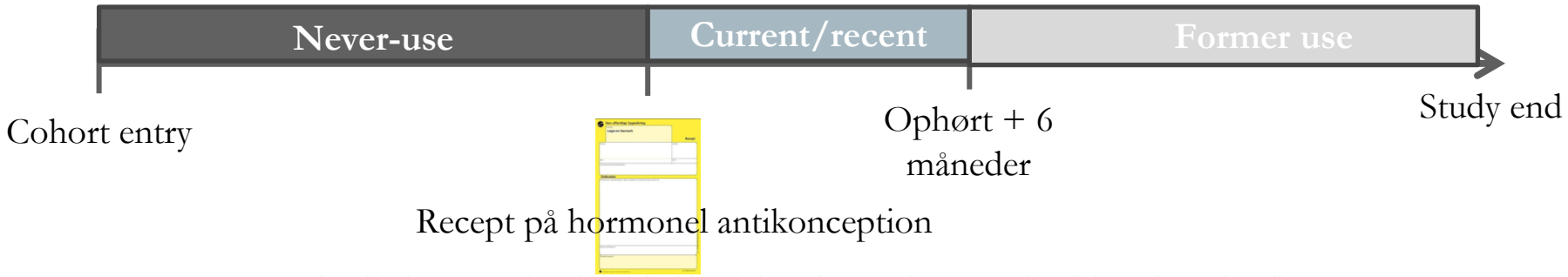
Inddeling ift. eksponeringsstatus

Per-protocol-like: der tages højde for ændringer i eksponeringsstatus

3 eksponeringskategorier

Never-use – Current or recent use - Former use

1 kvinde kan bidrage med person-tid i alle 3 kategorier!



Bidrag til eksponeringsgrupper

475 802 kvinder → mean follow-up: 8,3 år → 3 920 818 personår (PY)

TABLE 1. Clinical and Demographic Characteristics of Women Living in Denmark Who Turned 15 During the Study Period (1996–2013)

	Use of Hormonal Contraception							
Measure	Never		Current or Recent[a]		Former		All	
Suicide attempt	N		N		N		N	
Person-years	1,387,917		2,127,374		405,527		3,920,818	
Events	2,049		3,898		1,052		6,999	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Follow-up (years)	2.9	3.6	6.0	3.8	2.2	2.2	8.3	4.8
Age (years)	17.6	2.9	21.5	3.7	24.0	4.0	21.0	4.0
	N	%	N	%	N	%	N	%

(71 selvmord)

IR, never= 2049 events/1 387 917 PY = **1,48/1000 PY**

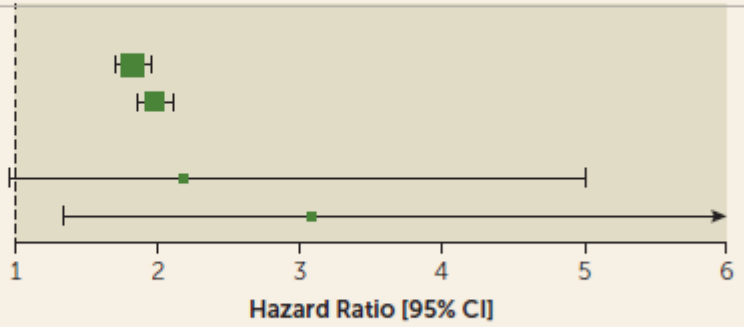
IR, current/recent = 3 898 events/ 2 127 374 PY= **1,83/1000PY**

IR, former = 1 052 / 405 527 PY = **2,6/1000PY**

Sammenhæng?

FIGURE 1. Relative Risk of a First Suicide Attempt and Suicide Among Current Users of Hormonal Contraception Compared With Never-Users[a]

	Person-Years	Events	p	Hazard Ratio [95% CI]
Suicide attempt				
Adjusted 1	2,127,374	3,898	<0.0001	1.82 [1.71, 1.94]
Adjusted 2	2,127,374	3,898	<0.0001	1.97 [1.85, 2.10]
Suicide				
Adjusted 1	2,154,887	42	0.067	2.17 [0.95, 5.00]
Adjusted 2	2,154,887	42	0.067	3.08 [1.34, 7.08]



[a] Adjusted 1: age as underlying time, and adjusted for calendar year; adjusted 2: age as underlying time, and adjusted for calendar year, education, polycystic ovary syndrome, and endometriosis. For suicide attempt, never use (reference; hazard ratio=1.0) person-years=1,387,917, events=2,049. For suicide, never use (reference; hazard ratio=1.0) person-years=1,393,940, events=8.

Samme studie som case-kontrol?

Cases: personer med selvmord/selvmordsforsøg

Kontroller: personer uden selvmord/selvmordsforsøg

Hyppighed af brug af hormonel antikonceptiva forud for indexdato i de to grupper bestemmes

En sammenhæng vil vise sig som hyppigere brug af antikonceptiva hos cases end kontroller (OR > 1)

I et typisk kohortestudie sammenlignes helbredsudviklingen i to eller flere grupper gennem en periode, idet grupperne er karakteriseret ved deres eksponeringsforhold ved undersøgelsens start.

Hvis eksponeringen har helbredsmæssige konsekvenser, skal det vise sig ved forskellig helbredsudvikling i grupperne.

S. Juul et al. Epidemiologi og Evidens. 3. udg.

SPØRGSMÅL?

Dansk Selskab for Farmakoepidemiologi / Danish Society for Pharmacoepidemiology, dsfe@dsfe.dk