BIAS

...

Kursus i basal farmakoepidemiologi 2018

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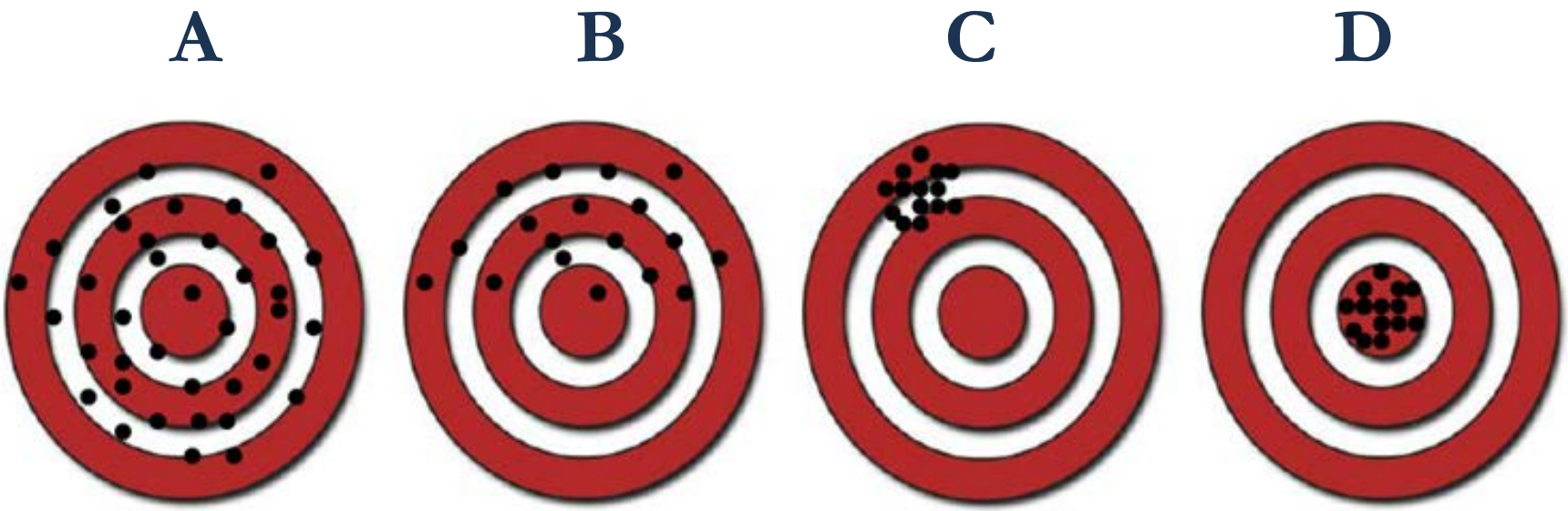
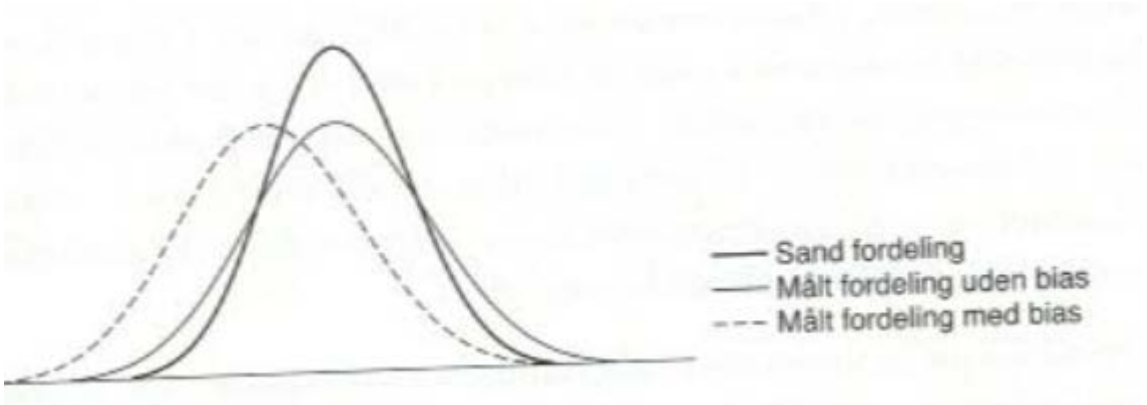
Hvad er bias?

Studiets resultat
≠
”det sande resultat”

En systematisk over- eller undervurdering af en sammenhæng

Pga. en systematisk fejl i studiets udførelse


A
B
C
D


Sand fordeling
Målt fordeling uden bias
Målt fordeling med bias

Typer af bias

Selektionsbias

Informationsbias

Confounding

Typer af bias

Selektionsbias

Informationsbias/misklassifikationsbias

Reverse causation

Detektionsbias

Selektionsbias

Bias der kommer **UDEFRA** materialet, på grund af selektiv rekruttering/inklusion af individer med særlige karakteristika (i forhold til eksponering eller outcome)

Selektionsbias

Når **"at deltage"** (vs. ikke at deltage) hænger sammen med risikoen/sandsynligheden for outcome eller eksponering

Deltagelse: at blive "valgt", selv at vælge deltagelse

Selektionsbias - selvselektion

Eksempel

Undersøgelse af effekten af screening på c.coli dødelighed

Deltagere: frivillige (skal selv melde sig)
Sammenligningsgrundlag: baggrundsbefolkning

Antagelse: uden screening er deres risiko ens

???

Selektionsbias - selvselektion

Dem der deltager har formentlig en risiko for død af c. coli der afviger fra baggrundsbefolkningen selv uden screening!

Lavere risiko: motiveret pga. generel "health-seeking behavior"
Højere risiko: Motiveret pga. konkret bekymring, familiær disposition

Forskel i risiko skyldes ikke (kun) screeningen → resultatet er biased af karakteristika der førte til deltagelse

When an Entire Country Is a Cohort

Denmark has gathered more data on its citizens than any other country. Now scientists are pushing to make this vast array of statistics even more useful

For years, any woman who got an abortion had to accept more than the loss of her fetus: For some unknown reason, she also faced an elevated risk for breast cancer. At least that was what several small case-control studies had suggested before Mads Melbye, an epidemiologist at the Statens Serum Institute in Copenhagen, undertook the largest effort ever to explore the link. He and his colleagues obtained records on 400,000 women in Denmark's national Abortion Register, then checked how many of the same women were listed in the Danish Cancer Register. Their foray into the two databases led to a surprising result: As they reported in *The New England Journal of Medicine* in 1997, there appears to be no connection between abortion and breast cancer.

Their success underscores the value of a trove of data the Danish government has accumulated on its citizenry, which today totals about 5 million people. Other Scandinavian countries have created powerful database systems, but Denmark has earned a preeminent reputation for possessing the most complete and interwoven collection of statistics touching on almost every aspect of life. The Danish government has compiled nearly 200 databases, some begun in the 1930s, on everything from medical records to socioeconomic data on jobs and salaries. What makes the databases a plum research tool is the fact that they can all be linked by a 10-digit personal identification number, cal the CPR, that follows each Dane from cra to grave. According to Melbye, "our regist allow for instant, large cohort studies that impossible in most countries."

Graphic Omitted
Per Publisher
Bell & Howell
Information and Learning

Beauty in numbers. These Danish twins sta ety show at the turn of the 20th century; medical records, part of a database, that are

But Melbye and other scientists think tl can extract even more from this data g mine. They argue that not enough money being spent on maintaining and expand existing databases, and they say that red t is hampering studies that require correlat of health and demographic data. The probl is that, while they have unfettered access more than 80 medical databases maintai

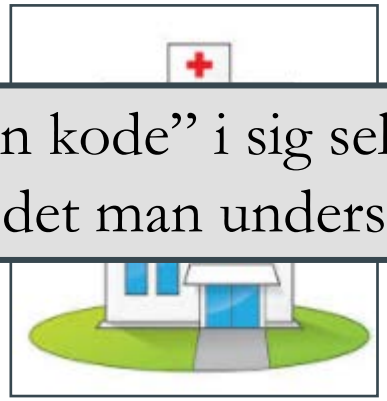
by the Danish Board of Health and public hospitals, their use of 120 demographic databases overseen by the agency Statistics Denmark is tightly restricted. Statistics Den-

Selektionsbias og ”population-based”?

Eks.: Danske diabetes patienter

70%

30%



Selektionbias: risiko hvis det ”at have en kode” i sig selv er associeret med en anderledes risiko for ”det man undersøger”

Studie på danske diabetes patienter

Inklusionskriterium: diagnosekode på diabetes

Informations/misklassifikationsbias

Bias der opstår **INDENI** materialet
som resultat af ukorrekt/inkomplet information om deltagerne (i forhold til eksponering eller outcome)

Differentieret

Ikke-differentieret

Misklassifikation

Sand status	≠	Klassificering i studiet
Syg		Ikke-syg
Ikke-syg		Syg
Eksponeret		Ueksponeret
Ikke-eksponeret		Eksponeret

Afhænger af hvor gode vores datakilder/antagelser er til at adskille:
Syge fra ikke-syge
Eksponerede fra ueksponerede

Misklassifikation: det vigtige spørgsmål

Virker det sandsynligt at graden af korrekt/forkert klassifikation er forskellig for de to grupper man sammenligner i studiet?

Klassifikation af outcome i kohortestudiet
Klassifikation af eksponeringen i case-kontrol studiet

Nej → Non-differentieret misklassifikation

”Lige meget” misklassifikation i grupperne

Grupperne kommer til at ligne hinanden mere ift. det ”man måler på”

Bias mod nul (ingen forskel)

Suicide attempts are known to be underreported (21), but there is no reason to believe that the underreporting would be distributed differently among users and never-users of hormonal contraception, so this circumstance is not likely to affect the associations assessed.

Ja → differentieret misklassifikation

Klassifikation af det vi måler på (fx eksponering) afhænger af hvilken gruppe patienten er i (fx cases i et case-kontrol studie)

Kan give bias i begge retninger

Det klassiske eksempel: recall bias

Mødre til børn med misdannelser vil være bedre til at genkalde sig oplysninger om lægemiddelforbrug and kvinder hvis børn er raske

Detektionsbias: differentieret misklassifikation af outcome

Når sandsynligheden for at få diagnosen øges hvis man er eksponeret

Pga. overvågning, lavere tærskel for undersøgelse

Særlig risiko når kendte/mistænkte lægemiddeleffekter undersøges

Henvisningsbias

Surveillancebias

Detektionsbias, eksempel

Ny forskning: Nye p-piller øger risiko for blodprop

Størstedelen af de danske kvinder er skiftet til ældre typer p-piller på grund af risiko for blodprop. Ny forskning dokumenterer risikoen ved de nyere piller.

MANDAG D. 1. JUNI 2015 KL. 17:07

17-årig fik blodprop: Jeg tænkte slet ikke, at p-piller var farlige

Emilie Rytter fulgte myndighedernes samt lægens anbefaling og fik en recept på en lavrisiko p-pille, så der kunne komme styr på en problematisk menstruation. Alligevel fik hun en blodprop i benet.

Detektionsbias, eksempel

Kvinder med vage symptomer på en dyb venetrombose har højere sandsynlighed for at blive udredt for DVT hvis de tager p-piller

Mindre grad af misklassifikation af milde tilfælde blandt eksponerede

Får associationen "p-piller og blodpropper" til at se stærkere ud

Håndtering/kvalificering: Subgruppeanalyse kun med tilfælde der altid vil føre til hospitalisering/udredning uanset eksponering

Reverse causation

Når en umiddelbar sammenhæng mellem eksponering og outcome faktisk skyldes at outcomet fører til eksponeringen (og ikke omvendt)

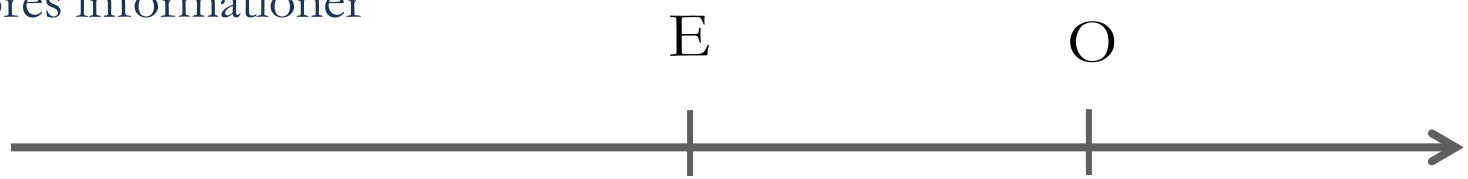
Når eksponeringen bruges til at behandle et tidligt (=før diagnose) symptom på outcomet

= protopatisk bias

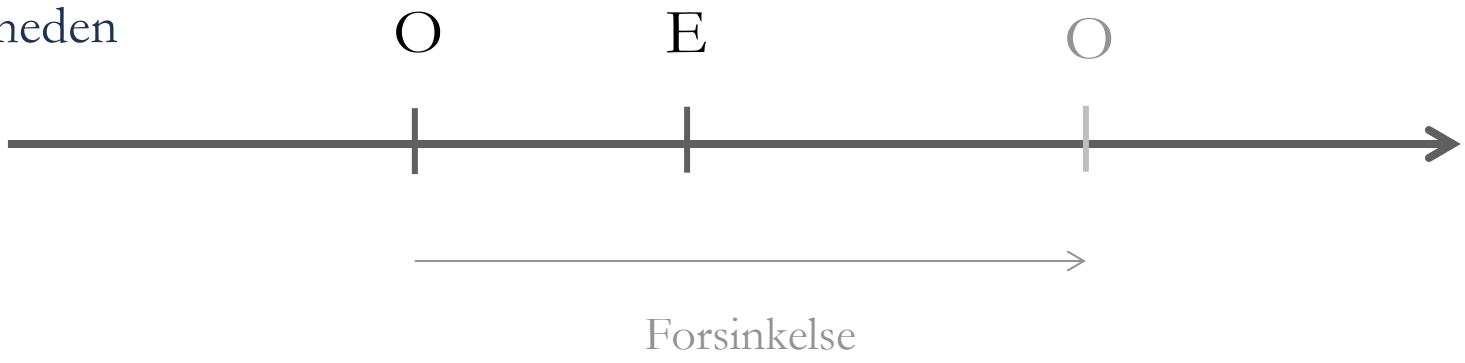
Reverse causation

Misklassifikation af tidspunkt for outcome

Ifølge vores informationer

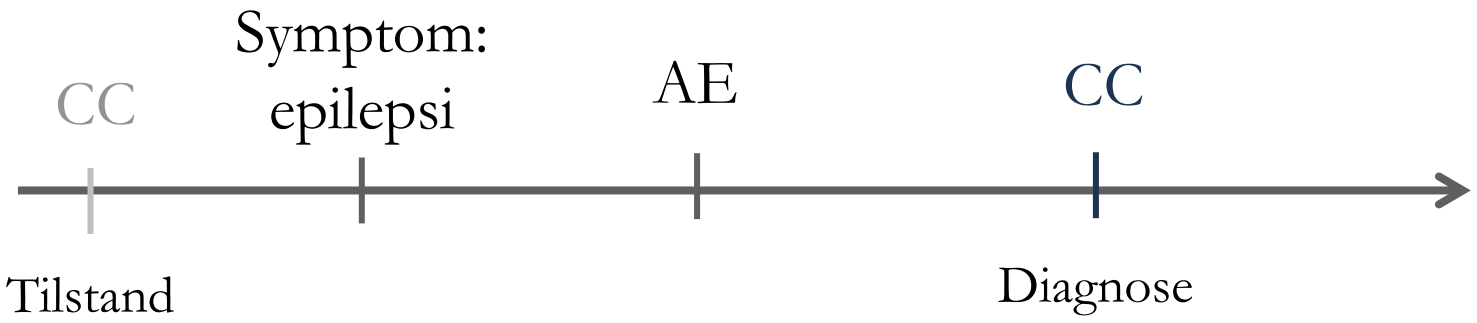


Virkeligheden



Reverse causation, eksempel

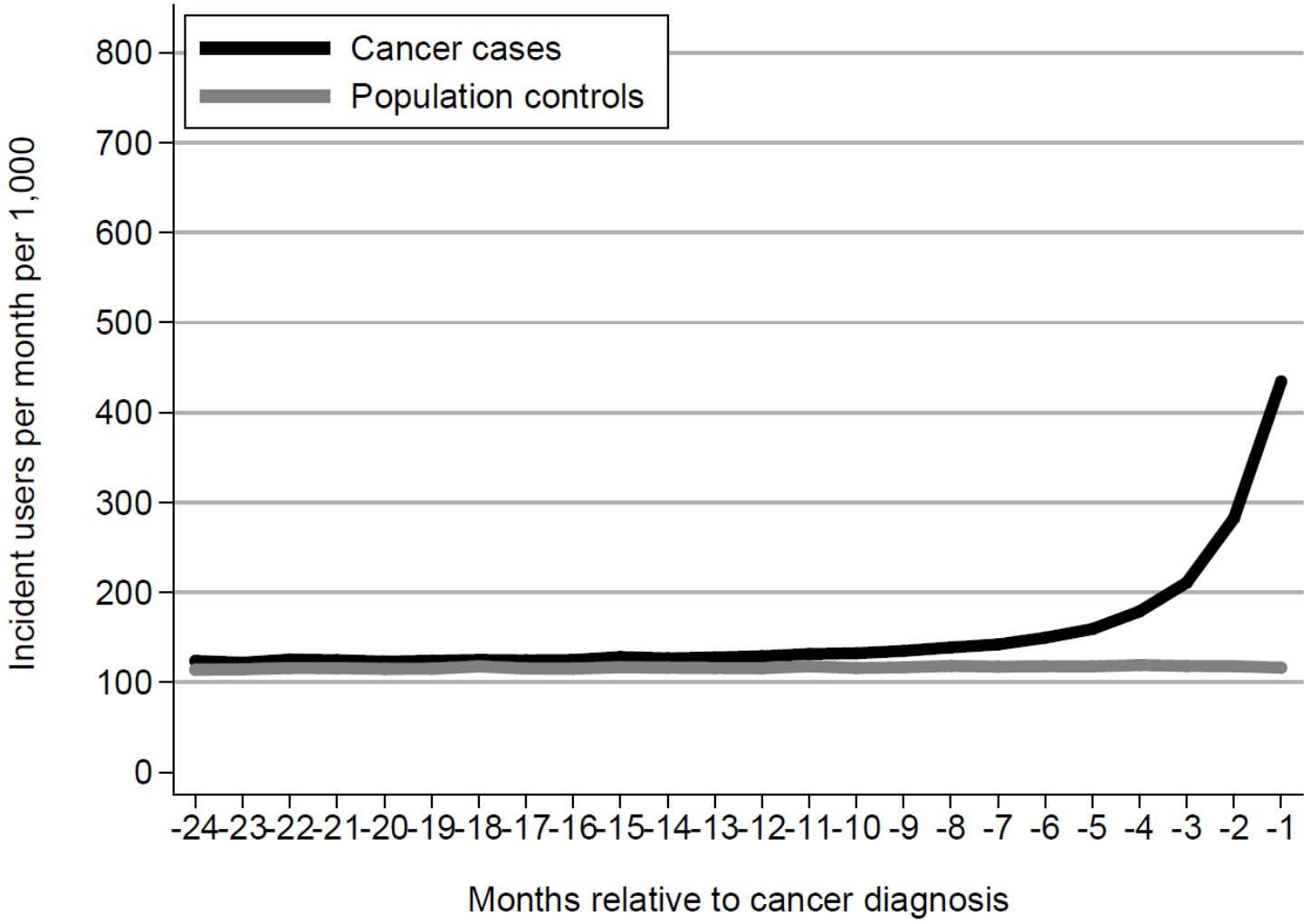
Antiepileptika (AE) og cancer i hjernen (CC)



Andre eksempler

NSAID og risiko for abort

Lægemidler mod overaktiv blære og risiko for blærecancer


Cancer cases
Population controls
Incident users per month per 1,000
800
700
600
500
400
300
200
100
0
-24 -23 -22 -21 -20 -19 -18 -17 -16 -15 -14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1
Months relative to cancer diagnosis

Reverse causation

Få mistanken når risikoen stiger jo nærmere man kommer på outcome

Tænk på patofysiologien og sygdomsforløb for outcome

Cancerstudier: brug induktionsperioder

> In all analyses, we disregarded prescriptions redeemed within 1 year prior to the index date. This was done to reduce the possibility of reverse causation (Jørgensen *et al*; Csizmadl *et al*, 2007), and the improbability that very recent exposure would be associated with cancer development (Burstein and Schwartz, 2008).

Take home message

Bias medfører en systematisk undervurdering eller overvurdering af en sammenhæng ift. det sande resultat

Selektionsbias: når studiedeltagerne risiko for eksponering/outcome er sammenhængende med grunden til at de deltager frem for andre

Informationsbias: når ukorrekt/inkomplet information om deltagerne fører til misklassifikation af deres status ift. eksponering/outcome

Kan kvalificeres (og potentielt håndteres) ved subgruppe og/eller sensitivitetsanalyser

Overvej og diskutér

assessing the association between hormonal contraceptive use and suicide attempt.

Strengths and Weaknesses

We assessed a nonselected cohort of women living in Denmark turning age 15 during the period of 1996–2013. By using data from the Danish national registers, we were able to follow these women for a mean of 8 years with no follow-up loss. The large study population allowed assessment of rare events such as suicide and suicide attempts. The information on redeemed prescriptions of hormonal contraception was obtained through bar codes from all Danish pharmacies, eliminating recall bias. It also allowed daily assessment of hormonal contraceptive use with time-dependent variables. Considering that the women paid for the contraception, the proportion of women not using the redeemed contraception is assumed to be minimal; moreover, the majority of women had repeated prescriptions and were assumed to be users only during the time the redeemed prescription was valid.

By using the personal identification number assigned to all persons in Denmark, which allows reliable linkage of data between different registers, we were able to ensure that we detected incident events of suicide attempt. Because suicide attempts are recorded by public hospitals when patients are brought in, independently of the patient's general practitioner and level of health insurance (all people in Denmark are covered by the public health insurance), it is unlikely that use of hormonal contraception would suggest better access to medical care and therefore a greater likelihood of a suicide attempt being recorded in the registers. Suicide attempts are

became sexually active before age 17, and, of these, 69% used a condom their first time (22), which suggests that for many, sexual relationships start under use of contraceptive methods other than hormonal contraception. The reference group of never-users included women using a copper intrauterine device, women using barrier methods, and women relying on natural methods, such as rhythm methods and interrupted intercourse. Thus, this group also constitutes sexually active women. In short, sexual activity does not seem to be an important confounder for the relationship between use of hormonal contraception and suicide attempt or suicide.

The influence of postpartum depressions was diminished by censoring women temporarily during pregnancy and 6 months after delivery (23, 24). We were not able to adjust for parental suicide/suicide attempt, which is a known risk factor for suicide or suicide attempt (25, 26). To address this concern, we conducted a quantitative bias analysis to assess how strong and how common an unknown binary risk factor for suicide attempt should be if it explained our results. The analysis showed that the unknown risk factor should be very strong, with a high odds ratio for use of hormonal contraception and a prevalence in the study population of one-third, to be able to explain the observed association. We find it unlikely that there would be such a strong unmeasured confounder that at the same time had a prevalence of one-third in the population.

One could speculate on whether other risk factors for suicide or suicide attempt might be less common among the never-users of hormonal contraception, thereby potentially causing an overestimation of our results—for example, certain personality traits or religious subgroups causing both never use of hormonal contraception and a lower risk of

SPØRGSMÅL?

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