How serious are the hazards of hazards ratios ?

Michal Abrahamowicz[1]

Distinguished James McGill Professor of Biostatistics

with: **Marie-Eve Beauchamp[2], Emily K Roberts[3] & Jeremy M G Taylor[4]**

on behalf of STRATOS TG8 'Survival Analysis'

[1] **McGill University, Department of Epidemiology & Biostatistics**
Montreal, Canada

[2] Research Institute of the McGill University Health Centre, Canada

[3] University of Iowa, Department of Biostatistics, USA

[4] University of Michigan, Department of Biostatistics, USA

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Outline

- **Background:**
  - M. Hernán's "*Hazards of hazard ratios (HR)*" commentary [*Epidemiology* 2010]: Arguments & Evidence
  - Outstanding Questions
- **"Generic" Simulations:** Impact of Unmeasured Frailty on HR estimates
- **"Targeted" Simulations:** assessing Plausibility of Hernán's Interpretations
- Possible **Alternative Explanations** of RCT results discussed by Hernán
- **Conclusions**

Objectives

- OVERALL Goal:

  To systematically re-assess the impact of Unmeasured Frailty on the Hazard Ratio (HR) estimates using Empirical Evidence

- Specific Aims:

  1. Investigate: Frailty-induced **Bias & artificial Time-Varying changes** in HRs
  2. **Re-assess the plausibility of** M. Hernan's influential **arguments on "*Hazards of Hazard Ratios*"** [*Epidemiology* 2010]
  3. Provide **Real-world examples of clinically plausible and interpretable time-varying changes in HR**

General Paradigm: 2 inter-connected Challenges for Advanced Analyses of Data on Human Health

1. Choose the **Accurate way of MODELLING Complex Processes*** underlying the Occurrence, Progression, Treatment and Outcomes of the Disease of interest**

   ** usually Dynamic & Multi-factorial*

   *** often Sensitivity Analyses are necessary as No single "optimal" model can be defined*

2. Try to **propose a Clinically Plausible & "Analytically Valid" INTERPRETATION of the RESULTS**

   (requires Both Statistical & Substantive Expertise)

   (or *Alternative Interpretations*)

Background I

- **Hazards and Hazard Ratios (HRs) have been the mainstays of Survival Analysis for >50 years [e.g., Andersen et al, *Stat Med* 2021 (STRATOS guidance paper)]**
- **In 2010, M. Hernán's very influential commentary "Hazards of hazard ratios" [*Epidemiology 2010*] warned about '*built-in selection bias*' of hazard ratios**
- **Hernán's commentary, cited >1,460 times** (Google Scholar), and related more recent 'recommendations' by Stensrud & Hernan [*JAMA* 2020 (*470 citations*); *Am J Epi* 2025], **led to concerns about the validity of Cox PH estimates and hazard-based models**
- Yet, **Empirical Evidence presented by Hernán is limited to Selected Results of a Single RCT [Manson et al, *NEJM 2003*]**

Background II

- Hernán's cornerstone argument [2010] is that **HRs suffer from "Built-in Selection Bias"** where:
  an unobserved risk factor ('*Susceptibility*' or '*Frailty*') automatically induces:

  (i) a systematic underestimation (Bias to the Null) of the PH model-based HR for the exposure/treatment (even if Randomization ensures balanced distribution of frailty…)

  (ii) a gradual decrease of period-specific HRs during follow-up, possibly leading to 'crossing hazards'

Example used by Hernán [2010]:
CHD risks in RCT of Hormone Therapy

- **RCT of Hormone therapy (Estrogen + Progestin *vs* Placebo) in primary prevention of Coronary Heart Disease (CHD)**
  [JA Manson et al, *NEJM* 2003: 349: 523-34]
- **N= 16,608** postmenopausal Women, aged 50-79 yrs at randomization
- Design: Parallel-groups, Double Blinded RCT
- Outcome = **Time to 1st major CHD event** (non-fatal MI or CHD death)
- Follow-up: median 5.6 yrs, maximum = 8.6 yrs
- CHD Events: (*Total Incidence = 335 events, only 2.0%* !)
  188 in 8,506 women on **Hormone Therapy (3.9/1,000 PY)**
  vs.
  147 in 8,102 women on **Placebo (3.3/1,000 PY)**

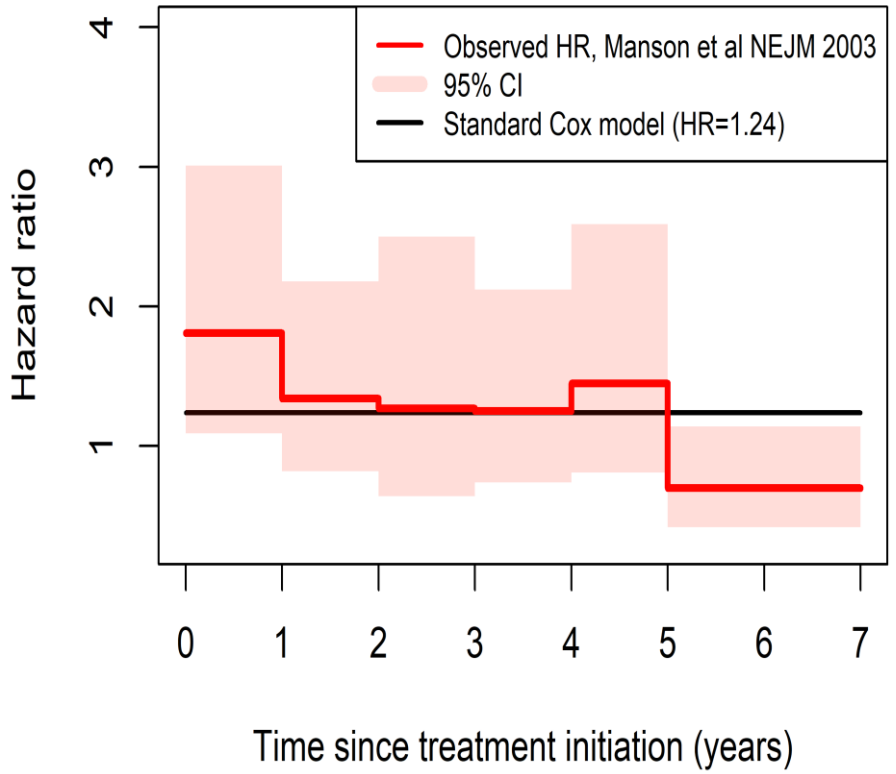
Main Results of Manson et al's [2003] RCT

- Primary ITT analyses reported by Manson et al [2003] based on Cox PH model (stratified by age and CHD at baseline):
  HR (Hormone/PB) = 1.24 [95% CI: 0.97-1.60]

- However, **year-specific HRs decreased 'significantly'** with increasing follow-up

  from HR=1.81 in year 1 (1.09-3.01),
  to HR = 1.27 in year 3, and then
  to HR = 0.7 (0.42-1.14) in years 6-8 [p. 528 & Table 2 in Manson et al, 2003]

Year-specific HRs* in Manson et al's RCT



* year-specific *HR(t)* is estimated by: (a) using only women 'at risk' at the start of year *t,* and (b) censoring women with NO event during year *t* at the end of the year

Selected Citations (re: **Interpretation of Decreasing HRs**) from M. Hernán's Commentary [*Epidemiology* 2010]:

- *"... this **apparently protective effect** * of hormone therapy **after year 5 * is hardly surprising** if one bears in mind that **women vary in their susceptibility to heart disease**."* [* year-specific HR = 0.7 for yrs 6-8 of the trial]

- *"... **built-in selection bias** (of period-specific HRs) **makes them difficult to interpret as** a measure of **time-varying effect**..."*

- "***Hazards may cross*** *(e.g.* from HR>1 to HR<1) *at some point* ***because of depletion of susceptibles***"

- OVERALL: **Hernán argues that important changes over time in year-specific HRs (& "crossing hazards"), observed in Manson et al's RCT, reflect simply Unobserved *Susceptibility* (rather than true "causal" changes in the impact of treatment)**

Need for more “solid” Evidence?

- However, **Hernán’s interpretation is based only on (i) results of a Single Empirical study and (ii) general (qualitative) arguments ****

  ** whereas the Bias-to-Null induced by ‘omitted covariate’ (‘Frailty’ or ***‘Susceptibility’***) is well established in statistical survival analysis literature, is it unclear under what (plausible) assumptions, it can lead to “crossing hazards”

- In many trials, there may be **Other, Plausible Reasons for HR(Treated/Placebo) to Change Systematically** with Increasing Follow-up Time, including e.g.:
  - Gradually *decreasing* Adherence (with longer follow-up)
  - Cumulative Effects (*increasing* with treatment duration)
  - Developing Tolerance to treatment effects
  - Effect Modification with Disease Stage/Progression…

Outstanding Questions

- **Is it plausible that the dramatic HRs changes (& "crossing hazards") observed in Manson et al's RCT [*NEJM* 2003] reflect simply Unobserved *Susceptibility i.e. Built-in Selection Bias* (as implied by Hernan [2010])?**

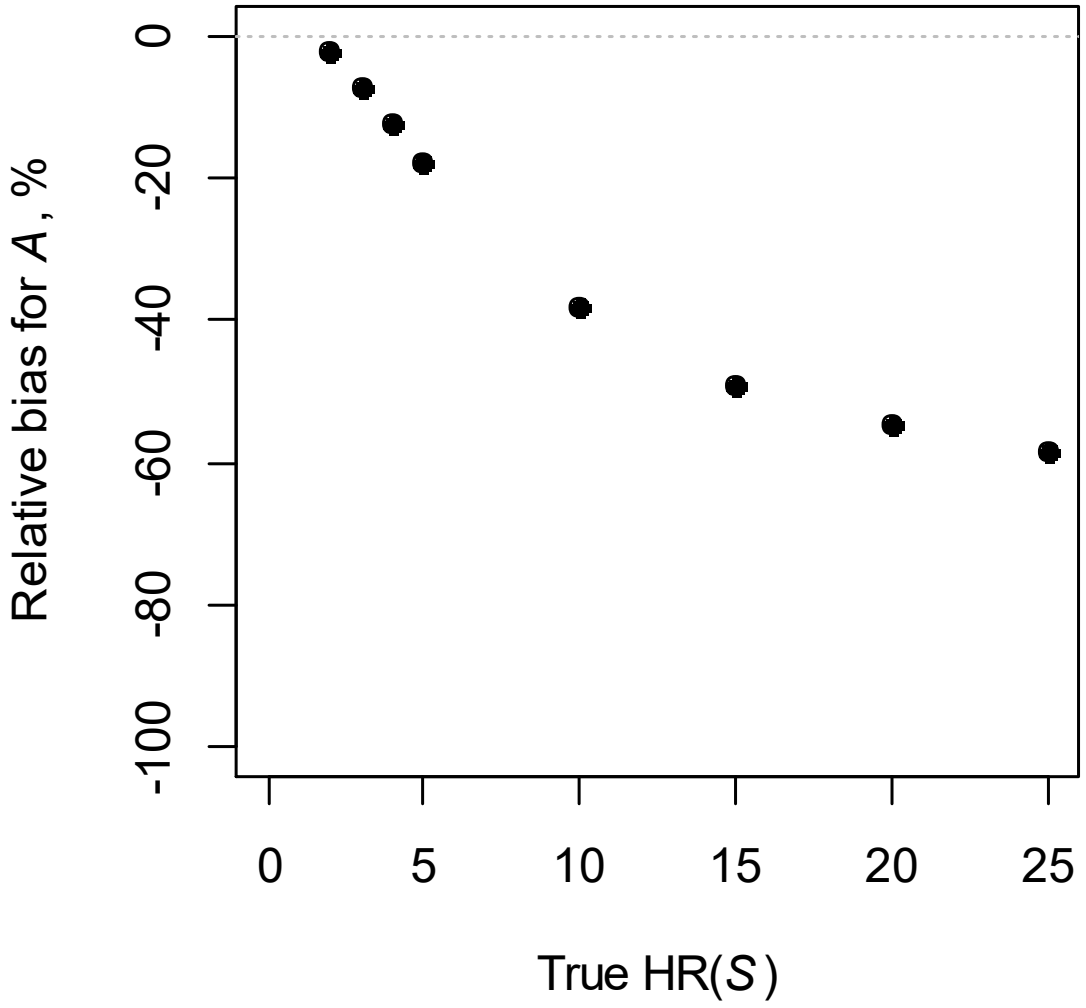
- **OR**

Could these results reflect True Changes over Time in the Impact of Treatment, due to its true (Biological) Time-Dependent Effect and/or some features of this specific RCT?

➢ **We have addressed these questions by 2 series of simulations:**

"Generic" & "Targetted"

Results of "Generic" Simulations: **HR(*S*) vs mean relative Bias:** (1000 samples: HR(*A*)=2; P(*S*=1)=0.5, Cum. Inc. = 35%-60%)



Main Results of our 'Generic' Simulations

[Abrahamowicz et al, EJE 2025]

- **Our 'Generic' Simulations explored how the impact of omitting an important independent risk factor (S) on the treatment's HR estimates from the Cox PH model depend on (i) strength of S' effect, (ii) prevalence of S, and (iii) incidence of events.**
- Results demonstrated that, for Cox-model HRs: **Unmeasured Susceptibility/Frailty (*S*):**

(1) induces (1a) serious Bias-to-Null, & (1b) gradual decay of year-specific HRs, ONLY IF it has a VERY STRONG association with the Hazard

(2) has a much Weaker Impact IF (2a) its Prevalence (P(*S*)=1) is Low And/Or

(2b) Overall Survival is High (implying Low Incidence of the events)

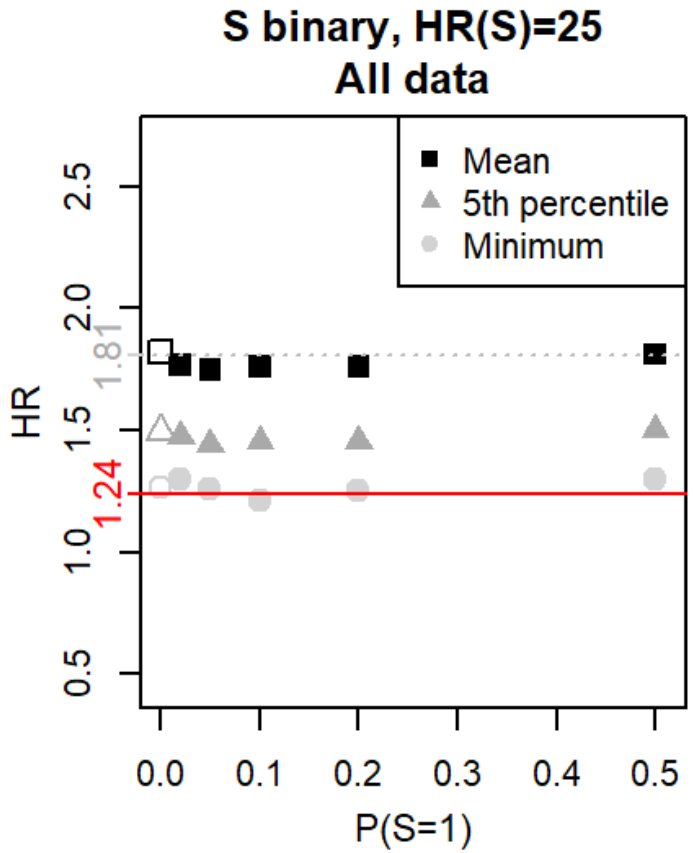
These Empirical findings motivated us to Re-Assess ** the Plausibility of M. Hernan's Interpretation of Manson et al's RCT results
(** using **'Targeted' Simulations** that follow**)**

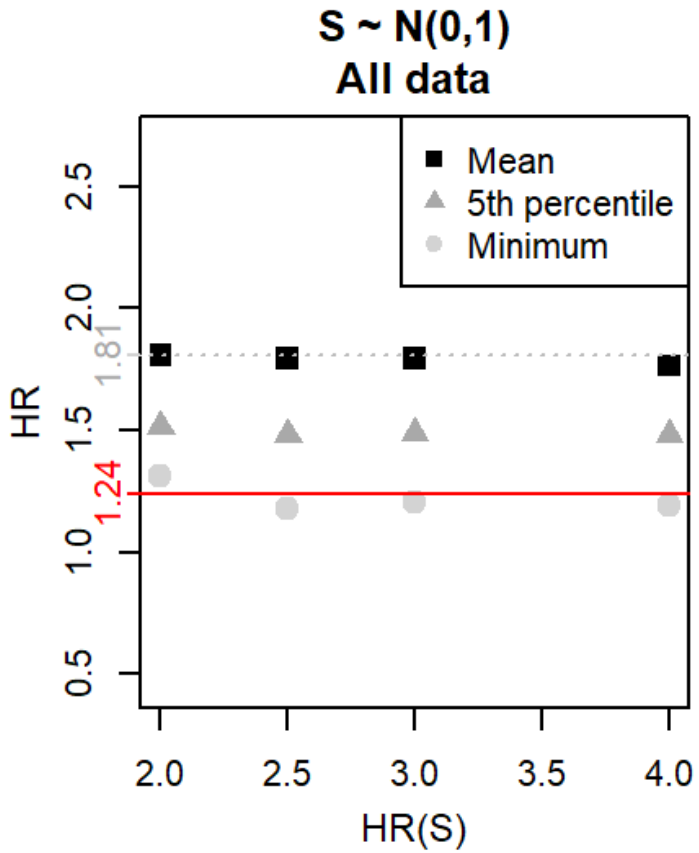
"Targeted" Simulations to Re-assess Mason's RCT results: main Assumptions

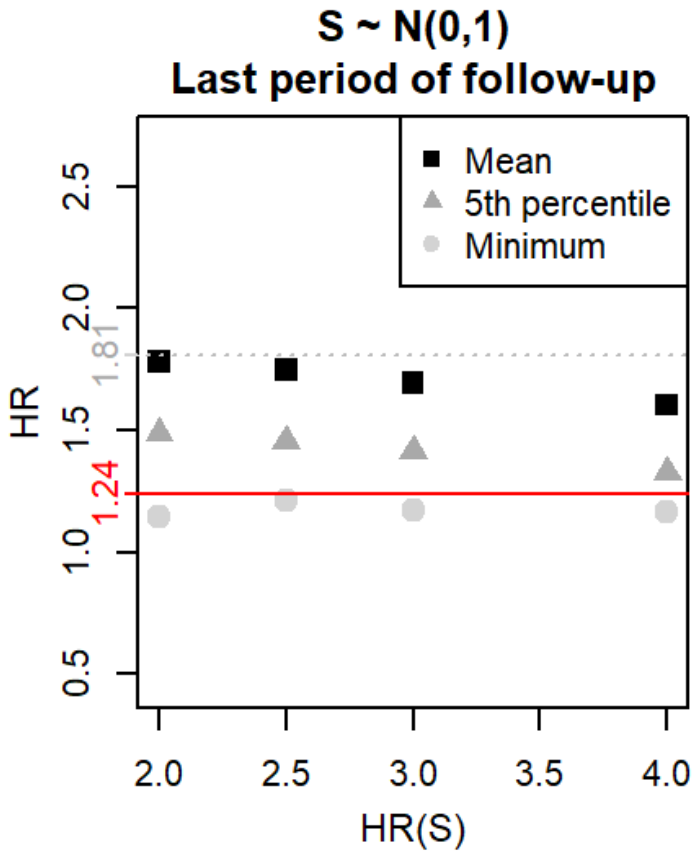
'Targetted' simulations replicated all important features of the original RCT [Mason et al, *NEJM* 2005], highlighted by Hernan [2010]:

- N = 16,600 (P(A=1) = P(A=0) = 0.5)
- Up to 10 years of follow-up
- Overall Cumulative Incidence = 2.0% (335 Events per sample)
- ~ 65 events in the last period (last 2 years)
- True HR(A)= 1.81 (1st-yr estimate, assumed to be the 'true' impact of the hormone therapy [Hernan, *Epidemiology* 2010]
- To make results most favorable to Hernan, we assumed Very Strong Impact of Unmeasured S (e.g. **HR(S)=25 for a binary S**) while varying its prevalence

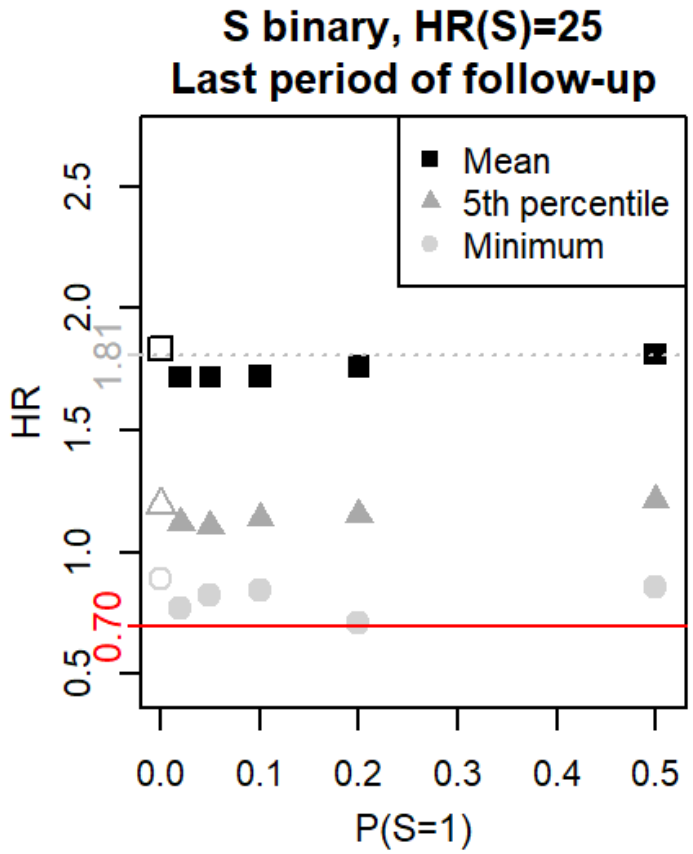
Simulation results: Even with the most exceptionally strong frailty (e.g. HR(S)=25 for Binary S in Leftmost panel) the overall HR is extremely unlikely to be as low as 1.24 reported by Mason et al!!

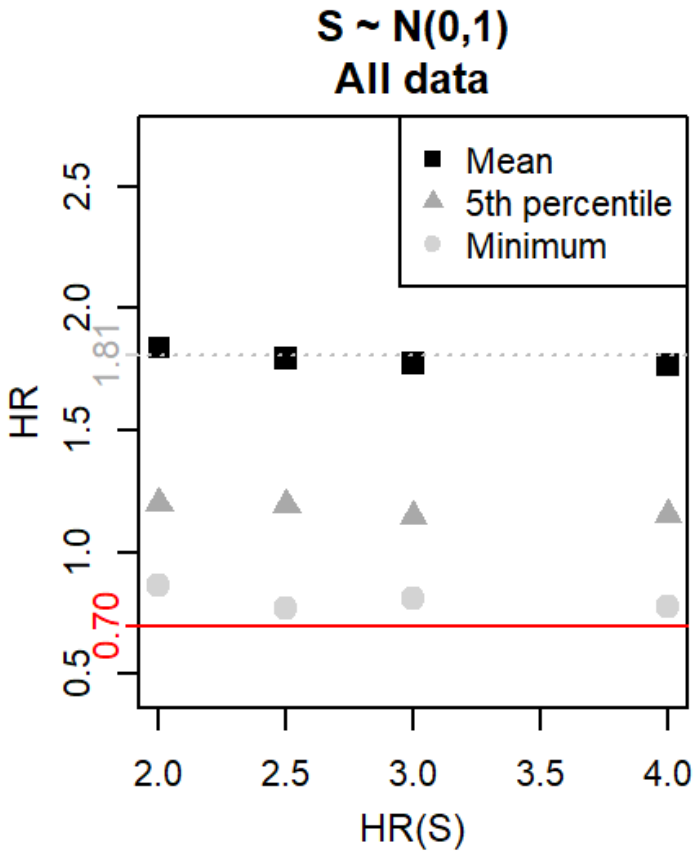


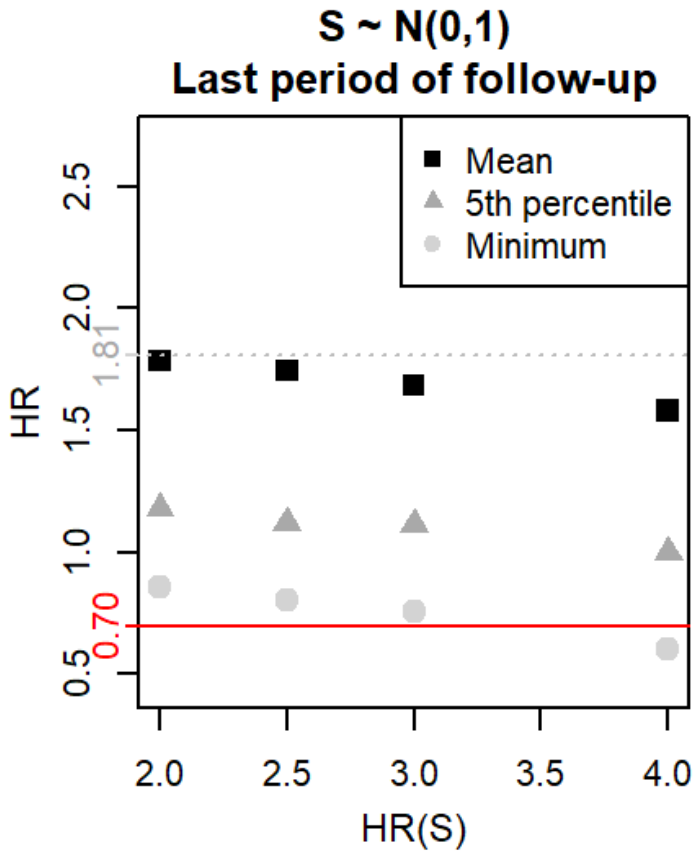




Further Simulation results: similarly, year-specific HR for the last period extremely unlikely to get as low as 0.70 reported by Mason!!







Possible **Alternative Explanations** of Manson's RCT results: **increasing Tx Non-Adherence ?**

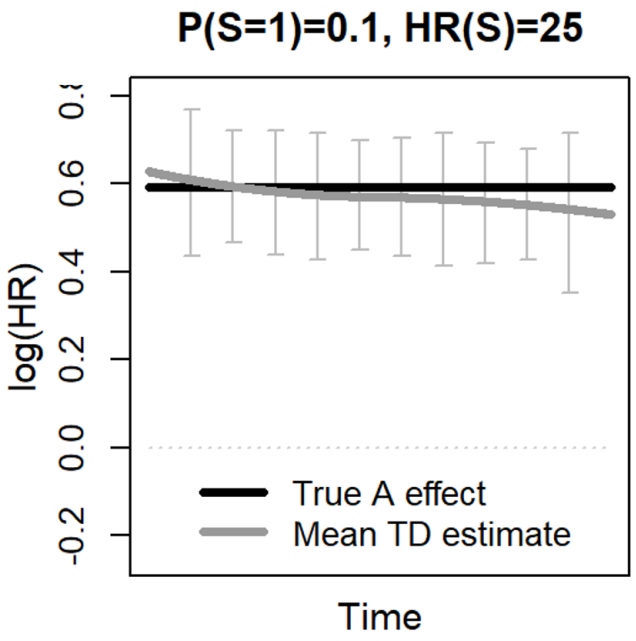
- Importantly, **Manson et al report** [*NEJM*, p.526]: *"relatively **High Rate of Discontinuation*** ***of Hormone Tx*** *"* (***42% by yr 5** **!**) [1]

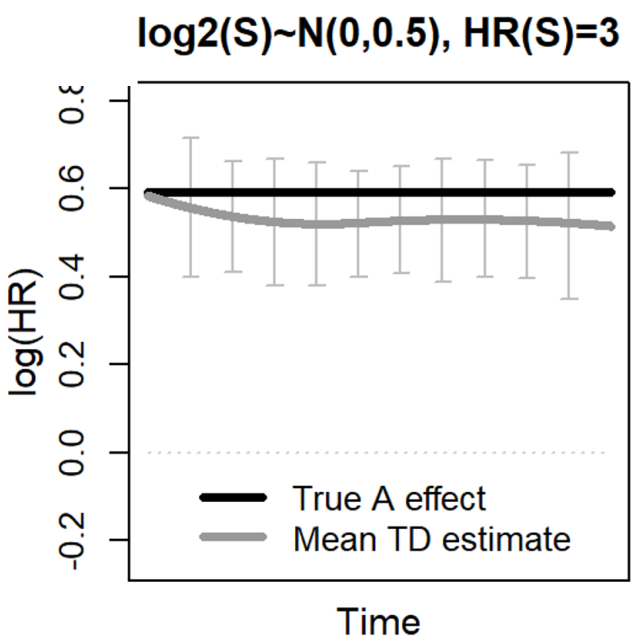
- & their secondary **analyses on Fully Adherent women yielded** **HR = 1.50 (1.14-1.97)** [p. 528],
  i.e. **50% stronger effect than ITT-based HR=1.24 (0.97-1.54)!** [1]

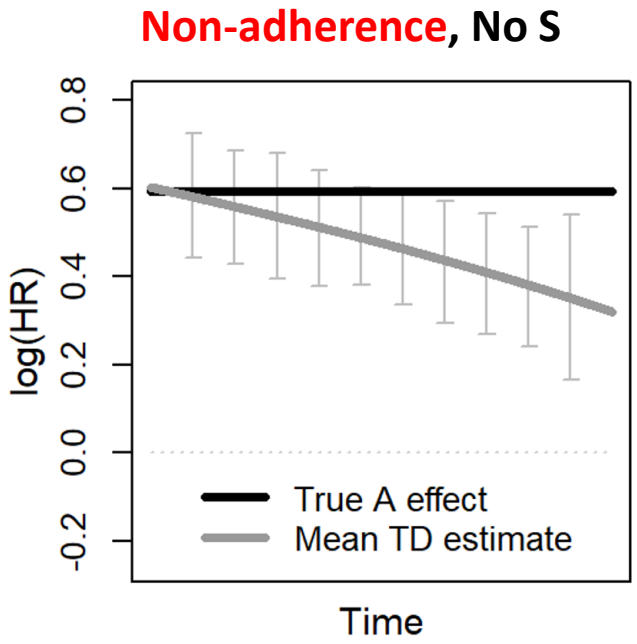
- **Thus, ~ 50% of "Bias" leading to Decaying-over-time HRs in Manson et al's RCT can be explained by Increasing-over-Time Non-Adherence with Hormone Therapy** [1]

[1] ***None of these facts is mentioned by Hernan*** [Epidemiology 2010]

In Simulations: Non-Adherence** consistent with Manson's RCT
(6% of women in Hormone Tx arm stop Tx each year > 42% after 7 yrs)
(**Rightmost graph) impacted the estimates much more than even very strong S







Possible CLINICAL/Biological **Explanations** of Manson et al's RCT results ?

- **Yet, HR = 1.50 (1.14-1.97) for Fully Adherent women is still considerably lower than the 1st-year HR=1.81 (1.09-3.01)** [Manson, *NEJM* 2003]. Thus:
  Non-Adherence *cannot* fully explain the decrease in Tx HRs in later years!
  and there may be more 'substantive' clinical/biological reasons…

- Recently, Prentice & Aragaki [*Stat Sciences* 2022] presented time-varying re-analyses of the Manson et al's RCT and suggested searching for the biological cause for the harmful hormone Tx impact decaying over time

- **Indeed, imaging studies show that hormone therapy reduces coronary artery plaque but only after several years of Tx** [Akhrass et al. *J Clin Endocrinol Metab* 2003; Barett-Connors et al. *Menopause* 2005]

- Further, a comprehensive review reports that **decaying, and possibly 'crossing' HRs for Hormone Tx** (i) **are consistent with 2 other RCTs of same Tx** & a large cohort (Nurses Studies), & (ii) **may have a biological basis** [Hodis & Mack 2007]

Benefits of flexible modeling of time-varying HRs

- Interestingly, **Hernan does Not mention a possibility of a genuine biological change in the treatment effect [*Epidemiology* 2010]** !

- Yet, since 1990's statisticians working in Survival Analysis developed & validated **several flexible extensions of Cox's model that allow for Time-Dependent (TD) Hazard Ratios ** (with log(HR(t)) = $\beta(t)$ modeled using different Splines)** e.g.:

  [Zucker & Karr, *Ann Stat* 1990]; [Gray, *JASA* 1992]; [Hastie & Tibshirani, *JRSS* 1993]; [Hess, *Statistics in Medicine* 1994]; [Grambsch & Therneau, *Biometrics* 1994]; [Verweij & van Houwelingen, *Biometrics* 1995]; [Kooperberg, Stone & Truong, *JASA* 1995]; [Luo, He, Wu & Taylor, *SMMR* 2023]; [Abrahamowicz, MacKenzie & Esdaile *JASA* 1996] …

- **Hundreds of real-life applications of these models**, in many diseases, yielded strong evidence of Time-Dependent HRs for several Prognostic Factors, Exposures and Treatments**

- **Could they All be due Exclusively to Unmeasured Susceptibilities ??**

(** **Hernan & Stensrud argued AGAINST such TD analyses [*JAMA* 2020]**…)

Conclusions

- **General:**

  Using Empirical Results (especially of a *Single* Study…) to support Methodological Postulates requires a careful examination of All relevant aspects of the study (including limitations of data and/or analyses)

- **Specific:**

  Concerns expressed in Epidemiological literature about "*Hazards of Hazard Ratios*" are somewhat exaggerated and not well supported by evidence

  Flexible modeling of time-varying HRs, combined with Clinical/Biological expertise about the underlying exposure-outcome relationships, may yield important new insights into the etiology, progression or treatment of many diseases

Thank you = Gamsahamnida

Michal.Abrahamowicz@McGill.ca

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