

Source-faithful replication protocol: menopausal hormone therapy and long-term mortality

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Abstract

Pre-data manuscript scaffold. Registered methods and planned displays are prepared; all empirical results and evidence-dependent conclusions remain unfilled.

Keywords: Registered study, results pending

PRE-DATA DRAFT: empirical placeholders are not findings.

Title

Systemic menopausal hormone therapy and long-term mortality: a source-faithful replication registration

Abstract

Objective. To reconstruct the mortality analyses specified in the Danish nationwide cohort study by Mikkelsen and colleagues, while preserving unresolved disagreements between its paper, supplement and supplied analysis code.

Design and setting. Later replication registration of an observational register cohort in Denmark. The question, outcomes and analyses are fixed by the source. No confidential records have been accessed in preparing this manuscript.

Participants and measurements. The source includes women born 1950–1977, alive and resident in Denmark at 45, with the stated immigration-history and pre-entry treatment, disease and surgery exclusions. Systemic MHT is measured from redeemed prescriptions as a time-varying ever-use process and cumulative duration. All-cause death is ascertained from person registration through 31 July 2023; cause-specific follow-up ends 31 December 2022. Models use age as the time axis. The original sister, surgical and treatment comparisons are retained.

Results. All current empirical results are unfilled. The manuscript is prepared to report the original descriptive quantities, counts, person-years, incidence rates, hazard

ratios and 95% confidence intervals. Source ambiguity, unavailable input and operational failure have distinct reporting dispositions. Published numbers are comparison references only.

Conclusion. The conclusion will be limited to the source-aligned associations actually reconstructed. Coverage and compilation do not establish replication agreement or causal treatment effects.

Keywords

Registered study; results pending.

Introduction

Mikkelsen and colleagues framed systemic menopausal hormone therapy in the context of effective symptom treatment, concerns about adverse outcomes and differences between the women enrolled in historical trials and women starting treatment near menopause. Their study chose all-cause mortality as an integrated severe outcome and used long register follow-up to examine cumulative treatment duration, formulations, regimens and women with previous gynaecological surgery. The original background contrasts the Women's Health Initiative trials with observational studies in Denmark and Sweden, noting differences in ages, treatments, outcome definitions and follow-up. We retain that motivation without converting those studies into new replication experiments or making a current clinical recommendation [1].

The present task is extraction and faithful reconstruction of that published question. The full article, its supplementary definitions and residual plot, and all 969 lines of a user-supplied R script form the scientific source set. The source article and supplementary PDFs were supplied by hash; the code is available but its publisher-file provenance has not been independently verified. An older audit saying that analysis code was not found in a previous public bundle is historical and is not the current access state.

This distinction matters because a detailed script can expose scientific uncertainty as well as resolve it. The supplied program depends on derived files and contains model-reference, population-timing and output-assembly disagreements. A faithful reconstruction must retain a missing result where the necessary source decision is not known. It must also retain supported components of the same analysis, such as counts or crude associations, without treating them as substitutes for an unresolved adjusted result.

Data and methods

Population and follow-up

The source cohort consists of Danish women born 1950–1977, alive and living in Denmark on their 45th birthday; immigrants are required to have arrived before 25. Exclusions concern prior systemic MHT, bilateral oophorectomy, thrombophilia, liver disease, arterial or venous thrombosis and the source-defined breast/endometrial/ovarian cancer group. Follow-up extends to the first relevant death or censoring event, with

an administrative end of 31 July 2023. The primary analysis does not censor for a newly developed MHT contraindication. A separate source sensitivity does so.

The nominal calendar-day specification and the script's 365.2-day age conversion, three-decimal rounding, entry exclusions at or before start and migration/status rules are not assumed equivalent. The script also contains an unquoted date expression. Those choices remain explicit gates in the registration; no reconstructed cohort size or time at risk may be reported until the required source history and timing are established. Exclusion-reason counts overlap and therefore are presented separately from their union.

Treatment measurement

Systemic estrogen alone or combined with progestogen is identified from prescription redemptions. The source considers oral and transdermal combination products and the stated estrogen-only forms; low-dose vaginal estrogen is outside its exposure definition. Separately prescribed progestogen may create combined treatment. Women contribute unexposed time until the first qualifying prescription and remain ever-exposed thereafter. The source duration groups are 0, <1, 1–2.9, 3–4.9, 5–9.9 and ≥ 10 years; selected subgroup and cause analyses collapse exposure to 0, <5 and ≥ 5 years.

The supplied code aggregates product supply into episodes, assigns APK times VOLUME to episode starts, and classifies dominant form and regimen from cumulative quantities. Its commented episode construction, VOLUME units, prospectively accumulated use and simultaneous-progestogen matching require reconciliation with the paper and source exports. Tied dominant categories and the ungrouped forward fill do not authorize an invented tie rule. The primary exposure categories and these unresolved decisions are registered in full, rather than replaced by a convenient prescription-count proxy.

Outcomes, covariates and analysis

The primary endpoint is all-cause death from person registration. Cardiovascular, cancer and other deaths are secondary cause-specific endpoints using underlying cause in the source death register, with follow-up through 31 December 2022. They are analysed with source cause-specific Cox models, not a new cumulative-incidence estimator. The source's older and newer cause-file mappings, duplicate selection, missing-cause classification and calendar filter must be reconciled before affected outputs are computed.

Cox models use woman's start–stop age intervals, with the source time-dependent covariates and calendar groups 1995–2001, 2002–2008, 2009–2015 and 2016–2023. The source includes parity, education, income quartile, country of birth, diabetes, hypertension, hypercholesterolaemia, atrial fibrillation, heart failure, valvular disease and a marker for at least three hospital contacts between 44 and 45. The program also includes civil status, visible in the supplementary residual plot but absent from printed table adjustment lists; exact printed-model attribution remains unresolved. The cardiovascular adjustment set is narrower, with its own text/footnote discrepancy. We do not select either competing set for convenience.

The source pregnancy input is `gravdb_steen`, not a documented direct extract of the current MFR tables. Its pregnancy coding and provenance affect parity, BMI and smoking. Education/country/civil crosswalks, income row scope and the distinction between source-mode imputation and hard-coded mode categories also remain explicit prerequisites. The 531-table planning boundary permits investigation of candidate mappings, but does not prove any historical extract or link equivalent or mounted.

Where the source specification is resolved, we preserve its Cox software semantics, source 95% confidence intervals and its two-sided $P < .05$ descriptive convention. No replication tolerance, equivalence margin, power calculation, additional estimator, multiplicity adjustment or numerical PH acceptance rule is introduced. The residual diagnostic is the original binary-exposure primary-model display, with all 14 source terms. Its plotting code consumes approved residual/curve output and cannot fit or repair a model.

Source comparisons and sensitivities

The contraindication sensitivity sensors at the source contraindications. The as-treated sensitivity sensors after the source cessation construction with 90 days of extension; it does not redefine the primary analysis. The sibling design retains maternal sister groups discordant in eventual exposure, including each sister's original time-varying history; the adjusted code stratifies baseline hazards by mother, whereas its crude fit does not, creating a source discrepancy for that target.

Surgical analyses concern hysterectomy at any age and bilateral oophorectomy at 45–54 or ≥ 55 . Hysterectomy and oophorectomy groups can overlap. Source breast/gynaecological cancer censoring is retained. The code's retrospective designation of women with eventual older surgery conflicts with a postoperative interpretation and is not silently repaired. Age-at-death summaries in the younger BSO group refer only to women who died and do not estimate life expectancy.

Treatment-form, progestogen-regimen and initiation-age analyses use their original categories and never-use comparators. They are not randomized head-to-head treatment comparisons. Code-only calendar, surgery-adjusted, age-hysterectomy, BMI and smoking specifications are inventoried separately from published table results. The smoking fits and merged output reference BMI objects; no corrected smoking model is introduced. The other-cause adjusted display extracts an older-BSO all-cause model despite fitting an other-cause model; both references are documented and the adjusted other-cause target remains unestimated pending source clarification.

Reporting, access and governance

Each component has an estimate/interval or an explicit availability disposition. Completed, partial and boundary are coverage states, not statistical conclusions. Computational failure remains operational `no_result`. Comparisons with the publication may report arithmetic differences and printed rounding once genuine reconstructed values exist, but no numerical agreement criterion has been invented.

The original article reports restricted register access and its own ethics/reporting arrangements. This conversion has accessed only public source material and schema

documentation, not confidential rows or computed study outcomes. It creates no new access approval. Event-count and residual disclosure must follow governed release rules. Source-provided values are kept outside all current replication-result slots. The two-stage lane has no independent scientific reviewer; source-fidelity self-checks and build checks do not establish scientific acceptance.

Results

Cohort, treatment uptake and age55 characteristics

The Figure1 flow will report eligibility, the union and overlapping reasons for exclusion, and final treatment-duration groups. Current numerical flow: [[RESULT:flow_report]]. Follow-up distribution: [[RESULT:followup]]. End-use frequency, birth-year uptake and cumulative duration: [[RESULT:uptake]]. Deaths in the cohort: [[RESULT:cohort_deaths]]. Treatment use at55 in the two source calendar windows: [[RESULT:landmark_uptake]]. Landmark group sizes: [[RESULT:landmark_n]].

Table1 presents the source landmark characteristic roster without balance tests. For each cell the reporting rule is a count/percentage or source parity mean/SD; an unresolved variable or denominator remains explicit rather than selecting a replacement variable.

Characteristic	Past/present MHT at55	No MHT at55
Birthplace: Denmark	[[RESULT:t1_03_0]]	[[RESULT:t1_03_1]]
Birthplace: Other	[[RESULT:t1_04_0]]	[[RESULT:t1_04_1]]
Birthplace: Unknown	[[RESULT:t1_05_0]]	[[RESULT:t1_05_1]]
Birthplace: Mean parity (SD)	[[RESULT:t1_06_0]]	[[RESULT:t1_06_1]]
Parity category: 0	[[RESULT:t1_08_0]]	[[RESULT:t1_08_1]]
Parity category: 1-2	[[RESULT:t1_09_0]]	[[RESULT:t1_09_1]]
Parity category: 3	[[RESULT:t1_10_0]]	[[RESULT:t1_10_1]]
Marriage status: Unmarried	[[RESULT:t1_12_0]]	[[RESULT:t1_12_1]]
Marriage status: Married	[[RESULT:t1_13_0]]	[[RESULT:t1_13_1]]
Marriage status: Divorced	[[RESULT:t1_14_0]]	[[RESULT:t1_14_1]]
Marriage status: Unknown	[[RESULT:t1_15_0]]	[[RESULT:t1_15_1]]
Highest completed educational degree: Primary or lower secondary school	[[RESULT:t1_17_0]]	[[RESULT:t1_17_1]]
Highest completed educational degree: Upper secondary school	[[RESULT:t1_18_0]]	[[RESULT:t1_18_1]]

Characteristic	Past/present MHT at55	No MHT at55
Highest completed educational degree: Bachelor's degree or equivalent	[[RESULT:t1_19_0]]	[[RESULT:t1_19_1]]
Highest completed educational degree: Master's degree or equivalent	[[RESULT:t1_20_0]]	[[RESULT:t1_20_1]]
Highest completed educational degree: Unknown	[[RESULT:t1_21_0]]	[[RESULT:t1_21_1]]
Income quartile* 1st	[[RESULT:t1_23_0]]	[[RESULT:t1_23_1]]
Income quartile* 2nd	[[RESULT:t1_24_0]]	[[RESULT:t1_24_1]]
Income quartile* 3rd	[[RESULT:t1_25_0]]	[[RESULT:t1_25_1]]
Income quartile* 4th	[[RESULT:t1_26_0]]	[[RESULT:t1_26_1]]
Year of 55th birthday: 2002-2008	[[RESULT:t1_28_0]]	[[RESULT:t1_28_1]]
Year of 55th birthday: 2009-2015	[[RESULT:t1_29_0]]	[[RESULT:t1_29_1]]
Year of 55th birthday: 2016-2023	[[RESULT:t1_30_0]]	[[RESULT:t1_30_1]]
Year of 55th birthday: Diabetes	[[RESULT:t1_31_0]]	[[RESULT:t1_31_1]]
Year of 55th birthday: Hypertension	[[RESULT:t1_32_0]]	[[RESULT:t1_32_1]]
Year of 55th birthday: Hypercholesterolemia	[[RESULT:t1_33_0]]	[[RESULT:t1_33_1]]
Year of 55th birthday: Atrial fibrillation	[[RESULT:t1_34_0]]	[[RESULT:t1_34_1]]
Year of 55th birthday: Heart failure	[[RESULT:t1_35_0]]	[[RESULT:t1_35_1]]
Year of 55th birthday: Valvular disease	[[RESULT:t1_36_0]]	[[RESULT:t1_36_1]]
Year of 55th birthday: Three or more hospital contacts between age 44 and 45 years	[[RESULT:t1_37_0]]	[[RESULT:t1_37_1]]
Year of 55th birthday: Earlier hysterectomy	[[RESULT:t1_38_0]]	[[RESULT:t1_38_1]]
Year of 55th birthday: Earlier bilateral oophorectomy	[[RESULT:t1_39_0]]	[[RESULT:t1_39_1]]

All-cause mortality and original comparisons

The following table preserves the source Table2 block and row order. Summary cells report events, person-years and deaths per10000person-years. HR cells report the specified estimate and95%CI, or the exact source/input boundary. A reference is labelled as such only when its source risk set is established. The denominator/summary and each model remain separately available; no missing adjusted result is replaced by1 or by the crude estimate.

Analysis and exposure	Events; person-years; IR	Crude HR (95%CI)	Adjusted HR (95%CI)
Primary analysis — Never used	[[RESULT:t2_primary_0_a]]	[[RESULT:t2_primary_0_a]]	[[RESULT:t2_primary_0_a]]
Primary analysis — Past or present use	[[RESULT:t2_primary_1_a]]	[[RESULT:t2_primary_1_a]]	[[RESULT:t2_primary_1_a]]
Primary analysis stratified by duration of use — 0 years	[[RESULT:t2_duration_0_a]]	[[RESULT:t2_duration_0_a]]	[[RESULT:t2_duration_0_a]]
Primary analysis stratified by duration of use — <1 year	[[RESULT:t2_duration_1_a]]	[[RESULT:t2_duration_1_a]]	[[RESULT:t2_duration_1_a]]
Primary analysis stratified by duration of use — 1-2.9 years	[[RESULT:t2_duration_2_a]]	[[RESULT:t2_duration_2_a]]	[[RESULT:t2_duration_2_a]]
Primary analysis stratified by duration of use — 3-4.9 years	[[RESULT:t2_duration_3_a]]	[[RESULT:t2_duration_3_a]]	[[RESULT:t2_duration_3_a]]
Primary analysis stratified by duration of use — 5-9.9 years	[[RESULT:t2_duration_4_a]]	[[RESULT:t2_duration_4_a]]	[[RESULT:t2_duration_4_a]]
Primary analysis stratified by duration of use — 10 years	[[RESULT:t2_duration_5_a]]	[[RESULT:t2_duration_5_a]]	[[RESULT:t2_duration_5_a]]
Sensitivity analysis: censored at MHT contraindication† — Never used	[[RESULT:t2_contraindication_0_a]]	[[RESULT:t2_contraindication_0_a]]	[[RESULT:t2_contraindication_0_a]]

Analysis and exposure	Events; person-years; IR	Crude HR (95%CI)	Adjusted HR (95%CI)
Sensitivity analysis: censored at MHT contraindication‡ — Past or present use	[[RESULT:t2_contraindication_0_a]]	[[RESULT:t2_contraindication_0_a]]	[[RESULT:t2_contraindication_0_a]]
Sensitivity analysis: sibling analysis — Never used	[[RESULT:t2_sibling_0_a]]	[[RESULT:t2_sibling_0_a]]	[[RESULT:t2_sibling_0_a]]
Sensitivity analysis: sibling analysis — Past or present use	[[RESULT:t2_sibling_1_a]]	[[RESULT:t2_sibling_1_a]]	[[RESULT:t2_sibling_1_a]]
Sensitivity analysis: ‘as treated’ analysis (censored at MHT cessation) — Never used	[[RESULT:t2_cessation_0_a]]	[[RESULT:t2_cessation_0_a]]	[[RESULT:t2_cessation_0_a]]
Sensitivity analysis: ‘as treated’ analysis (censored at MHT cessation) — Past or present use	[[RESULT:t2_cessation_1_a]]	[[RESULT:t2_cessation_1_a]]	[[RESULT:t2_cessation_1_a]]
Subgroup of women who had undergone hysterectomy§ — 0 years	[[RESULT:t2_hyst_0_a]]	[[RESULT:t2_hyst_0_a]]	[[RESULT:t2_hyst_0_a]]
Subgroup of women who had undergone hysterectomy§ — <5 years	[[RESULT:t2_hyst_1_a]]	[[RESULT:t2_hyst_1_a]]	[[RESULT:t2_hyst_1_a]]
Subgroup of women who had undergone hysterectomy§ — 5 years	[[RESULT:t2_hyst_2_a]]	[[RESULT:t2_hyst_2_a]]	[[RESULT:t2_hyst_2_a]]

Analysis and exposure	Events; person-years; IR	Crude HR (95%CI)	Adjusted HR (95%CI)
Subgroup of women who had undergone bilateral oophorectomy between age 45-54 years§ — 0 years	[[RESULT:t2_bso_45_54_0_a]]	[[RESULT:t2_bso_45_54_0_a]]	[[RESULT:t2_bso_45_54_0_a]]
Subgroup of women who had undergone bilateral oophorectomy between age 45-54 years§ — <5 years	[[RESULT:t2_bso_45_54_1_a]]	[[RESULT:t2_bso_45_54_1_a]]	[[RESULT:t2_bso_45_54_1_a]]
Subgroup of women who had undergone bilateral oophorectomy between age 45-54 years§ — 5 years	[[RESULT:t2_bso_45_54_2_a]]	[[RESULT:t2_bso_45_54_2_a]]	[[RESULT:t2_bso_45_54_2_a]]
Subgroup of women who had undergone bilateral oophorectomy at age 55 years or older§ — 0 years	[[RESULT:t2_bso_ge55_0_a]]	[[RESULT:t2_bso_ge55_0_a]]	[[RESULT:t2_bso_ge55_0_a]]
Subgroup of women who had undergone bilateral oophorectomy at age 55 years or older§ — <5 years	[[RESULT:t2_bso_ge55_1_a]]	[[RESULT:t2_bso_ge55_1_a]]	[[RESULT:t2_bso_ge55_1_a]]
Subgroup of women who had undergone bilateral oophorectomy at age 55 years or older§ — 5 years	[[RESULT:t2_bso_ge55_2_a]]	[[RESULT:t2_bso_ge55_2_a]]	[[RESULT:t2_bso_ge55_2_a]]

Analysis and exposure	Events; person-years; IR	Crude HR (95%CI)	Adjusted HR (95%CI)
Stratified analysis: by treatment form most used — Never used	[[RESULT:t2_route[[RESULT:t2_route[[RESULT:t2_route_0_a]]		
Stratified analysis: by treatment form most used — Oral	[[RESULT:t2_route[[RESULT:t2_route[[RESULT:t2_route_1_a]]		
Stratified analysis: by treatment form most used — Transdermal	[[RESULT:t2_route[[RESULT:t2_route[[RESULT:t2_route_2_a]]		
Stratified analysis: by treatment form most used — Other formulation	[[RESULT:t2_route[[RESULT:t2_route[[RESULT:t2_route_3_a]]		
Stratified analysis: by progestogen regimen most used — Never used	[[RESULT:t2_regime[[RESULT:t2_regime[[RESULT:t2_regimen_0_a]]		
Stratified analysis: by progestogen regimen most used — Oestrogen monotherapy	[[RESULT:t2_regime[[RESULT:t2_regime[[RESULT:t2_regimen_1_a]]		
Stratified analysis: by progestogen regimen most used — Oestrogen+cyclic progestogen	[[RESULT:t2_regime[[RESULT:t2_regime[[RESULT:t2_regimen_2_a]]		
Stratified analysis: by progestogen regimen most used — Oestro- gen+continuous progestogen	[[RESULT:t2_regime[[RESULT:t2_regime[[RESULT:t2_regimen_3_a]]		
Stratified analysis: by age of initiation — Never use	[[RESULT:t2_initia[[RESULT:t2_initia[[RESULT:t2_initiation_0_a]]		
Stratified analysis: by age of initiation — 45-51 years	[[RESULT:t2_initia[[RESULT:t2_initia[[RESULT:t2_initiation_1_a]]		

Analysis and exposure	Events; person-years; IR	Crude HR (95%CI)	Adjusted HR (95%CI)
Stratified analysis: by age of initiation — 52-56 years	[[RESULT:t2_initiation_2_a]]	[[RESULT:t2_initiation_2_a]]	[[RESULT:t2_initiation_2_a]]
Stratified analysis: by age of initiation — 57 years	[[RESULT:t2_initiation_3_a]]	[[RESULT:t2_initiation_3_a]]	[[RESULT:t2_initiation_3_a]]

Sister-cohort size and share: [[RESULT:sibling_population]]. The BSO45–54 death count is [[RESULT:bso_deaths]]. Their age-at-death distributions by MHT at death are [[RESULT:bso_death_age]].

Cause-specific mortality

The cardiovascular, cancer and other-cause rows follow Table3 and use the shorter register horizon. Cause proportions: [[RESULT:cause_proportions]]. The other-cause adjusted target remains explicitly unresolved under the m92/m222 conflict until source-supported clarification; available crude or other-cause components would not resolve it.

Cause and exposure	Events; person-years; IR	Crude HR (95%CI)	Adjusted HR (95%CI)
Cardiovascular mortality† — 0 years	[[RESULT:t3_cardiovascular_0_a]]	[[RESULT:t3_cardiovascular_0_a]]	[[RESULT:t3_cardiovascular_0_a]]
Cardiovascular mortality† — <5 years	[[RESULT:t3_cardiovascular_1_a]]	[[RESULT:t3_cardiovascular_1_a]]	[[RESULT:t3_cardiovascular_1_a]]
Cardiovascular mortality† — 5 years	[[RESULT:t3_cardiovascular_2_a]]	[[RESULT:t3_cardiovascular_2_a]]	[[RESULT:t3_cardiovascular_2_a]]
Cancer mortality† — 0 years	[[RESULT:t3_cancer_0_a]]	[[RESULT:t3_cancer_0_a]]	[[RESULT:t3_cancer_0_a]]
Cancer mortality† — <5 years	[[RESULT:t3_cancer_1_a]]	[[RESULT:t3_cancer_1_a]]	[[RESULT:t3_cancer_1_a]]
Cancer mortality† — 5 years	[[RESULT:t3_cancer_2_a]]	[[RESULT:t3_cancer_2_a]]	[[RESULT:t3_cancer_2_a]]
Other mortality† — 0 years	[[RESULT:t3_other_0_a]]	[[RESULT:t3_other_0_a]]	[[RESULT:t3_other_0_a]]
Other mortality† — <5 years	[[RESULT:t3_other_1_a]]	[[RESULT:t3_other_1_a]]	[[RESULT:t3_other_1_a]]
Other mortality† — 5 years	[[RESULT:t3_other_2_a]]	[[RESULT:t3_other_2_a]]	[[RESULT:t3_other_2_a]]

Additional source descriptions and diagnostics

The source's description of deaths preceded by contraindications is [[RESULT:contraindication_deaths]]; median age at the end of follow-up is [[RESULT:end_age]]. Source final-row demographic missingness is [[RESULT:missing_demographics]].

The supplementary residual plot will display the original 14 panels and the source uncertainty curves when approved inputs and model attribution are resolved. Diagnostic disposition and qualitative assessment: [[RESULT:ph_report]]. Source supplementary table 1 definitions are incorporated into the methods and registration; they are not empirical results.

Discussion

Interpretation conditional on the reconstructed evidence

For population mortality, the discussion will state the actual binary and duration-specific estimates with their uncertainty and applicable source sensitivities: [[RESULT:interpretation_1]]. If only counts or crude associations are available, the text will explicitly state that the published adjusted association has not been reconstructed. If all components are available, their directions and intervals will be described separately without converting complete coverage into agreement.

The sibling comparison will be interpreted within the selected discordant-family sample: [[RESULT:interpretation_2]]. An imprecise or different sibling association would be retained alongside the population association. It would not prove the presence or removal of all confounding, and a missing sister link would be a data boundary rather than a mortality finding.

Surgery-specific evidence will retain the separate risk populations and intervals: [[RESULT:interpretation_3]]. The younger BSO death-age distribution is conditioned on death and cannot establish increased life expectancy. Any unresolved older-BSO risk-set specification prevents a result for that target even if the younger group is fully reported.

Treatment heterogeneity will be described using the registered never-use comparisons: [[RESULT:interpretation_4]]. No treatment is ranked as causally superior from separate observational HRs. Unresolved dominant-category ties do not authorize selective publication of a favorable category or speculative new contrasts.

Cause-specific interpretation will preserve all three endpoint identities: [[RESULT:interpretation_5]]. Opposing or uncertain cause patterns are not averaged into a synthetic score. No main all-cause estimate or available cardiovascular/cancer output fills the adjusted other-cause gap.

Strengths, limits and relation to the source

The source design seeks long follow-up and time-varying treatment measurement in a nationwide register population. Those are intended features, not validated properties of data accessible in this conversion. Successful future record linkage and model

execution would still leave treatment indication, residual confounding, exposure measurement and informative selection/censoring as limits of observational interpretation. The source’s symptom-treatment and policy discussion does not turn this registration into medical guidance.

The supplied program narrows many implementation questions but does not provide a self-contained reproduction environment. Its precomputed histories, gravdb provenance and source/code conflicts limit exact reconstruction. The extraction explicitly separates these constraints from statistical uncertainty. It also distinguishes publication reference numbers from newly reconstructed observations and does not choose a scientifically different model simply because it would run.

The discussion will compare any reconstructed values to the original publication with exact source labels and rounding. The paper specifies no replication equivalence band; none is introduced. A difference, similar point estimate, wide interval, operational failure or unavailable target will be described for what it establishes within its scope. The separate original studies discussed by Mikkelsen et al. remain contextual comparisons; they are not independently reproduced here.

Conclusion

This prepared manuscript will report only the original analyses that can be reconstructed with established source definitions and approved inputs. It will retain unresolved targets and partial evidence. Final scientific conclusions remain unfilled until empirical evidence exists; no claim of causal treatment benefit, clinical safety or replication agreement is predetermined.

Source-code analysis appendix

The rows below preserve the additional specifications present in the supplied R code, which have no printed numerical result in the supplied paper/supplement. They remain in the original analysis modules and are not converter-added robustness analyses. Source-conflicting smoking and surgery-age targets retain their no-estimate dispositions; faithful component siblings remain separately reportable.

Source-code target and exposure	Events; person-years; IR	Crude HR (95%CI)	Adjusted HR (95%CI)
Code-only calendar interval- start<2003 — Never used	[[RESULT:code_cal interval_start<2003 never_used]]	[[RESULT:code_cal interval_start<2003 never_used]]	[[RESULT:code_cal interval_start<2003 never_used]]
Code-only calendar interval- start<2003 — Past or present use	[[RESULT:code_cal interval_start<2003 past_or_present_use]]	[[RESULT:code_cal interval_start<2003 past_or_present_use]]	[[RESULT:code_cal interval_start<2003 past_or_present_use]]

Source-code target and exposure	Events; person-years; IR	Crude HR (95%CI)	Adjusted HR (95%CI)
Code-only calendar interval- start>=2003 — Never used	[[RESULT:code_calen]]	[[RESULT:code_calen]]	[[RESULT:code_calen]]
Code-only calendar interval- start>=2003 — Past or present use	[[RESULT:code_calen]]	[[RESULT:code_calen]]	[[RESULT:code_calen]]
Code-only additional hyst/BSO adjustment — Never used	[[RESULT:code_sur]]	[[RESULT:code_sur]]	[[RESULT:code_sur]]
Code-only additional hyst/BSO adjustment — Past or present use	[[RESULT:code_sur]]	[[RESULT:code_sur]]	[[RESULT:code_sur]]
Code-only hysterectomy- age<55; comment45-54 unresolved — 0 years	[[RESULT:code_hys]]	[[RESULT:code_hys]]	[[RESULT:code_hys]]
Code-only hysterectomy- age<55; comment45-54 unresolved — <5 years	[[RESULT:code_hys]]	[[RESULT:code_hys]]	[[RESULT:code_hys]]
Code-only hysterectomy- age<55; comment45-54 unresolved — 5 years	[[RESULT:code_hys]]	[[RESULT:code_hys]]	[[RESULT:code_hys]]
Code-only hysterectomy- age>=55 — 0 years	[[RESULT:code_hys]]	[[RESULT:code_hys]]	[[RESULT:code_hys]]

ATC	Regimen	Form	Replication proportion (%)
G03CA03	Oestrogen	Nose spray	[[RESULT:s2_04]]
G03CA03	Oestrogen + Separate cyclic progestin	Transdermal	[[RESULT:s2_05]]
G03CA03	Oestrogen + Separate cyclic progestin	Oral	[[RESULT:s2_06]]
G03CA03	Oestrogen + Separate cyclic progestin	Injection	[[RESULT:s2_07]]
G03CA03	Oestrogen + Separate cyclic progestin	Nose spray	[[RESULT:s2_08]]
G03CA03	Oestrogen + Separate continuous progestin	Transdermal	[[RESULT:s2_09]]
G03CA03	Oestrogen + Separate continuous progestin	Oral	[[RESULT:s2_10]]
G03CA03	Oestrogen + Separate continuous progestin	Injection	[[RESULT:s2_11]]
G03CA03	Oestrogen + Separate continuous progestin	Nose spray	[[RESULT:s2_12]]
G03CA04	Oestrogen	Oral	[[RESULT:s2_13]]
G03CA04	Oestrogen + Separate cyclic progestin	Oral	[[RESULT:s2_14]]
G03CA04	Oestrogen + Separate continuous progestin	Oral	[[RESULT:s2_15]]
G03CA53	Oestrogen	Oral	[[RESULT:s2_16]]
G03CA53	Oestrogen + Separate cyclic progestin	Oral	[[RESULT:s2_17]]

ATC	Regimen	Form	Replication proportion (%)
G03FA01	Oestrogen and continuous progestin	Oral	[[RESULT:s2_18]]
G03FA01	Oestrogen and continuous progestin	Transdermal	[[RESULT:s2_19]]
G03FA11	Oestrogen and continuous progestin	Oral	[[RESULT:s2_20]]
G03FA12	Oestrogen and continuous progestin	Oral	[[RESULT:s2_21]]
G03FA15	Oestrogen and continuous progestin	Oral	[[RESULT:s2_22]]
G03FA17	Oestrogen and continuous progestin	Oral	[[RESULT:s2_23]]
G03FB01	Oestrogen and cyclic progestin	Oral	[[RESULT:s2_24]]
G03FB05	Oestrogen and cyclic progestin	Oral	[[RESULT:s2_25]]
G03FB05	Oestrogen and cyclic progestin	Transdermal	[[RESULT:s2_26]]
G03FB06	Oestrogen and cyclic progestin	Oral	[[RESULT:s2_27]]
G03FB09	Oestrogen and cyclic progestin	Oral	[[RESULT:s2_28]]
G03FB11	Oestrogen and cyclic progestin	Oral	[[RESULT:s2_29]]

Provenance, availability and references

This manuscript was prepared during Stage1 source conversion. It has no new empirical findings, no independent scientific reviewer and no original-author approval. The converter’s self-audit is separate from future model or publication validation. The supplied code is identified by its recorded hash and source line locators and is not redistributed here. Data access and analysis require a governed environment. The original article and supplement are referenced, not copied wholesale. Generated paper/report LaTeX, PDFs and ZIP are owned by the Transcriber and host.

The original article is the primary scientific reference [1]. Supplementary table1, table2 and figure1 are cited by page in the registration; the user-supplied analysis script is cited by line and recorded provenance. Bibliographic background claims in

this manuscript describe the original paper’s positioning rather than claiming a new systematic review.

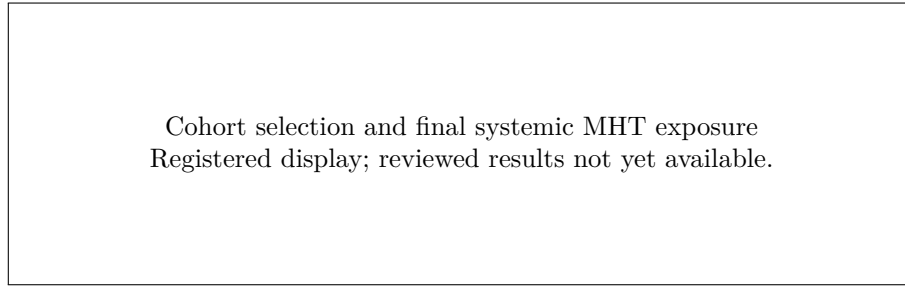


Fig. 1 Original cohort-selection flow and final treatment-duration groups. Counts remain unfilled until source-equivalent cohort and exposure construction is established. Exclusion reasons overlap; the union is supplied independently. Numerical cohort disposition: `[[RESULT:flow_report]]`. Missing values appear with numbered, fully retained reasons and are never inferred from neighboring boxes. Figure identity follows P Figure1; geometry is a meaning-preserving layout translation.

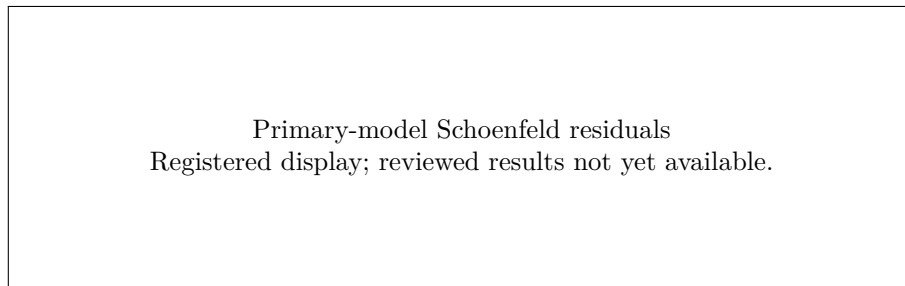


Fig. 2 Source primary binary-MHT model diagnostic in the14 printed term order. Residuals, fitted curve, uncertainty curves and P-values must come from the resolved source `m02/cox.zph/ggcox.zph` method; this renderer only draws supplied quantities. Diagnostic disposition: `[[RESULT:ph_report]]`. No residuals, smoother or P-value are estimated here. Unavailable terms retain their place and complete numbered reasons. There is no new numerical PH acceptance rule or corrective model. Two-column layout preserves the original panel content.

References

- [1] Mikkelsen, A. P., Bergholt, T., Lidegaard, . & Scheller, N. M. Menopausal hormone therapy and long term mortality: nationwide, register based cohort study. *BMJ* **392**, e085998 (2026).