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Time-varying treatment effect modification of oral analgesic effectiveness by depressive symptoms in knee osteoarthritis: an application of structural nested mean models in a prospective cohort

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Study objective

- Knee osteoarthritis (OA) is a leading cause of physical disability and is associated with substantial unmet medical care needs.
- Treatments include: weight loss, joint replacement, oral analgesics, etc.
- Depressive symptoms are common in Knee OA.
- Depressive symptoms could be a source of heterogeneity, increasing knee pain severity and influencing oral analgesic effectiveness.
- This study aims to assess if there is effect modification of depressive symptoms in the causal effect of oral analgesic in Knee OA.

Data

Data source:

- Osteoarthritis Initiative (OAI) prospective cohort study from 2004 to 2010
- Inclusion: 1) patients aged 45 - 79 years

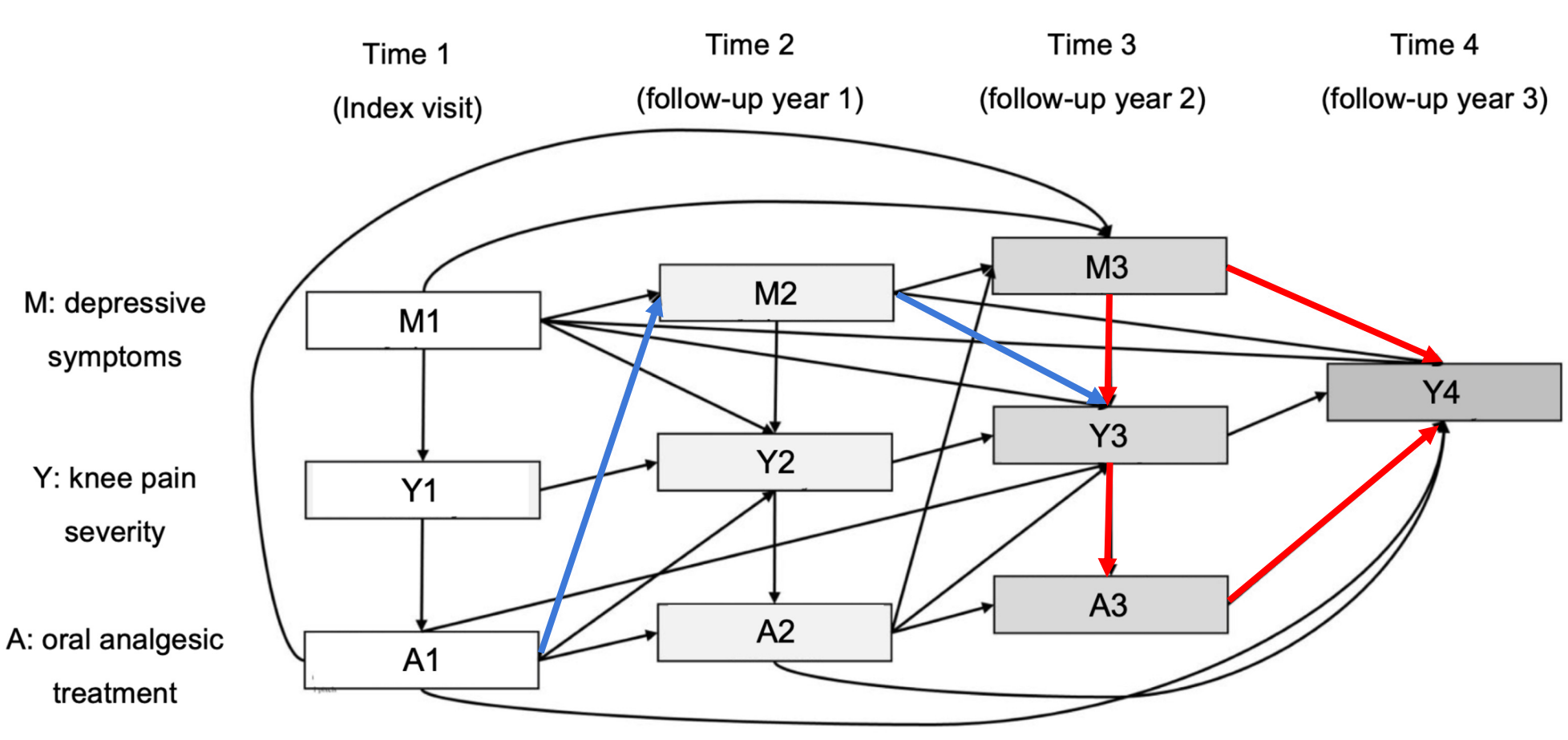
  2) patients with no oral analgesic treatment at baseline

Variables:

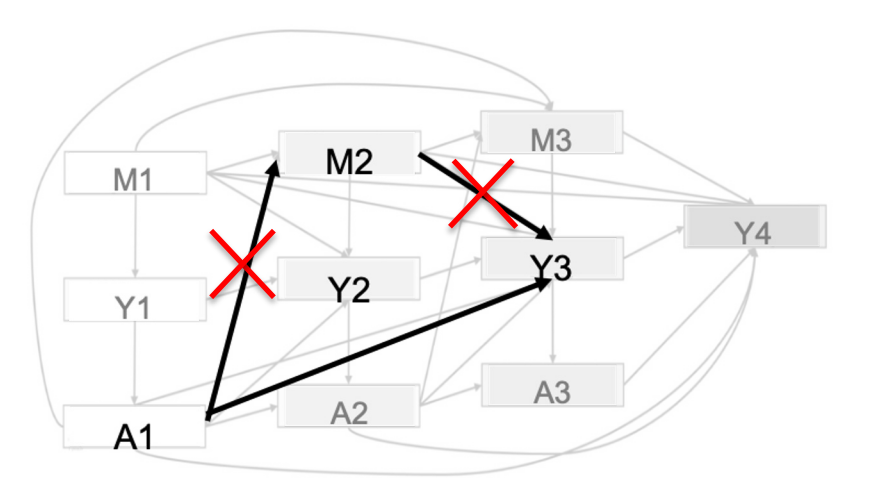
- **Exposure (A):** use of oral analgesic medications (Yes/No)
- **Effect modifier(M):**
  - depressive symptoms score > 16 (Yes/No)
  - quantified by the Center for Epidemiologic Studies Depression (CES-D) Scale
- **Outcome(Y):**
  - knee pain severity score (0-100)
  - Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
- **Confounders(L):**
  - Time-fixed: age, sex, race, marital status, education, employment status, health insurance, smoking, alcohol consumption, etc.
  - Time-dependent: BMI, knee injuries, physical performance, etc.

Study design

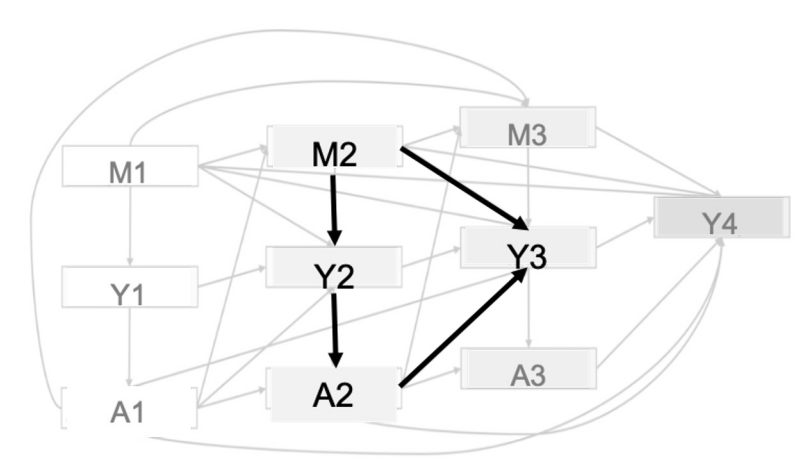
3-year longitudinal cohort study



Study design



(A)



(B)

M2 is a mediator, conditioning on M2:
- blocks the causal pathway: A1 → M2 → Y3

M2 is a common cause, not conditioning on M2:
- opens the non-causal pathway: A2 ← Y2 ← M2 →Y3

Marginal structural model: works for marginal effect

Of interest: subgroup risk difference, treatment effect **with and without** depressive symptoms

Estimand: $E(Y_t|A_t = 1, M_t) - E(Y_t|A_t = 0, M_t)$

Model: IPTW-RWR SNMM

Inverse-probability-of-treatment weighted regression-with-residuals structural nested mean model

Step 1: Treatment/Observation models

- **Inverse probability treatment weight:** regress A on covariates at and before time t
- **Inverse probability observation weight:** account for missing data

Step 2: Regress-with-residual procedure

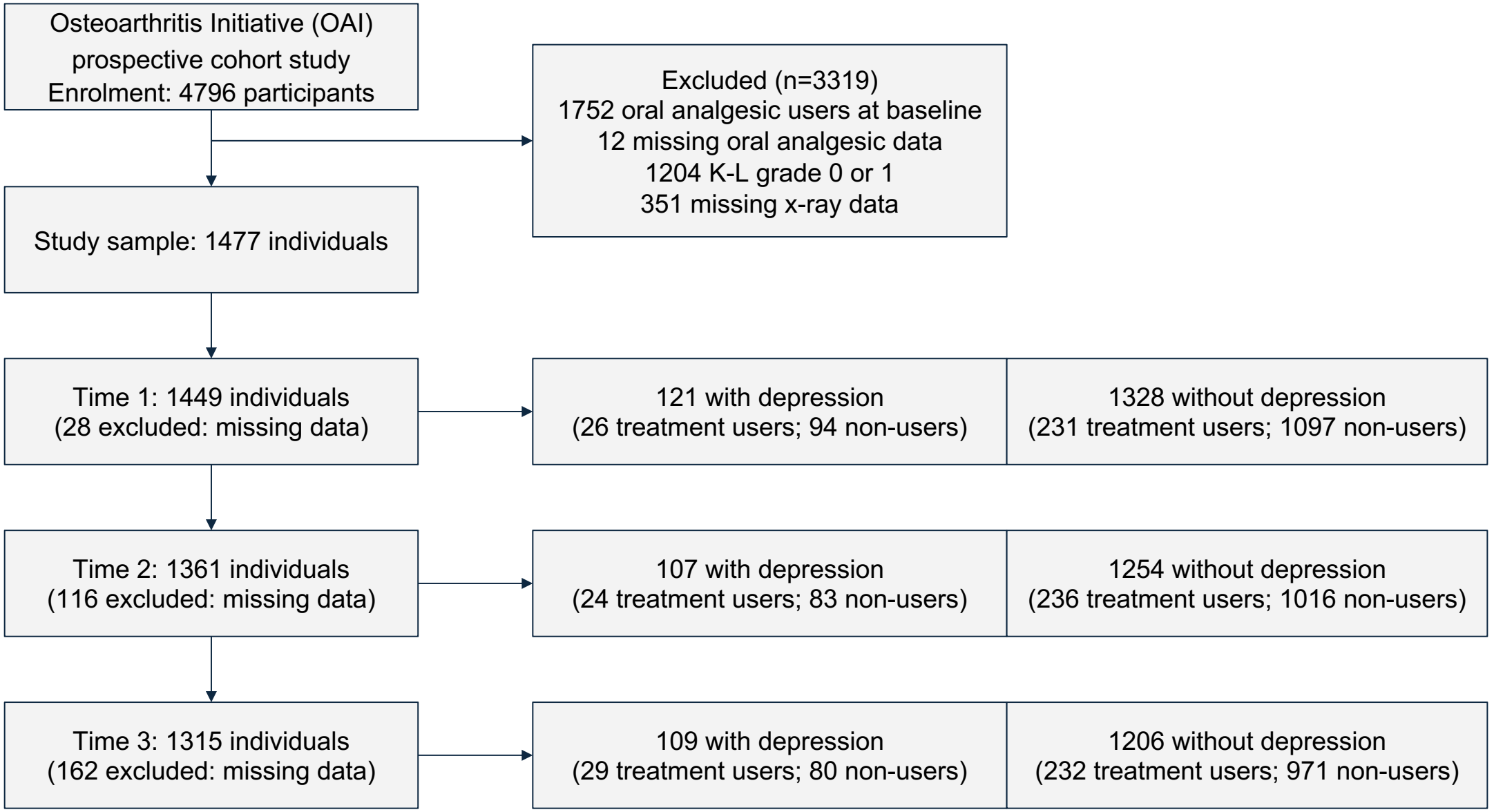
Directly conditioning on M is problematic. Instead, condition on the residual (which is independent of A and keeps the indirect effect)

$$\hat{\delta}(M_t) = M_t - \hat{E}(M_t \mid M_{t-}, A_{t-1})$$

Step 3: Outcome model

$$E(Y_T|A_t, M_t, \forall t) = \alpha_0 + \sum_{t=1}^{T} \alpha_t A_t + \sum_{t=1}^{T} \beta_t \hat{\delta}(M_t) + \sum_{t=1}^{T} \gamma_t A_t M_t$$

Results


Osteoarthritis Initiative (OAI)
prospective cohort study
Enrolment: 4796 participants
Excluded (n=3319)
1752 oral analgesic users at baseline
12 missing oral analgesic data
1204 K-L grade 0 or 1
351 missing x-ray data
Study sample: 1477 individuals
Time 1: 1449 individuals
(28 excluded: missing data)
121 with depression
(26 treatment users; 94 non-users)
1328 without depression
(231 treatment users; 1097 non-users)
Time 2: 1361 individuals
(116 excluded: missing data)
107 with depression
(24 treatment users; 83 non-users)
1254 without depression
(236 treatment users; 1016 non-users)
Time 3: 1315 individuals
(162 excluded: missing data)
109 with depression
(29 treatment users; 80 non-users)
1206 without depression
(232 treatment users; 971 non-users)

Results

Pain severity during follow-up

		No depressive symptoms, mean			Depressive symptoms, mean		
Treatment	Pain assessment	Not treated	Treated	SMD	Not treated	Treated	SMD
T1	T2	10.25	16.01	0.359	17.26	22.39	0.266
T2	T3	9.25	14.38	0.352	16.35	20.00	0.205
T3	T4	9.43	16.23	0.448	18.85	23.39	0.211

Pain was consistently higher among individuals

- with treatment than without
- with depression than without

Results

Average causal effects of treatment on pain severity in individuals with and without depressive symptoms from an structural nested mean model

Treatment	Pain assessment	Depressive symptoms, μ (95% CI)	No depressive symptoms, μ (95% CI)	Difference, μ (95% CI)
T1	T2	–0.10 (–9.94, 9.74)	1.00 (–1.22, 3.21)	–1.10 (–11.19, 9.00)
T2	T3	–6.01 (–16.34, 4.32)	–0.77 (–3.24, 1.71)	–5.24 (–15.88, 5.39)
T3	T4	–16.67 (–26.33, –7.01)	–0.14 (–3.33, 3.06)	–16.53 (–26.75, –6.31)
T1–T2	T3	–5.38 (–20.62, 9.85)	–2.14 (–5.10, 0.83)	–3.25 (–18.62, 12.13)
T1–T3	T4	–2.76 (–24.11, 18.60)	–0.75 (–6.61, 5.11)	–2.01 (–24.08, 20.06)

- Time-specific estimates: at each time, the causal effect of treatment on pain severity is larger among individuals with depression than without
- Cumulative estimates: the average causal effects for 2 years and 3 years of treatment are larger among individuals with depression than without

Discussion

Strength:

- Careful thinking of casual DAG
- Comprehensive collection of covariates
- Appropriate approach used to deal with time-varying effect modification

Limitations:

- Limited number of patients with depressive symptoms
- No sensitivity analysis and checking treatment assignment weight overlapping
- Depression is associated with poorer medication adherence, but no information was available on medication adherence between time points
- The authors did not investigate the effect of the level of depression, but combined them into one group instead. It may lead to wide CIs