Symptom Instability as an Early Warning Sign of Transition to Severe Depression

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Background

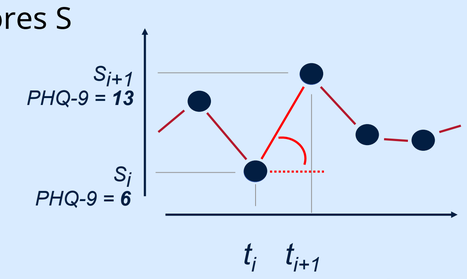
Beyond severity, clinical instability—fluctuations in symptom severity over time—is an important prognostic factor across psychiatric conditions.

This study investigates whether instability in PHQ-9 scores can predict transition to severe depression:

1. **Between-individuals analysis to evaluate if individuals with higher instability are at greater risk** of transitioning to severe depression.
2. **Within-individual analysis to examine whether instability increases** in the period leading up to transition.

Instability

- **Definition:** time-corrected RMSSD
- **Intuition:** *Slope* between successive scores S



- **Data source:** PHQ-9 scores, from de-identified EHRs in NeuroBlu

1. Between-individuals

Cohort selection

- **Inclusion:** Individuals diagnosed with MDD (ICD-9/10)
- **Observation window:** ≥5 PHQ-9 scores within 6 months

Statistical methods

- **Main analysis:** Cox model adjusted for baseline severity (mean PHQ-9), age, sex, race and psychiatric comorbidities
- Secondary models assess item-level instability (adjusted for baseline severity only)
- **2 outcomes:** 12-month risk of transition to more severe depression (PHQ-9 > 14 or PHQ-9 > 19)

2. Within-individual (temporal nature)

Cohort selection

- **Inclusion:** Individuals diagnosed with MDD (ICD-9/10)
- **Observation window:** ≥15 PHQ-9 scores, 5 within 6 months

Statistical methods

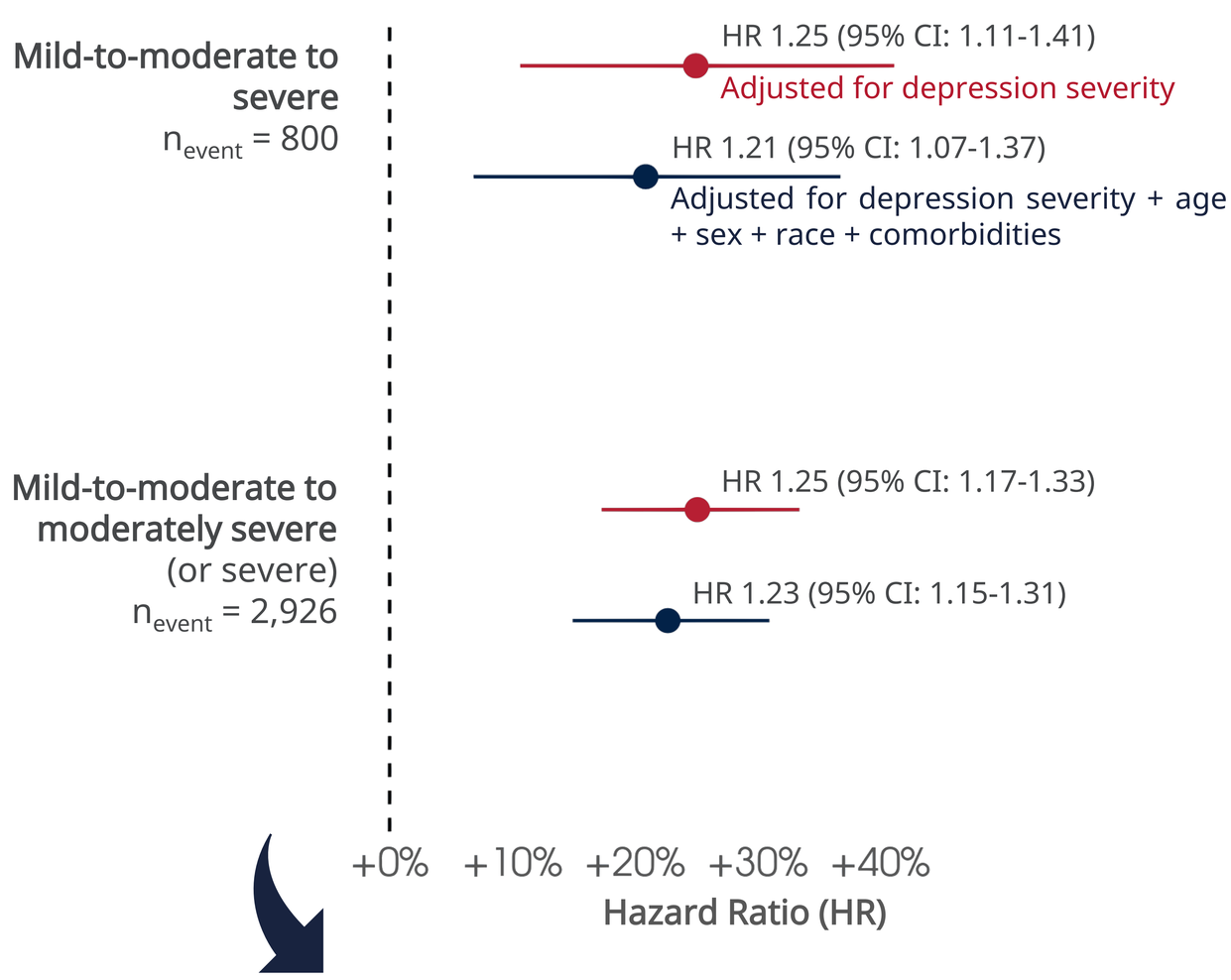
- Compared across 6 overlapping time windows relative to patient-specific baseline
- **Analysis:** Relative increase in instability from baseline, compared using paired t-tests

Results

Between individuals, higher instability in depressive symptoms linked to an increased risk of transition

21%/23% increase in risk of transition to moderately severe/severe depression for every 2 SD increase in instability.

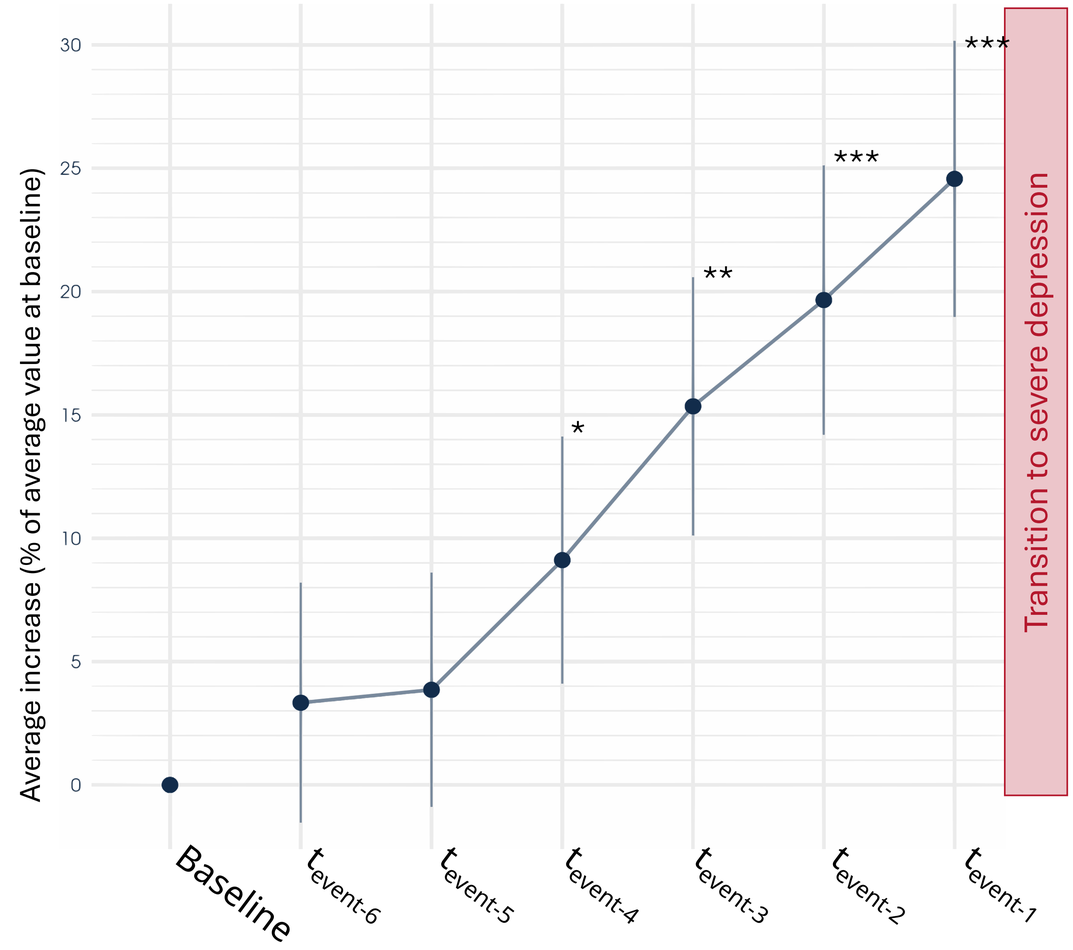
17,935 individuals (70% female, mean age 42.3 ± 18.5)



Within-individual, instability consistently rises in the weeks leading up to severe depression

Instability increased by **25% from baseline**, with significant differences observed **starting from the fourth visit before the event** ($p < 0.05$).

2,142 individuals (74.6% female; mean age 44.5 ± 17.6)



Instability in suicidal symptoms is a particularly strong predictor

Instability in all PHQ-9 items (except for psychomotor changes) was linked to higher risk. Suicidal ideation showed the strongest effect, with **70% increase in risk** for every 2 SD increase in instability.

1,189 individuals (70% female; mean age 44.3 ± 19.2)

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Disclosures: At the time of this study: TDD reports no conflicts of interest to disclose. MT has received consultancy fees from Holmusk Inc and from Cristal Health Ltd. NL reports employment with and equity ownership in KKT Technologies Pte. Ltd., or its subsidiaries. AJR has received consulting fees from Compass Inc., Curbstone Consultant LLC, Emmes Corp., Evecxia Therapeutics, Inc., Holmusk Technologies, Inc., ICON, PLC, Johnson and Johnson (Janssen), Liva-Nova, MindStreet, Inc., Neurocrine Biosciences Inc., Otsuka-US; speaking fees from Liva-Nova, Johnson and Johnson (Janssen); and royalties from Wolters Kluwer Health, Guilford Press and the University of Texas Southwestern Medical Center, Dallas, TX (for the Inventory of Depressive Symptoms and its derivatives). He is also named co-inventor on two patents: U.S. Patent No. 7,795,033: Methods to Predict the Outcome of Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S, Wilson AS; and U.S. Patent No. 7,906,283: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S.

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