

CUMULATIVE DOPAMINE-AGONIST EXPOSURE AND INCIDENT IMPULSE-CONTROL DISORDERS IN PARKINSON'S DISEASE: A THREE-COHORT LONGITUDINAL CAUSAL-MODELLING STUDY

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BACKGROUND

- Impulse-control disorders (ICDs)** - gambling, hypersexuality, compulsive buying/eating, hobbyism, punding, walkabout - consistently affect a substantial minority of people with Parkinson's disease (PD) and cause major psychosocial harm ^[1,2,3,4].
- Dopaminergic therapy, in particular, **dopamine agonists (DAs)** are implicated due to their effects on mesolimbic reward circuits ^[1,5,6].
- Gap:** most evidence is single-cohort, cross-sectional; reproducibility, DA-specificity and independence from the non-motor phenotype remain open ^[7,8].

AIMS:

- Test whether ICD prevalence and its DA-exposure association **replicate across three independent PD cohorts**, characterising the exposure–incidence and exposure–severity relationship.

METHODS:

- Cohorts:** Parkinson's Progression Markers Initiative (n = 1,052)^[9], OPDC Discovery (n = 992)^[10], Tracking P3 (n = 1,938) ^[11];
- Outcome:** Harmonised QUIP: binary, 0-7 full severity
- Exposure:** Dated DA/other medication episodes → active, cumulative-days & dose-burden windows (6/12/24m, lifetime).
- Covariates (C-full):** Age, sex, duration, MDS-UPDRS I & II, autonomic (SCOPA-AUT), anxiety, depression, sleepiness, function
- Analysis:** Next-visit incident modelling using patient-clustered GEE; FDR; IPTW MSMs; random-effects meta-analysis.

RESULTS:

ICD prevalence replicates
~21% baseline; **43–45% ever-positive** in all three datasets
Hobbyism, eating, punding and hypersexuality are most common; gambling and walkabout rarest, the rank is consistent across datasets

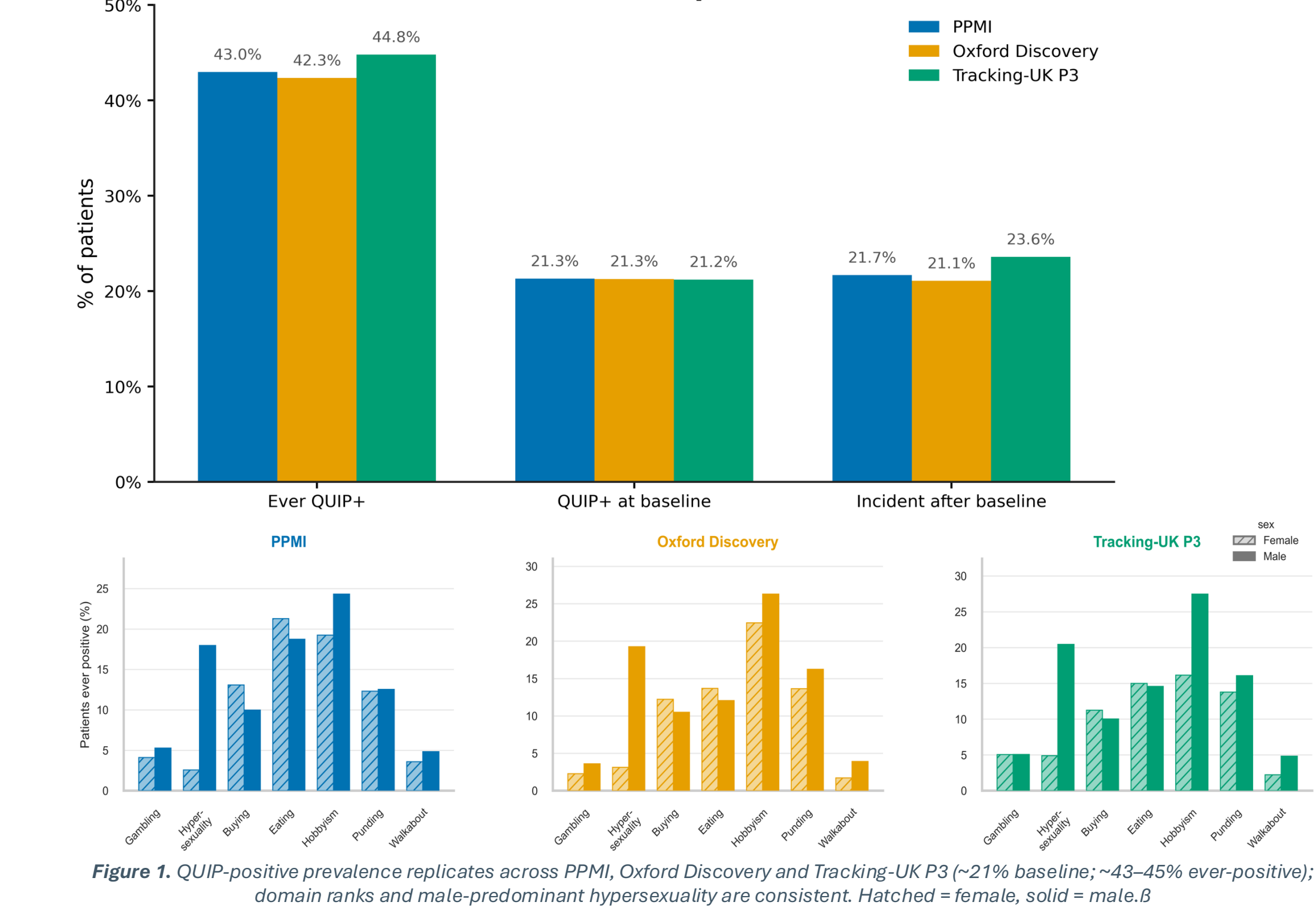
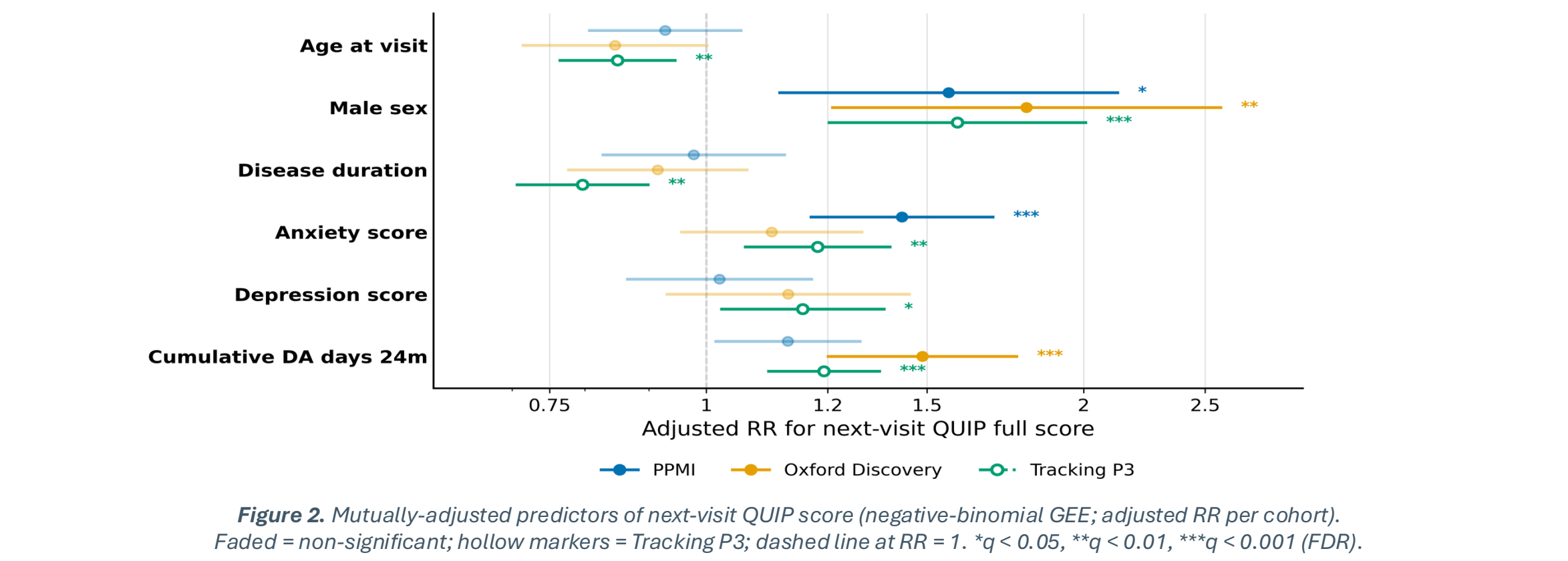


Figure 1. QUIP-positive prevalence replicates across PPMI, Oxford Discovery and Tracking-UK P3 (~21% baseline; ~43–45% ever-positive); domain ranks and male-predominant hypersexuality are consistent. Hatched = female, solid = male.

Cohort	Patients, n	Age, mean (SD)	Female, n (%)	Mean visits / patient	Mean days between visits
PPMI	1,052	62.4 (8.5)	390 (37.1)	4.8	405
Oxford Discovery	992	67.4 (8.5)	352 (35.5)	4.1	665
Tracking-UK P3	1,938	67.6 (9.2)	675 (34.8)	3.5	587

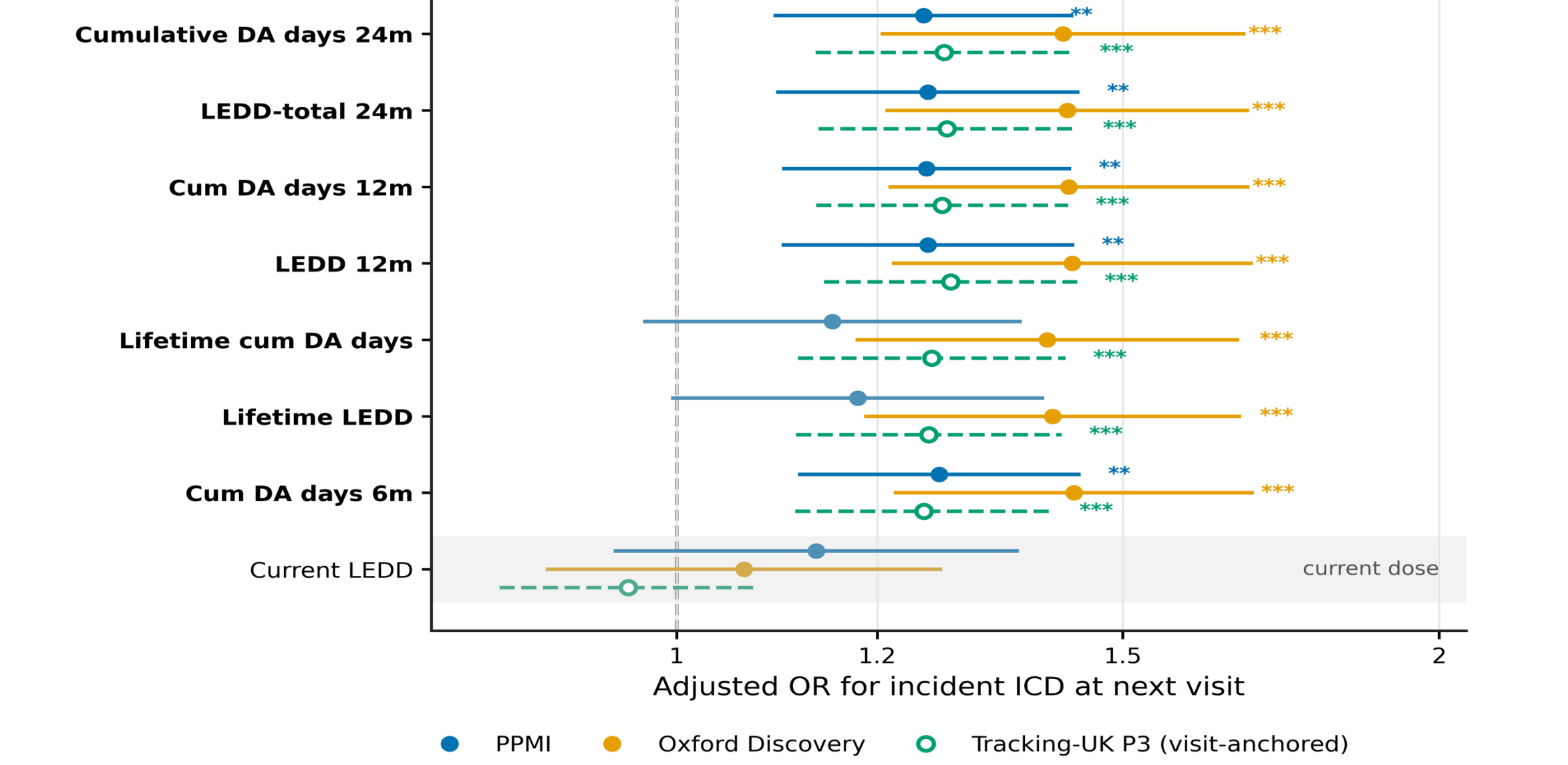
Who develops ICD?

Independent baseline correlates of next-visit incident ICD were consistent across cohorts: **male, younger age / earlier diagnosis, anxiety & depression**. The cumulative-DA effect is **independent of this phenotype**.

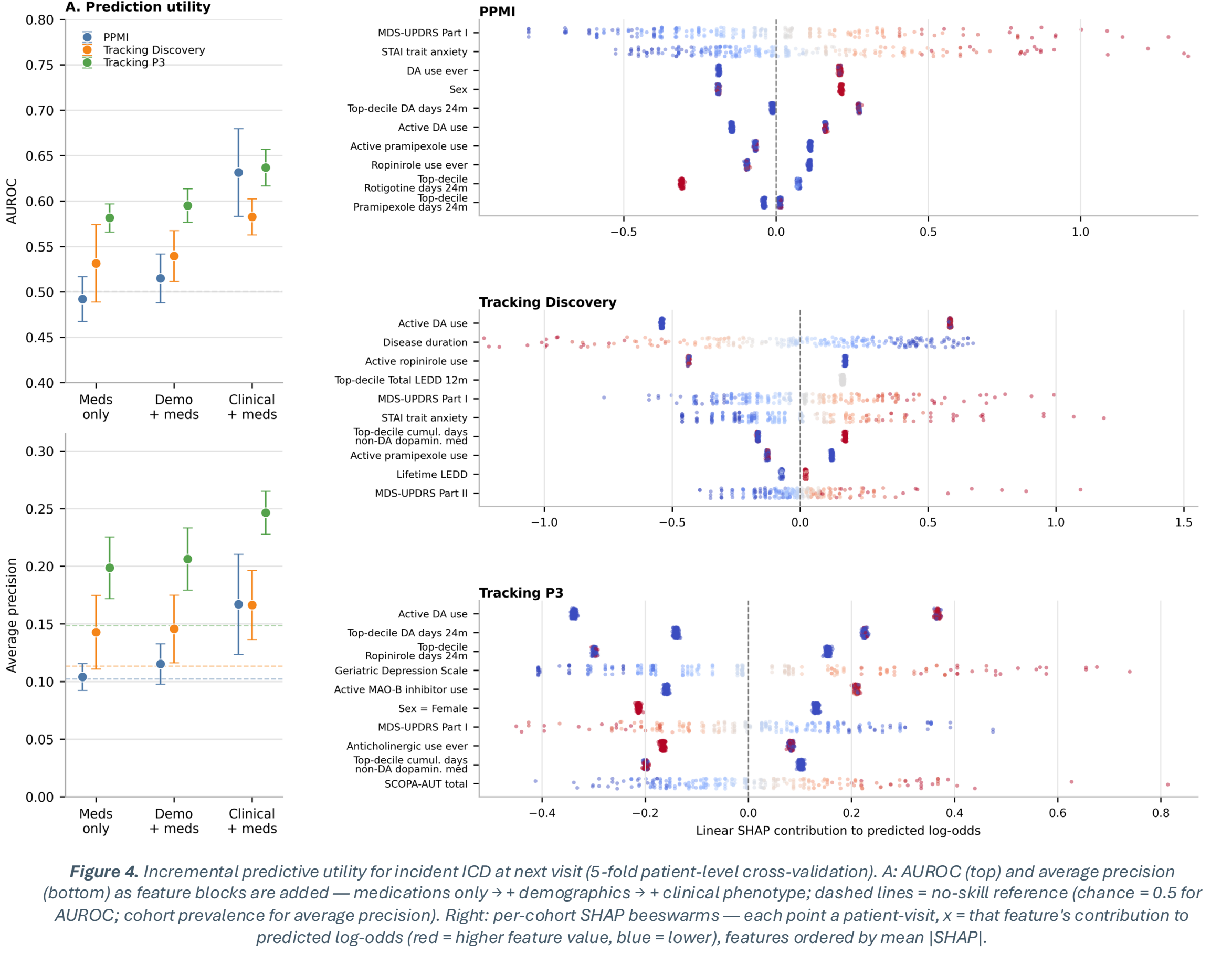


Cumulative exposure, not current dose

Cumulative DA exposure tracked ICD more strongly than a current-dose snapshot, even after covariate adjustment:

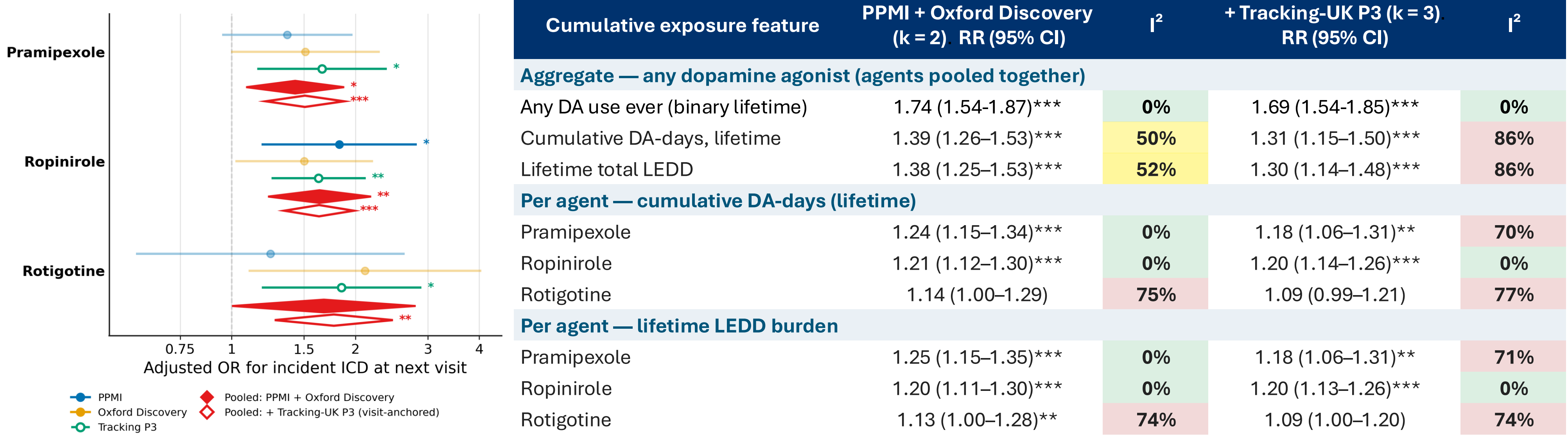


Clinical phenotype is necessary for the prediction



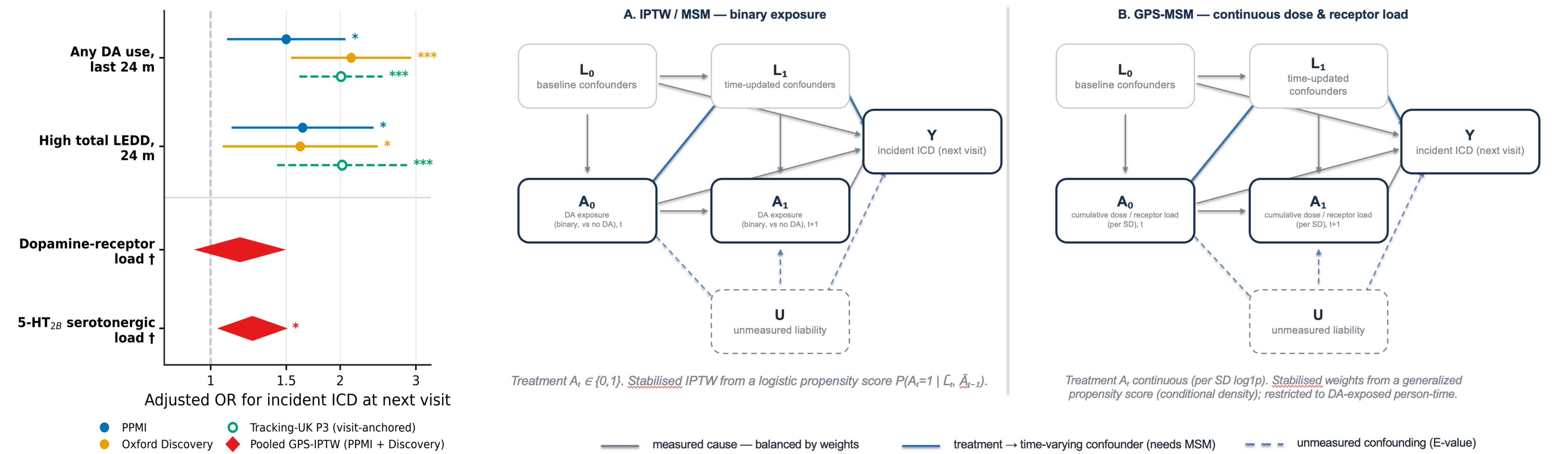
Heterogeneity of DA exposure collapses under per-agent decomposition

- Aggregate any-DA cumulative exposure pools with **high between-cohort heterogeneity** ($I^2 \approx 86\%$, $k=3$). In the exact-window primary pool (PPMI + Oxford Discovery), decomposing by agent removes it for **pramipexole and ropinirole** ($I^2 = 0\%$); residual heterogeneity sits only in **rotigotine**, which is prescribed sparsely.
- Adding Tracking-UK P3 as a visit-anchored sensitivity ($k = 3$) **re-introduces heterogeneity for pramipexole** (I^2 $0\% \rightarrow 70\%$), which might be because P3 has no prescription-episode dates and its windows are reconstructed at visit midpoints, while **ropinirole stays consistent** ($I^2 = 0\%$). All effects are positive throughout.



Does the association survive causal adjustment?

- DA exposure causally raises incident ICD:** under IPTW/MSM (time-varying-confounding adjustment, next-visit incident), any recent DA use raises ICD risk ~1.5–2.3× and high cumulative LEDD ~1.6–2.0× in all three cohorts (all FDR-significant).
- Effect is **threshold-like (exposure), not dose-graded** : a continuous-dose GPS-MSM among already-exposed person-time was null/inconclusive (per-SD ORs ~1.0–1.2, every pooled CI crosses 1) => risk is threshold-like (on a DA vs not), not "more drug, more risk."
- Class-wide effect:** per-agent and active-comparator IPTW show no agonist hierarchy (head-to-head is positivity-limited).
- Candidate serotonergic mechanism (exploratory):** receptor-load GPS-IPTW: dopamine-subtype load null and not separable (D2/D3/D4 collinear); 5-HT_{2B} serotonergic load OR 1.25 (1.05–1.50), $q=0.028$.



CONCLUSION:

- Across three independent cohorts, **ICDs were common and reproducible** (~21% baseline, 43–45% ever) and **predicted by a consistent phenotype: male sex, younger/earlier-onset disease, and prominent anxiety and depression**.
- Cumulative DA exposure** was strongly associated with **incident ICD and causally robust (IPTW/MSM; OR ≈ 1.5 –2.3, all cohorts)**, strongest for any recent exposure and high cumulative LEDD, but a **graded dose–response and agonist-specific effects were not confirmed** (GPS-MSM) => a **threshold-like (high DA-LEDD), class-wide effect** independent of phenotype.
- The **affective risk phenotype** and **5-HT_{2B} receptor-load signal** both implicate **serotonin**. Across agonists and doses; non-motor symptoms help flag higher-risk patients, but individual prediction needs the full clinical phenotype^[2,12].

LIMITATIONS:

- The data are **observational**, so residual **confounding by indication cannot be excluded**; its potential influence was quantified using E-values.
- Tracking-UK P3 **did not record** prescription start and stop dates, so its exposure windows were reconstructed around visits => reported as a **sensitivity analysis**.
- Per-agent and receptor-specific** comparisons were constrained by **limited positivity**, and the active-comparator analysis was **estimable in only one cohort**.
- QUIP** is a screening questionnaire rather than a diagnostic assessment and may **under-detect ICDs**, partly because **stigma around these behaviours discourages disclosure**^[13,14].

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