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BACKGROUND

- Alzheimer's disease (AD), the most common form of dementia, will affect 14 million by 2060; with an estimated cost of \$305 billion.
- Traditional drug development is high-investment, high-risk, and time-consuming;
- 500+ Randomized controlled trials in the past two decades for AD, only 7 approved by FDA: including 4 treatments for symptoms (donepezil, rivastigmine, galantamine, memantine) and 2 anti-amyloid agents that slow AD progression (Lecanemab, Donanemab)
- Drug repurposing may hold the key to meeting the urgent need for new ADRD treatments
- Previous studies of proton pump inhibitors (PPIs) and dementia have reported inconsistent results. Whether PPIs affect dementia risk and whether such effects vary across subgroups remains unclear.
- We applied the high-dimensional iterative causal forest (hdiCF) machine learning subgrouping algorithm to assess heterogeneous treatment effects (HTEs) of PPIs on dementia.

OBJECTIVE

- To assess the average treatment effect in the treated (ATT) and HTE of PPI on incident ADRD.

METHODS

- We emulated a target trial using 24 monthly sequential trials (2009–2010) with UK Biobank (UKB) primary care data, comparing PPI initiators and non-initiators aged ≥ 55 years.
- Individuals initiated PPI before enrolment in UKB were excluded to mitigate immortal time bias.
- Participants were followed from baseline until dementia, death, loss to follow-up, or 10 years, whichever occurred first. The primary outcome was AD; secondary outcomes included all-cause and vascular dementia.
- To control confounding, we applied high-dimensional propensity score (hdPS)-matching using ~ 200 ordinal high-dimensional variables identified from six linked electronic-health-record domains along with age, sex, 3 genetic modifiers: APOE genotype, an AD polygenic risk score excluding the APOE region (nonAPOE-PRS), and CYP2C19 phenotypes (rapid, intermediate, or poor metabolizers) in each trial.
- We then pooled the hdPS-matched trials into a single cohort for assessing average and heterogeneous treatment effects. We then applied hdiCF with 448 high-dimensional variables and the 5 predefined variables to identify subgroups and estimated 10-year adjusted risk differences (aRDs) using inverse-probability-treatment weight and the Aalen–Johansen estimator (Fig 1).

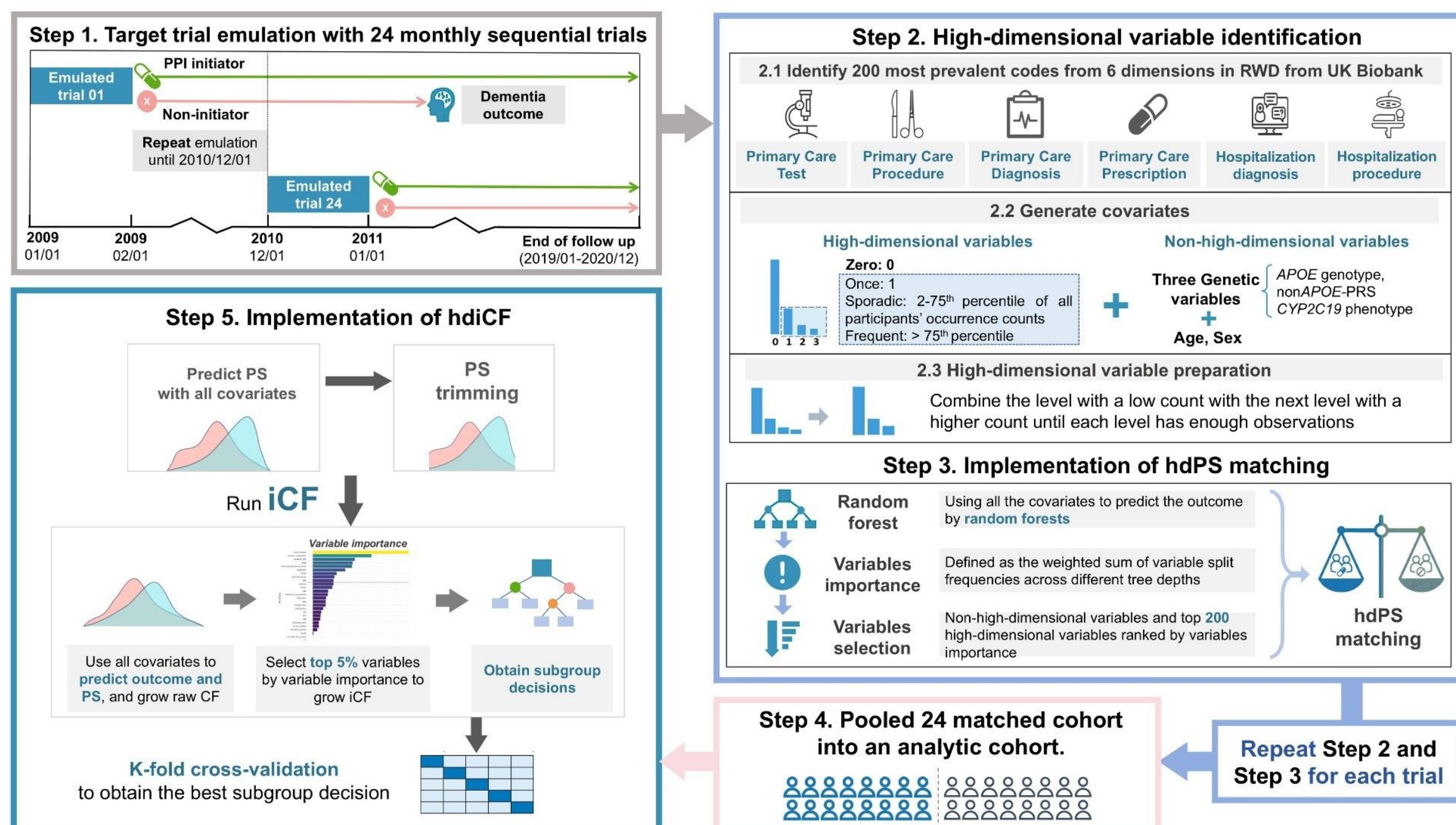


Fig 1. The workflow for leveraging high-dimensional Biobank data to assess the ATT and HTE of PPI on ADRD risk.

RESULTS

- Covariates are well balanced after in the hdPS-matched cohort (Fig 2).
- hdiCF selected top 5% (n=23) covariates by variable importance (VI), with APOE genotype emerging as the most important variable (Fig 3).
- The overall 10-year aRD was 0.04% (95% CI [-0.23%, 0.31%]; risks 0.92% vs. 0.88%) for AD among 10,368 PPI initiators and 10,368 non-initiators. Corresponding aRDs were -0.05% (-0.44%, 0.35%) for all-cause dementia and -0.03% (-0.21% to 0.14%) for vascular dementia.
- HTE analyses suggested a potential increased AD risk among APOE $\epsilon 4$ carriers (2773 vs 2750; aRD 0.69% [-0.32%, 1.71%]) (Fig 4) and a potential protective effect among CYP2C19 rapid metabolizers (3334 vs 3308; all-cause dementia: aRD -0.87% [-1.63%, -0.11%]) (Fig 5).

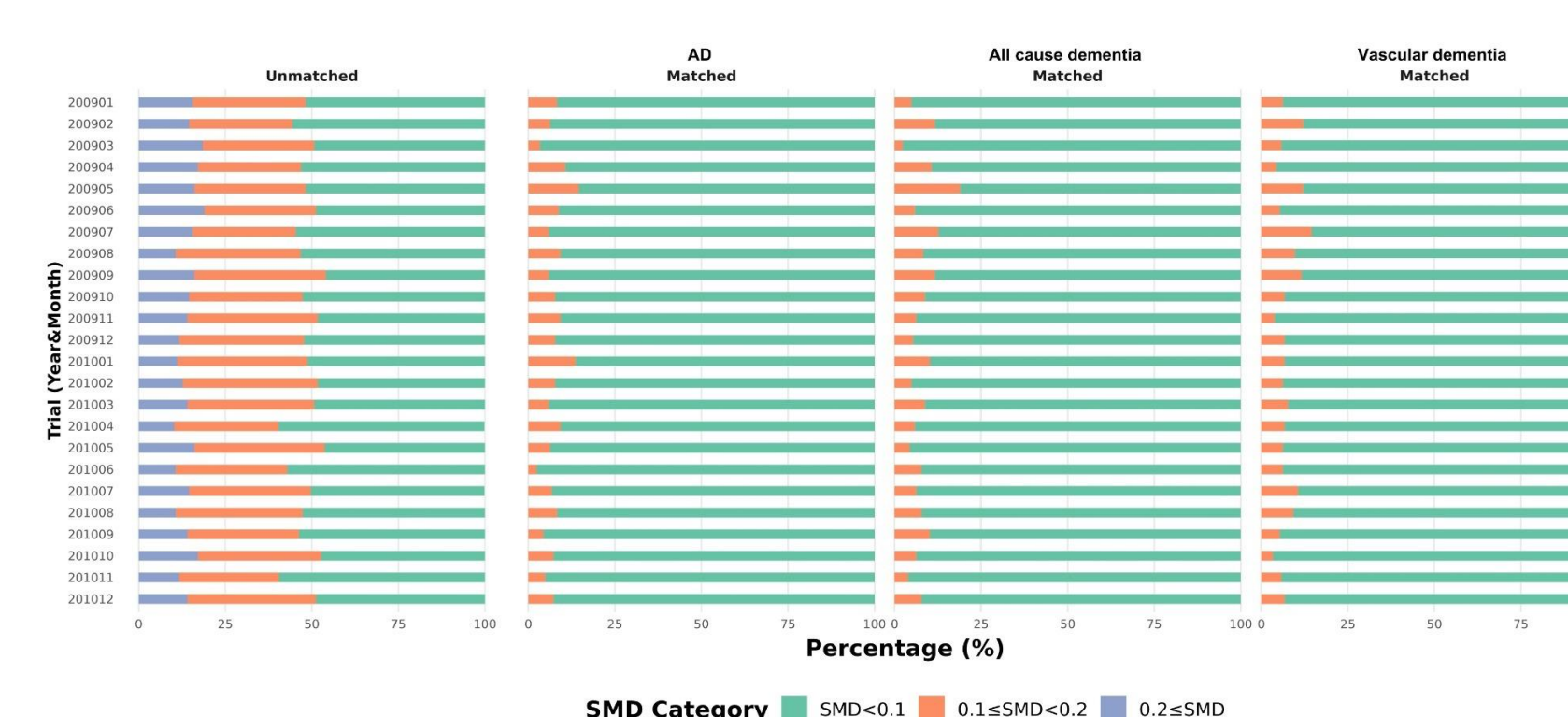


Fig 2. Proportion of selected HD variables within specified SMD ranges before and after hdPS matching.

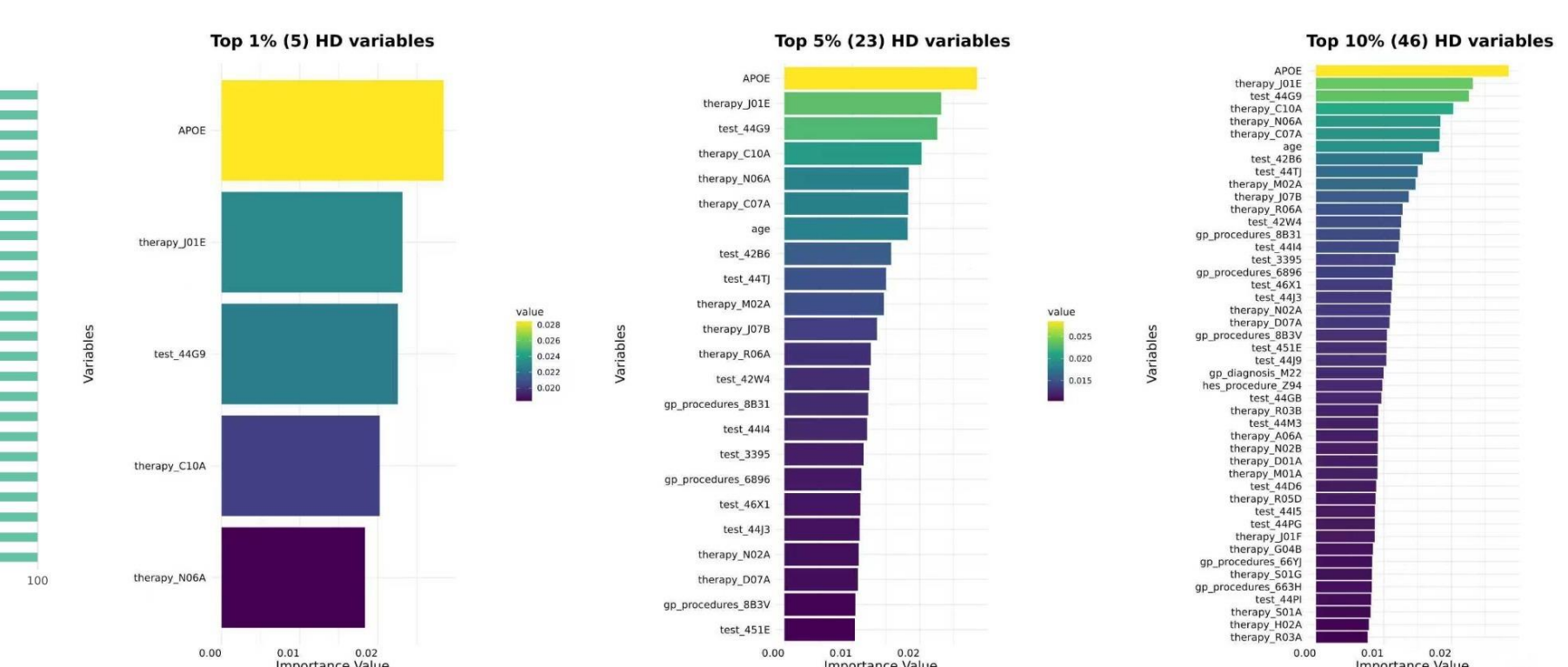


Fig 3. Variable importance of top-ranked variables from a raw causal forest for AD Outcome.

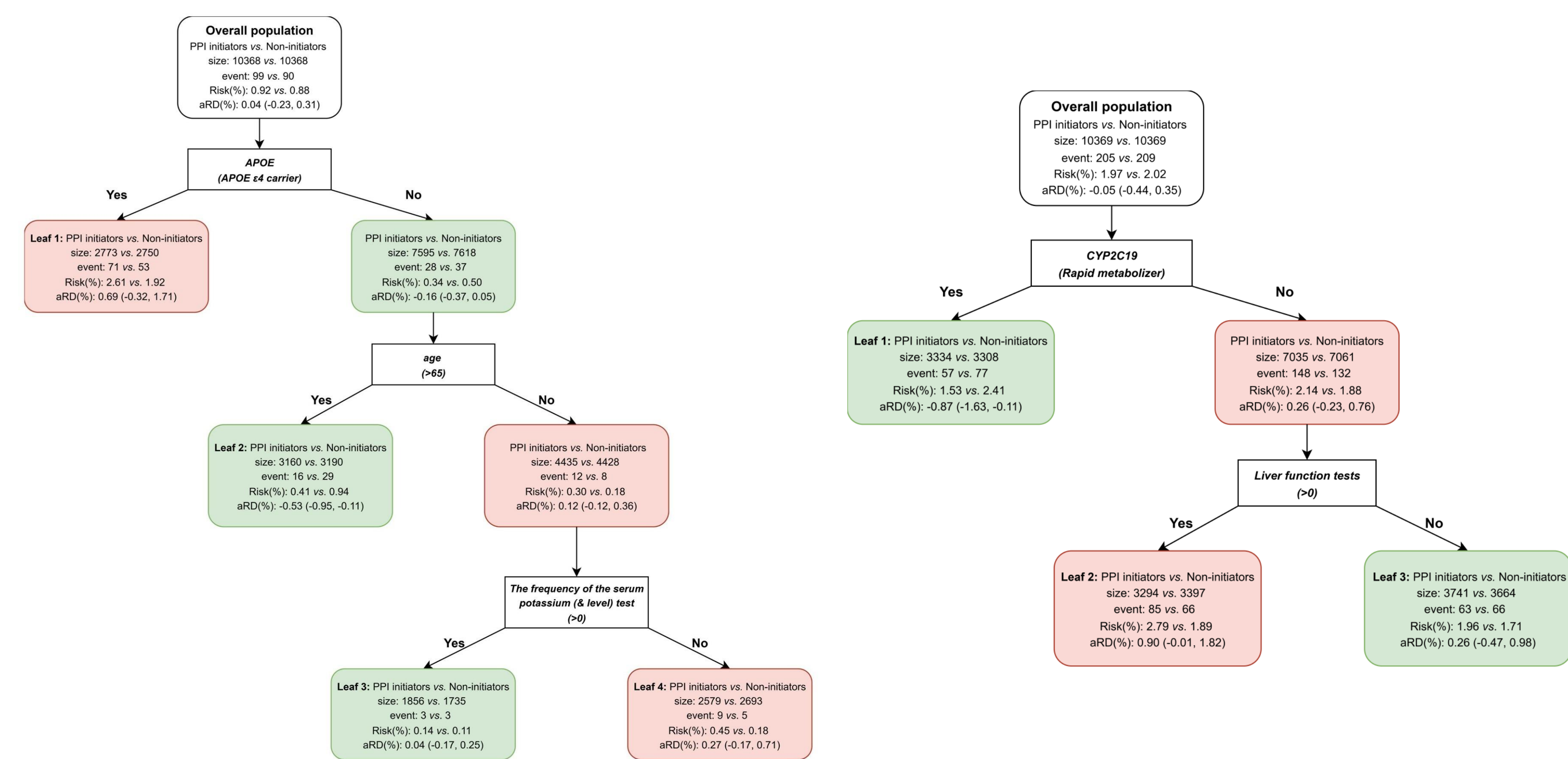


Fig 4. Subgroup decision from hdiCF analyses for AD outcome in the primary analysis.

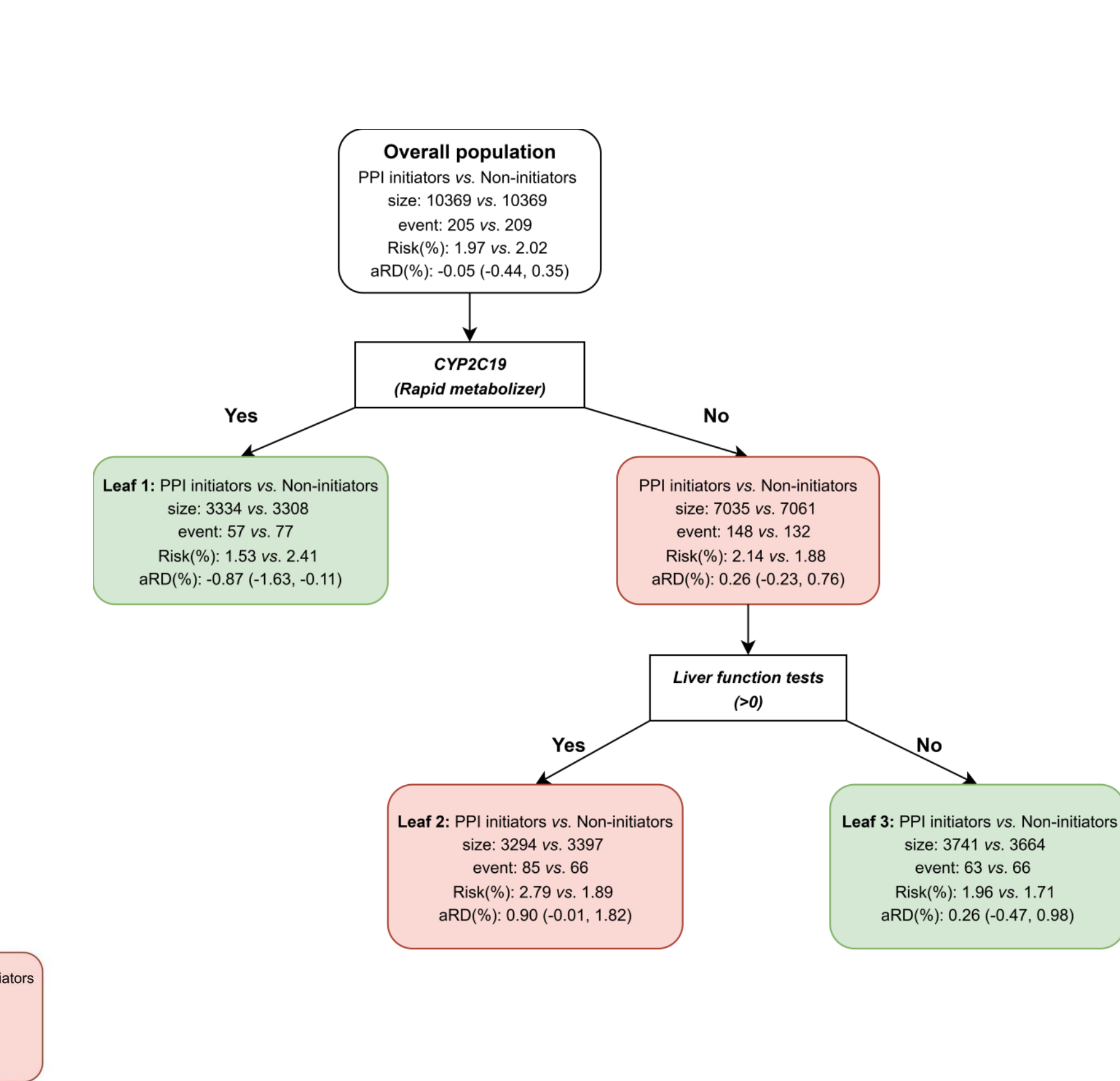


Fig 5. Subgroup decision from hdiCF analyses for all-cause dementia outcome in the primary analysis.

CONCLUSIONS

- PPI use was not associated with dementia risk in overall population. However, cognitive effects may differ across genetic subgroups, with potential harm among APOE $\epsilon 4$ carriers and possible benefit among CYP2C19 rapid metabolizers. Together, these findings suggest that PPI exposure may confer differential cognitive effects across subpopulations, but require further validation before informing genetic risk stratification and PPI prescribing.

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