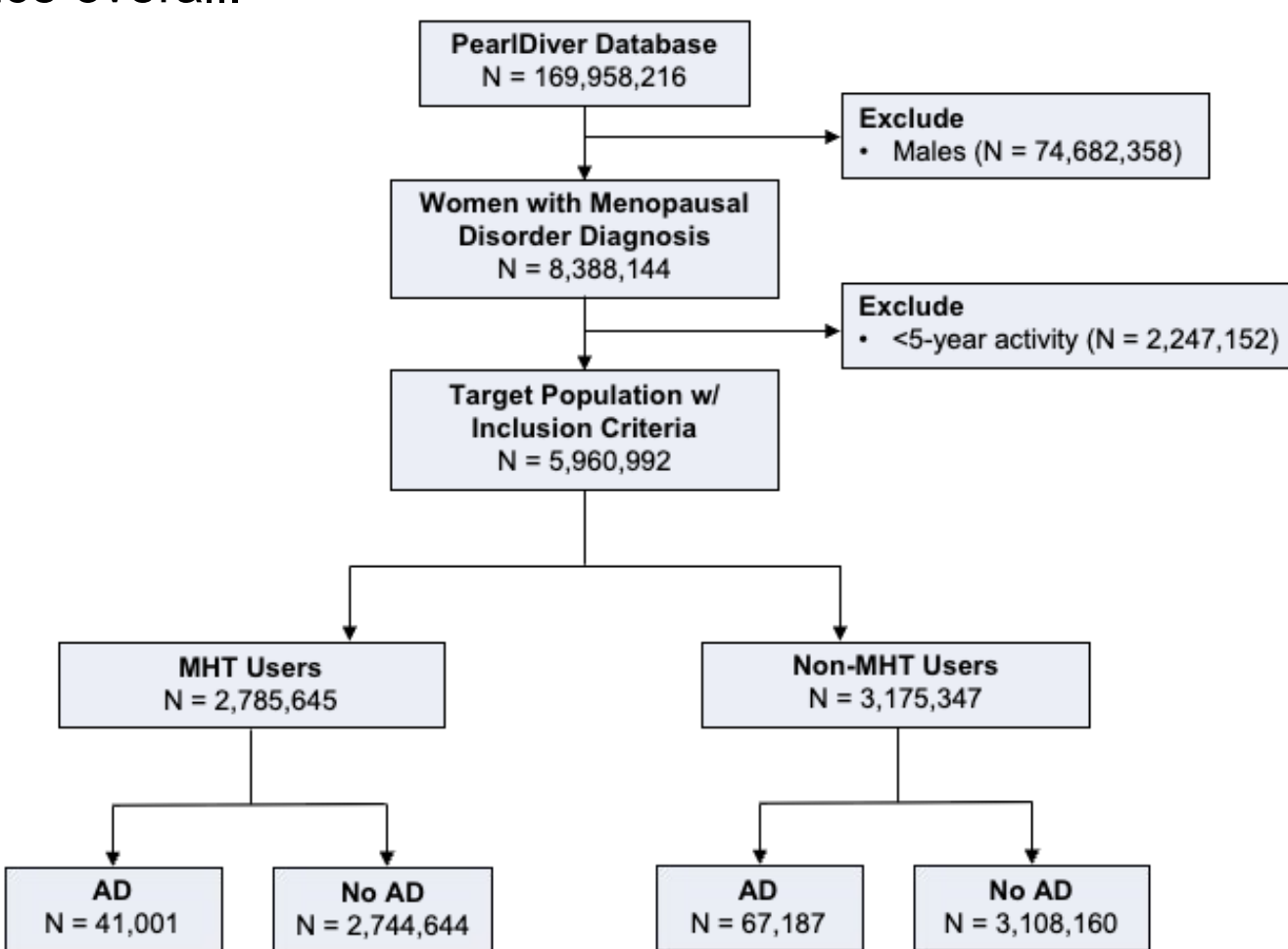


INTRODUCTION

- Alzheimer's disease (AD) is a major public health challenge that disproportionately affects women, who account for nearly two-thirds of diagnosed cases¹. Beyond longevity differences, biological sex-specific risk factors, particularly the menopausal transition, have been implicated in this disparity, yet targeted therapeutic strategies remain underexplored².
- The menopausal transition, characterized by a decline in ovarian estrogen production and a shift in brain bioenergetic capacity, has been identified as a critical window of vulnerability for AD risk^{3,4}. Menopausal hormone therapies (MHTs) have therefore emerged as promising candidates for mitigating AD development, with evidence suggesting that initiation timing and formulation class influence efficacy⁵.
- However, the translatability of the most commonly prescribed MHT to mechanistic outcomes in a preclinical humanized genetic risk model of AD remains poorly defined.

METHODS

- The US-based Mariner claims database (~170 million patients) was queried using the PearlDiver analytics platform to identify women with a menopause ICD-10 diagnosis and prescribed MHTs. Patients with follow up <5 years were excluded. MHT users were stratified by therapy formulation (estrogen-only, combined estrogen-progestogen, estrogen-androgen, estrogen-SERM (selective estrogen receptor modulators), other hormones, and SERM) and age at first MHT exposure.
- Age distributions at first MHT prescription were compared between women who subsequently developed AD (N=41,001) and those who did not (N=2,744,644). Relative risk ratios with 95% confidence intervals were calculated to evaluate associations between MHT use and AD incidence overall.

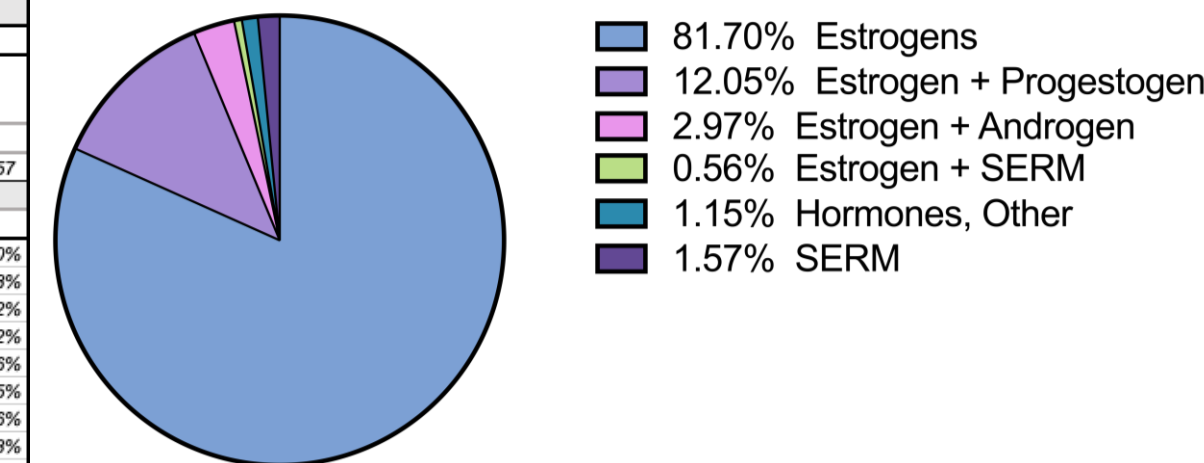


- Since population-level findings indicated estrogen-based therapy as the predominant MHT class, we conducted a preclinical study in 24 14-month-old female humanized (h) *APP/hAPOE3* and *hAPP/hAPOE4* mice.
- Animals were randomized by cycling status: regular (pre-menopause) or irregular (perimenopause) to subcutaneous 17 β -estradiol (E2, 0.09 mg 60-day slow-release pellet; Innovative Research of America) or sham surgery, with 30 days of exposure prior to sacrifice.
- Metabolic and physiological outcomes commonly disrupted in both AD and menopause were assessed, including body weight, body composition (EchoMRI), fasting blood glucose and ketones, cycling status (vaginal cytology), and ovarian estradiol (mass spectrometry).
- Statistical analyses included two-way ANOVA with Tukey's multiple comparisons test correction. Significance is denoted as *p<0.05 and **p<0.01.

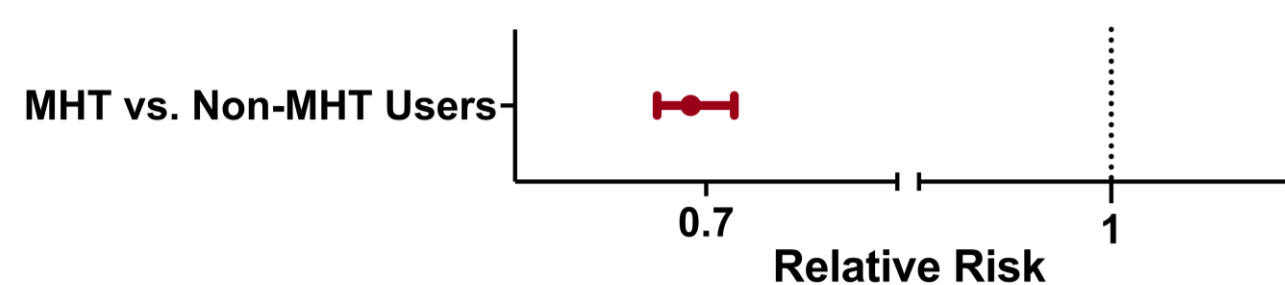
Menopausal hormone therapy (MHT) use is associated with a 30.9% reduced risk of AD diagnosis compared to non-MHT users.

Patient Profiles of MHT Users

	Menopausal Hormone Therapies											
	Estrogen		Estrogen + Progestogen		Estrogen + Androgen		Estrogen + SERM		Hormones, Other		SERM	
	n	%	n	%	n	%	n	%	n	%	n	%
Number of Patients (N=2,785,645)	2,591,730	81.70	382,096	12.05	94,146	2.97	17,889	0.56	36,480	1.15	49,714	1.57
Age at First MHT Exposure												
<40 (N=103,296)	99,732	105.93%	6,736	46.81%	6,404	17.55%	403	0.81%	1,167	3.20%	844	1.70%
40 to 44 (N=152,166)	142,612	151.48%	19,888	111.11%	8,784	24.08%	1,063	2.14%	2,537	6.95%	2,128	4.28%
45 to 49 (N=376,865)	345,468	366.95%	69,943	390.76%	17,728	48.60%	4,363	8.78%	7,413	20.32%	7,218	14.52%
50 to 54 (N=642,463)	578,833	614.82%	131,786	736.00%	23,186	63.96%	7,408	14.90%	13,981	35.86%	15,871	31.52%
55 to 59 (N=528,022)	486,060	516.28%	81,009	452.59%	17,806	48.81%	3,206	6.45%	7,721	21.77%	13,054	26.26%
60 to 64 (N=389,945)	366,809	389.62%	40,411	225.77%	11,592	31.78%	997	2.01%	2,900	7.95%	6,635	13.35%
65 to 69 (N=286,469)	276,469	293.65%	19,936	111.38%	5,877	16.11%	330	0.66%	1,139	3.12%	2,565	5.16%
70 to 74 (N=252,974)	246,728	262.07%	10,033	66.05%	2,671	7.32%	112	0.23%	426	1.17%	1,156	2.33%
>74 (N=49,416)	48,527	51.54%	404	2.26%	98	0.27%	17	0.03%	96	0.26%	243	0.49%

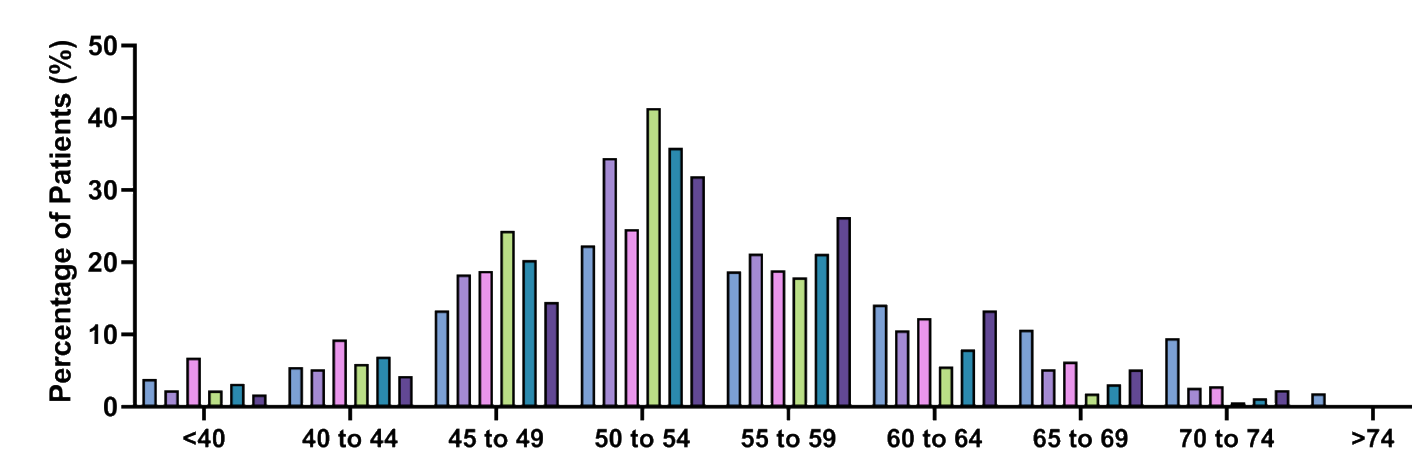


Relative Risk Ratio of AD in MHT Users vs Non-MHT Users

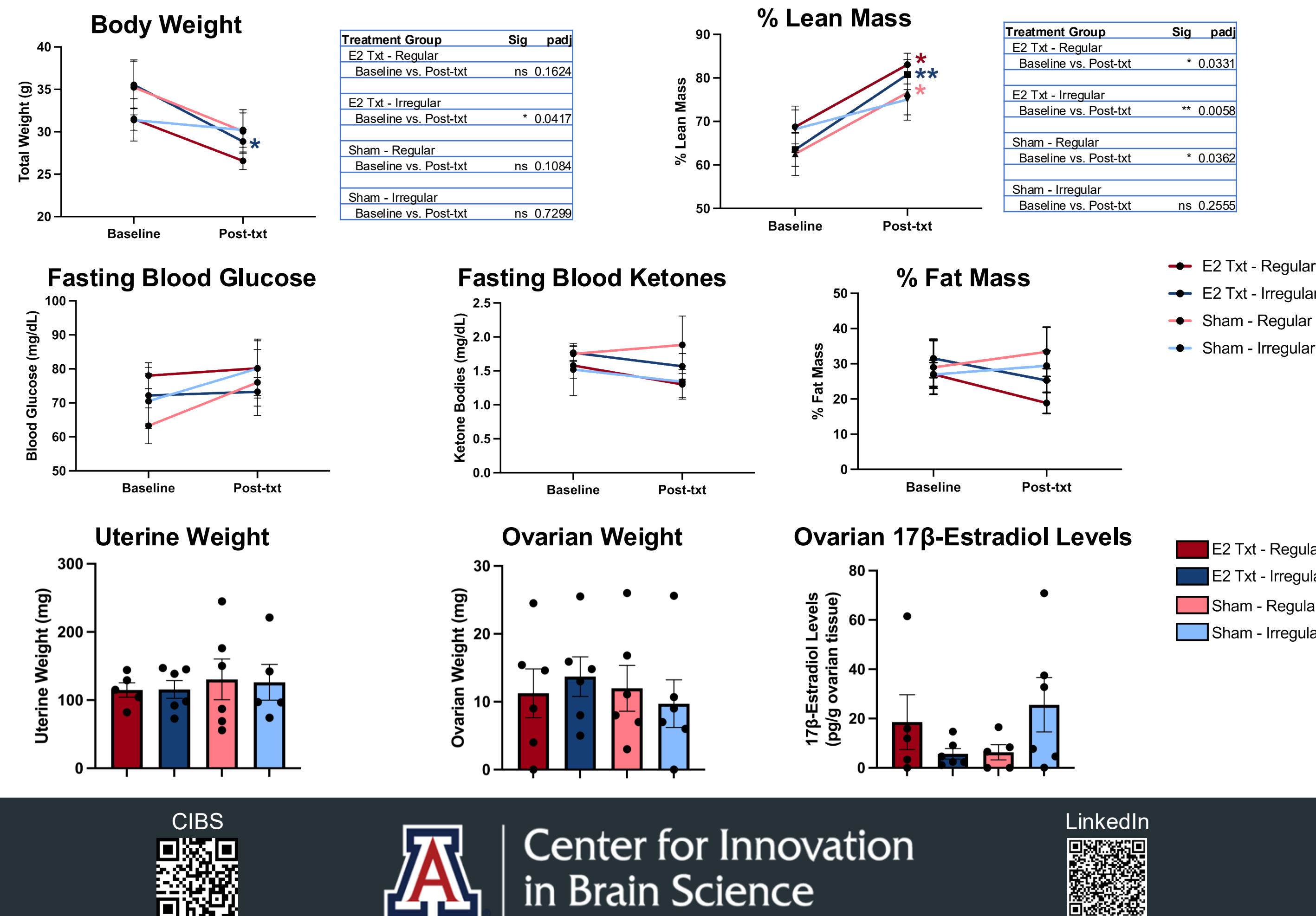


	AD	No AD
Treatment	N = 108,188	N = 5,852,804
MHT Users	41,001	2,744,644
Non-MHT Users	67,187	3,108,160
Relative Risk (MHT vs Non-MHT)	0.696	
95% CI	0.6872-0.7041	
p-value	<0.0001	

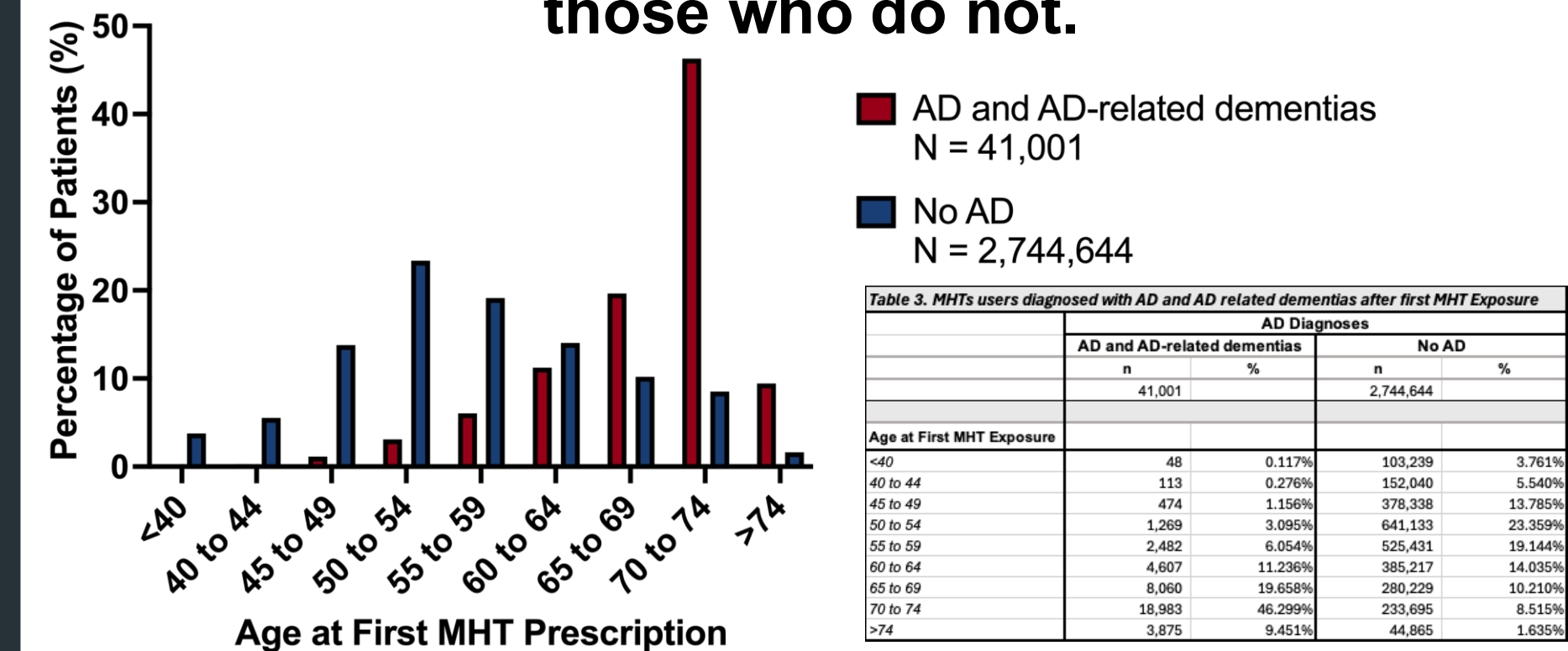
Age at First MHT Prescription



Short-term 17 β -estradiol treatment selectively modulates body composition in irregular cyclers during the perimenopausal transition.



Women who develop AD initiate MHT later than those who do not.



RESULTS

- Medical informatics analyses of insurance claims data revealed distinct AD risk profiles across MHT classes, with estrogen-based therapies representing 81.7% of prescribed MHTs and peak initiation age at 50-54 across most MHT classes.
- MHT use was associated with 30.9% reduced AD risk compared to non-users. Non-AD MHT users' peak initiation was at 50-54 (perimenopause) while AD MHT users' peak initiation was at 70-74 (post menopause).
- E2 treatment significantly reduced body weight by 34% in irregular cyclers and increased % lean mass in regular and irregular cyclers, as well as sham regular cyclers; sham irregular cyclers did not show this effect.

DISCUSSION

- Timing of MHT formulation impact AD risk. Medical informatics analysis support the critical window hypothesis that women who initiate MHT later are overrepresented in the AD group.
- The absence of lean mass preservation in sham irregular cyclers suggests that the perimenopausal transition creates a body composition deficit that E2 treatment rescues.
- Null findings in peripheral metabolic and reproductive endpoints suggest the E2 dose/duration selectively targets body composition pathways without broadly disrupting endocrine or metabolic homeostasis.
- The interaction between cycling status and treatment supports the critical window hypothesis, aligning with the population-level finding that earlier MHT initiation is associated with lower AD risk.
- By correlating population-level patterns of MHT use with targeted interventions in a genetic AD risk model, this work informs ongoing studies aimed at elucidating the biological pathways implicated in the most translationally relevant window of elevated AD risk in women.

ACKNOWLEDGEMENTS

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