

Multi-modal Precision Medicine Protocol for Cognitive Decline: Personalized Assessment and Intervention

AI-Driven Living Evidence Synthesis Framework for Modifiable Risk Factors and Longitudinal Progression Biomarkers in Alzheimer's Disease

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Developing Topics: Dementia Care and Psychosocial Factors

Challenge: Transforming the Preclinical Window into Empowered Prevention

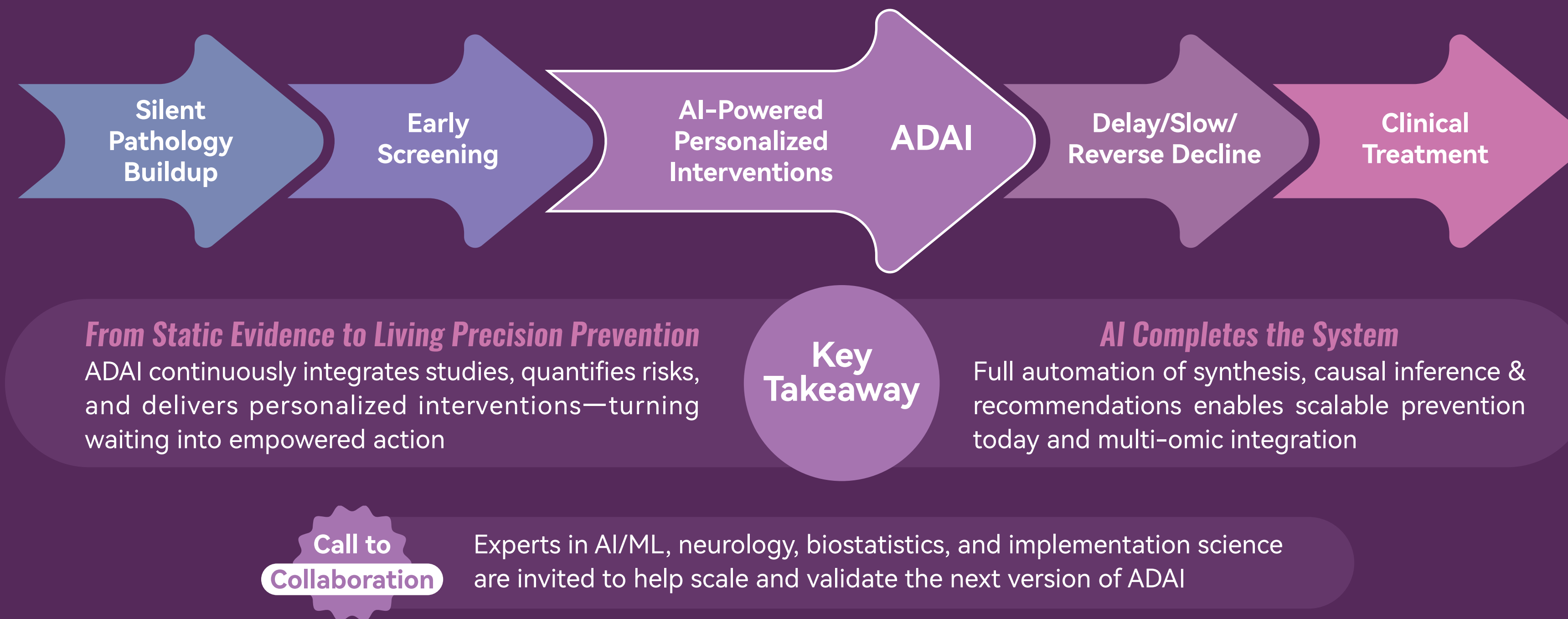
Alzheimer's disease features a critical 10–15-year preclinical window where pathology develops silently before symptoms appear. Seven stages of Alzheimer's outlined by Dr. Reisberg, of which Stages 1–3 are the predementia stages. Traditional "watchful waiting" leaves patients unsupported, while evidence on modifiable risk factors remains fragmented and underused (www.alzinfo.org).

ADAI—an AI-powered Cognitive Function Protection Agent—bridges this gap

It dynamically synthesizes living evidence on modifiable risk factors (supported by Lancet Commission findings that up to 45% of dementia cases may be preventable), delivers personalized non-drug interventions, and tracks biomarkers in real time (Livingston et al., 2024).

Significance

This scalable, self-updating platform makes early screening truly meaningful, empowering individuals to delay, slow, or potentially reverse cognitive decline today—while accelerating precision prevention research.

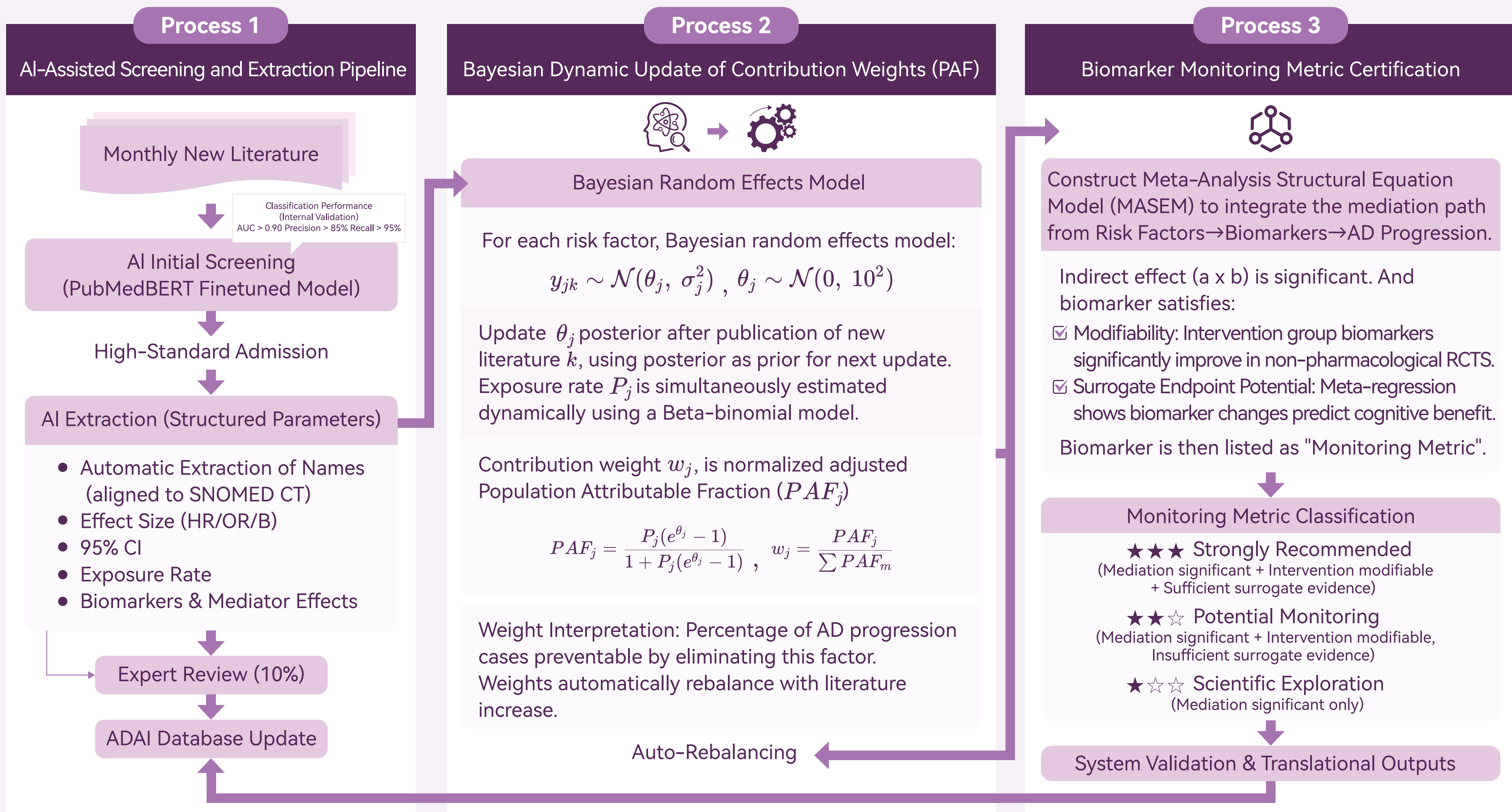


Our Solution: A Dynamic, Data-Driven Platform

We developed a "living evidence" synthesis framework designed to:

- Continuously synthesize high-quality evidence on modifiable risk factors and biomarkers for AD progression through an automated pipeline.
- Dynamically quantify the precise contribution and certainty of each risk factor, providing a clear hierarchy for intervention.
- Validate and grade actionable biomarkers for their utility as monitoring tools and surrogate endpoints in clinical trials.
- Continuously refine risk estimates, evidence certainty, and clinical recommendations in near real-time as the evidence base evolves.

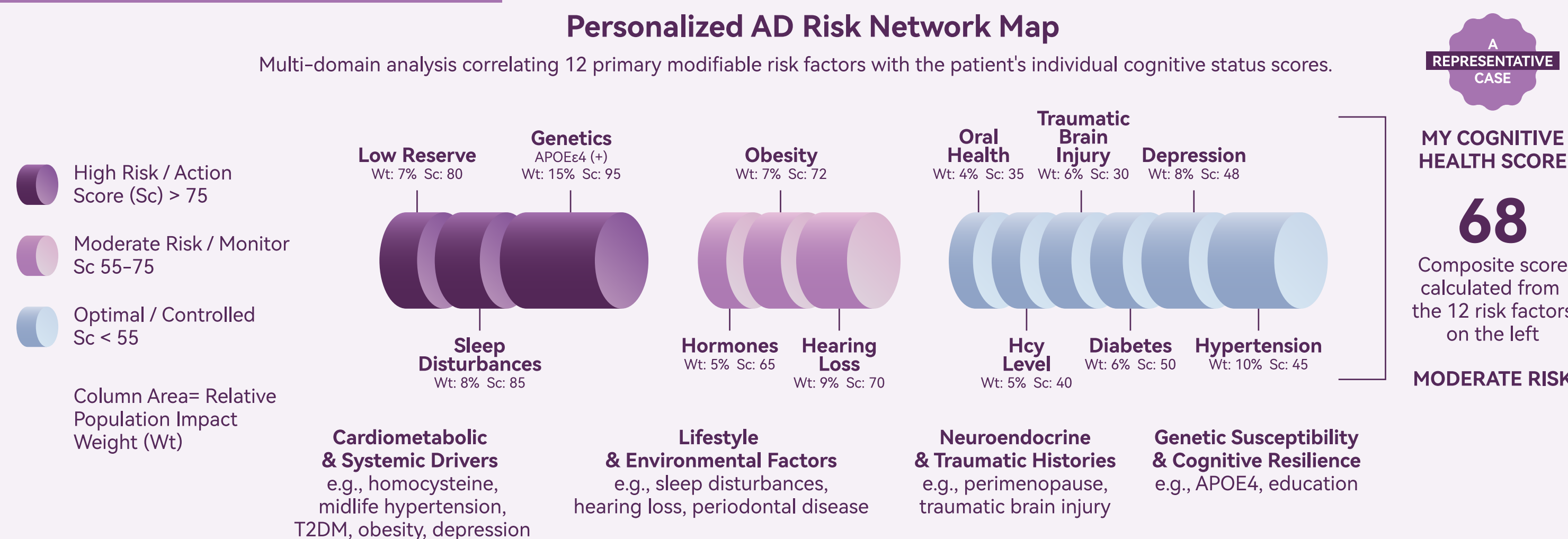
Dynamic Monitoring and Classification System of AD Prevention Factors



Platform in Action: From Risk Mapping to a Specific Case Example

Evidence from the HUNT study (Stubs et al., 2024) identifies CogDrisk as having the highest discriminative ability among current dementia risk indices. We therefore adopted this framework, valued for its comprehensive inclusion of modifiable risk factors, as the basis for our work.

Our living evidence platform then extends this framework by structuring and quantifying these factors into a multi-dimensional map of the AD risk landscape.



About ADAI: ADAI is a dedicated Cognitive Function Protection Agent. She bridges the gap between early screening and active clinical care to protect human memories. **Website:** www.adaineuro.com

“Where memories dwell, love never fades.”
— ADAI'S ORIGINAL ASPIRATION

Case Example: Applying the Living Evidence Synthesis Framework to Dysglycemia and AD Progression

1 Literature Curation

From an initial retrieval of 40,000 articles, the AI classifier (PubMedBERT) applied pre-specified, high-standard eligibility criteria. After a rigorous 10% manual audit to ensure classification fidelity, 152 high-quality articles directly addressing dysglycemia subtypes and AD progression were included in the living database.

2 Dysglycemia Subtype Definitions

- Diabetes: Physician diagnosis, HbA1c $\geq 6.5\%$ (≥ 48 mmol/mol), or fasting plasma glucose ≥ 7.0 mmol/L.
- Glycemic Peaks & Variability: Elevated postprandial 2-hour glucose, increased continuous glucose monitoring (CGM)-derived peak glucose, or an elevated glycemic coefficient of variation (CV).
- Severe Hypoglycemia: Events requiring external assistance or documented glucose levels < 3.0 mmol/L accompanied by clinically significant cognitive symptoms.

3 Dynamic Contribution Weights

Pooled hazard ratios from Bayesian meta-analysis, combined with exposure prevalence, are used to estimate confounder-adjusted PAFs and derive normalized contribution weights.

Dysglycemia Subtype	Pooled HR (95% CI)	Prevalence	PAF (%)	Contribution Weight
Diabetes	1.53 (1.41–1.65)	18%	7.8	0.42
Glycemic Peaks & Variability	1.31 (1.18–1.45) per SD	25% (upper quartile)	5.2	0.28
Severe Hypoglycemia	1.78 (1.49–2.13)	4%	2.9	0.16
Other glycemic factors	—	—	2.6	0.14

Note: Weights are normalized within the dysglycemia domain. Diabetes carries the largest contribution, but glycemic variability and hypoglycemia show independent, clinically significant effects. The entire weight spectrum recalibrates quarterly. Prevalence of 25% represents the population in the upper quartile of glycemic variability; the corresponding PAF was derived using the estimated effect size for this threshold.

4 Identifying & Grading Actionable Biomarkers

We applied Meta-Analytic Structural Equation Modeling (MASEM) to test which biomarkers lie on the causal pathway from intervention to clinical benefit, rather than merely being correlated with risk.

Biomarker	Monitoring Grade	Core Evidence
Glycemic Variability (CGM-CV)	★★★ Strongly Recommended	Complete Causal Chain: Linked to cognitive decline, proven to be modifiable in RCTs, and its reduction correlates with clinical benefit.
Time-in-Range (TIR)	★★★ Strongly Recommended	Strong Surrogate Evidence: Meta-regression validates that improving TIR is a powerful predictor of slowed clinical progression.
Plasma p-tau217	★★☆ Potentially Recommended	Pathological Response Marker: Reflects post-intervention pathological change (d=0.35), but evidence as a full surrogate is still accumulating.
FDG-PET Brain Metabolism	★☆☆ Exploratory	Associated but Insufficient: Linked to synaptic dysfunction but lacks direct validation as a surrogate for cognitive endpoints.
CSF Insulin Resistance Index	★☆☆ Exploratory	Mechanistic Insight: Informs on central pathology but lacks a direct, validated link to cognitive outcomes.

5 Generating Evidence-Based Recommendations

The platform integrates all evidence layers to generate tiered, actionable management recommendations weighted by risk contribution.

Priority (by Weight)	Clinical Target	Actionable Recommendation
Primary Target (0.42)	Diabetes & Glycemic Control	Implement medical nutrition therapy & structured exercise. Assess HbA1c and Time-in-Range (TIR > 70%) every 6 months.
Key Dynamic Monitoring (0.28)	Minimize Glycemic Variability	Deploy CGM-guided low-glycemic diets. Maintain a glycemic CV < 36% as a primary neuroprotective target.
Safety Floor (0.16)	Prevent Severe Hypoglycemia	Mandate CGM with low-glucose alerts for high-risk patients. Initiate medication de-escalation protocols upon any recurrent episode.
Biomarker Tracking	Monitor Neurodegeneration	Track fluid biomarkers (e.g., p-tau217) to evaluate treatment response. Measure every 6–12 months.

6 Living Evidence Status: A Dynamic Framework

This is not a static report. The platform demonstrates the power of "living evidence":

- Evolving Precision:** As of June 2026, the 95% confidence interval for the estimated effect of diabetes has narrowed by 15% compared to 2020, reflecting increased certainty.
- Discovery of New Risks:** Following the integration of high-quality Mendelian randomization studies in 2023, glycemic variability was formally established as an independent risk factor.
- Next Scheduled Update:** The next automated evidence synthesis and recalibration cycle is scheduled for September 2026.

References:

- <https://www.alzinfo.org/understand-alzheimers/clinical-stages-of-alzheimers/>
- Livingston G, et al. Lancet. 2024;404:572–628.
- Stubs J, et al. J Prev Alzheimers Dis. 2025;12:100326.

Conflicts of Interest: This platform and research project were developed and funded by ADAI.