MAYO CLINIC

Sex Differences in Brain Disorders:
Emerging Transcriptomic Evidence and Implications for Therapeutic Development

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Part B: Neurodevelopmental and Neurodegenerative Disorders

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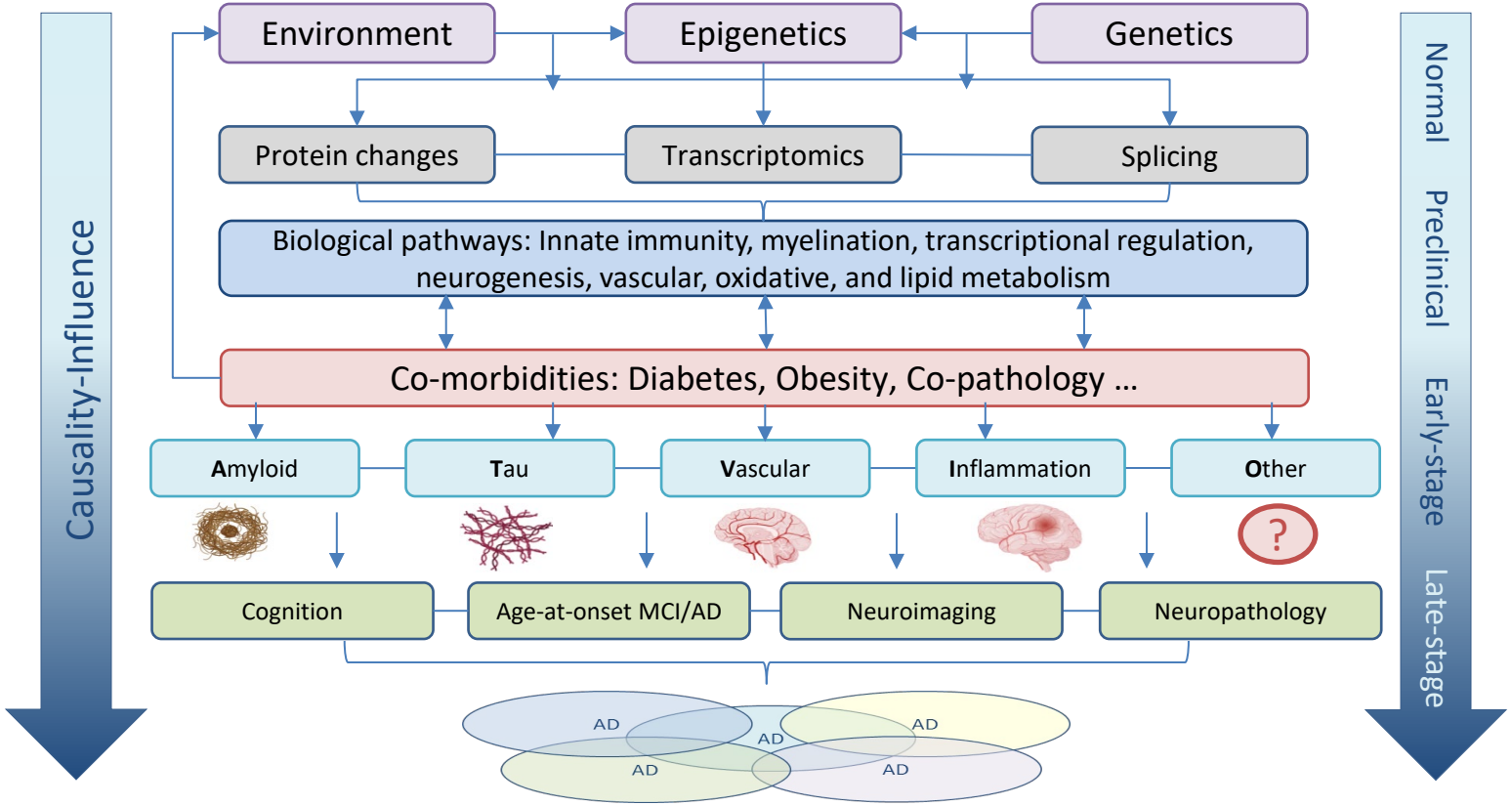
A (Simplified) Model of Neurodegenerative Diseases



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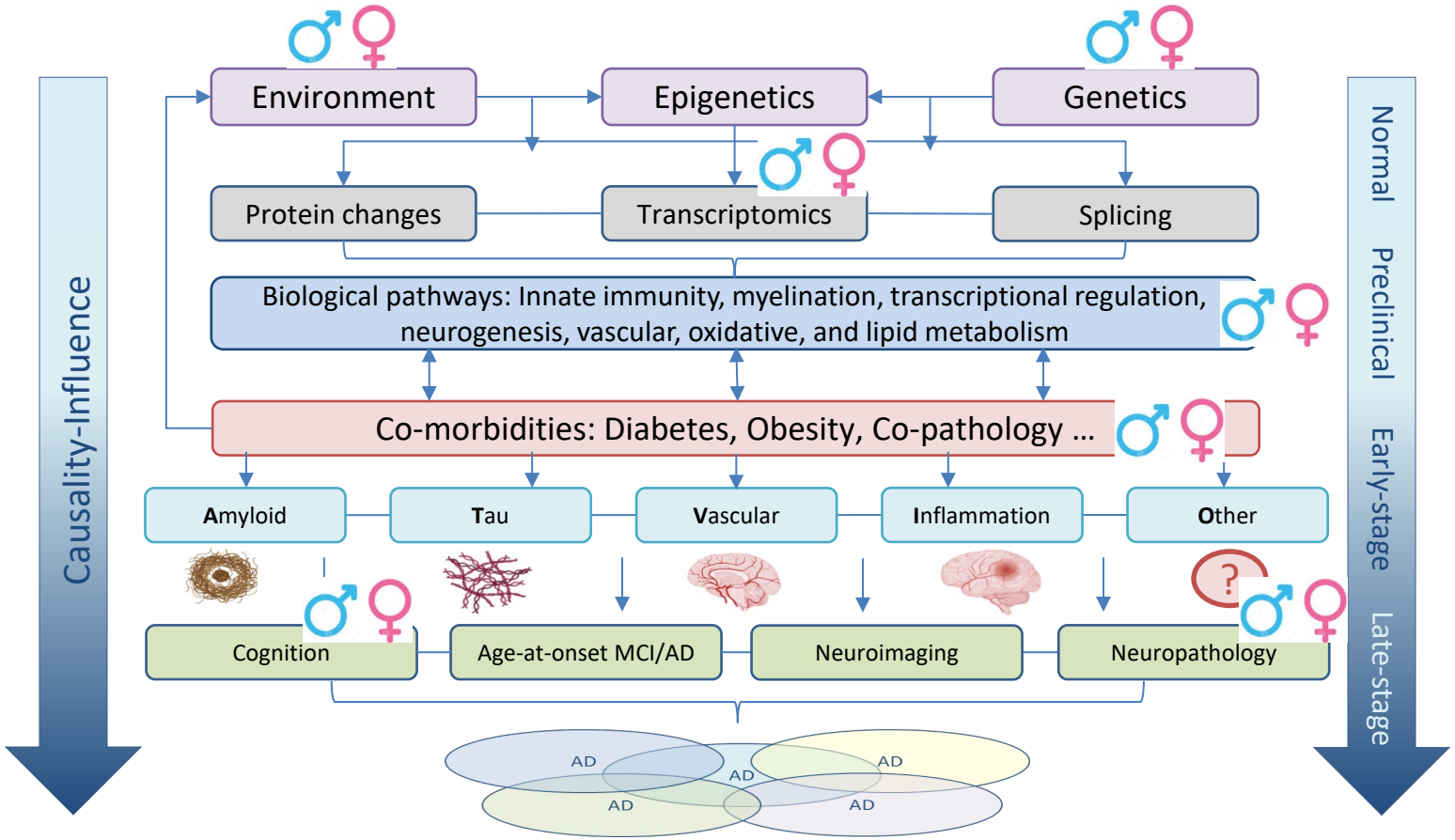
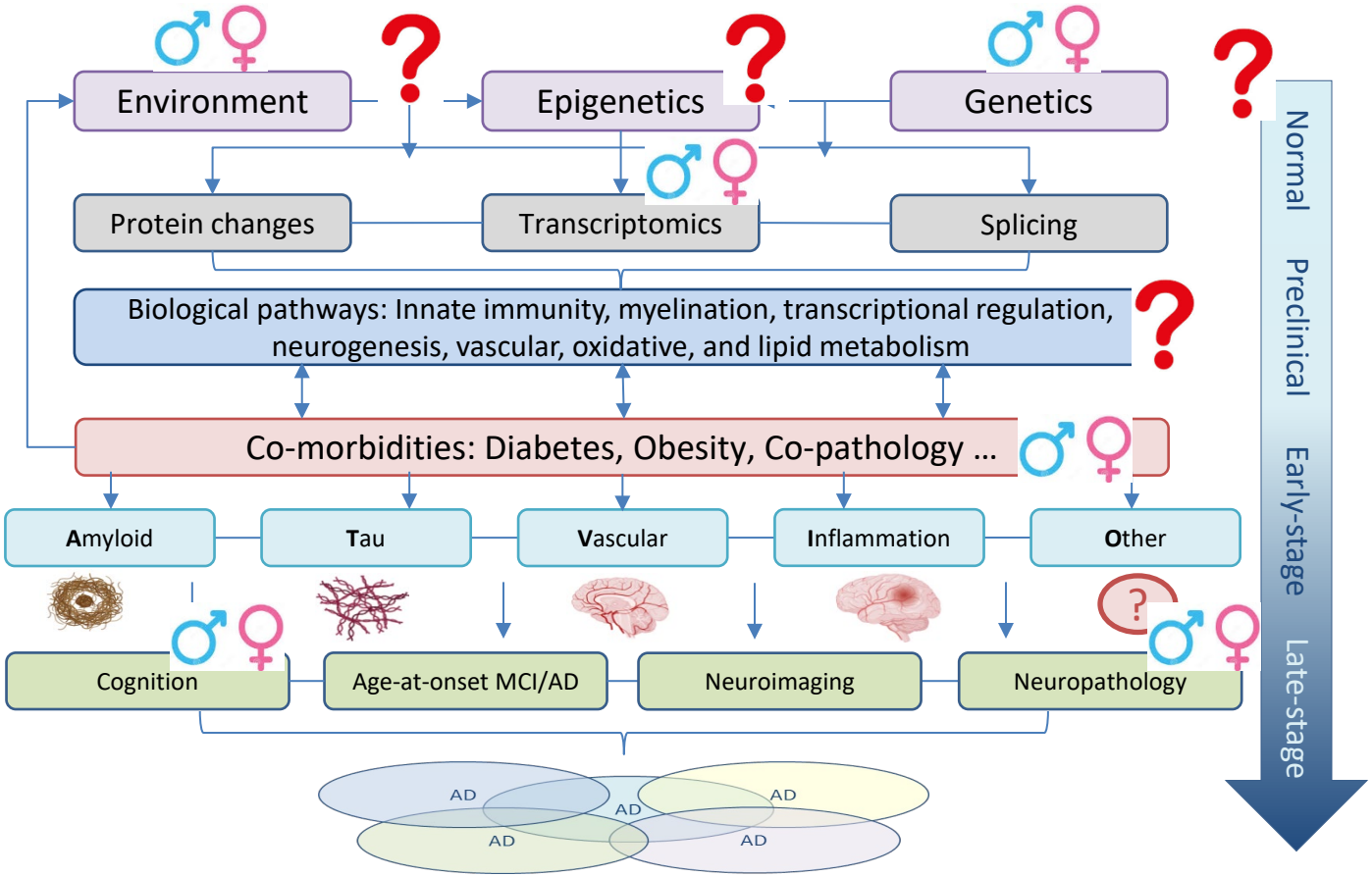


Evidence for Sex Differences in Alzheimer's Disease – "It's complicated"

- **Epidemiology:**
  - Women have 2x lifetime risk of Alzheimer's disease (AD) than men.
  - Higher prevalence in women-but not all geographical regions.
  - Higher incidence in low/middle income countries for women.
  - Suggested explanations: Lower education in women, survival bias against men (death due to cardiovascular disease higher in middle age), genetic, hormonal, but no definitive studies.
- **Symptomatology:**
  - Women with AD show higher rates of cognitive decline.
  - Some studies show greater rates of behavioral symptoms and dependence in women with AD.
- **Neuropathology:**
  - Some but not overwhelming evidence for differences in tau or Aß by neuropathology or biomarker studies (CSF, imaging).
  - However, for given AD neuropathology or biomarker levels, women have higher odds of dementia and faster cognitive decline.

Sex Differences – Knowledge Gaps



- Effect of sex-differences in environment on epigenome -> transcriptome -> disease pathways.
- Impact of lifelong changes in hormonal status.
- Longitudinal changes in peripheral transcriptome -> disease progression/outcomes.
- Sex differences in multi-ethnic populations.

Sex Differences in Brain Disorders – Bridging the Gap to Therapies

- **Establish and enhance well-powered longitudinal cohorts:**
  - Peri-menopausal to post-menopausal aged women and age-matched men.
  - Repeated measures of clinical, cognitive, biomarker outcomes.
  - Peripheral (blood, saliva, CSF) multi-omics (transcriptome, epigenetic, proteome, metabolome) and genetic data.
  - Ideally matched brain tissue/data.
  - Enhance inclusion of underrepresented populations.
- **Integrative analyses:**
  - Effects of hormonal status, education, socio-economic factors on multi-omics and disease outcomes.
  - Role of genetic factors on multi-omics and (eQTL, mQTL, pQTL) disease outcomes.
  - Sex-stratified and sex-interaction analysis of all data (in addition to sex-adjusted analysis).
- **Model systems to study sex-differences:**
  - Investigate role of chromosomal sex, gonadal sex and hormones on disease-related outcomes, transcriptional and epigenetic changes in brain and peripheral tissue of model systems.
  - Study effects of chromosomal sex in iPSC-based neuronal and glial cellular and organoid models based on samples collected from male and female participants from multi-ethnic groups who represent the full disease spectrum.