Clinical Trials in the Prodromal Phase of Alzheimer's Disease: Methodological Challenges and Clinical Outcomes

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What is a prodrome?

An early set of symptoms heralding a developing disease or a recurrent attack which is about to occur.

- wordnetweb.princeton.edu/perl/webwn;
- en.wiktionary.org/wiki/prodromal
- en.wikipedia.org/wiki/Prodrome;en.wiktionary.org/wiki/prodrome
- www.everydayhealth.com/pain-management/headache/glossary-of-headache-terms.aspx
- dmv.ca.gov/dl/driversafety/lapes_glossary_terms.htm
- www.birthingtouch.com

Examples of short-interval prodromes:

- Malaise, headache, muscle pains, and anorexia preceding **the full manifestation of viral infections, such as the flu**, by hours or days;
- Attenuated symptoms of herpes zoster preceding **a full attack** by hours or days;
- Changes in mood and appetite preceding an **attack of migraine** by hours or days;
- Tiredness, vague complains, mild and diffuse chest pains preceding an **MI** by days or weeks.

Examples of short-interval prodromes in CNS

- Vague anxiety or discomfort preceding an **epileptic attack** by days;
- Non-specific neurological symptoms preceding an **attack of MS** by days or weeks;
- Poor sleep and anxiety preceding a psychotic attack in **schizophrenia** by days;
- TIA preceding a **stroke** by days, weeks or, months.

Examples of long-interval prodromes in CNS

- Impaired olfaction, constipation and cardiac sympathetic denervation, preceding motor symptoms of **Parkinson's** disease by months or years ;
- Subtle deviation from norms in cognitive performance, behavior, and emotions preceding the first episode of psychosis in **schizophrenia** by months or years;
- Behavioral disturbances during childhood preceding **anti-social personality disorder** by years.

Exapmles of histological/biochemical prodromes

- Cell dysplasia preceding epithelial cancers by years:
  - Colon polyps
  - Breast nodule
  - Others
- Abnormal or exaggerated lipids and protein deposits in the coronary artery walls;
- Abnormal and/or exaggerated protein deposits in the brain's arterial wall and parenchyma.

What defines the prodrome?

- Time lag between the prodrome and the event it heralds;
- Inevitability of the event;
- PPV for the event;
- Symptomatic resemblance to the full-blown illness (is AP prodromal to a small MI and a small MI prodromal to a larger MI?) ;
- Pathophysiological relationship between the prodrome and the disease (the prodrome is (or is not) on casual path to the disease).

Are we looking for prodrome or something else?

- Sequential but unrelated association of common diseases (ex. Age-dependent CVD and dementia)
- Independent risks (ex. CVD modulating the pathophysiological process causing AD)
- Cumulative risks (ex. CVD lowering the threshold for manifesting dementia)

- (Bio)markers or predictors (a) indicating that the disease has started and (b) which can be reliably detected before irreversible damage has occurred

(Bio)markers*

- **Surrogate (bio)markers:**
  - a laboratory or a physical finding that is used in therapeutic trials **as a substitute for a clinically meaningful endpoint** that is a direct measure of how patients feel, function, or survive, and is expected to predict the effect of therapy e.g. BP, cholesterol, tumor size (DO THEY DO THE JOB?).
- **Non-surrogate (bio)markers:**
  - used as a screening and/or diagnostic test or as an ancillary tool in drug development.

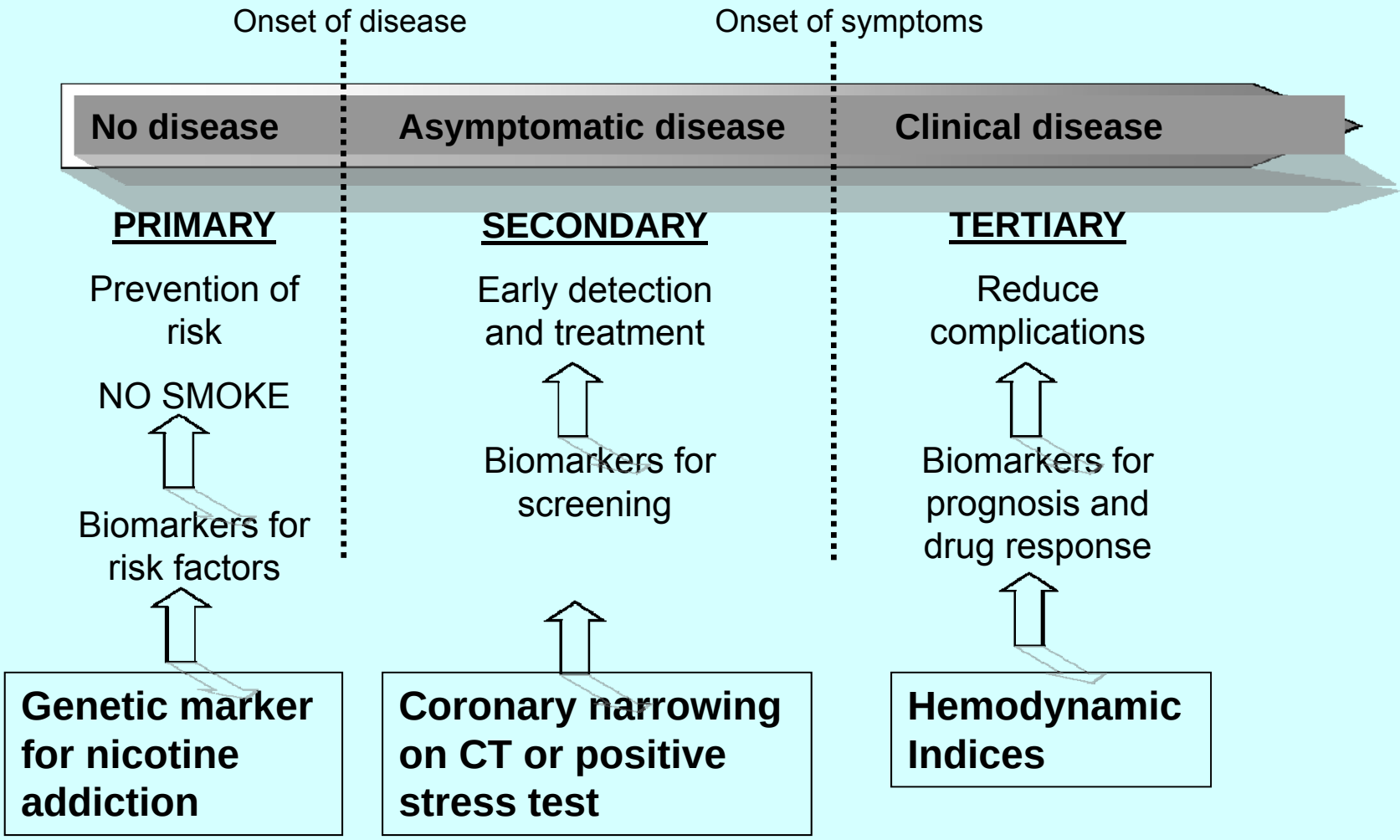
**** characteristics that are objectively measured as indicators of normal biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention (NIH).***

(Bio)markers: on the pathway to the disease or technology driven progress?

- **Glucose tolerance test** for diabetes
- **Blood lipids** for atherosclerotic processes
- **Hypertension** for Left Ventricular Hypertrophy
- **CBF** in AD

Use of non-surrogate (bio)markers in prevention

e.g. Myocardial Infarction



Considerations in using (bio)markers for screening and early diagnosis

Should populations or only high risk individuals be tested?

- **Risks depend on:**
  - Medical risks of the procedure
  - Financial costs
  - Harm to individuals previously unaware of illness
  - Misinterpretation of symptoms/signs
  - False reassurance by negative tests
  - Impact on life (insurance, career, independent living
- **Benefits depend on:**
  - (Bio)markers accuracy in predicting the event
  - Consequences of the event
  - Availability of treatment

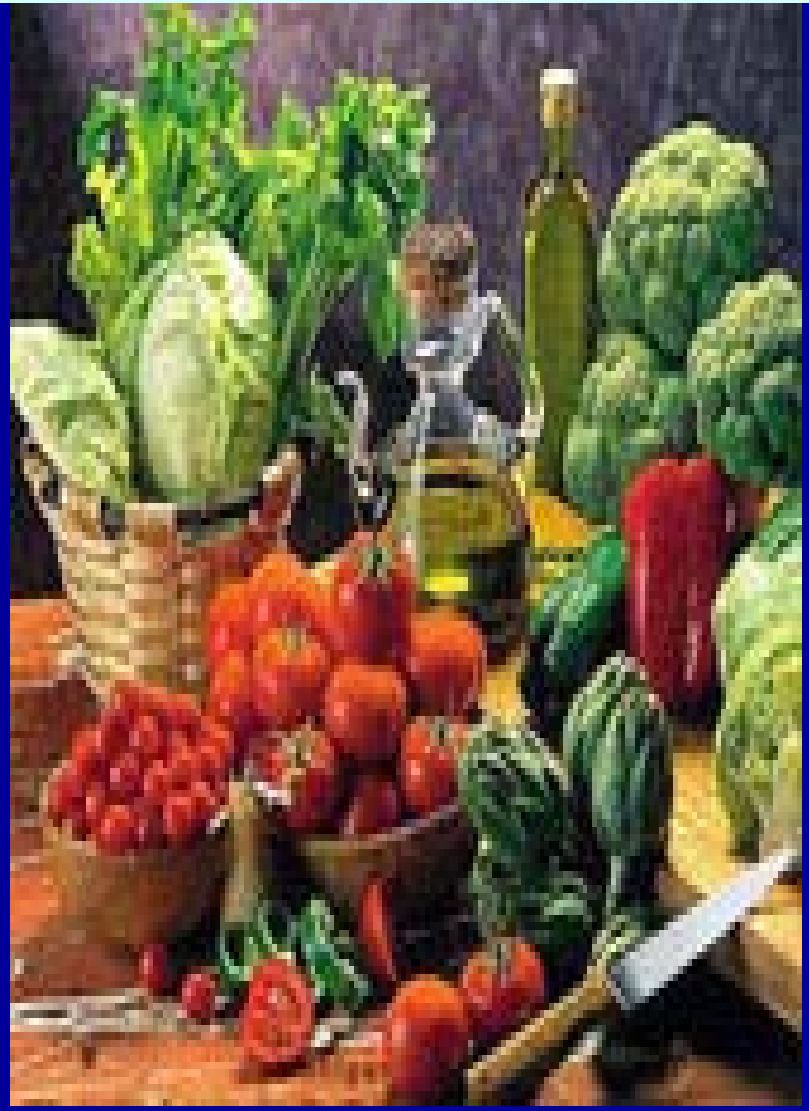
Use and *mis*use of non-surrogate (bio)markers in drug development

- Use
  - High-risk therapeutic areas, such as CNS, to reduce frequency of futile and non-conclusive phase II trials;
  - Drug targets not pharmacologically proven in man, to understand mechanisms and improve trial design;
  - Trials in pathophysiological heterogeneous diseases, to identify populations responsive to the Rx and reduce the N;
  - Slow developing diseases, to shorten the trial;
  - Trials targeting prevention.
- Misuse
  - * Non fully validated markers;
  - No predetermine go/no-go criteria.

**** Using a new biomarker is like walking across a frozen lake without knowing how thick the ice is" Baker M. Nature Biotechnology 2005***

Cardiovascular Risk Factors and Dementia

Prodromal, risk, or (bio)markers - these are easy to recommend.



However, the effects are only moderate

Prevention in cardiovascular

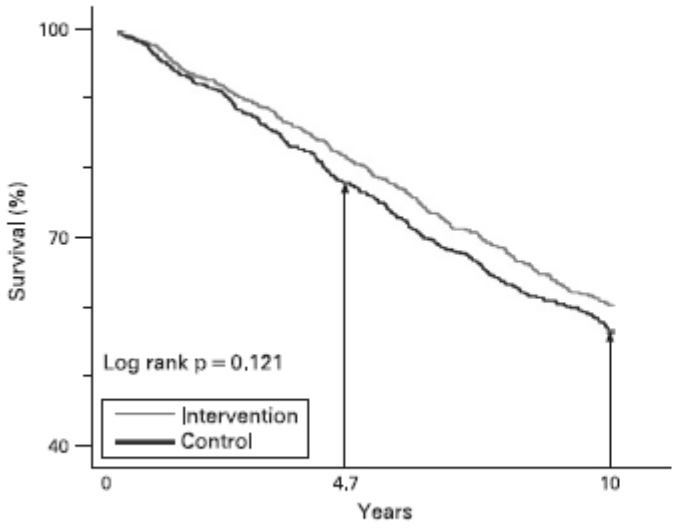


Figure 2 Kaplan Meier survival plot for total mortality by group.

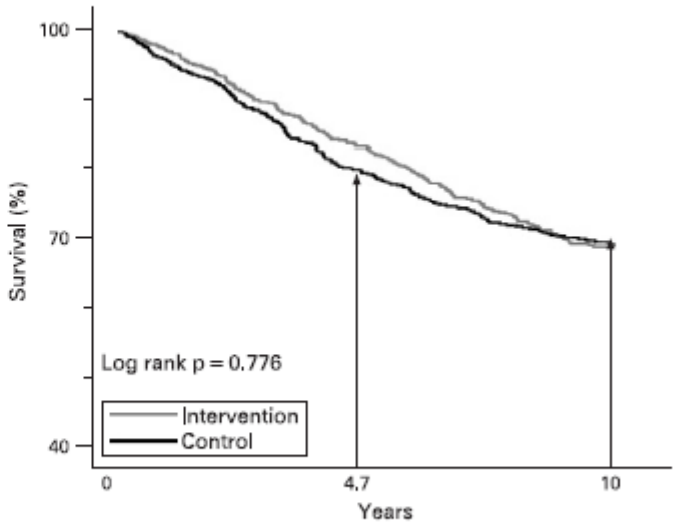
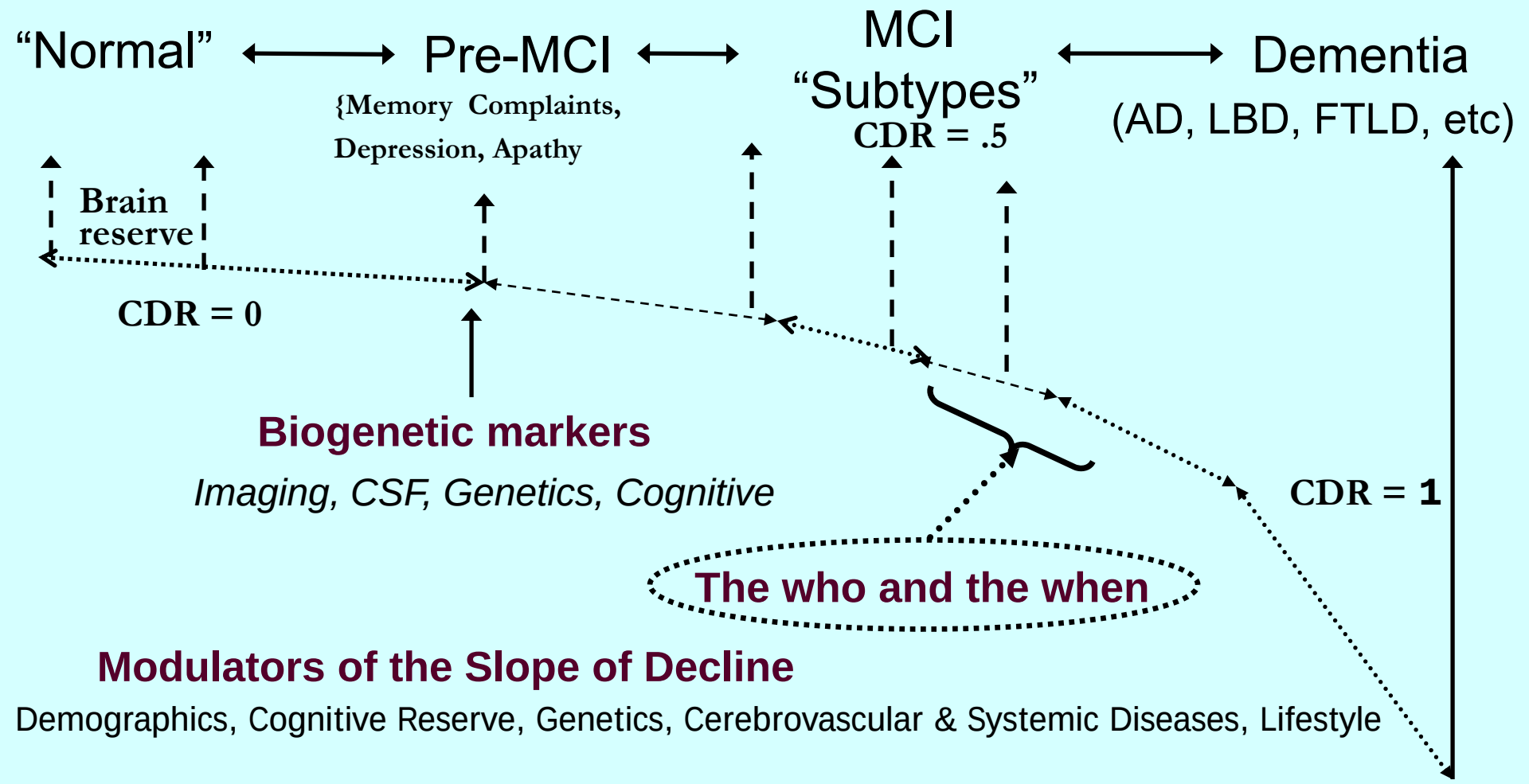


Figure 3 Kaplan Meier survival plot for coronary events (coronary deaths and non fatal myocardial infarctions) by group.

Minor differences at 1 year,

no differences at 10 years.

Is there any human affliction, besides traumatic accidents, which is not gradual?



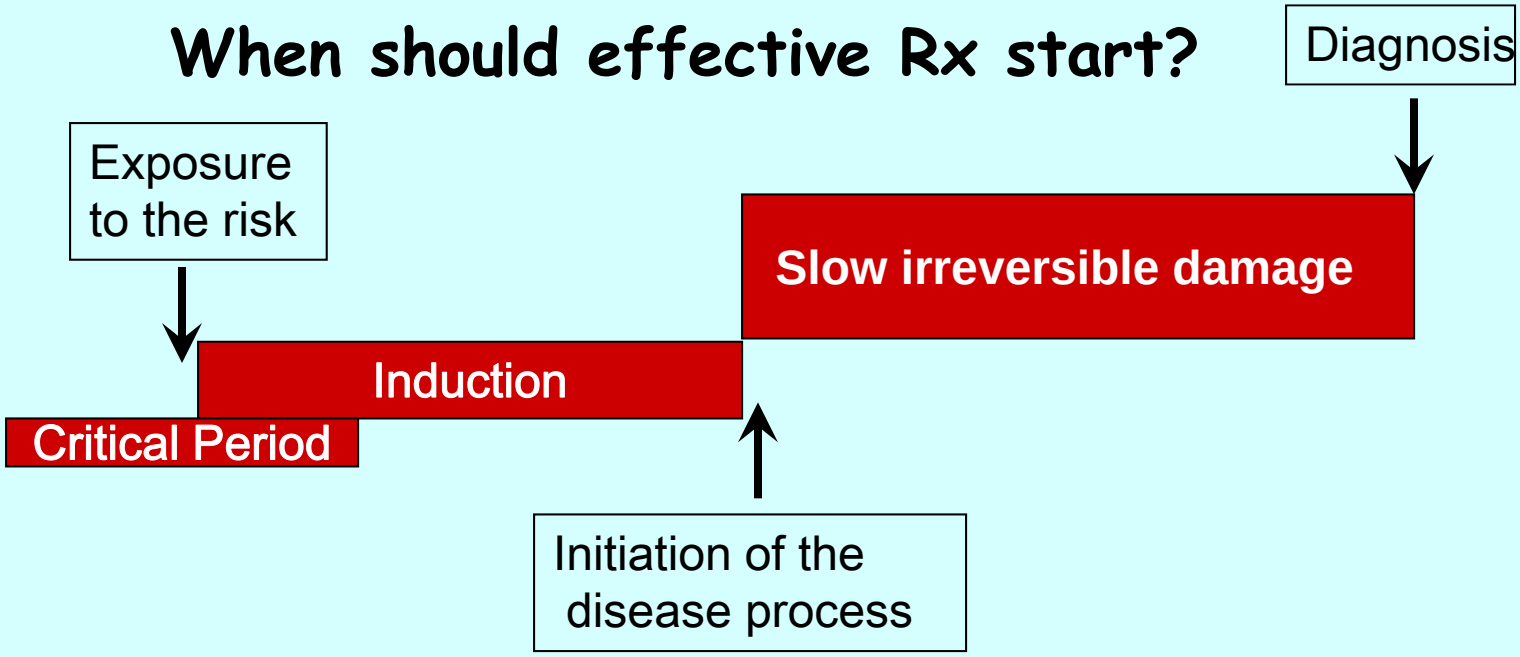
Which one is an AD prodrome and which one is a (bio)marker?

1. Poor brain reserve, AAMI, amnesic MCI, multi-domain MCI, CDR 0.5;
2. Depression, anxiety, personality changes;
3. Braak I-III stage(s) tangles;
4. Sub-threshold but crescendo synaptic degeneration;
5. “Light” but accumulating load of amyloid plaques (PET);
6. Sub-threshold brain atrophy (MRI);
7. Decrease global and regional metabolism (blood flow by PET and SPECT);
8. CSF which is low for amyloid and high for Tau.

What can we infer about the prodrome from the discrepancies between observational and prospective trials?

High cholesterol in mid-life increases risk for AD in observational studies but there is no benefit from statins given to elderly AD patients

Exposure to NSAID or estrogen reduces risk for AD in observational studies but not in prospective trials.



A timeline perspective on the prevention of AD H. Fillit

Disease	Biomarker discovered As potential target for treatment	Are treatments available to modify the biomarker?	Are drugs available to reduce the risk of sequelae of the disease?	Do lifestyle interventions reduce the risk of disease sequelae?	Are drugs available to prevent the onset of disease (primary prevention)?
Essential hypertension	1900: blood pressure	1900: low Na diet, 1940s': (guanethidine, hydralazine)	1960s': severe hypertension identified as a treatable risk factor for stroke 1980s': treatment and lifestyle management of mild hypertension prevents heat attacks and stroke	Yes, for some forms of essential hypertension, based on randomized clinical trials	No
Type 1 diabetes	1920s': glucose 1960s': hemoglobin A1C	Early 1920s': insulin	1920: insulin prevents hyperglycemia 1970s': insulin and lifestyle management of hyperglycemia reduces risk of secondary complications of diabetes	Yes, for type 2 diabetes based on randomized clinical trials	No
Coronary artery disease	1950s': cholesterol	1970s': bile acid sequestrants 1980s': statins, others	1980s': regression of coronary artery disease by cholesterol-lowering 1990s': consensus develops on lowering cholesterol to prevent heart disease	Yes, based on randomized clinical trials	Primary prevention for those with high cholesterol partially possible with combined lifestyle and drug Cholesterol-lowering (~30% reduction in relative risk with statins)
AD	1990s': potential biomarkers first identified (cerebrospinal fluid β-amyloid/tau); longitudinal structural and positron emission tomography amyloid neuroimaging	2000s': anti-amyloid and other agents in phase III	No for disease progression Symptomatic agents treat some sequelae of the disease, e.g., cognitive and functional impairment, and behavior	Tentatively yes, primarily based on epidemiologic studies	No