Using Joint Models to Disentangle the Treatment Effect in an Alzheimer Clinical Trial

Floor van Oudenhoven & Dimitris Rizopoulos
Department of Biostatistics, Erasmus University Medical Center, Rotterdam

d.rizopoulos@erasmusmc.nl

@drizopoulos

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Treatment Effects from Joint Models

1.1 Objectives & Standard Analysis

- The LipiDidiet trial: Investigate the effects of Souvenaid on cognition and related measures
  - ▷ *Sample:* 311 individuals with prodromal Alzheimer's Disease
  - ▷ *Intervention:* Souvenaid vs. placebo
  - ▷ *Design:* randomized, controlled, double-blind, parallel-group
  - ▷ *Period:* 36 months

1.1 Objective & Standard Analysis (cont'd)

- Longitudinal outcomes
  - ▷ **Neuropsychological Test Battery (NTB):** 5-item composite (z-score)
  - ▷ Clinical Dementia Rating: Sum of boxes (CDR-SB)
  - ▷ **Magnetic Resonance Imaging (MRI)**: hippocampal volume, ventricular volume and whole brain volume

  measured at: 0, 6, 12, 24 and 36 months

1.1 Objective & Standard Analysis (cont'd)

- Previous Analysis: Separate linear mixed models analysis for each longitudinal outcome
  - ▷ *ignored* biological relationships between the outcomes
  - ▷ *dropout* assumed missing at random,
    - * start open-label medication use $\rightarrow$ proxy for disease progression

1.1 Objective & Standard Analysis (cont'd)

Objective: How the intervention affects the time to start open-label medication use

while taking into account the biological mechanisms between the longitudinal outcomes

1.2 Joint Models

- Outcomes
  - ▷ Hippocampal volume left (*longitudinal*)
  - ▷ NTB memory domain (*longitudinal*)
  - ▷ Open-label medication (*time-to-event*)
  - ▷ Dropout (*time-to-event*)

1.2 Joint Models (cont'd)

- We want to quantify the treatment effect by linking
  - ▷ *time-to-event* outcomes, with
  - ▷ *longitudinal* outcomes

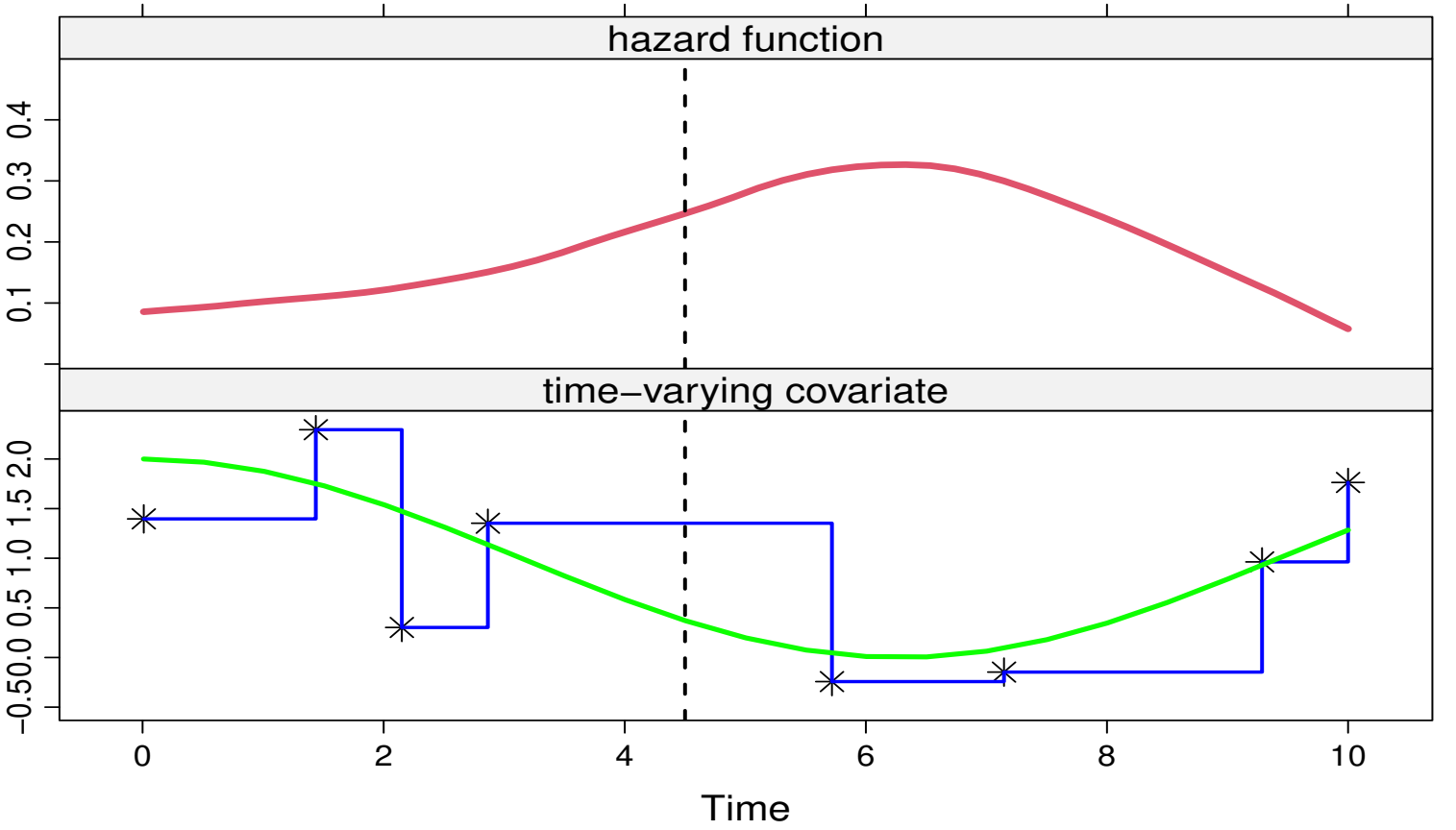
- Longitudinal outcomes $\Rightarrow$ time-varying covariates
  - ▷ endogenous type
  - ▷ existence of the covariates is related to the failure status

1.2 Joint Models (cont'd)

Standard (time-varying) Cox models not appropriate

Joint Models for Longitudinal and Time-to-Event Data

1.2 Joint Models (cont'd)

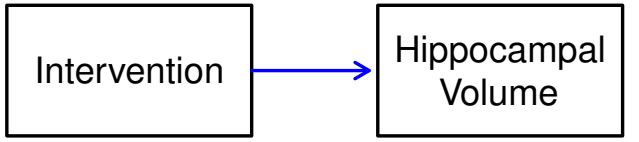


1.3 Hippocampal Volume Sub-Model

- Intervention is assumed to improve hippocampal volume

$$\begin{aligned} \texttt{HV}_i(t) &= HV_i(t) + \varepsilon_i(t) \\ &= \beta_0 + \beta_1 t + \beta_2 \texttt{Int}_i + \beta_3 \{t \times \texttt{Int}_i\} + b_{i0} + b_{i1} t + \varepsilon_i(t) \end{aligned}$$

1.3 Hippocampal Volume Sub-Model (cont'd)

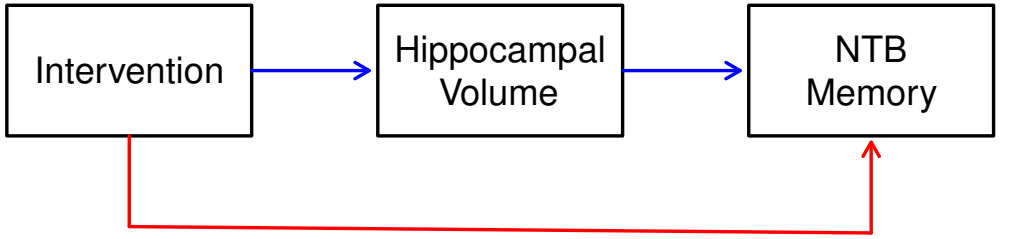


1.4 NTB Memory Sub-Model

- Intervention is assumed to
  - ▷ directly improve NTB memory
  - ▷ improve NTB memory via hippocampal volume

$$
\begin{aligned}
\texttt{NTB}_i(t) &= NTB_i(t) + \epsilon_i(t) \\
&= \gamma_0 + \gamma_1 t + \gamma_2 \texttt{Int}_i + \gamma_3 \{t \times \texttt{Int}_i\} + u_{i0} + u_{i1} t + \xi HV_i(t) + \epsilon_i(t) \\
&= \gamma_0 + \gamma_1 t + \gamma_2 \texttt{Int}_i + \gamma_3 \{t \times \texttt{Int}_i\} + u_{i0} + u_{i1} t \\
&\quad + \xi \Big(\beta_0 + \beta_1 t + \beta_2 \texttt{Int}_i + \beta_3 \{t \times \texttt{Int}_i\} + b_{i0} + b_{i1} t \Big) + \epsilon_i(t)
\end{aligned}
$$

1.4 NTB Memory Sub-Model (cont'd)



1.5 Open-Label Medication Sub-Model

- Open-label medication and dropout treated as *Competing Risks*

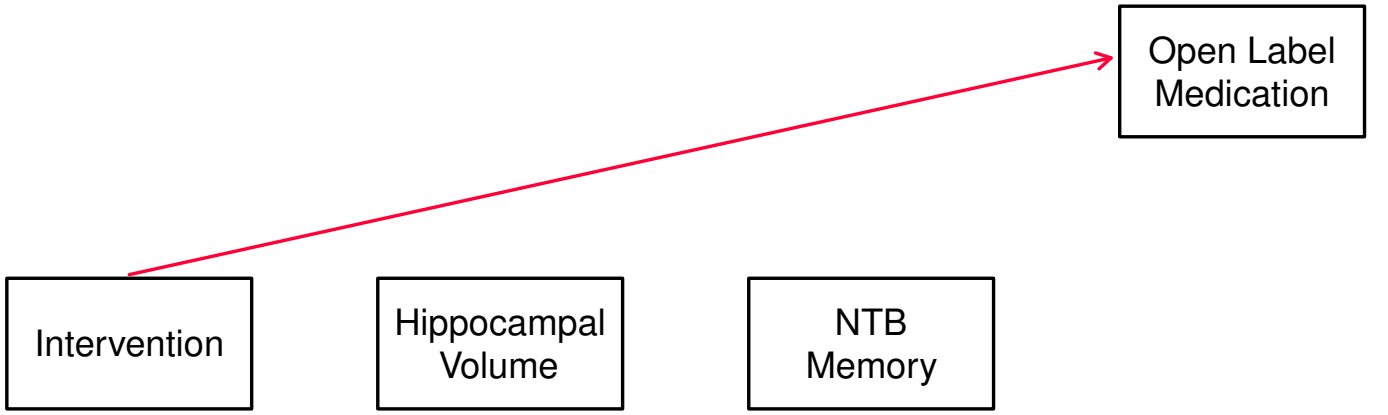
- Separate hazard models for Open-label medication and dropout
  - ▷ linked with intervention
  - ▷ hippocampal volume and NTB memory

1.5 Open-Label Medication Sub-Model (cont'd)

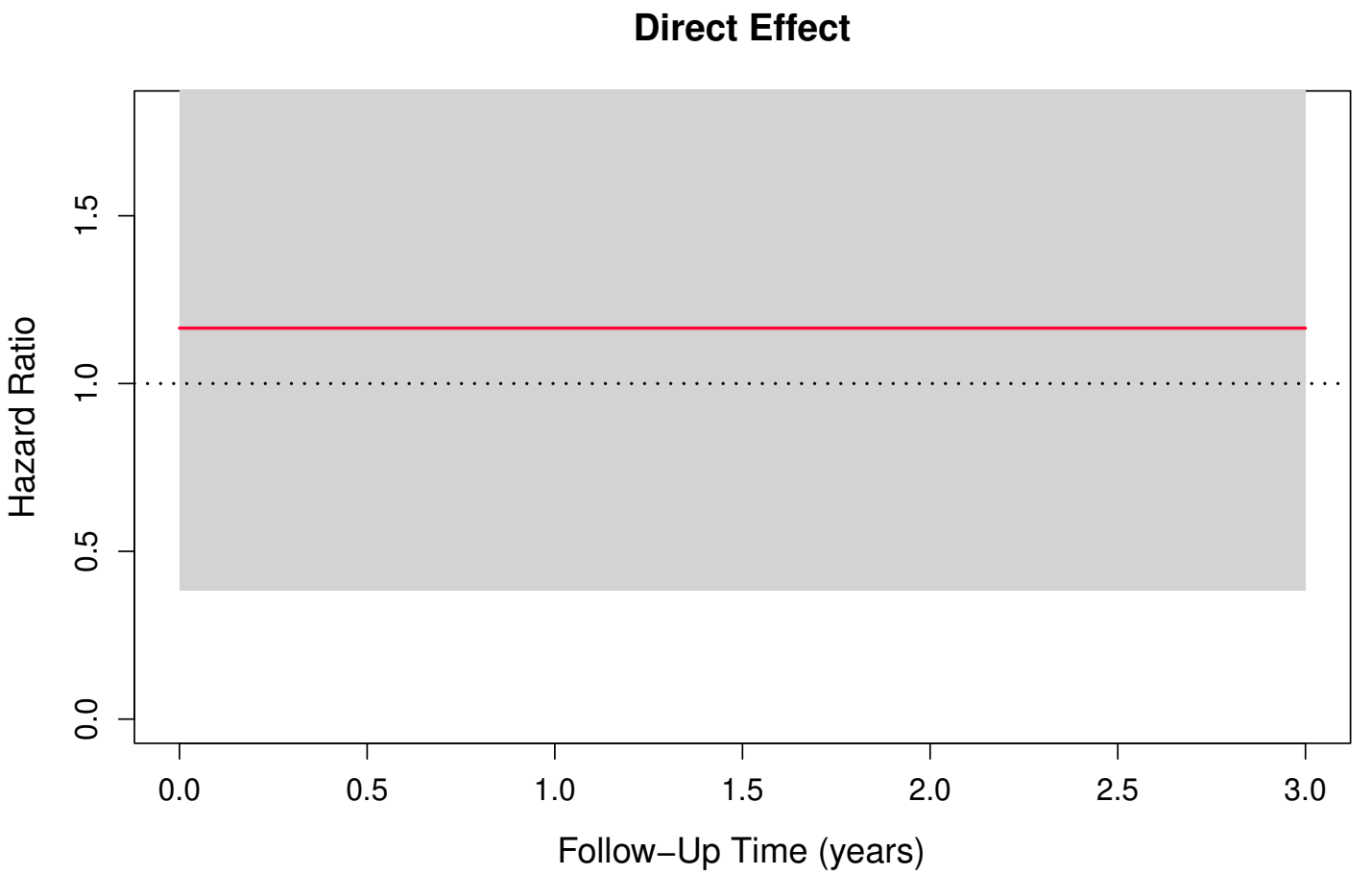
- Open-Label Medication

$$h_i(t) = h_0(t) \exp\Big\{ \delta \texttt{Int}_i \qquad \Big\}$$

1.5 Open-Label Medication Sub-Model (cont'd)



1.5 Open-Label Medication Sub-Model (cont'd)

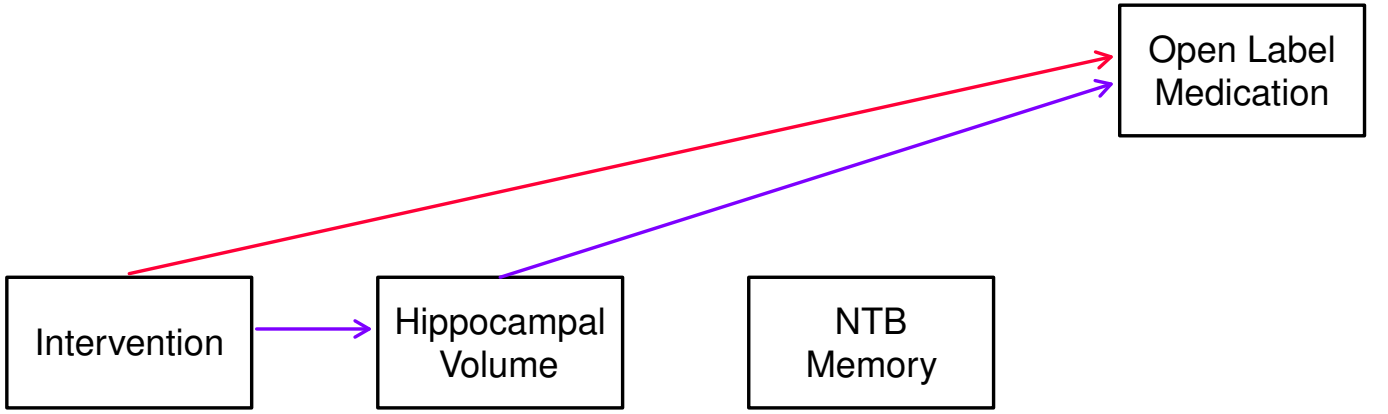


1.5 Open-Label Medication Sub-Model (cont'd)

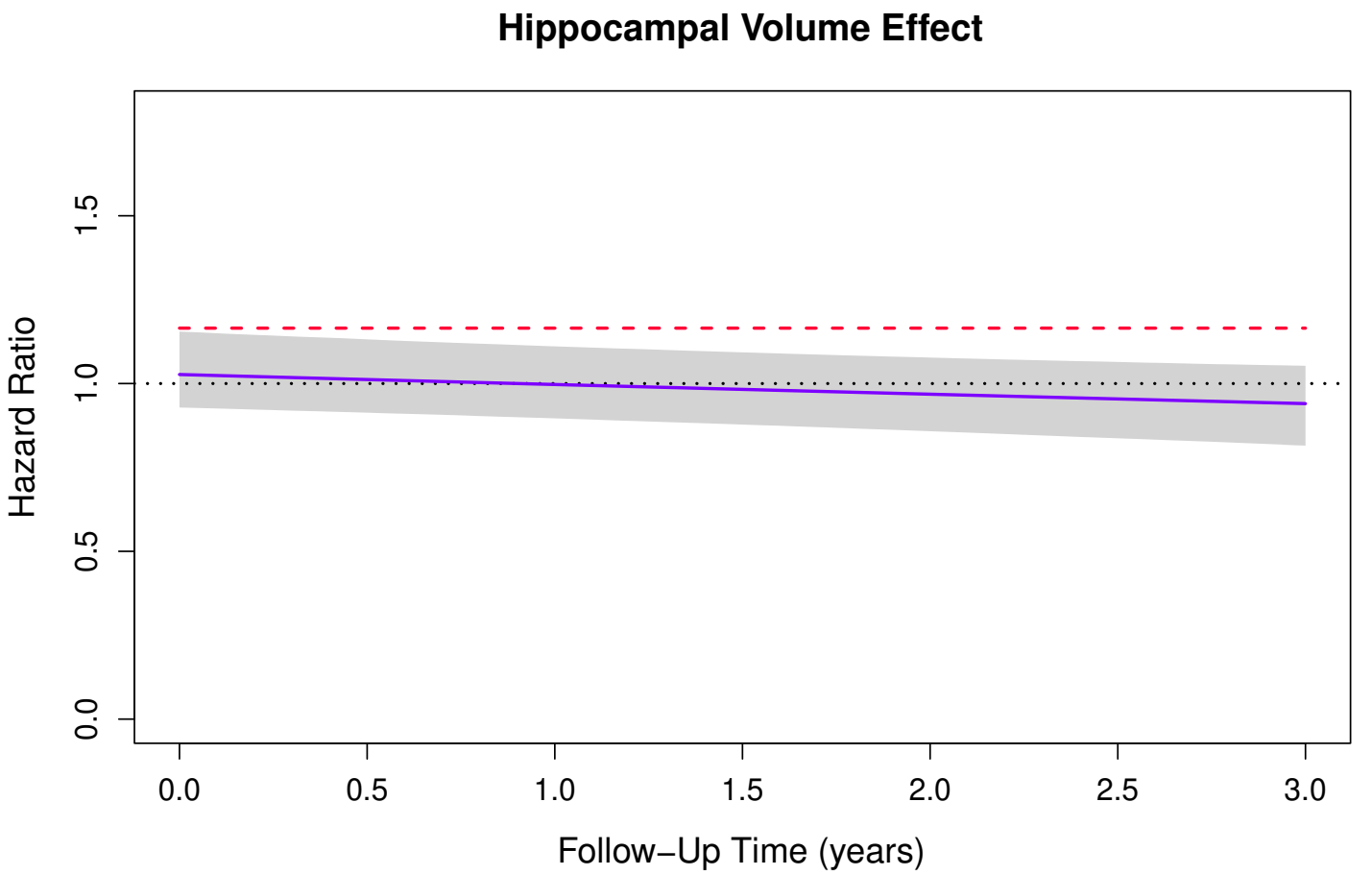
- Open-Label Medication

$$h_i(t) = h_0(t) \exp\Big\{ \delta \texttt{Int}_i + \alpha HV_i(t) \Big\}$$

1.5 Open-Label Medication Sub-Model (cont'd)



1.5 Open-Label Medication Sub-Model (cont'd)

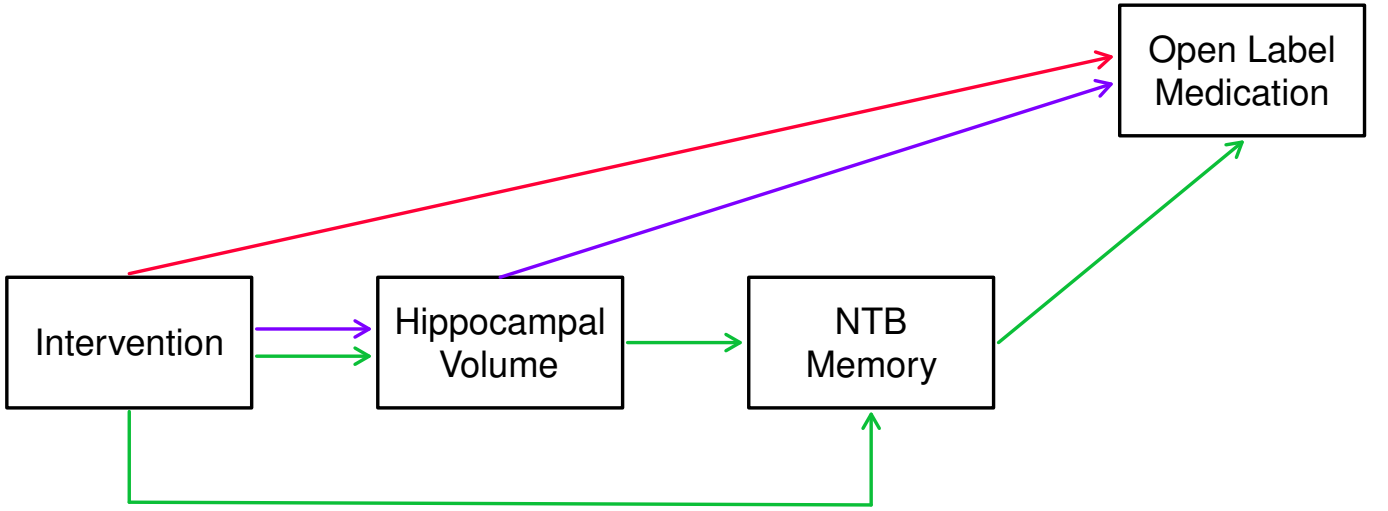


1.5 Open-Label Medication Sub-Model (cont'd)

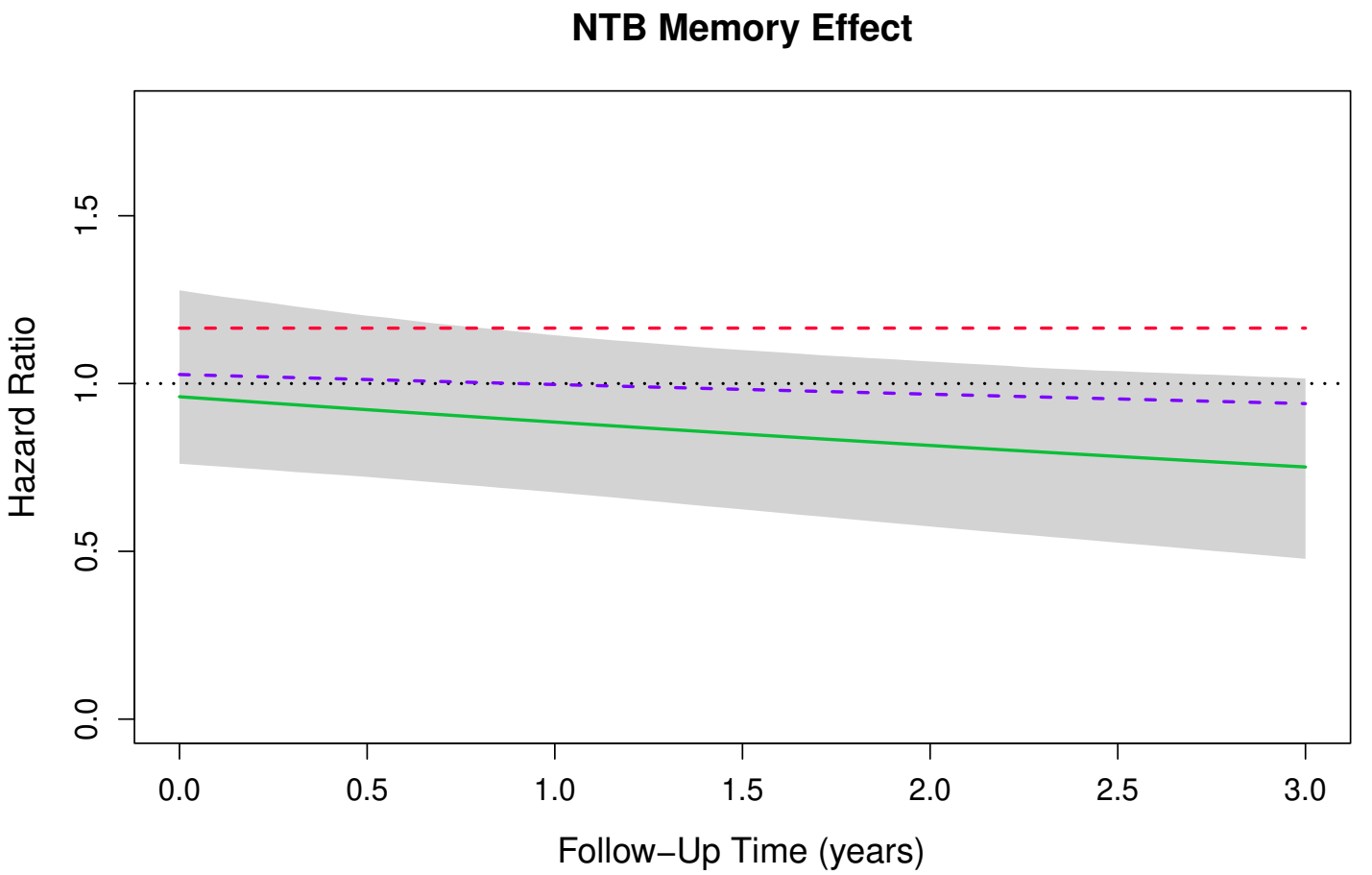
- Open-Label Medication

$$h_i(t) = h_0(t) \exp\Big\{ \delta \texttt{Int}_i + \alpha HV_i(t) + \psi NTB_i(t) \Big\}$$

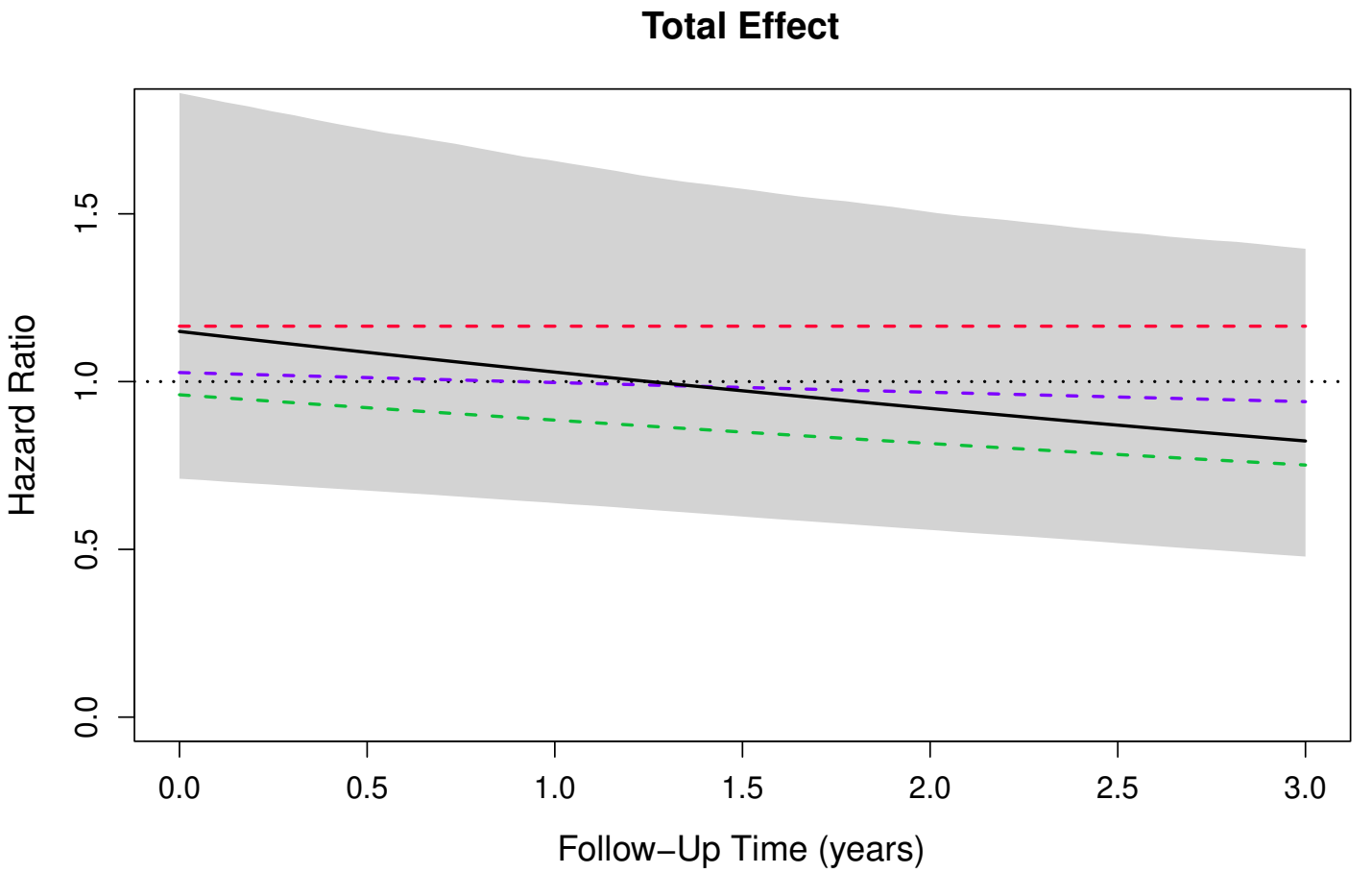
1.5 Open-Label Medication Sub-Model (cont'd)



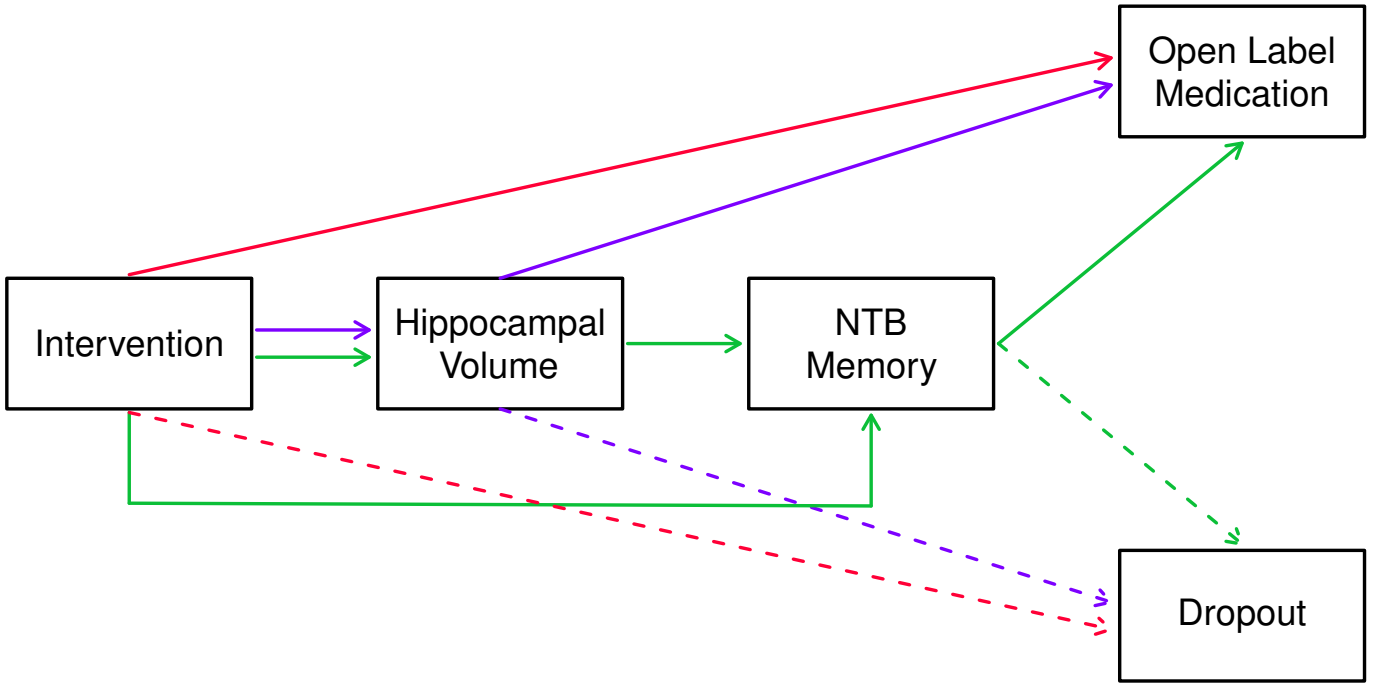
1.5 Open-Label Medication Sub-Model (cont'd)



1.5 Open-Label Medication Sub-Model (cont'd)



1.5 Open-Label Medication Sub-Model (cont'd)



1.6 Discussion & Extensions

- Joint Models **Advantages**
  - ▷ allow to disentangle treatment effects, accounting for biological mechanisms
  - ▷ account for MNAR dropout

- Joint Models **Challenges**
  - ▷ need to define the separate models
  - ▷ challenging to fit

1.6 Discussion & Extensions (cont'd)

- Consider relevant functional forms
  - ▷ e.g., cumulative effect of hippocampal volume

- Account for non-proportional hazards
  - ▷ time-varying coefficients

Thank for your attention!

http://www.drizopoulos.com/