PRM144

A model for Alzheimer's disease in the prevention setting

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Background

Shifting the focus of clinical trials testing disease-modifying interventions against Alzheimer's disease (AD) from the dementia stages of the disease to pre-symptomatic stages may increase the likelihood of success for these trials.

Objective

To develop a model for the pre-symptomatic time course of the disease to inform design of clinical trials in the prevention setting.

Methods

- Time to event (TTE), with event defined as diagnosis of mild cognitive impairment (MCI) or dementia due to AD, was modelled with a Weibull parametric survival function.
- Progression of the Alzheimer's Prevention Initiative Preclinical Composite (APCC)[1] was modelled with two mixed-effects models:
  1. For converters, i.e. participants with a diagnosis of MCI or dementia within 8 years: non-linear in time
  2. For non-converters: linear in time

TTE model for first diagnosis of MCI or dementia

Input

Simulation of APCC progression for converters and non-converters

Figure 1. Schematic for the AD prevention model

- Covariates incorporated in the model were selected from an initial list of clinically relevant variables by backward elimination based on Akaike's information criterion (AIC)[2]:
  - age
  - sex
  - apolipoprotein E ε4 (APOE4) carrier status, i.e. having no allele (non-carrier), one allele (heterozygous) or two alleles (homozygous)
  - cognition at baseline (BL)
  - years of education
- Validation of model structure
  - TTE model: Weibull survival function was compared with exponential, Gompertz and piece-wise exponential survival functions
  - APCC model for converters: non-linear power model was compared with linear and quadratic model
  - APCC model for non-converters: linear model was compared with quadratic model
- Data used to develop the model: cohorts from the Rush Alzheimer's disease center (ROS, MAP and MARS) and the National Alzheimer's Coordinating Center (NACC)

Results

Results of covariate selection

	APCC at BL	Education	APOE4 status	Sex	Age
TTE model	×	×	×		× (at BL)
APCC model for converters					
Intercept	×	×		×	× (at event)
Rate	×	×	×		
APCC model for non-converters					
Intercept	×	×		×	× (at BL)
Rate	×	×	×	×	× (at BL)

Table 1. Covariates selected by backward elimination based on AIC

Results of model structure validation

- TTE model: Weibull model performed best in terms of AIC (see Figure 2)
- APCC model for converters: power model performed best in terms of AIC (see Figure 3)
- APCC model for non-converters: linear model performed best in terms of AIC (graph not shown)

Results cont'd

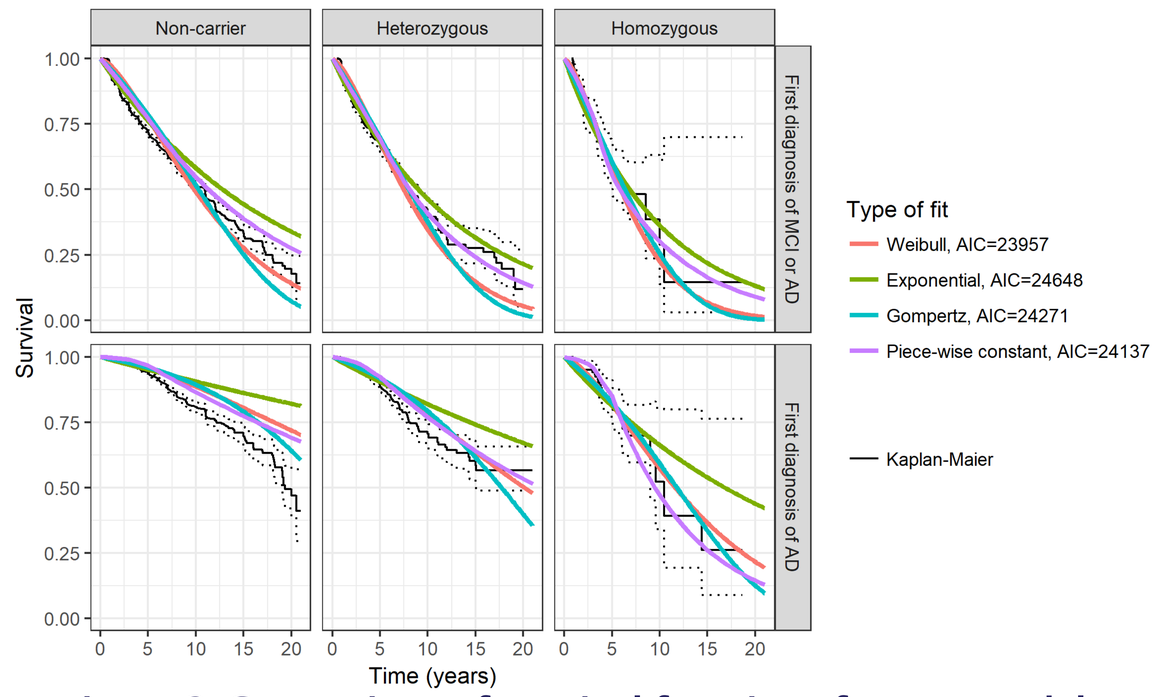

Figure 2. Comparison of survival functions for TTE model

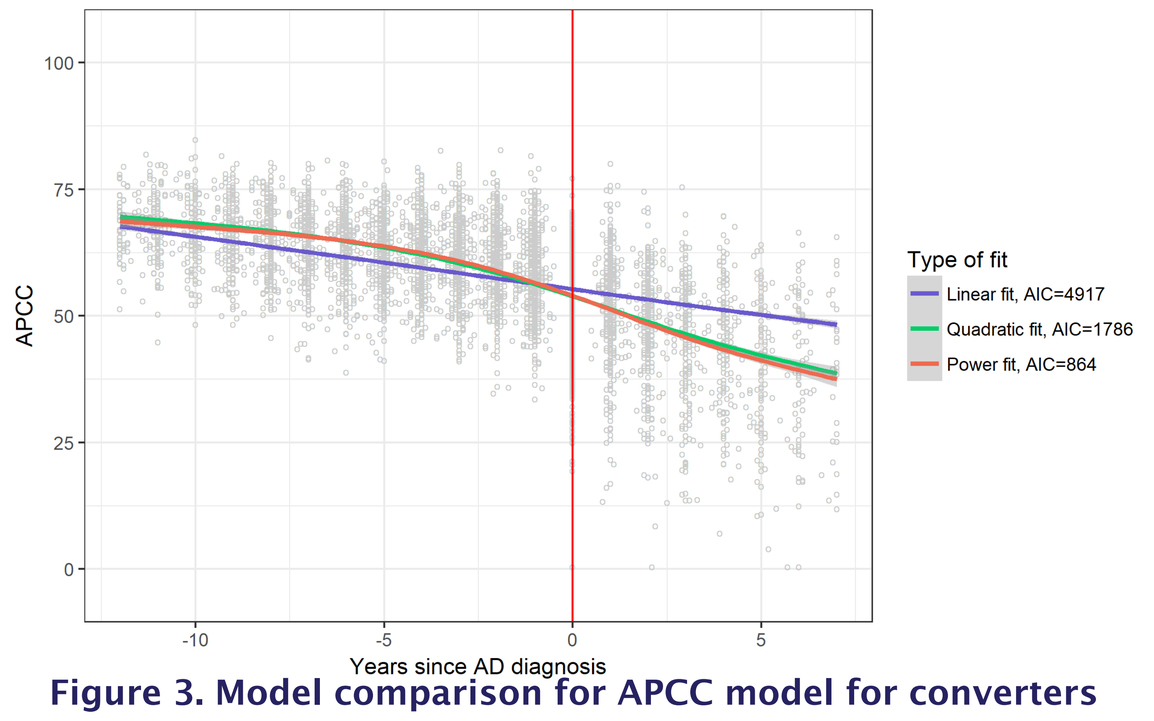

Figure 3. Model comparison for APCC model for converters

A simulation platform was developed to investigate clinical trial design options and properties of APCC and TTE as endpoints

- Developed on a slightly different model for TTE and APCC
- To investigate clinical trial design options and properties of APCC and TTE as endpoints
- To investigate and optimize population characteristics
- To explore the impact of population characteristics on event rates and power to optimize the enrichment strategy

Results of clinical trial simulations

- 1000 clinical trials simulated to investigate power
- Each run simulates placebo (natural course) as well as multiple active arms corresponding to different treatment effects formulated as hazard ratio (HR) from 0.9 to 0.6, i.e. risk reduction of 10 to 40%
- HR = 0.7 corresponds to around 1 year delay in 5 years (the 5 years risk for placebo will only be observed about one year later in active)
- Age has a major impact on the event rate and hence, on power
- Investigation of the relationship between age distribution and power supported the definition of the target trial population

Conclusion

- This is the first AD disease progression model describing pre-symptomatic stages of the disease, linking time to first diagnosis of MCI or dementia with longitudinal decline in cognition.
- The model captures prognostic factors, chosen by clinical and statistical relevance.
- It can be used in the context of optimizing design of clinical trials in the prevention setting.
- Further refinements of the model may include:
  - Incorporate biomarkers such as amyloid-β and τ as covariates
  - External validation of the model on other AD databases
  - Addition of a health economic module

References

1. Langbaum JB et al. *An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease*. Alzheimers Dement. 2014 Nov;10(6):666-74.
2. Vaida F and Blanchard S. *Conditional Akaike information for mixed-effects models.* Biometrika. 2005 Jun;92(2):351–370.

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