Evidence synthesis for a single randomized controlled trial and observational data in small populations

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InSPiRe
Innovative methodology for small populations research

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Motivation

- Randomized controlled trials (RCTs) are widely accepted as the gold standard design of clinical research to assess therapeutic interventions.
- Usually two independent RCTs are required to demonstrate efficacy and safety for marketing authorization.
- In small populations the conduct of a single RCT with a sufficient sample size might be extremely difficult or not feasible.
- This is particularly the case
  1. in paediatric studies,
  2. if the intervention is to treat a rare disease, or
  3. if randomization is challenging.

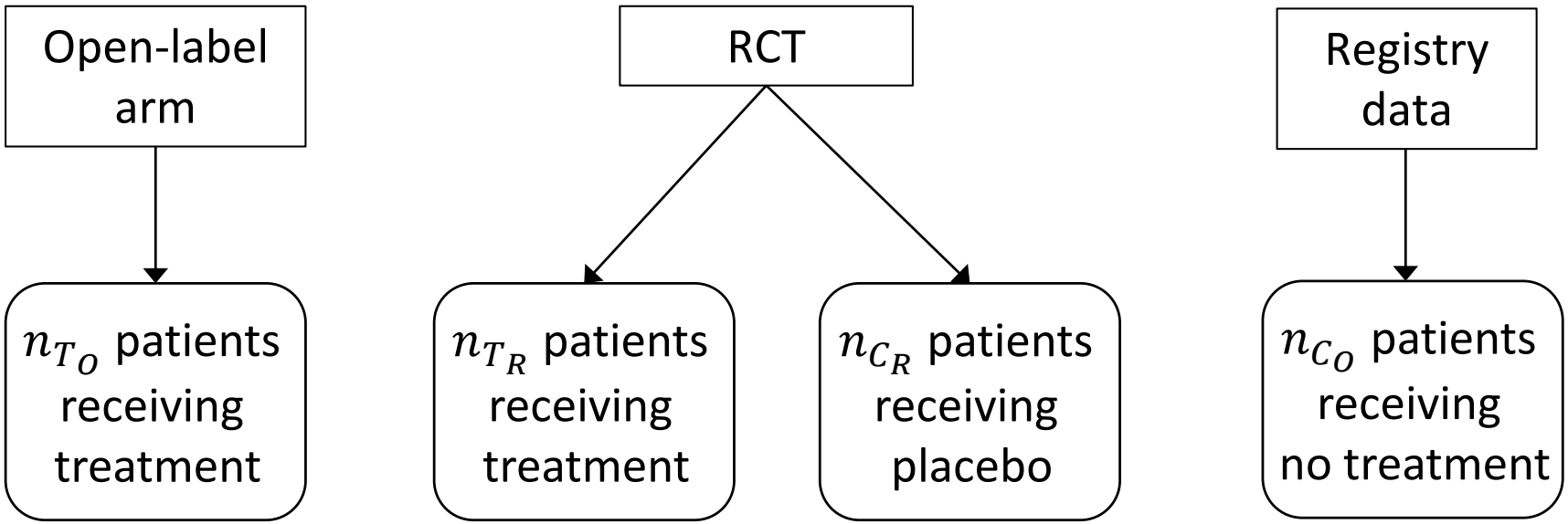
Alport syndrome

- Alport syndrome (AS) is a rare genetic disorder that inevitably leads to end-stage kidney disease.
- There is no known cure for AS. About 50% of patients develop end-stage kidney disease by the age of 20 years.
- Observational data suggest that the angiotensin-converting enzyme inhibitor ramipril delays renal failure and improves life-expectancy in Alport patients with proteinuria.
- The ongoing EARLY PRO-TECT Alport study is the first double-blind RCT that assesses the safety and efficacy of early therapy onset with ramipril in paediatric Alport patients (ClinicalTrials.gov identifier: NCT01485978).

The EARLY PRO-TECT trial and observational data

- The course of the disease, its hereditary nature and persuasive observational data affect the willingness of patients to consent to randomization.
- One could randomize patients in a 2:1 ratio to ramipril or placebo and combine the treatment effect estimate in the control arm with Alport registry data.
- Alport registries:
  1. Alport Syndrome Treatments and Outcomes Registry (ASTOR), located at the University of Minnesota.
  2. European Alport Therapy Registry - European Initiative Towards Delaying Renal Failure in Alport Syndrome.
- In addition, evidence from an open-label arm of patients receiving ramipril will be available.

Trial design



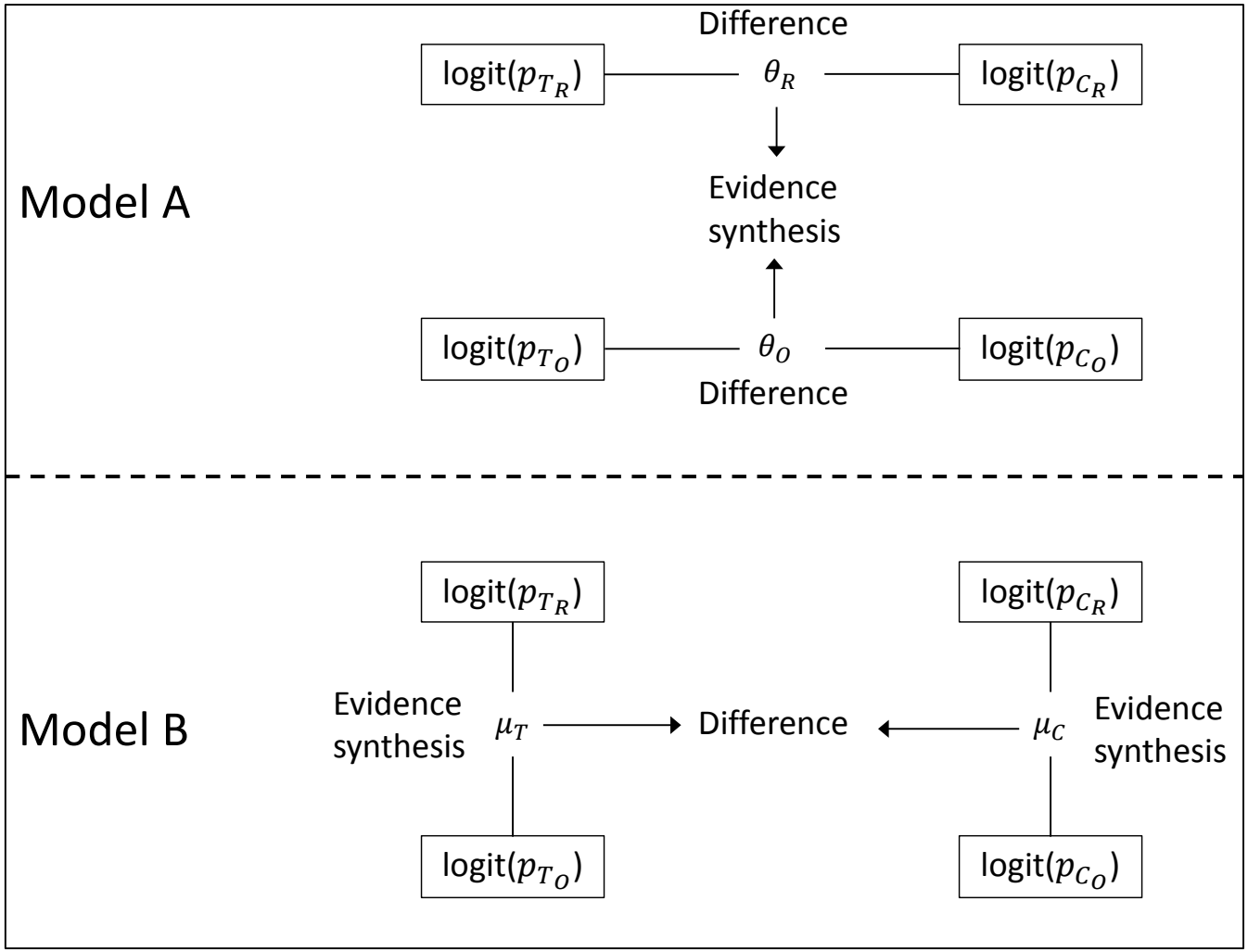
Data

- We consider a binary endpoint.
- Randomized arms: let X_{i_R} be the number of events and p_{i_R} denote the probability of an event in group i $(i = T, C)$.
- Non-randomized arms: let X_{i_O} be the number of events and p_{i_O} denote the probability of an event in group i $(i = T, C)$.
- Binomial model:

$$X_{i_j} \sim \mathcal{B}(n_{i_j}, p_{i_j}) \ , \quad i = T, C; j = R, O \ .$$

- Let $\theta_R = \log\left(\frac{p_{T_R}(1-p_{C_R})}{p_{C_R}(1-p_{T_R})}\right)$ and $\theta_O = \log\left(\frac{p_{T_O}(1-p_{C_O})}{p_{C_O}(1-p_{T_O})}\right)$ denote the log odds ratio for the randomized and observational data, respectively.

Model frameworks



Evidence synthesis

- The hierarchical structure of model A may be stated as

$$y_j|\theta_j, s_j \sim \mathcal{N}(\theta_j, s_j^2) \ ,$$
$$\theta_j|\mu, \tau \sim \mathcal{N}(\mu, \tau^2) \ , \quad j = R, O \ ,$$

  where y_j is an estimate of θ_j and s_j is its standard error.

  The θ_j differ from study to study and are distributed around a common mean μ with between-study-type variability or heterogeneity τ.

- The framework for model B consists of two hierarchical structures with parameters (μ_T, τ_T) and (μ_C, τ_C).

  The overall treatment effect is computed as a contrast: $\mu_T - \mu_C$.

Generating data

RCT	Treatment	Control
No event	31	9
Event	9	11
$\sum$	$n_{T_R} = 40$	$n_{C_R} = 20$

Log odds ratio $y_R = 1.4374$
Standard error $s_R = 0.5877$

Observational data	Treatment	Control
No event	29	29
Event	11	31
$\sum$	$n_{T_O} = 40$	$n_{C_O} = 60$

Log odds ratio $y_O = 1.0361$
Standard error: $s_O = 0.4383$

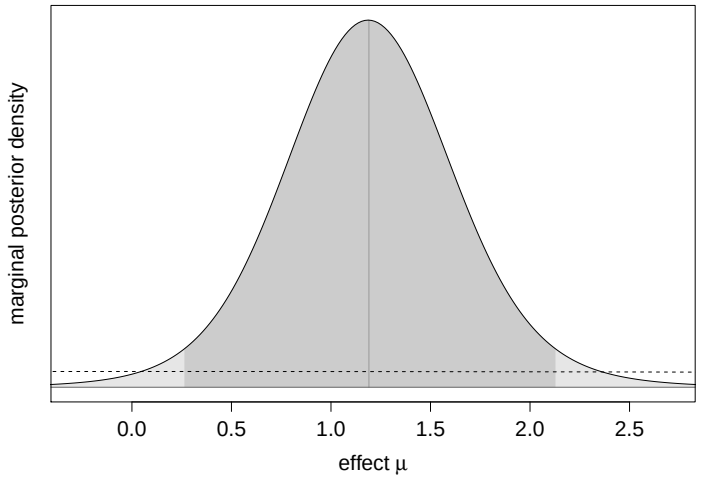
Fitting model A

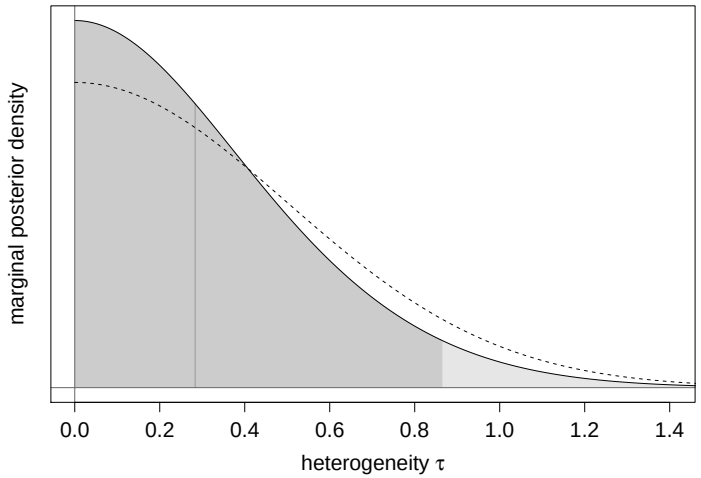
- We use a Bayesian approach for fitting the hierarchical models.
- Inference for μ and τ is captured by the joint posterior distribution, from which the marginal distribution of μ is used to derive point estimates and probability intervals for μ.
- Our approach requires prior distributions for μ and τ:
  - For μ one may use a noninformative (improper) uniform prior or a normal prior with mean zero and large variance.
  - For τ we use half-normal (HN) prior distributions.
- The R package `bayesmeta` provides a collection of functions to facilitate Bayesian inference in the random-effects meta-analysis model.

Fitting model A (2)

- `bma <- bayesmeta(y, s, mu.prior.mean=0, mu.prior.sd=10, tau.prior=function(t){dhalfnormal(t,scale=0.5)})`
- Marginal posterior summary:

	tau	mu
mode	0.0000	1.1870
median	0.2833	1.1960
mean	0.3428	1.1931
sd	0.2680	0.4699
95% lower	0.0000	0.2637
95% upper	0.8651	2.1278





Fitting model B

- Compute estimates for the logits(p_{i_j}) ($i = T, C; j = R, O$) and associated standard errors.

- ```
  bma.t <- bayesmeta(y=yt, s=st, labels=names(yt),
                     mu.prior.mean=0, mu.prior.sd=10,
                     tau.prior=function(t){dhalfnormal(t, scale=0.1)})

  bma.c <- bayesmeta(y=yc, s=sc, labels=names(yc),
                     mu.prior.mean=0, mu.prior.sd=10,
                     tau.prior=function(t){dhalfnormal(t, scale=0.5)})
  ```

- Compute the convolution, that is, the distribution of the difference (treatment - control).
  ```

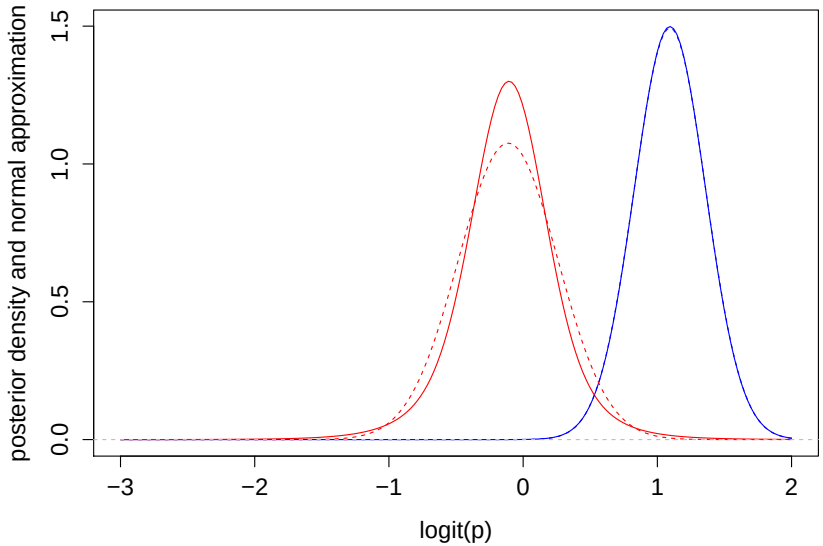
Fitting model B (2)

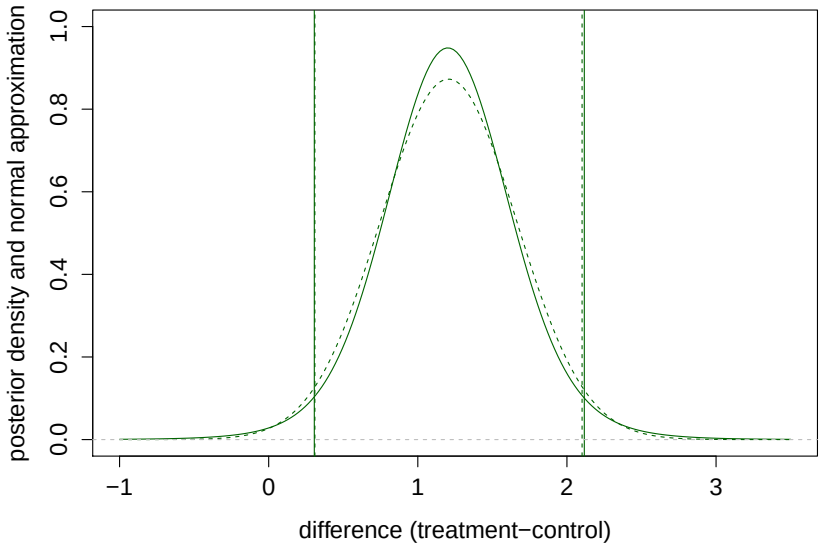
- Difference

mean	standard error
1.2056	0.4571

Model A

mean	sd
1.1931	0.4699





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	2.5%	97.5%
Normal.approx	0.3097	2.1015
Convolution	0.3059	2.1165
Model A	0.2637	2.1278

Summary and future work

- We have synthesized evidence from a single RCT and observational data in small populations.
- External data that can be used on the
  1. experimental arm could come from an additional non-randomized arm receiving the treatment;
  2. on the control arm could come from a registry.
- Recent computational advances in evidence synthesis facilitate the application of hierarchical models.
- A meta-analysis of only two studies is a challenging problem, in particular the choice of a prior distribution for τ.
- Current work involves the inclusion of covariates and the comparison of the performance of model frameworks A and B.
- In the future, we will also consider continuous and time-to-event endpoints.

References


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