Multi-state modelling of indirect chronic disease data to inform health impact models

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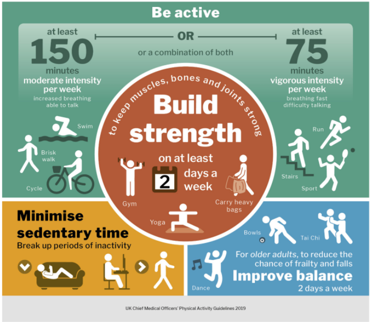
Modelling impacts of chronic disease prevention

What if?

Everyone did the recommended amount of physical activity?



(for able-bodied adults)

Modelling impacts of chronic disease prevention

What if?

40% of car trips in a city switched to walk/bike?

Modelling impacts of chronic disease prevention

What if?

Food manufacturers achieved salt reduction targets?

Modelling impacts of chronic disease prevention

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Impacts on

Lives saved / healthy life expectancy (“QALY” / “DALY”)

Modelling impacts of chronic disease prevention

What if?

Food manufacturers achieved salt reduction targets?

Impacts on

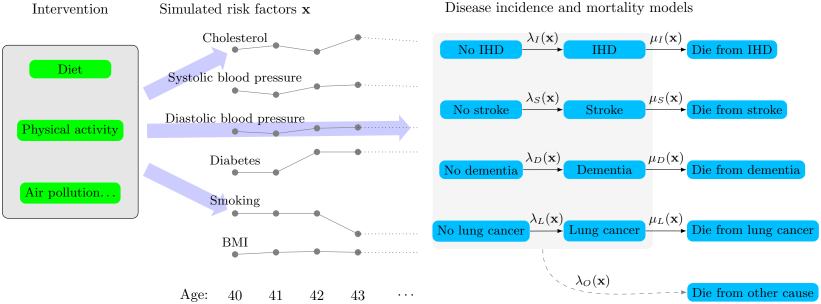
Health / social care costs, inequalities. . .

Modelling impacts of chronic disease prevention

What if?

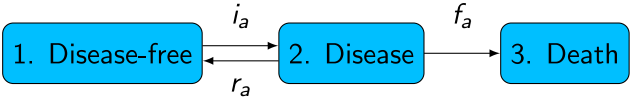
. . . Impacts on . . .

Models describe the mechanism for the impacts of prevention scenarios



Simulate outcomes under different scenarios or policy decisions

Common approach: multi-state lifetable model



1. Disease-free

i_a

r_a

2. Disease

f_a

3. Death

- Represent a disease as a 3-state Markov model
- Defined by rates by age a of
  - incidence i_a , case fatality f_a , (sometimes) remission r_a
- For some population stratum (e.g. area, gender)
- Population simulated assuming multiple diseases independent

Statistical challenge: data often indirect

- Prevalence (proportion with the disease) but not incidence i_a (rate of new cases)
- Mortality (deaths among whole population) but not case fatality f_a (risk for people who have the disease)

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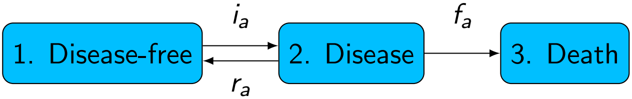

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Health impact models for transport policies and scenarios

Motivating example

- ITHIM (Integrated Transport and Health Impact model) and variants (MRC Epidemiology Unit)
- Used to inform transport policy in settings around the world (Sao Paulo, San Francisco, Nashville, Accra, Delhi...)
- Version under development (METAHIT) to inform "active transport" policy (walk, bike) for the city regions of England
- Model diseases affected by physical activity, air pollution, noise exposure (also road injury)
- Need city region-specific data on disease incidence and case fatality to inform multi-state progression model

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Global Burden of Disease study (Institute of Health Metrics and Evaluation, University of Washington)

Publishes estimates of incidence, prevalence, mortality, risk factors but not case fatality

- . . . for hundreds of diseases / conditions
- . . . for countries, and regions within countries, covering the whole world. Local authority level in UK
- Synthetic / model-based estimates with credible intervals
  - ensure consistency / comparability between outcomes and settings

Also published tools for estimating the multi-state disease model with indirect data

- DisMod II (Barendregt et al 2001)
  - friendly Windows interface, widely used, poorly understood statistical basis
- DisMod-MR (Flaxman et al 2015)
  - Bayesian, code less accessible, only been used internally

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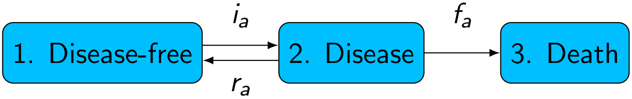
This work



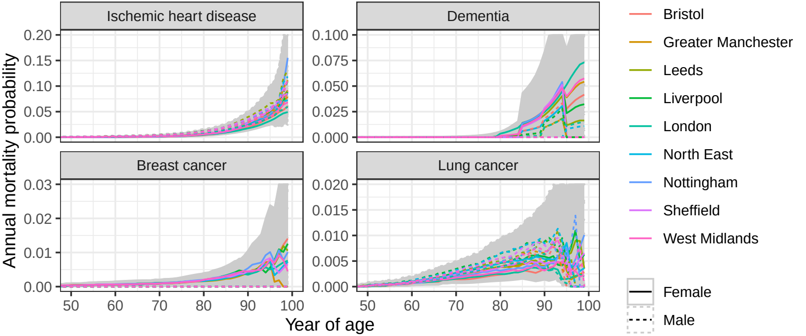
Methodological

- explained statistical basis behind DisMod inference methods
- extended the methods to make them more flexible
- provided accessible software as R package `https://chjackson.github.io/disbayes`

Application

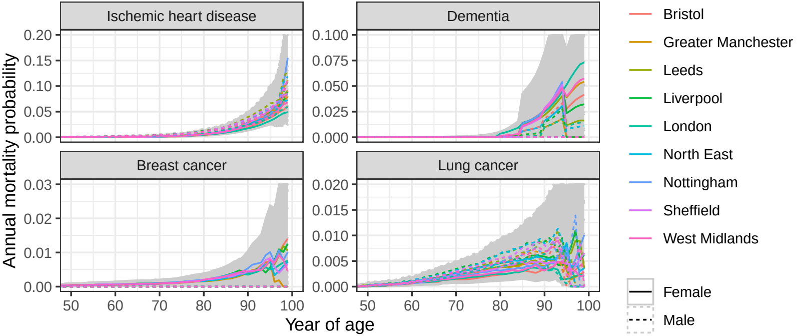
- estimate case fatality given mortality / prevalence for England city regions
- to inform transport health impact modelling for those areas

Data (incidence, mortality, prevalence, remission)



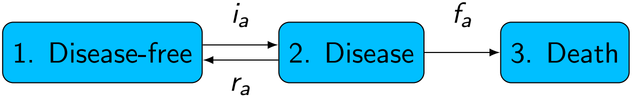
- 17 diseases, by 5-year age group, gender and local authority
- Incidence, mortality, prevalence from GBD.
- Cancer remission from 10-year survival rates published by ONS

Data (incidence, mortality, prevalence, remission)



- Data in form of estimated rates + credible intervals
- Converted to annual probabilities p, hence to implicit count of r events per year with denominator n
  - assuming CIs for p describe the Beta posterior from "data" $r \sim Bin(n, p)$. n describes the uncertainty.
- Counts for 5-year age groups smoothly disaggregated to 1-year age groups, and aggregated over city regions

Estimating multi-state transition rates from data



- Annual mortality, incidence, (remission) and prevalence as counts/denominators.
- Modelled as Binomial, with probabilities $p_a^{(mort)}, p_a^{(inc)}, p_a^{(prev)}, (p_a^{(rem)})$, for each age a
- Probabilities defined as complex functions of the parameters of interest i_a, f_a, (r_a).
  - via annual transition probability matrix P_a between 3 states
  - continuous-time Markov chain theory / analytic ODE solution
- How are rates for different ages/genders/areas related?

Relating rates from different ages, areas, genders

- Age-dependence of rates through smooth spline functions, e.g.

$$log(f_a) = \beta_0 + \beta_1 a + \sum_{k=2}^{K} \beta_k g_k(a)$$

  where $g_k()$ are basis functions (generated by `mgcv` R package)
- β_0, β_1 have vague priors, $\beta_2, \ldots, \beta_K \sim N(0, \lambda)$,
- $\lambda \sim Gamma(2, s)$ controls smoothness / deviation from linearity
- f_a assumed to be constant under a specific age if the data are insufficient (30, 50, 70 depending on the disease)
- Areas modelled independently or hierarchically (β_0 becomes random effect) with area-constant or area-dependent effect of gender

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Computation and implementation

Stan `https://mc-stan.org`

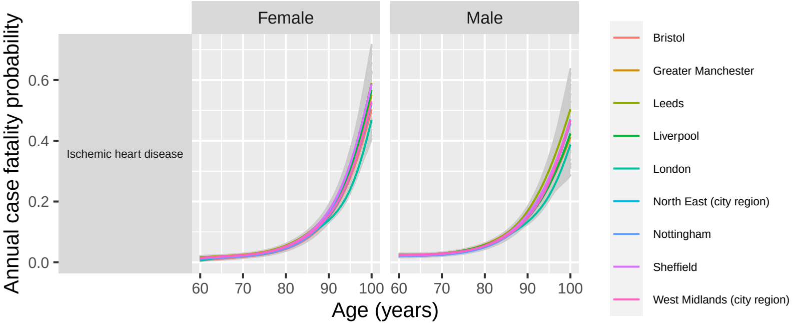
- Hamiltonian MCMC to obtain sample from posterior — for "final" results (minutes to hours)
- Optimisation to estimate the posterior mode, with normal approximation to posterior
  - instant, useful for model development

R package that embeds the Stan models

`https://chjackson.github.io/disbayes`

- Intended to be $\geq$ friendly / principled / flexible as previous DisMod packages

Examples of case fatality estimates under our models



- Area/gender specific case fatality curves produced for: ischemic heart disease, stroke, lung cancer, colorectal cancer, breast cancer, dementia, COPD, diabetes, Parkinson's disease, liver cancer, non-rheumatic valvular heart disease.
- National estimates by gender for: stomach cancer, liver cancer, uterine cancer, cardiomyopathy and myocarditis, multiple myeloma

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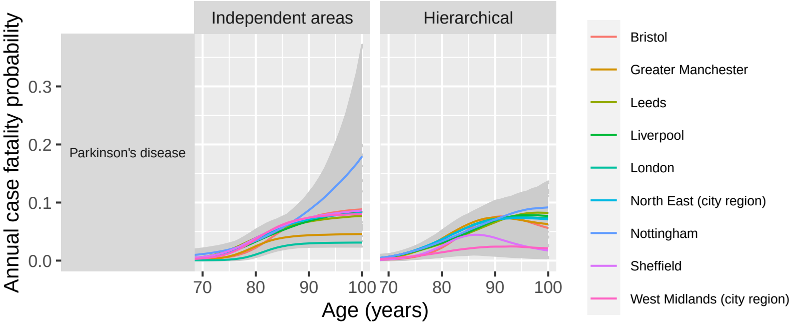

- Hierarchical models for area variations had limited utility.
- Same estimates as non-hierarchical models, except for some shrinkage at oldest ages.
- Identifiability problems for rarest diseases
- Cross-validatory comparison ("LOO-PSIS" method, Vehtari et al.) generally favoured non-hierarchical

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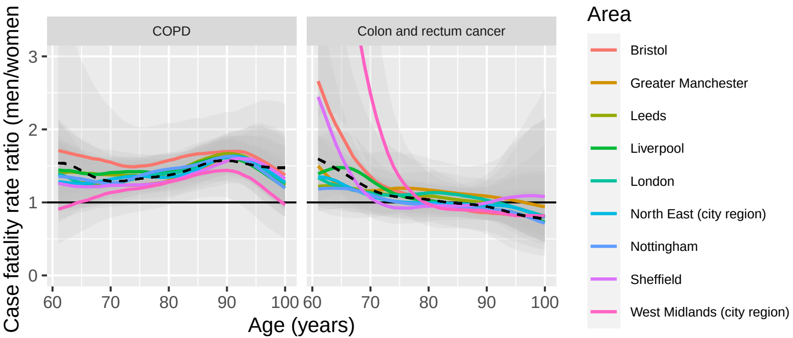
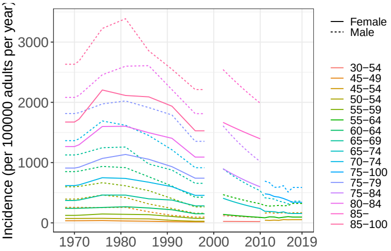
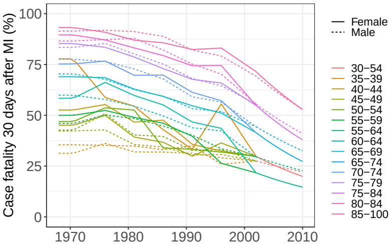


- Rate ratio between men and women, as a function of age, in the hierarchical models
- Dotted lines show model where this ratio is the same for each area.
  - Cross-validatory criterion generally prefers this

Trends through calendar time in disease risks





- Incidence and case fatality from ischemic heart disease declined in last 50 years (evidence from a variety of publications)
- Trends are age-dependent (previous "DisMod" software didn't account for this)
- Can adjust for this in the (non-hierarchical) model, assuming rate in a previous year is a fixed multiplier of the current rate (age-specific, from smoothing/interpolating published data)
- Different inferred rates under different assumptions

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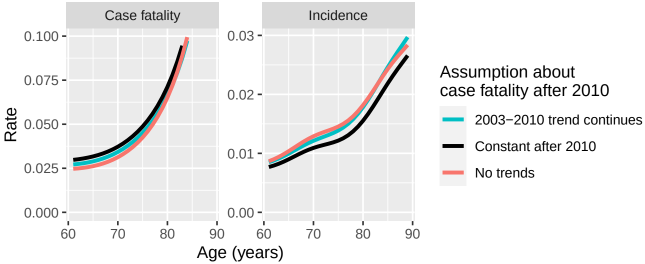

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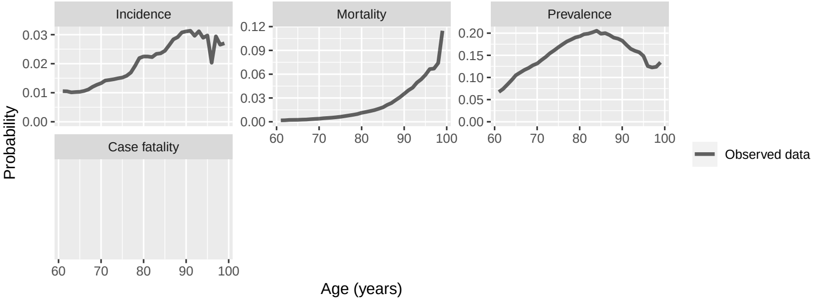
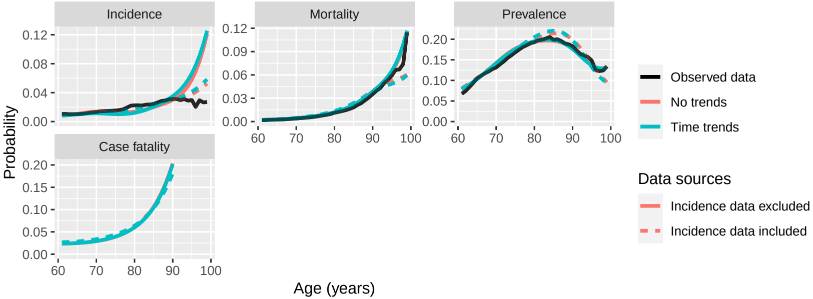
Consistency between estimates and different data sources



- The model synthesises observed data on current prevalence, mortality and incidence
  - to produce estimates of (unobserved) case fatality
  - estimates of prevalence, mortality and incidence also produced that are coherent with all data sources
- Check fit of model-based estimates to the direct data on incidence, prevalence and mortality
- Fit of the model estimates to the mortality and prevalence

Consistency between estimates and different data sources



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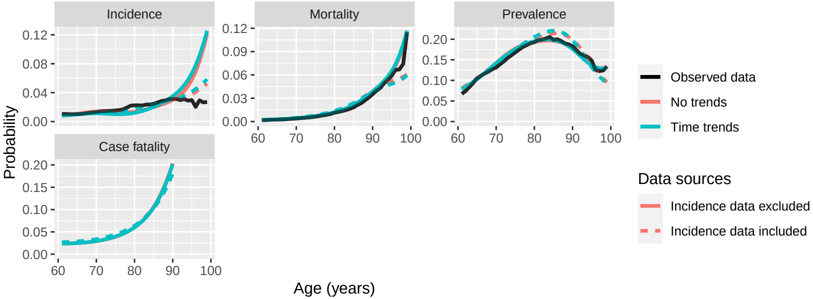
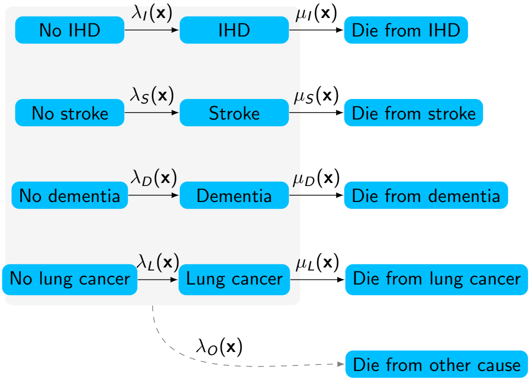


- Fit of the model estimates to the mortality and prevalence data is better if the incidence data are excluded from the evidence synthesis
- Current incidence data (new cases) in conflict with current prevalence (old cases), even if we adjust for time trends
  - Conflicts remaining between data sources, including the time trend data
  - Case fatality estimates not greatly affected though

Combining multiple diseases: "multistate lifetable"



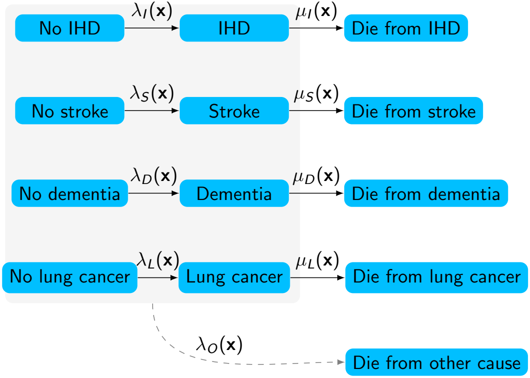
A common approach

- Parallel multistate models
- Assumes multiple diseases independent, neglecting multimorbidity effects
- Exposure (physical activity, air pollution...) may modify incidence and case fatality

Simulate at aggregate level

- proportion of population with each disease at each time
- accumulate health-adjusted life expectancy / costs to compare policies / scenarios

Combining multiple diseases: “multistate lifetable”



A common approach

Requires case fatality and effect of exposures on case fatality, needing data which attributes death to a specific cause

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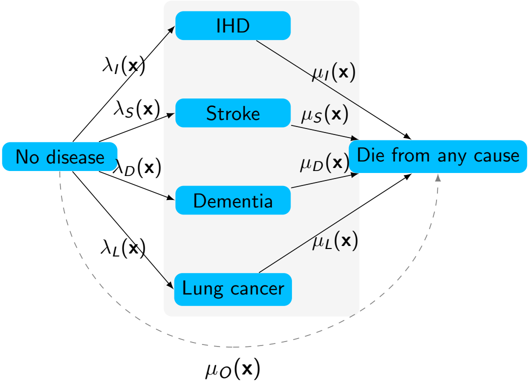
Combining multiple diseases: competing risks framework?



Simulate at individual-level ("microsimulation") rather than aggregate level

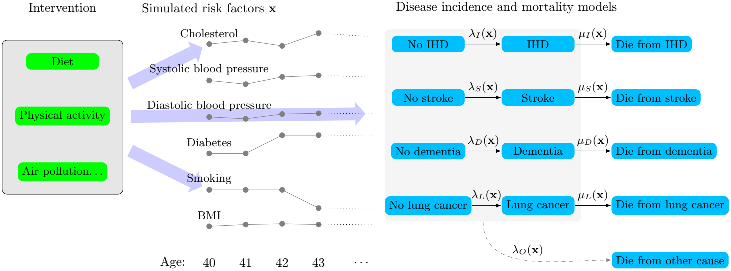
Alternative framework

- People can transition to only one disease state
- First disease that they get determines their outcome

Needs all-cause mortality rate μ for people with each disease
(and exposure effects on this)

- Easier to measure than cause-specific mortality?
- Multimorbidity effects included in each μ

Summary



Challenges of disease burden modelling to inform health impacts

- Long timespans, multiple diseases
- Disparate data sources, covering multiple populations

Further work on different aspects of this impact modelling picture

Paper soon, see `https://chjackson.github.io/disbayes` for software