Lifetime risk, prevalence, and incidence estimates from ATN model after optimzation

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Contents

1 Methods

A multistate model for Alzheimer's disease (AD) dementia using the dichotomous factors amyloidosis (A), tauopathy (T), neurodegeneration (N) and mild cognitive impairment (MCI) is shown in Figure 1. We refer to this model as the *ATN model*. The transitions $r_{ij}(a)$ are the one-year transition probabilities from state i to state j, conditional on surviving to age $a+1$. To calculate *lifetime risks* of AD dementia, we estimate the transition rates $r_{ij}(a)$ using available information.

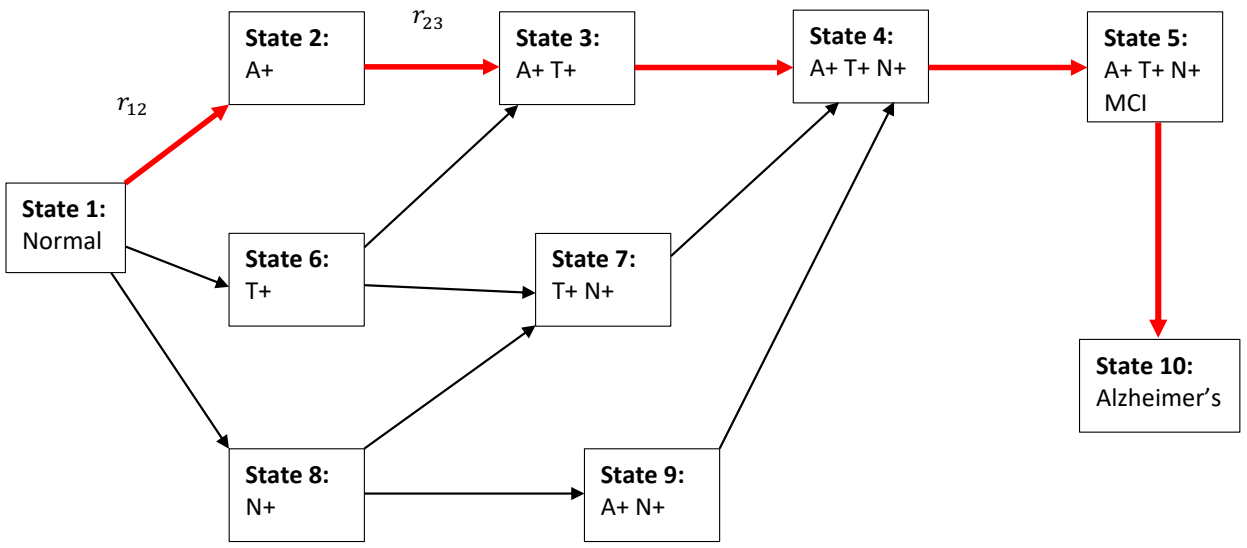


Figure 1: Multistate model for AD dementia with Amyloid (A+), Tauopathy (T+), Neurodegeneration (N+), and mild cognitive impairment (MCI)

1.1 Data and notation

We incorporate three sources of Alzheimer's disease (AD) dementia information into our analysis. These include age- and state-specific prevalence rates $Pc_i(a)$ (Jack Jr et al. 2017), age-specific incidence rates of AD dementia $I(a)$ (Brookmeyer et al. 2007), and age-specific probabilities $C(a)$ of being in a preclinical state (Brookmeyer and Abdalla 2019). The prevalences $Pc_i(a)$ are conditional on being preclinical, i.e. no MCI has developed. The probabilities $C(a)$ were calculated using a multistate model for AD dementia using only the factors A, N, and MCI, which we refer to as the *AN model*.

We will use the following notation throughout:

- $r_{ij}(a)$ is the one-year transition probability of a person at age a going from state i to state j;
- $Pc_i(a)$ is to the prevalence of state i for individuals age $a, a = 50, \ldots, 95$, conditional on being preclinical and alive(Jack Jr et al. 2017),
- $Pu_i(a)$ is the prevalence of state i for individuals age $a, a = 50, \ldots, 95$, only conditional on being alive. These were calculated as $Pu_i(a) = Pc_i(a) * C(a)$, where $C(a)$ is the probability of being preclinical as calculated using the AN model (Brookmeyer and Abdalla 2019);
- $I(a)$ is the incidence of AD dementia for individuals age $a, a = 65, \ldots, 90$ (Brookmeyer et al. 2007); its functional form is $I(a) = .00117 \exp(0.126a)$.
- $\boldsymbol{k}$ is the vector of all transition parameters $\boldsymbol{k} = (k_{012}, k_{112}, \ldots, k_{05,10}, k_{15,10})$
- k_{0ij} and k_{1ij} are transition parameters from state i to state j such that $r_{ij}(a) = k_{0ij} \exp(k_{1ij}a)$

Table 1: Lifetime risk of AD for women by age and disease state

Age	Normal	A	A+T	A+T+N	A+T+N + MCI	T	T+N	N	A+N
60	17.8 %	30.07 %	54.75 %	58.37 %	95.63 %	38.8 %	27.26 %	10.06 %	28.69 %
65	16.49 %	28.4 %	51.96 %	56.18 %	93.57 %	36.72 %	24.09 %	9.46 %	26.7 %
70	14.66 %	25.9 %	47.92 %	52.79 %	90.06 %	33.63 %	20.32 %	8.57 %	23.97 %
75	12.25 %	22.41 %	42.29 %	47.85 %	84.71 %	29.32 %	16.07 %	7.35 %	20.42 %
80	9.28 %	17.8 %	34.74 %	40.83 %	76.19 %	23.59 %	11.52 %	5.76 %	16.02 %
85	6.07 %	12.39 %	25.38 %	31.6 %	63.81 %	16.7 %	7.16 %	3.94 %	11.07 %
90	3.24 %	7.16 %	15.56 %	20.98 %	46.68 %	9.85 %	3.66 %	2.24 %	6.42 %

- $\widehat{Pc}_i(\boldsymbol{k}, a)$, $\widehat{Pu}_i(\boldsymbol{k}, a)$, and $\widehat{I}(\boldsymbol{k}, a)$, are estimates of these quantities from the multistate model for a given set of transition parameters $\boldsymbol{k}$

1.2 Estimating transition rate parameters $\boldsymbol{k}$

There are 14 total transitions r_{ij}, including 12 preclinical transitions, r_{45}, and $r_{5,10}$. We assume $r_{5,10}(a) = 0.3$ for all ages a. To estimate the parameters k_{045} and k_{145} we first notice that

$$r_{45}(a) = \lambda(a)\widetilde{r}_{45}(a), \tag{1}$$

where $\lambda(a) = \frac{P_4(a)}{P_4(a)+P_9(a)}$ is the proportion of those with both A+N+ that also have T+, and $\widetilde{r}_{45}(a)$ is the transition from State 4 (A+N+) to State 5 (A+N+ MCI) **in the AN model**. The ATN model assumes that only those with A+T+N+ can develop MCI, so we assume that those transitioning to MCI in the AN model were only coming from the subpopulation of A+N+ subjects that also had T+. Having calculated $r_{45}(a)$ using (1), we assume a log-linear form and perform a simple optimization to find the parameters k_{045} and k_{145}.

1.3 Lifetime Risks

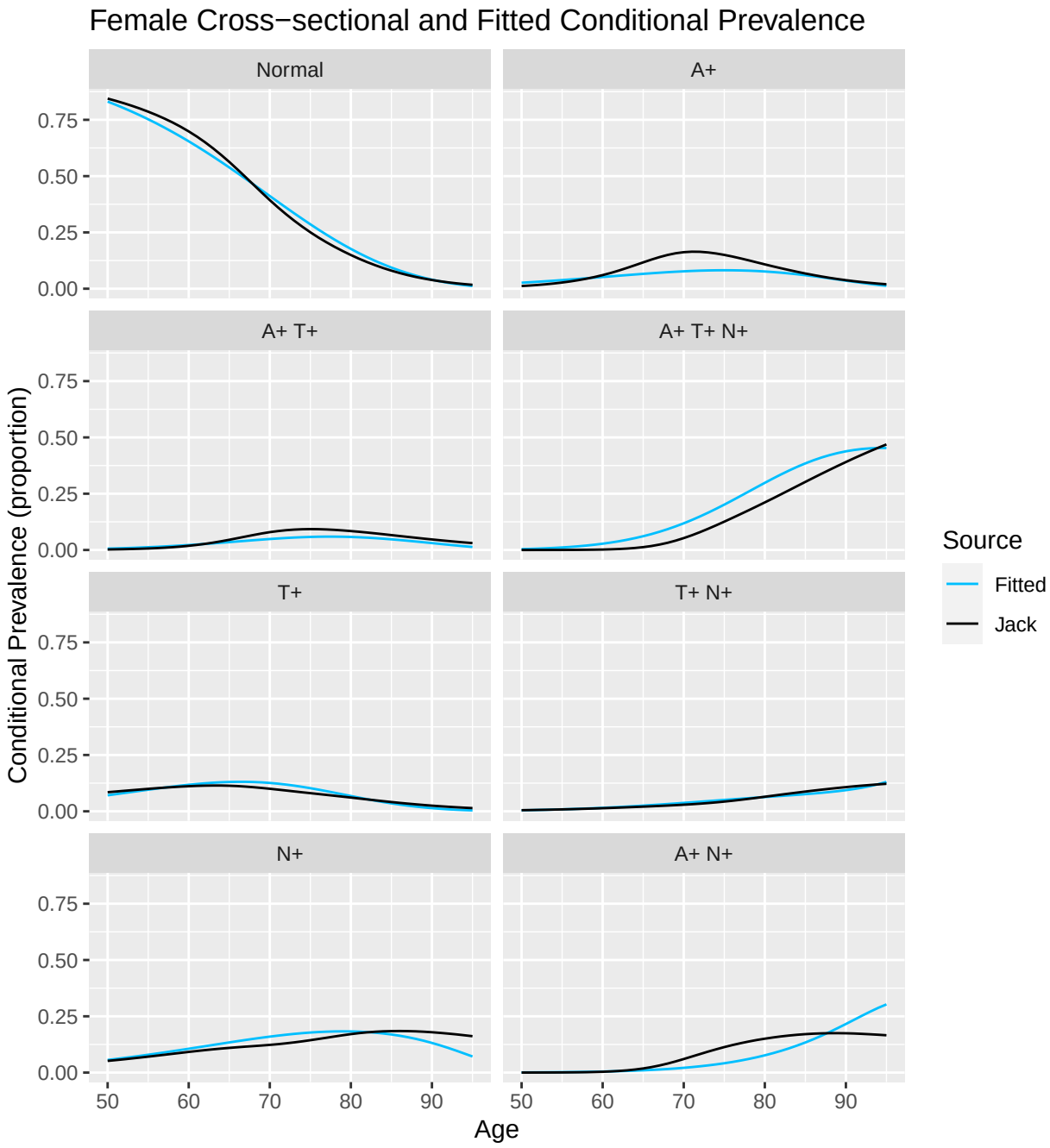
Let's first look at lifetime risks for males and females.

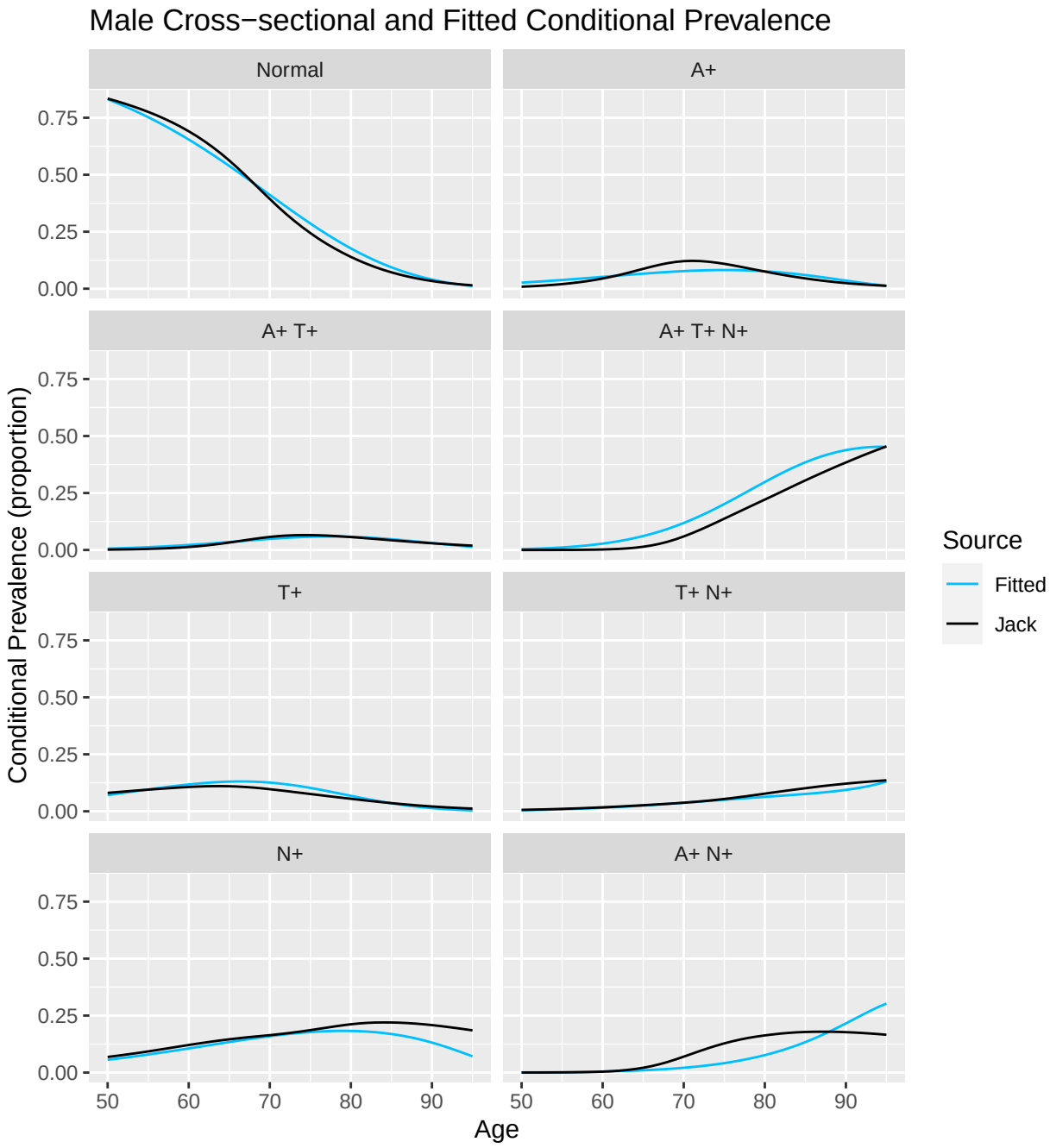
Table 2: Lifetime risk of AD for men by age and disease state

Age	Normal	A	A+T	A+T+N	A+T+N + MCI	T	T+N	N	A+N
60	12.09 %	21.94 %	45.32 %	49.39 %	92.93 %	29.87 %	20.65 %	6.42 %	21.35 %
65	11.17 %	20.71 %	42.84 %	47.49 %	90.37 %	28.19 %	18.1 %	6.05 %	19.83 %
70	9.82 %	18.72 %	39.04 %	44.27 %	85.99 %	25.55 %	15.04 %	5.45 %	17.63 %
75	8.05 %	15.94 %	33.82 %	39.59 %	79.54 %	21.89 %	11.64 %	4.61 %	14.79 %
80	5.9 %	12.31 %	26.98 %	33.02 %	69.91 %	17.11 %	8.09 %	3.53 %	11.3 %
85	3.66 %	8.21 %	18.97 %	24.79 %	56.66 %	11.62 %	4.81 %	2.31 %	7.53 %
90	1.77 %	4.38 %	10.91 %	15.73 %	40.15 %	6.35 %	2.29 %	1.21 %	4.08 %

1.4 Conditional Prevalence

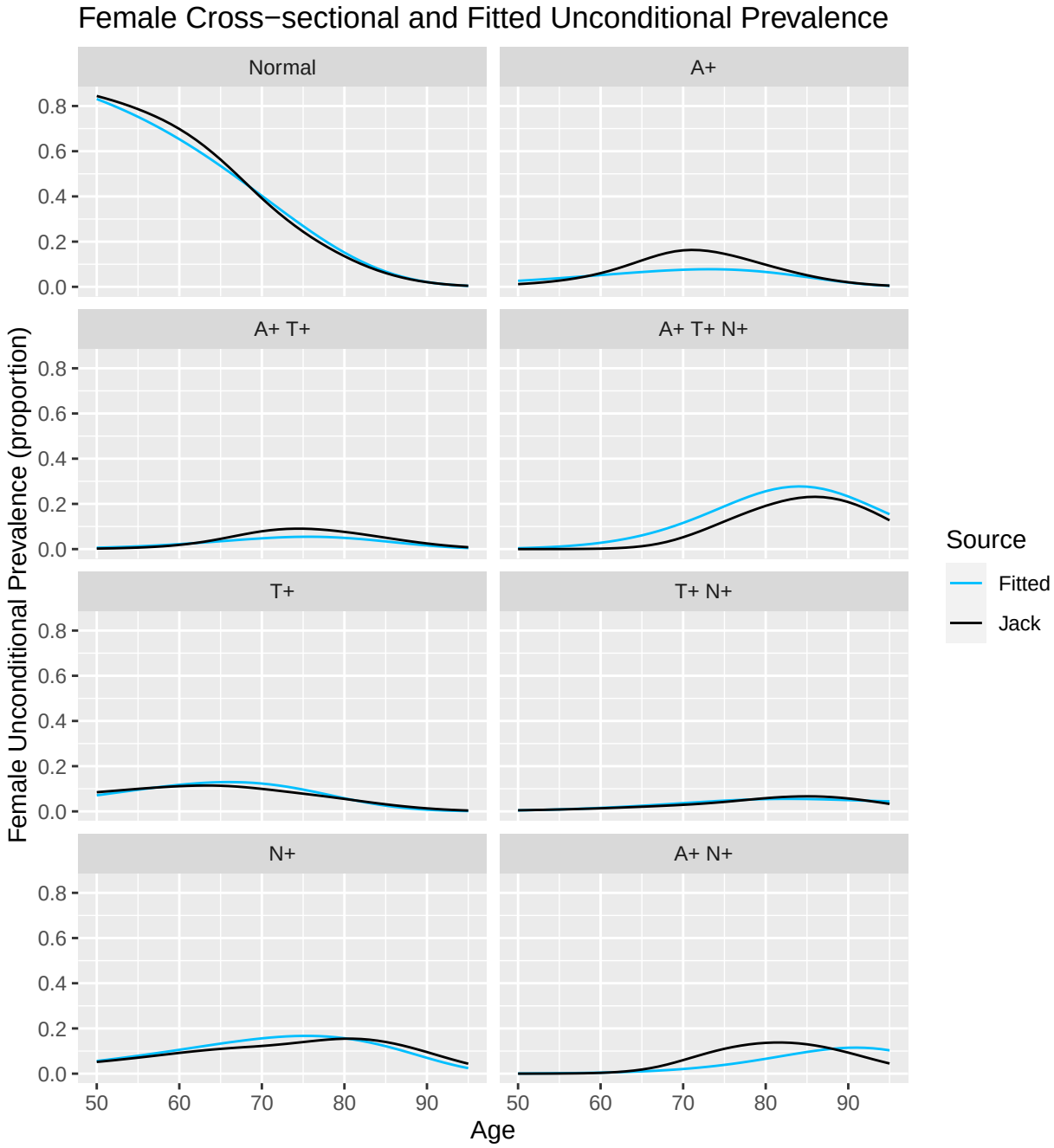
Female and male prevalence rates, conditional on being alive and in a preclinical state.

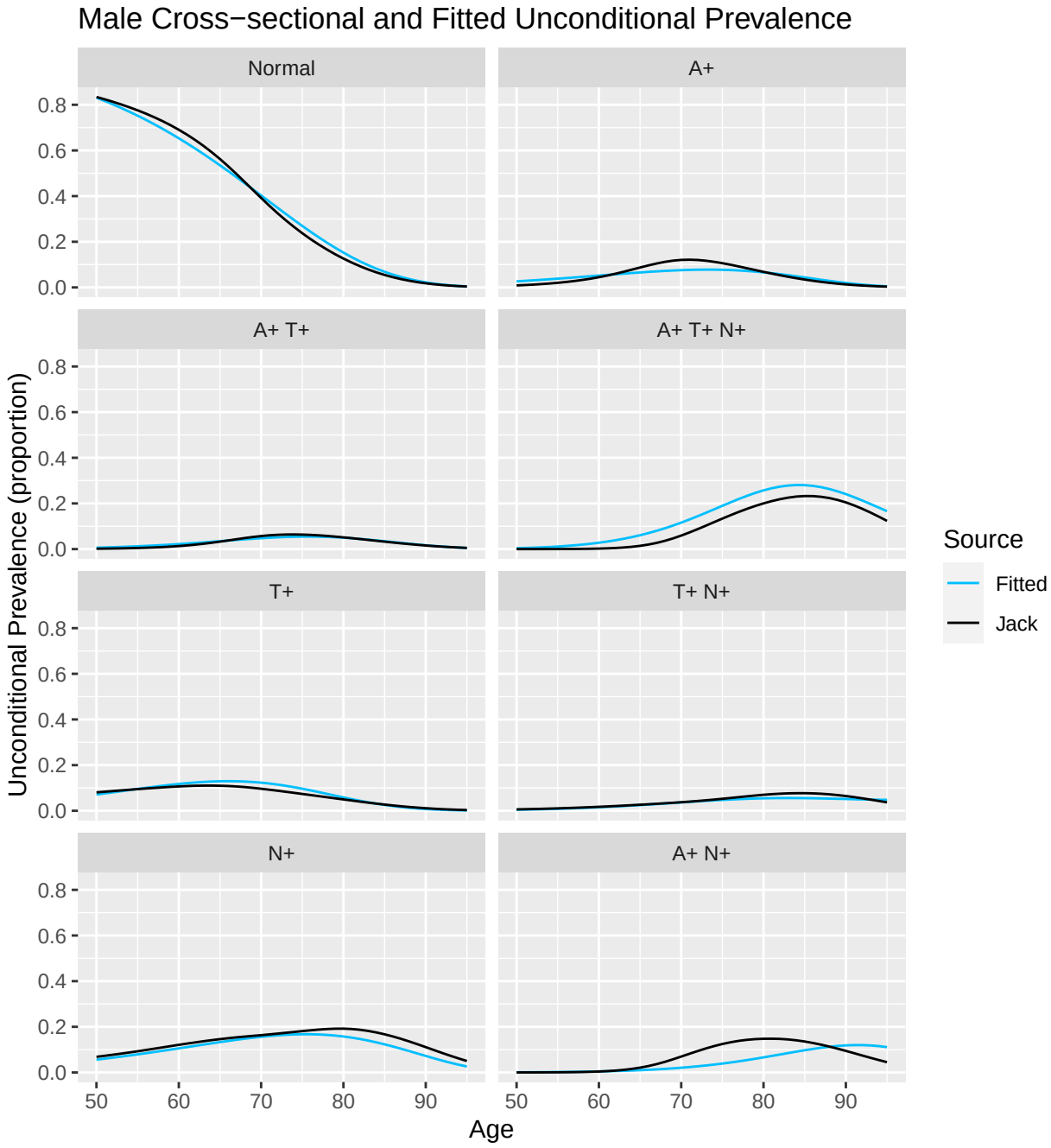

Female Cross−sectional and Fitted Conditional Prevalence
Normal
A+
A+ T+
A+ T+ N+
T+
T+ N+
N+
A+ N+
Conditional Prevalence (proportion)
0.00
0.25
0.50
0.75
50
60
70
80
90
Age
Source
Fitted
Jack


Male Cross−sectional and Fitted Conditional Prevalence
Normal
A+
A+ T+
A+ T+ N+
T+
T+ N+
N+
A+ N+
Conditional Prevalence (proportion)
0.00
0.25
0.50
0.75
50
60
70
80
90
Age
Source
Fitted
Jack

1.5 Unconditional prevalence

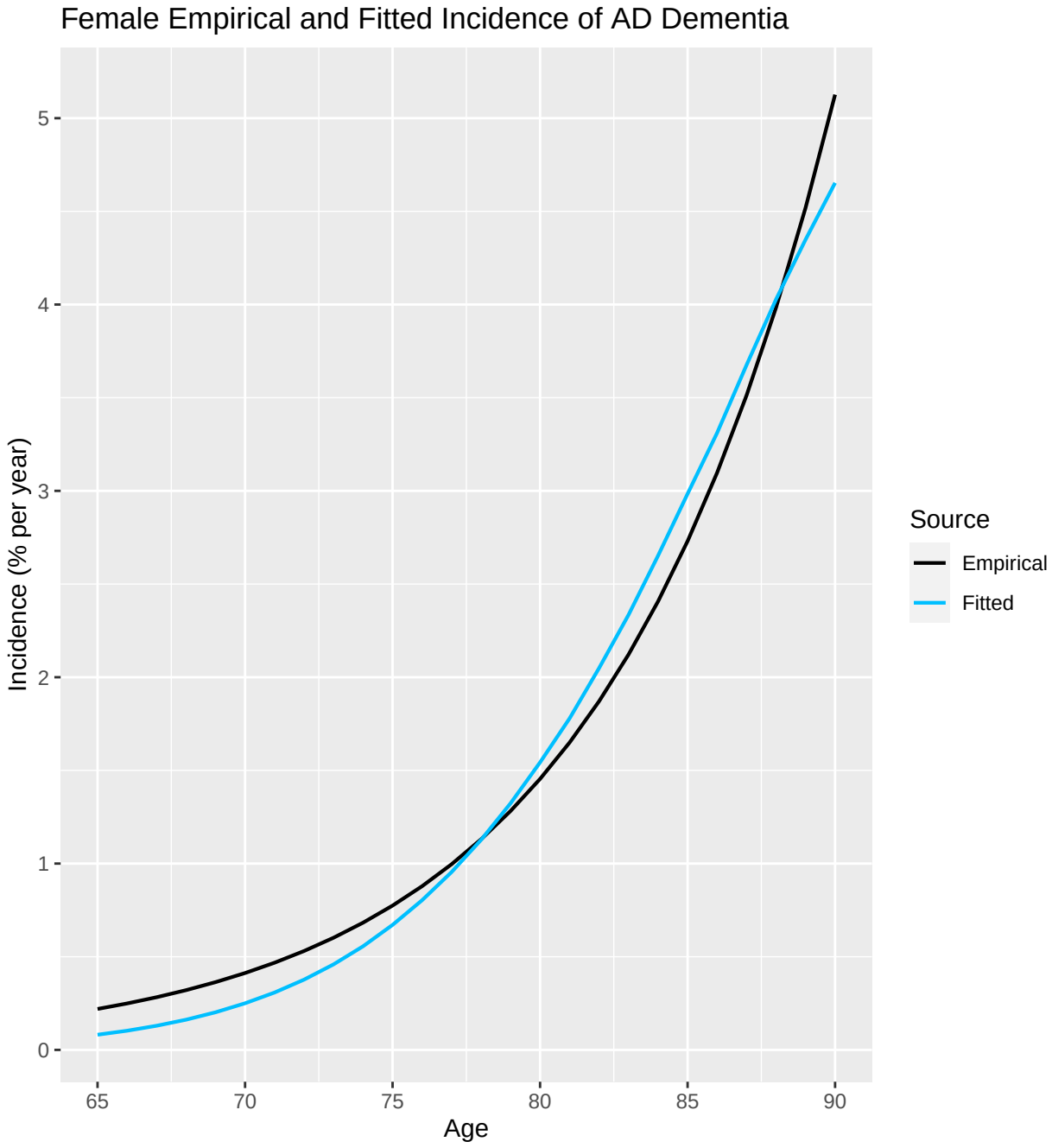
Female and male prevalence rates, conditional only on being alive.

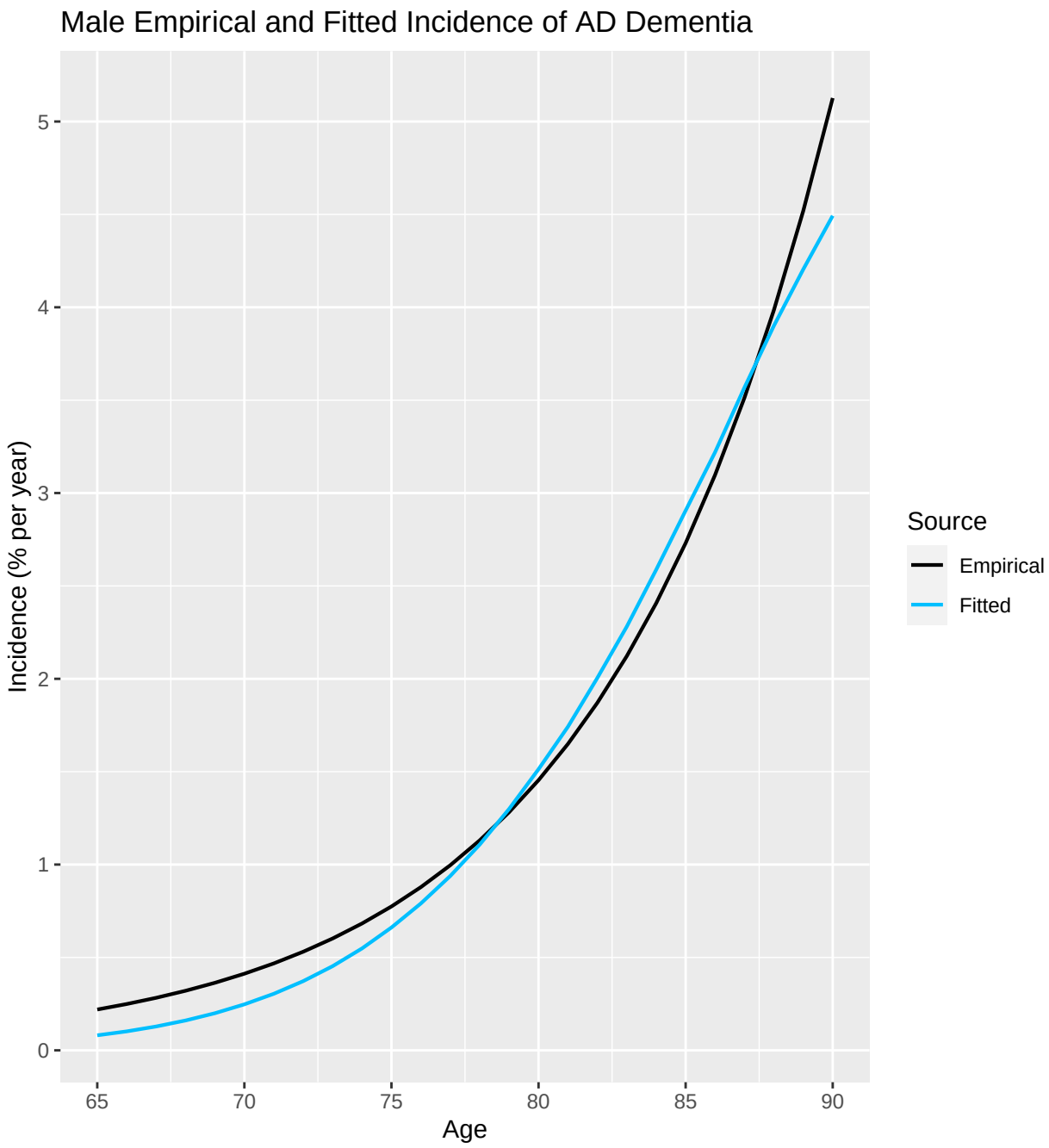



Male Cross−sectional and Fitted Unconditional Prevalence
Normal
A+
A+ T+
A+ T+ N+
T+
T+ N+
N+
A+ N+
Unconditional Prevalence (proportion)
0.0
0.2
0.4
0.6
0.8
50
60
70
80
90
Age
Source
Fitted
Jack

1.6 Incidence of AD

Female and male incidence rates as compared with the empirically estimated rate. Note that the empirical rate is the same in each plot, as it is sex-agnostic.





References

Brookmeyer, Ron, and Nada Abdalla. 2019. "Multistate Models and Lifetime Risk Estimation: Application to Alzheimer's Disease." *Statistics in Medicine* 38 (9): 1558–65.

Brookmeyer, Ron, Elizabeth Johnson, Kathryn Ziegler-Graham, and H Michael Arrighi. 2007. "Forecasting the Global Burden of Alzheimer's Disease." *Alzheimer's & Dementia* 3 (3): 186–91.

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