Risk and Timing of Age-Related Conditions in Individuals with Down Syndrome

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BACKGROUND

- Down syndrome (DS) is the most frequent chromosomal abnormality among live-born infants in the United States[1]
- The lifespan of individuals with DS has more than doubled to approximately 60 over the past 40 years, but remains much lower than in typically developing individuals[2,3]
- Disparity in aging presents a significant methodological challenge in DS-related case-control studies, complicating traditional age-matching methods
- **Comprehensive data on comorbidities and disease timing among individuals with DS are scarce, challenging the development of tailored healthcare guidelines for this group, especially as they age**

DESIGN/METHODS

The objectives of this study were to:

(1) Estimate the relative risk of a group of conditions experienced by aging individuals and
(2) Examine the timing of select conditions across the lifespan to inform tailored care and screening efforts

COHORTS

This was a retrospective study of 5,926 patients with DS (335,340 encounters) and 58,963 controls (1,655,740 encounters) seen at Advocate Health between January 2005 and May 2025. The control cohort was exact-matched 10:1 based on: age, sex, race / ethnicity, utilization percentile for year of entry into system, and state of residence

Table 1. Demographics and Baseline Characteristics

	IwDS (N=5,926)	Controls (N=58,963)
Age Mean (SD)	24.56 (18.34)	25.87 (18.18)
Total Encounters Mean (SD)	32.15 (43.50)	16.33 (31.30)
Sex		
Male	3,051 (51.48%)	30,288 (51.37%)
Female	2,875 (48.52%)	28,667 (48.63%)
Race		
NH White	3,748 (68.71%)	36,542 (69.48%)
NH Black	553 (10.14%)	5,073 (9.65%)
Hispanic	892 (16.35%)	8,360 (15.90%)
NH Other	262 (4.80%)	2,619 (4.98%)
Missing	471	6,369
Insurance		
Commercial	2,557 (43.15%)	48,021 (81.44%)
Medicare	1,794 (30.27%)	1,529 (2.59%)
Medicaid	1,575 (26.58%)	9,413 (15.96%)

ANALYSES

- Time to event modeling was conducted to estimate relative risk of conditions via semi-parametric Cox Proportional Hazards models fit with interval censoring. The model for age at death was fit using a traditional Cox PH model since exact death dates were known.
- All Cox PH models were adjusted for sex, race, ethnicity, and year of AH Heathcare system entry.
- Model assumptions were tested and time transformation terms (death model) or stratification by sex (osteoporosis) was used to resolve any violations.
- Restricted Mean Survival Time (RMST) or Restricted Mean Event-Free Age (RMEA) were used to estimate the average event-free years lived by each cohort up to a horizon (tau) of 80 years[4]
- All analyses were run in R v4.5.1[5]

RESULTS

Table 2. Hazards Model Results and RMEA/RMST Estimates

	IwDS (N=5,926)	Controls (N=58,963)
A. CATARACTS		
Observed Events (%)	139 (2.4%)	312 (0.5%)
Age Range at Time of Event	16.3 – 74.9	18.2 – 87.8
Hazard Ratio	4.0**	ref
Restricted Mean Event-Free Age	74.4 [73.2, 75.7]	78.0 [77.7, 78.3]
B. COGNITIVE DECLINE		
Observed Events (%)	502 (8.5%)	209 (0.4%)
Age Range at Time of Event	15.1 – 72.1	35.4 – 87.8
Hazard Ratio	24.5**	ref
Restricted Mean Event-Free Age	63.9 [63.0, 64.8]	78.6 [78.4, 78.8]
C. DEATH		
Observed Events (%)	545 (9.2%)	615 (1.0%)
Age Range at Time of Event	0 - 87.5	0 - 98.8
Hazard Ratio	2.0*	ref
Restricted Mean Survival Time	63.1 [62.4, 63.8]	77.3 [77.0, 77.6]
Median Age at Time of Event	57.7 [56.8, 58.7]	81.1 [78.7, 83.8]
D. MENOPAUSE		
Observed Events (%)	72 (2.5%)	713 (2.4%)
Age Range at Time of Event	23.8 – 64.5	21.8 – 91.7
Hazard Ratio	0.9	ref
Restricted Mean Event-Free Age	76.0 [75.0, 76.9]	75.0 [74.6, 75.4]
E. OSTEOPOROSIS		
Observed Events (%)	81 (1.4%)	222 (0.4%)
Age Range at Time of Event	21.2 – 80.4	7.4 – 88.1
Hazard Ratio	3.8**	ref
Restricted Mean Event-Free Age	75.5 [74.0, 76.9]	78.7 [78.5, 78.9]

*p<0.01, **p<0.001, 95% CIs in brackets where applicable.

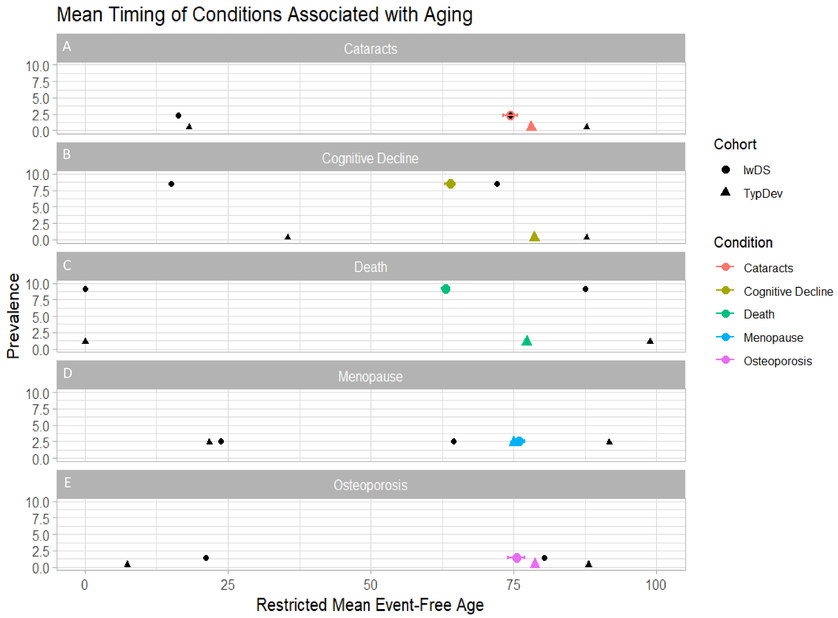

Figure 1: Restricted Mean Event-free Age (RMEA) for each condition of interest. Estimated RMEAs are presented for individuals with Down syndrome (IwDS, circles) and typically developing individuals (TypDev, triangles), color coded by each condition. Minimum and maximum observed values are presented in black for each cohort and condition.

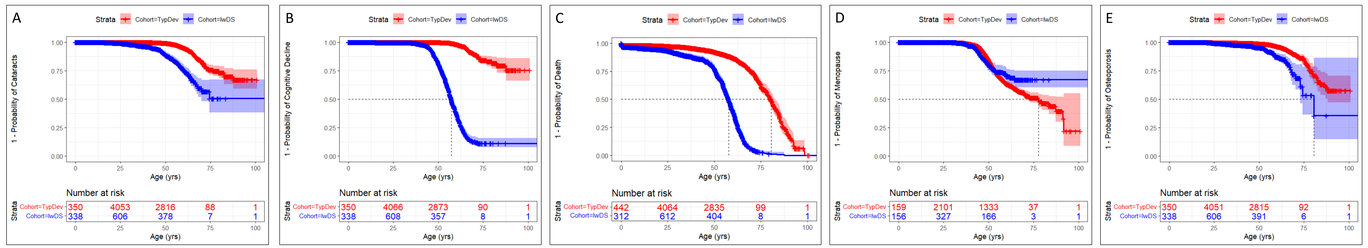

Figure 2: Kaplan-Meier time-to-event curves for each condition of interest as patients age. Event curves for individuals with Down syndrome (IwDS) are in blue, while those of typically developing individuals are in red. Curves depict the probability of each event not occurring over time (1 – p). Number of individuals at risk for each cohort are detailed along the bottom of each plot in 25-year intervals and reflect age-specific sample sizes due to interval censoring.

DISCUSSION

- Timing of death and age-related conditions differs significantly in IwDS and by large margins of time:
  - Death occurs >20yrs sooner
  - Key age-related conditions can occur >10yrs sooner
- Timing of cognitive decline and death are the most disparate between cohorts, but relative timing is close within each cohort
- Excluding menopause…
  - All conditions occur earlier in IwDS
  - All conditions are at higher prevalence in IwDS
- Cataracts, osteoporosis, and menopause occur at more similar ages across cohorts than death and cognitive decline

CONCLUSIONS

- Following standard care guidelines based on TypDev populations may lead care teams to miss important prevention and screening windows when treating IwDS
- Ongoing work – Characterize relative 'aging trajectories' and how we can better compare IwDS to TypDev counterparts in matched and adjusted analyses

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