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Addressing Common Statistical Issues

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Lead, CTSA Workgroup on Inclusion of Older Adults as a Model for Special Populations

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Study and data analytic design: Lenses to magnify clinical and translational research that includes older adults

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Do older adults seriously complicate study analysis and interpretation?

- Common wisdom
  - Older adults only selectively participate
  - Older adults' data are "messy"
  - Older adult health complicates study interpretation

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Do older adults seriously complicate study analysis and interpretation?

- **Older adult inclusion has real benefits to study analysis and interpretation!**
  - They are **dedicated** study participants
  - Heightened event rates may enhance study **power**
  - Addressing complexities challenging interpretation in older adults provides a **roadmap for addressing complexities** in others
  - Clearly understanding mechanisms in older adults as a "point of the spear" for adverse outcomes may provide general **mechanistic insights**

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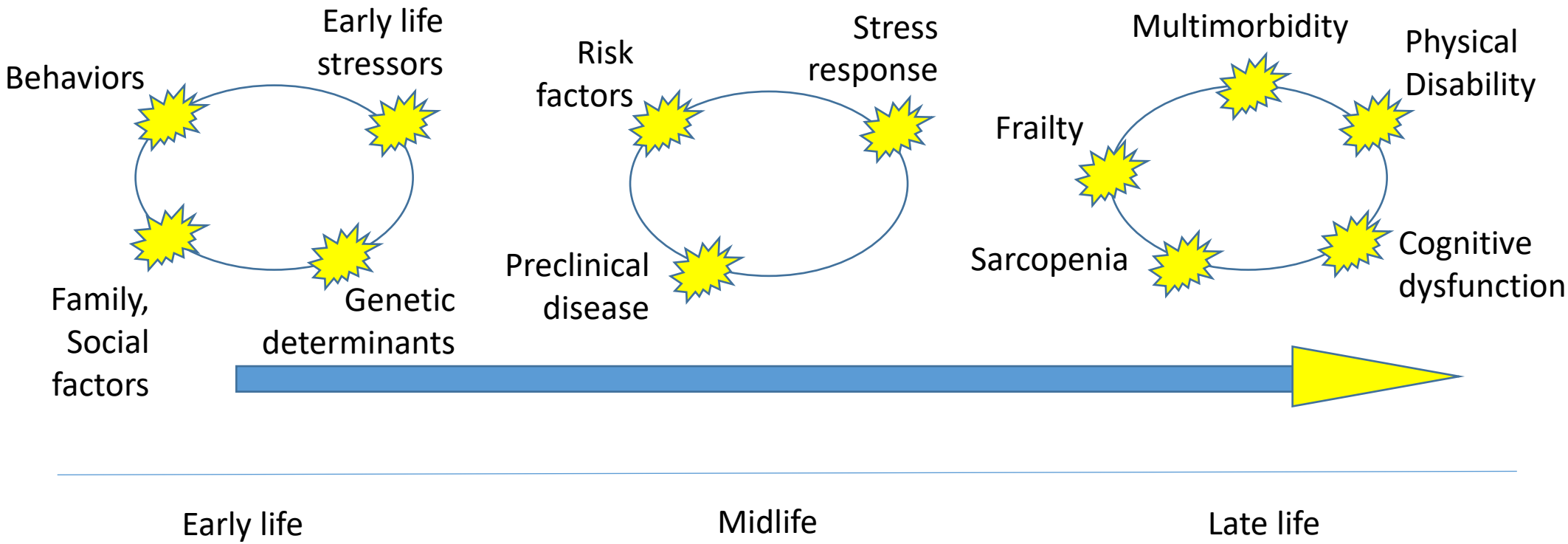

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Objectives

- Sampling of highest-profile challenges
- Three methodological strategies
  - Pilot studies
  - Design
  - Data analysis
- Take home messages / Challenges / Gaps

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Selective participation / Dropout

Study-wise

THREATS	OPPORTUNITIES	PILOT STUDIES	DESIGN	ANALYSIS
• **Mis-represents the intended population** • **Sample loss** • *Anecdote: Is there honestly negligible frailty incidence as people age?*				

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			• **Innovations to reduce barriers**
			• **Foot-in-door questionnaire**
			• **Auxiliary data**
				• **"Crosswalks" the observed data to the intended population**
				  • Inverse-probability weighting
				  • Selection modeling
				  • Sensitivity analysis

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Selective participation

Measure-wise: Same as study-wise, plus:

THREATS	PILOT STUDIES	DESIGN	ANALYSIS

• **Bias in estimating relationships**
• **Loss of power and precision**
	• **Coordinator-focused interviews**	• **Prioritize key measures early in the assessment**
		• *Anecdote: Running out of time*
		• **Record reasons for data missingness**
			• **Maximize data inclusion, minimize biases**
			  • Multiple imputation
			  • FIML
			  • Acknowledging “couldn’t” versus “didn’t”

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Competing risks / Death

THREATS	OPPORTUNITIES	PILOT STUDIES	DESIGN	ANALYSIS
• **Flawed, misleading interpretation of study findings** • *Anecdote: Hydrochloroquine?*				

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Competing risks / Death

THREATS	OPPORTUNITIES	PILOT STUDIES	DESIGN	ANALYSIS
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	• **Richer delineation of treatment impacts**	• **Document, prepare for death rate**	• **Sample size considerations**
			• **Interim measurements**
				• **Aims to explicitly account for "competition"**
				• **Address all risks**
				  • Composite outcomes
				  • Cause-specific relative hazard
				  • Subdistribution (incidence)
				  • Latent variable methods

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Measurement issues

THREATS	OPPORTUNITIES	PILOT STUDIES	DESIGN	ANALYSIS

• **Conflation of intended outcome with measurement modality**
• **Invalid inferences**
• *Anecdote: Cognitive testing and sensory impairment*
	• **Wearables**
	• **Sensors**
	• **Implantables**
		• **Multi-trait multi-method studies**	• **Bridging subsets**
			• **Thoughtful tailoring of measures to, and across, subpopulations**
				• **Aims to faithfully characterize the target of measurement**
				• **Bridge measurement differences**
				• **Explore error ramifications for effect estimation**
				  • Harmonization, latent variables
				  • Error “calibration”
				  • Modeling of variance in terms of the mean
				  • “Functional” data analysis

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Multimorbidity, Polypharmacy, Etc.

THREATS	OPPORTUNITIES	PILOT STUDIES	DESIGN	ANALYSIS
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	• **"Leverage" heterogeneity creates for estimating relationships**
		• **Literature review**
		• **Secondary data analyses to identify key suspects**
			• **Sample size considerations by strata**
			• **Identification of variables where strength can be borrowed**
			• *Anecdote: Flu vaccines and baseline pro-inflammatory, immune status*
				• **Reduce noise due to heterogeneity**
				• **Leverage heterogeneity to learn about mechanisms**
				  • Baseline covariate adjustment (*trials*)
				  • Propensity scores, instrumental variables, sensitivity analyses (*observational studies*)
				  • Testing, advanced model selection to identify effect modification
				  • Mixture models

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Leveraging Older Age as the "Point of the Spear" on Health

OPPORTUNITIES	PILOT STUDIES	DESIGN	ANALYSIS

• **Insights into treatment / health mechanisms**	• **Hone protocols to make design elements practical**	• **Include gerontological outcomes in assessments**
		  • Synthetic – markers of overall functional / health status
		  • Geriatric "vital signs"
		  • Function, cognition, frailty, sarcopenia, falls, …
		• **Measure outcomes repeatedly**
			• **Consider effect modification by age (akin to multimorbidity, polypharmacy, etc.)**
			• **Backward time analyses**
			• **Trajectory, transition analyses**

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Exhortation for our colleagues

- Engage statisticians and epidemiologists
  - They will love contributing to thinking about optimal strategies.
- It's not all bad
  - Added insights lurk
  - Solutions generalize to younger participants
  - Complexities relative to younger participants overblown?
- There's a lot of good!
  - Older adults are dedicated study participants
  - Added heterogeneity translates into heightened leverage, event rates in subsets
  - Aging is a point of the spear that can generate insights earlier in the lifespan

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Do older adults seriously complicate study analysis and interpretation?

- Gaps
  - Study designs to buffer informative dropout
  - Study designs to maximize information while limiting burden
  - Addressing heterogeneous treatment, exposure effects
  - Additional challenges?