# Multidimensional Sleep Health and Mortality in Older Adults

MEREDITH WALLACE, PHD
DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF PITTSBURGH
PITTSBURGH, PA

## How did you sleep last night?



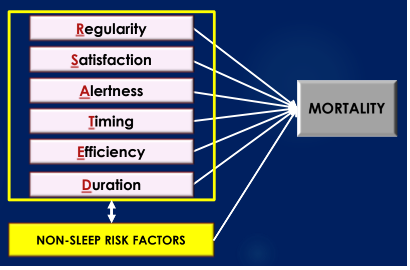

## Reality: Sleep is Multidimensional

- Regularity
- Satisfaction
- Alertness
- Timing
- Efficiency
- Duration

RU-SATED?
(Buysse, Sleep Health 2014)

## Reality: Sleep is Multidimensional

4




## Statistical Challenges

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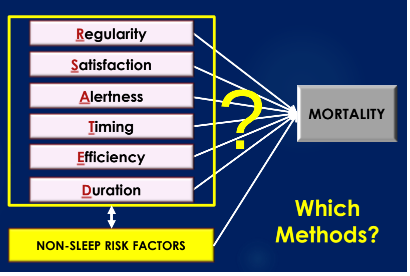
- Multiple characteristics
- Multiple domains
- Multiple data types
- Complex associations




6

| Overarching Goal | What is the question? | Methods I am Using |
|---|---|---|
| Explaining Associations | What is the importance of MDSH for mortality relative to other established risk factors? | • Tree models<br>• Random forest techniques |
| | Which sleep characteristics predict mortality? | |
| | Do MDSH phenotypes exist? | • Clustering followed by regression (or other model) |
| | Do MDSH phenotypes predict mortality? | |
| Individual Predictions | Which individuals are at risk for mortality based on their MDH? | • Random Forest<br>• Other Machine Learning |

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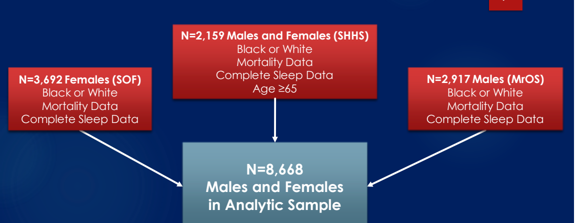
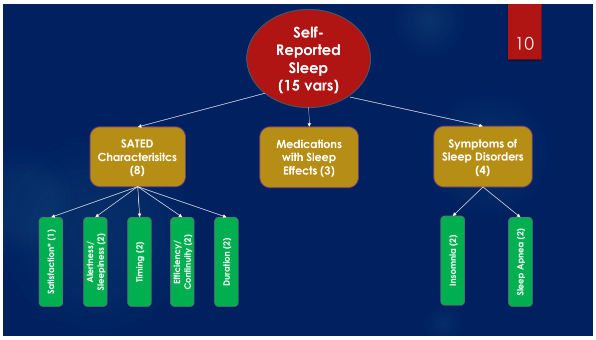
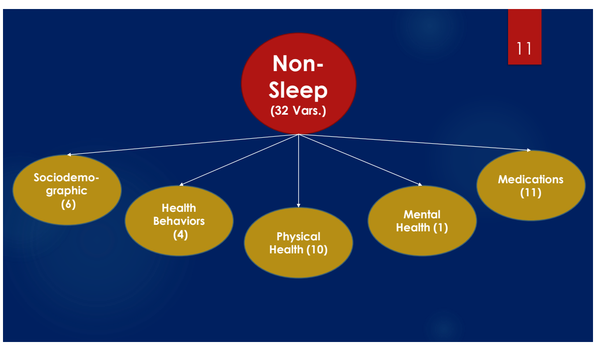
| | Which sleep characteristics predict mortality? | |

**Who cares?**
- Few major health guidelines include sleep
- Incorporate into health screening tools?
- Prediction + modifiability = Novel Target








## Random Survival Forest

12

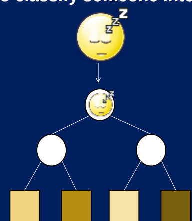
- Machine learning approach
- Models complex, non-linear associations

Ishrawan, et al. 2008, *Ann Appl Stat*

## Random Survival Forest

13

- **Single Tree Model: Empirically derived set of decision rules (e.g., is age < 80?) to classify someone into a mortality risk group**




## Random Survival Forest

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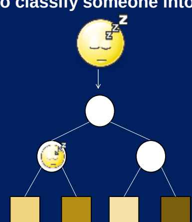


## Random Survival Forest

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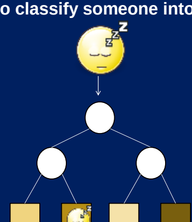
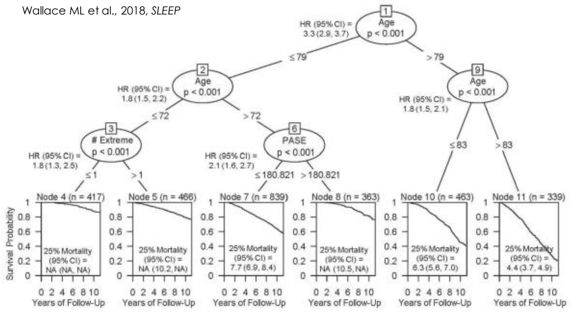
- **Single Tree Model: Empirically derived set of decision rules (e.g., is age < 80?) to classify someone into a mortality risk group**

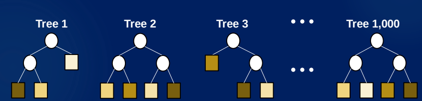
Wallace ML et al., 2018, *SLEEP*




## Random Survival Forest



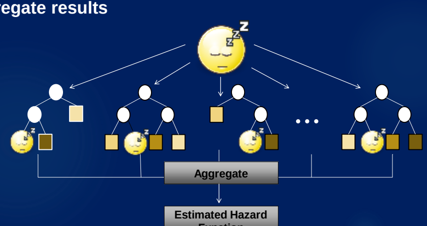
- Create hundreds of bootstrap samples
- Divide each sample into “in-bag” / “out of bag” (OOB) sets
- Fit tree model to each “in-bag” sample to create forest




## Random Survival Forest



- Send new case down each tree in the “forest”
- Aggregate results



## Prediction Error of Model

17

**Can the model discriminate which of two randomly selected individuals will have a worse survival outcome? (1 - Harrell's C)**

- **In-bag** prediction error (cases used to grow trees)
- **OOB** prediction error (cases used to grow other trees)
- **Cross-Validation or External Validation** (not used to grow any trees)

## Variable Importance (VIMP)

18

1. **Grow random forest (uses in-bag data)**
2. **Estimate OOB Error of Model with Real "X"**:
3. **Estimate OOB Error of Model with Permuted "X"**
4. **Compare (larger → "X" more predictive)**

- Can compute VIMPs for groups of variables (e.g., MDSH)
- **Confidence intervals**: stratified subsampling with jackknife estimates of standard errors (Ishrawan & Lu, *Stat Med*, in press)

## Variable Importance (VIMP)

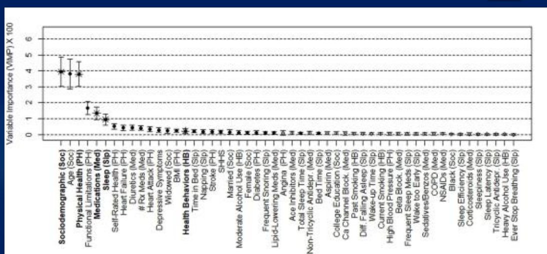
22

- Use OOB data to enhance computational efficiency
- VIMPs of correlated measures artificially inflated
- Assess relative predictive accuracy by refitting random forest with vs without predictor(s)

**Computationally burdensome!!**

## VIMPs (99% CIs) for All-Cause Mortality

19



Wallace, Buysse et al., 2019, *J Gerontol A Biol Sci Med Sci*

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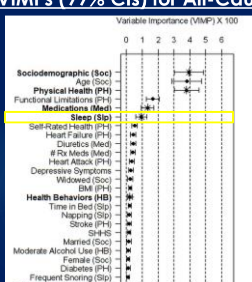
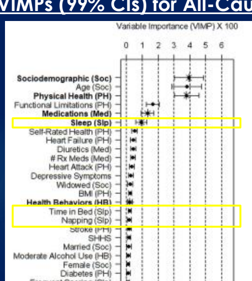



**Top-Tier Predictors:**
1. Socio-demographic Domain
2. Age
3. Physical Health Domain

**Second-Tier Predictors:**
3. Functional Limitations
4. Medication Domain
5. Sleep Domain
6. Self-Rated Health Status
7. Heart Failure
8. Diuretics
9. # Rx Medications
10. Heart Attack
11. Depressive Symptoms

## VIMPs (99% CIs) for All-Cause Mortality

21



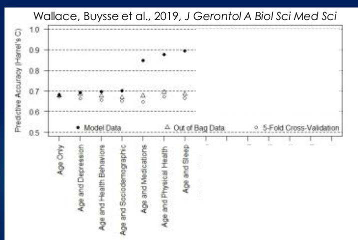

**Second-Tier Predictors (continued):**

12. Widowed
13. BMI
14. Health Behaviors Domain
15. Time in Bed
16. Napping
17. Stroke

…

…

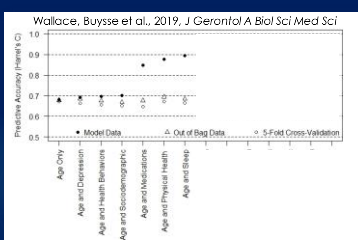
27. Total Sleep Time
28. Antidepressants
29. Bed Time




23

**<u>Compare Models</u>:**
Age
vs.
Age + One Domain

**<u>3 Metrics:</u>**
Model (In-Bag) Data
OOB Data
5-Fold XV

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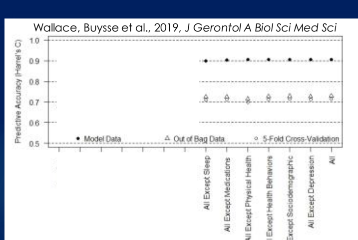
- ***Adding* any 1 domain doesn't notably *improve* accuracy**
- **Don't assess accuracy with the "in-bag" data!**




23

- ***Removing* any 1 domain doesn't notably *decrease* accuracy**
- **Don't assess accuracy with the "in-bag" data!**

## Why do we care?

- Need to start asking older adults about their sleep
- Not only sleep duration!
- Screening tools incorporating MDSH should be developed
- Other ages?
- MDSH Modifiability + Predictive Ability = Novel Target for Improving Health

25

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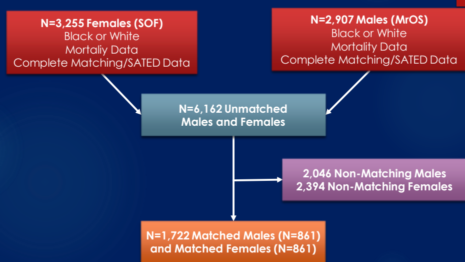
## Why do we care about phenotypes?

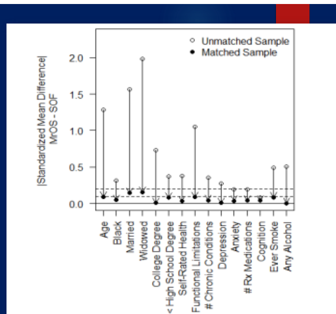
26

- Clarify understanding of sleep challenges
- Motivate the development of novel treatments
- Phenotypes stronger and more meaningful predictors?
- Suggest hypotheses for underlying disease mechanisms




**Matched Males**

Older
More likely to be black
Less education
Less likely to be married
Less Smoking/Drinking
Worse physical health
Worse mental health





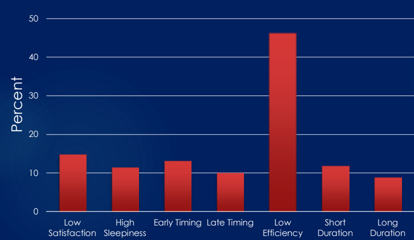

## SATED Framework (Buysse 2014, Sleep Health)

| Domain | Sleep Characteristic |
|---|---|
| Satisfaction | Poor Quality (Poor/ Very Poor on PSQI item)* |
| Alertness/ Sleepiness | High Sleepiness (Epworth > 10)* |
| Timing | Sleep Midpoint<br>Early (<02:00)*<br>Middle (02:00 -04:00)<br>Late (>04:00)* |
| Efficiency | Low Sleep Efficiency (<85%)* |
| Duration | Total Sleep Time<br>Short (<6 hours)*<br>Medium (6-8 hours)<br>Long (>8 hours)* |

*Potentially adverse sleep characteristic

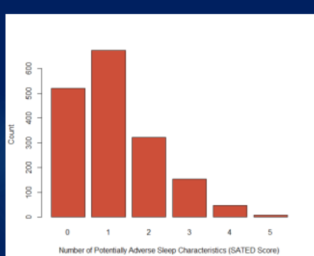
## SATED Sleep Characteristics






## SATED Score






## Common SATED Combinations?



**By hand**

- ~~$2^3$ x $3^2$ = 72 po... ...ATED patterns~~
- ~~Tabulate all ...nen...~~

**Use LCA to identify most common patterns**

- Model-based
- Maximize likelihood to estimate unknown parameters (e.g., class probabilities)

## Latent Class Analysis

33

**How many classes?**

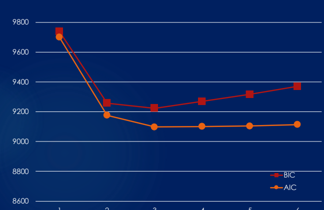
- Fit models with 1- 6 classes
- Examine relative goodness of fit with AIC and BIC
- Bootstrap Likelihood Ratio (McLachlan 1987, *Applied Stat*)

**Evaluate Stability and Class Separation of Final Model**

- Jaccard Coefficient for stability of each class (Hennig 2007, *Comp Stat Data Anal*)
- Model Entropy (Ramaswamy et al., 1993, *Marketing Science*)

## How Many Classes?

34




| Bootstrap Likelihood Ratio Test | |
|---|---|
| 1 vs. 2 Classes | <0.001 |
| 2 vs. 3 Classes | <0.001 |
| 3 vs. 4 Classes | 0.207 |

## 3-Class Solution

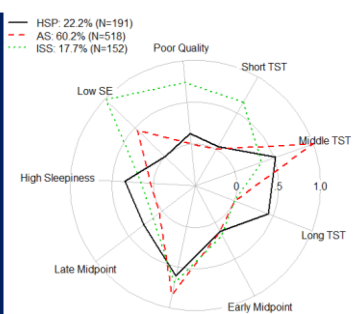
High Sleep Propensity (HSP)

Average Sleep (AS)

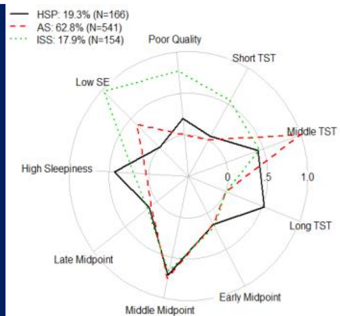
Insomnia + Short Sleep (ISS)

| Jaccard Coefficient<br>0 = least stable<br>1 = most stable | |
|---|---|
| HSP | 0.44 |
| AS | 0.70 |
| ISS | 0.79 |

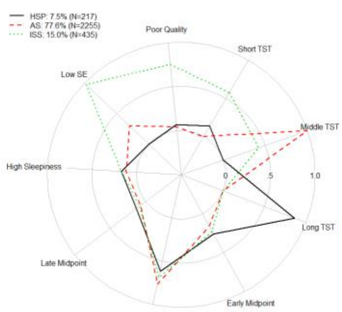
**Model Entropy = 0.59**
0 = low class separation
1 = high class separation



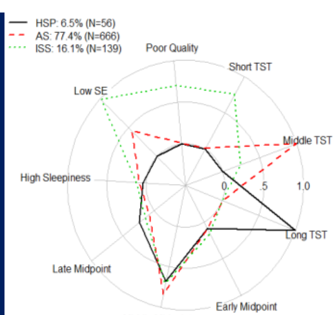
Matched Males (N=861)



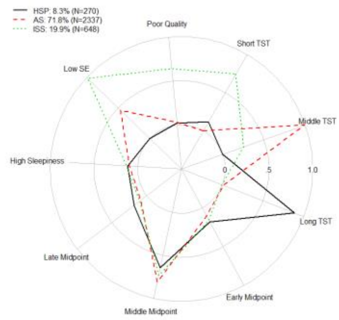

MrOS Males (N=2,907)




Matched Females (N=861)



## SOF Females (N=3,255)




## Stability of HSP Phenotype

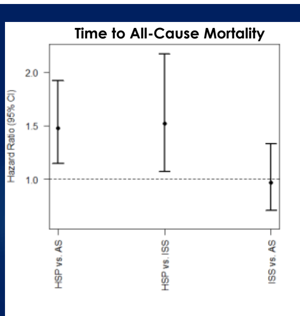


| | HSP Phenotype |
|---|---|
| Matched Sample | |
| Matched Males | |
| Matched Females | |
| MrOS Males | |
| SOF Females | |


## Characterization of Phenotypes



| | d/h > \|.20\| |
|---|---|
| Anxiety (GADS) | ISS > (HSP, AS) |
| Depression (GDS-15) | ISS > (HSP, AS) |
| Cognition (26-item mMMSE) | |
| Self-Rated Health (1 = Excellent; 5=Very Poor) | ISS > AS |
| Number of Functional Limitations | (ISS, HSP) > AS |
| Number of Chronic Conditions | ISS > (HSP, AS) |
| Number of Prescription Medications | ISS > AS |




41

- **Associations stronger among women**
- **Findings generalize to other samples (smaller effects in MrOS/SOF)**
- **Other sleep health approaches (SATED scale, multivariable regression) not predictive**

## Moving Forward

42

- Objective data types (Actigraphy, PSG)
- Does MDSH also predict other health outcomes?
- Mechanisms linking HSP or MDSH to mortality
- Create a MDSH measures that is good enough for multiple outcomes or populations

## Thank you!

lotzmj@upmc.edu

43

**University of Pittsburgh**
Dan Buysse, MD
Martica Hall, PhD

**California Pacific Medical Center**
Katie Stone, PhD
Terri Blackwell, MA

**Brigham and Women's Hospital**
Susan Redline, MD, MPH
Mike Rueschman, MPH

Data from the Osteoporotic Fractures in Men (MrOS) Study is publicly available on the MrOS Online website.

For more information or to download data, please visit:

http://mrosdata.sfcc-cpmc.net



## Grants


- Wallace: NIA grant R01 AG056331
- The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128.
- The National Heart, Lung, and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study "Outcomes of Sleep Disorders in Older Men" under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839.
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- SHHS : U01HL53916, U01HL53931, U01HL53934, U01HL53937, U01HL53938, U01HL53940, U01HL53941, U01HL64360)
- National Sleep Research Resource (NSRR): NHLBI grant HL114473
- SIR study: AG047139



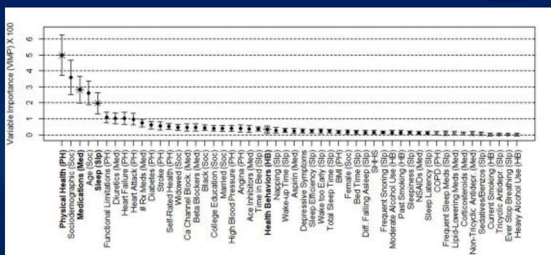

## Sample Characteristics

**Sample Characteristics**

- Mean (SD) age = 78.7 (6.7)
- 8% Black (N=718)
- 54% Female (N=4,682)
- 41% All-cause mortality (N=3,552)
- 13% Cardiovascular mortality (N=1,079)

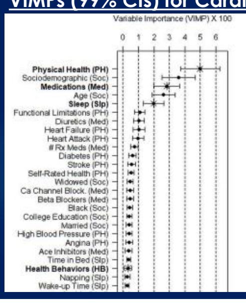
## VIMPs (99% CIs) for Cardiovascular Mortality

47




## VIMPs (99% CIs) for Cardiovascular Mortality

48

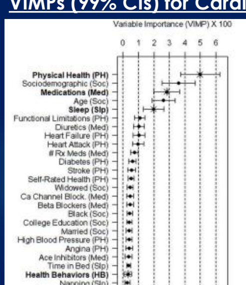



**Top-Tier Predictors:**
1. Physical Health Domain
2. Sociodemographic Domain

**Second-Tier Predictors:**
3. Medications Domain
4. Age
5. Sleep Domain
6. Functional Limitations
7. Diuretics
8. Heart Failure
9. Heart Attack
10. # Rx Medications
11. Diabetes
12. Stroke

## VIMPs (99% CIs) for Cardiovascular Mortality

49

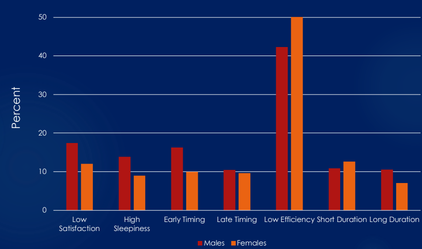



**Second-Tier Predictors (continued):**

13. Self-rated health status
14. Widowed
15. Ca Channel Blockers
16. Beta Blockers
17. Black (vs. white)
18. College Education
19. Married
20. High BP
21. Angina
22. Ace Inhibitors
23. Time in Bed
24. Health behaviors domain
25. Napping
26. Wake-up time

## SATED Sleep Characteristics

50




## Characterization of Phenotypes

51

| | HSP | AS | ISS | d/h > \|.20\| |
|---|---|---|---|---|
| Anxiety (GADS) | 0.85(1.73) | 0.92(1.76) | 2.46(2.86) | ISS > (HSP, AS) |
| Depression (GDS-15) | 2.27(2.26) | 1.87(2.22) | 2.97(2.66) | ISS > (HSP, AS) |
| Cognition (26-item mMMSE) | 23.8(2.67) | 24(2.21) | 23.89(2.24) | |
| Self-Rated Health (1 = Excellent; 5=Very Poor) | 1.96(0.77) | 1.86(0.67) | 2.08(0.71) | ISS > AS |
| Number of Functional Limitations (Range 0 – 5) | 0.84(1.22) | 0.61(1.07) | 1.01(1.41) | (ISS, HSP) > AS |
| Number of Chronic Conditions | 1.75(1.46) | 1.6(1.24) | 2.12(1.55) | ISS > (HSP, AS) |
| Number of Prescription Medications | 4.41(3.09) | 4(2.9) | 5.06(3.59) | ISS > AS |