

# Generalized Linear Mixed Model Analysis of Multistate Sleep Transition Data: The Sleep Heart Health Study

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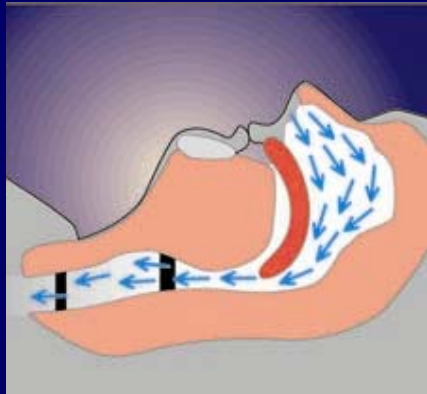
# Acknowledgements

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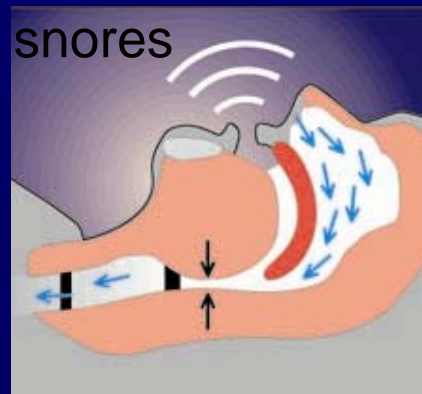
# Sleep

- Represents 1/3 of the human lifespan
- Is crucial for maintaining physical and mental health
- Sleep disturbance, poor sleep or sleep deprivation have been associated with
  - Daytime sleepiness
  - Decrements in cognition, mood and work performance
  - Glucose intolerance
  - Hypertension
  - Insulin resistance
  - Impaired immune function
  - Altered gene expression for important neurological genes
  - Increased mortality rates
- Despite its importance, sleep and its physiologic effects remain, on the whole, poorly understood.

# Sleep disordered breathing

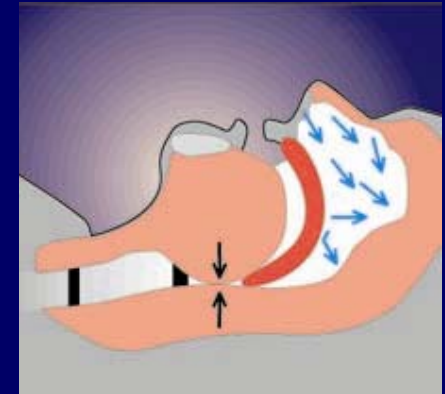


Normal



Partial Collapse

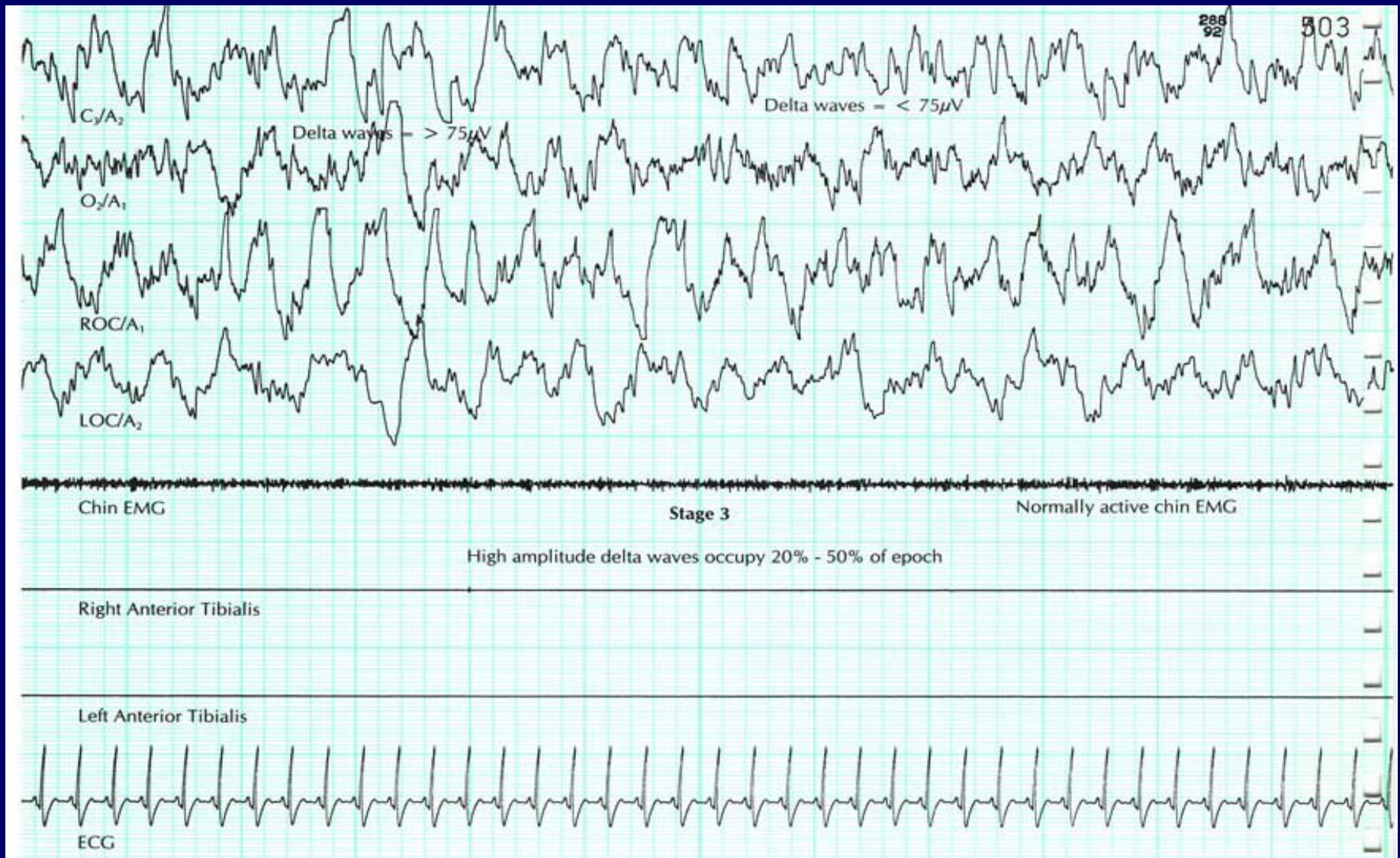
Hypopneas



Complete Collapse

Apneas

# Measurement of sleep



# Sleep states scoring

Wake

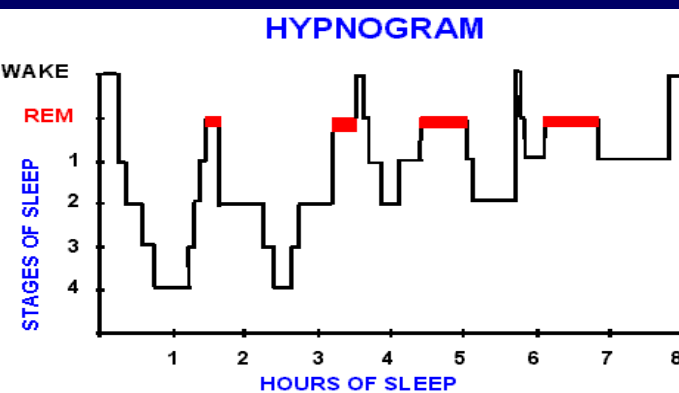
REM

Non REM — | Stage I  
Stage II  
Stage III  
Stage IV

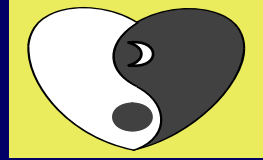
- REM – Rapid Eye Movement, 20-25% of sleep
  - brain activity similar to wake
  - Vivid dreams occur during this phase
  - No muscle movement
  - REM sleep function remains an active area of research
- Stage I – 3-8% Near wakefulness
- Stage II – 45-55% Transition to slow-wave
- Stage III-IV – 15-20% Slow-wave sleep

Transitions between all states (including wake) are possible

States are generally recorded in 30 second “epochs” by a trained technician

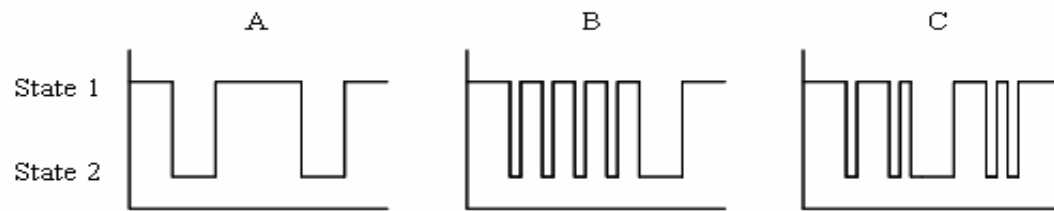
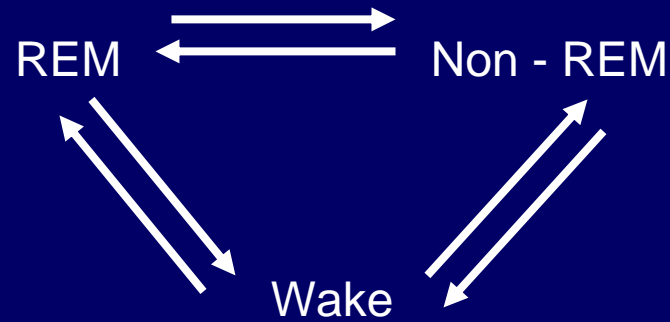


# The Sleep Heart Health Study



- A multi-center cohort study studying the cardiovascular effects of sleep disturbance
- In-home polysomograms completed on 6,441 subjects at baseline
- Mean age of the cohort was 62.9 years
- 52.9% Male
- Mean BMI of 28.5

# Studying sleep transition rates

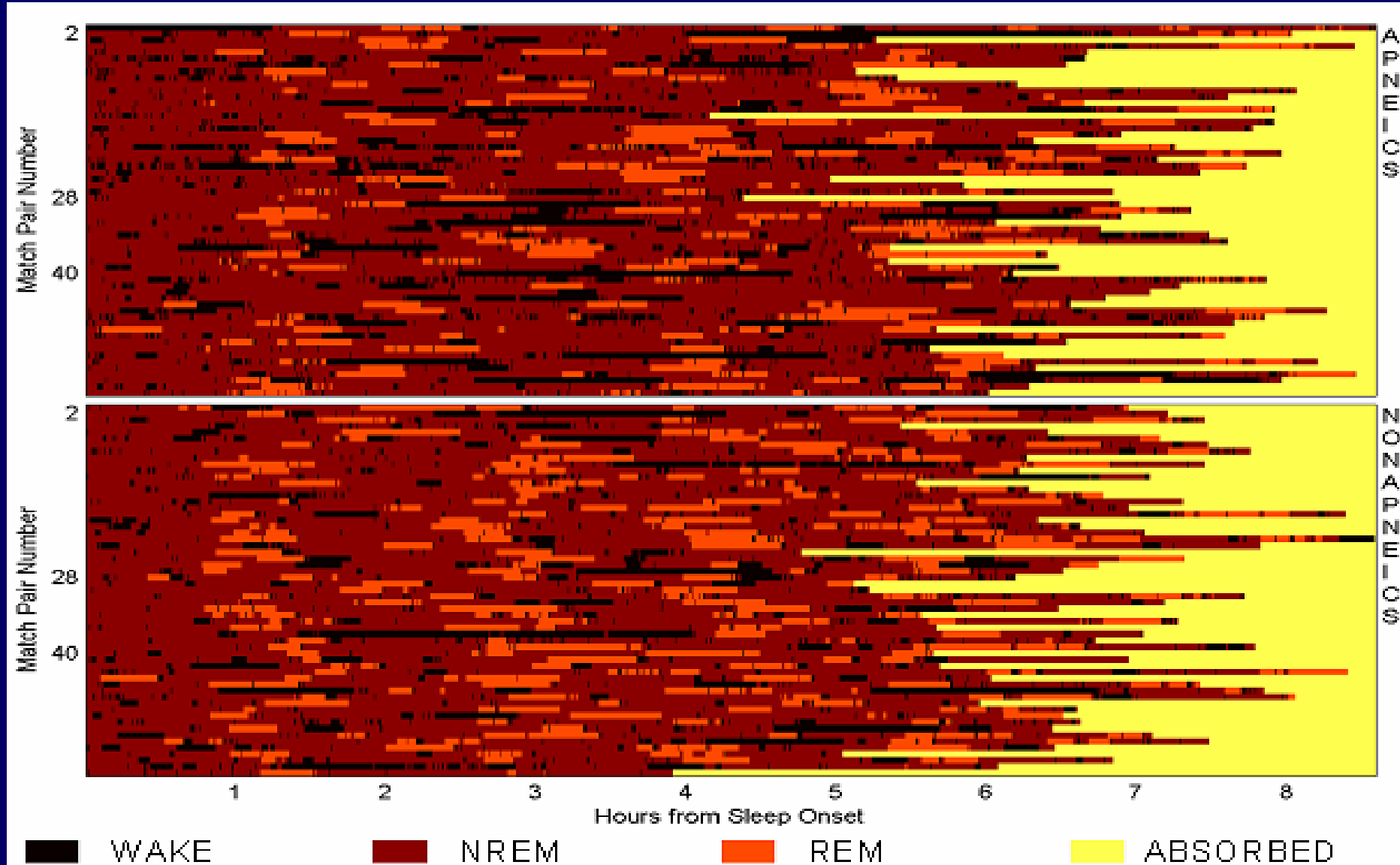


Total time recorded	A	=	B	=	C
Total time in State 2	A	=	B	=	C
No. of transitions from State 1 to State 2*	A	≠	B	=	C
Time to transition from State 1 to State 2**	A	≠	B	≠	C

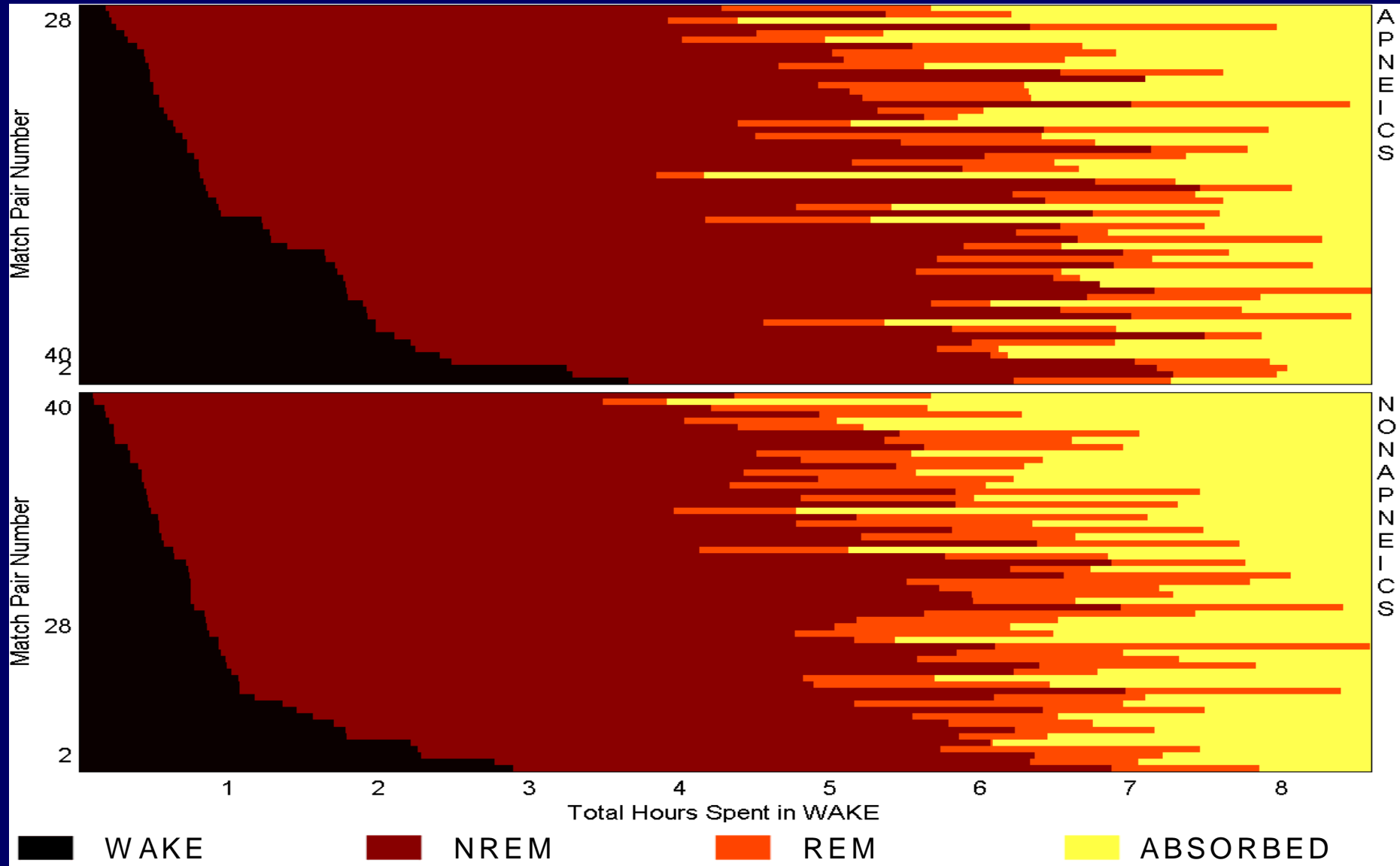
\* Differences detectable with log-linear modeling

\*\* Differences detectable with multi-state survival analysis

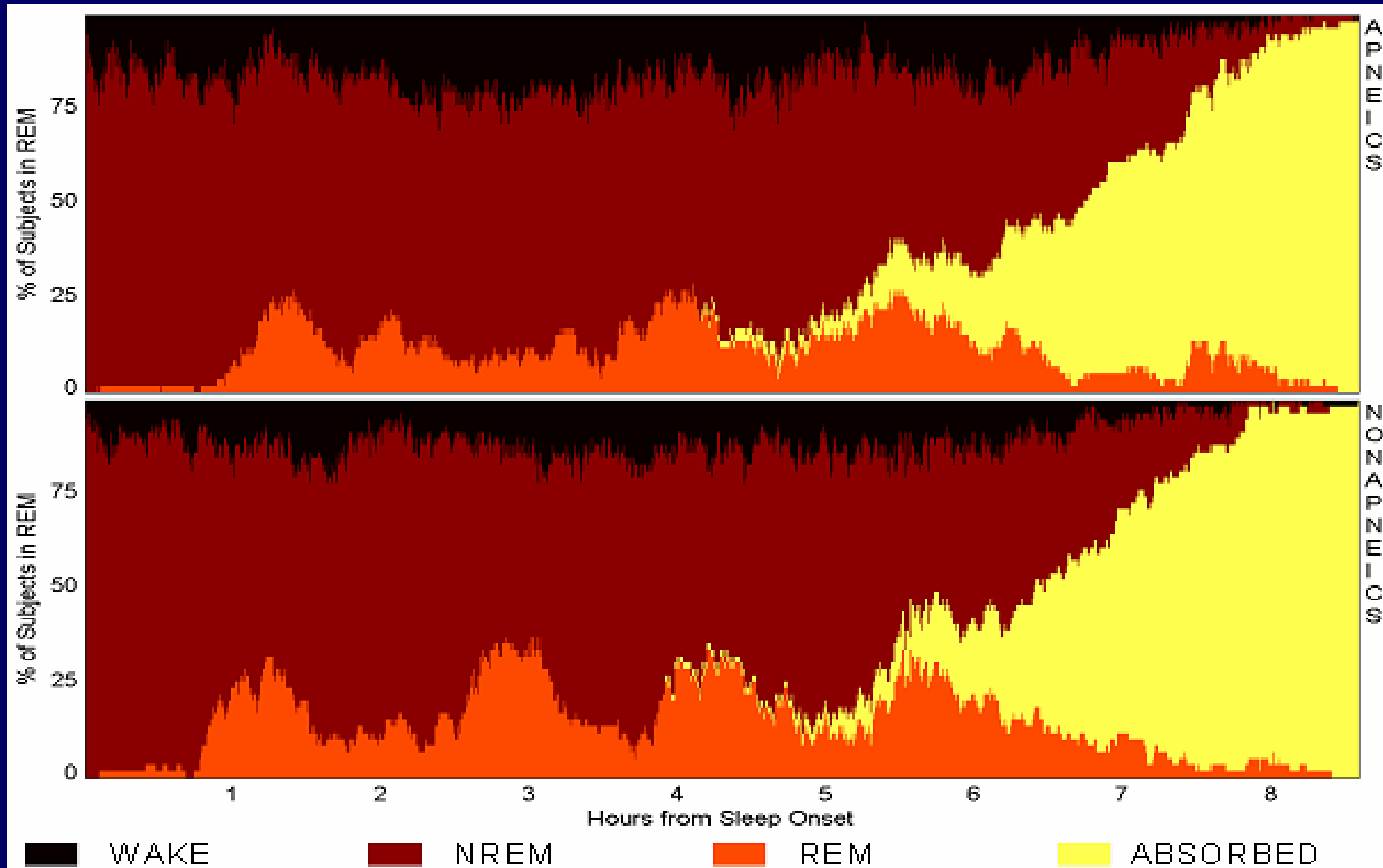
# HMVVs for SDB / No-SDB



# Strand sorting



# Vertically sorted HMMs



Variable	SDB	No-SDB	<i>p</i> -value*
Demographic			
Age (yrs)	62.7 ± 10.8	62.3 ± 10.6	0.31
Male gender, N (%)	38 (63.3%)	38 (63.3%)	1.00
Caucasian race, N (%)	52 (86.7%)	52 (86.7%)	1.00
Body mass index (kg/m <sup>2</sup> )	30.7 ± 5.21	29.2 ± 4.46	< 0.0001

Variable	SDB	No-SDB	<i>p</i> -value*
Polysomnographic			
AHI, events/hr	34.0 ± 12.1	0.63 ± 0.37	< 0.0001
Total sleep time (minutes)	353.3 ± 59.5	362.9 ± 56.3	0.38
Sleep latency <sup>†</sup> (minutes)	20.5 ± 15.7	22.1 ± 18.5	0.69
Sleep efficiency, %	81.9 ± 10.3	83.0 ± 9.2	0.98
Stage1 <sup>§</sup> sleep, %	6.5 ± 4.46	5.7 ± 3.50	0.21
Stage2 <sup>§</sup> sleep, %	58.6 ± 10.5	57.3 ± 11.8	0.52
Slow wave <sup>§</sup> sleep, %	15.6 ± 11.6	16.0 ± 12.5	0.86
REM <sup>§</sup> sleep, %	19.2 ± 7.14	21.0 ± 5.59	0.09

# Multistate proportional hazards models

- Stratified Cox proportional hazards model, with six strata-specific baseline hazards for each kind of transition  
(WR, WN, NW, NR, RW, RN)
- The duration in the current states are modeled as the outcome, with actual transitions treated as observed outcomes and potential transitions treated as censored
- Sandwich variance estimates used to handle within-subject correlations

## More about time

- Different time scales of interest
  - Time of night (circadian effects)
  - Time since sleep onset
  - Duration in current state
- The multistate Cox proportional Hazards approach analyzes the durations in the current state
- Time of night and time since sleep onset can be accounted for as proportional offsets in the hazard model

# Poisson-log linear models

		Previous state			
		REM	NREM	WAKE	TAR*
Current state	REM	-	7	4	7.5
	NREM	3	-	1	5.0
	Wake	1	2	-	2.5

Transition Type	R-N	R-W	N-R	N-W	W-R	W-N
Count	7	4	3	1	1	2
Time at risk	7.5	7.5	5.0	5.0	2.5	2.5

TAR\* = Total time at risk for transitioning from this state

# Poisson GLMM

- Log time at risk for transitioning included as an offset in the linear predictor
- Added a hierarchical random effect structure to account for the pair matching and the within-subject correlation
- Likelihood equivalent to a proportional hazards frailty model with constant strata-specific baseline hazards
- More complex baseline hazard models can be fit by dividing the times at risk for transitioning into bins
- Fit in R by MCMC placing diffuse inverted gamma priors on the variance components and diffuse gamma priors on the mean effects

# Results Diseased to Non-Diseased

Model	W-N	N-W	N-R	R-W	R-N	W-R
LL	1.07 <b>1.26</b> 1.48	1.11 <b>1.32</b> 1.56	0.81 <b>1.02</b> 1.29	0.91 <b>1.17</b> 1.50	0.90 <b>1.20</b> 1.59	1.02 <b>1.42</b> 1.96
MCPH	1.02 <b>1.10</b> 1.20	1.30 <b>1.50</b> 1.74	0.68 <b>1.04</b> 1.57	1.51 <b>2.26</b> 3.40	0.89 <b>1.57</b> 2.77	0.49 <b>0.86</b> 1.50
Poiss. 1	0.87 <b>1.01</b> 1.17	1.17 <b>1.35</b> 1.56	0.83 <b>1.02</b> 1.24	1.07 <b>1.32</b> 1.62	1.01 <b>1.43</b> 1.84	0.95 <b>1.24</b> 1.62
Poiss. 1*	0.87 <b>1.04</b> 1.22	1.17 <b>1.39</b> 1.65	0.84 <b>1.04</b> 1.29	1.08 <b>1.34</b> 1.67	1.11 <b>1.46</b> 1.93	0.95 <b>1.27</b> 1.68
Poiss. 2	0.92 <b>1.01</b> 1.10	1.02 <b>1.13</b> 1.23	0.75 <b>0.89</b> 1.04	0.91 <b>1.07</b> 1.27	0.88 <b>1.14</b> 1.45	0.92 <b>1.17</b> 1.49

# Summary

- Poisson glmms and multistate proportional hazards models can shed considerable light on sleep transition data
- Considering transitions highlights a different aspect of sleep behavior than architecture
- In subjects matched on architecture and other demographics, differences in transition rates can be found between diseased and non-diseased subjects
- Follow up analyses will use subject-specific random effect predictions as regressors to predict cardiac outcomes