The value of stratified economic analysis in cohort-level models: A case study on interventions for obstructive sleep apnea

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Disclosure

No actual or potential conflict of interest in relation to this topic or presentation.

Cohort-Level Modelling

- Many “cohort-level” models in economic evaluation
- All rely on an *Homogeneity* assumption
  - Aggregate, based on identifying similarities between individuals
- Subgroup effects may exist that is largely ignored in such models

Objective

To illustrate the importance of conducting stratified economic analysis to incorporate subgroup effects through the example of treatments for obstructive sleep apnea.

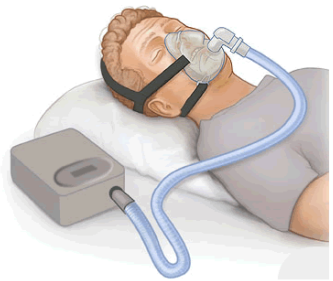
Stratified vs Partly stratified vs Non-stratified analyses

Obstructive Sleep Apnea (OSA)

- Relatively common disorder characterized by the narrowing and collapse of the upper airway during sleep
  - Severity categorized by apnea-hypopnea index (AHI):

- If left untreated, there is significant morbidity and mortality consequences

OSA Treatment Reviewed



PAP devices
(e.g., CPAP)

Oral appliances
(i.e., MAD)

Weight Loss*

No treatment

Surgery
(MMA ± GTA)

Additional interventions considered:

Exploratory analyses-
ePAP, positional therapy

CADTH conducted an Optimal Use review to address the question of "which treatment- **for whom**?"

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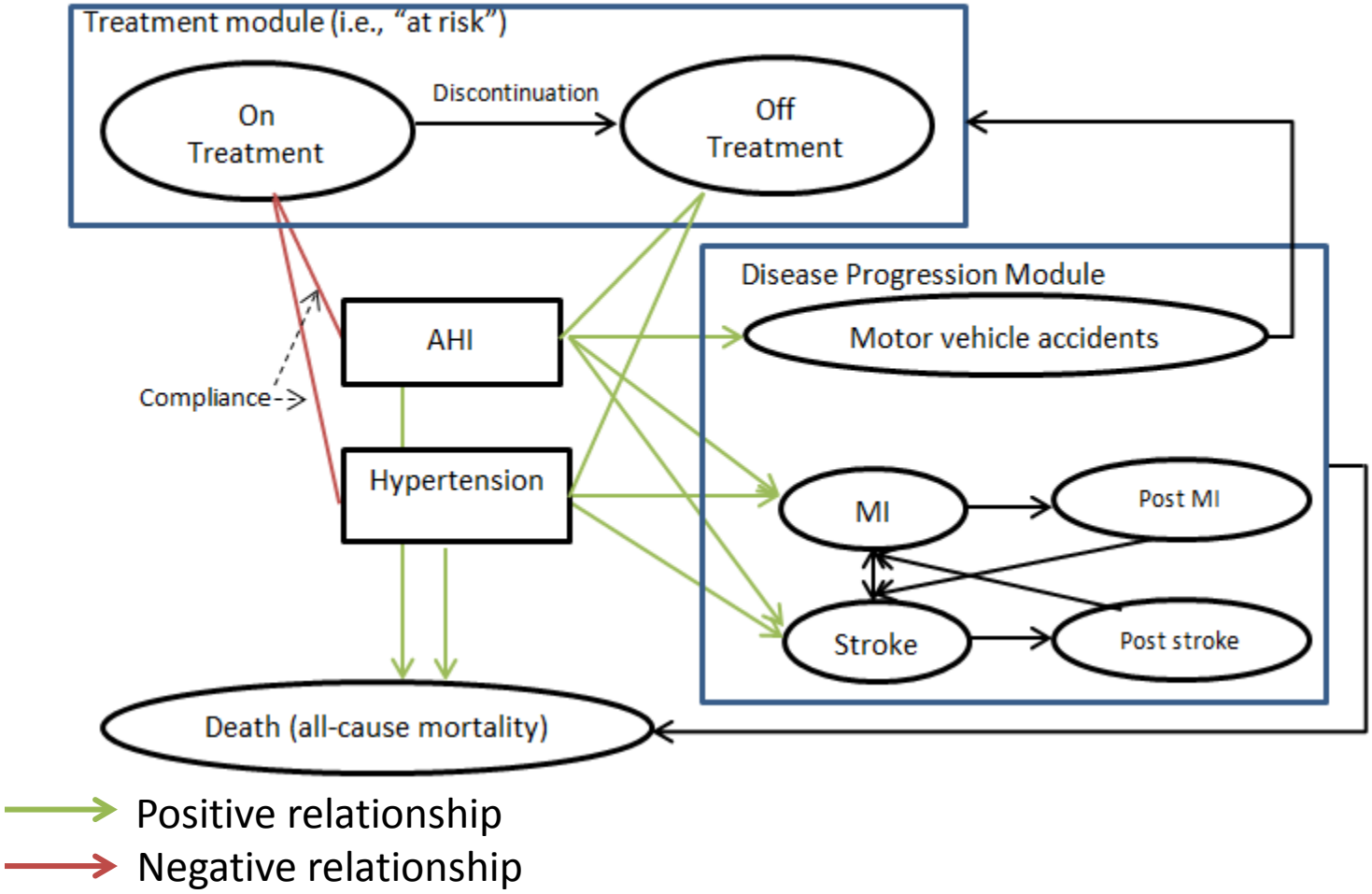
CPAP = continuous positive airway pressure; ePAP= exploratory positive airway pressure; GTA = Genial tubercle advancement; MAD = mandibular advancement devices; MMA = Maxillomandibular advancement

*Only suitable in patients who are overweight

Economic Model Structure



AHI = apnea hypopnea index; MI = myocardial infarction

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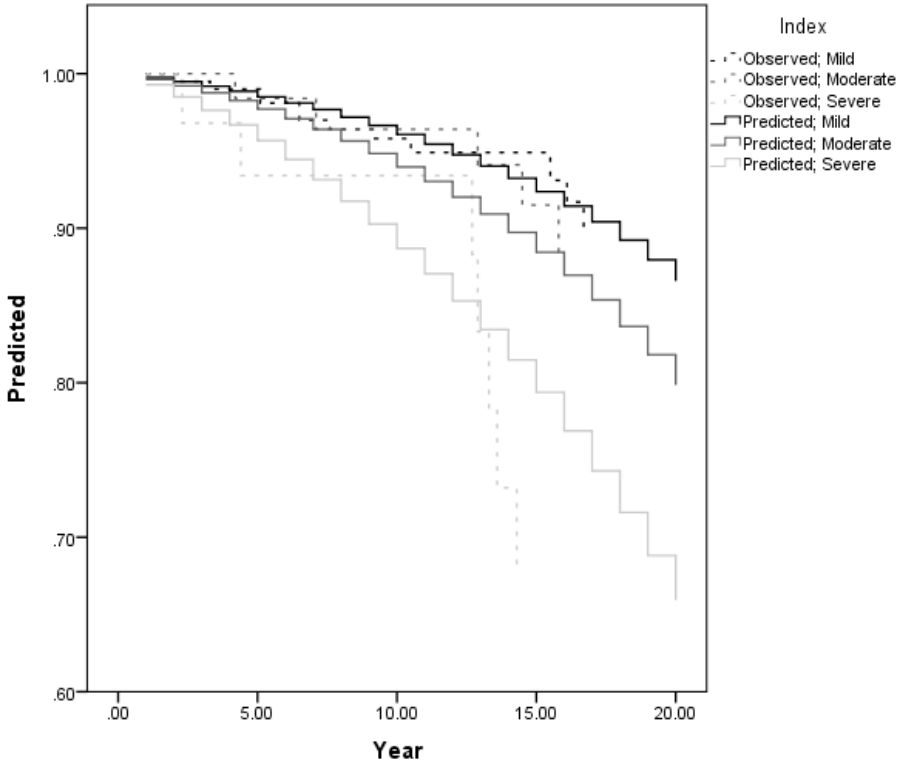
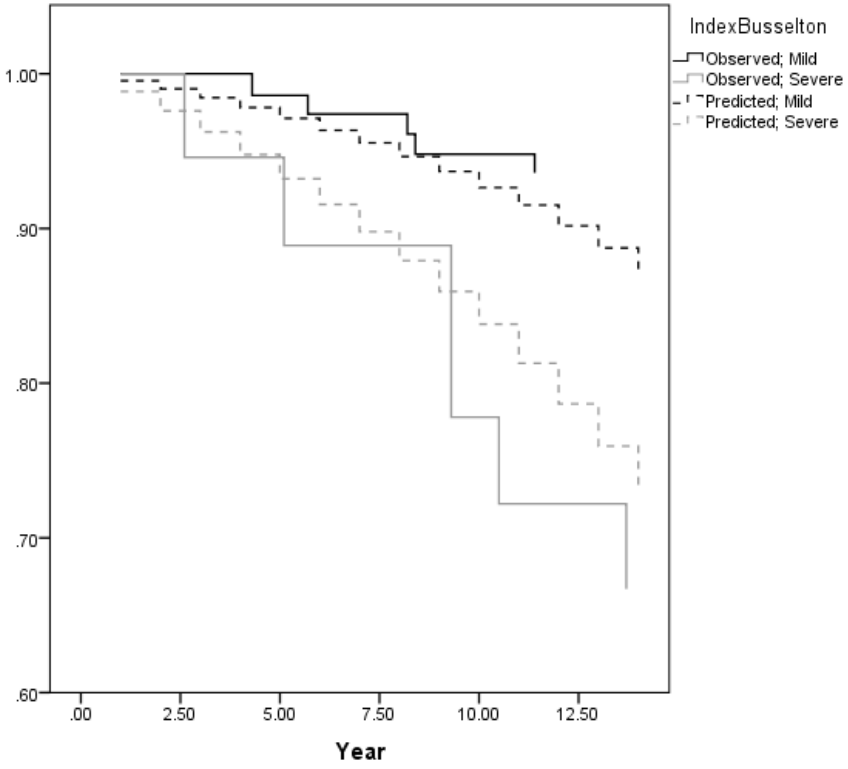
External Validation

Survival curve

A. Wisconsin Sleep Cohort Study



B. Busselton Study



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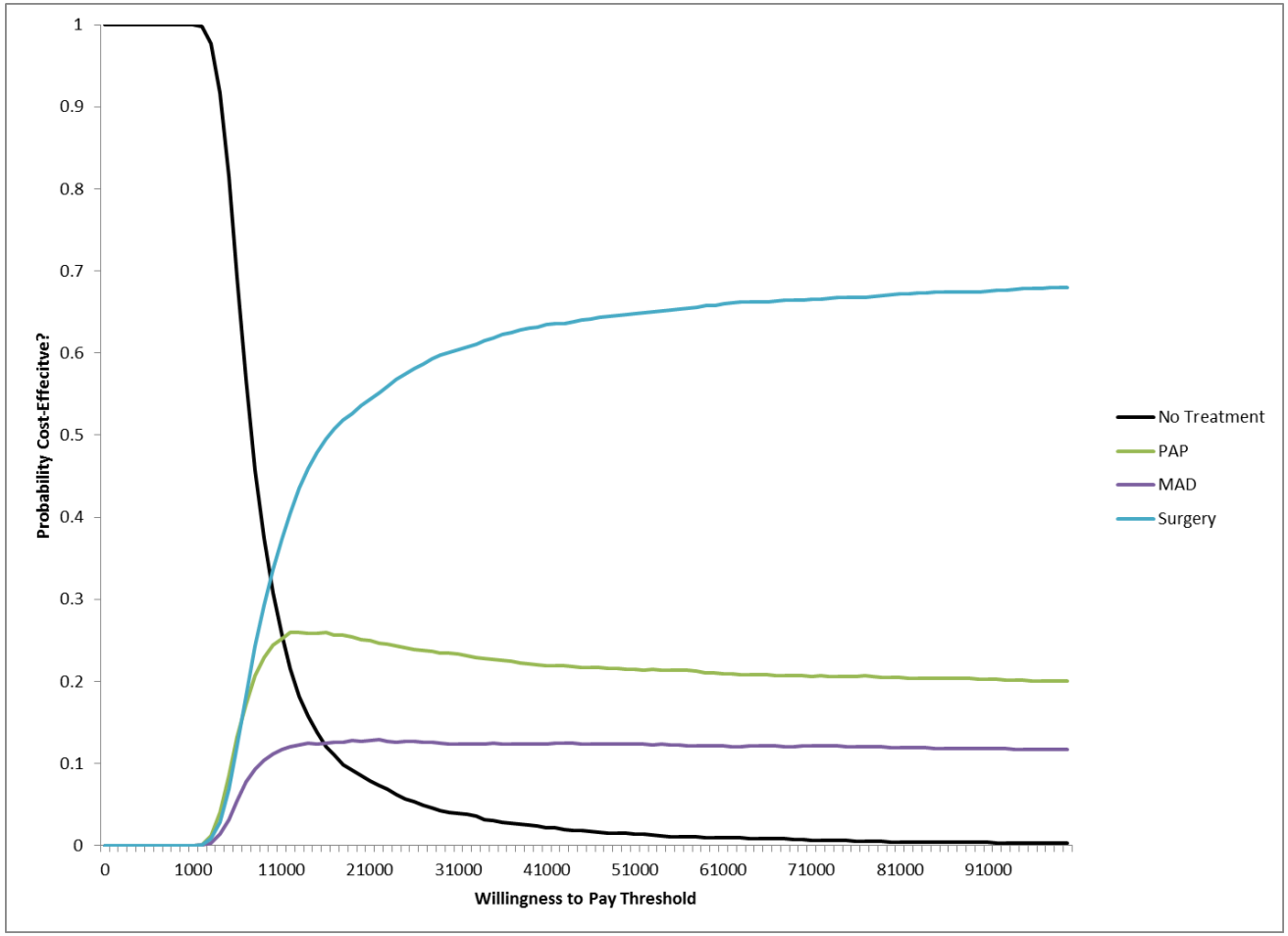
Non-stratified Analysis

No stratification by natural history or by treatment effect



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Modelling OSA Natural History

- All-cause mortality: based on Canadian lifetables for general population (age- and gender-specific)

  Also impacted by AHI:

  RR (severe OSA vs no OSA*) = 1.6
  RR (moderate OSA vs. no OSA*) = 1.2
  RR (mild OSA vs. no OSA*) ~ 1

- Cardiovascular event: based on Framingham risk equation

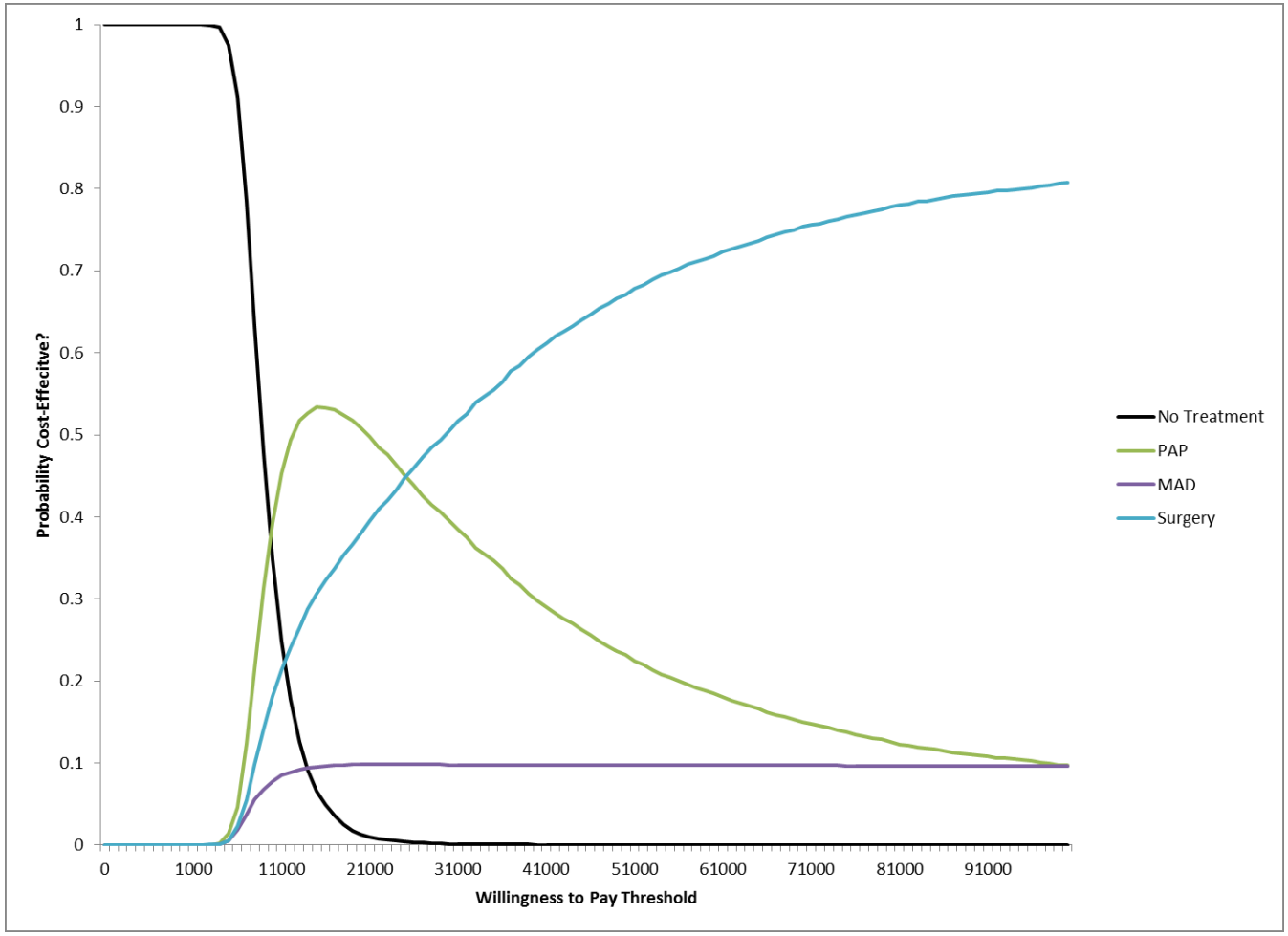
  Predictive equation of probability of MI or stroke based on gender, age, systolic blood pressure, smoking status, total cholesterol, HDL, diabetes status and ECG

  Also indirectly impacted by AHI, RR incident hypertension:

	Male	Female
Mild	1.19	1.37
Moderate	1.61	1.79
Severe	1.66	1.90

Partly Stratified Analysis

Stratify by natural history but not by treatment effects



Baseline AHI
33

Mild OSA

Severe OSA

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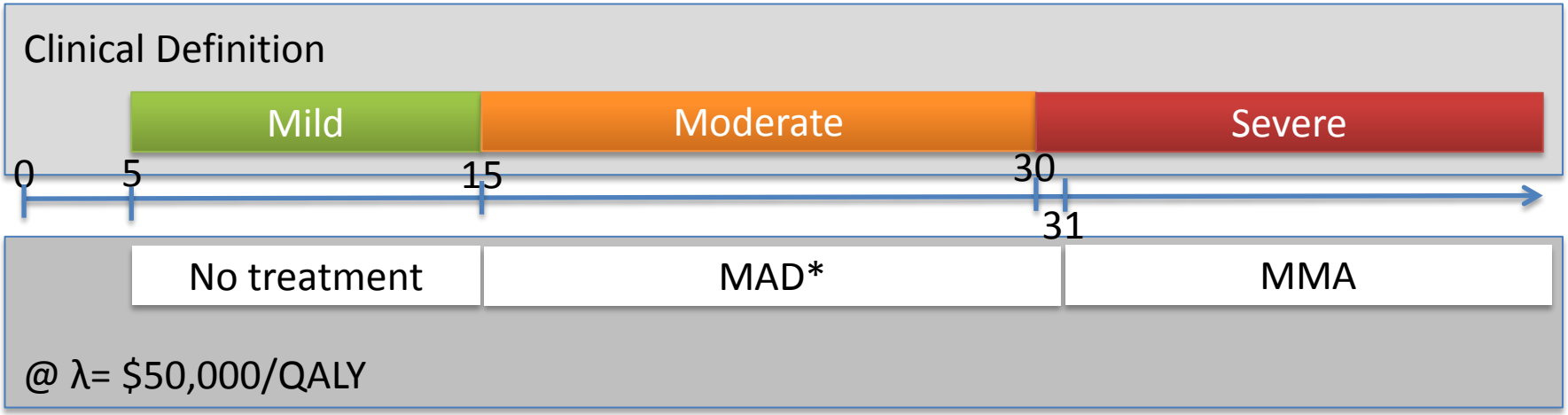
Summary of Partly Stratified Analysis



*Considerable parameter uncertainty at baseline AHI value 22 to 30 as no strategy emerged as most likely cost-effective at prob>60% (CPAP was most likely cost-effective at 25≤AHI≤27)

Non-stratified Treatment Effect

Intervention	Mean reduction in AHI					Mean reduction in BP
	Compared to "no treatment"					
PAP-based therapy	**NMA** -25.27 (-22.03, -28.52)					**NMA** -2.5 (-1.5, -3.5)
MAD	**NMA** -15.20 (-10.91, -19.50)					**NMA** -2.1 (-0.8, -3.4)
Surgery	**Probability** (by baseline AHI)					
		<30	30<AHI<60	60<AHI<90	AHI>90	-3.5 (-19, 11)
	Cure (AHI <5)	0.557	0.458	0.28	0.195	
	Success (AHI <15 and 50% ↓ in baseline AHI)	0.836	0.88	0.727	0.707	

Stratified Treatment Effect

Intervention	Mean reduction in AHI					Mean reduction in BP
	Compared to "no treatment"					
	Stratified by baseline AHI					
PAP-based therapy	**MA** Mild: -2.4 (-3.7, -1.1) Moderate: -13.7 (-16.1, -11.2) Severe: -33.0 (-39.8, -33.0)					**NMA** -2.5 (-1.5, -3.5)
MAD	**MA** Mild: -7.8 (-16.4, -1.1) Moderate: -10.7 (-14.6, -6.9) Severe: -8.0 (-16.0, 0.0)					**NMA** -2.1 (-0.8, -3.4)
Surgery	**Probability**					-3.5 (-19, 11)
		<30	30<AHI<60	60<AHI<90	AHI>90	
	Cure (AHI <5)	0.557	0.458	0.28	0.195	
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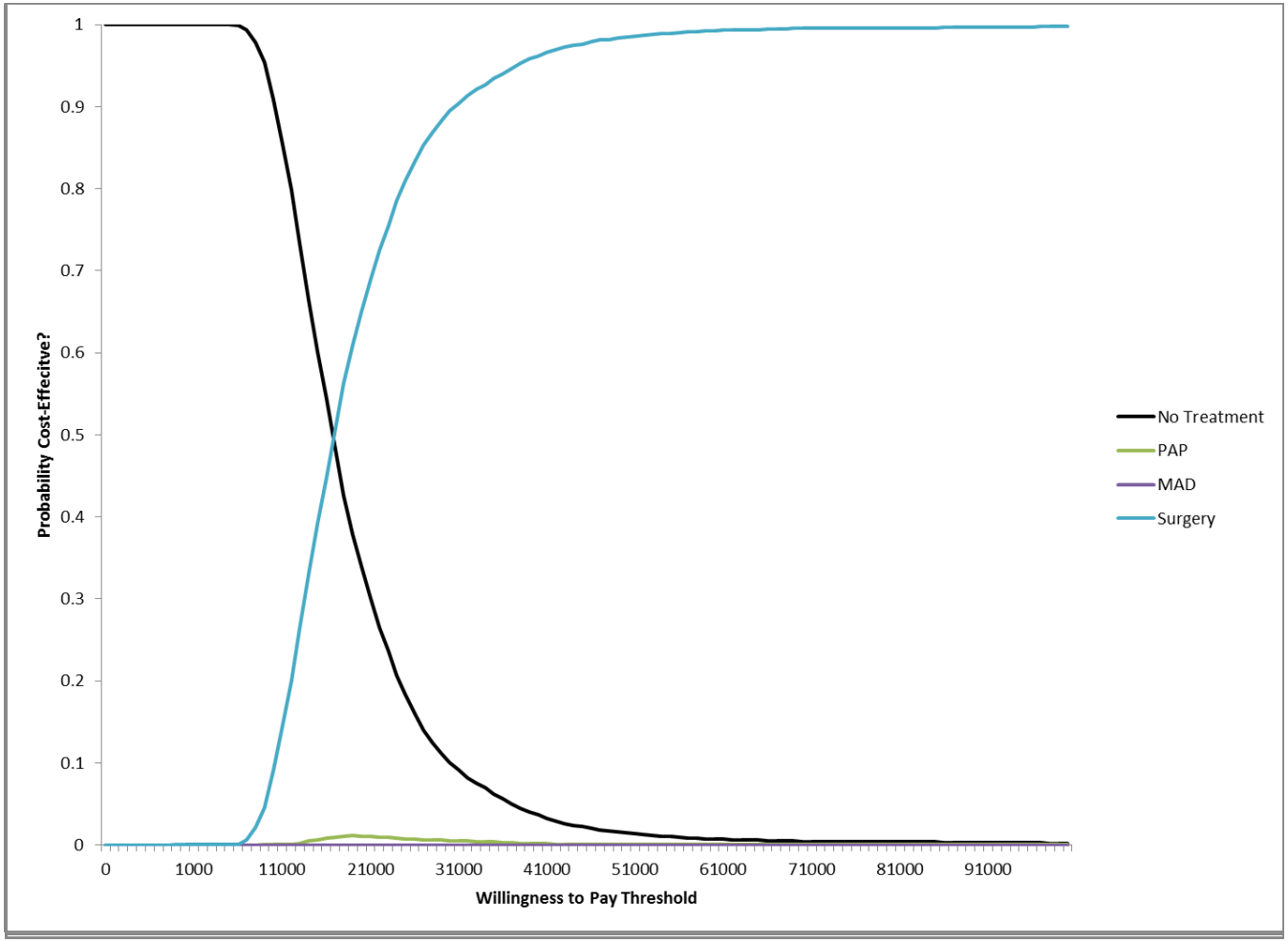
Fully Stratified Analysis

Stratify by natural history and by treatment effect



Baseline AHI
60

Mild OSA

Severe OSA

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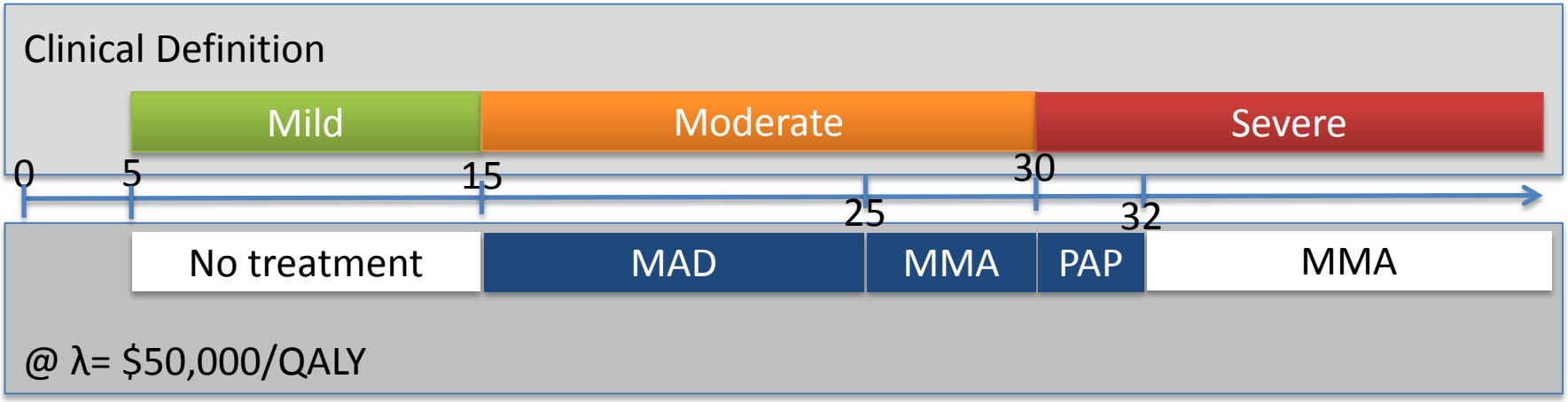
Summary of Fully Stratified Analysis



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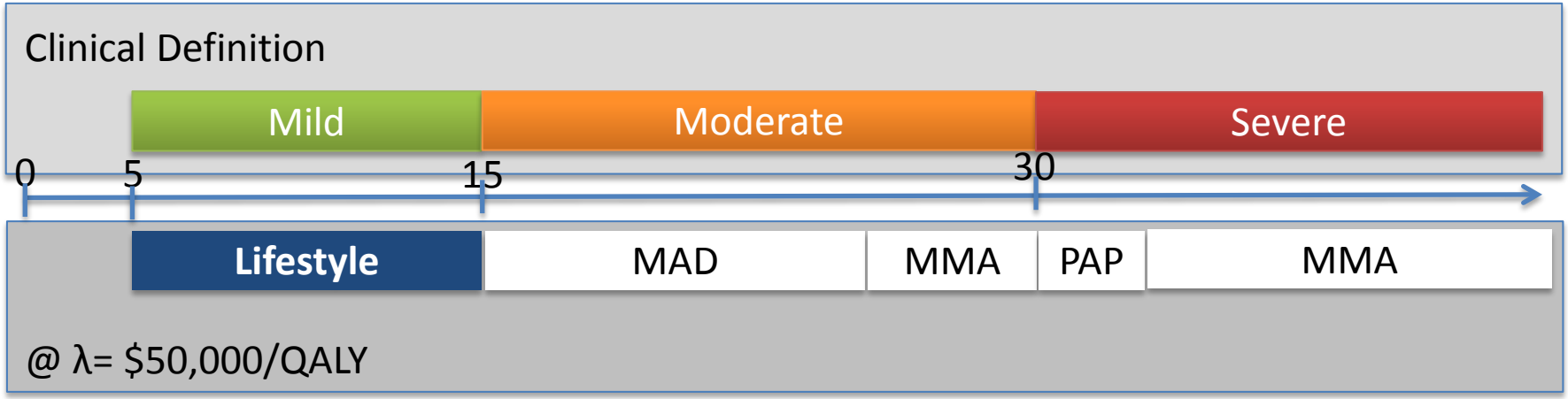
Subgroup: Overweight/Obese patients

- Rationale: Clinical experts and inclusion criteria from clinical review inclusion suggest lifestyle is a suitable option for patients who are overweight/obese
- Results: Lifestyle emerges as the most likely cost-effective interventions for patients with mild OSA



Discussion

- By ignoring heterogeneity in patient characteristics or in treatment effects, different results reached.
  - Observed uncertainty in CEAC driven by heterogeneity.
- In this example, value of conducting stratified analyses arose when:
  - Heterogeneity in natural history,
  - Differential treatment effects by subgroups,
  - Clinical criteria exist regarding the suitability of a treatment.
- In reality, heterogeneity can be with any type of parameter inputs.

Challenge with Stratification

- Challenge remains with cohort-level models given the potentially large number of analysis required

  Independent: $\sum n_m$

  Dependent: $\prod n_m$

  n= number of dimensions

  m= number of levels within dimension

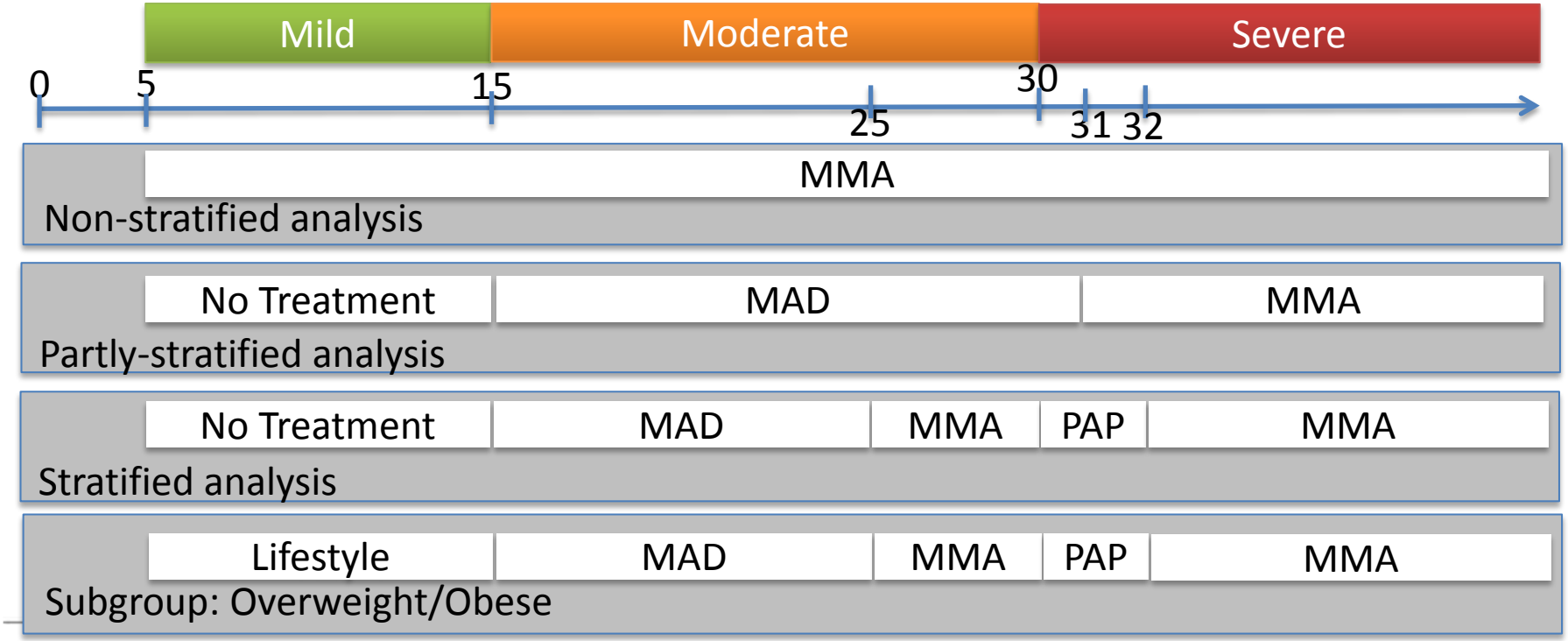
  Solution: Patient-level microsimulation

- How does one select which variables to factor with respect to heterogeneity in stratified analyses?

Conclusions

- Different economic findings when factoring patient-specific characteristics, with potential implication to policy-making.

At λ =$50,000/QALY:



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