Hearing Changes in Meniere's Disease: Categorizing Patterns of Change Over Time

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Outline

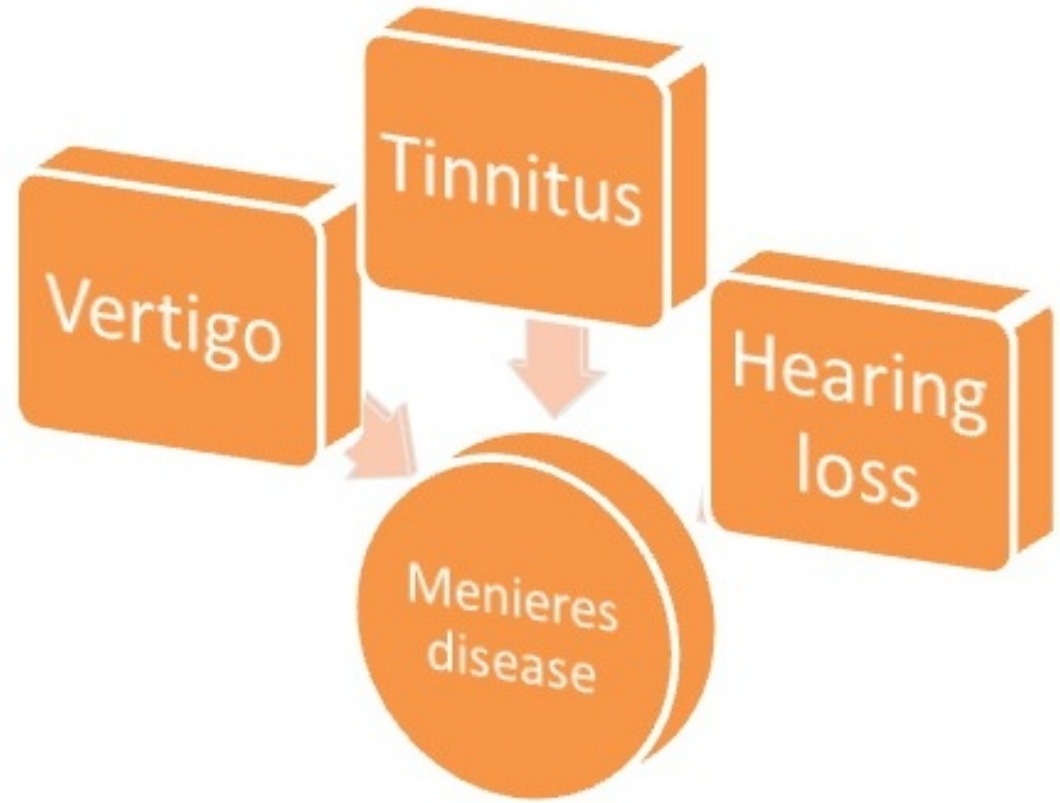
- Meniere's Disease and measurement of hearing loss
  - Primary complaint: vertigo
  - Traditional phenotype: pure-tone average
- Data
  - Retrospectively obtained hearing tests
  - Hearing affected by both disease and age
- Analysis

Why conduct these analyses of hearing data in Meniere's?

- Hypotheses of pathology affecting function
- Clinical trial endpoints
- Select useful metrics for genetic studies
  - Appropriately identify disease states
    - Medical history of symptom development OR
    - Single hearing measurement OR
    - Time to a specific hearing loss
    - Disease progression

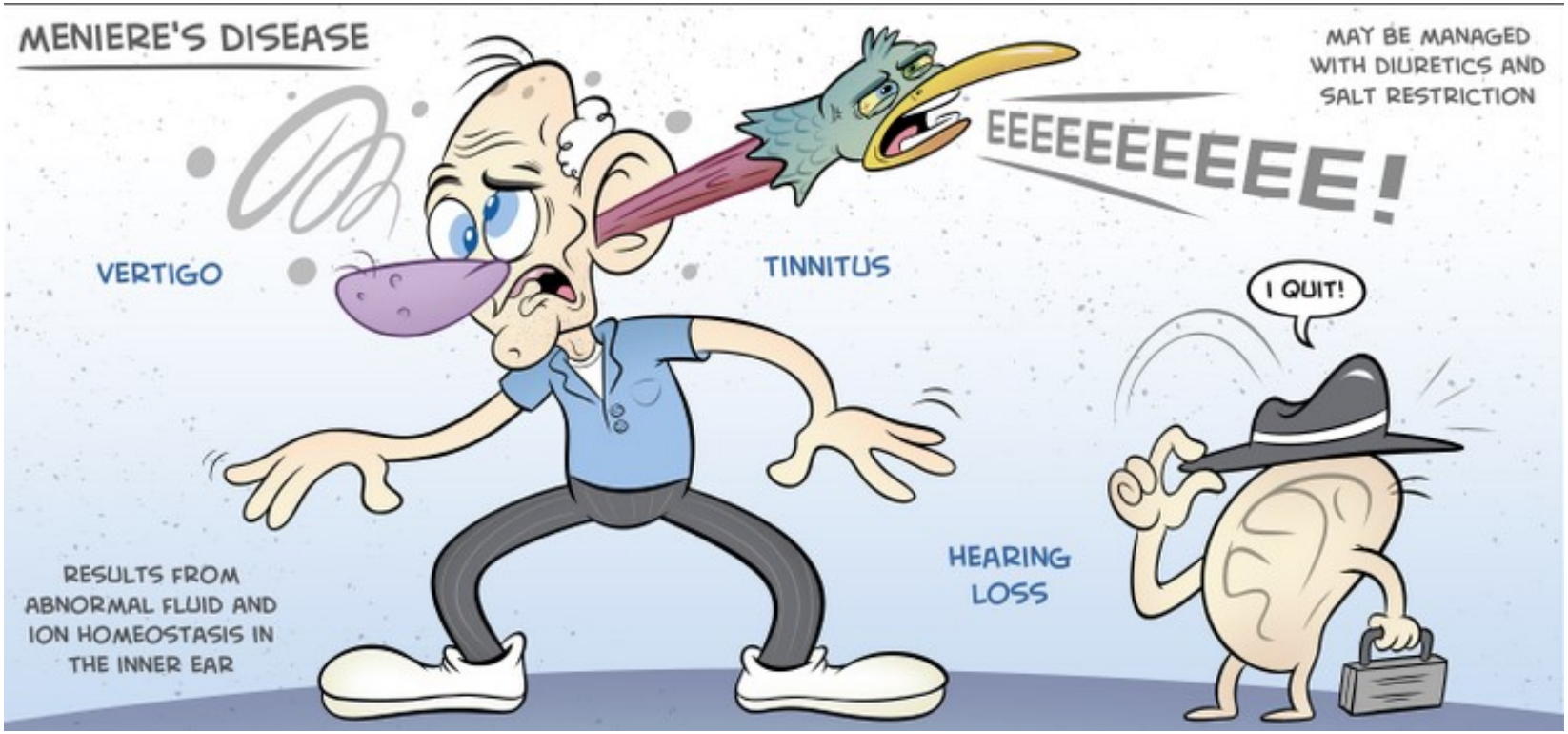
What is Meniere's Syndrome?

With or without vertigo



Hearing loss in one or both ears

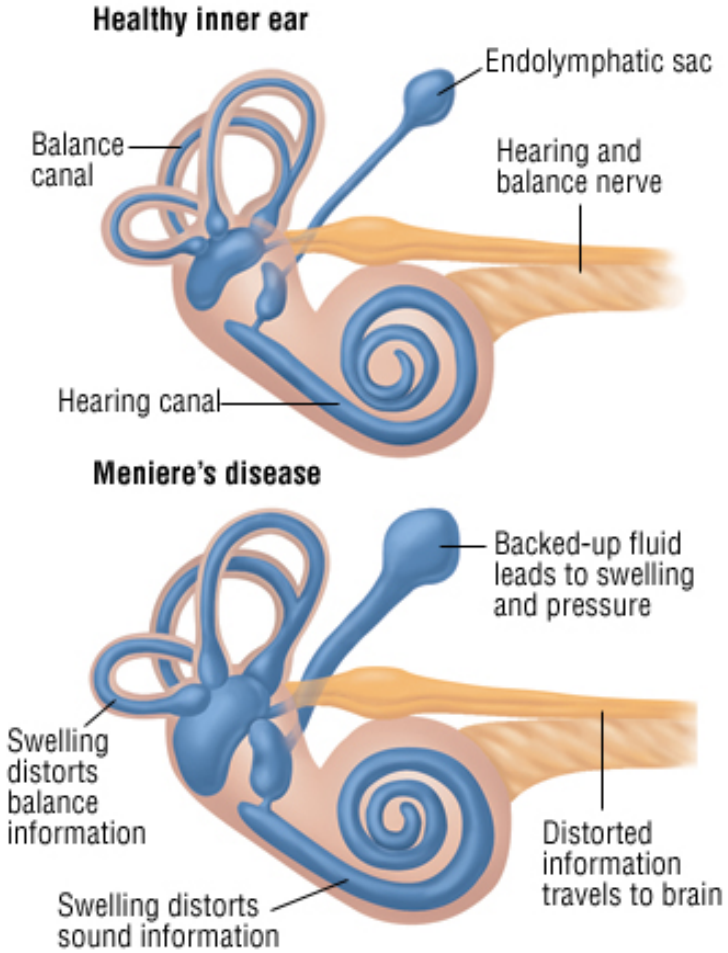
Meniere's = Miserable



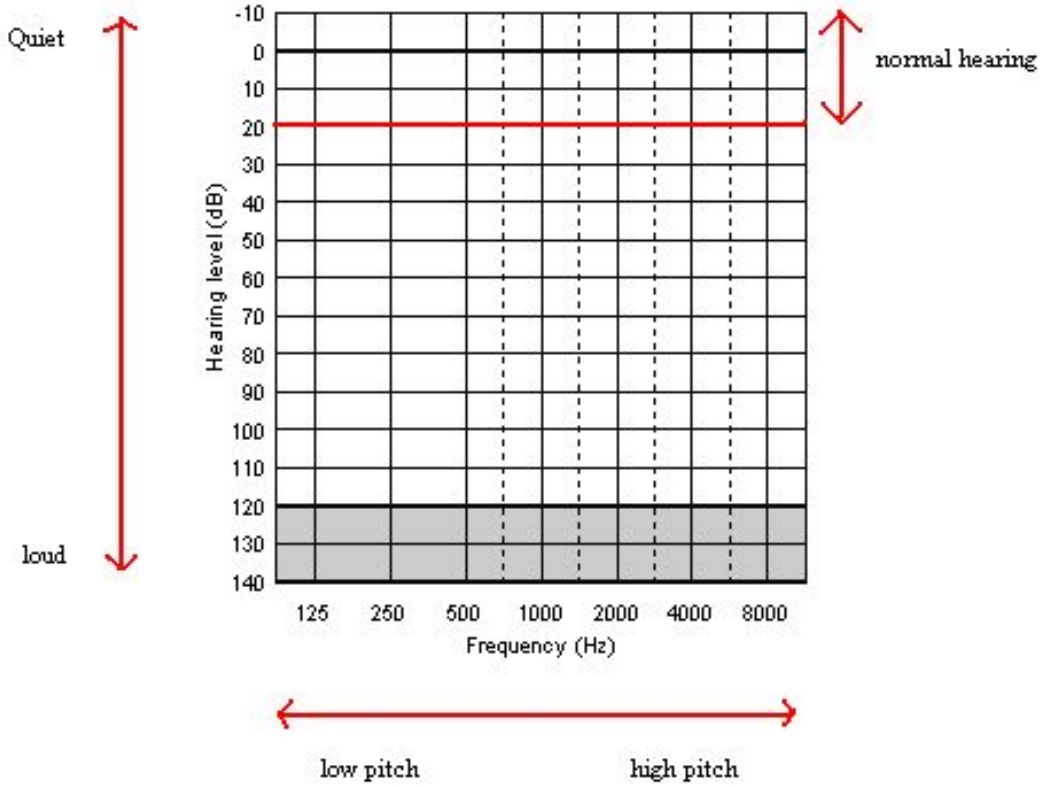
Who are the patients?

- Female/Male 2:1
- Average age first vertigo attack: 50-ish
- As few as 3:100,00 to 513:100,000
- Variations:
  - Hearing loss only
  - Both ears affected
  - Sudden onset, both ears

Pathophysiology of Meniere's



Measurement of Hearing by Ear



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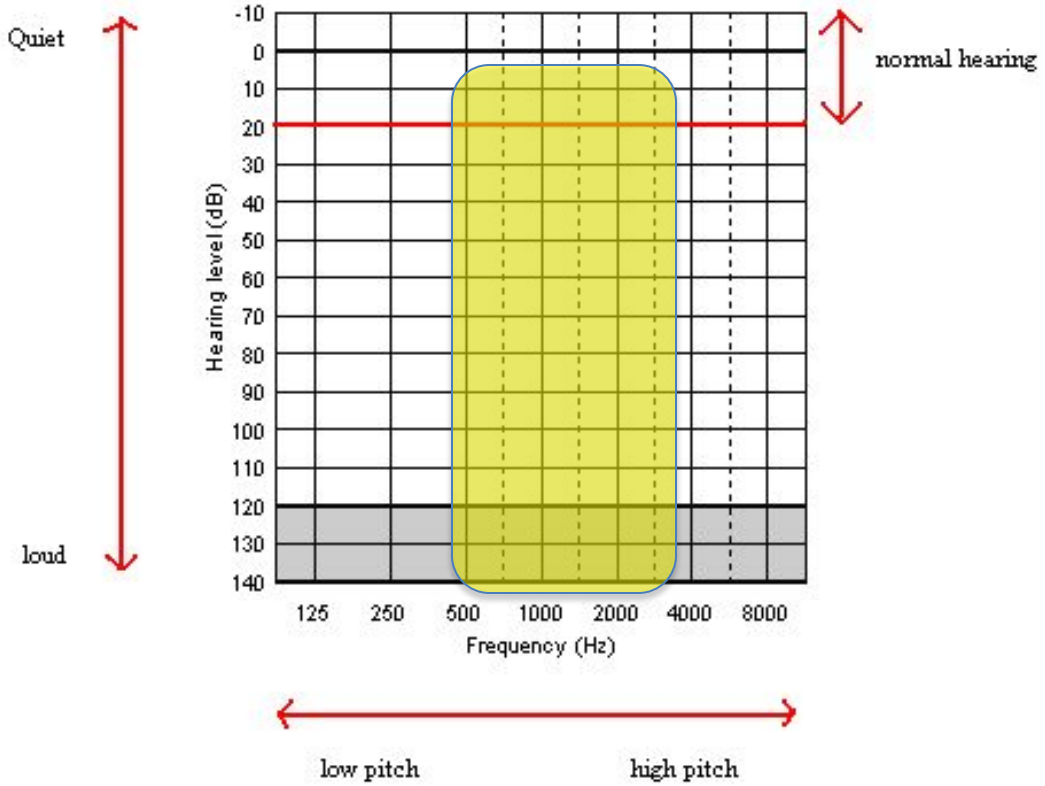
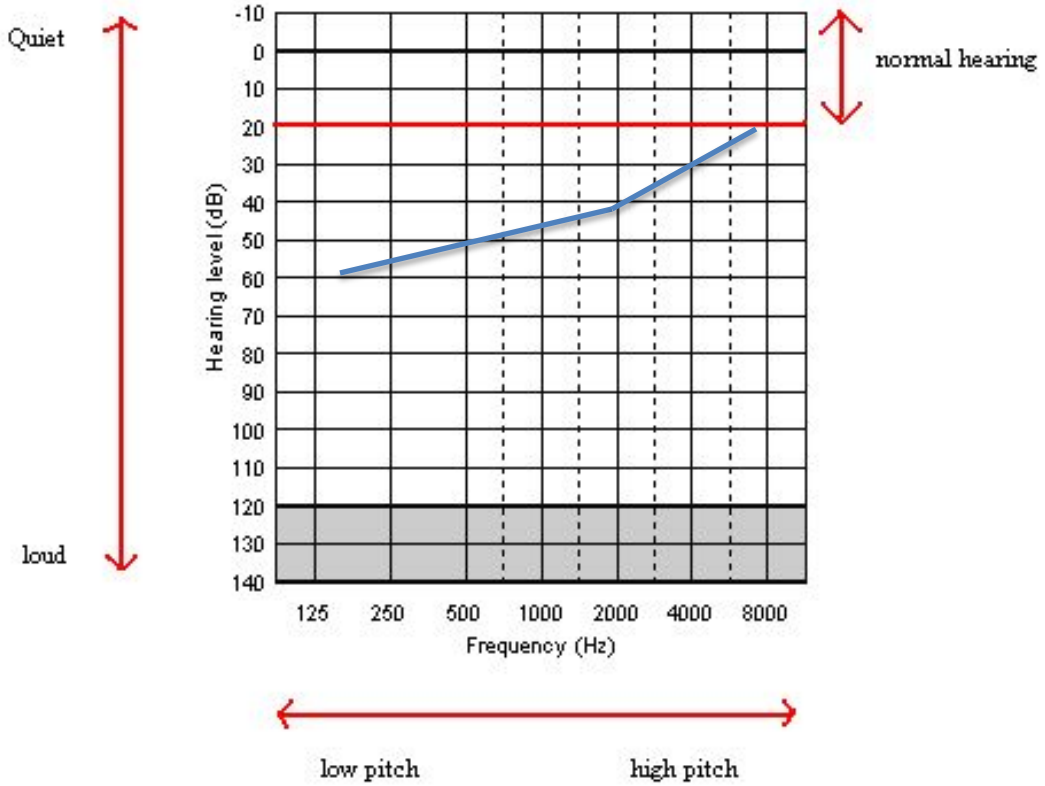
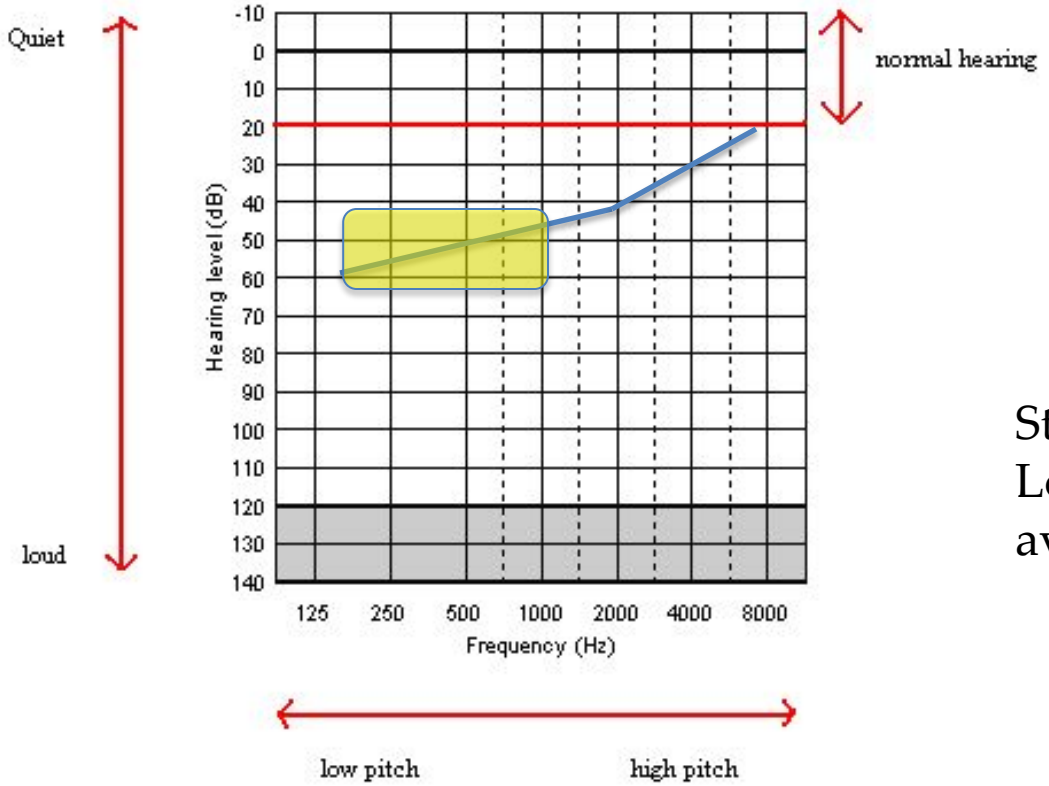


Measurement of Hearing by Ear

Typical Meniere's

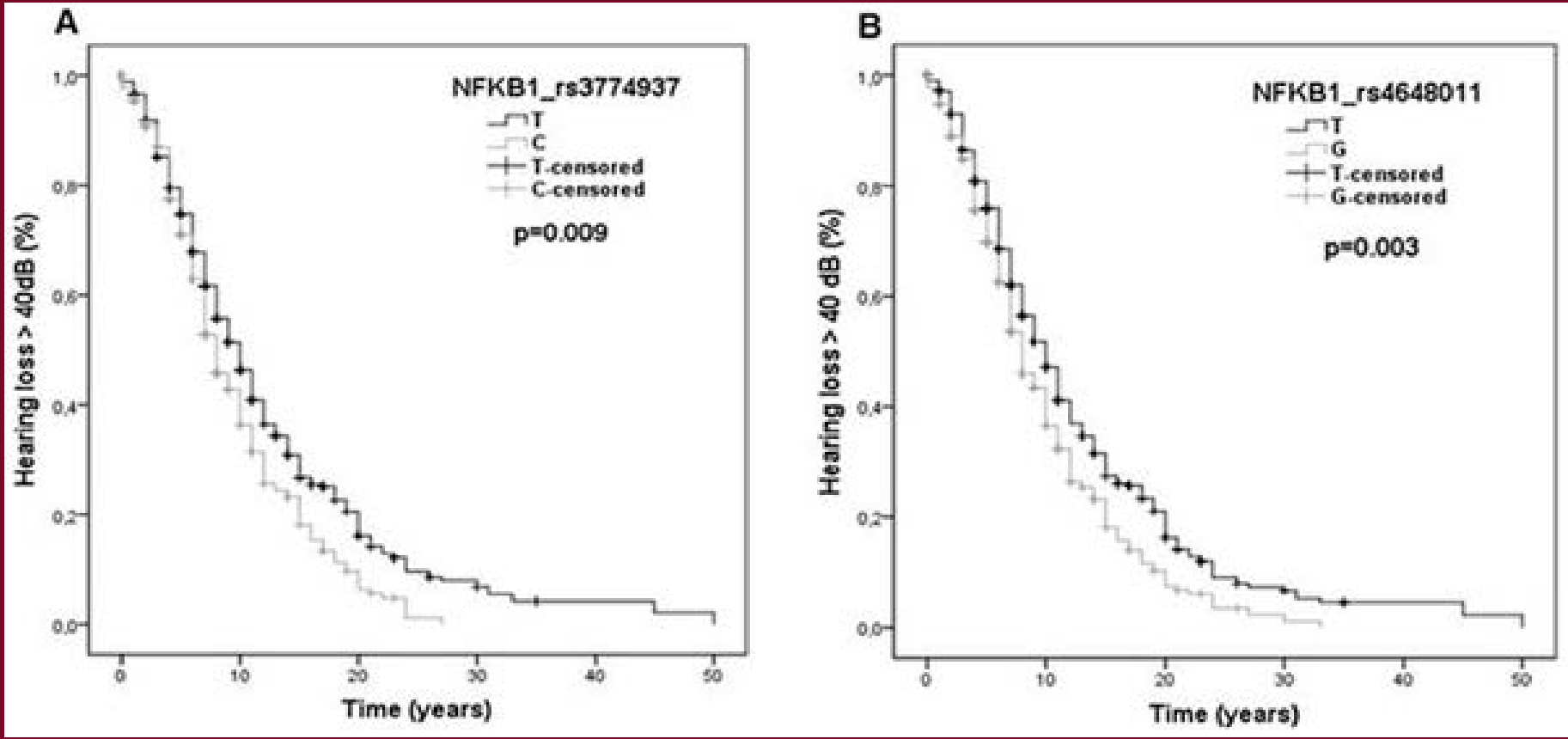


Conventional hearing measurement



Study endpoint
Low frequency average

Figure 1. Variants in NFKB1 gene and hearing outcome in patients with MD were compared by Kaplan-Meier survival curves and the log-rank test.



Cabrera S, Sanchez E, Requena T, Martinez-Bueno M, Benitez J, et al. (**2014**) Intronic Variants in the NFKB1 Gene May Influence Hearing Forecast in Patients with Unilateral Sensorineural Hearing Loss in Meniere's Disease. PLoS ONE 9(11): e112171.

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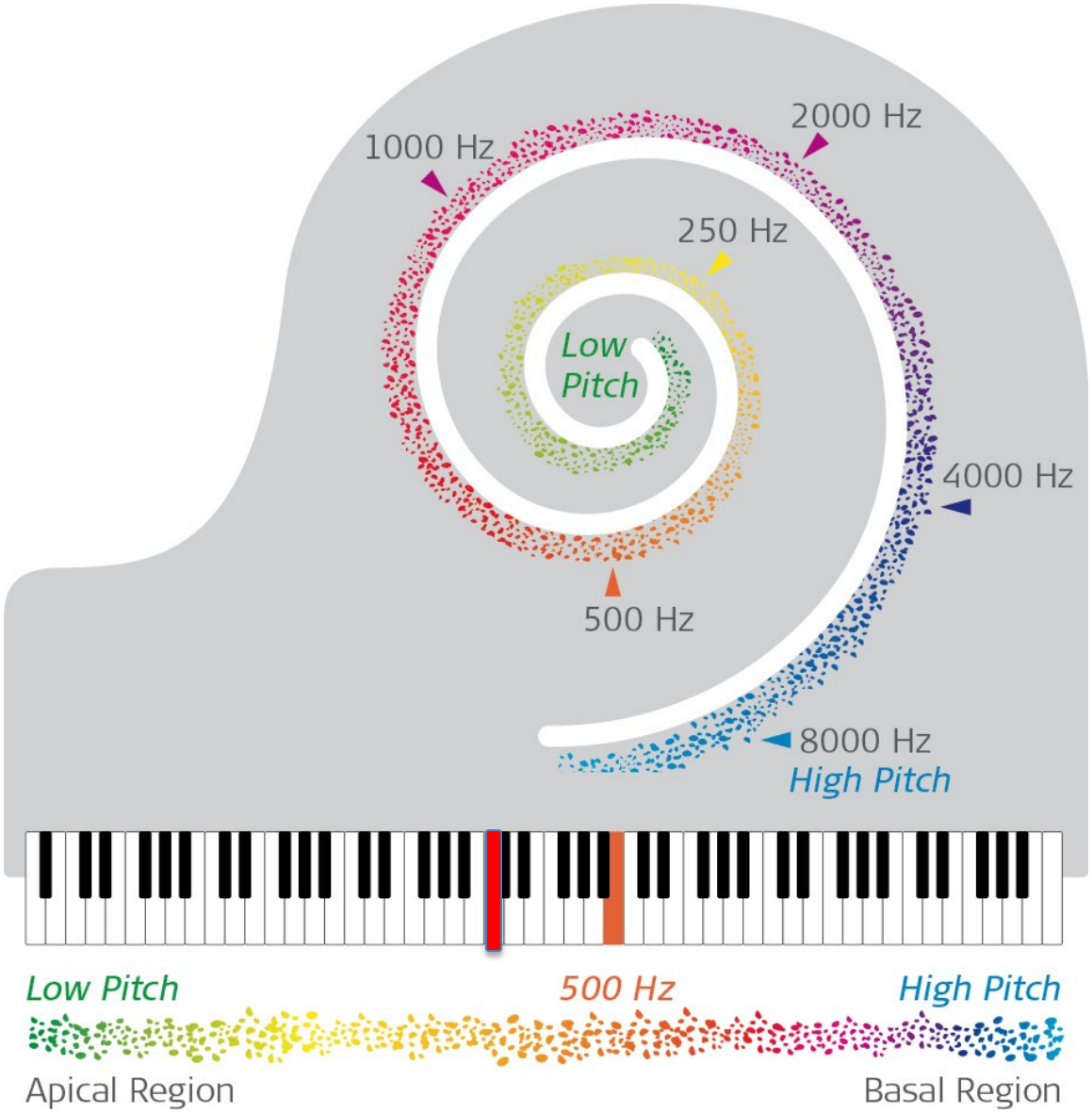
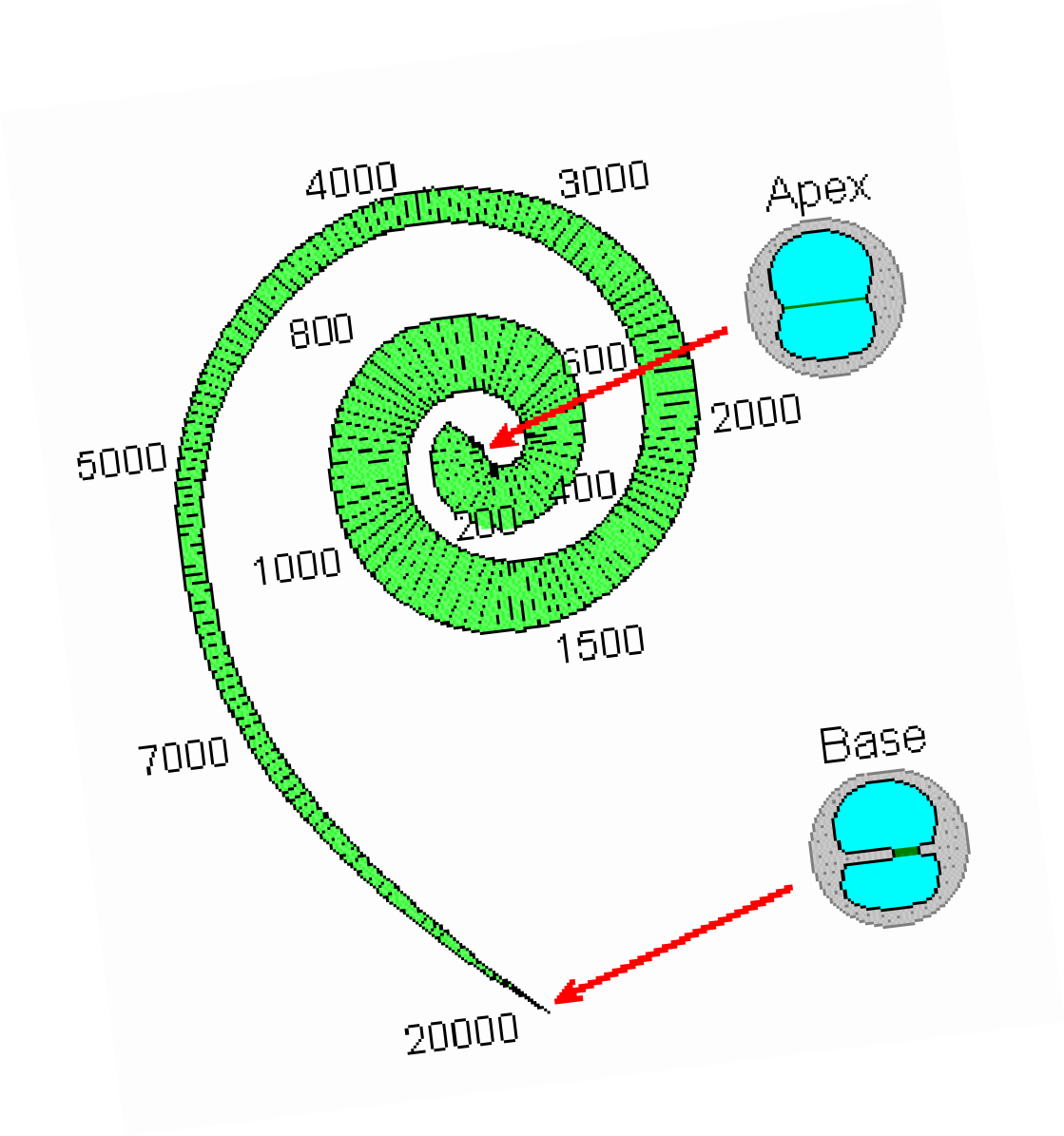
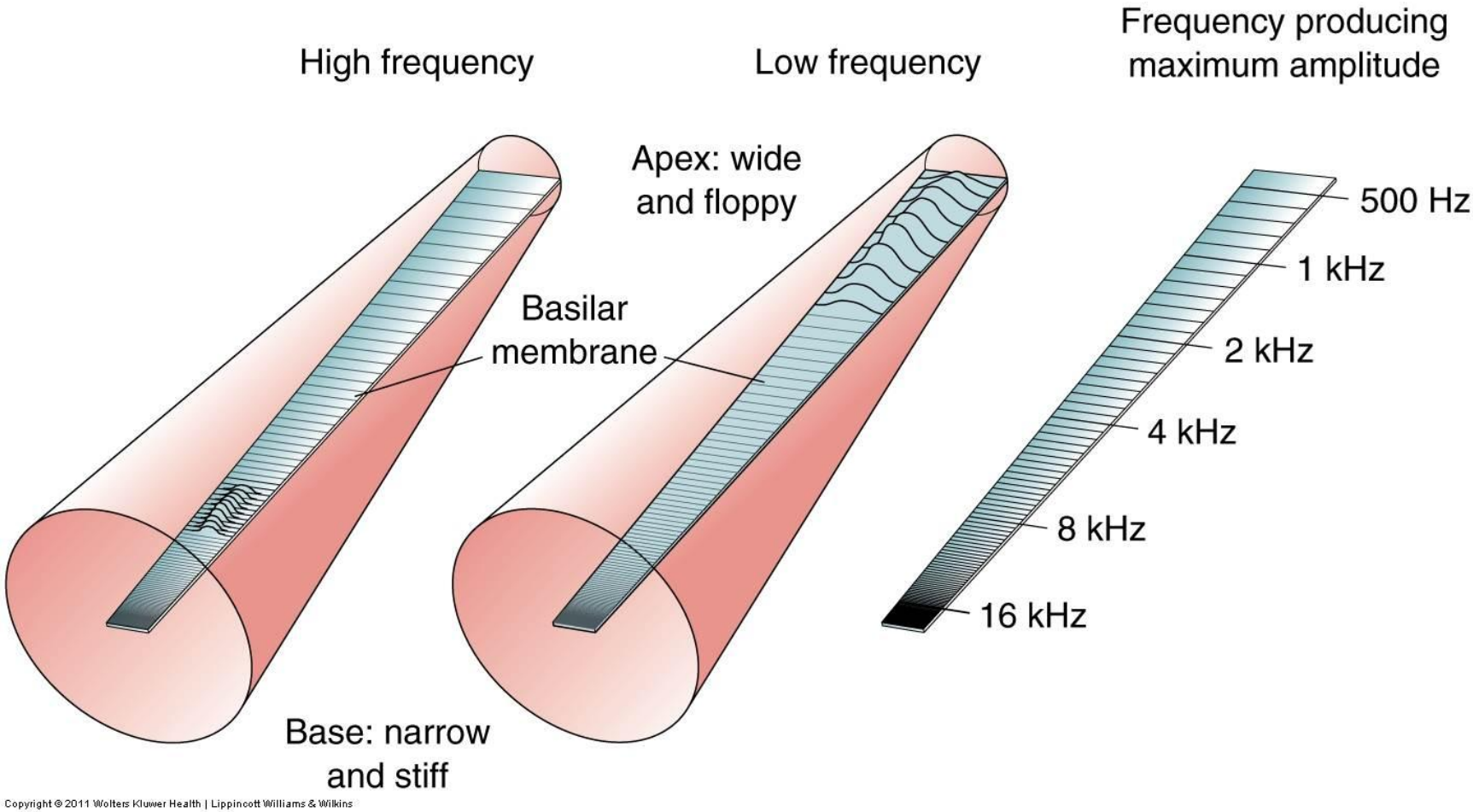
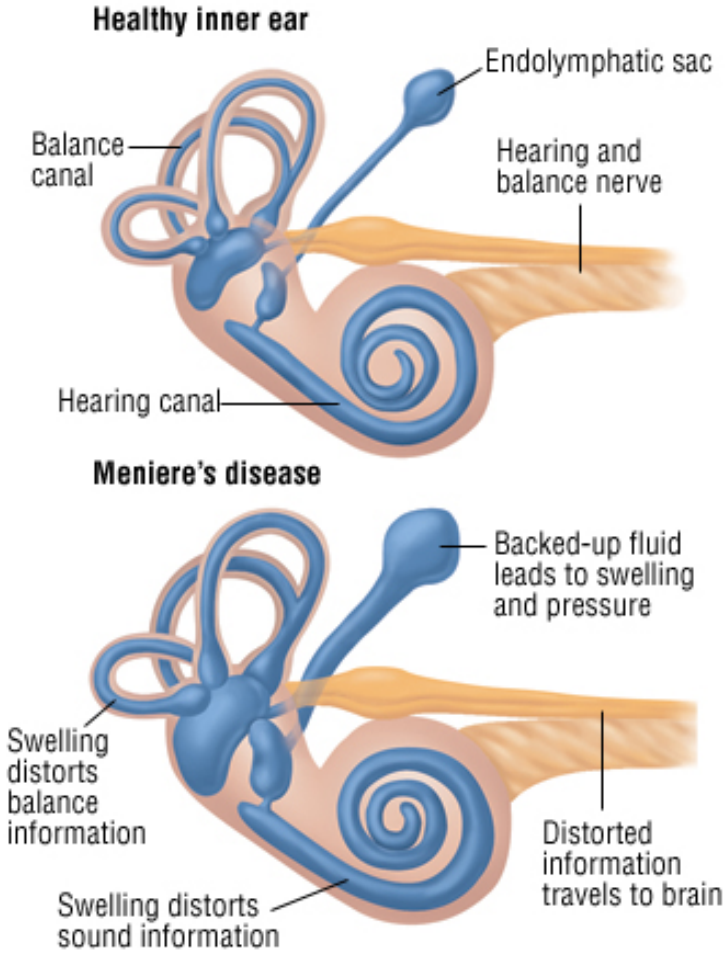

1000 Hz
2000 Hz
250 Hz
Low
Pitch
4000 Hz
500 Hz
8000 Hz
High Pitch
Low Pitch
500 Hz
High Pitch
Apical Region
Basal Region


4000
3000
Apex
800
600
2000
5000
400
200
1000
1500
7000
Base
20000

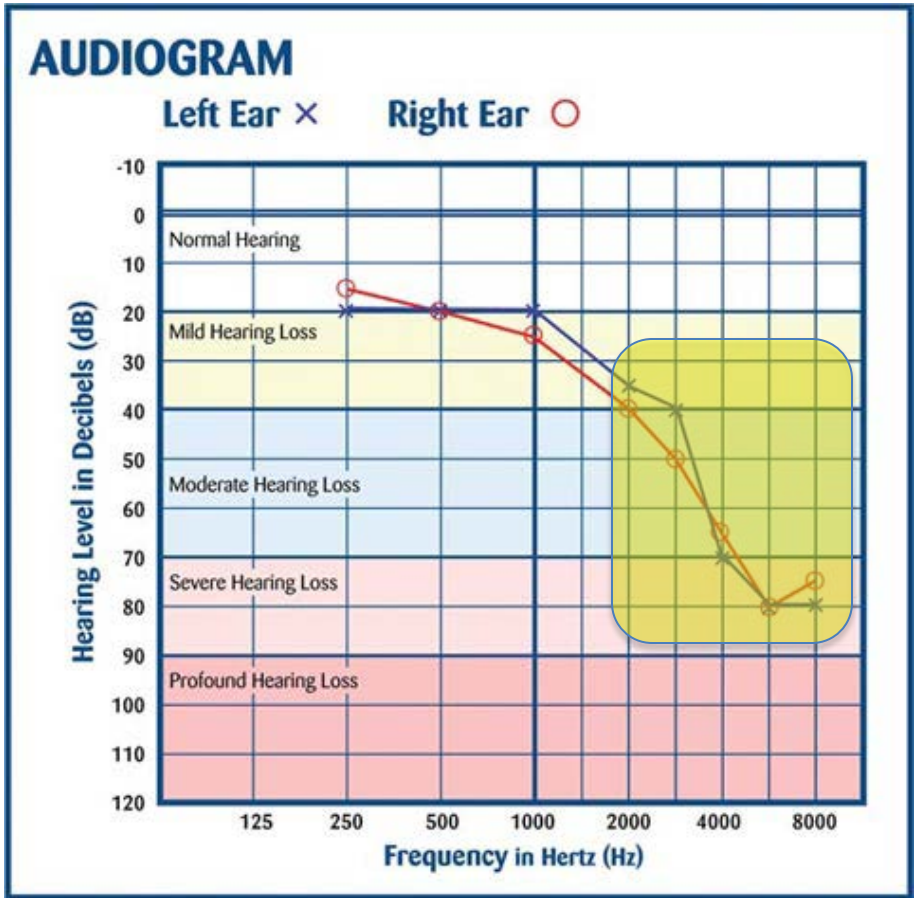
Differences in cochlea base to apex



Pathophysiology of Meniere's



Added complication: Age-related hearing loss



Symmetrical

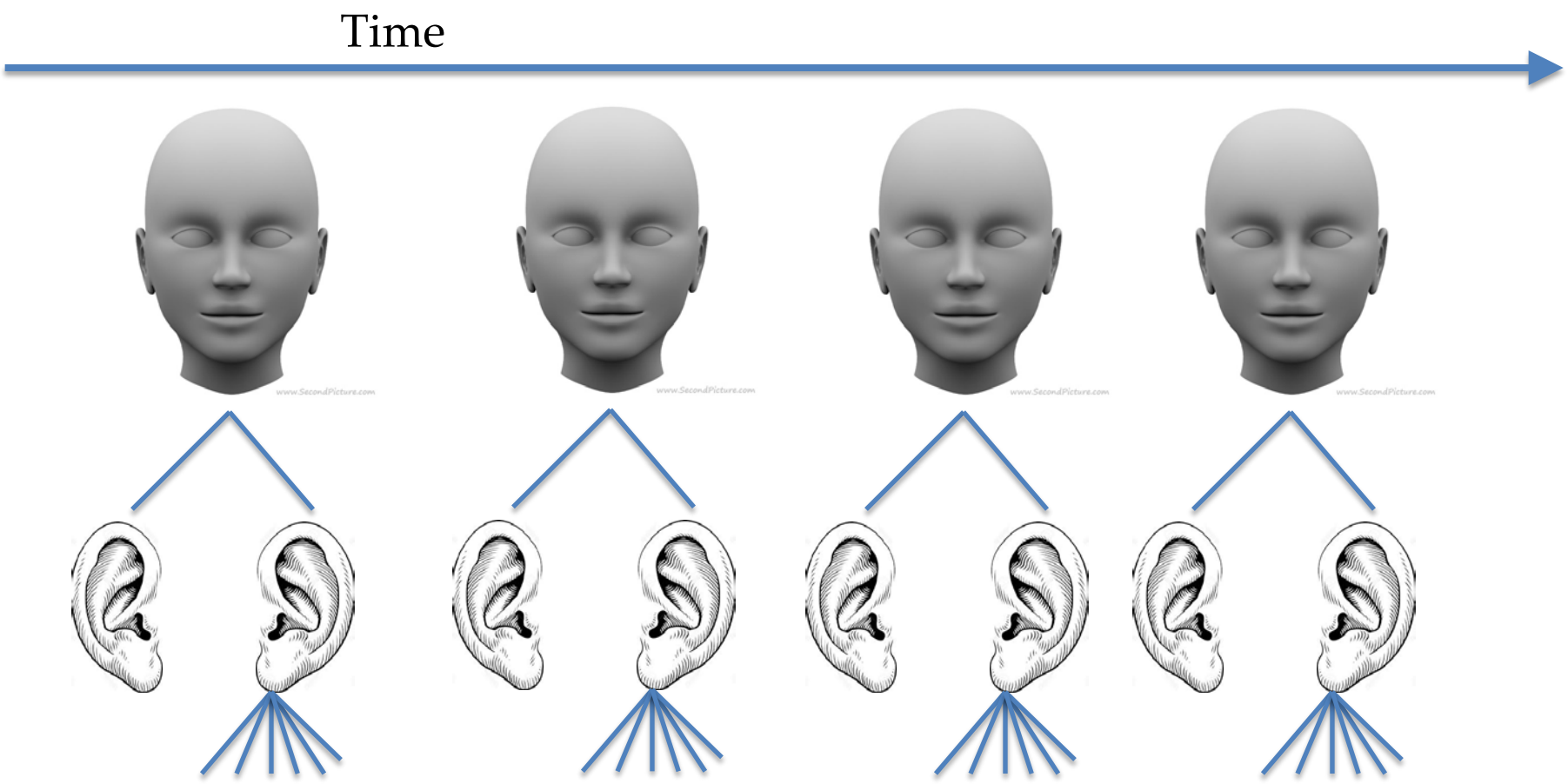
Research questions

- Low frequency affected by disease ONLY
- High frequency affected by age
- Or is high frequency affected by age and disease?

The Data

Data Cleaning

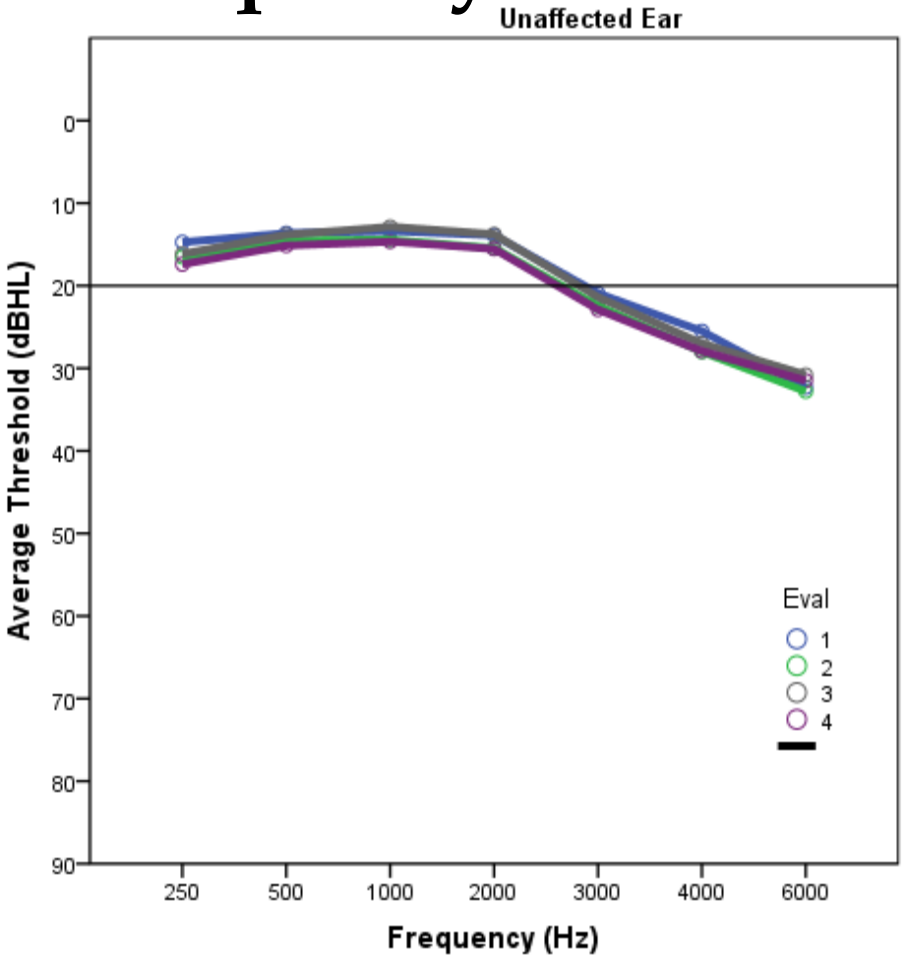
- Collected in 2 waves
- Clinical capture of data
  - Selected evaluations no more than 6 months apart
  - The highest frequency not measured consistently
  - Profound hearing loss (threshold >90 dBHL at any frequency)—coded as missing
  - Unilateral Meniere's patients only

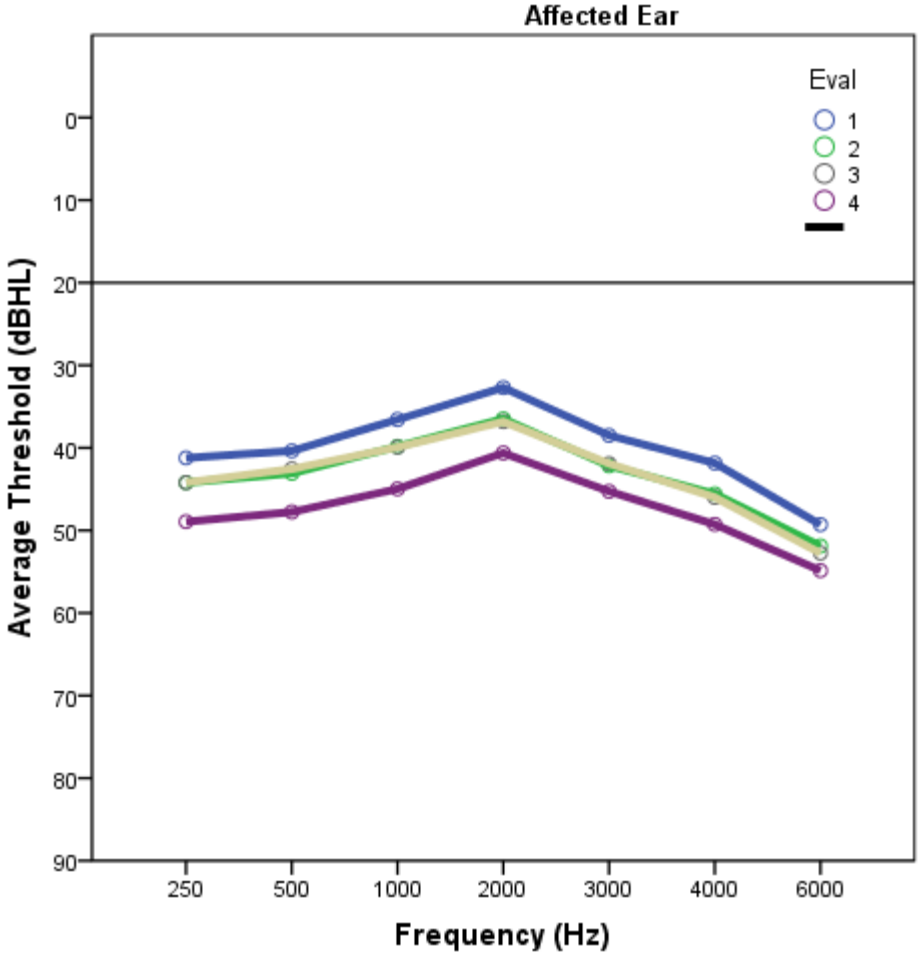

Time
Frequencies

Sample characteristics

- n=246 (unilateral)
  - 127 (52%) F, 119 (48%) M
  - Age, first evaluation: 49.6 (SD=12.7 years)
  - Word recognition score: 100%
  - Diagnosed with allergy 98 (40%)
  - 103 had up to 7 evaluations
    - Over 5 years

Raw averages across Evaluation and Frequency





Association of Age by Frequency

Unaffected Ear

Pearson Correlation

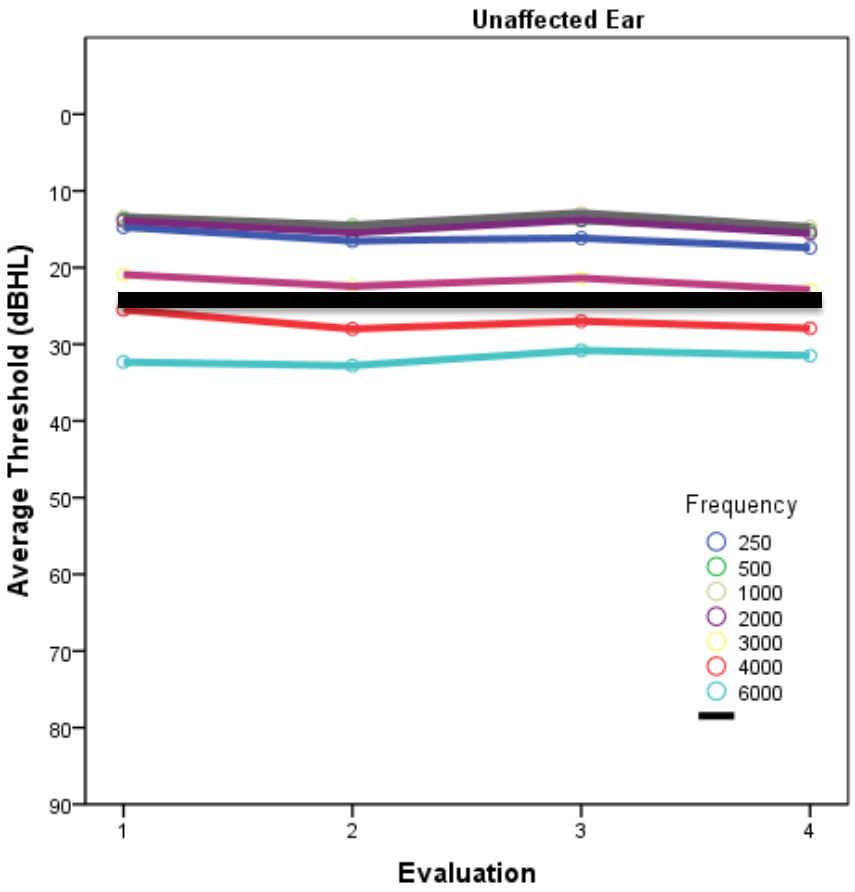
	age	f250	f500	f1k	f2k	f3k	f4k	f6k
age	1	.227**	.246**	.283**	.310**	.378**	.416**	.410**

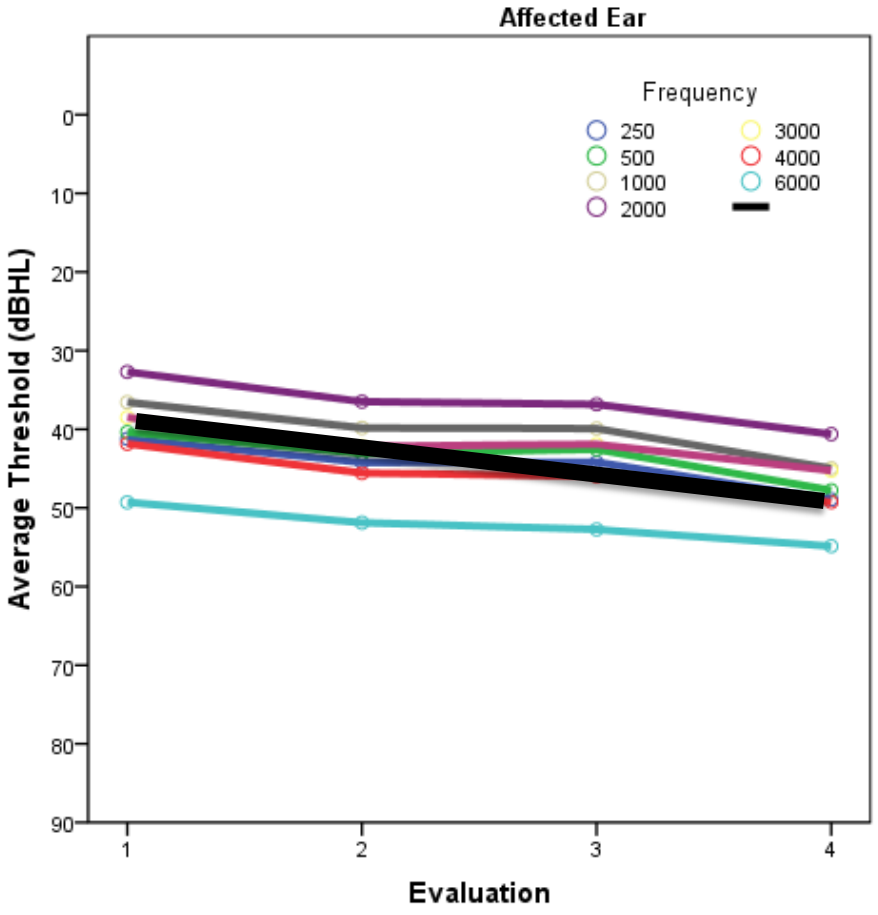
Affected Ear

Pearson Correlation

	age	f250	f500	f1k	f2k	f3k	f4k	f6k
age	1	.166**	.150**	.185**	.279**	.340**	.379**	.394**

By Frequency





Mixed Model

Null

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Repeated Measures	AR1 diagonal	204.481122	8.116542	25.193	.000	189.176059	221.024422
	AR1 rho	.652969	.014554	44.866	.000	.623512	.680575
freqN [subject = ID * earT]	Variance	485.204016	16.260746	29.839	.000	454.357695	518.144492

a. Dependent Variable: thrsh.

With Fixed

Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Repeated Measures	AR1 diagonal	141.938039	3.977222	35.688	.000	134.353018	149.951280
	AR1 rho	.520044	.014449	35.992	.000	.491156	.547789
freqN [subject = ID * earT]	Variance	304.109023	9.687282	31.393	.000	285.702862	323.700984

a. Dependent Variable: thrsh.

The Analysis

Analysis

- Descriptive questions
  - Change in level (intercept) or pattern across evaluation (slope) ?
  - Groups of similar patterns of change in low and high frequencies over time?
  - Within a group, are low and high frequency changes associated? I.e., the entire cochlea is affected by disease?
  - Demographic characteristic differences by group?

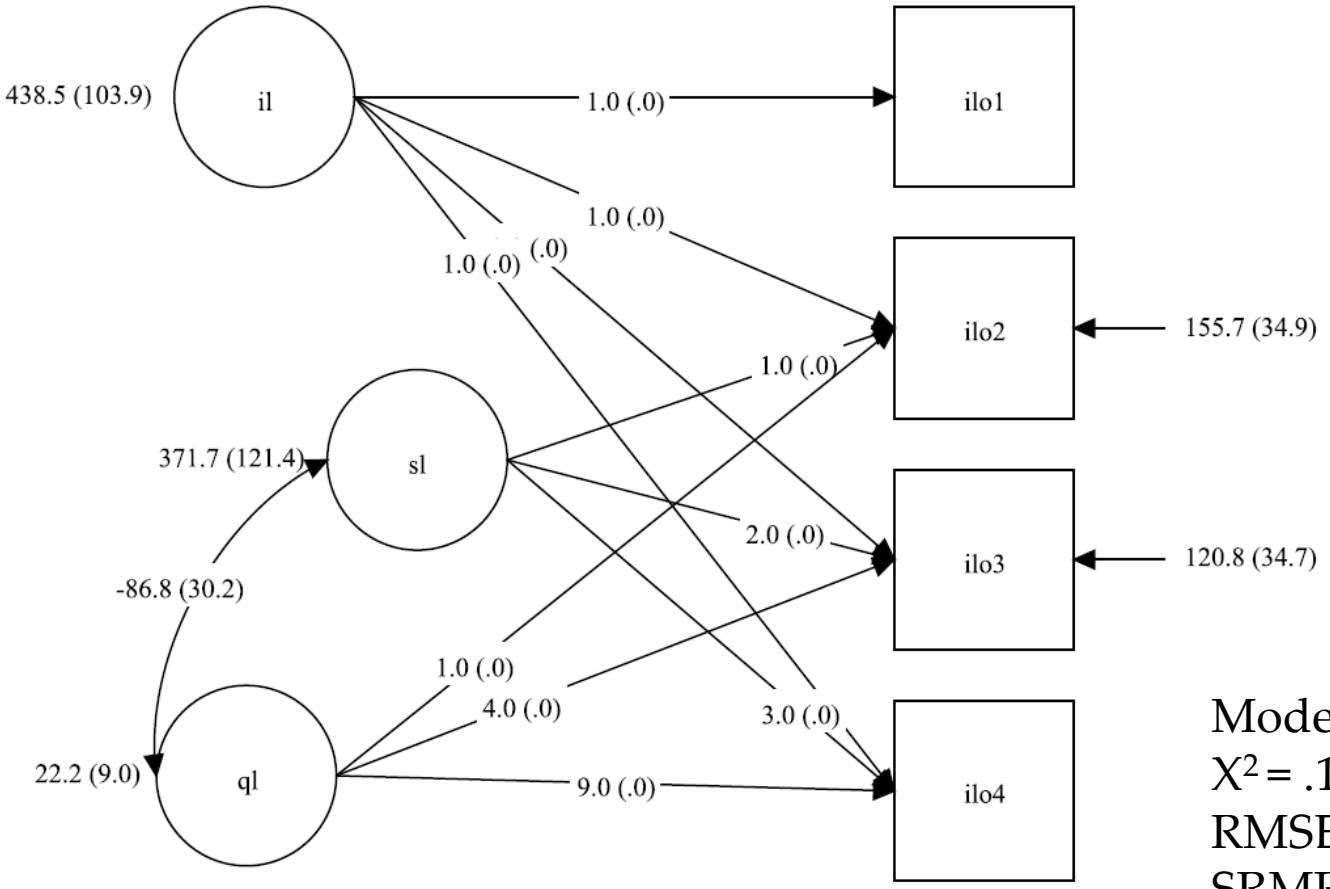
Dimension reduction

- Appears that in the non-diseased ear ~no change
- Modeling only diseased ear
- Created Low and High frequency variables from regressions of frequency on threshold
  - Low = 250, 500, 1000 Hz
  - High = 2000, 3000, 4000, 6000 Hz
  - Unstandardized intercepts (level)

Growth models assembled in stages

- Change in low frequency threshold
- Change in high frequency threshold
- Parallel change low and high frequency threshold
- Finally: LCA/mixture

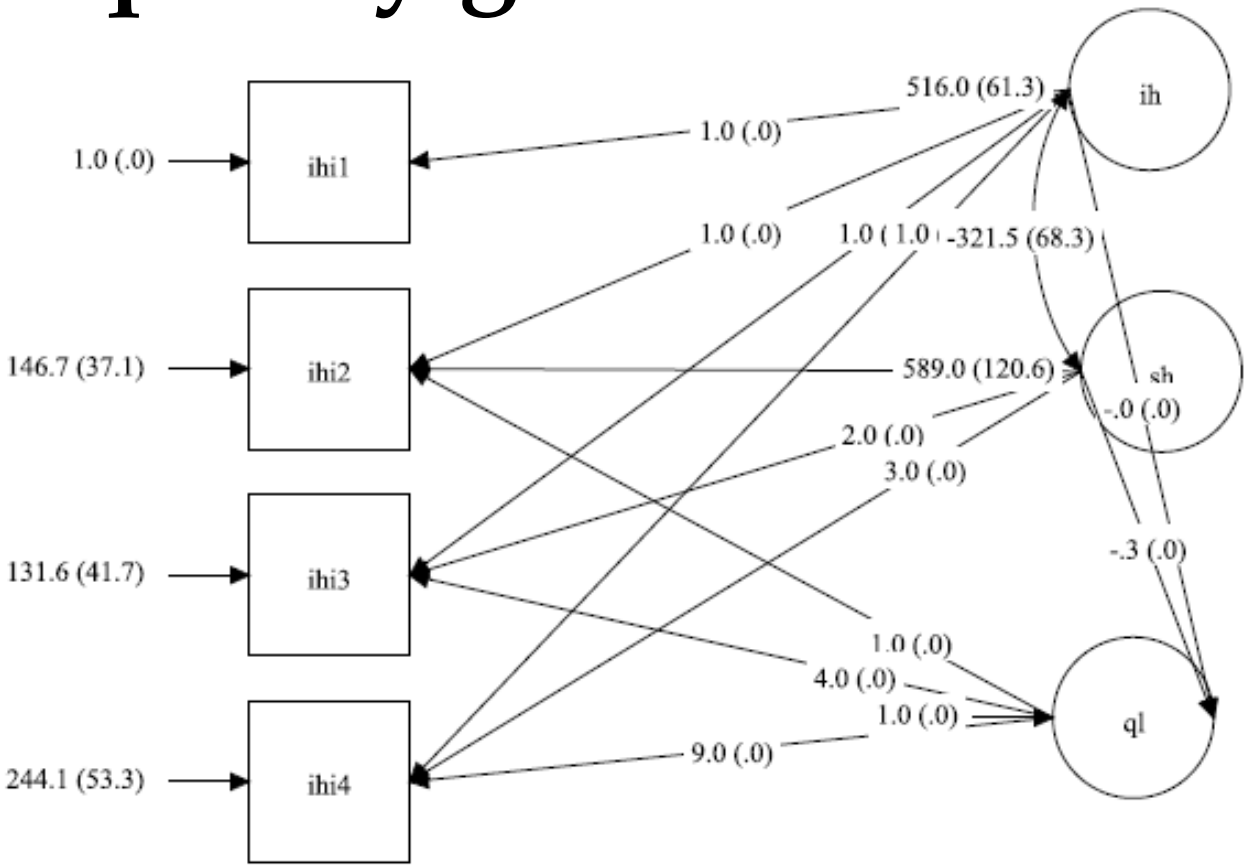
Low frequency growth



Model Fit
X^2 = .112, p=n.s.
RMSEA = .0001
SRMR = .0004

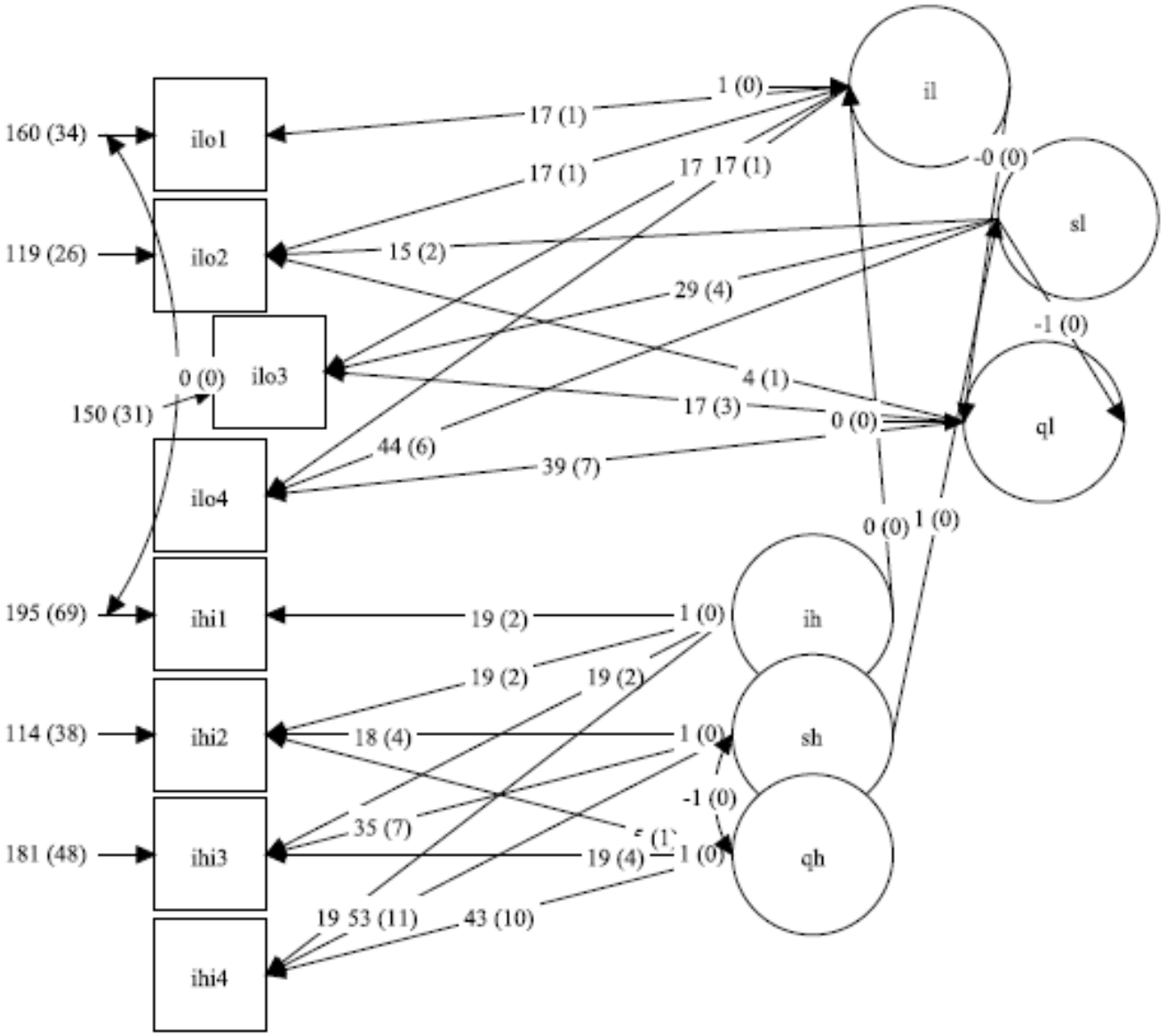
High frequency growth

Model Fit
X2=3.2, p=n.s
RMSEA=.018
SRMR=.044



Parallel Process Model

Model fit
$X^2 = 20.5$, p=n.s
RMSEA=.05
SRMR=.07



Mplus Growth Mixture Model

```
MODEL:
    %OVERALL%
    il sl | ilo1@0 ilo2@1 ilo3@2 ilo4@3;
    ih sh | ihi1@0 ihi2@1 ihi3@2 ihi4@3;
    ilo1 with ihi1;
    ilo2 with ihi2;          suggestion from Mplus discussion board
    ilo3 with ihi3;
    ilo4 with ihi4;
    il with ih@.5;
    il with sh@0;            constrained all classes to have equal loadings
    ih with sl@0;
    sl with sh;
    ih with sh@.5;
    il with sl;
    sh@1;
    [sh@0];
    ih@1;
```

Selecting number of classes

		Classification probabilities				
Class	BIC	1	2	3	4	5
3 class	10482	.93	.92	.93		
4 class	10466	.83	.82	.91	.93	
5 class	10468	.88	.94	.73	.610	.772
Entropy				.815	.772	.745
k-1 test				p<.00001	p<.00001	p<.00001

6 class solution not significantly different from the 5 class

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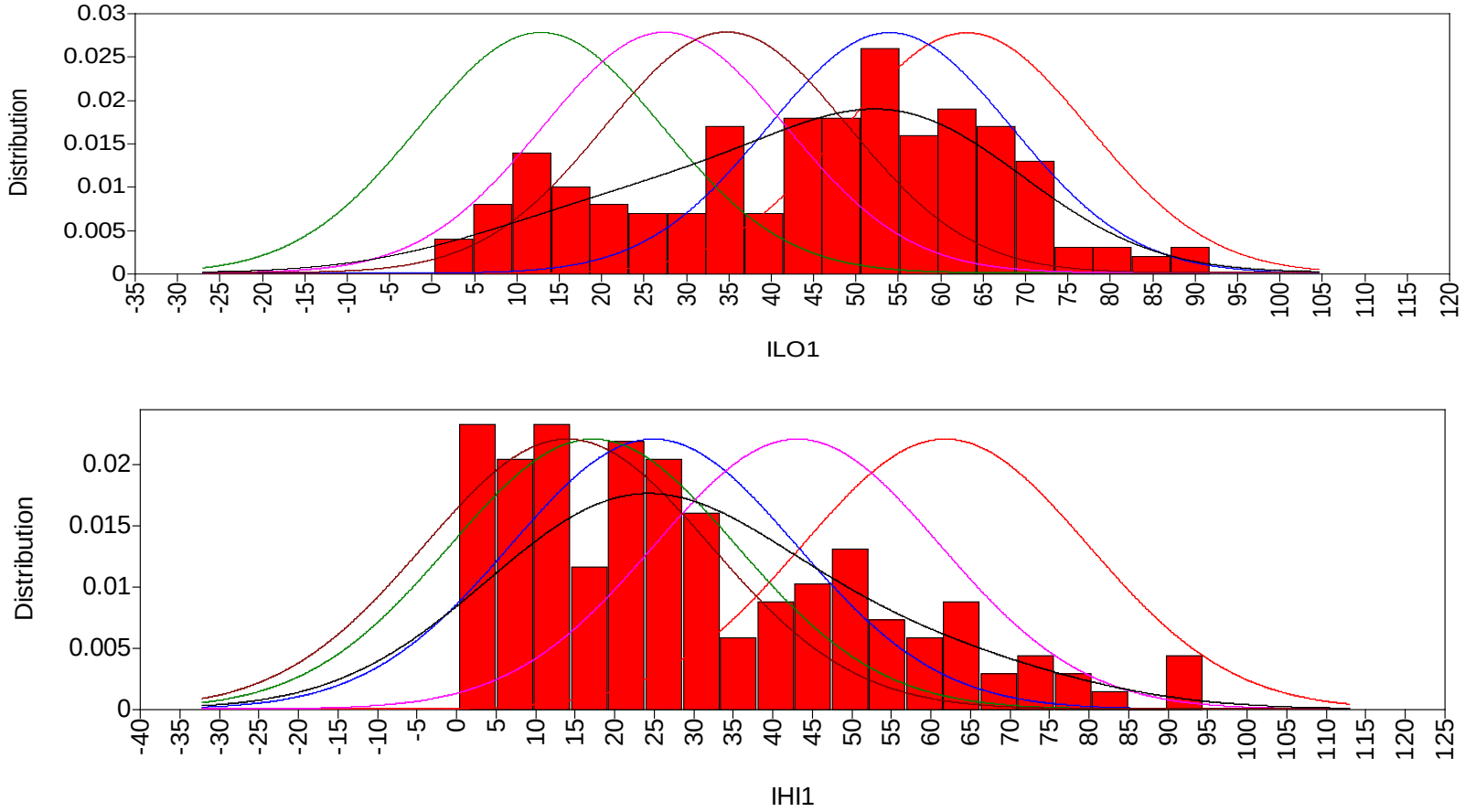
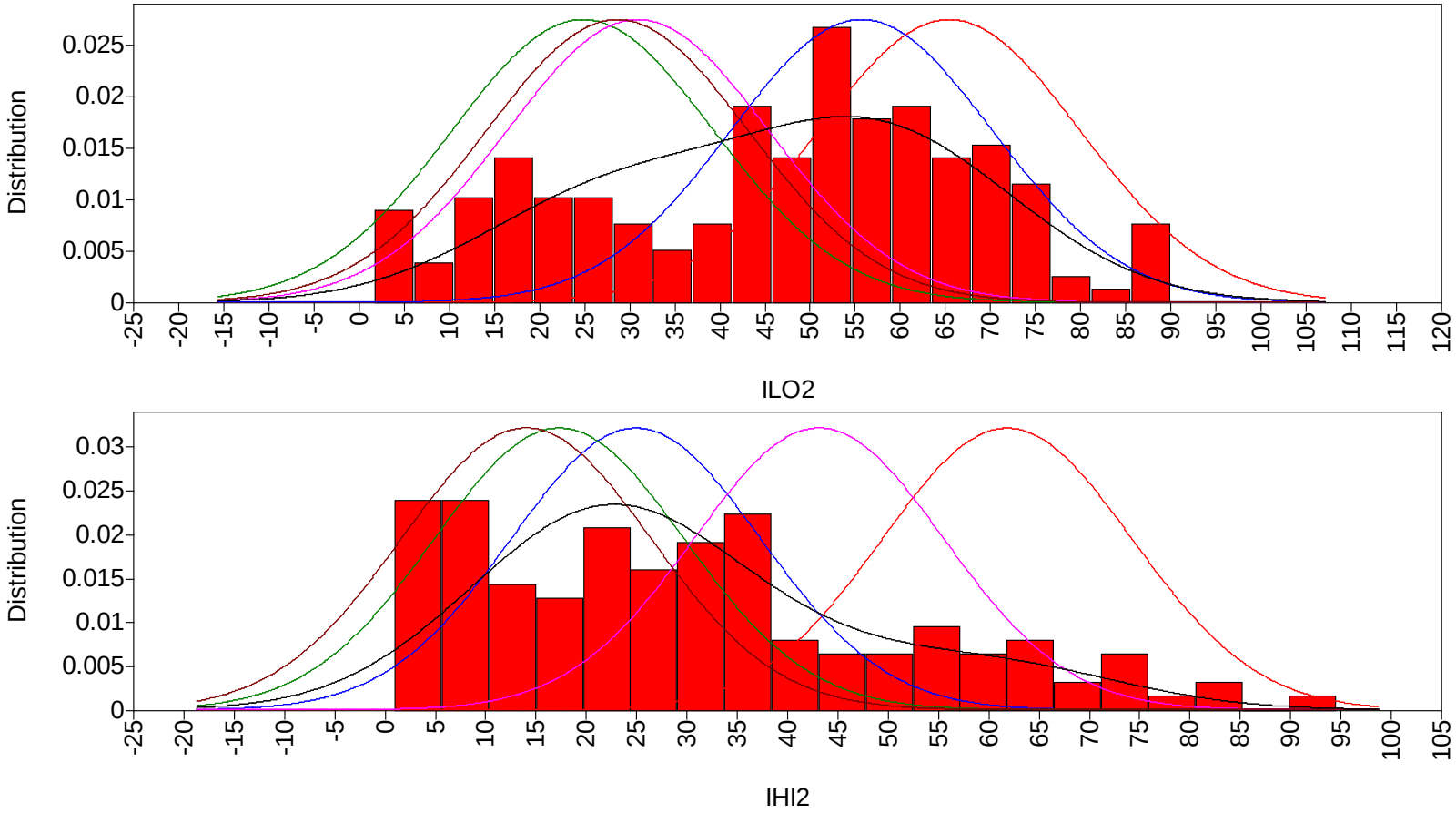
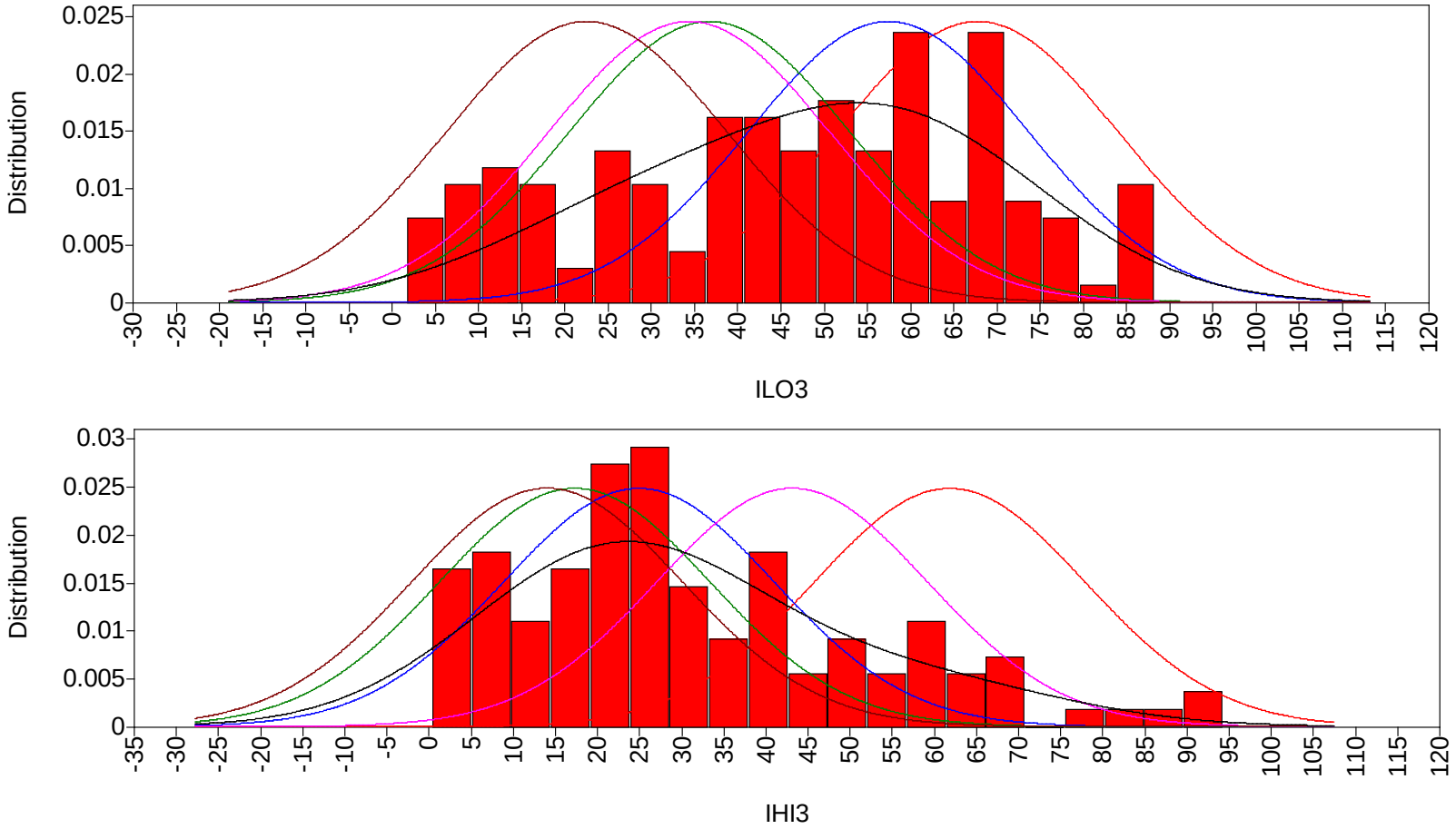
5 Class distributions Eval 1



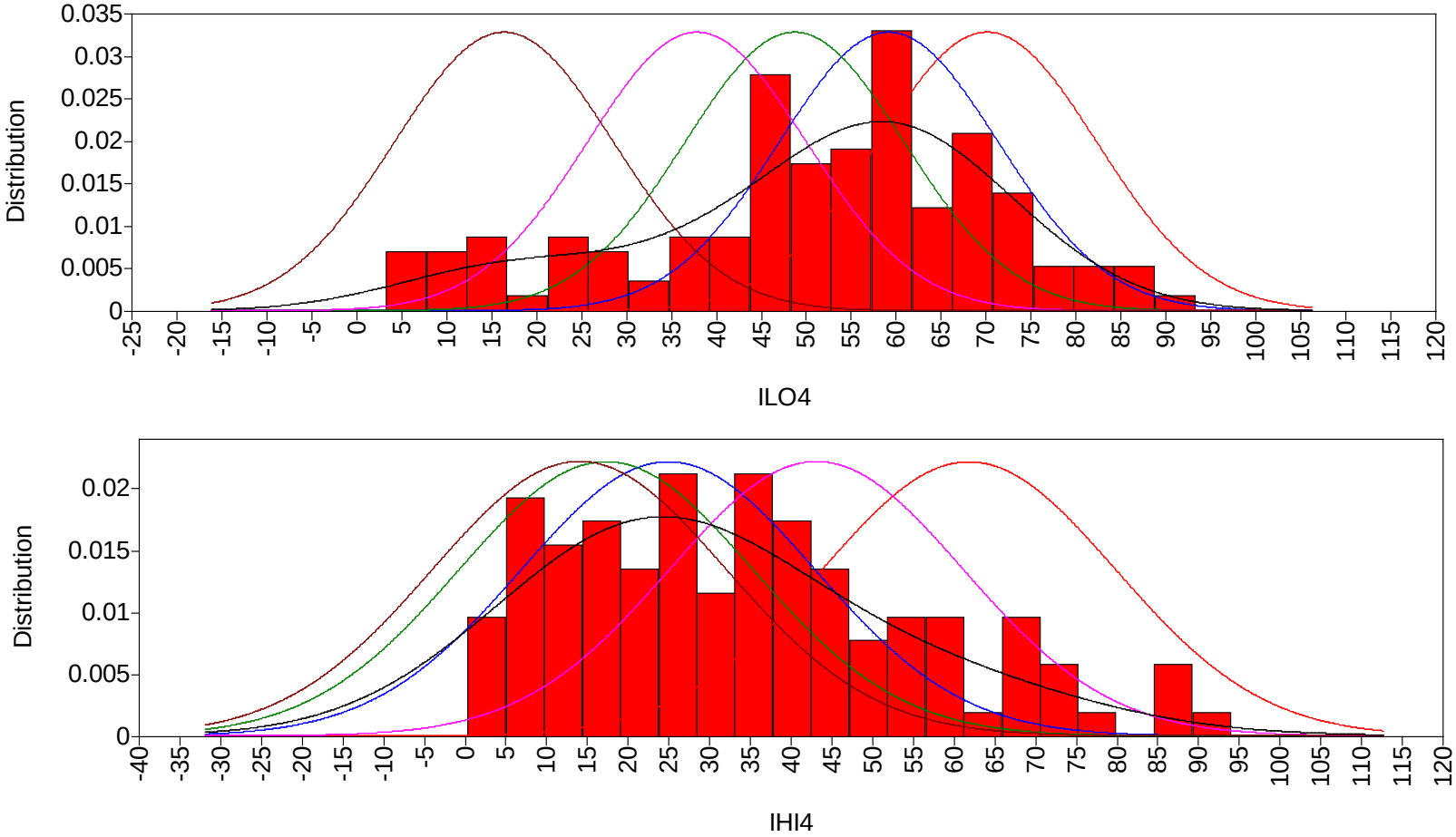
5 Class distributions Eval 2



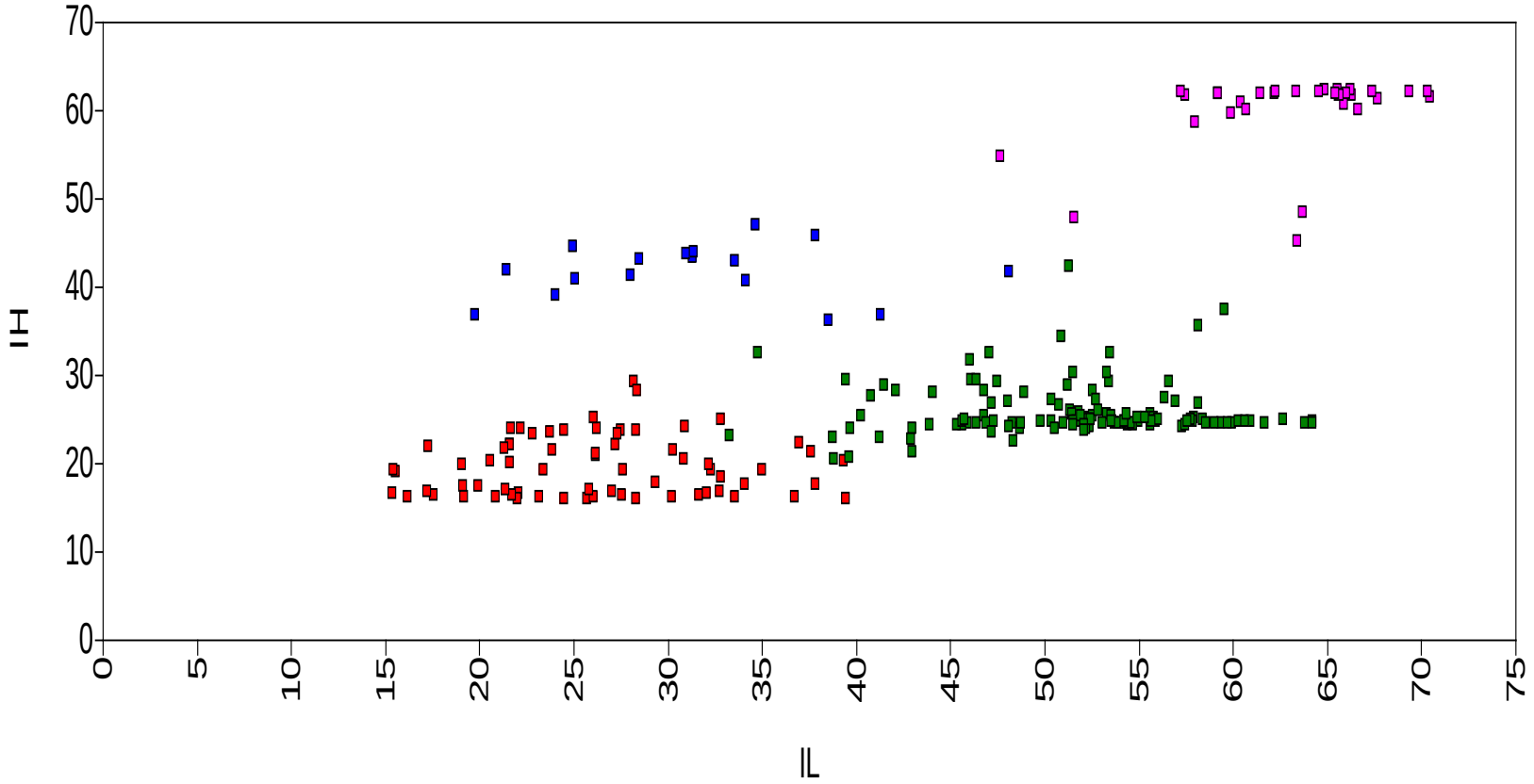
5 class distributions Eval 3



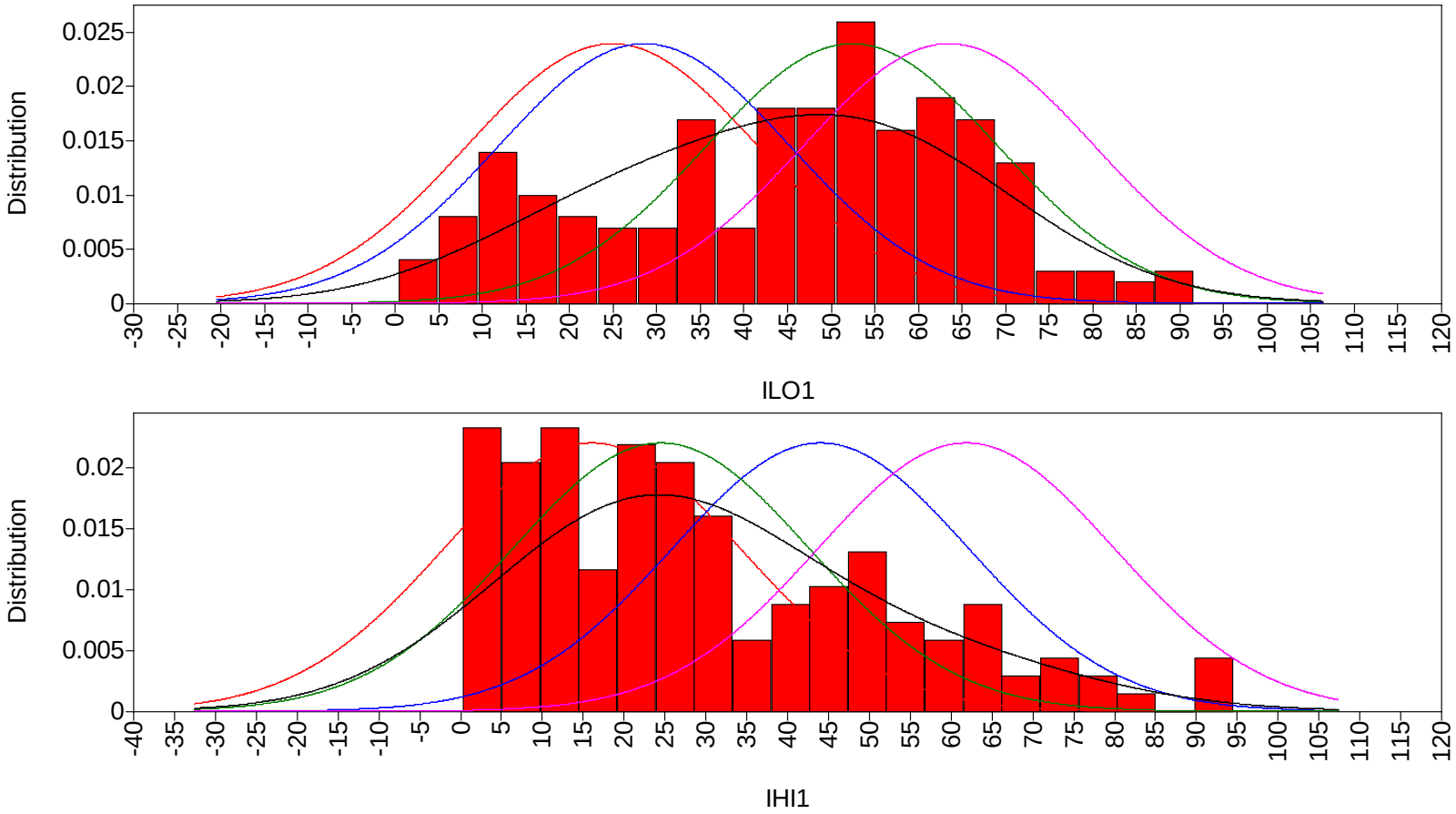
5 class distributions Eval 4



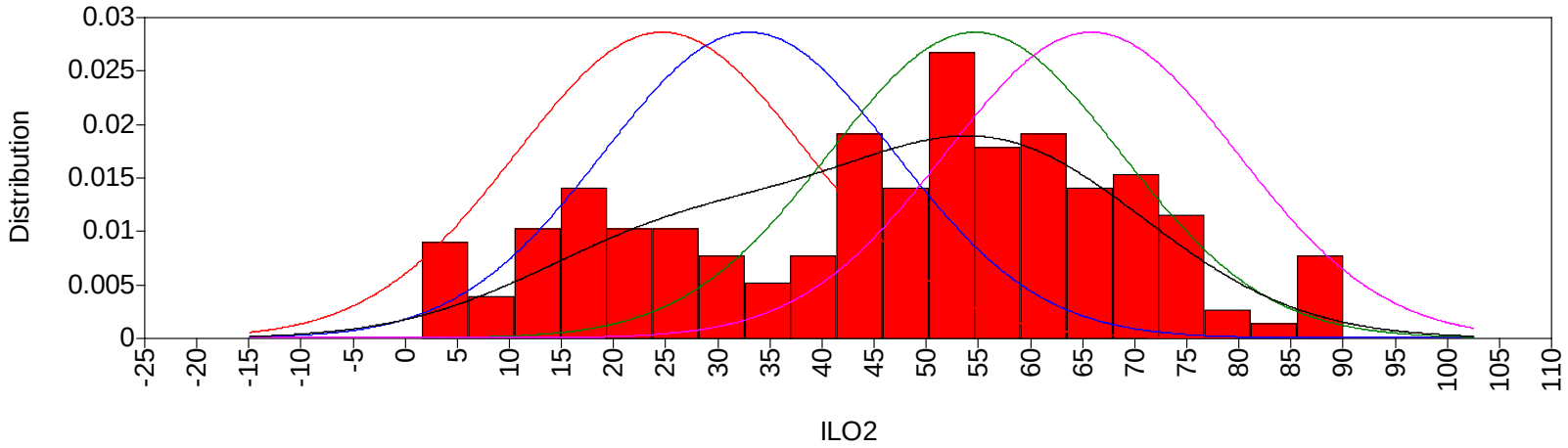
4 Class Low Frequency Factor Scores

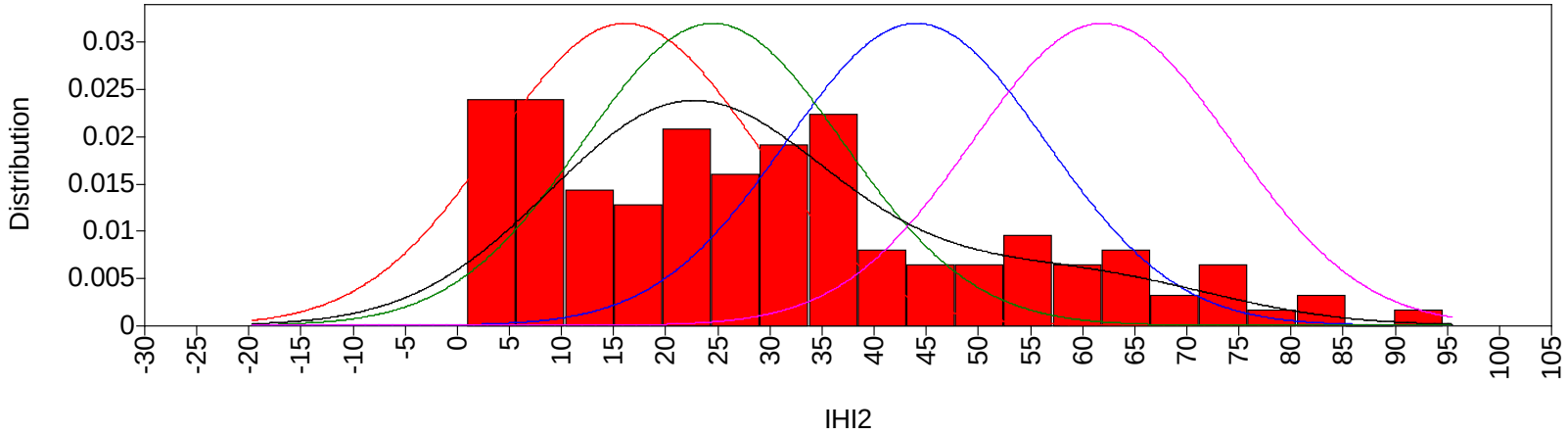


4 Class distributions Eval 1

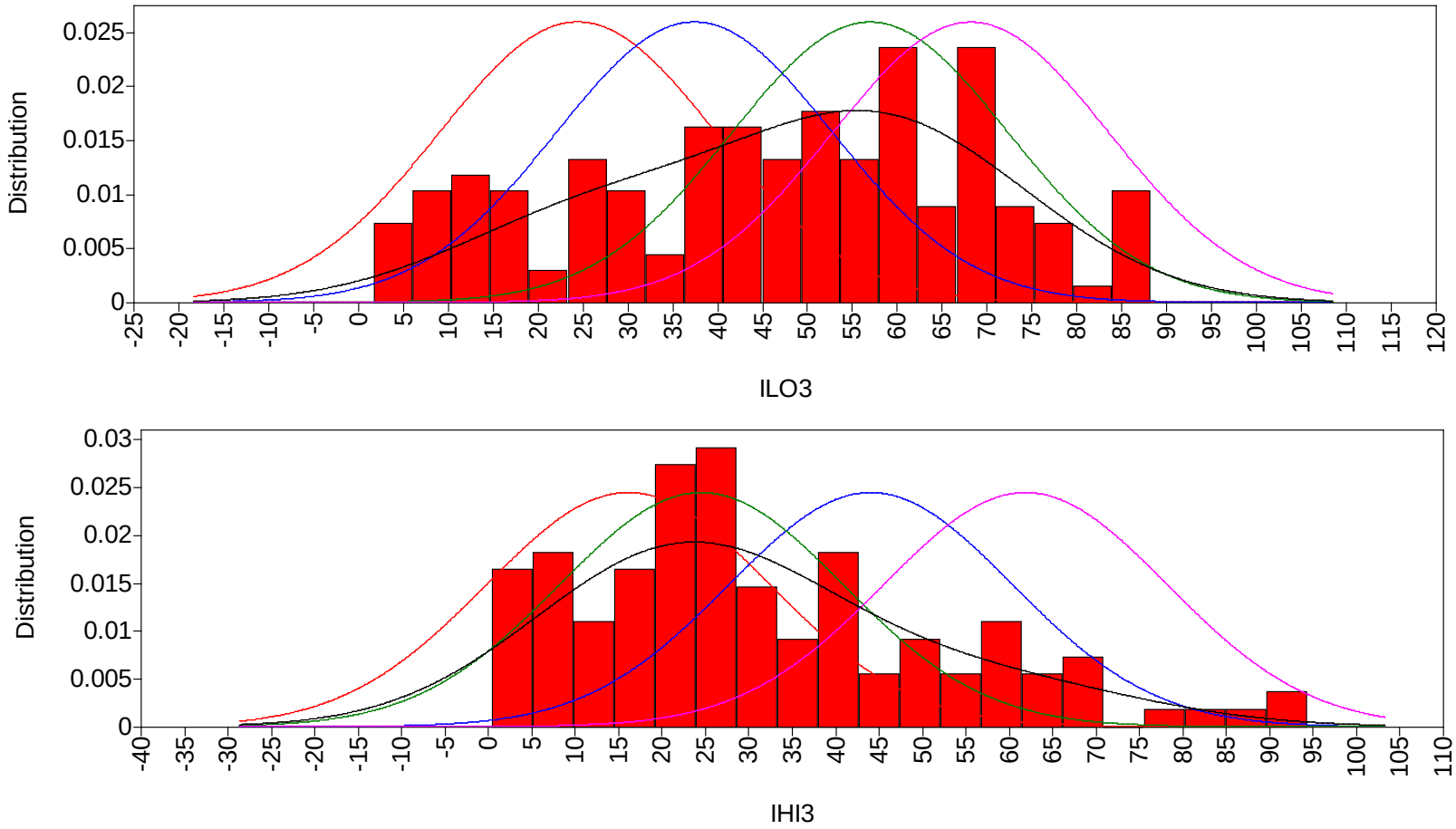


4 Class distributions Eval 2

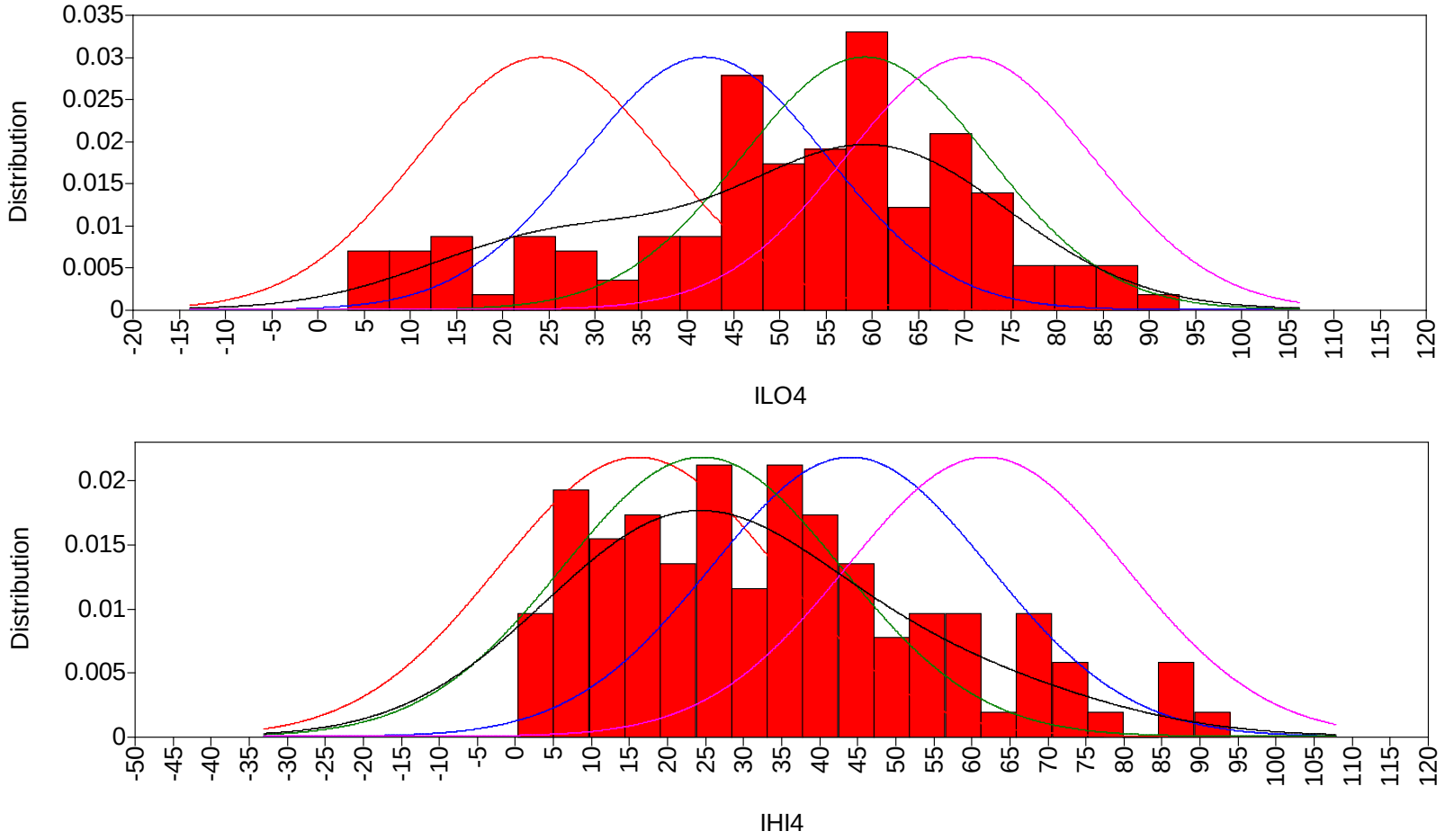




4 Class distributions Eval 3



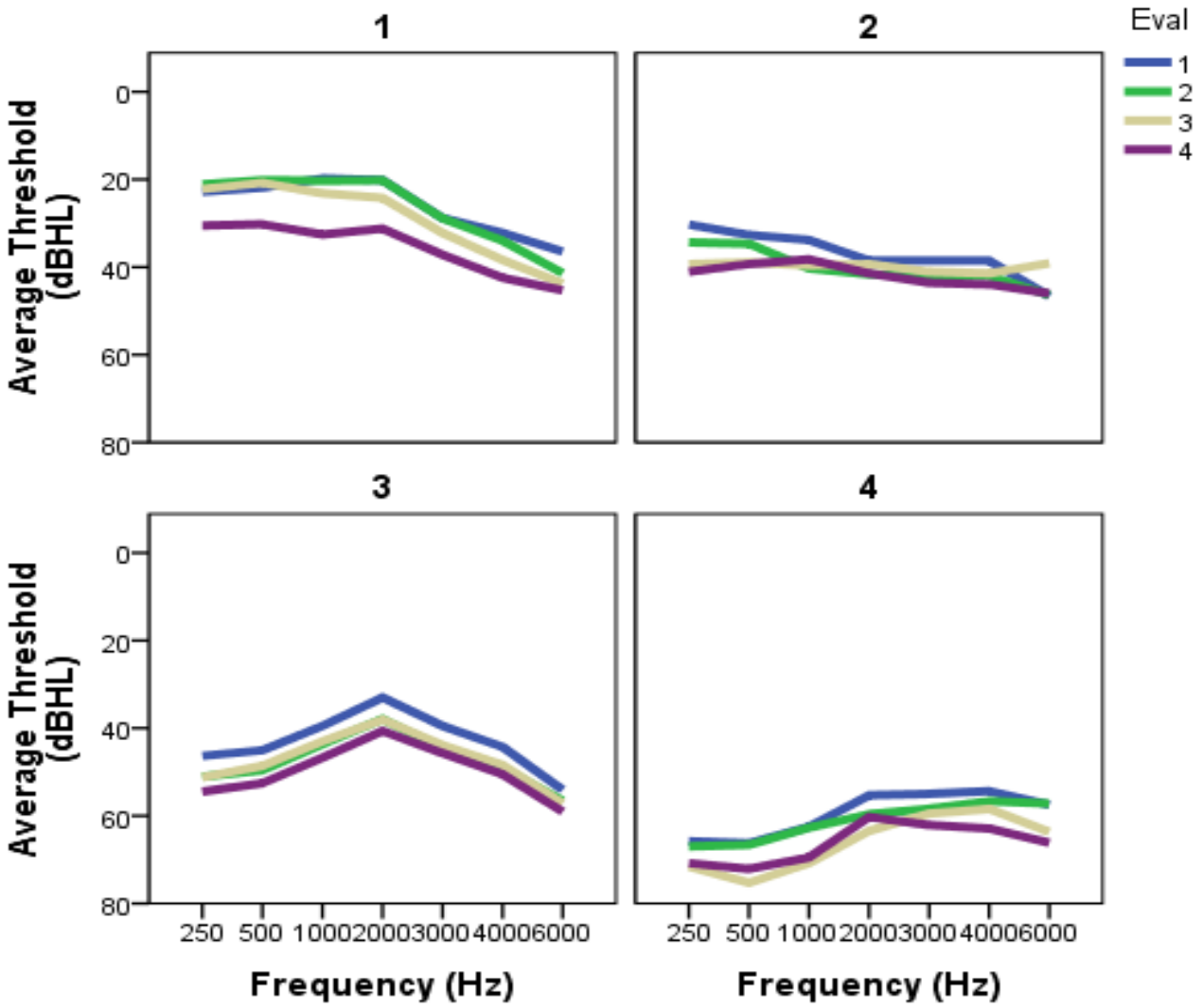
4 Class distributions Eval 4



4 class model

Class size

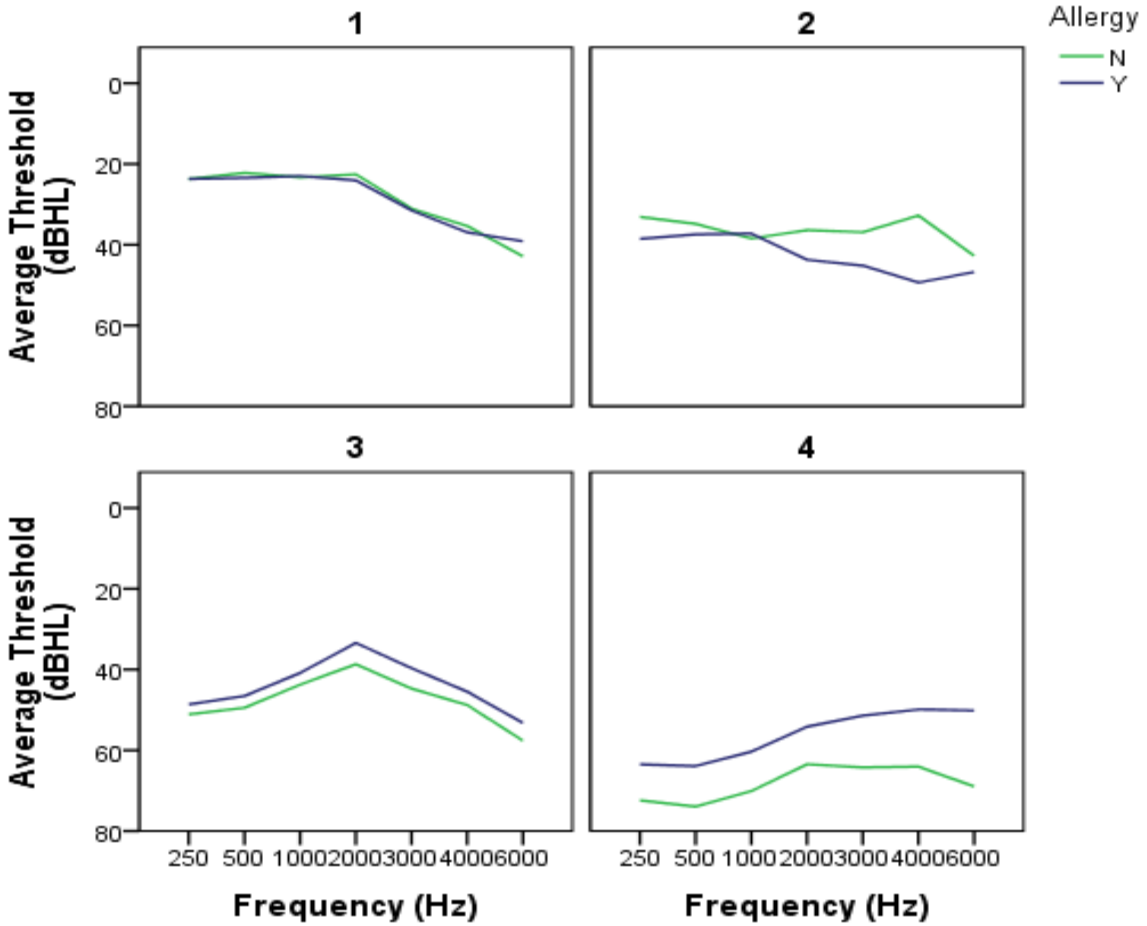
1	17	7%
2	32	13%
3	128	52%
4	68	28%



4 Class Demographics

Hearing Class	Age (years)	Sex	Allergy (N,Y)
1 Best	49.6	47% M/53% F	53% N/47% Y
2	48.7	29% M/71% F	47% N/53% Y
3	54.3	51% M/49% F	66% N/34% Y
4 Worst	47.6	50% M/50% F	56% N/44% Y

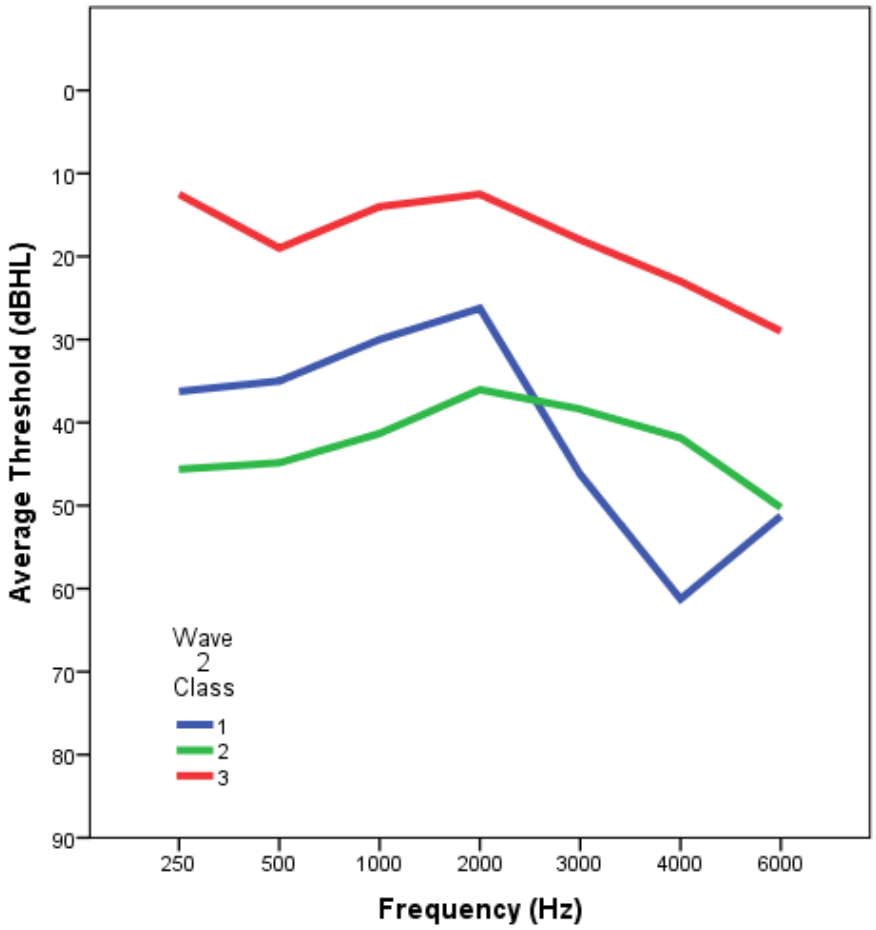
Allergy diagnosis/treatment by Class



Wave 2

- Two evaluations
- Need more evaluations to confirm the 4 class solution

Wave 2: 3 Class solution



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  - Groups of similar patterns of change in low and high frequencies over time? YES
  - Within a group, are low and high frequency changes associated? I.e., the entire cochlea is affected by disease? YES
  - Demographic characteristic differences by group? YES

Challenges to conventional understanding of Meniere's

- No one path of disease progression for hearing
- Parallel growth model suggests the entire cochlea is involved
  - Follows the cochlear pathology
- Class with poorest hearing youngest patients
  - More aggressive disease?

Challenge to conventional understanding of Meniere's

- Allergy diagnosis/treatment actually has a protective affect on hearing for 2 classes of hearing loss
- Supports controversial immunological hypothesis
- LCA revealed salient subtypes of the disease
  - Targeted treatments

In Memoriam

John K. Niparko, MD