Getting to grips with the real issues in OME

# Behaviour sequelae of OM(E): some new looks at an old issue

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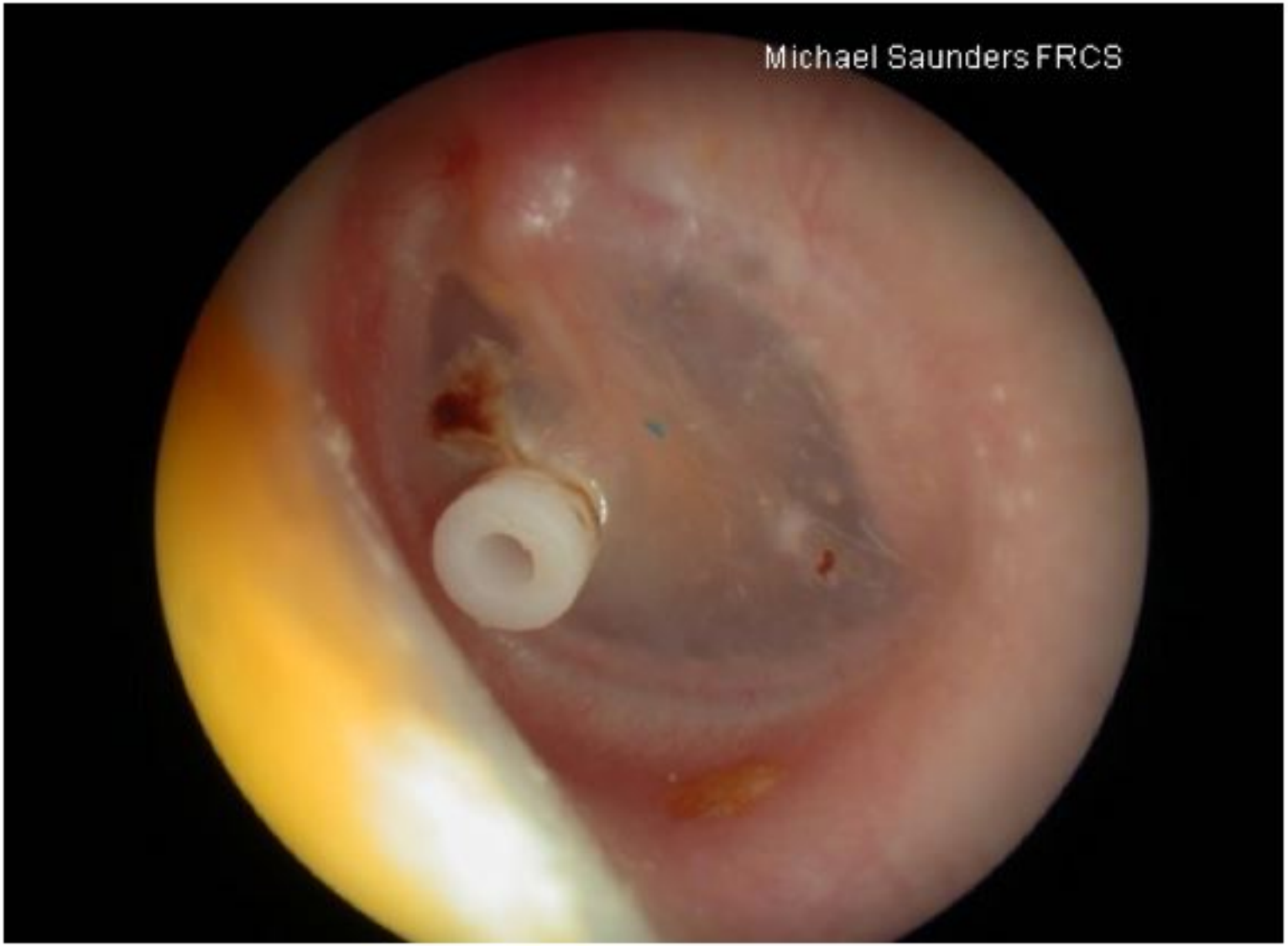
UNIVERSITY OF CAMBRIDGE 800 YEARS 1209–2009

# Appropriate OME/RAOM cases for treating by ventilation tubes: issue is still unclear



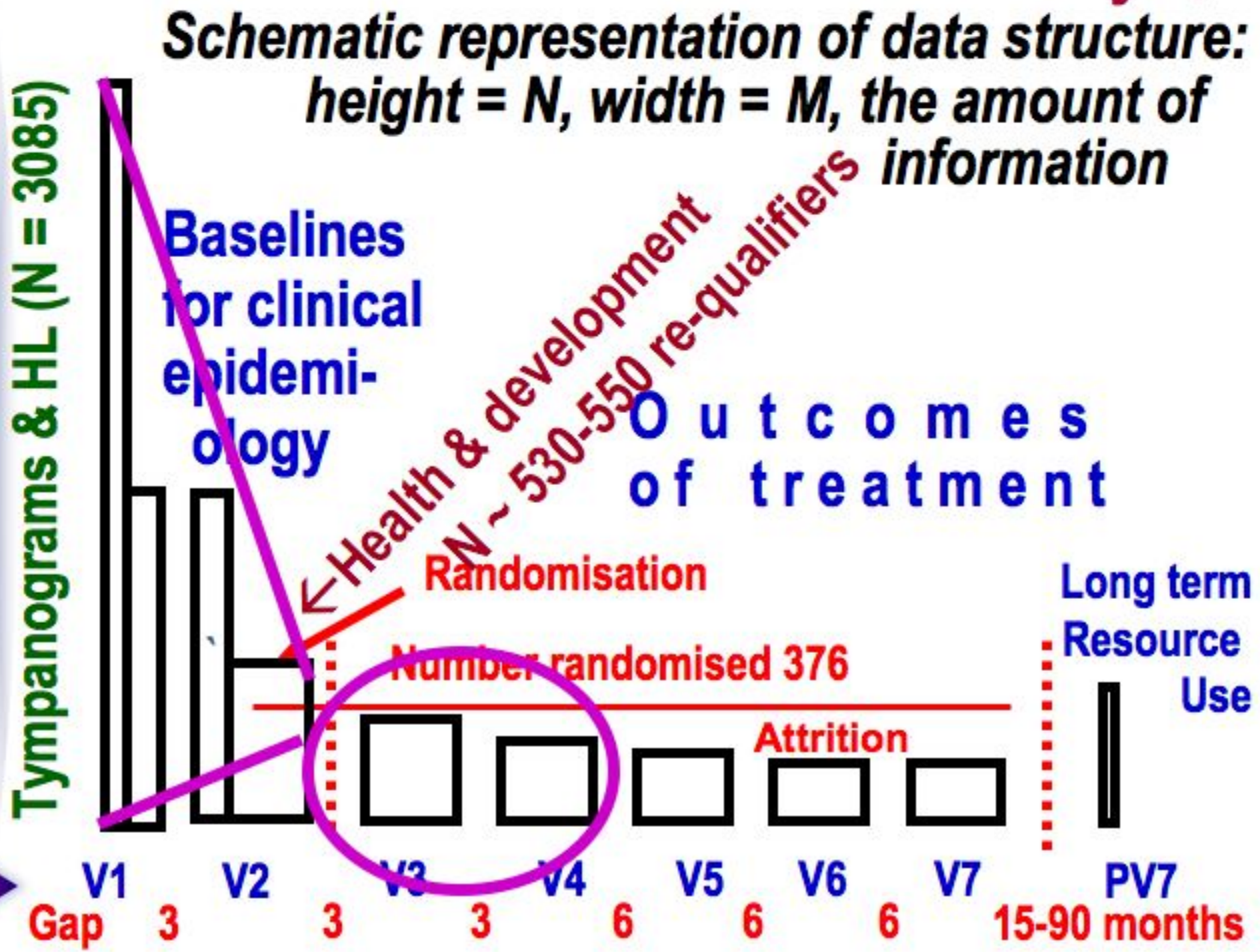
# The Holy Grail of OME treatment research (as endorsed by last Cochrane Review)

## Evidence-based indicators

***Aka*** **effect modifiers**
***Aka*** **predictors of benefit**
***Aka*** **statistical interactions with treatment**
***Aka*** **clinical sub-groups**

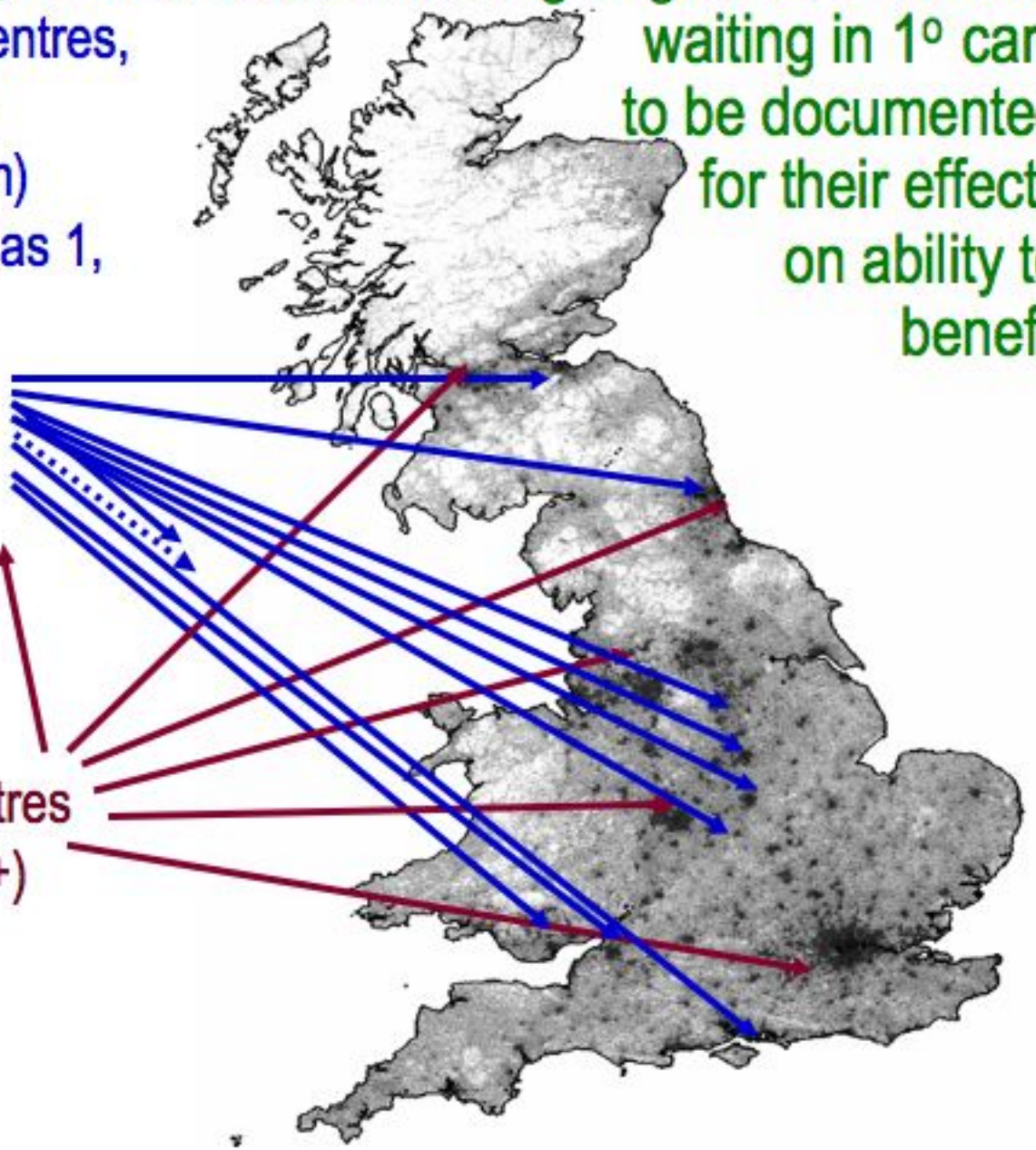
**Essentially, a difference between two differences, or diverging regressions, which**

# TARGET database as a vehicle for many Qs



## Geographical spread enabled differing degrees of watchful waiting in 1° care to be documented for their effects on ability to benefit

10 randomising centres,
all medium-large
cities (0.25-0.75m)
(Belfast analysed as 1,
but can be seen
as 2 centres for
some purposes)



+ 6 further
baseline clinical
epidemiology centres
3 large cities (1m+)
1 medium-large
1 rural
1 suburban

# ~10dB range in caseload averages at 1st visit !

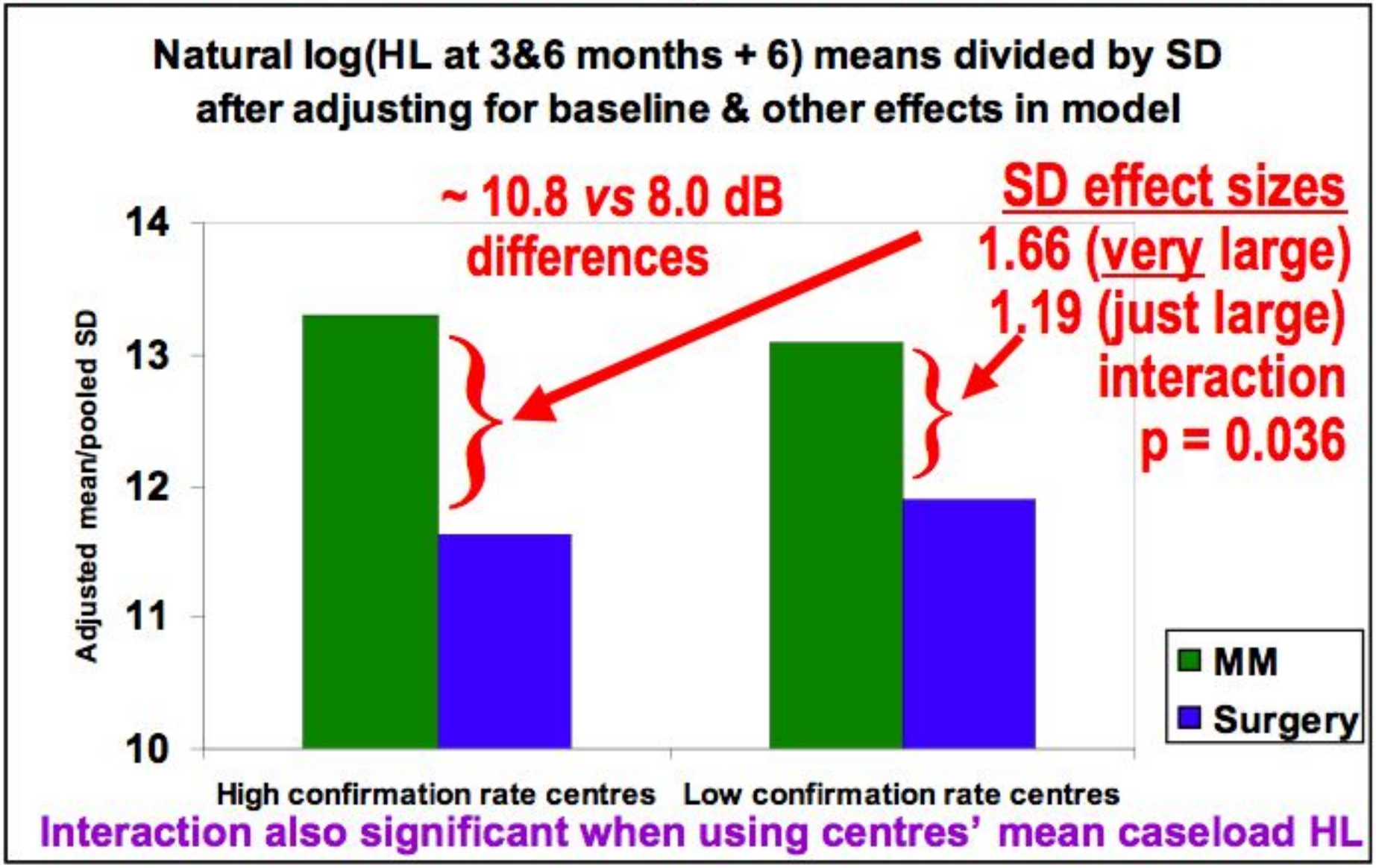
## High correlation of means of HL & ACET* (adj for season, source & delay)

| Centre | Mean ACET* | Mean HL | Diffs > 2dB |
|---|---|---|---|
| 1 Glasgow | 29.555 | 30.823 | |
| 2 Belfast | 25.497 | 25.366 | |
| 3 Birmingham | 28.477 | 24.630 | HL lower |
| 4 Bristol | 28.965 | 31.217 | HL higher |
| **5 Leicester** | **30.431** | **31.733** | |
| 6 Manchester | 27.095 | 27.777 | |
| 7 Nottingham | 25.075 | 25.960 | |
| 8 Sheffield | 28.035 | 28.490 | |
| 9 Newcastle | **24.657** | **24.116** | |
| **10 Coventry** | **24.723** | **30.791** | **HL 6dB higher** |
| 11 Edinburgh | 26.517 | 29.391 | HL higher |
| 12 Cardiff | 25.355 | 28.454 | HL higher |
| 13 Portsmouth | 28.181 | 26.505 | |
| 14 Sunderland | 21.646 | 21.464 | |
| 15 Epsom | 25.948 | 21.395 | HL lower |
| **16 Enniskillen (Tyrone)** | **21.413** | **19.076** | HL lower |

N=2698 with all data required. *ACET = 2 ear tymp states converted to binaural HL( IJPORL '08). Diffs (small) in R column are partly due to ACET scale compression; the one large exception has small N

*International Journal of Pediatric Otorhinolaryngology (2009) 73, 21—42

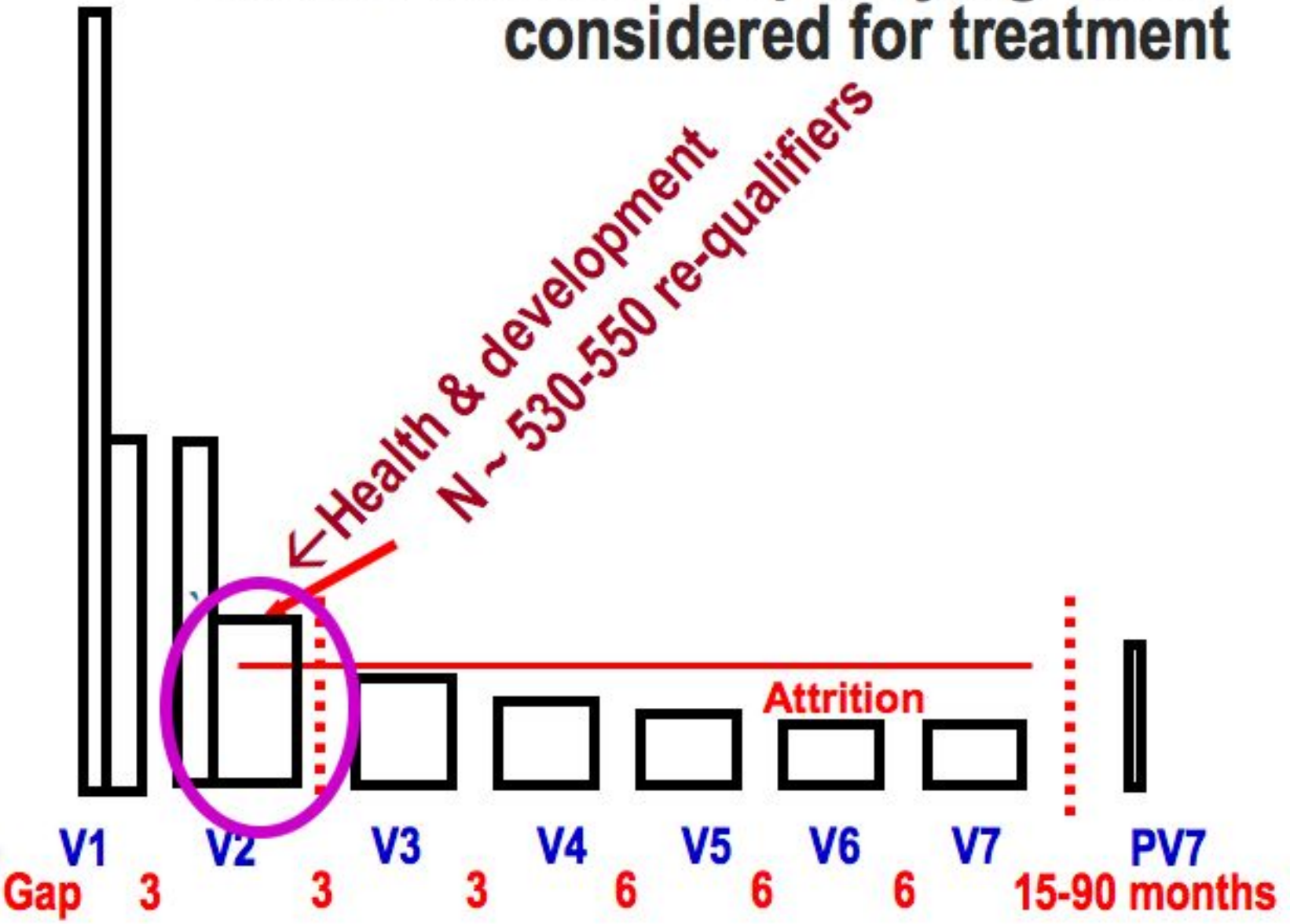
# Issue for community paediatrics, benefit to HL from VTs 3-6 months depends on catchment



# Principles make facts interpretable — 2 main considerations here

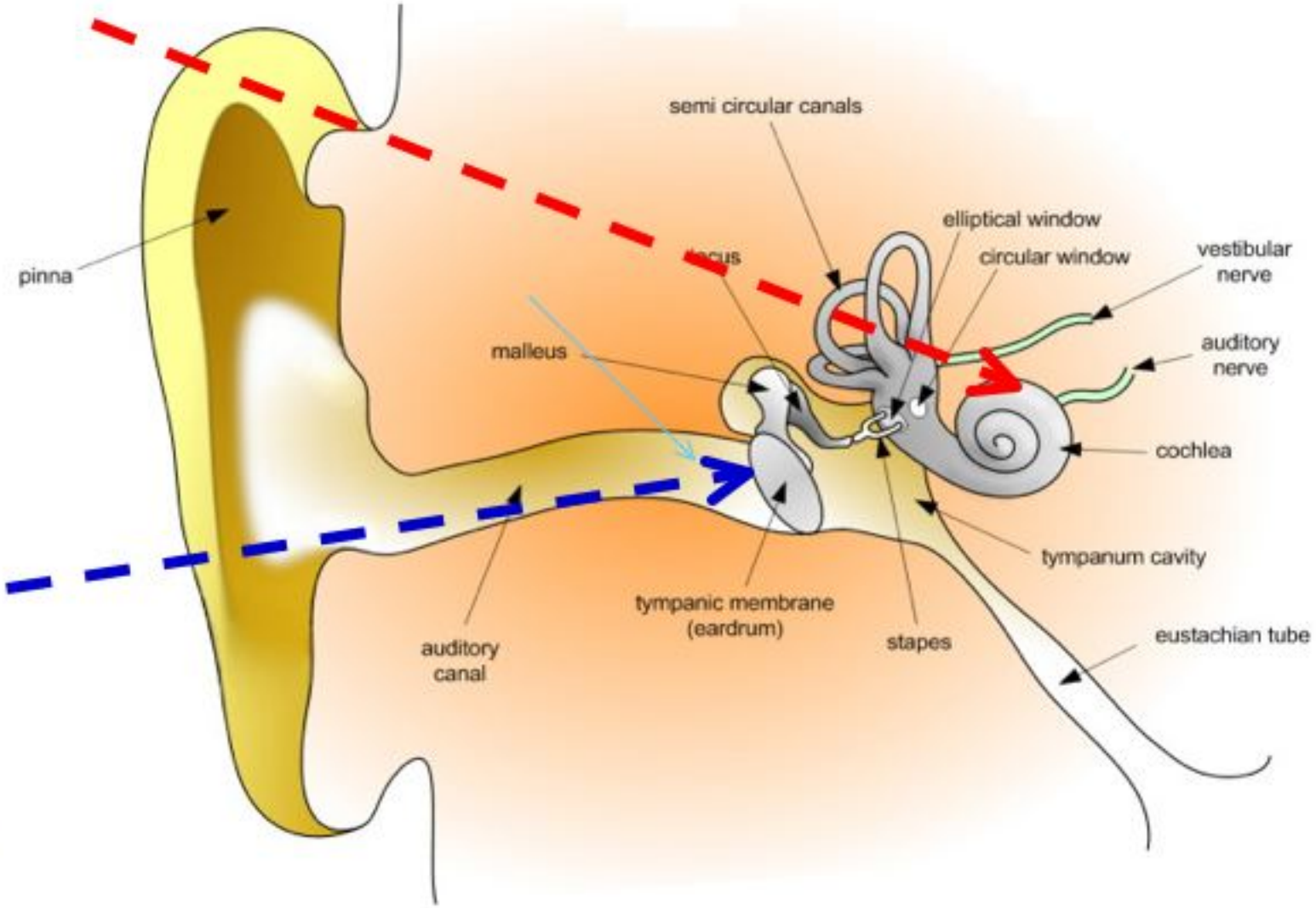
- A compressed form of the variation seen between countries: wide variation in mean HL of children referred for ears or hearing with ENT criteria frozen
- Children from catchments with better "hit rate" (PPV) get more benefit from ventilation tubes:
  - Biomedical fallacy: a difference in the operation ?
  - No, system differences in pre-selection give the children "baggage" <u>irrespective of indvidual HL</u>
- In catchments of centres with high HL &/or PPV (confirmation rate), children undergo more watchful waiting, selecting the persistent cases

# Moving from the presenting caseload to smaller number of qualifying cases considered for treatment

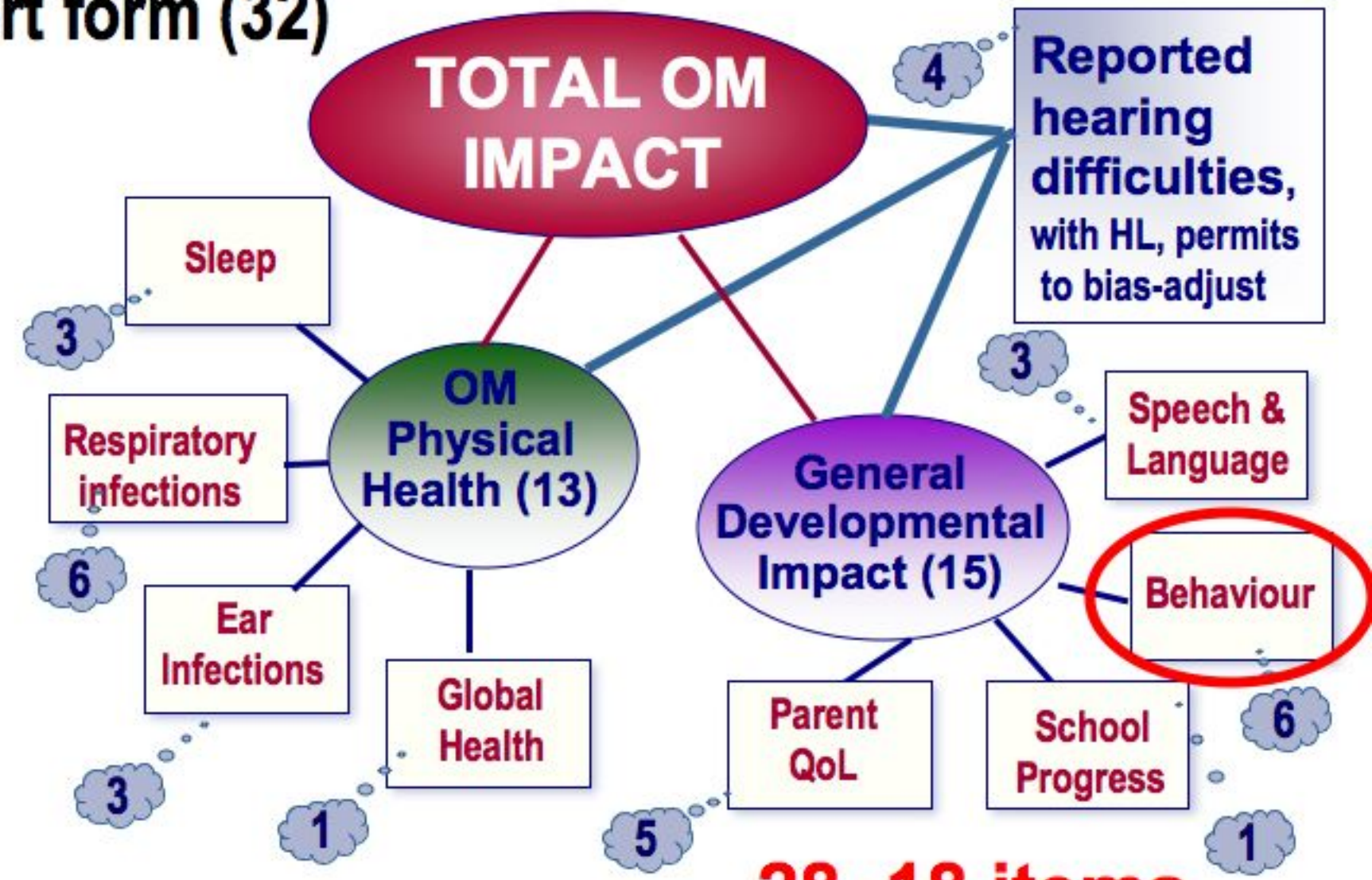


# A needed simplifying definition:

## Air-bone gap (ABG) = current conductive loss



# General structure of long-form (76) outcome measures in TARGET is mirrored in OM8-30 short form (32)



# Development is a reason to intervene, so we must understand its mechanisms (& their timescales)

Reported length of history < 1 yr

(Age)

TM retraction *still* present – (marking past severity & duration of OM?)

HL 3 months before or ABG & BC ?

Season

URTI

Sleep pattern

Response bias

**Developmental Impact (TARGET V2)**
Weighted sum of scores on 4 behaviour facets, speech & language, balance, schooling, parent QoL (49 Q-aire items; N=519)

Remote past | Past | Recent (3-6 m) | Current < 3 m

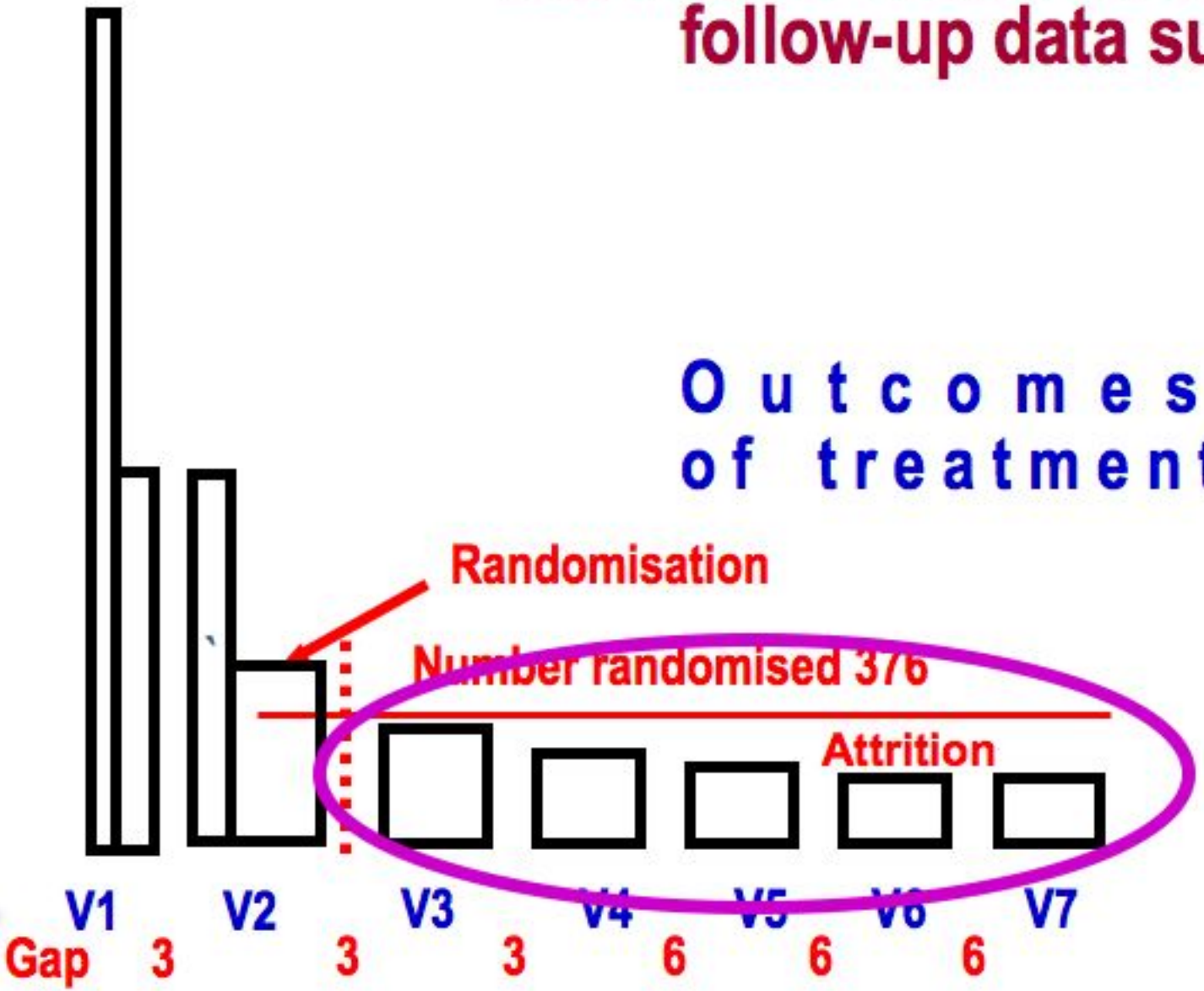
(Assumed) time frame over which influence acts →

# Evidence justifying this account: 9 highly significant predictors in multiple regression → 45% of dev variance

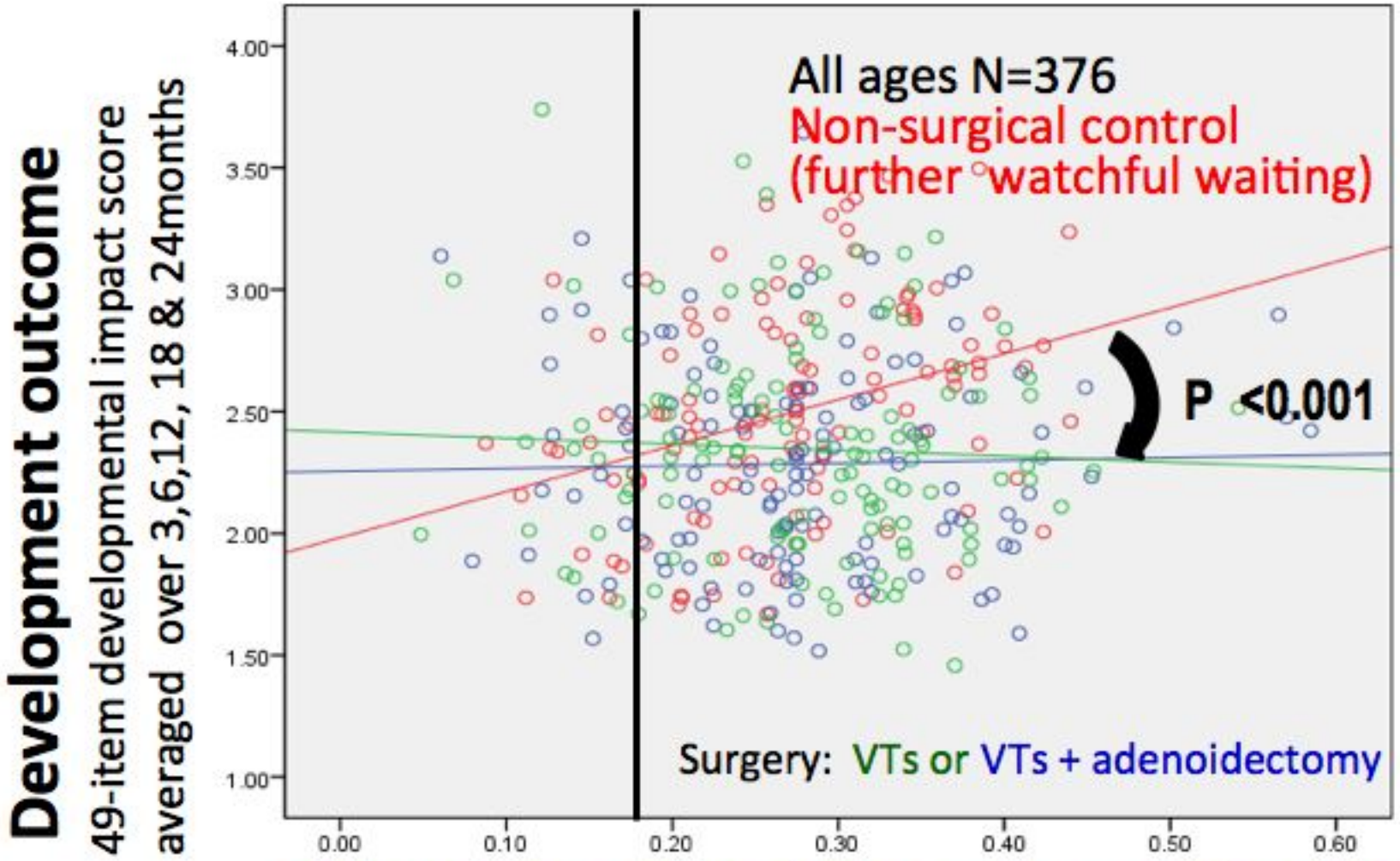
'OMDev trio'

| | | | | | 95% Confidence Interval | | |
|---|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound | Partial Square |
| Intercept | 99 | | | | 98 | 0 | .428 |
| [seas | 1.00 | 52 | 23 | 27 | 7 | 06 | .010 |
| [seas2_di7=2.00] | 0[a] | . | . | . | . | . | . |
| [howlong5=1.00] | .101 | .056 | 1.791 | .074 | -.010 | .211 | .006 |
| [howlong5=2.00] | -.063 | .025 | -2.527 | .012 | -.111 | -.014 | .012 |
| [howlong5=3.00] | 0[a] | . | . | . | . | . | . |
| agev2_v1otts_sincontrols_new_inrange | -.006 | .001 | -5.220 | .000 | -.009 | -.004 | .051 |
| lr_retv1_graded_imp_newi_655_sq | .007 | .002 | 3.101 | .002 | .002 | .011 | .019 |
| resp_colds_sep_guard4_g2i_655 | .012 | .005 | 2.283 | .023 | .002 | .022 | .010 |
| sleepg2i_655 | | 005 | 8.029 | 000 | 032 | 053 | .113 |
| abg1 | .008 | .001 | 5.356 | .000 | .005 | .011 | .053 |
| bonecondav1 | .009 | .003 | 3.229 | .001 | .003 | .014 | .020 |
| newbiasv2 | -.135 | .016 | -8.443 | .000 | -.166 | -.103 | .123 |

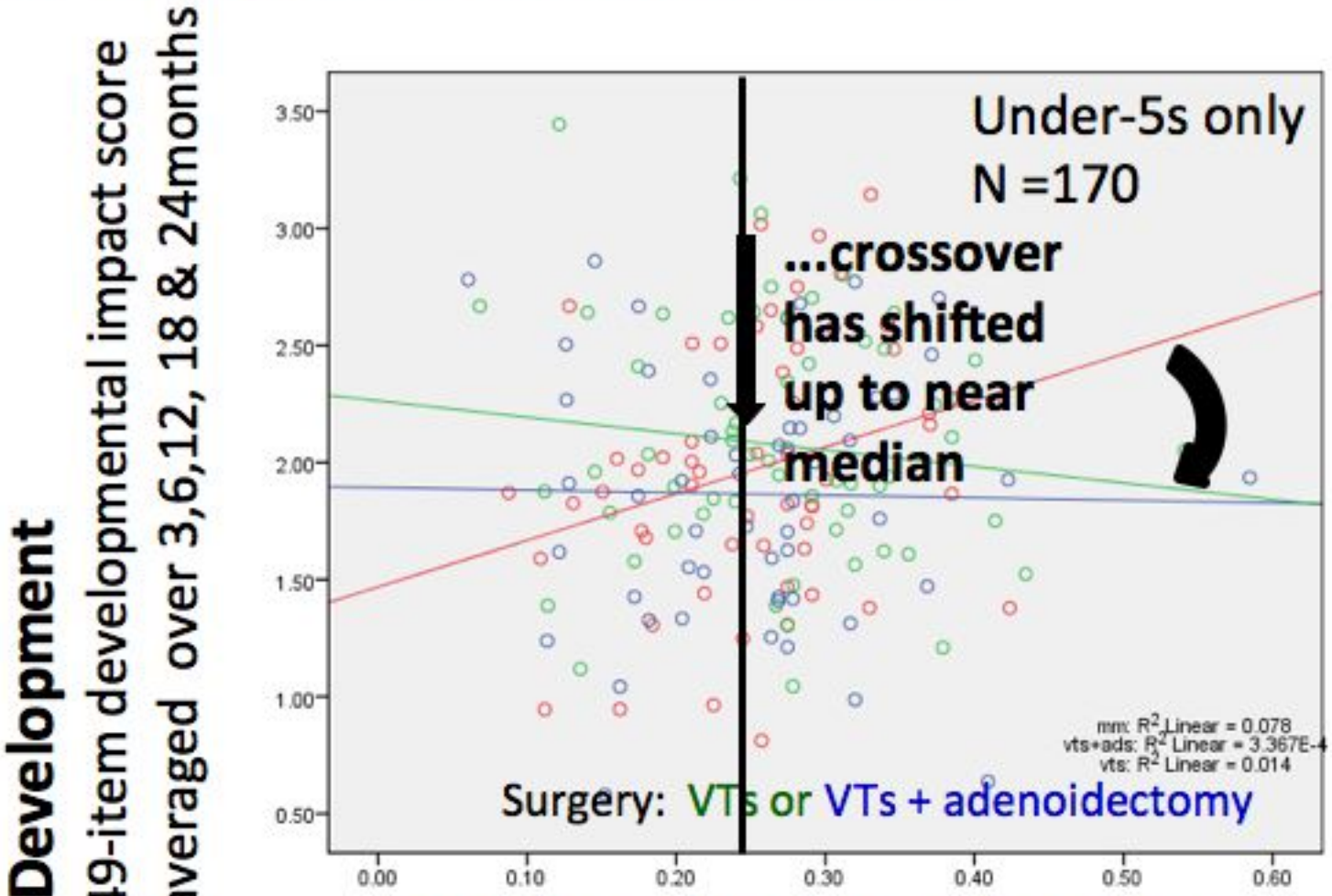
# Now applying the OMDEV trio measure from baseline to treatment in the follow-up data subset



# Interaction confirms therapeutic action, despite low overall benefit to development & absence of indication from baseline



# Over-5s, benefit in development (*ie* overall),so **Focus for this selection is in under-5s.** Fortunately, that would work OK




**OM Dev trio part of baseline**

# Is using ABG reinventing an old wheel?

But inventing appropriate novel *uses* for a concept can be equally important

The distinction between BC & ABG as parts of HL became important >70 years ago *for diagnosis*

# HALF-TIME SUMMARY

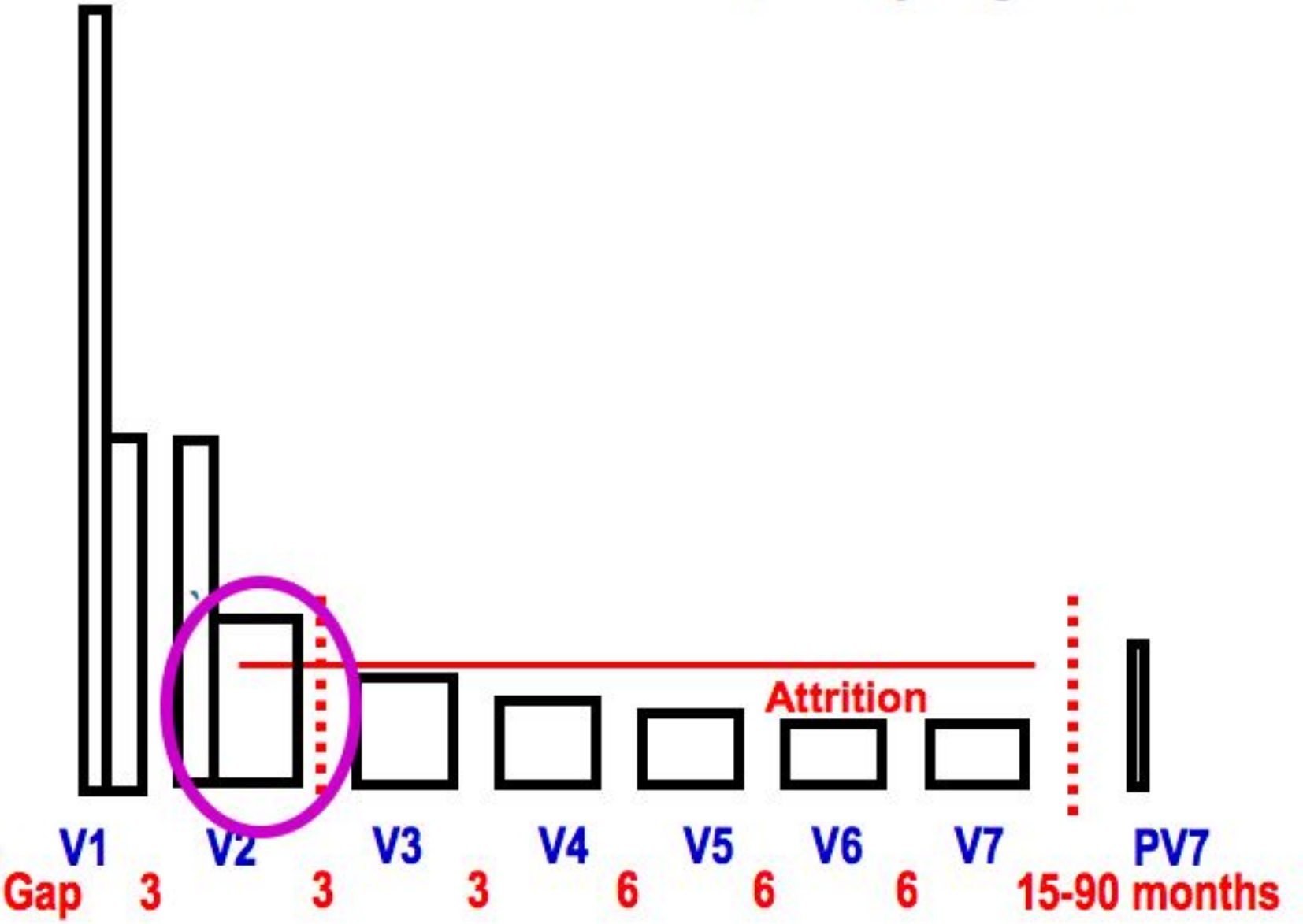
We have adding to the list of markers of the cumulative auditory deprivation in OME

The HL measured today is only one such marker, & a poor one, especially relative to HL 3 months ago, & relative to ABG

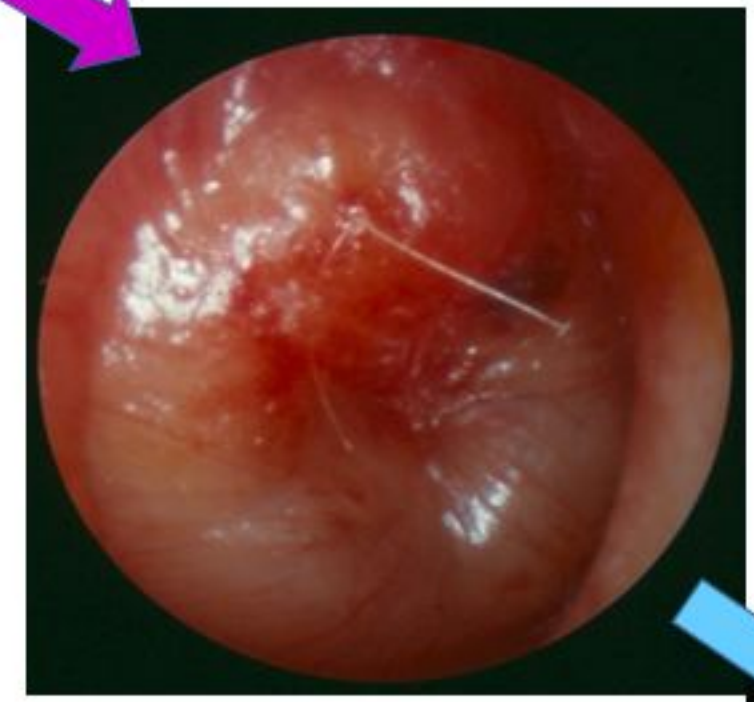
Our 3 OMDev trio markers collectively predict both the impact (sequelae) & ability to benefit from VTs, as VTs directly affect this basis. We name this score 'LCL', Lasting Conductive Loss

Within nominally 'conductive' losses the normal BC variation can still be influential

# Moving back from outcome follow-up to qualifying cases



# Measurement of impact needs to heed the causal cascade — familiar from diagnosis

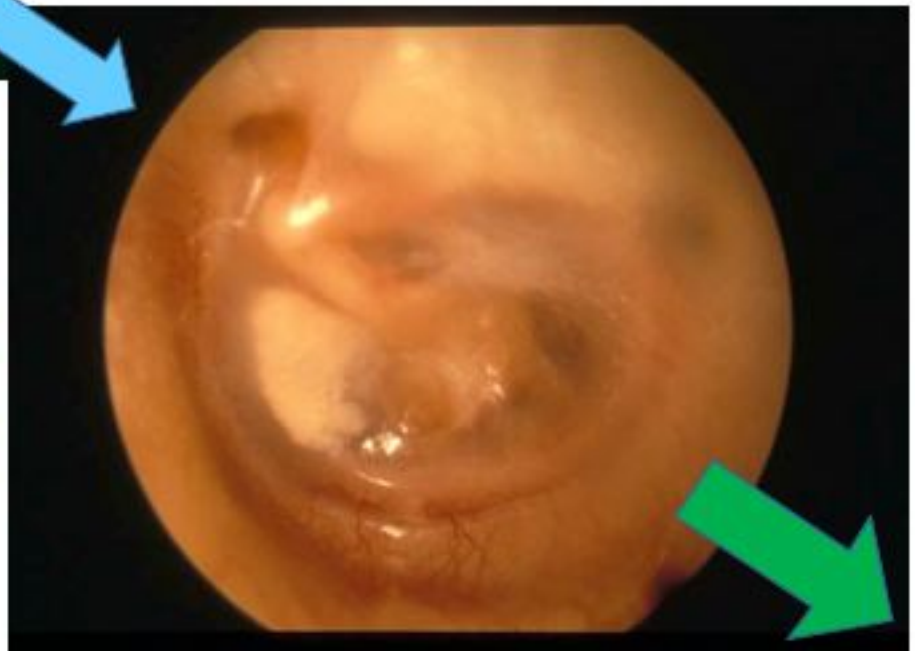


← AOM:

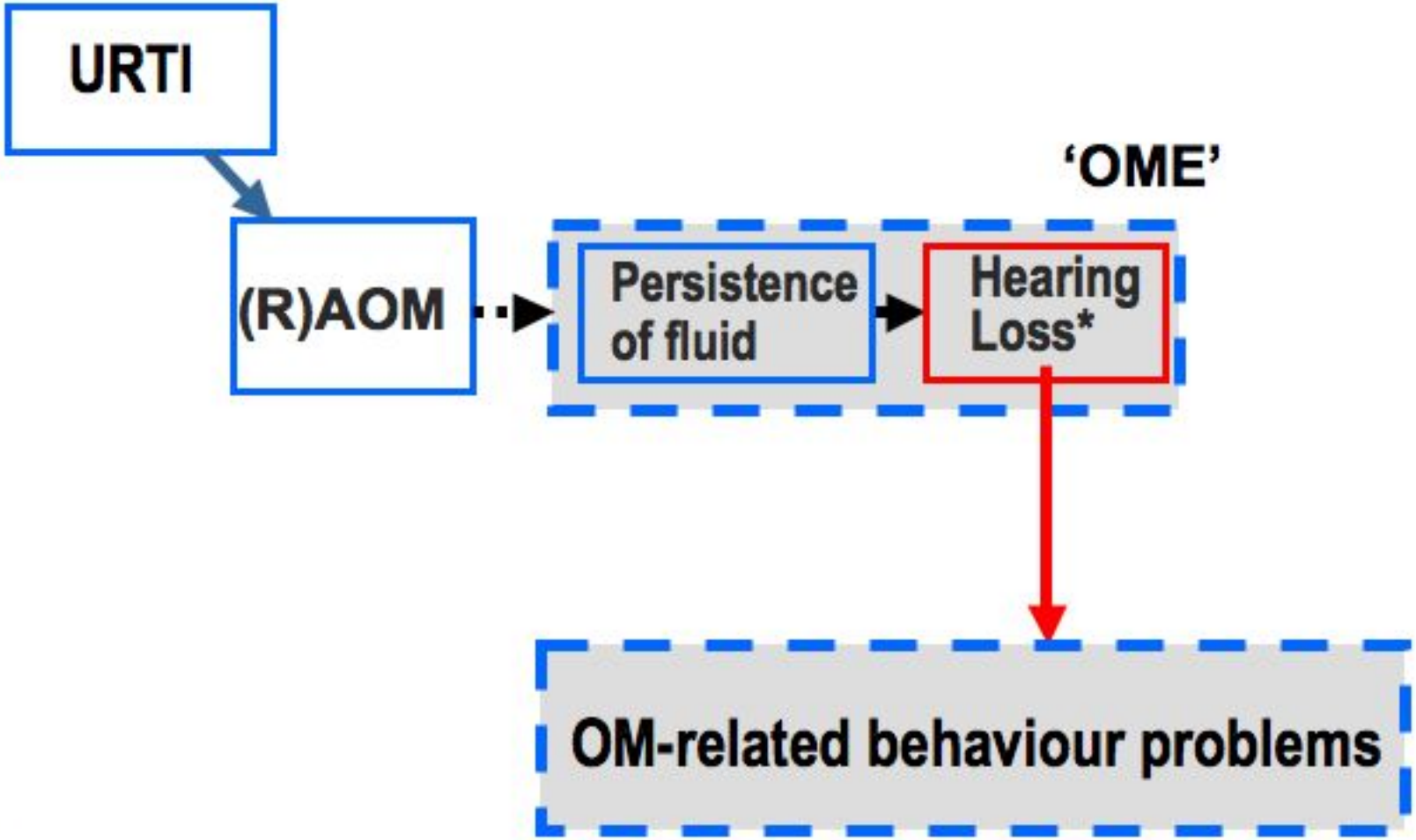
Fever; pain; irritability; bulging eardrum (TM); inflammation

SOM/OME →

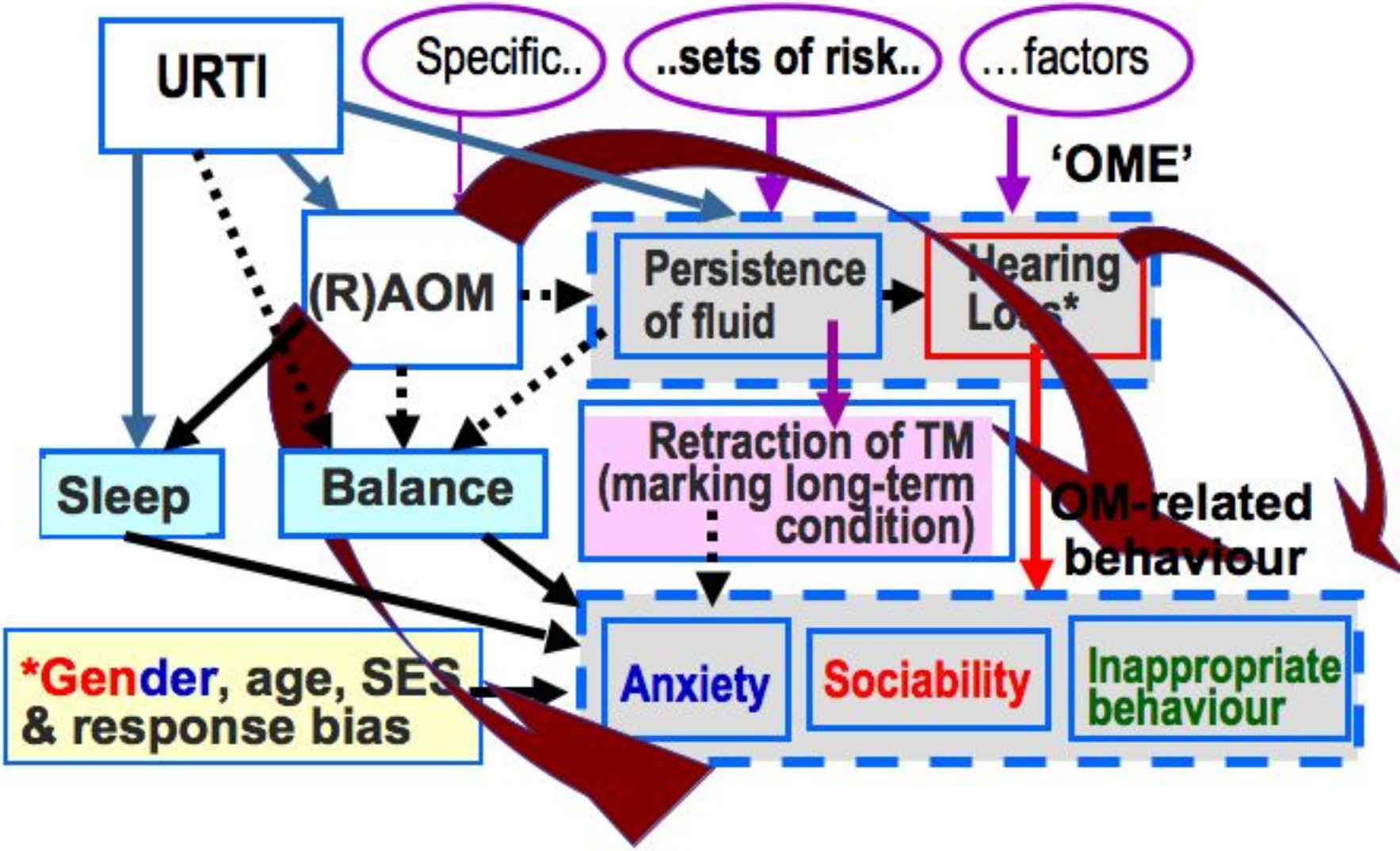
Fluid blocking TM motion, based on tympanometry/ otoscopy; hearing loss



# An extension to the cascade that is based in evidence but largely implicit — other paths also exist



# Full cascade is rather complicated but the evidence supports the expected links



# Analyses justifying this model

Grow a set of models back from the final model for what predicts Behaviour 18 analogous to the overall one just shown for all development

Run part-models and versions for what may predict each behaviour facet in the model

Apply this principle recursively

# BEH-18 model at baseline with BC & ABG separated — slightly better* than with HL

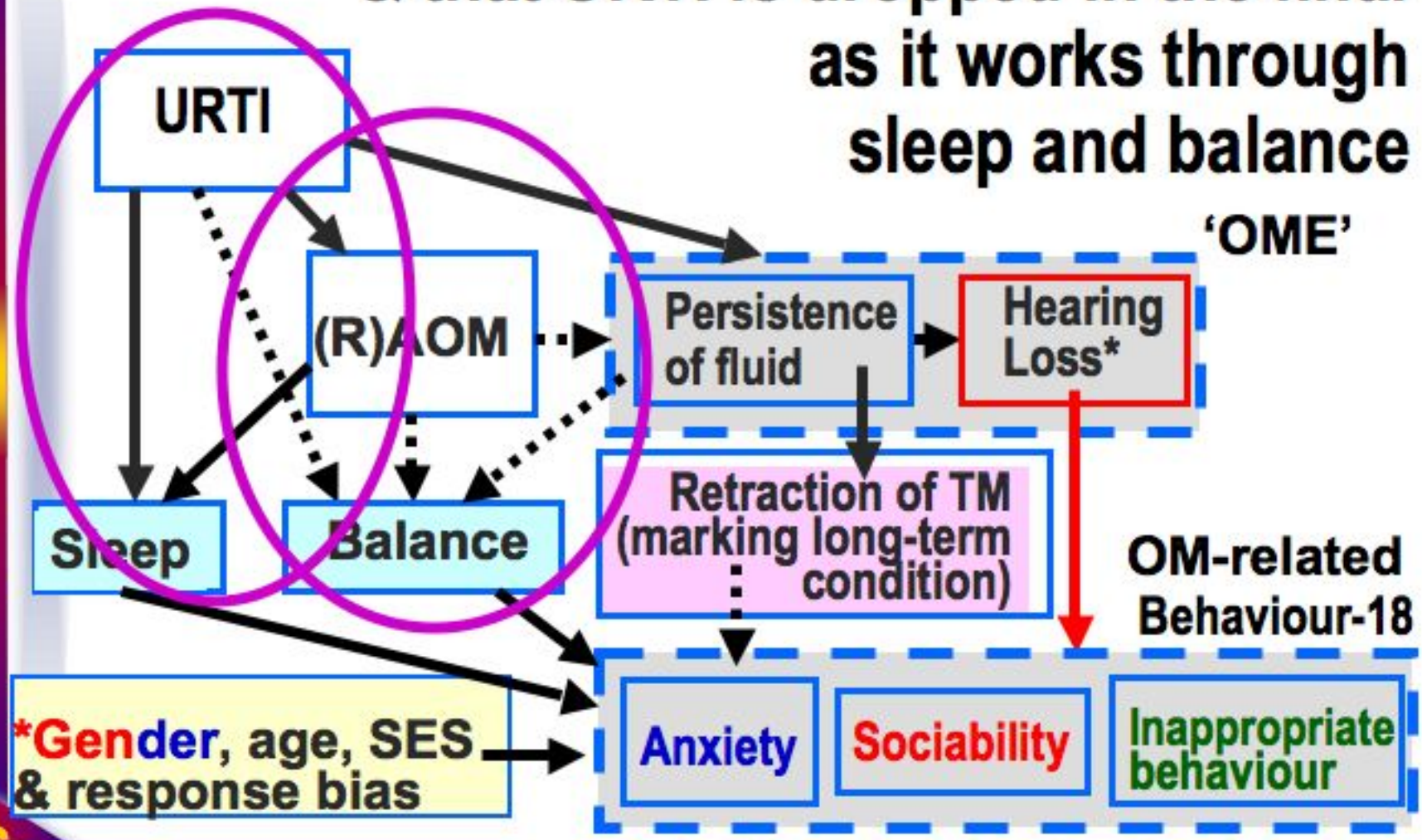
| Parameter | B | Std. Error | t | Sig. | 95% Confidence Interval | | Partial Eta Squared |
|---|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound | |
| Intercept | 3.669 | .177 | 20.782 | .000 | 3.322 | 4.016 | .450 |
| [manual4=.00] | .382 | .102 | 3.725 | .000 | .180 | .583 | .026 |
| [manual4=1.00] | .202 | .043 | 4.669 | .000 | .117 | .287 | .040 |
| [manual4=2.00] | 0[a] | . | . | . | . | . | . |
| agev2_v1otts_sinco | -.005 | .002 | -2.394 | .017 | -.009 | .000 | .011 |
| balg12 | .051 | .008 | 6.610 | .000 | .036 | .067 | .077 |
| abg1 | .009 | .002 | 3.428 | .001 | .004 | .013 | .022 |
| boneconda v1 | .021 | .005 | 4.465 | .000 | .012 | .030 | .036 |
| sleepq12i_655 | .065 | .010 | 6.277 | .000 | .045 | .085 | .070 |
| lr_retv1_graded_im | .010 | .004 | 2.739 | .006 | .003 | .017 | .014 |
| newbiasv2 | -.110 | .027 | -4.036 | .000 | -.164 | -.057 | .030 |

*Split adds 1% to % variance explained; itcan do so as contributions not equal here, & ABG/BC can now combine differently with other variables

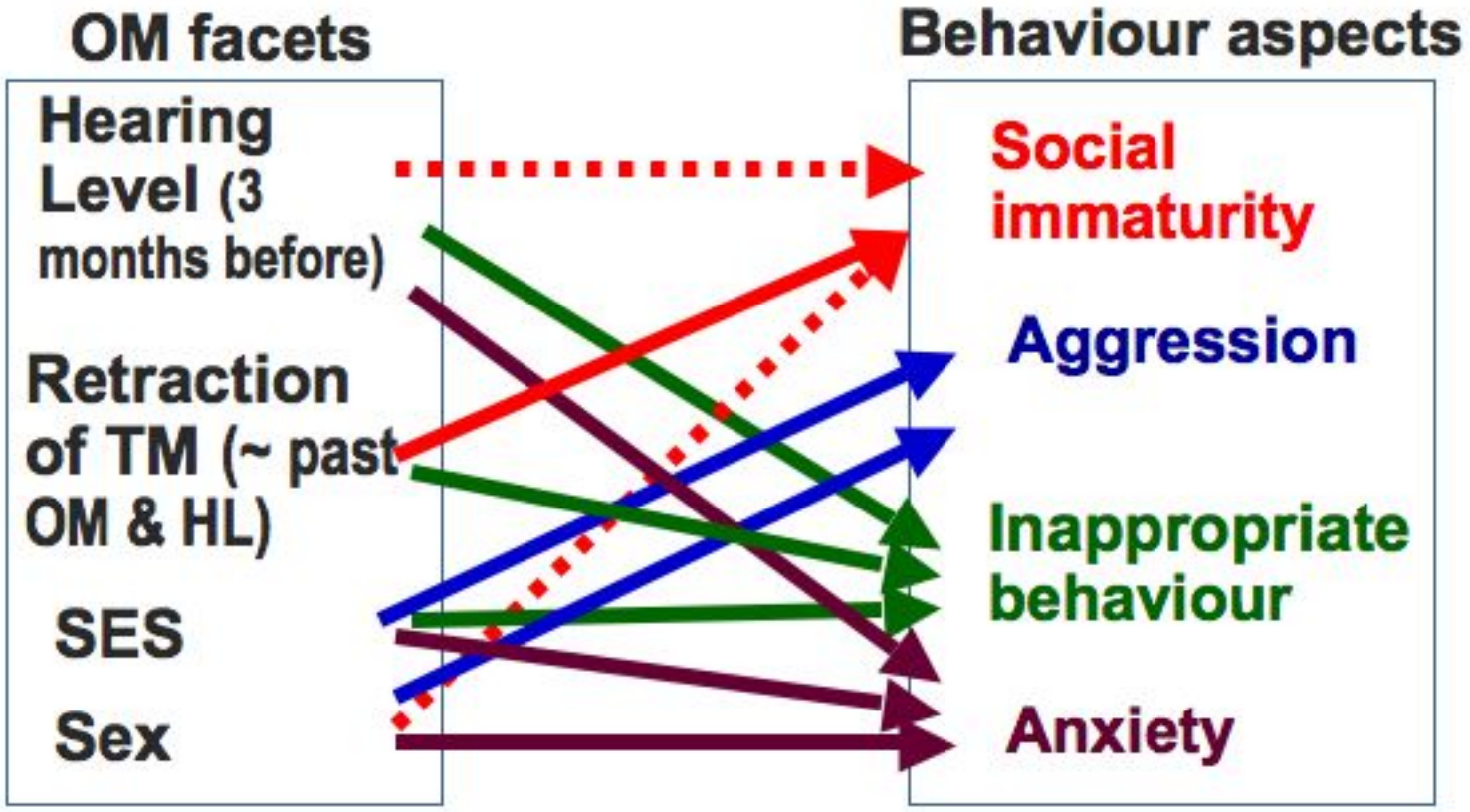
# Comparator model not splitting HL as BC & ABG shows similar determinants as for development, but overall slightly weaker (as only 18/49 items)

| Adj Rsq 0.355 Parameter | B | Std. Error | t | Sig. | 95% Confidence Interval | | Partial Eta Squared |
|---|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound | |
| Intercept | 6.237 | 1.461 | 4.270 | .000 | 3.368 | 9.107 | .033 |
| [manual4=.00] | 3.082 | .851 | 3.620 | .000 | 1.410 | 4.754 | .024 |
| [manual4=1.00] | 1.678 | .363 | 4.625 | .000 | .965 | 2.391 | .038 |
| [manual4=2.00] | 0(a) | . | . | . | . | . | . |
| agev2_v1otts_sinc ontrols_new_inr | -.050 | .018 | -2.857 | .004 | -.085 | -.016 | .015 |
| balg12 | .447 | .065 | 6.851 | .000 | .319 | .576 | .081 |
| **avehl1i_655** | .059 | .021 | 2.848 | .005 | .018 | .100 | .015 |
| sleepq12i_655 | .570 | .087 | 6.536 | .000 | .399 | .742 | .074 |
| **lr_retv1_graded_i mp_newi_655_sq** | .071 | .031 | 2.281 | .023 | .010 | .132 | .010 |
| newbiasv2 | -.871 | .231 | -3.776 | .000 | -1.325 | -.418 | .026 |

# Part regressions, as well as that final one, show which arrows need to be drawn, & that URTI is dropped in the final as it works through sleep and balance

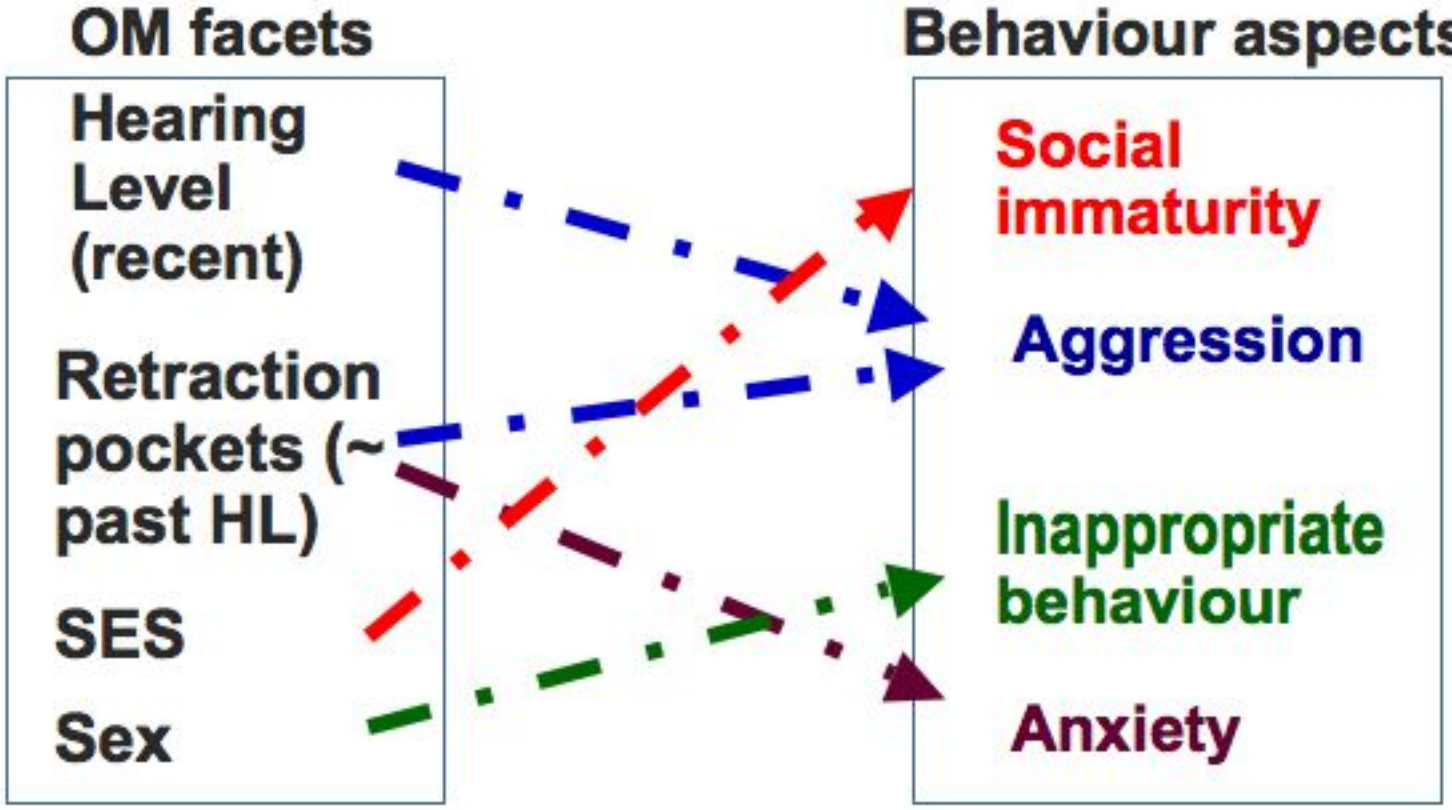


# At the margin of reliability, individual behaviour facets show plausible patterns: differential pattern of 9 of 16 possible paths of influence on specific behaviours




Linear (& logistic for social immaturity) regression analyses on 481 identical cases with all variables present. → = significant link, …= marginal or masked by collinearity. Age is seen as a methodological obligatory control with development but is reversed (NS) for aggression.

# Divergent validity: easier to see the 5/16 that don't appear in the data



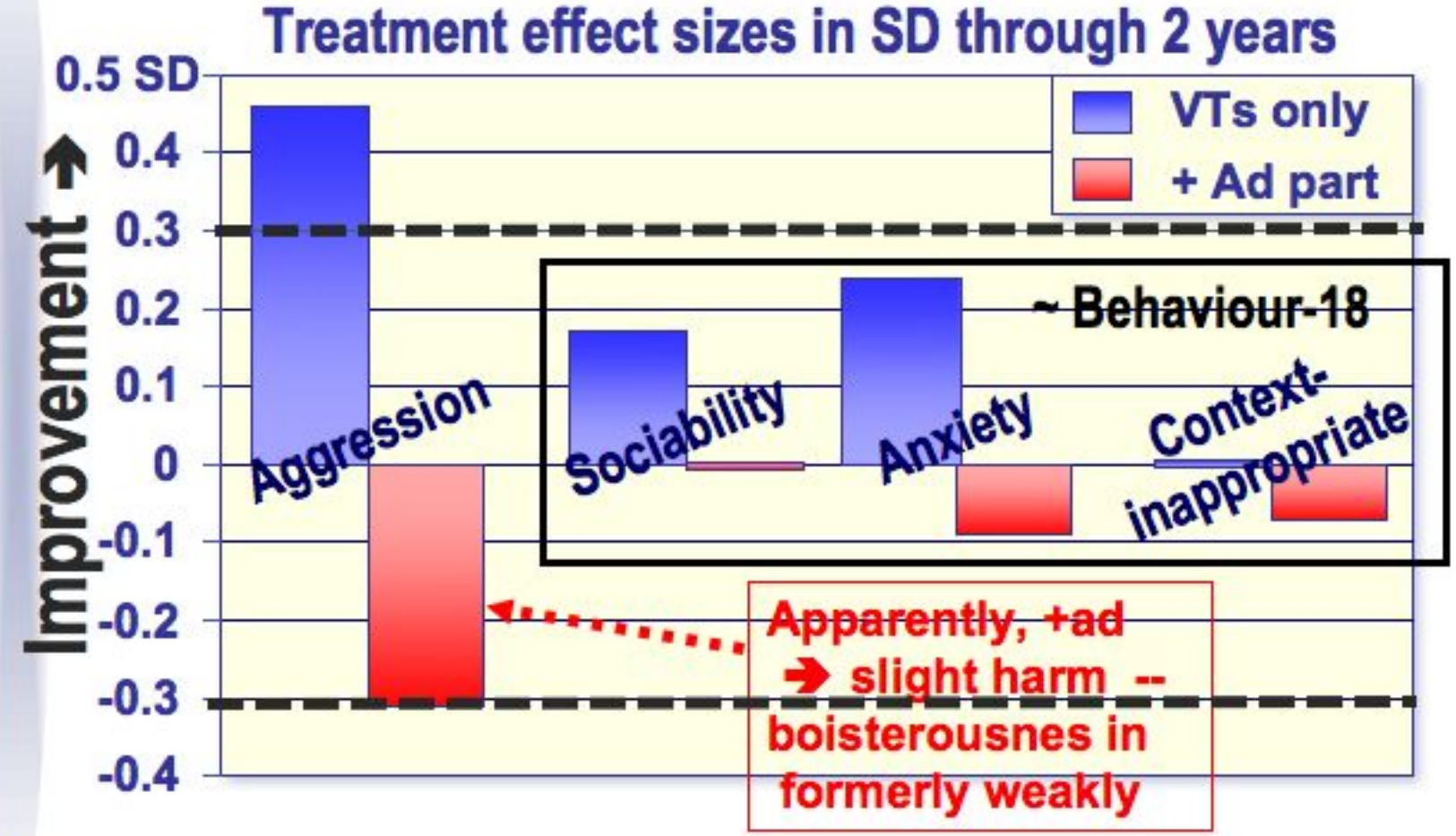

1: aggression may not be related to OM at all

2: anxiety relates to OM over short time-scale, social maturity over long

3: demographics are important, replicating classical findings (girls more anxious, boys more aggressive) & confirm ing some expected ones

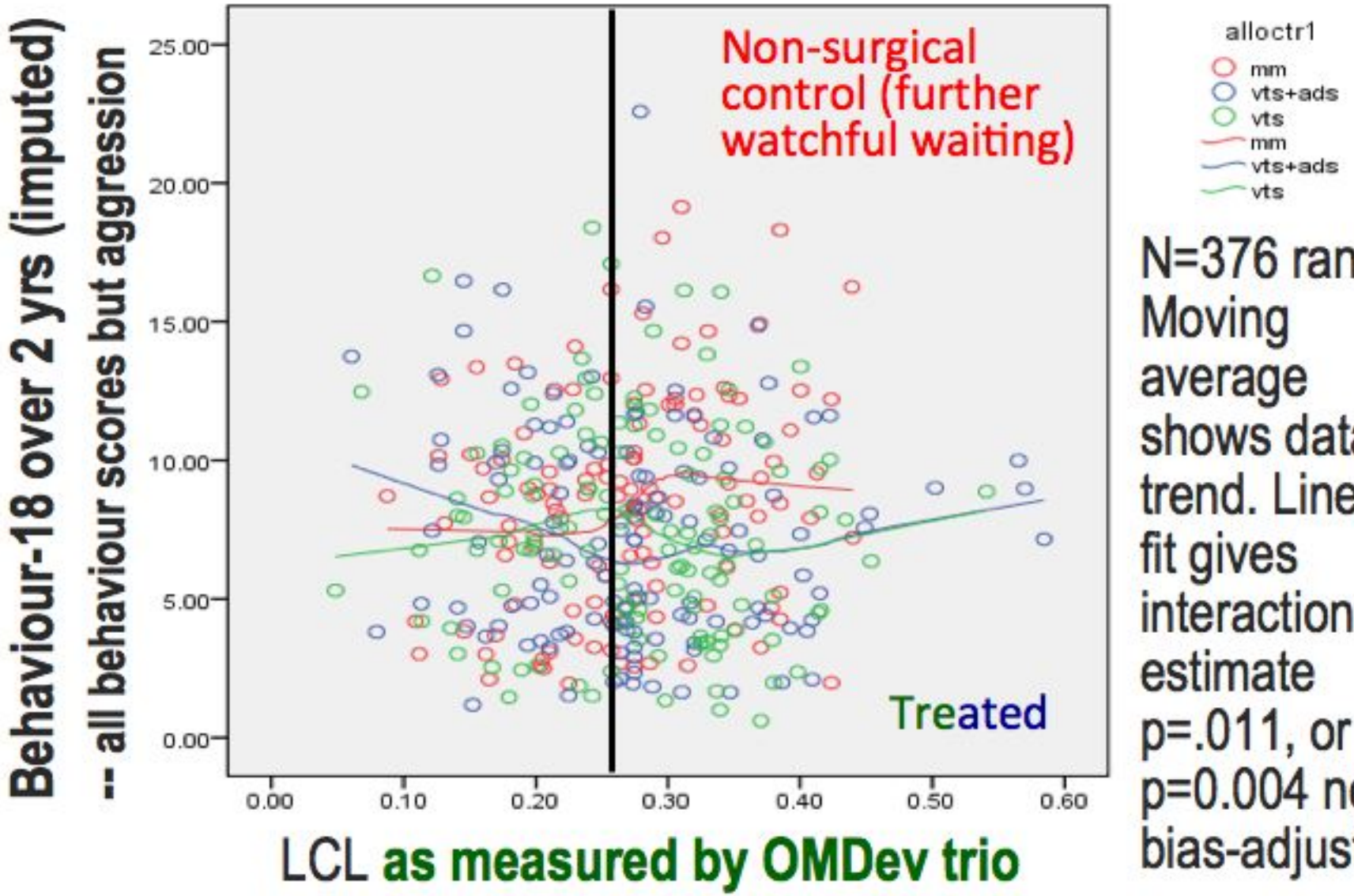
# Aid to interpreting results on scores in associations or treatment analyses where N of items fewer than about 7

# Treatments appear to affect behaviour less than HL or physical health do... but zero ?




TARGET complete-data cases but not imputed or bias-adjusted; summated over 2 years by former AUC7 formula (Ns 127–200)

# LCL does predict ability to benefit (over 2 years, all ages) but severity of baseline behaviour problems does not




N=376 rand. Moving average shows data trend. Linear fit gives interaction estimate p=.011, or p=0.004 not bias-adjusted

# FULL-TIME SUMMARY

**We have a generalised causal cascade model of pathogenesis of OME & its sequelae, which can be compressed in its number of stages and/or expanded in the detail of markers involved**

**Despite reliability problems with narrow facets (due to few items in an all-purpose set of outcome variables), the fine-structure of relationships for behaviour facets is plausible**

**Overall (BEH-18), and in particular facets this plausibility carries forward into treatment results, although benefits to behaviour are small**

# Further implications of this

- Behaviour: we understand the process better now:
  - Move on from that narrow language emphasis in OM(E)
  - Physical health not just HL influential
  - Role for normally varying BC as for other impacts (developmental & cognitive*) restrict scope for HL to predict treatment benefit with VTs, which don't affect BC
- Important modification of principle: not the baseline but treatment-relevant aspects provide best indicator
- A coherent 3-pass clinical algorithm now assigns VTs, VTs+ad justifiably to about 88% of group (≥ 20dB HL)
  - Single items could never have indicated treatment (low reliability), but LCL and URTI scores use tractably few
  - BC needed for ABG on definable cases



*Cf Welch and Dawes population study; HL within normal range → cognitive tests

# We have to be ready, on seeing the Light, to change tactics & strategy

# Special thanks


- Data collection
  - MRC Multi-centre Otitis-Media Study Group as published elsewhere
- This work especially
  - Helen Spencer (Statistical analysis)
  - Josie Higson (Database, audiology, writing)
- Financial Support
  - Medical Research Council UK
  - Deafness Research UK
  - BACO and ENT-UK