EUSPR MEETING NOV 2013 PARIS
UNDERSTANDING DIFFERENCES IN PREVENTION OUTCOMES

FOR WHOM DO THEY WORK? UNDERSTANDING MODERATORS OF OUTCOME IN FAMILY AND PARENTING INTERVENTIONS

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Acknowledgements

Funders
National Institutes of Health- NIDA, NIMH (US)
Health Foundation (UK)
NIHR- Public Health Research (UK)
Swedish Board of Health & Welfare

Collaborators
Danny Shaw – Pittsburgh
Tom Dishion – Oregon & Arizona
Mel Wilson – Virginia
Arin Connell – Case Western
Judy Hutchings – Bangor
Patty Leijten – Oxford & Amsterdam

Examples of moderator analyses from randomised trials

Which subgroups benefit most from:

- Welfare to work programs in US (Michalopoulos & Schwartz, 2000)
- Whole school interventions in NYC to reduce violence (Aber, 2003)
- Parenting interventions in Wales & US to prevent antisocial behaviour (Gardner et al., 2009; 2010)
- Conditional cash transfers in Mexico for attending school (Skoufias et al., 2001)

Outline, Aims

What are moderator effects?

Motivations for investigating moderators

Theories, questions about subgroups

Findings on moderators in family interventions

Methodological challenges

- Single trials
- Synthesising across trials in systematic reviews

How to take the field forward?

What are moderator effects?

- Question: for whom does it work?
- Are there differential effects of interventions, by subgroup? Do outcomes differ by level of participant baseline characteristics (e.g., gender, social background, ethnicity, severity of problem)
- Within randomised trials that test main effects – seen as secondary analyses
- Also known as: effect modifiers, subgroup analyses, differential effects

Motivations for moderators (1)

Understanding prevention theory, practice, policy

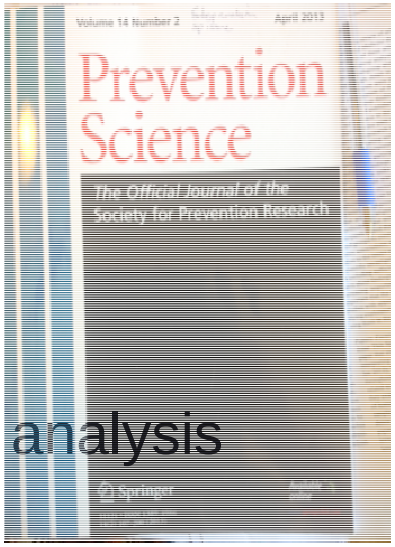
- Subgroups where intervention is suitable
- Subgroups where intervention does less good — need extra effort
- Subgroups where intervention does harm

Policy interest in what works for whom

More targeted, tailored interventions

Maximise efficiency, minimise risk

e.g. US federal interagency group in 2010, led to a special issue of Prevention Science 2013 on subgroup analysis



Motivations for moderators (2)

As interventions go to scale – ask wider questions about effects of interventions on social disparities

Do they disproportionately benefit certain groups?

If so, could they serve to increase social disparities?
Or narrow the gaps?

eg: Sure Start UK evaluation — despite focus on low-income families, uptake and outcome of family support services were better for higher income families (Rutter, 2006)

Motivations for moderators (3)

Basic science: understanding mechanisms of change

By identifying those who respond differentially to intervention, we may then be able to explore distinct causal mechanisms in these subgroups (Hinshaw, 2002).

→ Interplay of moderators & mediating mechanisms (Rothman, 2013; Stoltz,2013)

Moderators may be social, behavioural or biological - for example, genetic markers hypothesised to predict differential responsivity to intervention effects
(eg Bakermans-Kranenburg, 2008;
Brody et al, 2009 - in parenting field).

What are moderators—formally

Within a randomised trial…..

- "Moderator" = a baseline or pre-treatment variable which is hypothesised to modify the causal relationship between intervention and outcome (e.g., social, family or demographic characteristics)
- Statistically: treatment by covariate interaction in a linear regression, used to explain variation in the relation between intervention and outcome.
- Moderators can be *categorical* or *continuous* (e.g., gender, pints per week).

What aren't they? Moderators are distinct from:

'Predictors' of outcome:

- Associated with outcome in whole sample, or treatment group only.
- More limited, don't compare randomised groups, nor test for interaction.

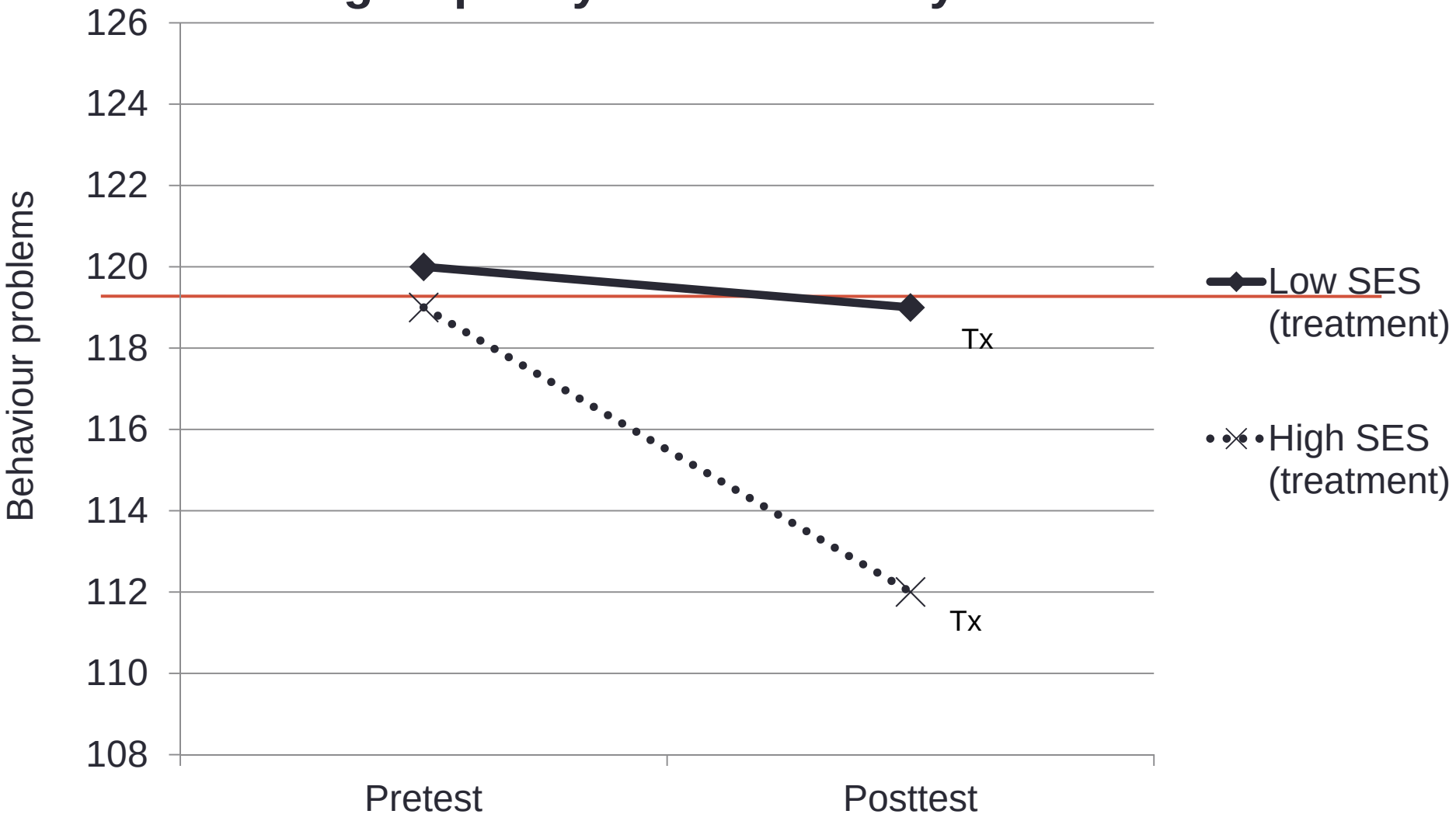
Mediators of outcome:

- On causal path between intervention & outcome, explain **how** it works
- Post- randomisation, intervention processes
- Can help us understand moderation: if we set up hypotheses about variation in processes within subgroups – (mediated moderation; eg Tein, Sandler et al 2004)

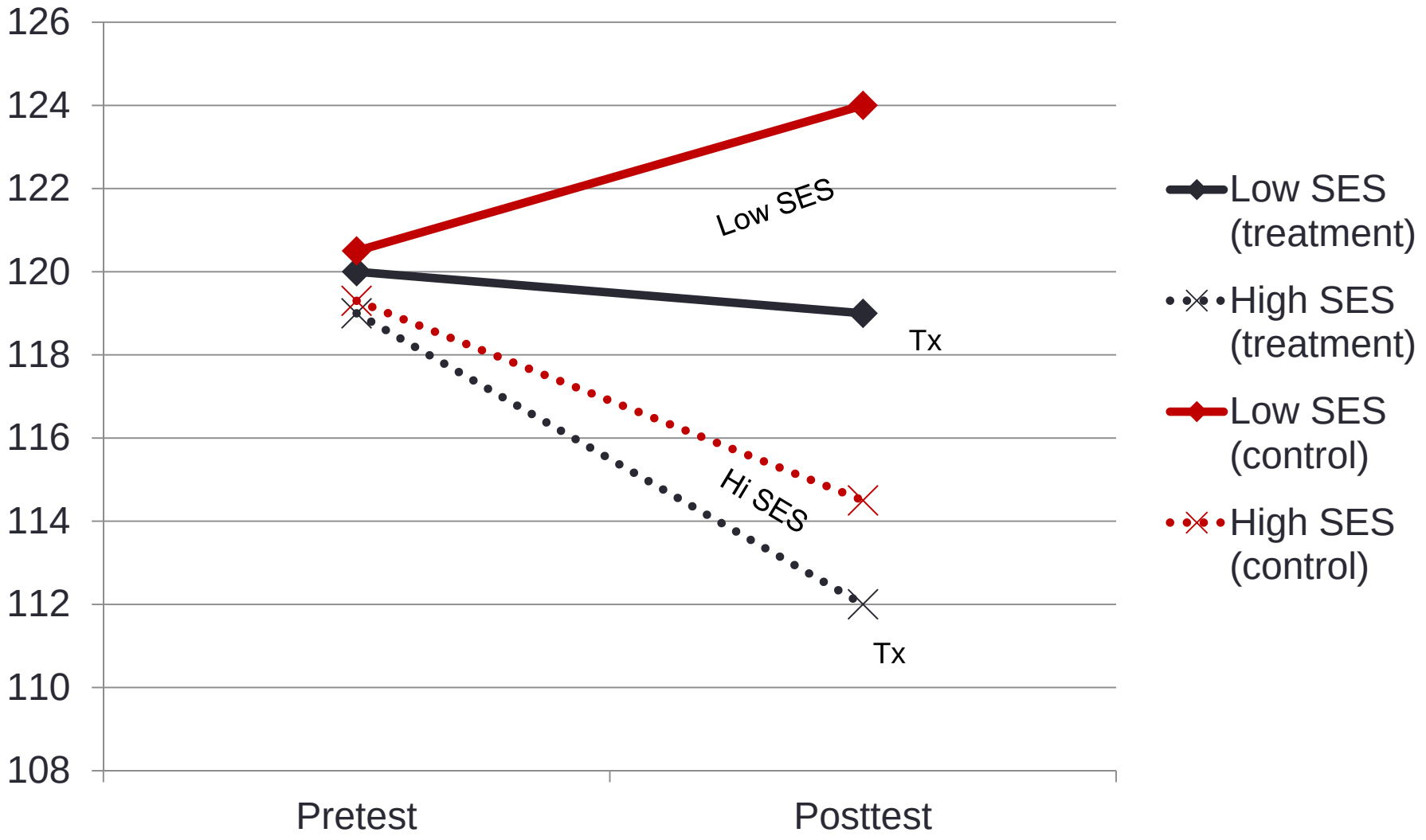
Clarifying the formal definition:

Does it really matter whether you do a moderator analysis or a ‘predictor’ analysis?

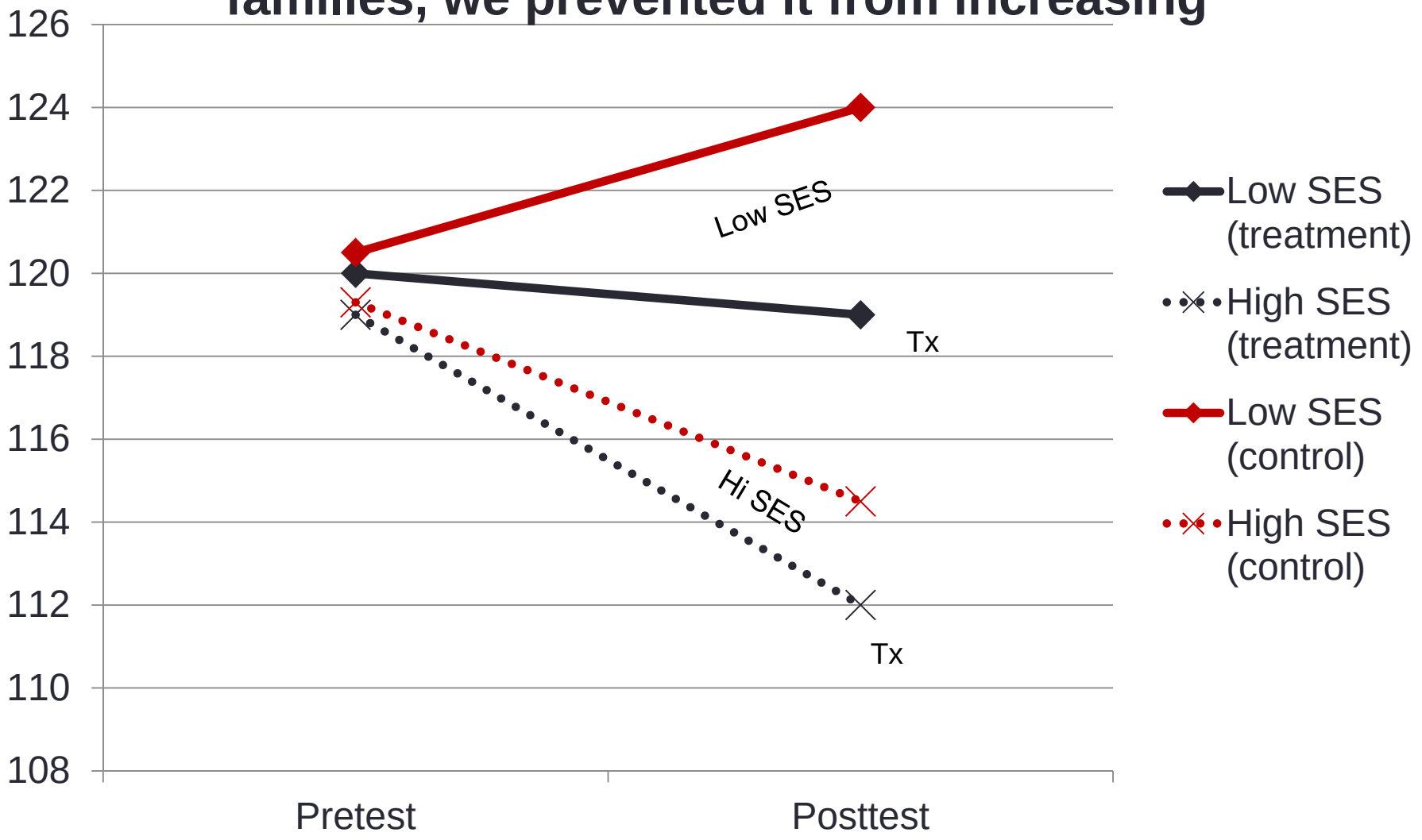
For whom does it work? In RCT of parenting intervention, using SES as a *predictor* of behaviour problem outcome, in treatment group only. What would you conclude?



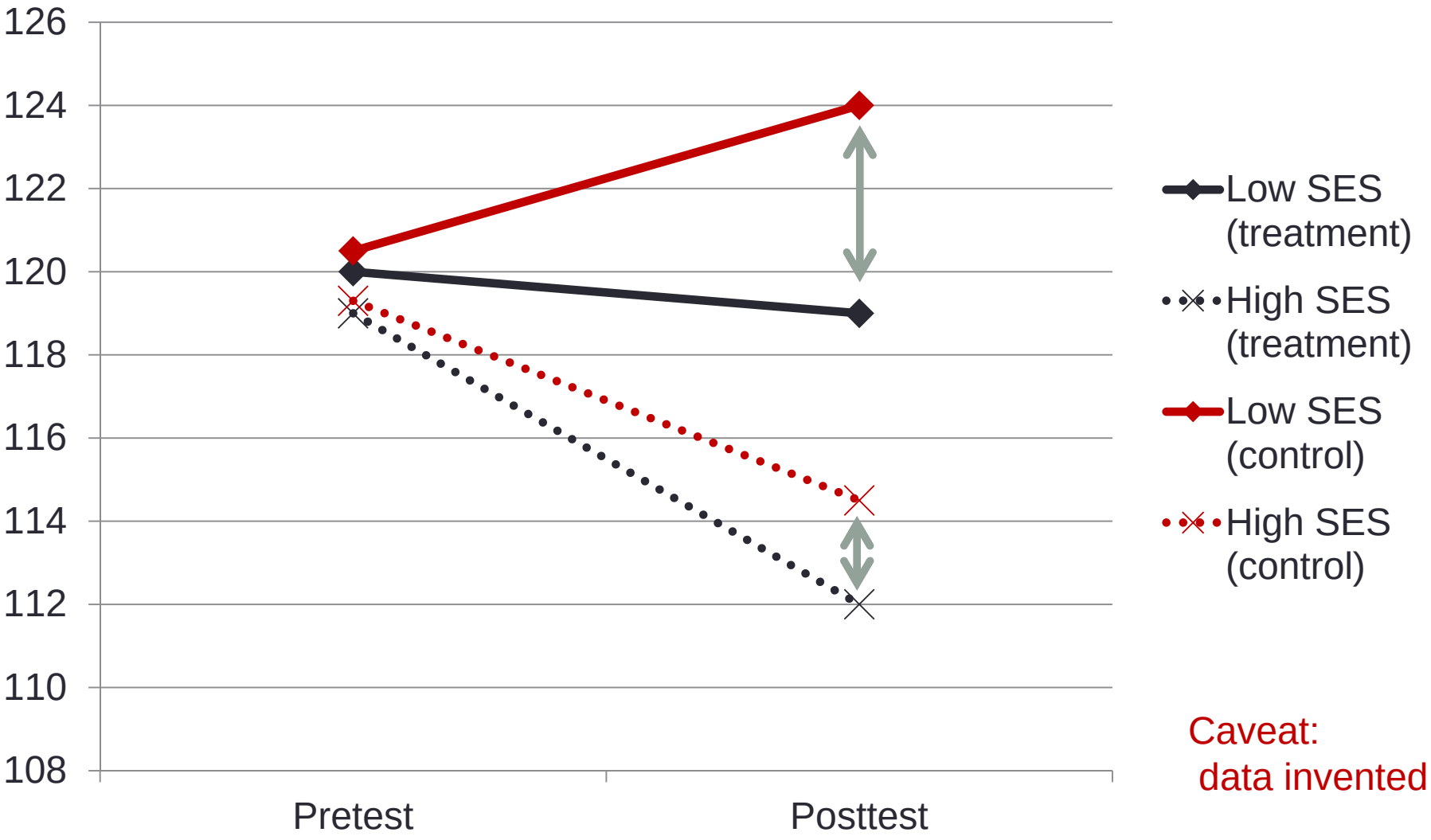
When we include the control group data, how would you interpret it now?



By including control condition, get a different picture- although problem behaviour not improving in low SES families, we prevented it from increasing



Moreover, treatment effects (vs. control group effects) are *stronger* in low SES families than high SES families



Caveat:
data invented!

Questions, theories about subgroups?

Will focus on:

- Family & parenting interventions for problem behaviour
- Social disadvantage as a moderator

i) Practical policy questions about benefit, harm, efficiency, tailoring and adaptation of interventions

ii) Hypotheses from literature on risk & protective factors for child outcomes—do factors that raise risk for poor outcome also predict poor intervention response?

iii) Focus on social disparities in public health ('equity'):

Inverse care law: some interventions may benefit more advantaged groups more, and thus serve to widen disparities - smoking a good example

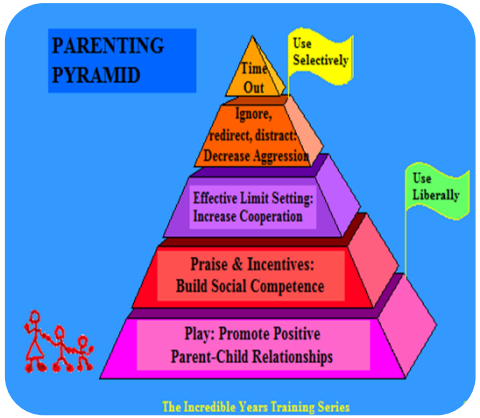
To illustrate moderator analyses…

Does social disadvantage influence the outcome of family and parenting interventions?

What evidence is there from trials and systematic reviews?

Parenting interventions—background

- Mainly based on social learning theory
- Shown to be effective in:
  - many randomised controlled trials
  - many countries
- Preventing & reducing problem behaviours in children
  (eg, conduct problems, delinquency, alcohol use; Cochrane reviews: Furlong 2012, Foxcroft, 2003)
- Many branded & unbranded versions trialled:
  (e.g., Incredible Years, Parent Management Training—Oregon, Triple P, Strengthening Families, etc.)
- Tested in many different formats and settings



Systematic reviews of moderator effects

Two well-cited meta-analyses of moderator/ predictor effects in parenting interventions:

Lundahl et al. 2006, n=63 trials -329 cites

Reyno & McGrath 2006, n=31 trials - 239 cites

- **Tested moderators**: poverty, lone parent, maternal low education, depression
- **Findings**: more distressed & disadvantaged families did worse
- Apparently clear-cut finding despite combining across disparate small trials
- Not good if these effective interventions show weaker effects on more disadvantaged families given the goals of the interventions, not good for disparities, improving equity .....

570 citations means many people repeating this: how do the data stand up.....?

Data from our recent trials look a bit different...

Moderators in two RCTs of preventive parenting interventions, for children at risk of conduct problems

- Early Steps trial (US): At risk toddlers, Dishion's Family Check-Up
- Sure Start trial (North Wales): 3-4 year olds showing early behavior problems, Incredible Years

Do more distressed /disadvantaged families do worse?

Gardner, Connell, Trentacosta, Shaw, Dishion, Wilson (2009). Moderators of outcome in a brief family-centred intervention for preventing early problem behaviour. *Journal Consulting & Clinical Psychology, 77,* 543-553.

Gardner, Hutchings, Bywater, Whitaker (2010). Who benefits and how does it work? Moderators and mediators of outcomes in a randomised trial of parenting interventions in multiple 'Sure Start' services. *Journal Clinical Child & Adolescent Psychology*, *39, 568-80.*

Potential moderator variables for our studies

Theoretically and clinically important risk factors known to predict poor outcomes:

Family disadvantage factors:
Mother a lone parent; a teen parent; low education level, very low income.

Parent well being:
depression, stress, history of drug problems, partner relationship problems.

Individual child factors:
Gender, high levels of problem behaviour, including conduct problems, ADHD, Callous-Unemotional traits

Early Steps trial of Family Check-Up

- Brief, home-based preventive parenting intervention in USA
- 731 two year olds selected by risk criteria related to distress & disadvantage (family or child domain).
- Randomised to intervention, vs. none.
- Brief Family Check-Up intervention, consists of:
  - full assessment (annual check up)
  - personalisation of parenting goals & delivery,
  - use of motivational strategies (MI, Rollnick).
- Average 3 sessions

Dishion et al, 2008; 2013

Gardner et al, 2009- moderators

www.pitt.edu/ppcl/PUBLICATIONS.HTML

Early Steps:

Moderator effects on child conduct problem outcomes

Found main effects, but for most variables—no moderator effects: i.e. families equally likely to respond at all levels of disadvantage/ distress

Two sig moderators found – out of 7:

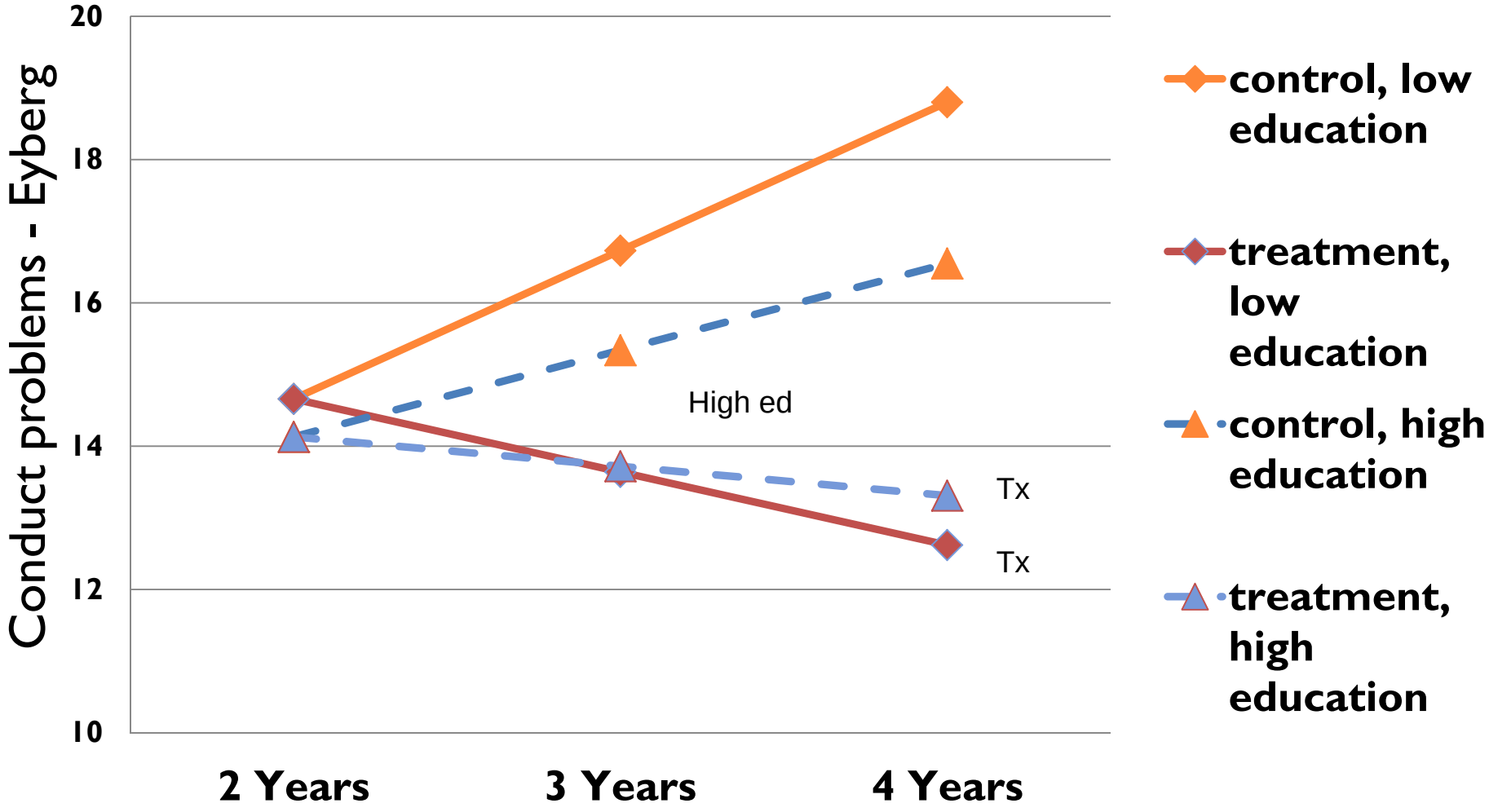
- Children of low educated mothers did better
- Children of single mothers did worse

No moderator effect when combined predictors into single risk index

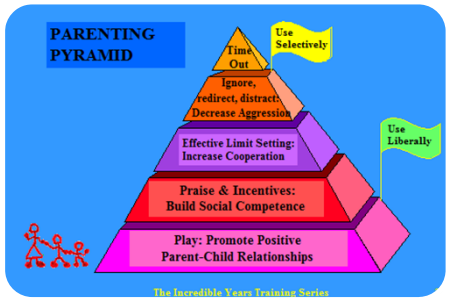
Large study, more optimistic picture than the 2006 reviews

Family Check Up trial: effects on child conduct problems by parent education level

Gardner et al 2009 (ES = .2 hi vs .7 for low ed)



Moderator effects in the North Wales Incredible Years Sure Start trial (Gardner et al., 2010)



Design

- Incredible Years 12 session group based parenting programme, multi-agency effectiveness trial in 11 ‘Sure Start’ areas
- 153 kids age 3-4, screened for high levels of problem behaviour
- Randomised to intervention, vs wait-list
- Moderators: family and child risk factors as moderators of change in conduct problems from pre to post-intervention

Hutchings et al., 2007, BMJ

Moderator effects in the North Wales Incredible Years parenting trial (Gardner, Hutchings et al. 2010)

Findings:

- Boys, & children with most depressed mothers, showed **greatest** improvement in conduct problems post intervention
- Other risk factors: teen or lone parent, very low income, showed **no** predictive effects

Conclusion:

- Intervention as successful at helping the most disadvantaged families, compared to more advantaged - Very distressed parents did better

Discrepant findings from trials

- Both our trials, one very large, found little evidence of moderation by social disadvantage
- For most ways of grouping by social disadvantage, no differential effects. Where there was sig moderation, it was more likely to favour the more distressed or disadvantaged families.

Is it only our trials? No ...

- Two large pooled data sets from Incredible Years trials (N= 500 & 800) found no differential effects by social disadvantage (Beauchaine 2005; Baydar 2003); Parents with drug or mental health problems did better.

Why discrepant from the highly cited reviews?

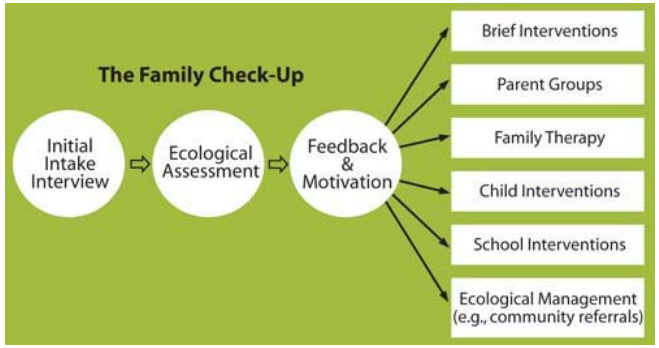
Why the discrepant findings?

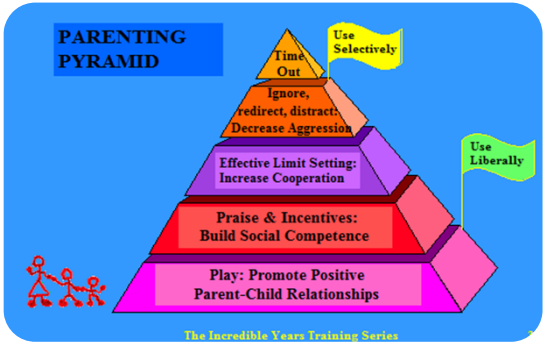
1. **Limitations of the highly cited 2006 meta-analyses**
   - Most analysed predictors, not moderators
   - Didn't examine heterogeneity of effects by intervention 'brand': some might be good at reaching the most distressed
   - Incomplete picture
2. **Depends which intervention?**
   - 4 omitted trials tell different story
   - N's in 3 studies *larger* than combined Ns in Reyno meta-analysis
   - Are the interventions different? Do they reach low income families better?
3. **Reviews reaching different conclusions**- ie no differential effects
   - Shelleby 2013; Menting et al., 2013; Furlong 2012 Cochrane review; Leijten, 2013

Depends which intervention?

Do programme differences mean some interventions better at reaching more disadvantaged families?

- Some interventions pay more attention to strategies for engaging and motivating very disadvantaged, hard to reach families
- eg Incredible Years uses collaborative group approach; Family Check Up uses personalised, home-based intervention (Dishion et al., 2008)
- The 4 trials not included in the 2006 meta-analyses





How to deal with these mixed findings?

What lessons from these studies to help us interpret and improve methods for moderators?

1. Consider limitations of analysing moderators at trial level

- Low power: trials powered for main effects
- Cherry picking: no pre-specified hypotheses
- Evidence that reporting bias is common in main effects analyses in trials (Dwan et al., 2008), likely more so when it comes to secondary analyses
- Failure to adequately adjust for multiple testing
- Moderators confounded

Long history of misgivings about moderator analyses in trials

"Only one thing is worse than doing subgroup analyses -- believing the results" Richard Peto

To prevent tempting cherry picking need: Explicit pre-specification of hypotheses: confirmatory or exploratory, plus rationale (Rothwell, 2005; Wang & Ware, 2013).

Need pre-registering, not just specifying somewhere.. ORCHIDS a model for us all

Chhangur and Weeland *et al. BMC Public Health* 2012, **12**:917
http://www.biomedcentral.com/1471-2458/12/917

BMC Public Health

STUDY PROTOCOL Open Access

ORCHIDS: an Observational Randomized Controlled Trial on Childhood Differential Susceptibility

Rabia R Chhangur†, Joyce Weeland†, Geertjan Overbeek*, Walter C H J Matthys and Bram Orobio de Castro

Abstract

Background: A central tenet in developmental psychopathology is that childhood rearing experiences have a major impact on children's development. Recently, candidate genes have been identified that may cause children to be differentially susceptible to these experiences (i.e., susceptibility genes). However, our understanding of the differential impact of parenting is limited at best. Specifically, more experimental research is needed. The ORCHIDS study will investigate gene-(gene-)environment interactions to obtain more insight into a) moderating effects of polymorphisms on the link between parenting and child behavior, and b) behavioral mechanisms that underlie these gene-(gene-)environment interactions in an experimental design.

Methods/Design: The ORCHIDS study is a randomized controlled trial, in which the environment will be manipulated with an intervention (i.e., Incredible Years parent training). In a screening, families with children aged 4–8 who show mild to (sub)clinical behavior problems will be targeted through community records via two Dutch regional healthcare organizations. Assessments in both the intervention and control condition will be conducted at baseline (i.e., pretest), after 6 months (i.e., posttest), and after 10 months (i.e., follow-up).

Discussion: This study protocol describes the design of a randomized controlled trial that investigates gene-(gene-) environment interactions in the development of child behavior. Two hypotheses will be tested. First, we expect that children in the intervention condition who carry one or more susceptibility genes will show significantly lower levels of problem behavior and higher levels of prosocial behavior after their parent(s) received the Incredible Years training, compared to children without these genes, or children in the control group. Second, we expect that children carrying one or more susceptibility genes will show a heightened sensitivity to changes in parenting behaviors, and will manifest higher emotional synchronization in dyadic interchanges with their parents. This may lead to either more prosocial behavior or antisocial behavior depending on their parents' behavior.

Trial registration: Dutch Trial Register (NTR3594)

Keywords: Randomized controlled trial, Externalizing behavior, Child behavior, Parenting, Gene-environment interaction, Differential susceptibility

Background

A central tenet in developmental psychopathology is that childhood rearing experiences have a major impact on children's development across life [1]. At the same time, we know that not all children are equally susceptible to these experiences [2]. Grounded in a diathesis-stress model, there has been growing attention for research on individuals' genetic susceptibility to parenting. The diathesis-stress model holds that some children, due to a specific vulnerability, are more likely to be negatively affected by environmental risk, such as with parental harshness, than others [3-5].

A typical characteristic of these studies is that they only examined environmental adversity and negative child outcomes. It may therefore be that we, for a long time, only studied so-called *dandelions*; the resilient children

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What do we normally when there are lots of data, but with low power and mixed findings?

Easy - do a good systematic review, and where appropriate, meta-analyse data across trials..?

For many questions, yes.. but

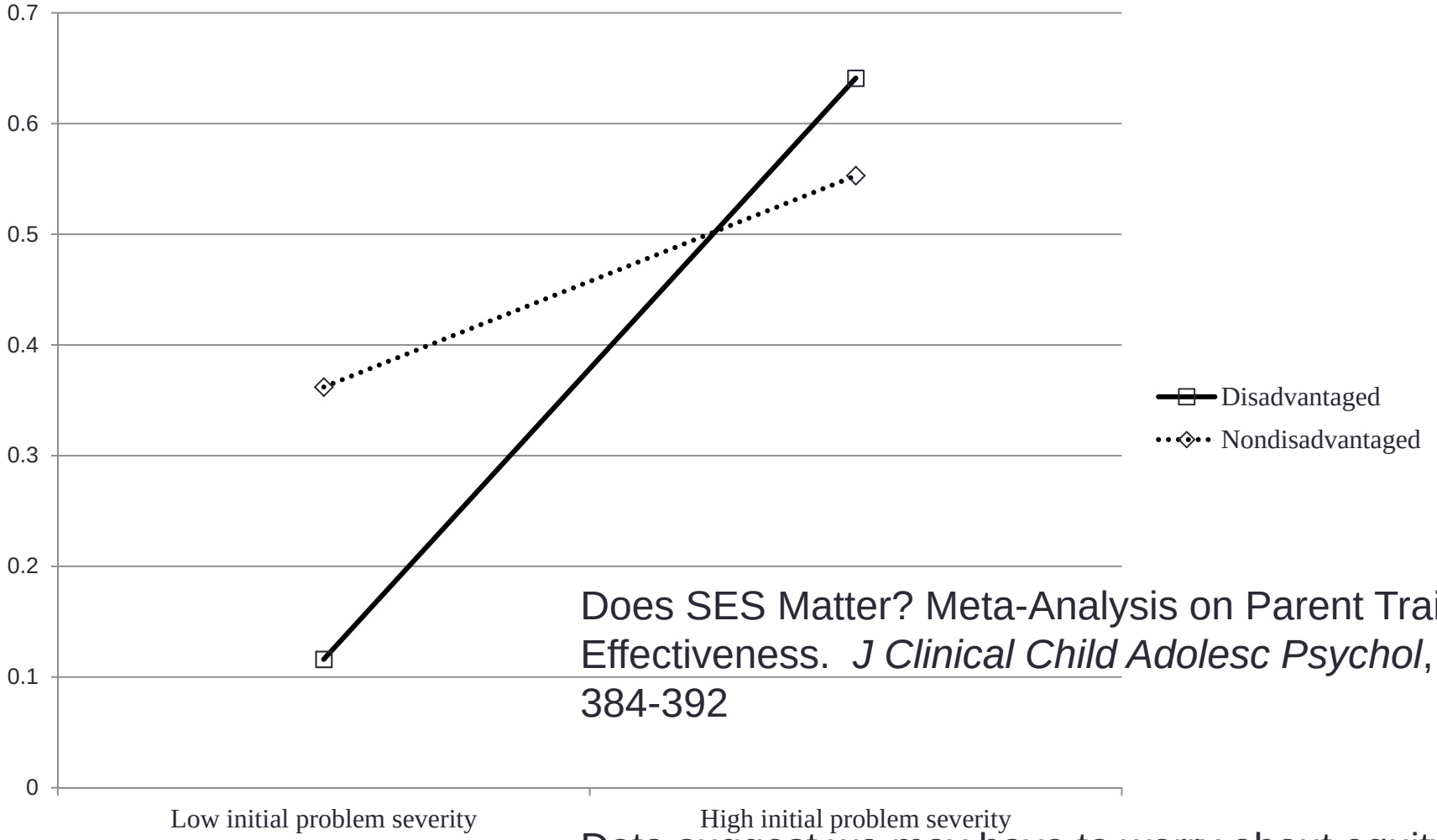
2. Consider limitations of analysing moderators in systematic reviews

- Power still low: although total Ns may be higher, subgroups are coded at trial level, meaning all variability *within* trials in participant characteristics is masked.

- Cherry picking: risk lower?

- Moderators still confounded (Lipsey, 2003); one meta-analysis attempted to overcome this - Leijten et al., 2013, examined how SES moderator effects were confounded by other risk factors, such as problem severity.

Confounded moderators:
Leijten, Raaijmakers, de Castro, Matthys (2013).



Does SES Matter? Meta-Analysis on Parent Training Effectiveness. *J Clinical Child Adolesc Psychol*, *42*, 384-392

Data suggest we may have to worry about equity effects, but only at the universal prevention end

Lots of data, quite a muddle.... is it due to program differences, low power, cherry picking, confounding, crude meta-analysis? What to do...?

- We could do bigger trials - build on what we know, so pre-planned and powered for moderator analyses
- We could do more trials - so more power for meta-analysis

Yes, or....

Use what we already have....

Pool data from lots of trials – using individual level data.
Many advantages:

- Makes full use of within-trial variability in characteristics
- Greatly increases power for subgroup analyses, especially rarer groups
- More power to control for confounders
- Transparency—help prevent cherry picking
- Can examine between and within trial sources of variance-contextual vs individual effects
- Wider generalisability across communities, contexts, regions

(Cooper & Patall, 2009; Brown et al 2013)
(also known as IPD, IDA)

Pooling data…

- Scientific benefits of sharing, collaboration between many investigator teams: wider influx of ideas to generate questions, build theoretical models, interpret findings = better science.
- Climate now is right?

  Big push from funders, journals, govts to share data to increase transparency, reduce fraud (ESRC, NIH, Ben Goldacre, AllTrials campaign) .
- Example NIMH Collaborative Data synthesis for Adolescent Depression Trials (Brown et al, 2013)

Pooling data from 13 European trials of Incredible Years (NIHR- PHR)

To what extent can parenting programmes improve child antisocial behaviour & reduce social inequalities?

We will examine:

(1) moderators: to what extent parenting interventions benefit the most socially disadvantaged families

(2) the wider public health benefits and potential harms of parenting interventions

(3) what mediates the effects on child outcome

Conclusions 1

- Moderator analyses worth doing, compared to predictor effects, but need to be pre-specified & adequately powered, and cautious in interpreting

- For family & parenting interventions, main effects clear but moderator data is mixed. However, some cause for optimism from large trials about equity effects

- Mixed findings may reflect real program differences - some may be better at helping disadvantaged families

Conclusions 2

- Mixed findings may reflect inadequate methods?

- Some common limitations in trials & meta-analysis for moderators:
  - power, cherry picking, confounding

- Unique limitation of meta-analysis: makes use only of between-trial variability in social factors; ignores huge within-trial variability

For moderator questions, need pooled individual-level data analysis to take field forward

Thank you!

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Director, Graduate programme in Evidence Based Social Intervention (come and do our MSc or Doctorate...)

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Family Check Up Model (Dishion et al 2008)