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Modelling multiple outcomes to improve the detection of causal mediation effects in complex intervention trials

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Outline:

The ProActive trial and intervention

Mediation methods and results

Factors influencing precision

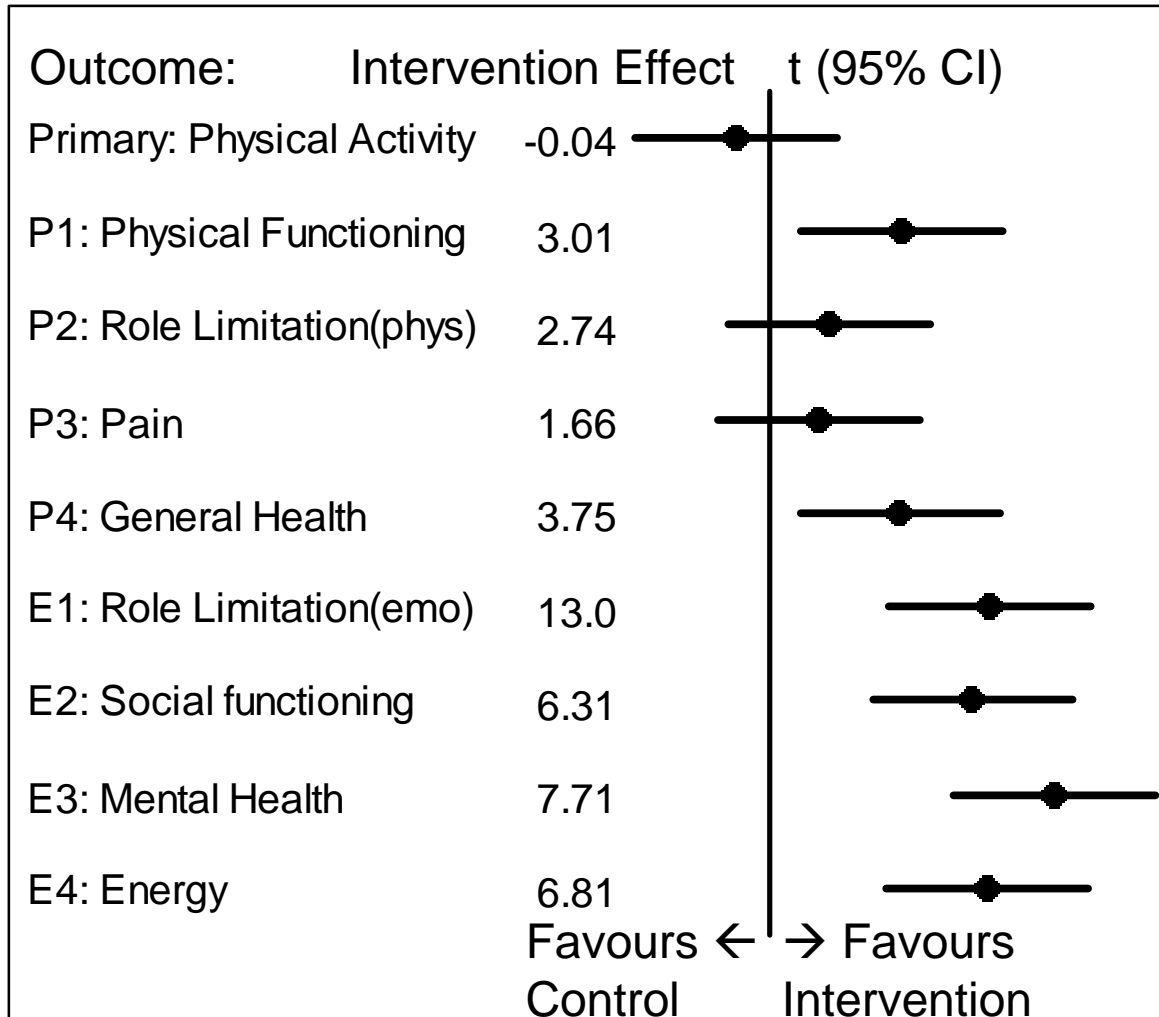
Key points

ProActive – Trial of a complex intervention

Who: N=365; 30-50y; parent with T2 Diabetes; sedentary

Aim: to increase physical activity in 1 year (25 min walk/day)

How: RCT parallel; control arm; intervention arms (combined)



SF36 effects genuine?

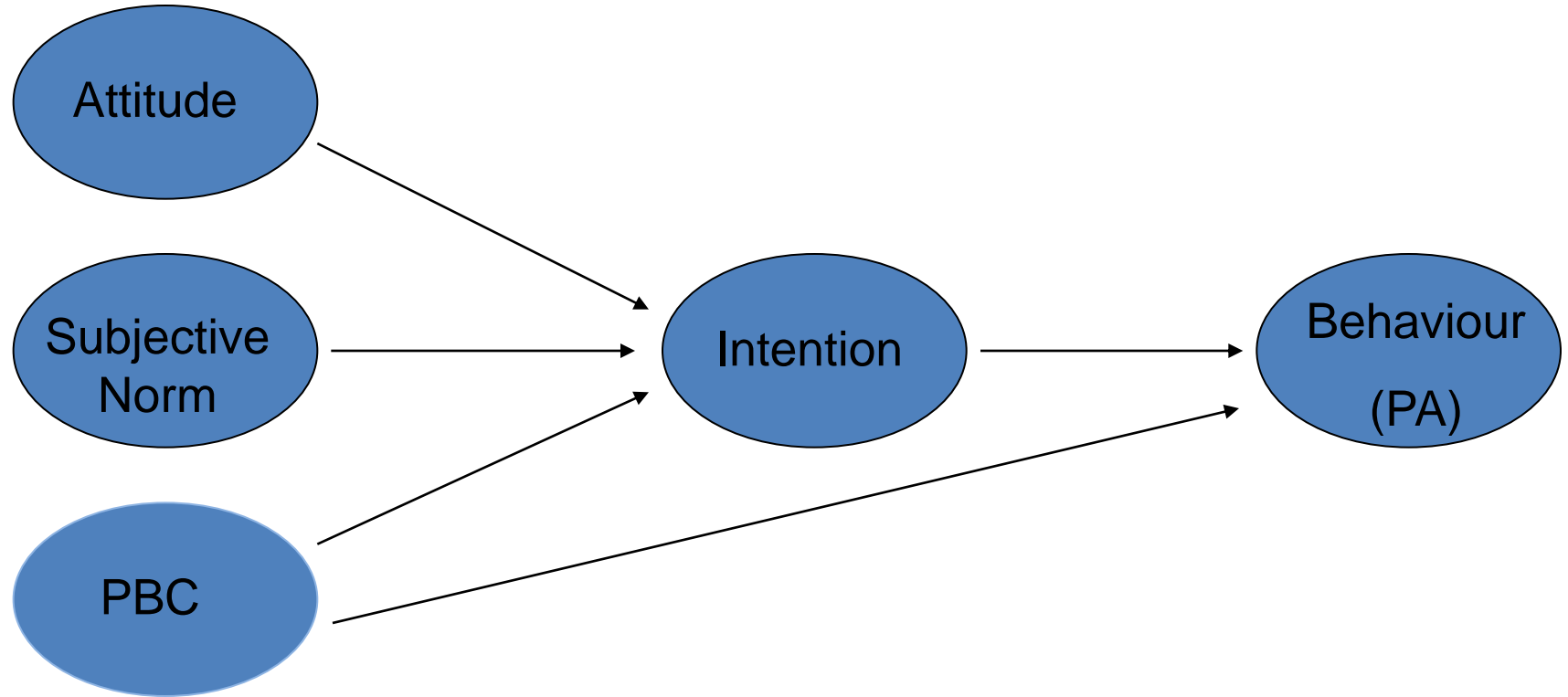
- through intervention

- self report bias

- chance

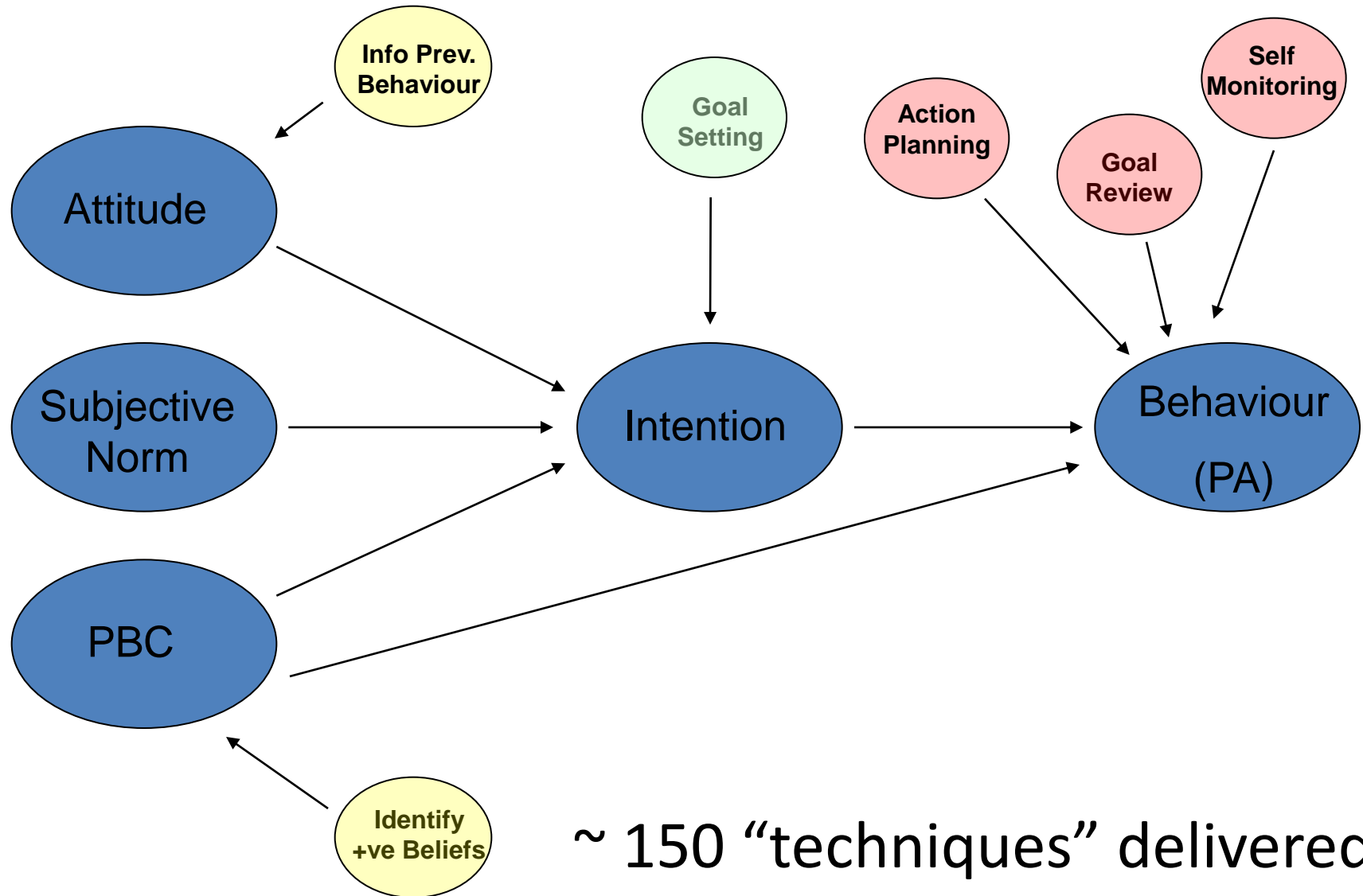
Intervention based on Theory of Planned Behaviour

Relationships are assumed to exist



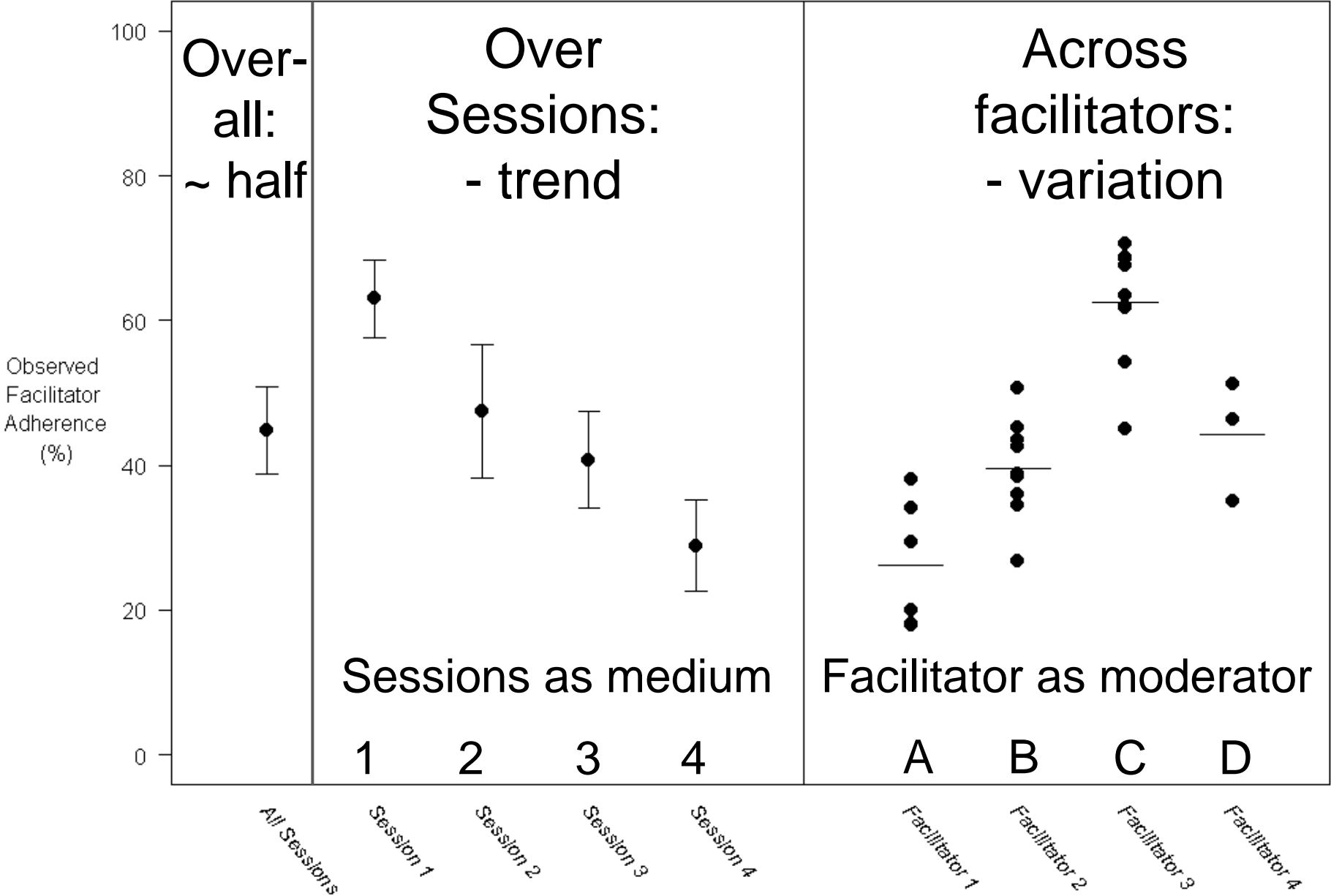
Meta-analyses support the “TPB” for physical activity. Previously developed MV meta-analysis methods to show “Intention – Behaviour” link stronger.

Intervention components: developed to target TPB

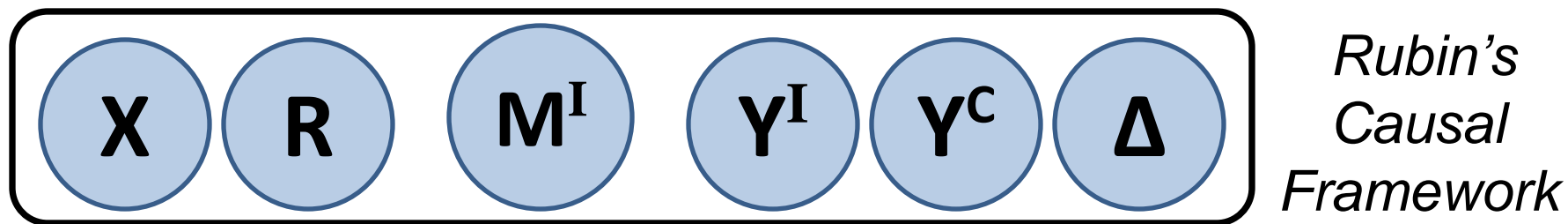
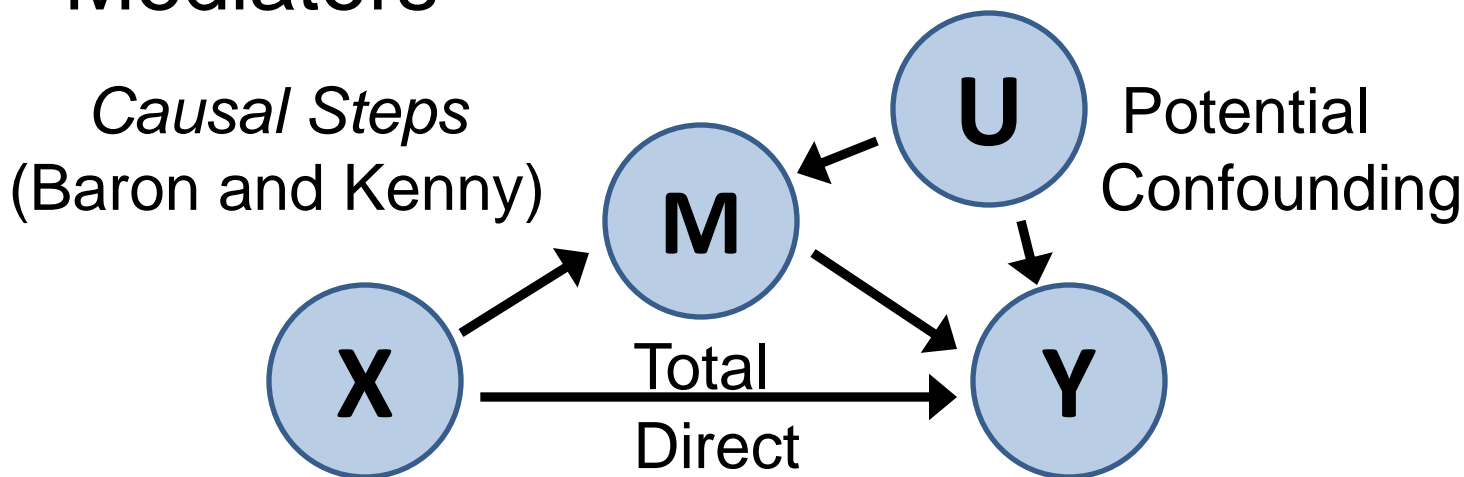


~ 150 “techniques” delivered across sessions by facilitators

Intervention delivered (“fidelity”): taped 10% sample



Mediators



SMM approach with two-stage LS estimation algorithm

1. Within arm, regress:

Y on X to predict Y^I, Y^C, Δ_i

M on X to predict M_i

2. Model Causal structure

$$\Delta_i = \beta M_i$$

$$\Delta_{ij} = \beta M_i \quad j=1\dots4$$

SE from Bootstrap [B=1000]

Multivariate SMM: GEE or lme

Why jointly analyse four outcomes?

Improve precision by estimating common effect

Bring more complex models within reach

Justify: SF36 outcomes have been aggregated before

$$\begin{pmatrix} 1 & 0.48 & 0.48 & 0.50 \\ 0.48 & 1 & 0.45 & 0.26 \\ 0.48 & 0.45 & 1 & 0.36 \\ 0.50 & 0.26 & 0.36 & 1 \end{pmatrix}$$

'SF-36 - Physical'

$$\begin{pmatrix} 1 & 0.67 & 0.52 & 0.41 \\ 0.67 & 1 & 0.60 & 0.48 \\ 0.52 & 0.60 & 1 & 0.64 \\ 0.41 & 0.48 & 0.64 & 1 \end{pmatrix}$$

'SF-36 - Emotional'

Correlations not implausibly low to weaken the justification

Correlations low enough to offer gains

Estimated β (SE): increase in SF36 outcomes* / session attended

* SF36 outcomes scaled to make each have SD=10 (~ halved)

SF36 Physical		SF36 Emotional	
P1	0.46 (0.18)	E1	0.84 (0.23)
P2	0.27 (0.25)	E2	0.77 (0.20)
P3	0.20 (0.22)	E3	0.89 (0.20)
P4	0.49 (0.20)	E4	0.90 (0.23)

Test assumption of common beta: MV Wald test (3 df)

Physical: p=0.34 Emotional: p=0.96

Estimated β (SE): increase in SF36 outcomes* / session attended

* SF36 outcomes scaled to make each have SD=10 (~ halved)

SF36 Physical		SF36 Emotional	
P1	0.46 (0.18)	E1	0.84 (0.23)
P2	0.27 (0.25)	E2	0.77 (0.20)
P3	0.20 (0.22)	E3	0.89 (0.20)
P4	0.49 (0.20)	E4	0.90 (0.23)
MV	0.40 (0.15)	MV	0.89 (0.18)

Test assumption of common beta: MV Wald test (3 df)

Physical: p=0.34 Emotional: p=0.96

MV: Linear mixed effects model – general correlation structure

SE reduced: Physical: 27% Emotional: 16%

Alternative causal model structures

(1) $\Delta_i = \beta M_i$ Single mediator model

(2) $\Delta_i = \alpha + \beta M_i$ With effect not all through mediator

(3) $\Delta_i = \beta M_i + \beta_{MF} MF_i$ With effect moderated by facilitator

Poor precision for estimates from (2) with SE typically X 15

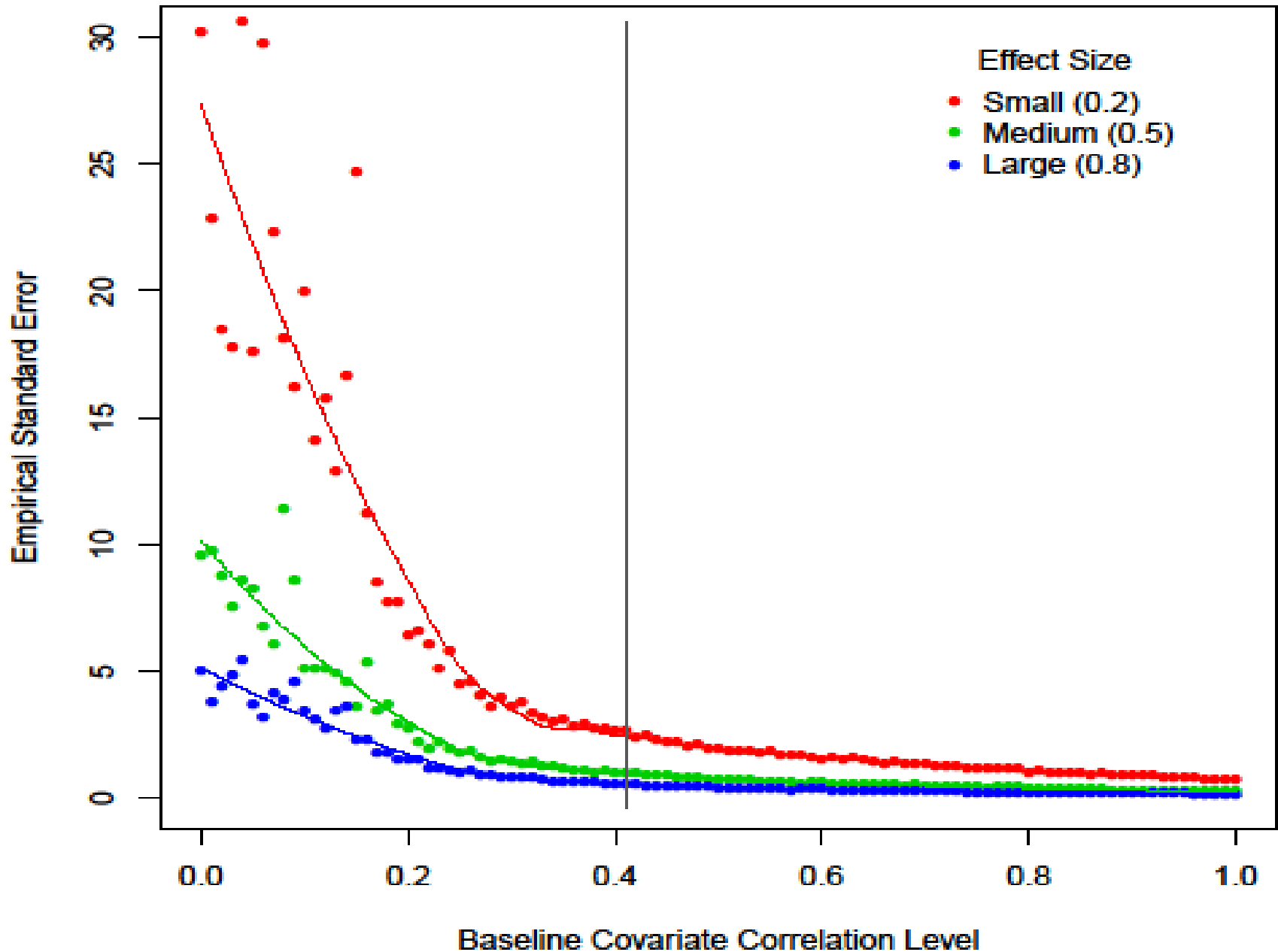
Monte Carlo Simulation study:

Trial Effect Size ($R \rightarrow Y$) is influential

for ability to detect mediation effects

using dose-response model (1)

For (2) $\Delta_i = \alpha + \beta M_i$ both $R \rightarrow Y$ and $X \rightarrow M^I$ strength matter



Key points

Power to detect mediation is larger when trial effect is larger

Mediation is detectable using Model (1)

Precision can increase by up to 40% using MV SMM

Very low power to detect mediation with Model (2)

Baseline covariate correlation > 0.3 (0.8) helps bit (lot)

MV SMM of multiple outcomes helps more

Need for baseline covariates predictive of session attendance

For ProActive, from model (1) with assumption

SF36 effects seem more likely genuine after
undertaking the mediation analysis

Complex intervention references

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