Pitfalls in precision medicine:

How do we know individuals differ in their response to a health intervention?

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Definitions and Scope

- Precision (Personalised) Medicine
  - *Using information about a person, e.g. genes, to precisely target interventions to persons who are most likely to benefit and least likely to experience adverse effects*
    (Pletcher, 2017)
- This talk is about **individual response** to interventions and treatments rather than individual risk for future disease
- My bias is on **exercise interventions** but principles are quite **generalizable**

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Progress in Cardiovascular Diseases

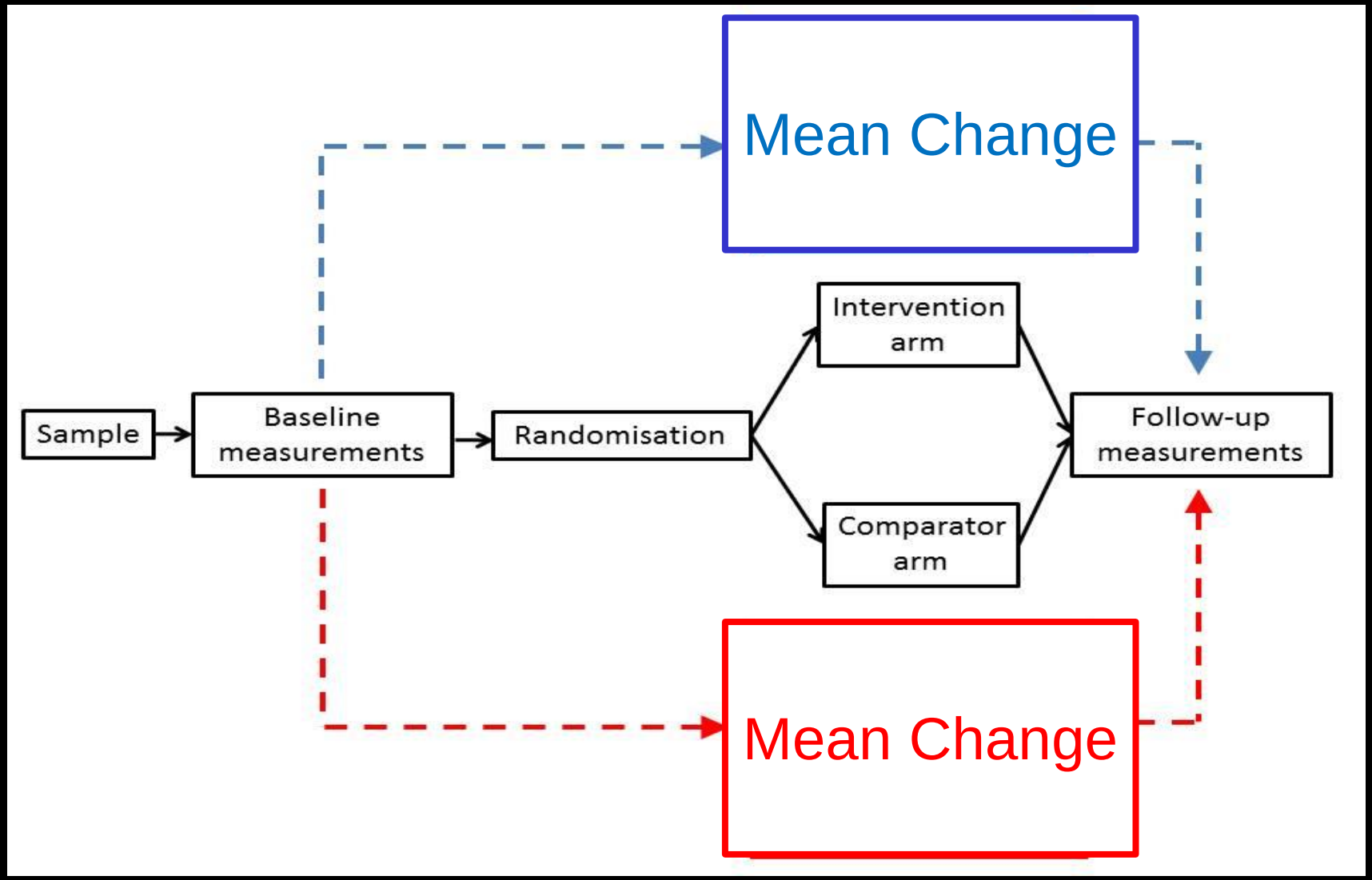
Personalized Preventive Medicine: Genetics and the Response to Regular Exercise in Preventive Interventions

Claude Bouchard[a,*], Ligia M. Antunes-Correa[b], Euan A. Ashley[c,d], Nina Franklin[e], Paul M. Hwang[f], C. Mikael Mattsson[c,g], Carlos E. Negrao[b,h], Shane A. Phillips[e], Mark A. Sarzynski[a], Ping-yuan Wang[f], Matthew T. Wheeler[c,d]

The mean response of a sample "*fails to recognize that there are considerable inter-individual differences in responses to any exercise program*"

(Bouchard *et al*., 2014; p.2).

A typical RCT on diastolic blood pressure response to exercise



Results for sample mean response

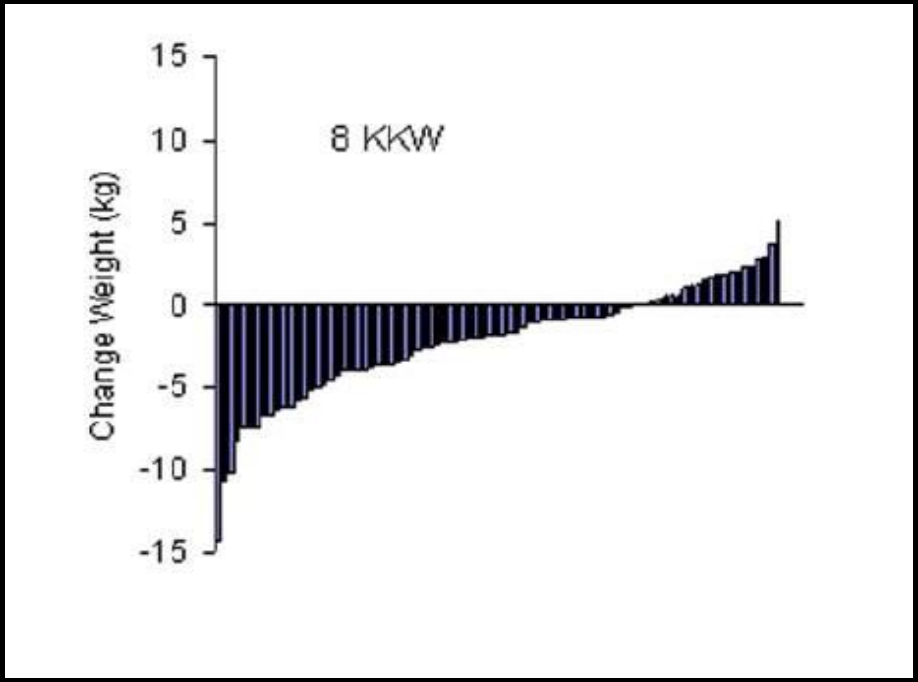
- Our minimum clinically important reduction in BP is 5 mmHg
- Intervention arm:
  - Mean (SD) decrease from 75.6 (19.2) mmHg to 70.4 (18.9) mmHg Reduction of 5.2 mmHg
- Comparator arm:
  - Mean (SD) change from 75.4 (18.9) to 75.6 (19.2) mmHg Slight rise of 0.2 mmHg
- Baseline-adjusted (ANCOVA) mean (95%CI) difference in changes: 5.4 (4.8-6.1) mm Hg

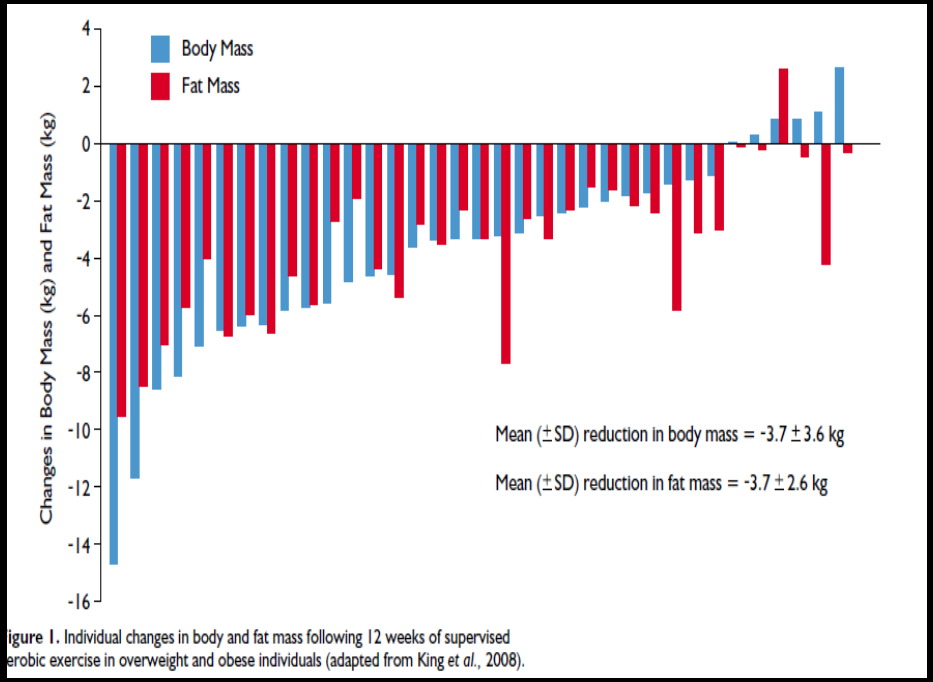
Mean response is above MCID indicating a successful intervention in this case

Researchers tend to get more excited about individual differences in treatment response when the really lovely result above is **not found**

Hmmmmmm!

How individual differences are presented in the literature

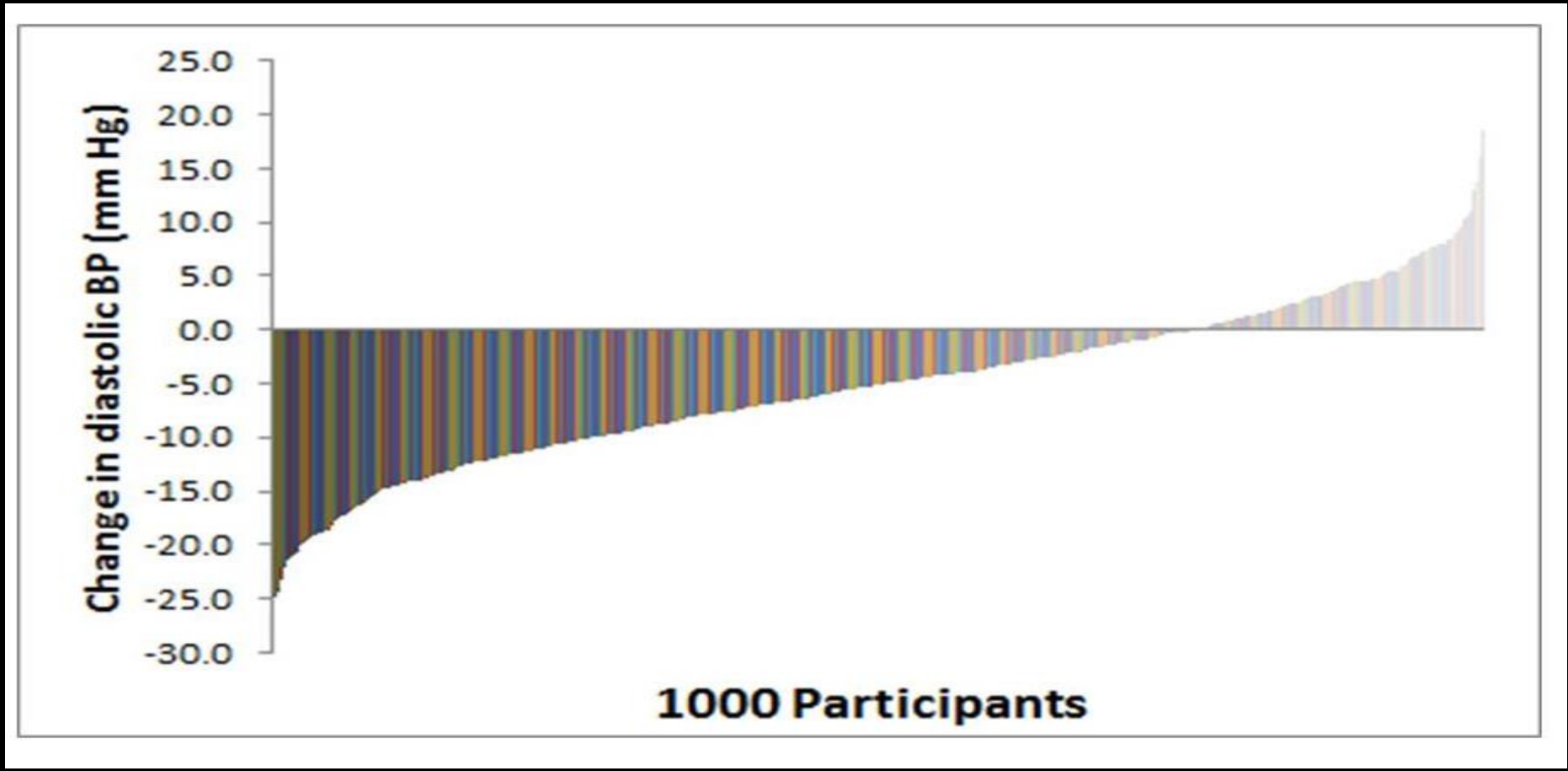




Church TS, *et al. PLoS ONE* 2009; 4: e4515.

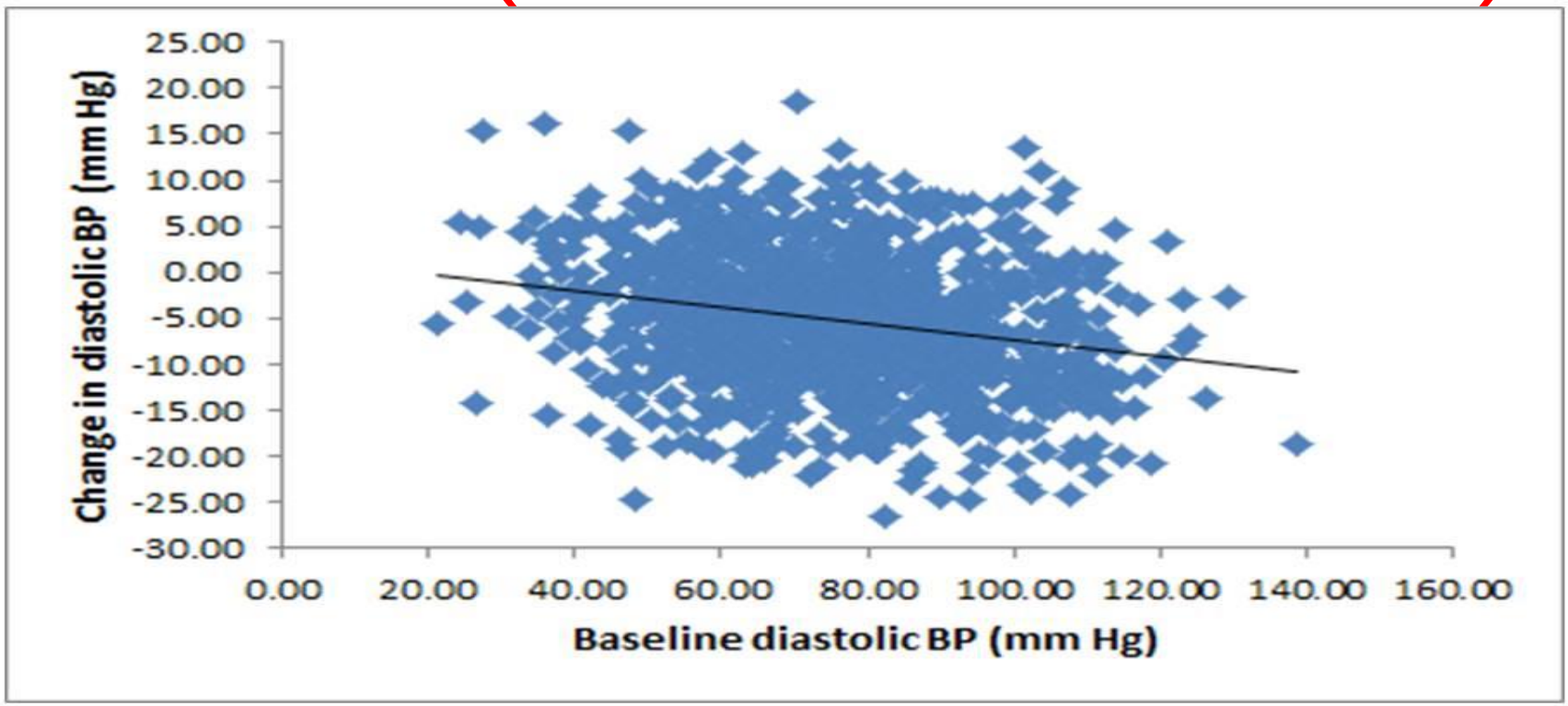
King, N., *et al. Int J Obes*. 2008; 32: 177–184

Individual differences in BP response in our intervention arm



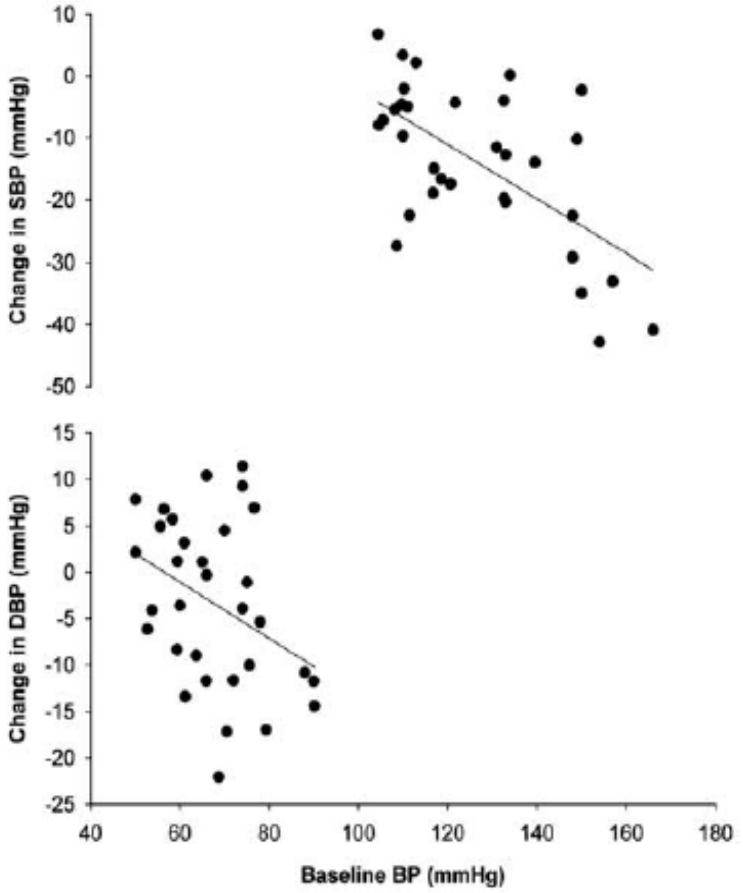
Our BP "responders" have a higher baseline BP and *vice versa (Personalised Medicine)*

r = -0.23 (95% CI: -0.29 to -0.17)



Great! – agrees with position statements

ACSM position statement "The variable that makes the largest contribution to the change in BP after exercise appears to be the pre-exercise value."



I conclude.....

- There is s<u>tantial</u> individ variation in the bloo ure resp n exerci ro
- Almost ha a BP response to g that is <u>less than</u> the M
- Exercis for people an ex blood pressure aseline
- Let's now secure <u>£££</u> to do some genomics

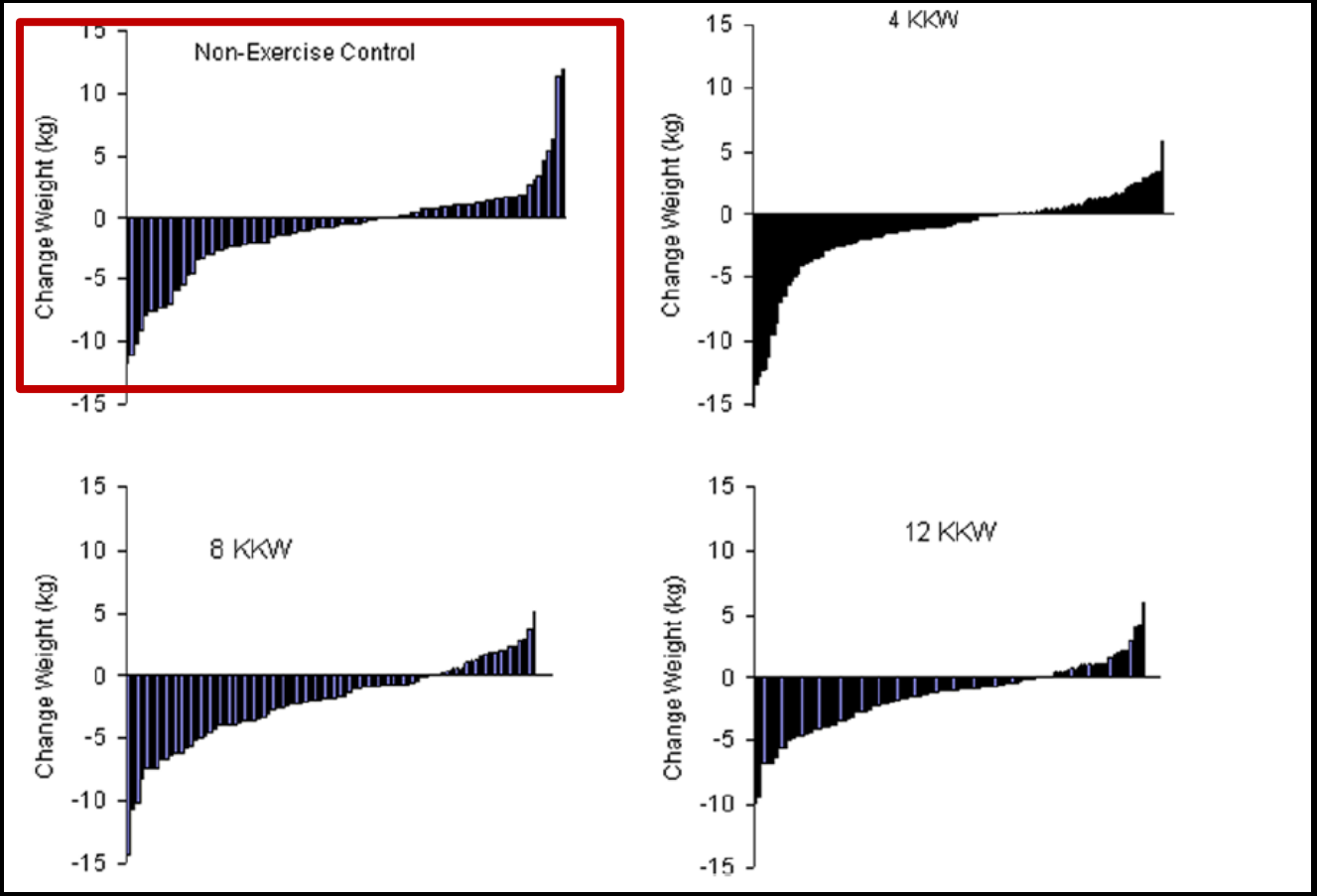
The truth is that BP response is exactly the same for everyone

-5 mmHg for everyone!

Individual differences

	True baseline	True follow-up	Error in baseline	Error in follow-up	Observed baseline	Observed follow-up	Observed change
1	67.29	62.29	15.08	-6.46	82.37	55.83	-26.54
2	44.57	39.57	3.76	-16.03	48.33	23.54	-24.80
3	82.22	77.22	11.88	-7.72	94.10	69.50	-24.60
4	78.45	73.45	11.62	-7.78	90.07	65.67	-24.40
5	106.20	101.20	1.63	-17.44	107.83	83.76	-24.07
994	70.82	65.82	-7.86	10.25	62.96	76.07	13.12
995	80.11	75.11	-3.94	14.45	76.17	89.56	13.39
996	110.88	105.88	-9.33	9.29	101.55	115.18	13.62
997	60.30	55.30	-12.83	7.48	47.47	62.78	15.31
998	41.42	36.42	-13.85	6.66	27.57	43.08	15.51
999	48.93	43.93	-12.89	8.20	36.04	52.13	16.08
1000	80.95	75.95	-10.73	12.87	70.22	88.82	18.59
M	75.45	70.45	0.13	-0.10	75.58	70.35	-5.23
SD	18.38	18.38	5.11	5.12	19.23	18.92	7.39

We MUST look at control data to see if response diffs > random within-subjects variability



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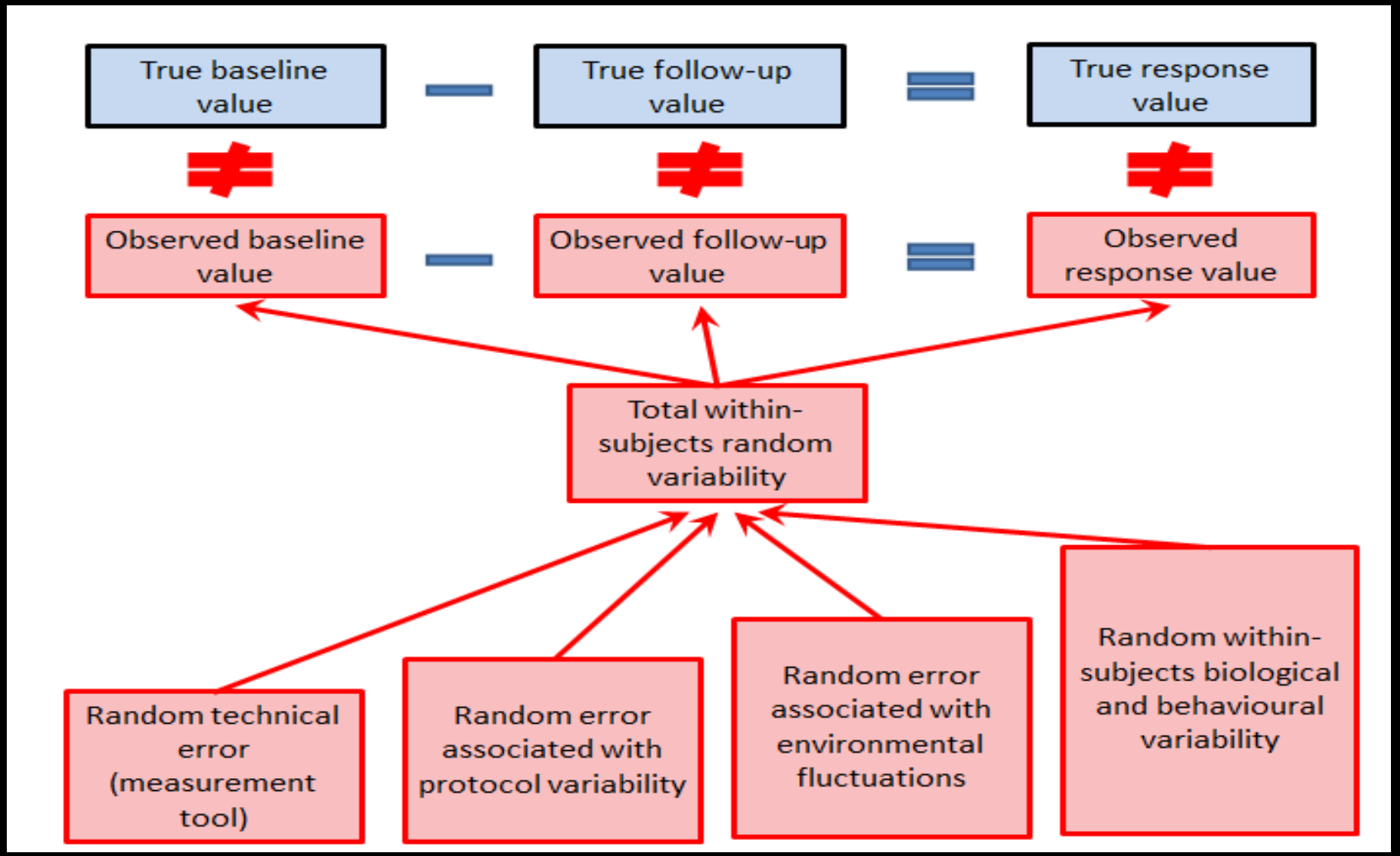
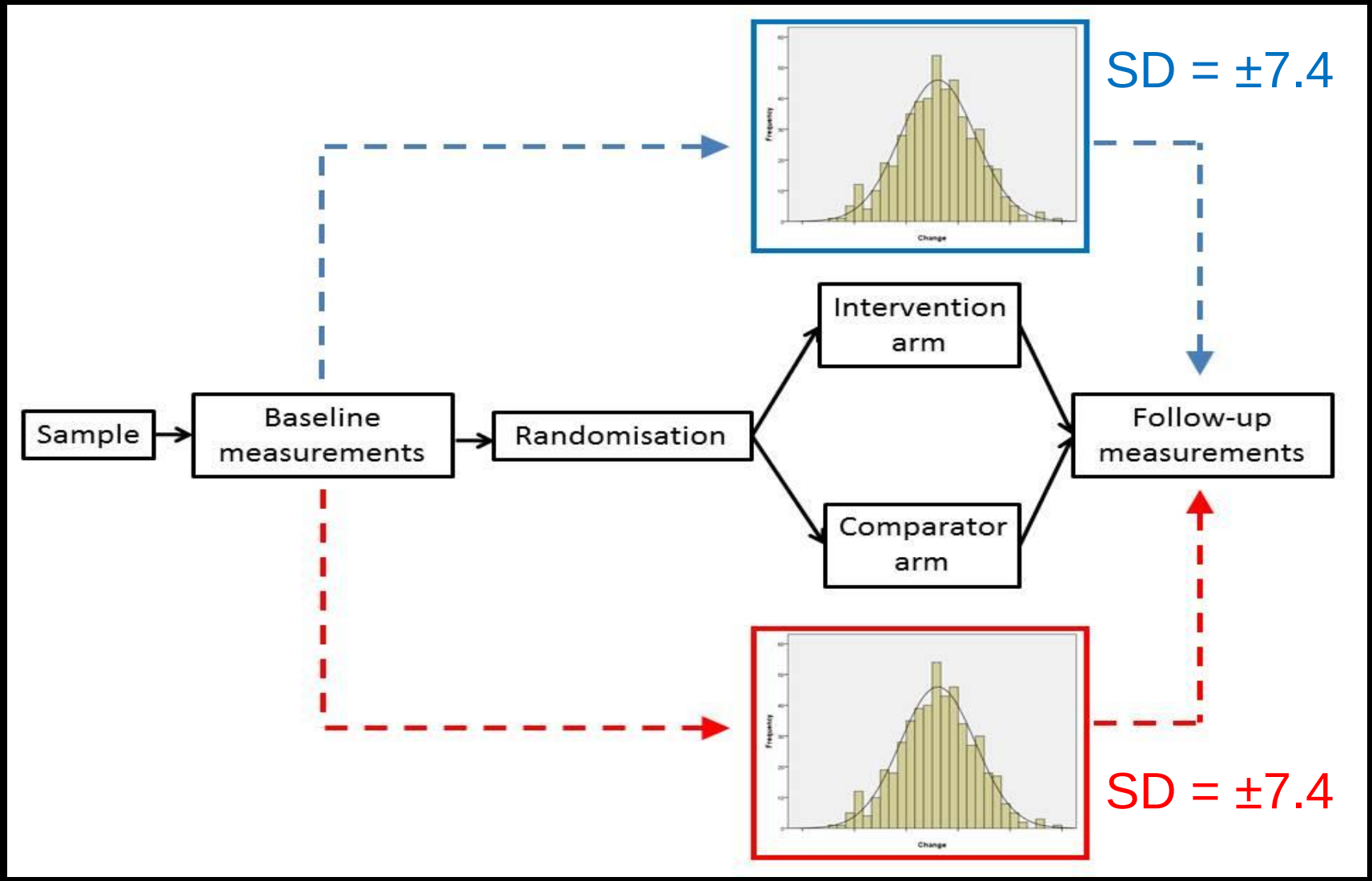
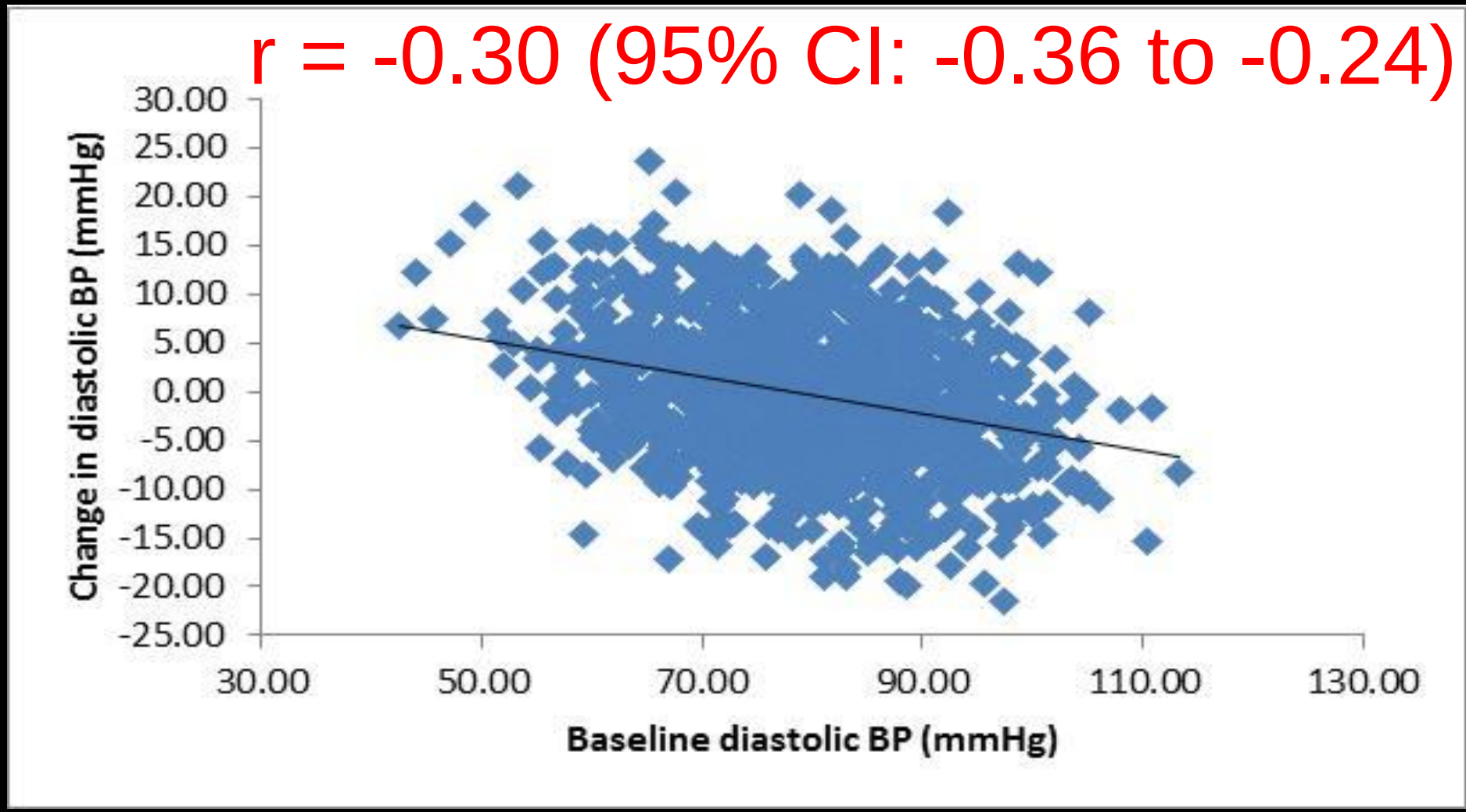
We're NOT just talking about "measurement errors" here



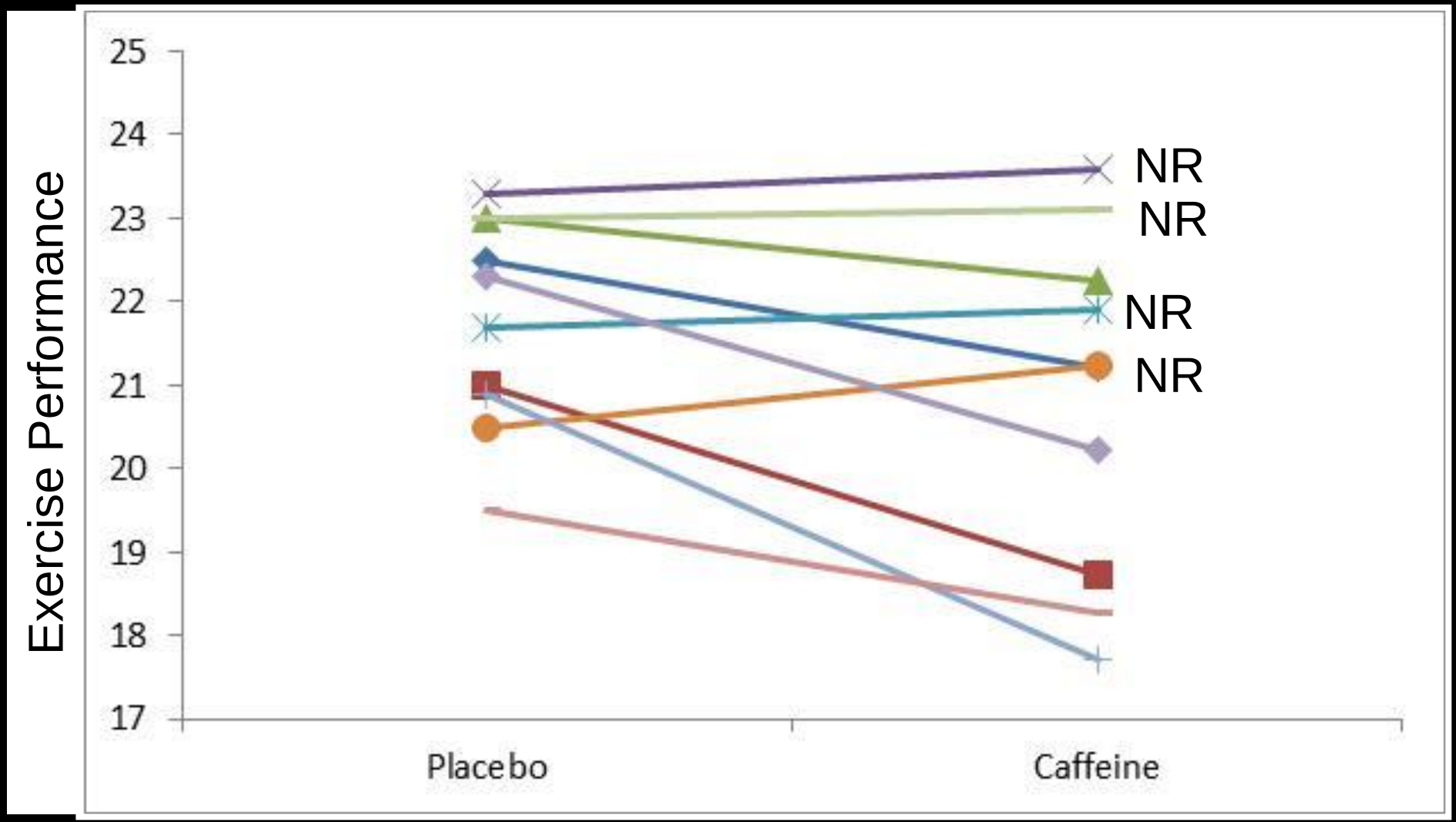
Individual differences in intervention must be compared against those in control



P.S. This observed association is <u>just regression to the mean</u> (Same result as before also in control group)



Same with crossover studies (acute):
No individual response differences here
Just trial-trial random variation



Replicate crossover trials needed in this case

Interindividual responses of appetite to acute exercise: a replicated crossover study

Fernanda R. Goltz [1,2], Alice E. Thackray [1,2], James A. King [1,2], James L. Dorling [1,2], Greg Atkinson [3], David J. Stensel [1,2]

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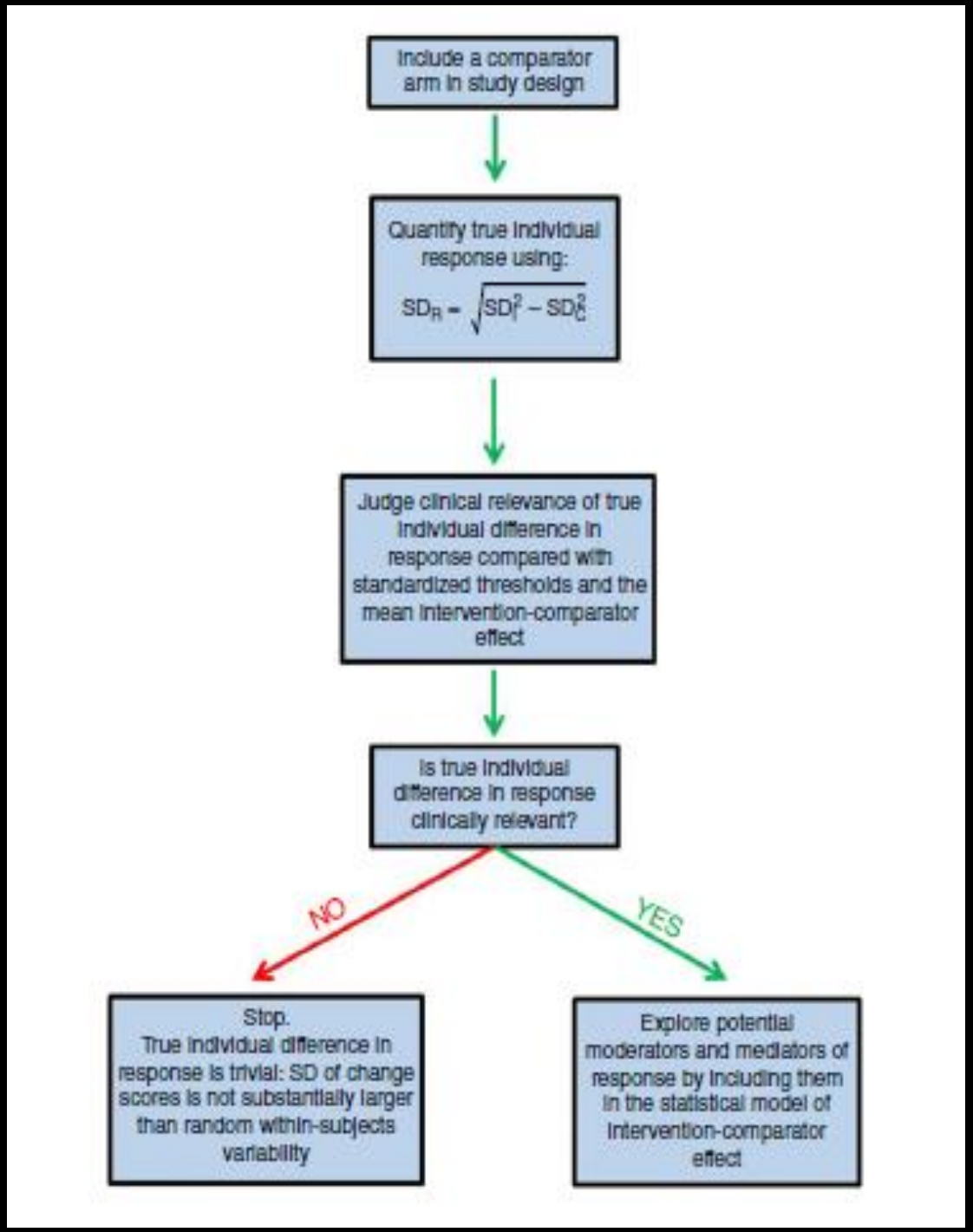
We maintain that

- It is **no good whatsoever** just looking at treatment responses **only** in the treatment group
- **Control data** are needed (just like for analysis of mean differences)
- Typical random variability between baseline and follow-up can **masquerade** as response differences
- Regression to mean can **masquerade** as responses predictors
- Response differences need to be known to be "**true**" and clinically important **BEFORE** we do anything else

Our "Road-Map"


Include a comparator arm in study design
Quantify true individual response using:
$SD_R = \sqrt{SD_I^2 - SD_E^2}$
Judge clinical relevance of true individual difference in response compared with standardized thresholds and the mean intervention-comparator effect
Is true individual difference in response clinically relevant?
NO
YES
Stop.
True individual difference in response is trivial: SD of change scores is not substantially larger than random within-subjects variability
Explore potential moderators and mediators of response by including them in the statistical model of intervention-comparator effect

Are we too late?

Sports Medicine

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Inter-Individual Responses of Maximal Oxygen Uptake to Exercise Training: A Critical Review

Authors | Authors and affiliations

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Review Article

First Online: 17 January 2017

The mean response of a sample "*fails to recognize that there are considerable inter-individual differences in responses to any exercise program*" (Bouchard *et al*., 2014; p.2).

Thank you for your attention

(which probably showed individual variation)