DANONE NUTRICIA RESEARCH

Challenges in the interpretation of Real World Data analysis

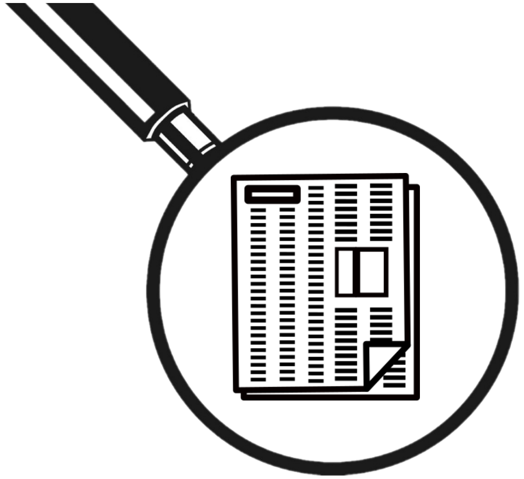
SOPHIE SWINKELS

SEPTEMBER 2022

RWE STUDY DESIGNS

RWE "STRICT"

Studies **available** real-world data



- Electronic health records (EHRs)
- Claims and billing databases
- Product and disease registries
- Data gathered from biosensors in computers, mobile devices and wearables

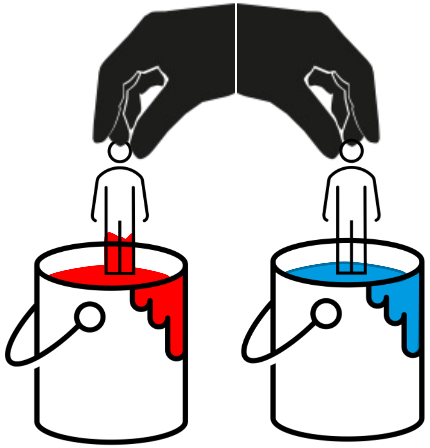
DESIGNS

Experimental / Interventional studies

"forced" intervention

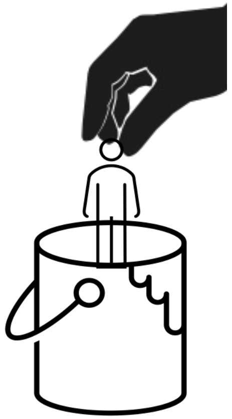
Randomized

Experimental



Non-randomized

Quasi-experimental



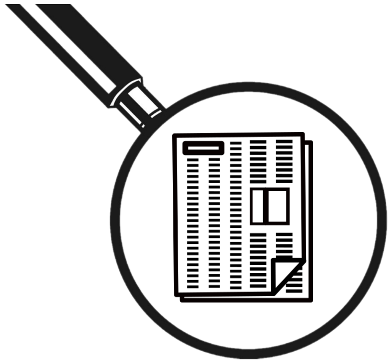
Non-experimental

Data collected on subjects

Observational

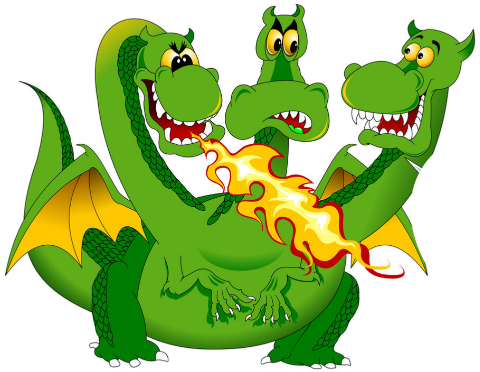
Based on existing data

RWE **"strict"**



MANY STUDY DESIGN ELEMENTS ARE INTENDED TO PREVENT DISTORTIONS

DISTORTIONS



Selection bias
At start: selectively enrolment

Performance bias
During conduct: different exposure to factors / care provided

Attrition bias
Nonrandom withdrawals

- **Subjects not representative**
- **“Unfair” comparison**

Observer bias:
Subjects act or report differently when studied

Response bias
People want to please

We cannot trust the measurements

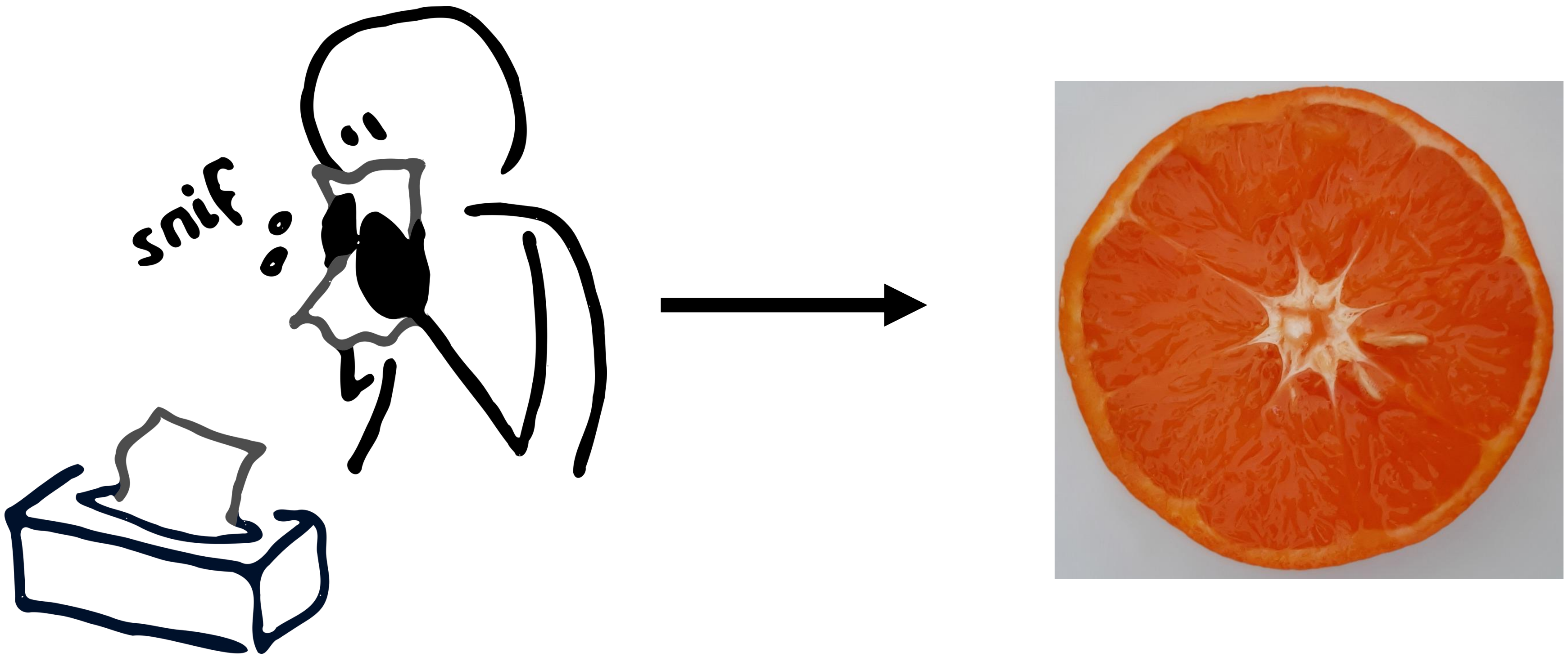
Time bias:
Change happens because of time passing

Confounding
Other factor driving results

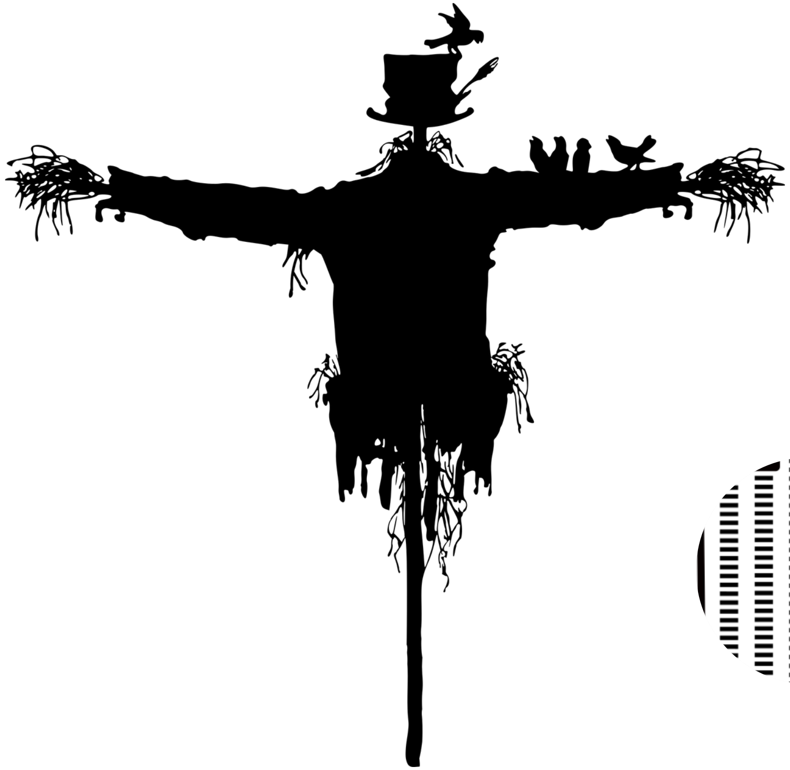
Wrong conclusion

REVERSE CAUSATION

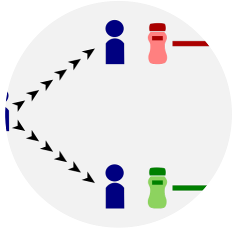
After noticing symptoms, people are more motivated to use certain products



DESIGN ELEMENTS THAT FIGHT DISTORTIONS

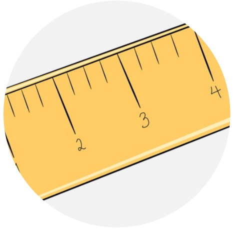


Randomise



Control arm

Product assignment

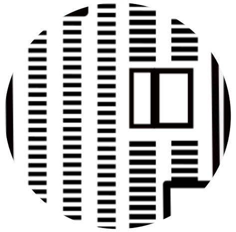


Baseline measurement

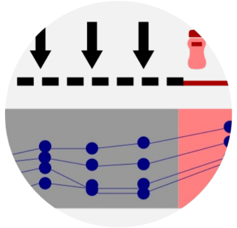
Allocation concealment

Prospective

Blind



Trial registry



Repeated measurements

Crossover

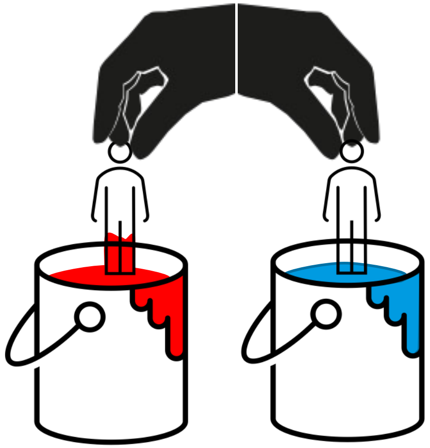
Objective outcome

Experimental / Interventional studies

Non-experimental

Randomized

Experimental



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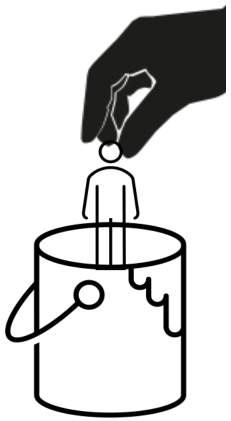
Quasi-experimental

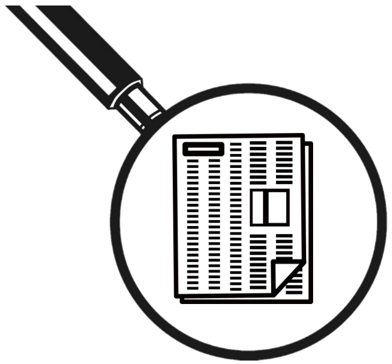


Data collected on subjects

Observational

Based on existing data

RWE **“strict”**

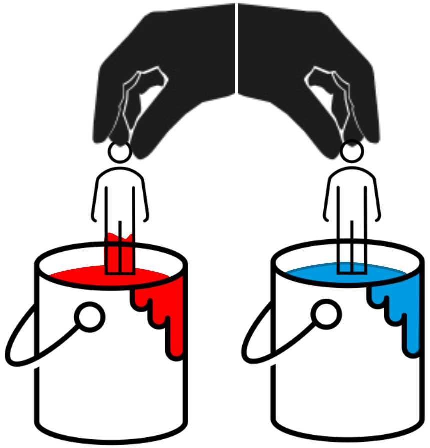


design elements that fight distortions

Experimental / Interventional studies

Randomized

Experimental



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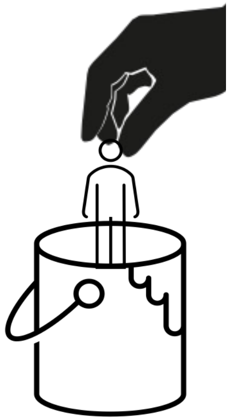

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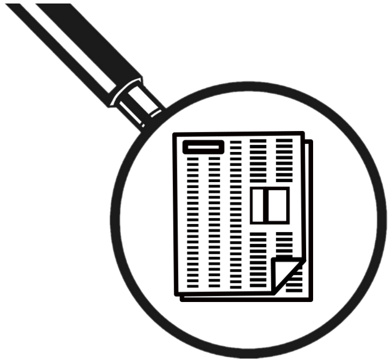

Chance of distortions

	Data
Pro-spectively	Measurements specifically for this study
	Clinical practice measurements
	Subject provides data during the study
	Digital device / AI provides data during the study

Retro-spectively	Existing registries / databases

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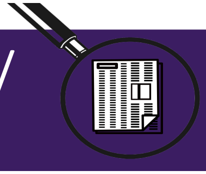
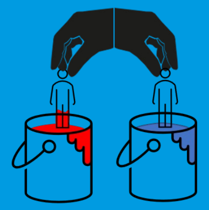
Retro-spectively	Existing registries / databases 	RWE “strict”

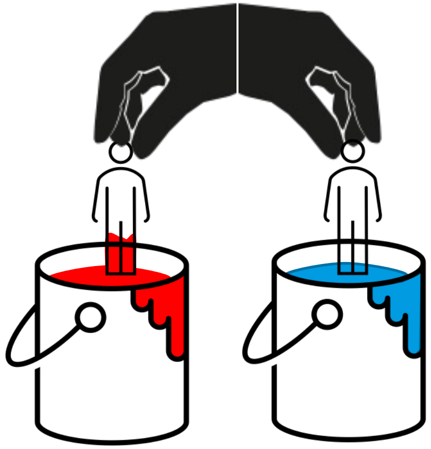
Design / Data		Experimental 	Quasi-experimental 	Observational 
Pro-spectively	Measurements specifically for this study		RWE “broad”	
	Clinical practice measurements	RWE “broad”		
	Subject provides data during the study			
	Digital device / AI provides data during the study			
Retro-spectively	Existing registries / databases	RWE		

RWE "broad"

Experimental / Interventional studies

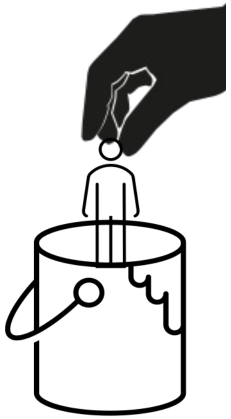
Randomized

Experimental



Non-randomized

Quasi-experimental



Non-experimental

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Observational

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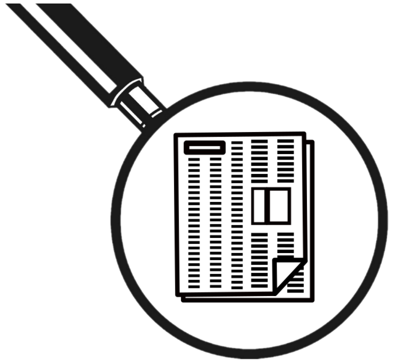
RWE "strict"

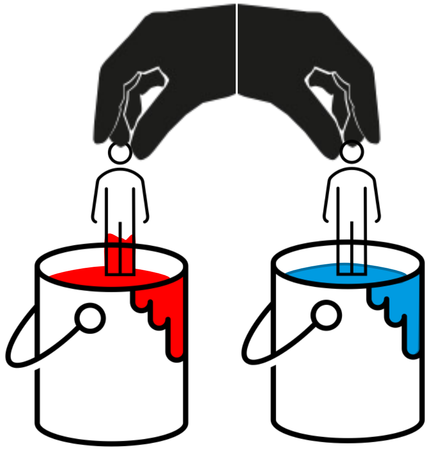


OPTIONS FOR DESIGN

Pragmatic clinical trial

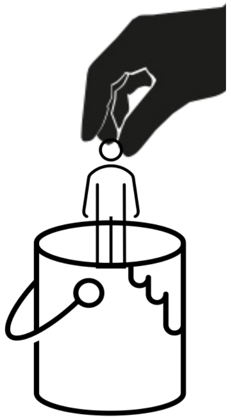
Randomized

Experimental



Non-randomized

Quasi-experimental



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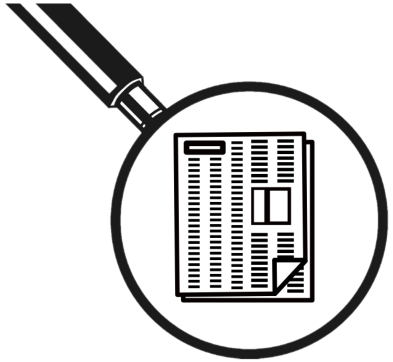
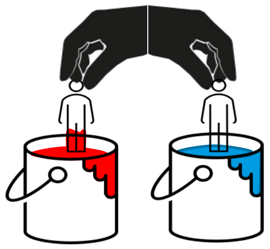
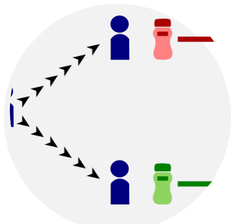




EXPERIMENTAL DESIGNS

PRAGMATIC CLINICAL TRIAL



Controlled

Randomise

Blinding

Relaxed in- and exclusion criteria,
Visits and measurements regular clinical practice

Advantages

- Real-world setting.
- Wider population: easier recruitment

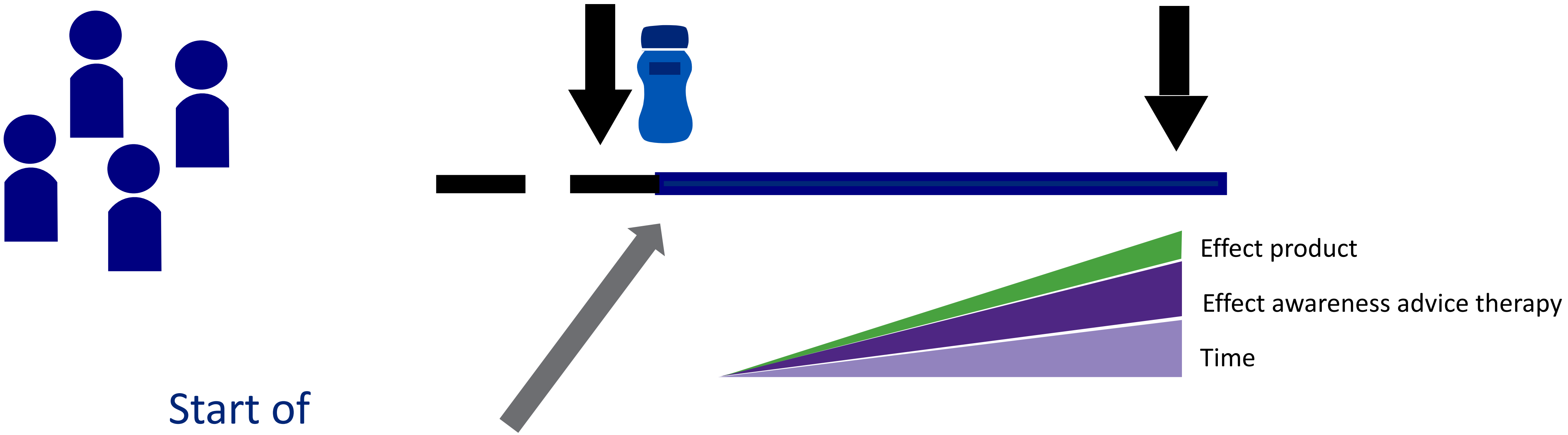
Disadvantages

- More noise in data: more challenging to find effect

PRE – POST DESIGN

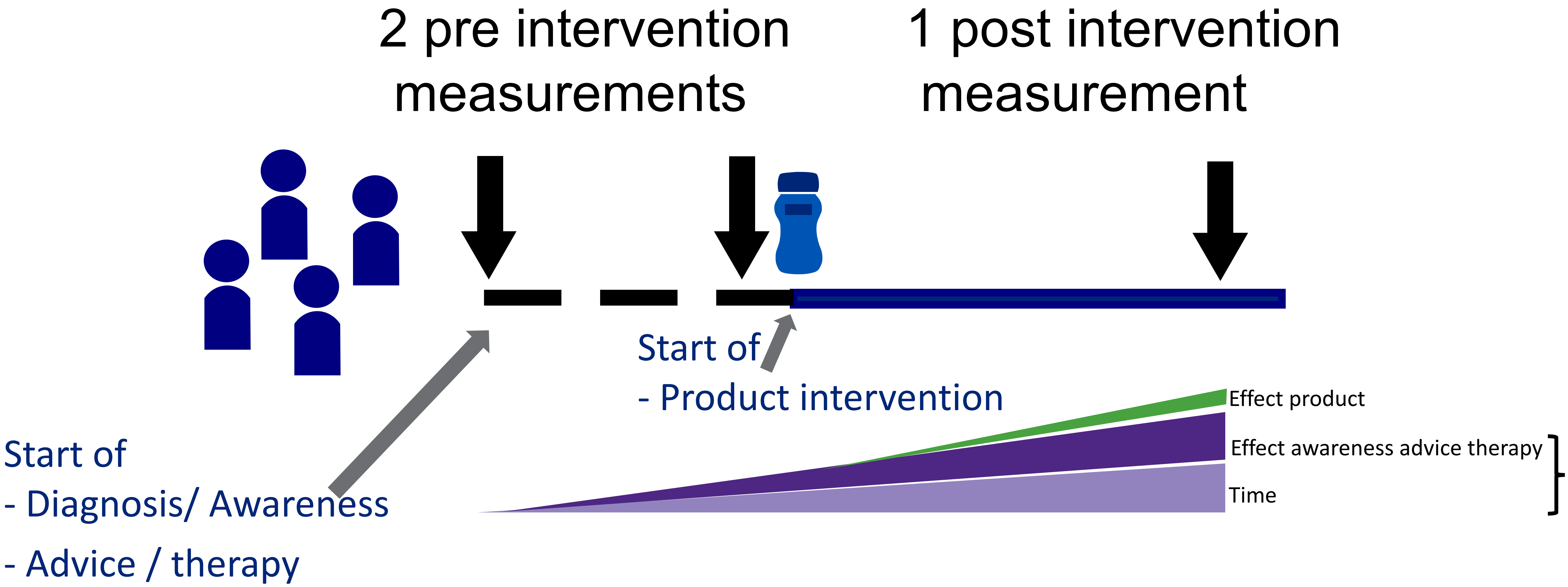
1 pre intervention measurement

1 post intervention measurement



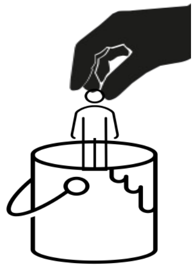
Start of
- Diagnosis / awareness
- Advice / therapy
- Product intervention

PRE – POST DESIGN

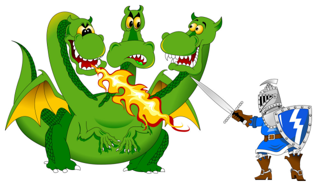


Two baseline measurement can give you an idea of some effects.

You can subtract this to get a “purer” idea of the effect of the product.

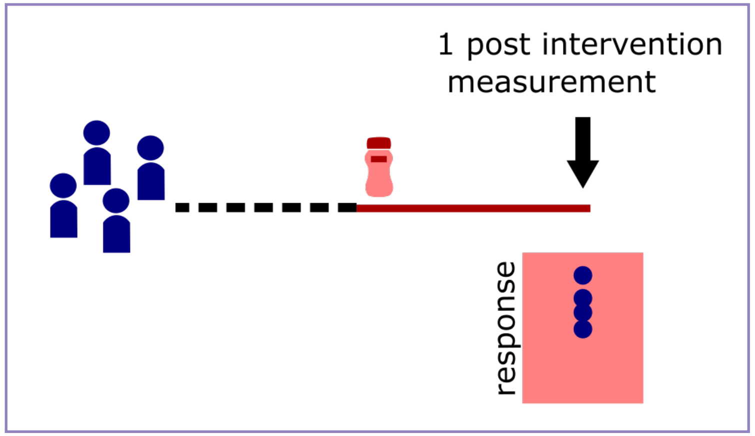


QUASI-EXPERIMENTAL DESIGN

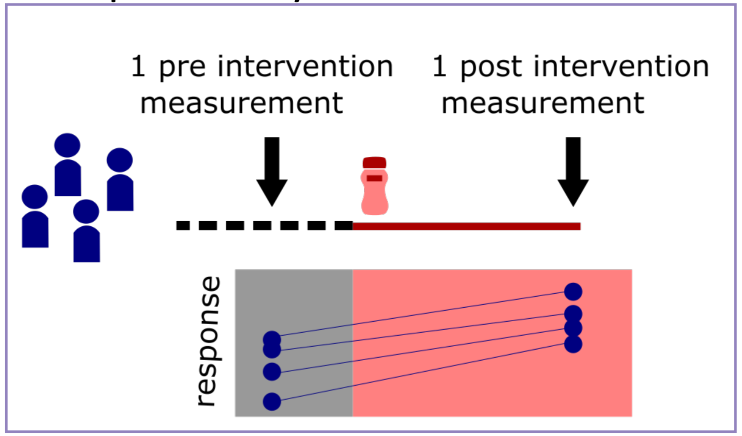


More measures over time

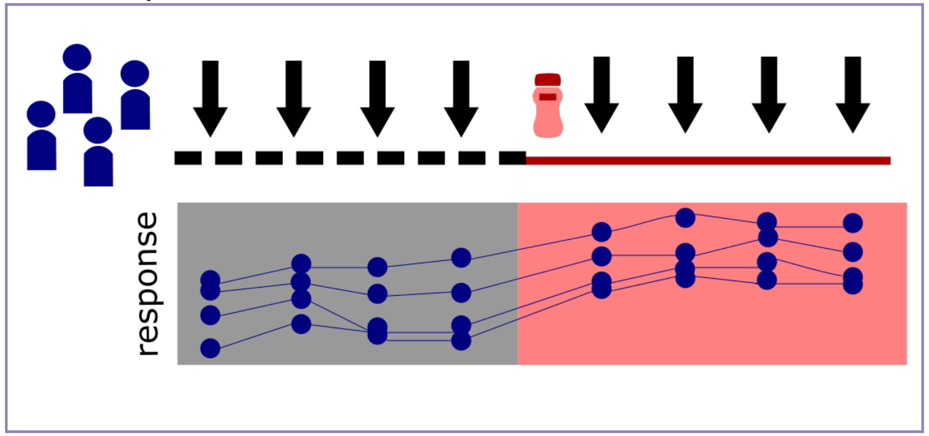
can help deal with time bias



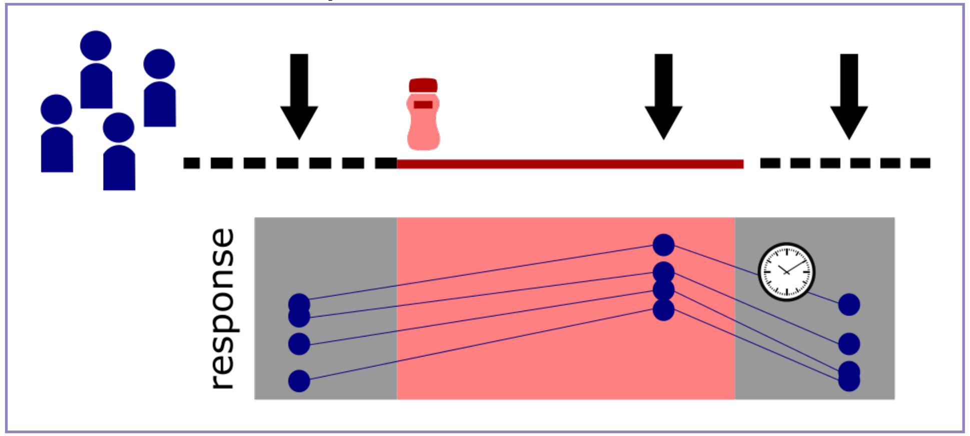
Pre–post study

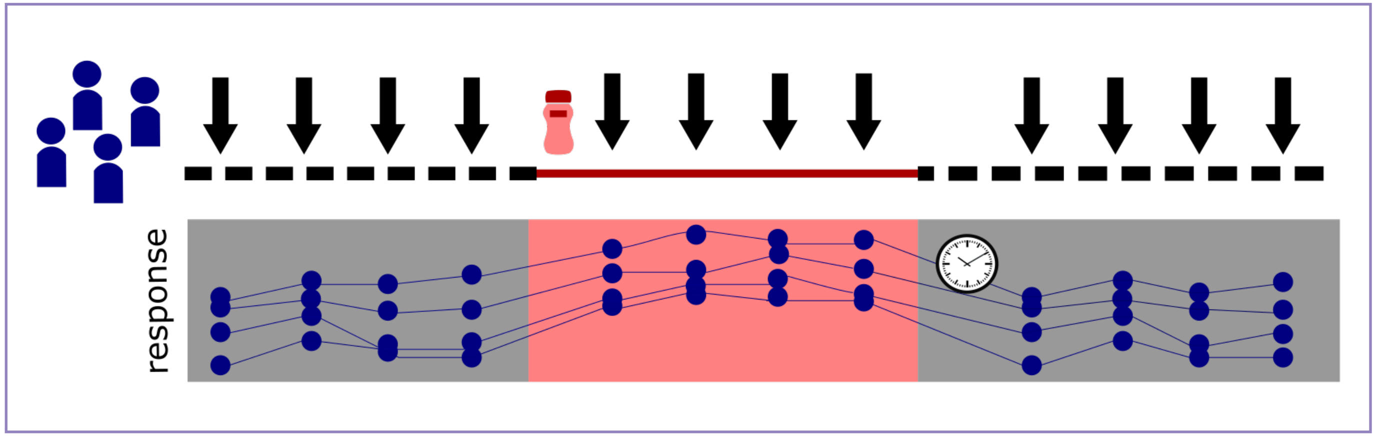


Interrupted time series



Cross-over study



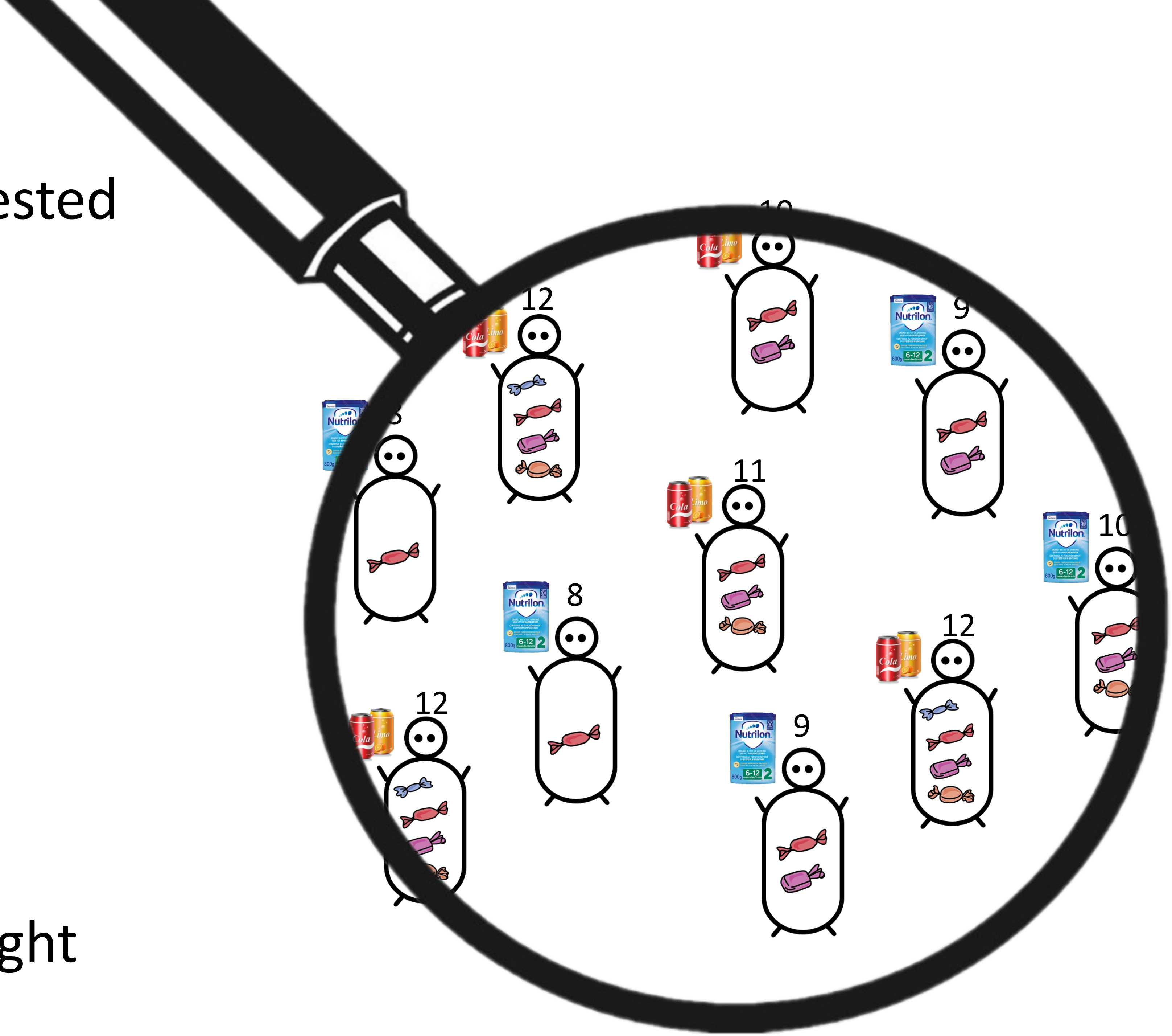


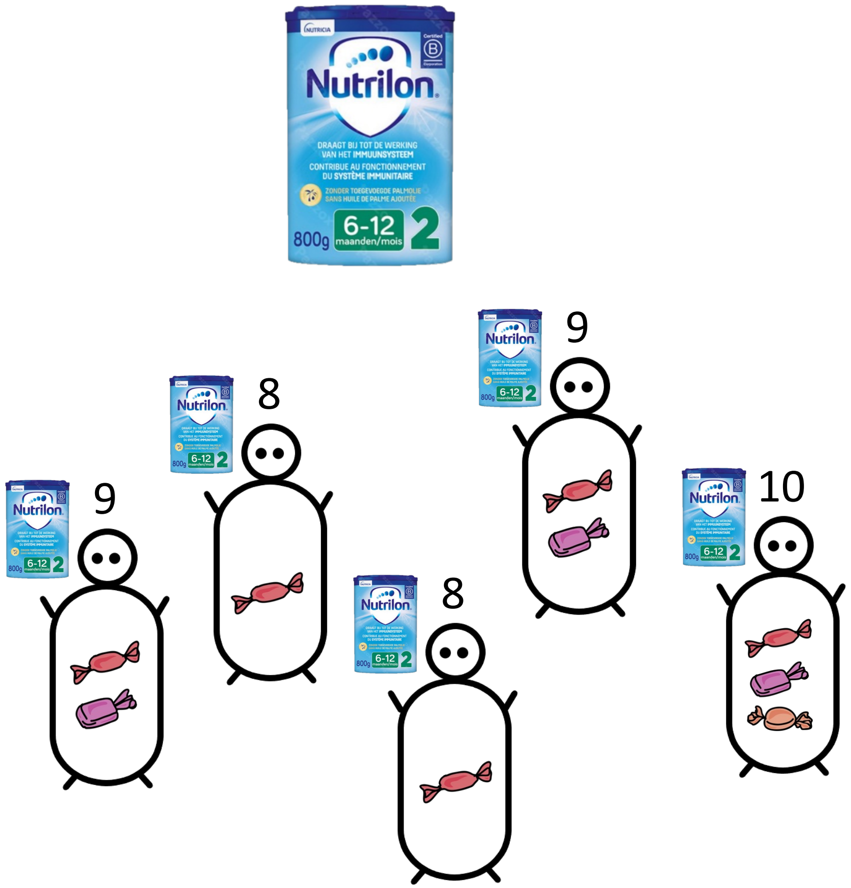
STATISTICAL SOLUTIONS FOR HANDLING BIAS

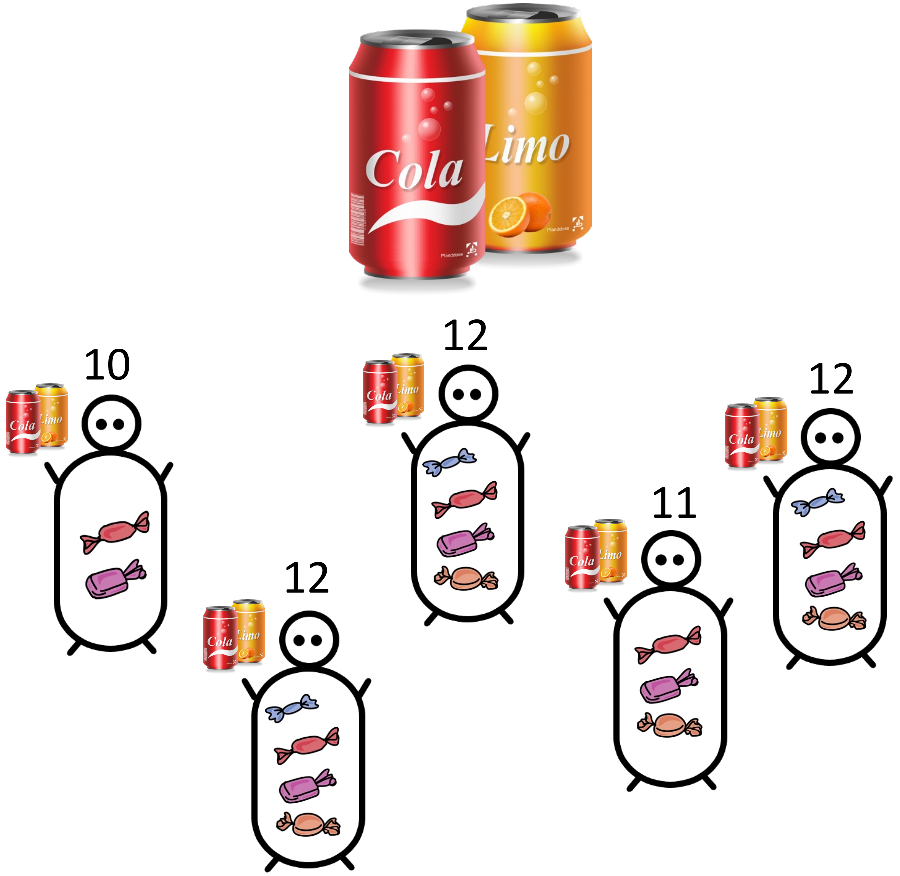
We are interested in

versus

effect on weight



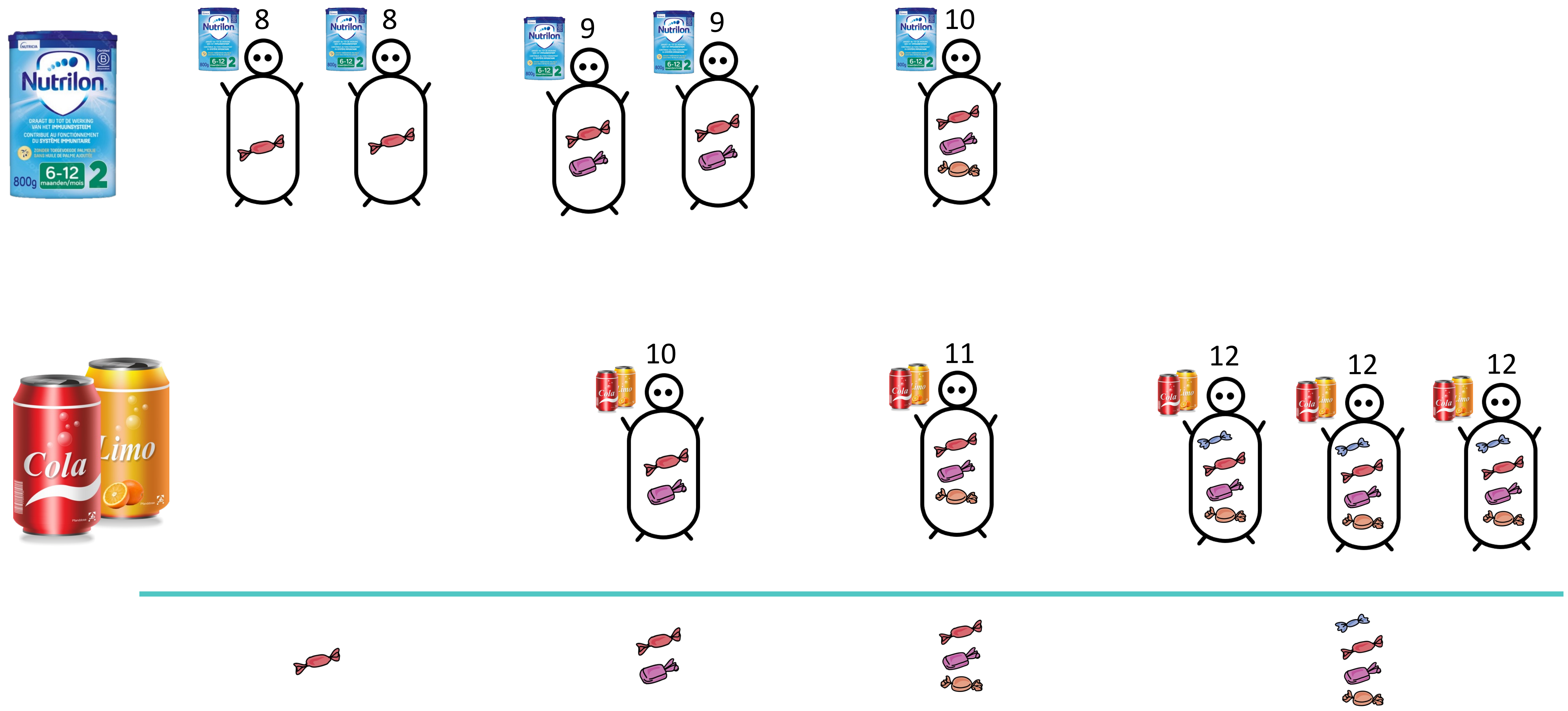


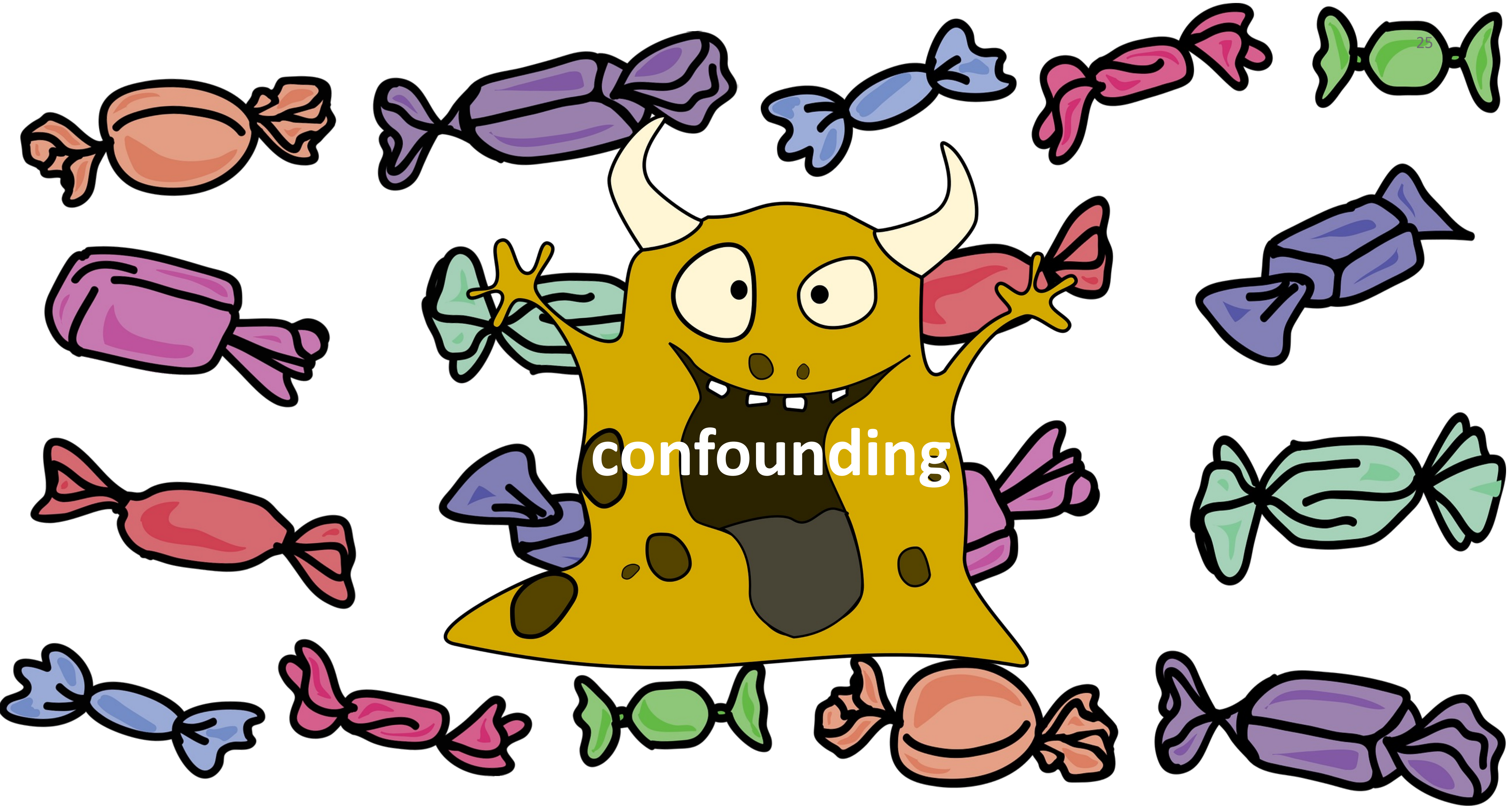


Average weight:
(8+8+9+9+10)/5 = 8,8

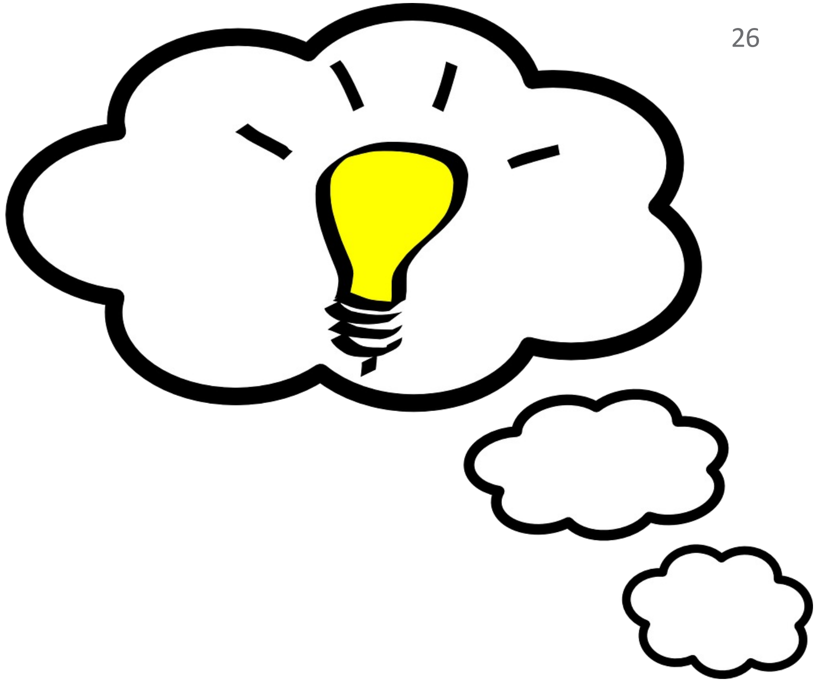
Average weight:
(10+11+12+12+12)/5 = 11,4

$\boxed{11{,}4 - 8{,}8 = 2{,}6}$ => Real effect?


Nutrilon
6-12
maanden/mois
800g
2
8
8
9
9
10
Cola
Limo
10
11
12
12
12


confounding

OPTIONS FOR HANDLING CONFOUNDING



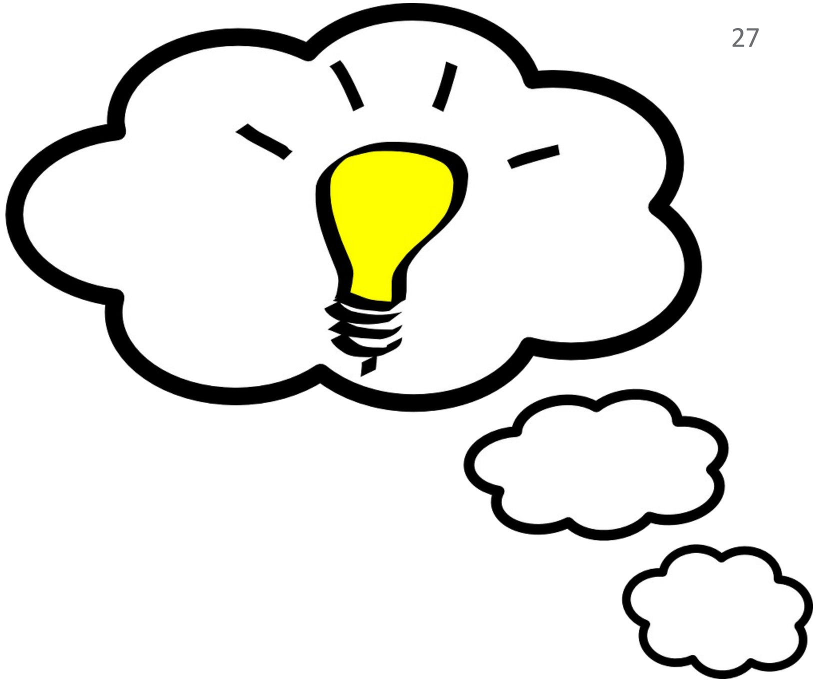
Traditional methods

- Regression models
- Subclassification, matching and weighting
- Combination => Doubly robust methods
- Instrumental variable methods

Advanced methods

- Predicting outcomes
- TMLE: Targeted maximum likelihood estimation
- Machine Learning estimation for causal inference
- Ensemble methods

OPTIONS FOR HANDLING CONFOUNDING



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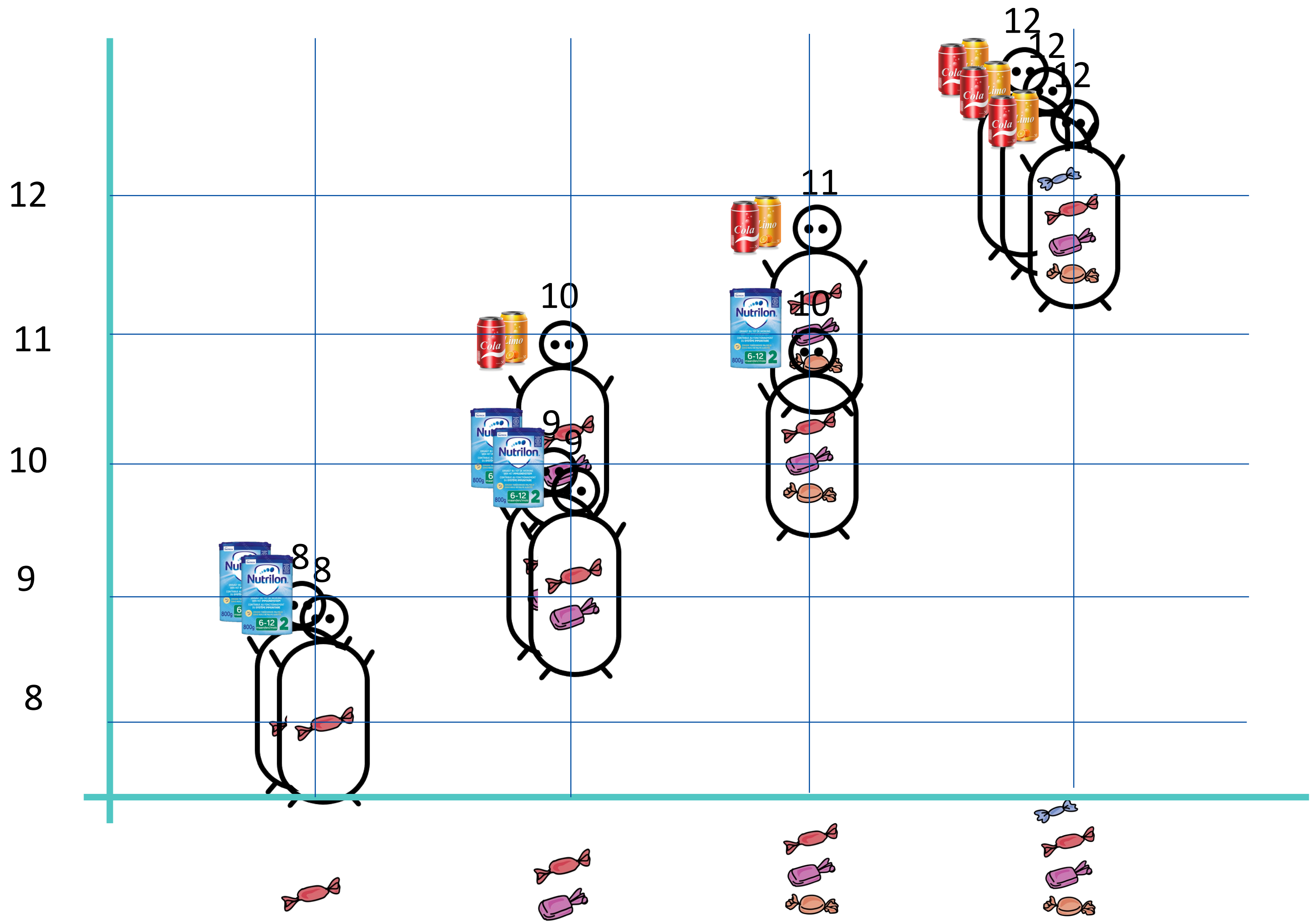
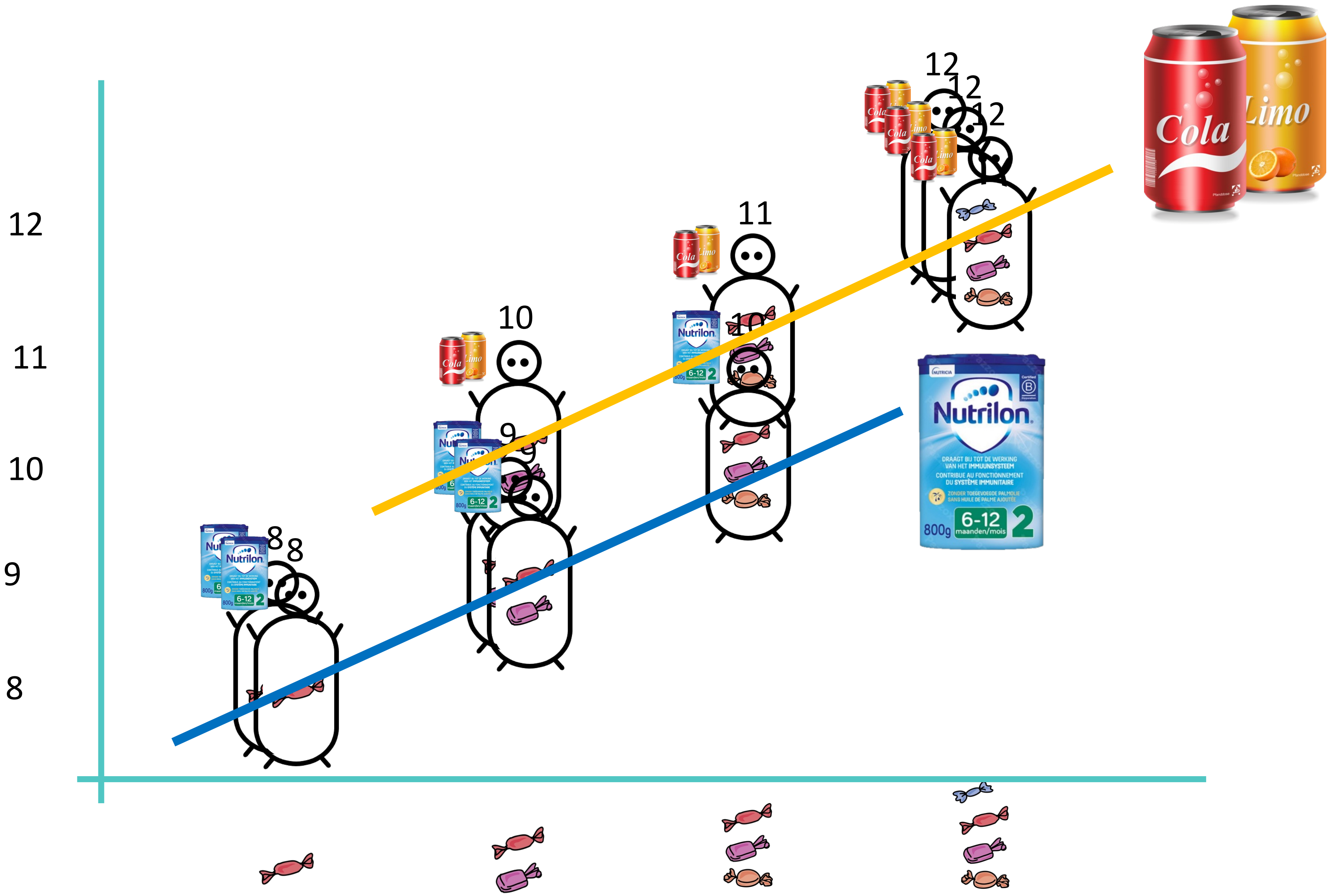
REGRESSION ADJUSTMENT



REGRESSION ADJUSTMENT



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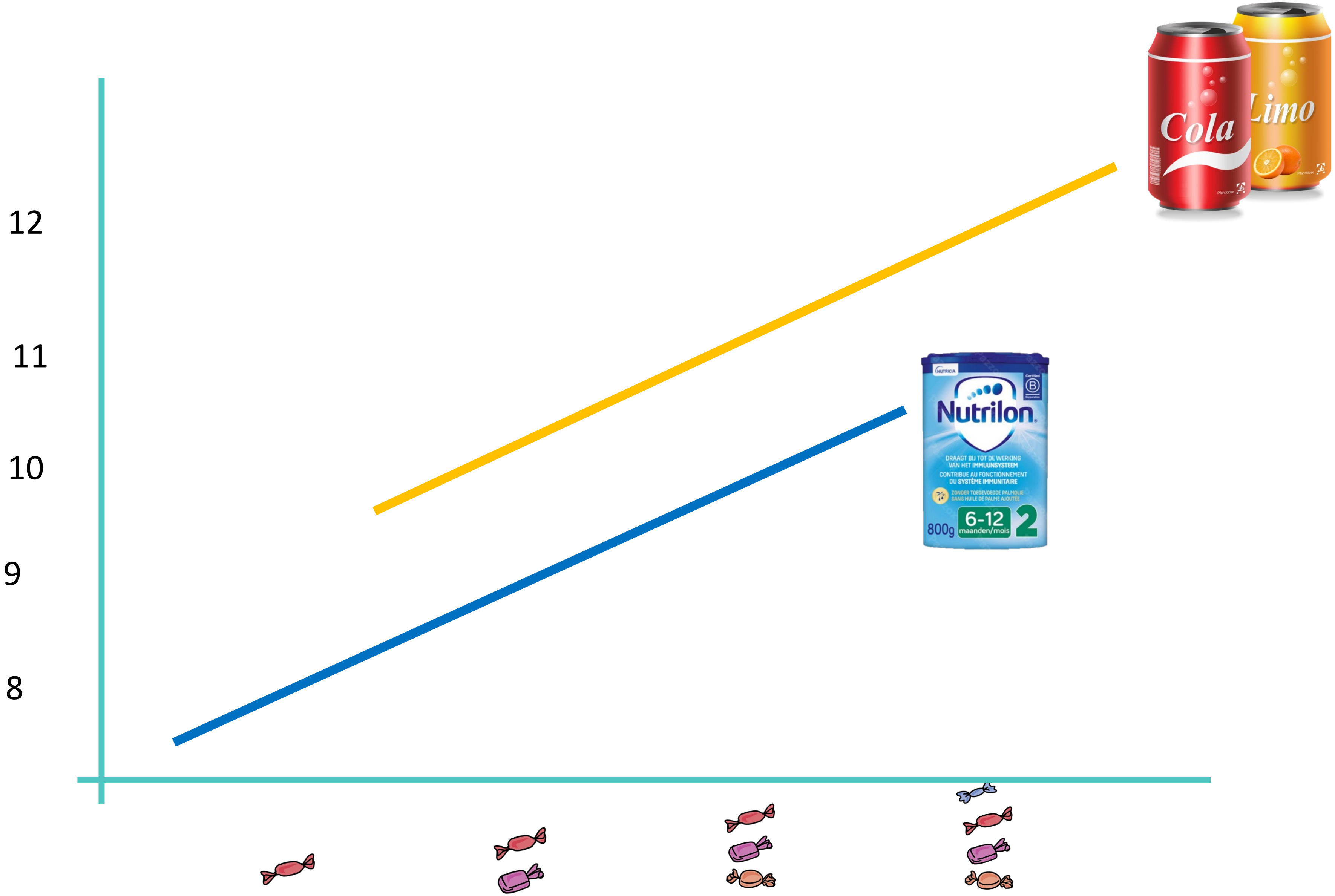
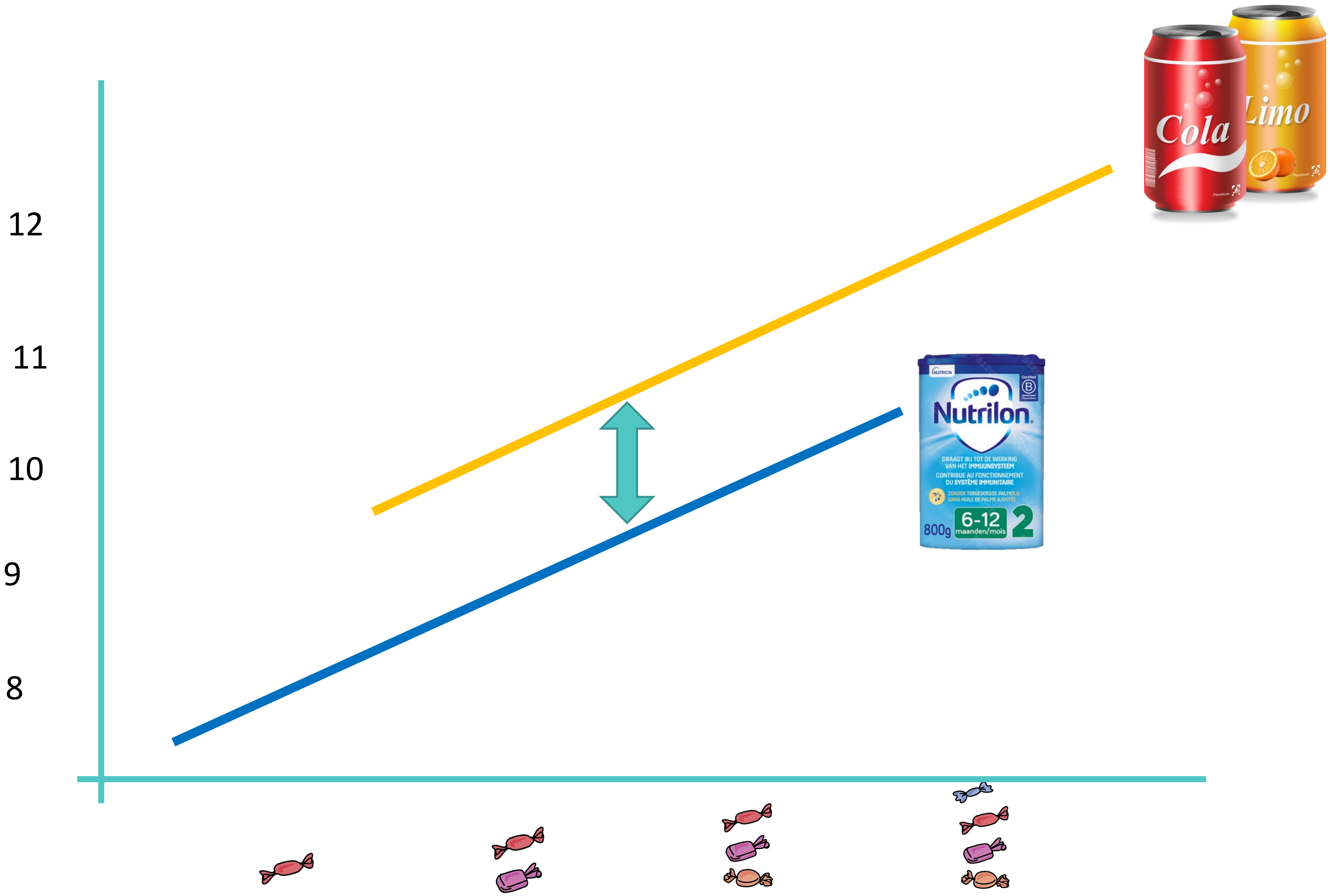
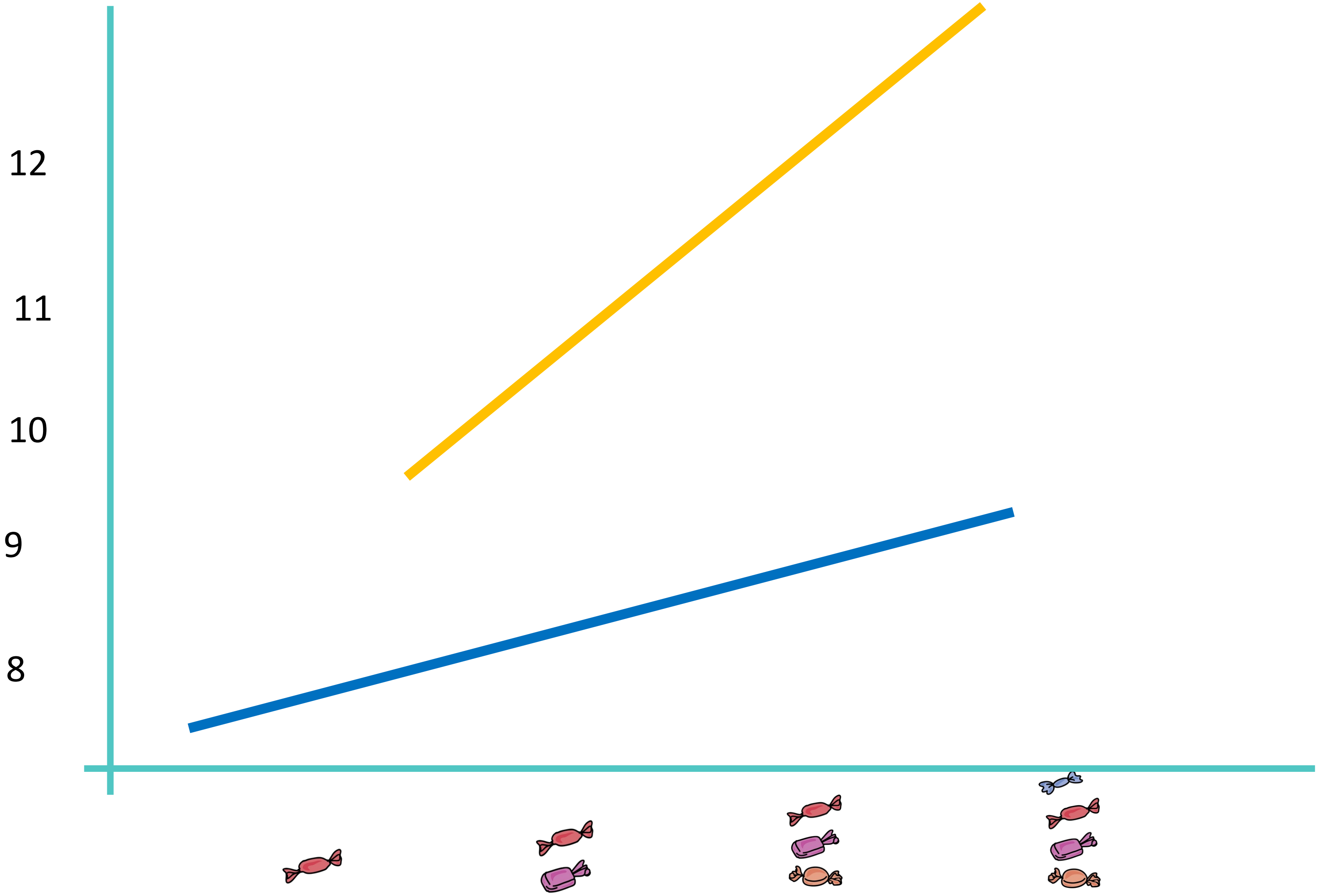


REGRESSION ADJUSTMENT



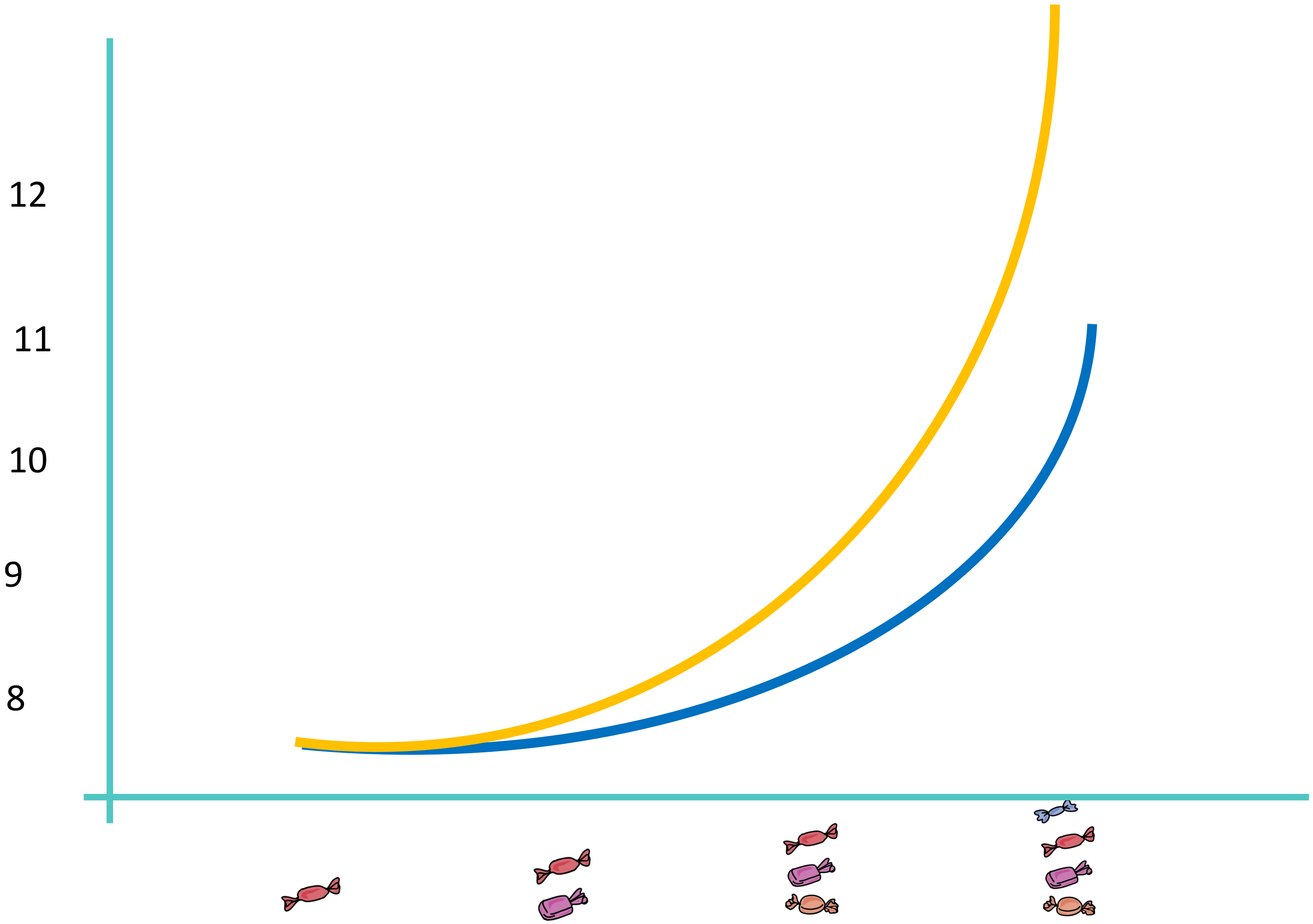
Effect versus = difference between the lines = 1

WHAT IF:



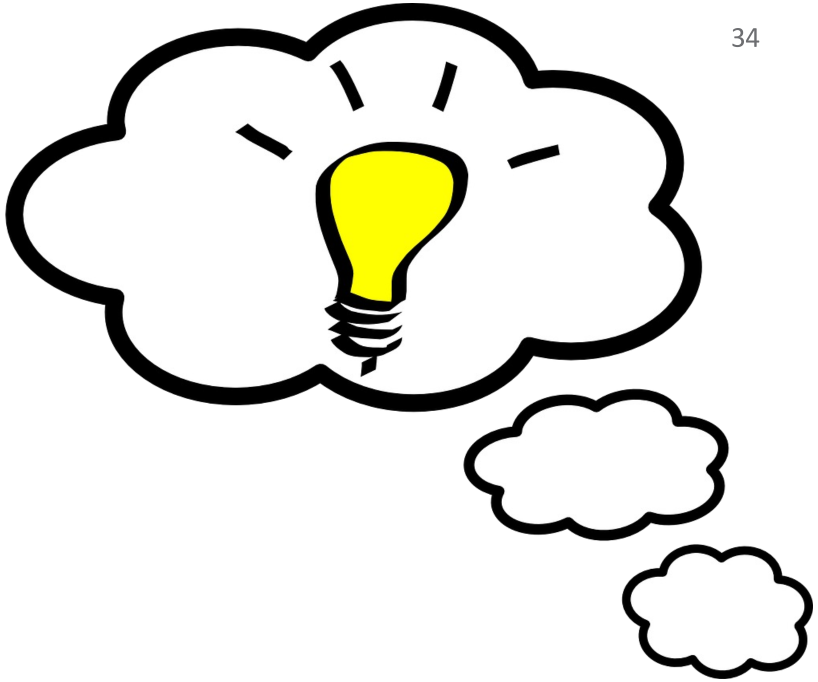
What is the difference between the lines?

WHAT IF:



What is the difference between the lines?

OPTIONS FOR HANDLING CONFOUNDING



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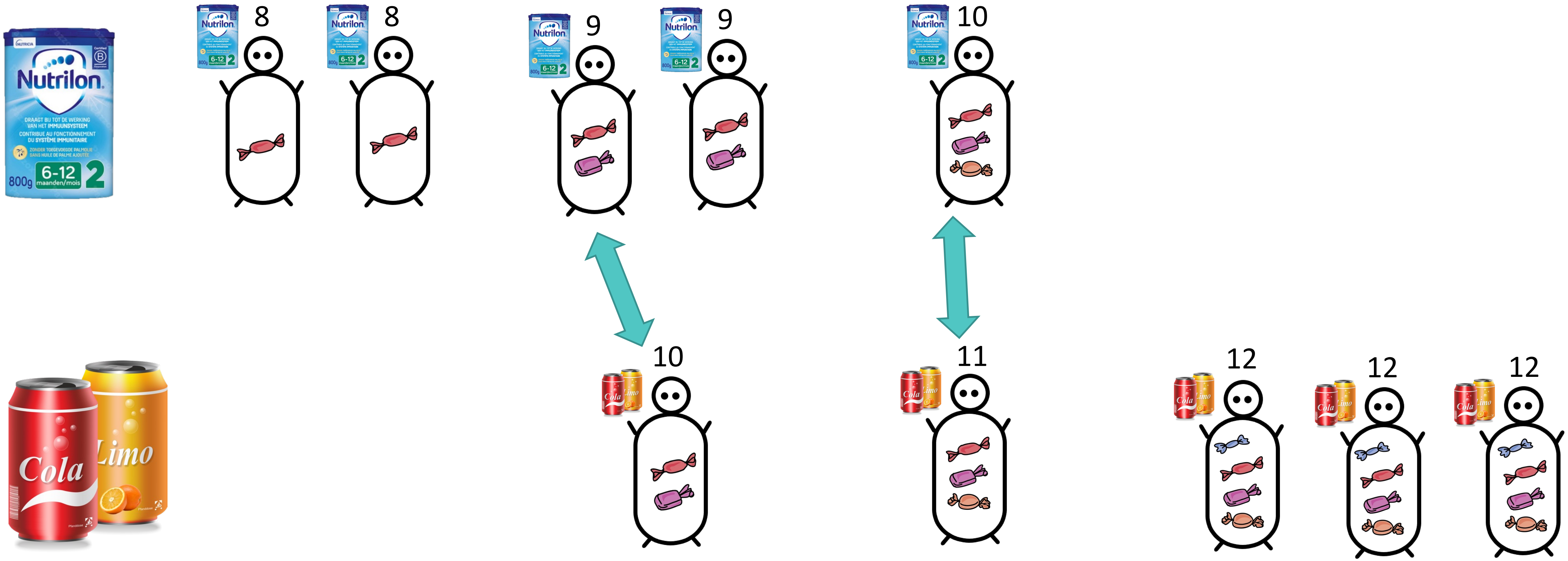
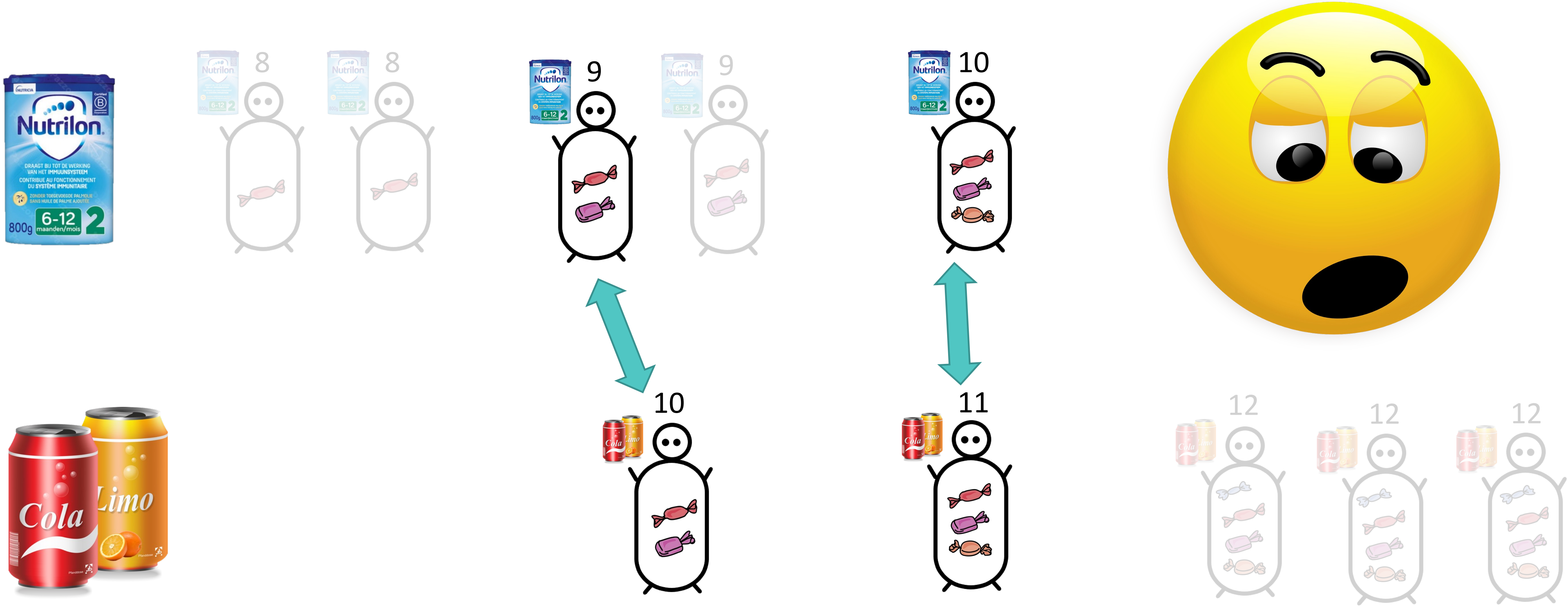
CASE CONTROL MATCHING



$10 - 9 = 1$

$11 - 10 = 1$

CASE CONTROL MATCHING



$10 - 9 = 1$

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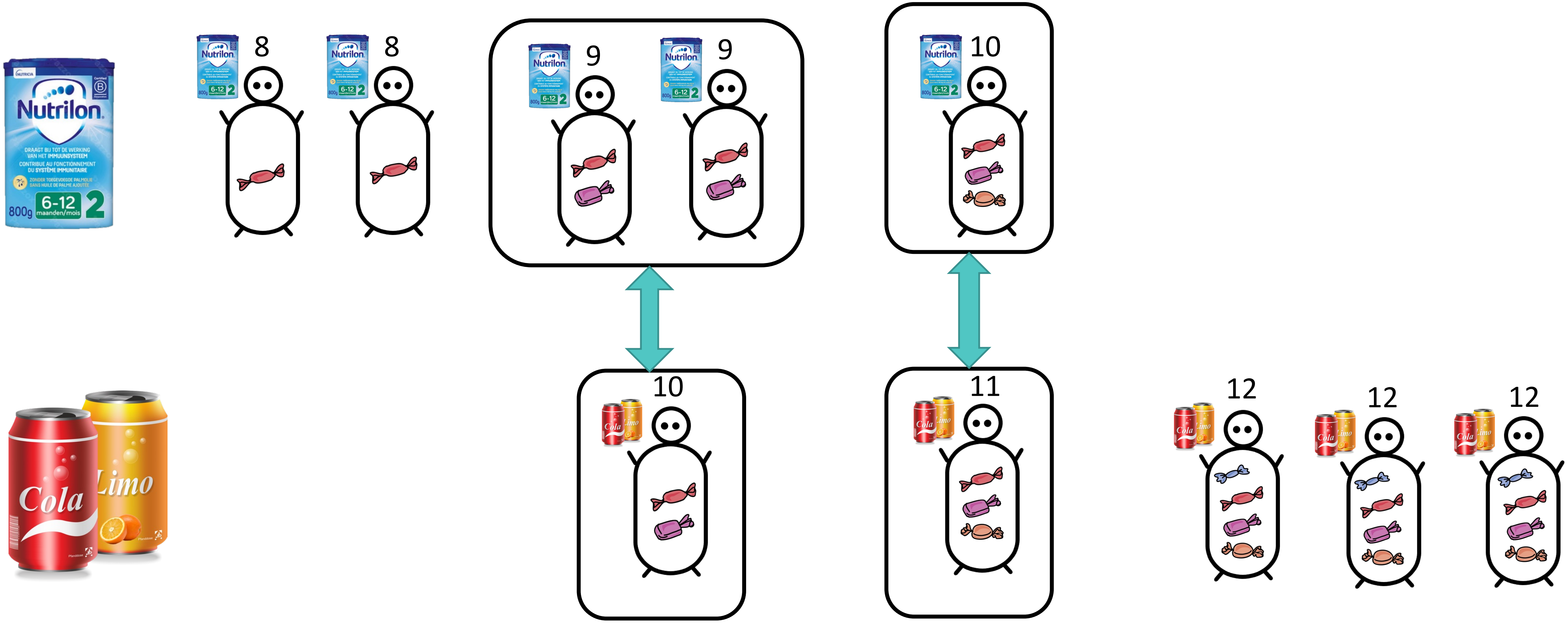
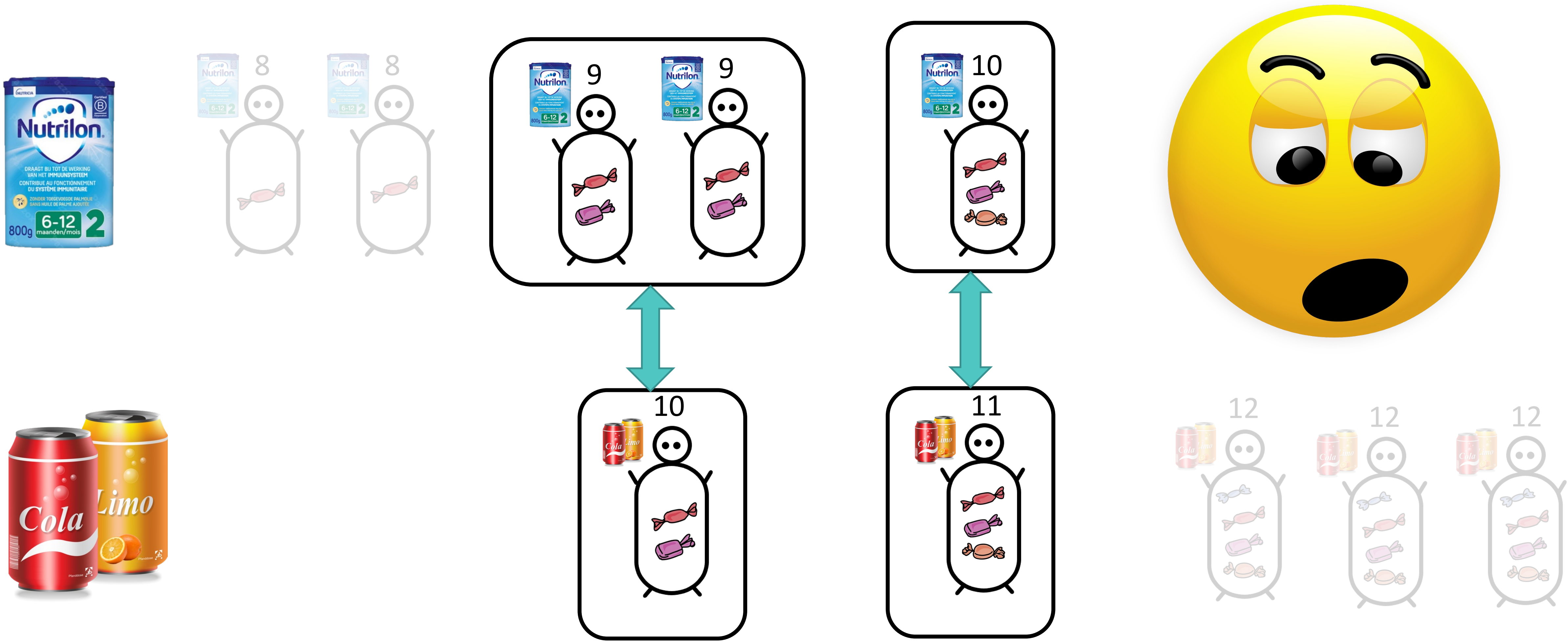
STRATIFICATION (SUBGROUP ANALYSIS)



$10 - ((9+9)/2) = 1$

$11 - 10 = 1$

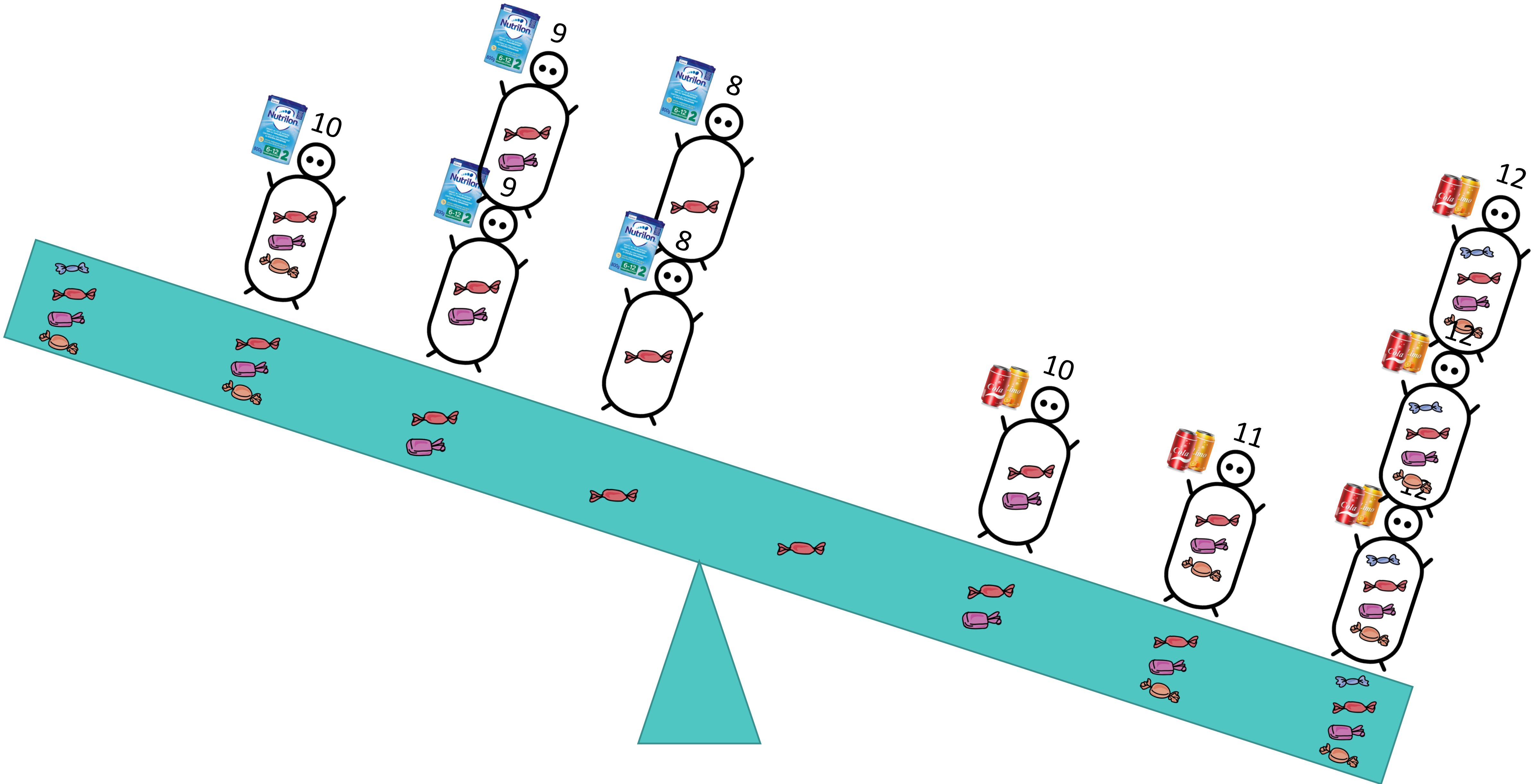
STRATIFICATION (SUBGROUP ANALYSIS)



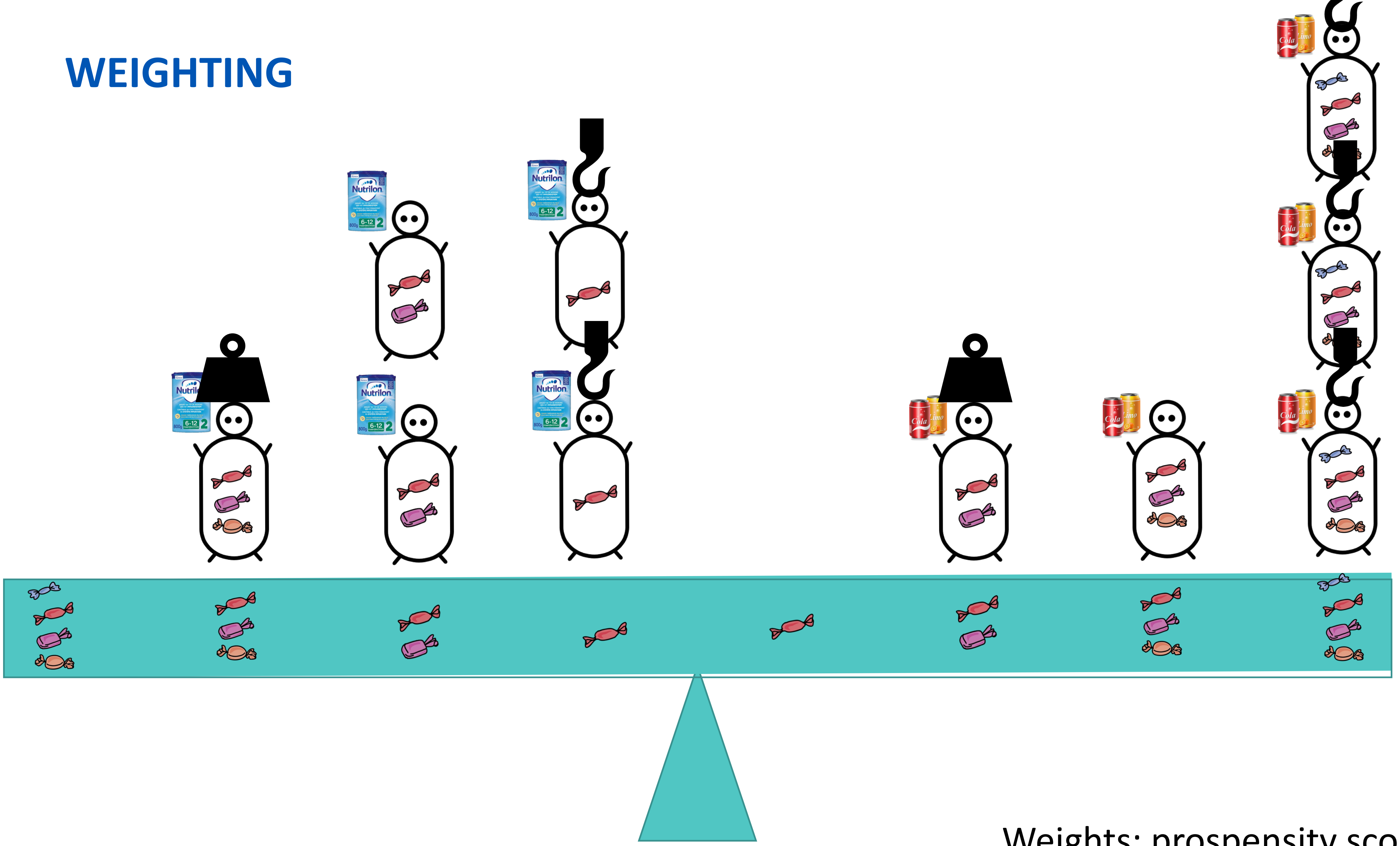
$10 – ((9+9)/2) = 1$

$11 – 19 = 1$

WEIGHTING

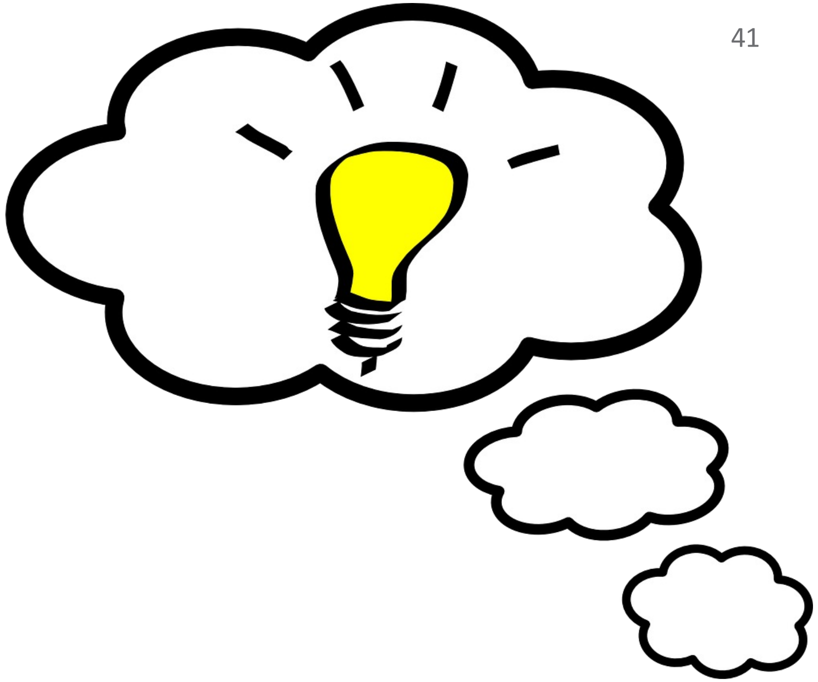


WEIGHTING



Weights: prospensity scores

OPTIONS FOR HANDLING CONFOUNDING



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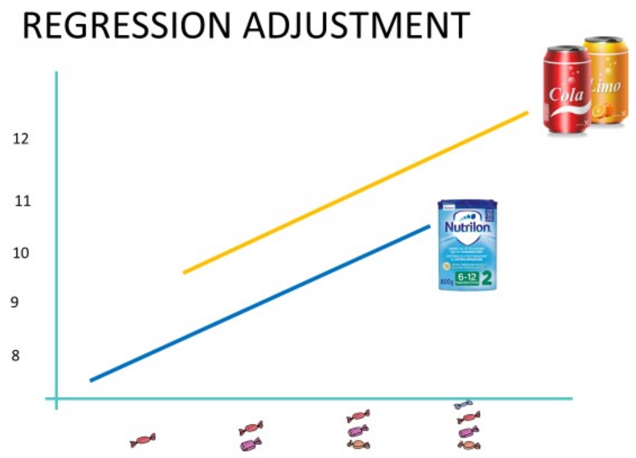
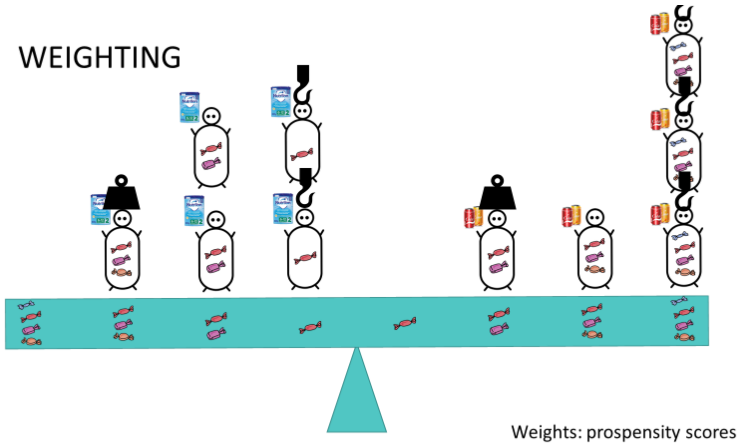
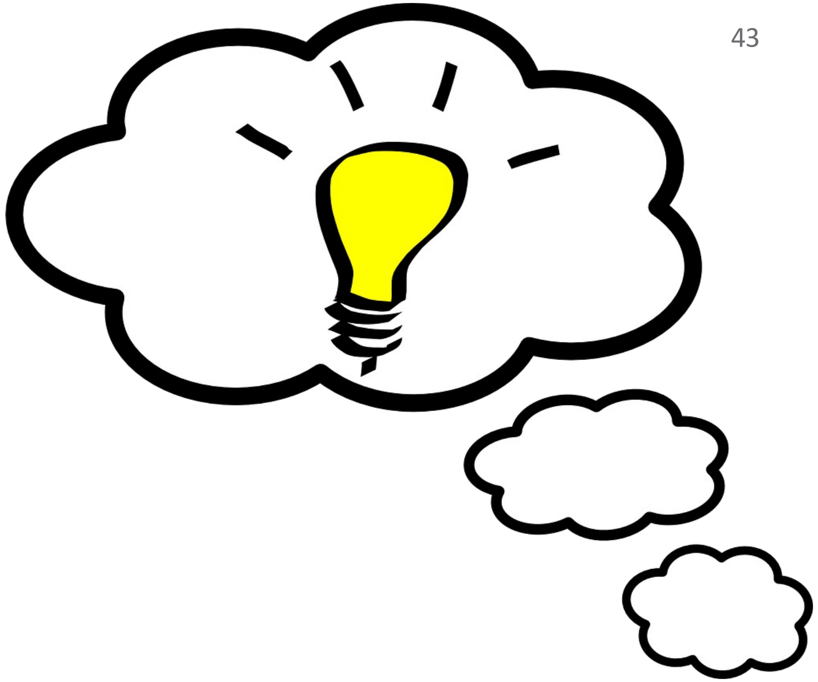
DOUBLY ROBUST METHODS





=> both = Doubly robust models

OPTIONS FOR HANDLING CONFOUNDING



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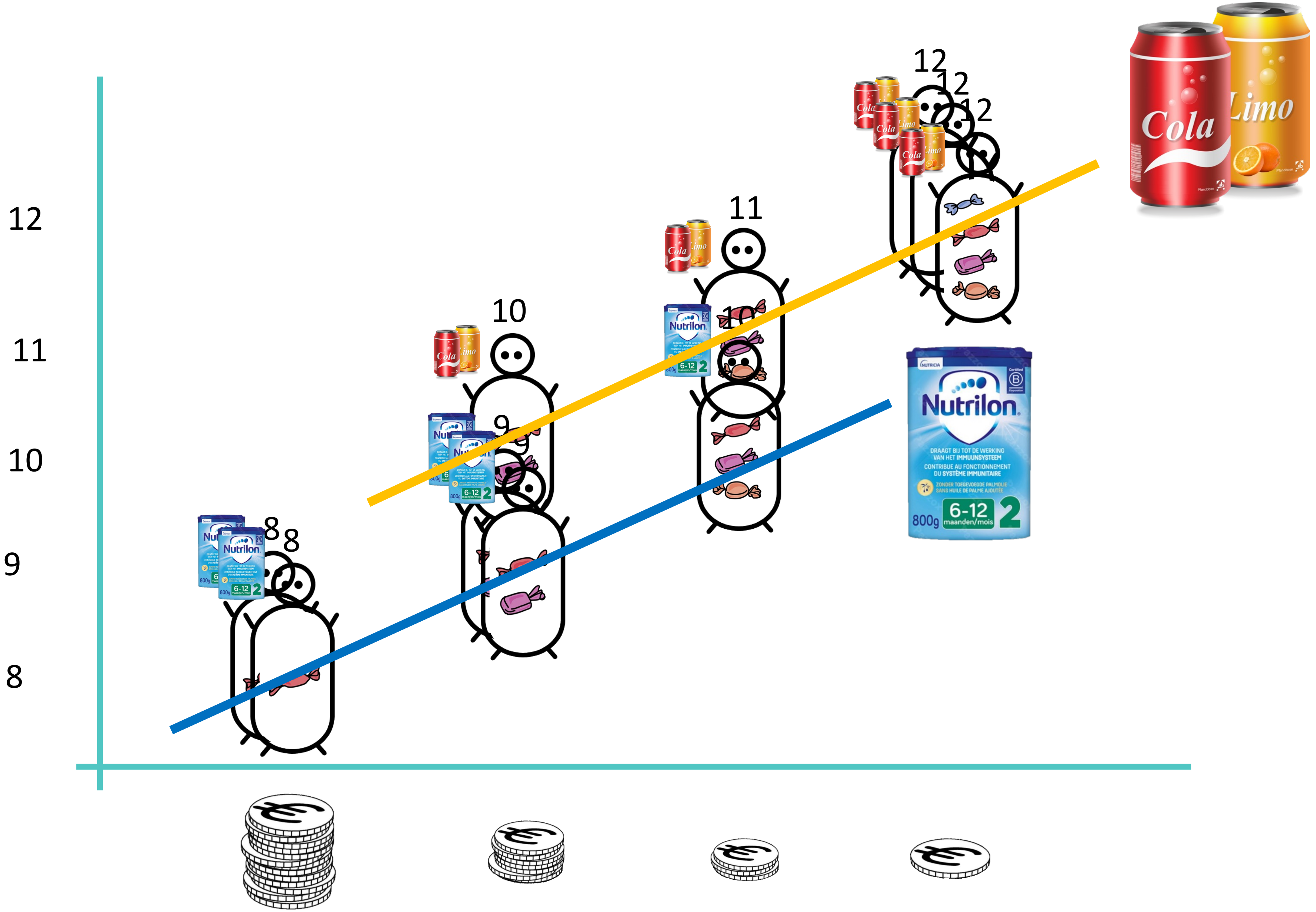
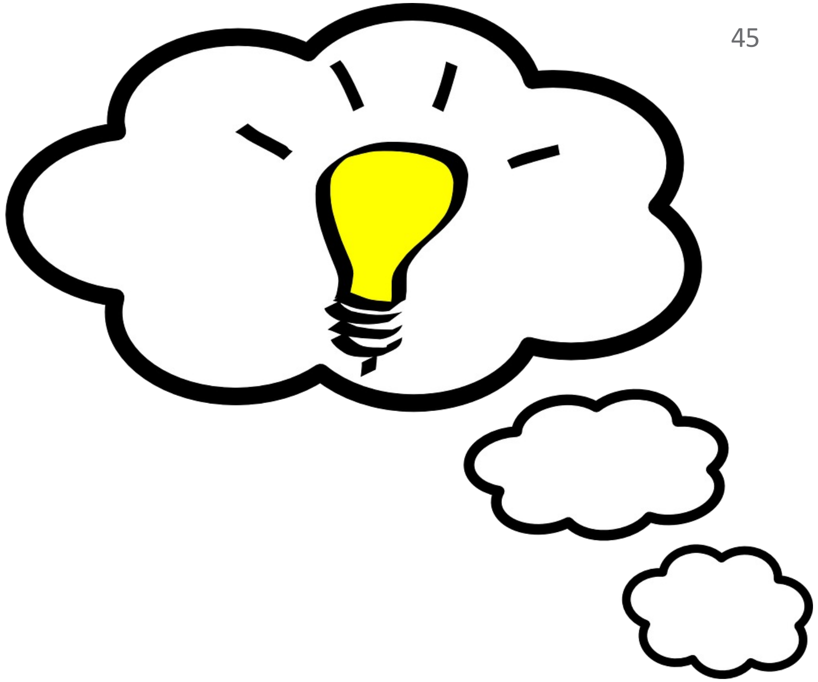
- Ensemble methods

INSTRUMENTAL VARIABLE



OPTIONS FOR HANDLING CONFOUNDING



Traditional methods

- Regression models
- Subclassification, matching and weighting
- Combination => Doubly robust methods
- Instrumental variable methods

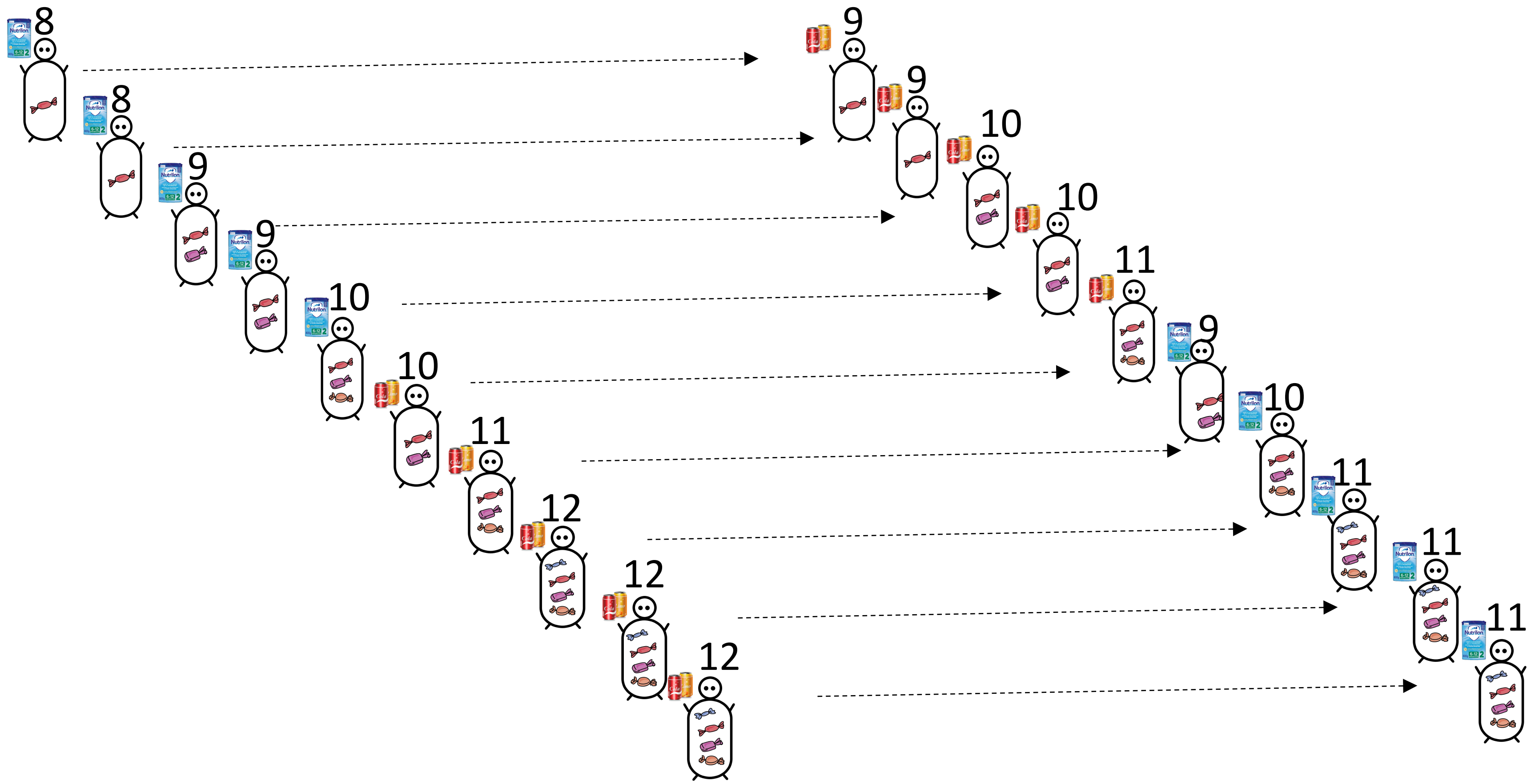
Advanced methods

- **Predicting outcomes**
- TMLE: Targeted maximum likelihood estimation
- Machine Learning estimation for causal inference
- Ensemble methods

PREDICTING OUTCOMES (G COMPUTATION)

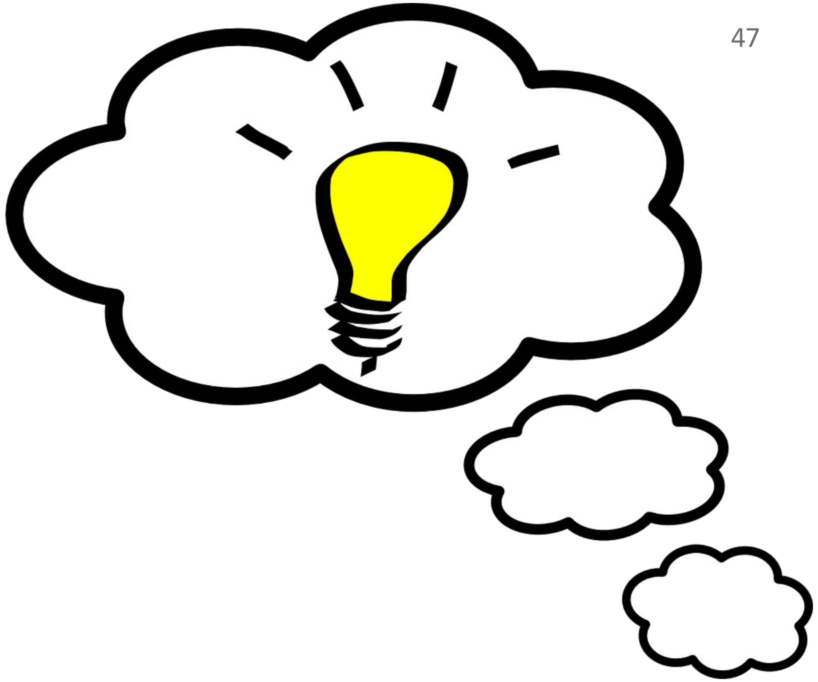
What we observed

What we estimate



Difference gives estimate of averaged effect

OPTIONS FOR HANDLING CONFOUNDING



Traditional methods

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WARNING

We can (statistically) deal with distortion factors that we directly or indirectly measured

but not with unknown, unmeasured confounding

TAKE HOME MESSAGE

1

Data, even of good quality,
do not necessarily translate into credible evidence

2

Design elements of RCTs help prevent drawing false conclusions.
If not possible in your RWE study, there are some (statistical) fixes but none perfect.

→ Cautious conclusions


THANK
YOU!