Factors influencing the outcome of human intervention trials

A case study using studies examing the effects of whole grain consumption on blood pressure in humans

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DE VRIES NUTRITION SOLUTIONS

Mondelēz International

StCoyfdesigingfactdrsgnto pharmexperitical study principles

Epidemiological studies as hypothesis generator for human intervention studies

Hypothesis
- Background of hypothesis

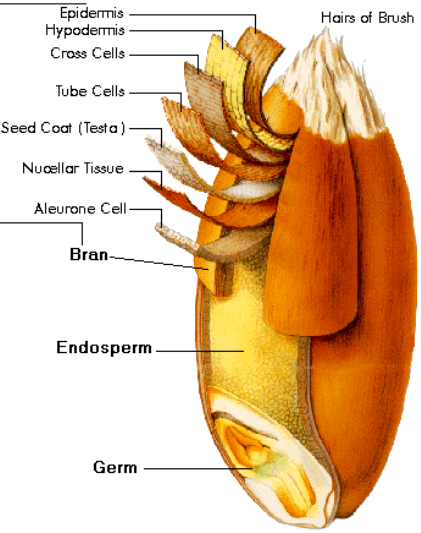
Individuals
- Healthy, at risk, ill, …
- Age, antropometric charac.
- Background diet
- Inclusion / exclusion criteria

Study design
- Randomization, methods
- Parallel or cross-over, controlled or not
- Run in, background diet
- Duration
- Number or samples
- Moment of sampling

Intervention
- Proper intervention
- Proper control
- Characterization of intervention
- Use of intervention
- Compliance to intervention

Parameters
- Relation ship to hypothesis
- Methodology for measurement
- Variability of measurement
- Variability in individuals
- Is paramamter appropriate?

Outcomes



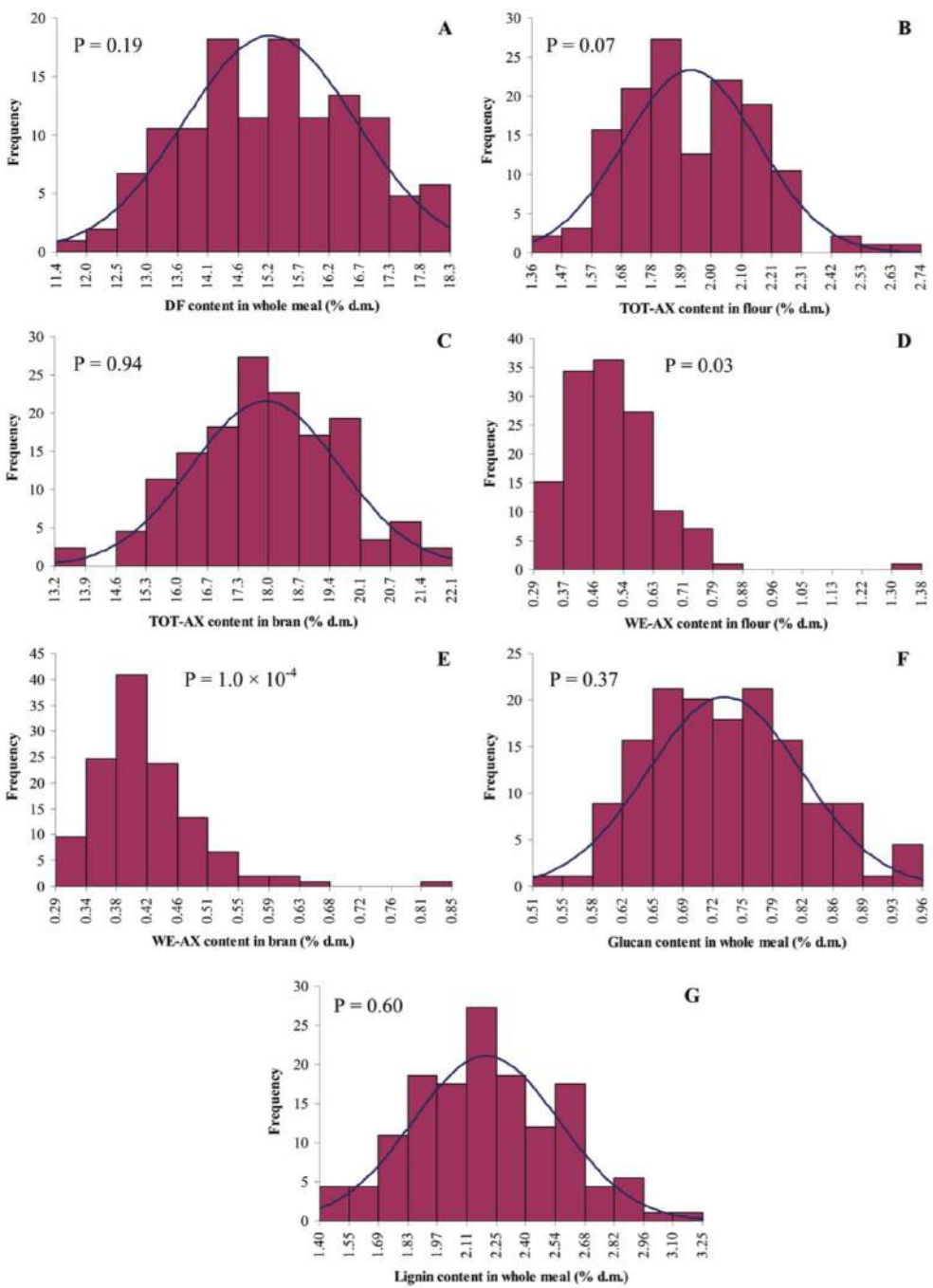


Figure 1. Frequency histograms (bars) for contents of DF in whole meal (**A**), TOT-AX in flour (**B**), and bran (**C**), WE-AX in flour (**D**) and bran (**E**), β-glucan in whole meal (**F**), and lignin in whole meal (**G**) from winter wheats. For the normally distributed data (Anderson–Darling P value > 0.05) also the corresponding normal distribution curves are shown.

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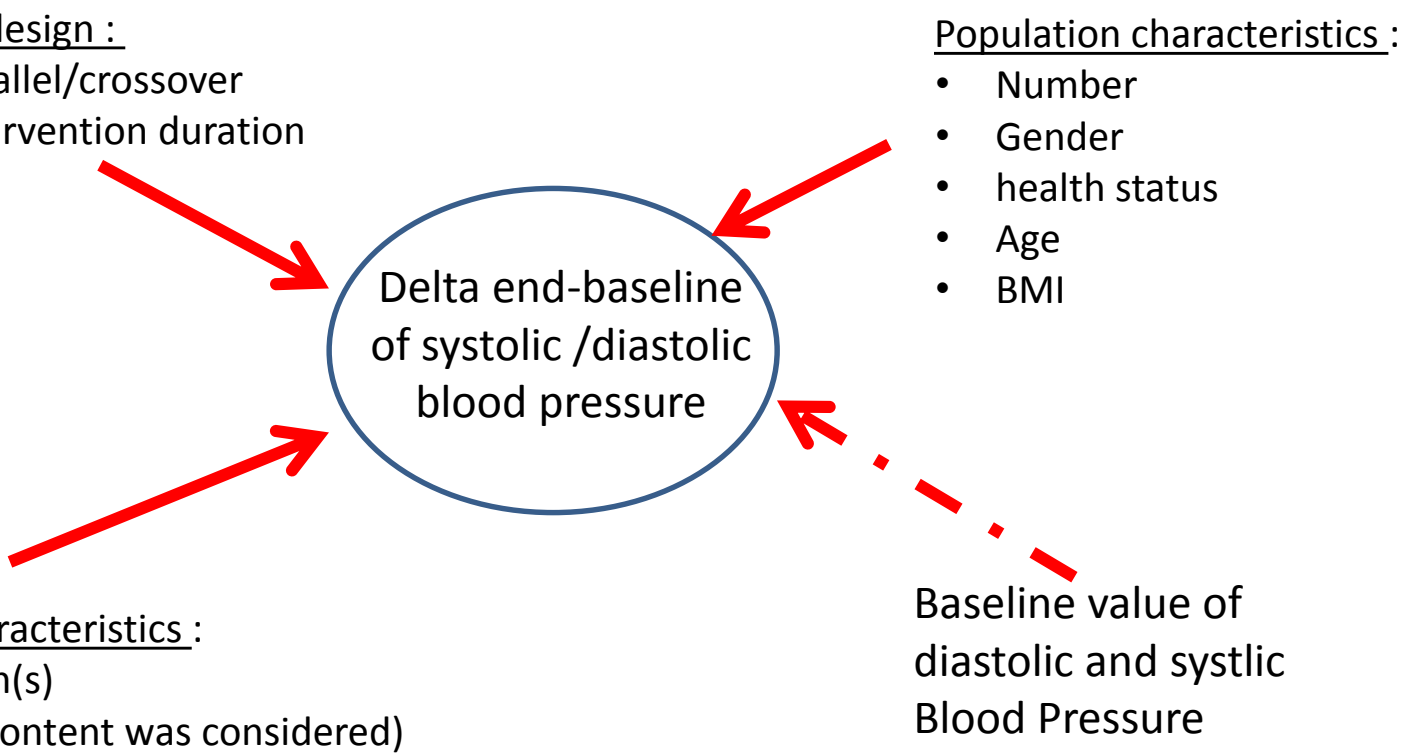
/east, bacteria)

Analytical method used for the first analysis

- **A Multiple Linear Regression analysis has been applied to the data in order to evaluate and quantify the impact of study design factors on blood pressure results**



Variability of participants

Physiological characteristics	# studies	Average age (y)	DBP t=0 (mmHg)	SBP t=0 (mmHg)	BMI (kg/m^2)	Use medication	Study design
Healthy	5	26-59	65-81	109-130	21,6-30,3	0	CO/nb, PAR/nb-db
Hypertension	3	45-63	83-93	135-140	28,8-32.6	2	PAR nb-db
Overweight/obese	2	57-61	84-87	132-139	29,2-30,4	1	PAR/nb-sb)
Type 2 diabetes	1	63	77-81	131-137	26,7	1	Single arm
Metabolic syndr	1	50	85-86	129	25,4-25,9	0	PAR/nb
Variable	1	52	76-79	126-132	27-28	0	PAR/sb

Variability of interventions

- Combination of whole grain products (probably mostly wheat) (n=2)
- Oat meal and oat squares and other types of products (n=6)
- Whole wheat bread (n=2)
- Whole wheat + brown rice + barley
- Brown rice
- Not decribed in detail (could be wheat or rye!)

- *Levels of intervention expressed as gram dietary fiber (varies between 2,6-19 g/d)*

Gender

- Both sexes (n=11)
- Female (n= 1)
- Male (n=1)

Multiple Linear Regression (SBP)

Terme	Estimation des coefficients codés	Erreur standard	t ratio	Prob. > |t|
Constante	-4,974134	1,420697	-3,50	0,0044 *
Gender[Both sexes]	1,6876969	1,507204	1,12	0,2847
Gender[Female]	1,5174493	1,453157	1,04	0,3170
Gender[Male]	-3,205146	2,317957	-1,38	0,1919
healthy vs at risk[0]	1,2446289	0,725282	1,72	0,1118
healthy vs at risk[1]	-1,244629	0,725282	-1,72	0,1118
ControlORinterventions[Control]	-1,60826	1,726527	-0,93	0,3700
ControlORinterventions[Intervention]	1,6082596	1,726527	0,93	0,3700
Age	0,6582045	0,80709	0,82	0,4307
BMI	-0,099693	0,907588	-0,11	0,9143
Gender[Both sexes]*ControlORinterventions[Control]	3,0470732	1,842209	1,65	0,1240
Gender[Both sexes]*ControlORinterventions[Intervention]	-3,047073	1,842209	-1,65	0,1240
Gender[Female]*ControlORinterventions[Control]	0	0	0,00	1,0000
Gender[Female]*ControlORinterventions[Intervention]	0	0	0,00	1,0000
Gender[Male]*ControlORinterventions[Control]	-3,047073	1,842209	-1,65	0,1240
Gender[Male]*ControlORinterventions[Intervention]	3,0470732	1,842209	1,65	0,1240
healthy vs at risk[0]*ControlORinterventions[Control]	-0,036627	0,725282	-0,05	0,9606
healthy vs at risk[0]*ControlORinterventions[Intervention]	0,036627	0,725282	0,05	0,9606
healthy vs at risk[1]*ControlORinterventions[Control]	0,036627	0,725282	0,05	0,9606
healthy vs at risk[1]*ControlORinterventions[Intervention]	-0,036627	0,725282	-0,05	0,9606
ControlORinterventions[Control]*(Age-51,772)	-1,957865	0,80709	-2,43	0,0320 *
ControlORinterventions[Intervention]*(Age-51,772)	1,9578653	0,80709	2,43	0,0320 *
ControlORinterventions[Control]*(BMI-28,636)	0,9372794	0,907588	1,03	0,3221
ControlORinterventions[Intervention]*(BMI-28,636)	-0,937279	0,907588	-1,03	0,3221
Systolic Baseline	1,3456074	1,088793	1,24	0,2402
ControlORinterventions[Control]*(Systolic Baseline-129,408)	0,3066323	1,088793	0,28	0,7830
ControlORinterventions[Intervention]*(Systolic Baseline-129,408)	-0,306632	1,088793	-0,28	0,7830

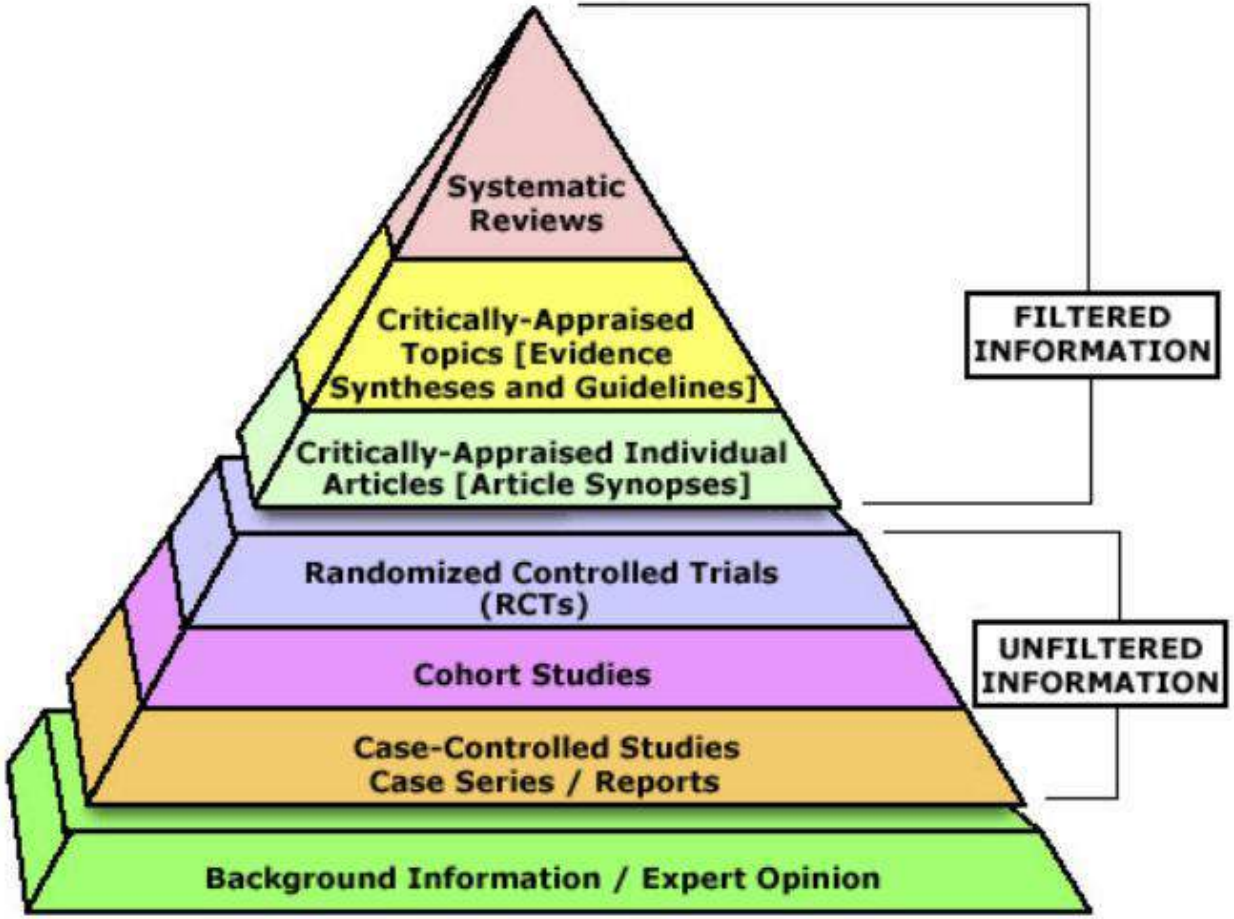
Multiple Linear Regression (DBP)

Terme	Estimation des coefficients codés	Erreur standard	t ratio	Prob. > |t|
Constante	-2,620365	1,090203	-2,40	0,0333 *
Gender[Both sexes]	0,4318079	1,156732	0,37	0,7154
Gender[Female]	-1,10876	1,179466	-0,94	0,3657
Gender[Male]	0,6769519	1,839252	0,37	0,7192
healthy vs at risk[0]	0,6348205	0,485325	1,31	0,2154
healthy vs at risk[1]	-0,634821	0,485325	-1,31	0,2154
ControlORinterventions[Control]	-0,558862	1,334854	-0,42	0,6829
ControlORinterventions[Intervention]	0,5588619	1,334854	0,42	0,6829
Age	1,3425952	0,59839	2,24	0,0445 *
BMI	0,5998506	0,644469	0,93	0,3703
Diastolic Baseline	1,1336687	0,733062	1,55	0,1479
Gender[Both sexes]*ControlORinterventions[Control]	1,5106447	1,440657	1,05	0,3150
Gender[Both sexes]*ControlORinterventions[Intervention]	-1,510645	1,440657	-1,05	0,3150
Gender[Female]*ControlORinterventions[Control]	0	0	0,00	1,0000
Gender[Female]*ControlORinterventions[Intervention]	0	0	0,00	1,0000
Gender[Male]*ControlORinterventions[Control]	-1,510645	1,440657	-1,05	0,3150
Gender[Male]*ControlORinterventions[Intervention]	1,5106447	1,440657	1,05	0,3150
healthy vs at risk[0]*ControlORinterventions[Control]	0,127623	0,485325	0,26	0,7970
healthy vs at risk[0]*ControlORinterventions[Intervention]	-0,127623	0,485325	-0,26	0,7970
healthy vs at risk[1]*ControlORinterventions[Control]	-0,127623	0,485325	-0,26	0,7970
healthy vs at risk[1]*ControlORinterventions[Intervention]	0,127623	0,485325	0,26	0,7970
ControlORinterventions[Control]*(Age-51,772)	-1,173276	0,59839	-1,96	0,0735
ControlORinterventions[Intervention]*(Age-51,772)	1,1732758	0,59839	1,96	0,0735
ControlORinterventions[Control]*(BMI-28,636)	1,4004531	0,644469	2,17	0,0505
ControlORinterventions[Intervention]*(BMI-28,636)	-1,400453	0,644469	-2,17	0,0505
ControlORinterventions[Control]*(Diastolic Baseline-80,296)	0,4733011	0,733062	0,65	0,5307
ControlORinterventions[Intervention]*(Diastolic Baseline-80,296)	-0,473301	0,733062	-0,65	0,5307

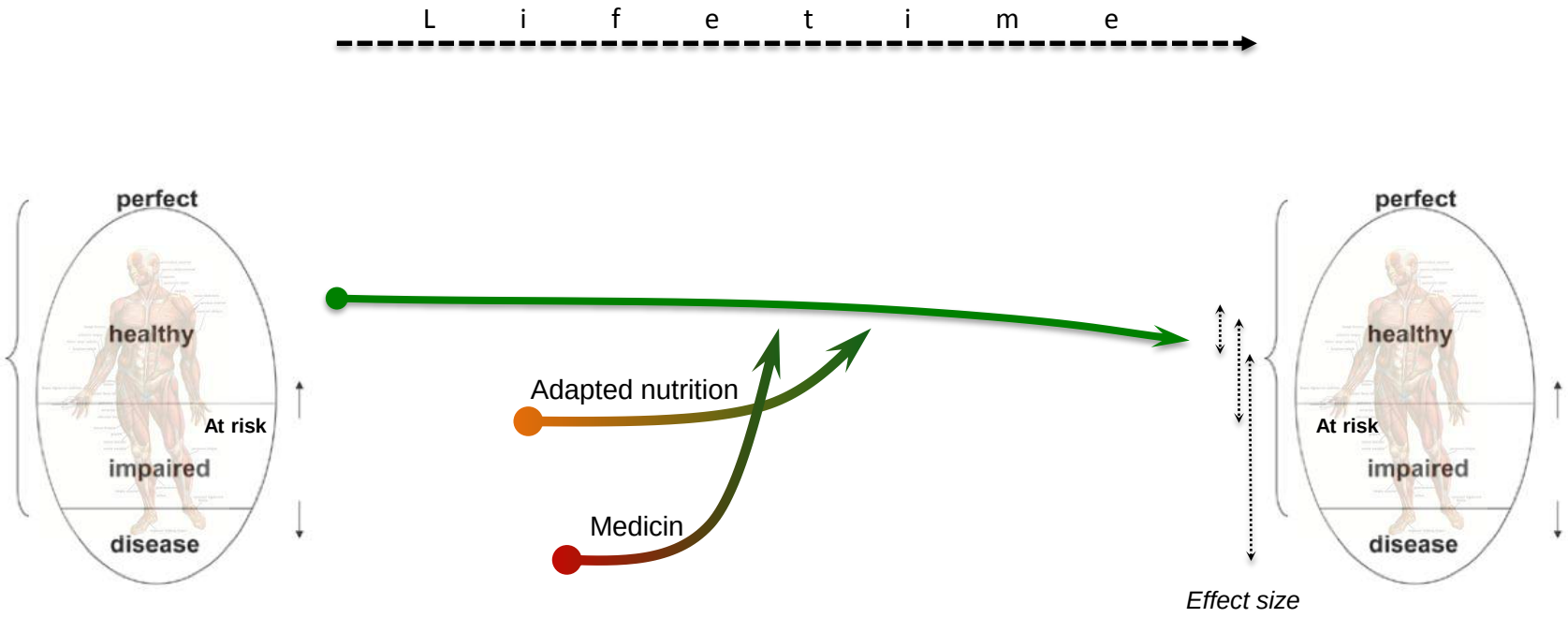
WHY look for confounding in experimental studies?

THE MODEL OF SCIENCE THAT NUTRITION IS GENERALY FORCED INTO DOES NOT COVER THE NEEDS FOR NUTRITION SCIENCES

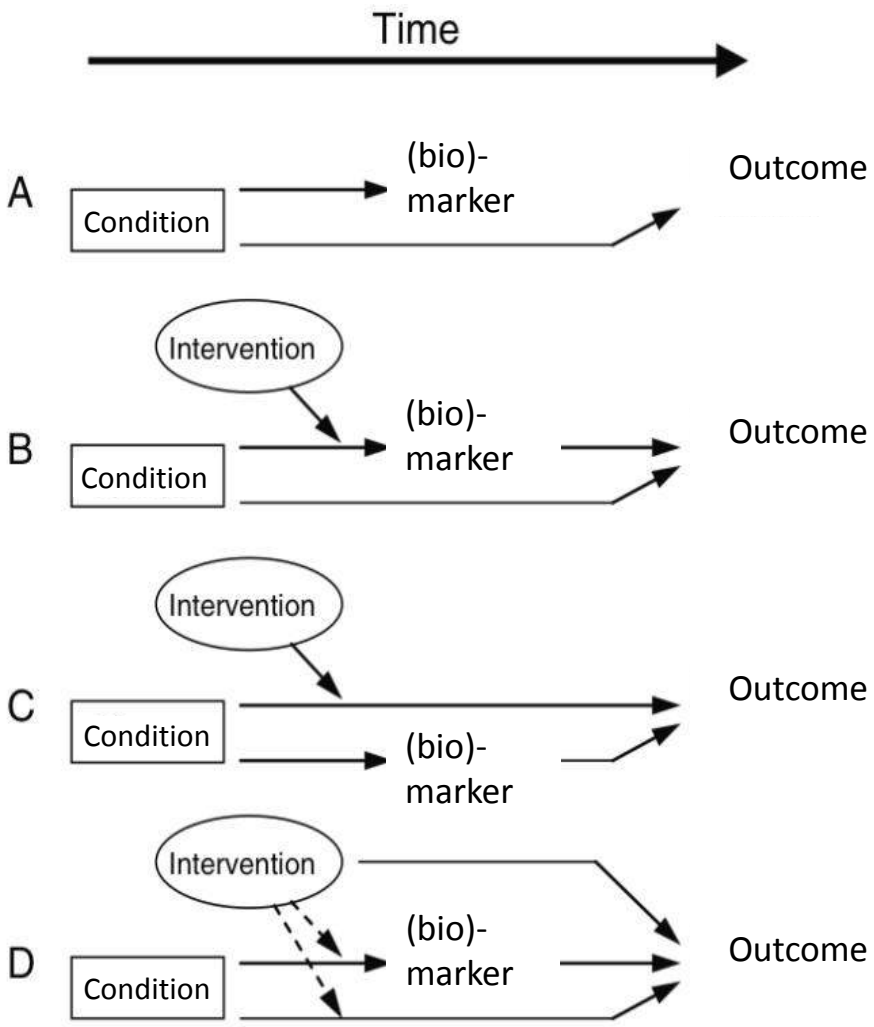
Evidency base Pyramid



Evidence based approach



Biomarkers and predictability of future outcome



A. The surrogate is not in the causal pathway of the process.

B. Of several causal pathways, the intervention affects only the pathway mediated through the surrogate.

C. The surrogate is not on the pathway of the intervention's effect or is insensitive to its effect.

D. The intervention has mechanisms of action independent of the process that results in the outcome. Dotted lines = mechanisms of action that might exist. (Adapted from Fleming, 1996).

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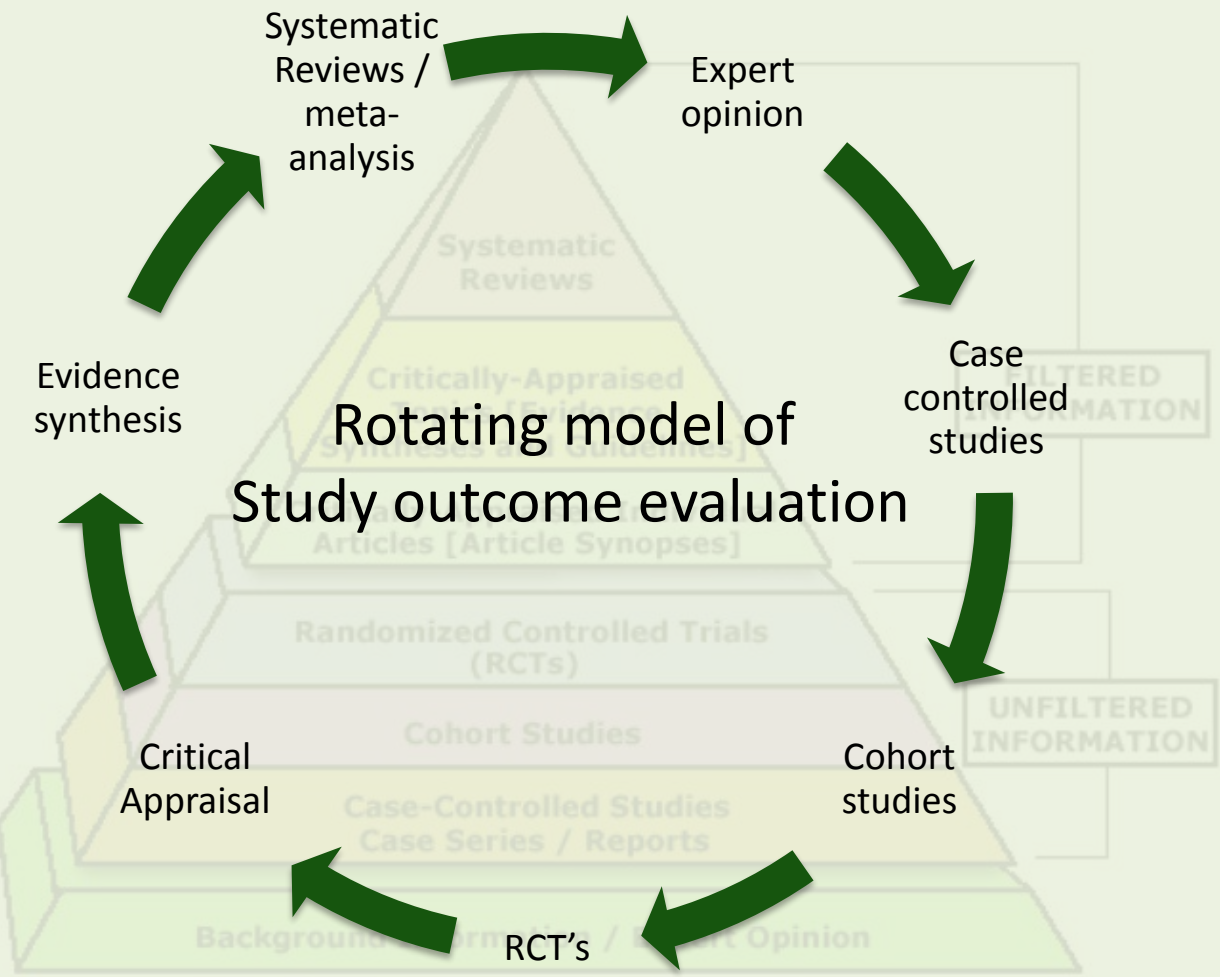
Evidency base Pyramid the right model for nutrition sciences?



Discussion

Epidemiology:

- Whole grain = whole grain

Intervention studies:

- Whole grain ≠ whole grain

Question:

- Is it surprising that experimental studies can not consistently support epidemiological findings!?

Questions

1. Usually outcomes from epidemiological studies are questioned with respect to cause-effect relationship.
   - However how valid are the outcomes of human intervention studies?
   - What is a cause-effect relationship?
2. Is cause-effect relationship essential in the communication of lifelong prevention? (*this is about deceit*)
3. Would there be THE ultimate intervention study to proof a cause-effect relationship of whole grain?
4. What is the level of evidence that is needed for preventive effects of nutrition in relation to lifelong healthiness?
5. May be more important: what do we consider as EVIDENCE?

Closing Quote

"All scientific work is incomplete, whether it be observational or experimental.

All scientific work is liable to be upset by advancing knowledge.

That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

Sir Austin Bradford Hill, Proc R Soc Med 1965, vol 58, p. 300