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diabetes foreningen

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Transportability

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Replacement of Red and Processed Meat With Other Food Sources of Protein and the Risk of Type 2 Diabetes in European Populations: The EPIC-InterAct Study

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OBJECTIVE

There is sparse evidence for the association of suitable food substitutions for red and processed meat on the risk of type 2 diabetes. We modeled the association between replacing red and processed meat with other protein sources and the risk of type 2 diabetes and estimated its population impact.

weak. This result is in line with a previous finding that serum ferritin may partly mediate the association between intake of red meat and risk of type 2 diabetes in the EPIC-Potsdam study (9). There are, however, alternative explanations for the potential benefits of substituting red meat with other protein sources. BMI could be regarded as a mediator. We found that most of our estimates were attenuated after adjustment for BMI, as was also observed in a

have been prevented if the population had replaced 1 serving/day of red and processed meat with 1 serving/day of cheese, yogurt, or nuts. This is relevant for public health. Our study paid close attention to accounting for a range of potential confounding factors and addressed a number of potential biases. Our study was undertaken in meat-consuming European populations, and the results cannot, therefore, necessarily be generalized to non-European populations with different dietary habits. Although studies suggest that red and processed meat intake is positively associated with the development of type 2 diabetes (6), this may also depend on the consumption levels of other foods consumed in the diet, such as fiber- or calcium-rich foods, and whether red and processed meats are consumed

Author Contributions. The EPIC-InterAct study was coordinated by N.J.W., S.J.S., and N.G.F. with N.J.W. as chief investigator. D.B.I., M.S., F.I., K.O., and N.G.F. conceived the research question. D.B.I., M.S., F.I., K.O., M.B.S., B.B., M.G., and N.G.F. designed the analysis plan. D.B.I. performed the data analysis. M.S., F.I., and S.J.S. provided statistical supervision. D.B.I. drafted the manuscript with supervision from N.G.F. All authors interpreted the results and critically revised the article for important intellectual content and gave final approval of the version to publish. N.G.F. and N.J.W. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract

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have been prevented if the population had replaced 1 serving/day of red and processed meat with 1 serving/day of cheese, yogurt, or nuts. This is relevant for public health. Our study paid close attention to accounting for a range of potential confounding factors and addressed a number of potential biases. Our study was undertaken in meat-consuming European populations, and the results cannot, therefore, necessarily be generalized to non-European populations with different dietary habits. Although studies suggest that red and processed meat intake is positively associated with the development of type 2 diabetes (6), this may also depend on the consumption levels of other foods consumed in the diet, such as fiber- or calcium-rich foods, and whether red and processed meats are consumed within an overall healthy diet (35).

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1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843

Imagine this was a randomized controlled trial…

(this simply makes the whole situation simpler, as we will assume the results are internally valid)

Randomized controlled trial

- We want to know what works
- Designed to reduce threats to internal validity
  - Restriction of participants
  - Randomization
  - Standardized outcome
  - Specific treatment regime

Internal validity

"The degree to which the results of a study are correct for the sample of individuals being studied."

External validity

"The degree to which the results of an observation hold true in other settings."

Fletcher and Fletcher, Clinical Epidemiology: The Essentials, 4th Ed

Imagine you work for a non-European country and need to use the results to make a recommendation.

Can you use the results for your population? Why, why not?

Who are we??

- **Policy makers**
  - Regulators, guideline makers
- **Payers**
  - Public, private
- **Purchasers**
  - Healthcare systems
- **Providers**
  - Clinicians, pharmacist, specialist
- **Patients**

Now take a meta-analysis of 21 RCTs showing a HR of 1.11 (95% CI: 1.05, 1.23) for higher intake of red meat on T2D risk

Can you use the results for your population? Why, why not?

Where do we go from here? Implement the intervention? Will we get the same results?

This is where transportability methods comes in. We can ask: *"what would be the effect in my target population?"*

Target population = a population in which we want to learn the effect of a treatment

Different decision-makers have different target populations

External validity and target populations

- A trial identifies an internally valid average causal effect where the sample is the trial population.
- We are rarely interested in the trial population for its own sake, yet we rarely formally identify a target population.
- In fact, there isn't just one target population. Each decision makers' target population is different
- A treatment effect is externally valid if the true treatment effect from the trial is equal to the true treatment effect in the target population

When do we have external validity issues

- If the trial population differs systematically from the target population, i.e., there are different “types” of people

AND

- If the characteristics that differ between the trial and target populations modify the effect of the treatment

Different characteristics

We want to make guideline for European population

Target population

60% men & 40% women

RR = 0.5 in men
RR = 0.9 in women

RCT in the US finds RR = 0.52

Randomized trial population

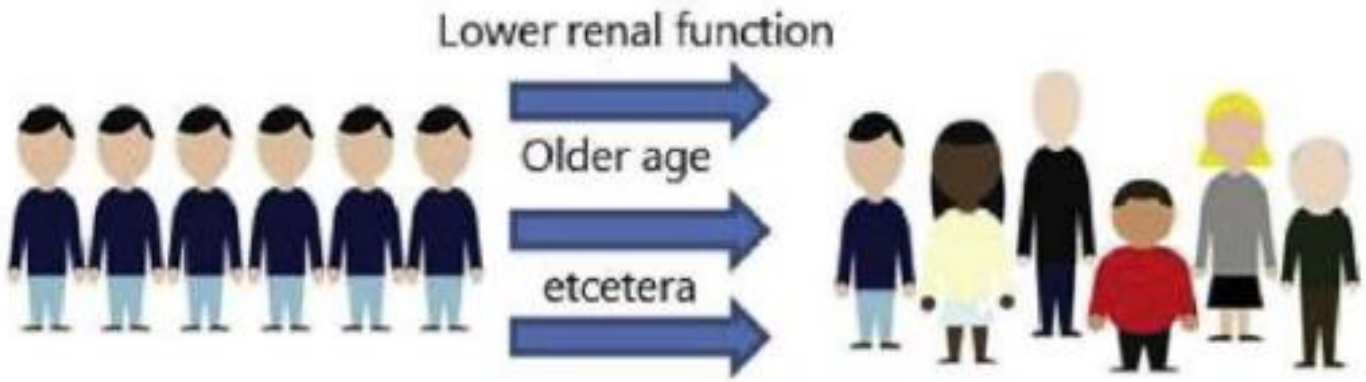
95% men & 5% women

Solution = new weighted average
RR = 0.6 * 0.5 + 0.4 * 0.9 = 0.66

Weighted average
RR = 0.95 * 0.5 + 0.05 * 0.9 = 0.52

Effect modification

Modifiers of treatment effects
(i.e., treatment effect heterogeneity)



Trial population

Target population: Clinical practice

Approaches to address external validity issues

- Assume external validity
- Discuss impact of inclusion/exclusion criteria
- Note lack of generalizability

OR

- Transportability analysis using trial and target population data

What do you need to carry out a transportability analysis?

- To understand if a treatment effect estimate reported in a randomized trial is valid in a different target population (i.e., would the effect estimate reported in the randomized trial be the same if the trial was carried out in our target population)
- RCT data (data on the assigned treatment, outcomes, and baseline covariates for everyone enrolled in the trial)
- Target population data (need data baseline covariates for the target population)

What do you need to carry out a transportability analysis?

- RCT data
- Baseline covariate data from our target population
- Apply transportability methods
  - Standardization/G-formula
  - Weighting
  - assumptions

Assumptions

- Internally valid estimates (=that was we we use the RCT, just stronger assumption with cohorts)

Assumption	
Exchangeability	Participants in the study are exchangeable with individuals in the target population, perhaps conditional on covariates X
Consistency	Treatment versions should not differ between the trial and target population
Positivity	All individuals in the target population have a non-zero probability of participating in the trial

Notation

- S indicates trial participation (0 = no, 1 = yes)
- L is some vector of covariates
- Y indicated the outcome (0 = no, 1 = yes)
- A indicates treatment assignment (0 = no treatment, 1 = treatment)
- Pr[Y=1|A=1] mean the probability of Y=1 among those with A=1
- $Pr[Y^{A=1}]$ means the probability of Y=1 if all individual had A=1

Estimators

- Our goal is to estimate Pr[Y^a=1|S=0]
- We know Pr[Y^a=1|L,S=1] from the trial
- We know Pr[L=l|S=0] from registry
- G-formula/standardization:

$$\Pr[Y^a = 1|S = 0] = \frac{1}{n}\sum_{i=1}^{n} \Pr[Y|A = a, L, S = 1] \times \Pr[L = l|s = 0]$$

By hand – in trial

	Randomized trial, S= 1, L = 0	Randomized trial, S= 1, L = 1
$Pr[Y^{A=1}\|L=l]$	0.30	0.75
$Pr[Y^{A=0}\|L=l]$	0.50	0.75
$Pr[Y^{A=1}\|L=l] - Pr[Y^{A=0}\|L=l]$	-0.20	0

- L = 0 is 85 % of patients
- $Pr[Y^{A=1}|L=0] = 0.30$
- L = 1 is 15 % of patients
- $Pr[Y^{A=1}|L=1] = 0.75$

- $Pr[Y^{A=a}] = \sum_L Pr[Y = 1|L = l, A = a]Pr[L = l]$
- $Pr[Y^{A=1}] = (0.3 \times 0.85) + (0.75 \times 0.15) = 0.37$

By hand – standardize to new population

What if the **distribution of patients with previous stroke (L) is 40 % in the general population** Pr(L=1|S=0), **compared to 15% in my original study location** Pr(L=1|S=1) ?

	Randomized trial, S= 1, L = 0	Randomized trial, S= 1, L = 1
$Pr[Y^{A=1}]$	0.30	0.75
$Pr[Y^{A=0}]$	0.50	0.75
$Pr[Y^{A=1}] - Pr[Y^{A=0}]$	-0.20	0

Standardized to new population (S = 0):

- $Pr[Y^{A=a}|S=0] = \sum_L Pr[Y=1|L=l,A=a,S=1]Pr\,[L=l|S=0]$
- $Pr[Y^{A=1}|S=0] = \sum_L Pr[Y=1|L=l,A=1,S=1]Pr\,[L=l|S=0] = 0.48$
- $Pr[Y^{A=0}|S=0] = \sum_L Pr[Y=1|L=l,A=0,S=1]Pr\,[L=l|S=0] = 0.5 \times 0.6 + 0.75 \times 0.4 = 0.60$

By hand – comparison

Standardized estimates	Original study (S=1)	New population (S=0)
$Pr[Y^{A=1}]$	0.37	0.48
$Pr[Y^{A=0}]$	0.54	0.60
$Pr[Y^{A=1}] - Pr[Y^{A=0}]$	-0.17	-0.12
$Pr[Y^{A=1}]/Pr[Y^{A=0}]$	0.68	0.80

With models

- We fit our model for the outcome, conditional on treatment and covariates, allowing for interactions in S=1
- We then predict the probability of the outcome in the dataset for our target population (S=0) under each treatment regime
- Average these treatment specific outcomes
- Bootstrap for inference

ID	A	L1	L2…	Y
1	1	1	2	1
2	0	1	5	0
3…	0	0	13	1

S=1

A	L1	L2…	Y	YA0	YA1
-	1	2	-	0.80	0.20
-	1	5	-	0.85	0.11
-	0	13	-	0.29	0.75

S=0

e.g. Pr[Y = 1|A, S=1, L1, L2] = a0 +a1A + a2L1 + a3L2 + a4A*L1 + a5A*L2

YA0_pred = *model0* Pr[Y = 1|A=0, L1=l1i, L2=l2i] for all i

YA1_pred = *model1* Pr[Y = 1|A=1, L1=l1i, L2=l2i] for all

$Pr[Y^{A=0}|S=0]=1/n\sum YA0\_pred = 0.65$

With models

1. Fit a logistic regression model for the outcome, conditional on treatment and covariates among participants in the randomized trial - Fit a model for Pr[Y|L, S = 1, A=a]
2. Use this model to predict the outcomes under each treatment in the entire target population - Estimates conditional risk for each individual Pr[Yi|Li, S = 1, A=a]
3. Take the average of these predictions for each treatment
4. Calculate the risk difference
5. 95 % CI by boostrapping this process

Let’s try in R

Thank you

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Collaborators

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