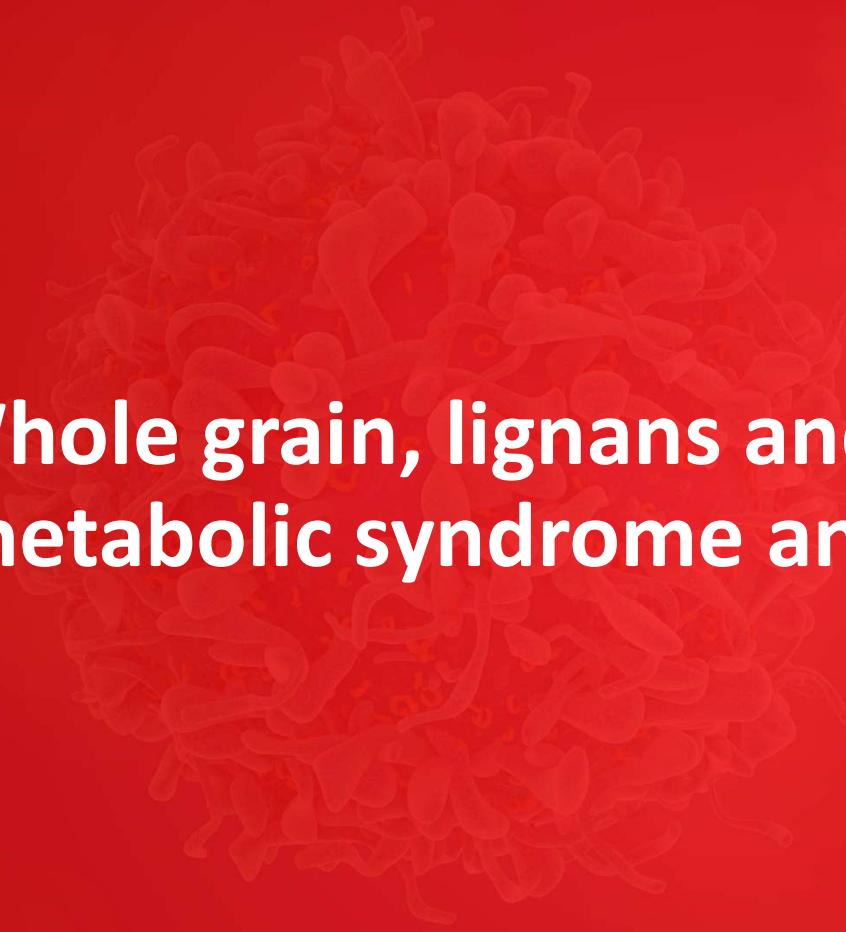




Whole grain, lignans and enterolactone in metabolic syndrome and type 2 diabetes

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Nordic Rye Forum, November 21-22, Gothenburg



DOCTORAL THESIS No. 2019:25
FACULTY OF NATURAL RESOURCES AND AGRICULTURAL SCIENCES

The role of whole grains and lignans in
lifestyle diseases – emphasis on
prostate cancer and type 2 diabetes
and their risk factors

ANNE KIRSTINE ERIKSEN

MAY 3RD 2019



Agenda



Background

- Whole grains, lignans and enterolactone
- Metabolic syndrome and type 2 diabetes



Crossover intervention among men with metabolic syndrome

- Whole-grain rye vs. whole-grain wheat
- High vs. low lignan content

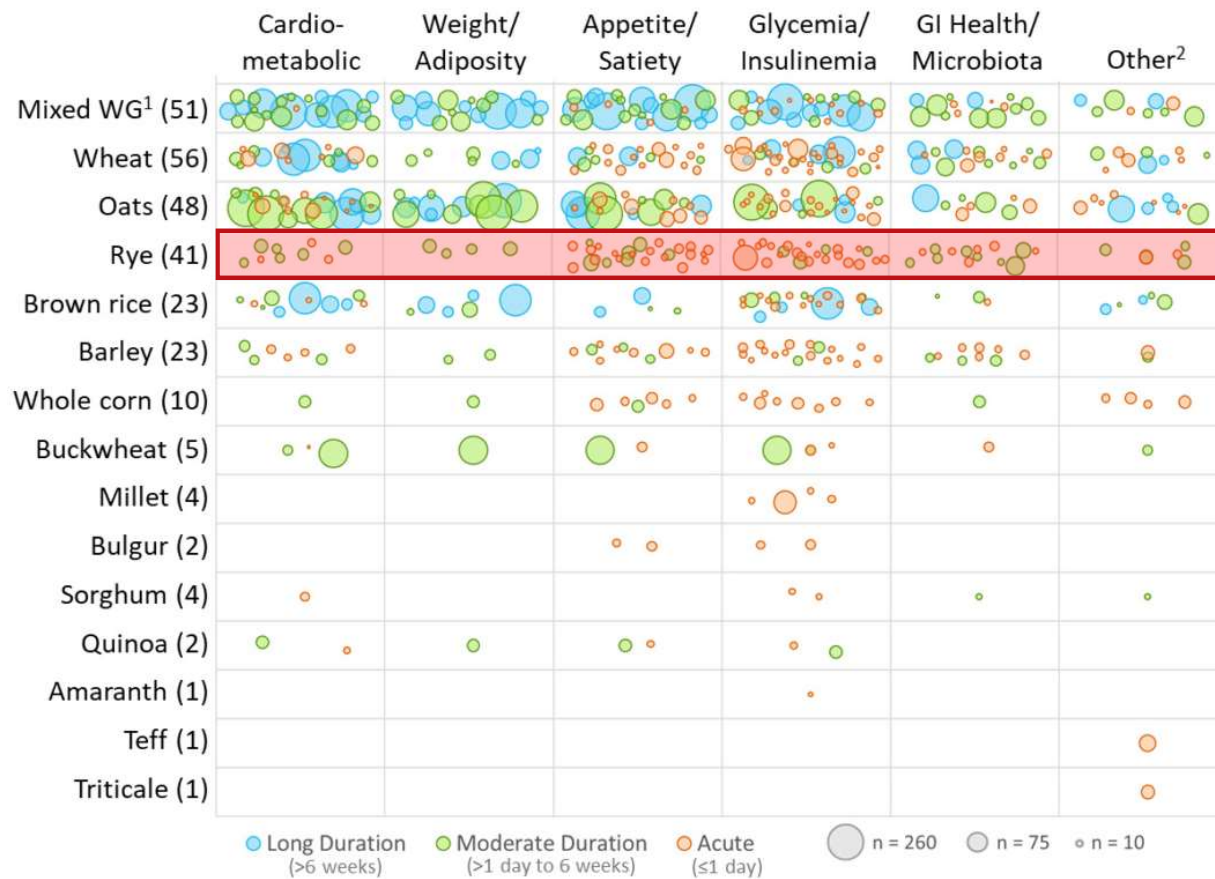


Pre-diagnostic enterolactone and T2D mortality

- What is the association between enterolactone concentrations and mortality?



Whole-grain interventions



Sawicki *et al.* 2018



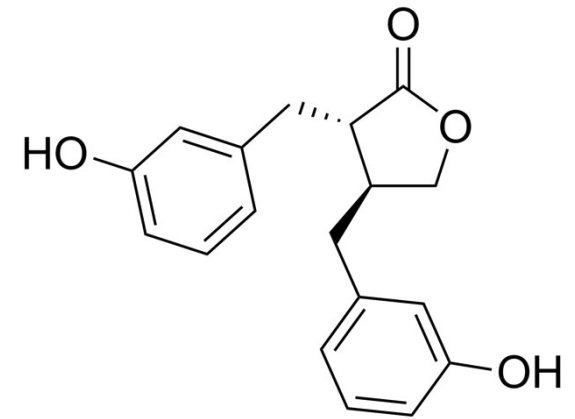
Background - lignans

Source	Lignan content ($\mu\text{g}/100\text{ g}$)
Flaxseed	300 000
Sesame seeds	39 000
Whole-grain rye flour	458
Dark rye bread	320
Whole-grain wheat bread	121
Wheat flour	99
Rolled oats	107
Whole-grain rice	40
Cabbages	600
Strawberry	334
Dark chocolate	44
Coffee	25
Tea	58
Beer	26
Wine	56

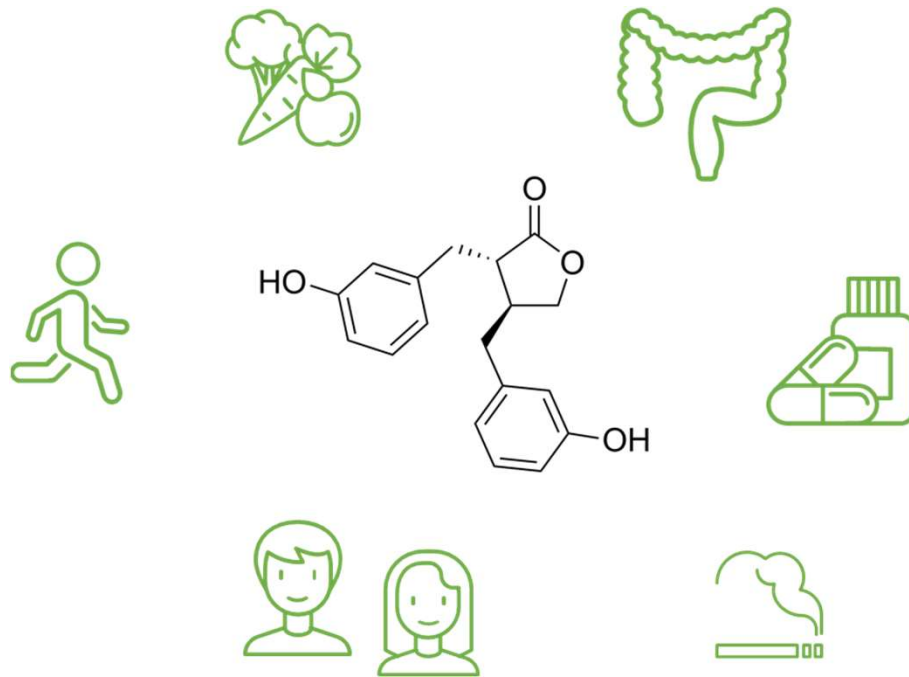


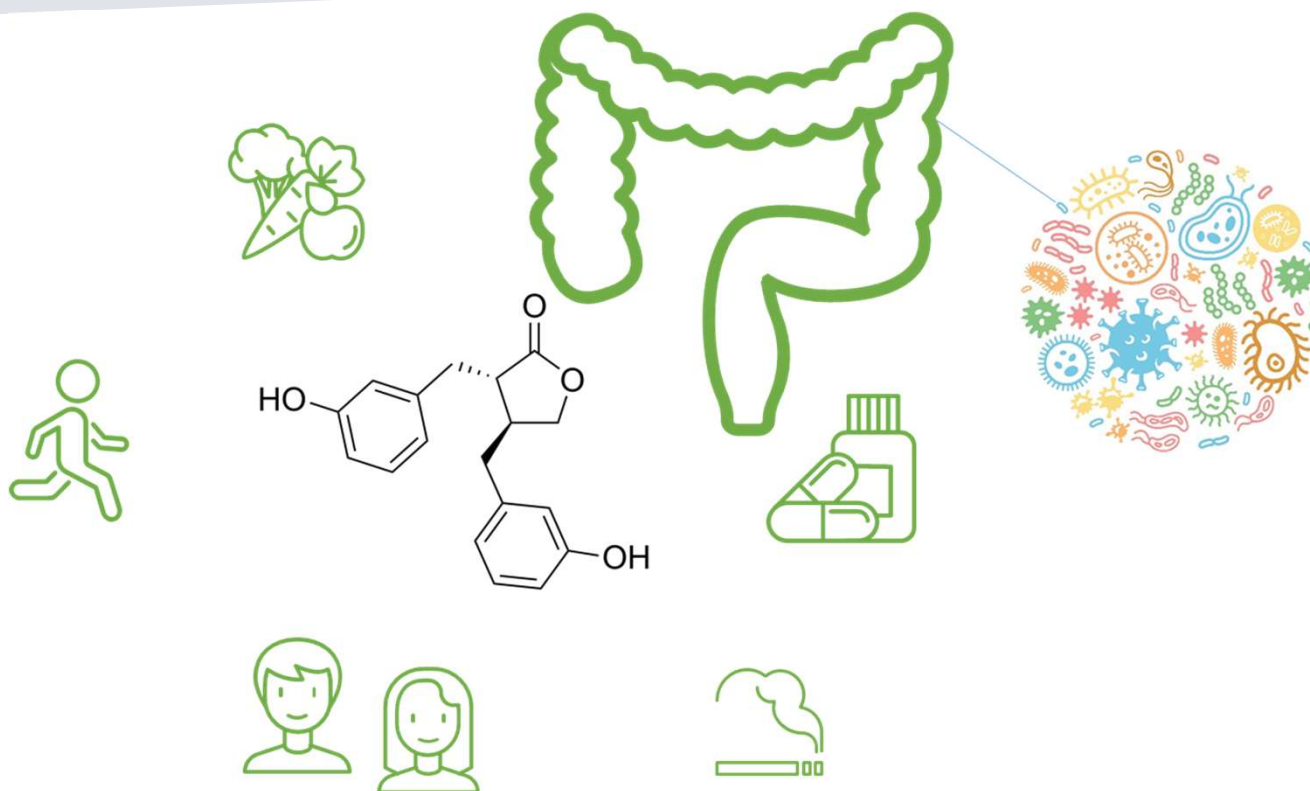
Background - enterolactone

- The final metabolite of plant lignans
- Measurable in blood and urine
- Structural similarities to estrogens
- Several proposed health beneficial properties
 - Weak estrogenic/anti-estrogenic receptor interaction
 - Antioxidant
 - Anti-cancer effects (growth factor modulating)



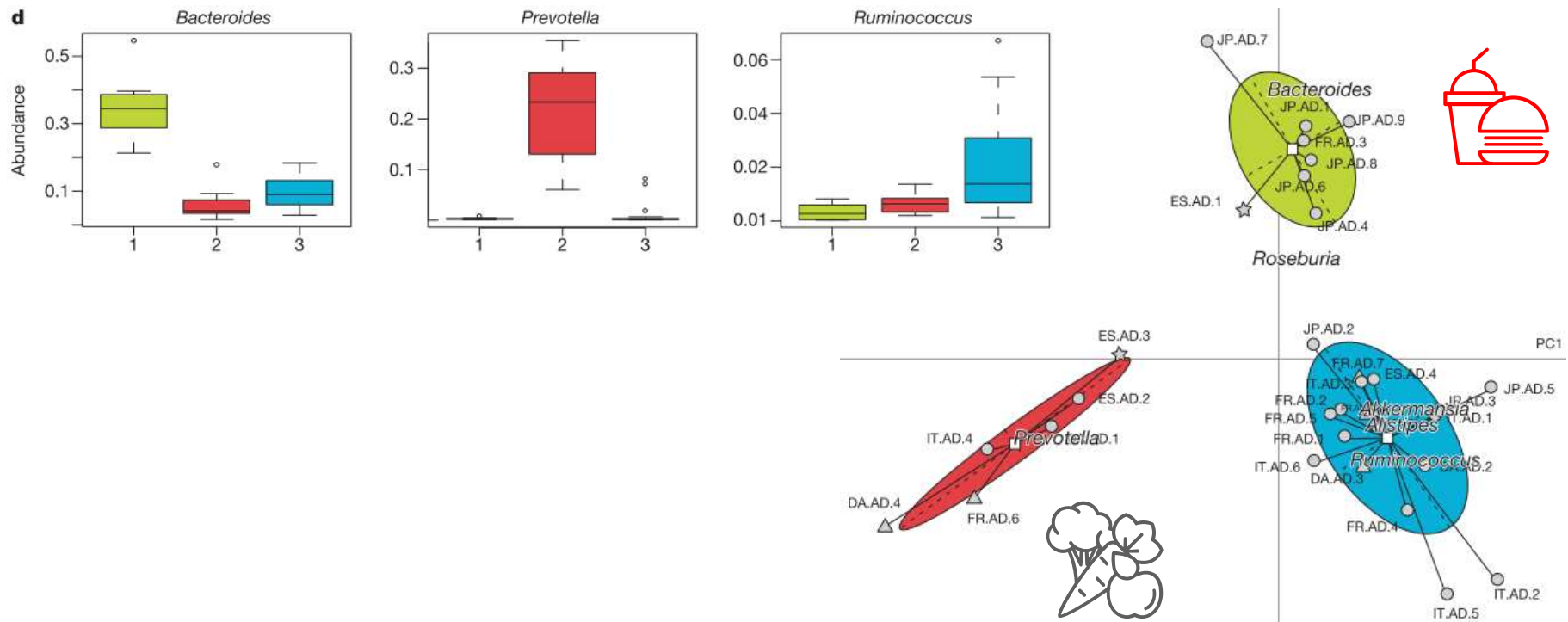
Background - enterolactone





Microbiota enterotypes

Arumugam *et al.* 2011



The whole-grain/lignan intervention study

Study aim and objectives

- To investigate the effects of whole-grain rye and wheat diets, with high vs. low lignan content, on cardio-metabolic risk factors
 - Main outcome: glucose and insulin response after OGTT
 - Secondary outcomes: blood lipids, blood pressure, waist etc.
 - Exploratory analyses: the role of microbiota/enterotype in response to diet
- Study population: middle-aged Swedish men with (or with signs of) metabolic syndrome
 - Central obesity, insulin resistance, hypertension, dyslipidemia
 - Risk factors: physical inactivity, diet and overweight/obesity



Intervention

Recruitment

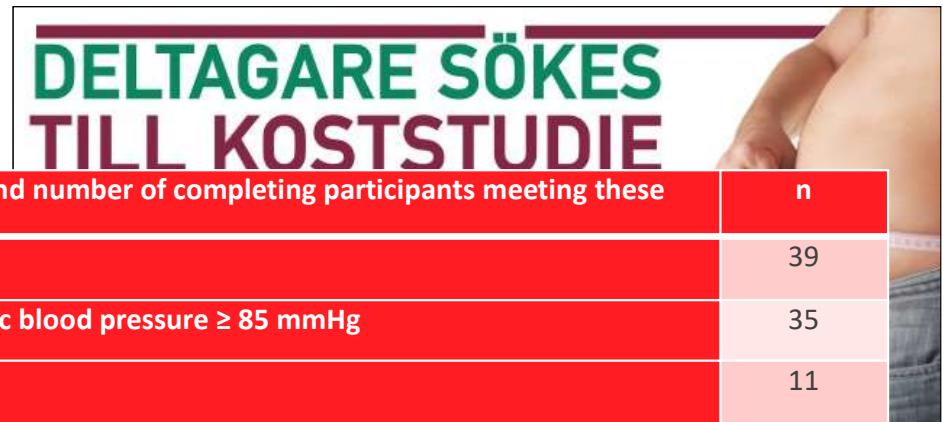
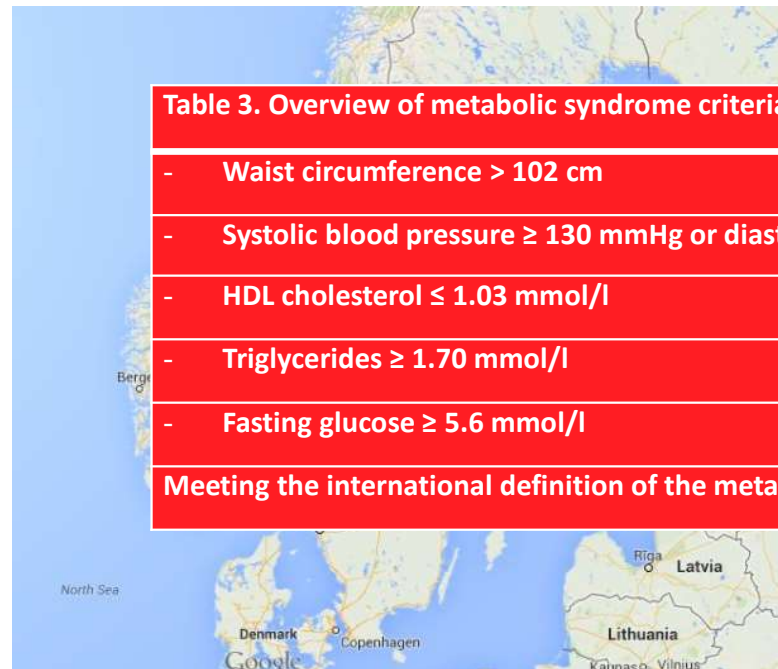
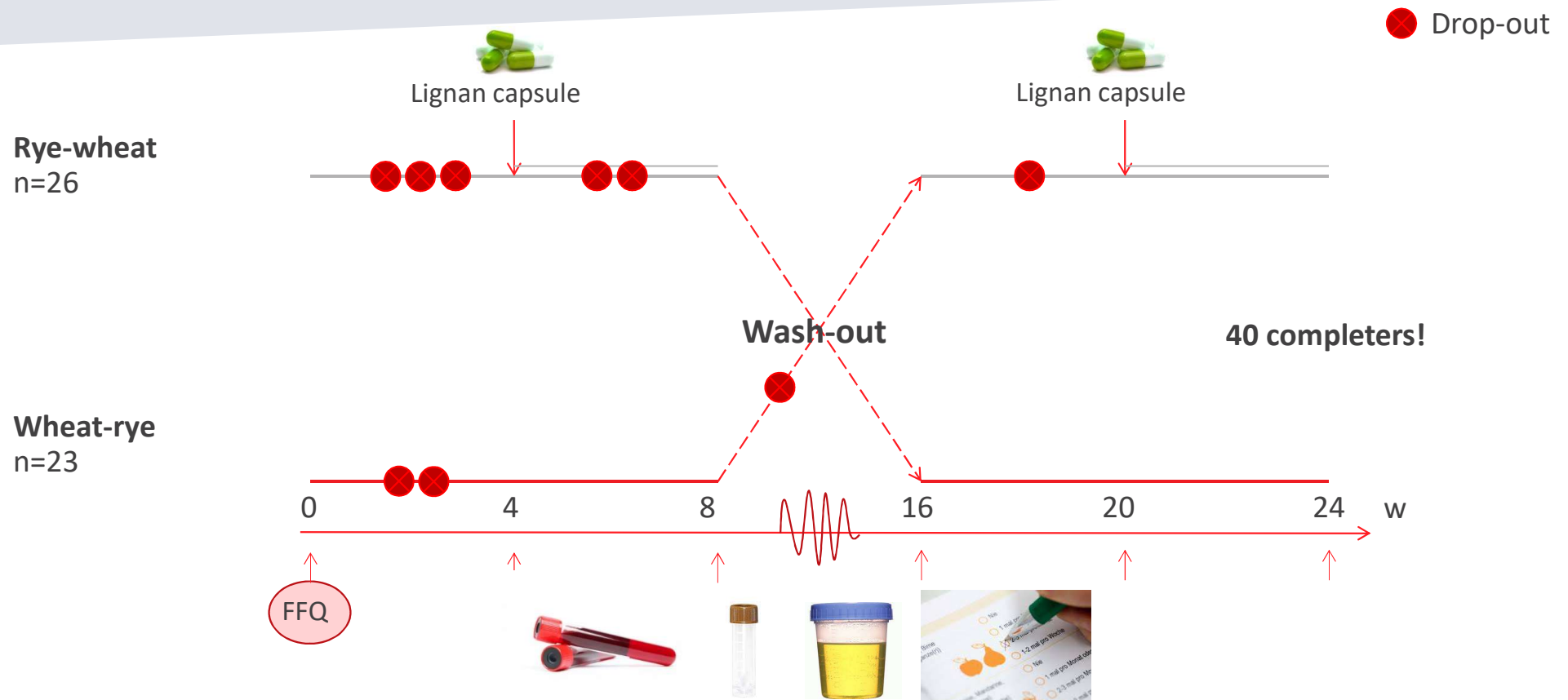


Table 3. Overview of metabolic syndrome criteria and number of completing participants meeting these	n
- Waist circumference > 102 cm	39
- Systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85 mmHg	35
- HDL cholesterol $\leq$ 1.03 mmol/l	11
- Triglycerides $\geq$ 1.70 mmol/l	7
- Fasting glucose $\geq$ 5.6 mmol/l	38
Meeting the international definition of the metabolic syndrome	33



Intervention

Study design



Intervention diets

+ 300,000 μg



RYE

Fibre $\approx 35 \text{ g}/800 \text{ kcal}$

Lignans: 12,000 μg

$\approx 800 \text{ kcal}$

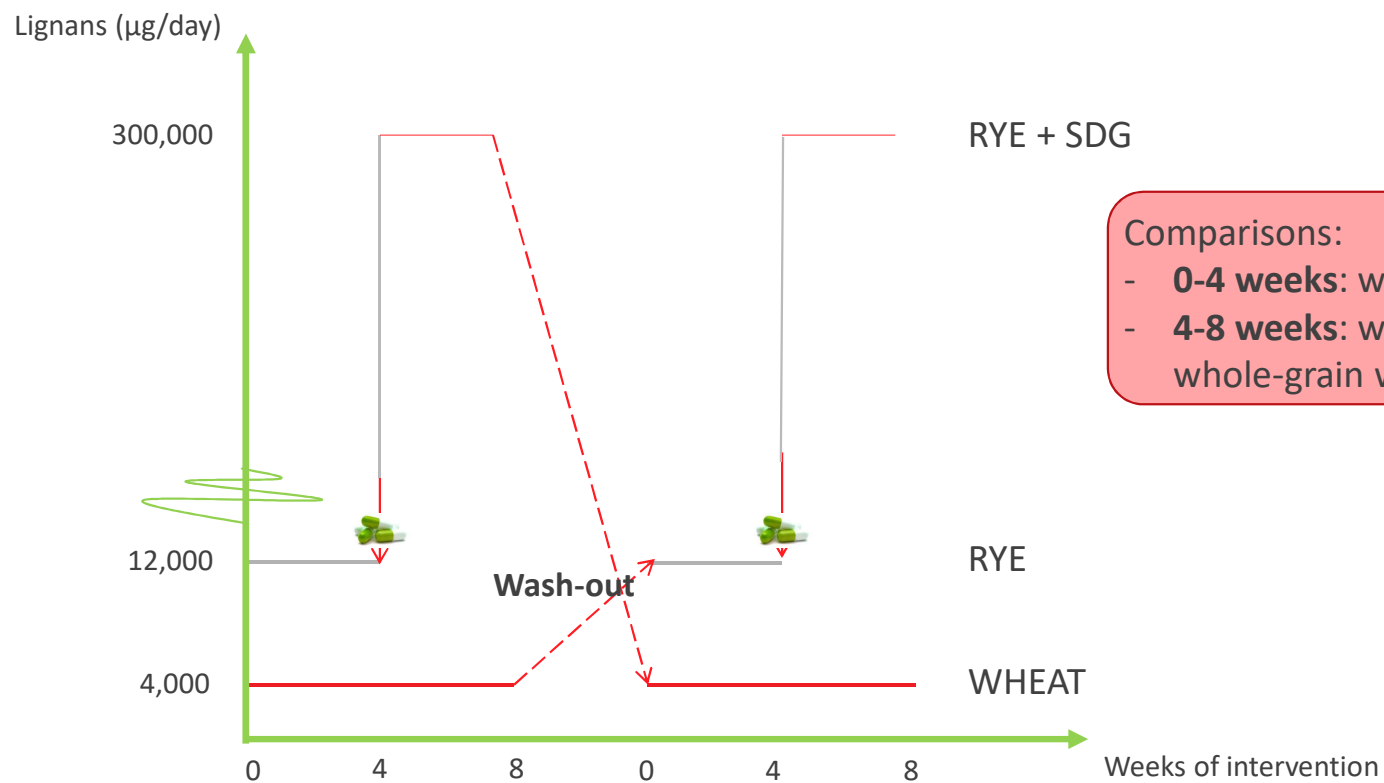


WHEAT

Fibre $\approx 34 \text{ g}/800 \text{ kcal}$

Lignans: 4000 μg

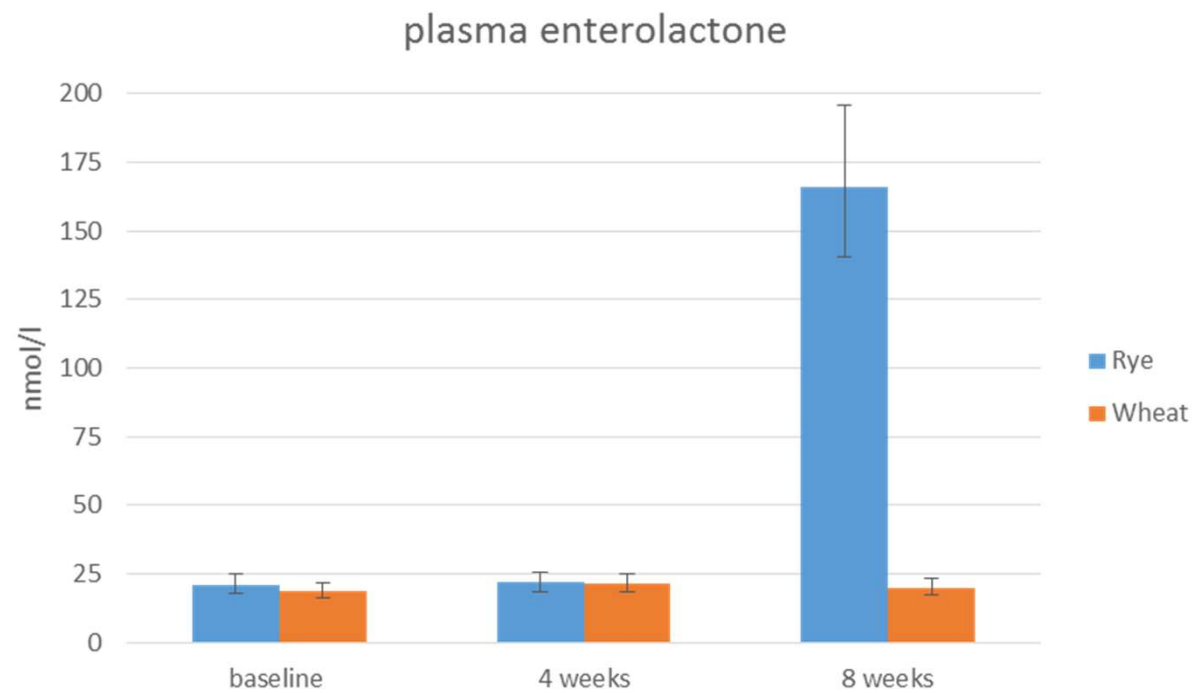
Lignan content during the intervention



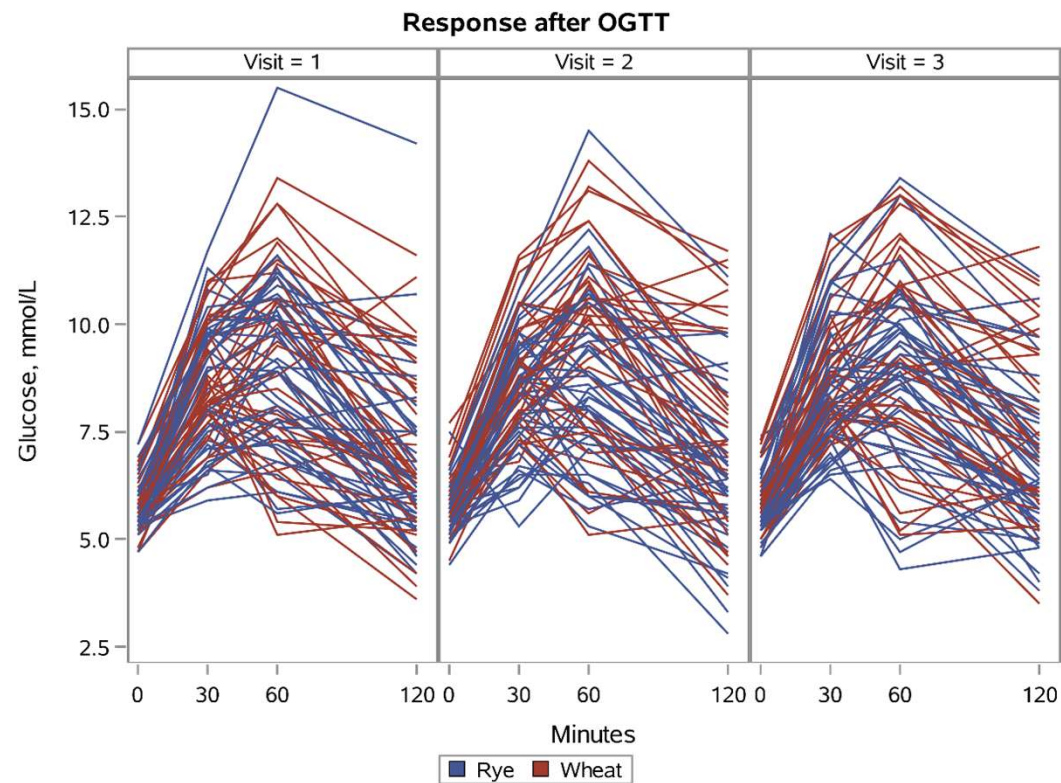
Comparisons:

- **0-4 weeks:** whole-grain rye vs. wheat
- **4-8 weeks:** whole-grain rye + lignans vs. whole-grain wheat

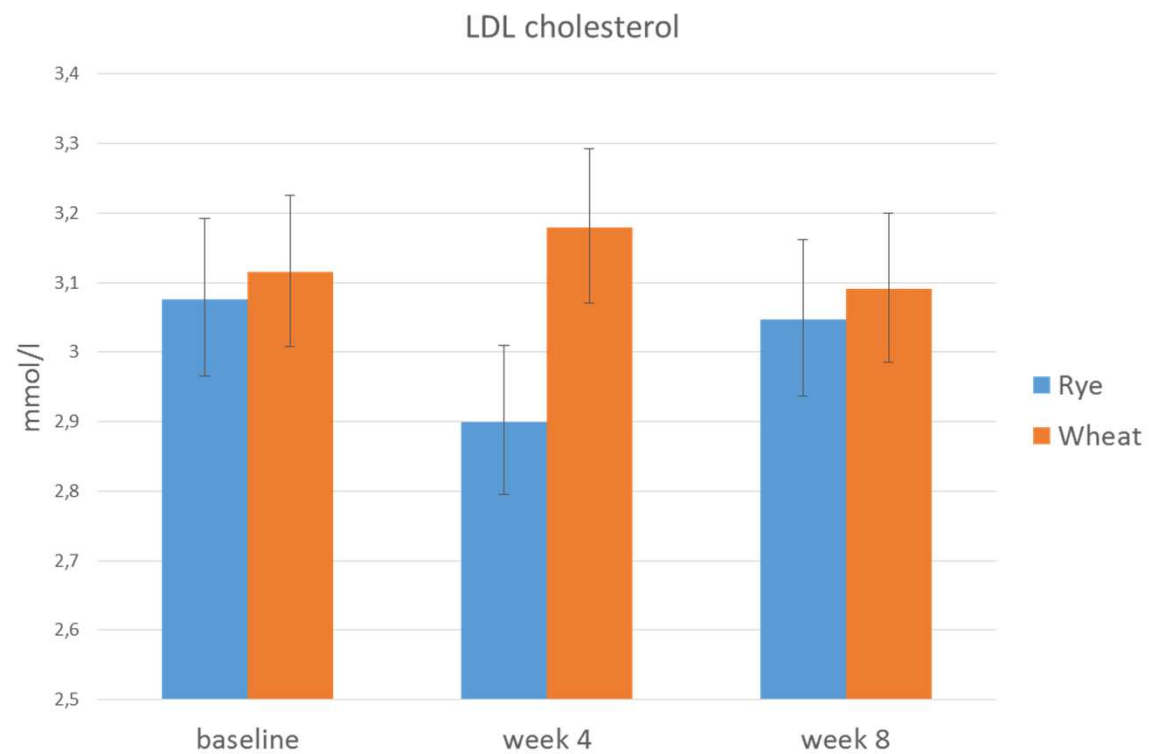
Enterolactone concentration



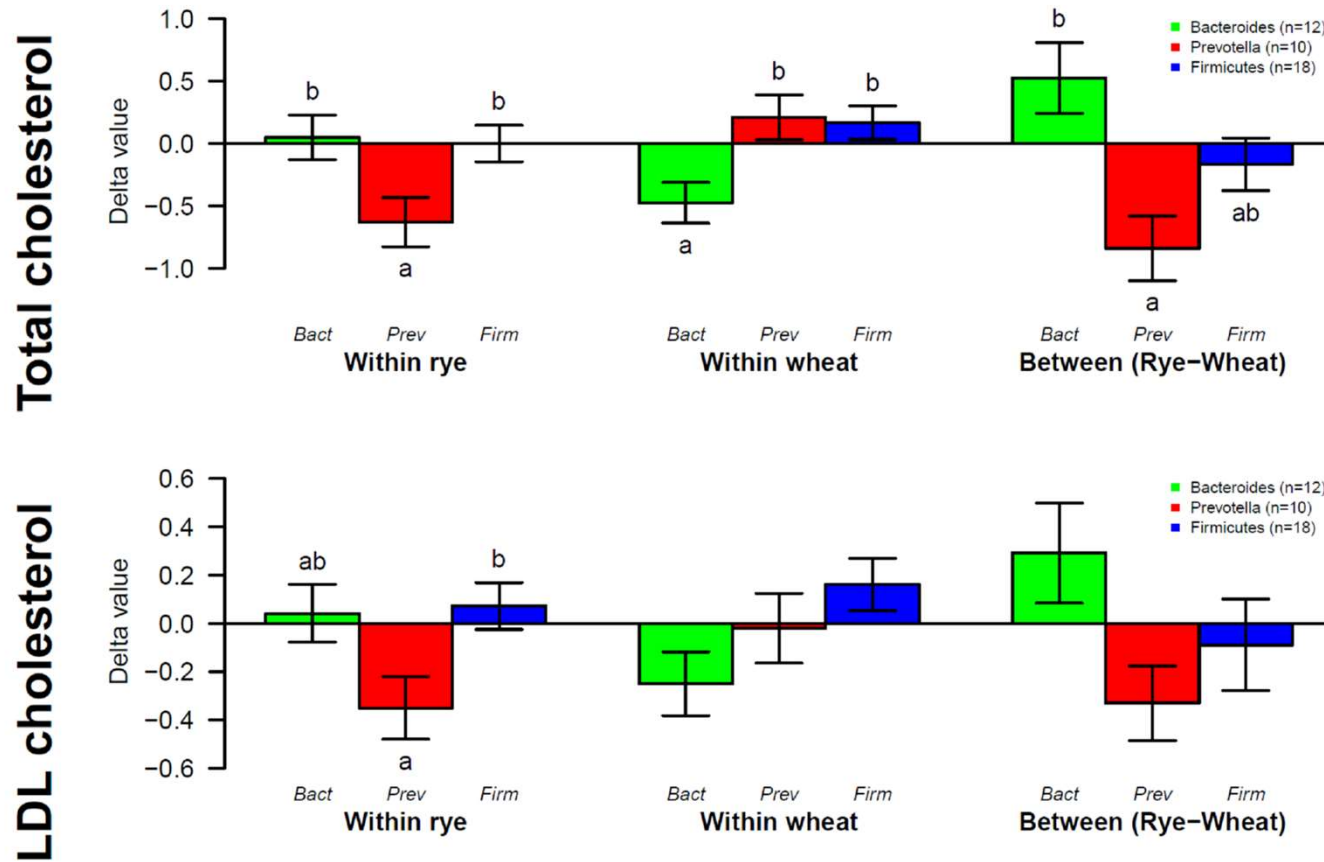
Glucose tolerance – 2h after OGTT



LDL cholesterol



Enterotypes and response to treatment



Enterolactone and mortality

Type 2 diabetes

Diabetologia
<https://doi.org/10.1007/s00125-019-4854-9>

ARTICLE



Pre-diagnostic plasma enterolactone concentrations are associated with lower mortality among individuals with type 2 diabetes: a case-cohort study in the Danish Diet, Cancer and Health cohort

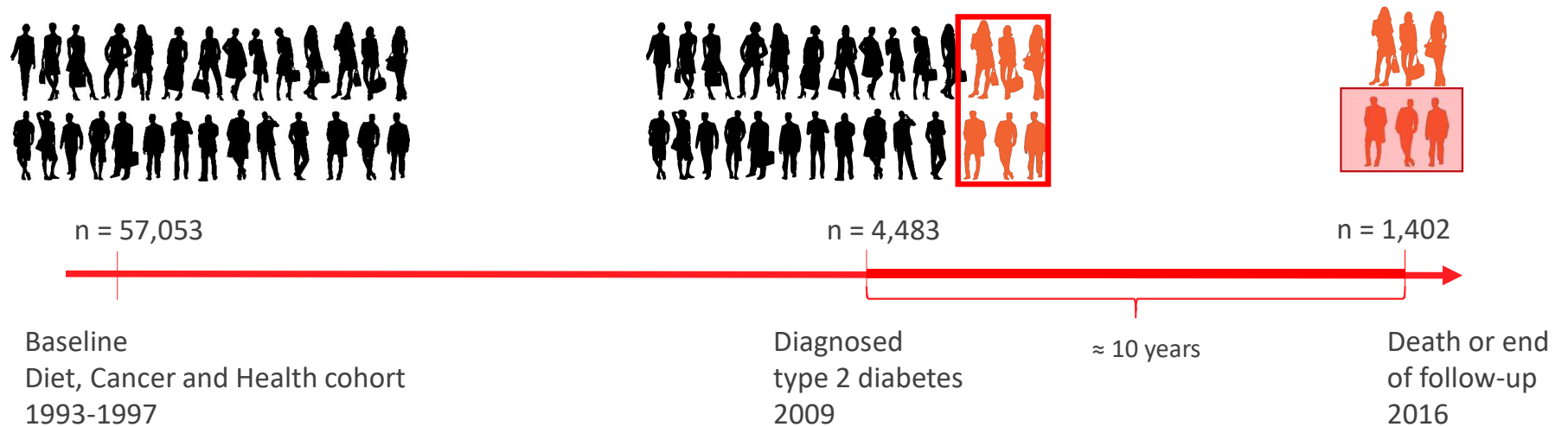
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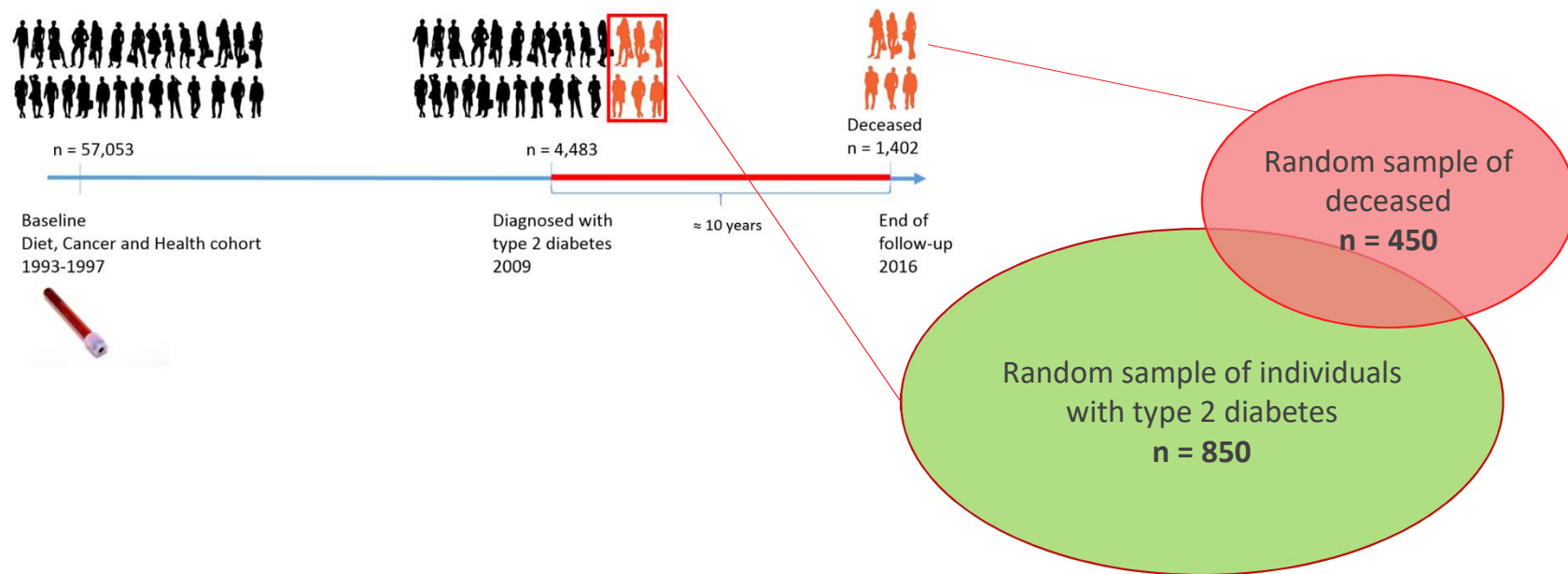
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A prospective study based on the Diet, Cancer and Health cohort

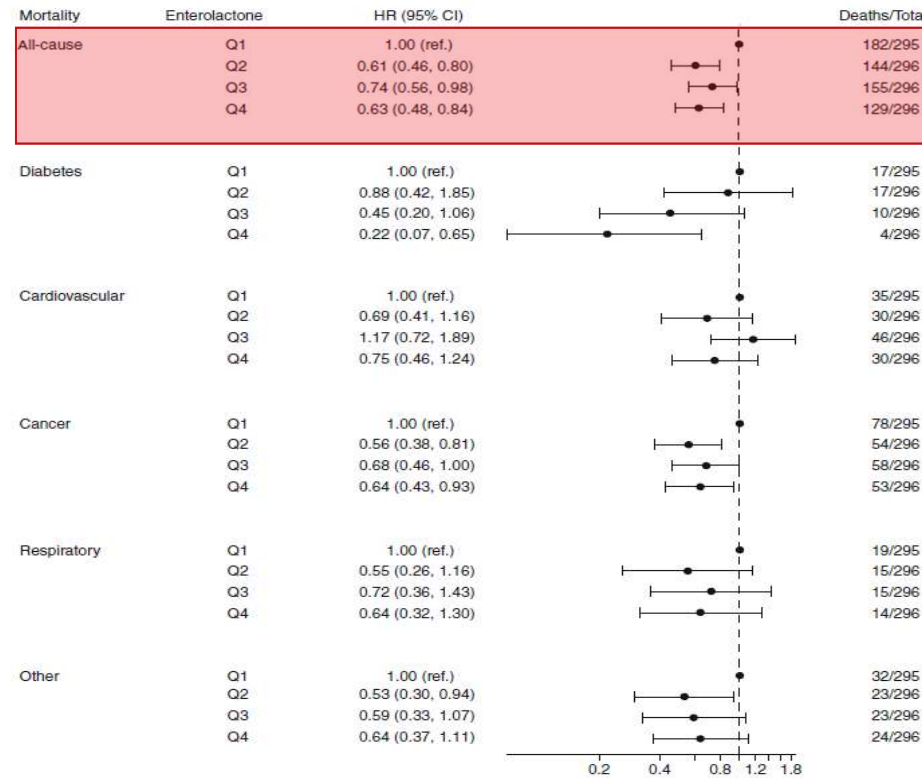


A case-cohort design



Enterolactone and mortality

Forest plot of all-cause and cause-specific mortality



Higher enterolactone concentration - lower mortality

How might this impact on clinical practice in the foreseeable future?

- The new findings suggest that high enterolactone concentrations are beneficial for diabetes prognosis. Enterolactone concentrations can be increased by diets with high lignan content. As existing evidence supports health benefits from cereal fibre (an important lignan source) on variables of diabetes management, the importance of promoting a diet rich in cereal fibre and lignans should be emphasised for people with type 2 diabetes

Linear estimate per doubling in concentration: HR 0.91 (95% CI 0.85, 0.96)



Thank you

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- Natalja Nørskov
- Knud Erik Bach Knudsen

- **All the participants in the studies!!**





VI VIL ET LIV **UDEN KRÆFT**



Background – enterolactone

- Whole-grain interventions:
 - Mainly oats (cholesterol)
 - Rye in the Nordic countries: "the rye factor", satiety and weight loss
- Observational studies on whole grains:
 - Lower morbidity and mortality (CHD, CVD, cancer, diabetes..)
- Lignan interventions:
 - Blood pressure↓
 - C-reactive protein↓
 - Cholesterol concentrations (LDL)↓
- Observational studies on enterolactone:
 - Enterolactone associated with lower mortality from CHD/CVD

Hollaender et al. 2015
Jonsson et al. 2018

Aune et al. 2016,
Zong et al. 2016

Aune et al. 2016,
Zong et al. 2016

Aune et al. 2016,
Zong et al. 2016



Effect modification by healthy lifestyle?

Diabetologia

Table 4 HR (95% CI) for pre-diagnostic enterolactone concentrations and all-cause mortality by health-score category in people with type 2 diabetes: a case-cohort study based on the Diet, Cancer and Health cohort

Variable	Health score		
	Low	Middle	High
Individuals, <i>n</i>	483	443	257
Deaths, <i>n</i>	284	222	104
Quartile of enterolactone concentration			
Q1 (0–4.97 nmol/l)	1.00 (ref)	0.65 (0.42, 0.99)	0.47 (0.25, 0.87)
Q2 (4.98–10.27 nmol/l)	0.52 (0.35, 0.78)	0.49 (0.31, 0.76)	0.38 (0.22, 0.64)
Q3 (10.28–21.54 nmol/l)	0.63 (0.42, 0.95)	0.60 (0.39, 0.93)	0.35 (0.21, 0.57)
Q4 (21.55–296.30 nmol/l)	0.66 (0.43, 1.01)	0.39 (0.25, 0.60)	0.33 (0.20, 0.55)
Linear, by doubling in enterolactone concentration (log ₂)	0.92 (0.86, 0.99)	0.89 (0.82, 0.96)	0.91 (0.81, 1.02)

Adjusted for sex, age (5 year bands), alcohol intake (alcohol abstain yes/no, intake among users, linear)

Brug af grafik

- Kopier grafik til ønsket slide.
- Skift fyldfarve til ønsket farve.
- Hold shift nede ved skalering, så holder grafikken proportioner.

