Experiences from a PFAS hot spot in Sweden

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This presentation at a glance

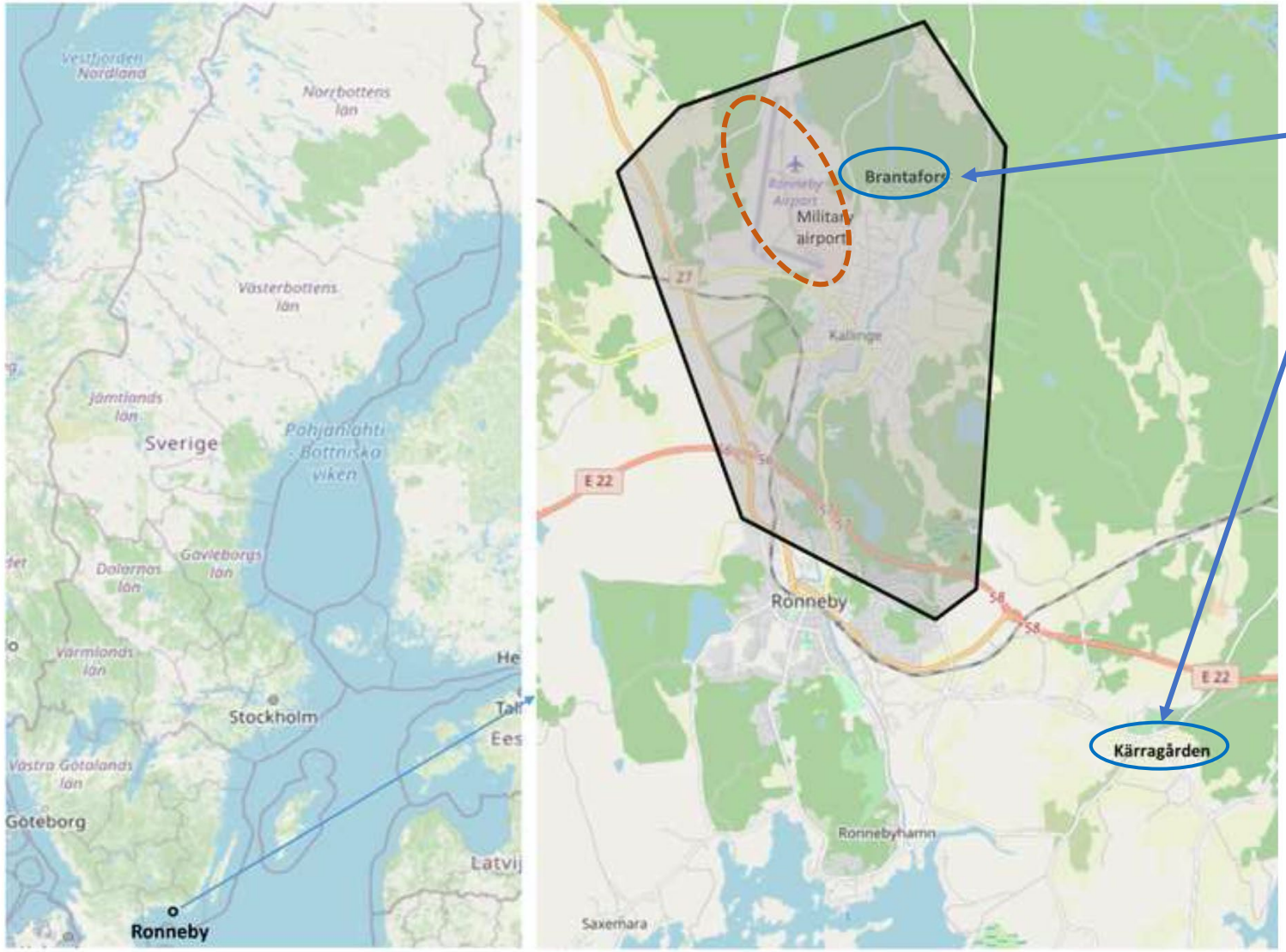
Ronneby PFAS Research Program (RPRP)

- Background
- Findings and ongoing research

Associations between PFAS exposure and health outcomes

- Findings in background vs hotspot populations
- Dose-response relationships
- Implications for risk assessment in different situations

Ronneby, southern Sweden December 2013



- PFAS in a municipal waterworks was unexpectedly discovered
- Clean drinking water was immediately provided from the other waterworks
- 1/3 of the households had been provided with contaminated water for decades
- Military airport in the middle of a large groundwater basin
- AFFF used since the mid-1980s but no details were available

Two waterworks in the municipality (≈30 000 inhabitants)

PFAS	Brantafors, Contaminated Waterworks in Ronneby (ng/L)[a]	Kärragården, Minimally contaminated waterworks in Ronneby (ng/L) [a]
PFPeA	38	10
PFHxA	320	3.6
PFHpA	32	1.4
PFOA	100	1.0
PFNA	<1	<1
PFDA	<1	<1
PFUnDA	<10	<10
PFDoDA	<10	<10
PFBS	130	<2.6
PFHxS	1700	4.6
PFHpS	60	<1
PFOS	8000	27
Sum of PFAS [d]	10,380	47.6

> 10 000 ng/L **≈50 ng/L**

\- No previous analyses of PFAS in groundwater wells or in the outgoing drinking water

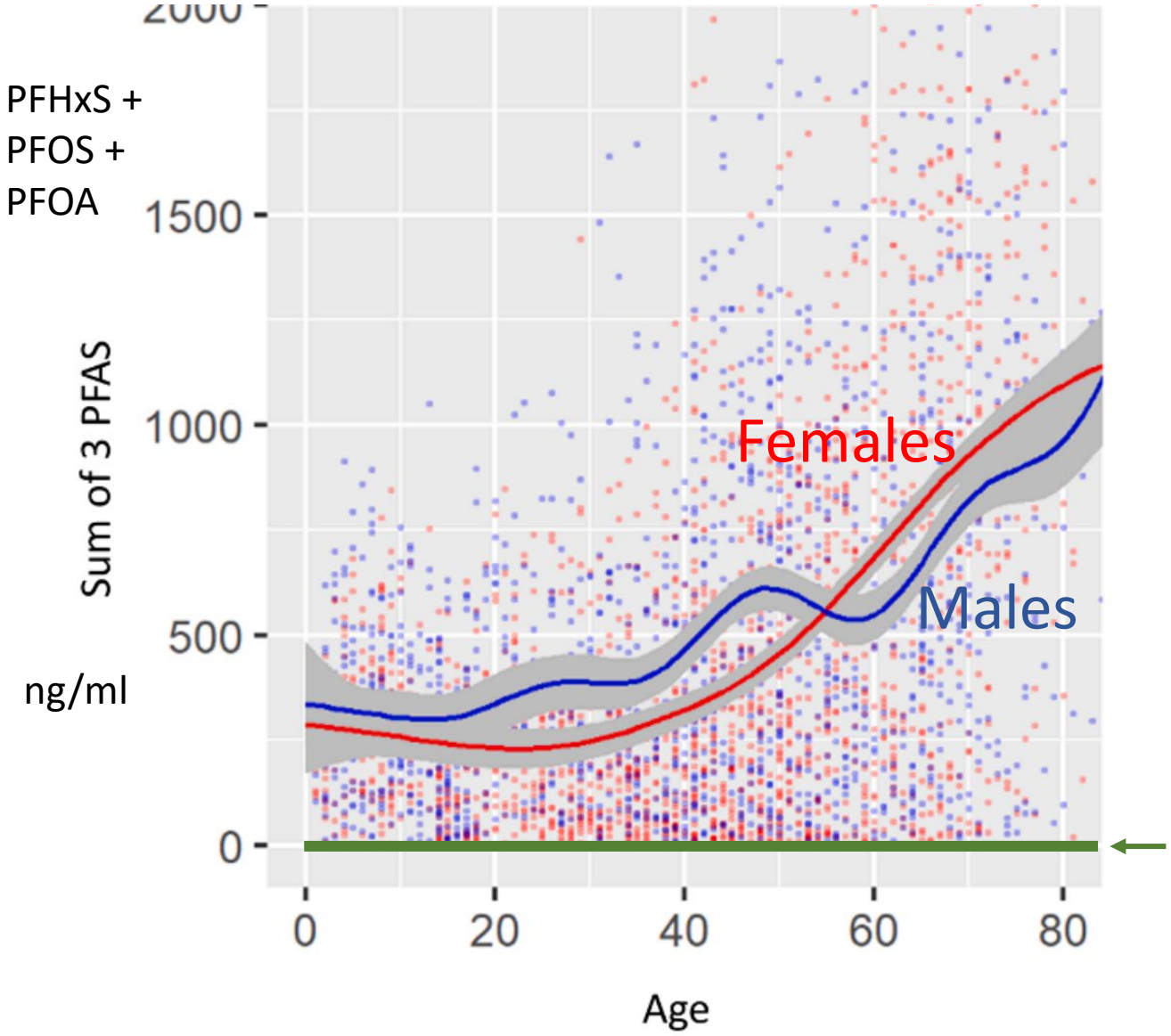
\+ Yearly address information on drinking water distribution from the two waterworks

\+ Personal ID and yearly address information for the entire Ronneby population since 1980 (n≈65,000)

RPRP cohort

1/3 of the households had been provided with contaminated water for decades – a natural experiment

Ronneby PFAS Biomarker Cohort

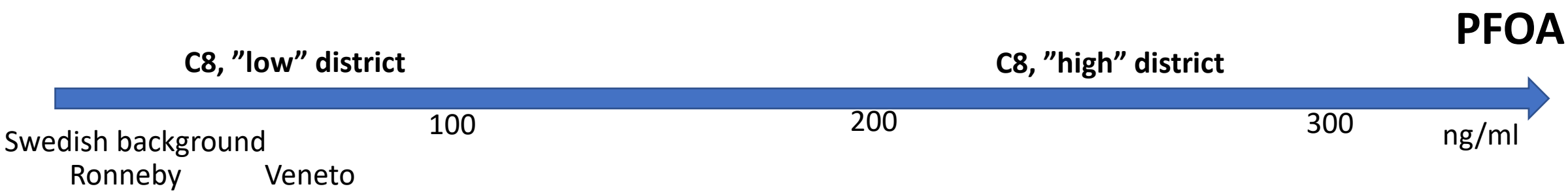


Assessment of exposure:
Open blood sampling 2014-2015

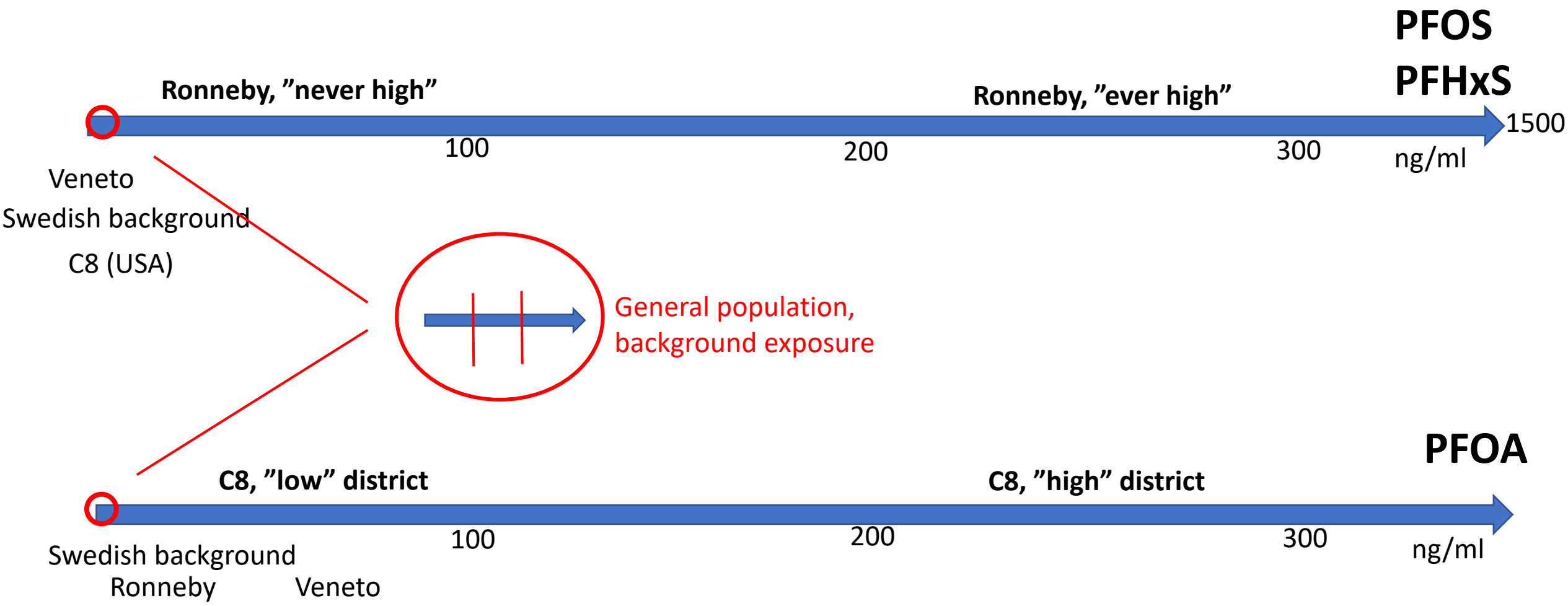
Biobank for research; N=3,293

Reference group from Karlshamn, background exposure only; N=219

Average serum levels in population-based studies



Average serum levels in population-based studies

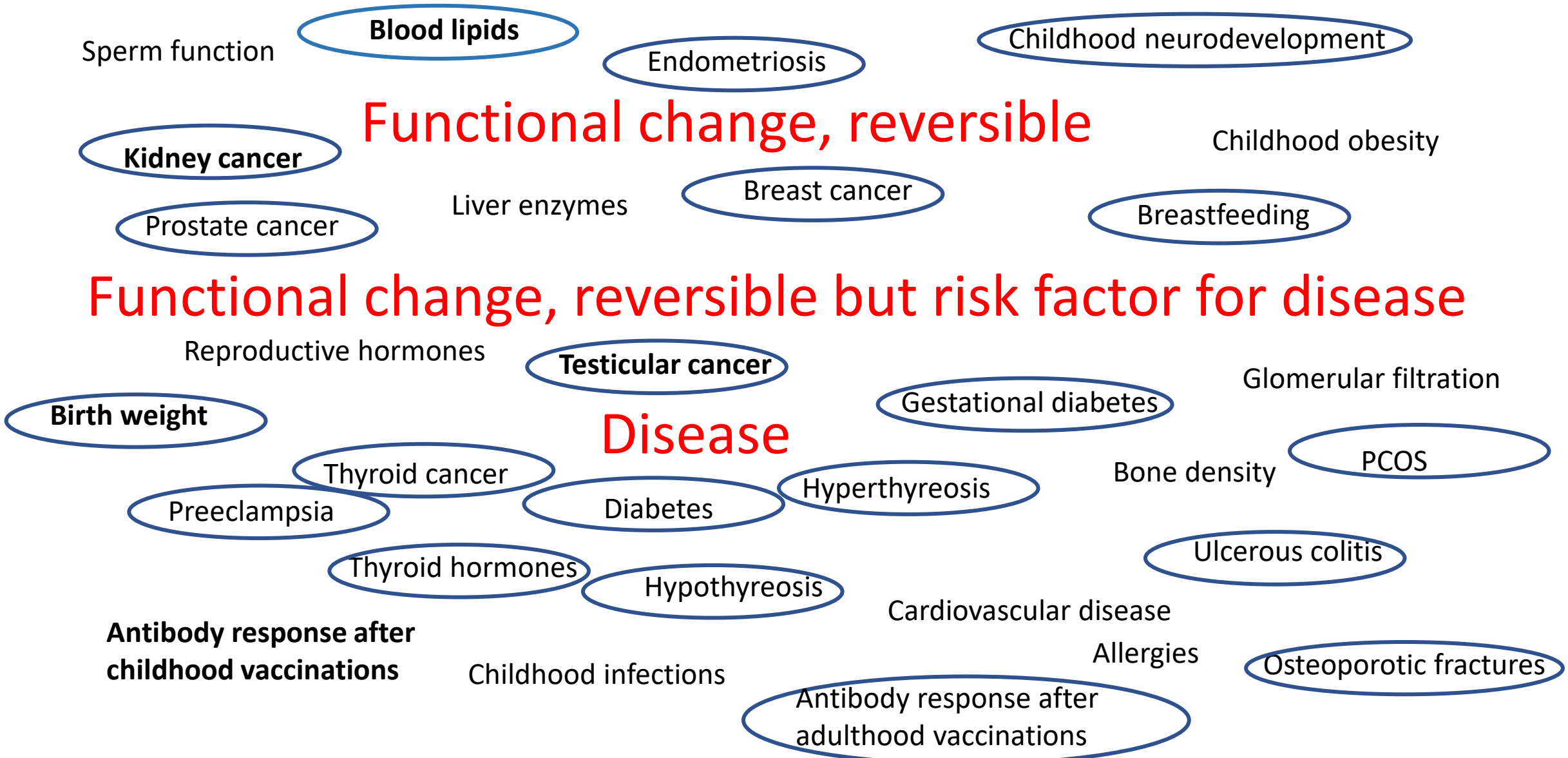


Most previous studies: associations at background exposure levels

- Simultaneous measurement of exposure and outcome
  - Crossectional prevalence studies
  - Case-control studies
- Longitudinal studies
  - Children: Mother-child cohorts
  - Adults: Re-use of other cohorts with biobanked serum samples

Can studies with larger exposure contrasts help the evaluation of causality?

Outcomes of interest – RPRP publications at present



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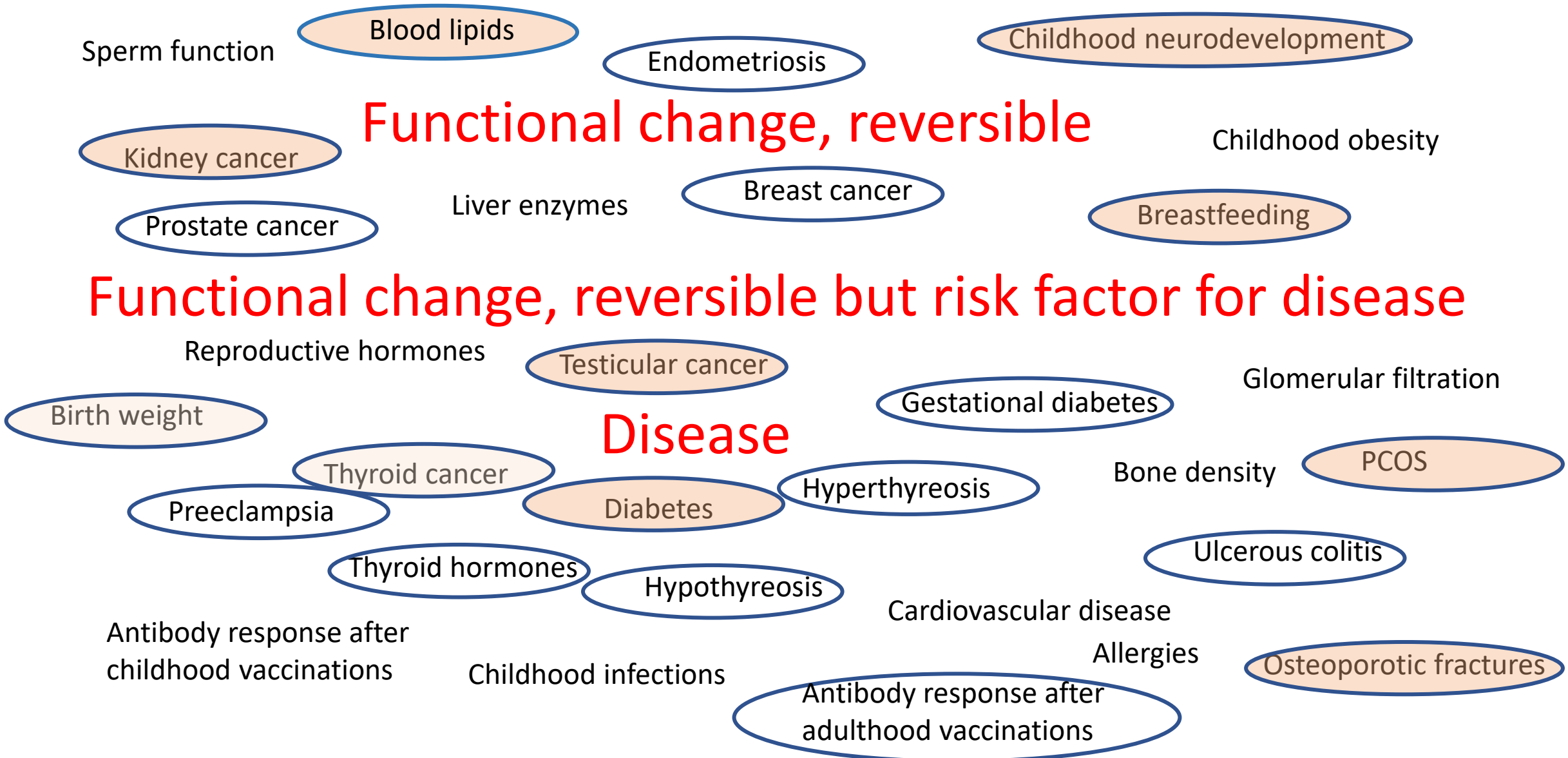


Can studies with larger exposure contrasts help the evaluation of causality?

	PFOA	PFOS, PFHxS
CANCER	**C8**	**RPRP**
Prostate	no	no
Breast	no	no
Kidney	yes	yes
Testicular	yes	(yes)
Thyroid	(yes)	(yes)

DISEASES	**C8**	**RPRP**
Diabetes	no	yes
Hypertension	no	-
Cardiovascular	no	-
Thyroid	(yes)	no
Fractures	-	yes
Liver	no	-
Colitis ulcerosa	yes	no

REPRODUCTION	**C8**	**RPRP**
Birth weight	no	(no)
Gest. diabetes	no	no
Preeclampsia	yes	no
Endometriosis	-	no
PCOS	-	yes
Uterine fibroids	-	(yes)

BIOMARKERS	**C8**	**RPRP**	**Veneto**
Cholesterol	yes	yes	yes
Thyroid hormones	no	no	no
Ab after vacc., children	-	-	-
Ab after vacc., adults	(yes)	no	-

Very different effect estimates for birth weight

Measured; background exposure

-5 g per 1 ng/ml increase in PFOA
(Fei 2007)

-11 g per 1 ng/ml increase in PFOS
(Steenland 2018)

-19 g per 1 ng/ml increase in PFOA
(Johnson 2014)

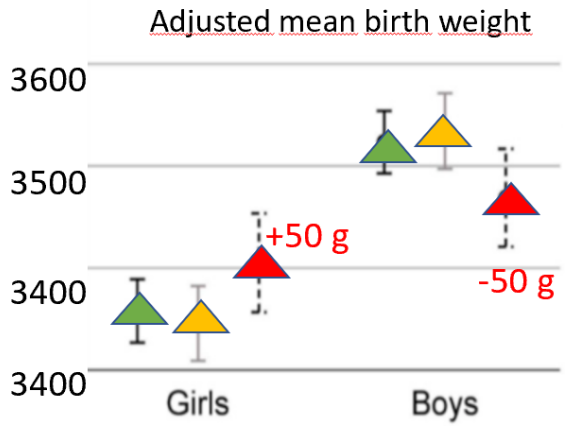
-50 g per 3-fold increase in PFOS
(Negri 2017)

-142 g per 1th to 4th quartile of PFOS (girls only)
(Wikström 2020)

Address based exposure assessment

- Blekinge county (n=9,692)
- Ronneby, not highly contaminated water; n=3,452)
- Ronneby, contaminated water; n=823)

Engström, 2021



Rough estimates for PFOS per 1 ng/mL increase
−0.50 g (boys), +0.50 g (girls)

Only for births 2005-2013;

No difference for births 1995-2004

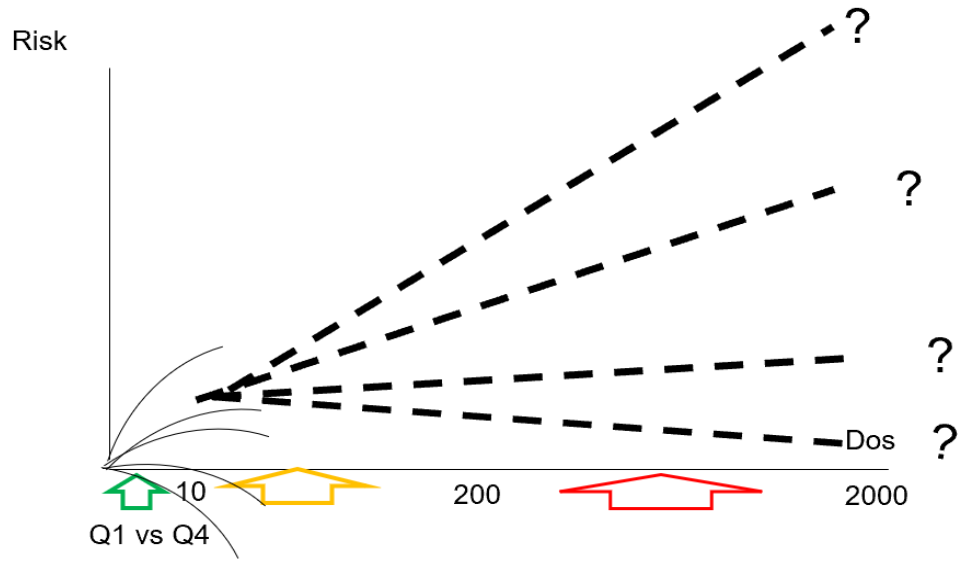
What is the shape of the dose-response curve?

Extrapolate ”upwards”? ⇒ **Risk?**

PFAS levels

Studies within a narrow exposure range may be more prone to inaccuracy of a measured exposure and misclassifications

Studies using biomarkers of exposure may be more prone to confounding and reverse causation



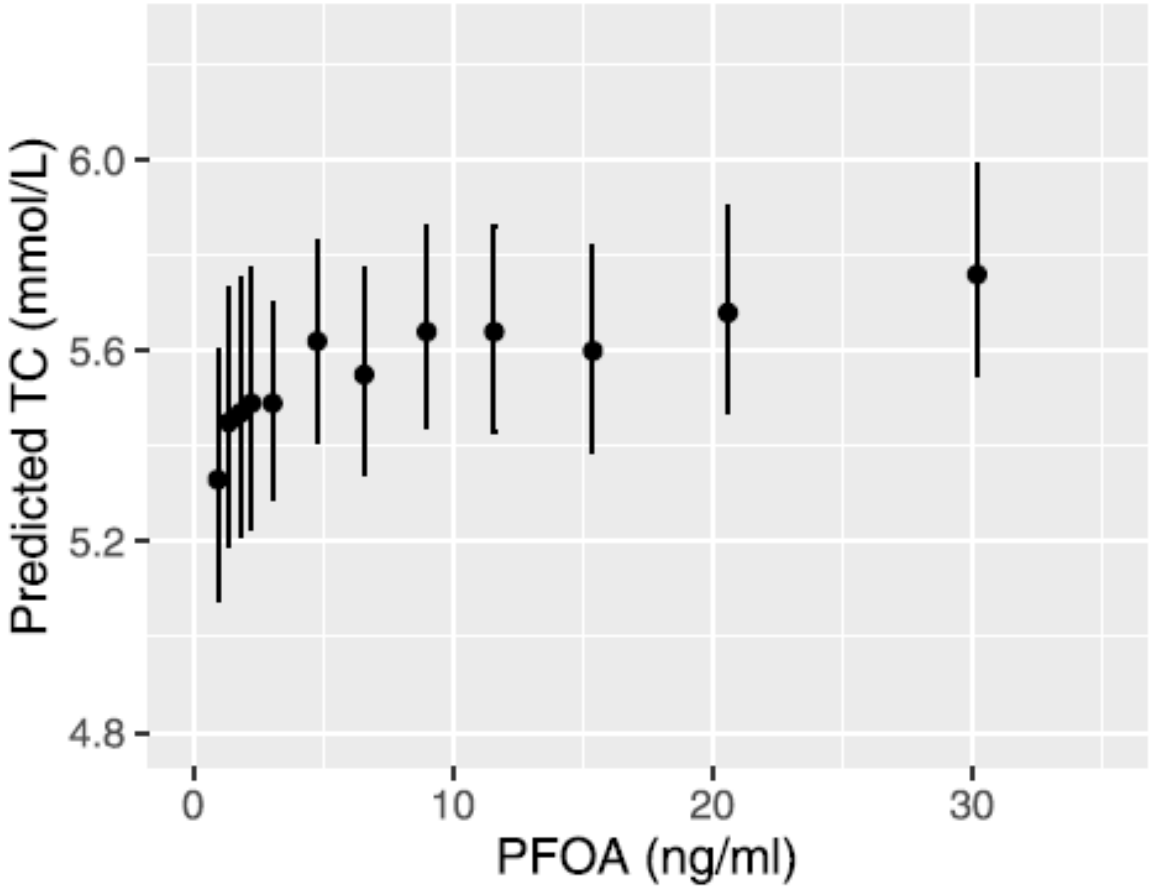
Non-linear dose-response – PFOA and cholesterol

Danish general population
At an increase of 4 ng/ml PFOA
(median 7 ng/ml)
+2 % (Eriksen et al, 2013)

C8 population, PFOA
At an increase of 15 ng/ml
(lowest decile to median 27 ng/ml)
+3-4 % (Steenland et al 2009)

PFOA workers
At an increase of 1000 ng/ml
+3% (Olsen et al 2003)
+2% (Sakr 2007)

RPRP biomarker study, Li et al, 2020



Ronneby **P**FAS **R**esearch **P**rogram

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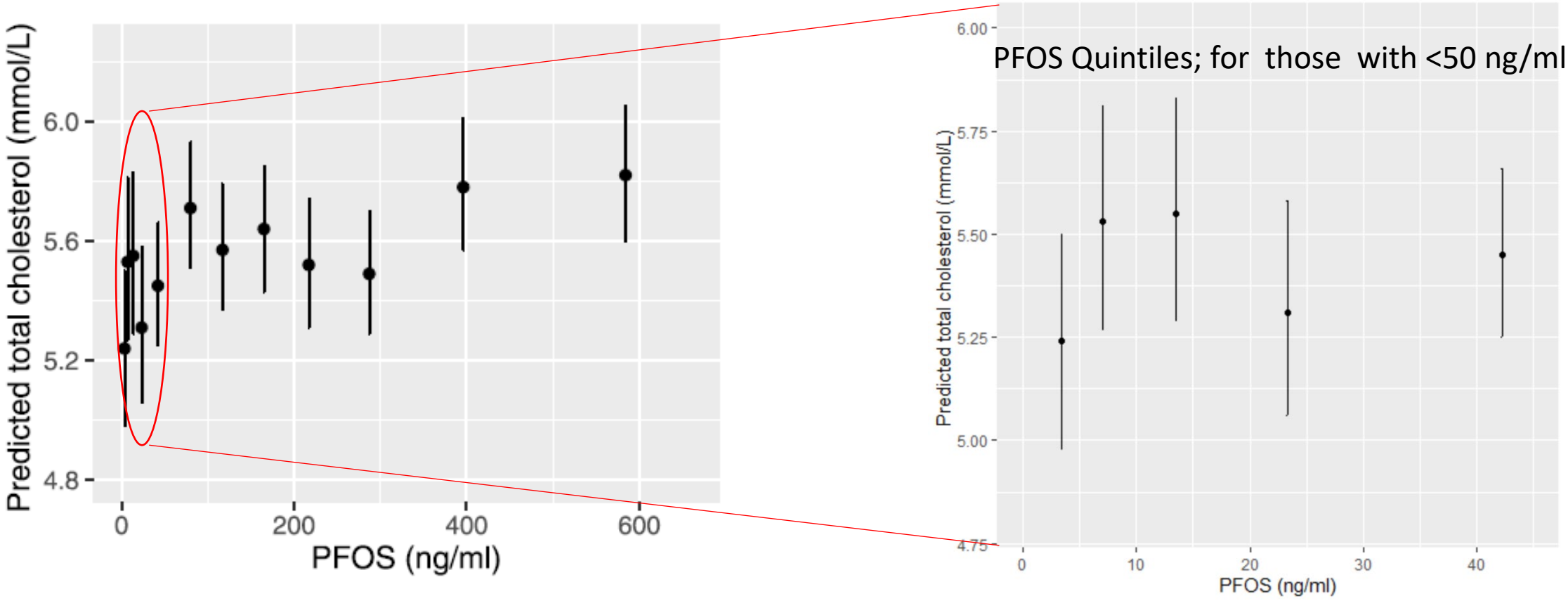
Steeper rise at low levels, but not over the whole range of exposures

(predicted TC, adjusted)

RPRP biomarker study, Li et al, 2020



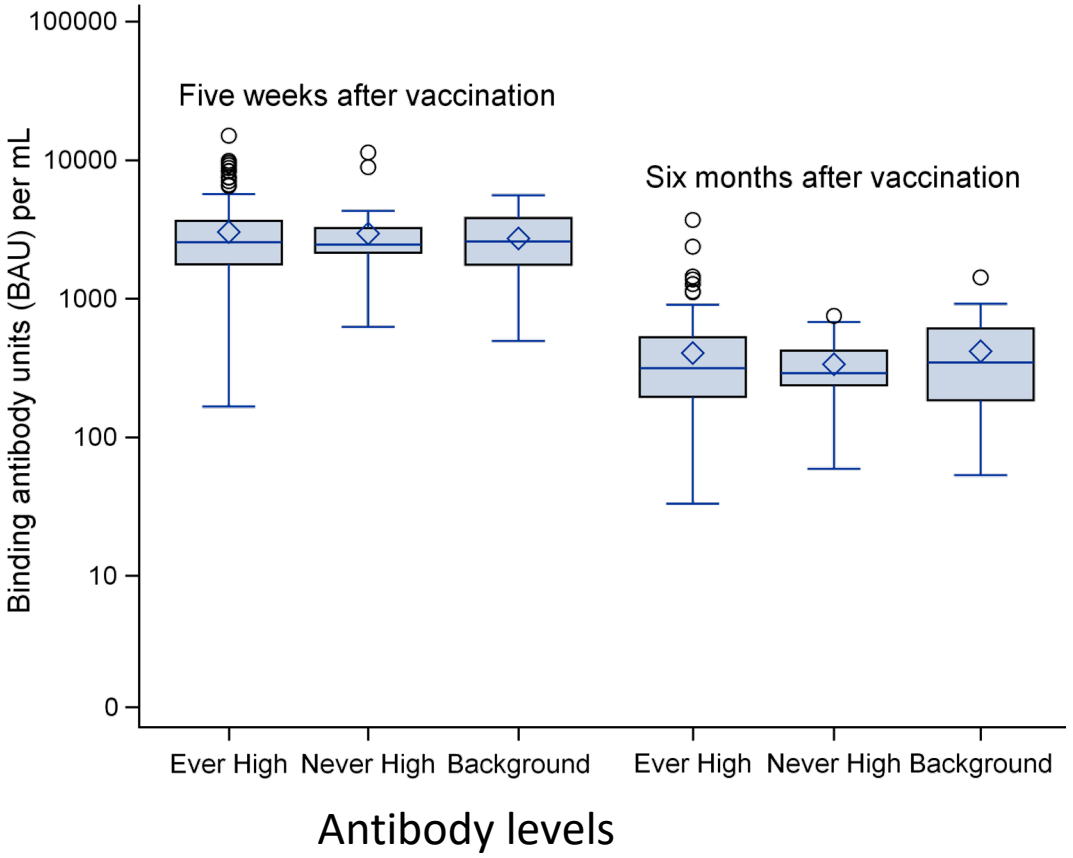
RPRP in summary so far….

- Some previously reported associations were confirmed, others not.
- Some new findings which need replication

- Manifold higher exposure levels did not result in manifold higher observed risks

- Decreased vaccination responses in childhood may not remain in adulthood

No decreased immune response in adults after vaccination against SarsCoV-2 (mRNA vaccine; Anderson et al. Env Health Perspect 2023)



Antibody levels

Compound	Median (ng/mL)		
	Ronneby		Karlshamn
	Ever High	Never High	Background
	n=245	n=63	n=40
PFHxS	**56**	**10**	**0.9**
PFOS	**54**	**14**	**4**
PFOA	**2**	**1**	**1**
PFHpS	3	0.6	0.1
PFNA	0.4	0.4	0.4
PFDA	0.2	0.2	0.2
PFUnDA	0.1	0.1	0.1

The findings are supported by others:
Shih et al. 2021; Faroe young adults, hepatitis A and B
Porter et al. 2022; Covid, various vaccines; workers
Bailey et al. 2023; Covid, mRNA

Risk assessment and risk communication in two very different situations

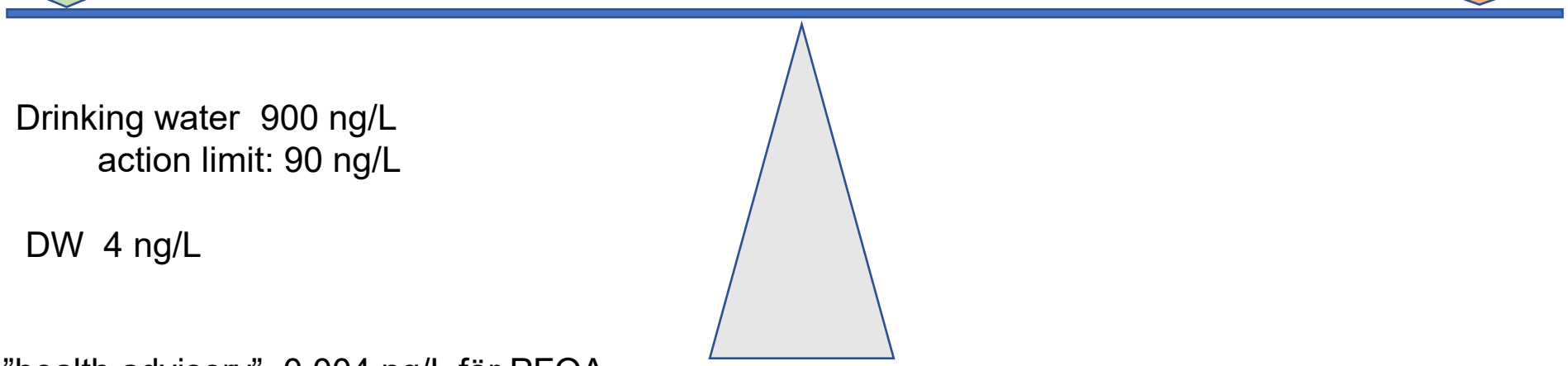
Tolerable Weekly Intake,

drinking water standards

Protect a population over generations

”Hotspot ”

Risk assessment and risk communication in a defined population with higher than background exposure



Sweden 2014: Drinking water 900 ng/L
action limit: 90 ng/L

Sweden 2022: DW 4 ng/L

US EPA 2022: ”health advisory” 0.004 ng/L för PFOA,
0.02 ng/L för PFOS

Why is it important to assess the shape of the dose-response curve?

Extrapolate ”upwards”? ⇒ **Risk?** ⇐ Extrapolate ”downwards”?

Studies within a narrow exposure range may be more prone to inaccuracy of a measured exposure and misclassifications

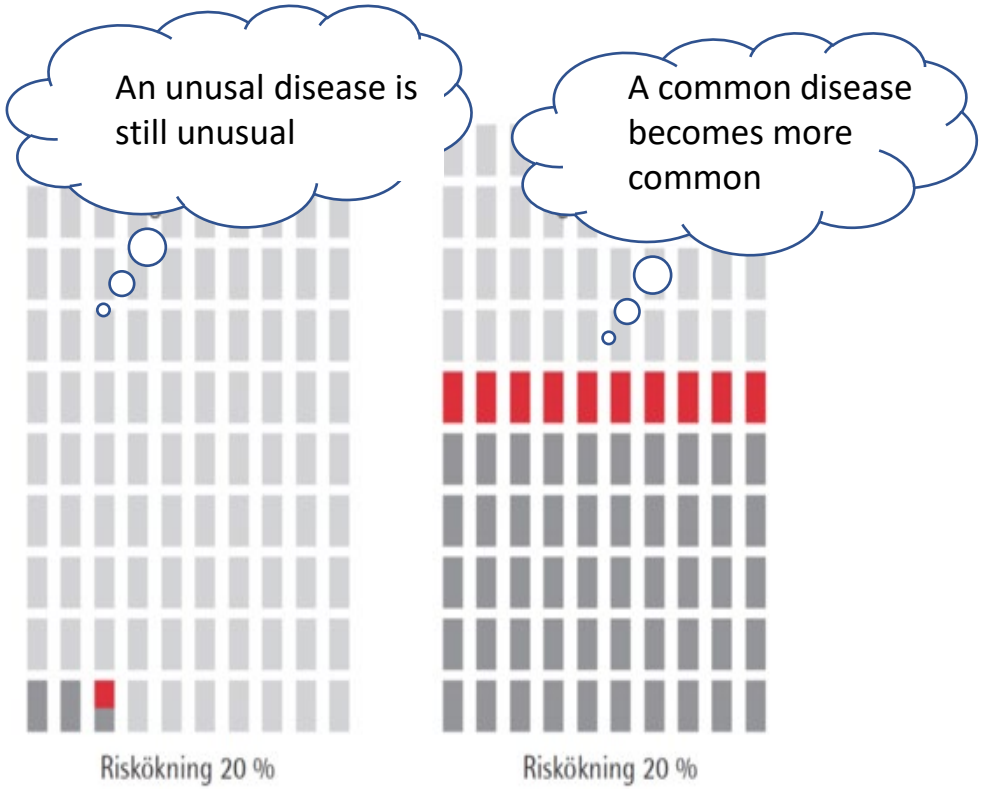
Studies using biomarkers of exposure may be more prone to confounding and reverse causation

Lack of mechanistical understanding.
Saturation? Threshold?
Other mechanisms?

The risk communication dilemma in a hotspot

- Is my illness due to PFAS
- Will I become ill
- Will my child become ill

- Risk on the individual level



- Absolute risk
- Excess risk

Research | Children's Health

Serum Perfluorooctanoic Acid and Perfluorooctane Sulfonate Concentrations in Relation to Birth Outcomes in the Mid-Ohio Valley, 2005–2010

Lyndsey A. Darrow,[1] Cheryl R. Stein,[2] and Kyle Steenland[2]

[1]Department of Epidemiology, Emory University, Atlanta, Georgia, USA; [2]Department of Preventive Medicine, Mount Sinai School of Medicine, New York, New York, USA; [3]Department of Environmental Health, Emory University, Atlanta, Georgia, USA

- Risk on group level
- Relative risk

Ronneby PFAS Research Program (RPRP)

Main funding:
- the Swedish Research Councils FORMAS, FORTE, and VR
- the national governmental ALF agreement for clinical research
- in-kind support from Lund University
- in-kind support from the University of Gothenburg
- in-kind support from the Regional Healthcare System

Other contributions :
- European Commission: Marie Sklodowska-Curie Actions postdoctoral fellowship
- Interreg Öresund-Kattegat-Skagerrak partnership
- Crafoord foundation
- Swedish Royal Physiographical Society
- Gothenburg Medical Society

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Longitudinal registry studies

Around 65 000 persons ever registered in Ronneby 1980-2013. Yearly addresses linked to continuously updated contaminated water at home and worknlace

- In- and outpatient hospital diagnoses, primary health care diagnosis

- Cancer incidence, causes of death

- Pharmaceutical registry 2005-

- Educational achievements, working life attachment

All children in Blekinge

- Medical birth registry

Extended exposure modelling using reconstruction of historical exposures

Focus on low-median exposure levels

Child health care*

All children in the municipality 1990-on

Childhood growth
Speech and psychomotor development

Mother-child cohort*

Transfer of PFAS mother-child
Duration of breastfeeding

Childhood growth
Speech and psychomotor development

Follow-up during childhood

Longitudinal vaccination response*

Routine vaccination program in children
Sars-CoV-2 in adults

Biobank* (serum, blood, urine, faeces, placenta, breast milk)

Exposure assessment

Biomarkers for (subclinical) effects

Mechanistical studies (genetics, metabolomics, immunology, epigenetics)

Collaborations

Reconstruction of historical exposures

Dry blood spots from neonates

Environmental investigations

* Includes reference population from Karlshamn with background levels of PFAS

Thank you for your attention

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