Dietary Contaminants in Nutritional Epidemiology

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Some examples of exposures

- Persistent Organochlorine Pollutants
- Cadmium
- PFAS
- Fluoride
- Pesticides
- (Mg/Ca in drinking water)
- (Acrylamide)

- We focus on preventable diseases of major public health concern

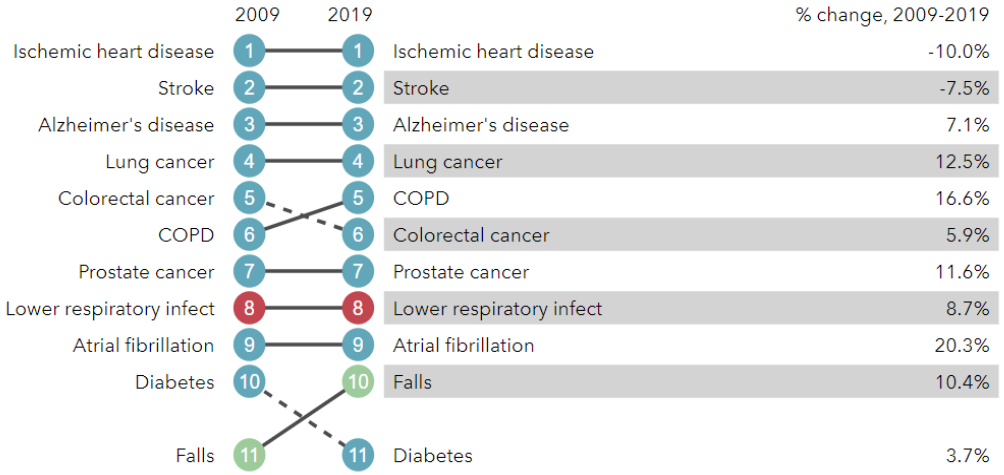
- We use population-based prospective cohorts, mainly
  - The Swedish Mammography Cohort
  - The Cohort of Swedish Men
  - n=100 000; comprehensive and repeated food frequency questionnaire data along with register-linkage on disease outcomes

Statistics for Sweden 2019 – The Global Burden of Disease

IHME Measuring what matters

What causes the most deaths?

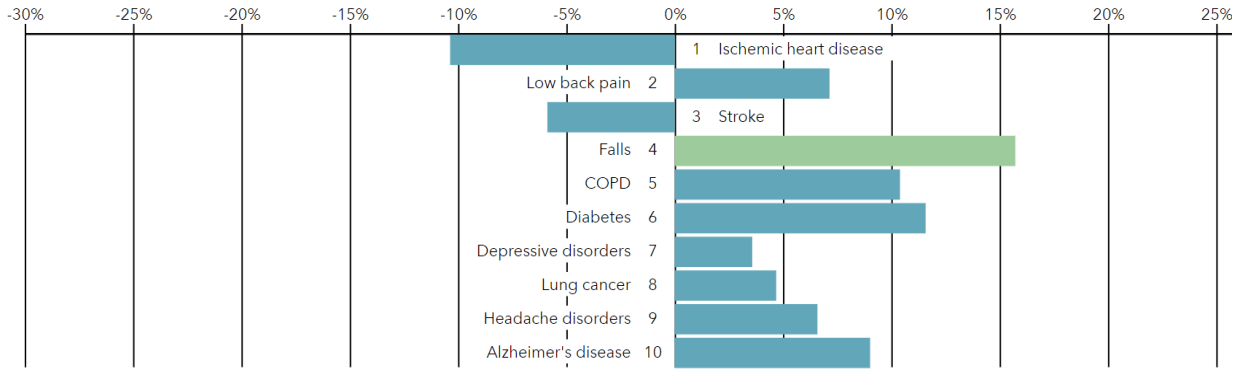
Communicable, maternal, neonatal, and nutritional diseases
Non-communicable diseases
Injuries



Top 10 causes of total number of deaths in 2019 and percent change 2009-2019, all ages combined

What causes the most death and disability combined?

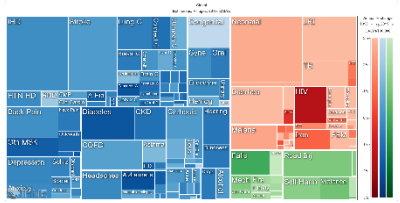
Communicable, maternal, neonatal, and nutritional diseases
Non-communicable diseases
Injuries



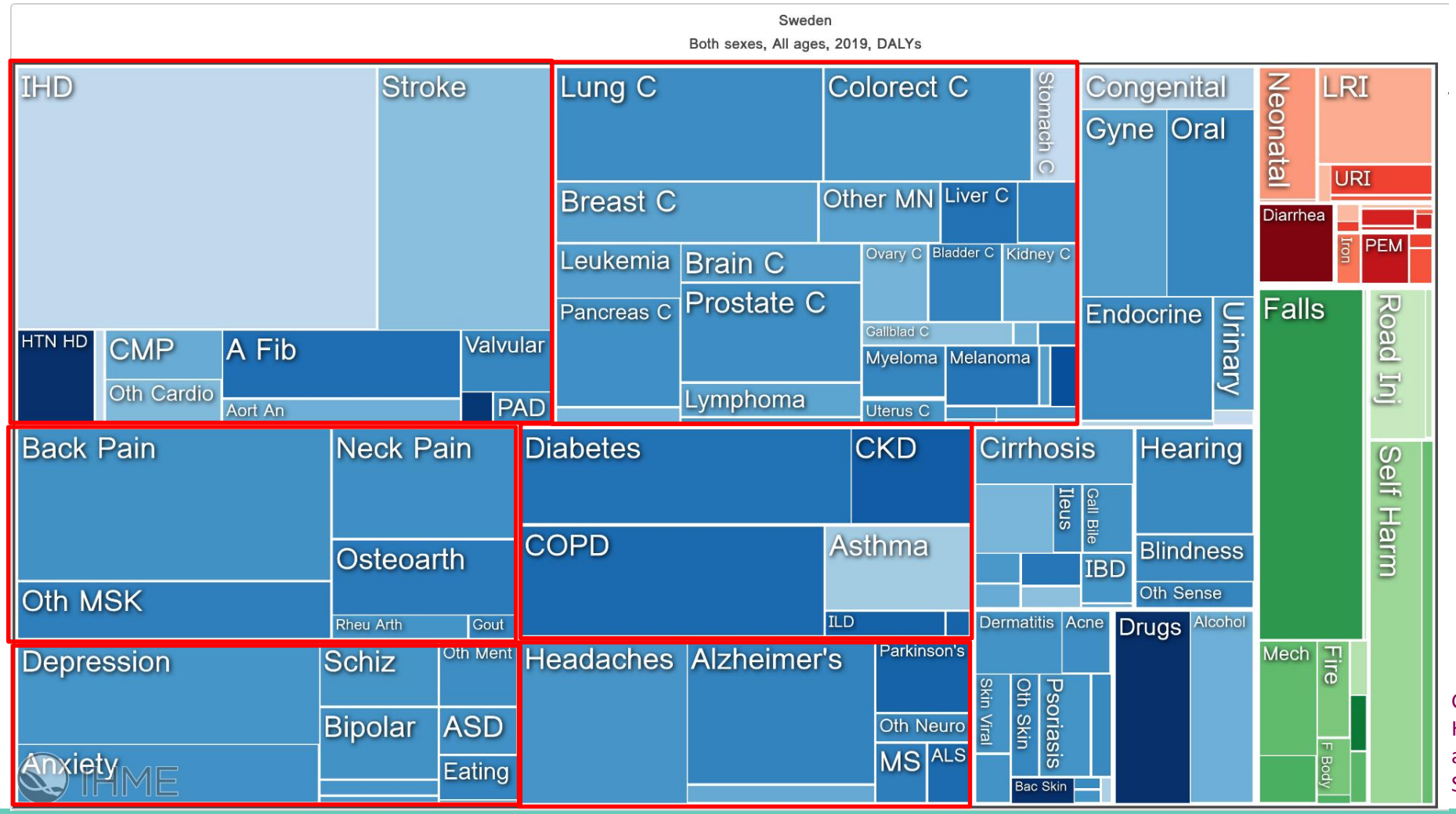
Top 10 causes of death and disability (DALYs) in 2019 and percent change 2009-2019, all ages combined

See related publication: https://doi.org/10.1016/S0140-6736(20)30925-9

The Institute for Health Metrics and Evaluation (IHME) – an independent global health research center at the University of Washington, Seattle



The Total Burden of Disease - Sweden 2019



GBD; Institute for Health Metrics and Evaluation, Seattle, USA

Major risk factors and how much do they explain?

IHME
Measuring what matters

What risk factors drive the most death and disability combined?

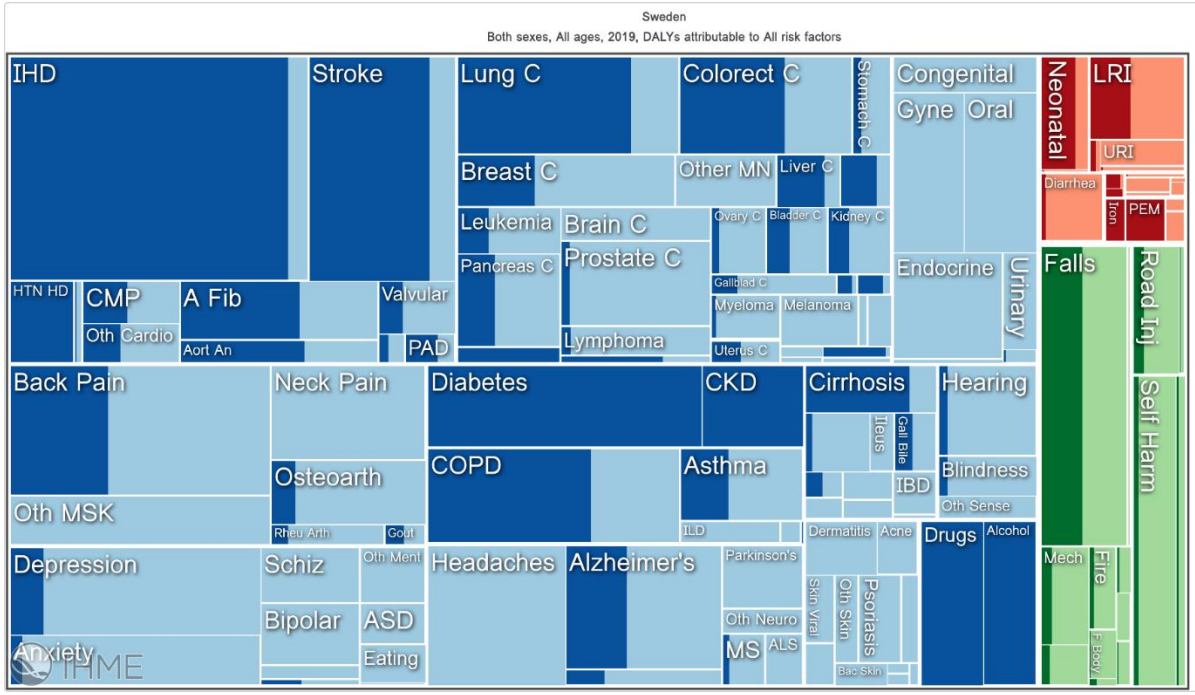
- Metabolic risks
- Environmental/occupational risks
- Behavioral risks

2009	2019		% change, 2009-2019
Tobacco	Tobacco	Tobacco	-1.3%
High blood pressure	High blood pressure	High blood pressure	-4.4%
Dietary risks	Dietary risks	Dietary risks	-5.8%
High fasting plasma glucose	High fasting plasma glucose	High fasting plasma glucose	6.2%
High body-mass index	High body-mass index	High body-mass index	11.0%
High LDL	Alcohol use	Alcohol use	1.2%
Alcohol use	High LDL	High LDL	-11.8%
Occupational risks	Occupational risks	Occupational risks	6.9%
Kidney dysfunction	Kidney dysfunction	Kidney dysfunction	4.0%
Non-optimal temperature	Drug use	Drug use	45.0%
Drug use	Non-optimal temperature	Non-optimal temperature	-5.0%

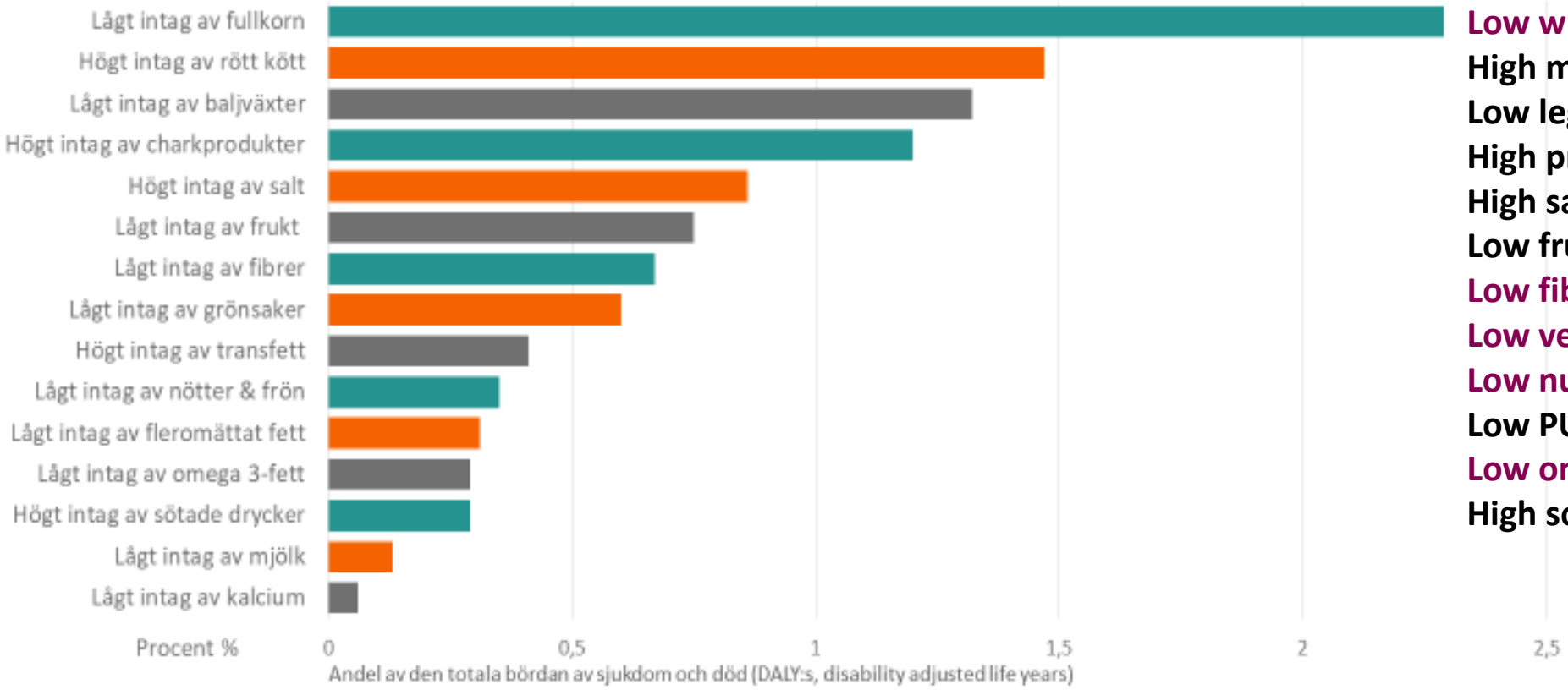
Top 10 risks contributing to total number of DALYs in 2019 and percent change 2009-2019, all ages combined

Dark blue = 1 or more risk factors

Light blue = unexplained



Largest dietary risk factors in Sweden



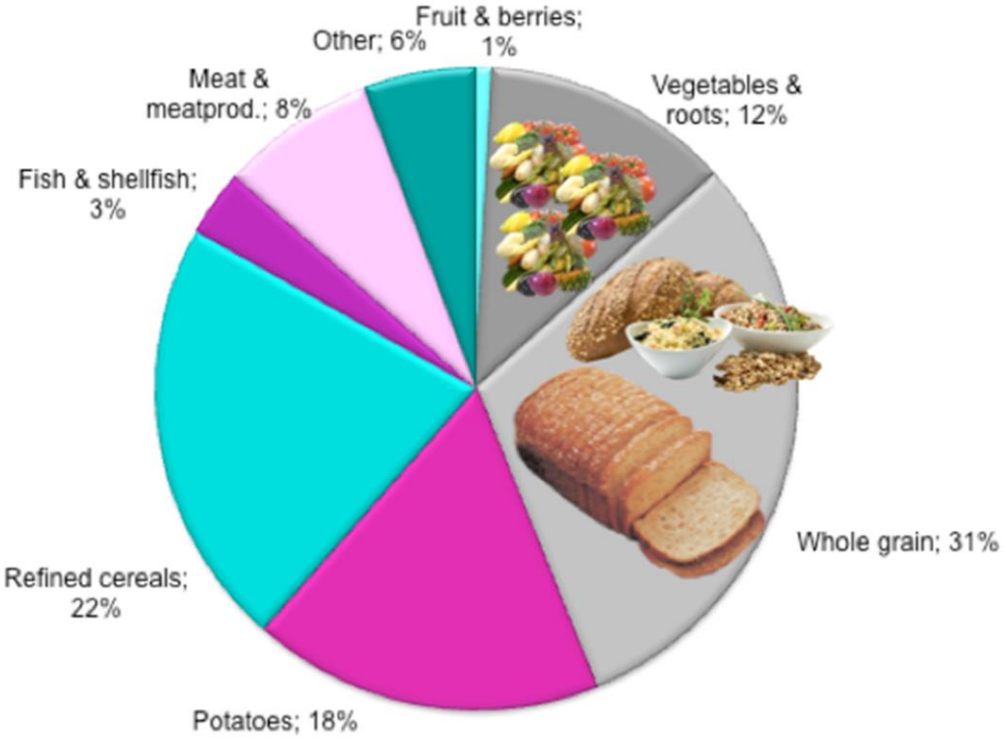
Low whole grain
High meat
Low legumes
High processed meat
High salt
Low fruit
Low fiber
Low veggies
Low nuts and seeds
Low PUFA
Low omega 3 PUFA
High soda

Livsmedelsverket

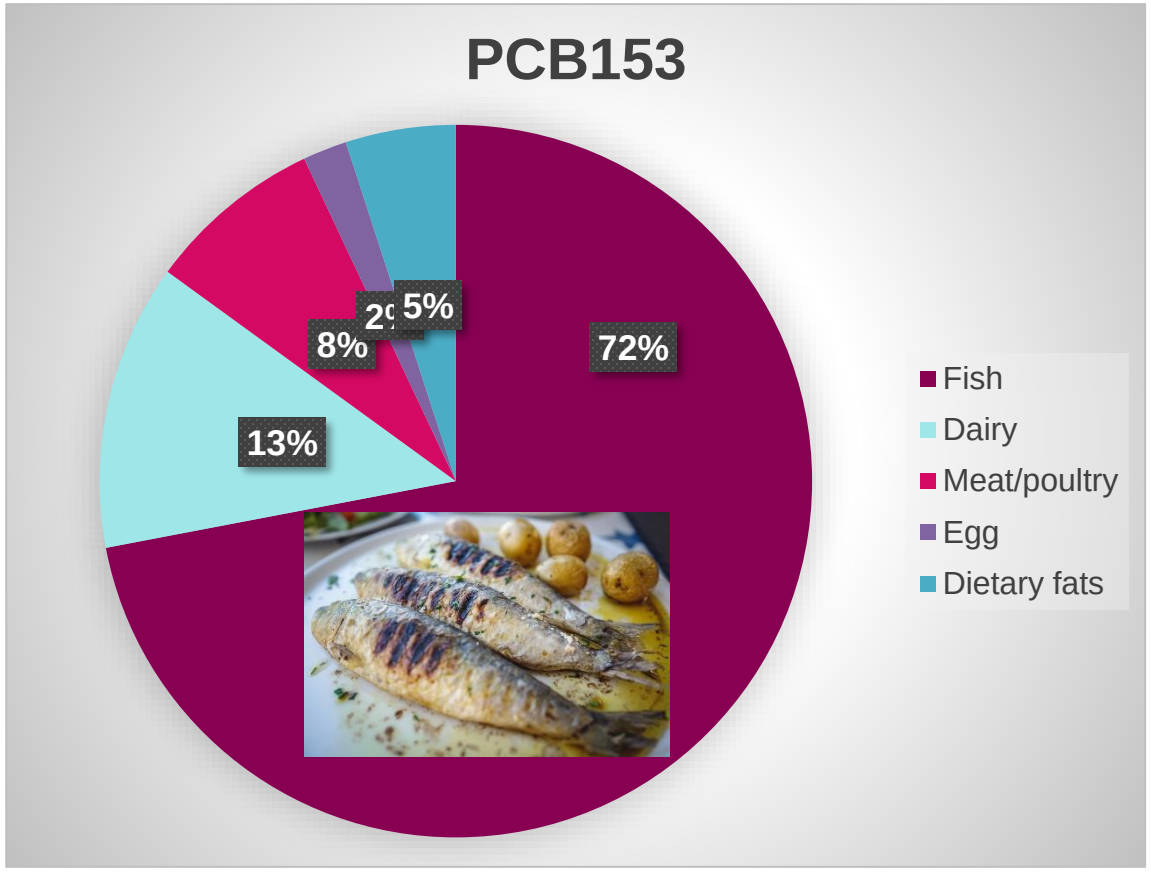
Bild: Livsmedelsverket, med data hämtad från Institute for Health Metrics and Evaluation

Emma Patterson 2022-01-19

Cadmium THE MAIN SOURCES POPs



Amzal et al, EHP 2009



Bergkvist et al, Mol Nutr Food Res, 2012

Can we estimate the exposure to a dietary contaminants via various dietary surveys/questionnaires well enough to use it in large epidemiological studies?

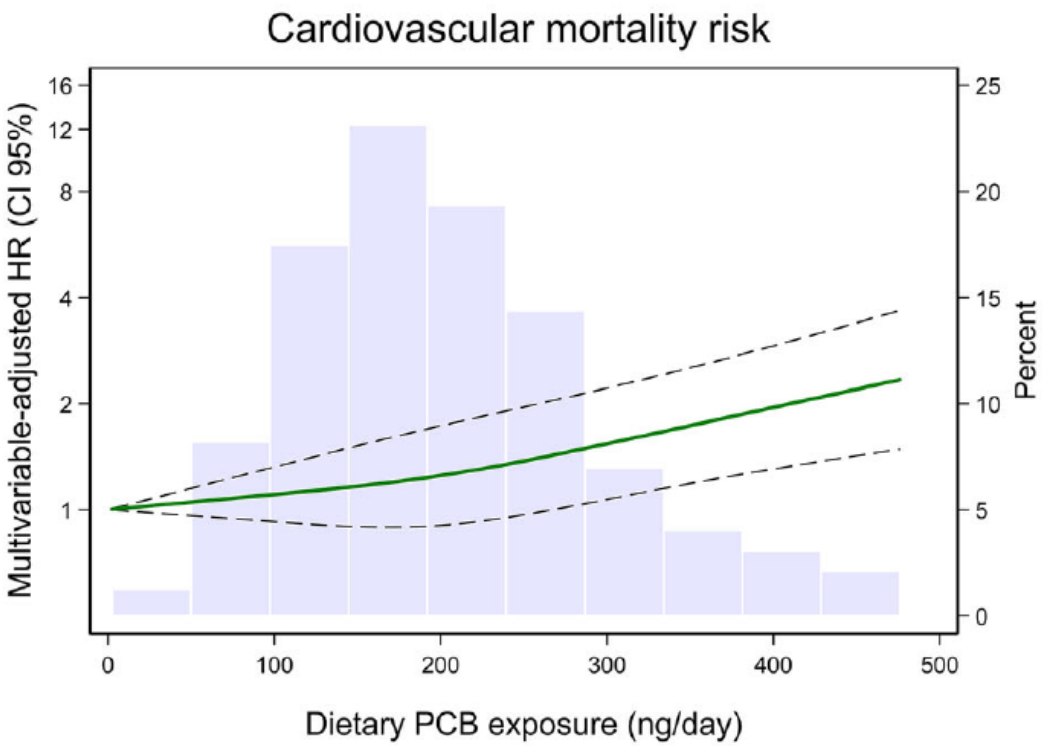
- It depends…
  - On the contaminant itself incl. the exposure level and the variation in levels within/btw foods, the availability of measured data in food, the quality of the dietary intake data available…
  - A validation study, correlating the dietary exposure against a biomarker, is needed to support the use

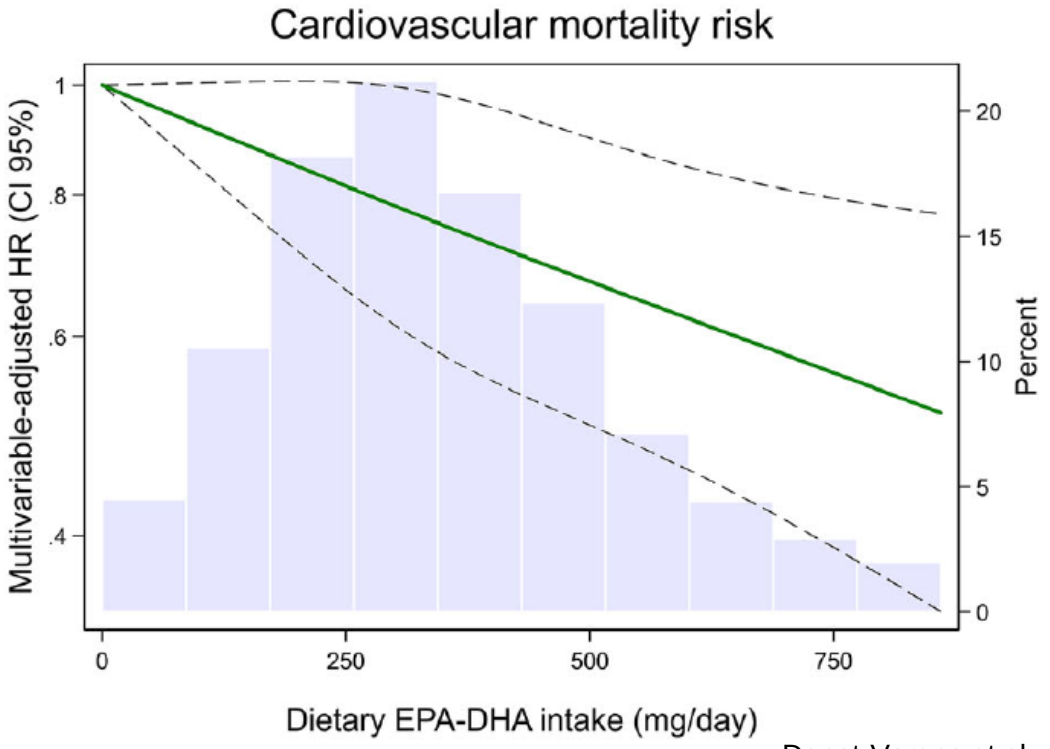
- If yes, what is the benefit?

Dietary POPs and Long-chain Fish Fatty Acids vs. Cardiosvascular Mortality

JIM PCBs, EPA-DHA and mortality / C. Donat-Vargas *et al.*

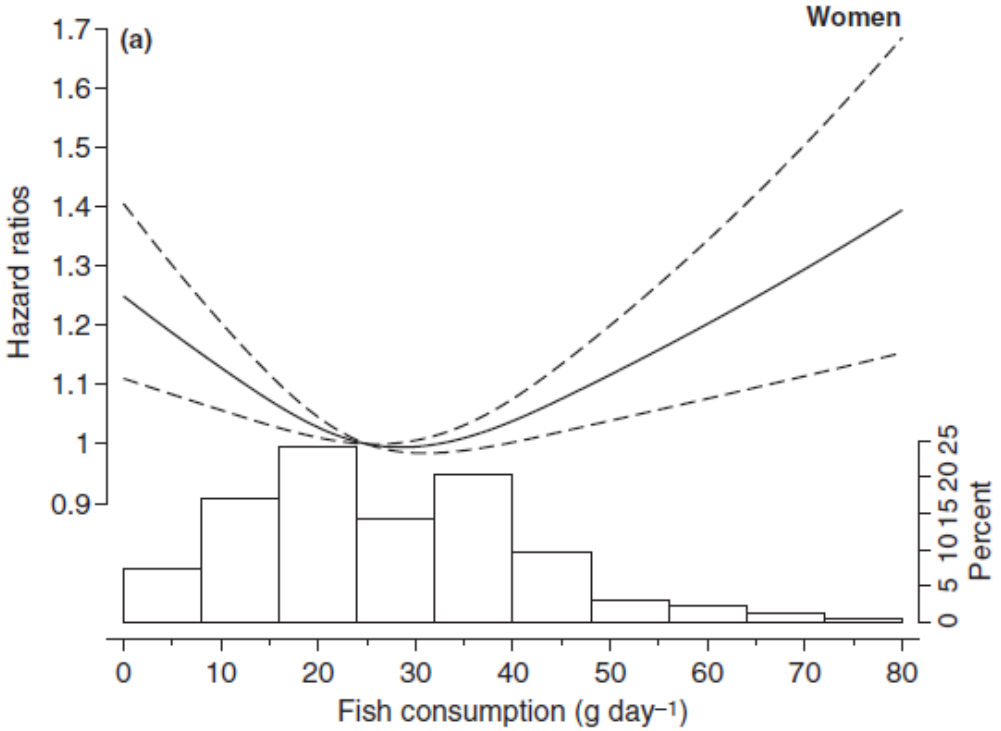
Based on 70,000 participants & 17,000 deaths





Donat-Vargas et al, J Intern Med, 2019

Fish consumption vs. mortality



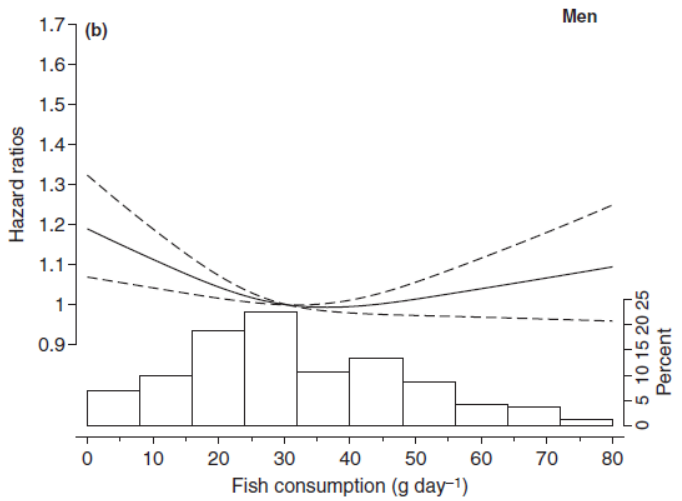


Fig. 1 *Hazard ratios of death as a function of fish consumption amongst Swedish women (A) and men (B). Data were fitted using Cox proportional hazard regression. Models were adjusted for BMI (in kg m^{-2}; <20, 20–24.9, 25–29 or ≥30), total physical activity (continuous variable; MET h day^{-1}), smoking status and pack-years of smoking (current ≥40, current 20–39, current <20, former ≥40, former 20–39, former <20 or never), alcohol consumption (never drinker, former drinker, <5, 5–10, 10.1–20 or >20 g day^{-1}), educational level (primary school, secondary school or university), total energy intake (continuous variable; kcal day^{-1}), fruit consumption (continuous variable; servings per day), vegetable consumption (continuous variable; servings per day), processed red meat consumption (continuous variable; g day^{-1}) and nonprocessed red meat consumption (continuous variable; g day^{-1}). Dashed lines represent 95% CIs. The reference values are 25 (A) and 30.5 g day^{-1} (B), and the histograms show the distributions of fish consumption.*

72 500 personer & 16 730 deaths

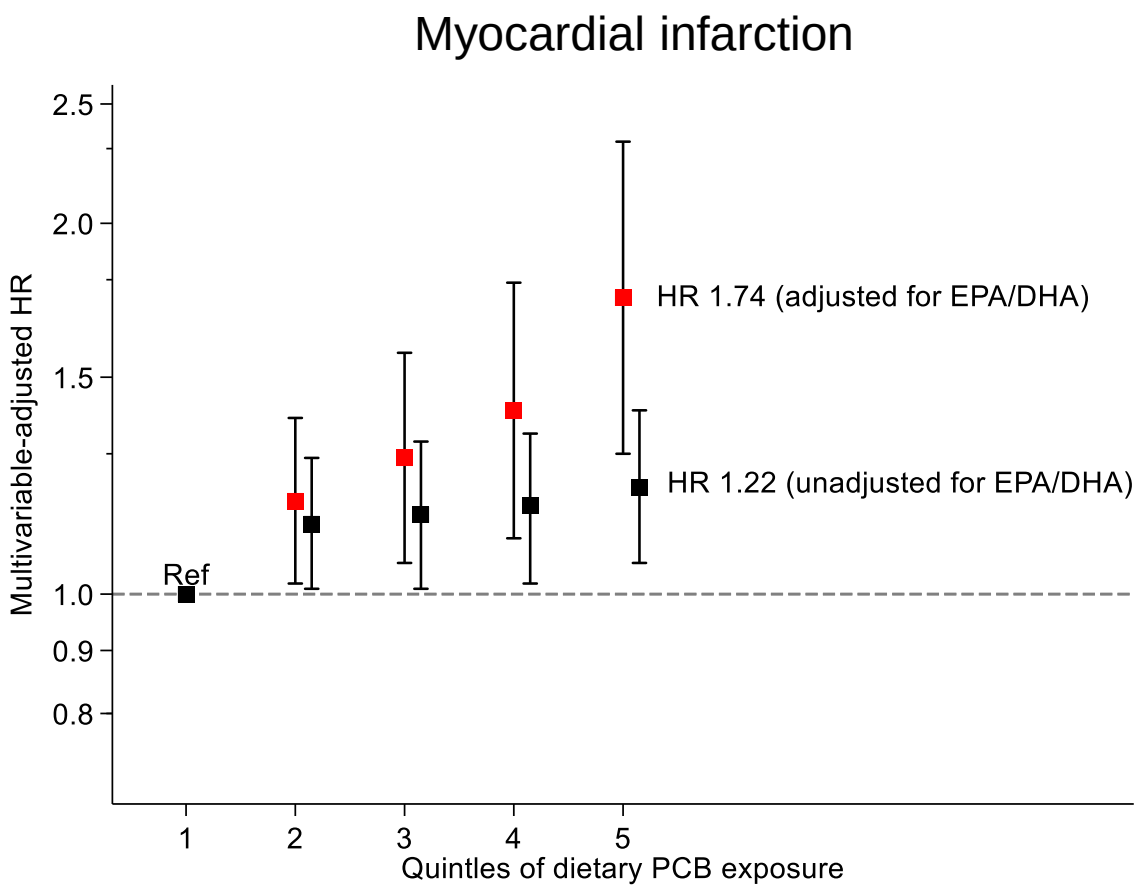
Bellavia, J Intern Med 2016

Dietary PCB exposure and CVD (Myocardial infarction, Stroke (ischemic / hemorragic))

- The risk of Stroke was higher in:
  - nulliparous women vs. multiparous
  - Lean vs. non-lean
  - Born after 1931 vs. born before
  - Higher for Hemorragic stroke than for Ischemic Stroke

- The risk of Myocardial Infarction was higher in
  - nulliparous women vs multiparous
  - Lean vs non-lean

Validation: Dietary vs Plasma PCBs: *rho* = 0.30-0.58



Bergkvist et al, J Intern Med, 2014; Bergkvist et al, Int J Cardiol, 2015; Bergkvist et al, Environ Int, 2016; Kippler et al, Environ Int, 2016; Bergkvist et al, 2012

DL-PCBs and Hypertension in 850 participants with 2 measurements 10-y apart

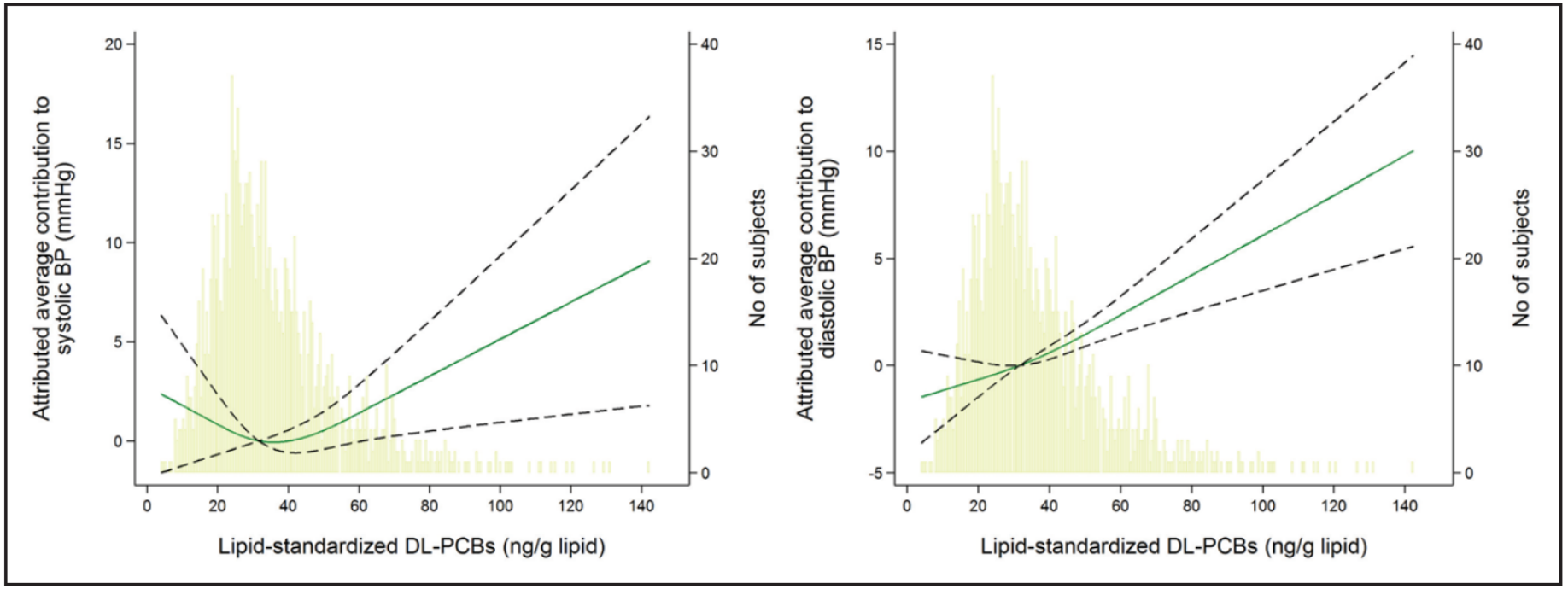


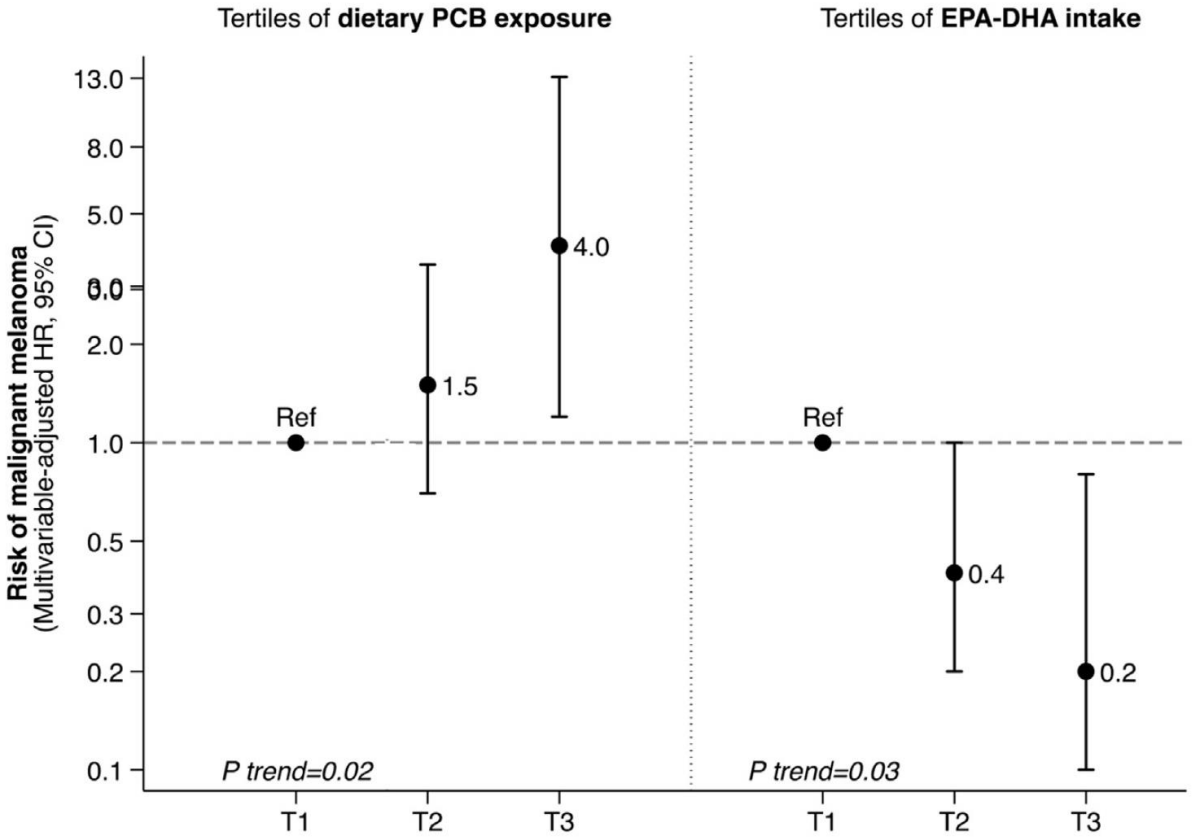
Figure 2. Continuous association between dioxin-like polychlorinated biphenyl (DL-PCBs) and blood pressure (BP). Multivariable-adjusted β coefficients of systolic (**A**) and diastolic (**B**) BP (solid lines) and their 95% confidence intervals (CI; dashed lines), as a continuous smooth function of lipid-standardized DL-PCBs. Data included the repeated measurements (both baseline and follow-up) and was fitted using multiple linear regression via generalized estimating equation methodology. Models were adjusted for gender, age, sample year, prediabetic status, total serum lipids, and body mass index. The median (31.7 ng/g lipids) was used as a reference and the histogram shows the distribution of the DL-PCBs. Plasma DL-PCB levels above the 99th percentile were excluded (n=3). Estimates are based on a single-pollutants analysis (ie, the different types of persistent organochlorine pollutants [POPs] were not mutually adjusted). Detailed data on the different POPs and different models for adjustment are given in the Table S5.

Donat-Vargas et al, 2018

Dietary PCB exposure and Malignant Melanoma

- IARC (2015) classified PCBs as Group 1 carcinogen.
- Occupational and accidental exposure and one case-control study on the general population

C. Donat-Vargas et al. / European Journal of Cancer 72 (2017) 137–143



Range	**< 141**	**141–188**	**> 188**	**< 0.24**	**0.24–0.35**	**> 0.35**
Age-standardised rate per 100,000 person-year	70.3	58.3	81.3	81.7	60.7	70.3

PFAS & Public Health

- TWI - Decreased response of the immune system to vaccination the most critical human health effect.
  - Several studies observed PFOS and PFOA to be associated with reduced antibody response to vaccination.

- Epidemiological studies provide clear evidence for an association between exposure to PFOS, PFOA and PFNA and increased serum cholesterol (previous *critical effect).*
  - Insufficient evidence to conclude on CVD risk

- The most consistent endpoint in animals was increased liver weight. Disturbances in lipid metabolism, including hepatocellular steatosis and hepatotoxic effects at higher dose levels.

PFAS

- Cardiometabolic disease and type 2 diabetes (T2D)
- Cardiovascular disease (CVD); myocardial infarction & stroke
  - In the general population

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Plasma metabolites associated with exposure to perfluoroalkyl substances and risk of type 2 diabetes – A nested case-control study

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Type 2 Diabetes
Nested case-control study

ABSTRACT

Perfluoroalkyl substances (PFAS) are widespread persistent environmental pollutants. There is evidence that PFAS induce metabolic perturbations in humans, but underlying mechanisms are still unknown. In this exploratory study, we investigated PFAS-related plasma metabolites for their associations with type 2 diabetes (T2D) to gain potential mechanistic insight in these perturbations.

We used untargeted LC-MS metabolomics to find metabolites related to PFAS exposures in a case-control study on T2D (n = 187 matched pairs) nested within the Västerbotten Intervention Programme cohort. Following principal component analysis (PCA), six PFAS measured in plasma appeared in two groups: 1) perfluorononanoic acid, perfluorodecanoic acid and perfluoroundecanoic acid and 2) perfluorohexane sulfonic acid, perfluorooctane sulfonic acid and perfluorooctanoic acid. Using a random forest algorithm, we discovered metabolite features associated with individual PFAS and PFAS exposure groups which were subsequently investigated for associations with risk of T2D.

PFAS levels correlated with 171 metabolite features ($0.16 \leq |r| \leq 0.37$, false discovery rate (FDR) adjusted $p < 0.05$). Out of these, 35 associated with T2D ($p < 0.05$), with 7 remaining after multiple testing adjustment (FDR < 0.05). PCA of the 35 PFAS- and T2D-related metabolite features revealed two patterns, dominated by glycerophospholipids and diacylglycerols, with opposite T2D associations. The glycerophospholipids correlated positively with PFAS and associated inversely with risk for T2D (Odds Ratio (OR) per 1 standard deviation (1-SD) increase in metabolite PCA pattern score = 0.2; 95% Confidence Interval (CI) = 0.1–0.4). The diacylglycerols also correlated positively with PFAS, but they associated with increased risk for T2D (OR per 1-SD = 1.9; 95% CI

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Associations between repeated measure of plasma perfluoroalkyl substances and cardiometabolic risk factors

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Plasma perfluoroalkyl substances
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Prospective assessment

ABSTRACT

Background: Perfluoroalkyl substances (PFAS) are persistent synthetic chemicals that may affect components of metabolic risk through the peroxisome proliferator-activated receptor but epidemiological data remain scarce and inconsistent.
Objective: To estimate associations between repeated measurements of the main PFAS in plasma and total cholesterol, triglycerides and hypertension among the control subjects from a population-based nested case-control study on diabetes type 2 in middle-aged women and men.
Methods: Participants (n = 187) were free of diabetes at both baseline and follow-up visits to the Västerbotten Intervention Programme, 10 years apart: during 1990 to 2003 (baseline) and 2001 to 2013 (follow-up). Participants left blood samples, completed questionnaires on diet and lifestyle factors, and underwent medical examinations, including measurement of blood pressure. PFAS and lipids were later determined in stored plasma samples. Associations for the repeated measurements were assessed using generalized estimating equations.
Results: Six PFAS exceeded the limit of quantitation. Repeated measures of PFAS in plasma, cardiometabolic risk factors and confounders, showed an average decrease of triglycerides from −0.16 mmol/l (95% confidence interval [CI]: −0.33, 0.02 for PFOA) to −0.26 mmol/l (95% CI: −0.50, −0.08 for PFOS), when comparing the highest tertile of PFAS plasma levels with the lowest. Associations based on average PFAS measurements and follow-up triglycerides revealed similar inverse associations, although attenuated. The estimates for cholesterol and hypertension were inconsistent and with few exception non-significant.
Conclusions: This study found inverse associations between PFAS and triglycerides, but did not support any clear link with either cholesterol or hypertension.

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Perfluoroalkyl substances and risk of type II diabetes: A prospective nested case-control study

Carolina Donat-Vargas[a], Ingvar A. Bergdahl[b], Andreas Tornevi[b], Maria Wennberg[c], Johan Sommar[b], Hannu Kiviranta[d], Jani Koponen[d], Olov Rolandsson[e], Agneta Åkesson[a,*]

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Environmental risk factors
Diabetes
Insulin resistance
Endocrine disruption
Environmental epidemiology
Nested case-control study
Prospective assessment

ABSTRACT

Background: Perfluoroalkyl substances (PFAS) have drawn much attention due to bioaccumulation potential and their current omnipresence in human blood. We assessed whether plasma PFAS, suspected to induce endocrine-disrupting effects, were prospectively associated with clinical type 2 diabetes (T2D) risk.
Methods: We established a nested case-control study within the Swedish prospective population-based Västerbotten Intervention Programme cohort. Several PFAS were measured in plasma from a subset of 124 case-control pairs at baseline (during 1990–2003) and at 10-year follow-up. T2D cases were matched (1:1) according to gender, age and sample date with participants without T2D (controls).

Conditional logistic regressions were used to prospectively assess risk of T2D by baseline PFAS plasma concentrations. Associations between long-term PFAS plasma levels (mean of baseline and follow-up) and insulin resistance (HOMA2-IR) and beta-cell function (HOMA2-B%) at follow-up were prospectively explored among 178 and 181 controls, respectively, by multivariable linear regressions.
Results: After adjusting for gender, age, sample year, diet and body mass index, the odds ratio of T2D for the sum of PFAS (Σ z-score PFAS) was 0.52 (95% confidence interval, CI: 0.20, 1.36), comparing third with first tertile; and 0.92 (95% CI: 0.84, 1.00) per one standard deviation increment of sum of log-transformed PFAS. Among the controls, the adjusted β of HOMA2-IR and HOMA-B% for the sum of PFAS were −0.26 (95% CI: −0.52, −0.01) and −9.61 (95% CI: −22.60, 3.39) respectively comparing third with first tertile.
Conclusions: This prospective nested case-control study yielded overall inverse associations between individual PFAS and risk of T2D, although mostly non-significant. Among participants without T2D, long-term PFAS exposure was prospectively associated with lower insulin resistance.

PFAS and Cardiovascular disease

ehp Environmental Health Perspectives

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Per- and Polyfluoroalkyl Substances and Risk of Myocardial Infarction and Stroke: A Nested Case–Control Study in Sweden

Tessa Schillemans, Carolina Donat-Vargas, Christian H. Lindh, Ulf de Faire, Alicja Wolk, Karin Leander, and Agneta Åkesson

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Abstract

Background: Per- and polyfluoroalkyl substances (PFAS) are widespread and persistent pollutants that have been associated with elevated cholesterol levels. However, data on incident cardiovascular disease (CVD) is lacking.

Objectives: We investigated the association of exposure to PFAS with risk of myocardial infarction and stroke and, subsidiary, with baseline blood lipids.

Methods: This population-based nested case–control study included first incident myocardial infarction and stroke cases with matched controls from two Swedish cohorts: the Swedish Mammography Cohort-Clinical (SMC-C) and the Cohort of 60-year-olds (60YO). Baseline blood sampling occurred during 2003–2009 and 1997–1999 with follow-up through 2017 and 2014 for the SMC-C and the 60YO, respectively. Eight plasma PFAS concentrations were measured using targeted liquid chromatography–triple quadrupole mass spectrometry. Five of these were quantifiable in both cohorts; individual values and their standardized sum were categorized into tertiles based on the controls. First incident myocardial infarction (n = 345) and ischemic stroke (n = 354) cases were ascertained via linkage to the National Inpatient Register and the Cause of Death Register. Controls were randomly selected from each cohort after matching for age, sex, and sample date. Baseline blood lipids were measured in plasma or serum after overnight fasting.

Results: Among the 1,528 case–control subjects, the mean (standard deviation) age was 66 (7.7) y and 67% of them were women. In multivariable-adjusted analyses, the third tertile of the standardized sum of five PFAS associated with higher cholesterol and lower triglyceride levels among controls at baseline (n = 631). The corresponding results were odds ratios = 0.70 [95% confidence interval (CI): 0.53, 0.93] for CVD, 0.60 (95% CI: 0.39, 0.92) for myocardial infarction, and 0.83 (95% CI: 0.46, 1.50) for stroke.

Discussion: This study indicated that exposure to PFAS, although associated with increased cholesterol levels, did not associate with an increased risk of myocardial infarction, stroke, or their composite end point. The findings improve our knowledge on potential health effects of environmental contaminants in the CVD context. https://doi.org/10.1289/EHP9791

- Nested case-control study with biobanked samples from 2 prospective cohorts
- 699 cases & 829 matched controls
  - 345 Myocardial infarction cases
  - 354 Stroke cases

Results: Lipids

- Baseline data (i.e. cross-sectional)

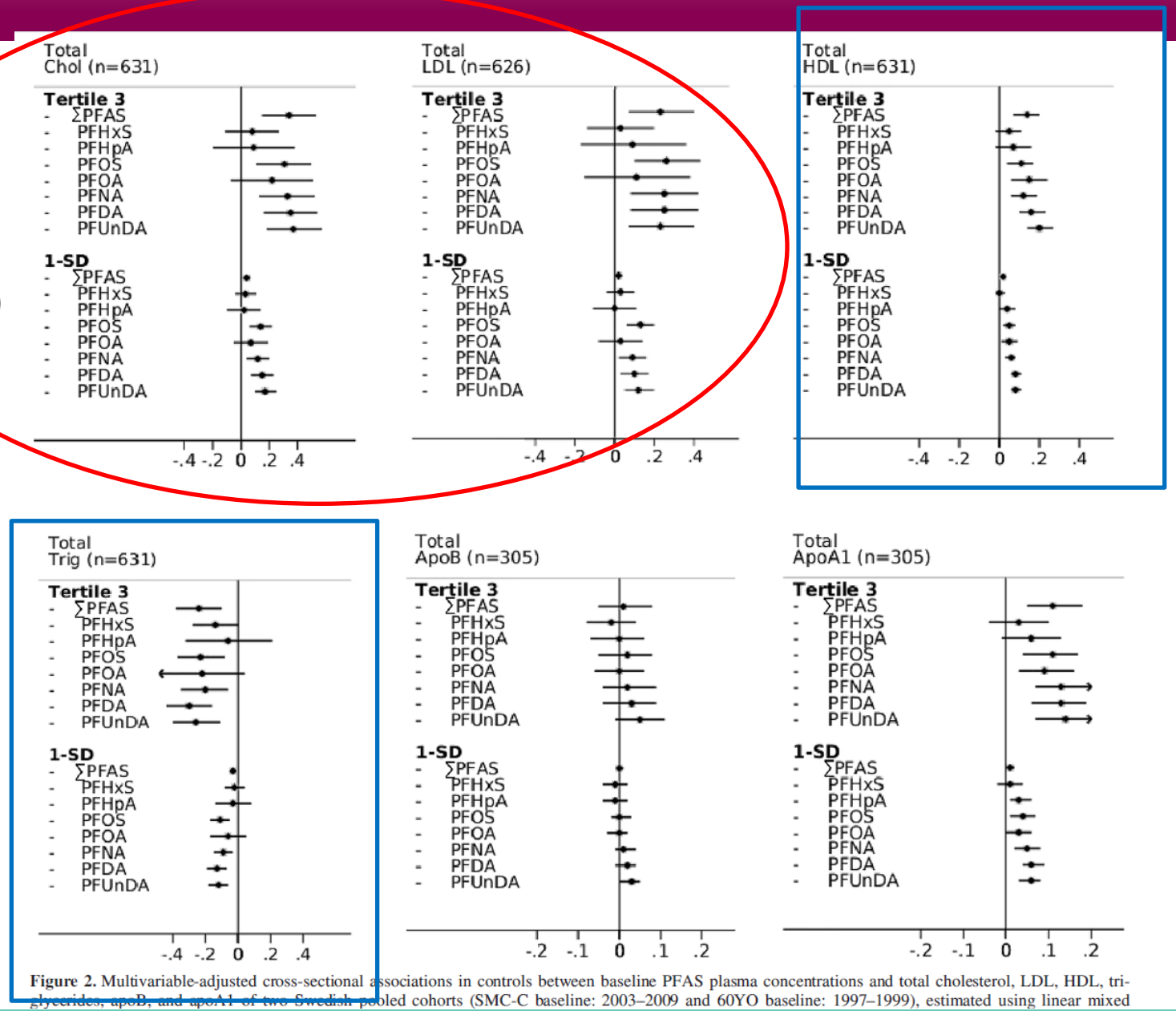


Figure 2. Multivariable-adjusted cross-sectional associations in controls between baseline PFAS plasma concentrations and total cholesterol, LDL, HDL, triglycerides, apoB, and apoA1 of two Swedish pooled cohorts (SMC-C baseline: 2003–2009 and 60YO baseline: 1997–1999), estimated using linear mixed

Schillemans, et al. EHP 2022

PFAS and risk of composite CVD

- OR <1.0 for all PFAS

Myocardial infarction ← Risk of → Stroke

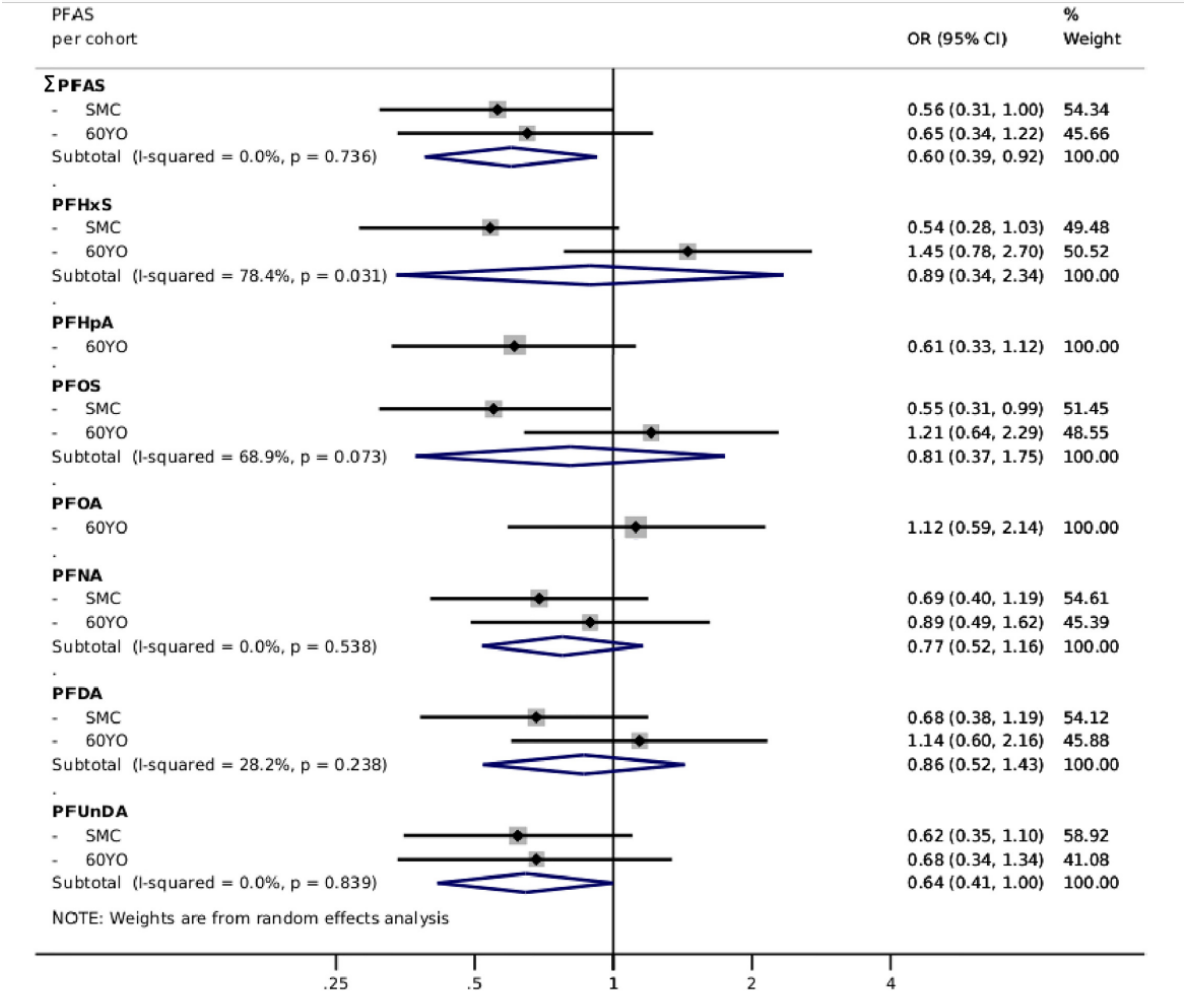


Figure 3. Multivariable-adjusted risk of myocardial infarction, presented as pooled ORs (95% CIs) from two Swedish cohorts (SMC-C: $n = 398$ and 60YO: $n = 422$) using random effects meta-analysis, comparing the third tertile of each PFAS with the first tertile—PFHpA and PFOA results are from the 60YO

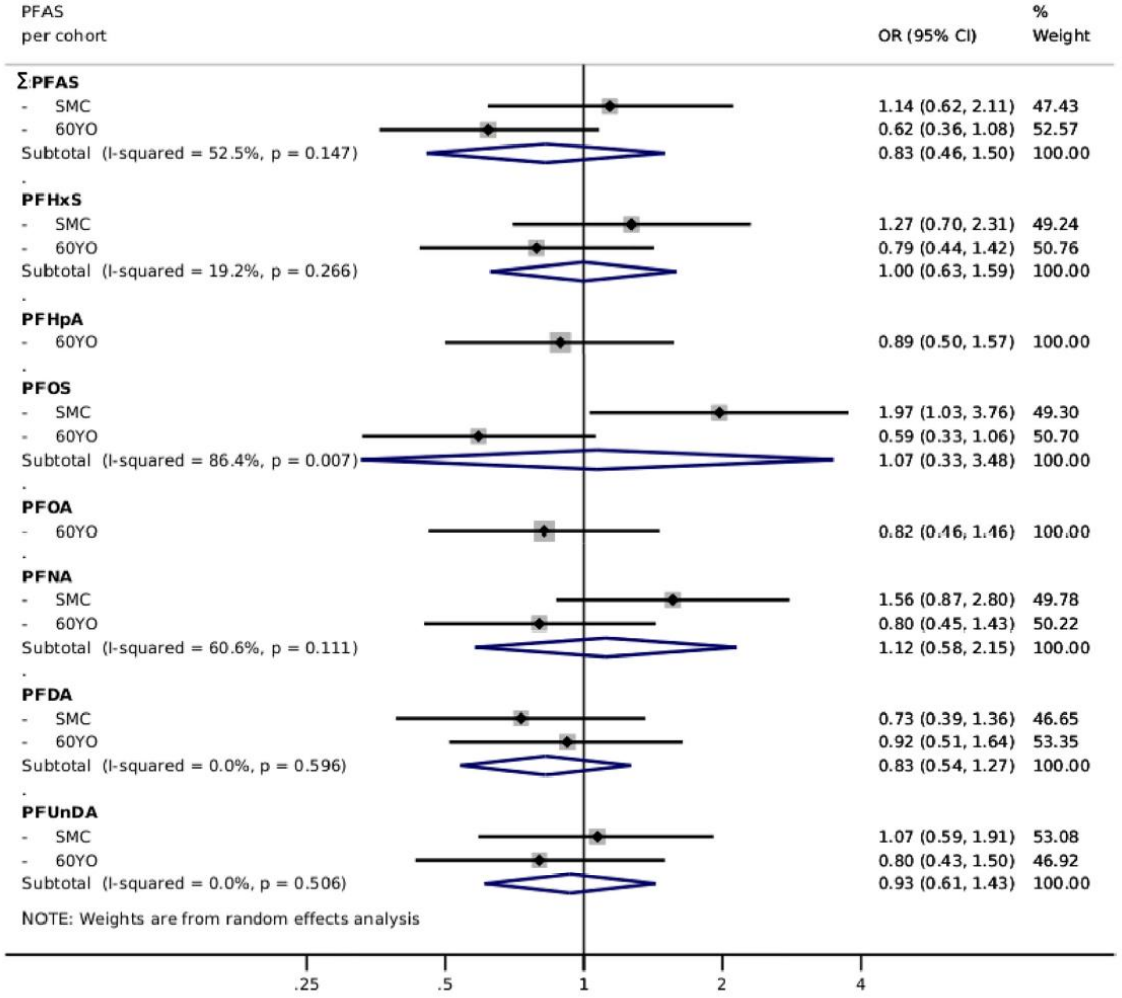


Figure 4. Multivariable-adjusted risk of stroke, presented as pooled ORs (95% CIs) from two Swedish cohorts (SMC-C: $n = 344$ and 60YO: $n = 364$) using ran-

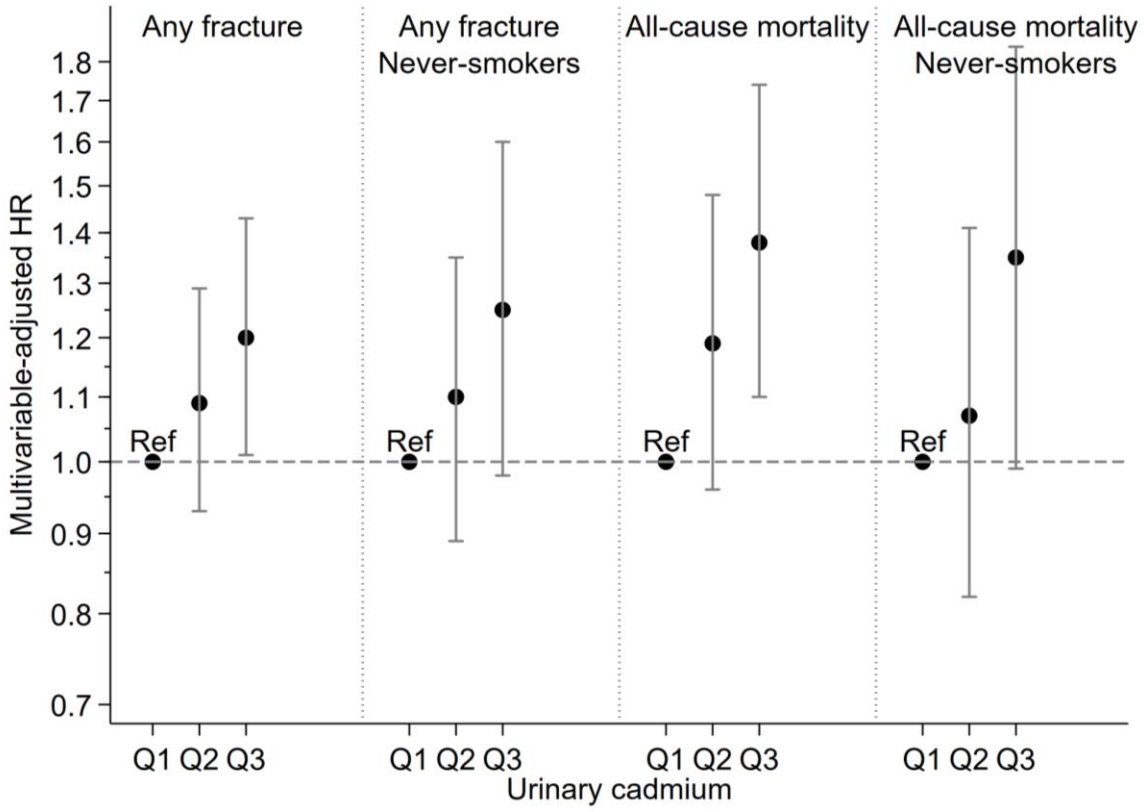
Summary PFAS

- We confirmed PFAS cross-sectional associations with elevated cholesterol among those without CVD. However, this did not translate into increased CVD risk in the prospective study.
- Overall inverse associations (mostly non-significant) between individual PFAS and the prospective risk of T2D. Among participants without T2D, long-term PFAS exposure was prospectively associated with lower insulin resistance.

Cadmium vs. Fractures and Mortality

- Low correlation between dietary Cd and U-Cd
- Dietary cadmium exposure linked to fractures
  - Some hormone-related cancers (e.g., endometrium)

U-Cd in 4000 women based on 11 years of follow-up



Tägt et al, Env Int. 2022

Fluoride

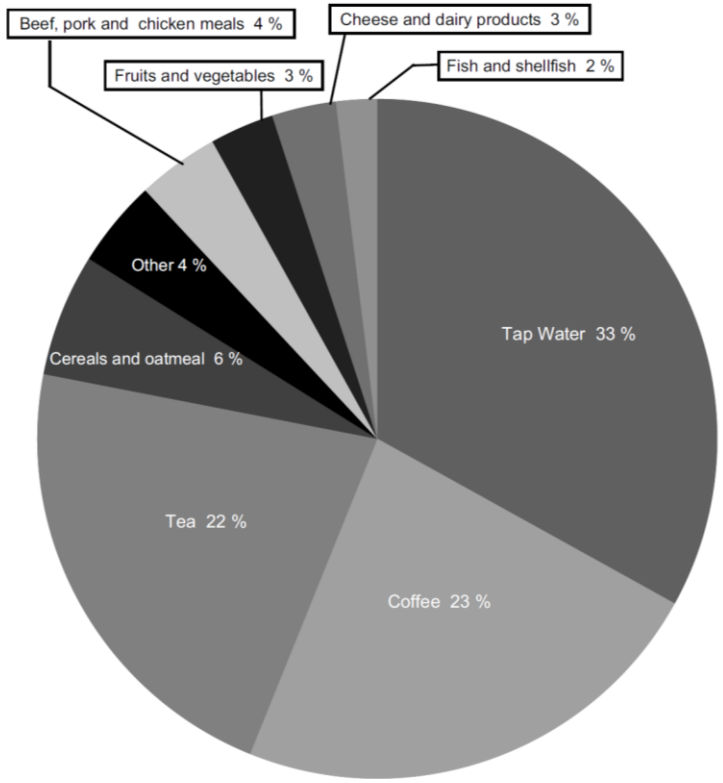
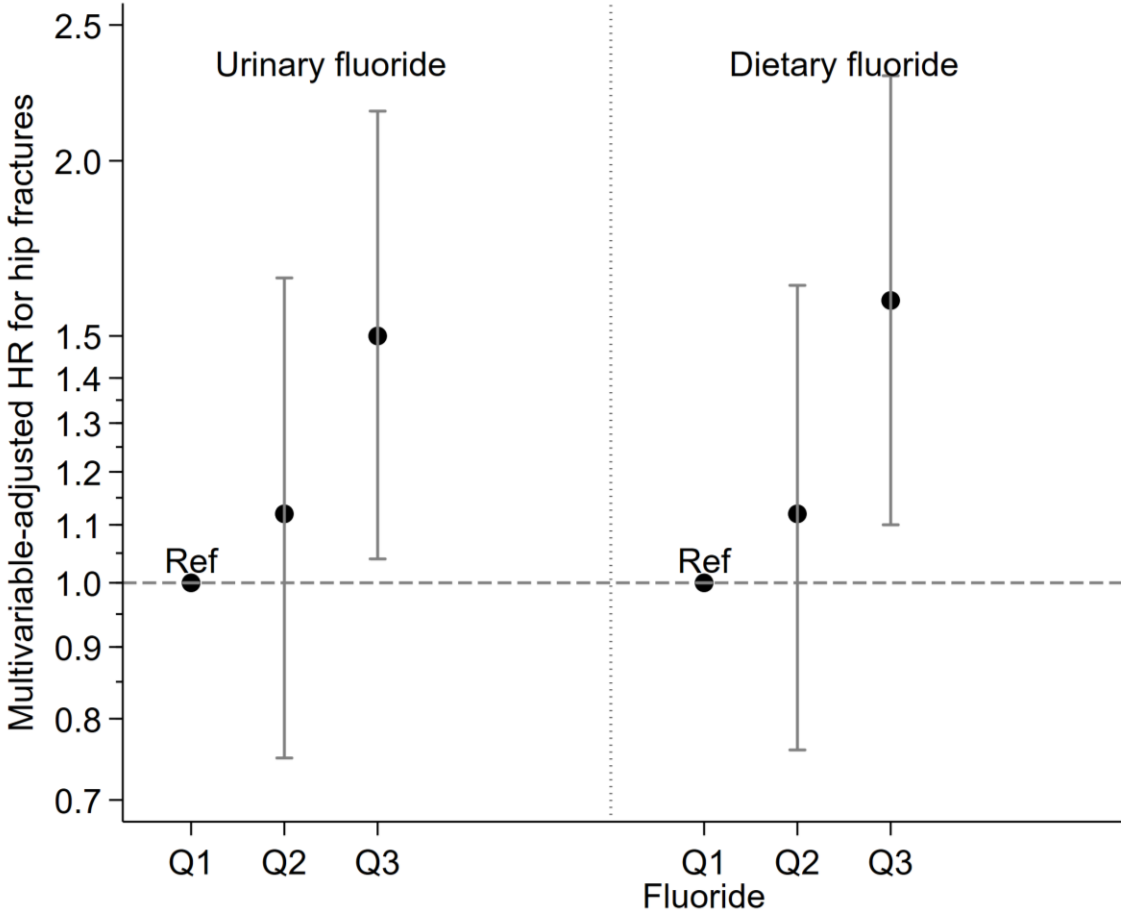


Figure 2. Major sources of dietary fluoride intake estimated for 4,072 women of the Swedish Mammography Cohort–Clinical. Tap water refers to tap water consumed as drinking water and coffee and tea brewed with tap water.

Environmental Health Perspectives 047005-5 129(4) April 2021

Fluoride & hip fractures (4000♀)



Helte et al, EHP 2021

Thank you

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