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LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE

Serum PFOA and PFOS levels and liver  
function biomarkers in the C8 Science Panel  
Study


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## Background

- ▶ Pefluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are man-made compounds used during the manufacture of fluoropolymer, including
  - ▶ Non-stick cookware
  - ▶ Breathable, yet waterproof, fabrics
- ▶ Or they can result from the metabolism of fluorinated telomers, used for
  - ▶ Food package coatings
  - ▶ Carpet treatment
  - ▶ Stain-resistant fabrics tratment
- ▶ PFOA and PFOS persist in the environment



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## Sources of exposure

- ▶ Potential sources of exposure in humans
  - ▶ Drinking water
  - ▶ Dust
  - ▶ Breast milk
  - ▶ Food packaging
  - ▶ Ambient air
  - ▶ Occupational exposure



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## Animal data

- ▶ In rodents, PFOA and PFOS have been associated with liver enlargement
- ▶ In rats, they have been associated with hepatocellular adenomas
- ▶ One of the biological effects is the activation of the proxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), a ligand-activated transcription factor that regulates gene expression, lipid modulation, glucose homeostasis, cell proliferation, and inflammation



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## Previous studies

- ▶ Previous occupational and population-based studies reported inconsistent association between PFOA, PFOS and liver enzymes [transaminase (ALT, AST), gamma glutamyltransferase (GGT), and bilirubin]



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## Aim and setting

- ▶ Aim of this study is to explore the association between PFOA and PFOS and liver function enzymes in adults in a cross-sectional analysis of a large population base study
- ▶ A chemical plant in the Mid-Ohio Valley (WV) was responsible for emitting PFOA in the surrounding environment from 1950 to 2005
- ▶ As part of a pre-trial settlement following a class action against the plant, a baseline survey of 69,000 inhabitants was carried out in 2005-06 by the C8 Health Project



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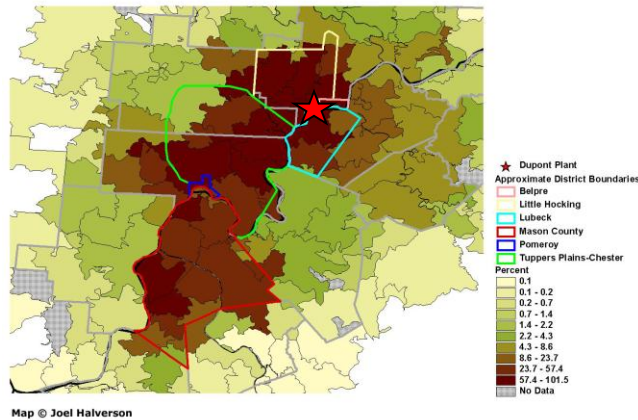


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## Study population

Percent of C8 Study Participants in Relation to Total 2000 Census Population  
For ZIP Code Tabulation Areas (ZCTAs)



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## Choice of lab parameters

<b>ALANINE AMINOTRANSFERASE (ALT)</b>	Together with aspartate aminotransferase (AST) are released after liver parenchymal cell injury and are elevated in serum during active liver damage. ALT was used as proxy for hepatocellular injury as more specific for hepatic damage than AST
<b>γ-GLUTAMYLTRANSFERASE (GGT)</b>	is found in cell membranes (particularly hepatic and renal and those of the bile ducts). Used as proxy for cholestatic disorder as elevation occurs at an earlier stage and is more persistent than that of alkaline phosphatase (ALP)
<b>BILIRUBIN</b>	Mostly derived from the metabolism of haemoglobin, the increase in serum of the direct component is highly specific for liver or bile duct disease



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## Statistical analysis

- ▶ Association between PFOA and PFOS and ALT, GGT, and direct bilirubin was investigated by fitting
  - ▶ Linear regression models
  - ▶ Logistic regression models using cut offs above normal levels
- ▶ All analyses were repeated in three models
  - ▶ **Model 1**: including age and gender only
  - ▶ **Model 2**: additionally including alcohol consumption, socio-economic status, fasting status, ethnicity, and month of blood sample collection
  - ▶ **Model 3**: additionally including, smoking status, BMI, physical activity, and insulin resistance
- ▶ **Between-Water District analysis**



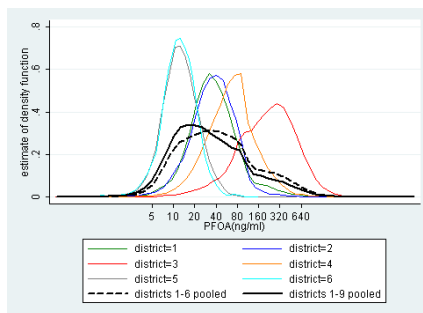
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## Between-Water District analysis



- ▶ Lack of consistency between shapes of an association at individual and at water district level might suggest the presence of unmeasured residual confounding at **individual level** (i.e. physical activity) or at **water district level** (i.e. healthcare access/facilities)

# Results



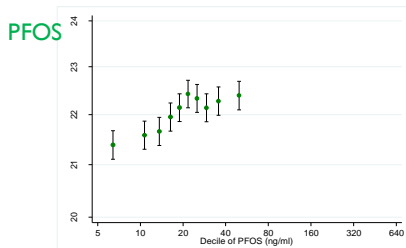
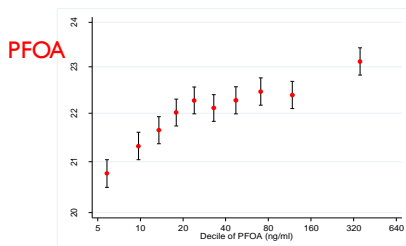
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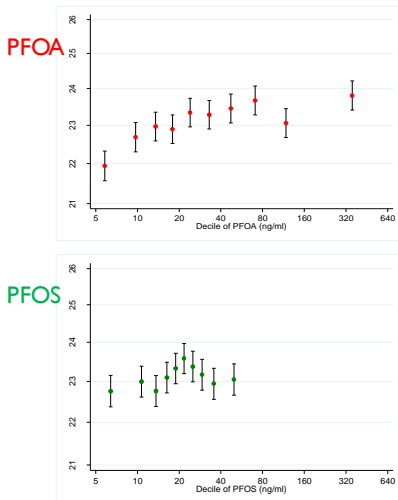
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## Hepatocellular injury (ALT)



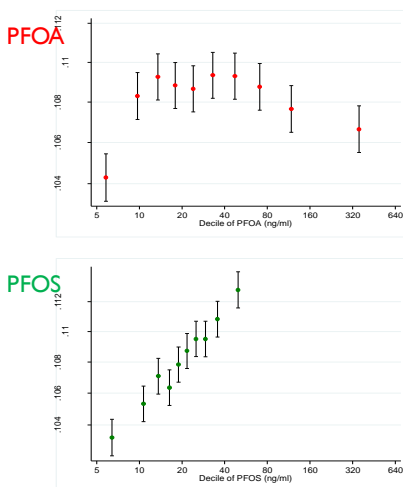
	PFOA	PFOS
<b>Linear regression</b>	Coefficient per In-unit 0.024 (95% C.I. 0.020-0.028)	Coefficient per In-unit 0.022 (95% C.I. 0.014-0.030)
<b>Logistic regression</b>	OR per In-unit 1.10 (95% C.I. 1.07-1.13)	OR per In-unit 1.13 (95% C.I. 1.07-1.18)

## Cholestasis (GGT)



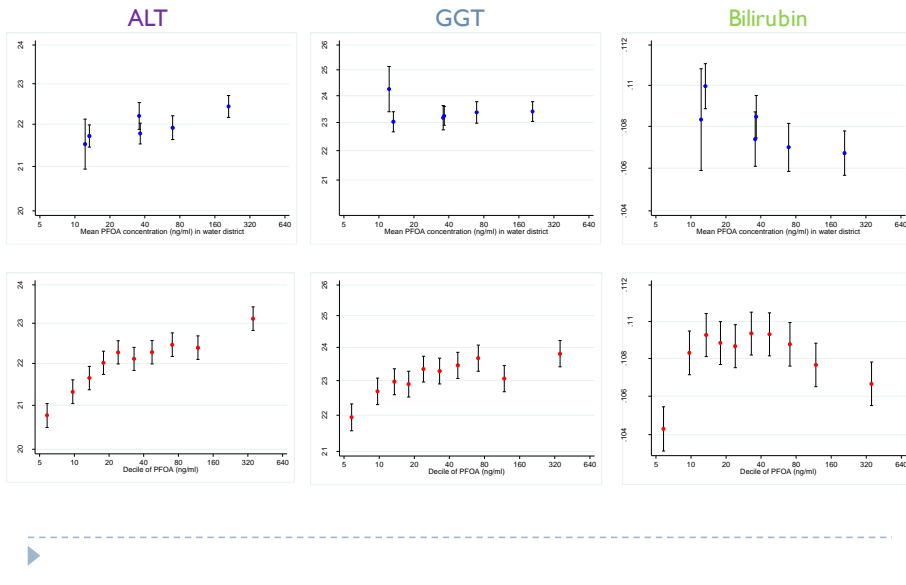
	PFOA	PFOS
<b>Linear regression</b>	Coefficient per ln-unit 0.015 (95% C.I. 0.009-0.020)	Coefficient per ln-unit 0.008 (95% C.I. -0.002-0.019)
<b>Logistic regression</b>	OR per ln-unit 1.01 (95% C.I. 0.99-1.04)	OR per ln-unit 0.98 (95% C.I. 0.94-1.02)

## Direct bilirubin



	PFOA	PFOS
<b>Linear regression</b>	Coefficient per ln-unit -0.002 (95% C.I. -0.006-0.002)	Coefficient per ln-unit 0.029 (95% C.I. 0.022-0.035)
<b>Logistic regression</b>	OR per ln-unit 0.97 (95% C.I. 0.90-1.05)	OR per ln-unit 1.11 (95% C.I. 0.96-1.28)

## Between-Water District analysis



## Conclusions on ALT

- ▶ Results show a **positive association between PFOA, PFOS and concentrations of ALT, a marker of hepatocellular damage**
- ▶ The linear association between the In-transformed values is consistently replicated in all analysis showing a **monotonic increase in logistic regression**
- ▶ The presence of a **consistent association between and within water districts** increases the strength of evidence for a true association



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## Conclusions on GGT

- ▶ There is some suggestion of an association between PFOA and GGT in linear regression models; however, these were not replicated in logistic regressions
- ▶ The instability of linear regression coefficient might be especially due to a **confounding effect of diet, or residual confounding of alcohol**
- ▶ Also the absence of any trend between WD suggest the presence of **confounding effect at individual level**



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## Conclusions on direct biliruin

- ▶ The relationship between PFOA and direct bilirubin is suggestive of an **increase of bilirubin increasing PFOA concentrations up to 40 ng/mL followed by a decrease of biliruin levels after this peak (inverse U-shaped)**
- ▶ **Negative associations observed in some occupational studies** might be due inclusion of subjects in the higher range of exposure, missing the first part of the inverse U-shaped curve
- ▶ **Between-district comparison is compatible with the suggested inverse U-shaped association**



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## Conclusions

- ▶ A small but monotonic linear association between PFOA and PFOS serum concentrations and ALT, a marker of hepatocellular injury, was observed in this large population-based sample of individuals with exposure to perfluoroalkyl acids. These results are consistent with some previous findings and warrant further investigation, in particular on the potential health consequence of long-term exposure and potential accumulation of damage.
- ▶ No clear conclusions can be drawn on the association between PFOA and PFOS with GGT and bilirubin



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Thank you very much for your  
attention!

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