

Air Pollution-induced Diabetes is Mediated via Macrophages in the Gut

PD Dr. Claudia Cavelti-Weder

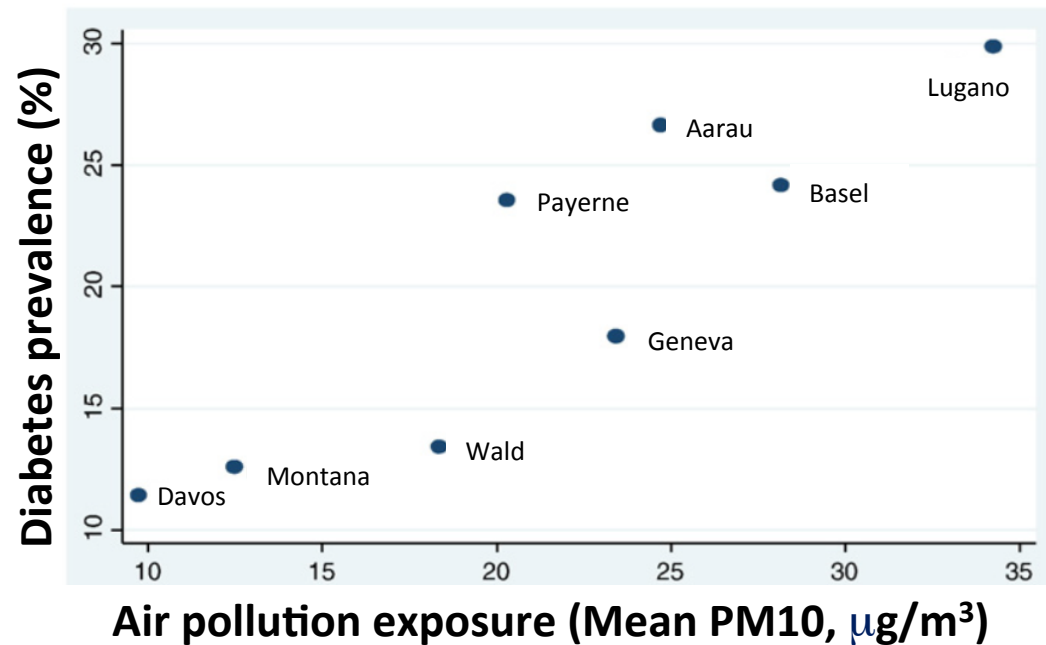
23rd ETH-Conference on Combustion Generated Nanoparticles

Increased diabetes prevalence with air pollution

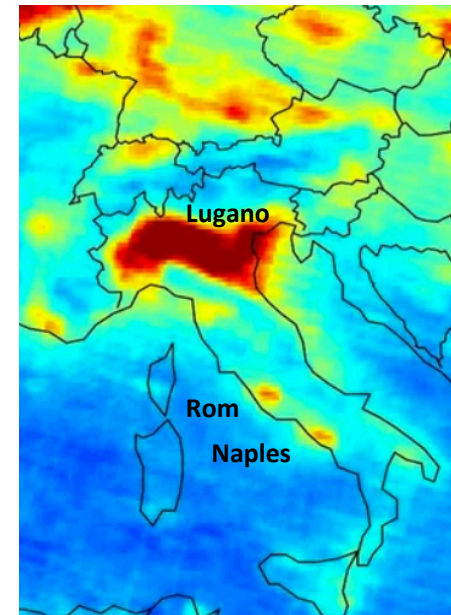
TagesAnzeiger

06.05.2016

Strassenverkehr macht zuckerkrank



Eze, Environment International. 2014

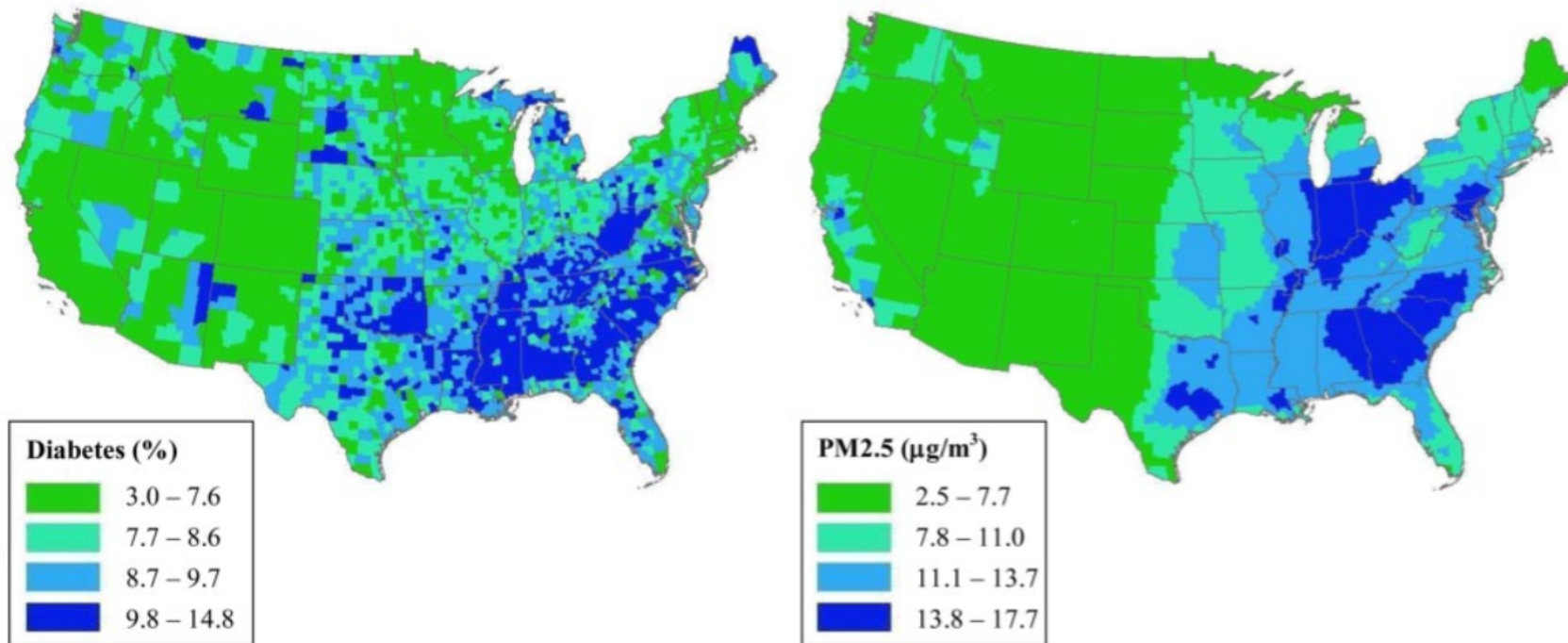


IUP Heidelberg, NO2 levels over Europe

Increased diabetes prevalence with air pollution

Ecological study

- County-level prevalence of diabetes
- PM_{2.5}



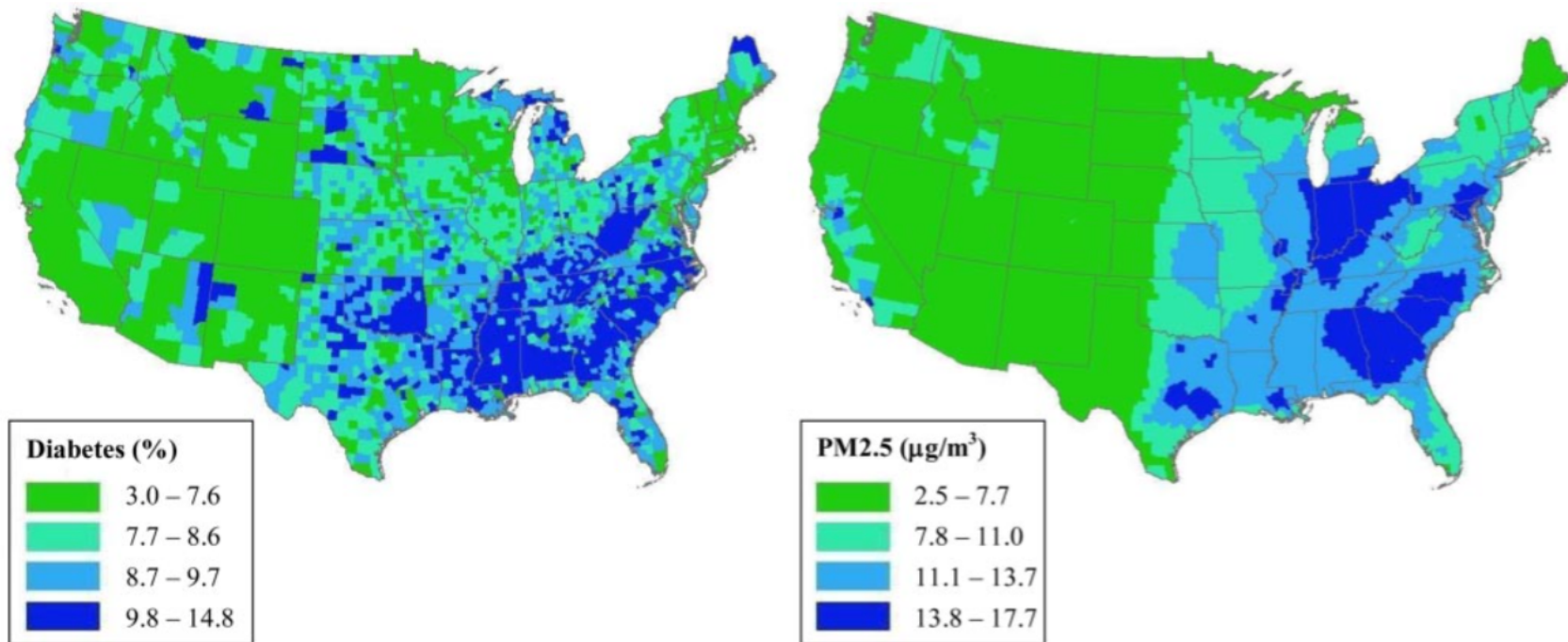
Pearson et al., Diabetes Care. 2010

- **Worldwide phenomenon** (USA, CA, DE, SE, DK, NL, IT, China).
- A similar association exists for **smoking** and **increased diabetes risk**. Willi, JAMA. 2007
- Air pollution is also associated with an **increased cardiovascular risk**. Brook, Circulation. 2010

Increased diabetes prevalence with air pollution

Ecological study

- County-level prevalence of diabetes
- $PM_{2.5}$



Pearson et al., Diabetes Care. 2010

Correlation or causation?

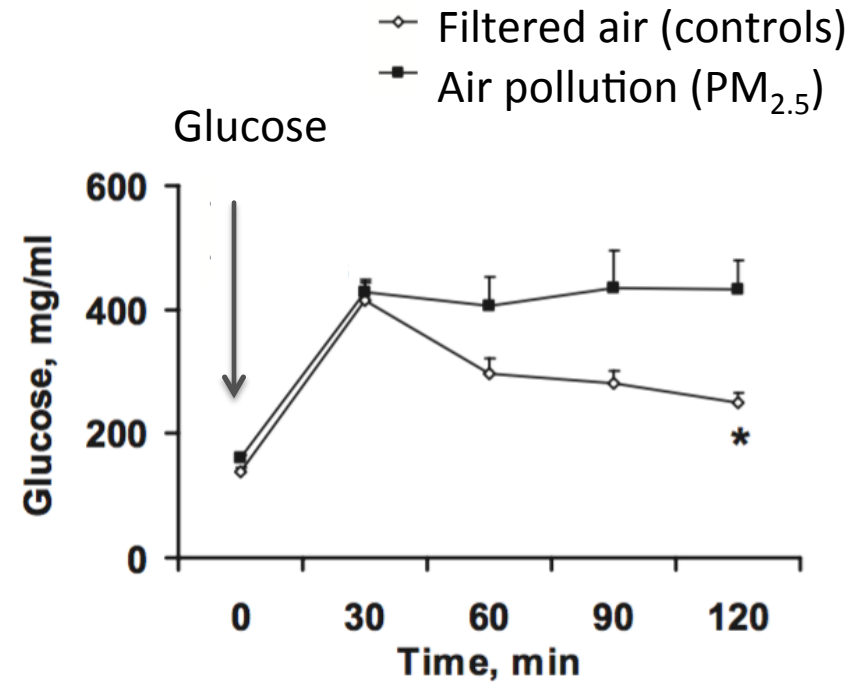
Physical inactivity, unhealthy food, poor socioeconomic status, genetic disposition

Mouse studies confirm increased diabetes risk with air pollution

Inhalation chambers in mice



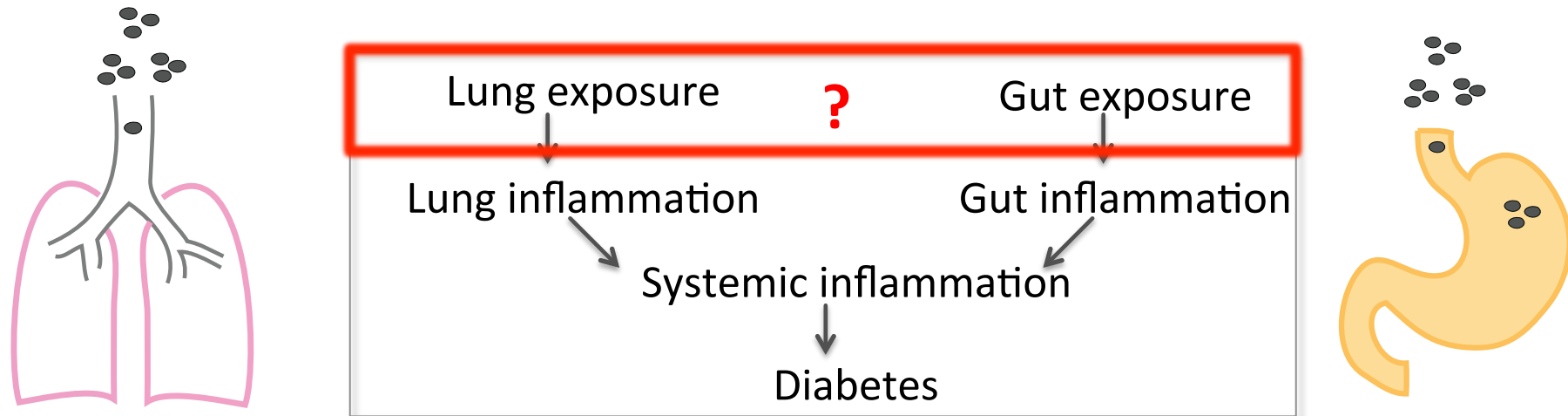
Concentrated ambient air during 6 hours/day



Sun, Circulation. 2009

- **Mouse studies** support that air pollution leads to diabetes.
- **The mechanism** how air pollution causes diabetes is unknown.

Hypothesis and Research Question



Current dogma:

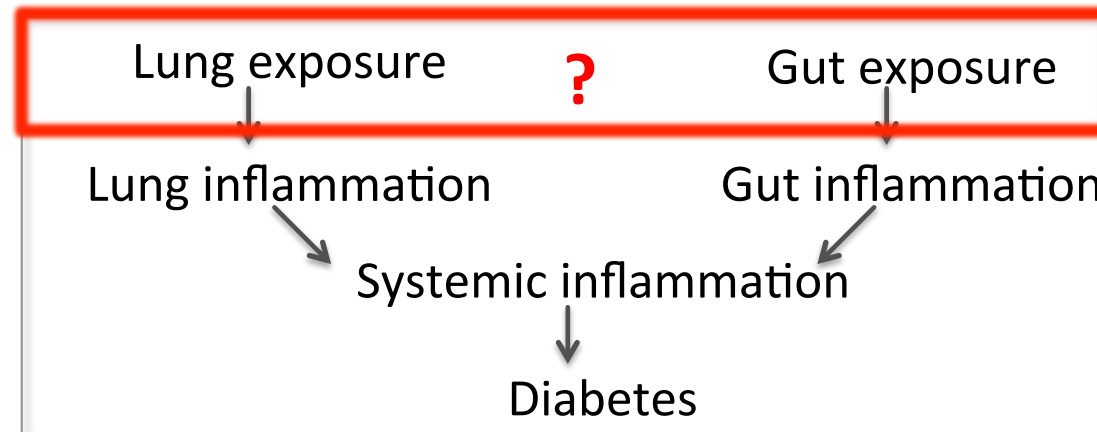
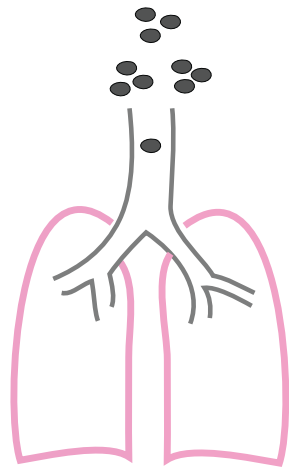
- Lung = primary target organ of air pollution

Rationale to look at the gut:

- Particles reach the gut
- Increased gut permeability
- Altered gut microbiota
- More GIT-diseases with air pollution

Is air pollution-induced diabetes mediated via gut or lung exposure?

Hypothesis and Research Question



Question 1: Is air pollution-induced diabetes mediated via the lung?

Question 2: Is air pollution-induced diabetes mediated via the gut?

Question 3: Is diabetes due to insulin secretion defect or insulin resistance?

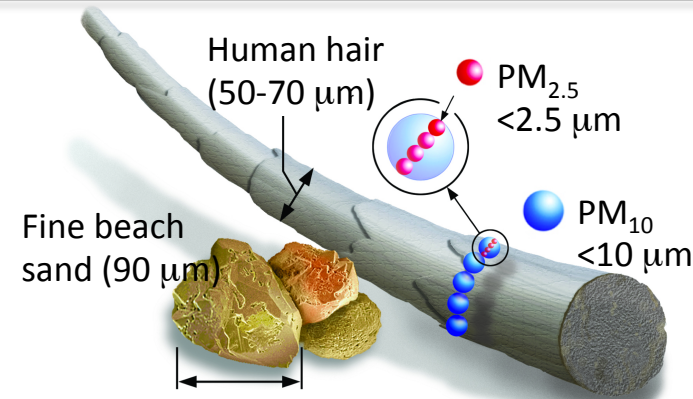
Question 4: Is innate immunity involved in air pollution-induced diabetes?

Question 5: Is adaptive immunity involved in air pollution-induced diabetes?

Methods

Solid form of air pollution

- **PM: Particulate matter** (“Feinstaub”)
 - PM_{2.5} (particles <2.5 µm)
 - PM₁₀ (particles <10 µm)
- **DEP: Diesel exhaust particles**



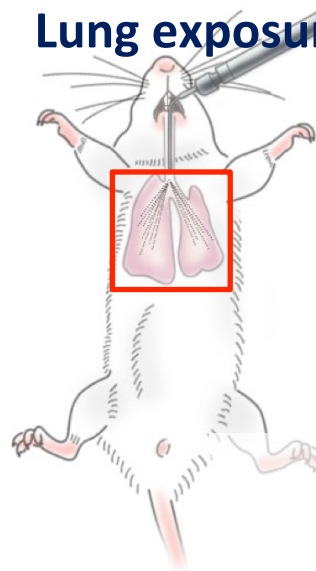
United States Environmental Protection Agency

Particulate matter
Diesel exhaust particles



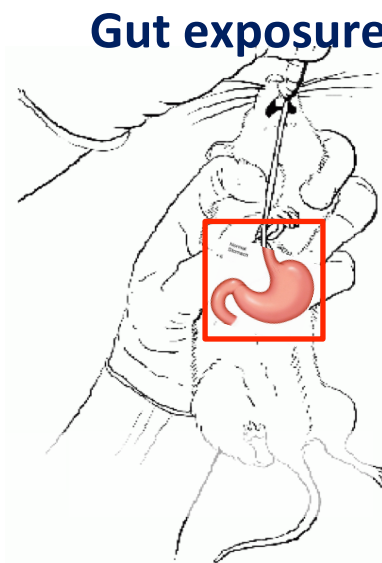
(“standardized”)

Lung exposure



2 x 30 (=60) µg/week

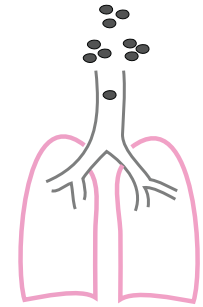
Gut exposure



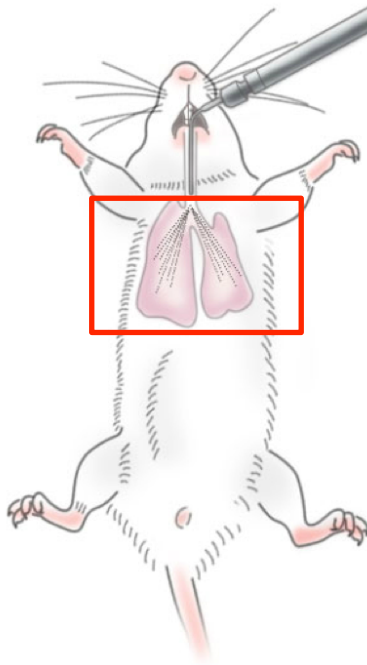
5 x 12 (=60) µg/week

Question 1:

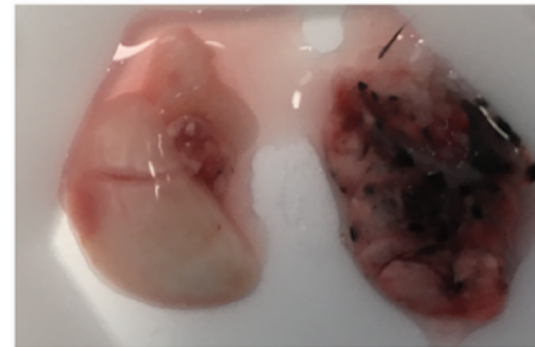
Is air pollution-induced diabetes mediated via the lung?



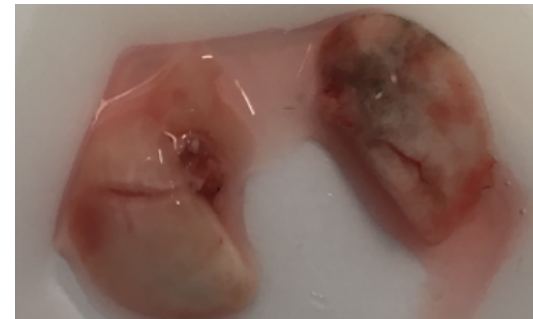
Lung exposure
Intratracheal instillation



Control (PBS) **Diesel exhaust particles**

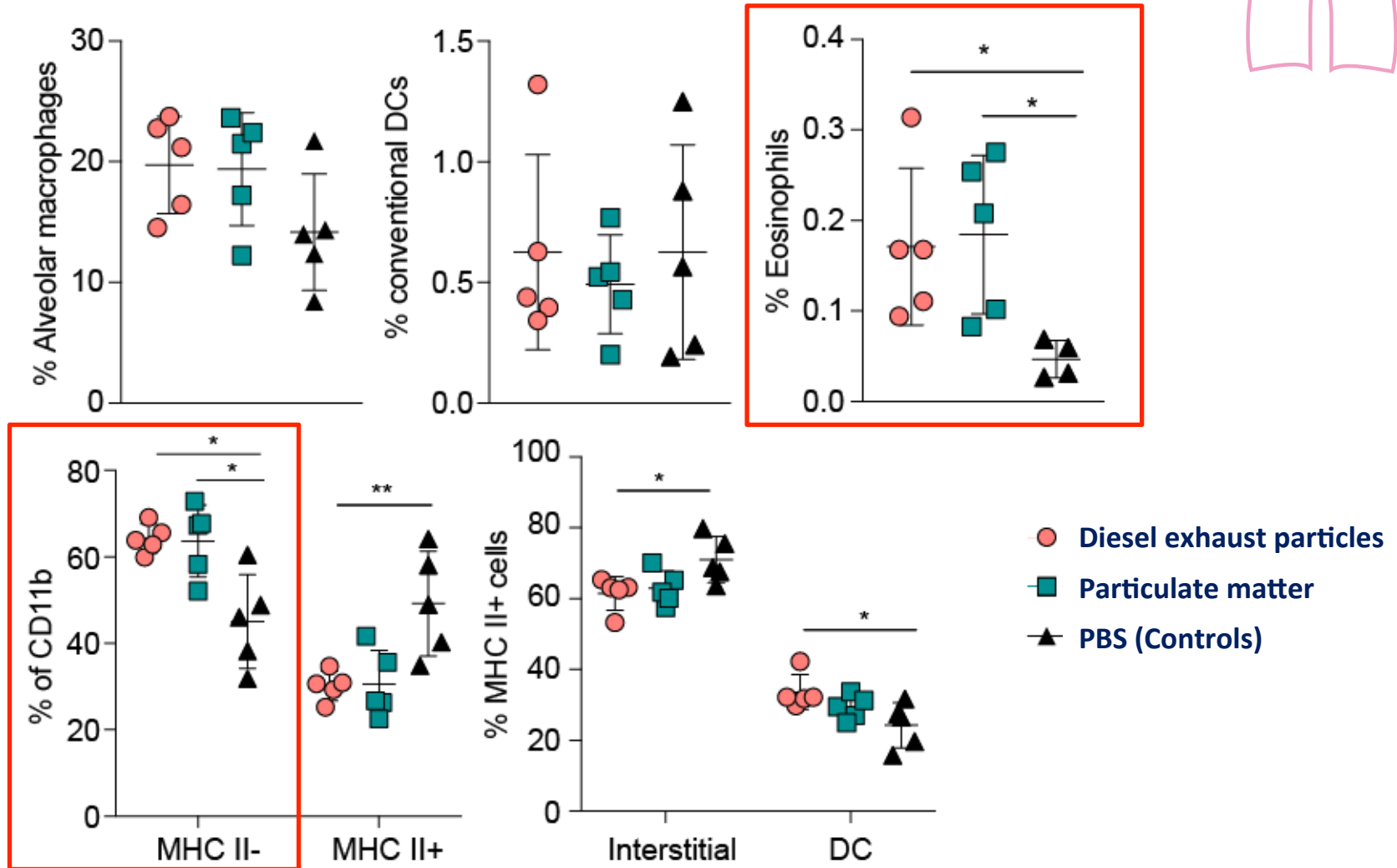
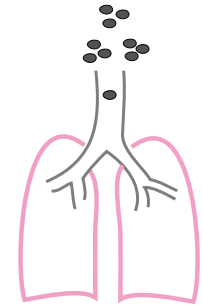


Control (PBS) **Particulate matter**



Question 1:

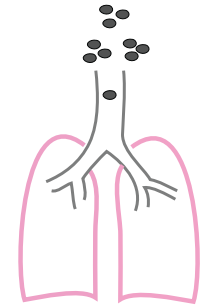
Is air pollution-induced diabetes mediated via the lung?



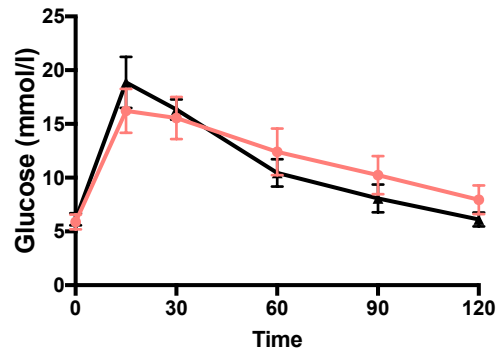
⇒ Lung exposure causes lung inflammation

Question 1:

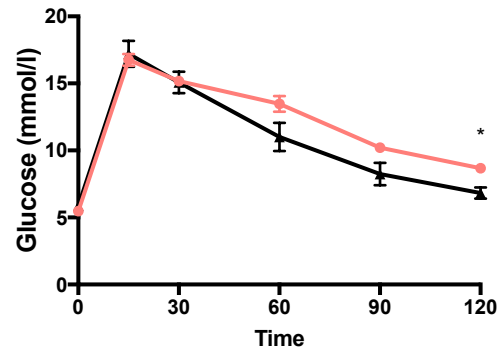
Is air pollution-induced diabetes mediated via the lung?



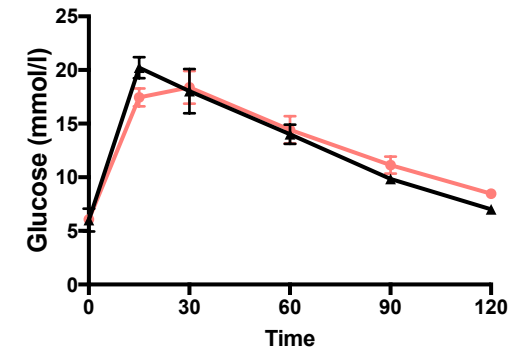
Glucose tolerance tests
1 month



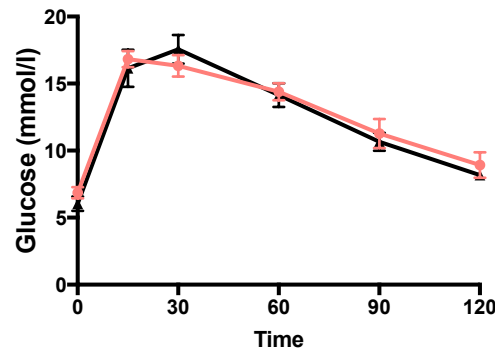
2 months



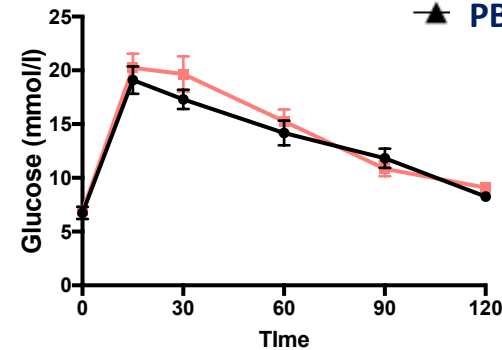
3 months



4 months



5 months



● Diesel exhaust particles
▲ PBS (Controls)

⇒ Lung exposure causes lung inflammation, but not diabetes

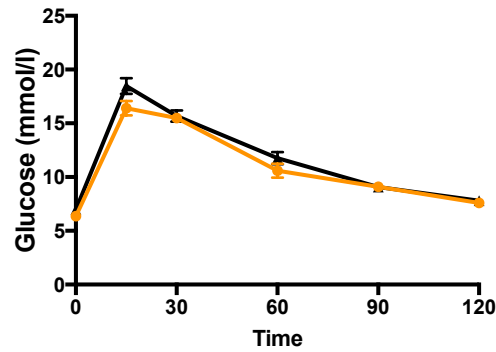
Question 2:

Is air pollution-induced diabetes mediated via the gut?

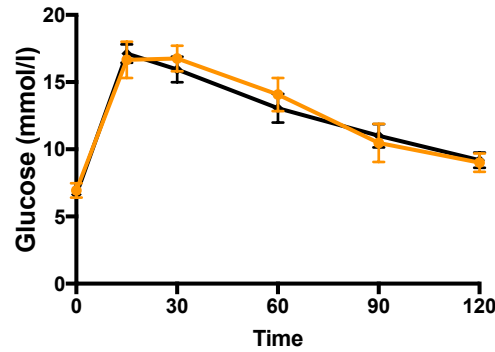


Glucose tolerance tests

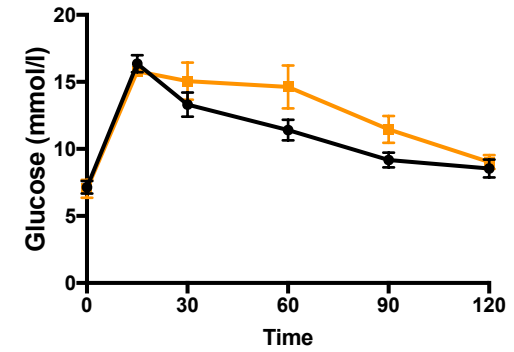
1 month



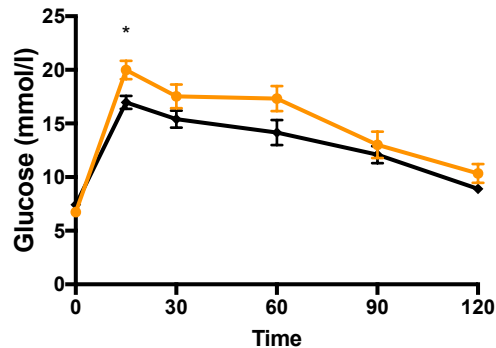
2 months



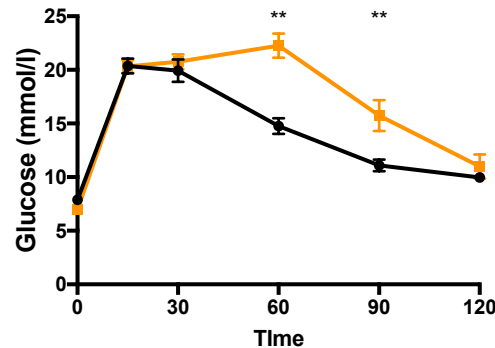
3 months



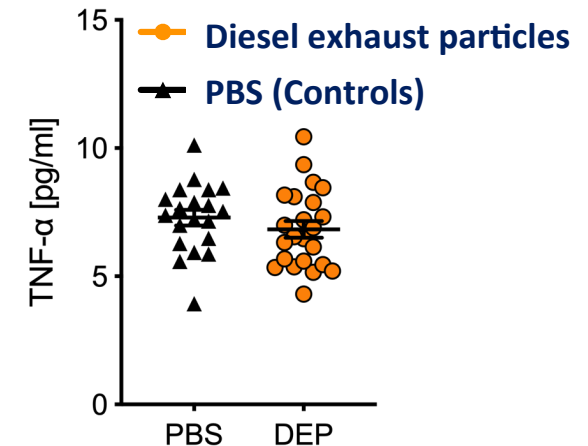
4 months



5 months



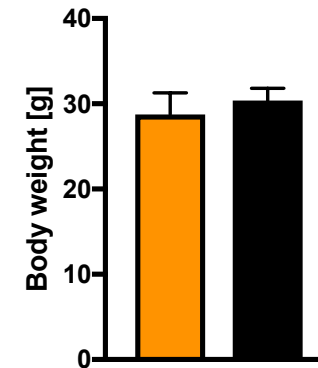
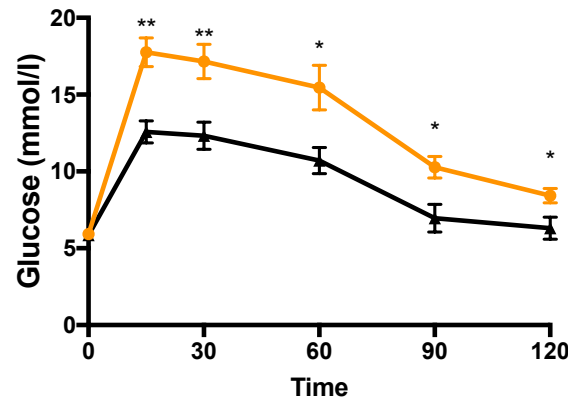
Systemic inflammation



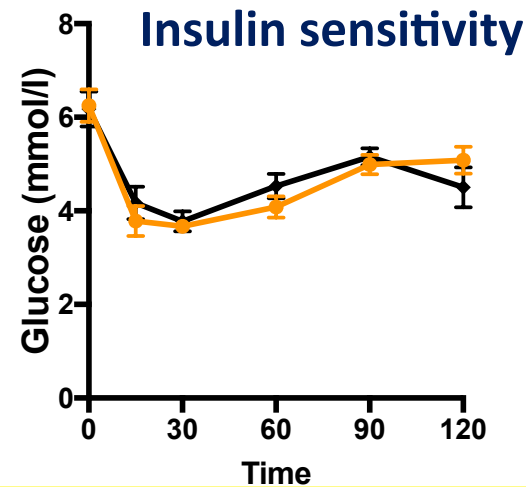
⇒ Gut exposure causes diabetes, but not via systemic inflammation

Question 3:

Is diabetes due to insulin secretion defect or insulin resistance?



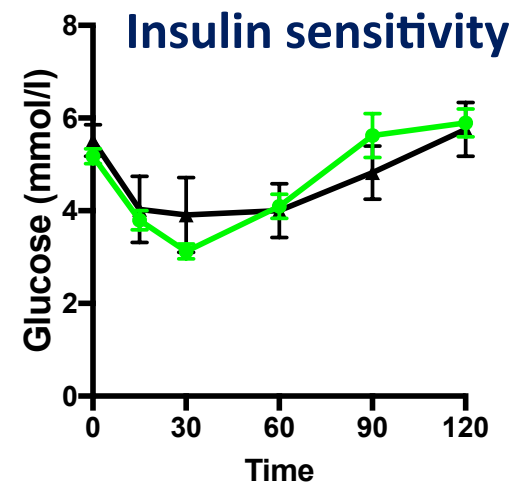
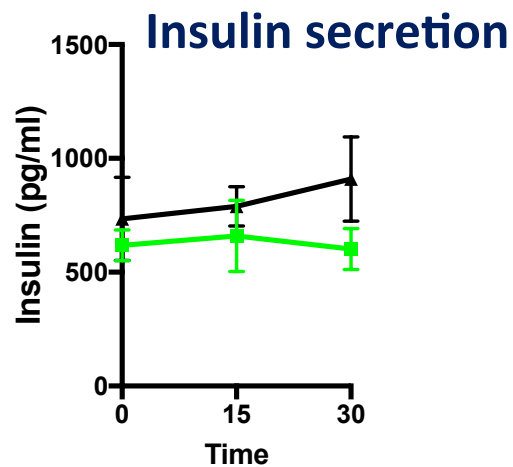
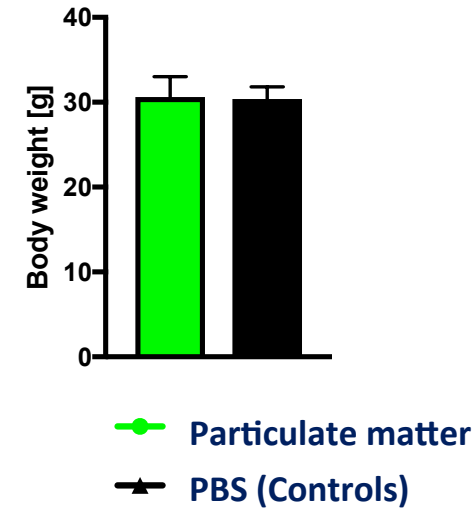
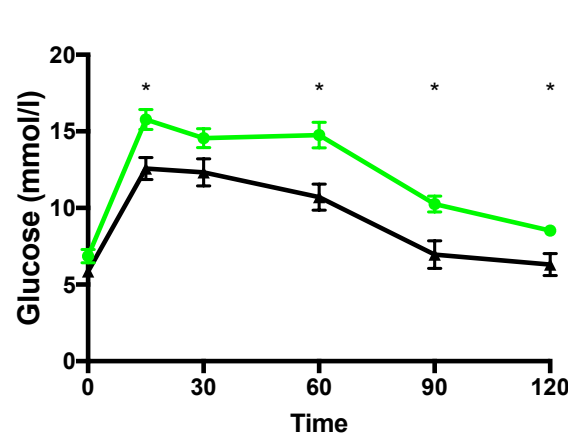
● Diesel exhaust particles
▲ PBS (Controls)



⇒ Insulin secretion defect, no “metabolic disease” phenotype

Question 3:

Is diabetes due to insulin secretion defect or insulin resistance?

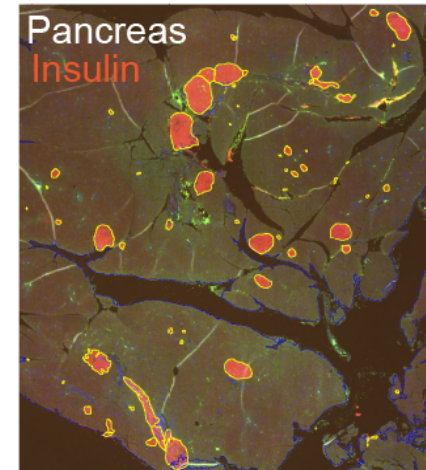
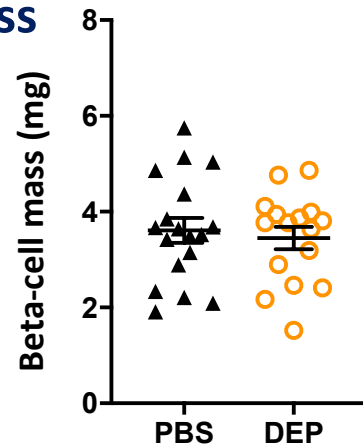


⇒ Insulin secretion defect, no “metabolic disease” phenotype

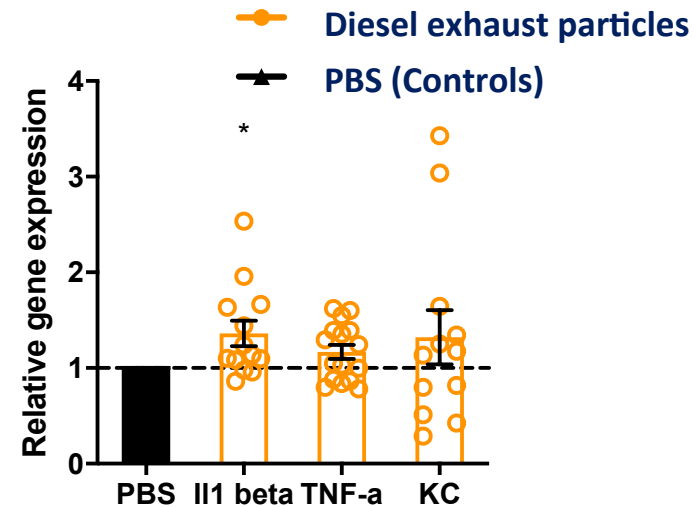
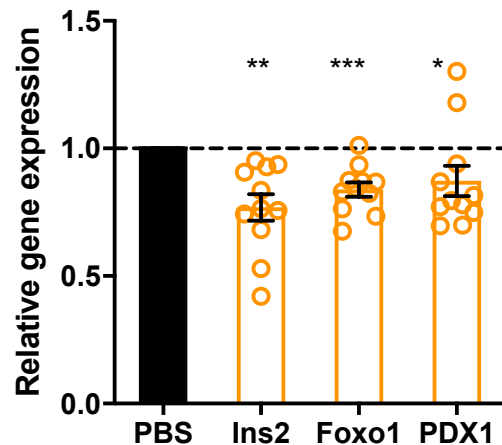
Question 3:

Is diabetes due to insulin secretion defect or insulin resistance?

Beta-cell mass



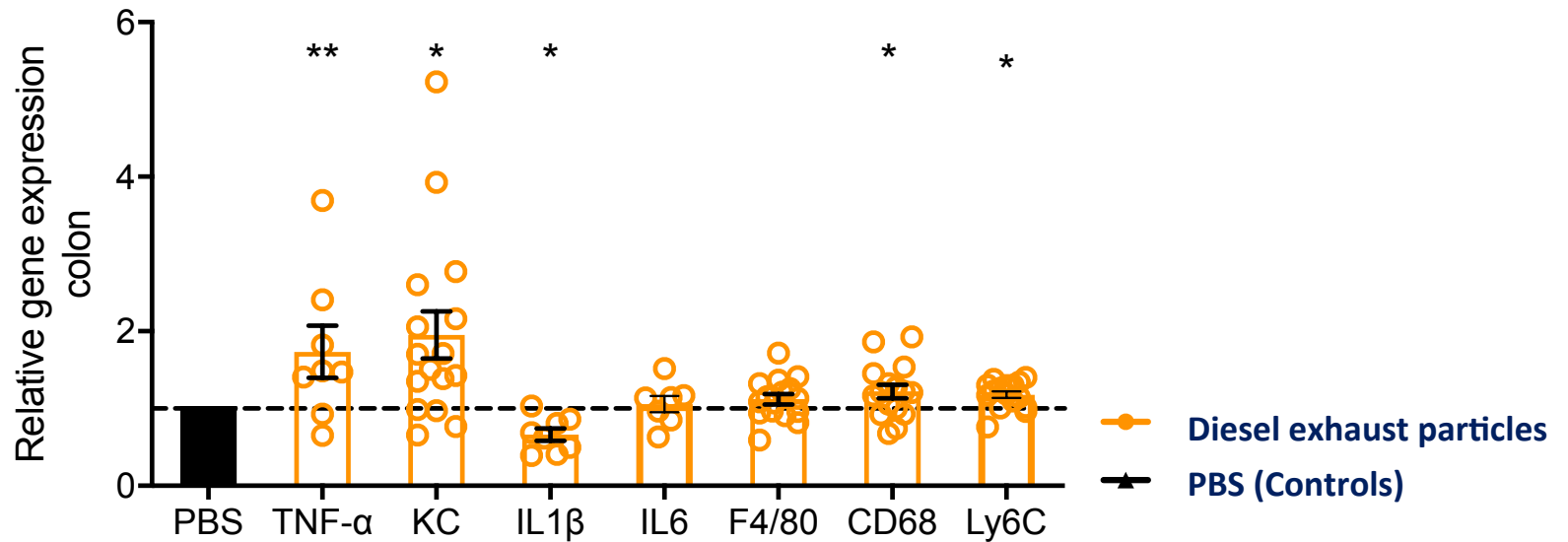
Islet gene expression



⇒ Insulin secretion defect not due to less beta-cells, but functional insulin secretion defect

Question 4: Is innate immunity of the gut involved in air pollution-induced diabetes?

Gut gene expression

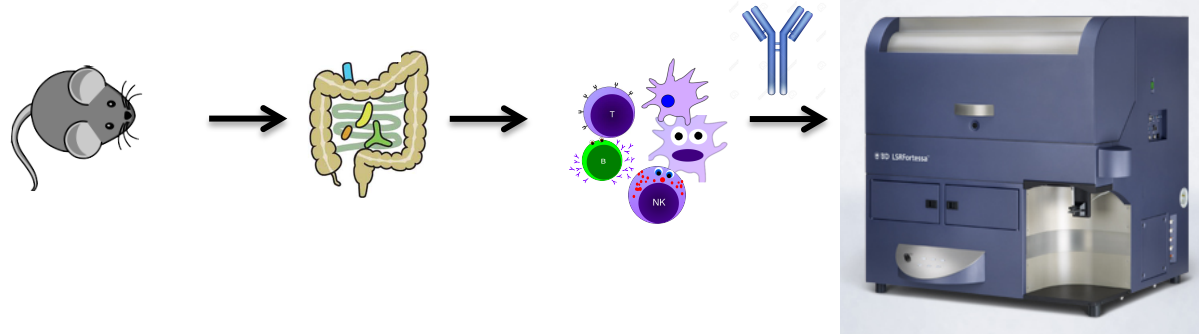


Flow cytometry

Air pollution

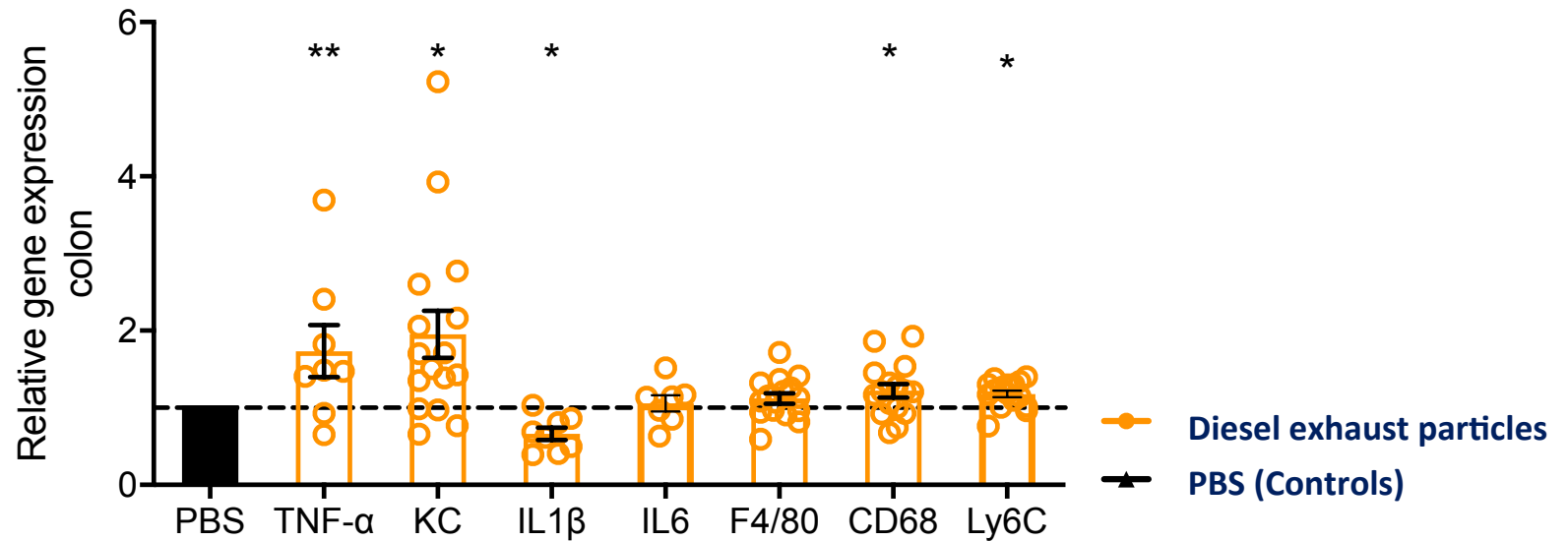
Isolation of lamina propria cells

Staining for flow cytometry

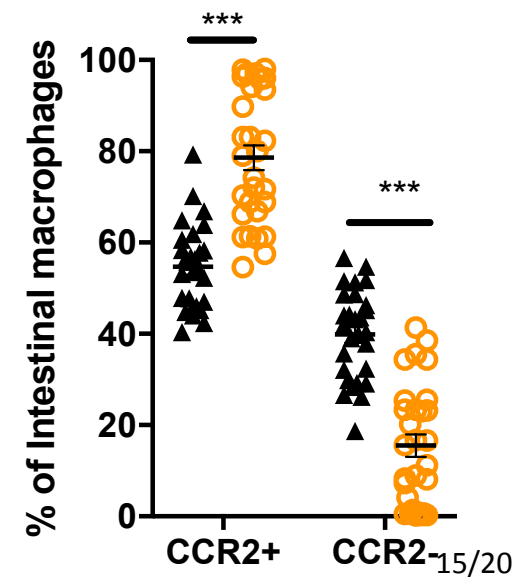
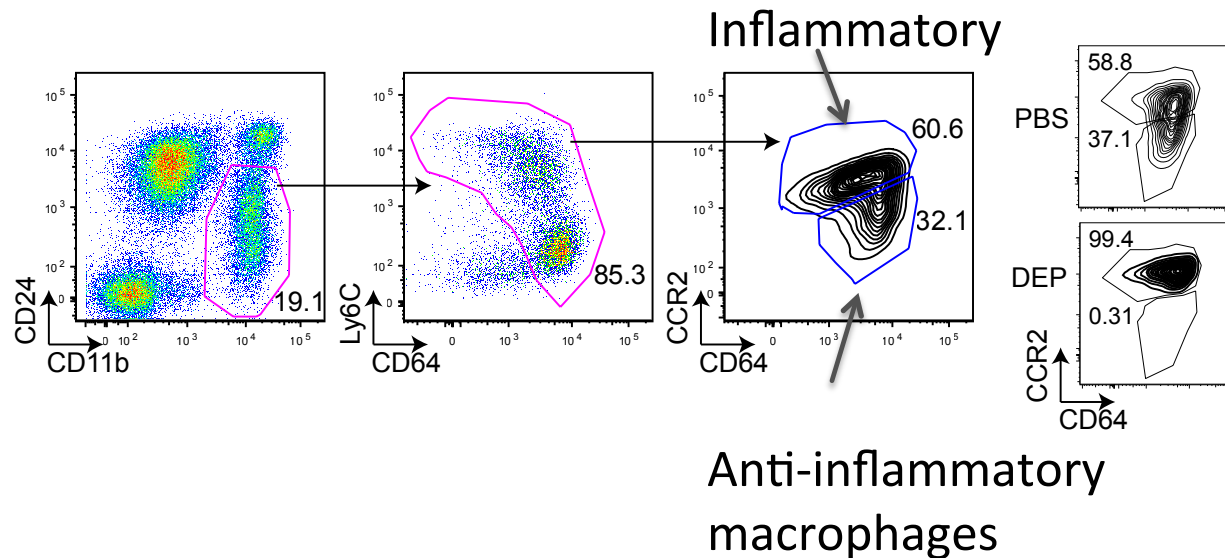


Question 4: Is innate immunity of the gut involved in air pollution-induced diabetes?

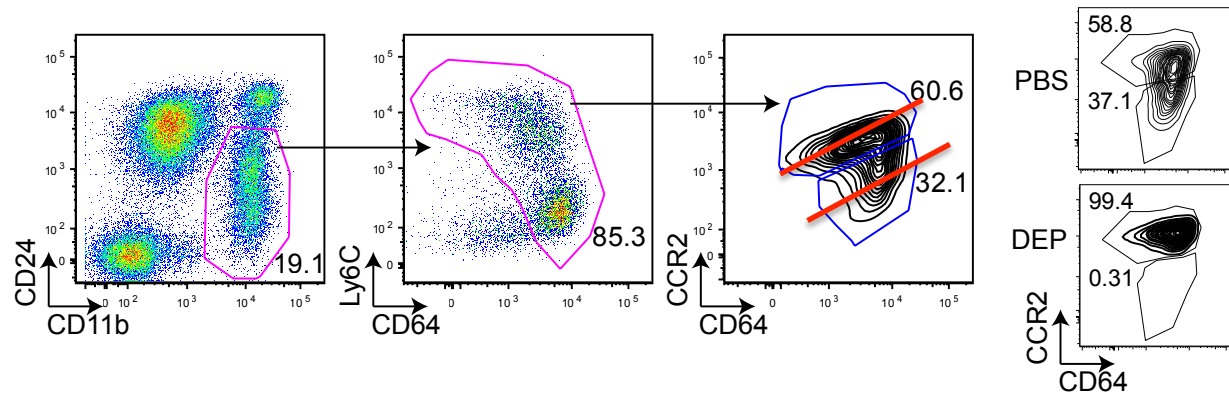
Gut gene expression



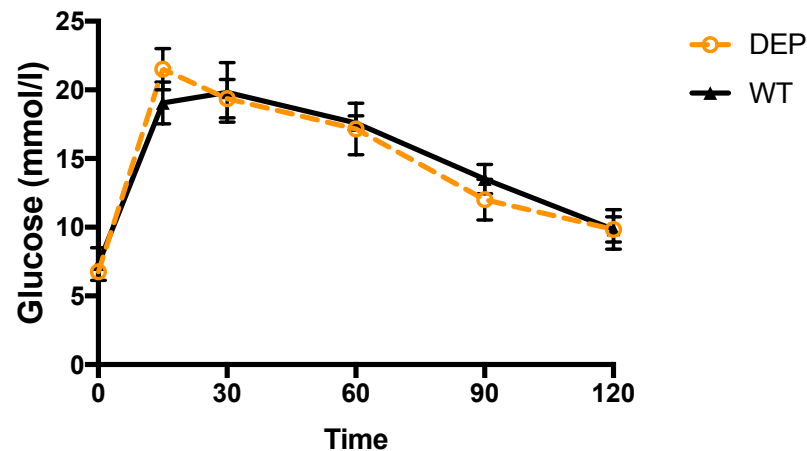
Flow cytometry: loss of anti-inflammatory macrophages



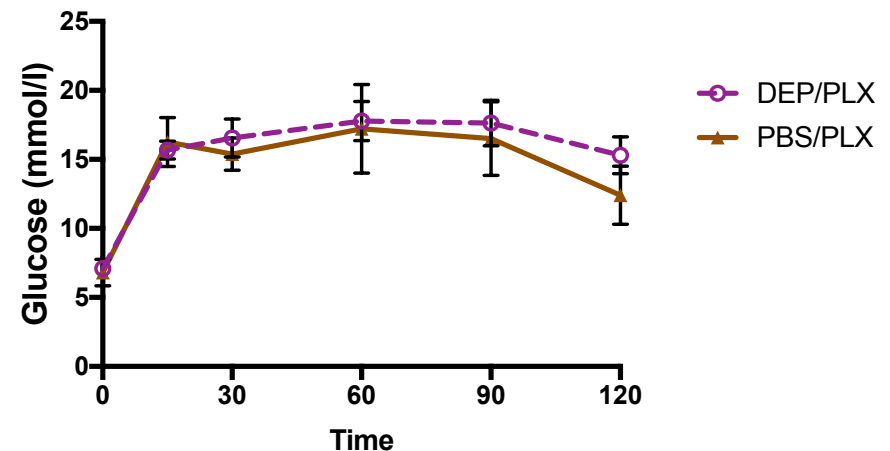
Question 4: Is innate immunity of the gut involved in air pollution-induced diabetes?



CCR2^{-/-} mice
lack inflammatory macrophages



CSF1R inhibitor
depletes both subgroups



⇒ **Loss of anti-inflammatory macrophages upon air pollution; mouse models with low macrophage numbers are**

Question 5: What about the role of adaptive immunity in the gut?

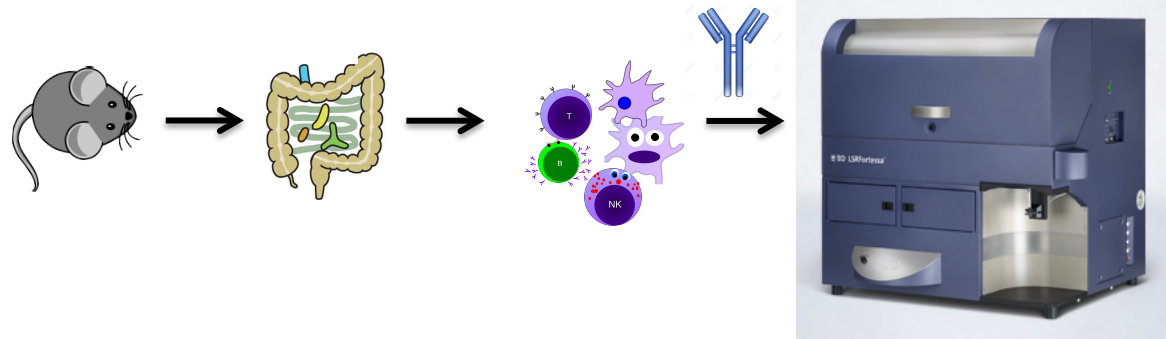
Flow cytometry

=> No changes in adaptive immune cell populations upon air pollution

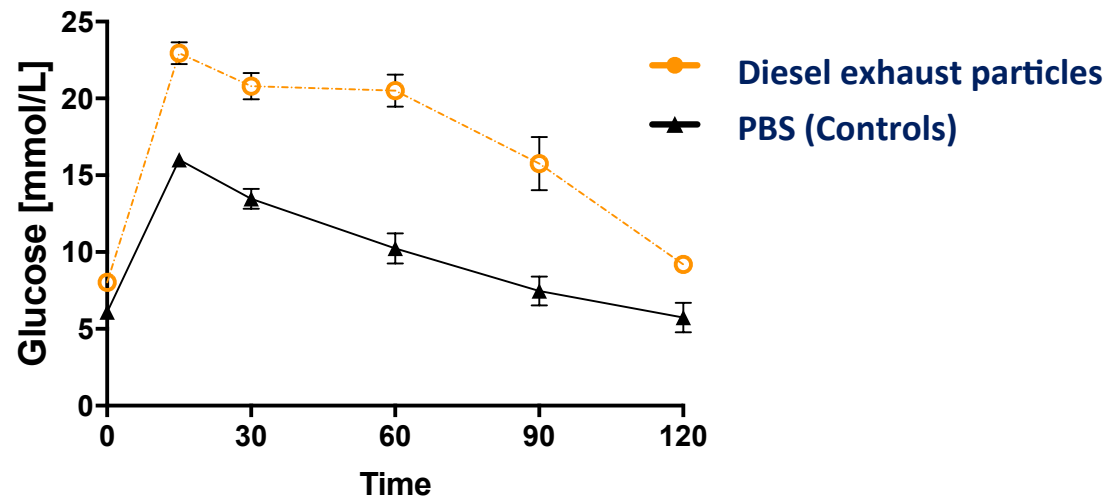
Air pollution

Isolation of lamina propria cells

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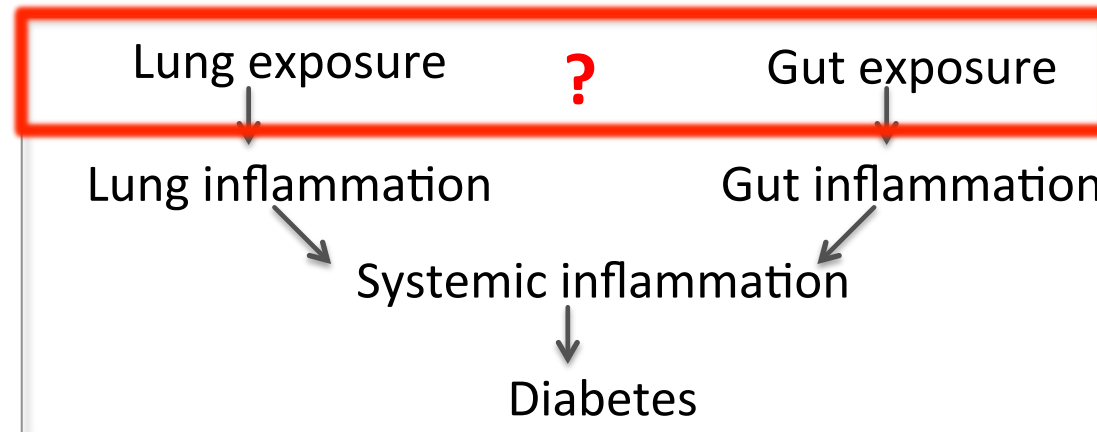
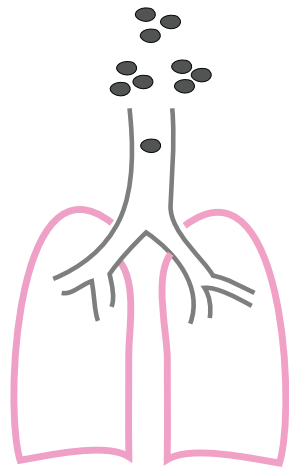


Rag2^{-/-} mice
lack adaptive immunity



**Gut adaptive immunity is not altered upon air pollution;
Adaptive immunity is not required for air pollution-induced diabetes**

Answers to Research Questions



Question 1: Is air pollution-induced diabetes mediated via the lung? ❌

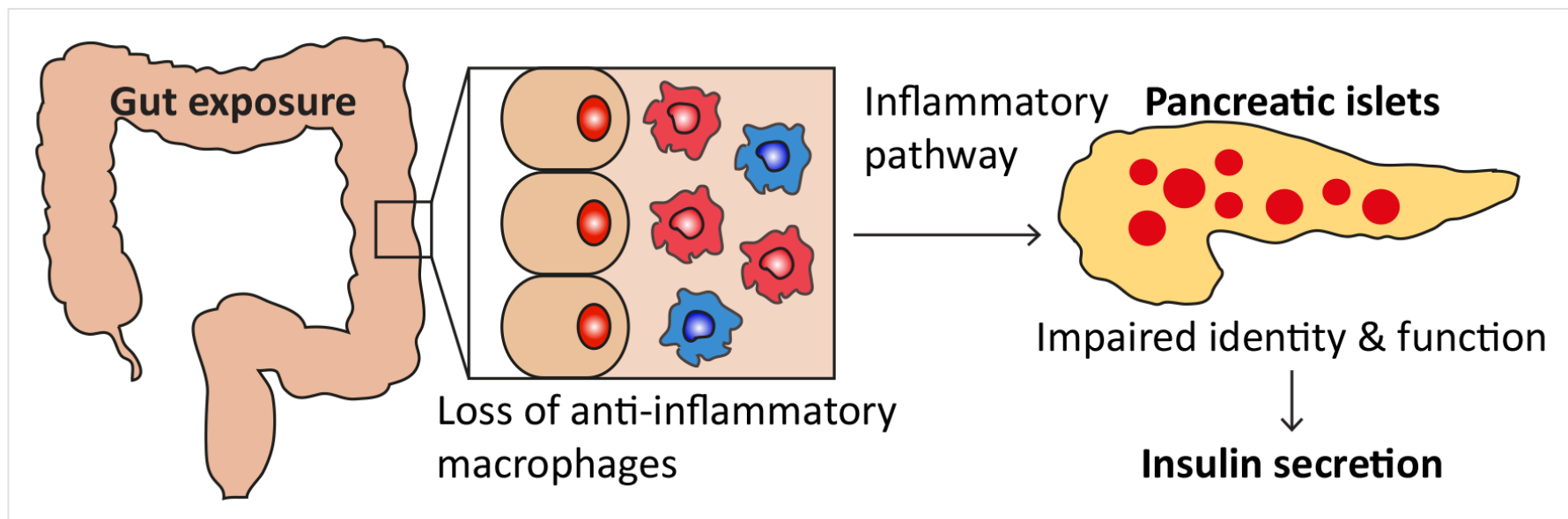
Question 2: Is air pollution-induced diabetes mediated via the gut? ✅

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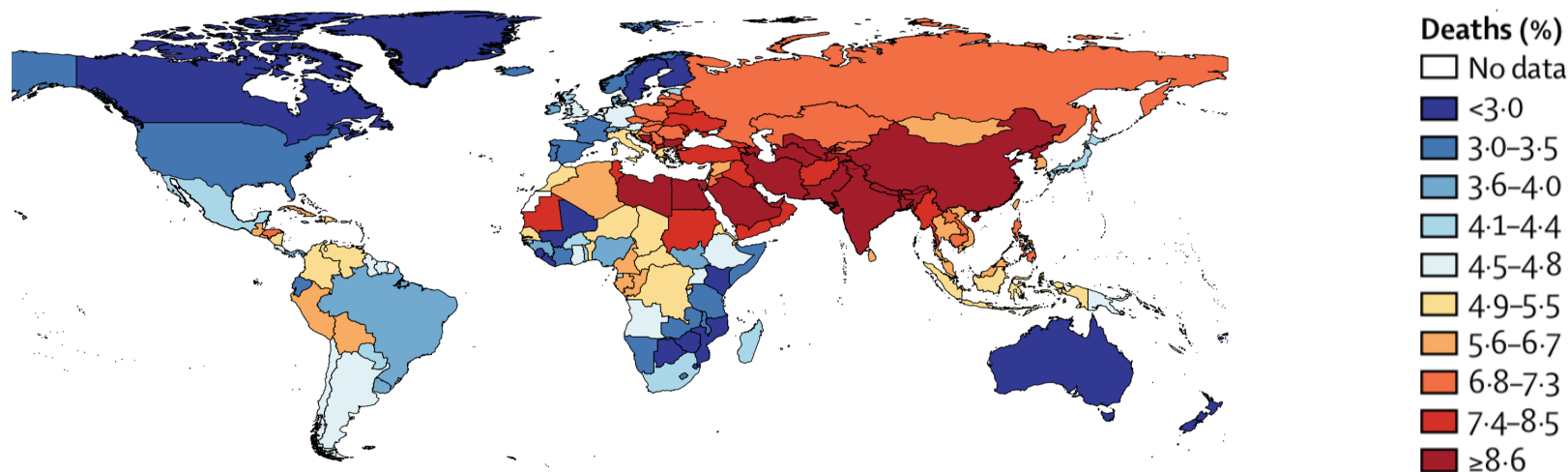
Question 4: Is innate immunity ✅ involved in air pollution-induced diabetes?

Question 5: Is adaptive immunity involved in air pollution-induced diabetes? ❌

Summary



Impact: 16% of global mortality is due to pollution



Thank you for your attention

Laboratory Translational Diabetes



Acknowledgements

Translational Diabetes

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Zora Baumann

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RIVM

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