TNO innovation for life

Beneficial effects of alternate dietary regimen on liver inflammation, atherosclerosis and renal activation

Peter Wielinga, Gopala Yakala, Peter Heeringa, Robert Kleemann, Teake Kooistra


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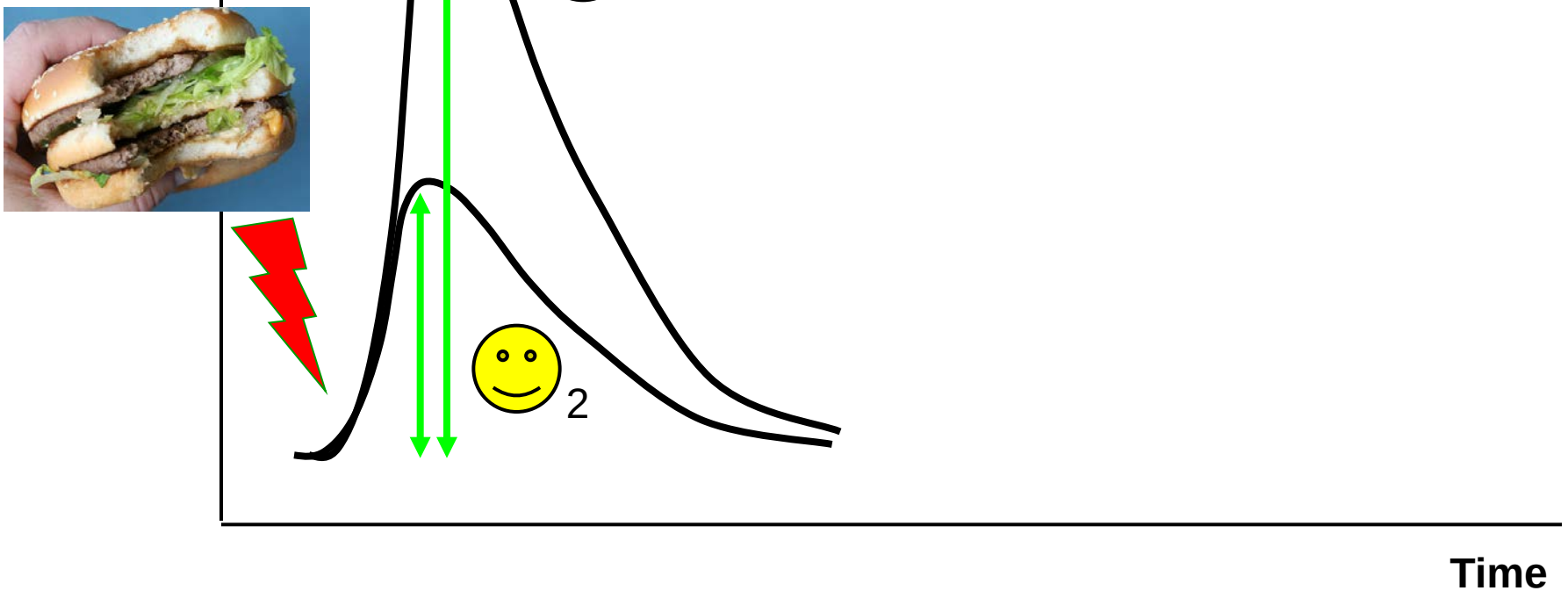
Metabolic flexibility

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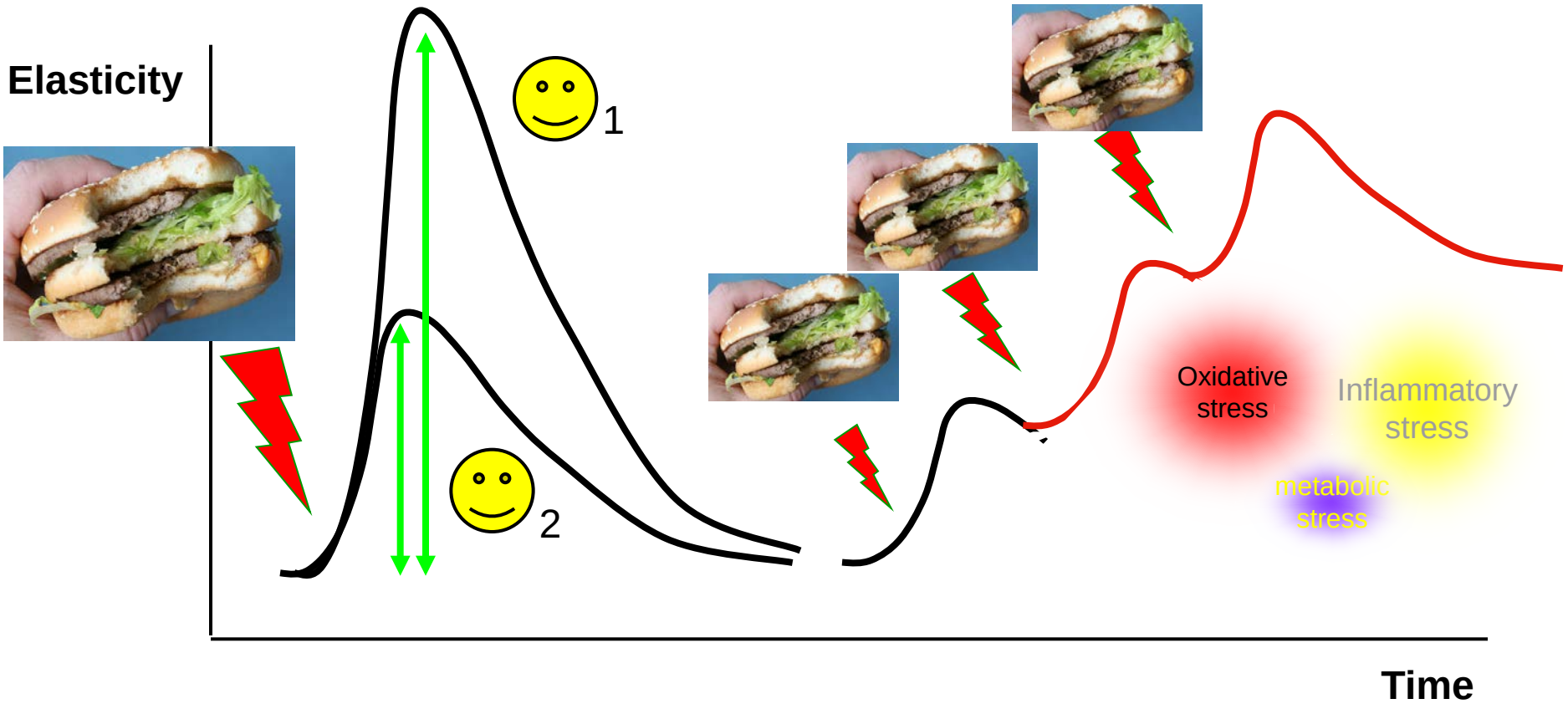
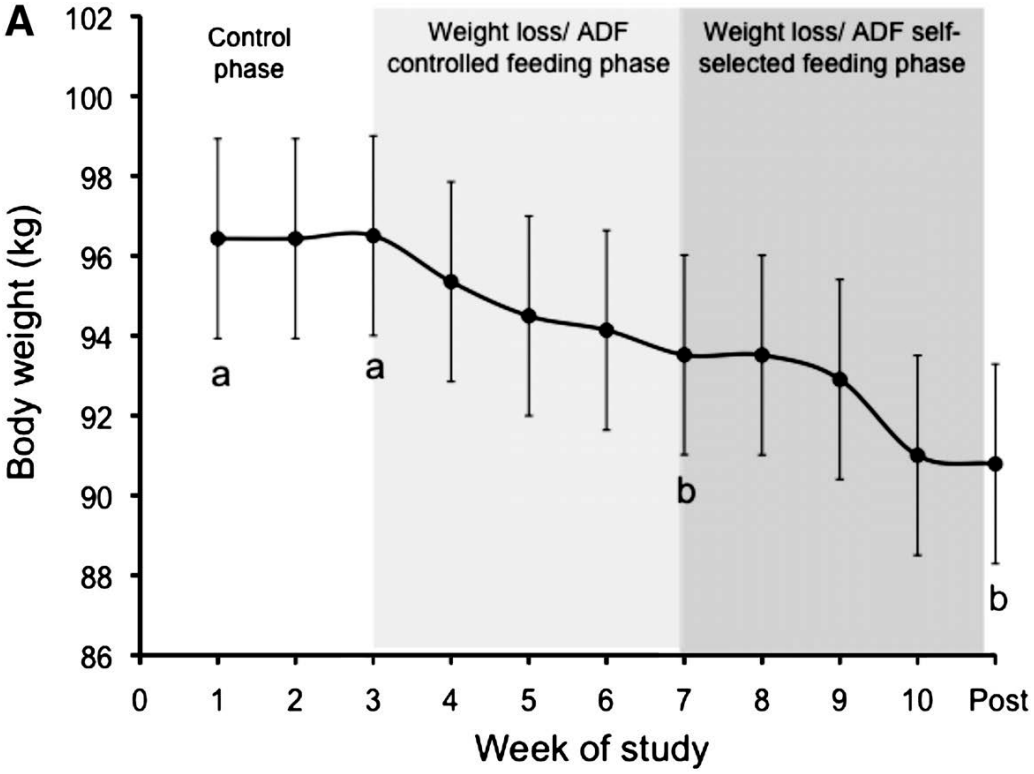
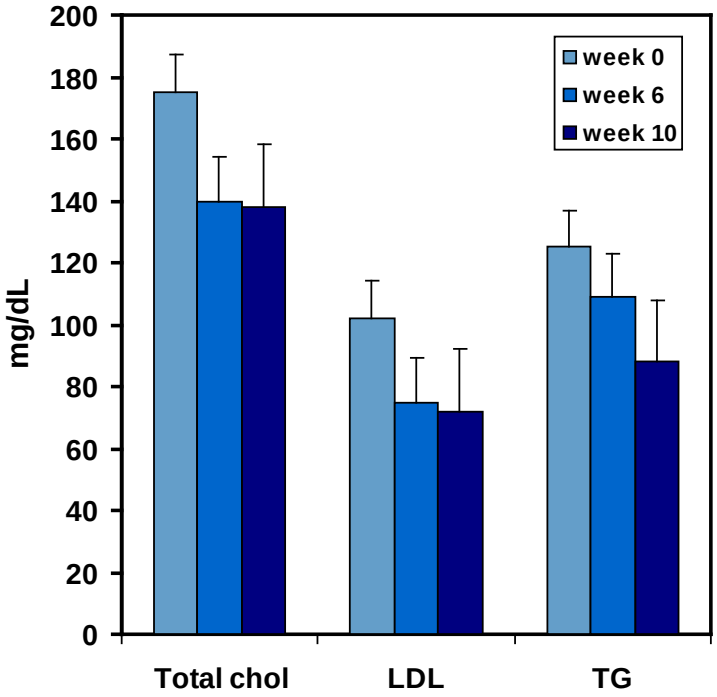
Chronic metabolic overload leads to disease, such as diabetes and CVD



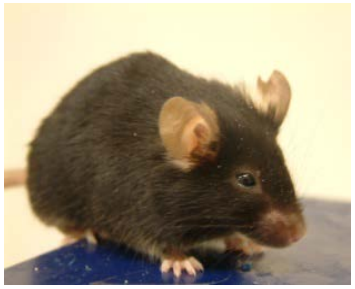

Alternate-day fasting successful strategy to reduce body weight and CVD risk factors





› **Compliance difficult**

(Varady et al, Am J Clin Nutr 2009)

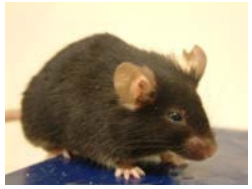
New approach

- **Hypothesis**: Alternate dietary composition is beneficial for metabolic health

- **Experiment:** Effects of alternating high cholesterol diet with cholesterol-free diet on liver health, macro- and microvascular function in humanized mouse model for atherosclerosis, the ApoE*3Leiden (E3L) mice


Experimental set-up

16 weeks



High cholesterol diet (HC)

disease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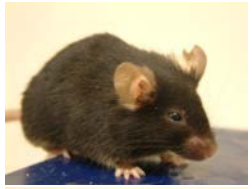
Experimental set-up

16 weeks

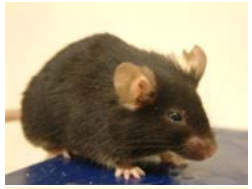



High cholesterol diet (HC) → disease

Cholesterol-free diet (CON) → healthy


Experimental set-up

16 weeks



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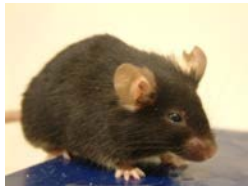
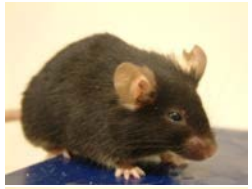


Alternating HC /CON (ALT) → disease??

4d 3d 4d 3d 4d 3d 4d 3d etc

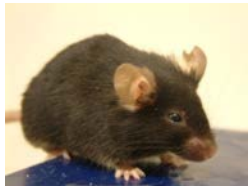

Experimental set-up

16 weeks

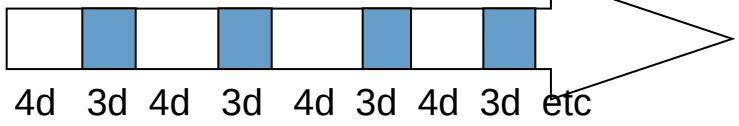


High cholesterol diet (HC) → disease

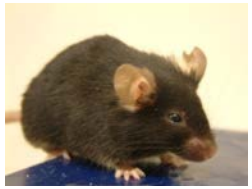
Cholesterol-free diet (CON) → healthy



Alternating HC /CON (ALT)



→ disease??



Medium cholesterol diet (MC) → Similar cholesterol intake ALT group

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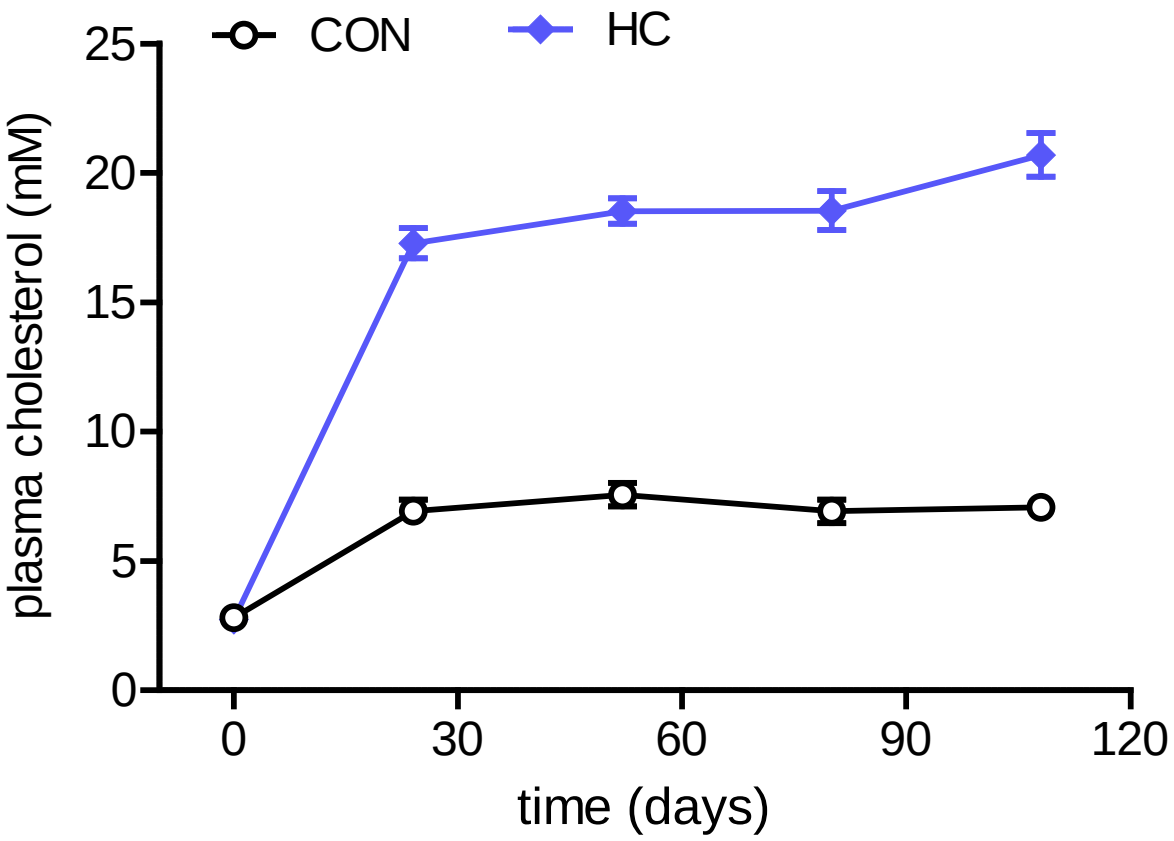
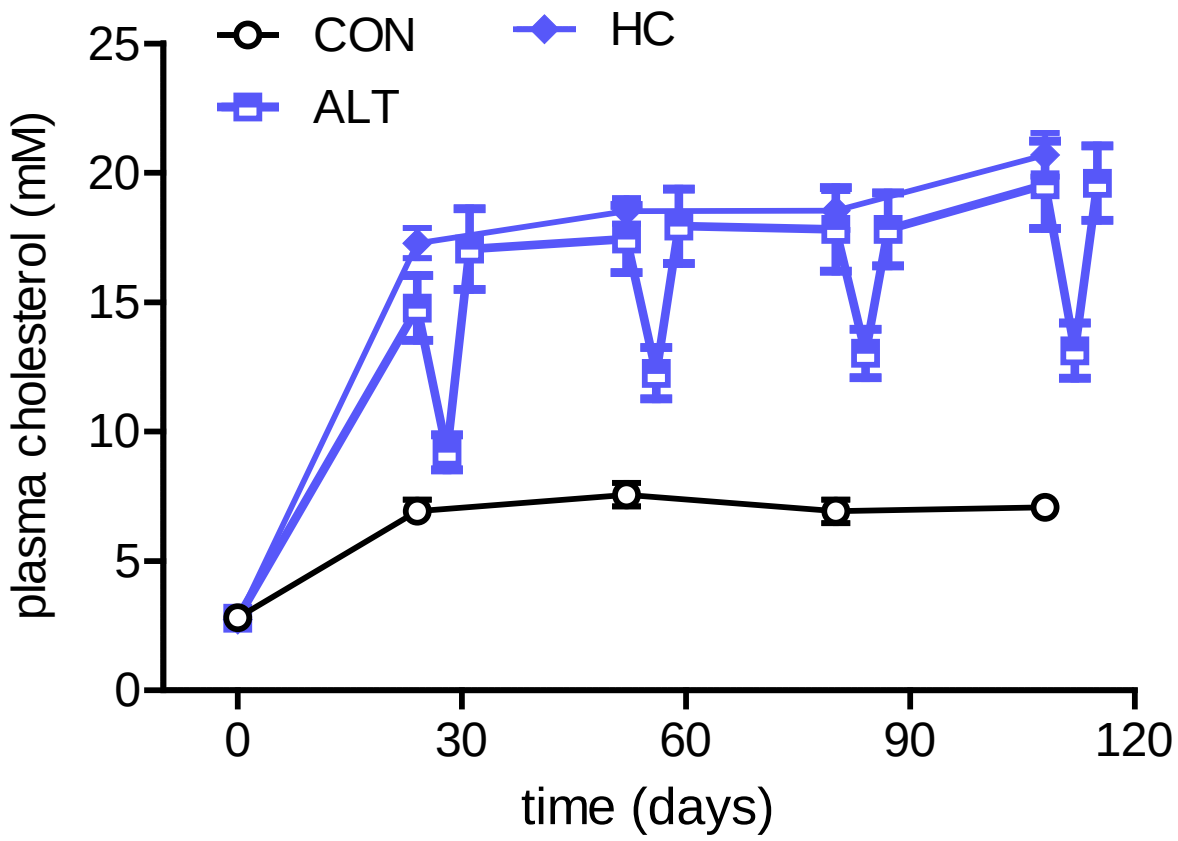
Plasma cholesterol



Wielinga et al., PLoS ONE, 2011


Plasma cholesterol



Wielinga et al., PLoS ONE, 2011

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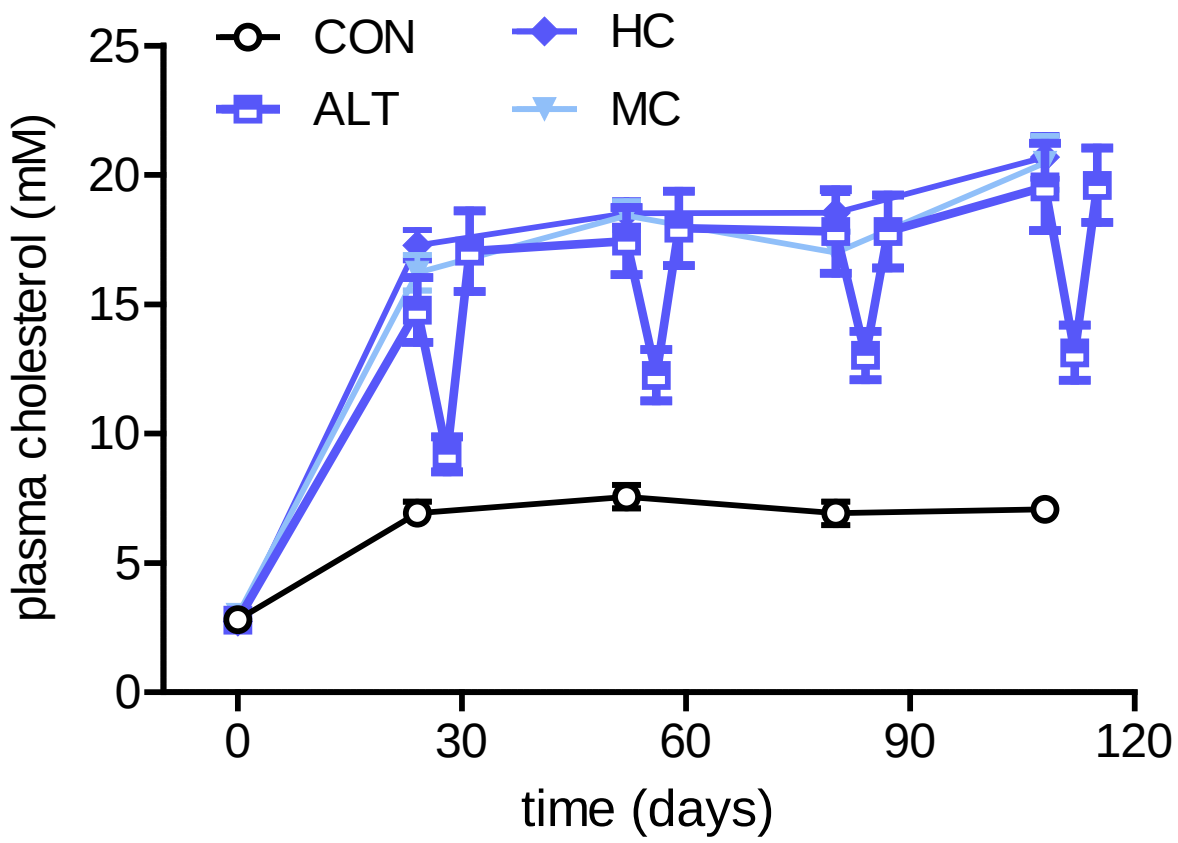
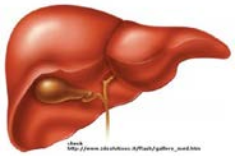
Plasma cholesterol

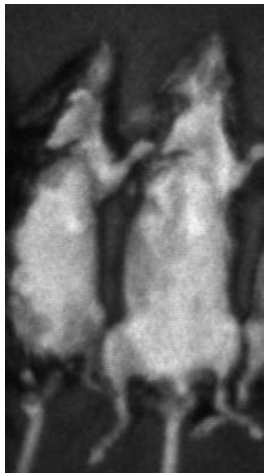
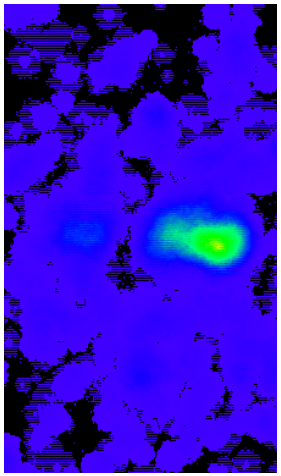


Wielinga et al., PLoS ONE, 2011

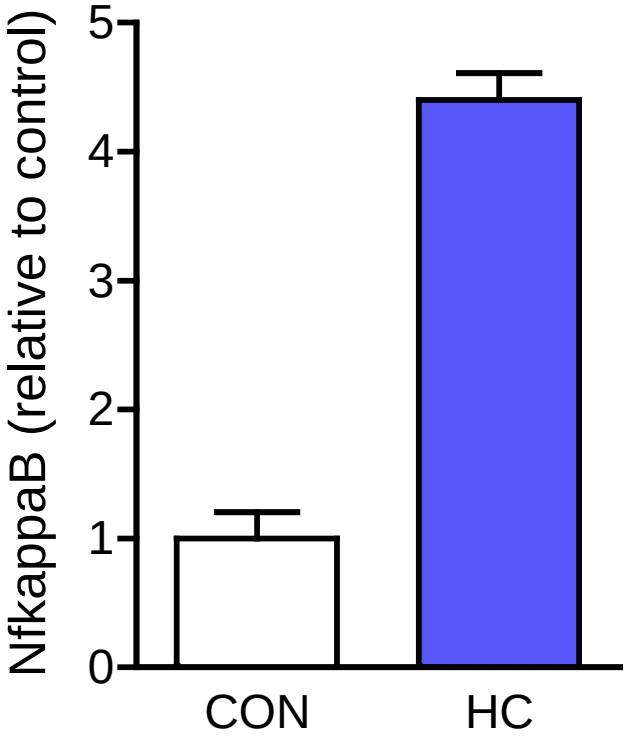




High cholesterol induces liver inflammation

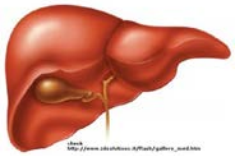



Con **1%** **Con** **1%**

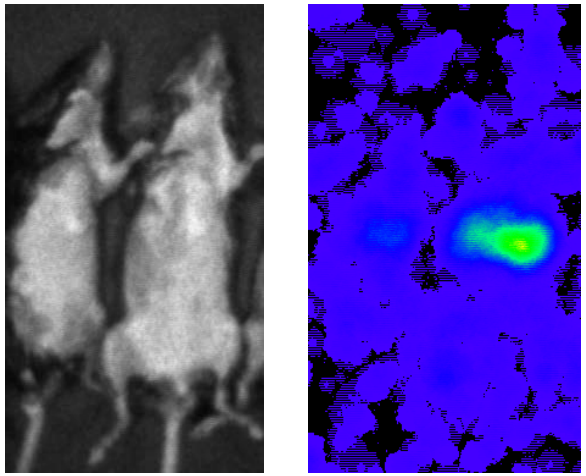


Wielinga et al., PLoS ONE, 2011

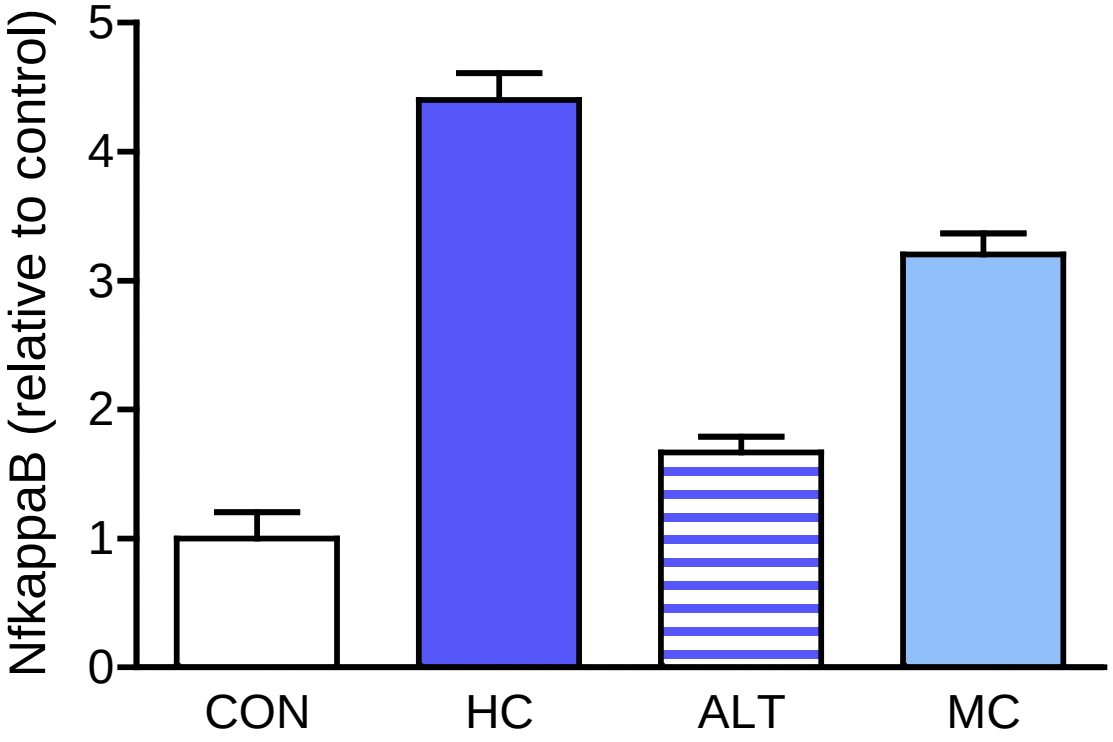




Alternate diet normalizes liver inflammation

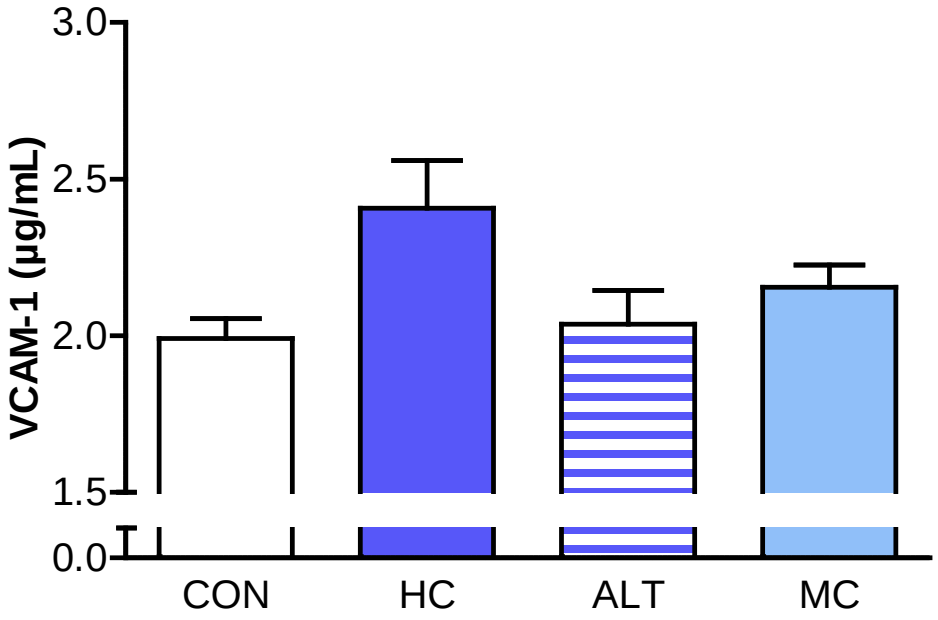


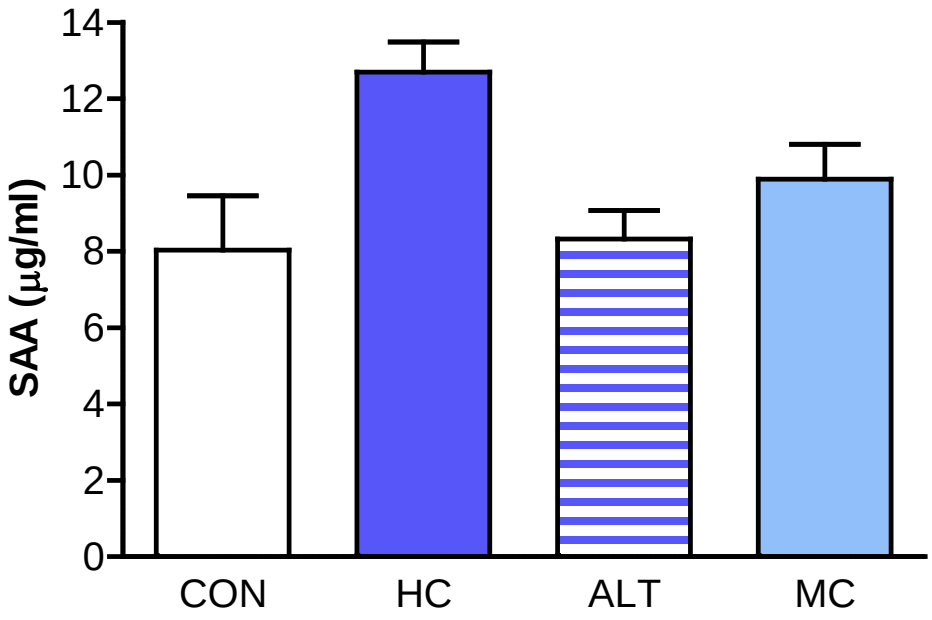
Con **1%** **Con** **1%**



Wielinga et al., PLoS ONE, 2011

Vascular and systemic inflammation normalized by ALT





Wielinga et al., PLoS ONE, 2011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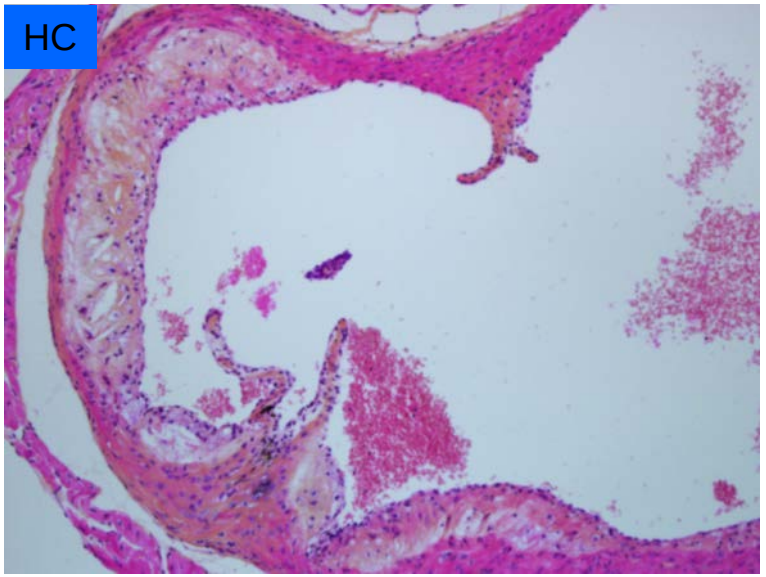
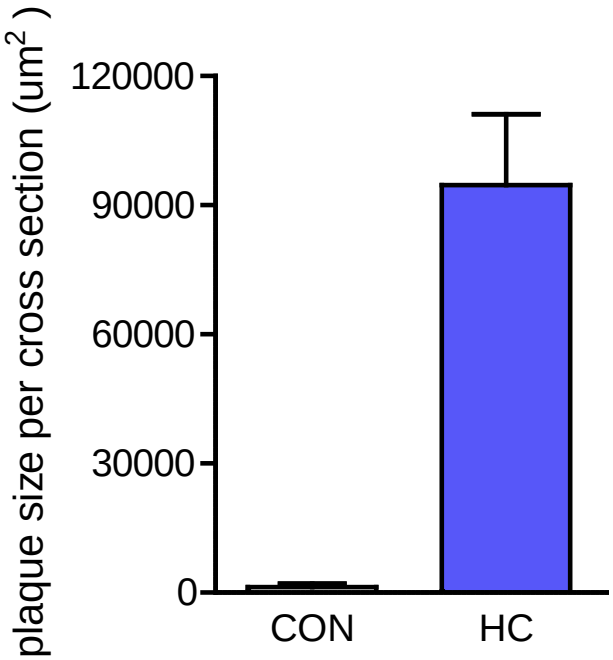
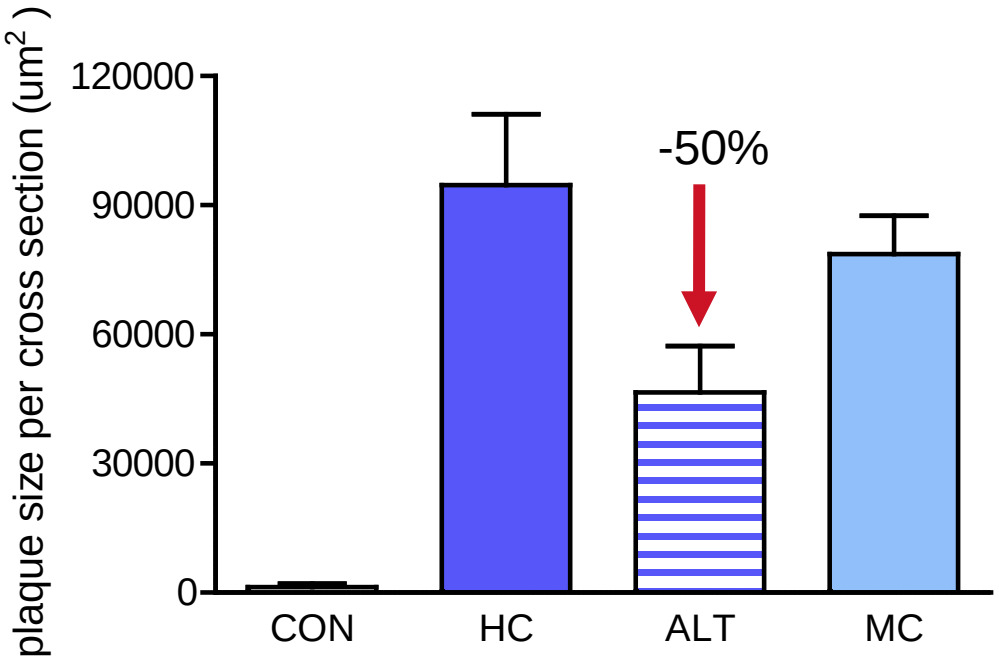
HC results in severe atherosclerosis

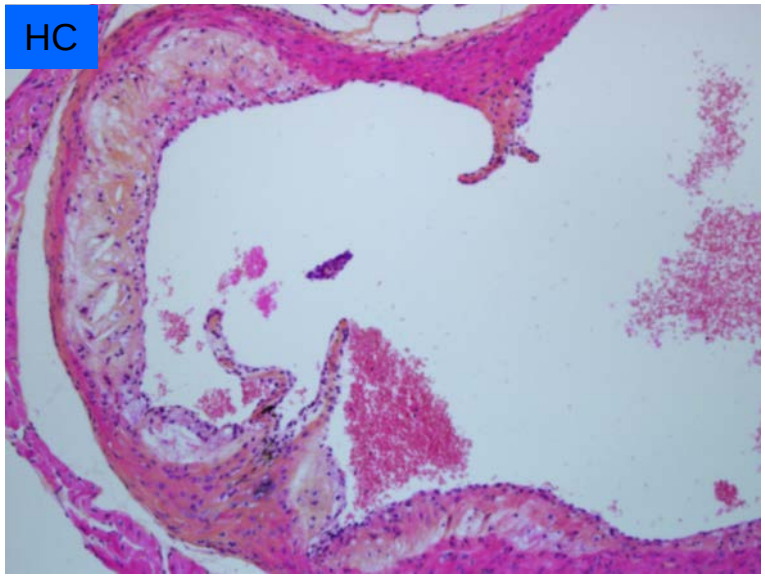


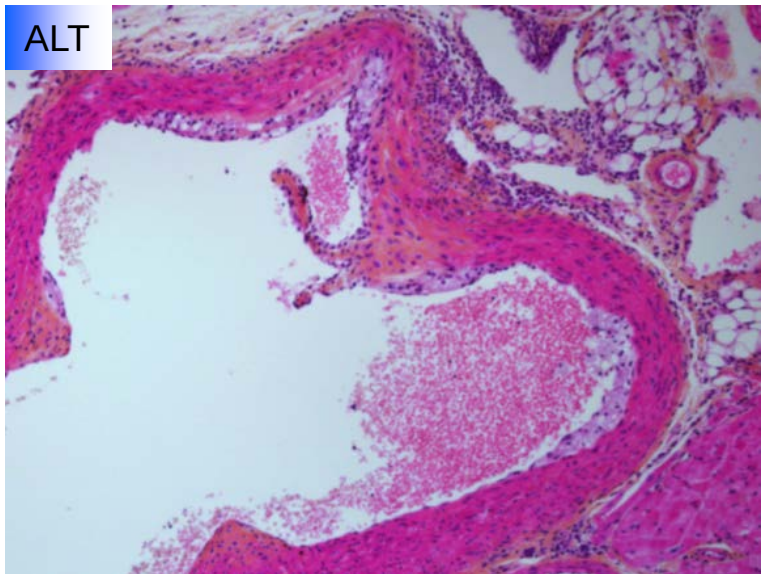


Wielinga et al., PLoS ONE, 2011

ALT strongly reduces atherosclerosis



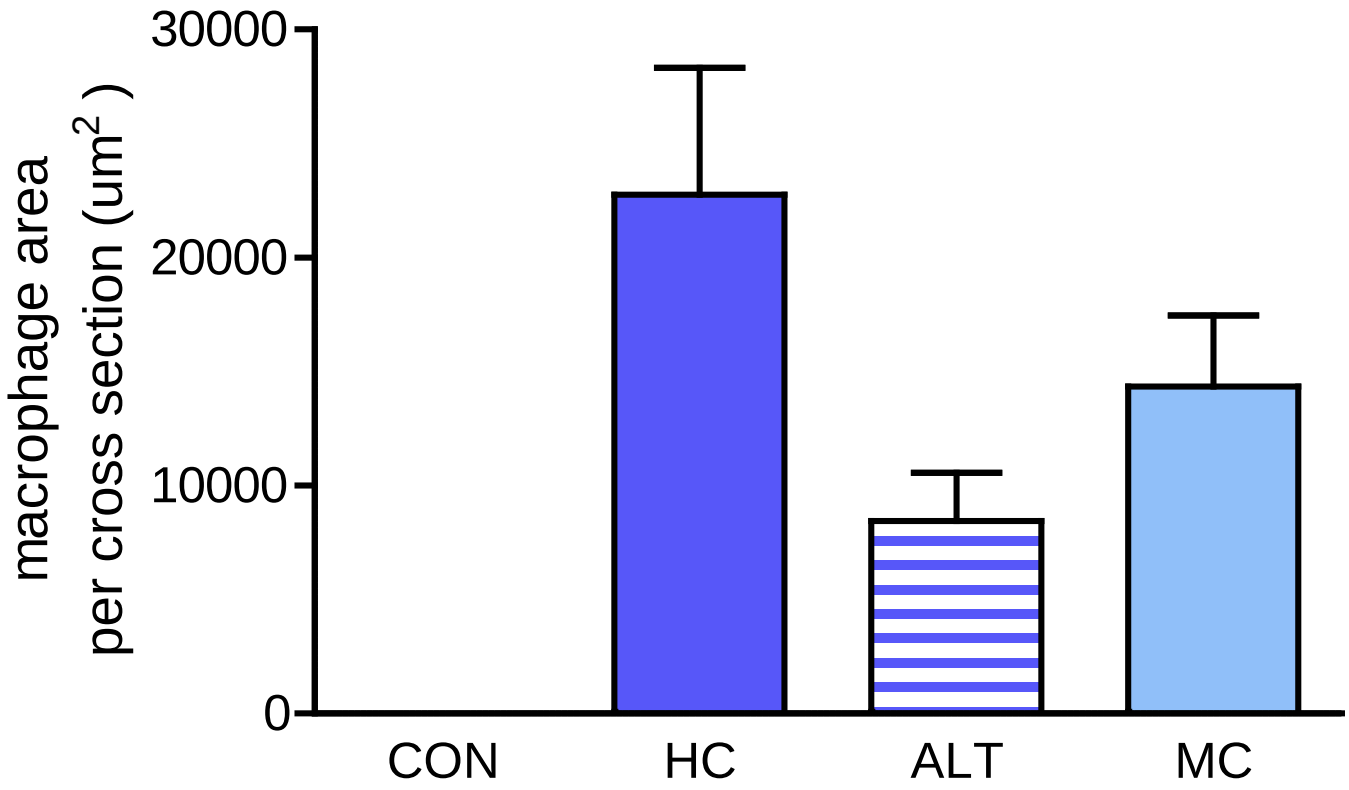




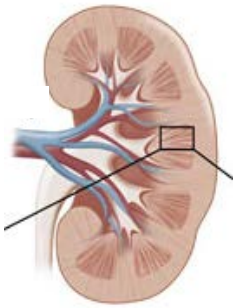
Wielinga et al., PLoS ONE, 2011



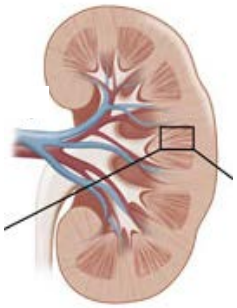
Lesional macrophages area strongly reduced by ALT



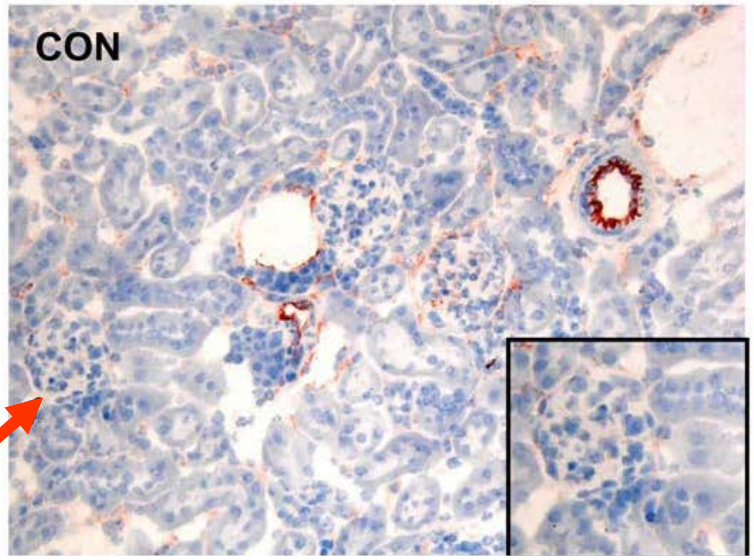
Wielinga et al., PLoS ONE, 2011

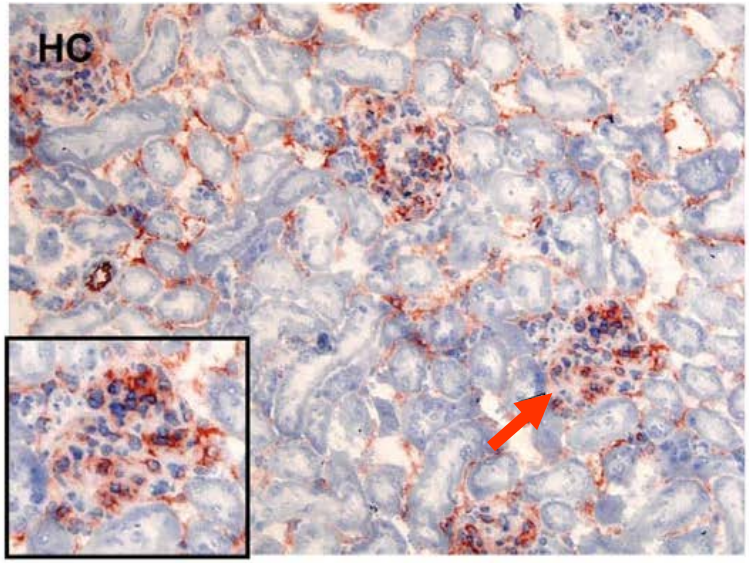


Wielinga et al.,
PLoS ONE, 2011

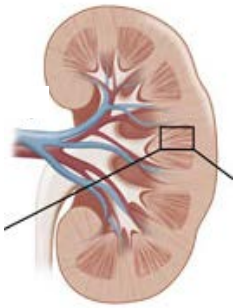


VCAM-1 expression in kidney by high cholesterol





Wielinga et al., PLoS ONE, 2011



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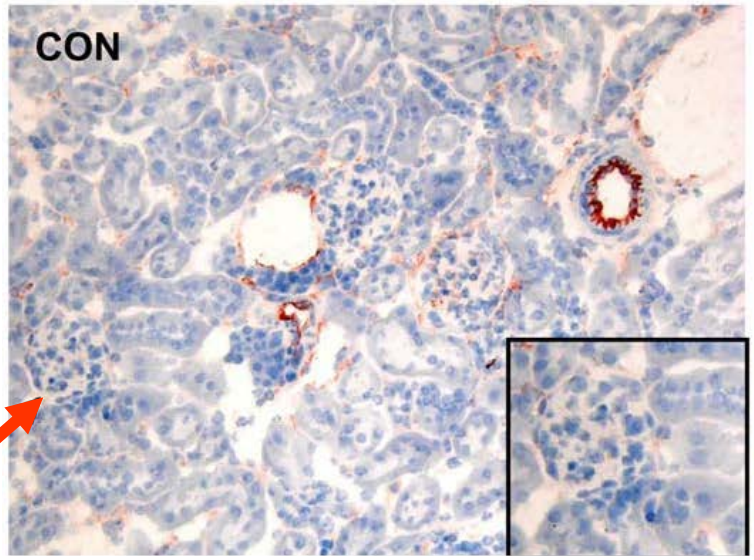
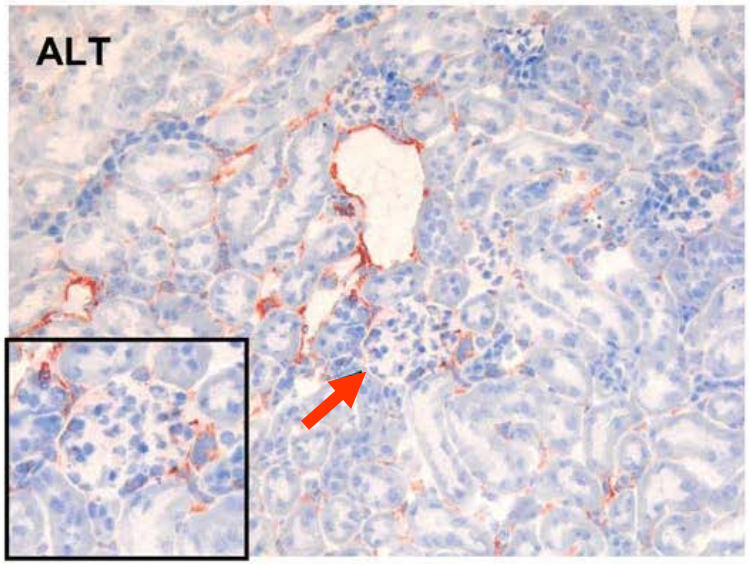
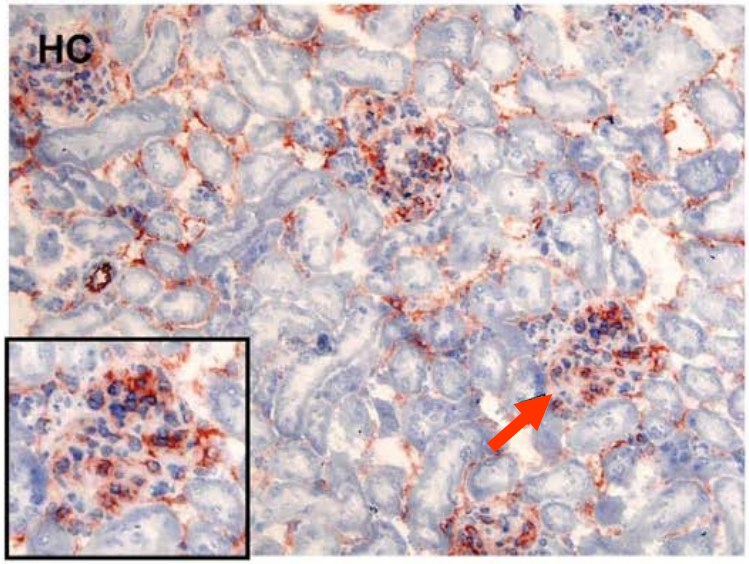
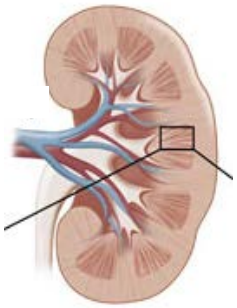


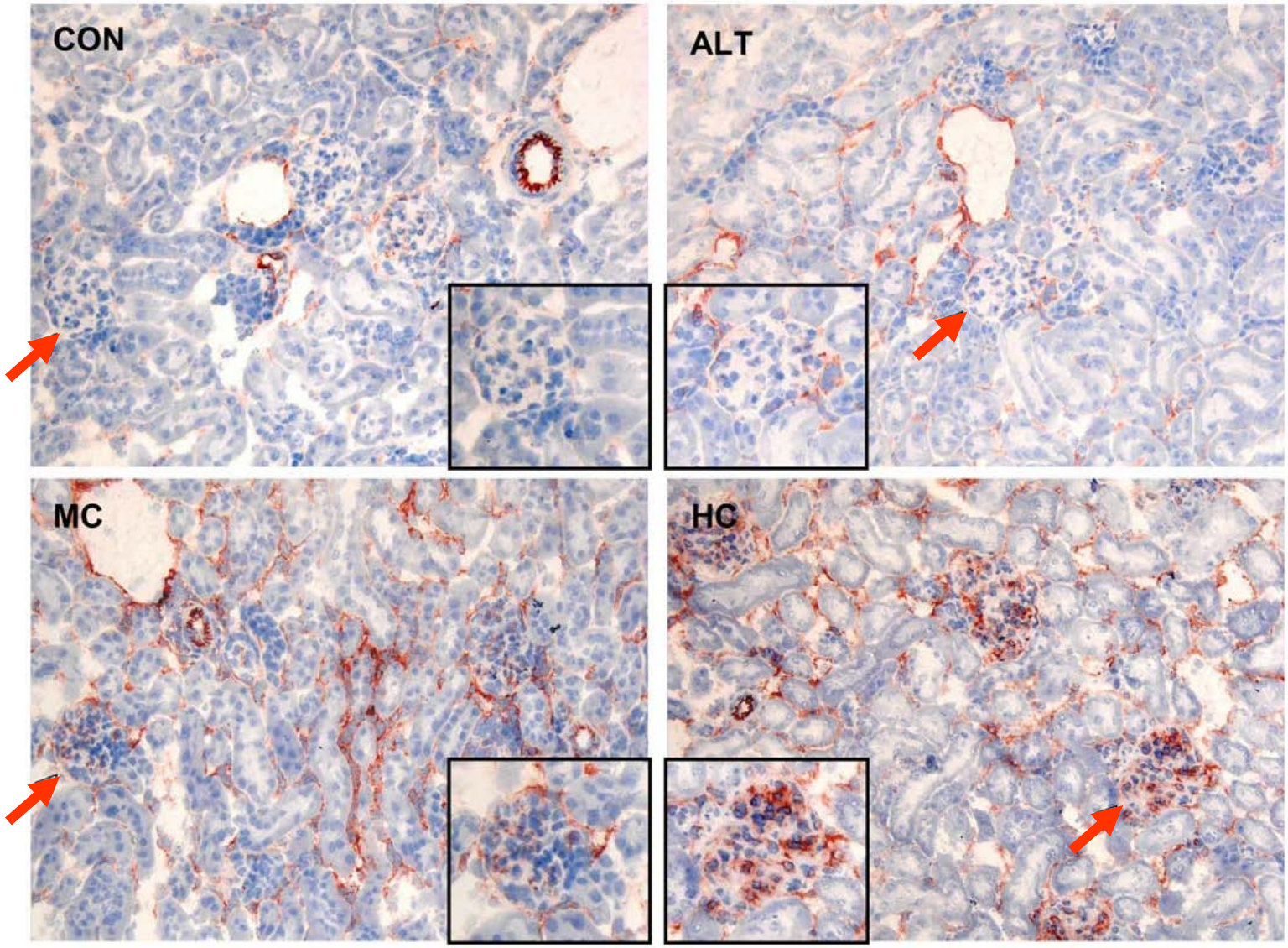




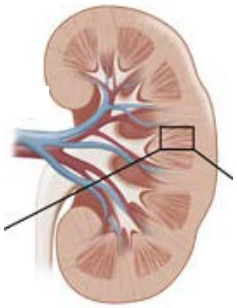
Wielinga et al., PLoS ONE, 2011



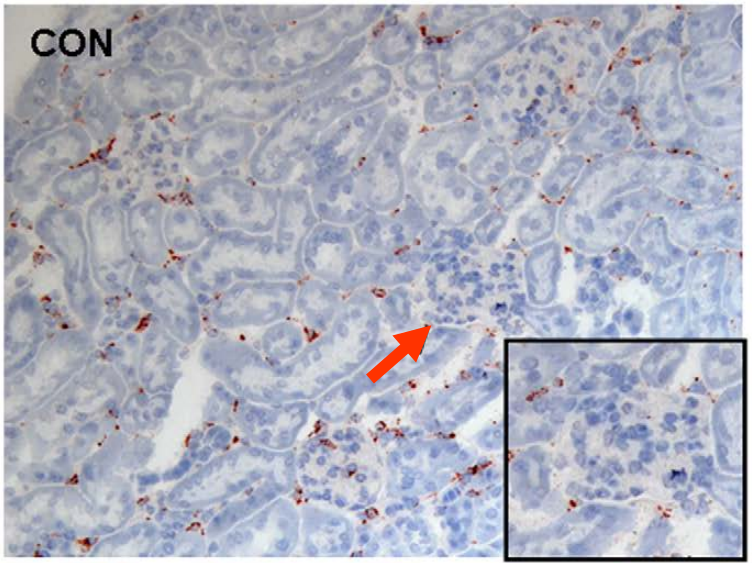
VCAM-1 expression in kidney normalized by ALT

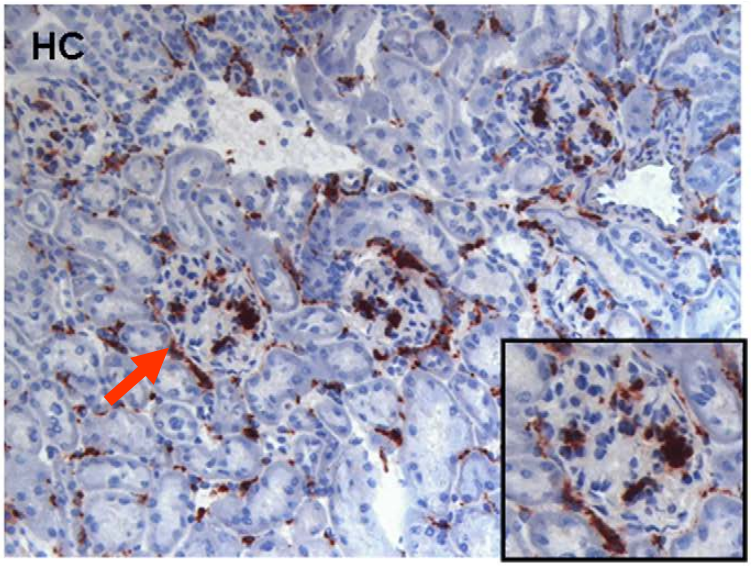


Wielinga et al., PLoS ONE, 2011

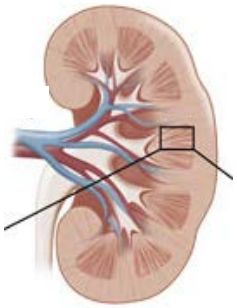


Macrophage accumulation by high cholesterol





Wielinga et al., PLoS ONE, 2011



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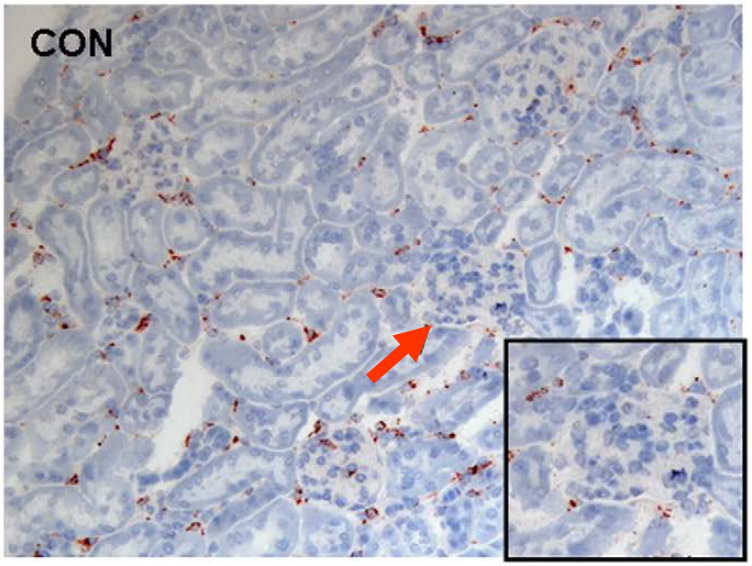
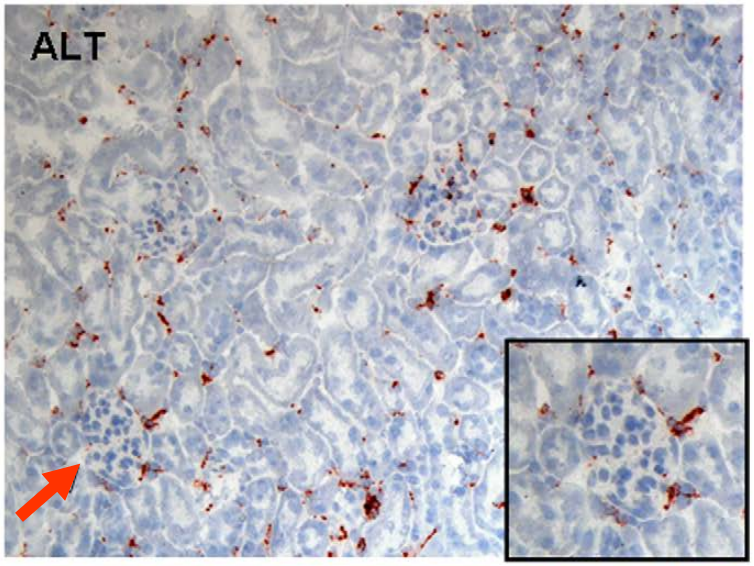
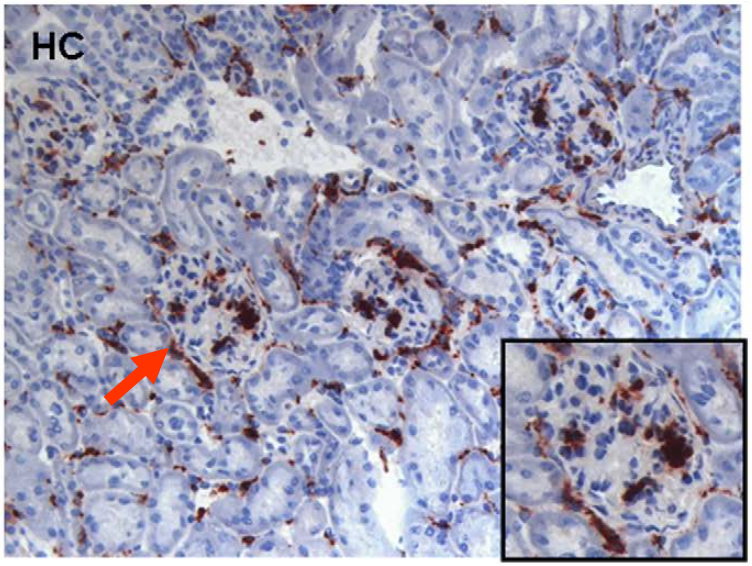
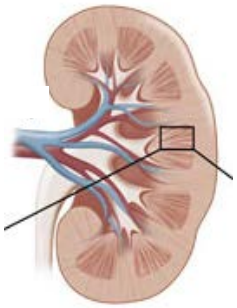


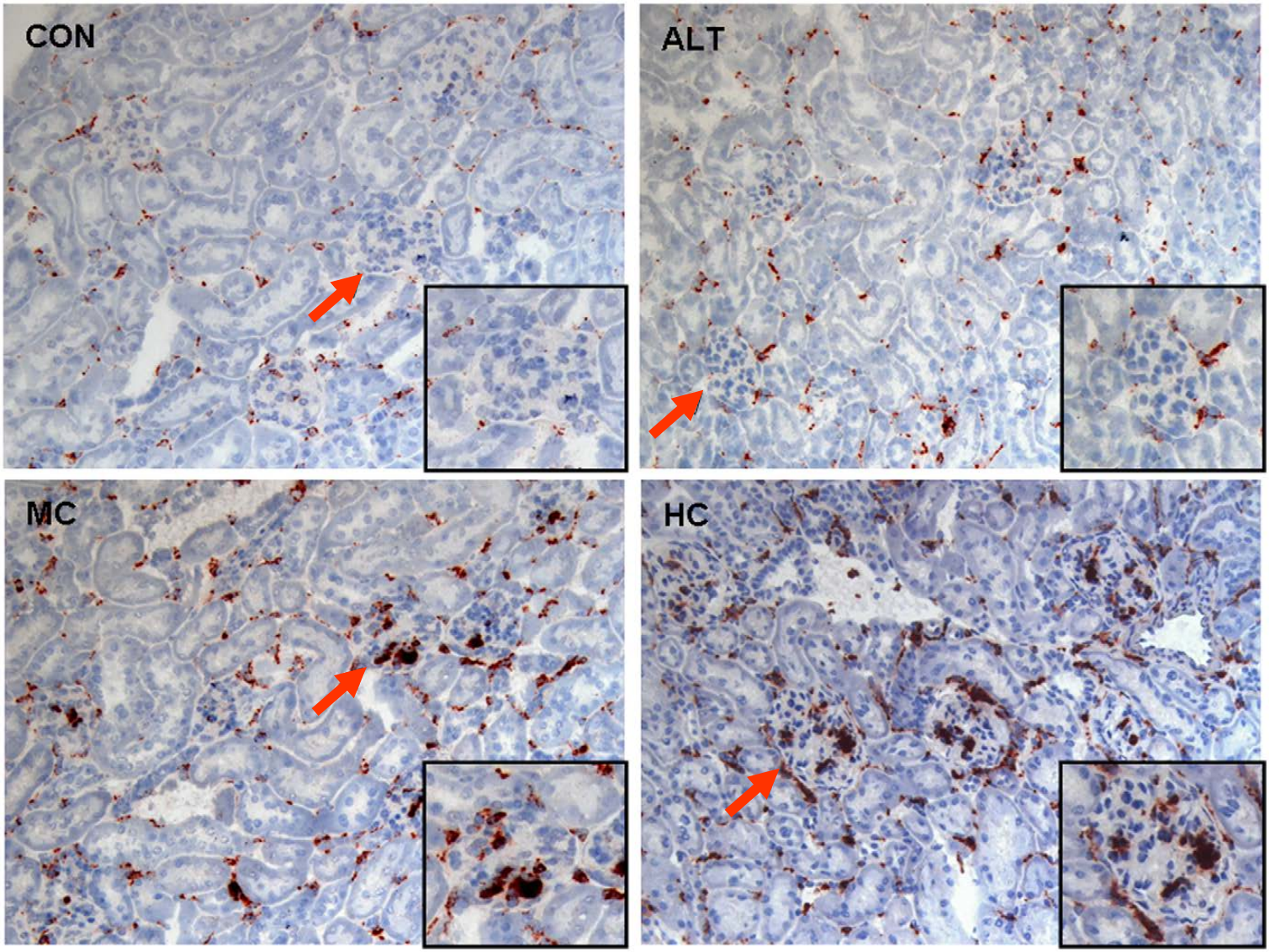




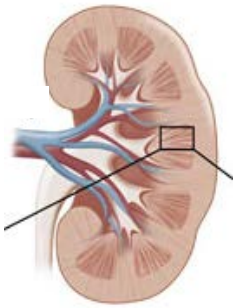
Wielinga et al., PLoS ONE, 2011



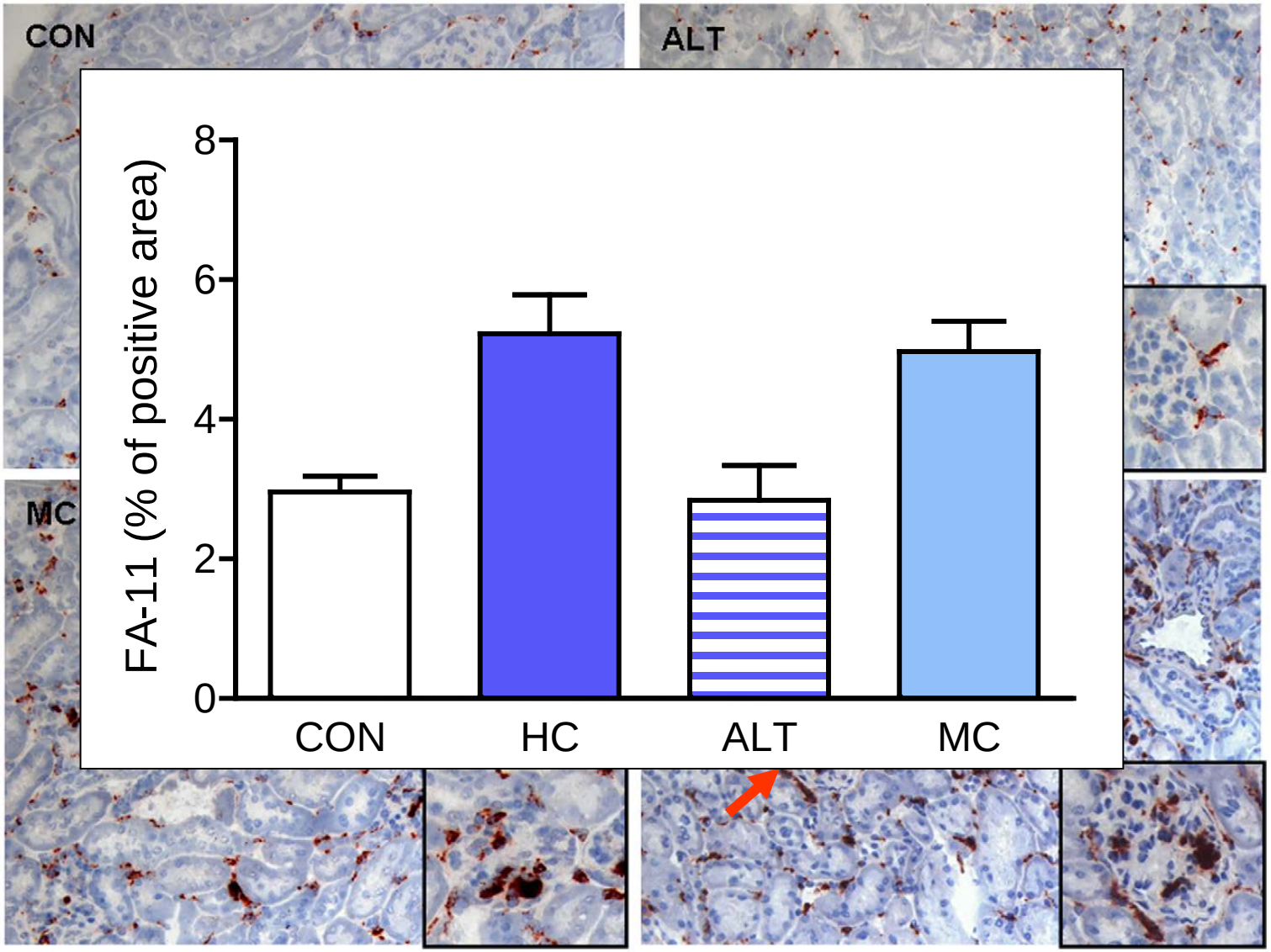
Macrophage accumulation normalized by ALT



Wielinga et al., PLoS ONE, 2011



Macrophage accumulation normalized by ALT



Wielinga et al., PLoS ONE, 2011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Summary

- Alternating high cholesterol with cholesterol-free diet reproduced most of the beneficial effects of cholesterol-free diet:
  - Systemic, hepatic, vascular and renal inflammation strongly diminished
  - Reduced atherosclerosis by 50%
- Findings suggest that alternating diet regimens can effectively modulate metabolic risk factors → potential attractive strategy to protect against adverse effects of unhealthy diets
- Next steps
  - Human study
  - Mechanism?

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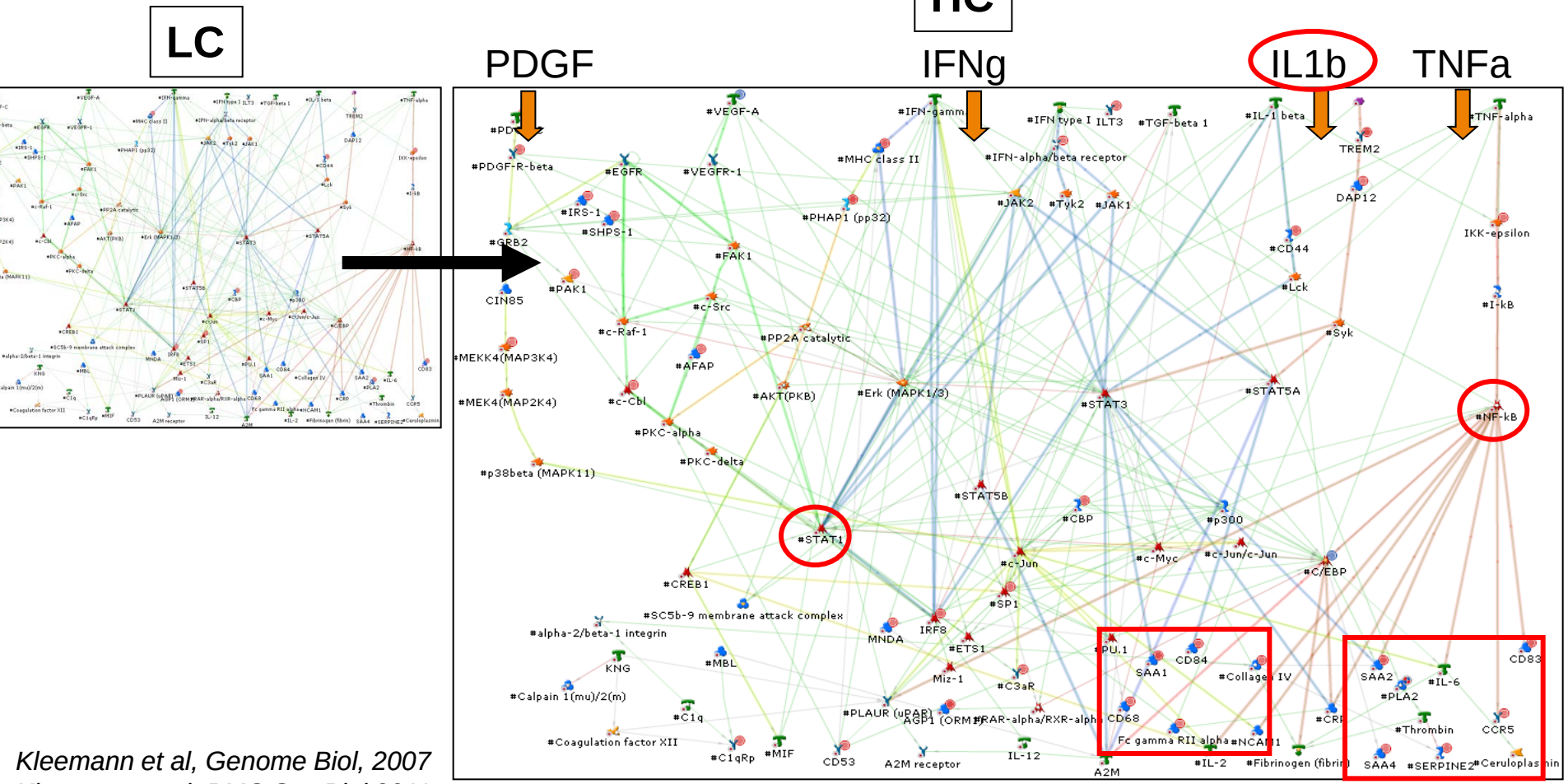
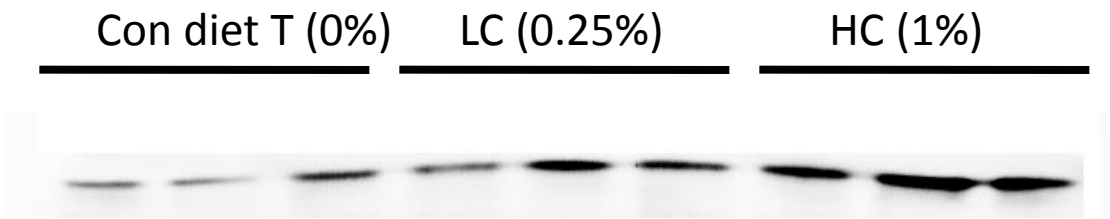
Transition from low cholesterol to high cholesterol feeding results in activation of 4 major inflammatory pathways

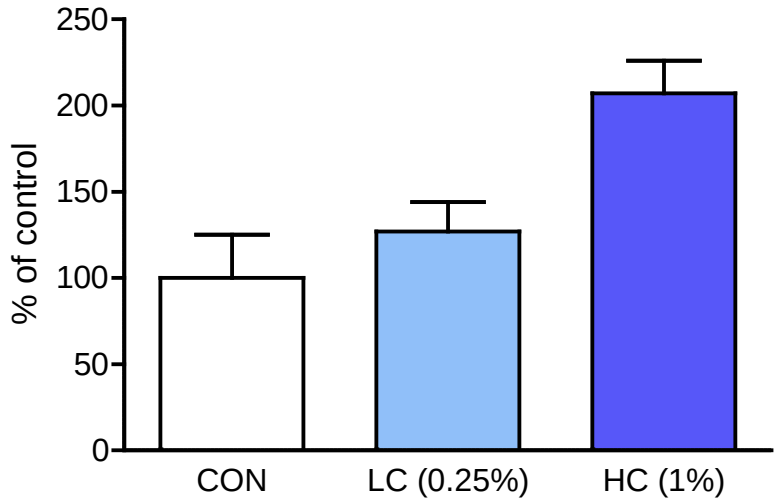


Kleemann et al, Genome Biol, 2007
Kleemann et al, BMC Sys Biol 2011

Activation of IL1-beta in response to cholesterol



IL1b (17 kD) active



ALT diet feeding has levels comparable low as the ones seen with LC → no induction of IL1b (current experiments) → possibly inflammasome involved

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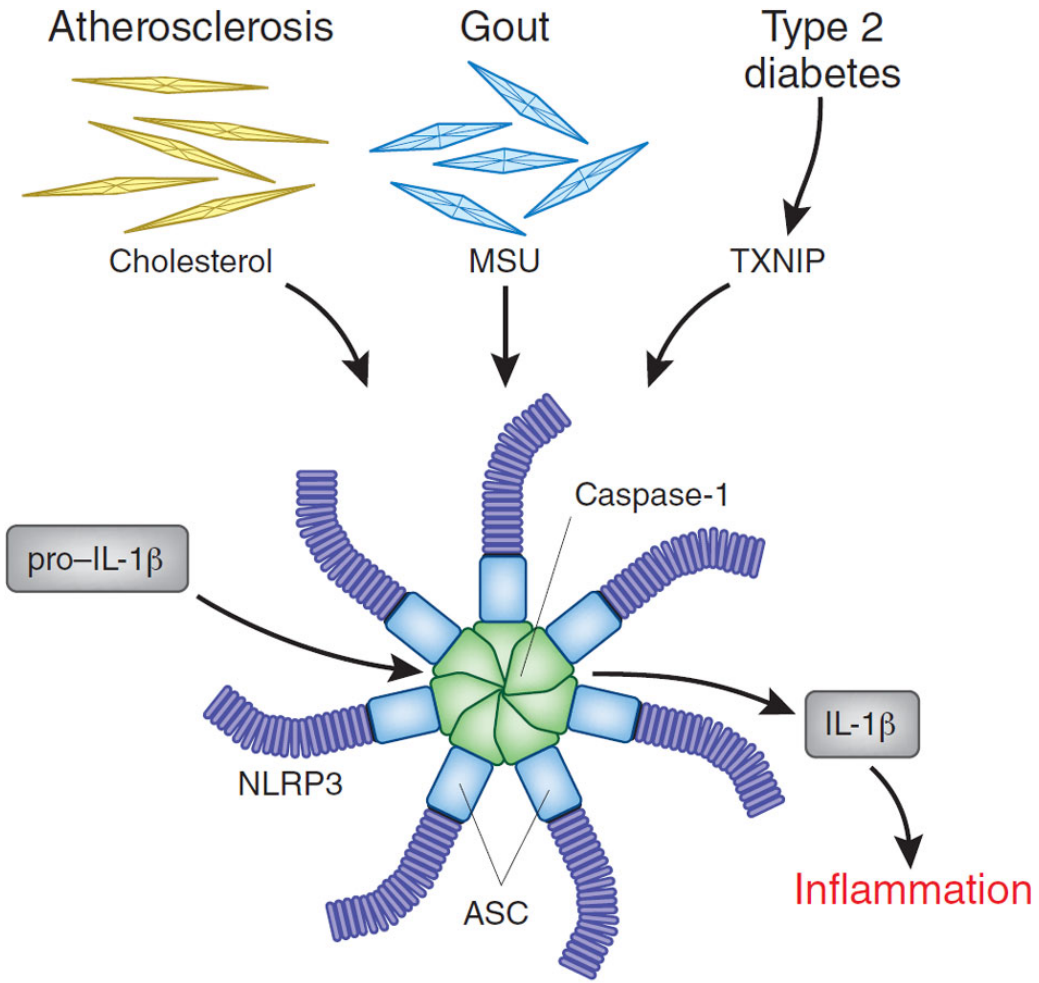
NLRP3-Inflammasome considered to play a *key* role in metabolic diseases



Hansson & Klareskog, Nat Med 2011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