Perinatal DDT Exposure Impairs Energy Expenditure and Metabolism in Adult Female Mice

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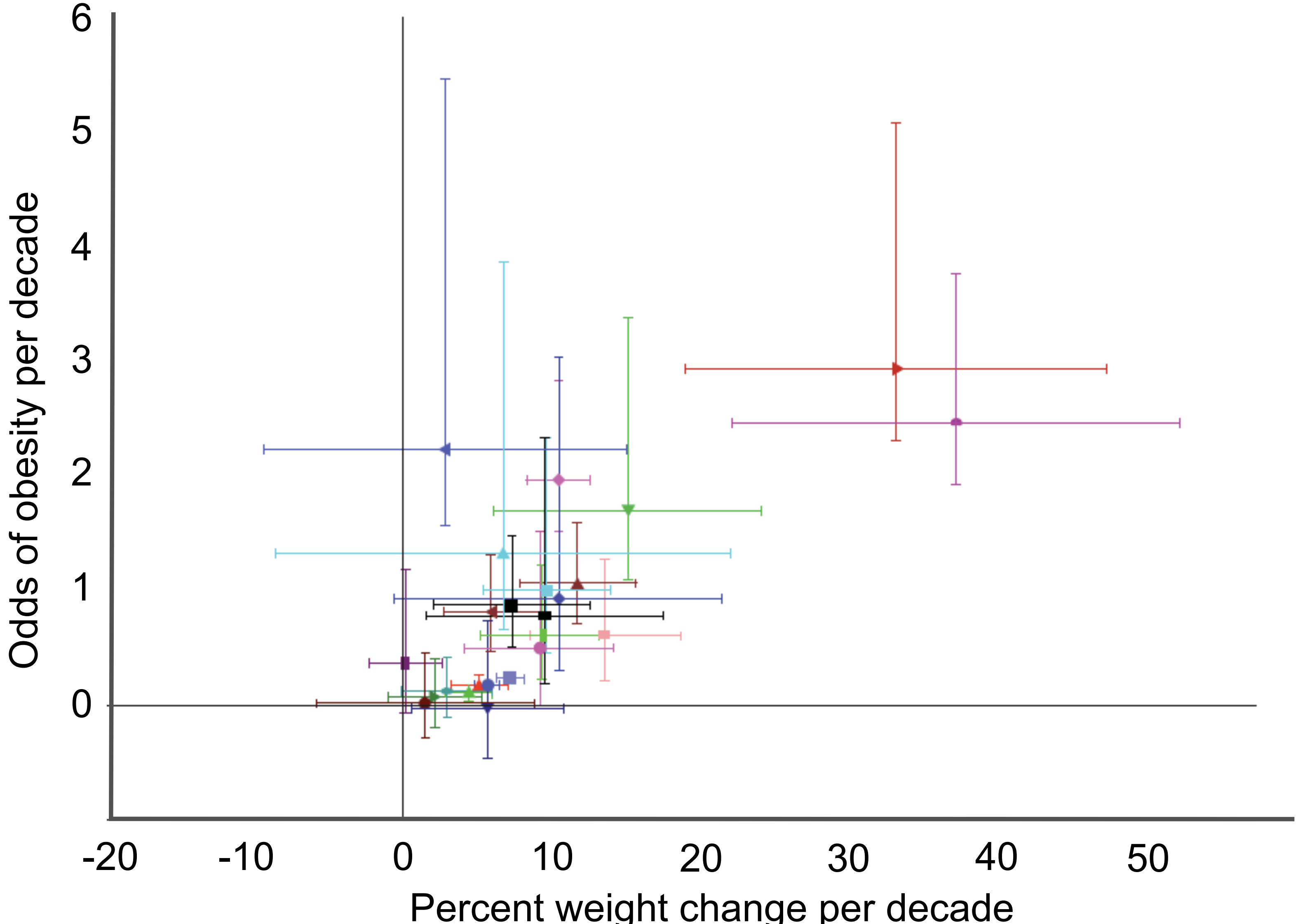
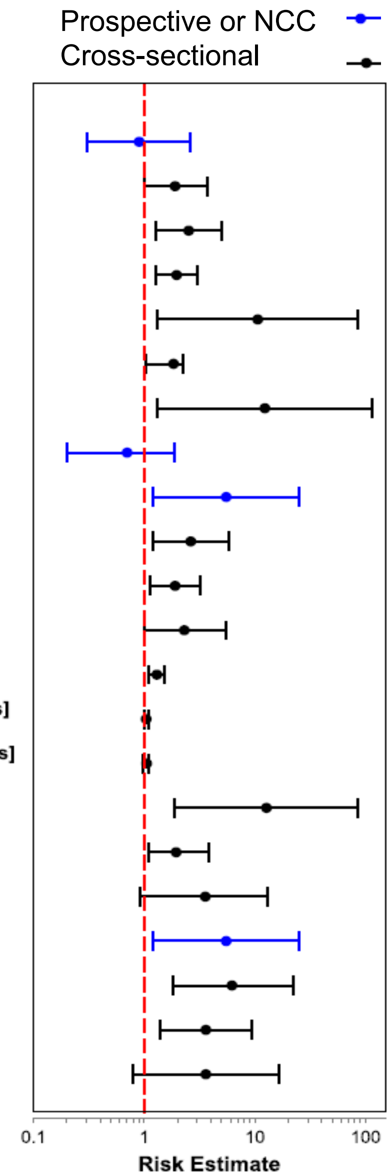
Average Body Weight & Obesity Has Been Rising in Animals Over Time



Klimentidis 2010

DDTs and Risk of Diabetes

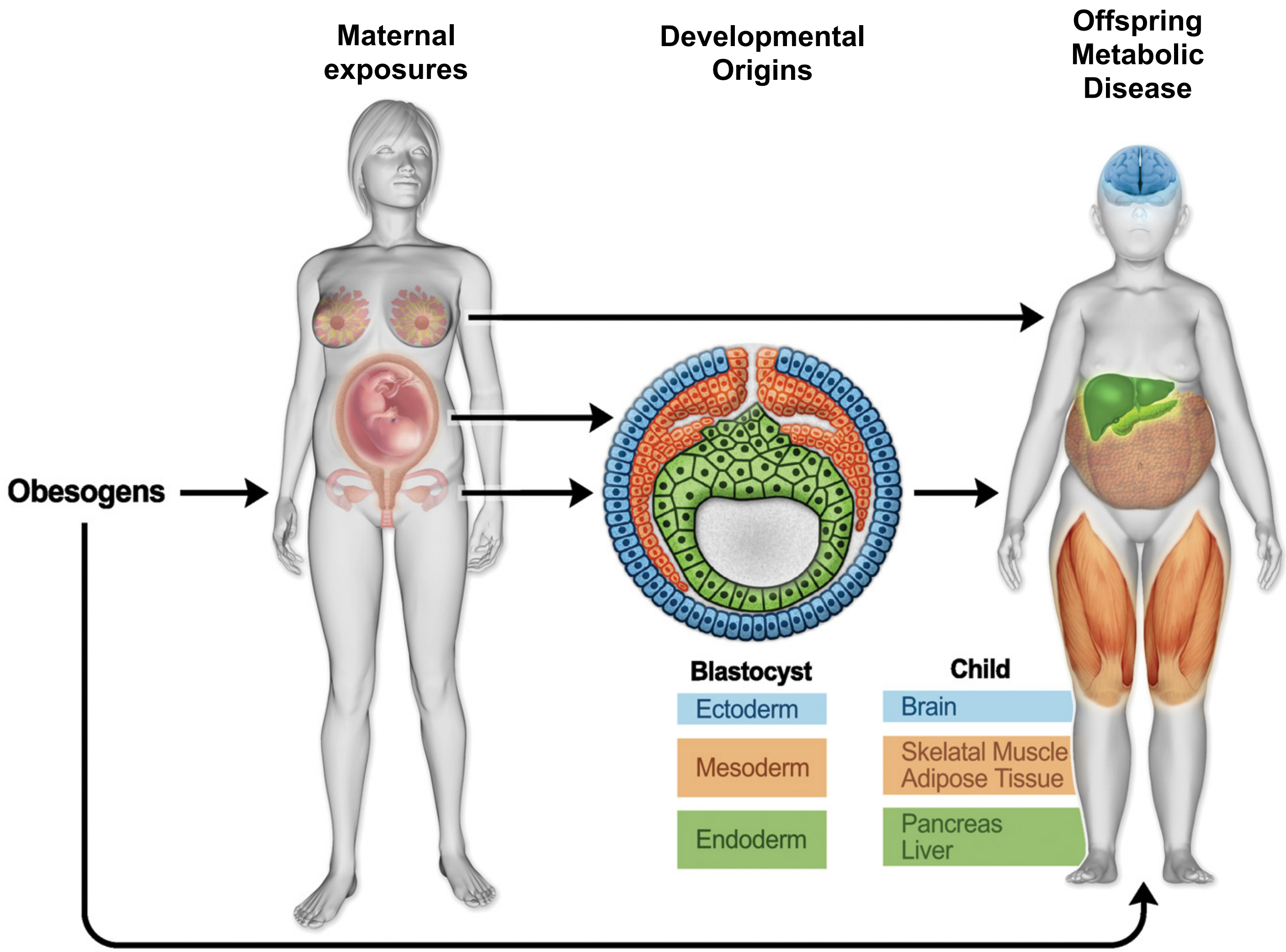
Reference	*Study Description (n)*	*Chemical*	*Diagnostic*	*Risk Estimate adjOR (95% CI)*	*Exposure*
Lee et al. 2010	US (multi-site) CARDIA nested CC, ≥18y ♂♀ (180)	DDT, -p,p'	FBG, meds	0.9 (0.3, 2.6)	Q4 vs Q1 pg/g (serum)
Cox et al. 2007	US (HHANES 82-84) CS, ≥20y ♂♀ (1,303)	DDT, -p,p'	SR	1.9 (1, 3.7)	≥2 vs <2.0 ng/g (serum)
Everett et al. 2007	US (NHANES 99-02) CS, ≥20y ♂♀ (1,830)	DDT, -p,p'	SR, HbA1c	1.17 (0.95, 1.45)	20.8-26.6 vs ≤20.7 ng/g lipid (serum)
Everett et al. 2010	US (NHANES 99-04) CS, ≥20y ♂♀ (3,049)	DDT, -p,p'	SR, HbA1c	1.96 (1.29, 2.98)	≥20.7 vs <20.7 ng/g lipid (serum)
Son et al. 2010	S. Korea (Uljin) CS, ≥40y ♂♀ (80)	DDT, -p,p'	FBG, meds	10.6 (1.3, 84.9)	36.2 (med, T3) vs 12.1 (med, T1) ng/g lip (serum)
Ukropec et al. 2010	Slovakia (eastern, polluted) CS, ≥21y ♂♀ (2,047)	DDT, -p,p'	FBG, 2hr glucose	1.84 (1.03, 2.27)	39-60 (Q3) vs 4-26 (Q1) ng/g lipid (serum)
Son et al. 2010	S. Korea (Uljin) CS, ≥40y ♂♀ (80)	DDT, -o,p'	FBG, meds	12.3 (1.3, 113.2)	5.4 (med, T3) vs 0.9 (med, T1) ng/g lip (serum)
Lee et al. 2010	US (multi-site) CARDIA nested CC, ≥18y ♂♀ (180)	DDE, -p,p'	FBG, medication	0.7 (0.2, 1.9)	>5,731 (Q4) vs ≤2153 (Q1) pg/g (serum)
Rignell-Hydbom et al. 2009	Sweden (Lund) WHILA nested CC, ♀ (742)	DDE, -p,p'	OGTT	5.5 (1.2, 25)	>4,600 vs ≤4,600 pg/ml (serum)
Cox et al. 2007	US (HHANES 82-84) CS, ≥20y ♂♀ (1,303)	DDE, -p,p'	self report	2.63 (1.2, 5.8)	>58.6 (>75th) vs <22.81 (<25th) ng/g (serum)
Everett et al. 2010	US (NHANES 99-04) CS, ≥20y ♂♀ (3,049)	DDE, -p,p'	self report, HbA1c	1.9 (1.13, 3.18)	≥168.6 vs <168 ng/g lipid (serum)
Lee et al. 2006	US (NHANES 99-02) CS, ≥20y ♂♀ (2,106)	DDE, -p,p'	FBG, self report	2.3 (1, 5.5)	1,560 (75 to <90th) vs ND ng/g lipid (serum)
Rignell-Hydbom et al. 2007	Sweden (east/west coast) CS, fisherman's wives ♀ (543)	DDE, -p,p'	self report	1.3 (1.1, 1.5) per 100 ng/g ↑	110 (56,250)[med (5th-95th), cases] ng/g lipid (serum)
Rylander et al. 2005	Sweden (nat'l registry) CS, fisherman's wives ♀ (184)	DDE, -p,p'	self report	1.05 (1.01, 1.10) per 100 ng/g ↑	990 (300-5,300)[med (5th-95th), cases] ng/g lipid (serum)
Rylander et al. 2005	Sweden (nat'l registry) CS, fisherman ♂ (196)	DDE, -p,p'	self report	1.05 (0.98, 1.11) per 100 ng/g ↑	1100 (390-2,400)[med (5th-95th), cases] ng/g lipid (serum)
Son et al. 2010	S. Korea (Uljin) CS, ≥40y ♂♀ (80)	DDE, -p,p'	FBG, medication	12.7 (1.9, 83.7)	667.4 (med, T3) vs 162.2 (med, T1) ng/g lip (serum)
Ukropec et al. 2010	Slovakia (eastern, polluted) CS, ≥21y ♂♀ (2,047)	DDE, -p,p'	FBG, 2hr glucose	1.94 (1.11, 3.78)	3,605-22,328 (Q5) vs 54-821 (Q1) ng/g lipid (serum)
Philibert et al. 2009	Canada (Northern Ontario) First Nation, ♂♀ (101)	DDE, -p,p'	SR	3.56 (0.91, 13.08)	>1,617 (>75th) vs ≤1,617 (≤75th) ng/g lipid
Turyk et al. 2009a	US (Great Lakes), prospective fish eaters, ♂♀ (471)	DDE	self report	5.5 (1.2, 25.1) IRR	2.3-5.3 (T2) vs <2.2 (T1) ng/g wet weight (serum)
Codru et al. 2007	US (Akwesasne) Mohawks CS, ♂♀ (352)	DDE	FBG, medication	6.2 (1.8, 21.9)	544.6 (T3) vs 246.1 (T1) ng/g lipid (serum)
Turyk et al. 2009b	US (Great Lakes) fish eaters CS, ♂♀ (503)	DDE	self report	3.6 (1.4, 9.4)	4.1-24.0 (Q4) vs <1.2 (Q1) ng/g (serum)
Son et al. 2010	S. Korea (Uljin) CS, ≥40y ♂♀ (80)	DDD, -p,p'	FBG, meds	3.6 (0.8, 16.3)	8.4 (med, T3) vs 2.7 (med, T1) ng/g lip (serum)



⊢ lower 95% confidence interval ⊣ upper 95% confidence interval ● risk estimate

Dr. Kris Thayer

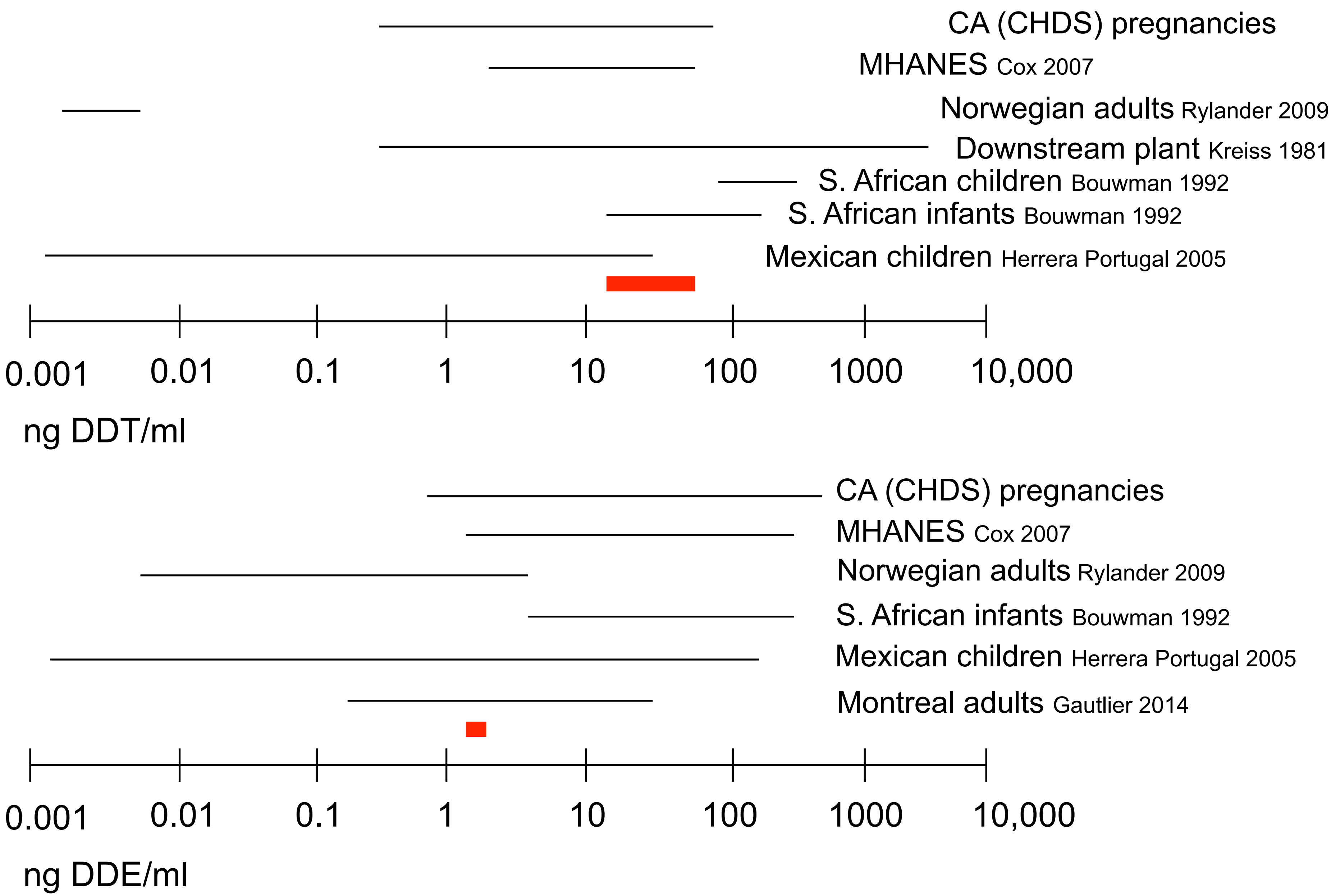
Developmental Origins of Metabolic Disease



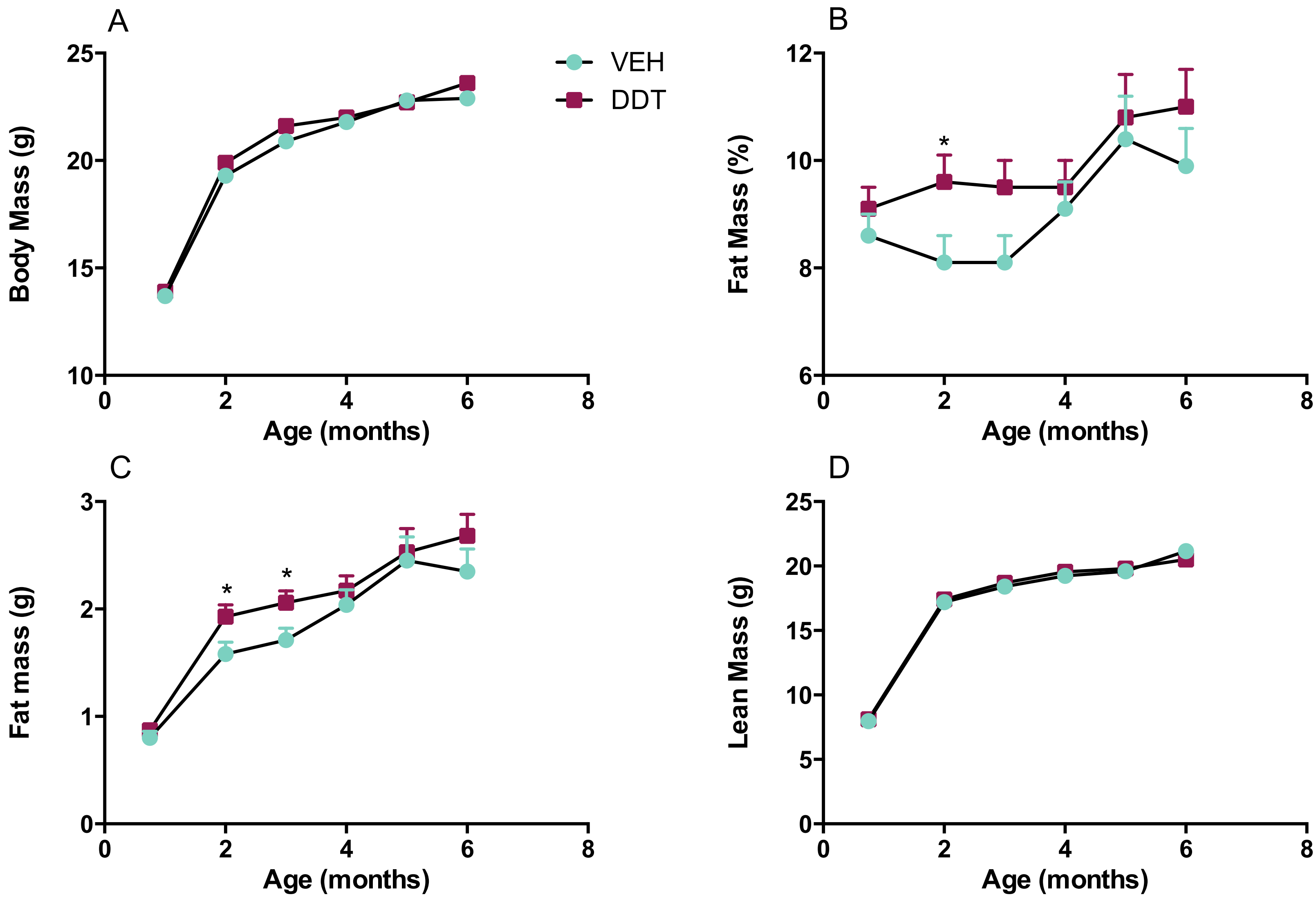
La Merrill & Birnbaum 2011

Could
Developmental Exposure to DDT
Increase Adult Risk of
Obesity and Diabetes?

Internal Dose in Range of Human Exposure



Perinatal DDT Increases Early Adult Adiposity



What Causes Excess Body Mass?

- The 1st Law of Thermodynamics!

  Excess Mass = Energy Intake > Energy Expenditure

- Energy Intake

  Food calories

- Energy Expenditure

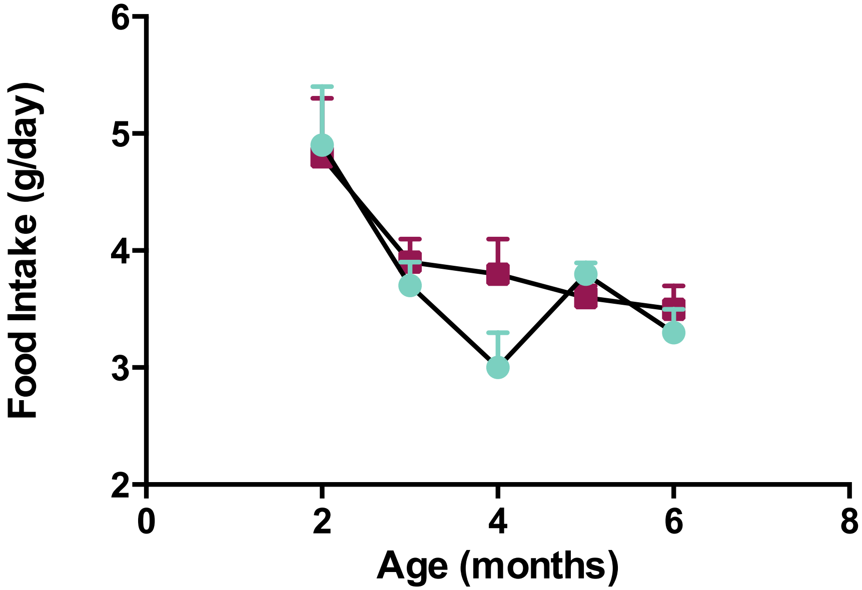
  10-30% physical activity

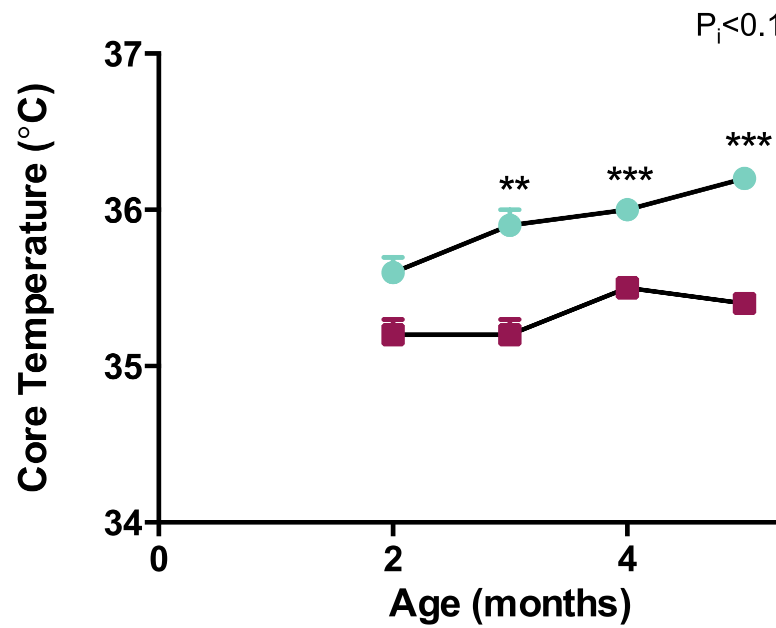
  60-80% resting metabolic rate (homeothermy)

  10% adaptive thermogenesis (response to cold and diet)

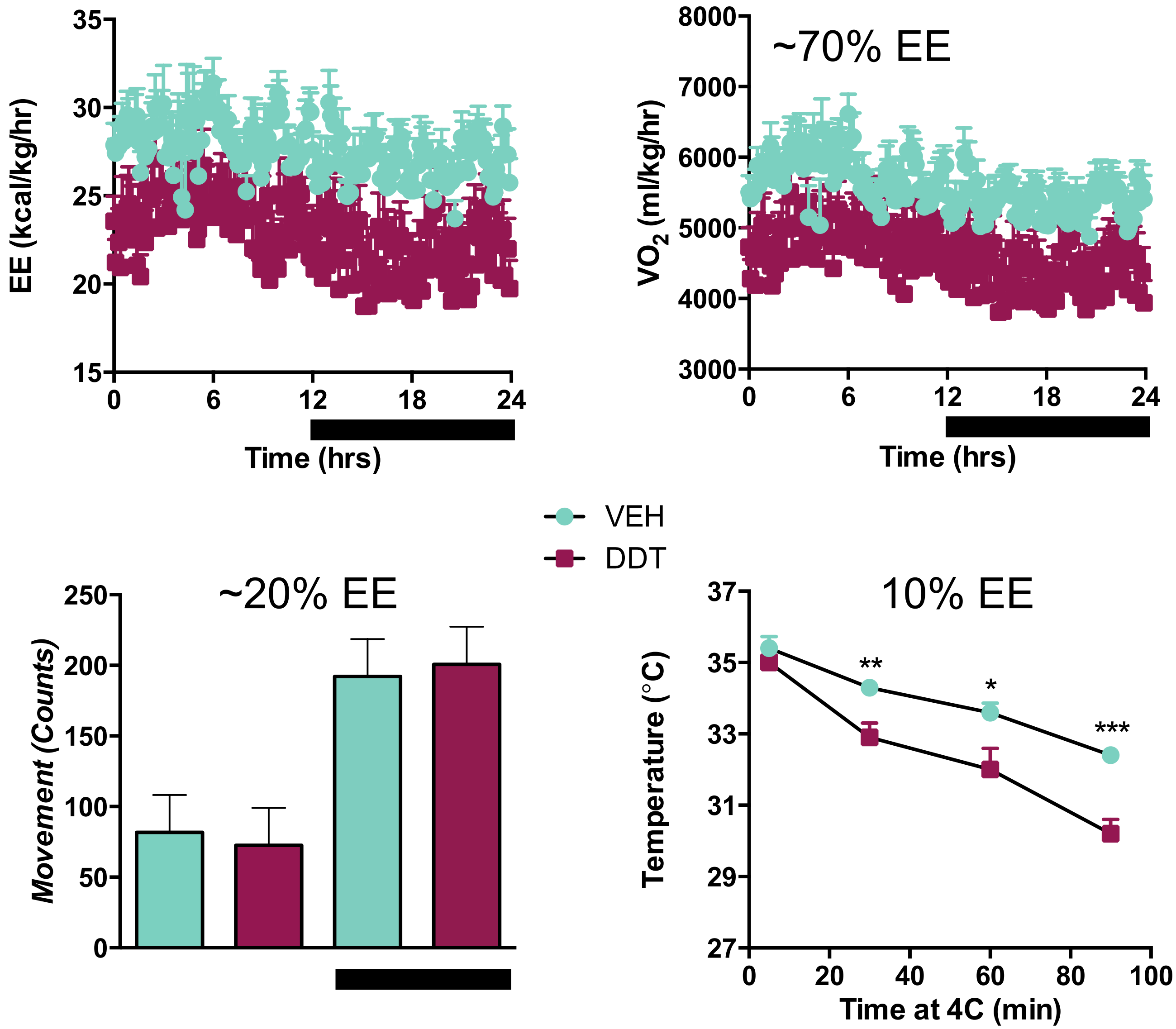
Landsberg 2012

Perinatal DDT Decreases Thermogenesis





Perinatal DDT Decreases Energy Expenditure

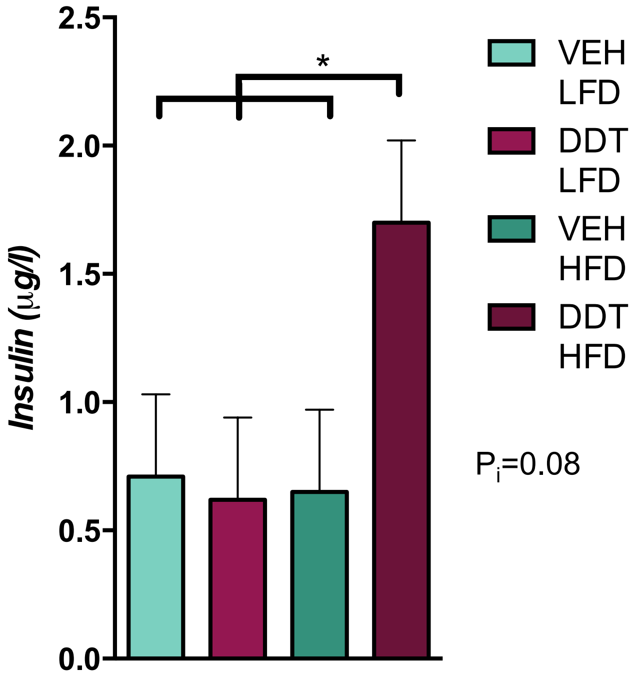


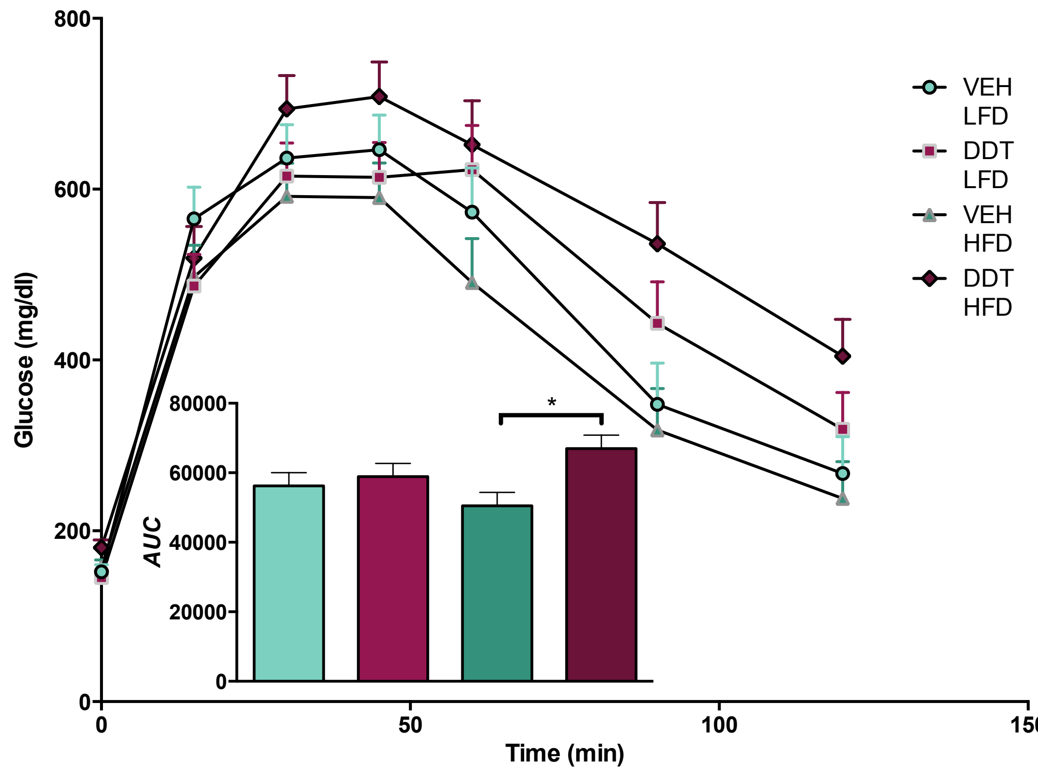
Mammalian body temperature maintenance is essential.

Therefore when thermogenic capacity is reduced, metabolic compensation occurs.

Does this metabolic compensation increase susceptibility to diet induced- metabolic disruption?

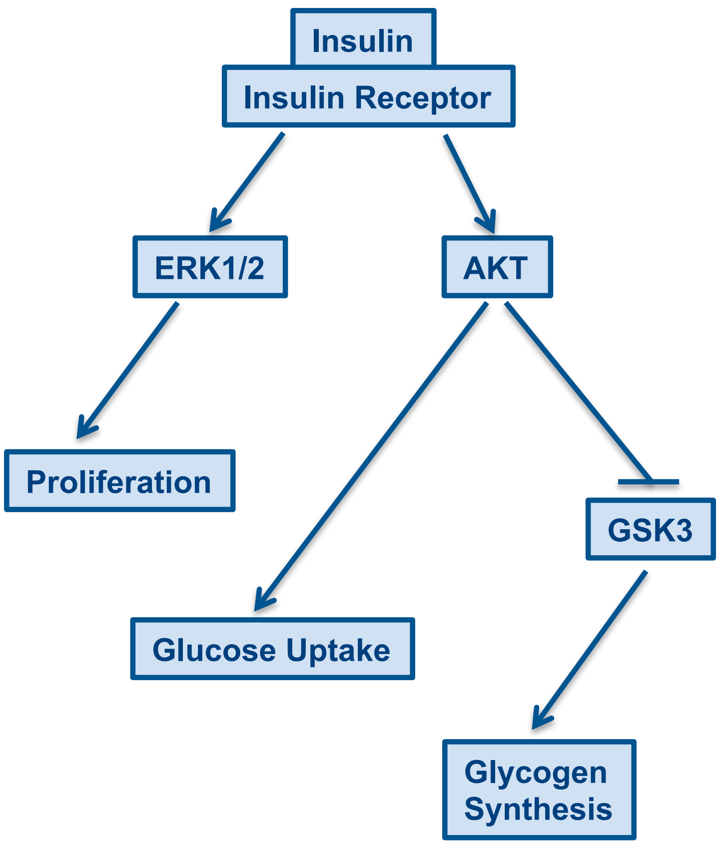
HFD Increases Susceptibility to Adult Insulin Resistance Induced by Perinatal DDT

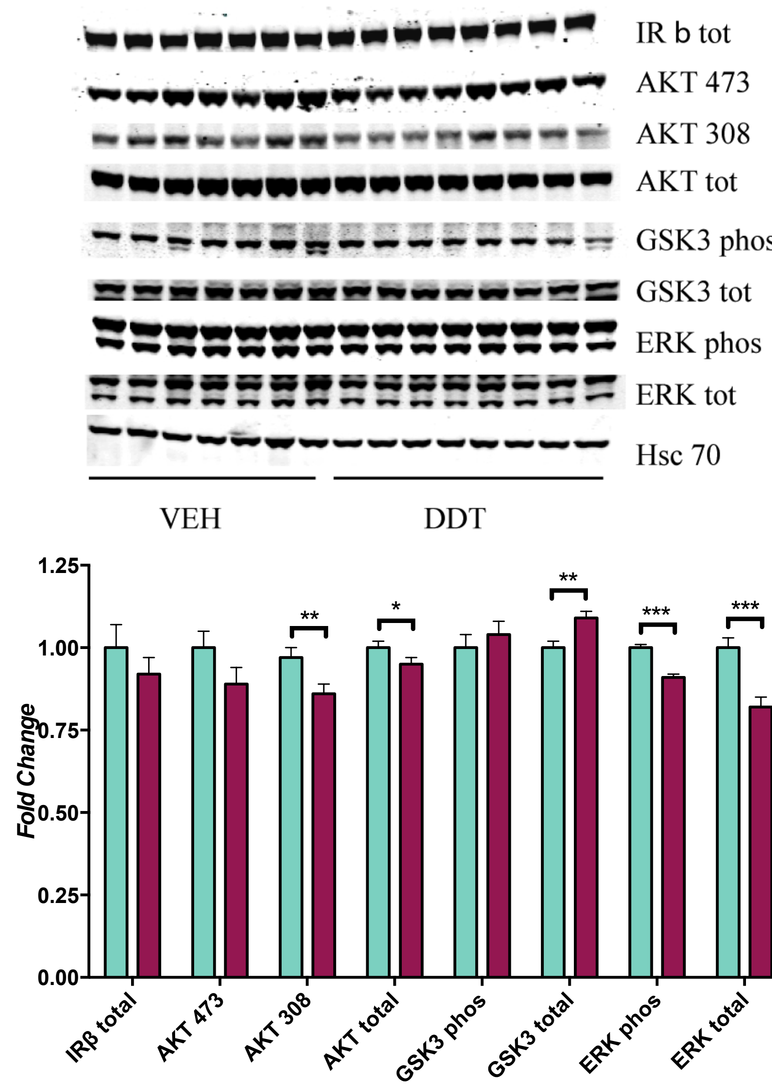




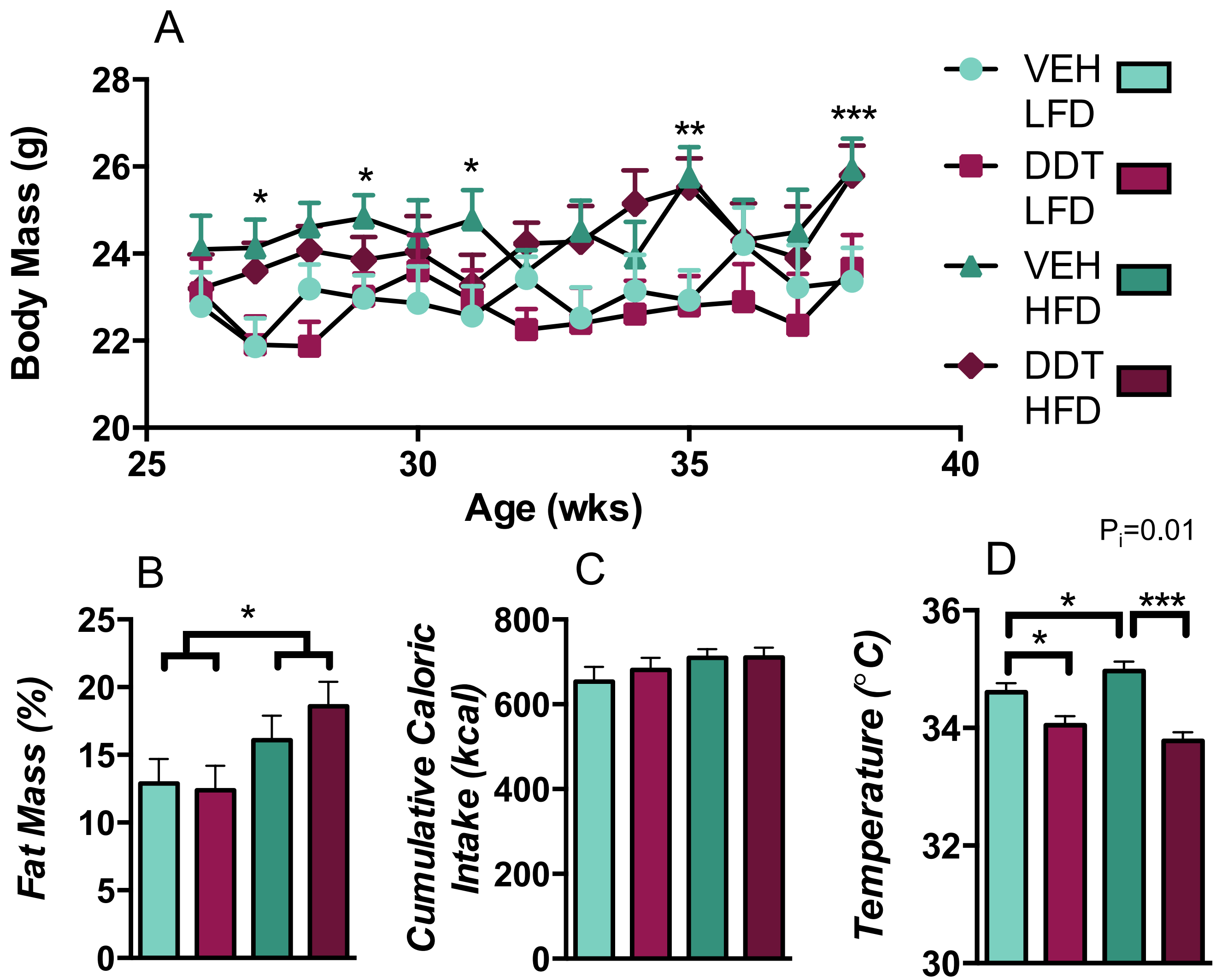
Perinatal DDT Reduces Hepatic Proteins Downstream of Insulin in HFD-fed Mice

Normal Insulin Signaling

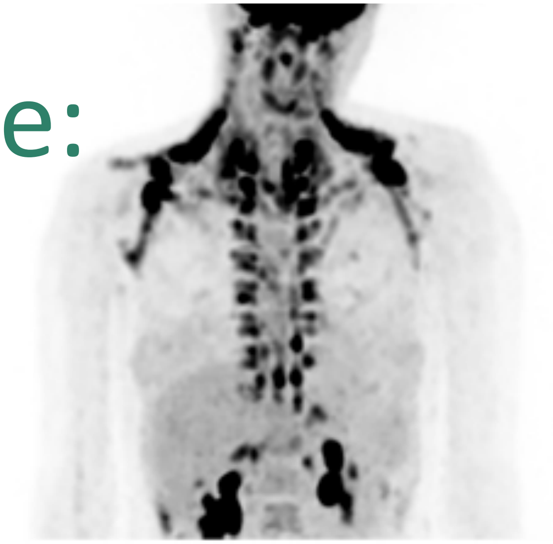




HFD Attenuates the Depressive Effect of Perinatal DDT on Thermogenesis



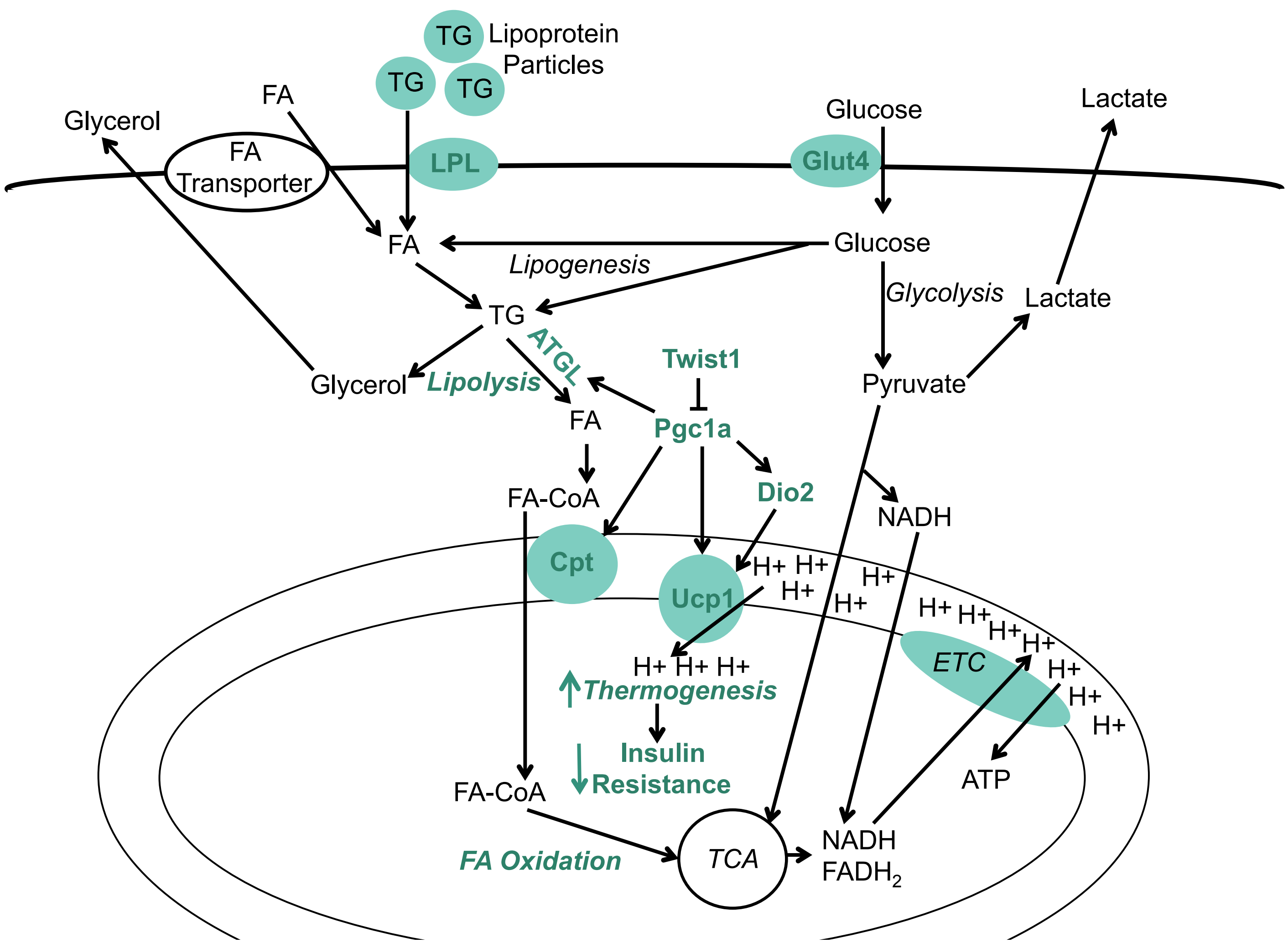
Brown Adipose Tissue: A Primer



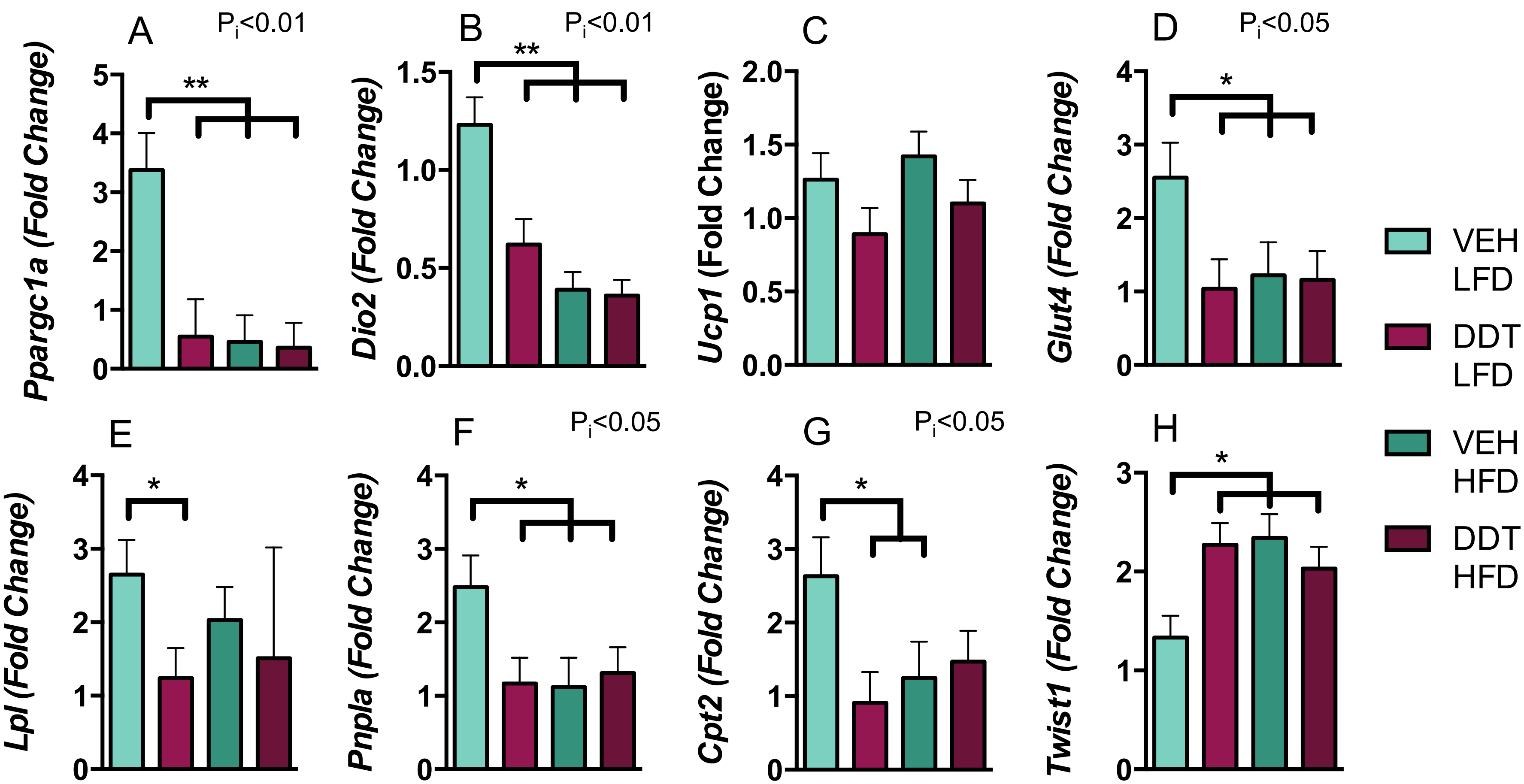
- BURNS energy to make heat
- Neonatal response to ambient temperature
- Recently discovered to be present and active in adult humans
  - Presence of BAT in adult humans associated with lower diabetes risk (A1C)
  - Activation of adult human BAT may contribute to loss of over 4 kg body fat annually

Matsushita 2013, Virtanen 2009

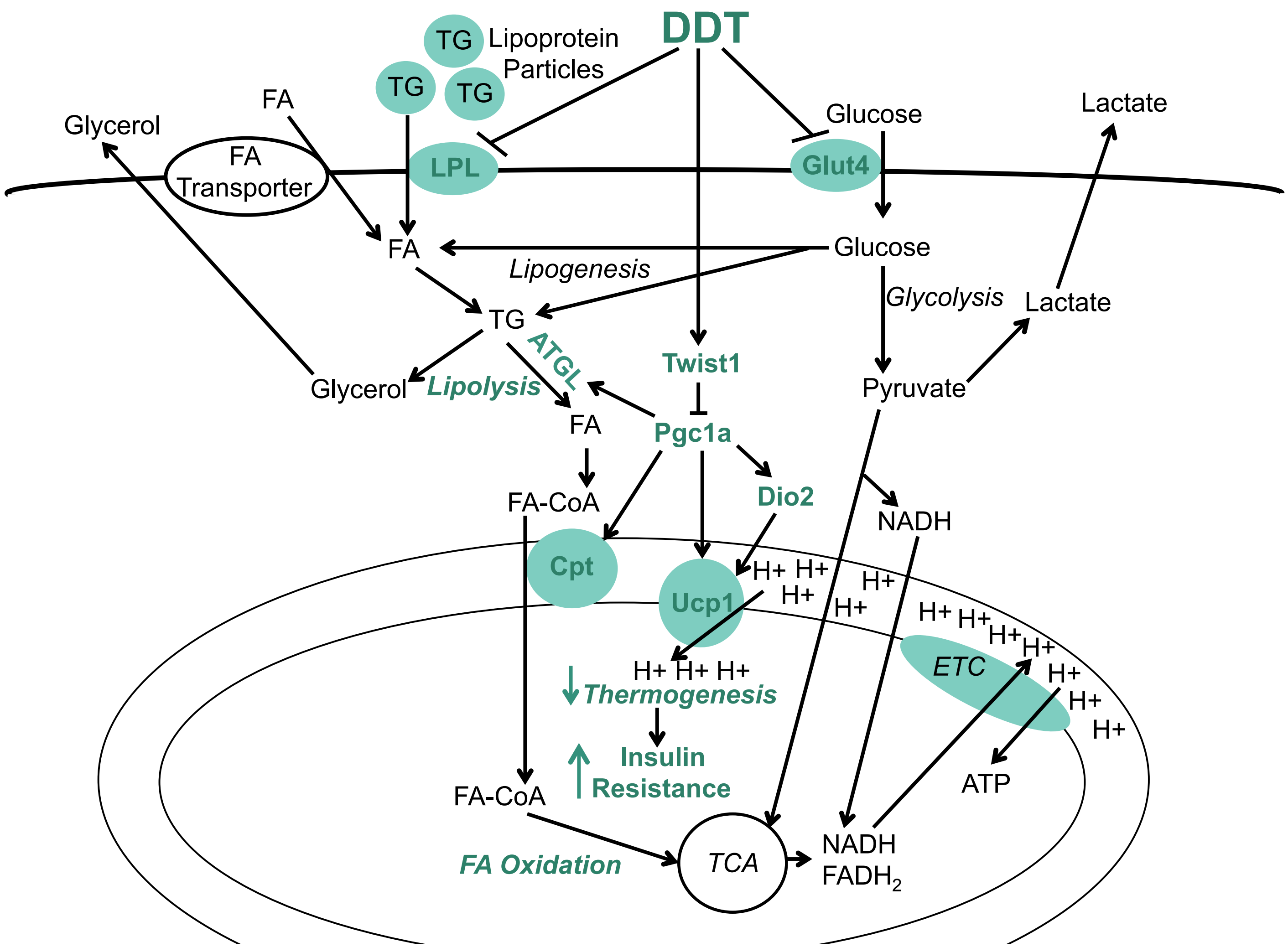
Pathway to Thermogenesis: Respiration and its Uncoupling in Brown Adipose



HFD Attenuates the Depressive Effect of Perinatal DDT on BAT Thermogenesis & Substrate Utilization



Working Model: Perinatal DDT Exposure Impairs Respiration and its Uncoupling in Brown Adipose

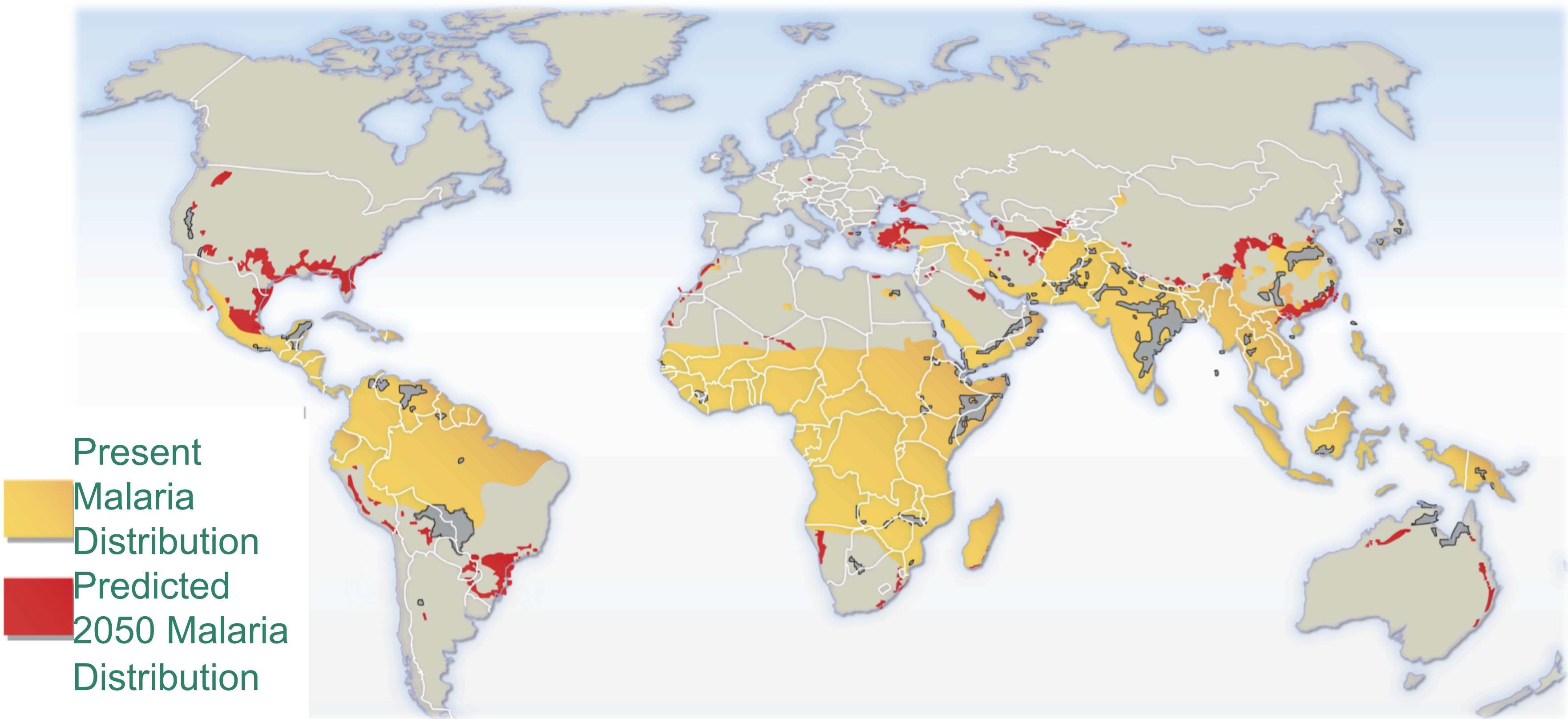


Results Summary

- Perinatal DDT exposure leads to…
  - Increased adipose in early adulthood
  - Decreased energy expenditure
    - Decreased thermogenesis
  - Susceptibility to HFD
    - Insulin resistance
    - Decreased thermogenesis
      - Defects in brown adipose substrate utilization implicated

Malaria & Climate Change

- Predictions about mosquitos carrying malaria
  - Larger numbers in existing range
  - Expanse of distribution

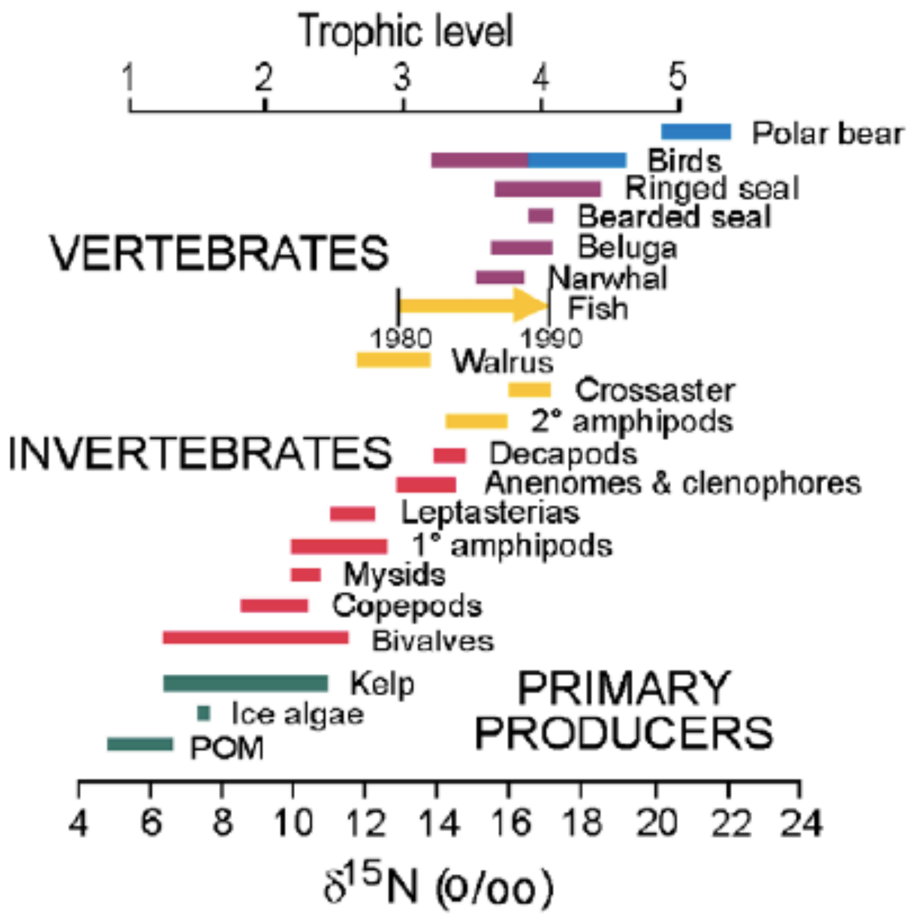


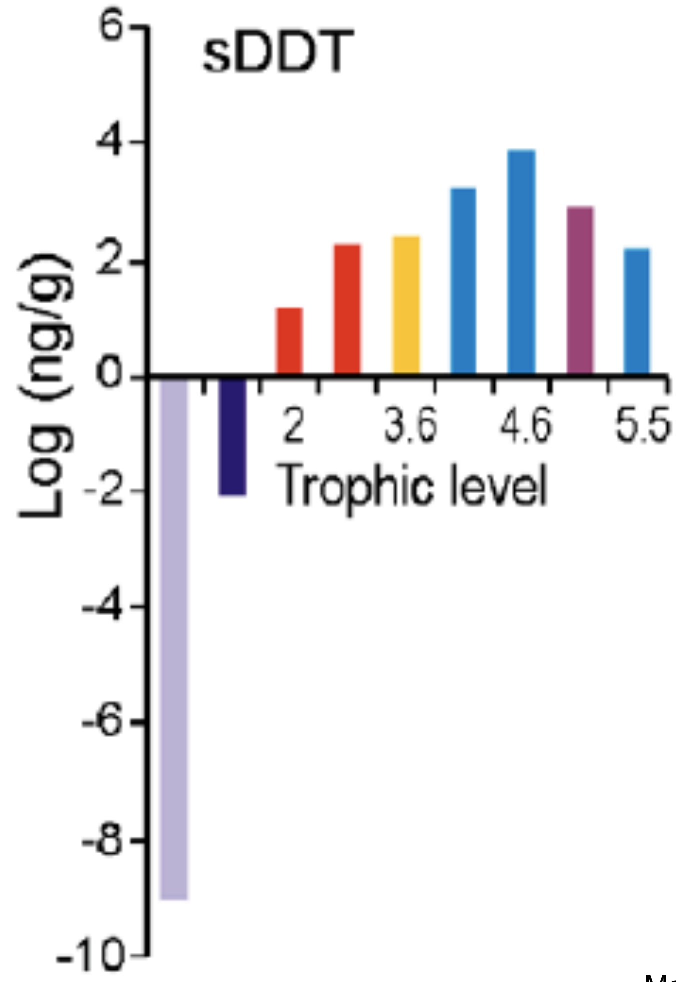
Rogers 2000, Kiszewski 2004, Pascual 2006, IPCC 2007, Siraj 2014, Noyes 2009

Melting glaciers are a source of marine DDTs:

≥ 60% to subalpine lakes

46% DDTs in Canadian Archipelago





Macdonald 2005

Thank you for your attention!

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No Conflicts of Interest