Why is type 2 diabetes linked to Alzheimer's disease?

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Disclosures

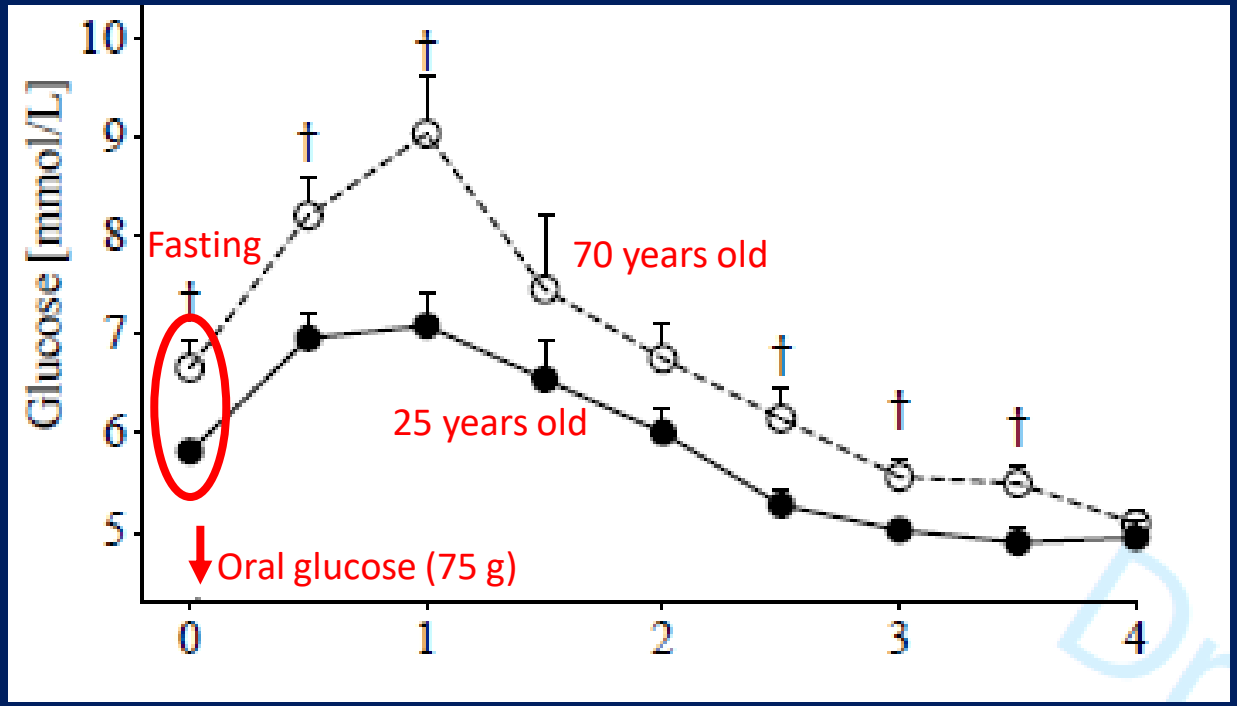
PUBLIC
CIHR, CRC, FRQS, MITACS, NSERC,
Research Center on Aging

PRIVATE
Nestlé Health Science
Abbott, Cargill, Cerecin, Swiss Re

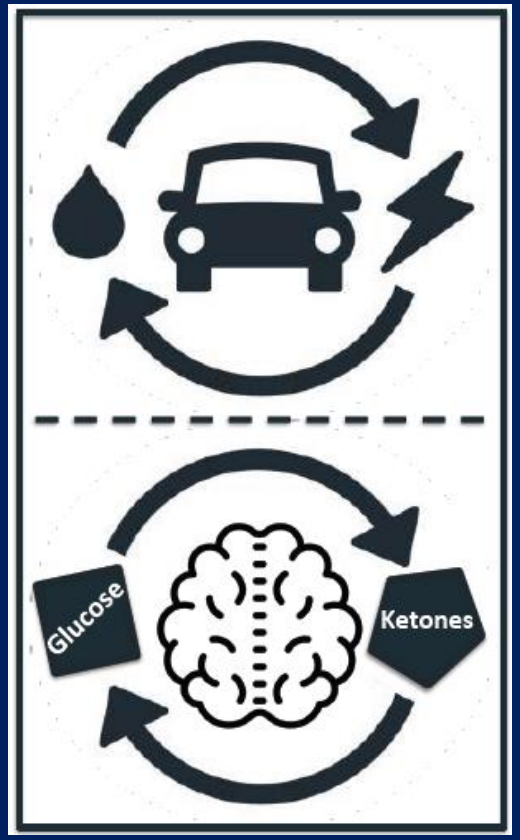
NON-PROFIT
Alzheimer Society Research Program (Canada)
Alzheimer Association (USA)

NOTE
The contents of this presentation are for research purposes only and should not be interpreted as nutritional or medical advice.

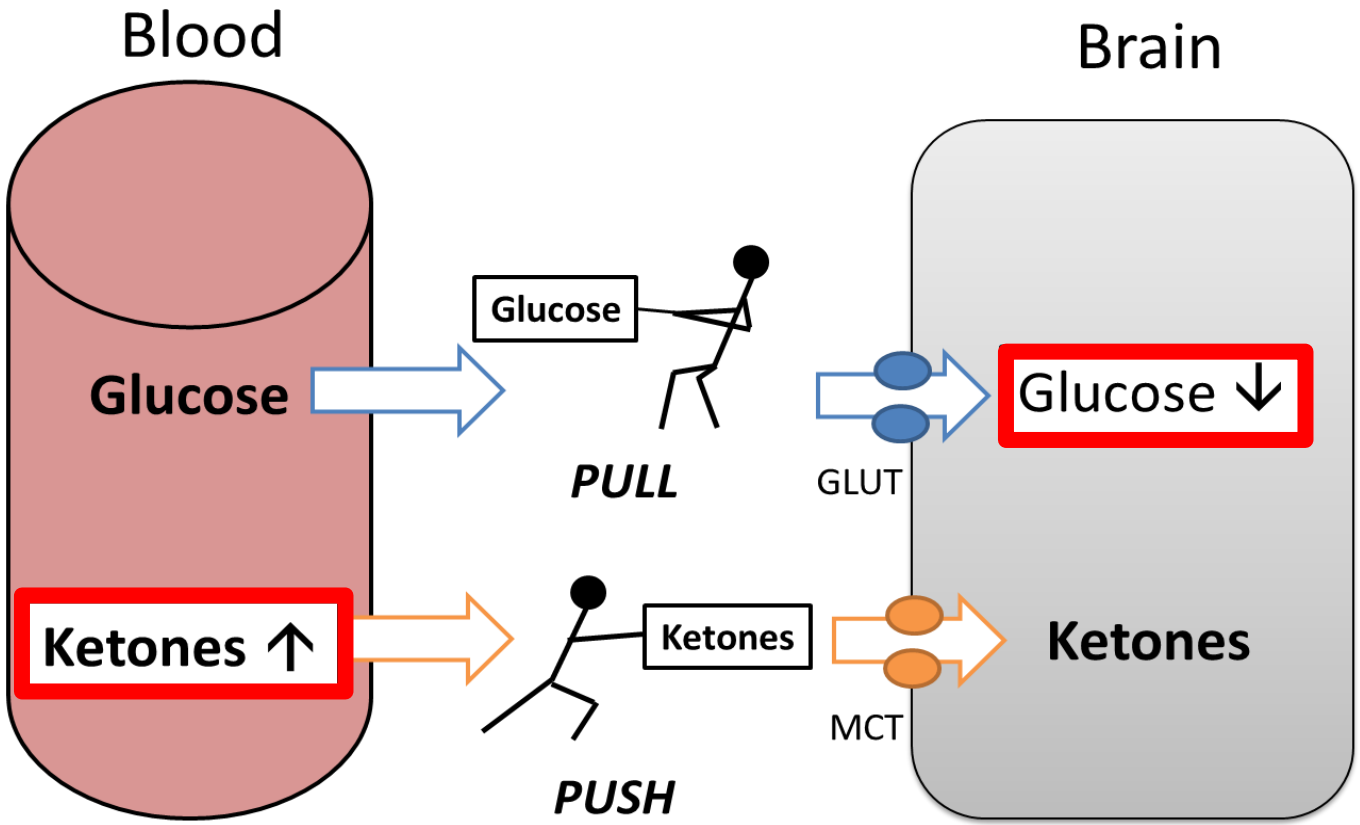
Glucose-insulin dysregulation: a major challenge as we age



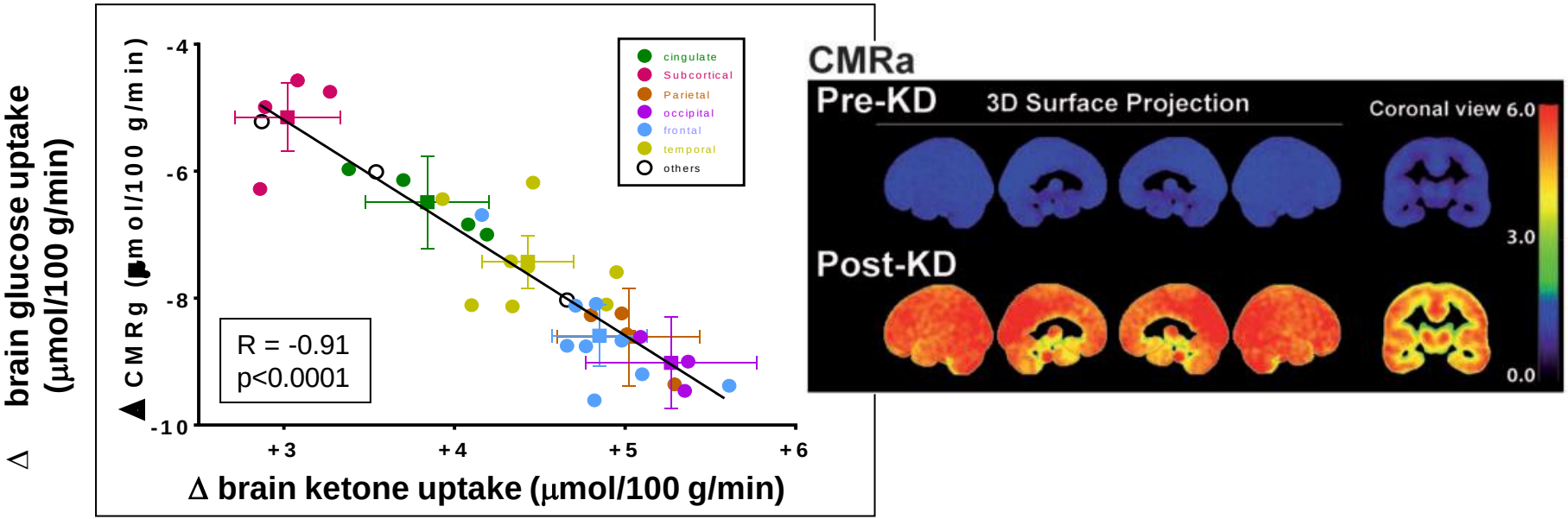
Metabolically, the brain is a hybrid car



Brain energy metabolism:
Two distinctly different strategies for the two main fuels



Ketones spare brain glucose uptake



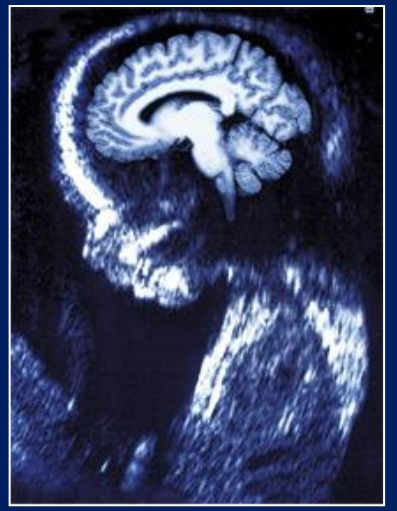
Healthy adults in short-term nutritional ketosis (n=10)

(Courchesne-Loyer et al., J Cerebral Blood Flow Metabolism, 2016)

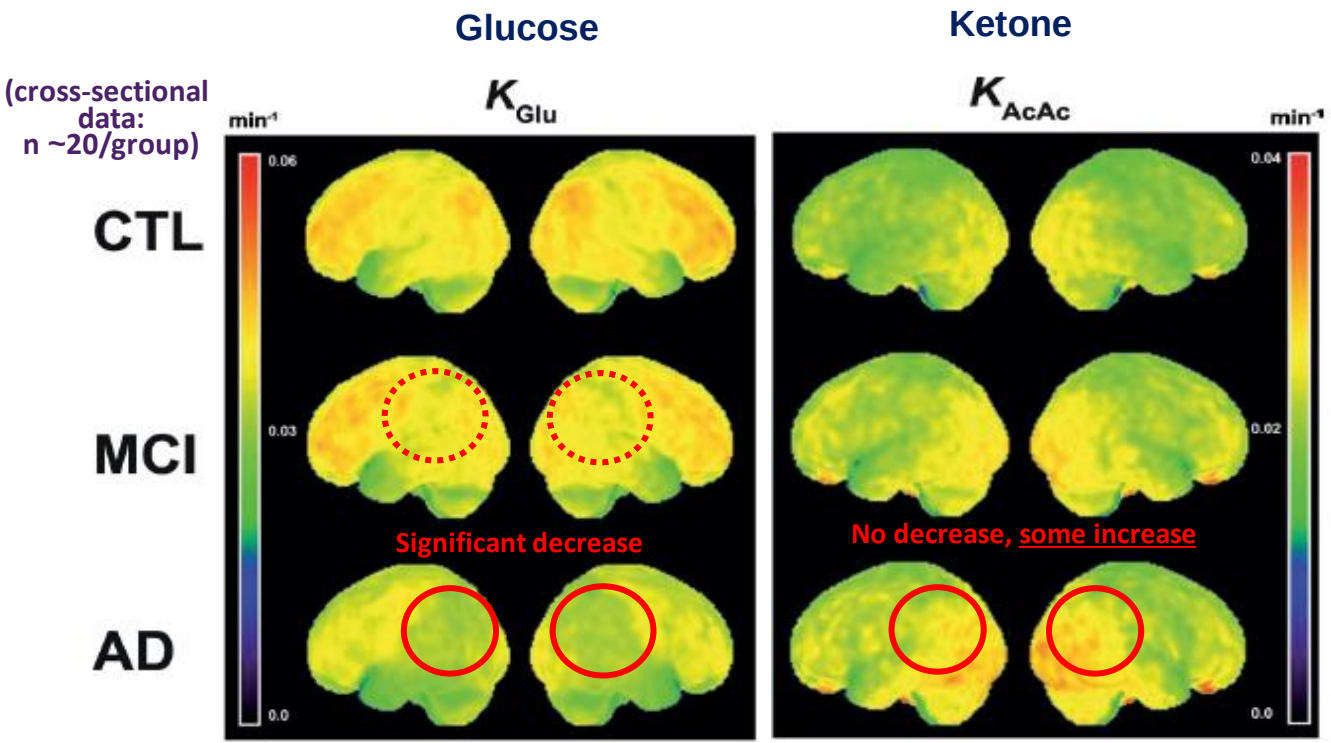
Ketones to improve (rescue) brain energy supply during aging: inspired by their role during brain development in infants

(Cunnane and Crawford, J Human Evolution, 2014)

- Mild hyperketonemia is normal in infants (0.5 – 1.0 mM ketones).
- 3-4 times more rapid brain ketone uptake in infants than in adults.
- Ketones supply ~30% of fetal, neonatal brain energy needs 24/7 *et al 1975, Bougnères et al 1985).*
- Ketones supply ~90% of the carbon to make brain cholesterol, fats *(Cunnane, 2003).*
- Ketones derived from medium chain fats (kMCT) in milk, long-chain fats in infant fat stores.



Impaired brain energy metabolism in MCI and AD is specific to glucose; no brain deficit in the *capacity (K)* to take up ketones



(Cunnane et al. Nature Reviews Drug Discovery, 2020)

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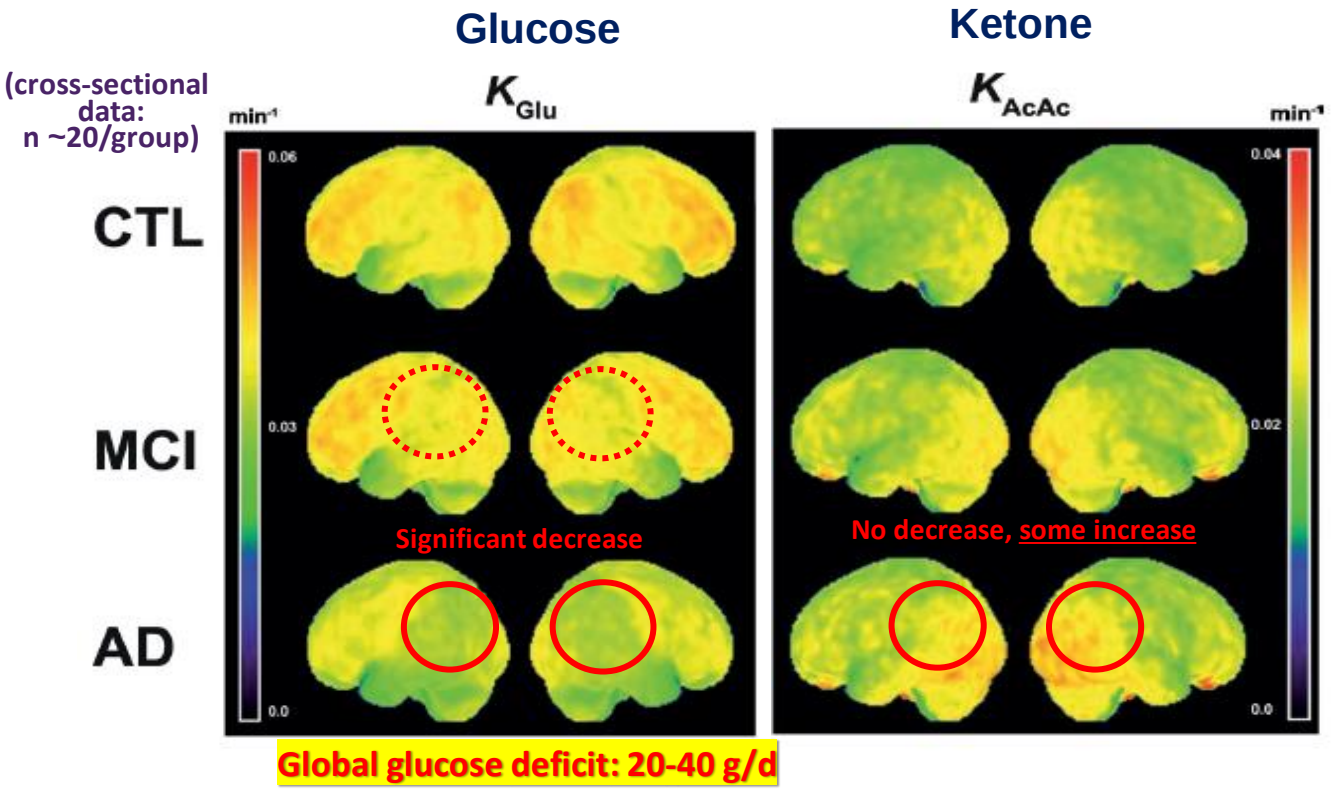

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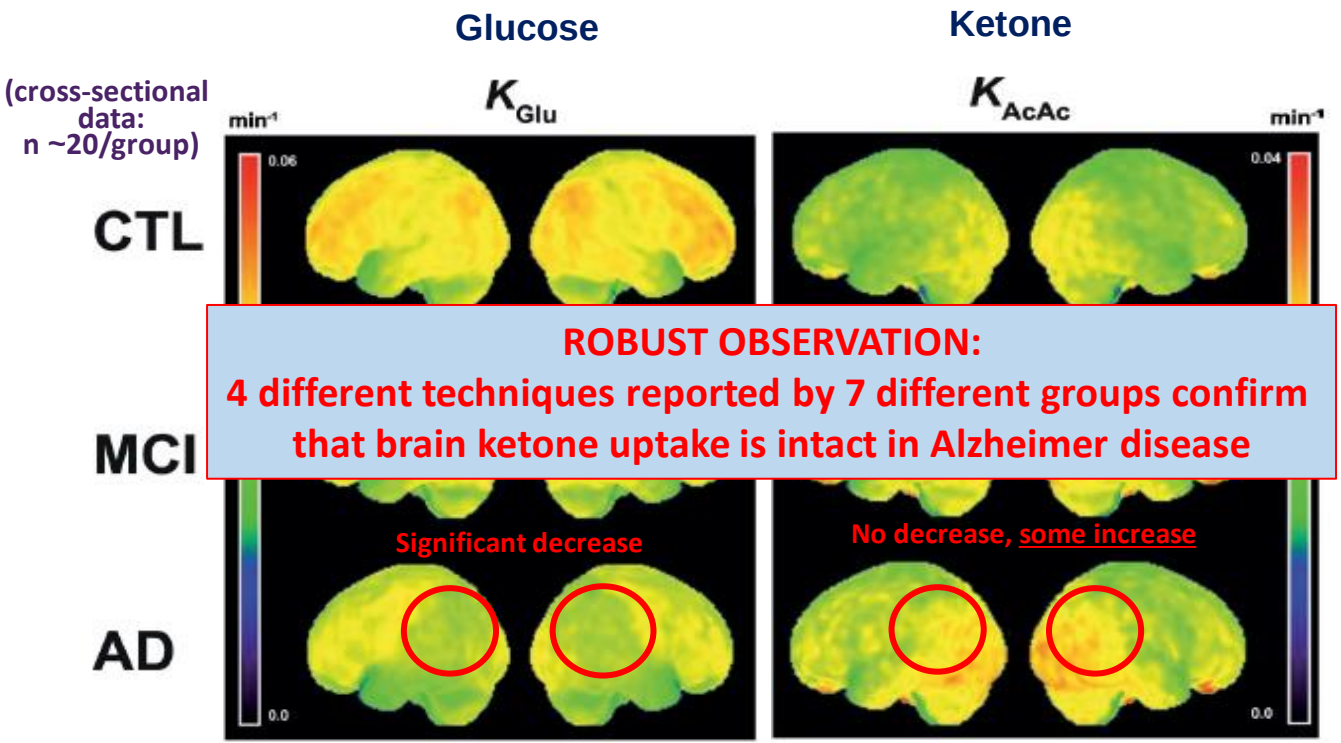
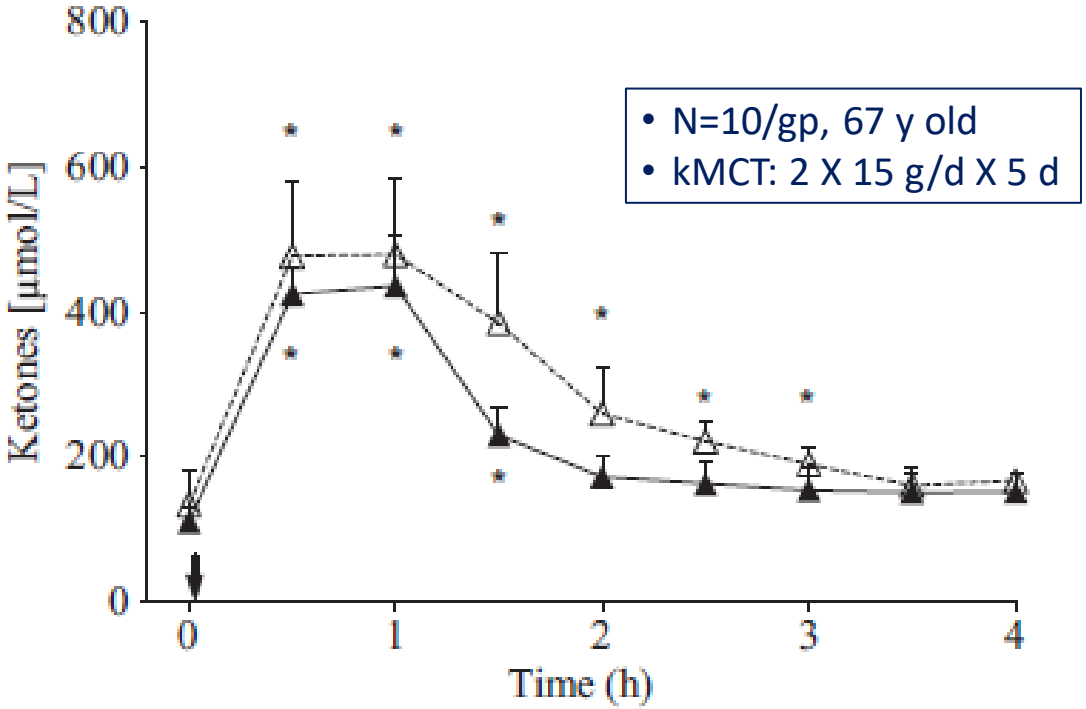


(Cunnane et al. Nature Reviews Drug Discovery, 2020)

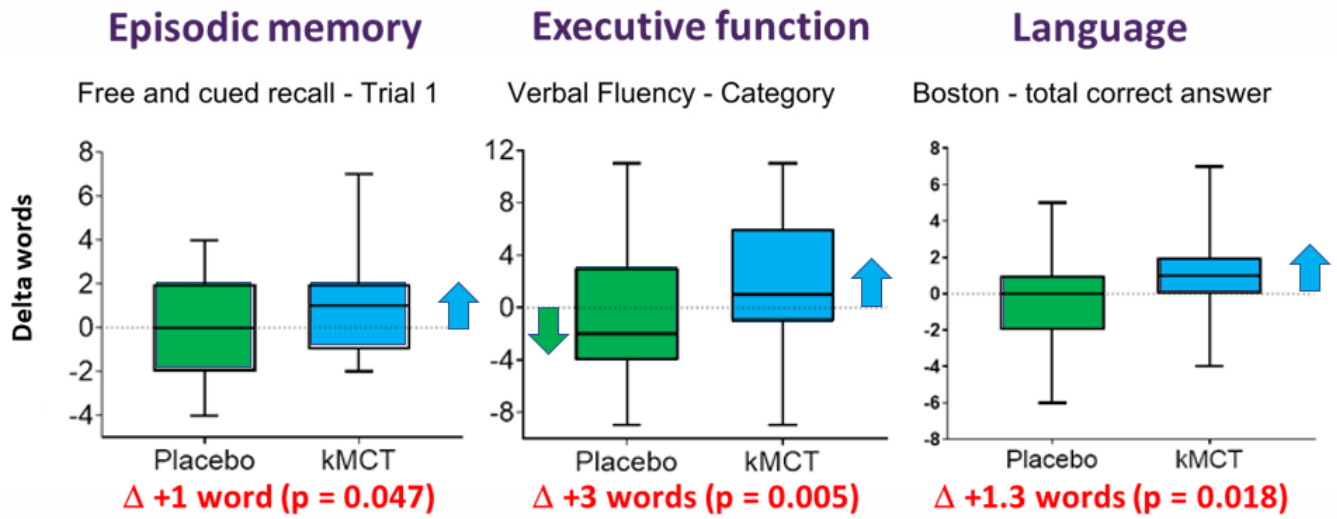
Ketogensis from MCT is largely intact in pre-diabetic older women

(Vandenberghe et al. Adv Physiol Nutr Metabolism, 2017)



Benefic: kMCT improved outcomes in 5/5 cognitive domains

(Fortier et al. Alzheimer's & Dementia, 2019, 2021)



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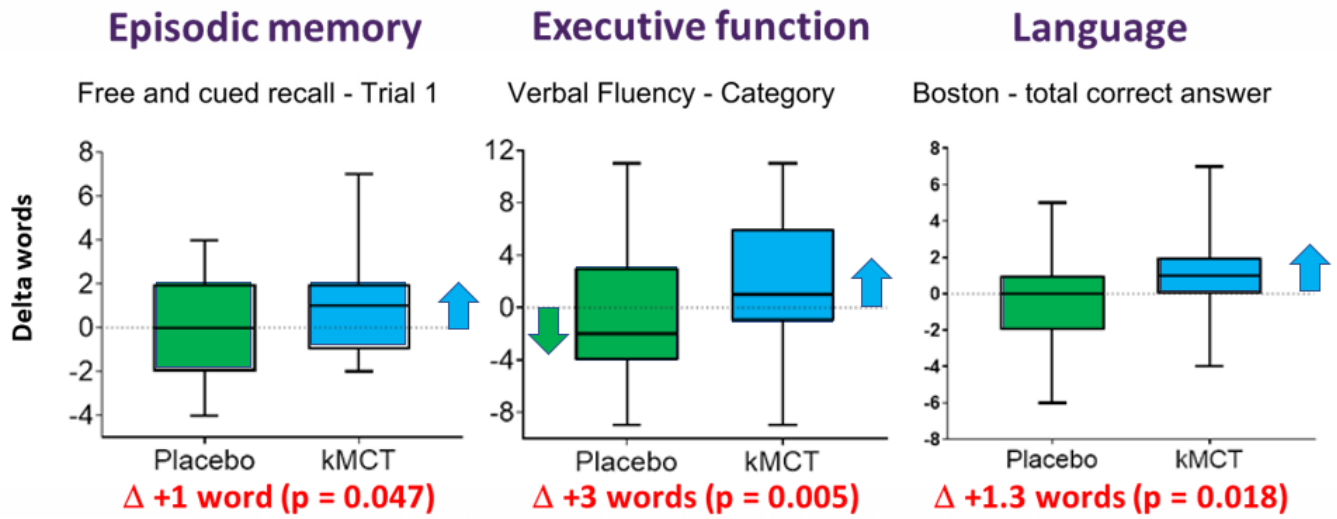
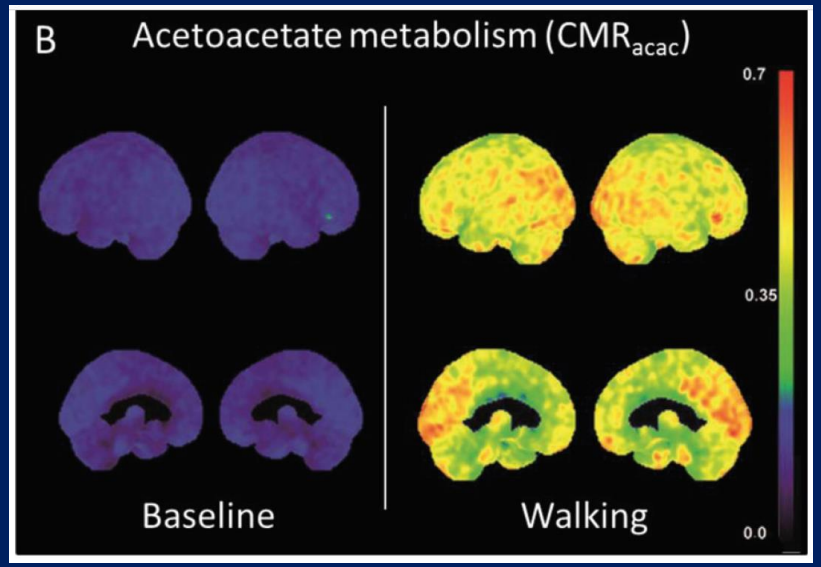
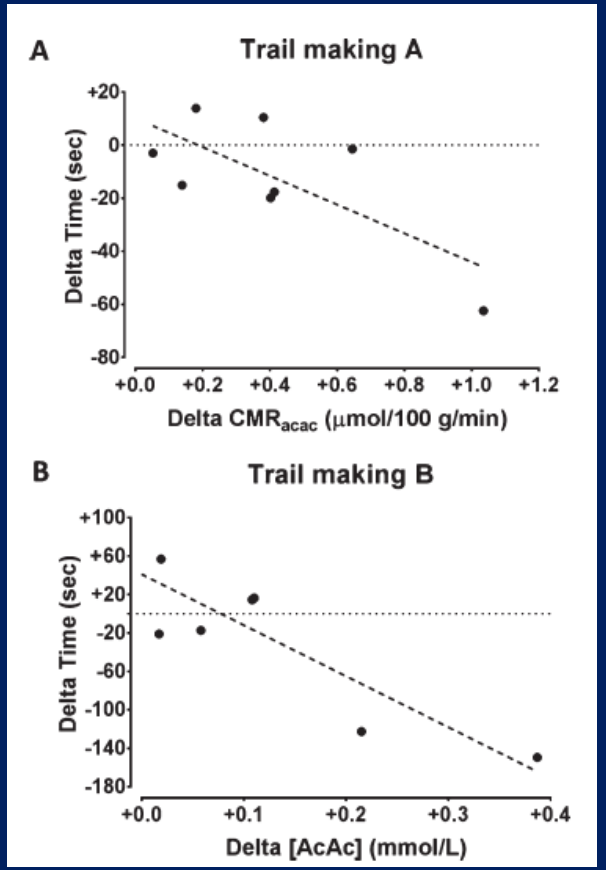


A 1 word improvement in a 16-item episodic memory test has been predicted to delay AD onset by 1-3 years (Auriacombe et al. 2010, Grober et al. 2018)

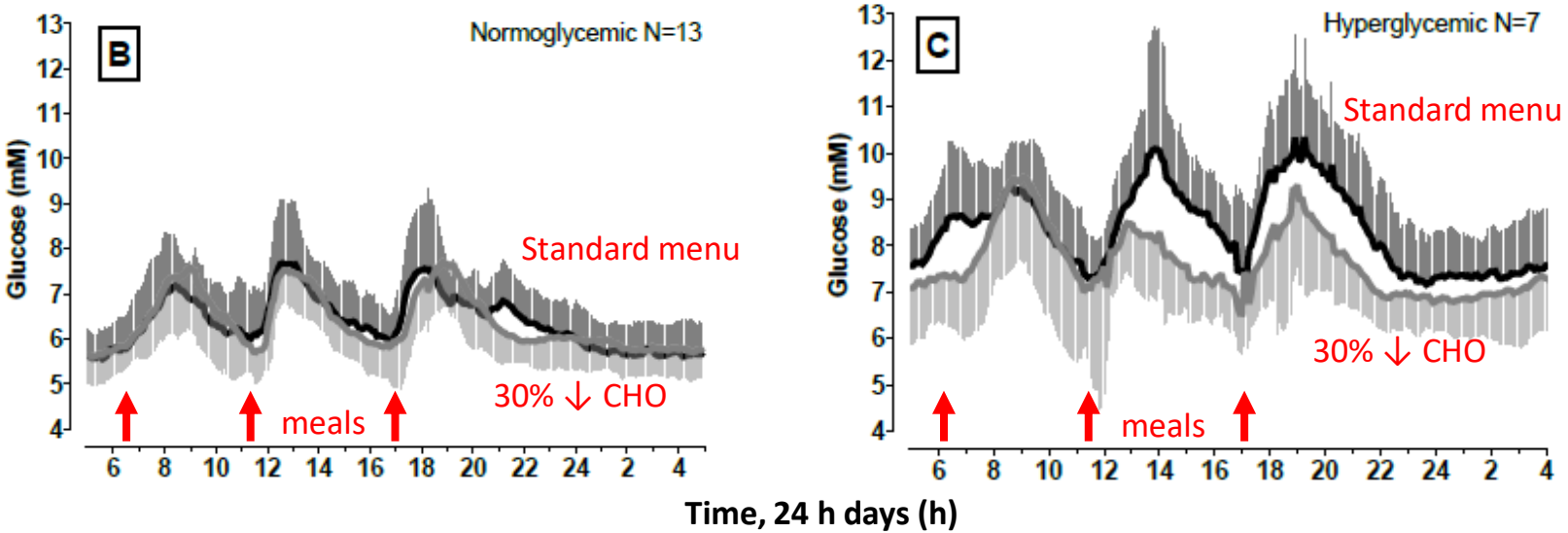
Brain ketone uptake doubles after a supervised walking intervention in Alzheimer's disease (n=10)

8 km/wk, 4 km/h, 12 wk
(Castellano et al. J Alz Disease, 2017)





Improving metabolic health in retirement homes: Can we protect against type 2 diabetes and Alzheimer disease?



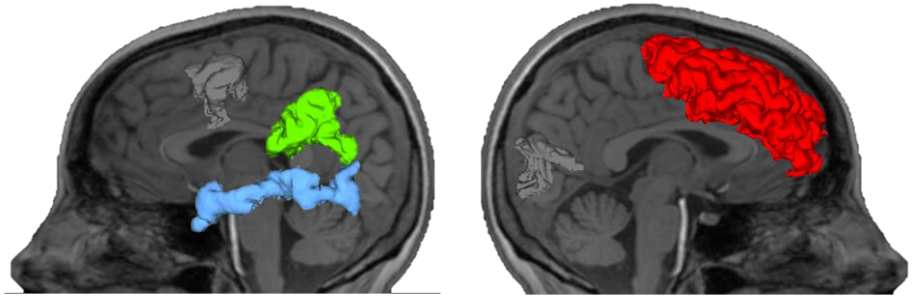
- 84 y old, 10 d feasibility study, 30% ↓ CHO intake
- ↓ post-prandial glucose AUC in hyperglycemics; n.c. in normoglycemics
- In progress: 2-months, 50% ↓ CHO

GOAL: scale up to multi-center trial, 1-year, combined with ketone supplement, with cognitive outcomes

Regional brain glucose hypometabolism in young women with insulin resistance due to polycystic ovary syndrome

(Castellano et al, PLOS1, 2016)

24 years old; normal BMI; mild deficit in working memory



~10% glucose hypometabolism in the parietal, temporal cortex; typical of early Alzheimer's

(Mosconi et al, Eur J Nucl Med Mol Imaging, 2005)

10-14% glucose hypometabolism in the frontal cortex; typical of normal aging

(Nugent et al, Am J Physiol Endocrinol Metab, 2014)

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Brain glucose deficit probably exists in mental illness; exacerbated by antipsychotic medication; as yet almost totally unexplored

metabolism
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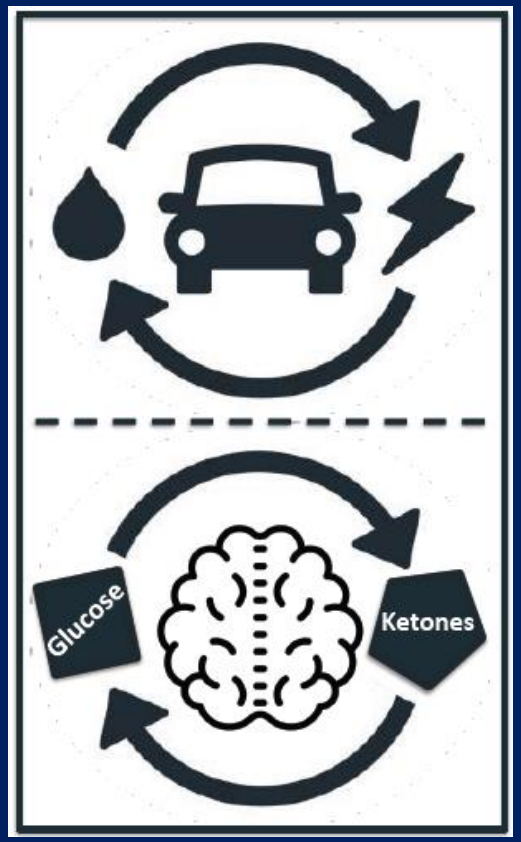
Metabolic health lets the hybrid car work as it should



- Dietary energy / carbohydrate restriction to allow endogenous ketogenesis.
- Never too young or too old to improve glucose regulation.
- Ketones can safely meet ≥75% of the brain's energy requirements.
- Ketone supplements (kMCT, salts, esters).
- Exercise combined with ketones.

Research team and collaborators

Funding partners

Particpants

THANK YOU!