

Developmental pharmacology of analgesics

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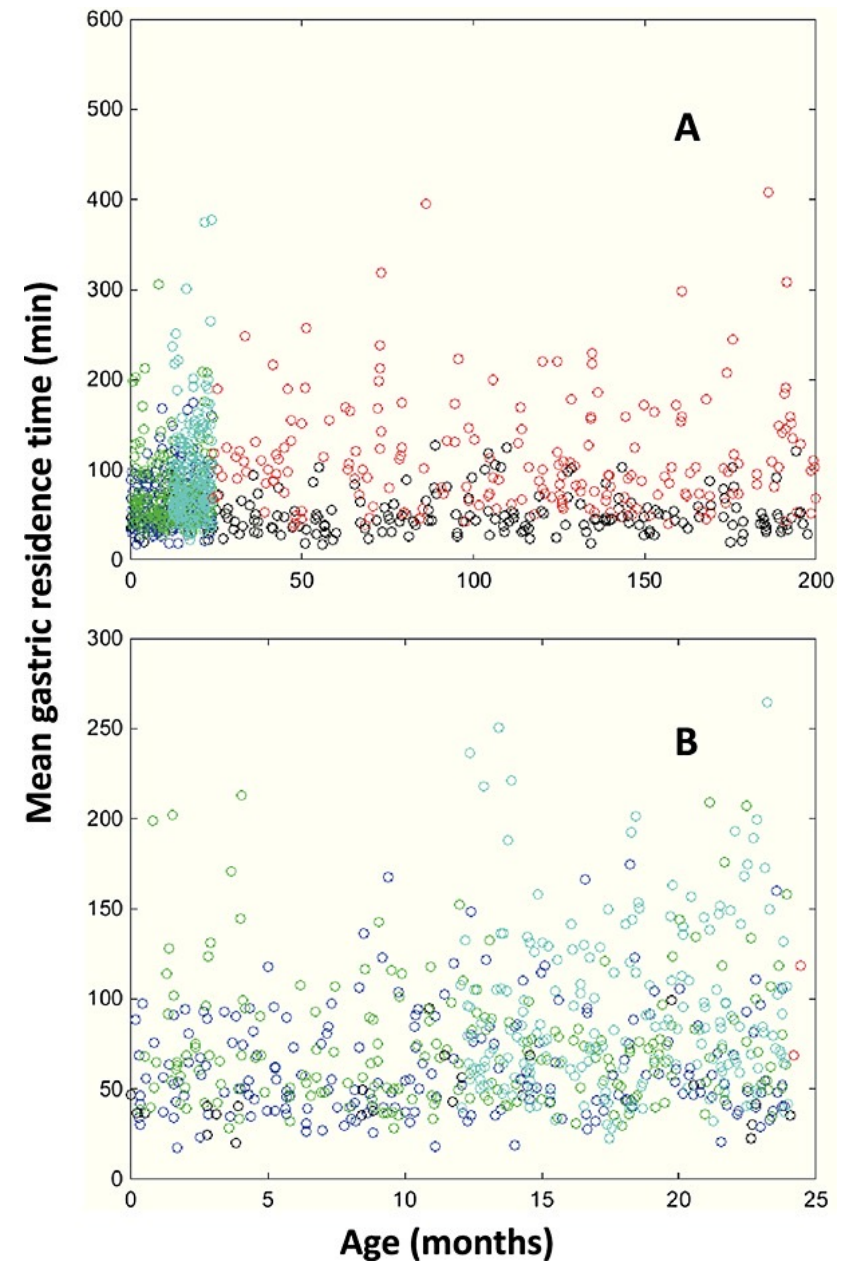
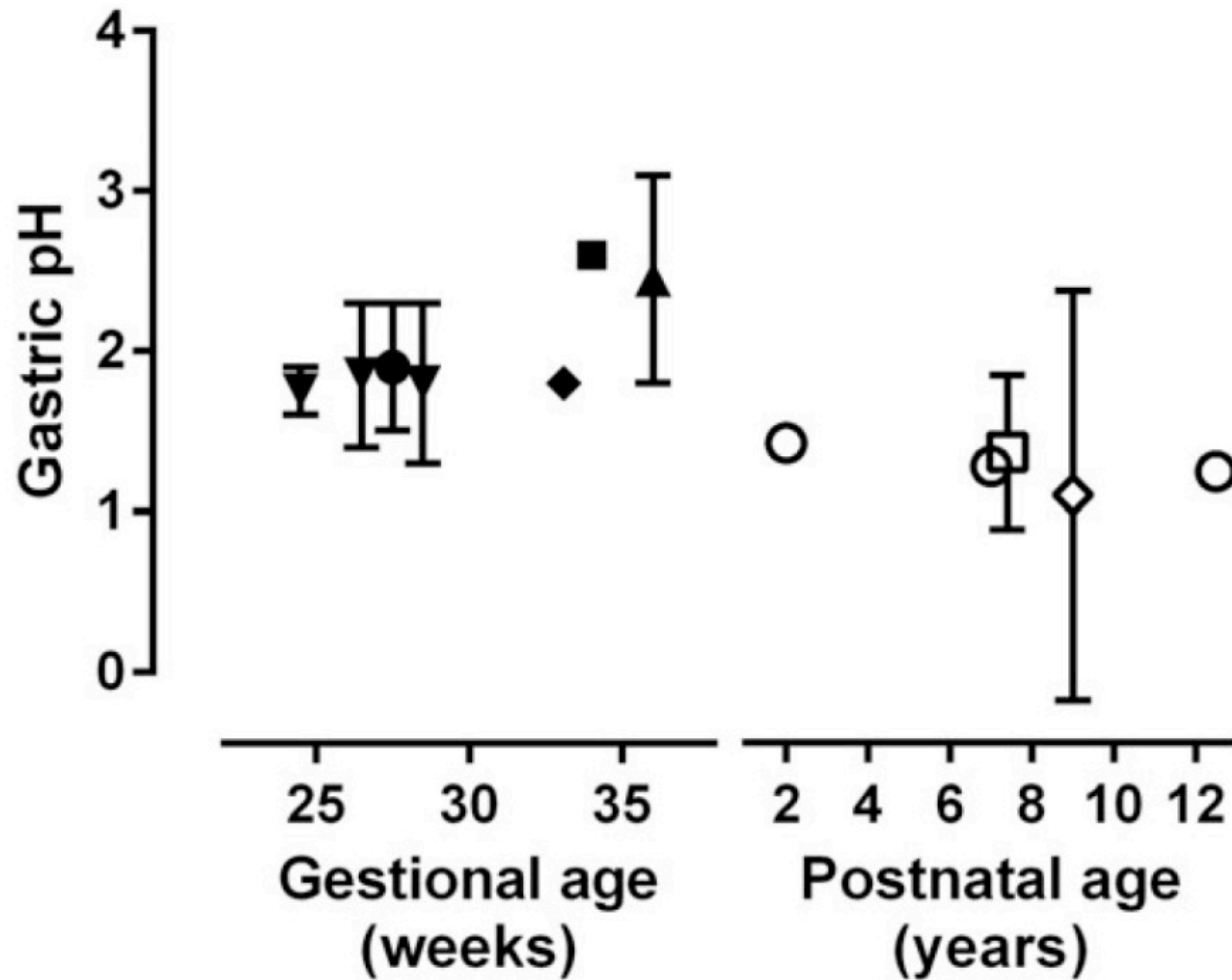


Disclosure statement

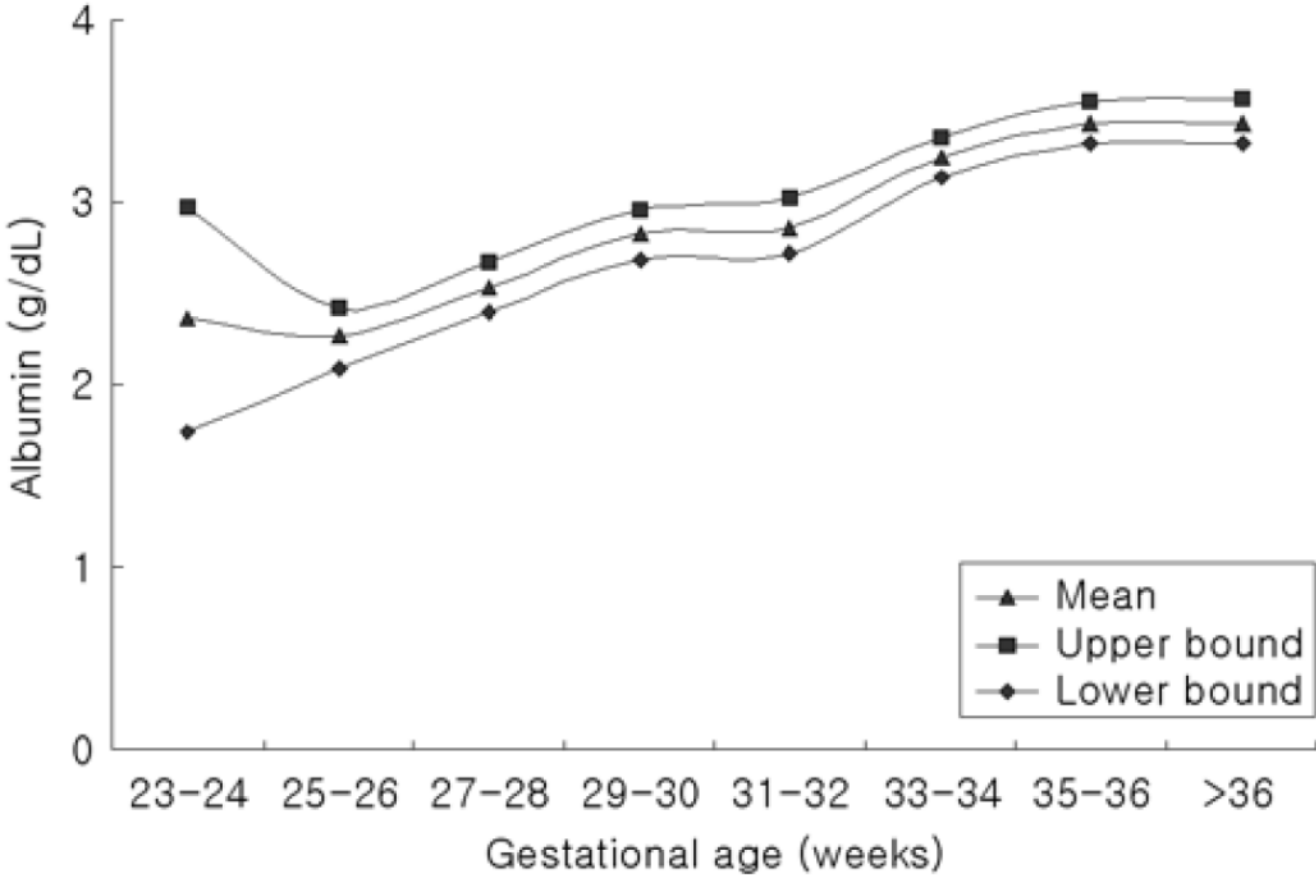
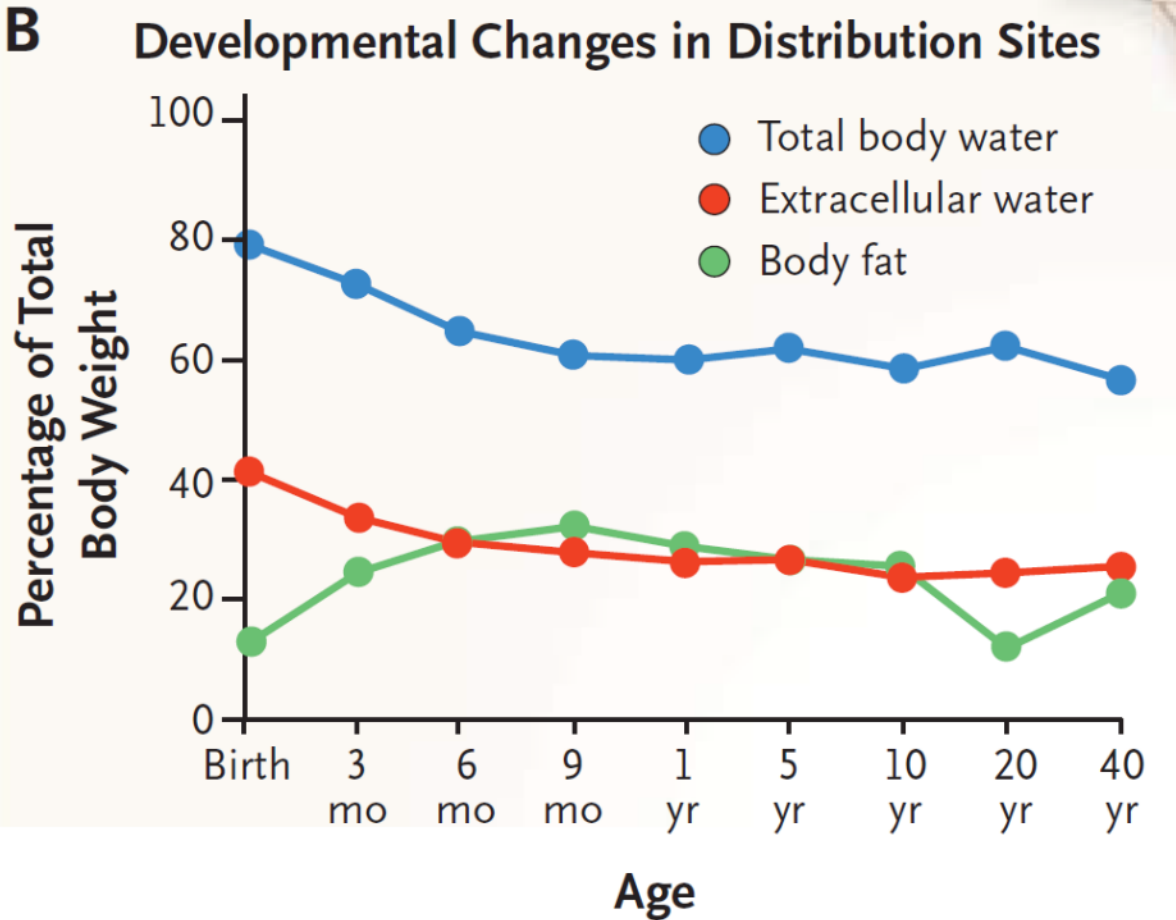
- I have no financial interests or conflicts of interest with any pharmaceutical company to disclose relating to this presentation
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies



Absorption

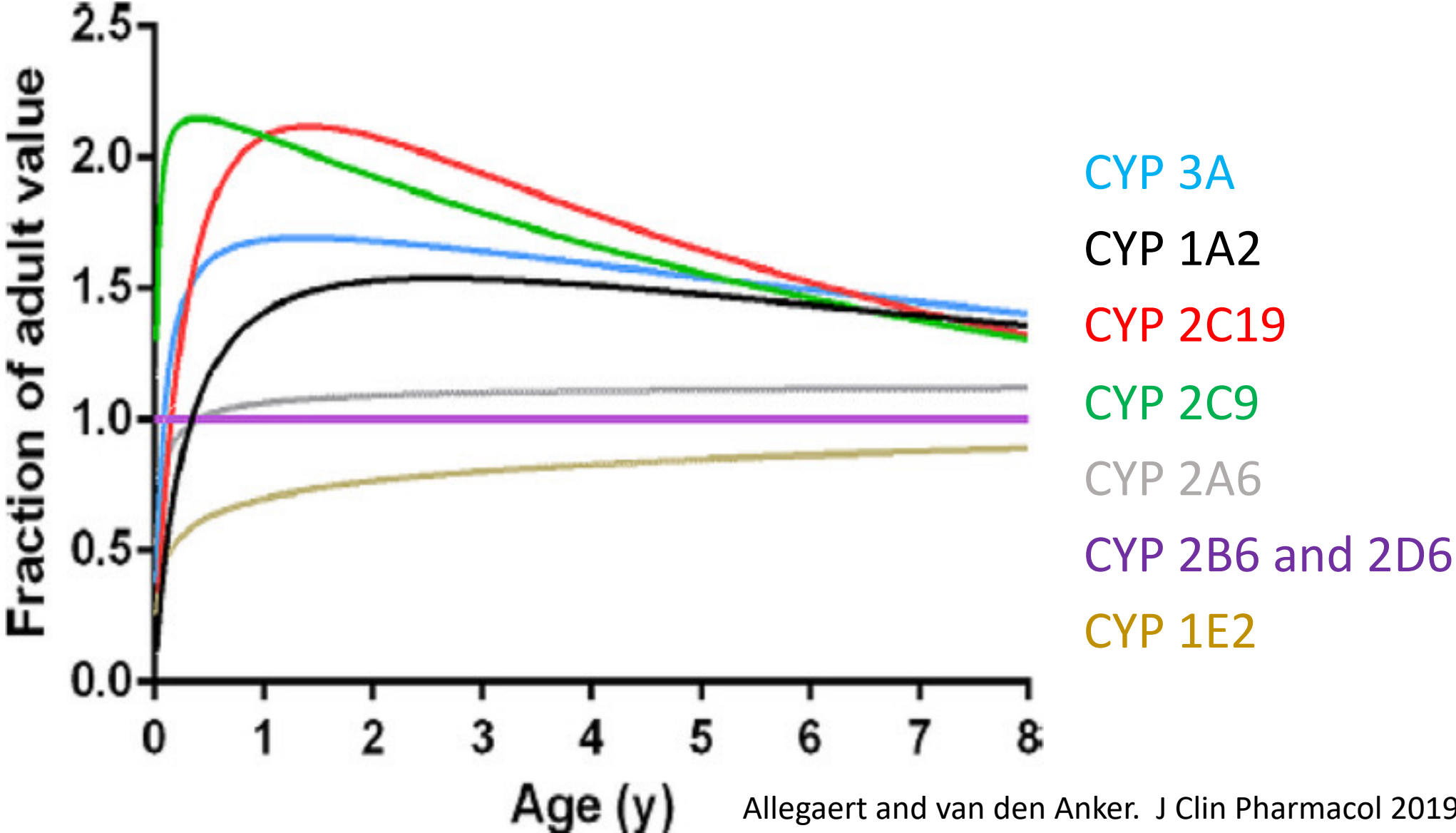


Distribution

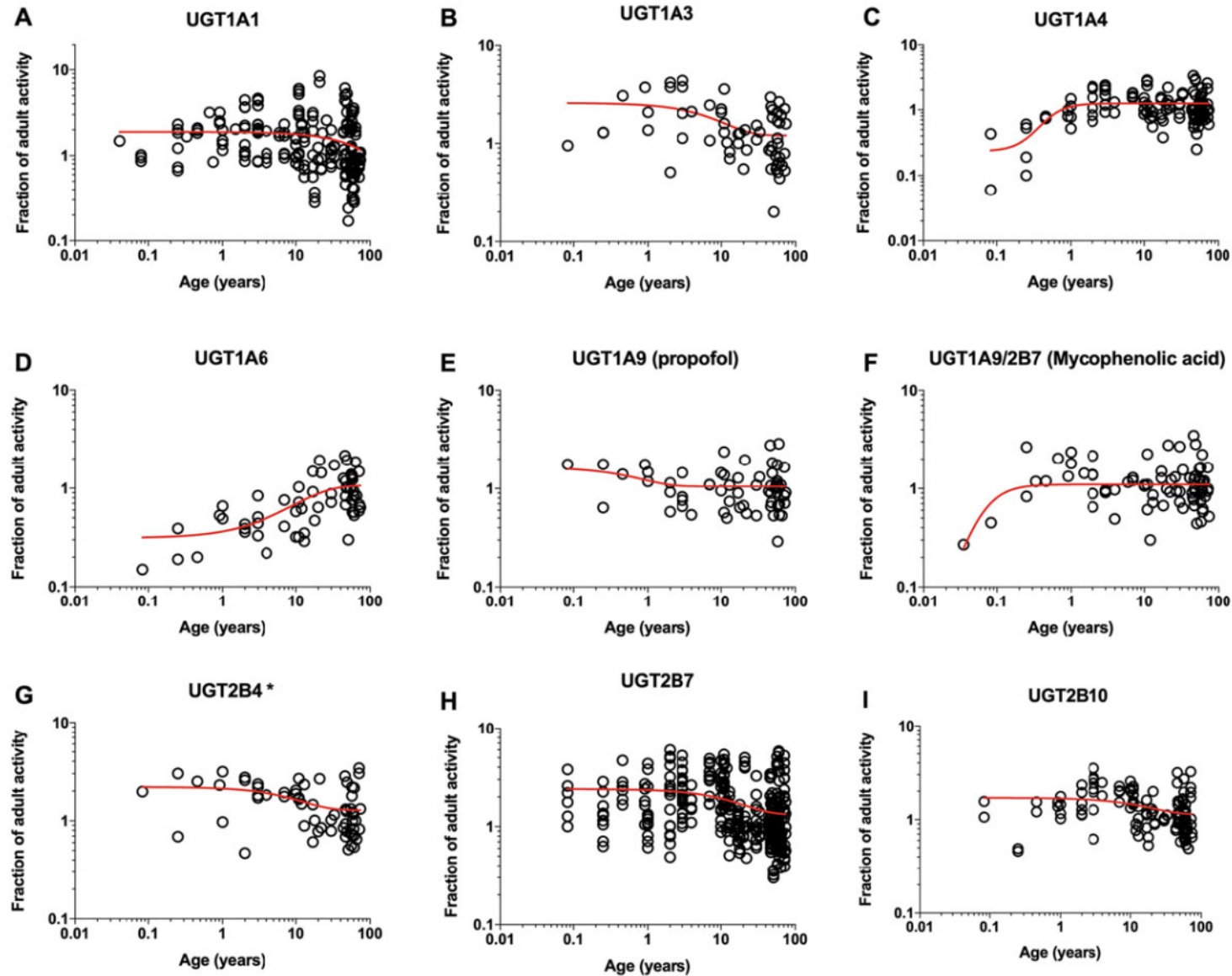


Kearnes et al. N Engl J Med 2003; 349: 1157-1167
 Lee et al. Korean J Pediatr 2005; 48: 148-153.

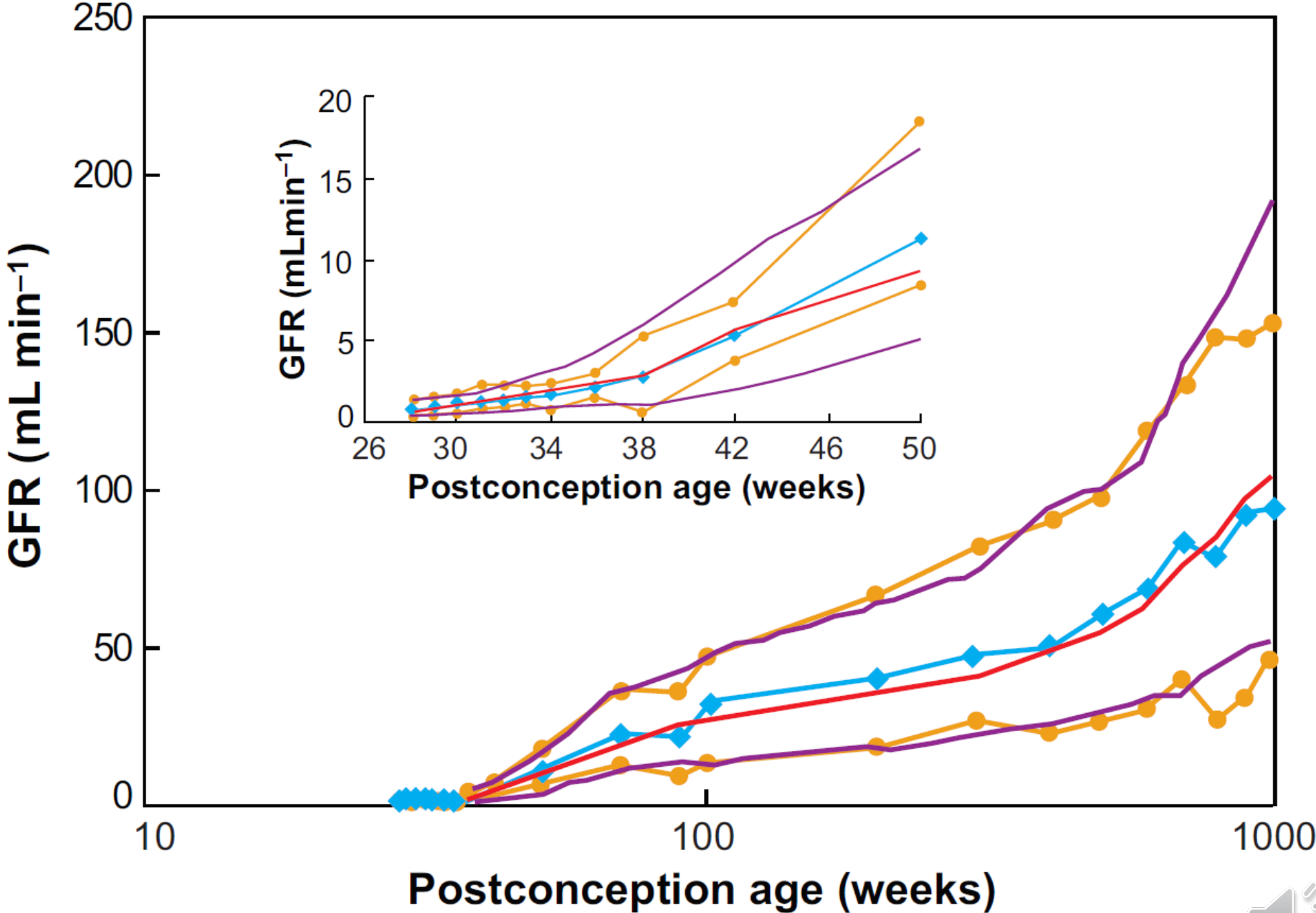
Metabolism – Phase I



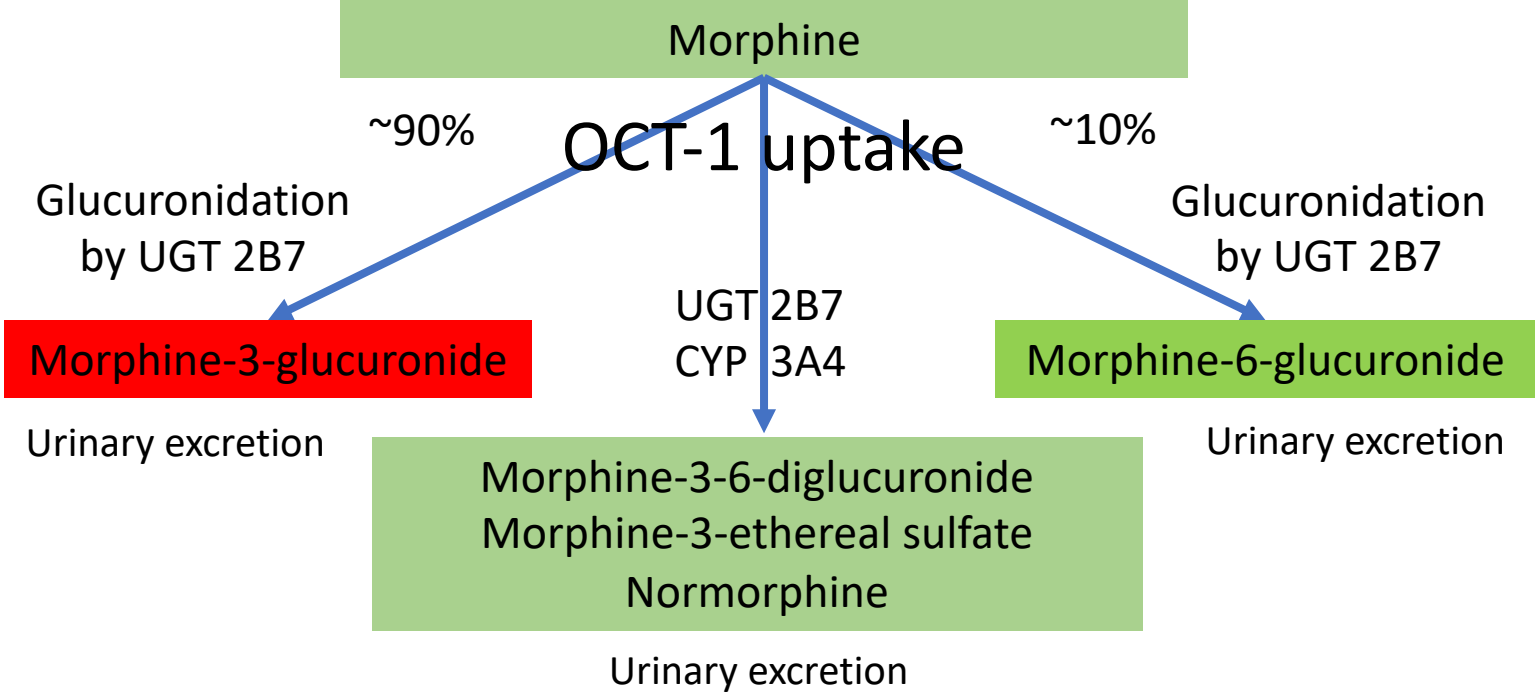
Metabolism – Phase II



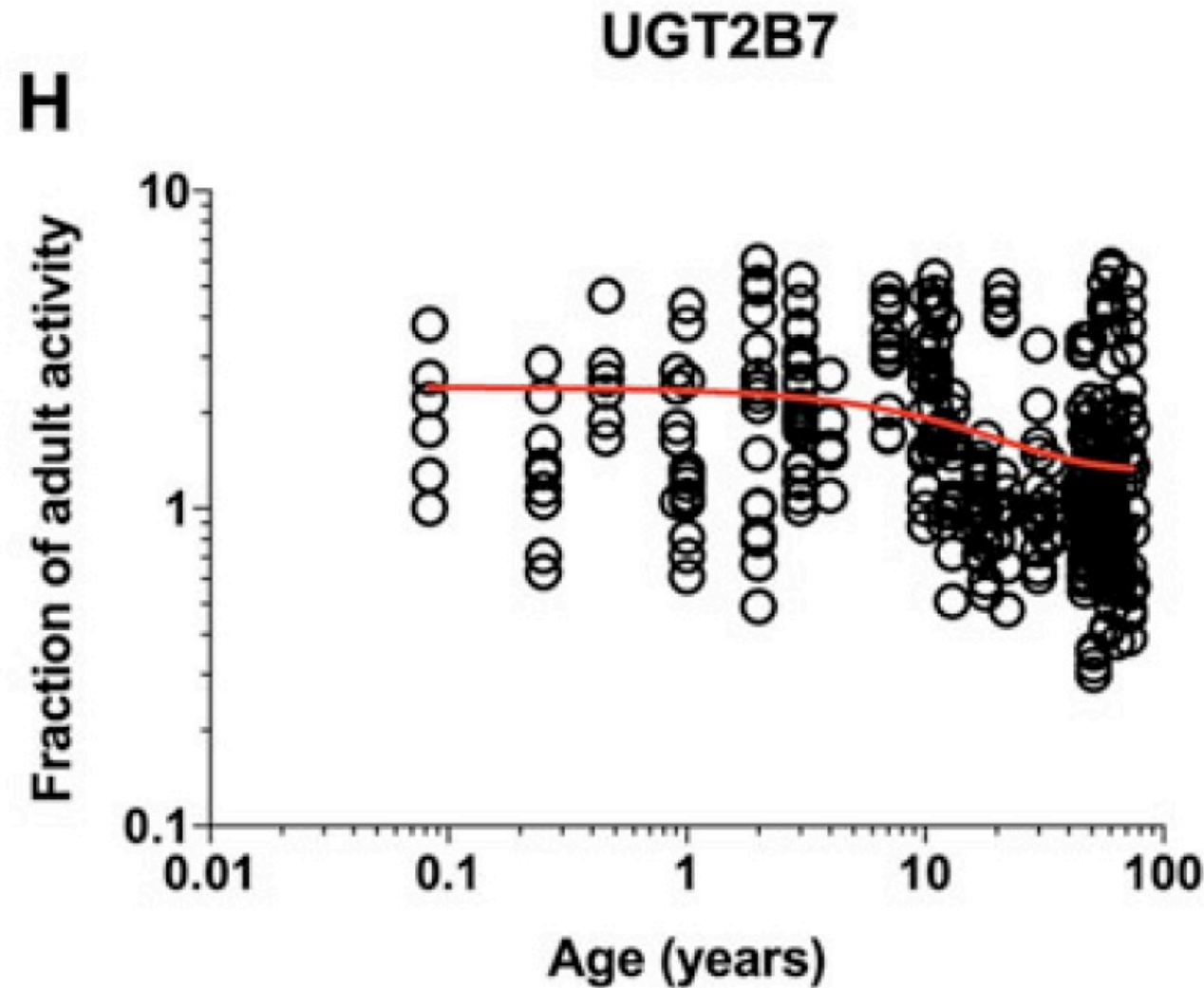
Excretion



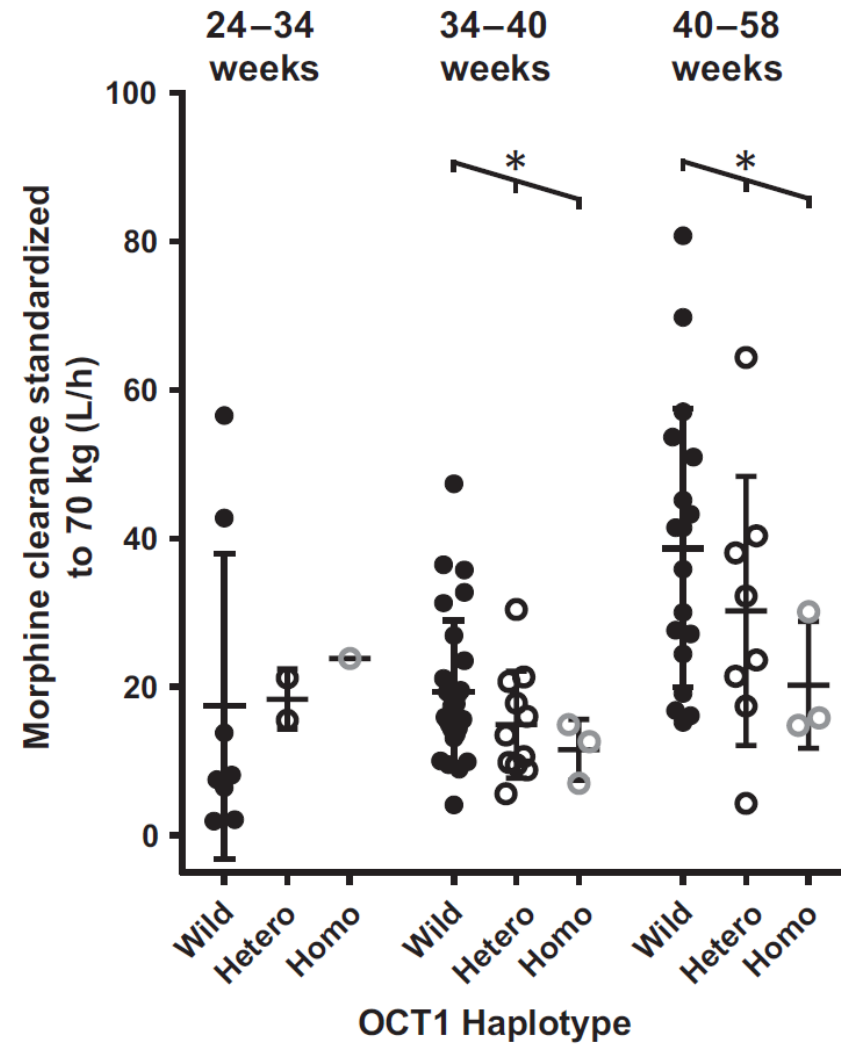
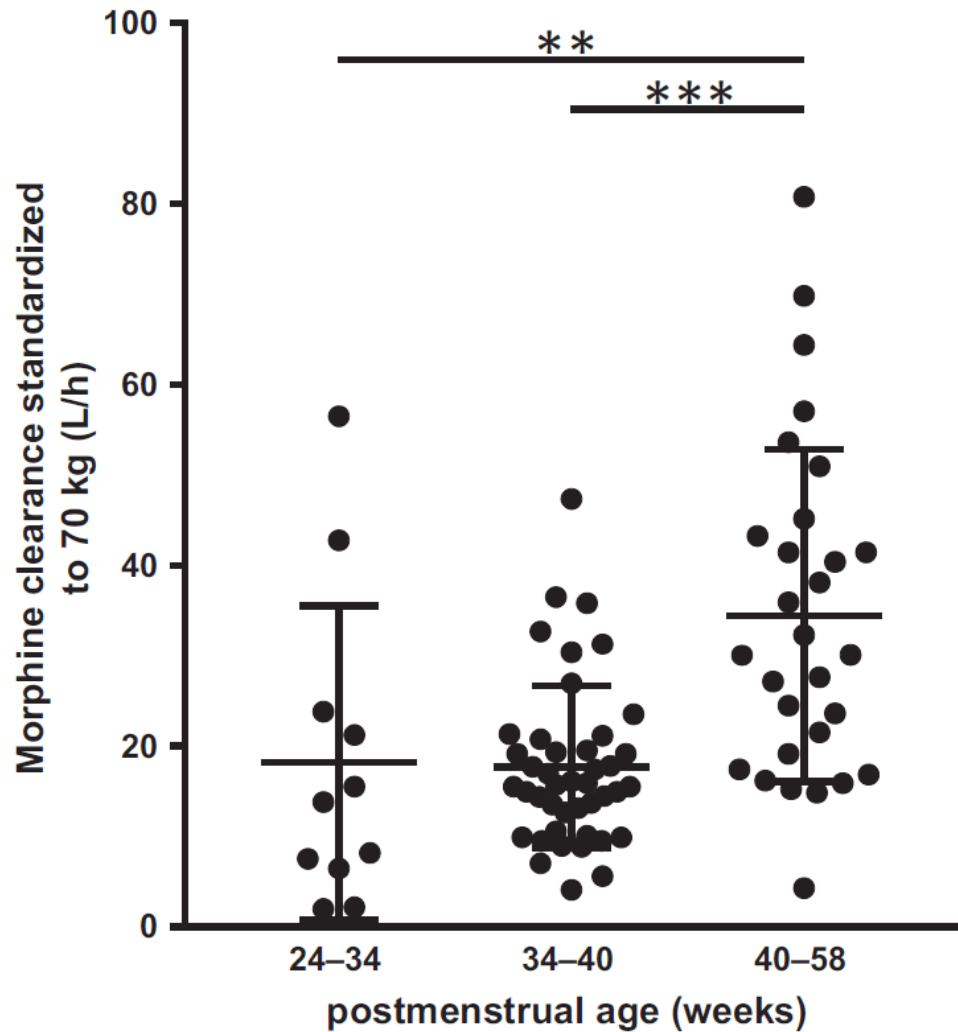
Opioid metabolism



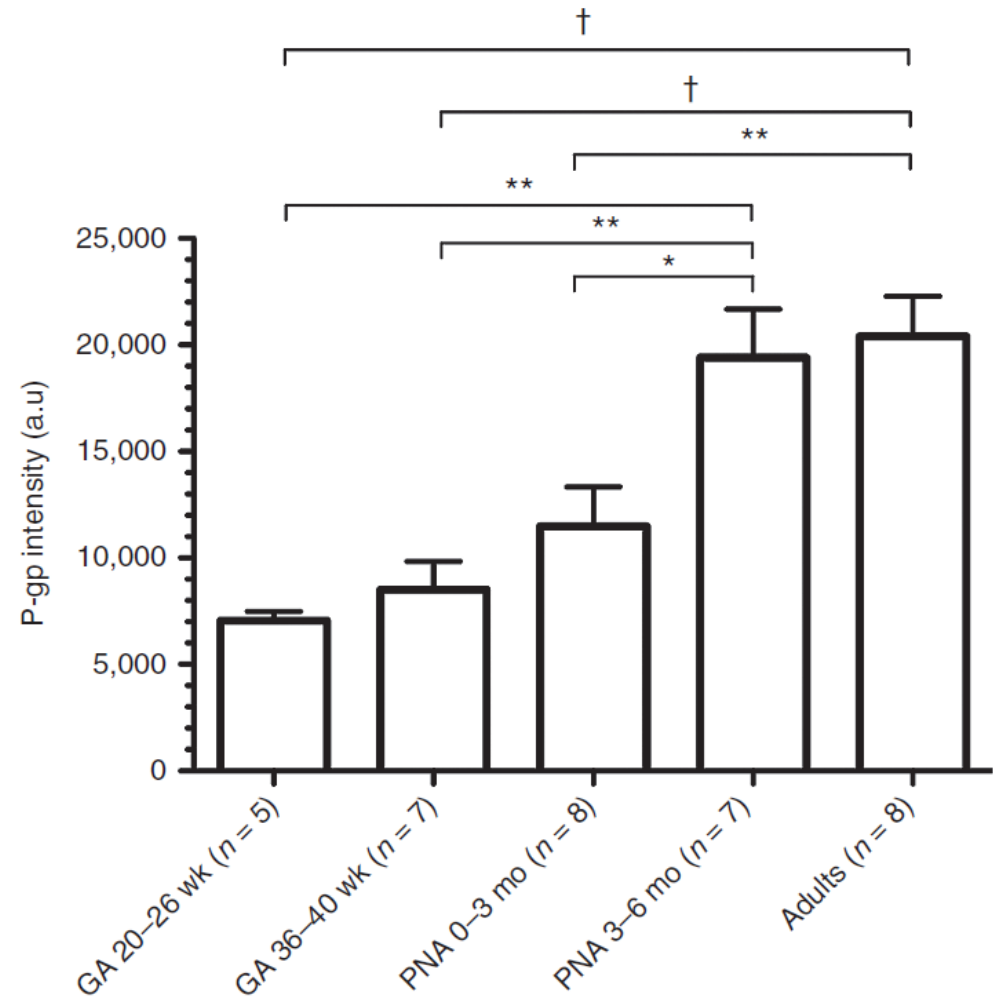
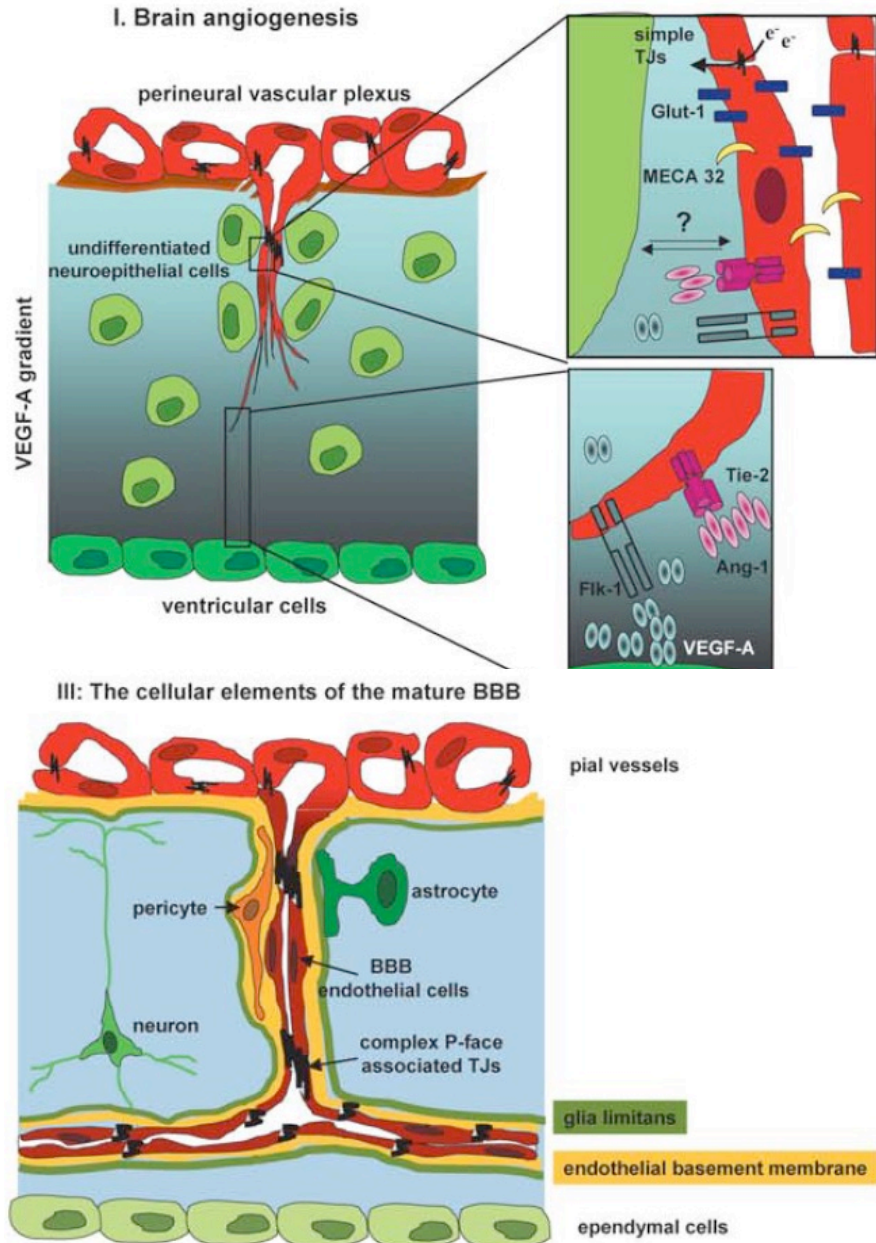
Ontogeny of morphine elimination pathways



Ontogeny of morphine elimination pathways



Serum opioid concentrations may not reflect CSF concentrations



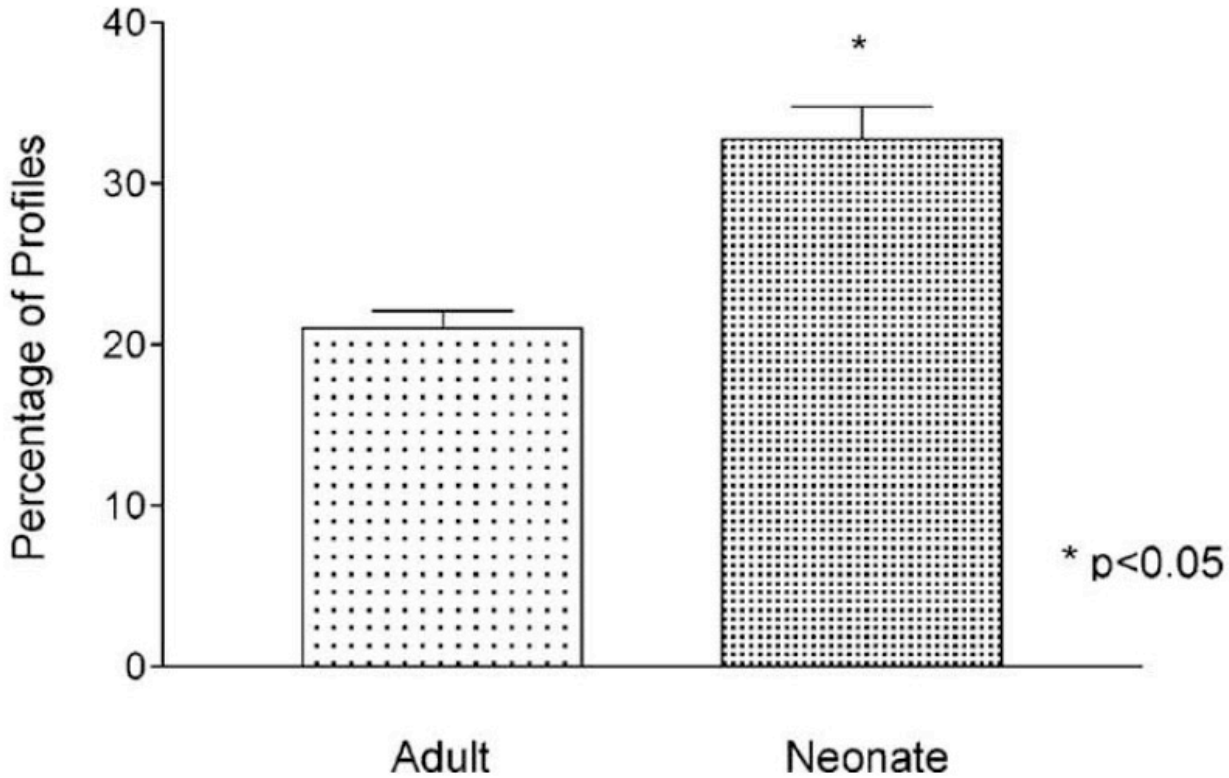
Developmental ages

Engelhardt. Cell Tissue Research 2003; 314: 119-129.

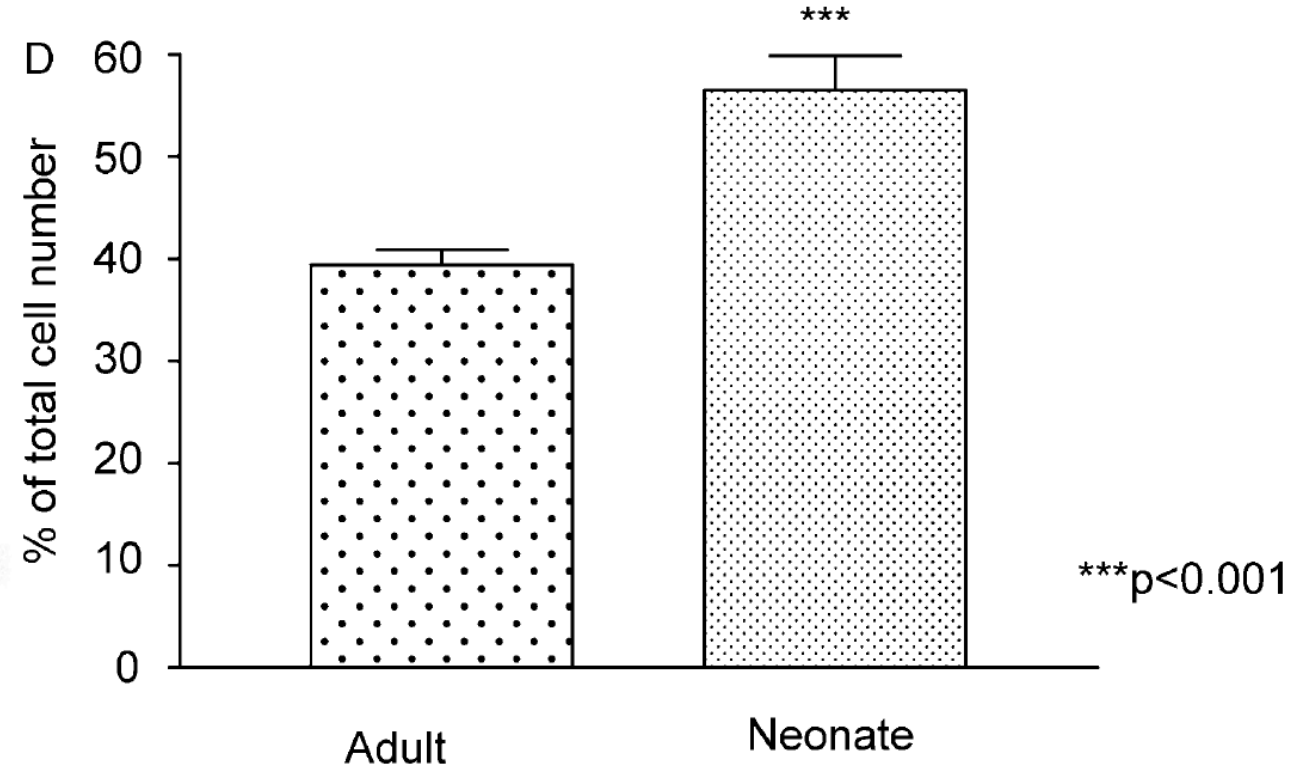
Lam et al. Pediatr Res 2015; 78: 417-421.



Opioid receptor ontogeny



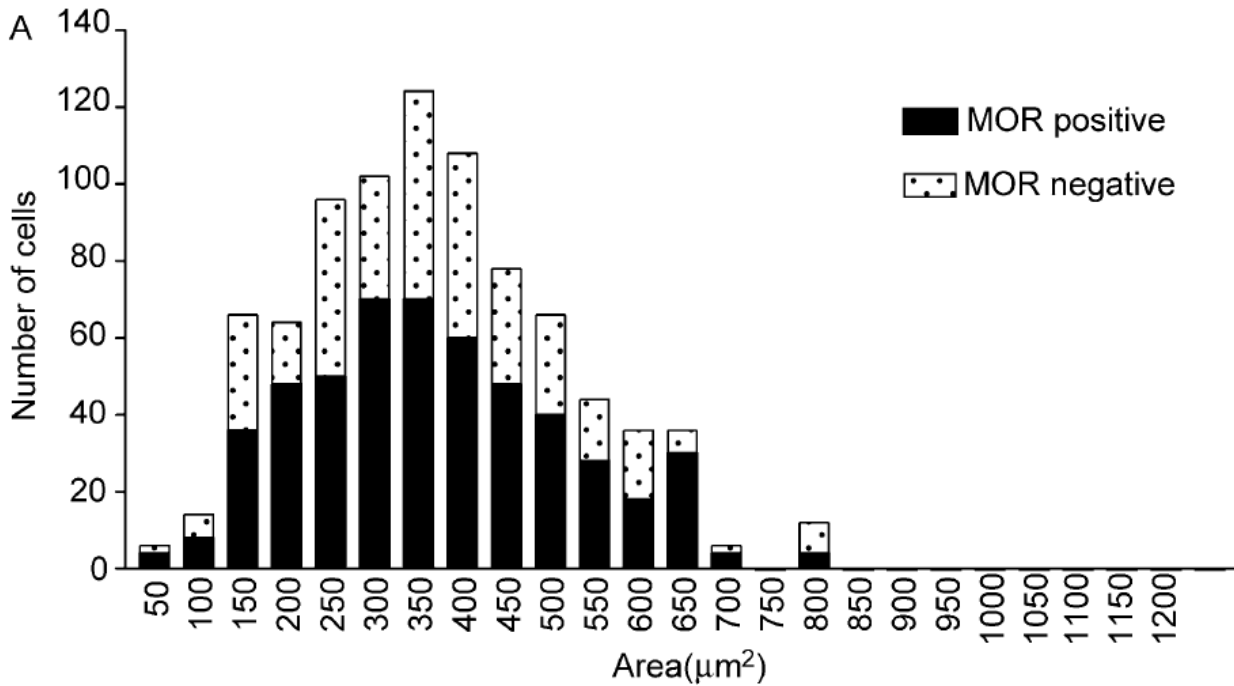
μ -opioid receptor expression in rat dorsal root ganglion



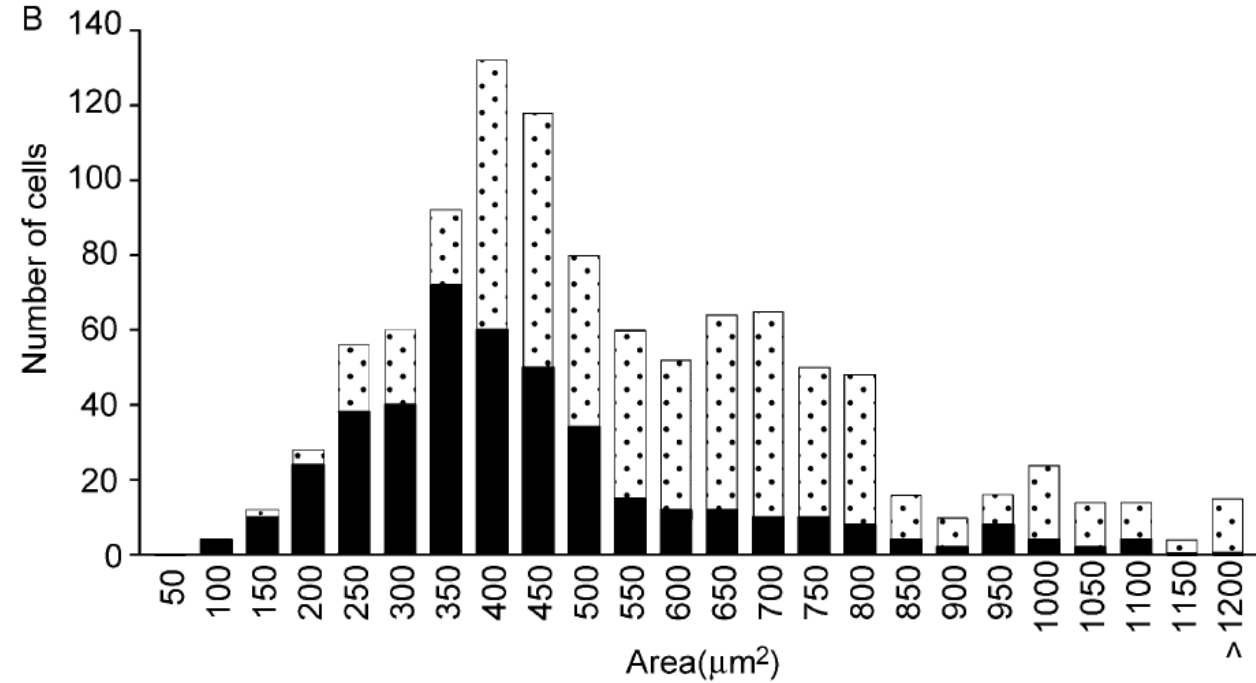
Opioid responsive cells in rat dorsal root ganglion



Opioid receptor ontogeny



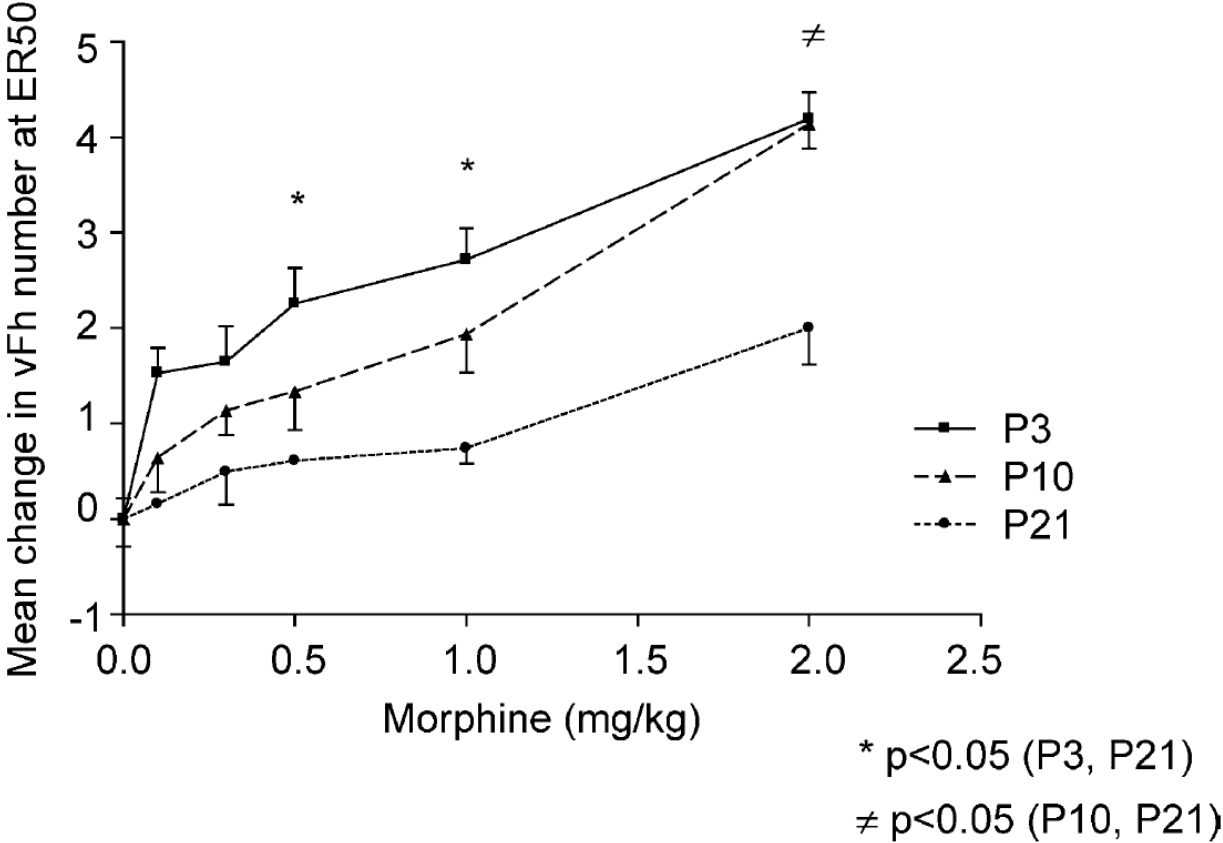
Adult rat dorsal root ganglion
(MOR positive small and medium cells)



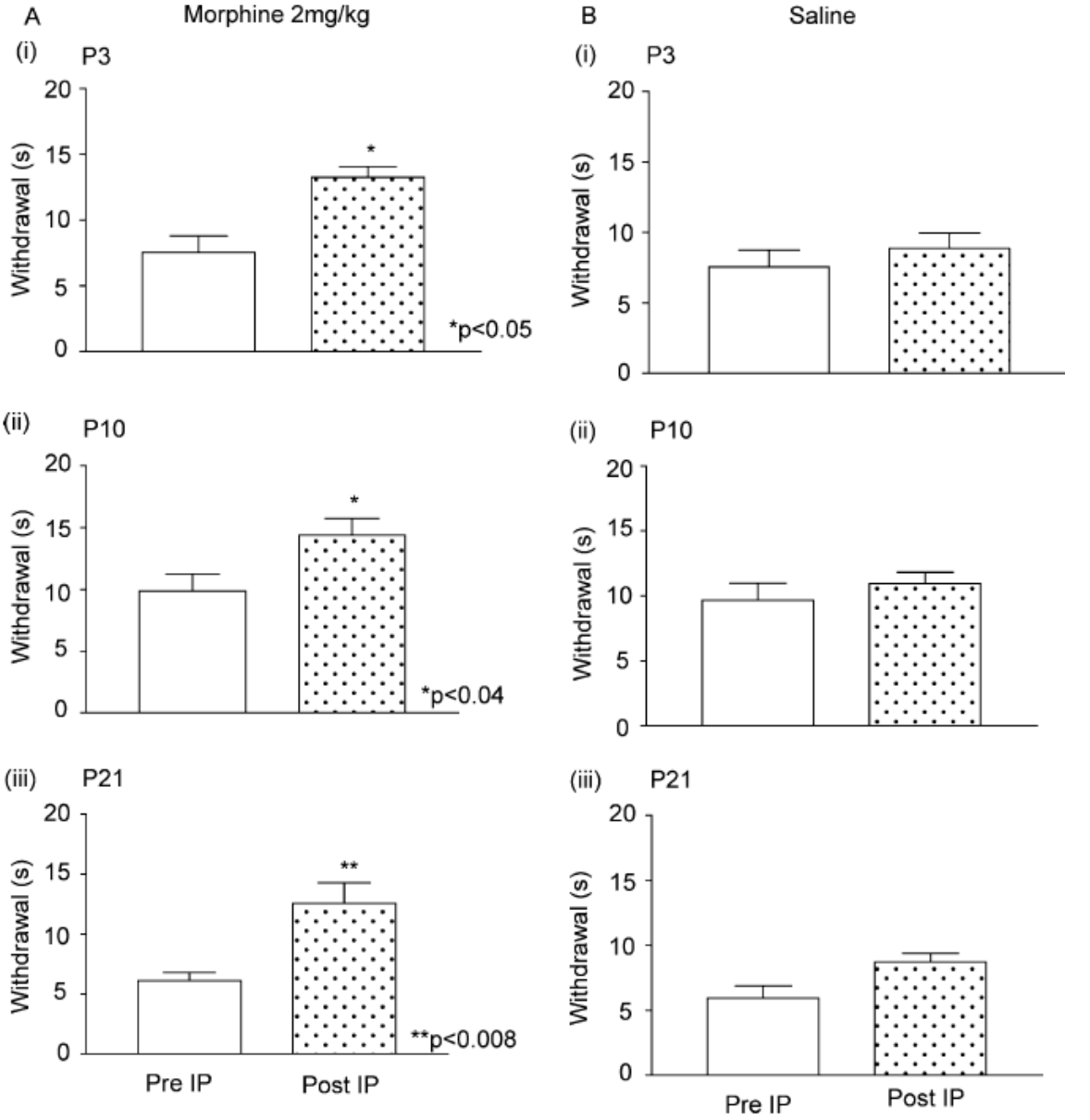
Neonatal rat dorsal root ganglion
(Diffuse distribution of MOR positive cells)



Opioid receptor ontogeny

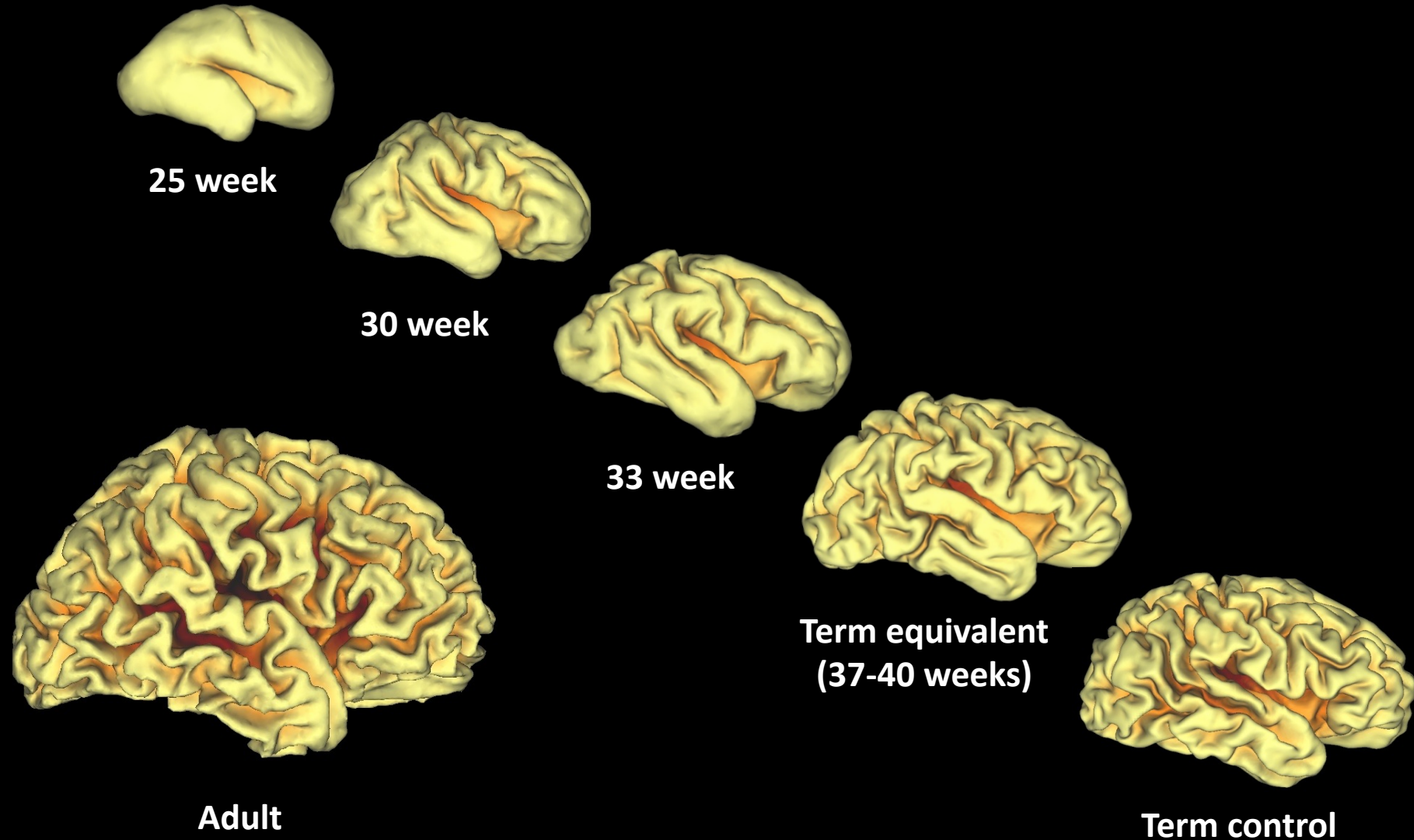


Decreased morphine sensitivity with age in the setting of mechanical stimulation

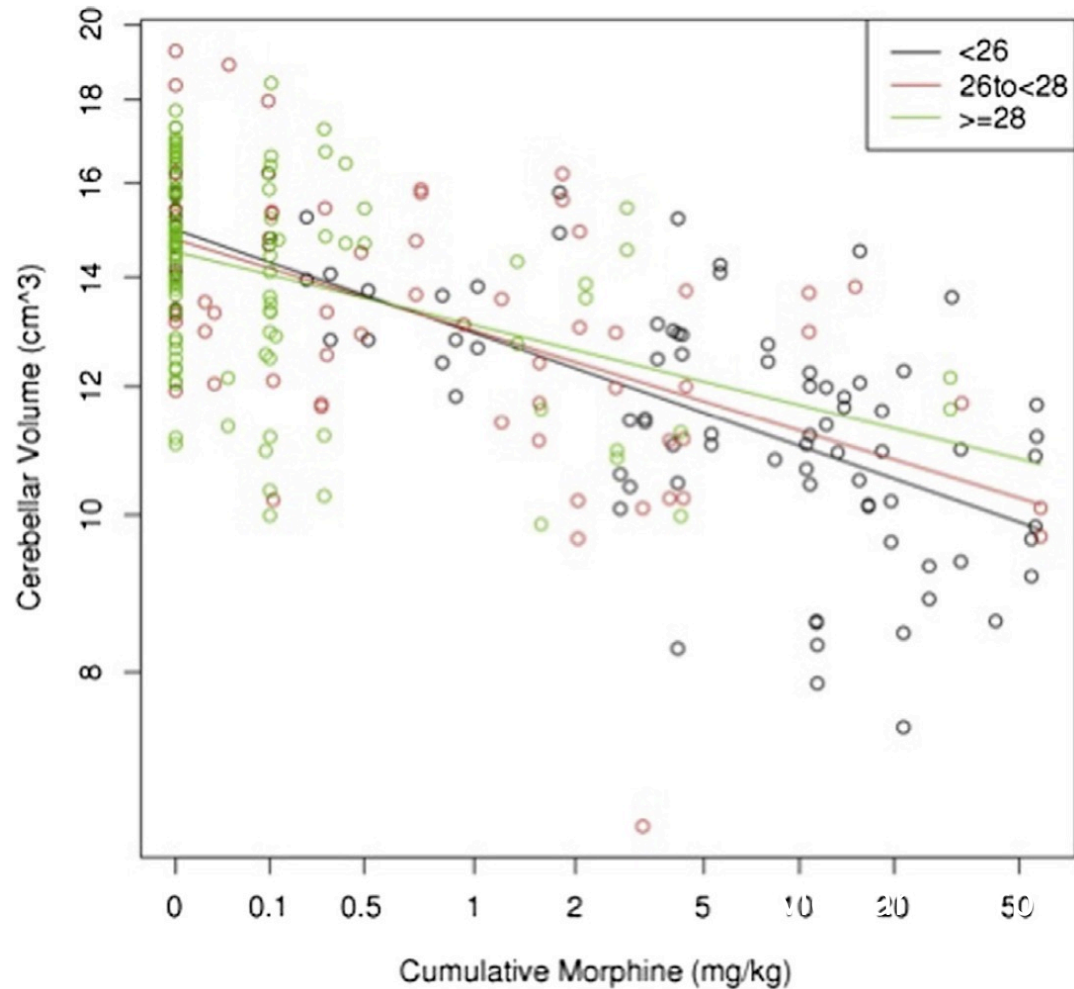


No difference in morphine sensitivity with age in the setting of thermal stimulation

Developmental impact



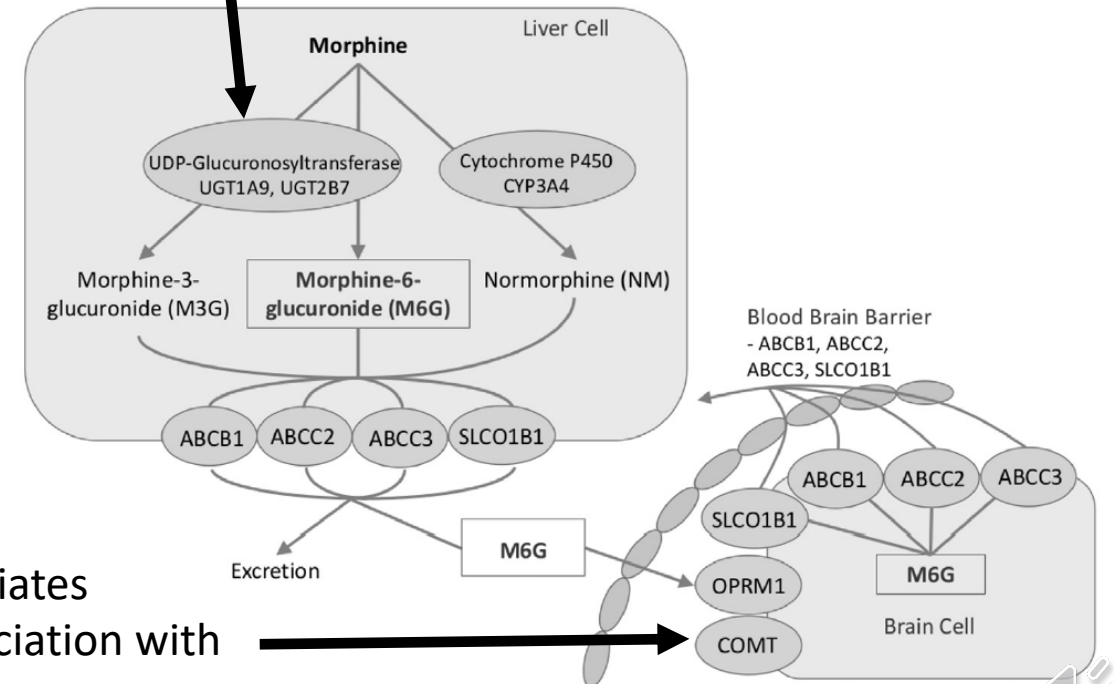
Morphine and developmental outcomes in preterm infants



Morphine exposure significantly associated with poorer motor scores ($p < 0.001$) and cognitive outcomes ($p = 0.006$) at 18 months CA

Mediates association with anxiety/depression

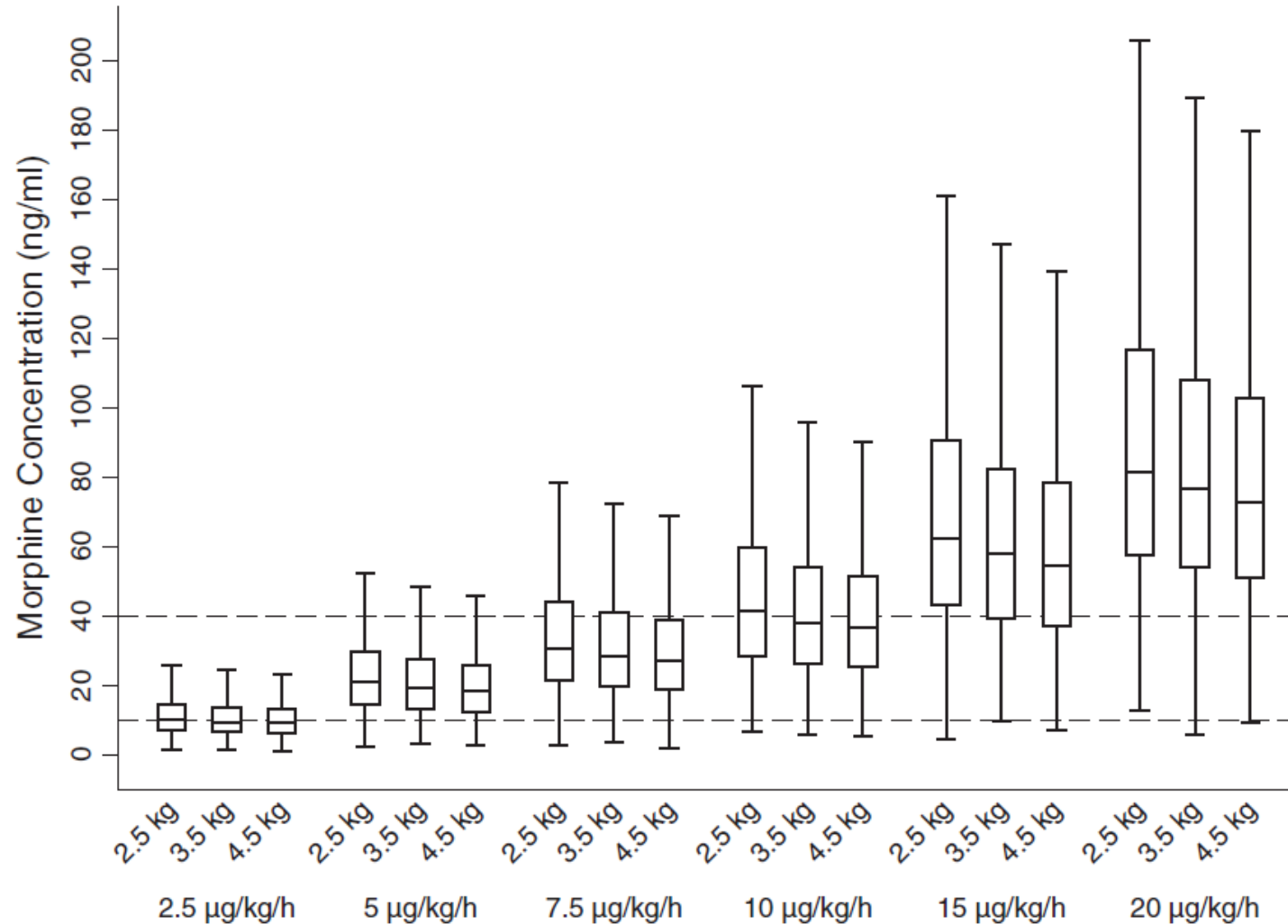
UGT 1A6?



Mediates association with acting out

Zwicker, Miller, et al. J Pediatr 2016; 172: 81-7.
Chau et al, Grunau. EBioMedicine 2019; 40: 655-62.

Morphine pharmacokinetics in therapeutic hypothermia

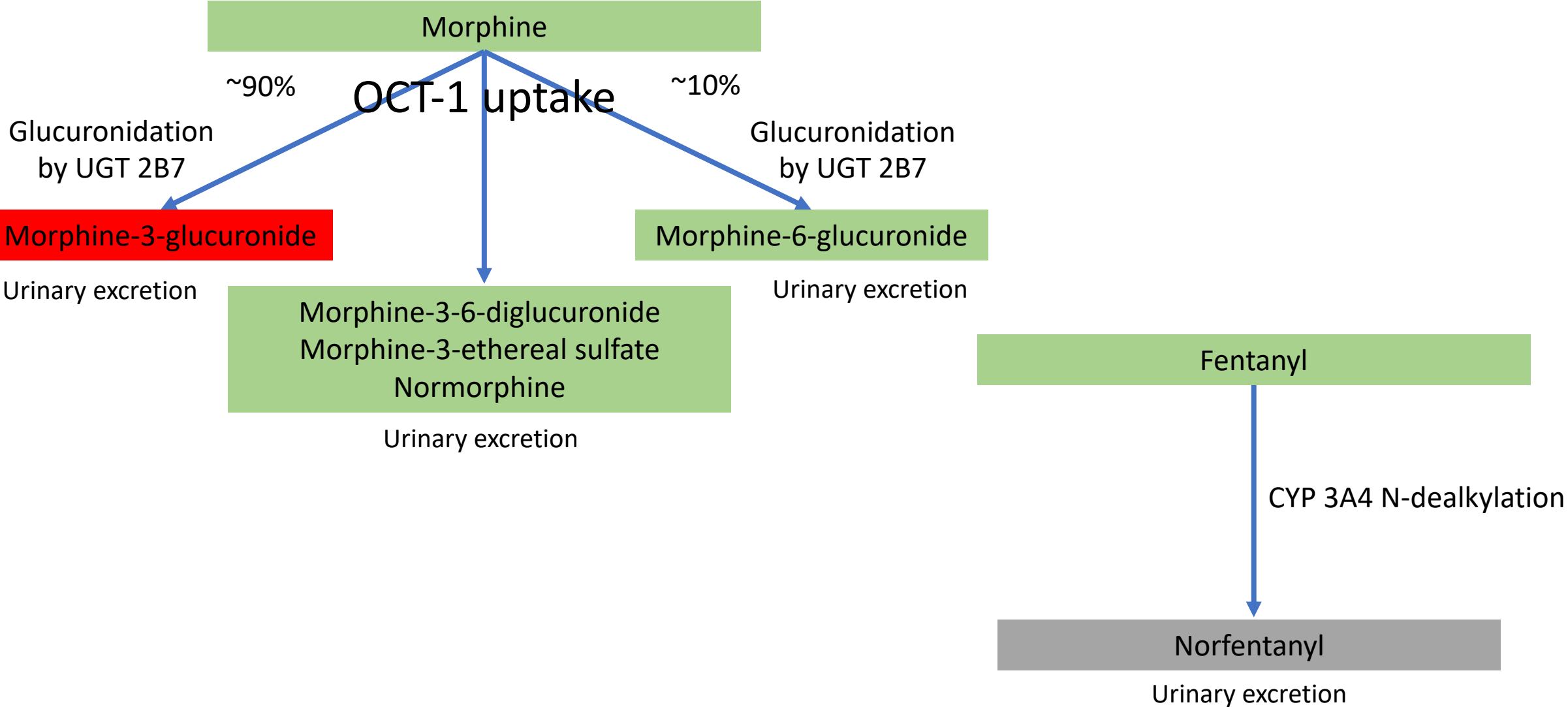


Frymoyer, Bonifacio, et al. *J Clin Pharmacol* 2017; 57: 64-76.

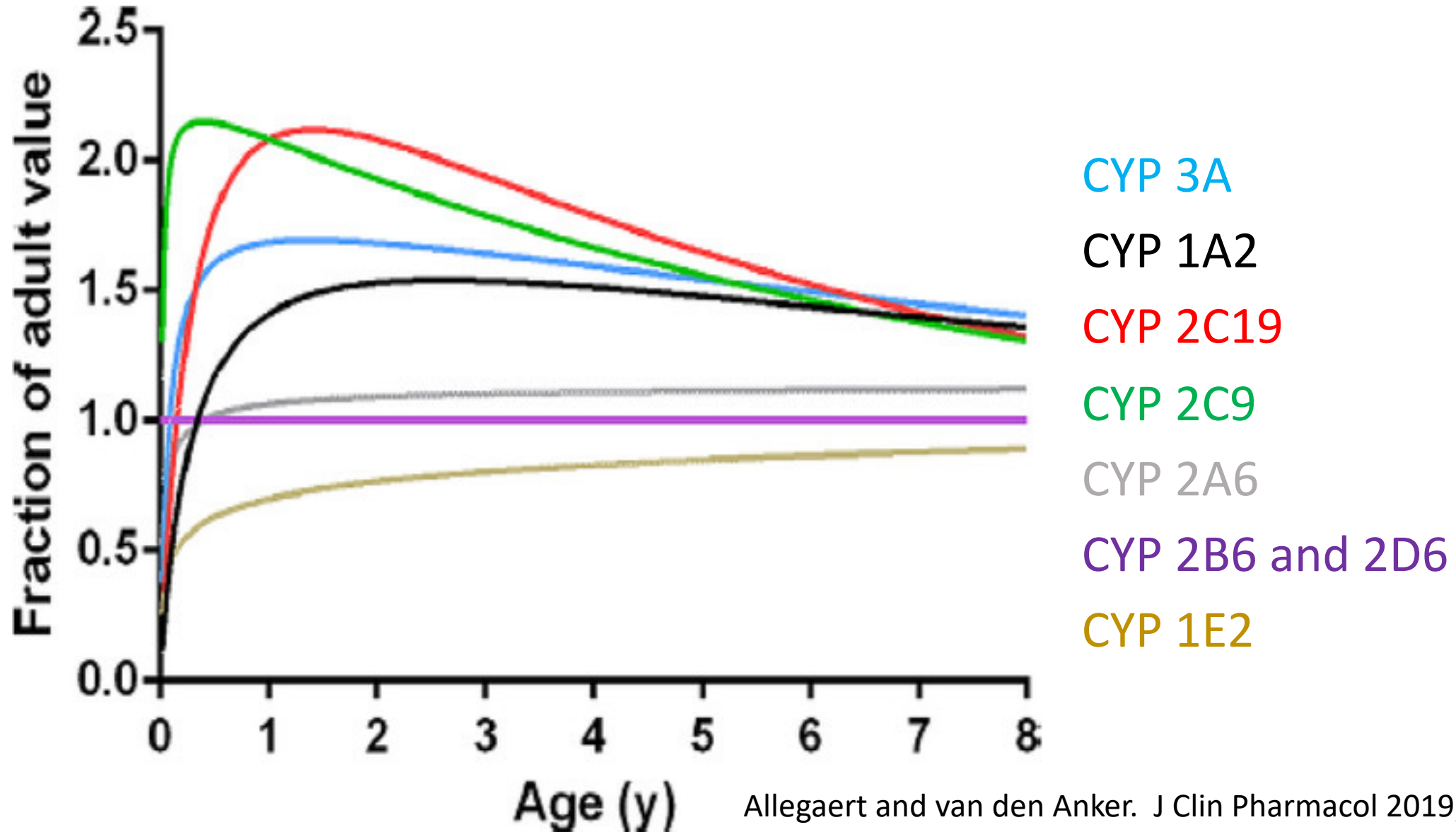
Favie, Groenendaal, the PharmaCool study group. *PLoS One* 2019; 14: e0211910.



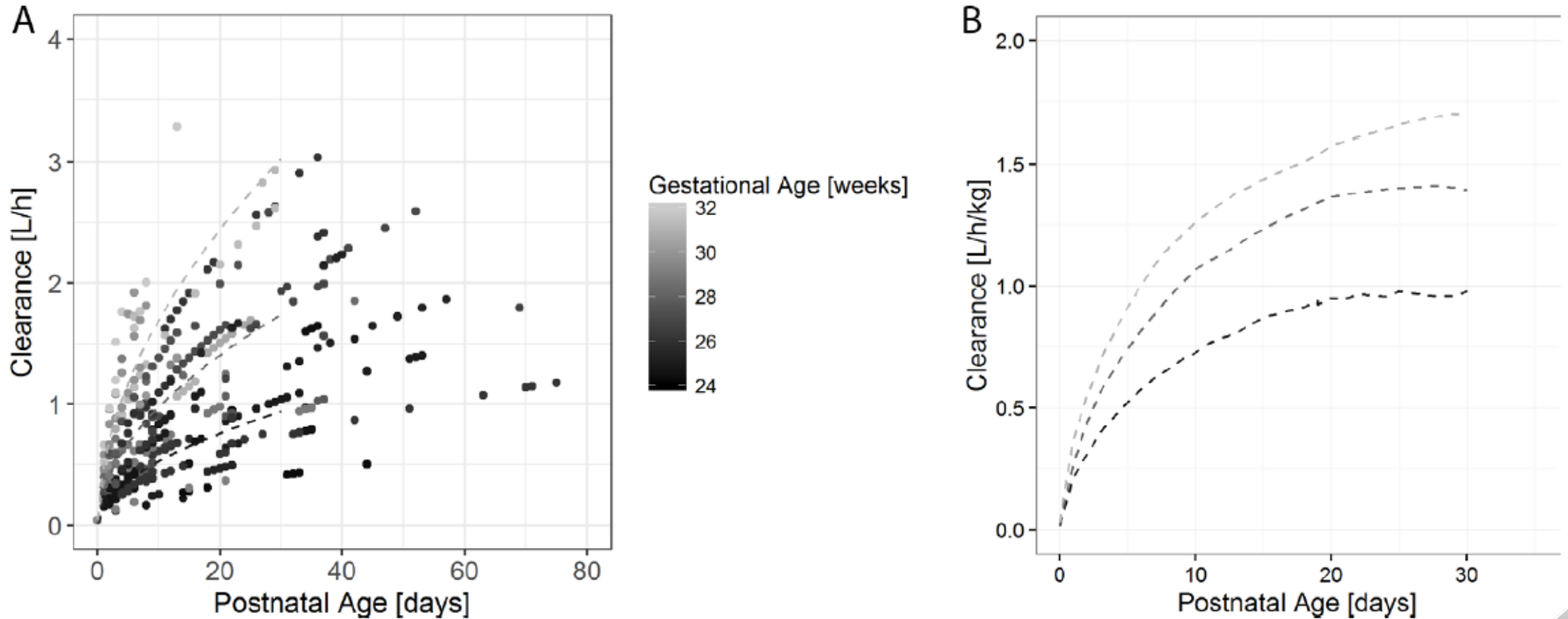
Opioid metabolism



Ontogeny of major hepatic CYP enzymes



Fentanyl pharmacokinetics in preterm neonates



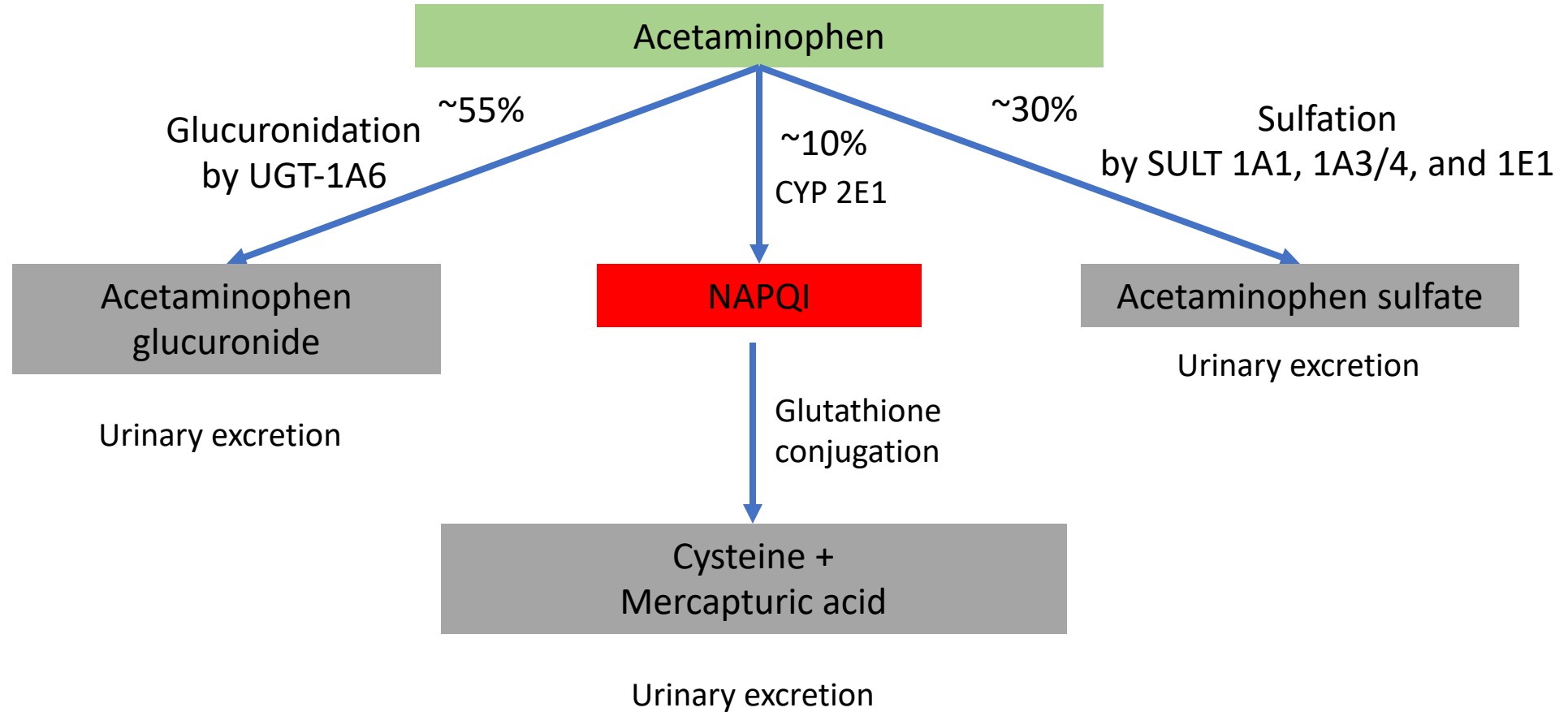
Developmental formulations

- $1 \text{ mcg/kg} \times 1 \text{ kg} \div 50 \text{ mcg/mL} = 0.02 \text{ mL}$

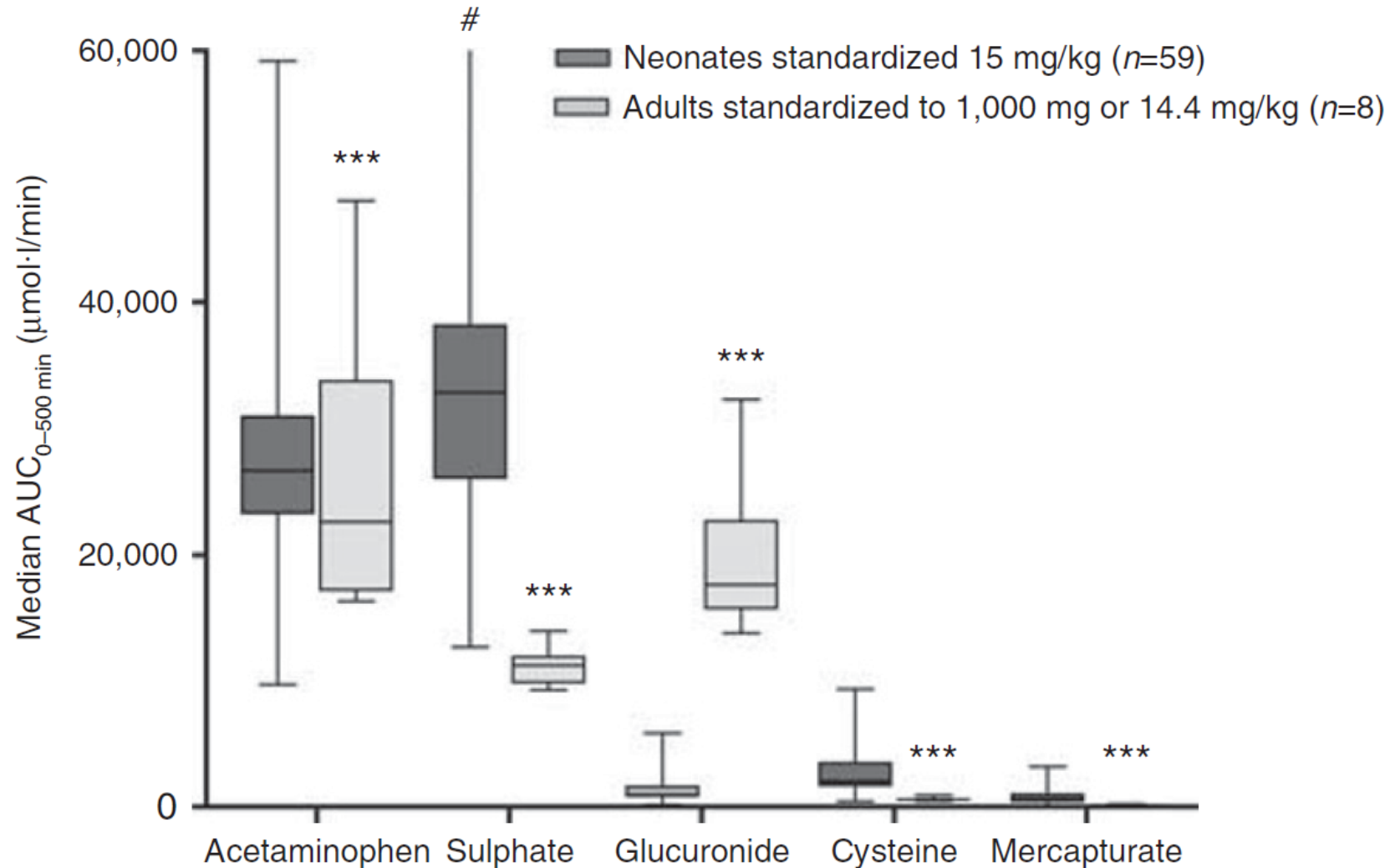
- $1 \text{ mcg/kg} \times 1 \text{ kg} \div 5 \text{ mcg/mL} = 0.2 \text{ mL}$



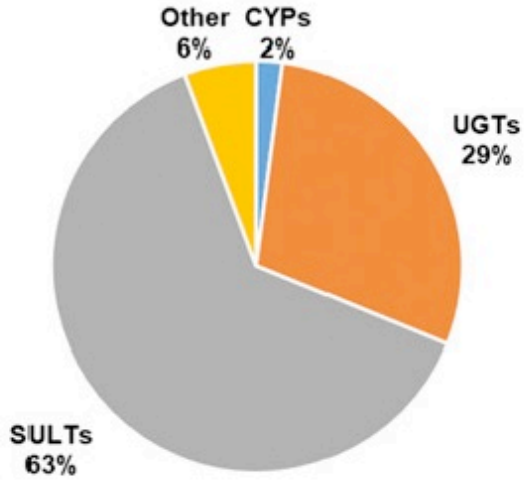
Acetaminophen metabolism



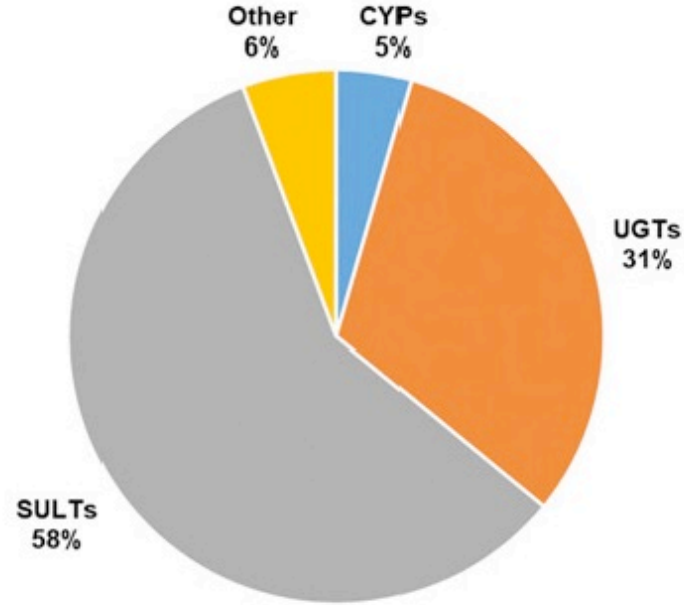
Ontogeny of acetaminophen elimination pathways in VPT neonates



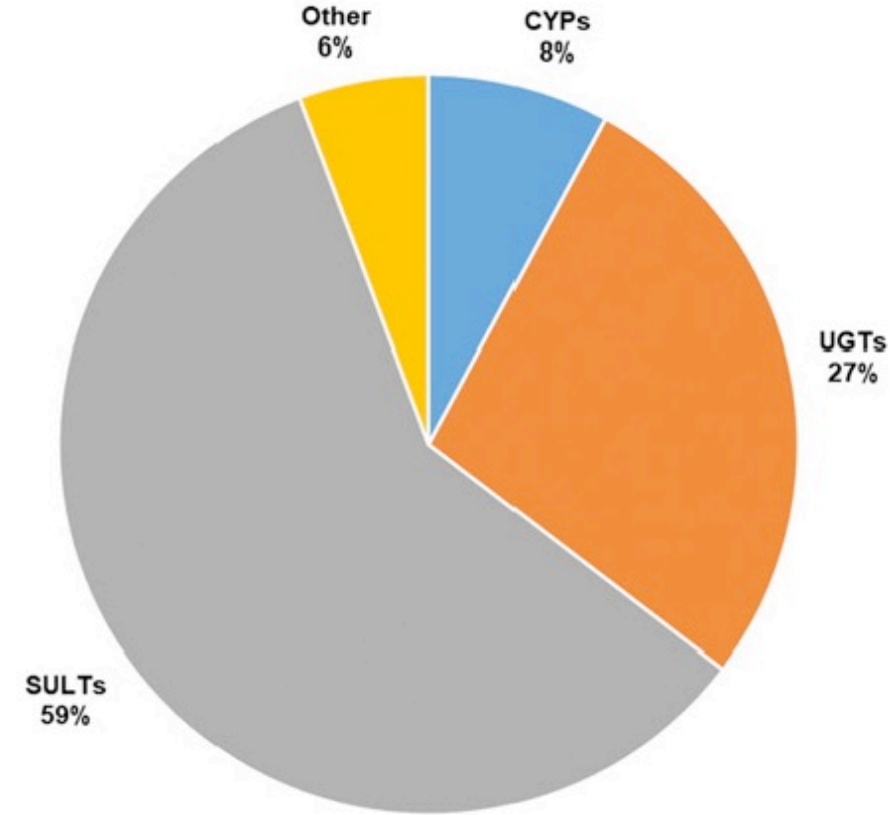
Neonatal (0 to 27 days)



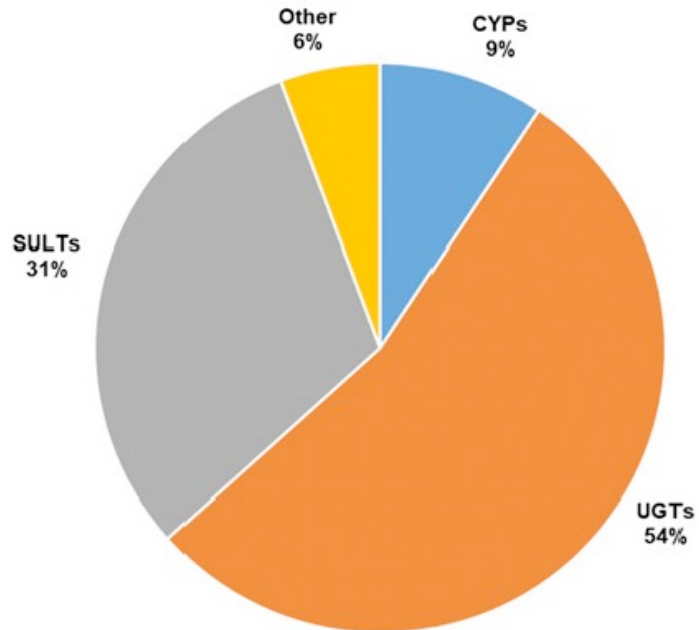
Infancy (28 to 364 days)



Early childhood (1 to <6years)



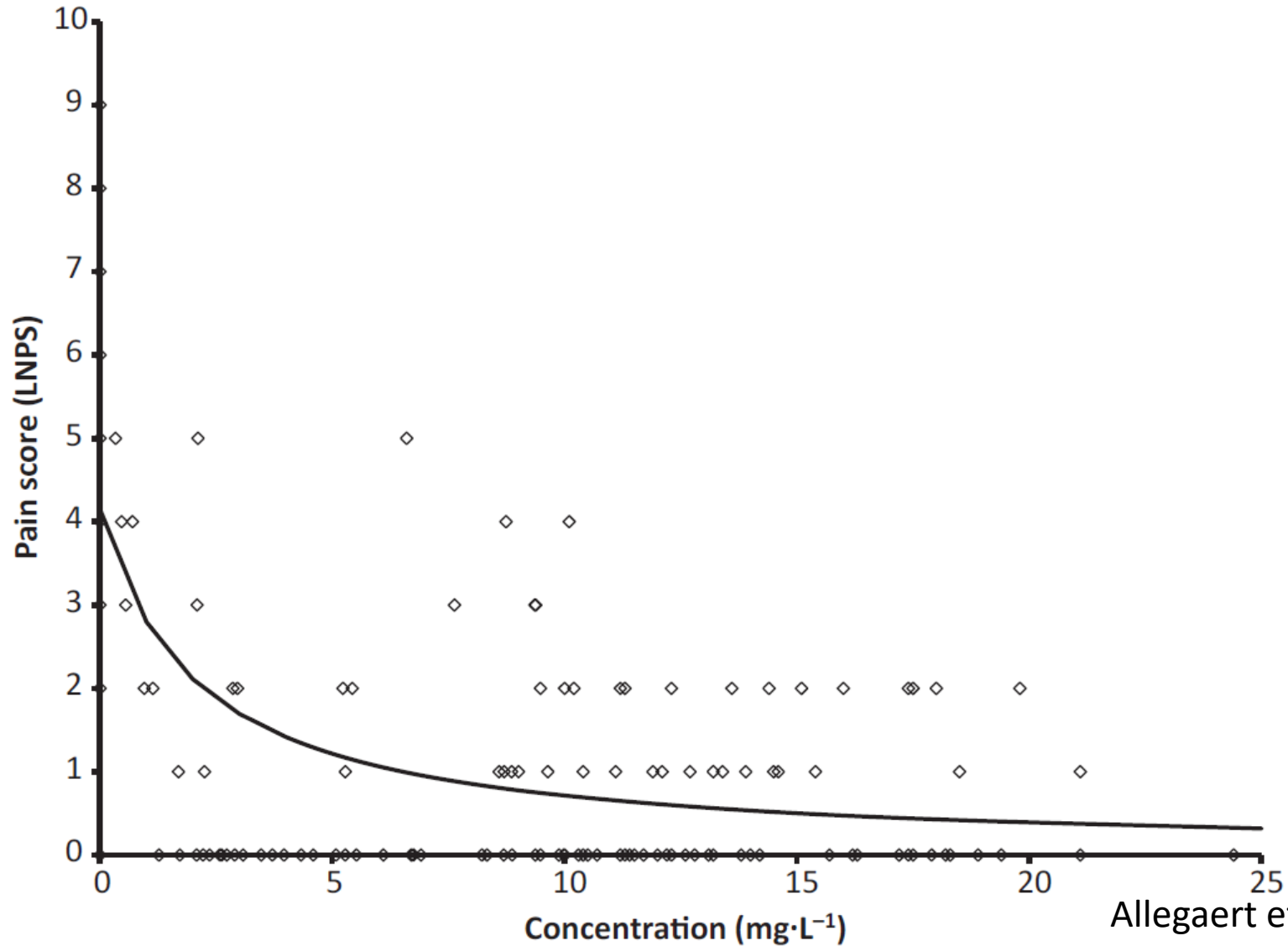
Adulthood (>18 years)



Ontogeny of acetaminophen elimination pathways



Acetaminophen PD

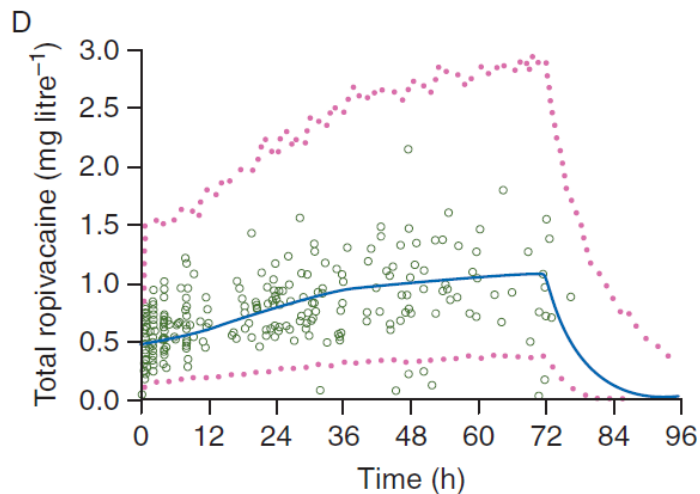
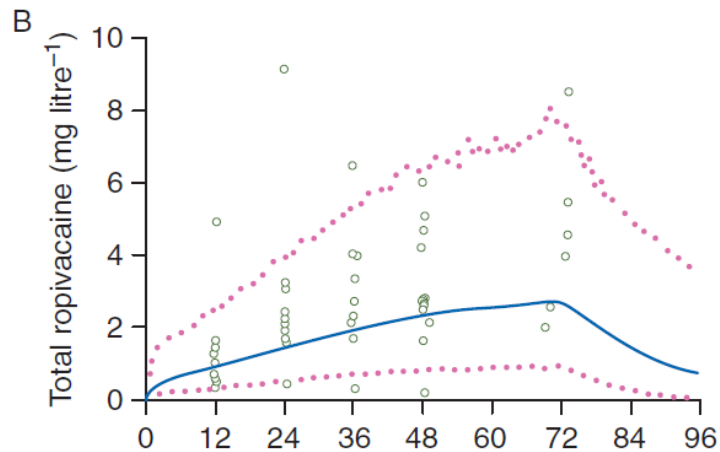
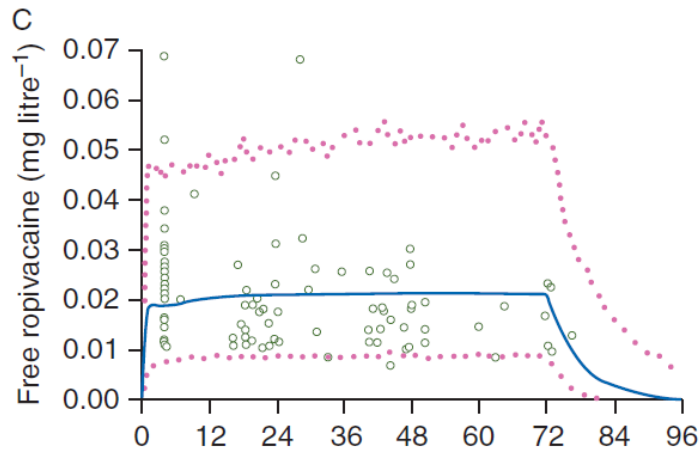
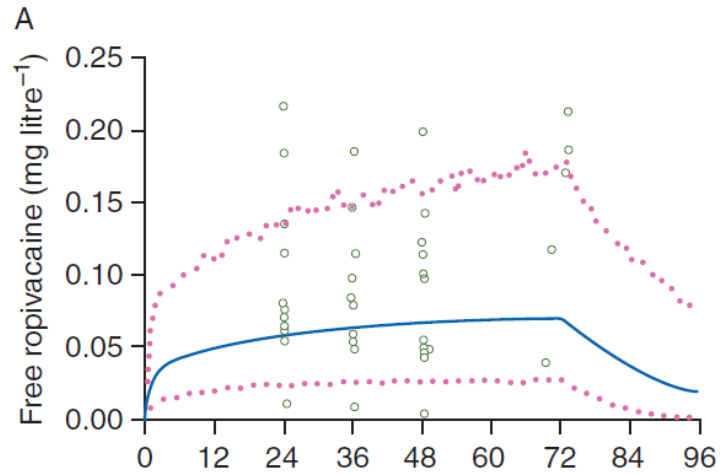


Local anesthetics in brief

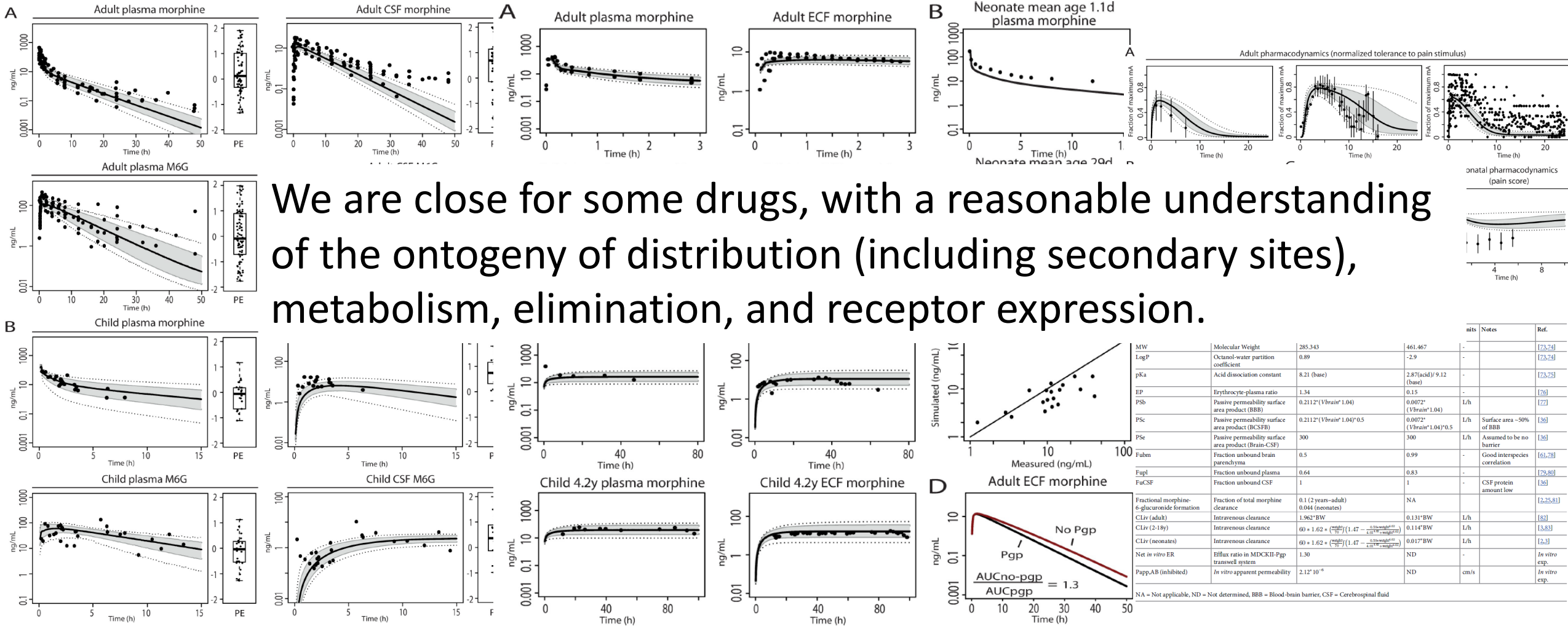
- Metabolism mediated by CYP enzymes, highly protein bound

0-1 month receiving 0.2 mg/kg/hr

1-12 years receiving 0.4 mg/kg/hr



Are we there yet?



We are close for some drugs, with a reasonable understanding of the ontogeny of distribution (including secondary sites), metabolism, elimination, and receptor expression.

My tentative conclusions

- We have made tremendous progress to understand the ontogeny of various systems impacting drug pharmacokinetics
 - Pharmacokinetic extrapolation across age groups is hindered by the importance of all aspects of developmental pharmacokinetics
- Larger gaps exist in our knowledge of effective site concentrations and receptor ontogeny.
- Different classes of drugs have different pitfalls.
- Both short-term and long-term safety studies are vital.
 - Formulation may influence short-term safety.

