



Choline and epigenetic mechanisms: potential for mediation of fetal alcohol spectrum disorders.

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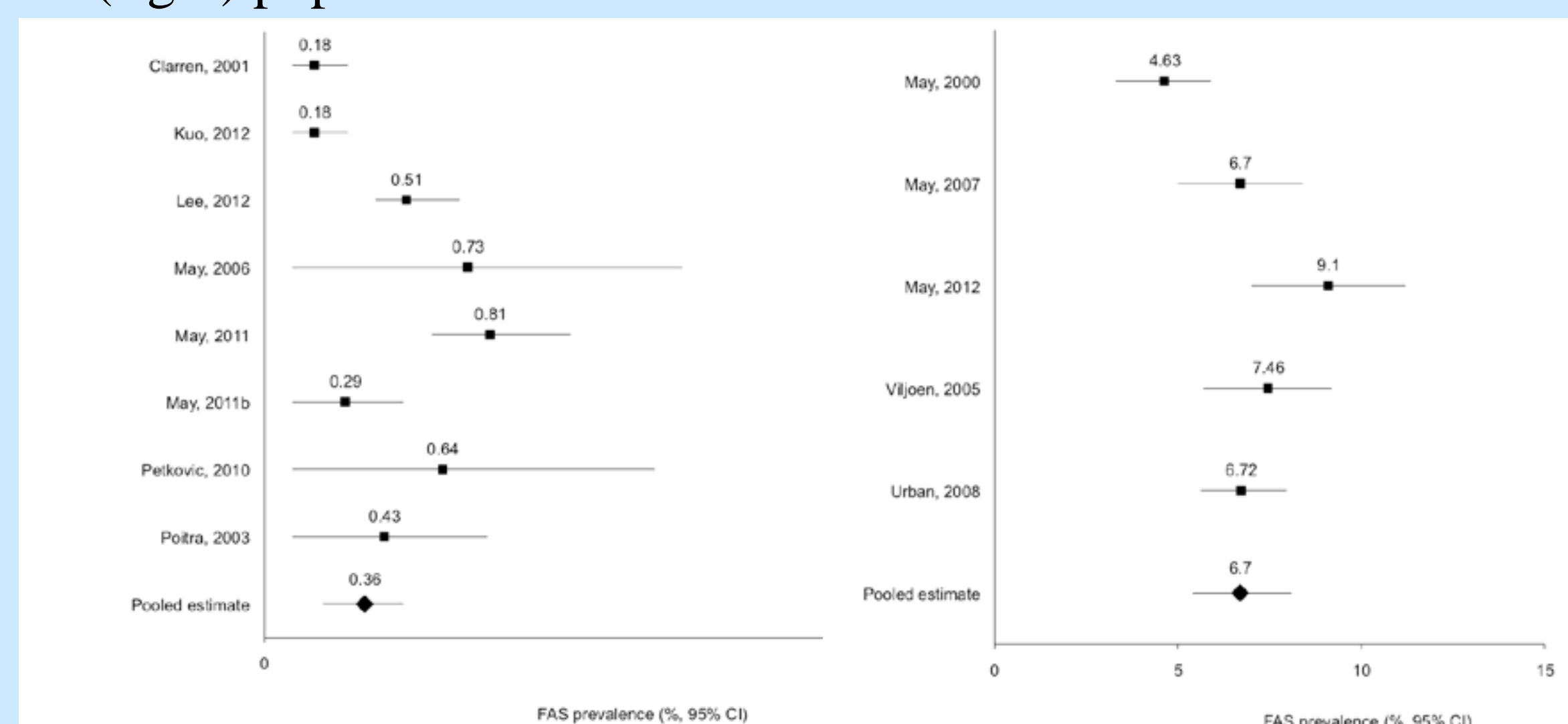


BACKGROUND

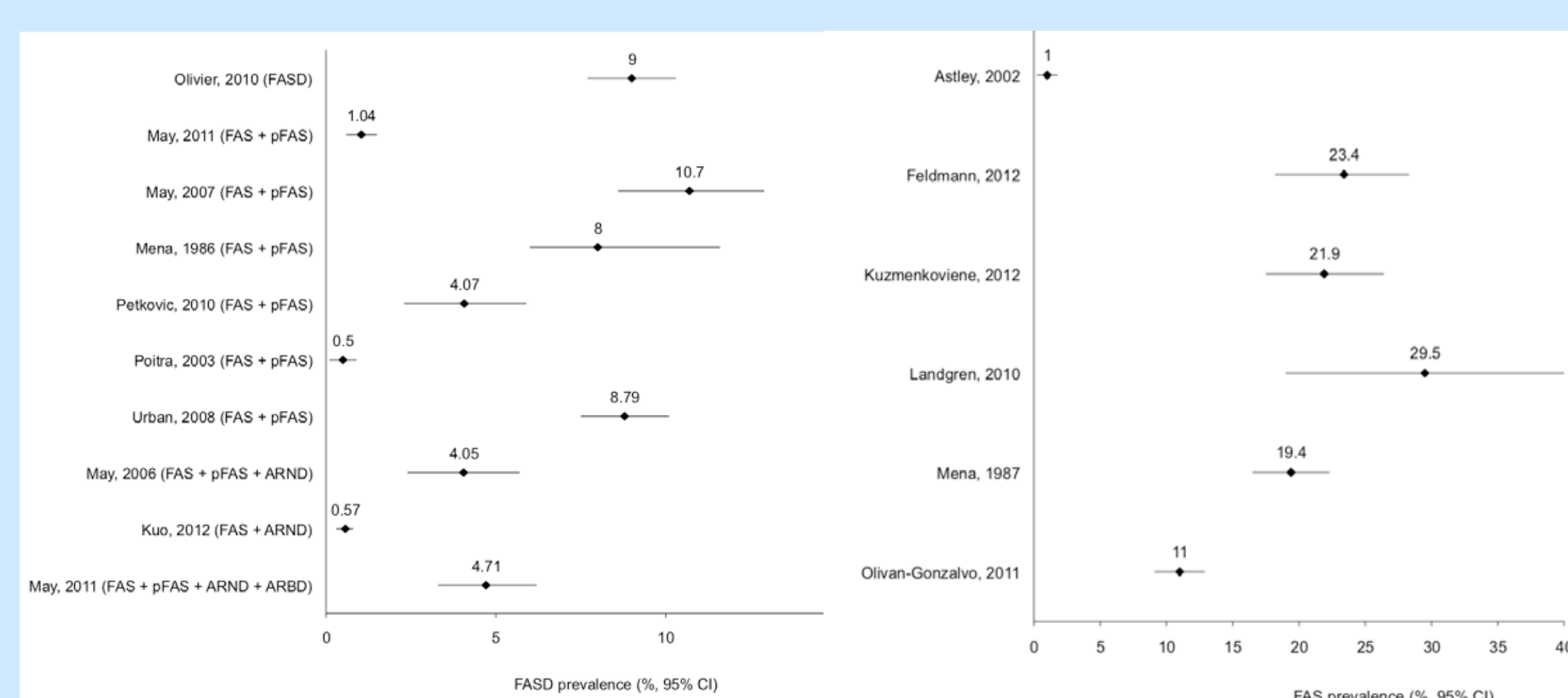
- Haycock (2009) posited that epigenetic mechanisms relate to fetal alcohol spectrum disorder (FASD) sequelae given the importance of the epigenome to nervous system development.
- Disruption of methylation and thus, gene expression during the embryonic period may negatively impact the developing fetus.
- Because alcohol disrupts liver 1-carbon metabolism resulting in a deficiency of the choline needed for methyl group transfer (Trimble et al., 1993), it is hypothesized that a similar disruption in methylation is occurring in the fetus in FASD.
- Poor nutrition status and irregularity of meals has been related to higher intake of alcohol (Santolaria et al., 2000). Thus, important nutrients may be low in chronic alcohol consumers.
- We propose that the positive effects of choline supplementation in alcohol-exposed fetuses and individuals are due to epigenetic mechanisms. The epigenome relies on methylation of DNA and on histone modification (Zeisel, 2009); choline is a major source of methyl groups (Zeisel, 2006).
- Here we provide the rationale for our hypothesis that epigenetic modifications enabled by choline supplementation will mitigate the effects of early alcohol exposure.

IMPORTANCE OF ISSUE

- FASD is a completely preventable developmental disorder.
- At first blush, prevalence may seem low (0.36%), but when one looks at rates in at-risk areas (6.7% in South Africa), at all diagnoses (5.14%), or at those in foster homes (17.7%), the reality for society becomes clearer.
- Prevalence from IHE review of the literature (Ospina & Dennett, 2013): non-South African (left) and South African (right) populations were assessed in schools.

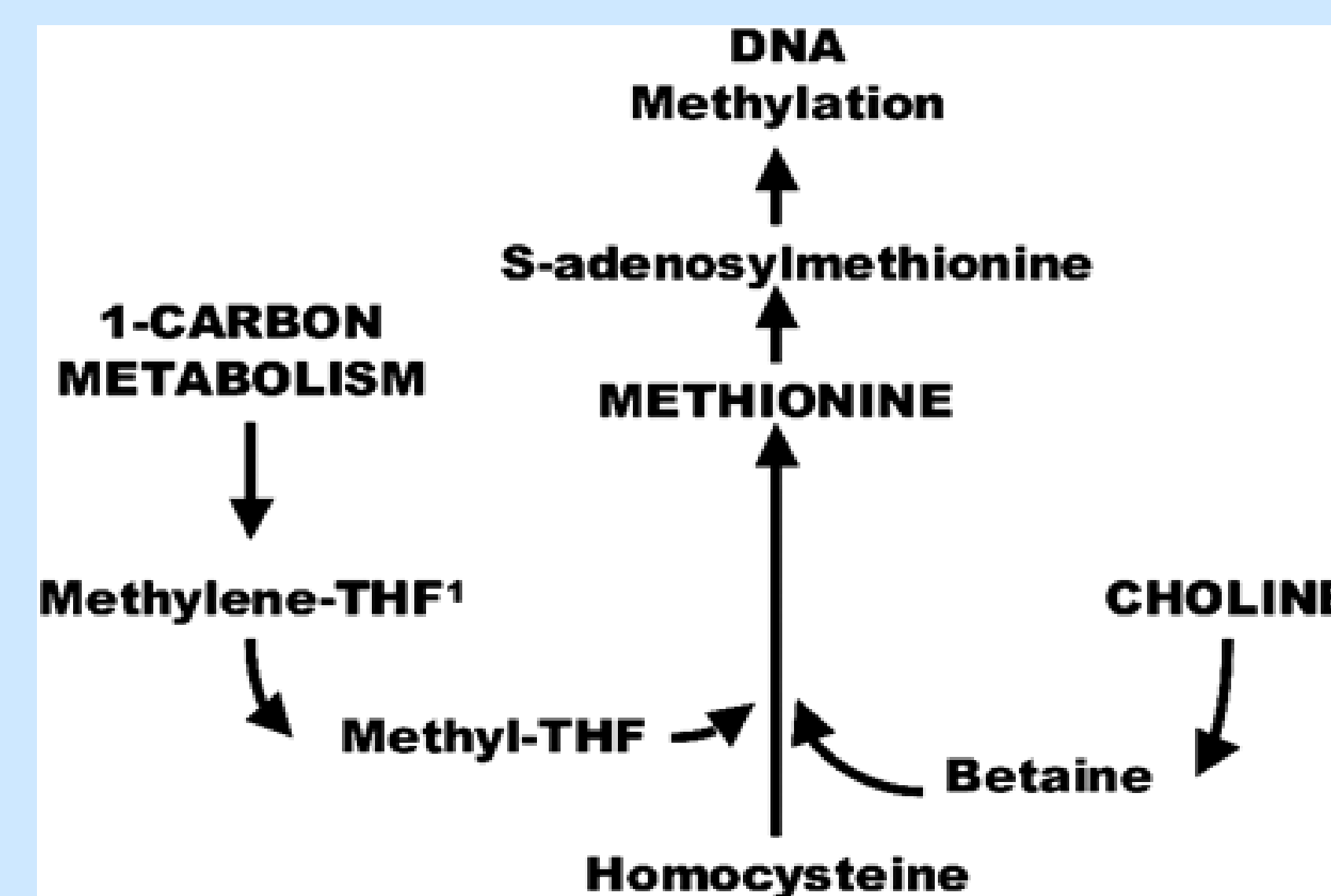
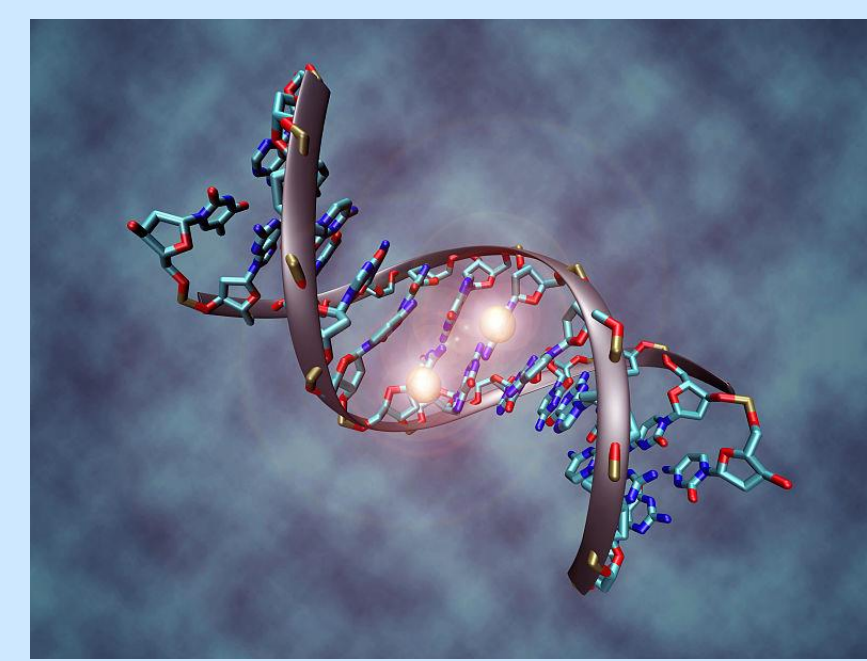


- Prevalence from IHE review of composite measures of effects (left) and those in foster homes (right).



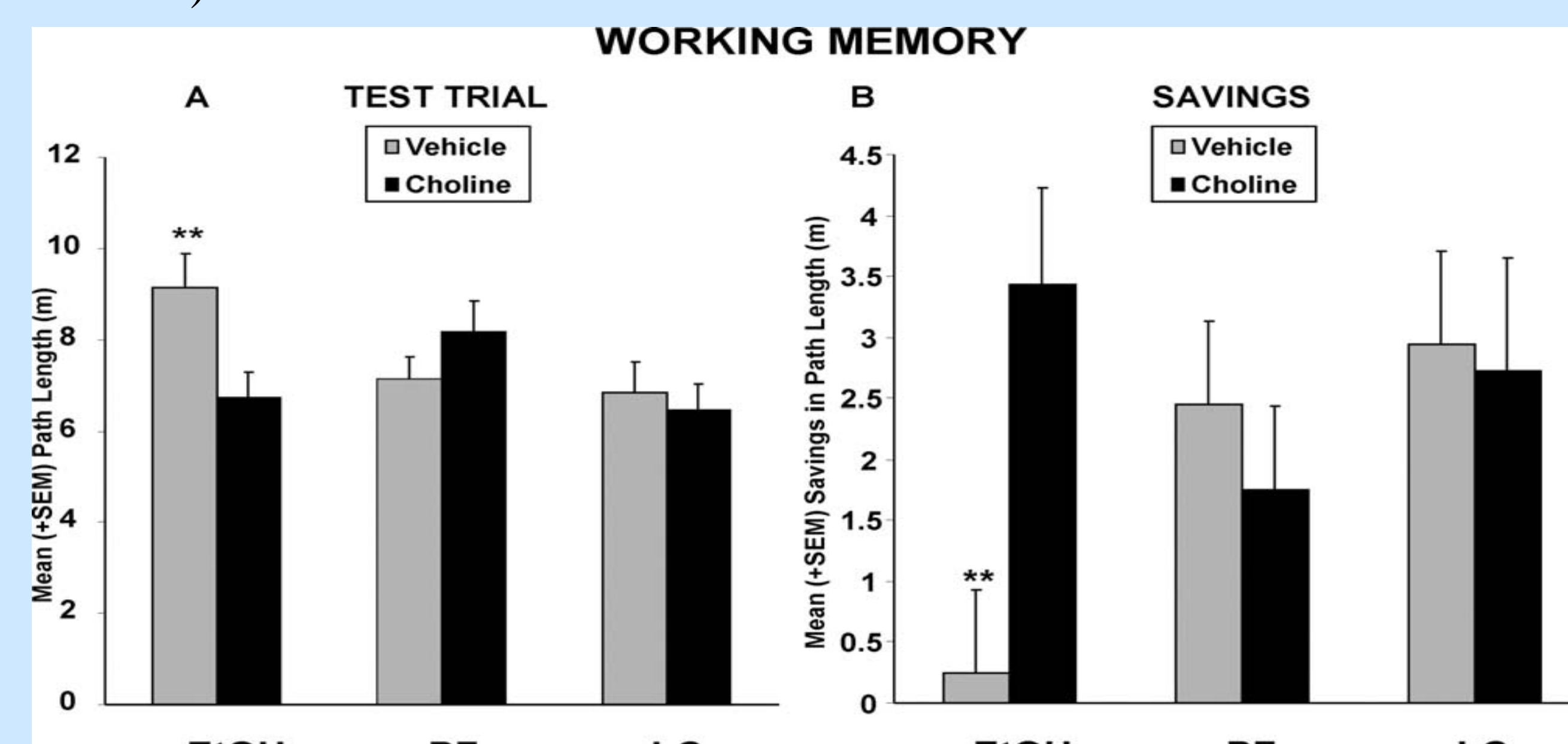
CHOLINE MECHANISMS

- Work in the Zeisel lab has shown that maternal dietary choline intake during late pregnancy modulates mitosis and apoptosis in stem cells of the fetal hippocampus and septum (Albright et al., 1999a, 1999b; Craciunescu et al., 2003) and alters the differentiation of neurons in fetal hippocampus (Albright et al., 1997, 1999a, 2001, 2003; Craciunescu et al., 2003).
- Choline deficiency (and resulting alterations in methylation) could be responsible, in part, for the reported differences in proliferation, differentiation, and plasticity of neurons and glia in the dentate gyri of alcohol-exposed individuals when compared to controls.
- Hippocampal-based cognition is disrupted with FASD (e.g., Willoughby et al., 2008), and maternal choline supplementation has been shown to improve the integrity of the hippocampus (e.g., Albright et al., 1999a, 1999b; Jones et al., 1999; Montoya et al., 2000).
- DNA methylation depends on the availability of choline and on 1-carbon metabolism (Niculescu & Zeisel 2002).

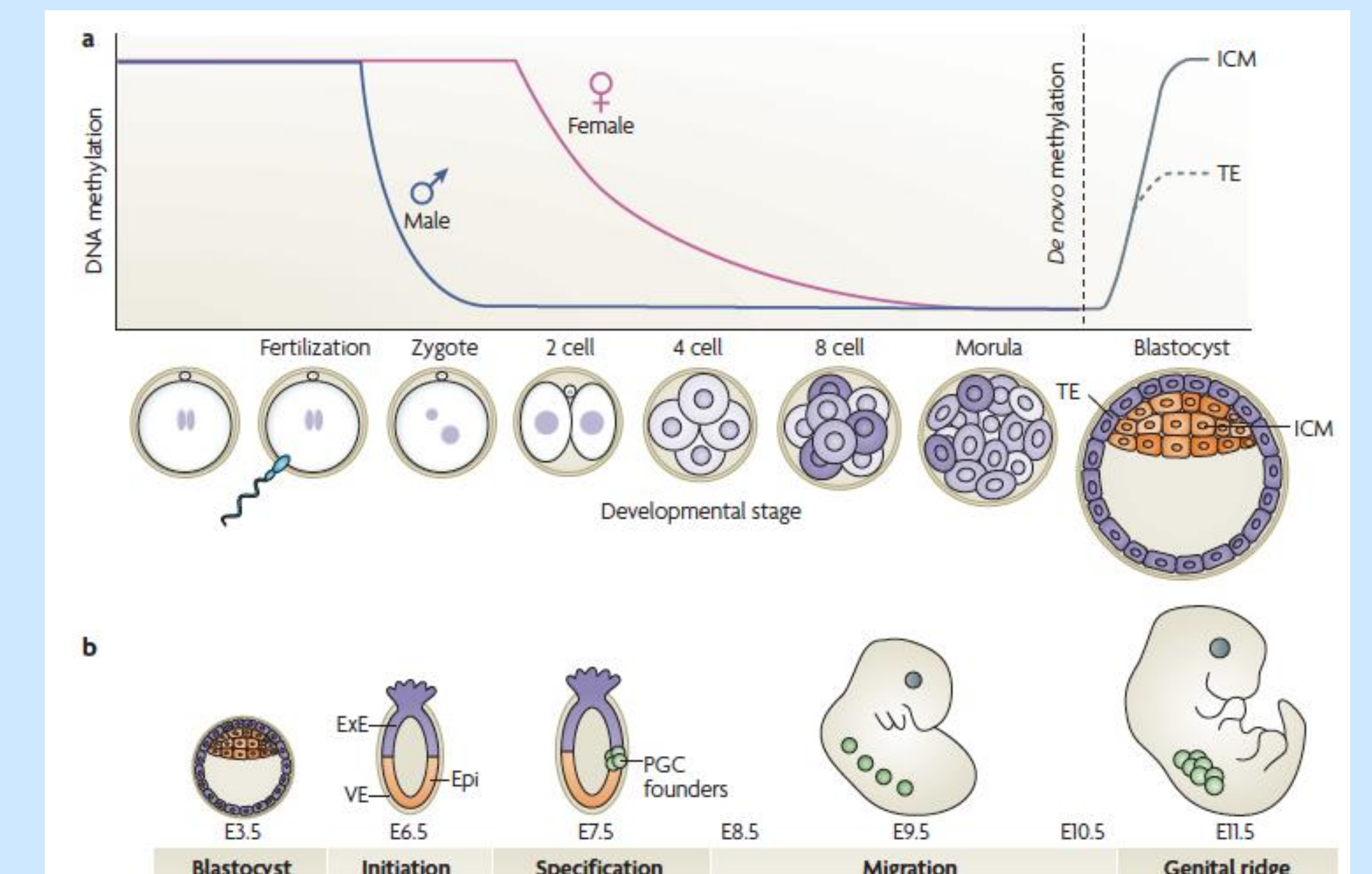


CHOLINE AND FASD

- The first evidence that choline supplementation can mitigate the effects of FASD comes from the Thomas laboratory.
- When choline supplementation was concurrent with neonatal alcohol exposure, there was marked improvement in a spatial discrimination task (Thomas, Garrison et al., 2004), but not in a motor coordination task (Thomas, O'Neill et al., 2004), indicative of hippocampal specificity.
- The closer the intervention is to the insult, the better the results, but choline supplementation also helps postnatally (Ryan et al., 2011).
- Spatial working memory deficits seen with ethanol exposure improved (see below) with prenatal maternal supplementation (Thomas et al., 2010).



EPIGENETICS



- The epigenetic code is transmitted by DNA methylation and is initially established during gastrulation. Demethylation and *de novo* methylation of the entire genome occurs soon after fertilization (see above illustration from Wu & Zhang, 2010).
- Early on, alcohol exposure during neurulation affects neural tube development and DNA methylation (Lui et al., 2009).
- Folate and choline are recommended before conception to prevent neural tube defects (Shaw et al, 2006; Zeisel, 2009).
- It follows that choline supplementation should begin before conception to alleviate FASD sequelae.
- Genome-wide hypomethylation has been shown to occur in GD 9-11 in fetal alcohol exposed mouse model. The resulting abnormal gene expression would lead to deleterious effects on brain development.
- Initial work in the Thomas lab shows that the hippocampus is hypermethylated in a neonate exposed to alcohol, and choline reduces that methylation (Otero et al., 2012).
- With an NIAAA funded K01, we will establish the connections between FASD, choline, and epigenetics.

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