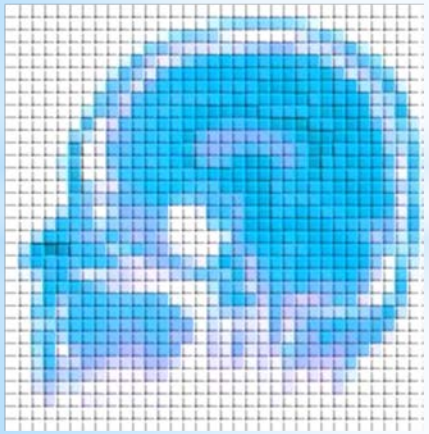
Choline as a neurodevelopmental intervention



Jeffrey R. Wozniak, Ph.D. (University of Minnesota)

Judith K. Eckerle, Birgit A. Fink, Christopher J. Boys, Anita J. Fuglestad, Neely C. Miller, Ann M. Brearley, Steven H. Zeisel, Michael K. Georgieff

CENTER FOR neuroBEHAVIORAL DEVELOPMENT

UNIVERSITY OF MINNESOTA
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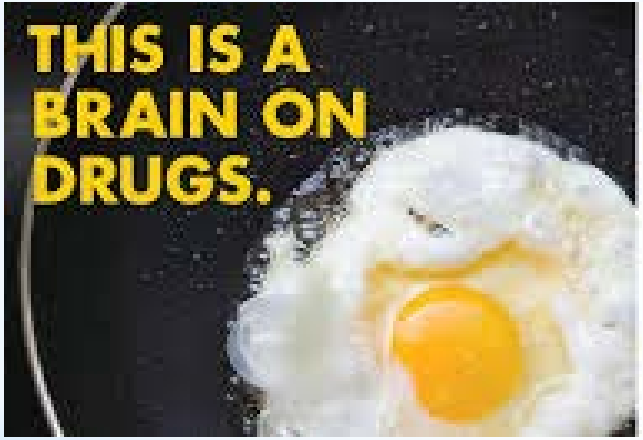
NIH National Institute on Alcohol Abuse and Alcoholism



ANY
QUESTIONS?

fetal alcohol brain - Goo

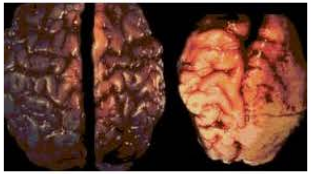
Secure | https://www.google.com/search?q=fetal+alcohol+brain&rlz=1C1CHWA_enUS630US630&espv=2&biw=1680&bih=948&source=lnms&tbm=isch&sa=X&ved=0ahUKEwianZay2KnSAhWBnBoKHQ0UCUQQ_AUIBigB

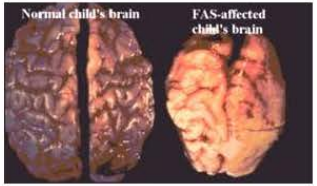
Google fetal alcohol brain

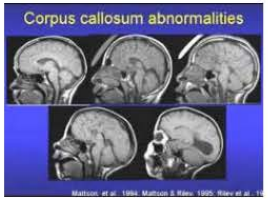
Sign in

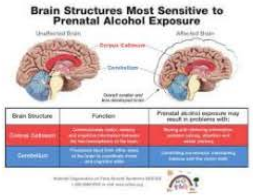
All | Images | News | Videos | Shopping | More | Settings | Tools | SafeSearch

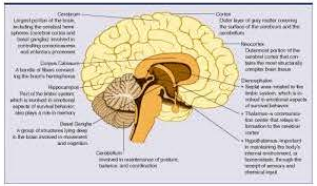
damaged | human body | alcoholic | baby | child | syndrom | alcohol withdrawal | brain scan | healthy | affected | pregnancy | foetal alcohol syndrome

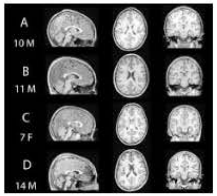


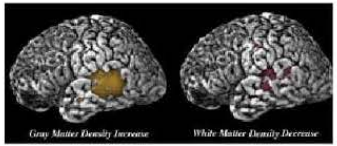


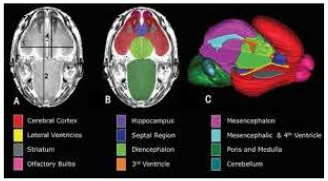


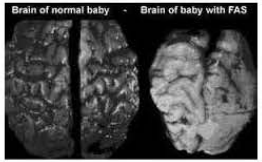


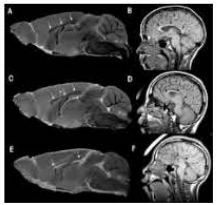


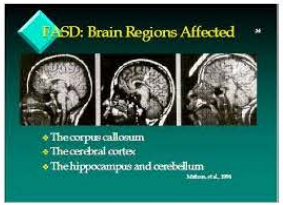


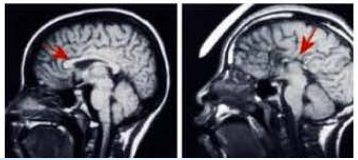


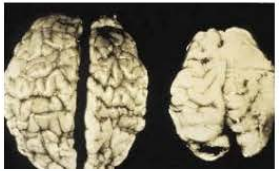













FASD in Minnesota
#FASDadvocate


make it happen
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THANK YOU

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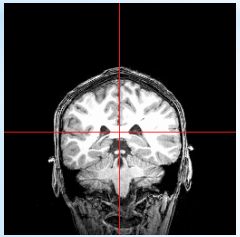
University of Minnesota FASD Program

Intervention research

Rationale:

- The only available treatments are behavioral / educational
- Current interventions are very specific / narrowly-focused
- Pre-clinical work suggests opportunities for nutrient intervention
- Focused intervention on hippocampus



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Dietary supplements??

Choline is an essential nutrient for humans

- Classified as essential nutrient (IOM, 1998) [Zeisel]
- All cells require it
    - Die by apoptosis without it
- Multiple needs:
    - Cell membrane
    - Lipid metabolism
    - Precursor to acetylcholine
    - Important methyl donor
- Endogenous supply & Diet
    - 550 mg per day (adult)
    - Mean adult intake in US = 312 mg. per day
    - 200 – 250 mg. for children under 8
- Brain development:
    - Choline and folate are linked
    - Deficiency -> neural tube disorders

(Albright et al., 1998; Eagle, 1955; Zeisel et al., 1997; Cho et al., 2006); Zeisel et al., 2003; (Shaw et al., 2004; Smithells et al., 1976; Zeisel, 2009b; (Albright et al., 1999a; Albright et al., 1999b

Behavioral Neuroscience
2007, Vol. 121, No. 1, 120–130

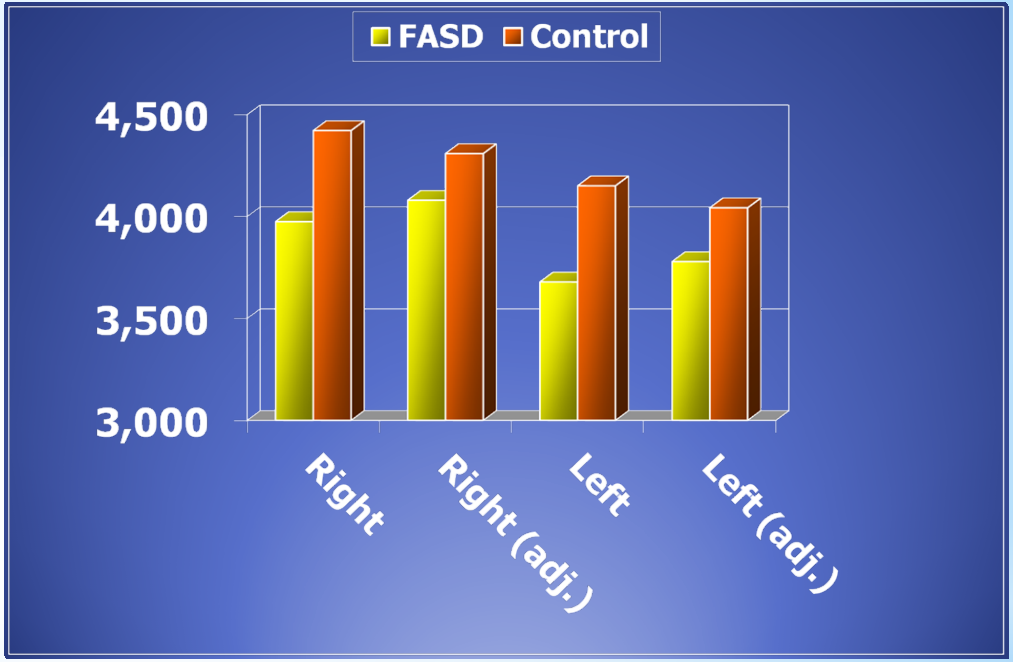
0735-7044/07/$12.00 DOI: 10.1037/0735-7044.121.1.120

Choline Supplementation Following Third-Trimester-Equivalent Alcohol Exposure Attenuates Behavioral Alterations in Rats

Jennifer D. Thomas, Jeremy S. Biane, Kelly A. O'Bryan, Teresa M. O'Neill, and Hector D. Dominguez
San Diego State University

Despite the known adverse consequences of prenatal alcohol exposure, some pregnant women continue to drink alcohol, making it imperative to identify treatments for children with fetal alcohol spectrum disorders. The authors recently reported that perinatal choline supplementation can reduce some fetal alcohol effects (J. D. Thomas, M. Garrison, & T. M. O'Neill, 2004), and the present study examined whether choline supplementation is effective when administered after third-trimester-equivalent ethanol treatment. Rat pups were exposed to 6.0 g/kg/day ethanol during the neonatal brain growth spurt (Postnatal Days [PD] 4–9) and treated with choline chloride (0, 10, 50, or 100 mg/kg) from PD 10–30.

- In prenatally-exposed rats, choline reduced cognitive deficits
  - Choline could be given in the diet to pups
  - Memory, behavior, aspects of learning
  - Earlier supplementation was more beneficial
  - But, later supplementation had some effects (out to "childhood" in rats



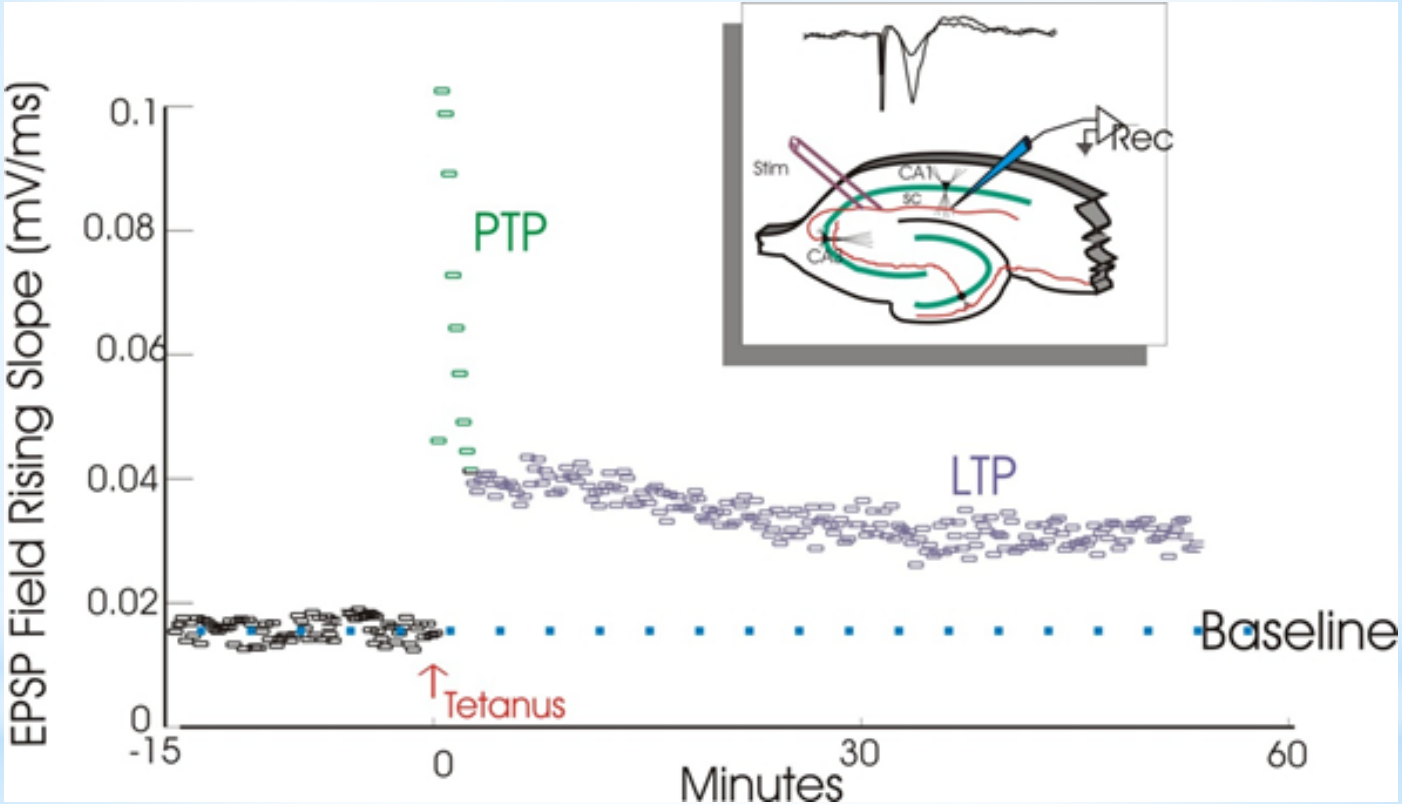
Hippocampal volumes in children with FASD vs. controls (raw volumes and volumes adjusted for total intracranial volume)

Shutterstock

How can choline impact a damaged brain??

- Hippocampus (memory)
  - Effects on LTP (biochemical basis of memory)
  - Building block of acetylcholine
- Gene expression
- Decrease apoptosis
- Role in the repair of myelin
- Animal models show permanent effects

Barnes D.E. & Walker, D.W. (1981). Brain Res.; Miller (1995), ACER; Tan, S.E. et al. (1990). Alcohol; Livy, D.J. et al. (2003); Neurotox Teratol.; Nardelli et al. (2011) ACER.; Coled et al. (2011) Brain & Cognition.


EPSP Field Rising Slope (mV/ms)
0.1
0.08
0.06
0.04
0.02
0
PTP
LTP
Baseline
Tetanus
-15
0
30
60
Minutes
Stim
Rec
CA1
sc

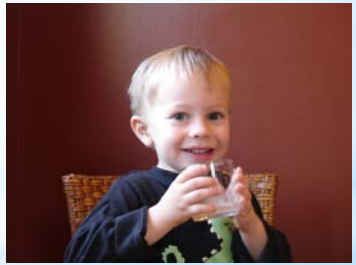
How the brain is built during pregnancy has an impact throughout the lifespan

Images: Huffington Post, Getty Images

Delivery system development

- Allocated Interventions (2-arms)
  - 500 mg. choline vs. placebo per day
    - Randomization is 1:1
    - Supplement dose based on adequate intake of 200-250 mg. per day
  - Fruit-flavored drink mix
  - Daily intake for 9 month duration
  - FDA Investigational New Drug (IND) exemption in place



NUTRITION RESEARCH 33 (2013) 897–904

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www.nrjournal.com

Choline supplementation in children with fetal alcohol spectrum disorders has high feasibility and tolerability

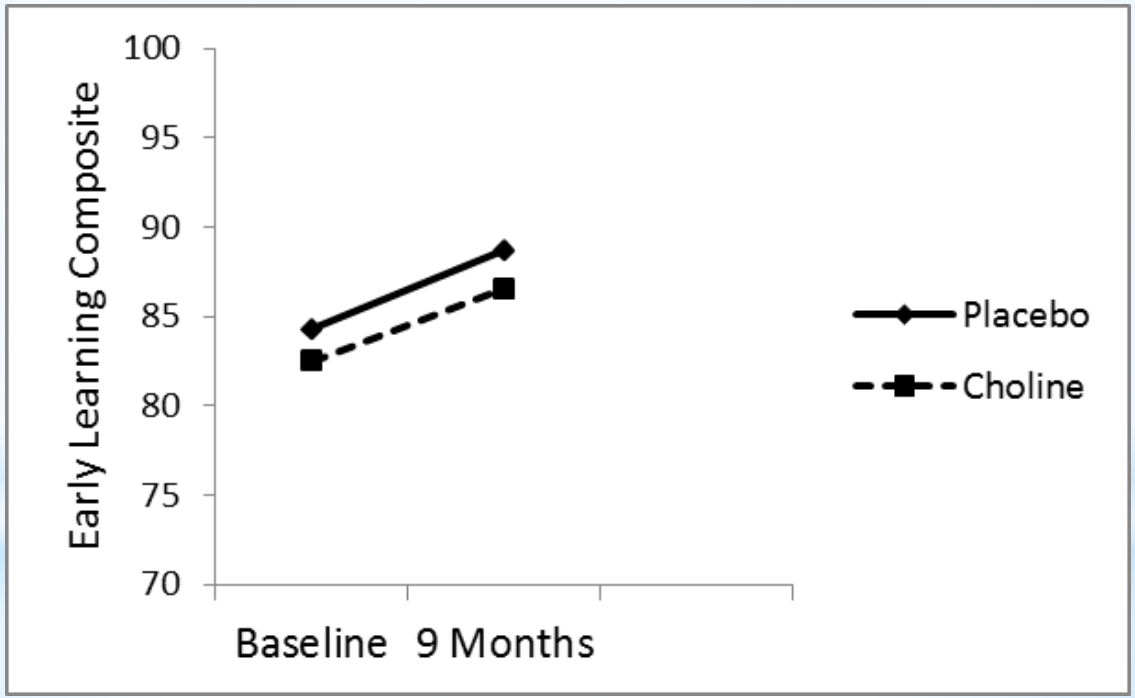
Jeffrey R. Wozniak[a,*], Anita J. Fuglestad[a], Judith K. Eckerle[a], Maria G. Kroupina[a], Neely C. Miller[a], Christopher J. Boys[a], Ann M. Brearley[a], Birgit A. Fink[a], Heather L. Hoecker[b], Steven H. Zeisel[c], Michael K. Georgieff[a]

- Randomization was accepted by parents
- Compliance with choline was excellent and no different than placebo
- 85% completed the study
- No differential drop-out
- Oral choline dramatically increased serum choline levels
- Adverse events were very minimal (no SAEs)

University of Minnesota Post-natal Choline Trial

No treatment effect for Global Cognitive Functioning

- Choline: 82(baseline) -> 87 (9 months)
- Placebo: 84(baseline) -> 89 (9 months)



Elicited Imitation (memory) performance

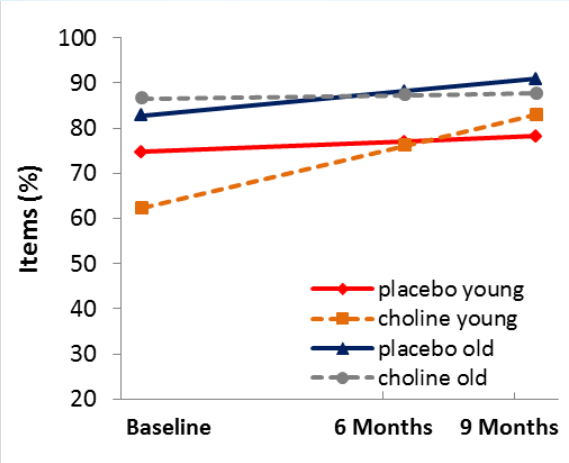


Fig 1. EI items after short delay

- **21 point increase for young choline**
- 2 point increase for young placebo
- 2 point increase for old choline
- 9 point increase for old placebo

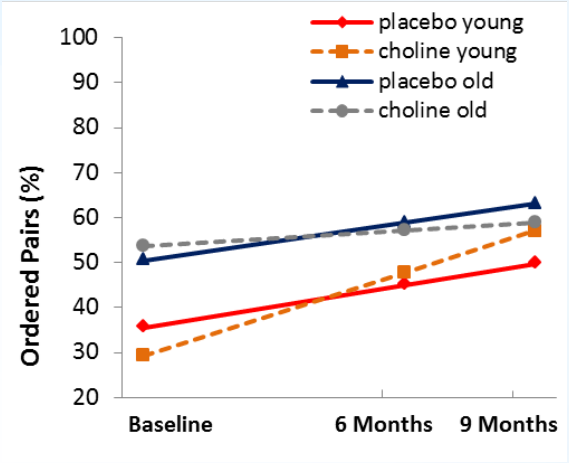
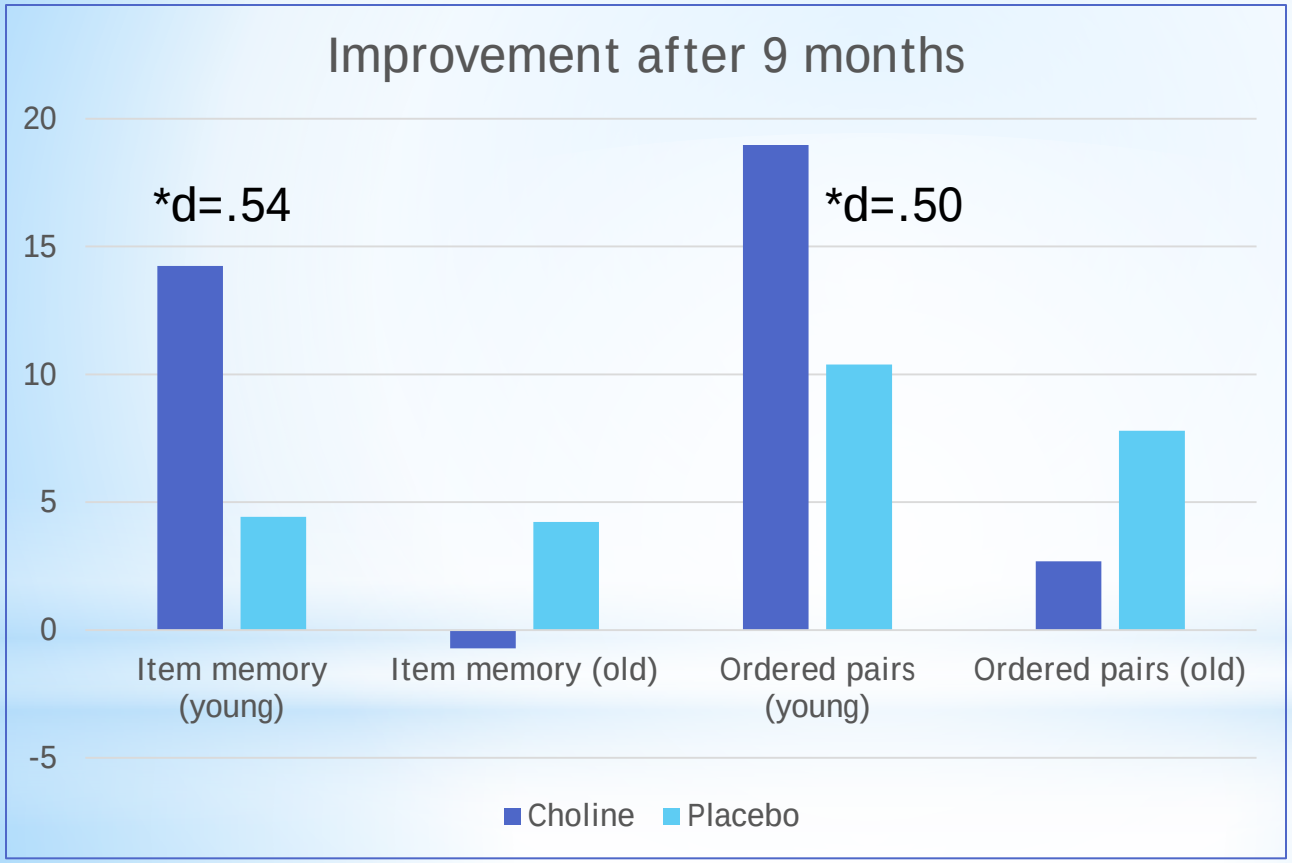


Fig 2. EI ordered pairs

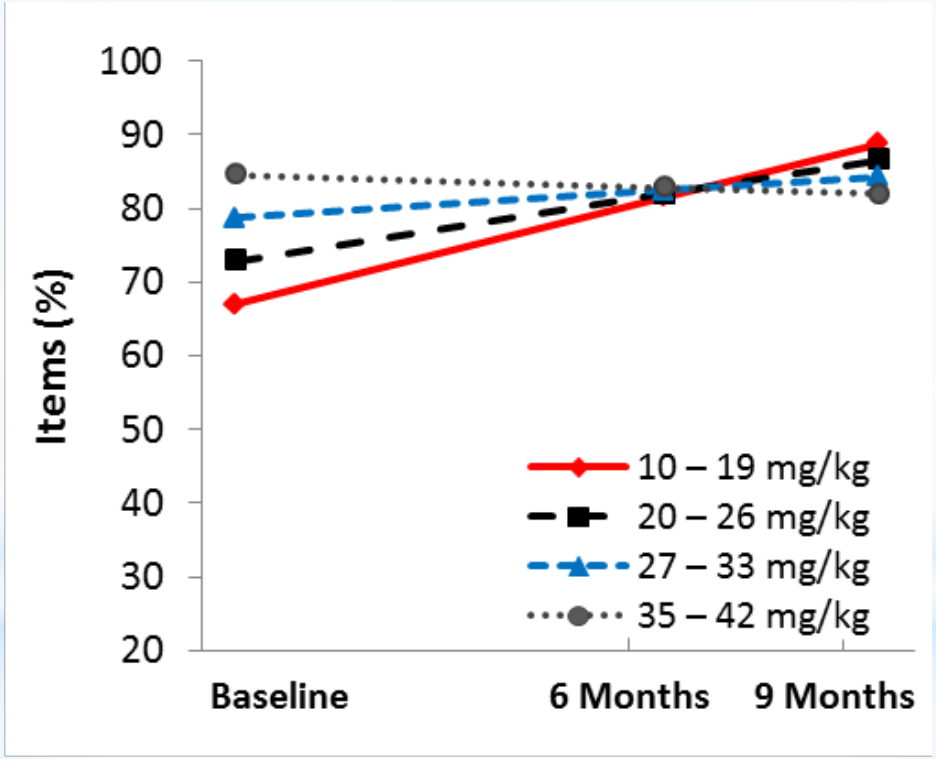
- Trend toward steeper improvement in young choline group

γ= -16.05, 95% CI [-31.71, -0.40], $t(84.7)= -2.09$, $p=0.045$.



Elicited imitation memory performance: Baseline to 9 months

Elicited imitation performance by weight-adjusted / compliance-adjusted dose



γ = -0.64, 95% CI [-1.21, -0.06], $t(34.4) = -2.26$, $p = .030$

What are other human choline intervention studies showing?

Matern Child Health J
DOI 10.1007/s10995-015-1779-x

CrossMark

Dose and Timing of Prenatal Alcohol Exposure and Maternal Nutritional Supplements: Developmental Effects on 6-Month-Old Infants

Claire D. Coles[1,7] · Julie A. Kable[1] · Carl L. Keen[2] · Kenneth Lyons Jones[3] · Wladimir Wertelecki[3,4,5,6] · Irina V. Granovska[5] · Alla O. Pashtepa[6] · Christina D. Chambers[3] · the CIFASD

- Multivitamin supplements given to heavy-drinking women in Ukraine
- 367 participated
- Range 1.5 to 10 drinks per day (all had some binge episodes)
- Outcome measure: Bayley Scales of Infant Development
- Multivitamin and Multivitamin + choline were examined

Matern Child Health J
DOI 10.1007/s10995-015-1779-x

Dose and Timing of Prenatal Alcohol Exposure and Maternal Nutritional Supplements: Developmental Effects on 6-Month-Old Infants

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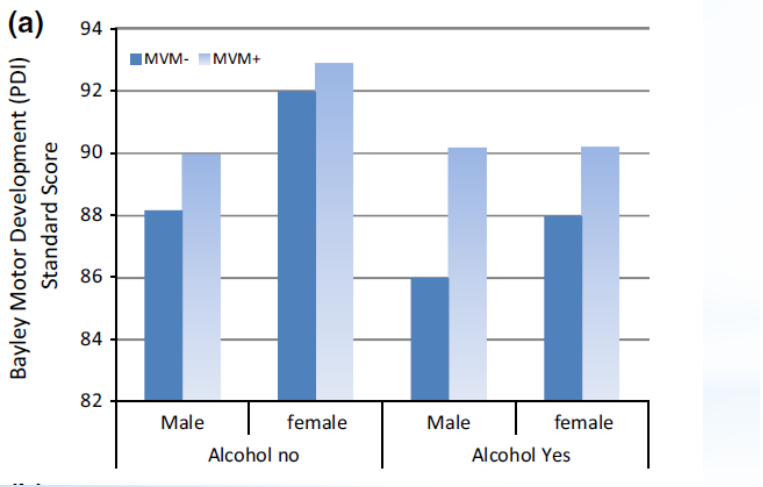
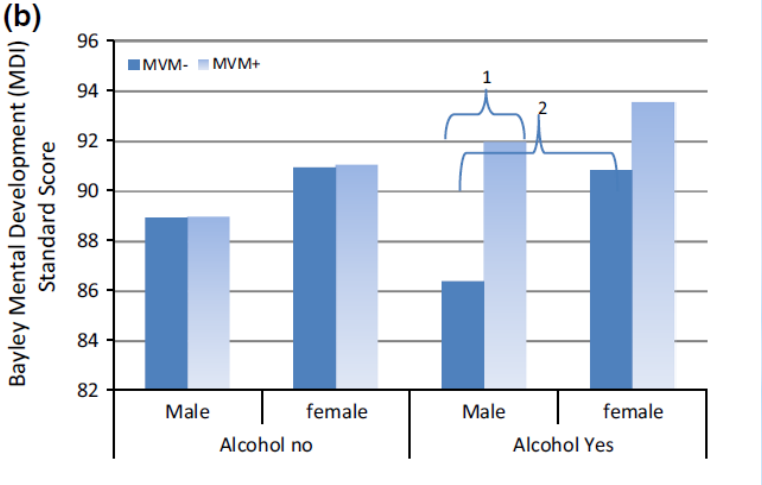


No difference in Bayley motor score



Multivitamin protected Bayley mental score (especially in males)

Randomized, double-blind, placebo-controlled clinical trial of choline supplementation in school-aged children with fetal alcohol spectrum disorders[1]

Tanya T Nguyen, Rashmi D Risbud, Sarah N Mattson, Christina D Chambers, and Jennifer D Thomas

Am J Clin Nutr 2016;104:1683–92

- Short-term supplementation (6 weeks)
- Older sample (5-10 years old) of children with PAE
- 625 mg per day
- Spatial memory, executive functioning, attention, fine motor speed outcomes

RESULTS:

- No effects of choline on cognitive outcome

Contents lists available at ScienceDirect

Alcohol

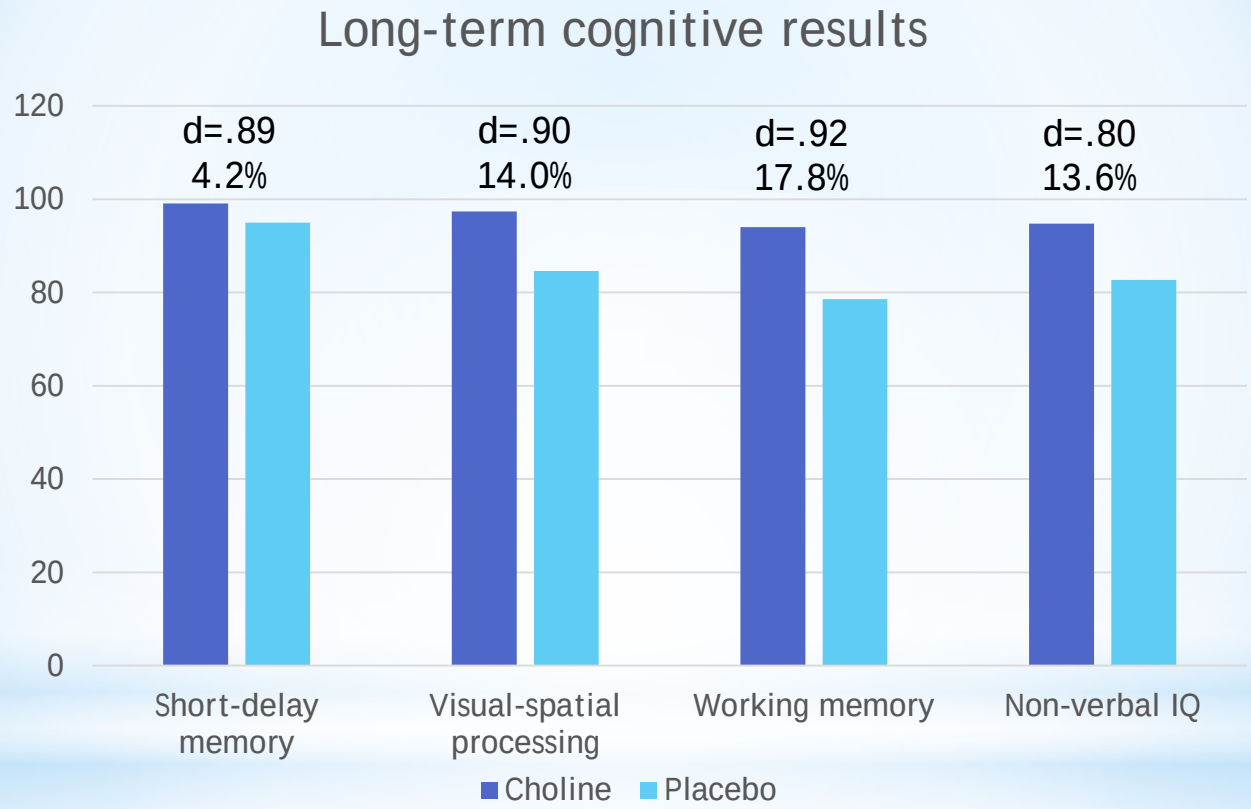
journal homepage: http://www.alcoholjournal.org/

The impact of micronutrient supplementation in alcohol-exposed pregnancies on information processing skills in Ukrainian infants

J.A. Kable [a,b,*], C.D. Coles [a,b], C.L. Keen [c], J.Y. Uriu-Adams [c], K.L. Jones [d], L. Yevtushok [f], Y. Kulikovsky [f], W. Wertelecki [d,g], T.L. Pedersen [h], C.D. Chambers [d,e] CIFASD

- Second study of the Ukraine cohort of women
- Outcome measure designed for infants
  - 1. Baby is habituated to a stimuli
  - 2. New stimulus is introduced
  - 3. Heart rate goes down indicating attention and recognition that the stimuli has changed
- Choline exposure during gestation caused <u>larger</u> response in the infants (better attention / discrimination capacity)

Images courtesy of the New York Times and isabelgranic.com



Follow-up of 23 participants at 3.95 years post study termination; matched groups

Collaborators

Judith K. Eckerle, Birgit A. Fink, Marisa Whitley, Maria G. Kroupina, Neely C. Miller, Christopher J. Boys, Ann M. Brearley, Heather L. Hoecker, Steven H. Zeisel, & Michael K. Georgieff

National Institute on Alcohol Abuse and Alcoholism

Funding

NIAAA: 5R21AA019580; R33AA019580

Dana Foundation

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