Is there a safe amount of alcohol consumption during pregnancy?

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'It is not appropriate to tell women it is safe to drink alcohol during pregnancy, but it is also not appropriate to have extreme messages, which could scare women into having abortions'

- Todorow et al, *J Popul Ther Clin Pharmacol* 17:e323-330, 2010
  - Exposing one's own child, albeit unintentionally, to a teratogenic substance can cause severe guilt and anxiety in the mother.
  - Evidence-based information regarding the actual magnitude of the risk of low level alcohol exposure during gestation is necessary in order that women can be counseled accurately and sensitively, to avoid potentially harmful feelings of guilt and stress in the mother, and to allow women to make informed decisions.
  - On the other hand, misinformation derived from inadequately designed studies that minimizes the risk of low level exposure can also be extremely counterproductive because mothers may be encouraged to continue drinking throughout their pregnancy, potentially causing harm to the fetus.

Some recent headlines….

…even conscientious pregnant women have been known to have an occasional beer or glass of wine while carrying a child. How risky is that?

Nursing IN PRACTICE

Drinking while pregnant "does not affect" baby's development

THE NEW AGE www.thenewage.co.za

Pregnant women can drink up to one glass of wine a day without harming their child's neurodevelopment, a new British study claims

FOX NEWS .com Fair & Balanced

Light drinking during pregnancy may benefit baby

New York Post: One glass of wine a day is A-OK for pregnant women: study

London Evening Standard

Light drinking during pregnancy will not be a mother's ruin

Belfast Telegraph.co.uk

"A drink or two may be good for baby….Light drinking during pregnancy does not affect children's behaviour or cause mental impairment, and may help them in some ways, according to new study."

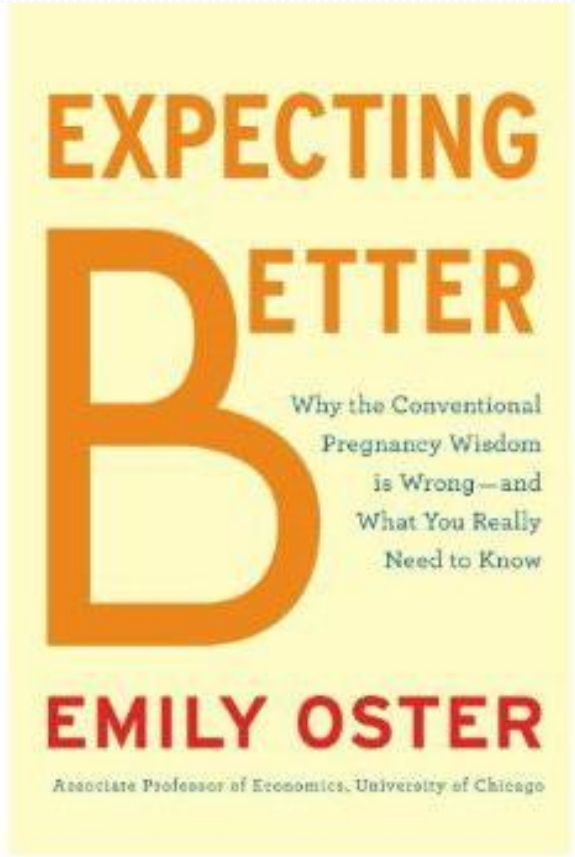
Medical Daily: Moderate consumption of alcohol by pregnant women appeared not to harm their children's brain development in a new large-scale study of families in southwestern England

The INDEPENDENT

Light drinking during pregnancy may lead to calm babies, says study

Emily Oster:

Why the conventional wisdom is wrong - and what you really need to know



"In fact, there is virtually no evidence that drinking a glass of wine a day has negative impacts on pregnancy or child outcomes…Of course, this is a little sensitive to timing — 7 drinks a week does not mean 7 shots of vodka in an hour on a Saturday night."

"I am not knocking her, but it would be nice if she would meet some people living with FASD … instead of reading a piece of paper, a book or a file," said Liz Kulp, 27, who said she was diagnosed with fetal alcohol syndrome at age 12.

THE GLOBE AND MAIL

A few drinks while pregnant isn't bad, but the new maternal puritanism is

Both women decided that the mandate to drink absolutely no alcohol is extremely overblown.

Ms. Oster ends up advising that women have "no more than one drink a day," while Ms. Geddes (a British science journalist) is ok with "one or two units, once or twice a week."

Both found that the subjects of most studies on Fetal Alcohol Syndrome Disorder are alcoholics, binge drinkers or also using drugs, making them irrelevant to most women.

Meanwhile, one Danish team proclaimed that the five-year-old kids of well-educated moms who drank lightly (up to four drinks a week) were actually less likely to have behavioural problems, hyperactivity, peer problems and emotional difficulty than the children of mothers who abstained entirely.

Cheers to that!

More headlines…

Nigerian Tribune

No amount of beer is safe in pregnancy

"…experts warn that no amount of alcohol is safe during pregnancy…"

The Telegraph

Glass or two of wine a week could damage baby

The Independent

Researchers have found that a single unit of alcohol a week resulted in less intelligent babies

Recent studies suggesting **NO EFFECTS** of light-moderate drinking on child outcomes

Light = 1-2/wk or /occasion; 1-4/wk; 2-6/wk
Moderate = 3-7/wk; 5-8/wk; 7-10/wk; 1-2/day

- ***BJOG: An International Journal of Obstetrics and Gynaecology*, 2012 (N=1628)**
  - No effects of low-moderate alcohol during pregnancy on neurodevelopment (**intelligence, attention, executive function**) in **5 yr old children** (5 articles)
- **Humphriss et al, *BMJ Open*, 2013 (N=6915)**
  - No strong evidence of a specific effect (either adverse or beneficial) of low-moderate alcohol during pregnancy on **balance at 11 yrs**.
  - Self-reported *higher* total maternal alcohol use generally associated with *better* offspring balance outcomes
- **Kelly et al., *Int J Epidemiol*, 2009; *J Epidemiol Community Health*, 2010; *BJOG*, 2013 (N=10,534 - 12,495)**
  - Children born to light drinkers show no increased risk of clinically relevant **behavioral difficulties or cognitive deficits at 3, 5, or 7 yrs** vs children of Abstainers

Recent studies suggesting **NO EFFECTS** of light-moderate drinking on child outcomes (cont'd)

- **Robinson et al., *BJOG,* 2010 (N=2370)**
  - Light-moderate drinking in first 3 mos gestation associated **with CBCL** scores (by parent report) indicative of **positive behavior** after adjusting for maternal and sociodemographic characteristics (2-14 yrs of age)
  - Clinically *lower* risk of total, externalizing, and internalizing behavioral problems *vs non-drinkers*
- **Sayal et al, *Arch Dis Child,* 2013 (13,171)**
  - Light drinking in pregnancy (1st trimester) does not appear to be associated with adverse **mental health or academic consequences at 11 yrs** of age
- **Rodriguez et al., J Child Psychol Psychiatry 2009 (N=21,678)**
  - Low-moderate drinking showed no risk for **attention deficit and hyperactivity** disorder

Recent studies suggesting **ADVERSE EFFECTS** of light-moderate drinking on child outcomes

- **Andersen et al., *Int J Epidemiol*, 2012 (N=92,719)**
  - Even low amounts of alcohol during **pregnancy increased the risk of spontaneous abortion** substantially
- **Day et al., *Alcohol Clin Exp Res*, 2013 (N=607)**
  - Effects on **behavior problems (CBCL) at 22 yrs** were dose related and significant at each trimester of pregnancy
  - Even at low-moderate levels, effects of PAE extend into young adulthood
- **Feldman et al, *Alcohol Clin Exp Res*, 2012 (N=992)**
  - Quantified specific risks for **minor malformations (FAS facial features) and growth deficiencies** based on patterns and timing of exposure – second half of first trimester most sensitive
  - Dose-related effects, without evidence of a threshold – "one drink is too many"
- **Sood et al, *Pediatrics,* 2001 (N=501)**
  - Even at low levels, alcohol consumption adversely related **to child behavior problems (CBCL)**
  - Dose-response relationship - effects observed with exposure as low as 1 drink/wk, controlling for confounding factors
- **Mullally et al, *BMC Prenancy and Childbirth*, 2011 (N=61,241)**
  - **Congenital abnormalities and dysmorphic features** similar across intake groups

What are the issues that can affect outcomes or interpretation of findings, both negative and positive?

Methodological issues 1:

Possible confounding by social, economic, psychological, lifestyle factors

- U- or J-shaped relationship (Kelly, Humphriss, Robinson)
  - Outcomes in children of low-moderate drinkers are *better* than those of abstainers although generally *worse* than heavy/binge drinkers
- U- or J-shaped relationship - not uncommon in relationship between alcohol consumption and adverse outcome (eg. cardiovascular disease) in adults

- Is there a "*protective effect*" of low-moderate drinking?

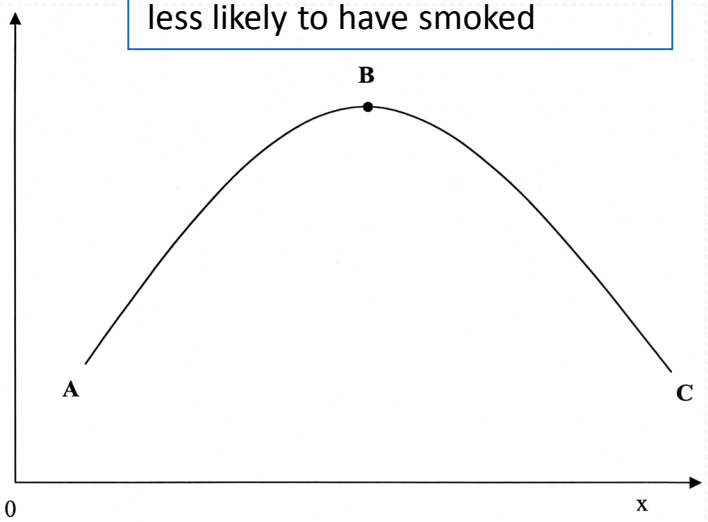
Possible confounding by social, economic, psychological, lifestyle factors (cont'd)

- **Kelly et al:**
  - Drinking socially patterned: (also **Lewis et al., 2012**)
  - Behavioral problems socially patterned:
  - After statistical adjustment for potential confounding or mediating factors (mom age, planned pregnancy, smoking, birth order, ethnicity, lone parent family, life quality), differences attenuated or largely disappeared
- **Robinson:** Mothers who drink in moderation mentally healthier than both abstainers and addicts; self-efficacy and self-management required for moderating substance intake
- **Humphriss**: Paradoxical 'beneficial' effects found in some analyses were most likely a reflection of residual confounding by factors related to social position; ie non-causal.

U-shaped relationship (Kelly et al)

Drinking is socially patterned:

B. Light drinkers better educated, from higher income households, less likely to have smoked

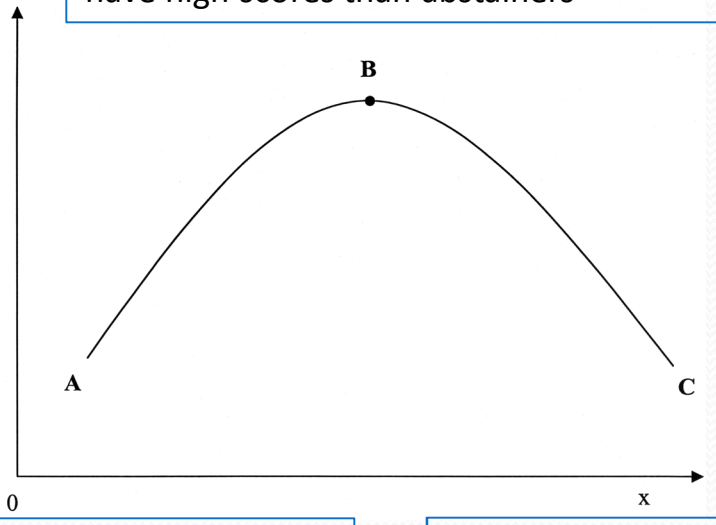


A. Abstainers less well educated, from lower income households, more likely to have smoked

C. Heavy/binge drinkers younger, from low income households, smokers

Relationship between drinking and high SDQ total difficulties score

B. Children of light drinkers less likely to have high scores than abstainers



A. Children of abstainers have high scores

C. Children of heavy/binge drinkers more likely to have high scores than abstainers

*After statistical adjustment for potential confounding or mediating factors (mom age, planned pregnancy, smoking, birth order, ethnicity, lone parent family, life quality), differences attenuated or largely disappeared

Methodological issues 2: Design and outcome measures

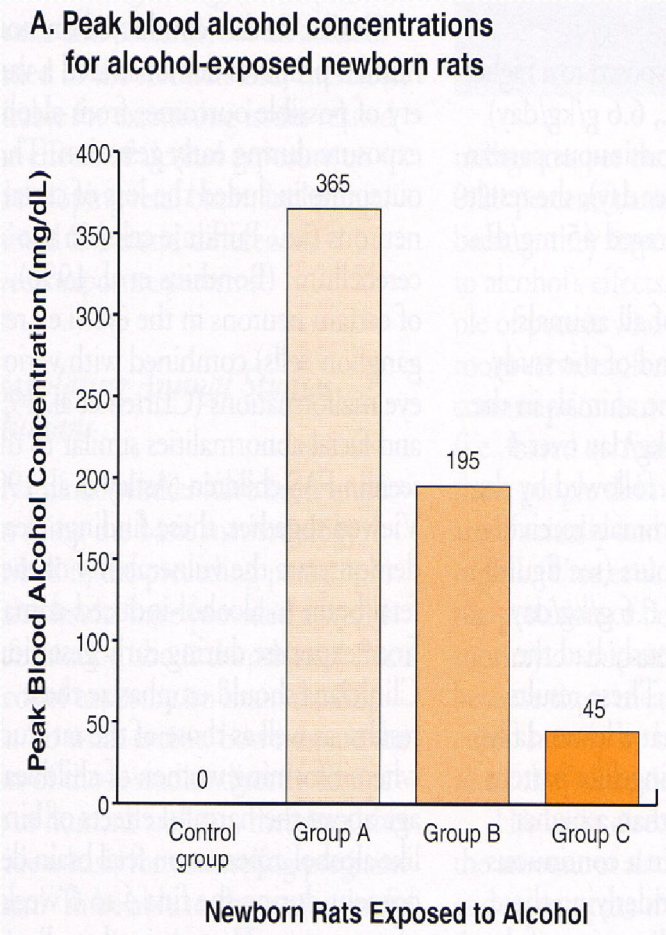
- "Absence of evidence is not evidence of absence" – ie. a statistically non-significant difference does not necessarily mean that there is no difference; study may be underpowered
- Self-report of intake
  - Often underestimated/under-reported
  - If retrospective, recall bias
- Selective attrition of participants
  - eg. Robinson et al – the 30% of mothers lost to follow-up were more socially disadvantaged, and thus more severe cases/ vulnerable children may have been lost
- Use of the CBCL (parental report) as only outcome measure
  - eg., mothers with depression/anxiety report more problem behavior
- Age of testing: children may be too young to measure full impact of alcohol on brain; effects may emerge over time

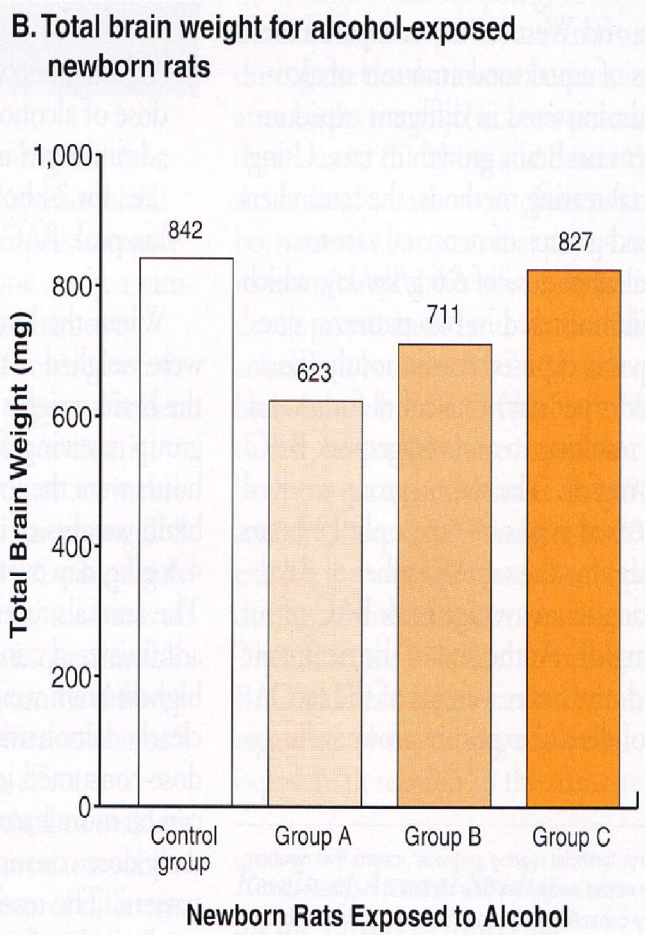
Methodological issues 2: Design and outcome measures (cont'd)

- Failure to account for pattern and timing of intake
  - Binging/dose per occasion, exposure early in development more serious
  - Mean daily intake/average daily volume may not represent the population, especially if broad range of intake from abstinent through heavy; can over- or under-estimate effects for any one individual
- Failure to include data on miscarriages, stillbirths, neonatal deaths
- Lack of sensitivity/age appropriateness of test instruments
- Generalizability of results
- Norms based on data collected (ie. above or below 90%ile for those data) rather than values previously validated in broader population

Pattern of Alcohol Intake and Peak Maternal BALs are Key Factors in Alcoholûs Teratogenic Effects

(From Maier & West, Alcohol Health & Research World 25:168-174, 2001)





- A = 4.5 g/kg over 4h
- B = 4.5 g/kg over 8 h
- C = 6.6 g/kg over 24 h

Methodological issues 3: Genetic variables

Must account for genetics and gene-environment interactions

- **Lewis et al, *PLOS ONE*, 2012:**
  - Population-based study, 11,086 mother-child pairs
  - Strong evidence that genetic variants in alcohol metabolizing genes in women and their children relate to child IQ at age 8, but only in women who drank
  - 4 variants among children and one variant in mothers were associated with child IQ
  - Variants in alcohol-metabolizing genes affect BALs achieved
  - However, these are modest effect of genotype (3.5 point difference in IQ); ie. subtle metabolic effects likely resulting in very small differences in peak BALs in women drinking < 1 unit of alcohol/day or /wk
- **Jacobson et al, J. Pediatrics, 2006**
  - 263 mother/child pairs (217 mothers and 239 children)
  - Maternal ADH1B*3 allele provides protective effects to the fetus on a broad range of alcohol-related cognitive and behavioral outcomes in infancy and at 7.5 years exposure
  - More rapid metabolism of alcohol – lower BALs

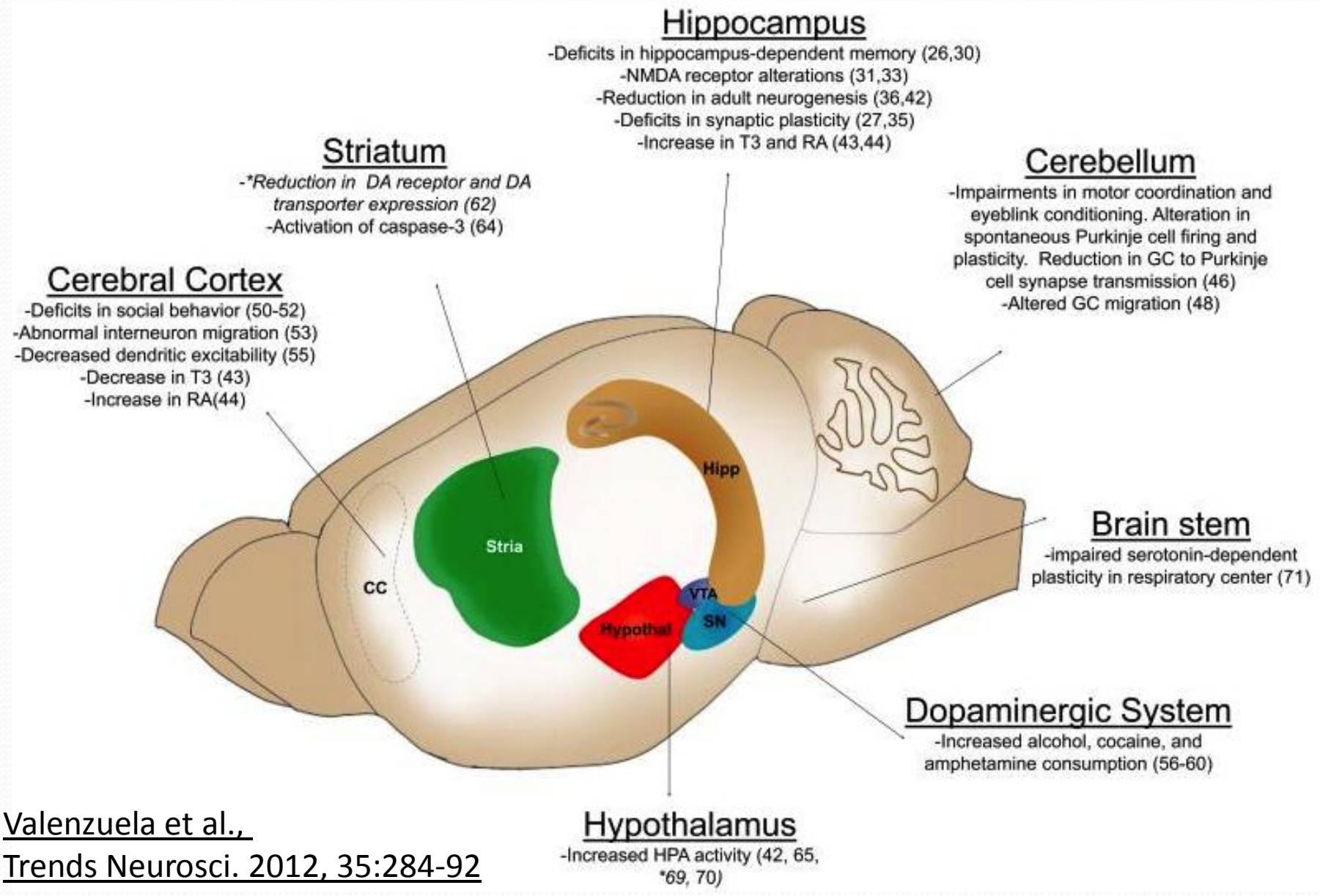
Confounds in studies reporting adverse effects as well

- Lack of rigorous criteria
  - eg., Feldman et al – focused on each outcome (facial features) individually
  - Astley definition requires all 3 features (smooth philtrum, thin upper lip, small palpebral fissures) for diagnosis of FAS
  - Of the 992 children, only 4 had all 3 features (< half of 1%)
- Possible mis-classification of people into intake groups/lack of understanding of what constitutes a 'unit' of alcohol
  - eg. Mullally found 3 cases of FAS in cohort of 61,241 women; one each in groups of low, moderate and high intake

Animal Models

- First developed to address initial skepticism that maternal alcohol consumption could cause FAS
  - Biological and neurobehavioral effects of prenatal alcohol exposure in animals consistent with clinical effects seen in humans
  - Can control timing, pattern, and level of alcohol exposure, genotype and environmental influences (nutrition, stress, drugs) – all of these matter
  - Data have demonstrated that alcohol is a teratogen
  - Effects are dose-dependent, exist on a continuum and are reproducible; low levels of intake can have adverse effects
- Well-defined animal models are valid and effective tools for examining outcomes and investigating mechanisms of alcohol's actions on fetus
  - Animal models allow us to explore brain and behavior in a way not possible in human studies
  - Control of environmental, genetic, nutritional, etc variables

Data from animal models demostrate that low-moderate (BALs 50-170 g/dl) alcohol intake can have adverse effects on brain and behavior:



Valenzuela et al.,
Trends Neurosci. 2012, 35:284-92

Conclusions:

Dr. Kathy Sulik: "Better safe than sorry" *BJOG*, 2012

- With alcohol being the drug of choice.., the desire for a "safe" amount to be identified is pervasive
- (However)..difficulties in human epidemiological studies regarding reliable and honest recall of alcohol consumption levels and patterns, knowledge of date of conception, generalizability of data across ethnic and racial groups/genetic factors, and confounding environmental variables, (makes it) highly unlikely that for any individual pregnancy a known safe amount of maternal alcohol consumption will be identified.
- The fact that the definition of a standard drink is widely variable, along with other potential individual risk factors…makes finding a universally correct answer impossible.
- Undoubtedly, it is better for women at all stages of pregnancy to be safe by avoiding alcohol consumption rather than being sorry for inadvertently damaging their children