

# Unique and common factors in risk development for alcohol use disorder (AUD) in earlier childhood

Implications and challenges for prevention

---

Robert A. Zucker, Ph.D.  
Addiction Research Center &  
Substance Abuse Section  
Department of Psychiatry  
University of Michigan Medical School

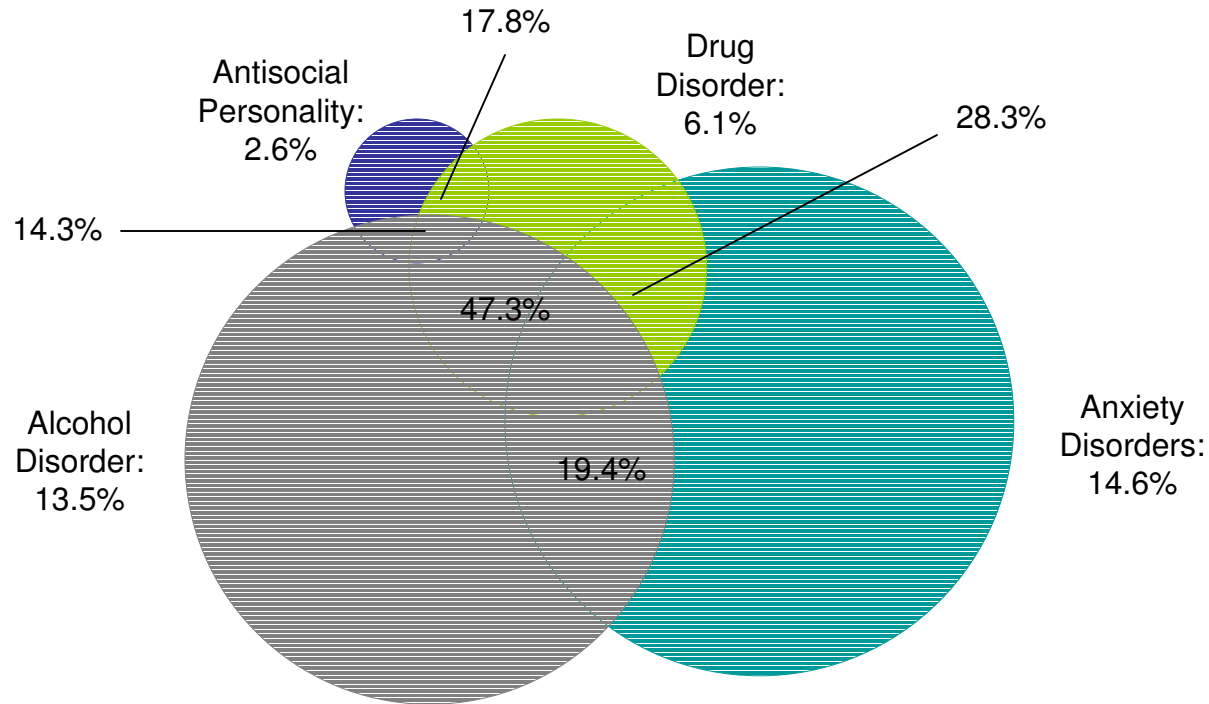


## Two risk domains

**Nonspecific risk:** precursive for a number of behavioral disorders and problem outcomes of youth and early adulthood, but is also a risk pathway to later alcohol problems and AUD

**Alcohol specific risk:** An alcohol involvement pathway, including risk manifestations identifiable well before drinking starts, also markers more proximal to drinking onset (e.g., drinking expectancies) as well as early drinking risk indicators—like bingeing.

# ECA Lifetime Comorbidity of any Alcohol Diagnosis, any Other Drug Diagnosis, Antisocial Personality Disorder and any Anxiety Disorders



Regier, D., Farmer, M., Rae, D., Locke, B., Keith, S., Judd, L., Goodwin, F. (1990). Comorbidity of Mental Disorders with Alcohol and Other Drug Abuse: Results from the Epidemiologic Catchment Area (ECA) Study, *JAMA*, 264(19), 2511-2518.

# The nonspecific risk domain

## **Two Core Nonspecific risky trait domains:**

---

**UNDERCONTROL:** Externalizing behaviors involving... impulsivity, high activity, aggressiveness, rule breaking

**NEGATIVE AFFECTIVITY:** Negative affective behaviors involving... internalizing behaviors... sadness, anxiety, depression, social inhibition

**Why these two?**

# Behavioral evidence from 7 longitudinal studies

**Kellam et al, 1980**

**Huesmann, Eron et al, 1984**

**Zucker et al., 1987, 2006, 2007**

**Cloninger, et al. 1988**

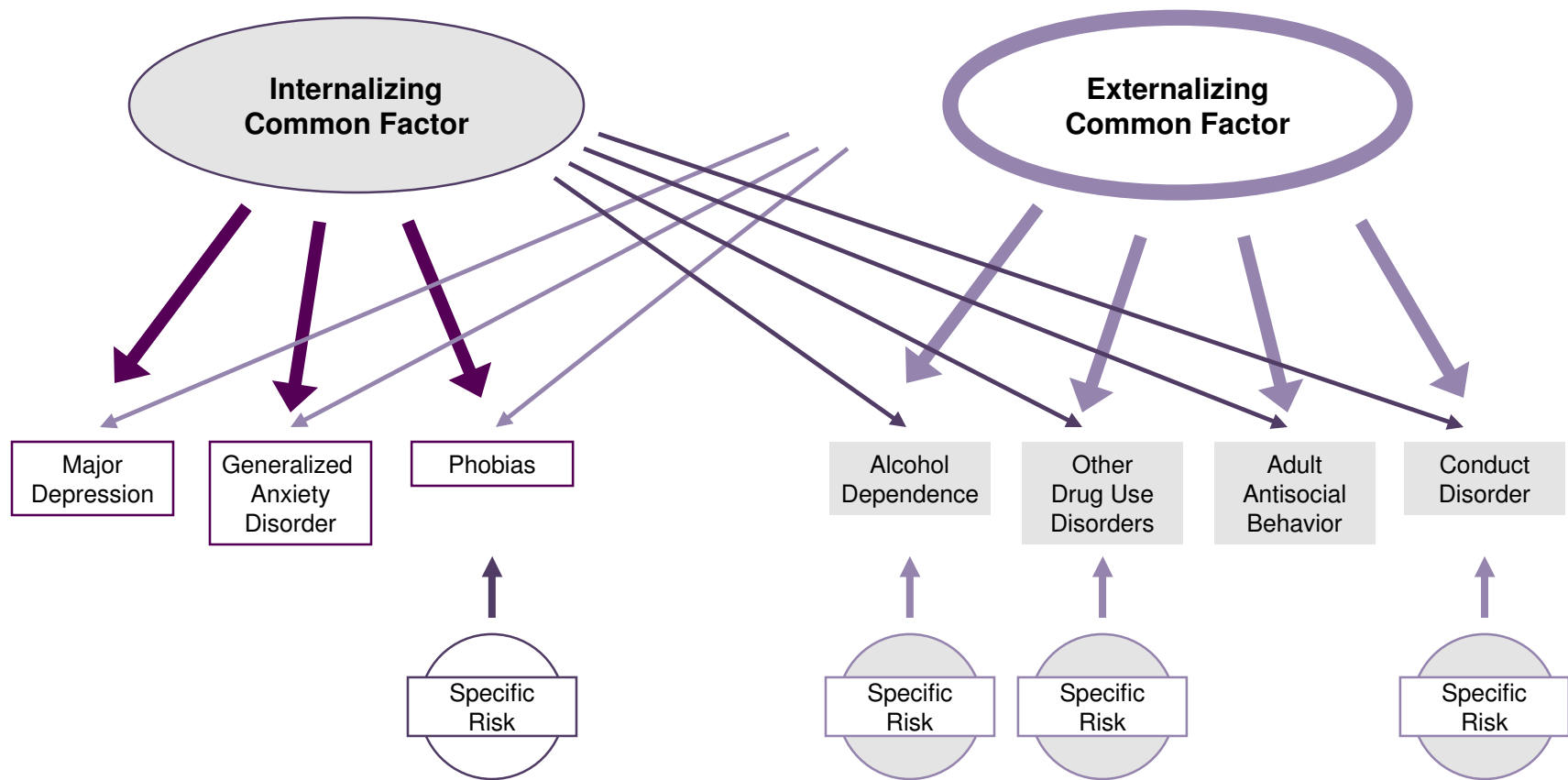
**Hawkins et al. 1992**

**Caspi et al, 1996**

**Tremblay et al. 1997**

Based on review in Zucker, R. A. (2006). Alcohol use and the alcohol use disorders: A developmental-biopsychosocial systems formulation covering the life course. In D. Cicchetti & D.J. Cohen (Eds.), *Developmental psychopathology: Vol. 3. Risk, disorder and adaptation* (2nd ed., pp. 620-656). New York: Wiley.

# Structure of common and disorder-specific genetic risk for common psychiatric and substance use disorders



Key: Width of arrows is an indicator of relative strength of the relationship.

Source: Figure 17.6, p. 639, in Zucker, R. A. (2006). Alcohol use and the alcohol use disorders: A developmental-biopsychosocial systems formulation covering the life course. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology: Vol. 3. Risk, disorder, and adaptation* (2nd ed., pp. 620-656). New York: Wiley. Adapted from Kendler, K.S., Prescott, C.A., Myers, J., & Neale, M.C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry*, 60, 929-937.

**Development**

## **Regulation and control systems developing between birth and middle childhood (0-11)**

---

- **Behavioral control and attendance to social rules**
- **Social regulation**
- **Self-regulation including emotional regulation**
- **Regulation of stress**

Neurocognitive and brain functional circuitry implicated in the development of these systems is

# Cortical and subcortical neural circuitry involved in self and social regulation, behavioral control, attendance to social rules (0-11)

---

- ability to suppress or to inhibit prepotent responses (Right inferior frontal cortex to basal ganglia (response inhibition)<sup>1</sup>)
- ability to suppress irrelevant information (dorsolateral prefrontal cortex and structures related to working memory<sup>2</sup>, and anterior cingulate cortex)<sup>3</sup>)
- ability to discriminate emotional facial expressions (Amygdala)<sup>4</sup>)

1. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. *J Child Psychol Psychiatry*. 1996; 37(1):51–87

2. Aron AR, Fletcher PC, Bullmore ET, et al. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat Neurosci*. 2003;6(2):115–116

3. Klingberg T, Forssberg H, Westerberg H. Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory capacity during childhood. *J Cogn Neurosci*. 2002;14(1):1–10

4. Thomas KM, Drevets WC, Whalen PJ, et al. Amygdala response to facial expressions in children and adults. *Biol Psychiatry*. 2001;49(4):309–316

## Parallelisms and predictions

---

- Interestingly, structural and functional changes in these same regions are seen in adult alcoholics
- Given that the nonspecific behavioral and emotional regulation domains that have been found to predict AUD risk map onto these structures, therefore...
- **Dysregulation of these neural systems should be related to AUD risk earlier than the adult disorder.**

# Michigan Longitudinal Study fMRI component on youth:<sup>5</sup>

An early test of this prediction

5. Heitzeg, M.M., Nigg, J.T., Yau, W-Y. W., Zubieta, J.K. & Zucker, R.A. (2008). Affective circuitry and risk for alcoholism in late adolescence: Differences in frontostriatal responses between vulnerable and resilient children of alcoholic parents. *Alcohol Clin Exp Res*, 32(3), 414–426.

# Risk and Resilience groups (M + F)

## Early Problem Alcohol Involvement

Low

High

Low:  
Not  
COA

**Controls**

**High  
Environmental  
Risk?**

Family risk  
(COA status)

High:  
COA

**Resilient**

**Vulnerable**

Source:Heitzeg, M.M., Nigg, J.T., Yau, W-Y. W., Zubieta, J.K. & Zucker, R.A. (2008). Affective circuitry and risk for alcoholism in late adolescence: Differences in frontostriatal responses between vulnerable and resilient children of alcoholic parents. *Alcohol Clin Exp Res*, 32(3), 414–426.

# Brain function of resilient youth in response to emotional stimuli: Ability to respond yet also to monitor

- Negative emotional stimuli; greater activation in:
  - **Insula activation**– evaluating internally generated emotions and monitoring ongoing internal emotional state. **Awareness** should be protective.
  - **Ventral striatum/extended amygdala activation**– activation involves response to **saliency** of the stimulus; unconscious emotional processing.
  - **Orbital frontal gyrus** – OFG involves **monitoring and evaluation of the affective value** of stimuli, allowing for appropriate behavioral responses. **Protective to monitor and evaluate**
  - OFG also activated for positive emotional stimuli.

# Brain function of resilient youth in response to emotional stimuli: Ability to respond yet also to monitor

- Summary: Resilient youth activate areas that evaluate and monitor internal stimuli. They also activate areas that respond to saliency (strength of the stimulus).
- These findings suggest an active emotional monitoring function, an ability to attend to affective input, and make judgments about level of arousal. This reflective capability would seem to be useful in making judgment calls about whether one has drunk enough, and would be essential processes in the regulation of drinking behavior as well as staying out of other trouble.

# Brain function of vulnerable youth in response to emotional stimuli; Active suppression & less awareness of saliency

- Negative emotional stimuli; greater activation in vulnerable group in:
  - Dorsomedial prefrontal cortex – related to conscious, voluntary control of emotional responses (e.g., involving the potential for suppression of emotion).

Positive emotional stimuli; Same as for negative stimulus response.. increased DMPFC response here;

In addition, decreased VS/Extended Amygdala response

–

decreased responding to saliency of stimulus; vulnerable had less responsivity; in contrast, resilient group had more.

# Brain function of vulnerable youth in response to emotional stimuli; Active suppression & less awareness of saliency

- Summary: The activation pattern observed here is consistent with a behavioral style involving active, voluntary suppression of emotional responses, which in turn would lead to a deficit in the ability to deal with emotional situations.
- The vulnerable group was also less responsive to emotional signal strength, another deficit with a strong potential to make difficulty in social situations.



# Development of early alcohol-specific risk

# Family history positive is a robust early marker

Children of Alcoholics have a  
4-10 fold increased risk  
for AUD<sup>6</sup>

6. Grant and Dawson. *J Subst Abuse*. 1998;10(2):163-73.

## Estimated Number and Percentage of Children in the Household Who Had One or More Parents Dependent on **Alcohol**, by Children's Ages (US Population)

Age Range	# in US Pop	# COA	% COA
Under 2	8,590,119	678,923	7.9
2 - 5	18,766,120	1,551,952	8.3
6 - 9	18,333,494	1,616,156	8.8
10-13	15,015,264	1,225,437	8.2
14-17	13,801,727	1,115,056	8.1
<b>Total</b>	<b>74,506,723</b>	<b>6,187,524</b>	<b>8.3</b>

Source: Office of Applied Studies, SAMHSA, National Household Survey on Drug Abuse, 1996.

**Early alcohol specific  
environmental effects on  
risk as a function of  
exposure**

# Alcohol-specific environmental risk in later childhood

Early exposure to heavy use leads to earlier onset and heavier use<sup>7,8,9</sup>

- Family exposure (greater parental drinking at ages 10-11)
- More involvement with peers who use

7. Hawkins JD, Graham JW, Maguin E, et al. Exploring the effects of age of alcohol use initiation and psychosocial risk factors on subsequent alcohol misuse. *J Stud Alcohol*. 1997; 58(3):280-290

8. Duncan, T.E., Duncan, S. E., Hops, H. The effects of family cohesiveness and peer encouragement on the development of adolescent alcohol use: A cohort-sequential approach to the analysis of longitudinal data. *J Stud Alcohol*. 1994; 55(5):588-599

9. Rhee S-H, Hewitt JK, Young, SE, Corley, RP, Crowley, TJ, Stallings, MC. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch Gen Psychiat* 2003, 60, 1256-1264

## **Alcohol-specific environmental risk in early childhood**

**Parental drinking very early in the child's life also has an early effect on children's understanding of drinking, and has a later effect on drinking outcomes <sup>10</sup>**

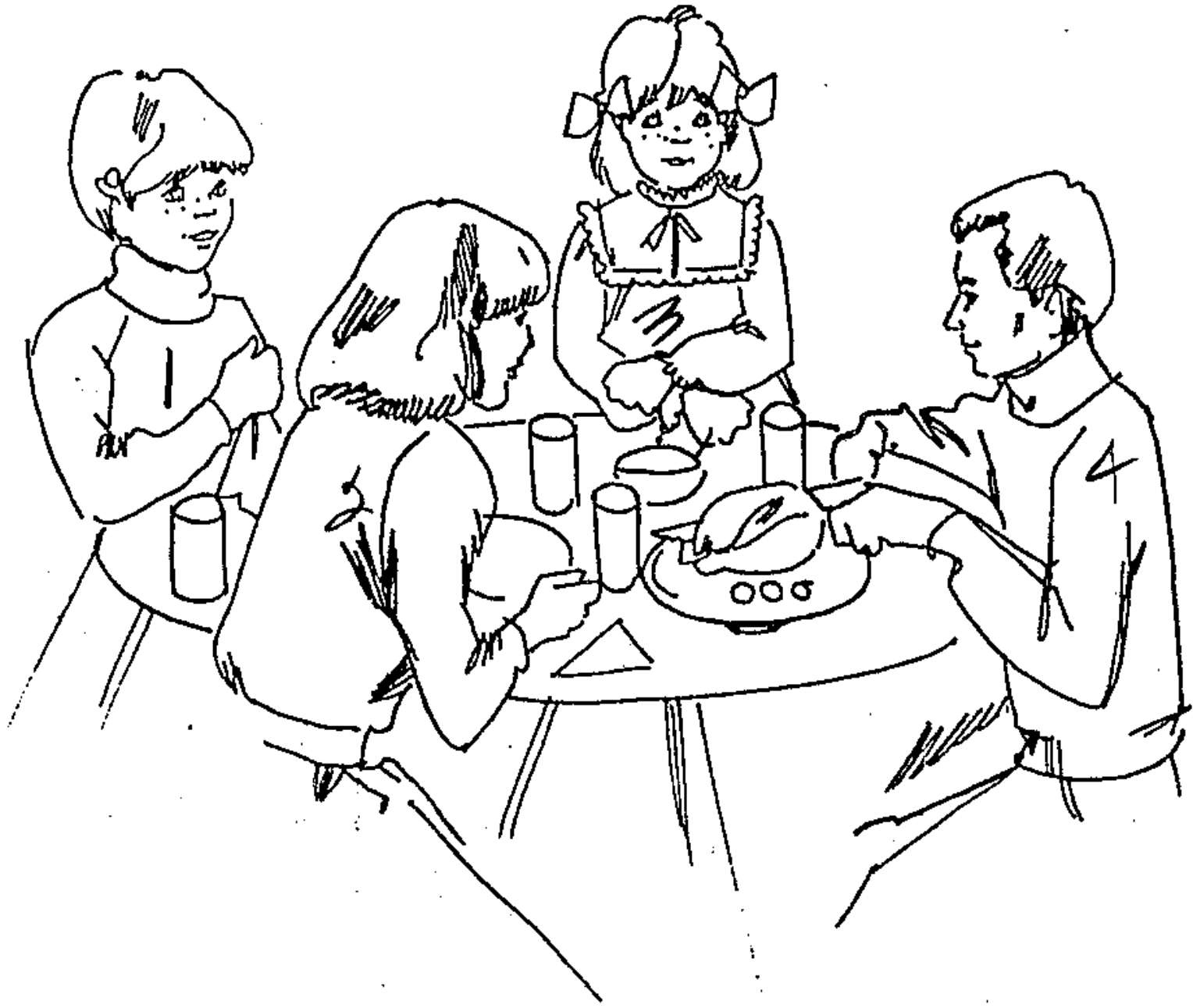
10. Zucker, R. A., Kincaid, S. B., Fitzgerald, H.E., & Bingham, C.R. (1995). Alcohol schema acquisition in preschoolers: Differences between children of alcoholic and children of nonalcoholics. *Alcohol: Clin Exp Res*, 19, 1011-1017.

# Alcohol schema development is a very early drug involvement indicator

- Alcohol an object in the social environment; for this reason, learning the “symptomatic behaviors” is different here than it is for learning the symptoms of depression.
- The development of concept formation about alcohol occurs at different rates among children and involves their ability to schematize and also develop scripts about use)
- Learning names (concept/schema formation) (assessed through ability to identify object by smell)
- Learning use patterns (scripts): assessed through the Appropriate Beverage Task







# Predicting child attributions of alcoholic beverage use at age 3-5: Hierarchical regressions of child's age and parental alcohol consumption on child attributions

	R <sup>2</sup>	R <sup>2</sup> change
<b>Attributions to adult males</b>		
Step 1. Child's age	0.03	0.03*
Step 2. Paternal alcohol Consumption	0.15	0.12**
Step 3. Maternal alcohol Consumption	0.16	0.01**
<b>Attributions to adult Females</b>		
Step 1. Child's age	0.01	0.01
Step 2. Maternal alcohol Consumption	0.04	0.03*
Step 3. Paternal alcohol Consumption	0.04	0.00*

F model: \*p<0.05;  
p<0.001.

10. Zucker, R.A. et al. (1995). *Alcohol Clin Exp Res* 19.

Predicting problem alcohol  
outcomes from alcohol  
schemas in preschool

# Extent of early childhood alcohol schema presence predicts early onset of drinking<sup>11</sup>

- Alcohol assignment at age 3-5 (# of alcoholic beverages assigned to adult males) was higher for later to be early drinkers compared to those who did not initiate alcohol use by age 14 ( $t = 2.81, p < .01$ )

11. Donovan, J.E., Leech, S.L., Zucker, R.A., Loveland-Cherry, C.J., Jester, J.J., Fitzgerald, H.E., Puttler, L.I., Wong, M.M. & Looman, W.S. (2004). Really underage drinking: Alcohol use among elementary students. *Alcohol: Clin Exp Res*, 28, 341-349

# Early alcohol schema development predicts early onset of drinking even with parent alcoholism and parental consumption are controlled <sup>11</sup>

11. Donovan, J.E., Leech, S.L., Zucker, R.A., Loveland-Cherry, C.J., Jester, J.J., Fitzgerald, H.E., Puttler, L.I., Wong, M.M. & Looman, W.S. (2004). Really underage drinking: Alcohol use among elementary students. *Alcohol: Clin Exp Res*, 28, 341-349

Prevention

# Why prevent early?

Drinking problems *and* AUD as visible behaviors are primarily a problem of youth and early adulthood

However, they are *developmental* disorders

The evidence is strong that the most damaging alcohol problem/AUD pathway is in place well before the start of high school

For these reasons, it is quite possible that middle childhood intervention may be too late. Is it?

This question has not yet been addressed. Given the magnitude of the problem, this is a critical question. Chronic disease management strategies in other areas (obesity, diabetes) would suggest that earlier is better.

## **Issues of Social and Political Policy related to early screening and intervention**

The problem of locating venues for early identification without increasing stigma.  
The need to identify practical pass-through points for screening as well as prevention/intervention.

## **Possible pass through points and intervention venues**

- Pediatric Emergency Departments
- Urgent Care
- District Courts adjudicating drunk driving
- Family Courts
- Schools in low income areas
- Primary health care settings
- **Substance Abuse Treatment Programs  
for the parents**

# Research needs I

A randomized trial to evaluate the efficacy of risk-reduction interventions begun in early childhood vs. middle childhood.

## Research needs II:

**The problem of nested risk; studies are needed to disaggregate the overlapping contributions of a number of known risk factors.**

- Parental comorbidity conveying increased nonspecific risk (antisociality, depression)
- Family conflict, violence, very early, as well as sustained later exposure to alcohol and other drugs
- Marital assortment
- Neighborhood assortment and longitudinal neighborhood effects
- Reluctance of high risk families to enter and/or stay in treatment; low compliance when in treatment

## **Research supported by:**

R37 AA07065 (Zucker)

RO1 AA12217 (Zucker & Nigg)

T32 AA07477 (Zucker)

K01 DA 20088 (Heitzeg)

Thank you