A life course approach to understanding sex differences in depression and inflammation in mid-life

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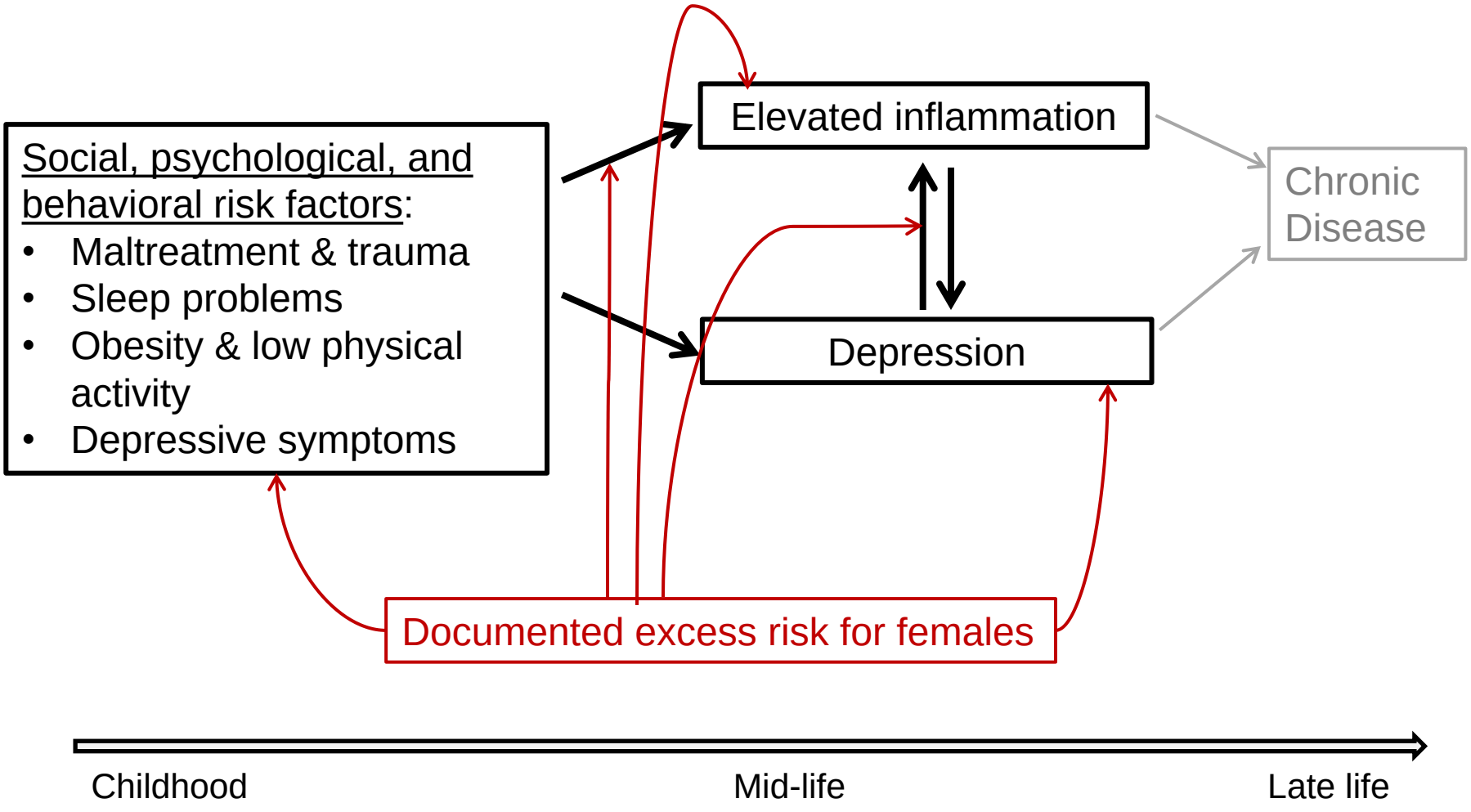
Life course model for sex differences in depression and inflammation in mid-life (Derry et. al.)



Source: Derry, Padin, Kuo, Hughes, & Kiekolt-Glaser, Curr Psychiatry Rep (2015) 17: 7.

Inflammation

- Individuals with inflammatory disorders are 3-4 times more likely to have depression.[1]
- Individuals with depression have elevated pro-inflammatory biomarkers[2]
- Inflammation: part of normal stress response system
  - Elevated levels are adaptive in short term, but detrimental over time[3]

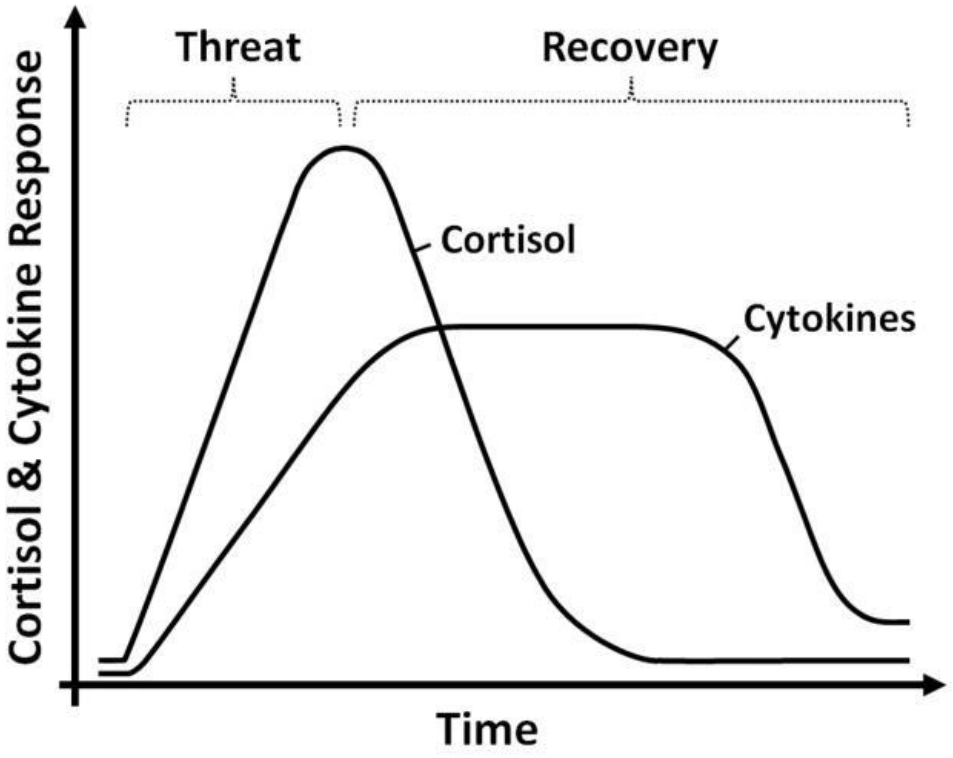


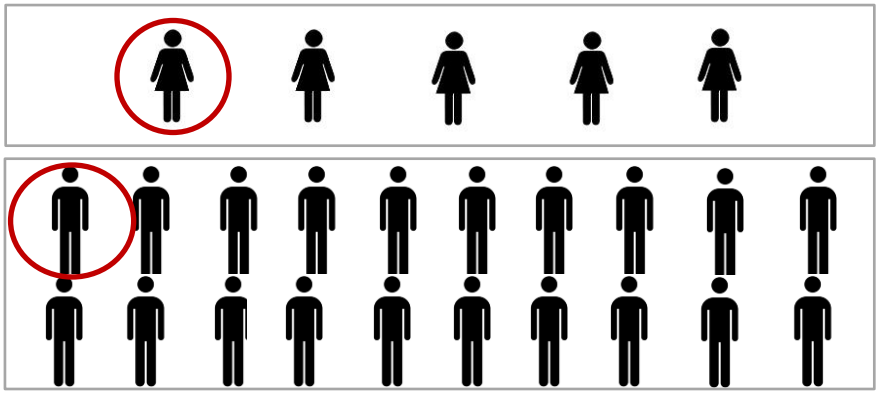
Image source: Slavich & Irwin, *Psychol Bull.* 2014;140(3):774-815.

[1]Moieni, et al. (2015), *Neuropsychopharmacology* 40 (7): 1709. [2]Howren et al, (2009), *Psychosomatic medicine* 71.2 :171-186.
[3]McEwen, B. S. (1998), N Engl J Med 338(3): 171-179.

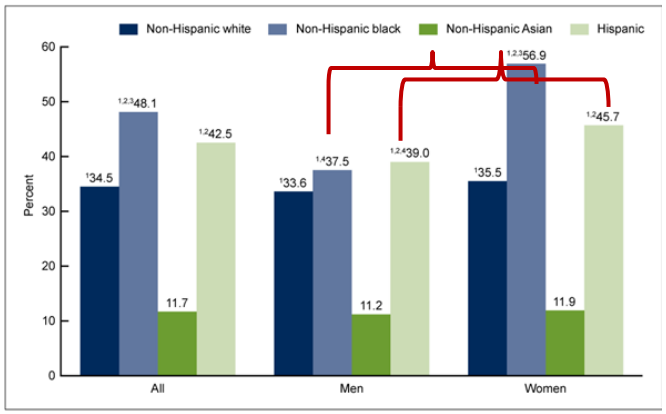
1. Women face excess risk for many shared risk factors for depression and inflammation in early life and beyond.

Females (vs. males) face excess risk for…

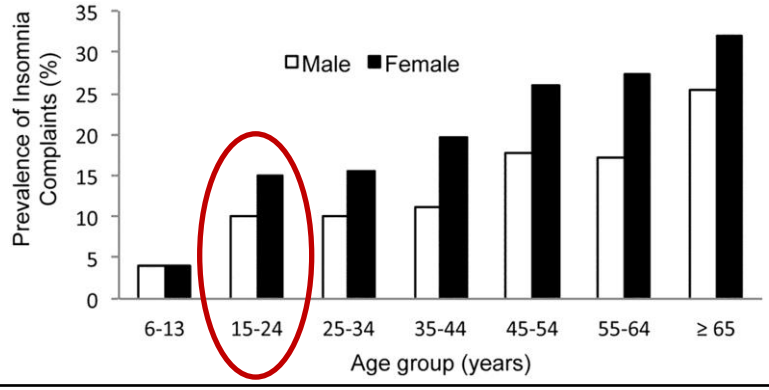
Childhood sexual abuse[1]



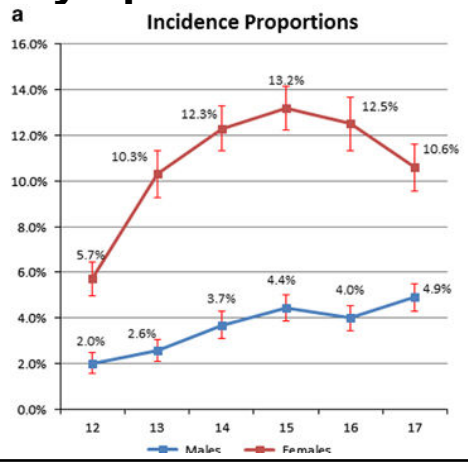
Obesity[2]



Sleep problems[3]



Depressive symptoms earlier in life[4]



[1] National Center for victims of crime: http://victimsofcrime.org/media/reporting-on-child-sexual-abuse/child-sexual-abuse-statistics; [2] Ogden et al. US Department of Health and Human Services, NCHS, 2015. [3]Mong, et al. *Journal of Neuroscience* 31.45 (2011): 16107-16116; ; [4]Breslau, et al. *Translational psychiatry*7.5 (2017): e1139.

2. Sex disparities in depression and inflammation emerge in adolescence.

Sex differences emerge in adolescence

Major depressive hazard rates by age and sex, into mid-life.

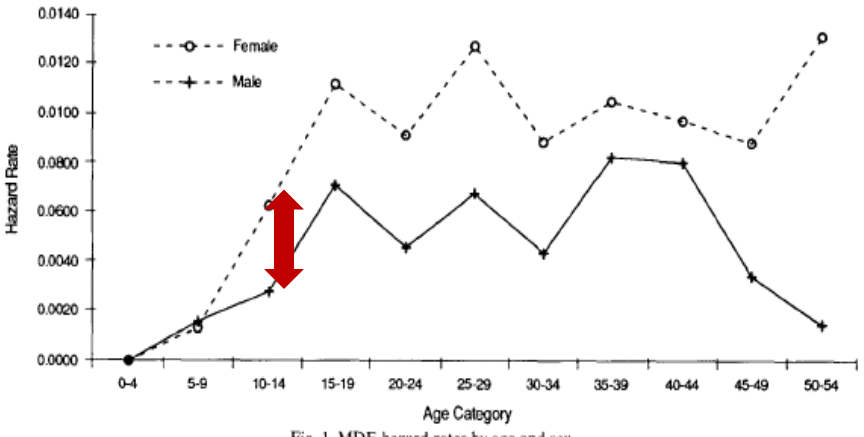
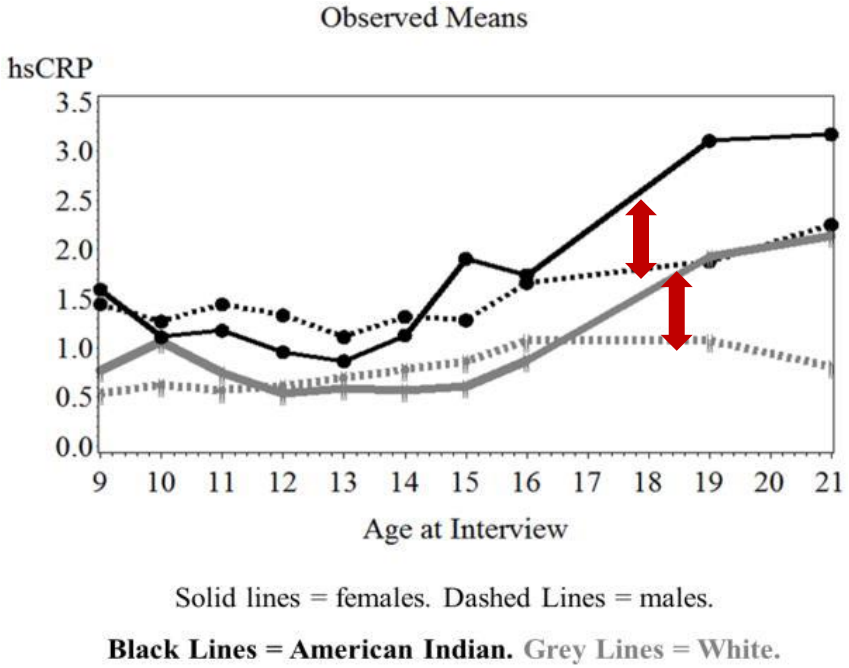


Fig. 1. MDE hazard rates by age and sex.

Data Source: National Comorbidity Study

Kessler et al. (1993). *J Affect Disord* **29** (2-3): 85-96.

Mean hs-CRP for American Indian and White females and males, ages 9 to 21.



Solid lines = females. Dashed Lines = males.

Black Lines = American Indian. Grey Lines = White.

Data Source: Great Smokey Mountain Study;

Shanahan et al, 2013. *Psychoneuroendocrinology*; 38(10): 2209–2217.

3. Psychological symptoms and inflammation are correlated, beginning early in the life course.

“Coupling” of psychological symptoms and inflammation in childhood & adolescence

Psychoneuroendocrinology (2013)

Internalizing and externalizing behaviors predict elevated inflammatory markers in childhood

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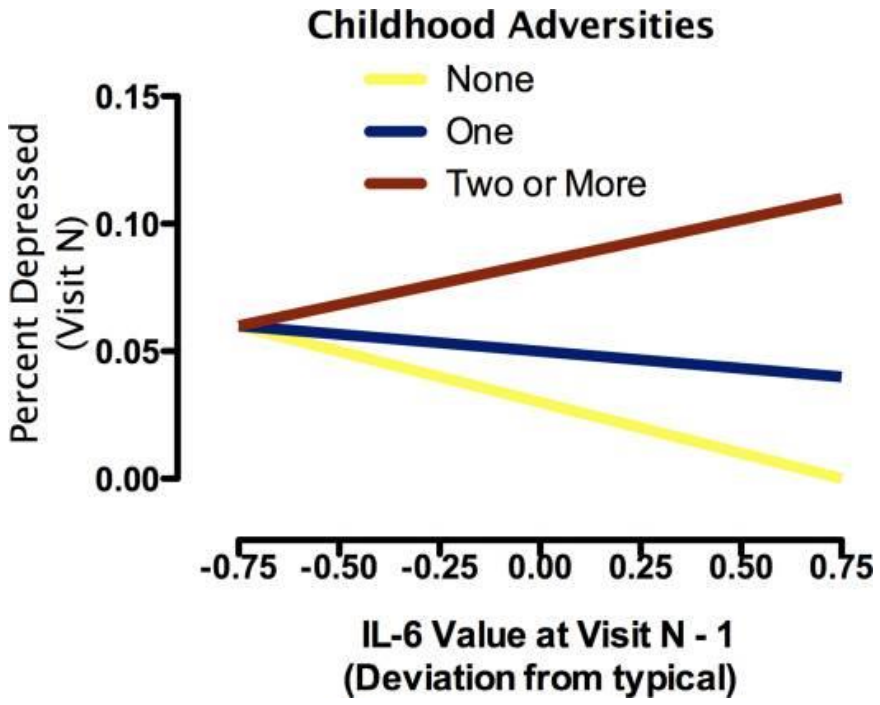
Table 2 Associations between age 8 internalizing and externalizing behaviors and C-reactive protein and Interleukin-6 levels at age 10.

	Simple model[a]		Adjusted for covariates[b]	
	β (SE)	p-Value	β (SE)	p-Value
Outcome: log C-reactive protein				
Internalizing z-score	0.04 (0.02)	0.02	0.03 (0.02)	0.06
Externalizing z-score	0.05 (0.02)	0.01	0.04 (0.02)	0.04
Outcome: log interleukin-6				
Internalizing z-score	0.06 (0.01)	<0.0001	0.05 (0.01)	<0.01
Externalizing z-score	0.05 (0.01)	<0.01	0.04 (0.01)	<0.01

[a] Simple linear regression models are adjusted for age and sex.
[b] Covariates include sex, ethnicity, age, current medication use, maternal education at gestation, family income at age 8. Sample sizes vary slightly due to missing information on inflammatory markers ($n = 4069$ for CRP and $n = 4061$ for IL-6). SE, standard error.

Prevalence of depression as a function of interleukin-6 and childhood adversity in 147 adolescent females.



Miller & Cole, Biol Psychiatry. 2012; 72(1): 34–40.

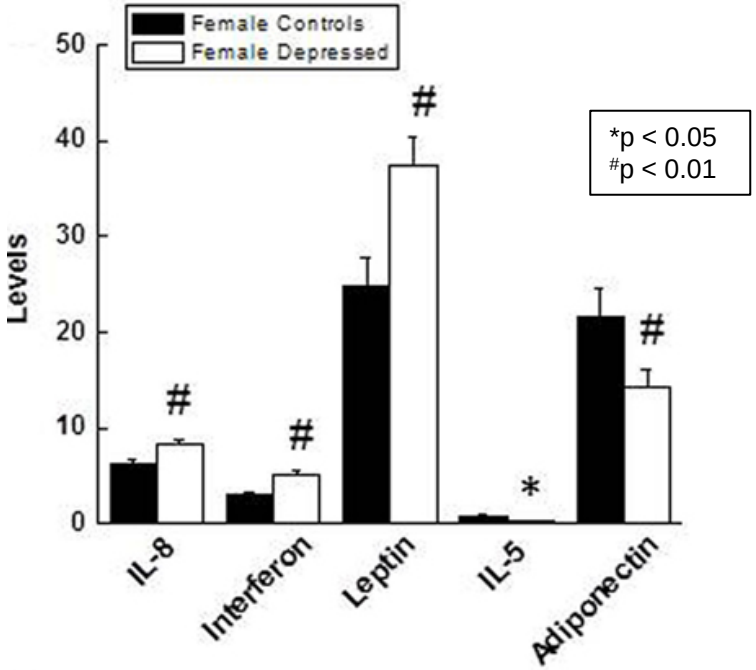
Additional reference (review article): O'Connor, T. G., et al. (2014). *Journal of Child Psychology and Psychiatry* 55(6): 615-631.

4. Inflammation may have a more pronounced influence on depression in women as compared to men.

Association between inflammation & depression may be modified by sex

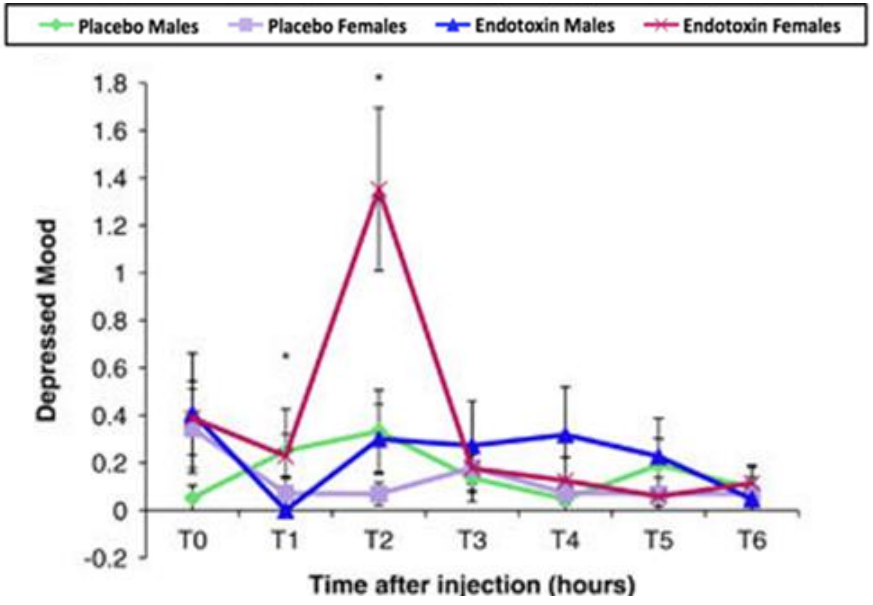
Sex differences in inflammatory biomarkers in patients with MDD vs. controls

- No significant differences between depressed males and control males



Birur, et al (2017), *Frontiers in psychiatry* 8 : 108.

Randomized Trial:
Changes over time in the endotoxin and placebo groups in depressed mood, by sex



Moieni et al (2015), *Neuropsychopharmacology* 40(7): 1709-16.

5. Social interventions can affect key biological domains implicated in the development of pro-inflammatory conditions and depression.

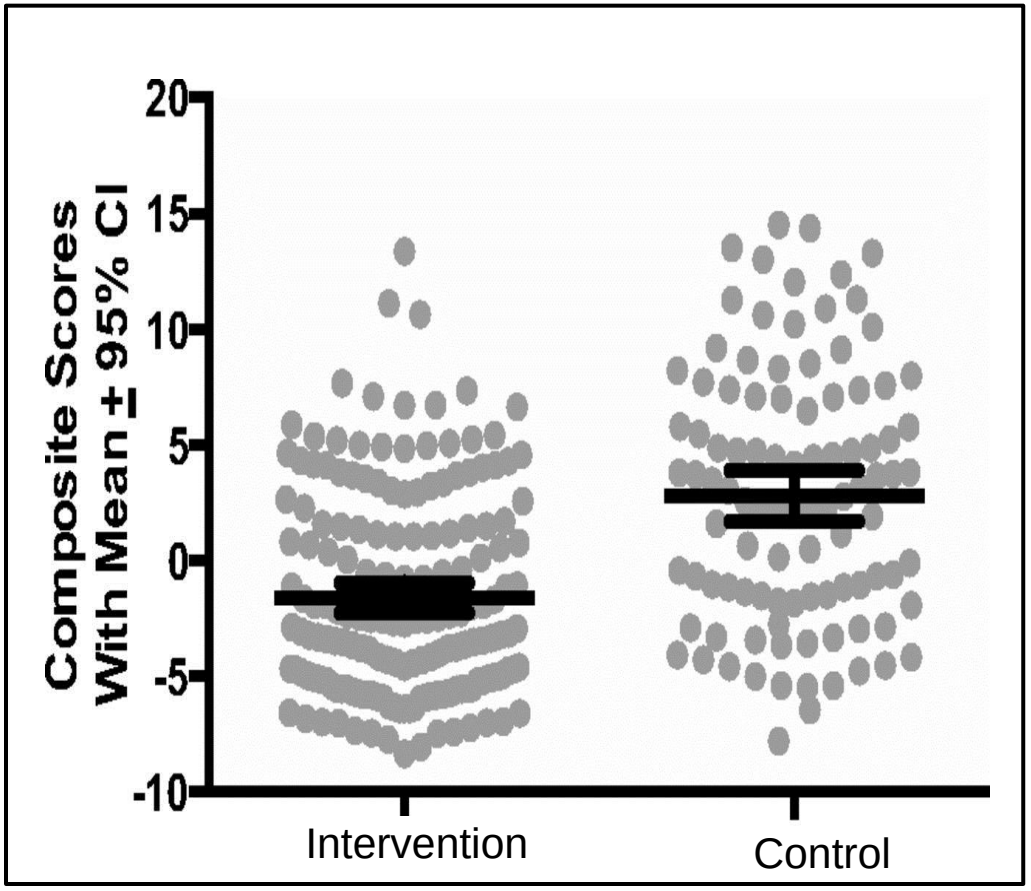
Family-oriented psychosocial intervention reduces inflammation in low-SES African American youth

Sample:
272 mothers and 11 yr-old children from rural Georgia (1/2 < FPL).

Random assignment to 7-wk psychosocial intervention

Outcome:
6 indicators of inflammation (evaluated individually and as a composite) measured at 19 years (8 years post-intervention).

Results:
Intervention youth had less inflammation on all 6 indicators relative to controls; improved parenting was a significant mediator.



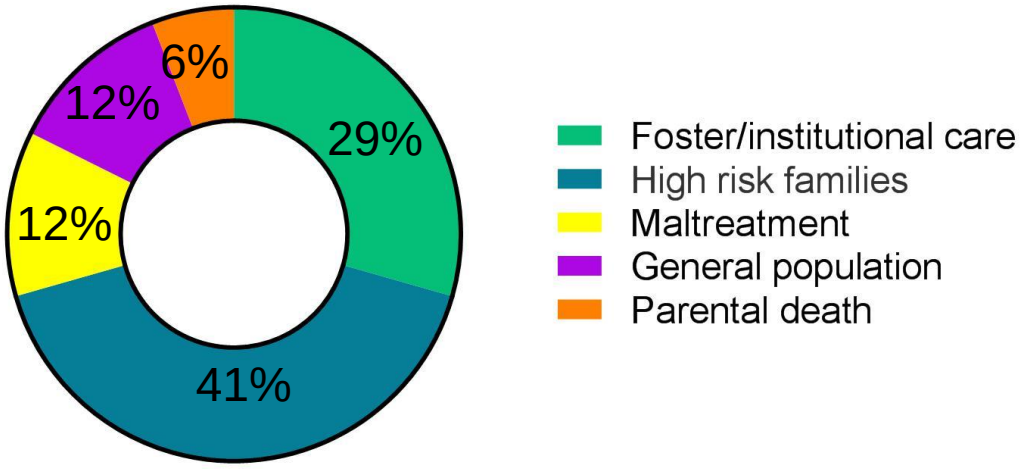
Miller, Brody, Yu, & Chen. PNAS 2014;111:11287-11292.

Interventions to improve cortisol regulation in children: A systematic review

Systematic review: identified 19 articles from 17 randomized or quasi-experimental studies:

1) designed to improve relationships, environments, or psychosocial functioning in children;

2) that examined cortisol as an outcome.



Slopen, McLaughlin, & Shonkoff, (2014), *Pediatrics,* 133: 312-326.

Interventions are effective

- 18 of 19 studies reported at least 1 difference in cortisol outcome between intervention and control participants.
- 8 studies included a low-risk comparison group: in all, post-intervention cortisol in the intervention group approximated low-risk comparison (& differed from usual care).
- Conclusion: cortisol activity can be altered by interventions.
- Promising evidence that it may be possible to protect and/or repair stress regulatory systems after early social adversity.

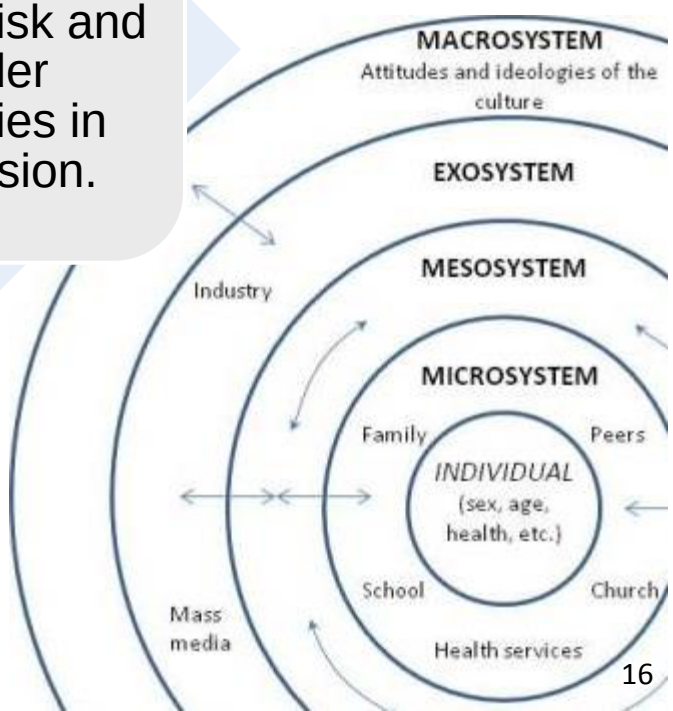
Slopen et al, (2014), *Pediatrics*, 133: 312-326.

Future Directions

Identification of mechanisms, sensitive periods, and moderators of early indicators of risk

Age-appropriate interventions

More effective reduction of disease risk and gender disparities in depression.



Thank you.

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