



Women's Health
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Stress, Depression and Physical Health

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Major Depressive Episode (DSM-IV)

- >5 Symptoms present during the same 2 wk
- A change from previous functioning
- Functional impairment and/or distress
- Symptoms not due to another cause
- The total of 5 symptoms must include
 - Depressed mood and/or
 - Loss of interest or pleasure
 - Plus...

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)*. Washington, DC: American Psychiatric Publishing, Inc; 1994.

Symptom Criteria for Diagnosis Major Depressive Episode



- Physical symptoms
- Appetite or weight change
- Insomnia or hypersomnia
- Psychomotor agitation or psychomotor retardation
- Fatigue
- Psychological symptoms
- Depressed mood
- Loss of interest or pleasure
- Feelings of worthlessness or guilt
- Diminished ability to think, concentrate, or make decisions
- Recurrent thoughts of death or suicide

The WHO Predicts by 2020 Major Depression will be the #1 Leading Cause of Disability



Leading Causes of Medical Disability in the US (1996)

Women

1. Ischemic heart disease
2. Unipolar major depression
3. Cerebrovascular disease
4. Lung, trachea, bronchus cancer
5. Osteoarthritis
6. Breast cancer
7. COPD
8. Dementia, other CNS disorders
9. Diabetes mellitus
10. Road traffic collisions

Men

1. Ischemic heart disease
2. Road traffic collisions
3. Lung, trachea, bronchus cancer
4. HIV/AIDS
5. Alcohol abuse/dependence
6. Cerebrovascular disease
7. Homicide and violence
8. COPD
9. Self-inflicted
10. Unipolar major depression

Having Depression Worsens the Prognosis for Other Health Problems Women Face



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| Cardiovascular Illness | Impact of Depression |
|---|--|
| Diabetes | 2.3x ↑ risk of diabetes |
| Hypertension | 3x ↑ morbid risk |
| Coronary artery disease | 40% ↑ risk of cardiac event |
| Unstable angina | 3x ↑ of cardiac death at 1 year |
| Stroke | 2.7x ↑ risk of stroke |
| Post-Myocardial infarction | 6x ↑ mortality |
| Congestive heart failure with LVEF < 20 | 50% survival vs 78% survival at 1 year |

Rabkin JG, et al. *Am J Psychiatry*. 1983;140:1072-1074; Carney RM, et al. *Psychosom Med*. 1988;50:627-633; Schleifer SJ, et al. *Arch Intern Med*. 1989;149:1785-1789; Frasure-Smith N, et al. *Circulation*. 1995;99:999-1005; Eaton WW. *Diabetes Care*. 1996;10:1097-1102; Kawakami N, et al. *Diabetes Care*. 1999;22:1071-1076; Albot F, Nouwen A. *Diabetes Care*. 2000;23:1556-1562; Larson SL, et al. *Stroke*. 2001;32:1979-1983; Frasure-Smith N, et al. *Herz*. 2006;64-8;



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Overlap: Depression and Other Medical/Physical Disorders

- 58% of MDD patients have co-occurring medical condition¹
- 13% of US women of reproductive age have MDD plus at least 1 additional chronic disease condition or risk factor ²
- Chronic Fatigue Syndrome, Fibromyalgia and Migraine highest comorbidity with MDD in the Senior population³
- Around the World, patient focus on Somatic Health⁴
 - ✓ n=1146 patients screened at primary care centers met MDD criteria
 - ✓ 69% reported only physical symptoms as the reason for their physician visit
 - ✓ 50% reported multiple unexplained somatic symptoms
 - ✓ 11% denied psychological symptoms of depression upon direct questioning

1. Pincus HA, et al. *Arch Gen Psychiatry* 1999;56:441–449

2. Farr SL, et al. *Prev Chronic Dis* 2011;8(6):A119.

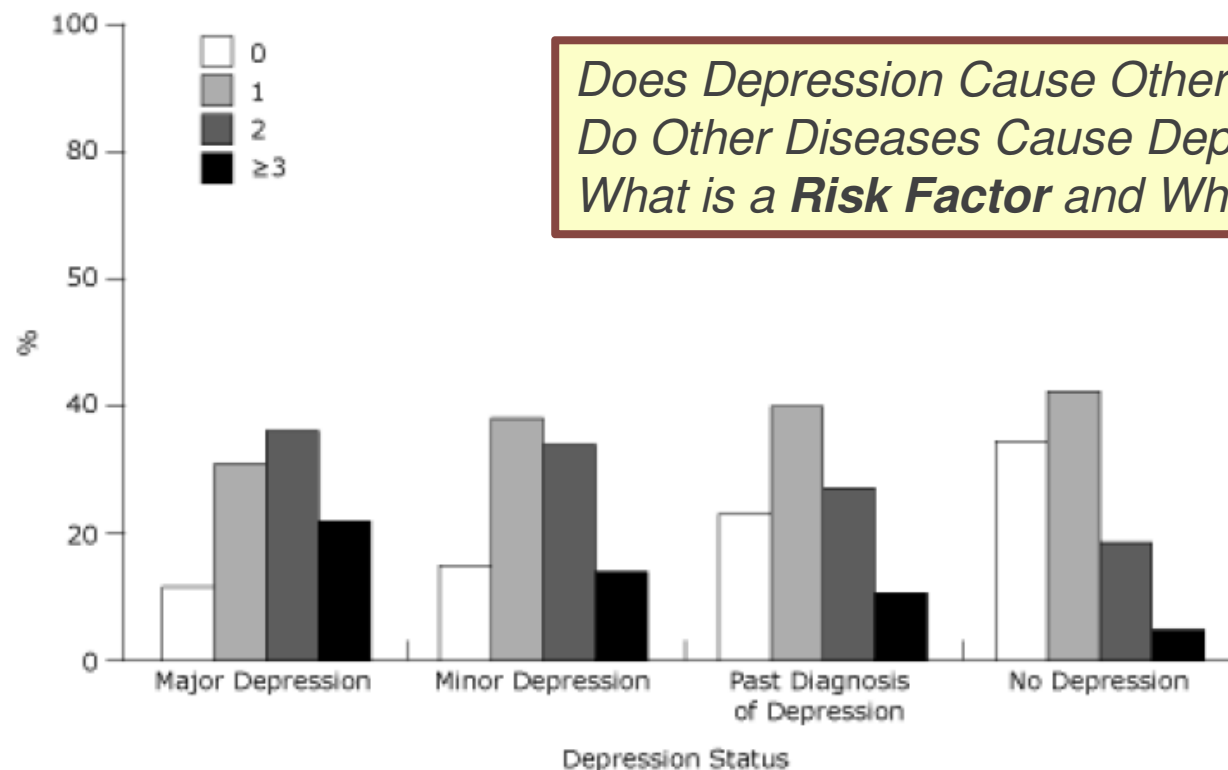
3. Fiest, et al. *J Affect Disord* 2010; 131(1-3): 172-8;

4. Simon GE. et al. *N Engl J Med*. 1999;341:1329-1335.

Diabetes, Obesity, Smoking, Drinking Alcohol, and Sedentary Lifestyle are Associated with Depression in Women



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*Does Depression Cause Other Diseases?
Do Other Diseases Cause Depression?
What is a **Risk Factor** and What is a **Consequence**?*

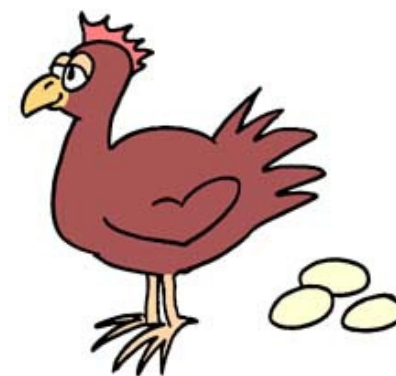


Figure. Prevalence and distribution of number of chronic conditions and risk factors by depression status. Conditions and risk factors included diabetes or prediabetes, current smoking, binge drinking or heavy drinking, overweight or obesity, and physical inactivity. $\chi^2 P < .001$. Source: Behavioral Risk Factor Surveillance System, 2006, 2008, and 2010.

Farr SL, et al. *Prev Chronic Dis* 2011;8(6):A119.

When Depression Strikes Early, the Outcome is Worse



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Earlier age onset of major depression is associated with greater illness burden:

- Never being married
- Social and occupational impairment
- Poorer quality of life
- Greater psychiatric comorbidity
- More negative outlook
- Greater number of depressive episodes
- Increased severity of depressive symptoms
- Increased suicidal ideation and attempted suicide
- *Greater medical comorbidity*

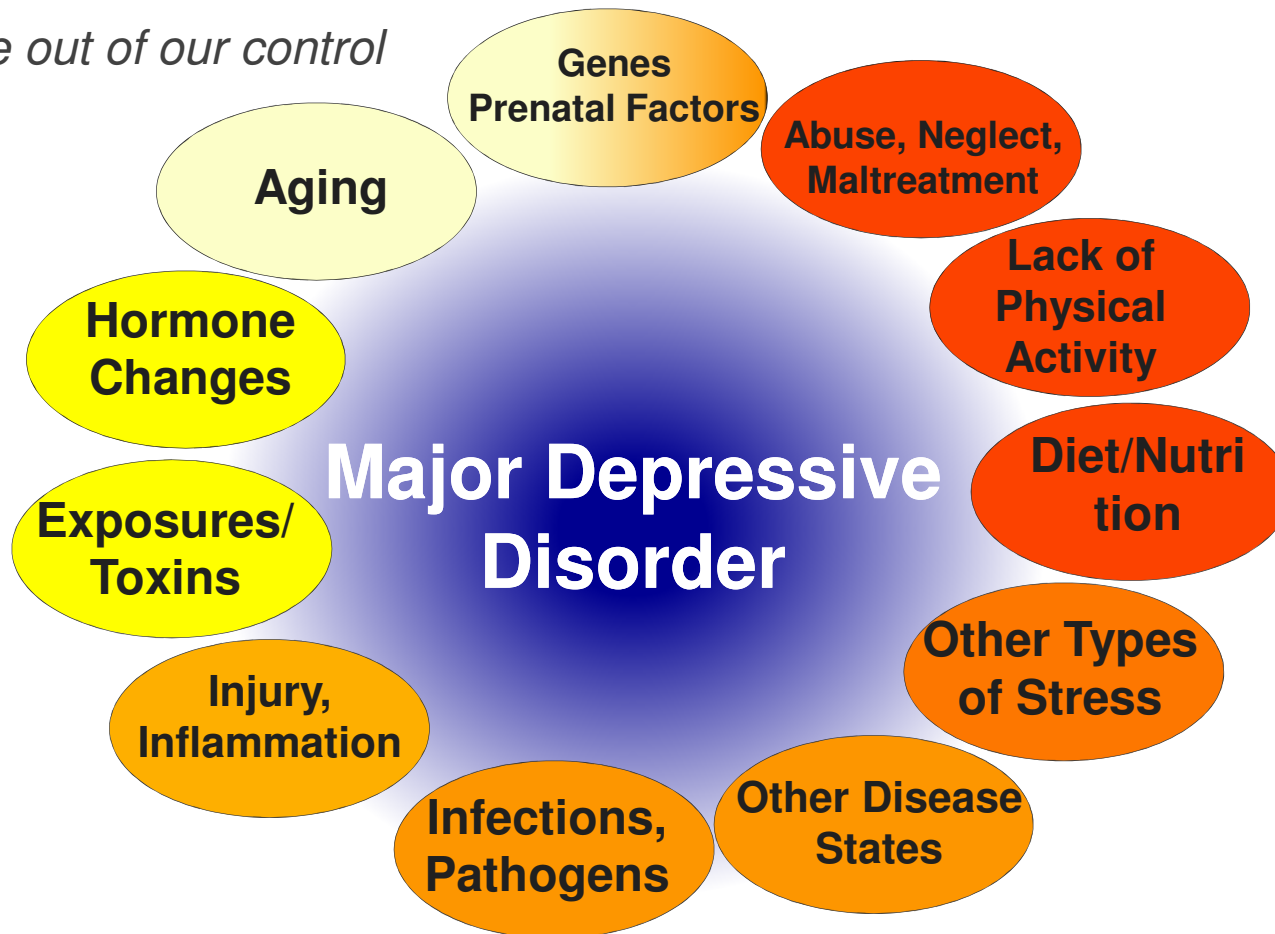


Depression is Probably “Caused” by Multiple Factors



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Some are out of our control



*Others pose
some
opportunity
for
prevention
or change*



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Childhood Stress is a Powerful Risk Factor (Abuse, Neglect, Maltreatment)

Associated with Depression at all ages

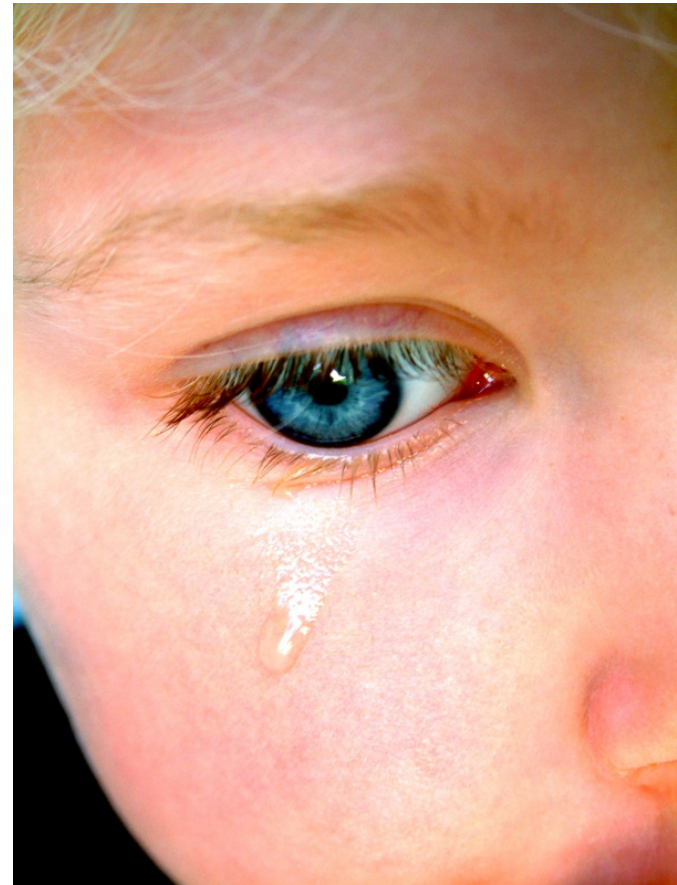
Associated with Suicide

Associated with Many Pain Syndromes

- Fibromyalgia Syndrome (FMS)
- Chronic Pelvic Pain (CPP)
- Chronic Refractory Low Back Pain
- Headache/Migraine
- Stomachache/Irritable Bowel Syndrome (IBS)

Associated with Adult Metabolic Syndrome

Sets a Course for Resistance to
Antidepressant Therapy in Adulthood



Childhood Adversity Sets the Course for Chronic Physical Health Disorders in Adulthood



| Variable | Heart Disease | Asthma | Diabetes Mellitus | Osteoarthritis | Chronic Spinal Pain (Back or Neck) | Frequent or Severe Headache |
|---|-------------------------|-------------------------|-------------------|-------------------------|------------------------------------|-----------------------------|
| Early-onset (ie, at age <21 years) mental disorders | | | | | | |
| Major depressive disorder | 1.82 (1.07-3.09) | 2.11 (1.51-2.93) | 1.14 (0.88-1.47) | 1.52 (1.26-1.85) | 1.59 (1.37-1.85) | 1.68 (1.40-2.03) |

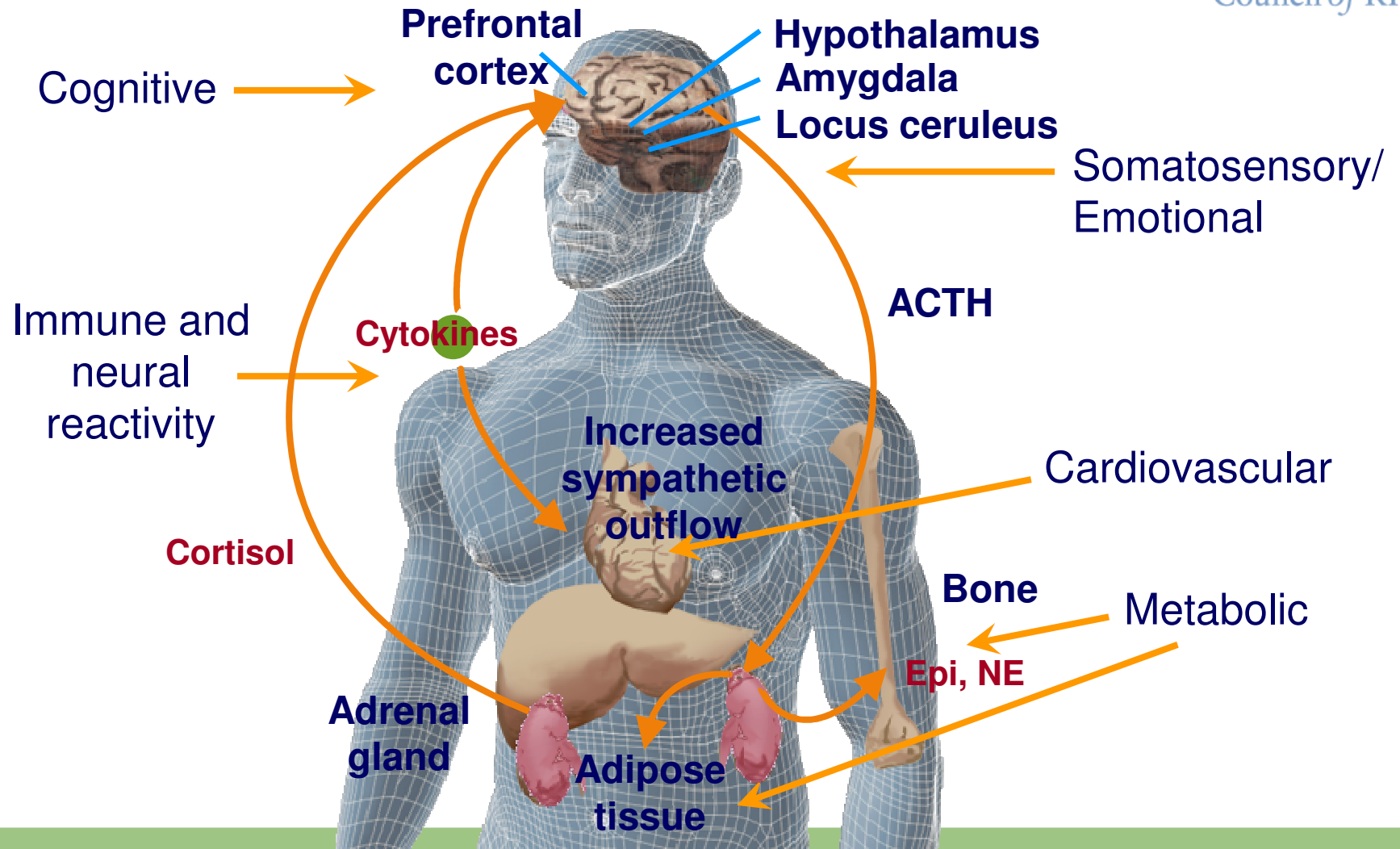
Early Onset MDD Independently Associated with Subsequent Chronic Physical Disorders

| Childhood adversity | Heart Disease | Asthma | Diabetes Mellitus | Osteoarthritis | Chronic Spinal Pain (Back or Neck) | Frequent or Severe Headache |
|-----------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|------------------------------------|-----------------------------|
| Physical abuse | 1.82 (1.37-2.43) | 1.92 (1.32-2.81) | 1.52 (1.16-2.00) | 1.42 (1.22-2.09) | 1.61 (1.43-1.82) | 1.64 (1.44-1.88) |
| Sexual abuse | 3.91 (2.40-6.39) | 1.26 (0.84-1.82) | 0.99 (0.63-1.55) | 1.64 (1.28-2.09) | 1.62 (1.28-2.06) | 1.73 (1.38-2.17) |
| Neglect | 1.37 (0.98-1.91) | 1.02 (0.70-1.49) | 1.02 (0.74-1.42) | 1.29 (1.08-1.55) | 1.33 (1.15-1.34) | 1.21 (1.02-1.43) |
| Parental death | 1.34 (1.05-1.70) | 1.34 (1.01-1.77) | 0.91 (0.71-1.18) | 1.02 (0.89-1.18) | 1.08 (0.95-1.22) | 1.10 (0.93-1.31) |
| Parental divorce | 1.31 (0.95-1.80) | 1.23 (0.84-1.82) | 1.37 (1.01-1.86) | 1.02 (0.86-1.22) | 1.16 (1.01-1.34) | 1.01 (0.84-1.22) |
| Other loss of parent ^c | 1.41 (1.03-1.93) | 1.36 (0.94-1.97) | 1.58 (1.12-2.23) | 1.26 (1.04-1.54) | 1.26 (1.08-1.48) | 1.29 (1.06-1.58) |
| Parental mental disorder | 1.58 (1.18-2.12) | 1.50 (1.05-2.17) | 1.04 (0.74-1.47) | 1.27 (1.07-1.51) | 1.42 (1.24-1.63) | 1.52 (1.25-1.83) |
| Parental substance use disorder | 1.75 (1.18-2.60) | 1.28 (0.83-1.97) | 1.30 (0.92-1.84) | 1.38 (1.14-1.67) | 1.31 (1.12-1.54) | 1.42 (1.18-1.71) |
| Violence in family | 1.31 (0.95-1.82) | 1.51 (1.05-2.17) | 1.16 (0.87-1.55) | 1.39 (1.16-1.67) | 1.52 (1.32-1.74) | 1.51 (1.30-1.76) |
| Criminal behavior in family | 1.47 (0.87-2.47) | 1.37 (0.82-2.31) | 1.81 (1.26-2.59) | 1.36 (1.07-1.71) | 1.32 (1.08-1.62) | 1.44 (1.10-1.88) |
| Family economic adversity | 1.41 (0.96-2.07) | 0.90 (0.61-1.33) | 1.44 (1.04-1.98) | 1.08 (0.93-1.26) | 1.13 (0.95-1.34) | 1.21 (0.98-1.48) |

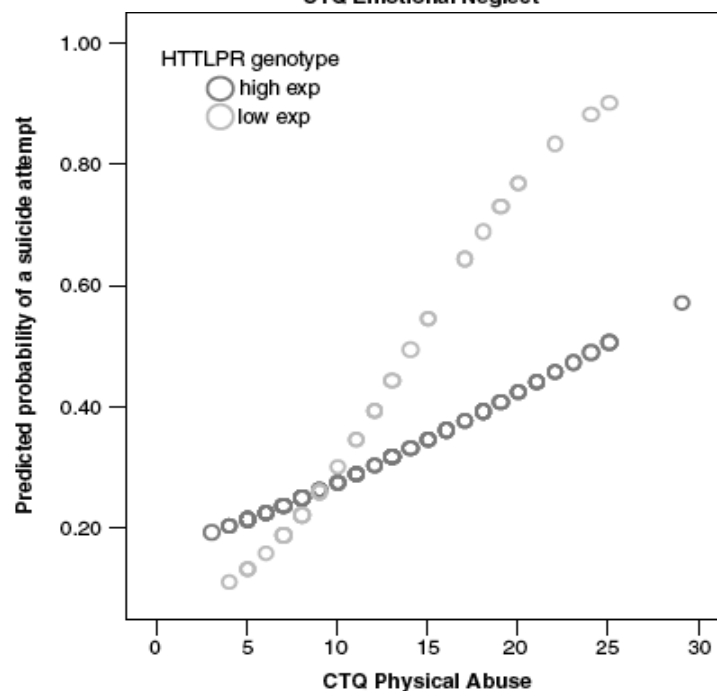
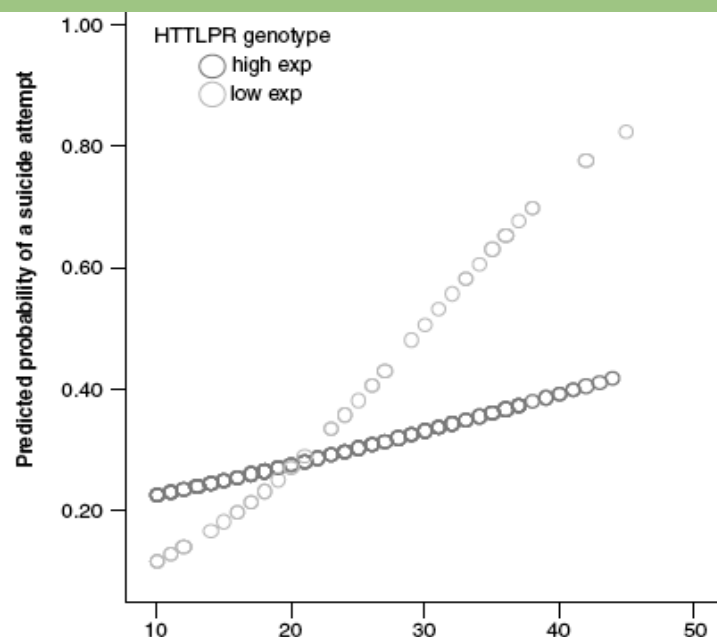
Depression Is a Condition Impacting the Whole Body, Not Just the Brain



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Adverse Childhood Environment and Genes Interact to Predict Suicide

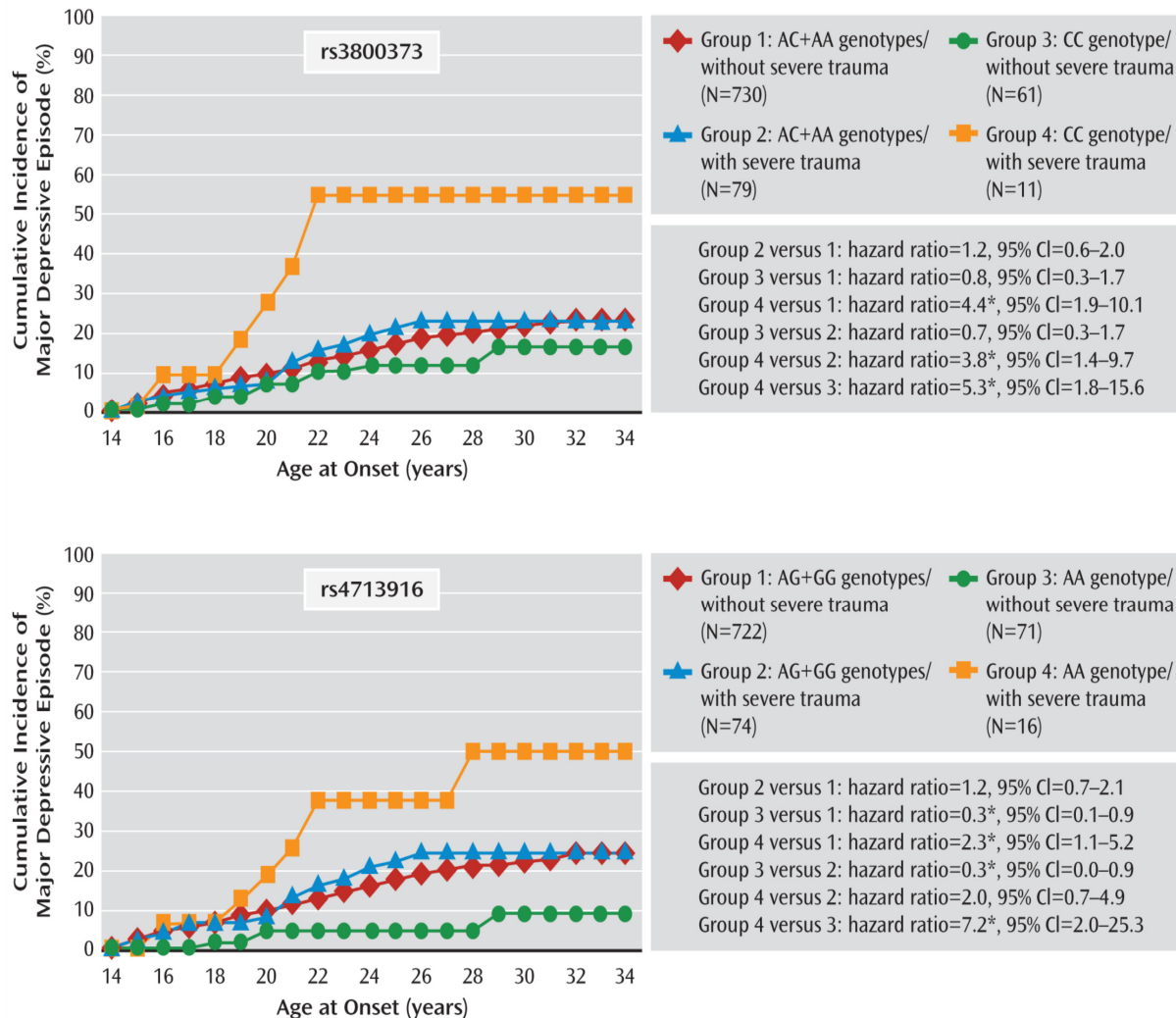


Ever attempted suicide

| | Yes N=81 | No N=176 | Group comparison |
|-----------------------|-------------|-------------|---------------------|
| Age (years) mean (SD) | 46.5 (7.2) | 44.9 (7.5) | $p=0.09$ |
| CTQ mean (SD) | | | |
| Physical abuse | 13.1 (6.5) | 10.2 (4.7) | $p<0.001$ |
| Emotional abuse | 12.1 (5.7) | 10.2 (5.1) | $p=0.001$ |
| Sexual abuse | 10.4 (6.1) | 8.7 (4.4) | $p=0.011$ |
| Physical neglect | 15.2 (6.2) | 13.5 (5.3) | $p=0.025$ |
| Emotional neglect | 26.0 (9.5) | 22.4 (8.8) | $p=0.003$ |
| Dependence | | | |
| Alcohol only | 10.6% | 9.0% | NS |
| Cocaine only | 14.9 | 18.4 | NS |
| Heroin only | 6.4 | 15.6 | NS |
| Multiple | 67.9 | 55.2 | $p=0.05$ |

Interaction of FKBP5 Gene Variants and Adverse Life Events in Predicting Depression Onset

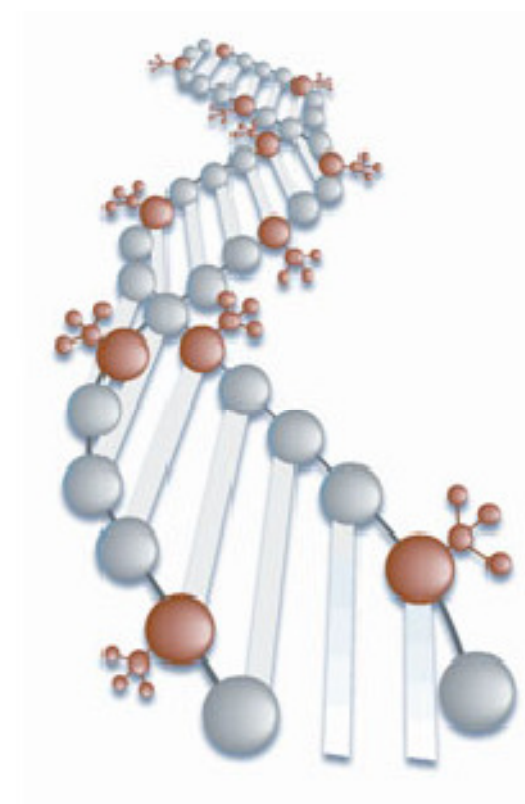
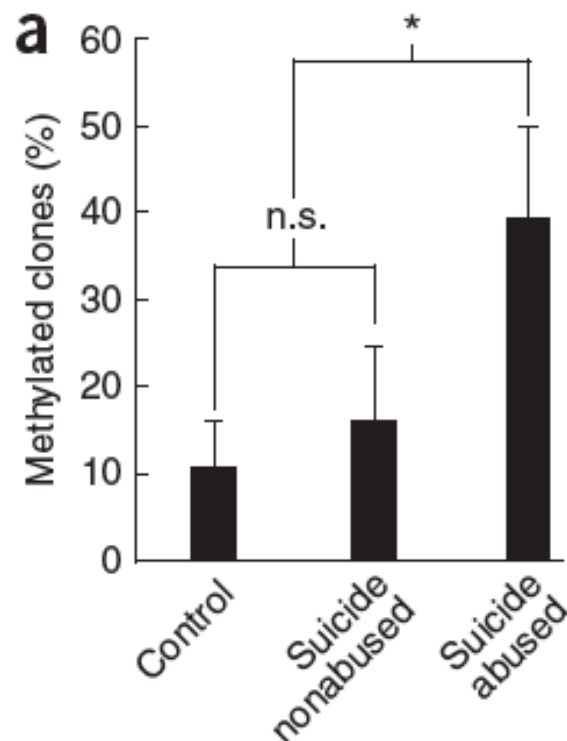
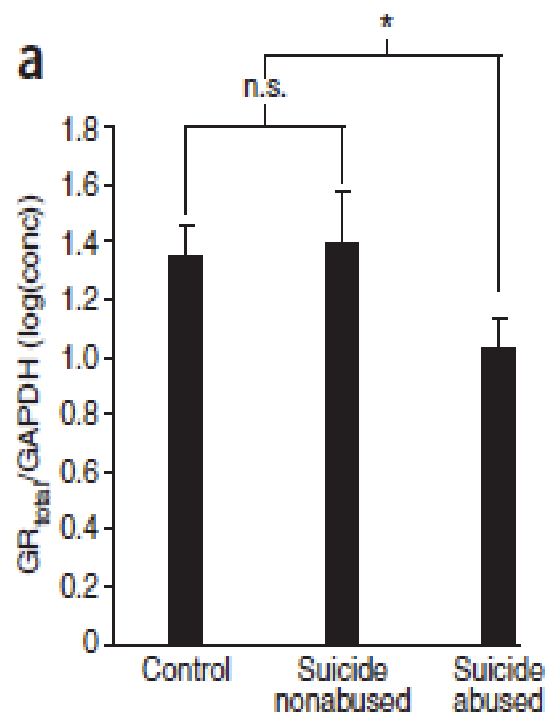
Results From a 10-Year Prospective Community Study



Brains of Suicide Victims with Childhood Abuse Reflect “Epigenetic Changes” – *Biological Mechanism Through Which Adverse Environment Confers Risk*

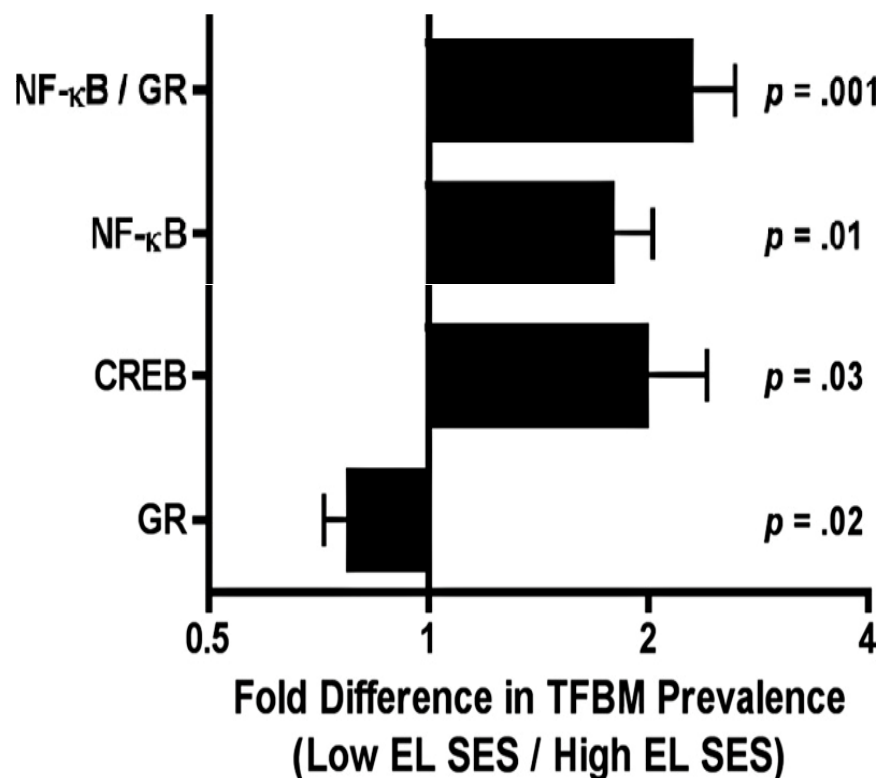


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McGowan et al., NATURE NEUROSCIENCE, VOLUME 12 [NUMBER 3] MARCH 2009

Low Socioeconomic Class During Childhood Leaves a Biological Residue that is Detectable in Genes of Healthy Adults – Genes Turned “On” or “Off”



Quality of Social Environment
Determines Biology Across the
Lifespan

Alter regulation of genes with
response elements for adrenergic
and cortisol stress response

Increase Pro-Inflammatory
Signaling Transcription Control
Pathways

Maternal Warmth Appears to Buffer
Effects of Low SEs

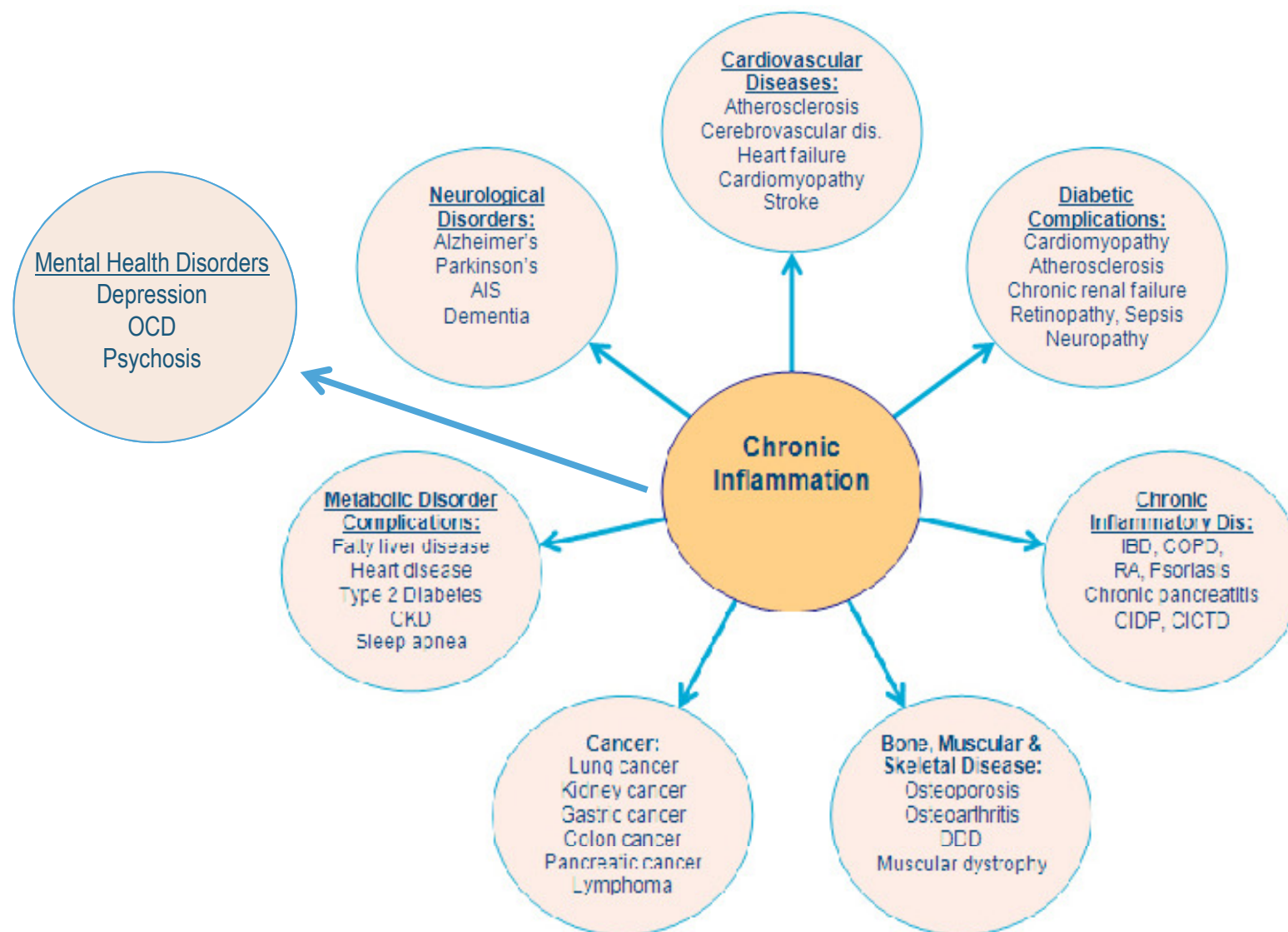
Miller GE et al. (2009) vol. 106 no. 34

Chen E et al. Molecular Psychiatry (2011) 16, 729–737

Depression As a Consequence of Inflammation



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Summary

- Major Depressive Disorder is a heterogeneous disorder, defined by physical and cognitive symptoms by DSM-IV
- MDD is Common and Profoundly Disabling for women around the world
- Tremendous Overlap exists between MDD and other “Medical” Disorders
- Comorbidity between Somatic and Mental Symptoms reflects both RISK factors for and CONSEQUENCES of disease states
- Early onset of MDD and Comorbidity leads to the worst health outcomes



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Summary, continued

- Exposure to stress in early life is a risk factor for depression and for many other medical disorders
- Adverse social environment may impact disease through epigenetic effects on genes that regulate physiological systems involved in stress and inflammation
- Identification and treatment of depression *early in life* may alter long-term health outcomes
- Interventions to reduce exposure to severe stress - and to promote protective factors - could be highly impactful in preventing depression and associated morbidity,.