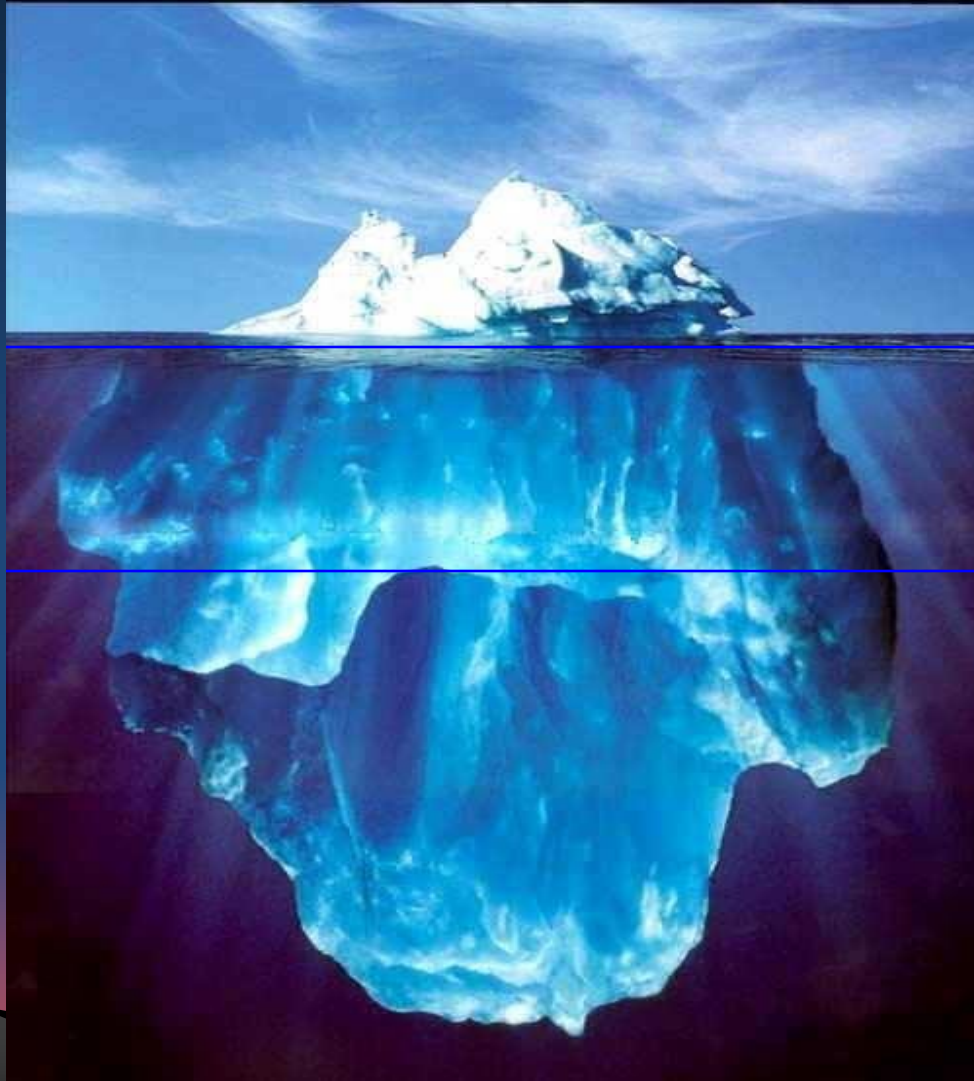


Genetic “Iceberg”



Recognized ADHD

Spectrum of ADHD

Unimpaired
(low loading,
high functioning family
members, “ADHD-like”)

Heredity – Family Studies

Evidence of Family Aggregation of the Disorder:

- 25-35% of siblings (hazard ratio [HR] = 8; 8x more likely than control siblings are to have ADHD. Same HR for dizygotic twins. Half-siblings = 2.3-2.8)
- 78-92% of identical twins (HR = 70)
- 15-20% of mothers
- 25-30% of fathers
- If parent is ADHD, 40-54% of offspring (odds = 8+)
- Parent of origin effects: (Goos et al., *Psychiatry Research*, 149, Jan. 2007)
 - If genes come from the mother, worse ADHD, ODD, & CD; girls have a higher risk of ADHD than if father has the disorder
 - If genes come from the father, worse depression, especially in girls

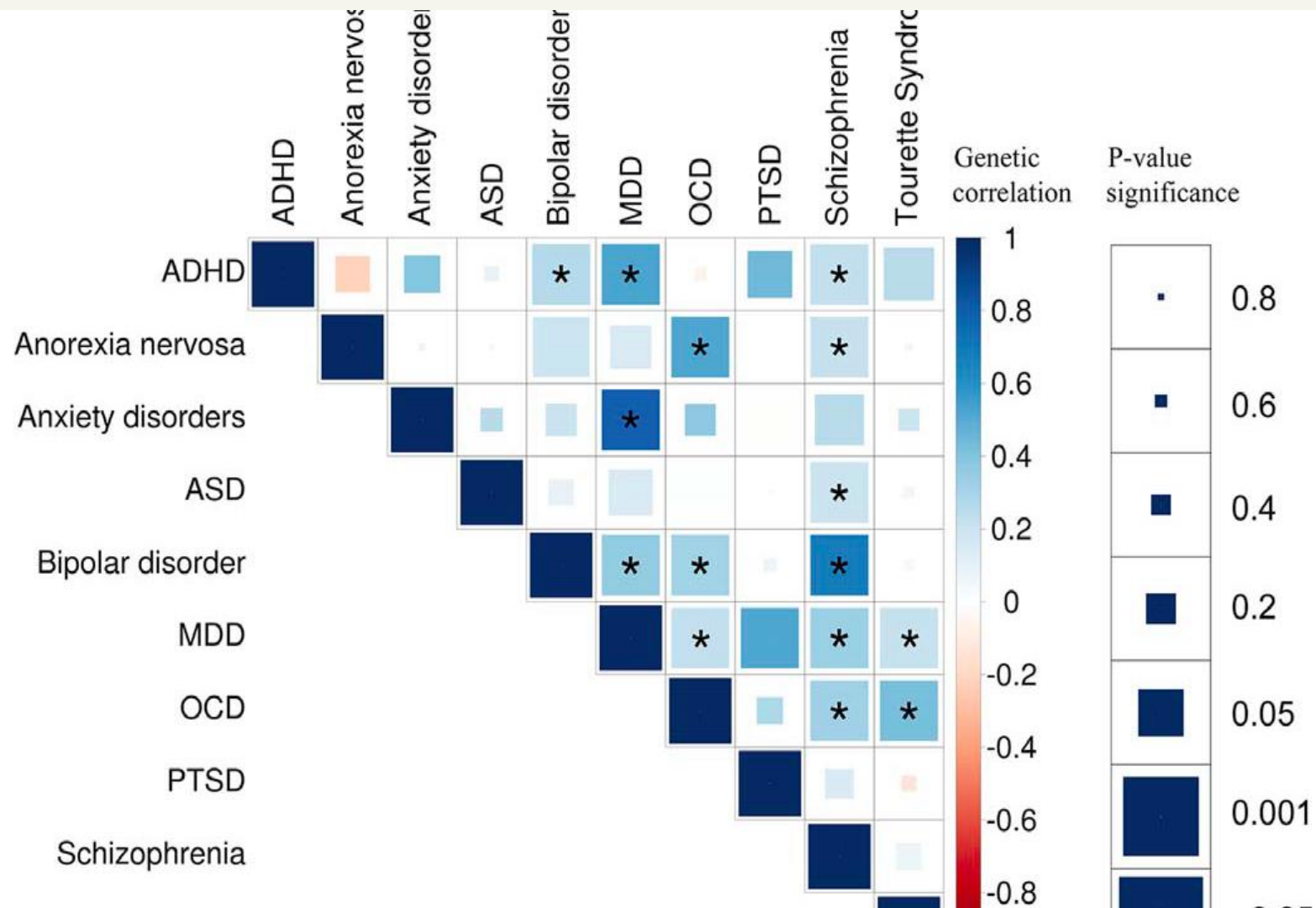
Heredity – Twin Studies^{1,2}

- Heritability (Genetic contribution)
 - 57-97% of individual differences (Mean 80%+)
 - (91-95%+ using DSM criteria)
- Shared Environment (common to all siblings)
 - 0-6% (Not significant in any study to date)
- Unique Environment (events that happen only to one person in a family)
 - 15-20% of individual differences
 - (but includes unreliability of measure used to assess ADHD)

1. Mick, E. & Faraone, S. V. (2008). *Child and Adolescent Psychiatric Clinics of North America*, 17 , 261-284.

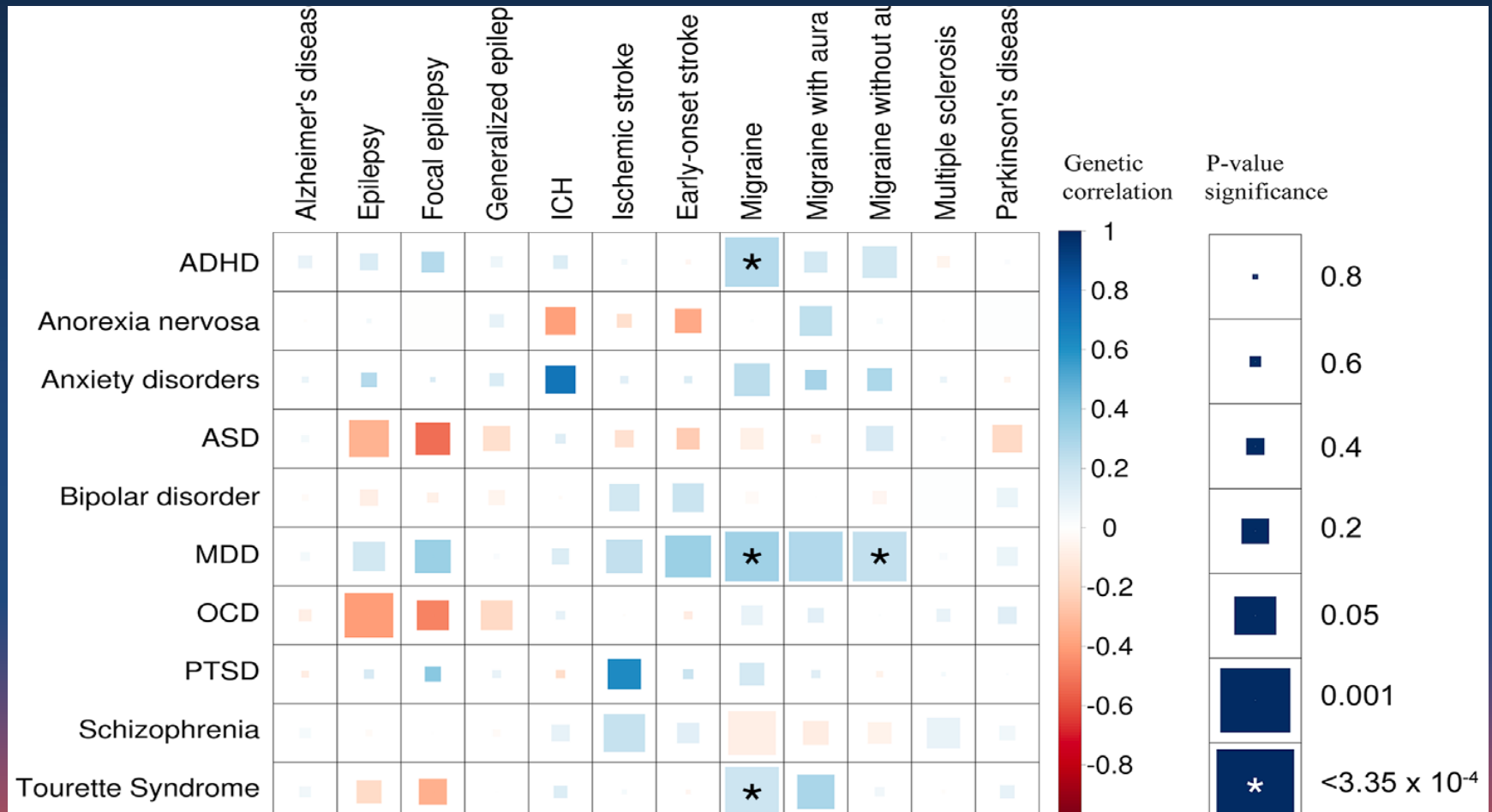
2. Tuvblad, C. (2009). *Journal of Abnormal Child Psychology*, 37, 153-167.

Genetic Correlations Across Psychiatric Disorders



The Brainstorm Consortium (2018). *Science*, 360, eaap8757. Ahead of print.

Genetic Correlations Between Psychiatric and Neurologic Disorders



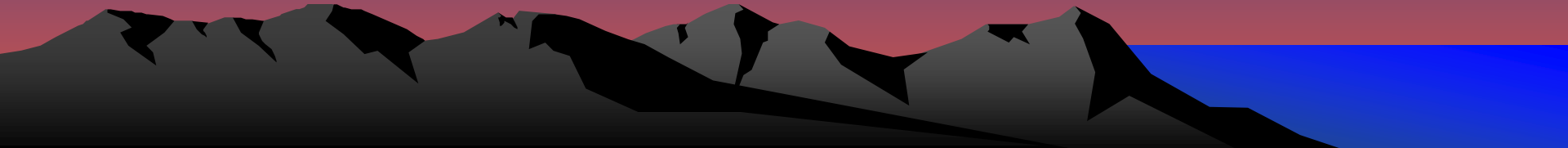
The Brainstorm Consortium (2018). *Science*, 360, eaap8757. Ahead of print.

Molecular Genetics

- **Genome wide scans** - suggest that 20-42 chromosome sites that may contain minor genes that are possible candidates² The most recent (Demontis et al., 2018) identified 12 reliable loci.
- Although candidate gene studies find a number of different genes as possibly associated with ADHD, such as those below, genome wide association studies have not supported these gene sites.
 - **DRD4 – 7+ repeat and 4 repeat absent (?)**: Related to novelty seeking, exploratory behavior, possibly human migration patterns; Longer genes blunt dopamine sensitivity. Those lacking 4 repeat do better on methylphenidate.⁶
 - **DAT1 – 480 bp (9/10 heterozygous differs from 9/9, 10/10)**: Function not well known; likely serving as a tag for other nearby functional gene regions; May build the dopamine transporter (reuptake pumps); Those with single copy 10 variants or with homozygous pairings (10/10) may respond less well to methylphenidate;⁶ 10 repeat interacts with maternal alcohol use to increase risk for ADHD; 9/10 pairing has marked effect on severity of ADHD across childhood to adulthood.
 - **DBH -- TaqI (A2 allele)**: May create chemical (DBH) that converts dopamine to norepinephrine
 - **MAO-A**: produces an mitochondrial enzyme that regulates presynaptic dopamine signals and other neurotransmitter systems
 - **LPHN3 (latrophilin) gene**: linked to G-protein-coupled receptors in amygdala, caudate, cerebellum, and cortex. Controls GABA release presynaptically; GABA is an inhibitory transmitter^{4,5}
 - **CHRNA7**: duplication in this gene at chromosome location 15q13.3 is involved the alpha-7 nicotinic acetylcholine receptor modulation that mediates calcium ion channel signaling that further affects dopamine release.⁷
 - **5-HTR gene variants**: Serotonin receptor gene – certain polymorphisms increase risk
- Instead, sites dealing with cell migration and support during brain development, synaptic connections, and networks relate to language and intelligence (FOX2P) are reliably linked to the disorder.

More on Molecular Genetics

- Genes involved in inattention (IN) overlap with those involved in hyperactive-impulsive (HI) symptoms yet some non-overlap (unique genetic effects) exists as well
- Genetic contribution increases with age; new genes contribute to later symptoms besides earlier genes
- Genes in ADHD are also risk genes for Depression, ODD, CD, and Reading and Language Disorders. Possibly Autism Spectrum Disorder as well



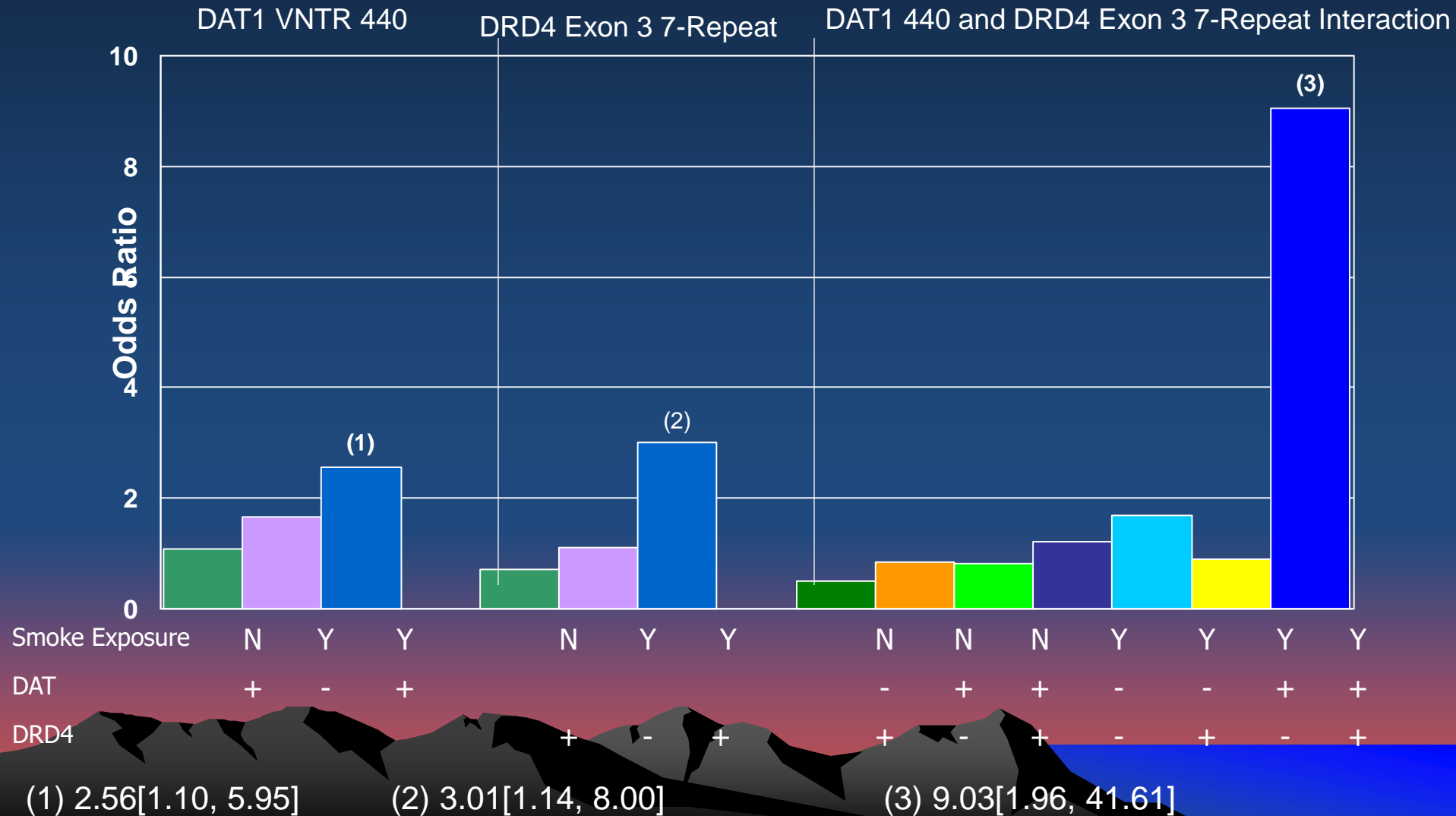
New Findings on Genetics

- Genes involved in ADHD affect not just dopamine and norepinephrine networks but pertain to brain neural cell growth and connections as well as connections of peripheral nerve cells to muscle junctions and feedback from muscles
 - May cause some overlap with Restless Leg Syndrome and possibly with Amyotrophic Lateral Sclerosis (ALS)
- New genetic mutations can arise in a child that contribute to ADHD risk that are not evident in parents (accumulated mutation model)
 - Likely accounts for some of the disparity in identical twins as well as newly genetic cases arising in previously unaffected families
- Some genes may predict drug response. And whether or not the gene has a methylated tag attached to it may further affect drug responding (e.g., DAT1 gene)

Genetic Risk May Interact with Risk From Environmental Toxins

Adjusted Odds Ratios for the Association Between Population Defined ADHD Combined Subtype and *In Utero* Maternal Smoking Exposure and Dopamine Pathway Genotypes (Todd, 2007)

Reference Group: No Smoking Exposure and genotype without risk allele

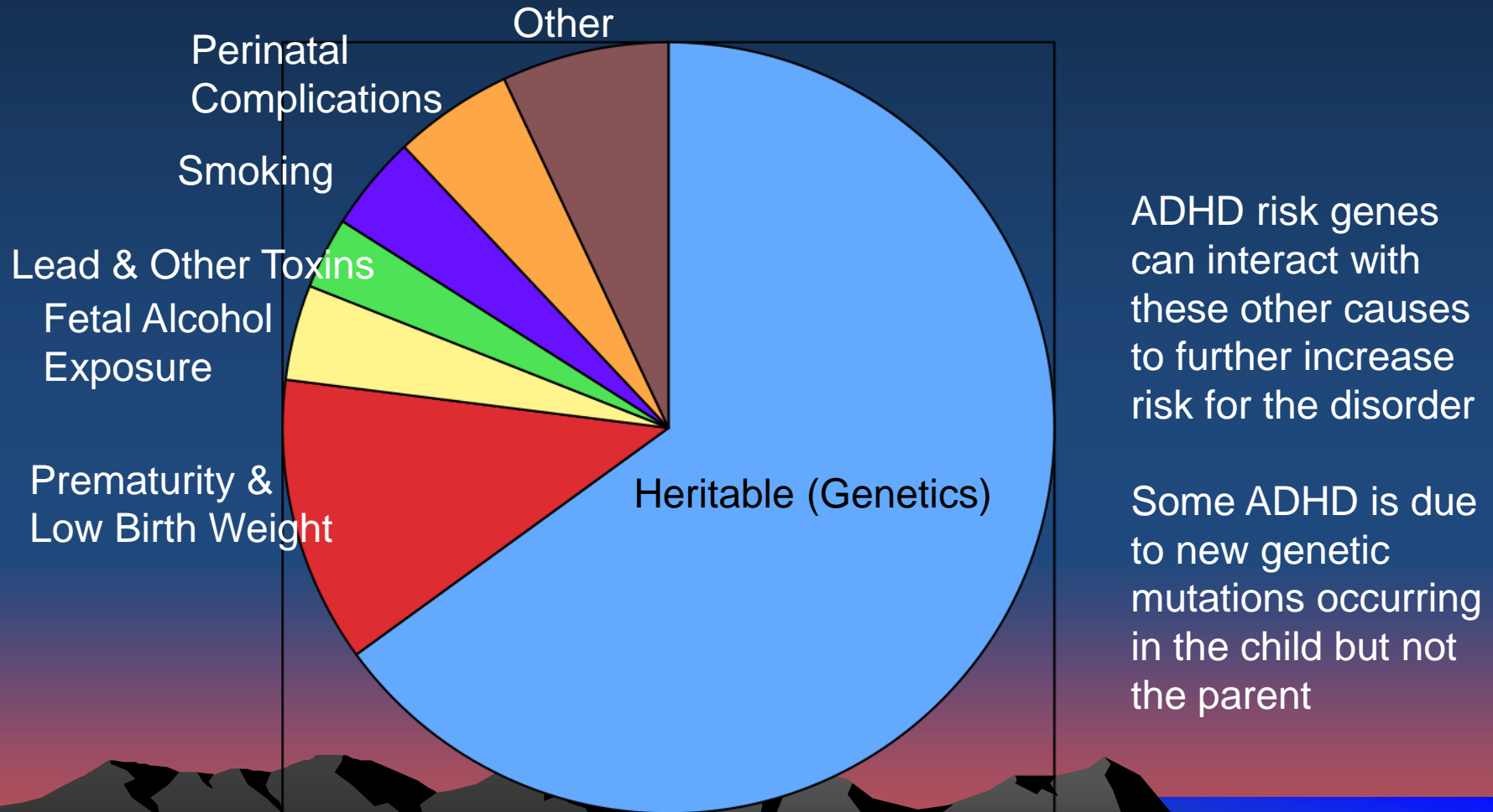


Expected Advances from Genetics

- Genetic testing to aid diagnosis
- Genetic subtyping of ADHD cases
- Better understanding and prediction of comorbidity
 - Genes already linked to risk for later smoking
- Evaluating gene x gene & gene x environment interactions:
 - In causing risk for the disorder
 - In predicting future risks for impairments and comorbidities
 - In predicting drug responses and side effects
 - DAT1 may predict response to MPH and ATX
 - In predicting response to psychosocial treatments
 - DRD4-7 allele related to response to parent behavior management training
- Developing new drugs targeted to genotypes
- Developing new psychosocial treatments for targeting specific phenotypes

Etiologies of ADHD

Adapted from Joel Nigg (2006), *What Causes ADHD?* New York: Guilford Press.

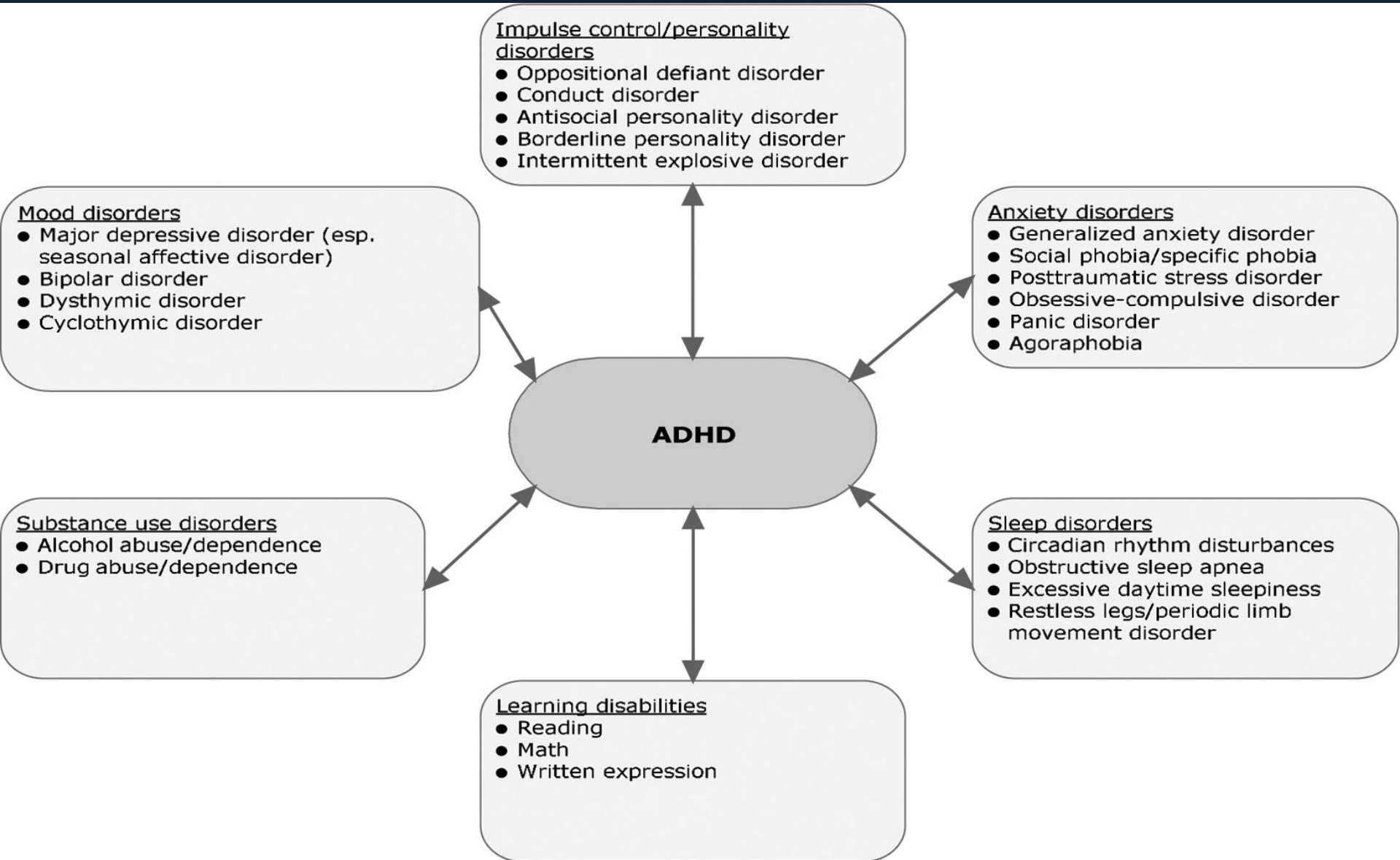


Conclusions on Etiology

- ADHD is a neurobiological disorder representing a single spectrum of symptoms in the human population
- Excessive symptoms result in impairment in major life activities resulting in a disorder of adaptive functioning
- Variation in the symptoms among people is largely the result of variation in genes that develop and operate the human brain
- But some variation in ADHD symptoms is the result of unique events, such as environmental biohazards, which may also cause ADHD

More Conclusions

- Some cases are due to gene x environment interactions (epi-genetic effects)
- Others are due to new (de novo) mutations arising in parental gametes that create ADHD risk in offspring
- No variation of the symptoms arises from within family factors
- The role of the psychosocial environment is not in causing ADHD but in determining:
 - risk for comorbidity,
 - degree of impairments in major life domains,
 - and access to professional resources for treatment



From Kooij, J. (2012) *Journal of Attention Disorders*, online first, April 12, 2012

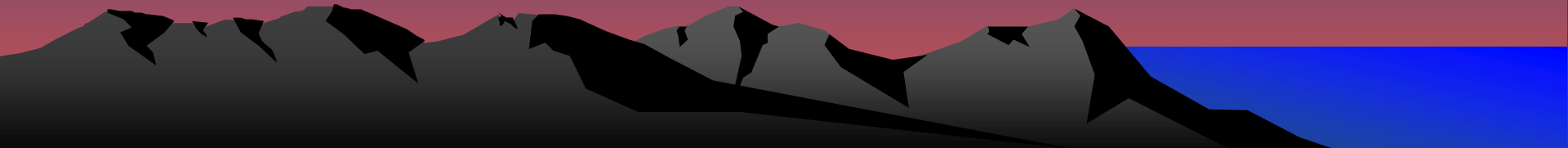
Comorbidity in ADHD

Comorbid Disorders

- Oppositional Defiant Disorder (40-84%; Mean = 65%)
- Conduct Disorder (15-56%; Mean = 45%)
 - Predicts personality disorders by age 27 - 10-21%; antisocial & borderline mostly
- Anxiety Disorders (20-35%; odds = 3.0): increases with age
- Major Depression (25-35%; odds = 5.5)
 - Suicidal ideation & attempts increase during high school; decrease by age 27
- Risk for substance use disorders (20-30%) by adolescence
- Autistic Spectrum Disorders (22%)
 - 28-52% of ASD cases have ADHD
- Bipolar Disorder (0-27%; likely 6-10% max.)
 - A one-way comorbidity? (80-97% BPDs have ADHD but only 2-3% of ADHD cases have BPD)
- Females have risk for bulimia – binge eating pathology (16%) and somewhat elevated risk for anorexia
- Personality Disorders by adulthood (related to CD):
 - Antisocial (11-21%)
 - Passive Aggressive (18%)
 - Histrionic (12%)
 - Borderline (14%)

Advances in Understanding the Life Course Outcomes of ADHD

What Are The Treatment
Implications?



Impairments Associated with Child ADHD



Educational Outcomes

- More grade retention (20-45%; MKE: 42 vs. 13)
 - Pagani et al. (2001) & Hauser (2007) show retention is harmful
- More placed in special educational (25-50%)
- More are suspended (40-60%; MKE: 60 vs. 19)
 - Reflects disciplinary action; more associated with CD
- Greater expulsion rate (10-18%; MKE: 14 vs. 6)
- Higher drop out rate (23-40%; MKE 32 vs 0)
- Lower academic achievement test scores
- Lower Class Ranking (MKE: 66% vs. 53%)
- Lower GPA (MKE: 1.8 vs. 2.4)
- Fewer enter college (MKE: 22 vs. 77%)
- Lower college graduation rate (5-10 vs. 35%)

Managing Educational Risks

- Educating teachers and school administrators on ADHD and associated academic risks
- Teacher training in behavior management strategies
- Implement ADHD school liaison
- Early screening and identification of ADHD cases at school entry
- Pre-referral assistance to regular classroom teachers on behavior management tactics
- Pre-referral curriculum adjustments
- If necessary, eventual referral for formal special educational services
- Earlier implementation of extended release medications as necessary
- Vocational assessment and job skills training during high school

Employment Problems

- Enter workforce at unskilled/semi-skilled level
- Greater likelihood of unemployment*
 - at age 21 (22 vs. 7%)
 - at age 27 (26% H+ADHD, 8% H-ADHD, 9% for controls)
- Use more sick days and report more days of under-productivity (22 days “out of role” more than others per year)**
- More likely to be dismissed or fired
 - 55 of ADHD cases vs. 23% of controls had been fired by age 21
 - Percent of jobs fired 43% (H+ADHD) vs. 30% (H-ADHD) vs .14% Controls (age 27)
- Change jobs more often
 - 2.6 (ADHD) vs. 1.4 times (Controls) over 4-8 years since high school (age 21)
 - 4.9 (H+ADHD) vs. 3.5 (H-ADHD) vs. 2.5 (Controls) (age 27)
- More ADHD/ODD symptoms on the job
 - As rated by current supervisors

*Sobanski et al. (2008). *European Psychiatry*, 23(2), 142-149.

** de Graaf et al. (2008). *Occupational and Environmental Medicine*, June issue.

Employment Outcomes

- Lower work performance ratings*
 - As reported by current supervisors
- By 30s, 35% may be self-employed**
- Lower job status rating and overall socio-economic status*
- Reduction in employment status (10-14 percentage pts)***
- 33% less earnings***
- Increased social assistance (15-17 percentage points)***
- Some outcomes partially related to reduced education and comorbid health problems but most is directly related to severity of ADHD***
- Onset before age 12 considerably worse in labor market outcomes than after age 12***
- Children from disadvantage backgrounds were worse off***

- *Barkley, R. et al. (2008). *ADHD in Adults: What the Science Says*. New York: Guilford.
- **NY Study by Mannuzza et al., *American Journal of Psychiatry*, 1993
- **Fletcher, J. (2013). *Health Economics*, January, online first, DOI: 10.1002/hec.2907 (N = 14,436)

Addressing Employment Risks

- Educate employers on nature of ADHD, workplace impact & risks, & workplace management
- Vocational assessment in high school for placement in technical training classes
- Counseling teen/adult for ADHD-friendly jobs
- Post-high school technical training if no plans for college enrollment
 - If college bound, consider community college as first step
- Military enlistment if not going on to college
- Make reasonable workplace adjustments
 - Similar to school behavior management tactics
- Medication management across longer periods
 - Extended release formulations; supplement with IR

Motor Vehicle Driving Risks

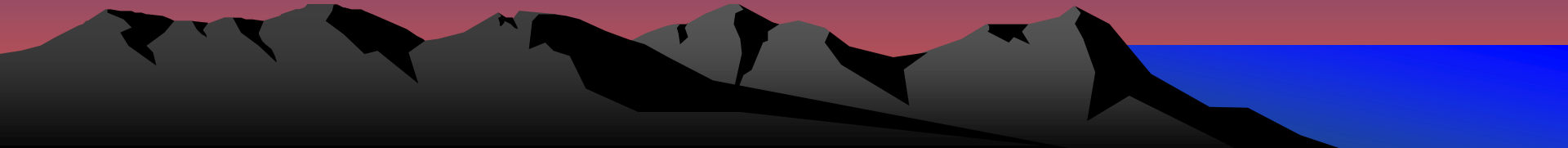
- Poorer steering, slower braking reaction time
- Rated by self, others, and driving instructors as using fewer safe driving habits
- More likely to drive before legally licensed
- More risk-taking, illegal actions, and distraction while driving
- More excessive sleepiness while driving (12% vs. 3%)
- More accidents (and more at faults) (2-3x risk)
 - % with 2+ crashes: 40 vs. 6; % with 3+ crashes: 26 vs 9
- More citations (Speeding - mean 4-5 vs. 1-2)
- Worse accidents (\$4200-5000 vs \$1600-2200)
 - (% having a crash with injuries: 60 vs 17%)
- More Suspensions/Revocations (Mean 2.2 vs 0.7)
 - (% suspended: 22-24 vs. 4-5%)
- Greater adverse impact of alcohol on driving
- More likely to participate in motorsports and to suffer injuries

Implications for Driving Risks

- Educate parents, teens, primary care physicians and motor vehicle agencies on driving risks
- Longer learner's permit period
- Graduated licensing approach
 - Daytime with adults, night-time with adults, alone, with peers, full independence (3-6 months at each stage, gradual independence)
- No (!) cell phone use or text messaging while driving – How to stop it? Block the cell phone signal when the car is running.
 - Cellcontrol.com (\$25 plus \$7.95 monthly fee) – blue tooth transmitter plugs into car diagnostic (OBDII) port and blocks calls when car is moving.
 - Key2SafeDriving.com – A bluetooth transmitter and car key case that shuts down driver's cell phone (\$99 – available for android phones)

More on Driving Treatment

- Greater supervision of vehicle use by parents
 - Chart intended vehicle use
 - Random spot checking on destinations
 - Critical incident cameras in vehicle (DriveCam Inc., San Diego, CA), or GPS car monitoring devices (MobileTeen GPS, AIG Insurance Co.).
- Behavior contracting for safe driving
 - (Barkley *Safe Driving Program*, Jones & Bartlett Publishing; Maureen Synder's book on ADHD and driving, addwarehouse.com)
- Use medication management
 - Extended release formulations with supplemental immediate release as needed – Substantial evidence shows a 40-50% decline in vehicular accidents in adults with ADHD when on their medication and improved driving behavior
- Avoid alcohol use while driving



Social Outcomes

- Fewer close friends
- Shorter duration of relations
- Rated by parents as more socially impaired
- Lower levels of marital satisfaction by both proband and partner
- Greater risk for extramarital affairs
- Increased intimate partner violence*
 - especially if CD is present
- Earlier child bearing
- Greater parenting stress in parental role
- Fang et al. (2010). *Archives of General Psychiatry*, 67, 1179-1186.

Lifestyles

- Spend more time talking on phone, watching TV and playing videogames, and socializing as teens
- ADHD children and young adults may be more prone to videogame dependency and Internet addiction*
- Spend less time reading, getting adult education, and exercising
- More likely to be homeless by age 41**
 - 24% vs. 4%
- Substantial problems with managing money and credit. This is related to degree of delay discounting, which is greater in those with ADHD***

*Bioulac et al. (2008). *European Psychiatry*, 23(2), 134-141.

**Murillo, L. G. et al., 2016, *J. of the American Academy of Child and Adolescent Psychiatry*, online first.)

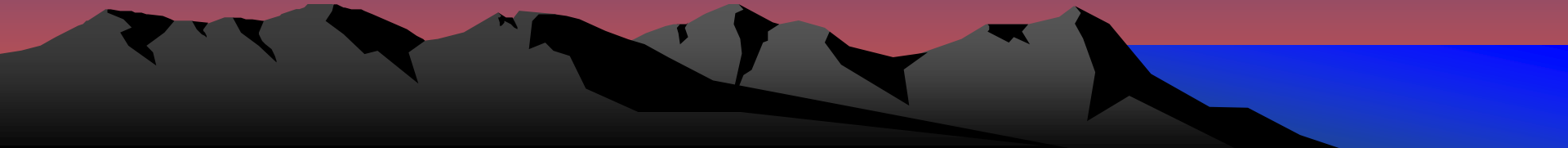
***Beauchaine et al. (2017). *PLoS One*, May 8;12(5):e0176933. doi: 10.1371/journal.pone.0176933. eCollection 2017.

ADHD, Sexual Behavior & Reproductive Risks

- No higher incidence of sexual disorders
- Begin sexual activity earlier (15 vs 16 yrs.)
 - especially If Conduct Disorder is comorbidity
- More lifetime sexual partners (13.6 vs. 5.4); 60% had 4+ partners vs. 28%
 - More partners in prior year (2.4 vs. 1.6)
 - Less time with each partner
- More casual sex (outside of committed relationships)(37 vs. 19%)
- Less likely to employ contraception
- Greater teen pregnancies (24-38 vs. 4-5%)
 - Odds:ages 12-15, females = 3.6, males 2.3; ages 16-19 – females 1.9, males 2.3*
- Ratio for number of births by age 21(37:1)
 - 54% Do Not Have Custody of Offspring
- By age 27, 51% have children vs. 13% for controls
- Higher risk for sexually transmitted disease (STDs) (17 vs. 4%)
- Overall riskier sexual behavior (RSB) in both sexes
 - Further exacerbated by presence of Conduct Disorder and/or substance use
 - RSB is linked to greater chance of sexual victimization in young adulthood in girls growing up with ADHD (even greater in Blacks than Whites)

Implications for Managing Risky Sexual Conduct

- Educate parents, primary medical care providers, and appropriate social service agencies on ADHD and risks for teen pregnancy & STDs
- Greater parental supervision of teen social and dating activities
- Delay couples dating in favor of group dating with multiple peers
- Educate teens on sex and risks
- Discuss use of contraception with teens & parents
- Medication management to reduce impulsive conduct and increase self-control
- Consider HPV immunization - To reduce future risks for cervical cancer in women with ADHD



Health Concerns

- Less healthy “Western style” diet
- More likely to be overweight and eat impulsively
 - Twice as likely to be obese by adulthood; risk increases with age
 - ADHD is over-represented in patients treated for obesity at eating disorders clinics (32% vs. 4% population prevalence)**
- Higher risk in females for eating disorders (10-20% of ADHD females vs. 0-5% of controls)* & increased eating pathology***
 - EDs are 3.5 x more likely in females with ADHD by adolescence
 - Bulimia is most likely subtype, being 5.6x more likely by age 16
 - ED linked to earlier impulsivity, peer rejection & harsh parenting,** and concurrent MDD, anxiety disorders, & ODD/CD*

*Biederman et al. (2007). *Journal of Developmental and Behavioral Pediatrics*, 28, 302-307.

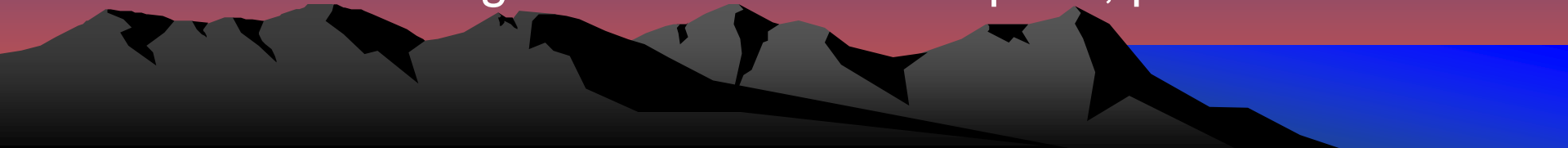
*Sobanski et al. (2008). *European Psychiatry*, 23, 142-149.

** *Journal of Obesity*, 2009, March issue.

***Mikami et al., (2008). *Journal of Abnormal Psychology*, 117, 225-235.

More Medical-Health Concerns

- Greater likelihood of smoking and alcohol use and greater frequency of using these substances*
- Growing risk of cardiovascular disease (CHD)*
 - Greater body mass index (higher percent obese), especially in females
 - Lower HDL cholesterol and higher Total/HDL ratio
 - Higher atherosclerotic risk to coronary arteries
 - Higher Framingham CHD risk percent over next 5 and 10 years
- Greater risk for developing dementia (5.5%) which is 3.4 times higher when controlling for other factors**
- Possibly greater risk for cancer ?
 - More smoking and alcohol consumption; poorer diet*



Implications for Health Risks

- Educate primary care providers and government health agencies on ADHD and related health and lifestyle risks
- Encourage greater use of preventive medical & dental care
- Focus more on accident prevention
- Provide assistance with managing legal substances
 - Smoking cessation programs
 - Alcohol abuse treatments
 - Substance abuse rehabilitation programs
- Discuss with parents and ADHD teens/adults the growing cardiovascular and cancer risks with age
- Encourage better health maintenance practices (better diet, routine physical exercise)

Life Course Impairments Linked to ADHD

Impaired Parenting Behavior

Marital/Cohabiting Problems & Violence*

Poorer Health – Obesity, CHD Risk

Occupational & Financial Difficulties

Delayed Transition to Independence

Driving Risks (speeding, crashes, DUI)

Accidental Injuries, Suicide

Risky Sexual Behavior – Early pregnancy

More Smoking, Marijuana & Alcohol Use and SUDs

Antisocial Behavior/Legal Problems

Peer Relationship Problems

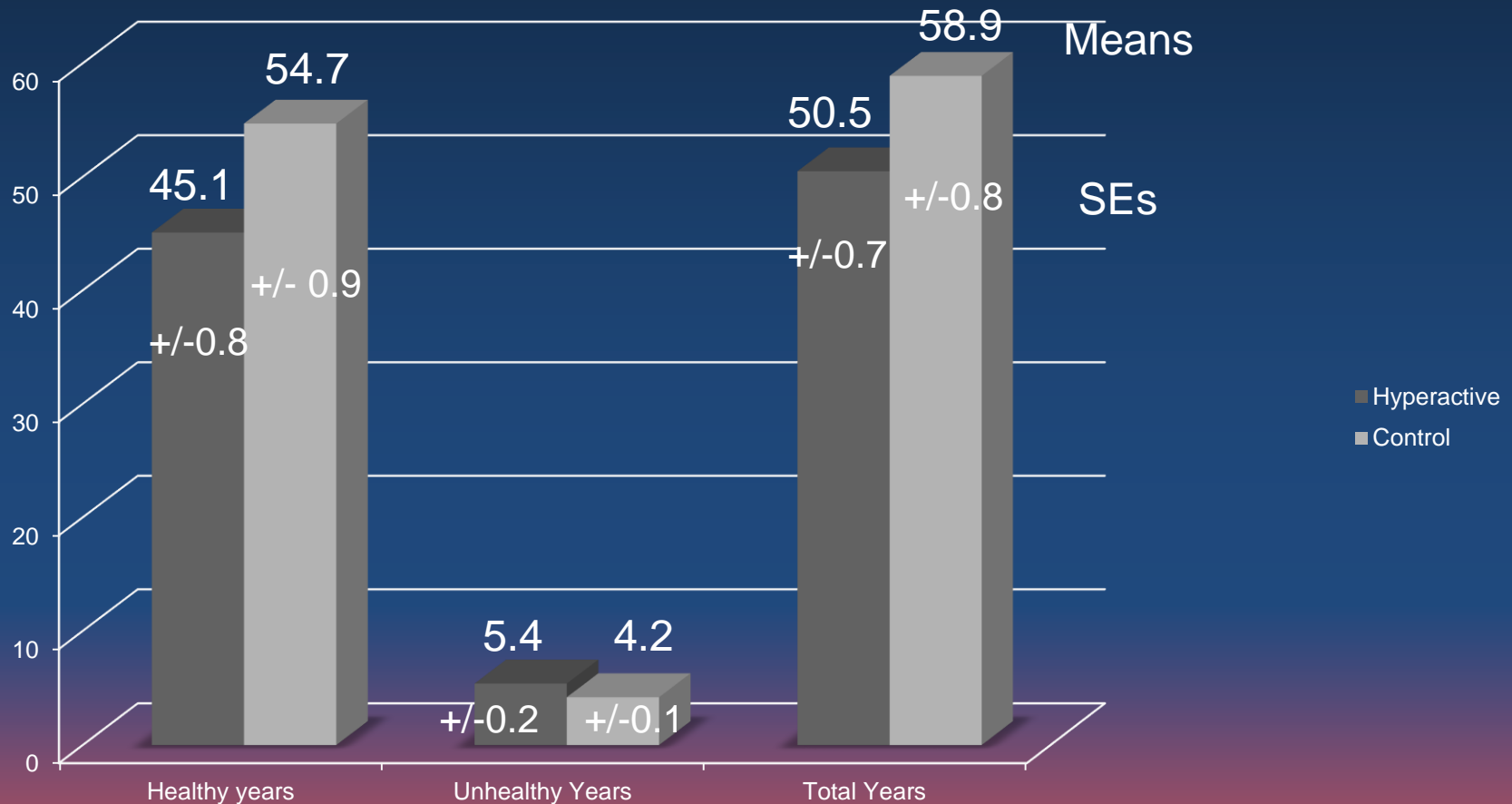
Greater Family Conflict/Stress

Limited Educational Success

Effect on Life-Expectancy?

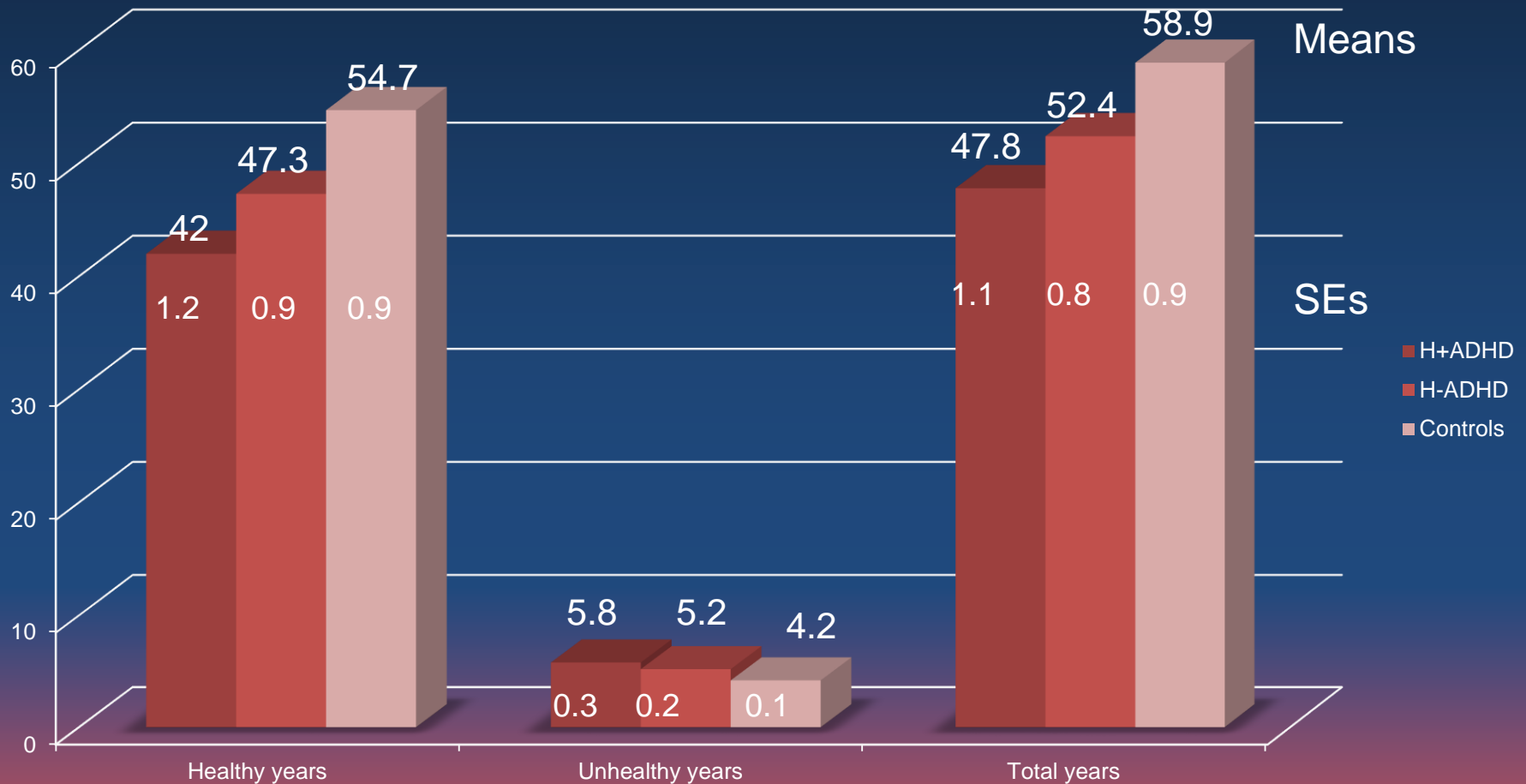
- Adults with ADHD are 1.8x more likely to die within childhood and 4.56x in adulthood than the general population. 3x more likely due to accidental death. Also due to suicide, to a lesser degree
- Other possible contributors to shortened life span? Greater smoking, alcohol, and substance abuse, increased aggression and crime, more intimate partner violence, higher suicide risk, greater obesity risk, lower health status. All are linked to low conscientiousness. Decreased child conscientiousness is associated with earlier death by all causes ($<25^{\text{th}}$ % = -7 years)
- ADHD is linked to very low conscientiousness ($<7\%$). So ADHD, should have an even greater reduction in life expectancy.

Estimated Life Expectancy (yrs. Left) Hyperactive (ADHD-C) Children vs. Controls



From Barkley, R. A. & Fischer, M. (2019). *Hyperactive child syndrome and estimated life expectancy at young adult follow-up: The role of adult ADHD and other potential predictors.* *Journal of Attention Disorders*, 23, 907-923.

Estimated Life Expectancy Persistent vs. Non-persistent ADHD



. From Barkley, R. A. & Fischer, M. (2019). *Hyperactive child syndrome and estimated life expectancy at young adult follow-up: The role of adult ADHD and other potential predictors*. *Journal of Attention Disorders*, 23, 907-923.

9 Malleable Factors in the Calculator Can Change ELE

- Years of Education (and hence income also)
- Weight
- Nutrition
- Exercise
- Sleep Duration
- Risky Driving
- Smoking
- Alcohol Use
- Current Health

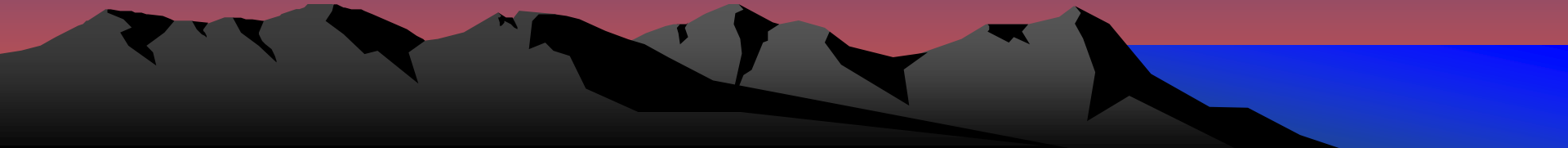


Behavioral Inhibition
(Conscientiousness)

So clinicians cannot just focus on the specific health concerns but must also address the underlying ADHD symptoms and particularly deficient behavioral inhibition and self-regulation

Implications

- ADHD is a serious public health problem; it accounts for greater reductions in ELE than any single risk factor of concern to public health and medical professionals, such as smoking, excess alcohol use, obesity, coronary heart disease, nutrition, sleep, exercise, or risky driving among other widely accepted health risks.
- It is 2.5x worse than even the top 4 above combined.
- Not surprisingly, ADHD is associated with \$26,000+ per year in increased costs for health, social care, crime, increased disability and other state benefits in comparison to siblings
- Treating ADHD and especially its behavioral inhibition deficits, such as with medications, may facilitate reduction in the associated health risks that may thereby improve estimated life expectancy
- Patients and families need to become aware of such risks so as to encourage more engagement in health risk reduction



More Implications

- Mental health professionals need to:
 - broaden their evaluations to include health, lifestyle, and other factors related to life expectancy
 - Include recommendations for reducing those first order risk factors as part of their treatment package
- Primary Care Providers need to:
 - recognize the role of ADHD in diminished health, wellness, and life expectancy in their practice
 - recognize that their patients who are failing in typical health improvement programs may have adult ADHD that is undermining their success
 - assess for adult ADHD, and
 - treat it or refer to others more expert in doing so to improve chances of responding to health and lifestyle self-improvement interventions
- Government agencies tasked to deal with public health issues, such as obesity, nutrition, exercise, substance use, sleep, and driving, among others, need to be aware of the important role that ADHD plays in these health domains and mediating success or failure in health improvement changes, encouraging screening for and treating it especially when prior efforts at self-improvement have failed.

Final Remarks

- ADHD is among the most treatable psychiatric disorders yet it is not recognized in primary care or by public health officials in their policies and programs as playing a critical role in health and healthy life style choices.
- The greatest problems currently are under-recognition and treatment of teen and adult ADHD, access to evidence-based treatments, cost, and getting patients to remain in treatment through the critical adolescent and adult years.

