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"Mortality of Psychiatric Disorders"

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Disclosures of Potential Conflicts

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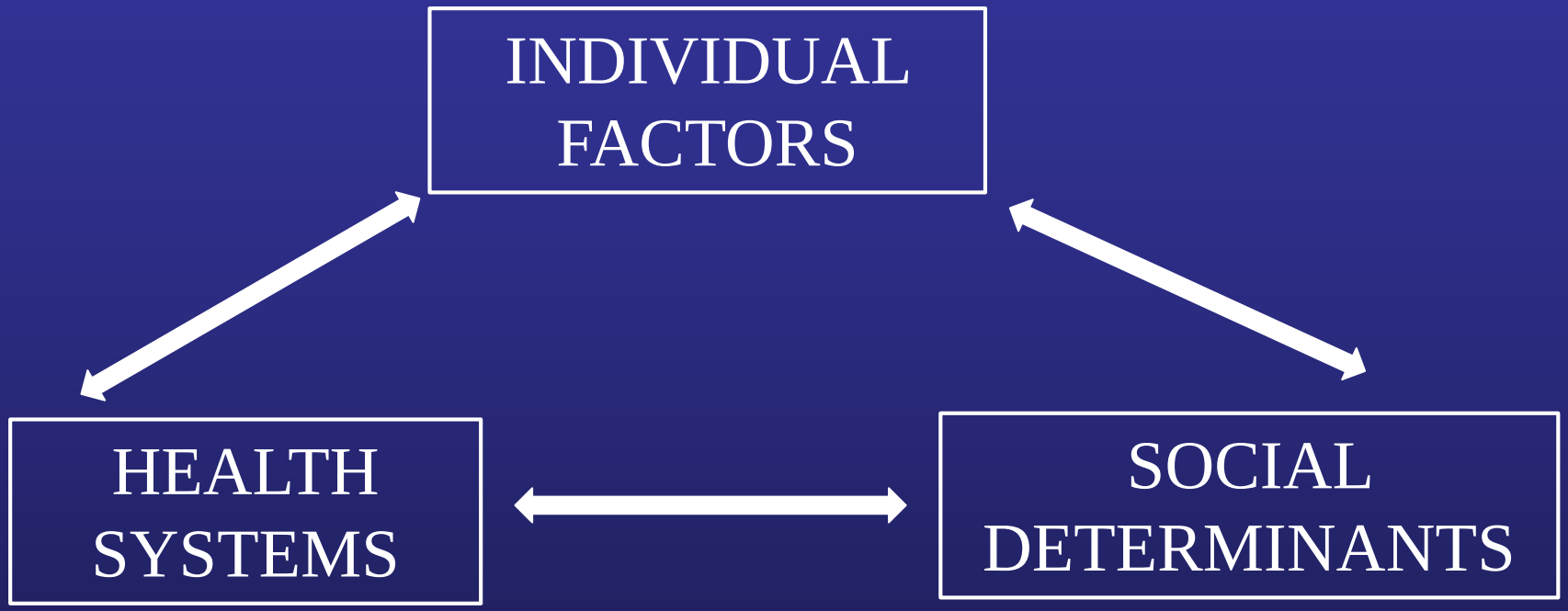
Oxford Books					Chapter			
PCIT International		X						

Objectives

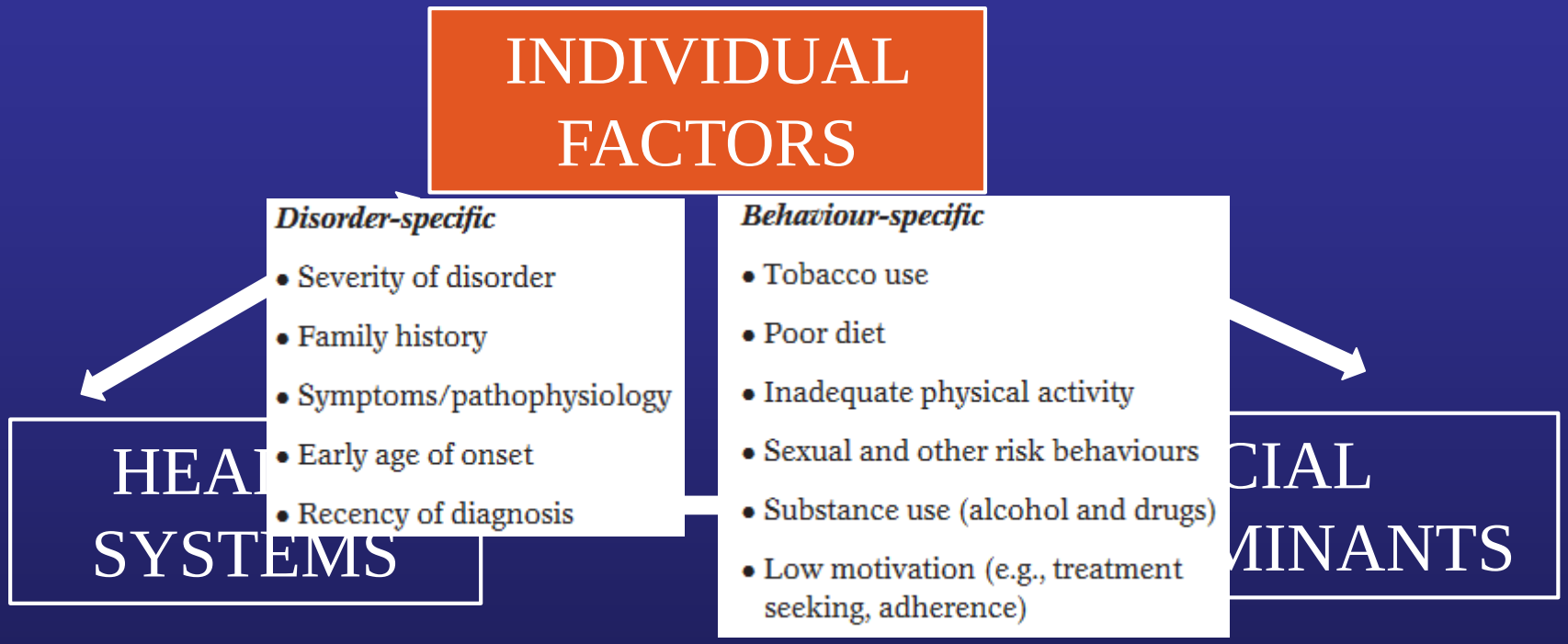
- Review overall multi-level mortality risk framework
- Review mortality risks associated with major psychiatric disorders
- Review association of common psychiatric disorders and general health conditions
- Discuss role of number and types of psychotropic medications in determining illness severity

Overall Mortality Risk Framework



(Source: Liu et al., 2017)

Overall Mortality Risk Framework



(Source: Liu et al., 2017, Table 1)

Overall Mortality Risk Framework

HEALTH SYSTEMS

AL
INANTS

Leadership

- Absence of relevant policies and guidelines

Financing

- Low investment in quality care

Information

- Limited health information systems

Service delivery

- Verticalization and fragmentation of health services
- Lack of care coordination and management
- Limited access to services

Human resources

- Poor quality service provision
- Negative beliefs/attitudes of workforce
- Poor communication

Medications

- Antipsychotic medications (no treatment, polypharmacy, higher than recommended dosages)

(Source: Liu et al., 2017, Table 1)

Overall Mortality Risk Framework

Public policies

- Discriminating policies
- Low financial protection and limited coverage in health packages

Socio-economic position

- Unemployment
- Homelessness
- Low health literacy

Culture and societal values

- Stigma and discrimination in society
- Negative perceptions about persons with SMD

Environmental vulnerabilities

- Infections, malnutrition
- Access to means of suicide
- Impoverished or unsafe neighbourhoods

Social support

- Limited family, social and community resources

HE
SYS

SOCIAL DETERMINANTS

(Source: Liu et al., 2017, Table 1)

Mortality Reduction: Multi-level Model

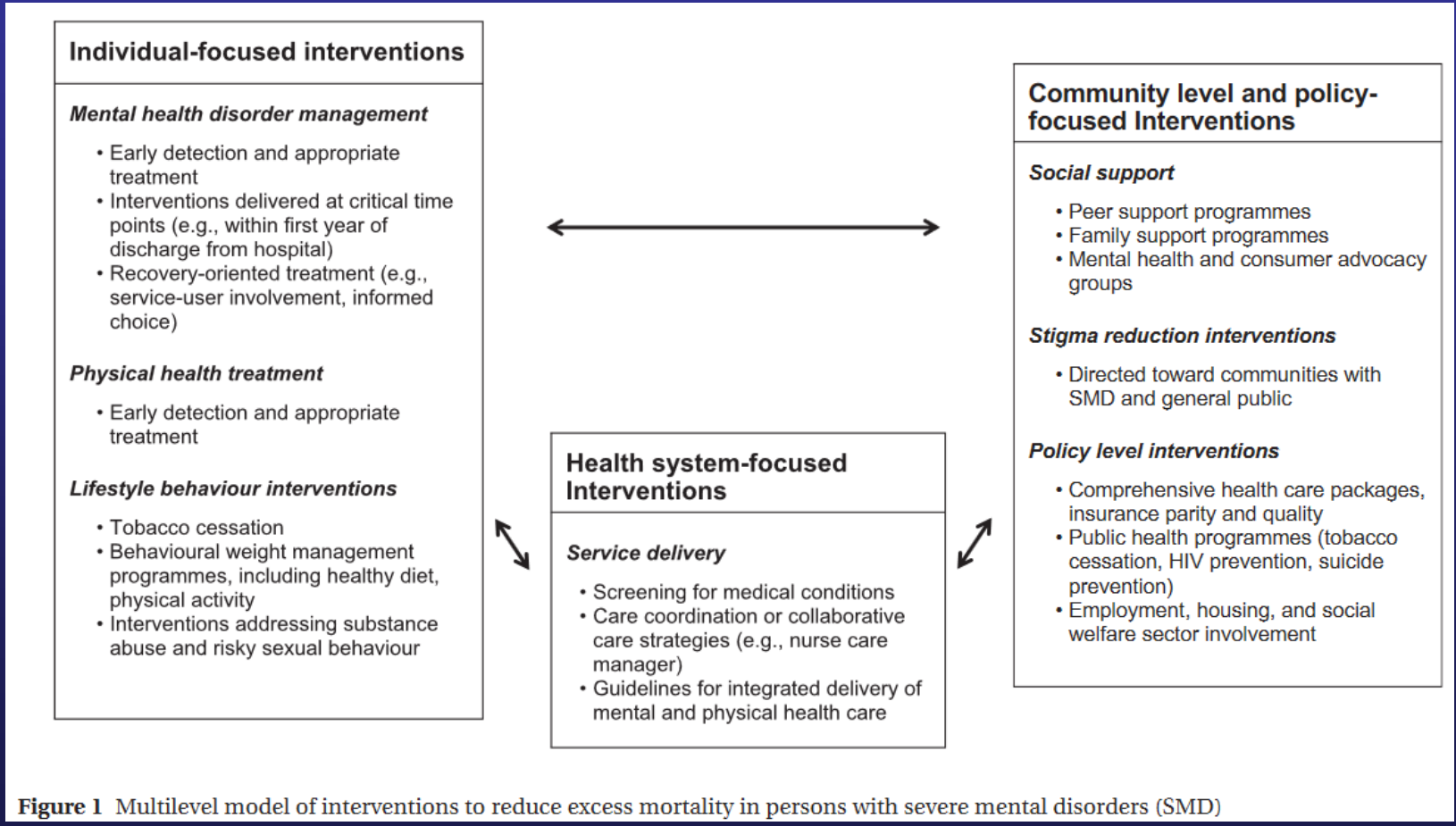
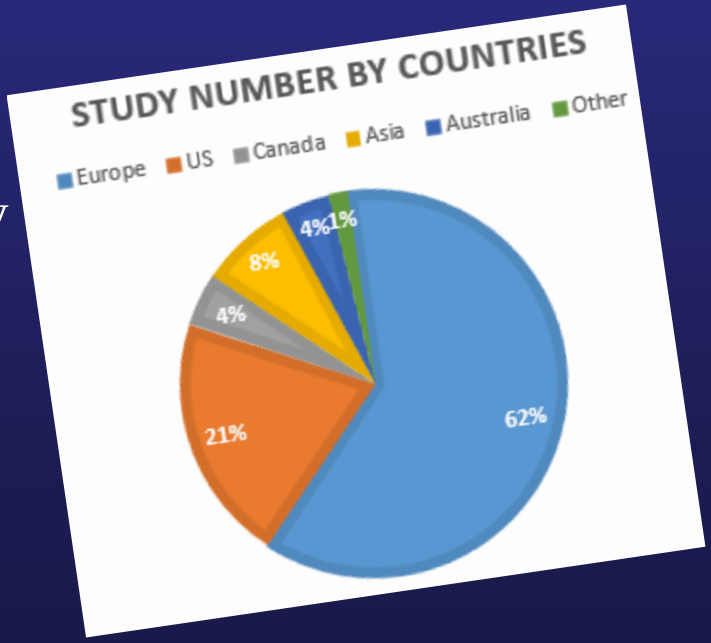


Figure 1 Multilevel model of interventions to reduce excess mortality in persons with severe mental disorders (SMD)

(Source: Liu et al., 2017, Figure 1)

Mortality in mental disorders, global findings

- Systematic review and meta-analysis of mortality among people with mental disorders from 29 countries
- 203 cohort design studies included, comparing those with diagnosed mental disorders to those without
- For all-cause mortality:
  - 91% report higher RR in PWMD
  - 9% report no difference
  - 0 report lower RR in PWMD
- Median years of potential life lost/life expectancy
  - All-cause - 10.1 years
  - Natural causes - 9.6 years
    - (acute or chronic illness related; 67.3% of deaths)
  - Unnatural causes - 21.6 years
    - (unintentional injury, suicide; 17.5% of deaths)



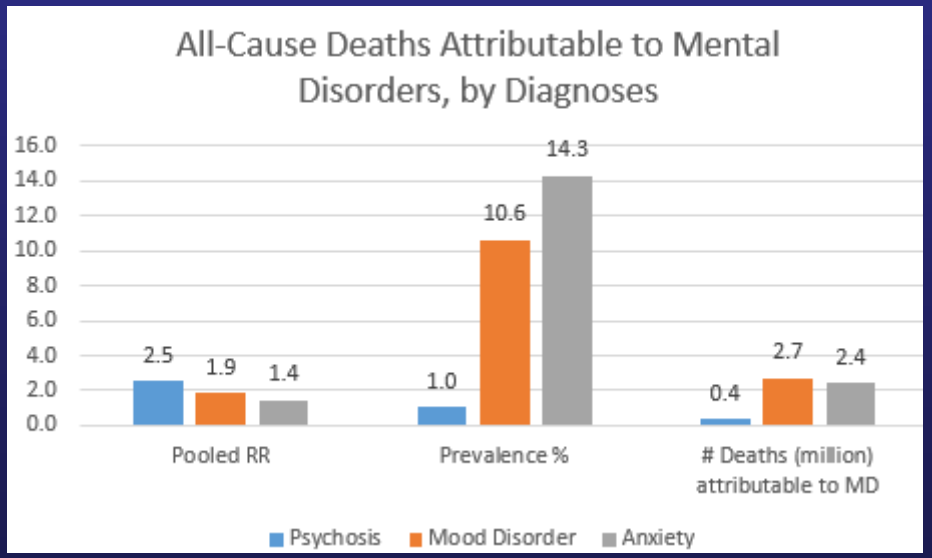
(Source: Walker et al., 2015)

Mortality in mental disorders, global findings

- All-cause mortality RR 2.22 (95% CI 2.12-2.33)
- No difference in mortality rate by geography, sample source or diagnostic system
- Relative risk differences by attributed causation

  RR 1.80 (95% CI 1.71-1.88) for natural causes

  RR 7.22 (95% CI 6.43-8.12) due to unnatural causes



- Differences by mental disorder:

  RR highest for psychosis

  Prevalence highest for anxiety

  8 Million attributable deaths due to mental disorders, based on WHO MD prevalence estimates of 26%

(Source: Walker et al., 2015)

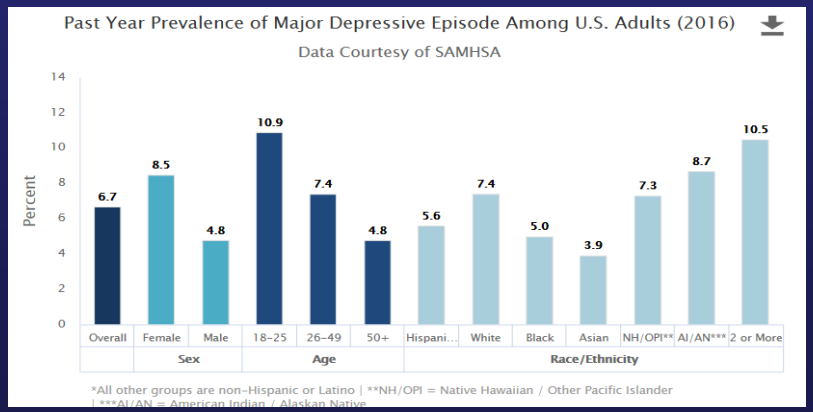
Depressive Disorders

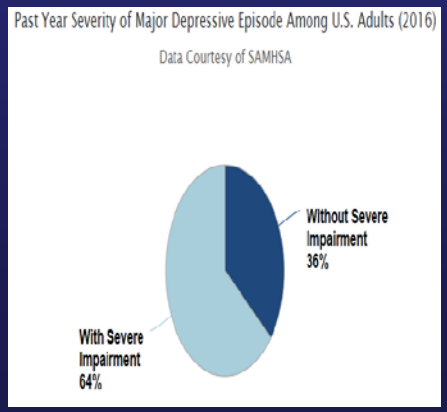
- Per DSM-5, includes
  - Disruptive mood dysregulation disorder
  - **Major depressive disorder (MDD)**
  - Persistent depressive disorder (dysthymia)
  - Premenstrual dysphoric disorder
  - Substance/medication-induced depressive disorder
  - Depressive disorder due to another medical condition
  - Other and unspecified depressive disorder
- Common feature: sad, empty or irritable mood, with cognitive and somatic changes that limit functioning
- Differences in timing, duration and presumed etiology
- MDD is among the most common mental disorders in U.S.

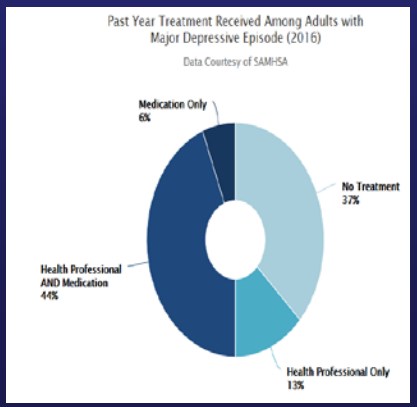
(Source: DSM-5, 2013)

Major Depressive Disorder

- Per 2016 National Survey on Drug Use and Health, MDD prevalence 6.7% of U.S. adults (16.2 million)
  - Higher in females (8.5%) than males (4.8%)
  - Highest among individuals aged 18-25 years (10.9%)
  - Highest among white (7.4%) and those with >=two races (10.5%)
- In 2016, an estimated 4.3% of U.S. adults had MDD with severe impairment (10.2 million)
- Of adults with MDD, 37% did not receive treatment (~5.9 million)





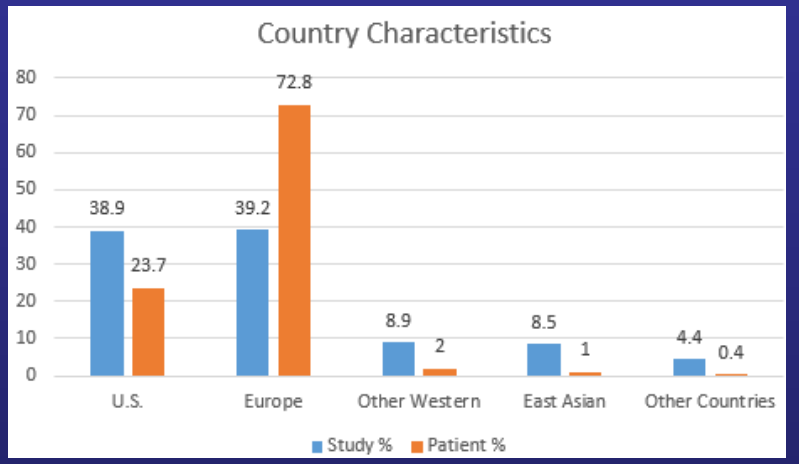


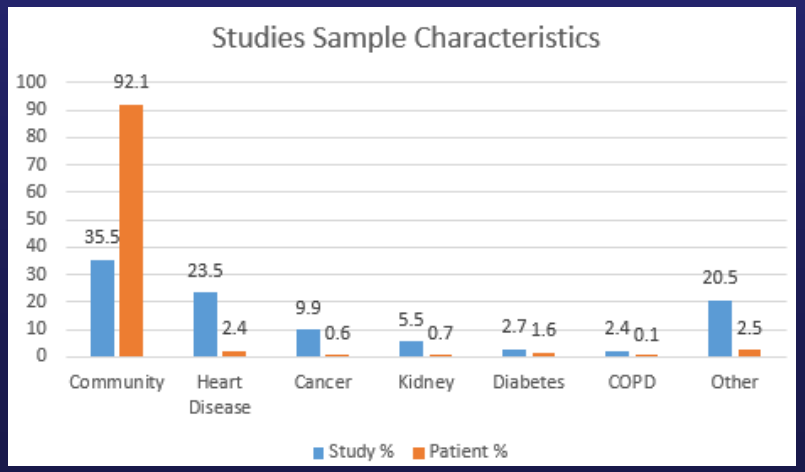
(Source: https://www.nimh.nih.gov/health/statistics/major-depression.shtml)

Major Depressive Disorder

- **Meta-analysis of 239 studies**
  - 35 countries
  - Varying decades of data collection
  - Various sample types, including community and disease-specific groups
- **Relative risk (RR) of all-cause mortality 1.52** (95% CI 1.45-1.59) in individuals with depressive disorder.
- **COPD associated with higher relative risk** than general population and other specific patient samples.
- **RR lower in longer f/up studies**

(Source: Cuijpers et al., 2014)





“Stirling” County Study

- Cohort study of 3,410 adults (Atlantic Canadian County)
- Three representative samples (1952, 1970 and 1992)
- Vital status through 2011 determined by linkages to Canadian Mortality Database

- Depression assessed through at-home interviews, based on DSM-III criteria, and requiring 1-month symptoms plus impairment

(Source: Gilman et al., 2017)

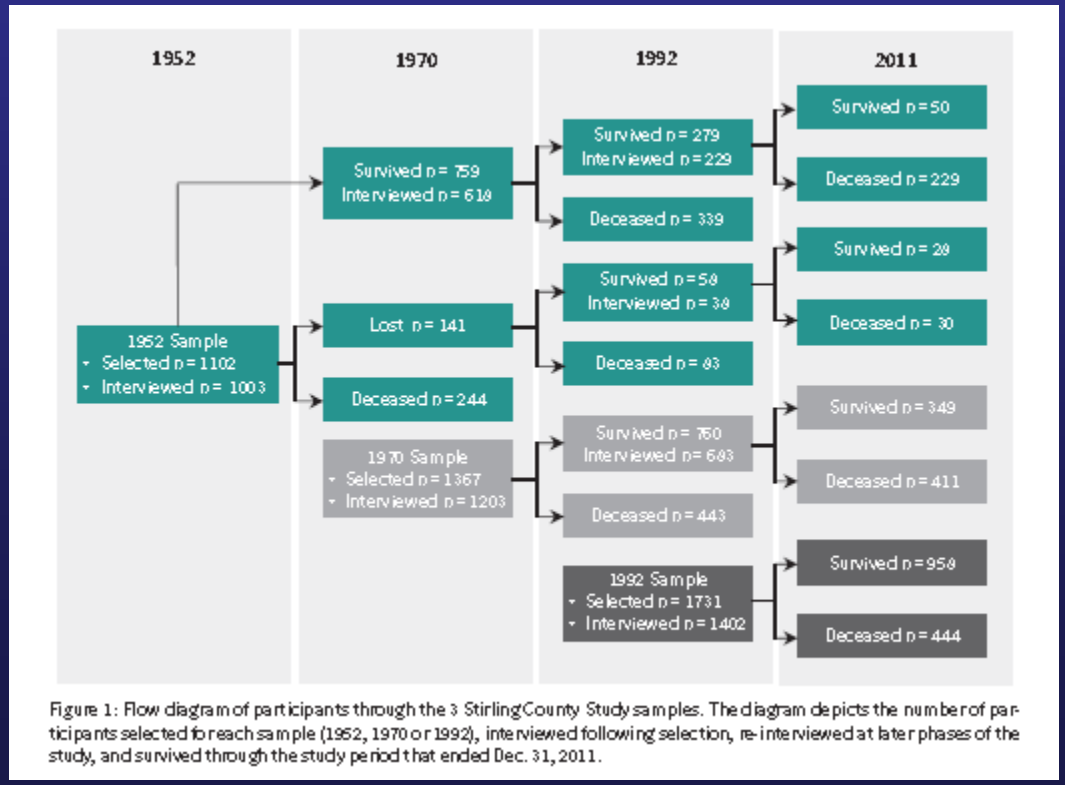
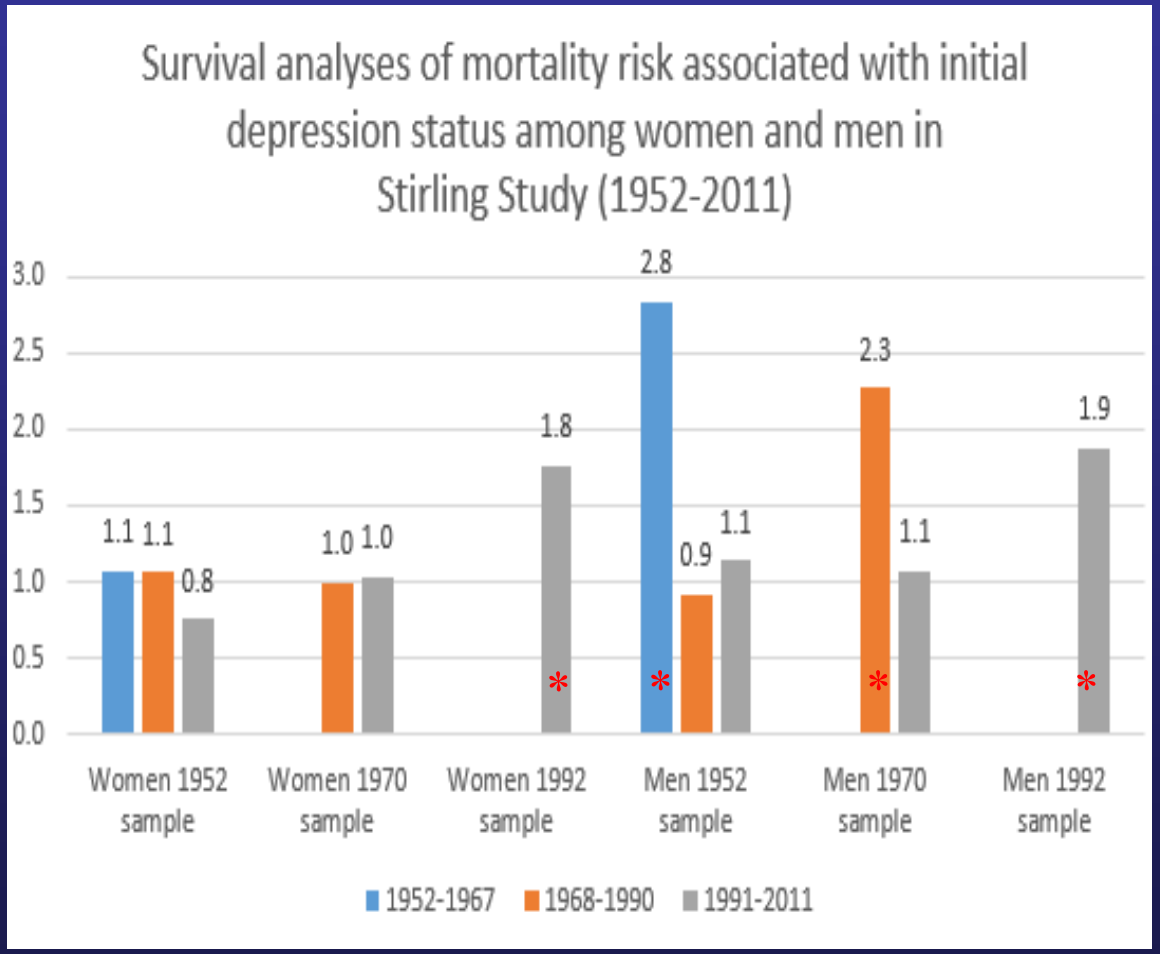


Figure 1: Flow diagram of participants through the 3 Stirling County Study samples. The diagram depicts the number of participants selected for each sample (1952, 1970 or 1992), interviewed following selection, re-interviewed at later phases of the study, and survived through the study period that ended Dec. 31, 2011.

"Stirling County" Study: Initial Status



- Depression confers mortality risk, which decays over time, unless recurrent episodes
- Secular trend by gender – women's mortality risk increased among depressed women, beginning in 1990s
- Mortality risk same for both genders by 1991-2011 period

(Source: Gilman et al., 2017)

Bipolar Disorder

- Was also referred to as “manic-depressive illness”
- Brain disorder causing unusual shifts in mood, energy and activity levels, and ability to carry out usual tasks
- Four basic types – with clear changes ranging from “up” (elated, energized) to “down” (sad, hopeless)
  - Bipolar I disorder (at least 7 days of mania, unless hospitalized)
  - Bipolar II disorder (less severe manic symptoms)
  - Cyclothymic disorder (less severe than hypomania, but mood swings lasting over 2 years – 1 year in children)
  - Other and unspecified bipolar and related disorder
- Mean age of onset 18 years for bipolar I; however, can occur in children and across the life cycle

(Source: DSM-5, 2013)

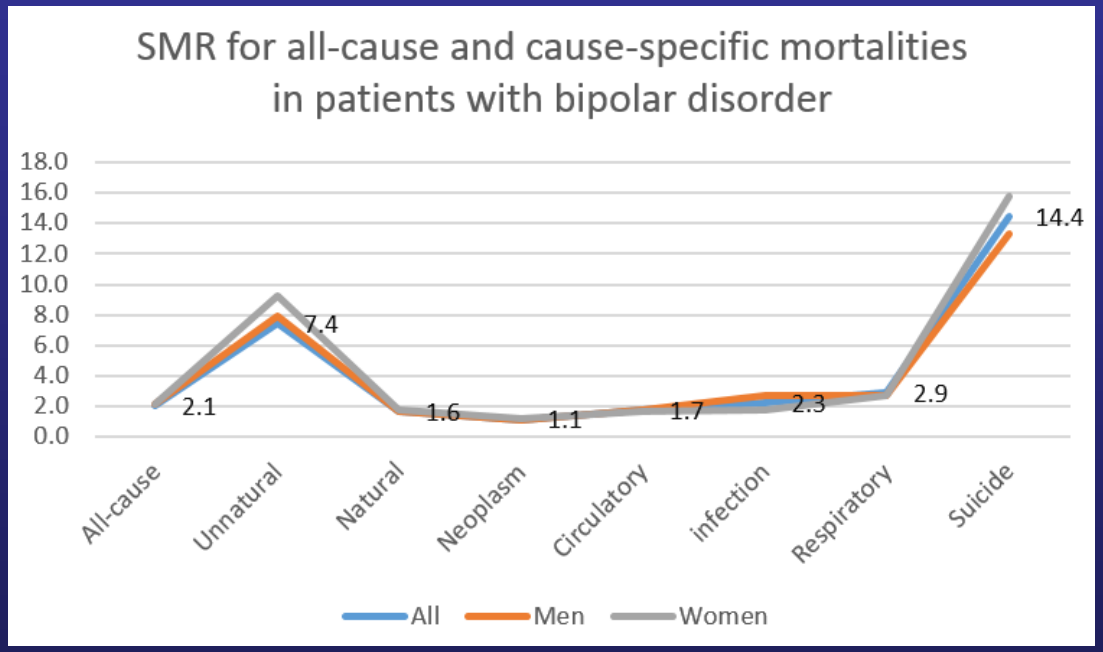
Bipolar Disorder

Meta-analysis of 31 studies

- Multiple countries
- Varying decades of data collection
- Various population types

All-cause and cause-specific SMR elevated in individuals with bipolar disorder relative to general population.

SMR has not improved over time.



(Source: Hayes et al., 2017)

Schizophrenia

- Characterized by disruptions in thought process and speech, perceptions, emotional responsiveness and social interactions
- Typically starts late adolescence or early adulthood, often after period of unusual behaviors and cognitive changes
- U.S. prevalence estimate ranges from 0.25% to 0.64%
- Among the top 15 leading causes of disability worldwide

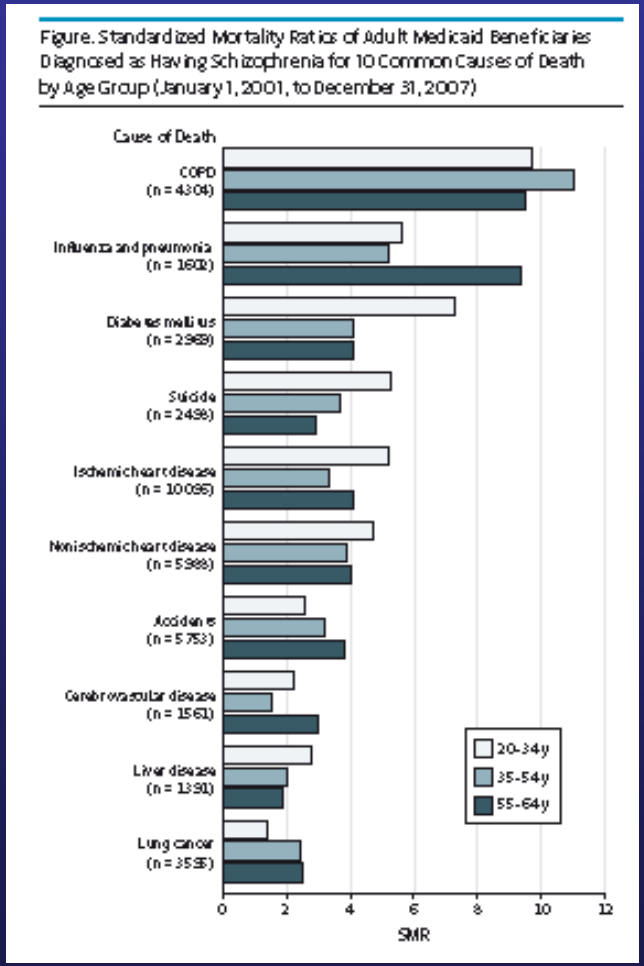
(Source: https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml)

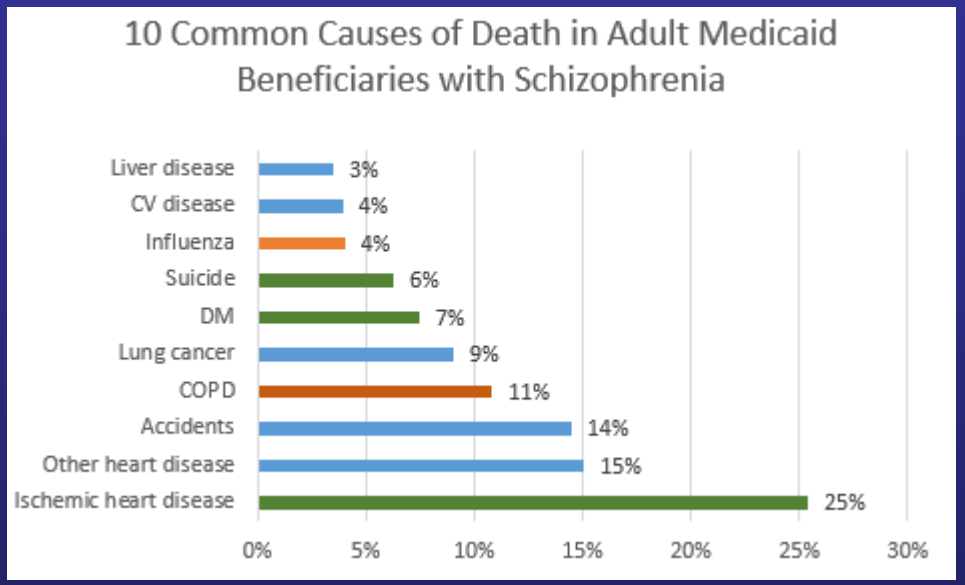
Schizophrenia

- Affected individuals are at increased risk for premature mortality
- Olfson et al. study:
  - Retrospective cohort study, 1,138,853 patients with schizophrenia ages 20-64 in Medicaid program, 1/1/2001 to 12/31/2007
  - 4,807,121 f/up years; 74 003 deaths (65 553 known cause)
  - Estimated average potential life lost in U.S. **28.5 years**
  - 3.5 times more likely to die during follow-up compared to general population
  - Mortality contributions by multiple chronic health conditions, smoking, unintentional injuries and suicide, as likely also by health effects of antipsychotic medications

(Source: Olfson et al., 2015)

Mortality Rates for 10 Common Causes of Death in Medicaid Patients with Schizophrenia





Mortality risk particularly elevated for COPD and Influenza/Pneumonia

Mortality risk particularly increased for younger adults for suicide, DM and ischemic heart disease

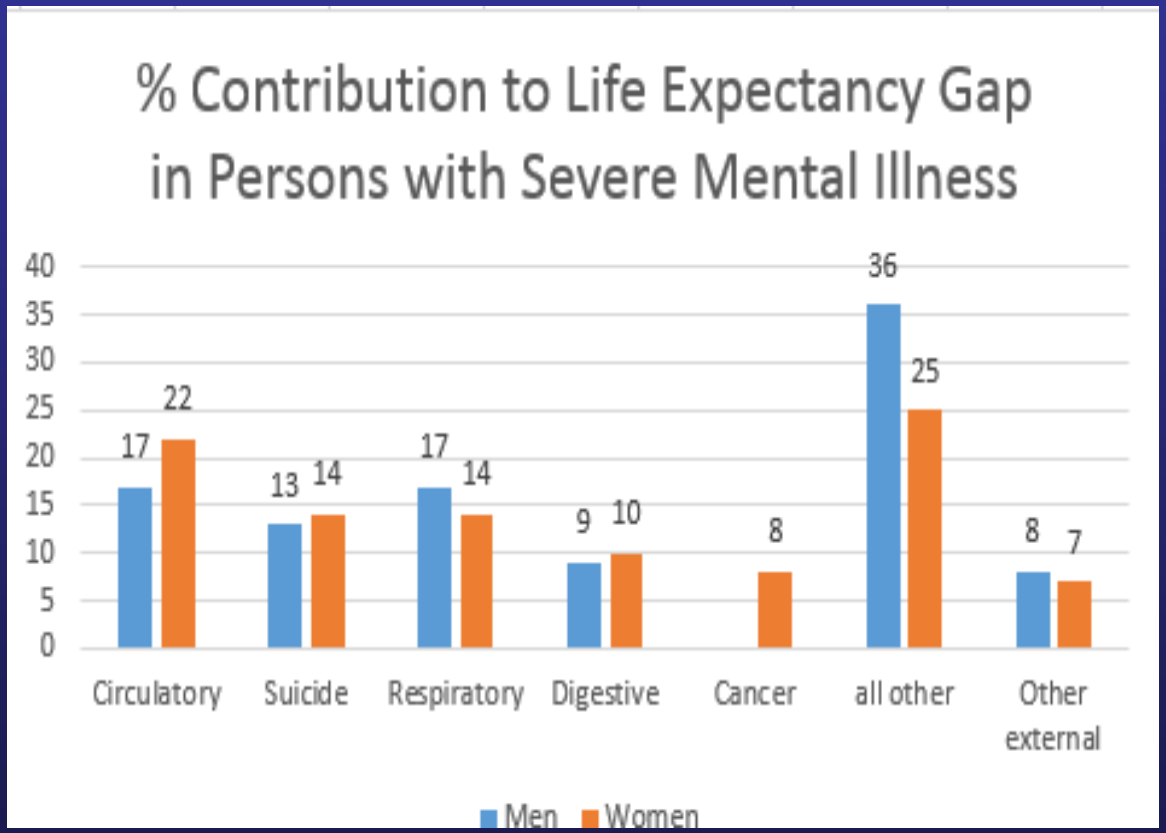
(Source: Olfson et al., 2015)

Contributions of specific causes of death to lost life-expectancy in SMI

- Case registry study, 2007 to 2012, England and Wales
- Age of death and primary cause of death were used to estimate life expectancy at birth for persons with SMI
- Gender- and age-specific norms were used to estimate contributions of specific causes to lost life expectancy
- Life expectancy was reduced by 10.6 years for men and 10.2 years for women with SMI
- Natural causes accounted for 79.2% of lost life-years in women and 78.6% in men

(Source: Jayatilleke et al., 2017)

% Contribution to Life-expectancy Gap in Persons with SMI



- Multiple causes contribute to reduced life expectancy
- Single-focus interventions unlikely to have meaningful effects
- "Package of care" to reduce health inequalities

(Source: Jayatilleke et al., 2017, Table 1)

Association of psychiatric disorders with chronic health conditions

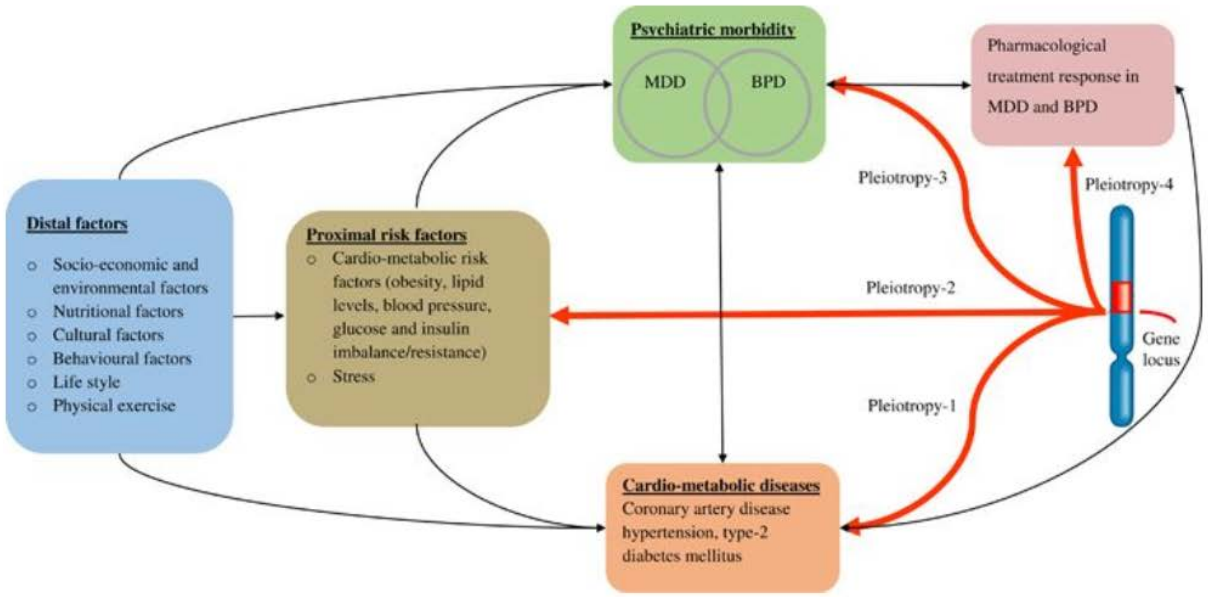
- Epidemiological studies show strong associations between psychiatric disorders and multiple chronic health conditions
- The associations are not unique to specific mental disorder; e.g., increased rates of coronary artery disease, cancer, or diabetes have been variably reported for schizophrenia, depression and bipolar disorder (e.g., Gale et al., 2014; Currier & Nemeroff, 2013; Rustad et al., 2010; Roshanaei-Moghaddam & Katon, 2010)
- Further complicating the picture is multimorbidity of these various conditions beyond comorbidity of one mental and one physical disorder (e.g., Barnett et al., 2012)

Potential shared mechanisms of physical and mental disorder "comorbidities"

- Genetics – see recent review of genetic overlap between mood disorders and cardiometabolic diseases, Amare et al. 2017

Figure 1

From: The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies



“Cardiometabolic Mood Disorder hub genes”

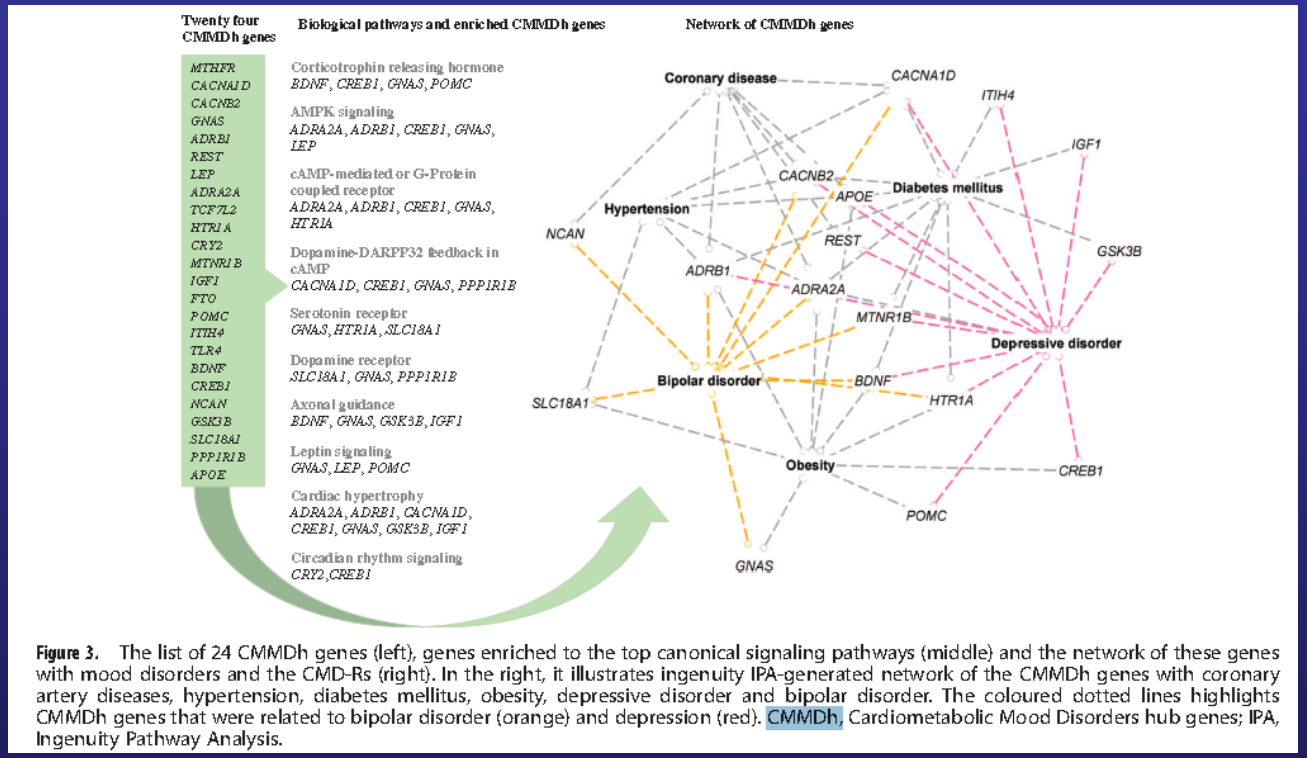
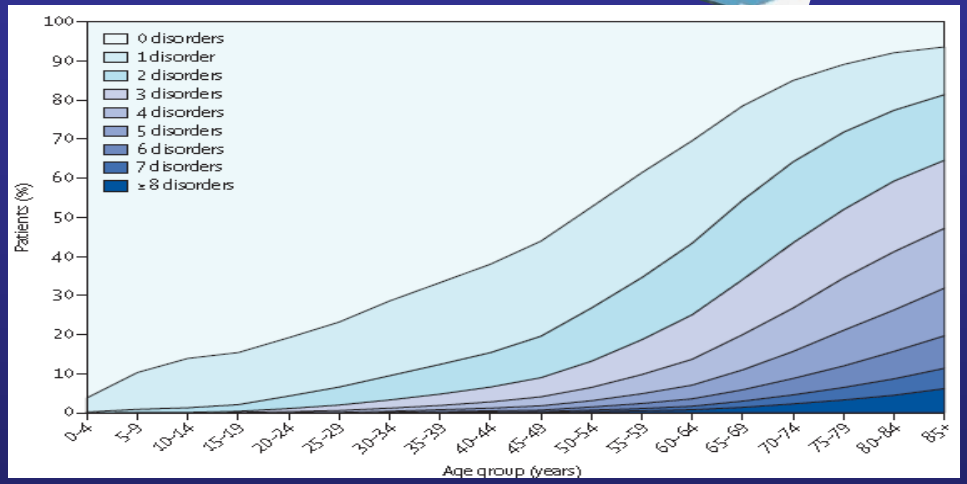


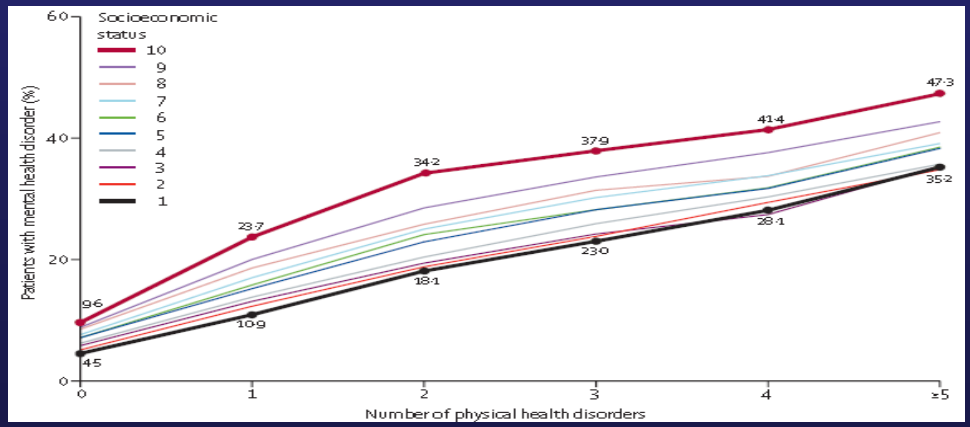
Figure 3. The list of 24 CMMDh genes (left), genes enriched to the top canonical signaling pathways (middle) and the network of these genes with mood disorders and the CMD-Rs (right). In the right, it illustrates ingenuity IPA-generated network of the CMMDh genes with coronary artery diseases, hypertension, diabetes mellitus, obesity, depressive disorder and bipolar disorder. The coloured dotted lines highlights CMMDh genes that were related to bipolar disorder (orange) and depression (red). CMMDh, Cardiometabolic Mood Disorders hub genes; IPA, Ingenuity Pathway Analysis.

Note: not my specialty area, but highly relevant to disentangling comorbidity findings – suggest future presentation by genetics expert

Multimorbidity findings

- Cross-sectional study
- 1,75 million patients of all ages registered in 314 practices (Scotland)
- % with physical-mental comorbidity ranged from 0.5% (under 25 y/o) to 30.8% (over 84 y/o)
- Presence of MHD strongly associated with number of physical disorders and SES gradient





Multimorbidity findings

- Depression, anxiety and pain conditions were more common comorbidities in patients living in deprived areas than in affluent peers
- MHD was predicted by female gender (OR 1.4), increasing age decade (OR 1.6), increasing deprivation (gradient up to OR 2.3 for most deprived) and number of physical conditions (gradient up to 6.7 for more than 4)

Figure 4: **Selected comorbidities in people with four common, important disorders in the most affluent and most deprived deciles**

COPD=chronic obstructive pulmonary disease. TIA=transient ischaemic attack.

Can MH interventions improve outcomes of chronic health conditions?

- Variable findings
  - Collaborative care (CC) in patients with depression and chronic medical conditions shows CC more effective than care as usual to improve chronic condition outcomes (e.g., van Eck van der Sluijs et al., 2018; Rossom et al., 2017)
  - Systematic literature review of various treatment studies showed no evidence that "screen-and-treat" strategy for depression in adults with chronic diseases improved the health outcomes (e.g., Health Quality Ontario, 20123)
- More research needed –see next example!

Depression Treatment and 1-year Mortality after AMI

- TRIUMPH study (Translational Research Investigating Underlying disparities in AMI Patients' Health Status)
- Observational multicenter cohort study in 24 US hospitals
- 4,062 patients with AMI between 4/2005 and 12/2008
- Depression assessed with PHQ-9 (score >=10) at index AMI admission
- Compared 1-year mortality between patients without depression (81%), treated (5.7%) and untreated depression (16.0%)
- "Treatment" could consist of antidepressant medication administered for depression, or of counseling/therapy

Depression Treatment and 1-year Mortality after AMI

- Unadjusted 1-year mortality rates were 6.1%, 6.7% and 10.8% for patients without depression, with treated depression and untreated depression, respectively
- After adjusting for demographics SES, disease severity and other clinical variables 1-year mortality
  - in patients with treated depression was not different from those without depression (HR 1.12, 95% CI 0.63-1.99)
  - In patients with untreated depression was significantly increased (HR 1.91, 95% CI 1.39-2.62)

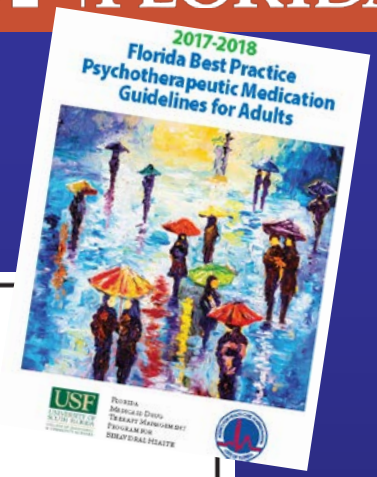
Polypharmacy and Illness Severity

Can you assume a patient on multiple psychotropic medications has more severe illness?

YES (mostly)

- Example: polypharmacy in depressive disorder
  - Indicated for more severe presentations, for example, with psychotic or catatonic features
  - Utilized for treatment resistant depression
  - May indicate co-occurrence of other disorders (e.g., anxiety, PTSD, ADHD etc.)

Treatment Guidelines for depression



Level 1 **Initial Treatment:**

- Evidence-based psychotherapy [Cognitive-Behavioral Therapy (CBT), Interpe
  Psychotherapy (IPT), Behavioral Activation]

Note: Manualized-based psychotherapies are preferred (where available) as first-line treatment for major depressive disorder (MDD) of mild severity.

- Monotherapy 4-8 week trial at adequate dose and evaluate*:
  - Selective serotonin reuptake inhibitor (SSRI)**, serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine
  - Bupropion or mirtazapine
- If partial response at 4 weeks, may continue for another 2 to 4 weeks or go to Level 2.
- If no response at 4 weeks, ensure dose optimization and go to Level 2.

Notes:

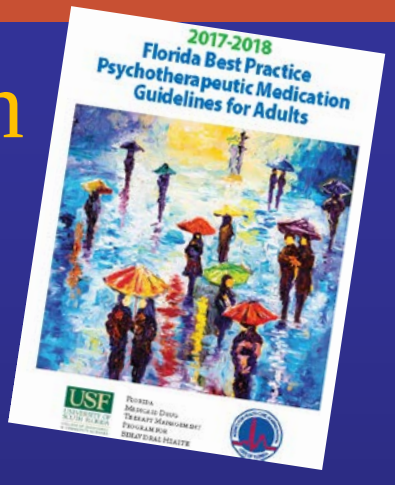
**Medication response is more pronounced in moderate to severe depression.*

***Consider propensity for drug-drug interactions and differential risk for teratogenicity.*

Initiate combination therapy for individuals with recurrent depression, persistent depressive disorder, and history of trauma.

Source: Medicaidmentalhealth.org

Treatment Guidelines for depression



Level 2 **If Level 1 Is Ineffective and/or not well tolerated:**

- Evaluate adherence
- Ensure dose optimization of medication used in Level 1.
- Switch to different monotherapy agent from different or same class (SSRI, SNRI, bupropion, or mirtazapine).
- Combine existing monotherapy with:
  - Evidence-based psychotherapy (e.g., CBT, IPT)
  - Second-generation antipsychotic FDA-approved for augmentation therapy for major depressive disorder (MDD) (i.e., aripiprazole or brexpiprazole)
  - An antidepressant (do not combine SSRI and SNRI)

Note: FDA-approved adjunctive agents for MDD are select atypical antipsychotics. Preliminary evidence evaluating comparative effectiveness of adjunctive antidepressant versus adjunctive atypical antipsychotic medications indicates superior efficacy for adjunctive antipsychotics and superior tolerability for adjunctive antidepressants.

Level 3 **If Levels 1 and 2 are Ineffective and/or not well tolerated:**

- Evaluate adherence
- Seek psychiatric consultation
- (SSRI or SNRI) + quetiapine (tolerability concerns)
- (SSRI or SNRI) + (lithium or T3)
- (SSRI or SNRI) + (L-methylfolate or S-adenosylmethionine)
- Tricyclic antidepressant (TCA)
- Monoamine oxidase inhibitor (MAOI)
- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)*

**Note: TMS only has Level 1 evidence for acute treatment.*

Level 4 **If Levels 1 – 3 are Ineffective and/or not well tolerated:**

- Re-evaluate diagnosis if patient has failed to respond to 2 or more treatments
- Monoamine oxidase inhibitor (MAOI) augmentation **(AVOID CONTRAINDICATED COMBINATIONS)**
- L-methylfolate augmentation
- Triple drug combination (little evidence exists supporting or refuting this strategy)
  - (SSRI or SNRI) + mirtazapine + bupropion
  - (SSRI or SNRI) + mirtazapine + lithium*
  - (SSRI or SNRI) + bupropion + second generation antipsychotic (SGA)
- Other neuromodulatory approaches [e.g., vagus nerve stimulation (VNS)]
- Intravenous ketamine (at specialized centers only and in accordance with best practices)

**Note: Caution should be used when prescribing lithium due to increased risk to the fetus with use during pregnancy (i.e., Ebstein's anomaly).*

Source: Medicaidmentalhealth.org

Antipsychotics and Illness Severity

Can you assume that receipt of antipsychotic medications indicates more severe psychiatric illness?

YES (mostly)

1. Most psychiatric illnesses for which antipsychotic medications have FDA-approved indications are considered in category of "severe mental illness" (e.g., schizophrenia and other psychotic disorders, bipolar and related disorders)
2. For neurodevelopmental disorders, like autistic disorder or Tourette, used for more severe presentations
3. Off-label use in other conditions usually if more severe presentations (PTSD; disruptive disorder; depression; anxiety; OCD; neurocognitive disorders; etc.)

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Thank you – questions?