

Metabolic Comorbidities in Major Depressive Disorder (MDD)



This program is paid for by
Otsuka Pharmaceutical Development &
Commercialization, Inc. (OPDC) and Lundbeck, LLC.

Objectives



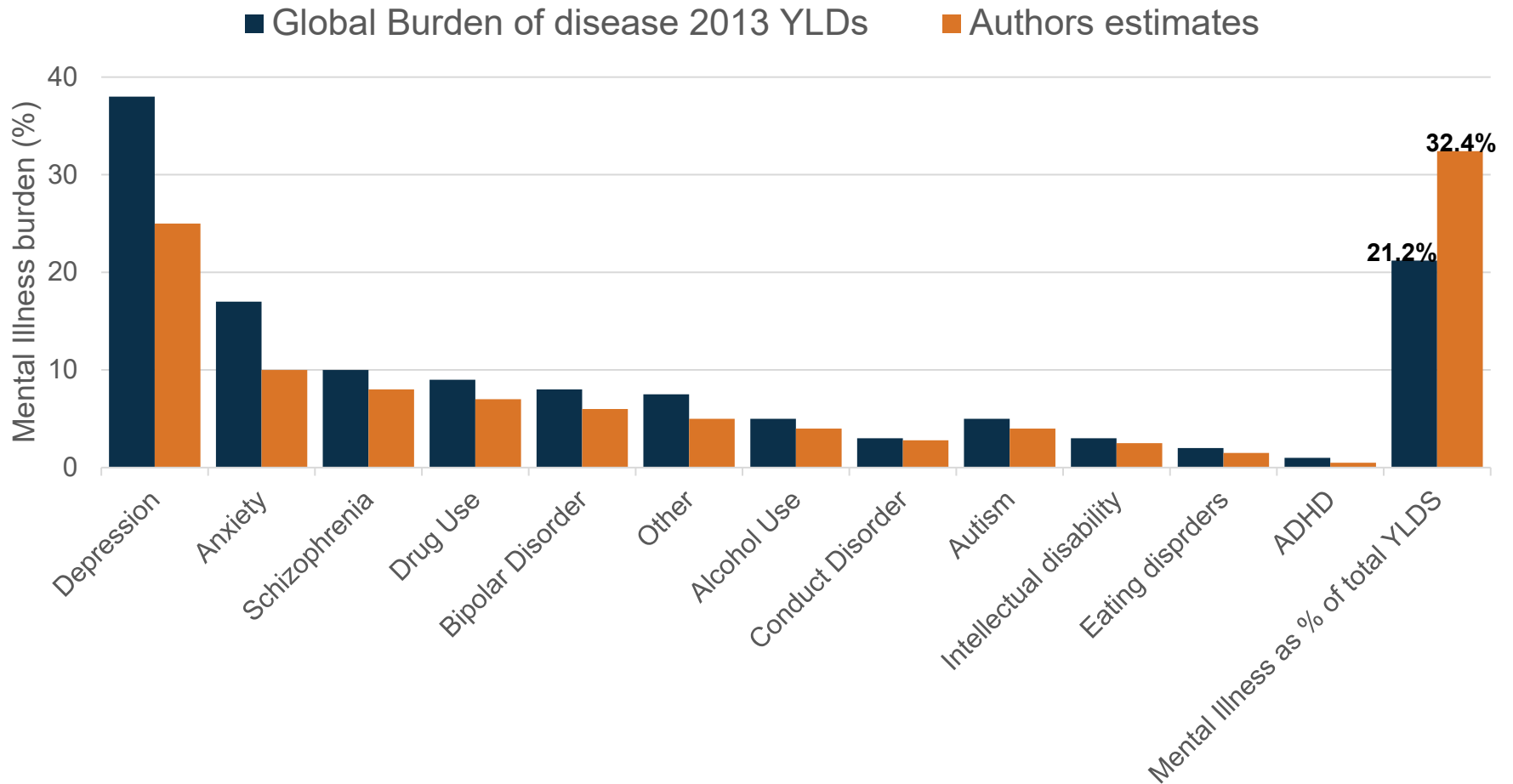
Describe the Mortality in MDD

Identify Metabolic Comorbidities: Weight and Obesity

Identify Metabolic Comorbidities: Diabetes

Identify Metabolic Comorbidities: Cardiovascular Disease and the parameters of Dyslipidemia

Global Burden of Mental Illness



Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry. 2016 Feb;3(2):171-8.

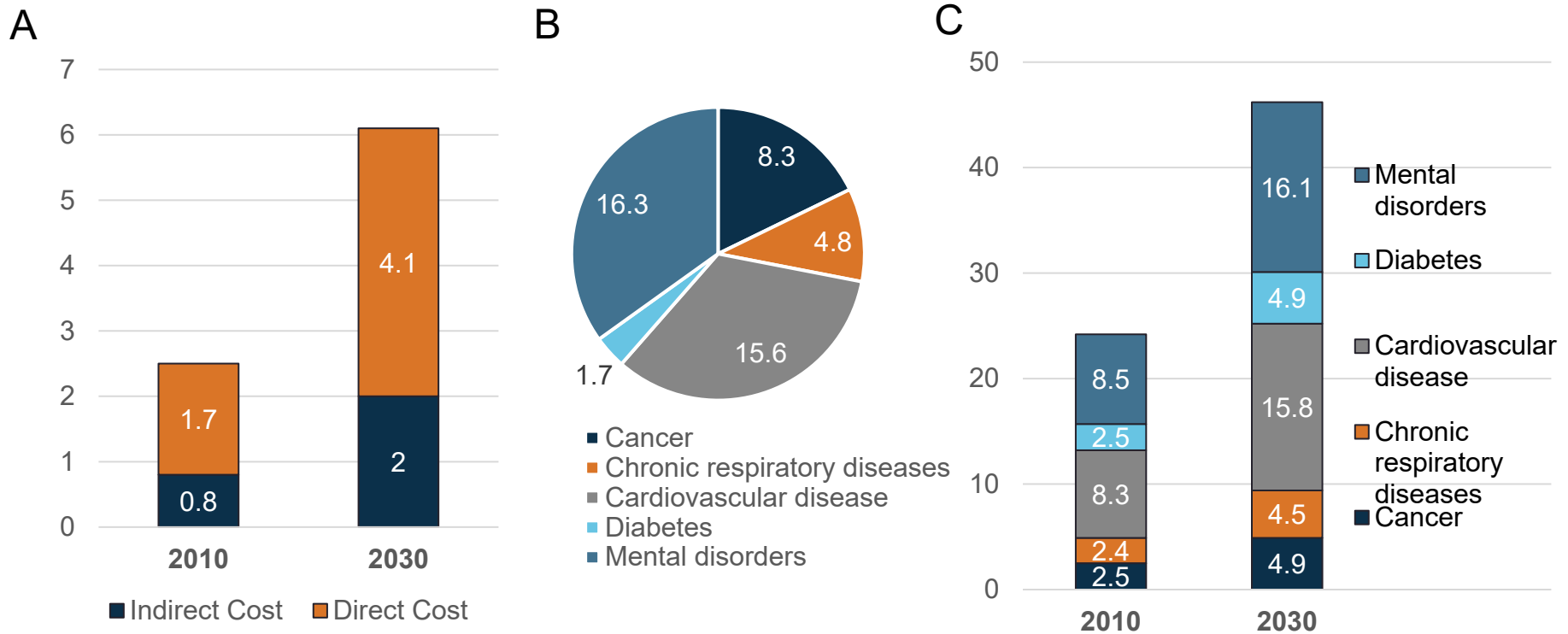
The Global Burden: Disability-adjusted life years (DALYs)

- Mental, neurological, and substance use disorders accounted for 258 million DALYs in 2010,
 - This was equivalent to 10.4% of total all-cause DALYs.
- Proportion of DALYs within mental, neurological, and substance use disorders:
 - Mental disorders = 56.7%
 - Neurological disorders = 28.6%
 - Substance use disorders = 14.7%
- DALYs occurred across the lifespan of all three groups;
 - however, there was a peak in early adulthood (between ages 20 and 30 years) for mental and substance use disorders compared to neurological disorders, where DALYs were more constant across age groups.

Whiteford Ha. et al (2015) The Global Burden of Mental, Neurological and Substance Use Disorders: An Analysis from the Global Burden of Disease Study 2010. PLOS ONE 10(2): e0116820.

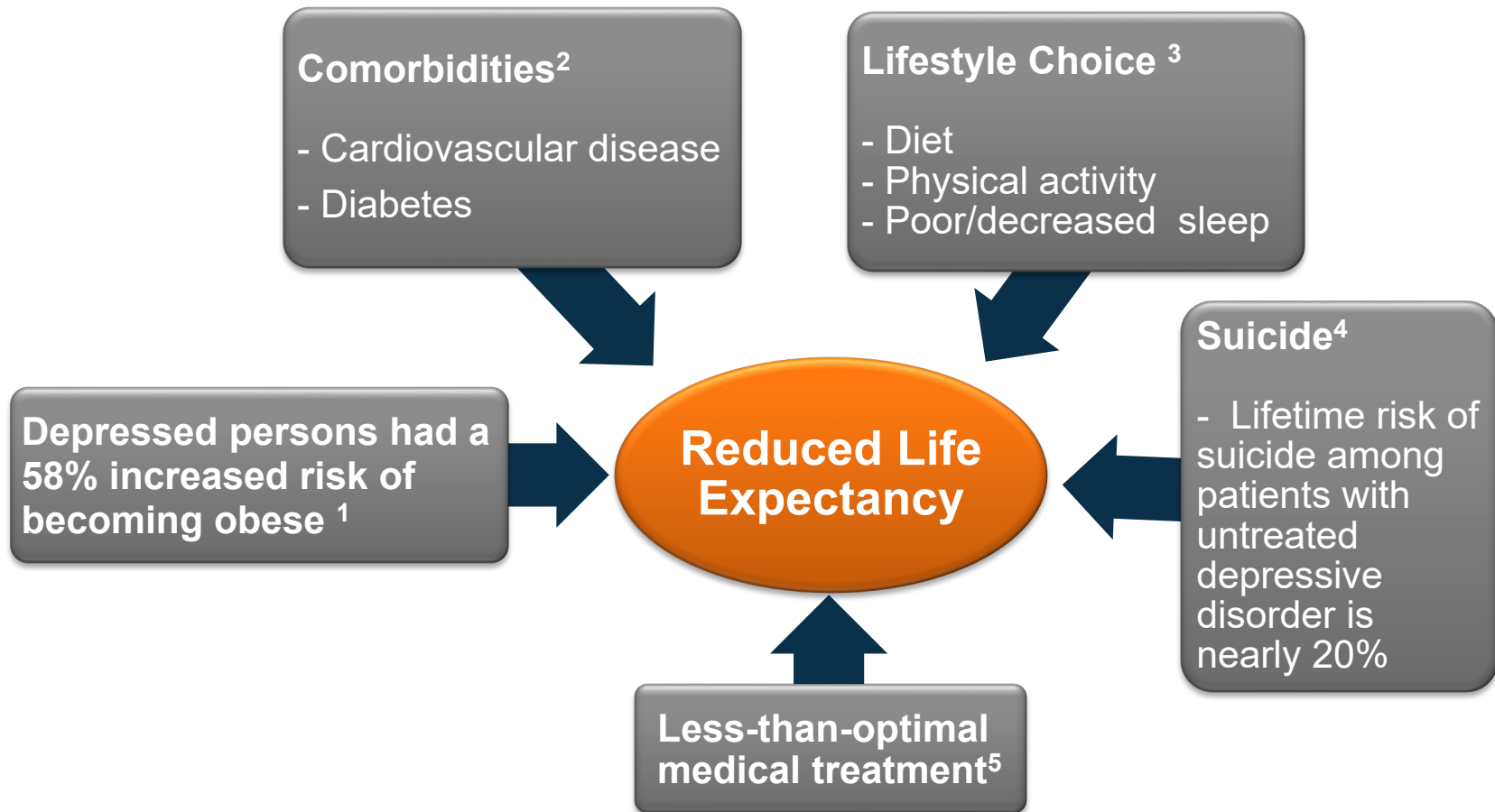
Economic Costs of Mental Disorders

Economic costs of mental disorders in trillion US\$ using three different approaches: direct and indirect costs (A), impact on economic growth (B), and value of statistical life (C)



Trautmann S, et al. The economic costs of mental disorders: Do our societies react appropriately to the burden of mental disorders?. EMBO Rep. 2016;17(9):1245–1249

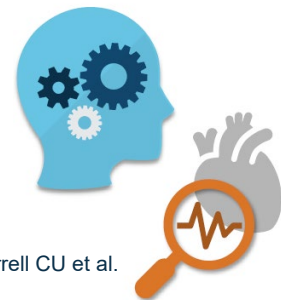
Mortality in MDD



1. Luppino, et al. Gen Psychiatry. 2010;67(3):220–229 2. Topic R et al. Croat Med. 2013; 54:453–459 3. Sarris J et al, BMC Psychiatry. 2014;14:107 4. What Is the Suicide Rate Among Persons with Depressive Disorder (clinical Depression)? 5. <https://www.medscape.com/answers/286759-14675/what-is-the-suicide-rate-among-persons-with-depressive-disorder-clinical-depression> 6. Lemelin J et al. Fam Physician. 1994;40:104–108.

Metabolic Comorbidities in Patients with Severe Mental Illness

- Severe mental illness is associated with increased:
 - Burden of CV mortality and morbidity ¹
 - Prevalence of CV Risk factors, such as obesity and Type 2 Diabetes Mellitus, compared with the general population. ^{2,3}
- Antipsychotics, antidepressants and mood stabilizers can further adversely affect CV risk in patients with severe mental illness ^{2,4}
 - Although some antipsychotics are described as “metabolic neutral” they are still capable of inducing metabolic side effects ⁵



1. Abosi O et al. Horm Mol Biol Clin Invest. 2018;20170065. 2. Bak M et al. Plos ONE. 2014;9:e94112. 3. Mamakou V et al. Psychiatriki. 2018;29(1):64-73. 4. Correll CU et al. World Psychiatry. 2015;14:119. 5. Sifakis S et al. Curr Neuropharmacol. 2018;16:1210

Metabolic Comorbidities: Weight & Obesity

Key Objectives



Epidemiology

Relationship between Obesity and Mental
Illness

Associated Physical Consequences

Recognized Need for Obesity Treatment in
the Mental Health Population

Defining Adult Overweight and Obesity

- Body Mass Index (BMI) is a person's weight in kilograms divided by the square of height in meters.
- BMI appears to be strongly correlated with various metabolic and disease outcomes.¹
- Weight that is higher than what is considered as a healthy weight for a given height is described as overweight or obese.²

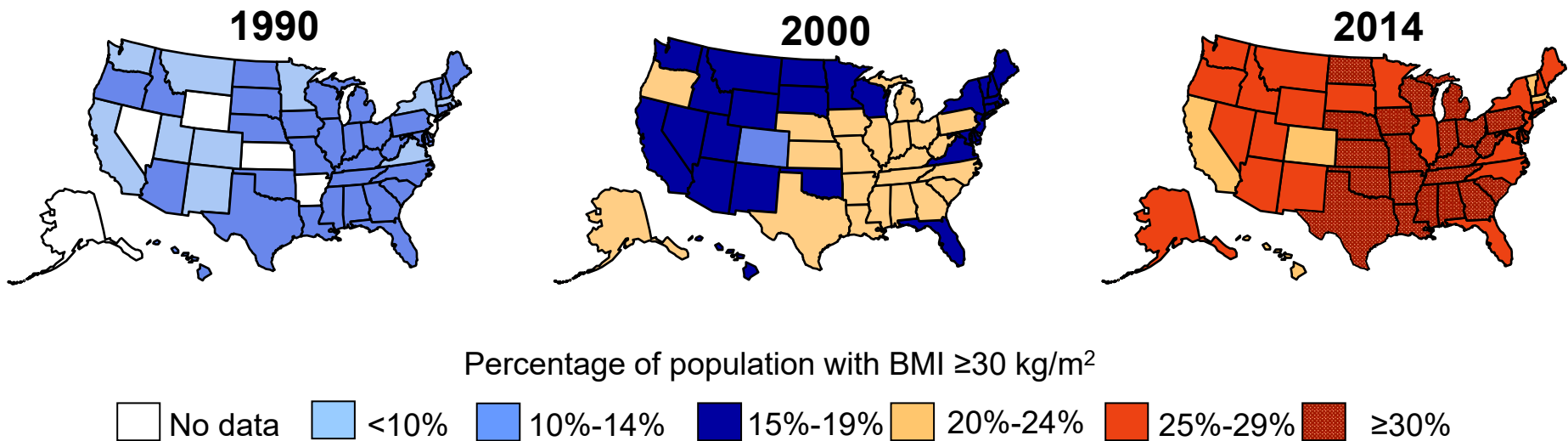
BMI ²	Range
18.5	Underweight
18.5 to <25	Normal
25.0 to <30	Overweight range
30.0	Obese

1. About Adult BMI. https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

2. Defining Adult Overweight and Obesity. <https://www.cdc.gov/obesity/adult/defining.html>

One-third of Adult Americans Are Obese¹

The prevalence of obesity is increasing in the United States, with an overall age-adjusted prevalence of 37% in 2014²

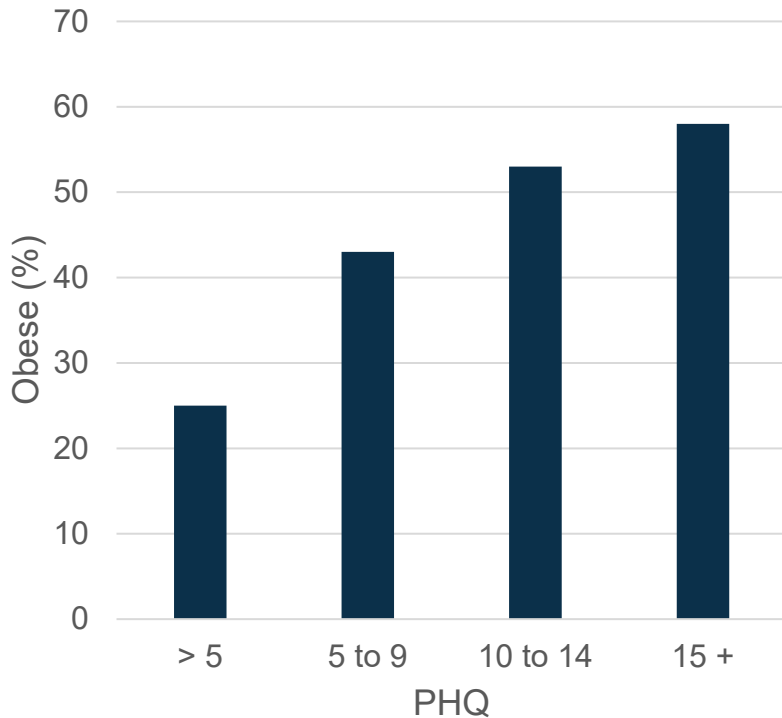


BMI, body mass index.

1. Centers for Disease Control and Prevention. <https://www.cdc.gov/nchs/data/databriefs/db219.pdf>. Accessed April 24, 2017.
2. Flegal et al. *JAMA*. 2016;315:2284-2291.
3. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm. Accessed April 27, 2017

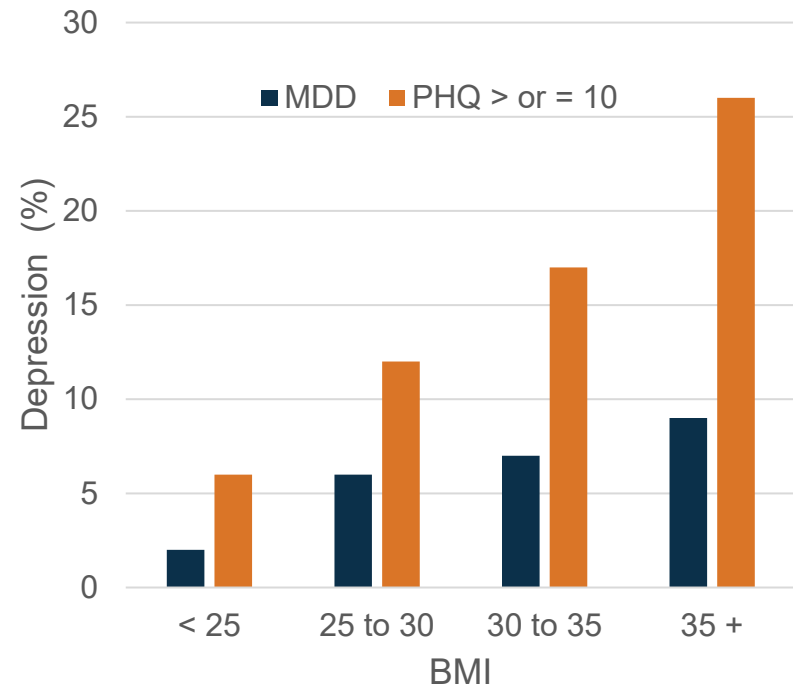
Bidirectional Relationship between Obesity and Depression

Depression Associated with Obesity



Prevalence of obesity (BMI \geq 30) according to PHQ depression score

Obesity Associated with Depression



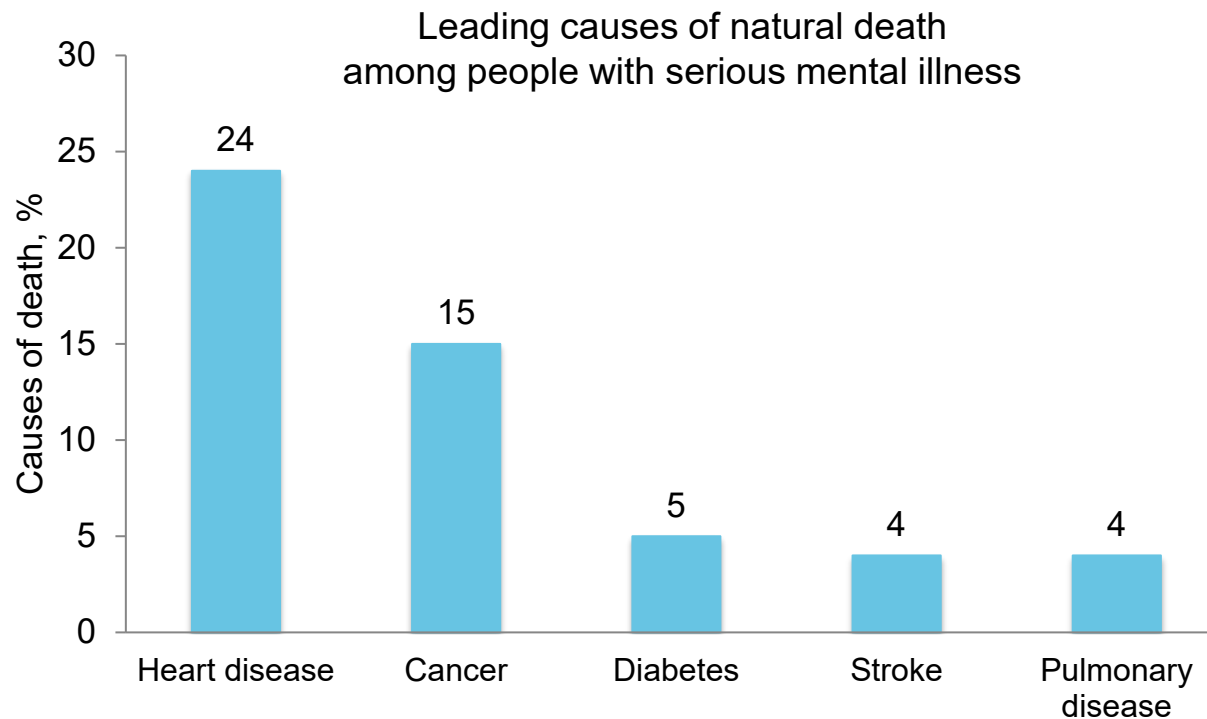
Prevalence of current depression according to Body Mass Index

BMI = Body Mass Index; PHQ = Patient Health Questionnaire

Simon GE General Hosp Psychiatry 2008;30(1):32-39

Obesity Contributes to Mortality in People With Mental Illness

The most common causes of death among people with serious mental illness were attributable to conditions linked with obesity^{1,2}



1. Daumit et al. *Psychiatry Res.* 2010;176:242-245.

2. Centers for Disease Control and Prevention. <https://www.cdc.gov/vitalsigns/adultobesity/infographic.html>. Accessed April 24, 2017.

Addressing Obesity in Patients with Mental Illness

Nonpharmacological interventions have been shown to reduce antipsychotic-associated weight gain and cardiometabolic perturbations¹

- Interventions such as nutritional counseling, exercise interventions, and cognitive behavioral therapy were associated with significant improvements in weight, body mass index, waist circumference, body fat, insulin levels, fasting glucose levels, and total cholesterol compared with controls

More recent data also indicate a positive effect of lifestyle interventions targeting weight loss in patients with serious mental illness²

- However, many of the interventions assessed were resource-intensive and time limited

Further research is needed to identify specific strategies that positively impact obesity and assess long-term maintenance of health benefits in individuals with mental illness. There is currently limited data assessing the efficacy and safety of commonly used diets or other weight-loss strategies in patients with mental health.

1. Caemmerer et al. *Schizophrenia Research*. 2012;140:159-168. 2. Aschbrenner et al. *J Soc Social Work Res*. 2016;7:289-313.

Metabolic Side Effects: Weight Gain

Antipsychotics

- Antipsychotics have been associated with clinically relevant weight gain ($\geq 7\%$)¹
- The propensity for weight gain differs between antipsychotics, however, no agent should be considered “weight-neutral”²
- Some agents can stimulate appetite³

Antidepressants

- Antidepressants have been associated with mild or moderate weight gain¹
- Some agents can stimulate appetite³



Combination therapy

- Combination therapy has been associated with weight gain ($\geq 7\%$)⁴
- The adverse effect of weight gain shared by antipsychotics and antidepressants could be potentially additive⁵

1. Correll CU et al. *World Psychiatry*. 2015;14:119.
2. Carey M et al. *Pilot and Feasibility Studies*. 2018;4:186.
3. Hasnain M et al. *Postgrad Med*. 2012;124:154-167.

4. Brunner E et al. *Neuropsychopharm*. 2014;39:2549.
5. Mao Y and Zhang D. *Neuropsychiatry Dis Treat*. 2015;11:701-713.

Metabolic Comorbidities: Diabetes

Key Objectives



Epidemiology



Relationship between Diabetes
and Mental Illness



Recognizing Diabetes in Mental
Health



Guidelines for Diabetes and
Mental illness

ADA: Recognizing Diabetes

	Type 1 diabetes	Type 2 diabetes	Gestational diabetes
Cause/Definition¹	Autoimmune process causes insulin deficiency	Progressive insulin resistance	Pregnancy-related diabetes (usually 2nd or 3rd trimester)
Nature of the disease	Rapid onset; incurable ²	Slower onset; often unnoticed ²	High blood sugar from placental hormones ¹
Key risk factors^{2,3}	<ul style="list-style-type: none"> • Genetics • Family history • Environmental factors 	<ul style="list-style-type: none"> • Genetics • Family history • Physical inactivity • Excessive body weight • Older age • Prior gestational diabetes • Elevated prolactin in men and nonpregnant women³ 	<ul style="list-style-type: none"> • Previous diagnosis of gestational diabetes • Certain indigenous populations • Age (>25 years) • Family over personal history of type 2 diabetes • Overweight or obesity

ADA, American Diabetes Association.

1. American Diabetes Association. *Diabetes Care*. 2017;40(suppl 1):S11-S24. 2. International Diabetes Foundation. <http://www.diabetesatlas.org>. Accessed April 26, 2017. 3. Therkelsen et al. *J Am Heart Assoc*. 2016;5:e002640. 3. Mayo Clinic. <http://www.mayoclinic.org/diseases-conditions/gestational-diabetes/symptoms-causes/dxc-20317176>. Accessed May 23, 2017.

ADA: Evaluating Risk and Diagnosing Diabetes

ADA recommendations for prediabetes or diabetes testing in asymptomatic adults

- Overweight or obese adults (BMI ≥ 25 kg/m²) with other risk factors
- All adults, beginning at 45 years of age
- Repeat tests with normal results every 3 years

Metabolic test	Prediabetes	Diabetes
FPG	100 to 125 mg/dL	≥ 126 mg/dL*
OR 2-hour plasma glucose	140 to 199 mg/dL	≥ 200 mg/dL
OR HbA1c	5.7% to 6.4%	$\geq 6.5\%$
OR Random plasma glucose	–	≥ 200 mg/dL with classic hyperglycemia symptoms

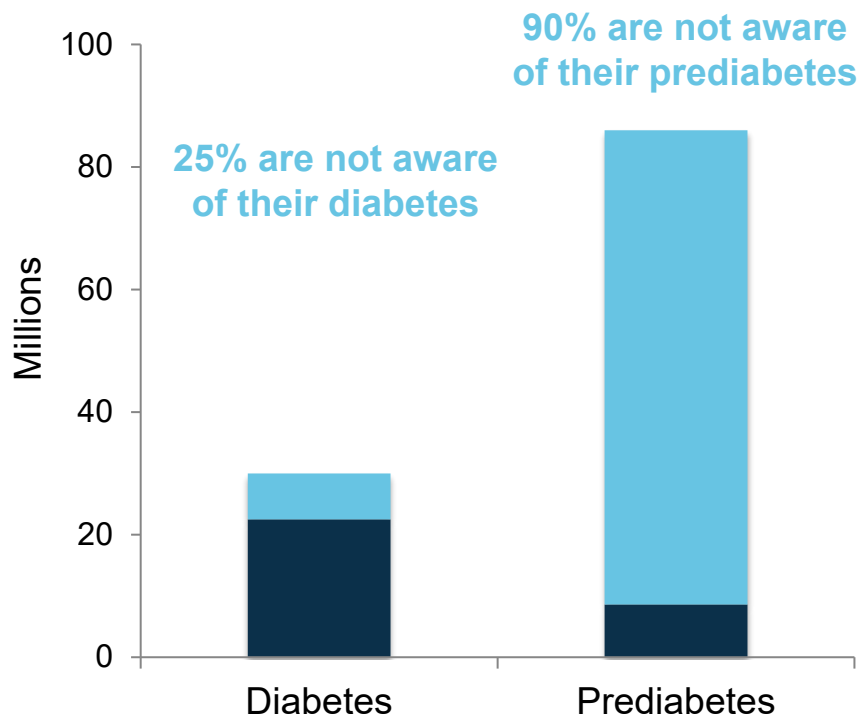
ADA, American Diabetes Association; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

*In the absence of unequivocal hyperglycemia, repeat testing should be performed to confirm result.

American Diabetes Association. *Diabetes Care*. 2017;40(suppl 1):S11-S24.

Diabetes Mellitus: an American Epidemic

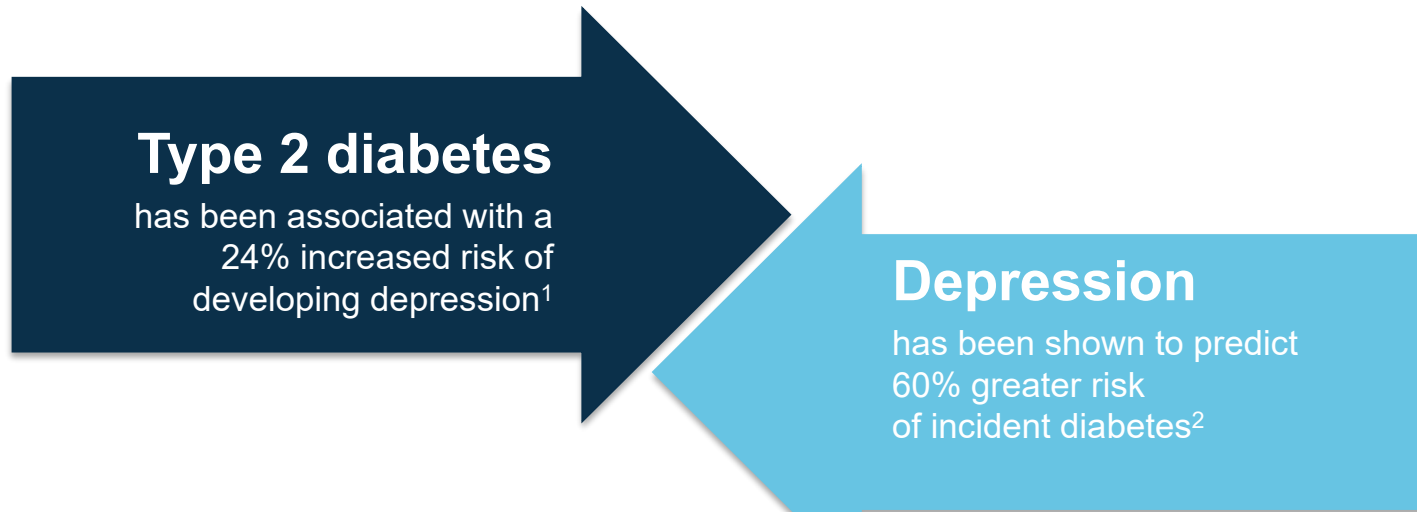
Many Americans are not aware of their glycemic control risk



- Nearly 30 million US adults have diabetes
 - Another 86 million have prediabetes
- Diabetes was the 7th leading cause of death in the United States in 2013
 - More than 20% of US healthcare spending is related to diabetes management

Centers for Disease Control and Prevention. <https://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2016/diabetes-aag.pdf>. Accessed April 26, 2017.

Diabetes and Depression: an Inextricable Relationship



Approximately 16% of US adults
with diabetes have depression³
Patients with depression have
higher rates of incident diabetes
than those without⁴

1. Nouwen et al. *Diabetologia*. 2010;53:2480-2486. 2. Mezuk et al. *Diabetes Care*. 2008;31:2383-2390. 3. Li et al. *Diabetes Care*. 2008;31:105-107. 4. Rotella and Mannucci. *J Clin Psychiatry*. 2013;74:31-37.

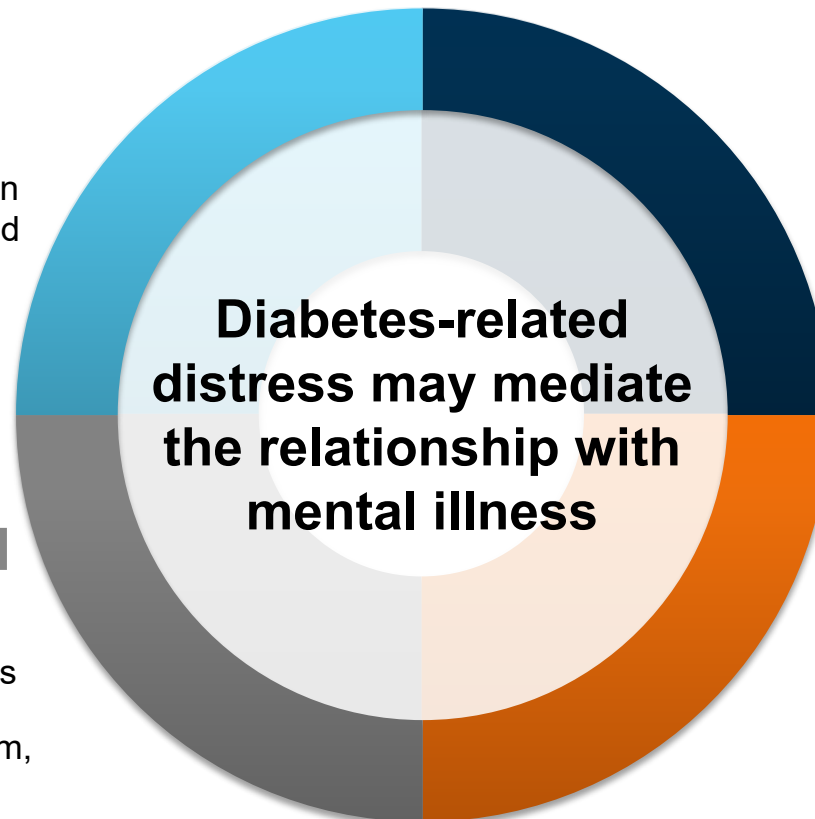
Proposed Mechanisms of the Relationship Between Diabetes and Mental Illness

Biologic pathways

Shared physiological factors such as inflammation, circadian rhythms, insulin resistance, and the hypothalamic pituitary-adrenal axis

Behaviors and risk factors

Shared challenges such as reduced physical activity, self-neglect, low self-esteem, and increased smoking



Socioeconomics and environment

Shared factors such as lower income and greater social adversity

Burden of chronic disease

The psychological burden of dealing with a chronic disease

Moulton et al. *Lancet Diabetes Endocrinol.* 2015;3:461-471.

ADA and APA: Coordinating Mental Health Care and Diabetes Care

The APA and ADA recommend routine screening of patients and communication among mental and physical health care providers^{1,2}

- APA and ADA recommend healthcare providers screen for common medical conditions and counsel patients to reduce preventable cardiovascular risk factors¹
 - Annual screening for patients taking atypical antipsychotics and careful monitoring of patients taking second-generation antipsychotics²
 - Annual screening and coordination with mental health care provider²

Examples of triggers and flags for anxiety, depression, and disordered eating behaviors

- ✓ Fear of hypoglycemia
- ✓ Fear of insulin or injections
- ✓ Fear of serious complications
- ✓ Hypoglycemia unawareness
- ✓ Avoidance behaviors
- ✓ Social withdrawal
- ✓ Onset of complications
- ✓ Significant change in medical status
- ✓ Unexplained hyperglycemia
- ✓ Unexplained weight loss

ADA, American Diabetes Association; APA, American Psychiatric Association.

1. American Psychiatric Association. <http://apps.psychiatry.org/pdfs/position-statement-role-of-psychiatrists.pdf>. Accessed April 27, 2017.

2. American Diabetes Association. *Diabetes Care*. 2017;40(suppl 1):S25-S32.

Metabolic Side Effects: Diabetes

Antipsychotics

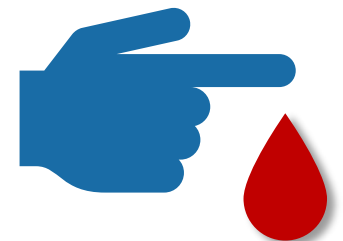
- Antipsychotics have been significantly associated with hyperglycemia, which can result in T2DM, metabolic acidosis or ketosis^{1,2}
- The associated increased risk for diabetes may occur independent of weight gain¹

Antidepressants

- A meta-analysis showed a significant link between antidepressants and diabetes, but the strength of this association varied between studies³

Combination therapy

- Some studies have reported increased blood glucose levels with combination therapy versus antidepressants alone^{4,5}
- Other studies, however, have reported no changes in blood glucose levels with combination therapy⁶




T2DM, type 2 diabetes mellitus.

1. Correll CU et al. *World Psychiatry*. 2015;14:119.
2. Llorente MD and Urrutia V. *Clinical Diabetes*. 2006;24:18-24.
3. Salvi V et al. *PLoS ONE*. 2017;12:e0182088;

4. Earley WR et al. *Psychopharmacol Bull*. 2018;48:62.
5. Brunner E et al. *Neuropsychopharm*. 2014;39:2549.
6. Berman RM et al. *Neuropsychiatric Dis Treat*. 2011;7:303.

Metabolic Comorbidities: CVD

Key Objectives



Epidemiology – Prevalence



Bidirectional Relationship between CVD and MDD



Pathophysiology and Guidelines

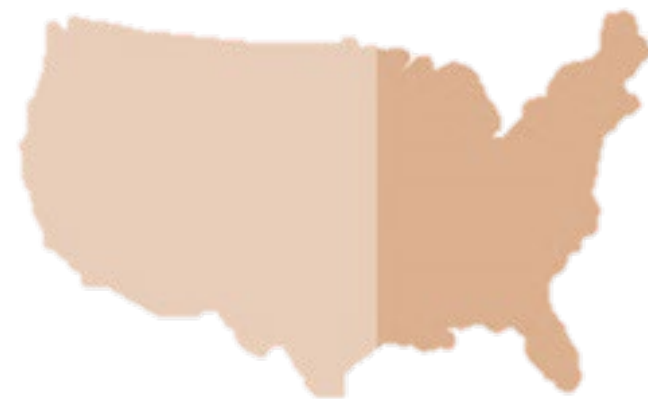


Lipids & Metabolic Syndrome

Cardiovascular diseases affect nearly half of American adults

By 2035, more than **130** million adults, or **45.1%** of the US population, are projected to have some form of Cardiovascular Disease.

Total costs of CVD are expected to reach \$1.1 trillion in 2035, with direct medical costs projected to reach \$748.7 billion and indirect costs estimated to reach \$368 billion.

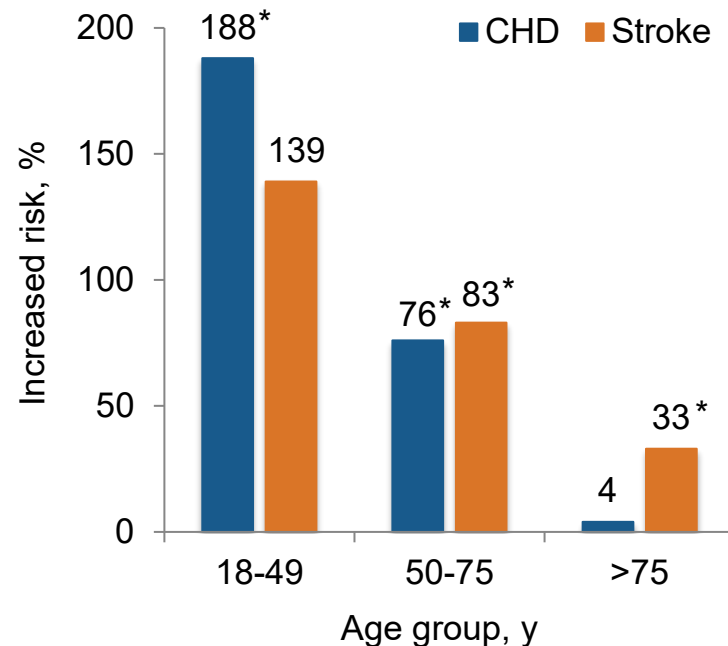
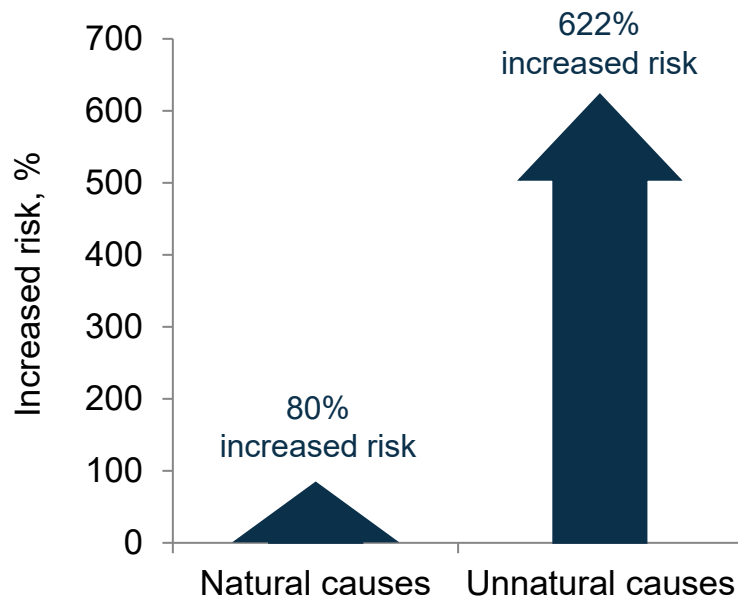


Benjamin EJ et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019 Mar 5;139(10):e56-e528

Mental Illness Bears Excess Mortality Risk, Including From Heart Disease and Stroke

People with mental disorders had 122% higher all-cause mortality relative risk compared with general population controls¹

Higher relative risk of mortality overall and from heart disease or stroke^{1,2}

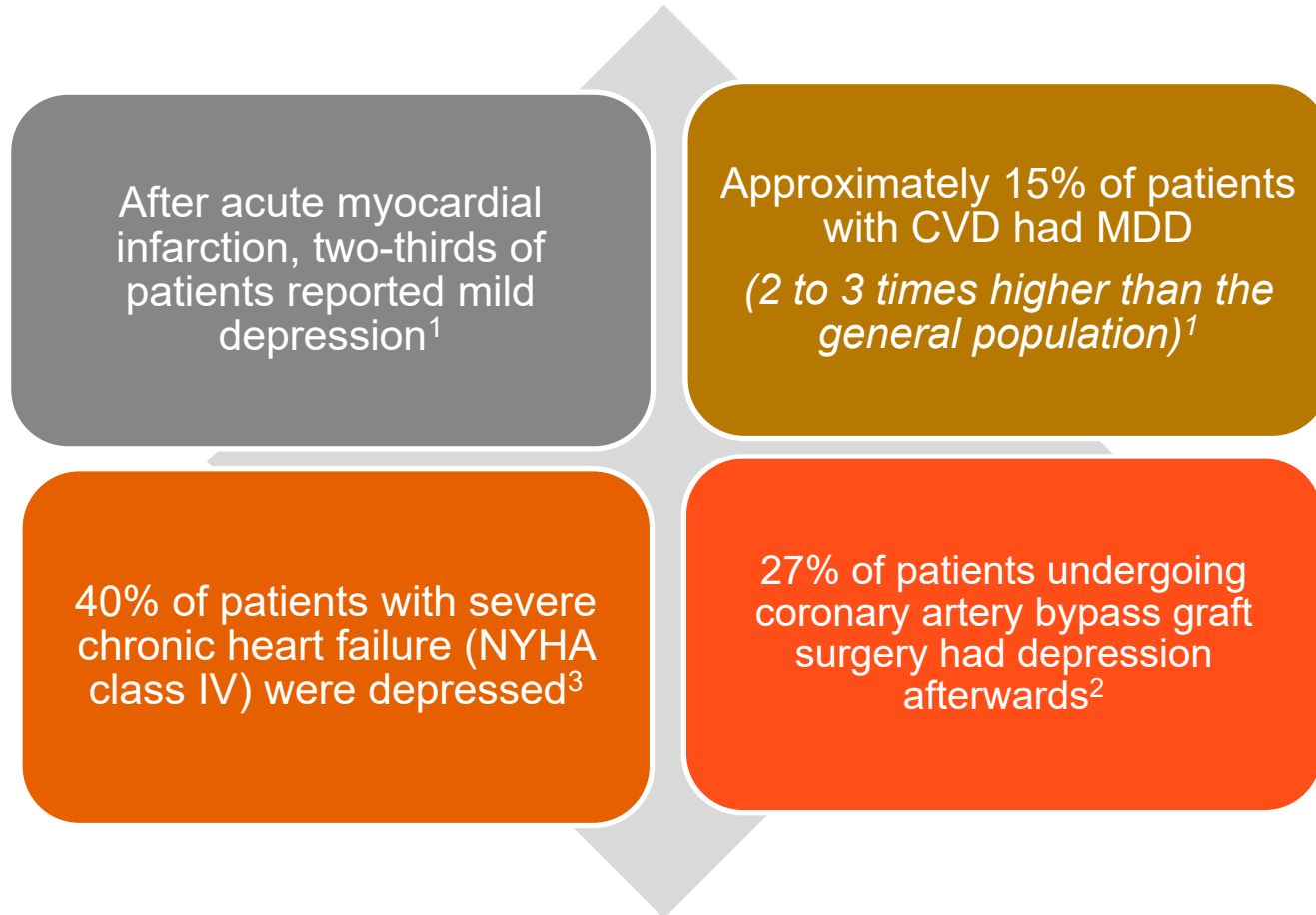


CHD, coronary heart disease.

*95% confidence interval does not include 1.0.

1. Walker et al. *JAMA Psychiatry*. 2015;72:334-341.
2. Osborn et al. *Arch Gen Psychiatry*. 2007;64:242-249.

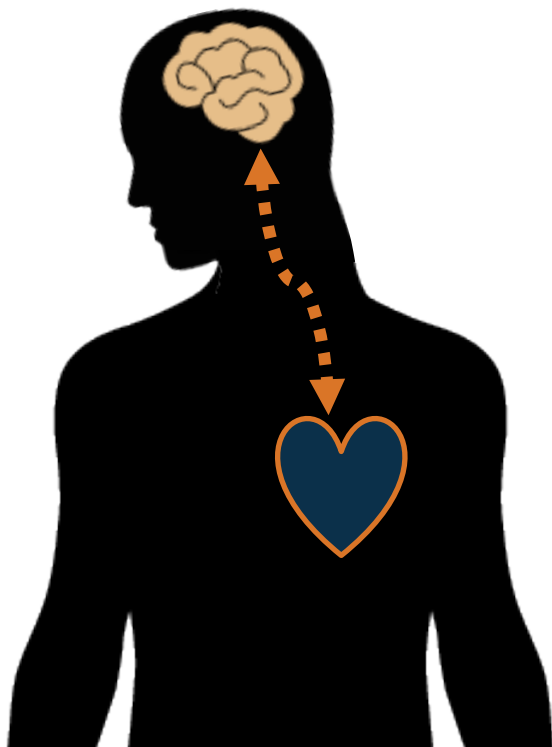
Depression Is Highly Prevalent in Patients With Cardiovascular Disease



CVD, cardiovascular disease; MDD, major depressive disorder; NYHA, New York Heart Association.

1. Hare et al. *Eur Heart J*. 2014;35:1365-1372. 2. Khawaja et al. *Psychiatry* 2009;6:38-51. 3. Rutledge et al. *J Am Coll Cardiol* 2006;48:1527-1537

Depression and Cardiovascular Disease: A Bidirectional, Multifaceted Relationship



Depression doubles the risk of developing new cardiovascular disease¹ and may be associated with greater cardiac complications²

Depression is 3 times more frequent in patients after an acute MI than in the general community and may be associated with worse prognosis³

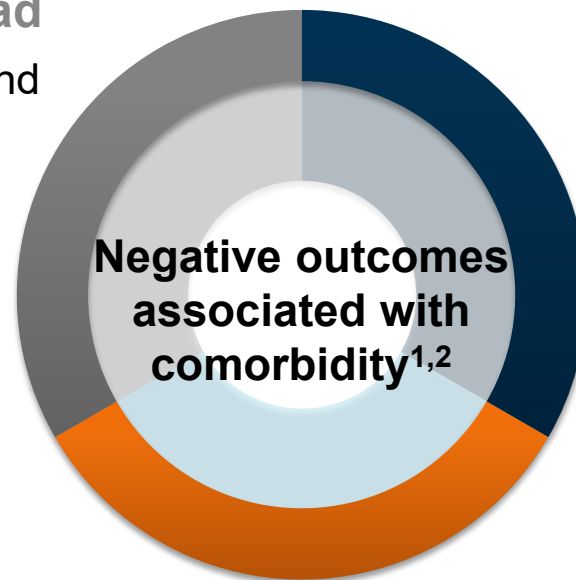
MI, myocardial infarction.

1. Hare et al. *Eur Heart J*. 2014;35:1365-1372. 2. Khawaja et al. *Psychiatry* 2009;6:38-51. 3. Lichtman et al. *Circulation*. 2008;118:1768-1775.

Depression and Cardiovascular Disease Comorbidity Is Associated With Poor Outcomes

After myocardial infarction, patients with depression had

- More medical comorbidities and cardiac complications¹
- 3-fold increase in mortality²
- 41% higher 1-year health costs¹



Patients with acute coronary syndrome and history of depression reported¹

- Triple the physical limitations
- Almost triple the risk of diminished health-related quality of life
- Twice the rate of angina

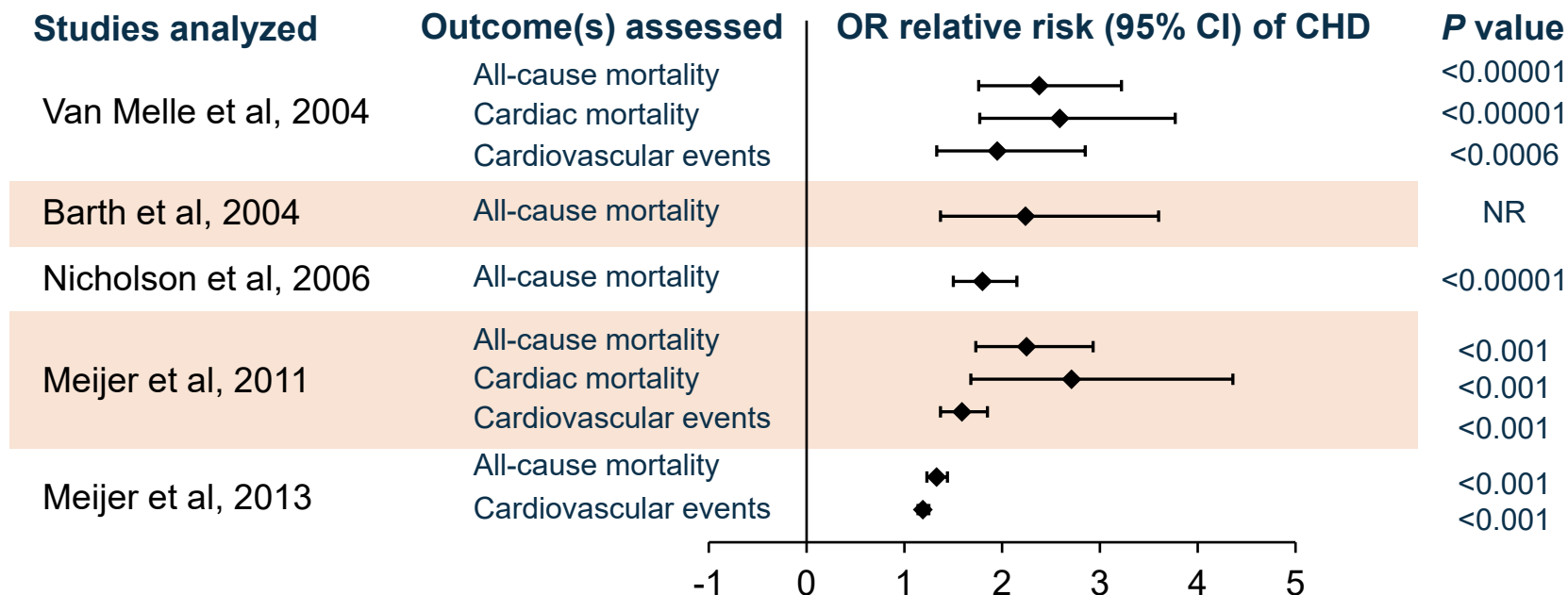
Patients with chronic heart disease and depression reported¹

- Depression as the most important correlate of diminished quality of life
- More days in bed due to illness
- More ambulatory and emergency room visits
- Increased functional disability

1. Davidson. *ISRN Cardiology*. 2012;2012:1-18. 2. Hare et al. *Eur Heart J*. 2014;35:1365-1372.

Depression Is a Predictor of Mortality in Patients With Established Coronary Heart Disease

In patients with established CHD, depression was predictive of all-cause mortality and cardiac-related mortality¹



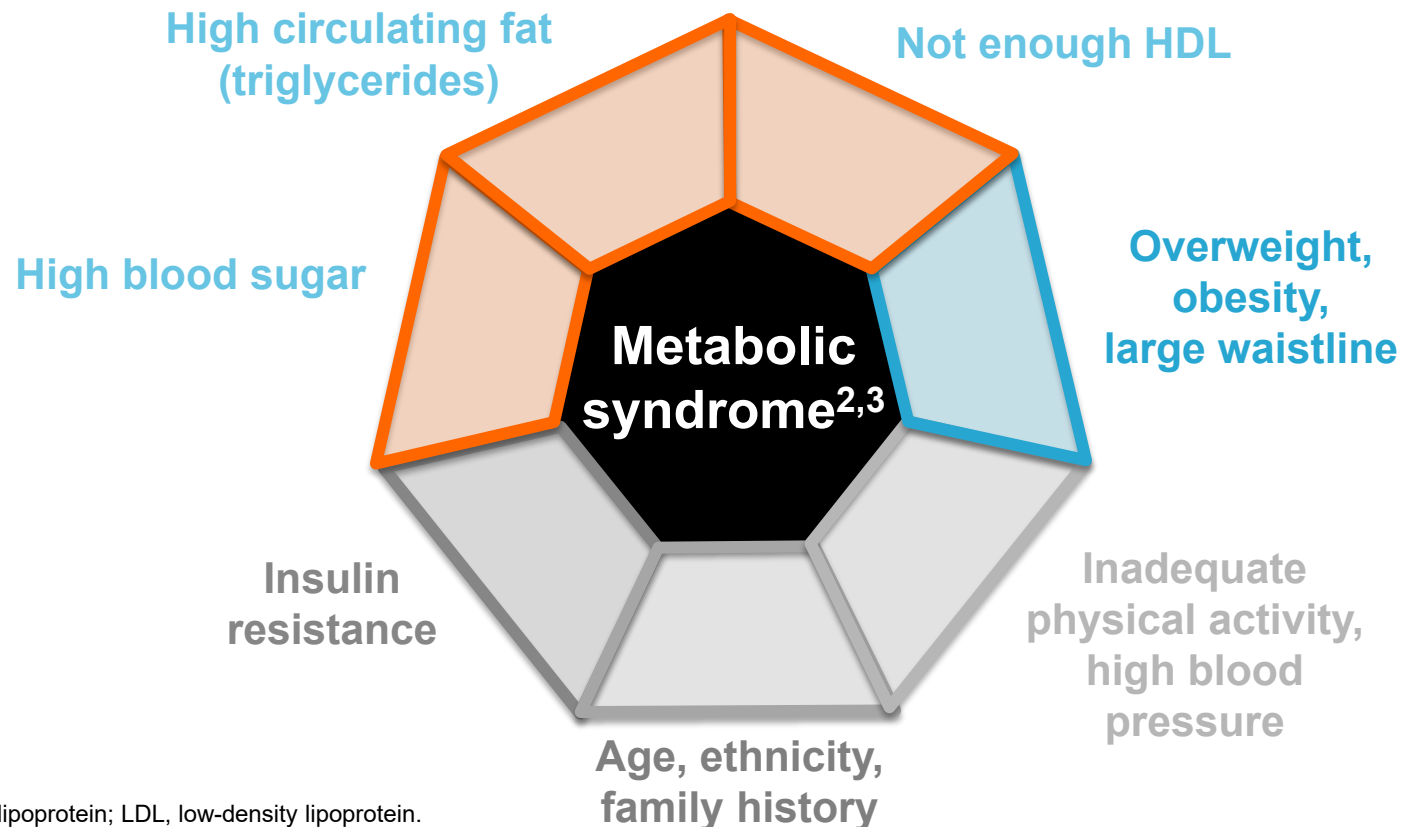
Following a meta-analysis of 53 studies, an AHA expert panel recommended that depression be elevated to the status of a risk factor for poor prognosis in patients with ACS²

ACS, acute coronary syndrome; AHA, American Heart Association; CHD, coronary heart disease; CI, confidence interval; NR, not reported; OR, odds ratio.

1. Carney and Freedland. *Nat Rev Cardiol.* 2017;14:145-155. 2. Lichtman et al. *Circulation.* 2014;129:1350-1369.

Lipids and Metabolic Syndrome

Triglycerides are stored fat, which, like cholesterol, does not dissolve in the bloodstream and contributes to a constellation of metabolic risk factors¹



HDL, high-density lipoprotein; LDL, low-density lipoprotein.

1. Mayo Clinic. <http://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/in-depth/triglycerides/art-20048186?p=1>. Accessed June 5, 2017. 2. National Heart, Lung, and Blood Institute. <https://www.nhlbi.nih.gov/health/health-topics/topics/ms/causes>. Accessed May 5, 2017. 3. NHLBI. <https://www.nhlbi.nih.gov/health/health-topics/topics/ms/diagnosis>. Accessed May 5, 2017.

High Lipid Levels Are a Warning Sign of Risk for Heart Disease

A lipid panel can diagnose hyperlipidemia, but additional cardiovascular risk factors should be considered simultaneously

Hyperlipidemia from the lipid panel¹

TOTAL CHOLESTEROL
≥240 mg/dL

LDL CHOLESTEROL
160 to 189 mg/dL (high)
≥190 mg/dL (very high)

HDL CHOLESTEROL
<40 mg/dL



Other major risk factors²

FACTORS BEYOND LDL

- ✓ Age (men ≥45 y, women ≥55 y)
- ✓ Blood pressure 140/90 mmHg
- ✓ Cigarette smoking
- ✓ Family history of premature CHD

CLINICAL ATHEROSCLEROSIS

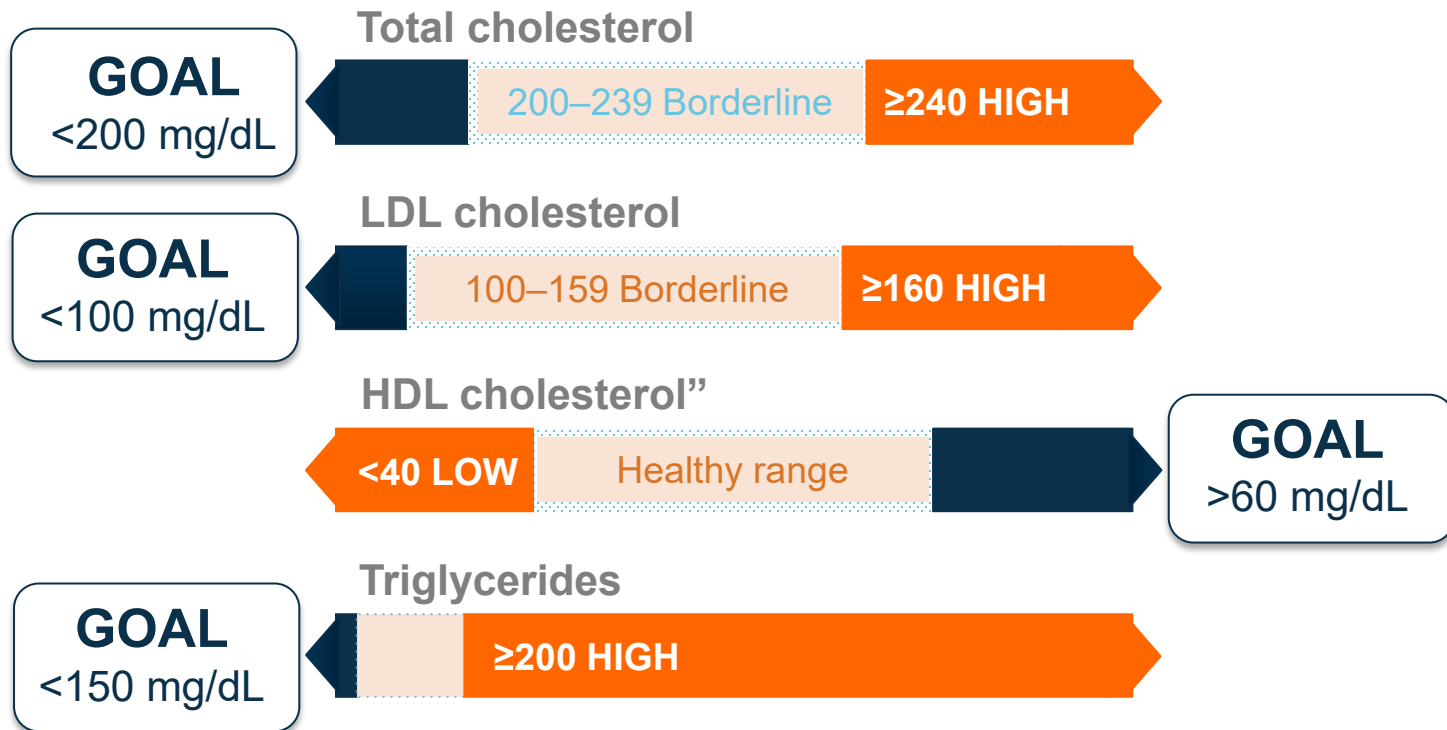
- ✓ CHD
- ✓ Symptomatic carotid artery disease
- ✓ Peripheral arterial disease
- ✓ Abdominal aortic aneurysm

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

1. National Heart, Lung, and Blood Institute. <https://www.nhlbi.nih.gov/health/health-topics/topics/hbc/diagnosis#>. Accessed May 16, 2017. 2. National Heart, Lung, and Blood Institute. <https://www.nhlbi.nih.gov/health-pro/guidelines/current/cholesterol-guidelines/quick-desk-reference.html>. Accessed May 5, 2017.

National Heart, Lung, and Blood Institute ATP III Guidelines

LDL levels are the most prominent determinant of management decisions for lifestyle and pharmacotherapy strategies



ATP III, Adult Treatment Panel III; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

National Heart, Lung, and Blood Institute. <https://www.nhlbi.nih.gov/health-pro/guidelines/current/cholesterol-guidelines/quick-desk-reference.html>. Accessed May 5, 2017.

Metabolic Side Effects: Dyslipidemia

Antipsychotics

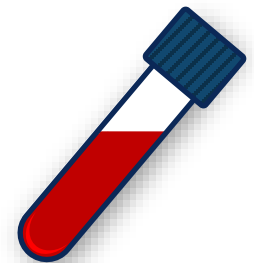
- Antipsychotics have been associated with varying degrees of dyslipidemia, which can precede weight gain¹
- The most common abnormalities are decreased HDL-C and increased triglyceride levels²

Antidepressants

- Antidepressants may not be directly associated with dyslipidemia; however, weight gain is a risk factor for lipid abnormalities¹

Combination therapy

- Some studies showed increased lipid levels with combination therapy versus antidepressants alone^{3,4}
- Other studies, however, have shown no differences in lipid levels after starting combination therapy^{5,6}



HDL-C, high-density lipoprotein cholesterol.

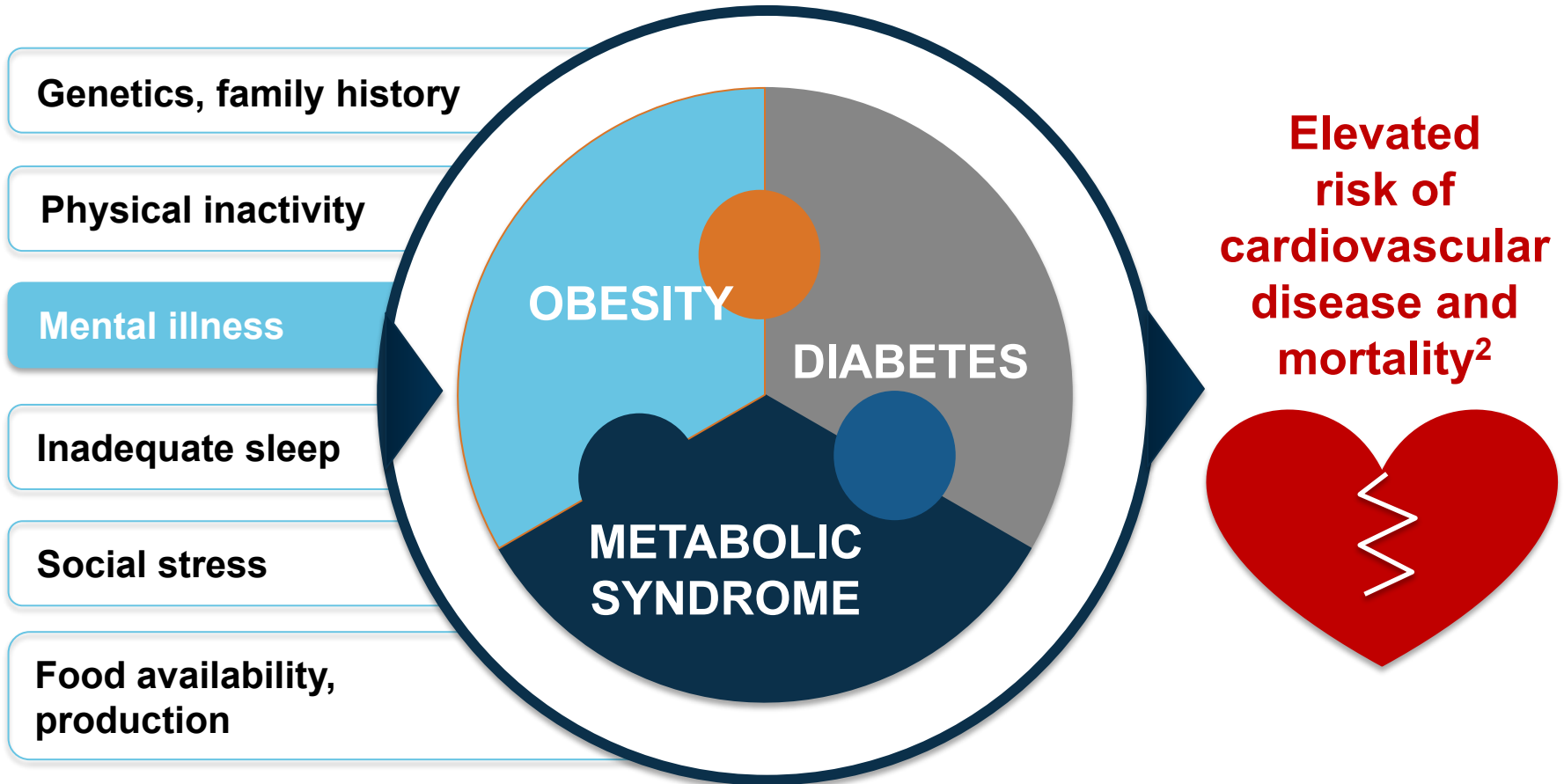
1. Correll CU et al. *World Psychiatry*. 2015;14:119.
2. Lambert T et al. *Aust Prescr*. 2011;4:97-99.
3. Thase ME et al. *J Clin Psychiatry*. 2015;76:1224.

4. Earley WR et al. *Psychopharmacol Bull*. 2018;48:62.
5. Brunner E et al. *Neuropsychopharm*. 2014;39:2549.
6. Berman RM et al. *Neuropsychiatric Dis Treat*. 2011;7:303.

Monitoring Metabolic markers



Mental Illness and Obesity Are Key Contributors to Cardiovascular Risk¹



1. Padwal and Sharma. *Can J Cardiol.* 2010;26(suppl C):18-20. 2. American Heart Association. http://www.heart.org/HEARTORG/Conditions/More/Diabetes/WhyDiabetesMatters/Cardiovascular-Disease-Diabetes_UCM_313865_Article.jsp/#.WP5owRiZMb0. Accessed April 24, 2017.

Monitoring for Metabolic Parameters

International guidelines suggest that patients taking atypical antipsychotics should be monitored regularly by their mental health care provider for basic metabolic markers¹

Basic monitoring	United States ¹	Canada ²	United Kingdom ²	Australia ²
Medical and family history	✓	✓	✓	✓
Weight (BMI)	✓	✓	✓	✓
Waist circumference	✓	✓	✓	✓
Blood pressure	✓		✓	✓
Fasting glucose	✓	✓	✓	✓
Fasting lipids	✓	✓	✓	✓

BMI, body mass index.

1. American Diabetes Association et al. *Diabetes Care*. 2004;27:596-601. 2. Chwastiak et al. *Lancet Psychiatry*. 2015;2:465-476.

ADA and HEDIS: Metabolic Monitoring Standards for Patients With Mental Illness

ADA guidelines and HEDIS quality measures are aligned regarding the care of patients with metabolic, cardiovascular, and mental health concerns^{1,2}

ADA recommendations¹

- ✓ Annual screening for prediabetes or diabetes in patients taking atypical antipsychotics
- ✓ Regular monitoring of weight, glycemic control, and cholesterol levels in adults and adolescents with diabetes taking second-generation antipsychotics
- ✓ Include diabetes monitoring and self-care in management goals of patients with diabetes and serious mental illness

Related HEDIS measures^{2,3}

1. Diabetes screening in the past year for adults with schizophrenia or bipolar disorder taking an antipsychotic medication
2. HbA1c and LDL tests in the past year for adults with schizophrenia and diabetes
3. LDL test in the past year for adults with schizophrenia and cardiovascular disease
4. Metabolic testing in the past year for children and adolescents taking an antipsychotic medication

ADA, American Diabetes Association; HbA1c, glycated hemoglobin; HEDIS, Healthcare Effectiveness Data and Information Set; LDL, low-density lipoprotein

1. American Diabetes Association. *Diabetes Care*. 2017;40(suppl 1):S25-S32. 2. National Committee for Quality Assurance. <http://www.ncqa.org/report-cards/health-plans/state-of-health-care-quality/2016-table-of-contents/schizophrenia>. Accessed May 12, 2017. 3. National Committee for Quality Assurance. <http://www.ncqa.org/report-cards/health-plans/state-of-health-care-quality/2016-table-of-contents/metabolic-monitoring-for-children-and-adolescents-on-antipsychotics>. Accessed May 12, 2017.

Conclusions

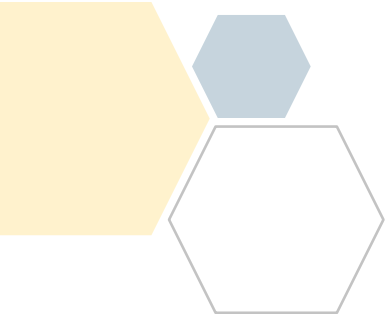
- Severe mental illness is associated with increased:
 - Burden of CV mortality and morbidity ¹
 - Prevalence of CV Risk factors ^{2,3}
- Major depressive disorder (MDD) shares a highly co-morbid, complex, multifactorial, bidirectional relationship with Cardiovascular disease, Obesity, and Diabetes Mellitus.
- Psychosocial, biological, and behavioral mechanisms may underlie the shared pathophysiology between MDD and cardiovascular disease.

1. Abosi O et al. *Horm Mol Biol Clin Invest*. 2018;20170065.

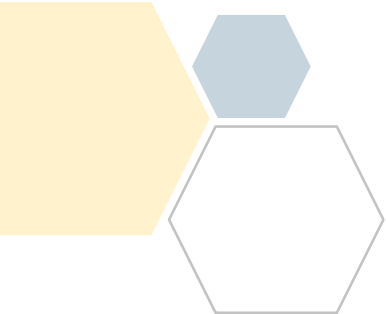
2. Bak M et al. *Plos ONE*. 2014;9:e94112.

3. Mamakou V et al. *Psychiatriki*. 2018;29(1):64-73.

Backup slides

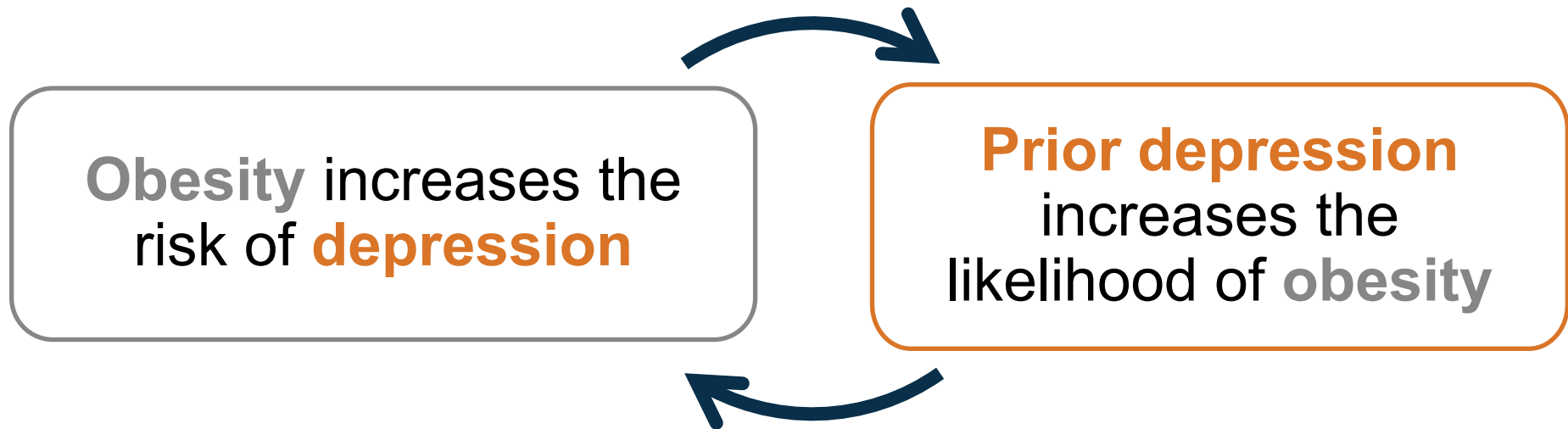


Weight gain and obesity



There Is a Bidirectional Relationship Between Obesity and Mental Illness

Obesity and depression, for example, are each well known to increase the risk of the other



1. Luppino et al. *Arch Gen Psychiatry*. 2010;67:220-229.

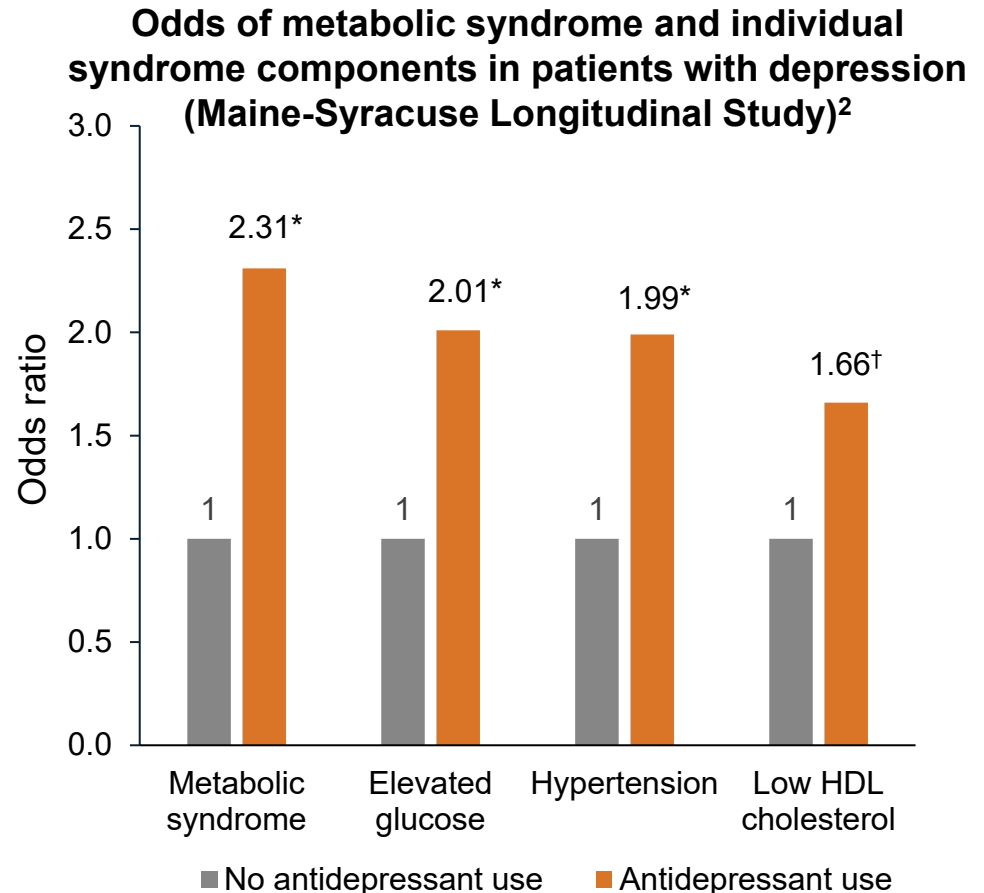
Relationship between Weight Change and Major Depression Diagnosis?

- Appetite and/or weight change is considered one of the DSM 5 criterion for diagnosing major depressive disorder
 - “Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day”¹

1. Medicaid Mental Health. (2017-2018). DSM-5 Criteria: Major Depressive Disorder [PDF file]. Retrieved from https://medicaidmentalhealth.fmhi.usf.edu/_assets/file/Guidelines/2017-2018%20Treatment%20of%20Adult%20Major%20Depressive%20Disorder.pdf

Antidepressants Have Been Associated With Weight Gain and Metabolic Abnormalities

- Weight gain is a common side effect of acute and long-term antidepressant use¹
 - TCAs and MAOIs are more likely to cause weight gain than SSRIs
- Antidepressant use may be associated with²
 - Metabolic syndrome
 - Metabolic syndrome components

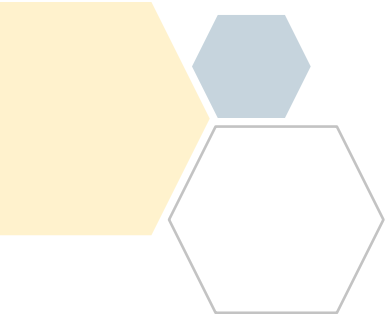


HDL, high-density lipoprotein MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

* $P < 0.01$ vs patients not using antidepressants. † $P < 0.05$.

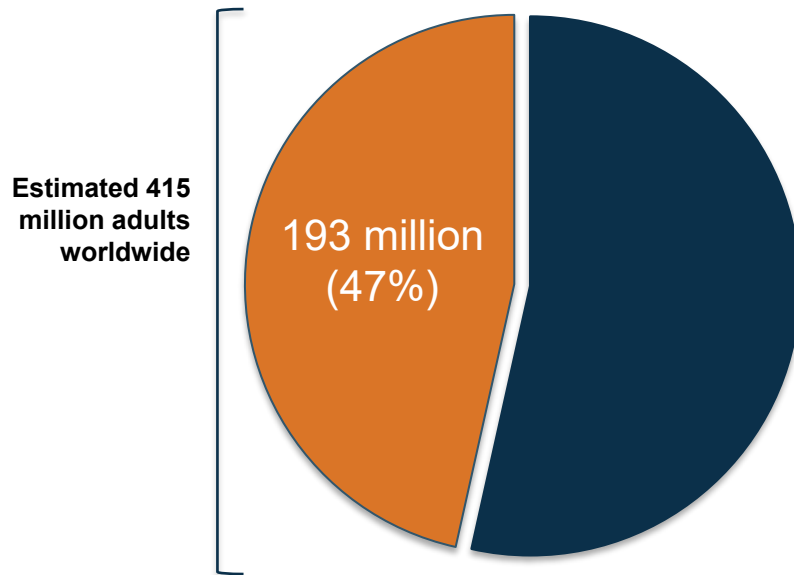
1. Fava. *J Clin Psychiatry*. 2006;61(Suppl11):37-41. 2. Crichton et al. *BMC Public Health*. 2016;16:502.

Diabetes



Diabetes Mellitus: A Global Epidemic

Nearly half of adults with diabetes are undiagnosed

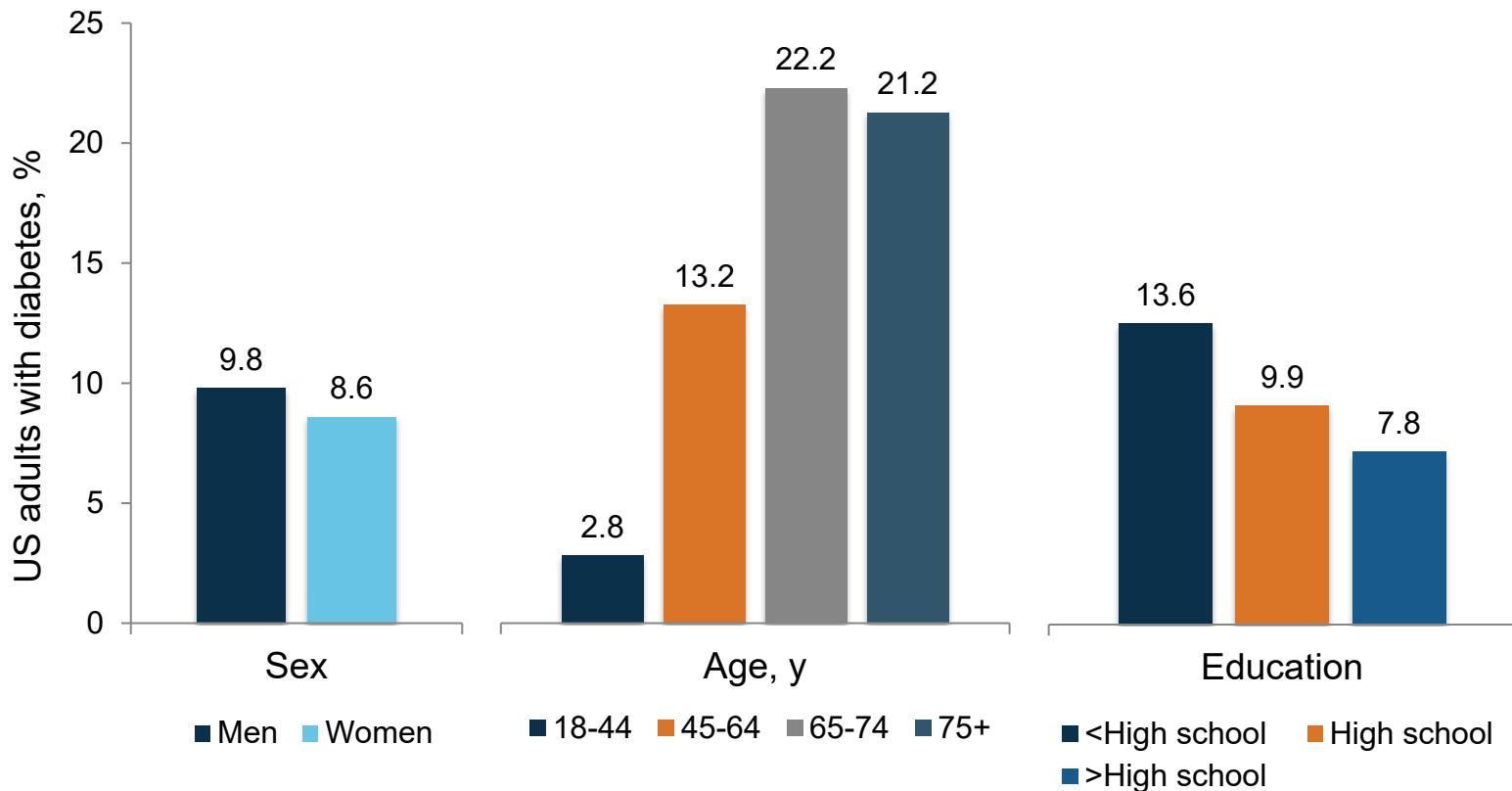


- In 2015
 - 1 in 11 adults worldwide had diabetes
 - Another 300 million had impaired glucose tolerance
 - 5 million deaths were attributable to diabetes

1. International Diabetes Foundation. <http://www.diabetesatlas.org>. Accessed April 26, 2017.

Prevalence Trends Among Americans

In 2014, approximately 9% of Americans had diabetes, with greater prevalence among men, older age groups, and the less educated.



Centers for Disease Control and Prevention. <https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html>. Accessed April 26, 2017.

Effect of Treatments for Mental Health

Atypical antipsychotics have been shown to be associated with obesity and diabetes, which are adversely affected by worsening mental illness^{1,2}

Rates of incident diabetes increased with antipsychotic polypharmacy³

Number of antipsychotics	Incident diabetes risk vs no antipsychotic
1	+48%
2	+68%
3	+96%
4	+138%
5	+241%

- Patients with depression had worse diabetes self-management⁴
- Lifetime depression and anxiety were associated with worse glycemic control, BMI, and other cardiometabolic risk factors²

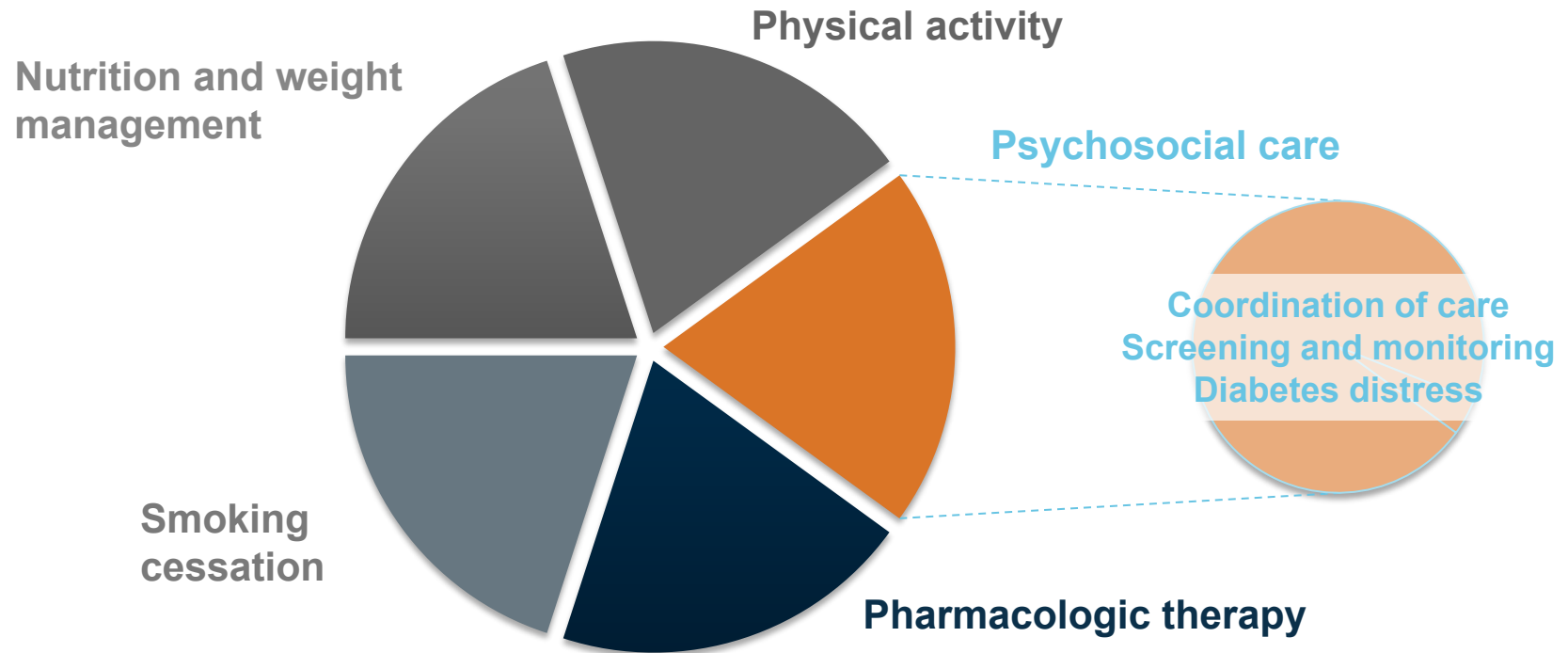
BMI, body mass index.

1. American Diabetes Association et al. *Diabetes Care*. 2004;27:596-601. 2. Whitworth et al. *Diabetes Res Clin Pract*. 2016;122:190-197.

3. Kessing et al. *Brit J Psychiatry*. 2010;197:266-271. 4. Shin et al. *J Diabetes Complications*. 2017;31:880-885.

ADA: Preventing and Managing Diabetes

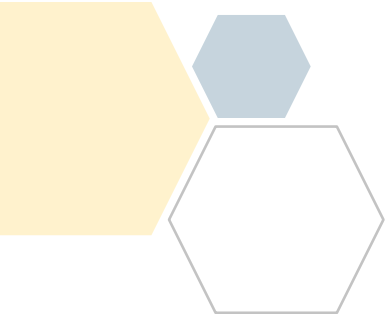
**Self-management education and support
are important factors of diabetes care**



ADA, American Diabetes Association.

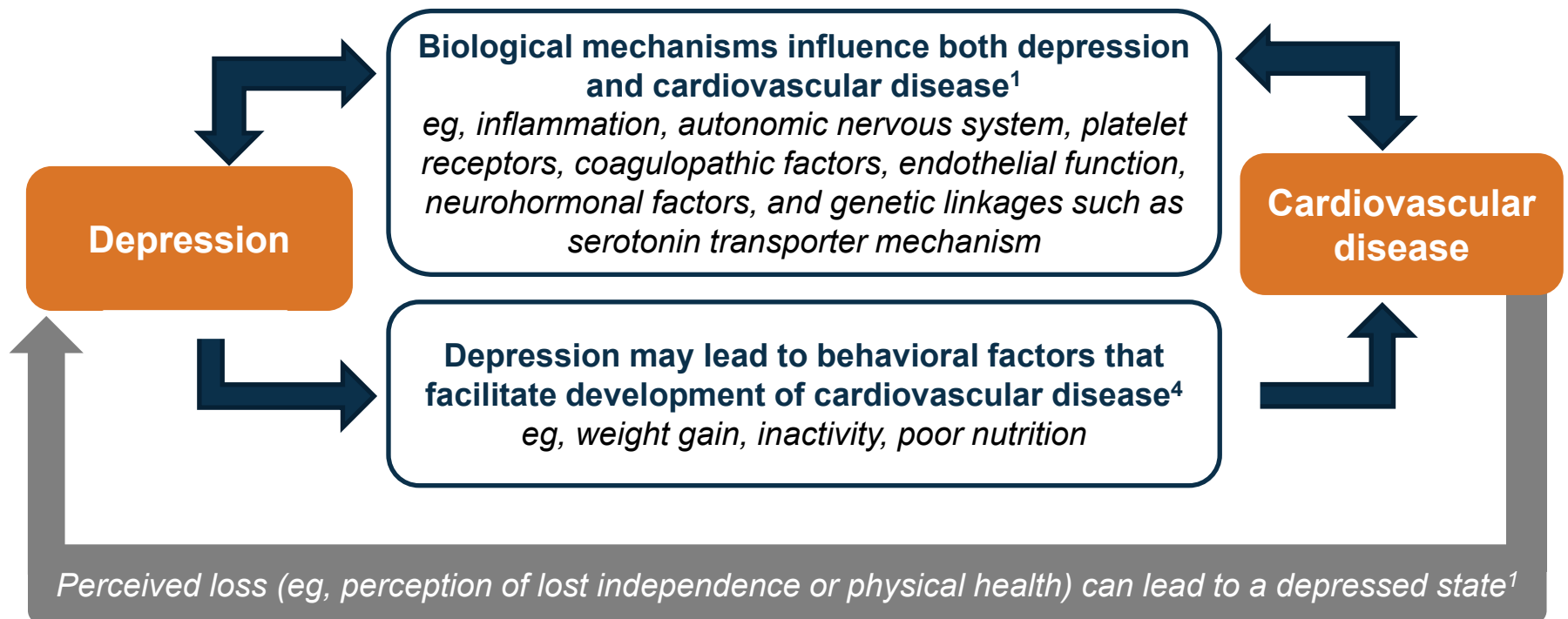
American Diabetes Association. *Diabetes Care*. 2017;40(suppl 1):S33-S43.

Cardiovascular Disease



Complex Relationship Between Depression and Cardiovascular Disease¹

Psychosocial stress can lead to **chronic inflammation** throughout the body, contributing to both depression² and cardiovascular disease³



1. Hare et al. *European Heart Journal*. 2014;35:1365-1372. 2. Miller et al. *Nat Rev Immunol*. 2016;16:22-34. 3. Puzianowska-Kuźnicka et al. *Immun Ageing*. 2016;13:21. 4. Crichton et al. *BMC Public Health*. 2016;16:502.

Cardiovascular Side Effects of Antidepressants

Examples of cardiovascular side effects of antidepressants^{1,2}

- Lengthening of cardiac myocyte action potentials
- Increases in heart rate
- Increases in blood pressure
- Orthostatic hypertension
- Arrhythmias
- Tachycardia
- Hypertensive crisis

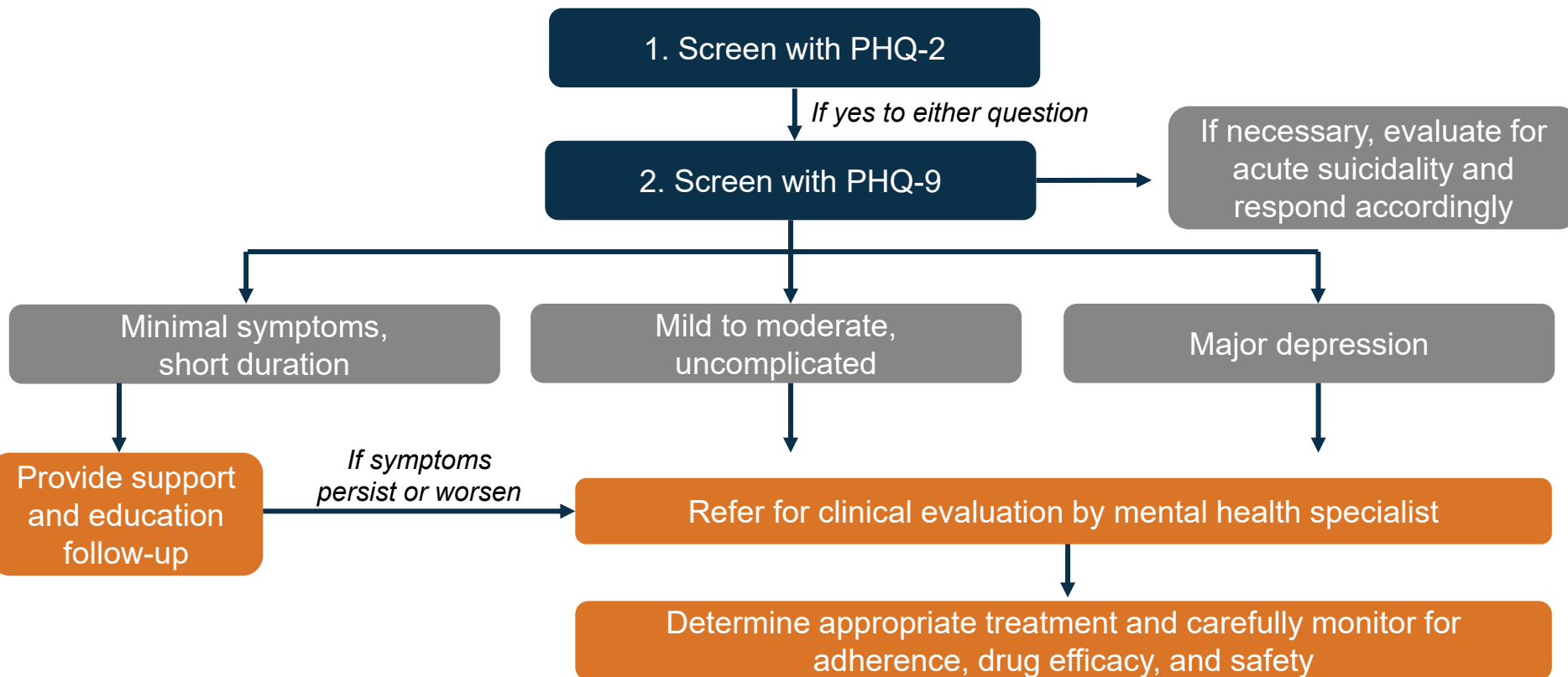
Tricyclic antidepressants and monoamine oxidase inhibitors are contraindicated in many patients with comorbid cardiac conditions because they may cause cardiotoxic side effects³

Determining optimal therapy for patients with chronic heart failure may be challenging. For example, when the QTc interval is borderline, the physician may choose to examine the potential for improved quality of life against potential arrhythmic risk¹

1. Hare et al. *Eur Heart J*. 2014;35:1365-1372. 2. American Psychiatric Association. *Practice Guidelines for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. 2010. 3. Lichtman et al. *Circulation*. 2008;118:1768-1775.

Routine Depression Screening Is Recommended for Patients With Coronary Heart Disease

The AHA and APA suggest screening for depressive symptoms in patients with CHD to identify patients who may require further assessment and treatment



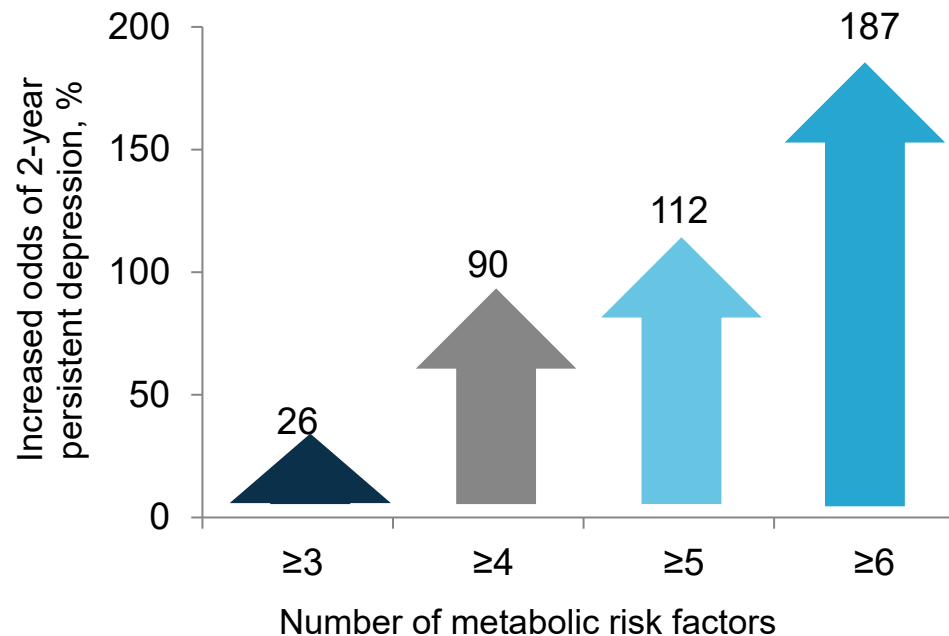
AHA, American Heart Association; APA, American Psychiatric Association; CHD, coronary heart disease; PHQ, Patient Health Questionnaire

Lichtman et al. *Circulation*. 2008;118:1768-1775.

Lipids and Obesity May Affect Response to Antidepressants

Depression was more likely to persist despite antidepressant use in people with higher triglycerides, larger waist circumference, and lower HDL

Treatment-resistant depression was more likely with an increasing number of metabolic risk factors



HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Vogelzangs et al. *Neuropsychopharmacol.* 2014;39:1624-1634.

Lipid Management Guidelines

Dyslipidemia management guidelines are generally consistent among international societies with a few specific differences.

ACC/AHA 2013¹ (USA)

ESC/EAS 2016² (EU)

NICE 2014³ (UK)

CCS 2016⁴ (Canada)

AACE/ACE 2017⁵ (USA)

Major differences among guidelines¹⁻⁶

Risk assessment tools and underlying studies

Use of different underlying study populations, endpoints, and outcome predictors (all use different methods)

“Treat-to-target” recommendations

ESC/EAS, CCS, and AACE recommend LDL-based treatment targets; ACC/AHA and NICE recommend statin therapy intensity based on risk category

Cholesterol and risk levels for statin therapy

LDL and 10-year risk levels prompting lipid-lowering therapy vary across organizations

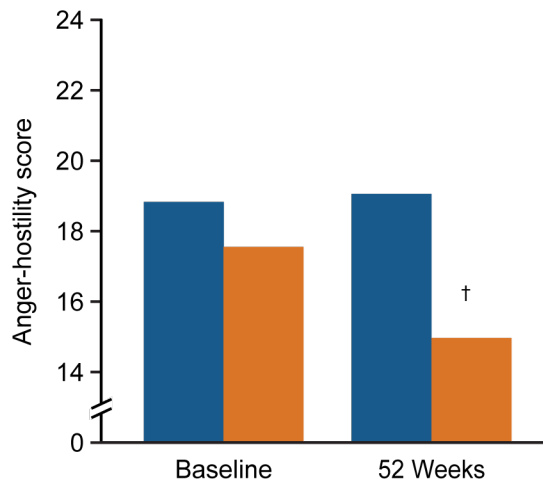
AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL, low-density lipoprotein; NICE, National Institute for Health and Care Excellence.

1. Stone et al. *Circulation*. 2014;63(25 Part B):2889-2934. 2. Catapano et al. *Eur Heart J*. 2016;37:2999-3058. 3. National Institute for Health and Care Excellence. <https://www.nice.org.uk/guidance/cg181/chapter/1-Recommendations>. Accessed May 30, 2017. 4. Anderson et al. *Can J Cardiol*. 2016;32:1263-1282. 5. Jellinger et al. *Endo Pract*. 2017;23(suppl 2):1-87. 6. Naylor and Vasan. *Circulation*. 2016;133:1795-1806.

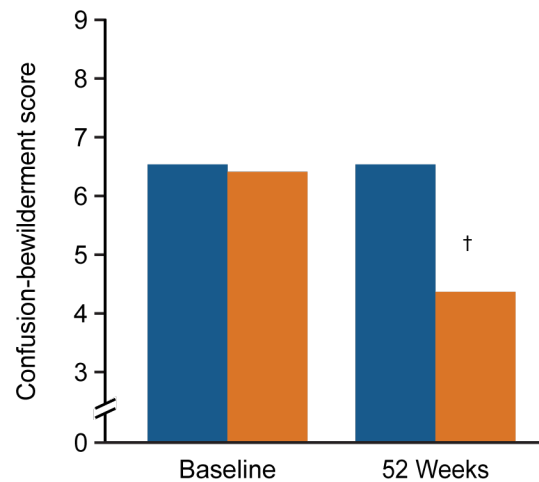
Low-Fat Diet Has Shown 1-Year Improvements in Mood-Related Measures

Mood improvements observed with a low-fat, energy-restricted diet were significantly greater compared with a low-carbohydrate diet after 1 year*

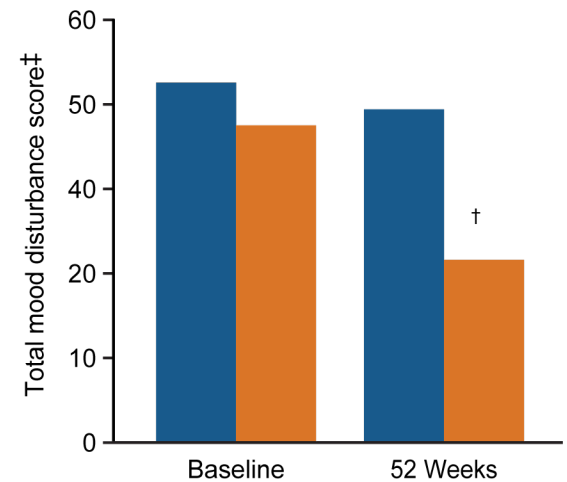
Anger-Hostility



Confusion-Bewilderment



Total mood disturbance



■ Low-carbohydrate diet ■ Low-fat diet

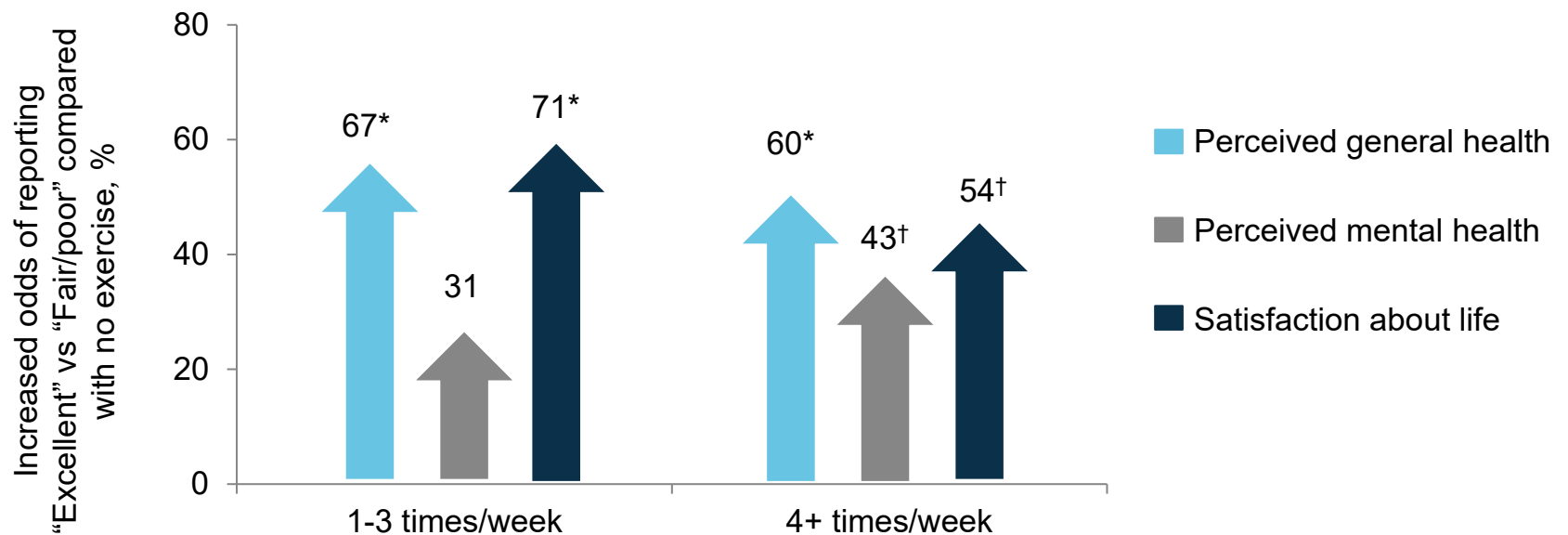
*Based on an Australian study of 118 adults with abdominal obesity and ≥ 1 additional metabolic syndrome risk factor. Although 55 patients were randomized to the low-carbohydrate diet and 52 patients randomized to the low-fat diet, 32 and 33 adults, respectively, completed 1 year of treatment. † $P < 0.05$ vs low-fat diet. ‡Y axis as shown in publication.

Brinkworth et al. *Arch Intern Med.* 2009;169:1873-1880.

Physical Activity in Mood Disorders

Regular exercise is thought to benefit mood regulation and cognitive function by increasing orexin-A and brain-derived neurotrophic factor¹

Only about half of patients with mood disorders exercised at least once a week, but they reported better health and satisfaction with life²



* $P < 0.001$. † $P < 0.05$.

1. Chieffi et al. *Front Physiol.* 2017;8:85. 2. Pelletier et al. *Health Promot Chronic Dis Prev Can.* 2017;37:149-159.



Metabolic Comorbidities in Major Depressive Disorder (MDD)