



# Head & Heart Health in Mental Illness

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**make  
history.**



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# Mental illness and Chronic conditions

People with mental illness are dying prematurely

**> 10,000 people with mental illness die prematurely from chronic diseases each year. Equivalent to 28 people/day.**

**Chronic diseases cause 10 times more premature deaths than suicide for people with mental illness.**

Includes heart disease and stroke, cancer, type 2 diabetes, chronic kidney disease and respiratory conditions.

**Unacceptable life-expectancy gap of up to 15 years between people with mental illness and people in the general population.**

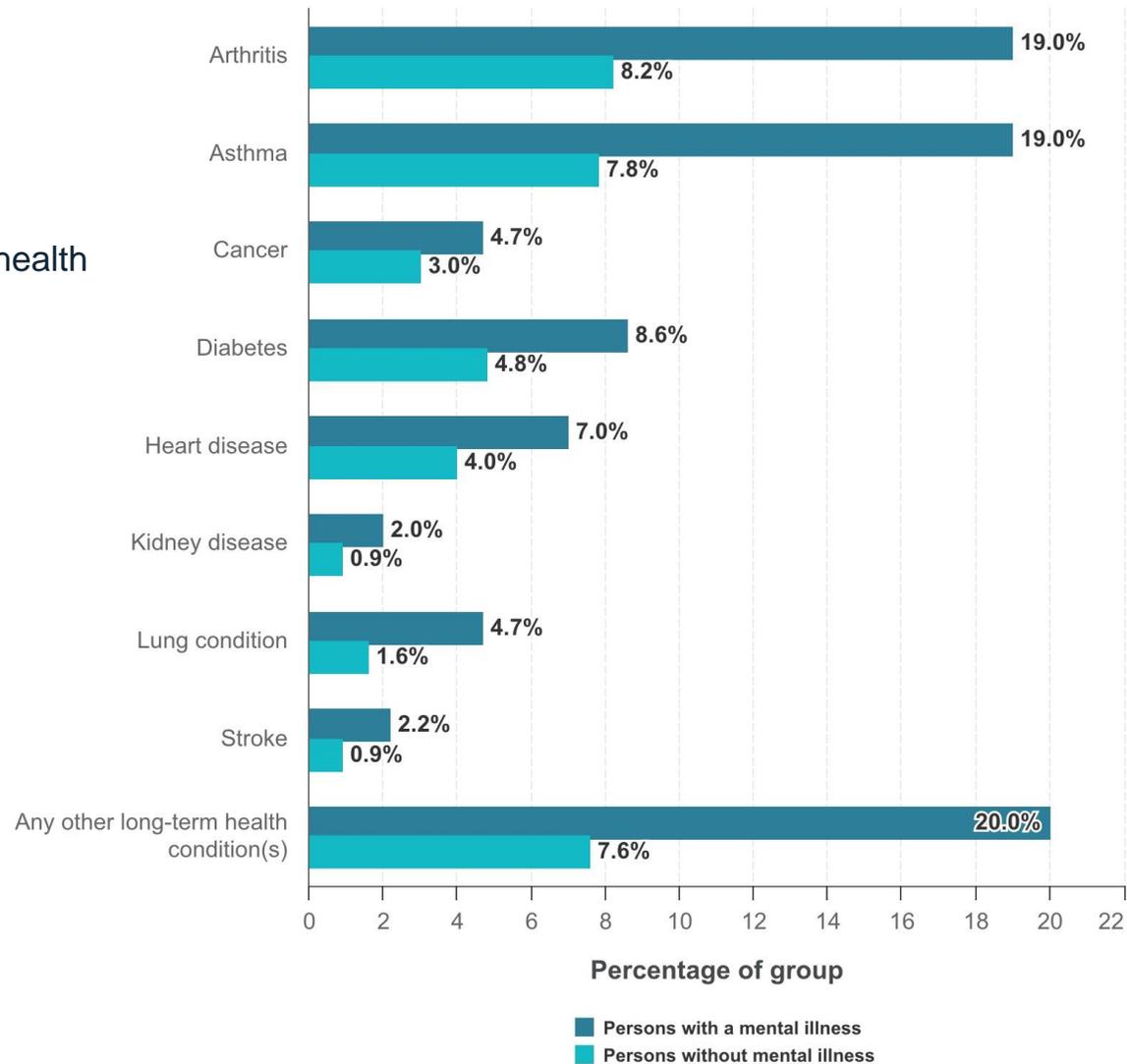
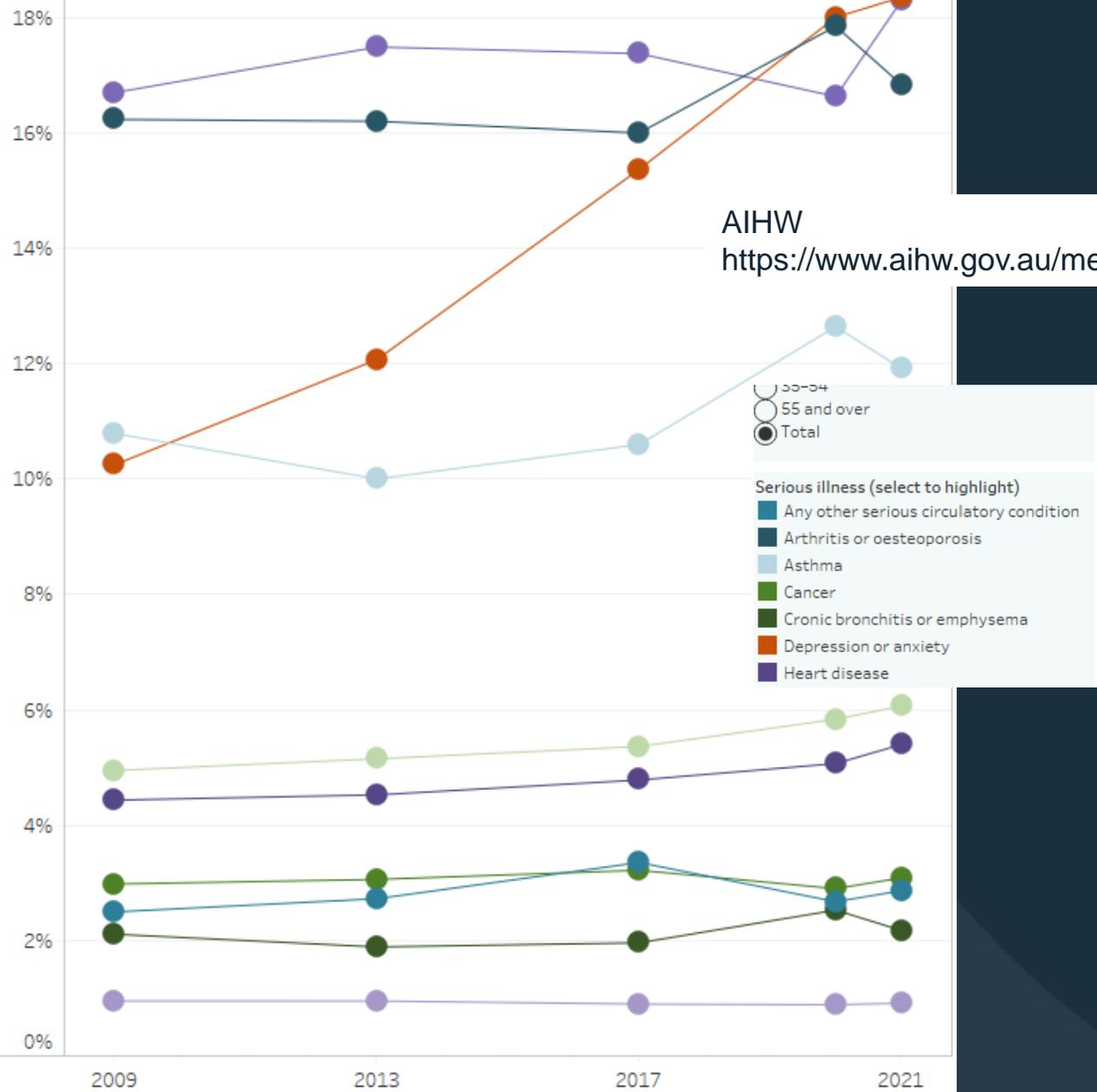
Their mental health conditions are treated but their physical health is neglected.

**80% of people with mental illness also have a serious physical health condition, which is often not diagnosed or treated.**

**People with mental illness not in full-time employment and from lower socio-economic areas are up to 5 times more likely to die prematurely.**

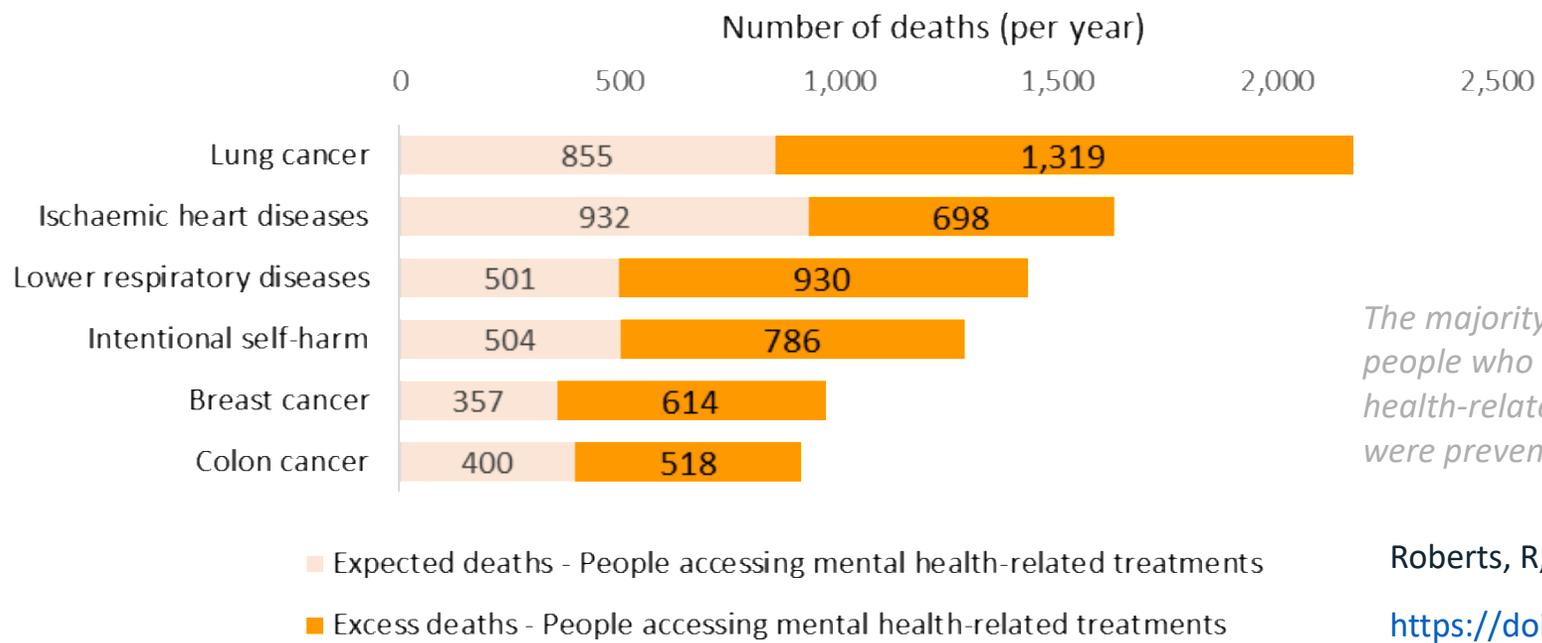
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Figure 1: Long-term health conditions reported by persons with and without mental illness



1. Mental illness includes anxiety and depression.
2. Diabetes excludes gestational diabetes; Cancer includes remission; Heart Disease includes heart attack and angina; Lung condition includes Chronic obstructive pulmonary disease (COPD) or emphysema; Other long-term health condition(s) excludes dementia, Alzheimer's disease and mental illness.

Figure 2: Estimated proportion of Australians reporting serious illnesses, by sex and age group, 2009–2021.



The majority of deaths of people who accessed mental health-related treatments were preventable.

Roberts, R, et al. (2024). *Unequally Unwell: Shorter life expectancies...*  
<https://doi.org/10.17605/OSF.IO/Q5CXJ>

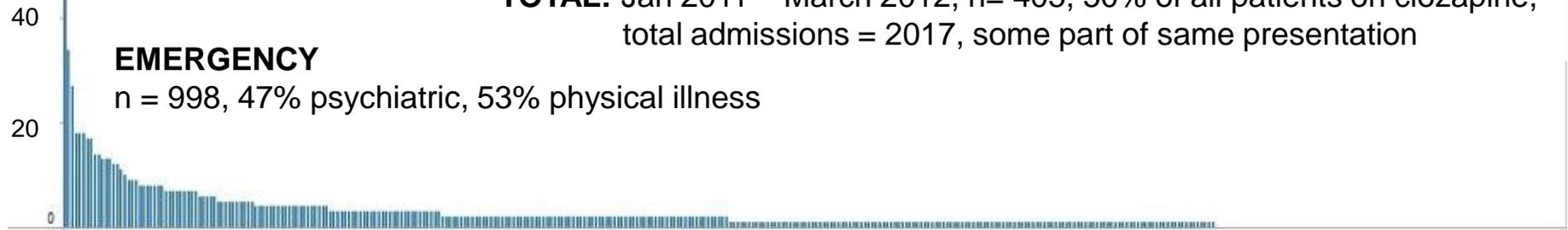
Meta-analytic results of cross-sectional studies		
Disorder	Adjusted odds ratio	95% Confidence Interval (P value)
Schizophrenia	<b>1.52</b>	<b>1.48-1.56 (P&lt;0.001)</b>
Bipolar disorder	0.94	0.79-1.11 (P =0.49)
Major depressive disorder	<b>2.52</b>	<b>1.81-3.52 (P &lt;0.001)</b>
Severe mental illnesses (pooled)	<b>1.51</b>	<b>1.47-1.55 (P &lt;0.001)</b>
Meta-analytic results of longitudinal studies		
Disorder	Adjusted hazard ratio/relative risk	95% Confidence Interval (P value)
Schizophrenia	<b>1.59</b>	<b>1.08-2.35 (P =0.02)</b>
Bipolar disorder	1.16	0.76-1.78 (P =0.49)
Major depressive disorder	<b>1.63</b>	<b>1.33-2.00 (P &lt;0.0001)</b>
Severe mental illnesses (pooled)	<b>1.54</b>	<b>1.30-1.82 (P &lt;0.0001)</b>
Anxiety disorder	<b>1.41</b>	<b>1.23-1.61 (P &lt;0.0001)</b>
Posttraumatic stress disorder	<b>1.27</b>	<b>1.08-1.49 (P &lt;0.05)</b>

De Hert et al. Dialog. in Clin Neurosc. - Vol 20 . No. 1 . 2018

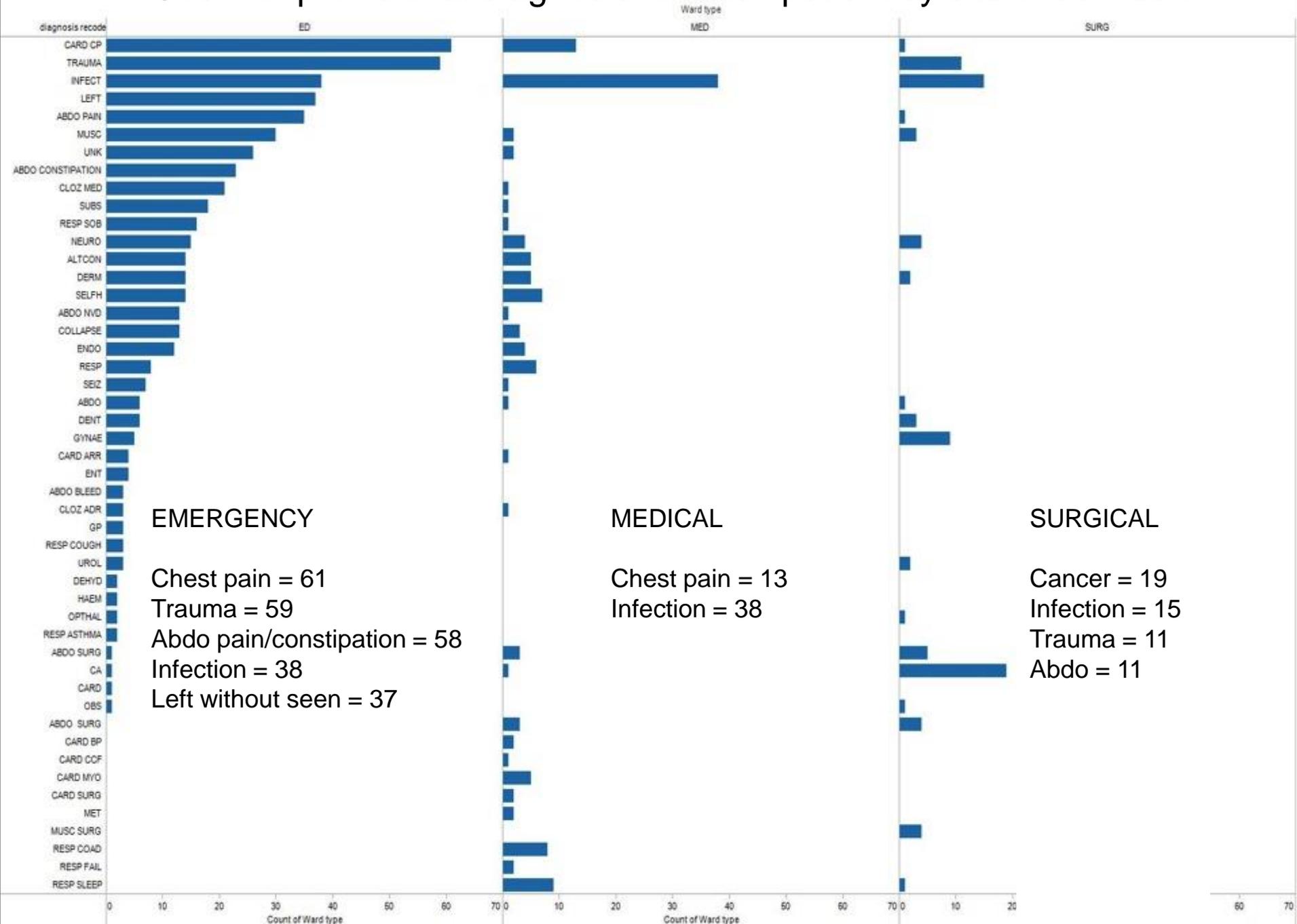
**Table I.** Meta-analytic results of studies on coronary heart disease risk of patients with severe or other mental illnesses.<sup>16,54,60</sup> Statistically significant results are indicated in bold

# Count of hospital admissions for each patient by site of admission

**TOTAL:** Jan 2011 – March 2012, n= 405, 50% of all patients on clozapine, total admissions = 2017, some part of same presentation



# Count of provisional diagnosis for each patient by site of admission



# Risk factors and access disparities for people with mental illness

Many chronic diseases share modifiable risk factors like smoking, overweight and obesity, poor diet, physical inactivity, alcohol consumption, high blood pressure, high cholesterol, and high blood sugar.

People with mental illness have much lower rates of health service access for screening, treatment, and surgical interventions.

People with a mental illness have a much higher prevalence of certain risk factors compared to the general population:

Women with mental illness are nearly **70 percent** more likely to smoke. Men are nearly **40% more likely to smoke**.

Women with mental illness are **eight percent more likely to be inactive**. Men with mental illness are **11% more likely to be inactive**.

Around one in three people with mental illness are obese, compared to around one in four people in the general population.

In people with **psychosis**, **obesity rates can be as high as 45%**

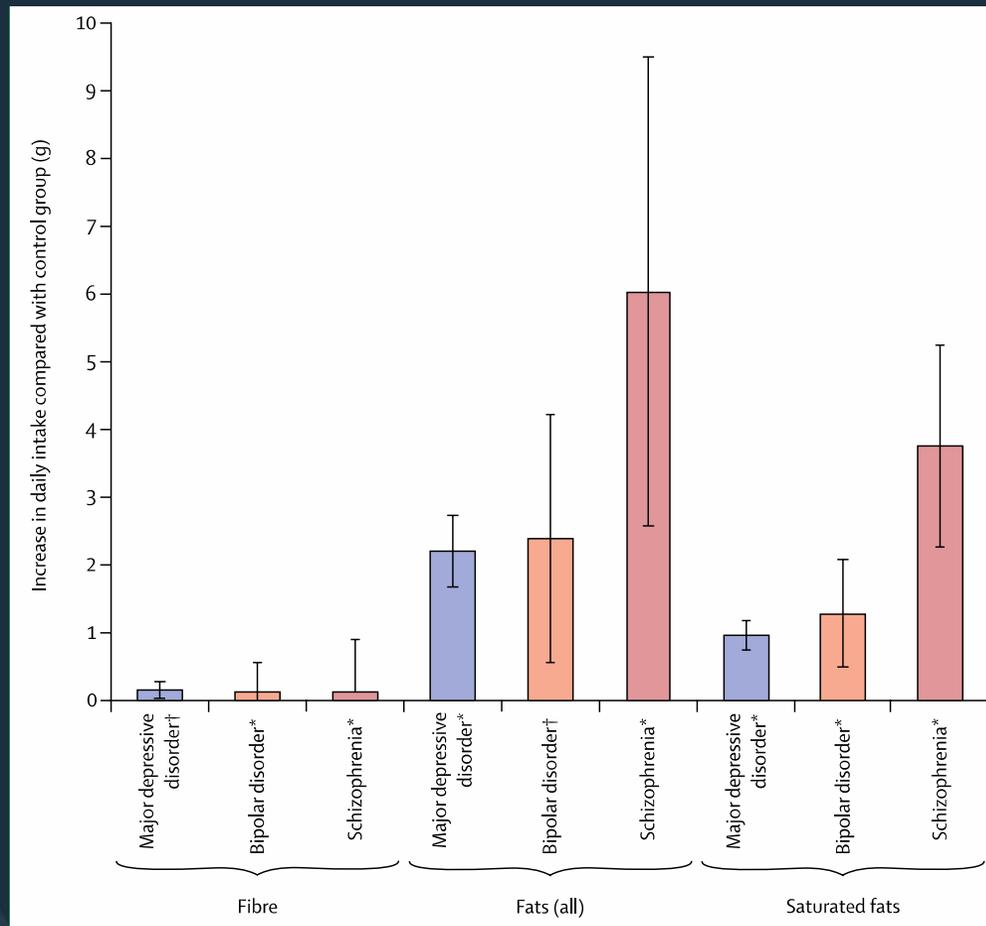
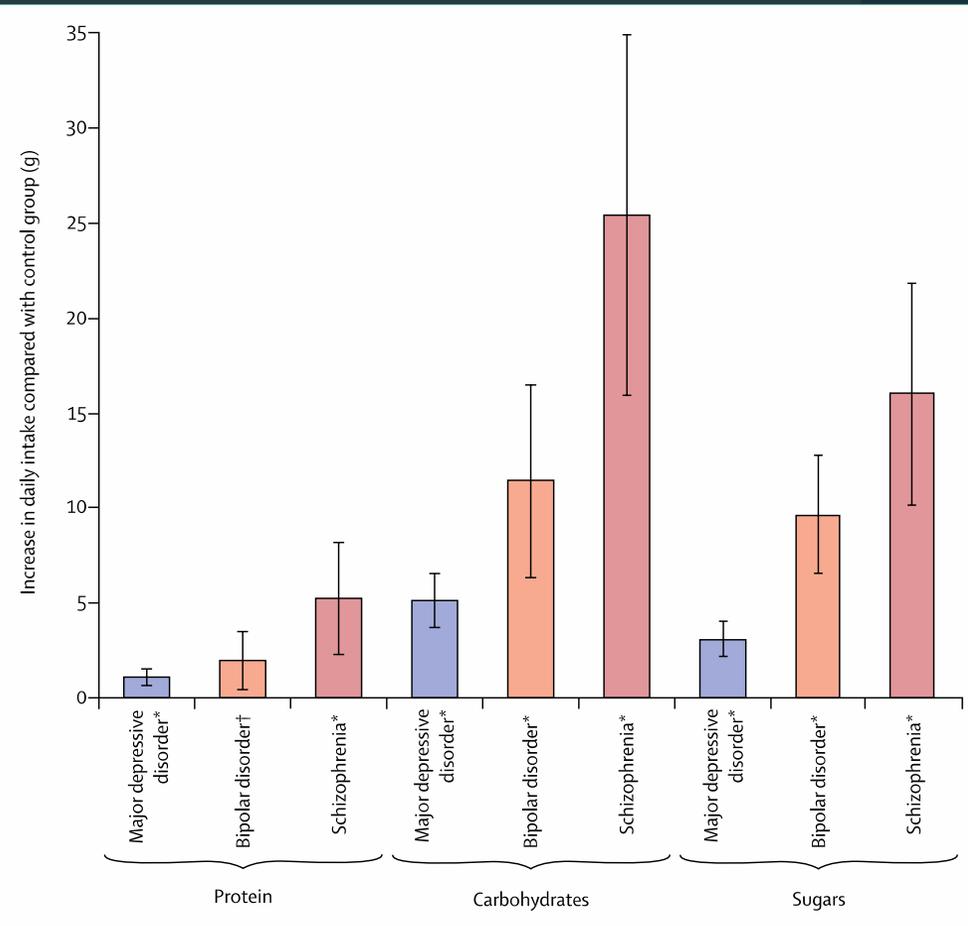


Firth et al. 2019, *The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry* 2019; 6: 675–712

	Alcohol	Tobacco use	Physical activity	Sedentary behaviour	Poor diet	Poor sleep
Major depression	SR: around 30% of patients have or have had alcohol use disorder <sup>124</sup>	SR: patients are more likely to smoke and be dependent on nicotine, are less likely to quit, and are more likely to relapse <sup>125</sup>	MA: around 60–70% of patients do not meet physical activity guidelines <sup>126,127</sup>	MA: patients are sedentary for 8.5 h per day <sup>127</sup>	ES: patients have significantly higher food intake and poorer diet quality than the general population <sup>128</sup>	ES: patients have significantly poorer continuity of sleep and reduced sleep depth compared with healthy controls <sup>129</sup>
Anxiety disorders	ES: 17.9% of patients have alcohol dependence or misuse <sup>130</sup>	MA: 41% increase in risk of regular smoking and 58% increase in risk of nicotine dependence <sup>131</sup>	ES: individuals with panic disorders, social phobia, and agoraphobia report significantly less activity <sup>132</sup>	SR: inconsistent evidence for increased sedentary time in people with anxiety <sup>133</sup>	Insufficient evidence	MA: anxiety disorders <sup>129,134</sup> and obsessive-compulsive disorder <sup>135</sup> are associated with reduced sleep quality
Bipolar disorder	MA: 1 in 3 patients have or have had alcohol use disorder <sup>136</sup>	MA: increased rates of current smoking (higher than in patients with major depression but lower than in patients with schizophrenia) <sup>137</sup>	MA: the majority of patients meet physical activity guidelines and are no different to the general population <sup>81,126</sup>	MA: patients are sedentary for more than 10 h per day <sup>81,126</sup>	MA: patients consume more than the general population per day <sup>138</sup>	MA: even between episodes, people with bipolar disorder have increased sleep-wake disturbance, similar to patients with insomnia <sup>139</sup>
Schizophrenia	MA: 1 in 5 patients have or have had alcohol use disorder <sup>140</sup>	MA: significantly higher rates of current smoking, heavy smoking, and nicotine dependence <sup>141</sup>	MA: the majority of patients do not meet physical activity guidelines <sup>108,126</sup>	MA: patients are sedentary for around 11 h per day <sup>142</sup>	MA: patients consume around 400 calories more than the general population per day <sup>138</sup>	MA: patients have significantly reduced sleep time and quality of sleep <sup>129,134</sup>
First-episode psychosis	MA: 27% of patients have or have had alcohol use disorder or alcohol dependence <sup>143</sup>	MA: 58% of patients use tobacco, which is a significantly higher prevalence than in matched controls <sup>144</sup>	MA: patients are less active than individuals with long-term schizophrenia <sup>108</sup>	Insufficient evidence	Insufficient evidence	MA: patients have significantly reduced sleep time and quality of sleep <sup>134</sup>
Post-traumatic stress disorder	SR: increased prevalence of comorbid alcohol misuse (10–61%) compared with the general population <sup>145</sup>	MA: patients are 22% more likely to be current smokers than the general population <sup>98</sup>	MA: patients are 9% less likely to be physically active than the general population <sup>98</sup>	Insufficient evidence	MA: patients are 5% less likely to have a healthy diet than the general population <sup>98</sup>	MA: significantly poorer continuity of sleep and reduced sleep depth compared with healthy controls <sup>129</sup>

Results described as significant had p<0.05. Comparisons are with the general population unless otherwise stated. SR=systematic review of case-control, clinical, or epidemiological research. MA=meta-analysis of multinational data. ES=large-scale epidemiological studies.

**Table 2: Prevalence of behavioural risk factors across different mental health diagnoses**



Firth et al. 2019, *The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry* 2019; 6: 675–712

Lifestyle interventions have variable efficacy MDD>Bipolar>Schizophrenia



**TABLE 1. Risk of weight gain with conventional antidepressants<sup>a</sup>**

Risk of Weight Gain	Antidepressants
High	Amitriptyline, citalopram, clomipramine, fluvoxamine, mirtazapine, nortriptyline, paroxetine, phenelzine
Moderate	Desipramine, duloxetine, escitalopram, sertraline, venlafaxine
Low	Agomelatine, desvenlafaxine, gepirone, levomilnacipran, moclobemide, selegiline, tranylcypromine, vilazodone, vortioxetine
Neutral or weight loss	Bupropion, dextromethorphan-bupropion, esketamine, fluoxetine, zuranolone

<sup>a</sup> Risk categorization is based on primary reports, meta-analytic evidence, product monographs, and expert opinion.

**TABLE 2. Risk of weight gain with antipsychotics<sup>a</sup>**

Risk of Weight Gain	Antipsychotics
High	Clozapine, olanzapine
Moderate	Chlorpromazine, olanzapine/samidorphan combination, paliperidone, quetiapine, risperidone
Low	Amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, haloperidol, iloperidone, ziprasidone
Neutral or weight loss	Lumateperone, lurasidone

<sup>a</sup> Risk categorization is based on primary reports, meta-analytic evidence, product monographs, and expert opinion.

**TABLE 3. Risk of weight gain with lithium and anticonvulsants<sup>a</sup>**

Risk of Weight Gain	Lithium and Anticonvulsants
High	Valproate (valproic acid)
Moderate	Lithium
Low	Carbamazepine, gabapentin, oxcarbazepine, pregabalin
Neutral or weight loss	Lamotrigine, topiramate

<sup>a</sup> Risk categorization is based on primary reports, meta-analytic evidence, product monographs, and expert opinion.

## Approximate relative frequency of common adverse effects of antipsychotics [NB1] [NB2] [NB3] [NB4]

Drug	Anticholinergic effects	Cardiometabolic effects	Extrapyramidal effects [NB5]	Hyperprolactinaemia	Orthostatic hypotension [NB5]	Sedation [NB5]	QT-interval prolongation
amisulpride	-	+	+	+++	- to +	+	++ to +++
aripiprazole	+	- to +	+	-	+	- to +	+
asenapine	+	+	+ to ++	+	+	+	+
brexpiprazole	- to +	- to +	+	-	- to +	- to +	-
chlorpromazine	++	++ to +++	++	++	++	++ to +++	++
clozapine [NB6]	+++	+++	-	-	+++	+++	+ to ++
flupentixol	++	++	++ to +++	- to +	+	+	++
haloperidol	+	+ to ++	+++	++	+ to ++	+	+++
lurasidone	- to +	- to +	+ to ++	+	- to +	+	- to +
olanzapine	++	+++	- to +	+	+ to ++	++	+ to ++
paliperidone	+	++	+	+++	+ to ++	+	+
periciazine	+++	++	+	+++	++	+++	limited or no data
quetiapine	+++	++ to +++	- to +	- to +	++	++ to +++	+ to ++
risperidone	+	++	+	+++	+ to ++	+	+ to ++
ziprasidone	+	+	+	+	+	++	+++
zuclopenthixol	++	++	++ to +++	+++	+	+++	limited or no data

Approximate frequencies of adverse effects: - = negligible or absent; + = infrequent; ++ = moderately frequent; +++ = frequent

NB1: The information in this table is based on a combination of reported adverse effect data and expert opinion; it is intended as a guide only and should be interpreted in the context of the patient (eg concurrent drugs, drug history, physical health, interindividual variation in pharmacokinetics). Adverse effects are similar with oral and long-acting injectable formulations, and are more likely with high doses. Consult a drug information resource for comprehensive information on antipsychotic adverse effects.

NB2: A rare adverse effect of antipsychotics is neuroleptic malignant syndrome.

NB3: Limited data suggest adverse effects may be more severe in children than in adults.

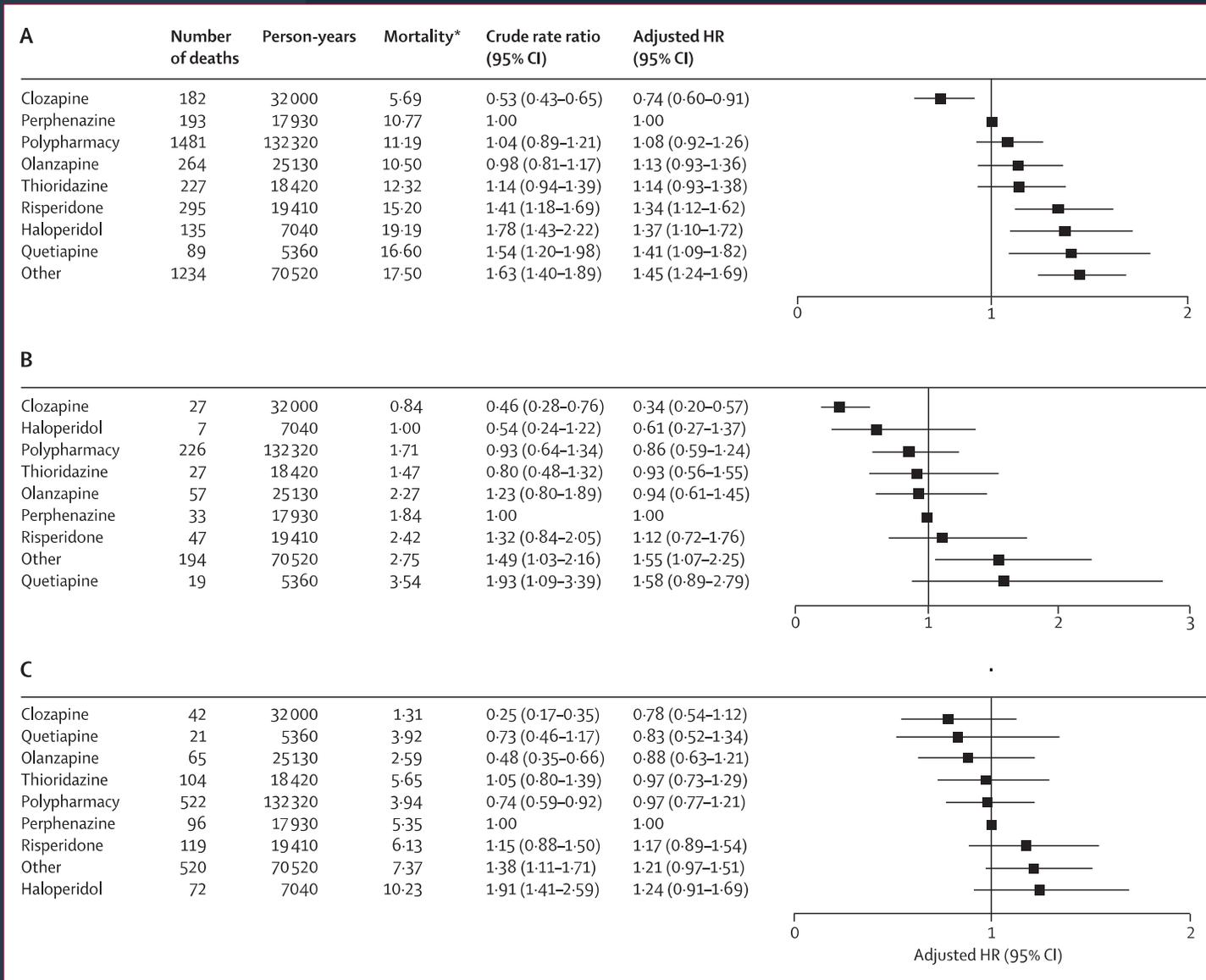
NB4: This table lists the approximate relative frequency of adverse effects, not the intensity with which they occur.

NB5: This adverse effect is generally more frequent when starting an antipsychotic or with a rapid dose increase, or starting or stopping an interacting drug.

NB6: For additional information on clozapine adverse effects, see 'Clozapine for treatment-resistant schizophrenia in adults and young people' in *Therapeutic Guidelines*.

# Antipsychotic related mortality

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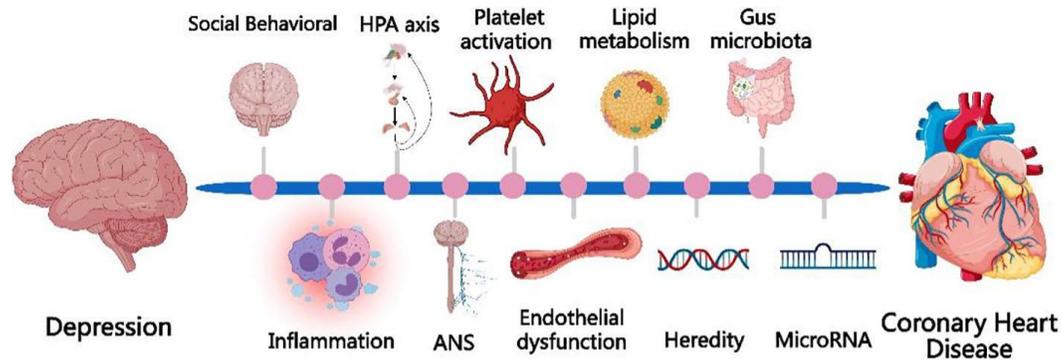
**Figure 1: Risk of death during current monotherapies**

(A) Risk of death from any cause. (B) Risk of death from suicide. CIs for haloperidol and quetiapine are wide because of the low number of incidents in patients using these drugs. (C) Risk of death from ischaemic heart disease. \*Mortality=unadjusted absolute risk per 1000 person-years. HR=hazard ratio. Other=rarely used antipsychotic drugs.

Tiihonen et. al., 2009 FIN 11 study



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**FIGURE 1**  
The currently proposed mechanisms of depression causing CHD include socio-behavioral mechanisms and physiological mechanisms, such as over-activation of the inflammatory response, autonomic dysfunction, endothelial dysfunction, abnormal HPA axis function, platelet over-activation, and genetics, microRNA, gut microbiota.

Xu L, et al.(2024) Front. Psychiatry 15:1328048.

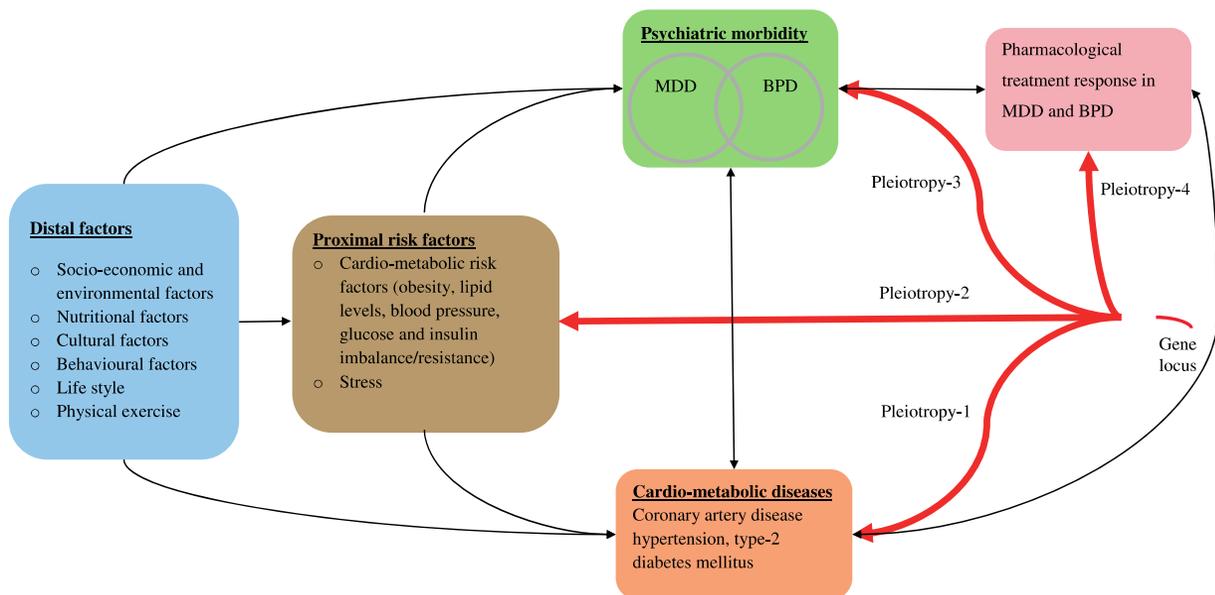


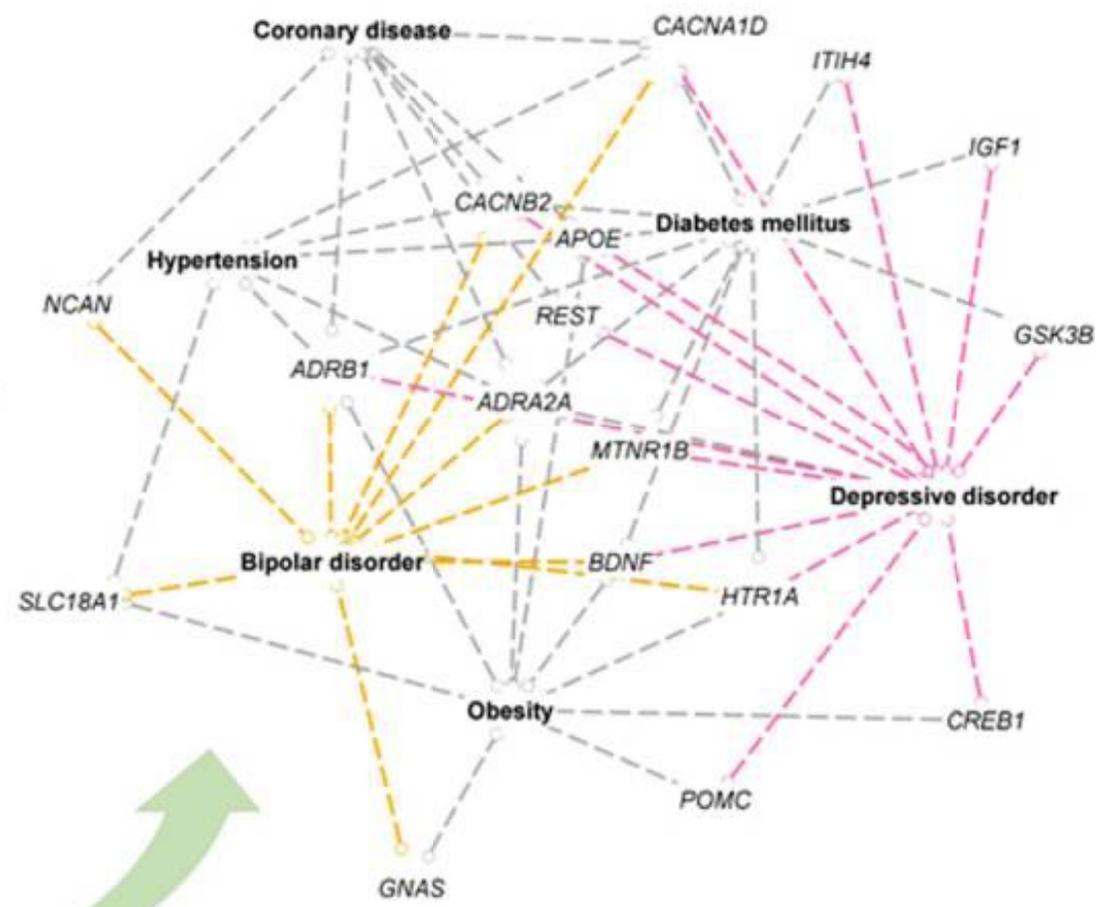
Figure 1. Schematic model for the potential pleiotropic effects of a shared gene locus that is associated with mood disorders and cardiometabolic diseases. The distal and proximal factors are obtained from the literature. Red bold lines represent the pleiotropic effect of a genetic locus on cardiometabolic diseases and associated risk factors, psychiatric morbidity, i.e. mood disorders and pharmacological treatment response in MDD and BPD. The bi-directional arrows indicate bidirectional epidemiological relationships between the cardiometabolic diseases and mood disorders. BPD, bipolar disorder; MDD, major depressive disorder.

Twenty four CMMDh genes

Biological pathways and enriched CMMDh genes

<i>MTHFR</i>	Corticotrophin releasing hormone
<i>CACNA1D</i>	<i>BDNF, CREB1, GNAS, POMC</i>
<i>CACNB2</i>	AMPK signaling
<i>GNAS</i>	<i>ADRA2A, ADRB1, CREB1, GNAS, LEP</i>
<i>ADRB1</i>	
<i>REST</i>	
<i>LEP</i>	cAMP-mediated or G-Protein coupled receptor
<i>ADRA2A</i>	<i>ADRA2A, ADRB1, CREB1, GNAS, HTR1A</i>
<i>TCF7L2</i>	
<i>HTR1A</i>	
<i>CRY2</i>	Dopamine-DARPP32 feedback in cAMP
<i>MTNR1B</i>	<i>CACNA1D, CREB1, GNAS, PPP1R1B</i>
<i>IGF1</i>	
<i>FTO</i>	
<i>POMC</i>	Serotonin receptor
<i>ITIH4</i>	<i>GNAS, HTR1A, SLC18A1</i>
<i>TLR4</i>	
<i>BDNF</i>	Dopamine receptor
<i>CREB1</i>	<i>SLC18A1, GNAS, PPP1R1B</i>
<i>NCAN</i>	Axonal guidance
<i>GSK3B</i>	<i>BDNF, GNAS, GSK3B, IGF1</i>
<i>SLC18A1</i>	
<i>PPP1R1B</i>	Leptin signaling
<i>APOE</i>	<i>GNAS, LEP, POMC</i>
	Cardiac hypertrophy
	<i>ADRA2A, ADRB1, CACNA1D, CREB1, GNAS, GSK3B, IGF1</i>
	Circadian rhythm signaling
	<i>CRY2, CREB1</i>

Network of CMMDh genes



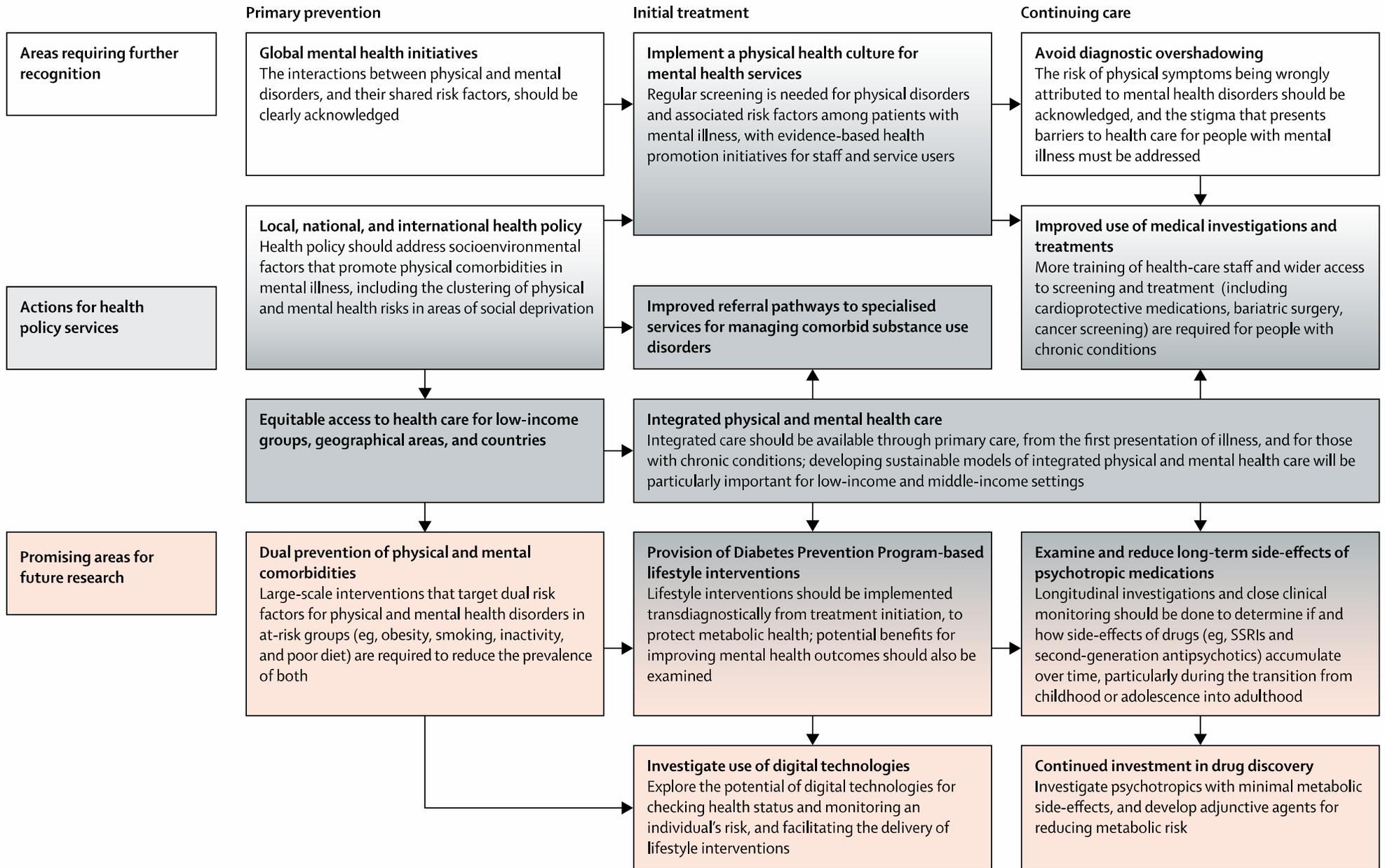
A pathway analysis of genes known to be associated with cardiometabolic diseases and mood disorders revealed significant pathways: corticotrophin-releasing hormone signaling, AMPK signaling, cAMP-mediated or G-protein coupled receptor signaling, axonal guidance signaling, serotonin or dopamine receptors signaling, dopamine-DARPP32 feedback in cAMP signaling, circadian rhythm signaling and leptin signaling

**Fig 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

What can we do?



Mental health treatment stage



Firth et al. 2019, *The Lancet Psychiatry*  
**Commission: a blueprint for protecting physical health in people with mental illness.**  
*Lancet Psychiatry* 2019; 6: 675–712

# Suggested schedule for monitoring antipsychotic adverse effects

## at 1 month

measure weight, waist circumference and BMI

ask about and assess for extrapyramidal effects

measure prolactin concentration

ask about sexual and reproductive problems

## at 2 months

measure weight, waist circumference and BMI

## at 3 months

measure blood pressure and heart rate

measure fasting blood glucose and glycated haemoglobin (HbA1c) concentrations

measure weight, waist circumference and BMI

ask about and assess for extrapyramidal effects

## at 6 months

measure blood pressure and heart rate

measure fasting blood glucose and glycated haemoglobin (HbA1c) concentrations

measure fasting lipid levels

measure weight, waist circumference and BMI

ask about and assess for extrapyramidal effects

measure prolactin concentration

ask about sexual and reproductive problems

## at 12 months and thereafter

measure blood pressure and heart rate; repeat **every 6 months**

measure fasting blood glucose and glycated haemoglobin (HbA1c) concentration; repeat **every 6 months**

measure fasting lipid levels; repeat **every 6 months**

measure weight, waist circumference and BMI; repeat **every 6 months**

perform ECG; repeat **annually**

measure full blood count; repeat **annually**

ask about and assess for extrapyramidal effects; repeat **every 6 months**

measure prolactin concentration; repeat **annually**

ask about sexual and reproductive problems; repeat **annually**

Adapted Table 8.32 Therapeutic Guidelines July 2022

# A case series considering personalized titration risk factors

Case	Sex	Age	Day Troponin Positive	Ethnicity	Obese	Elevated CRP On Initiation	Smoking Cessation	Concomitant Medication	Confirmed Echocardiography or MRI	Suspected Metaboliser Status**	Dose (mg) at week 2 <sup>#</sup>	Personalised Maximum Dose mg (week 2)**
1*	Male	19	18	Caucasian	Yes	No	Yes	Olanzapine, Sodium Valproate	Confirmed MRI	Poor	200	100-200 (75)
2	Female	44	20	Caucasian	Yes	Yes	No	Quetiapine, Paliperidone LAI, Paroxetine	Confirmed MRI	Poor	250	100-200 (75)
3	Male	27	19	Caucasian	No	No	No	Aripiprazole, Fluoxetine	Confirmed MRI	Normal	200	200-400 (200)
4	Male	44	16	Caucasian	Yes	Yes	No	Paliperidone LAI, Apixaban	No	Poor	175	100-200 (75)
5*	Female	37	20	Asian	Yes	No	No	Olanzapine, Paliperidone LAI, OCP	Echo Normal	Poor	225	75-150 (50)

**Table 1:** Demographics and risk factors for CAM cases, C-reactive protein – CRP, long-acting injection – LAI, Echocardiography – Echo, Oral Contraceptive Pill - OCP. \* case 1 and 5 were successfully rechallenged. \*\*based on De Leon et al., female non-smokers are thought best managed at the lower end of the personalised dose range (de Leon et al., 2022a; de Leon et al., 2022b). <sup>#</sup>SA Health guideline recommendation is 200 mg at 14 days. From day 14 the dose can be increased in 50 mg intervals every two to three days depending on efficacy and side effects. Maximum dose is 900 mg per day.

July 2021 to June 2022 CALHN-wide medical record review: 217 clozapine commencements - 53 elevated Troponin T results >12 ng/L in females > 16 ng/L in males, 35 of admitted to CALHN inpatient units, 14 with accompanied elevation in CRP. 5 cases received a discharge diagnosis of CAM. Troponin range 70-330, CRP range 34-226

# Personalised Clozapine Titration

**Table 1** Summary of international clozapine titration guideline for adult inpatients according to ancestry groups with updates

	Asians/Native Americans		Europeans/Western Asians		Afro-Americans	
	PMs*	Non-PMs	PMs*	Non-PMs	PMs*	Non-PMs
<b>Target</b>	75–150 mg/day	175–300 mg/day	100–200 mg/day	250–400 mg/day	150–300 mg/day	300–600 mg/day
<b>Week 1</b>						
Day 1	6.25 mg/day	12.5 mg/day	12.5 mg/day	25 mg/day	12.5 mg/day	25 mg/day
↑ D by	6.25 mg/day	12.5 mg/day	12.5 mg/day	25 mg/day	12.5 mg/day	25 mg/day
Day 7	25 mg/day	50 mg/day	50 mg/day	100 mg/day	50 mg/day	100 mg/day
Alert C	<118 ng/mL	<105 ng/mL	<175 ng/mL	<140 ng/mL	<117 ng/mL	<117 ng/mL
<b>Week 2</b>						
↑ D by	12.5 mg	12.5 mg/day	12.5 mg/day	25 mg/day	25 mg/day	50 mg/day
Day 14	50 mg/day	100 mg/day	75 mg/day	200 mg/day	100 mg/day	200 mg/day
Alert C	<235 ng/mL	<210 ng/mL	<263 ng/mL	<280 ng/mL	<233 ng/mL	<234 ng/mL
<b>Week 3</b>						
↑ D by	12.5 mg	25 mg/day	25 mg/day	25/50 mg/day	25 mg/day	50 mg/day
Day 21	75 mg/day	150 mg/day			150 mg/day	300 mg/day
NS ♀			100 mg/day	250 mg/day		
Other			125 mg/day	300 mg/day		
Alert C	<353 ng/mL	<315 ng/mL	<350 ng/mL	<350 ng/mL	<291 ng/mL	<351 ng/mL
<b>Week 4</b>						
NS ♀	75 mg/day	150 mg/day	100 mg/day	250 mg/day	150 mg/day	300 mg/day
C	C 1 week later	C 1 week later	C 1 week later	C 1 week later	C 1 week later	C 1 week later
Other	75–150 mg/day	175–300 mg/day	100–200 mg/day	250–400 mg/day	150–300 mg/day	300 mg/day
↑ D by	25 mg/day	25/50 mg/day	25/50 mg/day	25/50 mg/day	25/50 mg/day	25/100 mg/day
C	C 1 week later	C 1 week later	C 1 week later	C 1 week later	C 1 week later	C 1 week later

- Adverse events occur when titration rate is not matched to metabolism and peak levels are high
- Titration based on gender, inflammation risk, ethnicity, drug interactions
- Poor metabolisers:
  - Obesity (inflammation),
  - Oral contraceptives, valproate, flupentixol, olanzapine, perphenazine, quetiapine
- Alert clozapine levels at week 1
- Steady state levels at week 4

de Leon J, et al. General Psychiatry 2022;35:e100773

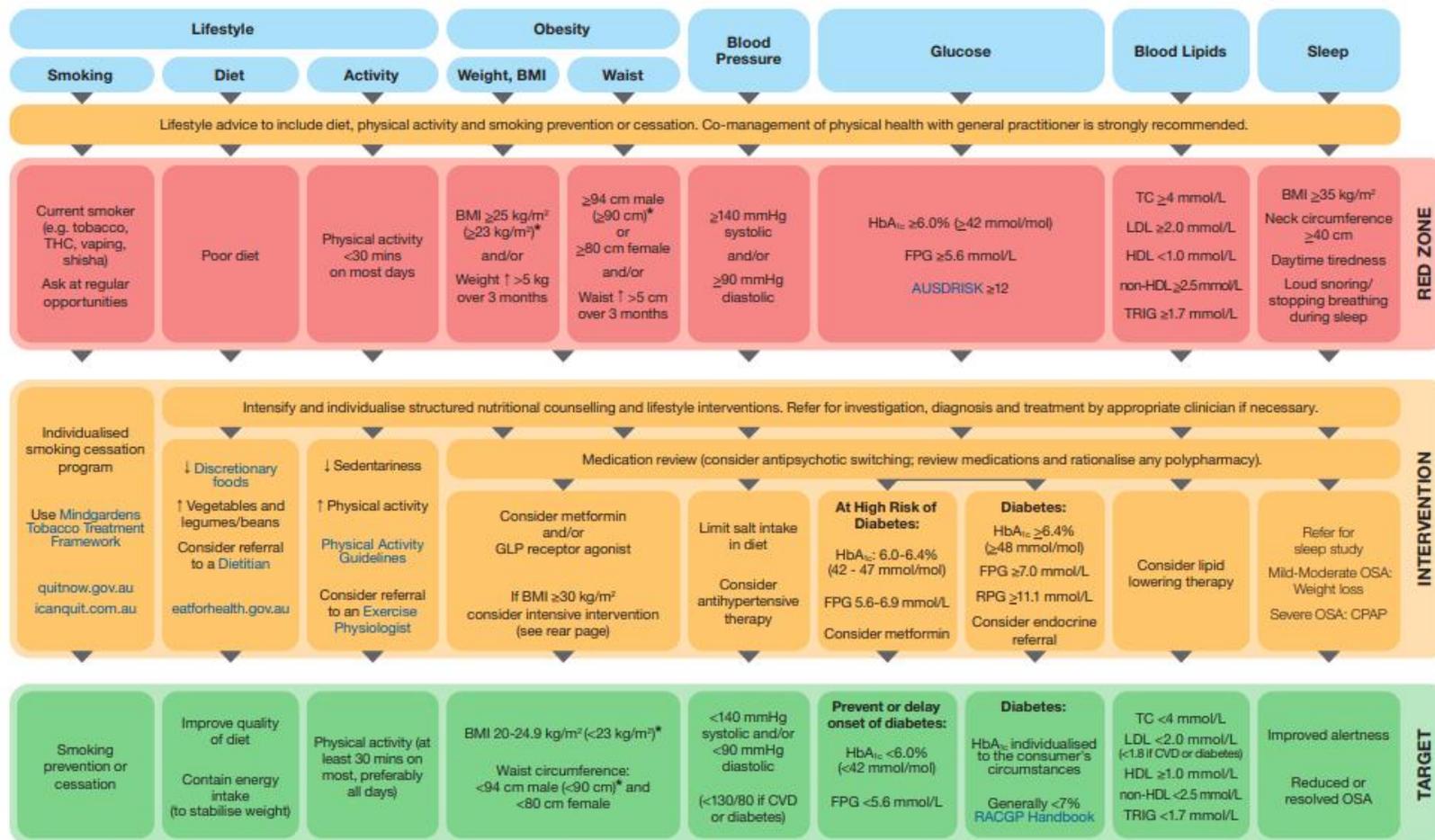


# Managing metabolic syndrome



## Positive Cardiometabolic Health Resource

An early intervention framework for people on psychotropic medication



\*For South Asian, Chinese, Japanese, Ethnic South and Central Americans. | BMI = Body Mass Index | CVD = Cardiovascular disease | FPG = Fasting Plasma Glucose | GLP = Glucagon-like Peptide | HbA<sub>1c</sub> = Glycated Haemoglobin | HDL = High Density Lipoprotein | LDL = Low Density Lipoprotein | OSA = Obstructive Sleep Apnoea | RPG = Random Plasma Glucose | TC = Total Cholesterol | TRIG = Triglycerides



# Managing metabolic syndrome



## Positive Cardiometabolic Health Resource

An early intervention framework for people on psychotropic medication

Access the guide and complete list of references online either by scanning the QR code or by visiting [mindgardens.org.au/KBIMResources](http://mindgardens.org.au/KBIMResources)



### History and examination following initiation or change of psychotropic medications

**History:** Seek history of smoking, poor diet (e.g. high calorie, high fat/sugar), physical activity and sedentariness (e.g. screen time), sleep, and polycystic ovary syndrome. Ask about family history (diabetes, obesity, early CVD), gestational diabetes. Note ethnicity.

**Investigations:** Fasting estimates of plasma glucose (FPG), HbA1c, and lipids (total cholesterol, LDL, HDL, non-HDL, triglycerides). If fasting samples are impractical then non-fasting samples are satisfactory for most measurements except for triglycerides.

**Frequency:** At a minimum, those starting or changing antipsychotics should be monitored as below. After 12 months, continue to monitor at 6-month intervals, with increased frequency if abnormalities emerge, which should then prompt appropriate action and/or continuing review at least every 3 months.

#### Monitoring Intervals

	Baseline	Weekly*	3 months	6 months	9 months	12 months	Continue 6 monthly
<b>Personal/Family History</b>	✓					✓	✓
<b>Lifestyle Review</b>	✓	✓	✓	✓	✓	✓	✓
<b>Weight</b>	✓	✓	✓	✓	✓	✓	✓
<b>Waist</b>	✓		✓	✓	✓	✓	✓
<b>Blood pressure</b>	✓		✓	✓	✓	✓	✓
<b>FPG, RPG, HbA<sub>1c</sub></b>	✓		✓	✓		✓	✓
<b>Lipid profile</b>	✓		✓	✓		✓	✓
<b>Vitamin D</b>	✓			✓		✓	✓

\*Weight should be assessed weekly to fortnightly in the first 6 – 8 weeks following initiation or change of medication. Commencing antipsychotics is a time of particular risk of rapid weight gain and this may predict severe weight gain in the longer term.

#### Other Considerations:

Other baseline investigations are not included here and need to be performed as clinically required (e.g. TFTs, UECs, FBC, ECHO). Additional monitoring requirements apply for those on mood stabilisers and clozapine (e.g. medication plasma levels). Prolactin measurement is only recommended if symptomatic. Consider ECG/cardiology review if concern regarding QT prolongation or cardiovascular risk factors present.

Screen for polycystic ovary syndrome in all women: No menstrual cycle for 3 months, acne, hirsutism. Check prolactin, consider metformin and endocrine referral. Treatment may restore fertility, ensure contraception is discussed. Some medications used to treat metabolic disorder are contraindicated in pregnancy (e.g. some antihypertensives and lipid lowering drugs).

Other issues such as sexual health, blood borne virus screening, oral health, vaccination status, and substance use have not been included in this resource though are important to discuss with all consumers.

## DON'T JUST SCREEN INTERVENE for all people in the 'red zone'

Decision making surrounding screening and agreed interventions should be made with the consumer and include consultation with carers, families, and key stakeholders (e.g. general practitioner, mental health clinicians, and community providers).

### Review of antipsychotic and mood stabiliser medications

- Choose lower metabolic liability medication first line where possible
- Review diagnosis and ensure ongoing need for all psychotropic medications
- Consider switching to a more weight neutral medication where possible
- Avoid antipsychotic polypharmacy
- Avoid off-label use of antipsychotic medications
- Changing antipsychotic medication requires careful clinical judgement to weigh any benefits against the risk of relapse of psychosis

#### Review should be a priority if there is:

- Rapid weight gain (e.g. 5 kg < 3 months) following antipsychotic initiation or change
- Rapid development (< 3 months) of abnormal lipids, BP, or glucose

If consumer has not successfully reached targets after 3 months, then consider specific pharmacological interventions

### Intensive Interventions

Intensive interventions to support weight loss may be considered with a BMI of  $\geq 30$  kg/m<sup>2</sup> or if unsuccessful in reducing weight or has regained weight using lifestyle approaches. Intensive interventions may include:

- Metformin and/or GLP receptor agonist
- Very low energy diets for 8-16 weeks under medical supervision, replacing one or more meals per day with food or formulas that provide a specified number of kilojoules (e.g. 1675-3350 kJ/day)
- Referral to obesity clinic
- Consider referral for assessment for bariatric surgery

### Specific pharmacological interventions

#### Consider metformin trial for:

- Impaired fasting glucose
- Obesity or rapid weight gain
- Polycystic ovary syndrome

Note that **off-label use** requires documented informed consent

#### Metformin therapy:

Start at 250 mg before dinner for two weeks, then increase to 250 mg bd. Dose can be increased by 500 mg per week to a maximum of 3 grams daily (taken in split doses with meals). If side-effects of nausea or abdominal cramping shift to after meal (or the XR preparation)

#### Lipid lowering therapy:

Co-management with GP recommended. Consider lipid lowering therapy (use PBS guidelines). If severe hyperlipidaemia or other risk factors, consider specialist referral

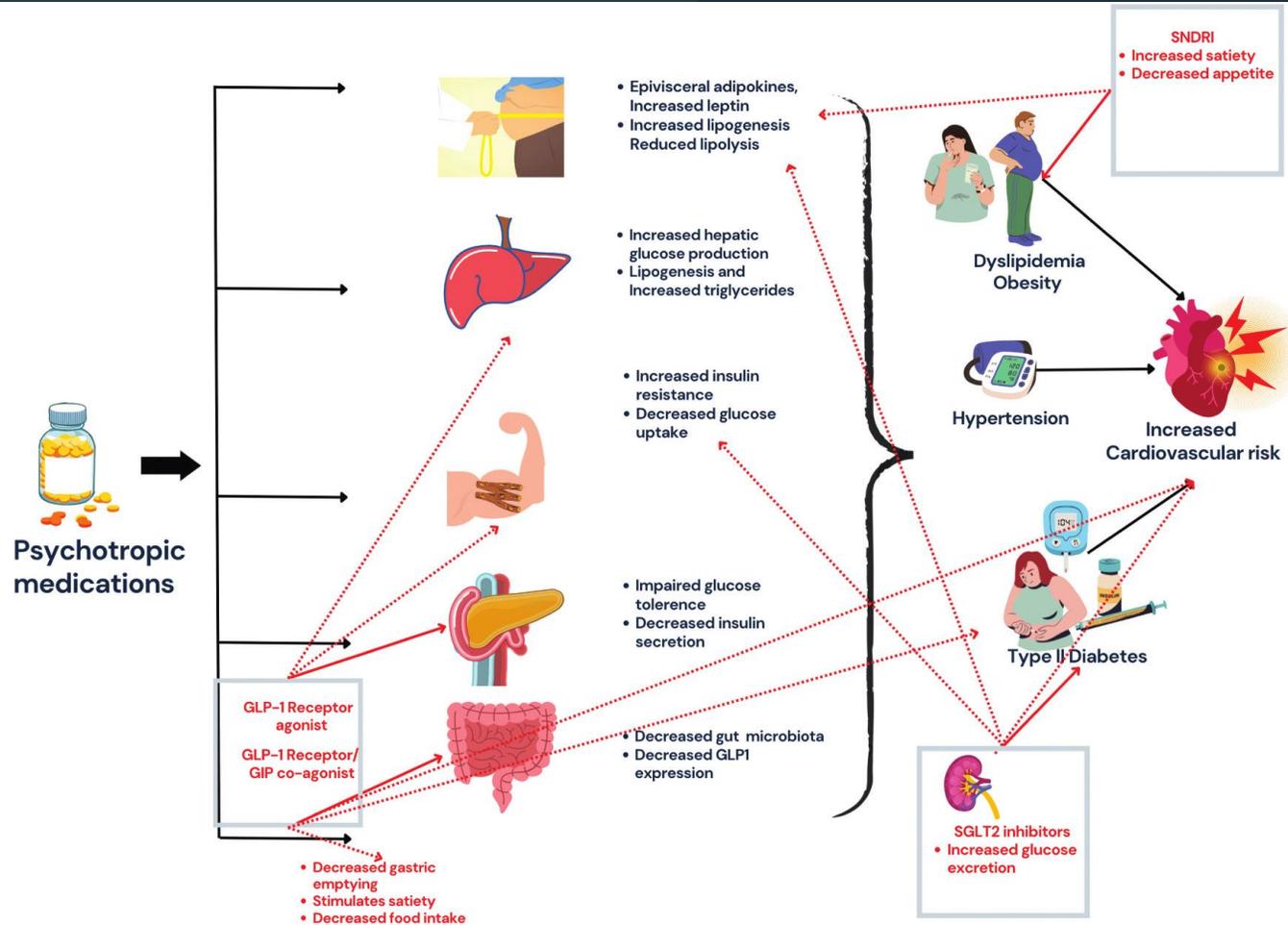
#### Antihypertensive therapy:

Refer to general practitioner or specialist

#### Vitamin D:

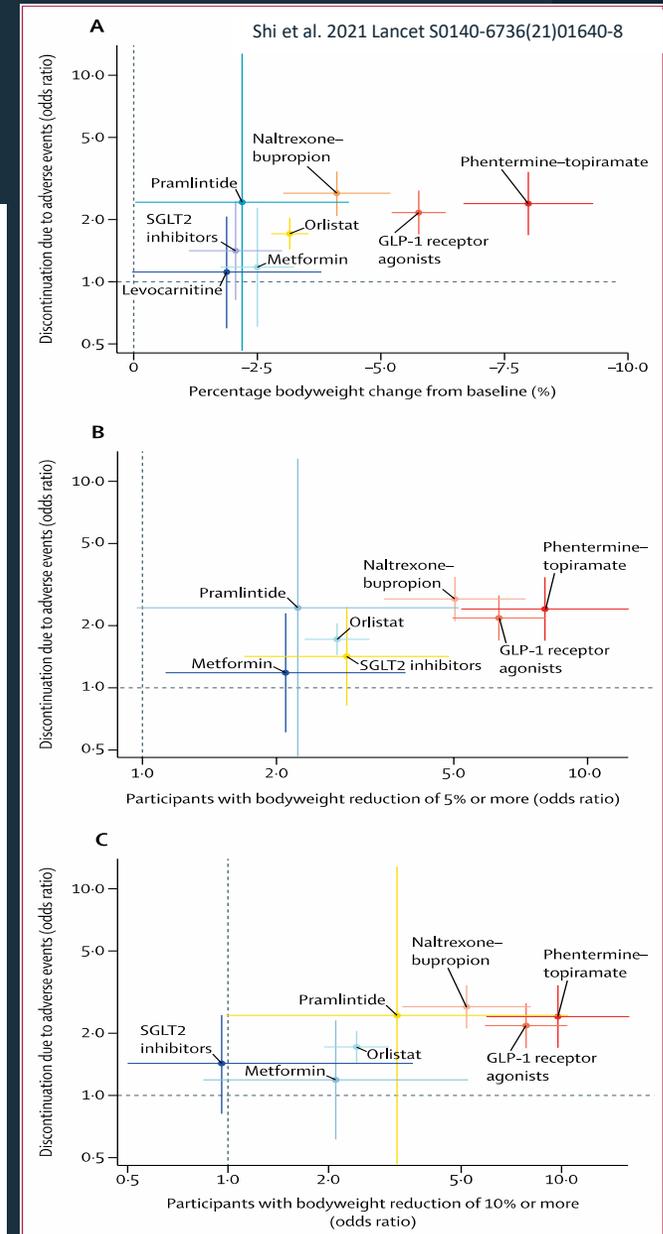
- <50 nmol/L: **Cholecalciferol treatment** 3000-5000 IU daily for 6-12 weeks to replenish stores followed by a maintenance dose of 1000-2000 IU daily
- Target: >80 nmol/L

# Emerging interventions



**Figure 1.** An overview of mechanisms of weight gain in individuals on psychotropic drugs including mechanism of action and effects of promising drugs highlighted in the review [73–75].

Note: "Bold red arrow-primary mechanism of action, dotted red arrow-possible/postulated mechanisms of action".



**Figure 5: Two-dimensional graphs of efficacy versus safety of weight-lowering drugs**  
 (A) Percentage change in bodyweight from baseline versus discontinuation due to adverse events. (B) Bodyweight reduction of 5% or more versus discontinuation due to adverse events. (C) Bodyweight reduction of 10% or more versus discontinuation due to adverse events. Effect sizes for drugs are represented by coloured nodes, with bars representing the corresponding 95% CI.

# Schizophrenia and Weight Improvement From Tirzepatide (SWIFT)

- Siskind, D. et al. MRFF \$3,839,117.60
- Hypothesis: In patients with schizophrenia with comorbid obesity, who fail to achieve 5% body weight loss with metformin over 16 weeks, adding semaglutide for 24 weeks will lead to significantly greater reduction in body weight compared to placebo.
- Primary Aim: To examine whether, compared to placebo, Tirzepatide, will lead to significantly lower 24-week endpoint weight adjusted for baseline.
- Secondary Aims: To (1) test whether, compared to placebo, among overweight/obese people with schizophrenia on antipsychotics, Tirzepatide will lead to:
  - a) an improvement in metabolic syndrome components (waist circumference, High Density Lipoprotein (HDL) cholesterol, triglycerides (TG), blood pressure and fasting glucose);
  - b) higher proportions of participants with weight loss >5% of body weight;
  - c) reduction in visceral adiposity and hepatic steatosis on Magnetic Resonance Imaging (MRI);and (2) examine participant preference, safety and tolerability regarding Tirzepatide.

# Hearts and Minds: A 3-arm Multicentre, Randomised, Double-Blind, Placebo-Controlled Study of Metformin and Atorvastatin for the Treatment of Depression

- Burke M. et al. MRFF \$10,000,000 MAGNET Trials network
- Hypothesis: Statins and Metformin are protective against depression
  - Statins - Geelong Osteoporosis Study (GOS). In a community sample of 1,491 adult women followed over 10 years, the age-adjusted odds ratio for major depressive disorder (MDD) among statin users was 0.13 (95% CI 0.02 to 1.02)
  - Metformin - anti-inflammatory as well as antioxidant properties, improves mitochondrial dysfunction, enhances neurotrophins like BDNF, antidepressant effects appeared to be linked to its capacity to reduce inflammation through inhibition of NF Kappa B and NLRP3 inflammasome activation.
- Primary Aim: determine the effectiveness of atorvastatin or metformin for the treatment of adults with MDD who remain symptomatic (MADRS $\geq$ 20) after an adequate (6 week) trial of established antidepressant therapy in a 16-week randomised, double-blind trial.



# Summary

- Mental illness is associated with excess cardiovascular morbidity and mortality
- Poor outcomes are associated with lifestyle and genetic factors but also lack of access to evidence-based care
- Psychotropic drugs contribute significantly to metabolic syndrome
- **Monitoring and intervening is critical !!!!!**
- Lifestyle interventions may not be successful in those with serious mental illness
- Known and emerging treatment for metabolic syndrome can reduce risk and may also target common mechanisms of mood disorders
- GPs, Cardiologists and Psychiatrists alike need to consider the bidirectional nature of mental illness and physical health



## OUR CONSENSUS

This page represents our *Consensus Statement* on the physical health of people living with a mental illness.

Our vision is to improve the quality of life of people living with mental illness by providing equity of access to quality health care, with the ultimate aim of bridging the life expectancy gap between people living with mental illness and the general population.

We commit to making the physical health of people living with mental illness a priority at all levels: national, state/territory and regional. We commit to bringing the importance of physical wellbeing across the spectrum of health – from promotion and prevention to treatment, for people of all ages across our whole society – to public attention, to spur change. We commit to partnering with consumers and carers, service providers (government, non-government and private), planners, policy makers and funders, to achieve our vision.

We will improve the physical health of people living with mental illness by acting to deliver:

1. a holistic, person centred approach to physical and mental health and wellbeing
2. effective promotion, prevention and early intervention
3. equity of access to all services
4. improved quality of health care
5. care coordination and regional integration across health, mental health and other services and sectors which enable a contributing life
6. the monitoring of progress towards improved physical health and wellbeing.

**We call on organisations across Australia to pledge to support this change – and encourage individuals to proactively seek the right services at the right time and in the right place.**

To sign up to this *Consensus Statement*, please go to [www.equallywell.org.au](http://www.equallywell.org.au)

# Equally Well Consensus Statement