Multimorbidity involving psychiatric disorders and insulin resistance:

clinical burden, shared genetic architecture, and mechanistic insights

Giuseppe Fanelli

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door

Giuseppe Fanelli
geboren op 21 december 1988
te Manduria (Italië)

Promotoren:
Prof. dr. Barbara Franke

Copromotoren:
Dr. Janita Bralten
Dr. Alessandro Serretti (Università degli Studi di Enna "Kore", Italië)
Dr. Chiara Fabbri (Università di Bologna, Italië)

Manuscriptcommissie:
Prof. dr. Arnt Schellekens (voorzitter)
Prof. dr. Nic van der Wee (Universiteit Leiden)
Dr. Yuri Milaneschi (Amsterdam UMC)

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by

Giuseppe Fanelli
born on December 21, 1988
in Manduria (Italy)

Supervisors:
Prof. dr. Barbara Franke

Co-supervisors:
Dr. Janita Bralten
Dr. Alessandro Serretti (Kore University of Enna, Italy)
Dr. Chiara Fabbri (University of Bologna, Italy)

Manuscript Committee:
Prof. dr. Arnt Schellekens (Chair)
Prof. dr. Nic van der Wee (Leiden University)
Dr. Yuri Milaneschi (Amsterdam UMC)

To my daughter,

May you never stop dreaming and striving
to achieve even the most challenging and arduous goals.
May your curiosity always be your guide,
leading you to new discoveries and adventures.
And may your mind remain free,
to question, to explore, and to shape your own path in life.

With all my love

A mia figlia,

Che tu non smetta mai di sognare e lottare
per raggiungere anche gli obiettivi più difficili e ardui.
Che la tua curiosità sia sempre la tua guida,
conducendoti verso nuove scoperte e avventure.
E che il tuo pensiero rimanga sempre libero,
per interrogarti, esplorare e tracciare il tuo cammino nella vita.

Con tutto il mio amore

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Chapter 1

General introduction

Background and rationale

Psychiatric disorders are a major cause of global disease burden, affecting hundreds of millions of individuals annually (GBD, 2022). Epidemiological research ranks these conditions among the leading contributors to disability-adjusted life years (DALYs), illustrating the magnitude of their public health impact (GBD, 2022). Beyond their contribution to functional impairment, psychiatric disorders impose considerable societal and economic costs, including direct healthcare expenditures and indirect losses linked to reduced productivity, unemployment, and caregiving demands (GBD, 2022).

Psychiatric disorders encompass a wide range of conditions with heterogeneous symptom profiles and variable clinical courses. While they are classified as distinct diagnostic entities, substantial heterogeneity and symptom overlap complicate both diagnosis and treatment (Zald & Lahey, 2017), and comorbidity is frequent. Their aaetiology is multifactorial, arising from the interplay between genetic predisposition, biological processes, and environmental influences (Panariello et al., 2022).

Psychiatric disorders do not occur in isolation. Growing evidence indicates that individuals with psychiatric disorders experience worse overall health outcomes, which cannot be explained by psychiatric symptoms alone. This adds an extra layer of difficulty to understanding these conditions as well as their clinical management.

Convergence of symptomatology and transdiagnostic dimensions in neuropsychiatric disorders

Despite differences in diagnostic criteria and clinical trajectories, psychiatric disorders share overlapping symptom dimensions, including mood instability, cognitive impairments, compulsivity, and alterations in social-behavioural regulation (see also **Table 1**; Guineau et al. (2023); Zald and Lahey (2017)). These transdiagnostic dimensions suggest that psychiatric conditions may not be entirely distinct entities but rather exist along a spectrum of shared cognitive and affective dysfunctions.

Mood instability and emotional dysregulation are observed across multiple psychiatric conditions, including major depressive disorder (MDD), bipolar disorder (BD), borderline personality disorder (BPD), and attention-deficit/hyperactivity disorder (ADHD). MDD is primarily characterised by persistent low mood, anhedonia, fatigue, and disturbances in sleep and appetite, but it is also frequently associated with cognitive dysfunction, including impairments in attention, executive function, and decision-making, which contribute to long-term disability (Marx et al., 2023). BD also involves mood instability, though it is episodic in nature, alternating between depressive and manic or hypomanic states. Manic episodes

include elevated mood, hyperactivity, impulsivity, and, in some cases, psychotic symptoms such as delusions of grandeur, while depressive episodes closely resemble those of MDD (Nierenberg et al., 2023). Outside acute mood episodes, BD is associated with persistent cognitive impairments, particularly in executive function, which persist across illness phases (Dickinson et al., 2017). Beyond mood disorders, emotional dysregulation in BPD and ADHD leads to heightened reactivity to stress, impulsivity, and difficulties in modulating mood, further demonstrating that affective instability is not limited to mood disorders (Richard-Lepouriel et al., 2016). However, while BD is characterised by episodic mood shifts, BPD and ADHD involve more chronic patterns of affective instability (Moukhtarian et al., 2018). This distinction highlights the need to consider mood dysregulation not only within the framework of mood disorders but also across conditions traditionally classified as neurodevelopmental or personality disorders.

Beyond mood dysregulation, cognitive dysfunction represents a core transdiagnostic feature spanning multiple disorders, including schizophrenia, neurodevelopmental conditions, and obsessive-compulsive spectrum disorders. Cognitive deficits are central to schizophrenia, where impairments in executive function, working memory, and attentional control are major contributors to functional impairment (Kahn et al., 2015). While delusions and hallucinations represent hallmark positive symptoms, schizophrenia also involves negative symptoms such as anhedonia, social withdrawal, and emotional blunting, which significantly overlap with features observed in depressive and anxiety disorders.

Notably, cognitive inflexibility is also a shared trait across multiple conditions, contributing to difficulties in set-shifting, problem-solving, and adapting to changing environmental demands. This is particularly evident in neurodevelopmental disorders such as ADHD and autism spectrum disorder (ASD), where deficits in cognitive flexibility and executive functioning are well documented (Lord et al., 2020; Thye et al., 2018). Individuals with ADHD frequently struggle with cognitive rigidity, particularly in adapting to new rules or shifting between tasks, reflecting impairments in set-shifting and response inhibition (Lord et al., 2020; Pearson et al., 2013). Similarly, ASD is characterised by atypical social communication, repetitive behaviours, and sensory processing abnormalities, alongside rigid cognitive patterns that further impair adaptive functioning (Lord et al., 2020; Thye et al., 2018). Given that schizophrenia shares developmental vulnerabilities with ADHD and ASD, it is increasingly conceptualised within a neurodevelopmental framework, where early disruptions in brain maturation, synaptic pruning, and neuroinflammatory processes are thought to contribute to disease onset in late adolescence or early adulthood (Owen & O'Donovan, 2017).

Table 1. Phenotypic overlap among neuropsychiatric disorders. This table provides an overview of core clinical manifestations, overlapping symptomatology, estimated age of onset, and cognitive features associated with selected neuropsychiatric disorders. Diagnostic classifications and symptomatology are based on criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA, 2013) and the International Classification of Diseases, 11th Revision (ICD-11) (WHO, 2019). The examples of overlapping symptoms with other psychiatric conditions illustrate shared features but do not represent an exhaustive list.

Disorder	Core symptoms	Overlapping symptoms across disorders	Typical onset	Primary cognitive observations
Alzheimer's Disease (AD)	Progressive cognitive decline with episodic memory impairment, executive dysfunction, disorientation, and aphasia. Later stages involve aphasia, apraxia, agnosia, and neuropsychiatric symptoms such as apathy, agitation, psychosis, and behavioural disinhibition.	MDD (apathy, cognitive slowing manifesting as "pseudodementia"); Schizophrenia (early-stage cognitive deficits, though distinct from neurodegenerative progression).	Typically >65 years	Severe impairment in episodic memory (encoding, consolidation, retrieval); progressive deficits in semantic memory manifests as anomia, category fluency deficits, and lexical retrieval failures. Executive dysfunction includes impairments in cognitive flexibility, response inhibition, and planning. As the disease advances, visuospatial disorientation and attentional deficits become more pronounced.
Attention-Deficit/ Hyperactivity Disorder (ADHD)	Impairments in sustained attention, excessive motor activity, impulsivity, and difficulties with inhibitory control. Symptoms must be present across multiple settings.	ASD (attention deficits, difficulties in social interaction); BD (impulsivity, risk-taking behaviours in manic episodes); Borderline personality disorder (impulsivity, emotional dysregulation); MDD (attention deficits).	Typically childhood	Deficits in working memory, sustained attention, inhibitory control, and response selection. Increased intra-individual variability in reaction times and difficulty with task persistence.
Anorexia Nervosa (AN)	Severe restriction of caloric intake leading to significantly low body weight, intense fear of gaining weight, and distorted body image.	OCD (obsessional preoccupations and compulsive behaviours related to food and weight control); ASD (rigid thought patterns, restricted interests); MDD (low mood, anhedonia).	Adolescence	Set-shifting deficits, cognitive inflexibility, perfectionistic thinking, and attentional biases toward weight-related stimuli.

Table 1. Continued

Disorder	Core symptoms	Overlapping symptoms across disorders	Typical onset	Primary cognitive observations
Autism Spectrum Disorder (ASD)	Social communication deficits, restricted/repetitive behaviours, interests or activities.	ADHD (attention deficits, impulsivity); OCD (ritualistic and repetitive behaviours); AN (cognitive rigidity, restricted interests), Schizophrenia (social withdrawal, emotional blunting).	Early childhood	Deficits in theory of mind, executive function (particularly cognitive flexibility), and social cognition.
Bipolar Disorder (BD)	Cyclical episodes of mania/ hypomania and depression, with potential for psychotic symptoms during severe episodes. Impulsivity, and reduced need for sleep are common.	Borderline personality disorder (emotional dysregulation, impulsivity, rapid mood shifts); ADHD (impulsivity, attentional deficits); Schizophrenia (psychotic symptoms during mood episodes); MDD (depressive episodes, possible psychotic features).	Late adolescence to early adulthood	Mood-state-dependent cognitive dysfunction: impaired attentional control, impulsivity during manic states, and psychomotor retardation during depressive episodes. Executive function deficits persist in euthymia.
Obsessive-Compulsive Disorder (OCD)	Presence of intrusive, distressing obsessions and repetitive compulsions aimed at reducing anxiety.	ASD (repetitive behaviours); AN (perfectionism, rigid cognitive style); TS (tic-related compulsions).	Late adolescence to early adulthood	Impaired cognitive flexibility, excessive error monitoring, heightened attentional bias toward threat-related stimuli, and deficits in set-shifting.
Major Depressive Disorder (MDD)	Persistent low mood, anhedonia, fatigue, sleep disturbances, psychomotor retardation, guilty feelings, and cognitive slowing. Severe cases may present with psychotic features.	Anxiety disorders (cognitive deficits); AD (pseudodementia); BD (shared depressive symptoms, psychotic features in severe cases); Schizophrenia (negative symptoms, e.g. anhedonia and social withdrawal)	Late adolescence to adulthood	Slowed processing speed, working memory deficits, and executive function. Attentional impairments are state-dependent and often improve with remission. Impaired reward responsiveness.

Table 1. Continued

Disorder	Core symptoms	Overlapping symptoms across disorders	Typical onset	Primary cognitive observations
Schizophrenia	Positive symptoms (hallucinations, delusions, disorganised thought) and negative symptoms (avolition, anhedonia, blunted affect, alogia), cognitive impairment.	BD (psychotic symptoms); OCD (obsessive thoughts); ASD (social cognition impairments, restrictive interests, limited reciprocity, avoidance of eye contact); MDD (social withdrawal, anhedonia and avolition, though with distinct neurocognitive profile).	Late adolescence to early adulthood	Deficits in executive function, working memory, and social cognition. Reduced processing speed and impaired contextual integration of information. Deficits persist independent of symptom fluctuations.
Tourette Syndrome (TS)	Chronic presence of multiple motor and vocal tics, often preceded by premonitory urges.	OCD (compulsions, intrusive urges); ADHD (impulsivity, inattention); ASD (stereotyped and repetitive behaviours).	Childhood	Deficits in response inhibition, increased cognitive load when suppressing tics, and abnormalities in sensorimotor integration. Some evidence of impaired attentional control and executive dysfunction.

References

APA. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. American psychiatric association.

WHO. (2019). International classification of diseases eleventh revision (ICD-11). Geneva: World Health Organization; 2022. License: CC BY-ND 3.0 IGO. In.

Beyond cognitive rigidity, compulsivity represents another transdiagnostic dimension with overlapping but distinct characteristics. While cognitive rigidity refers to difficulties in adapting to new information and shifting cognitive strategies, compulsivity is characterised by repetitive behaviours driven by an urge to reduce distress or avoid negative outcomes (Luigjes et al., 2019). Obsessive-compulsive disorder (OCD) exemplifies this pattern, with individuals experiencing intrusive, distressing thoughts (obsessions) and ritualistic behaviours (compulsions) aimed at reducing anxiety (Stein et al., 2019). However, compulsivity extends beyond OCD and is observed in schizophrenia, eating disorders, and other psychiatric conditions. In schizophrenia, compulsive-like behaviours often stem from cognitive inflexibility and impaired set-shifting rather than an anxiety-driven threat response, distinguishing them from the compulsions seen in OCD (McTeague et al., 2017; Mushtaq et al., 2011; Norman et al., 2019). Similarly, anorexia nervosa (AN), a disorder characterised by restrictive eating patterns and intense fear of weight gain, presents with disturbances in reward processing, interoception, and compulsivity, further illustrating cognitive-affective dysregulation and compulsivity as a shared feature across psychiatric illness (Zipfel et al., 2015).

Although psychiatric disorders primarily affect mood, cognition, and behaviour, neurodegenerative conditions such as Alzheimer's disease (AD) also present with significant psychiatric symptoms. AD is primarily characterised by progressive memory loss and executive dysfunction, yet depressive symptoms, anxiety, apathy, and agitation are commonly observed throughout its course (Scheltens et al., 2021). Additionally, psychotic symptoms, such as paranoic delusions, can emerge in later stages of AD, resembling those seen in primary psychotic disorders (Ismail et al., 2022). This overlap suggests that cognitive and affective dysfunctions span both psychiatric and neurodegenerative conditions, further supporting the need for a dimensional, rather than purely categorical, understanding of mental illness.

Given these substantial areas of symptom convergence, psychiatric comorbidity—the co-occurrence of two or more mental disorders within the same individual—is frequently observed in clinical practice (Nordgaard et al., 2023). For instance, BD and ADHD frequently co-occur, with studies suggesting a strong link between these conditions (Schiweck et al., 2021). This overlap is particularly evident in impulsivity, emotional dysregulation, and executive dysfunction, which persist across illness phases, although impulsivity is most pronounced during manic or hypomanic episodes in BD and represents a core trait of ADHD (Faraone et al., 2015; Vieta et al., 2018). Similarly, OCD and Tourette's syndrome (TS) show high rates of comorbidity, with TS often involving repetitive behaviours and intrusive urges that may resemble compulsions but are typically driven by premonitory sensory experiences rather than obsessive thoughts (Shitova et al., 2023). Other notable

examples of comorbidity include MDD and anxiety disorders, which frequently co-occur due to overlapping stress-response dysregulation and heightened sensitivity to negative affect (Davies et al., 2023). AN is frequently comorbid with OCD, with shared characteristics including cognitive rigidity, perfectionism, and compulsive behaviours related to food intake and body image (Sternheim et al., 2022). In psychotic disorders, schizophrenia and substance use disorders (SUDs) often co-occur, with some estimates suggesting that over 25% of individuals with schizophrenia experience a comorbid SUD (Nesvag et al., 2015). This association is particularly problematic, as substance use can worsen psychotic symptoms, increase relapse risk, and interfere with treatment adherence (Miller et al., 2009).

Despite its widespread recognition, psychiatric comorbidity remains a concept in need of theoretical refinement (Nordgaard et al., 2023). Nosological frameworks such as the Diagnostic and Statistical Manual of Mental disorders (DSM) and International Classification of Diseases (ICD) classify neuropsychiatric disorders as distinct categorical entities, yet substantial evidence suggests that many co-occurring conditions may not be truly independent disease processes. Instead, they may reflect shared pathophysiological mechanisms or transdiagnostic dimensions of psychopathology, spanning multiple diagnostic categories (Lai et al., 2019; Pearlson, 2015; see **Table 1**)..

Beyond the theoretical challenges, psychiatric comorbidity has significant clinical implications. Individuals with multiple psychiatric diagnoses exhibit greater symptom severity, higher rates of functional impairment, and poorer treatment outcomes (Archer et al., 2019; Barlattani et al., 2023; Ziobrowski et al., 2021). As for the latter, treatment of comorbid conditions often requires more complex strategies, as different disorders may demand competing therapeutic approaches. For instance, selective serotonin reuptake inhibitors (SSRIs) are first-line treatments for depression and anxiety but can induce manic episodes in individuals with BD, necessitating careful medication management (Ott, 2018). Similarly, cognitive-behavioural therapy interventions targeting obsessive-compulsive symptoms in ASD or AN may need to be adapted to account for the distinct cognitive and emotional processing styles observed in individuals with these conditions (Flygare et al., 2020).

Among the treatment challenges, therapeutic response is an additional topic complicated by comorbidity and shared aaetiology. Despite the availability of pharmacological and psychological treatments, response rates in psychiatric disorders generally remain suboptimal (Howes et al., 2022; Solmi et al., 2023). Unlike other areas of medicine, where diagnoses are often grounded in clear pathophysiological mechanisms, psychiatric disorders continue to be classified based on symptomatology rather than underlying aaetiology (Jablensky, 2016). This

contributes to variability in treatment response. Indeed, a significant proportion of individuals with mood disorders, including MDD and BD, fail to achieve remission despite receiving guideline-concordant treatment, a phenomenon termed treatment resistance (Solmi et al., 2023). In MDD, treatment-resistant depression (TRD), defined as the failure to respond to at least two adequate trials of antidepressants, affects approximately 30% of patients (McIntyre et al., 2023). TRD is associated with greater symptom severity, higher rates of comorbid anxiety and substance use disorders, and poorer overall functioning (Brenner et al., 2020). Similar challenges are observed across other psychiatric conditions. For instance, up to 20–50% of individuals with schizophrenia are classified as treatment-resistant, often requiring clozapine, a medication associated with significant metabolic side effects (Nucifora et al., 2019). In ADHD, treatment adherence and efficacy are frequently limited by side effects and comorbid conditions (Kamimura-Nishimura et al., 2019), while ASD interventions often fail to address core symptoms (McCracken et al., 2021), reflecting the substantial unmet therapeutic needs in these populations. Shared disorder dimensions and comorbidity are part of the problem, as they can make it difficult to determine whether a lack of response to treatment reflects true pharmacological resistance or diagnostic misclassification. For instance, individuals with BD who present with comorbid anxiety or obsessive-compulsive symptoms may not only fail to respond to standard antidepressant treatments but may also experience worsening mood instability (Amerio et al., 2019; Mucci et al., 2018). Similarly, individuals with schizophrenia who exhibit persistent negative symptoms and cognitive dysfunction despite treatment may be misdiagnosed with comorbid depression, leading to inappropriate pharmacological interventions.

The challenges listed above highlight the urgent need for research aiming to improve our understanding of the mechanisms underlying psychiatric symptomatology, especially of shared pathophysiological processes. Identifying these mechanisms is important not only for refining diagnostic classification but also for improving treatment response predictions and developing biologically informed therapeutic strategies (Quinlan et al., 2020). One can envisage future hierarchical diagnostic models incorporating trait vs. state distinctions, longitudinal symptom trajectories, and neurobiological correlates, which may enhance clinical decision-making, but these approaches critically depend on first clarifying the biological mechanisms linking different psychiatric conditions (Nordgaard et al., 2023). Reliable biomarkers and mechanistically driven classifications based on biologically meaningful entities across (and within) disorders with distinct therapeutic responses will be needed for the development of precision medicine approaches. Incorporating mechanistic insights from molecular 'omics' and

neurobiology will be essential for improving treatment personalisation and clinical outcomes.

Comorbidity between neuropsychiatric disorders and insulin resistance-related conditions

While comorbidity among psychiatric disorders is well established, psychiatric disorders also frequently co-occur with physical health conditions, leading to psychiatric–somatic multimorbidities. Among these, the co-occurrence of psychiatric disorders with metabolic and cardiovascular conditions is particularly frequent (Nielsen et al., 2021; Rajan & Menon, 2017). The psychiatric-somatic association extends beyond the impact of lifestyle factors or medication effects, as research suggests that psychiatric and metabolic conditions might share biological mechanisms that influence their co-occurrence and clinical outcomes (Garrido-Torres et al., 2021).

Individuals with severe mental illness, including schizophrenia, BD, and MDD, face a significantly reduced life expectancy, with estimates suggesting a lifespan reduction of approximately 15 years compared to the general population (Walker et al., 2015). A meta-analysis of mortality in psychiatric disorders found a pooled relative risk of 2.22 for all-cause mortality, indicating the substantial public health burden posed by these conditions (Walker et al., 2015). While suicide is a major contributor to premature mortality, the majority of excess deaths in psychiatric populations result from natural causes, including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and also chronic respiratory conditions (Walker et al., 2015). Importantly, psychiatric disorders are associated with a higher prevalence of adverse health behaviours, such as physical inactivity, poor diet, smoking, and substance use, which contribute to elevated cardiometabolic risk (Walker et al., 2015). In addition to lifestyle-related risks, structural barriers in healthcare access exacerbate disparities in medical outcomes. People with psychiatric disorders often receive suboptimal medical care, with lower rates of preventive screenings, delayed diagnoses, and undertreatment of medical conditions (Scott & Happell, 2011). Moreover, diagnostic overshadowing — where physical symptoms are misattributed to mental illness — further complicates appropriate medical management (Hallyburton, 2022). This contributes to disparities in mortality rates that persist despite advancements in medical treatments. While effective interventions targeting psychiatric disorders exist, their impact on longevity remains limited unless medical comorbidities are simultaneously addressed (Walker et al., 2015).

Large-scale cohort studies have demonstrated that individuals diagnosed with MDD, BD, schizophrenia, ADHD, and other psychiatric disorders exhibit higher rates

of metabolic conditions, especially obesity, T2DM, and metabolic syndrome (MetS), than the general population (Penninx & Lange, 2018; Vancampfort et al., 2015; Wimberley et al., 2022). Likewise, metabolic conditions have been associated with an increased risk for developing psychiatric disorders, suggesting a bidirectional relationship potentially driven by overlapping physiological and behavioural factors (Wimberley et al., 2022). Adverse health behaviours and other environmental factors have been implicated in the psychiatric-metabolic comorbidity, but also intrinsic metabolic dysfunctions have been identified as contributing factors (Mazereel et al., 2020). Notably, metabolic dysregulation often precedes the onset of psychiatric illness, challenging the notion that this dysregulation is a consequence of psychotropic medication exposure (Mazereel et al., 2020). Longitudinal studies in drug-naïve individuals with psychiatric disorders have demonstrated that elevated fasting glucose, altered lipid profiles, and insulin resistance (IR) — a condition in which peripheral tissues become less responsive to insulin, leading to impaired glucose regulation — can be observed before the onset of psychiatric symptoms or the initiation of psychotropic treatment (Garrido-Torres et al., 2021). This evidence is consistent with intrinsic biological vulnerabilities contributing to the observed metabolic dysfunction.

While metabolic abnormalities can present prior to psychiatric illness onset, psychotropic medications — particularly second-generation antipsychotics and certain antidepressants, with high affinity for histamine and serotonin 2C receptors — exacerbate metabolic risk by inducing weight gain, IR, and dyslipidaemia (Pillinger et al., 2020; Virk et al., 2004). This pharmacologically induced metabolic burden further compounds the risk for cardiometabolic disease, especially in individuals with pre-existing vulnerabilities. These findings emphasise the need for integrated treatment approaches that take into account both psychiatric symptom management and metabolic health, rather than treating them as separate entities.

That metabolic dysfunction can present before psychiatric illness onset likely has developmental origins. Indeed, maternal IR-related conditions, including T2DM, gestational diabetes mellitus, and obesity, are associated with an elevated risk for psychiatric disorders in offspring (Kong, Chen, et al., 2020; Kong, Nilsson, et al., 2020). Large-scale cohort studies have demonstrated that prenatal exposure to maternal metabolic dysregulation is linked to a heightened risk for ASD, ADHD, mood disorders, and conduct disorders in children (Kong, Nilsson, et al., 2020). Additionally, maternal pre-pregnancy obesity has been implicated in a two- to three-fold increased risk for schizophrenia in offspring (Kong, Chen, et al., 2020). The association between maternal obesity and offspring eating disorders has also been documented, with prospective cohort studies showing a positive correlation between early pregnancy BMI and eating disorder risk in offspring (Kong, Chen, et al., 2020). These findings

highlight the potential for intergenerational transmission of metabolic and psychiatric vulnerability, reinforcing the need for early identification of at-risk individuals.

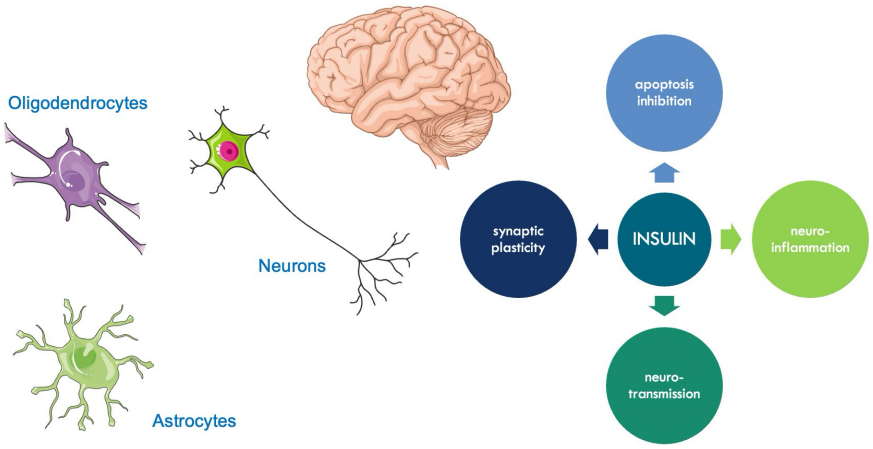

Figure 1. Insulin signalling in the brain: roles in neuronal and glial function.

Insulin crosses the blood-brain barrier and binds to insulin receptors on neurons, astrocytes, and oligodendrocytes, influencing multiple neurobiological processes. In the central nervous system, insulin plays a key role in synaptic plasticity, neurotransmission, apoptosis inhibition, and neuroinflammation regulation. Through its interactions with neurotransmitter systems such as serotonin and dopamine, insulin modulates neuronal survival, function, and communication, highlighting its relevance in both cognitive processes and neuropsychiatric disorders.

Insulin signalling in the brain

The co-occurrence of psychiatric disorders and metabolic dysfunction suggests a need to examine shared biological mechanisms, and previous literature points to a potential involvement of insulin signalling (Milstein & Ferris, 2021). Insulin plays a dual role in peripheral metabolism and central nervous system (CNS) function. Insulin crosses the blood-brain barrier, and it is also produced locally in the brain, where it binds to insulin receptors expressed on neurons and glial cells (Csajbok & Tamas, 2016). Insulin signalling within the CNS regulates synaptic plasticity, neurotransmission, neuroinflammation, and neuronal survival (Fanelli & Serretti, 2022) (see **Figure 1**).

Disruptions in brain insulin signalling can lead to dopaminergic dysfunction, particularly affecting the mesolimbic reward circuit, which modulates hedonic responses (Gruber et al., 2023). Such alterations may contribute to anhedonia, characterised by a diminished ability to experience pleasure and reduced motivation, which is a core symptom of depression that is often resistant to available pharmacotherapies (Gruber et al., 2023; Martone et al., 2024). Insulin receptors

are highly expressed in the mesolimbic dopamine system, including the ventral tegmental area (VTA), nucleus accumbens (NAc), and striatum, which regulate reward processing and motivation (Gruber et al., 2023). Under normal physiological conditions, insulin enhances dopamine clearance by increasing dopamine transporter (DAT) expression, while simultaneously reducing glutamatergic excitatory input, ultimately regulating extracellular dopamine levels (Gold, 2015; Gruber et al., 2023). However, IR impairs these mechanisms. IR reduces DAT expression, leading to excess extracellular dopamine, particularly in the NAc and striatum. Although transient increases in dopamine might initially enhance reward sensitivity, chronic dysregulation disrupts synaptic plasticity, blunting hedonic response (Carter & Swardfager, 2016). Neuroimaging studies in individuals with IR consistently show diminished responsivity of reward-related brain regions, supporting the association between metabolic dysfunction and anhedonia (Carter & Swardfager, 2016; Gruber et al., 2023). The phosphoinositide 3-kinase (PI3K)/Akt (protein kinase B) pathway, which is a component of insulin signalling, regulates dopamine clearance by modulating DAT expression and function. Experimental studies demonstrate that acute insulin application in the VTA enhances DAT activity through PI3K and mammalian target of rapamycin (mTOR) signalling pathways, reducing somatodendritic dopamine levels (Fanelli et al., 2025; Gruber et al., 2023). However, chronic hyperglycaemia and prolonged IR impair these regulatory mechanisms, leading to glutamatergic dysregulation and neurotoxicity in the medial prefrontal cortex (mPFC), a region implicated in mood regulation and cognitive control (Fanelli et al., 2025). Insulin signalling also influences corticostriatal circuits, which regulate reward anticipation, effort-based decision-making, and goal-directed behaviour. Disruptions in these pathways are linked to reduced motivation, a defining feature of motivational anhedonia (Gold, 2015). Preclinical models of diet-induced IR demonstrate deficits in effort-based reward tasks, mirroring the behavioural phenotypes observed in individuals with MDD (Gruber et al., 2023).

In addition to insulin, insulin-like growth factor-1 (IGF-1) plays a role in neuronal function and mood regulation (Fanelli et al., 2025). Despite structural similarities between insulin and IGF-1, these hormones exhibit distinct spatial distribution and functional roles within the CNS (Werner & LeRoith, 2014). Both insulin and IGF-1 activate overlapping intracellular pathways, such as PI3K/Akt and mitogen-activated protein kinase (MAPK) cascades, yet their receptor distribution varies, influencing their distinct contributions to neurobiology (Fanelli et al., 2025). Insulin receptors are abundantly expressed in the hippocampus, cerebral cortex, hypothalamus, and cerebellum — regions involved in learning, memory, and emotional regulation. IGF-1 receptors, while also widely distributed, are particularly concentrated in the cortex, hippocampus, and thalamus, with moderate expression in the olfactory

bulb, hypothalamus, and cerebellum (Fanelli et al., 2025). Experimental findings indicate that IGF-1 promotes hippocampal neurogenesis, and reduced IGF-1 levels are associated with depressive-like behaviours in animal models (Fanelli et al., 2025). Furthermore, IGF-1 interacts with serotonin receptors, including the 5-HT3 receptor, facilitating neurogenesis and exerting antidepressant-like effects independent of traditional serotonin reuptake mechanisms (Fanelli et al., 2025).

An additional disorder-overarching trait associated with altered insulin-mediated dopamine regulation is impulsivity, a defining feature of ADHD, BD, and substance use disorders (Eckstrand et al., 2017). Insulin signalling in the striatum influences dopamine clearance and synaptic availability, and its dysregulation leads to heightened impulsivity in addition to impaired reward processing (Daws et al., 2011). In individuals with IR, blunted insulin responses correlate with dopaminergic dysfunction, potentially predisposing them to impulsivity-driven behaviours (Eckstrand et al., 2017; Gruber et al., 2023). Beyond psychiatric conditions, insulin dysfunction has also been linked to impulsivity in obesity, where alterations in reward sensitivity and impulse control contribute to disinhibited eating behaviours and compulsive reward-seeking (Sfera et al., 2017). Neuroimaging studies indicate that individuals with high impulsivity scores exhibit structural and functional abnormalities in the orbitofrontal cortex and prefrontal regions, areas critical for decision-making and self-regulation (Sfera et al., 2017). These deficits, observed in both psychiatric impulsivity and obesity-related behaviours, suggest a shared metabolic-neurobehavioural vulnerability. Additionally, epidemiological studies report that obese individuals display increased risk-taking behaviours, supporting an association between metabolic dysfunction and impulsivity (Sfera et al., 2017). The connection between IR, impulsivity, and altered reward processing extends beyond metabolic conditions and is particularly evident in ADHD, where deficits in impulse control manifest in difficulties with academic performance (Faraone et al., 2015). Impaired insulin signalling may further exacerbate impulsivity in BD and SUDs, where dysregulated reward sensitivity is a core component of the underlying pathophysiology (Gomez-Coronado et al., 2018).

Beyond its role in reward, motivation, and impulsivity, IR has also been implicated in cognitive inflexibility, a feature observed in ASD, schizophrenia, OCD, and AD, as previously mentioned (Barlattani et al., 2023). This executive dysfunction is characterised by rigid thought patterns, difficulty adapting to new information, and repetitive behaviours. Preclinical studies suggest that IR impairs behavioural adaptation and decision-making by altering neuronal signalling within corticostriatal pathways, which regulate habit formation, goal-directed behaviour, and cognitive flexibility (Sullivan et al., 2023). For example, high-fat diet-induced IR in rodents has been shown to increase perseverative responding and reduce

behavioural flexibility, closely mirroring cognitive impairments observed in OCD and ASD (Yao et al., 2023). Moreover, TALLYHO/JngJ mice, a preclinical model of T2DM, exhibit behavioural phenotypes suggestive of compulsivity, a trait often associated with cognitive rigidity. (Sullivan et al., 2023; van de Vondervoort et al., 2019). These findings support the hypothesis that metabolic dysfunction may contribute to impaired cognitive flexibility and suggest that metabolic dysregulation may be a contributing factor to cognitive dysfunction across multiple psychiatric conditions, underscoring the need for integrative approaches in psychiatric research.

IR is also increasingly recognised as a contributing factor to neurodegeneration. In AD, impaired insulin signalling in the brain has gained attention, leading some researchers to describe AD as "type 3 diabetes" due to its overlap with T2DM in terms of insulin receptor dysfunction, glucose metabolism deficits, and neuroinflammation (De Sousa et al., 2020; Nguyen et al., 2020). Defective insulin signalling in AD contributes to amyloid-β aggregation, tau hyperphosphorylation, and neuroinflammatory cascades, all of which lead to synaptic dysfunction and neuronal loss (De Sousa et al., 2020; Kellar & Craft, 2020). Importantly, markers of altered insulin signalling are detectable even in preclinical stages of AD, suggesting a role in disease progression (Stanley et al., 2016). Given such evidence, therapeutic approaches targeting insulin pathways have been explored: intranasal insulin administration has been shown to improve cognitive function in individuals with mild cognitive impairment and AD, with some studies indicating modulation of amyloid-β levels and insulin signalling pathways (Arnold et al., 2018). Interestingly, the cognitive benefits of intranasal insulin appear genotype-dependent, with APOE ε4 non-carriers experiencing more pronounced improvements (Arnold et al., 2018). Neuroimaging studies have demonstrated that intranasal insulin enhances resting-state functional connectivity in the hippocampus and increases regional cerebral blood flow, further supporting its potential role in mitigating AD-related neuropathology (Arnold et al., 2018). While AD provides a prominent example of the link between insulin dysregulation and cognitive impairment, there is growing recognition that similar mechanisms, such as neuroinflammation and disrupted glucose metabolism, may also play roles in mood disorders, schizophrenia, and OCD, as previously mentioned (Fernandes et al., 2022; Kapogiannis et al., 2019; Martin et al., 2021; van de Vondervoort et al., 2016).

Although the exact mechanisms linking psychiatric and IR-related conditions remain under investigation, existing research underscores the importance of understanding possible shared biological pathways, of which insulin signalling is one, more thoroughly. Investigating these mechanisms could provide a foundation for identifying biomarkers and developing early intervention strategies to mitigate the burden of psychiatric-metabolic multimorbidity. Considering psychiatric

disorders within a broader framework of diseases of the body and not only of the mind can thus contribute to refined diagnostic models, improved treatment strategies, and better patient outcomes.

Importance of genetic studies in psychiatry and cross-disorder findings among psychiatric disorders

Psychiatric disorders are heritable, as demonstrated by twin and family-based studies. Estimates suggest that genetic factors explain up to 80% of the phenotypic variability for certain psychiatric disorders (Watson et al., 2020). A way to find out which genetic factors contribute to psychiatric disorders is to perform genome-wide association studies (GWASs), as has been done for schizophrenia, BD, and MDD, and many other psychiatric conditions (Howard et al., 2019; Mullins et al., 2021; Trubetskoy et al., 2022). In GWASs, millions of common genetic variants — i.e., single-nucleotide polymorphisms (SNPs) with a minor allele frequency exceeding 1% in the population) — are systematically examined across the genome and tested for allele frequency differences between individuals with a certain condition and those without it, in order to identify susceptibility loci. While individual common genetic variants typically exert small effects on disorder risk, their cumulative contribution accounts for a substantial proportion of genetic liability (Trubetskoy et al., 2022).

Two important insights have emerged from GWAS investigations in the conditions of interest for this thesis. First, psychiatric disorders display high levels of polygenicity, meaning that risk is conferred by numerous, possibly thousands, of variants spread throughout the genome, each with a small effect. SNP-based heritability estimates from GWASs indicate that common variants explain only a part of disorder liability, e.g. approximately 8.4% of MDD liability (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Electronic address & Major Depressive Disorder Working Group of the Psychiatric Genomics, 2025) and 24% for schizophrenia (Trubetskoy et al., 2022). The polygenic patterns also extend to IR-related conditions, such as obesity and T2DM, which rank among the most heritable common diseases. Twin studies estimated the heritability of adiposity measures at 50–90% and that of T2DM at 72% (Bouchard, 2021; Willemsen et al., 2015). Large-scale GWASs have identified multiple genomic loci associated with these conditions and related traits (Mahajan et al., 2022; Pulit et al., 2019; Watanabe et al., 2019). Second, extensive genetic overlap is observed among different psychiatric disorders.

Cross-disorder genomic analyses have e.g. revealed significant positive genetic correlations of schizophrenia with BD, as well as with MDD, albeit to a lesser extent, suggesting shared underlying risk factors (Cross-Disorder Group of the Psychiatric

Genomics Consortium, 2019). Similarly, moderate genetic correlation has been observed between AN, OCD, and TS, indicating that phenotypic comorbidity in clinical settings may, at least in part, reflect shared genetic architecture (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Beyond disorder-specific genetic relationships, a general psychopathology factor (p-factor) has been proposed as a single latent dimension that captures shared genetic liability across multiple psychiatric disorders (Sprooten et al., 2022). Based on structural equation modelling (SEM) and principal component analysis, the polygenic p-factor explains between 20% and 43% of SNP effects across disorders (Sprooten et al., 2022). This genomic dimension reflects pleiotropic effects of common genetic variants, meaning that many risk loci contribute to multiple disorders rather than being disorder-specific. Building upon this framework, recent cross-disorder genomic studies using refined statistical techniques, such as genomic SEM and transcriptome-wide SEM (T-SEM), have further refined our understanding of shared and distinct genetic architectures. Recent work by Grotzinger et al. (2023) applied T-SEM to analyse 13 major psychiatric disorders and identified five transdiagnostic genomic factors, which group psychiatric disorders based on shared genetic risk: thought disorders (schizophrenia, BD), compulsive disorders (OCD, AN, TS), internalising disorders (MDD, anxiety disorders, post-traumatic-stress disorder), neurodevelopmental disorders (ADHD, ASD), and SUDs (Grotzinger et al., 2023). These results support the view that genetic psychiatric risk factors do not conform to categorical diagnostic boundaries but rather contribute to shared biological liabilities across disorders, challenging conventional diagnostic classifications.

Beyond disorder-specific constructs, genetic influences extend to broader traits with transdiagnostic relevance. For instance, neuroticism and sensitivity to early-life stress, both traits with substantial heritability, are strongly correlated with mood and anxiety disorders (Nagel et al., 2018). This shared heritability underscores the idea that genetic liability is distributed along continuous dimensions rather than restricted to discrete diagnostic categories, another piece of evidence supporting the need for a shift toward dimensional or transdiagnostic conceptualisations of psychiatric conditions. Polygenic scores (PGSs), which are derived from large GWAS summary statistics, provide a means to quantify genetic risk along such dimensions. PGSs aggregate the effects of multiple common genetic variants into a single score, estimating an individual's genetic predisposition to a particular trait or disorder (Kullo et al., 2022; Oliva et al., 2023). PGSs are instrumental in studying genetic overlap among psychiatric conditions; for the time being, their predictive value remains limited due to low variance explained and limited generalisability across populations, with current models capturing only a small proportion of disease risk in psychiatric disorders (Lewis & Vassos, 2020). Although PGSs have been used to

examine transdiagnostic liability, their role in risk stratification and personalised treatment remains under investigation (Kullo et al., 2022; Oliva et al., 2023).

GWASs have successfully been used to identify multiple psychiatric risk genomic loci; translating these associations into biological disease mechanisms is the current challenge. Several factors contribute to this difficulty, which include the following: most genome-wide significant loci are located in non-coding regions, making it unclear how they influence gene expression and neur(on)al function (Schipper & Posthuma, 2022); moreover, pleiotropy — where a single genetic variant influences more than one trait — complicates causal inference, making it challenging to determine whether a specific genetic variant contributes directly to disease risk or reflects broader transdiagnostic liability (Hemani et al., 2018). Integrative approaches that combine genetic findings with transcriptomic, epigenomic, and functional data are needed to infer causal mechanisms and identify biologically relevant pathways associated with psychiatric disorders (Gallagher & Chen-Plotkin, 2018). These approaches can help refine our understanding of how genetic variation translates into disease risk, setting the stage for more mechanistic insights into psychiatric pathology. In addition, imaging genetics studies have provided insights into how polygenic risk influences brain structure and function, helping to bridge the gap between GWAS findings and neurobiological mechanisms (Gallagher & Chen-Plotkin, 2018).

Two decades of genome-wide studies and extension into other molecular 'omics' approaches have advanced our understanding of genetic risk in psychiatric disorders considerably, but many open questions remain. Among them is the question how genetic influences extend beyond the CNS. The extent to which psychiatric-somatic (e.g., IR-related metabolic) comorbidity reflects shared genetic factors remains unresolved. The next steps involve exploring whether the same or related genetic factors and related mechanistic pathways predispose individuals to both psychiatric and IR-linked phenotypes.

Research objectives

Above, I have argued that psychiatric disorders represent a significant global health challenge, characterised by diverse clinical manifestations and overlapping transdiagnostic traits, substantial personal and societal costs, as well as reduced life expectancy. High rates of comorbidity among psychiatric disorders, frequent psychiatric-somatic comorbidity, and the high prevalence of suboptimal treatment response and outcome complicate clinical management. This all emphasises the urgent need for research that integrates biological, clinical, and epidemiological

perspectives to move beyond categorical diagnostic frameworks toward a dimensional, biological mechanism-informed understanding of psychiatric disorders that offers room for shared symptom domains and physical comorbidities.

Addressing this need, the overarching goal of this thesis was to investigate how psychiatric disorders and IR-related metabolic conditions influence clinical progression, treatment response, and overall multimorbidity in patients, and to determine whether these highly heritable neuropsychiatric and somatic conditions share genetic risk factors and biological mechanisms. As previously mentioned, recent insights suggest that the influence of insulin extends beyond peripheral tissues and modulates central processes such as neurotransmission and neuroplasticity (Milstein & Ferris, 2021). Parallel findings indicate that numerous psychiatric conditions display considerable polygenic risk overlaps (Grotzinger, Mallard, et al., 2022; Lee et al., 2021), which may potentially also extend to somatic conditions like obesity and T2DM. Here, I focused on investigating how the comorbidity between neuropsychiatric and IR-related conditions influences both the clinical trajectory and treatment outcomes of affected individuals, and whether the observed comorbidity reflects shared genetic and biological pathways. My thesis addresses three core objectives, integrating clinical and genomic methodologies to systematically investigate the intersections of psychiatric and IR-related conditions:

Objective 1: examine the clinical burden and phenotypic associations between psychiatric and insulin resistance-related conditions

The first objective was to assess the clinical, cognitive, and treatment-related burden associated with the comorbidity between psychiatric disorders and IR-related conditions. In **Chapters 2** to **4**, I approached this question through systematic reviews, longitudinal analyses, and large-scale observational studies. These chapters evaluated how dysregulated glucose and insulin parameters coincide with cognitive impairment, treatment resistance, and distinct symptom profiles in mood disorders, aiming to clarify the clinical consequences of this comorbidity.

Objective 2: investigate the genetic architecture that underpins psychiatric-insulin resistance multimorbidity

The second objective was to determine the extent to which genetic factors contribute to the observed comorbidity between psychiatric disorders and IR-related metabolic conditions. This was explored in **Chapters 5** to **7**, in which I assessed global and regional genetic overlap between psychiatric and metabolic traits. Additionally, latent transdiagnostic genetic factors were examined to

determine whether shared genetic liability contributes to multimorbidity across psychiatric and IR-related metabolic conditions.

Objective 3: identify potential biological mechanisms underlying the comorbidity and explore therapeutic targets through integrative genomic approaches

Third, in this thesis, I evaluated whether the convergent genetic and biological processes — once identified — might be leveraged for improving personalised treatment interventions. Building on novel genomic findings, in **Chapters 6** and **7**, I investigated how shared genetic risk translates into dysregulated molecular processes. Furthermore, **Chapter 3** examined whether existing pharmacological compounds, such as antidiabetic medications, could be repurposed for psychiatric disorders. More broadly, I evaluated throughout the thesis potential druggable targets shared between psychiatric and metabolic conditions, providing preliminary insights into novel therapeutic interventions, which will need further validation in future studies.

In this work, I adopted an interdisciplinary approach, systematically linking clinical, genomic, and other -omics data to elucidate how metabolic dysfunction intersects with the pathophysiology of psychiatric disorders. By bridging metabolic and psychiatric research domains, I aimed to provide a deeper understanding of the biological processes that contribute to psychiatric and IR-related metabolic multimorbidity. My findings lay the groundwork for future studies focused on improving risk stratification, early detection, treatment personalisation, and the development of interventions for individuals with increased susceptibility to both psychiatric and metabolic conditions.

General overview of methods and datasets

Different methods were adopted in this thesis to investigate the association of metabolic conditions IR-related with psychiatric disorders and related symptomatology. The studies described in **Chapters 2** through **7** collectively draw upon literature reviews, large-scale primary care databases, and publicly available summary statistics from extensive GWASs. The methodological frameworks and participant samples used across **Chapters 2** through **7** are summarised here, with detailed descriptions provided in the respective chapters.

Systematic review approach on IR-related conditions and cognitive functioning (Chapter 2)

A systematic review was conducted to consolidate evidence on the relationship between IR-related somatic conditions and cognition within the UK Biobank cohort. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021), the review protocol was pre-registered in PROSPERO (CRD42022335139). Comprehensive searches were performed across PubMed, Scopus, and Web of Science using structured queries designed to capture studies investigating the phenotypic relationship between IR-related conditions, including T2DM, obesity, MetS, and various measures of glycaemic and lipidaemic control, and cognitive outcomes. The search was limited to peer-reviewed studies published up to April 2022. Included studies were assessed for quality and risk of bias using the Newcastle-Ottawa Scale (Herzog et al., 2013; Wells et al., 2000), ensuring a rigorous appraisal of both longitudinal and cross-sectional findings. This systematic review established the epidemiological and cognitive correlates of IR-related conditions in a population-based sample, providing an evidence-based foundation for subsequent analyses.

Review of longitudinal evidence and Mendelian randomisation studies on mood disorders and type 2 diabetes mellitus (Chapter 3)

To investigate the bidirectional relationship between mood disorders, including MDD and BD, and T2DM, **Chapter 3** reviewed evidence from longitudinal and Mendelian randomisation (MR) studies. Longitudinal studies were prioritised for their ability to evaluate temporal associations and provide insights into the directionality of the relationship between these conditions. MR studies, which leverage genetic variants strongly associated with T2DM or mood disorders as instrumental variables, were also reviewed to explore whether these associations might reflect underlying causal relationships. Additionally, the review included a qualitative synthesis of studies examining how comorbid T2DM and mood disorders impact the clinical progression of either condition, along with an evaluation of the effects of psychotropic medications on diabetes risk and the potential therapeutic repurposing of antidiabetic drugs for mood disorders. By integrating these lines of evidence, this chapterexamined the relationship between mood disorders and T2DM, with attention to causality, temporality, and potential implications for treatment.

Analyses on the UK Biobank primary care-linked data focusing on IR-related conditions and depression treatment outcomes (Chapter 4)

Analyses in **Chapter 4** leveraged data from the UK Biobank, a prospective cohort study of approximately 500,000 individuals aged 40–69 years at recruitment (2006–2010), encompassing diverse genetic, lifestyle, and clinical data (Bycroft et al., 2018). This study specifically utilised the subset of 230,096 participants with linked primary care records. Diagnostic and prescription codes from Read V2, CTV3, and BNF systems were used to identify depression diagnoses, IR-related conditions (e.g., obesity, T2DM), antidepressant prescriptions, and treatment outcomes. Antidepressant response/resistance was operationalised based on prescription records and antidepressants switches. Additionally, temporal relationships between diagnoses of MDD and IR-related conditions were evaluated to distinguish between MDD-first and IR-first scenarios. To complement phenotypic analyses, PGSs for IR-related traits (e.g., body mass index, T2DM, fasting glucose, triglycerides, homeostasis model assessment for IR [HOMA-IR]) were computed using PRS-CS-auto (Ge et al., 2019). PGSs were derived using the largest GWAS summary statistics available. Statistical models assessed the associations of IR-related conditions and related PGSs with antidepressant treatment outcomes, adjusting for covariates such as age, sex, socioeconomic status, smoking, and population structure (via principal components).

Pairwise global genetic correlations and stratified genetic covariance analyses (Chapter 5)

This analysis leveraged the largest available GWAS summary statistics to explore shared heritable risks between neuropsychiatric disorders and IR-related conditions. Disorders such as AD, ASD, OCD, and others were compared with IR phenotypes, including T2DM, MetS, and obesity, as well as IR-related traits like HOMA-IR and fasting glucose. Genome-wide genetic correlations were quantified using Linkage Disequilibrium Score Regression (LDSC) (Bulik-Sullivan et al., 2015), a robust method that estimates the extent of genetic liability shared across phenotypes. To refine these findings, GNOVA (GeNetic cOVariance Analyser) (Lu et al., 2017) was employed to perform stratified genetic covariance analyses focused on gene sets relevant to insulin signalling. These complementary approaches provided both global and pathway-specific insights into the genetic interplay between psychiatric and IR-related traits, advancing the understanding of potential shared biological mechanisms.

Local genetic correlation, functional annotation, and colocalisation analyses (Chapter 6)

Chapter 6 employed the Local Analysis of [co]Variant Association (LAVA) (Werme et al., 2022) to identify genomic loci demonstrating significant local genetic correlations between IR-related metabolic conditions (i.e., obesity, T2DM, and MetS) and psychiatric disorders (e.g., mood disorders, OCD). Colocalisation analyses were then conducted within these loci to assess whether shared causal variants could explain the observed correlations. These analyses used robust Bayesian colocalisation frameworks, such as SuSiE (Wallace, 2021), to account for multiple causal variants within each region. GWAS summary statistics for both IR-related conditions and psychiatric disorders were harmonised using consistent genome builds (GRCh37/hg19) to ensure methodological rigor. Subsequent functional annotation and gene mapping were performed using tools like Functional Mapping and Annotation of GWASs (FUMA) (Watanabe et al., 2017) and SNPnexus (Oscanoa et al., 2020). Gene mapping incorporated positional and expression quantitative trait loci (eQTL) data from brain-relevant tissues, as defined by Genotype-Tissue Expression (GTEx), to identify genes potentially driving the associations. Furthermore, druggability analyses were integrated into the pipeline, leveraging databases such as GeneCards, DrugBank, and Drug–Gene Interaction Database (DGIdb) to assess whether the identified genes represented viable pharmacological targets. This step aimed to identify candidate genes with therapeutic relevance, expanding the translational potential of the findings.

Genomic and transcriptome-wide structural equation modelling, and drug repurposing analyses (Chapter 7)

Chapter 7 employed genomic SEM (Grotzinger et al., 2019) to uncover latent genetic factors underlying the shared liability between psychiatric disorders and IR-related conditions. This multivariate framework utilised GWAS summary statistics from five psychiatric disorders (e.g., ADHD, MDD, OCD) and three IR-related conditions (e.g., T2DM, obesity, MetS), leveraging SNP-based heritability estimates and genetic covariance matrices derived from LDSC. Exploratory and confirmatory factor analyses identified a latent multimorbidity factor, reflecting shared genetic risk across these conditions. This latent factor was then linked to brain morphometric traits, expanding the analysis to neuroanatomical correlates of the shared genetic architecture. T-SEM (Grotzinger, de la Fuente, et al., 2022) extended this analysis by incorporating tissue-specific gene expression data. This approach utilised eQTL datasets from brain regions (e.g., hippocampus, prefrontal cortex) and the pituitary gland, as well as transcriptomic data from external resources like GTEx and PsychENCODE. The analyses allowed the identification

of genes whose expression in neural and peripheral tissues contributed to the shared genetic liability. To enhance translational relevance, prioritised genes from the multivariate GWAS and T-SEM were analysed for therapeutic potential using PharmOmics (Chen et al., 2022), a platform for drug repurposing that integrates transcriptomic and pharmacological data. Drugs targeting prioritised genes were filtered based on criteria such as blood-brain barrier permeability, cross-species concordance, and opposing gene regulation patterns to disease-related changes, offering a framework for potential therapeutic applications.

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PART I

Clinical and phenotypic interfaces of psychiatric–insulin resistance multimorbidity

Chapter 2

The link between cognition and somatic conditions related to insulin resistance in the UK Biobank study cohort: a systematic review

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#Contributed equally to this work

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Abstract

Clinical and genomic studies have shown an overlap between neuropsychiatric disorders and insulin resistance (IR)-related somatic conditions, including obesity, type 2 diabetes, and cardiovascular diseases. Impaired cognition is often observed among neuropsychiatric disorders, where multiple cognitive domains may be affected. In this review, we aimed to summarise previous evidence on the relationship between IR-related diseases/traits and cognitive performance in the large UK Biobank study cohort. Electronic searches were conducted on PubMed, Scopus, and Web of Science until April 2022. Eighteen articles met the inclusion criteria and were qualitatively reviewed. Overall, there is substantial evidence for an association between IR-related cardio-metabolic diseases/traits and worse performance on various cognitive domains, which is largely independent of possible confoundings. The most consistent findings referred to IR-related associations with poorer verbal and numerical reasoning ability, as well as slower processing speed. The observed associations might be mediated by alterations in immune-inflammation, brain integrity/connectivity, and/or comorbid somatic or psychiatric diseases/traits. Our findings provide impetus for further research into the underlying neurobiology and possible new therapeutic targets.

Introduction

The main feature of somatic diseases and traits linked to insulin resistance (IR) is a deficient response to insulin in peripheral tissues. IR is prominently involved in the pathophysiology of obesity, type 2 diabetes mellitus, and cardiovascular diseases (e.g., atherosclerosis, hypertension, coronary artery disease), as well as related traits, such as elevated glycated haemoglobin levels, high body mass index (BMI), and increased systolic blood pressure (Mancusi et al., 2020; Ormazabal et al., 2018). These conditions frequently coexist and are considered modern-day epidemics due to their increasingly high prevalence as a result of, amongst others, unhealthy diets and sedentary lifestyle (Seidell, 2000). While the role of IR in these somatic diseases and traits is well established (DeFronzo & Ferrannini, 1991; Mancusi et al., 2020; Ormazabal et al., 2018), it is becoming clearer that insulin also plays an important role in the central nervous system. For example, insulin is involved in important brain processes like neurotransmission, synaptic plasticity, and neuroprotection (Klinedinst et al., 2019). A growing body of studies shows evidence of both clinical and genetic overlap between IR-related somatic diseases and neuropsychiatric disorders (Bralten et al., 2020; Fanelli et al., 2022; (Wimberley et al., 2022). For example, many studies have linked Alzheimer's disease to altered insulin signalling, and some people even refer to Alzheimer's disease as type 3 diabetes mellitus (Kroner, 2009). In addition, studies in rat models have shown that local administration of insulin in the hippocampus modulates cognitive function, including spatial memory, and that selective blockade of the insulin signalling pathway leads to dysfunction of memory abilities, as also occurs following IR induced by a high-fat diet (McNay et al., 2010). These observations indicate a potential role for insulin-related processes on cognitive phenotypes, like cognitive impairment and dementia. Cognitive impairment and IR-related somatic diseases are important contributors to reduced quality of life and life expectancy and constitute major health and economic burdens for society (Kazukauskiene et al., 2021). Another relevant issue is that cognitive deficits are commonly seen in individuals with neuropsychiatric disorders and are seldom alleviated by currently available pharmacotherapies, usually persisting even in individuals who show a good overall response to treatment (Hori et al., 2020; Vinasi et al., 2021).

The recent availability of very large, population-based, well-phenotyped cohorts makes it possible to extend analyses beyond clinically defined phenotypes, allowing for a better investigation of the relationship of IR with cognition in humans. The largest of these cohorts addressing cognition and IR-related conditions is the UK Biobank cohort, which is a deeply phenotyped, large prospective study aimed at studying the general health of middle-aged and older people (≥40 years old)

across the United Kingdom (Sudlow et al., 2015). From 2006 to 2010, approximately 500,000 individuals were recruited for baseline assessments, which included detailed characterisation of sociodemographic, lifestyle, environmental factors, medical history, physical measures, and cognition. The richness of this data collection makes the UK Biobank study particularly useful to address the relationship between IR-related somatic diseases and traits with cognition. Cognitive function was initially measured by the pairs matching and reaction time tests using fully automated, unsupervised touchscreen questionnaires. Additional cognitive tests were later added to the baseline assessment and therefore administered only to a subsample of participants, namely prospective memory, numeric memory, and fluid intelligence tests. A subset of 20,000 participants was invited to repeat the assessment of baseline measures (between 2012 and 2013), which included the same baseline tests as cognitive measures, excluding the numeric memory test. Several cognitive function tests (i.e., fluid intelligence, pairs matching, and numeric memory tests) were later re-implemented as web-based questionnaires (completed between 2014 and 2015 by around 110,000 participants), and two additional tests were included, the trail making and the symbol digit substitution tests. Starting in 2016 and with ongoing recruitment, a subsequent imaging assessment visit has been introduced, where participants are also assessed on additional cognitive domains by tests such as the tower rearranging, the matrix pattern completion, and the trail making tests, for example. A further detailed description of the UK Biobank cognitive tests can be found in Lyall et al. (2016).

With UK Biobank making its collected data available to the research community, many studies had the ability to investigate the cognitive phenotypes in this cohort in combination with somatic IR-related disorders and traits. While multiple studies included parts of this exploration in their analyses, the literature still lacks a good overview of the gathered information. Therefore, we performed a literature review to identify and summarise the studies that investigated the relationship between IR-related diseases and traits and different cognitive domains in the UK Biobank study cohort, the largest population cohort addressing both a wide range of cognitive measures as well as diverse IR-traits and diseases on the same individual.

Methods

Study protocol

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement (Page et al., 2021). The full review protocol was registered on the international Prospective

Register Of systematic reviews (https://www.crd.york.ac.uk/prospero, PROSPERO ID: CRD42022335139).

Searching strategy

An electronic search of the literature was conducted on the PubMed, Scopus, and Web of Science databases looking for studies investigating the relationship between IR-related diseases/traits and cognitive functioning in the UK Biobank study cohort. We used the Polyglot Search Translator tool to transform the PubMed query into formats appropriate to other databases (Clark et al., 2020). We included papers published until April 2022, when the databases were last searched. We used search terms related to cognition and to IR-related traits and diseases, including terms encompassing glycaemic and lipidaemic control/homeostasis, diabetes mellitus, obesity and obesity-related measures, metabolic syndrome, cardiovascular disease, Cushing's syndrome, and polycystic ovary syndrome. The search was restricted to studies conducted using the UK Biobank study cohort and where any of the search terms appeared in the title or abstract. The full search queries used are provided in the **Supplementary Materials**. Duplicates were removed using EndNote 20.2 (Clarivate, Philadelphia, PA).

Two reviewers (GF and NRM) independently screened the results retrieved from the search query to identify potentially relevant studies by evaluating titles and abstracts. The full text of the selected studies and those of uncertain relevance were obtained and thoroughly evaluated to ascertain the pertinence of each study. In the event of disagreement during the study selection process, a decision was made through open discussion (and, in the case of persistent inconsistency of judgement, with the involvement of a third reviewer (JB)).

Inclusion and exclusion criteria

Studies were included if: 1) they investigated the phenotypic relationship between cognition and IR-related traits/diseases; 2) the analyses were conducted within the population-based UK Biobank cohort; 3) written in English. Reasons for exclusion were: 1) being a meta-analysis or review; 2) being a preprint (not yet peer-reviewed); 3) being a commentary, a letter, a congress abstract, or an editorial; 4) not having the outcomes of interest measured/reported.

Study quality and risk of bias assessment

The Newcastle-Ottawa Scale (NOS) for cohort studies (Wells et al., 2000) and its version adapted for cross-sectional studies (Herzog et al., 2013) were used to assess the quality and risk of bias of each included study (longitudinal or cross-sectional, respectively) by two independent reviewers (GF and NRM) (Herzog et al., 2013). A maximum score of 9 points (NOS for cohort studies) or 10 points (NOS adapted

for cross-sectional studies) could be assigned to a study. Studies with 0 to 4 points were deemed to be of unsatisfactory quality, 5 to 6 points to be of adequate quality, 7 to 8 points to be of good quality, and 9 to 10 points to be of very good quality. Regardless of the NOS score, all studies were considered for qualitative synthesis. Any disagreements were settled through consensus among reviewers.

Table 1. Description of the cognitive function tests administered throughout the UK Biobank study. Further information on how each test was conducted can be found at: https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100026.

UK Biobank cognitive tests	Cognitive domains [a]	UK Biobank Field ID(s) used by reviewed studies	Cognitive assessment time point (number of participants with valid data) [b]
Prospective memory	Prospective Memory	Field ID: 20018 Prospective memory result	Baseline (subsample: N=117,517) Repeat (subsample: N=20,329) Imaging (subsample: N=48,178)
Trail Making Test, part A (TMT-A) §	Executive function, divided attention, visual scanning, processing speed	Field ID: 6348 Duration to complete numeric path (trail #1)	Imaging (subsample: N=35,663)
Trail Making Test, part B (TMT-B) §	Executive function (and more specifically, set shifting/ cognitive flexibility, and working memory (short-term memory)), divided attention, visual scanning, conceptual tracking, processing speed	Field ID: 6350 Duration to complete alphanumeric path (trail #2)	Imaging (subsample: N=35,663)
Tower rearranging	Executive function (and more specifically, planning, working memory (short-term memory), problem solving, and response inhibition), visuospatial memory, procedural and skill learning	Field ID: 21004 Number of puzzles correct	Imaging (subsample: N=34,933)
Numeric memory	Working memory (short-term memory), attention	Field ID: 4282 Maximum digits remembered correctly	Baseline (subsample: N=51,799) Imaging (subsample: N=36,535)
Pairs matching	Visual declarative memory (short-term memory)	Field ID: 399 Number of incorrect matches in round	Baseline (subsample: N=497,791) Repeat (subsample: N=20,344) Imaging (subsample: N=48,202)

Table 1. Continued

UK Biobank cognitive tests	Cognitive domains [a]	UK Biobank Field ID(s) used by reviewed studies	Cognitive assessment time point (number of participants with valid data) [b]
Fluid intelligence	Verbal and numerical reasoning	Field ID: 20016 Fluid intelligence score (i.e., sum of the correct answers given)	Baseline (subsample: N=165,430) Repeat (subsample: N=20,110) Imaging (subsample: N=47,291)
Matrix pattern completion	Non-verbal reasoning	Field ID: 6373 Number of puzzles correctly solved	Imaging (subsample: N=35,243)
Reaction time	Processing speed	Field ID: 20023 Mean time to correctly identify matches Field ID: 404[c] Duration to first press of snap-button in each round	Baseline (subsample: N=496,590) Repeat (subsample: N=20,254) Imaging (subsample: N=47,878) Baseline (subsample: N=493,160) Repeat (subsample: N=20,265) Imaging (subsample: N=47,926)
Symbol digit substitution	Processing speed, attention	Field ID: 23324 Number of symbol digit matches made correctly	Imaging (subsample: N=35,264)

[a] Different cognitive test may correlate with one another because they can measure the same cognitive domain or general cognitive ability. Definitions of associated cognitive domains to each test are according to Fawns-Ritchie and Deary (2020) and Lezak (2012).

[b] Baseline (N=502,536), repeat assessment (N=20,346), and/or imaging assessment visit (tot N=37,102). Maximum sample size (N) for each cognitive assessment visit and test according to UK Biobank data Showcase: https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100026).

[c] Used only by Morys et al. (2021); Talboom et al. (2021).

§ The Trail Making Test difference (TMT part B - part A) score removes the speed and completion time component from the evaluation of shifting ability; the Trail Making Test B/A ratio score (TMT part B/ part A) better captures set-switching ability.

Results

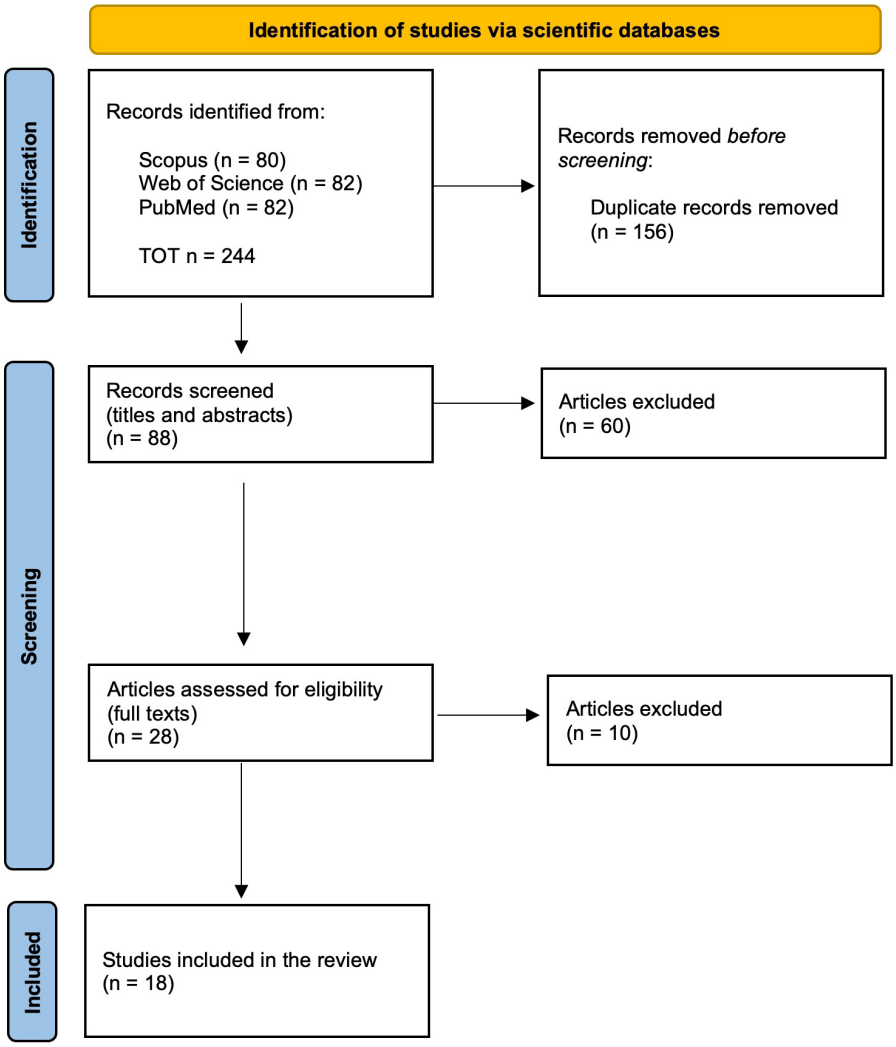

Figure 1. PRISMA flow diagram of the systematic review process.

The initial literature search yielded 244 results; these articles were screened to determine whether they met the inclusion criteria. After removing 156 duplicates, the remaining 88 studies were screened for possible inclusion. After the title and abstract inspection, 28 studies were selected as potentially relevant to our research topic and their full texts were collected. Finally, after careful assessment of full texts and discussion between reviewers, 18 pertinent studies matching the inclusion criteria were identified and reviewed (**Figure 1**). The quality of the included studies, according to the NOS assessment tool (Herzog et al., 2013; Wells et al., 2000), ranged from adequate to very good, indicating a low risk of bias (**Table 2**).

Results are reported in detail in the following paragraphs, grouping evidence regarding obesity, diabetes mellitus, and cardiovascular diseases and their related traits. With regard to diabetes mellitus, most of the studies included in this review did not make a clear distinction between type 2 diabetes mellitus and other (much less prevalent) types of diabetes, such as type 1 diabetes mellitus, and gestational diabetes mellitus, among others. Only three reviewed studies (Garfield et al., 2021; Hagenaars et al., 2017; Whitelock et al., 2021) report having applied additional algorithms and/or filtering inclusion criteria in order to retain as cases mainly those with type 2 diabetes, for example by excluding cases diagnosed before a certain age or those that started insulin therapy soon after diagnosis (features more commonly associated with type 1 diabetes mellitus). However, despite the lack of clear distinguishing measures by the other studies, it should be taken into consideration that it has been reported that 90% of all confirmed cases of diabetes mellitus in the UK population are type 2 diabetes mellitus, about 8% are type 1 diabetes mellitus, and the other forms account for the remaining 2% (Whicher et al., 2020). Therefore, for practical and readability reasons, hereafter we will refer to findings involving either type 2 diabetes mellitus or diabetes mellitus not otherwise specified simply as 'diabetes'.

Obesity and related measures

BMI is the most used quantitative measure to diagnose and classify obesity. BMI was significantly associated with performance in several cognitive domains in the UK Biobank study. Higher BMI has been associated with worse performance on fluid intelligence (Ferguson et al. (2020); Hagenaars et al. (2017); Olivo et al. (2019), but not by Morys et al. (2021)), numeric memory (Morys et al., 2021; Olivo et al., 2019), matrix pattern completion (Ferguson et al., 2020), trail making (i.e., higher Trail Making Test B/A ratio; Olivo et al. (2019)), and symbol digit substitution tests (Ferguson et al., 2020). On the other hand, no association between BMI and prospective memory was found (Morys et al., 2021). Interestingly, the association between BMI and numeric memory was partially mediated (9%) by

Table 2. Summary of included studies investigating the association of diseases and traits linked to IR and cognition in the UK Biobank study cohort.

Reference [Study Quality Assessment [a]]	Sample size [b] and assessment time point	Somatic IR-related phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Cross-sectional studies					
Feng et al. (2020) [***]	N=42,392 – 133,439 (baseline)	Hypertension	Fluid intelligence, prospective memory, and numeric memory	Age, sex, Townsend deprivation index, alcohol use, smoking status, and educational qualifications	History of hypertension was associated with reduced performance in fluid intelligence and in prospective and numeric memories
Ferguson et al. (2020) [***]	N=28,412 (imaging assessment visit)	BMI and SBP	Fluid intelligence, pairs matching, matrix pattern completion, symbol digit substitution, tower rearranging, and reaction time	Age, sex, assessment centres, Townsend deprivation index, self-reported medication (for dyslipidaemia, heart rate rhythm, oral contraceptive, or insulin), apolipoprotein e4 genotype, ever-smoking, population stratification, and genotypic array	BMI was associated with reduced fluid intelligence, matrix pattern completion, symbol digit substitution, and reaction time performance and with better pairs matching performance SBP was associated with reduced intelligence and matrix pattern completion performances
Garfield et al. (2021) [**]	N=449,973 (baseline)	Diabetes (considering prediabetes and undiagnosed and known diabetes status)	Reaction time and pairs matching	Age, sex, ethnicity, Townsend deprivation index, educational attainment, smoking status, BMI, baseline cardiovascular disease, and antihypertensive medication and statin use	Prediabetes, undiagnosed and known diabetes were associated with slower reaction time compared to normoglycaemic Known diabetes was associated with better pairs matching performance

Table 2. Continued

Reference [Study Quality Assessment [a]]	Sample size [b] and assessment time point	Somatic IR-related phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Hagenaars et al. (2017) [**]	N=up to 36,035 (baseline)	BMI, SBP, CAD, and diabetes	Fluid intelligence	Age, sex, genetic batch and array, and population stratification	All somatic IR-related phenotypes tested were associated with worse performance on fluid intelligence
Lyall et al. (2017) [**]	N=158,631 – 474,129 (baseline)	Diabetes, CAD, and hypertension	Fluid intelligence, reaction time, and pairs matching	Age, sex, ethnicity, Townsend score, education, depression, smoking status, alcohol intake, cholesterol/ blood pressure/insulin medication use, and BMI	Diabetes, CAD, and hypertension, alone or in comorbidity, were associated with worse fluid intelligence and reaction time performances Non-comorbid CAD and comorbid CAD + hypertension and diabetes + hypertension (but not non-comorbid hypertension or diabetes) were associated with worse pairs matching performance Overall, an increasing number of somatic IR-related diseases had an additive deleterious dose effect on the cognitive measures
Lyall et al. (2019) [***]	N=70,988 – 324,725 (baseline, for fluid intelligence and reaction time; imaging assessment, for TMT A and B, and symbol digit substitution)	Severe obesity (BMI ≥40)	Fluid intelligence, reaction time, TMT A and B, symbol digit substitution	Age, sex, genotypic array (also CAD, hypertension, diabetes, education, and Townsend deprivation index for the fully adjusted model)	Severe obesity was associated with worse reaction time, worse TMT part B, worse fluid intelligence, and worse symbol digit substitutions performances in the partially adjusted model These associations were no longer significant after additional covariates (i.e., CAD, hypertension, diabetes, education - university college degree -, Townsend deprivation index) were added to the model

Table 2. Continued

Reference [Study Quality Assessment [a]]	Sample size [b] and assessment time point	Somatic IR-related phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Newby et al. (2021) [***]	N=155,151 – 437,794 (baseline) N=18,801 – 29,628 (imaging assessment visit)	Hypertension	Fluid intelligence, pairs matching, reaction time, difference between TMT part B and part A (TMT B–A), matrix pattern completion, symbol digit substitution, tower rearranging	Age, sex, education, ethnicity, assessment centres, BMI, smoking status, diabetes, hyperlipidaemia, and interactions between sex and age and age^2 (non-linear effects: sex*age and sex*age^2)	Hypertension was associated with worse performance on fluid intelligence (both on baseline and on imaging assessment data), and on reaction time and pairs matching (only on baseline data) tests
Newby and Garfield (2022) [**]	N=24,402 – 36,323 (imaging assessment visit)	Diabetes (irrespective of comorbidity status), non-comorbid diabetes and hypertension, and comorbid diabetes + hypertension	Fluid intelligence, pairs matching, reaction time, TMT B–A, matrix pattern completion, symbol digit substitution, and tower rearranging	Age, sex, Townsend deprivation index, educational attainment, ethnicity, smoking, BMI, hypertension, and high cholesterol	Diabetes was associated with worse performance on fluid intelligence, reaction time, TMT B–A, matrix pattern completion, and symbol digit substitution Individuals with diabetes, both with and without comorbid hypertension, performed worse on reaction time and symbol digit substitution than individuals with non-comorbid hypertension or none of these diseases Individuals with non-comorbid diabetes had better performance on fluid intelligence than individuals with comorbid diabetes + hypertension

Table 2. Continued

Reference [Study Quality Assessment [a]]	Sample size [b] and assessment time point	Somatic IR-related phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Olivo et al. (2019) [***]	N=42,102 –167,730 (baseline)	BMI, overweight and obesity	Fluid intelligence, numeric memory, pairs matching, and TMT	Age, sex, education, ethnicity, smoking status, alcohol consumption, physical activity	Increasing BMI was associated with worse performance on fluid intelligence, numeric memory, pairs matching, and TMT Overweight and obesity were associated with worse performance on fluid intelligence, numeric memory, and pairs matching tests, while only obesity (but not overweight) was similarly associated with TMT
Shen et al. (2020) [**]	N=19,364 (imaging assessment visit)	"Vascular burden" latent variable that included BMI, diabetes, hypercholesterolemia, hypertension, and smoking	"Cognition" latent variable, that included fluid intelligence, pairs matching, reaction time, prospective memory, and numeric memory scores	Age, sex, Townsend deprivation index, education, ethnicity, and white matter hyperintensity	Vascular burden was no longer associated with the cognition latent variable after controlling for global efficiency (i.e., a measure of brain network integration). Mediation analysis further supports the (partially) mediating role of global efficiency in the relationship between vascular burden and cognition
Suzuki et al. (2019) [**]	N=8,312 (imaging assessment visit)	Number of following conditions present: obesity, diabetes, hypertension, and frequent alcohol use	Fluid intelligence, reaction time, and pairs matching	Age, sex, and ethnicity	Participants reporting the presence of all four conditions studied had worse performance on pairs matching test than those without any of those conditions; this association was partially mediated by lower grey matter volume in the posterior cingulate cortex

Table 2. Continued

Reference [Study Quality Assessment [a]]	Sample size [b] and assessment time point	Somatic IR-related phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Talboom et al. (2021) [**]	N=158,245 (baseline)	Diabetes, stroke, and hypertension	Reaction time	Age, sex, diabetes, handedness, stroke, hypertension, smoking status, dizziness, educational attainment, and a first-degree family history of Alzheimer's disease	Diabetes, stroke, and hypertension were associated with slower reaction time
van Gennip et al. (2021) [***]	N=87,075 (baseline)	Diabetes	Reaction time and pairs matching	Age, sex, and education	Diabetes was associated with worse reaction time performance
Veldsman et al. (2020) [**]	N=up to 22,059 (imaging assessment visit)	Diabetes, use of antihypertensive medication, use of cholesterol-lowering medication, WHR, and SBP	Continuous latent variable representing executive function (predictive of performance in the reaction time and the pairs matching tests)	Age and Townsend deprivation index	Diabetes, use of antihypertensive medication and increasing SBP were associated with worse performance on the continuous latent variable
Whitelock et al. (2021) [**]	N=47,468 (baseline)	Diabetes	fluid intelligence, reaction time, pairs matching, numeric memory, prospective memory	Age, sex, ethnicity, Townsend deprivation index, smoking status, alcohol consumption, physical activity, and antidiabetic medications use	Diabetes was associated with worse performance on numeric memory
Longitudinal studies					
Garfield et al. (2021) [*]	N=18,809 (for cognitive decline; repeat cognitive assessment)	Diabetes (considering prediabetes and undiagnosed and known diabetes status)	Cognitive decline, which was derived from the follow-up assessment of the pairs matching task	Age, sex, years of education and time between the two assessments	Prediabetes and known diabetes were associated with an increased risk of cognitive decline

Table 2. Continued

Reference [Study Quality Assessment [a]]	Sample size [b] and assessment time point	Somatic IR-related phenotypes	Cognitive phenotypes	Covariates included in the models	Main findings
Klinedinst et al. (2019) [*]	N=4,431 (baseline plus two additional assessments at 2-year intervals)	Visceral adipose mass, non-visceral adipose mass, and lean muscle mass	Fluid intelligence - changes in performance over a 6-year period	Education, socio-economic status (average total household income)	More visceral and non-visceral adipose mass independently predicted fluid intelligence decline, while more lean muscle mass predicted gains in fluid intelligence performance over time
Li et al. (2020) [**]	N=1,175 (baseline, 5-year follow-up and imaging assessment visit)	Cardiovascular disease and diabetes	Reaction time intraindividual variability	Age, BMI, lifestyle factors (smoking, alcohol, fruit/vegetables consumption), sex, socio-economic factors (employment, education, ethnicity, income)	The model including 'diabetes and cardiovascular diseases' had a significant, although weak, performance in predicting reaction time intraindividual variability over time
Morys et al. (2021) [*]	N=6,803 – 17,094 (baseline, for obesity and blood measures; imaging assessment visit, for cognitive tests)	BMI, WHR, and body fat percentage	Fluid intelligence, pairs matching, reaction time, numeric memory, tower rearranging, and prospective memory	Age, sex, average household income, Townsend deprivation index, education, depression, frequency of drinking alcohol, physical activity, and smoking status	BMI associated with worse numeric memory, and better pairs matching and tower rearranging test performances WHR was associated with worse fluid intelligence and numeric memory performances Body fat percentage was associated with worse numeric memory and with better pairs matching performances

Abbreviations: body mass index (BMI), coronary artery disease (CAD), diastolic blood pressure (DBP), glycated haemoglobin (HbA1c), high-density lipoprotein (HDL), insulin resistance (IR), systolic blood pressure (SBP), trail making test (TMT), waist-to-hip ratio (WHR).

[a] Study Quality Assessment according to the Newcastle-Ottawa Scale (NOS) for cohort studies (Wells et al., 2000) or its adapted version for cross-sectional studies (Herzog et al., 2013): *** indicates very good (9-10 points), ** indicates good (7-8 points), and * indicates adequate (5-6 points) qualities.

[b] For some studies, the sample size is presented as a range instead of a single numeric value. This can happen due to the varying number of participants that completed each individual cognitive task. See the Introduction section for a more detailed description of the cognitive assessment procedure in UK Biobank.

brain white matter hyperintensity (WMH) load (Morys et al., 2021). Similarly, the association between BMI and symbol digit substitution was found to be mediated (approximately 19%) by WMH, along with grey matter volume and a general factor of mean diffusivity (Ferguson et al., 2020).

Results were mixed for the association between BMI and slower reaction time, with one study finding an association (Ferguson et al., 2020), and another one not (Morys et al., 2021). Similarly, no consistent results were found regarding BMI and pairs matching and tower rearranging tests. While one study found increasing BMI associated with worse performance in the pairs matching test at the baseline assessment (Olivo et al., 2019), two studies examined the data collected during the imaging assessment visit, available only from a subset of participants, and found that BMI was associated with better performance on this test (Ferguson et al., 2020; Morys et al., 2021). Regarding the tower rearranging test, while one study found no association with BMI (Ferguson et al., 2020), another, using more limited sample size, found increasing BMI associated with better performance (Morys et al., 2021).

When BMI was used to categorise individuals, those with overweight (BMI: 25 kg/m2 to 29.9 kg/m2) or obesity (BMI ≥30 kg/m2) showed worse cognitive performance compared to normal-weight individuals (BMI: 18.5 to 24.9 kg/m2). In particular, both overweight and obesity were associated with poorer performance on fluid intelligence, numeric memory, and pairs matching, while only obesity (but not overweight) was associated with worse performance on the trail making (Trail Making Test B/A ratio (Olivo et al., 2019)). Severe obesity (BMI ≥40 kg/m2) was associated with worse performance on reaction time, TMT part B (but not part A), fluid intelligence, and symbol digit substitutions (Lyall et al., 2019). The presence of obesity, when combined with diabetes, hypertension, and frequent alcohol use, was associated with worse performance on the pairs matching task, and this association was found to be partially mediated by lower grey matter volume in the posterior cingulate cortex (Suzuki et al., 2019).

Considering other continuous obesity-related measures, increasing waist-to-hip ratio (WHR) has been associated with worse performance on fluid intelligence and numeric memory tasks, but no association was found with reaction time, prospective memory, pairs matching, and tower rearranging tasks (Morys et al., 2021). The authors suggested that the association between WHR and numeric memory and fluid intelligence were partially mediated by brain WMH load (7% and 12%, respectively). No association was found between WHR and a continuous latent variable representing executive function (i.e., predicting reaction time and pairs matching performances) (Veldsman et al., 2020). Body fat percentage, in turn, has been associated with worse numeric memory and better pairs matching performance, while no association was found with fluid intelligence,

reaction time, prospective memory, and tower rearranging (Morys et al., 2021). The associations found with body fat percentage were found to be partially mediated (9%) by WMH load.

Adipose mass is another quantitative measure related to obesity. A longitudinal study found that more visceral and non-visceral adipose mass independently predicted a decline in fluid intelligence performance over a period of six years, both in men and women (Klinedinst et al., 2019). Conversely, the presence of greater lean muscle mass favoured gains in fluid intelligence across time. Interestingly, they show important immune system-related mediation effects as the association between visceral adipose mass and fluid intelligence was either partially (men) or fully (women) mediated by changes in leukocyte subpopulation counts (Klinedinst et al., 2019).

Diabetes and related measures

Diabetes has been associated with worse performance on fluid intelligence, both at baseline (Lyall et al., 2017) and on follow-up data from the imaging assessment visit (Newby and Garfield, 2022). Others, however, did not find such an association (Whitelock et al., 2021). Intriguingly, when comorbidity with hypertension was considered, individuals with only diabetes had worse performances on fluid intelligence than those with comorbid diabetes and hypertension (Newby and Garfield, 2022).

Diabetes has also been repeatedly associated with slower reaction time (Garfield et al., 2021; Lyall et al., 2017; Talboom et al., 2021; van Gennip et al., 2021), although this was not always the case (Whitelock et al., 2021). These results were shown to be independent of possible confounders, such as socio-economic and demographic variables, depression, medications use, and BMI (Garfield et al., 2021; Lyall et al., 2017). Furthermore, diabetes has also been associated with worse performance on a latent executive function continuous variable, representing reaction time and pairs matching test scores (Veldsman et al., 2020). In addition to participants with known diabetes (i.e., self-reported, diagnosed by a doctor and/or hypoglycaemic medications use), those classified with either prediabetes (i.e., HbA1c 42-48 mmol/mol) or undiagnosed diabetes (i.e., HbA1c≥48 mmol/mol) at baseline also showed slower reaction time than normoglycaemic participants (i.e., HbA1c ≥35 and <42 mmol/mol; Garfield et al. (2021)). The association between diabetes and worse reaction time performance has been replicated using data from the imaging visit assessment and individuals with comorbid diabetes+hypertension showed worse performance than individuals with non-comorbid hypertension or neither diabetes nor hypertension (Newby and Garfield, 2022). Noteworthy, another study showed that the higher the number of cardio-metabolic risk variables found within the normal

ranges (i.e., HbA1c, blood pressure, and BMI), the least reaction time impairment difference was found between individuals with and without diabetes (van Gennip et al., 2021). A machine learning approach was used to examine whether diabetes and cardiovascular disease could predict reaction time intraindividual variability (RT-IIV) over time (i.e., across baseline and two follow-up assessments). This was considered a sensitive measure of cognitive change over time, with greater RT-IIV used as an indicator of longitudinal cognitive decline. Although it was outperformed by alternative models whose variables captured psychiatric phenotypes (i.e., anxiety and depression models, with an area under the curve (AUC) of 0.68 and 0.63, respectively), the 'diabetes and cardiovascular' model showed a significantly better classification performance than randomness (AUC=0.60; Li et al. (2020)).

The results about the relationship between diabetes and the pairs matching test, however, have been less consistent. While some reported an association between known diabetes and better baseline performance on this test (Garfield et al., 2021), others found an association with worse performance only when diabetes was comorbid with hypertension (no association otherwise) (Lyall et al., 2017), and others reported no association in smaller sample sizes from baseline (van Gennip et al., 2021; Whitelock et al., 2021) or imaging assessment visit data (see **Table 2**) (Newby and Garfield, 2022).

Interestingly, the same study that showed an outperformance of individuals with diabetes in the pairs matching task at baseline, further combined this data with the scores obtained during the UK Biobank follow-up assessment to address cognitive decline (i.e., measured by regressing the follow-up scores on the baseline scores). This longitudinal analysis indicated that participants with prediabetes and with known diabetes might be subject to a faster deterioration rate of pairs matching abilities than normoglycaemic individuals, suggesting a higher risk for cognitive decline (Garfield et al., 2021).

Using baseline data, Whitelock and colleagues (2021) found that participants with diabetes showed worse performance on numeric memory compared to those without diabetes, while they did not differ in terms of prospective memory performance. No differences between those with and without diabetes at the imaging assessment visit were found on tower rearranging performance either (Newby and Garfield, 2022).

At the imaging assessment visit, participants with diabetes performed worse on symbol digit substitution, trail making (i.e., trail making test B–A), and matrix pattern completion than those without diabetes (Newby and Garfield, 2022). When comorbidity with hypertension was considered, both the group of participants with only diabetes and those with comorbid diabetes+hypertension performed worse on symbol digit substitution compared to those with only hypertension or none

of these diseases (Newby and Garfield, 2022). Interestingly, when cardiovascular confounders were considered (i.e., smoking, BMI, hypertension, high cholesterol), the associations between diabetes and worse cognitive performance were attenuated, in particular matrix pattern completion and symbol digit substitution performances (Newby and Garfield, 2022). On this note, others have shown that the association between diabetes and cognitive performance was partially mediated (between 10 and 59%) by cardiovascular diseases (i.e., hypertension, thromboembolism, stroke, coronary artery disease (CAD)), depressive symptoms, and to a lesser extent by visceral obesity (i.e., WHR), possibly via immune-inflammatory dysregulation that is commonly present in each of these three conditions (Whitelock et al., 2021).

Lastly, the effect of diabetes and other cardio-metabolic diseases on cognition was found to be additive, meaning that an increasing number of concomitant cardio-metabolic diseases was associated with greater cognitive impairment (Lyall et al., 2017). Furthermore, a latent variable composed of BMI, diabetes, hypercholesterolaemia, hypertension, and smoking, was found to be associated with a cognition latent variable (composed of fluid intelligence, pairs matching, reaction time, prospective memory, and numeric memory scores). However, this association was no longer significant after controlling for brain global efficiency, a measure of brain network integration (Shen et al., 2020). Further investigation through mediation analysis supported the (partially) mediating role of global efficiency in the relationship between vascular burden and cognition (Shen et al., 2020).

Cardiovascular diseases and traits

CAD, defined as (self-reported) presence of angina and/or myocardial infarction diagnosis, was associated with poorer performance on fluid intelligence (Hagenaars et al., 2017; Lyall et al., 2017) and on pairs matching and reaction time tests (Lyall et al., 2017). These associations remained significant independently from the presence of other cardio-metabolic diseases (i.e., diabetes and/or hypertension) and after the adjustment for socio-economic and demographic variables, depression, medication use, and BMI (Lyall et al., 2017). In addition, stroke was also associated with worse processing speed on the reaction time test (Talboom et al., 2021).

Hypertension has also been repeatedly associated with worse cognitive performance. Although hypertension may have diverse underlying pathophysiology, it has been estimated that 60-70% of hypertension cases during adulthood may be directly attributed to adiposity and IR (Jameson et al., 2018). Furthermore, IR has been shown to contribute to hypertension by impairing vascular peripheral resistance and endothelial function (Mancusi et al., 2020). A history of hypertension (i.e., self-reported having previously received hypertension diagnosis by a doctor) has been

associated with poorer performance in fluid intelligence (Lyall et al., 2017) and slower reaction time (Lyall et al., 2017; Talboom et al., 2021). Regarding the pairs matching task, no association was found with a history of non-comorbid hypertension, but associations with worse performance were observed when hypertension was comorbid with either diabetes or CAD (Lyall et al., 2017). When taking multiple combined measures to define hypertension (i.e., SBP ≥140 mmHg and diastolic blood pressure ≥90 mmHg and/or use of blood pressure medication and/or self-reported history of a hypertension diagnosis by a doctor), results replicated the associations with fluid intelligence and reaction time and in turn also revealed an association with worse performance on the pairs matching task (Newby et al., 2021). However, no association was found with symbol digit substitution, matrix pattern completion, tower rearranging, and trail making (difference between part B and part A) tasks, for which data was acquired during the imaging assessment visit and thus was only available from a subset of UK Biobank participants (Newby et al., 2021). Data from hospital admission records for hypertension treatment has also been used to classify UK Biobank participants regarding hypertension. A history of hospitalisation for hypertension treatment was associated with lower fluid intelligence scores, corroborating previous findings. Additionally, it was associated with reduced prospective and numeric memories (Feng et al., 2020). Of note, this association with prospective memory was found to be partially mediated by reduced brain functional connectivity, which explained 11.5% of the association between hypertension and these cognitive task results (Feng et al., 2020).

When assessing the effect of systolic blood pressure as a continuous measure rather than a dichotomous hypertension diagnosis, (higher) SBP was associated with (lower) fluid intelligence (Ferguson et al., 2020; Hagenaars et al., 2017) and matrix pattern completion (Ferguson et al., 2020) scores, while no significant association was found with reaction time, symbol digit substitution, tower rearranging, and pairs matching tests (Ferguson et al., 2020). It is suggested that the association between SBP and fluid intelligence is, at least partially, mediated by differences in brain morphometry and connectivity/integrity (Ferguson et al., 2020). Furthermore, increasing SBP was associated with a graded reduction in performance on a continuous latent variable representing executive function (i.e., corresponding to reaction time and pairs matching tasks) in participants not taking antihypertensive medication (Veldsman et al., 2020). This was especially true for mid-aged participants (44-69 years) and less so for older ones (>70 years). For the participants taking antihypertensive medication (which can be considered as a proxy for hypertension diagnosis), however, executive performance was stable for the SBP range <140 mmHg, while increasing SBP above this threshold was associated with a decline in performance (Veldsman et al., 2020).

Discussion

This literature review aimed to summarise previous evidence on the relationship between somatic diseases and traits linked to insulin resistance and cognitive performance across several domains based on studies conducted in the large population-based UK Biobank study cohort. Overall, there is substantial evidence for an association between IR-related cardio-metabolic diseases and traits and general worse performance on various cognitive domains, which is largely independent of possible confounding factors, such as general socio-economic and demographic factors and the use of medications.

Worse fluid intelligence performance consistently associated with IR-related diseases/traits

The most consistent finding across studies within the UK biobank cohort is the association between the presence of IR-related diseases and traits with worse performance on fluid intelligence. This test was designed to evaluate verbal and numerical reasoning, which refers to the ability to derive logical inferences and solve novel problems through evaluation, abstraction, and integration of information and hypothesis testing. Fluid intelligence was initially assessed on a subsample of UK Biobank participants at baseline, with follow-up assessments at different time points. Despite encompassing a smaller sample size compared to other tasks (**Table 1**), it shows largely consistent findings for all the IR-related phenotypes reviewed (i.e., obesity, diabetes, cardiovascular disease, and their related traits), independent of the methods and corrections for confounders applied. Verbal and numerical reasoning have been linked to the activity of the dorsolateral and medial prefrontal cortex (which is part of the frontal lobe) and the posterior parietal cortex in previous studies in samples other than UK Biobank (Kolb and Wishaw, 2012). In line with this evidence, Ferguson and colleagues reported a mediating effect of frontal lobe volumes in the association between high SBP and poor verbal and numerical reasoning (Ferguson et al., 2020). Noteworthy, impairment in this cognitive domain has been associated with higher psychopathological severity across psychiatric disorders, a recent diagnosis of specific phobia, bipolar disorder and impulse-control disorders among adolescents (Keyes et al., 2017), and depressive symptoms in elderly individuals (Murray et al., 2013). Moreover, fluid intelligence deficits significantly contribute to worse performance in executive tasks among patients with Parkinson's disease, frontotemporal dementia, and schizophrenia (Roca et al., 2014).

Slower reaction time also associated with IR-related phenotypes

Similarly, the associations between IR-related phenotypes and slower reaction time have been quite consistent in the UK biobank literature. The reaction time task constitutes one of the tasks with the largest sample size in the UK Biobank, being assessed in the whole baseline cohort, in addition to the follow-up assessments. The reaction time task measures processing speed, which is the ability to quickly perform a variety of cognitive, perceptual, and motor processes, whose impairment has been linked to white matter integrity (Papanicolaou, 2017). Processing speed deficit is an important characteristic of Parkinson's disease and several major psychiatric disorders, such as autism spectrum disorder, mood disorders, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, obsessive-compulsive disorder, and panic disorder (Millan et al., 2012), which in turn have been shown to overlap (clinically and genetically) with IR-related somatic diseases (Fanelli et al., 2022; Wimberley et al., 2022).

Better pairs matching performance: a counterintuitive finding?

A less consistent but perhaps more intriguing finding concerns the associations with better performance on the pairs matching test for individuals with IR-related somatic phenotypes, which was assessed at baseline for the whole cohort and included in all cognitive reassessments. The pairs matching test assesses visual short-term memory, which is the ability to retain information from a visual stimulus for a short period of time after the stimulus has ceased and allows the comparison of perceptual information of objects separated in time and space (Hollingworth & Luck, 2008). Impairment in visual memory is a typical characteristic of Alzheimer's disease, and it is also commonly present in ADHD, although it has been less strongly reported in other neuropsychiatric disorders (Millan et al., 2012). The seemingly counterintuitive association with pairs matching outperformance was found with higher BMI (Ferguson et al., 2020; Morys et al., 2021), body fat percentage (Morys et al., 2021), and diabetes (Garfield et al., 2021). Although others have not replicated these findings (see the Results section), the repeated association of IR-related diseases and traits with better cognitive performance seems to be unique for pair matching, but a pathophysiological explanation behind such findings does not appear to be obvious at present. Noteworthy is the fact that the pairs matching task did not present a good test-retest reliability between baseline and a repeat assessment (in a subsample of 20,000 participants) about four years apart (Lyall et al., 2016). Furthermore, an intriguing finding arises from a longitudinal study showing that, despite a baseline association with better performance on this test, individuals with diabetes had a steeper decline in performance on follow-up assessment compared to individuals without diabetes (Garfield et al., 2021).

Possible underlying mechanisms linking IR and cognition

Several mechanisms have been suggested as possibly underlying the link between IR and cognition, including the insulin modulation of some neurotransmitter systems (among others, the cholinergic and glutamatergic systems having a major role in cognition), immune-inflammation and oxidative stress, and altered hypothalamus-pituitary axis function (Butterfield & Halliwell, 2019; De Felice et al., 2022). In particular, insulin has been implicated in the modulation of synaptic plasticity and memory through its effects on the expression and presentation on the plasma membrane of glutamatergic receptors (De Felice et al., 2022). Furthermore, insulin is responsible for glucose uptake in the hippocampus and some cortical areas through the membrane translocation of glucose transporter type 4 (GLUT4) (Koepsell, 2020), whose inhibition was shown to hinder the procognitive insulin's action on working memory in rats (De Felice et al., 2022). It is also important to consider that obesity and diabetes lead to a state of systemic inflammation with an increase in proinflammatory cytokines that is also reflected in the brain (Lyra et al., 2019). Here, microglia activation results in the production of proinflammatory cytokines, such as interleukin (IL)-6, tumour necrosis factor-α, IL-1β, which may interfere with insulin signalling (Kullmann et al., 2016). Interestingly, a UK Biobank study showed that the association between fluid intelligence and lean muscle or visceral adipose mass was mediated by the levels of different leukocyte subpopulations (Klinedinst et al., 2019).

Interestingly, it has been suggested that accumulation of amyloid-β oligomers, which is a hallmark of Alzheimer's disease neuropathology, may lead to cognitive impairment through defective brain insulin signalling (Tumminia et al., 2018). Animal studies have shown that impairments in insulin signalling following intracerebroventricular infusion of amyloid-β oligomers were accompanied by memory deficits in several behavioural tasks. In turn, IR may accelerate amyloid-β production and brain accumulation (Tumminia et al., 2018). IR may also result in microcirculation damage and atherosclerosis, leading to brain reduced oxygen supply and tissue suffering, as also revealed by widespread white matter and functional connectivity alterations, as well as regional brain volumes variations seen in individuals with diabetes or obesity, also in UK Biobank (Ferguson et al., 2020; Garfield et al., 2021; Hsu et al., 2012; Morys et al., 2021; Suzuki et al., 2017). These neuroimaging correlates and cardiovascular alterations may mediate the relationship between IR and worse cognitive performance, as repeatedly suggested by some authors (Feng et al., 2020; Ferguson et al., 2020; Morys et al., 2021; Suzuki et al., 2017; Whitelock et al., 2021). In fact, recent studies further suggest that white matter integrity may mediate the link between cognitive performance and

both variations in HbA1c levels (Repple et al., 2021) and genetic liability to type 2 diabetes (Repple et al., 2022).

Interestingly, one study in the UK Biobank also suggested that depressive symptoms may mediate the relationship between diabetes and cognitive function (Whitelock et al., 2021). Of note, depression and diabetes are both predisposing factors for each other, and common molecular pathways have been proposed (Nguyen et al., 2018). In addition, oral hypoglycaemic medications used in diabetes, such as liraglutide, have shown clinical usefulness in improving cognitive function in people with depression (Fanelli & Serretti, 2022). As a result, it is possible to speculate that biological factors common to diabetes and depression may have an influence on cognition.

Strengths and limitations

This review should be considered in light of clear strengths and limitations. The UK Biobank represents the largest population-based cohort where both cognitive measures and IR-related somatic diseases and traits have been deeply phenotyped. While large-scale Danish/Scandinavian population-based registries include information on clinical diagnoses and prescribed medication to identify cardio-metabolic and psychiatric conditions, they do not contain information on cognitive measures (Schmidt et al., 2019) or only do so for a very limited subsample derived from smaller clinical/follow-up studies on specific patient groups (e.g., patients with dementia or diabetes) that are then linked to national registries (Fereshtehnejad et al., 2015; Wium-Andersen et al., 2019). The richness of the phenotypes measured in UK Biobank allows going beyond clinical comparisons and addressing the full spectrum of phenotypes as a continuum in the general population. In order to allow cognitive assessment of an unprecedented number of individuals under the same protocol, some of the most widely used and clinician-rated cognitive instruments were specifically adapted for the UK Biobank study. Thus, a possible limitation is that the cognitive measures under the UK Biobank protocol were obtained by concise, unsupervised touchscreen assessments and not under traditional standardised conditions (Sudlow et al., 2015). It is important, however, to also weigh in as a clear strength of this approach the possibility of addressing several facets of cognition in a short period of time and that, despite the adapted nature of this protocol, the UK Biobank tests showed overall good validity, demonstrating moderate-to-high test-retest reliability and substantial correlation with the reference tests from which they were derived (Fawns-Ritchie and Deary, 2020). However, it is worth considering that the UK Biobank sample population was recruited on a voluntary basis and is not fully representative of the general UK population. In fact, participants were generally healthier, less likely to smoke or consume alcohol, and resided in less socio-

economically deprived areas than non-participants (Fry et al., 2017). Nevertheless, because of its large sample size and variety of exposure measurements, it can still provide valid scientific inferences about the link between exposures and health outcomes that are generalisable to other populations (Fry et al., 2017). Another possible point of attention is that the derivation of the diabetes phenotype was heterogeneous across different studies, sometimes pooling type 1 and type 2 diabetes mellitus, or even other types of diabetes, which have partially or entirely different aetiopathogenetic mechanisms. This may have added noise to the results of individual studies, contributing to some of the inconsistent findings described in this review. Last but not least, the study design was cross-sectional in most of the reviewed studies, limiting any interpretation of a temporal and/or causal link between IR-related diseases and cognitive changes. Cardio-metabolic diseases may have a deleterious impact on cerebral blood flow and, consequently, on cognitive function, while individuals with poorer cognitive abilities may be less likely to engage in healthy lifestyles and behaviours that prevent cardio-metabolic diseases. Although a causal relationship between IR-related cardio-metabolic diseases and impaired cognitive function is likely, data from the UK Biobank calls for caution for the time being. Studies on independent cohorts are required to clarify any causal relationship.

Directions for future research

In addition to focusing on better understanding the causal relationship between cognitive impairment and cardio-metabolic diseases linked to IR, both at the genomic and clinical levels, future research should also examine the potential contribution of immune-inflammatory, oxidative, and central insulin signalling mechanisms. Genomic research examining the pleiotropic effect of genes implicated in insulin signalling, immune-inflammation, and HPA axis modulation on both cognition and IR-somatic diseases might aid in unravelling the mechanisms behind the phenotypic associations highlighted in this review. Additional studies are also needed to further investigate the possible underlying mechanisms (and/or alternative explanations) for the seemingly counterintuitive findings associating IR-related conditions and better performance on visual memory tasks. Functional analyses, possibly including (animal) modelling, could provide further answers to the underlying pathological mechanisms involved in the differential effects observed for specific cognitive domains. Future research could benefit from a more homogeneous classification of participant diagnostic groups (e.g., better distinction between type 2 diabetes mellitus cases from those with other types of diabetes) to allow better interpretation of the findings and/or uncovering of possible underlying biology. Furthermore, despite the lack of clear

knowledge on the causal relationship between IR-related conditions and cognitive performance nor the identification of (possible) shared underlying factors so far, growing evidence suggests a potential future use of hypoglycaemic drugs, such as metformin, proliferator-activated receptor-γ (PPAR-γ) agonists, and glucagon-like peptide 1 receptor agonists (GLP1RA), in the treatment of cognitive deficits seen in various neuropsychiatric disorders (Fanelli & Serretti, 2022; Zhang et al., 2020). However, large-scale randomised clinical trials are required to confirm their efficacy and safety, which could possibly also inform on the shared pathophysiological mechanisms. Cognitive impairment is still one of the most challenging symptom domains to tackle with available pharmacological therapy (Fanelli & Serretti, 2022). As a result, gaining a deeper understanding of the processes underlying the reported links between IR and cognitive impairment will be critical in identifying potential new targets for pharmacological and/or behavioural intervention in patients with neuropsychiatric disorders.

Conclusion

In conclusion, this literature review of UK Biobank studies found substantial evidence for an association between an overall worse performance on various cognitive domains and cardio-metabolic traits and diseases related to insulin resistance, such as obesity, type 2 diabetes mellitus, hypertension, and CAD, in the general adult population. The most consistent findings are related to a detrimental influence on measures of verbal and numerical reasoning, as well as processing speed, while results for visual short-term memory have been mixed or indicated enhanced performance. It has been suggested that these associations might be mediated by alterations in immune-inflammation or white matter integrity/connectivity or brain volumes. Considering the worldwide increasing levels of multimorbidity and public health concerns about rising rates of cognitive decline, our findings offer important suggestions for future research in this crucial field and draw the attention of clinicians to the importance of primary and secondary prevention in people with cardio-metabolic diseases.

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Chapter 3

Clinical insights into the cross-link between mood disorders and type 2 diabetes: a review of longitudinal studies and Mendelian randomisation analyses

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Abstract

Mood disorders and type 2 diabetes mellitus (T2DM) are prevalent conditions that often co-occur. We reviewed the available evidence from longitudinal and Mendelian randomisation (MR) studies on the relationship between major depressive disorder (MDD), bipolar disorder and T2DM. The clinical implications of this comorbidity on the course of either condition and the impact of antidepressants, mood stabilisers, and antidiabetic drugs were examined. Consistent evidence indicates a bidirectional association between mood disorders and T2DM. T2DM leads to more severe depression, whereas depression is associated with more complications and higher mortality in T2DM. MR studies demonstrated a causal effect of MDD on T2DM in Europeans, while a suggestive causal association in the opposite direction was found in East Asians. Antidepressants, but not lithium, were associated with a higher T2DM risk in the long-term, but confounders cannot be excluded. Some oral antidiabetics, such as pioglitazone and liraglutide, may be effective on depressive and cognitive symptoms. Studies in multi-ethnic populations, with a more careful assessment of confounders and appropriate power, would be important.

Introduction

Mood disorders and type 2 diabetes mellitus (T2DM) are among the top leading causes of disability worldwide, affecting around 4% and 6% of the population, respectively (Dattani et al., 2021; Khan et al., 2019; Vos et al., 2020). In addition to their high prevalence, epidemiological studies showed that mood disorders and T2DM often co-occur (Wimberley et al., 2022). Compared to the general population, people with major depressive disorder (MDD) or bipolar disorder (BD) have twice the chance of being diagnosed with T2DM (Wimberley et al., 2022). Likewise, the risk of developing MDD or BD is almost doubled after a diagnosis of T2DM (Anderson et al., 2001; Wang et al., 2019; Wimberley et al., 2022). This comorbidity results in high social costs, reduced quality of life, and increased mortality (Holt et al., 2014; Molosankwe et al., 2012).

Many biological and behavioural/environmental factors may contribute to this comorbidity. Patients with mood disorders frequently lead an unhealthy lifestyle, e.g., altered sleep patterns, sedentariness, poor diet, and tobacco/substance use, which may predispose to insulin resistance and T2DM (Fanelli & Serretti, 2022). Second-generation antipsychotics are often prescribed for mood disorders, and they can have significant metabolic effects (Goncalves et al., 2015). In terms of biological mechanisms, genome-wide and locus-specific patterns of genetic overlap were found between MDD, BD and T2DM, suggesting co-heritability between these conditions, and pointing to the existence of common aetiopathogenetic mechanisms (Fanelli, Erdogan, et al., 2022; Fanelli, Franke, et al., 2022), as illustrated in **Figure 1**. These may include alterations in insulin signalling and inflammation, as well as hypothalamic-pituitary-adrenal (HPA) axis and gut microbiota dysregulations (Fanelli & Serretti, 2022). Insulin signalling plays a pivotal role in the brain, where it is involved in neuroprotection, neurogenesis, and synaptic plasticity (Nguyen et al., 2018). Of note, insulin from the periphery can cross the blood-brain barrier, but it is also centrally produced by the choroid plexus, and insulin receptors are present on both neurons and astrocytes (Lyra et al., 2019). Brain insulin resistance may impact the dopaminergic-mesolimbic reward circuit and the expression of glutamatergic receptors in the hippocampus, with detrimental effects on cognition and hedonic perceptions (Fanelli & Serretti, 2022). Both depressive and manic episodes were linked to persistent low-grade inflammation and elevated levels of circulating pro-inflammatory cytokines, such as interleukin-6 and tumour necrosis factor-α, which can lead to affective symptoms through HPA axis hyperactivity and changes in neurotransmission (Nguyen et al., 2018). A systemic inflammatory state, further induced by adipose tissue accumulation and a high-fat diet, may also disrupt insulin signalling, leading to the development of T2DM (Nguyen et al., 2018).

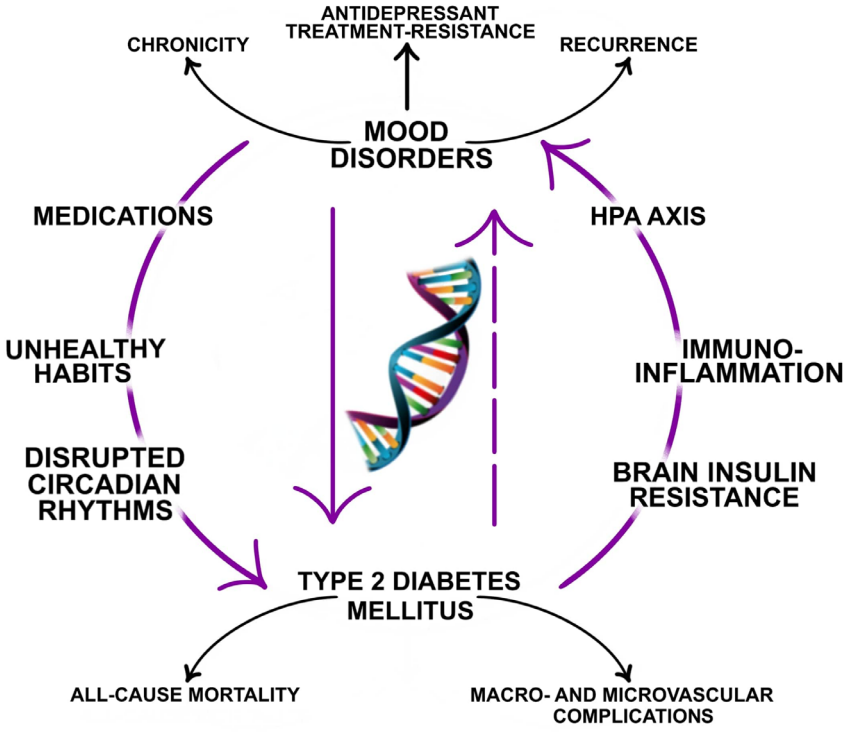

Figure 1. Summary of the evidence from epidemiological and MR studies.

Meta-analyses and cohort studies corroborated the hypothesis of a bidirectional relationship between mood disorders and T2DM. MDD predicts higher risk of subsequent T2DM, as confirmed by Mendelian randomisation studies. Results of studies on T2DM predicting incident mood disorders are contrasting. Many biological and behavioural/environmental factors may contribute to this correlation. The co-occurrence of T2DM and mood disorders can lead to worse outcomes for both conditions. Abbreviations: HPA, Hypothalamic–pituitary–adrenal; MR, Mendelian randomisation; T2DM, type 2 diabetes mellitus.

Given the considerable individual and socio-economic impact of the comorbidity between T2DM and mood disorders, and the steadily increasing prevalence of both these conditions in recent years (Holt et al., 2014; Molosankwe et al., 2012; World Health Organization, 2022), it is of paramount interest to clarify the presence of a possible causal link between them, to improve their prevention and treatment. To achieve this objective, we reviewed the literature on the association between mood disorders (MDD and BD) and T2DM. We specifically focused on longitudinal studies, as these are best suited to provide information about bidirectional and temporal relationships, and Mendelian randomisation (MR) studies, which use single-nucleotide polymorphisms (SNPs) associated with an exposure to examine

whether an association between the exposure and an outcome is compatible with a causal effect (Davies et al., 2018). In addition, we provided a qualitative synthesis of longitudinal studies on the impact of co-occurring mood disorders and T2DM, in terms of clinical course of either condition. Finally, we evaluated the potential beneficial or detrimental effects of psychotropic treatments in T2DM, as well as of antidiabetic drugs in mood disorders.

Methods

An electronic search of the literature was conducted on PubMed looking for studies investigating the relationship between T2DM and mood disorders, namely MDD and BD, and published from inception until September 2022. We used search terms related to mood disorders and diabetes mellitus, as well as antidepressants, mood stabilisers, and antidiabetic medications. The search was restricted to published only studies, written in English and conducted in human samples. The full search query used is available as **Supplementary Methods**. The final search was performed on October 3rd, 2022.

The records resulting from the search query were screened to find potentially relevant studies by inspecting titles and abstracts. The full text of the selected studies and those of uncertain relevance were retrieved and carefully examined to determine the pertinence of each study. Then the list of references in the included articles was screened to identify other potentially eligible studies not captured by the initial search. Studies whose samples consisted of patients with type 1 diabetes mellitus were excluded, as well as commentaries, letters and editorials. We only included longitudinal (i.e., observational studies and clinical trials), meta-analyses of longitudinal studies, and MR studies, as these are the best suited to study the temporality and direction of associations and possible causal effects.

The present review was narrative, as a quantitative synthesis and standardised quality assessment of the included articles were not within the scope of this work. The main reasons for this choice were the heterogeneity of the considered studies and the breadth of the research questions and methodologies. However, to provide a description of the results of our literature search, we synthesised the article selection process in **Figure S1**.

Results

The initial literature search identified 2,130 unique abstracts, out of which 232 full-text articles were evaluated to determine their eligibility. Ultimately, 84 papers were included in the review. The study selection process is summarised in **Figure S1**.

Epidemiological studies

Mood Disorders predicting incident T2DM

Previous meta-analyses of prospective studies supported the hypothesis of a link between depression and a subsequent diagnosis of T2DM (**Table S1**). In detail, a meta-analysis of nine studies with a mean follow-up of 9.4 years and a total of 174,035 individuals, found a relative risk (RR) of T2DM of 1.37 in the group with depression (95% CI 1.14-1.63) (Knol et al., 2006). This result is similar to what was reported by a later meta-analysis (RR 1.60, [95% CI 1.37-1.88]) that extended the total sample size to 222,019 individuals from 13 studies, with the same average duration of follow-up (Mezuk et al., 2008). The inclusion of an almost doubled total sample size did not change the result in a following meta-analysis (Rotella & Mannucci, 2013).

Other longitudinal studies were published after the mentioned meta-analyses, and they overall confirmed that depression increases the risk of incident T2DM in samples with various ethnic origins and clinical characteristics. Two studies used insurance claims/national registries in Asian samples, extracting data referred to 11,670 and 461,213 individuals, respectively, referred to ~7 years (Chen et al., 2013; Meng et al., 2018). Other studies confirmed the finding, but they showed a smaller sample size and/or shorter duration of follow-up, and/or they were performed in samples with specific clinical characteristics. Specifically, a study prescription of these 2981 individuals found an increased risk of incident T2DM within two years in those with depression or anxiety, particularly in those with both conditions. However, this association was attenuated after adjusting for risk factors of T2DM, such as plasma triglyceride levels and lifestyle (Atlantis et al., 2012). A study on a large cohort of 161,808 post-menopausal women reported consistent results, but it considered elevated depressive symptoms rather than a diagnosis of MDD, with a follow-up of 7.6 years (Ma et al., 2011). This limitation was balanced by the fact that the study evaluated the persistence of elevated depressive symptoms (baseline and year 3), which helped in distinguishing between transitory symptoms and probable MDD. Interestingly, only the group with persistently elevated depressive

symptoms (probable MDD) had an increased risk of incident T2DM after adjusting for confounders.

Other consistent evidence from the literature highlighted the synergistic interaction between metabolic dysregulation/prediabetes and comorbid depressive symptoms on the risk of T2DM (Deschenes et al., 2016; Schmitz et al., 2016). However, it should be noted that a recent study on a total of 1,766 individuals from a German nation-wide cohort, followed for 12 years, showed no increased risk of incident diabetes in the group with MDD (Nubel et al., 2022). The relatively small sample size of this study represents a limitation, but as discussed in the next section, longitudinal cohort studies are not free of potential limitations and risk of bias, therefore results (both positive and negative) should be interpreted carefully.

Although the cumulative evidence suggests a link between depression and incident T2DM, it is important to consider the influence of several confounding factors on the presented results. As mentioned before, adjusting for confounders reduced the effect size in studies that reported an association. The risk of bias coming from confounders is often not easy to evaluate, as the available studies were heterogeneous in terms of sample characteristics and covariates included.

Among potential confounders, undetected diabetes at baseline represents a relevant variable. Some studies relied on self-reported diabetes at baseline (e.g., Chen et al. (2013); Ma et al. (2011)), resulting in the risk of not controlling appropriately for this confounder. However, the exclusion of these studies did not change the pooled relative risk of T2DM compared to the overall estimate in an early meta-analysis (Knol et al., 2006). Other than undetected diabetes at baseline, there are risk factors for T2DM, such as overweight/obesity and lifestyle (e.g., physical activity and alcohol intake), that not all studies controlled for in an exhaustive way (Chen et al., 2013; Knol et al., 2006; Mezuk et al., 2008). Notably, many of these risk factors are shared between depression and T2DM (Milaneschi et al., 2020), therefore it is fundamental to adjust for them to avoid spurious or inflated results. Concomitant medications for depression are another important variable to take in account, as antidepressants and antipsychotics can have an impact on metabolic parameters (Goncalves et al., 2015; Rotella & Mannucci, 2013). However, most studies did not adjust for the prescription of these medications (Knol et al., 2006; Mezuk et al., 2008), and those that did adjust did not consider the specific medications but the class (e.g., Ma et al., (2011). Interestingly, antidepressant prescription was associated with an increased risk of incident T2DM, independent of depressive symptom severity (Andersohn et al., 2009; Kivimaki et al., 2010; Rubin et al., 2010). However, not all studies that reported an effect of antidepressant prescription adjusted for psychopathology (Pan et al., 2012). With one exception (Wium-Andersen et al., 2021), previous studies did not adjust for the concomitant

prescription of antipsychotics. Some antipsychotics are not rarely prescribed in depression and the prevalence of diabetes is ~12% among people taking antipsychotics (2-3 folds than the general population; Holt & Mitchell (2015)), therefore this variable should be considered as covariate in future studies.

Other modulating factors have been investigated in relation to the effect of depression on the risk of incident T2DM. Several studies considered the severity of depression and reported higher risk in case of severe and persistent depressive symptoms (Carnethon et al., 2003; Engum, 2007; Golden et al., 2008; Golden et al., 2004; Ma et al., 2011; Meng et al., 2018; Windle & Windle, 2013). Data about sex-specific correlations are contrasting - higher risk in women (Carnethon et al., 2003; Demmer et al., 2015) or in men (Mezuk et al., 2008) or no effect of sex (Chen et al., 2013)). Age seems to be a modulating factor, consistent with a couple of studies that found that the risk of incident T2DM becomes lower as age increases (Chen et al., 2013; Mezuk et al., 2008). Regarding socio-demographic factors, a lower education level was associated with increased risk (Mezuk et al., 2008), while social support does not seem to modify the risk of incident diabetes (Laursen et al., 2017).

Another relevant point to consider is the possible influence of unipolar vs bipolar depression on the risk of incident T2DM, as these disorders have largely different pathogenetic mechanisms (Johnston-Wilson et al., 2000). Unfortunately, there is much less literature on BD in this regard and no meta-analysis to the best of our knowledge. The available results are not univocal, and in most cases the potential effects of confounders do not seem appropriately accounted for. One of the available studies extracted insurance claims from a nation-wide database in Taiwan, to test the risk of initiation of antidiabetic medications within 10 years in people with MDD or BD at baseline vs matched controls (Bai et al., 2013). The authors reported an increased risk in BD but not in MDD; however, they did not control for prescription of psychotropic medications, body mass index (BMI), and other risk factors for T2DM, such as prediabetes at baseline. Further, the incidence of T2DM itself could have been underestimated, because the prescription of antidiabetic medications was the primary outcome, instead of T2DM diagnosis. Conversely, studies in the Danish registries found a similar increase in the risk of incident diabetes in both MDD and BD (Wimberley et al., 2022; Wium-Andersen et al., 2021). The results were confirmed when antidepressant/antipsychotic prescription and socio-demographic variables were considered (Wium-Andersen et al., 2021). However, these studies did not control for T2DM risk factors either, such as BMI, medical comorbidities, and lifestyle at baseline (Wimberley et al., 2022; Wium-Andersen et al., 2021). A smaller study with a 13-year follow-up included 475 patients with affective psychosis (bipolar or unipolar) and found no increased risk of incident T2DM after controlling for several confounders, including

medications, BMI, cholesterol, and inflammation levels (Dieset et al., 2019). Finally, in a Swedish nation-wide cohort of 6,587,036 individuals, people with a diagnosis of BD were found to have a ~1.5 fold increased risk of developing diabetes within 7 years, but BMI, lifestyle and medications were not considered as potential confounders (Crump et al., 2013). Therefore, studies with positive findings were larger but did not correct appropriately for confounding factors, the only negative study was smaller but adjusted the analyses for confounding factors in a more complete manner.

In conclusion, there is quite robust evidence of an increased risk of incident T2DM in people with depression (at least MDD), but this effect may be largely explained by shared risk factors between depression and T2DM and concomitant medications. Overall, epidemiological studies were not able to determine if there are depression-specific mechanisms that may link depression to the subsequent development of diabetes.

T2DM predicting incident mood disorders

The hypothesis of an increased risk of depressive disorders in people with a primary diagnosis of diabetes is controversial (**Table S1**), as available studies and meta-analyses reported small effect sizes and they suggested that medications for T2DM, characteristics of the disease and of individuals, lifestyle, and the modality used for diagnosis ascertainment could largely account for/modulate the observed (small) effects.

Two meta-analyses of longitudinal studies reported T2DM as a modest predictor of subsequent depression, with a pooled RR of 1.15 (95% CI 1.02-1.30) (Mezuk et al., 2008) and OR of 1.34 (95% CI 1.14-1.57) (Chireh et al., 2019). However, sensitivity analyses to test the robustness of findings showed that these results may be affected by confounders. Studies with clinical measures of depression indeed reported smaller effects than those using only self-reported data, and the exclusion of the latter group made the results no longer significant (Mezuk et al., 2008), similar to results found when considering self-reported diabetes (Chireh et al., 2019). Further, the exclusion of samples that had short (≤5 years) follow-ups also made the results no longer significant, suggesting that depressive symptoms may have been undetected at baseline, at least in part of the studies (Mezuk et al., 2008).

Individual studies found sex-specific effects (higher risk of depression/higher severity of depressive symptoms in women vs men (Jacob & Kostev, 2016; Lloyd et al., 2020; Salinero-Fort et al., 2018; Trento et al., 2015), age-related effects (Chen et al., 2013; Trento et al., 2015) and effects of lifestyle, medical comorbidities, and diabetes medications (e.g., (Golden et al., 2008; Jacob & Kostev, 2016; Salinero-Fort et al., 2018), though without univocal evidence. This underlines the

complexity of the relationship between depression and T2DM. For example, older age in patients with T2DM was found to have a negative impact on the severity of depressive symptoms (Trento et al., 2015), but older age is also associated with a longer duration of T2DM and a higher risk of having developed complications of the disease (e.g., retinopathy, neuropathy, coronary heart disease), which were associated with increased risk of depression (Jacob & Kostev, 2016; Lloyd et al., 2020). However, another study reported a higher risk of depression in younger patients (Chen et al., 2013). In this regard, it should be noted that the latter study considered new diagnoses of depression in patients with T2DM within a period of 7 years, while the previously mentioned work just assessed the severity of depressive symptoms at baseline and at follow-up (after 8 years) (Trento et al., 2015), therefore there is a substantial difference in study design.

Variables associated with T2DM severity were also suggested as modulators of the occurrence and the persistence of depressive symptomatology, such as worse glycaemic control (Fisher et al., 2008; Jacob & Kostev, 2016; Maraldi et al., 2007). Several lifestyle factors were also associated with a greater risk of depression, including physical inactivity (Lloyd et al., 2020; Salinero-Fort et al., 2018), higher BMI and unhealthy eating habits (Lloyd et al., 2020; Schmitz et al., 2013). Consistently with these findings, high levels of stress and reduced perceived health status were found to be markers of incident depression (Lloyd et al.; 2020). The association with the risk of incident depression or depressive mood seems stronger in subjects with treated vs untreated diabetes, especially in the case of insulin therapy, which could be a sign of worst glycaemic control or more severe complications/comorbidities (Golden et al., 2008; Lloyd et al., 2020; Pan et al., 2010). In addition, the psychological burden linked to the management of a complex therapy may contribute to depressed mood (Golden et al, 2008). On the contrary, another study demonstrated that the prescription of insulin and oral antidiabetic drugs did not affect the risk of depression (Jacob and Kostev, 2016).

The literature is much scarcer for incident BD in T2DM. To the best of our knowledge, there are only two large studies in population-based cohorts. An earlier study in a Taiwanese population-based cohort (~800,000 individuals) reported a 2.62-fold higher risk of a mood disorder (both MDD and BD) in patients with diabetes not taking any oral antidiabetic medication, but not in those taking an antidiabetic medication (Wahlqvist et al., 2012). A more recent study in the Danish registries confirmed increased odds of BD in patients with previous T2DM (hazard ratio [HR]=2.25, 95% CI 2.08-2.43), with an effect size comparable to that observed for incident MDD. The analyses were adjusted for sex, birth year, and family history of both mood disorders and T2DM, but they did not consider possible confounding and/or mediating effects of psychotropic medications and/or lifestyle (Wimberley et al., 2022).

Based on the discussed evidence, we can conclude that the relationship between T2DM and incident MDD and BD is complex and likely affected by multiple modulators. As discussed, a replicated finding was a higher risk of incident depression in women with T2DM compared to men. However, the most recent meta-analysis of incident depression in T2DM did not stratify the analyses by sex (Chireh et al., 2019), and a previous one did not identify sex effects (Mezuk et al., 2008), but it did not include the recent studies that highlighted the described higher risk in women (see above). This reflects the general difficulty in taking into account all the variables that modulate the link between T2DM and depression in epidemiological studies.

Mendelian randomisation studies

Several MR studies tested the two-way causal association between MDD and T2DM (**Table S2**), but none between BD and T2DM. A causal effect of MDD on T2DM was found by two well-powered two-sample MR studies, using summary statistics of genome-wide associations studies, including only subjects of European ancestry and a random-effect inverse-variance weighted (IVW) method (OR=1.22, 95% CI 1.09-1.36, and OR=1.26, 95% CI 1.10-1.43) (Tang et al., 2020; Tao et al., 2022). This effect was robust to sensitivity analyses that excluded possible horizontal pleiotropic effects, except for the less efficient Egger-MR –it frequently produces less precise estimates and suffers from a significant loss of power –, where the direction of the effect was nevertheless maintained. No causal association was shown in the opposite direction (T2DM → MDD) by the same studies (Tang et al., 2020; Tao et al., 2022). This negative finding is in line with an MR study using population-based individual-level data from a Scottish sample (N = 19,858) (Clarke et al., 2017). To the best of our knowledge, only one MR study reported a causal association of T2DM with MDD, using individual-level data from East-Asian ancestry subjects (N=11,506) (Xuan et al., 2018). The results showed a probable causal effect of T2DM on MDD (OR=1.83, 95% CI 1.25 - 2.70, and OR=1.57, 95% CI 1.04-2.37, derived using the Wald-type estimator with unweighted and weighted genetic scores for T2DM, respectively). The findings were confirmed by excluding pleiotropic variants and using the IVW method but not the Egger-MR, where the association was found to be non-significant and in the opposite direction (Xuan et al., 2018).

Overall, there is robust evidence of a causal effect of MDD on the risk of T2DM in European populations, while a causal effect in the opposite direction was found only by one study in East-Asian subjects, and it needs replication by more powerful studies. Further studies on ethnically diverse samples would be important.

Effects of mood disorders/T2DM comorbidity on the course of either condition

Given the chronic/relapsing nature of both mood disorders and T2DM, it is intriguing to better understand whether their co-occurrence may worsen the course of either condition.

Many prospective studies have explored depression trajectories in the context of T2DM, with the general conclusion that T2DM leads to a greater chronicity of depression, and worse depressive symptoms over time (**Table S1**). In this regard, an 8-year follow-up study found that patients with T2DM on insulin treatment experienced a mild but significant worsening of depressive symptomatology over time (Trento et al., 2015). This was corroborated by a 5-year study, showing that most patients with T2DM had low and persistent depressive symptoms, with a gradual worsening in 7.5% of cases (Whitworth et al., 2017). A lifetime history of MDD, followed by female sex, higher BMI, and younger age, were the strongest predictors for persistent depressive symptoms in T2DM (Whitworth et al., 2017). A number of social and clinical factors were also associated with the recurrence or relapse of depressive symptomatology in T2DM; for example, lack of home ownership, diabetes treatment complexity or dissatisfaction with antidepressant medications (de Groot et al., 2015), as well as poor control of glycaemic parameters (Ell et al., 2012; Maraldi et al., 2007). A recent study indicated that MDD occurring either before or after the diagnosis of T2DM may significantly increase the risk of dying by suicide (Huang et al., 2022).

No longitudinal studies investigated the relationship between T2DM and the clinical course and treatment outcomes of BD. Only one study conducted in the population-based Danish registries showed that women but not men with treatment-resistant depression (TRD) had a higher prevalence of a previous diabetes diagnosis than those without TRD. The risk of subsequent diabetes instead was increased for both sexes in individuals with TRD, after adjusting for the age at first antidepressant prescription and the number of other medical comorbidities (Madsen et al., 2021). However, there is still no longitudinal research investigating whether the presence of T2DM in BD or MDD may impact on treatment effects or may be related to specific symptom patterns.

Considering the consequences of depression on diabetes, many studies found that it may be associated with worse medical outcomes, e.g., more severe cardiovascular complications, and higher all-cause mortality (**Table S1**). This association may be at least partly mediated by poorer glycaemic control, which effect, despite small, may increase the risk of complications. An association between depressive symptoms and increased glycated haemoglobin (HbA1c) values was indeed observed in elderly patients at risk of depression or having

depression, in a longitudinal 1-year study (Sirirak et al., 2022). A sex-specific effect of MDD on glycaemic changes in T2DM was also suggested, with females but not males being less likely to return to normal glycaemic values (Nubel et al., 2022). However, studies on larger samples found no association between mood symptoms or lifetime MDD/BD and worse glycaemic control in T2DM (Aikens et al., 2009; Ismail et al., 2017; Speerforck et al., 2019; Whitworth et al., 2017).

As discussed, the effect of depression on glycaemic control seems negligible, but it may still considerably increase the risk of complications. In a cohort of elderly Mexican Americans, diabetes with comorbid depression predicted a greater risk of vascular complications, higher disability and mortality, as well as an earlier occurrence of these negative outcomes (Black et al., 2003). The risk of adverse outcomes increased with the severity of depression (Black et al., 2003). A number of other studies replicated these findings and showed that MDD in T2DM may increase the risk of advanced macrovascular complications, such as stroke, myocardial infarction, and heart failure (Ismail et al., 2017; Lin et al., 2010; Novak et al., 2016; Scherrer, Garfield, Chrusciel, et al., 2011), as well as microvascular complications, such as proliferative retinopathy and end-stage renal disease, compared to non-depressed patients with T2DM or patients with either diagnosis (Lin et al., 2010; Novak et al., 2016). Not surprisingly, in a 12-year follow-up study, baseline diabetes mellitus and lifetime moderate MDD were associated with an intensified antidiabetic treatment at follow-up (Speerforck et al., 2019). This was not found in diabetic patients with lifetime mild or severe MDD or lifetime BD (Speerforck et al., 2019). Most importantly, several studies confirmed a synergistic effect of comorbid depression and T2DM on increased mortality, even after controlling for sociodemographic, other health, and lifestyle variables (Huang et al., 2022; Jung et al., 2021; Naicker et al., 2017; Novak et al., 2016; Prigge et al., 2022; Sullivan et al., 2012; Zhang et al., 2005). The increased mortality in the presence of this comorbidity exceeded the sum of the risk associated with diabetes and depression alone (Prigge et al., 2022). Likewise, longitudinal studies focusing on BD and comorbid T2DM have corroborated these findings. In a 7-year follow-up study, subjects with BD had a higher risk of dying by a diabetes-specific cause than the general population, particularly in females (Crump et al., 2013). Additionally, there was an association between BD and premature mortality for diabetes mellitus (Crump et al., 2013). A more than 60% increase in the RR of mortality was also shown in patients with newly diagnosed BD and previous diabetes mellitus during a 3-year follow-up (Pan et al., 2016).

Do antidepressants and mood stabilisers impact on incident T2DM risk?

Many population-based studies found that individuals taking antidepressants have an increased risk of incident T2DM, especially in the long-term, as confirmed by a meta-analysis including studies with a mean follow-up of 5.8 years (OR 1.31, 95% CI 1.18–1.45) (Ma et al., 2011; Pan et al., 2010; Rotella & Mannucci, 2013). The association was stronger for selective serotonin reuptake inhibitors (SSRI) and multiple antidepressant users, while non-significant for other classes of antidepressants (mainly tricyclic antidepressants (TCAs)) in a study on middle-aged women followed for ~10 years; however, this could be due to the higher frequency of SSRIs prescription vs other classes (Pan et al., 2010). Another long follow-up study including individuals of both sexes found that those taking antidepressants were more likely to develop T2DM, regardless of the antidepressant class/molecule; participants were free of diabetes and cardiovascular diseases at baseline (Pan et al., 2012). However, the association was attenuated after adjusting for cardio-metabolic risk factors and BMI (Pan et al., 2012). The link between long-term use of antidepressants and increased diabetes risk was confirmed for both TCAs and SSRIs in other studies (Andersohn et al., 2009; Kivimaki et al., 2010; Rubin et al., 2010). Depressed patients on moderate-to-high daily doses of antidepressants for more than 24 months showed a nearly doubled risk of diabetes vs non-users, and this effect was independent of depression severity (Andersohn et al., 2009). In an 18-year study including ~6,000 middle-aged individuals, antidepressant use was associated with incident diabetes defined as use of antidiabetics or self-reported diagnosis, but not with diabetes detected during screenings of blood biomarkers or with increased glucose levels over time (Kivimaki et al., 2011). The analyses were adjusted for socio-demographic variables, other cardiovascular risk factors and medication use. These findings suggest that the association between antidepressant use and incident T2DM may be at least partly explained by the more frequent healthcare service use in patients with depression (Tusa et al., 2019), which increases the probability that T2DM is early diagnosed. This observation, together with the difficulty in adjusting for all the factors associated with long-term antidepressant use (e.g., lifestyle) suggests caution in concluding there may be an association with incident T2DM risk.

The evidence is scarcer regarding the use of lithium or valproate and the risk of incident T2DM. Existing studies do not show an increased risk of diabetes in patients taking lithium vs other mood stabilisers, taken individually or in combination, but the evidence is limited by a short duration of treatment or follow-up and the lack of a treatment-free/placebo control group (not feasible due to ethical reasons). In an early study, 460 patients with BD in long-term treatment with lithium were followed

for a period between 6 months and 6 years; there was no increase in diabetes mellitus risk, as observed by fasting blood glucose measurement, although weight gain was observed (Vestergaard & Schou, 1987). More recently, in a cohort of ~7,000 patients with BD, those receiving lithium showed no difference in the rate of T2DM compared to those treated with valproate, olanzapine, or quetiapine (Hayes et al., 2016). However, the median treatment duration was 1.48 years, which was a relevant limitation as T2DM develops typically in the longer term (Hayes et al., 2016). Lithium in combination with antipsychotics or anticonvulsants showed no evidence of increased cardiometabolic risk in patients with BD (Kohler-Forsberg et al., 2022); however, also this study had a relatively short follow-up (24 weeks).

Positive effects of treatments for depression and diabetes on either condition

The identification of effective treatment strategies for both mood disorders and T2DM is pivotal given the high comorbidity between the two conditions, as well as the common risk factors and aetiopathogenetic mechanisms (Fanelli & Serretti, 2022). Early studies investigated which drugs among those approved for MDD or BD had the best efficacy in patients with T2DM (e.g., Gulseren et al. (2005)). More recently, precision medicine and the development of a systemic vision of psychiatric disorders have become highly important. For example, several studies investigated the repurposing of antidiabetic drugs for treating mood disorders, as many of them cross the blood-brain barrier (Heneka et al., 2005; Kastin et al., 2002; Labuzek et al., 2010). An overview of studies on this topic is described in **Table S3**.

Antidepressants and mood-stabilisers

As expected, treatment with antidepressants showed an effect on depressive symptoms in samples of depressed patients with comorbid T2DM or altered glycaemic status (**Table S3**). The available clinical trials did not find differences in the decrease of depressive symptoms within 12 weeks when comparing an SSRI vs another SSRI (Gulseren et al., 2005; Khazaie et al., 2011). Two trials reported a higher benefit of agomelatine over an SSRI (sertraline or paroxetine) on depression scores after 12-16 weeks of treatment (Kang et al., 2015; Karaiskos et al., 2013). However, these studies did not provide an estimation of power to support sample size choice, and the statistical significance of the difference between the considered drugs seems doubtful. Other studies compared an antidepressant (SSRI or nortriptyline) vs placebo, and confirmed the benefit of the active treatment on depressive symptoms (Lustman et al., 2000; Lustman et al., 1997), despite one negative 6-month study on a small sample treated with sertraline (Echeverry et al., 2009). A couple of studies investigated the potential benefits of paroxetine in patients with

T2DM and subthreshold-mild depressive symptoms, finding no benefits on quality of life in the short term (10 weeks) or after 6 months (Paile-Hyvarinen et al., 2003, 2007). A recent network meta-analysis found that escitalopram, agomelatine and paroxetine have evidence of higher benefit on depression severity in patients with T2DM vs placebo, with escitalopram raking first; on the other hand, nortriptyline had a large but non-significant effect (Srisurapanont et al., 2022).

Data about antidepressant efficacy on glycaemic control (HbA1c) are conflicting. Although long-term antidepressant use was suggested to increase incident T2DM risk (see the previous paragraph), SSRIs may improve glycaemic control after 12 weeks, with similar benefits of citalopram and fluoxetine (Khazaie et al., 2011) and higher effect of sertraline over placebo at month 6 (Echeverry et al., 2009). However, no benefits over placebo were reported for citalopram (Nicolau et al., 2013), or no improvement in patients receiving fluoxetine or paroxetine (Gulseren et al., 2005). The results of a recent meta-analysis are helpful to interpret these conflicting results (Srisurapanont et al., 2022). The paper found that vortioxetine, escitalopram, agomelatine, sertraline, fluoxetine, and paroxetine reduced HbA1c significantly more than placebo, with vortioxetine ranking first, followed by escitalopram and agomelatine. The meta-analysis also reported that the hypoglycaemic benefits of agomelatine and vortioxetine were drawn from two trials with a moderate risk of bias. Interestingly, an open-label trial conducted in 93 patients with comorbid T2DM and MDD demonstrated that bupropion hydrochloride improved glycaemic control, BMI, as well as diabetes self-care in the acute phase (10 weeks), and this effect persisted during the maintenance phase (24 weeks) (Lustman et al., 2007). The improvement in glycaemic control in both the short- and medium-term was suggested to be potentially mediated by improvements in mood, although the findings must be interpreted with caution given the lack of a control arm and randomisation, as well as the small sample size (Lustman et al., 2007). Of note, in a large cohort of 93,653 individuals with depression, SSRIs, TCAs and other antidepressants prescribed for at least 12 weeks reduced the risk of incident myocardial infarction within a period of 8 years, with HRs ranging from 0.50 to 0.66 (Scherrer, Garfield, Lustman, et al., 2011).

To summarise, the available evidence suggests that antidepressants are effective in treating depression in patients with T2DM, and some antidepressants may have positive effects on glycaemic control, in the short term. Escitalopram seems to have good support for both depressive symptoms and glycaemic control. The positive impact of effectively treating depression in the long term should also be considered. Unfortunately, the studies that investigated the potential effects of mood stabilisers on HbA1c levels and T2DM complications are much scarcer. In patients with BD, mood stabilisers (including lithium) and antidepressants, in monotherapy or combination,

were associated with a decrease in HbA1c levels vs no psychotropic medication, independent from having a diagnosis of diabetes (Castilla-Puentes, 2007). On the contrary, antipsychotics in monotherapy or in combination with a mood stabiliser are known to have a negative effect on glycaemic control, while lithium monotherapy may be slightly better than lithium combination with another mood stabiliser (Castilla-Puentes, 2007; Kohler-Forsberg et al., 2022; Kuperberg et al., 2022).

Antidiabetic medications

Insulin

Insulin receptor knockout mice have depressive-like behaviours, and both depression and cognitive symptoms were associated with low insulin-like growth factor-1 in the elderly (Mueller et al., 2018). Therefore, it was hypothesised that insulin may have effects on both depressive and cognitive symptoms, particularly in the elderly. A previous study tested this hypothesis in type 2 diabetic elderly patients with poor glycaemic control, by randomising them to continuing oral medication, switching to insulin twice-a-day or basal insulin (Hendra & Taylor, 2004). The group that switched to basal insulin showed a decrease in depressive symptoms at months 1 and 3, though not at month 6; however, the study included only 19 patients per arm and the clinical significance and reproducibility of results seem doubtful. Another small study in elderly patients with poorly controlled T2DM adopted a similar design (though not randomised), with one group continuing oral medication and another switching to insulin. This study reported benefits on well-being and mood in the group that switched to insulin, however, as outlined, the study had relevant limitations (Reza et al., 2002).

Other studies tested intranasal insulin effects on mood and cognitive function in healthy individuals (Benedict et al., 2004), in euthymic BD (McIntyre et al., 2012) or in treatment-resistant depression (TRD) (Cha et al., 2017). These studies were also limited by small sample sizes. The first study reported an improvement in mood and memory after 8 weeks (vs placebo) in healthy individuals, consistently with the results of the second, which found an improvement in executive functioning in BD patients at week 8. On the contrary, the latter study did not find benefits on mood or neurocognitive functioning in TRD.

In conclusion, there is currently poor evidence in support of a possible effect of insulin on mood and neurocognitive functioning, since the results come from small and heterogeneous samples (**Table S3**).

Metformin

Metformin, a biguanide compound, is a commonly prescribed hypoglycaemic agent. Two recent meta-analyses of randomised clinical trials (RCTs) found metformin to have a neutral effect on mood symptomatology compared to placebo and inferior to active controls (Moulton et al., 2018; Nibber et al., 2022). Among the RCTs included in these meta-analyses, only one found metformin to be effective on depressive symptomatology, mainly by improving cognition (Guo et al., 2014). This result is in line with the meta-analytic finding that metformin was superior to placebo in improving cognitive function in patients with cognitive impairment (Nibber et al., 2022).

A recent randomised placebo-controlled study not included in the cited meta-analyses tested adjunctive metformin in a group of non-diabetic patients with treatment-resistant BD and insulin resistance (Calkin et al., 2022). The study reported a significant improvement in depression and anxiety, as well as in insulin resistance, although gastro-intestinal side effects were common.

In conclusion, metformin does not show consistent benefits on depressive symptoms (**Table S3**), and a relevant point for future research would be to test if it may improve specific depressive symptoms (e.g., cognitive symptoms) rather than the whole depressive spectrum. Another hypothesis worth further study is the possible preventing effects of oral antidiabetics on the development of mood disorders. This was suggested by a population-based study showing that the combination of metformin and sulfonylurea may reduce the risk of mood disorders in patients with T2DM, despite metformin alone did not show a protective role (Wahlqvist et al., 2012).

Thiazolidinediones

Thiazolidinediones, also known as peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, are oral hypoglycaemic agents that ameliorate insulin sensitivity by enhancing fatty acids storage and adipocytes differentiation (Raymond et al., 2014). A first meta-analysis included four RCTs and tested pioglitazone in MDD or BD, showing benefits vs control treatments, on both remission (OR 3.3, 95% CI 1.4-7.8) and symptom improvement (mean difference=2.8, 95% CI 1.4-4.3) (Colle et al., 2017). The benefit of pioglitazone on depressive symptomatology either alone or as an add-on treatment was confirmed by a following larger meta-analysis (Moulton et al., 2018). Interestingly, the improvement in depressive symptoms was predicted by the female sex, but not by the severity of depressive symptoms or by glycaemic control at baseline (Moulton et al., 2018). A significant reduction of depressive symptoms was also reported in three open-label studies, two testing

pioglitazone and one rosiglitazone (Kemp et al., 2012; Kemp et al., 2014; Rasgon et al., 2010). However, a double-blind placebo-controlled RCT (not included in the cited meta-analyses) failed to demonstrate the antidepressant effects of pioglitazone in 38 outpatients with bipolar depression, but it was limited by lack of power and the concurrent use of other psychotropic medications (Aftab et al., 2019).

Overall, there is suggestive evidence for a positive effect of pioglitazone on depressive symptomatology, regardless of a mood disorder diagnosis (**Table S3**). However, previous meta-analyses suffer from high heterogeneity, and future studies should include more homogeneous populations, particularly in terms of psychiatric diagnosis.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs)

Most studies on the neuropsychiatric effects of glucagon-like peptide (GLP-1) receptor agonists (GLP-1RAs) were conducted on animal models (e.g., (Chaves Filho et al., 2020). A previous meta-analysis considered the effect of GLP-1RAs on depression rating scales and found GLP-1RAs to be superior in reducing depression compared to control treatments, meta-analysing data that included both depressed and non-depressed patients with diabetes (Pozzi et al., 2019). Limitations of these results are the small number of included studies, the possibility of severe bias found for some studies, and the high heterogeneity.

As outlined for other anti-diabetic treatments, cognitive dysfunction represents a possible target symptom for GLP-1RAs as well. A four-week open-label trial tested the effectiveness of liraglutide on a sample of 19 non-diabetic patients with MDD or BD and below-average cognitive performance (Mansur et al., 2017). The results are clearly preliminary, but it is encouraging that a significant improvement in depressive symptoms and executive functions was observed, with no correlation with levels of glycaemia or insulin resistance (**Table S3**).

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a class of oral antidiabetics, also known as gliptins, which act by blocking the degradation of the incretin hormones (Kasina & Baradhi, 2022). These hormones regulate glycaemic homeostasis after food intake by increasing insulin secretion (Kasina & Baradhi, 2022). DPP-4 inhibitors also have anti-apoptotic, anti-inflammatory, and immunomodulatory actions on multiple tissues (Kasina & Baradhi, 2022). These mechanisms seem very promising in terms of a possible antidepressant effect; however, all the available studies provided negative results. An RCT in 44 middle-aged patients with T2DM assessed the effect of sitagliptin, a DPP-4 inhibitor, and found it was inferior to placebo in alleviating depressive symptoms at week 12 (Moulton et al., 2021). The RCT had, however, several

limitations, including an inadequate sample size, the exclusion of patients with very poor glycaemic control, and the use of a self-reported measure of depressive symptoms (Moulton et al., 2021). An observational study in 10 elderly patients with T2DM evaluated the effect of the DPP-4 inhibitor vildagliptin, as an add-on to metformin, with no evidence of benefits on depressive or cognitive symptoms at month 11 vs baseline (Tasci et al., 2013). Another RCT compared the DPP-4 inhibitor linagliptin to glimepiride, a hypoglycaemic drug of the sulphonylurea class, and found no differences on cognition, in 3163 middle-aged patients with T2DM, over a median of ~6 years of follow-up (Biessels et al., 2021).

Overall, there is currently no evidence to support the use of DPP-4 inhibitors for the treatment of depressive and cognitive symptoms (**Table S3**); however, there are only three available studies, two of them showed a small sample size, and each of them had a different design.

Non-pharmacological interventions

A Cochrane meta-analysis found a non-significant effect of psychological interventions vs usual care (including pharmacological treatment when indicated) on glycaemic control in individuals with both depression and diabetes, in the short-, medium- and long-term (Baumeister et al., 2012). This meta-analysis also outlined that the quality of the available evidence was low, and it was not possible to evaluate the impact of psychological interventions on the risk of diabetes complications.

When looking at individual studies, the evidence is heterogeneous. Psychotherapy (in particular cognitive-behavioural therapy [CBT]), combined with pharmacological treatment and/or lifestyle modifications, was associated with a higher rate of response in terms of depressive symptomatology, both in the short- (10-12 weeks) and medium-term (6-12 months) (de Groot et al., 2019; Huang et al., 2016; Lustman et al., 1998; Piette et al., 2011; Safren et al., 2014). Only a part of these studies also showed a benefit of the intervention on glycaemic control (de Groot et al., 2019; Huang et al., 2016; Safren et al., 2014). However, these studies were generally limited in sample size (<100 participants in most cases) and were heterogeneous in terms of inclusion criteria, type of intervention and type of control. For example, some studies compared CBT with diabetes self-management training (Lustman et al., 1998), or other forms of enhanced usual care (e.g., educational and self-help material (Piette et al., 2011)), while others used just usual care as control (e.g., Huang et al. (2016)).

On the other hand, psychoeducation or behavioural activation vs treatment as usual or other forms of enhanced treatment (e.g., physical exercise) does not seem to provide benefits in diabetic patients with subthreshold depression or

depression, according to previous studies in small samples (Pibernik-Okanovic et al., 2009; Pibernik-Okanovic et al., 2015; Schneider et al., 2016).

A recent meta-analysis (32 RCTs, including a total of 3,543 patients) contributed to clarify the cumulative evidence (van der Feltz-Cornelis et al., 2021). The results supported the efficacy of group-based therapy, psychotherapy, and collaborative care on glycaemic control in patients with diabetes and depressive symptomatology, with moderate heterogeneity among studies. High baseline depression and high baseline HbA1c were associated with a greater reduction in HbA1c. However, the meta-analysis also outlined that most studies had some risk of bias, mostly unclear reporting about randomisation and blinding. Moreover, the control group considered in each study was variable (e.g., waiting list, usual care). Another limitation of this and the meta-analysis discussed above (Baumeister et al., 2012) was the inclusion of RCTs of both type 1 and T2DM, despite the fact that these have different pathogenesis and treatment.

Discussion

Summary of findings

Meta-analyses and cohort studies corroborated the hypothesis of a bidirectional relationship between mood disorders and T2DM (**Figure 1**). MDD predicts a higher risk of subsequent T2DM, as confirmed by Mendelian randomisation studies, and this appears the finding with the strongest support emerging from this review. Evidence is scarcer for BD predicting the risk of incident T2DM, and the risk of confounding effects could not be excluded. Studies on T2DM predicting subsequent mood disorders outline a possible association, but show conflicting results, and further investigations are needed, particularly in patients with BD.

Independently from possible causal links, the available studies clearly demonstrated that the co-occurrence of T2DM and MDD can lead to worse outcomes for both conditions. T2DM leads to greater depression treatment resistance, chronicity, and more severe symptoms, while MDD leads to worse medical outcomes and higher mortality in T2DM. Both T2DM and mood disorders are associated with detrimental consequences on cognitive functioning and an increased risk of dementia (G. Fanelli et al., 2022; Jorm, 2000). Therefore, the promotion of a healthy lifestyle represents a clinical priority, with the Mediterranean diet and physical exercise having strong support for the prevention of both conditions (Strasser & Fuchs, 2015). The early detection and treatment of impaired glucose tolerance in patients with mood disorders are of similar importance, as well as of anxiety, depressed/irritable mood, or sleep alterations in patients with T2DM (Benasi et al., 2021).

Psychopharmacological treatments may contribute to an increased risk of developing T2DM in patients with mood disorders, particularly in the long term, and it is advisable to avoid combination therapies. However, certain antidepressants and mood stabilisers showed efficacy in treating mood symptoms in patients with T2DM, and they may also have beneficial effects on glycaemic control at least in the short term. Interestingly, promising results from clinical trials showed potential antidepressant benefits of hypoglycaemic drugs.

Modulators of the bidirectional association between mood disorders and T2DM

There are multiple confounders that should be taken into account when considering the bidirectional association between mood disorders and T2DM. As noted, these include cardiometabolic risk factors, such as cigarette smoking, which is frequent in mood disorders (Otte et al., 2016). MDD, particularly the atypical subtype, is often characterised by sedentary behaviour and increased appetite, leading to overweight/obesity (Otte et al., 2016). Patients with BD have disrupted circadian rhythms and a high rate of alcohol and substance consumption (Hunt et al., 2016). Several medical comorbidities may affect mood and increase the risk of T2DM, such as obesity, Cushing's disease, polycystic ovary syndrome, and hypothyroidism (Diez & Iglesias, 2012; Golden, 2007; Kolhe et al., 2022). Further, mood disorders are characterised by low adherence to pharmacological and non-pharmacological medical prescriptions, which may increase the likelihood of incident T2DM (Grenard et al., 2011). On the other hand, the prescription of some medications for mood disorders can increase the risk of metabolic alterations. Long-term treatment with antipsychotics, especially second-generation ones, increases the risk of T2DM (Burghardt et al., 2018; Vancampfort et al., 2016). Almost all the included studies considered some of the discussed confounders and provided adjusted analyses that substantially confirmed the initial results. However, as previously discussed, we noticed a high heterogeneity in the factors each study adjusted for.

Given the metabolic effects of some psychotropic drugs, another significant topic discussed in this review was the possible effect of antidepressant prescriptions in modulating the link between mood disorders and T2DM. The prescription of more than one antidepressant and for a longer period was associated with a higher risk of T2DM (Pan et al., 2010), corroborating the importance of preferring monotherapy when possible. On the other hand, antidepressant combinations prescribed over a long period could indicate a more severe form of depression, e.g., with chronicity and recurrence, which are predictors of T2DM (Andersohn et al., 2009; Rubin et al., 2010). Another issue that suggests the complexity of the illustrated relationship is the finding that antidepressant users may seek medical attention more frequently

than untreated or non-depressed people, increasing the likelihood of being diagnosed with medical conditions, including T2DM (Kivimaki et al., 2010). As previously stated, it is necessary to consider all the potential confounders and be cautious in stating that antidepressants may have a role in increasing the risk of diabetes.

Possible effects of medications for mood disorders and T2DM on the comorbid condition

Previous studies hypothesised that antidepressant prescription in patients with T2DM may ameliorate not only depression but also glycaemic control, despite conflicting data. Unfortunately, most antidepressant clinical trials excluded patients with T2DM, while those designed for comorbid mood disorders and T2DM are only a few and had small sample sizes. According to a meta-analysis of observational and cross-sectional studies in patients with T2DM and depression, individual characteristics may influence the probability of receiving an antidepressant prescription, such as sex, ethnicity, concurrent medications and comorbidities (Jeffery et al., 2021). Keeping in mind these limitations and modulating factors, the available evidence suggests that some SSRIs (particularly escitalopram), agomelatine, vortioxetine, and bupropion may have a positive impact on glycaemic control and in the prevention of cardiovascular complications, at least in the short-term (Lustman et al., 2007; Srisurapanont et al., 2022) (**Figure 2**).

Lithium is another medication that may have a positive effect in patients with mood disorders at risk of T2DM (**Figure 2**). Lithium acts on several molecular intracellular effectors of insulin signalling (Campbell et al., 2022). Indeed, lithium decreases the signalling of the phosphatidylinositol 3-kinase/Protein Kinase B (PI3K/Akt) pathway, by inhibiting the phosphatidylinositol cycle (PI-cycle) upstream and glycogen synthase kinase-3β (GSK3β) downstream (Campbell et al., 2022). Insulin resistance and related hyperinsulinaemia lead to chronic GSK3β overactivation, which negatively impacts on glycidic metabolism and energy production at the mitochondrial level (Campbell et al., 2022). Lithium could therefore be considered an insulin sensitiser for cells, as suggested also by animal studies (Lee & Kim, 2007; Rossetti, 1989). Markers of insulin resistance should be considered as possible predictors of lithium response in future studies.

Insulin signalling plays a critical role in the energy metabolism of both neurons and glia, in brain areas involved in mood regulation and cognition (Lyra et al., 2019), therefore antidiabetic medications may exert effects also in the brain (**Figure 2**). While insulin does not seem to improve mood, a procognitive action was hypothesised. Metformin was broadly tested for preventing or reducing the metabolic side effects of antipsychotics (Vancampfort et al., 2019) and it may

modulate the blood-brain barrier function with neuroprotective benefits (Takata et al., 2013). Nevertheless, clinical studies do not provide conclusive results on possible antidepressant or procognitive effects. On the other hand, encouraging evidence is available for PPAR-γ receptor agonists. Thiazolidinediones' activation of central PPAR-γ receptors protects neurons from oxidative stress and apoptosis, and it enhances mitochondrial energy generation (Hauner, 2002; Villapol, 2018). GLP-1RAs enhance neurogenesis via the 5' adenosine monophosphate-activated protein kinase (AMPK)-pathway and have very preliminary evidence of antidepressant benefits (Andreozzi et al., 2016). Intriguingly, thiazolidinediones and GLP-1RAs exhibit anti-inflammatory effects, attributed to a downregulation of pro-inflammatory genes (Kothari et al., 2016).

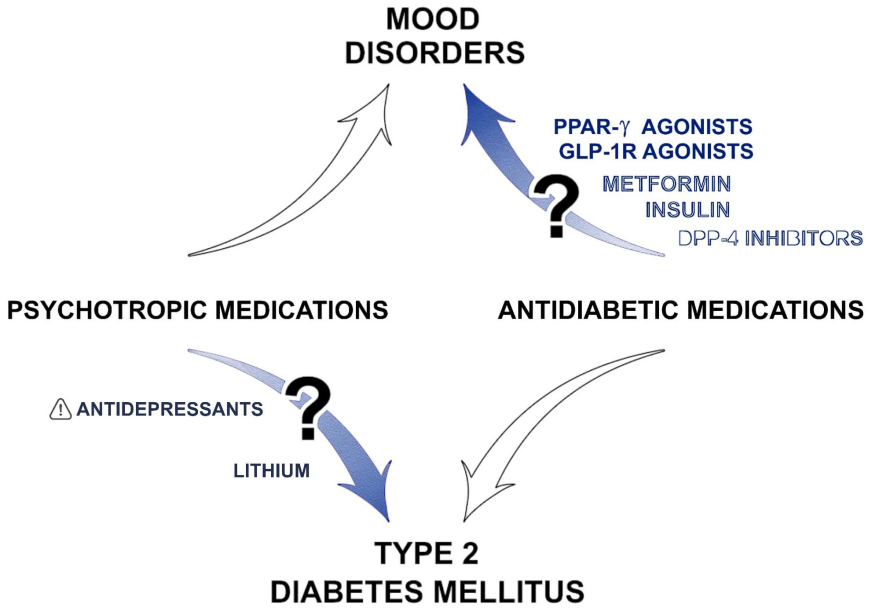

Figure 2. Effects of treatments for depression and diabetes on either condition.

Antidepressants, namely escitalopram, agomelatine, vortioxetine, and bupropion, may have a positive impact on glycaemic control, at least in the short-term, but the prescription of more than one antidepressant and for a long period may increase the risk of T2DM. Suggestive evidence indicates that lithium may improve glycaemic control, possibly by directly acting on the insulin signalling pathway. As shown at the top right of this figure, it has been hypothesised that drugs commonly prescribed for T2DM also exert effects on the brain. GLP-1R agonists and PPAR-γ agonists, such as liraglutide and pioglitazone, have shown promise in relation to their possible antidepressant effects. There is little evidence to support a possible effect of insulin and metformin on mood and neurocognitive functioning. No evidence supported the use of DPP-4 inhibitors for the treatment of depressive and cognitive symptoms. Abbreviations: PPAR-γ, peroxisome proliferator-activated receptor-γ; GLP-1R=glucagon-like peptide-1 receptor; DPP-4, dipeptidyl peptidase-4; T2DM, type 2 diabetes mellitus.

Limitations of the available studies

This review aimed to provide a comprehensive overview on the topic of interest; however, the reviewed studies showed several limitations that should be considered. Longer follow-ups would have been useful to intercept all cases of incident T2DM, which have typically an insidious onset, to better analyse the course of these chronic/relapsing conditions, and to detect the effects of medications on depressive and metabolic symptoms. The heterogeneous presentations of both mood disorders and T2DM should be better considered, to reduce the risk of stratification, and to disentangle possible differences due to disease subtypes (e.g., MDD with atypical vs melancholic features, BD type 1 vs 2), various disease stages (e.g., acute or remission phases, depressive or manic phases, earlier or later stages of T2DM), presence or absence of complications and/or other comorbidities. Another issue that came up as a possible limitation was the use of self-reported questionnaires for the diagnosis of depression in many studies, and the prescription of antidepressants as a proxy for depression in a few studies (e.g., (Ismail et al., 2017; Ma et al., 2011). Likewise, in several studies T2DM was self-reported or assessed using records of antidiabetic treatments (e.g., (Atlantis et al., 2010; Bai et al., 2013), which could result in an underestimation of the incidence of diabetes. Some studies did not differentiate between type 1 and type 2 diabetes. However, >95% of all diagnosed cases of diabetes are T2DM (World Health Organization, 2022). Finally, as previously outlined, common confounding variables, such as lifestyle and medication use, were not systematically considered in previous research, and some important topics were only marginally or not investigated. It is worth noting that, despite the evidence of brain insulin resistance being involved in BD aetiopathology (Mansur et al., 2021), there are no or few studies in BD for all the areas considered in this review. The paucity of studies could be explained by the lower prevalence of BD than MDD (Dattani et al., 2021), and the common use of screening and self-reported questionnaires in population studies, which have low positive predictive values for BD (Smith et al., 2011). Since cross-sectional studies have found that people with comorbid T2DM are more likely to experience a chronic course of BD, as well as rapid cycling, and are less prone to respond to lithium (Calkin et al., 2022; Calkin et al., 2015), future prospective studies should aim to elucidate the complex relationship between T2DM and BD and to treat more effectively these disabling forms of BD.

Conclusion

Epidemiological studies and meta-analyses consistently suggested an increased risk of incident T2DM in mood disorders and vice versa, with possible sex-specific effects. However, the evidence was less strong for the effect of T2DM on incident

depression, and these associations may be subject to undetected confounders. T2DM leads to greater treatment resistance, chronicity and more severe symptoms of depression, and depression leads to worse medical outcomes, micro- and macrovascular complications, and higher mortality in T2DM. Some antidepressants may improve glycaemic control in the short term; however, they may be associated with metabolic alterations in the long-term. Lithium may have protective effects on metabolic parameters vs other treatment options, but long-term studies are lacking. The use of some oral antidiabetics, such as thiazolidinediones and GLP-1RAs, may be beneficial in treating depressive and cognitive symptoms in mood disorders.

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Chapter 4

Insulin resistance and poorer treatment outcomes in depression: evidence from UK Biobank primary care data

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Abstract

Major depressive disorder (MDD) and insulin resistance (IR)-related conditions are major contributors to global disability. Their co-occurrence complicates clinical outcomes, increasing mortality and symptom severity. In this study, we investigated the association of IR-related conditions and related polygenic scores (PGSs) with MDD clinical profile and treatment outcomes, using primary care records from UK Biobank. We identified MDD cases and IR-related conditions, as well as measures of depression treatment outcomes (e.g., resistance) from the records. Clinical-demographic variables were derived from self-reports, and IR-related PGSs were calculated using PRS-CS. Univariable analyses were conducted to compare socio-demographic and clinical variables of MDD cases with (IR+) and without lifetime IR-related conditions. Multiple regressions were performed to identify factors, including IR-related PGSs, potentially associated with treatment outcomes, adjusting for confounders. Among 30,919 MDD cases, 51.95% were IR+. These had more antidepressant prescriptions and classes utilisation and longer treatment duration than patients without IR-related conditions ($p<0.001$). IR+ participants showed distinctive depressive profiles, characterised by concentration issues, loneliness and inadequacy feelings, which varied according to the timing of MDD diagnosis relative to IR-related conditions. After adjusting for confounders, IR-related conditions (i.e., cardiovascular diseases, hypertension, non-alcoholic fatty liver disease, obesity/overweight, prediabetes, and type 2 diabetes mellitus) were associated with antidepressant non-response/resistance and longer treatment duration, particularly when MDD preceded IR-related conditions. No significant PGS associations were found with antidepressant treatment outcomes. Our findings support an integrated treatment approach, prioritising both psychiatric and metabolic health, and public health strategies aimed at early intervention and prevention of IR in MDD.

Introduction

Major depressive disorder (MDD) and insulin resistance (IR)-related conditions rank among the leading causes of disability worldwide, and their incidence continues to grow to epidemic proportions (GBD, 2020). IR, which is characterised by diminished cellular response to insulin in muscles, fat, and liver, is a common feature underlying cardio-metabolic conditions like type 2 diabetes mellitus (T2DM), obesity, dyslipidaemia, and cardiovascular diseases (CVDs) (James et al., 2021). These conditions are increasingly recognised as significant risk factors for psychiatric disorders, notably MDD (Possidente et al., 2023).

The epidemiological link between MDD and IR-related conditions has been well-established (Rajan et al., 2020; Wimberley et al., 2022). The risk for IR-related conditions is higher among patients with MDD, and, in turn, people with T2DM and obesity have up to 4-fold higher risk for MDD (Possidente et al., 2023). Comorbidity with IR-related conditions in individuals with MDD adversely affects the clinical trajectory of depression, resulting in increased severity, greater chronicity, and higher mortality rates (Fanelli & Serretti, 2022; Possidente et al., 2023).

Recent studies have identified shared genetics and pathophysiological mechanisms between IR and MDD, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, chronic low-grade inflammation, alterations in the gut microbiota, and neurotransmitter systems, suggesting a bi-directional relationship where each condition may influence the onset of the other (Fanelli, Franke, et al., 2022; Fanelli & Serretti, 2022; Possidente et al., 2023). In MDD, chronic stress induces HPA axis hyperactivation, resulting in sustained cortisol elevation that promotes gluconeogenesis, impairs insulin-mediated glucose uptake in peripheral tissues, and elevates circulating free fatty acids, thereby contributing to IR (Fanelli et al., 2025). Concurrently, MDD-associated inflammation can disrupt insulin receptor signalling and contribute to metabolic dysfunction (Fanelli et al., 2025; Possidente et al., 2023). On the other hand, IR within the central nervous system impairs synaptic plasticity and affects mood-regulating neurotransmitter systems (Fanelli et al., 2025; Possidente et al., 2023). These shared pathophysiological mechanisms have also been linked to resistance to treatments (Borgiani et al., 2024; Murphy et al., 2017). The first exploration of insulin's effects in psychiatric disorders was unfortunately linked to insulin shock therapy, introduced in the mid-20th century as a treatment for severe psychiatric conditions; this approach was abandoned by the 1970s, due to the lack of therapeutic rationale and risks of prolonged hypoglycaemia and other side effects (Freudenthal & Moncrieff, 2022). As discussed above, in recent years, the study of IR in psychiatric disorders has been based on solid scientific evidence coming from both epidemiological and neurobiological studies.

Traditional antidepressant drugs are a cornerstone of MDD management. They address imbalances of distinct neurotransmitter systems but display inconsistent treatment efficacy. About 60% of treated individuals, in fact, do not reach complete clinical remission after a full course of treatment (De Carlo et al., 2016). This variability in response is partly attributed to the high clinical and pathophysiological heterogeneity of MDD, which is not restricted to monoamine system abnormalities (Oliva et al., 2023); one of the most studied MDD subgroups is characterised by metabolic disturbances, and it has been named immune-metabolic depression (Milaneschi et al., 2020). The presence of IR-related conditions in patients with MDD results in significant clinical challenges. The altered inflammatory and endocrine profile in these patients might reduce the effectiveness of standard antidepressant therapies, contributing to treatment-resistant depression (TRD) (Murphy et al., 2017). Therefore, understanding the influence of IR and related conditions on antidepressant response is essential for developing personalised treatment strategies, which is a key goal for precision psychiatry (van Dellen, 2024). Some antidepressants, like monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), may exacerbate metabolic disturbances, further complicating treatment (Fanelli & Serretti, 2022). This necessitates a careful balancing, to weight the expected benefits on mental health against the potential metabolic risks.

Genomic studies have highlighted the role of genetic predisposition in the development of both MDD and IR, hinting to their shared genetic aaetiology (Fanelli, Franke, et al., 2022). Polygenic scores (PGSs) quantify the cumulative effect of genetic variants associated with a particular trait or disease; they are a promising approach for studying the clinical/genetic heterogeneity and treatment response in depression (Oliva et al., 2023), heralding personalised medicine approaches based on individual genetic profiles.

Despite growing evidence supporting a link between IR and MDD, there is still a paucity of large-scale studies comprehensively exploring the association between IR-related conditions and treatment outcomes in MDD (Kraus et al., 2023; Madsen et al., 2021). Particularly, the temporal relationship between the onset of IR-related conditions and MDD, and how this sequence influences the clinical course of MDD and response to treatment, is not well-understood. This gap in knowledge hinders possible considerations for developing more well-tolerated and effective treatment strategies for patients with MDD and comorbid IR-related conditions.

The present study investigated whether IR-related conditions and their PGSs are associated with the clinical course of MDD or response to antidepressant treatment, considering also which condition was diagnosed earlier. This study leveraged data from the UK Biobank (UKB) cohort linked to primary care records, providing the opportunity to examine these relationships in a large population cohort.

Methods

UK Biobank cohort and linked primary care data

This study utilises data from the UKB, which is a large-scale, prospective cohort study providing extensive genetic, lifestyle, and health data from approximately 500,000 individuals across the UK, aged between 40 and 69 years at recruitment (2006-2010) (Bycroft et al., 2018). Primary care data were available for ~45% of the cohort (230,096 participants), reflecting regional and provider variability (UK Biobank, 2019). Missing or incomplete data were not imputed.

The UKB includes genotypes for 488,377 participants, who were genotyped using the Applied Biosystems UK BiLEVE and UK Biobank Axiom Arrays (Thermo Fisher Scientific Inc., Waltham, MA, USA) (Bycroft et al., 2018). Detailed methodologies for DNA extraction, genotyping, quality control, and imputation in UKB are reported elsewhere (UK Biobank, 2019).

As part of the UKB's comprehensive data collection, primary care data have been obtained for 230,096 participants, forming the basis of our study (UK Biobank, 2019). This subset includes electronic health records (EHRs) sourced from English, Scottish, and Welsh General Practitioner practices, employing various primary care information systems (EMIS, Vision, TPP). The records include dates and codes for primary care clinical events (e.g., consultations, diagnoses, referrals to specialists, or prescriptions events) coded using Read version 2 (V2) and Clinical Terms Version 3 (CTV3 or V3), the British National Formulary (BNF), and/or the Dictionary of Medicines and Devices (dm+d) (UK Biobank, 2019). These codes were used to identify MDD and IR-related conditions, the time at first diagnosis, and antidepressant prescriptions. In cases where prescription or diagnosis dates were missing or implausible (e.g., 01/01/1901, 07/07/2037), diagnostic codes were excluded from temporal analyses but retained for non-temporal analyses to maximise sample size, and prescription records were not considered for deriving treatment outcome variables. Potential biases arising from missing or incomplete primary care data are addressed in the Discussion section.

Ethics Statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human subjects/patients were approved by the Northwest Multi-centre Research Ethics Committee (MREC) with approval number 11/NW/0382.

Target population: MDD cases with or without IR-related conditions

We focused on a subset of UKB participants having at least one diagnostic record for a unipolar depressive disorder and at least one prescription code for an antidepressant medication, excluding those with bipolar, psychotic, and/or substance use disorders. These data were extracted according to the steps described in a previous work (Fabbri et al., 2021).

Similarly, IR-related conditions were defined based on diagnostic records. We considered the presence of at least one primary care Read code for coronary artery disease (CAD), cerebral ischaemia, CVDs, dyslipidaemia, polycystic ovary syndrome (PCOS), familiar dyslipidaemia, gestational diabetes, hypertension, non-alcoholic fatty liver disease (NAFLD), obesity/overweight, T2DM, and Cushing's disease. Read V2 and CTV3 codes used for the extraction of IR-related conditions are reported in **Tables S1-2**. These IR-related conditions were selected based on their established contribution to or pathogenic association with metabolic dysregulations commonly seen in IR (da Silva et al., 2020; Hill et al., 2021; James et al., 2021).

Outcomes of interest

The outcomes of interest were: 1) antidepressant non-response, defined as ≥1 switch between different antidepressant drugs, with each drug prescribed for at least six consecutive weeks to avoid drug switches due to side effects. We considered a time interval between consecutive prescriptions of no more than 14 weeks to ensure that treatment had not been suspended, following another recent study (Fabbri et al., 2021); 2) TRD, defined as ≥2 switches between different antidepressant drugs, with each drug prescribed at least for six consecutive weeks, to ensure an adequate duration of treatment before switching, and a time interval between prescriptions shorter than 14 weeks (Fabbri et al., 2021); 3) overall treatment time, used as proxy for MDD chronicity and calculated as the sum of time windows between two consecutive antidepressant prescriptions (if the time interval between two consecutive prescriptions was shorter than 14 weeks, otherwise it was considered a time window free from antidepressants).

Polygenic risk scores computation

PGSs were estimated in the UKB using PRS-CS-auto, a Bayesian method that applies continuous shrinkage priors on single-nucleotide polymorphism (SNP) effect sizes, bypassing the need to preselect a GWAS P-threshold for SNP inclusion (Ge et al., 2019). GWAS summary statistics used for the construction of PGSs were those for body mass index (BMI), CAD, T2DM, fasting plasma glucose (FPG), glucose levels 2 hours after an oral glucose challenge (2hGlu), glycated haemoglobin (HbA1C), high density lipoproteins (HDL), HOMA-IR, low density lipoproteins (LDL), and

triglycerides (TGL). GWAS summary statistics were selected based on the largest GWAS sample size available excluding UKB to avoid sample overlap between the input and target samples (**Table S3**).

Statistical analysis

We compared individuals with MDD having or not having IR-related comorbidities, also considering stratifying individuals based on the temporal sequence of MDD-first diagnosis relative to IR-related condition-first diagnosis, according to primary care records.

Univariable analyses were conducted using two-sample Student's t-test and Pearson's chi-square test, as appropriate, to examine differences in demographic, socio-economic, clinical, and lifestyle factors between individuals affected by MDD with and without IR-related conditions. The variables assessed included the age at MDD onset, follow-up duration, mean age during follow-up, patterns of antidepressant prescription, psychological symptoms, and treatment outcomes (see **Table S4** for information on variables and their coding). A subsequent one-way Analysis of Variance (ANOVA) was used to compare these variables across three defined groups of individuals: MDD without IR-related conditions (IR-), MDD after an IR-related condition diagnosis (MDD-after-IR), MDD diagnosis preceding IR-related conditions (MDD-before-IR). Post hoc analyses, employing Tukey's Honestly Significant Difference (HSD) test, were conducted to identify differences between group pairs.

To examine the association of IR-related conditions and their PGSs with treatment outcomes, we used multivariable linear or logistic regression models. These analyses were adjusted for assessment centre, mean age during follow-up, follow-up duration, sex, smoking status, Townsend deprivation index, and population principal components (the latter only for PGS analyses). PGS analyses were carried out in European individuals only (identified as in Fabbri et al. (2021)).

We quantified the variance explained in treatment non-response or resistance using Nagelkerke's pseudo-R^2. For models with overall treatment time as a continuous outcome, the variance was quantified using R^2. The Hosmer-Lemeshow χ^2 test was employed to evaluate the goodness of fit of logistic regression models, with $p \geq 0.05$ suggesting no significant difference between observed and predicted values, suggesting an adequate model fit. While the pseudo-R^2 in this study are anticipated to be low due to the multifactorial nature of depression treatment outcomes, and IR-related traits, goodness-of-fit metrics of the Hosmer-Lemeshow test can ensure that the predictions are reliable within the observed data.

This study was hypothesis-driven, building on prior evidence and well-established biological links between MDD and IR-related conditions. Although not

pre-registered, the analysis plan and the selection of the variables analysed was informed by previous literature (Fabbri et al., 2021; Possidente et al., 2023; Rashidian et al., 2021). To minimise the risk of type I errors due to multiple testing, a stringent Bonferroni correction was applied (α=0.0006), accounting for 27 predictors and three treatment outcomes.

All analyses were performed in R version 4.3.2 (2023-10-31), with data cleaning and manipulation streamlined by the *tidyverse 2.0* R package.

Results

Socio-demographics characteristics of the sample

Our study included 30,919 individuals with MDD, among whom 16,063 (51.95%) had a lifetime history of insulin resistance (IR)-related conditions (**Table S5**). The mean age during follow-up was 56.12 years (SD=8.35), with males comprising 31.8% of the cohort. A predominant majority (N=29,581; 95.67%) were of European descent. The most prevalent IR-related conditions included hypertension (N=9,499; 30,74%), obesity/overweight (N=5,243; 16.97%), CVDs (N=3,650; 11.81%), T2DM (N=3,092; 10.01%), and CAD (N=2,450; 7.92%) (**Table S5**). Of the cohort, 6,357 individuals (20.56%) received the first MDD diagnosis following an IR-related diagnosis. Conversely, 9,483 (30.67%) had MDD before any IR-related condition, and 14,856 (48.05%) had no history of IR-related conditions (**Table S5**).

Univariable analyses revealed significant socio-demographic differences among patients with MDD when stratified by the presence or absence of lifetime IR-related conditions (**Table 1**). Patients with lifetime IR-related conditions were older and were more frequently male compared to those without IR-related conditions (**Table 1**). These patients also reported lower levels of education and lower socioeconomic status, as indicated by the Townsend Deprivation Index and household income (**Table 1**). Stratification by IR-related diagnosis timing relative to MDD onset confirmed these findings (**Tables S7-S8**).

MDD clinical profile and insulin resistance

Individuals in the MDD IR+ group had a higher mean age at depression first diagnosis and longer duration of follow-up (**Table 1**). This group exhibited more frequently characteristics suggestive of unhealthy lifestyle, including higher rates of smoking and lower levels of moderate physical activity, but also lower alcohol intake frequency compared to the IR- group (**Table 1**). The IR+ group also showed higher prevalence of long-term illnesses and disability, as well as higher BMI (**Table 1**). BMI was highest in the MDD-after-IR group, followed by the MDD-before-IR group (**Table S9**).

Depressive symptoms and traits also varied between the groups. The IR+ group reported more feelings of loneliness and being fed-up, but reduced rumination over embarrassing situations, the latter especially in the MDD-after-IR group (**Table 1**; **Tables S7-S8**). Patients in the IR+ MDD-after-IR subgroup were characterised by fewer feelings of nervousness, worry/anxiety, guilt, and sensitivity to hurt, but increased feelings of inadequacy and concentration difficulties when compared to IR- individuals (**Table S8**). In contrast, those with pre-existing MDD exhibited higher levels of neuroticism compared to IR- individuals (**Table S7**).

Prescription patterns

IR+ individuals had a higher rate of antidepressant prescriptions per follow-up year, used more drug classes, and had more frequent antidepressant switches than those without any lifetime IR-related condition (**Table 1**). There were also differences in the prevalence of prescribed antidepressant classes between the groups. Specifically, individuals prescribed serotonin antagonist and reuptake inhibitors (SARIs - nefazodone and trazodone), serotonin-norepinephrine reuptake inhibitors (SNRIs - duloxetine and venlafaxine), tetracyclic antidepressants (i.e., mirtazapine), and tricyclic antidepressants (TCAs) were more numerous in the IR+ group, while the opposite was found for selective serotonin reuptake inhibitors (SSRIs); however, the number of prescriptions of individual antidepressants, including SSRIs, was higher in the IR+ group (**Table 1**). After stratifying the sample based on the timing of the first diagnosis of IR-related conditions in relation to the first MDD diagnosis, the higher antidepressant prescription and use of more different antidepressant classes was particularly evident in individuals having MDD onset before IR-related conditions (**Tables S7-S8**). A higher number of antidepressant switches and prescriptions of SARIs and SNRIs was found in patients with MDD preceding IR-related diagnoses versus the IR- group, but not in those with later MDD diagnosis (**Tables S7-S8**). Among individuals diagnosed with MDD following, but not preceding, an IR-related condition, a higher proportion were prescribed SSRIs compared to IR- individuals (**Tables S7-S8**). No differences were observed in antipsychotic use as adjunct treatments or other antidepressant classes among the groups.

Table 1. Differences in socio-demographic and clinical characteristics between patients with MDD not having a lifetime history of any IR-related condition (IR-) and patients with MDD having a history of any IR-related condition (IR+).

Student's two-sample t-tests and Pearson's Chi-square tests were used for continuous and categorical variables, as appropriate. Only statistically significant differences after Bonferroni correction are reported. Non-significant differences are detailed in **Table S6**.

Abbreviations: IR, insulin resistance-related conditions; SD, standard deviation; BMI, body mass index; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants. UK educational qualifications includes: 'College/University' degree, which covers undergraduate (Bachelor's degrees) and postgraduate degrees (Master's and Doctoral degrees); 'A/AS levels' (Advanced/Advanced Subsidiary levels), qualifications typically pursued by students aged 16 to 18 as a preparatory step for university or vocational training; 'GCSEs' (General Certificate of Secondary Education), the primary set of exams taken by students at the end of compulsory education around age 16, replacing the historical 'O levels' (Ordinary Levels) and 'CSEs' (Certificate of Secondary Education, a non-academic track phased out in 1988 alongside O Levels); 'NVQ' (National Vocational Qualifications), 'HND' (Higher National Diploma), and 'HNC' (Higher National Certificate), which are vocational qualifications offered post-secondary education to provide practical skills and training in various fields.

Variable	IR-	IR+	Test statistic	p-value
Alcohol intake frequency, N (%)	Daily or almost daily=2,593 (0.16) Three or four times a week=3,107 (0.19) Once or twice a week= 3,991 (0.25) One to three times a month/Special occasions only =3,896 (0.24) Never= 1,236 (0.07)	Daily or almost daily=2,502 (0.16) Three or four times a week=2,752 (0.17) Once or twice a week=3,875 (0.24) One to three times a month/Special occasions only=4,943 (0.31) Never=1,941 (0.12)	$\chi^2 = 259.77$	5.10e-55
Average household income, N (%)	>52,000£=2,751 (0.17) 31,000-51,999£=3,481 (0.22) 18,000-30,999£=3,283 (0.20) <18,000£=3,316 (0.21)	>52,000£=1,777 (0.11) 31,000-51,999£=2,775 (0.17) 18,000-30,999£= 3,701 (0.23) <18,000£=5,080 (0.32)	$\chi^2 = 675.44$	4.45e-146
BMI (kg/m^2), mean (SD)	26.21 (4.16)	30.15 (5.73)	t = -69.34	<5e-324
Age at first depression diagnosis (years), mean (SD)	46.29 (11.13)	49.47 (11.91)	t = -24.27	6.19e-129
Education qualifications, N (%)	College/University=4,603 (0.29) A/AS levels= 1,821 (0.11) O levels/GCSEs/CSEs=4,444 (0.28) NVQ/HND/ HNC/other professional qualifications=1,631 (0.10) none of the above=2,192 (0.14)	College/University=3,554 (0.22) A/AS levels= 1,530 (0.10) O levels/GCSEs/CSEs= 4,323 (0.27) NVQ/HND/ HNC/other professional qualifications= 2,151 (0.13) none of the above= 4,254 (0.26)	$\chi^2 = 852.9$	2.66e-183
Ever SARI prescriptions, prop. yes/no	0.06/0.94	0.07/0.93	$\chi^2 = 21.215$	4.11e-06

Table 1. Continued

Variable	IR-	IR+	Test statistic	p-value
Ever SNRI prescriptions, prop. yes/no	0.13/0.87	0.15/0.85	$\chi^2 = 32.455$	1.22e-08
Ever SSRI prescriptions, prop. yes/no	0.86/0.14	0.84/0.16	$\chi^2 = 27.322$	1.72e-07
Ever TCA prescriptions, prop. yes/no	0.5/0.5	0.58/0.42	$\chi^2 = 207.327$	5.26e-47
Ever tetracyclic antidepressant prescriptions, prop. yes/no	0.13/0.87	0.16/0.84	$\chi^2 = 34.637$	3.97e-09
Fed-up feelings, prop. yes/no	0.64/0.36	0.67/0.33	$\chi^2 = 22.973$	1.64e-06
Follow-up duration (years), mean (SD)	38.34 (13.11)	40.85 (13.79)	t = -16.37	5.22e-60
Loneliness, prop. yes/no	0.35/0.65	0.38/0.62	$\chi^2 = 24.745$	6.54e-07
Long-standing illness, disability or infirmity, prop. yes/no	0.35/0.65	0.56/0.44	$\chi^2 = 1339.24$	3.36e-293
Mean age during follow-up (years), mean (SD)	53.54 (8.21)	58.51 (7.74)	t = -54.57	<5e-324
N antidepressant classes ever used, mean (SD)	1.71 (0.88)	1.84 (0.95)	t = -12.01	3.64e-33
N antidepressant prescription records, mean (SD)	41.86 (59.28)	56.24 (71.64)	t = -19.29	1.94e-82
N antidepressant prescription records/ follow-up years, mean (SD)	1.26 (1.92)	1.59 (2.3)	t = -14.05	1.05e-44
N antidepressant switches, mean (SD)	1.77 (2.36)	2.07 (2.66)	t = -10.49	1.06e-25

Table 1. Continued

Variable	IR-	IR+	Test statistic	p-value
N days/week of moderate physical activity, mean (SD)	3.6 (2.37)	3.45 (2.43)	t = 5.2	1.99e-07
N depression diagnostic records/follow-up years, mean (SD)	0.11 (0.23)	0.1 (0.16)	t = 6.46	1.08e-10
N SNRI prescriptions, mean (SD)	3.4 (21.44)	4.8 (23.99)	t = -5.43	5.61e-08
N SSRI prescriptions, mean (SD)	26.41 (39.23)	31.82 (46.19)	t = -11.13	9.79e-29
N TCA prescriptions, mean (SD)	8.79 (26.29)	14.69 (37.47)	t = -16.12	3.08e-58
N tetracyclic antidepressant prescriptions, mean (SD)	1.91 (12.79)	3.07 (16.21)	t = -7.01	2.40e-12
Overall treatment time (weeks), mean (SD)	184.05 (229.77)	235.98 (262.19)	t = -18.55	1.97e-76
Recent trouble concentrating on things, prop. yes/no	0.36/0.64	0.4/0.6	$\chi^2 = 11.784$	5.97e-04
Sex (M/F, proportion)	0.26/0.74	0.37/0.63	$\chi^2 = 393.075$	1.77e-87
Smoking status, prop. yes/no	0.47/0.53	0.53/0.47	$\chi^2 = 94.106$	2.99e-22
Townsend deprivation index, mean (SD)	-1.27 (3.03)	-0.74 (3.23)	t = -14.79	2.46e-49
Treatment non-response, prop. yes/no	0.2/0.8	0.25/0.75	$\chi^2 = 98.393$	3.43e-23
Treatment resistance, prop. yes/no	0.08/0.92	0.12/0.88	$\chi^2 = 104.245$	1.79e-24

Treatment Outcomes

IR+ patients had overall longer treatment duration and poorer outcomes, including higher rates of TRD and non-response, than IR- counterparts (**Table 1**). After adjusting for confounders, specific IR-related conditions (i.e., CVDs, CAD, hypertension, NAFLD, obesity/overweight, prediabetes, and T2DM) were associated with increased odds of TRD and antidepressant non-response (**Figure 1a-b**; **Table S10a-b**). This pattern was consistent in the overall sample and in the subgroup of patients who developed MDD prior to each specific IR-related condition, but not in those who developed MDD after IR-related conditions (**Table S11**). Regarding the chronicity of MDD, proxied by the overall treatment time, a similar result was observed. The presence of IR-related conditions was associated with longer overall treatment time in the entire sample (**Figure 1c**; **Table S10c**), especially in individuals diagnosed with MDD before the IR-related condition (**Tables S11**). Conversely, in patients who developed MDD after IR diagnoses, a general association of poorer treatment outcomes and overall treatment time with the presence of any IR-related condition, rather than with specific IR-related conditions, was observed (**Table S12**).

We did not identify any association between the PGSs of IR-related diseases/traits and treatment outcomes or overall treatment time; we found nominal associations ($p<0.05$) with the PGSs of CAD, triglycerides, and BMI in certain subgroups defined by diagnosis timing (**Tables S13-S15**). The R^2/Nagelkerke's pseudo-R^2 values for models predicting treatment outcomes ranged from 1.3 to 3.9%, reflecting the complexity of multifactorial traits like depression treatment outcomes and IR-related conditions. Despite this, the Hosmer-Lemeshow χ^2 test indicated an acceptable fit for most models (**Tables S10–15**), supporting the validity of the observed associations.

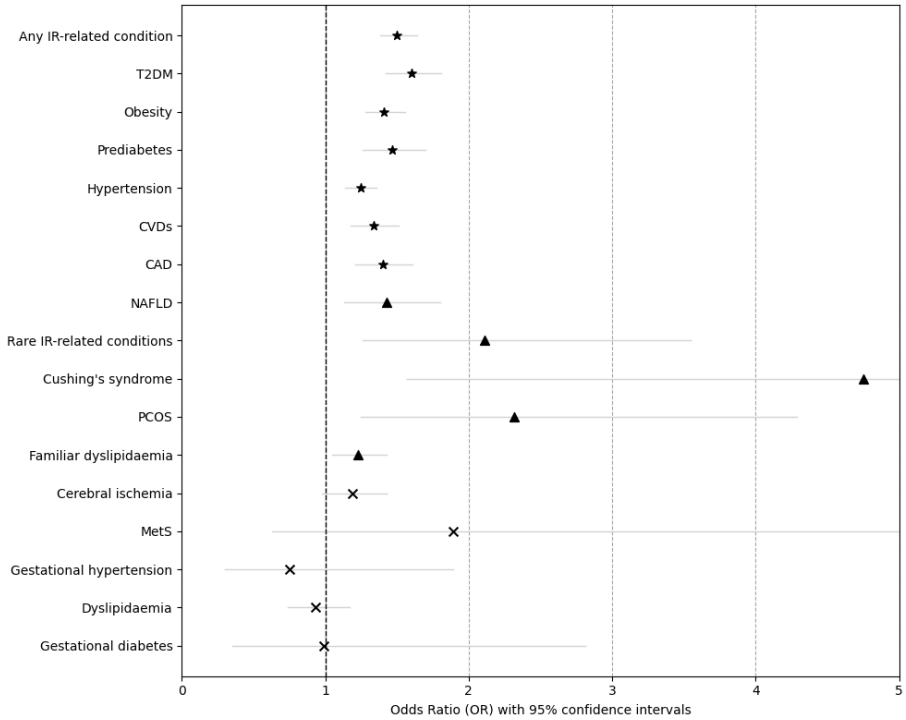

Figure 1a. Associations between insulin resistance-related conditions and treatment-resistant depression.

Odds ratios (ORs) along with their 95% confidence intervals are depicted for each insulin resistance-related conditions. Statistical significance is represented using different symbols: stars (★) for statistically significant results ($p < 0.0006$), triangles (▲) for nominally significant results ($p < 0.05$), and crosses (×) for non-significant results ($p \geq 0.05$). The findings are arranged in a gradient based on significance, with the most statistically significant results at the top, and non-significant results at the bottom of the plot. Abbreviations: CVDs, cardiovascular diseases; PCOS, polycystic ovary syndrome; MetS, metabolic syndrome; NAFLD, non-alcoholic steatohepatitis liver disease; T2DM, type 2 diabetes mellitus.

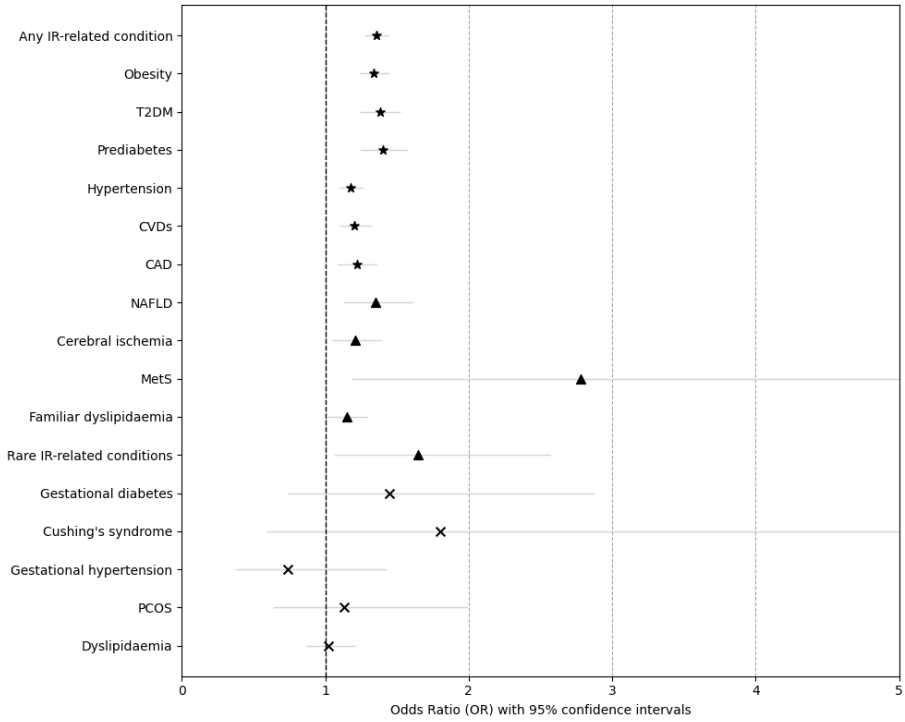

Figure 1b. Associations between insulin resistance-related conditions and antidepressant non-response.

Odds ratios (ORs) along with their 95% confidence intervals are depicted for each insulin resistance-related conditions. Statistical significance is represented using different symbols: stars (★) for statistically significant results ($p < 0.0006$), triangles (▲) for nominally significant results ($p < 0.05$), and crosses (✕) for non-significant results ($p \geq 0.05$). The findings are arranged in a gradient based on significance, with the most statistically significant results at the top, and non-significant results at the bottom of the plot. Abbreviations: CVDs, cardiovascular diseases; PCOS, polycystic ovary syndrome; MetS, metabolic syndrome; NAFLD, non-alcoholic steatohepatitis liver disease; T2DM, type 2 diabetes mellitus.

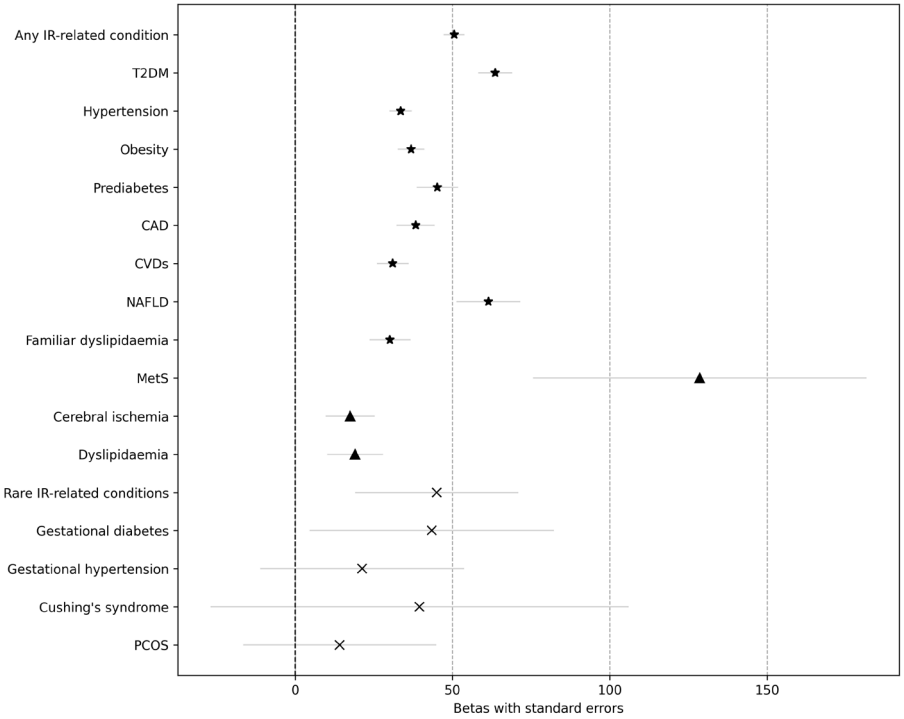

Figure 1c. Associations between insulin resistance-related conditions and overall treatment time in MDD.

β's and standard errors are depicted for each insulin resistance-related condition. Statistical significance is represented using different symbols: stars (★) for statistically significant results ($p < 0.0006$), triangles (▲) for nominally significant results ($p < 0.05$), and crosses (×) for non-significant results ($p \geq 0.05$). The findings are arranged in a gradient based on significance, with the most statistically significant results at the top, and non-significant results at the bottom of the plot. Abbreviations: CVDs, cardiovascular diseases; PCOS, polycystic ovary syndrome; MetS, metabolic syndrome; NAFLD, non-alcoholic steatohepatitis liver disease; T2DM, type 2 diabetes mellitus.

Discussion

Overview of main findings

This study, leveraging primary care-linked data from the UK Biobank, investigated the associations between IR-related conditions and treatment outcomes, prescription patterns, and clinical profiles of patients with MDD. Our analyses revealed a high prevalence of IR-related conditions among individuals with a history of MDD, emphasising the need to integrate metabolic health into psychiatric care. Those with IR-related comorbidities showed a later age at first MDD diagnosis, were less often females, and exhibited more unhealthy lifestyle factors. Our study is the first to utilise a large, real-world primary care sample with EHRs and genetic information, demonstrating the increased complexity in managing depression in this population. This complexity is evidenced by a higher number of antidepressant prescriptions, switches, and number of classes ever used among those with IR-related comorbidities. Most notably, the presence of IR-related conditions was associated with a higher likelihood of TRD, antidepressant non-response, and prolonged treatment duration, particularly when MDD preceded the onset of IR-related conditions.

Prevalence of IR-conditions in depression: mechanisms and unhealthy lifestyle

The high prevalence of hypertension, obesity/overweight, CVDs, and T2DM within our MDD sample aligns with existing research, underscoring the influence of these comorbidities on mental health (Kangethe et al., 2021; Kraus et al., 2023; Possidente et al., 2023; Wimberley et al., 2022). Metabolic dysregulation and MDD share overlapping pathophysiological mechanisms, including chronic inflammation, impaired insulin signalling, neuroendocrine dysfunction, and oxidative stress (e.g., Milaneschi et al. (2020)). These disturbances contribute to depressive symptomatology by disrupting neural circuits related to reward, verbal/numerical reasoning, and processing speed (Fanelli, Mota, et al., 2022; Milaneschi et al., 2019), thereby exacerbating core depressive symptoms such as anhedonia and cognitive dysfunction and hindering treatment response (Martone et al., 2024). Furthermore, behavioural and affective symptoms of depression may foster unhealthy lifestyle, predisposing individuals to IR-related conditions. This underscores the necessity of integrated treatment approaches.

The higher prevalence of unhealthy behaviours, such as smoking and reduced physical activity, in the IR+ group resonates with existing evidence linking lifestyle factors to both depression and metabolic disturbances (Kandola et al., 2019). This observation, coupled with the evidence indicating poorer treatment outcomes

in the same group, highlights the potential benefits of incorporating lifestyle interventions in MDD management (Kandola et al., 2019). However, lower alcohol intake frequency was noted, which aligns with certain clinical characteristics of the IR+ group. Given the comorbidities and more complex medication regimens in this group, it is likely that they prudently reduced alcohol intake for medical reasons (as form of tertiary prevention and to avoid possible pharmacokinetic interactions with their medications (Chan & Anderson, 2014)). The link between chronic health conditions like MDD and IR and lower SES is likely bi-directional. The risk of chronic diseases is increased in groups with lower SES (Sommer et al., 2015), but at the same time these conditions negatively impact wellbeing and social/work functioning, escalating medical expenses (Cabral et al., 2019).

Distinct clinical and emotional profiles

Our study also suggests that individuals with a lifetime history of both MDD and IR-related conditions exhibit a distinct clinical profile of depression. The higher mean age at MDD first diagnosis in the IR+ group could possibly result from an intersection of age-related reduction in insulin sensitivity, lifestyle, and psychosocial stressors inherent to aging, such as social isolation. Age-related factors, including chronic health challenges, retirement, and shifts in social roles, may contribute to the simultaneous emergence of depression and IR-related conditions (Stenholm et al., 2014). The prevalent feelings of loneliness and being fed-up in the MDD IR+ group resonate with the heightened susceptibility to perceived social isolation associated with atypical depression (Lojko & Rybakowski, 2017). This subtype of depression, frequently connected with inflammatory and metabolic disturbances, may also be reflected in the elevated BMI observed in the same group, consistent with the weight gain characteristic of atypical depression (Lojko & Rybakowski, 2017). The distinctive emotional profiles observed in relation to the timing of MDD-onset versus IR-related diagnoses provide potential hints for targeted preventive interventions. Higher neuroticism in individuals with pre-existing MDD suggests that these patients might have personality characteristics that could predispose not only to depression but also to metabolic changes. Neuroticism, characterised by a tendency towards anxiety, depression, and emotional instability, is a well-established risk factor for developing both mood disorders and cardio-metabolic conditions (Lee et al., 2022). Conversely, the reduced presence of classical anxiety-related symptoms, coupled with increased feelings of inadequacy and difficulty concentrating in the MDD-after-IR subgroup, could reflect the negative psychological impact of experiencing a chronic cardio-metabolic condition before depression. Living with a chronic IR-related condition may lead to adaptation to some emotional responses, shifting from anxiety and worry to feelings of

inadequacy and difficulty concentrating. This could be attributed to the constant coping and management demands of a chronic physical illness, which may lead to a sense of cognitive overload and being overwhelmed.

Prescription patterns and IR-related comorbidities

An increased prescription of SSRIs, SARIs, SNRIs, tetracyclic, and tricyclic antidepressants in the IR+ group was found, suggesting a more challenging treatment course. This is confirmed by the higher frequency of antidepressant switches and the use of a wider array of antidepressant classes, particularly in patients with MDD preceding IR-related diagnoses. The metabolic side effect profiles of these antidepressant classes warrant careful consideration. SSRIs are typically preferred for their relatively favourable side effect profile, especially in patients with comorbid medical conditions (Gold et al., 2020). SSRIs have been shown to improve glycaemic control in adults with comorbid MDD and T2DM in short-term studies, and have no long-term deleterious effects on glycaemic homeostasis (Possidente et al., 2023). Conversely, SNRIs, tetracyclic, and tricyclic antidepressants, despite their efficacy, are associated with significant cardio-metabolic side effects, such as hypertension, weight gain, and dyslipidaemia (Gold et al., 2020; Serretti & Mandelli, 2010), posing potential exacerbation risks in the presence of underlying IR predisposition. The use of TCAs in these patients, often a choice of last resort due to their lower tolerability, suggests a clinical pivot towards more pharmacodynamically complex treatment options when first-line treatments fail. Conversely, a less frequent use of some antidepressant classes in the MDD-after-IR group likely reflects clinicians' attention to the metabolic side effects of certain antidepressants, and a consequently more conservative approach. Overall, these findings emphasise the importance of a personalised treatment strategy for MDD, especially for individuals with a personal or familiar history of IR-related conditions. Antidepressant selection must carefully weigh the risk/benefit ratio, prioritising patient safety and overall health in the context of pre-existing or heightened risk of IR.

IR-related conditions and treatment outcomes in depression

The association between IR-related conditions and higher odds of poorer treatment outcomes and overall treatment duration supports the hypothesis that metabolic dysregulation may be linked with difficult-to-treat depression. The association with poorer treatment outcomes was particularly evident when MDD diagnosis preceded IR-related conditions. This trajectory may suggest that the neurobiological and behavioural effects of depression, including stress-related hormonal imbalances and reduced physical activity, may predispose individuals to metabolic disturbances, which likely worsen treatment response (Horstmann &

Binder, 2011; Milaneschi et al., 2020; Milaneschi et al., 2019). Chronic inflammation and oxidative stress, which are associated with IR, can impair serotonin signalling and synaptic plasticity, processes involved in antidepressant response (Mehdi et al., 2023; Milaneschi et al., 2020; Pilar-Cuellar et al., 2013). Notably, the observed higher prescription of antidepressants and diverse pharmacological classes in IR+ individuals raises questions about the potential of pharmacotherapy in triggering or worsening IR-related conditions; indeed, patients with difficult-to-treat MDD may be more frequently exposed to medications with metabolic side effects (Serretti & Mandelli, 2010). On the other hand, the observation in our sample that a broad phenotype of IR pathology – defined by the presence of any IR-related condition rather than specific ones – is linked to worse treatment outcomes when IR precedes MDD, may support a direct influence of metabolic health on psychiatric treatment effectiveness. Of note, the larger sample size of the cumulative IR phenotype likely increased the statistical power of this analysis, thus revealing associations not apparent in more narrowly defined groups. However, future research is needed to clarify whether IR-related conditions primarily aggravate depressive symptoms through metabolic dysregulation or directly impair antidepressant efficacy, as the current study design does not establish causality.

Polygenic scores and future directions

Our study did not identify significant associations between PGSs for IR-related conditions and treatment outcomes, although nominal associations were observed with PGS for CAD, TG, and BMI in certain subgroups. The multifactorial nature of treatment outcomes, with relatively modest contribution of common genetic variants (Pain et al., 2022), and methodological limitations may have impacted on the possibility to reach statistical significance for these results. For example, the used PGS approach was not biologically informed, i.e., it did not prioritise SNPs based on their known or predicted functional impact, which may improve PGS prediction accuracy (Sharew et al., 2024). Consistently with our findings, previous studies reported limited explanatory power of PGSs for IR-related conditions in antidepressant treatment outcomes. For instance, PGSs for CAD and BMI explained only 1.3% and 0.8% of SSRI treatment response variance, respectively, with notable cohort-specific and quartile-dependent differences in effect sizes (Amare et al., 2019). In one cohort, associations were evident only among individuals in the highest PGS quartile, while intermediate quartiles showed stronger effects in another (Amare et al., 2019). Similarly, research on PGSs for T2DM and depression has shown that significant associations were particularly evident in early-onset cases or only nominally significant across ancestrally diverse cohorts (Fanelli et al., 2025).

In addition to lifestyle modifications, addressing inflammatory-metabolic dysfunctions of MDD with new pharmacological interventions offers promising opportunities. Anti-inflammatory agents, such as anti-interleukin-6 antibodies, and tumor necrosis factor-α inhibitors have shown potential in alleviating depressive symptoms, particularly in individuals with elevated inflammatory biomarkers (Fanelli et al., 2025; Wittenberg et al., 2020). Similarly, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), like liraglutide, offer dual benefits by improving glycaemic control and reducing systemic inflammation, with preliminary evidence of antidepressant effects (Fanelli et al., 2025; Possidente et al., 2023). Integrating these pharmacological interventions with precision psychiatry tools, such as multivariable models incorporating more advanced PGS approaches, could optimise treatment personalisation.

Strengths and limitations

This study should be viewed in the context of its strengths and limitations. The strengths of this study lie in its large sample size and the use of a comprehensive dataset from the UK Biobank. The inclusion of primary care data enriched the findings, providing a real-world perspective on the management of MDD in relation to IR-related conditions. However, its observational nature precludes causal inferences, and generalisability of the findings may be limited to similar healthcare settings. While the results demonstrate a strong association between IR-related conditions and poorer treatment outcomes in MDD, they cannot determine whether IR-related conditions primarily aggravate MDD, directly contribute to resistance, or result from prolonged treatment resistance and pharmacological burden. Future longitudinal and experimental studies are required to disentangle the temporal and causal dynamics between IR conditions, MDD severity, and treatment outcomes. The demographic composition of the UK Biobank, predominantly consisting of females, older individuals, and those of higher socioeconomic status, does not mirror the general UK population (Fry et al., 2017). Additionally, our analysis relied on proxy measures such as antidepressant switches for treatment non-response/resistance. While these proxies are well-established in the literature (Lage et al., 2022; Wigmore et al., 2020), they depend on the completeness of EHRs and are not direct measures of treatment response. The interpretation of our results should consider possible biases introduced by missing data, such as gaps in prescription or diagnosis dates. Furthermore, our analysis did not consider prescription dosages, nor did it differentiate based on symptom severity or MDD phase (acute vs. non-acute). Regarding PGS calculation, to prevent results inflation we could not use some of the larger GWAS whose sample was overlapping with our target UK Biobank sample. While our findings demonstrate statistically significant associations

between various IR-related conditions and treatment outcomes in depression, the predictive impact of these associations, as indicated by Nagelkerke's pseudo-R^2 and R^2 values, was limited. This aligns with expectations for complex, multifactorial conditions like MDD and IR-related traits, where a substantial portion of variance arises from unmeasured genetic, environmental, and clinical factors. Nonetheless, the Hosmer-Lemeshow test results ($p>0.05$ in most models) indicated acceptable model fit, supporting the validity of the observed associations. Future research should incorporate other variables and advanced modelling approaches to better capture the full complexity of biopsychosocial factors that contribute to depression treatment outcomes.

Conclusion

In conclusion, this study highlights a substantial prevalence of IR-related conditions among individuals with a history of MDD, highlighting a demographic profile characterised by later age of MDD onset, a propensity towards unhealthy lifestyle, and a distinct clinical profile. Notably, the presence of IR-related conditions was associated with heightened complexity in managing depression, as evidenced by an increase in antidepressant prescriptions, treatment non-response/resistance, and prolonged treatment duration, particularly when MDD diagnosis preceded IR-related diagnoses. These results advocate for careful antidepressant selection, mindful of potential metabolic adverse effects. Overall, these insights endorse the implementation of a holistic care model that surpasses traditional psychiatric management, incorporating metabolic assessments and lifestyle interventions to improve outcomes in patients with MDD. It is important for healthcare providers to regularly monitor metabolic health in patients with MDD, as the early detection/treatment of IR-related conditions hold the potential to enhance psychiatric and physical outcomes, particularly in patients with persistent or treatment-resistant MDD.

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PART II

Genetic architecture and molecular mechanisms of psychiatric–insulin resistance multimorbidity

Chapter 5

Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders

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Abstract

The prevalence of somatic insulinopathies, like metabolic syndrome (MetS), obesity, and type 2 diabetes mellitus (T2DM), is higher in Alzheimer's disease (AD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD). Dysregulation of insulin signalling has been implicated in these neuropsychiatric disorders, and shared genetic factors might partly underlie this observed multimorbidity. We investigated the genetic overlap between AD, ASD, and OCD with MetS, obesity, and T2DM by estimating pairwise global genetic correlations using the summary statistics of the largest available genome-wide association studies for these phenotypes. Having tested these hypotheses, other potential brain "insulinopathies" were also explored by estimating the genetic relationship of six additional neuropsychiatric disorders with nine insulin-related diseases/traits. Stratified covariance analyses were then performed to investigate the contribution of insulin-related gene-sets. Significant negative genetic correlations were found between OCD and MetS (r_g=-0.315, p=3.9x10^{-8}), OCD and obesity (r_g=-0.379, p=3.4x10^{-5}), and OCD and T2DM (r_g=-0.172, p=3x10^{-4}). Significant genetic correlations with insulin-related phenotypes were also found for anorexia nervosa (AN), attention-deficit/hyperactivity disorder (ADHD), major depressive disorder, and schizophrenia (p<6.17x10^{-4}). Stratified analyses showed negative genetic covariances between AD, ASD, OCD, ADHD, AN, bipolar disorder, schizophrenia and somatic insulinopathies through gene-sets related to insulin signalling and insulin receptor recycling, and positive genetic covariances between AN and T2DM, as well as ADHD and MetS through gene-sets related to insulin processing/secretion (p<2.06x10^{-4}). Overall, our findings suggest the existence of two clusters of neuropsychiatric disorders, in which the genetics of insulin-related diseases/traits may exert divergent pleiotropic effects. These results represent a starting point for a new research line on "insulinopathies" of the brain.

Introduction

Mental disorders are characterised by a reduced life expectancy of approximately 10 years (Weye et al., 2020). In addition to violent causes of death, more than 67% of the increase in premature mortality is due to natural causes (Walker et al., 2015). The increased prevalence of insulin-related somatic diseases (i.e., type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome (MetS)) observed in mental disorders, with a resulting increased cardiovascular risk, contributes significantly to the lower life expectancy (Momen et al., 2020).

A number of studies have investigated this higher comorbidity, focusing mainly on metabolic disturbances as possible consequences of unhealthy lifestyles, sedentary habits, or the chronic use of psychotropic medication (Grajales et al., 2019). However, there is growing evidence for the presence of glycaemic and metabolic imbalances in drug-naïve acute psychiatric patients already at disease onset, suggesting that common pathogenic mechanisms may also be involved (Coello et al., 2019). Shared genetic factors may play a role, and genomic studies may help to unravel the biological underpinnings of the phenotypically observed comorbidity of neuropsychiatric disorders with somatic insulin-related diseases and traits.

The above-mentioned insulin-related and neuropsychiatric diagnostic groups consist of complex and heterogeneous diseases with a highly polygenic inheritance pattern; heritability estimates from twin and family studies range between 30% and 80% (Almgren et al., 2011; Wray et al., 2014). Large meta-analyses of genome-wide association studies (GWASs) have identified hundreds of disease-associated single nucleotide polymorphisms (SNPs), each contributing with a small effect to the overall risk for these diseases (Howard et al., 2019). Genetic sharing has already been highlighted between T2DM, obesity and MetS, as expected from their highly interrelated pathogenesis (Lind, 2019), and recent evidence has also revealed the presence of substantial pleiotropy among psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019).

A key feature that T2DM, obesity and MetS have in common is an impaired response to insulin stimulation in peripheral tissues, better known as insulin resistance (Petersen & Shulman, 2018). Abnormalities in insulin signalling might also link with neuropsychiatric disorders. Indeed, beyond the anabolic function of insulin at the peripheral level, where it promotes the glucose uptake in tissues while stimulating glycogenesis and lipogenesis, this hormone can also bind to insulin receptors (INSRs) on the surface of both neurons and glial cells in the central nervous system (CNS) (Petersen & Shulman, 2018), where insulin signalling is regulated among others by the neurotransmitters serotonin and dopamine

(Mazucanti et al., 2019). In the CNS, insulin plays a key role in synaptic plasticity and neurotransmission, apoptosis inhibition, and neuroinflammation (Arnold et al., 2018). Preclinical studies have suggested that an increase in the mammalian target of rapamycin (mTOR) activity, one of the major downstream effectors of the INSRs, may lead to reduced synaptic pruning, and thereby contributes to the cognitive inflexibility and perseverative/repetitive behaviours observed in those animals with *mTOR* genetic alterations (Hoeffer et al., 2008; Xu et al., 2019). Cognitive abnormalities of a similar nature were shown in TALLYHO/JngJ mice, an animal model of T2DM (van de Vondervoort et al., 2019).

Recently, dysregulation in insulin signalling has been suggested to contribute to neuropsychiatric disorders more widely. Evidence is strongest for Alzheimer's disease (AD) and autism spectrum disorder (ASD) (Bralten et al., 2020; Butterfield & Halliwell, 2019; Macklin et al., 2017; Stern, 2011; van de Vondervoort et al., 2016; Xiang et al., 2015). Our own recent work also suggested a link with obsessive-compulsive disorder (OCD) (Bralten et al., 2020; van de Vondervoort et al., 2016). In the case of AD, it has been shown that insulin sensitivity is altered even before the onset of cognitive decline or β-amyloid (Aβ) accumulation in the CNS (Macklin et al., 2017). The hyperactivity of the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/mTOR cascade, mediated by the phosphorylation of INSR via insulin binding to the neuronal surface, leads to the inhibition of autophagy processes and subsequent accumulation of damaged mitochondria and misfolded proteins seen in AD (Butterfield & Halliwell, 2019). The same PI3K/AKT/mTOR hyperactivity is also involved in ASD pathogenesis (Stern, 2011), and genes within the mTOR pathway were also shown to associate with brain volume variability and ASD (Arenella et al., 2020). Furthermore, offspring of mothers who have T2DM during pregnancy have a higher risk of developing ASD (Xiang et al., 2015). The integration of data from different types of genetic studies has also implicated CNS insulin signalling as one of the biological mechanisms underlying OCD, where this signalling pathway may modulate excitatory synaptogenesis and postsynaptic dendritic spine formation (van de Vondervoort et al., 2016). Also obsessive-compulsive symptoms in the general population have been associated with genes related to CNS insulin signalling (Bralten et al., 2020), and shared genetic aetiologies of peripheral insulin-related phenotypes (i.e., T2DM, glucose levels 2 hours after an oral glucose challenge (2hGlu), and fasting plasma insulin (FPI)) were found with both obsessive-compulsive symptoms and OCD (Bralten et al., 2020).

In light of the above evidence, we aimed to investigate the extent of the potential genetic sharing and contribution of insulin-related gene-sets in the observed comorbidity of neuropsychiatric disorders having preclinical evidence of insulin signalling dysregulation (i.e., AD, ASD, and OCD) with somatic diseases

related to insulin resistance, namely MetS, obesity, and T2DM. For this purpose, we performed Linkage Disequilibrium SCore regression (LDSC) and stratified GeNetic cOVariance Analyser (GNOVA) analyses (Bulik-Sullivan et al., 2015; Lu et al., 2017). In addition, we explored other potential brain "insulinopathies" by estimating the genetic overlap between other neuropsychiatric disorders and insulin-related somatic phenotypes.

Methods

Input datasets

As input for the analyses, we used summary statistic data of the largest GWASs available at the time of conducting our analyses for the phenotypes of interest (see also **Table 1** and the **Supplementary information**). We considered the most prevalent somatic diseases linked to insulin resistance (i.e., MetS, obesity, and T2DM), and neuropsychiatric disorders having preclinical evidence of insulin signalling dysregulation, namely AD, ASD, and OCD (Hoeffer et al., 2008; Macklin et al., 2017; van de Vondervoort et al., 2019). We also investigated insulin-related traits (i.e., 2hGlu, body mass index (BMI), fasting plasma glucose (FPG) and FPI, glycated haemoglobin (HbA1c), and homeostatic model assessment for insulin resistance (HOMA-IR)), and other six neuropsychiatric disorders, which are those best characterised genetically by the Psychiatric Genomic Consortium (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019) (i.e., attention-deficit hyperactivity disorder (ADHD), anorexia nervosa (AN), bipolar disorder (BD), major depressive disorder (MDD), schizophrenia (SCZ), and Tourette's syndrome (TS)). Data were downloaded from online repositories (see URLs), when publicly available, or requested (i.e., MetS) from the GWAS authors.

Genome-wide bivariate genetic correlation estimations

Bivariate LDSC (https://github.com/bulik/ldsc) analyses were performed to estimate the genetic correlation (r_g) ascribed genome-wide to common variants between AD, ASD, OCD and MetS, obesity, and T2DM, following the software guidelines (https://github.com/bulik/ldsc/wiki/Heritability-and-Genetic-Correlation). Also through LDSC, exploratory analyses were carried out to estimate the extent of the genetic sharing between other neuropsychiatric disorders (ADHD, AN, BD, MDD, SCZ, TS, along with AD, ASD, and OCD) and insulin-related somatic diseases/traits (i.e., 2hGlu, BMI, FPG and FPI, HbA1c, HOMA-IR, along with MetS, obesity, and T2DM). Further details on the quality control (QC) steps and the LDSC method are provided in the **Supplementary information**. LDSC is computationally robust to sample overlaps

between studies (Bulik-Sullivan et al., 2015). Bonferroni correction was applied, accounting for the number of analyses performed (α=0.05/(9x9)=6.17x10-4).

Genetic covariance analyses stratified by functional annotations

GNOVA (https://github.com/xtonyjiang/GNOVA) was used to investigate whether neuropsychiatric disorders were genetically correlated to MetS, obesity, or T2DM specifically through nine gene-sets involved in peripheral and/or CNS insulin signalling (gene-set sizes ranged from 27 to 137 genes; see **Tables S1-S2** for a complete list of genes included in each gene-set). Further details on the GNOVA method and the selection of the insulin signalling-related gene-sets are provided in the **Supplementary information**. GNOVA-computed covariance estimates are robust to sample overlaps (Lu et al., 2017). Bonferroni correction was applied to GNOVA results considering the nine tested gene-sets and the 27 pairwise combinations of three insulin-related somatic diseases and nine neuropsychiatric disorders for which GNOVA analyses were performed ($\alpha=0.05/(9x3x9)=2.06x10^{-4}$).

Results

Description of the input datasets

A description of the samples (with sample sizes, number of cases and controls, and the derived effective sample size) included in the analyses is provided in **Table 1**. Further information on the GWAS samples can be found in the **Supplementary information**.

Pairwise genome-wide genetic correlations between neuropsychiatric disorders and insulin-related somatic diseases and traits

A genetic correlation plot depicting the LDSC analyses results is shown in **Figure 1**; details on the genetic correlation estimates (r_g) for each pair and statistical significance are provided in **Table 2**. After correcting for multiple testing, negative genetic correlations were highlighted between OCD and MetS (r_g=-0.315, $p=3.9x10^{-8}$), OCD and obesity (r_g=-0.379, $p=3.6x10^{-5}$), and OCD and T2DM (r_g=-0.172, $p=3x10^{-4}$). Nominally significant genetic correlations were also found between AD and T2DM (r_g=0.155, p=0.048), and ASD and MetS (r_g=0.115, p=0.002).

When insulin-related somatic traits (i.e., 2hGlu, BMI, FPG, FPI, HbA1c, HOMA-IR) were considered, OCD was also found to be significantly negatively genetically correlated with BMI (r_g=-0.284, $p=2.6x10^{-11}$), but neither AD nor ASD showed significant correlations with the traits.

Table 1. Characteristics of the samples used for the linkage-disequilibrium score regression (LDSC) and GeNetic cOVariance Analyser (GNOVA) analyses.

Trait/Disorder	Author	Year	PMID	Consortium	Ancestry	N	Cases	Controls	Neff
2hGlu	Saxena et al.	2010	20081857	MAGIC	European	15,234			
BMI	Pulit et al.	2019	30239722	GIANT	European	697,734			
FGlu	Lagou et al.	2021	33402679	MAGIC	European	140,595			
FIns	Lagou et al.	2021	33402679	MAGIC	European	98,210			
HbA1c	Wheeler et al.	2017	28898252	MAGIC	European	123,665			
HOMA-IR	Dupuis et al.	2010	20081858	MAGIC	European	37,037			
MetS	Lind	2019	31589552		European	291,107	59,677	231,430	189,772.64
Obesity	Watanabe et al.	2019	31427789		European	244,890	9,805	235,085	37,649.69
T2DM	Mahajan et al.	2018	30297969	DIAGRAM	European	898,130	74,124	824,006	272,025.75
ADHD	Demontis et al.	2019	30478444	PGC	European	53,293	19,099	34,194	49,017.41
AD	Wightman et al.	2021	34493870	PGC	European	762,917	86,531	676,386	306,866.18
AN	Watson et al.	2019	31308545	PGC	European	72,517	16,992	55,525	52,041.91
ASD	Grove et al.	2019	30804558	PGC	European	46,350	18,381	27,969	44,366.62
BD	Mullins et al.	2021	34002096	PGC	European	413,466	41,917	371,549	150,669.89
OCD	OCGAS/ IOCDF-GC	2018	28761083	OCGAS/ IOCDF-GC	European	9,725	2,688	7,037	7,780.14
MDD	Wray et al./ Howard et al.	2019	29700475/ 29662059	PGC	European	500,199	170,756	329,443	449,855.91
SCZ	Pardinas et al.	2018	29483656	PGC+CLOZUK	European	105,318	40,675	64,643	99,863.42
TS	Yu et al.	2019	30818990	PGC	European	14,307	4,819	9,488	12,783.30

Abbreviations: 2hGlu, glucose levels 2 hours after an oral glucose challenge; BMI, body mass index; FGlu, fasting glucose; FIns, fasting insulin; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; ADHD, attention-deficit/ hyperactivity disorder; AD, Alzheimer's disease; AN, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; TS, Tourette's syndrome; N, total sample size; Neff, effective sample size [Neff = 4 / (1/Cases + 1/Controls)].

Analyses were also extended to other neuropsychiatric disorders (i.e., ADHD, AN, BD, MDD, SCZ, and TS) and significant genetic correlations were found between insulin-related diseases/traits and ADHD, AN, MDD, and SCZ (see **Figure 1** and **Table 2**).

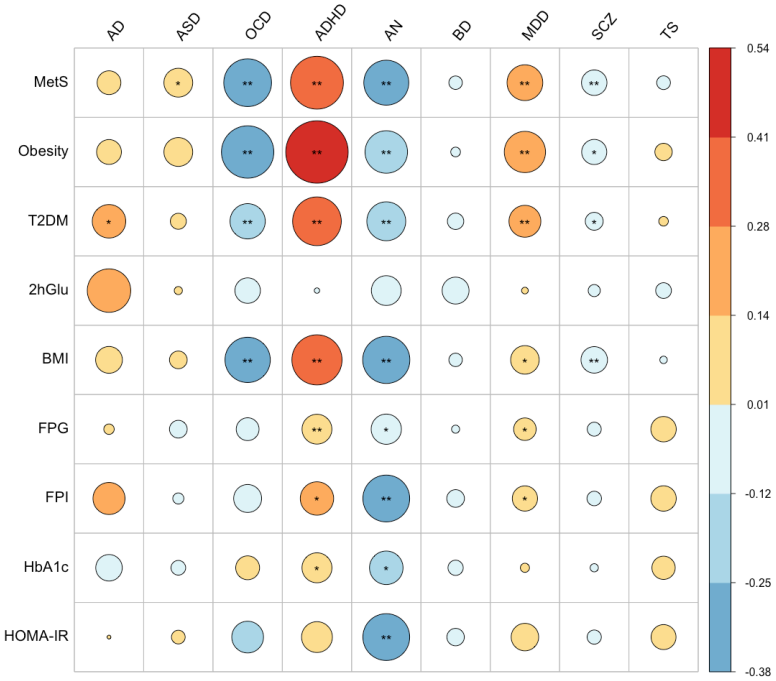

Figure 1. Genetic correlation plot summarising the results from the bivariate Linkage Disequilibrium Score regression (LDSC) analyses.

The size of the circle is proportional to the genetic correlation estimates, going from warmer to colder colours as the direction of the effect changes from positive to negative. Bonferroni multiple testing correction was applied, correcting for the number of analyses performed (α=0.05/(9*9)=6.17e-4). Abbreviations: AD, Alzheimer's disease; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; BD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; TS, Tourette's syndrome; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; 2hGlu, glucose levels 2 hours after an oral glucose challenge; BMI, body mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

** Statistically significant bivariate genetic correlation ($p<6.17x10^{-4}$).

* Nominally significant bivariate genetic correlation ($p<0.05$).

Genetic covariance between neuropsychiatric disorders and insulin-related somatic diseases stratified by insulin-related gene-sets

After Bonferroni correction, stratified GNOVA analyses highlighted significant negative genetic covariance between AD and obesity through the Reactome INSR

Table 2. Genetic correlation table reporting the detailed results derived from the bivariate Linkage Disequilibrium Score regression (LDSC) analyses.

Trait/Disorder	AD	ASD	OCD	ADHD	AN	BD	MDD	SCZ	TS
MetS	0.078 (0.239)	0.115 (0.002)*	-0.315 ($3.88x10^{-8}$)**	0.386 ($7.16x10^{-30}$)**	-0.279 ($3.43x10^{-15}$)**	-0.025 (0.321)	0.177 ($1.66x10^{-16}$)**	-0.090 ($1.41x10^{-5}$)**	-0.026 (0.496)
Obesity	0.085 (0.455)	0.115 (0.072)	-0.379 ($3.35x10^{-5}$)**	0.538 ($9.91x10^{-24}$)**	-0.250 ($7.60x10^{-6}$)**	-0.013 (0.749)	0.235 ($5.31x10^{-10}$)**	-0.087 (0.009)*	0.042 (0.552)
T2DM	0.155 (0.048)*	0.035 (0.403)	-0.172 ($3x10^{-4}$)**	0.328 ($3.24x10^{-28}$)**	-0.209 ($6.04x10^{-12}$)**	-0.037 (0.094)	0.141 ($4.65x10^{-11}$)**	-0.044 (0.016)*	0.013 (0.713)
2hGlu	0.261 (0.103)	0.009 (0.936)	-0.090 (0.591)	-0.004 (0.964)	-0.122 (0.221)	-0.100 (0.180)	0.006 (0.927)	-0.020 (0.743)	-0.034 (0.782)
BMI	0.099 (0.126)	0.043 (0.164)	-0.284 ($2.57x10^{-11}$)**	0.348 ($6.59x10^{-49}$)**	-0.308 ($6.38x10^{-38}$)**	-0.025 (0.167)	0.112 ($1.55x10^{-10}$)**	-0.097 ($7.95x10^{-11}$)**	-0.008 (0.801)
FPG	0.015 (0.828)	-0.043 (0.334)	-0.072 (0.339)	0.123 ($6x10^{-4}$)**	-0.126 (0.005)*	-0.009 (0.777)	0.070 (0.012)*	-0.027 (0.296)	0.089 (0.074)
FPI	0.142 (0.218)	-0.017 (0.797)	-0.108 (0.198)	0.154 (0.005)*	-0.303 ($4.17x10^{-7}$)**	-0.043 (0.319)	0.088 (0.045)*	-0.029 (0.464)	0.089 (0.190)
HbA1C	-0.097 (0.265)	-0.030 (0.619)	0.079 (0.367)	0.124 (0.006)*	-0.155 (0.003)*	-0.032 (0.379)	0.012 (0.722)	-0.009 (0.751)	0.075 (0.225)
HOMA-IR	0.002 (0.985)	0.026 (0.817)	-0.139 (0.255)	0.1313 (0.138)	-0.3029 ($1x10^{-4}$)**	-0.042 (0.505)	0.1044 (0.076)	-0.0278 (0.577)	0.086 (0.390)

Reported values are genetic correlation estimates – r_g – (p-values). Abbreviations: AD, Alzheimer's disease; ASD, autism spectrum disorders; OCD, obsessive-compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; BD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; TS, Tourette's syndrome; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; 2hGlu, glucose levels 2 hours after an oral glucose challenge; BMI, body mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

** Statistically significant bivariate genetic correlation ($p<6.17x10^{-4}$)

* Nominally significant bivariate genetic correlation ($p<0.05$)

recycling gene-set ($p=4.6x10^{-5}$), as well as between ASD and MetS through the Biocarta, KEGG, and PID insulin signalling pathways ($p\leq3.2x10^{-5}$). OCD showed negative genetic covariance with MetS and T2DM through the Reactome INSR recycling gene-set ($p\leq1.6x10^{-4}$).

When the other neuropsychiatric disorders were also considered, negative genetic covariance was found between BD and T2DM, BD and MetS, SCZ and MetS through the PID insulin signalling pathway ($p\leq2x10^{-5}$), as well as between AN and T2DM through the Biocarta insulin pathway ($p=1.26x10^{-5}$). Moreover, positive genetic covariance was highlighted between AN and T2DM through the Reactome insulin processing gene-set ($p=3.77x10^{-5}$), as well as between ADHD and MetS through the Reactome regulation of insulin secretion gene-set ($p=1.18x10^{-4}$) (see **Table 3**; detailed results are shown in **Tables S3-S11**).

Discussion

In this study, we investigated the genetic overlap of AD, ASD, OCD with somatic insulinopathies, namely MetS, obesity and T2DM, hypothesising an important role for gene-sets related to insulin signalling. Our genome-wide analyses indicate significant global negative genetic correlations between OCD and obesity, T2DM, and MetS. Gene-set stratified genetic covariance analyses of specific insulin-related pathways helped identify a genetic link of AD, ASD, and OCD with somatic insulinopathies. Moreover, our exploration of other potential brain "insulinopathies" yielded evidence for global genetic overlap of ADHD, AN, MDD, and SCZ with somatic insulin-related diseases/traits, while genetic covariance at the level of insulin-related gene-sets was identified between ADHD, AN, BD, SCZ and T2DM/MetS/obesity.

The previous clinical and epidemiological studies available to date indicate a higher prevalence of obesity, MetS, and T2DM in patients with OCD than the general population (Albert et al., 2013; Isomura et al., 2018). Furthermore, a mouse model for T2DM showed compulsive traits, as discussed above (Macklin et al., 2017). We thus had hypothesised a genetic correlation between OCD and somatic disorders characterised by insulin resistance to exist, which we indeed found in this study. The negative direction of the correlation we found was unexpected, as it might suggest a protective role of the genetics underlying OCD on the chance of having T2DM, MetS and/or obesity. However, for behavioural traits, environmental sources of variation may operate orthogonally to genetic factors, masking the effect of the genetics at the phenotypic level (Hadfield et al., 2007). Therefore, one hypothesis explaining our result can be that environmental

Table 3. Summary results of the genetic covariance analyses between neuropsychiatric disorders and somatic diseases linked with insulin-resistance stratified by insulin signalling gene-sets.

Gene-set name	n genes/ gene-set	Base phenotypes	ρ_g	SE ρ_g	p	h^2_{SNP} 1	h^2_{SNP} 2	annotated SNPs	total SNPs
BIOCARTA INSULIN PATHWAY	21	AN x T2DM	-0.00042 [a]	0.00010	$1.26x10^{-5}$ [b]	0.00078	0.00050	1,268	860,288
BIOCARTA INSULIN PATHWAY	21	ASD x MetS	-0.00041	0.00010	$1.96x10^{-5}$	0.00046	0.00068	1,520	968,964
KEGG INSULIN SIGNALLING PATHWAY	137	ASD x MetS	-0.00170	0.00041	$3.22x10^{-5}$	0.00261	0.00207	11,334	968,964
PID INSULIN PATHWAY	44	ASD x MetS	-0.00080	0.00018	$1.25x10^{-5}$	0.00012	0.00105	4,319	968,964
PID INSULIN PATHWAY	44	BD x T2DM	-0.00057 [a]	0.00013	$9.60x10^{-6}$ [b]	0.00054	0.00121	4,575	1,026,853
PID INSULIN PATHWAY	44	BD x MetS	-0.00076 [a]	0.00018	$2.03x10^{-5}$ [b]	0.00054	0.00109	4,580	1,027,553
PID INSULIN PATHWAY	44	SCZ x MetS	-0.00141	0.00032	$1.32x10^{-5}$	0.00155	0.00117	4,836	1,049,783
REACTOME INSULIN PROCESSING	27	AN x T2DM	0.00059 [a]	0.00014	$3.77x10^{-5}$ [b]	0.00216	0.00153	2,742	860,288
REACTOME REGULATION OF INSULIN SECRETION	77	ADHD x MetS	0.00174	0.00045	$1.18x10^{-4}$	0.00287	0.00156	9,850	986,120
REACTOME INSULIN RECEPTOR RECYCLING	26	AD x Obesity	-0.00079 [a]	0.00019	$4.61x10^{-5}$ [b]	0.00009	-0.00033	2,138	942,664
REACTOME INSULIN RECEPTOR RECYCLING	26	OCD x MetS	-0.00124	0.00028	$7.5x10^{-6}$	0.00316	0.00074	2,132	1,019,413
REACTOME INSULIN RECEPTOR RECYCLING	26	OCD x T2DM	-0.00100	0.00026	$1.6x10^{-4}$	0.00304	0.00128	2,130	1,019,648

Abbreviations: Alzheimer's disease (AD), attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa (AN), autism spectrum disorder (ASD), bipolar disorder (BD), obsessive-compulsive disorder (OCD), schizophrenia (SCZ), MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; SNPs, single nucleotide polymorphisms; ρ_g: genetic covariance estimate; SE ρ_g: standard error of the estimate of ρ_g; p: p-value from the statistical test for genetic covariance; r_g: genetic correlation estimate; h^2_{SNP} 1: SNP-based heritability estimate for the first phenotype; h^2_{SNP} 2: SNP-based heritability estimate for the second phenotype. Results are only reported for phenotype pairs when the stratified genetic covariance estimates were statistically significant after Bonferroni correction ($p<2.06x10^{-4}$).

[a] ρ_g corrected: genetic covariance estimates with sample overlap correction

[b] p corrected: p-value from the statistical test for genetic covariance with sample overlap correction

effects act in the opposite direction to genetics, causing an increased risk in the presence of protective genetics and resulting in variability in the phenotypic manifestations over time. Indeed, metabolic complications have been particularly associated with a longer duration of antipsychotics treatment in patients with OCD (Albert et al., 2013). It is also reasonable to assume that patients with more severe symptoms, having higher genetic load for OCD, are more likely to develop metabolic side effects of such treatments because they require higher doses and longer therapies, even though they might be genetically more protected against insulin-related/metabolic disturbances. The analyses considering insulin-related glycaemic/anthropometric traits also showed a negative correlation between OCD and BMI. This finding is consistent with previous evidence in smaller samples of a negative genetic relationship with a negative direction between OCD and body fat measures (Hubel et al., 2019); it also further supports the negative correlation trend that we observed between OCD and somatic insulinopathies. Zooming in through analyses of gene-sets related to insulin signalling, we found genes involved in the INSR recycling process involved in the genetic correlation of OCD with both MetS and T2DM. This molecular pathway mediates the recycling of the INSR and reintegration into the plasma membrane. After activation, the INSR-insulin complex is internalised into the cell within an endosome, and insulin is degraded, while INSR is dephosphorylated and reintegrated into the plasma membrane (Reactome). To our knowledge, this is the first study reporting involvement of the INSR recycling pathway in neuropsychiatric phenotypes. In this respect, it should be noted that endosomal recycling processes are relevant to the functioning of the brain. They are important for synaptic functioning and plasticity (and related glutamatergic neurotransmission) as well as for the maintenance of levels of membrane proteins, more generally (Chiu et al., 2017).

We did not observe significant genome-wide genetic correlations between AD and somatic insulin-related diseases, only nominally significant positive genetic correlations were seen with MetS and T2DM before multiple testing correction. Our results may add support for a predominant influence of environmental and epigenetic factors in the comorbidity observed between AD and somatic insulinopathies, although we cannot exclude the possible existence of patterns of local genetic correlation (Werme et al., 2021). It should be noted that ageing is considered the greatest risk factor for AD, and T2DM incidence also increases with ageing (Knopman et al., 2021). Processes linked to oxidative damage and ageing could trigger the onset of both diseases in a way that is partly independent from genetic effects (Butterfield & Halliwell, 2019). Air pollution, smoking, and low physical activity are also important risk factors for broadly defined dementia, and they also contribute to insulin resistance and cerebrovascular disease (Knopman

et al., 2021; Yang et al., 2020). The role of epigenetic modulation, including DNA methylation, histone modifications and non-coding RNAs, in the aetiopathogenesis of AD is also well recognised, and this may provide novel avenues for treatment in the upcoming years (Liu et al., 2018). A hypothesis is that the clinical heterogeneity of AD may have camouflaged the presence of genetic factors shared with somatic insulinopathies. In this regard, more deeply phenotyped samples might help better investigate the presence of pleiotropic effects in the future (Cummings, 2000). Alternatively or in addition, previous evidence may point to a role for insulin signalling specifically in individuals carrying *APOE* polymorphisms, suggesting that new insights may be derived from stratification of the AD population according to *APOE* genotype. Indeed, oral antidiabetics, such as thiazolidinediones and intranasal insulin have shown differential efficacy in AD depending on the *APOE*-ε4 genotype (Li et al., 2015), which is the strongest common genetic risk factor for late-onset AD (Yamazaki et al., 2019). Moreover, a previous study has also shown a strong regional genetic correlation between AD and T2DM for the genetic variants mapped to the apolipoprotein-E (*APOE*) locus (Zhu et al., 2019). However, the absence of genetic correlations at the genome-wide level does not preclude the existence of genetic sharing, as both positive and negative local genetic correlations may occur and potentially cancel each other out when summed at the genome-wide level (van Rheenen et al., 2019). In this regard, we demonstrated significant genetic covariance between AD and obesity at the INSR recycling gene-set level. Under physiological conditions, INSR is maintained in equilibrium between an internalising and an exposed state at the plasma membrane (Chen et al., 2019). Either excessive or insufficient surface INSR can lead to the development of insulin resistance (Chen et al., 2019). Our finding is in line with the evidence of an altered cellular distribution of INSRs in AD, resulting in a loss of INSRs at the neuronal membrane, suggesting that alterations in INSR recycling/trafficking are present (Moloney et al., 2010).

A role of metabolic dysregulation in ASD has been previously suggested by the increased risk for ASD and neurodevelopmental delays in the offspring of mothers who have metabolic conditions during pregnancy (Krakowiak et al., 2012). Nevertheless, our study did not find ASD to be significantly genetically correlated at the genome-wide level with either MetS, obesity or T2DM, in line with non-significant previous reports using smaller sample sizes (Grove et al., 2019). However, the stratification to insulin-specific gene-sets revealed significant localised negative genetic covariance of ASD with MetS through genes within insulin signalling pathways. Although further studies will be needed to disentangle the biological meaning of this finding, we could speculate that the observed pathway-level negative genetic covariance between ASD and MetS might reflect higher

complexity of reciprocal regulation between monoamine and insulin signalling at the CNS and peripheral level (Mazucanti et al., 2019). What we found at the gene-set level may also be consistent with prior findings of enhanced insulin signalling in the brain of a Drosophila model of Fragile X syndrome, which represents the most prevalent hereditary type of intellectual disability and autism (Monyak et al., 2017).

To extend the spectrum of potential brain "insulinopathies", LDSC analyses were performed considering six other neuropsychiatric disorders and diseases/traits related to insulin resistance. Our analyses identified several additional genetic correlations of the somatic insulin-related diseases with psychiatric disorders; negative genetic correlations were seen between MetS and both AN and schizophrenia, and positive genetic correlations were observed for MetS with both ADHD and MDD. Of note, the diagnosis of MetS is made when at least three out of the following co-occur: high systolic blood pressure, low levels of high-density lipoprotein (HDL), hyperglycaemia, high levels of triglycerides, and/or increased waist circumference (Lind, 2019). Our findings are consistent with previous evidence of pairwise genetic sharing between lipidaemic traits (HDL and triglycerides), waist circumference and AN, ADHD, and/or MDD (Demontis et al., 2019; Howard et al., 2019; Watson et al., 2019; Wray et al., 2018). In line with the negative genetic correlations that we observed between MetS and both AN and schizophrenia, Mendelian randomisation (MR) studies have previously identified AN and SCZ as causal for decreased fat mass (Hubel et al., 2019). This finding may suggest a prevalent contribution of environmental factors, such as the use of antipsychotics, unhealthy diet and lifestyle, reduced access to medical care on the epidemiological evidence of an increased risk of MetS, hypertension, and dyslipidaemia in patients with SCZ (Vancampfort et al., 2015). We also replicated and updated previous evidence of genetic sharing of ADHD, AN, and MDD with T2DM, as well as of ADHD, AN, MDD, and SCZ with both obesity and BMI (Bulik-Sullivan et al., 2015; Demontis et al., 2019; Howard et al., 2019; Hubel et al., 2019; So et al., 2019; Watson et al., 2019). With regard to SCZ and BMI, the negative direction of the genetic correlation corresponds to the previously reported evidence of a negative association of polygenic risk scores for SCZ with BMI (So et al., 2019). Exploring further the genetic links between these neuropsychiatric disorders and glycaemic traits linked to insulin resistance, we revealed a novel positive correlation between ADHD and FPG, as well as negative bivariate correlations between AN and both FPI and HOMA-IR that replicate and update previous findings (Hubel et al., 2019; Watson et al., 2019). A MR study had also previously shown that higher levels of FPI have a causal effect in reducing the risk of AN (Adams et al., 2020).

Interestingly, the local genetic covariance we have highlighted between neuropsychiatric disorders and somatic diseases linked to insulin resistance was

in most cases in the negative direction at the level of gene-sets related to insulin signalling, except for AN and ADHD. A negative direction means that genetic variability at the level of these gene-sets may result in an opposite pleiotropic effect on these two groups of diseases. However, the biological interpretation of these findings does not seem obvious at present and additional investigations at the gene and functional level will be necessary to clarify their biological significance.

This study comes with some strengths and limitations. The major strength is the investigation of the possible specific involvement of insulin-related gene-sets at the genomic level for the first time in the phenotypically observed comorbidity between neuropsychiatric disorders and somatic diseases related to insulin resistance. GNOVA provided us with more powerful statistical inference and more accurate genetic covariance estimates than LDSC and helped dissect the shared genetic architecture of the considered complex diseases, while giving us greater insights into the underlying biology. We exploited the largest public GWAS summary statistics (up to 898,130 individuals for T2DM) and used a strict Bonferroni correction to avoid type-1 errors. Our study may be limited by not having considered in our analyses the potential effect of environmental factors and epigenetic mechanisms, which are likely to mediate the relationship between neuropsychiatric and somatic insulinopathies, as well as potential sex effects due to the unavailability of publicly available sex-stratified data for all the traits/disorders tested and the loss of power for some of the phenotypes investigated. Another limitation is the inclusion of European-only datasets in our analyses, which limits the generalisability of our findings. In addition, the composition of insulin-related gene-sets, used as functional annotations in our stratified analyses, may be influenced by the current, still incomplete knowledge of the biology and functioning of the pathways to which they refer.

In conclusion, our study revealed the presence of genetic overlap between OCD and insulin-related somatic diseases, with a likely protective effect of the genetics underlying OCD on the chance of having MetS, obesity, and/or T2DM. However, environmental effects, such as psychotropic drug use, or a relatively unhealthy lifestyle, may act in the opposite direction to genetics, causing increased metabolic risk despite protective genetics. We pointed out that other neuropsychiatric disorders, besides OCD, represent potential brain "insulinopathies". Two distinct clusters of psychiatric disorders have emerged, in which the genetics of insulin-related traits/diseases may exert divergent pleiotropic effects: one consisting of AN, OCD, and SCZ, which showed negative genetic overlap with somatic insulin-related diseases and traits, and the other one comprising ADHD, and MDD, which showed positive genetic overlap with insulin-related diseases and traits. Finally, we demonstrated that insulin-related gene-sets may be pleiotropic for neuropsychiatric

disorders (i.e., AN, ADHD, ASD, BD, OCD, and SCZ) and somatic insulinopathies, suggesting that the cumulative effect of genetic variability within insulin-related gene-sets on the investigated neuropsychiatric disorders except for AN and ADHD is in the opposite direction to the effect on somatic insulinopathies. Our work might open up new directions for clinical and neuropsychopharmacological research by introducing insulin signalling as a possible mechanism underlying the multimorbidity of major mental disorders and somatic diseases. Further studies are warranted to investigate the biological meaning of the observed correlations and potential non-genetic effects contributing to insulin-related multimorbidity.

URLs

LDSC, https://github.com/bulik/ldsc; Pre-computed European LD scores, https://data.broadinstitute.org/alkesgroup/LDSCORE/; GNOVA, https://github.com/xtonyjiang/GNOVA;

GWAS summary statistics - ADHD, AN, ASD, BD, OCD, MDD, TS: https://www.med.unc.edu/pgc/download-results/; AD: https://ctg.cncr.nl/software/summary_statistics; SCZ: http://walters.psycm.cf.ac.uk/; 2hGlu, FPG, FPI, HbA1c, HOMA-IR: https://www.magicinvestigators.org/downloads/; BMI: https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files; MSigDB: https://www.gsea-msigdb.org/gsea/msigdb/index.jsp.

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Chapter 6

Local patterns of genetic sharing challenge the boundaries between neuropsychiatric and insulin resistance-related conditions

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Abstract

The co-occurrence of insulin resistance (IR)-related metabolic conditions with neuropsychiatric disorders is a complex public health challenge. Evidence of the genetic links between these phenotypes is emerging, but little is currently known about the genomic regions and biological functions that are involved. To address this, we performed Local Analysis of [co]Variant Association (LAVA) using large-scale (N=9,725-933,970) genome-wide association studies (GWASs) results for three IR-related conditions (type 2 diabetes mellitus, obesity, and metabolic syndrome) and nine neuropsychiatric disorders. Subsequently, positional and expression quantitative trait locus (eQTL)-based gene mapping and downstream functional genomic analyses were performed on the significant loci. Patterns of negative and positive local genetic correlations ($|r_g|$=0.21-1, p_{FDR}<0.05) were identified at 109 unique genomic regions across all phenotype pairs. Local correlations emerged even in the absence of global genetic correlations between IR-related conditions and Alzheimer's disease, bipolar disorder, and Tourette's syndrome. Genes mapped to the correlated regions showed enrichment in biological pathways integral to immune-inflammatory function, vesicle trafficking, insulin signalling, oxygen transport, and lipid metabolism. Colocalisation analyses further prioritised 10 genetically correlated regions for likely harbouring shared causal variants, displaying high deleterious or regulatory potential. These variants were found within or in close proximity to genes, such as *SLC39A8* and *HLA-DRB1*, that can be targeted by supplements and already known drugs, including omega-3/6 fatty acids, immunomodulatory, antihypertensive, and cholesterol-lowering drugs. Overall, our findings underscore the complex genetic landscape of IR-neuropsychiatric multimorbidity, advocating for an integrated disease model and offering novel insights for research and treatment strategies in this domain.

Introduction

Multimorbidity, defined as the co-occurrence of multiple conditions within an individual, poses substantial challenges to healthcare systems (Skou et al., 2022). An example is the observed co-occurrence of insulin resistance (IR)-related metabolic conditions, such as type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome (MetS), with neuropsychiatric disorders (Wimberley et al., 2022). This multimorbidity contributes to more severe physical and mental health outcomes, leading to reduced treatment effectiveness and higher mortality rates (Fanelli & Serretti, 2022; Kraus et al., 2023; Possidente et al., 2023). Moreover, IR is associated with detrimental effects on cognitive function, potentially worsening the cognitive impairment observed in various neuropsychiatric disorders (Fanelli, Mota, et al., 2022).

IR manifests as reduced tissue responsiveness to insulin stimulation, primarily disrupting blood glucose homeostasis and inducing long-term micro- and macrovascular complications, as well as peripheral nervous system damage (DeFronzo et al., 2015). Such a metabolic perturbation is a distinctive feature of T2DM, central obesity, and MetS (DeFronzo et al., 2015). Emerging evidence suggests that IR shares aetiological pathways with neuropsychiatric disorders, including Alzheimer's disease (AD), mood and psychotic disorders (Fanelli, Franke, et al., 2022; Hubel et al., 2019; Watson et al., 2019). The connection between IR-related conditions and neuropsychiatric disorders is supported by compelling epidemiological data (Leutner et al., 2023; Wimberley et al., 2022). Indeed, bidirectional phenotypic associations have been found between these two nosological groups (Wimberley et al., 2022). This evidence blurs the boundaries between traditional disease categories, advocating for a more integrated approach to research and clinical management (Chwastiak et al., 2015; Fanelli & Serretti, 2022). Consequently, a deeper comprehension of the mechanisms underlying this multimorbidity is essential.

Beyond shared environmental risk factors – including poor diet, sedentary lifestyle, and disturbed sleep (Marx et al., 2017; Ogilvie & Patel, 2018; Schuch et al., 2018), which could also be direct manifestations of psychopathology – shared genetic components have been identified (Fanelli, Franke, et al., 2022). Both IR-related conditions and neuropsychiatric disorders are highly heritable and polygenic (Mahajan et al., 2022; Trubetskoy et al., 2022), with heritability estimates, derived from twin and family studies, ranging from 40 to 80% (Almgren et al., 2011; Wray et al., 2014). Work by us and others disclosed global genetic correlations between neuropsychiatric disorders and IR-related conditions, indicative of shared genetic bases (Fanelli, Franke, et al., 2022; Hubel et al., 2019), though the effect

directions were not consistent across all phenotype pairs. Intriguingly, two clusters of neuropsychiatric disorders were identified, wherein the genetics of IR-related conditions showed opposite directions of genetic correlation. The first included attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder (MDD), which showed positive genetic correlations with IR-related conditions; the second included obsessive-compulsive disorder (OCD), anorexia nervosa (AN), and schizophrenia, which showed negative genetic correlations with IR-related conditions (Fanelli, Franke, et al., 2022). Genetic covariance was also highlighted within gene sets pertinent to insulin processing, secretion, and signalling, suggesting that several neuropsychiatric disorders could be reconceptualised as "insulinopathies" of the brain (Fanelli, Franke, et al., 2022). Strikingly, certain neuropsychiatric disorders, such as AD and bipolar disorder (BD), demonstrated no global genetic correlations with IR-related conditions, despite previous literature suggested a shared pathophysiology (Fanelli, Franke, et al., 2022; Shieh et al., 2020). However, global genetic correlation only encapsulates the average direction of genetic sharing across the genome, while the patterns of genetic correlations at the level of individual genomic regions can vary significantly (van Rheenen et al., 2019). Local genetic correlation can deviate from the genome-wide average, and regions of strong, local genetic correlation have been reported for multiple traits even in the absence of genome-wide correlation (van Rheenen et al., 2019; Werme et al., 2022). Therefore, the absence of genome-wide genetic correlations does not necessarily exclude shared genetics in specific regions, suggesting the importance to further study the possible genetic overlap between conditions without global genetic correlation, such as AD and IR-related traits (Fanelli, Franke, et al., 2022). Importantly, dissecting the local patterns of genetic sharing could shed light on specific genetic factors involved in IR-neuropsychiatric multimorbidity and new potential therapeutic targets for both groups of conditions. Recent advances in bioinformatics have facilitated a more detailed exploration of the genetic overlap across distinct phenotypes. Traditional global genetic correlation methods, like Linkage Disequilibrium Score regression (LDSC), assess shared genetic architecture between phenotypes across the entire genome (Bulik-Sullivan et al., 2015) but may fail in identifying phenotype pairs that share specific genomic regions potentially without showing global genome-wide genetic correlation (Bulik-Sullivan et al., 2015). Therefore, the utilisation of local genetic correlation analyses may offer more granular insights into shared genetic bases (Werme et al., 2022).

In this study, we aimed to dissect the genetic overlap between three IR-related metabolic conditions – namely, obesity, T2DM, and MetS - and nine psychiatric disorders by examining their pairwise patterns of local genetic correlation throughout semi-independent regions across the genome. Any shared genomic region was

further explored using positional and expression quantitative trait locus (eQTL)-based gene mapping techniques. This was followed by a functional annotation of the mapped genes, enabling a deeper exploration of biological mechanisms underlying IR-neuropsychiatric multimorbidity. Lastly, we investigated the shared (likely) causal variants possibly driving the pathophysiology of this multimorbidity.

Methods

Input datasets

We leveraged publicly available summary statistics from the largest genome-wide association studies (GWASs) on the three most prevalent IR-related conditions, namely obesity, MetS, and T2DM (n=244,890-933,970), and nine neuropsychiatric disorders, including AD, ADHD, AN, autism spectrum disorder (ASD), BD, MDD, OCD, schizophrenia, and Tourette's syndrome (TS) (n=9,725-933,970). These neuropsychiatric disorders were chosen because they are the best genetically characterised by the Psychiatric Genomics Consortium (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). Further details, including sample size of each GWAS, are reported in **Table 1**. To maintain consistency in genetic data, analyses were confined to individuals of European ancestry, employing the human genome build GRCh37/hg19 as a reference. All statistical analyses were performed using R v4.2.1 (2022-06-23).

Local genetic correlation analyses

We utilised the R package LAVA (Local Analysis of [co]Variant Association) (https://github.com/josefin-werme/LAVA) to perform pairwise local genetic correlation analyses between the three IR-related conditions and the nine neuropsychiatric disorders (Werme et al., 2022). Compared to traditional global correlation analysis methods (Bulik-Sullivan et al., 2015), LAVA estimates the genetic correlation at smaller genomic loci, which provides a more fine-grained overview of the genetic overlap between traits. In addition to providing insight into the potentially heterogeneous nature of the shared association patterns across the genome, LAVA allows identification of the regions from which the pleiotropy is originating (Werme et al., 2022). Further details regarding the LAVA analytical steps are provided in the **Supplementary information** (paragraph 1.1). Given the total number of bivariate tests performed across all phenotype pairs, local genetic correlations were deemed as statistically significant at a maximum acceptable false discovery rate (FDR) of q=0.05, following the approach of Hindley et al. (2022).

Table 1. Characteristics of genome-wide association study (GWAS) samples used as input for Local Analysis of [Co]variant Association (LAVA) and follow-up genomic analyses included in this study.

Phenotype	Authors	Year	PMID	Ancestry	N	Cases	Controls	N_{eff}
MetS	Lind	2019	31589552	European	291,107	59,677	231,430	189,772.81
Obesity	Watanabe et al.	2019	31427789	European	244,890	9,805	235,085	37,649.69
T2DM	Mahajan et al.	2022	35551307	European	933,970	80,154	853,816	293,100.50
AD	Wightman et al.	2021	34493870	European	762,917	86,531	676,386	306,866.18
ADHD	Demontis et al.	2023	36702997	European	225,534	38,691	186,843	128,213.80
AN	Watson et al.	2019	31308545	European	72,517	16,992	55,525	52,041.91
ASD	Grove et al.	2019	30804558	European	46,350	18,381	27,969	44,366.62
BD	Mullins et al.	2021	34002096	European	413,466	41,917	371,549	150,669.89
OCD	IOCDF-GC/OCGAS	2018	28761083	European	9,725	2,688	7,037	7,780.14
MDD	Howard et al.	2019	30718901	European	500,199	170,756	329,443	449,855.91
Schizophrenia	Trubetskoy et al.	2022	35396580	European	130,644	53,386	77,258	126,281.98
TS	Yu et al.	2019	30818990	European	14,307	4,819	9,488	12,783.30

Abbreviations: MetS metabolic syndrome, T2DM type 2 diabetes mellitus, AD Alzheimer's disease, ADHD attention-deficit/ hyperactivity disorder, AN anorexia nervosa, ASD autism spectrum disorder, BD bipolar disorder, MDD major depressive disorder, OCD obsessive-compulsive disorder, IOCDF-GC/OCGAS International OCD Foundation Genetics Collaborative/OCD Collaborative Genetics Association Studies, TS Tourette's syndrome, PMID PubMed ID, N total sample size, Neff effective sample size [Neff = 4/(1/Cases + 1/Controls)].

Positional and eQTL gene mapping

The biomaRt R package (version 2.54.1) (https://doi.org/doi:10.18129/B9.bioc.biomaRt) (Durinck et al., 2005) was used to annotate single-nucleotide polymorphisms (SNPs) within each genetically correlated region and positionally map them to genes. We used the Ensembl database (release 109, GRCh37/hg19, *homo sapiens*) as a reference for gene annotations. We defined filters to specify the genomic regions of interest based on their location (chromosome number, start and end positions).

For the eQTL-based gene mapping, the loci2path R package (version 1.3.1) (https://doi.org/doi:10.18129/B9.bioc.loci2path) (Xu et al., 2020) was used to identify eQTLs within the genetically correlated regions that may influence gene expression in 13 cortical, subcortical, and cerebellar brain regions (i.e., total brain cortex, frontal cortex BA9, hippocampus, hypothalamus, amygdala, anterior cingulate cortex BA24, caudate, nucleus accumbens, putamen, cervical spinal cord, substantia nigra, cerebellar hemisphere, cerebellum). We obtained the eQTL data from the Genotype-Tissue Expression (GTEx) project (GTEx V8, GRCh38/hg38) (https://gtexportal.org/home/dataset) and restricted our analysis to brain tissues due to their relevance to neuropsychiatric disorders. Prior to the analysis, we lifted the eQTL coordinates to the GRCh37/hg19 genomic build using the UCSC LiftOver tool (https://genome-store.ucsc.edu) to align with the used GWAS summary statistics.

Functional annotation of genetically correlated regions

Functional annotation analyses were conducted separately for each phenotype pair where genetically correlated regions were found. We employed the GENE2FUNC module within the Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA) platform (Watanabe et al., 2017), using default parameters and multiple testing correction (Watanabe et al., 2017). This approach served to examine important properties of the mapped genes, such as their tissue-specific and temporal expression profiles, enrichment in predefined gene sets, potential as drug targets, and previous trait/disease associations. Detailed information on the methods applied for these analyses are presented in the **Supplementary information** (paragraph 1.2).

To contextualise our findings within the broader landscape of known disease associations, we also investigated the overrepresentation of the identified genes within those previously associated with traits or diseases by querying the NHGRI-EBI GWAS Catalog (Buniello et al., 2019).

Colocalisation analyses

To identify the specific shared causal variants within each region showing local genetic correlation, we conducted robust Bayesian colocalisation analyses through the coloc R package (Giambartolomei et al., 2014) and the Sum of Single Effects (SuSiE) regression framework (Wallace, 2021) (https://chr1swallace.github.io/coloc/articles/a06_SuSiE.html). Notably, these approaches allow for simultaneous evaluation of multiple causal genetic variants within a genomic region and are therefore not limited by the single causal variant assumption that traditional colocalisation methods use. The input genomic regions were those showing evidence of local genetic correlation between each pair of IR-related condition and neuropsychiatric disorder. The detailed methodology is reported in the **Supplementary information** (paragraph 1.3).

Functional annotation of 95% credible sets of shared causal variants

We employed the SNPnexus web server (https://www.snp-nexus.org/) to further characterise the functional significance of the likely causal variants identified by colocalisation (Oscanoa et al., 2020). This tool integrates a wealth of genomic and functional annotation resources to elucidate the potential biological consequences of variants on gene structure, regulation, and function. The analysis encompassed several annotation categories, including gene annotations, regulatory elements (e.g., miRBASE, CpG islands), and non-coding scoring (i.e., deleteriousness Combined Annotation Dependent Depletion [CADD] scores), along with pathway enrichment analysis of credible set variants (Oscanoa et al., 2020). A detailed description of these steps is provided in the **Supplementary information** (paragraph 1.4).

Finally, the drugs/compounds that target genes mapped to likely causal variants were sourced from GeneCards, independent from their approved or investigational status. GeneCards is an online platform that gathers information from multiple databases including DrugBank, PharmaGKB, ClinicalTrials, DGIdb, the Human Metabolome Database, and Novoseek (Safran et al., 2010).

Results

a

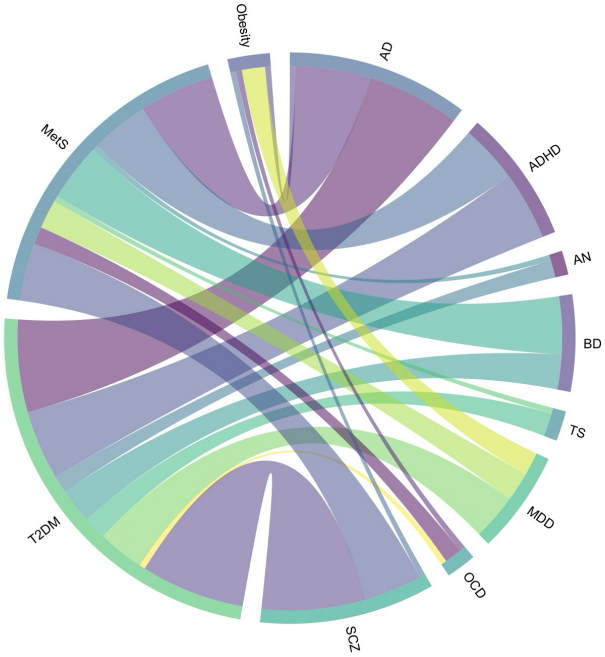


Figure 1. Local genetic correlations between neuropsychiatric and insulin resistance related conditions.

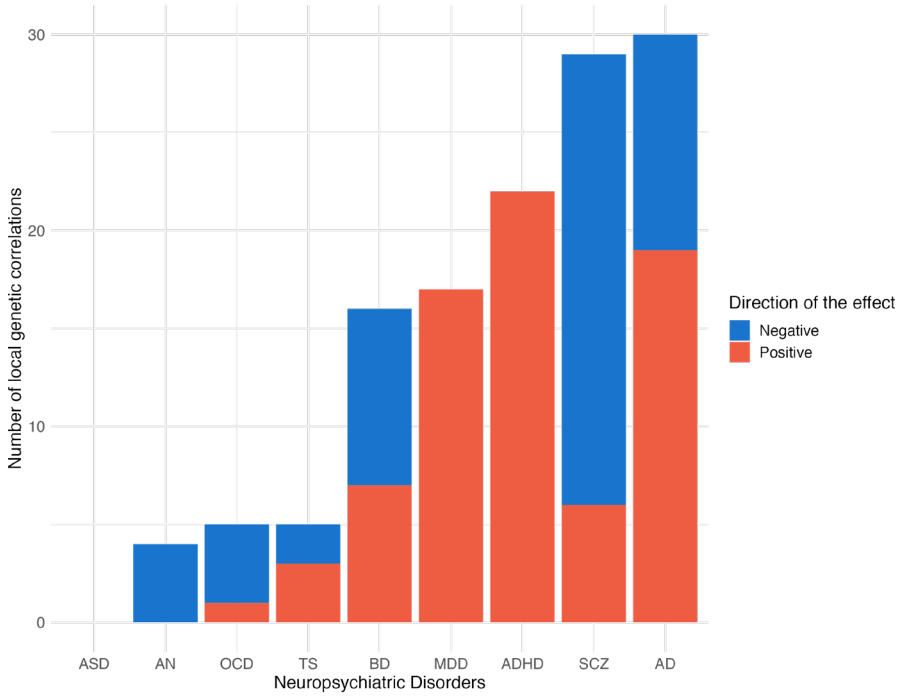
Abbreviations: AD, Alzheimer's disease; ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; MDD, major depressive disorder; MetS, metabolic syndrome, OCD, obsessive-compulsive disorder; T2DM, type 2 diabetes mellitus; SCZ, schizophrenia; TS, Tourette's syndrome.

a. Chord diagram representing the network of local genetic correlations between insulin resistance-related conditions and neuropsychiatric disorders. A higher width of a ribbon reflects a higher number of shared genetically correlated loci between two phenotypes, highlighting a substantial polygenic overlap and suggesting potential shared pathophysiological mechanisms between them. The colours of the ribbons are used purely for visual distinction and do not imply any additional significance or categorisation.

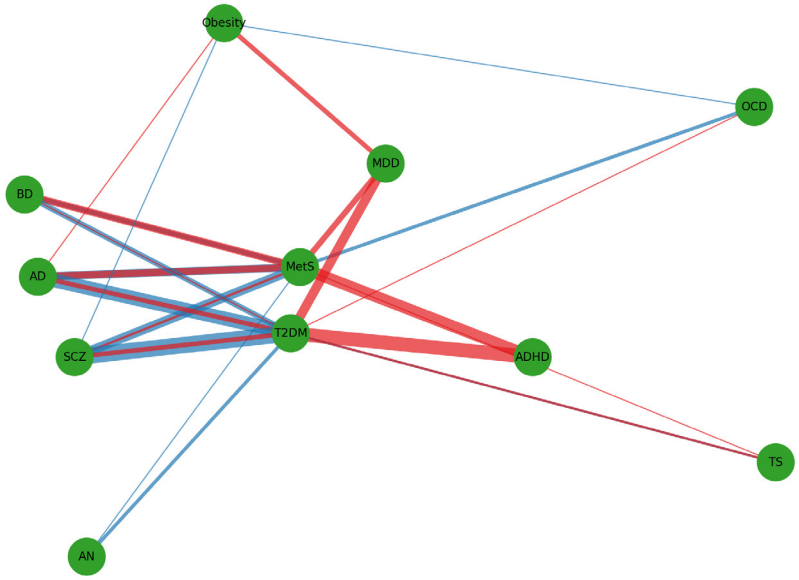
b. Bar plot presenting the number of local genetic correlations identified between neuropsychiatric disorders and insulin resistance-related conditions. Each bar corresponds to a different neuropsychiatric disorder, segmented by the direction of effect of local genetic correlations, with blue indicating negative and red indicating positive local genetic correlations between neuropsychiatric disorders and insulin resistance-related conditions. The height of each bar reflects the quantity of local genetic correlations detected for each disorder.

c. Network visualisation of local genetic correlations between a spectrum of neuropsychiatric disorders and insulin resistance-related conditions. Nodes represent distinct phenotypes for which local bivariate genetic correlations were evaluated. Edges connecting the nodes vary in width proportionally to the number of local genetic correlations identified between phenotype pairs. Edge colour denotes the direction of the genetic correlation estimate, with red indicating a positive correlation and blue indicating a negative correlation.

b


30
20
10
0
Number of local genetic correlations
ASD
AN
OCD
TS
BD
MDD
ADHD
SCZ
AD
Neuropsychiatric Disorders
Direction of the effect
Negative
Positive

c


Obesity
OCD
MDD
BD
MetS
AD
T2DM
SCZ
ADHD
TS
AN

Local patterns of genetic correlation between IR-related conditions and neuropsychiatric disorders

For each pair consisting of an IR-related condition and a neuropsychiatric disorder, bivariate local genetic correlation was evaluated in all genomic regions for which both phenotypes exhibited a univariate signal at $p<1x10^{-4}$, resulting in a total of 2,251 tests. Of note, only 19.6% of the regions with significant local SNP-based heritability (h^2_{SNP}) for both phenotypes showed a bivariate $p<0.05$, indicating that significant local h^2_{SNP} is often present without any local correlation signal between neuropsychiatric and IR-related conditions. After FDR correction, moderate to high degrees of local genetic correlations ($|r_g|=0.21\text{-}1$, $p_{FDR}<0.05$) were identified for 20 of the 27 phenotype pairs examined, across 109 unique semi-independent genomic regions (see **Figure 1** and **Table 2**). Noteworthy, local genetic correlations also emerged between IR-related conditions and neuropsychiatric disorders that had not shown significant global genetic correlations, namely AD, BD, and TS (Fanelli, Franke, et al., 2022). In total, 128 FDR-significant local genetic correlations were identified, of which 75 with a positive direction of the effect and 53 with a negative direction (**Table 2**; detailed results are provided in **Table S1**; see also **Figure 1b-c**). For 59 (46.1%) of the 128 local correlations, the 95% confidence intervals (CIs) for the explained variance included the value 1, consistent with a scenario where the local genetic signal for those phenotype pairs is entirely shared (**Table 2**). Interestingly, exclusively positive local genetic correlations were found between IR-related conditions and ADHD/MDD, while those detected between IR-related conditions and AN were all negative. No local genetic correlation was found between ASD and IR-related conditions. Conversely, a combination of positive and negative local genetic correlations was detected between all the other IR-related and neuropsychiatric conditions (**Figure 1**, **Table 2**), of which all but MetS-schizophrenia had no previous evidence of global genetic overlap (see **Table 2**).

Furthermore, fifteen out of the 109 unique regions were associated with more than one phenotypic pair (**Table S1**; we refer to these here as hotspots). The major hotspots showing significant bivariate local r_gs between multiple phenotypic pairs were the chr2:59251997-60775066 (between T2DM-ADHD, MetS-AN, MetS-MDD), chr6:31320269-31427209 (MetS-AD, T2DM-AD, T2DM-schizophrenia), and chr16:29043178-31384210 genomic regions (MetS-schizophrenia, obesity-schizophrenia, T2DM-schizophrenia) (see **Table S1** and **Figure S1**). Notably, 11.71% of the genetically correlated regions detected here (15/128) are located in the Major Histocompatibility Complex (MHC) region (chr6:28477797-33448354). All r_gs detected in the MHC were between T2DM/MetS and either schizophrenia, AD, or BP, with prevalence of a negative direction of the effect (**Table S1**).

Table 2. Summary of local genetic correlations between neuropsychiatric disorders and insulin resistance-related conditions.

Neuropsychiatric disorders	Insulin resistance-related conditions	Previous evidence of bivariate global genetic correlation	N loci with significant local h^2_{SNP} simultaneously for both phenotypes (% of loci tested)	N genetically correlated loci [b] (% of loci with significant [a] local h^2_{SNP} for both phenotypes)	N positively correlated loci (% of correlated loci for the pair)[b]	N negatively correlated loci (% of correlated loci for the pair)[b]	N genetic correlations estimates whose confidence intervals included 1 (% of correlated loci for the pair)[b]
AD	MetS	NO	306 (12.3%)	13 (4.2%)	6 (46.2%)	7 (53.8%)	2 (15.4%)
AD	Obesity	NO	34 (1.4%)	1 (2.9%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
AD	T2DM	NO	214 (8.6%)	16 (7.5%)	12 (75.0%)	4 (25.0%)	3 (18.8%)
ADHD	MetS	YES	94 (3.8%)	10 (10.6%)	10 (100.0%)	0 (0.0%)	9 (90.0%)
ADHD	Obesity	YES	30 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ADHD	T2DM	YES	88 (3.5%)	12 (13.6%)	12 (100.0%)	0 (0.0%)	7 (58.3%)
AN	MetS	YES	65 (2.6%)	1 (1.5%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
AN	Obesity	YES	40 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AN	T2DM	YES	73 (2.9%)	3 (4.1%)	0 (0.0%)	3 (100.0%)	2 (66.7%)
ASD	MetS	YES	21 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ASD	Obesity	YES	13 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ASD	T2DM	YES	12 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BD	MetS	NO	121 (4.8%)	10 (8.3%)	6 (60.0%)	4 (40.0%)	0 (0.0%)
BD	Obesity	NO	53 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
BD	T2DM	NO	107 (4.3%)	6 (5.6%)	1 (16.7%)	5 (83.3%)	1 (16.7%)
MDD	MetS	YES	95 (3.8%)	5 (5.3%)	5 (100.0%)	0 (0.0%)	3 (60.0%)
MDD	Obesity	YES	45 (1.8%)	4 (8.9%)	4 (100.0%)	0 (0.0%)	3 (75.0%)
MDD	T2DM	YES	83 (3.3%)	8 (9.6%)	8 (100.0%)	0 (0.0%)	4 (50.0%)
OCD	MetS	YES	71 (2.8%)	3 (4.2%)	0 (0.0%)	3 (100.0%)	2 (66.7%)
OCD	Obesity	YES	40 (1.6%)	1 (2.5%)	0 (0.0%)	1 (100.0%)	0 (0.0%)

Table 2. Contimued

Neuropsychiatric disorders	Insulin resistance-related conditions	Previous evidence of bivariate global genetic correlation	N loci with significant local h^2_{SNP} simultaneously for both phenotypes (% of loci tested)	N genetically correlated loci [b] (% of loci with significant [a] local h^2_{SNP} for both phenotypes)	N positively correlated loci (% of correlated loci for the pair)[b]	N negatively correlated loci (% of correlated loci for the pair)[b]	N genetic correlations estimates whose confidence intervals included 1 (% of correlated loci for the pair)[b]
OCD	T2DM	YES	54 (2.2%)	1 (1.9%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
Schizophrenia	MetS	YES	200 (8.0%)	10 (5.0%)	2 (20.0%)	8 (80.0%)	6 (60.0%)
Schizophrenia	Obesity	NO	89 (3.6%)	1 (1.1%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
Schizophrenia	T2DM	NO	172 (6.9%)	18 (10.5%)	4 (22.2%)	14 (77.8%)	10 (55.6%)
TS	MetS	NO	57 (2.3%)	1 (1.8%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
TS	Obesity	NO	27 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TS	T2DM	NO	47 (1.9%)	4 (8.5%)	2 (50.0%)	2 (50.0%)	3 (75.0%)
TOTAL			**2251**	**128 (5.7%)**	**75 (58.6%)**	**53 (41.4%)**	**59 (46.1%)**

For each neuropsychiatric disorder, the table presents the presence or absence of global genetic correlation with the specific insulin resistance-related condition, significant loci with h^2_{SNP} for both phenotypes tested, and the directionality of local genetic correlations with T2DM, Metabolic Syndrome (MetS), and obesity. The table further provides the number of local genetic correlations with confidence intervals that include 1, indicating completely overlapping genetic influences at specific loci. Abbreviations: AD, Alzheimer's disease; ADHD, attention-deficit/ hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; h^2_{SNP}, single-nucleotide polymorphism (SNP)-based heritability; MetS, metabolic syndrome; MDD, major depressive disorder; N, number of; OCD, obsessive-compulsive disorder; T2DM, type 2 diabetes mellitus; TS, Tourette's syndrome. [a]$p<1x10-4$; [b]False discovery rate (FDR) at maximum $q=0.05$.

Genes underlying IR-neuropsychiatric multimorbidity

In the regions where we detected significant local genetic correlations, we identified a total of 1,455 distinct genes were identified through eQTL-based mapping, and 1,495 unique protein-coding genes through positional mapping across all phenotype pairs (**Table S2-3**). Notably, the pseudogene *CYP21A1P* was recurrently eQTL-mapped across multiple phenotype pairs (AD-T2DM, AD-MetS, BD-T2DM, schizophrenia-T2DM). In total, 140 genes were mapped for at least three phenotype pairs, indicating a potentially broader relevance in the genetic landscape of IR-neuropsychiatric multimorbidity (**Table S3**). Within this subset, 20 genes, all located within the MHC region, were involved in immune-inflammation and vesicle metabolism/trafficking (e.g., *HLA-B, MICA, C4A, C4B, AGER, BTNL2, HLA-DRA, HLA-DRB1, HLA-DQA1, PSMB8, HLA-DRB5,* and *FLOT1*), and four genes were involved in insulin signalling and secretion (i.e., *STX1A, FLOT1, MAPK3,* and *PHKG2*) (see **Table S3**).

Functional annotation of the identified regions

Considering the genes mapped to the regions showing local correlation, 411 gene sets were significantly enriched (**Table S4**). Immune-related pathways were prominently represented for multiple phenotype pairs (i.e., AD-MetS/T2DM, BD-T2DM, TS-T2DM, schizophrenia-T2DM). Other biological pathways related to oxygen transport, lipid metabolism (including omega-3 and omega-6 polyunsaturated fatty acid levels (PUFAs)), embryonic/placental development, insulin receptor/phosphoinositide 3-kinase (PI3K), and vesicular function/secretion were enriched across different phenotype pairs (**Table S4**). Pharmacogenomic markers, notably genes genome-wide associated with response to metformin (i.e., *STX1B, STX4, ZNF668*), were enriched in regions shared between schizophrenia and MetS, obesity, and T2DM (**Table S5**).

In a more granular examination, we also evaluated enrichment of life-stage-specific expression profiles for genes mapped to the genetically correlated regions (**Tables S7-8**). Specifically, regions correlated between schizophrenia and obesity featured genes upregulated at 19 weeks post-conception. Conversely, regions associated with the schizophrenia-MetS pair exhibited a distinct pattern, with genes showing downregulation in brain samples from individuals at age 11. Furthermore, regions of overlap between OCD and MetS held genes upregulated in early adulthood brain tissues, while the genes in the overlapping regions marking the OCD-obesity pair exhibited gene downregulation in late childhood.

Detailed results for gene set analysis, spatio-temporal expression specificity of the mapped genes, and druggable gene annotations are reported in **Tables S4-S10**.

Shared causal variants between insulin resistance-related conditions and neuropsychiatric disorders

Of the 128 regions identified with local r_g, colocalisation analyses successfully pinpointed the likely causal variants driving this association in 10 regions (see **Tables S11-12**). For comprehensive functional annotations of 95% credible set variants within these 10 regions see **Tables S13-S23**.

Notably, one region on chromosome 4 and two on chromosome 6 showed the highest posterior probability for colocalisation, linking schizophrenia with MetS and AD with T2DM, respectively (**Tables S11-12**, **Fig. S2-4**). The schizophrenia-MetS relationship implicated the rs13107325 variant in the *SLC39A8* gene, which modulates the activity of the miRNA hsa-miR-374b-5p (**Tables S12-14**). For the AD-T2DM pair, the likely causal variants were rs9271608 and rs9275599, mapped to the *HLA-DRB1* and *MTCO3P1* genes, respectively. According to GeneCards, *HLA-DRB1* is targeted by immunosuppressive and anti-inflammatory drugs (e.g., azathioprine, lapatinib, interferons-β, and acetylsalicylic acid), as well as by statins and psychotropic drugs (e.g., carbamazepine, clozapine, and lamotrigine) (**Table S23**).

Further seven regions had good support for colocalisation (**Supplementary information**, paragraph 1.3); these regions showed local genetic correlations for the AD-T2DM, MDD-T2DM, BD-MetS, and schizophrenia-MetS pairs (**Tables S11-12**). Most of the identified variants were observed within or near genes pivotal to immune function, vesicle/small molecules trafficking, lipid metabolism, organ development, retinoic acid signalling, and DNA repair/apoptosis (**Tables S17-18**). They often had high CADD PHRED scores, suggesting highly deleterious effects (**Tables S13**). Genes mapping to these variants, like the *HLA-DQB1* and *FADS1/2* genes, are targeted by existing drugs and supplements, such as antihypertensive drugs, omega-3/6 PUFAs, and vitamin A (**Table S23**).

Discussion

In this study, we examined the genetic relationship between IR-related conditions – specifically, obesity, T2DM, and MetS – and nine neuropsychiatric disorders by investigating the pairwise patterns of local genetic correlation across the genome. At the same time, we explored the specific genetic factors and biological mechanisms underlying their multimorbidity. The results presented here offer novel insights into the shared genetic aaetiology between these phenotypes, unveiling a complex pattern of both positive and negative local genetic correlations. For the first time, we demonstrated that even in the absence of global genetic correlations, significant local correlations exist (i.e., between AD, BD, TS and IR-

related conditions). These findings expand the results of previous studies (Fanelli, Franke, et al., 2022; Hubel et al., 2019), with important implications for understanding the pathophysiology of these disorders and for developing targeted therapeutic interventions addressing IR-psychiatric multimorbidity. We identified 128 local genetic correlations across 109 unique genomic regions. Notably, the MHC region emerged as a particularly significant contributor in terms of shared genetic signal, as confirmed by enrichment in biological pathways related to immune function. In addition, genes mapped to the genetically correlated regions showed enrichment in pathways involved in lipid metabolism, insulin signalling, and vesicular function, among others.

Regarding the directions of the detected genetic correlations, we observed exclusively positive local genetic correlations for ADHD and MDD with IR-related conditions, indicating synergistic genetic effects that predispose to both neuropsychiatric symptoms and IR-related conditions. Our enrichment analyses of the genes mapped to these regions suggest that the genetic overlap might be mediated by genes involved in extracellular matrix organisation, vesicle trafficking, and oxygen transport/oxidative processes. These pathways are involved in both brain function and metabolic regulation (Dityatev et al., 2010; Rossetti et al., 2020; Zou et al., 2020). In particular, extracellular matrix molecules are implicated in synaptic plasticity and homeostasis (Dityatev et al., 2010) and may also influence tissue insulin sensitivity (Williams et al., 2015). Similarly, vesicle trafficking, integral to synaptic function and neurotransmission, could be a nexus where neuronal communication and insulin signalling intersect, contributing to the multimorbidity of the conditions (Zou et al., 2020). Conversely, we detected exclusively negative correlations between AN and IR-related conditions. These results align with the distinct phenotypic characteristics of AN, including increased insulin sensitivity and metabolic alterations related to undernutrition, which differ markedly from other neuropsychiatric disorders (Duriez et al., 2019; Ilyas et al., 2019).

While phenotypic overlap of AD and BD with IR-related conditions has been frequently reported (e.g., Santiago and Potashkin (2021); Wimberley et al. (2022))), previous genetic analyses did not find global genetic correlations between these phenotypes (Fanelli, Franke, et al., 2022). This may have occurred due to the averaging effect of global analyses. Our study, which is the first to report significant local genetic correlations between AD, BD, TS and IR-related conditions, suggests that positive and negative local correlations could neutralise each other in global correlation analyses, a phenomenon observed in other recent studies (Arenella et al., 2023; Fernandes et al., 2023). These heterogeneous patterns of genetic overlap could also point towards aetiologically distinct subgroups that warrant further exploration with deep phenotyping and functional validation. Such analyses could

bring us closer towards precision medicine, offering the potential for personalised healthcare and improved treatment success (Feczko & Fair, 2020).

Multiple genomic regions (15 out of 109) showed significant correlations for more than one phenotype pairs, implying a potentially more prominent and ubiquitous role in the IR-neuropsychiatric multimorbidity. Among the recurring regions, chr2:59251997-60775066, mapping to the *BCL11A* gene, was implicated in the correlation of T2DM with ADHD, MetS with AN, and MetS with MDD. *BCL11A* codes for a transcription factor essential for B cell function and haematopoiesis, as well as for neuronal development, regulating processes such as neurogenesis/axonogenesis, and neuronal migration (Bauer & Orkin, 2015; Dias et al., 2016). *BCL11A* variants have also been associated with neurodevelopmental disorders and impaired cognition, as well as with IR in *in vivo* and *in vitro* studies (Dias et al., 2016; Jonsson et al., 2013; Wiegreffe et al., 2022). Among other genes that were mapped across at least three phenotypic pairs, some (i.e., *STX1A, FLOT1, MAPK3*, and *PHKG2*) are pivotal in insulin signalling and secretion (Bagge et al., 2013; Jager et al., 2011; van de Vondervoort et al., 2016). These findings strengthen a molecular basis for linking neuropsychiatric disorders to altered insulin function (Fanelli, Franke, et al., 2022; Mota, 2024; van de Vondervoort et al., 2016)), which has also been tied to cognitive deficits, anhedonia, and reward processing alterations (Fanelli, Mota, et al., 2022; Fanelli & Serretti, 2022; Possidente et al., 2023).

Over 11% of the correlated genomic regions were located within the MHC region (chr6:28477797-33448354), where extensive pleiotropy has been demonstrated previously (Watanabe et al., 2019; Werme et al., 2022). This region is renowned for its high gene density, polymorphism, and involvement in immune-inflammatory responses (Matzaraki et al., 2017). The influence of the MHC region extends beyond autoimmune and infectious diseases susceptibility, being also associated with neuropsychiatric disorders, such as ASD, schizophrenia, and BD (Tamouza et al., 2021). Our findings point to a plausible genetic link between IR-related metabolic dysfunction, immune-inflammatory dysfunction, and neuropsychiatric disorders. This is consistent with previous findings indicating that central and peripheral inflammation may mediate the link between IR and neuropsychiatric conditions (Chan et al., 2019; Viardot et al., 2012). Inflammation may also impair brain insulin signalling, potentially resulting in neurobehavioural consequences (Gong et al., 2019). Notably, most of the local genetic correlations identified within the MHC region showed a negative direction of effect. We cannot provide a clear explanation of this finding, but it may lie in the balance of pro-inflammatory and anti-inflammatory factors in immune response, in which MHC genes play a role (Tamouza et al., 2021). Additionally, MHC class I (MHC-I) molecules, traditionally associated with immune functions, have also been implicated in synapse pruning, a process important for refining neural

circuits during development (McAllister, 2014). MHC-I molecules are expressed in neurons and modulate microglia-mediated synapse elimination by marking less active synapses for phagocytosis (Deivasigamani et al., 2023; Faust et al., 2021). This activity-dependent mechanism shapes functional neuronal networks and has been implicated in pathological synapse loss in neurodegenerative conditions (Faust et al., 2021; Zalocusky et al., 2021). Dysregulated MHC-I signalling can lead to aberrant synaptic pruning, implicated in disorders such as schizophrenia and ASD (McAllister, 2014). Hence, the dual role of MHC-encoded molecules in both immune modulation and synaptic plasticity, as well as the potential differential expression of genes in the MHC region across different tissues and the lifespan may help explain the observed negative genetic correlations (Shen & Zhang, 2021). Experimental validation of our findings will be necessary to determine the exact functional implication of the observed genetic associations.

Relatedly, our study identified multiple genes related to the human leukocyte antigen (HLA) system, innate immunity, and immunomodulation (i.e., *HLA-B, HLA-DRA, HLA-DRB1, HLA-DQA1, HLA-DRB5, MICA, C4A, C4B, AGER, PSMB8,* and *BTNL2*), supporting their possible influence on IR-neuropsychiatric multimorbidity. Of note, immunomodulatory drugs (e.g., non-steroidal anti-inflammatory drugs and monoclonal antibodies) have shown some efficacy as add-on treatments in psychoses and MDD, and might have higher efficacy in people with IR-neuropsychiatric multimorbidity (Drevets et al., 2022; Jeppesen et al., 2020). Another gene recurrently mapped across various phenotype pairs was the *CYP21A1P* pseudogene, located within the MHC region. Intergenic recombination of *CYP21A1P* leads to altered glucocorticoid and androgen production (Carvalho et al., 2021); glucocorticoids possess anti-inflammatory/immunosuppressive effects, and regulate glucose metabolism and the body's stress response (Balsevich et al., 2019). Specifically, glucocorticoids counteract insulin by decreasing peripheral glucose uptake and stimulating hepatic gluconeogenesis, leading to IR under conditions of excessive release, such as in chronic stress (Fichna & Fichna, 2017). Prolonged exposure to glucocorticoids can induce neurotoxic effects, possibly involved in the development of psychiatric disorders (Chiba et al., 2012; Ding et al., 2022). These hormones also modulate the serotonergic system, which is strongly implicated in psychiatric disorders and insulin signalling (Betari et al., 2021; Prouty et al., 2019). Interestingly, gene set enrichments within correlated regions between schizophrenia and IR-related conditions were related to the response to metformin, a frontline oral medication for T2DM. This implies a potential overlap in therapeutic targets between schizophrenia and T2DM, which could lead to a reassessment of treatment strategies for these patients. Previous randomised-controlled trials (RCTs) confirmed the efficacy of metformin in combating antipsychotic-induced metabolic side effects in individuals with psychoses (Agarwal

et al., 2021; de Silva et al., 2016), while improving psychiatric and cognitive symptoms in the same population (Battini et al., 2023).

Another significant finding of this study was the identification of colocalisation signals. Among the 128 regions demonstrating local genetic correlation, 10 regions were prioritised for their high posterior probabilities of harbouring the same causal variants shared between IR-related conditions and neuropsychiatric disorders. This was instrumental for further elucidating shared pathophysiological mechanisms and novel potential drug targets for IR-neuropsychiatric multimorbidity (Belyaeva et al., 2021; Karki et al., 2017). The two most likely shared causal variants were located in the chr4:102544804-104384534 and chr6:32586785-32629239/chr6:32682214-32897998 regions, suggesting novel cross-links between schizophrenia and MetS, and AD and T2DM, respectively. The identified shared causal variant (rs13107325) between schizophrenia and MetS maps to the *SLC39A8* gene, encoding the ZIP8 metal cation transporter. Previous studies demonstrated its association with altered brain manganese levels and protein complexity in schizophrenia, brain morphology and dendritic spine density, as well as a broader impact on various conditions, including developmental, neuropsychiatric and cardio-metabolic diseases/traits (Hermann et al., 2021; Li et al., 2022; Mealer et al., 2020; Nebert & Liu, 2019). Our findings also highlight SLC39A8's potential as a therapeutic target via zinc chloride/sulphate (Wishart et al., 2018). Interestingly, RCTs have shown beneficial effects of zinc sulphate in reducing symptoms of ADHD, MDD, and SCZ (Behrouzian et al., 2022; Bilici et al., 2004; Salari et al., 2015), as well as improving glucose handling in prediabetes (Islam et al., 2016). In the AD-T2DM context, the rs9271608 variant mapping to the *HLA-DRB1* gene presented compelling causal candidacy, pointing to the potential for immunosuppressive drugs such as azathioprine, lapatinib, and interferons-β to influence AD-T2DM manifestations. The administration of intranasal treatment with interferon-β was shown to improve anxious/depressive-like behaviours by modulating microglia polarisation in AD rat models (Farhangian et al., 2023). Of note, the rs9271608 also shows broad biological relevance as it is active as a promoter across numerous cell types and tissues, including various immune and neuronal progenitors (Zerbino et al., 2015). The remaining regions of notable colocalisation underpin associations between AD and T2DM, MDD and T2DM, BD and MetS, and schizophrenia and MetS, hinting at potential targetable mechanisms for current drugs and supplements, including antihypertensive drugs, omega-3/6 PUFAs, vitamin A (Wishart et al., 2018). Several antihypertensive drugs have been associated with a reduced risk of depression (Kessing et al., 2020), and omega-3 PUFAs showed beneficial effects on depression symptoms in a meta-analysis of RCTs (Liao et al., 2019). Genes associated with omega-3/omega-6 PUFAs were enriched when considering the regions showing correlation between BD and MetS, in line with their relevance in the multimorbidity. Finally, vitamin A inhibits amyloid β

protein deposition, tau phosphorylation, neuronal degeneration and improves spatial learning and memory in AD mouse models (Ono & Yamada, 2012). It is worth noting that a significant local genetic correlation without detectable colocalisation does not necessarily mean that there are no shared causal variants; this may reflect limitations in the power of the colocalisation analysis, particularly in scenarios with complex patterns of associations, which are often observed in highly polygenic traits (Werme et al., 2022).

Our study should be viewed considering some limitations. Although it may serve as a starting point by highlighting potential shared causal variants and proposing biological mechanisms through which shared genetic regions might impact both mental and metabolic health, the functional interpretation of our findings remains largely speculative; future *in vitro* and animal model studies will be necessary to validate our findings and provide more definitive mechanistic insights. The high LD in the MHC region may have led to spurious pleiotropy, not necessarily implying the presence of the same shared causal SNPs (Lee et al., 2021). Rare genetic variants were not considered, and population-specific effects may not be adequately captured by our analyses, which were limited to European ancestry. While the available GWAS summary statistics were generally obtained in samples of adequate size for this kind of study, the GWAS summary statistics for OCD were based on a relatively small sample size, potentially influencing the number of significant local genetic correlations detected by LAVA.

In conclusion, our study provides novel insights into the shared genetic underpinnings of neuropsychiatric and IR-related conditions, challenging traditional notions of their separate pathophysiology. Our result support a more integrated disease model, and the need to move beyond the conventional view of distinct aetiologies. The implications of our findings extend to clinical practice, emphasising the need for a holistic approach in the screening and management of IR-neuropsychiatric multimorbidity. For example, the importance of lifestyle interventions for both metabolic and psychiatric health, and of developing pharmacological treatments that target both conditions. The discovery of shared causal variants, particularly in genes like *SLC39A8* and *HLA-DRB1*, opens new avenues for targeted therapeutic interventions. The convergence of genetic findings on mechanisms related to immune-inflammation, insulin signalling, lipid metabolism, vesicle trafficking, among others, provides a compelling direction for future research. Overall, our study not only unveils the shared genetic landscape of neuropsychiatric and IR-related conditions but also establishes a foundation for integrated research and treatment approaches, contributing to a paradigm shift towards comprehensive care strategies that address the issue of multimorbidity.

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Chapter 7

The multivariate genetic architecture of psychiatric and insulin resistance multimorbidity

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# Contributed equally to this work

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Abstract

Psychiatric disorders frequently co-occur with insulin resistance (IR)-related conditions, including obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS). Although pairwise genetic correlations have been observed, the shared genetics underlying this multimorbidity remains underexplored. Here, we investigate the joint genetic architecture of psychiatric-IR multimorbidity, explore tissue-specific gene expression associations, and identify potential underlying biological mechanisms and repurposable drugs. We applied genomic structural equation modelling (SEM) to genome-wide association study (GWAS) data (N=9,725–933,970) from five psychiatric disorders (attention-deficit/hyperactivity disorder, anorexia nervosa, major depressive disorder, obsessive-compulsive disorder, and schizophrenia) and three IR-related conditions (MetS, obesity, T2DM). Factor analyses revealed a 2-factor solution, where one of the factors was composed by all psychiatric disorders (excluding schizophrenia) and IR-related conditions (the Psych-IR factor), representing the shared genetics of these psychiatric and IR-conditions. This factor showed genetic correlations with the inferior temporal, lateral occipital, and total cortical brain surface areas. A multivariate GWAS of the Psych-IR factor identified 150 risk loci and 366 associated genes (128 novel). The significant gene-set associations included the insulin binding and the Notch signalling pathways, while the gene-property tissue expression implicated the cerebellum, brain cortex, and pituitary gland, particularly involving the brain during prenatal development stages. Transcriptome-wide SEM (T-SEM) assessed tissue-specific gene expression associations and identified 499 genes (191 novel), including MHC-related genes. Drug repurposing analysis using PharmOmics suggested six potential candidates, including memantine and rosiglitazone. Associated genes derived from the Psych-IR factor multivariate GWAS and T-SEM results were combined for enrichment analyses, which highlighted the involvement of the chr16p11.2 region, BDNF signalling, and lipid metabolism. The identified Psych-IR factor offers novel insights into the shared genetic and biological mechanisms underlying psychiatric-IR multimorbidity, providing a foundation for future research on precision medicine and prevention approaches.

Introduction

The co-occurrence of psychiatric disorders and somatic insulin resistance (IR)-related conditions, such as obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS), is often observed (Perry et al., 2021; Wimberley et al., 2022). Population-based studies have demonstrated that obesity not only increases the risk of developing T2DM and metabolic syndrome but also elevates the likelihood of receiving a psychiatric diagnosis (Leutner et al., 2023). Moreover, large-scale Danish registry data reveal bidirectional associations between T2DM and various psychiatric disorders, including neurodevelopmental, mood, and psychotic disorders (Wimberley et al., 2022). This observed multimorbidity between IR-related conditions and psychiatric disorders complicates clinical trajectories (Kraus et al., 2023; Skou et al., 2022) and is linked to more severe clinical outcomes; for instance, T2DM has been associated to more severe depression and, conversely, depression is linked to higher rates of complications and mortality in T2DM (Fanelli and Serretti, 2022; Possidente et al., 2023).

Of note, IR generally refers to a reduced response to insulin stimulation on peripheral tissues, resulting in elevated blood glucose levels (DeFronzo et al., 2015; Gluvic et al., 2017). However, it is increasingly evident that insulin signalling disruption also has significant effects on the brain (Agrawal et al., 2021). Insulin receptors are expressed in most brain regions (Sullivan et al., 2023), and insulin is involved in important brain processes like synapse formation, neuroprotection, and neuronal survival (Pomytkin et al., 2018). A growing body of evidence links IR-related conditions with cognitive deficits across multiple domains (Fanelli et al., 2022b; Ottomana et al., 2023) and suggests that central IR affects key neurotransmitter systems, such as dopamine signalling, which is involved in reward-seeking behaviour and cognitive function (Gruber et al., 2023). Additionally, IR affects brain structures that are part of the mesolimbic pathway (i.e., the ventral tegmental area and nucleus accumbens), as well as the hippocampus (Lyra E Silva et al., 2019), influencing both hedonic perceptions and cognitive functions (Fanelli and Serretti, 2022; Gruber et al., 2023). The prefrontal cortex is also susceptible to the effects of IR, which can result in impaired cognitive flexibility and working memory deficits (Arnold et al., 2018a; Willette et al., 2013). IR is also associated with brain regional atrophy in Alzheimer's disease, particularly in the bilateral parietal-occipital junction and medial temporal regions, hippocampal and ventromedial prefrontal cortex volumes in bipolar depression and healthy subjects (Mansur et al., 2021; Morris et al., 2014; Mullins et al., 2017).

While many studies attribute metabolic disturbances in psychiatric patients to unhealthy lifestyles, sedentary habits, or the chronic use of psychotropic

medications (e.g., Grajales et al. (2019)), evidence suggests that these associations are not merely by-products of such factors. Glycaemic and metabolic imbalances have been detected even in drug-naïve psychiatric patients at disorder onset, implying the potential involvement of shared pathogenic mechanisms (Garrido-Torres et al., 2021). Genetic studies reinforce the hypothesis of a shared biological basis for this multimorbidity showing significant genetic correlations between several psychiatric disorders—including attention-deficit/hyperactivity disorder (ADHD), anorexia nervosa (AN), obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and schizophrenia (SCZ)—and IR-related conditions such as MetS, obesity, and T2DM (Fanelli et al., 2022a). Subsequent local genetic correlation analyses further demonstrated that these genetic overlaps are not always evenly distributed throughout the genome highlighting the complex genetic landscape of IR-neuropsychiatric multimorbidity (Fanelli et al., 2025). Additionally, a family-based study indicated that relatives of individuals with a psychiatric disorder have an increased risk for T2DM (Wimberley et al., 2024). These findings suggest that shared underlying mechanisms are important for the multimorbidity between psychiatric disorders and IR-related conditions.

While bivariate genetic analyses have been instrumental for identifying shared genetic aetiologies between pairs of psychiatric and IR-related conditions, the global joint genetic architecture and biological substrates underlying the multimorbidity across these two groups of conditions has not been explored. To address this gap, we employed genomic structural equation modelling (genomic SEM), a novel multivariate approach that enables analysing the shared genetic architecture of multiple complex traits simultaneously (Grotzinger et al., 2019). This method allows for the identification of genetic variants associated with a common underlying genetic factor, shown to capture loci that are missed by traditional univariate genome-wide association study (GWAS) approaches (Grotzinger et al., 2019). Given that many genetic loci identified through GWAS likely exert their effects via modulation of gene expression (e.g., as expression quantitative trait loci or eQTLs; (Westra et al., 2013)), transcriptome-wide association studies (TWASs) can be helpful to quantify the effect of gene expression on complex traits (Gusev et al., 2016). Transcriptome-wide structural equation modelling (T-SEM) extends genomic SEM by modelling tissue-specific gene expression within a multivariate network of genetically overlapping traits, providing further insights into the molecular mechanisms involved (Grotzinger et al., 2022a). These transcriptomic results can also be integrated with open-source databases to identify potential, novel drug candidates (Y.-W. Chen et al., 2022).

In this study, we aimed to elucidate the joint genetic architecture underlying the multimorbidity of psychiatric disorders and somatic IR-related conditions. We

applied genomic SEM to explore the genetic factor structure best explaining the shared genetics between five psychiatric disorders and three IR-related metabolic conditions that have previously shown significant pairwise genetic correlations (Fanelli et al., 2022a). Using the genomic SEM framework, we also examined the genetic relationships between the identified latent multimorbidity factor and brain morphometry (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019), as well as estimated the effects of single-nucleotide polymorphisms (SNPs), genes, and gene sets on such a latent multimorbidity factor. Furthermore, employing T-SEM, we specifically investigated the association between brain-specific transcriptomic patterns and the identified multimorbidity factor, aiming to uncover genes whose tissue-specific gene expression might overlap with brain molecular signatures of repurposable drugs.

Methods

Input univariate GWAS summary statistics

In order to explore the joint genetic architecture underlying the multimorbidity of psychiatric disorders and somatic IR-related conditions, we used GWAS summary statistics of European ancestry datasets of five psychiatric disorders (i.e., ADHD, AN, MDD, OCD, and SCZ) and three somatic IR-related conditions (i.e., MetS, obesity, and T2DM) that showed significant pairwise genetic correlations (Fanelli et al., 2022a) as input for the genomic factor analyses and further genomic SEM and T-SEM analyses (**Table 1**; see also **Figure 1a**). SNP-based heritability was estimated using Linkage Disequilibrium Score Regression (LDSC; (Bulik-Sullivan et al., 2015)) and is reported on the liability scale. For details regarding sample ascertainment, phenotype description, quality control, and related procedures, we refer the reader to the corresponding univariate GWAS original publications listed on **Table 1**.

Table 1. Contributing univariate genome-wide association study (GWAS) datasets.

Univariate GWAS	Cases	Controls	Total sample	Population prevalence	SNP-based heritability (SE)	GWAS reference
ADHD	38,691	186,843	225,534	0.087	0.213 (0.010)	Demontis et al., 2023
AN	16,992	55,525	72,517	0.009	0.165 (0.011)	Watson et al., 2019
MDD	170,756	329,443	500,199	0.21	0.290 (0.045)	Howard et al., 2019
OCD	2,688	7,037	9,725	0.02	0.094 (0.004)	IOCDF-GC/ OCGAS, 2018)
SCZ	53,386	77,258	130,644	0.01	0.223 (0.008)	Trubetskoy et al., 2022
MetS	59,677	231,430	291,107	0.25	0.201 (0.011)	Lind, 2019
Obesity[a]	9,805	235,085	244,890	0.39	0.267 (0.025)	Watanabe et al., 2019
T2DM	80,154	853,816	933,970	0.1	0.174 (0.008)	Mahajan et al., 2022

Note. Population prevalences were used for the liability scale conversion and were retrieved from their original publications and/or Grotzinger et al. (2019) for the psychiatric traits, from O'Neill and O'Driscoll (2015) for MetS, from World Health Organization (2018) for obesity, and from Kumar et al. (2024) for T2DM.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; SE, standard error; GWAS, genome-wide association study.

[a]GWAS ATLAS ID: 3687, UK Biobank phenotype field 41204 (41204_E66), which refers to the trait 'Diagnoses - secondary ICD10: E66 Overweight and obesity'.

Genomic structural equation modelling

Genomic factor analyses

A multivariate extension of LDSC (Bulik-Sullivan et al., 2015) within genomic SEM; (Grotzinger et al., 2019) was used to estimate genetic correlations between all pairwise combinations of the studied phenotypes (**Figure 1a**) and to generate three covariance matrix sets, which were based on the odd, even, or all autosomal chromosomes. Genomic SEM is not biased by sample overlap and is capable of accounting for differences in sample sizes among the univariate GWASs that are used as input. Standard procedures were followed and default filtering parameters for this munging step, such as retaining only SNPs that overlap with HapMap3 SNPs outside of the major histocompatibility complex (MHC) region and excluding SNPs with imputation quality (INFO) <0.9 and/or with minor allele frequency (MAF) <1%,

were applied whenever such information was available for the univariate GWAS summary statistics. As basis for the multivariate LDSC, we used precalculated LD scores derived from the 1000 Genomes (Phase 3) European reference population (1000 Genomes Project Consortium et al., 2015; Bulik-Sullivan et al., 2015). The sample prevalence for all phenotypes was set to 0.5 in the LDSC estimation step since we used the effective number of samples as the sample size for the munge step, following the instructions provided in genomic SEM GitHub page (2.1 Calculating Sum of Effective Sample Size and Preparing GWAS Summary Statistics · GenomicSEM/GenomicSEM Wiki · GitHub). The assigned population prevalence of each phenotype can be found in **Table 1**.

In order to model the genomic factor structure underlying the psychiatric and somatic IR-related conditions investigated here, we conducted a series of factor analyses based on the genetic covariance matrices derived from LDSC analyses within genomic SEM. We first conducted exploratory factor analyses (EFA) on the output of the LDSC analyses with odd chromosomes using the *factanal* function of R with promax rotation, which allows factors to be correlated. We tested solutions up to three latent factors, while retaining factors that explained at least 20% of the variance. Based on the results of the EFA in odd chromosomes, we performed follow-up confirmatory factor analyses (CFA) for the one-factor and two-factor models using the genetic covariance matrix from the LDSC with even chromosomes, where factors were assigned to traits when their standardised loading exceeded 0.20 in the corresponding EFA. The model uses Diagonally Weighted Least Square (DWLS) and was specified so that the variance of each latent factor is fixed to 1 (i.e., unit variance identification).

Model fit was assessed using standard measures in structural equation modelling, as described in Grotzinger et al. (2019), where values >0.9/0.95 for the comparative fit index (CFI) and <0.10/0.05 for the standardised root mean square residual (SRMR) were considered reflective of an acceptable/good fit model. The Akaike Information Criterion (AIC) is a relative fit index, which can be used to compare models (i.e., lower AIC values indicating better fit). Chi-square p-values are often significant in genomic SEM analyses due to the high power of current GWASs; however, chi-square estimates may still be informative for comparing competing models (i.e., lower chi-square values indicating better fit). Finally, the CFA model with best fit in even chromosomes was also assessed for all autosomes.

Genetic correlation with brain morphometry

We used genomic SEM to assess the genetic link between the identified latent multimorbidity factor(s) and brain morphological traits. More specifically, we modelled the genetic covariances and correlations between the factor and the

GWAS summary statistics of 1) the bilateral averages of cortical thickness and surface area (SA) of 34 brain regions and the total brain (N=33,992; Grasby et al. (2020)); and 2) eight subcortical volumes (Hibar et al., 2017; Satizabal et al., 2019), namely nucleus accumbens (N=32,562), amygdala (N=34,431), brainstem (N=28,809), caudate nucleus (N=37,741), globus pallidus (N=34,413), putamen (N=37,571), thalamus (N=34,464), and hippocampus (N=33,536). All brain morphometry-related GWAS summary statistics underwent standard filtering and processing through the munge function of LDSC in genomic SEM, as detailed above. We refer the reader to the original publications Grasby et al. (2020), for cortical thickness and SA; Satizabal et al. (2019) and Hibar et al. (2017) for the eight subcortical volumes) for details about how these brain-related univariate GWAS were performed. Bonferroni correction was applied to account for multiple comparisons, thus adjusting the significance threshold (α_{Bonf}=0.05/78 brain phenotypes=6.41x10^{-4}).

We further computed heterogeneity statistics (Q_{trait}) for the associations of the latent factor with the brain morphological traits, as described in Grotzinger et al. (2022b). For each brain phenotype, the Q_{trait} heterogeneity index evaluates to which extent that trait operates through the latent factor. This is done by comparing a model in which the brain trait predicted the factor only to one in which it predicted the individual disorders/conditions that compose the latent factor. A significant Q_{trait} ($P<6.41x10^{-4}$) indicates that the pattern of associations between the brain trait and the individual disorders/conditions is not well accounted for by the factor.

Multivariate GWAS of the multimorbidity factor

After identifying the CFA that best explained the observed genetic covariances among the psychiatric disorders and the IR-related somatic conditions, we used genomic SEM (Grotzinger et al., 2019) to conduct a multivariate GWAS, estimating individual SNP effects on the identified latent multimorbidity factor. Quality control procedures of the univariate GWAS summary statistics were performed following genomic SEM guidelines, which included restricting to SNPs with an INFO score >0.6 (when available) and to SNPs with MAF >1% in the 1000 Genomes phase 3 European reference panel (1000 Genomes Project Consortium et al., 2015). Only genetic variants present in all input univariate GWAS summary statistics were used. For this step, we used unit loading identification to scale the latent factor(s) (instead of unit variance identification used in the CFA), which also allows deriving the effective number of samples (N_{eff}) for the latent factor(s) (N_{eff} was estimated as described in Mallard et al. (2022).

Similarly to the Q_{trait} statistics described above, we also performed SNP-level tests of heterogeneity (Q_{SNP}) to evaluate whether each SNP had consistent pleiotropic effects on the factor components (i.e., input disorders/conditions) that effectively

only operate via the shared liability (null hypothesis) or whether there was evidence of heterogeneity, indicating that the SNP effect is not fully mediated by the factor (Grotzinger et al., 2019).

Gene, gene-set, and gene-property analyses of the Psych-IR multivariate GWAS results

The results of the multivariate GWAS of the multimorbidity latent factor were submitted to Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA; version v1.5.6; Watanabe et al. (2017)), using default parameters (if not otherwise specified). We used the FUMA SNP2GENE module to identify independent genomic risk loci, and independent genome-wide significant SNPs within each locus, employing the standard clumping algorithm (Watanabe et al., 2017). After the removal of all significant Q_{SNPs} ($P< 5x10-8$), as well as any SNP in LD with those ($r2>0.1$, 250Kb), from the multivariate GWAS summary statistics, this module was also used to implement Multi-marker Analysis of Genomic Annotation (MAGMA; v.1.08; De Leeuw et al. (2015)) gene-based, gene-set, and gene-property (tissue expression) analyses. Gene-based p-values were computed for protein-coding genes by mapping SNPs located within genes according to Ensembl v110. MAGMA gene-set association analysis uses the complete gene-based results, (thus differing from enrichment analyses of prioritised genes, described below) to perform one-sided (positive) association tests for 17,023 gene sets from the Molecular Signatures Database (MSigDB v2023.1.Hs; Liberzon et al. (2011a)). Bonferroni correction was used to set the genome-wide significance threshold for the gene-based and gene-set analyses. MAGMA gene-property tissue expression analyses also use the gene-based results to test the associations with highly expressed genes in specific tissues, while conditioning on average expression across all tissue types. These tissue expression analyses were performed across 30 general tissues and 54 tissues types (GTEx v8; The GTEx Consortium et al. (2020)), as well as 29 different ages of brain samples and 11 general developmental stages of the brain (BrainSpan; Kang et al. (2011)); (for more detailed information, please see Watanabe et al. (2017)). We also ran the FUMA analyses on the eight GWAS summary statistics of the individual phenotypes that served as input for genomic SEM, in order to compare the significant loci and genes identified for the multivariate GWAS. Genomic loci and genes associated with the latent factor that did not overlap with those associated with the individual phenotypes were considered as novel/unique to the multimorbidity factor.

Transcriptome-wide structural equation modelling (T-SEM)

T-SEM (Grotzinger et al., 2022a) was employed to investigate the effects of tissue-specific gene expression on the multimorbidity factor representing the shared genetics of psychiatric disorders and IR-related conditions. This method enables the examination of tissue-specific gene expression within a multivariate model of genetically overlapping traits.

First, to ensure sufficient SNP-level overlap with the tissue-specific expression weights, the univariate GWAS summary statistics of the eight input phenotypes (**Table 1**) were reprocessed using the LDSC munging function, this time using the 1000 Genomes SNPs as reference (1000 Genomes Project Consortium et al., 2015) (as recommended by the developers guidelines for T-SEM; https://github.com/GenomicSEM/GenomicSEM/wiki/7.-Transcriptome-wide-SEM-(T-SEM)). The genetic and sampling covariance matrices of these munged summary statistics were estimated by multivariate LDSC as implemented in genomic SEM and are used as input to T-SEM (Grotzinger et al., 2019).

Univariate, summary-based TWASs were then performed using FUSION (Gusev et al., 2016) to test the association between predicted tissue-specific gene expression and each individual trait. This association was estimated as a weighted linear combination of GWAS Z-statistics using pre-compiled functional weights from external reference datasets containing both tissue-specific gene expression and genotype data. In particular, we used 15 tissue-specific functional weight datasets, including 13 referring to brain tissues (i.e., amygdala, anterior cingulate cortex, caudate, cerebellar hemisphere, cerebellum, cortex, frontal cortex, hippocampus, hypothalamus, nucleus accumbens, putamen, cervical spinal cord C1, substantia nigra) and one to the pituitary gland from the GTEx v8 (The GTEx Consortium et al., 2020), as well as one referring to the brain prefrontal cortex from PsychENCODE (Gandal et al., 2018). The selection of pituitary and brain tissues for these analyses was supported by the tissue specificity of genes from the multivariate GWAS of the multimorbidity factor (described above).

The tissue-specific gene expression estimates for each gene produced by univariate TWASs were used to expand both the genetic covariance and sampling covariance estimated previously. Specifically, the *read_fusion* function in genomic SEM was employed to standardise the gene expression estimates relative to the phenotypic variance, thus integrating them into the LDSC genetic covariance matrices. We then applied the *userGWAS* function to evaluate the effect of gene expression on the previously identified factor representing the shared genetic liability across psychiatric disorders and IR-related conditions.

Lastly, T-SEM was used to examine the associations of tissue-specific gene expression with the multimorbidity latent factor. We applied a Bonferroni correction

to adjust for multiple testing across 16,542 unique genes, resulting in a significance threshold of $\alpha_{Bonf}=3.02x10^{-6}$. To identify genes with potentially trait-specific effects, we also computed gene heterogeneity statistics (Q_{Gene}) as a chi-square difference test between a common pathways model (where gene expression predicts the multimorbidity latent factor) and an independent pathways model (where the gene expression only predicts specific psychiatric or IR-conditions defining the factor) (Grotzinger et al., 2022a). To ensure robustness, we excluded from the list of significantly associated genes those with significant Q_{Gene} values using the same Bonferroni corrected threshold.

The MHC region was excluded from follow-up analyses due to its highly complex LD structure, which may confound genetic association signals and inflate the number of false-positive findings (Miretti et al., 2005). However, we conducted parallel T-SEM T-SEM analyses both excluding and including the MHC region to provide a comprehensive assessment of its potential impact on the results, and findings from the both T-SEM analyses are presented to ensure transparency and completeness in reporting.

Drug repurposing analysis

To identify potential therapeutic candidates for the psychiatric-IR multimorbidity, we used PharmOmics, a comprehensive online platform for drug repurposing (https://mergeomics.research.idre.ucla.edu/runpharmomics.php#; (Y.-W. Chen et al., 2022)). PharmOmics is a species- and tissue-specific drug signature database that leverages transcriptomic data to facilitate the identification of repurposable drugs by comparing user-provided gene signatures for a trait of interest (i.e., the multimorbidity factor, in our case) with a curated database of drug-induced gene expression profiles (Y.-W. Chen et al., 2022). The PharmOmics database integrates transcriptomic data from human, mouse, and rat studies across more than 20 tissues, compiling over 18,000 drug-induced gene signatures for 941 drugs and chemicals. This database was curated from multiple sources, including the Gene Expression Omnibus (GEO), ArrayExpress, TG-GATEs, and DrugMatrix repositories. For our analysis, we used the list of genes derived from significant tissue-specific gene expression associations from our T-SEM results as input into the PharmOmics platform ((Y.-W. Chen et al., 2022). These genes were classified into upregulated and downregulated groups based on their respective T-SEM Z scores and submitted separately to PharmOmics. Specifically, a gene-overlap analysis was conducted (Y.-W. Chen et al., 2022) to determine the degree of overlap between the input gene lists (upregulated and downregulated genes) and the drug-induced gene signatures in the database. This analysis included calculating odds ratios to quantify the strength of association between the list of genes resulting from T-SEM and drug-specific gene expression

signatures in the PharmOmics database. Fisher's exact tests were used to assess the statistical significance of these overlaps, determining the likelihood that the observed overlaps occurred by chance. A signed Jaccard score was employed to evaluate the direction of the overlap between the gene sets. A positive signed Jaccard score indicates that the drug and T-SEM gene sets overlap with congruent expression changes (e.g., both upregulated or both downregulated), while a negative signed Jaccard score suggests that the drug and T-SEM gene set overlap with opposite expression changes (e.g., one upregulated and the other downregulated). The therapeutic relevance depends on the direction of the gene regulation and the desired therapeutic objective. For example, if a pathway is upregulated in psychiatric-IR multimorbidity, a drug that induces a negative signed Jaccard score (indicating an opposite regulation of the overlapping genes) may be of therapeutic interest to counteract the disease-related up-/down-regulation.

We selected drug repurposing candidates based on the following stringent criteria: 1) individual pharmacological molecules already approved by the Food and Drug Administration (https://www.accessdata.fda.gov/) for conditions other than psychiatric disorders; 2) those with evidence of blood-brain barrier permeability (ADMET features from https://www.drugbank.com/; https://github.com/12rajnish/DeePred-BBB); 3) drugs with available molecular signatures derived from nervous tissues in the PharmOmics database; 4) candidates showing consistent Jaccard scores and P-value significance across species, ensuring cross-species concordance and eliminating discordant effects; and 5) candidates with significant P-values and negative Jaccard scores, indicating an opposing gene regulation pattern that could potentially reverse disease-related molecular changes.

Enrichment analyses of prioritised genes

The significantly associated genes identified by the MAGMA gene-based analysis of the multivariate GWAS were combined with genes whose tissue-specific expression was associated with the genomic latent multimorbidity factor in T-SEM analysis to compose a list of prioritised genes. This combined list of genes was used as input for the GENE2FUNC module in FUMA (version v1.5.6; Watanabe et al. (2017)) to conduct enrichment analyses to test for overrepresentation of the prioritised genes in pre-defined gene sets from the MsigDB (v2023;(Liberzon et al., 2011b)), which include hallmark gene sets (MsigDB h), positional gene sets (MsigDB c1), curated gene sets (MsigDB c2), regulatory target gene sets (MsigDB c3), computational gene sets (MsigDB c4), ontology gene sets (MsigDB c5), oncogenic signature gene sets (MsigDB c6), immunologic signature gene sets (MsigDB c7) and cell type signature gene sets (MsigDB c8), as well as sets of reported genes from the GWAS-catalog (MacArthur et al., 2017). For the list of all gene sets tested, please see

(https://fuma.ctglab.nl/tutorial#gene2func). Genes located within the MHC region were excluded from the analyses due to the extensive high linkage disequilibrium pattern in the region and hypergeometric tests were used for these evaluations. The background gene set, against which the prioritised genes were tested, consisted of all other (i.e., non-prioritised) protein-coding genes and the option of excluding the MHC region in FUMA was selected. Multiple testing correction was performed using the Benjamini–Hochberg (FDR) method by default, with corrections applied per data category or subcategory (e.g., hallmark genes, positional genes, different subcategories of curated gene sets, and so on). FUMA reported gene sets with an adjusted $P_{FDR}<0.05$ and where the number of prioritised genes overlapping with the gene set was greater than two.

Results

Genetic factor structure underlying psychiatric and somatic IR-related conditions

We formally modelled the genetic covariance structure of the five psychiatric (ADHD, AN, MDD, OCD, and SCZ) and three somatic IR-related phenotypes (MetS, obesity, and T2DM) which are genetically correlated ((Fanelli et al. (2022); and **Figure 1a**). Descriptives of the input data can be found in **Table 1**. Exploratory factor analyses suggested the two-factor solution as the best model (variance explained: R^2(F1)=32.1%, R^2(F2)=20%, R^2(Total)=52.1%), since the one-factor solution explained only 31.4% of the variance, while the third factor in a three-factor model explained only 15.2% of the variance and was not retained (**Table S1**). Confirmatory factor analyses, both in the even chromosomes as in the full set of autosomes, confirmed that a two correlated factors model fits the data well (for all autosomes: χ^2=78.559, df=15, Pχ^2=1.28x10-10, AIC=120.559, CFI=0.978, SRMR=0.053; **Table S2**; see also **Table S3**) and revealed a small negative genetic correlation between the two factors (r_g=-0.204; SE=0.043; P=2.02x10-6; **Figure 1b**). The first factor consists of all psychiatric disorders, except schizophrenia, and all somatic IR-related conditions investigated. This factor is hereafter referred to as the psychiatric and IR-related (Psych-IR) multimorbidity factor. The second factor consists of all five psychiatric disorders investigated, but none of the somatic ones.

Given our aim of unravelling the genetic architecture underlying the psychiatric and IR-related multimorbidity, subsequent results are focused on the Psych-IR multimorbidity factor, which was taken forward to investigate its relationship with brain morphometry, to conduct a multivariate GWAS, exploring it at multiple levels, as well as to conduct T-SEM and drug repurposing analysis.

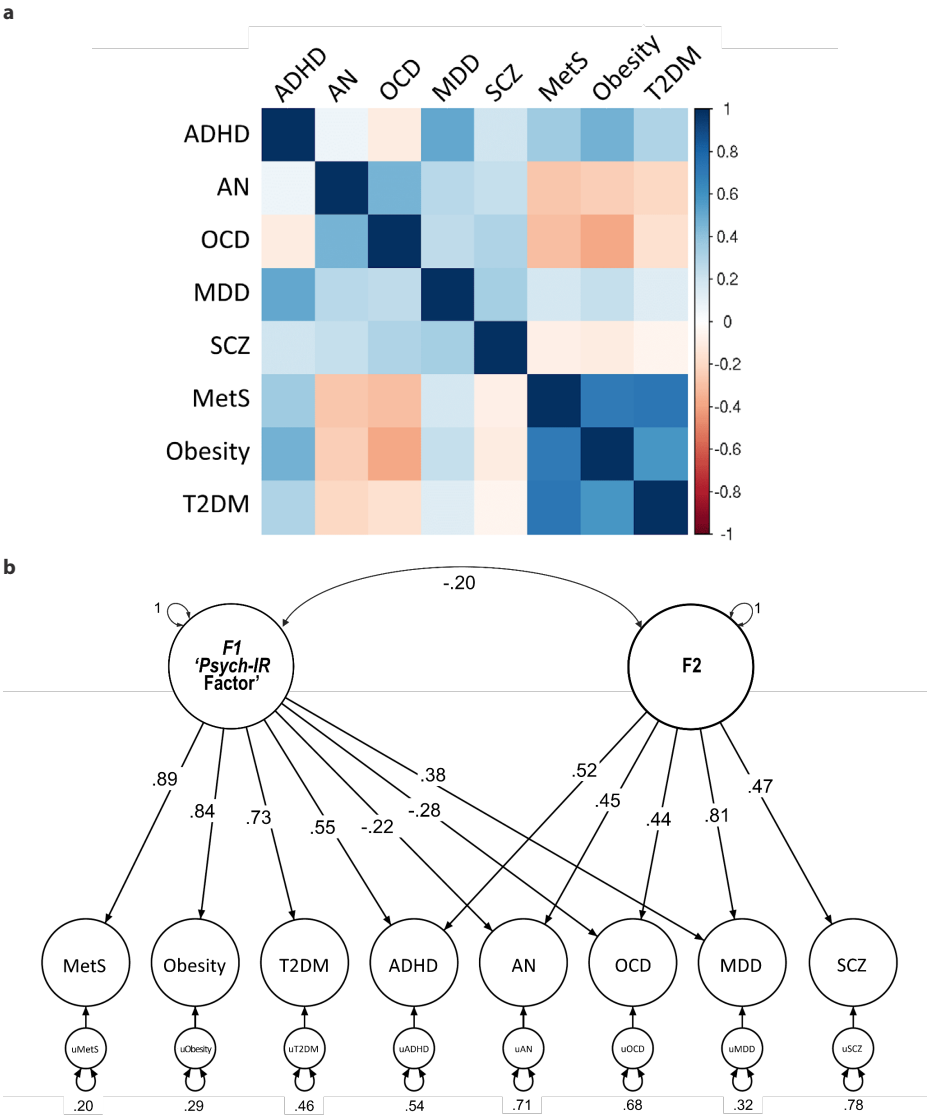

Figure 1. Multivariate genetic architecture of five psychiatric disorders and three somatic IR-related conditions.

a. Heatmap of pairwise genetic correlations based on all autosomes estimated using LDSC regression within genomic SEM; **b.** Path diagram for the final confirmatory factor model with standardised parameter estimates. Circles represent the genetic components of each disorder, condition, or common genetic factor. One-headed arrows represent regression relationships from the independent variables pointing towards the dependent variables. Two-headed arrow between variables represent a covariance relationship. Two-headed arrows connecting the variable to itself represents residual variance. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; OCD, obsessive-compulsive disorder; MDD, major depressive disorder; SCZ, schizophrenia; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus.

Genetic overlap between the Psych-IR multimorbidity factor and brain morphometry

We examined patterns of genomic correlations between the Psych-IR multimorbidity factor and brain morphometry (**Figure S1**). We observed significant negative genetic correlations between the Psych-IR multimorbidity factor and total SA (r_g=-0.151; SE=0.033; P=4.89x10^{-6}) and inferior temporal SA (r_g=-0.183; SE=0.045; P=4.60x10^{-5}), while the factor had a positive genetic correlation with lateral occipital SA (r_g=0.113; SE=0.032; P=5.01x10^{-4}) (**Figure 2**). Follow-up Q_{trait} analyses were conducted to examine whether the genetic associations between the brain traits and the disorders/conditions are well accounted for by the identified latent factor. Q_{trait} index analyses revealed no significant sign of heterogeneity involving the three significant genetically correlated brain traits, indicating that the implication of these brain structures are indeed via the common pathway of the Psych-IR multimorbidity factor (rather than independent pathways of individual psychiatric disorders and somatic IR-related conditions). **Table S4** provides genetic correlation estimates and Q_{trait} results for all brain traits analysed.

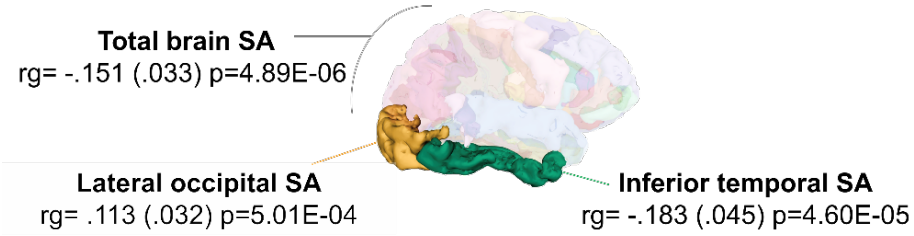

Figure 2. Genetic correlations (rg) between the Psych-IR multimorbidity factor and brain morphometric traits.

Areas highlighted indicate the significant genetic correlations with total brain surface area (SA), lateral occipital SA, and inferior temporal SA. Visualisation was performed using the ENIGMA-Vis tool (Shatokhina et al., 2021).

Multivariate GWAS of the Psych-IR multimorbidity factor

Through a multivariate GWAS of the Psych-IR multimorbidity factor (N_{eff}=622,007.6), we identified 11,672 genome-wide significant SNPs, which were distributed across 168 independent risk loci (**Table S5**). We also performed Q_{SNP} heterogeneity tests in order to identify SNPs that act not through a common multimorbidity factor of psychiatric and IR-related somatic conditions, but directly on one or more of its components. There were 9,324 significant Q_{SNPs} (of which, 2,539 were genome-wide significant SNPs for the Psych-IR factor), indicating that the effects of these SNPs are not fully mediated by the latent genomic factor. Since we are interested

in understanding the shared genetic basis of this multimorbidity, significant Q_{SNPs} were removed from downstream analyses (in order to reduce heterogeneity), along with those in LD (r^2>0.1, 250Kb) with them. The final Psych-IR factor multivariate GWAS summary statistics contains 8,834 genome-wide significant SNPs, distributed across 150 independent loci (**Figure 3; Figure S2**). Out of the 150 independent genomic loci identified, 46 of them did not overlap with the genomic loci associated in the input univariate GWAS of the psychiatric and somatic IR-related conditions that compose the latent factor (**Table S6**).

Genes, gene sets and gene-property associations with the Psych-IR multimorbidity factor

Gene-based analysis identified 366 genome-wide associated genes (**Figure 3**). About one third of the associated genes (N=128) are considered novel, in the sense that they were not significantly associated with the individual phenotypes that compose the factor (i.e., genes were not significant in the individual input GWAS; **Table S7**). Gene-set analyses revealed six gene sets associated with the Psych-IR multimorbidity factor after Bonferroni correction for multiple testing, including one representing insulin binding (GOMF_INSULIN_BINDING; MsigDB M26667) and one implicating NOTCH signalling (REACTOME_SIGNALLING_BY_NOTCH; MsigDB M10189), in addition to four gene sets of general Gene Ontology (GO) Biological Processes (**Table 2**).

Table 2. Gene sets significantly associated with the Psych-IR multimorbidity factor.

Significant gene sets	N_{genes}	P	P_{Bonf}
GOBP_POSITIVE_REGULATION_OF_RNA_METABOLIC_PROCESS	1,657	$1.38x10^{-7}$	0.0023
GOBP_NEGATIVE_REGULATION_OF_BIOSYNTHETIC_PROCESS	1,390	$1.89x10^{-7}$	0.0032
GOBP_POSITIVE_REGULATION_OF_ MACROMOLECULE_BIOSYNTHETIC_PROCESS	1,723	$5.48x10^{-7}$	0.0093
REACTOME_SIGNALLING_BY_NOTCH	183	$7.60x10^{-7}$	0.0129
GOBP_NEGATIVE_REGULATION_OF_NUCLEOBASE_ CONTAINING_COMPOUND_METABOLIC_PROCESS	1,316	$9.03x10^{-7}$	0.0153
GOMF_INSULIN_BINDING	5	$1.58x10^{-6}$	0.0268

Abbreviations: N_{genes}, number of genes included in the gene set; P, MAGMA gene-set association P-value; P_{Bonf}, P-value after Bonferroni multiple testing correction for all the MsigDB gene sets tested.

Furthermore, MAGMA gene-property tissue expression analyses were performed to identify tissue specificity of the gene-based associations of the Psych-IR multimorbidity factor. Upon testing the relationships between the Psych-IR gene-based association results and tissue specific gene expression profiles, there were

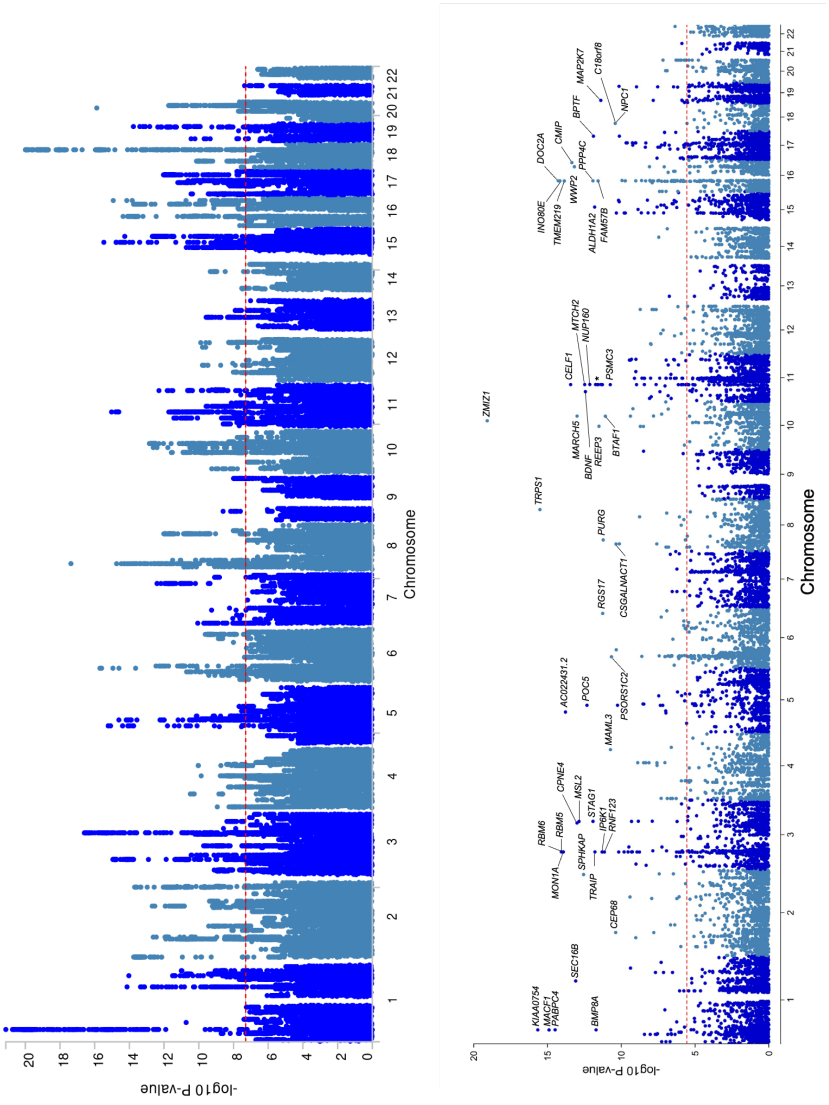

Figure 3. SNP-based (top) and gene-based (bottom) Manhattan plots of the Psych-IR multimorbidity factor multivariate GWAS.
Dotted red line represents the genome-wide significance threshold of 5x10-8 for the SNP-based plot and of 2.78x10-6 (i.e., αBonf=0.05/17,977 protein coding genes) for the gene-based plot. Gene names are shown for the top 50 out of the 366 genome-wide significant genes. The * on chromosome 11 represents the *FNBP4, SPI1, NDUFS3, AGBL2, SLC39A13* genes, in descending order. For a full list of significant genomic loci and associated genes, see **Tables S6** and **S7**.

associations with the brain and pituitary general tissues types (**Figure S3a**). A more fine-grained examination of the tissue types in question revealed that the Psych-IR factor was associated with highly expressed genes in specific brain tissues, namely the cerebellum, cerebellar hemisphere, cortex, and frontal cortex Brodmann Area (BA) 9, as well as the pituitary gland (**Figure S3b**). The tissue expression analyses across 11 different general developmental stages of the brain implicated early, early-mid, and late-mid-prenatal stages (**Figure S3c**), while no associations were found across the brain samples representing 29 different ages of the brain (BrainSpan; Kang et al. (2011)).

Multivariate TWAS

After excluding the MHC region and removing 31 unique genes (spanning 73 different gene-tissue pairs; **Table S9**) with significant Q_{Gene} values, T-SEM identified 462 unique genes whose expressions in the brain were associated with the Psych-IR multimorbidity factor (a heatmap of the most significant genes in each tissue and across tissues is depicted in **Figures S4** and **S5**, respectively; **Tables S10**). Among these, 188 were novel and not significant in any of the univariate TWASs of the input phenotypes (**Tables S11**). Among the top significant up-regulated genes, *MST1R*, *MTCH2*, *RNF123*, *RP11-69E11.4*, *SNF8*, and *BMP8A* were recurrent across several tissues (**Table S11** and **Figure S5**; see also a Miami plot of the analysis including the MHC region in **Figure 4**). These genes are implicated in various biological processes including cell survival, migration and activation of macrophages (*MST1R*); mitochondrial function, apoptosis regulation, and lipid homeostasis (*MTCH2*); vesicle-mediated transport and and protein ubiquitination (*SNF8, RNF123*), and energy balance regulation (*BMP8A*). Among the top significant down-regulated genes, *RBM6*, *INO80E*, *RPAP1*, *C18orf8*, *VPS11*, and *MAPK3* were recurrent across tissues (**Table S11**). These genes are involved in post-transcriptional modification (*RBM6*); chromatin remodelling (*INO80E*); vesicular trafficking (*VPS11*); and signal transduction (*MAPK3*). Of note, seven genes — *ANKDD1B, C17orf58, CRHR1, JMY, MAPT, PAM, and POC5* — demonstrated significant associations with the multimorbidity factor but showed discordant expression effects across different brain tissues (**Table S12**).

In the T-SEM analysis including the MHC region, 37 additional unique genes were significant (**Figure 4**; **Figures S6-S7**), including three novel genes (i.e., *HSD17B8, RPS18, UQCC2*) that were not significant in any of the univariate TWASs (**Table S13**). Among this region, the expression of the *HLA-DRB5* gene was the most frequently associated (significant across 14 tissues) with the multimorbidity factor, followed by *MICB* (12 tissues), and *CYP21A2* (11 tissues) (**Table S14**). Among the up-regulated MHC genes, the most significant were *HCG27* in the brain anterior cingulate cortex,

CYP21A2 in the putamen, and *AGER* in the ACC. *HCG27* is a long non-coding RNA gene involved in various metabolic diseases; *CYP21A2*, a cytochrome P450 monooxygenase involved in mineralocorticoids and glucocorticoids biosynthesis; *AGER* plays a role in inflammatory responses and cellular signalling. Among the down-regulated MHC genes, the most significant were *NOTCH4* in the hippocampus and cerebellum, *C4A* in the cortex, and *HLA-DRB1* in the nucleus accumbens. *NOTCH4*, part of the Notch signalling pathway, is important for cell differentiation, proliferation, and apoptosis; *C4A*, a component of the classic complement pathway, is involved in immune responses and inflammation; *HLA-DRB1*, a major histocompatibility complex class II gene, is involved in antigen presentation and immune system functioning (**Table S15**). These top three down-regulated genes were also the most significant ones among the whole set of MHC-related genes.

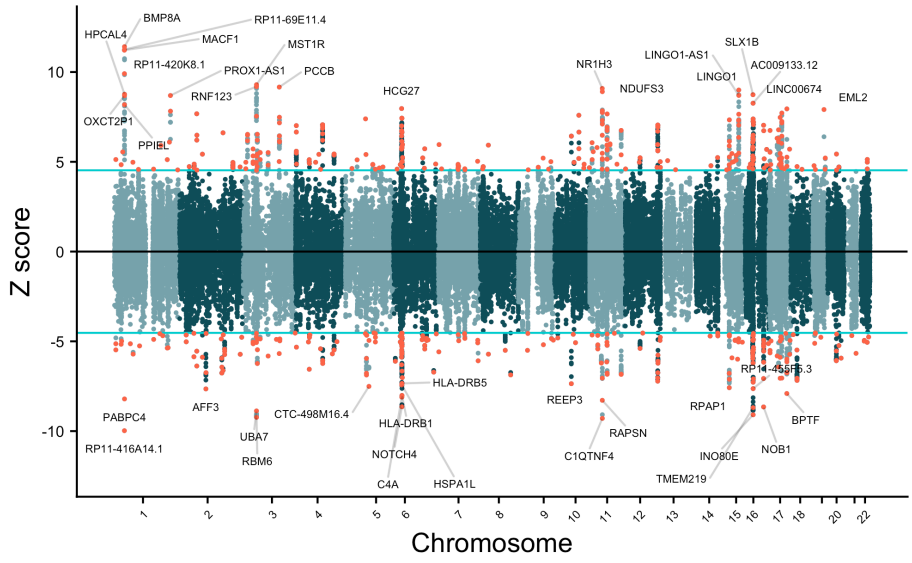

Figure 4. Miami plot of Z statistics for the estimated gene expression effects on the Psych-IR multimorbidity factor.

Z statistics are signed such that orange dots on the upper and lower half of the plot reflect genes whose up-regulated and down-regulated expression, respectively, is significantly associated with the multimorbidity factor. The light blue horizontal lines reflect the Bonferroni-corrected significance threshold. Genes exceeding this threshold are shown as orange dots. For genes significant in multiple tissues, only the most significant instance is highlighted in orange. Up to 40 unique Bonferroni-significant genes are labelled across tissues. Genes having significant Q_{Gene} statistics were not included in this plot.

Potential repurposable drugs

The overlap drug repurposing analysis using the PharmOmics platform identified six potential repurposable drugs for the Psych-IR multimorbidity factor (**Table S16**). Among the evaluated compounds, bevacizumab emerged as a candidate in *Homo sapiens* (human) and demonstrated significant gene overlap in brain tissues. In *Mus musculus* (mouse), the analysis highlighted memantine, rosiglitazone, levodopa, cyclophosphamide, and ceftriaxone as leading candidates for repurposing. Memantine and rosiglitazone, known for their neuroprotective and anti-diabetic properties, respectively, showed robust overlap with the multimorbidity factor gene signatures. Additionally, levodopa, a precursor of dopamine and a commonly used drug in Parkinson's disease, along with cyclophosphamide and ceftriaxone, both of which are involved in immune modulation and neuroprotection, also demonstrated significant overlap.

Enrichment analyses of the Psych-IR prioritised genes

There were 534 protein-coding genes used as input for the combined gene set enrichment analyses, comprising 215 significantly associated genes derived from MAGMA gene-based analysis of the Psych-IR multivariate GWAS, 179 genes derived from the TSEM analyses, and 140 genes that were overlapping between these two approaches. There were 518 genes with unique Entrez IDs, which were compared against a total of 18,605 unique Entrez background protein-coding genes. After FDR correction for multiple testing within category/subcategory, we observed significant enrichments in 110 pre-computed sets from MsigDB (encompassing 104 unique gene sets) and in 201 sets of reported genes from the GWAS-Catalog (**Table S8**). More specifically, these include the significant enrichments in 14 (MsigDB c1) positional gene sets. The most significant enrichment was in position chr16p11, which also had the highest proportion of overlapping genes with the gene set (i.e., 39 overlapping genes out of 97 in the gene set). There were also four significantly enriched (MsigDB c2) curated gene sets, two of which are also related with the chr16p11 region: the WP_16P112_PROXIMAL_DELETION_SYNDROME and the WP_16P112_DISTAL_DELETION_SYNDROME gene sets (both also significant in the analyses within the MsigDB c2:All Canonical Pathways (CP) and the MsigDB c2:CP/WikiPathways subcategories). Additional enrichments were found for three gene sets within the MsigDB c2:CP/WikiPathways subcategory, one of them related to the brain-derived neurotrophic factor (BDNF) signalling pathway and two related to familial hyperlipidaemia; one MsigDB c5:GO:molecular functions gene set; three MsigDB c8 cell type signatures gene sets; and 79 MsigDB c3:Transcription Factor targets gene sets. No significant enrichment was observed among the MsigDB h, MsigDB c2:BioCarta, MsigDB c2:KEGG, MsigDB c2:Reactome, MsigDB c3:microRNA

targets, MsigDB c4:All computational, MsigDB c4:Cancer gene neighborhoods, MsigDB c4:Cancer gene modules, MsigDB c5:GO:biological processes, MsigDB c5:GO:cellular components, MsigDB c6, and MsigDB c7 gene sets.

Discussion

This study leverages state-of-the-art multivariate genomic and transcriptomic methods, including genomic SEM and T-SEM, to explore the genetic architecture underlying the frequent co-occurrence of psychiatric disorders and somatic IR-related conditions. We identified a latent Psych-IR multimorbidity factor representing the shared genomic liability across ADHD, AN, MDD, OCD, MetS, obesity, and T2DM, which provides novel insights into the biological underpinnings of their multimorbidity. The multivariate GWAS of the Psych-IR factor revealed 150 genomic loci and 366 associated genes, with many of these considered novel (i.e., not previously identified by the univariate GWASs that compose the factor). The insulin binding and the Notch signalling pathways were implicated with the Psych-IR factor. Genetic correlation analyses linked the Psych-IR multimorbidity factor to brain morphometry, including structures involved in visual and sensory processing. In addition, a series of tissue specificity analyses implicated specific brain areas, including the cerebellum, the brain cortex, and the pituitary gland. The integration of transcriptomic data by T-SEM revealed that the expression of 462 genes in the brain and pituitary gland is associated with the multimorbidity factor; these included 188 not previously detected in univariate TWASs. Top up-regulated genes, such as *MST1R*, *MTCH2*, and *BMP8A*, suggest roles for immune modulation, mitochondrial function, and energy balance, while down-regulated genes like *RBM6*, *INO80E*, and *MAPK3* highlight disruptions in chromatin remodelling and signal transduction.

Our findings advance the current understanding of the genetic underpinnings of psychiatric and IR-related multimorbidity, building upon previous studies that primarily explored pairwise correlations between psychiatric disorders and IR-related conditions (Fanelli et al., 2022a, 2025; Hübel et al., 2019), which, while informative, do not capture the joint genetic architecture underlying these multiple conditions. Our multivariate approach reveals that psychiatric disorders share common genetic variants and mechanisms with IR-related conditions, albeit with opposite loadings on the Psych-IR factor, highlighting the presence of a joint genetic architecture underlying the multimorbidity. Both the positive loadings for ADHD and MDD on the Psych-IR factor, as well as the negative loading of AN and OCD, are consistent with the direction of their pairwise genetic correlations (Fanelli

et al., 2022a). The divergent pleiotropic effect observed with AN is also consistent with most clinical observations for AN, which is mainly characterised by weight loss, as opposed to the IR-related conditions (Walsh et al., 2023; American Psychiatric Association, 2013). While epidemiological data showed increased co-occurrence of OCD and T2DM (Wimberley et al., 2022), recent familial analyses indicate that parental T2DM was significantly less frequent in individuals with OCD, in line with negative genetic correlations, and indicating that phenotypic associations might be explained by other factors (like psychiatric comorbidities, shared environment or lifestyle factors) (Wimberley et al., 2024). Despite the well-documented clinical overlap between schizophrenia and metabolic dysregulation, particularly in the context of antipsychotic medication use, schizophrenia exhibited a weaker genetic loading and was ultimately not included in the Psych-IR multimorbidity factor. This may reflect the underlying genetic complexity given that previous local genetic correlation analyses indicate both positive and negative genetic local genetic correlations between schizophrenia and IR-related conditions (Fanelli et al., 2025). In addition, the metabolic side effects of antipsychotic medications used for treating schizophrenia include significant weight gain and IR, which are well-established but are likely driven by pharmacological mechanisms rather than by the genetic factors.

A key contribution of this study is the identification of genetic loci implicated in the psychiatric-IR multimorbidity, including novel genes that were not previously associated with individual psychiatric or IR-related phenotypes, while also reinforcing the involvement of established candidate biological pathways implicated in psychiatric-IR multimorbidity. In particular, among the top genes identified by the multivariate GWAS of the Psych-IR factor, the most significantly associated gene was *ZMIZ1*, which regulates transcription factors and interacts with nuclear hormone receptors. This gene shows genome-wide significant association also in the univariate T2DM GWAS and has recently been appointed as a novel regulator of brain development associated with ASD and intellectual disability (K. C. et al., 2024). *DOC2A*, located in the chr16p11 region, is involved with Ca^{2+}-dependent neurotransmitter release and is mainly expressed in the brain. Other top genes are involved with interactions of cytoskeletal elements (e.g., *MACF1*), encoding transcription factors (e.g., *TRPS1*), mRNA stability (e.g., PABPC4), and tumor suppression (e.g., *RBM5, RBM6*). In terms of novel genes, the top three genes (*KCTD13, GDPD3, MAPK3*) are situated in the chromosome 16p11.2 region, discussed in more details below. These are followed by *MST1*, whose receptor, *MST1R*, was the top up-regulated gene in the T-SEM results and is directly involved in immune-inflammatory pathways (Huang et al., 2020). Among the other T-SEM top up-regulated genes across several tissues, *MTCH2* is involved in adipocyte

differentiation and energy production (Peng et al., 2024). *RNF123/KPC1* and *SNF8* are linked to maintaining cellular homeostasis and regulating immunity (Kravtsova-Ivantsiv et al., 2015; Kumthip et al., 2017). Among the top down-regulated genes, *RBM6* and *INO80E* are involved in DNA repair and splicing/chromatin remodelling (Conaway and Conaway, 2009; Machour et al., 2021), pointing to disruptions in gene expression regulation. Among the novel genes, *STX4, EHD4*, and *USP46* participate in neurotransmission and insulin signalling, indicating a dual function in neuronal activity and glucose metabolism, and *ZNF268, MCM9* are involved in transcriptional regulation and genomic stability. Collectively, the novel genes highlight mechanisms that intersect both central nervous system function and peripheral metabolic regulation.

While analyses including the MHC region need to be interpreted cautiously given the genetic complexity due to the extensive LD, high gene density, and considerable allelic diversity of this region, they also highlighted immune-related genes as well. Among them, *HLA-DRB5* is involved in regulating immune responses and has been implicated in various brain-related and metabolic conditions, including SCZ, MDD, Parkinson's disease, and both type 1 diabetes and T2DM (Ahmed et al., 2012; Jacobi et al., 2020; Santiago et al., 2023; Zhao et al., 2016). In addition, the *MICB* gene is a marker of cellular stress and tag cells for elimination triggering the activation of natural killer and CD8+ T cells (Derby et al., 1992) and its association might support the idea that cellular stress-induced immune dysregulation might be a common mechanism in psychiatric-IR multimorbidity. *CYP21A2* is involved in the biosynthesis of glucocorticoids and mineralocorticoids (Slominski et al., 2020). Glucocorticoids affect neuroplasticity and the expression of BDNF, essential for synaptic integrity and cognitive function (Tsimpolis et al., 2024). These findings related to the MHC region align with previous evidence highlighting key genes emerging from genetic annotations of loci correlated between psychiatric and IR-related conditions (Fanelli et al., 2025).

Our gene-set analysis on the Psych-IR multivariate GWAS results highlighted an association with the insulin binding and the Notch signalling pathways, reinforcing the hypothesis that metabolic dysregulation is central to the shared biological basis underlying the multimorbidity observed between psychiatric and IR-related conditions. The insulin binding gene set comprises five genes, three of which - *IDE*, *IGF1R*, and *INSR* - show genome-wide significant associations themselves in the gene-based analyses. *IDE* encodes the insulin-degrading enzyme which has been associated with T2DM, but also plays a role in cognitive processes and neurodegeneration (Henderson and Poirier, 2011) *INSR* encodes for the insulin receptor and insulin binding to this receptor activates pathways such as the PI3K-AKT/PKB pathway, responsible for most metabolic actions, and the Ras-MAPK pathway, which regulates gene expression and cell growth (Boucher et al., 2014).

Dysregulation of these pathways has been implicated in both metabolic and neuropsychiatric outcomes, suggesting a shared mechanistic pathway (Borrie et al., 2017; Chen et al., 2024). *IGF1R* encodes the insulin-like growth factor 1 receptor, which is involved in neurogenesis, synaptic plasticity, and neuroprotective processes (Cardoso et al., 2021; Dyer et al., 2016). Although IGF1R's role has been explored in relation to various cognitive functions (Cardoso et al., 2021), its specific link to the genetic architecture of psychiatric and metabolic comorbidity represents a novel finding in our study, as it was not identified as significant in any of the input univariate GWAS datasets. While the potential involvement of insulin signalling in psychiatric disorders is not a new concept (McIntyre et al., 2010), our findings clearly highlight the association of such a core insulin-related gene set with a genetic latent factor encompassing both conditions. This reinforces the need to explore this pathway further as a gateway for managing the co-occurrence of psychiatric disorders and somatic IR-related conditions.

Another gene set that showed significance to the Psych-IR factor was the Notch signalling pathway, which has also garnered attention for its potential role in both IR and the brain. Notch signalling is involved in the regulation of metabolic processes, particularly in the liver and adipose tissues. For instance, active Notch signalling correlates with IR and nonalcoholic fatty liver disease, indicating that Notch signalling may influence glucose metabolism through its effects on hepatic function (Valenti et al., 2013). Additionally, a mouse model overexpressing the Notch intracellular domain in adipocytes led to severe IR, thereby establishing a direct link between Notch signalling and metabolic dysregulation (Chartoumpekis et al., 2018). Noteworthy, Notch signalling was also involved in learning, memory, and social behaviour, which are often disrupted in psychiatric disorders (Salazar et al., 2020), and it has also been implicated in neurodevelopment, neuronal connectivity and neurogenesis (Zhang et al., 2018), although a direct link with psychiatric disorders is currently missing (Salazar et al., 2020).

Subsequently, when combining the genome-wide significant genes from the Psych-IR multivariate GWAS with the associated genes from the T-SEM analyses, additional gene sets were implicated through the significant enrichment of our prioritised genes. Noteworthy are the ones related to proximal and distal chromosome 16p11.2 deletion syndrome, the BDNF signalling pathway, and the ones related to familial hyperlipidaemia (types 3 and 4). Both the proximal and distal 16p11.2 deletion syndromes are rare genetic conditions caused by the deletion of around a 600kb and a 220 kb region, respectively, of chromosome 16 (OMIM#611913 and OMIM#613444, respectively). They are both characterised by symptoms related to both psychiatric and IR-related phenotypes, and mild intellectual disability and speech problems are also frequent among individuals

with 16p11.2 deletion syndromes. Over 80% of the carriers of the proximal 16p11.2 deletion exhibit psychiatric disorders and obesity is a major comorbidity, affecting 50% of the carriers by age 7 and with a penetrance of 70% among adults (Zufferey et al., 2012). In a study comparing different 16p11.2 deletions, the vast majority of the individuals with proximal 16p11.2 deletion syndrome had developmental delays (85.5%), 19.4% autism spectrum disorder (ASD), 27.3% ADHD, 29.5% obesity, and 41% reported hyperphagia (Vos et al., 2024). In the same study, cases with distal 16p11.2 deletion showed the most severe obesity phenotype (73.7% obesity), with most cases presenting hyperphagia (61.1%), 40% intellectual disability, and 22.2% ASD (Vos et al., 2024). The enrichment of the BDNF signalling pathway also highlights a potential role of BDNF in bridging metabolic and psychiatric disorders. During development, the protein encoded by the *BDNF* gene promotes neuronal survival and differentiation and regulates synaptic plasticity, essential for adaptive neuronal responses, including long-term potentiation, and homeostatic regulation of excitability (Park and Poo, 2013; Rutherford et al., 1998). Its involvement in psychiatric conditions such as MDD, SCZ, and anxiety disorders is well-documented (Castrén and Kojima, 2017; Molendijk et al., 2014). Beyond its neural functions, BDNF plays a significant role in metabolic regulation. BDNF signalling intersects and shares downstream mechanisms with insulin pathways through its binding to tyrosine kinase B (TrkB) receptor (Bathina and Das, 2015). Moreover, low BDNF levels are associated with glucose impairment and lipid dysregulation, further implicating BDNF in metabolic health (Krabbe et al., 2007; Xia et al., 2022). This interaction is reinforced by findings that IR promotes neuroinflammation, which can impair BDNF signalling, creating a vicious cycle that exacerbates both metabolic and psychiatric conditions (Lima Giacobbo et al., 2019; Wei et al., 2021). Interventions such as exercise, which increase BDNF levels, have been shown to improve both insulin sensitivity and cognitive function (Dadkhah et al., 2023). Therefore, pharmacological strategies targeting BDNF signalling pathways could offer new avenues for treating metabolic and psychiatric disorders concurrently. We also observed significant enrichment of gene sets associated with familial hyperlipidaemia types 3 and 4. Type 3 primarily involves impaired clearance of intermediate-density lipoproteins (IDL) due to mutations in the *APOE* gene, of which the protein plays a role in lipid transport and metabolism (Javvaji et al., 2024). *APOE* is also one of the Psych-IR genome-wide significant genes, and the most well-known risk gene for Alzheimer's disease (Jackson et al., 2024). Familial hyperlipidaemia type 4, or familial hypertriglyceridaemia, involves increased levels of VLDL in the blood, driven by both enhanced production and decreased clearance (Goyal et al., 2024). Dyslipidaemia is a common feature in both psychiatric conditions, such as MDD and SCZ, and somatic ones like MetS, where lipid abnormalities may exacerbate IR

by promoting chronic inflammation, oxidative stress, and endothelial dysfunction (Higashi, 2023; Zorkina et al., 2024). The enrichment of these gene sets suggests a role for lipid metabolism in the pathophysiology of the multimorbidity of psychiatric and IR-related conditions.

In terms of brain morphometry implication, our analysis revealed significant negative genetic correlations between the Psych-IR multimorbidity factor and both total SA and inferior temporal SA. The inferior temporal cortex is primarily involved in visual processing, especially object and face recognition (Conway, 2018), as well as the retrieval of visual memories (Mruczek and Sheinberg, 2007). This region has been closely linked to metabolic dysfunctions, including obesity and IR (Morris et al., 2014; Opel et al., 2021). For instance, a Mendelian randomisation study demonstrated that higher waist-hip ratio causally reduces the surface area of the inferior temporal cortex (Chen et al., 2023). In addition, positive genetic correlation was found for the Psych-IR multimorbidity factor and the lateral occipital cortex, which is involved in the perception of shapes and forms, as well as the processing of visual stimuli in a multisensory context (Zhang et al., 2004). Altered glucose metabolism in this region has been linked to cognitive impairments in various conditions, including SCZ and T2DM (Wijtenburg et al., 2019). Studies have demonstrated that hypoperfusion in the occipital regions, including the lateral occipital cortex, correlates with higher IR and deficits in visual memory performance, particularly in patients with T2DM (Cui et al., 2017). This aligns with findings that neuronal IR biomarkers are significantly associated with memory measures and brain glucose levels, particularly in visual processing areas like the lateral occipital cortex (Wijtenburg et al., 2019). Consistent with our findings, previous studies found that IR is associated with smaller cortical gray matter volume, but not with subcortical gray matter volume in individuals with MetS (Lu et al., 2021). Another link to the brain is found in the tissue expression specificity of the Psych-IR gene associations, where our findings reveal that the Psych-IR multimorbidity factor is significantly associated with genes highly expressed in the pituitary gland and brain tissues, implicating specifically the cerebellum/cerebellar hemisphere, and cortex/frontal cortex BA 9. While the cerebellum and cerebellar hemisphere have traditionally been linked to motor control, recent studies increasingly recognise their roles in cognitive and emotional regulation, as evidenced by studies linking cerebellar dysfunction to various psychiatric conditions, including mood disorders (Adamaszek et al., 2017; Schmahmann, 2019). Recent evidence indicates that individuals with high IR exhibit reduced gray matter volume and altered functional connectivity in the cerebellum, suggesting that IR can lead to significant neuroanatomical and functional connectivity changes in this region (Chen et al., 2014; H.-Y. Zhang et al., 2024). IR also correlates with reduced glucose metabolism

in the cerebellum and frontal regions (Y. Chen et al., 2022). The frontal cortex, particularly BA 9, plays a role in executive functions, including decision-making, working memory, and cognitive control (Friedman and Robbins, 2022; Miller and Cohen, 2001), all of which are processes heavily implicated in psychiatric disorders. Previous work indicates that insulin signalling is essential for maintaining synaptic plasticity and neuronal health in the frontal cortex, and disruptions in insulin signalling can impair cognitive functions linked to the frontal cortex (Arnold et al., 2018b; Fanelli et al., 2022b; Kleinridders et al., 2014). The observed association with gene expression in the pituitary gland might suggest a link to the hypothalamic-pituitary-adrenal (HPA) axis, which regulates both the stress response and metabolic function. Dysregulation of the HPA axis is a well-established factor in psychiatric disorders and metabolic conditions, and might indicate a shared pathway that influences both groups of phenotypes and their co-occurrence (Joseph and Golden, 2017; Stetler and Miller, 2011). Moreover, the association of gene expression with early, early-mid, and late-mid prenatal developmental stages suggests that the genetic factors underlying the Psych-IR factor may exert their effects during critical periods of brain development. This finding aligns with the hypothesis that prenatal or early-life factors can shape the long-term risk for both metabolic and psychiatric disorders (Edlow, 2017). Prenatal exposures, such as maternal stress, poor nutrition, or gestational diabetes, could interact with genetic predispositions to alter brain development, thereby increasing susceptibility to both psychiatric disorders and metabolic dysregulation in offspring (Van Lieshout et al., 2011).

From a clinical perspective, our results indicating a shared genetic aetiology between multiple psychiatric and psychiatric and IR-related somatic conditions highlights the need for a holistic approach in medicine, integrating both worlds in clinical care. Through the genomic approaches addressed in this manuscript we identified potential drug repurposing candidates, including memantine, rosiglitazone, levodopa, cyclophosphamide, bevacizumab, and ceftriaxone, that could offer possibilities for developing targeted therapeutic strategies aimed at addressing both psychiatric symptoms and IR. Memantine, an NMDA receptor antagonist, has shown efficacy in improving cognitive and negative symptoms in SCZ, as well as in counteracting excessive glutamate neurotransmission and related neurotoxicity in Alzheimer's disease (Czarnecka et al., 2021; Zheng et al., 2018), and rosiglitazone, a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, enhances neuronal insulin receptor function and provides neuroprotective effects (McIntyre et al., 2007; Pipatpiboon et al., 2012). Cyclophosphamide, an immunosuppressive agent, shows promise in managing severe IR and autoimmune encephalitis, which often accompany psychiatric symptoms (Dinoto et al., 2022; Yang et al., 2017). Bevacizumab, an anti-VEGF monoclonal antibody, could

enhance glucose uptake via the upregulation of glucose transporters in response to the induced hypoxia, and it has been shown to improve cognitive function in a Alzheimer's disease animal models (Heijmen et al., 2014; Kuang et al., 2017; M. Zhang et al., 2024). Other drug repurposing candidates might need careful consideration, like levodopa, used for Parkinson's disease management due to its potential to exacerbate IR and disrupt glucose regulation, particularly in patients with pre-existing metabolic conditions (Smith et al., 2004). Ceftriaxone, a third generation cephalosporin antibiotic, presents challenges due to its impact on gut microbiota, which can lead to dysbiosis and decreased short-chain fatty acid production, ultimately exacerbating IR (Holota et al., 2019; Miao et al., 2021). Future research might prioritise the most promising candidates, which could be considered for further investigation in randomised-controlled trials as potential therapies for psychiatric-IR multimorbidity.

The strengths of this study lie in the use of large-scale GWAS datasets, advanced genomic SEM techniques, and the integration of transcriptomic data, which collectively provide a robust and comprehensive analysis of the genetic underpinnings of psychiatric and IR-related multimorbidity. These approaches allowed us to identify shared genetic factors that may not be detectable through traditional, univariate GWAS/TWAS analyses, thereby offering novel insights into the genetic and biological bases of psychiatric-IR multimorbidity. However, this study also has some limitations. First, our understanding of the functions of the identified genes and their roles in molecular pathways remains incomplete. While the discovery of novel loci is promising, further research is needed to elucidate their precise biological functions and how they contribute to the shared risk for psychiatric and IR-related conditions. Another limitation is the reliance on GWAS summary statistics derived from European ancestry populations, which may limit the generalisability of our findings to other populations. This issue highlights the need for more diverse genetic studies to ensure that our findings are applicable across different ethnic groups. The reliance on gene expression profiles from nervous tissues presents significant challenges, particularly given the often non-linear relationships between gene expression, protein function, and therapeutic efficacy (Munro et al., 2024). The T-SEM approach, while powerful in identifying tissue-specific gene expression effects across multiple genetically correlated traits, operates under the assumption that gene expression effects are consistent across all studied traits, potentially oversimplifying the complexity of biological interactions (Grotzinger et al., 2022a). In this respect, we employed the Q_{Gene} statistic in an attempt to mitigate the risk of false-positive findings that could arise from such assumptions (Grotzinger et al., 2022a). However, the dynamic nature of gene regulation, epigenetic modifications, and the impact of environmental exposures

can still exert tissue- or cell type-specific effects that might not be detected by our model (Pascual-Ahuir et al., 2020). Additionally, the drug repurposing results, while compelling, should be interpreted with much caution. Specific to drug repurposing, the relatively lower availability of human brain tissue samples remains a significant limitation. Moreover, the potential for off-target effects when repurposing drugs identified through gene expression overlaps must be carefully evaluated.

In conclusion, this study identified a common genetic factor underlying psychiatric and IR-related conditions, encapsulated by the Psych-IR multimorbidity factor. Overall, our findings suggest that the associated genetic factors are likely involved in pathways that regulate both brain function and metabolic processes, particularly during critical developmental windows. These findings have significant implications for our understanding of the co-occurrence between IR-related conditions and psychiatric disorders, providing new insights into the biological mechanisms that contribute to these comorbidities. Furthermore, the integration of genomic and transcriptomic data has identified potential candidate biomarkers and therapeutic targets, thereby providing the basis for the development of novel interventions. As research in this area continues to evolve, these findings have the potential to inform both scientific research and clinical practice, ultimately contributing to improved outcomes for patients with these co-occurring conditions.

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Chapter 8

General discussion

Overview of key findings

In this thesis, I investigated the relationship between insulin resistance (IR)-related conditions and neuropsychiatric disorders through a multi-layered approach integrating epidemiological, clinical, genomic, and transcriptomic analyses. Data sources included large-scale population studies, such as the UK Biobank, and well-powered genome-wide association studies (GWASs), complemented by advanced statistical methods to examine potential shared genetic architecture and biological pathways. Across **Chapters 2–7**, multiple research approaches converged to address the overarching question: to what extent do metabolic disturbances associated with IR contribute to neuropsychiatric disorders, and vice versa, at clinical, cognitive, and molecular levels?

In the first part of this thesis, I examined the epidemiological and clinical association of IR-related cardio-metabolic conditions and traits with cognitive functioning in a large population cohort, the UK Biobank. A systematic review of published studies using data from this cohort (**Chapter 2**) documented consistent evidence that type 2 diabetes mellitus (T2DM), obesity, hypertension, and other IR-related conditions correlate with poorer cognitive performance across multiple domains. The most consistent findings referred to IR-related associations with poorer verbal and numerical reasoning ability, as well as slower processing speed. These associations remained significant even after taking into account socio-demographic and lifestyle confounding variables. Potential mechanisms that could mediate the observed associations included neuroinflammation, cerebrovascular damage, and altered insulin signalling in the brain.

Expanding on this, the effects of metabolic dysfunction on psychiatric disorders, particularly mood disorders, were reviewed in **Chapter 3**. This chapter highlighted a bidirectional association between T2DM and major depressive disorder (MDD)/bipolar disorder (BD) based on longitudinal data. Individuals with T2DM exhibited higher rates of depression with more severe symptoms, while those with MDD or BD had an elevated risk of developing T2DM, along with higher rates of vascular complications and mortality. Mendelian randomisation (MR) studies demonstrated a causal effect of MDD on T2DM in Europeans, while a suggestive causal association in the opposite direction was found in East Asians (**Chapter 3**). These observations reinforce the hypothesis that shared pathophysiological mechanisms may underlie both conditions, contributing to their high comorbidity. Building upon these epidemiological and genetic insights, in **Chapter 4** I examined the potential clinical implications of IR-related conditions on depression treatment outcomes using primary care data linked to the UK Biobank. Analyses of prescription histories, IR-related conditions, and diagnostic codes indicated that individuals with T2DM,

obesity, or cardiovascular diseases (CVDs) show higher odds of treatment-resistant depression (TRD), more frequent antidepressant switches, and longer treatment durations than those without IR (**Chapter 4**). While these findings do not establish causal effects, they support the potential clinical relevance of incorporating metabolic biomarkers such as body mass index (BMI), fasting glucose, and glycated haemoglobin into psychiatric assessments. Furthermore, these findings raise the possibility that interventions targeting insulin sensitisation could be explored as adjunctive treatments for mood disorders.

While clinical and epidemiologic evidence (**Chapters 2**, **3**, and **4**) indicated a clear link of IR-related conditions with neuropsychiatric disorders and related traits, it was unclear whether genetic and biological factors were of importance for these associations. To address the option that part of the neuropsychiatric-IR multimorbidity is due to shared biological mechanisms, I devoted a major part of this thesis to the genetic dissection of shared liability of neuropsychiatric disorders and IR-related conditions (**Chapters 5**, **6**, and **7**). Using publicly available summary statistics of relevant large-scale GWASs as input, I was able to show that psychiatric disorders such as MDD and attention-deficit/hyperactivity disorder (ADHD), display positive global genetic correlations with IR-related conditions, thereby supporting a shared genetic basis for the observed epidemiological overlap (**Chapter 5**). In contrast, anorexia nervosa (AN), obsessive-compulsive disorder (OCD), and schizophrenia showed negative genetic correlations with IR-related conditions and traits, suggesting possible opposite genetic influences (**Chapter 5**). Despite the robust genetic associations observed between IR-related traits and several neuropsychiatric disorders, an apparent exception was AD. Although epidemiological studies had consistently reported a strong link between AD and IR-related metabolic disturbances (Ferreira et al., 2018), no significant global genetic correlation between AD and IR-related conditions was identified in these analyses. To explore this further, I used a more granular approach to dissect the genetic relationship between these conditions. I showed that for neuropsychiatric disorders where global genetic correlations with IR-related conditions were absent, local genetic analyses could find significant genetic correlations that were unobservable in global approaches (**Chapter 6**). Using Local Analysis of [co]Variant Association (LAVA) (Werme et al., 2022), heterogeneous local patterns of genetic overlap were identified across different genomic regions. Even in cases where no global genetic correlation was detected, local genetic correlations of opposite direction were observed at specific loci, indicating that shared genetic influences between psychiatric and metabolic conditions may be confined to discrete genomic regions rather than acting in a uniform manner across the genome. This regional dissection refined the global genetic correlation findings and demonstrated that the genetic

basis of psychiatric–metabolic multimorbidity is far from homogeneous, with both positive and negative genetic correlations observed at the locus-specific level (**Chapter 6**). Building upon these findings, in **Chapter 7**, I further expanded the genetic investigation by employing genomic SEM and T-SEM analyses to model the shared genetic architecture of psychiatric and IR-related conditions in a multivariate framework (Grotzinger et al., 2022; Grotzinger et al., 2019). I included genetic data of a total of five psychiatric disorders (ADHD, AN, MDD, OCD, and schizophrenia) and three IR-related conditions (metabolic syndrome [MetS], obesity, T2DM), for which global genetic correlations have previously been demonstrated (**Chapter 7**). This approach identified a latent multimorbidity factor reflecting shared genetic influences across psychiatric disorders—excluding schizophrenia—and IR-related conditions. Several novel genes that had not been found significant in any of the univariate GWASs and transcriptome-wide association studies (TWASs) of the individual disorders were identified, suggesting that the multimorbidity genetic factor captures biological processes that may not be fully detectable through single-trait analyses.

A deeper investigation of the biological pathways underlying this genetic overlap provided further insights into the molecular mechanisms linking psychiatric disorders and IR-related conditions. A major component of this shared genetic risk was traced to genomic regions enriched for immune-related genes, particularly within the major histocompatibility complex (MHC) region on chromosome 6 (**Chapter 6** and **7**). Findings in **Chapter 6** showed that these immune-related loci accounted for a substantial proportion of the genetic overlap between psychiatric and IR-related conditions, suggesting that dysregulated immune signalling may represent a core mechanism underlying this multimorbidity. The genetically correlated regions identified in **Chapter 6** were enriched in pathways implicated in immune-inflammatory processes, as well as in protein/vesicle trafficking, insulin signalling, lipid metabolism, and oxidative phosphorylation (energy production). To further assess whether these local genetic correlations reflect shared causal variants rather than linkage disequilibrium-driven associations, colocalisation analyses were performed (**Chapter 6**). Through these analyses, I identified specific loci where the same variants contribute to both psychiatric and IR-related conditions. The most notable colocalised signals mapped to genes regulating immune response, lipid metabolism, protein/vesicle trafficking, organ development, retinoic acid signalling, and DNA repair/apoptosis. Overlapping expression quantitative trait loci (eQTL) signals in immune/metabolic genes were also identified, suggesting that gene expression modulation in these loci could play a role in shaping both neuropsychiatric and metabolic disease risk (**Chapter 6**). In parallel, gene-set analyses of the latent multimorbidity factor (**Chapter 7**) also identified specific

biological pathways that may serve as mechanistic links between psychiatric and IR-related conditions. One of the most significant findings was the involvement of insulin-related pathways, particularly those regulating insulin binding. Additional candidate insulin-related pathways were identified using bivariate gene-set stratified genetic covariance analyses (**Chapter 5**). Specifically, genetic covariance was found between neuropsychiatric disorders and IR-related somatic conditions through the insulin receptor recycling, insulin processing, and regulation of insulin secretion pathways (**Chapter 5**). These results suggest that insulin signalling may be an important factor contributing to psychiatric–IR multimorbidity. The Notch signalling pathway emerged as another significant pathway associated with the multimorbidity factor, implicating cell fate determination, neurogenesis, and metabolic regulation processes (**Chapter 7**). Tissue-specific analyses in **Chapter 7** provided additional insights into the neurobiological substrates of psychiatric–IR multimorbidity. Genes associated with the multimorbidity genetic factor were enriched in genes expressed in the pituitary gland and brain, particularly in the cerebellum, cortex (including Brodmann Area 9), and frontal cortex. Among the most significant genes identified in the T-SEM analyses were *MST1R* and *MAPK3*, suggesting potential molecular mechanisms linking immune regulation, neuronal plasticity, and metabolic processes. Other strongly associated genes included *MTCH2*, involved in mitochondrial function and lipid homeostasis, and *SNF8*, which plays a role in vesicular transport. A complementary analysis of the transcriptomic data including the MHC region further highlighted other immune-related genes, such as *HLA-DRB5* and *MICB*, reinforcing the potential role of immune signalling in psychiatric–metabolic multimorbidity. The enrichment analysis of prioritised genes from genomic SEM and T-SEM results identified additional pathways of interest (**Chapter 7**). Notably, the strongest enrichment was observed for genes located in the chromosome 16p11.2 region, a locus previously implicated in both psychiatric disorders and metabolic dysregulation. This region has been linked to neurodevelopmental disorders, obesity, and cognitive dysfunction (Chung et al., 2021). Additional significant enrichments included the brain-derived neurotrophic factor (BDNF) signalling pathway, which plays a role in synaptic plasticity and neuronal survival, as well as pathways involved in lipid metabolism and familial hyperlipidaemia.

Considering the clinical associations found between mood disorders and IR-related conditions, an essential question explored in **Chapters 3**, **6**, and **7** was whether any pharmacological interventions targeting metabolic or other pathways could be useful in the context of psychiatric-IR multimorbidity. This was explored through the review of existing evidence, as well as new exploration of druggable genes and drug repurposing analyses. Several medications were highlighted in

these chapters, including metformin, pioglitazone, and Glucagon-like peptide-1 receptor agonists (GLP-1RAs) (**Chapter 3**), which have been investigated for their antidepressant and pro-cognitive properties. Metformin, primarily used as an insulin sensitiser, has been associated with improved depressive symptoms in individuals with metabolic dysfunction, possibly through mechanisms related to neuroinflammation and mitochondrial function. Pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, showed potential benefits in TRD, with some studies indicating effects on neurogenesis and inflammatory pathways. GLP-1RAs, such as liraglutide, have garnered attention for their neuroprotective and anti-inflammatory properties, with preliminary evidence suggesting cognitive benefits and antidepressive effects in individuals with IR-related conditions (Mansur et al., 2017; Pozzi et al., 2019). These findings suggest that metabolic interventions may hold promise in psychiatric treatment strategies, particularly in cases where standard psychotropic medications have shown limited effectiveness. Beyond these known metabolic agents, new drug repurposing opportunities were identified through colocalisation analyses (**Chapter 6**) and transcriptome-based drug screening (**Chapter 7**). Colocalisation analyses (**Chapter 6**) pinpointed genetic regions where the same causal variants likely contribute to both psychiatric and IR-related conditions, identifying druggable targets within immune function, lipid metabolism, vesicle trafficking, and DNA repair/apoptosis pathways. Among the genes mapped to the shared most likely causal variants, *HLA-DRB1* gene product is already targeted by multiple drugs, including immunosuppressants (azathioprine, interferons-β), anti-inflammatory agents (acetylsalicylic acid, statins), and psychotropic drugs (carbamazepine, lamotrigine). Other products of genes, such as *HLA-DQB1* and *FADS1/2*—involved in immune regulation and lipid metabolism, are already targeted by existing antihypertensive drugs, omega-3/6 polyunsaturated fatty acids (PUFAs), and vitamin A, indicating potential metabolic and neuroimmune intervention points. To extend these findings, transcriptome-based drug repurposing analyses (**Chapter 7**) identified pharmacological compounds with potential relevance for psychiatric–IR multimorbidity. Using the PharmOmics platform (Chen et al., 2022), six candidate drugs were highlighted, based on their ability to reverse disorder-associated gene expression signatures. In human data, bevacizumab was identified as a potential neurovascular modulator. In mouse models, the strongest candidates included memantine, rosiglitazone, levodopa, cyclophosphamide, and ceftriaxone. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is known for its neuroprotective properties and has been studied for cognitive dysfunction and treatment-resistant psychiatric disorders (Aljuwaiser et al., 2023). Rosiglitazone, a PPAR-γ agonist with insulin-sensitising and anti-inflammatory effects, showed strong overlap with genetic

signatures of psychiatric–IR multimorbidity, aligning with previous evidence of possible efficacy of pioglitazone on depressive symptoms (Moulton et al., 2018). Levodopa, a dopamine precursor commonly used in Parkinson's disease, emerged as another candidate, although its effects on glucose metabolism and IR require further investigation. Cyclophosphamide and ceftriaxone, both involved in immune modulation and neuroprotection, also demonstrated significant overlap with disease-relevant transcriptomic profiles. Taken together, these results suggest that existing metabolic and neuroimmune-modulating drugs may hold potential for addressing psychiatric–IR multimorbidity.

To summarise, these findings provide a coherent framework demonstrating convergent evidence for a bidirectional relationship between neuropsychiatric disorders and IR-related metabolic conditions at multiple levels. While conventional views often treat metabolic conditions and neuropsychiatric disorders as separate entities, the empirical observations and genomic findings described in this thesis reveal interconnected mechanisms. The identification of colocalised signals between neuropsychiatric disorders and IR-related conditions further refines this understanding, showing that some genetic variants are likely to exert a shared causal effect across metabolic and neuropsychiatric domains. The potential pharmacological relevance of these genes suggests that metabolic and antidiabetic and immune-targeting drugs may warrant further investigation in psychiatric conditions, particularly for individuals with high IR burden.

Contextualisation of findings within the existing literature and integration across chapters

The findings presented in **Chapters 2** to **7** provide converging evidence for a connection between neuropsychiatric disorders and IR-related conditions across multiple levels, ranging from epidemiological associations to shared genetic architecture and transcriptomic signatures. However, this relationship is not uniform across disorders, nor does it follow a simple linear association. Instead, the results reveal substantial heterogeneity in shared genetic risk across different neuropsychiatric and IR-related metabolic conditions. This heterogeneity is particularly evident in the contrasting patterns of global versus local genetic correlations, several biological pathways implicated in shared risk, and the varying degrees to which neuropsychiatric disorders align with or diverge from IR-related metabolic traits at the genetic level (**Chapters 5-7**).

Heterogeneity in genetic overlap between psychiatric disorders and metabolic dysregulation

Metabolic dysfunction emerges as a substantial determinant of psychiatric disorder trajectories, influencing cognitive outcomes, treatment response, and disorder chronicity. Observational data from **Chapters 2** to **4** demonstrated that individuals with IR-related conditions, including T2DM, obesity, and hypertension, exhibited poorer cognitive performance, increased rates of TRD, and more severe mood disorder phenotypes. Complementing these clinical findings, genetic analyses from **Chapters 5** to **7** demonstrated distinct patterns of genetic correlation between psychiatric and IR-related metabolic traits. While MDD and ADHD exhibited only positive genetic correlations with IR-related conditions at both global and local levels, the genetic relationship was more complex for AN, OCD, and schizophrenia. These three psychiatric disorders warrant specific attention because they deviate from the patterns observed in other psychiatric conditions. Schizophrenia presents a paradox: despite its high clinical burden of metabolic dysfunction (Freyberg et al., 2017; Manu et al., 2015), global genetic correlations indicate a protective effect, raising questions about the influence of environmental and pharmacological factors. In contrast, AN consistently shows negative genetic correlations with IR-related conditions at both the global and local levels, reflecting a metabolic profile that is distinct from most other psychiatric disorders. OCD, while also showing negative global genetic correlations, exhibits both negative and positive local genetic correlations. Clinical data indicate a heightened risk of metabolic complications in OCD (Isomura et al., 2018), suggesting that genetic and environmental factors interact in distinct ways across these disorders. Examining these contrasting patterns is important for understanding how genetic predisposition, medication effects, and physiological mechanisms contribute to metabolic variation in psychiatric conditions.

Schizophrenia, in particular, exhibited negative global genetic correlations with MetS and BMI, but no significant associations were observed with other IR-related diseases/traits (e.g., T2DM, fasting glucose, fasting insulin, glycated haemoglobin [HbA1c], and homeostatic model assessment for IR [HOMA-IR]). Nonetheless, clinical and epidemiological evidence suggests that individuals with schizophrenia are at increased risk of metabolic dysfunction (Freyberg et al., 2017; Manu et al., 2015), particularly in the context of antipsychotic treatment (Burschinski et al., 2023). This discrepancy raises the possibility that the protective genetic effects observed at the global level may be overridden by environmental and pharmacological factors, or that specific loci may interact with environmental exposures to increase the metabolic risk in patients with schizophrenia. Further supporting this hypothesis, a recent study identified shared genetic loci between antipsychotic-induced weight

gain and metabolic traits, primarily implicating loci involved in lipid pathways rather than insulin signalling mechanisms (Gezsi et al., 2024). This suggests that while genetic factors linked to schizophrenia itself may exhibit certain genetic protections against metabolic dysfunction, medication exposure introduces an additional layer of metabolic risk, with specific genetic variants (e.g., mapping to the *PEPD* and *PTPRD* loci) predisposing some individuals to antipsychotic-induced weight gain (Gezsi et al., 2024). Notably, the presence of both protective and risk-associated genetic influences within schizophrenia is further underscored by local genetic correlation analyses (**Chapter 6**), which reveal that certain genomic regions contribute to metabolic risk despite an overall negative genetic correlation with BMI and MetS. This heterogeneous pattern of local genetic correlations contrasts with AN, where all local correlations were consistently negative across loci as were global correlations with IR-related metabolic conditions (**Chapters 5** and **6**). This suggests that while schizophrenia may involve bidirectional genetic mechanisms that variably influence metabolic outcomes, AN appears to be characterised by a distinct genetic profile that is more markedly opposed to IR.

We can speculate that the heterogeneity in genetic correlations for schizophrenia and IR-related conditions may reflect variability in symptom domains, as studies have shown that dysglycaemia is particularly associated with greater severity of negative symptoms and cognitive impairments in schizophrenia, while positive symptoms showed mixed associations (Perry et al., 2017). Further supporting these findings, large-scale genomic analyses have highlighted distinct metabolic signatures associated with schizophrenia (Meer et al., 2024; Rodevand et al., 2023). An extensive study assessing the genetic overlap between psychiatric disorders and 249 circulating metabolic markers by using Linkage Disequilibrium Score Regression (LDSC) and bivariate Gaussian mixture modelling (MiXeR) found that MDD exhibited strong positive genetic correlations with lipid metabolites, amino acids, and inflammation-related markers, displaying a pattern similar to that observed between the same metabolites and T2DM, BMI and coronary artery disease. In contrast, schizophrenia and BD showed inverse genetic correlations with these metabolic traits. Notably, the overall pattern of genetic correlations across metabolic markers was strongly inversely related between MDD and schizophrenia ($r = -0.83$) and between MDD and BD ($r = -0.74$), indicating that while MDD shares genetics with metabolic traits, schizophrenia and BD exhibit an opposite pattern (Meer et al., 2024). Similarly, another study analysed genetic overlap between schizophrenia and CVD risk factors using MiXeR and conjunctional false discovery rate (conjFDR) analyses (Rodevand et al., 2023). The study identified extensive polygenic overlap between schizophrenia and smoking initiation and BMI, with mostly opposite effect directions for BMI. This could suggest that while schizophrenia may exhibit

an inverse genetic correlation with obesity, local genetic effects and environmental factors (e.g., smoking-related traits, antipsychotic-induced metabolic side effects) contribute to increased cardio-metabolic risk in affected individuals. Expanding on these insights, MR analyses further investigated the causal relationships between metabolic markers and psychiatric disorders (Rodevand et al., 2023). Findings indicated bidirectional effects between schizophrenia, MDD, and BD with specific metabolic markers, including docosahexaenoic acid (DHA) and glycoprotein acetyl—an inflammatory biomarker. However, the relationship with MDD was stronger than with schizophrenia and BD, with metabolic dysfunction playing a more pronounced role in its biological underpinnings (Meer et al., 2024).

In my work presented in **Chapter 5** and **6**, AN exhibited stronger and more consistent negative genetic correlations across IR-related traits and genomic loci than schizophrenia, which showed significant inverse correlations only with BMI and MetS. Unlike schizophrenia, where metabolic risk is influenced by both protective and risk-associated genetic factors and further modulated by environmental and pharmacological exposures, AN appears to follow a distinct genetic profile that is inherently opposed to the genetic risk for metabolic dysfunction (**Chapter 5** to **7**). The absence of local genetic correlations in a positive direction further supports this observation, suggesting that the genetic architecture of AN is more aligned with metabolic efficiency and insulin sensitivity rather than IR-related risk (**Chapter 6**). This genetic profile aligns with clinical and physiological findings that individuals with AN exhibit enhanced insulin sensitivity, increased lipid oxidation, and an adaptive energy conservation phenotype (Ilyas et al., 2019). Unlike other psychiatric disorders, where metabolic dysfunction is often associated with symptom severity and poorer clinical outcomes (**Chapter 3** and **4**), AN appears to be characterised by a metabolic state that is distinct from the broader psychiatric-IR multimorbidity spectrum (Ilyas et al., 2019; Kumar et al., 2023). These genetic findings are further supported by genomic SEM analyses (**Chapter 7**), which demonstrate that while AN is included in the latent factor of psychiatric-IR multimorbidity, it carries a negative loading. Initially, we had expected AN to form a separate factor based on the results of **Chapter 5**, which highlighted its distinct genetic correlations with metabolic traits. However, **Chapter 7** revealed that AN clustered within the same factor as other psychiatric disorders linked to IR, albeit with an opposite loading. This finding suggests that rather than representing a completely separate genetic entity, AN shares underlying genetic factors with psychiatric-IR multimorbidity, but these factors influence AN in a direction consistent with metabolic protection rather than risk. These genetic findings are consistent with clinical observations in individuals with AN undergoing weight restoration therapy. Despite the physiological stress of refeeding, overt IR is typically not observed in AN, although approximately 21% of

individuals show elevated HOMA-IR estimates (Kim et al., 2019). Increased glucose reactivity has been linked to visceral adiposity during recovery, suggesting that body fat distribution plays a role in metabolic adaptations (Prioletta et al., 2011). Nonetheless, insulin sensitivity remains preserved in most individuals with AN, likely due to higher circulating levels of adiponectin, a hormone that enhances insulin action (Karczewska-Kupczewska et al., 2010). Further evidence supporting the genetic divergence of AN from other psychiatric disorders comes from polygenic analyses linking T2DM with psychiatric risk. A nationwide multigenerational genetics study demonstrated that psychiatric disorders and T2DM share a familial risk component, with first-degree relatives of individuals with psychiatric disorders exhibiting a significantly higher risk of T2DM (parents: HR = 1.38; grandparents: HR = 1.14; aunts/uncles: HR = 1.19) (Wimberley et al., 2024). However, the study also found an inverse association between polygenic score (PGS) for T2DM and AN, reinforcing the hypothesis that AN follows a metabolic trajectory distinct from IR-related conditions, favouring enhanced insulin sensitivity rather than susceptibility to metabolic dysfunction (Ilyas et al., 2019; Wimberley et al., 2024). These findings collectively highlight that while most psychiatric disorders exhibit some degree of genetic overlap with IR-related traits, AN represents an exception, characterised by a genetic architecture opposite of IR-related metabolic dysfunction.

A disorder showing similar trends as AN in its global negative association with IR-related metabolic conditions is OCD. However, while AN exhibited a largely uniform genetic profile characterised by consistent negative correlations with IR-related traits, OCD presented a more complex pattern. Despite negative global genetic correlations with IR-related metabolic conditions suggesting protection (**Chapter 5**), clinical and epidemiological evidence indicates an elevated prevalence of metabolic disturbances in individuals with OCD (Wimberley et al., 2022). One potential explanation for this discordance is the contribution of external, environmental influences that may interact with genetic predisposition, as metabolic complications have been particularly associated with prolonged exposure to antipsychotic medications in patients with OCD (Albert, Aguglia et al. 2013, Isomura, Brander et al. 2018). Local genetic correlation and gene-set stratified covariance analyses provided additional insights, highlighting shared genetic factors between OCD and IR-related conditions in specific genomic regions or pathways (**Chapter 5** and **6**). Notably, gene-set stratified covariance analyses implicated pathways involved in insulin receptor recycling, a process important for maintaining insulin sensitivity (**Chapter 5**). This finding suggests that genetic variation affecting insulin receptor turnover may contribute to the observed genetic relationship between OCD and IR-related traits, despite the lack of a positive genome-wide correlation.

For AD, the findings described in this thesis highlight another layer of complexity. Although global genetic correlations between AD and IR-related conditions were non-significant, local genetic analyses identified significant regional overlaps, suggesting that positive and negative correlations at different loci may counterbalance each other at a global level (**Chapter 5** and **6**). Previous studies have reported strong regional genetic correlations between AD and T2DM, particularly for variants mapped to the *APOE* locus (Zhu et al., 2019). The absence of a genome-wide, global genetic correlation does not necessarily rule out biological links but instead suggests that shared mechanisms may operate at specific loci without a uniform direction of effect across the genome. Evidence from animal models supports this hypothesis, showing that transgenic mice carrying the APOE-ε4 allele exhibit impaired insulin signalling when exposed to a high-fat diet, whereas those carrying the APOE-ε3 allele do not (Zhao et al., 2017). Furthermore, pharmacological studies have demonstrated that the efficacy of insulin-modulating treatments for AD, such as thiazolidinediones and intranasal insulin, may depend on *APOE* genotype (Li et al., 2015), reinforcing the notion that genetic and environmental interactions influence the relationship between AD and IR-related conditions.

Taken together, the results observed in my thesis highlight the substantial heterogeneity in the genetic overlap between psychiatric disorders and IR-related conditions. While MDD and ADHD exhibit positive genome-wide genetic correlations with IR-related metabolic traits, AN presents a uniformly negative genetic profile, reflecting genetic opposition to IR-related metabolic dysfunction across both global and local genetic correlation analyses. In contrast, schizophrenia, OCD, and AD demonstrate more complex genetic relationships with IR-related traits. These disorders show both positive and negative local genetic correlations, suggesting that specific loci contribute to metabolic risk despite an overall lack of or even inverse genome-wide genetic correlation. On top of genetic factors - and potentially over-ruling those - environmental and pharmacological factors (e.g., antipsychotic-induced metabolic side effects in schizophrenia and OCD) may further shape the observed metabolic risk in affected individuals.

Insulin signalling and immune-inflammation as core mechanisms in psychiatric-insulin resistance multimorbidity

Two consistent biological mechanisms emerging from my work across genomic and transcriptomic analyses (**Chapters 5** to **7**) are the involvement of insulin signalling and immune-inflammatory mechanisms in the co-occurrence of psychiatric and IR-related conditions. The involvement of insulin signalling was first identified in **Chapter 5**, where gene-set stratified genetic covariance analyses revealed that

neuropsychiatric disorders and IR-related conditions show genetic covariance at the level of specific insulin-related pathways, including those involved in insulin receptor recycling, insulin secretion, and processing. These findings were complemented by results from **Chapter 6**, where gene mapping within genetically correlated regions identified genes such as *STX1A*, *FLOT1*, *MAPK3*, and *PHKG2*, which play roles in insulin secretion, receptor signalling, and vesicular function (Bagge et al., 2013; Jager et al., 2011; van de Vondervoort et al., 2016). While these associations do not establish causality, they suggest a genetic link between insulin-related processes and psychiatric-IR multimorbidity, consistent with prior research on insulin signalling dysfunction in psychiatric disorders (see **Chapter 1,** section 1.1.2.1). Additional support for this relationship was observed in **Chapter 7**, where genomic SEM analyses identified a significant association between insulin binding gene-set, including the *INSR*, *IGF1R*, and *IDE* genes, and the psychiatry-IR multimorbidity genetic factor. *INSR* and *IGF1R* are central to insulin signalling, also regulating neuronal metabolism, synaptic plasticity, and neurogenesis (Boucher et al., 2014; Cardoso et al., 2021). *IDE*, which encodes the insulin-degrading enzyme, is not only involved in insulin metabolism but has also been implicated in cognitive function and neurodegeneration, suggesting a neurobiological link between insulin dysregulation and neuropsychiatric symptoms (Henderson & Poirier, 2011). These findings suggest that genetic variability in insulin signalling is potentially involved in the pathophysiology of psychiatric-IR multimorbidity, aligning with previous evidence presented in **Chapter 1** regarding the involvement of insulin in brain functioning.

Although insulin signalling is important for psychiatric-IR multimorbidity, my findings in **Chapters 6** and **7** indicate that it does not act in isolation. Instead, immune-inflammatory mechanisms appear to be an additional biological link between psychiatric and IR-related conditions. In this regard, colocalisation analyses conducted in **Chapter 6** identified likely shared causal variants between psychiatric and IR-related conditions, which mapped to immuno-related genes such as *HLA-DQB1* and *HLA-DRB1*. Moreover, transcriptomic analyses further reinforced the potential role of immune signalling by implicating MHC-related genes, including *HLA-DRB5*, and *MICB*, whose expression is associated with psychiatric-IR multimorbidity; this suggests that immune system dysfunction may be a key mechanistic bridge between psychiatric disorders and IR-related conditions (**Chapter 7**). The relationship between immune-inflammatory pathways and insulin function is particularly relevant given the previously established bidirectional links between inflammatory cytokines and IR, which has been implicated in both metabolic dysfunction and neuropsychiatric symptoms (Al-Mansoori et al., 2022; Wu & Ballantyne, 2020). Interestingly, pro-inflammatory

cytokines, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α, may also interfere with insulin receptor signalling by promoting serine phosphorylation of insulin receptor substrate proteins, leading to IR in peripheral tissues and the brain (Andreozzi et al., 2007; Gao et al., 2002). Findings from other large-scale studies further support the role of immune-inflammatory dysregulation in psychiatric-IR multimorbidity, although the underlying biological mechanisms have yet to be fully elucidated. For example, Rodevand et al. (2023) and Meer et al. (2024) identified immune-related pathways among shared genetic loci between psychiatric disorders and metabolic traits, although their analytical approaches do not allow for definitive mechanistic conclusions. Rodevand et al. (2023) identified genetic overlap between schizophrenia and metabolic traits, including lipid metabolism, blood pressure regulation, and T2DM-related phenotypes, with shared genetic signals in the MHC region. Similarly, Meer et al. (2024) identified immune-related pathways among the shared genetic loci between psychiatric disorders and metabolic markers, as well as inflammatory-related metabolic markers such as glycoprotein acetyls causally related with psychiatric phenotypes. Further evidence supporting the immune-inflammatory hypothesis comes from clinical studies showing that individuals with MDD, BD, and schizophrenia exhibit elevated levels of pro-inflammatory cytokines, including IL-6 and TNF-α, which are also increased in individuals with obesity, MetS, and T2DM (Goldsmith et al., 2016; Liu et al., 2016; Popko et al., 2010). Chronic inflammation has also been linked to neurotransmitter dysregulation, synaptic plasticity impairments, and increased HPA axis activity, all of which contribute to psychiatric symptom severity and treatment resistance (Leonard, 2014; Rhie et al., 2020).

The influence of inflammation and insulin resistance on treatment outcomes: focus on depression

The link between immune-inflammatory dysregulation and treatment resistance has been particularly investigated in depression. Previous research has shown that elevated C-reactive protein (CRP) and IL-6 levels predict poorer response to antidepressants, and anti-inflammatory agents have been explored as adjunctive therapies for individuals with treatment-resistant symptoms (Fabbri et al., 2021). However, immune-inflammatory dysregulation has also been linked to symptom severity and treatment response in schizophrenia and BD (Murata et al., 2020). Findings from **Chapter 3** and **4** suggest that IR-related metabolic dysfunction, including T2DM and obesity, may interfere with antidepressant efficacy by potentially exacerbating neuroinflammatory processes, potentially explaining the higher rates of antidepressant switching and longer treatment duration observed in individuals with IR-related conditions. One possible mechanism involves the direct effect of inflammatory cytokines on monoaminergic signalling. Elevated levels of

IL-6 and TNF-α have been shown to reduce serotonin synthesis by increasing the activity of the enzyme indoleamine 2,3-dioxygenase (IDO), which shunts tryptophan metabolism toward the kynurenine pathway, reducing serotonin availability while increasing the production of neurotoxic metabolites such as quinolinic acid (Fanelli et al., 2019). These metabolites act as NMDA receptor agonists, contributing to glutamatergic excitotoxicity, oxidative stress, and synaptic dysfunction, all of which have been implicated in mood disorders and antidepressant nonresponse (Fanelli et al., 2019). Inflammation may also impair dopaminergic transmission, involved in motivation and reward processing, two domains commonly affected in TRD (Felger & Treadway, 2017). Beyond neurotransmitter alterations, inflammatory processes may interfere with antidepressant mechanisms by affecting intracellular signalling pathways. For example, inflammatory cytokines activate the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, which inhibit neurotrophic factor signalling, particularly BDNF and its receptor Tropomyosin receptor kinase B (TrkB). Reduced BDNF expression has been linked to impaired neuroplasticity, which is a key process involved in antidepressant efficacy (Andrade & Rao, 2010; Yang et al., 2020).

In the context of metabolic dysfunction, IR may amplify these neuroinflammatory effects. Indeed, insulin plays a role in modulating neurotrophic support and neurotransmission (Kleinridders et al., 2014; Stranahan et al., 2008), and IR has been associated with reduced hippocampal BDNF levels and impaired synaptic plasticity (Spinelli et al., 2019; Stranahan et al., 2008), which are involved in antidepressant response (Bjorkholm & Monteggia, 2016). Moreover, IR is linked with chronic low-grade inflammation, with increased levels of pro-inflammatory cytokines (Chen et al., 2015; Szukiewicz, 2023), which in turn can worsen neurotransmitter imbalances and further impair neurotrophic signalling (Leonard, 2014). The combination of neuroinflammation and IR may therefore create a loop that sustains antidepressant nonresponse and contributes to chronicity in mood disorders. These mechanisms provide a biological interpretation of the observed association between metabolic dysfunction and reduced antidepressant efficacy. The increased rates of antidepressant switching and prolonged treatment duration observed in individuals with IR-related conditions (**Chapter 4**) may reflect the inability of standard antidepressants to effectively counteract the combined effects of neuroinflammation, IR, and neurotransmitter dysregulation. These findings also raise the possibility that anti-inflammatory or insulin-sensitising interventions could enhance antidepressant efficacy in individuals with coexisting psychiatric and metabolic disturbances, a hypothesis that warrants further investigation.

In summary, the integration of findings from this thesis, together with recent large-scale genomic studies, indicates that psychiatric-IR multimorbidity is

characterised by shared biological pathways, with substantial heterogeneity in shared genetic risk across psychiatric conditions and at the level of individual genetic loci. Local genetic correlations can contrast with global trends. The findings underscore that psychiatric-IR multimorbidity cannot be explained by uniform genetic effects but rather by a complex balance of convergent and divergent genetic and biological effects, in addition to environmental influences.

Vision for future research and clinical implications

The findings presented in this thesis underscore the need for a refined, biologically informed approach to psychiatric research and clinical practice at the intersection of psychiatric disorders and IR-related conditions. The results indicate that psychiatric-IR multimorbidity is not a uniform phenomenon but rather a spectrum of convergent and divergent shared genetic and effects in interplay with environmental factors, with common mechanisms involving metabolic, immune-inflammatory, and neurotransmitter pathways. In this section, I will describe my view on three aspects I believe future research should aim to improve: 1) risk prediction, 2) refining biological subtyping, and 3) translating genetic insights into precision medicine approaches. These objectives necessitate integrative methodologies that leverage genomics, transcriptomics, proteomics, metabolomics, and digital health technologies to optimise diagnosis, prevention, and treatment strategies in psychiatric populations with metabolic dysregulation.

Advancing risk prediction models for psychiatric-IR multimorbidity

While PGSs have demonstrated clinical utility for some medical conditions, such as breast cancer and T2DM (Khera et al., 2018), their predictive value in psychiatric disorders remains small (Lewis & Vassos, 2020). This is likely due to the highly multifactorial nature of psychiatric conditions and the complex contribution of environmental factors, including feedback loops involving gene-environment interplay (correlations and interactions). Conditions such as breast cancer provide an example where PGSs are increasingly used in risk stratification to optimise screening strategies. Recent findings indicate that incorporating breast cancer PGS alongside family history can refine early screening recommendations, leading to increased life-years gained and a reduction in breast cancer mortality (van den Broek et al., 2021). These results illustrate how polygenic risk can be leveraged to improve clinical outcomes and underscore the potential for similar applications in psychiatric and metabolic medicine. A priority for future research is the development of multimorbidity-based predictive models that extend beyond

single-disorder risk estimation. The findings presented in **Chapter 7** suggest that a latent multimorbidity factor, identified through genomic SEM, captures shared polygenic risk across psychiatric and IR-related conditions. However, the clinical utility of this multimorbidity factor remains unexplored. One potential avenue for translating these findings into practice is the development of multimorbidity-based PGS, which could improve risk stratification and inform personalised treatment selection. Given the substantial pleiotropy observed in psychiatric-IR multimorbidity, such a multimorbidity-based PGS may outperform disorder-specific PGSs by capturing genetic effects that cut across conventional diagnostic categories. This hypothesis is supported by previous findings indicating that PGSs derived from multivariate GWASs outperform those based on single-trait GWAS in predictive accuracy (Grotzinger et al., 2019). To establish clinical validity, future studies should investigate whether a multimorbidity-based PGS, integrated with environmental and clinical variables, improves risk stratification in psychiatric patients with metabolic dysfunction. This requires integrating PGS with electronic health records (EHRs) to assess whether individuals with high multimorbidity-based PGS exhibit earlier disease onset, more severe clinical trajectories, increased treatment resistance, and/or adverse medication effects. Large-scale biobank datasets, such as the All of Us Research Program (All of Us Research Program et al., 2019), could be instrumental in refining these models across diverse populations. In clinical psychiatry, incorporating multimorbidity-based PGS into clinical workflows may help guide early intervention strategies, including metabolically informed psychotropic prescribing or preemptive lifestyle interventions. However, realising the full potential of PGS in the context of psychiatric-IR multimorbidity requires several methodological improvements. Current PGS approaches primarily rely on GWAS summary statistics, which assign equal weight to associated variants regardless of their functional significance (Choi et al., 2020). However, risk prediction models could be improved by integrating functional annotations, such as chromatin accessibility and eQTL data, to prioritise variants with stronger biological relevance (Pain et al., 2021; Zhang et al., 2024). Additionally, the predictive power of PGS remains constrained by multiple factors, including ancestry-related biases and the limited sample sizes of base GWAS, which result in suboptimal polygenic prediction (Lewis & Vassos, 2020).

To refine risk prediction, transcriptomic stratification approaches could be employed. The CASTom-iGEx framework has demonstrated the utility of incorporating transcriptomic data to define patient subgroups with distinct biological profiles and clinically relevant differences (Trastulla et al., 2024). Applying similar strategies to psychiatric-IR multimorbidity could improve risk stratification by prioritising variants with functional relevance in biological pathways implicated

in insulin signalling and immune function, among others, as identified in this thesis (**Chapters 5** to **7**). For example, genes such as *INSR*, *MAPK3*, *MST1R*, and *BDNF*, identified through transcriptomic analyses as significantly associated with psychiatric-IR multimorbidity (**Chapter 7**), may warrant differential weighting in future PGS models. However, additional research is needed to establish which variants are functionally relevant before making direct claims about their contribution to risk prediction.

Another advancement in PGS methodology is the integration of machine learning approaches, which can account for nonlinear interactions, gene-gene interactions, and complex multivariate patterns that traditional PGS methods may overlook (Zhou et al., 2023). Among these approaches, deep learning-based PGS utilises neural network architectures to model polygenic risk, leveraging large-scale genomic data to predict disease susceptibility. Unlike traditional PGS, which typically sums the weighted effects of independent variants, deep learning-based models can identify hidden patterns in genetic risk by incorporating epistatic interactions, functional annotations, and regulatory networks (Zhou et al., 2023). Zhou et al. (2023) demonstrated that deep learning-based PGS models significantly outperformed conventional PGSs in predicting AD risk, with an increase in predictive accuracy from AUC = 0.69 (traditional PGS) to AUC = 0.73 (deep learning-based PGS) (Zhou et al., 2023). The improvement was attributed to the model's ability to capture polygenic risk in a nonlinear, context-dependent manner, incorporating interactions between genetic variants, biological pathways, and endophenotypic traits. This suggests that applying deep learning to multimorbidity-based PGS could better capture shared genetic risk between psychiatric and IR-related conditions, which involve multiple, overlapping biological mechanisms. Importantly, deep learning approaches may enable stratification of genetic risk groups with distinct clinical trajectories, a finding with potential relevance to psychiatric-IR multimorbidity (Zhou et al., 2023). The model used by the authors not only predicted AD risk but also identified high-risk subgroups enriched for biological markers such as amyloid-beta and tau pathology, underscoring the potential of deep learning to infer disease-related endophenotypes. Given the multisystem involvement of psychiatric-IR multimorbidity, deep learning approaches could similarly refine risk prediction by identifying hidden patterns of genetic risk across metabolic, immune-inflammatory, and neurobiological pathways.

Despite possible methodological advancements, PGS should always be integrated with environmental and lifestyle data to improve clinical utility. The bidirectional relationship between psychiatric and metabolic conditions suggests that genetic predisposition interacts with modifiable risk factors, such as diet, physical activity, sleep disturbances, and chronic stress (Fanelli et al., 2025; Ferns,

2018). However, traditional PGS models do not incorporate these influences, which limits their predictive accuracy in clinical settings (Lewis & Vassos, 2020). Prior work has demonstrated that combined risk models incorporating both genetic and environmental factors can improve risk prediction. For instance, CVD prediction models that integrate PGS alongside conventional risk factors have shown improved predictive accuracy. Specifically, these models achieve a small but meaningful increase in their ability to distinguish individuals at higher vs. lower risk (measured as an increase in the C-index by 0.012, a metric that quantifies how well a model differentiates between outcomes). Additionally, integrating PGSs has led to a 10-12% improvement in correctly reclassifying individuals into more appropriate risk categories compared to models based solely on traditional predictors (Sun et al., 2021). Similarly, an analysis of breast cancer and CVD models demonstrated that environmental/clinical predictors such as BMI and smoking status contribute significantly to disease risk and that integrating genetic data further refines stratification (Dudbridge et al., 2018). While these findings illustrate the feasibility of multimodal prediction, their applicability to psychiatric-IR multimorbidity requires further validation. A multimodal risk model incorporating both genetic predisposition and longitudinal, real-time health data, such as actigraphy-based measures of physical activity, sleep patterns, and circadian rhythm stability, could further improve risk stratification and facilitate early identification of individuals at high risk for psychiatric-IR multimorbidity before clinical symptoms manifest. These dynamic predictors may complement genetic risk estimates, particularly given prior evidence that objective behavioural monitoring (e.g., actigraphy and smartphone-based digital phenotyping) is associated with mood symptomatology and treatment response (Gillett et al., 2021; Scott et al., 2020; Tazawa et al., 2019). Such an approach could support tailored intervention strategies, including preemptive lifestyle modifications or personalised metabolic risk mitigation. The integration of multimodal assessments may have broad implications for public health by shifting the focus from reactive treatment to proactive disease prevention.

Translation of predictive models into clinical practice will require addressing several challenges, including validation in diverse populations, integration into EHRs, and ensuring accessibility within routine healthcare settings. To maximise clinical impact, multimodal risk assessments should be implemented beyond research settings, ensuring that primary care and mental health services incorporate these tools in risk stratification and early intervention strategies. Future research should also explore how PGS can be incorporated into clinical decision support systems for individualised treatment selection. Potentially, psychiatric patients with high genetic risk for psychiatric-IR multimorbidity may benefit from metabolically neutral psychotropics, augmentation with anti-inflammatory agents, or insulin-

sensitising drugs, whereas those with low multimorbidity risk might tolerate more metabolically challenging treatments. By integrating PGS-driven metabolic risk profiles into EHRs, clinicians could receive data-driven recommendations tailored to an individual's psychiatric and metabolic risk. This could transform the management of psychiatric-IR multimorbidity, shifting away from trial-and-error prescribing towards precision medicine approaches that proactively mitigate/prevent metabolic complications.

An important factor that must be achieved to fulfil the potential of multimorbidity-based PGS is that it must account for both ancestral diversity and ethical considerations to ensure equitable clinical translation. Current polygenic prediction models are largely based on European-ancestry cohorts, limiting their generalizability across populations. Genetic findings from this thesis (**Chapters 5** to **7**) were derived from similar datasets, underscoring the need for replication in diverse ancestry groups. Given that PGS models underperform in non-European populations (Martin et al., 2019), future studies should integrate multi-ancestry cohorts, deep phenotyping, and prospective validation to ensure that PGS models are robust, generalizable, and clinically actionable. Trans-ethnic approaches are essential to prevent disparities in risk prediction and to ensure that precision medicine benefits all populations rather than disproportionately favouring those of European descent.

Beyond population-specific considerations, the ethical dimensions of PGS implementation must also be addressed. Ensuring equitable access to genetic-based risk assessments, preventing genetic determinism in clinical practice, and avoiding socioeconomic disparities in genomic medicine are critical challenges. PGS provides a probabilistic rather than deterministic measure of risk, yet misinterpretation by clinicians, patients, and policymakers may foster stigmatisation or fatalistic attitudes (Martin et al., 2019; Palk et al., 2019). This is particularly relevant in psychiatric disorders, where symptom heterogeneity, environmental influences, and modifiable lifestyle factors significantly shape disorder trajectories. If individuals at high polygenic risk for both psychiatric and metabolic conditions perceive their health outcomes as predetermined, they may be less likely to engage in preventive health behaviours. Public health strategies should therefore prioritise educational initiatives that emphasise the role of modifiable risk factors — including diet, physical activity, and stress management — to counteract potential misconceptions regarding genetic risk.

A further challenge lies in avoiding the reinforcement of socioeconomic disparities in healthcare access. If PGS-based risk stratification and early interventions become financially inaccessible to those in lower-resource settings, genomic medicine may exacerbate existing health inequities (Martin et al., 2019). This is particularly concerning given that psychiatric-IR multimorbidity is shaped by

both genetic and socioeconomic factors, including disparities in healthcare access, nutrition, and chronic stress exposure. To prevent the emergence of a two-tiered healthcare system, policymakers must prioritise the integration of PGS within universally accessible healthcare frameworks, ensuring that genomic medicine benefits all individuals, rather than being limited to affluent populations.

The challenges in genetically informed risk prediction ultimately reflect a broader issue in psychiatric classification: the limitations of current diagnostic categories.

Moving beyond symptom-based diagnoses: the need for biology-informed clinical subgroups

The new evidence on the genetic overlap between neuropsychiatric and IR-related conditions (**Chapter 5** to **7**), complemented by clinical evidence of a different clinical trajectory of psychiatric disorders co-occurring with IR (**Chapters 3** and **4**), suggests that conventional diagnostic classifications, such as those based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), may be insufficient to fully capture the biological complexity of these disorders. Furthermore, unravelling the clinical heterogeneity of some psychiatric disorders, such as MDD and schizophrenia, among others, could potentially help optimise their treatment and better understand their underlying biological basis (Buch & Liston, 2021).

As discussed in **Chapter 1** (section 1.1.1), psychiatric classification systems such as the DSM and International Classification of Diseases (ICD) have relied on symptom-based criteria, which, while clinically practical, do not map onto underlying neurobiological mechanisms. These frameworks have provided an essential structure for diagnosis and research, but they fail to account for the heterogeneous clinical presentations, high rates of multimorbidity with metabolic disorders, and variable treatment responses seen across psychiatric conditions. The findings presented in this thesis underscore the potential for a biology-informed approach, revealing shared genetic, metabolic, and immune-inflammatory pathways that challenge the conventional categorical distinction between psychiatric and somatic disorders.

The Research Domain Criteria (RDoC) framework (Insel et al., 2010) represents a shift toward redefining psychiatric disorders based on neurobiological dimensions rather than traditional diagnostic categories. However, RDoC primarily focuses on neural circuit dysfunction, while this thesis highlights the important roles of metabolic and immune-inflammatory pathways in psychiatric disorder pathophysiology. Future iterations of RDoC or similar frameworks should incorporate multi-omics findings, ensuring that psychiatric nosology is not limited to neurocircuitry alone but extends to systemic metabolic and immune mechanisms. By integrating genetic, transcriptomic, proteomic, and metabolomic

data, a revised nosology could help to reduce the artificial boundaries between mental and physical health, facilitating a more precise understanding of psychiatric disorders and enabling more targeted therapeutic strategies.

Integrating the assessment of somatic and metabolic traits into psychiatric practice may provide several advances, both in clinical decision-making and in refining disorder classification. Psychiatric symptoms are inherently subjective, relying on clinical interviews and self-report measures that are susceptible to reporting bias, variability in insight, and heterogeneity in symptom expression. In contrast, metabolic traits can be assessed through objective biochemical and physiological markers, including fasting glucose, insulin levels, HOMA-IR, lipid profiles (triglycerides, high-density lipoproteins [HDL], low-density lipoproteins [LDL]). These markers provide quantifiable data that help identify individuals with underlying metabolic disturbances that contribute to psychiatric symptomatology. Additionally, known intervention strategies for metabolic conditions, such as lifestyle modifications and pharmacological treatments targeting IR, could be repurposed for specific psychiatric subgroups. Another important consideration is that IR-related conditions, such as T2DM, typically develop later in life, whereas most psychiatric disorders emerge within early adulthood; this temporal pattern suggests that careful metabolic monitoring of individuals with psychiatric disorders, particularly those at genetic or clinical risk for metabolic dysfunction, could enable earlier intervention (and prevention) strategies aimed at reducing long-term morbidity.

If we can achieve a biologically informed classification system, this could facilitate the identification of specific psychiatric subtypes, such as immuno-metabolic depression, which has been increasingly recognised as a distinct depressive phenotype characterised by systemic inflammation, IR, and an increased risk for MetS, T2DM, and CVD (Penninx et al., 2025). Immuno-metabolic depression affects approximately 20–30% of individuals now diagnosed with depression, and it is marked by a combination of atypical depressive symptoms (hypersomnia, fatigue, hyperphagia), elevated inflammatory markers (CRP, IL-6, TNF-α), and metabolic dysfunction (dyslipidaemia, insulin and leptin resistance) (Penninx et al., 2025). Identifying this subgroup is of clinical importance, as it may help refine treatment strategies beyond standard antidepressant therapy. Recent randomised controlled trials (RCTs) have investigated targeted interventions for immuno-metabolic depression, providing mixed but informative findings. The INFLAMED trial is currently assessing the efficacy of the COX-2 inhibitor celecoxib as an add-on treatment for patients with immuno-metabolic depression features, specifically those with elevated CRP, atypical/energy-related symptoms of depression, and metabolic dysregulation, with the aim of determining whether targeting inflammation enhances antidepressant

response (Zwiep et al., 2023). However, prior trials such as the PREDDICT study, which tested celecoxib as an augmentation to the antidepressant vortioxetine and attempted to stratify patients based on inflammation levels, failed to demonstrate a consistent benefit of anti-inflammatory augmentation, suggesting that CRP alone may not be sufficient for identifying those who would benefit from this approach (Kavakbasi et al., 2024). These findings highlight the need for refined biomarkers that can better predict treatment response to anti-inflammatory interventions. Beyond pharmacological approaches, nutritional and metabolic interventions have also been explored as potential strategies for immuno-metabolic depression. The MooDFOOD trial, a large-scale RCT, investigated whether food-related behavioural activation therapy and multi-nutrient supplementation (omega-3 fatty acids and a multi-vitamin) could prevent depression onset or alleviate depressive symptoms. While primary outcomes showed no significant effect, secondary analyses indicated that food-related behavioural interventions may reduce somatic and energy-related depressive symptoms, aligning with the immuno-metabolic depression phenotype (Thomas-Odenthal et al., 2023). However, multi-nutrient supplementation did not demonstrate consistent benefits, and in some cases, participants reported greater severity of mood and energy-related symptoms following supplementation, raising questions about the appropriateness of generalised dietary interventions in this subgroup (Vreijling et al., 2021). These inconsistencies suggest that while dietary modifications may play a role in symptom management, nutritional interventions should be tailored to well-defined biological subgroups rather than applied as a universal strategy. The potential role of light therapy in individuals with immuno-metabolic depression has also been explored due to its effects on circadian rhythms, inflammation, and metabolic pathways. However, the LiDDia trial, which investigated the effects of light therapy in patients with immuno-metabolic depression and comorbid T2DM, found no significant improvements in atypical depressive symptom severity, inflammatory markers, or metabolic biomarkers (Vreijling et al., 2024). This suggests that while light therapy is effective for seasonal affective disorder, its benefits may not extend to individuals with immune-metabolic depression. These inconsistencies in treatment efficacy highlight the need for improved biomarker-based stratification, moving beyond CRP alone to incorporate multi-omics approaches, including genetic, transcriptomic, proteomic, and metabolomic profiling. A more comprehensive characterisation of immuno-metabolic depression may help delineate the biological mechanisms underlying psychiatric-metabolic interactions, allowing for a more precise classification of patients into biologically relevant subtypes.

One promising approach to achieve this is multimorbidity-based clustering analysis, which integrates genetic and clinical data to identify distinct psychiatric

subgroups with varying metabolic and inflammatory profiles. Further supporting the heterogeneity in psychiatric-IR interactions, such clustering analyses have identified distinct MDD-related subgroups with unique genetic and non-genetic risk profiles, some of which exhibit stronger genetic ties to inflammatory and metabolic pathways than others (Gezsi et al., 2024). In line with the findings described in this thesis, these observations suggest that psychiatric-IR comorbidity is not a uniform phenomenon but rather comprises biologically distinct subgroups with varying clinical trajectories. This underscores the importance of refining psychiatric classification systems by incorporating metabolic and immune-inflammatory profiles, alongside genetic risk markers, to better predict disorder course and treatment response. However, to translate these biologically defined subgroups into clinical practice, a deeper understanding of the molecular pathways driving these multimorbid conditions is necessary. Identifying the functional consequences of genetic variation and understanding how these interact with environmental exposures requires a multi-omics approach, integrating transcriptomics, epigenomics, proteomics, and metabolomics. These methodologies can help identify convergent biological mechanisms that may serve as therapeutic targets, thereby bridging the gap between classification and precision medicine.

Expanding -omics research to identify and validate candidate therapeutic targets

The genetic and transcriptomic findings presented in this thesis (**Chapters 5** to **7**) provide a strong foundation for understanding the shared biological mechanisms underlying neuropsychiatric disorders and IR-related conditions. However, these analyses alone offer only a partial view of the molecular processes contributing to disease. A fully integrative multi-omics approach, encompassing genomics, epigenomics, transcriptomics, proteomics, and metabolomics, is essential to develop a higher resolution understanding of multimorbidity and to further identify biologically relevant therapeutic targets. The need for multi-omics integration is particularly evident given the heterogeneity in genetic correlations and biological pathways identified in **Chapters 5** to **7**, which suggest that psychiatric-IR multimorbidity is influenced by multiple biological processes rather than a single common pathway.

A primary goal of future research should be the integration of epigenomic data to investigate how genetic risk factors interact with environmental influences to shape disorder susceptibility. While this thesis did not directly assess epigenetic modifications, results from **Chapter 7** indicate that genes associated with psychiatric-IR multimorbidity exhibit tissue-specific expression patterns in the brain, particularly in the cerebellum, frontal cortex (Brodmann Area 9), and the pituitary gland. These

findings suggest that genetic risk for multimorbidity may be mediated, at least in part, by transcriptional regulation in brain regions relevant to both psychiatric symptoms and metabolic function. Given that epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA regulation can influence gene expression without altering the underlying DNA sequence, future studies should explore whether metabolic dysfunction contributes to psychiatric symptoms through epigenetic modifications in these tissues. DNA methylation analyses in post-mortem brain samples and peripheral tissues (e.g., blood, adipose, liver) from individuals with psychiatric-IR multimorbidity could help determine whether specific epigenetic changes distinguish individuals who develop multimorbidity from those who do not.

Additionally, single-cell RNA sequencing (scRNA-seq) represents a promising approach for clarifying the cellular specificity of genetic risk factors. While the transcriptomic analyses presented in **Chapter 7** identified significant gene expression associations at the tissue level, they do not resolve which specific cell types contribute most strongly to multimorbidity risk. Future studies should employ scRNA-seq to identify which cell types contribute most strongly to multimorbidity risk. For instance, *in silico* scRNA-seq analyses of publicly available transcriptomic datasets from the human brain, peripheral immune cells, and metabolic tissues can further refine the understanding of cell-type-specific effects of the identified psychiatric-IR multimorbidity risk variants. This approach can clarify whether the genetic liability for this multimorbidity is primarily driven by specific neuronal or glial subpopulations within the different brain areas, or by systemic immune-metabolic dysfunction (Zhang et al., 2022).

Beyond single cell transcriptomics, proteomic and metabolomic studies will be important for translating genetic risk into biological function and actionable therapeutic targets. Psychiatric disorders and metabolic conditions are influenced by post-transcriptional modifications, protein-protein interactions, and metabolic flux alterations that are not fully captured by gene expression data alone (Appelman et al., 2021; Ganapathiraju et al., 2016; Khavari et al., 2024). Mass spectrometry-based proteomics in individuals with high genetic risk for psychiatric-IR multimorbidity could reveal altered protein abundance and signalling networks in both central and peripheral tissues. For instance, targeted proteomic analyses of serum, cerebrospinal fluid (CSF), and brain tissue could determine whether inflammatory markers (e.g., IL-6, TNF-α), insulin-related proteins (e.g., INSR, IGF1R, IRS1), or mitochondrial regulators (e.g., oxidative phosphorylation complexes, PGC-1α) are disrupted in individuals with multimorbidity. These findings could then inform the repurposing of existing metabolic or immunomodulatory drugs to restore disrupted pathways.

Metabolomics offers a complementary approach by characterising the small-molecule metabolic changes that bridge genetic risk with disorder pathology. Given the central role of insulin signalling and lipid metabolism, as well as immune and neurotransmitter pathways in psychiatric-IR multimorbidity, future studies should employ untargeted and targeted metabolomics to identify circulating metabolic signatures predictive of multimorbidity. Key areas of interest include aberrant glucose handling, altered lipid profiles, and disruptions in mitochondrial-derived metabolites such as lactate, ATP, and ketone bodies. Additionally, longitudinal metabolomic profiling could identify early metabolic alterations that precede the onset of psychiatric symptoms, offering new opportunities for disorder prevention and early intervention. Several studies have demonstrated the potential of metabolomics in elucidating the metabolic underpinnings of psychiatric disorders and their association with metabolic dysregulation. For instance, a large-scale prospective cohort study of over 200,000 individuals demonstrated that elevated glucose and triglyceride levels, as well as reduced HDL, were associated with an increased long-term risk of depression, anxiety, and stress-related disorders (Chourpiliadis et al., 2024). Notably, individuals who later developed psychiatric disorders exhibited persistently higher levels of glucose, triglycerides, and total cholesterol for up to 20 years before diagnosis. Another study conducted plasma metabolomics analysis in adolescents with MDD, BD, and schizophrenia revealing shared and distinct metabolic alterations across these conditions (Yin et al., 2024). Alterations in fatty acid, steroid hormone, purine, nicotinate, glutamate, tryptophan, arginine, and proline metabolism were common across all three disorders, while schizophrenia exhibited unique disturbances in glycolysis, glycerophospholipid, and sphingolipid metabolism. BD and MDD shared alterations in lysine, cysteine, and methionine metabolism, while BD and SCZ overlapped in disruptions of phenylalanine, tyrosine, and aspartate metabolism (Yin et al., 2024). These findings highlight the potential of metabolomics in distinguishing psychiatric subtypes and suggest that metabolic dysfunction in psychiatric disorders is heterogeneous rather than uniform. Further supporting the link between metabolic alterations and specific psychiatric symptom profiles, another metabolomics study in individuals with depression identified a distinct metabolic signature associated with atypical depressive symptoms, particularly those characterised by atypical symptoms, such as hypersomnia, hyperphagia, and weight gain (de Kluiver et al., 2023). This atypical/energy-related symptom profile was linked to elevated glycoprotein acetyls, isoleucine, very-low-density lipoprotein (VLDL) cholesterol, and saturated fatty acid levels, alongside reduced HDL cholesterol. Importantly, these metabolomic alterations closely resemble those observed in cardiometabolic conditions, further reinforcing the shared biological pathways between metabolic dysfunction and specific psychiatric phenotypes.

A major advantage of multi-omics integration is its ability to prioritise therapeutic targets with higher translational relevance. By integrating genomics, transcriptomics, proteomics, and metabolomics, researchers can prioritise targets that demonstrate convergent evidence across multiple biological layers. For instance, if a gene associated with multimorbidity shows genome-wide significance in GWAS, altered expression in brain transcriptomics, differential protein abundance in CSF, and metabolic dysregulation in patient-derived samples, it becomes a strong candidate for therapeutic targeting. In AD research, a deep learning framework called NETTAG (network topology-based deep learning framework to identify disease-associated genes) was developed to integrate GWAS with other -omics data. This integration led to the identification of gemfibrozil, an existing lipid-regulating drug, as a potential therapeutic agent for AD. Clinical data analysis revealed that gemfibrozil use was associated with a 43% reduced risk of AD compared to simvastatin, highlighting the power of multi-omics approaches in drug repurposing efforts (Xu et al., 2022). Similarly, in migraine research, a study combining GWAS with eQTL and proteomics data identified *GSTM4* as a potential druggable gene. This multi-omics integration provided a comprehensive understanding of *GSTM4*'s role in migraine pathophysiology, suggesting it as a promising therapeutic target (Sun et al., 2024). This multi-omics prioritisation framework could reduce the failure rate of drug discovery efforts by ensuring that candidate targets have robust biological support (Kim et al., 2023; Ramos et al., 2018).

Functional validation of genetic findings of my work (**Chapters 6** and **7**) will also be indispensable for bridging the gap between association studies and clinical application. Identifying genetic variants associated with psychiatric-IR multimorbidity is only the first step; their biological significance must be confirmed through experimental models. A central focus should be placed on key candidate genes and pathways identified through genomic SEM, T-SEM, and gene-set enrichment analyses. Genes such as *INSR*, *MST1R*, *MAPK3*, and *BDNF*, among many others, emerged as significant contributors to the shared genetic risk for psychiatric-IR multimorbidity. Each of these genes plays a role in insulin signalling, immune function, and neuroplasticity, but their precise mechanistic contributions to the multimorbidity remain to be elucidated. Functional validation should begin with cell-based studies using CRISPR-Cas9 gene editing, iPSC-derived neurons and astrocytes, and high-throughput functional genomics screening. CRISPR-Cas9 approaches offer a direct means of assessing the biological consequences of disorder-associated variants (Kim et al., 2024). Future studies should use CRISPR knockout and CRISPR activation techniques to manipulate genes such as *INSR* and *MAPK3* in relevant cell models, including neuronal, glial, and pancreatic β-cell lineages. For example, knocking out *INSR* in neuronal cultures could provide

additional insights into how insulin receptor dysfunction contributes to synaptic impairments, neurotransmitter alterations, and metabolic stress responses. Similarly, CRISPR activation of *MST1R* in microglia could help clarify its role in neuroinflammation and whether its upregulation in psychiatric-IR multimorbidity reflects a compensatory or pathological mechanism. Such studies would establish whether genetic variants influence psychiatric-IR multimorbidity via direct cellular effects or through broader immune-metabolic interactions.

Complementary approaches using induced pluripotent stem cell (iPSC)-derived neurons, astrocytes, and microglia are also relevant for examining cell-type-specific effects of risk variants (Cerneckis et al., 2024). Findings from **Chapter 7** demonstrated that several genes implicated in psychiatric-IR multimorbidity exhibit tissue-specific expression in the brain, particularly in the cerebellum, cortex (including Brodmann Area 9), and the pituitary gland. Moreover, colocalisation analyses in **Chapter 6** identified putative causal variants shared between schizophrenia, MetS, and type 2 diabetes in regions containing immune-related genes. However, these results do not establish a direct mechanistic link between these genes and psychiatric-IR multimorbidity but rather highlight regions of interest for further investigation. For instance, iPSC-derived astrocytes from individuals carrying high-risk alleles in *BDNF* and *MAPK3*, among the top genes identified in **Chapter 7**, could be analysed for altered metabolic and inflammatory responses, providing insights into how metabolic dysfunction and psychiatric symptoms co-evolve. While specific studies on these alleles are limited, research has shown that iPSC-derived astrocytes can model disease-specific neuroinflammatory and metabolic alterations. For example, astrocytes derived from iPSCs of patients with multiple sclerosis exhibit increased mitochondrial fission, elevated production of superoxide, and enhanced release of proinflammatory chemokines, reflecting a proinflammatory state (Ghirotto et al., 2022). Therefore, employing iPSC-derived models of neurons, astrocytes, and microglia may offer a promising avenue to dissect the cell-type-specific effects of genetic risk variants implicated in psychiatric-IR multimorbidity.

Moving beyond *in vitro* studies, animal models incorporating human disorder-associated genetic variants can be used for better understanding how the identified genes in **Chapters 6** and **7** influence behavioural, cognitive, and metabolic phenotypes. The creation of mouse models harbouring psychiatric-IR multimorbidity risk alleles could allow researchers to investigate disorder mechanisms in a physiologically relevant context. For example, *MST1R* (Macrophage Stimulating 1 Receptor/RON receptor; among the top up-regulated genes associated with the psychiatric-IR multimorbidity factor in **Chapter 7**) knock-in mice could be used to assess the impact of immune-inflammatory activation on insulin sensitivity, neuronal excitability, and depressive-like behaviours. Studies

have shown that mice lacking RON receptor signalling exhibit reduced obesity-related pathologies, including improved glucose tolerance and insulin sensitivity, when subjected to a high-fat diet (Stuart et al., 2015). Similarly, mice with *INSR* deletions specifically in the brain have been employed to elucidate how central insulin resistance contributes to neuropsychiatric and metabolic disturbances. Neuronal-specific *INSR* knockout mice display age-dependent anxiety and depressive-like behaviours, accompanied by mitochondrial dysfunction and altered dopamine turnover in the mesolimbic system (Kleinridders et al., 2015).

In summary, while this thesis has identified genetic and transcriptomic associations to psychiatric-IR multimorbidity, functional validation remains a required next step for establishing causal mechanisms.

Bridging the gap between genetic insights and precision medicine

The findings presented in **Chapters 6** and **7** indicate that psychiatric and IR-related conditions share fundamental biological pathways, including immune-inflammatory signalling, IR, mitochondrial dysfunction, and lipid metabolism. **Chapter 6** identified specific genomic regions where psychiatric and IR-related conditions exhibit local genetic correlations, implicating genes involved in immune regulation, lipid metabolism, and insulin signalling. Notably, genes such as *HLA-DRB1*, *C4A*, *FLOT1*, and *STX1A*, which were mapped within these regions, are targets of existing pharmacological agents, including immunosuppressants, statins, and certain psychotropic drugs. These findings suggest that existing pharmacological interventions targeting metabolic and immune-inflammatory pathways could be repurposed to improve psychiatric outcomes, particularly in TRD and other psychiatric symptoms (e.g., cognitive impairments, anhedonia, negative symptoms) that are poorly responsive to current psychotropic therapies.

Despite these insights, a major challenge remains identifying which patients would benefit most from such metabolic-targeted interventions. Multi-omics approaches integrating genetic, transcriptomic, proteomic, and metabolomic data could refine patient stratification and treatment response prediction. For instance, combining inflammatory and metabolic markers with PGSs may improve the identification of patients who are most likely to benefit from metabolic-targeted therapies (e.g., GLP-1RAs, metformin, statins). A precision psychiatry framework that aligns pharmacological interventions with genetic and metabolic risk profiles could move treatment selection beyond symptom-based classifications, allowing a more personalised approach.

As previously discussed (**Chapter 8**, section 8.3.2), CRP alone is an insufficient biomarker for predicting response to anti-inflammatory therapies, as demonstrated by mixed findings from RCTs such as the PREDDICT trial. However, biomarker-driven

RCTs have been proposed in personalised medicine to refine treatment selection (Park, 2022). These trials utilise biomarkers to select or stratify patients, aiming to predict which individuals are more likely to respond to specific interventions. Although such biomarker-stratified RCTs are common in other medical fields such oncology (LoRusso & Freidlin, 2023), their application in psychiatry is still emerging (Kavakbasi et al., 2024). Large-scale clinical trials should prioritise this approach, while evaluating whether immune- and insulin-targeting drugs may not only ameliorate psychiatric symptoms but also mitigate cognitive, compulsive, and reward-related symptoms, among others, in metabolically vulnerable individuals.

One of the most promising future directions involves therapies that simultaneously target psychiatric and metabolic pathways. Given that antidepressants, antipsychotics, and mood stabilisers frequently induce metabolic side effects (Himmerich et al., 2015), an integrated pharmacological approach is necessary to mitigate these effects while preserving psychiatric efficacy. Several combination strategies should be prioritised for clinical evaluation. For example, co-administration of metformin with SSRIs or SNRIs may enhance antidepressant response while reducing metabolic burden. Similarly, pairing GLP-1RAs with atypical antipsychotics may counteract weight gain and IR while improving cognitive outcomes (Horska et al., 2022). Preclinical and clinical studies should systematically test whether metabolically protective drugs enhance the efficacy of psychiatric treatments, particularly in individuals showing treatment resistance or metabolic comorbidities.

As suggested in **Chapter 3**, insulin-sensitising agents such as metformin and GLP-1RAs have emerged as promising therapeutic candidates in psychiatric populations. Metformin has been extensively studied for its effects on glucose metabolism and mitochondrial function, but accumulating evidence suggests it also modulates neuroinflammatory pathways and enhances synaptic plasticity, processes directly implicated in psychiatric disorders (Cao et al., 2022). In preclinical and clinical studies, metformin has demonstrated efficacy in improving cognitive function, depressive symptoms, and antipsychotic-induced weight gain, suggesting that its therapeutic benefits extend beyond metabolic regulation (Dodd et al., 2022). GLP-1RAs (e.g., liraglutide, semaglutide) represent another promising class of metabolic-based interventions for psychiatric disorders. These drugs exert anti-inflammatory, neuroprotective, and appetite-regulating effects by modulating insulin signalling in both central and peripheral tissues. Preclinical studies suggest that GLP-1RAs improve synaptic function, reduce neuroinflammation, and enhance neurogenesis in the hippocampus (Au et al., 2025; Detka & Glombik, 2021; Diz-Chaves et al., 2022), processes that are disrupted in MDD and BD. Emerging clinical trials indicate that GLP-1RAs reduce anhedonia, cognitive deficits, and inflammation-associated depressive symptoms in patients with metabolic

dysfunction (Badulescu et al., 2024; Tempia Valenta et al., 2024). Given the evidence from this thesis linking IR to poorer treatment response and cognitive dysfunction in depression, future studies should investigate whether GLP-1RAs can improve psychiatric outcomes even in patients without overt metabolic disease by targeting central insulin signalling pathways.

Beyond pharmacological interventions, lifestyle-based therapies should be systematically integrated into psychiatric treatment protocols to address the metabolic burden of psychiatric disorders. Evidence suggests that dietary interventions, including the Mediterranean diet, ketogenic diet, and intermittent fasting, confer antidepressant and cognitive benefits by modulating neuroinflammation, insulin sensitivity, and neurotransmitter metabolism (Al Shamsi et al., 2024; Devranis et al., 2023; Gudden et al., 2021). Other specific dietary interventions have been investigated for their potential role in modulating neuroinflammation and cognitive function. A cohort study found that higher nut consumption (≥3 servings per week) was associated with a smaller decline in general cognitive performance over two years in older adults at risk of cognitive decline (Ni et al., 2023). Nuts are rich in unsaturated fatty acids, antioxidants, and anti-inflammatory compounds, which may attenuate neuroinflammation and metabolic dysregulation, making them a potential dietary adjunct for psychiatric-IR multimorbidity. Similarly, structured exercise programmes have been shown to enhance hippocampal plasticity and improve insulin sensitivity, making them promising adjuncts for psychiatric-IR multimorbidity (Patten et al., 2015). However, implementing these lifestyle interventions presents significant challenges, particularly for individuals with psychiatric conditions like ADHD, where executive dysfunction, impulsivity, and attentional deficits can impair adherence to structured exercise regimens. Clinical experience indicates that ADHD patients often struggle with time management, maintaining motivation, and sustaining physical activity habits—barriers that are consistent with research findings showing that, while exercise can improve ADHD symptoms, long-term adherence remains difficult (Ogrodnik et al., 2023). Given these obstacles, future studies should investigate whether combining pharmacological and lifestyle-based interventions enhances treatment response in psychiatric populations, particularly those with high genetic risk for psychiatric-IR multimorbidity.

A major challenge in translating these insights into clinical practice is the limited implementation of precision medicine approaches in psychiatry. Future clinical trials should prioritise biomarker-driven patient stratification to optimise treatment selection based on genetic, inflammatory, and metabolic risk markers. A multi-omics approach could enable the early identification of psychiatric subgroups who are most likely to benefit from metabolic-based interventions, ensuring more targeted and individualised treatment strategies.

Advancing an interdisciplinary, equitable, and inclusive framework for future research

A broader vision for future research on psychiatric-IR multimorbidity must involve interdisciplinary collaboration that brings together genetics/genomics experts, psychiatrists, endocrinologists, neuroscientists, nutritionists, and data scientists. The multifactorial nature of these conditions necessitates collaboration between different biomedical fields to unravel the shared biological mechanisms underlying these disorders and translate findings into effective, personalised interventions. Large-scale consortia have successfully implemented such interdisciplinary frameworks, as exemplified by the PRIME (*Prevention and Remediation of Insulin Multimorbidity in Europe*) consortium (https://prime-study.eu). PRIME has brought together genetic, epidemiological, and clinical data to investigate the role of IR in psychiatric disorders and develop personalised treatment approaches by integrating multi-omics data, real-world clinical evidence, and patient-centred research. The consortium has also emphasised patient-centred research, incorporating the perspectives of individuals with lived experiences to align research priorities with patient needs.

A critical step toward implementing precision psychiatry involves the development of decision support systems that integrate genetic, clinical, and lifestyle data. These systems could refine risk prediction models and optimise treatment selection, improving both efficacy and patient satisfaction. Collaborative care models that bring together psychiatrists, endocrinologists, and primary care providers will further ensure that patients receive comprehensive care addressing both psychiatric and metabolic health.

Ensuring equity in research and clinical practice is both a scientific and ethical priority. Expanding recruitment efforts to include underrepresented communities and adapting research methodologies to account for cultural and contextual differences will enhance the relevance and applicability of findings. Moreover, developing scalable and adaptable interventions for diverse healthcare settings will help ensure that the benefits of precision psychiatry reach all populations, regardless of socioeconomic or geographic barriers.

Overall conclusions

This thesis provides a comprehensive investigation into the genetic, biological, and clinical links between neuropsychiatric disorders and IR-related conditions, offering new insights into their shared aaetiology, pathophysiological mechanisms, and clinical implications. Through a multidimensional approach integrating large-

scale genetic analyses, transcriptomic profiling, and clinical epidemiology, this work challenges traditional compartmentalised views of psychiatric and IR-related somatic conditions, underscoring their shared genetics and biological mechanisms.

A key contribution of my work is the demonstration that psychiatric-IR multimorbidity is not a coincidental overlap of independent disorders but rather a manifestation of shared genetic liability. The identification of a latent multimorbidity factor via genomic SEM and the detection of local genetic correlations between psychiatric and IR-related conditions provide clear indications for potential common underlying biological pathways. These findings redefine the conceptual boundaries between psychiatric and IR-related conditions, supporting the potential usefulness of a biologically informed, rather than purely symptom-based, classification system. Furthermore, this thesis highlights the role of insulin signalling and immune-related processes as possible fundamental axes of shared pathology, with potential implications for guiding novel interventions. It also illustrates how large datasets (e.g., UK Biobank, GWAS summary statistics) and advanced computational tools (e.g., LDSC, LAVA, genomic SEM, and T-SEM) may be leveraged for dissecting complex multimorbidity patterns, emphasising the importance of refining statistical approaches to capture biologically meaningful genetic overlap.

From a clinical point of view, this thesis establishes that metabolic dysfunction is not merely a secondary consequence of psychiatric illness or psychotropic treatment but can be a fundamental modifier of disorder trajectories. Findings from **Chapters 2** to **4** indicate that IR-related conditions predict poorer psychiatric outcomes, including increased risk for treatment resistance, greater cognitive impairment, and heightened chronicity. This underscores the need for integrated clinical management strategies that simultaneously address both psychiatric and metabolic dysfunction, moving beyond conventional siloed treatment approaches.

The findings described in this thesis support the need for metabolic risk screening in psychiatric practice, particularly in individuals presenting with systemic inflammation or other early markers of metabolic dysfunction. Given the observed genetic overlap between psychiatric and IR-related conditions, future research should explore whether PGSs can contribute to risk stratification. However, given the current limitations of PGSs in clinical psychiatry, their direct application remains uncertain. Rather than advocating for immediate implementation, this thesis underscores the importance of validating multimorbidity-based genetic risk models in large, diverse clinical cohorts before they can be integrated into routine care. If proven robust, such tools could eventually aid in personalised treatment selection, guiding clinicians toward metabolically neutral psychotropic agents, adjunctive metabolic interventions, or anti-inflammatory strategies tailored to an individual's broader health risk profile.

From a methodological perspective, my work advances the field by leveraging state-of-the-art genomic and transcriptomic approaches to dissect psychiatric-IR multimorbidity. The application of LAVA, Genomic and transcriptome-wide SEM, and cross-trait gene-set enrichment analyses enables a fine-grained dissection of shared mechanisms. These results highlight the power of tissue-specific and pathway-based analyses in uncovering potential targetable biological processes that bridge psychiatric and metabolic dysfunction. On the genetic and molecular front, the findings spotlight both positive and negative genetic correlations between neuropsychiatric and IR-related conditions, identifying candidate genes and pathways for pharmacological intervention and future functional validation. They also provide potential clinical correlates among patients who exhibit both psychiatric and IR conditions, suggesting the possible utility of insulin-related biomarkers for tailoring interventions.

While this work makes significant strides in elucidating psychiatric-IR bidirectional links, it also highlights several key areas for future research. First, the causal pathways linking IR, inflammation, and psychiatric symptoms remain incompletely understood. Future research should employ multivariate MR and experimental validation (e.g., CRISPR gene-editing, patient-derived iPSC models) to dissect the mechanistic role of insulin signalling in psychiatric disorders. Second, the integration of multi-omics approaches—including metabolomics, proteomics, and epigenomics—will be important for capturing the dynamic interplay between genetic risk and environmental exposures. Third, translating these findings into clinical interventions requires rigorous, large-scale RCTs testing metabolic-targeting therapies in psychiatric populations.

In conclusion, my work makes significant contributions to the understanding of psychiatric-IR multimorbidity, linking genetic, biological, and clinical perspectives to advance scientific knowledge and clinical practice. By emphasising the importance of shared genetic and biological mechanisms, integrated care models, and biologically informed diagnostics, it lays the groundwork for a new era of precision, metabolic psychiatry. Future research must now focus on translating these discoveries into clinical applications, ensuring that emerging genomic and metabolic insights inform efforts to improve outcomes for individuals with psychiatric disorders.

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Appendix

English summary

Psychiatric disorders are prevalent mental health conditions that frequently co-occur with insulin resistance (IR)-related somatic conditions, like obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS). Although lifestyle factors and pharmacotherapeutic side effects have long been posited as the principal mechanisms underlying such multimorbidity, accumulating evidence indicates that intrinsic dysregulation of insulin signalling in the central nervous system may also play a role. The overarching aim of this thesis is to clarify how IR-related metabolic conditions intersect with psychiatric disorders from both clinical and genetic standpoints. By integrating epidemiological research, primary care data, and large-scale genomic analyses, this work uncovers how IR-related conditions shape clinical trajectories of psychiatric disorders and share essential molecular mechanisms with them. Two central parts delineate this effort, beginning with in-depth clinical and phenotypic perspectives on psychiatric-IR multimorbidity (**Part I**) and advancing to its underlying genetic architecture and molecular mechanisms (**Part II**).

PART I: Clinical and phenotypic interfaces of psychiatric–insulin resistance multimorbidity (Chapters 2–4)

Part I provides a clinical and phenotypic framework for understanding how IR adversely influences cognitive function, risk for mood disorders, and treatment outcomes in depression. **Chapter 2** systematically reviews empirical findings from the UK Biobank, focusing on the relationship between IR-related conditions and cognition. A pronounced negative impact on multiple cognitive domains—including reasoning ability and processing speed—emerges among individuals with IR-related conditions, suggesting that IR might exacerbate cognitive deficits commonly associated with psychiatric disorders. **Chapter 3** evaluates the bidirectional link between T2DM and mood disorders, integrating both evidence from longitudinal studies and Mendelian randomisation analyses. The results demonstrate that T2DM confers a more severe depressive course, whereas mood disorders in turn accelerate cardiovascular and metabolic complications in T2DM, likely through inflammatory and hypothalamic–pituitary–adrenal axis dysregulation. **Chapter 4** leverages primary care records from the UK Biobank to address how concurrent IR conditions influence the clinical profile, antidepressant treatment response, and overall management of depression. Participants with IR-related comorbidities exhibit delayed improvement under antidepressants and require more complex pharmacological regimens, underscoring that metabolic disturbances not only potentiate morbidity but also hinder therapeutic success.

PART II: Genetic architecture and molecular mechanisms of psychiatric–insulin resistance multimorbidity (Chapters 5–7)

Part II shifts toward the genetic and molecular dimensions of psychiatric–IR multimorbidity, employing state-of-the-art genomic approaches to pinpoint shared biological pathways. **Chapter 5** investigates genome-wide association studies (GWAS) to explore genetic correlations between psychiatric disorders and IR-related conditions. These analyses reveal a spectrum of genetic relationships, with some disorders—such as major depressive disorder and ADHD—exhibiting positive genetic correlations with IR conditions and traits, while others, including anorexia nervosa and obsessive-compulsive disorder, demonstrate negative correlations. **Chapter 6** further dissects these relationships through local genetic correlation analyses across semi-independent genomic regions, highlighting specific loci with pleiotropic effects. Even in the absence of global genetic correlations for some disorders (e.g., bipolar disorder or Alzheimer's disease), shared regions implicate biological pathways related to immune-inflammatory responses, insulin receptor recycling, and lipid metabolism. **Chapter 7** synthesises this understanding through genomic and transcriptome-wide structural equation modelling, uncovering a latent multimorbidity factor capturing shared genetic liability across psychiatric and IR-related phenotypes. This factor implicates pathways related to insulin binding, Notch signalling, and immune-inflammatory regulation, with tissue-specific gene expression analyses highlighting roles for the cerebellum, cortex, and pituitary gland. These findings point toward early neurodevelopmental and endocrine mechanisms underlying the observed multimorbidity. Drug repurposing analyses identify potential therapeutic candidates, including memantine and rosiglitazone, which target intersecting neuroprotective, metabolic, and immune mechanisms.

Conclusion

The collective results from **Chapters 2–7** clarify that IR-related conditions substantially worsen psychiatric outcomes, including poorer cognition, heightened symptom severity, and suboptimal treatment response. Beyond clinical implications, genomic analyses confirm that psychiatric disorders and somatic insulinopathies converge on shared loci and pathways—including insulin signalling, immune responses, and vesicle-mediated synaptic regulation—highlighting a convergence that was not fully appreciated through earlier, single-phenotype approaches. These findings endorse the view that certain neuropsychiatric disorders can be fruitfully reconceptualised as "insulinopathies of the brain", where potentially central insulin signalling deficits amplify risk or severity. The perspective that metabolic

and psychiatric pathologies are mutually reinforcing, with a partial common genomic basis, stimulates new strategies for prevention and care. Interventions targeting both metabolic health and psychiatric stability—ranging from lifestyle modifications to immunomodulatory and insulin-sensitising agents—appear promising. Future investigations should verify these candidate pathways through experimental models, expand sampling to multi-ethnic cohorts, and systematically evaluate drug repurposing options. Ultimately, this thesis contributes a cohesive framework for understanding and mitigating the burden of psychiatric–IR multimorbidity in the era of precision medicine.

Nederlandse samenvatting (Dutch summary)

Psychiatrische aandoeningen zijn veelvoorkomende stoornissen die vaak gepaard gaan met somatische aandoeningen die verband houden met insulineresistentie (IR), zoals obesitas, type 2 diabetes mellitus (T2DM) en het metabool syndroom (MetS). Hoewel leefstijlfactoren en bijwerkingen van psychofarmacologische behandellingen lange tijd als de voornaamste verklaring voor deze multimorbiditeit werden beschouwd, wijst toenemend bewijs erop dat intrinsieke ontregeling van de insulinesignalering in het centrale zenuwstelsel hier wellicht ook een rol in kan spelen. Het overkoepelende doel van dit proefschrift is om de klinische en genetische samenhang tussen IR-gerelateerde metabole aandoeningen en psychiatrische aandoeningen te verduidelijken. Door epidemiologisch onderzoek, gegevens uit de eerstelijnszorg en grootschalige genetische analyses te combineren, draagt dit werk bij aan onze kennis over hoe IR-gerelateerde aandoeningen de klinische trajecten van psychiatrische stoornissen beïnvloeden, en essentiële moleculaire mechanismen met hen delen. Dit proefschrift is opgedeeld in twee delen: het eerste deel richt zich op de klinische en fenotypische dimensies van psychiatrische en IR-gerelateerde multimorbiditeit (**Deel I**), terwijl het tweede deel zich richt op de onderliggende genetische architectuur en moleculaire mechanismen (**Deel II**).

DEEL I: Klinische en fenotypische dimensies van psychiatrische en insulineresistentie multimorbiditeit (Hoofdstukken 2–4)

Deel I biedt een klinisch en fenotypisch kader voor het begrijpen van de invloed van IR op cognitieve functies, risico op stemmingsstoornissen en behandeluitkomsten bij depressie. **Hoofdstuk 2** geeft een systematisch overzicht van empirische bevindingen in de UK Biobank en onderzoekt de relatie tussen IR-gerelateerde aandoeningen en cognitie. Personen met IR-gerelateerde aandoeningen vertonen minder goede prestaties in verschillende cognitieve domeinen, waaronder redeneervermogen en verwerkingssnelheid, wat suggereert dat IR cognitieve problemen, zoals vaak waargenomen bij psychiatrische stoornissen, kan verergeren. **Hoofdstuk 3** evalueert de bidirectionele relatie tussen T2DM en stemmingsstoornissen, waarbij zowel longitudinale studies als Mendeliaanse randomisatie analyses worden geïntegreerd. De resultaten tonen aan dat T2DM gepaard gaat met een ernstiger beloop van depressie, terwijl stemmingsstoornissen op hun beurt het risico op cardiovasculaire en metabole complicaties bij T2DM verergeren, waarschijnlijk door ontregeling van inflammatie mechanismen en de hypothalamus-hypofyse-bijnier (HPA)-as. **Hoofdstuk 4** maakt gebruik van eerstelijnszorggegevens uit het UK Biobank project om te onderzoeken hoe gelijktijdige IR-aandoeningen de klinische kenmerken, antidepressieve behandelrespons en de algemene controle over depressie beïnvloeden. Personen met

IR-gerelateerde comorbiditeiten vertonen een vertraagde respons op antidepressiva en vereisen complexere farmacologische behandellingen, wat aantoont dat metabole ontregeling niet alleen de ziektelast verhoogt, maar ook de effectiviteit van behandellingen ondermijnt.

DEEL II: Genetische architectuur en moleculaire mechanismen van psychiatrische en insulineresistentie multimorbiditeit (Hoofdstukken 5–7)

Deel II richt zich op de genetische en moleculaire dimensies van psychiatrische en IR-gerelateerde multimorbiditeit en maakt gebruik van geavanceerde genetische methodologieën om gedeelde biologische mechanismen te identificeren. **Hoofdstuk 5** gebruikt genome-wide associatie studies (GWAS) om genetische correlaties tussen psychiatrische stoornissen en IR-gerelateerde aandoeningen in kaart te brengen. Deze analyses onthullen een spectrum aan genetische relaties, waarbij sommige stoornissen – zoals depressie en ADHD – positieve genetische correlaties met IR-gerelateerde aandoeningen en kenmerken vertonen, terwijl andere, zoals anorexia nervosa en obsessieve-compulsieve stoornis, negatieve correlaties laten zien. **Hoofdstuk 6** gaat dieper in op deze relaties via lokale genetische correlatieanalyses in semi-onafhankelijke genetische regio's en identificeert specifieke loci met pleiotrope effecten. Zelfs in afwezigheid van globale genetische correlaties voor sommige aandoeningen (bijv. bipolaire stoornis of de ziekte van Alzheimer), wijzen gedeelde genetische regio's op biologische mechanismen die verband houden met ontsteking, insuline-receptor recycling en vetmetabolisme.

Hoofdstuk 7 integreert deze inzichten met behulp van genetische en transcriptoom-brede analyses en modellen, wat leidt tot de identificatie van een genetische latente multimorbiditeitsfactor die gedeelde genetische kwetsbaarheid over psychiatrische en IR-gerelateerde fenotypes weergeeft. Deze factor omvat onder andere genen die verband houden met insuline binding, Notch-signalering en ontsteking, met specifieke genexpressiepatronen in de kleine hersenen, cortex en hypofyse. Deze bevindingen suggereren dat vroege hersenontwikkeling en endocriene processen mogelijk bijdragen aan de waargenomen multimorbiditeit. Daarnaast wordt via mogelijke medicatie herbestemming-analyses een reeks potentiële therapeutische kandidaten geïdentificeerd, waaronder memantine en rosiglitazon, die mogelike neuroprotectieve, metabole en immuunmodulerende werkingsmechanismen kunnen combineren.

Conclusie

De bevindingen uit de **hoofdstukken 2–7** verduidelijken dat IR-gerelateerde aandoeningen een negatieve invloed hebben op psychiatrische uitkomsten, waaronder verminderde cognitieve functies, ernstigere symptomen en een suboptimale behandelrespons. Naast deze klinische implicaties bevestigen genetische analyses dat psychiatrische stoornissen en somatische insulinepathologieën overlappen op gedeelde genetische loci en biologische mechanismen – waaronder insulinesignalering, ontstekingsregulatie en synaptische transportprocessen – wat een diepere mate van convergentie onthult dan eerdere benaderingen gebaseerd op een enkel psychiatrisch fenotype konden aantonen.

Deze resultaten ondersteunen de hypothese dat bepaalde psychiatrische aandoeningen kunnen worden heroverwogen als 'insulinopathieën van de hersenen', waarbij mogelijk centrale insulineontregeling het risico of de ernst van de aandoening vergroot. Dit onderstreept dat psychiatrische en metabole aandoeningen elkaar wederzijds beïnvloeden en deels een gemeenschappelijke genetische basis delen. Deze inzichten vormen een stimulans voor de ontwikkeling van geïntegreerde behandelstrategieën die zowel de metabole als psychiatrische gezondheid verbeteren.

Preventieve en therapeutische benaderingen die metabole stabiliteit en psychiatrisch welzijn bevorderen – variërend van leefstijlinterventies tot immunmodulerende en insuline-sensibiliserende behandellingen – lijken veelbelovend. Toekomstig onderzoek dient deze kandidaat-mechanismen verder te valideren via experimentele modellen, de populaties uit te breiden naar multi-etnische cohorten en systematisch de mogelijkheden voor medicatie herpositionering te evalueren. Dit proefschrift biedt een coherente structuur voor het begrijpen van psychiatrische en –IR-gerelateerde multimorbiditeit en draagt bij aan de ontwikkeling van gepersonalieerde behandellingen in de psychiatrie.

Description of research data management

ETHICS and PRIVACY

1. Type of research

☒ Medical-scientific research with human participants not subject to Medical Research Involving Human Subjects Act (non-WMO)

☒ Medical-scientific research without human participants

2. Evaluation of research by medical ethics board (applicable to **Chapter 4** only**)**

Chapter 4: Evaluated by: North West Multi-centre Research Ethics Committee (MREC); Approval number: 11/NW/0382; Approval date: initially granted in 2011, renewed in 2016 and 2021

Chapters 5, 6, and 7: Analysis of secondary data (genome-wide association study summary statistics) that does not involve individual-level human participation

3. Privacy of participants

☒ Data were pseudonymised (for **Chapter 4** using UK Biobank data)

- Pseudonymisation tool: UK Biobank's Research Analysis Platform
- Methodology: Randomised unique identifiers (EIDs) assigned to participants and distinct for each access application
- Key file storage: Managed by UK Biobank, inaccessible to researchers

☒ Data were anonymised (for GWAS summary statistics in **Chapters 5-7**)

DATA COLLECTION and STORAGE

4. Data Reuse

☒ My research reuses existing data sources

- **Chapter 4**: UK Biobank primary care records
- **Chapter 5, 6**, and **7**: Summary statistics from publicly available GWAS on psychiatric disorders and IR-related conditions
- Sources: GWAS Catalog, UK Biobank, Psychiatric Genomics Consortium (PGC), Diabetes Genetics Replication and Meta-analysis Consortium (DIAGRAM), Gene Identification for ANthropometric Traits (GIANT), Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)

5. Data collection and analysis

☒ Extraction from (electronic) health records (UK Biobank primary care records; **Chapter 4**)
☒ R-scripts (statistical analyses in all chapters)
☒ Excel (data handling and variable preparation for analyses in **Chapter 4**)
☒ GWAS summary statistics (genetic correlation and multi-omics analyses in **Chapters 5-7**)
☒ Other statistical tools: LDSC, GNOVA, LAVA, FUMA, coloc/SuSiE, SNPNexus, genomic SEM, T-SEM, MAGMA, PharmOmics

Remarks:
Data in **Chapter 4** were extracted from UK Biobank primary care records. **Chapters 5, 6, and 7** utilised public GWAS summary statistics.

6. Data storage

☒ Surfsara Snellius High Performance Computer (HPC)
☒ Institutional workstation

DATA SHARING, ACCESS, and RE-USE

7. Data sharing, access and reuse:

☒ Data from GWAS summary statistics (**Chapters 5-7**) are publicly available
☒ Individual-level UK Biobank data (**Chapter 4**) is not publicly shareable and is available only through UK Biobank access procedures
☒ Open Access Publications
- **Chapters 2, 3, 4, 5** (CC BY 4.0)
  DOI: 10.1016/j.neubiorev.2022.104927 (**Chapter 2**),
  DOI: 10.1016/j.neubiorev.2023.105298 (**Chapter 3**)
  DOI: 10.1192/bjp.2025.82 (**Chapter 4**)
  DOI: 10.1038/s41398-022-01817-0 (**Chapter 5**)

- **Chapters 6** and **7** (CC-BY-NC-ND 4.0)
  DOI: 10.1038/s41398-025-03349-9 (**Chapter 6**)
  DOI: 10.1101/2024.10.02.24314704 (**Chapter 7**)

Data locations and agreed time of storage

8. Time specification of data availability

☒ GWAS summary statistics used in this thesis (**Chapters 5–7**) are publicly available and will remain accessible indefinitely via their respective repositories.

☒ Individual-level UK Biobank data (**Chapter 4**) is only accessible through UK Biobank access procedures and cannot be shared. UK Biobank maintains participant data indefinitely under its research policies, but access requires a separate application.

☒ Preprint data (**Chapters 7**) on medRxiv will remain publicly available for the foreseeable future, subject to the policies of the preprint server.

☒ Open-access publications and supplementary materials will remain available indefinitely under their respective licenses.

☒ Scripts and analytical code used for genetic analyses (e.g., LDSC, LAVA, genomic SEM, T-SEM, and related pipelines) are available on GitHub. Scripts will remain available indefinitely unless repository policies change.

Curriculum vitae

Giuseppe Fanelli is a medical doctor specialised in psychiatry with a research background in psychiatric genomics, neuropsychobiology, and precision psychiatry. He obtained his MD from the University of Bari "Aldo Moro" in 2016, graduating cum laude (110/110) with a thesis on glutamatergic polygenic risk scores for schizophrenia and their association with cognitive function and brain activity in healthy individuals, supervised by Prof. Alessandro Bertolino and Prof. Antonio Rampino. During his medical studies, he trained in psychiatric genomics at the Psychiatric Neuroscience Group of the University of Bari and participated in an Erasmus+ program at the Medical University of Plovdiv, Bulgaria.

After completing his medical degree, he specialised in Psychiatry at the University of Bologna, earning his residency diploma in 2020 with cum laude distinction (110/110). His thesis investigated the genetic relationship between insulin resistance-related somatic conditions and neuropsychiatric disorders. During his specialisation, he worked in inpatient and outpatient psychiatric settings, focusing on mood and psychotic disorders, treatment-resistant depression, and suicidal behaviour. His research on genetic predictors of antidepressant response and suicidal behaviour was supervised by Prof. Alessandro Serretti and Prof. Chiara Fabbri. He also trained at Radboud University Medical Center (Nijmegen, Netherlands), where he joined the Multifactorial Research Group, Department of Human Genetics, as a Visiting Researcher (2019–2020) under the supervision of Prof. Barbara Franke and Dr. Janita Bralten.

Between 2021 and 2023, he was a Research Fellow at the University of Bologna, focusing on genetic predictors of antidepressant response, suicidal behaviour, and psychiatric multimorbidity. His role included genomic and clinical analyses, postgraduate supervision, and teaching in psychiatry. During this period, he also worked as a private psychiatrist in an outpatient setting, providing diagnostic assessment, pharmacological management, and psychotherapeutic support for patients with various psychiatric disorders. Additionally, he served as a psychiatry consultant at Bologna General Hospital "Maggiore", offering counselling and clinical management for patients admitted to medical and surgical units or presenting to the emergency department.

Since 2023, he has been a (fixed-term) Junior Assistant Professor (RTD-A) at the University of Bologna, working on the PNRR (National Recovery and Resilience Plan/Next Generation EU)–funded MNESYS project (*A Multiscale Integrated Approach to the Study of the Nervous System in Health and Disease*). His research integrates genetic and clinical data to advance precision medicine in psychiatry. He oversees biological sample collection, manages research funding, and collaborates

on large-scale genomic studies. He lectures in Psychiatry at the University of Bologna, teaching undergraduate and postgraduate courses and supervising psychiatric trainees.

He was actively involved in several high-profile European research initiatives, including the Horizon 2020-funded PRIME (*Prevention and Remediation of Insulin Multimorbidity in Europe*) project, where he investigated the shared genetic architecture between insulin resistance-related conditions and major psychiatric disorders; PRISM2 (*Psychiatric Ratings using Intermediate Stratified Markers 2) project*, where he was responsible for imaging genomic analyses linking social behaviour with functional brain networks.

Since December 2024, he holds the National Scientific Qualification for the role of Associate Professor in Psychiatry in the Italian national academic system. This qualification acknowledges his scientific contributions and enables him to apply for tenured professorship positions at Italian universities.

He serves as Managing Editor for International Clinical Psychopharmacology and Associate Editor for Frontiers in Psychiatry (Mood Disorders Section).

He has received multiple research awards, including the European College of Neuropsychopharmacology (ECNP) Excellence Award in 2024 and 2020, the World Federation of Societies of Biological Psychiatry (WFSBP) Young Investigator Award in 2021, the Collegium Internationale Neuro-Psychopharmacologicum (CINP) Student Encouragement Award in 2022, and the International Society of Psychiatric Genetics (ISPG) Early Career Investigator Award in 2021. He is Chair of the ECNP Network on Suicide Research and Prevention and collaborates in multiple international psychiatric genomics research initiatives.

Portfolio

Name PhD candidate: Giuseppe Fanelli
Graduate School: Donders Graduate School
PhD period: 01-01-2021 – 01-01-2025

1. Courses & workshops

- 6-16 June 2022 | University of Colorado Boulder (Virtual Course) - *2022 International Statistical Genetics Workshop on Statistical Genetic Methods for Human Complex Traits* | *Attendee*
- 16 May & 7 June 2024 | Radboudumc Health Academy (Virtual Course) - Scientific Integrity Course for PhD Candidates | *Attendee*
- 9-31 March 2022 | University of Cambridge, Online - *Mendelian Randomisation Course* | *Attendee*
- August 2020 | Virtual - Online Machine Learning School by the European College of Neuropsychopharmacology (ECNP) Neuroimaging Network | Attendee
- May 2020 | Radboud University Medical Center, Nijmegen, Netherlands (remote) - Presentation Skills Course | Attendee
- April 2020 | Radboud University Medical Center, Nijmegen, Netherlands (remote) - Grant Writing and Presenting for Funding Committees | Attendee

2. Conferences and scientific presentations

- 28-30 April 2025 | Bordeaux, France – *ECNP School on "Precision Psychiatry: -omics and imaging biomarkers of major psychiatric disorders" by the ECNP Networks on Pharmacogenomics and transcriptomics & Suicide Research and Prevention* | *Organiser of the ECNP School and Chair* | *Symposium: "Suicidality under the lens: neuroimaging, genetic, and biologic evidence"; Facilitator* | *Practical on "Imaging genomics of suicide"*
- 11 April 2025 | Udine, Italy - *Knots and joints in psychiatry XVII edition 2025 "Mens sana in corpore sano: the immune-metabolic face of psychiatric disorders"* | *Speaker* | *Lecture: "Multimorbidity between psychiatric disorders and insulin resistance: clinical impact, shared genetics, and biological mechanisms"*
- 11-13 December 2024 | Cologne, Germany - *6th General Assembly of the EU Horizon 2020 project "Prevention and Remediation of Insulin Multimorbidity in Europe" (PRIME)* | *Speaker* | *Talk: "Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders (summary of four years of studies)"*

- 30 September 2024 | Bari, Italy - *Personalising care: the role of metabolic psychiatry in precision medicine* | *Speaker* | *Talk: "Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders"*
- 13-15 May 2024 | Bologna, Italy - *5th General Assembly of the EU Horizon 2020 project "Prevention and Remediation of Insulin Multimorbidity in Europe" (PRIME)* | *Speaker* | *Talk: "Transcriptome-wide structural equation modelling of insulin resistance - neuropsychiatric multimorbidity"*
- 11-12 April 2024 | Deursen-Dennenburg, Netherlands - *The Royal Netherlands Academy of Arts and Sciences (KNAW) Symposium – MindYourBody!* | *Plenary speaker* | *Talk: "The link of insulin resistance with mood and psychosis: insights from the clinic"*
- 25 March 2024 | Istituto Superiore di Sanità (ISS), Rome, Italy - *Center for Behavioural Sciences and Mental Health seminars* | *Speaker* | *Talk: "Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders"*
- 21-23 February 2024 | Rome, Italy - *XXVIII National Congress of the Italian Society of Psychopathology (SOPSI)* | *Speaker* | *Symposium: "Physical well-being in patients with severe mental disorders: from genetics to personalised treatments"* | *Talk: "Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders"*
- 10-14 October 2023 | Montreal, Canada - *World Congress of Psychiatric Genetics (WCPG) 2023* | *Speaker* | *Talk: "Shared genetics linking sociability with the brain's default mode network"*
- 9 June 2023 | Brescia, Italy - *Conference: The results of the DIAPASON project* | *Speaker* | *Talk: "Prescribing patterns of antipsychotic drugs and correlation with physical activity levels"*
- 15 March 2023 | Remote - *Psychiatric Genomics Consortium (PGC) Suicide Working Group Meeting* | *Speaker* | *Talk: "Disentangling the genetic overlap between major psychiatric disorders, somatic diseases and suicide attempt"*
- 15-18 October 2022 | Vienna, Austria - *35th European College of Neuropsychopharmacology (ECNP) Congress 2022* | *Speaker* | *Symposium: "The role of insulin in the comorbidity between neuropsychiatric and somatic disorders"*
- 13-17 September 2022 | Florence, Italy - *World Congress of Psychiatric Genetics (WCPG) 2022* | *Poster presenter and mentor for early career researchers*
- 6-8 September 2022 | Castelldefels, Barcelona, Spain - *6th extended Horizon 2020 PRIME Steering Committee Meeting* | *Speaker*
- 8-12 June 2022 | Virtual & Taipei, Taiwan - *33rd CINP Hybrid World Congress of Neuropsychopharmacology (CINP 2022)* | *Speaker and poster presenter* | *Talk: "A meta-analysis of polygenic risk scores for mood disorders, neuroticism, and schizophrenia in antidepressant response"*

- 12 January 2022 | Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Netherlands (remote) - *Neurodevelopmental Disorders (NDD) event* | *Speaker*
- 10-14 October 2021 | Virtual - *Virtual World Congress of Psychiatric Genetics (WCPG) 2021* | *Poster presenter*
- 1-4 October 2021 | Lisbon, Portugal (hybrid) - *34th European College of Neuropsychopharmacology (ECNP) Congress Hybrid* | *Poster presenter*
- 27-29 June 2021 | Virtual - *15th World Congress of Biological Psychiatry (WFSBP Congress 2021)* | *Speaker and poster presenter*
- 28 June 2021 | Virtual - *51st Behaviour Genetics Association (BGA) Meeting 2021* | *Poster presenter*
- 25 February 2021 | Virtual - *International College of Neuropsychopharmacology (CINP) 2021 Virtual World Congress* | *Poster presenter*
- 11 February 2021 | Radboud University Medical Center, Nijmegen, Netherlands (remote) - *Radboudumc Theme Discussion* | *Speaker* | *Talk: "Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders"*

3. Organising committees for conferences or workshops

- 28-30 April 2025 - *"Precision Psychiatry: -omics and imaging biomarkers of major psychiatric disorders"*, Bordeaux School of Neuroscience, Bordeaux, France
- 35th World Congress of the Collegium Internationale Neuro-Psychopharmacologicum (CINP 2024) - May 23–26, 2024 | Tokyo, Japan - *Member of the International Scientific Program Committee*

4. Networks and affiliations

- 10/2024 – Present: European College of Neuropsychopharmacology (ECNP) *Subnetwork "Genetics to the clinic"*
- 06/2023 – Present: *Chair of the European College of Neuropsychopharmacology (ECNP) Network on Suicide Research and Prevention*
- 11/04/2022 – Present: *Member of the Collegium Internationale Neuro-Psychopharmacologicum (CINP)* (*Member No: 64060400*)
- 01/2020 – Present: *Member of the European College of Neuropsychopharmacology (ECNP) Network on Suicide Research and Prevention*
- 10/2018 – Present: *Member of the European College of Neuropsychopharmacology (ECNP)* (*Member No: M-03943*)
- 09/2018 – Present: *Member of the International Society of Psychiatric Genetics (ISPG)*

- 12/2024 – Present: *Member of the Hierarchical Taxonomy Of Psychopathology (HiTOP) Society*

5. Peer-reviewer activity

- Peer-reviewer for the Journal of Affective Disorders, International Clinical Psychopharmacology, International Journal of Psychiatry in Clinical Practice, Molecular Psychiatry, Neuropsychobiology, Neuroscience & Biobehavioural Reviews, Personalised Medicine in Psychiatry, Progress in Neuro-Psychopharmacology & Biological Psychiatry, Psychological Medicine, Psychiatric Genetics, The Lancet Psychiatry, The American Journal of Psychiatry, Translational Psychiatry, The International Journal of Neuropsychopharmacology, The World Journal of Biological Psychiatry, The British Journal of Psychiatry.
- Symposia peer-reviewer for the *International College of Neuropsychopharmacology (CINP) 2024 World Congress - Tokyo, Japan*
- Web of Science - Peer-review records: https://www.webofscience.com/wos/author/record/M-4050-2019 (more than 60 verified peer-reviews)

6. Editorial board membership

- 2021 - Present: *Managing Editor, International Clinical Psychopharmacology*
- 2022 - Present: *Review Editor for Mood Disorders, Frontiers in Psychiatry*
- 2024 - Present: *Associate Editor, Frontiers in Psychiatry*
- Web of Science - Editor records: https://www.webofscience.com/wos/author/record/M-4050-2019 (more than 149 verified editor records)

7. Teaching experience

- 2021 - Present: *"Cultore della materia"* in Psychiatry, University of Bologna, Italy
  (*In the Italian academic system, "Cultore della materia" is an honorary title given to a field expert appointed by the Faculty to serve on examination committees and contribute to teaching activities*)
- 01/03/2023 - Present: *Lecturer in Psychiatry, University of Bologna, Italy*
  University courses• 2022: *Module MED-BMS22 "Vanishing boundaries between neurodevelopmental disorders"*, Master's in Biomedical Sciences, Radboud University, Nijmegen, NL

- 2021 - 2023: Member of the examination committee for the *Psychiatry course, Module of Mental Health Studies (Combined Unit)*, 1st Cycle Degree/Bachelor's in Nursing, University of Bologna, Faenza, IT
- 2021 - 2023: Member of the examination committee for the *Psychiatry 3 course, Module of First Aid (Combined Unit)*, 1st Cycle Degree/Bachelor's in Health Professions for Rehabilitation, University of Bologna, Imola, IT
- 09/2022 - 2023: Member of the examination committee for the *Psychopathology of Emotional Disorders*, Master's in Applied Cognitive Psychology, University of Bologna, Bologna, IT
- 2023 - Present: *Psychiatry course, Module of Mental Health Studies (Combined Unit)*, 1st Cycle Degree/Bachelor's in Nursing, University of Bologna, Faenza, IT
- 09/2023 - Present: *Doctor-Patient Relationship*, Residency in Psychiatry, University of Bologna, Bologna, IT
- 2023 - Present: *Psychiatric Clinical Interview*, Residency in Psychiatry, University of Bologna, Bologna, IT
- 09/2023 - Present: *Supervisions in Psychotherapy II*, Residency in Psychiatry, University of Bologna, Bologna, IT
- 09/2023 - Present: *Psychiatry course, Module of Mental Health Studies (Combined Unit)*, 1st Cycle Degree/Bachelor's in Nursing, University of Bologna, Rimini Campus, Rimini, IT
- 09/2023 - Present: *Psychiatry course, Module of Neurosciences (Combined Unit)*, 1st Cycle Degree/Bachelor's in Speech and Language Therapy (Logopaedics), University of Bologna, Faenza, IT
- 10/2023 - Present: Member of the examination committee for the *Psychiatry course, Master's in Medicine and Surgery (English language)*, University of Bologna, Bologna, IT

Invited lectures

- 08/06/2024 - *Invited lecture on "Psychopharmacology and Multimorbidity"*, Residency in Community and Primary Care Medicine, University of Modena and Reggio Emilia, Modena, IT

Supervision of residents in psychiatry and research fellows

- Residents in psychiatry supervised: Actively involved in the supervision of 14 psychiatry residents, providing guidance in clinical psychiatry, psychiatric genomics, and psychopharmacology research.

- Research fellows (Co-supervised): Co-supervised four research fellows, supporting them in study design, data analysis, and scientific writing.

8. Outreach and impact

Media appearances or interviews

- Antenna Sud (Southern Italy TV broadcaster): https://www.youtube.com/watch?v=_ivvQEVr8Z4
- La Voce di Manduria (local newspaper): https://www.lavocedimanduria.it/articolo/da-un-ricercatore-maruggese-lesperanze-di-cura-per-i-disturbi-neuropsichiatrici_77443
- UK Science Media Center (roundups for journalists): https://www.sciencemediacentre.org/ expert-reaction-to-study-looking-at-semaglutide-liraglutide-and-suicidality/

Blogging or writing for a lay audience

- insulin resistance is associated with worse cognitive performance: https://prime-study.eu/news-events/publications/insulin-resistance-is-associated-with-worse-cognitive-performance/

List of publications

Peer-reviewed publications with major contribution (first, second, or last author)

 # = Shared first authorship
§ = Shared last authorship

Arenella, M., **Fanelli, G.**, Kiemeney, L. A., McAlonan, G., Murphy, D. G., & Bralten, J. (2023). Genetic relationship between the immune system and autism. Brain Behav Immun Health, 34, 100698. https://doi.org/10.1016/j.bbih.2023.100698

Borgiani, G., Possidente, C., Fabbri, C., Oliva, V., Bloemendaal, M., Arias Vasquez, A., Dinan, T. G., Vieta, E., Menchetti, M., De Ronchi, D., Serretti, A., & **Fanelli, G.** (2025). The bidirectional interaction between antidepressants and the gut microbiota: are there implications for treatment response? Int Clin Psychopharmacol, 40(1), 3-26. https://doi.org/10.1097/yic.0000000000000533

Fanelli, G., Benedetti, F., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., Serretti, A., & Fabbri, C. (2021). Higher polygenic risk scores for schizophrenia may be suggestive of treatment non-response in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry, 108, 110170. https://doi.org/10.1016/j.pnpbp.2020.110170

Fanelli, G., Benedetti, F., Wang, S. M., Lee, S. J., Jun, T. Y., Masand, P. S., Patkar, A. A., Han, C., Serretti, A., Pae, C. U., & Fabbri, C. (2019). Reduced CXCL1/GRO chemokine plasma levels are a possible biomarker of elderly depression. J Affect Disord, 249, 410-417. https://doi.org/10.1016/j.jad.2019.02.042

Fanelli, G., Benedetti, F., Wang, S. M., Lee, S. J., Jun, T. Y., Masand, P. S., Patkar, A. A., Han, C., Serretti, A., Pae, C. U., & Fabbri, C. (2020). Reduced plasma Fetuin-A is a promising biomarker of depression in the elderly. Eur Arch Psychiatry Clin Neurosci, 270(7), 901-910. https://doi.org/10.1007/s00406-019-01090-1

Fanelli, G., Domschke, K., Minelli, A., Gennarelli, M., Martini, P., Bortolomasi, M., Maron, E., Squassina, A., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., De Ronchi, D., Baune, B. T.,…Fabbri, C. (2022). A meta-analysis of polygenic risk scores for mood disorders, neuroticism, and schizophrenia in antidepressant response. Eur Neuropsychopharmacol, 55, 86-95. https://doi.org/10.1016/j.euroneuro.2021.11.005

Fanelli, G., Franke, B., De Witte, W., Ruisch, I. H., Haavik, J., van Gils, V., Jansen, W. J., Vos, S. J. B., Lind, L., Buitelaar, J. K., Banaschewski, T., Dalsgaard, S., Serretti, A., Mota, N. R., Poelmans, G., & Bralten, J. (2022). Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders. Transl Psychiatry, 12(1), 59. https://doi.org/10.1038/s41398-022-01817-0

Fanelli, G.[#], Mota, N. R.[#], Salas-Salvadó, J., Bulló, M., Fernandez-Aranda, F., Camacho-Barcia, L., Testa, G., Jiménez-Murcia, S., Bertaina-Anglade, V., Franke, B., Poelmans, G., van Gils, V., Jansen, W. J., Vos, S. J. B., Wimberley, T., Dalsgaard, S., Barta, C., Serretti, A., Fabbri, C., & Bralten, J. (2022). The link between cognition and somatic conditions related to insulin resistance in the UK Biobank study cohort: a systematic review. Neurosci Biobehav Rev, 143, 104927. https://doi.org/10.1016/j.neubiorev.2022.104927

Fanelli, G., Raschi, E., Hafez, G., Matura, S., Schiweck, C., Poluzzi, E., & Lunghi, C. (2025). The interface of depression and diabetes: treatment considerations. Transl Psychiatry, 15(1), 22. https://doi.org/10.1038/s41398-025-03234-5

Fanelli, G., & Serretti, A. (2019). The influence of the serotonin transporter gene 5-HTTLPR polymorphism on suicidal behaviours: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry, 88, 375-387. https://doi.org/10.1016/j.pnpbp.2018.08.007

Fanelli, G., & Serretti, A. (2022). Depression, antidepressants, and insulin resistance: which link? Eur Neuropsychopharmacol, 60, 4-6. https://doi.org/10.1016/j.euroneuro.2022.04.011

Fanelli, G., Sokolowski, M., Wasserman, D., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., De Ronchi, D., Serretti, A., & Fabbri, C. (2022). Polygenic risk scores for neuropsychiatric, inflammatory, and cardio-metabolic traits highlight possible genetic overlap with suicide attempt and treatment-emergent suicidal ideation. Am J Med Genet B Neuropsychiatr Genet, 189(3-4), 74-85. https://doi.org/10.1002/ajmg.b.32891

Fanelli, G., Bralten, J., Franke, B., Mota, N. R., Atti, A. R., De Ronchi, D., Monteleone, A. M., Grassi, L., MNESYS - Mood and Psychosis Sub-Project (Spoke 5), Serretti, A., & Fabbri, C. (2025). Insulin resistance and poorer treatment outcomes in depression: evidence from UK Biobank primary care data. Br J Psychiatry, 1–10. Advance online publication. https://doi.org/10.1192/bjp.2025.82

Fanelli, G.[#], Robinson, J.[#], Fabbri, C., Bralten, J., Roth Mota, N., Arenella, M., Sprooten, E., Franke, B., Kas, M., Andlauer, T. F., & Serretti, A. (2025). Shared genetics linking sociability with the brain's default mode network. Psychol Med, 55, e157. https://doi.org/10.1017/S0033291725000832

Fanelli, G., Franke, B., Fabbri, C., Werme, J., Erdogan, I., De Witte, W., Poelmans, G., Ruisch, I. H., Reus, L. M., van Gils, V., Jansen, W. J., Vos, S. J. B., Alam, K. A., Martinez, A., Haavik, J., Wimberley, T., Dalsgaard, S., Fóthi, Á., Barta, C., Fernandez-Aranda, F., … Bralten, J. (2025). Local patterns of genetic sharing between neuropsychiatric and insulin resistance-related conditions. Translational psychiatry, 15(1), 145. https://doi.org/10.1038/s41398-025-03349-9

Lippi, M., **Fanelli, G.**, Fabbri, C., De Ronchi, D., & Serretti, A. (2022). The dilemma of polypharmacy in psychosis: is it worth combining partial and full dopamine modulation? Int Clin Psychopharmacol, 37(6), 263-275. https://doi.org/10.1097/yic.0000000000000417

Olgiati, P., **Fanelli, G.**, Atti, A. R., De Ronchi, D., & Serretti, A. (2022). Clinical correlates and prognostic impact of binge-eating symptoms in major depressive disorder. Int Clin Psychopharmacol, 37(6), 247-254. https://doi.org/10.1097/yic.0000000000000422

Olgiati, P., **Fanelli, G.**, & Serretti, A. (2022). Obsessive-compulsive symptoms in major depressive disorder correlate with clinical severity and mixed features. Int Clin Psychopharmacol, 37(4), 166-172. https://doi.org/10.1097/yic.0000000000000396

Olgiati, P., **Fanelli, G.**, & Serretti, A. (2023a). Age or age of onset: which is the best criterion to classify late-life depression? Int Clin Psychopharmacol, 38(4), 223-230. https://doi.org/10.1097/yic.0000000000000472

Olgiati, P., **Fanelli, G.**, & Serretti, A. (2023b). Clinical correlates and prognostic implications of severe suicidal ideation in major depressive disorder. Int Clin Psychopharmacol, 38(4), 201-208. https://doi.org/10.1097/yic.0000000000000461

Oliva, V., **Fanelli, G.**, Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., De Ronchi, D., Fabbri, C., & Serretti, A. (2023). Melancholic features and typical neurovegetative symptoms of major depressive disorder show specific polygenic patterns. J Affect Disord, 320, 534-543. https://doi.org/10.1016/j.jad.2022.10.003

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Oliva, V., **Fanelli, G.**, Zamparini, M., Zarbo, C., Rocchetti, M., Casiraghi, L., Starace, F., Martinelli, A., Serretti, A., & de Girolamo, G. (2023). Patterns of antipsychotic prescription and accelerometer-based physical activity levels in people with schizophrenia spectrum disorders: a multicenter, prospective study. Int Clin Psychopharmacol, 38(1), 28-39. https://doi.org/10.1097/yic.0000000000000433

Panariello, F., **Fanelli, G.**, Fabbri, C., Atti, A. R., De Ronchi, D., & Serretti, A. (2022). Epigenetic Basis of Psychiatric Disorders: A Narrative Review. CNS Neurol Disord Drug Targets, 21(4), 302-315. https://doi.org/10.2174/1871527320666210825101915

Possidente, C., **Fanelli, G.**, Serretti, A., & Fabbri, C. (2023). Clinical insights into the cross-link between mood disorders and type 2 diabetes: A review of longitudinal studies and Mendelian randomisation analyses. Neurosci Biobehav Rev, 152, 105298. https://doi.org/10.1016/j.neubiorev.2023.105298

Scala, M., Del Rocío González Soltero, M., Bellido Esteban, A., Biscaia Fernández, J. M., Romero-Ferreiro, V., Serretti, A., **Fanelli, G.**§, & Rodriguez-Jimenez, R. (2025). Oropharyngeal microbiota in patients with psychotic disorders: A scoping review on compositional and functional alterations. Prog Neuropsychopharmacol Biol Psychiatry, 137, 111288. https://doi.org/10.1016/j.pnpbp.2025.111288

Scala, M., **Fanelli, G.**, De Ronchi, D., Serretti, A., & Fabbri, C. (2023). Clinical specificity profile for novel rapid acting antidepressant drugs. Int Clin Psychopharmacol, 38(5), 297-328. https://doi.org/10.1097/yic.0000000000000488

Peer-reviewed publications from collaborations

Bartova, L., Fugger, G., Dold, M., Kautzky, A., Bairhuber, I., Kloimstein, P., **Fanelli, G.**, Zanardi, R., Weidenauer, A., Rujescu, D., Souery, D., Mendlewicz, J., Zohar, J., Montgomery, S., Fabbri, C., Serretti, A., & Kasper, S. (2024). The clinical perspective on late-onset depression in European real-world treatment settings. Eur Neuropsychopharmacol, 84, 59-68. https://doi.org/10.1016/j.euroneuro.2024.03.007

Bartova, L., Fugger, G., Dold, M., Kautzky, A., **Fanelli, G.**, Zanardi, R., Albani, D., Weidenauer, A., Rujescu, D., Souery, D., Mendlewicz, J., Montgomery, S., Zohar, J., Fabbri, C., Serretti, A., & Kasper, S. (2023). Real-world characteristics of European patients receiving SNRIs as first-line treatment for major depressive disorder. J Affect Disord, 332, 105-114. https://doi.org/10.1016/j.jad.2023.03.068

Chiera, M., Draghetti, S., De Ronchi, D., Scaramelli, A. R., Fabbri, C., **Fanelli, G.**, & Serretti, A. (2023). Hyperthyroidism and depression: a clinical case of atypical thyrotoxicosis manifestation. Int Clin Psychopharmacol, 38(4), 269-272. https://doi.org/10.1097/yic.0000000000000438

De Donatis, D., Verrastro, M., **Fanelli, G.**, Fabbri, C., Maniscalco, I., Hart, X., Schoretsanitis, G., Mercolini, L., Ferri, R., Lanuzza, B., Serretti, A., Conca, A., & Florio, V. (2024). Mirtazapine blood levels and antidepressant response. Int J Psychiatry Clin Pract, 28(2), 102-106. https://doi.org/10.1080/13651501.2024.2409654

Fico, G., Oliva, V., De Prisco, M., Giménez-Palomo, A., Sagué-Vilavella, M., Gomes-da-Costa, S., Garriga, M., Solé, E., Valentí, M., **Fanelli, G.**, Serretti, A., Fornaro, M., Carvalho, A. F., Vieta, E., & Murru, A. (2022). The U-shaped relationship between parental age and the risk of bipolar disorder in the offspring: A systematic review and meta-analysis. Eur Neuropsychopharmacol, 60, 55-75. https://doi.org/10.1016/j.euroneuro.2022.05.004

Fugger, G., Bartova, L., Dold, M., Fabbri, C., **Fanelli, G.**, Zanardi, R., Kautzky, A., Zohar, J., Souery, D., Mendlewicz, J., Montgomery, S., Rujescu, D., Serretti, A., & Kasper, S. (2022). Evidence on sociodemographic and clinical correlates of antidepressant combination or augmentation with second-generation antipsychotics in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry, 114, 110480. https://doi.org/10.1016/j.pnpbp.2021.110480

Fugger, G., Bartova, L., Fabbri, C., **Fanelli, G.**, Dold, M., Swoboda, M. M. M., Kautzky, A., Zohar, J., Souery, D., Mendlewicz, J., Montgomery, S., Rujescu, D., Serretti, A., & Kasper, S. (2022). The sociodemographic and clinical profile of patients with major depressive disorder receiving SSRIs as first-line antidepressant treatment in European countries. Eur Arch Psychiatry Clin Neurosci, 272(4), 715-727. https://doi.org/10.1007/s00406-021-01368-3

Fugger, G., Bartova, L., Fabbri, C., **Fanelli, G.**, Zanardi, R., Dold, M., Kautzky, A., Rujescu, D., Souery, D., Mendlewicz, J., Zohar, J., Montgomery, S., Serretti, A., & Kasper, S. (2022). The sociodemographic and clinical phenotype of European patients with major depressive disorder undergoing first-line antidepressant treatment with NaSSAs. J Affect Disord, 312, 225-234. https://doi.org/10.1016/j.jad.2022.06.004

Kraus, C., Kautzky, A., Watzal, V., Gramser, A., Kadriu, B., Deng, Z. D., Bartova, L., Zarate, C. A., Jr., Lanzenberger, R., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., **Fanelli, G.**, Serretti, A., & Kasper, S. (2023). Body mass index and clinical outcomes in individuals with major depressive disorder: Findings from the GSRD European Multicenter Database. J Affect Disord, 335, 349-357. https://doi.org/10.1016/j.jad.2023.05.042

Laplace, B., Wong, W. L. E., Menchetti, M., De Ronchi, D., Fusar-Poli, P., **Fanelli, G.**, MNESYS - Mood and Psychosis Sub-Project (Spoke 5), Serretti, A., Lewis, C. M., & Fabbri, C. (2025). Factors associated with drug-drug interactions involving citalopram in the UK Biobank. Br J Psychiatry Open, 1–8. Advance online publication. https://doi.org/10.1192/bjo.2025.10060.

Luca, A., Luca, M., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Ferentinos, P., Rujescu, D., Mendlewicz, J., Zanardi, R., Ferri, R., Lanuzza, B., Pecorino, B., Baune, B. T., **Fanelli, G.**, Fabbri, C., & Serretti, A. (2025). Mild motor signs and depression: more than just medication side effects? European archives of psychiatry and clinical neuroscience. Advance online publication. https://doi.org/10.1007/s00406-025-02015-x

Luca, A., Luca, M., Kasper, S., Pecorino, B., Zohar, J., Souery, D., Montgomery, S., Ferentinos, P., Rujescu, D., Messina, A., Zanardi, R., Ferri, R., Tripodi, M., Baune, B. T., **Fanelli, G.**, Fabbri, C., Mendlewicz, J., & Serretti, A. (2024). Anhedonia is associated with a specific depression profile and poor antidepressant response. Int J Neuropsychopharmacol, 27(12). https://doi.org/10.1093/ijnp/pyae055

Luca, M., Luca, A., Messina, A., Bartova, L., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Ferentinos, P., Rujescu, D., Mendlewicz, J., Zanardi, R., Ferri, R., Lanuzza, B., Benedetti, F., Pecorino, B., Baune, B. T., **Fanelli, G.**, Fabbri, C., & Serretti, A. (2025). Specific symptomatology profile associated with treatment resistant depression: A multicentric study from the Group for the Study of Resistant Depression with a focus on sex. J Affect Disord, 375, 249-255. https://doi.org/10.1016/j.jad.2025.01.120

Martone, A., Possidente, C., **Fanelli, G.**, Fabbri, C., & Serretti, A. (2024). Genetic factors and symptom dimensions associated with antidepressant treatment outcomes: clues for new potential therapeutic targets? Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-024-01873-1

Oliva, V., De Prisco, M., Fico, G., Possidente, C., Fortea, L., Montejo, L., Anmella, G., Hidalgo-Mazzei, D., Grande, I., Murru, A., Fornaro, M., de Bartolomeis, A., Dodd, A., **Fanelli, G.**, Fabbri, C., Serretti, A., Vieta, E., & Radua, J. (2023). Correlation between emotion dysregulation and mood symptoms of bipolar disorder: A systematic review and meta-analysis. Acta Psychiatr Scand, 148(6), 472-490. https://doi.org/10.1111/acps.13618

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Oliva, V., Possidente, C., De Prisco, M., Fico, G., Anmella, G., Hidalgo-Mazzei, D., Murru, A., **Fanelli, G.**, Fabbri, C., Fornaro, M., de Bartolomeis, A., Solmi, M., Radua, J., Vieta, E., & Serretti, A. (2024). Pharmacological treatments for psychotic depression: a systematic review and network meta-analysis. Lancet Psychiatry, 11(3), 210-220. https://doi.org/10.1016/s2215-0366(24)00006-3

Oliva, V., Possidente, C., **Fanelli, G.**, Domschke, K., Minelli, A., Gennarelli, M., Martini, P., Bartolomasi, M., Squassina, A., Pisanu, C., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., Baune, B. T., Vieta, E., Serretti, A., & Fabbri, C. (2025). Predicted plasma proteomics from genetic scores and treatment outcomes in major depression: a meta-analysis. Eur Neuropsychopharmacol, 96, 17–27. https://doi.org/10.1016/j.euroneuro.2025.05.004

Rampino, A., Taurisano, P., **Fanelli, G.**, Attrotto, M., Torretta, S., Antonucci, L. A., Miccolis, G., Pergola, G., Ursini, G., Maddalena, G., Romano, R., Masellis, R., Di Carlo, P., Pignataro, P., Blasi, G., & Bertolino, A. (2017). A Polygenic Risk Score of glutamatergic SNPs associated with schizophrenia predicts attentional behaviour and related brain activity in healthy humans. Eur Neuropsychopharmacol, 27(9), 928-939. https://doi.org/10.1016/j.euroneuro.2017.06.005

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