

**A meta-analysis of potential genetic factors associated with antipsychotic-induced weight gain in adults with severe mental illness.**

WARNER-LEVY, John, BELSTON, Lleyton, ILLANGASEKERA, Yasitha, JAMESON, Adam <<http://orcid.org/0000-0002-3248-2302>>, MEEHAN, Cheyenne, WILKINS, Loren, LOUREIRO, Camila Marcelino <<http://orcid.org/0000-0002-0239-5064>>, SALUJA, Sushant, SHAKESPEARE, Mark, DALTON, Caroline <<http://orcid.org/0000-0002-1404-873X>>, REYNOLDS, Gavin <<http://orcid.org/0000-0001-9026-7726>> and HEALD, Adrian <<http://orcid.org/0000-0002-9537-4050>>

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## A Meta-analysis of Potential Genetic Factors Associated with Antipsychotic-Induced Weight Gain (AIWG) in Adults with Severe Mental Illness

Journal:	<i>Journal of Psychopharmacology</i>
Manuscript ID	JOP-2025-6435.R2
Manuscript Type:	Original Paper
Date Submitted by the Author:	29-Dec-2025
Complete List of Authors:	<p>Warner Levy, Julian; Salford Royal Hospitals NHS Trust, Endocrinology and Diabetes          Belston, Lleyton; Salford Royal Hospitals NHS Trust, Endocrinology and Diabetes          Illangasekera , Yasitha; Sheffield Hallam University, Genetics          Jameson, Adam; University of Bradford, School of Pharmacy and Medical Sciences          Meehan, Cheyenne; Salford Royal Hospitals NHS Trust, Endocrinology and Diabetes          Wilkins, Loren; Salford Royal Hospitals NHS Trust, Endocrinology and Diabetes          Loureiro, Camila; Universidade de São Paulo Faculdade de Medicina de Ribeirão Preto, Internal Medicine; Sheffield Hallam University, Biomolecular Sciences Research Centre          Saluja, Sushant; University of Manchester - The Victoria University of Manchester Campus, The School of Medicine and Manchester Academic Health Sciences Centre          Shakespeare, Mark; Rotherham Doncaster and South Humber NHS Foundation Trust, Research and Innovation          Dalton, Dr. Caroline; Senior Lecturer in Biomedical Science, Sheffield Hallam University, Biosciences and Chemistry          Reynolds, Gavin; Sheffield Hallam University, Biomolecular Sciences Research Centre          Heald, Adrian; Salford Royal Hospitals NHS Trust, Endocrinology and Diabetes; University of Manchester - The Victoria University of Manchester Campus, The School of Medicine and Manchester Academic Health Sciences Centre</p>
Please list at least 3 keywords which relate to your manuscript::	Antipsychotic, Weight gain, Genetics, Systematic review, Metaanalysis
Abstract:	<p>Introduction          Genetic factors are thought to play an important role in antipsychotic-induced weight gain (AIWG). This study conducted a meta-analysis of current research of the pharmacogenetic associations of adult AIWG.</p> <p>Methods</p>

The analysis included papers providing comparisons of weight gain across at least two allele combinations for at least one single nucleotide polymorphism (SNP). Inclusion criteria were, patients 18 years of age or older and had received a diagnosis of severe mental illness (SMI), for which antipsychotic medication was prescribed. The association with AIWG needed to be replicated across at least two papers reporting separate sample sets.

#### Results

223 papers were assessed for eligibility. Of the 223 papers, 148 were excluded, leaving 75 studies to be included.

Six SNPs in six different genes were identified as having significant associations ( $p < 0.05$ ) with AIWG. These were HTR2C rs3813929(TT + TC vs CC), Hedge's  $g$  0.76; MTHFR rs1801133(TC + TT vs CC), Hedge's  $g$  0.61; ADRA2A rs1800544(CC + CG vs GG), Hedge's  $g$  0.71; MC4R rs489693(CC + AC vs AA) Hedge's  $g$  0.127; LEPR rs1137101(GG + AG vs AA) Hedge's  $g$  0.18 and CNR1 rs104935 (GG + AG vs AA), Hedge's  $g$  0.55.

#### Conclusion

The study identified 6 SNPs that predispose adult individuals to AIWG, with HTR2C rs3813929 and ADRA2A rs1800544 showing the largest effect sizes. Five of these have a role in hypothalamic regulation of appetite/satiety.

Identification of these risk-associated SNPs may assist the development of a polygene/polyphenotypic risk score to identify individuals with psychosis with a heightened risk of experiencing AIWG.

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6 2 **A Meta-analysis of Potential Genetic Factors Associated with**  
7 **Antipsychotic-Induced Weight Gain (AIWG) in Adults with**  
8 **Severe Mental Illness**  
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Running Head: Genetics and Weight Gain in Treatment of Psychosis

18  
19 7 John Warner-Levy<sup>1</sup>, Lleyton Belston<sup>1</sup>, Yasitha Illangasekera<sup>2</sup>, Adam  
20 8 Jameson<sup>3</sup>, Cheyenne Meehan<sup>1</sup>, Loren Wilkins<sup>1</sup>, Camila Marcelino Loureiro<sup>2</sup>,  
21 9 Sushant Saluja<sup>4</sup>, Mark Shakespeare<sup>5</sup>, Caroline Dalton<sup>2</sup>, Gavin Reynolds<sup>2</sup>,  
22 10 Adrian Heald<sup>1,4</sup>  
23  
24  
25  
26  
27  
28 11

29 12 <sup>1</sup>Department of Endocrinology and Diabetes, Salford Royal Hospital, Salford,  
30 13 M6 8HD, UK

31 14 <sup>2</sup>Sheffield Hallam University, Biomolecular Sciences Research Centre,  
32 15 Sheffield, UK

33 16 <sup>3</sup>School of Pharmacy and Medical Sciences, University of Bradford, Bradford,  
34 17 UK.

35 18 <sup>4</sup>The School of Medicine and Manchester Academic Health Sciences Centre,  
36 19 Manchester University, Manchester, UK

37 20 <sup>5</sup>Rotherham Doncaster and South Humber NHS Foundation, UK  
38  
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48 23 Key words: Antipsychotic, Weight Gain, Psychosis, Gene, Association  
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52  
53 25 Corresponding author:

54 26 Adrian Heald

55 27 University of Manchester

56  
57 28 [adrian.heald@manchester.ac.uk](mailto:adrian.heald@manchester.ac.uk)  
58  
59  
60

29 Telephone: + 44 7470 532162

30 Word Count: 3987

31 Tables: 4; Figures: 1

## 32 **Abstract**

### 33 Introduction

34 Genetic factors are thought to play an important role in antipsychotic-induced  
35 weight gain (AIWG). This study conducted a meta-analysis of current  
36 research of the pharmacogenetic associations of adult AIWG.

### 38 Methods

39 The analysis included papers providing comparisons of weight gain across at  
40 least two allele combinations for at least one single nucleotide polymorphism  
41 (SNP). Inclusion criteria were, patients 18 years of age or older and had  
42 received a diagnosis of severe mental illness (SMI), for which antipsychotic  
43 medication was prescribed. The association with AIWG needed to be  
44 replicated across at least two papers reporting separate sample sets.

### 46 Results

47 223 papers were assessed for eligibility. Of the 223 papers, 148 were  
48 excluded, leaving 75 studies to be included.

49  
50 Six SNPs in six different genes were identified as having significant  
51 associations ( $p < 0.05$ ) with AIWG. These were *HTR2C rs3813929* (TT + TC vs  
52 CC), Hedge's  $g$  0.76; *MTHFR rs1801133* (TC + TT vs CC), Hedge's  $g$  0.61;  
53 *ADRA2A rs1800544* (CC + CG vs GG), Hedge's  $g$  0.71; *MC4R rs489693* (CC  
54 + AC vs AA) Hedge's  $g$  0.127; *LEPR rs1137101* (GG + AG vs AA) Hedge's  $g$   
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### 57 Conclusion

58 The study identified 6 SNPs that predispose adult individuals to AIWG, with  
59 *HTR2C rs3813929* and *ADRA2A rs1800544* showing the largest effect sizes.  
60 Five of these have a role in hypothalamic regulation of appetite/satiety.

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3 62 Identification of these risk-associated SNPs may assist the development of a  
4  
5 63 polygene/polyphenotypic risk score to identify individuals with psychosis who  
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7 64 are at heightened risk of experiencing AIWG.  
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10 65

## 11 66 **Introduction**

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13  
14  
15 67 Obesity in people with severe mental illness (SMI) shortens lives and is  
16  
17 68 associated with multiple comorbidities (De Hert et al, 2011). The social  
18  
19 69 disparities between those with a SMI and the broader society further  
20  
21 70 exacerbate inequity in health outcomes (Ngui et al, 2010). Antipsychotic  
22  
23 71 induced weight gain (AIWG) in people with SMI is a determinant of future  
24  
25 72 diabetes, dysmetabolic profile and increased cardiometabolic risk (Heald et  
26  
27 73 al, 2017; Zhang et al, 2013). Dyslipidaemia and hypertension may develop  
28  
29 74 within the first year of initiating antipsychotic therapy, exacerbating  
30  
31 75 cardiovascular risk. AIWG is linked to increased cardiovascular morbidity and  
32  
33 76 mortality (Doanne et al. 2022, Montejo et al. 2024). Weight gain can serve as  
34  
35 77 an early and recognisable signal of metabolic dysregulation and its prediction  
36  
37 78 through pharmacogenomic diagnostics could play a central role in the  
38  
39 79 management of antipsychotic drug treated patients.  
40

41 80  
42 81 Antipsychotic agents are prescribed for a range of SMI including, but not  
43  
44 82 limited to schizophrenia and bipolar disorder. Schizophrenia alone affects 1%  
45  
46 83 of the world's population. AIWG is a well-reported side effect of most  
47  
48 84 antipsychotics (Barton et al, 2020). Weight-gain is a modifiable risk, and  
49  
50 85 preventative treatment has been shown to be more effective than  
51  
52 86 retrospective treatment.  
53

54 87  
55 88 Numerous mechanisms underlying AIWG have been proposed, influenced by  
56  
57 89 a mixture of genetic, biological, psychological and behavioural factors  
58  
59 90 including sedentary lifestyle and dietary choices (Shrivastava et al, 2020;  
60  
91 Heald et al, 2015). AIWG also has a severe negative impact on patients' self-  
92  
93 92 esteem and can lead to non-adherence (Burschinski et al, 2023; Waite et al,  
93 2022; Klein et al 2020).

94

95 There is considerable variability in AIWG and metabolic effects between  
96 individuals in both the intermediate and longer term (Cooper et al, 2016).  
97 Young and antipsychotic-naïve individuals are at particularly high risk of  
98 AIWG in the short to intermediate term, as are women more than men (Correll  
99 et al 2009; Heald et al 2024). Genetic factors may play an important role in  
100 AIWG. Genome-wide association studies have reported the association of  
101 genes associated with obesity in the general population (Fall & Ingelsson  
102 2014). Furthermore, the expression of genes coding of components of  
103 metabolic pathways that modulate fat mass and weight gain in the shorter and  
104 longer term may be affected by genetic variants as described in recent years  
105 in seminal papers (Zhang & Malhotra; 2011 Zhang et al 2016).

106

107 Weight may show a steep upward trajectory following antipsychotic initiation,  
108 with up to 20% body mass increase in the first year (Lett et al, 2012). Early  
109 AIWG is a predictor of longer-term weight gain (Bioque et al, 2018), with the  
110 attendant long-term consequences including type 2 diabetes (T2D) premature  
111 cardiovascular disease (CVD) events and death. It is increasingly recognised  
112 that nutrition and physical health are closely aligned with mental health  
113 outcomes (Dayabandara et al 2017, Firth et al 2020 ) and genetic factors  
114 through their interaction with diet and other lifestyle factors, likely play a  
115 significant part in the degree to which AIWG occurs (Zhang & Malhotra; 2011  
116 Zhang et al 2016).

117

118 In relation to the genetic factors that may underlie weight gain in some  
119 individuals, we conducted a meta-analysis of the current research  
120 demonstrating the pharmacogenetic associations of AIWG. The longer-term  
121 goal is that individuals at risk of AIWG can be identified early to enable a  
122 balance between effective psychotropic treatment and physical health. The  
123 objective of the study was to perform a systematic review and meta-analysis  
124 of current literature to identify genetic variants most strongly predictive with  
125 AIWG.

126

127 **Methods**

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3 1284  
5 129 **Eligibility Criteria**6  
7 1308  
9 131 We included studies that examined the associations between specific single-  
10 132 nucleotide polymorphisms (SNPs) and AIWG in adults ( $\geq 18$  years). Studies  
11 133 needed to report genotype groupings for at least one SNP and provide body  
12 134 weight or Body Mass Index (BMI) data from a minimum of two time points,  
13 135 spaced at least four weeks apart. Only studies involving human participants  
14 136 receiving antipsychotic treatment for psychosis or severe mental illness (SMI)  
15 137 were eligible. We excluded animal studies, review articles, abstracts without  
16 138 full data, and studies lacking adequate weight or genotype information.17 139 Additionally, studies that focused on weight gain unrelated to antipsychotic  
18 140 treatment, such as comorbidities or lifestyle factors, were excluded.19  
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26 14127 142 **Information Sources and Search Strategy**28  
29 14330 144 We conducted a systematic literature search in PubMed, Embase, APA  
31 145 PsycINFO, and Web of Science. The search was registered with Covidence  
32 146 on 13 October 2022.33  
34  
35  
36 14737 148 The search included both free-text and controlled vocabulary (MeSH) terms  
38 149 related to genetics, psychiatry, weight-related outcomes, and antipsychotic  
39 150 medications. The final search was performed on May 13, 2024. The full  
40 151 search strategy was: (genetics OR gene\* OR polymorphisms OR "gene  
41 152 variants" OR 5HTC receptor OR pharmacogenetic\* OR SNP OR "single  
42 153 nucleotide polymorphism" OR "Human Genetics"[Mesh] OR "Polymorphism,  
43 154 Genetic"[Mesh] OR "Genetics, Medical"[Mesh] OR "Genetics,  
44 155 Behavioral"[Mesh]) AND (psych\* OR "biological psychiatry" OR schizophrenia  
45 156 OR "Psychotic Disorders"[Mesh] OR "Schizophrenia Spectrum and Other  
46 157 Psychotic") AND ("Weight Gain"[Mesh] OR "Body-Weight Trajectory"[Mesh]  
47 158 OR obes\* OR BMI OR cardiovascular OR diabetes) AND (antipsychotic\* OR  
48 159 "major tranquiliser\*" OR clozapine OR quetiapine OR risperidone OR  
49 160 amisulpride OR sertindole OR "Dopamine Antagonists"[Mesh] OR

1  
2  
3 161 "Olanzapine"[Mesh] OR "Aripiprazole"[Mesh] OR "Antipsychotic  
4 162 Agents"[Mesh]).  
5  
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7 163

8 164 References of selected studies were manually screened for additional  
9 165 relevant studies. For articles where only abstracts were available, every  
10 166 attempt was made to request the full text. Studies without full-text access  
11 167 were excluded from the final analysis. We did not apply any language or  
12 168 publication year restrictions.  
13  
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15  
16  
17 169

18 170 Duplicates were identified by screening the abstract text and authors. Studies  
19 171 conducted on children, adolescents and animals and those which had not  
20 172 been peer reviewed were excluded.  
21  
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23  
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26 174

### 27 175 **Study Selection and Data Extraction**

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29 176

30 177 Two independent reviewers screened titles, abstracts, and full texts, resolving  
31 178 disagreements via a third reviewer. Extracted data included SNP Identifier,  
32 179 genotype comparisons, sample size, the number of studies, direction and  
33 180 magnitude of weight change, and outcome measures (e.g., Hedges' g).  
34 181 Additionally, we collected information on study quality, participant  
35 182 demographics, and weight measurement methods (e.g., weight vs. BMI).  
36 183 Studies with multiple genotype comparisons for a given SNP were included,  
37 184 and all valid models were used in the analysis.  
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### 46 186 **Statistical Analysis**

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49 188 We performed a meta-analysis using the metafor package (version 4.4.8-0) in  
50 189 R (version 4.5.0). A random-effects model with the DerSimonian–Laird  
51 190 estimator was used to account for heterogeneity between studies. The  
52 191 primary outcome measure was the standardised mean difference (Hedges' g)  
53 192 with 95% confidence intervals (CIs) for weight change between genotype  
54 193 groups. .  
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## 195 **Heterogeneity and Bias Assessment**

196 Heterogeneity was quantified using  $I^2$  statistics, with thresholds of 25%, 50%,  
197 and 75% indicating low, moderate, and high heterogeneity, respectively. To  
198 evaluate potential publication bias, the Trim and Fill method was applied,  
199 which estimates the number of potentially missing studies and adjusts the  
200 overall effect size accordingly. Additionally, funnel plots were visually  
201 inspected for asymmetry to further evaluate publication bias (Duval et al,  
202 2000)

## 204 **Subgroup and Comparison Models**

206 Where feasible, dominant genetic models (e.g. AA + AG vs. GG) were  
207 analysed. In cases where studies presented multiple genotype comparisons,  
208 all valid models were incorporated into pooled analyses. SNPs with at least  
209 two studies and consistent genotype groupings were included in the analysis.

## 211 **Results**

### 212 *Selection of sources of evidence*

213 The literature search yielded 2091 results, 894 of which were duplicates,  
214 which were identified by screening the abstract text and author names.  
215 Studies conducted on children, adolescents and animals and those which had  
216 not been peer reviewed were excluded. This resulted in 1197 articles to be  
217 screened. 974 of these were excluded, as they did not relate specifically to  
218 AIWG. The remaining 223 papers were assessed for eligibility. Of the 223  
219 papers, 148 were excluded, leaving 75 studies to be included.

221 Figure One: PRISMA flowchart showcasing the flow of studies in our review.

223 Table 1 presents an overview of all 75 papers included in the analysis. Sample  
224 sizes in these studies ranged from 32 to 1991 participants, with the majority  
225 involving chronic schizophrenia (SCZ) or schizoaffective disorder (SZA)  
226 patients. Most studies were of short duration, typically between 4 weeks and 4  
227 months, though 16 studies (22%) included follow-up periods of one year or  
228 more. The patient populations were predominantly White or Asian, with 30

1  
2  
3 229 studies (41.7%) exclusively involving Asian participants. The most frequently  
4  
5 230 studied antipsychotics were olanzapine (52.8% of studies), risperidone  
6  
7 231 (41.7%), and clozapine (40.3%). Monotherapy was common, with 35 studies  
8  
9 232 examining a single antipsychotic, including clozapine (15 studies), olanzapine  
10  
11 233 (15 studies), risperidone (4 studies), and iloperidone (1 study). Nearly all  
12  
13 234 studies focused on people with schizophrenia (94.4%), although some included  
14  
15 235 participants with other psychiatric diagnoses.

16 236

17 237 Table 1: Overview of all papers included

18  
19 238 Table 1 lists the SNPs, along with their corresponding genes, chromosomal  
20  
21 239 positions and other relevant details. The major and minor alleles, as well as  
22  
23 240 minor allele frequencies (MAF), are provided based on available population  
24  
25 241 data. Among the SNPs, the *5-Hydroxytryptamine (Serotonin) Receptor 2C*  
26  
27 242 (*HTR2C*) polymorphism *rs3813929 (-759C/T)* was the most extensively  
28  
29 243 studied, with 17 studies involving 1,531 patients.

30 244

31 245 Table 1 here.

32 246

33  
34 247 Table 2 shows the list of genes and SNPs included in the meta-analysis. This  
35  
36 248 lists the included SNPs along with other relevant information including SNPs in  
37  
38 249 linkage disequilibrium.

39 250

40 251 Table 2 here.

41 252

42  
43  
44 253 Table 3a - Meta-analysis of longitudinal outcomes examining the association  
45  
46 254 between candidate SNPs and antipsychotic-induced weight gain (AIWG).] This  
47  
48 255 table presents combined effect sizes (Hedges' *g*) for continuous measures of  
49  
50 256 weight-related changes, including percentage weight change and baseline-to-  
51  
52 257 final BMI change. A dominant genetic model was used for each SNP (minor-  
53  
54 258 allele carriers vs. major-allele homozygotes). Positive effect sizes signify  
55  
56 259 greater weight gain linked to the minor-allele genotype; negative values indicate  
57  
58 260 less gain. For each SNP, the table reports the number of studies included, total  
59  
60 261 sample size, pooled effect size, 95% confidence interval, p-value, and

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3 262 heterogeneity statistics ( $I^2$ ). These analyses reflect the longitudinal influence of  
4 specific genetic variants on AIWG across adult psychosis cohorts.  
5 263

6 264

7  
8 265 Table 3a here.  
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10 266

11  
12 267 Table 3b - Meta-analysis of categorical outcomes assessing the association  
13 between SNPs and clinically significant antipsychotic-induced weight gain. This  
14 268 table summarises pooled effect sizes derived from categorical definitions of  
15 269 weight gain (e.g.,  $\geq 7\%$  increase from baseline), using a dominant genetic model  
16 270 (minor-allele carriers versus major-allele homozygotes). Effect sizes (Hedges'  
17 271  $g$ ) indicate the magnitude of difference in the likelihood of clinically relevant  
18 272 weight gain between genotype groups. For each SNP, the table includes the  
19 273 number of contributing studies, the combined sample size, the effect estimate,  
20 274 the 95% confidence interval, the p-value, and the heterogeneity statistic ( $I^2$ ).  
21 275 These analyses offer a categorical, clinically oriented perspective on the  
22 276 genetic contribution to AIWG.  
23 277

24 278

25 279 These correspond to the following proteins:

26 280 Serotonin (5-HT) receptor-2C

27 281 Methylenetetrahydrofolate reductase

28 282 Alpha-2 Adrenergic receptor A

29 283 Melanocortin-4 receptor

30 284 Leptin receptor

31 285 Cannabinoid receptor 1  
32

33 286

34 287 Table 3b here.  
35

36 288

37 289 Table 4 describes the orphan SNPs which therefore could not be included in  
38 290 the meta-analysis.  
39

40 291

41 292 Table 4 here.  
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43 293

44 294 **Discussion**  
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3 295 The study identified six SNPs that showed statistical significance in the meta-  
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5 296 analysis regarding predisposition of adult individuals to AIWG, of which  
6  
7 297 *ADRA2A rs1800544* and *HTR2C rs3813929* showed the largest effect size.  
8  
9 298 Five of these SNPs are implicated in hypothalamic regulation of appetite and  
10  
11 299 satiety. This contributes to our understanding of why some, but not all, people  
12  
13 300 experience an increase in body weight when started on an antipsychotic agent.  
14  
15 301 Genetic factors do not just add to the phenotype; they shape the range and  
16  
17 302 individual susceptibility to the obesogenic effects of psychotropic  
18  
19 303 pharmacotherapy and serve to address the substantial unexplained  
20  
21 304 interindividual variability in response to antipsychotic drug therapy that is not  
22  
23 305 explained by the other factors such as BMI, age, family history, diabetes and  
24  
25 306 polypharmacy. Furthermore, knowledge of genetic factors related to AIWG  
26  
27 307 would contribute towards a better understanding of the mechanisms of AIWG  
28  
29 308 and thus inform the potential development of targeted interventions.

309

310 Many genes have been studied for their proposed contribution to this very  
311  
312 prevalent side effect over the past 2 decades. In spite of mixed results for  
313  
314 some genetic studies, some genes have shown fairly consistent replication,  
315  
316 such as in the *MC4R*, *HTR2C*, *leptin*, *neuropeptide Y (NPY)* and *CNR1* gene  
(Shams et al, 2014), although a significant effect of *NPY* was not identified by  
our meta-analysis.

316

317 The majority of the studies examined here were not performed in people with  
318  
319 first episode psychosis (FEP). This is important, given that up to 50% weight  
320  
321 gain that occurs, does so in the months after initiation of antipsychotic  
treatment (Heald et al, 2023; Correll et al, 2023).

321

322 Five out of the six identified genes are linked to biological pathways  
323  
324 associated with hypothalamic regulation of appetite. Specifically, for *HTR2C*,  
325  
326 the gene codes for the 5-HT<sub>2C</sub> receptor at which several of the antipsychotic  
327  
328 drugs, most notably those associated with the greatest weight gain - clozapine  
and olanzapine - have antagonist or inverse agonist effects at this receptor.  
The 5-HT<sub>2C</sub> receptor is found in the hypothalamus, an area of the brain  
associated with appetite and satiety (Zanchi et al, 2017). Its blockade has

1  
2  
3 329 been proposed to be the major mechanism underlying olanzapine-induced  
4 330 weight gain (Reynolds et al, 2006). The SNP identified here, *rs3813929*, is in  
5 331 the promoter sequence of the gene and is thought to be involved in the control  
6 332 of transcription - the T-allele associated with less weight gain reportedly  
7 333 shows reduced transcriptional activity (Reynolds et al, 2006) probably by  
8 334 disrupting protein-DNA binding (Hill & Reynolds, 2011). This may therefore  
9 335 underlie allele-specific differences in the relative influence of 5-HT<sub>2C</sub>  
10 336 antagonism on hypothalamic function. Antipsychotics with lower metabolic risk  
11 337 lack 5-HT<sub>2C</sub> receptor antagonism (amisulpride, haloperidol) or have  
12 338 additional protective mechanisms, such as 5-HT<sub>1A</sub> partial agonism  
13 339 (aripiprazole, lurasidone, and ziprasidone) (Reynolds & McGowan, 2021).  
14 340

15 341 The ADRA<sub>2R</sub> is a heteroreceptor on 5-HT receptor terminals located in the  
16 342 hypothalamus. *ADRA2A rs1800544* was consistently associated with AIWG in  
17 343 our analysis. As it is situated in the regulatory promoter sequence of the gene,  
18 344 this polymorphism may influence transcription factor control of gene  
19 345 expression. This SNP may lie at a binding site for several transcription factors.  
20 346 In addition to its association with weight gain, a 2014 study reported that when  
21 347 individuals with schizophrenia were switched to either aripiprazole or  
22 348 ziprasidone from other antipsychotics, significant differences in reduction of  
23 349 BMI at 6 months associated with *rs1800544* of the *ADRA2A* gene (Roffeei et  
24 350 al, 2014). The underlying mechanism of the association that is observed in this  
25 351 study may relate to the role of the adrenergic system in maintaining energy  
26 352 balance via the control of thermogenesis and lipolysis.  
27 353

28 354 Leptin is an anorexigenic hormone secreted in adipose tissue proportional to  
29 355 weight gain. Leptin acts at the leptin receptor to activate hypothalamic MC4-  
30 356 receptors in order to inhibit food intake (Srisawat et al, 2014). Roffeei et al in  
31 357 2014 reported one marker from the promoter region of the leptin gene,  
32 358 *rs7799039* and one marker from the leptin receptor gene *rs1137101*. They  
33 359 described a significant association with *rs1137101* and the development of  
34 360 metabolic syndrome, but no association with *rs7799039*. Interestingly in a  
35 361 Brazilian study *LEPR rs1137101* was associated with a greater likelihood of  
36 362 higher circulating insulin levels and higher insulin resistance in overweight

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3 363 adolescents (Oliveira et al, 2013). Conversely Brandl et al (2012) did not find any  
4 364 association between *rs1137101* and weight gain in 181 people treated with  
5 365 various antipsychotic agents.  
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10 367 Regarding the melanocortin pathway, the fed state is signalled by abundance  
11 368 of circulating hormones such as leptin and insulin, which bind to receptors  
12 369 expressed at the surface of pro-opiomelanocortin (POMC) neurons to promote  
13 370 processing of POMC to the mature hormone  $\alpha$ -melanocyte-stimulating  
14 371 hormone ( $\alpha$ -MSH) (Malhotra et al, 2012). The  $\alpha$ -MSH released by POMC  
15 372 neurons then signals to decrease energy intake by binding to melanocortin-4  
16 373 receptor (MC4R) expressed by MC4R neurons innervating the paraventricular  
17 374 nucleus (PVN) of the hypothalamus. Conversely, in the 'starved state' activity  
18 375 of agouti-related neuropeptide (AgRP) and of neuropeptide Y (NPY)-  
19 376 expressing neurons is increased by decreased levels of circulating leptin and  
20 377 insulin and by the orexigenic hormone ghrelin to promote food intake (Baldini &  
21 378 Phelan, 2019).  
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32 379  
33 380 In several genome-wide association studies a genomic locus near *MC4R* was  
34 381 associated with obesity in the general population (Chambers et al, 2008; Zobel  
35 382 et al, 2009). *MC4R* mutations previously have been linked to extreme early-  
36 383 onset obesity (Farooqi and O'Rahilly, 2005). The *MC4R* gene, particularly  
37 384 variations in the *rs489693* and *rs17782313* polymorphisms, has been linked to  
38 385 increased AIWG, especially in individuals taking second-generation  
39 386 antipsychotics (SGAs) for schizophrenia. When accounting for the shared  
40 387 variance between emotional eating and depressed mood, a 2015 analysis  
41 388 revealed that eating behaviour alone - specifically emotional eating and food  
42 389 craving, accounted for the association between *rs17782313* and higher BMI in  
43 390 people who did not have a history of mental illness (Yilmaz et al, 2015). Thus,  
44 391 genetic variation appears to influence how the MC4R receptor, which is  
45 392 involved in energy balance and food intake, responds to second generation  
46 393 antipsychotic treatment, potentially leading to more weight gain in some  
47 394 individuals, as described by Malhotra et al (Malhotra et al, 2012).  
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3 396 The cannabinoid receptor 1 (CNR1) is expressed centrally in the hypothalamus  
4 and associated with appetite and satiety. Based on a report by Tiwari et al  
5 397  
6 (2010), Nurmi et al (2013) studied several *CNR1* SNPs in the same sample.  
7 398  
8 They investigated one SNP of the promoter region (rs806377) and three in the  
9 399  
10 coding region (rs806368 variable in its location in CNR1 transcripts, rs806378  
11 400  
12 and rs806377). They reported significant associations (that survived correction  
13 401  
14 for multiple testing) between rs806378 and rs1049353 with AIWG. A 2018  
15 402  
16 metanalysis reported that general population individuals with GA/AA genotype  
17 403  
18 of *CNR1 1049353* had significantly lower BMI (weighted mean difference = -  
19 404  
20 0.59 kg/m<sup>2</sup>, p<0.001) compared to those with the GG genotype with no  
21 405  
22 difference in dietary intake of fat, carbohydrate and protein (Sadeghian et al,  
23 406  
24 2018).  
25 407  
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27 409 The anti-obesity drug Rimonabant is a selective CNR1 receptor blocker causing  
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29 attenuation of hyperleptinemia in obese subjects with the consequence of  
30 411  
31 decreased leptin resistance (Despres et al, 2005) and associated diminished  
32 412  
33 central drive to eat.  
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35 414 Away from the hypothalamus, several polymorphisms of *MTHFR* have been  
36 415  
37 described in relation to association with weight gain in psychosis with evidence  
38 416  
39 particularly in younger people. Srisawat et al. (2013) reported an association  
40 417  
41 between the *MTHFR rs1801133* polymorphism and weight gain. Individuals  
42 418  
43 carrying the CC genotype gained more weight than those carrying the T allele  
44 419  
45 after treatment with antipsychotics. Therefore, the T allele appears to have a  
46 420  
47 protective effect (additional to that of the *HTR2C -759T* allele protective effect).  
48 421  
49 Several pharmacogenetic studies have indicated that individuals carrying the  
50 422  
51 677C allele (conferring higher MTHFR activity) experience greater  
52 423  
53 antipsychotic-induced increases in BMI and metabolic indices, especially  
54 424  
55 during early treatment (Su et al, 2021). This may be due to the role of MTHFR  
56 425  
57 in the one-carbon cycle (Ducker et al, 2017).  
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59 427 Whilst five of the six SNPs identified in the current meta-analysis were related  
60 428  
429 to the hypothalamic satiety pathways, it should be appreciated that weight  
regulation involves a broader neural circuitry beyond the hypothalamic satiety

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3 430 pathways resulting from a complex interplay of neurophysiological and  
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5 431 psychological factors such as mood and motivation. In particular the  
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7 432 mesocorticolimbic system consisting of dopaminergic projection play a central  
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9 433 role in motivation and food reward (Baik et al. 2021). In extracting studies for  
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11 434 analysis, we encountered a number of orphan SNPs which had only a single  
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13 435 study reporting association with AIWG- dopamine being one of them. Thus, our  
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15 436 null findings with regards to other genetic variants related to AIWG, reflect a  
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17 437 limitation of evidence extracted through our specific methodology rather than  
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19 438 an absence of genetic contribution.

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21 440 Our work builds on a previous metaanalysis by Zhang et al 2016. Overall, we  
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23 441 found fewer significant associations with AIWG. Possible reasons for this  
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25 442 included that we only looked at adults only, whereas Zhang et al considered  
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27 443 studies in both children and adults; The following SNPs were significant in the  
28  
29 444 previous Zhang etl metaanalysis but not in the current metaanalysis: Alpha-2  
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31 445 Adrenergic ReceptorB3 rs3994 (*ADRB3 rs3994*), Brain-Derived neurotrophic  
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33 446 factor rs6265 (*BDNF rs6265*), Dopamine Receptor D2 rs1799732 (*DRD2*  
34  
35 447 *rs1799732*), *DRD2 rs6275*, *DRD2 rs7131056*, Guanine nucleotide-binding  
36  
37 448 protein-3 rs5443 (*GNB3 rs5443*), Insulin Induced Gene 2 rs17047764 (*INSIG2*  
38  
39 449 *rs17047764*) and synaptosome associated protein 25 rs1051312 (*SNAP25*  
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41 450 *rs1051312*). The difference relates at least in part to contrasting inclusion  
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43 451 criteria: specifically the authors included individuals under 18 years of age,  
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45 452 which for certain SNPs led to the inclusion of more papers than in our analysis  
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47 453 that focussed on people aged 18 and above.

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46  
47 455 Many of the studies included in this meta-analysis have not looked at individuals  
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49 456 with first episode psychosis. However much of the weight gain occurs in the  
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51 457 early months after the first prescription of antipsychotic treatment (Correll et al,  
52  
53 458 2023). It is therefore important to determine the risk profile for early weight  
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55 459 gain as once weight has increased it is very difficult to reduce this (Firth et al  
56  
57 460 2020; Heald et al, 2024). The reduced gene effects during longer-term  
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59 461 antipsychotic treatment and follow-up could be explained by a reduced effect  
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462 size because of contributions from behavioural and environmental factors on  
463 weight trajectory.

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5 465 Regarding future developments, at the time of writing there is no clinically  
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7 466 applied gene-based algorithm that can reliably enable the identification of  
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9 467 individuals at greatest risk of weight gain in the early stages of psychosis is  
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11 468 being applied in every day clinical practice. However there is substantial  
12  
13 469 evidence that genetic factors can be used to predict AIWG. In the analysis of  
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15 470 Yoshida et al in 2023, nominal associations (uncorrected  $p < 0.05$ ) between  
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17 471 polygenic risk scores for BMI were found in the CAMH-Toronto study and the  
18  
19 472 CATIE study samples. The nominal associations of a polygenic risk score for  
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21 473 schizophrenia with AIWG - defined as the presence of  $>7\%$  weight change in  
22  
23 474 both the CATIE and CAMH-Toronto samples, pointed to shared genetic links  
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25 475 between genes underlying the pathogenesis of schizophrenia and those  
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27 476 associated with AIWG. However, it should be noted that coefficients were  
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29 477 opposite in two samples (0.714 in the CATIE sample and  $-0.483$  in the  
30  
31 478 CAMH-Toronto sample). Heterogeneity between the two samples (for  
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33 479 example the prescribed antipsychotic medications) may have contributed to  
34  
35 480 the discrepancy. While the results became non-significant after correction for  
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37 481 multiple testing, these findings suggest that polygenic risk score analyses  
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39 482 could contribute to identifying risk factors of AIWG and might help to elucidate  
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41 483 mechanisms at play in AIWG.

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#### 484 485 Limitations and strengths

486 A major limitation of this and previous meta-analyses in this area is that the  
487 majority of the studies examined were not performed in people with FEP,  
488 when the critical time in terms of determining innate biological predisposition  
489 to weight gain with antipsychotic treatment occurs. The variation in  
490 measurement timings reflect the constraints of the literature reviewed and the  
491 focus on  $\geq 4$  week time window was to allow for the inclusion of a broader set  
492 of studies whilst capturing treatment related weight change. Future studies  
493 should focus on weight trajectories in the early phases of treatment.

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495 We accept that there is a lack of ethnic diversity in some studies. However, we  
496 are limited by the studies that have been conducted. Also we have not  
497 examined epigenetic, transcriptomic data or gene/environment interactions.

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3 498 Another limitation is the way that different studies reported weight gain in  
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5 499 different ways, most by kg or percent change in weight but some applying a  
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7 500 categorical definition of weight change.  
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10 502 Metabolic syndrome is an important indicator of downstream cardiovascular  
11  
12 503 consequences. The present study protocol specifically focused on  
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14 504 absolute/relative weight/BMI change and hence did not include  
15  
16 505 pharmacogenomic studies on metabolic syndrome. Though body weight/BMI  
17  
18 506 has an indirect relationship to metabolic syndrome, future reviews should  
19  
20 507 incorporate specific genetic predictors of metabolic syndrome for a more  
21  
22 508 comprehensive understanding cardiometabolic risk.  
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25 510 The potential impact of publication bias on the meta-analysis findings are  
26  
27 511 considerable. Although some included studies in this meta-analysis reported  
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29 512 non-statistically significant findings between AIWG and associated genetic  
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31 513 variants, many studies with non-significant findings are not published and  
32  
33 514 therefore potentially underrepresented in the literature. Reliance on older  
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35 515 candidate gene studies further increases the risk of cumulative publication bias,  
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37 516 as the evidence base becomes focused on specific gene variants..  
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39 517

40 518 Conclusion

41 519 The study identified 6 SNPs that predispose individuals to weight gain  
42  
43 520 associated with antipsychotic treatment in adults, with *HTR2C rs3813929* and  
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45 521 *ADRA2A rs1800544* showing the largest effect sizes. Five of these have a  
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47 522 role in the hypothalamic regulation of appetite and satiety.  
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50 524 Identification of these risk-associated SNPs may assist the development of a  
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52 525 polygene/polyphenotypic risk score to identify individuals with psychosis who  
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54 526 are at heightened risk of experiencing AIWG.  
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57 528 **Figure Legends**

58 529 Figure 1: A modified PRISMA flowchart detailing our literature review  
59  
60 530 identification, screening, eligibility, and inclusion stages  
531

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3 532 **Acknowledgements**  
4

5 533 None  
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8 534  
9

10 535 **Funding**  
11

12 536 No external funding was obtained.  
13  
14

15 537  
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17 538 **Author Contributions**  
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19  
20 539 AHH conceived the study with GR and CD, with contributions in relation to  
21 540 design from AJ, CM, CML and CD. JWL, GR, SS and CD led on data analysis.  
22  
23 541 Data extraction was conducted by CM and AJ with the assistance of LB and  
24  
25 542 JWL. JWL constructed all the tables with support from LB and LW. All authors  
26  
27 543 contributed to the final version of the manuscript.  
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29 544  
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31 545 **Conflict of interest**  
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33 546 No author has any conflict of interest  
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38 548 **Data availability Statement**  
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40 549 The data that support the findings of this study are available from the  
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42 550 corresponding author upon reasonable request  
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552 **References**

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Table 1: Overview of publications included in meta-analysis

For Peer Review

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Study	Country	Genes	Rs numbers	n	Length	Mean age (SD)	Male (%)	Ethnicity	Diagnoses	Drug-Naive (%)	Medications	Outcome Variables
Alladi 2017	India	<i>HTR2C</i>	3813929	289	6 weeks	35.3 (10.0)	60.6	Indian	SCZ	NR	RIS	>5% weight gain
		<i>DRD2</i>	1799732									
Basile 2001	USA	<i>HTR2C</i>	6318	80	6 weeks	33.1 (8.4)	65	72% Caucasian, 28% African American	SCZ	NR	OLZ	Weight change (relative)
		<i>HTR2A</i>	6313, 6314									
		<i>ADRB3</i>	4994									
		<i>TNF</i>	1800629									
Basile 2002	Canada	<i>HTR2C</i>	3813929	80	6 weeks	NR	61.6	72.5% white, 27.5% black	SCZ	NR	CLZ	Weight change (absolute)
Bishop 2006	USA	<i>GNB3</i>	5443	42	6 weeks	35.6 (8.7)	81.0	NR	SCZ	NR	OLZ	Weight change (relative)
Brandl 2012	Canada	<i>LEP</i>	7799039, 10954173, 3828942	181	7.19 (3.47) weeks	35.9 (10.9)	65.2	70.2% European American, 23.8% African American, 5.0% others	SCZ, SCA	NR	Various APs	Weight change (relative)
		<i>LEPR</i>	1137101, 1327120									
Brandl 2013	Canada	<i>TBC1D1</i>	9852, 35859249	195	6 and 14 weeks	35.7 (10.8)	65.6	65.6% European, 28.2% African American, 4.1% others	SCZ, SCA	NR	Various APs	Weight change (relative)
Brandl 2014	Canada	<i>GCG</i>	1990761, 41368446, 13429709, 3761656	216	7.1 (3.4) weeks	36.2 (10.7)	65.7	69.9% European, 25.0% African American, 5.1% others	SCZ, SCA	NR	Various APs	Weight change (relative)
Brandl 2014	Canada	<i>PPARG</i>	2920500, 2960421, 17036160, 2120825, 3856806, 1797912, 4135268, 4135247, 12629751, 7620165, 4135256, 10865710, 7645903, 4135275, 6782475, 1801282, 4135258, 1175542, 7650895, 17793693, 709149, 1177809, 1152003	216	7.1 (3.4) weeks	36.2 (10.7)	65.7	69.9% European, 25.0% African American, 5.1% others	SCZ, SCA	NR	Various APs	Weight change (relative)
		<i>ADIPOQ</i>	12495941, 6773957, 3821799, 2241766, 822396, 3774261, 1501299, 1063539, 9882205, 822393, 2036373, 16861210, 182052, 7627128									
Brandl 2016	Canada	<i>OGFRL1</i>	9346455	86	6.1 (2.1) weeks	34.1 (9.4)	65.1	European	SCZ	NR	CLZ, OLZ	Weight change (relative)
		<i>IBA57</i>	1059778									
Chowdhury 2013	Canada	<i>MC4R</i>	11872992, 8087522, 17782313, 2229616	224	6-14 weeks	35.6 (10.5)	66.9	70.1% European Americans, 25% African Americans, 4.9% others	SCZ, SCA	NR	Various APs	Weight change (relative)
Chowdhury 2014	Canada	<i>POMC</i>	3754860, 6713532, 1042571	218	7.07 (3.5) weeks	36.2 (10.6)	66.5	69.7% European American, 25.2% African American, 5.0% others	SCZ, SCA	0	Various APs	Weight change (relative)
		<i>CART</i>	10515115, 3763153, 3857384, 11575893, 16871471									
		<i>AGRP</i>	1338993									
Czerwensky 2013	Germany	<i>MC4R</i>	17782313	173	4 weeks	39.3 (14.7)	37	NR	Various diagnoses	28	Various APs	Weight change (absolute and relative) Body Mass Index (BMI) change (absolute and relative)
Czerwensky 2013	Germany	<i>MC4R</i>	489693	341	4 weeks	41.3 (15.0)	42.0	NR	Various diagnoses	NR	Various APs	Weight change (absolute and relative) BMI change (absolute and relative)
Daray 2017	Argentina	<i>HTR2C</i>	3813929	48	6 weeks	34.5 (13.1)	0	97.9% Caucasian, 2.1% unknown	68.8% SCZ, 31.3% other	60.4	Various APs	Weight change (relative) >7% weight gain
Ellingrod 2002	USA	<i>CYP2D6</i>	35742686, 3892097	11	Up to 47 weeks	35.5 (5.4)	100	Caucasian	SCZ	NR	OLZ	BMI change (absolute)
Ellingrod 2005	USA	<i>HTR2C</i>	3813929	42	6 weeks	NR	81	Caucasian	SCZ	NR	OLZ	Weight change (relative) >10% weight gain
	Venezuela	<i>LEP</i>	7799039	56	14 weeks	39.1 (9.0)	78.6	NR	SCZ	NR	CLZ	Weight change (absolute)

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3	Fernandez 2010		LEPR	1137101									BMI change (absolute)
4	5 6 7 8	Canada	IL-1 $\beta$	4849127, 13032029, 16944, 3136558, 1143634, 1143643	188	7.3 (3.5) weeks	35.8 (10.0)	67.0	68.1% European, 26.6% African, 5.4% others	SCZ, SCA	NR	Various APs	Weight change (relative)
5			IL-2	2069762, 2069778, 2069779, 2069772, 2069776									
6			IL-6	2069827, 1800795, 2069837, 2066992, 2069840, 2069861, 10242595									
7			BDNF	6265									
9	Godlewska 2009	Poland	HTR2C	3813929, 518147	107	6 weeks	29.3 (10.0)	49.5	Caucasian	SCZ	33.6	OLZ	BMI change (relative) >10% weight gain
10	Herken 2009	Turkey	PPARG	1801282	95	6 weeks	34.4 (13.0)	51.6	Turkish	SCZ	NR	OLZ	Weight change (absolute) BMI change (absolute)
11	12 13	Taiwan	HTR2A	6313	93	16 weeks	37.1 (8.2)	64.5	Chinese	SCZ	0	CLZ	Weight change (absolute)
12			HTR2C	6318									
13			5HT6	T267C									
14	Hong 2010	Taiwan	DRD2	1799978, 4350392, 7131056, 4245148, 12574471, 4648318, 4436578, 7350522, 2075652, 2734833, 6275, 2242591, 1800497	479	209.3 (120.8) weeks	47.2 (13.2)	61.0	Chinese	SCZ	NR	CLZ, OLZ, RIS	$\geq$ 7% weight gain
15	Huang 2011	Taiwan	TNF	1800629	500	216.7 weeks	43.9 (9.1)	60.2	Chinese	SCZ	NR	CLZ, OLZ, RIS	Weight change (relative) >7% weight gain
16	Kang 2008	South Korea	LEP	7799039	74	> 13 weeks	47.2 (11.6)	67.6	Korean	SCZ	NR	OLZ	Weight change (absolute) $\geq$ 7% weight gain
17	18 19	South Korea	HTR2C	3813929	113	>52 weeks	39.5 (8.3)	71.7	Korean	SCZ	0	Various APs	BMI change (absolute) >7% weight gain
19			LEP	7799039									
20	Kao 2014	Canada	MTHFR	1801133, 1801131	347	8.87 (3.6) weeks	36.2 (10.2)	52.7	81.0% Caucasian, 16.1% African American, 3.2% others	SCZ, SCA	19	Various APs	Weight change (absolute and relative)
21	22 23	Croatia	HTR2C	3813929	108	17.4 weeks	30.6 (11.5)	0	Croatian	SCZ	88.9%	OLZ, RIS	>7% weight gain
22			MDR1	2032582, 1045642									
23	Laika 2010	Germany	HTR2C	3813929	56	4 weeks	41.6 (15.9)	50	Caucasian	Various diagnoses	NR	OLZ	Weight change (relative and absolute), BMI change (absolute)
24	Lencz 2010	USA	DRD2	1799732	58	16 weeks	23.5 (4.9)	75.9	40% African American, 28% Caucasian (European), 19% Hispanic, 5% Asian, 8% Other	SCZ, SCA, Schizophreniform disorder	79	OLZ, RIS	Weight change (absolute) BMI change (absolute)
25	Liao 2020	China	MTHFR	1801133	356	2,4 and 8 weeks	30.5 (10.3)	53.4	Chinese	SCZ	NR	RIS	BMI change (absolute) >7% weight gain
26	Miller 2005	USA	HTR2C	3813929	41	26.1 weeks	35.6 (9.7)	63.4	85.4% Caucasian, 12.2% African American, 2.4% Hispanic	SCZ	0	CLZ	Weight change (absolute) BMI change (relative) >7% weight gain
27	28 29	Italy	CNR1	1049353	83	24 weeks	44.0 (10.5)	60.2	Italian	88.0% SCZ, 10.8% psychosis, 1.2% delusional disorder	0	Various APs	>7% weight gain
28			FAAH	324420									
29	Muller 2005	Canada	SNAP25	1051312, 3746544, 8636	59	11.2 (4.0) weeks	40.1 (9.5)	78.0	55.9% African American, 25.4% Caucasian, 13.6% Hispanic, 3.4% Asian Pacific, 1.7% American Indian	SCZ, SCA	0	CLZ, OLZ, HAL, RIS	Weight change (absolute) BMI change (absolute)
30	Muller 2012	Canada	DRD1	4532, 686, 265976	206	6 or 14 weeks	35.7 $\pm$ 10.4	68.4		SCZ, SCA	NR		Weight change (relative)

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3		DRD2	1799978, 1799732, 4630328, 4648317, 7131056, 4274224, 17529477, 1079598, 1076563, 1800498, 6275, 6277, 2234689, 1800497										>7% weight gain
4		DRD3	905568, 7620754, 2399504, 7611535, 1394016, 9825563, 1800828, 6280, 7633291, 167770, 2134655, 2399496, 2087017, 1025398					62.1% European, 28.2% African American, 9.7% other			Various APs		
5		DRD4	3758653, 11246226										
6		DRD5	10033951, 6283, 10001006										
7	Musil 2008	Germany	SNAP25	1051312, 3746544, 8636	162	5 weeks	34.2 (12.2)	57.4	Caucasian	SCZ, SCA	NR	Various APs	BMI change (absolute)
8	Ono 2015	Japan	GIPR	10423928	32	4 weeks	27.6 (10.5)	50.0	NR	SCZ	71.9	OLZ	BMI change (absolute)
9			HTR2C	3813929, 6318, 498207									
10	Opgen-Rhein 2009	Germany	INSIG2	17587100, 10490624, 17047764, 7566605	128	6 weeks	38.6 (12.0)	62.5	Caucasian	SCZ, SCA	17.2	Various APs	>7% weight gain
11			LEP	7799039									
12	Park 2006	South Korea	ADRA2A	1800544	62	>13 weeks	46.5 (11.1)	71.0	Korean	SCZ	NR	OLZ	Weight change (absolute and relative) BMI change (absolute) >10% weight gain
13	Park 2008	South Korea	HTR2C	3813929	79	>52 weeks	46.7 (12.3)	67.1	Korean	SCZ	NR	OLZ	Weight change (absolute) BMI change (absolute) >7% weight gain
14	Park 2009	South Korea	GNB3	5443	79	>13 weeks	46.6 (11.6)	67.1	Korean	SCZ	NR	OLZ	Weight change (absolute and relative) BMI change (absolute) >10% weight gain
15	Park 2011	South Korea	CNR1	1049353, 806368, 4707436	78	>13 weeks	46.4 (11.6)	66.6	Korean	SCZ	NR	OLZ	>7% weight gain
16			FTO	9939609									
17	Perez-Iglesias 2010	Spain	LEP	7799039	239	52 weeks	28.4 (8.3)	57.7	94.0% White	Schizophrenia spectrum disorders	100	Various APs	Weight change (absolute) BMI change (absolute)
18			LEPR	1137101									
19			SH2B1	7498665									
20	Popp 2009	Germany	HTR2C	6318	142	4 weeks	37.5 (13.7)	45.1	Caucasian	69.0% SCA, 23.2% SCZ, and 7.7% other	52	Various APs	BMI change (absolute)
21	Reynolds 2002	China	HTR2C	3813929	123	6 and 10 weeks	26.6 (7.7)	52.1	Chinese	SCZ	100	Various APs	BMI change (absolute) >7% weight gain
22	Reynolds 2003	China	HTR2C	3813929	32	6 weeks	NR	65.6	Chinese	SCZ	100	CLZ	BMI change (absolute)
23	Reynolds 2013	UK	FTO	9939609	93	52 weeks	25.5 (6.7)	72.0	Caucasian	Psychosis	100	Various APs	Weight change (absolute) BMI change (absolute)
24	Ryu 2007	South Korea	HTR2C	3813929	84	4 weeks	30.1 (7.4)	46.4	Korean	SCZ	69	Various APs	BMI change (relative and absolute) >7% weight gain
25	Schreyer 2023	Germany	MC4R	17782313	252	2 and 8 weeks	41.5 (11.4)	52	97.6% Caucasian, 2.4% unknown	SCZ, SCA, schizophreniform disorder	14.7	Amisulpride, OLZ	Weight change (absolute) BMI change (absolute)
26	Schroder 2019	Germany	FTO	7185735, 9939609	350	4 weeks	40.1 (15.0)	40.3	Caucasian	Various diagnoses	26	Various APs	Weight change (absolute and relative) BMI change (absolute and relative)
27	Shing 2014	Canada	FTO	1421085, 8050136, 9939609, 9930506	218	6 and 14 weeks	NR	66.1	69.2% European American, 25.7% African American, 5.0% others	SCZ, SCA	NR	Various APs	Weight change (relative)
28	Song 2014	China	FTO	9939609, 8050136, 1421085, 9930506	237	26.1 weeks	27.5 (7.6)	54.0	Chinese	SCZ	100	RIS	Weight change (absolute) BMI change (absolute)
29			PRKAA1	3805494, 1002424, 6882903									
30	Souza 2012	Canada	PRKAA2	10789038, 2746355, 2796528	208	7.19 (3.5) weeks	35.9 (10.3)	67.8	67.8 European American, 26.9% African Americans, 5.3% others	SCZ, SCA	NR	Various APs	Weight change (absolute and relative) >7% weight gain
31			PRKAB1	278152, 17408578									

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3		<i>PRKAB2</i>	3766522, 6689934										
4	Srisawat 2014	UK	<i>MTHFR</i>	1801133, 1801131	182	10 weeks	26.2 (7.4)	45.6	Chinese	SCZ	100	Various APs	BMI change (absolute)
5	Staeker 2012	Germany	<i>PPARG</i>	1801133, 1801131	72	13 weeks	25.4 (6.8)	73.6	Spanish				
6				1801282	170	4 weeks	Range of 18-89	42.9	NR	Various diagnoses	NR	OLZ, CLZ	Weight change (absolute) BMI change (absolute)
7	Su 2021	China	<i>MTHFR</i>	1801133	1821	6 weeks	30.8 (7.9)	50.7	Chinese	SCZ	26.3	Various APs	BMI change (relative) Weight change (relative)
8	Templeman 2005	Spain	<i>HTR2C</i> <i>LEP</i>	3813929 rs7799039	73	6,13 and 39.1 weeks	25.2 (0.8)	75.3	Caucasian	Psychosis	100	Various APs	BMI change (absolute) >7% weight gain
9	Tiwari 2010	Canada	<i>CNR1</i>	806378, 806380, 2180619, 9450902, 10485170	183	7.54 (3.55) weeks	36.1 (10.2)	67.8	63.9% Caucasian, 30.1% African American, 6% others	SCZ, SCA	NR	Various APs	Weight change (relative)
11	Tiwari 2010	Canada	<i>INSIG2</i>	7566605, 17587100, 10490624, 17047764	154	7.94 (3.74) weeks	35.8 (9.8)	71.4	57.8% European American, 35.1% African American, 7.1% others	SCZ, SCA	NR	CLZ, OLZ, RIS, HAL	Weight change (relative)
14	Tiwari 2010	Canada	<i>CCK</i> <i>CCKAR</i>	1868522, 747455 2968720, 915890, 1573596, 2725307, 2929183, 11040826, 1042048, 10769675	215	7.20 (3.4) weeks	35.8 (10.6)	67.0	68.4% European American, 26.5% African American, 5.1% other	SCZ, SCA	NR	Various APs	Weight change (relative)
16	Tiwari 2013	Canada	<i>NPY</i>	10551063, 16147, 5573, 5574, 16475	226	7.03 (3.4) weeks	35.8 (10.6)	66.8	69.9% European, 25.2% African, 4.8% other	SCZ, SCA	NR	Various APs	Weight change (relative)
18	Tiwari 2016	Canada	<i>HCRTR1</i> <i>HCRTR2</i>	77324737, 1056526, 12057176, 2271933, 10914457 4467775, 7771743, 10456181, 4364482, 7738215, 4571564, 6927478, 9370399, 7768760, 7775745, 3122163, 3134701, 12111375, 4142972, 6922310, 12662510, 9382464, 9357849, 9357850, 9475206, 3134712, 9396069, 7741664, 2811239, 2134294, 12111299, 2653349, 2653350, 3746544, 8636	218	7.09 (3.5) weeks	36.4 (10.4)	66.1	69.3% European American, 25.7% African American, 5.0% others	SCZ, SCA	NR	Various APs	Weight change (relative)
25	Tiwari 2018	Canada	<i>HRH1</i>	7639145, 729327, 17034136, 13064530, 347614, 346074, 901865, 346070	193	7.14 (3.59) weeks	NR	66.3	69.9% European American, 25.9% African American, 4.1% other	SCZ, SCA	NR	Various APs	Weight change (relative)
27	Tsai 2002	Taiwan	<i>5HT2C</i>	3813929	80	17.4 weeks	36.7 (8.4)	65	Chinese	SCZ, SCA	0	CLZ	Weight change (absolute and relative) BMI change (absolute and relative) >7% weight gain
29	Tsai 2003	Taiwan	<i>TNF</i>	1800629	99	17.4 weeks	36.8 (8.0)	65.7	Chinese	SCZ	NR	CLZ	Weight change (absolute and relative)
30	Tsai 2004	Taiwan	<i>GNB3</i> <i>ADRB3</i>	5443 4994	87	17.4 weeks	37.0 (8.2)	64.4	Chinese	Schizophrenic disorders	0	CLZ	Weight change (absolute and relative)
32	Tsai 2011	USA	<i>BDNF</i>	6265, 11030101, 12291186, 2030323	481	213.8 (122.5) weeks	43.9 (9.0)	60.9	Chinese	SCZ	0	CLZ, OLZ, RIS	Weight change (relative)
34	Van Winkel 2010	Holland	<i>MTHFR</i>	1801133, 1801131	104	6 and 13 weeks	31.3 (11.7)	68.3	NR	SCZ, SCA	NR	Various APs	Weight change (absolute)
35	Wang 2005	Taiwan	<i>ADRA2A</i>	1800544	93	14.0 (6.2) weeks	38.4 (8.1)	52.7	Chinese	SCZ	NR	CLZ	BMI change (absolute) >7% weight gain
36	Wang 2005	Taiwan	<i>GNB3</i>	5443	134	58.2 (2.2) weeks	38.5 (0.7)	59.7	Chinese	SCZ	0	CLZ	Weight change (absolute and relative)
37	Wang 2010	Taiwan	<i>TNF</i>	1800629	55	417 weeks	37.2 (7.7)	49.1	Chinese	SCZ	0	CLZ	Weight change (absolute) BMI change (absolute)
39	Zai 2012	USA	<i>BDNF</i>	7934165, 11030104, 6265, 1519480	257	6 weeks	34.7 (9.3)	73.2	Caucasian	SCZ, SCA	NR	Various APs	Weight change (absolute) >7% weight gain

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3	Zai 2015	Canada	<i>GABRA2</i>	16859227, 279858, 1442060, 3849591, 1442062, 16859354, 11503014, 6856130, 1372472	160	5.8 (2.1) weeks	33.3 (10.5)	63.8	European	SCZ, SCA	NR	Various APs	Weight change (relative)
4													
5	Zai 2017	Canada	<i>HTR3A</i>	10789980, 1150226, 1062613, 1150222, 2276302, 11214789, 10891613, 11608102	149	5.8 (2.1) weeks	35.3 (10.5)	62.4	European	SCZ, SCA	NR	Various APs	Weight change (relative)
6			<i>HTR3B</i>	3891484, 10789970, 11214763, 3758987, 1176744, 3782025, 1672717, 2011249, 6589400, 11606194, 1176758, 7129190, 7945619									
7													
8	Zhang 2003	China	<i>DRD2</i>	1800497	117	10 weeks	26.0 (8.0)	49.6	Chinese	SCZ	100	Various APs	Weight change (absolute) BMI change (absolute) >7% weight gain
9	Zhang 2007	China	<i>LEP</i>	7799039	102	349.5 (146) weeks	47.2 (6.3)	65.7	Chinese	SCZ	0	CLZ	BMI change (absolute)
10	Zhang 2008	USA	<i>BDNF</i>	6265	196	312.8 (104.3) weeks	NR	66.3	Chinese	SCZ	100	Various APs	BMI change (absolute)
11	Zhang 2019	China	<i>MC4R</i>	489693, 17782313	1991	6 weeks	32.0 (7.9)	50.2	Chinese	SCZ	28.5	Various APs	BMI change (relative) >7% weight gain
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Various APs = various antipsychotics, SCZ = schizophrenia, SCA = schizoaffective disorder, OLZ = olanzapine, RIS = risperidone, CLZ = clozapine, HAL= Haloperidol, NR= not reported, Drug-naïve refers to patients with no prior exposure to antipsychotic medication. All data is presented as mean (standard deviation) (SD).

Table 2: Key characteristics of genes and single nucleotide polymorphisms (SNPs) included in meta-analysis

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Gene	SNP number	No. of studies (No. of patients)	SNP	Chromosome	Position	Region	Major Allele	Minor Allele	Minor allele frequency
ADRA2A	rs1800544	3 (284)	-1291C/G	10	111076745		C	G	0.48
ADRB3	rs4994	2 (249)	Trp64Arg	8	37823798	(Missense)	T	C	0.10
BDNF	rs6265	5 (1060)	Val66Met	11	27658369	(Missense)	G	A	0.23
FTO	rs1421085	2 (454)		16	53767042				
	rs8050136	2 (454)		16	53782363				
	rs9930506	2 (454)		16	53796553				
	rs9939609	4 (681)		16	53820527	Intron	T	A	0.36
GNB3	rs5443	4 (469)	C825T	12	6954875	Exon (synon)	C	T	0.48
HTR2A	rs6313	4 (456)	102T/C	13	46895805	Intron	C	G	0.48
HTR2C	rs6318	5 (414)	Cys23Ser	X	113871991	Exon 5	G	C	0.17
	rs3813929	17 (1531)	-759C/T	X	113818520	Upstream, promoter	C	T	0.12
LEP	rs7799039	6 (792)	-2548A/G	7	128238730		G	A	0.43
LPR	rs1137101	2 (294)	Q223R	1	65592830	(Missense)	A	G	0.41
MC4R	rs1778231 3	3 (1837)		18	60183864		T	C	0.22
MTHFR	rs1801131	4 (492)	1298A/C	1	11794419	(Missense)	A	C	0.23
	rs1801133	6 (2907)	677C/T	1	11796321	(Missense)	C	T	0.33
PPARG	rs1801282	2 (309)	Pro12Ala	3	12351626	Intron (Missense)	C	G	0.07

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<i>TNF</i>	<i>rs1800629</i>	4 (728)	<i>G-308A</i>	6	31575254		G	A	0.10
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For Peer Review

Table 3a: Meta-analysis of longitudinal outcomes examining the association between candidate SNPs and antipsychotic-induced weight gain (AIWG).

Gene	SNP number	Number of studies (number of patients)	Genotype comparison	Hedges' g (95% CI)	P value	I <sup>2</sup>	Trim & Fill
<i>ADRA2A</i>	rs1800544	2 (155)	CC + CG vs GG	0.714 (0.37,1.05)	<0.0001	0%	0
		2 (155)	GG + CG vs CC	0.593 (0.159, 1.027)	0.007	0%	0
<i>ADRB3</i>	rs4994	2 (160)	TT + TC vs CC	0.456 (-0.213, 1.124)	0.182	58.1%	0
		2 (160)	CC + TC vs TT	0.520 (-1.453, 2.493)	0.532	23.42%	0
		2 (160)	CC + TC vs TT	-0.830 (-1.994, 0.333)	0.191	89.23%	0
<i>BDNF</i>	rs6265	4 (938)	GG + GA vs AA	0.053 (-0.727, 0.832)	0.894	90.6%	-0.134
		4 (938)	AA + GA vs GG	-0.135 (-0.526, 0.255)	0.497	83.8%	-0.135
<i>FTO</i>	rs1421085	2 (454)	CC + TC vs TT	-0.164 (-0.369, 0.040)	0.116	0%	0
	rs8050136	2 (454)	AA + AC vs CC	0.011 (-0.201, 0.224)	0.916	0%	0
	rs9930506	2 (454)	AA + AG vs GG	-0.085 (-0.281, 0.111)	0.396	0%	0

	rs9939609	4 (681)	AA + AT vs TT	-0.101 (-0.305, 0.104)	0.336	28.3%	-0.101
		3 (444)	TT + AT vs AA	0.086 (-0.213, 0.385)	0.574	38.1%	0.086
<i>GNB3</i>	rs5443	4 (342)	CC + CT vs TT	-1.095 (-2.689, 0.498)	0.178	96.5%	-1.095
		4 (342)	TT + CT vs CC	0.312 (-0.664, 1.288)	0.531	93%	0.584
<i>HTR2A</i>	rs6313	2 (170)	TT + TC vs CC	0.010 (-0.389, 0.409)	0.960	12.9%	0
		2 (170)	CC + TC vs TT	-0.052 (-0.392, 0.288)	0.766	0.3%	0
<i>HTR2C</i>	rs6318	2 (179)	CC + CG vs GG	0.069 (-0.267, 0.404)	0.689	0%	0.198
		3 (216)	GG + GC vs CC	-0.269 (-0.827, 0.289)	0.345	22.7%	-0.567
	rs3813929	12 (852)	TT + TC vs CC	0.757 (0.463, 1.050)	<0.0001	70.6%	-0.807
<i>LEP</i>	rs7799039	5 (590)	AA + AG vs GG	-0.001 (-0.758, 0.756)	0.998	0%	-0.918
		5 (664)	GG + AG vs AA	1.688 (-0.530, 3.906)	0.136	42.64%	0.128
<i>LEPR</i>	rs1137101	2 (324)	AA + AG vs GG	0.020 (-0.306, 0.347)	0.903	0%	0

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		2 (324)	GG + AG vs AA	0.180 (0.050,0.410)	<0.001	0%	0
<i>MC4R</i>	rs17782313	4 (2749)	TT + TC vs CC	-0.170 (-0.443, 0.103)	0.222	38%	-0.170
		4 (2749)	CC + TC vs TT	0.054 (-0.166, 0.274)	0.632	78.8%	0.054
	rs489693	2 (2332)	AA + AC vs CC	0.135 (-0.333, 0.602)	0.572	93.8%	0
		2 (2332)	CC + AC vs AA	0.127 (0.059,0.313)	<0.001	0%	0
<i>MTHFR</i>	rs1801133	5 (2907)	CC + TC vs TT	0.528 (0.438, 0.619)	<0.0001	98.9%	0.756
		5 (2907)	TT + TC vs CC	0.614 (0.518, 0.710)	<0.0001	99.52%	-0.199
	rs1801131	3 (492)	AA + AC vs CC	0.115 (-0.220, 0.450)	0.50	0%	-0.305
		2 (348)	CC + AC vs AA	-0.344 (-0.566, -0.123)	0.0023	86.62%	0.276
<i>PPARG</i>	rs1801282	3 (341)	GG + GC vs CC	-0.051 (-0.808, 0.707)	0.896	80.4%	-0.051
<i>TNF-alpha</i>	rs1800629	4 (728)	AA + AG vs GG	-0.311 (-0.777, 0.154)	0.190	74.2%	-0.311
		4 (728)	GG + AG vs AA	-0.208 (-0.924, 0.508)	0.569	3.5%	-0.208

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Table 3b: Meta-analysis of categorical outcomes assessing the association between SNPs and clinically significant antipsychotic-induced weight gain.

Gene	SNP number	Number of studies (number of patients)	Genotype comparison	Odds ratio (95% CI)	P value	I <sup>2</sup>	Trim & Fill
CNR1	rs1049353	2 (161)	AA + AG vs GG	1.06 (0.49 – 2.26)	0.005	0%	0
		2 (161)	GG + AG vs AA	0.55 (0.11 – 2.73)	0.003	0%	0
HTR2C	rs3813929	5 (551)	TT + TC + T vs CC + C	0.68 (0.16 – 2.72)	0.006	69.23%	0
		4 (439)	CC + TC + C vs TT + T	1.26 (-0.09 – 2.23)	0.706	52.32%	0

Table 4: Orphan single nucleotide polymorphisms (SNPs) not included in meta-analysis

Gene	SNP number
HTR2C	rs498207, rs3813928, rs518147
5HT6	rs1805054
5HT2A	rs6314
CNR1	rs806378, rs806380, rs2180619, rs9450902, rs10485170, rs4707436, rs806368
ADRA1A	rs1048101
MC4R	rs11872992, rs8087522

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3	<i>PRKAA1</i>	rs3805494, rs1002424, rs6882903
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5	<i>PRKAA2</i>	rs10789038, rs2746355, rs2796528
6		
7	<i>PRKAB1</i>	rs278152, rs17408578
8		
9	<i>PRKAB2</i>	rs3766522, rs6689934
10		
11	<i>BDNF</i>	rs11030101, rs12291186, rs7934165, rs11030104, rs1519480
12		
13	<i>CCK</i>	rs1868522, rs747455
14	<i>CCKAR</i>	rs2968720, rs915890, rs1573596, rs2725307
15		
16	<i>CCKBR</i>	rs2929183, rs11040826, rs1042048, rs10769675
17		
18	<i>LEP</i>	rs10954173, rs3828942
19		
20	<i>LEPR</i>	rs1327120
21	<i>HTR3A</i>	rs10789980, rs1150226, rs1062613, rs1150222, rs2276302, rs11214789, rs10891613, rs11608102
22		
23	<i>HTR3B</i>	rs3891484, rs10789970, rs11214763, rs3758987, rs1176744, rs3782025, rs1672717, rs2011249, rs6589400, rs11606194, rs1176758, rs7129190, rs7945619
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26	<i>DRD1</i>	rs4532, rs686, rs265975
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28		rs1799978, rs4350392, rs7131056, rs4245148, rs12574471, rs4648318, rs4436578, rs7350522, rs2075652, rs2734833, r 6275,
29	<i>DRD2</i>	rs2242591, rs1800497, rs1799732, rs4630328, rs4648317, rs4274224, rs17529477, rs1079598, rs1076563, rs1800498, rs6277, rs2234689
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33	<i>DRD3</i>	rs905568, rs7620754, rs2399504, rs7611535, rs1394016, rs9825563, rs1800828, rs6280, rs7633291, rs167770, rs2134655, rs2399496, rs2087017, rs1025398
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36	<i>DRD4</i>	rs3758653, rs11246226
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38	<i>DRD5</i>	rs10033951, rs6283, rs10001006
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3	<i>TBC1D1</i>	<i>rs9852, rs35859249</i>
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5	<i>FTO</i>	<i>rs7185735, rs1421085</i>
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7	<i>GCG</i>	<i>rs1990761, rs41368446, rs13429709, rs3761656</i>
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9	<i>GIPR</i>	<i>rs10423928</i>
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11	<i>GLP1R</i>	<i>rs9296291, rs10305432, rs13202369, rs910166, rs12528717, 2300616, rs10305439, rs10305491, rs926674, rs2254336, rs1126476, rs1042044, rs6923761, rs2206942, rs2268640, rs9283907, rs932443, rs4714210, rs2268646, rs7769547, rs2268650, rs2894420, rs2268657, rs2268639, rs2268641, rs2300613, rs3799707, rs10305516, rs7766663, rs10305525, rs9296274, rs10305416</i>
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15	<i>HRH1</i>	<i>rs7639145, rs729327, rs7639145, rs17034136, rs13064530, rs347614, rs346074, rs901865, rs346070</i>
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17	<i>HRH2</i>	<i>rs2067474</i>
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19	<i>POMC</i>	<i>rs3754860, rs6713532, rs1042571</i>
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21	<i>CART</i>	<i>rs10515115, rs3763153, rs3857384, rs11575893, rs16871471</i>
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23	<i>AGRP</i>	<i>rs1338993</i>
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25	<i>PPARG</i>	<i>rs2920500, rs2960421, rs17036160, rs2120825, rs3856806, rs1797912, rs4135268, rs4135247, rs12629751, rs7620165, rs4135256, rs10865710, rs7645903, rs4135275, rs6782475, rs4135258, rs1175542, rs7650895, rs17793693, rs709149, rs1177809, rs1152003</i>
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28	<i>ADIPOQ</i>	<i>rs12495941, rs6773957, rs3821799, rs2241766, rs822396, rs3774261, rs1501299, rs1063539, rs9882205, rs822393, rs2036373, rs16861210, rs182052, rs7627128, rs822391, rs1656930, rs266729</i>
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31	<i>MDR1</i>	<i>rs2032582, rs1045642</i>
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33	<i>FAAH</i>	<i>rs324420</i>
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35	<i>INSIG2</i>	<i>rs17587100, rs10490624, rs17047764, rs7566605</i>
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37	<i>SH2B1</i>	<i>rs7498665</i>
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39	<i>NPY</i>	<i>rs10551063, rs16147, rs5573, rs5574, rs16475</i>
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<b>GABRA2</b>	<i>rs16859227, rs279858, rs1442060, rs3849591, rs1442062, rs16859354, rs11503014, rs6856130, rs1372472</i>
<b>IL-1b</b>	<i>rs4849127, rs13032029, rs16944, rs3136558, rs1143634, rs1143643</i>
<b>IL-2</b>	<i>rs2069762, rs2069778, rs2069772, rs2069776</i>
<b>IL-6</b>	<i>rs2069827, rs1800795, rs2069837, rs2066992, rs2069840, rs2069861, rs10242595</i>
<b>OGFRL1</b>	<i>rs9346455</i>
<b>IBA57</b>	<i>rs1059778</i>
<b>HCRTR1</b>	<i>rs77324737, rs1056526, rs12057176, rs2271933, rs10914457</i>
<b>HCRTR2</b>	<i>rs4467775, rs3134701, rs4142972, rs6922310, rs12662510, rs2653350, rs7771743, rs10456181, rs4364482, rs7738215, rs4571564, rs6927478, rs9370399, rs7768760, rs7775745, rs3122163, rs12111375, rs9382464, rs9357849, rs9357850, rs9475206, rs9396069, rs7741664, rs2811239, rs2134294, rs12111299, rs2653349</i>
<b>SNAP-25</b>	<i>rs1051312</i>

PRISMA flowchart showcasing the flow of studies in our review.

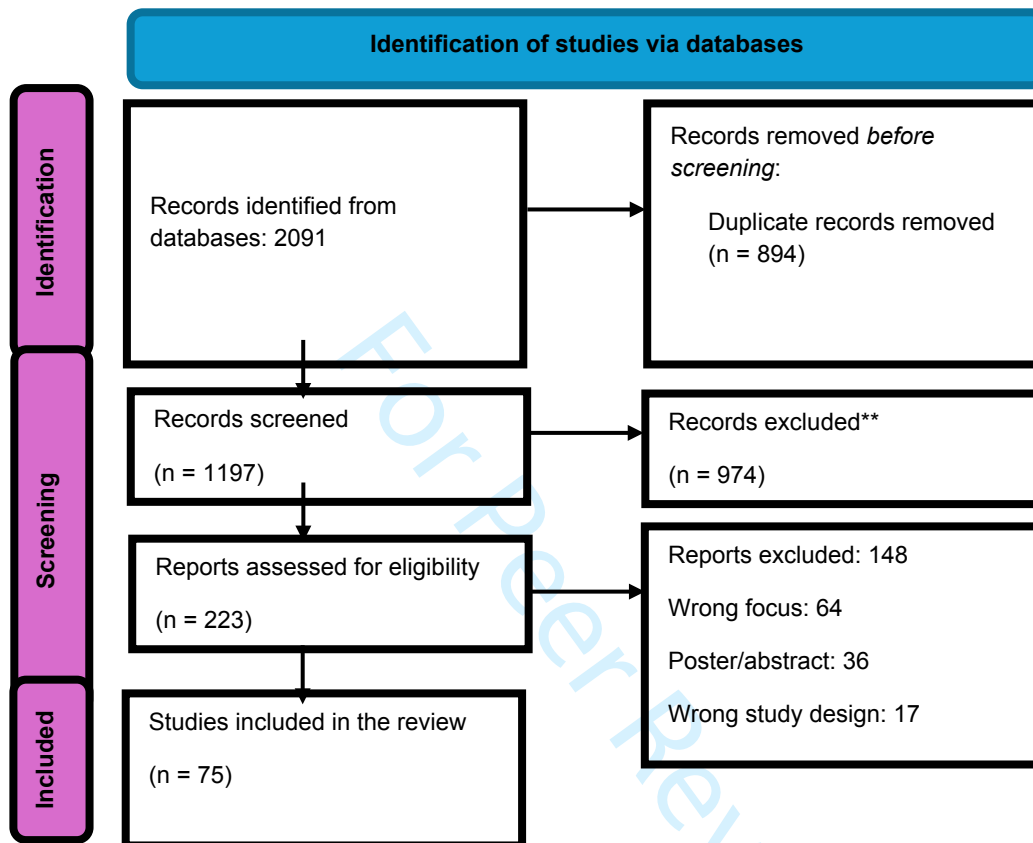


Figure 1: A modified PRISMA flowchart detailing our literature review identification, screening, eligibility, and inclusion stages

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**A Meta-analysis of Potential Genetic Factors Associated with  
Antipsychotic-Induced Weight Gain (AIWG) in Adults with  
~~Serious~~ Severe Mental Illness**

Running Head: Genetics and Weight Gain in Treatment of Psychosis

John Warner-Levy<sup>1</sup>, Lleyton Belston<sup>1</sup>, Yasitha Illangasekera<sup>2</sup>, Adam Jameson<sup>3</sup>, Cheyenne Meehan<sup>1</sup>, Loren Wilkins<sup>1</sup>, Camila Marcelino Loureiro<sup>2</sup>, Sushant Saluja<sup>4</sup>, Mark Shakespeare<sup>5</sup>, Caroline Dalton<sup>2</sup>, Gavin Reynolds<sup>2</sup>, Adrian Heald<sup>1,4</sup>

<sup>1</sup>Department of Endocrinology and Diabetes, Salford Royal Hospital, Salford, M6 8HD, UK

<sup>2</sup>Sheffield Hallam University, Biomolecular Sciences Research Centre, Sheffield, UK

<sup>3</sup>School of Pharmacy and Medical Sciences, University of Bradford, Bradford, UK.

<sup>4</sup>The School of Medicine and Manchester Academic Health Sciences Centre, Manchester University, Manchester, UK

<sup>5</sup>Rotherham Doncaster and South Humber NHS Foundation, UK

Key words: Antipsychotic, Weight Gain, Psychosis, Gene, Association

Corresponding author:

Adrian Heald

University of Manchester

[adrian.heald@manchester.ac.uk](mailto:adrian.heald@manchester.ac.uk)

29 Telephone: + 44 7470 532162

30 Word Count: 3987

31 Tables: 4; Figures: 1

## 32 **Abstract**

### 33 Introduction

34 Genetic factors are thought to play an important role in antipsychotic-induced  
35 weight gain (AIWG). This study conducted a meta-analysis of current  
36 research of the pharmacogenetic associations of adult AIWG.

### 38 Methods

39 The analysis included papers providing comparisons of weight gain across at  
40 least two allele combinations for at least one single nucleotide polymorphism  
41 (SNP). Inclusion criteria were, patients 18 years of age or older and had  
42 received a diagnosis of severe mental illness (SMI), for which antipsychotic  
43 medication was prescribed. The association with AIWG needed to be  
44 replicated across at least two papers reporting separate sample sets.

### 46 Results

47 223 papers were assessed for eligibility. Of the 223 papers, 148 were  
48 excluded, leaving 75 studies to be included.

50 Six SNPs in six different genes were identified as having significant  
51 associations ( $p < 0.05$ ) with AIWG. These were *HTR2C rs3813929* (TT + TC vs  
52 CC), Hedge's  $g$  0.76; *MTHFR rs1801133* (TC + TT vs CC), Hedge's  $g$  0.61;  
53 *ADRA2A rs1800544* (CC + CG vs GG), Hedge's  $g$  0.71; *MC4R rs489693* (CC  
54 + AC vs AA) Hedge's  $g$  0.127; *LEPR rs1137101* (GG + AG vs AA) Hedge's  $g$   
55 0.18 and *CNR1 rs104935* (GG + AG vs AA), Hedge's  $g$  0.55.

### 57 Conclusion

58 The study identified 6 SNPs that predispose adult individuals to AIWG, with  
59 *HTR2C rs3813929* and *ADRA2A rs1800544* showing the largest effect sizes.  
60 Five of these have a role in hypothalamic regulation of appetite/satiety.

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3 62 Identification of these risk-associated SNPs may assist the development of a  
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5 63 polygene/polyphenotypic risk score to identify individuals with psychosis who  
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7 64 are at heightened risk of experiencing AIWG.  
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## 11 66 **Introduction**

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14  
15 67 Obesity in people with severe mental illness (SMI) shortens lives and is  
16  
17 68 associated with multiple comorbidities (De Hert et al, 2011). The social  
18  
19 69 disparities between those with a SMI and the broader society further  
20  
21 70 exacerbate inequity in health outcomes (Nguie et al, 2010). Antipsychotic  
22  
23 71 induced weight gain (AIWG) in people with SMI is a determinant of future  
24  
25 72 diabetes, dysmetabolic profile and increased cardiometabolic risk (Heald et  
26  
27 73 al, 2017; Zhang et al, 2013). Dyslipidaemia and hypertension may develop  
28  
29 74 within the first year of initiating antipsychotic therapy, exacerbating  
30  
31 75 cardiovascular risk. AIWG is linked to increased cardiovascular morbidity and  
32  
33 76 mortality (Doanne et al. 2022, Montejo et al. 2024). Weight gain can serve as  
34  
35 77 an early and recognisable signal of metabolic dysregulation and its prediction  
36  
37 78 through pharmacogenomic diagnostics could play a central role in the  
38  
39 79 management of antipsychotic drug treated patients.  
40

41 80  
42 81 Antipsychotic agents are prescribed for a range of SMI including, but not  
43  
44 82 limited to schizophrenia and bipolar disorder. Schizophrenia alone affects 1%  
45  
46 83 of the world's population. AIWG is a well-reported side effect of most  
47  
48 84 antipsychotics (Barton et al, 2020). Weight-gain is a modifiable risk, and  
49  
50 85 preventative treatment has been shown to be more effective than  
51  
52 86 retrospective treatment.  
53

54 87  
55 88 Numerous mechanisms underlying AIWG have been proposed, influenced by  
56  
57 89 a mixture of genetic, biological, psychological and behavioural factors  
58  
59 90 including sedentary lifestyle and dietary choices (Shrivastava et al, 2020;  
60  
91 Heald et al, 2015). AIWG also has a severe negative impact on patients' self-  
92  
93 92 esteem and can lead to non-adherence (Burschinski et al, 2023; Waite et al,  
2022; Klein et al 2020).

94

95 There is considerable variability in AIWG and metabolic effects between  
96 individuals in both the intermediate and longer term (Cooper et al, 2016).  
97 Young and antipsychotic-naïve individuals are at particularly high risk of  
98 AIWG in the short to intermediate term, as are women more than men (Correll  
99 et al 2009; Heald et al 2024). Genetic factors may play an important role in  
100 AIWG. Genome-wide association studies have reported the association of  
101 genes associated with obesity in the general population (Fall & Ingelsson  
102 2014). Furthermore, the expression of genes coding of components of  
103 metabolic pathways that modulate fat mass and weight gain in the shorter and  
104 longer term may be affected by genetic variants as described in recent years  
105 in seminal papers (Zhang & Malhotra; 2011 Zhang et al 2016).

106

107 Weight may show a steep upward trajectory following antipsychotic initiation,  
108 with up to 20% body mass increase in the first year (Lett et al, 2012). Early  
109 AIWG is a predictor of longer-term weight gain (Bioque et al, 2018), with the  
110 attendant long-term consequences including type 2 diabetes (T2D) premature  
111 cardiovascular disease (CVD) events and death. It is increasingly recognised  
112 that nutrition and physical health are closely aligned with mental health  
113 outcomes (Dayabandara et al 2017, Firth et al 2020 ) and genetic factors  
114 through their interaction with diet and other lifestyle factors, likely play a  
115 significant part in the degree to which AIWG occurs (Zhang & Malhotra; 2011  
116 Zhang et al 2016).

117

118 In relation to the genetic factors that may underlie weight gain in some  
119 individuals, we conducted a meta-analysis of the current research  
120 demonstrating the pharmacogenetic associations of AIWG. The longer-term  
121 goal is that individuals at risk of AIWG can be identified early to enable a  
122 balance between effective psychotropic treatment and physical health. The  
123 objective of the study was to perform a systematic review and meta-analysis  
124 of current literature to identify genetic variants most strongly predictive with  
125 AIWG.

126

127 **Methods**

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3 1284 129 **Eligibility Criteria**5  
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7  
8 131 We included studies that examined the associations between specific single-  
9 132 nucleotide polymorphisms (SNPs) and AIWG in adults ( $\geq 18$  years). Studies  
10 133 needed to report genotype groupings for at least one SNP and provide body  
11 134 weight or Body Mass Index (BMI) data from a minimum of two time points,  
12 135 spaced at least four weeks apart. Only studies involving human participants  
13 136 receiving antipsychotic treatment for psychosis or severe mental illness (SMI)  
14 137 were eligible. We excluded animal studies, review articles, abstracts without  
15 138 full data, and studies lacking adequate weight or genotype information.  
16 139 Additionally, studies that focused on weight gain unrelated to antipsychotic  
17 140 treatment, such as comorbidities or lifestyle factors, were excluded.

18  
19 14120 142 **Information Sources and Search Strategy**21  
22 143

23 144 We conducted a systematic literature search in PubMed, Embase, APA  
24 145 PsycINFO, and Web of Science. The search was registered with Covidence  
25 146 on 13 October 2022.

26  
27 147

28 148 The search included both free-text and controlled vocabulary (MeSH) terms  
29 149 related to genetics, psychiatry, weight-related outcomes, and antipsychotic  
30 150 medications. The final search was performed on May 13, 2024. The full  
31 151 search strategy was: (genetics OR gene\* OR polymorphisms OR "gene  
32 152 variants" OR HT2RC-5HTC receptor OR pharmacogenetic\* OR SNP OR  
33 153 "single nucleotide polymorphism" OR "Human Genetics"[Mesh] OR  
34 154 "Polymorphism, Genetic"[Mesh] OR "Genetics, Medical"[Mesh] OR "Genetics,  
35 155 Behavioral"[Mesh]) AND (psych\* OR "biological psychiatry" OR schizophrenia  
36 156 OR "Psychotic Disorders"[Mesh] OR "Schizophrenia Spectrum and Other  
37 157 Psychotic") AND ("Weight Gain"[Mesh] OR "Body-Weight Trajectory"[Mesh]  
38 158 OR obes\* OR BMI OR cardiovascular OR diabetes) AND (antipsychotic\* OR  
39 159 "major tranquiliser\*" OR clozapine OR quetiapine OR risperidone OR  
40 160 amisulpride OR sertindole OR "Dopamine Antagonists"[Mesh] OR

1  
2  
3 161 "Olanzapine"[Mesh] OR "Aripiprazole"[Mesh] OR "Antipsychotic  
4 162 Agents"[Mesh]).

5  
6 163

7  
8 164 References of selected studies were manually screened for additional  
9 165 relevant studies. For articles where only abstracts were available, every  
10 166 attempt was made to request the full text. Studies without full-text access  
11 167 were excluded from the final analysis. We did not apply any language or  
12 168 publication year restrictions.

13  
14 169

15  
16 170 Duplicates were identified by screening the abstract text and authors. Studies  
17 171 conducted on children, adolescents and animals and those which had not  
18 172 been peer reviewed were excluded.

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### 23 175 **Study Selection and Data Extraction**

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26  
27 177 Two independent reviewers screened titles, abstracts, and full texts, resolving  
28 178 disagreements via a third reviewer. Extracted data included SNP Identifier,  
29 179 genotype comparisons, sample size, the number of studies, direction and  
30 180 magnitude of weight change, and outcome measures (e.g., Hedges' g).  
31 181 Additionally, we collected information on study quality, participant  
32 182 demographics, and weight measurement methods (e.g., weight vs. BMI).  
33 183 Studies with multiple genotype comparisons for a given SNP were included,  
34 184 and all valid models were used in the analysis.

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### 37 186 **Statistical Analysis**

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40  
41 188 We performed a meta-analysis using the metafor package (version 4.4.8-0) in  
42 189 R (version 4.5.0). A random-effects model with the DerSimonian–Laird  
43 190 estimator was used to account for heterogeneity between studies. The  
44 191 primary outcome measure was the standardised mean difference (Hedges' g)  
45 192 with 95% confidence intervals (CIs) for weight change between genotype  
46 193 groups. .

47  
48 194

## 195 **Heterogeneity and Bias Assessment**

196 Heterogeneity was quantified using  $I^2$  statistics, with thresholds of 25%, 50%,  
197 and 75% indicating low, moderate, and high heterogeneity, respectively. To  
198 evaluate potential publication bias, the Trim and Fill method was applied,  
199 which estimates the number of potentially missing studies and adjusts the  
200 overall effect size accordingly. Additionally, funnel plots were visually  
201 inspected for asymmetry to further evaluate publication bias (Duval et al,  
202 2000)

## 204 **Subgroup and Comparison Models**

206 Where feasible, dominant genetic models (e.g. AA + AG vs. GG) were  
207 analysed. In cases where studies presented multiple genotype comparisons,  
208 all valid models were incorporated into pooled analyses. SNPs with at least  
209 two studies and consistent genotype groupings were included in the analysis.

## 211 **Results**

### 212 *Selection of sources of evidence*

213 The literature search yielded 2091 results, 894 of which were duplicates,  
214 which were identified by screening the abstract text and author names.  
215 Studies conducted on children, adolescents and animals and those which had  
216 not been peer reviewed were excluded. This resulted in 1197 articles to be  
217 screened. 974 of these were excluded, as they did not relate specifically to  
218 AIWG. The remaining 223 papers were assessed for eligibility. Of the 223  
219 papers, 148 were excluded, leaving 75 studies to be included.

221 Figure One: PRISMA flowchart showcasing the flow of studies in our review.

223 Table 1 presents an overview of all 75 papers included in the analysis. Sample  
224 sizes in these studies ranged from 32 to 1991 participants, with the majority  
225 involving chronic schizophrenia (SCZ) or schizoaffective disorder (SZA)  
226 patients. Most studies were of short duration, typically between 4 weeks and 4  
227 months, though 16 studies (22%) included follow-up periods of one year or  
228 more. The patient populations were predominantly Caucasian-White or Asian,

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2  
3 229 with 30 studies (41.7%) exclusively involving Asian participants. The most  
4  
5 230 frequently studied antipsychotics were olanzapine (52.8% of studies),  
6  
7 231 risperidone (41.7%), and clozapine (40.3%). Monotherapy was common, with  
8  
9 232 35 studies examining a single antipsychotic, including clozapine (15 studies),  
10  
11 233 olanzapine (15 studies), risperidone (4 studies), and iloperidone (1 study).  
12  
13 234 Nearly all studies focused on people with schizophrenia (94.4%), although  
14  
15 235 some included participants with other psychiatric diagnoses.

16  
17 236

18 237 Table 1: Overview of all papers included

19 238 Table 1 lists the SNPs, along with their corresponding genes, chromosomal  
20  
21 239 positions and other relevant details. The major and minor alleles, as well as  
22  
23 240 minor allele frequencies (MAF), are provided based on available population  
24  
25 241 data. Among the SNPs, the *5-Hydroxytryptamine (Serotonin) Receptor 2C*  
26  
27 242 (*HTR2C*) polymorphism *rs3813929 (-759C/T)* was the most extensively  
28  
29 243 studied, with 17 studies involving 1,531 patients.

30  
31 244

32 245 Table 1 here.

33  
34 246

35 247 Table 2 shows the list of genes and SNPs included in the meta-analysis. This  
36  
37 248 lists the included SNPs along with other relevant information including SNPs in  
38  
39 249 linkage disequilibrium.

40  
41 250

42 251 Table 2 here.

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44 252

45 253 Table 3a - Meta-analysis of longitudinal outcomes examining the association  
46  
47 254 between candidate SNPs and antipsychotic-induced weight gain (AIWG).] This  
48  
49 255 table presents combined effect sizes (Hedges' *g*) for continuous measures of  
50  
51 256 weight-related changes, including percentage weight change and baseline-to-  
52  
53 257 final BMI change. A dominant genetic model was used for each SNP (minor-  
54  
55 258 allele carriers vs. major-allele homozygotes). Positive effect sizes signify  
56  
57 259 greater weight gain linked to the minor-allele genotype; negative values indicate  
58  
59 260 less gain. For each SNP, the table reports the number of studies included, total  
60  
261 sample size, pooled effect size, 95% confidence interval, p-value, and

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2  
3 262 heterogeneity statistics ( $I^2$ ). These analyses reflect the longitudinal influence of  
4 specific genetic variants on AIWG across adult psychosis cohorts.  
5 263

6 264

7  
8 265 Table 3a here.  
9

10 266

11  
12 267 Table 3b - Meta-analysis of categorical outcomes assessing the association  
13 between SNPs and clinically significant antipsychotic-induced weight gain. This  
14 268 table summarises pooled effect sizes derived from categorical definitions of  
15 269 weight gain (e.g.,  $\geq 7\%$  increase from baseline), using a dominant genetic model  
16 270 (minor-allele carriers versus major-allele homozygotes). Effect sizes (Hedges'  
17 271  $g$ ) indicate the magnitude of difference in the likelihood of clinically relevant  
18 272 weight gain between genotype groups. For each SNP, the table includes the  
19 273 number of contributing studies, the combined sample size, the effect estimate,  
20 274 the 95% confidence interval, the p-value, and the heterogeneity statistic ( $I^2$ ).  
21 275 These analyses offer a categorical, clinically oriented perspective on the  
22 276 genetic contribution to AIWG.  
23 277

24 278

25 279 These correspond to the following proteins:

26 280 Serotonin (5-HT) receptor-2C

27 281 Methylenetetrahydrofolate reductase

28 282 Alpha-2 Adrenergic receptor A

29 283 Melanocortin-4 receptor

30 284 Leptin receptor

31 285 Cannabinoid receptor 1  
32

33 286

34 287 Table 3b here.  
35

36 288

37 289 Table 4 describes the orphan SNPs which therefore could not be included in  
38 290 the meta-analysis.  
39

40 291

41 292 Table 4 here.  
42

43 293

44 294 **Discussion**  
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3 295 The study identified six SNPs that showed statistical significance in the meta-  
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5 296 analysis regarding predisposition of adult individuals to AIWG, of which  
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7 297 *ADRA2A rs1800544* and *HTR2C rs3813929* showed the largest effect size.  
8  
9 298 Five of these SNPs are implicated in hypothalamic regulation of appetite and  
10  
11 299 satiety. This contributes to our understanding of why some, but not all, people  
12  
13 300 experience an increase in body weight when started on an antipsychotic agent.  
14  
15 301 Genetic factors do not just add to the phenotype; they shape the range and  
16  
17 302 individual susceptibility to the obesogenic effects of psychotropic  
18  
19 303 pharmacotherapy and serve to address the substantial unexplained  
20  
21 304 interindividual variability in response to antipsychotic drug therapy that is not  
22  
23 305 explained by the other factors such as BMI, age, family history, diabetes and  
24  
25 306 polypharmacy. Furthermore, knowledge of genetic factors related to AIWG  
26  
27 307 would contribute towards a better understanding of the mechanisms of AIWG  
28  
29 308 and thus inform the potential development of targeted interventions.

309

310 Many genes have been studied for their proposed contribution to this very  
311  
312 prevalent side effect over the past 2 decades. In spite of mixed results for  
313  
314 some genetic studies, some genes have shown fairly consistent replication,  
315  
316 such as in the *MC4R*, *HTR2C*, *leptin*, *neuropeptide Y (NPY)* and *CNR1* gene  
(Shams et al, 2014), although a significant effect of *NPY* was not identified by  
our meta-analysis.

316

317 The majority of the studies examined here were not performed in people with  
318  
319 first episode psychosis (FEP). This is important, given that up to 50% weight  
320  
321 gain that occurs, does so in the months after initiation of antipsychotic  
treatment (Heald et al, 2023; Correll et al, 2023).

321

322 Five out of the six identified genes are linked to biological pathways  
323  
324 associated with hypothalamic regulation of appetite. Specifically, for *HTR2C*,  
325  
326 the gene codes for the 5-HT<sub>2C</sub> receptor at which several of the antipsychotic  
327  
328 drugs, most notably those associated with the greatest weight gain - clozapine  
and olanzapine - have antagonist or inverse agonist effects at this receptor.  
The 5-HT<sub>2C</sub> receptor is found in the hypothalamus, an area of the brain  
associated with appetite and satiety (Zanchi et al, 2017). Its blockade has

1  
2  
3 329 been proposed to be the major mechanism underlying olanzapine-induced  
4 330 weight gain (Reynolds et al, 2006). The SNP identified here, *rs3813929*, is in  
5 331 the promoter sequence of the gene and is thought to be involved in the control  
6 332 of transcription - the T-allele associated with less weight gain reportedly  
7 333 shows reduced transcriptional activity (Reynolds et al, 2006) probably by  
8 334 disrupting protein-DNA binding (Hill & Reynolds, 2011). This may therefore  
9 335 underlie allele-specific differences in the relative influence of 5-HT<sub>2C</sub>  
10 336 antagonism on hypothalamic function. Antipsychotics with lower metabolic risk  
11 337 lack 5-HT<sub>2C</sub> receptor antagonism (amisulpride, haloperidol) or have  
12 338 additional protective mechanisms, such as 5-HT<sub>1A</sub> partial agonism  
13 339 (aripiprazole, lurasidone, and ziprasidone) (Reynolds & McGowan, 2021).

14 340

15 341 The ADRA<sub>2R</sub> is a heteroreceptor on 5-HT receptor terminals located in the  
16 342 hypothalamus. *ADRA2A rs1800544* was consistently associated with AIWG in  
17 343 our analysis. As it is situated in the regulatory promoter sequence of the gene,  
18 344 this polymorphism may influence transcription factor control of gene  
19 345 expression. This SNP may lie at a binding site for several transcription factors.  
20 346 In addition to its association with weight gain, a 2014 study reported that when  
21 347 individuals with schizophrenia were switched to either aripiprazole or  
22 348 ziprasidone from other antipsychotics, significant differences in reduction of  
23 349 BMI at 6 months associated with *rs1800544* of the *ADRA2A* gene (Roffeei et  
24 350 al, 2014). The underlying mechanism of the association that is observed in this  
25 351 study may relate to the role of the adrenergic system in maintaining energy  
26 352 balance via the control of thermogenesis and lipolysis.

27 353

28 354 Leptin is an anorexigenic hormone secreted in adipose tissue proportional to  
29 355 weight gain. Leptin acts at the leptin receptor to activate hypothalamic MC<sub>4</sub>-  
30 356 receptors in order to inhibit food intake (Srisawat et al, 2014). Roffeei et al in  
31 357 2014 reported one marker from the promoter region of the leptin gene,  
32 358 *rs7799039* and one marker from the leptin receptor gene *rs1137101*. They  
33 359 described a significant association with *rs1137101* and the development of  
34 360 metabolic syndrome, but no association with *rs7799039*. Interestingly in a  
35 361 Brazilian study *LEPR rs1137101* was associated with a greater likelihood of  
36 362 higher circulating insulin levels and higher insulin resistance in overweight

1  
2  
3 363 adolescents (Oliveira et al, 2013). Conversely Brandl et al (2012) did not find any  
4 364 association between *rs1137101* and weight gain in 181 people treated with  
5 365 various antipsychotic agents.  
6  
7  
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9 366

10 367 Regarding the melanocortin pathway, the fed state is signalled by abundance  
11 368 of circulating hormones such as leptin and insulin, which bind to receptors  
12 369 expressed at the surface of pro-opiomelanocortin (POMC) neurons to promote  
13 370 processing of POMC to the mature hormone  $\alpha$ -melanocyte-stimulating  
14 371 hormone ( $\alpha$ -MSH) (Malhotra et al, 2012). The  $\alpha$ -MSH released by POMC  
15 372 neurons then signals to decrease energy intake by binding to melanocortin-4  
16 373 receptor (MC4R) expressed by MC4R neurons innervating the paraventricular  
17 374 nucleus (PVN) of the hypothalamus. Conversely, in the 'starved state' activity  
18 375 of agouti-related neuropeptide (AgRP) and of neuropeptide Y (NPY)-  
19 376 expressing neurons is increased by decreased levels of circulating leptin and  
20 377 insulin and by the orexigenic hormone ghrelin to promote food intake (Baldini &  
21 378 Phelan, 2019).  
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32 380 In several genome-wide association studies a genomic locus near *MC4R* was  
33 381 associated with obesity in the general population (Chambers et al, 2008; Zobel  
34 382 et al, 2009). *MC4R* mutations previously have been linked to extreme early-  
35 383 onset obesity (Farooqi and O'Rahilly, 2005). The *MC4R* gene, particularly  
36 384 variations in the *rs489693* and *rs17782313* polymorphisms, has been linked to  
37 385 increased AIWG, especially in individuals taking second-generation  
38 386 antipsychotics (SGAs) for schizophrenia. When accounting for the shared  
39 387 variance between emotional eating and depressed mood, a 2015 analysis  
40 388 revealed that eating behaviour alone - specifically emotional eating and food  
41 389 craving, accounted for the association between *rs17782313* and higher BMI in  
42 390 people who did not have a history of mental illness (Yilmaz et al, 2015). Thus,  
43 391 genetic variation appears to influence how the MC4R receptor, which is  
44 392 involved in energy balance and food intake, responds to second generation  
45 393 antipsychotic treatment, potentially leading to more weight gain in some  
46 394 individuals, as described by Malhotra et al (Malhotra et al, 2012).  
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3 396 The cannabinoid receptor 1 (CNR1) is expressed centrally in the hypothalamus  
4 and associated with appetite and satiety. Based on a report by Tiwari et al  
5 397  
6 (2010), Nurmi et al (2013) studied several *CNR1* SNPs in the same sample.  
7 398  
8 They investigated one SNP of the promoter region (rs806377) and three in the  
9 399  
10 coding region (rs806368 variable in its location in *CNR1* transcripts, rs806378  
11 400  
12 and rs806377). They reported significant associations (that survived correction  
13 401  
14 for multiple testing) between rs806378 and rs1049353 with AIWG. A 2018  
15 402  
16 metanalysis reported that general population individuals with GA/AA genotype  
17 403  
18 of *CNR1 1049353* had significantly lower BMI (weighted mean difference = -  
19 404  
20 0.59 kg/m<sup>2</sup>, p<0.001) compared to those with the GG genotype with no  
21 405  
22 difference in dietary intake of fat, carbohydrate and protein (Sadeghian et al,  
23 406  
24 2018).  
25 407  
26 408

27 409 The anti-obesity drug Rimonabant is a selective CNR1 receptor blocker causing  
28 410  
29 attenuation of hyperleptinemia in obese subjects with the consequence of  
30 411  
31 decreased leptin resistance (Despres et al, 2005) and associated diminished  
32 412  
33 central drive to eat.  
34 413

35 414 Away from the hypothalamus, several polymorphisms of *MTHFR* have been  
36 415  
37 described in relation to association with weight gain in psychosis with evidence  
38 416  
39 particularly in younger people. Srisawat et al. (2013) reported an association  
40 417  
41 between the *MTHFR rs1801133* polymorphism and weight gain. Individuals  
42 418  
43 carrying the CC genotype gained more weight than those carrying the T allele  
44 419  
45 after treatment with antipsychotics. Therefore, the T allele appears to have a  
46 420  
47 protective effect (additional to that of the *HTR2C -759T* allele protective effect).  
48 421  
49 Several pharmacogenetic studies have indicated that individuals carrying the  
50 422  
51 677C allele (conferring higher *MTHFR* activity) experience greater  
52 423  
53 antipsychotic-induced increases in BMI and metabolic indices, especially  
54 424  
55 during early treatment (Su et al, 2021). This may be due to the role of *MTHFR*  
56 425  
57 in the one-carbon cycle (Ducker et al, 2017).  
58 426

59 427 Whilst five of the six SNPs identified in the current meta-analysis were related  
60 428  
429 to the hypothalamic satiety pathways, it should be appreciated that weight  
regulation involves a broader neural circuitry beyond the hypothalamic satiety

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2  
3 430 pathways resulting from a complex interplay of neurophysiological and  
4  
5 431 psychological factors such as mood and motivation. In particular the  
6  
7 432 mesocorticolimbic system consisting of dopaminergic projection play a central  
8  
9 433 role in motivation and food reward (Baik et al. 2021). In extracting studies for  
10  
11 434 analysis, we encountered a number of orphan SNPs which had only a single  
12  
13 435 study reporting association with AIWG- dopamine being one of them. Thus, our  
14  
15 436 null findings with regards to other genetic variants related to AIWG, reflect a  
16  
17 437 limitation of evidence extracted through our specific methodology rather than  
18  
19 438 an absence of genetic contribution.

439

20  
21 440 Our work builds on a previous metaanalysis by Zhang et al 2016. Overall, we  
22  
23 441 found fewer significant associations with AIWG. Possible reasons for this  
24  
25 442 included that we only looked at adults only, whereas Zhang et al considered  
26  
27 443 studies in both children and adults; The following SNPs were significant in the  
28  
29 444 previous Zhang etl metaanalysis but not in the current metaanalysis: Alpha-2  
30  
31 445 Adrenergic ReceptorB3 rs3994 (*ADRB3 rs3994*), Brain-Derived **natriuretic**  
32  
33 446 **neurotrophic** factor rs6265 (*BDNF rs6265*), Dopamine Receptor D2 rs1799732  
34  
35 447 (*DRD2 rs1799732*), *DRD2 rs6275*, *DRD2 rs7131056*, Guanine nucleotide-  
36  
37 448 binding protein-3 rs5443 (*GNB3 rs5443*), Insulin Induced Gene 2 rs17047764  
38  
39 449 (*INSIG2 rs17047764*) and synaptosome associated protein 25 rs1051312  
40  
41 450 (*SNAP25 rs1051312*). The difference relates at least in part to contrasting  
42  
43 451 inclusion criteria: specifically the authors included individuals under 18 years of  
44  
45 452 age, which for certain SNPs led to the inclusion of more papers than in our  
46  
47 453 analysis that focussed on people aged 18 and above.

454

46  
47 455 Many of the studies included in this meta-analysis have not looked at individuals  
48  
49 456 with first episode psychosis. However much of the weight gain occurs in the  
50  
51 457 early months after the first prescription of antipsychotic treatment (Correll et al,  
52  
53 458 2023). It is therefore important to determine the risk profile for early weight  
54  
55 459 gain as once weight has increased it is very difficult to reduce this (Firth et al  
56  
57 460 2020; Heald et al, 2024). The reduced gene effects during longer-term  
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59 461 antipsychotic treatment and follow-up could be explained by a reduced effect  
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462 size because of contributions from behavioural and environmental factors on  
463 weight trajectory.

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5 465 Regarding future developments, at the time of writing there is no clinically  
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7 466 applied gene-based algorithm that can reliably enable the identification of  
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9 467 individuals at greatest risk of weight gain in the early stages of psychosis is  
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11 468 being applied in every day clinical practice. However there is substantial  
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13 469 evidence that genetic factors can be used to predict AIWG. In the analysis of  
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15 470 Yoshida et al in 2023, nominal associations (uncorrected  $p < 0.05$ ) between  
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17 471 polygenic risk scores for BMI were found in the CAMH-Toronto study and the  
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19 472 CATIE study samples. The nominal associations of a polygenic risk score for  
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21 473 schizophrenia with AIWG - defined as the presence of  $>7\%$  weight change in  
22  
23 474 both the CATIE and CAMH-Toronto samples, pointed to shared genetic links  
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25 475 between genes underlying the pathogenesis of schizophrenia and those  
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27 476 associated with AIWG. However, it should be noted that coefficients were  
28  
29 477 opposite in two samples (0.714 in the CATIE sample and  $-0.483$  in the  
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31 478 CAMH-Toronto sample). Heterogeneity between the two samples (for  
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33 479 example the prescribed antipsychotic medications) may have contributed to  
34  
35 480 the discrepancy. While the results became non-significant after correction for  
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37 481 multiple testing, these findings suggest that polygenic risk score analyses  
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39 482 could contribute to identifying risk factors of AIWG and might help to elucidate  
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41 483 mechanisms at play in AIWG.

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#### 484 485 Limitations and strengths

486 A major limitation of this and previous meta-analyses in this area is that the  
487 majority of the studies examined were not performed in people with FEP,  
488 when the critical time in terms of determining innate biological predisposition  
489 to weight gain with antipsychotic treatment occurs. The variation in  
490 measurement timings reflect the constraints of the literature reviewed and the  
491 focus on  $\geq 4$  week time window was to allow for the inclusion of a broader set  
492 of studies whilst capturing treatment related weight change. Future studies  
493 should focus on weight trajectories in the early phases of treatment.

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495 We accept that there is a lack of ethnic diversity in some studies. However, we  
496 are limited by the studies that have been conducted. Also we have not  
497 examined epigenetic, transcriptomic data or gene/environment interactions.

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3 498 Another limitation is the way that different studies reported weight gain in  
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5 499 different ways, most by kg or percent change in weight but some applying a  
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7 500 categorical definition of weight change.

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10 502 Metabolic syndrome is an important indicator of downstream cardiovascular  
11  
12 503 consequences. The present study protocol specifically focused on  
13  
14 504 absolute/relative weight/BMI change and hence did not include  
15  
16 505 pharmacogenomic studies on metabolic syndrome. Though body weight/BMI  
17  
18 506 has an indirect relationship to metabolic syndrome, future reviews should  
19  
20 507 incorporate specific genetic predictors of metabolic syndrome for a more  
21  
22 508 comprehensive understanding cardiometabolic risk.

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25 510 The potential impact of publication bias on the meta-analysis findings are  
26  
27 511 considerable. Although some included studies in this meta-analysis reported  
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29 512 non-statistically significant findings between AIWG and associated genetic  
30  
31 513 variants, many studies with non-significant findings are not published and  
32  
33 514 therefore potentially underrepresented in the literature. Reliance on older  
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35 515 candidate gene studies further increases the risk of cumulative publication bias,  
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37 516 as the evidence base becomes focused on specific gene variants..

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40 518 Conclusion

41 519 The study identified 6 SNPs that predispose individuals to weight gain  
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43 520 associated with antipsychotic treatment in adults, with *HTR2C rs3813929* and  
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45 521 *ADRA2A rs1800544* showing the largest effect sizes. Five of these have a  
46  
47 522 role in the hypothalamic regulation of appetite and satiety.

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49 523

50 524 Identification of these risk-associated SNPs may assist the development of a  
51  
52 525 polygene/polyphenotypic risk score to identify individuals with psychosis who  
53  
54 526 are at heightened risk of experiencing AIWG.

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57 528 **Figure Legends**

58 529 Figure 1: A modified PRISMA flowchart detailing our literature review  
59  
60 530 identification, screening, eligibility, and inclusion stages

61 531

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3 532 **Acknowledgements**  
4

5 533 None  
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8 534  
9

10 535 **Funding**  
11

12 536 No external funding was obtained.  
13  
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15 537  
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17 538 **Author Contributions**  
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19  
20 539 AHH conceived the study with GR and CD, with contributions in relation to  
21 540 design from AJ, CM, CML and CD. JWL, GR, SS and CD led on data analysis.  
22  
23 541 Data extraction was conducted by CM and AJ with the assistance of LB and  
24  
25 542 JWL. JWL constructed all the tables with support from LB and LW. All authors  
26  
27 543 contributed to the final version of the manuscript.  
28

29 544  
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31 545 **Conflict of interest**  
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33 546 No author has any conflict of interest  
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38 548 **Data availability Statement**  
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40 549 The data that support the findings of this study are available from the  
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42 550 corresponding author upon reasonable request  
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7 Reply to Reviewer 1  
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9 Please see the replies below  
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13 Reviewer: 1  
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15 Comments to the Author

16 The authors have followed the most important suggestions. Remaining points are:

- 17  
18 • line 4 - please change "serious mental illness" to "severe mental illness" in the title

19 Done

- 20 • line 152 - was "HT2RC" really used as a term during the searches?

21 Point taken. The search term was 5-HT receptor as now described  
22

- 23 • line 228 - please change "Caucasian" to "white"

24 Done

- 25 • line 445 – please change "natriuretic" to "neurotrophic".

26 Done  
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29 Thank you for pointing out the further improvements to this paper  
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11 **7 September 2025**  
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15 Dear colleagues  
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18  
19 **Re: A Metanalysis of Potential Genetic Factors Associated with Antipsychotic-**  
20 **Induced Weight Gain (AIWG) in Adults with Psychosis**  
21

22  
23  
24 We would be grateful if this paper could be considered for the Journal of  
25 Psychopharmacology.  
26

27 Antipsychotic induced weight gain (AIWG) in individuals with severe mental illness (SMI)  
28 shortens life expectancy and is associated with multiple comorbidities. Genetic factors are  
29 thought to play an important role in AIWG.  
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32 We conducted a meta-analysis of the current research demonstrating the pharmacogenetic  
33 associations of AIWG.  
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35  
36 The study identified six SNPs that showed statistical significance in the metanalysis  
37 regarding predisposition of individuals to weight gain associated with antipsychotic treatment  
38 in adults, of which *ADRA2A rs1800544* and *HTR2C rs3813929* showed the largest effect  
39 size. Five of these SNPs are implicated in hypothalamic regulation of appetite and satiety.  
40 This contributes to our understanding of why some, but not all, people experience an  
41 increase in body weight when started on an antipsychotic agent.  
42  
43

44 Thank you for considering this submission which we feel does add to our understanding of  
45 the factors influencing weight gain in adults treated for psychosis,  
46

47  
48 Yours sincerely,  
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53

54 Professor Adrian Hugh Heald  
55 Salford Royal Hospital  
56 07470 532162  
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