Impact of Early Antipsychotic Prescription Choice on Weight Gain in the First 5 Years of Psychotic Illness: a Retrospective Cohort Study

HEALD, Adrian <http://orcid.org/0000-0002-9537-4050>, TILSTON, George, WARNER-LEVY, John Julian, WILKINS, Loren, WILLIAMS, Richard, PILLINGER, Toby, DEAKIN, William, LONGSON, Damien, HASSAN, Lamiece, DALTON, Caroline <http://orcid.org/0000-0002-1404-873X>, REYNOLDS, Gavin P <http://orcid.org/0000-0001-9026-7726> and FIRTH, Joseph

Neurol Ther (2025) 14:1657–1670
https://doi.org/10.1007/s40120-025-00780-4

ORIGINAL RESEARCH

Impact of Early Antipsychotic Prescription Choice on Weight Gain in the First 5 Years of Psychotic Illness: a Retrospective Cohort Study

Adrian Heald · George Tilston · John Julian Warner-Levy · Loren Wilkins · Richard Williams · Toby Pillinger · William Deakin · Damien Longson · Lamiece Hassan · Caroline Dalton · Gavin P. Reynolds · Joseph Firth

Received: April 9, 2025 / Accepted: May 22, 2025 / Published online: June 19, 2025

ABSTRACT

Introduction: We analysed the effects of antipsychotic drug prescribing in year 1 of treatment for psychosis on future weight gain over 5 years.
Methods: We studied how weight changed over 5 years after the first diagnosis of psychosis/schizophrenia/schizoaffective disorder/delusional disorder/affective psychosis in 17,570 individuals and investigated its association with antipsychotic drug treatments prescribed in year 1 following diagnosis, over 30 years.
Results: The majority (65%) were aged 20–59 years at the time of first antipsychotic prescription. Mean baseline body-mass-Index (BMI) was similar in women versus men. Substantial increases in BMI were observed, with the greatest categorical changes seen in the obese (BMI ≥ 30 kg/m^2) subjects, increasing from 30 to 43% for women and from 26% to 39% for men, while 42% of people did not significantly increase their weight. Individuals prescribed perphenazine/fluphenazine/amisulpride were most likely to remain at normal-BMI, while individuals prescribed aripiprazole/quetiapine/olanzapine/risperidone in the first year were most likely to gain weight/transition to overweight (25.0–29.9 kg/m^2)/obese (≥ 30.0 kg/m^2) from a normal BMI. The 'typical' agents thioridazine/chlorpromazine/flupenthixol/trifluoperazine/haloperidol were associated with an intermediate likelihood of BMI category change. In multivariate linear regression, factors associated with weight-gain were younger age/female sex(both $p < 0.001$), number of antipsychotic agents prescribed in 1st year ($p < 0.001$), plus specific agents aripiprazole (including 75% co-prescription or as 2nd line/3rd line)/olanzapine/thioridazine ($p < 0.001$), risperidone/quetiapine ($p < 0.05$).

A. Heald (✉)
The School of Medicine and Manchester Academic Health Sciences Centre, Manchester University, Manchester, UK
e-mail: adrian.heald@manchester.ac.uk

A. Heald · J. J. Warner-Levy · L. Wilkins
Department of Endocrinology and Diabetes, Salford Royal Hospital, Salford M6 8HD, UK

G. Tilston · R. Williams
Division of Informatics, Imaging and Data Science, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

T. Pillinger
Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

W. Deakin · L. Hassan · J. Firth
Division of Psychology and Mental Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

D. Longson
Greater Manchester Mental Health, Prestwich Hospital, Greater Manchester, UK

C. Dalton · G. P. Reynolds
Sheffield Hallam University, Sheffield, UK

In multivariate logistic regression (weight increase ≥ 7%), the specific medication factors were similar, with odds ratios(OR) for specific medications ranging from quetiapine 1.09 (CI 1.00–1.21) to thioridazine 1.45 (CI 1.20–1.74).
***Conclusion*:** Younger women were at elevated risk for weight gain as were people prescribed multiple antipsychotics in the 1st year. Some older antipsychotics associated with as much weight gain as the newer prescribed agents. More than 40% of people did not put on weight.

Keywords: Psychosis; Longitudinal; Weight gain; BMI; Prescribing; Antipsychotic; Sex difference

Key Summary Points

Why we carried out this study?
Weight gain with all its adverse health consequences has come to define the life experience of many people with schizophrenia and other serious mental illnesses (SMI).
There are limited data on the longer-term profile of weight change in people with a history of treated psychosis and in particular how medications may differentially influence the weight change that people experience over time.
We have examined the effects of antipsychotic prescribing in the first year of treatment for psychosis on future weight gain over an average period of 5 years from first prescription.
What we learnt from the study?
A notable finding was the association of polypharmacy in the first year following diagnosis with psychosis. Some older antipsychotics associated with as much weight gain as the newer prescribed agents.
Younger women were at elevated risk for weight gain.
42% of people did not significantly increase their weight.

INTRODUCTION

Weight gain with all its adverse health consequences has come to define the life experience of many people with schizophrenia and other serious mental illnesses (SMI) [1, 2]. Early weight gain predicts weight gain in the longer term [3], with factors such as female sex and young age at diagnosis associated with risk of greater weight gain [4–7]. Genetic factors are a likely influence modulating the degree of weight gain [8].

The prediction of who is going to gain weight following antipsychotic initiation remains a challenge for healthcare professionals working in psychiatry, and for service users. There are limited data on the longer-term profile of weight change in people with a history of treated psychosis, and in particular how medications may differentially influence the weight change that people experience over time.

We previously reported a more than 20-year perspective on weight change post-SMI diagnosis in Greater Manchester, UK [7], with particular focus on a history of psychosis versus bipolar affective disorder. This showed that the changes in BMI with treatment of non-affective psychosis versus bipolar disorder are not significantly different, while 43% maintained a healthy weight in the first 5 years following antipsychotic prescription.

We have now progressed to examine the effects of antipsychotic prescribing in the first year of treatment for psychosis on future weight gain over an average period of 5 years from first prescription. We did not include antipsychotic dose in the analysis as there is little evidence of a dose effect on weight change at clinically therapeutic doses [9].

Methods

Deidentified data was extracted from the Greater Manchester Care Record (GMCR) database. This is an integrated database across primary care, secondary care and mental health trusts (https://gmwearebettertogether.com/research-and-planning/) [10] covering a population of approximately 2.85 million people. Data were available from 433 of 435 (99.5%) general practices.

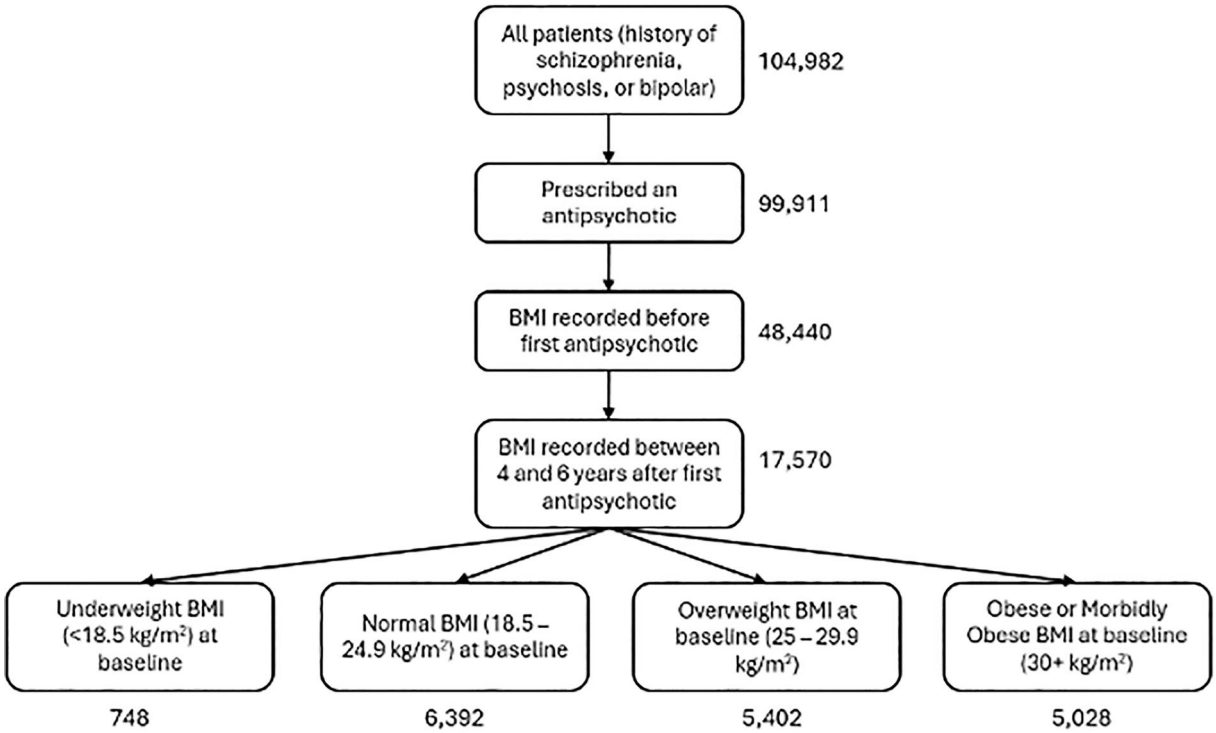

Fig. 1 Flowchart indicating how the study cohort was the derived from the full dataset

The ICD-10 classifications were: schizophrenia, schizotypal and delusional disorders. F20 (schizophrenia), F21 (schizotypal disorder), F22 (persistent delusional disorders), F23 (acute and transient psychotic disorders), F24 (induced delusional disorder), F25 (schizoaffective disorders), F27 (other psychotic disorders not due to a substance or known physiological condition), F28 (other nonorganic psychotic disorders), and F29 (unspecified nonorganic psychosis) [11].

A favourable ethical opinion was provided by the GMCR [12] (reference: IDCR-RQ-036). Deidentified data were used, as per the Health Research Authority's Governance arrangements and in accordance with the Declaration of Helsinki. Human ethics and consent to participate declarations were not applicable.

We included health records of people aged 18 years or more who had been diagnosed for the first time with first episode psychosis, schizoaffective disorder, schizophrenia, delusional disorder, psychosis associated with depression or bipolar affective disorder between 1 January 1997 and 1 January 2018. Anyone with a diagnosis of dementia was excluded. Given that the data were from primary care, SNOMED and READ codes were applied. Drug-induced psychosis was not included in these codes.

Body mass index (BMI) in the time before and after the first antipsychotic prescription was determined. The 'data window' was anywhere between 1998 and 2023. Townsend Index [13] as a measure of socioeconomic situation was included. In order to include data from an individual they must have had at least one BMI measurement prior to the first antipsychotic prescribed prescription date, and had at least one other BMI measurement between 4 and 6 years later. BMI measurements of < 12 or > 70 kg/m^2 were excluded.

Figure 1 shows a breakdown of the cohort from the entire dataset, down to the cohort used for modelling. The dataset is comprised of 104,982 individuals, which represents any person with a history of the above conditions who has been prescribed an antipsychotic medication, living in Greater Manchester.

After filtering the entire dataset to individuals who were prescribed an antipsychotic agent between April 1990 and June 2022, and had BMI recorded before the first antipsychotic prescription and at 5e-year follow-up (between 4 and 6 years), the cohort was filtered down to 17,570 individuals (Fig. 1). The analysis in this study focused on individuals that with 'healthy' or 'overweight' BMI at baseline (18.5–30 kg/m^2).

As this analysis focuses on antipsychotic prescriptions, we determined which antipsychotic agent each person had been prescribed within the first year of follow-up, as this is likely to be the period that has the most impact on subsequent weight gain after 5 years [3]. Several columns were created to indicate, for each individual antipsychotic, whether the individual had been prescribed it in the first year of follow-up.

Statistical Analysis

Regression analyses (both univariate and multivariate) were conducted to determine how BMI changes over time related to the prescription of antipsychotic agents in the first year. In the multiple regression analysis, we included factors that might influence weight trajectory over time. The exact numbers in each analysis differed slightly in relation to the specific analysis conducted.

Tables have been produced to show the proportional changes in BMI categories between baseline and 5-year follow-up. Regression analyses were also performed to investigate which antipsychotics and which demographics have significant impact on BMI increase. A kernel density plot was produced to visualise the change in weight gain percentage between baseline and 5-year follow-up. A sensitivity analysis was performed which considered all prescriptions of each antipsychotic during the 5-year follow-up, rather than just the first year.

All analysis was performed using R version 1.4.1103.

RESULTS

Baseline characteristics (relating to the closest point to initiation of the first antipsychotic prescription) are provided in Table 1.

Most people were in the age group 20–59 years old when the first antipsychotic agent was prescribed. BMI at baseline was similar in men and women. 5 years after baseline, BMI had increased more in women than in men. The % BMI change by category was greatest for the obese (BMI ≥ 30 kg/m^2) category at 30–43% for women and 26–39% for men. This likely included both people transitioning from normal BMI to obese and from overweight as a category to obese, while 42% of people did not significantly increase their weight.

There was minimal change in those recorded as underweight (BMI < 18.5 kg/m^2). A higher proportion of mean (78%) than women (69%) were smokers. For those with a measured HbA1c, this was higher in men then in women at baseline with the difference maintained at 5-year follow-up when HbA1c was 6–7 mmol/mol higher than at baseline.

In Fig. 2, we show the relative change in BMI for those of normal BMI (18–24.9 kg/m^2) and those overweight (25.0–29.9 kg/m^2). There was overall slightly less increase in BMI for those who were overweight at baseline versus those with a normal range BMI at baseline.

Tables 2 and 3 show the proportion of individuals moving between BMI categories between baseline and 5-year follow-up, split by most prescribed antipsychotic in the first year of follow-up after anti-psychotic treatment initiation. The tables show the top 12 most prescribed medications. Six medications (levomepromazine, sulpiride, clozapine, zuclopenthixol, pimozide, paliperidone) were excluded due to low numbers of individuals being prescribed them or in the case of clozapine having the prescription recorded in the primary care record (less than 100 prescriptions).

Table 2 shows the numbers of individuals in each BMI category at 5-year follow-up for individuals that had a normal BMI (18.5–24.9 kg/m^2) at baseline. The rows relate to individual antipsychotics that were prescribed to the

Table 1 Breakdown of demographics and laboratory tests for cohort of individuals that have the necessary baseline and follow-up BMI information

		Female	%	Male	%
	Total	10,443	59%	7143	41%
Ethnicity	White	8753	84%	5754	81%
	Black	217	2%	228	3%
	Asian	700	7%	599	8%
	Mixed	93	1%	82	1%
	Other	373	4%	274	4%
	Not available	307	3%	206	3%
Avg baseline BMI, kg/m^2 (*n*)		27.5 (10,443)		27.1 (7143)	
Avg 5-year BMI, kg/m^2 (*n*)		29.7 (10,443)		29 (7143)	
Avg baseline diastolic BP, mmHg (*n*)		77.4 (10,066)		78.2 (6678)	
Avg 5-year diastolic BP, mmHg (*n*)		77.9 (6348)		78.5 (4606)	
Avg baseline systolic BP, mmHg (*n*)		124 (10,066)		128 (6678)	
Avg 5-year systolic BP, mmHg (*n*)		124 (6348)		128 (4606)	
Avg baseline HbA1c, mmol/mol (*n*)		31.0 (1875)		34.1 (1490)	
Avg 5-year HbA1c, mmol/mol (*n*)		38.1 (4883)		40.1 (4036)	
Ever smoked	Yes	7231	69%	5585	78%
Age at first antipsychotic (years)	0–19	3939	38%	2457	34%
	20–39	2880	28%	2528	35%
	40–59	3155	30%	1877	26%
	60–79	299	3%	159	2%
	80+	2707	26%	1708	24%
Age at 2020 (years)	0–19	14	0%	19	0%
	20–39	1857	18%	1269	18%
	40–59	4449	43%	3228	45%
	60–79	3220	31%	2206	31%
	80+	903	9%	421	6%
Baseline BMI category	Underweight	469	4%	281	4%
	Normal	3939	38%	2457	34%
	Overweight	2880	28%	2528	35%
	Any obesity	3155	30%	1877	26%
5-year BMI category	Underweight	299	3%	159	2%
	Normal	2707	26%	1708	24%
	Overweight	2997	29%	2525	35%
	Any obesity	4440	43%	2751	39%

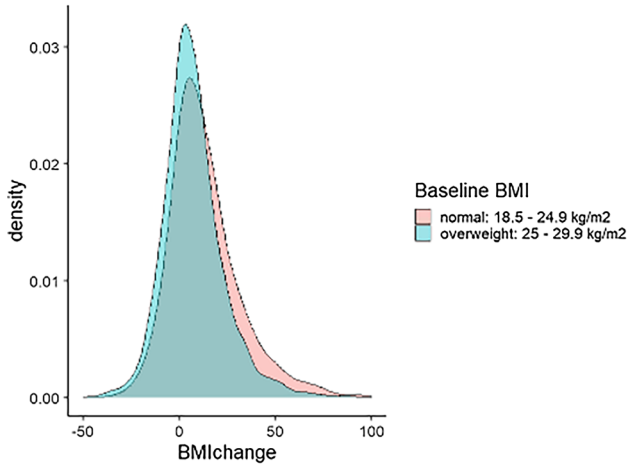

Fig. 2 Kernel density plot showing percentage BMI change for individuals with *normal* or *overweight* BMI at baseline

individual in the first year of follow-up ordered by most prescribed antipsychotic agent.

The first prescriptions of antipsychotic agents over the whole period of follow-up by individual were as follows: olanzapine 54%, risperidone 12%, quetiapine 10%, aripiprazole 6%, amisulpride 4%, haloperidol 4%, chlorpromazine 2% and other antipsychotic 8%.

Prescription of perphenazine, fluphenazine, flupenthixol and amisulpride in the first year after diagnosis associated with the least weight gain. Prescription of olanzapine, risperidone or aripiprazole (75% of aripiprazole was

Table 2 BMI category changes at 5-year follow-up, for individuals with a normal BMI at baseline

Antipsychotic in year 1 (any prescription)	No change (remained normal BMI	%	Change to Overweight	%	Change to any obesity	%	Change to under weight	%	Total
Quetiapine	663	44	568	37	242	16	45	3.0	1518
Flupentixol	769	58	410	31	104	8	34	2.6	1317
Olanzapine	594	44	499	37	219	16	37	2.7	1349
Risperidone	356	44	301	38	116	14	28	3.5	801
Chlorpromazine	282	55	165	32	54	11	9	1.8	510
Aripiprazole	210	40	199	38	109	21	10	1.9	528
Thioridazine	182	57	112	35	24	7	< 5	1.2	322
Trifluoperazine	157	55	102	36	22	8	5	1.7	286
Haloperidol	161	54	98	33	26	9	13	4.4	298
Perphenazine	80	61	41	31	9	7	< 5	1.5	132
Amisulpride	78	56	41	29	18	13	< 5	2.1	140
Fluphenazine	59	56	36	34	7	7	< 5	2.9	105

Values less than 5 have been changed to < 5 to protect individual confidentiality. An individual can appear in multiple rows if they were prescribed multiple medications in the first year of follow-up. This table is ordered by total prescriptions.

co-prescribed or prescribed as a 2nd- or 3rd-line agent) associated with greater likelihood to gain weight. Transition from a normal range BMI to overweight (25.0–29.9 kg/m^2) or obese (≥ 30.0 kg/m^2) was also associated with prescription of these agents. Quetiapine was also associated with a higher proportion of individuals showing change in BMI category (normal to overweight or normal to obese).

Prescription of the first-generation agents chlorpromazine, thioridazine, trifluoperazine and haloperidol was associated with an intermediate likelihood of weight gain.

Table 3 shows parallel information to Table 2, but only for individuals that had an overweight BMI (25–29.9 kg/m^2) at baseline. Overall trends were similar, although risperidone was associated with a lower proportion of people transitioning from overweight to obese BMI versus normal to overweight/obese categories, with thioridazine associated with a high proportion of people transitioning from overweight to obese versus other antipsychotic agents. Some first-generation oral antipsychotics were also associated with a higher proportion of people transitioning from overweight to obese. Again, perphenazine was associated with the lowest proportion of people transitioning to a higher BMI category (overweight to obese).

Linear regression analysis was used to further understand the association between each antipsychotic and weight gain, as well as the impact of demographic factors on these associations. The results of the univariate and multivariate linear regression are displayed in Tables 4 and 5, respectively. A total of 359 individuals in the final cohort were either missing ethnicity information or deprivation scores (due to missing location information) or both. These individuals were excluded from the regression analysis.

The main findings from the univariate analysis are consistent with Tables 2 and 3. Aripiprazole in co-prescription or following olanzapine or quetiapine (as the second or third agent prescribed—75% of aripiprazole prescriptions) had the greatest significant positive association with weight gain followed by olanzapine and quetiapine, while haloperidol and perphenazine had

Table 3 BMI category changes for individuals with an overweight BMI at baseline

Antipsychotic in year 1 (any prescription)	No change (remained overweight)	%	Changed to any obesity	%	Changed to normal or underweight	%	Total
Quetiapine	546	43	547	43	175	14	1268
Flupentixol	598	54	379	34	127	12	1104
Olanzapine	444	45	420	43	122	12	986
Risperidone	264	50	157	30	104	20	525
Chlorpromazine	266	53	178	36	57	11	501
Aripiprazole	162	37	222	51	51	12	435
Trifluoperazine	134	52	94	36	31	12	259
Haloperidol	113	40	118	42	53	19	284
Thioridazine	106	46	106	46	19	8	231
Perphenazine	76	60	40	31	11	9	127
Amisulpride	54	46	48	41	16	14	118
Fluphenazine	46	51	33	37	11	12	90

An individual can appear in multiple rows if they were prescribed multiple medications in the first year of follow-up. This table is ordered by number of prescriptions for each medication

Table 4 Univariate linear regression results for predicting BMI percentage increase

Variable	Estimate	*p* value	95% confidence interval	Significance
Sex: male (reference: female)	− 1.97	< 0.001	− 2.67 to − 1.28	***($p < 0.001$)
Age	− 0.27	< 0.001	− 0.29 to − 0.25	***($p < 0.001$)
Ethnicity: Black	2.16	0.056	− 0.06 to 4.37	($p < 0.1$)
Ethnicity: Asian	− 0.18	0.792	− 1.51 to 1.15	
Ethnicity: Mixed	3.45	0.065	− 0.21 to 7.12	($p < 0.1$)
Ethnicity: Other	2.31	0.013	0.49 to 4.13	*($p < 0.05$)
Ever s moked: Yes (reference: no)	0.3	0.462	− 0.49 to 1.09	
Total antipsychotics in year 1	0.12	< 0.001	0.09 to 0.14	***($p < 0.001$)
Townsend score	0.27	< 0.001	0.18 to 0.36	***($p < 0.001$)
Amisulpride	− 0.09	0.94	− 2.45 to 2.27	
Aripiprazole (co-prescription)	6.11	< 0.001	4.85 to 7.36	***($p < 0.001$)
Chlorpromazine	− 1.68	0.070	− 2.92 to − 0.45	**($p < 0.01$)
Flupentixol	− 3.27	< 0.001	− 4.13 to − 2.42	***($p < 0.001$)
Fluphenazine	− 2.44	0.080	− 5.15 to 0.26	($p < 0.1$)
Haloperidol	− 3.26	< 0.001	− 4.86 to − 1.65	***($p < 0.001$)
Olanzapine	3.66	< 0.001	2.79 to 4.52	***($p < 0.001$)
Perphenazine	− 3.23	0.006	− 5.59 to − 0.88	**($p < 0.01$)
Quetiapine	2.93	< 0.001	2.12 to 3.74	***($p < 0.001$)
Risperidone	1.38	0.012	0.32 to 2.44	*($p < 0.05$)
Thioridazine	− 0.40	0.634	− 2.03 to 1.24	
Trifluoperazine	− 2.12	0.013	− 3.76 to − 0.47	*($p < 0.05$)

The specific antipsychotic medication variables refer to any prescribed in the first year of follow-up for each individual, e.g. 1 if a patient was prescribed the medication, and 0 if not

* p < 0.05; ** p < 0.01; *** p < 0.001

the least strong association with weight gain in univariate analysis.

Other antipsychotics with a low association with weight gain at 5-year follow-up, included chlorpromazine, trifluoperazine and flupenthixol. Some of the key findings were consistent across the univariate and multivariate models, such as men and older people gaining less weight and aripiprazole in co-prescription or following other antipsychotics associated with the greatest weight gain, followed by olanzapine. Thioridazine had a strong positive association with weight gain in multivariate but not univariate analysis. The older antipsychotic agents were largely associated with less weight again in univariate analysis with no significant association with weight gain in multivariate analysis.

Townsend deprivation score (increasing social disadvantage) was associated with weight again in univariate analysis, and the number of antipsychotics prescribed in the first year of follow-up was associated with weight gain in univariate and multivariate analysis. Black/Black British ethnicity was associated (not quite reaching significance) with weight gain in univariate but not multivariate analysis, whereas 'ever smoked' was not associated with weight change. Younger age and female sex were associated with greater weight gain in both univariate and multivariate analysis.

Table 5 Multivariate linear regression results for predicting BMI percentage increase

Variable	Estimate	*p* value	95% Confidence interval	Significance
Sex: male (reference: female)	− 2.60	< 0.001	− 3.30 to − 1.89	***$p < 0.001$
Age	− 0.25	< 0.001	− 0.27 to − 0.23	***$p < 0.001$
Ethnicity: Black	− 0.02	0.988	− 2.20 to 2.17	
Ethnicity: Asian	− 2.16	0.002	− 3.51 to − 0.81	**$p < 0.01$
Ethnicity: Mixed	0.57	0.755	− 2.99 to 4.13	
Ethnicity: Other	1.40	0.120	− 0.27 to 3.17	
Ever Smoked: yes (reference: no)	0.06	0.878	− 0.74 to 0.86	
Total antipsychotics year 1	0.06	< 0.001	0.01 to 0.09	***$p < 0.001$
Townsend score	0.01	0.794	− 0.08 to 0.11	
Amisulpride	− 0.11	0.924	− 2.48 to 2.26	
Aripiprazole (co− prescription)	3.75	< 0.001	2.44 to 5.07	***$p < 0.001$
Chlorpromazine	0.53	0.447	− 0.84 to 1.91	
Flupentixol	0.04	0.951	− 1.13 to 1.20	
Fluphenazine	0.91	0.521	− 1.87 to 3.70	
Haloperidol	− 0.58	0.501	− 2.27 to 1.11	
Olanzapine	2.75	< 0.001	1.71 to 3.79	***$p < 0.001$
Perphenazine	1.28	0.304	− 1.16 to 3.72	
Quetiapine	1.17	0.029	0.12 to 2.21	*$p < 0.05$
Risperidone	1.22	0.041	0.05 to 2.38	*$p < 0.05$
Thioridazine	3.02	< 0.001	1.23 to 4.81	***$p < 0.001$
Trifluoperazine	0.61	0.498	− 1.15 to 2.36	

The specific antipsychotic medication variables refer to any prescribed in the first year of follow-up for each individual, e.g. 1 if a patient was prescribed the medication, and 0 if not

* p < 0.05; ** p < 0.01; *** p < 0.001

A sensitivity analysis was performed which considered all prescriptions of each antipsychotic during the 5-year follow-up, rather than just the first year. Supplementary Tables 1 and 2 show the univariate and multivariate regression results respectively, for this sensitivity analysis. No major differences were observed compared to the primary analysis which focuses on prescriptions in the first year of follow-up. With the addition of multicollinearity checks, there was no material change in the results.

In Table 6 we report the results of multivariate logistic regression modelling with the outcome of weight increase ≥ 7%. Asian/Asian British ethnicity was associated with less likelihood to put on 7% or more in weight as was female sex and younger age. The specific medication factors were similar to the multivariate linear regression with odds-ratios (OR) for individual medications

Table 6 Multivariate logistic regression predicting 7 + % BMI increase

Variable	Estimate	*p* value	Odds ratio	95% Confidence interval	Significance
Sex: male (reference: female)	− 0.24	< 0.001	0.79	0.72–0.95	***$p < 0.001$
Age	− 0.02	< 0.001	0.98	0.98–0.98	***$p < 0.001$
Ethnicity: Black	− 0.04	0.715	0.96	0.75–1.22	
Ethnicity: Asian	− 0.22	0.003	0.80	0.69–0.93	**$p < 0.01$
Ethnicity: Mixed	− 0.23	0.256	0.79	0.54–1.18	
Ethnicity: Other	0.23	0.024	1.26	1.03–1.54	*$p < 0.05$
Ever smoked: yes (reference: no)	− 0.02	0.728	0.98	0.90–1.08	
Total antipsychotics year1	0.00	< 0.001	1.00	1.00–1.00	***$p < 0.001$
Townsend score	0.00	0.831	1.00	0.99–1.01	
Amisulpride	0.18	0.095	1.20	0.97–1.48	
Aripiprazole (co− prescription)	0.33	< 0.001	1.39	1.24–1.58	***$p < 0.001$
Chlorpromazine	0.05	0.426	1.05	0.92–1.20	
Flupentixol	0.00	0.966	1.00	0.90–1.12	
Fluphenazine	0.19	0.204	1.21	0.90–1.62	
Haloperidol	0.09	0.256	1.09	0.94–1.29	
Olanzapine	0.24	< 0.001	1.27	1.15–1.40	***$p < 0.001$
Perphenazine	0.05	0.689	1.05	0.81–1.36	
Quetiapine	0.09	0.058	1.09	1.00–1.21	$p < 0.1$
Risperidone	0.12	0.039	1.13	1.01–1.25	*$p < 0.05$
Thioridazine	0.37	< 0.001	1.45	1.20–1.74	***$p < 0.001$
Trifluoperazine	0.20	0.030	1.22	1.02–1.45	*$p < 0.05$

* p < 0.05; ** p < 0.01; *** p < 0.001

ranging from quetiapine 1.09 (CI 1.00–1.21) to aripiprazole 1.39 (CI 1.24–1.58) (75% as co-prescription or 2nd/3rd line) and thioridazine 1.45 (CI 1.20–1.74).

DISCUSSION

The results of this real-world longitudinal cohort study suggest that the changes in BMI with treatment of psychosis are modulated by medication, independent of demographic factors, highlighting the importance of regular physical health checks for all people treated with antipsychotics, not just those with a diagnosis of schizophrenia, with consideration of change in medication if the medication is thought to be a contributory factor to weight gain.

A notable finding is the association of polypharmacy in the first year following diagnosis with psychosis/first prescription of an antipsychotic agent, with longer-term weight gain, both on linear regression and logistic regression analysis (vs. weight increase of 7% or more). In

a previous paper, we described increasing polypharmacy over time in relation to prescribing for people with a diagnosis of psychosis [14]. Furthermore the increase in HbA1c seen over the 5-year follow-up period looked at here, albeit in a relatively small portion of those being monitored, supports the observation that progressive dysglycaemia is a feature for some people who are treated for psychosis [1].

We found an association of aripiprazole in both univariate and multivariate analysis with weight gain, given that it is known to be relatively weight neutral on the basis of clinical trial evidence [2]. If aripiprazole is used as first-line, it may be targeted towards people who are already overweight or obese who already have a predisposition to weight gain, i.e. the choice of aripiprazole may be based on the physical health profile of the individuals.

Some 75% of aripiprazole prescriptions were as co-prescribing or following other agents, which may account for the strong association with weight gain seen here. Aripiprazole may be used as an augmentation agent in cases of treatment resistance (persisting symptoms of psychosis) [15], while aripiprazole may be added to combat weight gain when this has already occurred with a view to facilitating some weight reduction [4, 16]. Review of randomised controlled trial evidence indicates that mean weight gain with aripiprazole is low compared to other second-generation antipsychotic agents with the exception of cariprazine and lurasidone [17, 18]. Thus, what we report here may link to prescribing choices for aripiprazole.

It is of relevance that Parabiaghi et al. reported [19] that the prescription of aripiprazole did not significantly reduce the rates of metabolic syndrome over 12 months. The intention-to-treat analysis found no significant differences in the rate of metabolic syndrome between aripiprazole (37%), olanzapine (47%) and haloperidol (42%).

Both univariate and multivariate analyses showed a clear pattern for a spectrum of predisposition for weight gain across the prescribed antipsychotic agents. As in our previous study [7], greater weight gain was associated with female sex and younger age. Greater social disadvantage was associated with more weight gain in univariate analysis.

The finding of only slightly less weight gain for people taking some 'typical' = first-generation = older antipsychotics versus 'atypical' or second-generation antipsychotics in the first year after diagnosis with psychosis is in keeping with what is already known, i.e. that some of 'typical' antipsychotics such as chlorpromazine, thioridazine and flupentixol were associated with significant weight gain when they were used as mainline antipsychotic agents [20].

The period of time in which the data contributing to our analysis were collected (starting in the 1990s in relation to the first prescription) corresponds with the transition from typical to atypical antipsychotic prescribing in relation to routine prescribing practice in the United Kingdom (UK) [21]. The choice of antipsychotic agent has multiple influences [4, 18, 21, 22] with knock-on effects on physical health (23).

Strengths/Limitations

A major strength of this study is that we have linked the prescription date of a particular medication with the closest weight/BMI and with subsequent weight/BMI checks in the in the subsequent weeks following initiation of that medication as recorded in primary care.

In the analysis, we have looked at weight change by category. We accept that this results in small changes in BMI, for example 24.9–25.1 kg/m^2 associated with changes in category. However, these categories are associated with well-established future cardiometabolic risk estimates.

We do not have specific information regarding dosage variability, which is a limitation of this study. Nevertheless, we feel that our findings are relevant, given the number of people followed-up in this study.

We did not have access in a reliable way to information about clozapine prescribing which, in the UK, is only undertaken by specialist psychiatry services and therefore rarely recorded in the primary care record. This is also the case for depot antipsychotic medication. Nevertheless, we have analysed in detail the duration of antipsychotic prescribing in the first year after diagnosis/first prescription, and have been able to describe the first antipsychotic agent prescribed. This would

generally not include clozapine or depot antipsychotic medication.

Additional limitations include the lack of serial BMI information for some individuals, so the cohort was smaller than it might otherwise have been. We also had no access to reliable information on family history of obesity, which would have been a sensible variable to include in the regression models, nor did we have data on physical activity.

CONCLUSION

Our conclusion is that there are differences between agents in relation to weight gain, but that the interaction between drugs and predisposition to weight gain is complex.

The implication of this longitudinal population study, is that, while we know that, in randomised controlled trials, there is a clear hierarchy in relation to weight gain, in a real-world evaluation, the association between prescribing choice and cardiometabolic outcomes is determined by multiple other factors and is more complex, as we have outlined here.

A significant number of people (42%) remain relatively weight-stable in the 5 years after starting antipsychotic medication. Weight gain particularly occurred in people prescribed multiple antipsychotics in the first year and in younger women. Some first-generation = older antipsychotics associate with as much weight gain as second-generation antipsychotic agents. The association of aripiprazole with weight increase likely relates to clinician choice to switch to this treatment after initial weight gain or its use in augmentation (co-prescription) or as a weight-reducing medication once weight gain has occurred. Thus, what we report here likely links to appropriate prescribing choices for aripiprazole.

We have here provided further evidence in a long-term follow-up real-world study for the way that antipsychotic agents may increase the likelihood of individuals experiencing weight gain in the years after the first prescription of an antipsychotic agent.

Author Contributions. Adrian Heald conceived the study with Gavin Reynolds and led on the project. George Tilston led on data analysis and constructed all the Tables and Figures with support from Richard Williams, Lamiece Hassan and Loren Wilkins. Loren Wilkins provided clinical and scientific context as did John Warner-Levy. Joseph Firth provided essential grounding from a service user point of view and inputted to all sections. Toby Pillinger, William Deakin, Chris Daly and Damien Longson provided editorial input and clinical perspective as did Caroline Dalton from a scientific point of view. All authors reviewed the manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Data Availability. The data that support the findings of this study are available from the corresponding author in summary from upon reasonable request.

Declarations

Conflict of Interest. Adrian Heald, George Tilston, John Julian Warner-Levy, Loren Wilkins, Richard Williams, Toby Pillinger, William Deakin, Damien Longson, Lamiece Hassan, Caroline Dalton, Gavin P Reynolds and Joseph Firth have no conflict of interest.

Ethical Approval. A favourable ethical opinion was provided by Greater Manchester Care Record Board (reference: IDCR-RQ-036). Deidentified data was used, as per the Health Research Authority's Governance arrangements nd in accordance with the Declaration of Helsinki. Human Ethics and Consent to Participate declarations were not applicable.

REFERENCES

1. Heald AH, Martin JL, Payton T, Khalid L, Anderson SG, Narayanan RP, De Hert M, Yung A, Livingston M. Changes in metabolic parameters in patients with severe mental illness over a 10-year period: a retrospective cohort study. Australian New Zealand J Psychiatr. 2017;51:75–82.

2. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2013;16:1205–18.

3. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatr. 1999;156:1686–96.

4. Cooper SJ, Reynolds GP; With expert co-authors (in alphabetical order):; Barnes T, England E, Haddad PM, Heald A, Holt R, Lingford-Hughes A, Osborn D, McGowan O, Patel MX, Paton C, Reid P, Shiers D, Smith J. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. J Psychopharmacol. 2016; 30: 717–48

5. Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. JAMA Psychiatr. 2014;71:1350–63.

6. Harrison RNS, Gaughran F, Murray RM, Lee SH, Cano JP, Dempster D, Curtis CJ, Dima D, Patel H, de Jong S, Breen G. Development of multivariable models to predict change in body mass index within a clinical trial population of psychotic individuals. Sci Rep. 2017;7:14738.

7. Heald A, Daly C, Warner-Levy JJ, Williams R, Meehan C, Livingston M, Pillinger T, Hussain L, Firth J. Weight change following diagnosis with psychosis: a retrospective cohort study in Greater Manchester, UK. Ann Gen Psychiatr. 2024;23(1):1.

8. Brandl EJ, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotics. Can J Psychiatr. 2014;59:76–88.

9. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. J Clin Psychiatr. 2009;70:1041–50.

10. https://gmwearebettertogether.com/gm-care-record/: Accessed 1 Aug 2024.

11. https://www.who.int/standards/classifications/classification-of-diseases: Accessed 14 May 2025.

12. https://healthinnovationmanchester.com/thegmcarerecord/the-gm-care-record-for-secondary-uses-research: Accessed 21 Aug 2024.

13. Dolan SA, Jarman B, Bajekal M, Davies PM, Hart D. Measuring disadvantage: changes in the underprivileged area, Townsend, and Carstairs scores 1981–91. J Epidemiol Community Health. 1995;49 Suppl 2(Suppl 2):S30–3

14. Heald A, Livingston M, Yung A, De Hert MA. Prescribing in schizophrenia and psychosis: Increasing polypharmacy over time. Hum Psychopharmacol. 2017;32(2):e2579.

15. Wagner E, Kane JM, Correll CU, Howes O, Siskind D, Honer WG, Lee J, Falkai P, Schneider-Axmann T, Hasan A, TRRIP Working Group. Clozapine combination and augmentation strategies in patients with schizophrenia -recommendations from an international expert survey among the treatment response and resistance in psychosis (TRRIP) working group. Schizophr Bull. 2020;46(6):1459–70.

16. Gupta B, Chee KS, Neo LQ, Tang C, Hariram J, Tan GC, Verma S, Basu S, Appan DP, Ting CC, Abdin E, Lee J. Effect of aripiprazole as an adjunct to atypical antipsychotics on weight and metabolic profile: a 12-week open-label trial. Ther Adv Psychopharmacol. 2021. https://doi.org/10.1177/20451253211046765.

17. Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva VA. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr Dis Treat. 2017;13:2231–41.

18. Barton BB, Segger F, Fischer K, Obermeier M, Musil R. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. Expert Opin Drug Saf. 2020;19(3):295–314.

19. Parabiaghi A, Tettamanti M, D'Avanzo B, Barbato A, GiSAS study group. Metabolic syndrome and drug discontinuation in schizophrenia: a randomized trial comparing aripiprazole olanzapine and haloperidol. Acta Psychiatr Scand. 2016;133(1):63–75.

20. Matei VP, Mihailescu A, Paraschiv G, Al-Bataineh R, Purnichi T. Weight gain and antipsychotics. Data from eufest study. Acta Endocrinol (Buchar). 2016;12(2):177–84.

21. Barton BB, Segger F, Fischer K, Obermeier M, Musil R. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. Expert Opin Drug Saf. 2020;19:295–331.

22. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, Beck K, Natesan S, Efthimiou O, Cipriani A, Howes OD. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatr. 2020;7:64–77.

23. Firth J, Siddiqi N, Koyanagi A, Siskind D, Rosenbaum S, Galletly C, Allan S, Caneo C, Carney R, Carvalho AF, Chatterton ML, Correll CU, Curtis J, Gaughran F, Heald A, Hoare E, Jackson SE, Kisely S, Lovell K, Maj M, McGorry PD, Mihalopoulos C, Myles H, O'Donoghue B, Pillinger T, Sarris J, Schuch FB, Shiers D, Smith L, Solmi M, Suetani S, Taylor J, Teasdale SB, Thornicroft G, Torous J, Usherwood T, Vancampfort D, Veronese N, Ward PB, Yung AR, Killackey E, Stubbs B. The lancet psychiatry commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatr. 2019;6(8):675–712.