Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: population based cohort study

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ABSTRACT

OBJECTIVE
To evaluate the long term association between antidepressant prescribing and body weight.

DESIGN
Population based cohort study.

SETTING
General practices contributing to the UK Clinical Practice Research Datalink, 2004-14.

PARTICIPANTS
136 762 men and 157 957 women with three or more records for body mass index (BMI).

MAIN OUTCOME MEASURES
The main outcomes were antidepressant prescribing, incidence of ≥5% increase in body weight, and transition to overweight or obesity. Adjusted rate ratios were estimated from a Poisson model adjusting for age, sex, depression recording, comorbidity, coprescribing of antiepileptics or antipsychotics, deprivation, smoking, and advice on diet.

RESULTS
In the year of study entry, 17 803 (13.0%) men and 35 307 (22.4%) women with a mean age of 51.5 years (SD 16.6 years) were prescribed antidepressants. During 1 836 452 person years of follow-up, the incidence of new episodes of ≥5 weight gain in participants not prescribed antidepressants was 8.1 per 100 person years and in participants prescribed antidepressants was 11.2 per 100 person years (adjusted rate ratio 1.21, 95% confidence interval 1.19 to 1.22, P<0.001). The risk of weight gain remained increased during at least six years of follow-up. In the second year of treatment the number of participants treated with antidepressants for one year for one additional episode of ≥5% weight gain was 27 (95% confidence interval 25 to 29). In people who were initially of normal weight, the adjusted rate ratio for transition to overweight or obesity was 1.29 (1.25 to 1.34); in people who were initially overweight, the adjusted rate ratio for transition to obesity was 1.29 (1.25 to 1.33). Associations may not be causal, and residual confounding might contribute to overestimation of associations.

CONCLUSION
Widespread utilisation of antidepressants may be contributing to long term increased risk of weight gain at population level. The potential for weight gain should be considered when antidepressant treatment is indicated.

Introduction

Obesity is an increasing concern worldwide. Between 1975 and 2014 the global prevalence of obesity increased from 3.2% to 10.8% for men and from 6.4% to 14.9% for women.[1] The United States and United Kingdom have among the highest rates of obesity in the world: 69% of US adults are overweight or obese and 36% are obese,[2] and 61% of UK adults are overweight or obese, with the prevalence of obesity increasing from 15% in 1993 to 26% in 2016.[3] Severe obesity is strongly associated with socioeconomic inequality in both the US and the UK.[4] Weight gain and obesity are important public health problems, being associated with increased risk of chronic disease and mortality.[5 6] Once obesity is established, it is difficult to achieve substantial and sustained weight loss.[7]

Antidepressants are increasingly being prescribed.[8] In a primary care population 23% of 1.5 million participants were prescribed an antidepressant on at least one occasion between 1995 to 2011.[9] The number of antidepressant prescriptions issued nearly doubled over the same period, although some of the increase might be explained by extended duration of courses of treatment.[9] Obesity is associated with depression, which is particularly common in patients with severe obesity.[10 11] Antidepressant treatment may also be associated with weight gain,[12] through mechanisms that are only partially understood.[13] The current high prevalence of antidepressant use could have potentially important public health impacts through the association with body weight gain, but the nature of this association is poorly described. Although a systematic review of antidepressant use and weight gain collated evidence from 116 clinical trials and clinical cohort studies,[14] fewer than half of the studies contributed data for more than three months of follow-up and it was not reported how many studies included more than 12 months of follow-up. The review also drew attention to the heterogeneity among different antidepressant drugs, with bupropion and fluoxetine being associated with lower weight gain

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Obesity is global and antidepressant use is increasingly widespread

Short term studies suggest strong associations between antidepressant use and weight gain

No robust data exist on the long term risks of weight gain or the relative risks of weight gain for individual antidepressants

WHAT THIS STUDY ADDS

Antidepressant treatment is associated with a sustained increase in risk of weight gain over at least five years

Associations with subsequent weight gain appear to vary widely within and between antidepressant classes

Risk of weight gain should be considered when antidepressants are to be prescribed

than mirtazapine and nortriptyline.[14] Most studies have reported on weight change in depressed patients treated in clinical settings, but few population based studies have investigated the potential population impact of widespread antidepressant treatment on weight gain. One study evaluated weight change after initiation of antidepressant treatment in 5932 patients registered with the Group Health system in Washington state, USA, and found that weight gain persisted for at least two years.[15] A UK study analysed data for 268 patients treated with antidepressants from a general practice with 11 994 registered patients, and concluded that weight gain persisted during long term treatment, with, in some instances, prescriptions maintained for several years.[16] Another US study evaluated weight gain in the 12 months after initiation of antidepressant treatment in 22 610 adults treated in clinics in New England and found differences in the propensity of individual antidepressants to result in weight gain.[17]

In this study we used primary care electronic health records to evaluate non-randomised evidence on the long term association of antidepressant prescribing with weight gain. We also evaluated the associations in different subgroups and whether individual antidepressant drugs might be associated with greater risks of weight gain.

Methods

Data source

We carried out a population based cohort study in the UK Clinical Practice Research Datalink (CPRD). The CPRD is one of the world's largest databases of primary care electronic health records, with participation of about 7% of UK general practices and with ongoing collection of anonymised data from 1990. The registered active CPRD population is generally representative of the UK population in terms of age, sex, and regional distribution.[18] During 2004-14, the annual count of the CPRD registered population aged 20 years and older peaked at 3.7 million, with a total of 7.1 million participants aged 20 years or older registered at any time during the period. Data collected into CPRD comprise clinical diagnoses; records of clinical measurements, including body mass index (BMI) and body weight records taken during primary care consultations[19]; prescriptions; results of investigations; and referrals to specialist services.

Participants and cohort selection

The sample was drawn from the population of 2 006 296 patients registered with general practices participating in CPRD between 1 November 2004 and 31 October 2014 inclusive, who were aged 20 years or older and had three or more BMI measurements ever recorded.[7] To provide a sample for analysis, we stratified eligible participants according to their first recorded BMI measurement (kg/m^2): 18.5-24.9 (normal weight), 25.0-29.9 (overweight), 30.0-34.9 (obese), 35.0-35.9 (severe obesity), 40.0-44.9 (morbid obesity), and ≥45.0 (super obesity). Using the "sample" command in Stata,

we selected a random sample of up to a maximum of 30 000 participants from each category of BMI and sex, resulting in 314 477 participants, for whom data were extracted for 314 449 participants. Fewer than 30 000 women had a BMI of ≥45 and fewer than 30 000 men had a BMI of ≥40. We then extracted full CPRD records for this sample. In the analysis phase we computed additional BMI values from recorded weight and height, permitting a greater number of participants to be represented in some BMI categories. We excluded participants with no BMI records for 1 November 2004 to 31 October 2014.

Main outcome measures

Antidepressant prescriptions were the exposure of interest. We initially classified these according to section 4.3 of the *British National Formulary*,[20] including tricyclic and related antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs), and other antidepressant drugs. We then analysed individual antidepressant drugs: mirtazapine, duloxetine, sertraline, venlafaxine, citalopram, fluoxetine, escitalopram, trazodone, amitriptyline, paroxetine, nortriptyline, and dosulepin.

Body weight was the outcome of interest. We evaluated all records of body weight, height, and BMI. If a body weight value was recorded that indicated a weight increase of ≥5% compared with the previous year, we classified the calendar year as being associated with weight gain. In the analysis we retained person time not associated with recorded body weight values, incorporating the assumption that weight gain had not occurred. In a sensitivity analysis, we excluded person time with no weight records, so as to provide a "complete case" analysis.

We included several variables as known confounders or effect modifiers in the relation between antidepressant use and subsequent weight gain: sex; initial BMI category; age; smoking status; coprescribing of antiepileptics or antipsychotics; and comorbidities of diabetes, coronary heart disease, stroke, cancer, and depression. Classifications of presence or absence of cancer, coronary heart disease, and stroke were recorded clinically, or if the participant had been referred to specialist services for management of any of these conditions. We classified diabetes as being present if the condition had been recorded in the dataset clinically, the participant had been prescribed a drug for the control of insulin dependent or non-insulin dependent diabetes, or the participant had been referred to a diabetes clinic. Participants were classified as depressed in each year of follow-up if they were recorded as having depression in a given year.[21] Smoking status was taken from the clinical records, or inferred from referrals to smoking cessation clinics or from prescriptions of devices or drugs for smoking cessation.[22] We also included whether participants had received advice about weight management or diet.[23] Deprivation classification was based on fifths

of the English index of multiple deprivation (2010), which evaluates social and material deprivation across seven domains. For subgroup analyses we categorised age into 10 year groups.

Statistical analyses

The unit of analysis was person years, with each participant's record being divided into calendar years of follow-up. We classified person time for each calendar year as "exposed" if one antidepressant prescription or more was issued in that year. In univariate analyses, we estimated the incidence of ≥5% body weight gain per 100 person years for participants treated or not treated with antidepressants. The number needed to harm (NNH) was computed as the reciprocal of the risk difference. We conducted Poisson regression analyses using person years as observations. The outcome was incidence of ≥5% gain in body weight, the exposure

was antidepressant use in a year, and the log of person time was included as offset. To allow for correlation of repeated observations on participants we used robust variance estimates. We estimated adjusted rate ratios along with confidence intervals. The models included the quadratic term age^2. The final fully adjusted model adjusted for sex, initial BMI category, age, age^2, diabetes, coronary heart disease, stroke, cancer, depression, smoking status, coprescribing of antiepileptics or antipsychotics, diet advice, year, region of residence, and fifth of deprivation. For adjusted analyses, we calculated the NNH by applying the adjusted rate ratio to the incidence of weight gain in participants not treated with antidepressants, enabling estimation of the risk difference and its reciprocal the NNH. Forest plots present measures of association for subgroups and individual antidepressants and for antidepressant classes. To evaluate heterogeneity by

Table 1 | Characteristics of participants according to antidepressant prescribing. Values are numbers (row percentages) unless stated otherwise

Characteristics	No Antidepressant	Antidepressant
Total	241 609 (82.0)	53 110 (18.0)
Men	118 959 (87.0)	17 803 (13.0)
Women	122 650 (77.7)	35 307 (22.4)
Age group (years):		
20-29	29 597 (84.8)	5305 (15.2)
30-39	33 260 (80.1)	8247 (19.9)
40-49	44 955 (78.9)	12 061 (21.2)
50-59	48 131 (80.1)	11 988 (20.0)
60-69	46 218 (83.7)	9003 (16.3)
70-79	29 184 (86.2)	4691 (13.9)
≥80	10 264 (85.0)	1815 (15.0)
BMI category (kg/m^2):		
14.0-18.4	433 (79.9)	109 (20.1)
18.5-24.9	44 857 (86.1)	7266 (13.9)
25.0-29.9	50 264 (85.4)	8620 (14.6)
30.0-34.9	48 273 (82.9)	9942 (17.1)
35.0-39.9	45 358 (80.7)	10 828 (19.3)
40.0-44.9	32 393 (78.0)	9140 (22.0)
>45.0	20 031 (73.6)	7205 (26.5)
Comorbidity:		
Coronary heart disease	24 122 (81.4)	5516 (18.6)
Diabetes	42 122 (79.8)	10 682 (20.2)
Stroke	4903 (74.9)	1645 (25.1)
Cancer	12 940 (81.9)	2865 (18.1)
Depression recordings	2036 (12.4)	14 400 (87.6)
Coprescribing:		
Antiepileptic	3730 (62.8)	2211 (37.2)
Antipsychotic	2412 (38.9)	3794 (61.1)
Smoking status:		
Non-smoker	117 874 (84.2)	22 101 (15.8)
Former smoker	61 906 (83.5)	12 245 (16.5)
Current smoker	61 829 (76.7)	18 764 (23.3)
Index of multiple deprivation fifth:		
1st (least deprived)	37 639 (84.2)	7056 (15.8)
2nd	45 778 (82.9)	9451 (17.1)
3rd	50 768 (82.0)	11 138 (18.0)
4th	55 504 (81.5)	12 603 (18.5)
5th (most deprived)	51 920 (80.1)	12 862 (19.9)
Country:		
England	186 976 (82.7)	39 052 (17.3)
Northern Ireland	7945 (77.9)	2257 (22.1)
Scotland	24 389 (79.0)	6472 (21.0)
Wales	22 299 (80.7)	5329 (19.3)

Table 2 | Baseline characteristics by antidepressant prescribing and weight gain. Values are frequencies except unless stated otherwise

Characteristics	No antidepressant			Antidepressant		
	Person years	≥5% weight gain	Incidence/ 100 person years	Person years	≥5% weight gain	Incidence/ 100 person years
Total	1 454 909	118 462	8.1	381 543	42 839	11.2
Men	728 208	54 494	7.5	129 862	13 398	10.3
Women	726 701	63 968	8.8	251 680	29 441	11.7
Age group (years):						
20-29	101 633	11 163	11.0	19 792	2993	15.1
30-39	163 285	15 704	9.6	44 017	6048	13.7
40-49	252 218	22 289	8.8	79 302	9988	12.6
50-59	290 131	23 880	8.2	88 597	10 109	11.4
60-69	314 516	24 403	7.8	78 431	7957	10.1
70-79	229 011	14 976	6.5	48 182	4065	8.4
≥80	104 116	6047	5.8	23 221	1679	7.2
BMI category (kg/m^2):						
14.0-18.4	4959	101	2.0	1571	40	2.5
18.5-24.9	250 546	12 507	5.0	47 916	3269	6.8
25.0-29.9	329 117	23 307	7.1	67 697	6413	9.5
30.0-34.9	308 812	23 573	7.6	76 823	7575	9.9
35.0-39.9	264 974	22 320	8.4	76 047	8172	10.7
40.0-44.9	176 339	18 110	10.3	59 696	7731	14.0
≥45.0	120 163	18 544	15.4	51 793	9639	18.6
Comorbidity:						
Coronary heart disease	172 445	13 471	7.8	49 570	4989	10.1
Diabetes	314 672	26 708	8.5	100 183	10 704	10.7
Stroke	37 882	3041	8.0	15 115	1555	10.3
Cancer	112 346	8048	7.2	30 356	2871	9.5
Depression recorded	7215	737	10.2	66 660	7740	11.6
Coprescribing:						
Antiepileptic	24 657	2360	9.6	16 240	1993	12.3
Antipsychotic	14 676	1740	11.9	24 815	3591	14.5
Index of multiple deprivation fifth:						
1st (least deprived)	237 325	17 874	7.5	53 146	5735	10.8
2nd	280 343	22 523	8.0	69 182	7638	11.0
3rd	300 334	24 207	8.1	77 382	8503	11.0
4th	324 533	26 771	8.2	88 440	10 096	11.4
5th (most deprived)	312 373	27 087	8.7	93 392	10 867	11.6
Current smoker	326 618	27 992	8.6	117 164	13 796	11.8
Diet advice	403 929	48 006	11.9	114 533	18 538	16.0

both antidepressant class and overall we conducted random effects meta-analyses. We used Stata version 14.2[24] and R version 3.4.2[25] for statistical analyses.

Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. We received input into the report from Patient and Public Involvement representatives who commented on the relevance of the design question, the readability of the report, and the potential impact of the outcomes on their treatment.
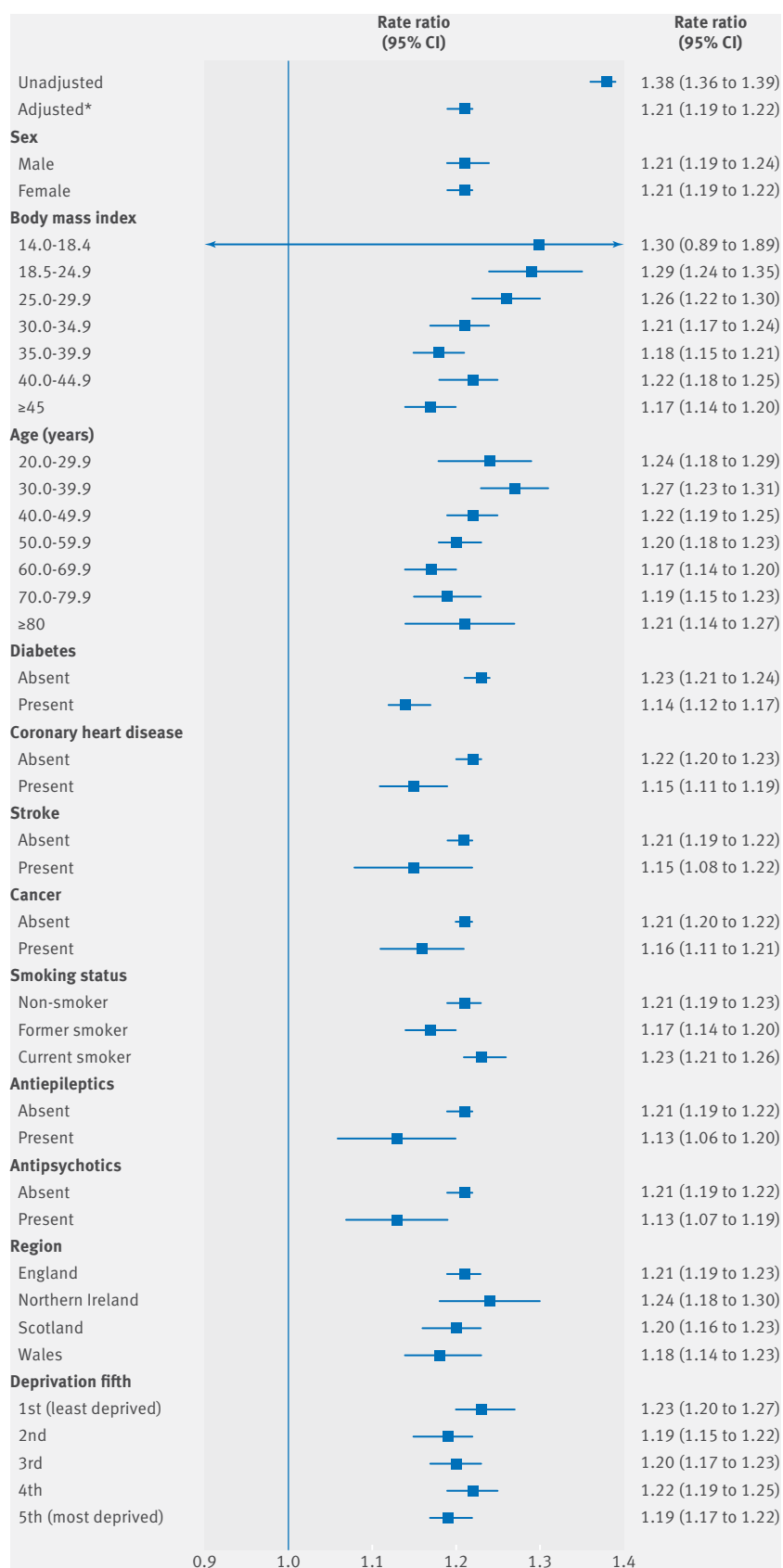
Results
The initial cohort comprised 314 449 participants. We excluded all person time for 3809 (1.2%) participants with insufficient records for analysis; 2404 (0.8%) with an ever record of bariatric surgery for treatment of obesity; 13 517 (4.3%) with no BMI values recorded between 2004 and 2014 or no record of smoking status; and person time for women who had given birth during a period defined as 280 days (40 weeks) before and after the recorded date of delivery. The final sample for analysis included 294 719 (93.7%) participants.

Table 1 presents the characteristics of participants at their entry to the study according to antidepressant prescribing status. Among 294 719 participants, 53 110 (18.0%) were prescribed antidepressants in their first calendar year of study entry. The proportion prescribed antidepressants was greater in women (22.4%) than in men (13.0%) and was highest between the ages of 30 and 59 years. Antidepressant use was strongly associated with BMI category, being lowest in those of normal body weight (13.9%) and increasing with BMI category up to 26.5% in those with a BMI of ≥45. Antidepressant use was greater in patients with comorbidity and coprescriptions, particularly with diagnoses of stroke and diabetes or coprescribing of antiepileptics or antipsychotics, than in those without. Antidepressant use was also associated with current smoking and higher deprivation category.

Table 2 presents the distribution of person time for the whole sample and for subgroups by covariates, together with the number of new cases of ≥5% weight

	Rate ratio (95% CI)	Rate ratio (95% CI)
Unadjusted		1.38 (1.36 to 1.39)
Adjusted*		1.21 (1.19 to 1.22)
Sex		
Male		1.21 (1.19 to 1.24)
Female		1.21 (1.19 to 1.22)
Body mass index		
14.0-18.4		1.30 (0.89 to 1.89)
18.5-24.9		1.29 (1.24 to 1.35)
25.0-29.9		1.26 (1.22 to 1.30)
30.0-34.9		1.21 (1.17 to 1.24)
35.0-39.9		1.18 (1.15 to 1.21)
40.0-44.9		1.22 (1.18 to 1.25)
≥45		1.17 (1.14 to 1.20)
Age (years)		
20.0-29.9		1.24 (1.18 to 1.29)
30.0-39.9		1.27 (1.23 to 1.31)
40.0-49.9		1.22 (1.19 to 1.25)
50.0-59.9		1.20 (1.18 to 1.23)
60.0-69.9		1.17 (1.14 to 1.20)
70.0-79.9		1.19 (1.15 to 1.23)
≥80		1.21 (1.14 to 1.27)
Diabetes		
Absent		1.23 (1.21 to 1.24)
Present		1.14 (1.12 to 1.17)
Coronary heart disease		
Absent		1.22 (1.20 to 1.23)
Present		1.15 (1.11 to 1.19)
Stroke		
Absent		1.21 (1.19 to 1.22)
Present		1.15 (1.08 to 1.22)
Cancer		
Absent		1.21 (1.20 to 1.22)
Present		1.16 (1.11 to 1.21)
Smoking status		
Non-smoker		1.21 (1.19 to 1.23)
Former smoker		1.17 (1.14 to 1.20)
Current smoker		1.23 (1.21 to 1.26)
Antiepileptics		
Absent		1.21 (1.19 to 1.22)
Present		1.13 (1.06 to 1.20)
Antipsychotics		
Absent		1.21 (1.19 to 1.22)
Present		1.13 (1.07 to 1.19)
Region		
England		1.21 (1.19 to 1.23)
Northern Ireland		1.24 (1.18 to 1.30)
Scotland		1.20 (1.16 to 1.23)
Wales		1.18 (1.14 to 1.23)
Deprivation fifth		
1st (least deprived)		1.23 (1.20 to 1.27)
2nd		1.19 (1.15 to 1.22)
3rd		1.20 (1.17 to 1.23)
4th		1.22 (1.19 to 1.25)
5th (most deprived)		1.19 (1.17 to 1.22)

0.9 1.0 1.1 1.2 1.3 1.4

Fig 1 | Forest plot for association of antidepressant prescribing with ≥5% weight gain for whole cohort and subgroups. *Rate ratios were adjusted for sex, body mass index category, age, age², diabetes, coronary heart disease, stroke, cancer, depression, smoking status, coprescribing of antiepileptics or antipsychotics, diet advice, year, region, and fifth of deprivation

gain. Over a 10 year period there was a total of 1 836 452 person years of follow-up. For 1 454 909 person years not associated with antidepressant use, the incidence of ≥5% weight gain was 8.1 per 100 person years, whereas for 381 543 person years associated with antidepressant use the incidence was 11.2 per 100 person years. The unadjusted rate ratio was 1.38 (95% confidence interval 1.36 to 1.39, P<0.001). Table 2 also presents data for subgroups by sex, age, initial BMI, comorbidity, coprescribing, deprivation, smoking, and diet advice. While the risk of weight gain without antidepressant use decreased with age and increased with increasing BMI category, the incidence of weight gain was higher for participants treated with antidepressants than for those not treated with antidepressants across all subgroups.

Figure 1 presents unadjusted and adjusted rate ratios for weight increase according to antidepressant use, as well as estimates for subgroups of covariates. After adjustment for covariates, the rate ratio was 1.21 (95% confidence interval 1.19 to 1.22, P<0.001) indicating that during the entire period of follow-up the risk of ≥5% weight gain was 21% higher during antidepressant treatment than at other times. The absolute risk of weight gain without antidepressant use was 8.1 per 100 person years; a rate ratio of 1.21 is consistent with an absolute risk of weight gain with antidepressant use of 9.8 per 100 person years. The risk difference of 1.7 per 100 person years is consistent with a NNH of 59 (95% confidence interval 57 to 65) patient years treated with antidepressants for one episode of weight gain, assuming the association is causal.

Supplementary table 1 shows the results of a sensitivity analysis to evaluate the effect of excluding person time in which there were no weight records. Weight records were available for 67.1% of person years in the antidepressant group and 64.2% of person years in the no antidepressant group. Consequently, omitting person time with no weight records disproportionately reduced the denominator for the no antidepressant group leading to a lower adjusted rate ratio estimate of 1.16 (1.16 to 1.17). The finding that antidepressant use is associated with weight gain is robust to varying assumptions about person time without weight records.

Adjusted rate ratios for weight gain associated with antidepressant treatment were consistent across subgroups of age, BMI, region of residence, deprivation level, coprescribing of antipsychotics or antiepileptics, and smoking status (fig 1). However, rate ratios for weight gain tended to be slightly lower for participants with diabetes mellitus or coronary heart disease compared with those without comorbidity. No similar association was seen in those participants with cancer.

Figure 2 presents adjusted rate ratios according to years of antidepressant treatment. Participants with one or more years of treatment showed an increased risk of weight gain that was maintained during six years of follow-up. Adjusted rate ratios were 1.46 (1.43 to 1.49) in the second year of follow-up and 1.48 (1.45
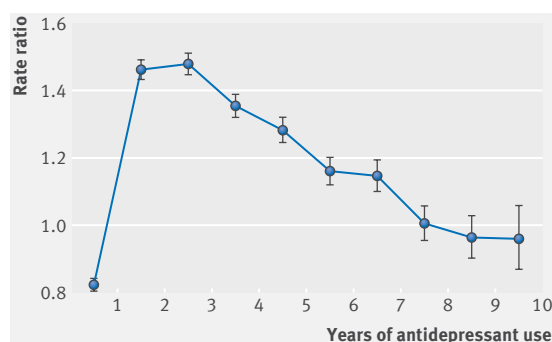
Fig 2 | Adjusted rate ratios for ≥5% weight gain by number of years of antidepressant treatment. Rate ratios were adjusted for sex, body mass index category, age, age², diabetes, coronary heart disease, stroke, cancer, depression, smoking status, coprescribing of antiepileptics or antipsychotics, diet advice, year, region, and fifth of deprivation. Whiskers represent 95% confidence intervals

to 1.51) in the third year. Adjusted rate ratios then declined; from year 7 onwards there was no evidence for an increased risk of weight gain. During the second year of treatment, the risk of one additional episode of ≥5% weight gain may be expected for every 27 (25 to 29) patients treated.

Table 3 shows the association of antidepressant treatment with risk of increase in BMI category. In people who were initially of normal weight (BMI 18.5-24.9), the adjusted rate ratio for transition to overweight or obesity was 1.29 (1.25 to 1.34); in people who were initially overweight (BMI 25.0-29.9), the adjusted rate ratio for transition to obesity was 1.29 (1.25 to 1.33). These secondary analyses confirm that antidepressant use might be associated with clinically important weight gain when evaluated using different categories for weight increase.

A random effects meta-analysis was conducted (fig 3) to evaluate heterogeneity within and between antidepressant classes. SSRI and TCA classes were heterogeneous (I^2=92.8%, P<0.001 and I^2=75.0%, P=0.018, respectively). Weak evidence of heterogeneity was found for the SNRI class (venlafaxine and duloxetine) (I^2=64.3%, P=0.094). Given the heterogeneity within classes of antidepressants, the relation between individual antidepressants and

weight gain was explored (figs 3 and 4). Mirtazapine appeared to be associated with the greatest adjusted rate ratio of weight gain (1.50, 95% confidence interval 1.45 to 1.56). Figure 4 shows the relative frequencies of prescribing compared with the adjusted rate ratio for individual antidepressants—in order of frequency of use: amitriptyline (25.9%), citalopram (19.8%), fluoxetine (16.0%), sertraline (9.0%), venlafaxine (6.4%), paroxetine (5.5%), mirtazapine (4.5%), dosulepin (3.9%), escitalopram (3.7%), trazodone (1.9%), duloxetine (2.1%), and nortriptyline (1.1%).

Discussion

This population based cohort study reports data for participants registered in primary care who had three or more measurements for body mass index (BMI), with sampling stratified by BMI category. Analysis reveals a high prevalence of exposure to antidepressant drugs. Considering the entire period of follow-up (10 years), participants who were prescribed an antidepressant had an increased risk of ≥5% weight gain compared with those who had never been prescribed an antidepressant, after allowing for differences in case mix. This association was consistently observed across a wide range of population subgroups. Participants of normal weight showed an increased risk of transitioning to overweight or obesity, and overweight participants were more likely to become obese if they were treated with an antidepressant. The risk of weight gain was substantially increased during the second and third years of treatment. Less than 12 months' use of antidepressants did not appear to be associated with weight gain, but this might be an artefact from incomplete data recording. Pharmacological classes of antidepressants displayed intraclass heterogeneity for later risk of weight gain. Mirtazapine was associated with the highest incidence rate ratio of weight gain, although the drug was relatively infrequently prescribed.

### Strengths and limitations of this study

This study used data from a large nationally representative primary care database in the United Kingdom. Use of electronic health records enabled us to comprehensively ascertain whether participants had received prescriptions for antidepressants. We used clinical records of weight, height, and BMI. These

Table 3 | Association of antidepressant prescription with increase in body mass index (BMI) category. Values are frequencies unless stated otherwise

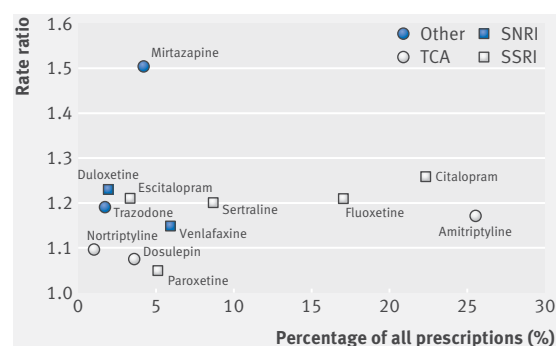| Variables	Initial BMI category (kg/m2)*				
	18.5-24.9	25.0-29.9	30.0-34.9	35.0.39.9	40.0-44.9
No antidepressant:					
Person years	264728	309434	297714	275752	192405
Increase in BMI category	14940	18440	20205	21824	16337
Antidepressant:					
Person years	50763	64152	73014	78907	66040
Increase in BMI category	3751	5265	6562	8028	7095
Unadjusted rate ratio (95% CI)	1.31 (1.26 to 1.36)	1.38 (1.34 to 1.42)	1.32 (1.29 to 1.36)	1.29 (1.25 to 1.32)	1.27 (1.23 to 1.30)
Adjusted rate ratio (95% CI)†	1.29 (1.25 to 1.34)	1.29 (1.25 to 1.33)	1.23 (1.19 to 1.26)	1.22 (1.19 to 1.25)	1.21 (1.17 to 1.24)

*163 542 person years were accounted for by initial BMI categories of <18.5 or ≥45.0.
†Adjusted for age, sex, depression recording, comorbidity, coprescribing of antiepileptics or antipsychotics, deprivation, smoking, and advice on diet.
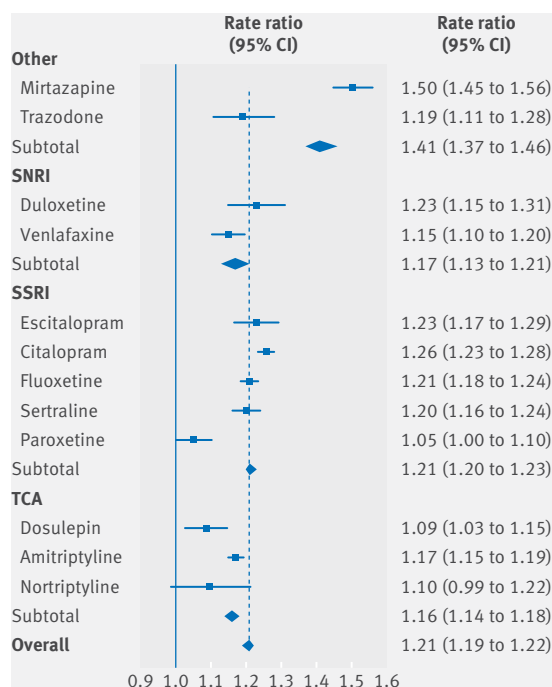
Fig 3 | Adjusted rate ratios (95% confidence intervals) for ≥5% weight gain by antidepressant type. Rate ratios were adjusted for sex, body mass index category, age, age^2, diabetes, coronary heart disease, stroke, cancer, depression, smoking status, coprescribing of antiepileptics or antipsychotics, diet advice, year, region, and fifth of deprivation. SNRI=serotonin-noradrenaline (norepinephrine) reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic and related antidepressants

Fig 4 | Scatter plot of adjusted rate ratios for ≥5% weight gain by number of prescriptions. Rate ratios were adjusted for sex, body mass index category, age, age^2, diabetes, coronary heart disease, stroke, cancer, depression, smoking status, coprescribing of antiepileptics or antipsychotics, diet advice, year, region, and fifth of deprivation. SNRI=serotonin-noradrenaline (norepinephrine) reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors; TCA=tricyclic and related antidepressants

measures are not always systematically recorded in primary care.[19] Infrequent recording of BMI could lead to underestimation of associations if weight gain occurred but no measurement was taken; conversely, confounding of measurement by indication might occur if family doctors are more likely to record body weight when there has been weight gain. The direction of any possible bias from incomplete recording of body weight is difficult to anticipate. We initially selected participants who had at least three BMI measurements recorded, leading to over-representation of those with comorbidity; participants with no comorbidities being less likely to have BMI recorded than those with concurrent illnesses. Patients with comorbidities such as diabetes mellitus or coronary heart disease may be more likely to be enrolled in self management interventions that focus on diet, exercise, and weight control and this could modify estimated associations. Also, in this non-randomised study, residual confounding might lead to bias. Confounding by indication might occur if the propensity to be prescribed antidepressants is also associated with the propensity to gain weight. The present data show that 94% of treated patients had a diagnosis of depression. However, antidepressant drugs can be prescribed for several disorders, and depression might not always have been the sole indication for prescription. We cannot exclude the possibility that depressive symptoms rather than antidepressant treatment were the reason for changes in body weight. Analyses were based on antidepressant prescription, but non-adherence might be common and could diminish estimated associations.[26] However, clinical trials in depressed patients show that antidepressant treatment is associated with weight gain.[14] The strong temporal association between initiation of antidepressant treatment and weight gain also suggests a causal association. This dataset reflects prescribing habits over a decade. During this time a switch occurred from older tricyclic antidepressants to selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors. Older generation drugs, including monoamine oxidase inhibitors and tricyclic antidepressants, are generally more associated with weight gain than are the newer SSRIs, but the older generation drugs are only infrequently prescribed. Associations with weight gain might depend on drug dose, but it was not possible to reconstruct dosage information for this study.

Comparison with other studies

A systematic review analysed short term studies and estimated weight increases over eight months' follow-up.[14] Another study evaluated weight gain up to two years using electronic health records,[15] with estimates consistent with a 2.1 kg weight gain with fluoxetine treatment and about a 4.8 kg increase with setraline. These figures suggest that increases of ≥5% body weight are plausible. Our study adds to previous data by providing longer follow-up (up to 10 years) of antidepressant treatment, showing that the risk of weight gain is increased for at least the first five years of treatment. Our study also adds a comparison with a general population sample that was not treated with antidepressant drugs, showing an association between

antidepressant use and transitions to overweight and obesity. Weight gain is a well recognised side effect of antipsychotic treatment,[27] but prescribing guidelines generally devote less attention to weight management in the context of antidepressant treatment.[28] Obesity and depression are common, often coexist, and are associated with physical comorbidity and worse health outcomes.[5] Researchers have observed that the negative perceptions associated with either a depression diagnosis or an obesity diagnosis may be potentiated when the conditions overlap.[29] This makes weight management and obesity prevention particularly important in this population. The relation between depression symptoms and health behaviours that might contribute to weight gain is also a relevant concern.[30]

From a population perspective, these results suggest that the widespread use of antidepressants might be an important factor contributing to increasing body weight. These results should be set in the context of increasing BMI in the general population. Data from the health survey for England show that between 2004 and 2014 the prevalence of obesity in adults increased from 23% to 26%, and mean BMI increased from 26.9 to 27.2.[3] From a clinical perspective, these observations reinforce the need for active body weight management to accompany antidepressant treatment,[31] although this might often be met with limited success. The potential for weight gain may also be a consideration in the selection of individual antidepressant drugs.

Conclusions and policy implications

Initiation of antidepressant drugs shows a strong temporal association with weight gain, which is greatest during the second and third years of treatment. During the second year of treatment, the risk of ≥5% weight gain is 46.3% higher than in a general population comparison group. These associations are consistent across a wide range of clinical, social, and demographic characteristics. The increasingly widespread use of antidepressants is of concern in the context of the increasing prevalence of obesity.

Rates of antidepressant use and obesity are rising simultaneously in the UK. The results of this study show that the two phenomena are closely linked and that the greatest risk of a ≥5% weight gain occurs during the second and third years of treatment and remains elevated for up to six years after initiation of treatment (see supplementary infographic).

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Supplementary information: appendix table 1
Infographic: summary of findings in graphic format