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SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up study

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Abstract

Objective To examine the association between antidepressant use and weight gain, as well as the interaction with lifestyle factors.

Design Longitudinal study

Setting and participants We used data from 2334 adults from two stages (4.4 years apart) of the North West Adelaide Health Study, including validated diet and lifestyle questionnaires, measured body weight, and linked pharmaceutical data.

Main outcome measures Body weight change

Results 188 (8.1%) participants had a mean annual number of 1-2 antidepressant prescriptions, and 212 (9.1%) had over 2 prescriptions. The mean annual weight gain was 0.12, 0.18 and 0.28 kg in non-users, low (1-2 prescriptions/year) and high (>2 prescriptions/year) antidepressant users, respectively. In multivariable regression models, antidepressant use was positively associated with weight gain: high antidepressant users gained an extra 0.22 (95%CI 0.00-0.44) kg per year. This association was caused by selective serotonin reuptake inhibitor (SSRI) use. High SSRI users gained 0.48 (95%CI 0.20-0.76) kg more than non-users. There was no association between tricyclics or other antidepressant use and weight gain. The association between SSRI use and weight gain was mainly seen among those with high intake of Western diet, sedentary activity, and smoking.

Conclusions Exposure to SSRIs potentiates weight gain, exceeding what occurs in the context of Western diet, sedentarism, and smoking without antidepressant exposure.

Strengths and limitations of this study

- Measurement of body weight by health workers at both time points with a mean of 4.4 years of follow-up;
- Ability to adjust for detailed lifestyle factors and chronic conditions.
- The total number of antidepressant users was relatively small, which limited our power to conduct detailed subgroup analyses.
- Dietary intake was only assessed at follow-up; therefore, we were unable to adjust for dietary change during follow-up.

Keywords Antidepressant, cohort study, body weight, dietary patterns, smoking

1. Introduction

Obesity is a major global health problem almost entirely caused by excess dietary intake and reduced energy expenditure. It is estimated that up to 205 million men and 297 million women over the age of 20 years worldwide are obese [1]. In Australia, the prevalence of obesity class I (BMI 30-34.9 kg/m^2) and obesity class II or III (BMI ≥35 kg/m^2) has respectively doubled and almost tripled since 1980 [2]. Currently it is estimated that 28.3% of Australian adults are obese [3]. One of the most important health consequences of high and rising trends in global obesity prevalence has been the increased risk of developing depression [4]. Indeed, data from the Global Burden of Disease (GBD) study suggest that major depression disorder was the second leading cause accounting for 8.2% of global years lived with disability (YLDs) in 2010 [5].

Several population based cohort studies have consistently shown a positive relationship between antidepressant use and weight gain in countries such as the USA [6-8] Canada [9] and Australia [10]. This is valuable information for public health policy makers and researchers given that the prevalence of antidepressant use is high in Australia and the USA (5-12%) [7 11], and frequently used by people without depressive or anxiety disorders [12].

The underlying cause of weight gain due to long-term antidepressant use is poorly understood [13]. In rodents, data from our lab showed that the combination of chronic stress and short-term antidepressant treatment, followed by high-fat diet results in long-term weight gain that is greater than that caused by stress and high-fat diet, without antidepressant exposure [14]. In our animal paradigm, antidepressant exposure potentiated weight gain caused by an obesogenic diet. Based on those findings and the high rates of antidepressant use, we have hypothesised that increased antidepressant exposure might be a contributory factor to the obesity pandemic [13]. Data from a recent

cross-sectional population-based study showed that antidepressant use was associated with increased energy intake [15]. Poor diet, sedentary lifestyle, obesity, and depression often cluster together; however, association studies between antidepressant use and obesity have been mostly based on registry data or short-term clinical trials, which limited their capacity to understand interactions [6-10]. Therefore, it is unknown whether interactions between antidepressant use and lifestyle factors influence human obesity on a long-term, ongoing basis.

This study was designed to specifically examine the association between antidepressant use and weight gain, as well as the interaction with diet and other lifestyle factors in adults participating in large-population based prospective cohort study.

2. Methods

2.1 Data source and study participants

This study was approved by the Queen Elizabeth Hospital Human Research Committee and, where appropriate, by the Aboriginal Health Research Ethics Committee, Adelaide, South Australia, Australia. The North West Adelaide Health Study (NWAHS) is an ongoing community based cohort study among adults living in the North West region of Adelaide, South Australia. The detailed description of this cohort has been published elsewhere [16]. The current study analysed data from both stage 2 (2004-2006) and stage 3 (2008-2010) data collections. A total of 2334 participants had information on body weight at both time points.

2.2 Outcome variable-change in body weight

At both stages 2 and 3, height and body weight were measured in light clothing and shoeless by trained clinic staff, to the nearest 0.1 cm and 0.1 kg, respectively. Overweight and obesity were defined respectively as 25 $kg/m^2 \geq$ BMI <30 kg/m^2 and BMI ≥ 30 kg/m^2.

2.3 Exposure variable- prospective antidepressant use

Information on medication use according to the Anatomical Therapeutic Chemical (ATC) Classification was obtained from Medicare Australia (Pharmaceutical Benefits Scheme (PBS)) by confidential unit record linkage for the study period. Antidepressants (ATC code N06A) were categorized into three groups: tricyclic antidepressants (TCAs) (ATC code N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB) and other antidepressants (ATC code N06AF, N06AG,

and N06AX). For each participant the mean annual number of antidepressant prescriptions, calculated by adding the number of prescriptions and dividing it by the follow-up duration between stages 2 and 3, was categorized into three groups: non-user, low user (1-2 prescriptions/year), or high user (>2 prescriptions/year).

2.4 Covariates

2.4.1 Baseline and follow-up covariates: The Centre for Epidemiologic Studies Depression Scale (CES-D) was used to measure depressive symptoms. CES-D scores were categorised as no depression (<16), mild depression (16-26) or moderate to severe depression (>26) [17]. Smoking behaviour was determined by self-report and coded as non-smoker, ex-smoker or current smoker. Self-reported income was recoded into three levels (<$20,000, $20,000-$60,000 or >$60,000 AUD). Physical activity questions from the Australian National Health Surveys were used to classify participants as sedentary, or having low, moderate or high levels of physical activity [18].

2.4.2 Follow-up only covariates Dietary intake during the previous 12 months was assessed by the Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies (DQES-V3.1 (FFQ)). The FFQ was previously validated in an Australian population, and is widely used in epidemiological studies. In the analysis the daily intake of 128 food items were collapsed into 41 food groups as previously described [19]. Dietary patterns were identified by factor analysis using the principal component method. Varimax rotation was used to assist the interpretability of the factor solution. Based on the Eigen value (>1), scree plot and interpretability, two dietary patterns were constructed. The prudent pattern was characterised by high loadings of fruit and

vegetable (Supplemental **Figure S1**) and the Western pattern had high intake of processed meat, snacks, and fast food.

2.5 Statistical analyses

Chi square test and ANOVA were used respectively to compare differences between categorical variables, and in continuous variables between groups. The linear regression model was used to assess the longitudinal association between antidepressant use and annual weight change. Three models were employed: model 1 was adjusted for age and gender, model 2 was further adjusted for income, smoking, physical activity, and follow-up duration, and model 3 was further adjusted for depression status at baseline and follow-up, and dietary patterns (continuous). Multiplicative interaction between antidepressant use, lifestyle factors (dietary patterns, smoking and physical activity) and age was conducted by inputting the product terms of these variables and antidepressant use in the regression models. The interaction between antidepressant use and age was graphically represented using the *marginsplot* command in STATA 14 (Stata Corporation, College Station, TX, USA).

Sensitivity analyses were conducted using mixed linear modelling to assess the association between antidepressant use and weight status adjusted for depression and smoking status as time-varying variables, while considering antidepressant use, physical activity, dietary patterns, and gender as time-invariant variables. We also assessed the association (incident rate ratio) between antidepressant use and five percent weight gain over five years using Poisson regression with robust variance.

All analyses were performed using STATA 14 (Stata Corporation), and statistical significance was set at $P<0.05$ (two sided).

3. Results

The mean age of the sample was 54.1 (SD 14.1) years (**Table 1**). The mean duration of follow-up was 4.4 (SD 0.4) years. Women had a higher prevalence of depression and a higher mean level of antidepressant use than men. In the sample, 188 (8.1%) and 212 (9.1%) participants had a mean annual number of 1-2, and more than 2 antidepressant prescriptions, respectively. Out of 400 antidepressant users, 225 (56.3%) were SSRI users, and in high SSRI users the mean annual number of SSRI prescriptions was 5.9 (SD 3.1) (Supplemental **Table S1**).

The mean annual weight gain was 0.12, 0.18 and 0.28 kg in non-users, low and high antidepressant users, respectively. Compared with non-users, high antidepressant users had higher energy intake (9160 vs 8628 kJ/day) and higher Western dietary pattern scores after adjusting for age and gender (Supplemental **Table S2**).

In multivariable regression models adjusted for age, gender, income, smoking, physical activity, follow-up duration and dietary patterns, antidepressant use was positively associated with weight gain. High users gained 0.22 (95%CI 0.00-0.44) kg per year when compared with non-users, and this association was related to SSRI use (**Table 2**). In the fully adjusted model, high SSRI users gained 0.48 (95%CI 0.20-0.76) kg more than non-users. No association was found between TCA and other antidepressant use and weight gain.

In relation to annual weight gain, significant interactions were found between SSRI use and three lifestyle factors: Western dietary pattern, smoking, and sedentary activity (**Table 3**). The association between SSRI use and weight gain was mainly seen among those with unhealthy lifestyle, and a strong dose response relationship between SSRI use and weight gain was observed among those with high intake of

Western diet: the regression coefficients were 0.00, 0.46 (95%CI 0.05-0.88), and 0.84 (95%CI 0.43-1.24) kg for non-users, low users and high users, respectively. This association was not seen in those with low intake of Western diet. There was a significant interaction between antidepressant use and age in relation to weight gain (Supplemental **Figure S2**). The positive association between high antidepressant use and weight gain was mainly seen among those aged below 50 years. Among those with sedentary lifestyles, high SSRI use was associated with 1.01 (95%CI 0.52-1.50) kg higher weight gain per year than non-users. A consistent positive association between SSRI use and weight gain was only observed among smokers: low and high SSRI use was respectively associated with 0.44 (95%CI 0.05-0.84) and 0.66 (95%CI 0.23-1.10) kg higher weight gain per year than non-users.

In the multivariable mixed regression model adjusted for time-varying depression status, smoking, age, and income as well as time-invariant dietary patterns, physical activity, and gender, antidepressant use was associated with weight status (Supplemental **Table S3**). Compared with non-use, high use was associated with an extra body weight of 4.40 kg (any antidepressant, $P= 0.002$), 4.20 kg (SSRI, $P= 0.007$) and 7.14 kg (other antidepressant, $P< 0.001$), respectively. TCA use was not associated with body weight. No interaction between antidepressant use and gender was found.

Overall, 27.2% of the participants had weight gain above 5% over five years. In fully adjusted model, the incident rate ratio (IRR) for 5% weight gain were 1.00, 1.09 (95%CI 0.83-1.44) and 1.37 (95%CI 1.10-1.70) for non-users, low users and high users of antidepressant, respectively. A dose response association between SSRI use and 5% weight gain was found in fully adjusted model: IRRs were 1.00, 1.37 (95%CI

1.03-1.81) and 1.43 (95%CI 1.10-1.86) (p trend <0.001) for non-users, low users and high users of SSRI, respectively.

4. **Discussion**

In this prospective study, we found that antidepressant use was positively associated with weight gain, which was influenced by significant interactions between SSRI use, age and unhealthy lifestyle factors, including western dietary pattern, sedentary activity and smoking.

The mean annual weight gain among antidepressant users during this 4.4-year study was around 0.2 kg, which is similar to those reported in the literature for shorter studies [6 7 9 10 20]. However, in those previous population studies, lifestyle factors were either lacking or treated as confounding factors [6 7 9 10]. None of those studies had adjusted for dietary intake, an important factor for weight gain.

Only one previous study assessed differences in energy intake and physical activity between antidepressant users and non-users, employing data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES). It showed that after adjusting for potential confounding factors, antidepressant users had an extra 215 kcal/day of energy intake and were 77% more likely to use a computer for ≥2 hour/day than non-users [15]. The authors hypothesized that increased energy intake and sedentary activity could contribute to weight gain associated with antidepressant use. In the present study we also found a significant difference in energy intake between high antidepressant users and non-users. After adjusting for age and gender, high antidepressant users had a higher energy intake than non-users (9160 *vs* 8628 kJ/day). Furthermore, high antidepressant users had higher Western dietary pattern scores than non-users (0.14 *vs* -0.03). To the best of our knowledge, this is the first study that

systematically tested the interactions between antidepressant use and modifiable lifestyle factors. A significant positive dose response association between antidepressant use and weight gain was found in individuals with high intake but not in those with low intake of Western diet.

The interaction between antidepressant use and smoking in relation to weight gain was consistent with that reported by Arterburn *et al.* who found that bupropion-treated smokers gained an extra 14.2 lbs compared to fluoxetine-treated non-smokers during a two-year follow-up study [8]. We observed an intriguing interaction between antidepressant use and age in relation to weight gain, which may be related to the fact that younger people are more likely to eat a Western diet. In our sample, age was inversely associated with Western dietary pattern scores (data not shown).

The lack of association between TCA use and weight gain was also reported in the Netherlands Study of Depression and Anxiety as well as the Rotterdam Study [20 21]. However, previous studies have reported an association between TCA use and weight gain [6 13]. Our null association between TCA use and weight gain may be due to the fact that age was positively associated with TCA use ($P<0.001$). The mean age was 53.6, 62.2 and 65.6 years among non-users, low and high users of TCA (data not shown). However, there was no significant age difference between SSRIs users and non-users.

The strengths of this study include: 1) measurement of body weight by health workers at both time points with a mean of 4.4 years of follow-up; 2) ability to adjust for detailed lifestyle factors and chronic conditions. The main limitation of the study compared to other registry-based studies was that the total number of antidepressant users was relatively small, which limited our power to conduct detailed subgroup

analyses. The effect size of the antidepressant use on weight gain may be under estimated due to the fact that some of the low cost antidepressants (below co-payment level) were not recorded by the PBS system before 2012. Furthermore, dietary intake was only assessed at follow-up; therefore, we were unable to adjust for dietary change during follow-up.

Antidepressants are widely used, representing the most prescribed drug class in the USA [22]; in Australia 11.6% of the country's population is on antidepressants [23]. Antidepressant-related weight gain is an outcome of public health relevance, as it may contribute to increased rates of obesity. Here we provide evidence that antidepressant use potentiates weight gain, especially among those with unhealthy lifestyles, resulting in body weight that is higher than that associated solely with those same lifestyle factors, in the absence of antidepressants. As a matter of public health relevance, SSRI use ought to be clinically recognized as a risk factor for obesity. Therefore, SSRI use should be accompanied by pro-active efforts to avoid weight gain. We suggest that reducing Western diet consumption, increasing physical activity and smoking cessation may mitigate antidepressant-related weight gain.

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Conflicts of interest: We declare that we have no conflicts of interest.

Author contributions: ZS contributed to the conception, analysis, and interpretation of data; drafting of the report; and have given approval of the final version for publication. EA, AWT, TKG, KP, SA, MLW and JL contributed to analysis and

interpretation of the data, commented on the report, revising the manuscript and approving the final version for publication.

Availability of data and material

Data from the North West Adelaide Healthy Study (NWAHS) were accessed from a third party. The authors confirm that for approved reasons, some access restrictions apply to the data underlying the findings. To gain access to the data for this manuscript, ethics approval was sought and granted. Enquiries regarding requests for the NWAHS data can be directed to Prof Robert Adams, Principal Investigator (Clinical) (<robert.adams@adelaide.edu.au>).

Figure legends

Supporting Information **Figures**

Figure S1: Factor loadings of dietary patterns

Figure S2: Interaction between any antidepressant use and age in relation to weight gain.

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Table 1 Sample characteristic by sex *

	Male	Female	Total	*P* value
n (%)	1095 (46.9)	1239 (53.1)	2334	
Age (years)	54.0 (14.4)	54.3 (13.8)	54.1 (14.1)	0.648
Baseline weight (kg)	87.2 (15.3)	73.5 (16.1)	79.9 (17.2)	<0.001
Follow-up weight (kg)	87.9 (16.0)	74.0 (16.2)	80.5 (17.5)	<0.001
Annual weight gain (kg)	0.17 (1.35)	0.12 (1.46)	0.14 (1.41)	0.449
Baseline BMI status				
Normal	21.9	34.5	28.6	<0.001
Overweight	48.9	34.2	41.1	
Obese	29.2	31.2	30.3	
Baseline income ($)				
<20000	196 (17.9)	332 (26.9)	528	
20000-60000	529 (48.4)	543 (44.0)	1072	
>60000	338 (31.0)	308 (24.9)	646	
Not stated	29 (2.7)	52 (4.2)	81	<0.001
Baseline smoking status				
Non smoker	444 (40.7)	642 (52.0)	1086	
Current or ex-smoker	647 (59.3)	593 (48.0)	1240	<0.001
Baseline physical activity				
Sedentary	252 (25.9)	345 (30.4)	597	
Low exercise level	323 (33.2)	448 (39.5)	771	
Moderate exercise level	291 (29.9)	285 (25.1)	576	
High exercise level	106 (10.9)	56 (4.9)	162	<0.001
Depression (baseline)				
No depressive symptoms	995 (91.3)	1043 (85.4)	2038	
Mild depression	61 (5.6)	122 (10.0)	183	
Moderate to severe depression	34 (3.1)	56 (4.6)	90	<0.001
Depression (follow-up)				
No depressive symptoms	907 (85.6)	958 (79.6)	1865	
Mild depression	101 (9.5)	151 (12.5)	252	
Moderate to severe depression	52 (4.9)	95 (7.9)	147	<0.001
Any antidepressant †	0.4 (1.7)	0.9 (2.5)	0.7 (2.2)	<0.001

TCAs †	0.1 (0.6)	0.2 (1.3)	0.1 (1.0)	<0.001
SSRIs †	0.2 (1.3)	0.4 (1.6)	0.3 (1.4)	0.019
Other antidepressant †	0.1 (0.8)	0.3 (1.5)	0.2 (1.2)	<0.001

* values are n (%) or mean (SD)

† Annual number of prescriptions

Table 2 Association (β 95%CI) between antidepressant use and annual weight gain

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
Any antidepressant				
n	1934	188	212	
Baseline weight (kg), mean (SD)	80.0 (17.0)	77.1 (16.5)	81.3 (19.1)	
Follow-up weight (kg), mean (SD)	80.6 (17.3)	78.0 (17.2)	82.5 (19.6)	
Annual weight change (kg), mean (SD)	0.12(1.32)	0.18(1.54)	0.28(1.99)	
Model 1 *	Ref	0.15(-0.06-0.36)	0.22(0.02-0.42)	0.022
Model 2 †	Ref	0.18(-0.04-0.40)	0.25(0.04-0.46)	0.009
Model 3 ‡	Ref	0.11(-0.11-0.34)	0.22(0.00-0.44)	0.044
SSRIs				
n	2109	114	111	
Baseline weight (kg), mean (SD)	79.8 (17.0)	79.7 (18.2)	82.2 (19.1)	
Follow-up weight (kg), mean (SD)	80.3 (17.3)	81.2 (18.0)	84.9 (21.2)	
Annual weight change (kg), mean (SD)	0.11(1.33)	0.38(2.11)	0.61(1.89)	
Model 1 *	Ref	**0.30(0.04-0.57)**	**0.53(0.27-0.80)**	**<0.001**
Model 2 †	Ref	**0.30(0.03-0.58)**	**0.58(0.30-0.85)**	**<0.001**
Model 3 ‡	Ref	**0.30(0.01-0.58)**	**0.48(0.20-0.76)**	**<0.001**
TCAs				
n	2212	79	43	
Baseline weight (kg), mean (SD)	80.1 (17.2)	76.3 (17.8)	77.3 (15.9)	
Follow-up weight (kg), mean (SD)	80.8 (17.5)	75.5 (17.3)	77.3 (16.4)	
Annual weight change	0.16(1.40)	-0.13(1.61)	-0.01(1.32)	

(kg), mean (SD)				
Model 1 *	Ref	-0.12(-0.44-0.19)	0.06(-0.36-0.49)	0.717
Model 2 †	Ref	-0.11(-0.44-0.22)	0.05(-0.39-0.50)	0.704
Model 3 ‡	Ref	0.02(-0.31-0.36)	0.03(-0.46-0.52)	0.908
Other antidepressants				
n	2210	57	67	
Baseline weight (kg), mean (SD)	79.8 (17.0)	80.0 (18.7)	82.9 (20.5)	
Follow-up weight (kg), mean (SD)	80.4 (17.4)	81.3 (17.6)	83.4 (21.2)	
Annual weight change (kg), mean (SD)	0.14(1.37)	0.35(1.88)	0.12(2.08)	
Model 1 *	Ref	0.23(-0.13-0.60)	-0.04(-0.38-0.29)	0.844
Model 2 †	Ref	0.32(-0.05-0.70)	-0.01(-0.36-0.35)	0.505
Model 3 ‡	Ref	0.42(0.03-0.80)	-0.19(-0.56-0.19)	0.926

* Model 1 adjusted for age and gender.

† Model 2 further adjusted for baseline income, smoking, physical activity, follow-up duration.

‡ Model 3 further adjusted for depression status at baseline and follow-up, dietary patterns (continuous).

Table 3 Interaction between SSRI use and lifestyle factors in relation to annual weight gain *

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* for interaction
Western dietary pattern				0.026
Low intake	0.00	0.11(-0.29-0.51)	0.14(-0.26-0.54)	
High intake	0.00	**0.46(0.05-0.88)** †	**0.84(0.43-1.24)**	
Prudent dietary pattern				0.635
Low intake	0.00	0.35(-0.07-0.78)	0.38(-0.02-0.78)	
High intake	0.00	0.23(-0.16-0.63)	**0.61(0.20-1.02)**	
Physical activity				0.039
Sedentary	0.00	0.15(-0.34-0.63)	**1.01(0.52-1.50)**	
Low	0.00	0.34(-0.13-0.82)	0.23(-0.27-0.72)	
Moderate/high	0.00	0.33(-0.27-0.94)	0.06(-0.49-0.61)	
Smoking				0.002
Non-smoker	0.00	-0.28(-0.73-0.16)	0.35(-0.03-0.72)	
Smoker	0.00	**0.44(0.05-0.84)**	**0.66(0.23-1.10)**	

* Models adjusted for age, gender, income, physical activity, smoking, depression status at baseline and follow-up. Stratifying variables were not adjusted in the corresponding models. Values represent regression coefficients (95%CI).

† Bold values represent p<0.05.

Supplemental materials

Table S1 Sample characteristic by SSRIs use *

	Non-user	Low user	High user	*P* value
n (%)	2109 (90.4)	114 (4.9)	111 (4.8)	
Age (years)	54.0 (14.3)	55.0 (11.6)	55.4 (12.6)	0.4818
Baseline weight (kg)	79.8 (17.0)	79.7 (18.2)	82.2 (19.1)	0.3717
Follow-up weight (kg)	80.3 (17.3)	81.2 (18.0)	84.9 (21.2)	0.0245
Annual weight gain (kg)	0.1 (1.3)	0.4 (2.1)	0.6 (1.9)	0.0002
Income ($)				
<20000	451 (21.5)	36 (31.6)	41 (36.9)	
20000-60000	981 (46.7)	45 (39.5)	46 (41.4)	
>60000	599 (28.5)	27 (23.7)	20 (18.0)	
Not stated	71 (3.4)	6 (5.3)	4 (3.6)	0.0008
Smoking status				
Non smoker	994 (47.3)	38 (33.3)	54 (48.6)	
Current or ex-smoker	1107 (52.7)	76 (66.7)	57 (51.4)	0.0131
Physical activity				
Sedentary	519 (27.3)	39 (37.1)	39 (37.9)	
Low exercise level	696 (36.7)	38 (36.2)	37 (35.9)	
Moderate exercise level	536 (28.2)	17 (16.2)	23 (22.3)	
High exercise level	147 (7.7)	11 (10.5)	4 (3.9)	0.0130
Depression (baseline)				
No depressive symptoms	1897 (90.7)	70 (63.6)	71 (65.1)	
Mild depression	138 (6.6)	19 (17.3)	26 (23.9)	
Moderate to severe depression	57 (2.7)	21 (19.1)	12 (11.0)	0.0000
Depression (follow-up)				
No depressive symptoms	1745 (85.3)	60 (53.6)	60 (56.1)	
Mild depression	196 (9.6)	27 (24.1)	29 (27.1)	
Moderate to severe depression	104 (5.1)	25 (22.3)	18 (16.8)	0.0000
Any antidepressant †	0.3 (1.5)	1.7 (2.7)	6.5 (3.2)	0.0000
TCAs †	0.1 (1.0)	0.3 (1.6)	0.1 (0.5)	0.0996
SSRIs †	0.0 (0.0)	0.8 (0.5)	5.9 (3.1)	0.0000
Other antidepressant †	0.2 (1.1)	0.6 (2.1)	0.4 (1.3)	0.0001

* Values are n (%) or mean (SD)
† Annual number of prescriptions

Table S2 Intake of macronutrients and dietary patterns by antidepressants use

	Non-user	Low user	High user	*P* value
Energy intake (kJ/d) *	8,628.2(62.3)	8,697.3(201.6)	9,160.1(189.4)	0.029
Fat (g/d) *	87.3(0.7)	87.3(2.3)	92.6(2.2)	0.064
Protein (g/d) *	94.8(0.7)	94.8(2.4)	98.6(2.3)	0.290
Carbohydrate (g/d) *	209.5(2.3)	214.0(7.3)	225.3(6.8)	0.085
Prudent pattern score *	0.02(0.02)	0.08(0.07)	-0.12(0.07)	0.103
Western pattern score *	-0.03(0.02)	-0.04(0.07)	0.14(0.06)	0.037
Sedentary (%)	27.0	34.7	34.5	0.013
Smoking status (%)				
Non-smoker	47.7	36.4	46.2	0.003
Ex-smoker	36.7	48.1	32.6	
Current smoker	15.6	15.5	21.2	

* Values are age and gender adjusted mean (SE).

Table S3 Association between antidepressant use and body weight *

	Non-user	Low user	High user	*P* value
Any antidepressant	Ref	-0.32(-2.81-2.16)	**4.40(1.97-6.83)**	0.002
TCAs	Ref	-2.81(-6.56-0.94)	0.87(-4.52-6.25)	0.571
SSRIs	Ref	1.45(-1.66-4.56)	**4.20(1.06-7.35)**	0.007
Other	Ref	2.88(-1.43-7.18)	**7.14(3.05-11.23)**	<0.001

* Values represent regression coefficients (95%CI). Results are from mixed linear models adjusted for age, sex, depression, smoking, physical activity, dietary patterns (follow-up).

Figure S1 Factor loadings of dietary patterns

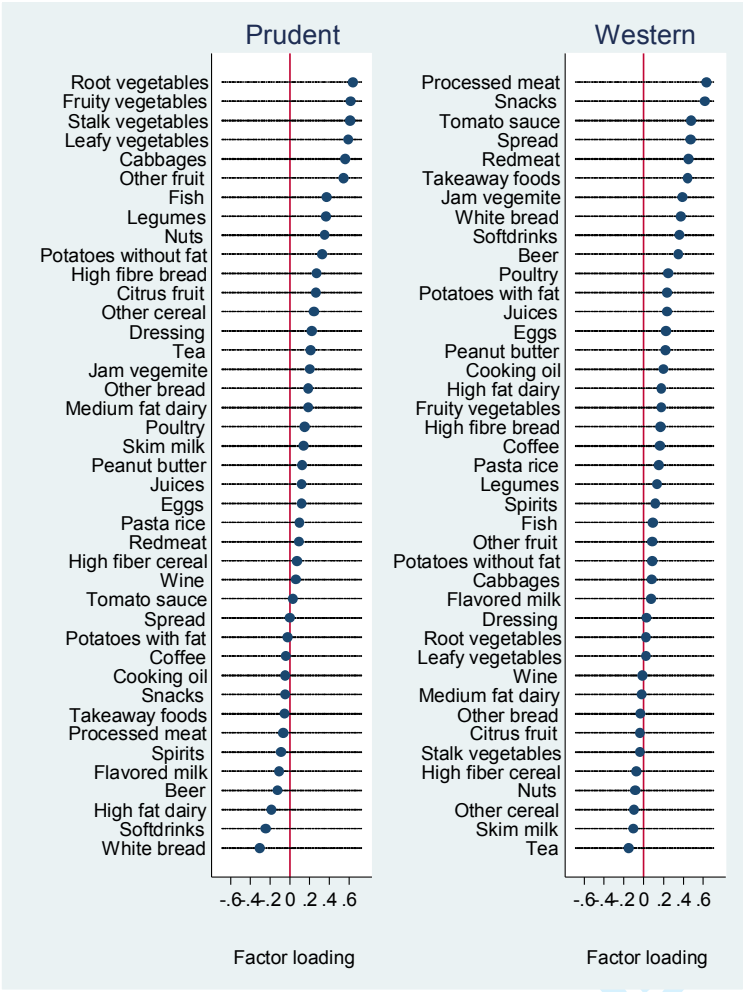
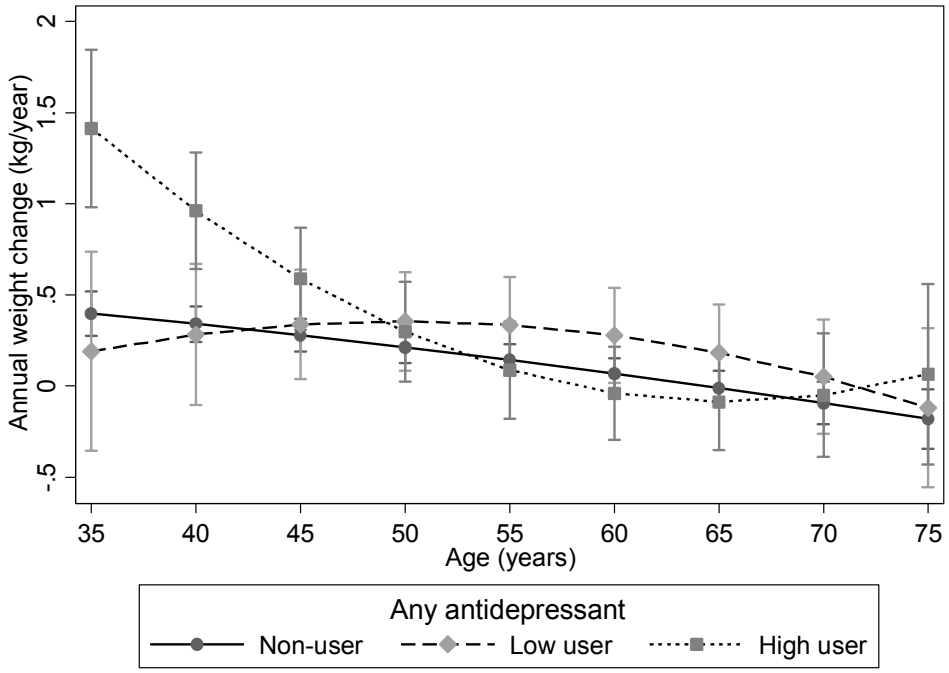


Figure S2 Interaction between any antidepressant use and age in relation to weight gain



Values adjusted for covariates included in model 3 of Table 3.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Paragraphs 1-3
Objectives	3	State specific objectives, including any prespecified hypotheses	Paragraph 4
Methods			
Study design	4	Present key elements of study design early in the paper	Paragraph 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Paragraph 1-2
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Cohort study: Paragraph 1
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Paragraphs 2-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Paragraphs 2-5
Bias	9	Describe any efforts to address potential sources of bias	Paragraphs 2-5
Study size	10	Explain how the study size was arrived at	Paragraph 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Paragraphs 2-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Paragraphs 6-7
		(*b*) Describe any methods used to examine subgroups and interactions	Paragraph 6
		(*c*) Explain how missing data were addressed	Paragraph 1
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Paragraph 1 (external linkage)

		(*e*) Describe any sensitivity analyses	Paragraph 6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods section: Paragraph 1
		(b) Give reasons for non-participation at each stage	Methods section: Paragraph 1 + cohort profile is referenced (Ref 16)
		(c) Consider use of a flow diagram	N/A- prior publication is referenced (Ref 16).
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results: Paragraph 1 & Table 1 & S1 Tables
		(b) Indicate number of participants with missing data for each variable of interest	Methods section: Paragraph 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Methods section: Paragraph 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1; Methods section: Paragraph 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2 & 3; Paragraph 3
		(*b*) Report category boundaries when continuous variables were categorized	Methods section Paragraph 3,4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results Paragraphs 4-5; S3 Tables, S2 Figure
Discussion			
Key results	18	Summarise key results with reference to study objectives	Paragraph 1

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Paragraphs 5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Paragraphs 2-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	Paragraphs 6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

BMJ Open

SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up study

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SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up study

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Abstract

Objective To examine the association between antidepressant use and weight gain, as well as the interaction with lifestyle factors.

Design Longitudinal study

Setting and participants We used data from 2334 adults from two stages (4.4 years apart) of the North West Adelaide Health Study, including validated diet and lifestyle questionnaires, measured body weight, and linked pharmaceutical data.

Main outcome measures Body weight change

Results 188 (8.1%) participants had a mean annual number of 1-2 antidepressant prescriptions, and 212 (9.1%) had over 2 prescriptions. The mean annual weight gain was 0.12, 0.18 and 0.28 kg in non-users, low (1-2 prescriptions/year) and high (>2 prescriptions/year) antidepressant users, respectively. In multivariable regression models, antidepressant use was positively associated with weight gain: high antidepressant users gained an extra 0.22 (95%CI 0.00-0.44) kg per year. This association was mainly due to selective serotonin reuptake inhibitor (SSRI) use. High SSRI users gained 0.48 (95%CI 0.20-0.76) kg more than non-users. There was no association between tricyclic or other antidepressant use and weight gain. The association between SSRI use and weight gain was mainly seen among those with high intake of Western diet, sedentary activity, and smoking.

Conclusions Exposure to SSRIs potentiates weight gain, exceeding what occurs in the context of Western diet, sedentarism, and smoking without antidepressant exposure.

Strengths and limitations of this study

- Measurement of body weight by health workers at both time points with a mean of 4.4 years of follow-up;
- Ability to adjust for detailed lifestyle factors and chronic conditions.
- The total number of antidepressant users was relatively small, which limited our power to conduct detailed subgroup analyses.
- Dietary intake was only assessed at follow-up; therefore, we were unable to adjust for dietary change during follow-up.

Keywords Antidepressant, cohort study, body weight, dietary patterns, smoking

1. Introduction

Obesity is a major global health problem almost entirely caused by excess dietary intake and reduced energy expenditure. It is estimated that up to 205 million men and 297 million women over the age of 20 years worldwide are obese [1]. In Australia, the prevalence of obesity class I (BMI 30-34.9 kg/m^2) and obesity class II or III (BMI ≥35 kg/m^2) has respectively doubled and almost tripled since 1980 [2]. Currently it is estimated that 28.3% of Australian adults are obese [3]. One of the most important health consequences of high and rising trends in global obesity prevalence has been the increased risk of developing depression [4]. Indeed, data from the Global Burden of Disease (GBD) study suggest that major depression disorder was the second leading cause accounting for 8.2% of global years lived with disability (YLDs) in 2010 [5].

Several population based cohort studies have consistently shown a positive relationship between antidepressant use and weight gain in countries such as the USA, [6-8] Canada [9] and Australia [10]. This is valuable information for public health policy makers and researchers given that the prevalence of antidepressant use is high in Australia and the USA (5-12%) [7 11], and frequently used by people without depressive or anxiety disorders [12].

The underlying cause of weight gain due to long-term antidepressant use is poorly understood [13]. In rodents, data from our lab have shown that the combination of chronic stress and short-term antidepressant treatment, followed by high-fat diet results in long-term weight gain that is greater than that caused by stress and high-fat diet, without antidepressant exposure [14]. In our animal paradigm, antidepressant exposure potentiated weight gain caused by an obesogenic diet. Based on those findings and the high rates of antidepressant use, we have hypothesised that increased antidepressant exposure might be a contributory factor to the obesity pandemic [13].

Data from a recent cross-sectional population-based study showed that antidepressant use was associated with increased energy intake [15]. Poor diet, sedentary lifestyle, obesity, and depression often cluster together; however, association studies between antidepressant use and obesity have been mostly based on registry data or short-term clinical trials, which limited their capacity to understand interactions [6-10]. Therefore, it is unknown whether interactions between antidepressant use and lifestyle factors influence human obesity on a long-term, ongoing basis.

This study was designed to specifically examine the association between antidepressant use and weight gain, as well as the interaction with diet and other lifestyle factors in adults participating in a large-population based prospective cohort study.

2. Methods

2.1 Data source and study participants

This study was approved by the Queen Elizabeth Hospital Human Research Committee and, where appropriate, by the Aboriginal Health Research Ethics Committee, Adelaide, South Australia, Australia. The North West Adelaide Health Study (NWAHS) is an ongoing community based cohort study among adults living in the North West region of Adelaide, South Australia. A detailed description of this cohort has been published elsewhere [16]. The current study analysed data from both stage 2 (2004-2006) and stage 3 (2008-2010) data collections. A total of 2334 participants had information on body weight at both time points.

2.2 Outcome variable-change in body weight

At both stages 2 and 3, height and body weight were measured in light clothing and without shoe by trained clinic staff, to the nearest 0.1 cm and 0.1 kg, respectively. Annual weight gain was calculated by the difference of body weight (kg) between follow-up and baseline divided by the duration of follow-up (in years). Overweight and obesity were defined respectively as 25 $kg/m^2 \geq$ BMI <30 kg/m^2 and BMI ≥ 30 kg/m^2.

2.3 Exposure variable- prospective antidepressant use

Information on medication use (based on prescription) according to the Anatomical Therapeutic Chemical (ATC) Classification was obtained from Medicare Australia (Pharmaceutical Benefits Scheme (PBS)) by confidential unit record linkage for the study period (between baseline and follow-up). Antidepressants (ATC code N06A)

were categorized into three groups: tricyclic antidepressants (TCAs) (ATC code N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB) and other antidepressants (ATC code N06AF, N06AG, and N06AX). For each participant the mean annual number of antidepressant prescriptions, calculated by adding the number of prescriptions and dividing it by the follow-up duration between stages 2 and 3, was categorized into three groups: non-user, low user (1-2 prescriptions/year), or high user (>2 prescriptions/year).

2.4 Covariates

2.4.1 Baseline and follow-up covariates: The Centre for Epidemiologic Studies Depression Scale (CES-D) was used to measure depressive symptoms. CES-D scores were categorised as no depression (<16), mild depression (16-26) or moderate to severe depression (>26) [17]. Smoking behaviour was determined by self-report and coded as 1) non-smoker, and 2) current or ex-smoker. Self-reported income was recoded into three levels (<$20,000, $20,000-$60,000 or >$60,000 AUD). Physical activity questions from the Australian National Health Surveys were used to classify participants as sedentary, or having low, moderate or high levels of physical activity [18].

2.4.2 Follow-up only covariates: Dietary intake during the previous 12 months was assessed by the Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies (DQES-V3.1 (FFQ)). The FFQ was previously validated in an Australian population, and is widely used in epidemiological studies. In the analysis, the daily intake of 128 food items were collapsed into 41 food groups as previously described [19]. Dietary patterns were identified by factor analysis using the principal component method. Varimax rotation was used to assist the interpretability of the factor solution.

Based on the Eigenvalue (>1), scree plot and interpretability, two dietary patterns were constructed: 1) the prudent pattern was characterised by high loadings of fruit and vegetable (Supplemental **Figure S1**) and 2) the Western pattern had high intake of processed meat, snacks, and fast food. Scores of each dietary pattern were calculated as the sum of the products of factor loading coefficients and standardized daily intake of the food intake. Dietary pattern scores were dichotomised as low and high.

2.5 Statistical analyses

Chi square test and ANOVA were used respectively to compare differences between categorical variables, and in continuous variables between groups (gender, categories of antidepressant use). Linear regression models was used to assess the longitudinal association between antidepressant use and annual weight change. Three models were employed: model 1 was adjusted for age and gender, model 2 was further adjusted for income, smoking, physical activity, and follow-up duration, and model 3 was further adjusted for depression status at baseline and follow-up, and dietary patterns (continuous). Participants with missing information of depression were excluded in the corresponding analyses. Multiplicative interaction between SSRI use, lifestyle factors (dietary patterns, smoking and physical activity) and age (continuous, or below/above 50 years) was conducted by inputting the product terms of these variables and antidepressant use in the regression models. The interaction between antidepressant use and age (continuous) was graphically represented using the *marginsplot* command in STATA 14 (Stata Corporation, College Station, TX, USA).

Sensitivity analyses were conducted using mixed linear modelling to assess the association between antidepressant use and weight status adjusted for age, income, depression, and smoking status as time-varying variables, while considering antidepressant use, physical activity, dietary patterns, and gender as time-invariant variables. We also assessed the association (incident rate ratio) between antidepressant use and five percent weight gain over five years using Poisson regression with robust variance.

All analyses were performed using STATA 14 (Stata Corporation), and statistical significance was set at $P<0.05$ (two sided).

3. Results

The mean age of the sample was 54.1 (SD 14.1) years (**Table 1**). The mean duration of follow-up was 4.4 (SD 0.4) years. Women had a higher prevalence of depression and a higher mean level of antidepressant use than men. In the sample, 188 (8.1%) and 212 (9.1%) participants had a mean annual number of 1-2, and more than 2 antidepressant prescriptions, respectively. Information on antidepressant usage was based on prescription information; out of 400 antidepressant users, 225 (56.3%) were SSRI users, and in high SSRI users the mean annual number of SSRI prescriptions was 5.9 (SD 3.1) (Supplemental **Table S1**). The mean annual weight gain was 0.12, 0.18 and 0.28 kg in non-users, low and high antidepressant users, respectively.

Compared with non-users, high antidepressant users had higher energy intake (9160 vs 8628 kJ/day) and higher Western dietary pattern scores after adjusting for age and gender (Supplemental **Table S2**).

In multivariable regression models adjusted for age, gender, income, smoking, physical activity, follow-up duration, and dietary patterns, antidepressant use was positively associated with weight gain. High users gained 0.22 (95%CI 0.00-0.44) kg per year when compared with non-users, and SSRI use was related to weight gain (**Table 2**). In the fully adjusted model, high SSRI users gained 0.48 (95%CI 0.20-0.76) kg more than non-users. No association was found between TCA and other antidepressant use and weight gain.

In relation to annual weight gain, significant interactions were found between SSRI use and three lifestyle factors: Western dietary pattern, smoking, and sedentary activity (**Table 3**). The association between SSRI use and weight gain was mainly seen among those with unhealthy lifestyle, and a strong dose response relationship

between SSRI use and weight gain was observed among those with high intake of Western diet: the regression coefficients were 0.00, 0.46 (95%CI 0.05-0.88), and 0.84 (95%CI 0.43-1.24) kg for non-users, low users and high users, respectively. This association was not seen in those with low intake of Western diet. There was a significant interaction between antidepressant use and age in relation to weight gain (Supplemental **Figure S2**). The positive association between high antidepressant use and weight gain was mainly seen among those aged below 50 years. Among those with sedentary lifestyles, high SSRI use was associated with 1.01 (95%CI 0.52-1.50) kg higher weight gain per year than non-users. A consistent positive association between SSRI use and weight gain was only observed among smokers: low and high SSRI use was respectively associated with 0.44 (95%CI 0.05-0.84) and 0.66 (95%CI 0.23-1.10) kg higher weight gain per year than non-users. No significant interaction between SSRI use and the prudent dietary pattern was found.

In the multivariable mixed regression model adjusted for time-varying depression status, smoking, age, and income as well as time-invariant dietary patterns, physical activity, and gender, antidepressant use was associated with weight status (Supplemental **Table S3**). Compared with non-use, high use was associated with an extra body weight of 4.40 kg (any antidepressant, $P= 0.002$), 4.20 kg (SSRI, $P= 0.007$) and 7.14 kg (other antidepressant, $P< 0.001$), respectively. TCA use was not associated with body weight. No interaction between antidepressant use and gender was found (data not shown).

Overall, 27.2% of the participants had weight gain above 5% over five years. In fully adjusted model, the incident rate ratio (IRR) for 5% weight gain were 1.00, 1.09 (95%CI 0.83-1.44) and 1.37 (95%CI 1.10-1.70) for non-users, low users and high users of antidepressant, respectively. A dose response association between SSRI use

and 5% weight gain was found in fully adjusted model: IRRs were 1.00, 1.37 (95%CI 1.03-1.81) and 1.43 (95%CI 1.10-1.86) (p trend <0.001) for non-users, low users and high users of SSRI, respectively (data not shown).

4. **Discussion**

In this prospective study, we found that antidepressant use was positively associated with weight gain, which was influenced by significant interactions between SSRI use, age and unhealthy lifestyle factors, including western dietary pattern, sedentary activity and smoking.

The mean annual weight gain among antidepressant users during this 4.4-year study was around 0.2 kg, which is similar to those reported in the literature for shorter studies [6 7 9 10 20]. However, in those previous population studies, lifestyle factors were either lacking or treated as confounding factors [6 7 9 10 20]. None of those studies had been adjusted for dietary intake, an important factor for weight gain.

Only one previous study assessed differences in energy intake and physical activity between antidepressant users and non-users, employing data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES). It showed that, after adjusting for potential confounding factors, antidepressant users had an extra 215 kcal/day of energy intake and were 77% more likely to use a computer for ≥2 hour/day than non-users [15]. The authors hypothesized that increased energy intake and sedentary activity could contribute to weight gain associated with antidepressant use. In the present study we also found a significant difference in energy intake between high antidepressant users and non-users. After adjusting for age and gender, high antidepressant users had a higher energy intake than non-users (9160 *vs* 8628 kJ/day). Furthermore, high antidepressant users had higher Western dietary pattern scores than

non-users (0.14 *vs* -0.03). To the best of our knowledge, this is the first study that systematically tested the interactions between antidepressant use and modifiable lifestyle factors. A significant positive dose response association between antidepressant use and weight gain was found in individuals with high intake but not in those with low intake of Western diet. Clustering of unhealthy behaviours and chronic diseases, including depression, may partly explain the interaction between unhealthy lifestyle and weight gain among those using antidepressant.

The interaction between antidepressant use and smoking in relation to weight gain was consistent with that reported by Arterburn *et al.* who found that bupropion-treated smokers gained an extra 14.2 lbs compared to fluoxetine-treated non-smokers during a two-year follow-up study [8]. We observed an intriguing interaction between antidepressant use and age in relation to weight gain, which may be related to the fact that younger people are more likely to eat a Western diet. In our sample, age was inversely associated with Western dietary pattern scores (data not shown).

The lack of association between TCA use and weight gain was also reported in the Netherlands Study of Depression and Anxiety as well as the Rotterdam Study [20 21]. However, previous studies have reported an association between TCA use and weight gain [6 13]. Our null association between TCA use and weight gain may be due to the fact that age was positively associated with TCA use ($P<0.001$). The mean age was respectively 53.6, 62.2 and 65.6 years among non-users, low and high users of TCA (data not shown). However, there was no significant age difference between SSRIs users and non-users. Another explanation could be that doctors may be more likely to prescribe SSRIs to people who are worried about weight gain as TCA use has been linked to weight gain in clinical trials.

The strengths of this study include: 1) measurement of body weight by health workers at both time points with a mean of 4.4 years of follow-up; 2) ability to adjust for detailed lifestyle factors and chronic conditions. The main limitation of the study compared to other registry-based studies was that the total number of antidepressant users was relatively small, which limited our power to conduct detailed subgroup analyses. The effect size of the antidepressant use on weight gain may be under estimated due to the fact that some of the low cost antidepressants (below co-payment level) were not recorded by the PBS system before 2012. The PBS dataset only provides information on dispensing not the actual use of antidepressants. Furthermore, dietary intake was only assessed at follow-up; therefore, we were unable to adjust for dietary change during follow-up. There may also be an under or over estimate of energy intake due to the use of FFQ and the inherent issues surrounding recall. Finally, the sample power may be limited for the analyses of TCA and other antidepressants.

Antidepressants are widely used, representing the most prescribed drug class in the USA [22]; in Australia 11.6% of the country's population is on antidepressants [23]. Antidepressant-related weight gain is an outcome of public health relevance, as it may contribute to increased rates of obesity. Here we provide evidence that antidepressant use potentiates weight gain, especially among those with unhealthy lifestyles, resulting in body weight that is higher than that associated solely with those same lifestyle factors, in the absence of antidepressants. As a matter of public health relevance, SSRI use should be accompanied by pro-active efforts to avoid weight gain. We suggest that reducing Western diet consumption, increasing physical activity and smoking cessation may mitigate antidepressant-related weight gain.

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Conflicts of interest: We declare that we have no conflicts of interest.

Author contributions: ZS contributed to the conception, analysis, and interpretation of data; drafting of the report; and have given approval of the final version for publication. EA, AWT, TKG, KP, SA, MLW and JL contributed to analysis and interpretation of the data, commented on the report, revising the manuscript and approving the final version for publication.

Availability of data and material

Data from the North West Adelaide Healthy Study (NWAHS) were accessed from a third party. The authors confirm that for approved reasons, some access restrictions apply to the data underlying the findings. To gain access to the data for this manuscript, ethics approval was sought and granted. Enquiries regarding requests for the NWAHS data can be directed to Prof Robert Adams, Principal Investigator (Clinical) (robert.adams@adelaide.edu.au).

Figure legends

Supporting Information **Figures**

Figure S1: Factor loadings of dietary patterns

Figure S2: Interaction between any antidepressant use and age in relation to weight gain.

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Table 1 Sample characteristic by sex *

	Male	Female	Total	*P* value
n (%)	1095 (46.9)	1239 (53.1)	2334	
Age (years)	54.0 (14.4)	54.3 (13.8)	54.1 (14.1)	0.648
Baseline weight (kg)	87.2 (15.3)	73.5 (16.1)	79.9 (17.2)	<0.001
Follow-up weight (kg)	87.9 (16.0)	74.0 (16.2)	80.5 (17.5)	<0.001
Annual weight gain (kg)	0.17 (1.35)	0.12 (1.46)	0.14 (1.41)	0.449
Baseline BMI status				
Normal	21.9	34.5	28.6	<0.001
Overweight	48.9	34.2	41.1	
Obese	29.2	31.2	30.3	
Baseline income ($)				
<20000	196 (17.9)	332 (26.9)	528	
20000-60000	529 (48.4)	543 (44.0)	1072	
>60000	338 (31.0)	308 (24.9)	646	
Not stated	29 (2.7)	52 (4.2)	81	<0.001
Baseline smoking status				
Non smoker	444 (40.7)	642 (52.0)	1086	
Current or ex-smoker	647 (59.3)	593 (48.0)	1240	<0.001
Baseline physical activity				
Sedentary	252 (25.9)	345 (30.4)	597	
Low exercise level	323 (33.2)	448 (39.5)	771	
Moderate exercise level	291 (29.9)	285 (25.1)	576	
High exercise level	106 (10.9)	56 (4.9)	162	<0.001
Depression (baseline)				
No depressive symptoms	995 (91.3)	1043 (85.4)	2038	
Mild depression	61 (5.6)	122 (10.0)	183	
Moderate to severe depression	34 (3.1)	56 (4.6)	90	<0.001
Depression (follow-up)				
No depressive symptoms	907 (85.6)	958 (79.6)	1865	
Mild depression	101 (9.5)	151 (12.5)	252	
Moderate to severe depression	52 (4.9)	95 (7.9)	147	<0.001
Any antidepressant †	0.4 (1.7)	0.9 (2.5)	0.7 (2.2)	<0.001

TCAs †	0.1 (0.6)	0.2 (1.3)	0.1 (1.0)	<0.001
SSRIs †	0.2 (1.3)	0.4 (1.6)	0.3 (1.4)	0.019
Other antidepressant †	0.1 (0.8)	0.3 (1.5)	0.2 (1.2)	<0.001

* values are n (%) or mean (SD)

† Annual number of prescriptions

Table 2 Association (β 95%CI) between antidepressant use and annual weight gain

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
Any antidepressant				
n	1934	188	212	
Baseline weight (kg), mean (SD)	80.0 (17.0)	77.1 (16.5)	81.3 (19.1)	
Follow-up weight (kg), mean (SD)	80.6 (17.3)	78.0 (17.2)	82.5 (19.6)	
Annual weight change (kg), mean (SD)	0.12(1.32)	0.18(1.54)	0.28(1.99)	
Model 1 *	Ref	0.15(-0.06-0.36)	0.22(0.02-0.42)	0.022
Model 2 †	Ref	0.18(-0.04-0.40)	0.25(0.04-0.46)	0.009
Model 3 ‡	Ref	0.11(-0.11-0.34)	0.22(0.00-0.44)	0.044
SSRIs				
n	2109	114	111	
Baseline weight (kg), mean (SD)	79.8 (17.0)	79.7 (18.2)	82.2 (19.1)	
Follow-up weight (kg), mean (SD)	80.3 (17.3)	81.2 (18.0)	84.9 (21.2)	
Annual weight change (kg), mean (SD)	0.11(1.33)	0.38(2.11)	0.61(1.89)	
Model 1 *	Ref	**0.30(0.04-0.57)**	**0.53(0.27-0.80)**	**<0.001**
Model 2 †	Ref	**0.30(0.03-0.58)**	**0.58(0.30-0.85)**	**<0.001**
Model 3 ‡	Ref	**0.30(0.01-0.58)**	**0.48(0.20-0.76)**	**<0.001**
TCAs				
n	2212	79	43	
Baseline weight (kg), mean (SD)	80.1 (17.2)	76.3 (17.8)	77.3 (15.9)	
Follow-up weight (kg), mean (SD)	80.8 (17.5)	75.5 (17.3)	77.3 (16.4)	
Annual weight change	0.16(1.40)	-0.13(1.61)	-0.01(1.32)	

(kg), mean (SD)				
Model 1 *	Ref	-0.12(-0.44-0.19)	0.06(-0.36-0.49)	0.717
Model 2 †	Ref	-0.11(-0.44-0.22)	0.05(-0.39-0.50)	0.704
Model 3 ‡	Ref	0.02(-0.31-0.36)	0.03(-0.46-0.52)	0.908
Other antidepressants				
n	2210	57	67	
Baseline weight (kg), mean (SD)	79.8 (17.0)	80.0 (18.7)	82.9 (20.5)	
Follow-up weight (kg), mean (SD)	80.4 (17.4)	81.3 (17.6)	83.4 (21.2)	
Annual weight change (kg), mean (SD)	0.14(1.37)	0.35(1.88)	0.12(2.08)	
Model 1 *	Ref	0.23(-0.13-0.60)	-0.04(-0.38-0.29)	0.844
Model 2 †	Ref	0.32(-0.05-0.70)	-0.01(-0.36-0.35)	0.505
Model 3 ‡	Ref	0.42(0.03-0.80)	-0.19(-0.56-0.19)	0.926

* Model 1 adjusted for age and gender.

† Model 2 further adjusted for baseline income, smoking, physical activity, follow-up duration.

‡ Model 3 further adjusted for depression status at baseline and follow-up, dietary patterns (continuous).

Table 3 Subgroup analyses of the association between SSRI use and annual weight gain *

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* for interaction
Western dietary pattern				0.026
Low intake	0.00	0.11(-0.29-0.51)	0.14(-0.26-0.54)	
High intake	0.00	**0.46(0.05-0.88)** †	**0.84(0.43-1.24)**	
Prudent dietary pattern				0.635
Low intake	0.00	0.35(-0.07-0.78)	0.38(-0.02-0.78)	
High intake	0.00	0.23(-0.16-0.63)	**0.61(0.20-1.02)**	
Physical activity				0.039
Sedentary	0.00	0.15(-0.34-0.63)	**1.01(0.52-1.50)**	
Low	0.00	0.34(-0.13-0.82)	0.23(-0.27-0.72)	
Moderate/high	0.00	0.33(-0.27-0.94)	0.06(-0.49-0.61)	
Smoking				0.002
Non-smoker	0.00	-0.28(-0.73-0.16)	0.35(-0.03-0.72)	
Current or ex-smoker	0.00	**0.44(0.05-0.84)**	**0.66(0.23-1.10)**	

* Models adjusted for age, gender, income, physical activity, smoking, depression status at baseline and follow-up. Stratifying variables were not adjusted in the corresponding models. Dietary pattern scores are dichotomised as low or high intake. Values represent regression coefficients (95%CI).

† Bold values represent p<0.05.

Supplemental materials

Table S1 Sample characteristic by SSRIs use *

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
n (%)	2109 (90.4)	114 (4.9)	111 (4.8)	
Age (years)	54.0 (14.3)	55.0 (11.6)	55.4 (12.6)	0.4818
Baseline weight (kg)	79.8 (17.0)	79.7 (18.2)	82.2 (19.1)	0.3717
Follow-up weight (kg)	80.3 (17.3)	81.2 (18.0)	84.9 (21.2)	0.0245
Annual weight gain (kg)	0.1 (1.3)	0.4 (2.1)	0.6 (1.9)	0.0002
Income ($)				
<20000	451 (21.5)	36 (31.6)	41 (36.9)	
20000-60000	981 (46.7)	45 (39.5)	46 (41.4)	
>60000	599 (28.5)	27 (23.7)	20 (18.0)	
Not stated	71 (3.4)	6 (5.3)	4 (3.6)	0.0008
Smoking status				
Non smoker	994 (47.3)	38 (33.3)	54 (48.6)	
Current or ex-smoker	1107 (52.7)	76 (66.7)	57 (51.4)	0.0131
Physical activity				
Sedentary	519 (27.3)	39 (37.1)	39 (37.9)	
Low exercise level	696 (36.7)	38 (36.2)	37 (35.9)	
Moderate exercise level	536 (28.2)	17 (16.2)	23 (22.3)	
High exercise level	147 (7.7)	11 (10.5)	4 (3.9)	0.0130
Depression (baseline)				
No depressive symptoms	1897 (90.7)	70 (63.6)	71 (65.1)	
Mild depression	138 (6.6)	19 (17.3)	26 (23.9)	
Moderate to severe depression	57 (2.7)	21 (19.1)	12 (11.0)	0.0000
Depression (follow-up)				
No depressive symptoms	1745 (85.3)	60 (53.6)	60 (56.1)	
Mild depression	196 (9.6)	27 (24.1)	29 (27.1)	
Moderate to severe depression	104 (5.1)	25 (22.3)	18 (16.8)	0.0000
Any antidepressant †	0.3 (1.5)	1.7 (2.7)	6.5 (3.2)	0.0000
TCAs †	0.1 (1.0)	0.3 (1.6)	0.1 (0.5)	0.0996

SSRIs †	0.0 (0.0)	0.8 (0.5)	5.9 (3.1)	0.0000
Other antidepressant †	0.2 (1.1)	0.6 (2.1)	0.4 (1.3)	0.0001

* Values are n (%) or mean (SD)

† Annual number of prescriptions

Table S2 Intake of macronutrients, dietary patterns and lifestyle factors by antidepressants use

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
Energy intake (kJ/d) *	8,628.2(62.3)	8,697.3(201.6)	9,160.1(189.4)	0.029
Fat (g/d) *	87.3(0.7)	87.3(2.3)	92.6(2.2)	0.064
Protein (g/d) *	94.8(0.7)	94.8(2.4)	98.6(2.3)	0.290
Carbohydrate (g/d) *	209.5(2.3)	214.0(7.3)	225.3(6.8)	0.085
Prudent pattern score *	0.02(0.02)	0.08(0.07)	-0.12(0.07)	0.103
Western pattern score *	-0.03(0.02)	-0.04(0.07)	0.14(0.06)	0.037
Sedentary (%)	27.0	34.7	34.5	0.013
Smoking status (%)				
Non-smoker	47.7	36.4	46.2	0.003
Ex-smoker	36.7	48.1	32.6	
Current smoker	15.6	15.5	21.2	

* Values are age and gender adjusted mean (SE).

Table S3 Association between antidepressant use and body weight from mixed linear model *

	Non-user	Low user	High user	*P* value
Any antidepressant	Ref	-0.32(-2.81-2.16)	**4.40(1.97-6.83)**	0.002
TCAs	Ref	-2.81(-6.56-0.94)	0.87(-4.52-6.25)	0.571
SSRIs	Ref	1.45(-1.66-4.56)	**4.20(1.06-7.35)**	0.007
Other	Ref	2.88(-1.43-7.18)	**7.14(3.05-11.23)**	<0.001

* Values represent regression coefficients (95%CI). Results are from mixed linear models adjusted for age, sex, income, depression, smoking, physical activity, dietary patterns (follow-up).

Figure S1 Factor loadings of dietary patterns

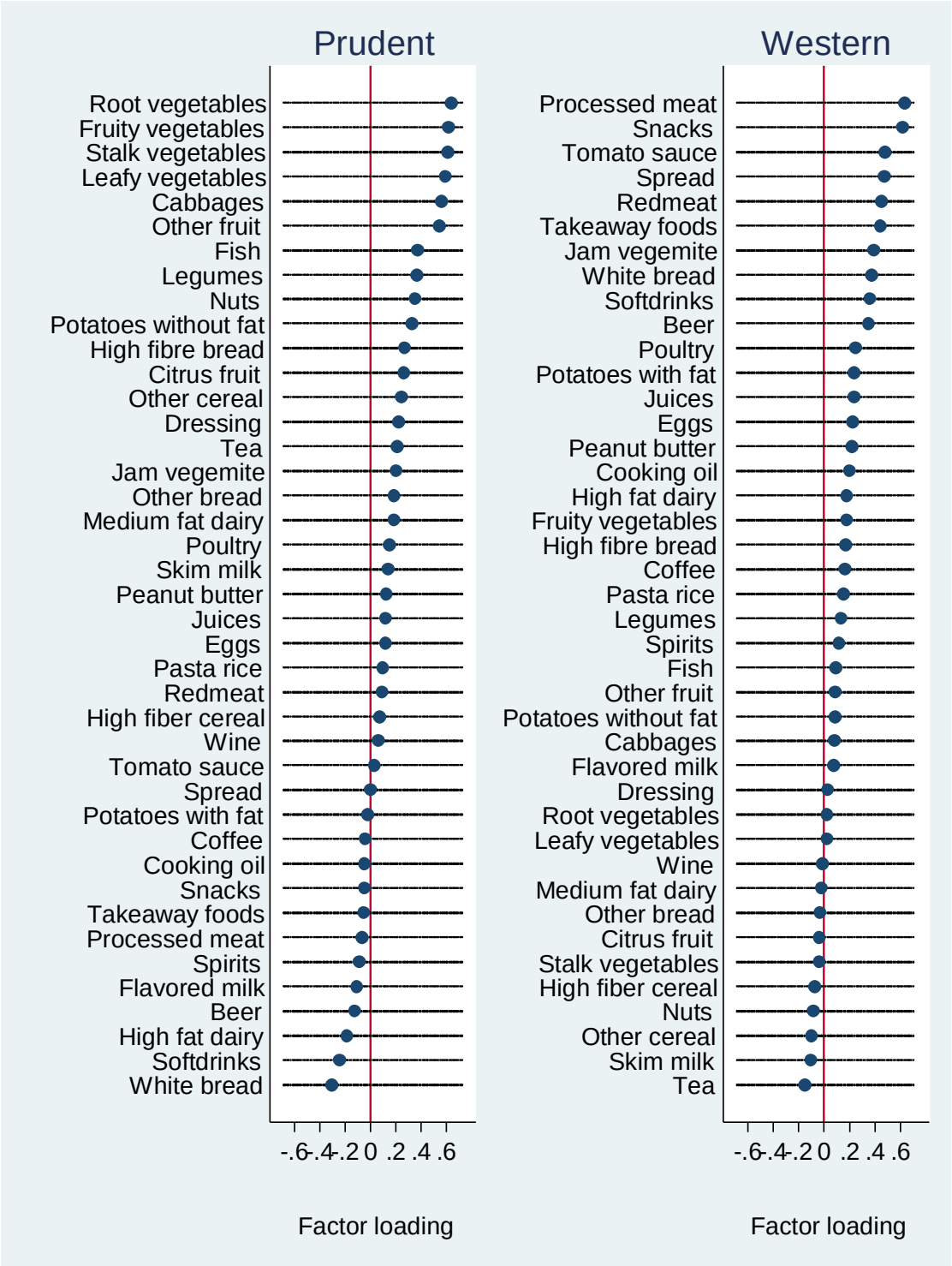
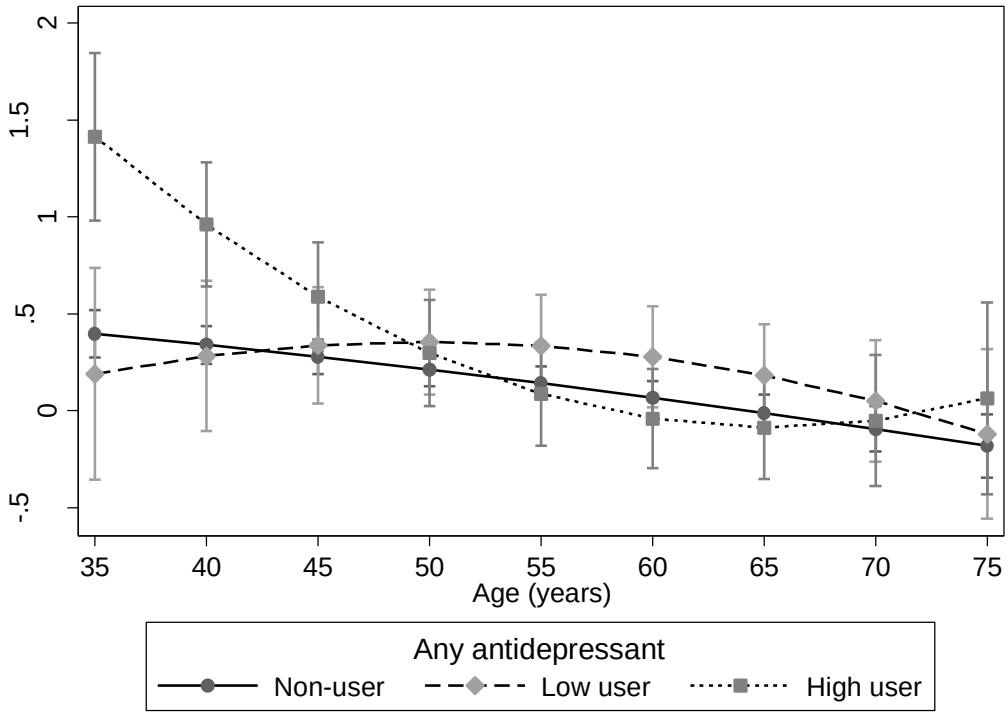


Figure S2 Interaction between any antidepressant use and age in relation to weight gain



Values adjusted for covariates included in model 3 of Table 3.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Paragraphs 1-3, page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Paragraph 4, page5
Methods			
Study design	4	Present key elements of study design early in the paper	Paragraph 1, page6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Paragraph 1-2, page6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Cohort study: Paragraph 1 Page 6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Paragraphs 2-5, page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Paragraphs 2-5, Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	Paragraphs 2-5, Page 6-8
Study size	10	Explain how the study size was arrived at	Paragraph 1, Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Paragraphs 2-5, Page 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Paragraphs 6-7, Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	Paragraph 6, Page 8
		(*c*) Explain how missing data were addressed	Page 6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Paragraph 1 (external

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	linkage)
		(*e*) Describe any sensitivity analyses	Paragraph 6, page 8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods section: Paragraph 1, page 10
		(b) Give reasons for non-participation at each stage	Methods section: Paragraph 1 + cohort profile is referenced (Ref 16)
		(c) Consider use of a flow diagram	N/A- prior publication is referenced (Ref 16).
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results: Paragraph 1 & Table 1 & S1 Tables
		(b) Indicate number of participants with missing data for each variable of interest	Methods section: Paragraph 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Methods section: Paragraph 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1; Methods section: Paragraph 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2 & 3; Paragraph 3, Page 10
		(*b*) Report category boundaries when continuous variables were categorized	Methods section Paragraph 3,4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results Paragraphs 4-5; S3 Tables, S2 Figure
Discussion			
Key results	18	Summarise key results with reference to study objectives	Paragraph 1, page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Paragraphs 5, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Paragraphs 2-6, Page 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Paragraphs 6, page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

BMJ Open

SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up study

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SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up study

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Abstract

Objective To examine the association between antidepressant use and weight gain, as well as the interaction with lifestyle factors.

Design Longitudinal study

Setting and participants We used data from 2334 adults from two stages (4.4 years apart) of the North West Adelaide Health Study, including validated diet and lifestyle questionnaires, measured body weight, and linked pharmaceutical prescription data.

Main outcome measures Body weight change

Results 188 (8.1%) participants had a mean annual number of 1-2 antidepressant prescriptions, and 212 (9.1%) had over 2 prescriptions. The mean annual weight gain was 0.12, 0.18 and 0.28 kg in non-users, low (1-2 prescriptions/year) and high (>2 prescriptions/year) antidepressant users, respectively. In multivariable regression models, antidepressant use was positively associated with weight gain: high antidepressant users gained an extra 0.22 (95%CI 0.00-0.44) kg per year. This association was mainly due to selective serotonin reuptake inhibitor (SSRI) use. High SSRI users gained 0.48 (95%CI 0.20-0.76) kg more than non-users. There was no association between tricyclic or other antidepressant use and weight gain. The association between SSRI use and weight gain was stronger among those with high intake of Western diet, greater sedentary activity, and who smoked.

Conclusions Exposure to SSRIs potentiates weight gain in the presence unhealthy behaviours including Western diet, sedentarism, and smoking.

Strengths and limitations of this study

- Measurement of body weight by health workers at both time points with a mean of 4.4 years of follow-up;
- Ability to adjust for detailed lifestyle factors and chronic conditions.
- The total number of antidepressant users was relatively small, which limited our power to conduct detailed subgroup analyses.
- Dietary intake was only assessed at follow-up; therefore, we were unable to adjust for dietary change during follow-up.

Keywords Antidepressant, cohort study, body weight, dietary patterns, smoking

1. Introduction

Obesity is a major global health problem almost entirely caused by excess dietary intake and reduced energy expenditure. It is estimated that up to 205 million men and 297 million women over the age of 20 years worldwide are obese [1]. In Australia, the prevalence of obesity class I (BMI 30-34.9 kg/m^2) and obesity class II or III (BMI ≥35 kg/m^2) has respectively doubled and almost tripled since 1980 [2]. Currently it is estimated that 28.3% of Australian adults are obese [3]. One of the most important health consequences of high and rising trends in global obesity prevalence has been the increased risk of developing depression [4]. Indeed, data from the Global Burden of Disease (GBD) study suggest that major depression disorder was the second leading cause accounting for 8.2% of global years lived with disability (YLDs) in 2010 [5].

Several population based cohort studies have consistently shown a positive relationship between antidepressant use and weight gain in countries such as the USA, [6-8] Canada [9] and Australia [10]. This is valuable information for public health policy makers and researchers given that the prevalence of antidepressant use is high in Australia and the USA (5-12%) [7 11], and frequently used by people without depressive or anxiety disorders [12] .

The underlying cause of weight gain due to long-term antidepressant use is poorly understood [13]. In rodents, data from our lab have shown that the combination of chronic stress and short-term antidepressant treatment, followed by high-fat diet results in long-term weight gain that is greater than that caused by stress and high-fat diet, without antidepressant exposure [14]. In our animal paradigm, antidepressant exposure potentiated weight gain caused by obesity promoting diet. Thus, increased antidepressant exposure might be a contributory factor to the obesity pandemic [13]. It is supported by the change of energy intake related to antidepressant use. Data from a

recent cross-sectional population-based study showed that antidepressant use was associated with increased energy intake [15]. Poor diet, sedentary lifestyle, obesity, and depression often cluster together; however, association studies between antidepressant use and obesity have been mostly based on registry data or short-term clinical trials, which limited their capacity to understand interactions [6-10]. Therefore, whether specific antidepressant medications interaction with lifestyle risk factors (poor diet, inadequate physical activity, and smoking) partially explain the development of human obesity long term is still unclear. Identifying the potential mechanism by which antidepressant medication increases the risk of obesity may could help develop targeted strategies for prevention.

This study was designed to specifically examine the association between antidepressant use and weight gain, as well as the interaction with diet and other lifestyle factors (e.g. smoking, sedentary activity) in adults participating in a large-population based prospective cohort study.

2. Methods

2.1 Data source and study participants

This study was approved by the Queen Elizabeth Hospital Human Research Committee and, where appropriate, by the Aboriginal Health Research Ethics Committee, Adelaide, South Australia, Australia. The North West Adelaide Health Study (NWAHS) is an ongoing community based cohort study among adults living in the North West region of Adelaide, South Australia. A detailed description of this cohort has been published elsewhere [16]. The current study analysed data from both stage 2 (2004-2006) and stage 3 (2008-2010) data collections. A total of 2334 participants had information on body weight at both time points.

2.2 Outcome variable-change in body weight

At both stages 2 and 3, height and body weight were measured in light clothing and without shoe by trained clinic staff, to the nearest 0.1 cm and 0.1 kg, respectively. Annual weight gain was calculated by the difference of body weight (kg) between follow-up and baseline divided by the duration of follow-up (in years). Overweight and obesity were defined respectively as 25 $kg/m^2 \geq$ BMI <30 kg/m^2 and BMI ≥ 30 kg/m^2.

2.3 Exposure variable- prospective antidepressant use

Information on medication use (based on prescription) according to the Anatomical Therapeutic Chemical (ATC) Classification was obtained from Medicare Australia (Pharmaceutical Benefits Scheme (PBS)) by confidential unit record linkage for the study period (between baseline and follow-up). Antidepressants (ATC code N06A)

were categorized into three groups: tricyclic antidepressants (TCAs) (ATC code N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB) and other antidepressants (ATC code N06AF, N06AG, and N06AX). For each participant the mean annual number of antidepressant prescriptions, calculated by adding the number of prescriptions and dividing it by the follow-up duration between stages 2 and 3, was categorized into three groups: non-user, low user (1-2 prescriptions/year), or high user (>2 prescriptions/year). Exposure of specific antidepressants was assessed independent of one or more antidepressants.

2.4 Covariates

2.4.1 Baseline and follow-up covariates: The Centre for Epidemiologic Studies Depression Scale (CES-D) was used to measure depressive symptoms. CES-D scores were categorised as no depression (<16), mild depression (16-26) or moderate to severe depression (>26) [17]. Smoking behaviour was determined by self-report and coded as 1) non-smoker, and 2) current or ex-smoker. Self-reported income was recoded into three levels (<$20,000, $20,000-$60,000 or >$60,000 AUD). Physical activity questions from the Australian National Health Surveys were used to classify participants as sedentary, or having low, moderate or high levels of physical activity [18]. Respondents were asked about the amount of walking, moderate and vigorous activity they had undertaken in the past two weeks.

2.4.2 Follow-up only covariates: Dietary intake during the previous 12 months was assessed by the Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies (DQES-V3.1 (FFQ)). The FFQ was previously validated in an Australian population, and is widely used in epidemiological studies. In the analysis, the daily intake of 128 food items were collapsed into 41 food groups as previously described

[19]. Dietary patterns were identified by factor analysis using the principal component method. Varimax rotation was used to assist the interpretability of the factor solution. Based on the Eigenvalue (>1), scree plot and interpretability, two dietary patterns were constructed: 1) the prudent pattern was characterised by high loadings of fruit and vegetable (Supplemental **Figure S1**) and 2) the Western pattern had high intake of processed meat, snacks, and fast food. Scores of each dietary pattern were calculated as the sum of the products of factor loading coefficients and standardized daily intake of the food intake. Dietary pattern scores were dichotomised as low and high (i.e. below or above zero).

2.5 Statistical analyses

Chi square test and ANOVA were used respectively to compare differences between categorical variables, and in continuous variables between groups (gender, categories of antidepressant use). Linear regression models was used to assess the longitudinal association between antidepressant use and annual weight change. Three models were employed: model 1 was adjusted for age and gender, model 2 was further adjusted for income, smoking, physical activity, and follow-up duration, and model 3 was further adjusted for depression status at baseline and follow-up, and dietary patterns (continuous). Participants with missing information of depression were excluded in the corresponding analyses.

As the association between antidepressant use and weight gain was mainly due to SSRI, we further looked at the interaction between SSRI use and lifestyle factors. Multiplicative interaction between SSRI use, lifestyle factors (categorical variables of dietary patterns (low or high), smoking (non-smoker, current or ex-smoker) and

physical activity (sedentary, low, moderate/high)) was conducted by inputting the product terms of these variables and antidepressant use in the regression models. The analysis was subsequently stratified for the lifestyle factors. The interaction between antidepressant use and age (continuous) was graphically represented using the *marginsplot* command in STATA 14 (Stata Corporation, College Station, TX, USA).

Sensitivity analyses were conducted using mixed linear modelling to assess the association between antidepressant use and body weight (baseline and follow-up adjusted for age, income, depression, and smoking status as time-varying variables, while considering antidepressant use, physical activity, dietary patterns, and gender as time-invariant variables. We also assessed the association (incident rate ratio) between antidepressant use and five percent weight gain over five years using Poisson regression with robust variance.

All analyses were performed using STATA 14 (Stata Corporation), and statistical significance was set at $P<0.05$ (two sided).

3. Results

The mean age of the sample was 54.1 (SD 14.1) years (**Table 1**). The mean duration of follow-up was 4.4 (SD 0.4) years. Women had a higher prevalence of depression and a higher mean level of antidepressant use than men. In the sample, 188 (8.1%) and 212 (9.1%) participants had a mean annual number of 1-2, and more than 2 antidepressant prescriptions, respectively. Information on antidepressant usage was based on prescription information; out of 400 antidepressant users, 225 (56.3%) were SSRI users, and in high SSRI users the mean annual number of SSRI prescriptions was 5.9 (SD 3.1) (Supplemental **Table S1**). The mean annual weight gain was 0.12, 0.18 and 0.28 kg in non-users, low and high antidepressant users, respectively.

Compared with non-users, high antidepressant users had higher energy intake (9160 vs 8628 kJ/day) and higher Western dietary pattern scores after adjusting for age and gender (Supplemental **Table S2**).

In multivariable regression models adjusted for age, gender, income, smoking, physical activity, follow-up duration, and dietary patterns, antidepressant use was positively associated with weight gain. High users gained 0.22 (95%CI 0.00-0.44) kg per year when compared with non-users, and SSRI use was related to weight gain (**Table 2**). In the fully adjusted model, high SSRI users gained 0.48 (95%CI 0.20-0.76) kg more than non-users. No association was found between TCA and other antidepressant use and weight gain.

In relation to annual weight gain, significant interactions were found between SSRI use and three lifestyle factors: Western dietary pattern, smoking, and sedentary activity (**Table 3**). The association between SSRI use and weight gain was mainly seen among those with unhealthy lifestyle, and a strong dose response relationship

between SSRI use and weight gain was observed among those with high intake of Western diet: the regression coefficients were 0.00, 0.46 (95%CI 0.05-0.88), and 0.84 (95%CI 0.43-1.24) kg for non-users, low users and high users, respectively. This association was not seen in those with low intake of Western diet. No significant interaction between SSRI use and the prudent dietary pattern was found. Among those with sedentary lifestyles, high SSRI use was associated with 1.01 (95%CI 0.52-1.50) kg higher weight gain per year than non-users. A consistent positive association between SSRI use and weight gain was only observed among smokers: low and high SSRI use was respectively associated with 0.44 (95%CI 0.05-0.84) and 0.66 (95%CI 0.23-1.10) kg higher weight gain per year than non-users.

There was a significant interaction between antidepressant use and age in relation to weight gain (Supplemental **Figure S2**). The positive association between high antidepressant use and weight gain was mainly seen among those aged below 50 years.

In the multivariable mixed regression model adjusted for time-varying depression status, smoking, age, and income as well as time-invariant dietary patterns, physical activity, and gender, antidepressant use was associated with body weight (baseline and follow-up)(Supplemental **Table S3**). Compared with non-use, high use was associated with an extra body weight of 4.40 kg (any antidepressant, $P = 0.002$), 4.20 kg (SSRI, $P = 0.007$) and 7.14 kg (other antidepressant, $P < 0.001$), respectively. TCA use was not associated with body weight. No interaction between antidepressant use and gender was found (data not shown).

Overall, 27.2% of the participants had weight gain above 5% over five years. In fully adjusted model, the incident rate ratio (IRR) for 5% weight gain were 1.00, 1.09 (95%CI 0.83-1.44) and 1.37 (95%CI 1.10-1.70) for non-users, low users and high

users of antidepressant, respectively. A dose response association between SSRI use and 5% weight gain was found in fully adjusted model: IRRs were 1.00, 1.37 (95%CI 1.03-1.81) and 1.43 (95%CI 1.10-1.86) (p trend <0.001) for non-users, low users and high users of SSRI, respectively (data not shown).

4. **Discussion**

In this prospective study, we found that antidepressant use was positively associated with weight gain, which was influenced by significant interactions between SSRI use, age and unhealthy lifestyle factors, including western dietary pattern, sedentary activity and smoking.

The mean annual weight gain among antidepressant users during this 4.4-year study was around 0.2 kg, which is similar to those reported in the literature for shorter studies [6 7 9 10 20]. However, in those previous population studies, lifestyle factors were either lacking or treated as confounding factors [6 7 9 10 20]. None of those studies had been adjusted for dietary intake, an important factor for weight gain.

Only one previous study assessed differences in energy intake and physical activity between antidepressant users and non-users, employing data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES). It showed that, after adjusting for potential confounding factors, antidepressant users had an extra 215 kcal/day of energy intake and were 77% more likely to use a computer for ≥2 hour/day than non-users [15]. The authors hypothesized that increased energy intake and sedentary activity could contribute to weight gain associated with antidepressant use. In the present study we also found a significant difference in energy intake between high antidepressant users and non-users. After adjusting for age and gender, high antidepressant users had a higher energy intake than non-users (9160 *vs* 8628 kJ/day).

Furthermore, high antidepressant users had higher Western dietary pattern scores than non-users (0.14 *vs* -0.03). To the best of our knowledge, this is the first study that systematically tested the interactions between antidepressant use and modifiable lifestyle factors. A significant positive dose response association between antidepressant use and weight gain was found in individuals with high intake but not in those with low intake of Western diet. Clustering of unhealthy behaviours and chronic diseases, including depression, may partly explain the interaction between unhealthy lifestyle and weight gain among those using antidepressant.

The interaction between antidepressant use and smoking in relation to weight gain was consistent with that reported by Arterburn *et al.* who found that bupropion-treated smokers gained an extra 14.2 lbs compared to fluoxetine-treated non-smokers during a two-year follow-up study [8]. We observed an intriguing interaction between antidepressant use and age in relation to weight gain, which may be related to the fact that younger people are more likely to eat a Western diet. In our sample, age was inversely associated with Western dietary pattern scores (data not shown).

The lack of association between TCA use and weight gain was also reported in the Netherlands Study of Depression and Anxiety as well as the Rotterdam Study [20 21]. However, previous studies have reported an association between TCA use and weight gain [6 13]. Our null association between TCA use and weight gain may be due to the fact that age was positively associated with TCA use ($P<0.001$). The mean age was respectively 53.6, 62.2 and 65.6 years among non-users, low and high users of TCA (data not shown). The SSRI fluoxetine entered medical use in 1986; TCAs were the gold standard for depression treatment before SSRIs became popular. It is likely that older patients started their treatment with TCA and those that were treated with and responded to TCAs for many years before SSRIs became available may have

been reluctant to be switched to SSRIs. However, there was no significant age difference between SSRIs users and non-users. Another explanation could be that doctors may be more likely to prescribe SSRIs to people who are worried about weight gain as TCA use has been linked to weight gain in clinical trials.

The strengths of this study include: 1) measurement of body weight by health workers at both time points with a mean of 4.4 years of follow-up; 2) ability to adjust for detailed lifestyle factors and chronic conditions. The main limitation of the study compared to other registry-based studies was that the total number of antidepressant users was relatively small, which limited our power to conduct detailed subgroup analyses. The effect size of the antidepressant use on weight gain may be under estimated due to the fact that some of the low cost antidepressants (below co-payment level) were not recorded by the PBS system before 2012. The PBS dataset only provides information on dispensing not the actual use of antidepressants. Furthermore, dietary intake was only assessed at follow-up; therefore, we were unable to adjust for dietary change during follow-up. There may also be an under or over estimate of energy intake due to the use of FFQ and the inherent issues surrounding recall. Finally, the sample power may be limited for the analyses of TCA and other antidepressants.

Antidepressants are widely used, representing the most prescribed drug class in the USA [22]; in Australia 11.6% of the country's population is on antidepressants [23]. Antidepressant-related weight gain is an outcome of public health relevance, as it may contribute to increased rates of obesity. Here we provide evidence that antidepressant use potentiates weight gain, especially among those with unhealthy lifestyles, resulting in body weight that is higher than that associated solely with those same lifestyle factors, in the absence of antidepressants. As a matter of public health relevance, SSRI use should be accompanied by pro-active efforts to avoid weight gain.

We suggest that reducing Western diet consumption, increasing physical activity and smoking cessation may mitigate antidepressant-related weight gain. General practitioners should encourage their patients adopt healthy lifestyle while treating depression with antidepressants or cognitive behaviour therapy.

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Conflicts of interest: We declare that we have no conflicts of interest.

Author contributions: ZS contributed to the conception, analysis, and interpretation of data; drafting of the report; and have given approval of the final version for publication. EA, AWT, TKG, KP, SA, MLW and JL contributed to analysis and interpretation of the data, commented on the report, revising the manuscript and approving the final version for publication.

Availability of data and material

Data from the North West Adelaide Healthy Study (NWAHS) were accessed from a third party. The authors confirm that for approved reasons, some access restrictions apply to the data underlying the findings. To gain access to the data for this manuscript, ethics approval was sought and granted. Enquiries regarding requests for the NWAHS data can be directed to Prof Robert Adams, Principal Investigator (Clinical) (robert.adams@adelaide.edu.au).

Figure legends

Supporting Information **Figures**

Figure S1: Factor loadings of dietary patterns

Figure S2: Interaction between any antidepressant use and age in relation to weight gain.

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Table 1 Sample characteristic by sex *

	Male	Female	Total	*P* value
n (%)	1095 (46.9)	1239 (53.1)	2334	
Age (years)	54.0 (14.4)	54.3 (13.8)	54.1 (14.1)	0.648
Baseline weight (kg)	87.2 (15.3)	73.5 (16.1)	79.9 (17.2)	<0.001
Follow-up weight (kg)	87.9 (16.0)	74.0 (16.2)	80.5 (17.5)	<0.001
Annual weight gain (kg)	0.17 (1.35)	0.12 (1.46)	0.14 (1.41)	0.449
Baseline BMI status				
Normal	21.9	34.5	28.6	<0.001
Overweight	48.9	34.2	41.1	
Obese	29.2	31.2	30.3	
Baseline income ($)				
<20000	196 (17.9)	332 (26.9)	528	
20000-60000	529 (48.4)	543 (44.0)	1072	
>60000	338 (31.0)	308 (24.9)	646	
Not stated	29 (2.7)	52 (4.2)	81	<0.001
Baseline smoking status				
Non smoker	444 (40.7)	642 (52.0)	1086	
Current or ex-smoker	647 (59.3)	593 (48.0)	1240	<0.001
Baseline physical activity				
Sedentary	252 (25.9)	345 (30.4)	597	
Low exercise level	323 (33.2)	448 (39.5)	771	
Moderate exercise level	291 (29.9)	285 (25.1)	576	
High exercise level	106 (10.9)	56 (4.9)	162	<0.001
Depression (baseline)				
No depressive symptoms	995 (91.3)	1043 (85.4)	2038	
Mild depression	61 (5.6)	122 (10.0)	183	
Moderate to severe depression	34 (3.1)	56 (4.6)	90	<0.001
Depression (follow-up)				
No depressive symptoms	907 (85.6)	958 (79.6)	1865	
Mild depression	101 (9.5)	151 (12.5)	252	
Moderate to severe depression	52 (4.9)	95 (7.9)	147	<0.001
Any antidepressant †	0.4 (1.7)	0.9 (2.5)	0.7 (2.2)	<0.001

TCAs †	0.1 (0.6)	0.2 (1.3)	0.1 (1.0)	<0.001
SSRIs †	0.2 (1.3)	0.4 (1.6)	0.3 (1.4)	0.019
Other antidepressant †	0.1 (0.8)	0.3 (1.5)	0.2 (1.2)	<0.001

* values are n (%) or mean (SD)

† Annual number of prescriptions

Table 2 Association (β 95%CI) between antidepressant use and annual weight gain

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
Any antidepressant				
n	1934	188	212	
Baseline weight (kg), mean (SD)	80.0 (17.0)	77.1 (16.5)	81.3 (19.1)	
Follow-up weight (kg), mean (SD)	80.6 (17.3)	78.0 (17.2)	82.5 (19.6)	
Annual weight change (kg), mean (SD)	0.12(1.32)	0.18(1.54)	0.28(1.99)	
Model 1 *	Ref	0.15(-0.06-0.36)	0.22(0.02-0.42)	0.022
Model 2 †	Ref	0.18(-0.04-0.40)	0.25(0.04-0.46)	0.009
Model 3 ‡	Ref	0.11(-0.11-0.34)	0.22(0.00-0.44)	0.044
SSRIs				
n	2109	114	111	
Baseline weight (kg), mean (SD)	79.8 (17.0)	79.7 (18.2)	82.2 (19.1)	
Follow-up weight (kg), mean (SD)	80.3 (17.3)	81.2 (18.0)	84.9 (21.2)	
Annual weight change (kg), mean (SD)	0.11(1.33)	0.38(2.11)	0.61(1.89)	
Model 1 *	Ref	**0.30(0.04-0.57)**	**0.53(0.27-0.80)**	**<0.001**
Model 2 †	Ref	**0.30(0.03-0.58)**	**0.58(0.30-0.85)**	**<0.001**
Model 3 ‡	Ref	**0.30(0.01-0.58)**	**0.48(0.20-0.76)**	**<0.001**
TCAs				
n	2212	79	43	
Baseline weight (kg), mean (SD)	80.1 (17.2)	76.3 (17.8)	77.3 (15.9)	
Follow-up weight (kg), mean (SD)	80.8 (17.5)	75.5 (17.3)	77.3 (16.4)	
Annual weight change	0.16(1.40)	-0.13(1.61)	-0.01(1.32)	

(kg), mean (SD)				
Model 1 *	Ref	-0.12(-0.44-0.19)	0.06(-0.36-0.49)	0.717
Model 2 †	Ref	-0.11(-0.44-0.22)	0.05(-0.39-0.50)	0.704
Model 3 ‡	Ref	0.02(-0.31-0.36)	0.03(-0.46-0.52)	0.908
Other antidepressants				
n	2210	57	67	
Baseline weight (kg), mean (SD)	79.8 (17.0)	80.0 (18.7)	82.9 (20.5)	
Follow-up weight (kg), mean (SD)	80.4 (17.4)	81.3 (17.6)	83.4 (21.2)	
Annual weight change (kg), mean (SD)	0.14(1.37)	0.35(1.88)	0.12(2.08)	
Model 1 *	Ref	0.23(-0.13-0.60)	-0.04(-0.38-0.29)	0.844
Model 2 †	Ref	0.32(-0.05-0.70)	-0.01(-0.36-0.35)	0.505
Model 3 ‡	Ref	0.42(0.03-0.80)	-0.19(-0.56-0.19)	0.926

* Model 1 adjusted for age and gender.

† Model 2 further adjusted for baseline income, smoking, physical activity, follow-up duration.

‡ Model 3 further adjusted for depression status at baseline and follow-up, dietary patterns (continuous).

Table 3 Subgroup analyses of the association between SSRI use and annual weight gain *

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* for interaction
Western dietary pattern				0.026
Low intake	0.00	0.11(-0.29-0.51)	0.14(-0.26-0.54)	
High intake	0.00	**0.46(0.05-0.88)** †	**0.84(0.43-1.24)**	
Prudent dietary pattern				0.635
Low intake	0.00	0.35(-0.07-0.78)	0.38(-0.02-0.78)	
High intake	0.00	0.23(-0.16-0.63)	**0.61(0.20-1.02)**	
Physical activity				0.039
Sedentary	0.00	0.15(-0.34-0.63)	**1.01(0.52-1.50)**	
Low	0.00	0.34(-0.13-0.82)	0.23(-0.27-0.72)	
Moderate/high	0.00	0.33(-0.27-0.94)	0.06(-0.49-0.61)	
Smoking				0.002
Non-smoker	0.00	-0.28(-0.73-0.16)	0.35(-0.03-0.72)	
Current or ex-smoker	0.00	**0.44(0.05-0.84)**	**0.66(0.23-1.10)**	

* Models adjusted for age, gender, income, physical activity, smoking, depression status at baseline and follow-up. Stratifying variables were not adjusted in the corresponding models. Dietary pattern scores are dichotomised as low or high intake. Values represent regression coefficients (95%CI).

† Bold values represent p<0.05.

Supplemental materials

Table S1 Sample characteristic by SSRIs use *

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
n (%)	2109 (90.4)	114 (4.9)	111 (4.8)	
Age (years)	54.0 (14.3)	55.0 (11.6)	55.4 (12.6)	0.4818
Baseline weight (kg)	79.8 (17.0)	79.7 (18.2)	82.2 (19.1)	0.3717
Follow-up weight (kg)	80.3 (17.3)	81.2 (18.0)	84.9 (21.2)	0.0245
Annual weight gain (kg)	0.1 (1.3)	0.4 (2.1)	0.6 (1.9)	0.0002
Income ($)				
<20000	451 (21.5)	36 (31.6)	41 (36.9)	
20000-60000	981 (46.7)	45 (39.5)	46 (41.4)	
>60000	599 (28.5)	27 (23.7)	20 (18.0)	
Not stated	71 (3.4)	6 (5.3)	4 (3.6)	0.0008
Smoking status				
Non smoker	994 (47.3)	38 (33.3)	54 (48.6)	
Current or ex-smoker	1107 (52.7)	76 (66.7)	57 (51.4)	0.0131
Physical activity				
Sedentary	519 (27.3)	39 (37.1)	39 (37.9)	
Low exercise level	696 (36.7)	38 (36.2)	37 (35.9)	
Moderate exercise level	536 (28.2)	17 (16.2)	23 (22.3)	
High exercise level	147 (7.7)	11 (10.5)	4 (3.9)	0.0130
Depression (baseline)				
No depressive symptoms	1897 (90.7)	70 (63.6)	71 (65.1)	
Mild depression	138 (6.6)	19 (17.3)	26 (23.9)	
Moderate to severe depression	57 (2.7)	21 (19.1)	12 (11.0)	0.0000
Depression (follow-up)				
No depressive symptoms	1745 (85.3)	60 (53.6)	60 (56.1)	
Mild depression	196 (9.6)	27 (24.1)	29 (27.1)	
Moderate to severe depression	104 (5.1)	25 (22.3)	18 (16.8)	0.0000
Any antidepressant †	0.3 (1.5)	1.7 (2.7)	6.5 (3.2)	0.0000
TCAs †	0.1 (1.0)	0.3 (1.6)	0.1 (0.5)	0.0996

SSRIs †	0.0 (0.0)	0.8 (0.5)	5.9 (3.1)	0.0000
Other antidepressant †	0.2 (1.1)	0.6 (2.1)	0.4 (1.3)	0.0001

* Values are n (%) or mean (SD)

† Annual number of prescriptions

Table S2 Intake of macronutrients, dietary patterns and lifestyle factors by antidepressants use

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
Energy intake (kJ/d) *	8,628.2(62.3)	8,697.3(201.6)	9,160.1(189.4)	0.029
Fat (g/d) *	87.3(0.7)	87.3(2.3)	92.6(2.2)	0.064
Protein (g/d) *	94.8(0.7)	94.8(2.4)	98.6(2.3)	0.290
Carbohydrate (g/d) *	209.5(2.3)	214.0(7.3)	225.3(6.8)	0.085
Prudent pattern score *	0.02(0.02)	0.08(0.07)	-0.12(0.07)	0.103
Western pattern score *	-0.03(0.02)	-0.04(0.07)	0.14(0.06)	0.037
Sedentary (%)	27.0	34.7	34.5	0.013
Smoking status (%)				
Non-smoker	47.7	36.4	46.2	0.003
Ex-smoker	36.7	48.1	32.6	
Current smoker	15.6	15.5	21.2	

* Values are age and gender adjusted mean (SE).

Table S3 Association between antidepressant use and body weight (kg) from mixed linear model *

	Non-user	Low user	High user	*P* value
Any antidepressant	Ref	-0.32(-2.81-2.16)	**4.40(1.97-6.83)**	0.002
TCAs	Ref	-2.81(-6.56-0.94)	0.87(-4.52-6.25)	0.571
SSRIs	Ref	1.45(-1.66-4.56)	**4.20(1.06-7.35)**	0.007
Other	Ref	2.88(-1.43-7.18)	**7.14(3.05-11.23)**	<0.001

* Values represent regression coefficients (95%CI). Results are from mixed linear models adjusted for age, sex, income, depression, smoking, physical activity, dietary patterns (follow-up). In the model, age, income, depression and smoking were treated as time-variant variables.

Figure S1 Factor loadings of dietary patterns

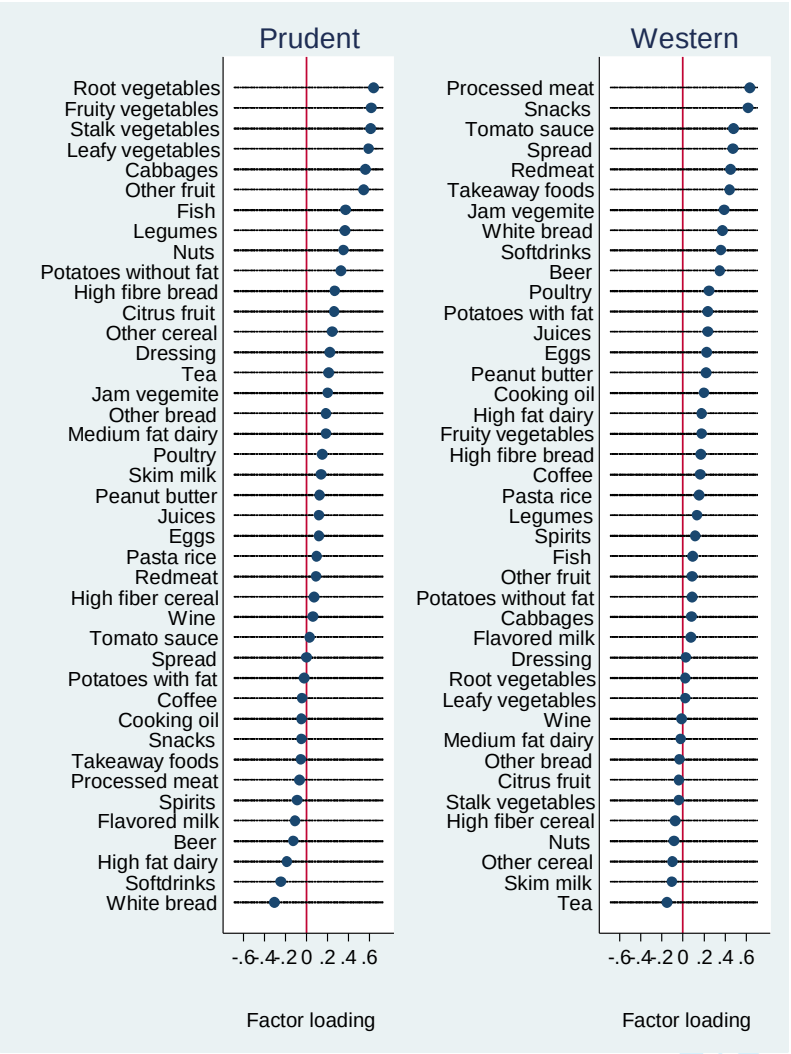
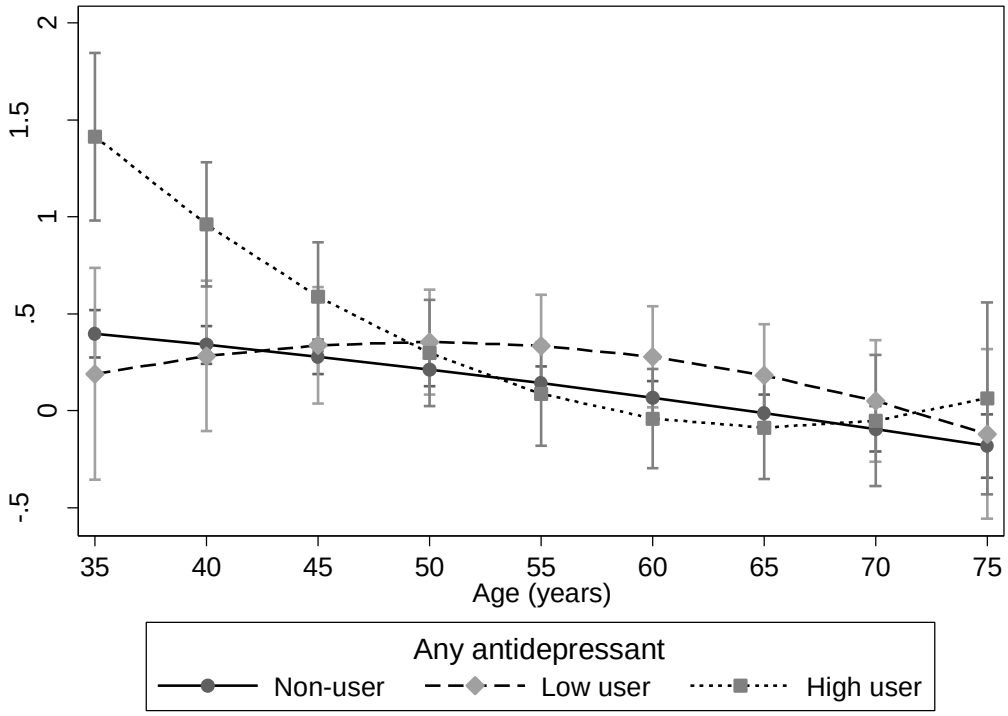


Figure S2 Interaction between any antidepressant use and age in relation to weight gain



Values adjusted for covariates included in model 3 of Table 3.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Paragraphs 1-3, page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Paragraph 4, page5
Methods			
Study design	4	Present key elements of study design early in the paper	Paragraph 1, page6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Paragraph 1-2, page6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Cohort study: Paragraph 1 Page 6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Paragraphs 2-5, page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Paragraphs 2-5, Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	Paragraphs 2-5, Page 6-8
Study size	10	Explain how the study size was arrived at	Paragraph 1, Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Paragraphs 2-5, Page 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Paragraphs 6-7, Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	Paragraph 6, Page 8
		(*c*) Explain how missing data were addressed	Page 6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Paragraph 1 (external

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	linkage)
		(*e*) Describe any sensitivity analyses	Paragraph 6, page 8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods section: Paragraph 1, page 10
		(b) Give reasons for non-participation at each stage	Methods section: Paragraph 1 + cohort profile is referenced (Ref 16)
		(c) Consider use of a flow diagram	N/A- prior publication is referenced (Ref 16).
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results: Paragraph 1 & Table 1 & S1 Tables
		(b) Indicate number of participants with missing data for each variable of interest	Methods section: Paragraph 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Methods section: Paragraph 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1; Methods section: Paragraph 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2 & 3; Paragraph 3, Page 10
		(*b*) Report category boundaries when continuous variables were categorized	Methods section Paragraph 3,4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results Paragraphs 4-5; S3 Tables, S2 Figure
Discussion			
Key results	18	Summarise key results with reference to study objectives	Paragraph 1, page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Paragraphs 5, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Paragraphs 2-6, Page 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Paragraphs 6, page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

BMJ Open

SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up study

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Keywords:	Antidepressant, cohort study, body weight, dietary pattern

SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up study

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Abstract

Objective To examine the association between antidepressant use and weight gain, as well as the interaction with lifestyle factors.

Design Longitudinal study

Setting and participants We used data from 2334 adults from two stages (4.4 years apart) of the North West Adelaide Health Study, including validated diet and lifestyle questionnaires, measured body weight, and linked pharmaceutical prescription data.

Main outcome measures Body weight change

Results 188 (8.1%) participants had a mean annual number of 1-2 antidepressant prescriptions, and 212 (9.1%) had over 2 prescriptions. The mean annual weight gain was 0.12, 0.18 and 0.28 kg in non-users, low (1-2 prescriptions/year) and high (>2 prescriptions/year) antidepressant users, respectively. In multivariable regression models, antidepressant use was positively associated with weight gain: high antidepressant users gained an extra 0.22 (95%CI 0.00-0.44) kg per year. This association was mainly due to selective serotonin reuptake inhibitor (SSRI) use. High SSRI users gained 0.48 (95%CI 0.20-0.76) kg more than non-users. There was no association between tricyclic or other antidepressant use and weight gain. The association between SSRI use and weight gain was stronger among those with high intake of Western diet, greater sedentary activity, and who smoked.

Conclusions SSRIs use was associated with weight gain in the presence unhealthy behaviours including Western diet, sedentarism, and smoking.

Strengths and limitations of this study

- Measurement of body weight by health workers at both time points with a mean of 4.4 years of follow-up;
- Ability to adjust for detailed lifestyle factors and chronic conditions.
- The total number of antidepressant users was relatively small, which limited our power to conduct detailed subgroup analyses.
- Dietary intake was only assessed at follow-up; therefore, we were unable to adjust for dietary change during follow-up.

Keywords Antidepressant, cohort study, body weight, dietary patterns, smoking

1. Introduction

Obesity is a major global health problem almost entirely caused by excess dietary intake and reduced energy expenditure. It is estimated that up to 205 million men and 297 million women over the age of 20 years worldwide are obese [1]. In Australia, the prevalence of obesity class I (BMI 30-34.9 kg/m^2) and obesity class II or III (BMI ≥35 kg/m^2) has respectively doubled and almost tripled since 1980 [2]. Currently it is estimated that 28.3% of Australian adults are obese [3]. One of the most important health consequences of high and rising trends in global obesity prevalence has been the increased risk of developing depression [4]. Indeed, data from the Global Burden of Disease (GBD) study suggest that major depression disorder was the second leading cause accounting for 8.2% of global years lived with disability (YLDs) in 2010 [5].

Several population based cohort studies have consistently shown a positive relationship between antidepressant use and weight gain in countries such as the USA, [6-8] Canada [9] and Australia [10]. This is valuable information for public health policy makers and researchers given that the prevalence of antidepressant use is high in Australia and the USA (5-12%) [7 11], and frequently used by people without depressive or anxiety disorders [12] .

The underlying cause of weight gain due to long-term antidepressant use is poorly understood [13]. In rodents, data from our lab have shown that the combination of chronic stress and short-term antidepressant treatment, followed by high-fat diet results in long-term weight gain that is greater than that caused by stress and high-fat diet, without antidepressant exposure [14]. In our animal paradigm, antidepressant exposure potentiated weight gain caused by obesity promoting diet. Thus, increased antidepressant exposure might be a contributory factor to the obesity pandemic [13]. It is supported by the change of energy intake related to antidepressant use. Data from a

recent cross-sectional population-based study showed that antidepressant use was associated with increased energy intake [15]. Poor diet, sedentary lifestyle, obesity, and depression often cluster together; however, association studies between antidepressant use and obesity have been mostly based on registry data or short-term clinical trials, which limited their capacity to understand interactions [6-10]. Therefore, whether specific antidepressant medications interaction with lifestyle risk factors (poor diet, inadequate physical activity, and smoking) partially explain the development of human obesity long term is still unclear. Identifying the potential mechanism by which antidepressant medication increases the risk of obesity may could help develop targeted strategies for prevention.

This study was designed to specifically examine the association between antidepressant use and weight gain, as well as the interaction with diet and other lifestyle factors (e.g. smoking, sedentary activity) in adults participating in a large-population based prospective cohort study.

2. Methods

2.1 Data source and study participants

This study was approved by the Queen Elizabeth Hospital Human Research Committee and, where appropriate, by the Aboriginal Health Research Ethics Committee, Adelaide, South Australia, Australia. The North West Adelaide Health Study (NWAHS) is an ongoing community based cohort study among adults living in the North West region of Adelaide, South Australia. A detailed description of this cohort has been published elsewhere [16]. The current study analysed data from both stage 2 (2004-2006) and stage 3 (2008-2010) data collections. A total of 2334 participants had information on body weight at both time points.

2.2 Outcome variable-change in body weight

At both stages 2 and 3, height and body weight were measured in light clothing and without shoe by trained clinic staff, to the nearest 0.1 cm and 0.1 kg, respectively. Annual weight gain was calculated by the difference of body weight (kg) between follow-up and baseline divided by the duration of follow-up (in years). Overweight and obesity were defined respectively as 25 $kg/m^2 \geq$ BMI <30 kg/m^2 and BMI ≥ 30 kg/m^2.

2.3 Exposure variable- prospective antidepressant use

Information on medication use (based on prescription) according to the Anatomical Therapeutic Chemical (ATC) Classification was obtained from Medicare Australia (Pharmaceutical Benefits Scheme (PBS)) by confidential unit record linkage for the study period (between baseline and follow-up). Antidepressants (ATC code N06A)

were categorized into three groups: tricyclic antidepressants (TCAs) (ATC code N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB) and other antidepressants (ATC code N06AF, N06AG, and N06AX). For each participant the mean annual number of antidepressant prescriptions, calculated by adding the number of prescriptions and dividing it by the follow-up duration between stages 2 and 3, was categorized into three groups: non-user, low user (1-2 prescriptions/year), or high user (>2 prescriptions/year). Exposure of specific antidepressants was assessed independent of one or more antidepressants.

2.4 Covariates

2.4.1 Baseline and follow-up covariates: The Centre for Epidemiologic Studies Depression Scale (CES-D) was used to measure depressive symptoms. CES-D scores were categorised as no depression (<16), mild depression (16-26) or moderate to severe depression (>26) [17]. Smoking behaviour was determined by self-report and coded as 1) non-smoker, and 2) current or ex-smoker. Self-reported income was recoded into three levels (<$20,000, $20,000-$60,000 or >$60,000 AUD). Physical activity questions from the Australian National Health Surveys were used to classify participants as sedentary, or having low, moderate or high levels of physical activity [18]. Respondents were asked about the amount of walking, moderate and vigorous activity they had undertaken in the past two weeks.

2.4.2 Follow-up only covariates: Dietary intake during the previous 12 months was assessed by the Cancer Council Victoria Dietary Questionnaire for Epidemiological Studies (DQES-V3.1 (FFQ)). The FFQ was previously validated in an Australian population, and is widely used in epidemiological studies. In the analysis, the daily intake of 128 food items were collapsed into 41 food groups as previously described

[19]. Dietary patterns were identified by factor analysis using the principal component method. Varimax rotation was used to assist the interpretability of the factor solution. Based on the Eigenvalue (>1), scree plot and interpretability, two dietary patterns were constructed: 1) the prudent pattern was characterised by high loadings of fruit and vegetable (Supplemental **Figure S1**) and 2) the Western pattern had high intake of processed meat, snacks, and fast food. Scores of each dietary pattern were calculated as the sum of the products of factor loading coefficients and standardized daily intake of the food intake. Dietary pattern scores were dichotomised as low and high (i.e. below or above zero).

2.5 Statistical analyses

Chi square test and ANOVA were used respectively to compare differences between categorical variables, and in continuous variables between groups (gender, categories of antidepressant use). Linear regression models was used to assess the longitudinal association between antidepressant use and annual weight change. Three models were employed: model 1 was adjusted for age and gender, model 2 was further adjusted for income, smoking, physical activity, and follow-up duration, and model 3 was further adjusted for depression status at baseline and follow-up, and dietary patterns (continuous). Participants with missing information of depression were excluded in the corresponding analyses.

As the association between antidepressant use and weight gain was mainly due to SSRI, we further looked at the interaction between SSRI use and lifestyle factors. Multiplicative interaction between SSRI use, lifestyle factors (categorical variables of dietary patterns (low or high), smoking (non-smoker, current or ex-smoker) and

physical activity (sedentary, low, moderate/high)) was conducted by inputting the product terms of these variables and antidepressant use in the regression models. The analysis was subsequently stratified for the lifestyle factors. The interaction between antidepressant use and age (continuous) was graphically represented using the *marginsplot* command in STATA 14 (Stata Corporation, College Station, TX, USA).

Sensitivity analyses were conducted using mixed linear modelling to assess the association between antidepressant use and body weight (baseline and follow-up adjusted for age, income, depression, and smoking status as time-varying variables, while considering antidepressant use, physical activity, dietary patterns, and gender as time-invariant variables. We also assessed the association (incident rate ratio) between antidepressant use and five percent weight gain over five years using Poisson regression with robust variance.

All analyses were performed using STATA 14 (Stata Corporation), and statistical significance was set at $P<0.05$ (two sided).

3. Results

The mean age of the sample was 54.1 (SD 14.1) years (**Table 1**). The mean duration of follow-up was 4.4 (SD 0.4) years. Women had a higher prevalence of depression and a higher mean level of antidepressant use than men. In the sample, 188 (8.1%) and 212 (9.1%) participants had a mean annual number of 1-2, and more than 2 antidepressant prescriptions, respectively. Information on antidepressant usage was based on prescription information; out of 400 antidepressant users, 225 (56.3%) were SSRI users, and in high SSRI users the mean annual number of SSRI prescriptions was 5.9 (SD 3.1) (Supplemental **Table S1**). The mean annual weight gain was 0.12, 0.18 and 0.28 kg in non-users, low and high antidepressant users, respectively.

Compared with non-users, high antidepressant users had higher energy intake (9160 vs 8628 kJ/day) and higher Western dietary pattern scores after adjusting for age and gender (Supplemental **Table S2**).

In multivariable regression models adjusted for age, gender, income, smoking, physical activity, follow-up duration, and dietary patterns, antidepressant use was positively associated with weight gain. High users gained 0.22 (95%CI 0.00-0.44) kg per year when compared with non-users, and SSRI use was related to weight gain (**Table 2**). In the fully adjusted model, high SSRI users gained 0.48 (95%CI 0.20-0.76) kg more than non-users. No association was found between TCA and other antidepressant use and weight gain.

In relation to annual weight gain, significant interactions were found between SSRI use and three lifestyle factors: Western dietary pattern, smoking, and sedentary activity (**Table 3**). The association between SSRI use and weight gain was mainly seen among those with unhealthy lifestyle, and a strong dose response relationship

between SSRI use and weight gain was observed among those with high intake of Western diet: the regression coefficients were 0.00, 0.46 (95%CI 0.05-0.88), and 0.84 (95%CI 0.43-1.24) kg for non-users, low users and high users, respectively. This association was not seen in those with low intake of Western diet. No significant interaction between SSRI use and the prudent dietary pattern was found. Among those with sedentary lifestyles, high SSRI use was associated with 1.01 (95%CI 0.52-1.50) kg higher weight gain per year than non-users. A consistent positive association between SSRI use and weight gain was only observed among smokers: low and high SSRI use was respectively associated with 0.44 (95%CI 0.05-0.84) and 0.66 (95%CI 0.23-1.10) kg higher weight gain per year than non-users.

There was a significant interaction between antidepressant use and age in relation to weight gain (Supplemental **Figure S2**). The positive association between high antidepressant use and weight gain was mainly seen among those aged below 50 years.

In the multivariable mixed regression model adjusted for time-varying depression status, smoking, age, and income as well as time-invariant dietary patterns, physical activity, and gender, antidepressant use was associated with body weight (baseline and follow-up)(Supplemental **Table S3**). Compared with non-use, high use was associated with an extra body weight of 4.40 kg (any antidepressant, $P = 0.002$), 4.20 kg (SSRI, $P = 0.007$) and 7.14 kg (other antidepressant, $P < 0.001$), respectively. TCA use was not associated with body weight. No interaction between antidepressant use and gender was found (data not shown).

Overall, 27.2% of the participants had weight gain above 5% over five years. In fully adjusted model, the incident rate ratio (IRR) for 5% weight gain were 1.00, 1.09 (95%CI 0.83-1.44) and 1.37 (95%CI 1.10-1.70) for non-users, low users and high

users of antidepressant, respectively. A dose response association between SSRI use and 5% weight gain was found in fully adjusted model: IRRs were 1.00, 1.37 (95%CI 1.03-1.81) and 1.43 (95%CI 1.10-1.86) (p trend <0.001) for non-users, low users and high users of SSRI, respectively (data not shown).

4. **Discussion**

In this prospective study, we found that antidepressant use was positively associated with weight gain, which was influenced by significant interactions between SSRI use, age and unhealthy lifestyle factors, including western dietary pattern, sedentary activity and smoking.

The mean annual weight gain among antidepressant users during this 4.4-year study was around 0.2 kg, which is similar to those reported in the literature for shorter studies [6 7 9 10 20]. However, in those previous population studies, lifestyle factors were either lacking or treated as confounding factors [6 7 9 10 20]. None of those studies had been adjusted for dietary intake, an important factor for weight gain.

Only one previous study assessed differences in energy intake and physical activity between antidepressant users and non-users, employing data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES). It showed that, after adjusting for potential confounding factors, antidepressant users had an extra 215 kcal/day of energy intake and were 77% more likely to use a computer for ≥2 hour/day than non-users [15]. The authors hypothesized that increased energy intake and sedentary activity could contribute to weight gain associated with antidepressant use. In the present study we also found a significant difference in energy intake between high antidepressant users and non-users. After adjusting for age and gender, high antidepressant users had a higher energy intake than non-users (9160 *vs* 8628 kJ/day).

Furthermore, high antidepressant users had higher Western dietary pattern scores than non-users (0.14 *vs* -0.03). To the best of our knowledge, this is the first study that systematically tested the interactions between antidepressant use and modifiable lifestyle factors. A significant positive dose response association between antidepressant use and weight gain was found in individuals with high intake but not in those with low intake of Western diet. Clustering of unhealthy behaviours and chronic diseases, including depression, may partly explain the interaction between unhealthy lifestyle and weight gain among those using antidepressant.

The interaction between antidepressant use and smoking in relation to weight gain was consistent with that reported by Arterburn *et al.* who found that bupropion-treated smokers gained an extra 14.2 lbs compared to fluoxetine-treated non-smokers during a two-year follow-up study [8]. We observed an intriguing interaction between antidepressant use and age in relation to weight gain, which may be related to the fact that younger people are more likely to eat a Western diet. In our sample, age was inversely associated with Western dietary pattern scores (data not shown).

The lack of association between TCA use and weight gain was also reported in the Netherlands Study of Depression and Anxiety as well as the Rotterdam Study [20 21]. However, previous studies have reported an association between TCA use and weight gain [6 13]. Our null association between TCA use and weight gain may be due to the fact that age was positively associated with TCA use ($P<0.001$). The mean age was respectively 53.6, 62.2 and 65.6 years among non-users, low and high users of TCA (data not shown). The SSRI fluoxetine entered medical use in 1986; TCAs were the gold standard for depression treatment before SSRIs became popular. It is likely that older patients started their treatment with TCA and those that were treated with and responded to TCAs for many years before SSRIs became available may have

been reluctant to be switched to SSRIs. However, there was no significant age difference between SSRIs users and non-users. Another explanation could be that doctors may be more likely to prescribe SSRIs to people who are worried about weight gain as TCA use has been linked to weight gain in clinical trials.

The strengths of this study include: 1) measurement of body weight by health workers at both time points with a mean of 4.4 years of follow-up; 2) ability to adjust for detailed lifestyle factors and chronic conditions. The main limitation of the study compared to other registry-based studies was that the total number of antidepressant users was relatively small, which limited our power to conduct detailed subgroup analyses. The effect size of the antidepressant use on weight gain may be under estimated due to the fact that some of the low cost antidepressants (below co-payment level) were not recorded by the PBS system before 2012. The PBS dataset only provides information on dispensing not the actual use of antidepressants. Furthermore, dietary intake was only assessed at follow-up; therefore, we were unable to adjust for dietary change during follow-up. There may also be an under or over estimate of energy intake due to the use of FFQ and the inherent issues surrounding recall. Finally, the sample power may be limited for the analyses of TCA and other antidepressants.

Antidepressants are widely used, representing the most prescribed drug class in the USA [22]; in Australia 11.6% of the country's population is on antidepressants [23]. Antidepressant-related weight gain is an outcome of public health relevance, as it may contribute to increased rates of obesity. Here we provide evidence that antidepressant use was associated with weight gain, especially among those with unhealthy lifestyles, resulting in body weight that is higher than that associated solely with those same lifestyle factors, in the absence of antidepressants. As a matter of public health relevance, SSRI use should be accompanied by pro-active efforts to avoid weight gain.

We suggest that reducing Western diet consumption, increasing physical activity and smoking cessation may mitigate antidepressant-related weight gain. General practitioners should encourage their patients adopt healthy lifestyle while treating depression with antidepressants or cognitive behaviour therapy.

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Conflicts of interest: We declare that we have no conflicts of interest.

Author contributions: ZS contributed to the conception, analysis, and interpretation of data; drafting of the report; and have given approval of the final version for publication. EA, AWT, TKG, KP, SA, MLW and JL contributed to analysis and interpretation of the data, commented on the report, revising the manuscript and approving the final version for publication.

Availability of data and material

Data from the North West Adelaide Healthy Study (NWAHS) were accessed from a third party. The authors confirm that for approved reasons, some access restrictions apply to the data underlying the findings. To gain access to the data for this manuscript, ethics approval was sought and granted. Enquiries regarding requests for the NWAHS data can be directed to Prof Robert Adams, Principal Investigator (Clinical) (robert.adams@adelaide.edu.au).

Figure legends

Supporting Information **Figures**

Figure S1: Factor loadings of dietary patterns

Figure S2: Interaction between any antidepressant use and age in relation to weight gain.

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Table 1 Sample characteristic by sex *

	Male	Female	Total	*P* value
n (%)	1095 (46.9)	1239 (53.1)	2334	
Age (years)	54.0 (14.4)	54.3 (13.8)	54.1 (14.1)	0.648
Baseline weight (kg)	87.2 (15.3)	73.5 (16.1)	79.9 (17.2)	<0.001
Follow-up weight (kg)	87.9 (16.0)	74.0 (16.2)	80.5 (17.5)	<0.001
Annual weight gain (kg)	0.17 (1.35)	0.12 (1.46)	0.14 (1.41)	0.449
Baseline BMI status				
Normal	21.9	34.5	28.6	<0.001
Overweight	48.9	34.2	41.1	
Obese	29.2	31.2	30.3	
Baseline income ($)				
<20000	196 (17.9)	332 (26.9)	528	
20000-60000	529 (48.4)	543 (44.0)	1072	
>60000	338 (31.0)	308 (24.9)	646	
Not stated	29 (2.7)	52 (4.2)	81	<0.001
Baseline smoking status				
Non smoker	444 (40.7)	642 (52.0)	1086	
Current or ex-smoker	647 (59.3)	593 (48.0)	1240	<0.001
Baseline physical activity				
Sedentary	252 (25.9)	345 (30.4)	597	
Low exercise level	323 (33.2)	448 (39.5)	771	
Moderate exercise level	291 (29.9)	285 (25.1)	576	
High exercise level	106 (10.9)	56 (4.9)	162	<0.001
Depression (baseline)				
No depressive symptoms	995 (91.3)	1043 (85.4)	2038	
Mild depression	61 (5.6)	122 (10.0)	183	
Moderate to severe depression	34 (3.1)	56 (4.6)	90	<0.001
Depression (follow-up)				
No depressive symptoms	907 (85.6)	958 (79.6)	1865	
Mild depression	101 (9.5)	151 (12.5)	252	
Moderate to severe depression	52 (4.9)	95 (7.9)	147	<0.001
Any antidepressant †	0.4 (1.7)	0.9 (2.5)	0.7 (2.2)	<0.001

TCAs †	0.1 (0.6)	0.2 (1.3)	0.1 (1.0)	<0.001
SSRIs †	0.2 (1.3)	0.4 (1.6)	0.3 (1.4)	0.019
Other antidepressant †	0.1 (0.8)	0.3 (1.5)	0.2 (1.2)	<0.001

* values are n (%) or mean (SD)

† Annual number of prescriptions

Table 2 Association (β 95%CI) between antidepressant use and annual weight gain

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
Any antidepressant				
n	1934	188	212	
Baseline weight (kg), mean (SD)	80.0 (17.0)	77.1 (16.5)	81.3 (19.1)	
Follow-up weight (kg), mean (SD)	80.6 (17.3)	78.0 (17.2)	82.5 (19.6)	
Annual weight change (kg), mean (SD)	0.12(1.32)	0.18(1.54)	0.28(1.99)	
Model 1 *	Ref	0.15(-0.06-0.36)	0.22(0.02-0.42)	0.022
Model 2 †	Ref	0.18(-0.04-0.40)	0.25(0.04-0.46)	0.009
Model 3 ‡	Ref	0.11(-0.11-0.34)	0.22(0.00-0.44)	0.044
SSRIs				
n	2109	114	111	
Baseline weight (kg), mean (SD)	79.8 (17.0)	79.7 (18.2)	82.2 (19.1)	
Follow-up weight (kg), mean (SD)	80.3 (17.3)	81.2 (18.0)	84.9 (21.2)	
Annual weight change (kg), mean (SD)	0.11(1.33)	0.38(2.11)	0.61(1.89)	
Model 1 *	Ref	**0.30(0.04-0.57)**	**0.53(0.27-0.80)**	**<0.001**
Model 2 †	Ref	**0.30(0.03-0.58)**	**0.58(0.30-0.85)**	**<0.001**
Model 3 ‡	Ref	**0.30(0.01-0.58)**	**0.48(0.20-0.76)**	**<0.001**
TCAs				
n	2212	79	43	
Baseline weight (kg), mean (SD)	80.1 (17.2)	76.3 (17.8)	77.3 (15.9)	
Follow-up weight (kg), mean (SD)	80.8 (17.5)	75.5 (17.3)	77.3 (16.4)	
Annual weight change	0.16(1.40)	-0.13(1.61)	-0.01(1.32)	

(kg), mean (SD)				
Model 1 *	Ref	-0.12(-0.44-0.19)	0.06(-0.36-0.49)	0.717
Model 2 †	Ref	-0.11(-0.44-0.22)	0.05(-0.39-0.50)	0.704
Model 3 ‡	Ref	0.02(-0.31-0.36)	0.03(-0.46-0.52)	0.908
Other antidepressants				
n	2210	57	67	
Baseline weight (kg), mean (SD)	79.8 (17.0)	80.0 (18.7)	82.9 (20.5)	
Follow-up weight (kg), mean (SD)	80.4 (17.4)	81.3 (17.6)	83.4 (21.2)	
Annual weight change (kg), mean (SD)	0.14(1.37)	0.35(1.88)	0.12(2.08)	
Model 1 *	Ref	0.23(-0.13-0.60)	-0.04(-0.38-0.29)	0.844
Model 2 †	Ref	0.32(-0.05-0.70)	-0.01(-0.36-0.35)	0.505
Model 3 ‡	Ref	0.42(0.03-0.80)	-0.19(-0.56-0.19)	0.926

* Model 1 adjusted for age and gender.

† Model 2 further adjusted for baseline income, smoking, physical activity, follow-up duration.

‡ Model 3 further adjusted for depression status at baseline and follow-up, dietary patterns (continuous).

Table 3 Subgroup analyses of the association between SSRI use and annual weight gain *

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* for interaction
Western dietary pattern				0.026
Low intake	0.00	0.11(-0.29-0.51)	0.14(-0.26-0.54)	
High intake	0.00	**0.46(0.05-0.88)** †	**0.84(0.43-1.24)**	
Prudent dietary pattern				0.635
Low intake	0.00	0.35(-0.07-0.78)	0.38(-0.02-0.78)	
High intake	0.00	0.23(-0.16-0.63)	**0.61(0.20-1.02)**	
Physical activity				0.039
Sedentary	0.00	0.15(-0.34-0.63)	**1.01(0.52-1.50)**	
Low	0.00	0.34(-0.13-0.82)	0.23(-0.27-0.72)	
Moderate/high	0.00	0.33(-0.27-0.94)	0.06(-0.49-0.61)	
Smoking				0.002
Non-smoker	0.00	-0.28(-0.73-0.16)	0.35(-0.03-0.72)	
Current or ex-smoker	0.00	**0.44(0.05-0.84)**	**0.66(0.23-1.10)**	

* Models adjusted for age, gender, income, physical activity, smoking, depression status at baseline and follow-up. Stratifying variables were not adjusted in the corresponding models. Dietary pattern scores are dichotomised as low or high intake. Values represent regression coefficients (95%CI).

† Bold values represent p<0.05.

Supplemental materials

Table S1 Sample characteristic by SSRIs use *

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
n (%)	2109 (90.4)	114 (4.9)	111 (4.8)	
Age (years)	54.0 (14.3)	55.0 (11.6)	55.4 (12.6)	0.4818
Baseline weight (kg)	79.8 (17.0)	79.7 (18.2)	82.2 (19.1)	0.3717
Follow-up weight (kg)	80.3 (17.3)	81.2 (18.0)	84.9 (21.2)	0.0245
Annual weight gain (kg)	0.1 (1.3)	0.4 (2.1)	0.6 (1.9)	0.0002
Income ($)				
<20000	451 (21.5)	36 (31.6)	41 (36.9)	
20000-60000	981 (46.7)	45 (39.5)	46 (41.4)	
>60000	599 (28.5)	27 (23.7)	20 (18.0)	
Not stated	71 (3.4)	6 (5.3)	4 (3.6)	0.0008
Smoking status				
Non smoker	994 (47.3)	38 (33.3)	54 (48.6)	
Current or ex-smoker	1107 (52.7)	76 (66.7)	57 (51.4)	0.0131
Physical activity				
Sedentary	519 (27.3)	39 (37.1)	39 (37.9)	
Low exercise level	696 (36.7)	38 (36.2)	37 (35.9)	
Moderate exercise level	536 (28.2)	17 (16.2)	23 (22.3)	
High exercise level	147 (7.7)	11 (10.5)	4 (3.9)	0.0130
Depression (baseline)				
No depressive symptoms	1897 (90.7)	70 (63.6)	71 (65.1)	
Mild depression	138 (6.6)	19 (17.3)	26 (23.9)	
Moderate to severe depression	57 (2.7)	21 (19.1)	12 (11.0)	0.0000
Depression (follow-up)				
No depressive symptoms	1745 (85.3)	60 (53.6)	60 (56.1)	
Mild depression	196 (9.6)	27 (24.1)	29 (27.1)	
Moderate to severe depression	104 (5.1)	25 (22.3)	18 (16.8)	0.0000
Any antidepressant †	0.3 (1.5)	1.7 (2.7)	6.5 (3.2)	0.0000
TCAs †	0.1 (1.0)	0.3 (1.6)	0.1 (0.5)	0.0996

SSRIs †	0.0 (0.0)	0.8 (0.5)	5.9 (3.1)	0.0000
Other antidepressant †	0.2 (1.1)	0.6 (2.1)	0.4 (1.3)	0.0001

* Values are n (%) or mean (SD)

† Annual number of prescriptions

Table S2 Intake of macronutrients, dietary patterns and lifestyle factors by antidepressants use

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	*P* value
Energy intake (kJ/d) *	8,628.2(62.3)	8,697.3(201.6)	9,160.1(189.4)	0.029
Fat (g/d) *	87.3(0.7)	87.3(2.3)	92.6(2.2)	0.064
Protein (g/d) *	94.8(0.7)	94.8(2.4)	98.6(2.3)	0.290
Carbohydrate (g/d) *	209.5(2.3)	214.0(7.3)	225.3(6.8)	0.085
Prudent pattern score *	0.02(0.02)	0.08(0.07)	-0.12(0.07)	0.103
Western pattern score *	-0.03(0.02)	-0.04(0.07)	0.14(0.06)	0.037
Sedentary (%)	27.0	34.7	34.5	0.013
Smoking status (%)				
Non-smoker	47.7	36.4	46.2	0.003
Ex-smoker	36.7	48.1	32.6	
Current smoker	15.6	15.5	21.2	

* Values are age and gender adjusted mean (SE).

Table S3 Association between antidepressant use and body weight (kg) from mixed linear model *

	Non-user	Low user	High user	*P* value
Any antidepressant	Ref	-0.32(-2.81-2.16)	**4.40(1.97-6.83)**	0.002
TCAs	Ref	-2.81(-6.56-0.94)	0.87(-4.52-6.25)	0.571
SSRIs	Ref	1.45(-1.66-4.56)	**4.20(1.06-7.35)**	0.007
Other	Ref	2.88(-1.43-7.18)	**7.14(3.05-11.23)**	<0.001

* Values represent regression coefficients (95%CI). Results are from mixed linear models adjusted for age, sex, income, depression, smoking, physical activity, dietary patterns (follow-up). In the model, age, income, depression and smoking were treated as time-variant variables.

Figure S1 Factor loadings of dietary patterns

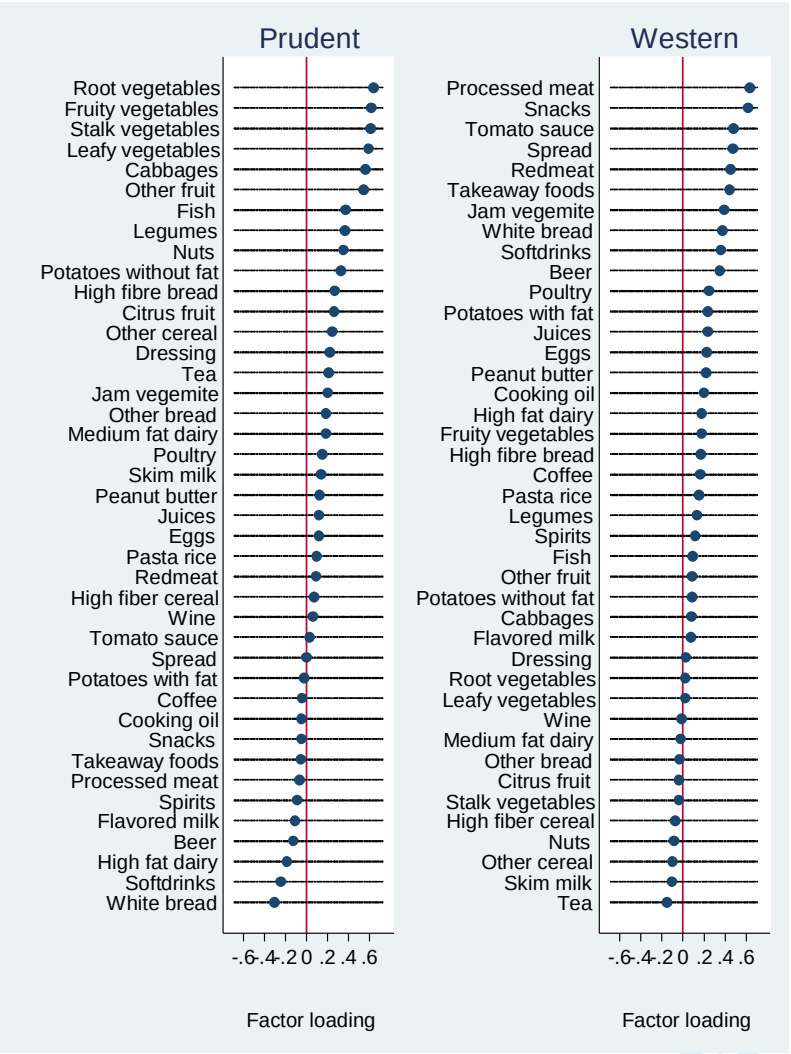
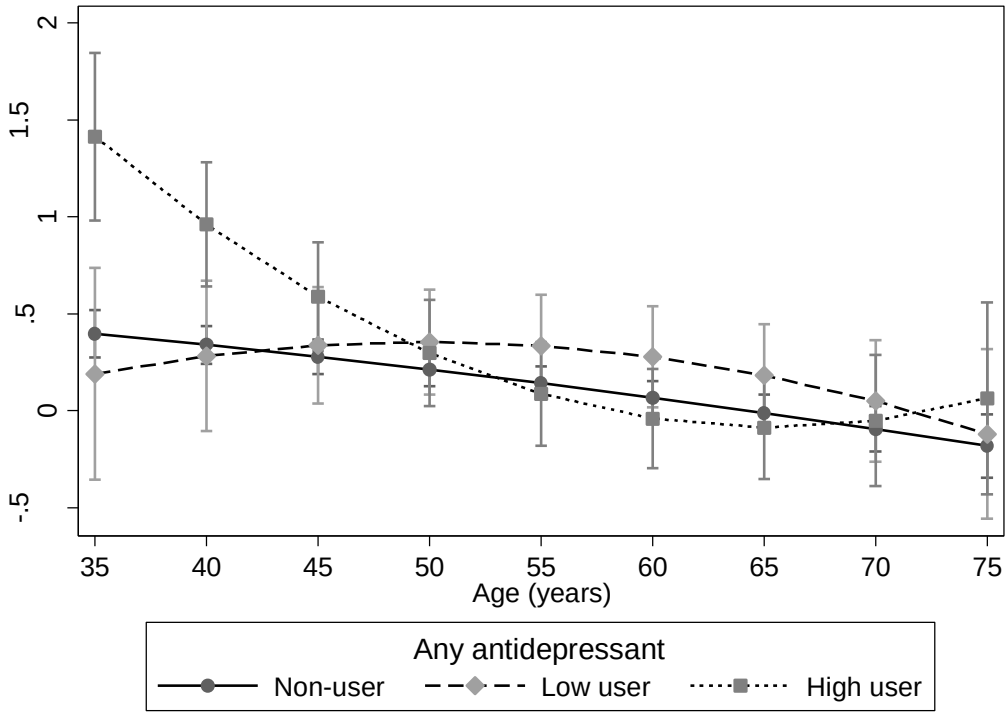


Figure S2 Interaction between any antidepressant use and age in relation to weight gain



Values adjusted for covariates included in model 3 of Table 3.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Paragraphs 1-3, page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Paragraph 4, page5
Methods			
Study design	4	Present key elements of study design early in the paper	Paragraph 1, page6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Paragraph 1-2, page6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Cohort study: Paragraph 1 Page 6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Paragraphs 2-5, page 6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Paragraphs 2-5, Page 6-7
Bias	9	Describe any efforts to address potential sources of bias	Paragraphs 2-5, Page 6-8
Study size	10	Explain how the study size was arrived at	Paragraph 1, Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Paragraphs 2-5, Page 6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Paragraphs 6-7, Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	Paragraph 6, Page 8
		(*c*) Explain how missing data were addressed	Page 6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Paragraph 1 (external

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	linkage)
		(*e*) Describe any sensitivity analyses	Paragraph 6, page 8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods section: Paragraph 1, page 10
		(b) Give reasons for non-participation at each stage	Methods section: Paragraph 1 + cohort profile is referenced (Ref 16)
		(c) Consider use of a flow diagram	N/A- prior publication is referenced (Ref 16).
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Results: Paragraph 1 & Table 1 & S1 Tables
		(b) Indicate number of participants with missing data for each variable of interest	Methods section: Paragraph 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Methods section: Paragraph 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 1; Methods section: Paragraph 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2 & 3; Paragraph 3, Page 10
		(*b*) Report category boundaries when continuous variables were categorized	Methods section Paragraph 3,4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results Paragraphs 4-5; S3 Tables, S2 Figure
Discussion			
Key results	18	Summarise key results with reference to study objectives	Paragraph 1, page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Paragraphs 5, page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Paragraphs 2-6, Page 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Paragraphs 6, page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A