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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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Complete List of Authors:	Shi, Zumin; The University of Adelaide, Discipline of Medicine Atlantis, Evan; Western Sydney University Taylor, Anne; University of Adelaide, School of Medicine Gill, Tiffany; School of Medicine, The University of Adelaide Price, Kay; University of South Australia, School of Nursing and Midwifery Appleton, Sarah L. ; University of Adelaide, School of Medicine Wong, Ma-Li; South Australia Health and Medical Research Institute (SAHMRI) Licinio, Julio; South Australia Health and Medical Research Institute (SAHMRI)
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3 **SSRI antidepressant use potentiates weight gain in the context of unhealthy**  
4 **lifestyles: Results from a four-year Australian follow-up study**  
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7 Zumin Shi, MD PhD <sup>1</sup>, Evan Atlantis, PhD <sup>2</sup>, Anne W Taylor, PhD <sup>1</sup>, Tiffany K Gill,  
8  
9 PhD <sup>1</sup>, Kay Price, PhD <sup>3</sup>, Sarah Appleton, PhD <sup>1</sup>, Ma-Li Wong, MD PhD <sup>4</sup>, Julio  
10  
11 Licinio, MD <sup>4</sup>  
12

13  
14 <sup>1</sup> Discipline of Medicine, University of Adelaide, L7 SAHMRI, North Terrace,  
15  
16 Adelaide, Australia

17  
18 <sup>2</sup> University of Western Sydney, Australia

19  
20 <sup>3</sup> University of South Australia, Australia

21  
22 <sup>4</sup> South Australia Health and Medical Research Institute (SAHMRI) and Flinders  
23  
24 University, Australia

25  
26 Email address:

27  
28 Zumin Shi: [Zumin.shi@adelaide.edu.au](mailto:Zumin.shi@adelaide.edu.au)

29  
30 Evan Atlantis: [E.Atlantis@westernsydney.edu.au](mailto:E.Atlantis@westernsydney.edu.au)

31  
32 Anne W Taylor: [anne.taylor@adelaide.edu.au](mailto:anne.taylor@adelaide.edu.au)

33  
34 Tiffany Gill: [tiffany.gill@adelaide.edu.au](mailto:tiffany.gill@adelaide.edu.au)

35  
36 Kay Price: [Kay.Price@unisa.edu.au](mailto:Kay.Price@unisa.edu.au)

37  
38 Sarah Louise Appleton: [sarah.appleton@adelaide.edu.au](mailto:sarah.appleton@adelaide.edu.au)

39  
40 Ma-Li Wong: [mali.wong@sahmri.com](mailto:mali.wong@sahmri.com)

41  
42 Julio Licinio: [Julio.Licinio@sahmri.com](mailto:Julio.Licinio@sahmri.com)  
43  
44

45  
46 **Corresponding Author:** A/Professor Zumin Shi

47  
48 Postal address; Discipline of Medicine, University of Adelaide, Level 7, SAHMRI,  
49  
50 North Terrace, Adelaide, Australia, 5005

51  
52 Phone: +61 8 8313 1188

53  
54 Fax: +61 8 8313 1228

55  
56 Email: [Zumin.shi@adelaide.edu.au](mailto:Zumin.shi@adelaide.edu.au)  
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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 <sup>1</sup>. In Australia, the prevalence of obesity class I (BMI 30-34.9 kg/m<sup>2</sup>) and obesity class II or III (BMI  $\geq 35$  kg/m<sup>2</sup>) has respectively doubled and almost tripled since 1980 <sup>2</sup>. Currently it is estimated that 28.3% of Australian adults are obese <sup>3</sup>. One of the most important health consequences of high and rising trends in global obesity prevalence has been the increased risk of developing depression <sup>4</sup>. 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 <sup>5</sup>.

Several population based cohort studies have consistently shown a positive relationship between antidepressant use and weight gain in countries such as the USA <sup>6-8</sup> Canada <sup>9</sup> and Australia <sup>10</sup>. 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%) <sup>7,11</sup>, and frequently used by people without depressive or anxiety disorders <sup>12</sup>.

The underlying cause of weight gain due to long-term antidepressant use is poorly understood <sup>13</sup>. 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 <sup>14</sup>. 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 <sup>13</sup>. Data from a recent

1  
2 cross-sectional population-based study showed that antidepressant use was associated  
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4 with increased energy intake<sup>15</sup>. Poor diet, sedentary lifestyle, obesity, and depression  
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6 often cluster together; however, association studies between antidepressant use and  
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8 obesity have been mostly based on registry data or short-term clinical trials, which  
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10 limited their capacity to understand interactions<sup>6-10</sup>. Therefore, it is unknown whether  
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12 interactions between antidepressant use and lifestyle factors influence human obesity  
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14 on a long-term, ongoing basis.  
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18 This study was designed to specifically examine the association between  
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20 antidepressant use and weight gain, as well as the interaction with diet and other  
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22 lifestyle factors in adults participating in large-population based prospective cohort  
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24 study.  
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## 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<sup>16</sup>. 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  $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$  and  $\text{BMI} \geq 30 \text{ kg/m}^2$ .

### 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,



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2 and N06AX). For each participant the mean annual number of antidepressant  
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4 prescriptions, calculated by adding the number of prescriptions and dividing it by the  
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6 follow-up duration between stages 2 and 3, was categorized into three groups: non-  
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8 user, low user (1-2 prescriptions/year), or high user (>2 prescriptions/year).  
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## 11 *2.4 Covariates*

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14 *2.4.1 Baseline and follow-up covariates:* The Centre for Epidemiologic Studies  
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16 Depression Scale (CES-D) was used to measure depressive symptoms. CES-D scores  
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18 were categorised as no depression (<16), mild depression (16-26) or moderate to  
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20 severe depression (>26)<sup>17</sup>. Smoking behaviour was determined by self-report and  
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22 coded as non-smoker, ex-smoker or current smoker. Self-reported income was  
23  
24 recoded into three levels (<\$20,000, \$20,000-\$60,000 or >\$60,000 AUD). Physical  
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26 activity questions from the Australian National Health Surveys were used to classify  
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28 participants as sedentary, or having low, moderate or high levels of physical activity  
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36 *2.4.2 Follow-up only covariates* Dietary intake during the previous 12 months was  
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38 assessed by the Cancer Council Victoria Dietary Questionnaire for Epidemiological  
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40 Studies (DQES-V3.1 (FFQ)). The FFQ was previously validated in an Australian  
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42 population, and is widely used in epidemiological studies. In the analysis the daily  
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44 intake of 128 food items were collapsed into 41 food groups as previously described  
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2 vegetable (Supplemental **Figure S1**) and the Western pattern had high intake of  
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4 processed meat, snacks, and fast food.  
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### 9 10 *2.5 Statistical analyses*

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12 Chi square test and ANOVA were used respectively to compare differences between  
13  
14 categorical variables, and in continuous variables between groups. The linear  
15  
16 regression model was used to assess the longitudinal association between  
17  
18 antidepressant use and annual weight change. Three models were employed: model 1  
19  
20 was adjusted for age and gender, model 2 was further adjusted for income, smoking,  
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22 physical activity, and follow-up duration, and model 3 was further adjusted for  
23  
24 depression status at baseline and follow-up, and dietary patterns (continuous).  
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28 Multiplicative interaction between antidepressant use, lifestyle factors (dietary  
29  
30 patterns, smoking and physical activity) and age was conducted by inputting the  
31  
32 product terms of these variables and antidepressant use in the regression models. The  
33  
34 interaction between antidepressant use and age was graphically represented using the  
35  
36 *marginsplot* command in STATA 14 (Stata Corporation, College Station, TX, USA).  
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40 Sensitivity analyses were conducted using mixed linear modelling to assess the  
41  
42 association between antidepressant use and weight status adjusted for depression and  
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44 smoking status as time-varying variables, while considering antidepressant use,  
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46 physical activity, dietary patterns, and gender as time-invariant variables. We also  
47  
48 assessed the association (incident rate ratio) between antidepressant use and five  
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50 percent weight gain over five years using Poisson regression with robust variance.  
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54 All analyses were performed using STATA 14 (Stata Corporation), and statistical  
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56 significance was set at  $P < 0.05$  (two sided).  
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### 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

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2 Western diet: the regression coefficients were 0.00, 0.46 (95%CI 0.05-0.88), and 0.84  
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4 (95%CI 0.43-1.24) kg for non-users, low users and high users, respectively. This  
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6 association was not seen in those with low intake of Western diet. There was a  
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8 significant interaction between antidepressant use and age in relation to weight gain  
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10 (Supplemental **Figure S2**). The positive association between high antidepressant use  
11  
12 and weight gain was mainly seen among those aged below 50 years. Among those  
13  
14 with sedentary lifestyles, high SSRI use was associated with 1.01 (95%CI 0.52-1.50)  
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16 kg higher weight gain per year than non-users. A consistent positive association  
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18 between SSRI use and weight gain was only observed among smokers: low and high  
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20 SSRI use was respectively associated with 0.44 (95%CI 0.05-0.84) and 0.66 (95%CI  
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22 0.23-1.10) kg higher weight gain per year than non-users.  
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28 In the multivariable mixed regression model adjusted for time-varying depression  
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30 status, smoking, age, and income as well as time-invariant dietary patterns, physical  
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32 activity, and gender, antidepressant use was associated with weight status  
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34 (Supplemental **Table S3**). Compared with non-use, high use was associated with an  
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36 extra body weight of 4.40 kg (any antidepressant,  $P= 0.002$ ), 4.20 kg (SSRI,  $P= 0.007$ )  
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38 and 7.14 kg (other antidepressant,  $P< 0.001$ ), respectively. TCA use was not  
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40 associated with body weight. No interaction between antidepressant use and gender  
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42 was found.  
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46 Overall, 27.2% of the participants had weight gain above 5% over five years. In fully  
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48 adjusted model, the incident rate ratio (IRR) for 5% weight gain were 1.00, 1.09  
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50 (95%CI 0.83-1.44) and 1.37 (95%CI 1.10-1.70) for non-users, low users and high  
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52 users of antidepressant, respectively. A dose response association between SSRI use  
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54 and 5% weight gain was found in fully adjusted model: IRRs were 1.00, 1.37 (95%CI  
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2 1.03-1.81) and 1.43 (95%CI 1.10-1.86) (p trend <0.001) for non-users, low users and  
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4 high users of SSRI, respectively.  
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#### 7 **4. Discussion**

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10 In this prospective study, we found that antidepressant use was positively associated  
11 with weight gain, which was influenced by significant interactions between SSRI use,  
12 age and unhealthy lifestyle factors, including western dietary pattern, sedentary  
13 activity and smoking.  
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16 The mean annual weight gain among antidepressant users during this 4.4-year study  
17 was around 0.2 kg, which is similar to those reported in the literature for shorter  
18 studies<sup>6 7 9 10 20</sup>. However, in those previous population studies, lifestyle factors were  
19 either lacking or treated as confounding factors<sup>6 7 9 10</sup>. None of those studies had  
20 adjusted for dietary intake, an important factor for weight gain.  
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23 Only one previous study assessed differences in energy intake and physical activity  
24 between antidepressant users and non-users, employing data from the 2005-2006  
25 National Health and Nutrition Examination Survey (NHANES). It showed that after  
26 adjusting for potential confounding factors, antidepressant users had an extra 215  
27 kcal/day of energy intake and were 77% more likely to use a computer for  $\geq 2$   
28 hour/day than non-users<sup>15</sup>. The authors hypothesized that increased energy intake and  
29 sedentary activity could contribute to weight gain associated with antidepressant use.  
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32 In the present study we also found a significant difference in energy intake between  
33 high antidepressant users and non-users. After adjusting for age and gender, high  
34 antidepressant users had a higher energy intake than non-users (9160 vs 8628 kJ/day).  
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36 Furthermore, high antidepressant users had higher Western dietary pattern scores than  
37 non-users (0.14 vs -0.03). To the best of our knowledge, this is the first study that  
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2 systematically tested the interactions between antidepressant use and modifiable  
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4 lifestyle factors. A significant positive dose response association between  
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6 antidepressant use and weight gain was found in individuals with high intake but not  
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8 in those with low intake of Western diet.  
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11 The interaction between antidepressant use and smoking in relation to weight gain  
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13 was consistent with that reported by Arterburn *et al.* who found that bupropion-treated  
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15 smokers gained an extra 14.2 lbs compared to fluoxetine-treated non-smokers during  
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17 a two-year follow-up study<sup>8</sup>. We observed an intriguing interaction between  
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19 antidepressant use and age in relation to weight gain, which may be related to the fact  
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21 that younger people are more likely to eat a Western diet. In our sample, age was  
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23 inversely associated with Western dietary pattern scores (data not shown).  
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28 The lack of association between TCA use and weight gain was also reported in the  
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30 Netherlands Study of Depression and Anxiety as well as the Rotterdam Study<sup>20,21</sup>.  
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32 However, previous studies have reported an association between TCA use and weight  
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34 gain<sup>6,13</sup>. Our null association between TCA use and weight gain may be due to the  
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36 fact that age was positively associated with TCA use ( $P<0.001$ ). The mean age was  
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38 53.6, 62.2 and 65.6 years among non-users, low and high users of TCA (data not  
39  
40 shown). However, there was no significant age difference between SSRIs users and  
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42 non-users.  
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47 The strengths of this study include: 1) measurement of body weight by health workers  
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49 at both time points with a mean of 4.4 years of follow-up; 2) ability to adjust for  
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51 detailed lifestyle factors and chronic conditions. The main limitation of the study  
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53 compared to other registry-based studies was that the total number of antidepressant  
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55 users was relatively small, which limited our power to conduct detailed subgroup  
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2 analyses. The effect size of the antidepressant use on weight gain may be under  
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4 estimated due to the fact that some of the low cost antidepressants (below co-payment  
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6 level) were not recorded by the PBS system before 2012. Furthermore, dietary intake  
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8 was only assessed at follow-up; therefore, we were unable to adjust for dietary change  
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10 during follow-up.  
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14 Antidepressants are widely used, representing the most prescribed drug class in the  
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16 USA <sup>22</sup>; in Australia 11.6% of the country's population is on antidepressants <sup>23</sup>.  
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18 Antidepressant-related weight gain is an outcome of public health relevance, as it may  
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20 contribute to increased rates of obesity. Here we provide evidence that antidepressant  
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22 use potentiates weight gain, especially among those with unhealthy lifestyles,  
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24 resulting in body weight that is higher than that associated solely with those same  
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26 lifestyle factors, in the absence of antidepressants. As a matter of public health  
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28 relevance, SSRI use ought to be clinically recognized as a risk factor for obesity.  
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30 Therefore, SSRI use should be accompanied by pro-active efforts to avoid weight  
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32 gain. We suggest that reducing Western diet consumption, increasing physical activity  
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34 and smoking cessation may mitigate antidepressant-related weight gain.  
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46  
47 international institutions  
48

49 **Conflicts of interest:** We declare that we have no conflicts of interest.  
50

51 **Author contributions:** ZS contributed to the conception, analysis, and interpretation  
52  
53 of data; drafting of the report; and have given approval of the final version for  
54  
55 publication. EA, AWT, TKG, KP, SA, MLW and JL contributed to analysis and  
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1  
2 interpretation of the data, commented on the report, revising the manuscript and  
3  
4 approving the final version for publication.  
5  
6

### 7 **Availability of data and material**

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9  
10 Data from the North West Adelaide Healthy Study (NWAHS) were accessed from a  
11  
12 third party. The authors confirm that for approved reasons, some access restrictions  
13  
14 apply to the data underlying the findings. To gain access to the data for this  
15  
16 manuscript, ethics approval was sought and granted. Enquiries regarding requests for  
17  
18 the NWAHS data can be directed to Prof Robert Adams, Principal Investigator  
19  
20 (Clinical) (<robert.adams@adelaide.edu.au>).  
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**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.

For peer review only

## References

1. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011;**377**(9765):557-67.
2. Atlantis E, Lange K, Wittert GA. Chronic disease trends due to excess body weight in Australia. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2009;**10**(5):543-53.
3. Australian Bureau of Statistics. 4364.0.55.001 - Australian Health Survey: First Results, 2011-12. , 2012.
4. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010;**67**(3):220-9.
5. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013;**10**(11):e1001547.
6. Kivimaki M, Hamer M, Batty GD, et al. Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetes Care* 2010;**33**(12):2611-6.
7. Blumenthal SR, Castro VM, Clements CC, et al. An electronic health records study of long-term weight gain following antidepressant use. *JAMA Psychiatry* 2014;**71**(8):889-96.
8. Arterburn D, Sofer T, Boudreau DM, et al. Long-Term Weight Change after Initiating Second-Generation Antidepressants. *J Clin Med* 2016;**5**(4).
9. Patten SB, Williams JV, Lavorato DH, et al. Weight gain in relation to major depression and antidepressant medication use. *J Affect Disord* 2011;**134**(1-3):288-93.
10. Paige E, Korda R, Kemp-Casey A, et al. A record linkage study of antidepressant medication use and weight change in Australian adults. *Aust N Z J Psychiatry* 2015;**49**(11):1029-39.
11. Atlantis E, Sullivan T, Sartorius N, et al. Changes in the prevalence of psychological distress and use of antidepressants or anti-anxiety medications

- 1  
2 associated with comorbid chronic diseases in the adult Australian population,  
3 2001-2008. *The Australian and New Zealand journal of psychiatry*  
4 2012;**46**(5):445-56.
- 5  
6  
7 12. Harris MG, Burgess PM, Pirkis J, et al. Correlates of antidepressant and anxiolytic,  
8 hypnotic or sedative medication use in an Australian community sample.  
9 *Australian and New Zealand Journal of Psychiatry* 2011;**45**(3):249-60.
- 10  
11 13. Lee SH, Paz-Filho G, Mastronardi C, et al. Is increased antidepressant exposure a  
12 contributory factor to the obesity pandemic? *Transl Psychiatry* 2016;**6**:e759.
- 13  
14 14. Mastronardi C, Paz-Filho GJ, Valdez E, et al. Long-term body weight outcomes of  
15 antidepressant-environment interactions. *Mol Psychiatry* 2011;**16**(3):265-72.
- 16  
17 15. Jensen-Otsu E, Austin GL. Antidepressant Use is Associated with Increased  
18 Energy Intake and Similar Levels of Physical Activity. *Nutrients*  
19 2015;**7**(11):9662-71.
- 20  
21 16. Grant JF, Taylor AW, Ruffin RE, et al. Cohort Profile: The North West Adelaide  
22 Health Study (NWAHS). *Int J Epidemiol* 2009;**38**(6):1479-86.
- 23  
24 17. Radloff LS. The CES-D scale: A self-report depression scale for research in the  
25 general population. *Applied Psychological Measurement* 1977;**1**:385-401.
- 26  
27 18. Australian Bureau of Statistics, editor. *National Health Survey: users' guide*.  
28 Canberra: ABS, 2003.
- 29  
30 19. Schoenaker DA, Dobson AJ, Soedamah-Muthu SS, et al. Factor analysis is more  
31 appropriate to identify overall dietary patterns associated with diabetes when  
32 compared with Treelet transform analysis. *J Nutr* 2013;**143**(3):392-8.
- 33  
34 20. Gibson-Smith D, Bot M, Milaneschi Y, et al. Major depressive disorder,  
35 antidepressant use, and subsequent 2-year weight change patterns in the  
36 Netherlands Study of Depression and Anxiety. *J Clin Psychiatry*  
37 2016;**77**(2):e144-51.
- 38  
39 21. Noordam R, Aarts N, Tiemeier H, et al. Sex-specific association between  
40 antidepressant use and body weight in a population-based study in older adults.  
41 *J Clin Psychiatry* 2015;**76**(6):e745-51.
- 42  
43 22. IMS Institute for Healthcare Informatics. *The Use of Medicines in the United*  
44 *States: Review of 2011*. Secondary *The Use of Medicines in the United States:*  
45 *Review of 2011* 2012.
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3 23. Mental health services in Australia. Mental health-related prescriptions.

4 Secondary Mental health-related prescriptions.

5 <https://mhsa.aihw.gov.au/resources/prescriptions/>.

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Table 1 Sample characteristic by sex \*

	Male	Female	Total	<i>P</i> value
<i>n</i> (%)	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

TCA <sup>s</sup> †	0.1 (0.6)	0.2 (1.3)	0.1 (1.0)	<0.001
SSRI <sup>s</sup> †	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

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Table 2 Association ( $\beta$  95%CI) between antidepressant use and annual weight gain

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	<i>P</i> value
<b>Any antidepressant</b>				
<i>n</i>	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
<b>SSRIs</b>				
<i>n</i>	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	<b>0.30(0.04-0.57)</b>	<b>0.53(0.27-0.80)</b>	<b>&lt;0.001</b>
Model 2 †	Ref	<b>0.30(0.03-0.58)</b>	<b>0.58(0.30-0.85)</b>	<b>&lt;0.001</b>
Model 3 ‡	Ref	<b>0.30(0.01-0.58)</b>	<b>0.48(0.20-0.76)</b>	<b>&lt;0.001</b>
<b>TCAs</b>				
<i>n</i>	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				
<i>n</i>	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	<i>P</i> for interaction
<b>Western dietary pattern</b>				0.026
Low intake	0.00	0.11(-0.29-0.51)	0.14(-0.26-0.54)	
High intake	0.00	<b>0.46(0.05-0.88) †</b>	<b>0.84(0.43-1.24)</b>	
<b>Prudent dietary pattern</b>				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)	<b>0.61(0.20-1.02)</b>	
<b>Physical activity</b>				0.039
Sedentary	0.00	0.15(-0.34-0.63)	<b>1.01(0.52-1.50)</b>	
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)	
<b>Smoking</b>				0.002
Non-smoker	0.00	-0.28(-0.73-0.16)	0.35(-0.03-0.72)	
Smoker	0.00	<b>0.44(0.05-0.84)</b>	<b>0.66(0.23-1.10)</b>	

\* 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	<i>P</i> value
<i>n</i> (%)	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	<i>P</i> 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	

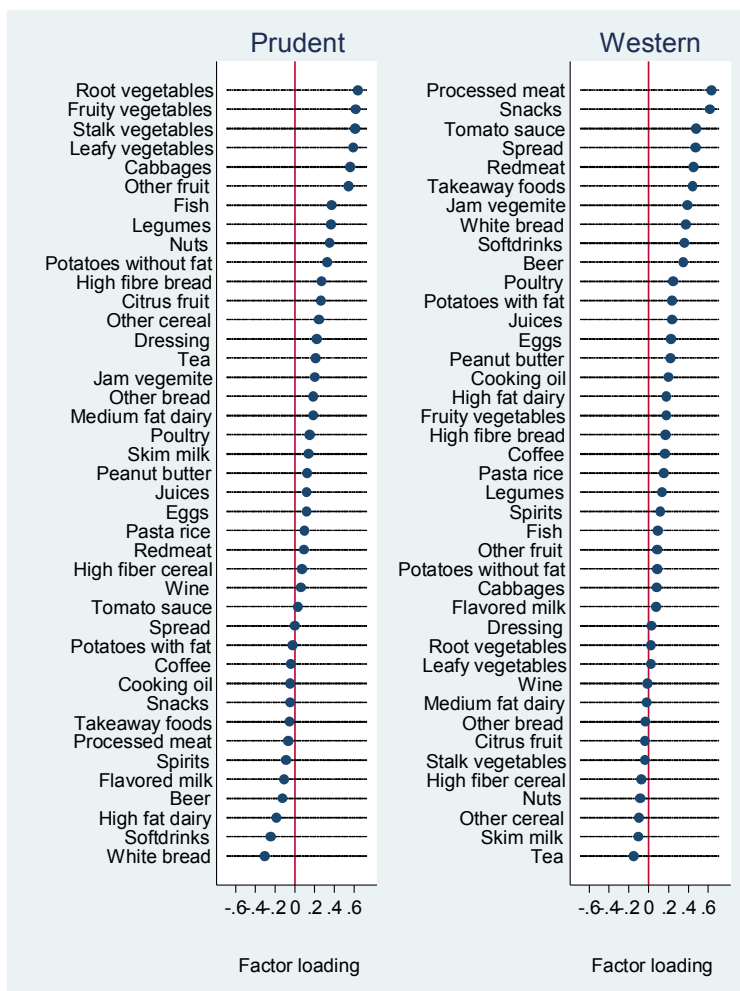
\* Values are age and gender adjusted mean (SE).

**Table S3** Association between antidepressant use and body weight \*

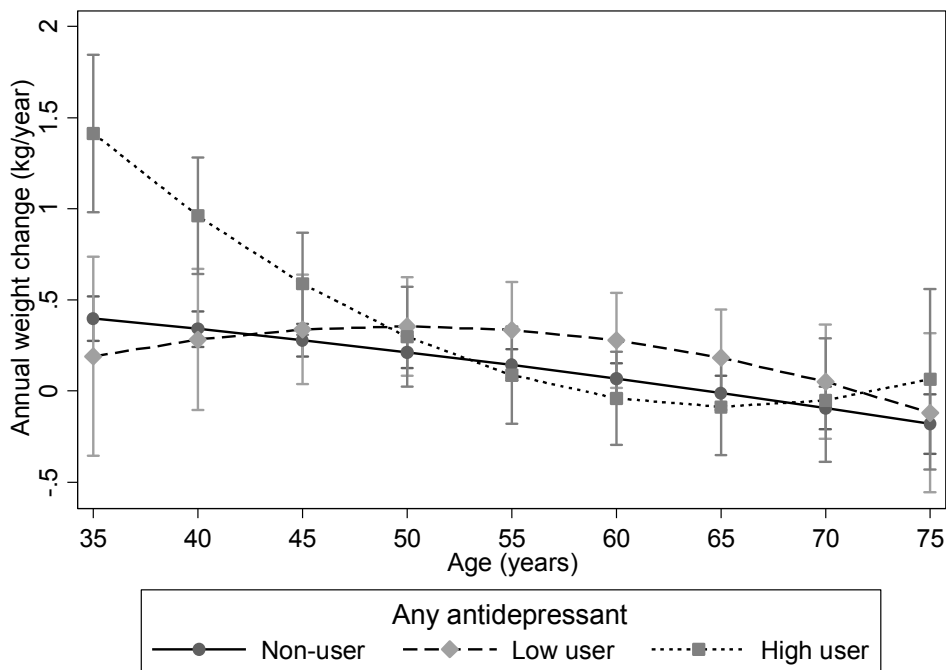
	Non-user	Low user	High user	<i>P</i> value
Any antidepressant	Ref	-0.32(-2.81-2.16)	<b>4.40(1.97-6.83)</b>	0.002
TCAs	Ref	-2.81(-6.56-0.94)	0.87(-4.52-6.25)	0.571
SSRIs	Ref	1.45(-1.66-4.56)	<b>4.20(1.06-7.35)</b>	0.007
Other	Ref	2.88(-1.43-7.18)	<b>7.14(3.05-11.23)</b>	<0.001

\* 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.

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## 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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Cohort study: Paragraph 1
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —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 (b) Give reasons for non-participation at each stage	Methods section: Paragraph 1 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 (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Results: Paragraph 1 & Table 1 & S1 Tables Methods section: Paragraph 1 Methods section: Paragraph 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Table 1; Methods section: Paragraph 1 N/A 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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2 & 3; Paragraph 3 Methods section Paragraph 3,4 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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Paragraph 1



1				
2	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
3				
4	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
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8	Generalisability	21	Discuss the generalisability (external validity) of the study results	Paragraphs 6
9				
10	<b>Other information</b>			
11	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
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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016224.R1
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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Epidemiology, Public health, Nutrition and metabolism, Mental health
Keywords:	Antidepressant, cohort study, body weight, dietary pattern

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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**

Zumin Shi, MD PhD <sup>1</sup>, Evan Atlantis, PhD <sup>2</sup>, Anne W Taylor, PhD <sup>1</sup>, Tiffany K Gill,  
PhD <sup>1</sup>, Kay Price, PhD <sup>3</sup>, Sarah Appleton, PhD <sup>1</sup>, Ma-Li Wong, MD PhD <sup>4</sup>, Julio  
Licinio, MD PhD <sup>4</sup>

<sup>1</sup> Discipline of Medicine, University of Adelaide, L7 SAHMRI, North Terrace,  
Adelaide, Australia

<sup>2</sup> University of Western Sydney, Australia

<sup>3</sup> University of South Australia, Australia

<sup>4</sup> South Australia Health and Medical Research Institute (SAHMRI) and Flinders  
University, Australia

Email address:

Zumin Shi: [Zumin.shi@adelaide.edu.au](mailto:Zumin.shi@adelaide.edu.au)

Evan Atlantis: [E.Atlantis@westernsydney.edu.au](mailto:E.Atlantis@westernsydney.edu.au)

Anne W Taylor: [anne.taylor@adelaide.edu.au](mailto:anne.taylor@adelaide.edu.au)

Tiffany Gill: [tiffany.gill@adelaide.edu.au](mailto:tiffany.gill@adelaide.edu.au)

Kay Price: [Kay.Price@unisa.edu.au](mailto:Kay.Price@unisa.edu.au)

Sarah Louise Appleton: [sarah.appleton@adelaide.edu.au](mailto:sarah.appleton@adelaide.edu.au)

Ma-Li Wong: [mali.wong@sahmri.com](mailto:mali.wong@sahmri.com)

Julio Licinio: [Julio.Licinio@sahmri.com](mailto:Julio.Licinio@sahmri.com)

**Corresponding Author:** A/Professor Zumin Shi

Postal address; Discipline of Medicine, University of Adelaide, Level 7, SAHMRI,  
North Terrace, Adelaide, Australia, 5005

Phone: +61 8 8313 1188

Fax: +61 8 8313 1228

Email: [Zumin.shi@adelaide.edu.au](mailto:Zumin.shi@adelaide.edu.au)

## 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 <sup>1</sup>. In Australia, the prevalence of obesity class I (BMI 30-34.9 kg/m<sup>2</sup>) and obesity class II or III (BMI  $\geq 35$  kg/m<sup>2</sup>) has respectively doubled and almost tripled since 1980 <sup>2</sup>. Currently it is estimated that 28.3% of Australian adults are obese <sup>3</sup>. One of the most important health consequences of high and rising trends in global obesity prevalence has been the increased risk of developing depression <sup>4</sup>. 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 <sup>5</sup>.

Several population based cohort studies have consistently shown a positive relationship between antidepressant use and weight gain in countries such as the USA, <sup>6-8</sup> Canada <sup>9</sup> and Australia <sup>10</sup>. 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%) <sup>7,11</sup>, and frequently used by people without depressive or anxiety disorders <sup>12</sup>.

The underlying cause of weight gain due to long-term antidepressant use is poorly understood <sup>13</sup>. 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 <sup>14</sup>. 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 <sup>13</sup>.

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2 Data from a recent cross-sectional population-based study showed that antidepressant  
3 use was associated with increased energy intake<sup>15</sup>. Poor diet, sedentary lifestyle,  
4 obesity, and depression often cluster together; however, association studies between  
5 antidepressant use and obesity have been mostly based on registry data or short-term  
6 clinical trials, which limited their capacity to understand interactions<sup>6-10</sup>. Therefore, it  
7 is unknown whether interactions between antidepressant use and lifestyle factors  
8 influence human obesity on a long-term, ongoing basis.  
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11 This study was designed to specifically examine the association between  
12 antidepressant use and weight gain, as well as the interaction with diet and other  
13 lifestyle factors in adults participating in a large-population based prospective cohort  
14 study.  
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## 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<sup>16</sup>. 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  $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$  and  $\text{BMI} \geq 30 \text{ kg/m}^2$ .

### 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)



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2 were categorized into three groups: tricyclic antidepressants (TCAs) (ATC code  
3 N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB) and  
4 other antidepressants (ATC code N06AF, N06AG, and N06AX). For each participant  
5 the mean annual number of antidepressant prescriptions, calculated by adding the  
6 number of prescriptions and dividing it by the follow-up duration between stages 2  
7 and 3, was categorized into three groups: non-user, low user (1-2 prescriptions/year),  
8 or high user (>2 prescriptions/year).  
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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)<sup>17</sup>. 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  
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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.

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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).

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2 Sensitivity analyses were conducted using mixed linear modelling to assess the  
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4 association between antidepressant use and weight status adjusted for age, income,  
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6 depression, and smoking status as time-varying variables, while considering  
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8 antidepressant use, physical activity, dietary patterns, and gender as time-invariant  
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10 variables. We also assessed the association (incident rate ratio) between  
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12 antidepressant use and five percent weight gain over five years using Poisson  
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14 regression with robust variance.  
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18 All analyses were performed using STATA 14 (Stata Corporation), and statistical  
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20 significance was set at  $P < 0.05$  (two sided).  
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### 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

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2 between SSRI use and weight gain was observed among those with high intake of  
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4 Western diet: the regression coefficients were 0.00, 0.46 (95%CI 0.05-0.88), and 0.84  
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6 (95%CI 0.43-1.24) kg for non-users, low users and high users, respectively. This  
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8 association was not seen in those with low intake of Western diet. There was a  
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10 significant interaction between antidepressant use and age in relation to weight gain  
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12 (Supplemental **Figure S2**). The positive association between high antidepressant use  
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14 and weight gain was mainly seen among those aged below 50 years. Among those  
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16 with sedentary lifestyles, high SSRI use was associated with 1.01 (95%CI 0.52-1.50)  
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18 kg higher weight gain per year than non-users. A consistent positive association  
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20 between SSRI use and weight gain was only observed among smokers: low and high  
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22 SSRI use was respectively associated with 0.44 (95%CI 0.05-0.84) and 0.66 (95%CI  
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24 0.23-1.10) kg higher weight gain per year than non-users. No significant interaction  
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26 between SSRI use and the prudent dietary pattern was found.  
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32 In the multivariable mixed regression model adjusted for time-varying depression  
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34 status, smoking, age, and income as well as time-invariant dietary patterns, physical  
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36 activity, and gender, antidepressant use was associated with weight status  
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38 (Supplemental **Table S3**). Compared with non-use, high use was associated with an  
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40 extra body weight of 4.40 kg (any antidepressant,  $P= 0.002$ ), 4.20 kg (SSRI,  $P= 0.007$ )  
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42 and 7.14 kg (other antidepressant,  $P< 0.001$ ), respectively. TCA use was not  
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44 associated with body weight. No interaction between antidepressant use and gender  
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46 was found (data not shown).  
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50 Overall, 27.2% of the participants had weight gain above 5% over five years. In fully  
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52 adjusted model, the incident rate ratio (IRR) for 5% weight gain were 1.00, 1.09  
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54 (95%CI 0.83-1.44) and 1.37 (95%CI 1.10-1.70) for non-users, low users and high  
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56 users of antidepressant, respectively. A dose response association between SSRI use  
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2 and 5% weight gain was found in fully adjusted model: IRRs were 1.00, 1.37 (95%CI  
3 1.03-1.81) and 1.43 (95%CI 1.10-1.86) (p trend <0.001) for non-users, low users and  
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7 high users of SSRI, respectively (data not shown).  
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#### 9 10 4. Discussion

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12 In this prospective study, we found that antidepressant use was positively associated  
13 with weight gain, which was influenced by significant interactions between SSRI use,  
14 age and unhealthy lifestyle factors, including western dietary pattern, sedentary  
15 activity and smoking.  
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21 The mean annual weight gain among antidepressant users during this 4.4-year study  
22 was around 0.2 kg, which is similar to those reported in the literature for shorter  
23 studies<sup>6 7 9 10 20</sup>. However, in those previous population studies, lifestyle factors were  
24 either lacking or treated as confounding factors<sup>6 7 9 10 20</sup>. None of those studies had  
25 been adjusted for dietary intake, an important factor for weight gain.  
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33 Only one previous study assessed differences in energy intake and physical activity  
34 between antidepressant users and non-users, employing data from the 2005-2006  
35 National Health and Nutrition Examination Survey (NHANES). It showed that, after  
36 adjusting for potential confounding factors, antidepressant users had an extra 215  
37 kcal/day of energy intake and were 77% more likely to use a computer for  $\geq 2$   
38 hour/day than non-users<sup>15</sup>. The authors hypothesized that increased energy intake and  
39 sedentary activity could contribute to weight gain associated with antidepressant use.  
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49 In the present study we also found a significant difference in energy intake between  
50 high antidepressant users and non-users. After adjusting for age and gender, high  
51 antidepressant users had a higher energy intake than non-users (9160 vs 8628 kJ/day).  
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56 Furthermore, high antidepressant users had higher Western dietary pattern scores than  
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2 non-users (0.14 vs -0.03). To the best of our knowledge, this is the first study that  
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4 systematically tested the interactions between antidepressant use and modifiable  
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6 lifestyle factors. A significant positive dose response association between  
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8 antidepressant use and weight gain was found in individuals with high intake but not  
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10 in those with low intake of Western diet. Clustering of unhealthy behaviours and  
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12 chronic diseases, including depression, may partly explain the interaction between  
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14 unhealthy lifestyle and weight gain among those using antidepressant.  
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18 The interaction between antidepressant use and smoking in relation to weight gain  
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20 was consistent with that reported by Arterburn *et al.* who found that bupropion-treated  
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22 smokers gained an extra 14.2 lbs compared to fluoxetine-treated non-smokers during  
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24 a two-year follow-up study<sup>8</sup>. We observed an intriguing interaction between  
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26 antidepressant use and age in relation to weight gain, which may be related to the fact  
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28 that younger people are more likely to eat a Western diet. In our sample, age was  
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30 inversely associated with Western dietary pattern scores (data not shown).  
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34 The lack of association between TCA use and weight gain was also reported in the  
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36 Netherlands Study of Depression and Anxiety as well as the Rotterdam Study<sup>20,21</sup>.  
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38 However, previous studies have reported an association between TCA use and weight  
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40 gain<sup>6,13</sup>. Our null association between TCA use and weight gain may be due to the  
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42 fact that age was positively associated with TCA use ( $P<0.001$ ). The mean age was  
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44 respectively 53.6, 62.2 and 65.6 years among non-users, low and high users of TCA  
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46 (data not shown). However, there was no significant age difference between SSRIs  
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48 users and non-users. Another explanation could be that doctors may be more likely to  
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50 prescribe SSRIs to people who are worried about weight gain as TCA use has been  
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52 linked to weight gain in clinical trials.  
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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 underestimated 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<sup>22</sup>; in Australia 11.6% of the country's population is on antidepressants<sup>23</sup>.

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](mailto:robert.adams@adelaide.edu.au)).

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3 **Figure legends**  
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5 Supporting Information **Figures**  
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8 **Figure S1:** Factor loadings of dietary patterns  
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11 **Figure S2:** Interaction between any antidepressant use and age in relation to weight  
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13 gain.  
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## References

1. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011;**377**(9765):557-67.
2. Atlantis E, Lange K, Wittert GA. Chronic disease trends due to excess body weight in Australia. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2009;**10**(5):543-53.
3. Australian Bureau of Statistics. 4364.0.55.001 - Australian Health Survey: First Results, 2011-12. , 2012.
4. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010;**67**(3):220-9.
5. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013;**10**(11):e1001547.
6. Kivimaki M, Hamer M, Batty GD, et al. Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetes Care* 2010;**33**(12):2611-6.
7. Blumenthal SR, Castro VM, Clements CC, et al. An electronic health records study of long-term weight gain following antidepressant use. *JAMA Psychiatry* 2014;**71**(8):889-96.
8. Arterburn D, Sofer T, Boudreau DM, et al. Long-Term Weight Change after Initiating Second-Generation Antidepressants. *J Clin Med* 2016;**5**(4).
9. Patten SB, Williams JV, Lavorato DH, et al. Weight gain in relation to major depression and antidepressant medication use. *J Affect Disord* 2011;**134**(1-3):288-93.
10. Paige E, Korda R, Kemp-Casey A, et al. A record linkage study of antidepressant medication use and weight change in Australian adults. *Aust N Z J Psychiatry* 2015;**49**(11):1029-39.
11. Atlantis E, Sullivan T, Sartorius N, et al. Changes in the prevalence of psychological distress and use of antidepressants or anti-anxiety medications

- 1  
2 associated with comorbid chronic diseases in the adult Australian population,  
3 2001-2008. *The Australian and New Zealand journal of psychiatry*  
4 2012;**46**(5):445-56.
- 5  
6  
7 12. Harris MG, Burgess PM, Pirkis J, et al. Correlates of antidepressant and anxiolytic,  
8 hypnotic or sedative medication use in an Australian community sample.  
9 *Australian and New Zealand Journal of Psychiatry* 2011;**45**(3):249-60.
- 10  
11 13. Lee SH, Paz-Filho G, Mastronardi C, et al. Is increased antidepressant exposure a  
12 contributory factor to the obesity pandemic? *Transl Psychiatry* 2016;**6**:e759.
- 13  
14 14. Mastronardi C, Paz-Filho GJ, Valdez E, et al. Long-term body weight outcomes of  
15 antidepressant-environment interactions. *Mol Psychiatry* 2011;**16**(3):265-72.
- 16  
17 15. Jensen-Otsu E, Austin GL. Antidepressant Use is Associated with Increased  
18 Energy Intake and Similar Levels of Physical Activity. *Nutrients*  
19 2015;**7**(11):9662-71.
- 20  
21 16. Grant JF, Taylor AW, Ruffin RE, et al. Cohort Profile: The North West Adelaide  
22 Health Study (NWAHS). *Int J Epidemiol* 2009;**38**(6):1479-86.
- 23  
24 17. Radloff LS. The CES-D scale: A self-report depression scale for research in the  
25 general population. *Applied Psychological Measurement* 1977;**1**:385-401.
- 26  
27 18. Australian Bureau of Statistics, editor. *National Health Survey: users' guide*.  
28 Canberra: ABS, 2003.
- 29  
30 19. Schoenaker DA, Dobson AJ, Soedamah-Muthu SS, et al. Factor analysis is more  
31 appropriate to identify overall dietary patterns associated with diabetes when  
32 compared with Treelet transform analysis. *J Nutr* 2013;**143**(3):392-8.
- 33  
34 20. Gibson-Smith D, Bot M, Milaneschi Y, et al. Major depressive disorder,  
35 antidepressant use, and subsequent 2-year weight change patterns in the  
36 Netherlands Study of Depression and Anxiety. *J Clin Psychiatry*  
37 2016;**77**(2):e144-51.
- 38  
39 21. Noordam R, Aarts N, Tiemeier H, et al. Sex-specific association between  
40 antidepressant use and body weight in a population-based study in older adults.  
41 *J Clin Psychiatry* 2015;**76**(6):e745-51.
- 42  
43 22. IMS Institute for Healthcare Informatics. *The Use of Medicines in the United*  
44 *States: Review of 2011*. *Secondary The Use of Medicines in the United States:*  
45 *Review of 2011 2012*.
- 46  
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23. Mental health services in Australia. Mental health-related prescriptions.  
Secondary Mental health-related prescriptions.  
<https://mhsa.aihw.gov.au/resources/prescriptions/>.

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Table 1 Sample characteristic by sex \*

	Male	Female	Total	<i>P</i> value
<i>n</i> (%)	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

1					
2	TCA <sub>s</sub> †	0.1 (0.6)	0.2 (1.3)	0.1 (1.0)	<0.001
3					
4	SSRIs †	0.2 (1.3)	0.4 (1.6)	0.3 (1.4)	0.019
5					
6	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

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Table 2 Association ( $\beta$  95%CI) between antidepressant use and annual weight gain

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	<i>P</i> value
<b>Any antidepressant</b>				
<i>n</i>	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
<b>SSRIs</b>				
<i>n</i>	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	<b>0.30(0.04-0.57)</b>	<b>0.53(0.27-0.80)</b>	<b>&lt;0.001</b>
Model 2 †	Ref	<b>0.30(0.03-0.58)</b>	<b>0.58(0.30-0.85)</b>	<b>&lt;0.001</b>
Model 3 ‡	Ref	<b>0.30(0.01-0.58)</b>	<b>0.48(0.20-0.76)</b>	<b>&lt;0.001</b>
<b>TCAs</b>				
<i>n</i>	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)	



1					
2					
3	(kg), mean (SD)				
4	Model 1 *	Ref	-0.12(-0.44-0.19)	0.06(-0.36-0.49)	0.717
5	Model 2 †	Ref	-0.11(-0.44-0.22)	0.05(-0.39-0.50)	0.704
6	Model 3 ‡	Ref	0.02(-0.31-0.36)	0.03(-0.46-0.52)	0.908
7					
8					
9	<b>Other antidepressants</b>				
10					
11	<i>n</i>	2210	57	67	
12	Baseline weight (kg),				
13	mean (SD)	79.8 (17.0)	80.0 (18.7)	82.9 (20.5)	
14	Follow-up weight (kg),				
15	mean (SD)	80.4 (17.4)	81.3 (17.6)	83.4 (21.2)	
16	Annual weight change				
17	(kg), mean (SD)	0.14(1.37)	0.35(1.88)	0.12(2.08)	
18	Model 1 *	Ref	0.23(-0.13-0.60)	-0.04(-0.38-0.29)	0.844
19	Model 2 †	Ref	0.32(-0.05-0.70)	-0.01(-0.36-0.35)	0.505
20	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	<i>P</i> for interaction
<b>Western dietary pattern</b>				0.026
Low intake	0.00	0.11(-0.29-0.51)	0.14(-0.26-0.54)	
High intake	0.00	<b>0.46(0.05-0.88)</b> †	<b>0.84(0.43-1.24)</b>	
<b>Prudent dietary pattern</b>				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)	<b>0.61(0.20-1.02)</b>	
<b>Physical activity</b>				0.039
Sedentary	0.00	0.15(-0.34-0.63)	<b>1.01(0.52-1.50)</b>	
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)	
<b>Smoking</b>				0.002
Non-smoker	0.00	-0.28(-0.73-0.16)	0.35(-0.03-0.72)	
Current or ex-smoker	0.00	<b>0.44(0.05-0.84)</b>	<b>0.66(0.23-1.10)</b>	

\* 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	<i>P</i> value
<i>n</i> (%)	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
TCAAs †	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

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

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	<i>P</i> 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	

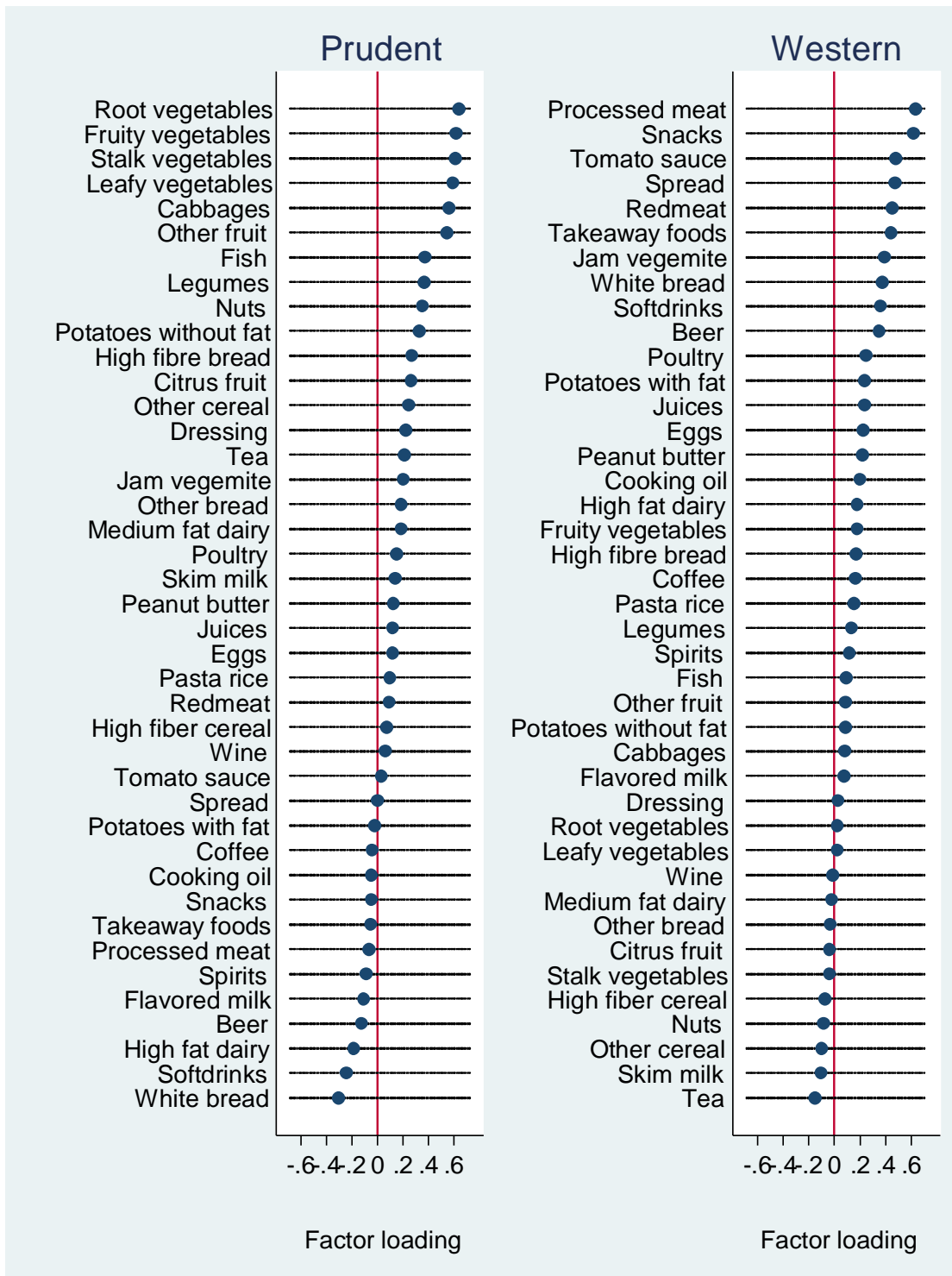
\* Values are age and gender adjusted mean (SE).

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

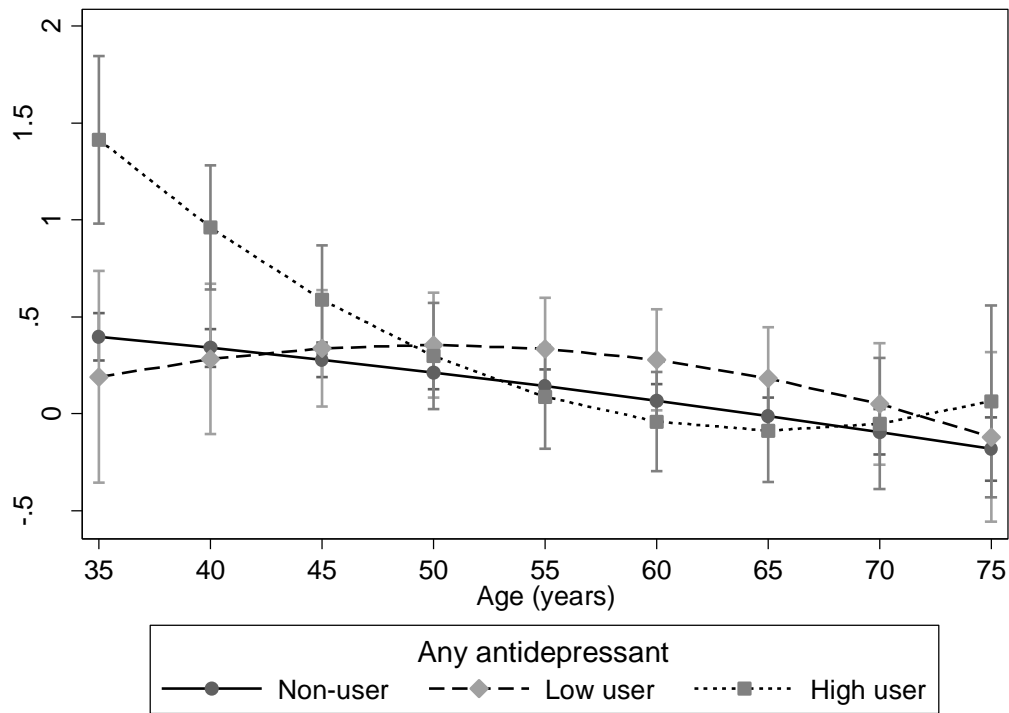
	Non-user	Low user	High user	<i>P</i> value
Any antidepressant	Ref	-0.32(-2.81-2.16)	<b>4.40(1.97-6.83)</b>	0.002
TCAs	Ref	-2.81(-6.56-0.94)	0.87(-4.52-6.25)	0.571
SSRIs	Ref	1.45(-1.66-4.56)	<b>4.20(1.06-7.35)</b>	0.007
Other	Ref	2.88(-1.43-7.18)	<b>7.14(3.05-11.23)</b>	<0.001

\* 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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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, page 5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Paragraph 1, page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Paragraph 1-2, page 6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Cohort study: Paragraph 1 Page 6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	Paragraph 1 (external

		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	linkage)
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	Paragraph 6, page 8-9
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Methods section: Paragraph 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Table 1; Methods section: Paragraph 1
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —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

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

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016224.R2
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Date Submitted by the Author:	13-Jun-2017
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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Epidemiology, Public health, Nutrition and metabolism, Mental health
Keywords:	Antidepressant, cohort study, body weight, dietary pattern

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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**

Zumin Shi, MD PhD <sup>1</sup>, Evan Atlantis, PhD <sup>2</sup>, Anne W Taylor, PhD <sup>1</sup>, Tiffany K Gill, PhD <sup>1</sup>, Kay Price, PhD <sup>3</sup>, Sarah Appleton, PhD <sup>1</sup>, Ma-Li Wong, MD PhD <sup>4</sup>, Julio Licinio, MD PhD <sup>4</sup>

<sup>1</sup> Discipline of Medicine, University of Adelaide, L7 SAHMRI, North Terrace, Adelaide, Australia

<sup>2</sup> University of Western Sydney, Australia

<sup>3</sup> University of South Australia, Australia

<sup>4</sup> South Australia Health and Medical Research Institute (SAHMRI) and Flinders University, Australia

Email address:

Zumin Shi: [Zumin.shi@adelaide.edu.au](mailto:Zumin.shi@adelaide.edu.au)

Evan Atlantis: [E.Atlantis@westernsydney.edu.au](mailto:E.Atlantis@westernsydney.edu.au)

Anne W Taylor: [anne.taylor@adelaide.edu.au](mailto:anne.taylor@adelaide.edu.au)

Tiffany Gill: [tiffany.gill@adelaide.edu.au](mailto:tiffany.gill@adelaide.edu.au)

Kay Price: [Kay.Price@unisa.edu.au](mailto:Kay.Price@unisa.edu.au)

Sarah Louise Appleton: [sarah.appleton@adelaide.edu.au](mailto:sarah.appleton@adelaide.edu.au)

Ma-Li Wong: [mali.wong@sahmri.com](mailto:mali.wong@sahmri.com)

Julio Licinio: [Julio.Licinio@sahmri.com](mailto:Julio.Licinio@sahmri.com)

**Corresponding Author:** A/Professor Zumin Shi

Postal address; Discipline of Medicine, University of Adelaide, Level 7, SAHMRI, North Terrace, Adelaide, Australia, 5005

Phone: +61 8 8313 1188

Fax: +61 8 8313 1228

Email: [Zumin.shi@adelaide.edu.au](mailto:Zumin.shi@adelaide.edu.au)

## 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 <sup>1</sup>. In Australia, the prevalence of obesity class I (BMI 30-34.9 kg/m<sup>2</sup>) and obesity class II or III (BMI  $\geq 35$  kg/m<sup>2</sup>) has respectively doubled and almost tripled since 1980 <sup>2</sup>. Currently it is estimated that 28.3% of Australian adults are obese <sup>3</sup>. One of the most important health consequences of high and rising trends in global obesity prevalence has been the increased risk of developing depression <sup>4</sup>. 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 <sup>5</sup>.

Several population based cohort studies have consistently shown a positive relationship between antidepressant use and weight gain in countries such as the USA, <sup>6-8</sup> Canada <sup>9</sup> and Australia <sup>10</sup>. 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%) <sup>7,11</sup>, and frequently used by people without depressive or anxiety disorders <sup>12</sup>.

The underlying cause of weight gain due to long-term antidepressant use is poorly understood <sup>13</sup>. 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 <sup>14</sup>. 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 <sup>13</sup>. It is supported by the change of energy intake related to antidepressant use. Data from a



1  
2 recent cross-sectional population-based study showed that antidepressant use was  
3 associated with increased energy intake <sup>15</sup>. Poor diet, sedentary lifestyle, obesity, and  
4 depression often cluster together; however, association studies between antidepressant  
5 use and obesity have been mostly based on registry data or short-term clinical trials,  
6 which limited their capacity to understand interactions <sup>6-10</sup>. Therefore, whether  
7 specific antidepressant medications interaction with lifestyle risk factors (poor diet,  
8 inadequate physical activity, and smoking) partially explain the development of  
9 human obesity long term is still unclear. Identifying the potential mechanism by  
10 which antidepressant medication increases the risk of obesity may could help develop  
11 targeted strategies for prevention.  
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24 This study was designed to specifically examine the association between  
25 antidepressant use and weight gain, as well as the interaction with diet and other  
26 lifestyle factors (e.g. smoking, sedentary activity) in adults participating in a large-  
27 population based prospective cohort study.  
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## 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<sup>16</sup>. 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  $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$  and  $\text{BMI} \geq 30 \text{ kg/m}^2$ .

### 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)

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2 were categorized into three groups: tricyclic antidepressants (TCAs) (ATC code  
3 N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB) and  
4 other antidepressants (ATC code N06AF, N06AG, and N06AX). For each participant  
5 the mean annual number of antidepressant prescriptions, calculated by adding the  
6 number of prescriptions and dividing it by the follow-up duration between stages 2  
7 and 3, was categorized into three groups: non-user, low user (1-2 prescriptions/year),  
8 or high user (>2 prescriptions/year). Exposure of specific antidepressants was  
9 assessed independent of one or more antidepressants.  
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## 20 21 *2.4 Covariates*

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24 *2.4.1 Baseline and follow-up covariates:* The Centre for Epidemiologic Studies  
25 Depression Scale (CES-D) was used to measure depressive symptoms. CES-D scores  
26 were categorised as no depression (<16), mild depression (16-26) or moderate to  
27 severe depression (>26)<sup>17</sup>. Smoking behaviour was determined by self-report and  
28 coded as 1) non-smoker, and 2) current or ex-smoker. Self-reported income was  
29 recoded into three levels (<\$20,000, \$20,000-\$60,000 or >\$60,000 AUD). Physical  
30 activity questions from the Australian National Health Surveys were used to classify  
31 participants as sedentary, or having low, moderate or high levels of physical activity  
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<sup>18</sup>. 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

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<sup>19</sup>. 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 were 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

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2 physical activity (sedentary, low, moderate/high)) was conducted by inputting the  
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4 product terms of these variables and antidepressant use in the regression models. The  
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6 analysis was subsequently stratified for the lifestyle factors. The interaction between  
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8 antidepressant use and age (continuous) was graphically represented using the  
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10 *marginsplot* command in STATA 14 (Stata Corporation, College Station, TX, USA).  
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14 Sensitivity analyses were conducted using mixed linear modelling to assess the  
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16 association between antidepressant use and body weight (baseline and follow-up  
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18 adjusted for age, income, depression, and smoking status as time-varying variables,  
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20 while considering antidepressant use, physical activity, dietary patterns, and gender as  
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22 time-invariant variables. We also assessed the association (incident rate ratio)  
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24 between antidepressant use and five percent weight gain over five years using Poisson  
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26 regression with robust variance.  
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30 All analyses were performed using STATA 14 (Stata Corporation), and statistical  
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32 significance was set at  $P < 0.05$  (two sided).  
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### 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

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2 between SSRI use and weight gain was observed among those with high intake of  
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4 Western diet: the regression coefficients were 0.00, 0.46 (95%CI 0.05-0.88), and 0.84  
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6 (95%CI 0.43-1.24) kg for non-users, low users and high users, respectively. This  
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8 association was not seen in those with low intake of Western diet. No significant  
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10 interaction between SSRI use and the prudent dietary pattern was found. Among those  
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12 with sedentary lifestyles, high SSRI use was associated with 1.01 (95%CI 0.52-1.50)  
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14 kg higher weight gain per year than non-users. A consistent positive association  
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16 between SSRI use and weight gain was only observed among smokers: low and high  
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18 SSRI use was respectively associated with 0.44 (95%CI 0.05-0.84) and 0.66 (95%CI  
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20 0.23-1.10) kg higher weight gain per year than non-users.  
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25 There was a significant interaction between antidepressant use and age in relation to  
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27 weight gain (Supplemental **Figure S2**). The positive association between high  
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29 antidepressant use and weight gain was mainly seen among those aged below 50 years.  
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33 In the multivariable mixed regression model adjusted for time-varying depression  
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35 status, smoking, age, and income as well as time-invariant dietary patterns, physical  
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37 activity, and gender, antidepressant use was associated with body weight (baseline  
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39 and follow-up)(Supplemental **Table S3**). Compared with non-use, high use was  
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41 associated with an extra body weight of 4.40 kg (any antidepressant,  $P= 0.002$ ), 4.20  
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43 kg (SSRI,  $P= 0.007$ ) and 7.14 kg (other antidepressant,  $P< 0.001$ ), respectively. TCA  
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45 use was not associated with body weight. No interaction between antidepressant use  
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47 and gender was found (data not shown).  
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51 Overall, 27.2% of the participants had weight gain above 5% over five years. In fully  
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53 adjusted model, the incident rate ratio (IRR) for 5% weight gain were 1.00, 1.09  
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55 (95%CI 0.83-1.44) and 1.37 (95%CI 1.10-1.70) for non-users, low users and high  
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2 users of antidepressant, respectively. A dose response association between SSRI use  
3 and 5% weight gain was found in fully adjusted model: IRRs were 1.00, 1.37 (95%CI  
4 1.03-1.81) and 1.43 (95%CI 1.10-1.86) (p trend <0.001) for non-users, low users and  
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9 high users of SSRI, respectively (data not shown).

#### 10 11 12 **4. Discussion**

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15 In this prospective study, we found that antidepressant use was positively associated  
16 with weight gain, which was influenced by significant interactions between SSRI use,  
17 age and unhealthy lifestyle factors, including western dietary pattern, sedentary  
18 activity and smoking.  
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22 The mean annual weight gain among antidepressant users during this 4.4-year study  
23 was around 0.2 kg, which is similar to those reported in the literature for shorter  
24 studies<sup>6 7 9 10 20</sup>. However, in those previous population studies, lifestyle factors were  
25 either lacking or treated as confounding factors<sup>6 7 9 10 20</sup>. None of those studies had  
26 been adjusted for dietary intake, an important factor for weight gain.  
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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  $\geq 2$   
hour/day than non-users<sup>15</sup>. 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).



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

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

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

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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 underestimated 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<sup>22</sup>; in Australia 11.6% of the country's population is on antidepressants<sup>23</sup>. 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.

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2 We suggest that reducing Western diet consumption, increasing physical activity and  
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4 smoking cessation may mitigate antidepressant-related weight gain. General  
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6 practitioners should encourage their patients adopt healthy lifestyle while treating  
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8 depression with antidepressants or cognitive behaviour therapy.  
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17  
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19  
20 international institutions

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

23  
24 **Author contributions:** ZS contributed to the conception, analysis, and interpretation  
25  
26 of data; drafting of the report; and have given approval of the final version for  
27  
28 publication. EA, AWT, TKG, KP, SA, MLW and JL contributed to analysis and  
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30 interpretation of the data, commented on the report, revising the manuscript and  
31  
32 approving the final version for publication.  
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### 34 35 **Availability of data and material**

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38 Data from the North West Adelaide Healthy Study (NWAHS) were accessed from a  
39  
40 third party. The authors confirm that for approved reasons, some access restrictions  
41  
42 apply to the data underlying the findings. To gain access to the data for this  
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44 manuscript, ethics approval was sought and granted. Enquiries regarding requests for  
45  
46 the NWAHS data can be directed to Prof Robert Adams, Principal Investigator  
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48 (Clinical) (robert.adams@adelaide.edu.au).  
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3 **Figure legends**  
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5 Supporting Information **Figures**  
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8 **Figure S1:** Factor loadings of dietary patterns  
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11 **Figure S2:** Interaction between any antidepressant use and age in relation to weight  
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13 gain.  
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## References

1. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011;**377**(9765):557-67.
2. Atlantis E, Lange K, Wittert GA. Chronic disease trends due to excess body weight in Australia. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2009;**10**(5):543-53.
3. Australian Bureau of Statistics. 4364.0.55.001 - Australian Health Survey: First Results, 2011-12. , 2012.
4. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010;**67**(3):220-9.
5. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013;**10**(11):e1001547.
6. Kivimaki M, Hamer M, Batty GD, et al. Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetes Care* 2010;**33**(12):2611-6.
7. Blumenthal SR, Castro VM, Clements CC, et al. An electronic health records study of long-term weight gain following antidepressant use. *JAMA Psychiatry* 2014;**71**(8):889-96.
8. Arterburn D, Sofer T, Boudreau DM, et al. Long-Term Weight Change after Initiating Second-Generation Antidepressants. *J Clin Med* 2016;**5**(4).
9. Patten SB, Williams JV, Lavorato DH, et al. Weight gain in relation to major depression and antidepressant medication use. *J Affect Disord* 2011;**134**(1-3):288-93.
10. Paige E, Korda R, Kemp-Casey A, et al. A record linkage study of antidepressant medication use and weight change in Australian adults. *Aust N Z J Psychiatry* 2015;**49**(11):1029-39.
11. Atlantis E, Sullivan T, Sartorius N, et al. Changes in the prevalence of psychological distress and use of antidepressants or anti-anxiety medications associated with comorbid chronic diseases in the adult Australian population,

- 2001-2008. The Australian and New Zealand journal of psychiatry  
2012;**46**(5):445-56.
12. Harris MG, Burgess PM, Pirkis J, et al. Correlates of antidepressant and anxiolytic,  
hypnotic or sedative medication use in an Australian community sample.  
Australian and New Zealand Journal of Psychiatry 2011;**45**(3):249-60.
13. Lee SH, Paz-Filho G, Mastronardi C, et al. Is increased antidepressant exposure a  
contributory factor to the obesity pandemic? *Transl Psychiatry* 2016;**6**:e759.
14. Mastronardi C, Paz-Filho GJ, Valdez E, et al. Long-term body weight outcomes of  
antidepressant-environment interactions. *Mol Psychiatry* 2011;**16**(3):265-72.
15. Jensen-Otsu E, Austin GL. Antidepressant Use is Associated with Increased  
Energy Intake and Similar Levels of Physical Activity. *Nutrients*  
2015;**7**(11):9662-71.
16. Grant JF, Taylor AW, Ruffin RE, et al. Cohort Profile: The North West Adelaide  
Health Study (NWAHS). *Int J Epidemiol* 2009;**38**(6):1479-86.
17. Radloff LS. The CES-D scale: A self-report depression scale for research in the  
general population. *Applied Psychological Measurement* 1977;**1**:385-401.
18. Australian Bureau of Statistics, editor. *National Health Survey: users' guide*.  
Canberra: ABS, 2003.
19. Schoenaker DA, Dobson AJ, Soedamah-Muthu SS, et al. Factor analysis is more  
appropriate to identify overall dietary patterns associated with diabetes when  
compared with Treelet transform analysis. *J Nutr* 2013;**143**(3):392-8.
20. Gibson-Smith D, Bot M, Milaneschi Y, et al. Major depressive disorder,  
antidepressant use, and subsequent 2-year weight change patterns in the  
Netherlands Study of Depression and Anxiety. *J Clin Psychiatry*  
2016;**77**(2):e144-51.
21. Noordam R, Aarts N, Tiemeier H, et al. Sex-specific association between  
antidepressant use and body weight in a population-based study in older adults.  
*J Clin Psychiatry* 2015;**76**(6):e745-51.
22. IMS Institute for Healthcare Informatics. The Use of Medicines in the United  
States: Review of 2011. Secondary The Use of Medicines in the United States:  
Review of 2011 2012.
23. Mental health services in Australia. Mental health-related prescriptions.  
Secondary Mental health-related prescriptions.  
<https://mhsa.aihw.gov.au/resources/prescriptions/>.

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Table 1 Sample characteristic by sex \*

	Male	Female	Total	<i>P</i> value
<i>n</i> (%)	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



1					
2	TCA <sup>s</sup> †	0.1 (0.6)	0.2 (1.3)	0.1 (1.0)	<0.001
3					
4	SSRI <sup>s</sup> †	0.2 (1.3)	0.4 (1.6)	0.3 (1.4)	0.019
5					
6	Other antidepressant †	0.1 (0.8)	0.3 (1.5)	0.2 (1.2)	<0.001

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

8 † Annual number of prescriptions

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Table 2 Association ( $\beta$  95%CI) between antidepressant use and annual weight gain

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	<i>P</i> value
<b>Any antidepressant</b>				
<i>n</i>	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
<b>SSRIs</b>				
<i>n</i>	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	<b>0.30(0.04-0.57)</b>	<b>0.53(0.27-0.80)</b>	<b>&lt;0.001</b>
Model 2 †	Ref	<b>0.30(0.03-0.58)</b>	<b>0.58(0.30-0.85)</b>	<b>&lt;0.001</b>
Model 3 ‡	Ref	<b>0.30(0.01-0.58)</b>	<b>0.48(0.20-0.76)</b>	<b>&lt;0.001</b>
<b>TCAAs</b>				
<i>n</i>	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)	

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3	(kg), mean (SD)				
4	Model 1 *	Ref	-0.12(-0.44-0.19)	0.06(-0.36-0.49)	0.717
5	Model 2 †	Ref	-0.11(-0.44-0.22)	0.05(-0.39-0.50)	0.704
6	Model 3 ‡	Ref	0.02(-0.31-0.36)	0.03(-0.46-0.52)	0.908
7					
8					
9	<b>Other antidepressants</b>				
10					
11	<i>n</i>	2210	57	67	
12	Baseline weight (kg),				
13	mean (SD)	79.8 (17.0)	80.0 (18.7)	82.9 (20.5)	
14	Follow-up weight (kg),				
15	mean (SD)	80.4 (17.4)	81.3 (17.6)	83.4 (21.2)	
16	Annual weight change				
17	(kg), mean (SD)	0.14(1.37)	0.35(1.88)	0.12(2.08)	
18	Model 1 *	Ref	0.23(-0.13-0.60)	-0.04(-0.38-0.29)	0.844
19	Model 2 †	Ref	0.32(-0.05-0.70)	-0.01(-0.36-0.35)	0.505
20	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	<i>P</i> for interaction
<b>Western dietary pattern</b>				0.026
Low intake	0.00	0.11(-0.29-0.51)	0.14(-0.26-0.54)	
High intake	0.00	<b>0.46(0.05-0.88) †</b>	<b>0.84(0.43-1.24)</b>	
<b>Prudent dietary pattern</b>				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)	<b>0.61(0.20-1.02)</b>	
<b>Physical activity</b>				0.039
Sedentary	0.00	0.15(-0.34-0.63)	<b>1.01(0.52-1.50)</b>	
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)	
<b>Smoking</b>				0.002
Non-smoker	0.00	-0.28(-0.73-0.16)	0.35(-0.03-0.72)	
Current or ex-smoker	0.00	<b>0.44(0.05-0.84)</b>	<b>0.66(0.23-1.10)</b>	

\* 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	<i>P</i> value
<i>n</i> (%)	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
TCAAs †	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

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

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	<i>P</i> 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).

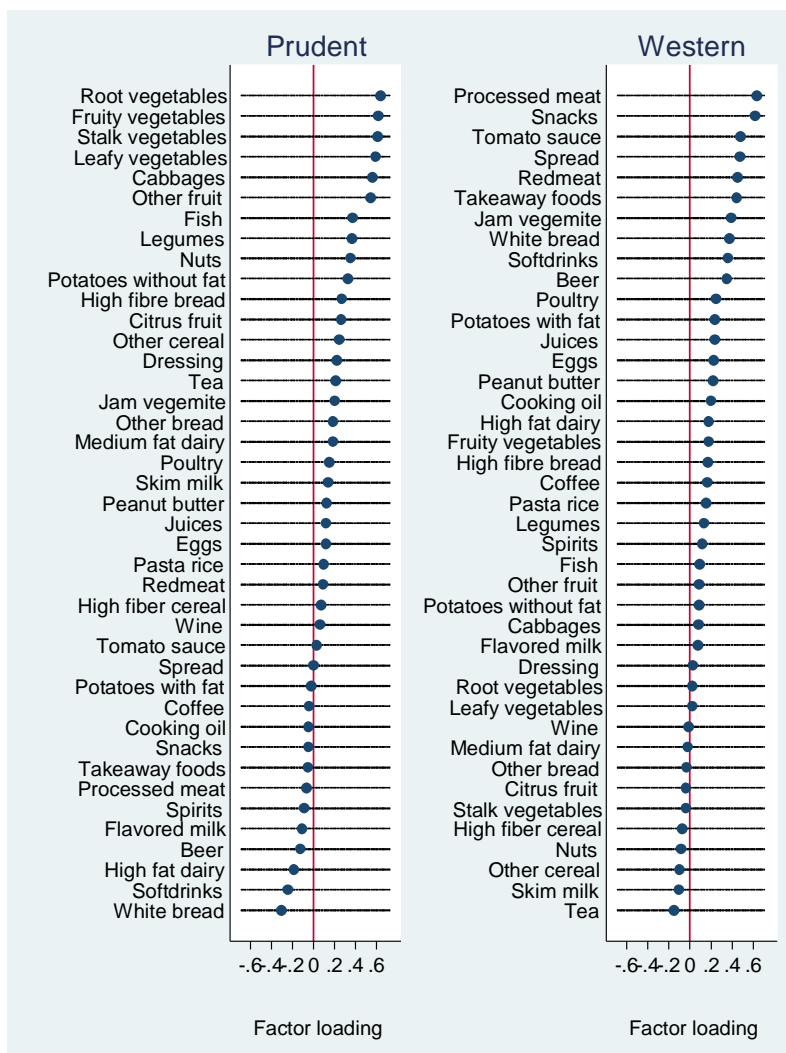
**Table S3** Association between antidepressant use and body weight (kg) from mixed linear model \*

	Non-user	Low user	High user	<i>P</i> value
Any antidepressant	Ref	-0.32(-2.81-2.16)	<b>4.40(1.97-6.83)</b>	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)	<b>4.20(1.06-7.35)</b>	0.007
Other	Ref	2.88(-1.43-7.18)	<b>7.14(3.05-11.23)</b>	<0.001

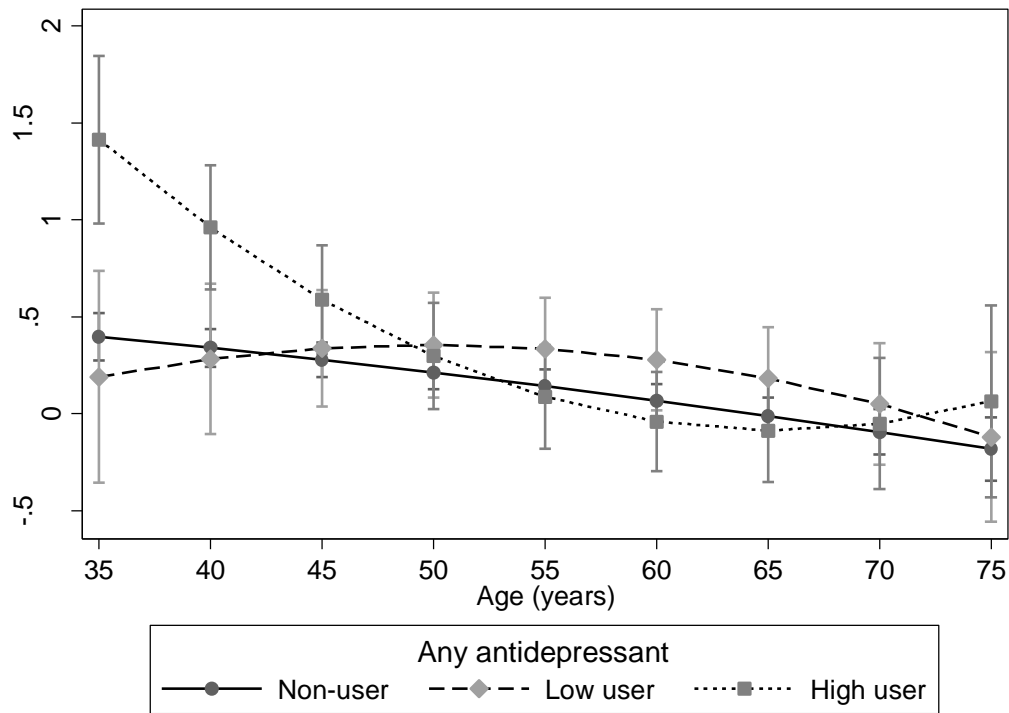
\* Values represent regression coefficients (95%CI). Results are from mixed linear models adjusted for age, sex, income, depression, smoking, physical activity, dietary patterns (follow-up). In the model, age, income, depression and smoking were treated as time-variant variables.



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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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, page 5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Paragraph 1, page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Paragraph 1-2, page 6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Cohort study: Paragraph 1 Page 6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	Paragraph 1 (external

		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	linkage)
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	Paragraph 6, page 8-9
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Methods section: Paragraph 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Table 1; Methods section: Paragraph 1
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —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

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

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016224.R3
Article Type:	Research
Date Submitted by the Author:	26-Jun-2017
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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Epidemiology, Public health, Nutrition and metabolism, Mental health
Keywords:	Antidepressant, cohort study, body weight, dietary pattern

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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**

Zumin Shi, MD PhD <sup>1</sup>, Evan Atlantis, PhD <sup>2</sup>, Anne W Taylor, PhD <sup>1</sup>, Tiffany K Gill,  
PhD <sup>1</sup>, Kay Price, PhD <sup>3</sup>, Sarah Appleton, PhD <sup>1</sup>, Ma-Li Wong, MD PhD <sup>4</sup>, Julio  
Licinio, MD PhD <sup>4</sup>

<sup>1</sup> Discipline of Medicine, University of Adelaide, L7 SAHMRI, North Terrace,  
Adelaide, Australia

<sup>2</sup> University of Western Sydney, Australia

<sup>3</sup> University of South Australia, Australia

<sup>4</sup> South Australia Health and Medical Research Institute (SAHMRI) and Flinders  
University, Australia

Email address:

Zumin Shi: [Zumin.shi@adelaide.edu.au](mailto:Zumin.shi@adelaide.edu.au)

Evan Atlantis: [E.Atlantis@westernsydney.edu.au](mailto:E.Atlantis@westernsydney.edu.au)

Anne W Taylor: [anne.taylor@adelaide.edu.au](mailto:anne.taylor@adelaide.edu.au)

Tiffany Gill: [tiffany.gill@adelaide.edu.au](mailto:tiffany.gill@adelaide.edu.au)

Kay Price: [Kay.Price@unisa.edu.au](mailto:Kay.Price@unisa.edu.au)

Sarah Louise Appleton: [sarah.appleton@adelaide.edu.au](mailto:sarah.appleton@adelaide.edu.au)

Ma-Li Wong: [mali.wong@sahmri.com](mailto:mali.wong@sahmri.com)

Julio Licinio: [Julio.Licinio@sahmri.com](mailto:Julio.Licinio@sahmri.com)

**Corresponding Author:** A/Professor Zumin Shi

Postal address; Discipline of Medicine, University of Adelaide, Level 7, SAHMRI,  
North Terrace, Adelaide, Australia, 5005

Phone: +61 8 8313 1188

Fax: +61 8 8313 1228

Email: [Zumin.shi@adelaide.edu.au](mailto:Zumin.shi@adelaide.edu.au)

## 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 <sup>1</sup>. In Australia, the prevalence of obesity class I (BMI 30-34.9 kg/m<sup>2</sup>) and obesity class II or III (BMI  $\geq 35$  kg/m<sup>2</sup>) has respectively doubled and almost tripled since 1980 <sup>2</sup>. Currently it is estimated that 28.3% of Australian adults are obese <sup>3</sup>. One of the most important health consequences of high and rising trends in global obesity prevalence has been the increased risk of developing depression <sup>4</sup>. 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 <sup>5</sup>.

Several population based cohort studies have consistently shown a positive relationship between antidepressant use and weight gain in countries such as the USA, <sup>6-8</sup> Canada <sup>9</sup> and Australia <sup>10</sup>. 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%) <sup>7,11</sup>, and frequently used by people without depressive or anxiety disorders <sup>12</sup>.

The underlying cause of weight gain due to long-term antidepressant use is poorly understood <sup>13</sup>. 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 <sup>14</sup>. 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 <sup>13</sup>. It is supported by the change of energy intake related to antidepressant use. Data from a

1  
2 recent cross-sectional population-based study showed that antidepressant use was  
3 associated with increased energy intake <sup>15</sup>. Poor diet, sedentary lifestyle, obesity, and  
4 depression often cluster together; however, association studies between antidepressant  
5 use and obesity have been mostly based on registry data or short-term clinical trials,  
6 which limited their capacity to understand interactions <sup>6-10</sup>. Therefore, whether  
7 specific antidepressant medications interaction with lifestyle risk factors (poor diet,  
8 inadequate physical activity, and smoking) partially explain the development of  
9 human obesity long term is still unclear. Identifying the potential mechanism by  
10 which antidepressant medication increases the risk of obesity may could help develop  
11 targeted strategies for prevention.  
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24 This study was designed to specifically examine the association between  
25 antidepressant use and weight gain, as well as the interaction with diet and other  
26 lifestyle factors (e.g. smoking, sedentary activity) in adults participating in a large-  
27 population based prospective cohort study.  
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## 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<sup>16</sup>. 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  $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$  and  $\text{BMI} \geq 30 \text{ kg/m}^2$ .

### 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)

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2 were categorized into three groups: tricyclic antidepressants (TCAs) (ATC code  
3 N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB) and  
4 other antidepressants (ATC code N06AF, N06AG, and N06AX). For each participant  
5 the mean annual number of antidepressant prescriptions, calculated by adding the  
6 number of prescriptions and dividing it by the follow-up duration between stages 2  
7 and 3, was categorized into three groups: non-user, low user (1-2 prescriptions/year),  
8 or high user (>2 prescriptions/year). Exposure of specific antidepressants was  
9 assessed independent of one or more antidepressants.  
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## 20 21 *2.4 Covariates*

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24 *2.4.1 Baseline and follow-up covariates:* The Centre for Epidemiologic Studies  
25 Depression Scale (CES-D) was used to measure depressive symptoms. CES-D scores  
26 were categorised as no depression (<16), mild depression (16-26) or moderate to  
27 severe depression (>26)<sup>17</sup>. Smoking behaviour was determined by self-report and  
28 coded as 1) non-smoker, and 2) current or ex-smoker. Self-reported income was  
29 recoded into three levels (<\$20,000, \$20,000-\$60,000 or >\$60,000 AUD). Physical  
30 activity questions from the Australian National Health Surveys were used to classify  
31 participants as sedentary, or having low, moderate or high levels of physical activity  
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<sup>18</sup>. 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

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<sup>19</sup>. 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 were 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

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2 physical activity (sedentary, low, moderate/high)) was conducted by inputting the  
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4 product terms of these variables and antidepressant use in the regression models. The  
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6 analysis was subsequently stratified for the lifestyle factors. The interaction between  
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8 antidepressant use and age (continuous) was graphically represented using the  
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10 *marginsplot* command in STATA 14 (Stata Corporation, College Station, TX, USA).  
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14 Sensitivity analyses were conducted using mixed linear modelling to assess the  
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16 association between antidepressant use and body weight (baseline and follow-up  
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18 adjusted for age, income, depression, and smoking status as time-varying variables,  
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20 while considering antidepressant use, physical activity, dietary patterns, and gender as  
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22 time-invariant variables. We also assessed the association (incident rate ratio)  
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24 between antidepressant use and five percent weight gain over five years using Poisson  
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26 regression with robust variance.  
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30 All analyses were performed using STATA 14 (Stata Corporation), and statistical  
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32 significance was set at  $P < 0.05$  (two sided).  
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### 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



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2 between SSRI use and weight gain was observed among those with high intake of  
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4 Western diet: the regression coefficients were 0.00, 0.46 (95%CI 0.05-0.88), and 0.84  
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6 (95%CI 0.43-1.24) kg for non-users, low users and high users, respectively. This  
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8 association was not seen in those with low intake of Western diet. No significant  
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10 interaction between SSRI use and the prudent dietary pattern was found. Among those  
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12 with sedentary lifestyles, high SSRI use was associated with 1.01 (95%CI 0.52-1.50)  
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14 kg higher weight gain per year than non-users. A consistent positive association  
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16 between SSRI use and weight gain was only observed among smokers: low and high  
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18 SSRI use was respectively associated with 0.44 (95%CI 0.05-0.84) and 0.66 (95%CI  
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20 0.23-1.10) kg higher weight gain per year than non-users.  
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25 There was a significant interaction between antidepressant use and age in relation to  
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27 weight gain (Supplemental **Figure S2**). The positive association between high  
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29 antidepressant use and weight gain was mainly seen among those aged below 50 years.  
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33 In the multivariable mixed regression model adjusted for time-varying depression  
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35 status, smoking, age, and income as well as time-invariant dietary patterns, physical  
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37 activity, and gender, antidepressant use was associated with body weight (baseline  
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39 and follow-up)(Supplemental **Table S3**). Compared with non-use, high use was  
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41 associated with an extra body weight of 4.40 kg (any antidepressant,  $P= 0.002$ ), 4.20  
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43 kg (SSRI,  $P= 0.007$ ) and 7.14 kg (other antidepressant,  $P< 0.001$ ), respectively. TCA  
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45 use was not associated with body weight. No interaction between antidepressant use  
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47 and gender was found (data not shown).  
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51 Overall, 27.2% of the participants had weight gain above 5% over five years. In fully  
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53 adjusted model, the incident rate ratio (IRR) for 5% weight gain were 1.00, 1.09  
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55 (95%CI 0.83-1.44) and 1.37 (95%CI 1.10-1.70) for non-users, low users and high  
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2 users of antidepressant, respectively. A dose response association between SSRI use  
3 and 5% weight gain was found in fully adjusted model: IRRs were 1.00, 1.37 (95%CI  
4 1.03-1.81) and 1.43 (95%CI 1.10-1.86) (p trend <0.001) for non-users, low users and  
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9 high users of SSRI, respectively (data not shown).

#### 10 11 12 **4. Discussion**

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15 In this prospective study, we found that antidepressant use was positively associated  
16 with weight gain, which was influenced by significant interactions between SSRI use,  
17 age and unhealthy lifestyle factors, including western dietary pattern, sedentary  
18 activity and smoking.  
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22 The mean annual weight gain among antidepressant users during this 4.4-year study  
23 was around 0.2 kg, which is similar to those reported in the literature for shorter  
24 studies<sup>6 7 9 10 20</sup>. However, in those previous population studies, lifestyle factors were  
25 either lacking or treated as confounding factors<sup>6 7 9 10 20</sup>. None of those studies had  
26 been adjusted for dietary intake, an important factor for weight gain.  
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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  $\geq 2$   
hour/day than non-users<sup>15</sup>. 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).

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

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

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

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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 underestimated 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<sup>22</sup>; in Australia 11.6% of the country's population is on antidepressants<sup>23</sup>. 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.

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2 We suggest that reducing Western diet consumption, increasing physical activity and  
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4 smoking cessation may mitigate antidepressant-related weight gain. General  
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6 practitioners should encourage their patients adopt healthy lifestyle while treating  
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8 depression with antidepressants or cognitive behaviour therapy.  
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15  
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17  
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19  
20 international institutions

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

23  
24 **Author contributions:** ZS contributed to the conception, analysis, and interpretation  
25  
26 of data; drafting of the report; and have given approval of the final version for  
27  
28 publication. EA, AWT, TKG, KP, SA, MLW and JL contributed to analysis and  
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30 interpretation of the data, commented on the report, revising the manuscript and  
31  
32 approving the final version for publication.  
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### 34 35 **Availability of data and material**

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38 Data from the North West Adelaide Healthy Study (NWAHS) were accessed from a  
39  
40 third party. The authors confirm that for approved reasons, some access restrictions  
41  
42 apply to the data underlying the findings. To gain access to the data for this  
43  
44 manuscript, ethics approval was sought and granted. Enquiries regarding requests for  
45  
46 the NWAHS data can be directed to Prof Robert Adams, Principal Investigator  
47  
48 (Clinical) (robert.adams@adelaide.edu.au).  
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3 **Figure legends**  
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5 Supporting Information **Figures**  
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8 **Figure S1:** Factor loadings of dietary patterns  
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11 **Figure S2:** Interaction between any antidepressant use and age in relation to weight  
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13 gain.  
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## References

1. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011;**377**(9765):557-67.
2. Atlantis E, Lange K, Wittert GA. Chronic disease trends due to excess body weight in Australia. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2009;**10**(5):543-53.
3. Australian Bureau of Statistics. 4364.0.55.001 - Australian Health Survey: First Results, 2011-12. , 2012.
4. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010;**67**(3):220-9.
5. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013;**10**(11):e1001547.
6. Kivimaki M, Hamer M, Batty GD, et al. Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetes Care* 2010;**33**(12):2611-6.
7. Blumenthal SR, Castro VM, Clements CC, et al. An electronic health records study of long-term weight gain following antidepressant use. *JAMA Psychiatry* 2014;**71**(8):889-96.
8. Arterburn D, Sofer T, Boudreau DM, et al. Long-Term Weight Change after Initiating Second-Generation Antidepressants. *J Clin Med* 2016;**5**(4).
9. Patten SB, Williams JV, Lavorato DH, et al. Weight gain in relation to major depression and antidepressant medication use. *J Affect Disord* 2011;**134**(1-3):288-93.
10. Paige E, Korda R, Kemp-Casey A, et al. A record linkage study of antidepressant medication use and weight change in Australian adults. *Aust N Z J Psychiatry* 2015;**49**(11):1029-39.
11. Atlantis E, Sullivan T, Sartorius N, et al. Changes in the prevalence of psychological distress and use of antidepressants or anti-anxiety medications associated with comorbid chronic diseases in the adult Australian population,

- 2001-2008. The Australian and New Zealand journal of psychiatry  
2012;**46**(5):445-56.
12. Harris MG, Burgess PM, Pirkis J, et al. Correlates of antidepressant and anxiolytic,  
hypnotic or sedative medication use in an Australian community sample.  
Australian and New Zealand Journal of Psychiatry 2011;**45**(3):249-60.
13. Lee SH, Paz-Filho G, Mastronardi C, et al. Is increased antidepressant exposure a  
contributory factor to the obesity pandemic? *Transl Psychiatry* 2016;**6**:e759.
14. Mastronardi C, Paz-Filho GJ, Valdez E, et al. Long-term body weight outcomes of  
antidepressant-environment interactions. *Mol Psychiatry* 2011;**16**(3):265-72.
15. Jensen-Otsu E, Austin GL. Antidepressant Use is Associated with Increased  
Energy Intake and Similar Levels of Physical Activity. *Nutrients*  
2015;**7**(11):9662-71.
16. Grant JF, Taylor AW, Ruffin RE, et al. Cohort Profile: The North West Adelaide  
Health Study (NWAHS). *Int J Epidemiol* 2009;**38**(6):1479-86.
17. Radloff LS. The CES-D scale: A self-report depression scale for research in the  
general population. *Applied Psychological Measurement* 1977;**1**:385-401.
18. Australian Bureau of Statistics, editor. *National Health Survey: users' guide*.  
Canberra: ABS, 2003.
19. Schoenaker DA, Dobson AJ, Soedamah-Muthu SS, et al. Factor analysis is more  
appropriate to identify overall dietary patterns associated with diabetes when  
compared with Treelet transform analysis. *J Nutr* 2013;**143**(3):392-8.
20. Gibson-Smith D, Bot M, Milaneschi Y, et al. Major depressive disorder,  
antidepressant use, and subsequent 2-year weight change patterns in the  
Netherlands Study of Depression and Anxiety. *J Clin Psychiatry*  
2016;**77**(2):e144-51.
21. Noordam R, Aarts N, Tiemeier H, et al. Sex-specific association between  
antidepressant use and body weight in a population-based study in older adults.  
*J Clin Psychiatry* 2015;**76**(6):e745-51.
22. IMS Institute for Healthcare Informatics. The Use of Medicines in the United  
States: Review of 2011. Secondary The Use of Medicines in the United States:  
Review of 2011 2012.
23. Mental health services in Australia. Mental health-related prescriptions.  
Secondary Mental health-related prescriptions.  
<https://mhsa.aihw.gov.au/resources/prescriptions/>.



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Table 1 Sample characteristic by sex \*

	Male	Female	Total	<i>P</i> value
<i>n</i> (%)	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

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3	TCA <sub>s</sub> †	0.1 (0.6)	0.2 (1.3)	0.1 (1.0)	<0.001
4	SSRIs †	0.2 (1.3)	0.4 (1.6)	0.3 (1.4)	0.019
5	Other antidepressant †	0.1 (0.8)	0.3 (1.5)	0.2 (1.2)	<0.001
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7 \* values are n (%) or mean (SD)

8 † Annual number of prescriptions

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Table 2 Association ( $\beta$  95%CI) between antidepressant use and annual weight gain

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	<i>P</i> value
<b>Any antidepressant</b>				
<i>n</i>	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
<b>SSRIs</b>				
<i>n</i>	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	<b>0.30(0.04-0.57)</b>	<b>0.53(0.27-0.80)</b>	<b>&lt;0.001</b>
Model 2 †	Ref	<b>0.30(0.03-0.58)</b>	<b>0.58(0.30-0.85)</b>	<b>&lt;0.001</b>
Model 3 ‡	Ref	<b>0.30(0.01-0.58)</b>	<b>0.48(0.20-0.76)</b>	<b>&lt;0.001</b>
<b>TCAs</b>				
<i>n</i>	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
<b>Other antidepressants</b>				
<i>n</i>	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	<i>P</i> for interaction
<b>Western dietary pattern</b>				0.026
Low intake	0.00	0.11(-0.29-0.51)	0.14(-0.26-0.54)	
High intake	0.00	<b>0.46(0.05-0.88)</b> †	<b>0.84(0.43-1.24)</b>	
<b>Prudent dietary pattern</b>				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)	<b>0.61(0.20-1.02)</b>	
<b>Physical activity</b>				0.039
Sedentary	0.00	0.15(-0.34-0.63)	<b>1.01(0.52-1.50)</b>	
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)	
<b>Smoking</b>				0.002
Non-smoker	0.00	-0.28(-0.73-0.16)	0.35(-0.03-0.72)	
Current or ex-smoker	0.00	<b>0.44(0.05-0.84)</b>	<b>0.66(0.23-1.10)</b>	

\* 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	<i>P</i> value
<i>n</i> (%)	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
TCAAs †	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

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

	Non-user	1-2 prescriptions/year	>2 prescriptions/year	<i>P</i> 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	

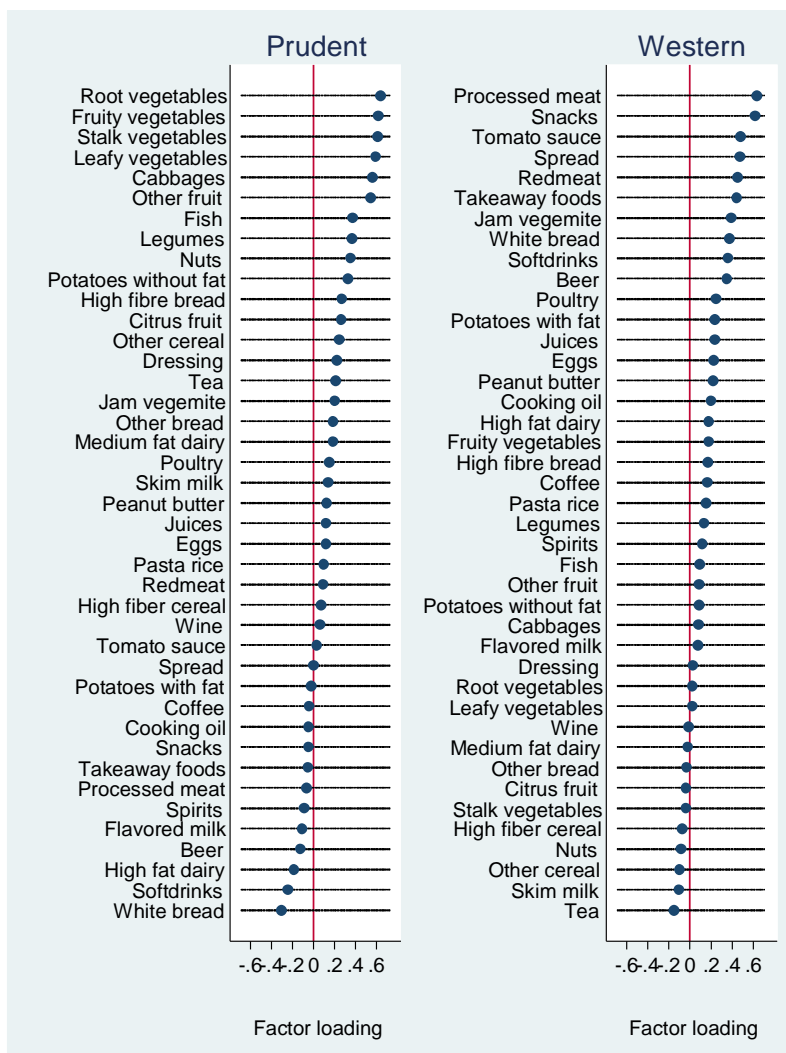
\* Values are age and gender adjusted mean (SE).

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

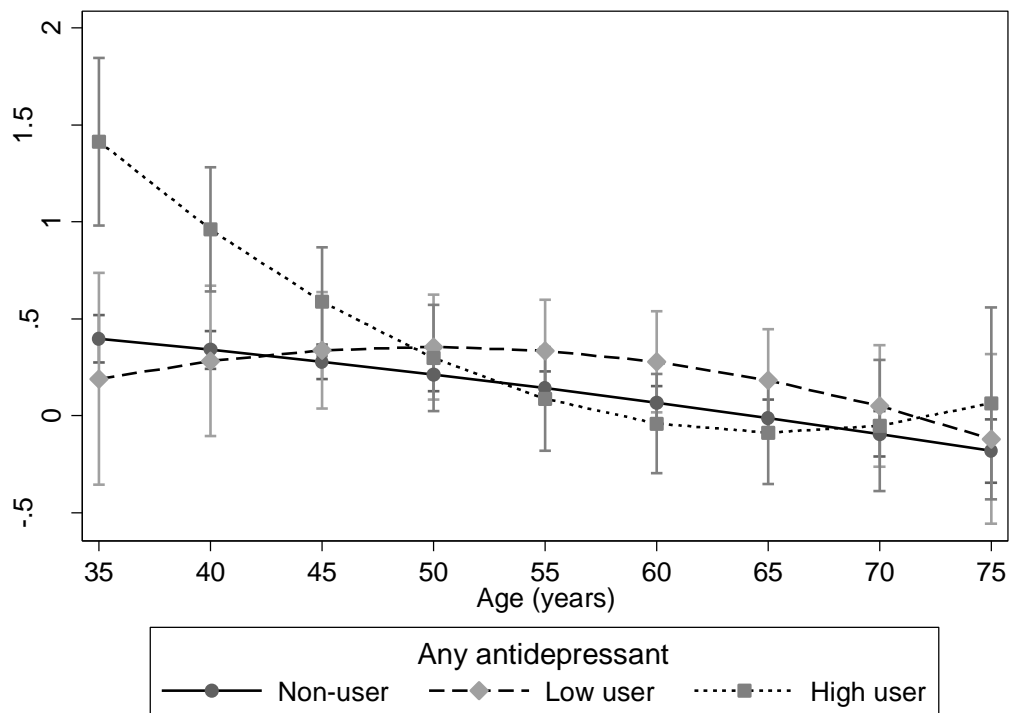
	Non-user	Low user	High user	<i>P</i> value
Any antidepressant	Ref	-0.32(-2.81-2.16)	<b>4.40(1.97-6.83)</b>	0.002
TCAs	Ref	-2.81(-6.56-0.94)	0.87(-4.52-6.25)	0.571
SSRIs	Ref	1.45(-1.66-4.56)	<b>4.20(1.06-7.35)</b>	0.007
Other	Ref	2.88(-1.43-7.18)	<b>7.14(3.05-11.23)</b>	<0.001

\* 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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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, page 5
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Paragraph 1, page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Paragraph 1-2, page 6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Cohort study: Paragraph 1 Page 6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	Paragraph 1 (external

		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	linkage)
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	Paragraph 6, page 8-9
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Methods section: Paragraph 1
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Table 1; Methods section: Paragraph 1
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	N/A
		<i>Cross-sectional study</i> —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

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