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Patterns of Antidepressant Usage and Their Association with Six-Year Body Weight Changes: A Prospective Population-Based Cohort Study

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Abstract

Therapy with antidepressants could contribute to increases in body mass, though extended-duration investigations remain scarce. The analysis incorporated 3,127 individuals (including 1,701 females) participating in the REGICOR cohort, with a mean age of 55.6 years (standard deviation 11.6) during the initial assessment period of 2003–2006, residing in northeastern Spain. Information was available from two assessments (initial and after a median interval of 6.3 years) regarding self-reported antidepressant medication, body mass, stature, along with initial data on tobacco use, leisure-time exercise, dietary patterns, educational attainment, marital status, and symptoms of depression evaluated via the Patient Health Questionnaire (PHQ-9) during the subsequent evaluation. Four patterns of antidepressant utilization were identified: no usage ever, commencement at the second assessment, cessation after initial usage, and ongoing usage across both assessments. Multivariable linear regression models were applied to evaluate links between these patterns and proportional changes in body mass. Among those without obesity initially (n = 2,404), associations with new-onset obesity at the later assessment were also examined.

Over the approximate 6-year period, participants experienced an average increase of 0.53 kg (equivalent to 1.01% of initial body mass), while 24.5% showed gains exceeding 5% of their starting weight. Most individuals (83.6%) reported no antidepressant usage, whereas 6.2% began treatment during the interval, 5.1% stopped after starting, and 5.1% indicated usage at both evaluations. After adjustments in multivariable models, relative to those with no usage, every pattern linked to higher mass increases: +1.78% (95% CI: 0.57, 2.98) for cessation after initial use, +2.08% (0.97, 3.19) for commencement at follow-up, and +1.98% (0.75, 3.20) for ongoing use. In participants free of obesity at start (n = 2,404), the odds ratio for developing obesity reached 2.06 (1.03, 3.96) with ongoing use, while results for other patterns lacked statistical significance. Within this community-based cohort of adults, persistent antidepressant utilization showed a robust link to increases in body mass. Both initiation and cessation patterns also connected to greater mass gains, though not significantly to new obesity cases. Amid rising global obesity rates and increasing antidepressant prescriptions, strategies for mass control and metabolic surveillance warrant inclusion in depression management protocols alongside medication regimens.

Keywords: Antidepressant, Weight change, Anthropometrics, Obesity, Prospective study

Introduction

Major depressive disorder stands as the leading psychiatric condition [1]. Worldwide estimates indicate that around 280 million individuals suffer from depression [2], corresponding to about 5% prevalence in adults over age 20. Females face nearly double the risk compared to males throughout their lives. The condition imposes severe impacts, contributing prominently to years lived with disability [1]. Primary treatment for major depression, combined with psychotherapy, involves antidepressant medications [3, 4]—now the most frequently prescribed drugs globally. Antidepressant regimens address both immediate (acute and continuation) and extended (maintenance) phases,

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potentially lasting from one year to indefinitely [5]. Records from the UK's primary care database reveal that 24% of individuals received at least one antidepressant prescription from 1995 to 2011, with higher rates in females and a doubling of prevalence over that timeframe [3]. In one Spanish region (Castile and León), recent figures show 8.6% yearly antidepressant utilization, reaching 12.1% among women versus 4.9% in men [6].

Although newer antidepressants offer better tolerance and acceptance, all carry potential adverse reactions in short- and long-term use, requiring careful risk-benefit evaluation [7]. Common side effects encompass sleep disturbances, drowsiness, vertigo, agitation, tremors, oral dryness, excessive perspiration, sexual dysfunction, gastrointestinal issues, and notably, alterations in body mass [5]. Increases in mass have emerged as a key factor leading to treatment cessation [8].

Globally, obesity impacts roughly 650 million adults, carrying broad health consequences [9]. Strong epidemiologic data point to a mutual association between obesity and depression: prospective research demonstrates obesity predicting future depression and certain symptoms [10], while depression elevates later obesity risk [10–13]. Proposed overlapping pathways include genetic factors, overactivity of the hypothalamic–pituitary–adrenal axis, leptin imbalances, insulin dysregulation, and intestinal microbiome disruptions [13]. Medication for depression represents another plausible link, as antidepressants may induce mass gains varying by type. Certain selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs), for instance, connect to increases, in contrast to agents like bupropion that may promote loss [14, 15]. Yet, much evidence derives from brief clinical trials (spanning weeks or months) [8, 16], with insufficient real-world prospective data on extended effects over years [16, 17]. The most extensive prior investigation, drawing on UK primary care records over 10 years, linked 1–6 years of antidepressant exposure to elevated odds of exceeding 5% mass gain [18]. Finnish research indicated that sustained high-dose antidepressant intake (>200 daily doses annually over 4 years) correlated with more substantial 4-year gains versus depressed non-users [19]. A Canadian analysis associated SSRIs and venlafaxine (but not TCAs) with heightened 10-year obesity risk [20]. One modest-scale study tied only SSRI exposure over 90 days to greater BMI rises compared to non-users, unlike TCAs or alternatives [21]. As far as known, prior work focused on aggregated exposure without exploring extended patterns like treatment discontinuation.

The objective here was to characterize patterns of antidepressant utilization separated by about 6 years and examine their relations to mass variations and obesity onset in a community-based prospective cohort of middle-aged Spanish adults.

Materials and Methods

Study design and participants

The REGICOR study (REgistre GIroni del COR, or Girona Heart Registry) represents a prospective, community-based cohort conducted in Girona province (population around 700,000) in northeastern Spain, primarily aimed at investigating cardiovascular disease occurrence and associated risk factors. A comprehensive description of the study methodology is available elsewhere [22]. In summary, residents from 42 localities—comprising 41 rural areas and the urban center of Girona—were randomly drawn from population registers and invited to join. Eligible individuals were aged 35–79 years, without terminal illness, not residing in institutions, and having spent at least six months annually in the region. Enrollment occurred across three phases: 1995, 2000, and 2005. Participation reached 73.8% among those invited for the initial examination. For the present analysis, baseline data were restricted to the 6,352 participants recruited in the third phase (2005). The subsequent evaluation occurred between 2007 and 2013, during which 2,072 individuals did not participate. No intermediate assessments were conducted, resulting in an average interval of 6 years between visits. Among those eligible for re-examination (alive, still residing in the area, and without severe illness), attendance was 78%. Ethical approval was granted by the Parc de Salut Mar Research Ethics Committee, with all participants providing written informed consent. Data collection involved standardized, validated instruments and protocols administered by trained nurses and interviewers, as detailed previously [20].

Assessment of exposure

Baseline medication information was obtained through self-report via an open-ended inventory. Antidepressants were identified as those categorized as selective serotonin reuptake inhibitors (SSRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), or tricyclic antidepressants (TCAs). At the follow-up assessment,

researchers documented psychotropic drug use through a dedicated query, classifying medications into categories such as antiepileptics, antiparkinsonian agents, antipsychotics, lithium, anxiolytics, hypnotics/sedatives, SSRIs, NDRIs, and other psychotropics. Antidepressant classification at follow-up was limited to SSRIs and NDRIs.

A four-level variable was constructed to capture antidepressant utilization patterns over the approximate 6-year period: no use at either time point, use only at baseline (subsequently discontinued), use only at follow-up (new initiation), and use at both time points (persistent). A parallel variable was generated specifically for SSRI trajectories, given consistent reporting across assessments and sufficient statistical power for the four-category structure.

Outcome measures

Trained nurses measured height and weight at both assessments following standardized procedures. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2), with obesity defined as BMI ≥30 kg/m^2 [23]. Percentage weight change was computed as [(follow-up weight − baseline weight) / baseline weight] × 100.

Covariates

Most covariates were measured at baseline, with the exceptions of depressive symptoms and marital status, which were collected at follow-up.

Self-reported data included smoking status (current, former, never), marital/cohabitation status (partnered, single/separated/widowed), and education (low, medium, high). Leisure-time physical activity was evaluated using the Spanish-validated Minnesota questionnaire [24, 25]. Nutritional habits were captured via a 157-item food frequency questionnaire [26], from which the relative Mediterranean diet adherence score (0–18 range) was derived [27]. Type 2 diabetes was identified by fasting glucose >126 mg/dl or use of insulin/oral hypoglycemic agents. Hypertension was diagnosed based on systolic blood pressure >140 mmHg, diastolic >90 mmHg, or antihypertensive treatment. Given potential links of diabetes and hypertension to body composition, lifestyle modifications, and mood disorders, they were included as adjusters. Antipsychotic use was also considered due to its known weight-promoting effects and possible co-prescription with antidepressants in depressed patients; however, only 39 participants reported baseline use and 34 at follow-up, suggesting limited confounding impact.

Depressive symptoms were measured with the Spanish-validated Patient Health Questionnaire-9 (PHQ-9) [28], scoring nine items from 0 ("not at all") to 3 ("nearly every day")—covering aspects like anhedonia, sleep disturbances, and self-deprecation—for a total of 0–27. A score ≥10 indicated probable depression [29]. Additionally, primary care electronic records from the Catalan Government's PADRIS program were linked for diagnoses between January 2008 and December 2016. Depression cases were defined by ICD-10 codes F32 (depressive episode) or F33 (recurrent major depressive disorder) occurring between baseline and follow-up. A combined "depression" indicator (elevated PHQ-9 symptoms or diagnosed episode during follow-up) served as a primary adjuster to isolate antidepressant effects from those of underlying depression on weight trajectories.

Statistical analysis

Baseline characteristics were summarized by antidepressant trajectory groups, as well as by age strata, sex, and initial BMI categories. Group differences were tested using ANOVA for continuous data and chi-square tests for categorical data, presented as means (standard deviations) or counts (percentages).

Percentage weight change was analyzed as a continuous dependent variable in generalized linear models, with antidepressant trajectory as the main categorical predictor (reference: no use). Model 0 adjusted for age and sex only. Model 1 added education, marital status, smoking, Mediterranean diet score, physical activity, diabetes, and hypertension. Continuous variables included age, diet score, and activity level; categorical variables comprised sex, education, marital status, smoking, diabetes, and hypertension. Model 2 incorporated depression status to separate its influence from medication effects. Model 3 further included baseline BMI. Sensitivity analyses added antipsychotic use adjustment. Potential interactions of antidepressant trajectories with age, sex, and baseline BMI were evaluated via likelihood ratio tests comparing nested models, with stratified estimates reported where relevant. Findings are shown as beta coefficients with 95% confidence intervals.

Clinically meaningful weight gain (>5%) was examined using multivariable logistic regression with identical covariate progression, enabling comparison with prior

work [18]. In participants without baseline obesity, incident obesity risk at follow-up was assessed similarly via logistic models. Results are reported as odds ratios with 95% confidence intervals.

Statistical significance was set at two-tailed $p < 0.05$. Analyses were conducted in R version 4.2.1.

Results and Discussion

The primary analytic sample consisted of 3,127 adults (including 1,701 females) with a mean age of 55.6 years (standard deviation 11.6) and complete data. Relative to individuals excluded from this investigation, the retained participants were younger, predominantly female, more often never-smokers, and less frequently had low educational attainment. No notable differences emerged, however, in dietary patterns, leisure-time physical activity, initial BMI, or antidepressant utilization.

The median duration to re-assessment was 6.3 years (interquartile range 5.7–6.8 years; 5th percentile: 5.3 years; 95th percentile: 9.9 years). In total, 16.4% of individuals reported antidepressant use at one or both assessments: 5.1% used them only at baseline (later discontinued), 6.2% started them by follow-up, and 5.1% reported use on both occasions. Across the follow-up period, the average weight increase was +0.53 kg (SD = 6.19), equating to +1.01% (SD = 7.88%) of baseline body weight. Baseline characteristics by group are shown in **Table 1**. In comparison to those with no antidepressant exposure, individuals with any use (across the other patterns) tended to be older, more often female and non-smokers, less likely to have higher education or a cohabiting partner, while those with persistent use exhibited reduced physical activity and lower Mediterranean diet scores. Participants with any antidepressant history also displayed elevated depressive symptoms, higher BMI at both time points, greater obesity rates, and more pronounced weight increases.

Table 1. Characteristics of participants in the REGICOR study included in the analysis, overall and across antidepressant use trajectories (N=3,127), Spain, 2005-2013.

	Overall	Never use	Initial use discontinued	New use at follow-up	Repeated use	p-Value[a]
n (%)	3,127	2,613 (83.6)	161 (5.1)	194 (6.2)	159 (5.1)	
Female (%)	1,701 (54.4)	1,313 (50.2)	113 (70.2)	148 (76.3)	127 (79.9)	<0.001
Age [mean (SD)]	55.56 (11.61)	55.10 (11.67)	56.51 (10.79)	57.82 (11.42)	59.32 (10.53)	<0.001
Educational level (%)						0.003
High	715 (22.9)	628 (24.0)	30 (18.6)	31 (16.0)	26 (16.4)	
Low	1,486 (47.5)	1,209 (46.3)	77 (47.8)	106 (54.6)	94 (59.1)	
Medium	926 (29.6)	776 (29.7)	54 (33.5)	57 (29.4)	39 (24.5)	
Living with a partner (%)	2,369 (75.8)	2,026 (77.5)	113 (70.2)	139 (71.6)	91 (57.2)	<0.001
Smoking status baseline (%)						<0.001
Never	1,695 (54.2)	1,368 (52.4)	90 (55.9)	129 (66.5)	108 (67.9)	
Current	630 (20.1)	547 (20.9)	31 (19.3)	29 (14.9)	23 (14.5)	
Ex-smoker	802 (25.6)	698 (26.7)	40 (24.8)	36 (18.6)	28 (17.6)	
Mediterranean diet score [mean (SD)]	8.72 (2.83)	8.76 (2.84)	8.41 (2.69)	8.79 (2.71)	8.16 (2.81)	0.032
Energy kcal/day [mean (SD)]	2,437.81 (654.57)	2,447.51 (648.56)	2,434.14 (708.74)	2,380.77 (709.30)	2,351.64 (622.10)	0.186
Physical activity METs.min/day [mean (SD)]	310.56 (341.61)	316.44 (332.54)	278.69 (376.14)	291.62 (277.62)	269.29 (489.37)	0.165
Hypertension	1,318 (42.1)	1,087 (41.6)	58 (36.0)	91 (46.9)	82 (51.6)	0.023
Diabetes	339 (10.8)	273 (10.4)	15 (9.3)	28 (14.4)	23 (14.5)	0.061
Body weight variables						
BMI baseline, kg/m^2 [mean (SD)]	27.29 (4.53)	27.22 (4.48)	27.52 (4.62)	27.24 (4.77)	28.33 (4.80)	0.024
BMI follow-up, kg/m^2 [mean (SD)]	27.49 (4.56)	27.35 (4.48)	28.01 (4.78)	27.88 (4.77)	28.78 (5.22)	<0.001

BMI change, kg/m^2 [mean (SD)]	0.19 (2.42)	0.13 (2.38)	0.49 (2.46)	0.64 (2.43)	0.45 (2.82)	0.005
Weight change, kg [mean (SD)]	0.53 (6.19)	0.39 (6.10)	1.29 (6.47)	1.39 (6.30)	1.01 (7.12)	0.035
Weight change, % [mean (SD)]	1.01 (7.88)	0.78 (7.56)	2.23 (8.84)	2.48 (9.57)	1.74 (9.42)	0.003
Weight gain >5% (%)	767 (24.5)	596 (22.8)	54 (33.5)	66 (34.0)	51 (32.1)	<0.001
Obese (BMI ≥ 30) baseline (%)	721 (23.1)	585 (22.4)	37 (23.0)	48 (24.7)	51 (32.1)	0.042
Obese (BMI ≥ 30) follow-up (%)	779 (24.9)	621 (23.8)	47 (29.2)	55 (28.4)	56 (35.2)	0.003
Depression variables						
PHQ-9 score at follow-up [mean (SD)]	3.06 (3.97)	2.62 (3.46)	5.07 (5.31)	5.46 (5.55)	5.33 (5.28)	<0.001
Depression during follow-up (%)	312 (10.0)	180 (6.9)	40 (24.8)	57 (29.4)	35 (22.0)	<0.001
Antidepressant use at baseline (%)	320 (10.2)	0 (0.0)	161 (100.0)	0 (0.0)	159 (100.0)	<0.001
Antidepressant use at follow-up (%)	353 (11.3)	0 (0.0)	0 (0.0)	194 (100.0)	159 (100.0)	<0.001

[a]p-Value for the ANOVA or chi-square test for the difference across the four trajectories of antidepressant use.

As illustrated in **Figure 1**, each of the three antidepressant utilization patterns showed higher weight increases relative to individuals who never used these medications, irrespective of the degree of covariate adjustment. In the fully adjusted Model 3, the largest proportional weight increase (relative to baseline body mass) occurred among those who initiated treatment at follow-up [+2.17% (95% CI: 1.05, 3.29), $p < 0.001$], closely followed by persistent users [+2.01% (0.78, 3.23), $p = 0.001$], and those who discontinued after baseline use [+1.83% (0.62, 3.04), $p = 0.003$]. Incorporating adjustment for depressive status over the follow-up period (Model 2) and initial BMI (Model 3) did not weaken these associations; instead, the estimates became slightly more pronounced across all three patterns. Additional control for antipsychotic medication use also left the coefficients largely unchanged. When the analysis was limited to SSRI trajectories, effect sizes remained comparable overall, though persistent SSRI use was linked to somewhat smaller weight gains than the other two patterns.

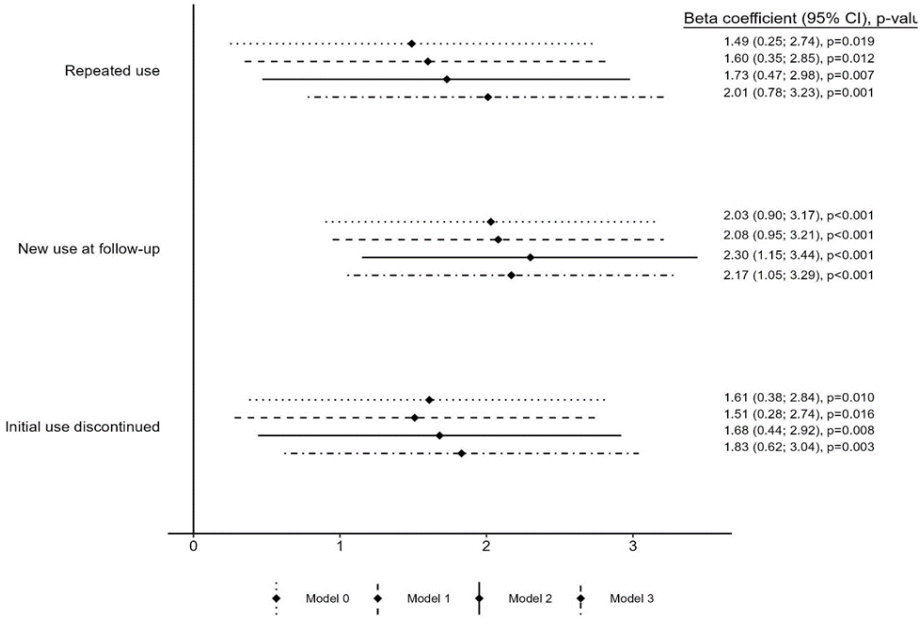
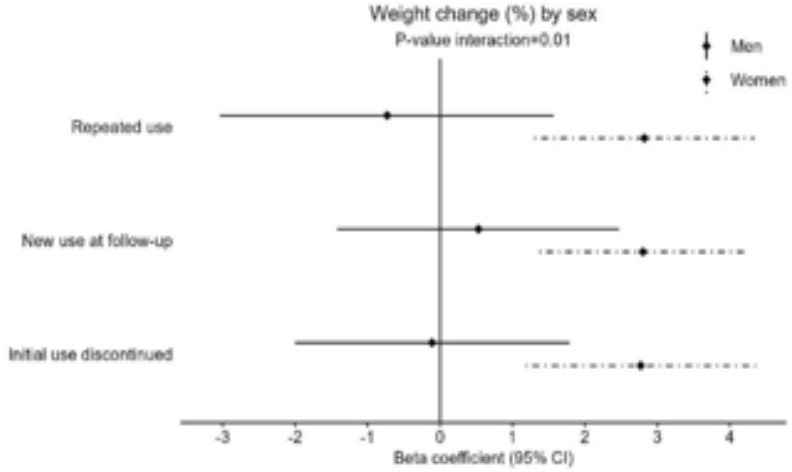


Figure 1. Linear relationships between patterns of antidepressant utilization and proportional weight variation over 6 years (relative to initial body mass). Model 0 adjusts for age and sex at baseline. Model 1 additionally controls for baseline age, sex, education, cohabitation status, smoking habits, leisure-time physical activity, Mediterranean diet score, diabetes, and hypertension. Model 2 incorporates depression status during the follow-up period. Model 3 further adjusts for baseline BMI.

As displayed in **Figure 2**, the links were stronger among participants under 55 years of age, non-smokers, and those with normal body weight (BMI < 25 kg/m²) [23] at the start of the study; the associations emerged clearly in females but not in males. Six-year weight trajectories varied according to initial characteristics: weight increases occurred exclusively in individuals with baseline BMI below 25 and those younger than 55 years. Females exhibited larger weight gains compared to males. Antidepressant utilization was more common in women and in those older than 55 years.



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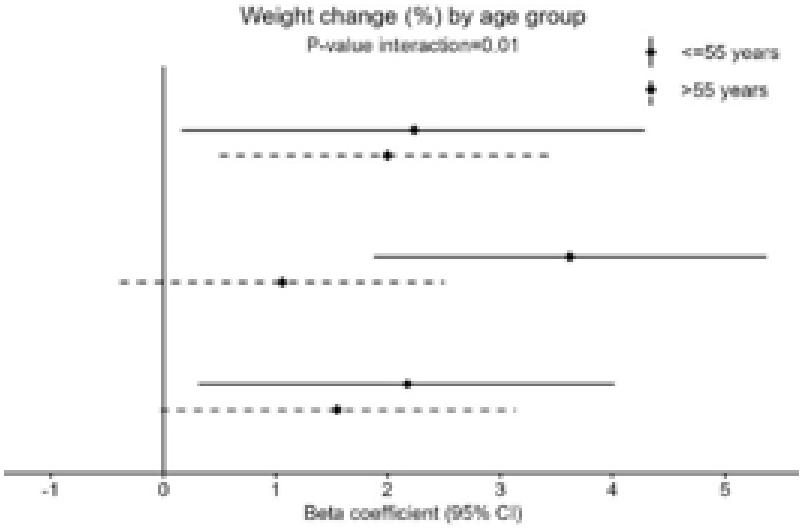

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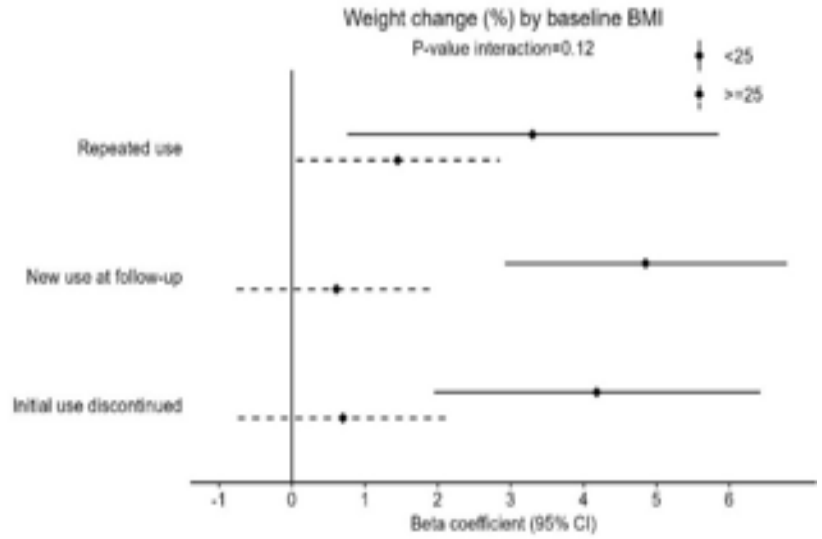

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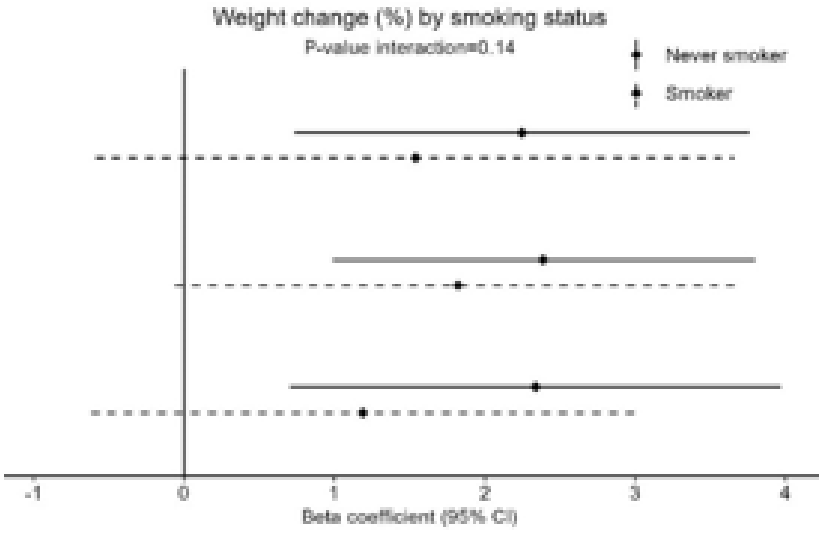

d)

Figure 2. Stratified analysis across sex, age, initial BMI category, and smoking habits, examining the linear relationships between patterns of antidepressant utilization and proportional weight variation over 6 years (relative to baseline body mass). The reference group is individuals with no antidepressant use. All estimates are fully adjusted (as appropriate) for baseline age, sex, education, cohabitation status, smoking, leisure-time physical activity, Mediterranean diet score, diabetes, hypertension, depressive status during follow-up, and baseline BMI (Model 3). Interaction p-values derive from likelihood ratio tests comparing nested models with and without terms for interaction between antidepressant trajectory and each stratifying variable: sex (categorical), age (continuous), baseline BMI (continuous), and smoking status (categorical).

Logistic regression findings indicated that any antidepressant exposure (across all three patterns) linked to elevated odds of exceeding 5% weight increase over 6 years, with comparable effect sizes: discontinued after baseline use OR = 1.80 (1.25, 2.56); initiation at follow-up OR = 1.93 (1.38, 2.68); and persistent use OR = 1.90 (1.31, 2.72).

Among those free of obesity at baseline (n = 2,404; **(Figure 3)**), persistent antidepressant use alone demonstrated a robust and statistically significant link to incident obesity: fully adjusted OR = 2.02 (1.00, 3.88) in

Model 3, whereas the remaining patterns showed smaller and less precise odds ratios. Additionally, depression itself correlated with greater obesity risk [unadjusted OR = 2.13 (1.40–3.17, p < 0.001), not shown in tables], and incorporating depression status into the models reduced the strength of associations between antidepressant patterns and new-onset obesity (comparison of Model 2 versus Model 1).

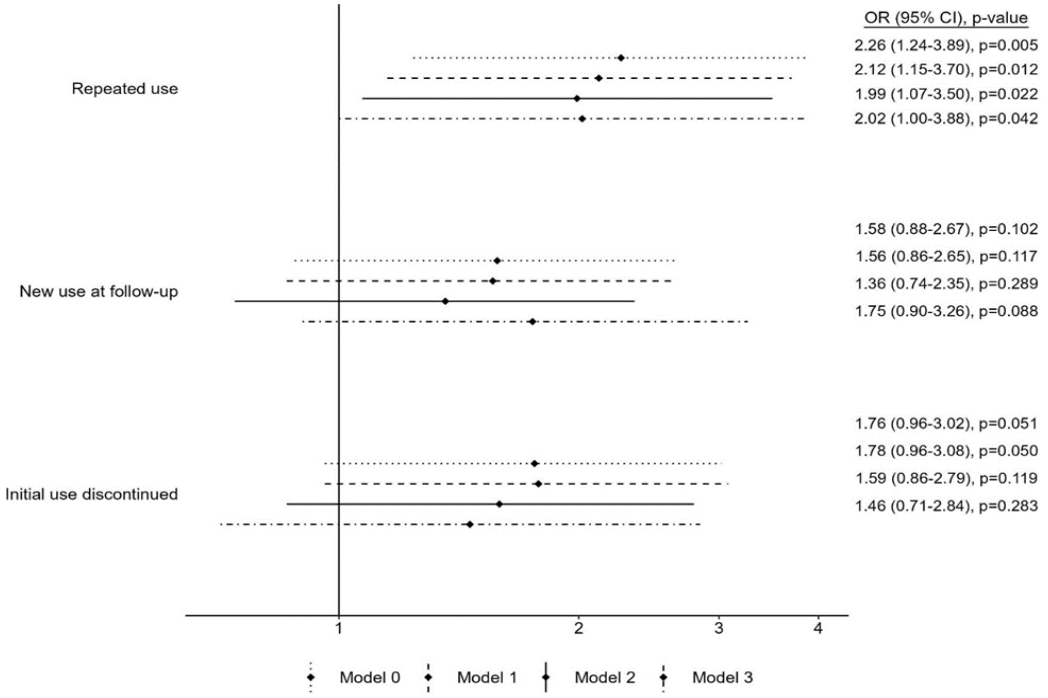

Figure 3. Links from multivariable logistic regression models between patterns of antidepressant utilization and risk of incident obesity among individuals without obesity at baseline (n = 2,404). The reference group is those with no antidepressant use. Model 0 controls for baseline age and sex. Model 1 additionally adjusts for baseline age, sex, education, cohabitation status, smoking, leisure-time physical activity, Mediterranean diet score, diabetes, and hypertension. Model 2 incorporates depression status during follow-up. Model 3 further includes baseline BMI.

In this community-based longitudinal investigation involving more than 3,000 middle-aged Spanish adults, antidepressant utilization—even when intermittent—was linked to larger weight increases over approximately 6 years, with proportional gains ranging from 1.78% to 2.08% higher than in those who never used these medications. These connections persisted after controlling for age, sex, socioeconomic variables, lifestyle behaviors, and depressive symptoms. The relationships appeared strongest in females, participants younger than 55 years, and those with normal body weight at the outset. In individuals free of obesity initially, persistent antidepressant use (reported at both assessments) correlated with elevated odds of developing obesity.

These observations add to accumulating evidence from investigations in the UK [18], Finland [19], Canada [20, 30], Australia [31], and the Netherlands [21], demonstrating that prolonged antidepressant exposure, especially SSRIs and possibly TCAs, connects to increased body mass over time. The extent of weight increase detected here aligns with, or exceeds, prior reports comparing users to non-users. Some have proposed that such patterns might stem from depression itself rather than the drugs, yet our findings—consistent with several others [18, 19, 21, 30, 31]—remain robust after adjustment for depressive symptoms. That said, depressive symptoms were assessed only at follow-up in our cohort. Among those initiating treatment during follow-up, undetected baseline symptoms could have prompted both weight gain and subsequent prescribing,

limiting our ability to fully separate these factors. The particularly marked association in new initiators might also reflect a stronger acute influence of antidepressants on body mass. Persistent users entered the study with higher average baseline BMI (28.3) than never-users or new initiators (27.2), implying that some medication-related weight accrual may have preceded enrollment. A higher starting weight could also constrain additional gains during observation.

Subgroup findings revealed associations primarily in women, aligning with one earlier report [21], though others detected no notable sex differences [18, 30]. Women in our sample displayed greater average weight increases and variability over 6 years, alongside higher antidepressant utilization rates, which likely accounts for the more evident links in this group. Heightened connections between new antidepressant exposure and weight gain in younger participants and those with lower initial BMI mirror observations by Gafoor *et al*. [18] and may relate to larger overall gains in these subgroups. Considering that depression often emerges in early adulthood, these results highlight the need for vigilant weight oversight when initiating antidepressants in younger patients, despite our cohort's minimum age of 35.

Among non-obese participants at baseline, incident obesity risk rose predominantly with persistent antidepressant use, while initiation or discontinuation showed unclear links. This suggests prioritizing close weight surveillance in long-term users to avert progression to obesity.

Multiple pathways may underlie these patterns, involving monoamine systems (serotonergic, adrenergic, dopaminergic, histaminergic, and muscarinic receptors) that modulate appetite hormones, feeding behavior, and metabolism [8]. For example, antagonism of histamine receptors by certain antidepressants can stimulate appetite through orexigenic signals such as ghrelin and neuropeptide Y. Regarding SSRIs, blockade of the serotonin transporter (SERT) has been tied to obesity and diabetes in animal models lacking SERT [32].

This investigation offers several advantages. It draws from a representative community cohort of substantial size in Girona province, northeastern Spain. Antidepressant prevalence (16.4%) matched rates in other affluent nations, including the UK (18%) [18] and Canada (13.7%) [30]. The extended follow-up enabled detection of chronic effects, unlike most trials limited to short- (weeks) or medium-term (around 6 months) outcomes [14]. Exposure and outcomes were rigorously assessed: anthropometrics were obtained via standardized measurements by trained personnel, and medication reports were collected and confirmed during visits. This surpasses many long-term studies relying on inconsistent clinical records [18], self-reported measures [19, 20], or dispensing data that may not confirm ingestion [18, 19, 31]. Our thorough adjustment for lifestyle elements (physical activity, diet, smoking)—potential confounders of adiposity—extends beyond most prior work, with only one study similarly accounting for them [31].

Limitations exist, however. Although prescription registries provide objective, frequent updates, we depended on self-reported use at just two assessments. Medication categorization varied slightly between time points (TCAs absent at follow-up), probably reflecting clinical shifts toward SSRIs/NDRIs [18]. We lacked granularity to examine trajectories by specific subclasses, treating "any antidepressant" as the primary exposure. Weight effects differ across classes—TCAs often implicated more strongly—yet emerging long-term data increasingly implicate SSRIs [18, 20, 21, 31], consistent with our SSRI-restricted sensitivity results. Absence of drug-specific details represents a drawback, particularly amid recent class-specific findings [15]. Low antipsychotic reporting precluded robust evaluation of combined use, though adjustment for it left antidepressant associations intact, indicating minimal confounding. Misclassification risks include inconsistent use among "persistent" categorizations or unreported interim exposure in "never" users. As in all observational designs, unmeasured confounding or collider stratification bias remain possible—for instance, via selective follow-up attendance. Nonetheless, non-attenders showed no significant baseline differences in BMI or antidepressant use.

Future investigations should extend beyond antidepressants to other psychotropics like antipsychotics. Ideally, integrating cohort designs with electronic records would enhance power, duration, confounder capture, medication trajectories, polypharmacy assessment, and inclusion of younger cohorts.

Conclusion

In summary, this community-based analysis of Spanish adults revealed that any antidepressant exposure over 6

years—even if discontinued—correlated with larger weight increases or heightened likelihood of >5% gain relative to non-use. Persistent use further linked to elevated obesity onset risk in initially non-obese individuals. Amid escalating global obesity and rising antidepressant prescriptions, incorporating weight oversight and metabolic checks into depression care protocols alongside medication is advisable.

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Conflict of Interest: None

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Ethics Statement: None

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