Adherence to Antidepressants Is Associated With Lower Mortality:
A 4-Year Population-Based Cohort Study

Amir Krivoy, MD[a,b,d,*]; Ran D. Balicer, MD, PhD[a,e]; Becca Feldman, PhD[a]; Moshe Hoshen, PhD[a]; Gil Zalsman, MD, MHA[b,d,f]; Abraham Weizman, MD[b,c,d]; and Gal Shoval, MD[a,b,d]

ABSTRACT

Objective: Despite the growing use of antidepressants and the potential grave consequences of inadequate treatment, little is known about the impact of adherence to antidepressant treatment on mortality in the general population. The objective of this study was to evaluate the association between adherence to antidepressants and all-cause mortality in a population-based cohort.

Methods: Data were extracted from the electronic medical record database of the largest health provider in Israel (53% of the nation's population) on a total of 251,745 patients aged 40 years and above who filled an antidepressant prescription at least once between 2008 and 2011. The main outcome measure was all-cause mortality during the study period. Adherence was measured as a continuous variable representing possession ratio (duration of filled antidepressant divided by duration of prescribed antidepressant). A polynomial model of proportional hazard Cox regression for multivariable survival analysis was used, adjusting for demographic and clinical variables that affect mortality.

Results: The association between adherence and the hazard ratio (HR) for mortality follows a quadratic model in which the lowest HR (0.66 [95% CI, 0.64–0.69]) is at a level of 60% adherence in respect to nonadherence.

Conclusions: Adherence to antidepressants is significantly associated with a corresponding decrease in the risk of mortality, controlling for relevant covariates. Physicians from all disciplines should actively improve their patients' adherence to antidepressants since their persistent use is associated with increased survival.

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[a]Clalit Research Institute, Chief Physician Office, Clalit Health Services, Tel Aviv, Israel
[b]Geha Mental Health Center, Petah Tiqva, Israel
[c]Felsenstein Medical Research Center, [d]Sackler Faculty of Medicine, Tel Aviv University, Israel
[e]Public Health Department, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel
[f]Division of Molecular Imaging and Neuropathology, Department of Psychiatry, Columbia University, New York, New York
**Corresponding author:* Amir Krivoy, MD, Geha Mental Health Center, PO Box 102, Petah Tiqva 49 100, Israel (amir.krivoy@gmail.com).

Antidepressants are indicated mainly for the treatment of highly prevalent mood and anxiety disorders. It is estimated that the current use of these medications in the general population varies between 4% and 13%,[1–4] and this rate is expected to increase over the next decade.[5] Adherence to antidepressants is essential for successful treatment outcomes[6]; however, poor adherence (none or partial) is commonly reported among patients treated with antidepressants,[7,8] ranging from 40%–75% in a 6-month period. Premature discontinuation of antidepressants is linked to relapse and chronicity,[6] as well as increased health care costs.[9] It has been suggested that adherence to treatment could reduce the overall burden of depression by 28%.[10] Consequently, improving adherence to antidepressants has been recognized by the World Health Organization (WHO) as a pressing need.[11]

Depressive and anxiety disorders are highly comorbid disorders, both concurrently and sequentially.[12,13] They share many similarities; specifically, they have common pathophysiology and biological therapies, and thus are often studied together.[12,14] They not only are major sources of lost productivity,[15,16] high health care costs,[15–17] and leading causes of burden,[18,19] but also are associated with increased mortality.[20–22] Ultimately, patients with depressive disorders have a 2-fold risk of death compared to the general population.[21]

Despite the growing use of antidepressants and the possible grave consequences of inadequate treatment, very little is known about the impact of antidepressant adherence levels on survival and mortality rates. Overall, there have been a few large-scale population-based cohort studies that have examined the association between the use of, but not adherence to, antidepressants and mortality.[23–25] Those that have been conducted vary greatly in their selected populations and methodology and yield conflicting results (Supplementary eTable 1).

The current study's primary objective was to evaluate the association between all-cause mortality rates and adherence to antidepressants, a more comprehensive clinical measure than use alone, among the patient population of Clalit Health Services (CHS). CHS insures and provides hospital and community-based services to approximately 4 million people (53% of the Israeli population), and it operates a comprehensive clinical and administrative electronic medical database. Using CHS's Electronic Medical Records (EMRs), we conducted a cohort study to examine the association between antidepressant adherence level and mortality with the largest sample size to date of antidepressant users.

METHODS

Population and Study Period

Healthcare in Israel is delivered primarily through 4 nationwide health plans (of which CHS is the largest with over 50% of the market share), which act as both providers and insurers to essentially the entire

Clinical Points

- Antidepressant drugs are commonly prescribed for several indications; however, data on long-term association between adherence and all-cause mortality are lacking.
- Study results show that adherence to antidepressants is positively associated with survival during a 4-year follow-up.
- Therefore, clinicians should actively promote greater adherence among their antidepressant-prescribed patients.

population. Through each plan, patients are guaranteed a legally mandated minimum package of medical services. CHS patients have a strong incentive to access primary care services and obtain prescription medications within the CHS system because primary care visits are free of charge to members and medications included in the benefit package are subject to greatly reduced copayments (approximately US $4–$7 per month for most medications and discounted further for disadvantaged subpopulations). Starting in 1998, data from all CHS ambulatory services on all CHS members were recorded in an integrated clinical EMR and administrative database using uniform software.

We retrospectively analyzed the entire CHS patient population during the study period and initially included all patients with at least 1 prescription for an antidepressant during that time (see Figure 1). Antidepressants included all those approved by Israel's Food and Drug Administration. Extraction was based on the WHO Anatomic Therapeutic Chemical code N06A (see Supplementary eTable 2). We included CHS members of all ages in the cohort. Patients were retrospectively monitored for medication adherence between January 1, 2008, and December 31, 2011 (the study period) and were enrolled in the study starting on the date of their first antidepressant prescription during the period (Figure 1). Preliminary analysis showed a total of 429,457 patients who were prescribed an antidepressant at least once during the study period (~10% of the CHS adult population). A total of 31,138 (7.3%) patients died during the follow-up period. The distribution of deaths across the age groups revealed that only 1.3% (n = 392) were below 40 years of age. Therefore, we limited our subsequent analysis to subjects aged 40 years and above (N = 334,663, 78% of the original sample). Since our independent variable was adherence, we analyzed data of antidepressant users and selected only those users who purchased at least one prescription (N = 251,745, 59% of the original sample).

Access to the data warehouse and the analysis were approved for this study by the CHS Review Board.

Measures

Outcome. Mortality was measured by a record (received from the Ministry of Interior Affairs) of death from any cause during the 4-year study period. Patient adherence was tracked until death or until the end of the study period.

Main predictor: adherence to antidepressants. The adherence measure was based on a medication possession ratio, which utilized data from filled prescriptions.[26,27] Filled-based measure of adherence has been found to be a reliable source of drug exposure.[28]

As previously described in detail by Singer et al,[29] adherence was defined as the ratio between the number of days covered by any antidepressant prescription filled (during the study period) divided by the time between the first and last prescriptions of antidepressant issued by the doctor, and thus reflected the period for which antidepressants were known to be prescribed. Adherence was calculated for all antidepressants; therefore, switching between antidepressant compounds was not taken into account. Adherence was reported as a continuous variable (0 to 1) and also as a percentage score for each patient. Adherence was capped at 1, such that patients who made excess purchases were attributed a score of 1. Adherence was calculated only for patients with at least 1 filled prescription. If there was only 1 prescription, without purchase, then the patient was not included in the analysis.

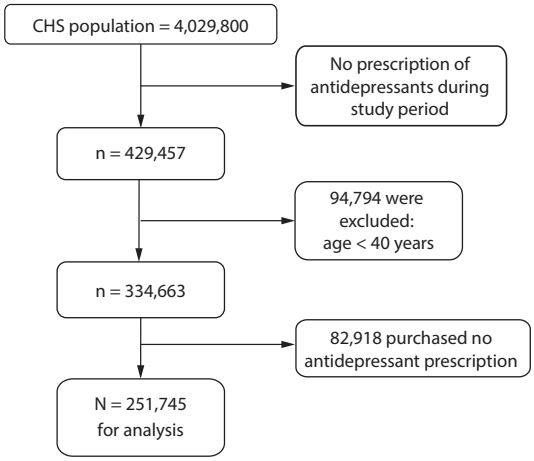
Based on generally accepted adherence categorization models,[30] patients with adherence below 20% were considered nonadherent, while patients with adherence above 80% were considered to have good adherence. Our adherence variable described the proportion of the duration of filled prescriptions over the duration of the prescribed dosage during the study period, whereas "use of antidepressant" was limited to a dichotomous rule ("used" or "did not use" antidepressants at study entry). We assumed that if the antidepressant was prescribed by the physician it was indicated for the condition it was prescribed for (ie, long-term prescription for chronic depression and short-term prescription for mild cases). The adherence measure depended both on the time intended to take the medication based on the prescription and on the length of time that the prescriptions were actually filled.

Covariates. We collected the following sociodemographic and clinical variables, recorded closest to the index date: age (categorized into age groups: 40–64, 65–74, 75–84, and 85+ years), sex, socioeconomic status (stratified into 3 levels: low, moderate, and high), and self-reported smoking status (categorized into 2 groups: those who had never smoked and those who had smoked or were currently smoking). In-hospital prescribing and dispensing data were not available for this study (because hospitalized patients received medication from the ward, and these data were not in the EMR); therefore, days of acute hospitalization over the course of the study were calculated and deducted from the duration of follow-up time. Physical status was assessed by the Charlson Comorbidity Index[31] (CCI), the most widely used clinical index for the evaluation of comorbidities, which weighs 20 chronic conditions as predictors of 1-year relative risk of death and provides scores from 1 to 20.

Analysis

Statistical analysis was conducted using SPSS version 20 (IBM Corp, Armonk, New York). We calculated descriptive statistics of sociodemographics, comorbidities, and

Figure 1. Flowchart of Study Population Selected for Analysis Among Clalit Health Services (CHS) Patient Population



adherence levels across the total study population, as well as across 4 adherence level groups (< 20%, 20%–50%, 50%–80%, and > 80%; non-, poor, moderate, and good adherence groups, respectively). We used univariate associations (logistic regression and Kaplan-Meier log rank) to assess the association between sociodemographics and clinical covariates and mortality during the study period. We used the multivariable Cox proportional hazard regression model to assess the adjusted association between risk of death and adherence level of antidepressant medication, controlling for confounders that demonstrated significance in the univariate analysis (age, sex, physical comorbidities modeled as CCI score, smoking status, and socioeconomic status). We tested the proportional hazard model assumption using log-log plots. We used the receiver operating characteristic curve of the individual hazard score created by the regression to test for a model's fit as a predictor of an event. Furthermore, we used an adjusted proportional hazard model to generate parameters for a quadratic polynomial regression equation. We then used the equation to form mortality log-hazard curves for adherence and covariates. We performed sensitivity analyses to test the assumptions with subpopulations, specifically among concomitant statin users and those with chronic depression, and to see whether duration of antidepressant adherence affected mortality, with either more than 3 or more than 18 months of follow-up (Supplementary eFigure 1). Hazard ratios (HRs) and their 95% CIs are reported. Significance was considered when $P < .001$, due to the extremely high-powered study.

RESULTS

Population Characteristics

Population characteristics and mortality events are shown in Table 1. Almost 50% of the study population was aged 40–64 years. The most prevalent comorbidities among the study population were hypertension (55.4%), diabetes mellitus (28.4%), ischemic heart disease (23.6%), and past stroke (11.7%). The most frequently used concomitant medications were statins (65.6%), acetylsalicylic acid (39%), anticonvulsants (19.4%), and antipsychotics (9.5%).

Table 1. Total Population (N = 251,745) Characteristics and Mortality Rates Across Sociodemographic and Clinical Variables

	Population		Mortality	
Variable	n	%	n	%
Total	251,745		23,419	9.3
Male	85,341	33.9	10,328	12.1*
Female	166,404	66.1	13,091	7.9
Age at study entry, y[a]				
40–64	124,376	49.4	3,114	2.5
65–74	51,955	20.6	4,089	7.9**
75–84	56,276	22.4	9,550	17**
> 85	19,138	7.6	6,666	34.8**
Native	221,273	87.9	20,679	9.3
Immigrant	30,472	12.1	2,740	9
Socioeconomic status[b]				
Low	84,381	33.5	7,681	9.1
Moderate	108,367	43	101,99	9.4
High	58,460	23.2	5,476	9.4
Charlson Comorbidity Index score				
0–2	181,452	72.2	9,999	5.5
3–4	44,692	17.8	6,481	14.5**
> 5	25,177	10	6,902	27.4**
Smoking status[b]				
Never	170,342	68.4	16,488	9.7*
Past or current	78,873	31.6	6,208	7.9

[a]Age distribution: mean ± SD = 62.1 ± 13.7, median = 60; 10th percentile = 45, 90th percentile = 82.
[b]Group total differs from the adherence total due to missing data in the electronic medical records.
*$P < .001$. **$P < .05$.

Men had a higher unadjusted mortality rate than women (12.1% vs 7.9%, $P < .0001$, respectively), and those with higher CCI scores also experienced higher mortality rates (27.4% with CCI scores > 5 vs 5.5% with CCI scores of 0–2, $P < .0001$).

Mean follow-up time of the study period was 26.8 ± 16 months (range, 1–47 months; median 30 months). Mean follow-up time of survivors was 27.9 ± 15.6 months, and mean time to death among those who did not survive was 16.6 ± 12 months.

Adherence

The results revealed that 54% of the study sample discontinued antidepressants within a month after receiving a prescription (ie, they had only a single prescription claim), and 79.6% of the study sample discontinued the medication after less than 6 months of use. Adherence level distribution and variables across adherence levels are shown in Table 2. The adherence distribution indicated that 32% of antidepressant users were nonadherent (n = 80,868), 17% had poor adherence (n = 42,794), 17% had moderate adherence (n = 43,964), and 33% had good adherence (n = 84,119).

Univariate Analysis

Unadjusted data show that the lowest mortality rate (6.6%) was among those with nonadherence, compared to the mortality rate of those with poor adherence (9.3%), moderate adherence (10.2%), or good adherence (12.2%;

Table 2. Population Characteristics Across Adherence Levels (N = 251,745)

	None (< 20%)[a]		Poor (20%–50%)[a]		Moderate (50%–80%)[a]		Good (> 80%)[a]		Total
Characteristic	n	%	n	%	n	%	n	%	
Sex									
Male	27,868	33	14,580	17	14,603	17	28,290	33	85,341
Female	53,000	32	28,214	17	29,361	18	55,829	34	166,404
Age at study entry, y									
40–64	46,225	37	22,567	18	21,328	17	34,256	28	124,376
65–74	16,050	31	8,521	16	9,041	17	18,343	35	51,955
75–84	14,287	25	8,860	16	10,008	18	23,121	41	56,276
> 85	4,306	22	2,846	15	3,587	19	8,399	44	19,138
Socioeconomic status[b]									
Low	32,706	39	15,051	18	13,559	16	23,065	27	84,381
Moderate	33,362	31	18,339	17	19,144	18	37,522	35	108,367
High	14,704	25	9,338	16	11,120	19	23,298	40	58,460
Smoking[b]									
Never	54,516	32	28,802	17	29,661	17	57,363	34	170,342
Past or current	25,662	33	13,649	17	13,881	18	25,681	33	78,873
Immigrant[b]									
No	10,828	36	5,820	19	5,328	17	8,496	28	30,472
Yes	70,040	32	36,974	17	38,636	17	75,623	34	221,273
CCI									
0	21,261	31	12,258	18	12,897	19	21,875	32	68,291
1	24,320	36	11,905	17	11,377	17	20,830	30	68,432
2	14,765	33	7,386	17	7,630	17	14,948	33	44,729
3	8,619	31	4,501	16	4,807	17	10,126	36	28,053
4	4,955	30	2,635	16	2,876	17	6,173	37	16,639
> 5	6,806	27	4,027	16	4,302	17	10,042	40	25,177
Mortality	5,289	23	3,632	16	4,224	18	10,274	44	23,419
Total	80,868	32	42,794	17	43,964	17	84,119	33	251,745

[a]Percentage represents proportions of variable across levels of adherence.
[b]Group total differs from the adherence total due to missing data in the electronic medical records.

$P < .001$). This was supported by a univariate Kaplan-Meier model. Older adults (> 75 years) were more likely to have good adherence than nonadherence (41.8% vs 24.7% respectively, $P < .001$). There were more severely physically ill patients (CCI > 5) in the good adherence group compared to the nonadherence group (40% vs 27%, respectively, $P < .001$).

Multivariable Analysis

The Cox proportional hazards model included mortality as the main outcome and variables that were significantly associated with mortality in the univariate analyses as covariates. Adjusted associations between adherence to the aggregate measure of antidepressants and mortality are shown in Figure 2. The association between adherence, as a continuous variable, and hazard of mortality, using an adjusted multivariate model, was found to follow a quadratic polynomial regression model (Figure 2). Using this model, the lowest HR for mortality (0.66 [95% CI, 0.64–0.69]) was among those who were 60% adherent. Thereafter, the HR trend was reversed and reached a level of 0.77 (95% CI, 0.7–0.84) among those who were 100% adherent. The same methodology for various covariates is demonstrated in Supplementary eFigure 2. Sensitivity analyses for populations with more than 3 or more than 18 months of follow-up time showed the same trend (Supplementary eFigure 1).

Looking at the categorized level of adherence, the adjusted HR for mortality among the poor, moderate, and good adherence groups was 0.93 (95% CI, 0.89–0.97), 0.83 (95% CI, 0.79–0.86), and 0.88 (95% CI, 0.85–0.91), respectively, compared to the nonadherence group, $P < .0001$ for all (Supplementary eFigure 3). The receiver operating characteristic curve of the survival function as a logistic predictor for mortality by the model was tested as a measure of model fit. The C-statistic was 0.65, which represents a moderate-to-good fit for a large population.

The adjusted HR for mortality among men was 1.5 (95% CI, 1.46–1.54) as compared to women. Other significant predictors of mortality were age (40–64 years: HR = 0.08 [95% CI, 0.08–0.09], 65–74 years: HR = 0.21 [95% CI, 0.2–0.21], and 75–84 years: HR = 0.43 [95% CI, 0.42–0.44] relative to age 85+, all $P < .001$); current or past smoking status (HR = 1.05 [95% CI, 1.02–1.08], $P = .003$); low socioeconomic status (HR = 1.13 [95% CI, 1.10–1.18], $P < .001$) and moderate socioeconomic status (HR = 1.05 [95% CI, 1.02–1.09], $P = .002$) compared to high socioeconomic status; and physical chronic comorbidity using CCI, with HR = 0.6 (95% CI, 0.58–0.62), $P < .001$ for the 0–2 scores and HR = 1.76 (95% CI, 1.70–1.82), $P < .001$ for the 5+ scores compared to scores 3–4.

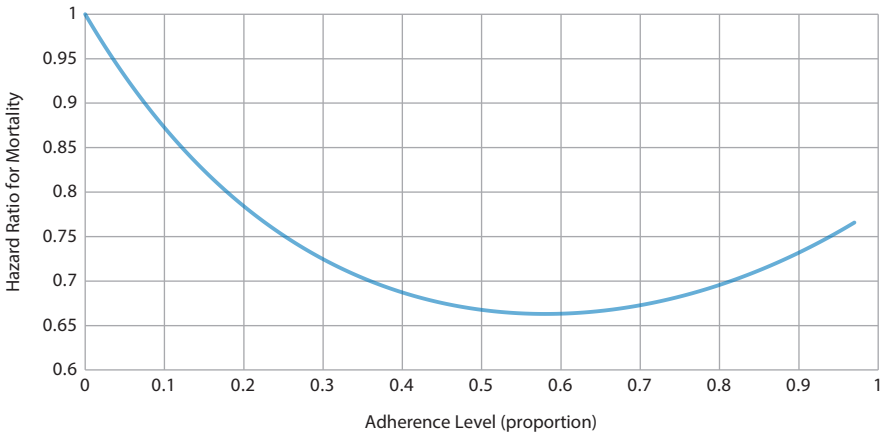
Sensitivity and Post hoc Analyses

We compared the impact of concomitant statin adherence on mortality to the impact of antidepressant adherence on mortality. We found that among statin users (n = 165,164; 65.6% of the sample), more than 50% statin adherence was associated with an adjusted HR for mortality of 0.58 (95% CI, 0.56–0.60) in comparison to less than 50% adherence. The same comparison between the same measure of adherence to antidepressants, in the same population, showed HR = 0.91 (95% CI, 0.88–0.95) for mortality. It is of note that among high antidepressant adherers, there was a rate of 81% of high statin adherence vs 62% in the low antidepressant-adherent group ($P < .0001$). There was a correlation between continuous adherence to antidepressants and statins ($r = 0.2$, $P < .0001$).

We further analyzed the effect of duration of adherence (as measured by filled prescriptions) on mortality rate. There was a strong correlation between adherence and duration of treatment ($r = 0.73$, $P < .0001$). The effect of this measure as a covariate in the multivariate model for mortality was found to be inversely related to mortality rate (B = −0.05, $P < .0001$), ie, longer duration of treatment was associated with a higher probability to survive. A treatment period of more than a year was associated with a HR of 0.54 (95% CI, 0.52–0.56) in comparison to a treatment period of less than 6 months in the multivariate model.

In another sensitivity analysis, we repeated the study in a subpopulation (n = 93,446) with diagnosis of chronic depression. Polynomial regression model of mortality hazard by

Figure 2. Relative Hazard Ratios Model of Mortality by Adherence Level[a] During 4 Years of Follow-Up (N = 251,745)[b]



[a]Nonadherence level serves as the reference.
[b]The quadratic equation is based on a log-log multivariate polynomial regression model adjusted for sex, age, smoking, socioeconomic status, and the Charlson Comorbidity Index score.

continuous adherence level, adjusted for age, sex, smoking status, socioeconomic status, and CCI score, either within the entire subpopulation or among those with more than 6 months of prescription (n = 77,157), as a measure of sufficient treatment, showed the same association between adherence and mortality (data shown in Supplementary eFigure 4).

DISCUSSION

The central, novel finding of our large population-based cohort study is that there is a significant inverse association between the level of adherence to antidepressants and the hazard of mortality during a 4-year follow-up period. There was a substantial decline in mortality HR from 1 (baseline) at 0% adherence level to 0.66 at the level of 60% adherence. Stratifying levels of adherence as good, moderate, and poor adherence showed increased chances for survival in respect to nonadherence (12%, 17%, and 7%, respectively). The results of the multivariable model analysis suggest that mortality significantly declines with increasing adherence after adjusting for other risk factors for mortality, such as age, sex, socioeconomic status, smoking status, and physical comorbidities.

Comparison With Previous Studies

To date, only 1 study has examined the effect of suboptimal treatment with antidepressants (a proxy variable of adherence) on the risk of mortality. A 7-year follow-up study of 4,037 patients with post–myocardial-infarction depression showed that subjects with inadequate, short-duration treatment for depression (less than 12 weeks of continuous antidepressant treatment) had a 3-fold higher mortality risk compared to sufficiently-treated depressed patients.[32] Although that study focused on a selected subpopulation of cardiac patients with depression, its findings corroborated ours. The current study evaluated a cohort of all 251,745 antidepressant users nested in a population of over 4 million CHS members for a 4-year follow-up period, thereby representing a much broader and larger antidepressant-using population.

Other related studies examined only the usage of antidepressants (as a dichotomous variable) rather than measuring longitudinal adherence with respect to mortality outcome (Supplementary eTable 1). Results of some of these studies suggested that antidepressant use might substantially decrease mortality risk. These studies, however, were limited to select populations, including those who have attempted suicide,[25] patients with depression,[33,34] older adults,[34] and cardiac patients.[33] In contrast, several publications[34,36,37] have found a null or inciting association between antidepressant use and mortality rates. An analysis of data from the Health in Men Study,[35] of 5,276 community-dwelling men with depression aged 68–88 years, revealed that the use of antidepressants was associated with a 30% increase in mortality independent of the presence of depression. Results from the Three City Study,[36] which followed 7,363 adults aged 65 years or older, suggested that antidepressant use was not associated with increased survival; however, the latter study lacked power to establish unequivocal conclusions, and none of these studies addressed directly the issue of medication adherence.

These previous contradictory findings, reported in relatively small samples of select populations adjusted for diverse covariates, strongly support the need for the present study. We measured antidepressant adherence level, rather than use alone, in a general population-based cohort. Controlling for the mortality-associated covariates was essential, since unadjusted results demonstrated a positive association between antidepressant adherence level and mortality. The importance of adjustment could be partially explained by the larger proportion of older and more physically ill patients in the good adherence group, which introduced confounding.

Our finding of an association between the level of antidepressant adherence and survival may be mediated through several direct and indirect pathways. Mortality risk in patients with depressive and anxiety disorders is only partially attributable to the elevated risk of suicide among this population,[21] but considerably attributable to an aggravation of life-threatening physical disorders such as ischemic heart disease.[37] This grave prognosis of physical disorders could be partially due to decreasing adherence to cardiac, antihypertensive,[38] and other comorbid medications[37] taken by this population compared to the nondepressed, as suggested by preliminary reports of small-scale studies.[37,39]

Depression and anxiety are recognized as risk factors for many diseases, such as cardiovascular disease and diabetes mellitus,[40,41] which lead to increased mortality rates.[16] In addition to disease, depression is also associated with suicidal behavior and neglecting health behavior; therefore, antidepressant use may improve those behaviors.[42,43] Furthermore, depression often causes fatal accidents due to a lack of concentration,[44] so ameliorating symptoms of depression could help prevent accidents.

Another possible explanation for our findings is that good antidepressant adherence represents a positive health behavior (eg, physical activity, healthy nutrition, etc) that mediates the association between antidepressant adherence and increased survival. In other words, it may be adherence itself, rather than antidepressants, that is protective. It is also possible that good and long-term adherence to antidepressants ameliorates symptoms of depression and anxiety and thus promotes adherence to other prescribed medication, as suggested by others.[39] Ultimately, this explanation could support the effect of antidepressant adherence on survival, as demonstrated in our study. These hypotheses should be tested in future studies.

Our results suggest a mild increase in HR for mortality in patients with antidepressant adherence greater than 60%, from 0.66 to 0.77 at 100% adherence level. It could be speculated that these patients share certain risk factors for mortality that we did not adjust for in our model; however, it is also possible that the beneficial effect of adherence to antidepressants maximizes at 60% and that in higher levels of adherence, there is no additive value, where high adherence might reflect intensity of the disease. Moreover, there is a clearly demonstrated relationship between the burden of general medical conditions, as reflected in this study by the CCI scores, and depression. Although the elderly are most likely to suffer heavier disease burden, they also have a stronger tendency to adhere to medication. Nevertheless, they often represent a medically fragile population; thus, antidepressants may ultimately not be effective in reducing mortality rates for them.

Strengths and Limitations of the Study

The findings of this pharmacoepidemiologic study should be interpreted in light of its limitations. We had only partial data regarding the indication for prescribing antidepressants; thus, such data were not included in the analysis. Furthermore, we did not have data on cause of death, which precluded us from studying their distribution among the cohort. For example, it would have been interesting to examine suicide outcomes; however, even among patients with depression and anxiety, suicide is not a primary cause of death.[21] Therefore, all-cause mortality is a preferable outcome measure to evaluate the long-term impact of antidepressant adherence on patients' survival. It should be noted that a correlation in an observational study does not imply a causal relationship, although one might exist. Finally, residual confounding by unmeasured variables, such as obesity and physical inactivity, could have also confounded our findings.

Despite these limitations, our study has several strengths. The large size (N = 251,745) encompassed a nationwide sample of all antidepressant users in the CHS database, which is generalizable to the general population. Moreover, the Israeli health care delivery system is similar to systems in other Western countries, and therefore our findings are generalizable to these settings as well. The 4-year follow-up period of the present study is substantial enough to unveil a broader set of adherence-related variables—most importantly, mortality as an outcome measure—while permitting a huge person-time denominator and the development of causal pathways. And finally, but of major importance, adherence was analyzed, for the first time, as a continuous variable too, and within multivariable analysis.

It should be emphasized that without proper adjustment, the simple association between adherence and mortality risk was positive. This potential for misleading results indicates the need to take the confounding effects of age, sex, and overall health status into account in such analyses.

CONCLUSIONS AND IMPLICATIONS FOR POLICY MAKERS

This study is the first to demonstrate the inverse association between adherence to antidepressants and all-cause mortality in a general-population–based large cohort (N = 251,745) for a period of 4 years. The findings have important implications for clinical practice. Even though the standardized effect size of antidepressants may be lower than previously thought,[45] the beneficial effect of adherence (even partial) on increasing survival should encourage clinicians of all disciplines, particularly general physicians, to improve their efforts to promote and sustain their patients' adherence to antidepressants, which may ultimately increase life-expectancy.

Depression is projected to become the second leading cause of disability worldwide by the year 2020.[5] Since suboptimal duration and inadequate dosing of antidepressant treatment can increase the risk for relapse, chronicity, and—as shown here—mortality, poor adherence is of considerable clinical, economic, and public health concern. This study, demonstrating a correlation between nonadherence to antidepressants and all-cause mortality rate, contributes new data that can have great implications on both clinical care and future health policies.

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Additional information: The original data set is available from Clalit Research Institute, Clalit Health Services, upon approval and permission of the database warehouse committee.

Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Adherence to Antidepressants Is Associated With Lower Mortality: A 4-Year Population-Based Cohort Study

Author(s): Amir Krivoy, MD; Ran D. Balicer MD, PhD; Becca Feldman, PhD; Moshe Hoshen, PhD; Gil Zalsman, MD, MHA; Abraham Weizman, MD; and Gal Shoval, MD

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List of Supplementary Material for the article

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Supplementary Table 1: Previous studies examining the association between antidepressants use and all-cause mortality

[a] HR for Selective Serotonin Reuptake Inhibitors:1.26 and for Other AD:1.67

[b] HR 1.22 for AD use and no dep., HR 2.97 for AD use with dep. compared to no AD use and no dep.

[c] HR For tricyclic antidepressant:0.5 and for Other AD:0.66

[d] Risk ratio for mortality of AD users vs. AD non users during 1 year.

Study	N	Sample	Country	variable	Maximal follow-up period	Covariates	HR for mortality
Scherrer et al. [33]	4,037	Post-MI & Dep.	USA	<12 wk. AD	7 yrs	SDV, Anxiety, HSU	0.33
Gallo et al. [35]	1,226	age>60 yrs & Dep.	USA	AD use vs. none	5 yrs	SDV, SmS, CCI, cognition, and suicidal ideation	0.67
Tiihonen et al. [26]	15,390	Hospitalized suicide attempters	Finland	AD use vs. none	7 yrs	SDV, no. of previous AD prescriptions, and no. of previous suicide attempts	0.64

Berkman et al. [34]	2,481	Post-MI & Dep.	USA	AD use vs. none	5 yrs	Age, baseline BDI score, Killip class, ejection fraction, creatinine level, previous MI, prior medical diagnoses	NS
Glassman et al. [39]	361	Acute coronary syndrome & Dep.	USA	AD use vs. none	7 yrs	Age, gender	0.42
Coupland et al. [24]	60,746	age>65 yrs & Dep.	UK	AD class use vs. none	12 yrs	SDV, previous dep., severity of index Dep., deprivation, SmS, comorbidities, use of other drugs and previous falls	1.16-1.67[a]
Almeida et al. [36]	5,276	68-88 yrs, men +/- Dep.	Australia	AD use -/+ dep. vs. no AD no dep.	7 yrs	age, education, migrant status, physical activity, SmS, alcohol use and CCI	1.22-2.97[b]
Ryan et al. [37]	7,363	Elderly	France	AD use vs. none	4 yr	SDV, cognition, alcohol consumption, SmS, disability, recent hospitalization, comorbidity, weight	2.22
Scherrer et al. [40]	93,653	Dep. w/o cardiac disease	USA	AD class 12 wk. use vs. less	7 yrs	SDV, Anxiety, Cardio-vascular indices, Dep. severity	0.5-0.66[c]
Bingefors et al. [41]	456	AD	Sweden	AD use vs. none	9 yrs	SDV, physical diseases	1.52

	AD vs. 912 MC	prescribed vs. MC					
Sundell et al. [25]	94,239	Age 20-34	Sweden	AD use vs. none	1 yr	Gender	4.39[d]

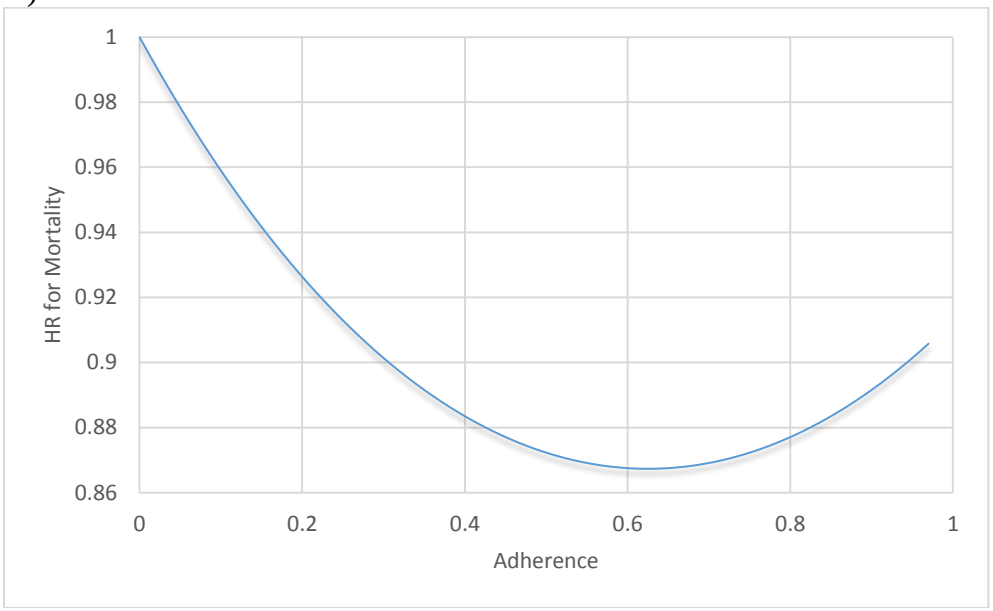
MI – Myocardial Infarction. Dep. – Depression, AD – Antidepressants, wk – Week, SDV – Socio-Demographic Variables,

HSU – Health Service Utilization, SmS - Smoking Status, CCI – Charlson Comorbidity Index, MC – Matched control,

HR – Hazard ratio, NS- Non Significant

Supplementary figure 1:

A)



B)

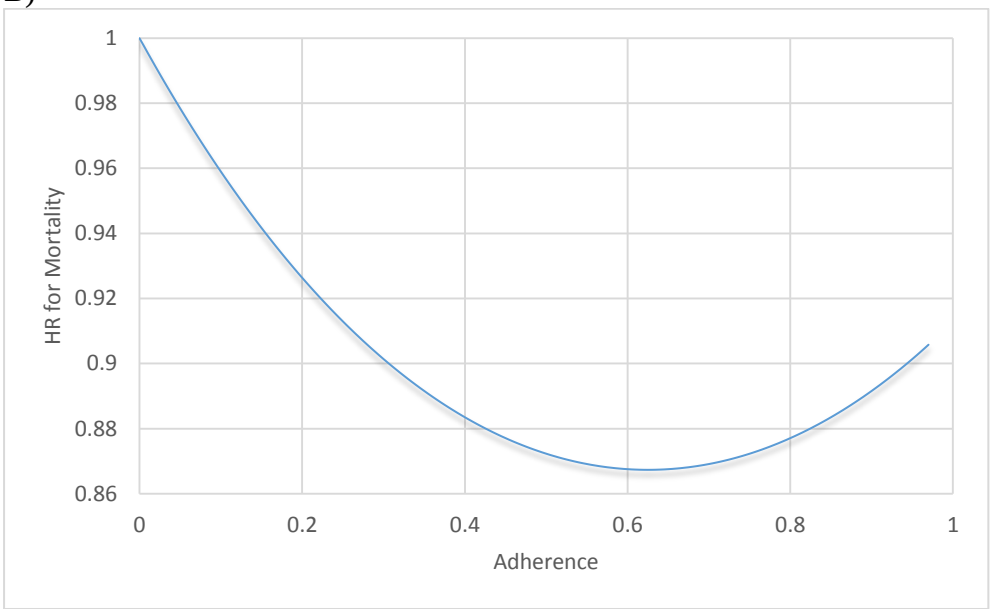
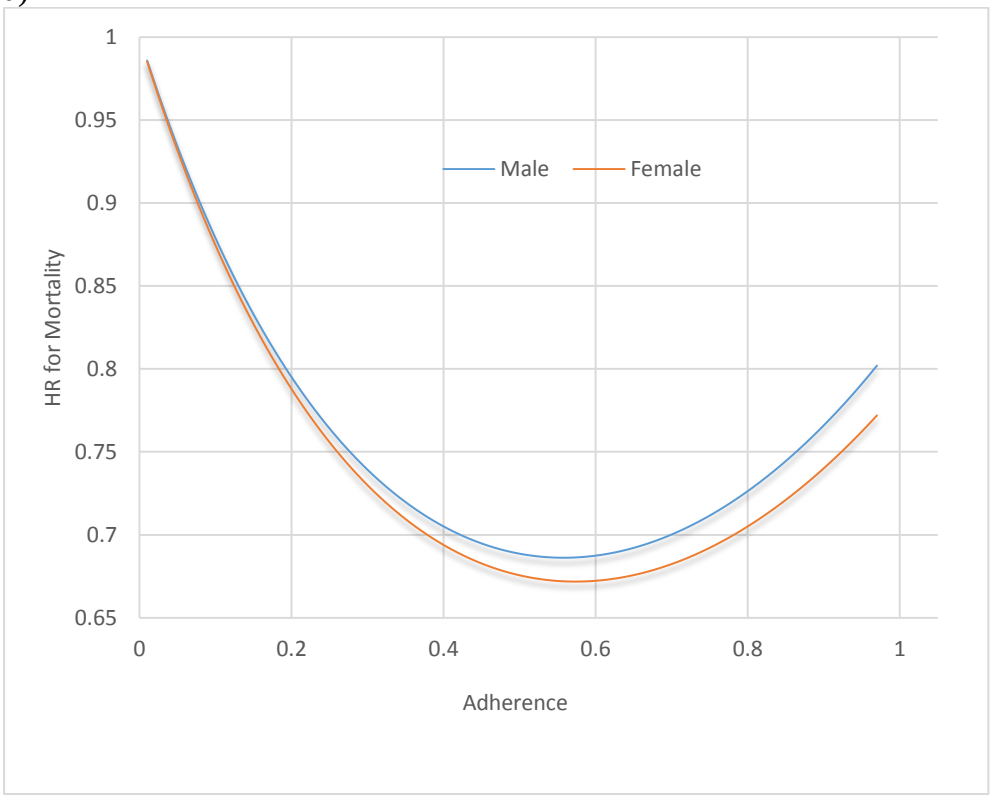


Figure 1: Polynomial regression model of mortality hazard by continuous adherence level, adjusted for age, gender, smoking status, socioeconomic status and Charlson comorbidity score: a) population with follow-up time of three months or more (n=236,262). b) Population with follow-up time of 18 months or more (n=166,812).

Supplementary Figure 2 –

a)



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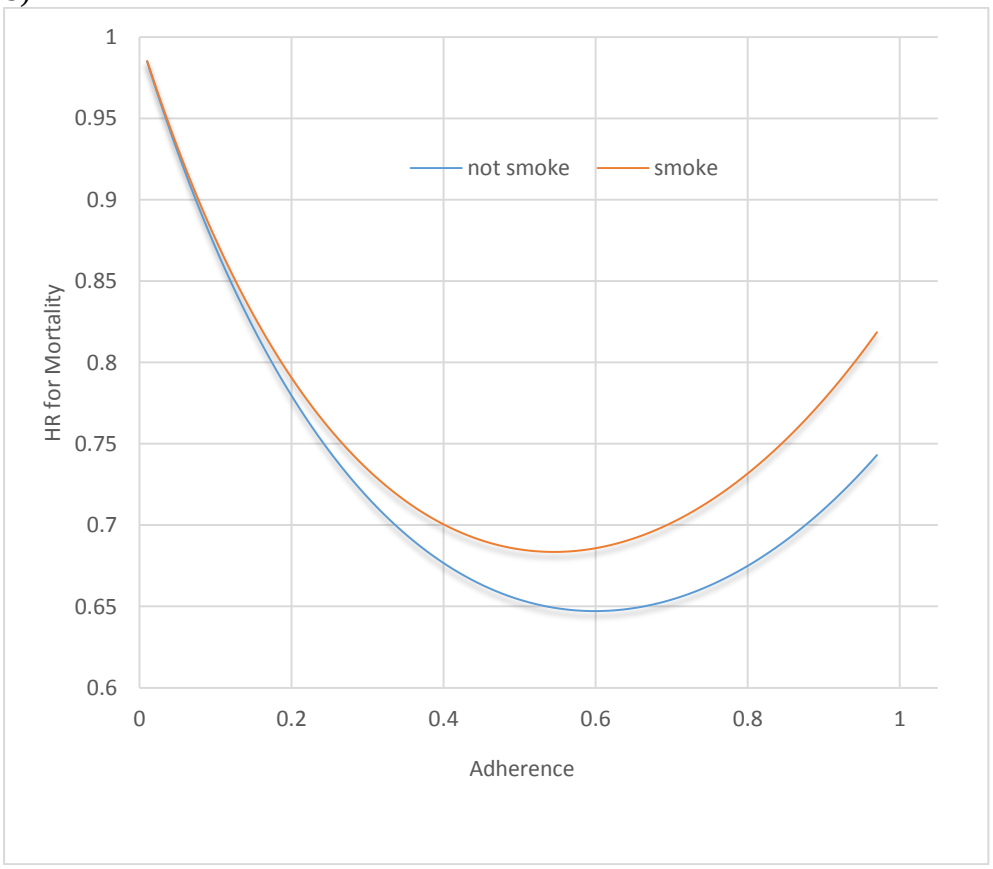

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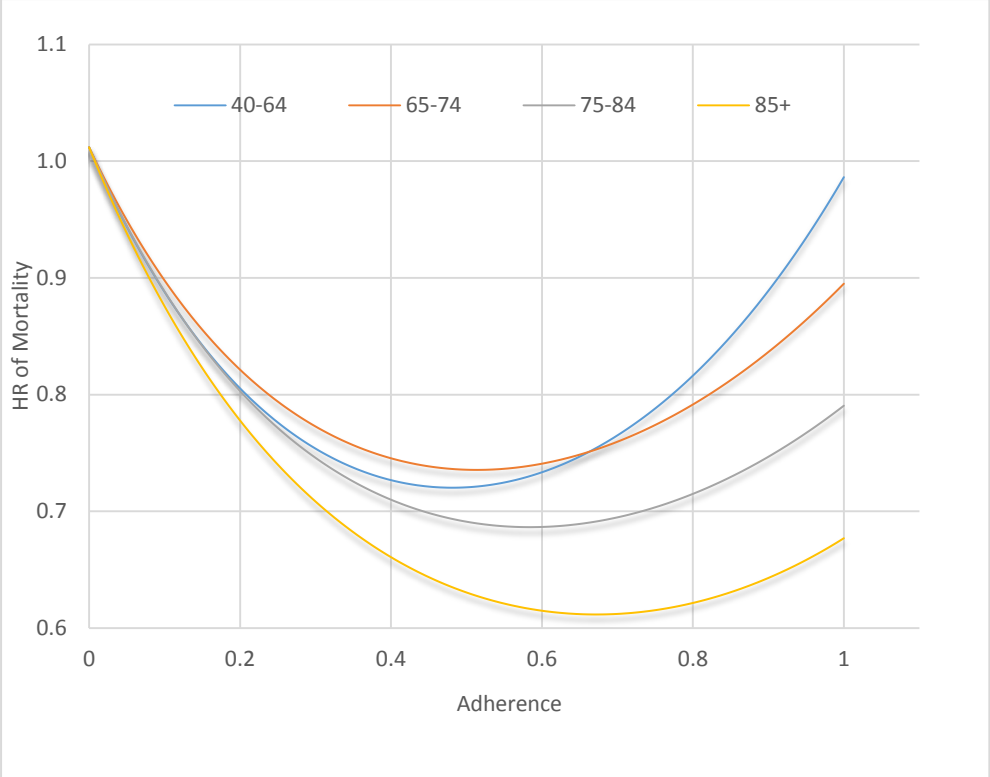


Figure 2S: Polynomial regression model of mortality hazard by continuous adherence level across: a) gender b) smoking status c) age group

Supplementary figure 3

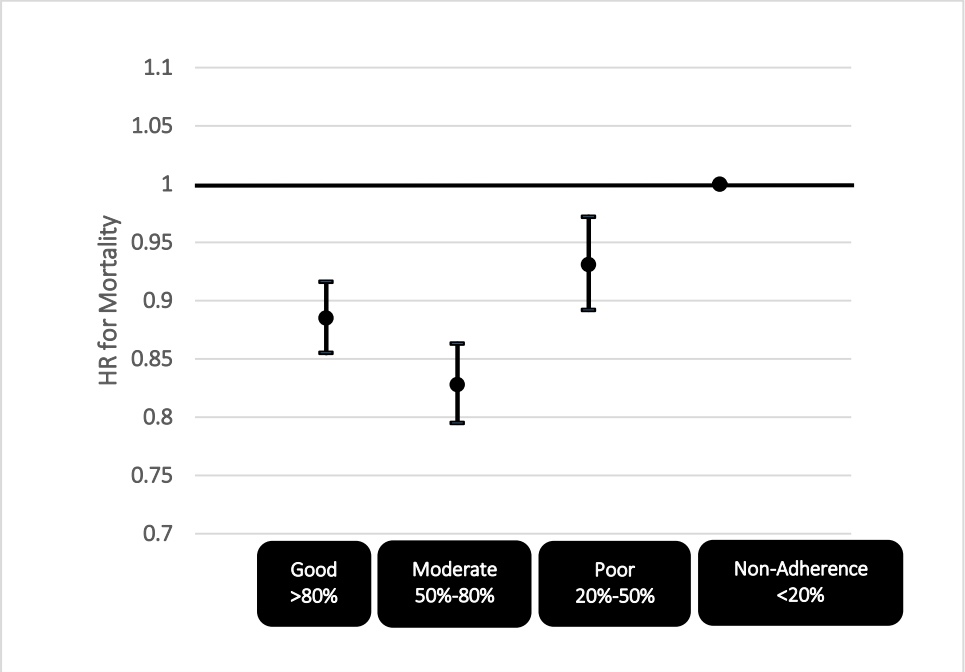


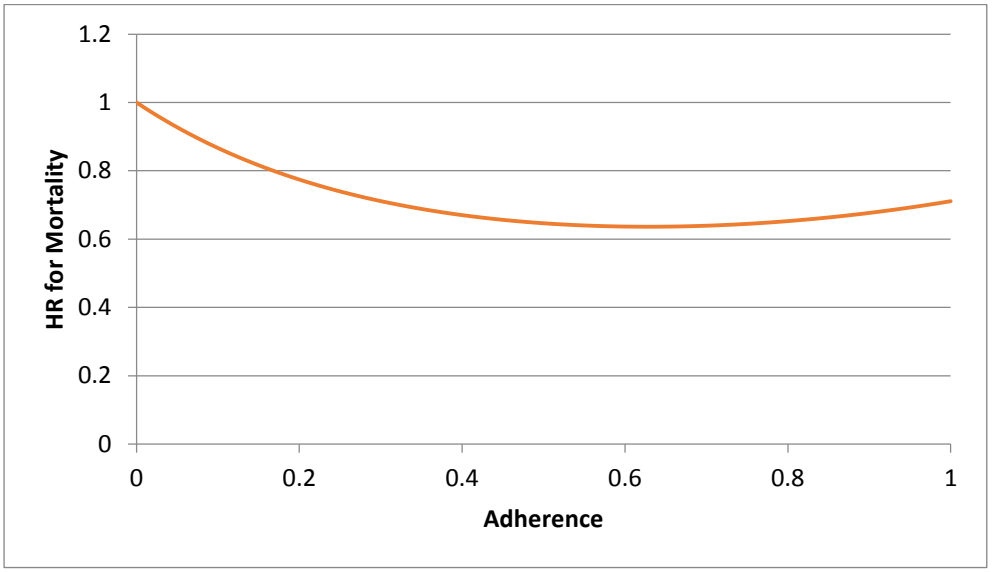
Figure 3s: Relative hazard ratios (HR) for mortality and 95% confidence intervals across clustered adherence levels during 4 years follow-up (N=251,745). Non adherence level (<20%) serves as the reference. Adjusted for sex, age, smoking status, socio-economic status and Charlson's comorbidity score

Supplementary Table 2: List of antidepressants and ATC codes and summary of users according to drug group.

DESIPRAMINE	N06AA01
IMIPRAMINE	N06AA02
CLOMIPRAMINE	N06AA04
OPIPRAMOL	N06AA05
DIBENZEPIN	N06AA08
AMITRIPTYLINE	N06AA09
NORTRIPTYLINE	N06AA10
DOXEPIN	N06AA12
MAPROTILINE	N06AA21
FLUOXETINE	N06AB03
CITALOPRAM	N06AB04
PAROXETINE	N06AB05
SERTRALINE	N06AB06
FLUVOXAMINE	N06AB08
ESCITALOPRAM	N06AB10
PHENELZINE	N06AF03
MOCLOBEMIDE	N06AG02
MIANSERIN	N06AX03
TRAZODONE	N06AX05
MIRTAZAPINE	N06AX11
BUPROPION	N06AX12
VENLAFAXINE	N06AX16
MILNACIPRAN	N06AX17
REBOXETINE	N06AX18
DULOXETINE	N06AX21
ST. JOHN'S WORT	N06AX30

Drug group	n	%
SSRI	192697	44.9
SNRI	35951	8.4
TCA	84761	19.7
MAO	123	0.0
Others	5021	1.2

Figure 4:
a)



b)

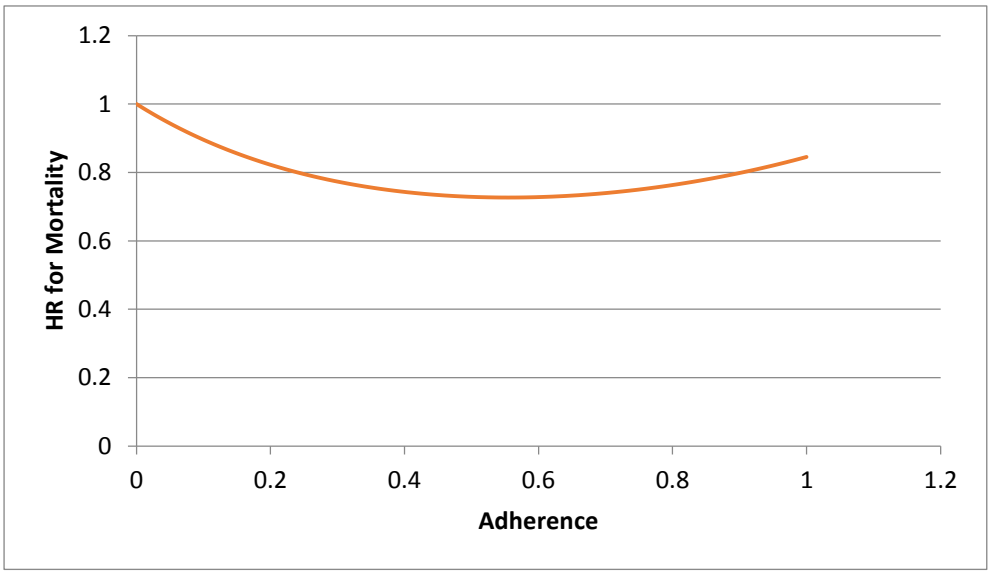


Figure 4: Polynomial regression model of mortality hazard by continuous adherence level, adjusted for age, gender, smoking status, socioeconomic status and Charlson's comorbidity score of population with chronic Depression diagnosis: a) entire population (n=93,446). b) Sub-population (n=77,157) with more than 6 months of prescription