

# The Mortality and Myocardial Effects of Antidepressants Are Moderated by Preexisting Cardiovascular Disease: A Meta-Analysis

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## Keywords

Antidepressant medications · All-cause mortality · Cardiovascular events

## Abstract

**Background:** Antidepressants (ADs) are commonly prescribed medications, but their long-term health effects are debated. ADs disrupt multiple adaptive processes regulated by evolutionarily ancient biochemicals, potentially increasing mortality. However, many ADs also have anticlotting properties that can be efficacious in treating cardiovascular disease. We conducted a meta-analysis assessing the effects of ADs on all-cause mortality and cardiovascular events in general-population and cardiovascular-patient samples. **Methods:** Two reviewers independently assessed articles from PubMed, EMBASE, and Google Scholar for AD-related mortality controlling for depression and other comorbidities. From these articles, we extracted information about cardiovascular events, cardiovascular risk status, and AD class.

We conducted mixed-effect meta-analyses testing sample type and AD class as moderators of all-cause mortality and new cardiovascular events. **Results:** Seventeen studies met our search criteria. Sample type consistently moderated health risks. In general-population samples, AD use increased the risks of mortality (HR = 1.33, 95% CI: 1.14–1.55) and new cardiovascular events (HR = 1.14, 95% CI: 1.08–1.21). In cardiovascular patients, AD use did not significantly affect risks. AD class also moderated mortality, but the serotonin reuptake inhibitors were not significantly different from tricyclic ADs (TCAs) (HR = 1.10, 95% CI: 0.93–1.31,  $p = 0.27$ ). Only “other ADs” were differentiable from TCAs (HR = 1.35, 95% CI: 1.08–1.69). Mortality risk estimates increased when we analyzed the subset of studies controlling for pre-medication depression, suggesting the absence of confounding by indication. **Conclusions:** The results support the hypothesis that ADs are harmful in the general population but less harmful in cardiovascular patients.

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## Introduction

Antidepressant (AD) medications are among the most frequently used medications, taken by 1 in 10 Americans aged  $\geq 12$  years [1]. They are the first-line intervention for depression [2], but they are commonly indicated for other mental disorders [3], as well as substance use problems, sleep disturbances, and chronic pain syndromes [4]. One factor contributing to the widespread use of ADs is that they are considered both effective and relatively safe, with mild or rare side effects that are preferred over the debilitating effects of untreated depression. Depression is widely considered a disorder that causes needless suffering [5], and it is associated with an elevated risk of mortality [6–8]. People with depression are more likely to suffer from many comorbid physical disorders, such as cardiovascular disease [8–10], and they are at elevated risk for suicide [11]. By alleviating depressive symptoms, ADs could lessen depression-related mortality [12–14].

Nevertheless, there are scientific and public debates about the role ADs play in current treatment guidelines [15–26] reflecting a wider discussion about their effects on health outcomes. All commonly prescribed ADs target one or more monoamines (serotonin, norepinephrine, and dopamine), which are ancient, phylogenetically conserved molecules that are homeostatically regulated by complex systems with multiple components [27–29]. These monoamine systems are functionally integrated in many biological processes.

In the brain, serotonin acts as a neurotransmitter, and it is recycled back to the serotonin-releasing neuron by a molecule called a *transporter* that promotes the reuptake of serotonin from the synaptic cleft. However, most of the body's serotonin is synthesized in the gut where it spills into the bloodstream, is distributed throughout the body [29], and is taken up by platelet cells and tissues by the serotonin transporter [30, 31], which is widely expressed [32–35]. Serotonin evolved in mitochondria [27], and, in many cell types, cellular uptake of serotonin depends on mitochondrial activity [36–40], which suggests serotonin supports many biological processes. Indeed, serotonin regulates growth, development, reproduction, neuronal activity, digestion, immune function, thermoregulation, tissue repair, maintenance, electrolyte balance, mitochondrial function, and the storage, mobilization and distribution of energetic resources [3, 27, 41]. By blocking the transporter in the brain and periphery, selective serotonin reuptake inhibitors (SSRIs), which are the most widely prescribed ADs, could potentially degrade many adaptive processes [3, 42].

This hypothesis is not restricted to serotonin and SSRIs. Tricyclic ADs (TCAs) also affect norepinephrine and to a lesser extent dopamine. Norepinephrine affects the sympathetic nervous system and parts of the brain involving attention and arousal [43, 44]. Dopamine has broad effects, including immune, endocrine, kidney, gastrointestinal, and pancreatic functions, as well as the regulation of body weight and life span length [45–48]. TCAs could also degrade the functioning of many adaptive processes.

For instance, both SSRIs and TCAs have cardiovascular side effects, although the specific effects and mechanisms may differ [49]. The clotting process involves platelet cell activation [50], which requires an intracellular store of serotonin that accrues through the serotonin transporter [51]. Norepinephrine also promotes clotting [52, 53], and both SSRIs and TCAs inhibit proaggregatory processes [54]. In people with an otherwise normal clotting process, this may increase the risk of abnormal bleeding and hemorrhagic stroke [55–58]. Additionally, SSRIs can cause bradycardia, syncope, and have potent antagonistic effects on cardiac ion channels [49]. TCAs also have antagonistic effects on cardiac ion channels, but they are more likely to cause orthostatic hypotension, tachycardia, irregular heart rhythms, and alterations in the standard electrocardiogram [49, 59].

More generally, although each AD has unique pharmacological effects [3, 60], they all interact with evolutionarily ancient biochemical systems that regulate multiple, adaptive processes throughout the brain and the periphery. Thus, while each AD probably has a distinct symptom profile, there is good reason to suspect that they all degrade the functioning of some adaptive processes in the body [3]. Consistent with this hypothesis, several cohort studies of community samples have associated AD use with an elevated risk of cardiovascular events and death, even after controlling for depressive symptoms and other comorbidities [6, 7, 57]. Although cohort studies cannot conclusively demonstrate causation, randomized controlled trials are often underpowered due to the rarity of death events and the limited duration of follow-up.

Meta-analyses are at risk of neglecting important individual differences that can moderate the outcomes of medical interventions [61, 62]. For instance, SSRIs and TCAs may have some beneficial effects in patients with diseases in which proaggregatory processes are pathologically activated, such as heart disease, diabetes, chronic kidney disease, and chronic obstructive pulmonary disease [54, 63–67]. For this paper, we refer to such conditions as cardiovascular diseases. By blocking the uptake

of platelet serotonin and norepinephrine, many ADs could potentially normalize proaggregatory processes in cardiovascular patients. Consistent with a protective effect, AD use has been associated with reduced mortality in some studies of cardiovascular patients [68–70].

The debates about the effects of AD use on health outcomes highlight the significant public health issues at stake [19, 20, 25]. Further information clarifying the effects of ADs in different populations is both scientifically and ethically warranted. Towards this end, we conducted a meta-analysis of published studies that assessed the mortality effects of ADs. Because ADs could affect all the processes regulated by monoamines, we focused on studies reporting all-cause mortality. We hypothesized that ADs would have different effects on mortality in general-population samples and samples with preexisting cardiovascular diseases. Specifically, because ADs disrupt the functioning of monoamines that regulate many adaptive processes, we predicted that they would be associated with increased mortality in general-population samples. Conversely, we predicted that ADs would be less harmful or even protective in cardiovascular patients due to the anticoagulating properties of many ADs.

As a secondary outcome, we examined the incidence of fatal and nonfatal cardiovascular events associated with AD use. We also hypothesized that their use would be associated with different effects on cardiovascular events in general-population and cardiovascular-patient samples. In general-population samples with otherwise normal clotting processes, ADs could inhibit clotting and increase the risk of cardiovascular events, particularly those associated with abnormal bleeding (e.g., hemorrhagic stroke). Conversely, in patients with preexisting cardiovascular diseases where proaggregatory processes are pathologically elevated, the anticoagulating properties of ADs could normalize those processes and reduce the risk of new cardiovascular events (e.g., myocardial infarction or ischemic stroke).

We also examined the effects of AD class on mortality. While each AD has unique pharmacological effects [3, 60], it is common to separate out the second-generation ADs with serotonin reuptake properties – the SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) – from the first-generation antidepressants such as the TCAs. As discussed above, TCAs have a broad range of side effects, including cardiotoxicity, and overdoses can be fatal [59]. But given the breadth of processes regulated by serotonin, including cardiovascular function, SSRIs could also have multiple effects [3]. We, therefore, predicted that AD classes would have similar effects on mortality and cardiovascular events despite their different mechanisms of action.

## Methods

We conducted this meta-analysis in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [71] (see online supplementary completed guideline checklist A8; for all online supplementary material, see [www.karger.com/doi/10.1159/000477940](http://www.karger.com/doi/10.1159/000477940)).

### Study Selection

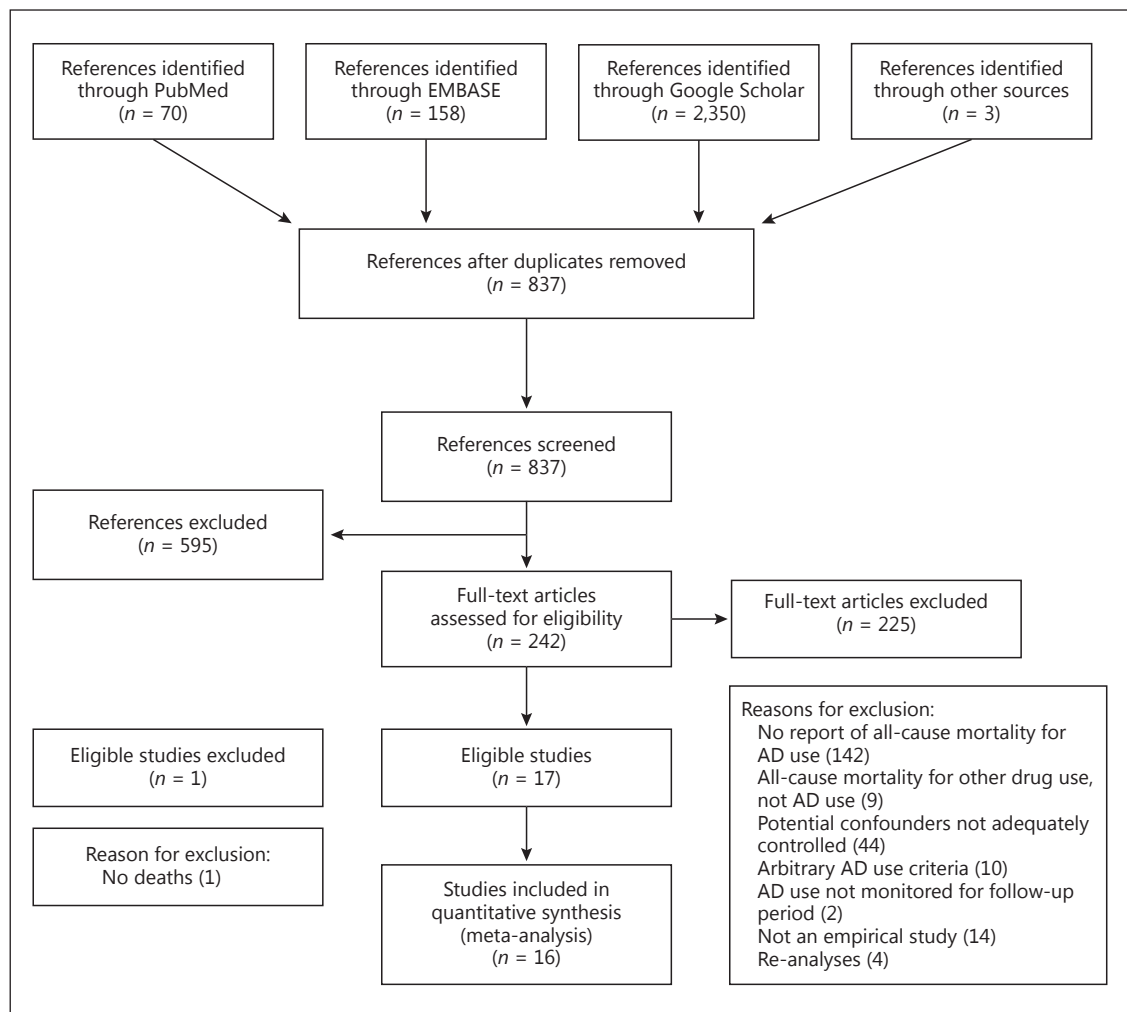
Studies included in our meta-analysis had to meet several criteria. First, the studies must have reported any statistics (e.g., hazard ratio [HR], odds ratio, or crude rates) comparing all-cause mortality in human users of prescribed ADs to all-cause mortality in a group not taking ADs. Studies that only compared ADs to other specific drugs were ineligible. We deemed any class or combination of ADs as eligible as long as the drugs were considered ADs and generally used as such. Since ADs are commonly used for conditions other than depression, studies estimating the all-cause mortality effects of ADs taken for any reason by any type of sample were eligible. Any dose or duration of AD use was acceptable unless there was evidence of overmedication, because we intended to estimate the mortality effects of AD use, not their misuse. Thus, studies reporting mortality in individuals who had overdosed were ineligible.

Second, researchers must have made an effort to isolate the mortality effects of ADs, either by using a randomized placebo-controlled design, restricting their analyses to a particular sample type, or adjusting the statistics for covariates in prospective or retrospective cohort designs. If statistical adjustment was used, the statistics must have been adjusted for variables that could have potentially affected all-cause mortality, such as demographic factors, medical and psychological comorbidities, and, in particular, conditions being treated by the ADs, most commonly depression.

Third, we included only empirical studies and excluded reviews, commentaries, or meta-analyses. To avoid double counting, we also excluded any report that was a re-analysis of data already included in our study.

### Data Sources and Searches

Two reviewers (M.J.R. and K.E.) independently conducted comprehensive searches of two scientific databases, PubMed and EMBASE, and one search engine, Google Scholar. Our search terms were “all-cause mortality” or “all-cause death” in combination with various classes or types of ADs. Online supplementary material A2 contains complete search instructions for each data source. All references generated through PubMed and EMBASE were included. Because we expected each search term to yield hundreds of study references in Google Scholar, we included only the first 50 references corresponding to each search term. We searched for all papers and conference abstracts published up to and on June 3, 2014. We also included 2 published studies we were aware of before we began searching [68, 72] and 1 study that was in press at the time of the search [73]. Each reviewer recorded the number of total references recovered from each data source. They imported the references into EndNote citation manager software and screened the references for duplicates. Figure 1 presents a flow diagram of the search procedure.



**Fig. 1.** Flow diagram for the search procedure. AD, antidepressant medication.

### Screening and Eligibility

After searching was complete, the two reviewers independently screened the abstracts of each reference to determine its relevance based on the study selection criteria. References deemed relevant by both reviewers were assessed for eligibility, and those deemed irrelevant by both reviewers were discarded. A third reviewer (M.M.M.) assessed all references with discrepant decisions between reviewers, and an additional 133 discrepant references were discarded.

After screening abstracts, the two primary reviewers independently obtained copies of the full articles for relevant references and read through each article to determine whether it was eligible for inclusion in the meta-analysis. The third reviewer monitored the eligibility decisions made by each reviewer, and any discrepancies were discussed until a consensus was reached. If a consensus could not be reached, a senior investigator (P.W.A.) made a decision. A list of the 16 studies included in the meta-analysis and all discrepant reviews and their corresponding decisions are de-

scribed in online supplementary material A3. Figure 1 summarizes information on the screening and eligibility rating process.

### Study Quality Assessment

We assessed the validity of each included study using the Cochrane Collaboration's "risk of bias" tool [74]. This tool assesses the risk of bias in intervention studies using 5 criteria: selection bias, which includes the adequate generation of a concealed allocation sequence in randomized studies, or the adequate control for potential confounders in nonrandomized studies; performance bias, the masking of participants; detection bias, masking of assessors; attrition bias, dealing with incomplete outcome data; and selective outcome reporting bias. When assessing nonrandomized studies for performance bias, we also considered the strategy researchers used to model AD exposure in treatment groups. We categorized studies at low risk of bias if they considered fluctuations in AD use; studies that examined any AD exposure in the follow-up period were high risk.

Additionally, we assessed each study using the “checklist for measuring study quality” [75]. This checklist provides a quantitative assessment of methodological quality and assigns each study a score out of 27.

#### Data Extraction

For each study, in addition to whether the study used a randomized controlled trial or a cohort design, we extracted 3 categories of relevant information to use in our analysis.

#### Summary Measures

We extracted summary measures describing the effect of AD use on all-cause mortality and cardiovascular events in their least aggregated form. For instance, if a study provided estimates for individual drugs, aggregated estimates for drug classes, as well as estimates for the use of any ADs [57], we extracted the estimates of individual drugs. These statistics were most commonly reported in the form of HRs and when they were not, we contacted the investigators to obtain data that could be converted into HRs. We also extracted confidence intervals (CIs) associated with the summary measures, unless only crude rates were provided. Strategies for obtaining HRs and CIs not provided in the articles are described in online supplementary material A4.

#### Participant Characteristics

We extracted information about the characteristics of participants the studies recruited. Of the final 17 studies, 1 included patients attempting to quit smoking. Several studies involved samples specifically selected for various sorts of cardiovascular diseases. One study [76] involved a sample that was at an increased risk of cardiovascular problems due to a high incidence of insulin resistance, obesity, smoking, diabetes, and hypertension, and a high Framingham risk score [77]. In the remaining studies, participants were recruited for depression or were community samples with depression. We split samples into two categories: “cardiovascular-patient samples”, which included those with or at high risk for cardiovascular problems, and “general-population samples”. Eleven studies fell into the “cardiovascular-patient” category (see online suppl. material A6.1). Samples in the “general-population” category could have had a variety of conditions for which ADs were used (e.g., depression, anxiety, pain, or cardiovascular disease), but these participants were not specifically selected for cardiovascular diseases.

#### Drug Class

We obtained information about the drug classes corresponding to the summary measures, and formed 3 classes: (1) SSRIs and SNRIs; (2) TCAs; and (3) “Other ADs” for drugs that were not in either of these categories (e.g., mirtazapine, bupropion, tianeptine, monoamine oxidase inhibitors, or trazodone). The classification of ADs in our included studies did not always map on to these predefined categories. Some studies provided estimates for unspecified drugs [7, 72, 78]. Because we could not place them in one of our specified categories, we placed them in an “undifferentiated” category. We did not include these estimates in any analysis involving AD class, but we included them in other analyses. In 2 studies [7, 78], some patients who were taking an SSRI or a TCA as their primary AD were also taking trazodone, nefazodone, or vilazodone. Since this was a small subset of patients, we reasoned that the estimates were largely unaffected by these ancillary drugs,

and we classified them according to the primary AD. Online supplementary material A6.2 presents drug type information from our included studies.

#### Data Synthesis and Analysis

##### Data Preparation

We transformed all summary measures into HRs (see online suppl. material B). In instances where only crude rates were available, we converted probabilities to the HR scale and obtained standard errors by running simple generalized linear models on the numbers of mortality or cardiovascular events and the total populations exposed in the treatment and control groups. We renormalized all HRs for control groups to a baseline of 1. In order to estimate standard errors of the HRs relative to baseline, we assumed the baseline and treatment group estimates were independent (because the original papers did not report correlations between these estimates). We also converted HRs and CIs found in the original sources to the log-hazard scale and back-transformed CIs into standard errors using the assumption that the errors were normally distributed on the log-hazard scale.

##### Data Analyses

We incorporated random effects at the level of both individual observations and published studies in our analyses, because we suspected heterogeneity both among groups within studies and among studies, and we intended to use multiple summary measures from single studies [7, 57, 76, 78, 79]. To test our two pre-specified hypotheses, we conducted mixed-effect meta-analyses examining whether sample type and AD class were significant moderators of all-cause mortality and new cardiovascular events. We estimated both the average effects in each group and the differences among groups. We also summarized the effects of AD use unstratified by sample type and AD class. For each analysis, we calculated  $I^2$  to measure the extent of the inconsistency of the effects between studies [80]. Larger  $I^2$  values suggest increasing heterogeneity, with 25% identified as low, 50% as moderate, and 75% as high. We also examined residuals graphically, generated quantile-quantile plots, and plotted Cook’s distance ( $D_i$ ) to identify influential data points that had a  $D_i > 1$  [81]. To assess the risk of publication or dissemination bias, we generated and inspected funnel plots. All statistical analyses were performed using the metafor package in R [82].

##### Sensitivity Analyses

In cohort studies that met our selection criteria, people who were prescribed ADs could have had higher baseline levels of depressive symptoms, which would make it difficult to disentangle the distinct effects of depression and ADs on mortality. To deal with confounding by indication, we conducted sensitivity analyses on the subset of studies that controlled for premedication depressive symptoms.

## Results

Seventeen studies met the inclusion criteria (see online suppl. material A6 for information regarding the eligible studies). After extracting the data, we removed

1 study with a very small sample size that reported no deaths in either the treatment or control group after 1 year of follow-up and thus provided no useful information on AD-related mortality [83]. The 16 remaining eligible studies with 50 available summary measures were included in the meta-analyses. These studies reported all-cause mortality for a total of 378,400 participants during the study follow-up periods (140,787 were AD users and 237,613 were not using ADs). Online supplementary material A6.1 contains a list of illnesses in the cardiovascular-patient samples. The drug classes and estimates we extracted are presented in online supplementary material A6.2 and A6.3. The covariates that were controlled for in each study are given in online supplementary material C.

The quality of the studies varied. A total of 11 studies were at high risk for selection bias, 9 had a high risk of performance bias, 2 had a high risk for attrition bias, and 1 study had a high risk of reporting bias. All the studies were at low risk for detection bias. The mean score for all studies on the “checklist for measuring study quality” [75] was 18.44, with a range from 10 to 24. Online supplementary material A5 includes complete bias assessment information.

#### *Sample Type as Moderator*

We assessed the health risks of using ADs stratified by sample type. Sample type was a significant moderator for both all-cause mortality,  $Q_M(1) = 11.22, p < 0.01$ , and cardiovascular events,  $Q_M(1) = 8.59, p < 0.01$  (for full results, see online suppl. material B1).

In cardiovascular-patient samples, AD use was associated with nonsignificant decreases in all-cause mortality (HR = 0.90, 95% CI: 0.76–1.07,  $p = 0.24$ ) and cardiovascular events (HR = 0.93, 95% CI: 0.82–1.06,  $p = 0.29$ ). However, in the general-population samples, ADs increased mortality risk by 33% (HR = 1.33, 95% CI: 1.14–1.55,  $p < 0.01$ ) and the risk of experiencing a cardiovascular event by 14% (HR = 1.14, 95% CI: 1.08–1.21,  $p < 0.01$ ). Figure 2 shows a forest plot of the all-cause mortality HRs for AD use with sample type as a moderator.

Heterogeneity between studies in their assessments of all-cause mortality was high ( $I^2 = 87\%$ ), but it was relatively low for cardiovascular events ( $I^2 = 26\%$ ). There were 6 influential data points ( $D_i > 1$ ) for all-cause mortality and 11 for cardiovascular events (these data points are described in online suppl. material A7). Multiple data points deviated from the quantile-quantile plots for both analyses. Online supplementary material B1 depicts these effects and shows funnel plots for the two sets of estimates

with sample type as moderators. Both distributions suggest an absence of bias [84].

#### *Antidepressant Class as Moderator*

Next, we collapsed the sample types together and tested whether AD class moderated the risks of all-cause mortality and cardiovascular events. AD class significantly moderated the risk of mortality,  $Q_M(2) = 6.82, p = 0.03$ , but not cardiovascular events,  $Q_M(2) = 1.52, p = 0.47$  (online suppl. material B2).

#### *Do the AD Classes Differ from Each Other?*

Using TCAs as the reference group, SSRI/SNRI did not have significantly different effects on all-cause mortality (HR = 1.10, 95% CI: 0.93–1.31,  $p = 0.27$ ) or cardiovascular events (HR = 1.07, 95% CI: 0.96–1.20,  $p = 0.24$ ). Other ADs did not significantly differ from TCAs on cardiovascular events (HR = 1.08, 95% CI: 1.92–1.27,  $p = 0.39$ ), but they did have a significantly higher effect on all-cause mortality (HR = 1.35, 95% CI: 1.08–1.69,  $p = 0.01$ ).

#### *How Does Each AD Class Compare to No AD Use?*

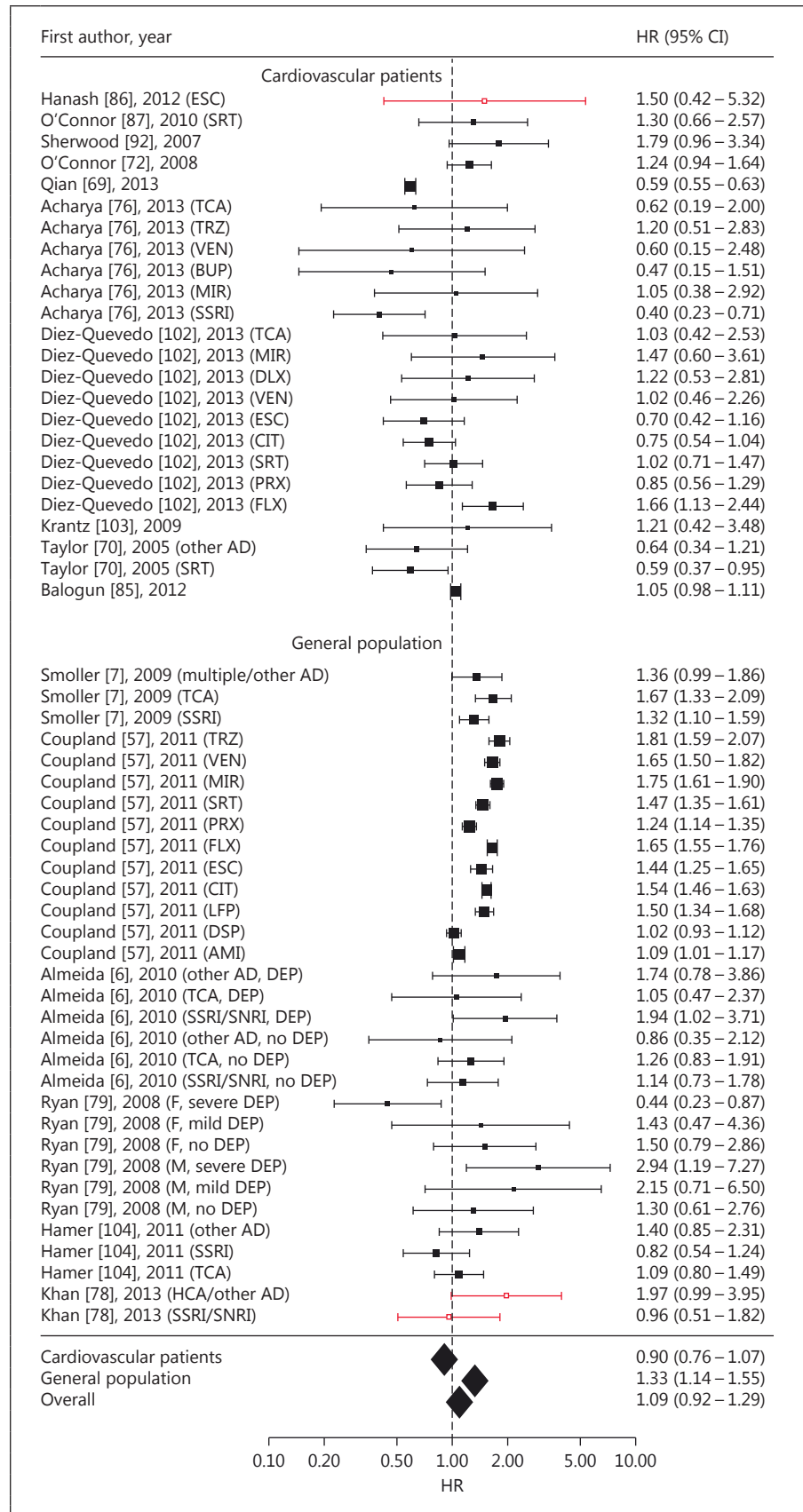
Relative to no AD use, none of the AD classes significantly affected mortality (SSRI/SNRI: HR = 1.06, 95% CI: 0.85–1.32,  $p = 0.61$ ; TCAs: HR = 0.96, 95% CI: 0.75–1.24,  $p = 0.77$ ; other ADs: HR = 1.30, 95% CI: 0.99–1.70,  $p = 0.06$ ) or the incidence of cardiovascular events (SSRI/SNRI: HR = 1.05, 95% CI: 0.90–1.24,  $p = 0.52$ ; TCAs: HR = 0.99, 95% CI: 0.83–1.18,  $p = 0.87$ ; other ADs: HR = 1.06, 95% CI: 0.87–1.29,  $p = 0.56$ ).

#### *Diagnostics*

Stratifying the data by AD class slightly reduced the heterogeneity between studies in their assessments of all-cause mortality ( $I^2 = 78\%$ ). The heterogeneity between studies in their assessments of cardiovascular events remained low ( $I^2 = 34\%$ ). Our diagnostic analysis revealed 5 influential data points ( $D_i > 1$ ) for all-cause mortality, and 2 for cardiovascular events (online suppl. material A7 and supplement B2). We also inspected the funnel plots (with AD class as moderators and the influential data points included) and found no evidence of bias (online suppl. material B2).

#### *Unstratified Data*

Although we did not have specific predictions about the overall effects of using ADs in our included studies, we analyzed our data unstratified by either sample type or AD class (online suppl. material B5). ADs did not signif-



**Fig. 2.** Forest plot of the mortality effects of antidepressants (ADs) and 95% confidence intervals (CIs) in the overall sample ( $n = 378,400$ ) and separated by cardiovascular-patient ( $n = 59,930$ ) and general-population ( $n = 318,470$ ) sample types. Red bars/open symbols indicate randomized placebo-controlled trials. AD, antidepressant medication; AMI, amitriptyline; BUP, bupropion; CIT, citalopram; DEP, depression; DLX, duloxetine; DSP, dosulepin; ESC, escitalopram; FLX, fluoxetine; HCA, heterocyclic ADs; HR, hazard ratio; LFP, lofepramine; MIR, mirtazapine; PRX, paroxetine; SNRI, serotonin-norepinephrine reuptake inhibitor; SRT, sertraline; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic ADs; TRZ, trazodone; VEN, venlafaxine. Study order is based on quality, from highest to lowest scoring studies on the “checklist for measuring study quality” [73].

icantly impact all-cause mortality (HR = 1.09, 95% CI: 0.92–1.29,  $p = 0.32$ ) and cardiovascular events (HR = 1.05, 95% CI: 0.92–1.20,  $p = 0.43$ ).

Removing the moderators increased the heterogeneity between studies ( $I^2 = 94\%$ ); however, it remained low for cardiovascular events ( $I^2 = 33\%$ ). There were 8 influential data points for all-cause mortality and 9 for cardiovascular events. When we inspected the funnel plots, we found no evidence of bias (online suppl. material B5 contains diagnostic information for this analysis).

#### *Controlling for Premedication Depression*

In our included studies, the most important potential source of confounding by indication is the possibility that the people taking ADs were also more depressed. If the risk estimates we have reported on all-cause mortality and new cardiovascular events were biased by confounding by indication, then they should decrease when controlling for premedication depression.

#### *Sample Type as a Moderator*

We first examined the effect of sample type on all-cause mortality using the 6 studies in which premedication depressive symptoms were controlled for (online suppl. material B3) [7, 57, 78, 85–87]. This reduced our number of summary measures from 55 to 16, and only 3 of the measures involved cardiovascular samples. Although underpowered for moderation analyses, our aim was to determine how controlling for premedication depression influenced the effect size of AD use in each sample type. Not surprisingly, sample type was not a significant moderator,  $Q_M(1) = 2.87$ ,  $p = 0.09$ . In cardiovascular-patient samples, ADs were associated with a small, nonsignificant increase in mortality (HR = 1.10, 95% CI: 0.82–1.48,  $p = 0.52$ ), whereas they significantly increased mortality in general-population samples by 44% (HR = 1.44, 95% CI: 1.31–1.58,  $p < 0.01$ ). Therefore, attempting to reduce an important potential source of confounding by indication by controlling for premedication depression did not decrease the all-cause mortality effect sizes as we had expected. Instead, it increased the effect sizes in both sample types.

Next, we tested the effect of sample type on the risk of new cardiovascular events (online suppl. material B3). However, only 1 study in the cardiovascular patient group controlled for premedication depression [86], so we restricted our analysis to the 28 summary measures from 2 general-population studies that controlled for premedication depression [7, 57]. AD use remained a significant predictor of the risk of experiencing a cardiovascular event (HR = 1.14, 95% CI: 1.08–1.20,  $p < 0.01$ ).

#### *AD Class as a Moderator*

We also reexamined AD class as a potential moderator, collapsing the sample types together. Restricting our analyses to the summary measures that controlled for premedication depression (online suppl. material B4), drug class remained a significant moderator of all-cause mortality,  $Q_M(2) = 7.60$ ,  $p = 0.02$ , but not cardiovascular events,  $Q_M(2) = 4.44$ ,  $p = 0.11$ . Using TCAs as the reference group, the mortality risk of SSRI/SNRIs was not significantly different (HR = 1.15, 95% CI: 0.97–1.39,  $p = 0.11$ ), although the mortality risk of other ADs was significantly higher (HR = 1.42, 95% CI: 1.10–1.82,  $p = 0.01$ ).

Using no AD use as the reference, each AD class was associated with a significant increase in the risk of mortality (SSRI/SNRIs: HR = 1.46, 95% CI: 1.31–1.62,  $p < 0.01$ ; TCAs: HR = 1.25, 95% CI: 1.08–1.45,  $p < 0.01$ ; other ADs: HR = 1.78, 95% CI: 1.45–2.18,  $p < 0.01$ ). The risk of cardiovascular events significantly increased with the use of SSRI/SNRIs (HR = 1.17, 95% CI: 1.10–1.24,  $p < 0.01$ ) and other ADs (HR = 1.21, 95% CI: 1.04–1.40,  $p = 0.01$ ); however, the effect of TCA use was not significant (HR = 1.05, 95% CI: 0.97–1.15,  $p = 0.22$ ).

#### *Unstratified Data*

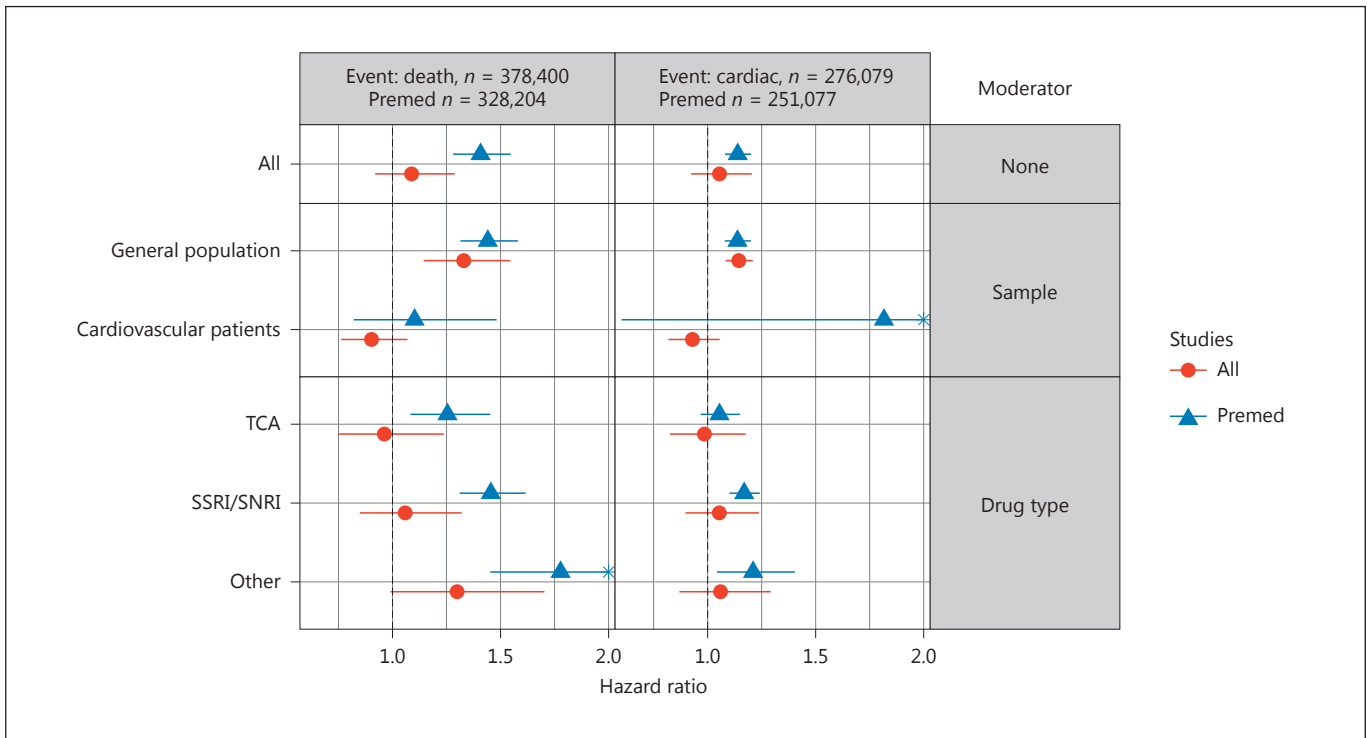
We reexamined the effects of AD use, unstratified by sample type or AD class, in studies that controlled for premedication depression. In this analysis, ADs were associated with a significant increase in all-cause mortality (HR = 1.41, 95% CI: 1.28–1.55,  $p < 0.01$ ) and cardiovascular events (HR = 1.14, 95% CI: 1.08–1.20,  $p < 0.01$ ).

Online supplementary material B3, B4, and B6 show forest plots of the HRs and CIs for these analyses, and contain heterogeneity, diagnostic, and risk of bias information.

#### *Exploratory Analyses*

As exploratory analyses, we tested whether sample type and drug class interacted to predict all-cause mortality or cardiovascular events (the interaction was not significant; see online suppl. B7 for the results). We then dropped the interaction and tested additive models of the moderators to predict mortality and cardiovascular events (online suppl. material B8). For AD class, we used TCAs as the reference group. SSRI/SNRIs did not significantly differ from TCAs for all-cause mortality (HR = 1.13, 95% CI: 0.95–1.34,  $p = 0.17$ ) or cardiovascular events (HR = 1.08, 95% CI: 0.97–1.21,  $p = 0.17$ ). Other ADs had a significantly higher risk of death than the TCAs (HR = 1.35, 95% CI: 1.08–1.69,  $p = 0.01$ ), but they did not increase the risk of new cardiovascular events (HR = 1.09,





**Fig. 3.** Summary of the estimates of antidepressant (AD) use on the risk of all-cause mortality (“death”) and cardiovascular events (“cardiac”). Three a priori analyses were conducted: no moderator variable (“none”), sample type as a moderator (“sample”), and AD class as a moderator (“drug type”). Finally, separate results are reported for all included studies (“all”) and the post hoc analyses of the subset of studies that controlled for premedication depression (“premed”). SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic ADs;

95% CI: 0.93–1.29,  $p = 0.30$ ). Sample type remained a significant moderator, with the risk of death and cardiovascular events higher in the general-population samples (see results in online suppl. material B8).

Next, we examined the health effects for each AD class stratified by sample type (online suppl. material B8). Using no AD use as the reference group, none of the AD classes significantly affected all-cause mortality in the cardiovascular patient samples, although TCAs were marginally protective (SSRI/SNRIs: HR = 0.86, 95% CI: 0.68–1.08,  $p = 0.19$ ; TCAs: HR = 0.76, 95% CI: 0.57–1.00,  $p = 0.05$ ; other ADs: HR = 1.02, 95% CI: 0.77–1.36,  $p = 0.88$ ). They also did not impact the risk of experiencing a new cardiovascular event, although the effect of TCAs was marginal (SSRI/SNRIs: HR = 0.92, 95% CI: 0.81–1.05,  $p = 0.24$ ; TCAs: HR = 0.85, 95% CI: 0.73–1.01,  $p = 0.05$ ; other ADs: HR = 0.93, 95% CI: 0.79–1.11,  $p = 0.43$ ). In general-population samples, however, SSRI/SNRIs and other ADs were associated with significant increases in

all-cause mortality (SSRI/SNRIs: HR = 1.58, 95% CI: 1.22–2.04,  $p < 0.01$ ; other ADs: HR = 1.32, 95% CI: 1.07–1.63,  $p = 0.01$ ), and the risk of cardiovascular events (SSRI/SNRIs: HR = 1.18, 95% CI: 1.03–1.35,  $p = 0.02$ ; other ADs: HR = 1.17, 95% CI: 1.09–1.25,  $p < 0.01$ ). TCAs did not have a significant effect on either all-cause mortality (HR = 1.17, 95% CI: 0.94–1.46,  $p = 0.16$ ) or cardiovascular events (HR = 1.08, 95% CI: 0.99–1.18,  $p = 0.10$ ). Because we did not set out to test the effects of AD classes within each sample type, these findings should be interpreted with caution and used only to guide future research [88].

## Discussion

In Figure 3, we summarize findings from our meta-analyses. This figure shows that the risk estimates of AD use are consistently higher in general-population than cardiovascular-patient samples, and they are higher in

the subset of studies that control for premedication depression. The risk of all-cause mortality also differs according to AD class; however, this effect appears to be driven by the difference between the use of TCAs and other ADs.

Our findings provide corroborative evidence that cardiovascular status moderates the health risks associated with AD use. In general populations, AD use was associated with a 33% increase in mortality and a 14% increase in the risk of new cardiovascular events. The baseline HR was not reported in every study, but Smoller et al. [7], for example, reported about 8 deaths per 1,000 person-years among older women (50–79 years old) not taking ADs. A 33% increased risk in mortality would correspond to an estimated additional 2.64 deaths per 1,000 person-years in this demographic category. Conversely, in samples with preexisting cardiovascular disease, AD use slightly reduced the risk of death and new cardiovascular events, though these effects did not reach statistical significance.

A recent meta-analysis provided converging evidence that ADs have different effects in cardiovascular and non-cardiovascular samples [89]. This paper, which was published after we conducted our search, reported all deaths that occurred after randomization in 9 randomized, placebo-controlled, double-blind trials of SSRIs and SNRIs. The data were obtained from UK and European regulatory agencies and the website of a pharmaceutical company and so would not have been picked up by our search criteria. This meta-analysis did not stratify the studies by the cardiovascular status of the participants, but it did provide the information to do so. We stratified their data by cardiovascular status (online suppl. material D) to compare their effect sizes to ours. Seven studies involved patients with affective conditions, and 2 involved patients with diabetes, which share chronic platelet activation in common with cardiovascular disease [66]. Although the sample sizes in this new meta-analysis are underpowered for significance testing of rare death events (there were only 13 deaths out of a total sample size of 2,944), our purpose was to examine the direction of the estimated effects and compare them to our estimates. The point estimates were in the same direction as our estimates. In the affective group, the estimated effect of ADs was harmful (HR = 2.48, 95% CI: 0.52–11.94,  $p = 0.26$ ), while the estimated effect was protective in the cardiovascular group (HR = 0.55, 95% CI: 0.08–3.93,  $p = 0.55$ ).

Due to the highly conserved nature of mammalian physiology, ADs should have similar effects in other mammals. While we know of no studies on prolonged AD use in animals with cardiovascular disease, a recent study ex-

amined the effects of chronic exposure to paroxetine in otherwise healthy mice. Male mice exposed to paroxetine in utero through early adulthood were 2.5 times more likely to die relative to controls [90]. This effect – which is similar in magnitude to the estimated effects of SSRIs and SNRIs on affective patients in the meta-analysis described in the preceding paragraph – was marginally significant ( $p = 0.07$ ). Again, both studies are underpowered to detect rare death events. The researchers also reported statistically significant negative effects of paroxetine on body mass (both sexes), the ability to hold territories (males), the likelihood of mating (both sexes), and the total number of offspring (males only). Such effects are ecologically important, yet they are rarely evaluated in human studies.

In our meta-analysis, AD class was a significant moderator of all-cause mortality. However, as predicted, SSRI/SNRIs and TCAs did not have significantly different effects on health risk outcomes. AD class came out as a significant moderator because the other AD category was significantly higher than the TCAs. This is against our prediction that all AD classes would have similar effects on all-cause mortality. However, we urge caution in interpreting this result. There is a paucity of studies in this category, and significance is driven by 2 estimates for mirtazapine and trazadone from the same study [57], both of which are influential data points (online suppl. material B2).

When using no AD use as the reference, the 3 AD classes did not significantly impact mortality or new cardiovascular events. This is not surprising, since these analyses collapsed the 2 sample types together, obscuring the effects of ADs in general-population samples. Our findings, therefore, demonstrate how different investigations into the long-term safety of AD use may result in seemingly contradictory findings when population characteristics, like cardiovascular status, are not properly controlled for [62]. If we had simply assessed the mortality effects of ADs unstratified by cardiovascular status, we would have concluded that ADs do not significantly increase the risk of death (Fig. 3). Our findings highlight the importance of attending to potentially influential patient characteristics when conducting meta-analytic research [61].

The fact that SSRI/SNRIs and TCAs had similar effects on health outcomes could be surprising to some readers. The widespread use of SSRIs is partly based on the belief that they are safer than the older TCAs, which have a variety of cardiotoxic effects [91]. However, our results support Pacher and Kecskemeti's [49] review, which outlines a number of negative cardiovascular effects of SSRIs (bra-

dyscardia, prolongation of the QT interval, and antagonism of cardiac ion channels) and urges greater caution in their use. Additionally, the serotonin transporter is widely expressed in the periphery, and SSRIs cannot be selectively directed towards the brain regions putatively involved in depression. Thus, even though the SSRIs selectively target the serotonin transporter, they are not selective enough. SSRIs, therefore, prevent many peripheral organs from taking up serotonin from the bloodstream, which may cause many other adverse effects that contribute to mortality risk [3, 27].

The results from our meta-analysis are affected by the quality of our included studies, and many were at high risk for selection bias. Some studies did not adequately account for gender [92], and 1 study used data from several randomized trials [78], some of which were not double blind or even placebo controlled. Nevertheless, each cohort study controlled for a large number of covariates, including demographics and health-related conditions, in an attempt to isolate the specific effects of ADs (online suppl. material C).

Although we may have missed some factors contributing to selection bias, we did address two potential sources. First, a potential source of confounding by indication is that a small proportion of people in the general-population samples will have cardiovascular diseases [93], and some of them will have taken ADs. However, since ADs are more protective in cardiovascular patients, the use of general-population samples should result in a conservative estimate of their mortality effects in people *without* preexisting cardiovascular disease.

Second, we also attempted to address the issue that people using ADs may have had higher premedication depression by reconducting our analyses using the subset of studies that controlled for premedication depression. If confounding by indication was inflating the all-cause mortality estimates of ADs, then the effect sizes should have gone down in these analyses. Contrary to that expectation, we found that controlling for premedication depression increased all of the effect sizes (Fig. 3). When stratified by sample type, AD use was estimated to increase the risk of death by 44% in general-population samples and 10% in cardiovascular samples. When we stratified by AD class, TCAs were estimated to increase the risk of death by 26%, SSRI/SNRIs by 49%, and other ADs by 75%. Even the overall effect of ADs (i.e., unstratified by either sample type or AD class) reached significance for all-cause mortality. Controlling for premedication depression also increased the effect sizes of AD use on the risk of new cardiovascular events (Fig. 3).

These results suggest that controlling for premedication depression increases the signal-to-noise ratio of the health effects of AD use. Put another way, controlling for depressive symptoms that are concurrent with AD use may cause researchers to underestimate the adverse health effects of AD use. One possible explanation is that AD use only leads to a transient reduction in depressive symptoms because they induce an oppositional tolerance (caused by mechanisms in the brain responsible for maintaining homeostasis) that interferes with spontaneous remission and prolongs episodes [19, 27, 94–96]. Under this hypothesis, depressive symptoms under prolonged AD use (i.e., months or longer) are higher than they would be without medication, and partialling out concurrent depression also partials out the negative health effects of ADs that covary with this iatrogenic depression.

Many studies were also at high risk for performance bias with respect to the way AD treatment was assessed. Most of the cohort studies treated any drug exposure during the follow-up period as a binary variable and did not allow patients to fluctuate in their AD status. Since differences in the onset and length of AD exposure likely affect mortality in different ways, studies that do not account for these differences may have produced less reliable estimates. To remedy this design flaw, we recommend prospective designs that treat AD use as a time-dependent covariate.

We did not explore how individual differences other than cardiovascular disease and AD class (which we targeted a priori) influence the mortality effects of ADs. The mortality estimates for AD use varied widely between studies. Although this is common in meta-analyses of studies that differ in sample type, study design, duration, and treatment administration, dosage, and measurement [97], the statistical heterogeneity we observed in all-cause mortality suggests that other nonmethodological factors are contributing to discrepancies in these effects. For instance, individual characteristics of study participants might play a role. One study included in our meta-analysis [79] found that AD use was associated with an increased risk of death in men but a decrease in women, whereas another study [7] reported an increased risk of death in women using ADs, as compared with women not using ADs. Furthermore, although we ensured that each study estimate controlled for age, the studies included in our meta-analysis tended to use an older age as a selection criterion, so our findings may not generalize to younger populations. Future research should investigate how individual differences such as gender and age group impact the mortality risk associated with AD use.

Some of the increased risk of death associated with AD use in general-population samples appears to be attributable to an increased risk of cardiovascular events. There are a number of other potentially contributing pathways [3], although the limited number of studies reporting causes of death precludes a formal evaluation. In the study by Coupland et al. [57], AD use was associated with an increased risk of suicide attempts, myocardial infarction, stroke, falls, fractures, upper gastrointestinal bleeding, seizures, adverse drug reactions, and hyponatremia. Each such event could contribute to mortality, but the cause-specific mortality effects of ADs were not estimated. Two studies reported the distribution of deaths [7, 79]. In both, most were caused by cardiovascular events, cancer, and other/unknown causes, and only a few were due to suicide. However, only one of these studies estimated the cause-specific risks of death associated with AD use [7]. In men, AD use was associated with a significant increase in the risk of death due to unknown causes. The authors suggested the difficulty in attributing a cause was due to a general decline in health where multiple factors were probably present. Thus, multiple causes may contribute to AD-related mortality in general-population samples.

We also found that ADs were less harmful in samples ascertained for preexisting cardiovascular illnesses, further suggesting that ADs have broad serotonergic effects outside of the brain. Their anticlotting properties may facilitate blood flow to the heart when blood vessels are blocked or constricted, decreasing the likelihood of cardiovascular events in samples exhibiting these types of pathologies, and thereby offsetting the negative effects of ADs. Another possibility is that ADs are harmful in both samples, except they provide psychological benefits to cardiovascular patients that are unrelated to the treatment of pathological vascular processes. Studies suggest that depression increases the risk of cardiovascular mortality in individuals with preexisting cardiovascular illnesses [98], and AD-related reductions in depression may increase well-being or positive affect, which in some cases can improve medical outcomes [99]. Arguing against this explanation is the evidence that ADs have limited efficacy in the treatment of depression [24]. Furthermore, when they are taken by individuals with preexisting illnesses, ADs have not been shown to improve medical outcomes; instead, they introduce the risk of harmful side effects and iatrogenic comorbidity [100]. Thus, although ADs are less harmful in cardiovascular patients, further research is needed into the mechanisms behind this effect.

The rates of AD use are high and appear to be increasing [2], and most ADs are prescribed by primary-care practitioners in the absence of a formal psychiatric diagnosis [101]. Our results suggest that health care providers should take greater care in evaluating the relative costs and benefits of ADs for each individual patient, including an assessment of cardiovascular status. ADs may be relatively safe for patients with known cardiovascular disease. However, when the patient has no cardiovascular disease, our results should give the prescriber pause because they suggest ADs increase health risks, including the risk of death. When recommending or prescribing ADs to patients, health care providers should also engage in informed consent discussions that more accurately describe these risks and benefits. Finally, our findings highlight the urgent need for more rigorous investigations into the mortality effects of ADs. They are too widely used to allow this basic question of safety to remain unanswered.

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## Author Contributions

P.W.A. designed the study. M.J.R. and K.E. conducted the search, M.J.R., K.E., M.M.M., and P.W.A. were involved in determining study eligibility. B.M.B., M.M.M., P.W.A., and S.D.H. analyzed the data; M.M.M. and P.W.A. had full access to all the data in the study and take responsibility for the integrity of the data and

the accuracy of the data analysis. G.M.S. contributed to the interpretation of the results. M.M.M., P.W.A., B.M.B., and M.J.R. drafted the manuscript. K.E., M.M.M., B.M.B., and M.J.R. drafted appendices. S.D.H., G.M.S., B.H.M., J.A.T., and Z.D. provided critical edits of the manuscript. All authors have read and approved the final manuscript.

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