ELECTRONIC SUPPLEMENTARY MATERIAL
A meta-analysis of the all-cause mortality effects of antidepressants

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1. INTRODUCTION

This supplement provides the information required to reproduce our meta-analysis. It also includes a list of articles that produced disagreements between our reviewers, and justifications for their final eligibility decisions.

2. SEARCH INSTRUCTIONS

We carried out our search using two academic databases and one search engine. Our search can be reproduced using the following instructions to search PubMed, EMBASE, and Google Scholar in order, including articles up to June 3rd, 2014.

In PubMed, using "Basic search", enter the following search term to generate 70 articles:

> ("all-cause mortality" OR "all cause mortality" OR "all-cause death" OR "all cause death") AND (antidepress* OR SSRI* OR SNRI* OR MAOI* OR "reuptake inhibitor" OR TCA* OR "monoamine oxidase inhibitor" OR "bupropion" OR "milnacipran" OR "venlafaxine" OR " desvenlafaxine" OR "duloxetine" OR "imipramine" OR "fluvoxamine" OR "desipramine" OR "paroxetine" OR "amitriptyline" OR "escitalopram" OR "citalopram" OR "clomipramine" OR "nortriptyline" OR "sertraline" OR "fluoxetine" OR "lithium")

In EMBASE, complete the search in two steps using the "Advanced search" option:

Step 1. Enter the following search term:

> 'all-cause mortality' OR 'all cause mortality' OR 'all-cause death' OR 'all cause death'
> Click "Search" and your search will be saved in "Search History".

Step 2. Enter the following search term:

> antidepress* OR SSRI* OR SNRI* OR MAOI* OR 'reuptake inhibitor' OR TCA* OR 'monoamine oxidase inhibitor' OR 'bupropion' OR 'milnacipran' OR 'venlafaxine' OR 'desvenlafaxine' OR 'duloxetine' OR 'imipramine' OR 'fluvoxamine' OR 'desipramine' OR 'paroxetine' OR 'amitriptyline' OR 'escitalopram' OR 'citalopram' OR 'clomipramine' OR 'nortriptyline' OR 'sertraline' OR 'fluoxetine' OR 'lithium'

Select "Search" to save the search in "Search History". To generate a final list of 158 articles, select searches 1 and 2 in "Search History" and select "Combine selections with: AND".

In Google Scholar, each search is completed by entering each search term one at a time, and combining the first five pages of references resulting from each search term for a combined total of 2350 articles. The search terms are:

> "all-cause mortality" AND (antidepressant OR SSRI)
> "all-cause death" AND (antidepressant OR SSRI)

"all-cause mortality" AND (SNRI OR "reuptake inhibitor")
"all-cause death" AND (SNRI OR "reuptake inhibitor")
"all-cause mortality" AND (MAOI OR TCA)
"all-cause death" AND (MAOI OR TCA)
"all-cause mortality" AND ("monoamine oxidase inhibitor" OR "bupropion")
"all-cause death" AND ("monoamine oxidase inhibitor" OR "bupropion")
"all-cause mortality" AND ("milnacipran" OR "venlafaxine")
"all-cause death" AND ("milnacipran" OR "venlafaxine")
"all-cause mortality" AND ("desvenlafaxine" OR "duloxetine")
"all-cause death" AND ("desvenlafaxine" OR "duloxetine")
"all-cause mortality" AND ("imipramine" OR "fluvoxamine")
"all-cause death" AND ("imipramine" OR "fluvoxamine")
"all-cause mortality" AND ("desipramine" OR "paroxetine")
"all-cause death" AND ("desipramine" OR "paroxetine")
"all-cause mortality" AND ("amitriptyline" OR "escitalopram")
"all-cause death" AND ("amitriptyline" OR "escitalopram")
"all-cause mortality" AND ("citalopram" OR "clomipramine")
"all-cause death" AND ("citalopram" OR "clomipramine")
"all-cause mortality" AND ("nortriptyline" OR "sertraline")
"all-cause death" AND ("nortriptyline" OR "sertraline")
"all-cause mortality" AND ("fluoxetine" OR "lithium")
"all-cause death" AND ("fluoxetine" OR "lithium")

All duplicates are removed, and 3 articles that we knew of before searching are added (O'Connor et al., 2008; Jorge et al., 2003; Ghassemi et al., 2014) to produce 837 articles.

3. DISCREPANT ELIGIBILITY REVIEWS

After the initial screening process, two reviewers independently assessed articles to decide whether each article was eligible to be included in our meta-analysis. A third reviewer periodically monitored eligibility decisions, and all reviewers discussed any articles that produced discrepant eligibility decisions with a third reviewer. Descriptions of these articles (and the final eligibility decisions) are listed here.

3.1. FINAL ASSESSMENT: ELIGIBLE

Taylor, C. B., Marston, E. Y., Catellier, D., Veith, R. C., Carney, R. M., Burg, M. M., … Jaffe, A. S. (2005). Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. *Archives of General Psychiatry, 62*, 792–798.

We considered whether this study adequately isolated the effects of antidepressant use on all-cause mortality. This study is a randomized controlled trial assessing the effect of an intervention for depressed and socially isolated individuals on depression-related outcomes and mortality. In the intervention and control groups, participants were free to seek antidepressant treatment. As part of this study, the researchers conducted an analysis of all-cause mortality associated with antidepressant use, regardless of which group participants were initially randomized to. We

considered that the two groups were not comparable, since more individuals in the antidepressant group received the intervention, but the researchers also reported that in a previous study (Investigators et al., 2003), this intervention did not affect all-cause mortality. Thus, we reasoned that this intervention was not a confounding variable.

Sherwood, A., Blumenthal, J. A., Trivedi, R., Johnson, K. S., O'Connor, C. M., Adams, K. F., ... & Hinderliter, A. L. (2007). Relationship of depression to death or hospitalization in patients with heart failure. *Archives of Internal Medicine, 167,* 367–373.

The authors isolated the effects of using antidepressants on all-cause mortality by adjusting their statistics for various variables, including depression in the form of BDI scores.

Coupland, C. A., Dhiman, P., Barton, G., Morriss, R., Arthur, A., Sach, T., & Hippisley-Cox, J. (2011). A study of the safety and harms of antidepressant drugs for older people: A cohort study using a large primary care database. *Health Technology Assessment, 15*(28), 1-202.

We considered that the researchers' decision to exclude patients not taking antidepressants in the past year from the analysis might be an arbitrary criteria for selecting their sample; however, antidepressant use was monitored for the follow up period, and the researchers controlled for the necessary confounding variables.

3.2. FINAL ASSESSMENT: ELIGIBLE BUT NOT INCLUDED

Elitzur, Y., Sharon, N., Ouzan, E., Pugatsch, T., ... & Lotan, C. (2011). Bupropion for smoking cessation in patients with acute coronary syndrome. *Archives of Internal Medicine, 171,* 1055-1060.

Although bupropion, the antidepressant used in the study, was used for smoking cessation and not to treat depression, we decided the study was eligible since our criteria included antidepressants used for any reason. We did not include this study in our analysis because there were no deaths in each group (likely due to a small sample size and a short follow-up period), and the study did not contribute any useful information.

3.3. FINAL ASSESSMENT: INELIGIBLE BECAUSE NO ALL-CAUSE MORTALITY ESTIMATE FOR ADM USE

Barnett, K., McCowan, C., Evans, J. M. M., Gillespie, N. D., Davey, P. G., & Fahey, T. (2011). Prevalence and outcomes of use of potentially inappropriate medicines in older people: cohort study stratified by residence in nursing home or in the community. *BMJ Quality and Safety, 20*, 275–281.

The authors were interested in the use of potentially inappropriate medications (PIMs) and assessed the mortality effects of multiple drugs (including certain ADMs such as fluoxetine and amitriptyline) together.

Chung, M. L., Dekker, R. L., Lennie, T. A., & Moser, D. K. (2013). Antidepressants do not

improve event-free survival in patients with heart failure when depressive symptoms remain. *Heart & Lung, 42*, 85–91.

This study presents statistics summarizing the effects of antidepressant use on event-free survival, not all-cause mortality.

Davidson, K. W., Burg, M. M., Kronish, I. M., Shimbo, D., Dettenborn, L., Mehran, R., …Rieckmann, N. (2010). Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. *Archives of General Psychiatry, 67*, 480–488.

The authors did not include an analysis of mortality based on ADM use.

Farrell, M., & Marsden, J. (2007). Acute risk of drug-related death among newly released prisoners in England and Wales. *Addiction, 103,* 251–255.

The authors did not include an analysis of mortality based on ADM use.

Lett, H. S., Blumental, J. A., Babyak, M. A., Catellier, D. J., Carney, R. M. Berkman, L. F., … & Schneiderman, N. (2007). Social support and prognosis in patients at increased psychosocial risk recovering from myocardial infarction. *Health Psychology, 26*, 418–427.

The authors did not include an analysis of mortality based on ADM use.

Meyer, T., Belnap, B. H., Herrmann-Lingen, C., He, F., Mazumdar, S., & Rollman, B. L. (2014). Benefits of collaborative care for post-CABG depression are not related to adjustments in antidepressant pharmacotherapy. *Journal of Psychosomatic Research, 76*, 28–33.

The authors did not include an analysis of mortality based on ADM use.

Zarse, K., Terao, T., Tian, J., Iwata, N., Ishii, N., & Ristow, M. (2011). Low-dose lithium uptake promotes longevity in humans and metazoans. *European Journal of Nutrition, 50*, 387–389.

The authors did not include an analysis of mortality based on ADM use.

Ahlehoff, O., Lindhardsen, J., Gislason, G. H., Olesen, J. B., Charlot, M., Skov, L., … & Hansen, P. R. (2012). Prognosis after percutaneous coronary intervention in patients with psoriasis: A cohort study using Danish nationwide registries. *BMC Cardiovascular Disorders, 12*:79.

The authors did not include an analysis of mortality based on ADM use.

Brumberg, G. E., ElSaid, A., Saba, S. & Shalaby, A. (2009). Psychiatric disorders impart poor prognosis to cardiac resynchronization therapy recipients. *Heart Rhythm, 6*, S24.

The authors did not include an analysis of mortality based on ADM use.

Fisher, M., Falqués, M., Rance, M., Taylor, D. C. A., & Lindner, L. (2013). Cost-effectiveness of linaclotide compared to antidepressants in the treatment of irritable bowel syndrome with constipation in Scotland. *Value in Health, 7*, A497.

The authors did not include an analysis of mortality based on ADM use.

Hak, E., Bont, J., & Verheik, T. J. M. (2005). Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. *Family Practice, 22,* 375–380.

The authors did not include an analysis of mortality based on ADM use.

Haugaa, K. H., Tarrell, R. F., Morlan, B. W., Carabello, P. J., & Ackerman, M. J. (2013). QT prolonging medications are frequent in patients with high risk of mortality. *Heart Rhythm, 10*, S208.

The authors did not include an analysis of mortality based on ADM use.

Takeshita, J., Masaki, K., Ahmed, I., Foley, D. J., Li, Y. Q., Chen, R., …& White, L. (2002). Are depressive symptoms a risk factor for mortality in elderly Japanese American men?: The Honolulu-Asia aging study. *American Journal of Psychiatry, 159*, 1127–1132.

The authors did not include an analysis of mortality based on ADM use.

Teremura-Gronblad, M., Bell, S. J., Poysti, M. M., Strandberg, T. E., Laurila, J. V., Tilvis, R. S., … & Pitkala, K. H. (2012). Risk of death associated with use of PPIs in three cohorts of institutionalized older people in Finland. *Journal of the American Medical Directors Association, 13,* 488.e9–488.e13.

The authors did not include an analysis of mortality based on ADM use.

Pan, A., Lucas, M., Sun, Q., van Dam, R. M., Franco, O. H., Willett, W. C., ... & Hu, F. B. (2011). Increased mortality risk in women with depression and diabetes mellitus. A*rchives of General Psychiatry, 68*, 42–50.

The authors did not include an analysis of mortality based on ADM use.

Fischer, M. J., Kimmel, P. L., Greene, T., Gassman, J. J., Wang, X., Brooks, D. H., … & AASK Study Group. (2011). Elevated depressive affect is associated with adverse cardiovascular outcomes among African Americans with chronic kidney disease. *Kidney International, 80*, 670–678.

This study examines the effect of depression on all-cause mortality, and not the effect of antidepressants on all-cause mortality.

Gisev, N., Hartikainen, S., Chen, T. F., Korhonen, M., & Bell, J. S. (2012). Effect of comorbidity

on the risk of death associated with antipsychotic use among community-dwelling older adults. *International Psychogeriatrics, 24*, 1058–1064.

The authors provided an all-cause mortality statistic with respect to the use of an antipsychotic. Although this drug involves the serotonin pathway, it is not classified and used as an antidepressant.

Kiviniemi, M., Suvisaari, J., Koivumaa-Honkanen, H., Kakkinen, U., Isohanni, M., & Hakko, H. (2013). Antipsychotics and mortality in first-onset schizophrenia: Prospective Finnish register study with 5-year follow-up. *Schizophrenia Research, 150*, 274–280.

The authors provided an all-cause mortality statistic with respect to the use of an antipsychotic. Although this drug involves the serotonin pathway, it is not classified and used as an antidepressant.

Trifirò, G., Verhamme, K. M. C., Ziere, G., Caputi, A. P., Ch Stricker, B. H., & Sturkenboom, M. C. J. M. (2007). All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. *Pharmacoepidemiology and Drug Safety, 16*, 538–544.

The authors provided an all-cause mortality statistic with respect to the use of an antipsychotic. Although this drug involves the serotonin pathway, it is not classified and used as an antidepressant.

Hennessy, S., Bilker, W. B., Knauss, J. S., Margolis, D. J., Kimmel, S. E., Reynolds, R. F., ... & Strom, B. L. (2002). Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: Cohort study using administrative data. *British Medical Journal, 325*, 1070–1072.

The authors provided an all-cause mortality statistic with respect to the use of an antipsychotic, and although this drug involves the serotonin pathway, it is not classified and used as an antidepressant.

3.4. FINAL ASSESSMENT: INELIGIBLE BECAUSE POTENTIAL CONFOUNDS WERE NOT ADEQUATELY CONTROLLED

Douglas, I.J., Evans, S.J.W., Hingorani, A.D., Grosso, A.M., Timmis, A., Hemingway, H., & Smeeth, L. (2012). Clopidogrel and interaction with proton pump inhibitors: Comparison between cohort and within person study designs. *British Medical Journal, 345*, e4388.

Initially, we considered this study to be eligible and included it in our meta-analysis. The researchers did not control for depression, but we assumed that the strong 2C19 inhibiting antidepressants were only used to aid in the treatment of cardiovascular issues (i.e., to prevent gastrointestinal bleeding), and not to treat depression. Given that this is a cohort study, we later realized that some participants still could have been prescribed these antidepressants for depression. In order to properly assess the mortality effects of these antidepressants, the researchers should have controlled for depression, therefore we excluded this study.

Ried, L. D., Tueth, M. J., & Jia, H. (2006). A pilot study to describe antidepressant prescriptions dispensed to veterans after stroke. *Research in Social and Administrative Pharmacy, 2*, 96–109.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Xiong, G. L., Jiang, W., Clare, R., Shaw, L. K., Smith, P. K., Mahaffey, K. W., …& Newby, L. K. (2006). Prognosis of patients taking selective serotonin reuptake inhibitors before coronary artery bypass grafting. *The American Journal of Cardiology, 98*, 42–47.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Bush, D. E., Ziegelstein, R. C., Tayback, M., Richter, D., Stevens, S., Zahalsky, H., & Fauerbach, J. A. (2001). Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *The American Journal of Cardiology, 88*, 337–341.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Zuidersma, M., Conradi, H. J., van Melle, J. P., Ormel, J., & de Jonge, P. (2013). Depression treatment after myocardial infarction and long-term risk of subsequent cardiovascular events and mortality: A randomized controlled trial. *Journal of Psychosomatic Research, 74*, 25–30.

The researchers did not adequately isolate the effects of antidepressant use on all-cause mortality. In this randomized controlled trial, a non-pharmacological intervention was employed in addition to antidepressants in the treatment group, and this intervention was not offered in the control group.

Blanchette, C. M., Simoni-Wastila, L., Shaya, F., Orwig, D., Noel, J., & Stuart, B. (2009). Health care use in depressed, elderly, cardiac patients and the effect of antidepressant use. *American Journal of Health-System Pharmacists, 66*, 366–372.

The authors did not isolate the effects of antidepressants on all-cause mortality, because they did not adequately control for depression. The researchers assumed that participants without a depression claim would not be using antidepressants; however, not all individuals using antidepressants are necessarily depressed. The authors reported that they assessed the mortality effects of using antidepressants restricting the sample to only those with a depression claim as assessed by an ICD-9 code, but unfortunately, they do not report this statistic in the study.

Ghassemi, M., Marshall, J., Singh, N., Stone, D. J., & Celi, L. A. (2014). Leveraging a critical care database: Selective Serotonin Reuptake Inhibitor use prior to ICU admission is associated with increased hospital mortality. *CHEST Journal*, *145*(4), 745-752.

This was a study we were also aware of prior to conducting this meta-analysis. Upon further review however, we decided that the researchers did not isolate the effects of antidepressant use

on all-cause mortality because they did not adjust the statistics for depression. The authors adjust their mortality statistics for co-morbidities using a composite Elixhauser score, that includes 30 conditions. Although the Elixhauser score includes depression, depression is not considered as a confound separately from other conditions.

Haukka, J., Arffman, M., Partonen, T., Sihvo, S., Elovainio, M., Tiihonen, J., … & Keskimaki, I. (2009). Antidepressant use and mortality in Finland: A register-linkage study from a nationwide cohort. *European Journal of Clinical Pharmacology, 65*, 715–720.

The authors did not isolate the effects of antidepressants on all-cause mortality, because they did not adequately control for depression. In their study, they qualify the presence of depression as being hospitalized for depression; however, most individuals with depression are not hospitalized for the condition.

Maust, D. T., Kim, H. M., Seyfried, L. S., Chiang, C., Kavanagh, J., Schneider, L., & Kales, H. C. (2014). Number needed to harm for antipsychotics and antidepressants in dementia. *American Journal of Geriatric Psychiatry, 22,* S119–120.

This study does not isolate the effect of using antidepressants on all-cause mortality. The researchers use antidepressant users as a reference category, comparing mortality rates of antidepressant users to users of other types of drugs.

Ahola, A. J., Harjutsalo, V., Saraheimo, M., Forsblom, C., & Groop, P. (2012). Purchase of antidepressant agents by patients with type 1 diabetes is associated with increased mortality rates in women but not in men. *Diabetologia, 55,* 73–79.

This study does not isolate the effects of antidepressant use on all-cause mortality. The authors considered all individuals taking antidepressants to be depressed, and they did not measure depression in any other way; they did not control for depression between the two groups.

Kelly, C. M., Juurlink, D. N., Gomes, T., Duong-Hua, M., Pritchard, K. I., Austin, P. C., & Paszat, L. F. (2010). Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: A population based cohort study. *British Medical Journal, 340,* c693.

This study does not present statistics summarizing the effects of antidepressant use on all-cause mortality, as compared with a control group not using antidepressants. This study examines changes in the risk of death as a function of an increasing overlap in using antidepressants and the drug, tamoxifen.

Carter, G., Reith, D. M., Whyte, I. M., & McPherson, M. (2005). Non-suicidal deaths following hospital-treated self-poisoning. *Australian and New Zealand journal of psychiatry, 39,* 101–107.

The all-cause mortality statistic presented in this study excluded deaths from suicide, and we disagreed on whether this statistic truly reflected death from all causes. Nevertheless, the study was not eligible because it did not adjust the statistic for potential confounding variables.

Chandra, R., Selim, A., Singh, B., & Zolty, R. (2010). Selective serotonin reuptake inhibitor use may reduce mortality in systolic heart failure patients. *Journal of Cardiac Failure, 16,* S99–S100.

This abstract does not present adjusted mortality statistics summarizing the effects of antidepressant use on all-cause mortality; it reports crude rates and p-values only, and it is unclear whether the analysis was adjusted for confounding variables.

Davidson, K. W., & Burg, M. M. (2013). Implementing an antidepressant treatment strategy for post-MI depression does not reduce risk of further cardiovascular events or mortality. *Evidence Based Mental Health*, *16*, 72.

This study does not isolate the effects of antidepressant use on all-cause mortality. The control group was free to seek treatment for depression, which may have included antidepressants.

Gallo, J. J., Bogner, H. R., Morales, K. H., Post, E. P., Lin, J. Y., & Bruce, M. L. (2007). The effect of a primary care practice–based depression intervention on mortality in older adults: A randomized trial. *Annals of Internal Medicine, 146,* 689–698.

In this study, the intervention tested was the assignment of a care manager, and not treatment with antidepressants. Antidepressant treatment was available to all participants in the study, even those in the control group, but care managers were only available in the treatment groups; as such, this study did not isolate the effects of antidepressants on all-cause mortality.

Leonard, C. E., Freeman, C. P., Newcomb, C. W., Bilker, W. B., Kimmel, S. E., Strom, B. L., & Hennessy, S. (2013). Antipsychotics and the risks of sudden cardiac death and all-cause death: Cohort studies in Medicaid and dually-eligible Medicaid-Medicare beneficiaries of five states. *Journal of Clinical & Experimental Cardiology, Supplementary 10, 1–9.*

The authors compare all-cause mortality in users of antidepressants as compared with users of an antipsychotic, and therefore do not isolate the effects of antidepressant use alone on mortality.

Stenman, M., Holzmann, M. J., & Sartipy, U. (2013). Antidepressant use before coronary artery bypass surgery is associated with long-term mortality. *International Journal of Cardiology*, *167*, 2958–2962.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Nielsen, T. J., Vestergaard, M., Christensen, B., Christensen, K. S., & Larsen, K. K. (2013). Mental health status and risk of new cardiovascular events or death in patients with myocardial infarction: a population-based cohort study. *British Medical Journal Open*, *3*, e003045.

In this study, the researchers considered the use of antidepressants as a marker for the presence of a depression diagnosis, and therefore did not isolate the effects of using antidepressants on

mortality separate from depression.

Tenback, D., Pijl, B., Smeets, H., van Os, J., & van Harten, P. (2012). All-cause mortality and medication risk factors in schizophrenia: a prospective cohort study. *Journal of Clinical Psychopharmacology*, *32*(1), 31–35.

This study does not isolate the effects of antidepressant use on all-cause mortality, because the researchers did not control for potential co-morbid depression in the treatment and control groups. Based on our research into another study (Tiihonen et al., 2012), we decided that in order to truly isolate the effects of using antidepressants in this sample, the researchers should have controlled their analysis for depression.

Huang, T. J., Wei, Y., Moyo, P., Zuckerman, I. H., Lucas, J., & Simoni-Wastila, L. (2013). Antipsychotic and antidepressant use and mortality among nursing home residents with Alzheimer's disease and related dementias. *Pharmacoepidemiology and Drug Safety, 22 (Supplementary 1),* 471.

We decided that the study (from the information reported in the abstract) does not sufficiently isolate the effects of antidepressant use on all-cause mortality in this particular sample. The authors did not adjust the statistics for demographic variables and medical co-morbidities. Additionally, there was an issue with selection bias. The authors used an arbitrary survival criteria, such that only participants who survived 100 days after being brought into the nursing home were allowed to enter the study. For these reasons, we did not include this abstract in our analysis.

Dias, A. M., Franco, E., Hebert, K., Mercedes, A., Gogichaishvili, I., Messina, D., & Quevedo, H. (2013). Impact of SSRIs as a treating for depression and anxiety in the survival of patients who suffered takotsubo cardiomyopathy. *Cardiology, 126,* 475.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Zimmermann-Viehoff, F., Kuehl, L. K., Danker-Hopfe, H., Whooley, M. A., & Otte, C. (2014). Antidepressants, autonomic function and mortality in patients with coronary heart disease: Data from the Heart and Soul Study. *Psychological medicine*, *44*, 2975–2984.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Wium-Andersen, M. K., Ørsted, D. D., & Nordestgaard, B. G. (2014). Elevated C-reactive protein, depression, somatic diseases, and all-cause mortality: A mendelian randomization study. *Biological psychiatry*, *76*, 249–257.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Tiihonen, J., Suokas, J. T., Suvisaari, J. M., Haukka, J., & Korhonen, P. (2012). Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Archives of General Psychiatry, 69*, 476–483.

This study does not isolate the effects of antidepressant use on all-cause mortality, because the researchers do not adjust the statistics for depression. Since the statistics were adjusted for schizophrenia, we considered that antidepressants may have been used in the treatment of schizophrenia. We reviewed the research on this topic, and found that when patients with schizophrenia display more negative symptoms, they are often more depressed (Jockets et al., 2005; Buckley et al., 2007). These negative symptoms seem to respond to antidepressant medication, but not antipsychotic medication (Jockets et al., 2005; Singh et al., 2010). The prescription of antipsychotics is therefore often accompanied with antidepressants, but antidepressants alone do not seem to be used to treat schizophrenia (Rothbard et al., 2003). We concluded that patients in this study were therefore likely using antidepressants to treat depression.

Abraham, N. S., Castillo, D. L., & Hartman, C. (2008). National mortality following upper gastrointestinal or cardiovascular events in older veterans with recent nonsteroidal anti-inflammatory drug use. *Alimentary Pharmacology & Therapeutics, 28*, 97–106.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Kuehl, L. K., Zimmermann-Viehoff, F., Danker-Hopfe, H., Whooley, M. A., & Otte, C. (2012). Tricyclic antidepressants, autonomic function and mortality in patients with coronary heart disease: Data from the heart and soul study. *European Journal of Psychotraumatology, 3*, SE-175 64.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Kivimaki, M., Gunnell, D., Lawlor, D. A., Davey Smith, G., Pentti, J., Virtanen, M., ... & Vahtera, J. (2007). Social inequalities in antidepressant treatment and mortality: A longitudinal register study. *Psychological Medicine, 37*, 373–382.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Cohen, H. W., Gibson, G., & Alderman, M. H. (2000). Excess risk of myocardial infarction in patients treated with antidepressant medications: Association with use of tricyclic agents. *The American Journal of Medicine, 108,* 2–8.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Gunnell, D., Irvine, D., Wise, L., Davies, C., & Martin, R. M. (2009). Varenicline and suicidal

behaviour: A cohort study based on data from the General Practice Research Database. *British Medical Journal, 339*, b3805.

Although the researchers report the mortality rates of individuals taking bupropion, they compare these rates to individuals taking nicotine replacement therapy, but they do not control for potential changes in smoking status or depression.

Haukka, J., Tiihonen, J., Härkänen, T., & Lönnqvist, J. (2008). Association between medication and risk of suicide, attempted suicide and death in nationwide cohort of suicidal patients with schizophrenia. *Pharmacoepidemiology and Drug Safety*, *17*, 686–696.

The researchers did not isolate the effects of antidepressant use on all-cause mortality, because they did not adjust the statistics for depression.

Zivin, K., Pfeiffer, P. N., Bohnert, A. S. B., Ganoczy, D., Blow, F. C., Nallamothu, B. K., Kales, H. C. (2013). Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *American Journal of Psychiatry, 170*, 642–650.

The authors did not include a control group with no ADM use.

Rigotti, N. A., Thorndike, A. N., Regan, S., McKool, K., Pasternak, R. C., Chang, Y., ... & Singer, D. E. (2006). Bupropion for smokers hospitalized with acute cardiovascular disease. *The American Journal of Medicine, 119*, 1080–1087.

We decided that this study isolates the effects of antidepressant use on all-cause mortality. Participants in the smoking cessation treatment group taking an antidepressant initially did not differ in smoking status from the control group (Table 1; Rigotti, 2006); however, after treatment, smoking cessation rates were significantly higher in the treatment group, which could have affected mortality rates at one year. The researchers also did not monitor antidepressant use in the two groups for the entire follow up period.

3.5. FINAL ASSESSMENT: INELIGIBLE BECAUSE OF HOW ADM USE WAS DEFINED

Cully, J. A., Zimmer, M., Khan, M. M., & Petersen, L. A. (2008). Quality of depression care and its impact on health service use and mortality among veterans. *Psychiatric Services, 59,* 1399–1405.

The mortality statistic the authors report compares patients with an 'adequate' and 'inadequate' treatment of ADM defined by Cully (2008), as well as a mortality statistic associated with 'adequate' ADM usage, rather than the effect of ADM use in general on mortality.

Jordan, N., Lee, T. A., Valenstein, M., Pirraglia, P. A., & Weiss, K. B. (2009). Effect of depression care on outcomes in COPD patients with depression. *CHEST, 135,* 626–632.

The authors arbitrarily defined ADM use as: "…an adequate supply of antidepressants to cover at least 84 days of the 114 days following the day of the first antidepressant prescription

associated with the qualifying depression event", rather than simply ADM use.

Walker, A. J., Grainge, M., Bates, T. E., & Card, T. R. (2012). Survival of glioma and colorectal cancer patients using tricyclic antidepressants post-diagnosis. *Cancer Causes Control, 23*, 1959–1964.

The authors arbitrarily defined ADM use as: "…a patient must have had a repeat prescription [of 2 or more] within the period being examined for exposure", rather than simply ADM use.

Fosbøl, E. L., Gislason, G. H., Poulsen, H. E., Hansen, M. L., Folke, F., Schramm, T. K., ... & Torp-Pedersen, C. (2009). Prognosis in heart failure and the value of beta-blockers are altered by the use of antidepressants and depend on the type of antidepressants used. *Circulation: Heart Failure*, *2,* 582–590.

This study qualified antidepressant use based on an arbitrary criteria (within 90 days of discharge from the hospital), and therefore did not meet our eligibility criteria.

Grunau, G. L., Ratner, P. A., Goldner, E. M., & Sheps, S. (2006). Is early- and late-onset depression after acute myocardial infarction associated with long-term survival in older adults? A population-based study. *Canadian Journal of Cardiology, 22*, 473–478.

The ADM-user cohort used by the authors includes individuals that may not currently use ADMs, such as those who had previously, but no longer use ADM.

3.6. FINAL ASSESSMENT: INELIGIBLE BECAUSE ADM USE WAS NOT FULLY MONITORED DURING THE FOLLOW-UP PERIOD

Jorge, R. E., Robinson, R. G., Arndt, S., & Starkstein, S. (2003). Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *American Journal of Psychiatry*, *160*, 1823-1829.

This was a study that we were aware of prior to conducting the meta-analysis. After reviewing it, however, we noted that the goal of the study is to assess the effect of taking antidepressants after a stroke and the authors only monitor antidepressant treatment in the first two years; however, they assess all-cause mortality associated with using antidepressants after 9 years.

Suominen, K., Haukka, J., Valtonen, H. M., & Lonnqvist, J. (2009). Outcome of patients with major depressive disorder after serious suicide attempt. *Journal of Clinical Psychiatry, 70*, 1372–1380.

In this study, the authors do not monitor antidepressant use during the follow up period.

3.7. FINAL ASSESSMENT: INELIGIBLE BECAUSE IT WAS NOT AN EMPIRICAL STUDY

Scheen, A. J. (2010). Cardiovascular risk-benefit profile of sibutramine. *American Journal of Cardiovascular Drugs, 10*, 321–334.

This is not an empirical study, and was missed during the initial sorting process.

Howard, M. P., Knight, C., Boler, A., & Baker, C. (2008). Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO simulation model. *Pharmacoeconomics, 26*, 497–511.

This is not an empirical study; rather, the researchers make predictions based on data collected in other studies according to a theoretical model.

3.8. FINAL ASSESSMENT: INELIGIBLE BECAUSE IT WAS A RE-ANALYSIS OF A STUDY THAT WAS ALREADY INCLUDED

Hamer, M., Batty, G. D., Seldenrijk, A., & Kivimaki, M. (2011). Antidepressant medication use and future risk of cardiovascular disease: the Scottish Health Survey. *European Heart Journal, 32*, 437–442.

This article is a copy of a study already included in our analysis (Hamer, 2011).

Writing Committee for the ENRICHD Investigators. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction. *ACC Current Journal Review*, *12*(5), 22–23.

This paper reports on the data used in the Taylor et al., 2005 study which we have already included in our analysis.

4. OBTAINING HAZARD RATIOS AND CONFIDENCE INTERVALS

4.1 STUDIES NOT REPORTING HAZARD RATIOS

Most studies reported their summary measures in the form of hazard ratios; however, researchers sometimes reported odds ratios (Acharya et al., 2013; Khan et al., 2013) or crude death rates (Hanash et al., 2012) instead. We contacted two researchers who reported odds ratios in order to obtain baseline odds, which were necessary to convert odds ratios into hazard ratios (Acharya et al., 2013; Khan et al., 2013). In both cases, the researchers provided us with crude rates. One of the studies for which we were unable to obtain baseline odds was a cohort study that adjusted its odds ratios for relevant covariates (Acharya et al., 2013). Because we were unable to adjust for these covariates when using the crude death rates provided by the authors, we computed odds ratios from the crude rates and compared them to the adjusted odds ratios reported in the study. We found the unadjusted and adjusted odds ratios to be qualitatively similar (see **Section 4.2** below), so we included the unadjusted odds ratios in our meta-analysis.

We also extracted confidence intervals associated with the mortality statistics, unless only crude rates were provided. We obtained hazard ratios and confidence intervals from a figure in one study (Almeida et al., 2010) using Data Thief, a data extraction software (Tummers et al., 2006). Two studies reported hazard ratios for different types of ADMs without presenting a combined

hazard ratio for ADM use in general (Coupland et al., 2011; Khan et al., 2013). Two studies also separated their sample by the presence of depression or its severity (Smoller et al., 2009; Ryan et al., 2008). We therefore extracted multiple summary measures from each of these studies to use in our meta-analysis.

4.2 CRUDE RATES FROM ACHARYA ET AL. (2012)

We were unable to obtain the baseline odds necessary to transform odds ratios into hazard ratios for one study included in our meta-analysis (Acharya et al., 2012). Instead, we received the following crude death rates directly from an email correspondence with the study's authors:

Drug	**Crude rate**
No ADM	44/472
SSRI	16/416
NASSA (Mirtazapine)	4/41
NDRI (Bupropion)	3/67
SNRI	2/35
SRA	6/54
TCA	3/51

The odds ratios reported in the study were adjusted for relevant covariates, and the hazard ratios we would calculate based on these death rates would be unadjusted. Therefore, we examined the degree to which adjusting for covariates affected the odds ratios. We computed unadjusted odds ratios, confidence intervals, and p-values, using the "oddsratio" function in the `epitools` package in R.

First, we created numeric vectors for each drug:

```
SSRI <- c(428, 44, 400, 16)
NASSA <- c(428, 44, 37, 4)
NDRI <- c(428, 44, 64, 3)
SNRI <- c(428, 44, 33, 2)
SRA <- c(428, 44, 48, 6)
TCA <- c(428, 44, 48, 3)
```

Next, we use the "oddsratio" function to generate the unadjusted odds ratios, confidence intervals, and p-values:

```
oddsratio(x=SSRI, y=NULL, conf.level=0.95, rev="neither", correction=FALSE, v
erbose=FALSE)
```

```
$data
          Outcome
Predictor  Disease1 Disease2 Total
  Exposed1      428       44   472
  Exposed2      400       16   416
  Total         828       60   888

$measure
          odds ratio with 95% C.I.
Predictor   estimate     lower     upper
```

```
  Exposed1 1.0000000        NA        NA
  Exposed2 0.3918827 0.2108449 0.6930534

$p.value
          two-sided
Predictor   midp.exact fisher.exact  chi.square
  Exposed1          NA           NA          NA
  Exposed2 0.001044842  0.001190937 0.001178439

$correction
[1] FALSE

attr(,"method")
[1] "median-unbiased estimate & mid-p exact CI"
```

```
oddsratio(x=NASSA, y=NULL, conf.level=0.95, rev="neither", correction=FALSE,
verbose=FALSE)
```

```
$data
          Outcome
Predictor  Disease1 Disease2 Total
  Exposed1      428       44   472
  Exposed2       37        4    41
  Total         465       48   513

$measure
          odds ratio with 95% C.I.
Predictor  estimate     lower    upper
  Exposed1 1.000000        NA       NA
  Exposed2 1.085387 0.3065927 2.886304

$p.value
          two-sided
Predictor  midp.exact fisher.exact chi.square
  Exposed1         NA           NA         NA
  Exposed2   0.884013    0.7859589  0.9270607

$correction
[1] FALSE

attr(,"method")
[1] "median-unbiased estimate & mid-p exact CI"
```

```
oddsratio(x=NDRI, y=NULL, conf.level=0.95, rev="neither", correction=FALSE, v
erbose=FALSE)
```

```
$data
          Outcome
Predictor  Disease1 Disease2 Total
  Exposed1      428       44   472
  Exposed2       64        3    67
  Total         492       47   539

$measure
          odds ratio with 95% C.I.
Predictor   estimate     lower    upper
  Exposed1 1.0000000        NA       NA
  Exposed2 0.4777096 0.1094002 1.365388

$p.value
          two-sided
Predictor  midp.exact fisher.exact chi.square
```

```
  Exposed1          NA           NA          NA
  Exposed2   0.1862344    0.2487991   0.1884209

$correction
[1] FALSE

attr(,"method")
[1] "median-unbiased estimate & mid-p exact CI"
```

```
oddsratio(x=SNRI, y=NULL, conf.level=0.95, rev="neither", correction=FALSE, v
erbose=FALSE)
```

```
$data
          Outcome
Predictor  Disease1 Disease2 Total
  Exposed1      428       44   472
  Exposed2       33        2    35
  Total         461       46   507

$measure
          odds ratio with 95% C.I.
Predictor   estimate      lower    upper
  Exposed1 1.0000000         NA       NA
  Exposed2 0.6306142 0.09252714 2.186142

$p.value
          two-sided
Predictor  midp.exact fisher.exact chi.square
  Exposed1          NA           NA          NA
  Exposed2   0.5158212    0.7590979   0.4733775

$correction
[1] FALSE

attr(,"method")
[1] "median-unbiased estimate & mid-p exact CI"
```

```
oddsratio(x=SRA, y=NULL, conf.level=0.95, rev="neither", correction=FALSE, ve
rbose=FALSE)
```

```
$data
          Outcome
Predictor  Disease1 Disease2 Total
  Exposed1      428       44   472
  Exposed2       48        6    54
  Total         476       50   526

$measure
          odds ratio with 95% C.I.
Predictor  estimate     lower    upper
  Exposed1 1.000000        NA       NA
  Exposed2 1.240135 0.4493711 2.876915

$p.value
          two-sided
Predictor  midp.exact fisher.exact chi.square
  Exposed1          NA           NA          NA
  Exposed2   0.6510206    0.6264672   0.6711131

$correction
[1] FALSE
```

```
attr(,"method")
[1] "median-unbiased estimate & mid-p exact CI"
```

```
oddsratio(x=TCA, y=NULL, conf.level=0.95, rev="neither", correction=FALSE, ve
rbose=FALSE)
```

```
$data
          Outcome
Predictor  Disease1 Disease2 Total
  Exposed1      428       44   472
  Exposed2       48        3    51
  Total         476       47   523

$measure
          odds ratio with 95% C.I.
Predictor   estimate     lower   upper
  Exposed1 1.0000000        NA      NA
  Exposed2 0.6362708 0.1447532 1.84095

$p.value
          two-sided
Predictor  midp.exact fisher.exact chi.square
  Exposed1         NA           NA         NA
  Exposed2  0.4412659    0.6059674  0.4145189

$correction
[1] FALSE

attr(,"method")
[1] "median-unbiased estimate & mid-p exact CI"
```

Next, we compared these unadjusted statistics to the adjusted statistics presented in Acharya et al., 2012, Figure 2:

	All Deaths		
Drug	Odds Ratio	95% CI	P value
SSRI	0.3735	0.1959 to 0.7123	0.0028
NASSA	1.7898	0.6434 to 4.9787	0.2647
NDRI	0.2456	0.0323 to 1.8681	0.175
SNRI	0	0.0000 to 0.0000	0.994
SRA	0.6924	0.2157 to 2.2226	0.5367
TCA	1.5912	0.5751 to 4.4021	0.371

In general, we found the unadjusted odds ratios to be qualitatively similar to the adjusted odds ratios, and decided that using unadjusted death rates was reasonable.

5. BIAS ASSESSMENT INFORMATION

5.1 'RISK OF BIAS' TABLES FOR EACH INCLUDED STUDY

Acharya 2013

Entry	Judgement	Support for judgement
Selection bias	High risk.	Estimates were adjusted for age, gender, depression, cardiovascular conditions. Depression was assessed while some participants may have been taking ADMs.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into account.
Detection bias	Low risk.	Information about mortality was likely taken from VA medical records.
Attrition bias	Unclear risk.	Information about attrition is not reported.
Reporting bias	Low risk.	All planned outcomes are reported.

Almeida 2010

Entry	Judgement	Support for judgement
Selection bias	High risk.	Estimates were adjusted for age, gender, depression, cardiovascular conditions. Depression was assessed while some participants may have been taking ADMs.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into account.
Detection bias	Low risk.	Information about mortality was taken from the Australian Bureau of Statistics.
Attrition bias	Low risk.	A small proportion of the sample (136/5276) had missing depression scores.
Reporting bias	Low risk.	All planned outcomes are reported.

Balogun 2012

Entry	Judgement	Support for judgement
Selection bias	Low risk.	Estimates were adjusted for age, gender, depression, cardiovascular conditions. Depression was likely diagnosed before ADM exposure.
Performance bias	Unclear risk.	ADM use was assessed using VA pharmacy dispensation records, but it is unclear whether fluctuations in ADM use were taken into account.
Detection bias	Low risk.	Information about mortality was taken from the VA registry.
Attrition bias	Low risk.	A small proportion of the sample (8%) had missing co-variate information.
Reporting bias	Low risk.	All planned outcomes are reported.

Coupland 2011

Entry	Judgement	Support for judgement
Selection bias	Low risk.	Estimates were adjusted for age, gender, depression, cardiovascular conditions. Depression was diagnosed before ADM use was initiated.
Performance bias	Low risk.	Fluctuations in ADM use were taken into account in the analyses.
Detection bias	Low risk.	Information about mortality was taken from primary care computer records.
Attrition bias	Unclear risk.	Attrition information was not reported.
Reporting bias	Low risk.	All planned outcomes are reported.

Diez-Quevedo 2013

Entry	Judgement	Support for judgement
Selection bias	High risk.	Estimates were adjusted for age, gender, depression, cardiovascular conditions. Depression was assessed while some participants may have been taking ADMs.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into

		account.
Detection bias	Low risk.	Information about mortality was taken from the database of the Spanish National System.
Attrition bias	Low risk.	A small number of participants (n=21) were excluded.
Reporting bias	Low risk.	All planned outcomes are reported.

Hamer 2011

Entry	**Judgement**	**Support for judgement**
Selection bias	High risk.	Estimates were adjusted for age, gender, cardiovascular conditions, and psychological distress (which includes depression) Depression was assessed while some participants may have been taking ADMs.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into account.
Detection bias	Low risk.	Information about mortality was taken from the Scottish National Database.
Attrition bias	High risk.	Study had a low response rate (60-76%), and non-responders were more likely to be using ADMs.
Reporting bias	High risk.	All-cause mortality was not a planned outcome (not referred to until the 'Results' section)

Hanash 2012

Entry	**Judgement**	**Support for judgement**
Selection bias	Low risk.	Double-blind, randomized, placebo controlled trial.
Allocation concealment	Low risk.	Allocation sequence was implemented using the consecutive number of the study medication.
Performance bias	Low risk.	Participants were masked.
Detection bias	Low risk.	Assessors were masked.
Attrition bias	Low risk.	Study had a high drop-out rate (27.2%), but drop-out rates did not differ in the two groups, and all participants were included in the analysis (intention-to-treat).

Reporting bias	Low risk.	All planned outcomes are reported.

Khan 2013

Entry	Judgement	Support for judgement
Selection bias	High risk.	Most studies included in the synthesis were not double-blind, and some were not placebo-controlled.
Allocation concealment	Unclear risk.	Strategies for allocation concealment were not reported.
Performance bias	High risk.	Most studies included were not double-blind, and the strategy for including studies in the synthesis is unclear.
Detection bias	Low risk.	It is unlikely that an assessment of mortality would be biased.
Attrition bias	Unclear risk.	Attrition information is not reported.
Reporting bias	Low risk.	All planned outcomes are reported.

Krantz 2009

Entry	Judgement	Support for judgement
Selection bias	High risk.	Estimates were adjusted for age, gender, cardiovascular conditions, depression. Depression was assessed while some participants may have been taking ADMs.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into account.
Detection bias	Low risk.	Assessors were masked and deaths were confirmed by death certificate.
Attrition bias	Low risk.	Study only included participants without missing data.
Reporting bias	Low risk.	All planned outcomes are reported.

O'Connor 2010

Entry	Judgement	Support for judgement
Selection bias	Low risk.	Double-blind, randomized, placebo controlled trial.

Allocation concealment	Low risk.	Allocation sequence was implemented using a centralized computerized interactive voice system (IVRS).
Performance bias	Low risk.	Participants were masked.
Detection bias	Low risk.	Information about mortality was obtained by telephone, mail, and the National Death Index.
Attrition bias	Low risk.	Drop-out rates did not differ in the two groups, and all participants were included in the analysis (intention-to-treat).
Reporting bias	Low risk.	All planned outcomes are reported.

O'Connor 2008

Entry	**Judgement**	**Support for judgement**
Selection bias	High risk.	Estimates were adjusted for age, gender, cardiovascular conditions, depression. Depression was assessed while some participants may have been taking ADMs.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into account.
Detection bias	Low risk.	Information about mortality was obtained by telephone, mail, and the National Death Index.
Attrition bias	Low risk.	Only 1 participant was excluded for having missing data and all participants were available for follow-up.
Reporting bias	Low risk.	All planned outcomes are reported.

Qian 2013

Entry	**Judgement**	**Support for judgement**
Selection bias	High risk.	Estimates were adjusted for age, gender, cardiovascular conditions, depression. Depression was assessed while some participants may have been taking ADMs.
Performance bias	Low risk.	Fluctuations in ADM use were taken into account in the analyses.
Detection bias	Low risk.	Information about mortality was obtained via Medicare claims.
Attrition bias	Unclear risk.	The researchers sampled 5% of the data, but it

		is unclear if all participants had complete information or whether there was missing data but this information was not reported.
Reporting bias	Low risk.	All planned outcomes are reported.

Ryan 2008

Entry	Judgement	Support for judgement
Selection bias	High risk.	Estimates were adjusted for age, gender, cardiovascular conditions, depression. Depression was assessed while some participants may have been taking ADMs.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into account.
Detection bias	Low risk.	Information about mortality was obtained from death registries and medical records (ICD-10).
Attrition bias	High risk.	1922/9294 participants were excluded due to missing data, and excluded participants were more likely to have been depressed and using ADMs.
Reporting bias	Low risk.	All planned outcomes are reported.

Sherwood 2007

Entry	Judgement	Support for judgement
Selection bias	High risk.	Estimates were adjusted for age, cardiovascular conditions, depression, but not gender. Depression was assessed while some participants may have been taking ADMs.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into account.
Detection bias	Low risk.	Information about mortality was obtained from hospital and emergency medical services records.
Attrition bias	Low risk.	No participants were lost to follow-up.
Reporting bias	Low risk.	All planned outcomes are reported.

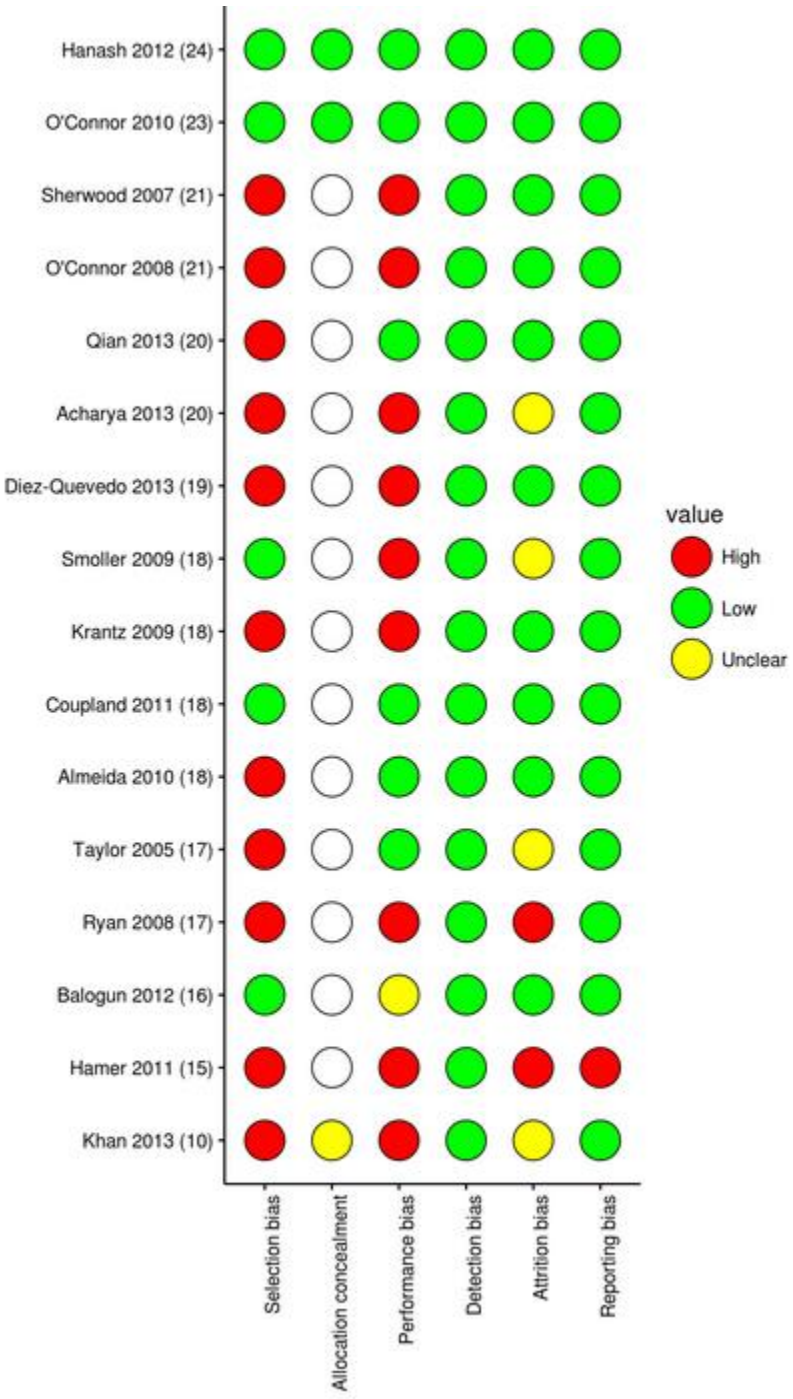
Smoller 2009

Entry	Judgement	Support for judgement
Selection bias	Low risk.	Estimates were adjusted for age, gender, cardiovascular conditions, depression. Depression was diagnosed before ADM use was initiated.
Performance bias	High risk.	ADM use was assessed at baseline and fluctuations in ADM use were not taken into account.
Detection bias	Low risk.	Information about mortality was obtained via telephone follow-up with proxy respondents and the National Death Index.
Attrition bias	Unclear risk.	Many participants were lost to follow-up, with no data comparing those lost to follow-up to participants who remained in the study.
Reporting bias	Low risk.	All planned outcomes are reported.

Taylor 2005

Entry	Judgement	Support for judgement
Selection bias	High risk.	Estimates were adjusted for age, cardiovascular conditions, depression, but not gender, which differed between the two groups (p=.02). Depression was assessed while some participants may have been taking ADMs.
Performance bias	Low risk.	Fluctuations in ADM use were taken into account in the analyses.
Detection bias	Low risk.	Assessors were masked.
Attrition bias	Unclear risk.	173 participants had missing information, but it is unclear what proportion of these participants used ADMs.
Reporting bias	Low risk.	All planned outcomes are reported.

5.2 ‘RISK OF BIAS’ SUMMARY



Note. Y-axis labels indicate the reference, with the corresponding ‘Checklist for assessing study quality’ (Downs & Black, 1998) score in parantheses.

6. ELIGIBLE STUDIES AND INFORMATION EXTRACTED

6.1 SAMPLE DESCRIPTION, SAMPLE CATEGORY, AND STUDY DESIGN

Reference	Sample description	Sample Category	Design
Acharya 2013	Veterans in Fresno at high risk of cardiovascular disease	Cardiovascular	Cohort
Almeida 2010	Community sample of older men living in Perth	General	Cohort
Balogun 2012	Chronic kidney disease	Cardiovascular	Cohort
Coupland 2011	60,746 depressed patients between ages 65 and 100	General	Cohort
Diez-Quevedo 2013	1017 patients with heart failure	Cardiovascular	Cohort
Hamer 2011	14, 784 community dwelling adults aged 35 or older	General	Cohort
Hanash 2012	Acute coronary syndrome	Cardiovascular	RCT
Khan 2013	Depressed patients	General	RCT
Krantz 2009	Coronary angiography	Cardiovascular	Cohort
O'Connor 2008	Heart failure	Cardiovascular	Cohort
O'Connor 2010	Heart failure	Cardiovascular	Cohort
Planer 2011**	Acute coronary syndrome	Cardiovascular	Cohort
Qian 2013	COPD	Cardiovascular	Cohort
Ryan 2008	Men without depression	General	Cohort
	Men without depression		
	Mildly depressed men		
	Mildly depressed men		
	Severely depressed men		
	Severely depressed men		
	Women without depression		
	Women without depression		
	Mildly depressed women		
	Mildly depressed women		
	Severely depressed women		
	Severely depressed women		
Sherwood 2007	Heart failure	Cardiovascular	Cohort
Smoller 2009	Not depressed	General	Cohort
	Depressed		
Taylor 2005	Coronary heart disease	Cardiovascular	Cohort

6.2 DRUG TYPE AND CLASSIFICATION INFORMATION

Study	SSRI/SNRI	TCA	Other ADMs	Undifferentiated
Acharya 2013	Sertraline Paroxetine Fluoxetine Citalopram Venlafaxine	Not specified	Trazodone Mirtazapine Bupropion	NA
Almeida 2010	Not specified	Not specified	Not specified	NA
Balogun 2012	Any ADMs (Not specified)			
Coupland 2011	Citalopram Escitalopram Fluoxetine Paroxetine Sertraline Venlafaxine	Amitriptyline Dosulepin Lofepramine	Mirtazapine Trazodone	NA
Diez-Quevedo 2013	Fluoxetine Paroxetine Sertraline Citalopram Escitalopram Venlafaxine Duloxetine	Not specified	Mirtazapine	NA
Hamer 2011	Not specified	Not specified	MAO inhibitors and other drugs	NA
Hanash 2012	Escitalopram	NA	NA	NA
Khan 2013	Sertraline Paroxetine Paroxetine CR Citalopram Escitalopram Venlafaxine Venlafaxine XR Duloxetine Desvenlafaxine in combination with Nefazodone /Trazodone /Vilazodone	NA	NA	Imipramine Amitryptiline Maprotiline Mirtazapine
Krantz 2009	Any ADMs (Not specified)			
O'Connor 2008	Citalopram Fluoxetine Paroxetine Sertraline	Any ADMs (Amitriptyline, Bupropion, Citalopram, Desipramine, Doxepine, Fluoxetine, Mirtazapine, Nefazodone, Nortriptyline, Paroxetine, Sertraline, Trazodone, Triavil, Venlafaxine)		

Qian 2013	Any ADMs (Unspecified SSRIs, Unspecified SNRIs, Bupropion, Unspecified TCAs, MAO Inhibitors, Trazodone, Maprotiline hydrochloride, Mirtazapine)			
Ryan 2008	Any ADMs (Unspecified SSRIs and TCAs)			
Sherwood 2007	Any ADMs (Unspecified SSRIs, TCAs, TeCAs, MAO Inhibitors)			
Smoller 2009	Not specified (in combination with Trazodone)	Not specified (in combination with Trazodone)	NA	Other or multiple
Taylor 2008	Sertraline	NA	NA	Not specified
O'Connor 2010	Sertraline	NA	NA	NA

6.3 COMPARISONS AND ALL-CAUSE MORTALITY SUMMARY MEASURES

Reference	Comparison	Exposure variable	Estimate*	95% CI
Acharya 2013	No ADM	1	CR=44/472	NA
	SSRI	1	CR=16/416	NA
	Venlafaxine	1	CR=2/35	NA
	Trazadone	1	CR=6/54	NA
	Mirtazapine	1	CR=4/41	NA
	Bupropion	1	CR=3/67	NA
	TCA	1	CR=3/51	NA
Almeida 2010	SSRI/SNRI	1	HR=1.14	0.73-1.78
	TCA	1	HR=1.26	0.83-1.91
	Other ADM	1	HR=0.86	0.36-2.18
	SSRI/SNRI	1	HR=3.59	1.96-6.59
	TCA	1	HR=1.95	0.88-4.18
	Other ADM	1	HR=3.21	1.48-6.86
Balogun 2012	No ADM	1	HR=1.07	1.01-1.13
	ADM	1	HR=1.12	1.09-1.15
Coupland 2011	Amitriptyline	1	HR=1.09	1.02-1.18
	Dosulepin	1	HR=1.02	0.95-1.14
	Lofemaprime	1	HR=1.5	1.34-1.69
	Citalopram	1	HR=1.54	1.46-1.63
	Escitalopram	1	HR=1.44	1.26-1.66
	Fluoxetine	1	HR=1.65	1.56-1.77
	Paroxetine	1	HR=1.24	1.14-1.36
	Sertraline	1	HR=1.47	1.35-1.61
	Mirtazapine	1	HR=1.75	1.61-1.9
	Venlafaxine	1	HR=1.65	1.5-1.82
	Trazodone	1	HR=1.81	1.59-2.07
Diez-Quevedo 2013	Fluoxetine	1	HR=1.66	1.13-2.44
	Paroxetine	1	HR=0.85	0.56-1.28
	Sertraline	1	HR=1.02	0.71-1.47

	Citalopram	1	HR=0.75	0.54-1.04
	Escitalopram	1	HR=0.7	0.42-1.16
	Venlafaxine	1	HR=1.02	0.46-2.25
	Duloxetine	1	HR=1.22	0.53-2.81
	Mirtazapine	1	HR=1.47	0.6-3.62
	TCA	1	HR=1.03	0.42-2.54
Hamer 2011	TCA	1	HR=1.09	0.8-1.49
	SSRI	1	HR=0.82	0.55-1.26
	Other AM	1	HR=1.4	0.85-2.31
Hanash 2012	No ADM	1	CR=4/119	NA
	Escitalopram	1	CR=6/120	NA
Khan 2013	No ADM	1	CR=11/6529	NA
	SSRI	1.55	CR=65/26000	NA
	HCA/Other ADMs	1.26	CR=29/6954	NA
Krantz 2009	ADM	1	HR=1.21	0.42-3.48
O'Connor 2008	ADM	1	HR=1.24	0.94-1.64
	SSRI	1	HR=1.1	0.81-1.5
O'Connor 2010	Sertraline	1	HR=1.3	0.66-2.58
Planer 2011**	No ADM	1	CR=0/76	NA
	ADM	1	CR=0/75	NA
Qian 2013	ADM	1	HR=0.59	0.55-0.63
Ryan 2008	No ADM	1	HR=1	NA
	ADM	1	HR=1.3	0.6-2.7
	No ADM	1	HR=1.3	0.9-2.1
	ADM	1	HR=2.8	1-7.7
	No ADM	1	HR=1.8	1-3.3
	ADM	1	HR=5.3	2.7-10.5
	No ADM	1	HR=1	NA
	ADM	1	HR=1.5	0.8-2.9
	No ADM	1	HR=1.4	0.9-2.2
	ADM	1	HR=2	0.7-5.4
	No ADM	1	HR=1.8	1.1-2.8
	ADM	1	HR=0.8	0.8-2.1
Sherwood 2007	ADM	1	HR=1.79	0.96-3.34
Smoller 2009	SSRI	1	HR=1.32	1.1-1.59
	TCA	1	HR=1.67	1.33-2.09
	Multiple/Other	1	HR=1.36	0.99-1.86
Taylor 2005	Sertraline	1	HR=0.59	0.37-0.96
	Other ADM	1	HR=0.64	0.34-1.22

6.4 COMPARISONS AND CARDIOVASCULAR EVENT SUMMARY MEASURES

Reference	Comparison	Event	Estimate*	95% CI
Acharya 2013	No ADM	CHF	CR=44/472	NA
	SSRI	CHF	CR=16/416	NA
	Venlafaxine	CHF	CR=2/35	NA
	Trazadone	CHF	CR=6/54	NA
	Mirtazapine	CHF	CR=4/41	NA
	Bupropion	CHF	CR=3/67	NA
	TCA	CHF	CR=3/51	NA
	No ADM	CVA or TIA	CR=44/472	NA
	SSRI	CVA or TIA	CR=16/416	NA
	Venlafaxine	CVA or TIA	CR=2/35	NA
	Trazadone	CVA or TIA	CR=6/54	NA
	Mirtazapine	CVA or TIA	CR=4/41	NA
	Bupropion	CVA or TIA	CR=3/67	NA
	TCA	CVA or TIA	CR=3/51	NA
	No ADM	CAD	CR=44/472	NA
	SSRI	CAD	CR=16/416	NA
	Venlafaxine	CAD	CR=2/35	NA
	Trazadone	CAD	CR=6/54	NA
	Mirtazapine	CAD	CR=4/41	NA
	Bupropion	CAD	CR=3/67	NA
	TCA	CAD	CR=3/51	NA
Almeida 2010	No ADM	CVE	CR=10.1/1000	1.02-1.68
	TCA	CVE	CR=15.4/1000	
	SSRI	CVE	CR=17.1/1000	
	Other	CVE	CR=19.3/1000	
Coupland 2011	Amitriptyline	MI	HR=1.1	0.92-1.39
	Dosulepin	MI	HR=1.05	1.3-0.86
	Lofemaprime	MI	HR=1.17	0.86-1.62
	Citalopram	MI	HR=1.1	0.94-1.29
	Escitalopram	MI	HR=1.31	0.88-1.93
	Fluoxetine	MI	HR=1.3	1.12-1.53
	Paroxetine	MI	HR=1.1	0.9-1.37
	Sertraline	MI	HR=0.88	0.67-1.2
	Mirtazapine	MI	HR=1.1	0.82-1.5
	Venlafaxine	MI	HR=1.03	0.78-1.4
	Trazodone	MI	HR=1.03	0.66-1.65
	Amitriptyline	CVA/TIA	HR=1	0.89-1.14
	Dosulepin	CVA/TIA	HR=0.95	0.83-1.1
	Lofemaprime	CVA/TIA	HR=1.25	1.02-1.54
	Citalopram	CVA/TIA	HR=1.21	1.11-1.35
	Escitalopram	CVA/TIA	HR=1.21	0.92-1.6
	Fluoxetine	CVA/TIA	HR=1.15	1.03-1.3

	Paroxetine	CVA/TIA	HR=1.07	0.93-1.25
	Sertraline	CVA/TIA	HR=1.21	1.03-1.44
	Mirtazapine	CVA/TIA	HR=1.37	1.15-1.66
	Venlafaxine	CVA/TIA	HR=1.5	1.23-1.79
	Trazodone	CVA/TIA	HR=1.09	0.82-1.49
Diez-Quevedo 2013	Fluoxetine	CVE	HR=1.9	1.19-3.05
	Paroxetine	CVE	HR=0.99	0.6-1.64
	Sertraline	CVE	HR=1.02	0.64-1.64
	Citalopram	CVE	HR=0.66	0.43-1.02
	Escitalopram	CVE	HR=0.6	0.3-1.21
	Venlafaxine	CVE	HR=0.55	0.13-2.3
	Duloxetine	CVE	HR=0.74	0.18-3.04
	Mirtazapine	CVE	HR=0.55	0.08-4.01
	TCA	CVE	HR=1.65	0.06-4.57
Hamer 2011	TCA	CVE	HR=1.39	0.85-2.28
	SSRI	CVE	HR=0.74	0.33-1.7
	Other ADM	CVE	HR=0.83	0.26-2.5
Hanash 2012	No ADM	ACS	CR=5/119	NA
	Escitalopram	ACS	CR=9/120	NA
Krantz 2009	ADM	CVE	HR=1.48	0.67-3.26
O'Connor 2010	No ADM	CVE	CR=65/235	NA
	Sertraline	CVE	CR=63/234	NA
Smoller 2009	SSRI	MI/CHD	HR=0.74	0.49-1.11
	TCA	MI/CHD	HR=1.02	0.59-1.77
	Multiple/Other	MI/CHD	HR=1.30	0.57-2.94
	SSRI	CVA	HR=1.36	0.88-2.1
	TCA	CVA	HR=1.35	0.71-2.59
	Multiple/Other	CVA	HR=1.32	0.66-2.6
Taylor 2005	Sertraline	MI	HR=0.53	0.32-0.9
	Other ADM	MI	HR=0.73	0.38-1.38

Note: COPD= Chronic obstructive pulmonary disease, ADM= antidepressant, CVE=cardiovascular event, CHF=congestive heart failure, CVA=cerebrovascular accident, TIA=transient ischemic attack, CHD=congenital heart defect.

* CR=crude rate, H=hazard, HR=hazard ratio

7. DIAGNOSTIC INFORMATION SUMMARIES

Effects of sample type and ADM class on all-cause mortality: Our diagnostic analysis revealed one influential data point showing a protective effect of SSRI use (Acharya et al., 2013).
Effect of sample type and ADM class on cardiovascular events: In this analysis, there were four influential data points, one showed a protective effect (Taylor et al., 2005) and three showed an increased risk of cardiovascular events (Diez-Quevedo et al., 2013; Coupland et al., 2011; Smoller et al., 2009; Taylor et al., 2005).

Sample type and all-cause mortality: There were six influential data points in this analysis (D_i>1). In cardiovascular patients, two showed protective effects (Acharya et al., 2013; Qian et al., 2013), and two showed an increased mortality risk (Diez-Quevedo et al., 2013; Sherwood et al., 2007); in the general population sample, one showed a protective effect (Ryan et al., 2008 [women with severe depression]), and one showed an increased mortality risk (Ryan et al., 2008 [men with severe depression]).
Sample type and cardiovascular events*:* Our diagnostic analysis revealed eleven influential data points (D_i>1). Six were in cardiovascular samples for the use of bupropion, mirtazapine, citalopram, fluoxetine, and sertraline (Acharya et al., 2013; Diez-Quevedo et al., 2013; Taylor et al., 2005). Five were in general population sample, related to the use of sertraline, dusolepin, mirtazapine, venlafaxine, and SSRIs (Coupland et al., 2011; Smoller et al., 2009).

Drug class and all-cause mortality:
There were five influential data points (D_i>1). One showed a protective effect of using SSRI/SNRIs (Acharya et al., 2013), and four showed increases in mortality related to the use of TCAs (Coupland et al., 2011; Smoller et al., 2009) and Other ADMs (Coupland et al., 2011).
Drug class and cardiovascular events:
There were two influential data points (D_i>1). One showed an increase in CVA/TIA associated with the use of other ADMs (Coupland et al., 2011), and one showed a protective effect of using an SSRI/SNRI (Taylor et al., 2005).

8. META-ANALYSIS OF OBSERVATIONAL STUDIES IN EPIDEMIOLOGY (MOOSE) GUIDELINES CHECKLIST

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5
2	Hypothesis statement	6
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6
5	Type of study designs used	5-6
6	Study population	5-6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	8, A2
9	Effort to include all available studies, including contact with authors	8, A4
10	Databases and registries searched	8
11	Search software used, name and version, including special features used (eg, explosion)	8, A4
12	Use of hand searching (eg, reference lists of obtained articles)	8
13	List of citations located and those excluded, including justification	Figure 1, A3
14	Method of addressing articles published in languages other than English	NA
15	Method of handling abstracts and unpublished studies	8
16	Description of any contact with authors	A4
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8, A3
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	10-11, A4
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	10-11, A4
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7-8, A3, A5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	9-10, A5
22	Assessment of heterogeneity	15, 16, 17, A7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	11-13

24	Provision of appropriate tables and graphics	Figures 1-2, Table 1, B
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2, B
26	Table giving descriptive information for each study included	A6
27	Results of sensitivity testing (eg, subgroup analysis)	17-19
28	Indication of statistical uncertainty of findings	13-19, B

Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	22-23, A5, B
30	Justification for exclusion (eg, exclusion of non-English language citations)	NA
31	Assessment of quality of included studies	22, 23
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	23
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	23
34	Guidelines for future research	23, 25
35	Disclosure of funding source	26

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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SUPPLEMENT B: R code and supplementary output

Ben Bolker, Marta Maslej, Paul Andrews

17:46 27 May 2017

- Bias scoring
- Effects plot (Table 1)
- References

(create HTML output via `render("maslej_MA.rmd")`, using the `rmarkdown` package, or by clicking the "Knit" button in RStudio)

All analyses done with the `metafor` package (Viechtbauer 2010); we have extended the output function to include the I^2 statistic ($I^2 = \max(0, 100 \times (1 - \mathrm{df}/Q))$) from Higgins et al. (2003).

Packages

```
library(metafor)
library(methods)
library(plyr)       ## arrange(), ...
library(reshape2)   ## melt()
library(lattice)    ## qqmath() etc.
library(ggplot2); theme_set(theme_classic())
library(ggstance)   ## pointrangeh, position_dodgev
library(gridExtra)  ## grid.arrange
library(RColorBrewer)
source("MA_funs.R")
sessionInfo()
```

```
## R version 3.3.3 (2017-03-06)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 14393)
##
## locale:
## [1] LC_COLLATE=English_Canada.1252  LC_CTYPE=English_Canada.1252
## [3] LC_MONETARY=English_Canada.1252 LC_NUMERIC=C
## [5] LC_TIME=English_Canada.1252
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
##  [1] RColorBrewer_1.1-2 gridExtra_2.2.1    ggstance_0.3
##  [4] ggplot2_2.2.1      lattice_0.20-34    reshape2_1.4.2
##  [7] plyr_1.8.4         metafor_1.9-9      Matrix_1.2-8
## [10] knitr_1.15.1
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_0.12.10     magrittr_1.5     munsell_0.4.3    colorspace_1.3-2
##  [5] stringr_1.2.0    tools_3.3.3      grid_3.3.3       gtable_0.2.0
##  [9] htmltools_0.3.5  yaml_2.1.14      lazyeval_0.2.0   rprojroot_1.2
## [13] digest_0.6.12    assertthat_0.1   tibble_1.2       purrr_0.2.2
## [17] evaluate_0.10    rmarkdown_1.3    stringi_1.1.2    scales_0.4.1
## [21] backports_1.0.5
```

```
debug <- FALSE
```

Read and process data

```
dd <- read.csv("Maslej_et_al_MA.csv")
dd <- dd[,!grepl("^X",names(dd))]  ## drop bogus columns
## this ref. does not control for depression ...
dd <- droplevels(subset(dd,REFERENCE!="Douglas 2012"))
```

- **Study**: Study number used to specify higher level random effect
- **Reference**: First author and date of study
- **Reference label**: Label used to specify drug type in forest plots
- **Study type**: identifies study as a cohort study or a randomized controlled trial
- **Sample**: identifies sample as cardiovascular (i.e, at high risk of cardiovascular illness) or general
- **Drug type**: Baseline (i.e., no drug), ADM (i.e., Unspecified antidepressant), Serotonergic agent (e.g., SSRI, SNRI), Heterocyclic (e.g., TCA), Other
- **Note**: more information on sample and control
- **DOW_BLA**: study quality score based on the Downs & Black tool

Non-standard baseline conversion example

Pull out just the first all-cause mortality non-standard baseline example and go step by step so we can see what's happening:

(R trick: putting parentheses around an assignment statement, as in `(dtmp <- stuff)`, prints the result in the output.)

```
## identify non-standard baseline examples; we will assume
## that each baseline value is followed by its corresponding
## non-baseline comparison
br_vals <- with(dd,which(DRUG.TYPE=="Baseline" & ACM_HR!=1.0))
(dtmp <- subset(dd[br_vals[1]+(0:1),],
                select=c(REFERENCE,ACM_HR,ACM_L_95CI,ACM_U_95CI)))
```

```
##      REFERENCE ACM_HR ACM_L_95CI ACM_U_95CI
## 7 Almeida 2010   1.85       1.47       2.32
## 8 Almeida 2010   3.59       1.96       6.59
```

```
## HR->logHR, CI -> logHR.se transformation
(dtmp <- transform(dtmp,
                logACMHR=log(ACM_HR),
                logACMHR.se = (log(ACM_U_95CI)-log(ACM_L_95CI))/(2*1.96)))
```

```
##      REFERENCE ACM_HR ACM_L_95CI ACM_U_95CI  logACMHR logACMHR.se
## 7 Almeida 2010   1.85       1.47       2.32 0.6151856   0.1164043
## 8 Almeida 2010   3.59       1.96       6.59 1.2781522   0.3093390
```

```
## baseline change
i <- 1
dtmp[i+1,"logACMHR"] <- dtmp[i+1,"logACMHR"]-dtmp[i,"logACMHR"]
dtmp[i+1,"logACMHR.se"] <- sqrt(sum(dtmp[i:(i+1),"logACMHR.se"]^2))
dtmp[i,"logACMHR"] <- 0
dtmp[i,"logACMHR.se"] <- NA
dtmp
```

```
##      REFERENCE ACM_HR ACM_L_95CI ACM_U_95CI  logACMHR logACMHR.se
## 7 Almeida 2010   1.85       1.47       2.32 0.0000000          NA
## 8 Almeida 2010   3.59       1.96       6.59 0.6629666   0.3305156
```

The lower and upper confidence interval columns are no longer meaningful, but we're not going to use them for anything else …

Data processing

Now back to our regular sequence.

Standardizing HR's and SE's

- take the natural log of each hazard rate (`logHR`)
- generate a standard error using each CI: (`log(upper CI) â log (lower CI)) / (2*1.96)`) (SE)

```
dd <- transform(dd,
                logACMHR=log(ACM_HR),
                logACMHR.se = (log(ACM_U_95CI)-log(ACM_L_95CI))/(2*1.96),
                logCVEHR=log(CVE_HR),
                logCVEHR.se = (log(CVE_U_95CI)-log(CVE_L_95CI))/(2*1.96))
```

Comparing HR's with baseline rates that do not equal 1

- take the ratio of the two HR's of interest (e.g., Mild depression, no ADM use vs. Mild depression, ADM use) and take the natural log of this ratio (`logHR`).
- take the square root of the sum of squares of the SE's: `sqrt( SE1^2 + SE2^2 )`

```
for (i in br_vals) {
    ## ASSUME consecutive data
    ## take difference of logHRs
    dd[i+1,"logACMHR"] <- dd[i+1,"logACMHR"]-dd[i,"logACMHR"]
    ## compute sqrt(sum_sq(SE)) to get (approx) SE of difference
    dd[i+1,"logACMHR.se"] <- sqrt(sum(dd[i:(i+1),"logACMHR.se"]^2))
    ## set baseline to rescaled values
    dd[i,"logACMHR"] <- 0
    dd[i,"logACMHR.se"] <- NA
}
```

Converting crude death rates into log hazards and SE's

- create a table with the crude death rates for each group in R:
- Run a generalized linear model with `link ="cloglog"` and obtain estimate and standard error for the treated group

```
crude_vals <- which(!is.na(dd$NUM_DEAD))
## iterate over *odd* elements of crude_vals
## (again assume that values are consecutive)
for (i in crude_vals[seq(1,length(crude_vals),by=2)]) {
    ## assume consecutive data
    nums <- t(sapply(strsplit(as.character(dd[i:(i+1),"NUM_DEAD"]),"/"),
                     as.numeric))
    if (debug) print(nums)
    hdata <- data.frame(dead=nums[,1],
                        alive=nums[,2]-nums[,1],
                        ttt=c("control","treat"),
                        EXPOSURE_TIME=dd[i:(i+1),"EXPOSURE_TIME"])
    g0 <- glm(cbind(dead,alive)~ttt,
              data=hdata,family=binomial(link="cloglog"),
              offset=log(EXPOSURE_TIME))
    vals <- coef(summary(g0))["ttttreat",c("Estimate","Std. Error")]
    dd[i+1,"logACMHR"] <- vals[1]
    dd[i+1,"logACMHR.se"] <- vals[2]
    dd[i,"logACMHR"] <- 1
    dd[i,"logACMHR.se"] <- NA
}
```

For the crude rates from Khan 2013, where exposure time differs by treatment, we have added an “exposure time” column to the data frame (which is 1 for all other studies) and used it to adjust the hazards. We add `log(exposure time)` as an offset in the model above (see e.g. this document (https://rpubs.com/bbolker/logregexp), or Harney et al. (2013) or Baetschmann and Winkelmann (2013)). Equivalently, we could the subtract the log of exposure time from the log hazard (*or* equivalently divide the hazards by exposure time before logging).

Converting cardiovascular event rates into log hazards and SE’s

- Repeat the same process to convert cardiovascular event rates (create a table for each group in R, run a generalized linear model, and obtain estimate and standard error for the treated group)

```
CVE_vals <- which(!is.na(dd$NUM_CVE))
for (i in CVE_vals[seq(1,length(CVE_vals),by=2)]) {
    nums2 <- t(sapply(strsplit(as.character(dd[i:(i+1),"NUM_CVE"]),"/"),
                      as.numeric))
    if (debug) print(nums2)
    hdata2 <- data.frame(HadCVE=nums2[,1],
                         NoCVE=nums2[,2]-nums2[,1],
                         ttt=c("control","treat"),
                         CVE_EXPOSURE=dd[i:(i+1),"CVE_EXPOSURE"])
    g1 <- suppressWarnings(glm(cbind(HadCVE,NoCVE)~ttt,
              data=hdata2,family=binomial(link="cloglog"),
              offset=log(CVE_EXPOSURE)))
    ## we know we will have non-integer event rates, so suppressWarnings()
    CVE_vals <- coef(summary(g1))["ttttreat",c("Estimate","Std. Error")]
    dd[i+1,"logCVEHR"] <- CVE_vals[1]
    dd[i+1,"logCVEHR.se"] <- CVE_vals[2]
    dd[i,"logCVEHR"] <- 1
    dd[i,"logCVEHR.se"] <- NA
}
```

Modifying labels

Unicode symbol information (http://xahlee.info/comp/unicode_sex_symbols.html)

```
## the symbol encoding we use here may be fragile;
## will depend on correct encoding, need to
## double-check that it comes out OK in final PDF ...
## msymb <- "M"; fsymb <- "F"
msymb <- "M"; fsymb <- "F"

rep_list <- cbind(
    ## target strings
    c("Citalopram","Fluoxetine","Paroxetine",
                    "Sample without","Sample with",
                    "Women","Men",
                    "With DEP",
                    "without", "with"),
    ## result strings
    c("CTP","FLX","PRX","No","With",
      fsymb,
      msymb,
      "DEP",
      ", no",
      ","))
dd$REFERENCE.LABEL <- as.character(dd$REFERENCE.LABEL)
for (i in 1:nrow(rep_list)) {
    dd <- transform(dd,
                    REFERENCE.LABEL=gsub(rep_list[i,1],
                    rep_list[i,2],
                    REFERENCE.LABEL))
}
```

delete the baseline rates and unnecessary columns

```
dd2 <- subset(dd,DRUG.TYPE!="Baseline",
              select=c(REFERENCE,REFERENCE.LABEL,SAMPLE,DRUG.TYPE,NOTE,
              STUDY.TYPE,DOW_BLA,logACMHR, logACMHR.se, logCVEHR, logCVEHR.se))
dd2 <- transform(dd2,id=factor(seq(nrow(dd2))))
levels(dd2$SAMPLE) <- c("Cardiovascular patients",
                        "General population")
```

Doing the meta-analysis

Utility functions:

```
## ASSUMES that studies come in blocks
## assign unique labels by study
unique_lab <- function(ref) {
    ref <- as.character(ref)
    unlist(lapply(split(ref,ref),
                  function(z) {
                      n <- length(z)
                      if (n==1) z else paste0(z," (",seq(n),")")
                  }))
}

make_lab <- function(x) {
    return(transform(arrange(x,REFERENCE),
                     uref=unique_lab(REFERENCE)))
}

## these functions look hacky, but something like this
##  is necessary due to the way metafor::rma.mv evaluates
##  data arguments ...
CVErma.fun <- function(data,...) {
    dd <- data
    r <- rma.mv(data=data, ..., yi=logCVEHR, V= logCVEHR.se^2,
           random= list(~1|REFERENCE,~1|id), method="REML",
           slab=with(dd,paste(REFERENCE,REFERENCE.LABEL)))
    ## hack labels to remove unnecessary disambiguation tags
    r$slab <- gsub("\\.[1-9]$","",r$slab)
    return(r)
}

ACMrma.fun <- function(data,...) {
    dd <- data
    r <- rma.mv(data=dd, ..., yi=logACMHR, V= logACMHR.se^2,
           random= list(~1|REFERENCE,~1|id), method="REML",
           slab=with(dd,paste(REFERENCE,REFERENCE.LABEL)))
    ## hack labels to remove unnecessary disambiguation tags
    r$slab <- gsub("\\.[1-9]$","",r$slab)
    return(r)
}
```

B1: Meta-analysis using sample type as a moderator

All-cause mortality

Studies with statistics presented for use of any antidepressant with a Sample variable (Cardiovascular or general) (i.e., using only studies that have ADM in the NOTES, and studies that do not have the SSRI estimate from O'Connor 2008)

```
dd3A <- subset(dd2, grepl("ADM", NOTE) &
                   NOTE !="SSRI only" & logACMHR != "NA")
## order by REFERENCE: see note below with forest.addcat
dd3A <- arrange(dd3A,REFERENCE)
nrow(dd3A)
```

```
## [1] 55
```

```
(ADMresult_1A <- ACMrma.fun(mods = ~ SAMPLE-1, data=dd3A))
```

```
##
## Multivariate Meta-Analysis Model (k = 55; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0136  0.1166     16     no  REFERENCE
## sigma^2.2  0.0417  0.2043     55     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 53) = 416.7432, p-val < .0001
##
## I(df = 53) = 87.2823
##
## Test of Moderators (coefficient(s) 1,2):
## QM(df = 2) = 15.1684, p-val = 0.0005
##
## Model Results:
##
##                                estimate      se     zval    pval    ci.lb
## SAMPLECardiovascular patients   -0.1021  0.0863  -1.1824  0.2370  -0.2712
## SAMPLEGeneral population         0.2850  0.0768   3.7108  0.0002   0.1345
##                                 ci.ub
## SAMPLECardiovascular patients  0.0671
## SAMPLEGeneral population       0.4356  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

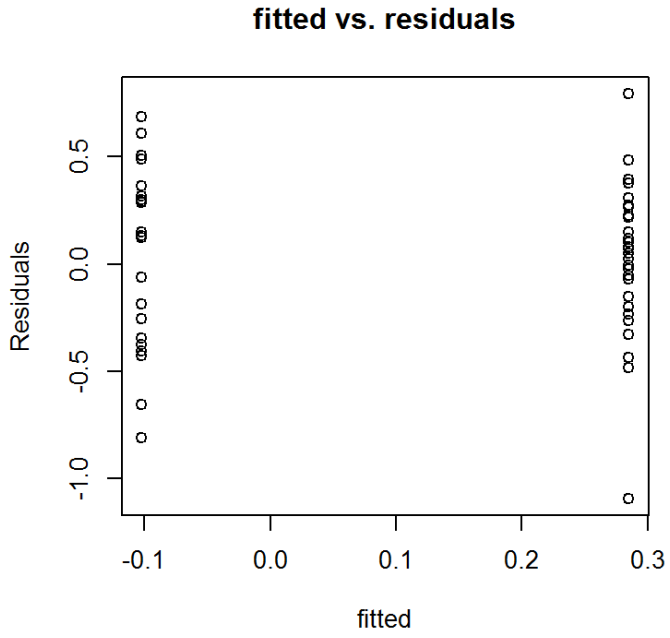
```
(ADMresult_1B <- ACMrma.fun(mods = ~ SAMPLE,   data=dd3A))
```

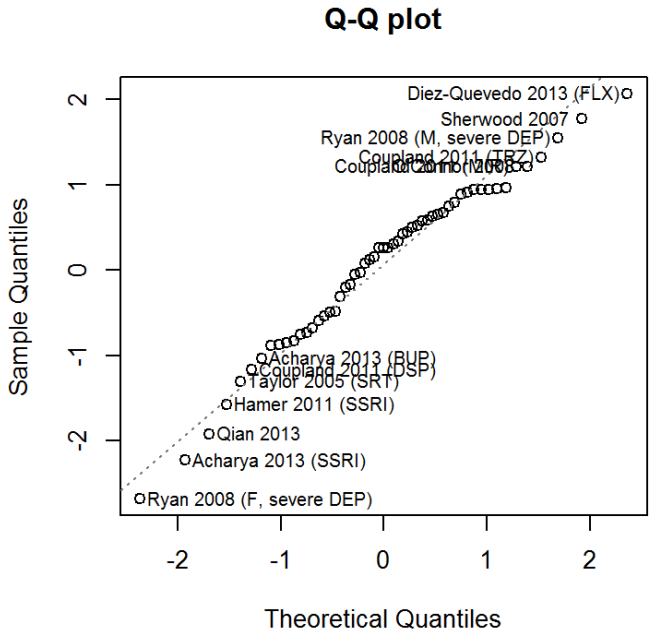
```
##
## Multivariate Meta-Analysis Model (k = 55; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0136  0.1166     16     no  REFERENCE
## sigma^2.2  0.0417  0.2043     55     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 53) = 416.7432, p-val < .0001
##
## I(df = 53) = 87.2823
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 11.2243, p-val = 0.0008
##
## Model Results:
##
##                           estimate      se     zval    pval    ci.lb
## intrcpt                    -0.1021  0.0863  -1.1824  0.2370  -0.2712
## SAMPLEGeneral population    0.3871  0.1155   3.3503  0.0008   0.1606
##                            ci.ub
## intrcpt                   0.0671
## SAMPLEGeneral population  0.6135  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

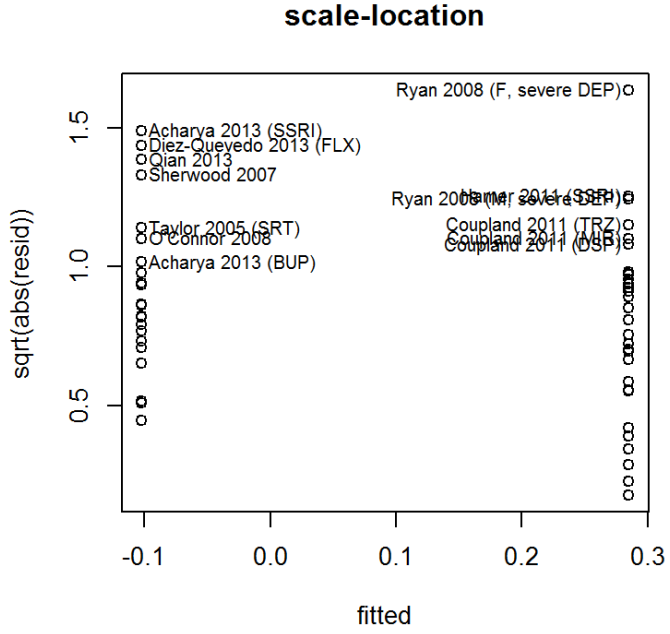
```
## remove drug labels?
## ADMresult_2B$slab <- gsub("\\((HCA|SRI|FLX/PRX|CIT|Other ADM)\\)","",
##                           ADMresult_2B$slab)
```

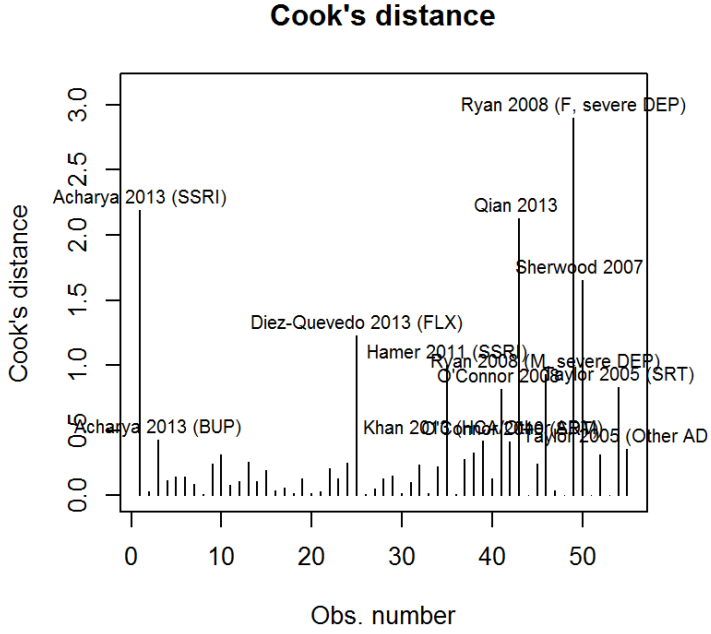
Diagnostics

```
plot(ADMresult_1B,id.n=13)
```



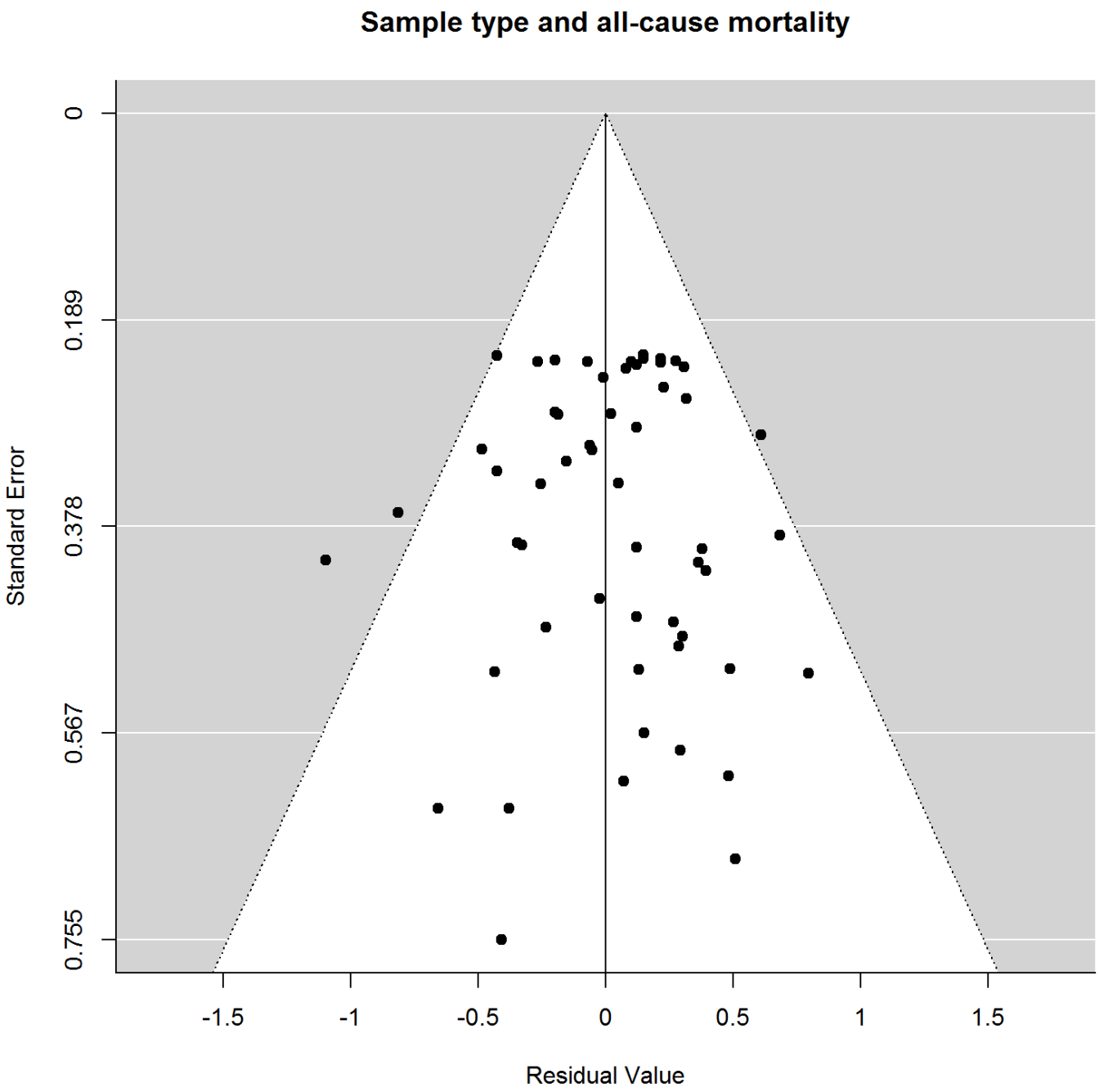






Funnel plot

```
funnel(ADMresult_1B, main= "Sample type and all-cause mortality")
```



Cardiovascular events

```
dd4A <- subset(dd2, grepl("ADM", NOTE) & logCVEHR != "NA")
## order by REFERENCE: see note below with forest.addcat
dd4A <- arrange(dd4A,REFERENCE)
nrow(dd4A)
```

```
## [1] 65
```

```
(ADMresult_9A <- CVErma.fun(mods = ~ SAMPLE-1, data=dd4A))
```

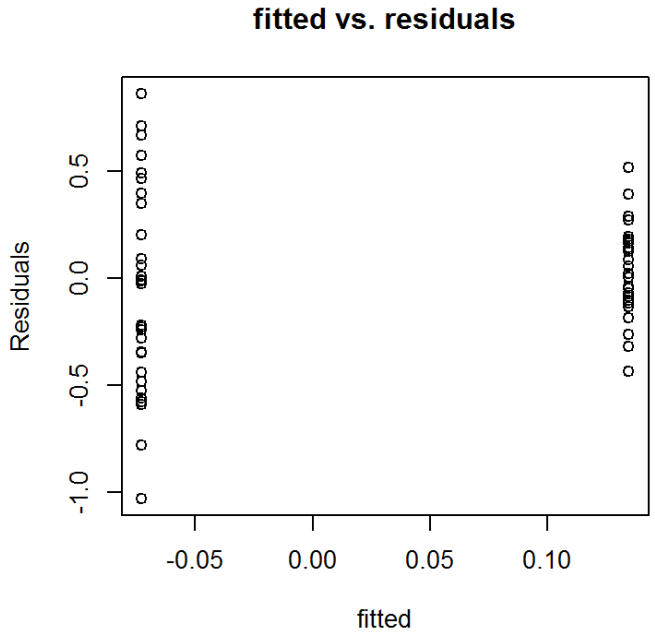
```
##
## Multivariate Meta-Analysis Model (k = 65; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      9     no  REFERENCE
## sigma^2.2  0.0082  0.0907     65     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 63) = 85.4317, p-val = 0.0315
##
## I(df = 63) = 26.2569
##
## Test of Moderators (coefficient(s) 1,2):
## QM(df = 2) = 24.3055, p-val < .0001
##
## Model Results:
##
##                               estimate      se     zval    pval    ci.lb
## SAMPLECardiovascular patients   -0.0728  0.0650  -1.1205  0.2625  -0.2002
## SAMPLEGeneral population         0.1347  0.0280   4.8010  <.0001   0.0797
##                                ci.ub
## SAMPLECardiovascular patients  0.0546
## SAMPLEGeneral population       0.1896  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

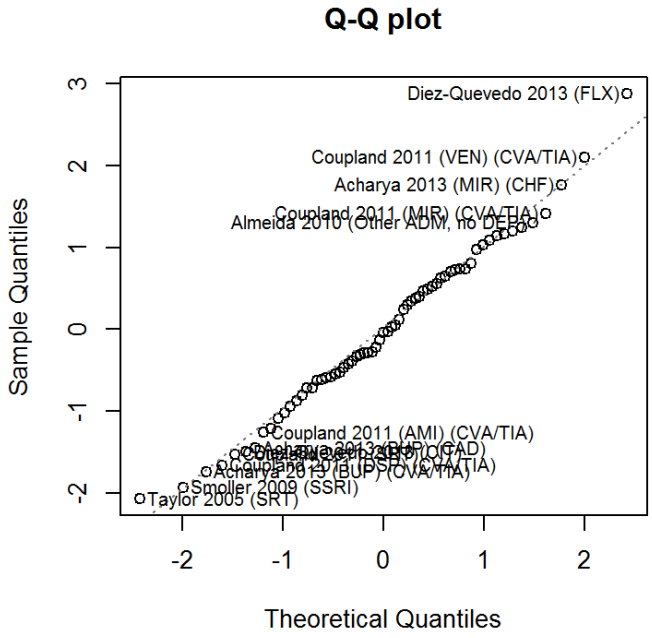
```
(ADMresult_9B <- CVErma.fun(mods = ~ SAMPLE,   data=dd4A))
```

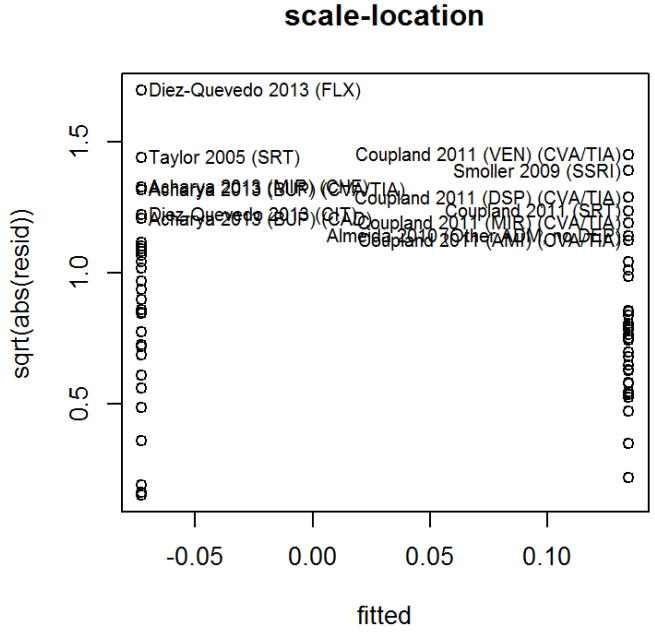
```
##
## Multivariate Meta-Analysis Model (k = 65; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      9     no  REFERENCE
## sigma^2.2  0.0082  0.0907     65     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 63) = 85.4317, p-val = 0.0315
##
## I(df = 63) = 26.2569
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 8.5916, p-val = 0.0034
##
## Model Results:
##
##                           estimate      se     zval    pval    ci.lb
## intrcpt                    -0.0728  0.0650  -1.1205  0.2625  -0.2002
## SAMPLEGeneral population    0.2075  0.0708   2.9311  0.0034   0.0687
##                            ci.ub
## intrcpt                   0.0546
## SAMPLEGeneral population  0.3462  **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

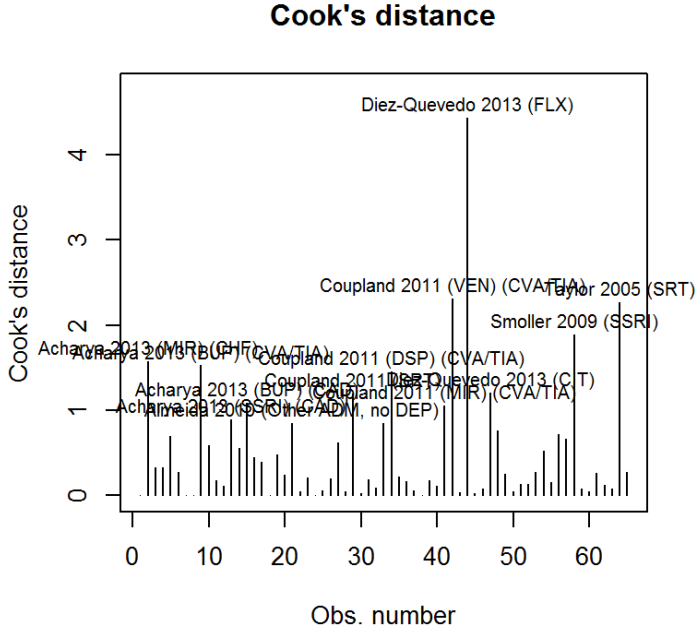
Diagnostics

```
plot(ADMresult_9B,id.n=13)
```



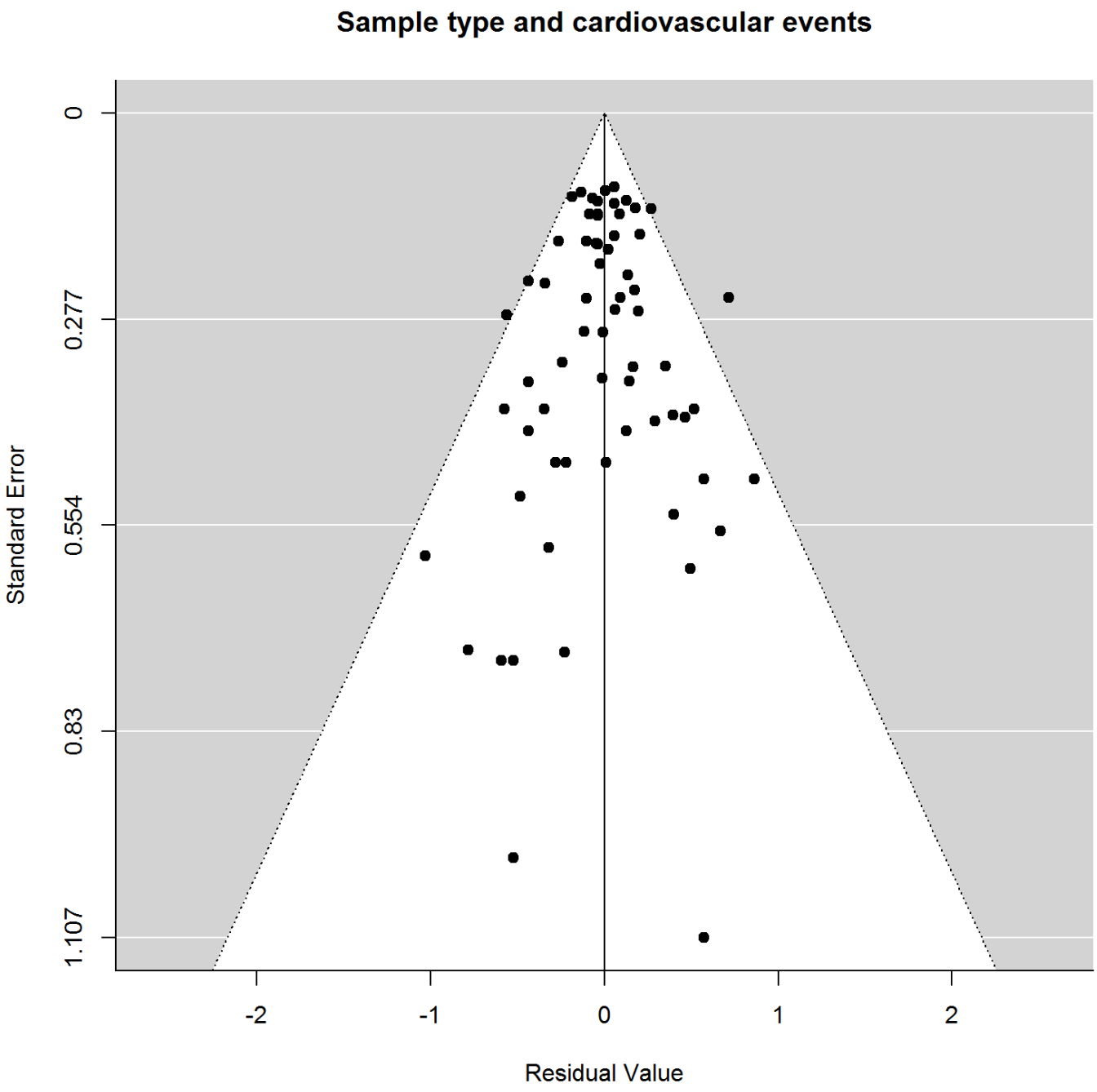






Funnel plot

```
funnel(ADMresult_9B, main= "Sample type and cardiovascular events")
```



B2: Meta-analysis using ADM class as a moderator

All-cause mortality

Studies with statistics presented for use of antidepressants, separated by drug class (SSRI/SNRI, TCA, Other) (Excluding studies that provided statistics for “Any ADM use” or the use of undifferentiated ADMs)

```
dd3B <- transform(subset(dd2,DRUG.TYPE != "ADM" & logACMHR != "NA" &
                           DRUG.TYPE != "Undifferentiated"),
                  DRUG.TYPE=factor(DRUG.TYPE,
                                   levels=c("TCA",
                                            "SSRI/SNRI",
                                            "Other")),
                  SAMPLE = factor (SAMPLE,
                                   levels=c("Cardiovascular patients",
                        "General population")))
dd3B <- arrange(dd3B,REFERENCE)
nrow(dd3B)
```

```
## [1] 43
```

```
(ADMresult_2A <- ACMrma.fun(mods = ~ DRUG.TYPE-1, data=dd3B))
```

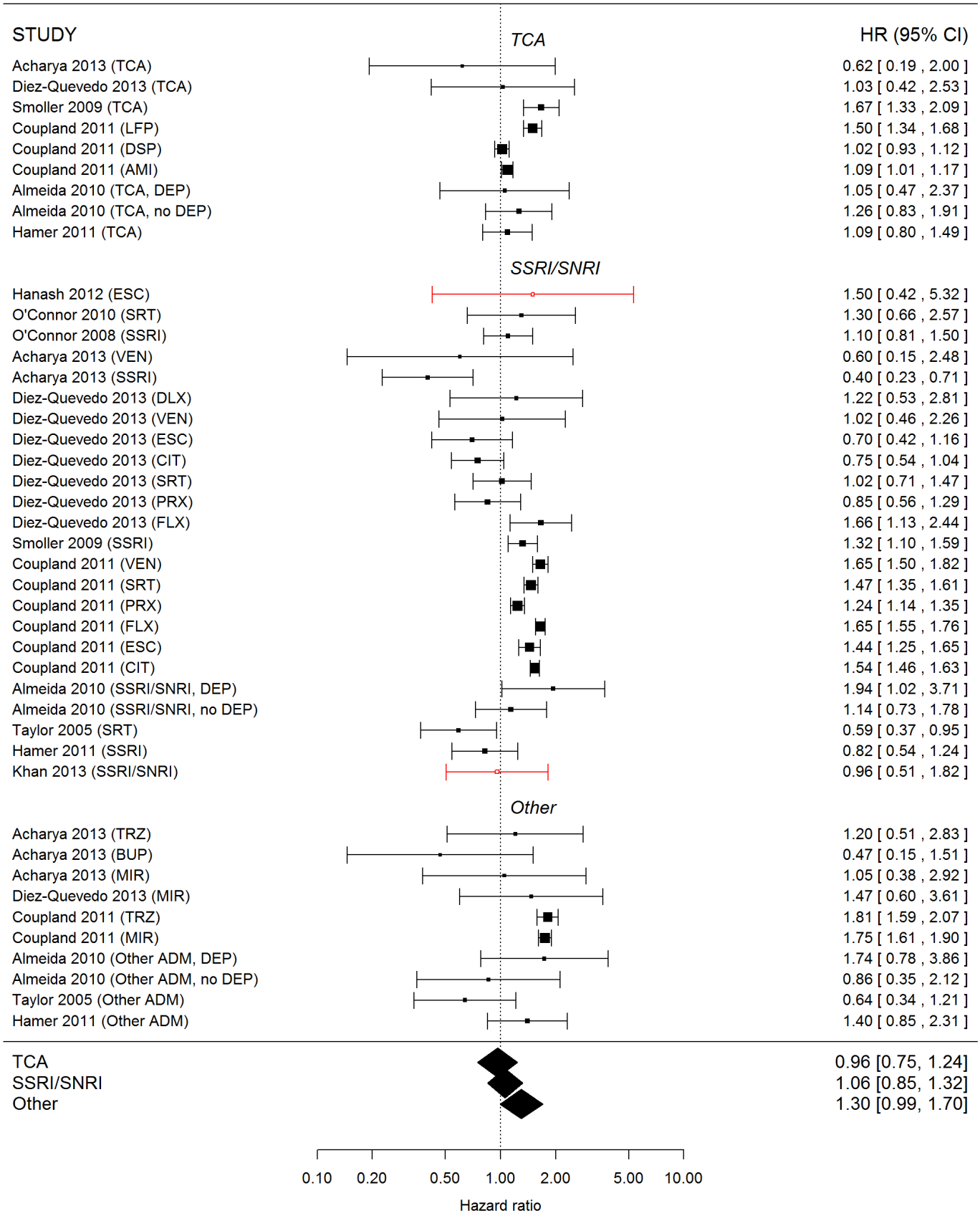
```
##
## Multivariate Meta-Analysis Model (k = 43; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0869  0.2948     11     no  REFERENCE
## sigma^2.2  0.0212  0.1455     43     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 40) = 183.5061, p-val < .0001
##
## I(df = 40) = 78.2024
##
## Test of Moderators (coefficient(s) 1,2,3):
## QM(df = 3) = 7.2177, p-val = 0.0653
##
## Model Results:
##
##                     estimate      se     zval    pval    ci.lb   ci.ub
## DRUG.TYPETCA         -0.0383  0.1284  -0.2987  0.7651  -0.2899  0.2132
## DRUG.TYPESSRI/SNRI    0.0570  0.1125   0.5070  0.6122  -0.1635  0.2776
## DRUG.TYPEOther        0.2617  0.1382   1.8938  0.0583  -0.0091  0.5325  .
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(ADMresult_2B <- ACMrma.fun(mods = ~ DRUG.TYPE,   data=dd3B))
```

```
##
## Multivariate Meta-Analysis Model (k = 43; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0869  0.2948     11     no  REFERENCE
## sigma^2.2  0.0212  0.1455     43     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 40) = 183.5061, p-val < .0001
##
## I(df = 40) = 78.2024
##
## Test of Moderators (coefficient(s) 2,3):
## QM(df = 2) = 6.8194, p-val = 0.0331
##
## Model Results:
##
##                     estimate      se     zval    pval    ci.lb   ci.ub
## intrcpt              -0.0383  0.1284  -0.2987  0.7651  -0.2899  0.2132
## DRUG.TYPESSRI/SNRI    0.0954  0.0872   1.0936  0.2741  -0.0756  0.2664
## DRUG.TYPEOther        0.3000  0.1155   2.5971  0.0094   0.0736  0.5264  **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

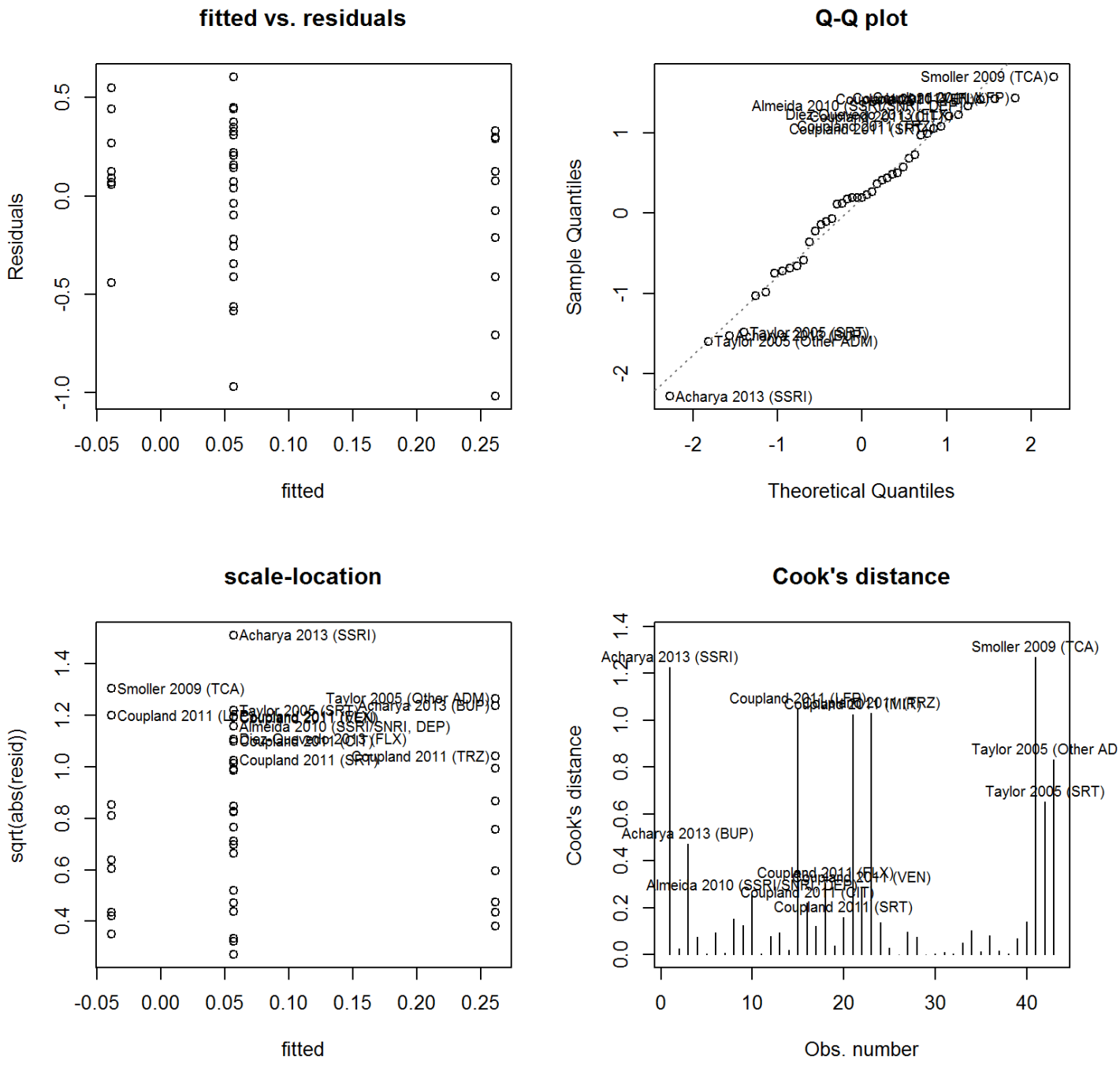
Forest plot

```
ffun(ADMresult_2B,dd3B,mod="DRUG.TYPE",add.fullpoly=FALSE,
          ss=as.numeric(dd3B$STUDY.TYPE))
```


STUDY
HR (95% CI)
TCA
Acharya 2013 (TCA) 0.62 [0.19 , 2.00]
Diez-Quevedo 2013 (TCA) 1.03 [0.42 , 2.53]
Smoller 2009 (TCA) 1.67 [1.33 , 2.09]
Coupland 2011 (LFP) 1.50 [1.34 , 1.68]
Coupland 2011 (DSP) 1.02 [0.93 , 1.12]
Coupland 2011 (AMI) 1.09 [1.01 , 1.17]
Almeida 2010 (TCA, DEP) 1.05 [0.47 , 2.37]
Almeida 2010 (TCA, no DEP) 1.26 [0.83 , 1.91]
Hamer 2011 (TCA) 1.09 [0.80 , 1.49]
SSRI/SNRI
Hanash 2012 (ESC) 1.50 [0.42 , 5.32]
O'Connor 2010 (SRT) 1.30 [0.66 , 2.57]
O'Connor 2008 (SSRI) 1.10 [0.81 , 1.50]
Acharya 2013 (VEN) 0.60 [0.15 , 2.48]
Acharya 2013 (SSRI) 0.40 [0.23 , 0.71]
Diez-Quevedo 2013 (DLX) 1.22 [0.53 , 2.81]
Diez-Quevedo 2013 (VEN) 1.02 [0.46 , 2.26]
Diez-Quevedo 2013 (ESC) 0.70 [0.42 , 1.16]
Diez-Quevedo 2013 (CIT) 0.75 [0.54 , 1.04]
Diez-Quevedo 2013 (SRT) 1.02 [0.71 , 1.47]
Diez-Quevedo 2013 (PRX) 0.85 [0.56 , 1.29]
Diez-Quevedo 2013 (FLX) 1.66 [1.13 , 2.44]
Smoller 2009 (SSRI) 1.32 [1.10 , 1.59]
Coupland 2011 (VEN) 1.65 [1.50 , 1.82]
Coupland 2011 (SRT) 1.47 [1.35 , 1.61]
Coupland 2011 (PRX) 1.24 [1.14 , 1.35]
Coupland 2011 (FLX) 1.65 [1.55 , 1.76]
Coupland 2011 (ESC) 1.44 [1.25 , 1.65]
Coupland 2011 (CIT) 1.54 [1.46 , 1.63]
Almeida 2010 (SSRI/SNRI, DEP) 1.94 [1.02 , 3.71]
Almeida 2010 (SSRI/SNRI, no DEP) 1.14 [0.73 , 1.78]
Taylor 2005 (SRT) 0.59 [0.37 , 0.95]
Hamer 2011 (SSRI) 0.82 [0.54 , 1.24]
Khan 2013 (SSRI/SNRI) 0.96 [0.51 , 1.82]
Other
Acharya 2013 (TRZ) 1.20 [0.51 , 2.83]
Acharya 2013 (BUP) 0.47 [0.15 , 1.51]
Acharya 2013 (MIR) 1.05 [0.38 , 2.92]
Diez-Quevedo 2013 (MIR) 1.47 [0.60 , 3.61]
Coupland 2011 (TRZ) 1.81 [1.59 , 2.07]
Coupland 2011 (MIR) 1.75 [1.61 , 1.90]
Almeida 2010 (Other ADM, DEP) 1.74 [0.78 , 3.86]
Almeida 2010 (Other ADM, no DEP) 0.86 [0.35 , 2.12]
Taylor 2005 (Other ADM) 0.64 [0.34 , 1.21]
Hamer 2011 (Other ADM) 1.40 [0.85 , 2.31]
TCA 0.96 [0.75, 1.24]
SSRI/SNRI 1.06 [0.85, 1.32]
Other 1.30 [0.99, 1.70]
0.10
0.20
0.50
1.00
2.00
5.00
10.00
Hazard ratio

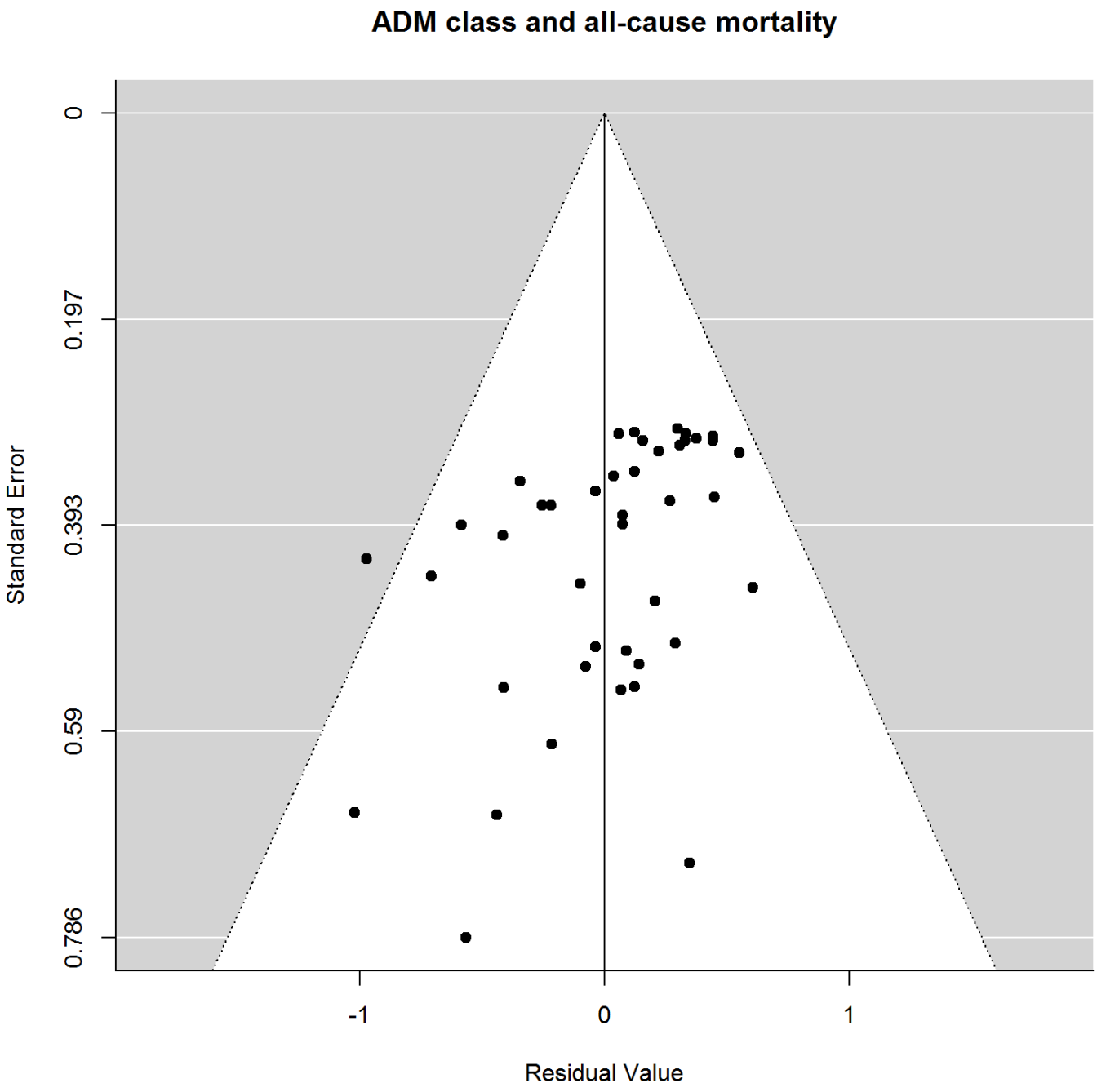
Diagnostics

```
plot(ADMresult_2B,id.n=13)
```



Funnel plot

```
funnel(ADMresult_2B, main= "ADM class and all-cause mortality")
```



Cardiovascular events

```
dd4B <- transform(subset(dd4A,!DRUG.TYPE %in% c("ADM","Undifferentiated") &
                              logCVEHR != "NA"),
                  DRUG.TYPE=factor(DRUG.TYPE,
                                   levels=c("TCA",
                                            "SSRI/SNRI",
                                            "Other")),
                  SAMPLE = factor (SAMPLE,
                                   levels=c("Cardiovascular patients",
                        "General population")))
dd4B <- arrange(dd4B,REFERENCE)

nrow(dd4B)
```

```
## [1] 62
```

```
(ADMresult_4A <- CVErma.fun(mods = ~ DRUG.TYPE-1, data=dd4B))
```

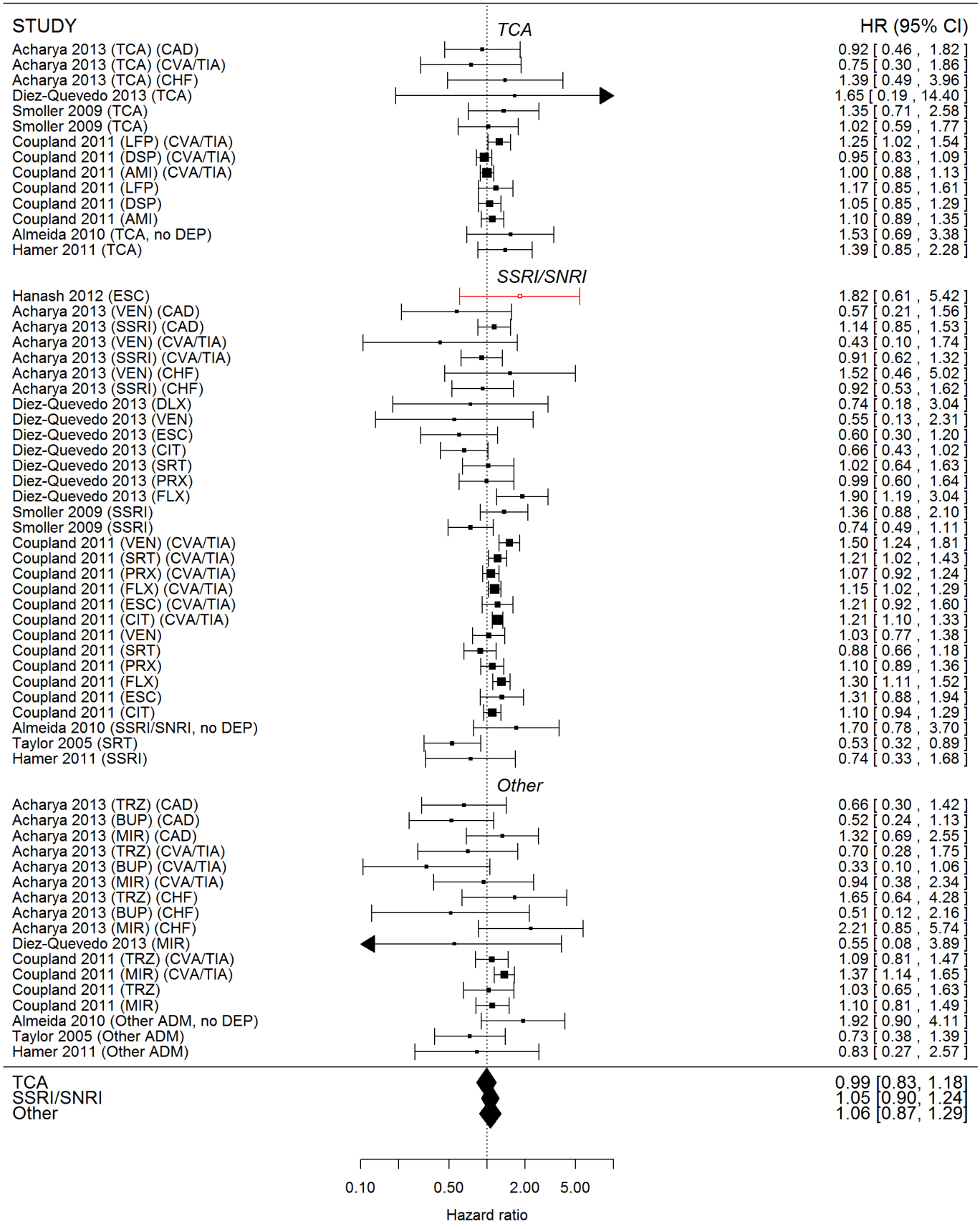
```
##
## Multivariate Meta-Analysis Model (k = 62; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0263  0.1621      8     no  REFERENCE
## sigma^2.2  0.0061  0.0780     62     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 59) = 89.5181, p-val = 0.0063
##
## I(df = 59) = 34.0915
##
## Test of Moderators (coefficient(s) 1,2,3):
## QM(df = 3) = 1.7508, p-val = 0.6257
##
## Model Results:
##
##                     estimate      se     zval    pval    ci.lb   ci.ub
## DRUG.TYPETCA         -0.0150  0.0904  -0.1662  0.8680  -0.1922  0.1622
## DRUG.TYPESSRI/SNRI    0.0527  0.0817   0.6443  0.5194  -0.1076  0.2129
## DRUG.TYPEOther        0.0582  0.1011   0.5762  0.5645  -0.1398  0.2563
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(ADMresult_4B <- CVErma.fun(mods = ~ DRUG.TYPE,   data=dd4B))
```

```
##
## Multivariate Meta-Analysis Model (k = 62; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0263  0.1621      8     no  REFERENCE
## sigma^2.2  0.0061  0.0780     62     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 59) = 89.5181, p-val = 0.0063
##
## I(df = 59) = 34.0915
##
## Test of Moderators (coefficient(s) 2,3):
## QM(df = 2) = 1.5167, p-val = 0.4684
##
## Model Results:
##
##                     estimate      se     zval    pval    ci.lb   ci.ub
## intrcpt              -0.0150  0.0904  -0.1662  0.8680  -0.1922  0.1622
## DRUG.TYPESSRI/SNRI    0.0677  0.0573   1.1812  0.2375  -0.0446  0.1800
## DRUG.TYPEOther        0.0733  0.0846   0.8658  0.3866  -0.0926  0.2391
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

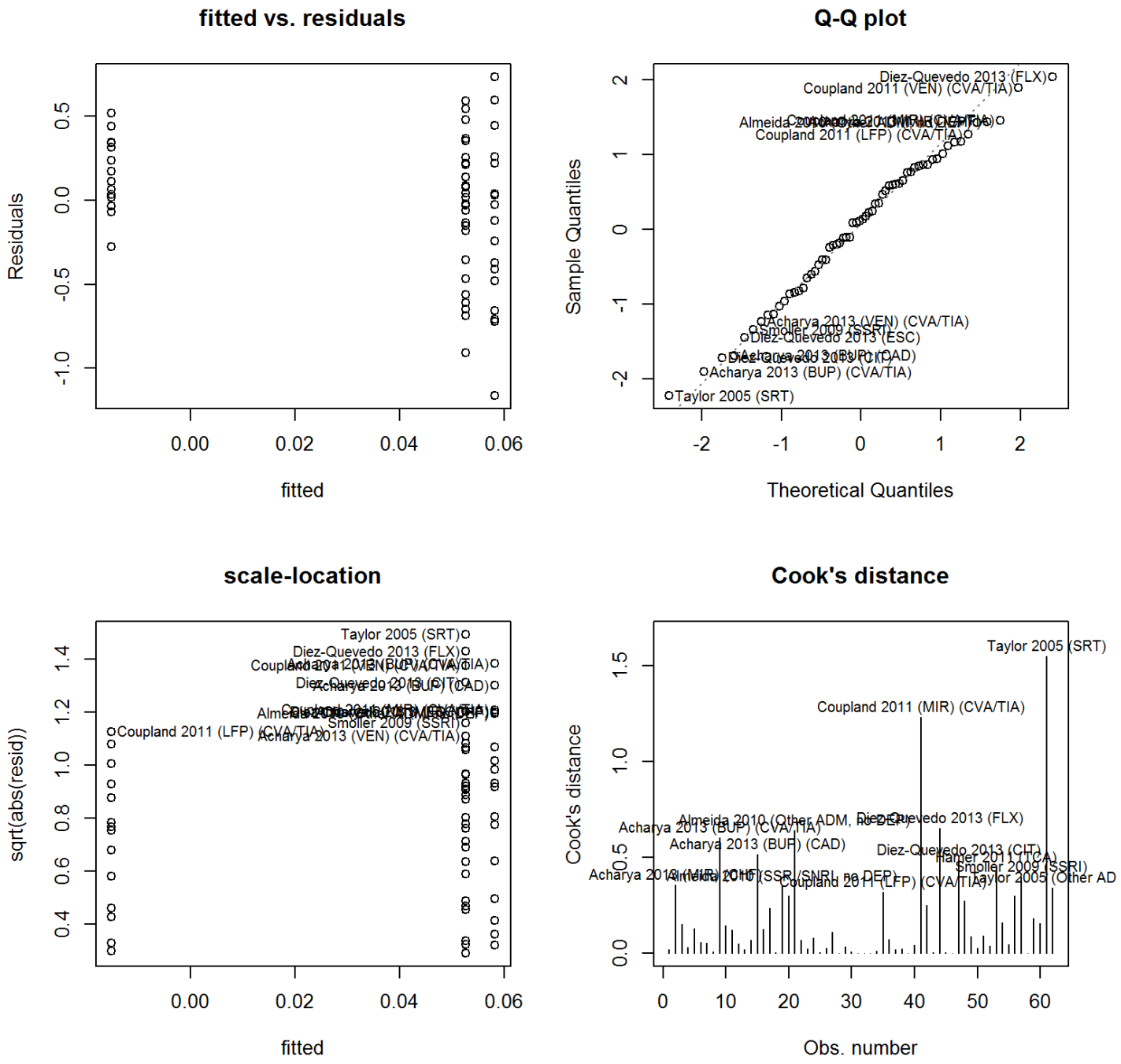
Forest plot

```
ffun(ADMresult_4B,dd4B,mod="DRUG.TYPE",add.fullpoly=FALSE,
          ss=as.numeric(dd4B$STUDY.TYPE))
```


STUDY
HR (95% CI)
TCA
Acharya 2013 (TCA) (CAD) 0.92 [0.46 , 1.82]
Acharya 2013 (TCA) (CVA/TIA) 0.75 [0.30 , 1.86]
Acharya 2013 (TCA) (CHF) 1.39 [0.49 , 3.96]
Diez-Quevedo 2013 (TCA) 1.65 [0.19 , 14.40]
Smoller 2009 (TCA) 1.35 [0.71 , 2.58]
Smoller 2009 (TCA) 1.02 [0.59 , 1.77]
Coupland 2011 (LFP) (CVA/TIA) 1.25 [1.02 , 1.54]
Coupland 2011 (DSP) (CVA/TIA) 0.95 [0.83 , 1.09]
Coupland 2011 (AMI) (CVA/TIA) 1.00 [0.88 , 1.13]
Coupland 2011 (LFP) 1.17 [0.85 , 1.61]
Coupland 2011 (DSP) 1.05 [0.85 , 1.29]
Coupland 2011 (AMI) 1.10 [0.89 , 1.35]
Almeida 2010 (TCA, no DEP) 1.53 [0.69 , 3.38]
Hamer 2011 (TCA) 1.39 [0.85 , 2.28]
SSRI/SNRI
Hanash 2012 (ESC) 1.82 [0.61 , 5.42]
Acharya 2013 (VEN) (CAD) 0.57 [0.21 , 1.56]
Acharya 2013 (SSRI) (CAD) 1.14 [0.85 , 1.53]
Acharya 2013 (VEN) (CVA/TIA) 0.43 [0.10 , 1.74]
Acharya 2013 (SSRI) (CVA/TIA) 0.91 [0.62 , 1.32]
Acharya 2013 (VEN) (CHF) 1.52 [0.46 , 5.02]
Acharya 2013 (SSRI) (CHF) 0.92 [0.53 , 1.62]
Diez-Quevedo 2013 (DLX) 0.74 [0.18 , 3.04]
Diez-Quevedo 2013 (VEN) 0.55 [0.13 , 2.31]
Diez-Quevedo 2013 (ESC) 0.60 [0.30 , 1.20]
Diez-Quevedo 2013 (CIT) 0.66 [0.43 , 1.02]
Diez-Quevedo 2013 (SRT) 1.02 [0.64 , 1.63]
Diez-Quevedo 2013 (PRX) 0.99 [0.60 , 1.64]
Diez-Quevedo 2013 (FLX) 1.90 [1.19 , 3.04]
Smoller 2009 (SSRI) 1.36 [0.88 , 2.10]
Smoller 2009 (SSRI) 0.74 [0.49 , 1.11]
Coupland 2011 (VEN) (CVA/TIA) 1.50 [1.24 , 1.81]
Coupland 2011 (SRT) (CVA/TIA) 1.21 [1.02 , 1.43]
Coupland 2011 (PRX) (CVA/TIA) 1.07 [0.92 , 1.24]
Coupland 2011 (FLX) (CVA/TIA) 1.15 [1.02 , 1.29]
Coupland 2011 (ESC) (CVA/TIA) 1.21 [0.92 , 1.60]
Coupland 2011 (CIT) (CVA/TIA) 1.21 [1.10 , 1.33]
Coupland 2011 (VEN) 1.03 [0.77 , 1.38]
Coupland 2011 (SRT) 0.88 [0.66 , 1.18]
Coupland 2011 (PRX) 1.10 [0.89 , 1.36]
Coupland 2011 (FLX) 1.30 [1.11 , 1.52]
Coupland 2011 (ESC) 1.31 [0.88 , 1.94]
Coupland 2011 (CIT) 1.10 [0.94 , 1.29]
Almeida 2010 (SSRI/SNRI, no DEP) 1.70 [0.78 , 3.70]
Taylor 2005 (SRT) 0.53 [0.32 , 0.89]
Hamer 2011 (SSRI) 0.74 [0.33 , 1.68]
Other
Acharya 2013 (TRZ) (CAD) 0.66 [0.30 , 1.42]
Acharya 2013 (BUP) (CAD) 0.52 [0.24 , 1.13]
Acharya 2013 (MIR) (CAD) 1.32 [0.69 , 2.55]
Acharya 2013 (TRZ) (CVA/TIA) 0.70 [0.28 , 1.75]
Acharya 2013 (BUP) (CVA/TIA) 0.33 [0.10 , 1.06]
Acharya 2013 (MIR) (CVA/TIA) 0.94 [0.38 , 2.34]
Acharya 2013 (TRZ) (CHF) 1.65 [0.64 , 4.28]
Acharya 2013 (BUP) (CHF) 0.51 [0.12 , 2.16]
Acharya 2013 (MIR) (CHF) 2.21 [0.85 , 5.74]
Diez-Quevedo 2013 (MIR) 0.55 [0.08 , 3.89]
Coupland 2011 (TRZ) (CVA/TIA) 1.09 [0.81 , 1.47]
Coupland 2011 (MIR) (CVA/TIA) 1.37 [1.14 , 1.65]
Coupland 2011 (TRZ) 1.03 [0.65 , 1.63]
Coupland 2011 (MIR) 1.10 [0.81 , 1.49]
Almeida 2010 (Other ADM, no DEP) 1.92 [0.90 , 4.11]
Taylor 2005 (Other ADM) 0.73 [0.38 , 1.39]
Hamer 2011 (Other ADM) 0.83 [0.27 , 2.57]
TCA 0.99 [0.83, 1.18]
SSRI/SNRI 1.05 [0.90, 1.24]
Other 1.06 [0.87, 1.29]
0.10
0.50
2.00
5.00
Hazard ratio

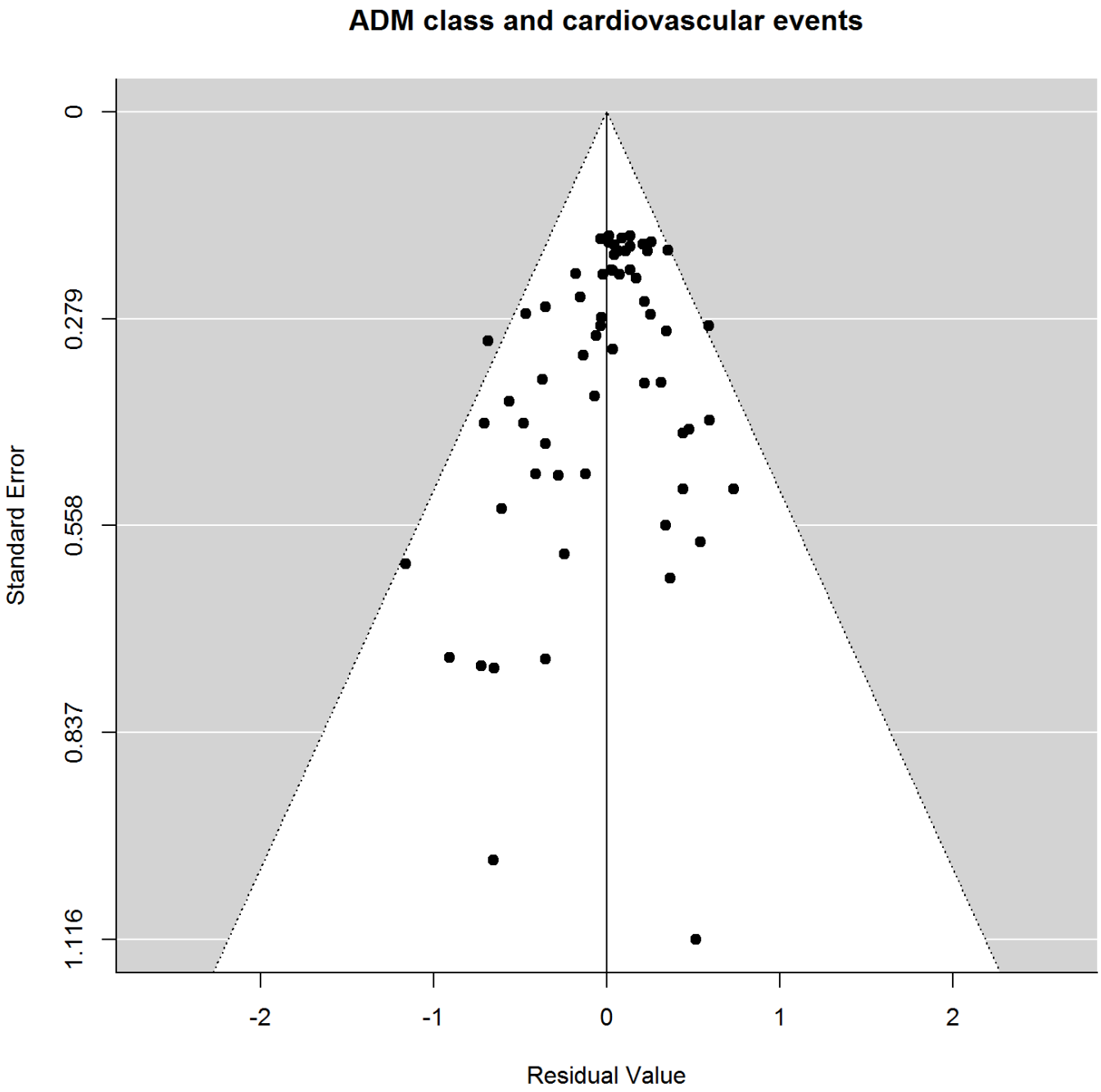
Diagnostics

```
plot(ADMresult_4B,id.n=13)
```



Funnel plot

```
funnel(ADMresult_4B, main= "ADM class and cardiovascular events")
```



B3: Meta-analysis of studies controlling for premedication depression, using sample type as a moderator

All-cause mortality

```
control_refs <- c("Smoller 2009","O'Connor 2010","Khan 2013","Hanash 2012",
                  "Coupland 2011","Balogun 2012")
dd3E <- droplevels(subset(dd3A, REFERENCE %in% control_refs))
dd3E <- arrange(dd3E, REFERENCE)
nrow(dd3E)
```

```
## [1] 19
```

```
(ADMresult_7A <- ACMrma.fun(mods = ~ SAMPLE-1, data=dd3E))
```

```
##
## Multivariate Meta-Analysis Model (k = 19; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      6     no  REFERENCE
## sigma^2.2  0.0276  0.1662     19     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 17) = 192.4680, p-val < .0001
##
## I(df = 17) = 91.1674
##
## Test of Moderators (coefficient(s) 1,2):
## QM(df = 2) = 60.6647, p-val < .0001
##
## Model Results:
##
##                                estimate      se    zval    pval    ci.lb
## SAMPLECardiovascular patients    0.0974  0.1509  0.6449  0.5190  -0.1985
## SAMPLEGeneral population         0.3654  0.0471  7.7620  <.0001   0.2732
##                                 ci.ub
## SAMPLECardiovascular patients  0.3932
## SAMPLEGeneral population       0.4577  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

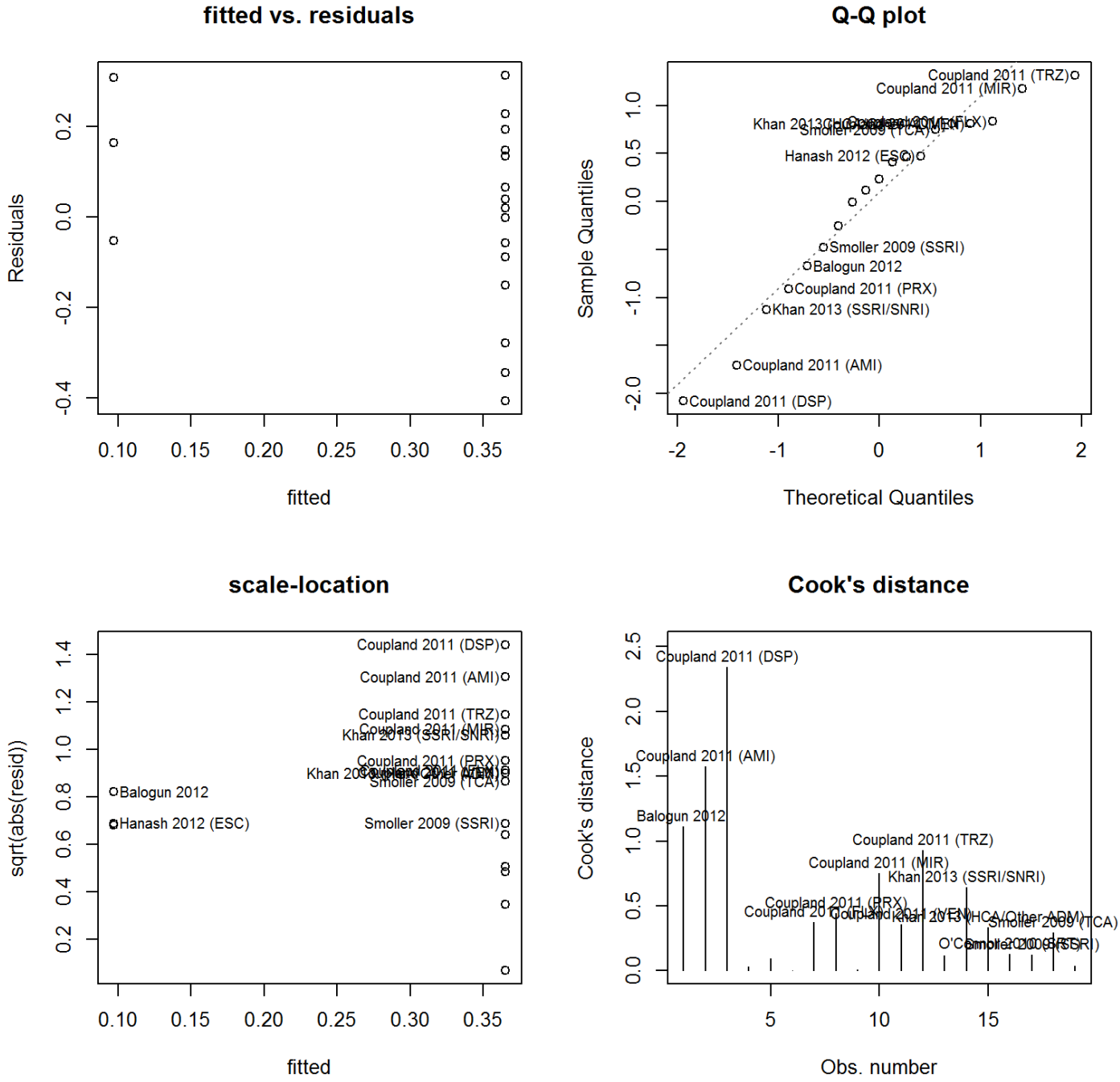
```
(ADMresult_7B <- ACMrma.fun(mods = ~ SAMPLE,   data=dd3E))
```

```
##
## Multivariate Meta-Analysis Model (k = 19; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      6     no  REFERENCE
## sigma^2.2  0.0276  0.1662     19     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 17) = 192.4680, p-val < .0001
##
## I(df = 17) = 91.1674
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 2.8747, p-val = 0.0900
##
## Model Results:
##
##                           estimate      se    zval    pval    ci.lb
## intrcpt                     0.0974  0.1509  0.6449  0.5190  -0.1985
## SAMPLEGeneral population    0.2681  0.1581  1.6955  0.0900  -0.0418
##                            ci.ub
## intrcpt                   0.3932
## SAMPLEGeneral population  0.5780  .
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
## remove drug labels?
## ADMresult_2B$slab <- gsub("\\((HCA|SRI|FLX/PRX|CIT|Other ADM)\\)","",
##                           ADMresult_2B$slab)
```

Diagnostics

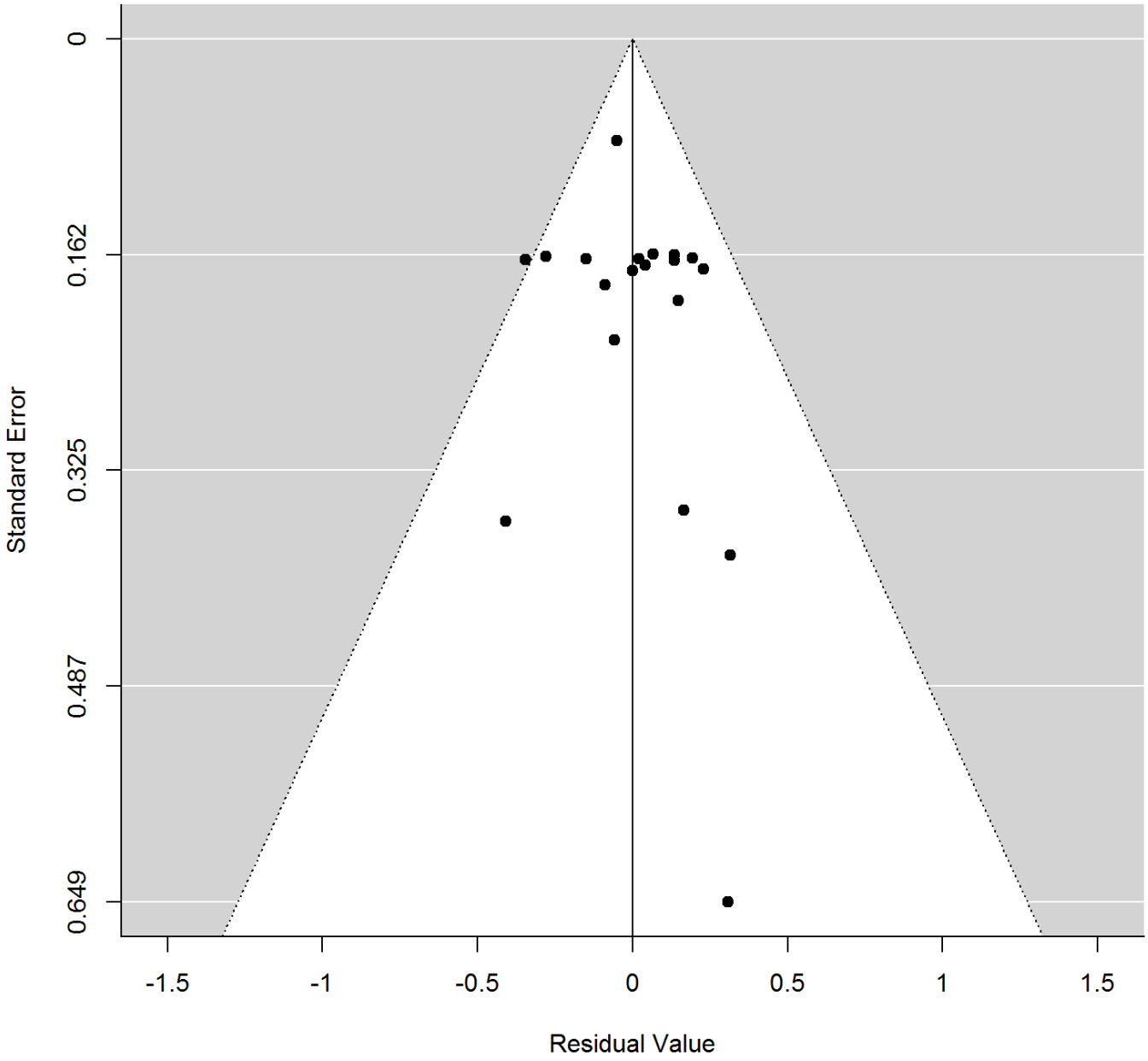
```
plot(ADMresult_7B,id.n=13)
```



Funnel plot

```
funnel(ADMresult_7B, main= "Mortality effects of any ADMs using sample type as a
 moderator in studies that control for pre-medication depressive symptoms")
```

ıny ADMs using sample type as a moderator in studies that control for pre-medicatio



Cardiovascular events

```
dd4E <- droplevels(subset(dd4A, REFERENCE %in% control_refs))
dd4E <- arrange(dd4E, REFERENCE)
nrow(dd4E)
```

```
## [1] 29
```

```
(ADMresult_12A <- CVErma.fun(mods = ~ SAMPLE-1, data=dd4E))
```

```
##
## Multivariate Meta-Analysis Model (k = 29; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      3     no  REFERENCE
## sigma^2.2  0.0067  0.0816     29     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 27) = 40.1019, p-val = 0.0501
##
## I(df = 27) = 32.6715
##
## Test of Moderators (coefficient(s) 1,2):
## QM(df = 2) = 23.8267, p-val < .0001
##
## Model Results:
##
##                               estimate      se    zval    pval    ci.lb
## SAMPLECardiovascular patients    0.5968  0.5638  1.0585  0.2898  -0.5082
## SAMPLEGeneral population         0.1294  0.0271  4.7651  <.0001   0.0762
##                                ci.ub
## SAMPLECardiovascular patients  1.7018
## SAMPLEGeneral population       0.1826  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

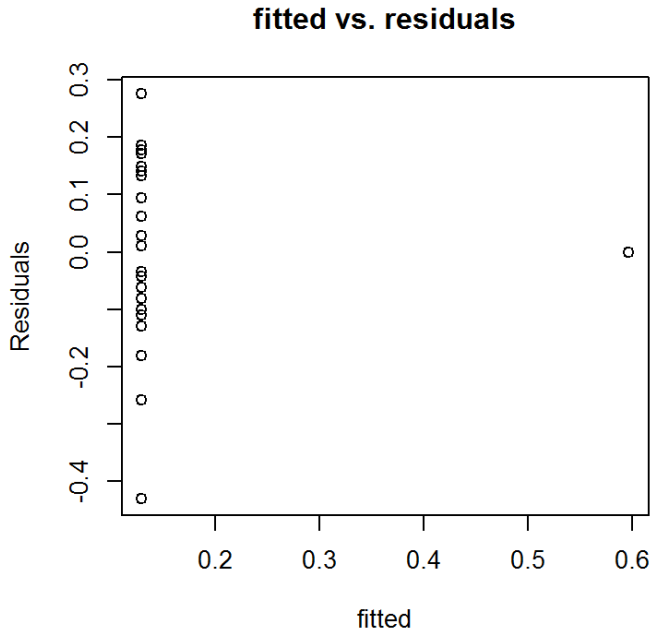
```
(ADMresult_12B <- CVErma.fun(mods = ~ SAMPLE,   data=dd4E))
```

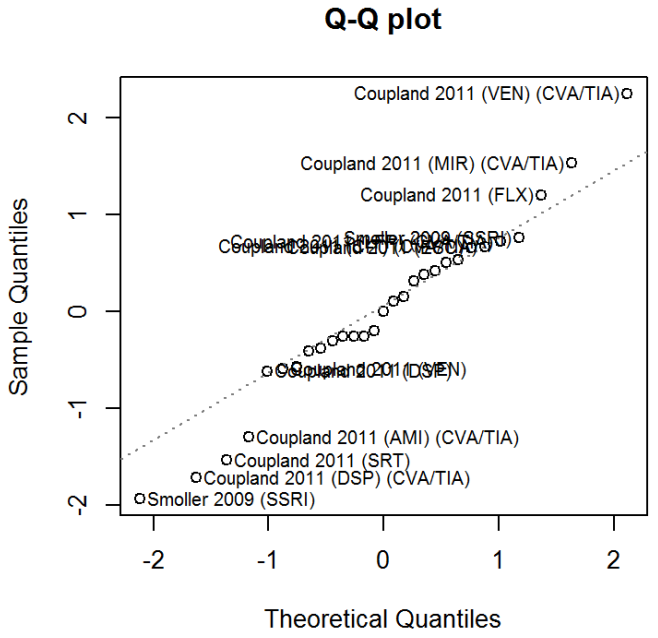
```
##
## Multivariate Meta-Analysis Model (k = 29; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      3     no  REFERENCE
## sigma^2.2  0.0067  0.0816     29     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 27) = 40.1019, p-val = 0.0501
##
## I(df = 27) = 32.6715
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 0.6857, p-val = 0.4076
##
## Model Results:
##
##                           estimate      se     zval    pval    ci.lb
## intrcpt                     0.5968  0.5638   1.0585  0.2898  -0.5082
## SAMPLEGeneral population   -0.4674  0.5644  -0.8281  0.4076  -1.5737
##                            ci.ub
## intrcpt                   1.7018
## SAMPLEGeneral population  0.6389
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

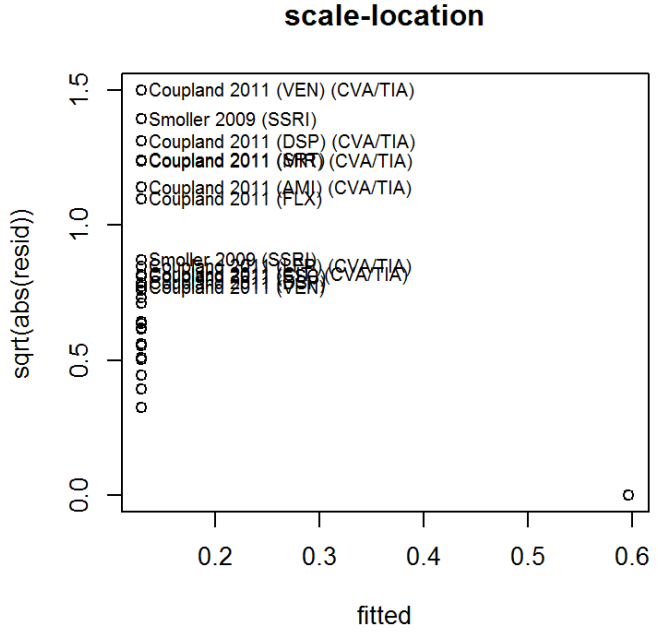
```
## remove drug labels?
## ADMresult_2B$slab <- gsub("\\((HCA|SRI|FLX/PRX|CIT|Other ADM)\\)","",
##                           ADMresult_2B$slab)
```

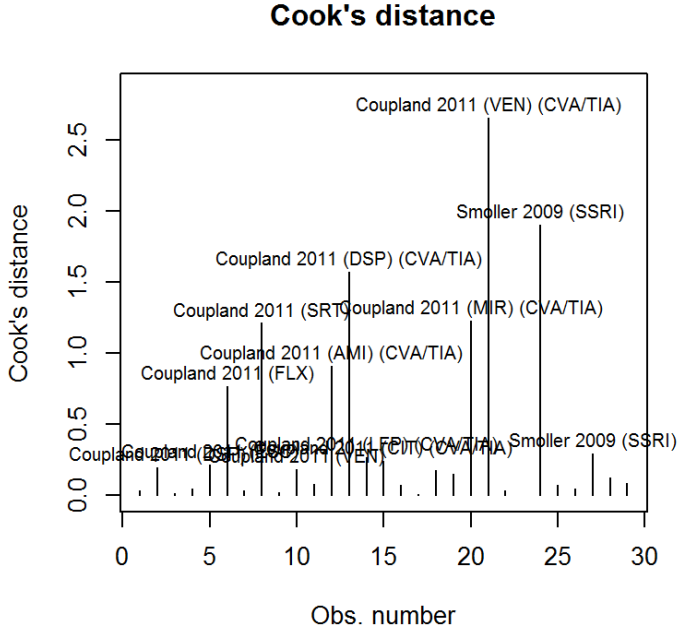
Diagnostics

```
plot(ADMresult_12B,id.n=13)
```



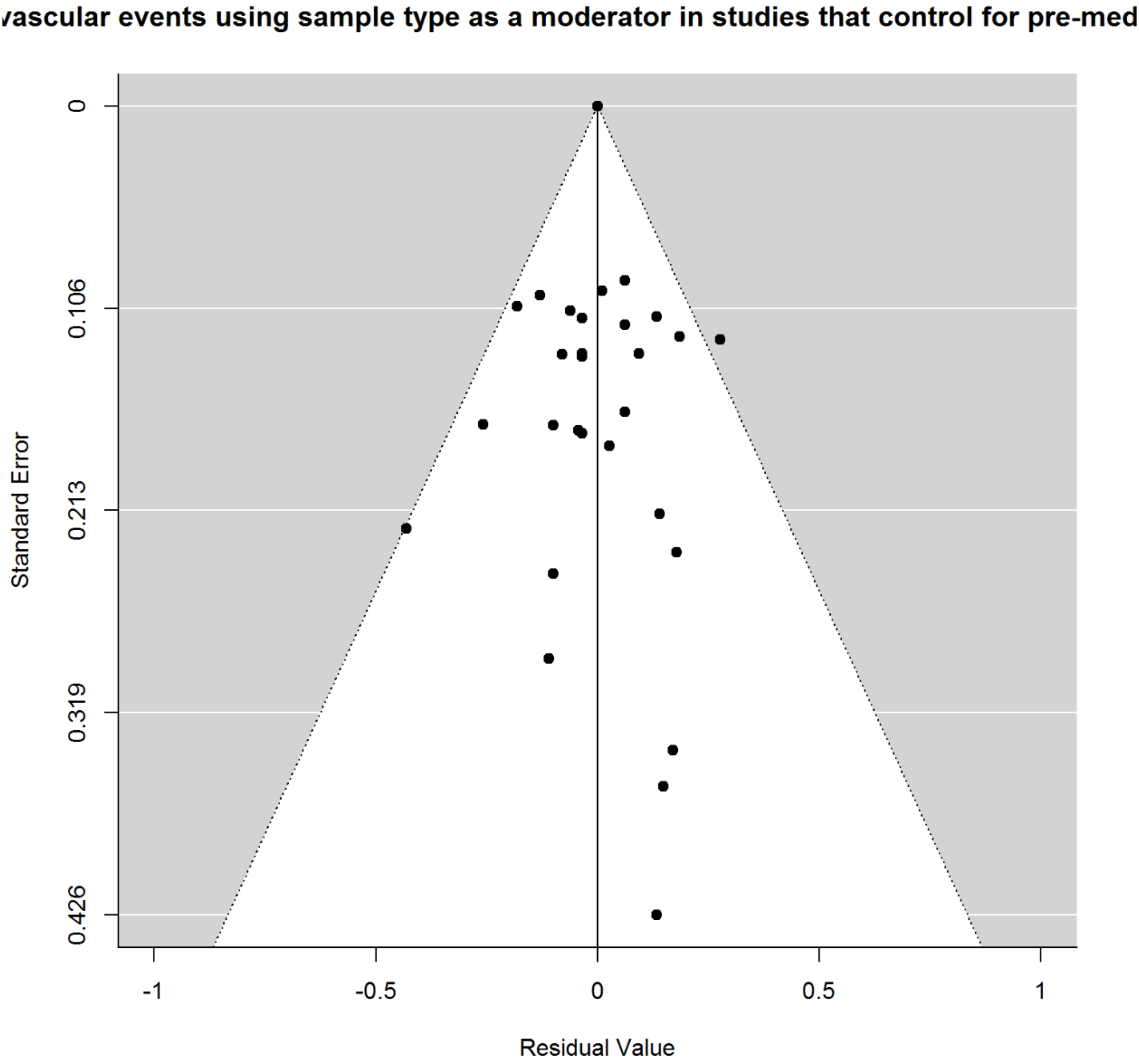






Funnel plot

```
funnel(ADMresult_12B, main= "Effect of ADMs on cardiovascular events using sampl
e type as a moderator in studies that control for pre-medication depressive symp
toms")
```



B4: Meta-analysis using ADM class as a moderator, with studies controlling for premedication depression

All-cause mortality

Studies with statistics presented for use of antidepressants, separated by drug class (SSRI/SNRI, TCA, Other) (Excluding studies that provided statistics for Any ADM use or the use of undifferentiated ADMs)

```
dd3F <- droplevels(subset(dd3B, REFERENCE %in% control_refs))
dd3F <- arrange(dd3F, REFERENCE)
nrow(dd3F)
```

```
## [1] 16
```

```
(ADMresult_5A <- ACMrma.fun(mods = ~ DRUG.TYPE-1, data=dd3F))
```

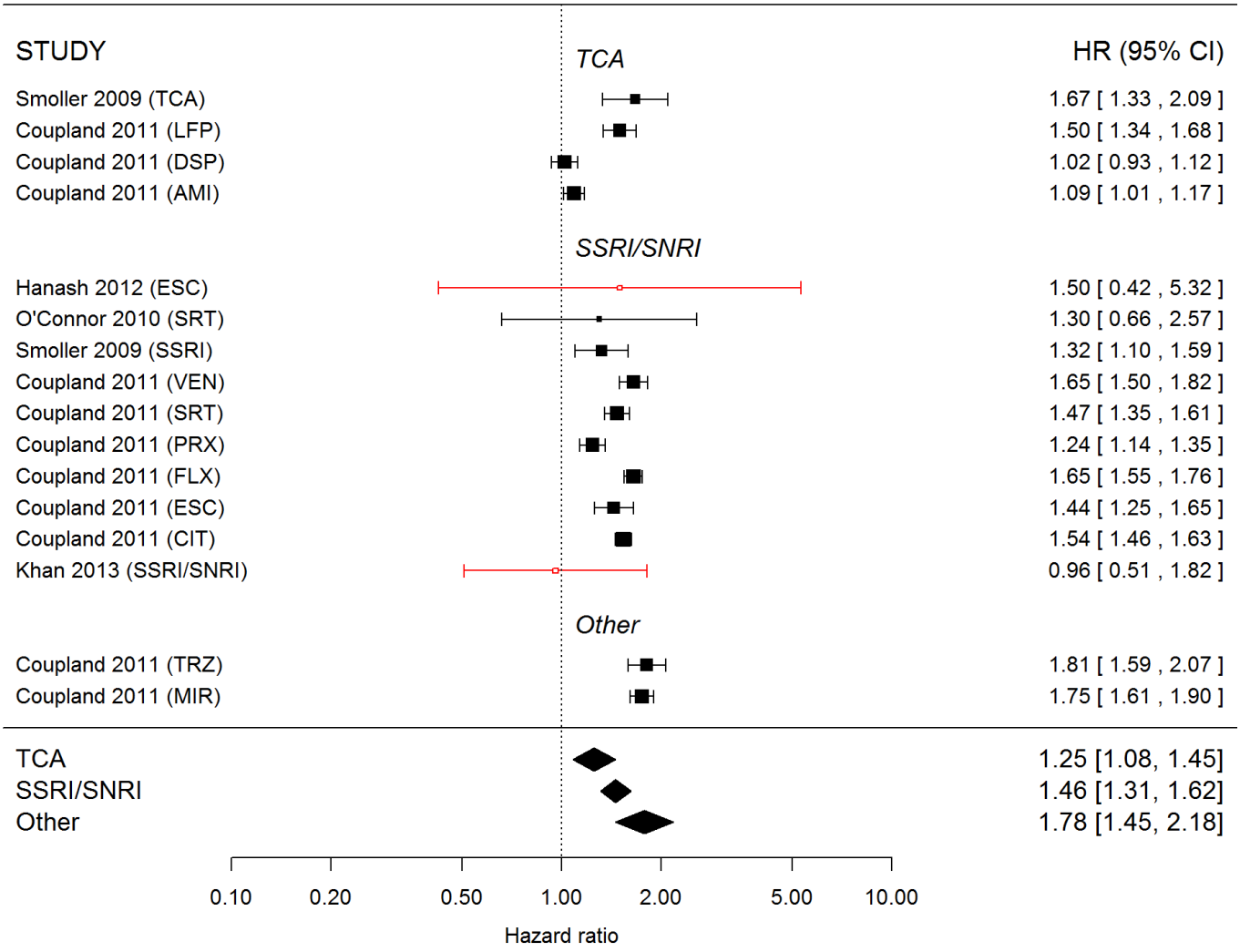
```
##
## Multivariate Meta-Analysis Model (k = 16; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      5     no  REFERENCE
## sigma^2.2  0.0182  0.1349     16     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 13) = 74.8912, p-val < .0001
##
## I(df = 13) = 82.6415
##
## Test of Moderators (coefficient(s) 1,2,3):
## QM(df = 3) = 89.5026, p-val < .0001
##
## Model Results:
##
##                     estimate      se    zval    pval   ci.lb   ci.ub
## DRUG.TYPETCA          0.2266  0.0750  3.0232  0.0025  0.0797  0.3735   **
## DRUG.TYPESSRI/SNRI    0.3752  0.0535  7.0168  <.0001  0.2704  0.4801  ***
## DRUG.TYPEOther        0.5754  0.1031  5.5792  <.0001  0.3733  0.7775  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(ADMresult_5B <- ACMrma.fun(mods = ~ DRUG.TYPE,   data=dd3F))
```

```
##
## Multivariate Meta-Analysis Model (k = 16; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      5     no  REFERENCE
## sigma^2.2  0.0182  0.1349     16     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 13) = 74.8912, p-val < .0001
##
## I(df = 13) = 82.6415
##
## Test of Moderators (coefficient(s) 2,3):
## QM(df = 2) = 7.6039, p-val = 0.0223
##
## Model Results:
##
##                     estimate      se    zval    pval    ci.lb   ci.ub
## intrcpt               0.2266  0.0750  3.0232  0.0025   0.0797  0.3735  **
## DRUG.TYPESSRI/SNRI    0.1486  0.0921  1.6141  0.1065  -0.0318  0.3291
## DRUG.TYPEOther        0.3488  0.1275  2.7356  0.0062   0.0989  0.5987  **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Forest plot

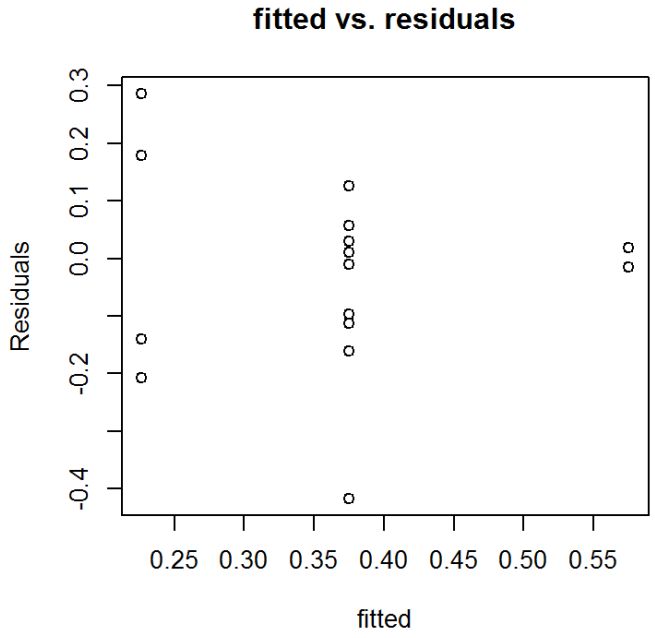
```
ffun(ADMresult_5B,dd3F,mod="DRUG.TYPE",add.fullpoly=FALSE,
          ss=as.numeric(dd3F$STUDY.TYPE))
```

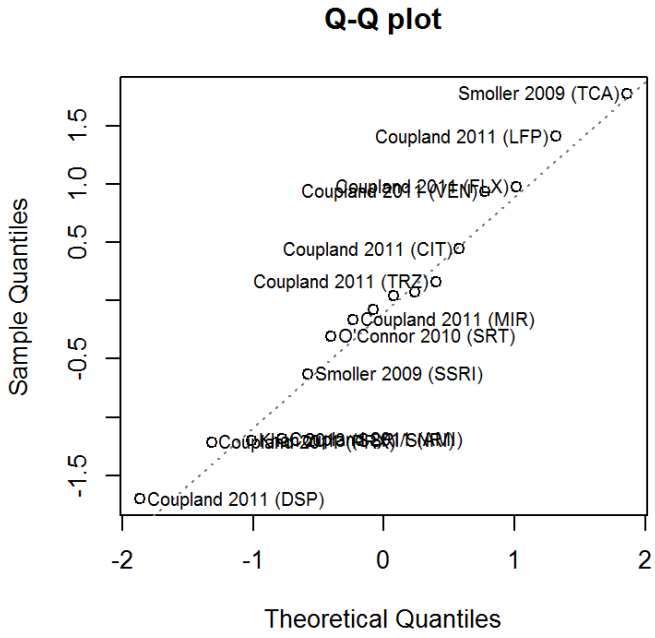


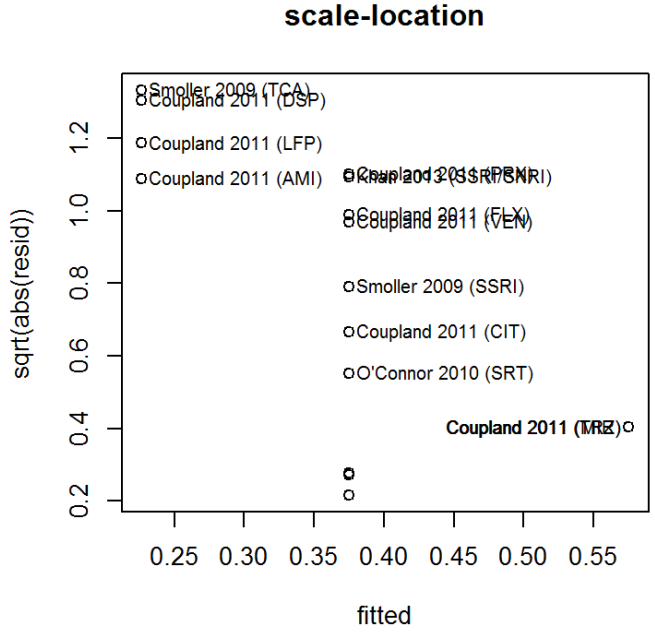
Diagnostics

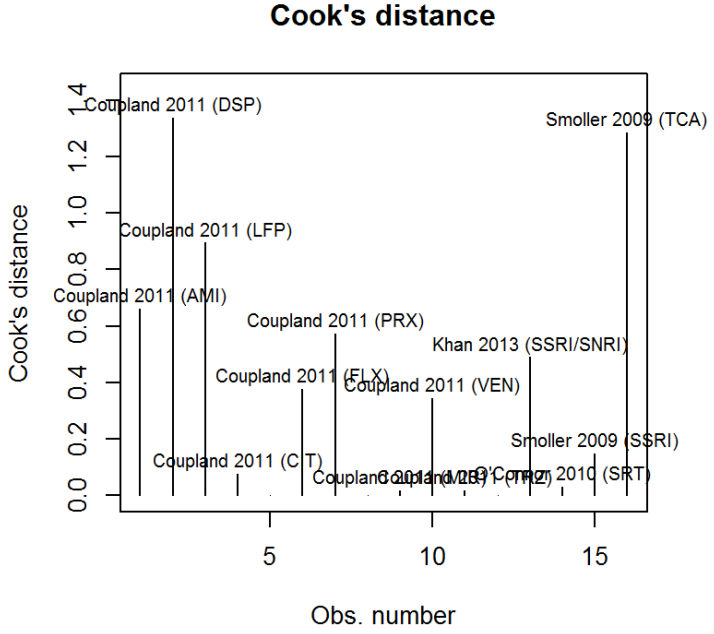
Coupland 2011 (MIR) is the only observation in the “Other” drug category, so it has infinite leverage and doesn’t show up on the Cook’s distance plot.

```
plot(ADMresult_5B,id.n=13)
```



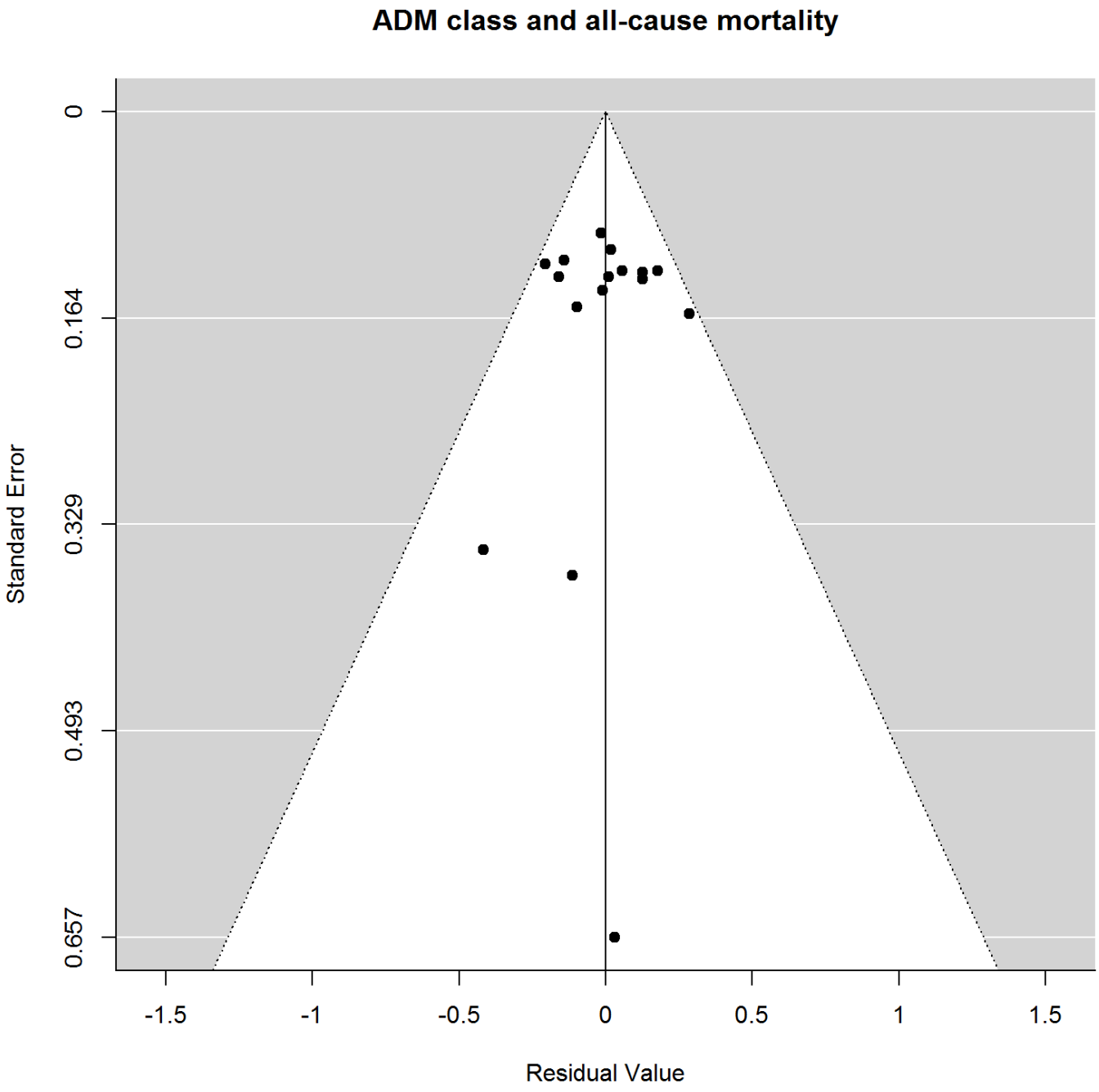






Funnel plot

```
funnel(ADMresult_5B, main= "ADM class and all-cause mortality")
```



Cardiovascular events

```
dd4F <- droplevels(subset(dd4B, REFERENCE %in% control_refs))
dd4F <- arrange(dd4F, REFERENCE)
nrow(dd4F)
```

```
## [1] 27
```

```
(ADMresult_11A <- CVErma.fun(mods = ~ DRUG.TYPE-1, data=dd4F))
```

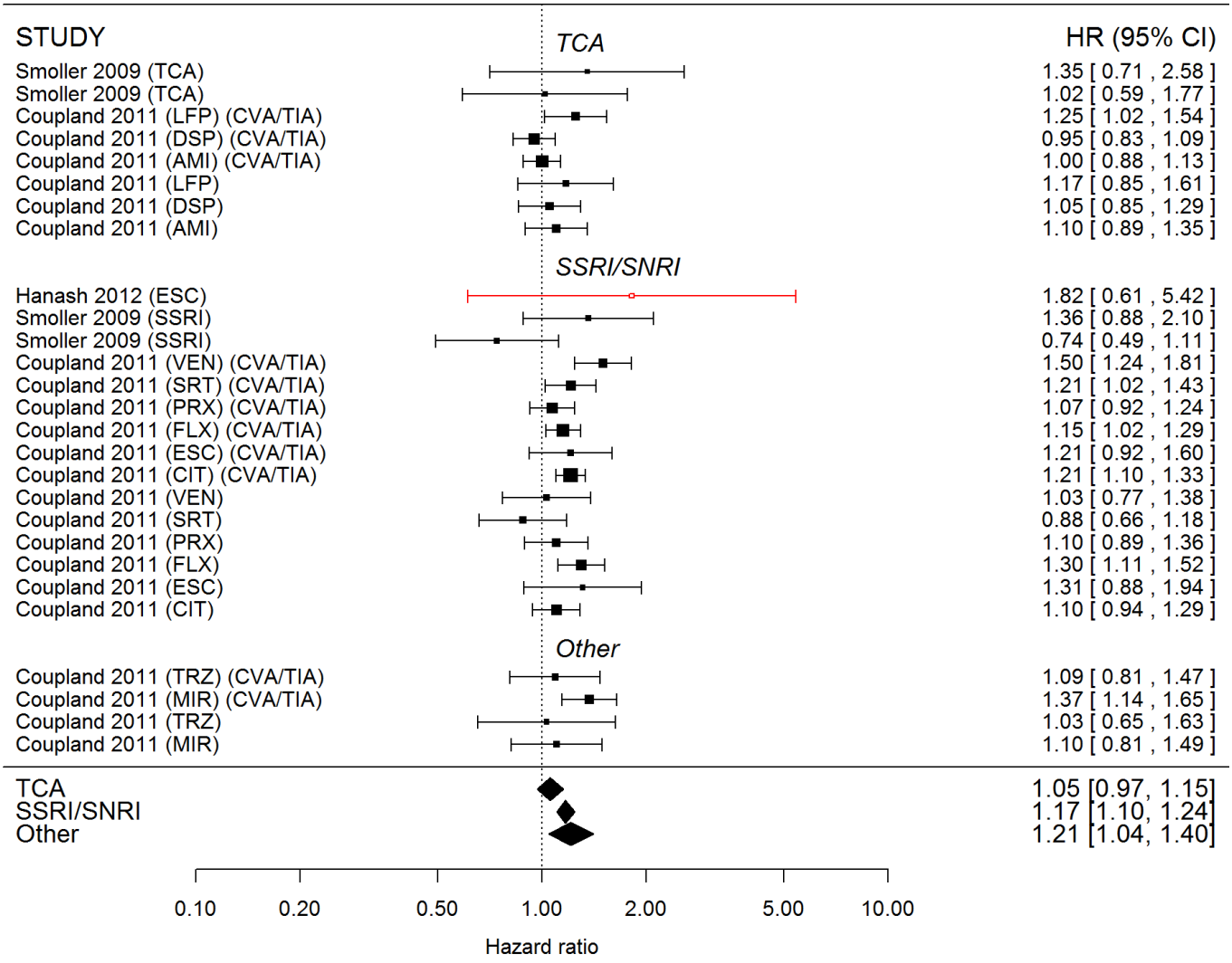
```
##
## Multivariate Meta-Analysis Model (k = 27; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      3     no  REFERENCE
## sigma^2.2  0.0033  0.0573     27     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 24) = 31.6948, p-val = 0.1347
##
## I(df = 24) = 24.2778
##
## Test of Moderators (coefficient(s) 1,2,3):
## QM(df = 3) = 33.9618, p-val < .0001
##
## Model Results:
##
##                     estimate      se    zval    pval    ci.lb   ci.ub
## DRUG.TYPETCA          0.0534  0.0439  1.2184  0.2231  -0.0325  0.1394
## DRUG.TYPESSRI/SNRI    0.1563  0.0306  5.1086  <.0001   0.0964  0.2163  ***
## DRUG.TYPEOther        0.1909  0.0756  2.5257  0.0115   0.0428  0.3391    *
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(ADMresult_11B <- CVErma.fun(mods = ~ DRUG.TYPE,   data=dd4F))
```

```
##
## Multivariate Meta-Analysis Model (k = 27; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      3     no  REFERENCE
## sigma^2.2  0.0033  0.0573     27     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 24) = 31.6948, p-val = 0.1347
##
## I(df = 24) = 24.2778
##
## Test of Moderators (coefficient(s) 2,3):
## QM(df = 2) = 4.4370, p-val = 0.1088
##
## Model Results:
##
##                     estimate      se    zval    pval    ci.lb   ci.ub
## intrcpt               0.0534  0.0439  1.2184  0.2231  -0.0325  0.1394
## DRUG.TYPESSRI/SNRI    0.1029  0.0535  1.9240  0.0544  -0.0019  0.2077  .
## DRUG.TYPEOther        0.1375  0.0874  1.5733  0.1157  -0.0338  0.3088
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

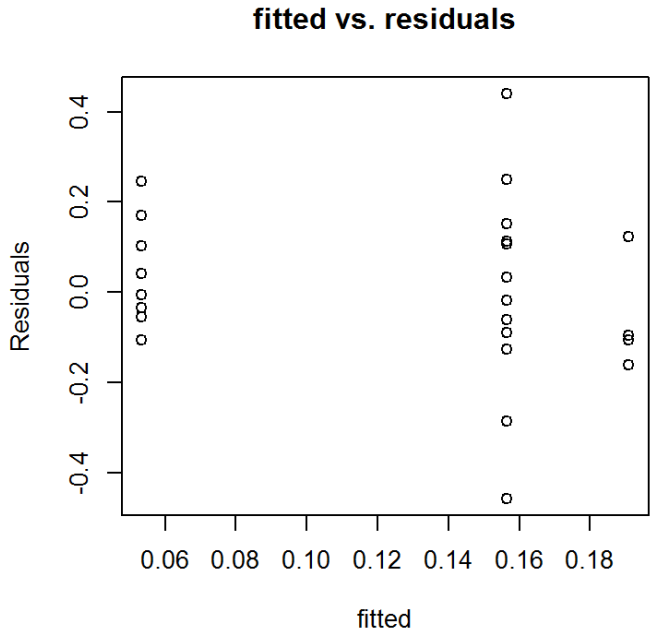
Forest plot

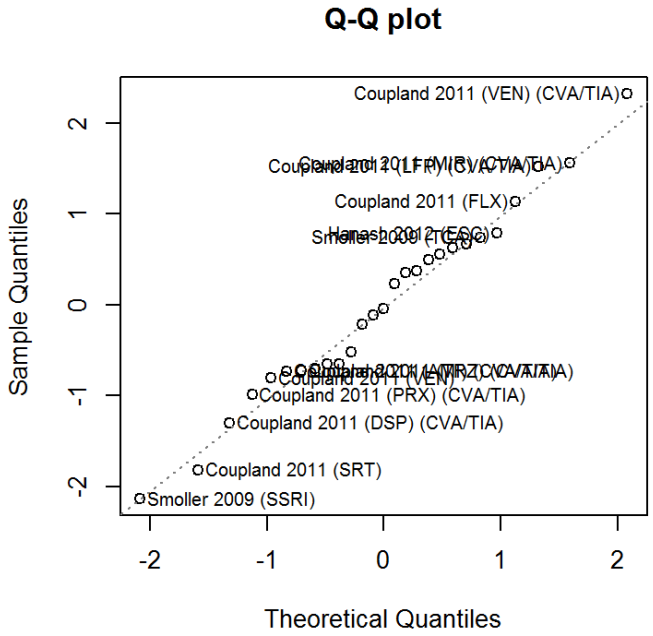
```
ffun(ADMresult_11B,dd4F,mod="DRUG.TYPE",add.fullpoly=FALSE,
          ss=as.numeric(dd4F$STUDY.TYPE))
```

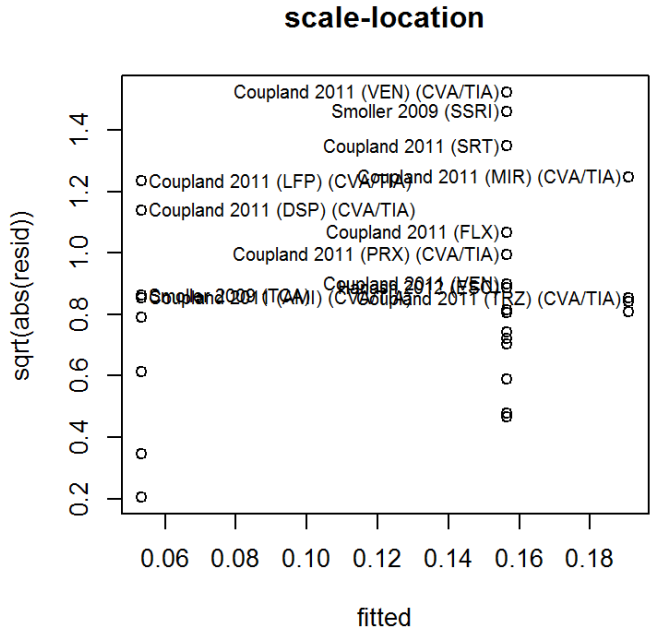


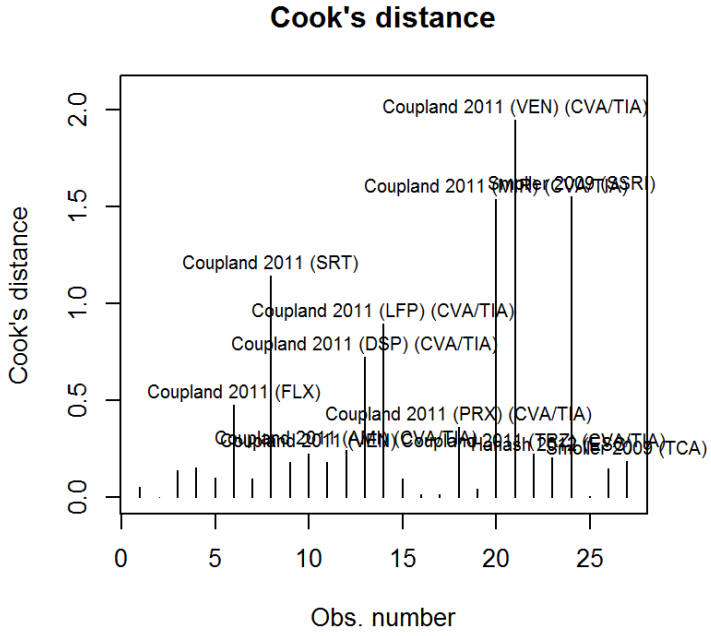
Diagnostics

```
plot(ADMresult_11B,id.n=13)
```



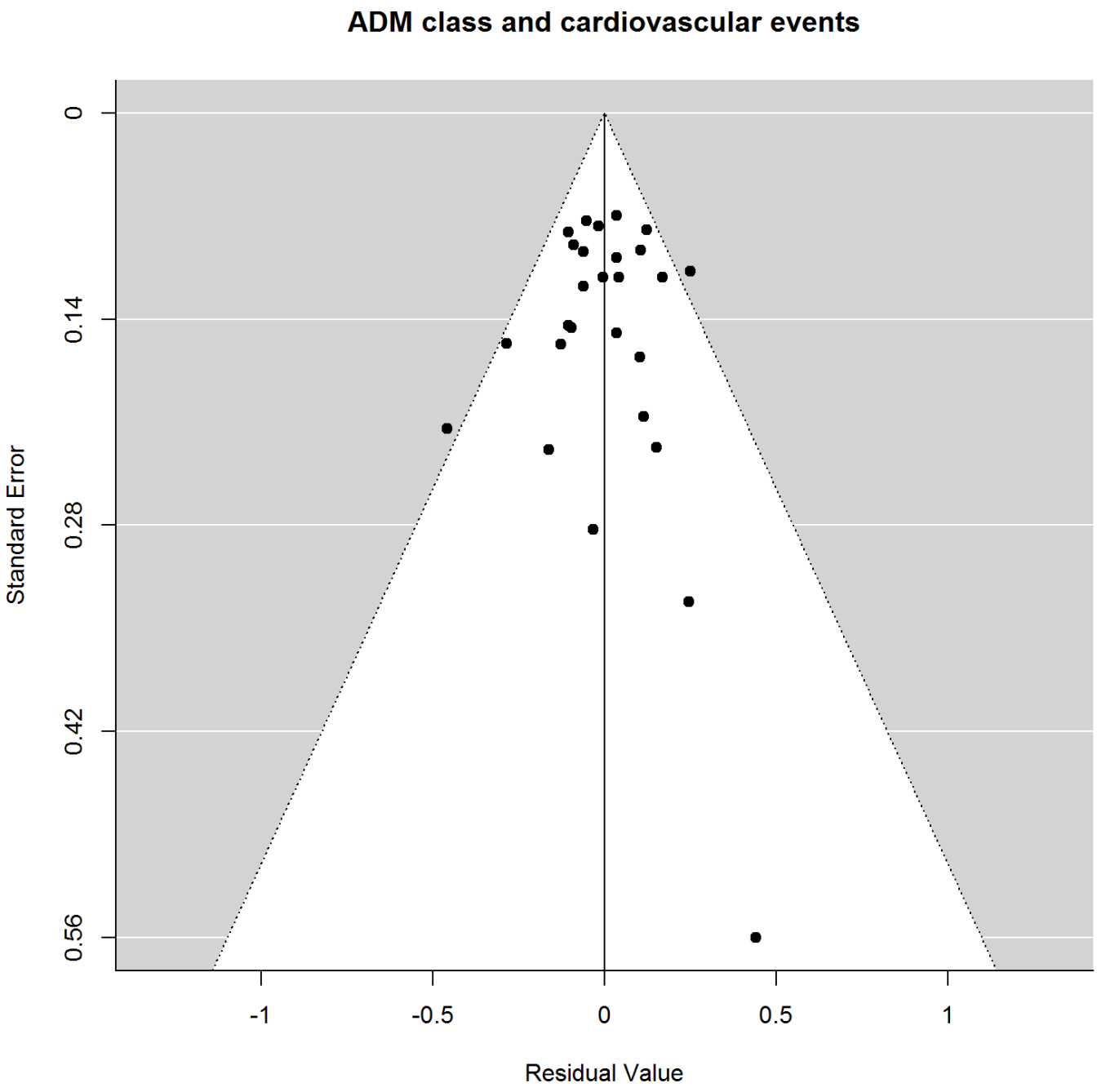






Funnel plot

```
funnel(ADMresult_11B, main= "ADM class and cardiovascular events")
```



B5: Meta-analysis of the overall data

All-cause mortality

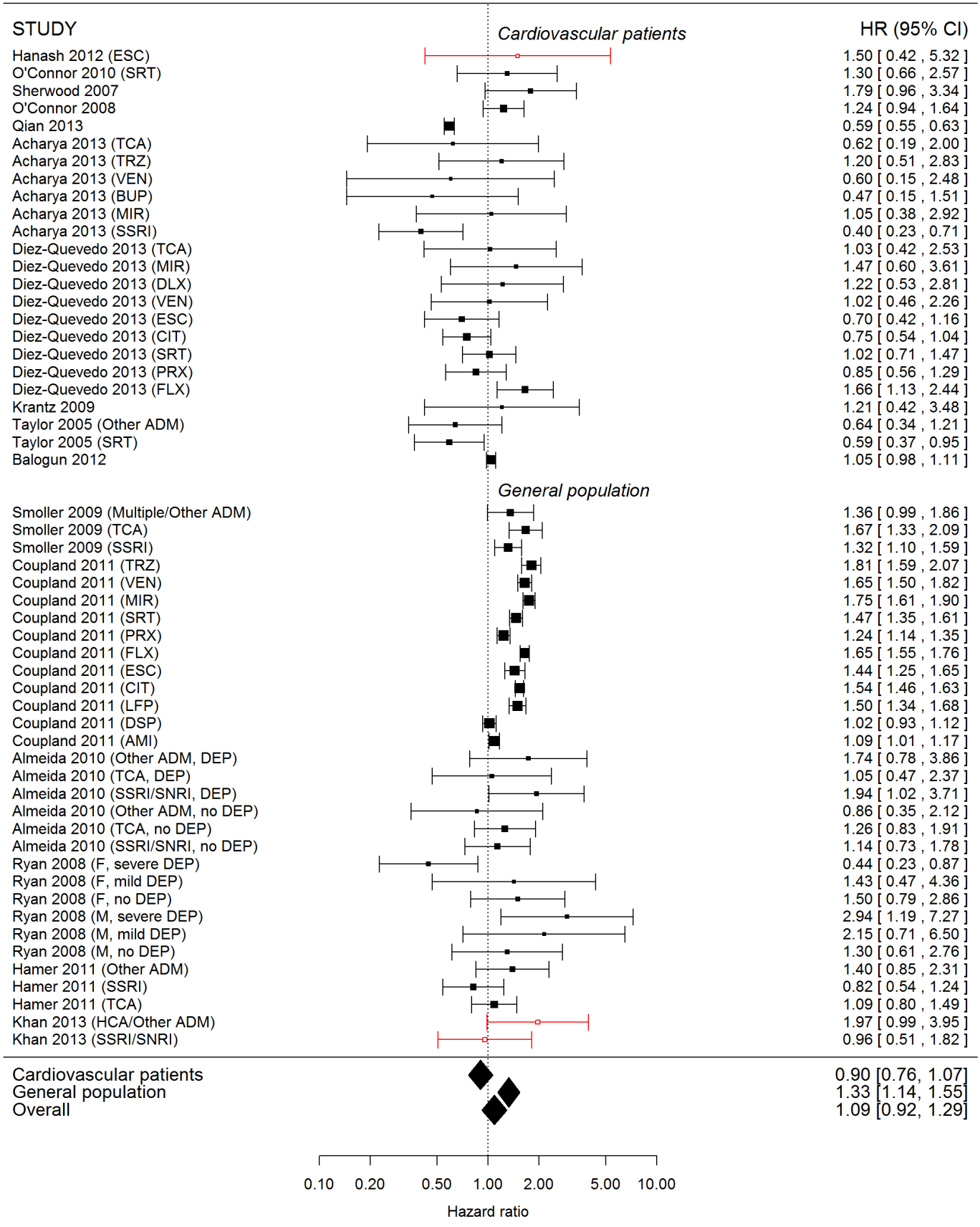
Although not of primary interest, we include for the sake of completeness a meta-analysis of all the data points, unsegregated by either sample type or ADM class.

```
(ADMresult_2 <- ACMrma.fun(data=dd3A))
```

```
##
## Multivariate Meta-Analysis Model (k = 55; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0672  0.2593     16     no  REFERENCE
## sigma^2.2  0.0355  0.1885     55     no         id
##
## Test for Heterogeneity:
## Q(df = 54) = 903.3781, p-val < .0001
##
## I(df = 54) = 94.0224
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##   0.0848   0.0858   0.9879   0.3232  -0.0835   0.2531
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

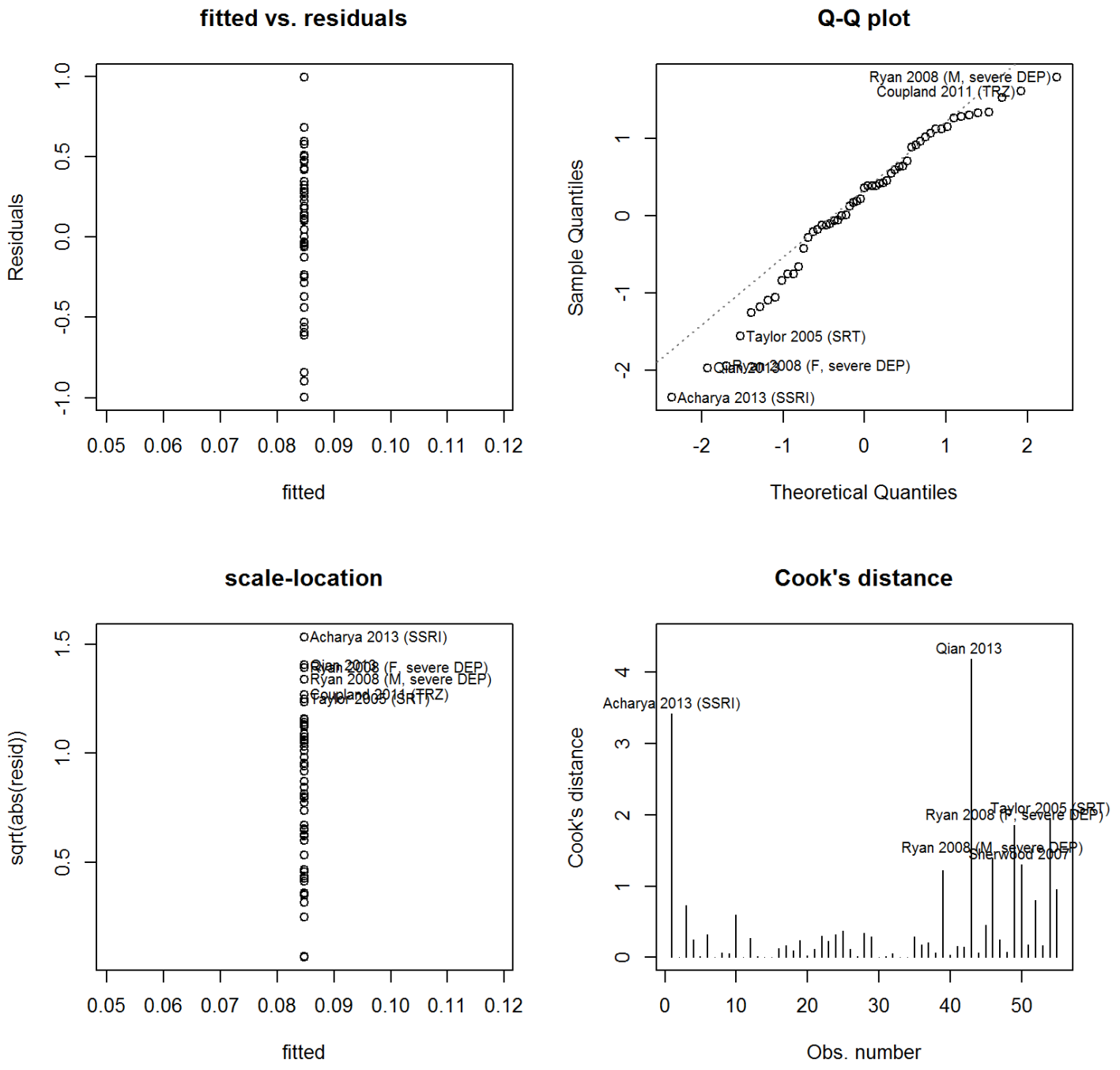
Forest plot

```
ffun(ADMresult_1B,dd3A,mod="SAMPLE",
     fullfit=ADMresult_2)
```


STUDY
HR (95% CI)
Cardiovascular patients
Hanash 2012 (ESC) 1.50 [0.42 , 5.32]
O'Connor 2010 (SRT) 1.30 [0.66 , 2.57]
Sherwood 2007 1.79 [0.96 , 3.34]
O'Connor 2008 1.24 [0.94 , 1.64]
Qian 2013 0.59 [0.55 , 0.63]
Acharya 2013 (TCA) 0.62 [0.19 , 2.00]
Acharya 2013 (TRZ) 1.20 [0.51 , 2.83]
Acharya 2013 (VEN) 0.60 [0.15 , 2.48]
Acharya 2013 (BUP) 0.47 [0.15 , 1.51]
Acharya 2013 (MIR) 1.05 [0.38 , 2.92]
Acharya 2013 (SSRI) 0.40 [0.23 , 0.71]
Diez-Quevedo 2013 (TCA) 1.03 [0.42 , 2.53]
Diez-Quevedo 2013 (MIR) 1.47 [0.60 , 3.61]
Diez-Quevedo 2013 (DLX) 1.22 [0.53 , 2.81]
Diez-Quevedo 2013 (VEN) 1.02 [0.46 , 2.26]
Diez-Quevedo 2013 (ESC) 0.70 [0.42 , 1.16]
Diez-Quevedo 2013 (CIT) 0.75 [0.54 , 1.04]
Diez-Quevedo 2013 (SRT) 1.02 [0.71 , 1.47]
Diez-Quevedo 2013 (PRX) 0.85 [0.56 , 1.29]
Diez-Quevedo 2013 (FLX) 1.66 [1.13 , 2.44]
Krantz 2009 1.21 [0.42 , 3.48]
Taylor 2005 (Other ADM) 0.64 [0.34 , 1.21]
Taylor 2005 (SRT) 0.59 [0.37 , 0.95]
Balogun 2012 1.05 [0.98 , 1.11]
General population
Smoller 2009 (Multiple/Other ADM) 1.36 [0.99 , 1.86]
Smoller 2009 (TCA) 1.67 [1.33 , 2.09]
Smoller 2009 (SSRI) 1.32 [1.10 , 1.59]
Coupland 2011 (TRZ) 1.81 [1.59 , 2.07]
Coupland 2011 (VEN) 1.65 [1.50 , 1.82]
Coupland 2011 (MIR) 1.75 [1.61 , 1.90]
Coupland 2011 (SRT) 1.47 [1.35 , 1.61]
Coupland 2011 (PRX) 1.24 [1.14 , 1.35]
Coupland 2011 (FLX) 1.65 [1.55 , 1.76]
Coupland 2011 (ESC) 1.44 [1.25 , 1.65]
Coupland 2011 (CIT) 1.54 [1.46 , 1.63]
Coupland 2011 (LFP) 1.50 [1.34 , 1.68]
Coupland 2011 (DSP) 1.02 [0.93 , 1.12]
Coupland 2011 (AMI) 1.09 [1.01 , 1.17]
Almeida 2010 (Other ADM, DEP) 1.74 [0.78 , 3.86]
Almeida 2010 (TCA, DEP) 1.05 [0.47 , 2.37]
Almeida 2010 (SSRI/SNRI, DEP) 1.94 [1.02 , 3.71]
Almeida 2010 (Other ADM, no DEP) 0.86 [0.35 , 2.12]
Almeida 2010 (TCA, no DEP) 1.26 [0.83 , 1.91]
Almeida 2010 (SSRI/SNRI, no DEP) 1.14 [0.73 , 1.78]
Ryan 2008 (F, severe DEP) 0.44 [0.23 , 0.87]
Ryan 2008 (F, mild DEP) 1.43 [0.47 , 4.36]
Ryan 2008 (F, no DEP) 1.50 [0.79 , 2.86]
Ryan 2008 (M, severe DEP) 2.94 [1.19 , 7.27]
Ryan 2008 (M, mild DEP) 2.15 [0.71 , 6.50]
Ryan 2008 (M, no DEP) 1.30 [0.61 , 2.76]
Hamer 2011 (Other ADM) 1.40 [0.85 , 2.31]
Hamer 2011 (SSRI) 0.82 [0.54 , 1.24]
Hamer 2011 (TCA) 1.09 [0.80 , 1.49]
Khan 2013 (HCA/Other ADM) 1.97 [0.99 , 3.95]
Khan 2013 (SSRI/SNRI) 0.96 [0.51 , 1.82]
Cardiovascular patients 0.90 [0.76, 1.07]
General population 1.33 [1.14, 1.55]
Overall 1.09 [0.92, 1.29]
0.10 0.20 0.50 1.00 2.00 5.00 10.00
Hazard ratio

Diagnostics

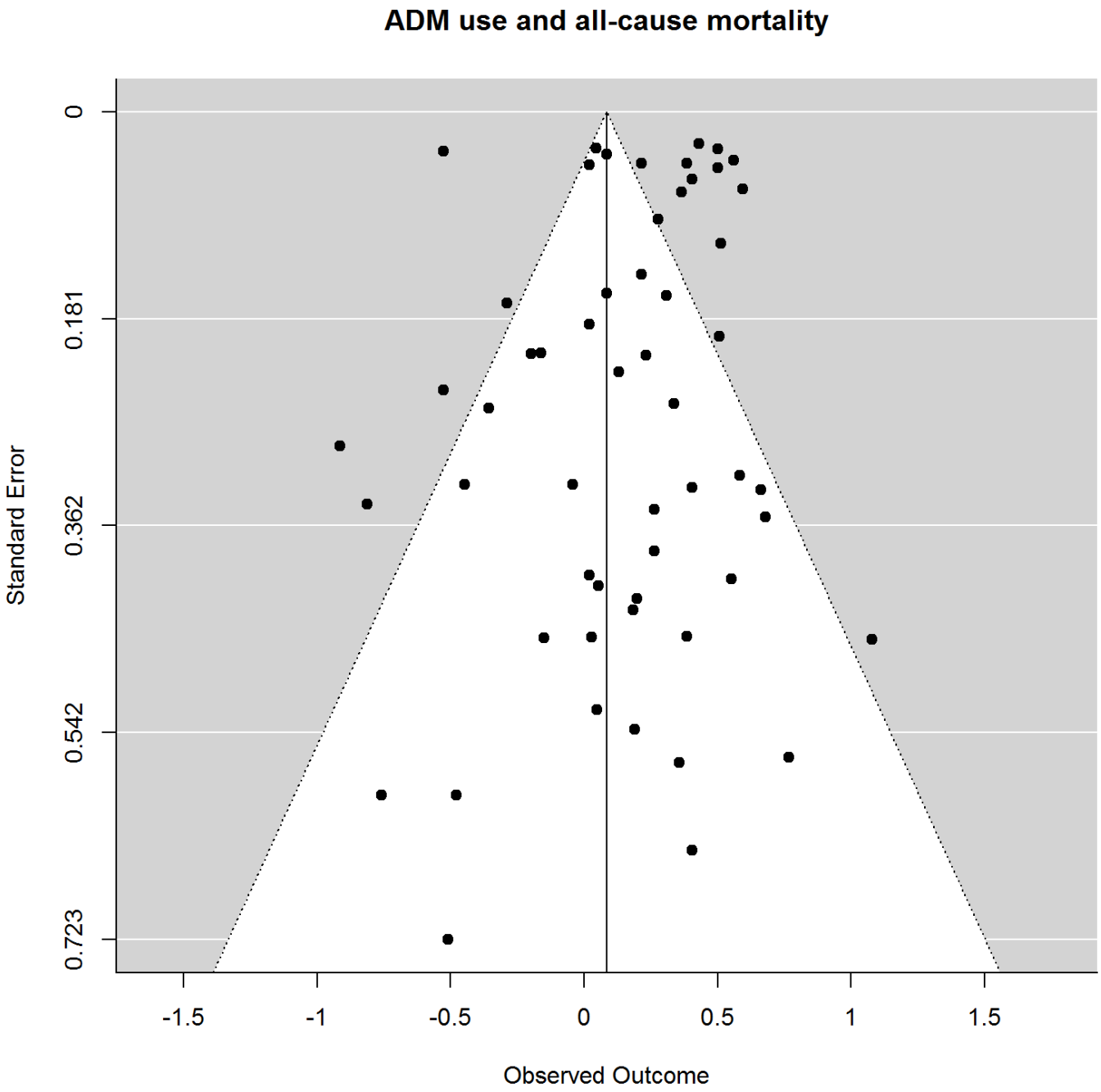
```
plot(ADMresult_2, id.n=6)
```



Here the fitted-vs-residual plot is completely boring since we only have a single category for this model (no modifiers). The Q-Q plot isn't perfect, but it's reasonable.

Funnel plot

```
funnel(ADMresult_2, main= "ADM use and all-cause mortality")
```



Cardiovascular events

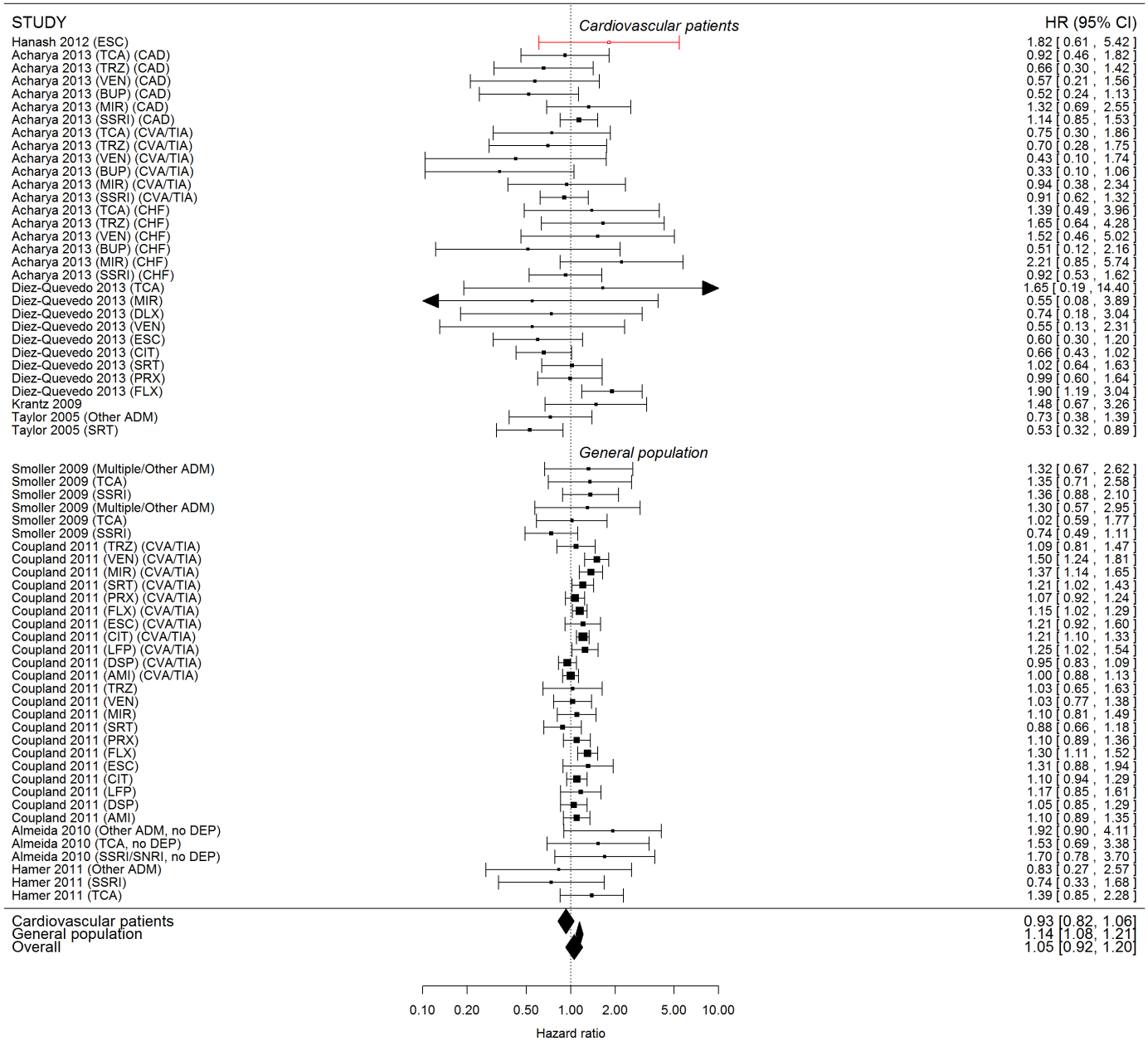
Studies with statistics presented for use of any antidepressant (i.e., using only studies that have “Any ADM” or “Depression and ADM use” in the `Notes` column)

```
(ADMresult_8 <- CVErma.fun(data=dd4A))
```

```
##
## Multivariate Meta-Analysis Model (k = 65; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0167  0.1292      9     no  REFERENCE
## sigma^2.2  0.0081  0.0899     65     no         id
##
## Test for Heterogeneity:
## Q(df = 64) = 95.1033, p-val = 0.0070
##
## I(df = 64) = 32.7048
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##   0.0534   0.0677   0.7893   0.4299  -0.0793   0.1862
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

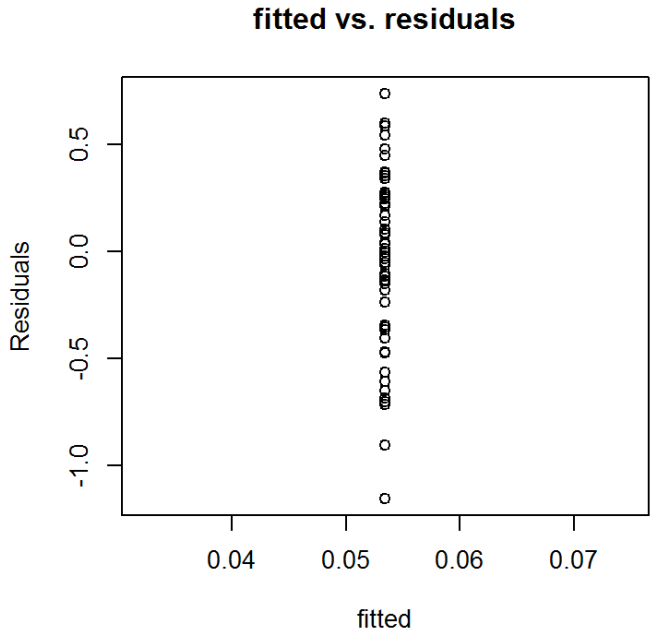
Forest plot

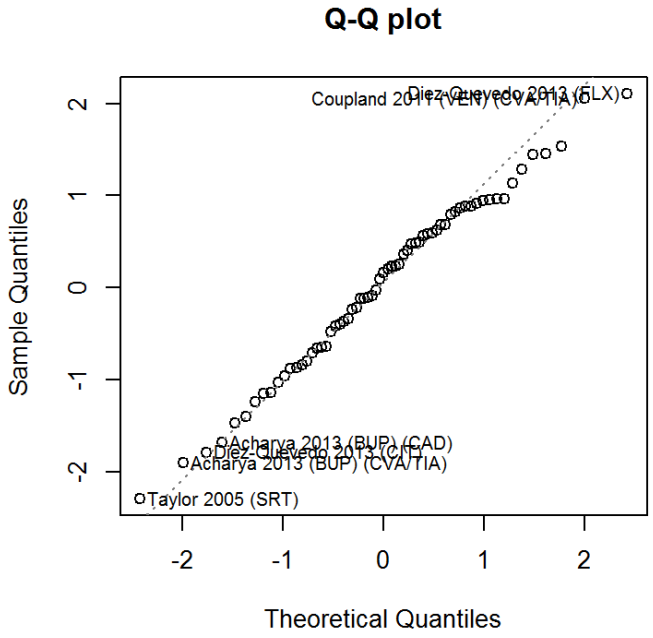
```
ffun(ADMresult_9B,dd4A,mod="SAMPLE",
     fullfit=ADMresult_8)
```

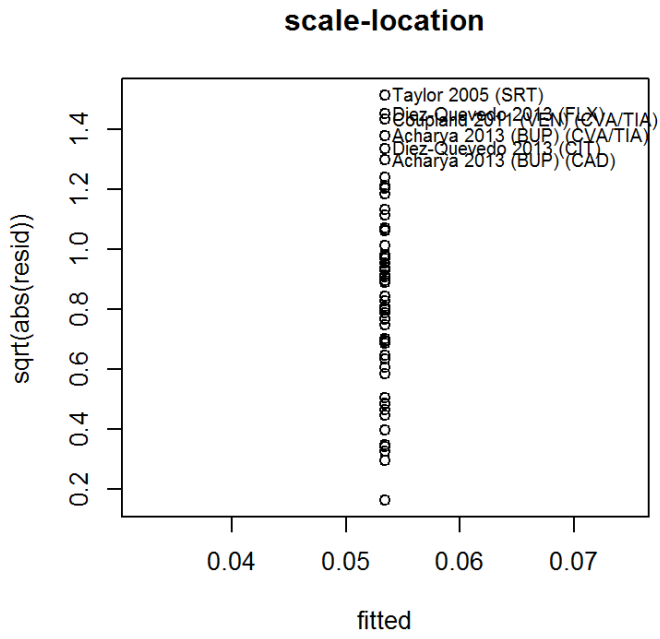


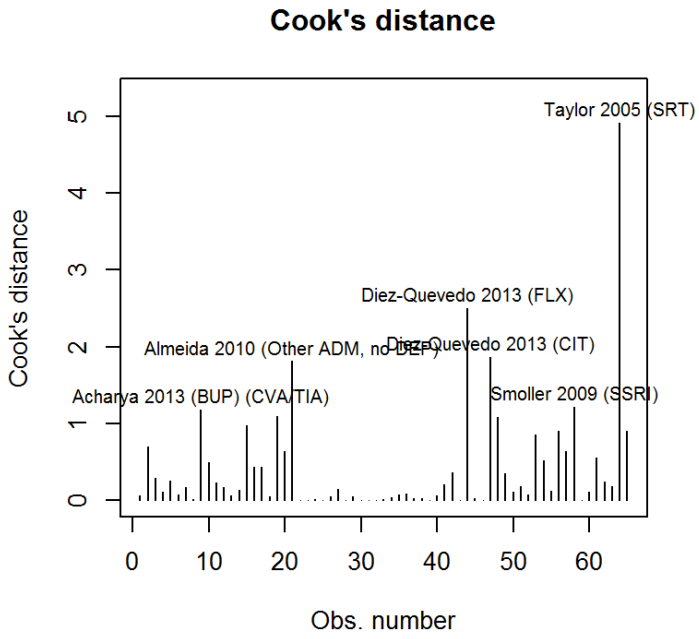
Diagnostics

```
plot(ADMresult_8, id.n=6)
```



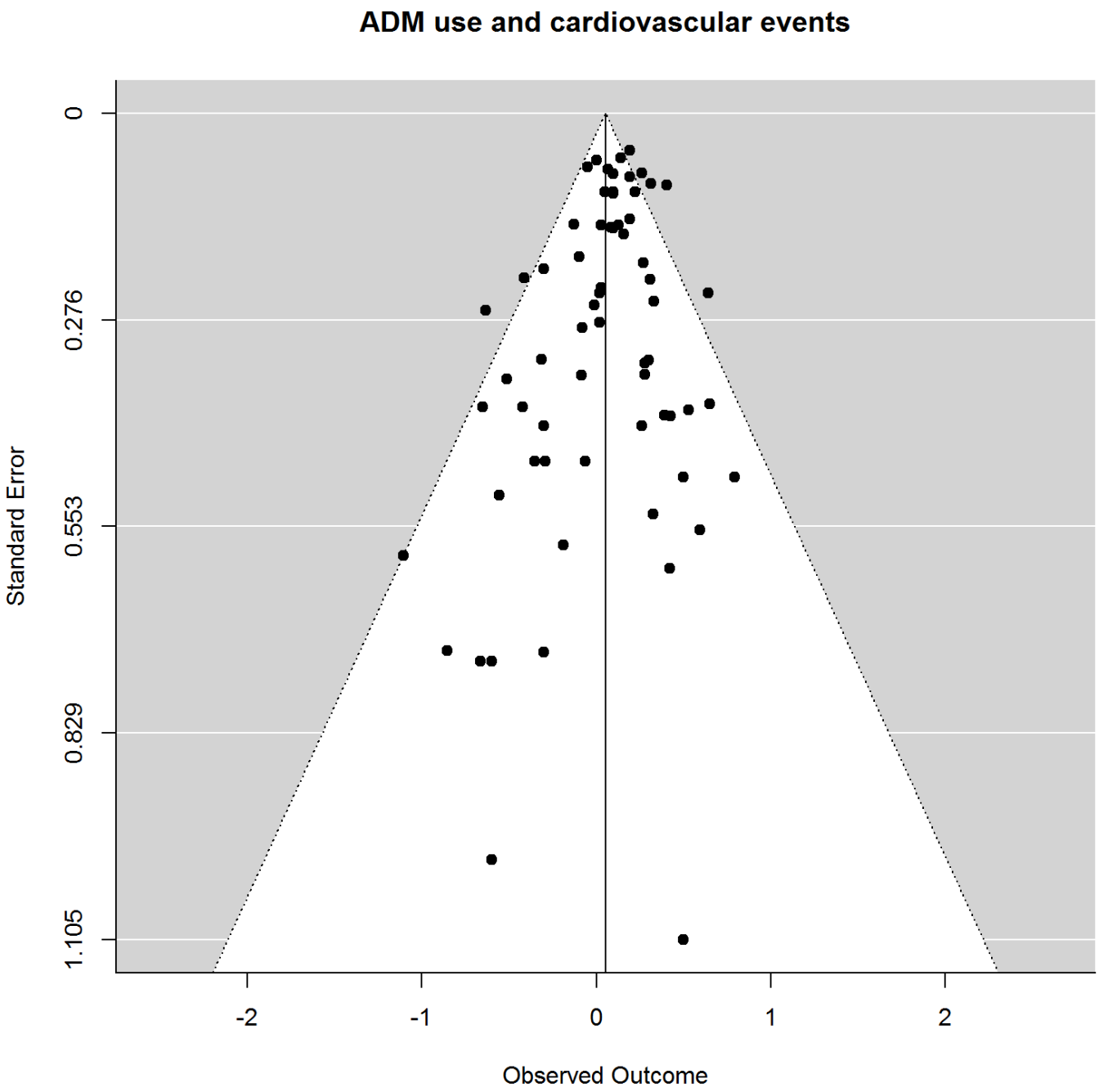






Funnel plot

```
funnel(ADMresult_8, main= "ADM use and cardiovascular events")
```



B6: Meta-analysis of studies controlling for premedication depression

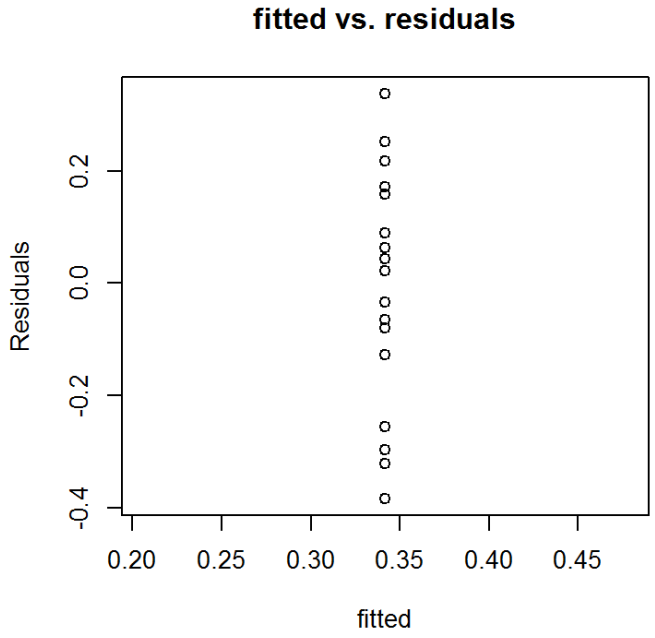
All-cause mortality

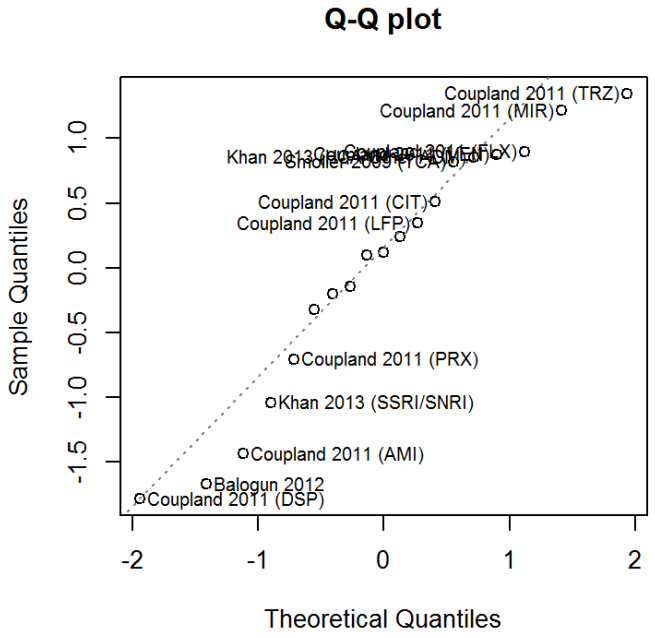
```
(ADMresult_6 <- ACMrma.fun(data=dd3E))
```

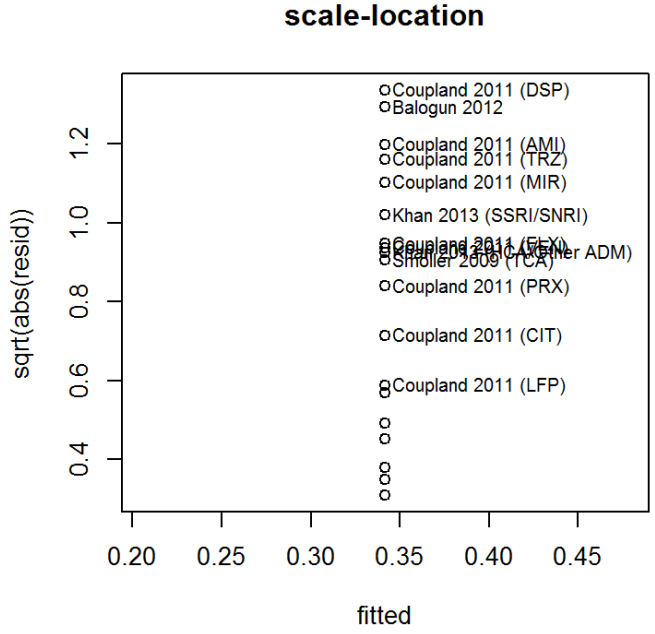
```
##
## Multivariate Meta-Analysis Model (k = 19; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      6     no  REFERENCE
## sigma^2.2  0.0327  0.1807     19     no         id
##
## Test for Heterogeneity:
## Q(df = 18) = 280.6046, p-val < .0001
##
## I(df = 18) = 93.5853
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##   0.3419   0.0483   7.0798   <.0001   0.2472   0.4365      ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

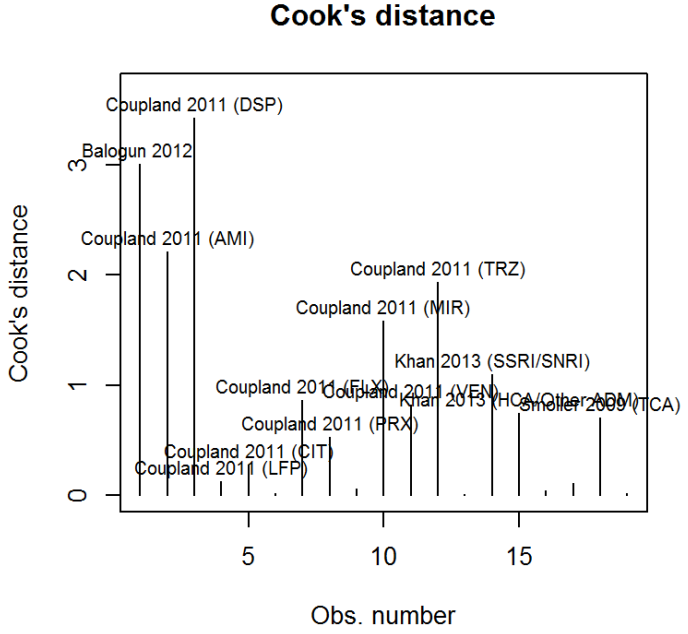
Diagnostics

```
plot(ADMresult_6,id.n=13)
```



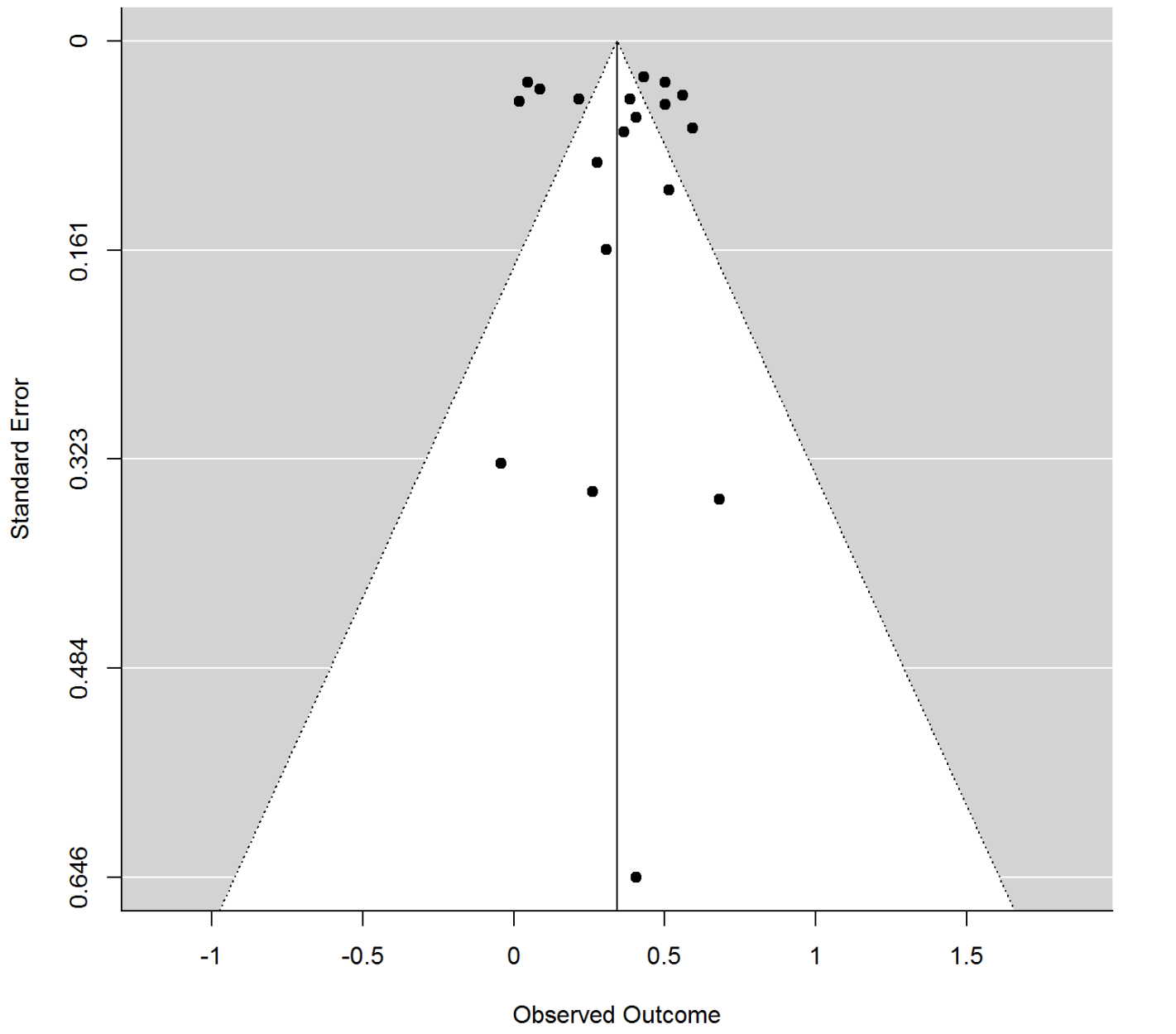






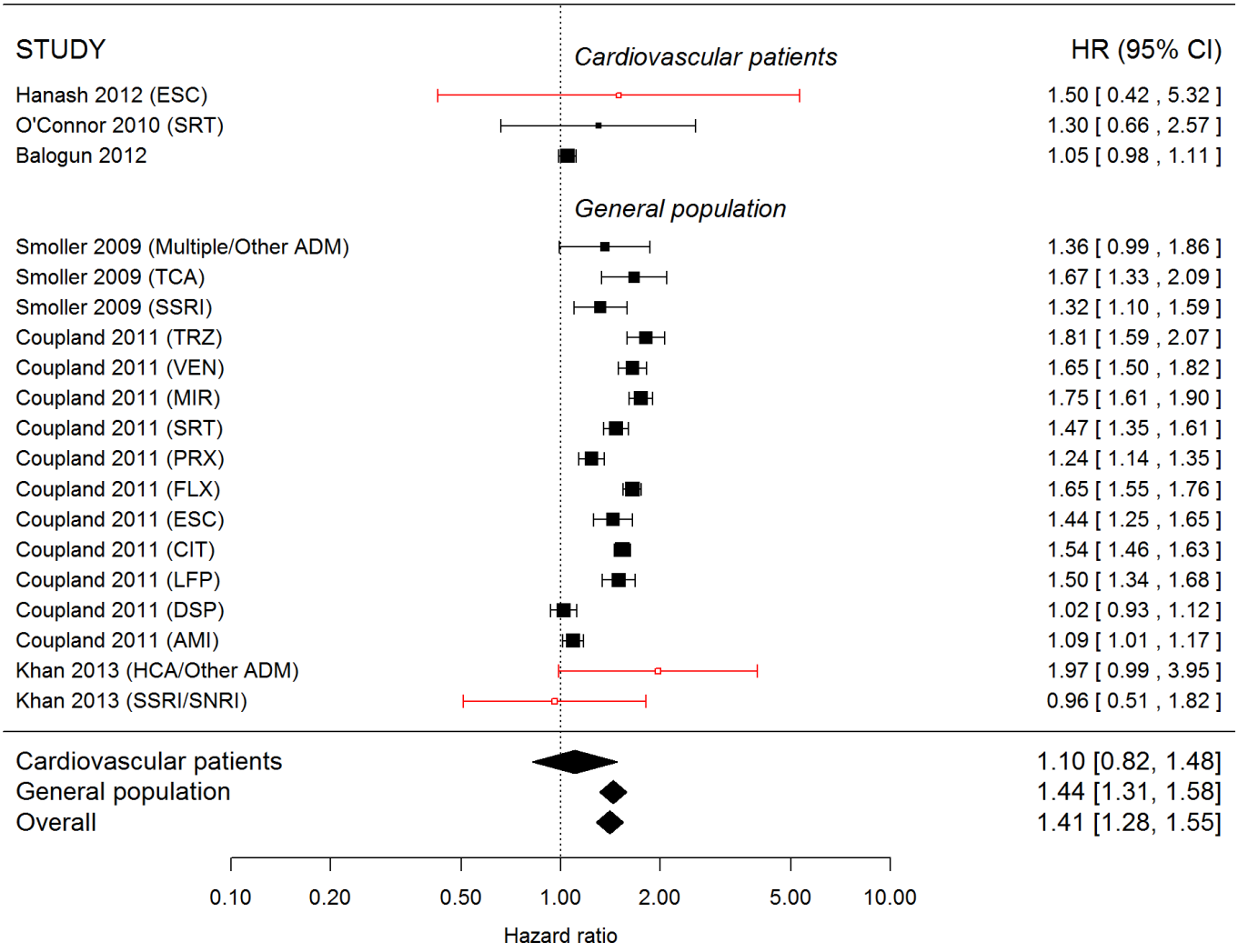
Funnel plot

```
funnel(ADMresult_6, main= "Mortality effects of ADMs in studies that control for
 pre-medication depressive symptoms")
```



Forest plot

```
ffun(ADMresult_7B,dd3E,mod="SAMPLE",
     fullfit=ADMresult_6)
```



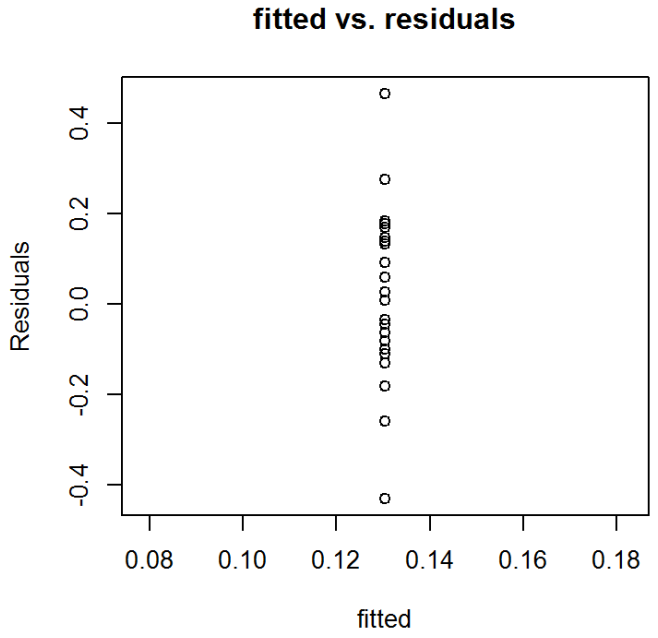
Cardiovascular events

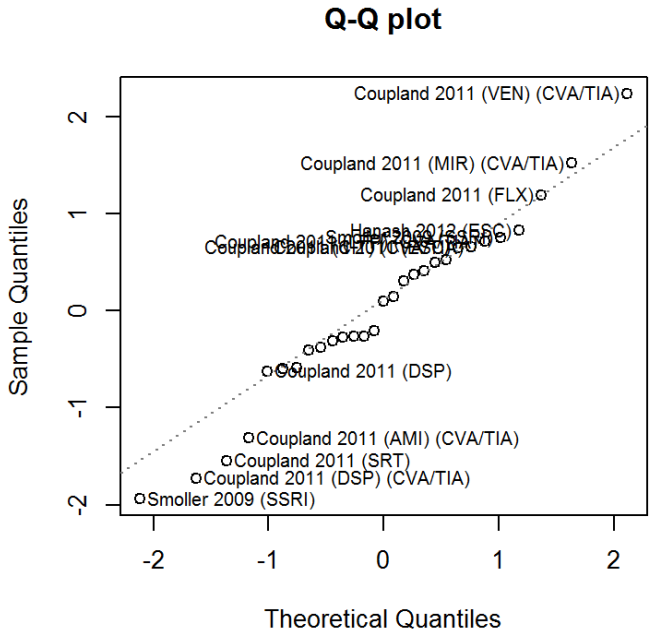
```
(ADMresult_11 <- CVErma.fun(data=dd4E))
```

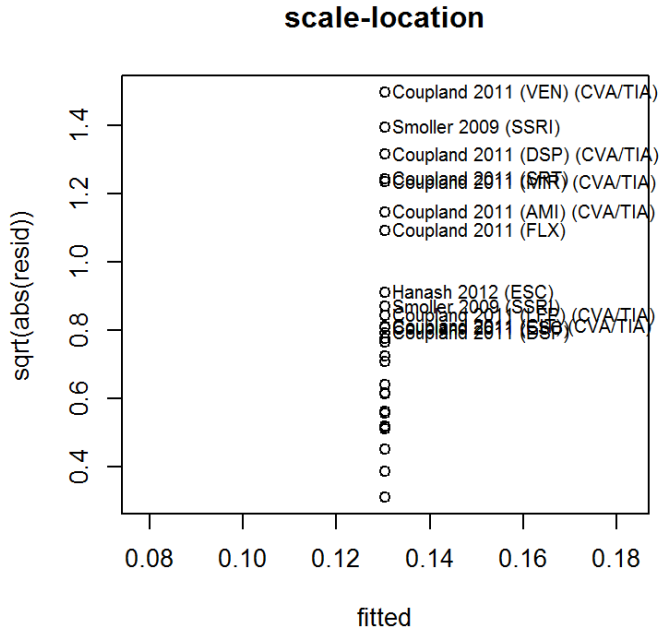
```
##
## Multivariate Meta-Analysis Model (k = 29; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      3     no  REFERENCE
## sigma^2.2  0.0066  0.0815     29     no         id
##
## Test for Heterogeneity:
## Q(df = 28) = 40.8007, p-val = 0.0560
##
## I(df = 28) = 31.3737
##
## Model Results:
##
## estimate       se     zval     pval    ci.lb    ci.ub
##   0.1305   0.0271   4.8129   <.0001   0.0773   0.1836      ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

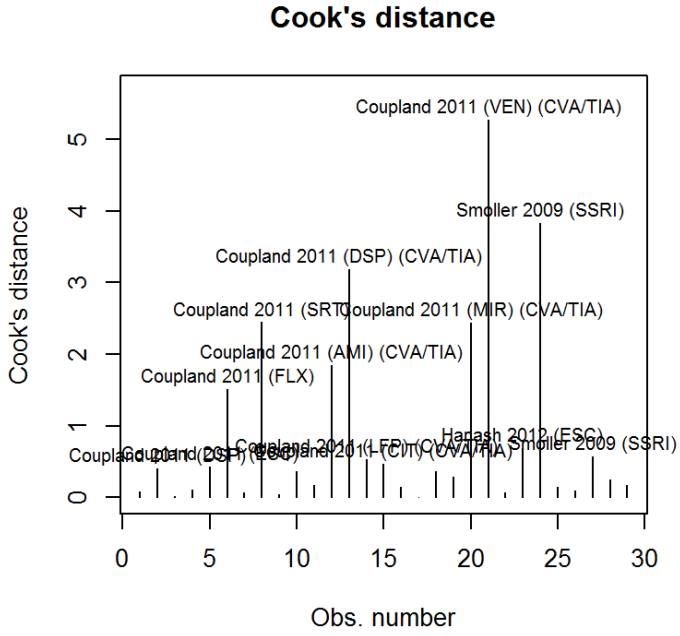
Diagnostics

```
plot(ADMresult_11,id.n=13)
```



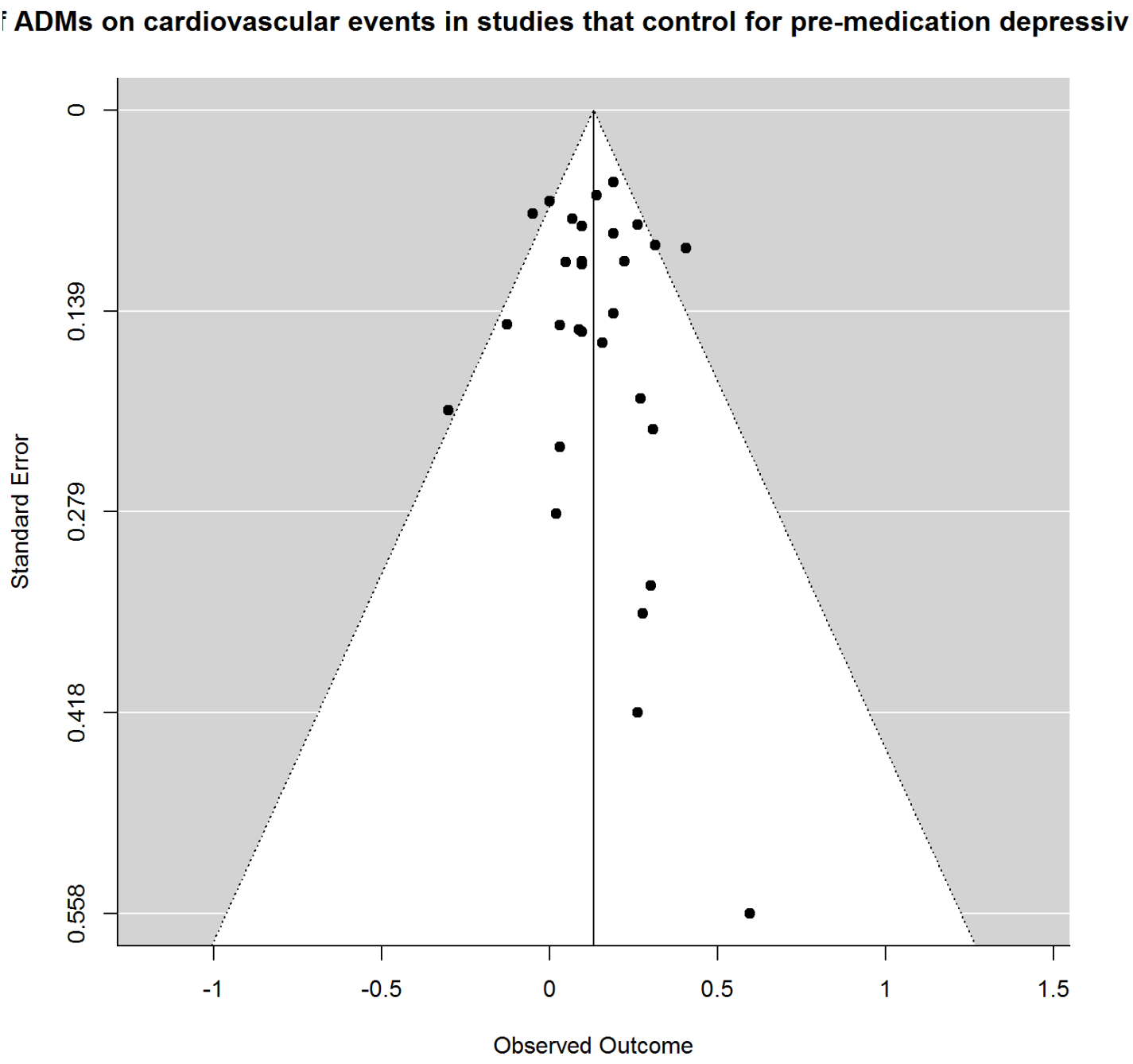






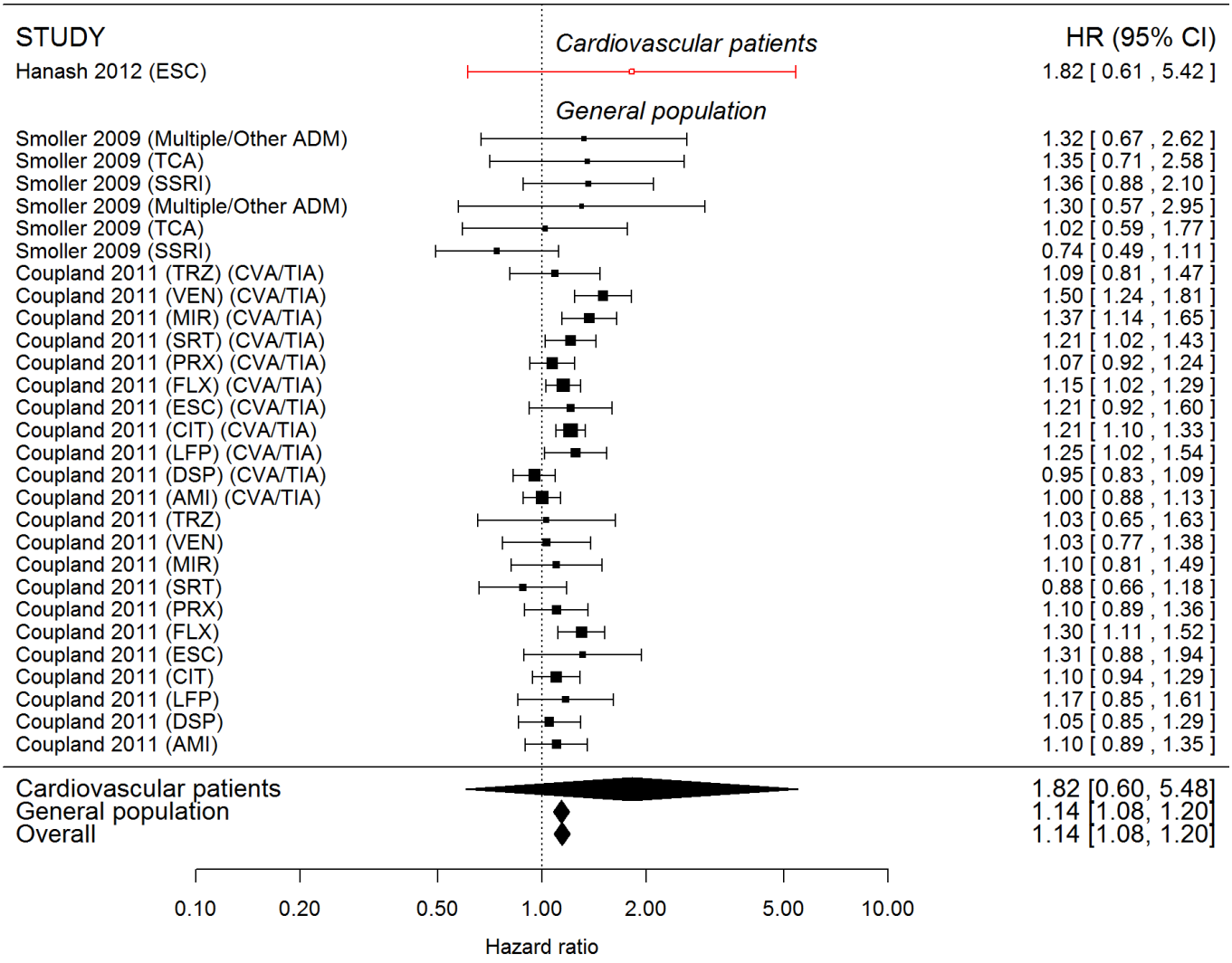
Funnel plot

```
funnel(ADMresult_11, main= "Effect of ADMs on cardiovascular events in studies t
hat control for pre-medication depressive symptoms")
```



Forest plot

```
ffun(ADMresult_12B,dd4E,mod="SAMPLE",
     fullfit=ADMresult_11)
```



B7: Meta-analysis testing an interaction between ADM class and sample type

All-cause mortality

```
(ADMresult_3C <- ACMrma.fun(mods = ~DRUG.TYPE*SAMPLE, data=dd3B))
```

```
##
## Multivariate Meta-Analysis Model (k = 43; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0279  0.1672     11     no  REFERENCE
## sigma^2.2  0.0220  0.1483     43     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 37) = 120.3500, p-val < .0001
##
## I(df = 37) = 69.2563
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 13.2821, p-val = 0.0209
##
## Model Results:
##
##                                           estimate      se     zval
## intrcpt                                    -0.1692  0.3928  -0.4307
## DRUG.TYPESSRI/SNRI                          0.0174  0.3914   0.0445
## DRUG.TYPEOther                              0.1490  0.4382   0.3401
## SAMPLEGeneral population                    0.3250  0.4088   0.7949
## DRUG.TYPESSRI/SNRI:SAMPLEGeneral population  0.1061  0.4020   0.2639
## DRUG.TYPEOther:SAMPLEGeneral population      0.1606  0.4555   0.3526
##                                             pval    ci.lb   ci.ub
## intrcpt                                   0.6667  -0.9391  0.6007
## DRUG.TYPESSRI/SNRI                        0.9645  -0.7497  0.7846
## DRUG.TYPEOther                            0.7338  -0.7099  1.0080
## SAMPLEGeneral population                  0.4267  -0.4763  1.1263
## DRUG.TYPESSRI/SNRI:SAMPLEGeneral population  0.7919  -0.6818  0.8940
## DRUG.TYPEOther:SAMPLEGeneral population      0.7244  -0.7321  1.0532
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(anova(ADMresult_3C, btt=c(5,6)))
```

```
##
## Test of Moderators (coefficient(s) 5,6):
## QM(df = 2) = 0.1260, p-val = 0.9390
```

Cardiovascular events

```
dd4A <- subset(dd2, grepl("ADM", NOTE) & logCVEHR != "NA")
## order by REFERENCE: see note below with forest.addcat
dd4A <- arrange(dd4A,REFERENCE)
nrow(dd4A)
```

```
## [1] 65
```

```
dd4B <- transform(subset(dd4A,!DRUG.TYPE %in% c("ADM","Undifferentiated") &
                           logCVEHR != "NA"),
                  DRUG.TYPE=factor(DRUG.TYPE,
                                   levels=c("TCA",
                                            "SSRI/SNRI",
                                            "Other")),
                  SAMPLE = factor (SAMPLE,
                                   levels=c("Cardiovascular patients",
                        "General population")))
dd4B <- arrange(dd4B,REFERENCE)

nrow(dd4B)
```

```
## [1] 62
```

```
(ADMresult_10C <- CVErma.fun(mods = ~DRUG.TYPE*SAMPLE, data=dd4B))
```

```
##
## Multivariate Meta-Analysis Model (k = 62; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      8     no  REFERENCE
## sigma^2.2  0.0058  0.0761     62     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 56) = 75.2634, p-val = 0.0439
##
## I(df = 56) = 25.5947
##
## Test of Moderators (coefficient(s) 2,3,4,5,6):
## QM(df = 5) = 12.6025, p-val = 0.0274
##
## Model Results:
##
##                                           estimate      se     zval
## intrcpt                                    -0.0281  0.2461  -0.1144
## DRUG.TYPESSRI/SNRI                         -0.0347  0.2578  -0.1347
## DRUG.TYPEOther                             -0.1347  0.2821  -0.4775
## SAMPLEGeneral population                    0.1006  0.2506   0.4013
## DRUG.TYPESSRI/SNRI:SAMPLEGeneral population  0.1146  0.2643   0.4335
## DRUG.TYPEOther:SAMPLEGeneral population      0.2582  0.2966   0.8707
##                                             pval    ci.lb   ci.ub
## intrcpt                                   0.9089  -0.5105  0.4542
## DRUG.TYPESSRI/SNRI                        0.8928  -0.5399  0.4705
## DRUG.TYPEOther                            0.6330  -0.6875  0.4181
## SAMPLEGeneral population                  0.6882  -0.3906  0.5918
## DRUG.TYPESSRI/SNRI:SAMPLEGeneral population  0.6647  -0.4034  0.6326
## DRUG.TYPEOther:SAMPLEGeneral population      0.3839  -0.3230  0.8394
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(anova(ADMresult_10C, btt=c(5,6)))
```

```
##
## Test of Moderators (coefficient(s) 5,6):
## QM(df = 2) = 0.9534, p-val = 0.6208
```

B8: Meta-analysis of sample type and ADM class as moderators (additive model)

All-cause mortality

```
(ADMresult_3B <- ACMrma.fun(mods = ~SAMPLE+DRUG.TYPE, data=dd3B))
```

```
##
## Multivariate Meta-Analysis Model (k = 43; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0293  0.1713     11     no  REFERENCE
## sigma^2.2  0.0211  0.1452     43     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 39) = 121.5487, p-val < .0001
##
## I(df = 39) = 67.9141
##
## Test of Moderators (coefficient(s) 2,3,4):
## QM(df = 3) = 13.2733, p-val = 0.0041
##
## Model Results:
##
##                          estimate      se     zval    pval    ci.lb
## intrcpt                   -0.2771  0.1420  -1.9511  0.0510  -0.5555
## SAMPLEGeneral population   0.4346  0.1557   2.7914  0.0052   0.1295
## DRUG.TYPESSRI/SNRI         0.1212  0.0874   1.3867  0.1655  -0.0501
## DRUG.TYPEOther             0.2993  0.1152   2.5990  0.0094   0.0736
##                           ci.ub
## intrcpt                  0.0013   .
## SAMPLEGeneral population  0.7398  **
## DRUG.TYPESSRI/SNRI        0.2926
## DRUG.TYPEOther            0.5250  **
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(anova(ADMresult_3B, btt=c(2)))
```

```
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 7.7921, p-val = 0.0052
```

```
(anova(ADMresult_3B, btt=c(3,4)))
```

```
##
## Test of Moderators (coefficient(s) 3,4):
## QM(df = 2) = 6.7563, p-val = 0.0341
```

```
(anova(ADMresult_3B, L=c(0,0,1,-1)))
```

```
##
## Hypothesis:
## 1: DRUG.TYPESSRI/SNRI - DRUG.TYPEOther = 0
##
## Results:
##    estimate     se    zval   pval
## 1:  -0.1781 0.1021 -1.7432 0.0813
##
## Test of Hypothesis:
## QM(df = 1) = 3.0388, p-val = 0.0813
```

```
#Cardiovascular samples:
(predict(ADMresult_3B, newmods=rbind(c(0,0,0), c(0,1,0), c(0,0,1))))
```

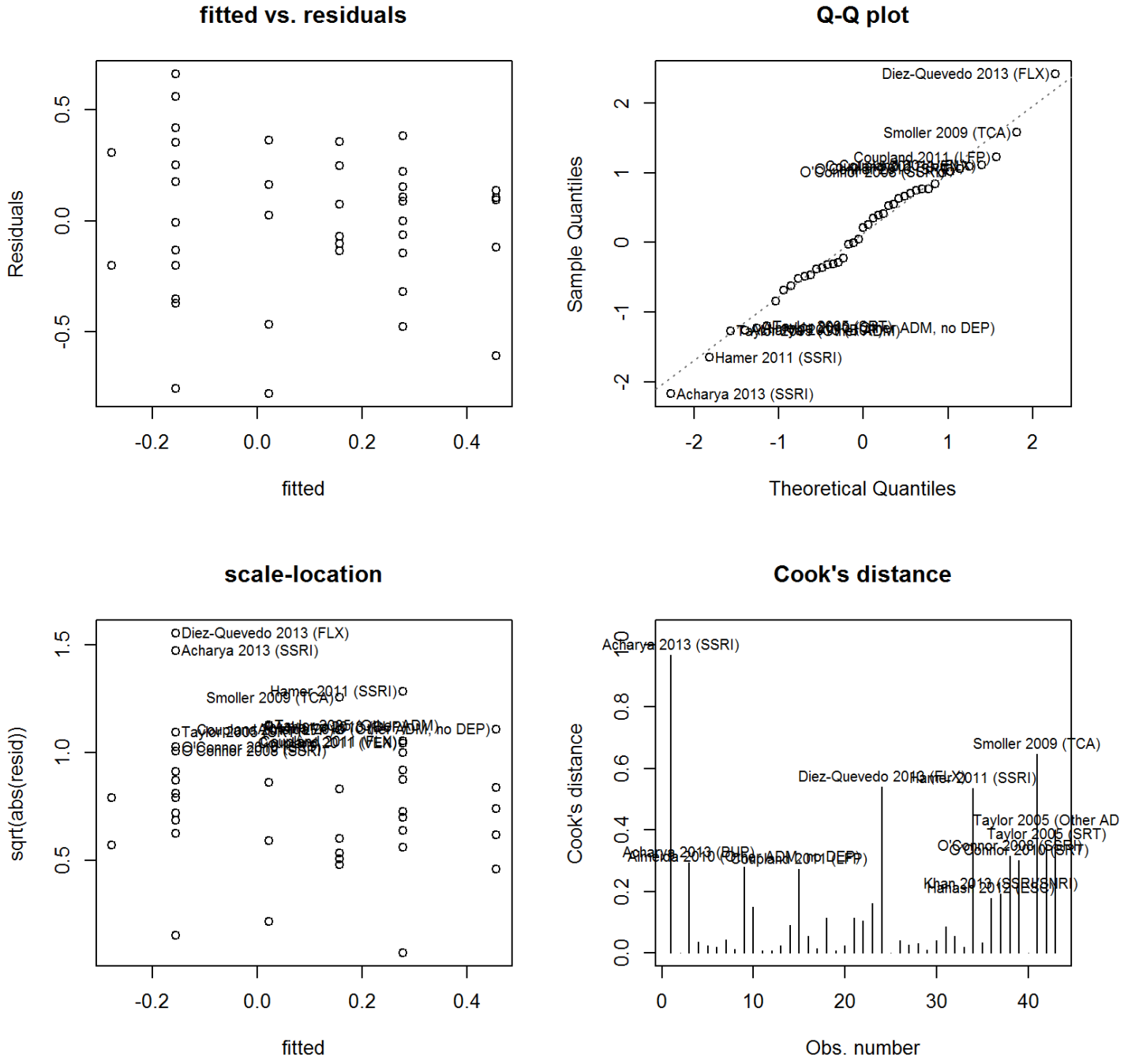
```
##      pred     se   ci.lb  ci.ub   cr.lb  cr.ub
## 1 -0.2771 0.1420 -0.5555 0.0013 -0.7979 0.2436
## 2 -0.1559 0.1178 -0.3868 0.0750 -0.6529 0.3411
## 3  0.0221 0.1438 -0.2596 0.3039 -0.5005 0.5447
```

```
#General population samples:
(predict(ADMresult_3B, newmods=rbind(c(1,0,0), c(1,0,1), c(1,1,0))))
```

```
##     pred     se   ci.lb  ci.ub   cr.lb  cr.ub
## 1 0.1575 0.1134 -0.0648 0.3797 -0.3356 0.6505
## 2 0.4568 0.1308  0.2003 0.7132 -0.0526 0.9661
## 3 0.2787 0.1066  0.0698 0.4876 -0.2085 0.7659
```

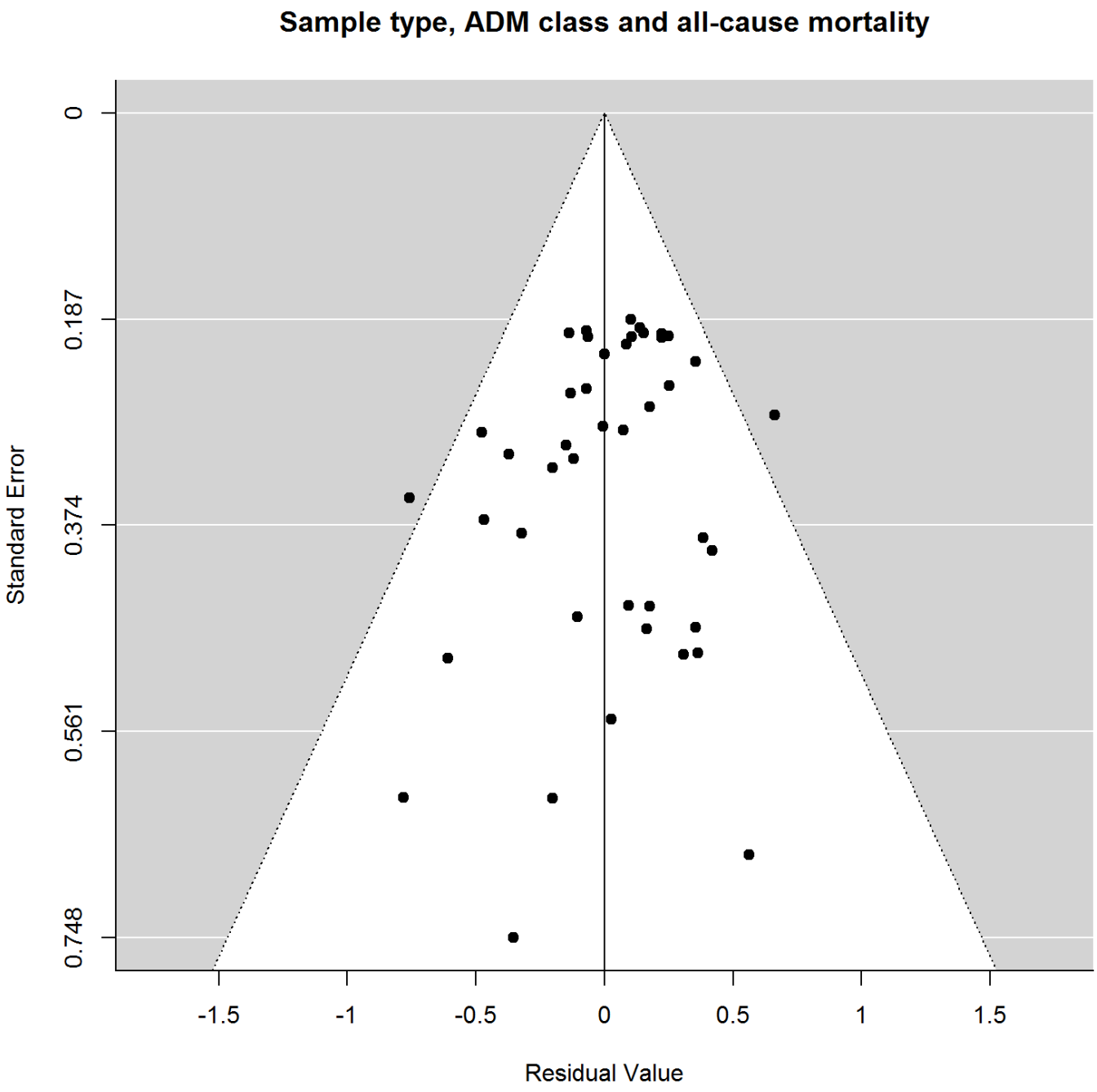
Diagnostics

```
plot(ADMresult_3B,id.n=13)
```



Funnel plot

```
funnel(ADMresult_3B, main= "Sample type, ADM class and all-cause mortality")
```



Cardiovascular events

```
(ADMresult_10B <- CVErma.fun(mods = ~SAMPLE+DRUG.TYPE, data=dd4B))
```

```
##
## Multivariate Meta-Analysis Model (k = 62; method: REML)
##
## Variance Components:
##
##             estim    sqrt  nlvls  fixed     factor
## sigma^2.1  0.0000  0.0000      8     no  REFERENCE
## sigma^2.2  0.0060  0.0774     62     no         id
##
## Test for Residual Heterogeneity:
## QE(df = 58) = 76.5686, p-val = 0.0517
##
## I(df = 58) = 24.2509
##
## Test of Moderators (coefficient(s) 2,3,4):
## QM(df = 3) = 11.5570, p-val = 0.0091
##
## Model Results:
##
##                           estimate      se     zval    pval    ci.lb
## intrcpt                    -0.1570  0.0832  -1.8879  0.0590  -0.3201
## SAMPLEGeneral population    0.2348  0.0713   3.2948  0.0010   0.0951
## DRUG.TYPESSRI/SNRI          0.0776  0.0572   1.3567  0.1749  -0.0345
## DRUG.TYPEOther              0.0875  0.0842   1.0382  0.2992  -0.0776
##                            ci.ub
## intrcpt                   0.0060    .
## SAMPLEGeneral population  0.3745  ***
## DRUG.TYPESSRI/SNRI        0.1896
## DRUG.TYPEOther            0.2526
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(anova(ADMresult_10B, btt=c(2)))
```

```
##
## Test of Moderators (coefficient(s) 2):
## QM(df = 1) = 10.8559, p-val = 0.0010
```

```
(anova(ADMresult_10B, btt=c(3,4)))
```

```
##
## Test of Moderators (coefficient(s) 3,4):
## QM(df = 2) = 2.0287, p-val = 0.3626
```

```
(anova(ADMresult_10B, L=c(0,0,1,-1)))
```

```
##
## Hypothesis:
## 1: DRUG.TYPESSRI/SNRI - DRUG.TYPEOther = 0
##
## Results:
##    estimate     se    zval   pval
## 1:  -0.0099 0.0754 -0.1311 0.8957
##
## Test of Hypothesis:
## QM(df = 1) = 0.0172, p-val = 0.8957
```

```
#Cardiovascular samples:
(predict(ADMresult_10B, newmods=rbind(c(0,0,0), c(0,1,0), c(0,0,1))))
```

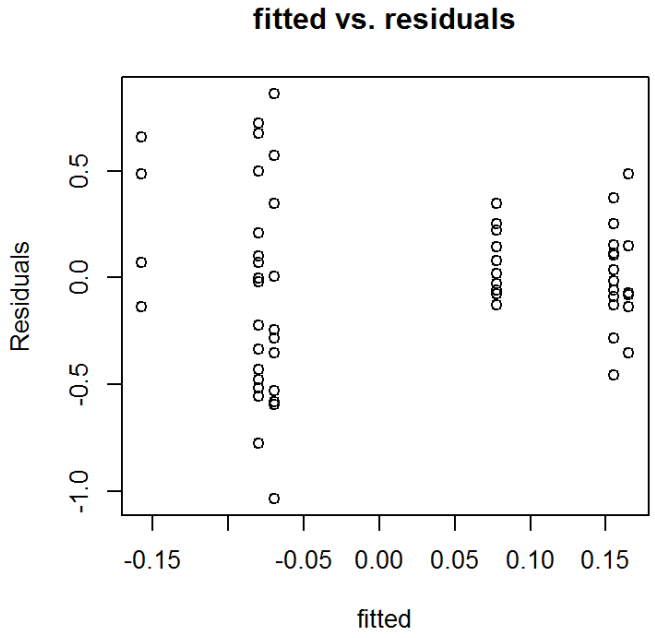
```
##      pred     se   ci.lb  ci.ub   cr.lb  cr.ub
## 1 -0.1570 0.0832 -0.3201 0.0060 -0.3797 0.0657
## 2 -0.0795 0.0672 -0.2111 0.0522 -0.2803 0.1214
## 3 -0.0696 0.0870 -0.2400 0.1009 -0.2978 0.1586
```

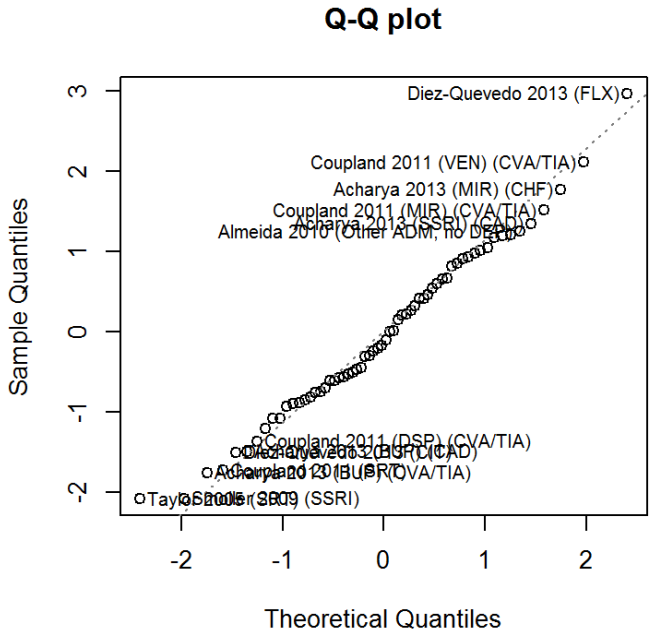
```
#General population samples:
(predict(ADMresult_10B, newmods=rbind(c(1,0,0), c(1,0,1), c(1,1,0))))
```

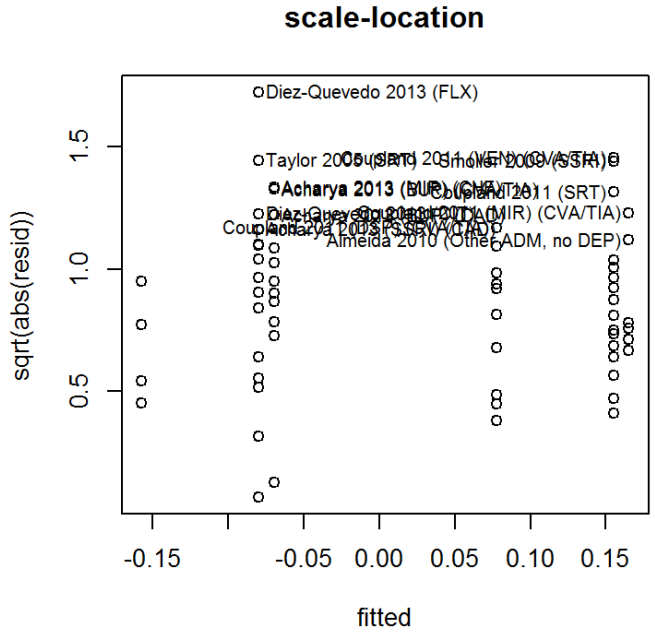
```
##     pred     se   ci.lb  ci.ub   cr.lb  cr.ub
## 1 0.0778 0.0470 -0.0143 0.1699 -0.0997 0.2553
## 2 0.1653 0.0706  0.0270 0.3035 -0.0400 0.3705
## 3 0.1554 0.0335  0.0897 0.2210 -0.0099 0.3207
```

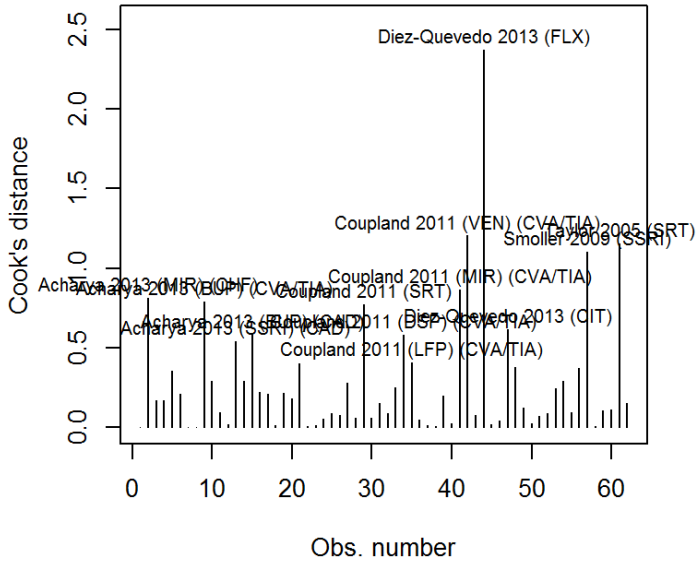
Diagnostics

```
plot(ADMresult_10B,id.n=13)
```



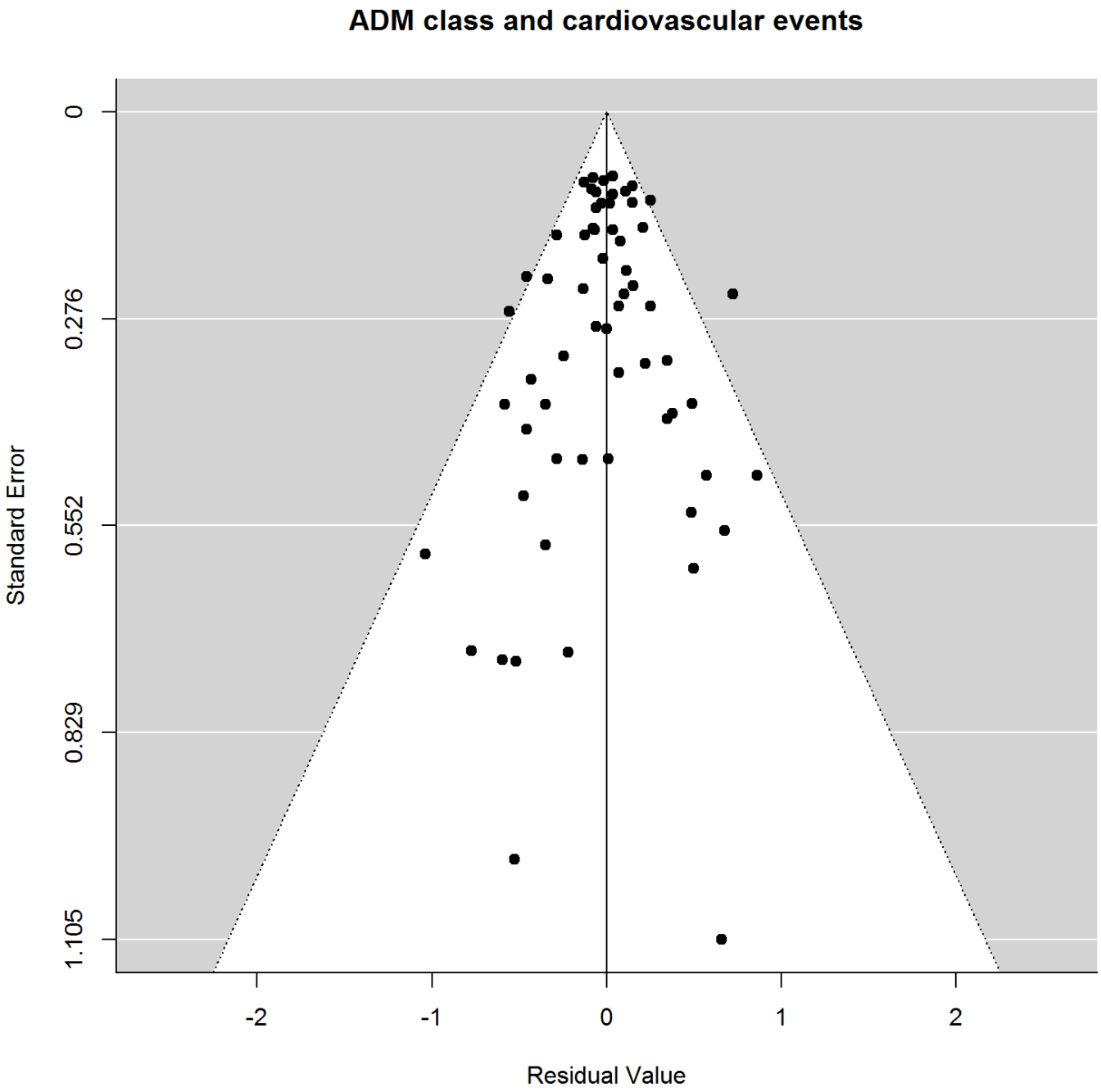






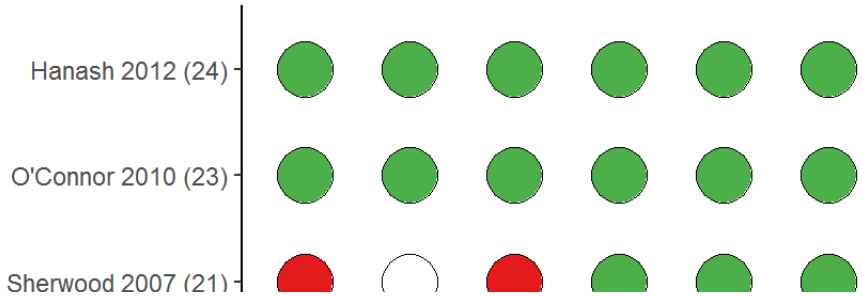
Funnel plot

```
funnel(ADMresult_10B, main= "ADM class and cardiovascular events")
```



Bias scoring

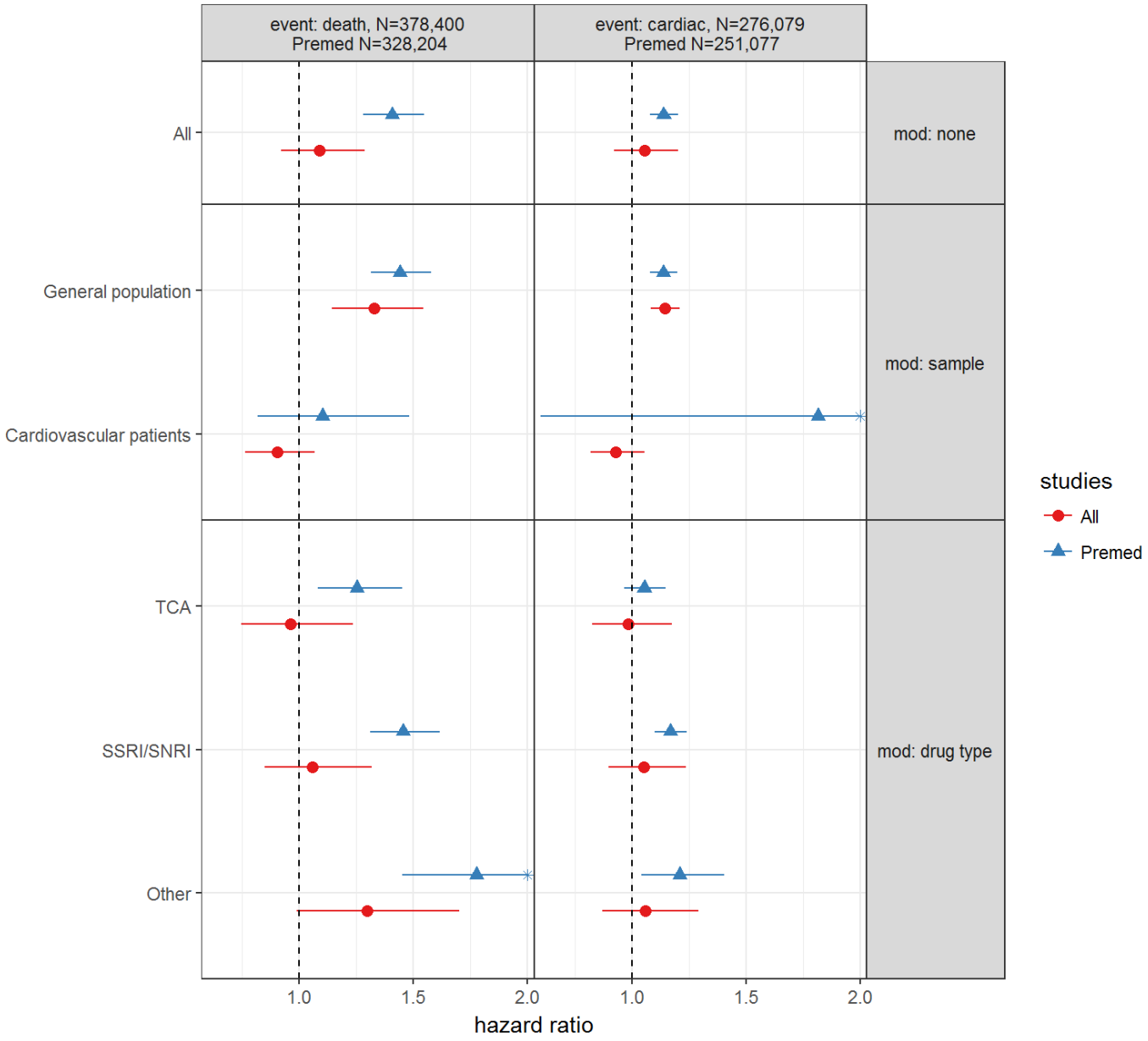
Y-axis labels indicate the reference, with the corresponding Downs and Black (1998) score in parentheses.




```
save(list=ls(pattern="ADM|dd3"),file="MA_results.rda")
```

Effects plot (Table 1)

```
## Warning: Removed 2 rows containing missing values (geom_point).
```




```
## Warning: Removed 2 rows containing missing values (geom_point).
```

References

Baetschmann, Gregori, and Rainer Winkelmann. 2013. “Modeling Zero-Inflated Count Data When Exposure Varies: With an Application to Tumor Counts.” *Biometrical Journal* 55 (5): 679–86. doi:10.1002/bimj.201200021 (https://doi.org/10.1002/bimj.201200021).

Downs, S. H., and N. Black. 1998. “The Feasibility of Creating a Checklist for the Assessment of the Methodological Quality Both of Randomised and Non-Randomised Studies of Health Care Interventions.” *J Epidemiol Community Health* 52: 377–84. doi:10.1136/jech.52.6.377

(https://doi.org/10.1136/jech.52.6.377).

Harney, Ewan, Tom J. M. Van Dooren, Steve Paterson, and Stewart J. Plaistow. 2013. “How to Measure Maturation: A Comparison of Probabilistic Methods Used to Test for Genotypic Variation and Plasticity in the Decision to Mature.” *Evolution* 67 (2): 525–38. doi:10.1111/j.1558-5646.2012.01758.x (https://doi.org/10.1111/j.1558-5646.2012.01758.x).

Higgins, Julian PT, Simon G. Thompson, Jonathan J. Deeks, and Douglas G. Altman. 2003. “Measuring Inconsistency in Meta-Analyses.” *BMJ: British Medical Journal* 327 (7414): 557. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/ (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC192859/).

Viechtbauer, Wolfgang. 2010. “Conducting Meta-Analyses in R with the metafor Package.” *Journal of Statistical Software* 36 (3): 1–48. http://www.jstatsoft.org/v36/i03/ (http://www.jstatsoft.org/v36/i03/).

SUPPLEMENT C
The list of covariates used in each study

Acharya et al., 2013:
We used crude death rates, because we were unable to obtain baseline odds that would have been adjusted for the following covariates:

age, sex, BMI, smoking history, metabolic syndrome, hypertension, diabetes mellitus, CAD, CVA, TIA, and CHF, and use of aspirin, b-blockers, calcium channel blockers, clopidogrel, angiotensinconverting enzyme inhibitors or angiotensin receptor blockers, statins, thiazide diuretics, benzodiazepines, antidepressants, atypical antipsychotics

Since we were unable to adjust for these covariates when using the crude death rates, we also computed odds ratios from the crude rates and compared them to the adjusted odds ratios reported in Acharya et al., 2013. We found the unadjusted and adjusted odds ratios to be qualitatively similar, so we included the unadjusted HRs in the meta-analysis. The computation of odds ratios and the comparisons are in Section 4.2 of Appendix A.

Almeida et al., 2010:
age, depression (as assessed by the GDS-15), completion of high school, born overseas, smoking status, arthritis, cancer, cardiovascular disease, diabetes, hypertension, pulmonary disease, Charlson co-morbidity index

This study involved only men, so it was not possible to include sex as a covariate

Balogun et al., 2012:
age, sex, race, marital status, insurance status, geographic location, diabetes, hypertension, cardiovascular disease, congestive heart failure, cerebrovascular disease, liver disease, chronic lung disease, Charlson comorbidity index, eGFR (estimated glomerular filtration rate)

Coupland et al., 2011:
sex, age (five year bands), year, severity of depression, depression before age 65, smoking status, Townsend deprivation score, coronary heart disease, diabetes, hypertension, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, epilepsy/seizures, statins, non-steroidal anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, hypnotics/anxiolytics, stroke/transient ischaemic attack at baseline

Diez Quevedo et al., 2012:
depressive symptoms during the first year of follow-up, sex, age, months since heart failure diagnosis, left ventricular ejection fraction, New York Heart Association functional class, ischemic etiology, comorbidities (diabetes mellitus, COPD, peripheral vasculopathy), creatinine clearance by Cockcroft formul (CrC), BMI, and treatments with ACE inhibitors, Angiotensin II

Receptor or beta-blockers

Hamer et al., 2011:
age, sex, psychological distress (GHQ-12 $\geq$ 4), psychiatric continuous inpatient stays, socioeconomic group, marital status, physical activity, smoking, alcohol, BMI, cardiovascular disease medication, hypertension

Khan et al., 2013:
We obtained crude death rates from the authors. Because this study involved randomized controlled trials, we included it even though no covariates were included.

Krantz et al., 2009:
age, race, BMI, marital status, high school graduate, use of anxiolytics, combination medication use, coronary artery disease severity score, smoking history, diabetes history, hypertension history, non-fatal MI history, dyslipidemia history, current hormone therapy use, baseline BDI scores, baseline anxiety scores (assessed by the STAI)

Only women were included in this study, so it was not possible to include sex as a covariate.

O'Connor et al., 2008:
age, sex, race, marriage status, baseline ejection fraction, New York Heart Association class, ischemic cause of heart failure, depression

O'Connor et al., 2010:
This was a randomized, controlled trial, but we used a heart failure that was adjusted for site, since the trial was carried out in the three different treatment centers.

Qian et al., 2013:
age, sex, race, ethnicity, region (i.e., northeast, north central, south, west), end-stage renal disease, asthma, diabetes mellitus, ischemic heart disease, congestive heart failure, hypertension, other cardiovascular disease, Alzheimer's disease and related disorders or senile dementia, anxiety, bipolar, schizophrenia, neuropathic pain, smoking cessation, respiratory cancer, other respiratory diseases, evidence of supplemental oxygen use, baseline severe depression diagnosis, evidence of depression hospitalization, nonpharmacological psychiatric health services

Ryan et al., 2008:
centre (this was a multicentre study conducted in three different cities), education, living status, cognitive impairment, high alcohol consumption, regular smoking, disability, recent hospitalisation, co-morbidity (considered 'yes' if participants had vascular diseases, including angina pectoris, myocardial infarction, stroke, cardiovascular surgery, bradycardia or palpitations, or other chronic illnesses, like asthma, diabetes, hypercholesterolaemia, hypertension and thyroid problems, and diagnoses of cancer within the past 2 years), underweight, obesity

This study reported separate estimates for men and women, so sex was inherently controlled for

Sherwood et al., 2007:
age, heart failure etiology, left ventricular ejection fraction, N-terminal pro–B-type natriuretic peptide, BDI score

Smoller et al., 2009:
age, race, income, log of depression screen score at baseline and follow-up, systolic blood pressure, high cholesterol level requiring treatment with pills, hypertension treatment, smoking status, physical activity, body mass index, alcohol use, diabetes treatment, history of myocardial infarction or stroke, hormone therapy use, migraine headaches, aspirin or nonsteroidal anti-inflammatory use, decile of propensity for any incident antidepressant use

Only women were included in this study, so it was not possible to include sex as a covariate

Taylor et al., 2005:
baseline age, baseline BDI score, Killip class, ejection fraction, creatinine value, previous myocardial infarction, prior diagnosis of congestive heart failure, stroke or transient ischemic attack, pulmonary disease, diabetes mellitus

SUPPLEMENT D
Data from Sharma et al. (2016)

Crude all-cause death rates from double-blind randomized controlled trials reported in Sharma et al. (2016).

		No. of Deaths/Total N	
Affective Samples	**Treatable condition**	**Drugs**	**Placebo**
Trial 3	Major depressive disorder	2/188	1/93
Trial 8	Major depressive disorder	1/175	0/90
Trial 16	Stress urinary incontinence	1/227	0/231
Trial 30	Post-traumatic stress disorder	0/160	1/162
Trial 31	Post-traumatic stress disorder	1/151	0/156
Trial 69	Major depressive disorder	1/167	0/83
Trial 70	Major depressive disorder	1/180	0/68
	Total	**7/1248**	**2/883**
Cardiovascular samples	**Treatable condition**	**Drugs**	**Placebo**
Trial 23	Diabetic peripheral neuropathic pain	2/342	1/115
Trial 62	Non-insulin-dependent diabetes mellitus	0/181	1/175
	Total	**2/523**	**2/290**