

Index

Note: page numbers in *italics* refer to figures and tables

- absolute risk reduction (ARR) 62
- α error 46, 52
 - arbitrary standard 52
- alternative hypothesis
 - of a difference 37, 38
 - rejection 52
- American College of Neuropsychopharmacology, suicidality risk with antidepressants 64, 64
- anonymity, peer review 113–14
- antidepressants
 - bipolar disorder
 - discontinuation in 14–16
 - meta-analysis 97–8
 - RCTs 84
 - stratification 27
 - efficacy, regression modeling 31–2
 - mania 97–8
 - negative confounding with substance abuse 17–18
 - post-stroke mortality
 - positive confounding 16–17
 - predictors 134–5
 - RCTs
 - bipolar disorder 84
 - meta-analysis 58–9
 - unipolar depression 124
 - suicide controversy 64–5, 66
 - American College of Neuropsychopharmacology 64, 64
 - lessons learned 66–7
 - treatment response 134–5
 - unpublished negative studies 124
- antipsychotics, relapse 132
- Arateus of Cappadocia 89
- association
 - consistency of 74
 - specificity of 74–5
 - strength of 74
- astrological signs, clinical trial subgroup effects 50
- Bayes, Thomas 101–2
- Bayes' theorem 101–2
 - attack on 102–3
 - subjectivity 102
- Bayesian decision-making 109–10
- Bayesian Id 110–11
- Bayesian statistics 101
 - application to scientific research 109
 - approach 106
 - diagnosis 103–6
 - diagnostic screening tests 107–8
 - null hypothesis 110–11
 - probability 101
 - psychiatric practice 103–6
- Belmont Report 128, 129
- beriberi 22
- Bernard, Claude 83
- β error 46, 52
 - arbitrary standard 52
- bias 5–7
 - clinical research 127
 - lung cancer and smoking 72
 - measurement 6, 7, 19–20
 - misclassification 20
 - null hypothesis (NH) 39
 - peer review 114
 - pharmaceutical
 - industry–doctor relationship 126
 - publication 96–7
 - p-values 42
 - researchers 126
 - selection 6–7
 - see also* confounding bias
- bioethics 127–30
 - Belmont Report 128, 129
- bipolar disorder
 - antidepressants
 - discontinuation 14–16
 - mania and substance
 - abuse negative confounding 17–18
 - meta-analysis 97–8
 - RCTs 84
 - stratification 27
 - diagnostic accuracy 108
 - diagnostic probability 105
 - diagnostic screening tests 107–8
 - divalproex
 - prophylaxis study design 57
 - RCT 25
 - lamotrigine unpublished
 - negative studies 125
 - maintenance studies 56–8
 - mania symptoms 108
 - olanzapine for mood episode
 - prevention 49–50
 - prior probability 108–9
 - rapid-cycling
 - antidepressant stratification 27
 - confounding factors 15
 - lamotrigine studies 125
 - SRI 24–5
 - underdiagnosis 108
- Bipolar Spectrum Diagnostic Scale (BSDS) 107–8
 - psychometric properties 108–9
- bivariate analysis 30, 32
- blinding 7
 - guessing outcome 19–20
 - measurement bias 19–20
 - outcomes 19
- Bonferroni correction 49, 50
- Cade, John 128–9
- case reports 10–11
- case series 10, 10–11
- causation 5, 8, 71
 - analogy 76
 - biological 77
 - biological gradient 75

- coherence 75
 concept 78
 consistency of association 74, 99
 definitive 25
 experiment 76
 experimental 83
 Hill's concepts 77, 73–7, 78
 philosophy of statistics 82–3
 plausibility 75
 practical 78–9
 RCTs 76, 83
 replication of studies 74
 smoking and lung cancer 72–3
 specificity of association 74–5
 strength of association 74
 temporality 75
 central limit theorem, randomization 23–4
 chance 5, 7
 clinical trials 46
 influence 36
 observed event 35
 p-value 36, 41
 chart reviews 67–8
 observational data 91
 retrospective observational studies 68
 cigarette smoking 3
 lung cancer 8
 bias 72
 causation 72–3, 76–7
 Doll's causation proof 76–7
 effect modification 18–19
 epidemiology 72–3
 Fisher's views 72
 stratification 27
 clinical experience 89
 clinical innovation 127–8
 Belmont Report 128
 clinical observation 88–9
 research 93
 clinical research 89
 bias towards 127
 decline 118
 diagnostic categories 125
 clinical significance 41
 clinical trials
 α error 46, 52
 arbitrary standard 52
 balance 58
 β error 46, 52
 arbitrary standard 52
 categorical assessments 46–7
 chance 46
 clinical innovation 128
 combination therapy 57–8
 continuous measurements 46
 design 45
 dropouts 54–5
 efficacy 56
 exclusion criteria 56
 false negatives 46, 47
 false positives 46, 47, 48, 54
 subgroup effects 50
 generalizability 55–6
 inclusion criteria 56
 outcome 49–50
 efficacy 49
 measures 49
 primary 45, 46–7, 49–50
 secondary 47, 49–50
 participation 56
 philosophy 13–14
 placebo use 56, 57, 58–9
 post-hoc analysis 47–8
 power analysis 51–3
 prophylaxis study design 57
 p-value 46
 inflation 48–9
 questions 45–6, 47–8
 side effects 53–4
 statistical power 46
 subgroup analysis 50
 legitimizing 50–1
 subgroup effects 47–8
 type I and type II errors 46
see also randomized clinical trials (RCTs)
 co-authorship 118, 122
 Cochrane Collaboration 92, 99
 meta-analyses 96
 coffee consumption 3
 cognitive behavioral therapy (CBT), TADS study 65–6
 Cohen, Jacob 42
 Cohen's d 62
 cohort studies 67
 prospective 67
 retrospective 67–8
 collinearity 32
 combination therapy studies 57–8
 Comte, Auguste 2, 84
 confidence intervals 38, 63–4
 concept 63
 definition 63
 hypothesis-testing 64
 for mean 63
 p-value relationships 64
 TADS study 65–6
 theoretical computation 63
 confirmation 3–4
 conflicting studies 28, 106
 confounding
 cutoff 25–6
 by indication 6–7, 14–16
 antidepressant
 discontinuation in bipolar depression 14–16
 negative 17–18
 positive 16–17
 residual 133
 confounding bias 3–4, 6, 5–7, 13–18
 A. Bradford Hill's views 130
 after completion of RCT 26
 antidepressants
 discontinuation in bipolar depression 15–16
 and post-stroke mortality 17
 clinical observation 88–9
 conflicting studies 28
 effect modification
 relationship 18, 32–3
 meta-analysis 96
 negative 14
 observation 6, 13–14
 positive 14
 prevention 13
 randomization 89
 RCTs 16
 regression modeling 28
 removal 13
 retrospective cohort studies 67
 stratification 27
 confounding factors 3, 6
 antidepressants and post-stroke mortality 17
 assessing 28

Index

- confounding factors (*cont.*)
 baseline assessment 16
 known 23
 magnitude of difference
 between groups 28
 p-values 28
 randomization 22–3
 rapid-cycling in bipolar
 depression 15
 strength of association 74
 Table One 25
 unknown 23
 confounding variables
 133–4
 regression 28–9
 counting patients 89
 covariate analyses,
 time-varying 131
 Cox regression 131–2
 cult of medicine 91
 cultural positivism 81
- data, adjusted 28–9
 data variability 96
 power analysis 51
 decision-making 109–10
 Bayesian 109–10
 depression
 recall bias of diagnosis 68
 see also bipolar disorder;
 unipolar depression
 diabetes, antidepressants and
 post-stroke mortality
 17
 diagnosis
 Bayesian statistics 103–6,
 107–8
 bipolar disorder 105, 108
 probability 104, 105
 evidence-based medicine
 (EBM) 90
 predictive values of
 screening tests 107
 recall bias 68
 diagnostic categories 125
 disease-mongering 125
 divalproex in bipolar
 depression 25
 prophylaxis study design 57
 Doll, Richard 72–3, 76–7
 dropouts from clinical trials
 54–5
 DSM-IV 90
- effect estimation 61
 antidepressants and suicide
 controversy 64–5
 chart reviews 67–8
 cohort studies 67
 number needed to treat
 62–3
 effect modification 19, 18–20
 confounding bias
 relationship 18, 32–3
 regression models 32–3
 effect size 29–30, 61–3
 absolute 29–30
 clinical significance 41
 power analysis 51–2
 relative 29–30
 standardized 62
 statistical power 51–2
 effectiveness 56
 efficacy, clinical trials 56
 Einstein, Albert 82
 epidemiological methods 41–2
 epidemiological two-by-two
 table 62
 epidemiology, smoking and
 lung cancer 72–3
 error *see* α error; β error; type
 I and type II errors
 evidence 91
 authoritative 92
 best available 92
 conflicting 11–12
 evidence levels 10, 9–12, 93
 specific 10–11
 evidence-based medicine
 (EBM) 9–12
 anti-statistics bias 90–1
 clinical observation 89, 93
 diagnosis 90
 ivory-tower 25, 69, 91
 levels of evidence 93
 limits of statistics 93
 opinion 9–10
 origins 9–10
 parachute use for
 gravitational challenge
 92–3
 pharmaceutical industry 90
 psychiatric nosology 90
 in psychiatry 87, 93
 real in retrospective
 observational studies
 68
- experiments 3–4
 causation 76
 external validity *see*
 generalizability
 extraneous factors 13
 Eysenck H. J. 98, 99–100
- facts
 interpretation 3–4
 theory-laden 81
 Feinstein, Alvan 92, 98–9
 nature of science 98–9
 Fisher, Ronald 2, 21–2
 cigarette smoking and lung
 cancer 72
 null hypothesis 39
 p-values 35–6, 37–8, 41
 hypothesis-testing 43
 science 115–16
 view of Bayes' theorem 102
 Fisher's fallacy 41
 Fletcher, William 22
 fluoxetine
 post-stroke 16–17
 TADS study 65–6
 lessons learned 66–7
 Framingham Heart Study 11,
 67
 French Encyclopedists 2
 frequentist statistics 101, 103,
 106
 conflicting studies 106
 Freud, Sigmund 82
 funding
 extramural/intramural 129
 National Institute of Mental
 Health 129
 pharmaceutical industry
 126
- Galen 87–8, 89
 medical dogmatism 91–2
 Galton, Francis 2
 general *versus* individual
 83–4
 generalizability
 bipolar disorder
 maintenance studies
 56–8
 clinical trials 55–6
 combination therapy 57–8
 ghost authorship 122
 proof 123–4

- harm 14
 heuristics 109–10
 Hill, A. Bradford 2, 8
 causation 72
 concepts 77, 73–7, 78
 consistency of association 99
 criteria 74–6
 practical 78–9
 clinical experience/clinical research 89
 conflicting studies 28
 confounding bias 130
 philosophy of the clinical trial 13–14
 randomization concept 21–2
 RCTs 92
 smoking and lung cancer 72–3
 statisticians and clinicians 130
 Hippocrates 88, 89
 humility 89
 hormone replacement therapy (HRT)
 confounding bias 5–6
 observational study 68–9
 Hume, David 35, 71, 76, 82
 causation 82
 Hume's fallacy 71
 humors, four 87–8
 hypotheses 3–4
 fact relationship 81
 generation 85
 hypothesis-testing 3–4, 7, 85
 assumptions 40
 confidence intervals 64
 faulty logic 42
 limits 43
 p-values 37–8, 43
 statistics abuse 66–7
 hypothesis-testing statistics 84–5
 illness, spontaneous resolution 58
 impact factor (IF) 117–18
 distorting effect 118
 improbability, illusion of attaining 42
 inclusion criteria 95–6
 individual *versus* general 83–4
 induction
 problem of 35
 scientific 82
 intent-to-treat (ITT) analysis 17, 54–5
 journal article publication 113–16
 co-authorship 118
 impact factor (IF) 117–18
 distorting effect 118
 letters to the editor 119
 peer review 113–14
 interpretations 114
 published 119
 quality of published papers 115–16
 reviewers 114–15
Journal of the American Medical Association (JAMA) 114
 Keynes, John Maynard 102–3, 109
 Koch's postulates 77
 Kuala Lumpur insane asylum study RCT 21–2
 Laplace, Pierre 2
 lamotrigine
 bipolar disorder
 unpublished negative studies 125
 lithium as active control 57
 side effects 53, 54
 last observation carried forward (LOCF) approach 55
 literature reviews 95–6
 lithium
 active control in lamotrigine studies 57
 Cade's discovery 128–9
 logic 84–5
 inductive 85
 modal 84
 predicate 84
 Louis, Pierre 11, 21
 numerical method 89
 lung cancer, cigarette smoking
 association 8
 bias 72
 causation 72–3, 76–7
 Doll's causation proof 76–7
 effect modification 18–19
 epidemiology 72–3
 Fisher's views 72
 stratification 27
 mania
 antidepressant-induced 97–8
 antidepressant-related and substance abuse
 multivariate regression modeling 18
 negative confounding 17–18
 symptoms and bipolar disorder diagnosis 108
 Marx, Karl 82
 material implication 77, 82–3
 means, confidence intervals 63
 measurement bias 6, 7, 19–20
 blinding 19–20
 side effects 19–20
 medical dogmatism 91–2
 medical effects 21
 medical knowledge 127–8
 medical writing companies 122
 medicine, cult of 91
 medicine, philosophy of 87–8
 Galenic 88, 89
 Hippocratic 88, 89
 meta-analysis 92, 95–100
 antidepressants
 bipolar depression 97–8
 RCT 58–9
 Cochrane Collaboration 96
 confounding bias 96
 data variability 96
 definition 96
 heterogeneity of studies 96, 99
 as interpretation 98
 publication bias 96–7
 randomization loss 96, 98
 sample sizes 96
 significance 99
 validity 98
 misclassification bias 20
 modern medicine 88
 Mood Disorders Questionnaire (MDQ) 107–8
 psychometric properties 108–9

Index

- mood events,
 treatment-emergent 53, 54
- multivariate regression 30–1, 131–2
 equation 32
 modeling of substance abuse and antidepressant-associated mania 18
 number of variables 32
 randomized clinical trials 51
 subgroup effects 51
 substance abuse and antidepressant-associated mania 18
- National Commission for the Protection of Human Subjects (Belmont Report) 128, 129
- National Institute of Mental Health (NIMH), funding 129
- Neyman, Jerzy 37–8, 63
- Neyman-Pearson approach 43
 p-value 37–8
- non-evidence-based medicine, history 87–8
- non-inferiority designs 39
- non-systematic reviews 95–6
- nortriptyline, post-stroke 16–17
- null hypothesis 36, 37, 38–9
 assumptions 40
 Bayesian approach 110–11
 bias 39
 conservatism assumption 39–40
 hypothesis-testing statistics 85
 non-inferiority designs 39
 prior probability 111
 refuting 82
 rejection probability 52
 significance testing 42
 statistical significance 40–1
 number needed to harm (NNH) 62, 63
 Osler's art of balancing probabilities 66
 suicide controversy and serotonin reuptake inhibitors 65
- number needed to treat (NNT) 62–3
 Osler's art of balancing probabilities 66
- numerical method 89
- Nurses Health Study 11, 67
- observation
 chance 36
 clinical 89
 evidence-based medicine 89, 93
 research 93
 confounding bias 6, 13–14
 fallibility 3
 regression concept 29
- observational data 91
- observational studies 10, 11
 benefits 69
 Cochrane Collaboration dismissal 92
 conflicting studies 28
 hormone replacement therapy (HRT) 68–9
 randomized clinical trial comparison 69
 retrospective 68
 side effects 53–4
 variables 15–16
- observations, clinical 88–9
- odds ratio 29–30
 effect size 62
 relative risk 61
- olanzapine
 clinical trial outcome 49–50
versus placebo 57
- opinion, evidence-based medicine 9–10
- Osler's art of balancing probabilities 65, 66, 84
- outcome
 blinding 19
 clinical trials 49–50
 efficacy 49
 measures 49
 primary 45, 46–7, 49–50
 secondary 47, 49–50
 effect modification 19
 false positives 48, 54
 multivariate regression 30–1
 objective 19
versus predictor 31, 32
- probability 29
 false positives 48, 54
 regression 31–2
 multivariate 30–1
 subjective 19
 treatment response 134–5
- parachute use for gravitational challenge 92–3
- Pearson, Egon 37–8
- Pearson, Karl 2
 view of Bayes' theorem 102
- peer review 113–14
 anonymity 113–14
 bias 114
 interpretations 114
 process 113
 published 119
 quality of published papers 115–16
 reviewers 114–15
- Peirce, Charles Sanders 22, 81, 82
 Bayesian probability 102–3
- penicillin, RCT for tuberculosis 92
- Peto, Richard 55
- pharmaceutical industry
 co-authorship 122
 disease-mongering 125
 doctor relationship 126
 evidence-based medicine 90
 funding 126
 ghost authorship 122
 proof 123–4
 influence on medical research 121
 negative studies 97
 unpublished 124–5
 publication 122
 methods 122–3
 RCT data analysis 122–3
 statisticians 122–3
- Pickering, Sir George 88
- placebo effect 58
- placebo use 56, 57
 clinical trials 58–9
 olanzapine study 57
- pooled analysis literature reviews 95–6
- Popper, Karl 81–2
- population characteristics 6
- positivism 1, 91

- power analysis
 clinical trials 51–3
 data variability 51
 sample size 51
 subjectivity 52–3
 power of a significance test 37
 precision 61
 predictive values, positive/
 negative 107, 107
 predictors 29
 antidepressant use 134–5
 multivariate regression 30–1
 outcome *versus* 31, 32
 regression 31–2
 number 32
 prestige 126
 probability
 art of balancing 65, 66, 84
 Bayesian statistics 101
 concepts 109–10
 conditional 101–2
 diagnosis 104
 hypothesis-testing 42
 Keynesian 109
 outcome 29
 personal 102–3
 posterior 102
 predictors 29
 prior 102–3, 108–9
 null hypothesis 111
 subjective judgment 101
 theory 2
see also p-value
 problem of induction 35
 prophylaxis study design 57
 psychiatric nosology 90
 psychiatric practice, Bayesian
 statistics 103–6
 publication
 ghost authorship 122
 proof 123–4
 journal articles 113–16
 pharmaceutical industry 122
 methods 122–3
 subgroup analyses 51
see also journal article
 publication
 publication bias 96–7
 p-value 7, 35–7
 arbitrariness 36
 assumptions 40
 bias 42
 chance 36, 41
 clinical trials 46
 inflation 48–9
 confidence interval
 relationships 64
 confounding by indication
 16
 confounding factor
 assessment 28
 cutoff point 35–6
 definition 36–7
 hypothesis-testing 37–8, 43
 inflation 48–9
 number of variables 32
 RCTs 41
 refutationism 82
 relevance 37
 scope 41
 statistical significance 40–1
see also null hypothesis
 Quetelet, Lambert Adolphe 2,
 23, 83
 randomization 7, 11, 21
 central limit theorem 23–4
 concept development 21–2
 confounding bias 89
 prevention 13
 confounding factors 22–3
 distribution of variables
 15–16
 loss in meta-analysis 96, 98
 process 22–3
 regression modeling 26
 sample size 23
 success
 measurement 23
 in RCTs 26, 33
 Table One 25, 26
 ten percent solution 25–6
 randomized clinical trials
 (RCTs) 3–4
 antidepressants
 in bipolar disorder 84
 meta-analysis 58–9
 and post-stroke mortality
 16–17
 unipolar depression 124
 causation 76, 83
 co-authorship 118
 confounding bias 16
 identified after
 completion 26
 data analysis 122–3
 divalproex in bipolar
 depression 25
 double-blind 10, 11, 12
 fetishization 91, 92
 hormone replacement
 therapy 5–6, 68–9
 Kuala Lumpur insane
 asylum study 21–2
 meta-analysis of
 antidepressants 58–9
 multivariate regression 51
 observational study
 comparison 69
 open 10, 11, 12
 penicillin for tuberculosis 92
 pharmaceutical industry
 data analysis 122–3
 positive confounding 16–17
 psychiatry 89
 p-values 41
 randomization success 26,
 33
 regression 33
 small 24–6
 SRIs in bipolar disorder
 24–5
 statistical significance
 application 72
 variable conditions 92
 randomized studies 15–16
 rapid-cycling in bipolar
 disorder
 antidepressant stratification
 27
 confounding factors 15
 lamotrigine studies 125
 recall bias
 diagnosis 68
 retrospective observational
 studies 68
 refutation 3–4
 refutationism 81, 82
 regression 27–8
 concept 29
 confounding variables 28–9,
 133
 effect modification 32–3
 equations 29–30
 number of variables 32
 predictor number 32
 RCTs 33
 visualizing 31–2

Index

- regression analysis
 cohort studies 67
 retrospective 67
see also multivariate
 regression
 regression models/modeling 3,
 7, 27–8
 adjustment 28–9
 assumptions 131–2
 backward deletion 136
 computerized methods
 136–7
 confounding bias 28
 removal 13
 confounding variables 28–9,
 133
 selection 133–6
 Cox 131–2
 forward selection 136
 handmade selection of
 variables 134–5
 kitchen sink method for
 variables 135–6
 linear 131
 logistic 131
 randomization 26
 residual confounding 133
 substance abuse and
 antidepressant-
 associated mania 18
 relative risk 22, 61
 TADS study 65–6
 replication of studies 8,
 79–80
 causation 74
 convergence of research 93
 research
 Bayesian statistics
 application 109
 bias 126
 clinical observation 93
 co-authorship 118
 impact factor 117–18
 distorting effect 118
 impact on practice 117–19
 negative studies 96–7
 pharmaceutical industry
 influence 121
 prestige 126
 replicated 93
 trivial 129–30
see also clinical research
 restriction 27
 results, crude 28–9
 reviews
 non-systematic 95–6
 systematic 95–6, 100
 rice, white/brown 22
 Rickert, Heinrich 83
 risk ratio 29–30
 effect size 62
 risperidone with
 antidepressants in
 unipolar depression 47
 Russell, Bertrand 77, 82–3
 Salsburg, David 35–6, 37
 sample size
 power analysis 51
 randomization 23
 Savage L. J. 102–3
 science 1
 Bayesian statistics
 application 109
 co-authorship 118
 complexity 1
 Fisher's views 115–16
 hypotheses 3–4, 93
 impact on practice 117–19
 knowledge 3
 misunderstanding 91
 nature of 98–9
 philosophy of 82
 replicated research 93
 revolution 2–3
 theory–fact
 interrelationships 85
see also research
 selection bias 6–7
 antidepressant
 discontinuation in
 bipolar depression
 14–16
 sensitivity analyses,
 stratification 27
 serotonin reuptake inhibitors
 (SRIs) in bipolar
 disorder 24–5
 serotonin reuptake inhibitors
 (SRIs), suicide
 controversy 64–5
 side effects 53–4
 lamotrigine 53, 54
 measurement bias 19–20
 significance hypothesis-testing
 54
 standard deviation 51–2,
 53
 statistical analysis 3–4
 statistical power
 clinical trials 46
 effect size 51–2
 mathematical notation 52
 statistical significance 40–1
 application 72
 statistical trends 40–1
 statistics
 benefits 3
 concepts 2
 history 1–2
 stepwise conditional regression
 136
 stratification 27
 confounding bias 27
 sensitivity analyses 27
 stroke, antidepressants and
 post-stroke mortality
 16–17
 study design, confounding bias
 prevention 13
 subgroup analyses
 false positive risks 50
 legitimizing 50–1
 a priori 50–1
 rate in publications 51
 subgroup effects 47–8
 multivariate regression 51
 subjectivity, Bayes' theorem
 102
 substance abuse and
 antidepressant-
 associated mania
 negative confounding 17–18
 regression models/modeling
 18
 suicide risk
 with antidepressants,
 American College of
 Neuropsychopharma-
 cology 64, 64
 controversy and serotonin
 reuptake inhibitors
 64–5
 TADS study 65–6
 lessons learned 66–7
 survival analysis 132
 dropouts 132–3
 sample size 132
 Swan-Ganz catheter 91

Index

- systematic error 5
 systematic reviews 95–6,
 100
 Systematic Treatment
 Enhancement Program
 for Bipolar Disorder
 (STEP-BD) project 67
 Table One randomization 25,
 26
 theory 81
 time-varying covariate analyses
 131
 Treatment of Adolescent
 Depression Study
 (TADS) 65–6
 Osler's art of balancing
 probabilities 66
 trends 40–1
 tuberculosis, RCT of penicillin
 92
 Tukey test 50
 type I and type II errors 46, 48,
 54
 uncertainty 3
 unipolar depression
 FDA database of
 antidepressant RCTs
 124
 risperidone with
 antidepressants 47
 univariate analysis 30,
 32
 validity 55
 verificationism 81
 vitamin E studies 79–80
 vote count method literature
 reviews 95–6
 Windelband, Wilhelm
 83
 withdrawal syndrome, placebo
 use 57
 Women's Health Initiative,
 hormone replacement
 therapy RCT 68–9