

Index

- A**
- ABO blood group, genotype–phenotype relationship, 19–20
 - ACE model, twin studies, 23, 32–33, 40, 53
 - ACHE*, 161
 - Additive genetic variance, 22
 - ADHD. *See* Attention-deficit/hyperactivity disorder
 - Adoption study design
 - overview, 71
 - strengths and limitations, 64
 - ALDH2*, 28, 31, 86, 171
 - Anacetrapib, 193
 - ANGPTL3*, 186, 201
 - ATP7A*, 16, 19, 21, 28
 - Attention-deficit/hyperactivity disorder (ADHD), 46–48, 54, 63–67, 71–72, 240, 243
- B**
- BCKD. *See* Branched-chain α -ketoacid dehydrogenase
 - BMI. *See* Body mass index
 - Body mass index (BMI)
 - breast cancer risk, 126
 - cardiovascular disease correlation, 94–95
 - vitamin D studies, 243
 - Branched-chain α -ketoacid dehydrogenase (BCKD), 86
 - Breastfeeding, 239
 - Broad heritability, 22
 - BSCL2*, 154
- C**
- CAD. *See* Coronary artery disease
 - CADD, 172
 - Causal analysis using summary effect estimates (CAUSE), 103
 - Causal inference
 - overview, 1–2
 - prediction comparison, 230
 - CAUSE. *See* Causal analysis using summary effect estimates
 - CETP, 193, 223
 - Cholesky decomposition twin model, 43–45
 - CHRNA5*, 97–98, 171
 - COL1A1*, 20
 - COL1A2*, 20
 - Coronary artery disease (CAD), 101
 - metabolome-wide Mendelian randomization, 156
 - polygenic risk score, 170
 - proteomics Mendelian randomization, 156
 - COVID-19, interleukin-6 receptor expression and outcomes, 9
 - C-reactive protein (CRP), 85, 99, 102
 - CRIP1*, 155
 - CRP. *See* C-reactive protein
- D**
- DAG. *See* Directed acyclic graph
 - Diabetes, 102, 155–156, 161, 191–192, 204, 223
 - Directed acyclic graph (DAG), 6–7, 92, 113–114, 230, 237
 - Direction of causation (DOC). *See* Mendelian randomization; Twin studies
 - Discordant sib pair study design
 - overview, 66–67
 - postnatal exposures, 67–68
 - prenatal exposures, 66
 - strengths and limitations, 64, 68
 - triangulation, 237–238
 - DOC. *See* Direction of causation
 - Dominance variance, 22
 - Drug development
 - failure rate of target-based drug development, 200–201
 - genome-wide association studies for drug target identification
 - limitations
 - breadth and depth of studies, 203
 - mechanistic considerations, 205
 - noncausal genes, 203–204
 - nondruggable genes, 204
 - therapeutic area limitations, 204–205
 - tractability of identified drug target, 204
 - overview, 201, 203
 - public data, 219
 - Mendelian randomization
 - drug development yield enhancement
 - compound specificity delineation, 223

Index

- Drug development (*Continued*)
- indication expansion, 222–223
 - preclinical drug target prioritization, 221
 - safety and efficacy phenotype identification, 221–222
 - drug target validation
 - absence of genetic variation, 219–220
 - biomarker-weighted analysis, 216
 - cis* and *trans* instruments, 215–217
 - drug target MR effect estimate interpretation, 213–214
 - evidence prioritization, 220–221
 - genetic weights and inferential target, 211–213
 - overview, 205, 210–211
 - pre-translational pleiotropy for validation, 216, 218–219
 - proteomics data utilization, 214–215
 - randomized controlled trial comparison, 206–210
 - scaling, 219–221
 - omics in drug development, 160–161
 - prospects in drug trials, 101–102, 223–224
 - overview of genomics-led drug development, 199–200
- E**
- eCAVIAR, 153, 174, 203
 - Environmental variance, 22
 - Epigenetics, complications in causality determination, 17
 - EpiGraphDB, 174
 - Epistasis variance, 22
- F**
- FATHMM, 172
 - Folate, supplementation, 240
- G**
- GBLUP. *See* Genetic best linear unbiased predictor
 - Genetic best linear unbiased predictor (GBLUP), 153
 - Genetic instrumental variable regression (GIV), 103
 - Genome-wide association study (GWAS). *See also* Mendelian randomization
 - consortia, 82–83
 - drug target identification. *See also* Mendelian randomization
 - limitations
 - breadth and depth of studies, 203
 - mechanistic considerations, 205
 - noncausal genes, 203–204
 - non-druggable genes, 204
 - therapeutic area limitations, 204–205
 - tractability of identified drug target, 204
 - overview, 201, 203
 - public data, 219
 - overview, 152
 - polygenic scores, 3, 29
 - polygenic traits, 28–29
 - summary statistics databases, 168–169
- GIV. *See* Genetic instrumental variable regression
- GWAS. *See* Genome-wide association study
- H**
- HDL-C. *See* High-density lipoprotein-cholesterol
 - Heritability
 - polygenic traits
 - family studies, 22–28
 - genomic approaches, 28–29
 - single-gene traits, 19–22
 - High-density lipoprotein-cholesterol (HDL-C), 2, 210, 223, 230–231
 - Hill's criteria, causal inference, 5, 7
 - HMG2A*, 29
 - HMGCR*, 161, 201, 223
- I**
- IL6R*, 9, 86, 222
 - IL12*, 161
 - IMPROVE-IT, 193
 - Instrument strength independent of direct effect (InSIDE), 115–116, 118, 120
 - Intelligence quotient (IQ), twin studies, 48
 - Interactionist consensus, 17
 - Inverse variance weighted estimator. *See* Polygenic Mendelian randomization
 - In vitro fertilization (IVF) study design
 - overview, 68–69
 - postnatal exposures, 70
 - prenatal exposures, 69–70
 - strengths and limitations, 64, 70–71
 - IQ. *See* Intelligence quotient
 - IVF study design. *See* In vitro fertilization study design
- L**
- LATE. *See* Local average treatment effect
 - Latent class variable (LCV), 173
 - LCV. *See* Latent class variable
 - LD clumping, 173–174
 - LD Hub, 170
 - LDL-C. *See* Low-density lipoprotein-cholesterol
 - Lmbr1*, 17
 - Local average treatment effect (LATE), 95

- Low-density lipoprotein-cholesterol (LDL-C), 155, 191–193, 204, 211–212, 215
- M**
- MAF. *See* Minor allele frequency
- Maraviroc, 203
- Maternal versus paternal exposure study design
 - overview, 65–66
 - strengths and limitations, 64, 66
- MELODI, 171
- Mendelian genetics
 - gene concepts, 16–17
 - overview, 2–3
 - single-gene traits, 19–22
- Mendelian randomization (MR). *See also*
 - Multivariable Mendelian randomization; Polygenic Mendelian randomization
 - applications, 77–81
 - assumptions
 - exclusion restriction assumption
 - overview, 84–85
 - pleiotropy effects, 97
 - sensitivity analyses, 85–88
 - independence/exchangeability assumption, 81, 84
 - misconceptions, 94–95
 - relevance assumption, 81
 - consortia for genome-wide association studies, 82–83
 - confounding factors and genetic variants, 96–97
 - direct genotype associations, 88
 - direction of causation model, 146–148, 239
 - drug development
 - drug target validation
 - absence of genetic variation, 219–220
 - biomarker-weighted analysis, 216
 - cis* and *trans* instruments, 215–217
 - drug target MR effect estimate interpretation, 213–214
 - evidence prioritization, 220–221
 - genetic weights and inferential target, 211–213
 - overview, 205, 210–211
 - pre-translational pleiotropy for validation, 216, 218–219
 - proteomics data utilization, 214–215
 - randomized controlled trial comparison, 206–210
 - scaling, 219–221
 - omics in drug development, 160–161
 - prospects in drug trials, 101–102, 223–224
 - yield enhancement
 - compound specificity delineation, 223
 - indication expansion, 222–223
 - preclinical drug target prioritization, 221
 - safety and efficacy phenotype identification, 221–222
 - extensions
 - horizontal pleiotropy, 93–94
 - informatic tools, 92–93
 - miscellaneous approaches, 91–92
 - family-based study integration
 - assortative mating, 138–139
 - bias control, 140–142
 - dynastic effects, 138
 - limitations, 142
 - overview, 137–138
 - residual population stratification, 140
 - within-families estimators, 142
 - gene–environment correlations, 31
 - limitations
 - canalization and time-varying effects, 100–101
 - cis* versus *trans* quantitative trait loci, 158–159
 - dependable instruments, 99
 - gene prioritization, 157–158
 - heritable confounders, 157
 - horizontal pleiotropy, 99
 - instrument bias, 100
 - optimal precision, 99–100
 - overview, 98
 - reliable polymorphisms for studying
 - modifiable exposures of interest, 98–99
 - tissue specificity, 158
 - winner’s curse, 100
 - maternal exposures and offspring outcomes, 142–146
 - metabolome-wide Mendelian randomization, 155–156
 - methylome-wide Mendelian randomization, 156–157
 - one-sample Mendelian randomization, 88–89
 - one- versus two-sample Mendelian randomization, 90–91
 - overview, 8, 30–32, 75–77
 - prospects, 9
 - automation, 104
 - causal inference and clinical end points, 102
 - disease modification of gene expression, 159
 - disease progression factor identification, 101
 - ethnic diversity, 103
 - gene regulatory networks of causal effects, 159–160
 - methodological innovations, 103
 - molecular mechanism elucidation, 102–103

Index

- Mendelian randomization (MR) (*Continued*)
 reproducibility and reporting, 104
 sex-specific analysis, 159
 proteomics Mendelian randomization, 156
 randomized controlled trial
 comparison, 96, 184–187
 Mendelian randomization study design,
 183–184, 192–194
 Mendelian randomization utility in trial
 design
 adverse events, 191–192
 background therapy, 191
 biomarkers, 189–190
 inclusion and exclusion criteria, 190–191
 intervention target, 187
 subgroups benefiting from intervention, 192
 reverse causation, 97–98
 transcriptome-wide Mendelian randomization,
 154–155
 triangulation, 238–239
 two-sample Mendelian randomization, 89–90
Metabolome-wide Mendelian randomization,
 155–156
Methylome-wide Mendelian randomization,
 156–157
Minor allele frequency (MAF), 29
MR. *See* Mendelian randomization
MRMix, 119
MR-PRESSO, 173
Multivariable Mendelian randomization (MVMR)
 advantages and limitations, 131–134
 data sources, 127
 exposure effects on outcomes, 129–130
 mediated effect estimation analysis
 difference method, 131
 overview, 130–131
 product of coefficients method, 131
 MV-IV1, 128
 MV-IV2, 128–129
 MV-IV3, 128–129
 overview, 125–129
 single-nucleotide polymorphisms, 127–130,
 133–134
MVMR. *See* Multivariable Mendelian randomization
- N**
- Narrow heritability, 22
Nonadditive genetic variance, 22
- O**
- Observational data, causal inference, 4–5, 7
OI. *See* Osteogenesis imperfecta
- Open Targets, 175
Osteogenesis imperfecta (OI), 20–21
- P**
- PAH, 22
PCSK9, 155, 161, 186, 193, 201, 204, 211–212
Phenotypic variance, 22
Phenylketonuria (PKU), 22
PKU. *See* Phenylketonuria
PLA2, 221
Polygenic Mendelian randomization
 Bayesian methods, 119–120
 heterogeneity and outlier detection, 115–116
 InSIDE assumption, 115–116, 118, 120
 inverse variance weighted estimator, 115–119,
 122
 median and mode estimators, 118–119
 MR-Egger regression, 116–118, 173, 216
 overview, 113–114
 polygenic score, 114–115
 single-nucleotide polymorphism selection,
 120–121
 zero modal pleiotropy assumption, 119, 121–122
Polygenic risk score (PRS), 170–171
Prediction, causal inference comparison, 230
Proteomics
 drug target Mendelian randomization, 214–215
 Mendelian randomization, 156
PRS. *See* Polygenic risk score
- R**
- Randomized controlled trial (RCT)
 design, 182–183
 Mendelian randomization
 drug target validation, 206–210
 comparison with trials, 96, 184–187
 study design, 183–184, 192–194
 utility in trial design
 adverse events, 191–192
 background therapy, 191
 biomarkers, 189–190
 inclusion and exclusion criteria, 190–191
 intervention target, 187
 subgroups benefiting from intervention,
 192
 triangulation, 236
RCT. *See* Randomized controlled trial
- S**
- SIFT, 172
SIMEX algorithm, 117

- Single-nucleotide polymorphism (SNP)
 heritability, 4
 Mendelian randomization, 8, 86, 88–90, 98–99
 molecular traits underlying disease, 152–153
 multivariable Mendelian randomization, 127–130, 133–134
 polygenic Mendelian randomization, 114–122
 polygenic trait analysis, 28–29
- Smoking, 1, 5, 7, 9, 46–47, 53, 62–71, 97–98, 126, 146, 171, 235–241
- SNP. *See* Single-nucleotide polymorphism
- SOCS5, 155
- T**
- Transcriptome-wide association study (TWAS), 153
- Transcriptome-wide Mendelian randomization (TWMR), 154–155
- Triangulation
 applications, 229–231
 bias sources, 241–242
 causal effect magnitude, 242
 causal inference study design, 233–234
 combining multiple approaches, 240
 examples in genetically informed designs
 breastfeeding, 239
 educational attainment, 239
 folate supplementation, 240
 smoking, 239–240
 lack of convergence, 242–243
 Mendelian randomization, 238–239
 prospects, 243–244
 smoking and low birth weight, 235
 study designs
 controls, 237
 different confounding structures, 237
 discordant siblings, 237–238
 incommensurable evidence, 238
 instrumental variables, 236
 natural experiments, 236–237
 randomized controlled trials, 236
 theory, 231–236
- TWAS. *See* Transcriptome-wide association study
- Twin studies
 ACE model, 23, 32–33, 40, 53
 confounding
 environmental exposure and genetic influence, 42
 nonshared environmental confounds, 53
 phenotypic correlations and genetic influence, 41
 context importance, 55
 cotwin control design
 comparison with classical twin decomposition, 47–48
 overview, 46–47
 direction of causation
 cross-sectional data, 49–51
 longitudinal data, 48–49
 environmental differences, 54
 experimental design, 53
 extended family designs
 children-of-twins-and-siblings models, 51–53, 63
 overview, 51
 measurement error, 55
 monozygotic versus dizygotic twins, 23, 33, 40
 multivariate twin models and causal inference, 43–46
 phenotypic causal inference, 7–8
 prospects for causality studies, 55–56
 statistical power, 54
 triangulation, 237
- TWMR. *See* Transcriptome-wide Mendelian randomization
- Z**
- ZEMPA. *See* Zero modal pleiotropy assumption
- Zero modal pleiotropy assumption (ZEMPA), 119, 121–122