guiding the selection of instruments. MR is then used to further evaluate whether these signals are compatible with a directional relationship between a molecular trait and a complex phenotype.

For loci with stronger supporting evidence, replication across independent datasets or conditions can help assess robustness. In multi-tissue or multi-omics settings, multivariable models may provide additional insight into overlapping pathways. Conversely, when evidence is limited or inconsistent, it is often more appropriate to return to earlier stages of analysis, such as fine-mapping or data harmonization, rather than proceeding directly to causal interpretation.

Overall, MR is best understood as part of a sequence of analytical steps rather than a standalone method. When combined with association analyses, colocalization, and functional annotation, it contributes to a gradual refinement of evidence, moving from statistical association toward more directed interpretation of genetic effects (Zuber et al., 2022).

6 An Integrated Pathway for Causal Inference

In studies of complex traits, different data types and analytical approaches each provide only partial information. Effective integration therefore requires a coherent analytical path through which initial genetic associations can be progressively refined into more interpretable results. Rather than functioning as independent tools, these methods operate in sequence, with each step narrowing the set of candidates and adding complementary evidence.

In practice, analyses often begin with GWAS signals and proceed by incorporating molecular and statistical constraints, gradually focusing from broad genomic regions to more specific genes or regulatory mechanisms.

6.1 From GWAS signals to candidate genes

Analyses typically start with GWAS summary statistics. Initial steps include harmonizing allele orientation, standardizing effect sizes, and selecting LD reference panels matched to the study population. Fine-mapping can then be applied to reduce the set of candidate variants and concentrate the analysis on more localized regions (Hormozdiari et al., 2016).

At this stage, incorporating molecular QTL data provides an additional layer of information. Colocalization analysis is used to assess whether GWAS and molecular signals within a region are consistent with a shared underlying variant, thereby helping to prioritize loci for further investigation. When such consistency is observed, expression-based models can be used to translate locus-level signals into gene-level associations, further narrowing the list of candidate genes (Porcu et al., 2019; Wainberg et al., 2019; Zhang et al., 2024).

Following this prioritization, selected variants can be used as instruments to evaluate relationships between molecular traits and complex phenotypes. Mendelian randomization is commonly applied at this stage to examine potential directionality and estimate effect sizes. Through this sequence, initial GWAS signals are progressively refined into more specific hypotheses, such as the involvement of particular genes or regulatory processes (Lessard et al., 2024).

In situations where data are incomplete-for example, when high-quality eQTL data are unavailable-the analytical path may need to be adapted. TWAS can provide an initial prioritization of candidate genes, which can later be revisited using external or newly generated datasets. In such cases, however, interpretation should remain cautious, particularly when moving toward causal claims (Wainberg et al., 2019).

Across the entire process, replication in independent populations or environments can help assess robustness. Combining multiple MR methods and diagnostic measures further contributes to a more comprehensive evaluation of the evidence (Porcu et al., 2019; Zuber et al., 2022).

6.2 Practical considerations in analysis

In applied settings, the choice of analytical strategy depends on data availability and quality. A key consideration is whether high-quality molecular QTL data are available in tissues relevant to the trait of interest, along with