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Figure 1. Study design and data sources used to investigate the effect of liver dysfunction (proxied by biomarkers: ALT, AST, ALP, and GGT) on type 2 diabetes or secondary outcomes (fasting glucose, fasting insulin, LDL-C, HDL-C, total cholesterol, and triglycerides) (Figure 1A) and the effect of predisposition to type 2 diabetes or insulin resistance on circulating liver function biomarkers (Figure 1B).

As shown in Figure 1A, the multivariable association of liver function markers with T2D risk (or related outcomes) was estimated by meta-analysing results from each data source using logistic regression models (or linear regression models in the case of secondary outcomes) with participant-level data from relevant studies within UCLEB consortium (BRHS, BWHHS, MRC-NHSD) and summary-level data from the published meta-analyses of Kunutsor et al (2013) and Fraser et al (2009). We also estimated the association of liver function markers with T2D risk (or secondary outcomes) using a Mendelian randomization approach. In Mendelian randomization analysis, we used different data sources to estimate the SNP-liver function marker association (UCLEB consortium — BRHS, BWHHS and MRC-NHSD —, Fenland study, and GWAS of liver function markers — Chambers et al (2011)) —, and SNP-T2D risk association (UCLEB — BRHS, BWHHS, CaPS, EAS, ELSA, MRC-NHSD, and WHII —,
and GWAS consortium) or SNP-secondary outcomes. As shown in figure 1B, the summary-level data for the association of SNP-T2D risk and SNP-fasting insulin for the reverse MR was extracted from GWAS consortia, and the association of SNP-liver function marker was extracted from Chambers et al (2011). ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BRHS: British Regional Heart Study; BWHS: British Women’s Heart and Health Study; CaPS: Caerphilly Prospective Study; DIAGRAM consortium: Diabetes Genetics Replication And Meta-analysis consortium; EAS: Edinburgh Artery Study; ELSA: English Longitudinal Study of Ageing; GGT: gamma-glutamyl transferase; GWAS: genome-wide association study; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; MRC-NSHD: National Survey of Health and Development; SNPs: single nucleotide polymorphisms; T2D: type 2 diabetes; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium; WHII: Whitehall II study.