

Effects of Mulberry Leaf Supplementation on Cardiometabolic Markers: A Systematic Review and Meta-Analysis

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Abstract

Background. Cardiometabolic dysfunction complicates diabetes management through impaired glycemic control, insulin resistance, and dyslipidemia. We evaluated the effects of mulberry leaf and its extract (ML/MLE) on glycated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance (HOMA-IR), and low-density lipoprotein cholesterol (LDL-C).

Methods. This systematic review and meta-analysis was preregistered on the Open Science Framework (n3bct). Randomized controlled trials were identified from ClinicalTrials.gov, Cochrane CENTRAL, PubMed, and PubMed Central. Trials comparing ML/MLE with control for at least 4 weeks and reporting HbA1c were eligible. Statistical meta-analysis was performed in RevMan 5.4.1 using random-effects models. To account for baseline HbA1c, HbA1c effects were examined by baseline glycemic subgroup and contextualized against oral glucose-lowering studies at comparable baseline levels using study-level regression.

Results. Eight randomized trials with 440 analyzed participants were included; the sample-size-weighted mean baseline HbA1c was 7.15%. ML/MLE reduced HbA1c versus control (MD -0.22 percentage points, 95% CI -0.39 to -0.06; $p = 0.009$). Baseline-stratified point estimates were 0.00 percentage points in non-diabetic, -0.14 in prediabetic, and -0.42 in diabetic trials. HOMA-IR decreased significantly in two trials (MD -0.64, 95% CI -1.27 to -0.02; $p = 0.04$; $I^2 = 18\%$). LDL-C showed a non-significant pooled decrease (MD -6.21 mg/dL, 95% CI -15.37 to 2.94; $p = 0.18$; $I^2 = 0\%$), with a concordant directional trend across all four trials. Seven of eight HbA1c estimates fell within the 50% prediction interval of oral-agent studies at comparable baseline HbA1c; the remaining estimate fell within the 80% interval.

Conclusions. ML/MLE showed promising effects on glycemic control and insulin resistance, with the largest HbA1c reduction in diabetic-baseline trials. The LDL-C signal was directionally favorable but imprecise. Baseline-adjusted comparison with oral glucose-lowering studies supports the clinical plausibility of the HbA1c effect without establishing therapeutic equivalence. Larger, longer trials using standardized preparations are needed to confirm the secondary outcomes and define reproducible dosing.

Research Insights

What is currently known about this topic?	• ML/MLE has shown glycemic effects in randomized clinical trials. • HOMA-IR and LDL-C add cardiometabolic context beyond HbA1c. • Higher baseline HbA1c predicts larger absolute treatment-associated reductions.
What is the key research question?	How does ML/MLE affect HbA1c, HOMA-IR, and LDL-C across glycemic states?
What is new?	• ML/MLE significantly reduced HbA1c and HOMA-IR. • All four LDL-C estimates favored ML/MLE, but the pooled effect was not significant. • HbA1c reductions were largest in diabetic-baseline trials, a descriptive subgroup trend.
How might this study influence clinical practice?	Clinicians may consider adjunctive ML/MLE for high HbA1c while larger trials confirm other effects.

Background

Diabetes is accompanied by interconnected abnormalities in glycemic control, insulin sensitivity, and lipid metabolism that contribute to cardiometabolic risk. HbA1c, HOMA-IR, and LDL-C provide complementary measures of these domains: HbA1c reflects longer-term glycemic exposure, HOMA-IR estimates fasting insulin resistance, and LDL-C reflects lipid-related atherosclerotic risk [1–4].

HbA1c is a clinically important marker of long-term glycemic status and is standardized through the NGSP to values traceable to the Diabetes Control and Complications Trial reference system [4]. HbA1c reflects average glycemia over approximately the preceding 2–3 months [5]. Longer follow-up therefore captures more of an eventual treatment response, but shorter trials can still detect meaningful change. Michaelis-Menten modeling reported by Kim et al. [5] predicts 34.2% of maximal treatment effect by 30 days, 56.6% by 60 days, and 71.4% by 90 days; the predicted 30-day effect is approximately half the 90-day effect. This supported the 4-week minimum while recognizing that shorter trials may underestimate the eventual HbA1c response.

Bloomgarden et al. [6] analyzed 61 studies spanning five major oral glucose-lowering drug classes, including metformin, and showed that higher baseline HbA1c is associated with larger apparent treatment-associated reductions. This baseline-response relationship provides a useful benchmark for interpreting HbA1c changes observed in ML/MLE trials without implying head-to-head equivalence.

Mulberry leaf and mulberry leaf extract (ML/MLE) have been investigated as complementary interventions for metabolic dysfunction. Their constituents include iminosugars such as 1-deoxynojirimycin (1-DNJ), D-fagomine, and 2-O- α -D-galactopyranosyl-DNJ, together with flavonoids, phenolics, and polysaccharides [7–10]. 1-DNJ is an α -glucosidase inhibitor, but whole-leaf or extract effects cannot be attributed to a single constituent [9]. Constituent abundance can also vary with

preparation and extraction conditions [8–10], making formulation standardization important when comparing trials.

Glycemic response may also depend on baseline status: across oral glucose-lowering studies, higher baseline HbA1c is generally associated with larger absolute HbA1c reductions [6]. Stratifying trials by mean baseline HbA1c can therefore provide clinically useful context for the pooled ML/MLE effect.

Accordingly, this systematic review and meta-analysis evaluated ML/MLE effects on the core cardiometabolic outcomes HbA1c, HOMA-IR, and LDL-C, while also examining whether HbA1c responses differed across baseline glycemic levels.

Methods

Search strategy

This review followed the project preregistration on the Open Science Framework (OSF; registration n3bct) and was reported in accordance with PRISMA 2020 [11]. Search reporting followed the PRISMA-S extension [12], and statistical methods followed the Cochrane Handbook for Systematic Reviews of Interventions [13]. PubMed, PubMed Central (PMC), Cochrane CENTRAL, and ClinicalTrials.gov were searched. The search strategy combined mulberry-related terms (including *Morus*, mulberry, *M. alba*, mulberry leaf/leaves, Mulberroside A, 1-deoxynojirimycin [1-DNJ/DNJ], and traditional or alternative names) with glycemic outcome terms (including HbA1c and related terminology, fasting or random glucose, fasting insulin, HOMA-IR, 2-hour glucose, and postprandial glucose). The complete search term is provided in Supplementary Methods S1. Duplicate records were identified by DOI matching when available.

Eligibility criteria and outcome hierarchy

Eligible studies were randomized controlled trials comparing ML/MLE with placebo or control for at least 4 weeks and reporting HbA1c. Combination interventions were excluded when the independent effect of ML/MLE could not be isolated. HbA1c was designated the primary outcome because it was the principal glycemic endpoint of the review. HOMA-IR and LDL-C were designated secondary/core outcomes to extend interpretation to insulin resistance and lipid-related risk. AST, ALT, FPG, FPI, HDL-C, insulin, total cholesterol, triglycerides, and VLDL were exploratory/tertiary outcomes. G.K., P.B., T.N., P.N., M.S., and P.P. participated in screening and data extraction from primary articles, tables, supplementary materials, and finalized project datasets. Intention-to-treat outcome data were used when reported; when a trial did not clearly identify ITT results, the available analyzed data were used and the uncertainty was considered in risk-of-bias assessment.

Data extraction and statistical analysis

HbA1c was reported on the NGSP scale. The NGSP standardizes HbA1c assay results to values traceable to the Diabetes Control and Complications Trial reference method [4]. HbA1c effects in this manuscript are expressed as percentage-point changes on the NGSP scale, not relative percentage changes; for example, a change from 7.5% to 7.0% is a decrease of 0.50 percentage points.

Change-from-baseline analysis compared the mean within-group change from baseline to follow-up between ML/MLE and control groups, whereas post-intervention analysis compared final follow-up means. Change-from-baseline data were used for HbA1c, HDL-C, HOMA-IR, fasting glucose measures, insulin, ALT, AST, and LDL-C. Post-intervention values were used for triglycerides, total cholesterol, FPI, and VLDL when a valid change-from-baseline SD was unavailable [13]. HOMA-IR was defined as $[FPI (\mu U/mL) \times FPG (mmol/L)]/22.5$ when glucose was reported in mmol/L and $[FPI (\mu U/mL) \times FPG (mg/dL)]/405$ when glucose was reported in mg/dL [3]. A study was included in the HOMA-IR meta-analysis only when HOMA-IR and a defensible variance estimate were available.

When a study reported baseline, final, and change-from-baseline SDs, the within-participant correlation coefficient (r) was calculated according to Cochrane Handbook section 6.5.2.8 [13]:

$$r = (SD_{baseline}^2 + SD_{final}^2 - SD_{change}^2) / (2 \times SD_{baseline} \times SD_{final})$$

The correlation coefficient describes the within-participant relationship between baseline and follow-up measurements; it is used to estimate change-from-baseline variability and does not measure an association between treatment and outcome. When the change-from-baseline SD was unavailable, it was imputed using the following Cochrane formula [13]:

$$SD_{change} = \sqrt{(SD_{baseline}^2 + SD_{final}^2 - 2 \times r \times SD_{baseline} \times SD_{final})}$$

Outcome-specific correlation coefficients were applied only when baseline and final SDs were reported but a direct change-from-baseline SD was unavailable. Directly reported change-from-baseline SDs were used whenever available. Random-effects meta-analysis was performed in Review Manager 5.4.1 (RevMan), with mean differences and 95% confidence intervals calculated for continuous outcomes.

For the contextual baseline-response analysis, ordinary least-squares regression was fitted to the study-level baseline HbA1c and HbA1c-change observations reported by Bloomgarden et al. [6]. ML/MLE trial points were overlaid for comparison but were not used to fit the model. Prediction intervals of 50%, 80%, and 95% were calculated for individual study-level observations; extension below the observed Bloomgarden baseline range was treated as linear extrapolation.

Baseline glycemic status was defined using American Diabetes Association thresholds: non-diabetic (<5.7%), prediabetic (5.7% to <6.5%), and diabetic ($\geq 6.5\%$) [14]. Each trial was assigned using its reported mean baseline HbA1c; both randomized groups fell within the same glycemic category in every included trial. Statistical heterogeneity was assessed using Cochran's Q (Chi-square) and I^2 statistics, and $p < 0.05$ was considered statistically significant.

Risk-of-bias assessments

Risk of bias was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [15]. The parallel-group version was used because all comparisons contributing to the meta-analysis were parallel-group comparisons; no crossover phase contributed to pooled outcomes. The five domains were bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Results

Study selection

The PRISMA 2020 flow diagram summarizes study selection (Figure 1) [11]. Database and registry searches identified 1,911 records, and citation searching identified 10 additional records. After 64 duplicate database/register records were removed, 1,847 records were screened and 1,833 reports were assessed for eligibility. The largest exclusion categories were no medical intervention (n = 893), not a clinical trial (n = 722), and an intervention that could not be isolated against an appropriate control (n = 154). Eight randomized trials were included in the final review.

Description of included studies

Table 1 summarizes the eight included randomized trials [16-23]. The HbA1c synthesis included 224 participants receiving ML/MLE and 216 controls, with analyzed trial sample sizes ranging from 17 to 100 participants. Using these analyzed group sizes, the sample-size-weighted mean baseline HbA1c was 7.15% overall (7.20% in ML/MLE groups and 7.09% in controls). Trials were conducted in Japan, Thailand, the Republic of Korea, Pakistan, Iran, and the United States and enrolled healthy adults, adults with impaired glucose regulation or borderline diabetes, and adults with type 2 diabetes. Intervention duration ranged from 4 weeks to 4 months, and formulations included beverages, tablets, extracts, powders, and teas. HbA1c was available for all eight trials, HOMA-IR was directly reported in two, and LDL-C was available in four; AST and the remaining outcomes were exploratory.

The measured outcomes represent distinct cardiometabolic processes. LDL-C is a cholesterol-carrying lipoprotein causally linked to atherosclerotic cardiovascular disease when exposure is elevated [1]. FPG measures glucose after fasting, whereas FPI measures circulating insulin under fasting conditions; HOMA-IR combines these measures to estimate insulin resistance [2,3]. AST is an aminotransferase enzyme involved in amino-acid metabolism and can increase with hepatocellular or muscle injury. Because AST is present in liver, cardiac muscle, and skeletal muscle, it is not liver-specific [24] and was interpreted as an exploratory tissue-related safety marker rather than a direct glycemic endpoint.

Study	Population	Intervention type	Baseline glycemic stratum	Measured outcomes
Asai 2011 [16]	Adults with impaired glucose metabolism	MLE	Prediabetic	HbA1c, LDL-C, FPG, insulin, AST
Momeni 2021 [17]	Adults with diabetes	Morus nigra leaf extract	Diabetic	HbA1c
Riche 2017 [18]	Adults with type 2 diabetes on stable oral therapy	MLE	Diabetic	HbA1c
Sohail 2020 [19]	Adults with type 2 diabetes on oral hypoglycemics	ML	Diabetic	HbA1c
Taghizadeh 2019/2022 [20]	Adults with type 2 diabetes	MLE	Diabetic	HbA1c, HOMA-IR, LDL-C, FPG, FPI, AST
Thaipitakwong 2019/2020 [21]	Obese persons with borderline diabetes	ML tablets	Prediabetic	HbA1c, HOMA-IR, FPG, FPI
Yang 2006 [22]	Adults with type 2 diabetes	MLE	Diabetic	HbA1c, LDL-C
Yasumoto 2022 [23]	Healthy adults in a safety study	MLE beverage	Non-diabetic	HbA1c, LDL-C, AST

Table 1. Characteristics of the eight randomized controlled trials included in the synthesis. The table summarizes population, intervention, baseline glycemic stratum, and measured outcomes. Asai et al. [16] reported fasting glucose and insulin but did not directly report HOMA-IR and was therefore not counted as a HOMA-IR outcome in the quantitative synthesis. Abbreviations: AST, aspartate aminotransferase; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; ML, mulberry leaf; MLE, mulberry leaf extract.

Primary outcome: HbA1c

Across eight trials [16-23], ML/MLE was associated with a statistically significant reduction in HbA1c (MD -0.22 percentage points, 95% CI -0.39 to -0.06; $p = 0.009$) (Figure 2). Seven of eight trial point estimates favored ML/MLE, a descriptive directional pattern rather than a separate significance test. The pooled confidence interval excluded the null value of 0. Study weights ranged from 2.2% to 21.2%, so no single trial dominated the estimate. Between-study heterogeneity was moderate ($I^2 = 51\%$), indicating variation in effect magnitude across populations and formulations.

HbA1c subgroup analysis by baseline HbA1c

Baseline glycemic strata included one non-diabetic trial, two prediabetic trials, and five diabetic trials [16-23] (Figure 3). The non-diabetic subgroup included 44 participants and showed no between-group difference (MD 0.00 percentage points, 95% CI -0.24 to 0.24; $p = 1.00$). The prediabetic subgroup included 119 participants and favored ML/MLE (MD -0.14 percentage points, 95% CI -0.28 to -0.00; $p = 0.04$; $I^2 = 0\%$). The diabetic subgroup included 277 participants and showed the largest reduction (MD -0.42 percentage points, 95% CI -0.66 to -0.18; $p = 0.0005$; $I^2 = 16\%$). Point estimates therefore became more favorable as baseline glycemic status worsened, though this was not a formal test of subgroup interaction.

Secondary outcomes: HOMA-IR and LDL-C

Two trials [20,21] directly reported HOMA-IR and contributed 57 ML/MLE participants and 54 controls. ML/MLE produced a statistically significant reduction in HOMA-IR (MD -0.64, 95% CI -1.27 to -0.02; $p = 0.04$; $I^2 = 18\%$) (Figure 4A). Both point estimates favored ML/MLE as a descriptive directional pattern, and heterogeneity was low. For Thaipitakwong et al. [21], the change-from-baseline SD was imputed using the HOMA-IR correlation coefficient of 0.769 derived from directly reported HOMA-IR change data. Asai et al. [16] reported fasting glucose and insulin but not HOMA-IR or the covariance information needed to reconstruct a defensible HOMA-IR variance [25]; it was therefore not pooled for this outcome.

Four trials [20-23] reported LDL-C, comprising 93 ML/MLE participants and 85 controls. All four point estimates favored ML/MLE, but the pooled reduction was not statistically significant (MD -6.21 mg/dL, 95% CI -15.37 to 2.94; $p = 0.18$; $I^2 = 0\%$) (Figure 4B). The direction was concordant and no heterogeneity was detected, but the confidence interval included the null value of 0. A correlation coefficient of 0.400 was used when LDL-C change-from-baseline SDs required imputation. Table 2 summarizes the primary, secondary, and selected exploratory outcomes.

Summary of Outcomes

Outcome	Studies	Analyzed n (ML/control)	Correlation coefficient used for imputation	Pooled mean difference (95% CI)	I ²
Overall HbA1c	8	224 / 216	0.433	-0.22% (-0.39 to -0.06)	51%
Non-diabetic HbA1c	1	22 / 22	0.433	0.00% (-0.24 to 0.24)	N/A
Prediabetic HbA1c	2	61 / 58	0.433	-0.14% (-0.28 to -0.00*)	0%
Diabetic HbA1c	5	141 / 136	0.433	-0.42% (-0.66 to -0.18)	16%
HOMA-IR	2	57 / 54	0.769	-0.64 (-1.27 to -0.02)	18%
LDL-C	4	93 / 85	0.400	-6.21 mg/dL (-15.37 to 2.94)	0%
AST	4	93/85	0.452	-1.23 U/L (-4.00 to 1.54)	34%

Table 2. Summary of outcomes. HbA1c values are NGSP percentage-point changes, not relative percentage changes. Correlation coefficients were used only to impute missing change-from-baseline SDs and should not be interpreted as treatment-outcome correlations [13]. The same HbA1c coefficient was used across glycemic strata because the subgroups came from the same outcome dataset. For HOMA-IR, Taghizadeh et al. [20] reported change-from-baseline SDs directly, and the outcome-specific coefficient of 0.769 was used for Thaipitakwong et al. [21]. For LDL-C, the coefficient used for imputation was 0.400. HOMA-IR is reported without a physical unit. *-0.00 is retained because this is the greatest precision displayed by RevMan 5.4.1.

Exploratory tertiary outcomes

Four trials [20-23] comprising 93 participants receiving ML/MLE and 85 controls contributed AST data. The pooled estimate favored ML/MLE but was not statistically significant (MD -1.23 U/L, 95% CI -4.00 to 1.54; $p = 0.38$; $I^2 = 34\%$). Descriptively, three study point estimates favored ML/MLE and one favored control. Because the confidence interval was compatible with either a small reduction or a small increase in AST, no treatment or hepatic safety effect could be established.

Other exploratory outcomes were assessed in the supplementary analyses. ALT showed no clear between-group difference across three trials (MD 1.99 U/L, 95% CI -2.08 to 6.07; $p = 0.34$; $I^2 = 12\%$) (Supplementary Figure S1). FPG likewise showed essentially no pooled difference across three trials (MD -0.07 mg/dL, 95% CI -4.69 to 4.55; $p = 0.98$; $I^2 = 22\%$) (Supplementary Figure S2). FPI was available from one trial and was not significantly different between groups (MD -1.63 μ U/mL, 95% CI -5.37 to 2.11; $p = 0.39$) (Supplementary Figure S3). HDL-C was not significantly different across four trials and showed

substantial heterogeneity (MD 2.83 mg/dL, 95% CI -6.89 to 12.56; $p = 0.57$; $I^2 = 90\%$) (Supplementary Figure S4). Insulin across two trials was also not significantly different and showed substantial heterogeneity (MD -1.05 μ U/mL, 95% CI -3.99 to 1.89; $p = 0.48$; $I^2 = 71\%$) (Supplementary Figure S5).

Total cholesterol was lower with ML/MLE across two post-intervention comparisons (MD -17.63 mg/dL, 95% CI -29.65 to -5.62; $p = 0.004$; $I^2 = 0\%$) (Supplementary Figure S6), whereas triglycerides showed a favorable but non-significant pooled reduction across four trials (MD -20.55 mg/dL, 95% CI -42.92 to 1.83; $p = 0.07$; $I^2 = 50\%$) (Supplementary Figure S7). VLDL was reported by a single trial and favored ML/MLE (MD -8.90 mg/dL, 95% CI -14.61 to -3.19; $p = 0.002$) (Supplementary Figure S8); this is a descriptive single-study result rather than pooled evidence. These exploratory analyses identify outcomes that should be measured more consistently in future trials.

Small-study effects

Formal publication-bias testing was not performed because fewer than 10 studies contributed to each analysis, a setting in which funnel-plot asymmetry tests are underpowered [13].

Risk of bias

Using RoB 2, overall risk of bias was low in 1 of 8 studies (12.5%), raised some concerns in 6 of 8 (75%), and was high in 1 of 8 (12.5%) (Figure 5). Measurement of the outcome was judged low risk in all studies. Most "some concerns" judgments reflected incomplete reporting of randomization procedures or prespecified analysis plans rather than direct evidence that the reported outcomes were selectively altered. Asai et al. [16] received the only high-risk judgment because the report did not clarify whether eight participants who did not complete the intervention were retained in an intention-to-treat analysis. Future trials should preregister protocols, describe randomization and allocation procedures, publish analysis plans, and report participant flow and ITT handling explicitly [15].

Contextual baseline-response analysis

In the Bloomgarden reference dataset [6], ordinary least-squares regression showed that higher baseline HbA1c was associated with a larger downward HbA1c change (Pearson $r = -0.35$; $p < 0.001$) (Figure 6). Seven of eight ML/MLE trial estimates fell within the model's 50% prediction interval at their respective baseline values, and the remaining trial fell within the 80% interval; all eight were within the 95% interval. ML/MLE points were not used to fit the regression. Because Bloomgarden observations began at 6.40%, the lower-baseline segment is a limited linear extrapolation. The comparison therefore supports clinical plausibility of the observed HbA1c magnitude but does not establish head-to-head equivalence with glucose-lowering medications.

Discussion

Across the three core cardiometabolic outcomes, HbA1c and HOMA-IR showed statistically significant pooled reductions, whereas LDL-C showed a consistent but non-significant favorable direction. The HbA1c subgroup point estimates were smallest in the non-diabetic stratum and largest in the diabetic stratum; this is a descriptive trend rather than evidence of a statistically tested interaction. The pattern is nevertheless compatible with the broader observation that glucose-lowering interventions often produce larger absolute reductions when baseline HbA1c is higher [6].

The baseline-response analysis adds clinical context to the HbA1c finding. All eight ML/MLE estimates fell within the 95% prediction interval of the oral glucose-lowering reference model, including seven within the 50% interval (Figure 6). Because this is a study-level comparison and the reference model required limited extrapolation below a baseline HbA1c of 6.40%, it supports plausibility of the observed magnitude rather than therapeutic equivalence [6].

The diabetic subgroup showed the largest HbA1c reduction, but between-trial differences in baseline severity, background therapy, diet, genetics, formulation, and duration may contribute to variation. The interventions included powders, tablets, standardized extracts, beverages, and tea-based preparations, and ML/MLE products can differ in iminosugars, flavonoids, phenolics, polysaccharides, and other constituents [8-10]. These differences limit direct dose comparison and may partly explain heterogeneity among similarly labeled interventions.

Formulation and extraction methods can alter the amount and composition of bioactive material delivered. Extraction yield varies with solvent composition, solvent-to-sample ratio, time, temperature, cultivar, harvest timing, and processing [8-10,26,27]; 1-DNJ content and alpha-glucosidase inhibitory activity also vary across cultivars and harvest periods [27]. Future trials should therefore report species or cultivar, extraction conditions, formulation, dose, and quantified constituents when available so that biological exposure can be compared across studies.

HOMA-IR extends the analysis beyond average glucose exposure by addressing insulin resistance, a cardiometabolic process closely linked to cardiovascular disease [2,3]. The pooled reduction was statistically significant (MD -0.64, 95% CI -1.27 to -0.02; $p = 0.04$; $I^2 = 18\%$), but only 111 participants contributed. This supports HOMA-IR as an important confirmatory endpoint while leaving substantial uncertainty about the magnitude and generalizability of the effect.

Asai et al. [16] illustrates why component fasting measures cannot automatically be converted into a meta-analyzable HOMA-IR outcome. The study reported fasting glucose and insulin, so a group-level HOMA-IR point estimate could be approximated using the standard equations described in Methods. However, the HOMA-IR SD depends on glucose and insulin variances and their covariance, and change-from-baseline variance also depends on within-participant covariance over time [25]. Those covariance terms and participant-level data were unavailable, so reconstructing an SD would have required unsupported assumptions and could have distorted study precision and meta-analytic weight.

LDL-C showed a consistent directional pattern: all four point estimates favored ML/MLE, with a pooled MD of -6.21 mg/dL (95% CI -15.37 to 2.94; $p = 0.18$; $I^2 = 0\%$). Because the CI included 0, this remains a promising signal rather than a confirmed effect. Preclinical work by Cao et al. [28] found that MLE and 1-DNJ improved glucose and lipid metabolism and cardiac function in a diabetic cardiomyopathy model while reducing myocardial fibrosis. That work provides mechanistic, not clinical, support for continued evaluation of lipid and cardiovascular outcomes.

Exploratory lipid outcomes provided additional context. Total cholesterol was lower with ML/MLE across two post-intervention comparisons (MD -17.63 mg/dL, 95% CI -29.65 to -5.62; $p = 0.004$; $I^2 = 0\%$) (Supplementary Figure S6). Triglycerides showed a favorable but non-significant pooled reduction across four trials (MD -20.55 mg/dL, 95% CI -42.92 to 1.83; $p = 0.07$; $I^2 = 50\%$) (Supplementary Figure S7). VLDL favored ML/MLE in one trial (Supplementary Figure S8). These findings are hypothesis-generating because the evidence base is small and exploratory.

Other tertiary outcomes were less consistent. AST showed no clear pooled effect (Table 2); ALT (Supplementary Figure S1) and FPG (Supplementary Figure S2) also showed little evidence of between-group effects. FPI was available from only one trial (Supplementary Figure S3), while HDL-C (Supplementary Figure S4) and insulin (Supplementary Figure S5) were non-significant and heterogeneous ($I^2 = 90\%$ and 71%). These patterns support measuring a standardized cardiometabolic panel in future trials rather than relying on isolated markers.

This review differs from the earlier ML/MLE glycemic meta-analysis by Cui et al. [7] by jointly prioritizing HbA1c, HOMA-IR, and LDL-C while excluding trials that were too short or did not permit isolation of the mulberry intervention. Under the current outcome definitions, both HbA1c and HOMA-IR showed statistically significant pooled reductions, whereas LDL-C showed a descriptively uniform favorable direction across all contributing trials and a pooled decrease of -6.21 mg/dL that was not statistically significant. Statistical significance should not be interpreted as proof that one outcome analysis is inherently more accurate than another; the HOMA-IR and LDL-C evidence bases remain small, and the precision of each estimate reflects the number and characteristics of the contributing trials.

An important direction for future research is the study of individual compounds found in mulberry leaf. One compound of particular interest is 1-deoxynojirimycin (1-DNJ), a potent alpha-glucosidase inhibitor found in mulberry leaves [29]. Asai et al. [16] used a mulberry leaf extract enriched in 1-DNJ, but increasing the concentration of one compound within a complex extract cannot determine whether that compound alone explains the clinical effect. A more informative next step would be a randomized trial evaluating isolated 1-DNJ as a separate intervention, with an appropriate comparator and standardized dose, rather than only enriching mulberry extract. Such a design would help distinguish the effects of 1-DNJ from those of flavonoids, phenolics, polysaccharides, iminosugars, and other constituents of ML/MLE [8-10,28].

Because ML/MLE contains multiple bioactive compounds, the present results should not be attributed to 1-DNJ alone [8-10,28]. The available trials were designed to test whole-leaf or extract formulations, not

isolated compounds. Therefore, any mechanistic interpretation remains provisional until individual constituents are evaluated directly in controlled clinical trials.

ML/MLE also has practical relevance because mulberry leaf is consumed in East Asia as herbal tea, while powders, extracts, and capsules are used as dietary supplements [8,30]. Mulberry-leaf tea can be prepared in a caffeine-free format [30]. These familiar formulations make tea and standardized MLE tablets or capsules practical formats for further controlled study. However, the current evidence is not sufficient to recommend routine supplementation; any future adjunctive role alongside established diet, lifestyle, and pharmacologic care requires confirmation of efficacy, safety, and preparation standardization.

Future randomized trials should prioritize participants with elevated HbA1c, while prospectively measuring HOMA-IR and LDL-C as key secondary outcomes. Studies should last longer than 4 weeks, use standardized ML/MLE preparations, quantify intervention composition, and report HbA1c, HOMA-IR, and LDL-C consistently so that effect magnitude and reproducibility can be established [8-10,26,27].

Taken together, ML/MLE remains a promising complementary intervention for impaired glycemic control, but the evidence is not yet sufficient to establish routine clinical use. The strongest current support is for HbA1c, with a smaller HOMA-IR evidence base and an encouraging but unconfirmed LDL-C signal. Larger standardized trials are needed before recommendations about formulation, dose, or target population can be made.

Limitations

Several limitations should be acknowledged. HOMA-IR was supported by only two trials and LDL-C by four, limiting precision. Formulations, species, doses, populations, and trial durations varied [8-10,26,27], and some change-from-baseline SDs required correlation-based imputation. Most trials were not designed around cardiovascular outcomes, which limited lipid data. Finally, most studies had at least some risk-of-bias concerns because randomization details or prespecified analysis plans were incompletely reported.

Conclusions

ML/MLE was associated with statistically significant reductions in HbA1c and HOMA-IR, while LDL-C showed a consistent but non-significant favorable signal. HbA1c reductions were largest in diabetic-baseline trials, although the subgroup pattern was descriptive rather than a formal interaction finding. The baseline-adjusted comparison with oral glucose-lowering studies supports clinical plausibility of the HbA1c response without demonstrating therapeutic equivalence.

The results support larger, longer, standardized randomized trials in populations with elevated HbA1c, with HOMA-IR and LDL-C measured prospectively as key secondary outcomes. Such studies should

define reproducible preparations and doses, confirm durability of the glycemic effect, and determine whether the HOMA-IR and LDL-C signals translate into clinically meaningful adjunctive benefit.

Abbreviations

AST, aspartate aminotransferase; CI, confidence interval; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA1c, hemoglobin A1c (glycated hemoglobin); HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; MD, mean difference; ML, mulberry leaf; MLE, mulberry leaf extract; NGSP, National Glycohemoglobin Standardization Program; RoB 2, Revised Cochrane risk-of-bias tool for randomized trials 2; SD, standard deviation; VLDL, very-low-density lipoprotein.

Declarations

Ethics approval and consent to participate

Not applicable. This systematic review and meta-analysis used published aggregate data only.

Consent for publication

Not applicable.

Availability of data and materials

All data analyzed in this review were derived from the cited published studies and are summarized in this article and its supplementary information.

Competing interests

No competing interests.

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Authors' contributions

G.K., J.K., and K.K. conceptualized the study and contributed to the formal analysis, project administration, supervision, and validation. G.K. and J.K. developed the methodology and performed the software-related work. G.K., J.K., P.B., B.A.N., A.T.N., M.S., and P.P. conducted data curation and investigation, listed in descending order of contribution to study screening. G.K. led the collection of quantitative data, raw data extraction, organization, and summarization of the meta-analytic dataset in

Google Sheets, while J.K. also conducted data extraction. G.K. prepared all visualizations and wrote the original manuscript draft. G.K., J.K., P.B., B.K., and K.K. reviewed and edited the manuscript.

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Not applicable.

Supplementary Information

Supplementary materials include the completed PRISMA 2020, PRISMA for Abstracts, and PRISMA-S checklists [11,12] and Supplementary Figures S1-S8. The relevance and quantitative findings for each supplementary forest plot are described in the Results section.

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Figures

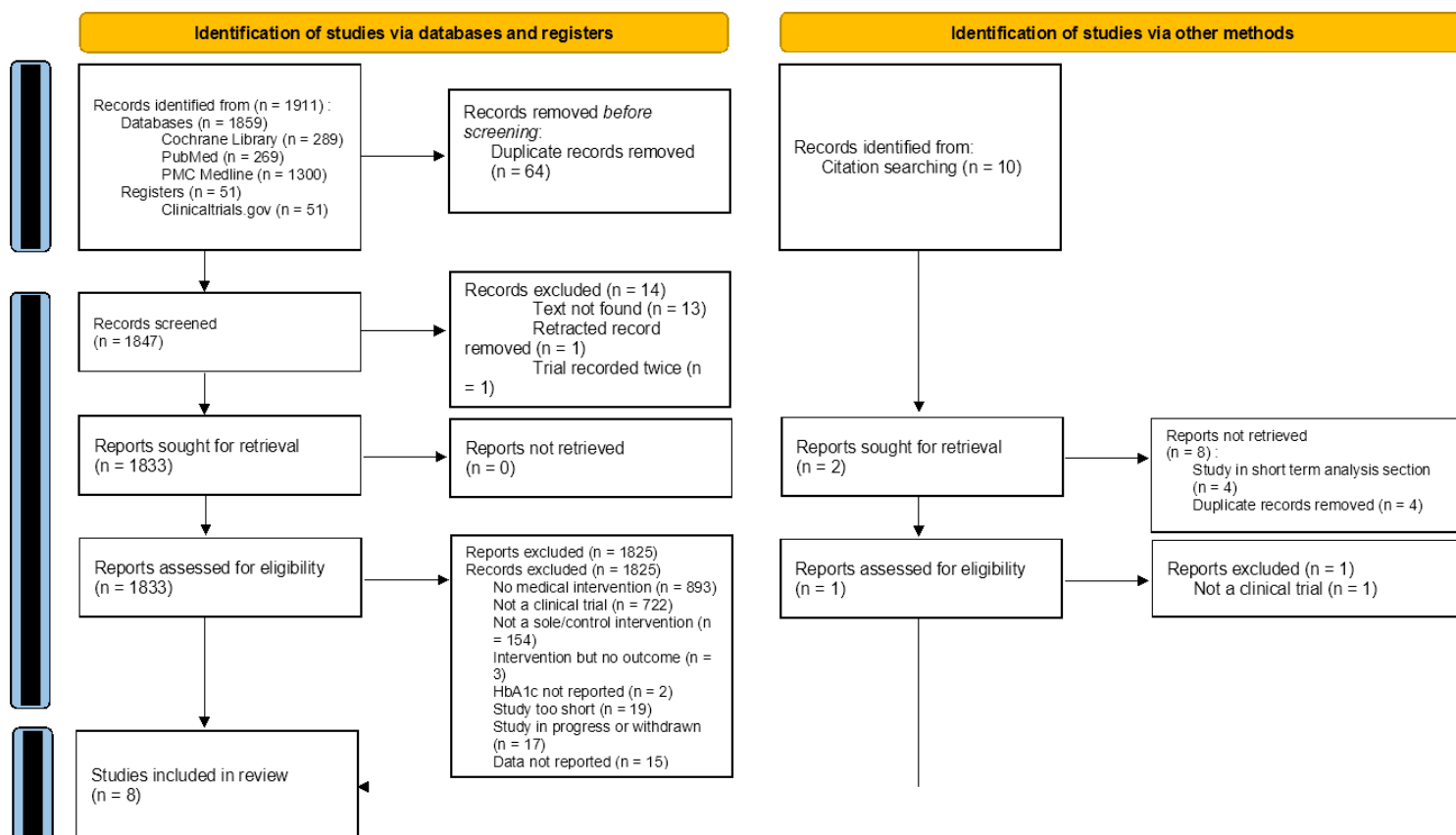


Figure 1

PRISMA 2020 flow diagram for the mulberry leaf review. The diagram shows the numbers of records identified, screened, excluded, and included through database and registry searching [11].

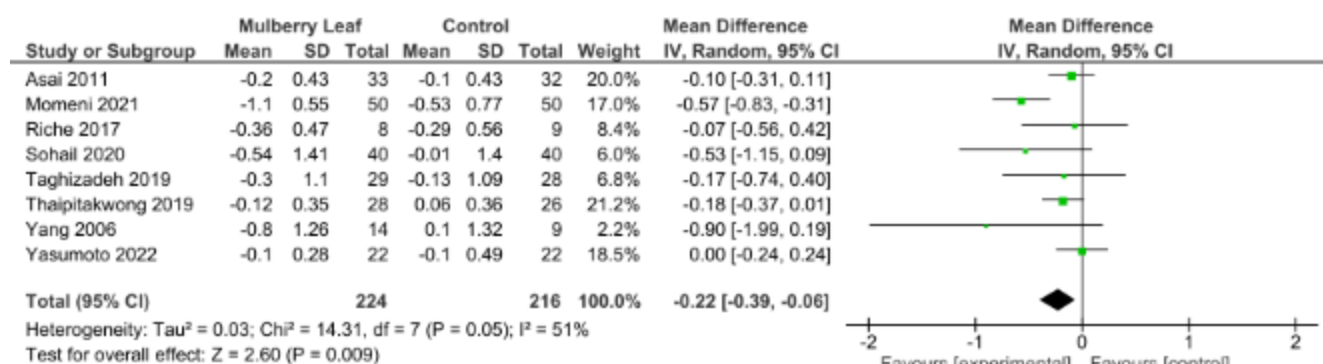
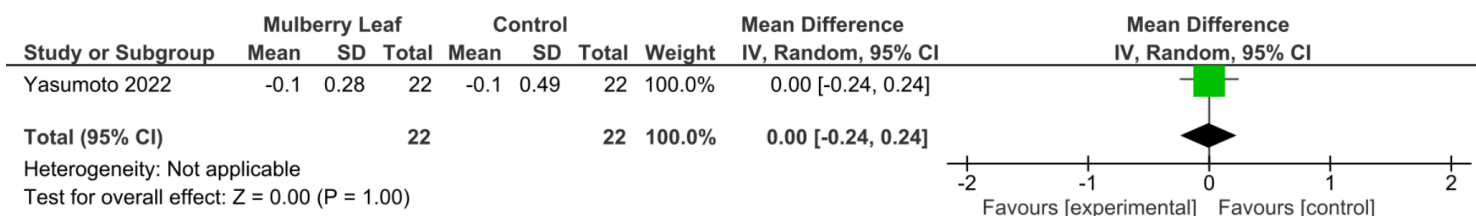


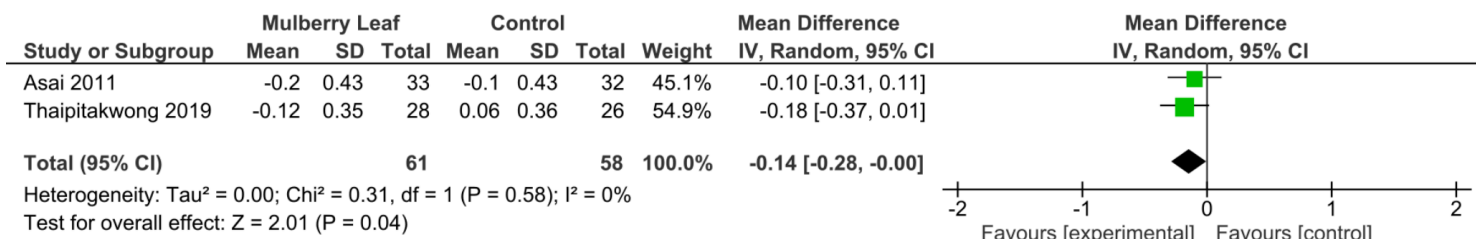
Figure 2

Forest plot of the overall effect of ML/MLE on HbA1c. The pooled mean difference was -0.22 percentage points (95% CI -0.39 to -0.06; $p = 0.009$), with moderate heterogeneity ($I^2 = 51\%$).

A.



B.



C.

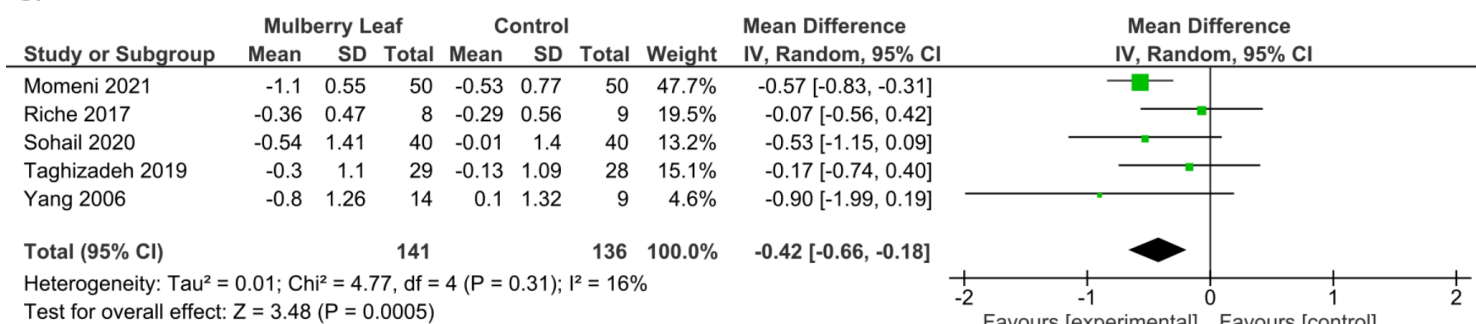
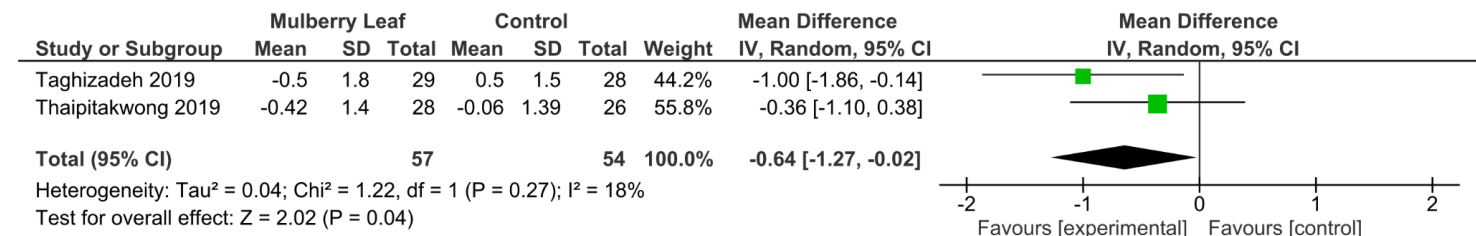


Figure 3

HbA1c subgroup analyses by mean baseline glycemic status: A, non-diabetic; B, prediabetic; C, diabetic. Point estimates became progressively more favorable across strata, but no formal subgroup-interaction test was performed.

A.



B.

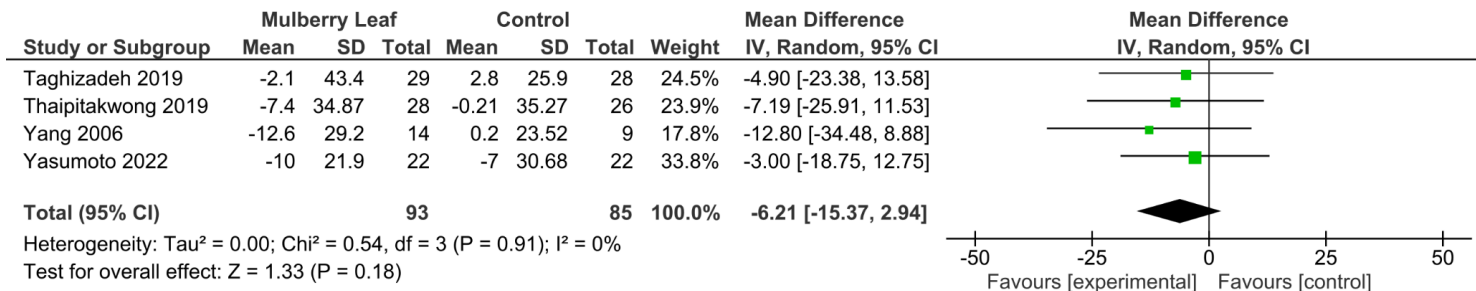


Figure 4

Secondary cardiometabolic outcomes. A, HOMA-IR: pooled MD -0.64 (95% CI -1.27 to -0.02; $p = 0.04$; $I^2 = 18\%$). B, LDL-C: pooled MD -6.21 mg/dL (95% CI -15.37 to 2.94; $p = 0.18$; $I^2 = 0\%$); the four point estimates showed a concordant directional trend, but the pooled CI included 0.

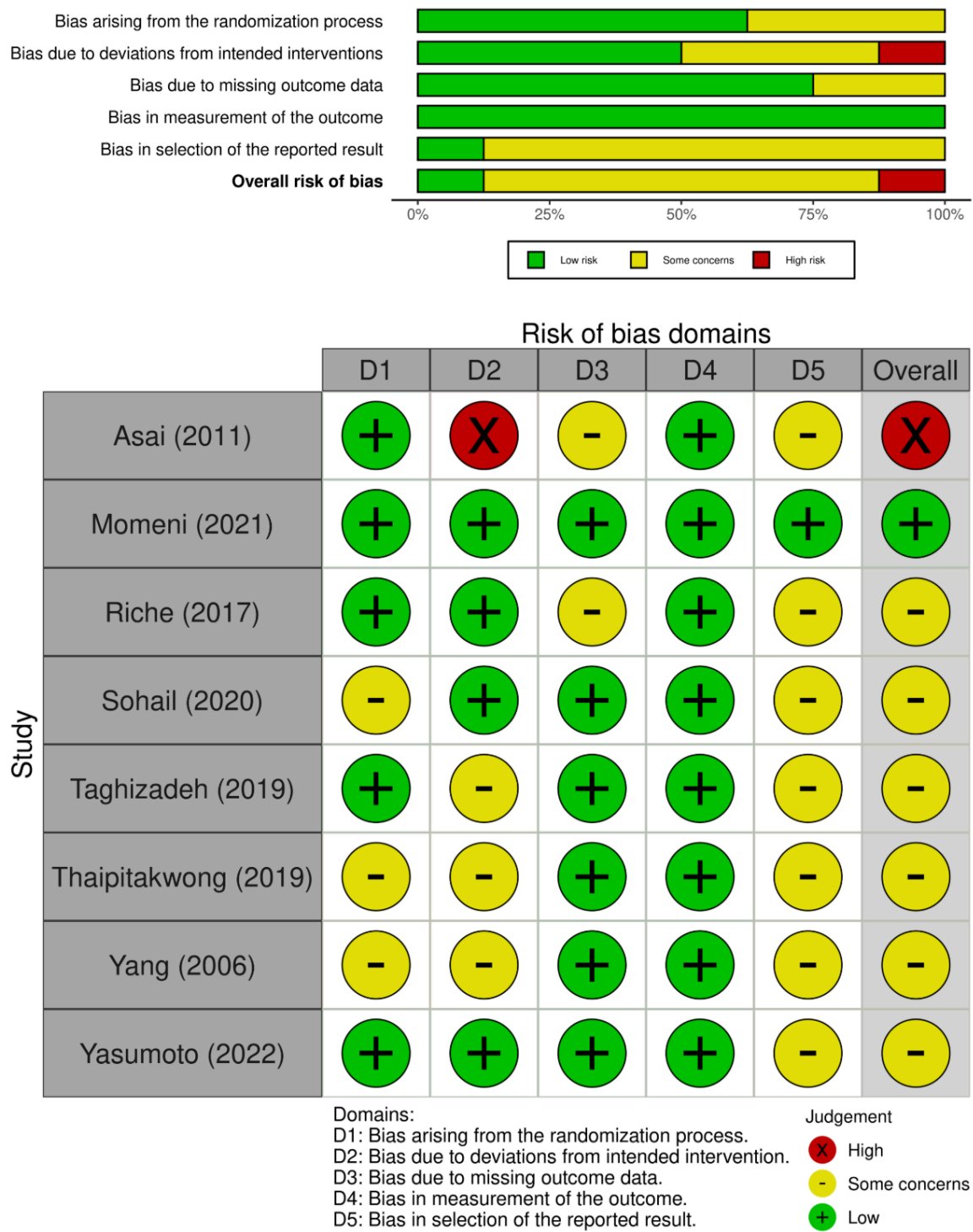


Figure 5

RoB 2 assessment of included trials. Top: proportion of judgments by domain. Bottom: trial-level traffic-light summary. Six of eight trials had some concerns overall, primarily from incomplete reporting of randomization or analysis plans; one trial was low risk and one was high risk.

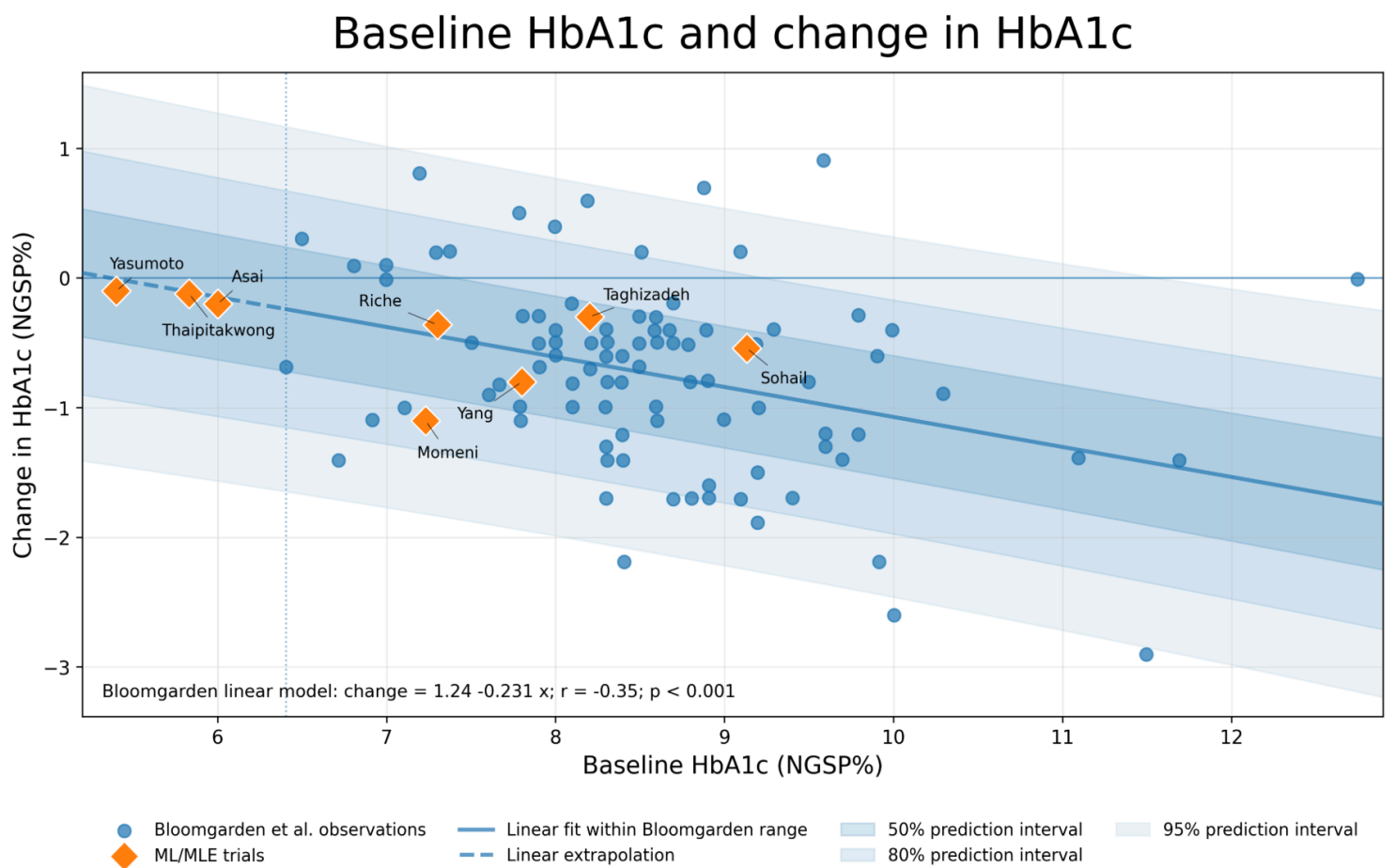


Figure 6

Baseline HbA1c and HbA1c change in Bloomgarden and ML/MLE trials. Circles represent Bloomgarden study-level observations, and enlarged diamonds identify the ML/MLE trials. The solid line shows the fitted linear association over the observed Bloomgarden baseline range, while the dashed segment extends the same model to lower baseline HbA1c values. The nested shaded bands indicate the 50%, 80%, and 95% prediction intervals for an individual Bloomgarden-like study-level observation, not the confidence interval for the mean trend or a within-trial confidence interval. ML/MLE points were not used to fit the model.

Supplementary Files

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