Meta-Analysis

Effect of honey on cardiometabolic risk factors: a systematic review and meta-analysis

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Context: *Excess calories from free sugars are implicated in the epidemics of obesity and type 2 diabetes. Honey is a free sugar but is generally regarded as healthy.* ***Objective:*** *The effect of honey on cardiometabolic risk factors was assessed via a systematic review and meta-analysis of controlled trials using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.* ***Data Sources:*** *MEDLINE, Embase, and the Cochrane Library databases were searched up to January 4, 2021, for controlled trials ≥1 week in duration that assessed the effect of oral honey intake on adiposity, glycemic control, lipids, blood pressure, uric acid, inflammatory markers, and markers of nonalcoholic fatty liver disease.* ***Data Extraction:*** *Independent reviewers extracted data and assessed risk of bias. Data were pooled using the inverse variance method and expressed as mean differences (MDs) with 95%CIs. Certainty of evidence was assessed using GRADE.* ***Data Analysis:*** *A total of 18 controlled trials (33 trial comparisons, N = 1105 participants) were included. Overall, honey reduced fasting glucose (MD = −0.20 mmol/L, 95%CI, −0.37 to −0.04 mmol/L; low certainty of evidence), total cholesterol (MD = −0.18 mmol/L, 95%CI, −0.33 to −0.04 mmol/L; low certainty), low-density lipoprotein cholesterol (MD = −0.16 mmol/L, 95%CI, −0.30 to −0.02 mmol/L; low certainty), fasting triglycerides (MD = −0.13 mmol/L, 95%CI, −0.20 to −0.07 mmol/L; low certainty), and alanine aminotransferase (MD = −9.75 U/L, 95%CI, −18.29*

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https://doi.org/10.1093/nutrit/nuac086

to −1.21 U/L; low certainty) and increased high-density lipoprotein cholesterol (MD = 0.07 mmol/L, 95%CI, 0.04–0.10 mmol/L; high certainty). There were significant subgroup differences by floral source and by honey processing, with robinia honey, clover honey, and raw honey showing beneficial effects on fasting glucose and total cholesterol. ***Conclusion:*** *Honey, especially robinia, clover, and unprocessed raw honey, may improve glycemic control and lipid levels when consumed within a healthy dietary pattern. More studies focusing on the floral source and the processing of honey are required to increase certainty of the evidence.*
Systematic Review Registration: *PROSPERO registration number CRD42015023580.*

INTRODUCTION

High intake of added or free sugars has been shown to contribute to the rise in obesity, type 2 diabetes, and cardiovascular disease.[1] Health and nutrition guidelines call for a reduction in consumption of added sugars, with health agencies recommending an intake of no more than 5% to 10% of total energy intake per day.[2,3] Most regulatory agencies, including the World Health Organization, the Heart and Stroke Foundation, and the US Food and Drug Administration, include honey within their definition of free or added sugars.[2–4] In contrast, honey is often regarded by the public as a healthier alternative to sugar, with the National Honey Board Consumer Attitudes and Usage Study of 2020 reporting that honey had surpassed white sugar as the preferred sweetener.[5,6]

Honey is a complex composition of sugars (common and rare), organic acids, enzymes, proteins, amino acids, minerals, vitamins, and bioactive substances made by honeybees from the nectar of flowers.[7,8] It has shown many benefits for cardiometabolic health in in vitro, animal, and clinical trials. Among these benefits are improvements in body weight, inflammation, lipid profile, and glycemic control. However, the evidence for this effect in human studies has not been systematically evaluated and quantified.[9,10] Furthermore, it is unclear whether the effect of honey differs by the type of honey, such as floral source, and whether honey is raw or processed. Therefore, a systematic review and meta-analysis of controlled trials was conducted to examine the effect of honey intake on adiposity, glycemia, lipids, blood pressure, markers of nonalcoholic fatty liver disease, and inflammatory markers and to assess the certainty of the evidence using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.

METHODS

This systematic review and meta-analysis was conducted according to the *Cochrane Handbook for Systematic Reviews of Interventions* (version 6.1) and reported using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (see Table S1 in the Supporting Information online).[11,12] The study protocol is registered at PROSPERO (registration number CRD42015023580).

Data sources and search strategy

The MEDLINE, Embase, and Cochrane Central Register of Controlled Studies databases were searched through January 4, 2021. Tables S2 and S3 in the Supporting Information online present the search strategy. Validated filters from the McMaster University Health Information Research Unit were applied to limit the database search to controlled studies only.[13] Electronic searches were supplemented with manual searches of references from included studies.

Study selection

Randomized and nonrandomized controlled feeding trials in humans of all health backgrounds and ages, with intervention periods of 7 days or more, that investigated the effect of oral honey intake on adiposity (body weight, body mass index [BMI], waist circumference), glycemic control (fasting glucose, fasting insulin, glycated hemoglobin [HbA_{1c}], homeostasis model assessment of insulin resistance [HOMA-IR]), lipids (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], fasting triglycerides, apolipoprotein B), blood pressure (systolic blood pressure [SBP], diastolic blood pressure [DBP]), uric acid, inflammatory markers (tumor necrosis factor α [TNF-α], interleukin 6 [IL-6], high-sensitivity C-reactive protein), and markers of nonalcoholic fatty liver disease (alanine aminotransferase [ALT], aspartate aminotransferase, and intrahepatocellular lipid content) were included. Trials in which honey was consumed with a cointervention (so that the

effect of honey itself could not be isolated) or studies that lacked an adequate comparator were excluded. No restrictions were placed on language.

Data extraction and quality assessment

The following data were extracted from each eligible study by at least 2 authors independently from a pool of 12 (A.A., D.L., Z.N., S.B., Z.A., S.Z., M.S., F.J., F.Q., F.Z., R.B., and S.A.): sample size, participant health status, participant age, study setting, study design, comparator, randomization method, floral source of honey, processing of honey, form in which honey was delivered, energy control (whether honey was added or substituted in the diet), energy balance, duration of intervention, funding source, and outcome data (see Table S4 in the Supporting Information online). Authors were contacted for missing outcome data when it was indicated that an outcome was measured but not reported. If outcome data were missing and it was not possible to obtain the original data from authors, values were extracted from figures using PlotDigitizer software, where available.[14]

Each eligible study was assessed independently for risk of bias by at least 2 authors from a pool of 12 (A.A., D.L., Z.N., S.B., Z.A., S.Z., M.S., F.J., F.Q., F.Z., R.B., and S.A.) using the Cochrane Risk of Bias Tool.[15] Six domains of bias were assessed (sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias [carryover effects]). Risk of bias was assessed as low (proper methods used to reduce bias), high (improper methods used that created bias), or unclear (insufficient information provided to determine the bias level). Crossover trials that did not have a washout period between interventions were assigned a high risk of bias in the "other" (carryover effects) category; otherwise, the trial was assigned a low risk of bias for this domain. All discrepancies were resolved through consensus or arbitration by the senior authors (T.A.K. and J.L.S.).

Outcomes

Mean differences (MDs) and standard errors between the intervention and control arms were extracted for each trial. If these values were not provided, they were calculated using published formulas.[11] Mean pairwise difference in change-from-baseline values were preferred over end values. When median data were reported, they were converted to mean data and variances using methods developed by Tiejun Tong and colleagues.[16–18]

Data syntheses and analyses

All analyses were performed using Stata software, version 16.1 (StataCorp; College Station, TX, USA). The principal effect measures were the mean pairwise differences in change from baseline (or, alternatively, end differences) between the oral honey intake arm and the comparator arm. Data were analyzed using the generic inverse variance method with the DerSimonian and Laird random-effects model.[19] A fixed-effects model was used when fewer than 5 trial comparisons were available.[20] Paired analyses were applied to all crossover trials by using a within-individual correlation coefficient between treatments of 0.5 for statistical efficiency.[21–23] When the intervention or control arms were used more than once, the sample size was divided by the number of times it was used to mitigate unit-of-analysis error.[11] Each pairwise comparison was considered a separate trial for the purpose of this analysis.

Heterogeneity was assessed using the Cochran Q statistic and quantified using the I^2 statistic.[11] Evidence of substantial heterogeneity was considered when I^2 was greater than 50% and P_Q (P value for heterogeneity) was less than 0.10.[11] Sources of heterogeneity were explored by sensitivity analysis and subgroup analysis. In sensitivity analysis, each trial was systematically removed from the meta-analyses, and then the summary effect estimate was recalculated. A study was considered influential when its removal explained the heterogeneity, changed the significance of the effect, or altered the effect size for an outcome by the minimally important difference or more.

Sensitivity analyses were also performed using correlation coefficients of 0.25 and 0.75 to determine whether the overall results were robust to the use of different correlation coefficients in crossover trials. When 4 or more trial comparisons were available, subgroup analyses were conducted using meta-regression, with significance at $P < 0.05$.[24] A priori subgroup analyses were conducted by floral source of honey, whether honey was processed, participant health status, type of comparator, dose of honey, duration of follow-up, study design, baseline BMI, and individual domains of risk of bias. Post hoc subgroup analyses were conducted by participant age, randomization method, feeding control, energy control, energy balance, and funding source. Meta-regression analyses were performed to assess the significance of each subgroup categorically, and continuously when possible. If there was effect modification by honey floral source or processing of honey, these effects were further explored by post hoc meta-analyses.

Dose-response analyses were performed using meta-regression to assess linear and nonlinear (restricted cubic splines) dose-response gradients (significance at $P < 0.05$) if there were 6 or more trials.[24]

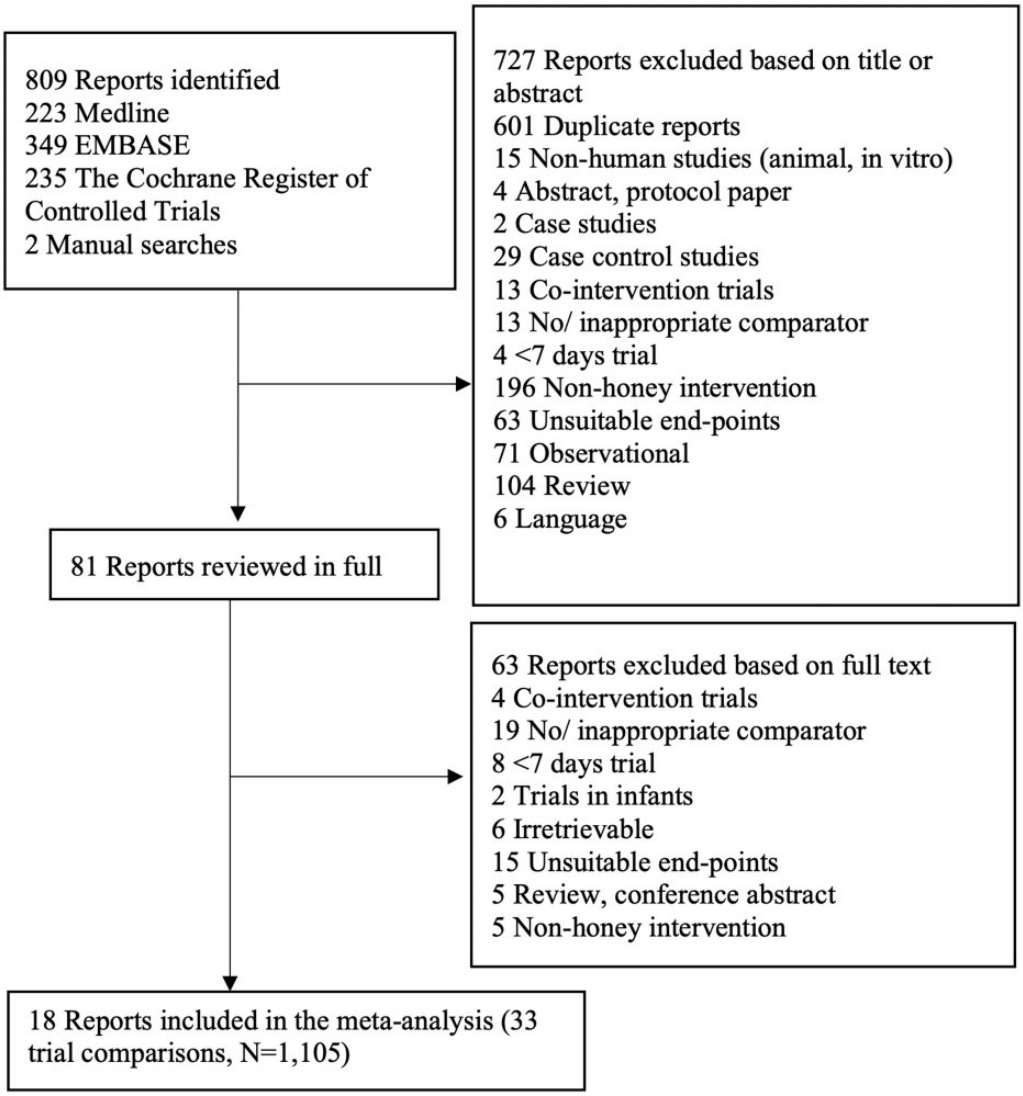

Figure 1 **Flow diagram of the literature search process.**

When at least 10 studies were available, publication bias was assessed by inspection of contour-enhanced funnel plots and formal testing with Egger and Begg tests (significance at $P < 0.10$).[25–27] If evidence of publication bias was suspected, the Duval and Tweedie trim-and-fill method was performed to adjust for funnel plot asymmetry by imputing missing study data and assessing for small-study effects.[28]

Certainty of the evidence

The GRADE approach was used to assess the certainty of the estimates and to produce evidence profiles, with the certainty of evidence graded as high, moderate, low, or very low (GRADEpro GDT software; McMaster University and Evidence Prime Inc, Hamilton, Ontario, Canada).[29–36] Controlled trials receive an initial grade of high certainty and are then downgraded on basis of the following prespecified criteria: risk of bias (assessed by the Cochrane Risk of Bias Tool[15]), inconsistency (substantial unexplained interstudy heterogeneity, $I^2 > 50\%$ and $P_Q < 0.10$), indirectness (presence of factors that limit the generalizability of the results), imprecision (the 95%CIs for effect estimates overlap the minimal important differences [MIDs] for benefit or harm), and publication bias (significant evidence of small-study effects). Criteria to upgrade the certainty of the evidence on the basis of the presence of a significant dose-response were applied.

RESULTS

Literature search

Figure 1 shows the flow of the literature search. In total, 809 reports were identified from databases and manual

searches, 727 of which were excluded on the basis of title and abstract. Of the 81 reports reviewed in full, 18 controlled feeding trials (33 comparisons) conducted in 1105 participants met the eligibility criteria.[37–54] These trials assessed the effect of honey on body weight (14 trial comparisons), BMI (10 trial comparisons), waist circumference (1 trial comparison), SBP (11 trial comparisons), DBP (11 trial comparisons), fasting glucose (20 trial comparisons), fasting insulin (8 trial comparisons), glycated hemoglobin (10 trial comparisons), HOMA-IR (7 trial comparisons), total cholesterol (29 trial comparisons), LDL-C (29 trial comparisons), HDL-C (29 trial comparisons), fasting triglycerides (29 trial comparisons), apolipoprotein B (1 trial comparison), high-sensitivity C-reactive protein (8 trial comparisons), IL-6 (5 trial comparisons), TNF-α (2 trial comparisons), uric acid (5 trial comparisons), and ALT (1 trial comparison).

Trial characteristics

Table 1 and Table S4 in the Supporting Information online show the trial characteristics for all studies included. Trial size ranged from 8 to 72 participants, with a median of 43 participants. Most floral sources of honey were polyfloral (24 trials), while the remainder were clover (3 trials), robinia (3 trials), or milk vetch (1 trial); 2 trials did not report the floral source. Processing of honey was mostly not reported (20 trials). Seven trials included processed honey, 5 trials included raw honey, and 1 trial examined honey that included both processed and raw samples. Forty-two percent of participants were healthy and of mixed weight (mix of BMIs indicating normal weight, overweight, or obesity), 12% had obesity or overweight, 21% had type 1 or type 2 diabetes, 10% were glucose intolerant, and 15% had a mixed health status. Participants tended to be middle-aged, with a median age of 41.2 years (range, 10.5–60.7 years) and approximately equal ratios of both sexes. Doses of daily oral honey intake ranged from 5 g to 125 g, with a median dose of 40 g. Trial comparisons included the participant's usual diet (70% of studies), sucrose (15%), high-fructose corn syrup (6%), and mixed comparators (9%). Almost all trials were randomized (94%), and the duration of follow-up ranged from 1 to 24 weeks (median of 8 weeks). Most trials were performed in an outpatient setting, with half of all trials conducted in the United States, Turkey, and Pakistan. Trials were agency funded (government, not-for-profit health agency, or university sources) (64%), industry funded (3%), or did not report a funding source (33%).

Trial quality

Figure S1 in the Supporting Information online shows the risk-of-bias assessments by the Cochrane Risk-of-Bias Tool. Owing to poor reporting, most trials were assessed as having unclear risk of bias for most domains. Few trials were assessed as having high risk of bias for each domain (7% for sequence generation, 10% for allocation concealment, 3% for blinding, 13% for incomplete outcome data, 0% for selective outcome reporting, and 7% for other types of bias). Overall, there was no serious summary risk of bias across the available trials.

Outcomes

Figure 2 and Figures S2 through S20 in the Supporting Information online show the effects of oral honey intake on cardiometabolic outcomes. Oral honey intake had a beneficial effect on all lipid outcomes: reductions were found in total cholesterol (29 trials; MD = −0.18 mmol/L [95%CI, −0.33 to 0.04 mmol/L], P_{MD} (*P* value for the mean difference) = 0.011; substantial heterogeneity, $I^2 = 65.1\%$, $P_Q < 0.001$), LDL-C (29 trials; MD = −0.16 mmol/L [95%CI, −0.30 to −0.02 mmol/L], $P_{MD} = 0.024$; substantial heterogeneity, $I^2 = 73.8\%$, $P_Q < 0.001$), fasting triglycerides (29 trials; MD = −0.13 mmol/L [95%CI, −0.20 to −0.07 mmol/L], $P_{MD} < 0.001$; substantial heterogeneity, $I^2 = 63.4\%$, $P_Q < 0.001$), along with an increase in HDL-C (29 trials; MD = 0.07 mmol/L [95%CI, 0.04 to 0.10 mmol/L], $P_{MD} < 0.001$; no substantial heterogeneity, $I^2 = 33.0\%$, $P_Q = 0.046$). Oral honey intake also decreased fasting glucose (20 trials; MD = −0.20 mmol/L [95%CI, −0.37 to −0.04 mmol/L], $P_{MD} = 0.017$; substantial heterogeneity, $I^2 = 76.8\%$, $P_Q < 0.001$) and ALT (1 trial; MD = −9.75 U/L [95%CI, −18.28 to −1.21 U/L], $P_{MD} = 0.025$). There was a significant increase in IL-6 (5 trials; MD, 0.37 pg/mL [95%CI, 0.01 to 0.74 pg/mL], $P_{MD} = 0.046$; no substantial heterogeneity, $I^2 = 0.0\%$, P_Q=0.847) and TNF-α (2 trials; MD = 1.44 pg/mL [95%CI, 0.24 to 2.64 pg/mL], $P_{MD} = 0.019$; no substantial heterogeneity, $I^2 = 22.9\%$, $P_Q = 0.255$). Oral honey intake had no significant effect on any of the remaining outcomes.

Sensitivity analyses

Table S5 and Figures S2 through Figures S20 in the Supporting Information online show the results of sensitivity analyses for the use of different correlation coefficients and the results of influence analysis for each outcome. The sensitivity analyses altered the significance of some outcomes. Specifically, they demonstrated instability in the estimates of HbA_{1c}, with the removal of Bahrami et al[39] resulting in a significant decrease in

Table 1 **Characteristics of the trials included in the systematic review**

Characteristic	Trial details[a]
No. of trial comparisons	33
Median no. of participants (range)	43 (8–72)
Underlying disease status (no. of studies)	Healthy mixed weight (n = 14), overweight/obesity (n = 4), T1DM/T2DM (n = 7), impaired glucose tolerance (n = 3), mixed health status (n = 5)
Female: male ratio (%)[b]	54:46
Median age in years (interquartile range)[b]	41.2 (10.55–60.7)
Age category (%; adult: children: mixed age)	90:10:0
Country (no. of comparisons)	Egypt (n = 2), Germany (n = 1), Greece (n = 1), Indonesia (n = 1), Iran (n = 4), Malaysia (n = 6), Pakistan (n = 5), Switzerland (n = 2), Turkey (n = 6), USA (n = 5)
Study setting (%; inpatients: outpatients: inpatients/outpatients)	12:92:6
Median baseline BMI in kg/m^2 (interquartile range)[b]	26 (20.7–40.2)
Study design (%; crossover: parallel)	30:70
Feeding control (%; metabolic: supplemented: dietary advice)	10:90
Randomization (%; yes: no: NR)	94:3:3
Median dose of oral honey intake in grams/day (interquartile range)	40 (25–70)
Median weeks of follow-up (range)	8 (1–24)
Funding sources (%; agency: industry: NR)	64:3:33
Honey floral source (no. of comparisons)	Polyfloral (n = 24), robinia (n = 3), clover (n = 3), milk vetch (n = 1), NR (n = 2)
Method of honey processing (no. of comparisons)	Raw (n = 5), processed (n = 7), mixed (n = 1), NR (n = 20)
Comparator (no. of comparisons)	Usual diet (n = 23), sucrose (n = 5), HFCS (n = 2), mixed (n = 3)
Energy control (no. of comparisons)	Substitution (n = 12), addition (n = 21)
Energy balance (no. of comparisons)	Neutral (n = 10), positive (n = 23)

Abbreviations: BMI, body mass index; HFCS, high-fructose corn syrup; NR, not reported; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
[a]Values rounded to the nearest whole number.
[b]Based on studies that reported data.

HbA_{1c}. Similarly, SBP and DBP were altered by the removal of Rasad et al,[49] resulting in a significant increase in both outcomes. Lastly, the significant decrease in LDL-C was eliminated through the individual removal of 6 trials, demonstrating some instability in this effect estimate as well.[37,45,47] The systematic removal of each trial did not alter the direction, magnitude, or significance of effect for any of the remaining outcomes.

Subgroup analyses

Figures S2 through S20 in the Supporting Information online show the results of subgroup analyses. Of the glycemic outcomes, fasting glucose demonstrated evidence of subgroup differences by honey floral source (decreasing effect for clover honey and for honey without a reported source, $P < 0.001$), processing of honey (decreasing effect for raw honey, $P < 0.001$), participant health status, and risk of bias in 1 domain, ie, allocation concealment. Similarly, there was evidence of subgroup differences by floral honey source for total cholesterol, LDL-C, and fasting triglycerides, with clover honey and robinia honey demonstrating a beneficial effect on these outcomes ($P < 0.05$). Total cholesterol, HDL-C, and fasting triglycerides additionally demonstrated evidence of subgroup differences by processing of honey, with raw honey showing a beneficial effect ($P < 0.05$). Lastly, SBP demonstrated subgroup differences by dose (decreasing effect of > 10% energy, $P = 0.002$), by the continuous subgroup of dose ($P = 0.010$), and by the continuous subgroup of BMI (for each unit increase in BMI, SBP increased by 0.62 mmHg; 95%CI, 0.18 to 1.07 mmHg, $P = 0.006$). The same results were not seen for DBP. There was no evidence of subgroup differences in any of the adiposity outcomes. Subgroup analyses were not performed for waist circumference, apolipoprotein B, TNF-α, or ALT, as there were fewer than 4 trials available.

Results by floral source and processing of honey

There were significant subgroup differences by honey floral source and raw honey for the effect on cholesterol and glycemic outcomes. As a result, the effect of robinia honey, clover honey, and raw honey on all outcomes was also assessed (Figures 3 and 4). Of importance, raw honey resulted in a reduction in fasting glucose (5 trials; MD = −1.05 mmol/L, 95%CI = −1.90 to −0.20 mmol/L), total cholesterol (5 trials; MD = −0.61 mmol/L, 95%CI = −1.07 to −0.14 mmol/L), and fasting triglycerides (5 trials; MD = −0.27 mmol/L, 95%CI, −0.43 to −0.10 mmol/L) and an increase in HDL-C (5 trials; MD = 0.11 mmol/L, 95%CI, 0.02 to 0.20 mmol/L) (Figure 3). Similarly, clover honey reduced fasting glucose (2 trials; MD = −1.82 mmol/L, 95%CI, −2.35 to

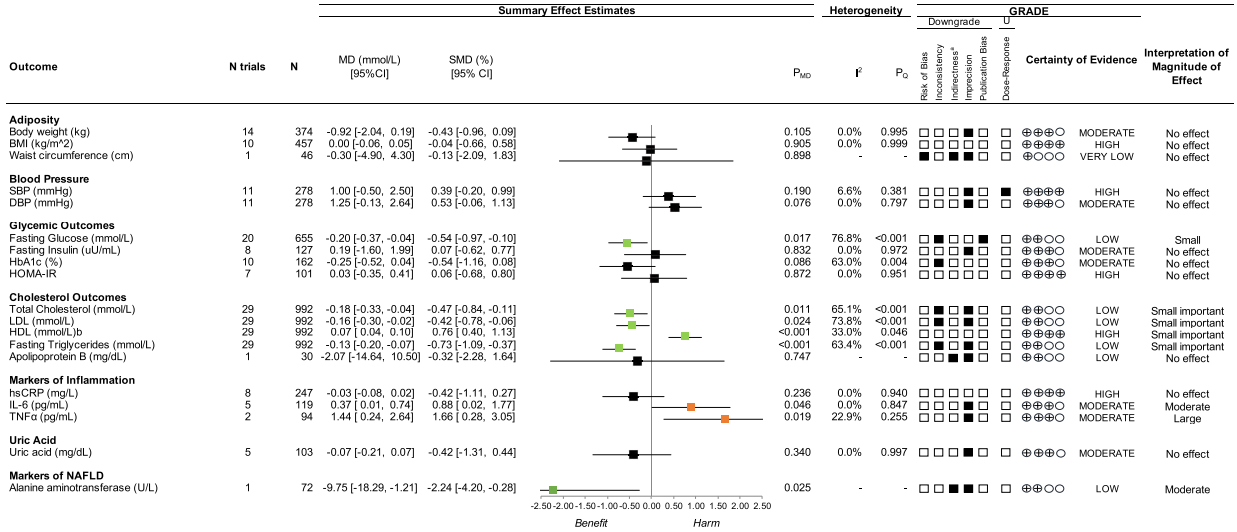

Figure 2 **Summary plot for the effect of honey consumption on cardiometabolic risk factors.** The white squares indicate no downgrades were made, while solid black squares indicate a single downgrade or upgrade was made for each outcome. *Abbreviations*: BMI, body mass index; DBP, diastolic blood pressure; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; LDL, low-density lipoprotein; MD, mean difference; NAFLD, nonalcoholic fatty liver disease; P_{MD}, *P* value for the overall effect; P_Q, Cochrane's *Q* statistic; SBP, systolic blood pressure; SMD, standard mean difference; TNF-α, tumor necrosis factor α.

*Data are weighted mean differences (95%CIs) for summary effects of honey consumption on metabolic outcomes. Analyses were conducted by generic, inverse-variance random-effects models (at least 5 trials available) or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane *Q* statistic, where $P_Q < 0.100$ is considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered evidence of substantial heterogeneity. The GRADE level of the certainty of evidence of randomized controlled trials is "high" and can be downgraded by 5 domains and upgraded by 1 domain.

[a]For the interpretation of the magnitude, minimally important differences (MIDs) were used to assess the importance of the magnitude of the point estimate using the effect size categories according to new GRADE guidance.

[b]An increase in HDL cholesterol signals a beneficial change in this outcome.

−1.30 mmol/L), total cholesterol (3 trials; MD = −0.44 mmol/L, 95%CI, −0.63 to −0.26 mmol/L), LDL-C (3 trials; MD = −0.38 mmol/L, 95%CI, −0.56 to −0.20 mmol/L), and fasting triglycerides (3 trials; MD = −0.31 mmol/L, 95%CI, −0.39 to −0.24 mmol/L) and increased HDL-C (3 trials; MD = 0.08 mmol/L, 95%CI, 0.02–0.15 mmol/L) (Figure 4). Robinia honey demonstrated beneficial effects on cholesterol outcomes, with reductions in total cholesterol (1 trial; MD = −0.69 mmol/L, 95%CI, −1.04 to −0.34 mmol/L), LDL-C (1 trial; MD = −0.52 mmol/L, 95%CI, −0.78 to −0.26 mmol/L) and fasting tryglycerides (1 trial; MD = −0.20 mmol/L, 95%CI, −0.37 to −0.03 mmol/L] observed (Figure 4).

Dose-response analyses

Figures S2 through S20 in the Supporting Information online show the results of linear and nonlinear dose-response analyses. There was a linear negative dose-response effect on SBP, ie, each 10-g increase in honey intake reduced SBP by 0.72 mmHg ($P = 0.010$). No dose-response gradient was found for any of the other outcomes. Dose-response analyses for waist circumference, apolipoprotein B, TNF-α, uric acid, and ALT were not performed because fewer than 6 unique studies were available.

Publication bias

Figures S2 through S20 in the Supporting Information online present the publication bias funnel plots and the results of trim-and-fill analyses. There was evidence of publication bias for fasting glucose (Begg test, $P = 0.194$; Egger test, $P = 0.033$), with the trim-and-fill method demonstrating small-study effects and the new 95%CI losing significance (MD = −0.10 mmol/L [95%CI, −0.30 to 0.09 mmol/L], $P = 0.303$). There was also evidence of publication bias for fasting triglycerides (Begg test, $P = 0.253$; Egger test, $P = 0.007$) and HDL (Begg test, $P = 0.626$; Egger test, $P = 0.024$), but it was not confirmed for either outcome using the trim-and-

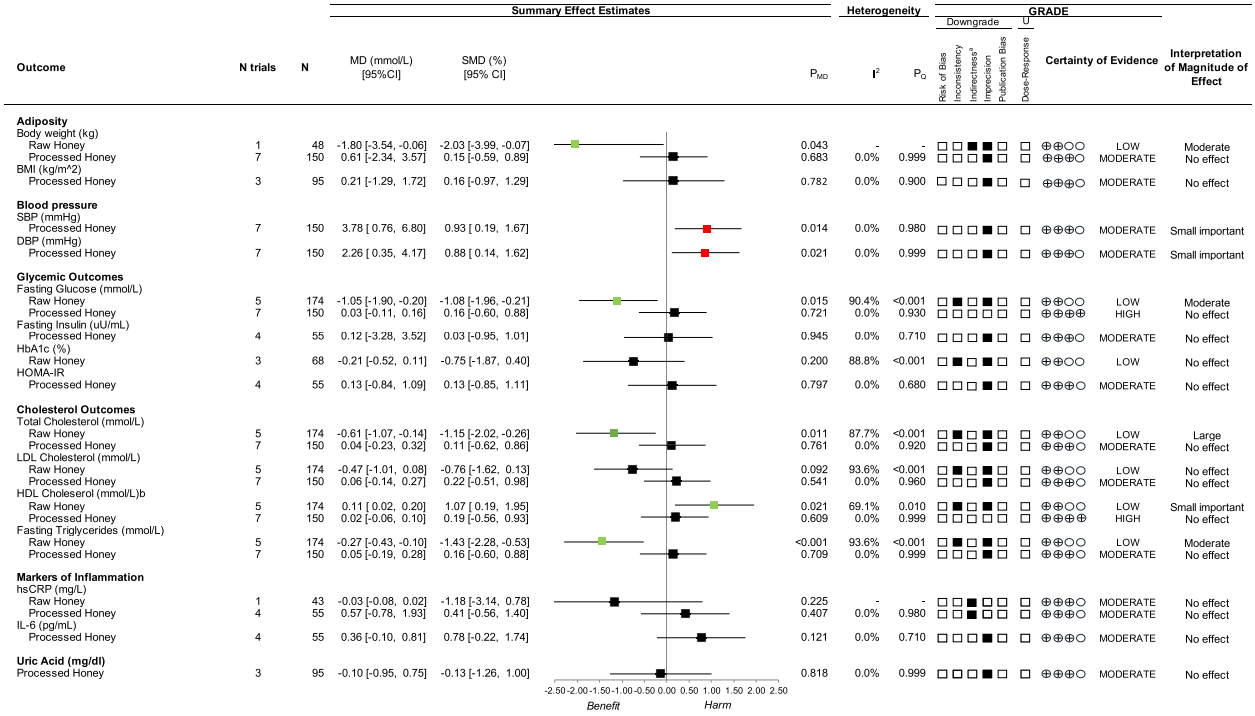

Figure 3 **Summary plot for the effect of raw vs processed honey consumption on cardiometabolic risk factors.** The white squares indicate no downgrades were made, while solid black squares indicate a single downgrade or upgrade was made for each outcome. *Abbreviations*: BMI, body mass index; DBP, diastolic blood pressure; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; LDL, low-density lipoprotein; MD, mean difference; NAFLD, nonalcoholic fatty liver disease; P_{MD}, *P* value for the overall effect; P_Q, Cochrane's *Q* statistic, SBP, systolic blood pressure, TNF-α, tumor necrosis factor α.

*Data are weighted mean differences (95%CIs) for summary effects of honey consumption on metabolic outcomes. Analyses were conducted by generic, inverse-variance random-effects models (at least 5 trials available) or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane *Q* statistic, where $P_Q < 0.100$ is considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered evidence of substantial heterogeneity. The GRADE level of the certainty of evidence of randomized controlled trials is "high" and can be downgraded by 5 domains and upgraded by 1 domain.

[a]For the interpretation of the magnitude, minimally important differences (MIDs) were used to assess the importance of the magnitude of the point estimate using the effect size categories according to new GRADE guidance.

[b]An increase in HDL cholesterol indicates a beneficial change in this outcome.

fill method. Lastly, there was evidence of publication bias for SBP (Begg test, $P = 0.937$; Egger test, $P = 0.021$), but it was not confirmed by the trim-and-fill method, which failed to demonstrate small-study effects. There was no evidence of publication bias for body weight, DBP, HbA_{1c}, total cholesterol, or LDL-C. Analyses for publication bias were not performed for BMI, waist circumference, SBP, DBP, fasting insulin, HOMA-IR, apolipoprotein B, high-sensitivity C-reactive protein, IL-6, TNF-α, uric acid, or ALT because there were fewer than 10 trials available.

GRADE assessment of evidence

Figure 2 and Table S6 in the Supporting Information online present the GRADE assessments for the certainty of evidence. The reduction in fasting glucose was rated as low, owing to downgrades for serious inconsistency and the presence of publication bias. The reductions in total cholesterol, LDL-C, and fasting triglycerides were also rated as low certainty, owing to downgrades for serious inconsistency and imprecision. The increase in HDL-C was graded as high certainty and was not downgraded for any of the domains. The dose-dependent reduction in SBP was rated as high certainty. Although it was downgraded for imprecision for the pairwise response, it was upgraded for the detection of a significant negative dose-response association. Similarly, the increases in IL-6 and TNF-α were graded as moderate certainty, owing to downgrades for serious imprecision. The reduction in ALT was graded as low certainty, owing to downgrades for serious indirectness and imprecision. The certainty of evidence varied from

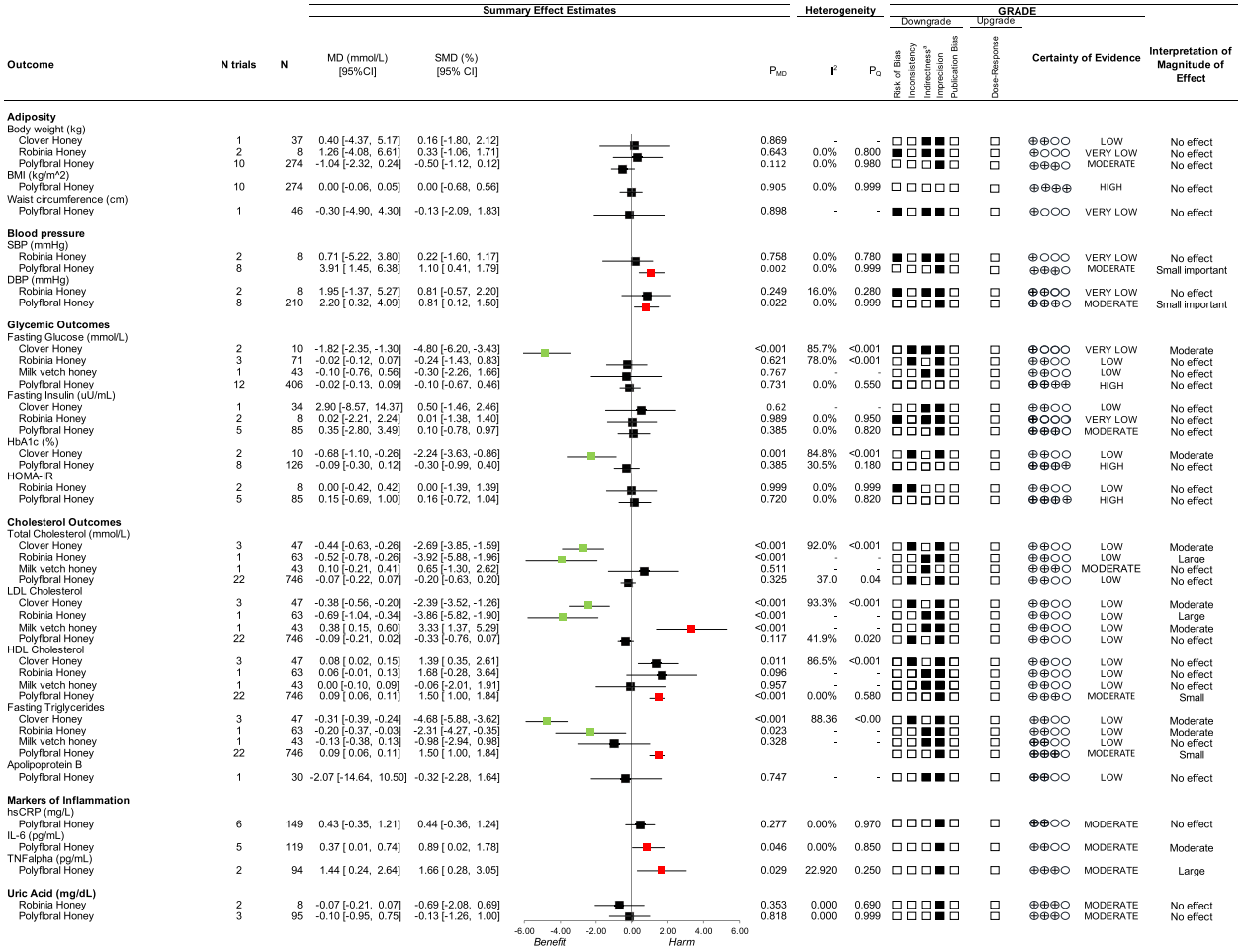

Figure 4 **Summary plot for the effect of difference floral sources of honey on cardiometabolic risk factors.** The white squares indicate no downgrades were made, while solid black squares indicate a single downgrade or upgrade was made for each outcome. *Abbreviations*: BMI, body mass index; DBP, diastolic blood pressure; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; LDL, low-density lipoprotein; MD, mean difference; P_{MD}, *P* value for the overall effect; P_Q, Cochrane's *Q* statistic, SBP, systolic blood pressure, TNF-α, tumor necrosis factor α.

*Data are weighted mean differences (95%CIs) for summary effects of honey consumption on metabolic outcomes. Analyses conducted by generic, inverse-variance random-effects models (at least 5 trials available) or fixed-effects models (fewer than 5 trials available). Between-study heterogeneity was assessed by the Cochrane *Q* statistic, where $P_Q < 0.100$ is considered statistically significant, and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is considered evidence of substantial heterogeneity. The GRADE level of the certainty of evidence of randomized controlled trials is "high" and can be downgraded by 5 domains and upgraded by 1 domain.

[a]For the interpretation of the magintude, minimally important differences (MIDs) were used to assess the importance of the magnitude of the point estimate using the effect size categories according to new GRADE guidance.

[b]An increase in HDL cholesterol indicates a beneficial change in this outcome.

high to very low for all other outcomes, owing to downgrades for inconsistency, imprecision, and indirectness.

Figures 3 and 4 and Tables S6 and S7 in the Supporting Information online present the GRADE assessments for the certainty of evidence of results by floral source and processing of honey. The reductions in fasting glucose, total cholesterol, and triglycerides and the increase in HDL-C observed with raw honey intake were graded as low certainty, mostly owing to downgrades for inconsistency and imprecision. Likewise, the reductions in fasting glucose, total cholesterol, LDL-C, and triglycerides and the increase in HDL-C observed with clover honey intake were graded as low certainty, also owing to downgrades for inconsistency and imprecision. The reductions in total cholesterol, LDL-C, and fasting triglycerides observed with robinia honey intake were downgraded for imprecision

and indirectness and were therefore graded as low certainty.

DISCUSSION

This systematic review and meta-analysis of 18 controlled feeding trials involving 33 trial comparisons in 1105 predominantly healthy participants of mixed weight assessed the effect of oral honey intake on cardiometabolic outcomes. The results showed that oral honey intake at a median dose of 40 g over a median period of 8 weeks resulted in beneficial reductions in fasting glucose, ALT, total cholesterol, LDL-C, and fasting triglycerides and a significant increase in HDL-C. There was also a significant increase in markers of inflammation, specifically IL-6 and TNF-α. There was effect modification by both the floral source of honey and the processing of honey. Intake of clover honey and raw honey appeared to have a beneficial effect on fasting glucose, while both clover honey and robinia honey produced beneficial reductions in total cholesterol, LDL-C, and fasting triglycerides. The processing of honey produced a further effect modification on total cholesterol, HDL-C, and fasting triglycerides, with raw honey resulting in a beneficial effect. While there was no significant effect of oral honey intake on SBP, linear dose-response analysis showed that SBP decreased with an increasing dose of honey.

Findings in relation to the literature

The overall beneficial effect of honey on glycemic and lipid outcomes is consistent with published literature on this topic. Previous review papers on honey have presented and argued for a wide-ranging benefit of honey on cardiometabolic outcomes.[9,10,55] In addition, a cross-sectional analysis of the Tianjin Chronic Low-Grade Systemic Inflammation and Health cohort study of 18 000 people in China showed that those who consumed honey regularly had lower odds of prediabetes.[56] In that study, the authors also demonstrated a dose-response relationship between honey intake and prediabetes, with more regular consumption of honey associated with a lower prevalence of prediabetes. A cross-sectional analysis from the same cohort showed that honey intake in moderate amounts was associated with lower prevalence of nonalcoholic fatty liver disease as measured via ultrasound, while a smaller cohort study (n = 665 men) from Caerphilly, United Kingdom, demonstrated that honey intake was associated with lower all-cause mortality in a 25-year follow-up study.[57,58]

A recent systematic review and meta-analysis of 23 controlled trials examining the effect of oral honey intake on lipid outcomes did not show any benefit of honey.[59] However, it included studies with complex interventions in which it was difficult to isolate the effect of honey, which may have led to a weakening of effect.[59] Another systematic review of 13 controlled and uncontrolled trials reported a beneficial effect of oral honey intake on adiposity, glycemia, and lipid profiles, although a quantitative assessment of the overall effect was not conducted.[60] Neither of these studies investigated the effect of honey intake by floral source or honey processing.

While research on oral consumption of honey by humans is relatively limited, animal studies examining the effect of oral honey intake have shown many benefits.[61] Rats with a diet high in honey content demonstrate reduced weight gain and reduced cholesterol levels, notably LDL-C and fasting triglycerides. It is important to note, however, that the doses of honey given to these animal subjects were extremely high, often 10% to 20% of their daily energy intake, and are therefore not replicable in humans.[62–68] Other studies in rats confirm a beneficial effect on glycemic outcomes, demonstrating a reduction in fasting blood sugar levels.[66,67,69,70] Most of the honey types used in these animal trials were also monofloral raw honey, confirming the benefits of unprocessed raw honey for a variety of outcomes.

Subgroup analyses showed that raw honey had a beneficial effect on lipid levels and fasting glucose compared with processed honey, indicating that processing might change the composition and bioactivity of honey. Conventional processing of honey involves several steps: straining and filtering for suspended and fine particles at 40°C; heating at 60° to 65°C for a short period to reduce moisture and yeast, which is responsible for the fermentation of honey; and then rapidly cooling to maintain flavor, color, and enzyme content.[71] Diastase, an enzyme found in honey, is responsible for the breakdown of starch to maltose and is sensitive to heat, with exposure to higher temperatures resulting in reduced quantities of this enzyme in honey.[72] The increased content of diastase in raw honey may contribute to better digestion of starch in individuals who consume significant amounts of honey, leading to the beneficial effects reported in this study. Similarly, hydroxymethyl furfural, an organic compound found in honey, is often also used as an indicator of honey quality. Heat treatment of honey results in increased amounts of hydroxymethyl furfural in processed honey.[73,74] Hydroxymethyl furfural is converted to 5-sulfoxymethylfurfural, a known genotoxic compound, in vivo and might mediate the lack of beneficial effect seen in processed honey.[75]

Raw honey also contains probiotic bacteria, including lactobacilli, which have been shown to improve

regulation of the immune system, reduce serum lipid levels, and help supply short-chain fatty acids to the intestine.[76] Therefore, raw honey may offer health benefits not provided by processed honey, as processing reduces the amounts of these probiotic bacteria.[76–79] Lastly, the processing of honey also affects its antioxidant capacity, leading to reductions in components of honey that may drive the demonstrated benefits in lipid levels and fasting glucose.[80] For example, a study examining the effects of processing on buckwheat honey demonstrated a 33% reduction in antioxidant capacity. Therefore, processing conducted at ambient temperatures, such as high-pressure processing, has been suggested as an alternative means of honey production.[80,81] A study comparing the effects of pressure vs thermal processing showed that honey subjected to high-pressure processing not only retained but increased its antioxidant activity, while honey subjected to thermal processing failed to maintain its antioxidant activity, confirming the negative effects of applying heat to honey.[81]

Monofloral honey types, specifically clover honey and robinia honey, demonstrated beneficial effects on lipid levels and fasting glucose compared with polyfloral honey types, possibly indicating a difference in the composition of these honeys. While both clover honey and robinia honey contain many of the same enzymes, flavonoids, and phenolic compounds as other monofloral honey types, they differ in relative quantities of these components and likely have their own unique compounds that may confer distinct properties. For example, Manuka honey from New Zealand exhibits strong antimicrobial properties that are attributed to a methylglyoxal compound that is unique to that honey.[82] Both robinia honey, also marketed as acacia honey, and clover honey have high fructose content (~40 to 44%).[38,83] As small catalytic doses of fructose have demonstrated a beneficial effect on fasting glucose levels, the high fructose content in robinia honey may be driving the benefit observed within the subgroup analyses.[84] Further, compositional analysis of clover honey has demonstrated the presence of the phenolic compound pinobanksin, a known inhibitor of LDL-C peroxidation, which may explain the beneficial effect of clover honey on cholesterol levels.[85–87] This highlights the importance of considering the floral source of honey when investigating any potential health benefits.[88,89]

Potential mechanisms of action

Several mechanisms can explain the observed effects of oral honey intake on fasting glucose, lipid outcomes, and markers of inflammation. Honey has a complex composition of organic acids, minerals, vitamins, enzymes, proteins, amino acids, and bioactive substances, all of which may mediate an effect on cardiometabolic outcomes.[8] It is approximately 80% sugar, the majority of which is fructose and glucose.[90] However, when considering the glycemic effects of honey, it is important to highlight that rare sugars constitute around 14% of the sugar content of honey.[91] These rare sugars are "monosaccharides and their derivatives that are present in limited quantities in nature."[92] With slight differences in their chemical structure, many of these rare sugars have demonstrated effects on short- and longer-term glycemic outcomes, through either inhibition of certain enzymes (eg, sucrase) or downregulation of glucose transporters.[93] Thus, the presence of a variety of rare sugars may contribute to the observed effects of honey on fasting glucose. The beneficial effect on fasting glucose may also be due to a catalytic effect, whereby fructose, present in small amounts in honey, and fructose epimers may increase the rate-limiting glucokinase activity, causing a subsequent increase in hepatic glucose metabolism.[84] Further, isomaltulose, a rare sugar present in honey, has been shown to act as a prebiotic by promoting the growth of *Lactobacillus acidophillus*, *Lactococcus lactis*, and *Saccharomyces cerevisae*, which are bacteria associated with a healthy gut microbiome.[94]

Honey is also rich in phenolic compounds and flavonoids, which may moderate the observed effects on total cholesterol, LDL-C, HDL-C, and fasting triglycerides.[95,96] Phenolic compounds, which have an array of pharmacological properties, including anti-inflammatory and anticancer effects, play a role in the apoptosis of preadipocytes, demonstrating an antiobesogenic effect, and have been show to inhibit lipid accumulation in adipocytes.[97] Similarly, flavonoids have been shown to inhibit nonenzymatic lipid peroxidation, thereby protecting against free radicals and associated diseases.[98] These compounds may play a role in promoting and maintaining a healthy lipid profile, thus contributing to the benefits of honey.

Analyses also showed an increase in IL-6 and TNF-α levels with honey intake. While it is generally accepted that chronic elevation of IL-6, common in people with metabolic dysregulation, may be associated with insulin resistance,[99] the glycemic and lipid benefits observed in this study are at odds with this narrow premise. A study in healthy people showed that IL-6 may play a role in maintaining normoglycemia by improving whole-body energy metabolism, increasing liver efficiency for nutrient delivery, and improving the uptake and utilization of glucose by the muscle.[100] Furthermore, IL-6 administration has been shown to increase lipid metabolism and maintain substrate supply for organs. In in vitro studies, specific proteins present in honey

resulted in the production of TNF-α via stimulation of Toll-like receptor 4 (TLR4), activating the body's innate immune system.[101] The pathway of TLR4 signaling also results in activation of nuclear factor kappa B, which leads to expression of inflammatory cytokines, including IL-6.[101] Therefore, specific components of honey may activate and improve the body's immune response. Previous studies examining the effect of fructose on markers of inflammation have also demonstrated that fructose consumption leads to increased levels of IL-6.[102] As roughly half of the sugar present in honey is fructose, it is possible that the high fructose content could have contributed to the elevated IL-6 levels observed in the analyses. More research is needed to assess the role of elevated IL-6 and TNF-α with honey intake.

Strengths and limitations

This systematic review and meta-analysis has several strengths. First, a comprehensive and reproducible literature search and selection process was employed. Second, the available evidence was collated and synthesized from a large body of controlled feeding trials (18 studies, N = 1105), a design that provides the greatest protection against bias. Third, possible sources of heterogeneity were explored comprehensively. Fourth, the shape and strength of the dose-response relationships was evaluated. Finally, the GRADE approach was used to assess the certainty of evidence.

This analysis also presented some limitations. First, there was evidence of serious risk of bias in the outcome of waist circumference because the single trial in this study did not randomize or conceal the allocation of treatment groups to participants, thereby increasing the risk of bias of the effects measured. Second, there was evidence of substantial unexplained heterogeneity in fasting glucose, total cholesterol, LDL-C, HDL-C, and fasting triglycerides. There was also evidence of substantial heterogeneity in HbA_{1c}, but this was partially explained by the subgroup analyses as well as by the removal of one study in the sensitivity analyses. Therefore, these outcomes were downgraded for the presence of serious inconsistency. Third, there was evidence of serious indirectness for waist circumference, apolipoprotein B, and ALT, as only one trial was included in the analyses of each of these outcomes. Fourth, there was evidence of serious imprecision for body weight, waist circumference, SBP, DBP, fasting insulin, total cholesterol, LDL-C, fasting triglycerides, apolipoprotein B, IL-6, TNF-α, uric acid, and ALT, where the 95% confidence intervals crossed the minimally important differences for benefit or harm and, thus, clinically trivial effects for these outcomes cannot be ruled out. Finally, there was evidence of publication bias for fasting glucose, as imputation of studies by the trim-and-fill method changed the significance of the findings. There was also evidence of publication bias for SBP, HDL-C, and fasting triglycerides, but it was not downgraded because imputation of studies by the trim-and-fill method did not demonstrate a change in the significance of the findings.

Weighing the strengths and limitations, the overall certainty of evidence was low for the reductions in fasting glucose, total cholesterol, LDL-C, fasting triglycerides, and ALT, high for the increase in HDL-C, and moderate for the increases in IL-6 and TNF-α. The certainty of evidence ranged from very low to high for all other outcomes.

Implications

These findings demonstrate that honey has a beneficial effect on fasting glucose and lipid outcomes while also increasing IL-6 and TNF-α levels. Honey is around 80% sugar, but the reduction in fasting glucose indicates that the rare sugars in honey moderate the effect of fructose and glucose and may also provide additional benefit for acute glycemic control. This potential effect is supported by the large reduction in HbA_{1c} of 0.25% in this study. Although this did not reach statistical significance at the traditional level ($P = 0.086$), the effect estimate and confidence interval were compatible with a large and consistent reduction. Further studies are expected to improve this estimate. The improvement in lipid outcomes also indicates that honey may have a potential lipid-lowering effect, though the benefit appears to be clinically trivial.

The floral source of honey is also important to consider because the source of nectar will determine the composition of honey and its bioactive components, which may selectively affect some of these cardiometabolic risk factors. For example, there were observed beneficial effects from clover honey and robinia honey on glycemic and cholesterol outcomes. Raw honey, compared with processed honey, demonstrated a beneficial effect on these outcomes as well, indicating that processing may lower the efficacy of honey by affecting the activity and quantity of both the enzymes and the bioactive phenolic compounds present in honey. This study demonstrates the importance of using unprocessed, specific monofloral honey types in research studies so that interventions can be replicated and results will be consistent across specific honey types.

The National Honey Board Consumer Attitudes and Usage Study of 2020 reports the greatest use of honey at breakfast, in beverages such as coffee and tea, and in baked goods.[5] Further, sales of raw honey have

increased by 32%, indicating greater consumption of honey in this form.[5] While the dose of honey consumed by the general population is not well reported, the median dose of honey in the present study was 40 g, which equates to roughly 2 tablespoons, and was often consumed through addition to foods or beverages as a sweetener. Therefore, replacing added free sugars in the diet with honey could lead to a meaningful reduction in fasting glucose and lipid levels.

CONCLUSION

This systematic review and meta-analysis showed that oral honey intake reduced fasting glucose, total cholesterol, LDL-C, fasting triglycerides, and ALT and increased HDL-C, IL-6, and TNF-α. The confidence in the effect of honey consumption on HDL-C is high, owing to no downgrades in the certainty of evidence, suggesting that the available evidence provides a good indication of the ability of honey to increase HDL-C. There is less confidence in the evidence for other outcomes, which was generally graded as moderate to low, owing mostly to serious inconsistency or imprecision in the evidence. Thus, there remains a need for larger, high-quality trials to improve the effect estimates. The subgroup analyses also demonstrated effect modification by both honey processing and the floral source of honey, with raw honey, clover honey, and robinia honey driving the reductions in fasting glucose and total cholesterol. An additional analysis separating honey by floral source as well as by processing confirmed these benefits. Overall, these findings warrant further research into the effects of honey consumption, particularly for the effects of floral source and processing. Further, the results do not support the consideration by policymakers and those who issue guidelines to designate honey as a free sugar, as honey, when taken in moderation, may offer a variety of benefits for glycemic control and lipid levels.

Acknowledgments

Author contributions. A.A., Z.T-N., T.A.K., and .J.L.S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. A.A., T.A.K., Z.T-N., D.L., S.B., Z.A., S.Z., M.S., F.J., F.Q., F.Z., R.B., S.A., M.T., and S.A. developed and executed the search strategy, extracted the data, and analyzed and interpreted the data. A.A., T.A.K., and Z.T-N. wrote the first draft of the manuscript. D.R., R.T., S.C., C.W.C.K., R.J.d.S., and J.L.S. participated in the analysis and interpretation of data and critically revised the manuscript for important intellectual content. T.A.K., C.W.C.K., and J.L.S. obtained the funding and were responsible for the original concept, design, and supervision of the work. All authors read and approved the final version of the manuscript.

Funding. This work was supported by the Canadian Institutes of Health Research (funding reference number, 129920) through the Canada-wide Human Nutrition Trialists' Network. The Diet, Digestive tract, and Disease (3-D) Centre, funded through the Canada Foundation for Innovation and the Ministry of Research and Innovation's Ontario Research Fund, provided the infrastructure for the conduct of this project. A.A. is funded by a Toronto 3D MSc. Scholarship and a Canadian Institutes of Health Research Canada Graduate Scholarship. T.A.K. is funded by a Toronto 3D Post-doctoral Fellowship Award. J.L.S. is funded by a Diabetes Canada Clinician Scientist award. The sponsors had no role in any aspect of the present study, including design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or the decision to publish. No other funders had a role in the design or conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; or the decision to publish.

Declaration of interest. T.A.K. has received research support from the Canadian Institutes of Health Research, the International Life Sciences Institute, and the National Honey Board.

D.R. has received research support from Pulse Canada, the Saskatchewan Pulse Growers Association, and the Ontario Bean Growers Association. He has no other relevant interests to declare.

J.L.S. has received research support from the Canadian Foundation for Innovation, the Ontario Research Fund, the Province of Ontario Ministry of Research and Innovation and Science, the Canadian Institutes of Health Research, Diabetes Canada, the PSI Foundation, the Banting and Best Diabetes Centre, the American Society for Nutrition (ASN), the International Nut and Dried Fruit Council Foundation (INC), the National Dried Fruit Trade Association, the National Honey Board (the US Department of Agriculture [USDA] Honey Checkoff program), the International Life Sciences Institute (ILSI), Pulse Canada, the Quaker Oats Center of Excellence, the United Soybean Board (USDA Soy Checkoff program), the Tate and Lyle

Nutritional Research Fund at the University of Toronto, the Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers), and the Nutrition Trialists Fund at the University of Toronto (a fund established by an inaugural donation from the Calorie Control Council). He has received in-kind food donations to support a randomized controlled trial from the Almond Board of California, the California Walnut Commission, the Peanut Institute, Barilla, Unilever/Upfield, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, WhiteWave Foods/Danone, and Nutrartis. He has received travel support, speaker fees, and/or honoraria from Diabetes Canada, the Dairy Farmers of Canada, FoodMinds LLC, the International Sweeteners Association, Nestlé, Pulse Canada, the Canadian Society for Endocrinology and Metabolism, the GI Foundation, Abbott, General Mills, Biofortis, American Society for Nutrition, the Northern Ontario School of Medicine, the INC Nutrition Research & Education Foundation, the European Food Safety Authority, the Comité Européen des Fabricants de Sucre (CEFS), Nutrition Communications, the International Food Information Council, the Calorie Control Council, and the Physicians Committee for Responsible Medicine. He has or has had ad hoc consulting arrangements with Perkins Coie LLP, Tate & Lyle, Wirtschaftliche Vereinigung Zucker e.V., Danone, and Inquis Clinical Research. He is a member of the European Fruit Juice Association Scientific Expert Panel and a former member of the Soy Nutrition Institute Scientific Advisory Committee. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, the European Association for the Study of Diabetes (EASD), the Canadian Cardiovascular Society, and Obesity Canada/Canadian Association of Bariatric Physicians and Surgeons. He serves or has served as an unpaid scientific advisor for the Food, Nutrition, and Safety Program and the Technical Committee on Carbohydrates of ILSI North America. He is a member of the International Carbohydrate Quality Consortium, an executive board member of the Diabetes and Nutrition Study Group of the EASD, and director of the Toronto 3D Knowledge Synthesis and Clinical Trials Foundation. His wife is an employee of AB InBev.

C.W.C.K. has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada, the Almond Board of California, Barilla, the Canadian Institutes of Health Research, the Canola Council of Canada, the International Nut and Dried Fruit Council, the International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd, the Peanut Institute, Pulse Canada, and Unilever. He has received in-kind research support from the Almond Board of California, Barilla, the California Walnut Commission, Kellogg Canada, Loblaw Companies, Nutrartis, Quaker (PepsiCo), the Peanut Institute, Primo, Unico, Unilever, and WhiteWave Foods/Danone. He has received travel support and/or honoraria from Barilla, the California Walnut Commission, the Canola Council of Canada, General Mills, the International Nut and Dried Fruit Council, the International Pasta Organization, Lantmannen, Loblaw Brands Ltd, the Nutrition Foundation of Italy, Oldways Preservation Trust, Paramount Farms, the Peanut Institute, Pulse Canada, Sun-Maid, Tate & Lyle, Unilever, and White Wave Foods/Danone. He has served on scientific advisory boards for the International Tree Nut Council, the International Pasta Organization, McCormick Science Institute, and Oldways Preservation Trust. He is a founding member of the International Carbohydrate Quality Consortium, an executive board member of the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes, is a director of the Toronto 3D Knowledge Synthesis and Clinical Trials Foundation, and is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD.

R.J.d.S. has served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on trans fats, saturated fats, and polyunsaturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012–2017 to present and discuss this work. He has presented updates of this work to the WHO in 2022. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the WHO, for which he received remuneration. He has received speaker's fees from the University of Toronto and from McMaster Children's Hospital. He has held grants from the Canadian Institutes of Health Research, the Canadian Foundation for Dietetic Research, the Population Health Research Institute, and the Hamilton Health Sciences Corporation as a principal investigator and is a coinvestigator on several funded team grants from the Canadian Institutes of Health Research. He has served as an independent director of the Helderleigh Foundation (Canada). He serves as a member of the Nutrition Science Advisory Committee to Health Canada (Government of Canada) and is a co-opted member of the Scientific Advisory Committee on

Nutrition (SACN) Subgroup on the Framework for the Evaluation of Evidence (Public Health England).

A.A., Z.T-N., D.L., S.B., Z.A., S.Z., M.S., F.J., F.Q., F.Z., R.B., S.A., M.T., S.A., R.T., and S.C. have no relevant interests to declare.

Ethical Approval

Ethical approval was not required for this research.

Data Availability

Full datasets can be obtained from the corresponding author at tauseef.khan@utoronto.ca.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **PRISMA 2020 checklist**.

Table S1 **Search strategy for controlled trials assessing the effect of oral honey intake on cardiometabolic outcomes.**

Table S2 **PICOTS framework of the search strategy for controlled trials assessing the effect of oral honey intake on cardiometabolic outcomes.**

Table S3 **Characteristics of controlled trials assessing the effect of oral honey intake on cardiometabolic outcomes.**

Table S4 **Sensitivity analyses of the use of correlation coefficients of 0.25 and 0.75 for crossover trials in the primary analysis of the effect of oral honey intake on cardiometabolic outcomes.**

Table S5 **GRADE certainty-of-evidence assessment for the effect of oral honey intake on cardiometabolic outcomes.**

Table S6 **GRADE certainty-of-evidence assessment for the effect of raw vs processed honey intake on cardiometabolic outcomes.**

Table S7 **GRADE certainty-of-evidence assessment for the effect of different floral sources of honey on cardiometabolic outcomes.**

Figure S1 **Risk-of-bias proportion graph for the effect of oral honey intake on cardiometabolic outcomes.**

Figure S2 **Body weight analyses.**

Figure S3 **Body mass index (BMI) analyses.**

Figure S4 **Waist circumference analyses.**

Figure S5 **Systolic blood pressure (SBP) analyses.**

Figure S6 **Diastolic blood pressure (DBP) analyses.**

Figure S7 **Fasting glucose analyses.**

Figure S8 **Fasting insulin analyses.**

Figure S9 **Glycated hemoglobin (HbA_{1c}) analyses.**

Figure S10 **Homeostasis model assessment of insulin resistance (HOMA-IR) analyses.**

Figure S11 **Total cholesterol analyses.**

Figure S12 **Low-density lipoprotein (LDL) cholesterol analyses.**

Figure S13 **High-density lipoprotein (HDL) cholesterol analyses.**

Figure S14 **Fasting triglycerides analyses.**

Figure S15 **Apolipoprotein B analyses.**

Figure S16 **High-sensitivity C-reactive protein (hsCRP) analyses.**

Figure S17 **Interleukin 6 (IL-6) analyses.**

Figure S18 **Tumor necrosis factor α (TNF-α) analyses.**

Figure S19 **Uric acid analyses.**

Figure S20 **Alanine transaminase (ALT) analyses.**

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