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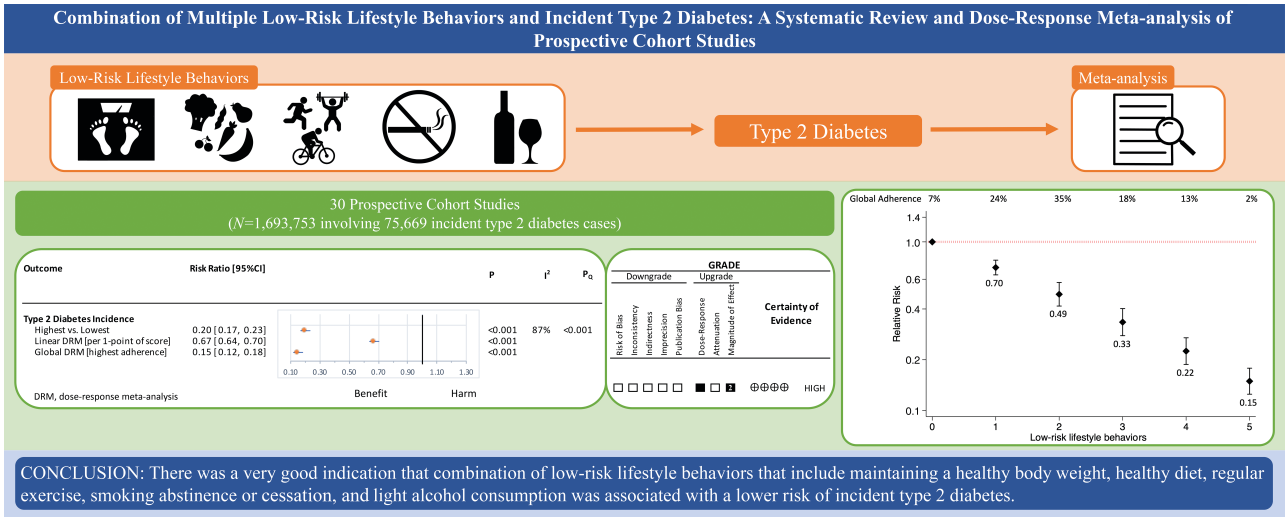

ARTICLE HIGHLIGHTS

- Low-risk lifestyle behaviors (LRLBs) are associated with a reduction in type 2 diabetes risk, but the extent of the total benefit when adhering to multiple LRLBs has not been systematically analyzed.
- In this meta-analysis of 30 cohort comparisons, maximum adherence to multiple LRLBs, including achieving and maintaining a healthy body weight, healthy diet, regular physical activity, smoking abstinence or cessation, and light alcohol consumption, was associated with an 85% reduction in type 2 diabetes risk.
- These findings affirm the need for encouraging combined LRLBs for the primary prevention of type 2 diabetes.

Combination of Multiple Low-Risk Lifestyle Behaviors and Incident Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of Prospective Cohort Studies

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OBJECTIVE

Combined low-risk lifestyle behaviors (LRLBs) have been associated with a reduction in type 2 diabetes risk. This relationship has not been systematically quantified.

RESEARCH DESIGN AND METHODS

A systematic review and meta-analysis was conducted to assess the association of combined LRLBs with type 2 diabetes. Databases were searched up to September 2022. Prospective cohort studies reporting the association between a minimum of three combined LRLBs (including healthy diet) with incident type 2 diabetes were included. Independent reviewers extracted data and assessed study quality. Risk estimates of extreme comparisons were pooled using a random-effects model. Global dose-response meta-analysis (DRM) for maximum adherence was estimated using a one-stage linear mixed model. The certainty of the evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations).

RESULTS

Thirty cohort comparisons (*n* = 1,693,753) involving 75,669 incident type 2 diabetes cases were included. LRLBs, with author-defined ranges, were healthy body weight, healthy diet, regular exercise, smoking abstinence or cessation, and light alcohol consumption. LRLBs were associated with 80% lower risk of type 2 diabetes (relative risk [RR] 0.20; 95% CI 0.17–0.23), comparing the highest with lowest adherence. Global DRM for maximum adherence to all five LRLBs reached 85% protection (RR 0.15; 95% CI 0.12–0.18). The overall certainty of the evidence was graded as high.

CONCLUSIONS

There is a very good indication that a combination of LRLBs that includes maintaining a healthy bodyweight, healthy diet, regular exercise, smoking abstinence or cessation, and light alcohol consumption is associated with a lower risk of incident type 2 diabetes.

Type 2 diabetes is an epidemic with a global (diagnosed and undiagnosed) prevalence of 9.3% (463 million 20- to 79-year-old people), which is expected to rise to

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META-ANALYSIS

11% by the year 2045 (1). A number of low-risk lifestyle behaviors (LRLBs), i.e., habits of daily routine, have been associated with lower risk of developing diabetes. These include achieving and maintaining healthy weight (2,3), healthy dietary pattern (4,5), regular physical activity (6), smoking abstinence or cessation (7), and light alcohol intake. The extent to which adherence to these LRLBs is additive has been investigated in various prospective cohort studies (8–10); however, these risk reductions have not been systematically quantified across populations using all available data.

To inform the development of new clinical practice guidelines for nutrition therapy, the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) commissioned two systematic reviews and meta-analyses to evaluate LRLB evidence in randomized controlled trials (11) and in prospective cohort studies. We present the systematic review and meta-analysis of prospective cohort studies of the association between adherence to multiple LRLBs and incident type 2 diabetes using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) to assess the certainty of the evidence.

RESEARCH DESIGN AND METHODS

We conducted a systematic review and meta-analysis according to the Cochrane Handbook for Systematic Reviews of Interventions (12), MOOSE (Meta-analysis Of Observational Studies in Epidemiology) (13), and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (14). The study protocol was registered (ClinicalTrials.gov identifier, NCT03234101).

Data Sources and Searches

The search strategy is outlined in Supplementary Table 1. MEDLINE, Embase, and Cochrane Library databases were searched until 7 September 2022. A manual search of the reference lists from included studies supplemented the database search. Google Scholar was used to identify any studies not captured by the above methods.

Study Selection

Titles and abstracts, followed by full-text reports, were reviewed by two reviewers in parallel. The inclusion criteria were prospective cohort studies examining the relationship between a combination of at least three LRLBs, including a healthy dietary pattern, with type 2 diabetes incidence in individuals from all health backgrounds with a minimum of 1-year follow-up duration. The other LRLBs could include achieving and maintaining a healthy body weight, regular physical activity, smoking abstinence or cessation, and light alcohol consumption. We did not prespecify cutoffs for the LRLBs but used study authors' own definitions. We excluded clinical trials and those cohort studies that did not report diet and/or combined lifestyle behaviors with clinical biomarkers of cardiometabolic risk.

Data Extraction and Quality Assessment

Two reviewers extracted relevant data from the selected reports and assessed the study quality using the Newcastle-Ottawa Scale (NOS) (15,16). Up to 9 points were awarded based on cohort selection (representativeness, selection of nonexposed cohort, exposure assessment, outcome not present at baseline), ascertainment of outcome (follow-up length, adequacy of follow-up, outcome assessment), and comparability (controlling for one prespecified primary [age] and four of six secondary confounding variables [sex, adiposity, smoking, family history, energy intake, physical activity]). These confounding variables were selected based on their association with diabetes risk (17,18). If a confounding variable was present as an exposure variable in the model, it was determined to be accounted for and not penalized, as outlined in Supplementary Table 2. Cohorts were adjudged high (score $\geq$7), moderate (score = 6) or low (score $\leq$5) study quality.

Data Synthesis and Analysis

All analyses were performed using Stata 16 software (StataCorp). Extreme contrast risk ratios (relative risk or RRs) comparing the maximum (three or more) versus minimum (zero, one, or two) combinations of LRLBs from the most adjusted model were used in the pairwise meta-analysis. Pooled RR was estimated using natural log-transformed RRs with DerSimonian and Laird random effects model (19). Heterogeneity was assessed by Cochrane Q statistic and quantified by the I^2 statistic, with $I^2 \geq 50\%$ and $P_Q < 0.1$ denoting substantial heterogeneity (20,21). We computed prediction intervals to assess clinical heterogeneity (22,23). Sources of heterogeneity were explored using influence analysis (systematic removal of each study) and a priori subgroup analysis. Subgroup analyses ($\geq$10 studies) were assessed for by sex, number of participants, follow-up duration, number of LRLBs, inclusion of alcohol intake, age, race/ethnicity, continent, study quality (NOS scale), and funding source using Q test of homogeneity (24). Comparison within categories was performed using meta-regression if the subgroup analysis showed significance at $P < 0.1$ (25). We also computed the E-value to ascertain the effect of an unmeasured or uncontrolled confounder on the exposure-outcome relationship (26).

We performed a dose-response meta-analysis (DRM) using a one-stage random-effects model (27,28). Each cohort's LRLBs score ranged from 0 to 5 depending on the number of LRLBs included, with a minimum score of 3. If a cohort gave different score to LRLBs (e.g., counting some LRLBs, such as diet, as 2 points), these were rescaled to match the num-

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ber of LRLBs included. The linear DRM was reported per-1-LRLB score, and the global DRM was assessed using the nonlinear association at the highest global population adherence of LRLBs. Global adherence was calculated by the percentage of people in each LRLB compared with the total people studied in all of the included cohorts.

If ≥10 cohort comparisons were available, we assessed publication bias by funnel plot and Egger and Begg tests with significance adjudged at $P < 0.1$. (29,30). We used the trim-and-fill method to assess the likely impact of missing studies (31).

Grading of the Evidence

We assessed the certainty and strength of the overall pooled evidence using GRADE (32). Included observational studies started as low and could be downgraded or upgraded based on established criteria. Criteria to downgrade included study quality (weight of studies show low study quality by NOS), inconsistency (substantial unexplained heterogeneity, $I^2 > 50\%$, $P_Q < 0.10$), indirectness (presence or absence of factors that limit generalizability based on populations, exposures, and outcomes), imprecision (95% CIs cross the minimally important difference of 5%), and publication bias (evidence of small study effects). Criteria to upgrade included a large magnitude of effect (large [RR < 0.5 or RR > 2] or very large [RR < 0.2 or RR > 5] in the absence of plausible confounders), a dose-response gradient, and attenuation by plausible confounders (33).

RESULTS

Search Results

Figure 1 outlines our systematic search. We included 19 reports (with 1 conference abstract [34]) containing 22 prospective cohort studies, with 30 cohort comparisons involving 1,693,753 participants and 75,669 incident type 2 diabetes cases in our analyses (8–10,34–49).

Study Characteristics

Table 1 describes the included cohort studies. Participants were a median age of 54 years (range 20–98), with a median follow-up of 12 years (range 5–34). The cohort populations included those with men only (*n* = 3 cohorts) (37,38,46,47), women only (*n* = 5) (35,37,38,46,47), and mixed (*n* = 14) (8–10,39–42,44,45,48,49). Incident diabetes cases were ascertained by medical records (*n* = 10) (8,34,36,37,39,43,44,48,49), self-report (*n* = 7) (35,37,38,40,45,46), and biochemical ascertainment using an oral glucose tolerance test (*n* = 5) (9,10,41,42,48). Participants were from the U.S. (*n* = 8) (37,38,40,41,43,46), followed by China (36,45,47) (*n* = 4), Finland (10,34), the U.K. (*n* = 2) (44,49), France (35), Netherlands (39), Germany (8), Sweden (9), Spain (48) and Australia (42) (*n* = 1 each). Fifteen cohorts included five LRLBs (9,34–41,43,45,46,48,49), while the remaining cohorts contained four (excluding light alcohol intake) (8,39,42) and three behaviors, respectively (excluding smoking cessation and alcohol intake) (10,44,47). Variable criteria were used by the included studies for defining healthy body weight (BMI <23 kg/m^2 to <30 kg/m^2, or waist circumference of <80 to <88 cm in women or <92 to <94 cm in men, or 5% weight reduction), healthy diet (daily intake of vegetables only to upper-2-quintiles of healthy dietary pattern scores that included higher intake of vegetables, fruits, nuts and legumes, whole grains, and polyunsaturated fatty acids, and lower intake of sugar-sweetened beverages, fruit juice, red/processed meat, *trans* fat, and sodium), regular physical activity (exercising twice per week to >30 min of moderate to vigorous exercise per day), smoking abstinence or cessation (never smoked to smoking cessation >6 months), and light alcohol consumption (0–30 g/day).

The incidence rates were <10% in all studies reporting odds ratios (40,44) and hazard ratios (8,34–36,39,41,42,45–47,49) and thus were assumed to be equal to RRs (50), except for one cohort (10) for which the hazard ratio was converted to RR (51). One study used incidence rates (37), while another reported population-attributable risk (43) for the combination of LRLBs; we converted these to RRs (52).

Diet was measured using food frequency questionnaires (*n* = 21) (8,9,34–49) or a food record (*n* = 1) (10). BMI was obtained through self-report (*n* = 10) (34–38,

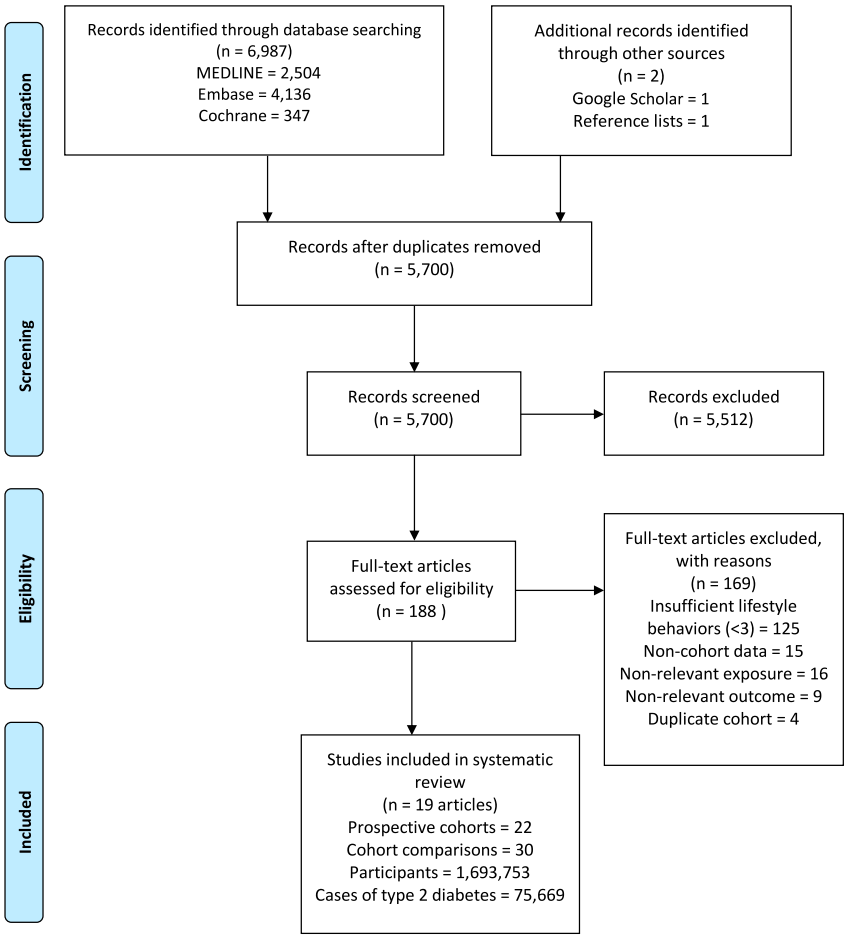

Figure 1—Systematic search and article selection.

Table 1—Cohort study characteristics investigating the association between a combinations of LRLBs and type 2 diabetes incidence

Cohort	Country	Predominant race/ethnicity	Sex	No.[a]	T2D cases	Age (years)[b]	Duration of study, year	Healthy dietary pattern[c]	Healthy body-weight (BMI, kg/m^2)[c]	Regular physical activity[c]	Smoking abstinence or cessation[c]	Light alcohol intake (g/day)[c]
Australian Diabetes, Obesity and Lifestyle Study (42)	Australia	Caucasian	Mixed	6,242	376	50 ± 12.5	12	Adherence to recommended intakes (includes high intake of fruits, vegetables, grains, dairy, proteins, no alcohol)	Waist circumference <94 cm for men; <80 cm for women	Physical activity ≥150 min/week	Nonsmoker	N/A
Cardiovascular Health Study (41)	U.S.	Caucasian	Mixed	4,883	337	72.7 ± 5.5	9	Diet score in upper 2 quintiles (includes high intake of fiber, PUFA-to- SFA ratio; lower intake of high glycemic index foods, *trans* fat)	<25 or waist circumference <92 cm for men; <88 cm for women	Total physical activity score ≥than median	Never smoked	>0
China Kadoorie Biobank (36)	China	Chinese	Men; women	189,153; 272,058	3,259; 5,525	30–79	9	Daily use of vegetables, fruits, wheat; less than daily use of red meat	18.5–23.9 and/or waist-to-hip ratio <0.90	Top quartile of physical activity based on METs	Nonsmoker	>0–30
Dongfeng-Tongji Cohort (45)	China	Chinese	Mixed	19,005	1,555	63.2	4.6	Vegetables and fruits every day; meat less than daily	18.5–23.9 and/or waist circumference <85 cm for men, <80 cm for women	>20 min per time and ≥7 h/week	Never smoked or stopped for >6 months	0
EPIC-E3N (35)	France	Caucasian	Women	74,522	2,692	43–68	18	≥5 servings/day of fruits and vegetables	18.5–25.0	≥20 MET-h/week of physical activity	Never smoked	≤10
EPIC-NL (39)	Netherlands	Caucasian	Mixed	10,758	796	20–70	14	DASH diet score in upper 2 quintiles (includes high intake of fruits, vegetables (except potatoes and legumes), nuts and legumes, low-fat dairy products, whole grains; lower intake of sodium, sugar-sweetened beverages, red/processed meats) in teetotalers	<25	>30 min/day	Nonsmoker	N/A
EPIC-Norfolk (44)	U.K.	Caucasian	Mixed	24,155	394	40–79	5	Fat intake <30% of total energy; saturated fat intake <10% of total energy; fiber intake ≥15 g/day	<25	Walking, cycling or light exercise >4 h/ week	N/A	N/A
EPIC-Potsdam (8)	Germany	Caucasian	Mixed	23,153	871	49.3 ± 8.8	12	Above the median sum *z* score (higher intake of fruits and vegetables, whole grain bread; lower intake of red meat)	<30	>3.5 h/week.	Never smoked	N/A
FINRISK Study (34)	Finland	Caucasian	Men; women	18,649; 20,052	950; 759	35–55	20	Daily use of vegetables	<25	Regular physical activity	Nonsmoker	Moderate intake

Continued on p. 647

Table 1—Continued

Cohort	Country	Predominant race/ethnicity	Sex	No.[a]	T2D cases	Age (years)[b]	Duration of study, year	Healthy dietary pattern[c]	Healthy body-weight (BMI, kg/m^2)[c]	Regular physical activity[c]	Smoking abstinence or cessation[c]	Light alcohol intake (g/day)[c]
Finnish Diabetes Prevention Study (10)	Finland	Caucasian	Mixed	522	130	55 ± 7.0	16	Fat intake <30% of total; saturated fat intake <10% of total energy; fiber intake >15 g/1,000 kcal	Weight reduction of 5% from baseline *z* score	>4 h of physical activity/week	N/A	N/A
Health Professionals Follow-up Study (38,46)	U.S.	Caucasian	Men	38,366	1,400	40–75	28	Alternate healthy eating index 2010 – top 40% of distribution (includes high intake of vegetables, fruits, nuts and legumes, whole grains, long-chain fats, and PUFA; low intake of sugar-sweetened beverages, fruit juice, red/processed meat, *trans* fat, and sodium)	18.5–24.9	Moderate-to-vigorous exercise >30 min/day	Nonsmoker	5–30
Hortega Study (48)	Spain	Caucasian	Mixed	830	51	48.5	13	Alternate Mediterranean Diet – top 40% of distribution	18.5–24.9	≥600 METs-min/ week performing moderate to vigorous activity	Never smokers	5–15 for women and 5–30 for men
Multiethnic Cohort (43)	U.S.	Caucasian Hawaiian Japanese	Men; women	36,075; 38,895	4,532; 4,010	45–75	12	Lowest quintile of processed red meat and dietary fiber intake	Overweight or obese (for Japanese American BMI <23)	Physical activity >4 h/week	Nonsmoker	≥0.4
NIH-AARP Diet and Health Study (40)	U.S.	Caucasian	Men; women	114,996; 92,483	11,031; 6,969	50–71	11	Upper 2 quantiles of diet score (includes foods with high fiber, PUFA-to-SFA ratio; low intake of foods with high glycemic index, *trans* fat)	<25	Physical activity >20 min 3 times/week.	Never smoked or ≥10 years nonsmoker	5–30
Nurses' Health Study I (38, 46)	U.S.	Caucasian	Women	73,196	4,494	30–55	34	Alternate healthy eating index 2010—top 40% of distribution (includes high intake of vegetables, fruits, nuts and legumes, whole grains, long-chain fats, and PUFA; low intake of sugar-sweetened beverages, fruit juice, red/processed meat, *trans* fat, and sodium)	18.5–24.9	Moderate-to-vigorous exercise >30 min/day	Nonsmoker	5–15
Nurses' Health Study II (38)	U.S.	Caucasian	Women	74,336	4,117	25–42	20	Alternate healthy eating index 2010 – top 40% of distribution (includes high intake of vegetables, fruits, nuts and legumes, whole grains, long chain fats, and PUFA; low intake of sugar-sweetened beverages, fruit juice, red/processed meat, *trans* fat, and sodium)	<25	Moderate-to-vigorous exercise >30 min/day	Nonsmoker	5–15

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Table 1—Continued

Cohort	Country	Predominant race/ethnicity	Sex	No.[a]	T2D cases	Age (years)[b]	Duration of study, year	Healthy dietary pattern[c]	Healthy body-weight (BMI, kg/m^2)[c]	Regular physical activity[c]	Smoking abstinence or cessation[c]	Light alcohol intake (g/day)[c]
Physicians' Health Study (37)	U.S.	Caucasian	Men	20,915	2,096	53.5	26	Upper 2 quintiles of sex-specific diet score (includes low intake of eggs and breakfast cereals)	<25	Exercise >2 times/ week.	Never smoked	0–28
Shanghai Men's Health Study (47)	China	Chinese	Men	56,691	3,315	40–74	9	Upper half of Chinese Food Pagoda Score (includes grains; vegetables and fruit; dairy products and beans and bean products; meat and poultry, fish and shrimp and eggs; and fats and oils and salt)	<24 and waist circumference <90 cm	Upper half of physical activity level	N/A	N/A
Shanghai Women's Health Study (47)	China	Chinese	Women	70,849	5,952	40–70	14	Upper half of Chinese Food Pagoda Score (includes grains; vegetables and fruits; dairy products and beans and bean products; meat and poultry, fish and shrimp and eggs; and fats and oils and salt)	<24 and waist circumference <85 cm	Upper half of physical activity level	N/A	N/A
UK Biobank Study (49)	U.S.	Caucasian	Mixed	321,225	5,368	40–70	9	Consumption of ≥4 of 7 commonly eaten diet components (including fruits ≥3 servings/day; vegetables ≥3 servings/day; fish ≥2 servings/ week; processed meats ≤1 serving/ week; unprocessed red meats ≤1.5 servings/week; whole grains ≥3 servings/day; refined grains ≤1.5 servings/day)	≥18.5 and <25 and waist circumference ≤102 cm for men and ≤88 cm for women	≥150 min/week moderate or ≥75 min/week vigorous or 150 min/week mixed (moderate + vigorous) activity or moderate ≥5 days/week or vigorous once/week	Nonsmoker	0–28 for men and 0–14 for women
Västerbotten Intervention Programme (9)	Sweden	Caucasian	Mixed	32,120	2,211	35–55	23	Fiber intake >15 g; fat intake <30% total of energy intake	<25	>34 MET-h/week for men >51 MET-h/ week for women	Nonsmoker	>0–20
Women's Health Study (37)	U.S.	Caucasian	Women	36,594	2,390	54.6	26	Upper 2 quintiles of sex-specific diet score (includes foods with high dietary fiber, high PUFA, low cholesterol, low *trans*-fat, low glycemic index)	<25	Top 2 quintiles of energy expenditure (MET-h/week.)	Never smoked	0–14

DASH, Dietary Approaches to Stop Hypertension; EPIC, European Prospective Investigation into Cancer and Nutrition; E3N, Etude Epidémiologique Auprès des Femmes de la Mutuelle Générale de l'Education Nationale; FINRISK, Finland Cardiovascular Risk Study; NIH-AARP, National Institutes of Health–American Association of Retired Persons; N/A, not available; SFA, saturated fatty acids; T2D, type 2 diabetes. [a]No. represents number of people followed up in the cohort. [b]Baseline age is represented as mean, mean (SD), or range as presented in the original article. [c]Cutoffs for each LRLB goal in the studies.

40,46) or direct measurement (n = 12) (8–10,39,41–45,47–49). Physical activity was measured by self-report (interview/questionnaire) (n = 12) (8,34–38,40,42–45) or by a validated questionnaire (n = 10) (9,10,39,41,46–49). Smoking and alcohol consumption were ascertained from self-report in all cohorts. When reporting extreme comparisons, 12 cohorts compared maximum adherence of all available LRLBs to none (8,10,36,37,41,44,46,47), while 10 cohorts compared maximum

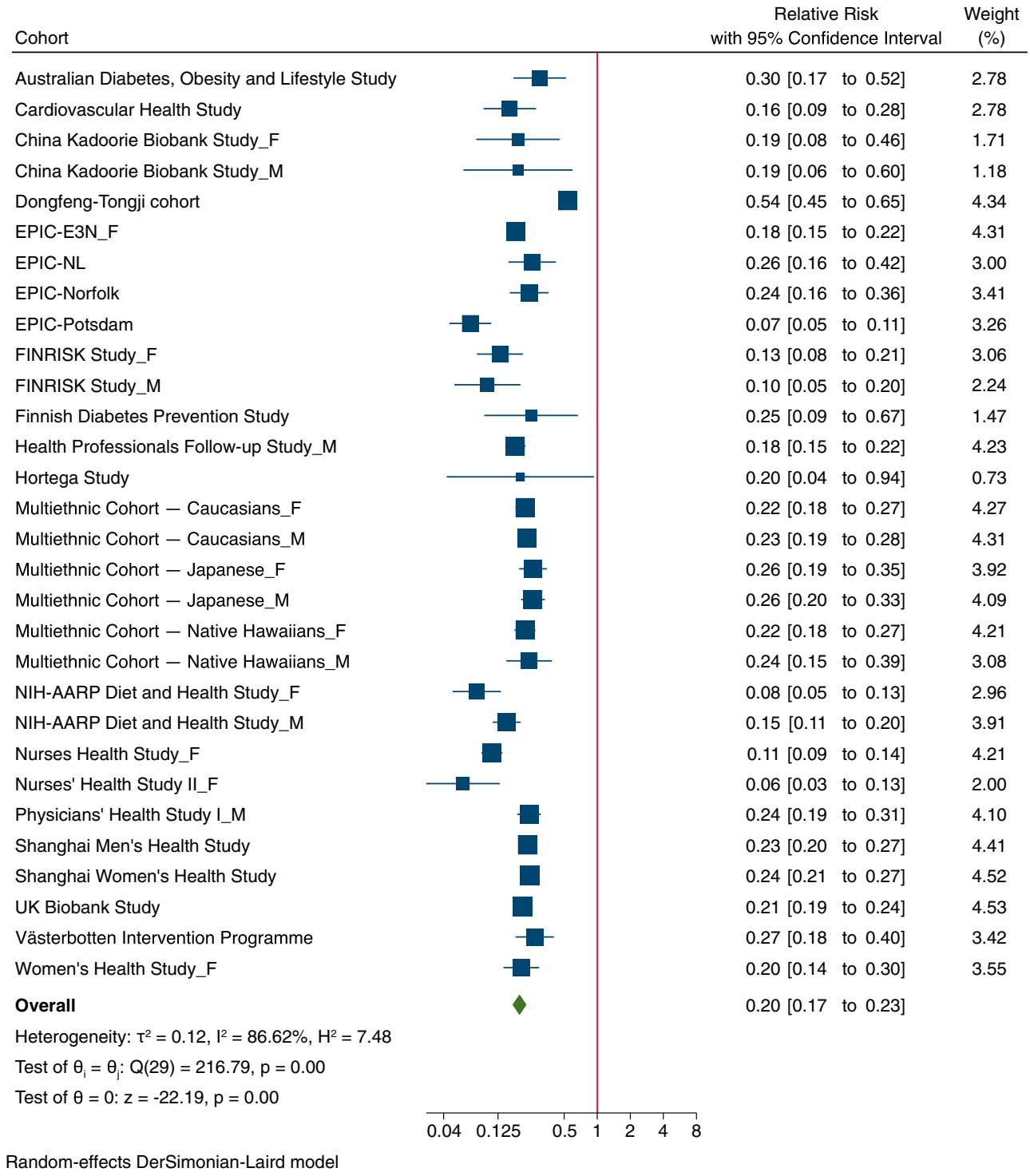

Figure 2—Forest plot of the association of multiple low-risk lifestyle behaviors with type 2 diabetes incidence with highest number (three or more) vs. lowest number of behaviors (three or less). The individual study relative risk (RR) estimates are indicated by blue squares; the size is proportional to its weight. The blue horizontal lines represent CIs. The overall pooled estimate is represented by the green diamond. Estimates $<$1.0 indicate protective association and RRs $>$1.0 indicate an adverse association. Comparison is between highest vs. lowest number of LRLBs. EPIC, European Prospective Investigation into Cancer and Nutrition; E3N, Etude Epidémiologique Auprès des Femmes de la Mutuelle Générale de l'Education Nationale; FINRISK, Finland Cardiovascular Risk Study; NIH-AARP, National Institutes of Health–American Association of Retired Persons; M, males/men; F, females/women.

behaviors to a minimum of combination that was higher than zero (i.e., one, two, or three LRLBs) (9,34,35,38–40,42,43,45, 48,49).

All studies received funding from an agency (8,9,35–49), with one study receiving partial funding through a mix of agency and industry (10); however, the authors maintained the sponsors had no role in the study or its publication. One study did not report its funding source (34).

Supplementary Table 2 shows the covariate adjustments. Of the 22 cohorts, 20 adjusted for the prespecified primary confounding variable of age (8–10,35–41,44–49), and a separate 20 adjusted (or were included in the model as part of a LRLB score) for at least four of six of the important secondary confounding variables: sex, adiposity, smoking, energy intake, family history of type 2 diabetes, and physical activity (8–10,35–42,44–49).

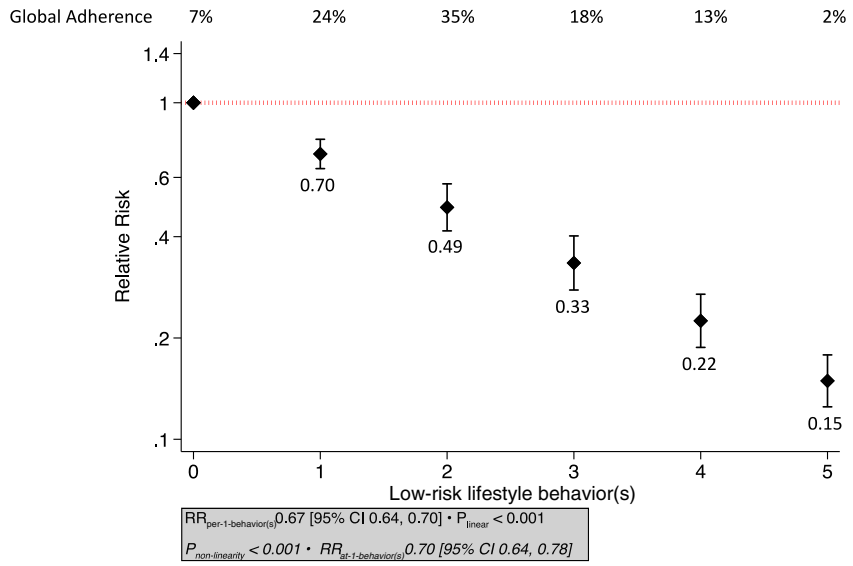

Figure 3—Dose-response plot of the association of the number of LRLBs with incident type 2 diabetes. The black boxes with vertical bars represent the aggregate relative risks (RRs) and 95% CIs for each LRLBs. Compared with adherence to no LRLBs, the estimated RRs were 0.70 (95% CI 0.64–0.78) for adherence to one LRLB, 0.49 (95% CI 0.42–0.57) for two combined LRLBs, 0.33 (95% CI 0.28–0.40) for three combined LRLBs, 0.22 (95% CI 0.19–0.27) for four-combined LRLBs, and 0.15 (95% CI 0.12–0.18) for all five combined LRLBs (global DRM at the highest adherence to global range of scores).

Study Quality Assessment

Supplementary Table 3 shows the NOS quality scores. No study was rated as low quality; however, for one study, the ascertainment of quality was not possible and was determined to be of low quality (34).

LRLBs and Type 2 Diabetes Risk

Figure 2 outlines the relationship between LRLBs and incident type 2 diabetes. Adherence to the maximum combination of LRLBs compared with the minimum reported (zero, one, two, or three) was associated with an 80% reduction in type 2 diabetes incidence (RR 0.20; 95% CI 0.17–0.23), with evidence of heterogeneity (I^2 = 87%; 95% CI 82–90; $P < 0.001$).

DRMs

Figure 3 shows the global adherence and the dose-response relationship between the number of LRLBs and diabetes incidence. Adherence was highest to one (24%), two (35%), and three (18%) LRLBs, while only 2% of the population adhered to all five LRLBs. There was an inverse linear association for adherence to multiple LRLBs and type 2 diabetes incidence in the linear DRM model, with 33% relative reduction per additional LRLB (RR 0.67; 95% CI 0.64–0.70; $P_{linear} < 0.001$), with the global DRM showing that the highest adherence to LRLBs over the global range of scores was associated with a 85% lower risk diabetes (RR 0.15; 95% CI 0.12–0.18). There was evidence of a nonlinear association ($P < 0.001$), with a minor deviation from linearity indicating slightly lower RR compared with linear as the LRLBs dose increased (Supplementary Fig. 1).

Sensitivity and Subgroup Analyses

Supplementary Table 4 shows the sensitivity analysis. Systematic removal of each cohort comparison did not alter the association (significance and direction) between combined LRLBs and incident diabetes.

Figure 4 shows the subgroup analyses. Within-subgroup analyses revealed a significant difference between the RR for combinations of lifestyle behaviors (extreme comparisons) and incident type 2 diabetes when stratifying by cohort size, race/ethnicity, age, funding, and time of exposure measurement. Increasing size of the study indicated more benefit (P = 0.07), although there was no difference with follow-up duration (P = 0.16). Younger baseline age was associated with more benefit (RR 0.14 [95% CI 0.10–0.21] for <50 years) compared with cohorts with older baseline age (RR 0.22 [95% CI 0.19–0.26] for ≥50 years; $P_{difference}$ = 0.03). Cohorts that updated exposure measurements during follow-up and had unknown funding sources indicated more benefit (P = 0.03 and P = 0.05, respectively). Meta-regression did not show any significant differences between any two races/ethnicities ($P > 0.05$). There were no significant differences when stratifying by sex (P = 0.21), follow-up period (P = 0.16), number of reported LRLBs (P = 0.81), inclusion of alcohol (P = 0.60), NOS score (P = 0.73), continent of study (P = 0.10), and dietary assessment type (P = 0.63).

We assessed the robustness of association to potential unmeasured and uncontrolled confounding using E-values. It showed that any potential confounding variable needed an RR of 9.47 (E-value) for the point estimate and 8.16 (E-value) for the CI, with both the exposure and outcome to explain away the highest versus lowest LRLBs association.

Publication Bias Analyses

Supplementary Fig. 2 shows the funnel plot. There was no evidence of publication bias on visual inspection or by formal testing with Begg test though Egger test showed some indication of small study effect (P = 0.06). However, trim and fill analysis (Supplementary Fig. 3) did not impute any missing studies.

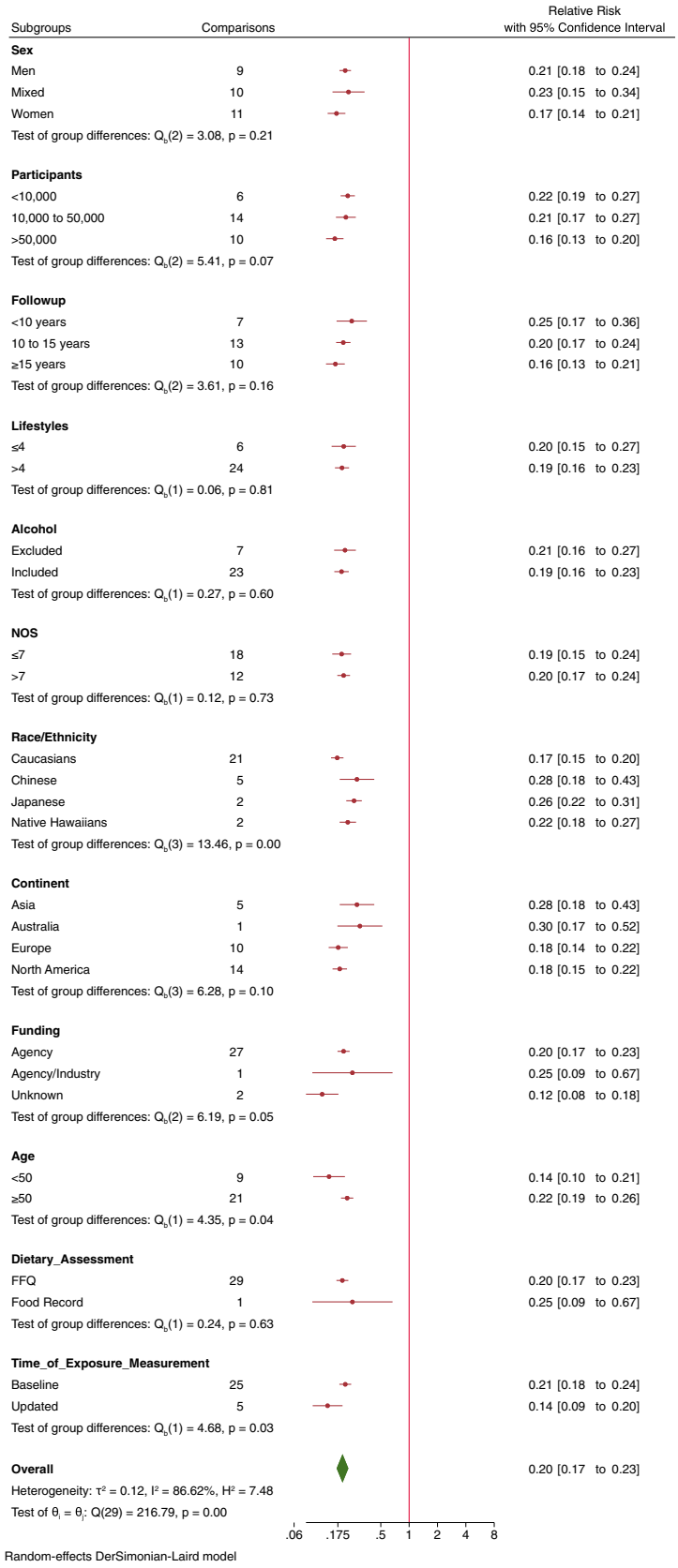

Figure 4—Subgroup analyses by sex, number of participants, duration of follow-up, number of LRLBs, exclusion of alcohol, NOS score, predominant race/ethnicity, continent, funding source, age, dietary assessment type, and time of exposure measurement with the relative risk of incident type 2 diabetes. Estimates at each subgroup level (red circles) indicate pooled effect estimates. The pooled effect estimate for the overall analysis is represented by the green diamond. Interstudy heterogeneity unexplained by the subgroup is represented by the residual I^2 value.

GRADE Assessment

Supplementary Table 5 shows the GRADE assessment. The certainty of evidence for the association of multiple LRLBs and type 2 diabetes was graded as "high" due to no downgrades for any of the domains (no serious risk of bias due to low study quality, inconsistency, imprecision, or publication bias), a double upgrade for a very large magnitude of effect (RR of 0.196 was less than threshold of 0.2), and a single upgrade for a significant dose-response gradient ($P_{linear} < 0.001$).

CONCLUSIONS

We performed a systematic review and DRM of 30 prospective cohort study comparisons involving 1,693,753 participants with 75,669 incident type 2 diabetes cases with a median follow-up of 12 years to quantify and evaluate the relationship between adherence to multiple LRLBs and incident type 2 diabetes. Our synthesis showed that adherence to a combination of LRLBs that included achieving and maintaining healthy body weight, healthy diet, regular physical activity, smoking abstinence or cessation, and light or no alcohol consumption was associated with an 80% lower incidence of type 2 diabetes. Furthermore, we found a strong inverse dose-response relationship, with each additional LRLB associated with a 33% RR reduction in diabetes, reaching a global reduction of 85% with maximum adherence to all five LRLBs.

Findings in the Context of the Literature

Two previous systematic reviews and meta-analyses showed a 75–78% lower risk of incident type 2 diabetes with adherence to a healthy lifestyle (53,54). However, one review included studies that did not exclude cases of prevalent diabetes at baseline (54), and both included biomarkers of cardiometabolic risk (e.g., blood lipids, blood glucose, and blood pressure) as part of lifestyle factors. As biomarkers are not "lifestyle behaviors," we excluded articles that combined biomarkers with lifestyle factors (Supplementary Table 6).

In our recent systematic review and meta-analysis of the available randomized trials of intensive lifestyle intervention programs (11), we showed that targeting up to three of five LRLBs (weight loss, a healthy dietary pattern, and regular physical activity) reduced incident type 2 diabetes by 47% in high-risk individuals with prediabetes (11). While smoking cessation and light alcohol intake were not part of any of the interventions, the weight reduction programs in such trials included alcohol reduction to reduce energy intake, and smoking prevalence was generally low. The smaller number of LRLBs targeted, the modest weight loss in these trials, shorter follow-up duration, and inclusion of only high-risk individuals may explain the difference in type 2 diabetes risk reduction from our results from observational studies (47% vs. 80%). The trials also showed that better adherence to lifestyle changes resulted in a lower incidence of type 2 diabetes, as an almost 80% reduction in the risk of type 2 diabetes was not unusual among the most adherent individuals in some trials (55–58). The evidence from the available randomized controlled trials of intensive lifestyle intervention programs, therefore, can be seen to fit well with our present synthesis of the prospective cohort studies.

Achieving and maintaining a healthy body weight (59,60), healthy dietary patterns (5,61), regular physical activity (62), and smoking cessation (7) have all been shown to be independently associated with lower risk of type 2 diabetes. Some meta-analyses of prospective cohort studies have observed a 30% lower diabetes incidence in individuals with moderate alcohol intake compared with nonconsumers (63–65), although recent Mendelian randomization studies have caused some doubt regarding the beneficial effect of alcohol intake (66,67).

There are biologically plausible mechanisms supporting the observed associations with lower risk of type 2 diabetes. Healthier diets that focus on fruits, vegetables, fiber consumption, nuts, polyunsaturated fatty acids (PUFAs), and low glycemic index foods have been associated with improved glycemic control, improved serum lipids, and weight loss (68,69). Weight reduction is associated with improved insulin sensitivity in the liver and peripheral tissues, blood pressure, serum lipids, and low-grade inflammation (60). Physical activity can improve serum lipids, peripheral insulin sensitivity, lower blood pressure, lower inflammation, and lead to weight loss (70–74). Smoking can impair pancreatic β-cell function and insulin sensitivity, induce inflammation, and can increase visceral adiposity compared with nonsmokers (75,76).

Although our findings show that light alcohol consumption as part of a combination of LRLBs is associated with a lower risk of type 2 diabetes, our subgroup analysis suggested no difference between studies that included alcohol as an LRLBs and those that did not. Owing to the potential harmful effects of alcohol consumption in disease (77) and public health outcomes (78,79), our results do not support the initiation of alcohol consumption in nonconsumers or the increase of alcohol consumption in existing consumers.

Strengths and Limitations

Strengths of our synthesis include the identification of all prospective cohorts, quantitative syntheses, and using GRADE to assess certainty of the evidence. The available prospective cohort studies provided a large sample size, long duration of follow-up, and adjustment for relevant confounders. We also upgraded the certainty of the evidence twice for a very large magnitude of RR reduction (RR < 0.2) and once for a significant linear dose-response gradient (33).

There were several limitations of our synthesis. Although prospective cohort studies represent the highest quality observational studies, the inability to remove residual confounding is inherent in all observational studies. Therefore, the GRADE assessment starts as low for observational studies. Although we showed substantial statistical heterogeneity in the pooled estimate, we did not downgrade for serious inconsistency due to the well demonstrated issue of increasing I^2 with the size of the studies due to nonoverlapping narrow CIs (80). Additionally, homogenous direction of study estimates, narrow 95% prediction intervals (0.10–0.40) (Supplementary Fig. 4), and robustness of the overall estimate to influence analysis demonstrated that the apparent statistical heterogeneity did not reflect clinical heterogeneity. Our studies adjusted for differing confounding variables, however, which did not reflect in a low score in NOS. In addition, we measured the E-values for our association, which is defined as the minimum strength of association on the RR

scale that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure-outcome association (26,81). In our study, the very large E-values meant that confounding associations were very unlikely to explain the association, and thus, our results are robust to unmeasured or uncontrolled confounding. Our analysis also did not include other emerging LRLBs that may have further contributed to lower diabetes incidence, including adequate sleep (82) and good dental hygiene (83), due to the small number of studies, none of which met our inclusion criteria.

Weighing the strengths and limitations, the certainty of the evidence was graded as high, suggesting that the true association is likely to be close to this estimate and that further research is unlikely to change the very large magnitude of the pooled estimate.

Implications

Individual LRLBs were unweighted in our analysis as each contributed a single dose; this was based on the original aggregate data from prospective cohort studies. An inherent additive assumption is presumed, but whether this is accurate biologically is unclear (e.g., Does regular exercise carry the same weight as healthy eating?). Such analysis requires individual patient data on each LRLB. So, while an assumption of a monotonic additive relationship can be considered a constraint, from the public health perspective, it is immensely practical to score each LRLB equally and focus on their implementation as a group set. Another important question that can be asked is: Do the LRLBs cluster and is there individual synergy between some of these LRLBs? Our study, while unable to answer the question of clustering, showed a small nonlinear association indicating a possible synergistic effect as the number of LRLBs cluster.

In addition, we were not able to assess the contribution of individual LRLBs from the LRLBs score as the cohort studies provided aggregate estimates of combined lifestyle behaviors (Supplementary Table 7). A minority of prospective cohort studies in our analysis also reported individual LRLBs and their association with type 2 diabetes (9,35,36,39–44), although this information was independent from the LRLBs score and could not be further assessed. Despite the constraints associated with aggregate data, the large reductions per lifestyle score in our dose-response relationship demonstrated the importance of combined behaviors for optimal risk reduction of type 2 diabetes.

Most of the participants adhered to up to three LRLBs (84%), while 13% adhered to four LRLBs, and only 2% achieved adherence to all five LRLBs in the included prospective cohort studies. This decreasing prevalence to achieve adherence to multiple LRLBs underscores the challenges in implementation and maintenance of a healthy lifestyle in an obesogenic environment. Similarly, population surveys from the U.K. (84,85), Germany (86,87), and other European countries (88–90) indicate that fewer than half of the people maintain adequate physical activity, more than half are former or nonsmokers, and only a quarter maintain a healthy body weight or eat a healthy dietary pattern. These data suggest an immense opportunity to improve adherence to LRLBs in Europe and worldwide to address the epidemic of type 2 diabetes and its downstream complications. Our results suggest that interventions need not target adherence to all five LRLBs, as benefits can be accrued in a dose-dependent manner such that the addition of each LRLB is associated with a 33% RR reduction. Furthermore, an incremental approach that targets one LRLB at a time may lead to the adoption of multiple LRLBs over the long-term (91). Our results also suggest that the five LRLBs can be defined differently depending on the population, with the RR reductions shown to be robust to variable criteria with no evidence of effect modification by region or ethnicity.

Conclusion

The findings from our systematic review and meta-analysis confirm that adherence to a combination of lifestyle behaviors that includes achieving and maintaining a healthy body weight, healthy dietary pattern, regular physical activity, smoking abstinence or cessation, and light alcohol intake can have a substantial impact, lowering the overall risk of developing type 2 diabetes by 85%. Our certainty in the evidence is highly based on the very large magnitude of the risk reduction and presence of a dose-response gradient, with further studies unlikely to change our confidence in the estimate. Taken together with the evidence from randomized controlled trials of intensive lifestyle interventions (11), this evidence provides a strong rationale for clinical and public health programs that target these LRLBs for the primary prevention of diabetes. With so few individuals engaging in multiple LRLBs, strategies to drive adherence, especially in those at high risk for type 2 diabetes, is imperative. As alcohol has been associated with increased net harm, it might be prudent to focus more on the promotion of the other four LRLBs. Future research is needed to assess the association of LRLBs minus the inclusion of alcohol intake with diabetes risk and assess any added benefit of including adequate sleep along with other emerging LRLBs.

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He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Obesity Canada/Canadian Association of Bariatric Physicians and Surgeons. He serves or has served as an unpaid member of the Board of Trustees and an unpaid scientific advisor for the Carbohydrates Committee of IAFNS. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His spouse is an employee of AB InBev. H.K. is Director of Clinical Research at the Physicians Committee for Responsible Medicine, a nonprofit organization that provides nutrition education and research. She is an Executive Board Member of the DNSG of the EASD. No other potential conflicts of interest relevant to this article were reported.

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