eTable 5. Dietary factors having probable or convincing evidence for causal relationships with cardiometabolic outcomes and standardized magnitudes of effect sizes.

Dietary Targets[a]	Cardiometabolic Outcome	No. of Studies in Each Meta-analysis	Unit of RR[b]	Relative Risk by Age (RR, 95% CIs)[c]					
				25-34 y	35-44 y	45-54 y	55-64 y	65-74 y	75+ y
Fruits (g/d)	↓ CHD	16 cohorts (22 estimates)	per 1 serving (100 g)/d	0.92 (0.87, 0.97)	0.92 (0.87, 0.97)	0.93 (0.89, 0.97)	0.94 (0.91, 0.98)	0.95 (0.92, 0.98)	0.97 (0.96, 0.99)
	↓ Ischemic stroke	9 cohorts (10 estimates)		0.83 (0.76, 0.90)	0.83 (0.77, 0.90)	0.86 (0.80, 0.92)	0.88 (0.83, 0.93)	0.90 (0.86, 0.94)	0.94 (0.92, 0.96)
	↓ Hemorrhagic stroke	5 cohorts (7 estimates)		0.63 (0.49, 0.81)	0.64 (0.5, 0.82)	0.69 (0.56, 0.84)	0.73 (0.61, 0.87)	0.77 (0.67, 0.89)	0.86 (0.8, 0.92)
Vegetables (g/d)	↓ CHD	9 cohorts (9 estimates)	per 1 serving (100 g)/d	0.93 (0.89, 0.97)	0.93 (0.9, 0.97)	0.94 (0.91, 0.97)	0.95 (0.93, 0.98)	0.96 (0.94, 0.98)	0.98 (0.97, 0.99)
	↓ Ischemic stroke	9 cohorts (10 estimates)		0.76 (0.64, 0.9)	0.77 (0.66, 0.9)	0.8 (0.7, 0.92)	0.83 (0.74, 0.93)	0.86 (0.78, 0.94)	0.92 (0.87, 0.96)
	↓ Hemorrhagic stroke	5 cohorts (7 estimates)		0.76 (0.61, 0.95)	0.77 (0.62, 0.95)	0.80 (0.67, 0.96)	0.83 (0.72, 0.96)	0.86 (0.76, 0.97)	0.92 (0.86, 0.97)
Nuts/seeds (g/d)	↓ CHD (fatal)	5 cohorts, 1 RCT (6 estimates)	per 1 serving (oz)/ wk	0.89 (0.85, 0.93)	0.89 (0.85, 0.93)	0.91 (0.87, 0.94)	0.92 (0.89, 0.95)	0.93 (0.91, 0.96)	0.96 (0.95, 0.97)
	↓ Diabetes	5 cohorts, 1 RCT (6 estimates)		0.95 (0.92, 0.98)	0.95 (0.93, 0.98)	0.96 (0.94, 0.98)	0.97 (0.95, 0.98)	0.97 (0.96, 0.99)	0.98 (0.98, 0.99)
Whole grains (g/d)	↓ CHD	6 cohorts (6 estimates)	per 1 serving (50 g)/d	0.95 (0.91, 0.99)	0.95 (0.92, 0.99)	0.96 (0.93, 0.99)	0.97 (0.94, 0.99)	0.97 (0.95, 0.99)	0.98 (0.97, 0.99)
	↓ Ischemic stroke[d]	7 cohorts (9 estimates)		0.88 (0.80, 0.96)	0.88 (0.81, 0.96)	0.90 (0.83, 0.97)	0.91 (0.86, 0.97)	0.93 (0.88, 0.98)	0.96 (0.93, 0.98)
	↓ Hemorrhagic stroke[d]	7 cohorts (9 estimates)		0.88 (0.80, 0.96)	0.88 (0.81, 0.96)	0.90 (0.83, 0.97)	0.91 (0.86, 0.97)	0.93 (0.88, 0.98)	0.96 (0.93, 0.98)
	↓ Diabetes	10 cohorts (10 estimates)		0.83 (0.76, 0.90)	0.83 (0.77, 0.90)	0.86 (0.80, 0.92)	0.88 (0.83, 0.93)	0.90 (0.86, 0.94)	0.94 (0.92, 0.96)
Red meats (g/d)	↑ Diabetes	9 cohorts (10 estimates)	per 1 serving (100 g)/d	1.3 (1.05, 1.60)	1.29 (1.05, 1.57)	1.24 (1.04, 1.47)	1.19 (1.03, 1.37)	1.16 (1.03, 1.30)	1.09 (1.02, 1.15)
Processed meats (g/d)	↑ CHD	5 cohorts (6 estimates)	per 1 serving (50 g)/d	1.62 (1.17, 2.18)	1.58 (1.16, 2.11)	1.47 (1.14, 1.88)	1.38 (1.11, 1.69)	1.30 (1.09, 1.54)	1.16 (1.07, 1.27)
	↑ Diabetes	8 cohorts (9 estimates)		1.86 (1.38, 2.46)	1.81 (1.36, 2.37)	1.65 (1.30, 2.08)	1.52 (1.24, 1.83)	1.41 (1.20, 1.65)	1.22 (1.12, 1.32)
SSBs (servings (8 oz)/d)	↑ BMI (baseline BMI <25)[e]	Original meta-analysis of 3 US prospective cohorts (NHS I, NHS II, HPFS)	per 1 serving (8 oz)/d	0.10 kg/m^2 (0.05, 0.15)	0.10 kg/m^2 (0.05, 0.15)	0.10 kg/m^2 (0.05, 0.15)	0.10 kg/m^2 (0.05, 0.15)	0.10 kg/m^2 (0.05, 0.15)	0.10 kg/m^2 (0.05, 0.15)
	↑ BMI (baseline BMI ≥25)[e]			0.23 kg/m^2 (0.14, 0.32)	0.23 kg/m^2 (0.14, 0.32)	0.23 kg/m^2 (0.14, 0.32)	0.23 kg/m^2 (0.14, 0.32)	0.23 kg/m^2 (0.14, 0.32)	0.23 kg/m^2 (0.14, 0.32)

eTable 5. Dietary factors having probable or convincing evidence for causal relationships with cardiometabolic outcomes and standardized magnitudes of effect sizes (continued)

Dietary Targets[a]	Cardiometabolic Outcome	No. of Studies in Each Meta-analysis	Unit of RR[b]	Relative Risk by Age (RR, 95% CIs)[c]					
				25-34 y	35-44 y	45-54 y	55-64 y	65-74 y	75+ y
	CHD-BMI mediated[e]	pooled analysis of APCSC, PSC, and ERFC international pooling projects	per 5 kg/m^2 increase in BMI	1.79 (1.56, 2.06)	1.66 (1.51, 1.84)	1.55 (1.46, 1.64)	1.44 (1.4, 1.48)	1.35 (1.32, 1.38)	1.19 (1.13, 1.25)
	HHD-BMI mediated[e]			2.30 (0.66, 7.95)	2.15 (0.80, 5.78)	2.02 (0.97, 4.21)	1.90 (1.17, 3.07)	1.81 (1.45, 2.26)	1.54 (1.20, 1.97)
	Ischemic stroke-BMI mediated[e]			2.09 (1.81, 2.40)	1.86 (1.67, 2.08)	1.67 (1.53, 1.81)	1.50 (1.40, 1.6)	1.35 (1.28, 1.41)	1.11 (1.06, 1.15)
	Hemorrhagic stroke-BMI mediated[e]			3.04 (2.24, 4.11)	2.54 (1.96, 3.28)	2.10 (1.66, 2.66)	1.75 (1.44, 2.13)	1.48 (1.29, 1.71)	1.13 (1.03, 1.23)
	Diabetes-BMI mediated[e]			3.55 (2.41, 5.23)	3.07 (2.28, 4.15)	2.66 (2.15, 3.30)	2.32 (2.04, 2.63)	2.03 (1.95, 2.11)	1.52 (1.40, 1.65)
	↑ CHD-BMI adjusted[e]	4 cohorts (4 estimates)	per 1 serving (8 oz)/d	1.33 (1.19, 1.47)	1.31 (1.18, 1.45)	1.26 (1.15, 1.37)	1.21 (1.13, 1.3)	1.17 (1.10, 1.24)	1.09 (1.06, 1.13)
	↑ Diabetes-BMI adjusted[e]	17 cohorts (17 estimates)		1.35 (1.14, 1.59)	1.33 (1.13, 1.56)	1.27 (1.11, 1.46)	1.22 (1.09, 1.36)	1.18 (1.07, 1.29)	1.10 (1.05, 1.15)
	↑ Diabetes-BMI unadjusted[e]	13 cohorts (13 estimates)		1.55 (1.25, 1.89)	1.52 (1.24, 1.85)	1.43 (1.20, 1.68)	1.34 (1.17, 1.54)	1.28 (1.14, 1.43)	1.15 (1.09, 1.22)
PUFA replacing Carbs (% E)[g]	↓ CHD	9 cohorts (12 estimates)	per 5 %E/d	0.86 (0.79, 0.92)	0.86 (0.8, 0.93)	0.88 (0.83, 0.94)	0.90 (0.86, 0.95)	0.92 (0.88, 0.96)	0.95 (0.93, 0.97)
PUFA replacing SFA (% E)[g]	↓ CHD	8 cohorts (11 estimates)	per 5 %E/d	0.87 (0.81, 0.93)	0.87 (0.82, 0.94)	0.89 (0.84, 0.95)	0.91 (0.87, 0.95)	0.92 (0.89, 0.96)	0.96 (0.94, 0.98)
SFA replacing PUFA (% E)[g]	↑ CHD	8 cohorts (11 estimates)	per 5 %E/d	1.15 (1.07, 1.24)	1.14 (1.06, 1.23)	1.12 (1.05, 1.19)	1.10 (1.05, 1.15)	1.08 (1.04, 1.13)	1.05 (1.02, 1.07)
Seafood ω-3 fats (mg/d)	↓ CHD	4 RCTs and 15 cohorts (19 estimates)	per 100 mg/d	0.79 (0.70, 0.88)	0.80 (0.71, 0.89)	0.82 (0.75, 0.90)	0.85 (0.79, 0.92)	0.87 (0.82, 0.93)	0.93 (0.90, 0.96)
Sodium (mg/d)	↑ SBP, main effect, white, normotensive[g]	103 RCTs (107 estimates)	per 2300 mg/d	1.64 mm Hg (-0.19, 3.46)	2.69 mm Hg (1.15, 4.23)	3.74 mm Hg (2.30, 5.17)	4.79 mm Hg (3.25, 6.33)	5.84 mm Hg (4.01, 7.66)	5.84 mm Hg (4.01, 7.66)
	↑ SBP, additional effect among Blacks[g]			2.49 mm Hg (0.13, 4.85)	2.49 mm Hg (0.13, 4.85)	2.49 mm Hg (0.13, 4.85)	2.49 mm Hg (0.13, 4.85)	2.49 mm Hg (0.13, 4.85)	2.49 mm Hg (0.13, 4.85)
	↑ SBP, additional effect among hypertensives[g]			1.87 mm Hg (0.12, 3.63)	1.87 mm Hg (0.12, 3.63)	1.87 mm Hg (0.12, 3.63)	1.87 mm Hg (0.12, 3.63)	1.87 mm Hg (0.12, 3.63)	1.87 mm Hg (0.12, 3.63)
	CHD-SBP mediated[g]	pooled analysis of APCSC and PSC	per 10 mmHg increase in SBP	1.81 (1.29, 2.56)	1.68 (1.29, 2.20)	1.56 (1.29, 1.89)	1.45 (1.29, 1.62)	1.33 (1.29, 1.38)	1.18 (1.09, 1.28)

eTable 5. Dietary factors having probable or convincing evidence for causal relationships with cardiometabolic outcomes and standardized magnitudes of effect sizes (continued)

Dietary Targets[a]	Cardiometabolic Outcome	No. of Studies in Each Meta-analysis	Unit of RR[b]	Relative Risk by Age (RR, 95% CIs)[c]					
				25-34 y	35-44 y	45-54 y	55-64 y	65-74 y	75+ y
		international pooling projects							
	HHD-SBP mediated[g]			3.29 (3.00, 3.60)	2.86 (2.67, 3.06)	2.49 (2.37, 2.61)	2.16 (2.09, 2.24)	1.88 (1.82, 1.94)	1.47 (1.42, 1.53)
	RHD-SBP mediated[g]			1.28 (1.11, 1.47)	1.24 (1.11, 1.38)	1.20 (1.11, 1.30)	1.17 (1.11, 1.23)	1.13 (1.09, 1.18)	1.08 (1.03, 1.12)
	CMM-SBP mediated[g]			1.51 (1.39, 1.64)	1.44 (1.35, 1.54)	1.37 (1.31, 1.43)	1.30 (1.26, 1.34)	1.24 (1.21, 1.28)	1.14 (1.11, 1.17)
	AF-SBP mediated[g]			1.51 (1.39, 1.64)	1.44 (1.35, 1.54)	1.37 (1.31, 1.43)	1.30 (1.26, 1.34)	1.24 (1.21, 1.28)	1.14 (1.11, 1.17)
	AA-SBP mediated[g]			1.62 (1.45, 1.80)	1.53 (1.40, 1.66)	1.44 (1.36, 1.53)	1.36 (1.31, 1.42)	1.29 (1.25, 1.32)	1.16 (1.12, 1.20)
	PVD-SBP mediated[g]			1.51 (1.39, 1.64)	1.44 (1.35, 1.54)	1.37 (1.31, 1.43)	1.30 (1.26, 1.34)	1.24 (1.21, 1.28)	1.14 (1.11, 1.17)
	Endocarditis-SBP mediated[g]			1.45 (1.26, 1.67)	1.39 (1.24, 1.55)	1.33 (1.22, 1.44)	1.27 (1.20, 1.34)	1.21 (1.17, 1.26)	1.12 (1.07, 1.17)
	Other cardiovascular and circulatory-SBP mediated[g]			1.51 (1.39, 1.64)	1.44 (1.35, 1.54)	1.37 (1.31, 1.43)	1.30 (1.26, 1.34)	1.24 (1.21, 1.28)	1.14 (1.11, 1.17)
	Ischemic stroke-SBP mediated[g]			2.30 (2.07, 2.56)	2.05 (1.89, 2.22)	1.83 (1.72, 1.93)	1.63 (1.57, 1.69)	1.44 (1.39, 1.50)	1.17 (1.13, 1.22)
	Hemorrhagic stroke-SBP mediated[g]			2.25 (1.67, 3.04)	2.11 (1.50, 2.98)	1.89 (1.43, 2.51)	1.66 (1.39, 1.98)	1.46 (1.36, 1.57)	1.19 (1.08, 1.3)

[a] Dietary factors with probable or convincing evidence, based on criteria for assessing causality,[11,13,14,86] for etiologic relationships with cardiometabolic outcomes including coronary heart disease (CHD), stroke, type 2 diabetes, body mass index (BMI), or systolic blood pressure (SBP).[9,10] Trans fats were not assessed due to limited national data on intakes as well as rapidly declining levels due to policy interventions. Dietary fiber was not included in the present analysis due to its overlap with its major food foods sources including fruits, vegetables, legumes, and whole grains.

[b] Associations with cardiometabolic outcomes were based on published or de novo meta-analyses of prospective cohorts or randomized clinical trials. Meta-analyses were evaluated based on design, number of studies and events, definition of dietary exposure and disease outcomes, statistical methods, evidence of bias, and control for confounders.[10] Relative risks (RRs) were standardized across individual studies per uniform servings of intake. No differential associations with incidence versus case-specific mortality were assumed; thus, for a given diet-disease relationship incidence estimates were used as a proxy, if mortality estimates were unavailable. We focused on dose-response meta-analyses. When necessary, original data were extracted from individual studies within each meta-analysis to perform de novo dose-response meta-analyses using all available data by means of generalized least squares (GLST) for trend estimation.

[c] Effect sizes are relative risks (RRs) (95% confidence intervals (CIs)) except for sugar-sweetened beverage (SSB) effects on BMI (absolute in kg/m^2) and sodium effects on SBP (absolute in mm Hg). Effect sizes correspond to the relationship between increased consumption of each dietary target per unit of RR and respective change in cardiometabolic risk (directionality in risk: ↑ increased, ↓ decreased). Most meta-analyses did not stratify by sex, and those that did found no significant differences in proportional relationships of dietary factors between men and women; in addition, the proportional relationships of most metabolic risk factors with chronic diseases appear similar by sex.[16-24] Thus, we incorporated similar proportional effect sizes (RRs) of dietary factors by sex. Conversely, our own and others' work has demonstrated that proportional relationships of major risk factors with cardiometabolic diseases vary by age, with an inverse log-linear age association.[4,5] We therefore derived and utilized age-group specific RRs for diet-CMD relationships based on the age patterns of RRs for metabolic risk factors and incident cardiometabolic

eTable 5. Dietary factors having probable or convincing evidence for causal relationships with cardiometabolic outcomes and standardized magnitudes of effect sizes (continued)

events, based on established Global Burden of Disease (GBD) methods.[4,5] Except as indicated (SSBs, sodium), we did not identify sufficient evidence for effect size modification by other factors beyond age, e.g. race, obesity, or overall diet quality.

[d] The RR on CVD from a de novo dose-response meta-analysis was used for ischemic and hemorrhagic stroke (similar to the RR on total stroke, which was based on a limited number of cohorts and events).[10]

[e] Consistent with GBD and available evidence for harms of high BMI on specific cardiometabolic outcomes the relationships of high intake of SSBs with CHD, hypertensive heart disease (HHD), ischemic stroke, hemorrhagic stroke (only when BMI ≥25 kg/m^2), and diabetes were estimated through their measured relationships with BMI (i.e., as mediated by BMI relationships).[5,6] Direct relationships with BMI (risk estimates are continuous changes in BMI, rather than RRs)[5,6] were included. The association of change in BMI with change in SSB consumption was assessed using multivariate linear regression accounting for within-person repeated measures, as described in earlier work;[6,7] separate linear relationships were estimated for BMI <25 and BMI ≥25 since the rate of increase in BMI due to SSB intake varies based on an individual's baseline BMI. Independently of this, additional direct relationships with type 2 diabetes (after adjustment for BMI) and CHD were included; total relationships with diabetes (direct plus mediated; after excluding BMI-mediated relationships with diabetes) were investigated in sensitivity analyses (see eFigure 18).[10]

[f] Estimated RRs are nearly identical for polyunsaturated fats (PUFA) replacing carbohydrates (Carbs) or saturated fats (SFA). For comparison, in sensitivity analyses we also evaluated the estimated mortality associated with excess SFA in place of PUFA. PUFA in place of carbs is the same as PUFA in place of carbs or SFA.

[g] Consistent with GBD and available evidence for harms of high BP on specific CVD outcomes the relationships of high intake of dietary sodium with CHD, ischemic stroke, hemorrhagic stroke, HHD, rheumatic heart disease (RHD), cardiomyopathy and myocarditis (CMM), atrial fibrillation and flutter (AF), aortic aneurysm (AA), peripheral vascular disease (PVD), endocarditis, and other cardiovascular and circulatory diseases were estimated through their measured effects on SBP (i.e., as mediated by SBP effects).[5,8] Direct effects on SBP are continuous changes in SBP, rather than RRs. For every year above or below age 50, there was 0.105 mm Hg (95%CI: 0.047, 0.164) larger or smaller BP reduction, respectively. No further interactions with SBP reduction were assumed below age 25 or above age 70, due to limited trial evidence outside this age range. Based on the evidence, we assumed a log-linear dose-response between SBP and CVD until a BP level of 115 mm Hg, below which we assumed no further contribution to risk.[8]