Combined lifestyle factors, all-cause mortality and cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies

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ABSTRACT

Introduction Unhealthy lifestyles caused a huge disease burden. Adopting healthy lifestyles is the most cost-effective strategy for preventing non-communicable diseases. The aim was to perform a systematic review and meta-analysis to quantify the relationship of combined lifestyle factors (eg, cigarette smoking, alcohol consumption, physical activity, diet and overweight/obesity) with the risk of all-cause mortality, cardiovascular mortality and incident cardiovascular disease (CVD).
Methods PubMed and EMBASE were searched from inception to April 2019. Cohort studies investigating the association between the combination of at least three lifestyle factors and all-cause mortality, cardiovascular mortality or incidence of CVD were filtered by consensus among reviewers. Pairs of reviewers independently extracted data and evaluated study quality. Random-effects models were used to pool HRs. Heterogeneity and publication bias were tested.
Results In total, 142 studies were included. Compared with the participants with the least-healthy lifestyles, those with the healthiest lifestyles had lower risks of all-cause mortality (HR=0.45, 95% CI 0.41 to 0.48, 74 studies with 2 584 766 participants), cardiovascular mortality (HR=0.42, 95% CI 0.37 to 0.46, 41 studies with 1 743 530 participants), incident CVD (HR=0.38, 95% CI 0.29 to 0.51, 22 studies with 754 894 participants) and multiple subtypes of CVDs (HRs ranging from 0.29 to 0.45). The associations were largely significant and consistent among individuals from different continents, racial groups and socioeconomic backgrounds.
Conclusions Given the great health benefits, comprehensively tackling multiple lifestyle risk factors should be the cornerstone for reducing the global disease burden.

INTRODUCTION

Lifestyle factors are often interrelated and associated with multiple non-communicable diseases (NCDs) including cardiovascular disease (CVD).[1] It was estimated that unhealthy behaviours accounted for over 23 million deaths and 36.5% of disability-adjusted life-years in 2017 globally.[2] Besides, adopting healthy lifestyle behaviours, including avoiding tobacco use and harmful alcohol consumption, as well as keeping a healthy diet, an optimal body weight and physically active, is the most cost-effective strategy for preventing NCDs.[3] Hence, understanding the associations of combined lifestyle factors with mortality and the incidence of CVD is of vital importance for health policymaking and medical resource allocation.

Many organisations have endorsed policies to reduce disease burden by diminishing unhealthy lifestyle factors.[4–6] Besides, an increasing number of studies investigated the associations of combined lifestyle factors with the risk of incident CVD, CVD mortality and all-cause mortality. However, given a relatively small number of original studies, previous meta-analyses did not investigate whether these associations were consistent among individuals with different baseline characteristics, and did not comprehensively evaluate the evidence on the subtypes of CVD.[7–12] Therefore, we conducted a systematic review and meta-analysis to evaluate the associations of combined lifestyle factors with total and subtypes of CVD mortality and morbidity as well as all-cause mortality, and whether these associations were consistent across individuals with different demographic characteristics.

METHOD

Data sources and searches

The study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in the Epidemiology Group (MOOSE) guidelines.[13 14] PubMed and EMBASE were searched from database inception to 26 April 2019. Reference lists of the included studies and relevant reviews were searched to identify additional publications. As the study was a section of a larger meta-analysis of the associations of combined lifestyle factors with mortality and major NCDs, the search terms included keywords in titles or abstracts and Medical Subject Heading terms related to 'combined', 'lifestyle', 'cohort study', 'mortality', 'cardiovascular disease', 'diabetes' and 'cancer'. Detailed search strategies were reported previously.[15] No language restriction was applied.

Study selection

We included cohort studies investigating the association of combined lifestyle factors with the incidence of total or subtypes of CVD, total or subtypes of CVD mortality, or all-cause mortality. The lifestyle factors included but were not limited to cigarette smoking, alcohol consumption, physical activity/sedentary behaviour, diet, overweight/obesity, sleep duration/quality. Several studies also included metabolic factors (eg, the Life's simple 7 (LS7) score defined by the American Heart Association included

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blood pressure, blood lipid level and blood glucose level, as well as smoking, physical activity, body weight and diet), which also reflected the overall lifestyle and remained in our main analysis. Online supplemental table A1 shows the components of three most common scores, defined as simple score (which gave equal weight to each lifestyle factor, eg, most studies assigned 1 or 0 to participants with or without a certain healthy behaviour),[16] LS7 score[17 18] and World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) score (which included physical activity, body weight, consumption of fast foods and other processed foods high in fat, starches or sugars, consumption of sugar-sweetened drinks, consumption of plant foods, consumption of animal foods, alcohol consumption, using supplements for cancer prevention, breastfeeding, and following recommendations after a cancer diagnosis).[19 20] We did not select studies according to the characteristics of the participants. We also included studies conducted in specific occupational groups or patients with certain diseases.

The exclusion criteria for this meta-analysis were as follows: (1) studies not investigating the combination of lifestyle factors or pre-decided outcomes, (2) ineligible publication types (such as reviews, protocols, cross-sectional studies and case–control studies) or not peer-reviewed publications (such as commentary, editorial and meeting abstracts), (3) studies focusing on an individual lifestyle factor or combinations of only two lifestyle factors, (4) studies with less than 1 year of follow-up, (5) studies aiming at formulating or validating prediction models, (6) duplicate publications or duplicate reporting from the same cohort and (7) studies not reporting the risk ratios with their CIs comparing the participants with the healthiest lifestyles versus those with the least-healthy lifestyles. We excluded conference abstracts from our analysis even if they reported the association of combined lifestyle factors with outcomes of interest. However, to avoid omitting any potential eligible studies, we searched online and contacted the authors to confirm whether the full texts of the conference abstracts had been accepted for publication.

Y-BZ filtered all citations, and another group of researchers including JC, AC, LX, YZ, JW and HL also performed the study selection independently. Any differences were resolved by consensus, or by consulting with a third investigator (AP).

Data extraction and quality assessment

The following information was extracted: first author, cohort, country, follow-up duration, the definitions of the healthy lifestyle factors, the definitions and attainments of outcomes, the number of participants and events, effect size with its CI, age, sex composition, race and ethnicity, education level and health status. Study quality was evaluated according to the Newcastle-Ottawa Scale.[21] Pairs of researchers independently conducted these procedures. Any differences were resolved by consensus, or by consulting with a senior investigator. We also made at least two attempts to contact the corresponding authors to obtain missing information.

Data synthesis and analysis

All analyses were performed by STATA software (version 13.0, StataCorp, College Station, Texas, USA). HR was used as an effect size for the pooled estimate, which was considered as interchangeable with relative risks and could be transformed from OR.[22] The score systems of different studies varied; however, most studies classified participants into three to six groups based on the distribution of the lifestyle score in the study population. Hence, we pooled HRs comparing the participants in the highest versus the lowest score group, to represent the risk estimates comparing individuals with the healthiest versus the least-healthy lifestyles. We used random-effects models to synthesise data, which allow heterogeneity among different studies.

Heterogeneity across studies was evaluated by I^2 statistic.[22] Pre-decided stratified analyses were conducted according to studies' characteristics (study locations, mean/median follow-up durations and lifestyle score systems) and populations' characteristics (average age, sex, race and ethnicity, education level and health status). Meta-regression was used to obtain p values for the difference between subgroups.[22] Publication bias was evaluated by the fail-safe N statistic, Begg's test and Egger's test.[22]

RESULTS

Study selection and characteristics

Based on the search strategy, we identified 82 230 unique citations and excluded 82 032 citations after screening for titles and abstracts. After reading the full text, 56 studies were excluded (online supplemental table A2 shows reasons). Finally, 87 studies (13 studies were only used for stratified analyses), 55 studies (14 were only used for stratified analyses), 25 studies (three were only used for stratified analyses) and 56 studies were respectively included for meta-analysis of all-cause mortality, CVD mortality, incident total CVD and subtypes of CVD (figure 1).

Among 94 studies used for the main analysis for all-cause mortality, CVD mortality and CVD (online supplemental tables A3–A5), 39 were from America, 36 from Europe, 15 from Asia, 2 from Oceania and 2 were global studies across several continents; 83 were from high-income countries. The mean baseline age ranged from less than 37.3 years to 81.3 years (median 55.9, IQR 11.8 years). The sample size ranged from 600 to 421 411. The mean/median follow-up duration ranged from 3.0 years to 33.9 years (median 10.3, IQR 7.3 years). Besides, several studies investigated coronary heart disease (CHD) mortality (10 studies), stroke mortality (4 studies) and the incidence of CHD (22 studies), stroke (18 studies), heart failure (9 studies), hypertension (6 studies), atrial fibrillation (2 studies) and peripheral artery disease (2 studies, online supplemental tables A6–A7). Newcastle-Ottawa Scale scores of all studies were no less than 5 (online supplemental table A8).

Association between combined lifestyle factors and all-cause mortality

The pooled HR comparing participants with the healthiest versus the least-healthy lifestyles for all-cause mortality was 0.45 (95% CI 0.41 to 0.48, I^2=91.0%, 74 studies with 2 584 766 participants and 304 130 deaths, figure 2 and online supplemental figure A1). The association was consistent in most stratified analyses. However, the associations seemed weaker in studies with shorter follow-up duration and in studies conducted among cancer survivors. Additionally, the association of the simple score (HR=0.41, 95% CI 0.37 to 0.45) with all-cause mortality was stronger than the LS7 score (HR=0.55, 95% CI 0.47 to 0.63) and WCRF/AICR score (HR=0.73, 95% CI 0.65 to 0.82). Also, the association of combined lifestyle factors with all-cause mortality was attenuated when the lifestyle score did not include smoking. The HRs were 0.45 (95% CI 0.38 to 0.54) for scores including all five factors versus 0.65 (95% CI 0.60 to 0.71) for scores not including smoking. P values for Egger's test and Begg's test were ≤0.05; however, the classic fail-safe N statistic indicated that additionally including 119

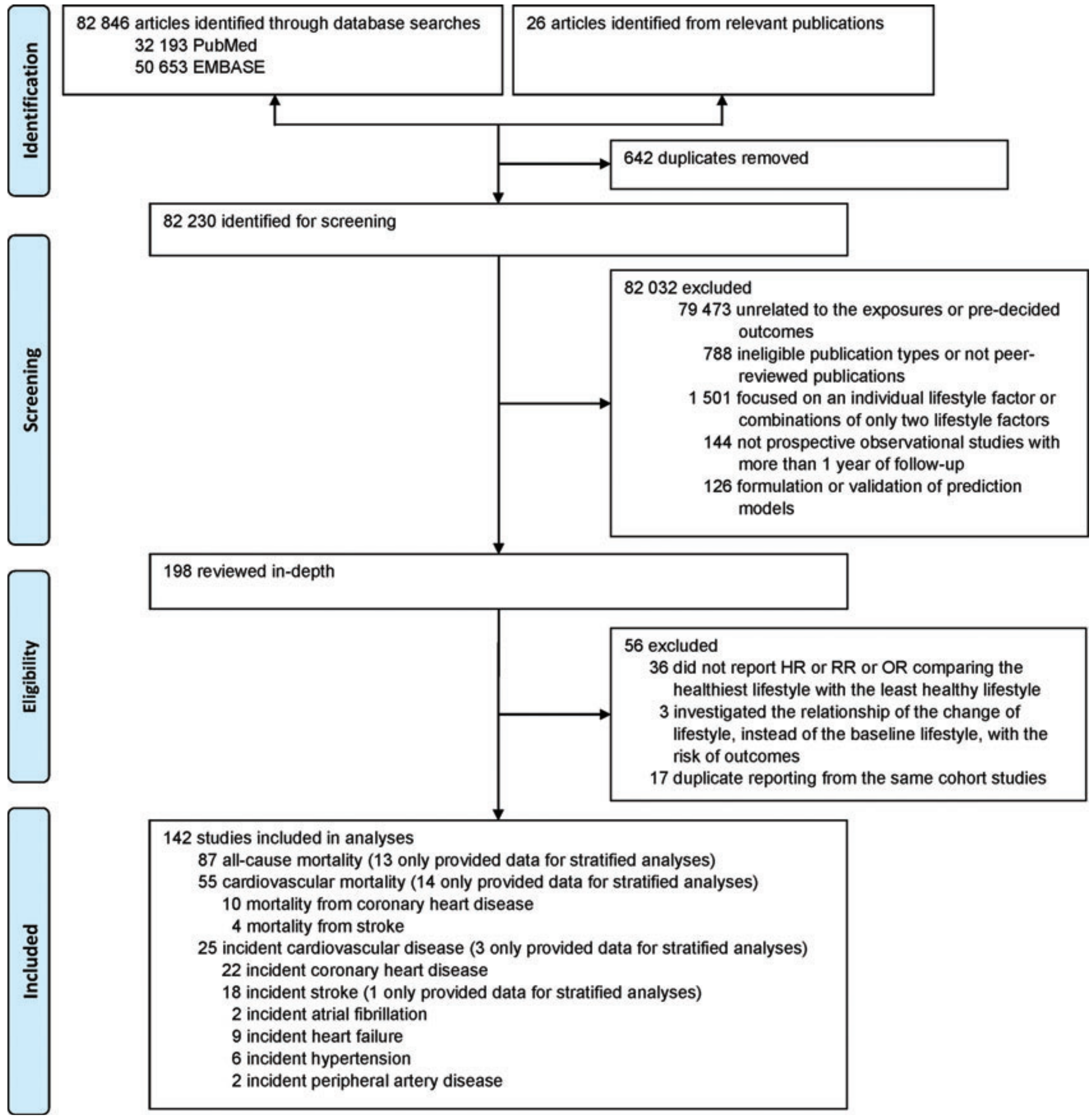


Figure 1 Flow chart of study selection. There were 64 studies reporting two or more outcomes, so the total number of studies for different outcomes exceeded 142. RR, risk ratio.

803 studies of null associations would make the pool result non-significant, which indicated that the influence of potential publication bias was mild (online supplemental table A9).

Association between combined lifestyle factors and CVD mortality

The pooled HR comparing participants with the healthiest versus the least-healthy lifestyles was 0.42 (95% CI 0.37 to 0.46, I^2=73.9%, 41 studies with 1 743 530 participants) for total CVD mortality, 0.40 (95% CI 0.30 to 0.53, I^2=68.6) for CHD mortality and 0.38 (95% CI 0.27 to 0.53, I^2=51.2) for stroke mortality (figure 3 and online supplemental figures A2–A4). The associations were statistically significant and consistent in most stratified analyses. However, the association seemed stronger in the younger population and in studies using the simple score and LS7 score compared with those using the WCRF/AICR score. Again, the association was stronger in studies with smoking included in the score than the others. P values for Egger's test were 0.001 for total CVD mortality and 0.04 for CHD mortality; however, the classic fail-safe N statistics were between 155 and 17 161 (online supplemental table A9).

Association between combined lifestyle factors and the risk of CVD

For the incidence of CVD, the HRs comparing participants with the healthiest versus the least-healthy lifestyles were 0.38 (95% CI 0.29 to 0.51, I^2=96.9, 22 studies with 754 894 participants) for total CVD, 0.31 (95% CI 0.24 to 0.40, I^2=93.0, 22 studies with 1 492 174 participants) for CHD, 0.45 (95% CI 0.37 to 0.54, I^2=80.0, 17 studies with 1 441 107 participants) for stroke, 0.29 (95% CI 0.24 to 0.35, I^2=80.3) for heart failure, 0.35 (95% CI 0.28 to 0.45, I^2=94.8) for hypertension, 0.44 (95% CI 0.31 to 0.61, I^2=50.2) for atrial fibrillation and 0.33 (95% CI 0.19 to 0.56, I^2=0) for peripheral artery disease (figures 4–5, online supplemental tables A10–A11and online supplemental figures A5–A11). The associations were statistically significant and consistent in most stratified analyses, except that the association of the LS7 score (HR=0.24, 95% CI 0.16 to 0.34) with total CVD was stronger than the simple score (HR=0.52, 95% CI 0.42 to 0.66).

Subgroup	Studies	Participants	Deaths	HR (95% CI)	P	I^2, %
All	74	2 584 766	304 130	0.45 (0.41 to 0.48)	<0.001	91.0
Continent*					$P_{between-group}$=0.01	
America	32	727 947	142 345	0.49 (0.44 to 0.55)	<0.001	93.1
Asia	12	438 746	36 408	0.45 (0.38 to 0.53)	<0.001	76.8
Europe	26	1 170 866	103 916	0.40 (0.36 to 0.46)	<0.001	89.8
Oceania	2	233 331	16 443	0.20 (0.14 to 0.29)	<0.001	0
High-income country*					$P_{between-group}$=0.27	
Yes	67	2 310 277	286 837	0.44 (0.40 to 0.47)	<0.001	91.2
No	5	260 613	12 275	0.53 (0.38 to 0.76)	<0.001	90.7
Ethnicity†					$P_{between-group}$=0.54	
Asian	11	398 038	33 369	0.43 (0.36 to 0.51)	<0.001	73.4
African-American	1	745	382	0.45 (0.23 to 0.88)	0.02	NA
White	47	1 753 758	226 704	0.44 (0.40 to 0.48)	<0.001	93.3
Mixed	12	153 461	23 821	0.51 (0.42 to 0.61)	<0.001	81.5
Missing	4	278 764	19 854	0.35 (0.20 to 0.62)	<0.001	90.7
Follow-up					$P_{between-group}$=0.02	
≥10 years	36	1 351 923	206 972	0.40 (0.36 to 0.44)	<0.001	94.4
<10 years	36	1 224 760	94 918	0.50 (0.45 to 0.56)	<0.001	80.9
Missing	2	8 083	2 240	0.38 (0.30 to 0.47)	<0.001	0
Average age†					$P_{between-group}$=0.41	
≥60 years old	33	>1 078 661‡	>111440‡	0.46 (0.40 to 0.52)	<0.001	94.0
<60 years old	44	>1 480 405‡	>157 941‡	0.43 (0.39 to 0.47)	<0.001	86.2
Sex†					$P_{between-group}$=0.61	
Men	32	>719 335‡	>92 518‡	0.40 (0.35 to 0.46)	<0.001	92.3
Women	34	>1 038 229‡	>106 208‡	0.44 (0.38 to 0.51)	<0.001	93.8
Both	33	680 372	59 013	0.45 (0.40 to 0.50)	<0.001	77.9
Proportion of high school graduates†					$P_{between-group}$=0.55	
≥80%	18	484 243	>90 674‡	0.49 (0.43 to 0.55)	<0.001	83.1
<80%	31	1 078 234	>101 474‡	0.45 (0.39 to 0.51)	<0.001	88.8
Missing	27	1 019 385	96 347	0.41 (0.35 to 0.48)	<0.001	93.9
Health status†					$P_{between-group}$=0.25	
General population	54	2 183 232	>270 364‡	0.43 (0.39 to 0.47)	<0.001	92.5
Patients with CVD	6	11 196	2 886	0.48 (0.40 to 0.59)	<0.001	21.9
Patients with CKD	3	8 244	2 366	0.55 (0.33 to 0.91)	0.02	59.2
Patients with cancer	8	24 990	8 374	0.58 (0.48 to 0.70)	<0.001	64.7
Score†					$P_{between-group}$=0.003	
Simple score	50	1 521 011	214 663	0.41 (0.37 to 0.45)	<0.001	92.2
LS7 score	15	582 387	41 817	0.55 (0.47 to 0.63)	<0.001	72.1
WCRF/AICR score	6	431 725	32 734	0.73 (0.65 to 0.82)	<0.001	67.9
Others	11	154 038	30 659	0.43 (0.36 to 0.52)	<0.001	87.3
Factors included in score†					$P_{between-group}$=0.37	
All five factors	16	362 393	80 309	0.45 (0.38 to 0.54)	<0.001	89.7
Alcohol drinking excluded	40	1 257 258	141 842	0.45 (0.41 to 0.51)	<0.001	90.2
Body weight excluded	26	1 161 270	104 806	0.42 (0.37 to 0.47)	<0.001	92.9
Diet excluded	18	800 786	86 793	0.47 (0.43 to 0.52)	<0.001	83.0
Physical activity excluded	3	205 837	26 629	0.45 (0.31 to 0.65)	<0.001	95.1
Smoking excluded	13	858 715	88 882	0.65 (0.60 to 0.71)	<0.001	84.5

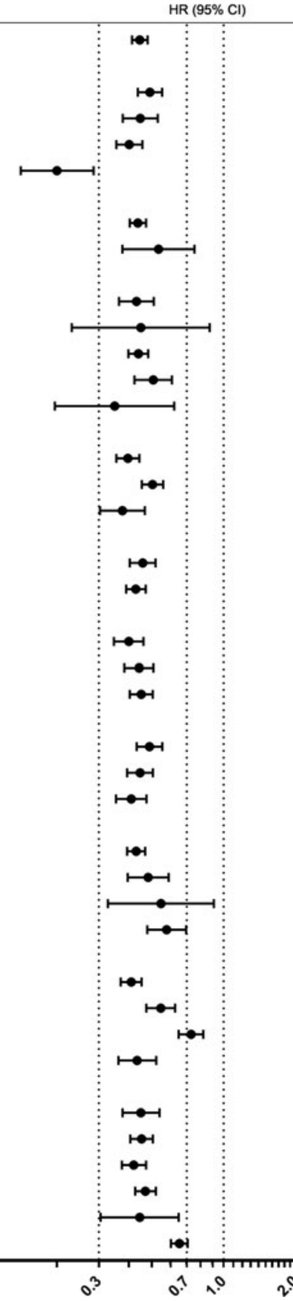


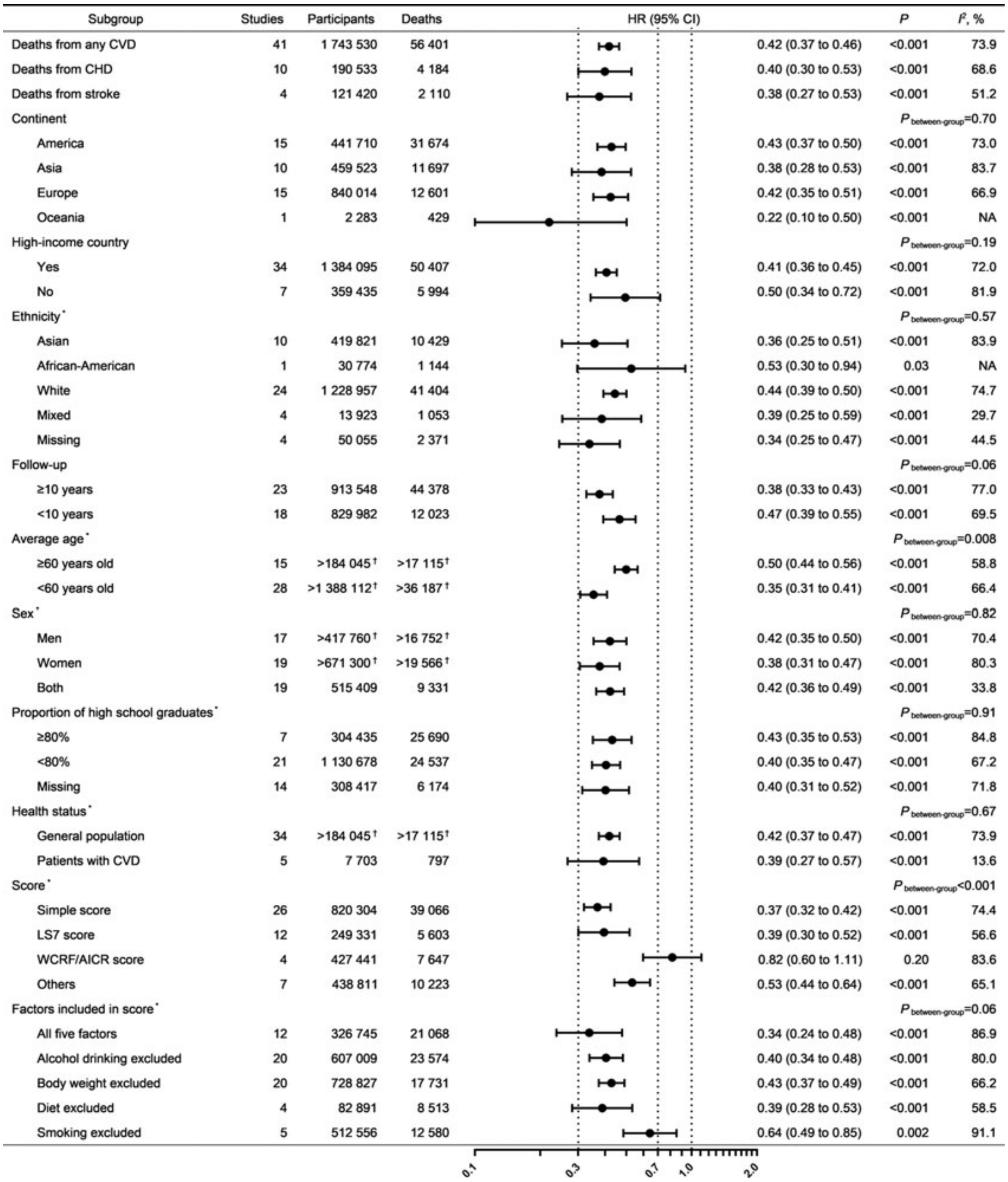
Figure 2 Association of combined lifestyle factors with all-cause mortality. *Two studies were global studies that included participants from different continents. † Studies from several cohorts conducted stratified analyses, and thusly the total number of the studies from different groups exceeded 74. ‡ Several studies did not report the number of participants and deaths in each subgroup. AICR, American Institute for Cancer Research; CKD, chronic kidney disease; CVD, cardiovascular disease; LS7, Life's Simple 7; NA, Not available; WCRF, World Cancer Research Fund.

P value for Egger's test was 0.04 for incident CHD; however, the classic fail-safe N statistics were between 2423 and 6550 (online supplemental table A9).

DISCUSSION

This systematic review and meta-analysis of cohort studies suggest that an overall healthy lifestyle was associated with a considerably lower risk of all-cause mortality, CVD mortality and incident CVD. Compared with the participants with the least-healthy lifestyles, those with the healthiest lifestyles had 55%, 58% and 62% lower risks of all-cause mortality, CVD mortality and incident CVD, respectively. Besides, adopting the healthiest lifestyles would have a 55–71% lower risk of fatal/total stroke, atrial fibrillation, hypertension, peripheral artery disease, fatal/total CHD and heart failure. The associations were largely consistent among populations from different continents, racial groups and socioeconomic backgrounds.

A meta-analysis published in 2012 (15 studies with 531 804 participants) reported that a combination of at least four healthy behaviours was associated with a 66% reduction in all-cause mortality, which was similar to our result but we included 74 studies with over 2.5 million participants.[11] Another meta-analysis concluded that adopting the healthiest behavioural pattern was associated with a 60–69% reduced risk for incident



Subgroup	Studies	Participants	Deaths	HR (95% CI)	P	I^2, %
Deaths from any CVD	41	1 743 530	56 401	0.42 (0.37 to 0.46)	<0.001	73.9
Deaths from CHD	10	190 533	4 184	0.40 (0.30 to 0.53)	<0.001	68.6
Deaths from stroke	4	121 420	2 110	0.38 (0.27 to 0.53)	<0.001	51.2
Continent					$P_{between-group}$=0.70	
America	15	441 710	31 674	0.43 (0.37 to 0.50)	<0.001	73.0
Asia	10	459 523	11 697	0.38 (0.28 to 0.53)	<0.001	83.7
Europe	15	840 014	12 601	0.42 (0.35 to 0.51)	<0.001	66.9
Oceania	1	2 283	429	0.22 (0.10 to 0.50)	<0.001	NA
High-income country					$P_{between-group}$=0.19	
Yes	34	1 384 095	50 407	0.41 (0.36 to 0.45)	<0.001	72.0
No	7	359 435	5 994	0.50 (0.34 to 0.72)	<0.001	81.9
Ethnicity*					$P_{between-group}$=0.57	
Asian	10	419 821	10 429	0.36 (0.25 to 0.51)	<0.001	83.9
African-American	1	30 774	1 144	0.53 (0.30 to 0.94)	0.03	NA
White	24	1 228 957	41 404	0.44 (0.39 to 0.50)	<0.001	74.7
Mixed	4	13 923	1 053	0.39 (0.25 to 0.59)	<0.001	29.7
Missing	4	50 055	2 371	0.34 (0.25 to 0.47)	<0.001	44.5
Follow-up					$P_{between-group}$=0.06	
≥10 years	23	913 548	44 378	0.38 (0.33 to 0.43)	<0.001	77.0
<10 years	18	829 982	12 023	0.47 (0.39 to 0.55)	<0.001	69.5
Average age*					$P_{between-group}$=0.008	
≥60 years old	15	>184 045†	>17 115†	0.50 (0.44 to 0.56)	<0.001	58.8
<60 years old	28	>1 388 112†	>36 187†	0.35 (0.31 to 0.41)	<0.001	66.4
Sex*					$P_{between-group}$=0.82	
Men	17	>417 760†	>16 752†	0.42 (0.35 to 0.50)	<0.001	70.4
Women	19	>671 300†	>19 566†	0.38 (0.31 to 0.47)	<0.001	80.3
Both	19	515 409	9 331	0.42 (0.36 to 0.49)	<0.001	33.8
Proportion of high school graduates*					$P_{between-group}$=0.91	
≥80%	7	304 435	25 690	0.43 (0.35 to 0.53)	<0.001	84.8
<80%	21	1 130 678	24 537	0.40 (0.35 to 0.47)	<0.001	67.2
Missing	14	308 417	6 174	0.40 (0.31 to 0.52)	<0.001	71.8
Health status*					$P_{between-group}$=0.67	
General population	34	>184 045†	>17 115†	0.42 (0.37 to 0.47)	<0.001	73.9
Patients with CVD	5	7 703	797	0.39 (0.27 to 0.57)	<0.001	13.6
Score*					$P_{between-group}$<0.001	
Simple score	26	820 304	39 066	0.37 (0.32 to 0.42)	<0.001	74.4
LS7 score	12	249 331	5 603	0.39 (0.30 to 0.52)	<0.001	56.6
WCRF/AICR score	4	427 441	7 647	0.82 (0.60 to 1.11)	0.20	83.6
Others	7	438 811	10 223	0.53 (0.44 to 0.64)	<0.001	65.1
Factors included in score*					$P_{between-group}$=0.06	
All five factors	12	326 745	21 068	0.34 (0.24 to 0.48)	<0.001	86.9
Alcohol drinking excluded	20	607 009	23 574	0.40 (0.34 to 0.48)	<0.001	80.0
Body weight excluded	20	728 827	17 731	0.43 (0.37 to 0.49)	<0.001	66.2
Diet excluded	4	82 891	8 513	0.39 (0.28 to 0.53)	<0.001	58.5
Smoking excluded	5	512 556	12 580	0.64 (0.49 to 0.85)	0.002	91.1

Figure 3 Association of combined lifestyle factors with CVD mortality. * Studies from several cohorts conducted stratified analyses, and thusly the total number of the studies from different groups exceeded 41. † Several studies did not report the number of participants and deaths in each subgroup. AICR, American Institute for Cancer Research; CHD, coronary heart disease; CVD, cardiovascular disease; LS7, Life's Simple 7; NA, not available; WCRF, World Cancer Research Fund.

CVD, stroke and heart failure.[12] However, the authors pooled all CVD subtypes together in the CVD analysis, while we only included studies using total CVD as the outcome, and results for subtypes were analysed separately. Additionally, we included more studies and additionally reported results for incident CHD, hypertension, atrial fibrillation and peripheral artery disease.

Four meta-analyses focused on LS7 and found ideal cardiovascular health profile was associated with a 46% lower risk for all-cause mortality (six studies), 70% for CVD mortality (six studies), 77% for incident CVD (four studies), 67% for incident stroke (five studies) and 79% for incident CHD (two studies), compared with poor cardiovascular health profile.[7–10] We included approximately twice more studies and further compared the lifestyle scores with vs without metabolic factors. As expected, the LS7 score was strongly related to incident CVD given that blood pressure, lipid and glucose levels were powerful predictors for incident CVD. However, the risk reductions for all-cause and CVD mortality related to LS7 were similar or even weaker compared with the simple score, indicating that more emphases should be given to the upstream lifestyle factors, in addition to the intermediate metabolic changes, for the prevention of premature deaths.

Evidence from randomised controlled trials regarding the effects of comprehensive lifestyle intervention on premature death and CVD is limited. The Da Qing Diabetes Prevention Outcome Study (577 Chinese adults with impaired glucose tolerance) found that participants receiving dietary and/or exercise interventions for 6 years had 26%, 33% and 26%

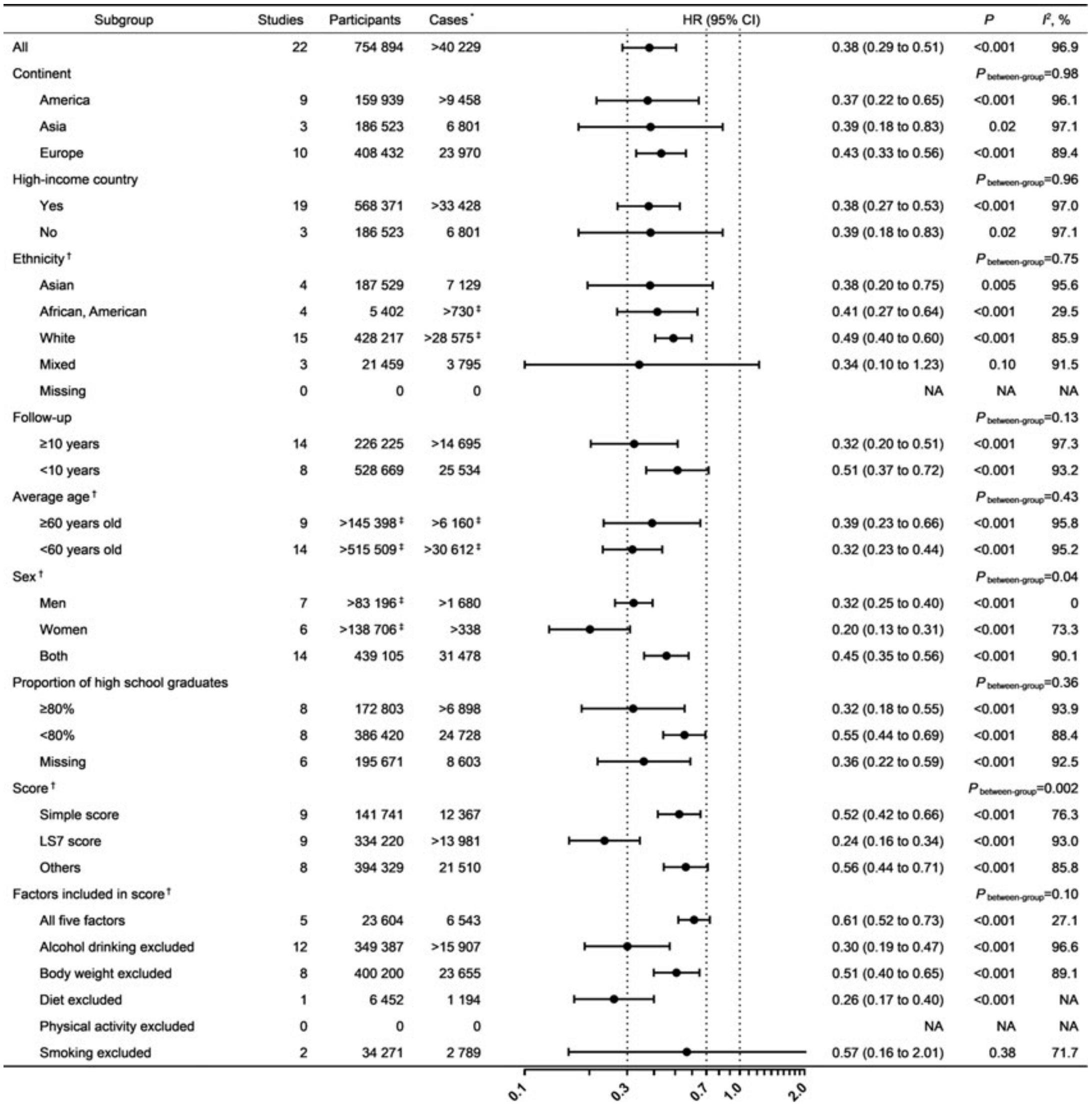


Figure 4 Association of combined lifestyle factors with the risk of total CVD, CHD and stroke. *The number of the incident CVD cases was not reported in Foraker *et al* (2016).[23] † Studies from several cohorts conducted stratified analyses, and thus the total number of the studies from different groups exceeded the number of studies used in the main analysis. ‡ Several studies did not report the number of participants and deaths in each subgroup. CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; LS7, Life's Simple 7; NA, not available.

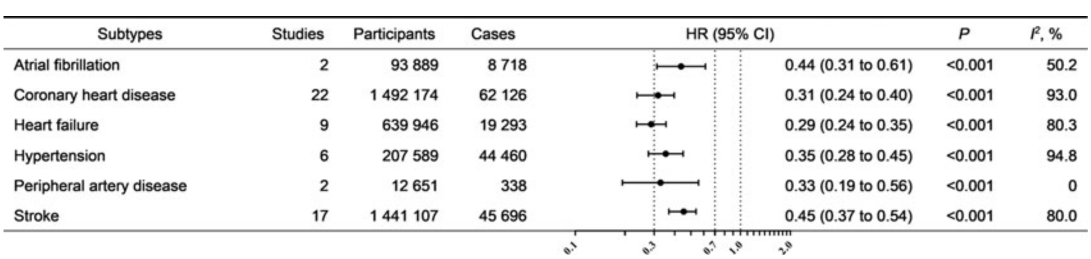


Figure 5 Association of combined lifestyle factors with the risk of atrial fibrillation, heart failure, hypertension and peripheral artery disease.

lower risks of CVD, CVD mortality and all-cause mortality after a 30-year follow-up, respectively.[24] Two studies reported that lifestyle interventions could reduce 20% and 38% risks of primary CVD outcomes and stroke in diabetic individuals, respectively.[25 26] However, studies applying lifestyle counselling reported inconsistent conclusions.[27–29] In patients with CVD, lifestyle interventions could reduce 48–81% risk of cardiovascular events,[30–32] but the effect on deaths remained controversial.[33–35] Generally, randomised controlled trials were conducted in relatively small groups of individuals or diseased populations and were followed up for relatively short periods. Besides, it was difficult for participants to follow the structured lifestyle, and the intervention period was short. Hence, high-quality evidence from cohort studies is essential for understanding the protective effects of healthy lifestyles.

To the best of our knowledge, this study is the first systematic review conducting stratified analyses according to the populations' characteristics to understand the relations of combined lifestyle factors with the risk of incident CVD, CVD mortality and all-cause mortality, which may have important public health implications. Considering that socioeconomic factors could be upstream determinants of lifestyles, individuals with different characteristics may perceive and choose healthy lifestyles differently.[4] However, our stratified analyses showed the associations were largely consistent across different regions, economic levels, races and ethnicities, sexes, and education levels. Notably, the stratified analyses showed that the association was stronger in studies with longer follow-up or among younger participants, indicating larger benefits could be obtained if people adopt healthy lifestyles at an early age and follow for a long time.

The associations between different lifestyle factors and the outcomes are varied. For instance, smoking showed a stronger association with all-cause and CVD mortality than other factors.[36 37] Accordingly, our stratified analysis showed that the associations were stronger in studies with smoking as a component of lifestyle score. Therefore, avoiding smoking should be prioritised when we make lifestyle-related recommendations or policies to prevent premature death.

This study also raised an important clinical issue of whether patients with certain diseases could also benefit from healthy lifestyles. Among individuals with CVD, associations between healthy lifestyles and all-cause mortality or CVD mortality were similar to those among the general population. The finding supports the recommendations from several organisations that lifestyle modification should be the cornerstone for the management of CVD.[5 6] However, the association between healthy lifestyles and all-cause mortality was weaker among cancer survivors, which might be because treatment is also an important predictor of prognosis among cancer survivors and thus the impact of lifestyle becomes relatively weaker. Nonetheless, the risk reductions were still substantial, indicating that lifestyle modifications are still meaningful and should be recommended for cancer survivors. With limited large randomised controlled trials investigating the effect of lifestyle intervention on mortality among individuals with cancer or CVD, evidence from high-quality cohort studies is urgently needed for formulating clinical guidelines in the diseased populations.

Based on a thorough search strategy and the standard procedures of PRISMA and MOOSE guidelines,[13 14] this study is the most comprehensive and up-to-date systematic review and meta-analysis to summarise the associations of combined lifestyle factors with all-cause mortality, CVD mortality and the risk of CVD. We had sufficient power to conduct many stratified analyses, and the results were largely consistent. These analyses could provide new clinical and public health viewpoints. However, several limitations should also be acknowledged. First, most studies were conducted in high-income countries and whites. Hence, more evidence from other populations is still needed. Second, the constructions of lifestyle scores varied across studies, which could generate potential heterogeneity. However, we only pooled risk ratios comparing the extreme groups, and most studies grouped participants into three to six groups according to the distribution of lifestyle scores. Besides, we also conducted stratified analyses according to score systems to explore the sources of heterogeneity. Third, there were possibilities of publication bias, and limited studies were available for incident atrial fibrillation, heart failure, hypertension and peripheral artery disease. Thus, the results should be interpreted cautiously. Fourth, some original studies did not fully control for socioeconomic status, psychological characteristics, comorbidities and medical treatment adherence at baseline, and thus residual cofounding in original studies might bias the results.

CONCLUSION

Adopting healthy lifestyles was associated with substantially lower risks of all-cause mortality, CVD mortality and incident CVD. The results were generally consistent among populations from different continents, racial groups and socioeconomic backgrounds. Given that the proportion of individuals adopting the healthiest lifestyles is low globally, all countries and regions should give high priority to the promotion of healthy lifestyles. Governments and other organisations should formulate policies and guidelines tailored to the preference of the locals to facilitate their adopting healthy lifestyles. Health workers should instruct patients, especially those with CVD, high-risk individuals and general populations to adopt healthy lifestyles for comprehensive prevention for CVD and premature death. Future studies should focus on non-high-income countries and non-white ethnicity, as well as the associations between combined lifestyle factors and the risk of subtypes of CVD.

What is already known on this subject

- Single healthy lifestyle factors are associated with lower risks of all-cause and cardiovascular mortality as well as incident cardiovascular disease.
- Lifestyle factors are often interrelated and associated with multiple non-communicable diseases, and thus, investigating the combined effects of multiple lifestyle factors, which could reflect the benefits of overall healthy lifestyles, might be more appropriate to account for interactions between lifestyle factors.

What this study adds

- In this systematic review and meta-analysis, compared with the participants with the least-healthy lifestyles, those with the healthiest lifestyles had 55%, 58% and 62% lower risks of all-cause mortality, cardiovascular mortality, and incident cardiovascular disease, respectively, as well as 55–71% lower risks of multiple subtypes of cardiovascular disease including fatal/total stroke, atrial fibrillation, hypertension, peripheral artery disease, fatal/total coronary heart disease and heart failure.
- The associations were largely consistent among populations from different continents, racial groups and socioeconomic backgrounds, and adopting healthy lifestyles could also benefit individuals with cardiovascular disease or cancer.
- Our findings indicated that comprehensively tackling multiple lifestyle risk factors should be the cornerstone for reducing the global disease burden.

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REFERENCES

1 Shankar A, McMunn A, Steptoe A. Health-related behaviors in older adults: relationships with socioeconomic status. *Am J Prev Med* 2010;38:39–46.
2 Stanaway JD, Afshin A, Gakidou E, *et al.* Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2018;392:1923–94.
3 World Health Organization. 'Best buys' and other recommended interventions for the prevention and control of noncommunicable diseases. Available http://www.who.int/iris/handle/10665/259232 (accessed 5 May 2019)
4 World Health Organization. Noncommunicable diseases progress monitor. 2017. Available https://www.who.int/nmh/publications/ncd-progress-monitor-2017/en/ (accessed 5 May 2019)
5 Carnethon MR, Pu J, Howard G, *et al.* Cardiovascular health in African Americans: a scientific statement from the American Heart Association. *Circulation* 2017;136: e393–e423-.
6 Turco JV, Inal-Veith A, Fuster V. Cardiovascular health promotion: an issue that can no longer wait. *J Am Coll Cardiol* 2018;72:908–13.
7 Aneni EC, Crippa A, Osondu CU, *et al.* Estimates of mortality benefit from ideal cardiovascular health metrics: a dose response meta-analysis. *J Am Heart Assoc* 2017;6:e006904.
8 Guo L, Zhang S. Association between ideal cardiovascular health metrics and risk of cardiovascular events or mortality: a meta-analysis of prospective studies. *Clin Cardiol* 2017;40:1339–46.
9 Na F, Jiang M, Yu F. Ideal cardiovascular health metrics and risk of cardiovascular disease or mortality: a meta-analysis. *Int J Cardiol* 2016;214:279–83.
10 Ramirez-Velez R, Saavedra JM, Lobelo F, *et al.* Ideal cardiovascular health and incident cardiovascular disease among adults: a systematic review and meta-analysis. *Mayo Clin Proc* 2018;93:1589–99.
11 Loef M, Walach H. The combined effects of healthy lifestyle behaviors on all cause mortality: a systematic review and meta-analysis. *Prev Med* 2012;55:163–70.
12 Barbaresko J, Rienks J, Nothlings U. Lifestyle indices and cardiovascular disease risk: a meta-analysis. *Am J Prev Med* 2018;55:555–64.
13 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
14 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-Analysis of Observational Studies in Epidemiology: a proposal for reporting. Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
15 Zhang Y, Pan XF, Chen J, *et al.* Combined lifestyle factors and risk of incident type 2 diabetes and prognosis among individuals with type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. *Diabetologia* 2020;63:21–33.
16 Li Y, Pan A, Wang DD, *et al.* Impact of healthy lifestyle factors on life expectancies in the US population. *Circulation* 2018;138:345–55.
17 Lloyd-Jones DM, Hong Y, Labarthe D, *et al.* Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation* 2010;121:586–613.
18 Folsom AR, Shah AM, Lutsey PL, *et al.* American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. *Am J Med* 2015;128:970–76.e2.
19 Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. *Proc Nutr Soc* 2008;67:253–6.
20 Romaguera D, Ward H, Wark PA, *et al.* Pre-diagnostic concordance with the WCRF/AICR guidelines and survival in European colorectal cancer patients: a cohort study. *BMC Med* 2015;13:107.
21 Cook DA, Reed DA. Appraising the quality of medical education research methods: the medical education research study quality instrument and the Newcastle-Ottawa scale-education. *Acad Med* 2015;90:1067–76.
22 Borenstein M, Hedges LV, Higgins JPT, *et al. Introduction to meta-analysis*. Chichester: John Wiley & Sons, Ltd, 2009.
23 Foraker RE, Abdel-Rasoul M, Kuller LH, *et al.* Cardiovascular health and incident cardiovascular disease and cancer: the women's health initiative. *Am J Prev Med* 2016;50:236–40.
24 Gong Q, Zhang P, Wang J, *et al.* Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019;7:452–61.
25 Gregg EW, Jakicic JM, Blackburn G, *et al.* Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the look ahead randomised clinical trial. *Lancet Diabetes Endocrinol* 2016;4:913–21.
26 Sone H, Tanaka S, Iimuro S, *et al.* Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). *Diabetologia* 2010;53:419–28.
27 Jorgensen T, Jacobsen RK, Toft U, *et al.* Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial. *BMJ* 2014;348:g3617.
28 Kim D, Yoon SJ, Lim DS, *et al.* The preventive effects of lifestyle intervention on the occurrence of diabetes mellitus and acute myocardial infarction in metabolic syndrome. *Public Health* 2016;139:178–82.
29 Ponzo V, Gentile L, Gambino R, *et al.* Incidence of diabetes mellitus, cardiovascular outcomes and mortality after a 12-month lifestyle intervention: a 9-year follow-up. *Diabetes Metab* 2018;44:449–51.
30 Giannuzzi P, Temporelli PL, Marchioli R, *et al.* Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network. *Arch Intern Med* 2008;168:2194–204.
31 Kono Y, Yamada S, Yamaguchi J, *et al.* Secondary prevention of new vascular events with lifestyle intervention in patients with noncardioembolic mild ischemic stroke: a single-center randomized controlled trial. *Cerebrovasc Dis* 2013;36:88–97.
32 Ornish D, Scherwitz LW, Billings JH, *et al.* Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* 1998;280:2001–7.
33 Lisspers J, Sundin O, Ohman A, *et al.* Long-term effects of lifestyle behavior change in coronary artery disease: effects on recurrent coronary events after percutaneous coronary intervention. *Health Psychol* 2005;24:41–8.
34 Marcos-Forniol E, Meco JF, Corbella E, *et al.* Secondary prevention programme of ischaemic heart disease in the elderly: a randomised clinical trial. *Eur J Prev Cardiol* 2018;25:278–86.
35 Wallner S, Watzinger N, Lindschinger M, *et al.* Effects of intensified lifestyle modification on the need for further revascularization after coronary angioplasty. *Eur J Clin Invest* 1999;29:372–9.
36 Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. *Arch Intern Med* 2012;172:837–44.
37 Mons U, Müezzinler A, Gellert C, *et al.* Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ* 2015;350:h1551.