SYSTEMATIC REVIEW

REVISED

The influence of socioeconomic status on the association between unhealthy lifestyle factors and adverse health outcomes: a systematic review [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background

Combinations of lifestyle factors (LFs) and socioeconomic status (SES) are independently associated with cardiovascular disease (CVD), cancer, and mortality. Less advantaged SES groups may be disproportionately vulnerable to unhealthy LFs but interactions between LFs and SES remain poorly understood. This review aimed to synthesise the available evidence for whether and how SES modifies associations between combinations of LFs and adverse health outcomes.

Methods

Systematic review of studies that examine associations between combinations of >3 LFs (eg.smoking/physical activity/diet) and health outcomes and report data on SES (eg.income/education/poverty-index) influences on associations. Databases (PubMed/EMBASE/CINAHL), references, forward citations, and grey-literature were searched from inception to December 2021. Eligibility criteria were analyses of prospective adult cohorts that examined all-cause mortality or CVD/cancer mortality/incidence.

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Any reports and responses or comments on the article can be found at the end of the article.

Results

Six studies (n=42,467–399,537; 46.5–56.8 years old; 54.6–59.3% women) of five cohorts were included. All examined all-cause mortality; three assessed CVD/cancer outcomes. Four studies observed multiplicative interactions between LFs and SES, but in opposing directions. Two studies tested for additive interactions; interactions were observed in one cohort (UK Biobank) and not in another (National Health and Nutrition Examination Survey (NHANES)). All-cause mortality HRs (95% confidence intervals) for unhealthy LFs (versus healthy LFs) from the most advantaged SES groups ranged from 0.68 (0.32–1.45) to 4.17 (2.27–7.69). Equivalent estimates from the least advantaged ranged from 1.30 (1.13–1.50) to 4.00 (2.22–7.14). In 19 analyses (including sensitivity analyses) of joint associations between LFs, SES, and all-cause mortality, highest all-cause mortality was observed in the unhealthiest LF-least advantaged suggesting an additive effect.

Conclusions

Limited and heterogenous literature suggests that the influence of SES on associations between combinations of unhealthy LFs and adverse health could be additive but remains unclear. Additional prospective analyses would help clarify whether SES modifies associations between combinations of unhealthy LFs and health outcomes.

Registration

Protocol is registered with PROSPERO (CRD42020172588;25 June 2020).

Keywords
Public Health, Epidemiology, Lifestyle, Health Behaviour, Healthcare Disparities, Socioeconomic Factors

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> **REVISED** **Amendments from Version 1**
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> We have responded to the reviewer's comments point by point. Key changes involved adding to the disucssion on the heterogeity of data in studies, adding to the strengths and limitations section, and altering the main figures (Figure 2 and Figure 3) to include the HR (95%CI) estimates and change the horizontal axes to a logarithmic scale.
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> **Any further responses from the reviewers can be found at the end of the article**

Introduction

Unhealthy lifestyle factors (LFs) (*e.g.*, smoking, alcohol, poor diet, low physical activity (PA)) are key modifiable risk factors for non-communicable diseases (NCDs) and mortality[1]. While single LFs have, by themselves, strong associations with NCDs and mortality, combinations of unhealthy LFs have stronger associations. Meta-analyses show that, compared with healthy LFs, combinations of at least three unhealthy LFs are associated with more than twice the risk of all-cause, cardiovascular disease (CVD), and cancer mortality, and CVD incidence[2,3]. Examining adverse health outcomes associated with combinations of LFs can help to capture 'real life' risks more completely as unhealthy LFs tend to cluster together - individuals with one unhealthy LF often have more than one[4,5]. And the impacts of one unhealthy LF may interact (additively or multiplicatively) with other unhealthy LFs[6–8].

In addition to examining the associations between combinations of LFs and adverse health outcomes (*e.g.*, all-cause, CVD, and cancer mortality, and CVD incidence), examining the effect of socioeconomic status (SES) on those associations can deepen understanding of the distribution of these lifestyle-related adverse health outcomes among populations. As with most health outcomes, all-cause, CVD, and cancer mortality, and CVD incidence all follow clear and long-recognised SES-health gradients where individuals of less advantaged SES (*e.g.*, those with lower educational attainment, lower income, or who live in areas of higher deprivation) tend to have higher rates of both morbidity and mortality[9,10]. SES is a theoretical construct that differentiates sections of society by their means and access to resources (*e.g.*, financial, educational, material) and by the ways in which they live (*e.g.*, occupation type or class, housing type/conditions, neighbourhood/post code area)[10]. The broad scope that SES encompasses means 1) there are numerous ways in which SES can be operationalised or measured[11,12]; and 2) there are numerous aspects of SES that could be expected to influence and have strong associations with both LFs and lifestyle-related adverse health outcomes[13,14]. For example, there is higher prevalence of unhealthy LFs in less advantaged SES groups and clustering of multiple unhealthy LFs in such population groups is often cited as an explanation for observed lifestyle-related adverse health inequalities[4]. However, 'differential exposure' to unhealthy LFs only partially explains lifestyle-related health inequalities; higher prevalence of unhealthy LFs is estimated to account for 6–80% of SES related mortality inequalities[4,15–18].

Beyond differential exposure, further explanations for lifestyle-related health inequalities may involve interactions between LFs and SES; so-called 'differential vulnerability'[17], where SES strengthens the association between lifestyle and adverse health outcomes. A study of over 300,000 UK Biobank (UKB) participants observed multiplicative interactions between a combination of unhealthy LFs and SES, where less advantaged SES groups had disproportionately higher lifestyle-related all-cause and CVD mortality[19]. Similar interactions between lifestyle and SES have been observed for single LFs: smoking, alcohol, and PA[20–22]. A multiplicative interaction between LFs and SES supports a vulnerability hypothesis, where less advantaged groups are disproportionately vulnerable to the adverse effects of unhealthy LFs[17,20]. Whereas additive interactions, where the effects of a combination of unhealthy LFs and SES are added rather than multiplied[23], can also highlight vulnerable groups and inform policy or interventions[24]. Mechanisms that explain differential lifestyle vulnerability or that explain how and why SES effects associations between lifestyle and adverse health outcomes are unclear but could include interactions with other factors associated with less advantaged SES (*e.g.*, stress, reduced access to health care) or accelerated biological ageing *via* greater cumulative risks over the life-course (*e.g.*, poorer childhood health or increased adverse childhood experiences)[25–27].

Aims

Understanding whether SES influences the association between combinations of unhealthy LFs and adverse health outcomes could help reduce excess risk in less advantaged populations by deepening understanding of how complex lifestyle risks vary across society and by identifying higher risk LF combinations. This could inform health policy, guide the development of interventions targeting more vulnerable groups, and support health care professionals managing multiple risk factors in their patient population. This systematic review aims to identify, describe, and synthesise the evidence for whether SES modifies associations between combinations of unhealthy LFs and adverse health outcomes (all-cause mortality, incidence and mortality from CVD or cancer). This review addresses the following research questions: Does SES modify the association between combinations of unhealthy LFs and adverse health outcomes? And if so, how?

An important linguistic caveat: 'lifestyle' can imply choices made freely by individuals, leading to potential stigma. However, resource scarcity and the wider socioeconomic environment experienced by those in less advantaged SES groups clearly influences choices, for example, by making healthier choices less likely[28,29]. Moreover, lifestyle choices in the context of poverty or material deprivation may represent 'optimal' choices given wider socioeconomic influences that shape decision making and abstract future planning[30,31]. Nevertheless, the word lifestyle

remains recognised in the context of modifiable behaviours and is therefore used here.

Methods

Search strategy and study selection

This review followed a protocol and was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[32–34]. The protocol is registered with a database of prospectively registered systematic reviews (PROSPERO CRD42020172588; 25 June 2020)[35,36].

Search strategies were developed with a specialist university librarian and adapted for three databases: PubMed (RRID: SCR_004846), EMBASE (RRID:SCR_001650), and EBSCO CINAHL (RRID:SCR_022707) (S1-3 Tables, which can be found as *Extended data*)[37]. The search strategy of a previous systematic review of combinations of LFs and type 2 diabetes served as a template and was adapted to include SES related terms[38]. As per that previous review, this current review focusses on combinations of LFs, and therefore search terms relating to LFs included general terms like 'lifestyle' or 'health behaviour' rather than terms for individual LFs like 'smoking' or 'alcohol'. Search terms also included terms for combinations of LFs (*e.g.*, 'combined', 'multiple', 'score'). Searches from inception (PubMed-1966; EMBASE-1947; CINAHL-1984) to 17th December 2021 were supplemented by searches of references, forward citations, and grey literature[36].

Eligibility criteria and screening

Inclusion criteria were developed using an adapted PICOS (population, intervention, comparator, outcome, study design) framework, with 'I' (intervention) replaced with 'E' (exposure)[39]. Inclusion criteria:

1) Population: any general adult population (age ≥18 years). Studies of participants with an index condition were excluded.

2) Exposure - examination of two main exposures:

    i. combination of ≥3 LFs: studies that also included metabolic/intermediate factors (*e.g.*, blood pressure/body mass index (BMI)) as part of their combination of LFs were included so long as the combination also included ≥3 'behavioural' LFs (*e.g.*, smoking/PA/diet).

    ii. SES: any SES measure (e.g., income/education/poverty-index).

3) Comparator: data for the influence of SES on associations between combinations of unhealthy LFs and adverse health.

4) Outcomes: at least one from: all-cause mortality, incidence and mortality from CVD or cancer.

5) Study design: prospective observational cohort. All types of analysis were included, and no study was excluded based on analysis method.

Exclusion criteria: not in English; abstracts/conference presentations only; ineligible design (*e.g.*, review/case-control/cross-sectional/qualitative). Studies were uploaded to 'DistillerSR' software (Version 2.38. DistillerSR Inc.; 2022. Accessed December 2021-February 2022; alternative software, Rayyan) and duplicates removed. Two reviewers (PP and HF/CO'D) screened titles and abstracts independently. Conflicts were resolved by discussion or included for full-text screening. Two reviewers (PP and HF) screened full-texts independently; conflicts resolved by discussion with a third reviewer (CO'D).

Data extraction

Two reviewers (HF and PP/CO'D) extracted data independently using a piloted proforma (S4 Table, which can be found as *Extended data*)[37]. After peer review, the proforma was adapted to include the distribution of type and number of unhealthy LFs among participants[36]. Quality was measured using the Newcastle-Ottawa Scale for cohort studies (NOS)[40]. The NOS was adapted to include assessments of confounder adjustment, sensitivity analysis, and missing data methodology (S5 Table, which can be found as *Extended data*)[36,37]. To compare study results, the following data from SES stratified analyses for each outcome was used to form our 'main comparator': 1) risk estimates for participants with the unhealthiest LF combination (using healthiest LF combination as reference) in the most advantaged SES group (*e.g.*, highest education, highest ranking occupation) were compared with 2) equivalent estimates (unhealthiest *versus* reference healthiest LF combination) in the least advantaged SES group (*e.g.*, lowest education, lowest ranking occupation). Studies frequently used more than two categories/quantiles of LF combinations, however only the estimates for the healthiest and unhealthiest categories were extracted. For example, for a study with a lifestyle score based on eight LFs, which study authors classified into five categories (scores 0–3, 4, 5, 6, and 7–8), the estimates for scores 0–3 and 7–8 were extracted. Estimates from SES stratified analyses were used for the main comparator because some studies did not report analyses examining combined influence of LF and SES using a single reference group (*i.e.*, analyses comparing all groups to the group with the healthiest combination of LFs and in the most advantaged SES group). However, results for these analyses were also extracted as they provide information on the combined influence of SES and lifestyle. To make direct comparisons, estimates from studies where the unhealthiest group was the reference were transformed to make the 'healthiest' group the reference. This transformation was achieved by dividing: 1) all hazard ratios (HRs) by the HR of the healthiest category (the healthiest category HR then becomes 1.00), 2) all lower confidence intervals (CIs) by the lower CI of the healthiest category, and 3) all upper CIs by the upper CI of the healthiest category. This then requires swapping the upper and lower CIs because transformed lower CIs become upper CIs.

Meta-analysis was not appropriate due to the heterogeneity of included studies. Instead, results were reported and synthesised according to Synthesis Without Meta-analysis (SWiM)

guidelines[41]. In accordance with transparent reporting of the synthesis methodology, this review adhered to the following approach - study results were grouped by outcome and compared by: 1) main models evaluating influence of SES; 2) model adjustment; 3) additional models, including sensitivity analyses; 4) tests for interactions; and 5) results for our main comparator.

Results

Results of the searches and screening are shown in a PRISMA flowchart (Figure 1).

Study populations

Six studies of five cohorts were included in this review (Table 1)[19,42–46]. Two studies analysed the same USA-based cohort, The Southern Community Cohort Study (SCCS), but each study examined different LFs and SES exposures and therefore both were included[42,44]. Similarly, two studies analysed UKB and examined different exposure variables and outcomes[19,46]. The remaining cohorts analysed were The Japan Collaborative Cohort Study (JCCS)[43], the National Health Interview Survey (NHIS)[45], and US National Health and Nutrition Examination Survey (NHANES)[46]. SCCS was designed to investigate ethnic inequalities in healthcare and 86% of participants were recruited from community health centres; JCCS, UKB, NHIS and NHANES are general population cohorts with NHIS and NHANES designed to be nationally representative[47,48]. Participants per study ranged from 42,467–399,537; mean age ranged from 46.5–56.8 years; and the proportion of women from 54.6–59.3%. Ethnic composition of populations analysed varied: SCCS cohort was 67% African American[42,44]; JCCS ethnicity was not reported, but likely predominantly Japanese[43];
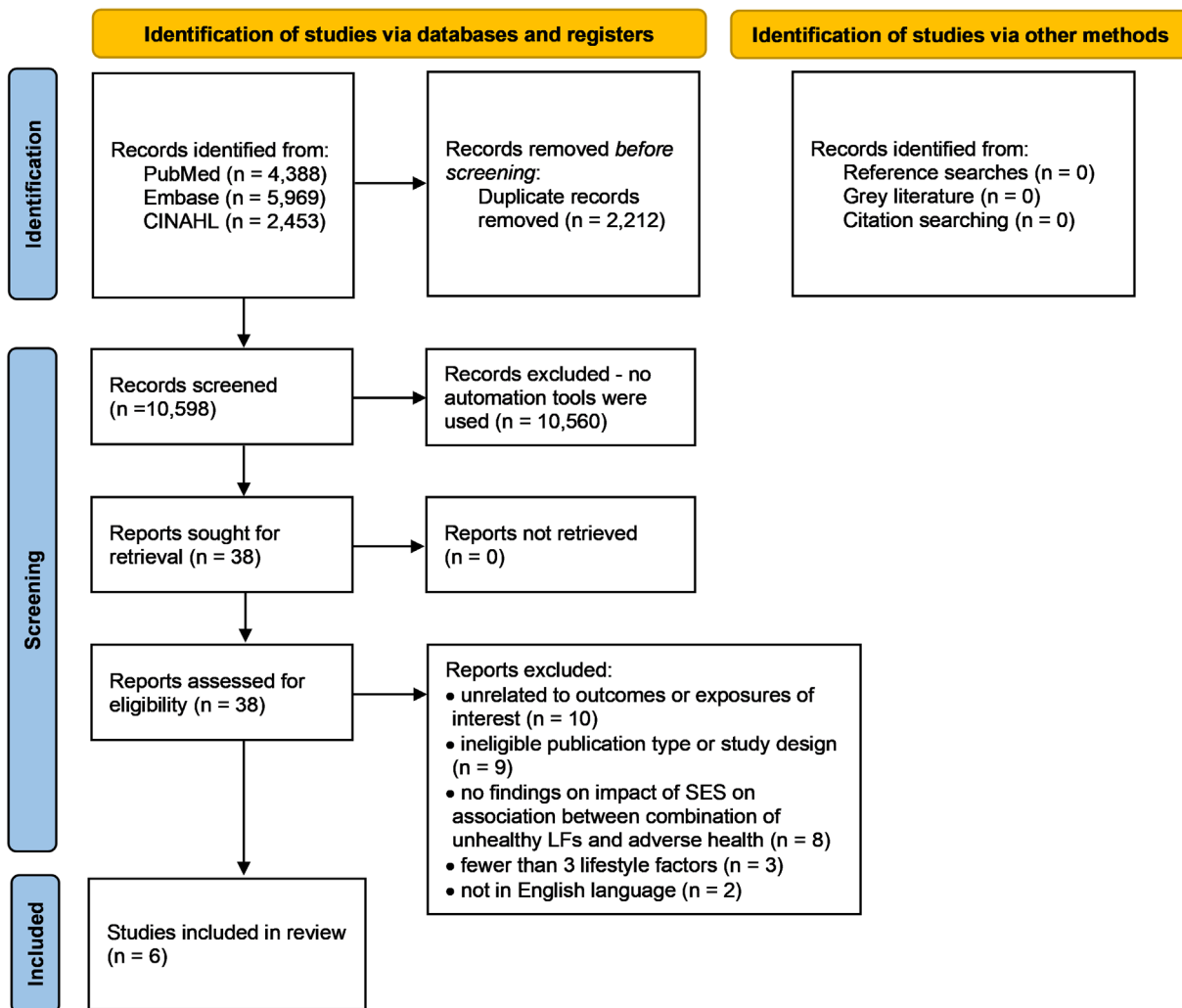
Figure 1. PRISMA flow chart of searches and screening results. CINAHL, Cumulative Index to Nursing and Allied Health Literature; SES, socioeconomic status; LFs, lifestyle factors.

Table 1. Characteristics of included studies.

Author, year	Cohort Country Type N	Age (years) Women (%) Ethnicity	Follow up length	Lifestyle factors and definitions of unhealthy (source or justification for unhealthy definition) Categories for analysis*	SES measure Categories for analysis	Outcome
Andersen et al., 2016[42]	Southern Community Cohort Study USA Prospective cohort designed to assess ethnic disparities in health outcomes, 86% recruited from community health centres 79,101 participants	Median age 51 (IQR 13) 59.3% women 67% African American	Max. 9 years (average not reported)	Self-reported at baseline Based on guidelines - i) current or former smoking (WHO) ii) alcohol intake >1 drink/d for women; >2 drinks/d for men (2010 Dietary Guidelines for Americans) iii) PA <150 min/wk moderate or <75 min/wk vigorous aerobic, or equivalent combination (2008 PA Guidelines for Americans) iv) sedentary time within 3 longest quartiles i.e., >5.75 h/d (Avoid inactivity and limit sedentary behaviours; American Cancer Society) v) diet quality (HEI) in 3 lowest quartiles i.e., <66.7 (USDA's Center for Nutrition Policy and Promotion and previous publication) Five categories according to the number of lifestyle factor guidelines met (0, 1, 2, 3, ≥4).	Income self-reported at baseline Dichotomised as </≥ $15,000 p.a.	i) All-cause mortality via linkage to national registry
Eguchi et al., 2017[43]	The Japan Collaborative Cohort Study Japan Prospective cohort of general population 42,647 participants	Mean age 56.8 (SD not reported) 56.8% women Likely to be mainly Japanese ethnicity	Median 19.3 years (IQR 11.6–20.8)	Self-reported at baseline i) current smoking ii) alcohol intake > 2 'gou'/d (>46 g ethanol/d) iii) PA: <0.5 h/d or <5 h/wk walking and/or in sports iv) sleep duration: <5.5 or >7.4 h/d v) BMI: <21 or >25 vi) fruit intake: <1x/d vii) fish intake: <1x/d viii) milk intake: <almost daily; Five categories: according to healthy lifestyle score with one point for each lifestyle factor threshold met (0–3, 4, 5, 6, 7–8)	Education level as age at last formal education self-reported at baseline Dichotomised as </≥ 16 years old	i) All-cause mortality ii) CVD mortality iii) CHD mortality iv) Stroke mortality v) Cancer mortality All via death certificate review

Author, year	Cohort Country Type N	Age (years) Women (%) Ethnicity	Follow up length	Lifestyle factors and definitions of unhealthy (source or justification for unhealthy definition) Categories for analysis*	SES measure Categories for analysis	Outcome
Andersen et al., 2018[44]	Southern Community Cohort Study USA Prospective cohort designed to assess ethnic disparities in health outcomes, 86% recruited from community health centres 77,896 participants	Median age 51 (IQR 13) 57.1% women 66.1% African American	Median 8 years (IQR not reported)	Self-reported at baseline Based on guidelines - i) alcohol intake >1 drink/d for women, >2 drinks/d for men (2010 Dietary Guidelines for Americans) ii) PA <150 min/wk moderate or <75 min/wk vigorous aerobic, or equivalent combination (2008 PA Guidelines for Americans) iii) sedentary time within 3 longest quartiles i.e., >6.5 h/d (Avoid inactivity and limit sedentary behaviours; American Cancer Society) iv) diet quality (HEI) in 3 lowest quartiles i.e., <65.5 (USDA's Center for Nutrition Policy and Promotion) Four categories: according to number of guidelines met (0, 1, 2, 3–4)	Neighborhood deprivation index (NDI): 2000 U.S. Census data linked to participant's residential address incorporating education, employment, housing, occupation, and poverty Quartiles	i) All-cause mortality via linkage to national registry
Foster et al., 2018[19]	UKB UK Prospective cohort of general population 328,594	Mean age 55.6 (SD 8.1) 54.6% women 95% White	Mean 4.9 years (SD 0.83, range 3.3–7.9) for all-cause and CVD mortality, 4.1 years (0.81 SD; range 2.4–7.0) for CVD incidence	Self-reported at baseline; Based on UK guidelines where available: i) current smoking ii) alcohol intake daily or almost daily iii) PA <150 min/wk moderate or <75 min/wk vigorous iv) TV viewing time ≥4 h/d v) sleep duration <7 or >9 h/d vi) fruits and vegetables <400g/d vii) oily fish <1 portion/wk viii) red meat >3 portions/wk ix) processed meat >1 portion/wk Three categories: according to lifestyle risk score with one point for each unhealthy definition met (0–2, 3–5, 6–9)	Townsend deprivation index: national census data incorporating car ownership, household overcrowding, owner occupation, and unemployment aggregated for and linked to participant postcode of residence Quintiles Secondary SES measures for sensitivity analyses: i) Household income (£p.a.) self-reported at recruitment Five categories: >100,000; 52,000-100,000; 30,000-51,999; 18,000-29,999; <18,000 ii) Educational attainment self-reported at recruitment Five categories: College/University degree; A levels or equivalent; O levels or equivalent; CSEs or equivalent; none of the above	i) All-cause mortality ii) CVD mortality iii) CVD incidence All via linkage to national registries

Author, year	Cohort Country Type N	Age (years) Women (%) Ethnicity	Follow up length	Lifestyle factors and definitions of unhealthy (source or justification for unhealthy definition) Categories for analysis*	SES measure Categories for analysis	Outcome
Choi et al., 2022[45]	National Health Interview Survey USA Prospective cohort of general population aged ≥30 years 189,087	Age ≥30 (average not reported) Proportion female not reported Ethnicity not reported	Mean 12.7 years	Self-reported at baseline: i) current smoker and ex-smokers who quit <20 years ago ii) weekly alcohol intake >14 drinks for men, >7 drinks for women (2016 NIAAA guidelines), or >5 drinks/d at least monthly iii) PA <150 min/wk moderate or <75 min/wk vigorous and/or strengthening activities <2 d/wk (2008 Physical Activity Guidelines for Adults) iv) BMI <18.5 or ≥35 Five categories according to the number of lifestyle factors: 0, 1, 2, 3, or 4	Household income as a ratio of family income to federal poverty level Dichotomised as < or ≥200% of federal poverty level	i) All-cause mortality via linkage to national registry

Author, year	Cohort Country Type N	Age (years) Women (%) Ethnicity	Follow up length	Lifestyle factors and definitions of unhealthy (source or justification for unhealthy definition) Categories for analysis*	SES measure Categories for analysis	Outcome
Zhang et al., 2021[46]	US National Health and Nutrition Examination Survey (NHANES) USA Prospective cohort of general population 44,462 & UKB UK Prospective cohort of general population 399,537	NHANES: Mean age 46.5 51.3% women 73.6% White UKB: Mean age 56.1 52.5% women 95.6% White	NHANES: Mean 11.2 years UKB: Mean 11.0 years for all-cause mortality, 8.8 years for CVD incidence	Self-reported at baseline; i) smoked >100 cigarettes in lifetime ii) daily alcohol intake >1 drink for women, 2 drinks for men (National guidelines for USA and UK) iii) leisure time physical activity at level of lower two thirds of study participants iv) diet quality (HEI) at level of lower 2/5th of participants for US NHANES (2015-20 Dietary Guidelines for Americans & 1992 food guide from US Department of Agriculture); meeting 5/10 diet recommendations for UKB (evidence-based recommendations) Three categories according to number of lifestyle factors (score): 0–1, 2, 3–4 Sensitivity analyses included: a weighted lifestyle score to account for differing magnitude of associations between each LF and outcomes; and a combination of LFs that included BMI outwith 18.5–24.9.	NHANES: i) family poverty to income ratio: low (≤1); middle (1-4); and high (≥4) ii) educational attainment: less than high school diploma; high school graduate or equivalent; and college or above iii) occupation (US socioeconomic index): upper (index ≥50); lower (index <50); and unemployment iv) health insurance: private; public only; none Variables i)-iv) were self-reported at recruitment and combined via latent class analysis to generate 3 latent classes/categories of low, medium, and high SES UKB: i) income (£p.a.): >100,000; 52,000-100,000; 30,000-51,999; 18,000-29,999; <18,000 ii) educational attainment: College/University degree; A levels or equivalent; O levels or equivalent; CSEs or equivalent; NVQ, HND, HNC, or equivalent; other professional qualifications; none of the above iii) employment: employed (including self-employed, retired, unpaid/voluntary work, full/part time students); unemployed Variables i)-iii) were self-reported at recruitment and combined via latent class analysis to generate 3 latent classes/categories of low, medium, and high SES Secondary SES measures in sensitivity analyses included: each SES factor individually, Townsend index (UKB only)	i) All-cause mortality ii) CVD mortality iii) CVD incidence iv) heart disease mortality, NHANES only v) coronary heart disease mortality, UKB only vi) stroke mortality, UKB only vii) myocardial infarction incidence, UKB only vii) stroke incidence, UKB only All via linkage to national registries

N, number of participants included in analysis; *Categories for analysis shows the number of categories used by study authors to analyse the associations between the combination of lifestyle factors and health outcome (e.g., a study of five lifestyle factors, with possible scores of 0 to 5, could be analysed using the score categories of 0, 1, 2, 3, and ≥4; i.e, with scores 4 and 5 grouped together); Outcomes, adverse health outcome used to assess interaction between lifestyle and SES (some studies reported additional health outcomes but these were not used to assess interaction); SES, socioeconomic status; IQR, Interquartile range; PA, physical activity; BMI, body mass index (kg/m²); WHO, World Health Organisation; d, day; wk, week; h, hours; min, minutes; $, US dollars; pa per annum; £, British pounds; TV, television; HEI, Healthy Eating Index, which measures adherence to the Dietary Guidelines for Americans. HEI is based on 12 dietary components: total fruits; whole fruits; total vegetables; greens and beans; whole and refined grains; dairy; total protein foods; seafood and plant proteins; fatty acids; sodium; and calories from solid fats, alcohol, and added sugars (range 0–100; higher values indicate healthier diet); CVD, cardiovascular disease; CHD, coronary heart disease; UKB, UK Biobank; NIAAA, National Institute on Alcohol Abuse and Alcoholism; A level, General Certificate of Education Advanced Level; O-level, General Certificate of Education Ordinary Level; CSE, Certificate of Secondary Education; NVQ, National Vocational Qualification; HND/HNC, Higher National Diploma/Certificate.

UKB was 95% White British[19,46]; NHIS ethnicity was not reported[45]; NHANES was 73.6% White[46]. Average follow-up time ranged from 4.3–19.3 years. In assessing the influence of SES on associations between combinations of unhealthy LFs and health outcomes, all studies examined all-cause mortality. In addition, three studies examined CVD mortality[19,43,46]; two examined CVD incidence[19,46]; one examined heart disease mortality and incidence of myocardial infarction and stroke[46]; two examined mortality from coronary heart disease (CHD), stroke, and cancer[43,46]; and one examined mortality from 'non-CVD and non-cancer' causes[43]. The non-CVD and non-cancer results are not reported here as they are outside the scope of this review.

Combinations of unhealthy lifestyle factors

The number of LFs comprising the combination in each study ranged from four to nine and included: smoking, alcohol, PA, sedentary time, television (TV) viewing time, various individual dietary factors, a dietary index, and sleep duration (Table 1). Two studies included BMI in main analyses and one study included BMI in a sensitivity analysis[43,45,46]. Alcohol and PA were included in all studies and dietary factors were missing from only one study[45]. Smoking was included in five studies but excluded from relevant analyses in the remaining study[44]. All LF data was collected *via* baseline questionnaire or interview.

Definition or classification of unhealthy for individual lifestyle factors

In each study individual LFs were dichotomised as healthy/unhealthy with one point per factor summed to create an unweighted score. Two studies also created weighted scores using the strength of association between individual LFs and outcomes[42,46]. However, only one of these examined the effect of SES on a weighted score for which results were extracted here[46]. Three studies summed healthy LFs to create 'healthy' scores[42,43,46], while the remaining three studies created 'unhealthy' scores (results were harmonised to show increasing risk with increasingly unhealthy lifestyle)[19,44,45].

The definition of unhealthy for each individual LF included in the LF combinations varied (Table 1). Unhealthy smoking status was defined as current smoking[19,43], current/any former smoking[42], current/quitting <20 years ago[45], and smoking more than 100 cigarettes in a lifetime[46]. Unhealthy alcohol intake was defined as: >1 drink/day for women or >2 drinks/day for men[42,44–46], >5 drinks/day monthly[45], >46 g alcohol/day[43], and 'daily/almost daily intake', respectively[19]. Unhealthy PA levels were defined as <150 minutes/week moderate or <75 minutes/week vigorous PA in four studies[19,42,44,45], as strengthening activities on <2 days/week[45], as not achieving either ≥0.5 hours/day walking or ≥5 hours/week walking/playing sports[43], and as having leisure time PA levels in the lower two thirds of study participants[46]. Unhealthy sedentary time, considered in two studies, was defined as the three quartiles with longest sedentary time (*i.e.*, >5.75 and >6.5 hours/day), respectively[42,44]. Unhealthy TV viewing time, examined in one study, was defined as ≥4 hours/day[19]. Unhealthy sleep duration, examined in two studies, was classified as <5.5/>7.4 hours/day[43] and <7/>9 hours/day[19], respectively.

Dietary factors examined varied considerably. Three studies of two USA-based cohorts used a national dietary index (comprising fruit, vegetables, grains, proteins, fatty acids, sodium, and calories from fats, alcohol, and added sugars), defining unhealthy as either belonging to the three lowest quartiles[42,44] or two lowest quintiles[46]. The Japanese cohort study included three dietary components, defining unhealthy as: fruit <once/day; fish <once/day; and milk <almost daily[43]. One of the studies examining the UK-based UKB included four components, classifying unhealthy as: fruit and vegetables <400 g/day; oily fish <1 portion/week; red-meat >3 portion/week; and processed-meat >1 portion/week[19]. Whereas the other study of UKB classified unhealthy as meeting at least five of 10 recommendations[46].

Justification for the classification of 'unhealthy' varied. One study cited WHO guidelines for the classification of unhealthy smoking[42]. Four studies of USA-cohorts used US national guidelines to define unhealthy alcohol intake and diet[42,44–46]. And of those, two also used US guidelines to define PA and sedentary time[42,44]. One study adapted a previous lifestyle score[49], using UK guidelines or standards from the original score[19]. One study did not report the basis for their definitions of unhealthy for eight LFs including a BMI outwith 21–25[43]. The other study that examined BMI in their main analyses based the definition of unhealthy (<18.5 or ≥35) on prior analysis of the data[45]. Unhealthy BMI (outwith 18.5–24.9) was based on previous research in the third study that included BMI in a sensitivity analysis[46].

Most studies had approximately normal distributions of the total number of unhealthy LFs among participants (S6 Table, which can be found as *Extended data*)[37]. One study of UKB, with nine LFs, had relatively few participants with six to nine unhealthy LFs[19]. The other study of UKB, with four LFs, had more participants with unhealthy LFs[46]. The proportion of study participants with specific unhealthy LFs also varied. For example, the proportion of study participants with unhealthy smoking status ranged from 9.6% to 64%; some of this discrepancy is likely due to differences in the definition of unhealthy (*i.e.*, current *versus* current/former smoking).

Socioeconomic status

SES measures varied by study (Table 1). For main analyses, two studies used area-based deprivation indices: Neighborhood deprivation index (NDI) and Townsend deprivation index (TDI)[19,44]. Data for both indices were obtained *via* national censuses from or near baseline. NDI comprises five 'domains': education, employment, housing, occupation, and poverty[44]. Whereas TDI comprises data on car ownership, household overcrowding, owner occupation, and unemployment[19]. Two studies used self-reported individual-level measures of income at recruitment[42,45] and one of these operationalised income as a ratio of family income to the USA federal poverty level[45]. One study used age at last formal education obtained *via* baseline self-report for the main analyses[43]. Finally, one study of two cohorts used latent class analysis to generate an overall SES variable from four SES measures (income, occupation, education, and health insurance) in analysis of one cohort and three SES measures (income, education, and employment

status) in analysis of the second cohort[46]. In sensitivity analyses, two studies examined alternative SES measures[19]. One study swapped area-based TDI for annual household income and, separately, individual-level educational attainment[19]. The second study performed multiple sensitivity analyses of alternative SES measures by replacing a latent class SES variable with 1) each SES measure (income, occupation, education, health insurance, and employment status) used to generate the latent class; 2) an SES score based on each single SES measure; 3) and TDI[46].

Categories for analysis

Categorisation of the two main exposures (combination of LFs and SES) used in analyses varied (Table 1). Categories for combinations of LFs ranged from three to five and were not always related to the number of LFs included and often influenced by the number of participants with unhealthy LFs. For example, one study examined nine LFs and split participants into three categories: 'healthy' (score 0–2), 'moderately healthy' (score 3–5), and 'unhealthy' (score 6–9)[19]; whereas another study included eight LFs and split participants into five categories[43].

For SES measures, the following categories were used: income dichotomised as $</\geq$ \$15,000 US dollars per annum[42]; age at last formal education dichotomised as $</\geq$ 16 years[43]; quartiles of NDI[44]; quintiles of TDI[44]; ratio of family income to federal poverty level dichotomised as $<$ or $\geq$200% of federal poverty level[45]; three latent classes of low, medium and high SES[46].

Analysis procedures

Each study conducted descriptive analyses, examining independent associations between combinations of LFs and outcomes and between SES and outcomes. All studies used Cox-proportional hazard models in their main analyses to estimate HRs and 95% confidence intervals (CIs) for outcomes for each LF combination category, stratified by SES (Table 1). Three studies additionally stratified these analyses; one by ethnicity and sex together (African American/White and female/male)[42], three by sex alone[43,44,46], one by ethnicity (White/Non-white)[46], and one by age ($\geq$60/$<$60 years)[46]. One study that stratified by sex alone, also performed a separate analysis on the total population (not stratified by sex)[43]. Two studies did not additionally stratify by sociodemographics[19,45]. The number of confounder variables chosen by studies ranged from five to 14 (Table 2). All studies adjusted for either age, age plus age squared, or used age as the time-varying covariate.

Studies varied in their additional analyses to investigate the influence of SES and included: single reference group analyses to investigate the joint associations of combinations of unhealthy LFs, SES, and outcomes[19,43,44,46]; Kaplan-Meier survival curves for combinations of unhealthy LFs stratified by SES[43]; tests for multiplicative interactions between combinations of unhealthy LFs and SES[19,42–46]; and tests for additive interactions (Table 2)[19,46].

Study quality

Results for study quality as measured by the adapted NOS ranged from 5–9 (max. 9; S7 Table, which can be found as *Extended data*)[37]. Only two studies examined more than one SES measure[19,46] and only three studies attempted to reduce the chance of reverse causality by demonstrating participants were free from disease at the start of the study[19,43,46].

The influence of socioeconomic status on lifestyle-associated health

Using the main comparator as an assessment of the influence of SES on the association between combinations of unhealthy LFs and outcomes, results across studies were mixed and varied by outcome (Figure 2 and Figure 3). A synthesis of results, including the main comparator, is structured by outcome below.

All-cause mortality. Estimates from 13 main analyses were available for the main comparator for all-cause mortality as some analyses were additionally stratified by sex or by both sex and ethnicity (Figure 2 and Table S8A Table, which can be found as *Extended data*). All studies observed that, compared with healthy LFs, combinations of unhealthy LFs were generally associated with higher all-cause mortality. However, the difference between the higher all-cause mortality associated with a combination of unhealthy *versus* that associated with healthy LFs was greater in the most advantaged SES group in seven analyses, but greater in the least advantaged group in the remaining six analyses (Figure 2 and Table S8A Table, which can be found as *Extended data*). However, there was considerable overlap of CIs from most and least advantaged SES groups and the difference between some estimates from most and least advantaged groups were similar. HRs (95%CIs) from the most advantaged groups ranged from 0.68 (0.32–1.45) to 4.17 (2.27–7.69); equivalent estimates from the least advantaged groups ranged from 1.30 (1.13–1.50) to 4.00 (2.22–7.14).

Two analyses were additionally stratified by sex alone and, for women, the difference in all-cause mortality associated with unhealthy *versus* healthy LFs was greater in the least advantaged group in one study[44] but greater in the most advantaged group in the other study[43] (and *vice versa* for men). The study that additionally stratified by both sex and ethnicity observed the difference in all-cause mortality associated with combinations of unhealthy *versus* healthy LFs was consistent for sex across two ethnic groups: greater in the least advantaged SES group for women of both African American and White ethnicity, but greater in the most advantaged SES group for men of both ethnicities[42]. One study stratified by sex for sensitivity analysis and observed similar all-cause mortality associated with combinations of unhealthy *versus* healthy LFs for both sexes in the most *versus* least advantaged groups[46]. However, the same study examined two cohorts and found that although the difference in all-cause mortality associated with combinations of unhealthy *versus* healthy LFs was small for men and women, it was greater in the most advantaged group in one cohort (NHANES) and in the least advantaged group

Table 2. Methods/results for influence of SES on association between combinations of unhealthy LFs and outcomes.
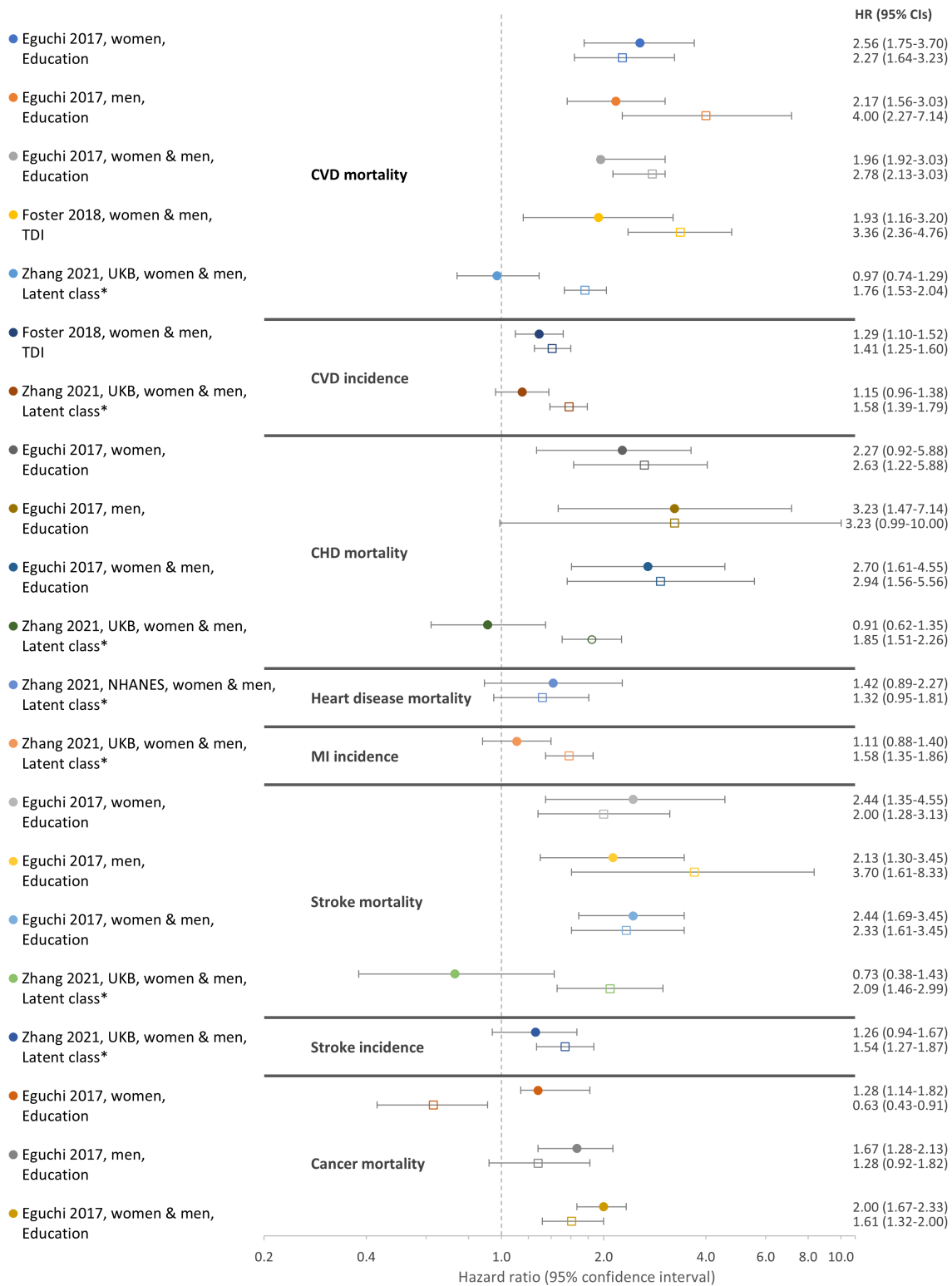
Study	Methods	Covariates (n)	Interaction tests between combinations of unhealthy LFs and SES	Main interaction results ($P_{interaction}$ or RERI)	Result summary
Andersen 2016[42]	1) Cox-proportional hazard models for all-cause mortality for combination of unhealthy LF categories 2) Models stratified by low/high income in sub-group analysis	Enrolment source, education, marital status, neighbourhood deprivation, and BMI (5)	Likelihood ratio tests, comparing main effects models with and without cross-product terms	All-cause mortality: 0.002 (African American men); 0.89 (African American women); 0.04 (White men); 0.49 (White women)	Significant multiplicative interaction for African American and White men only; highest HRs for combination of unhealthy LFs and high income Only stratified (sex, ethnicity) results available
Eguchi 2017[43]	1) Cox-proportional hazard models for outcomes for combinations of unhealthy LF categories, stratified by low/high education (analyses for total population and separate analyses further stratified by sex) 2) Cox-proportional hazard models for combinations of unhealthy LF categories and education level using single reference group (all-cause and CVD mortality only) 3) Kaplan-Meier survival curves for combinations of unhealthy LF categories, stratified by low/high education (all-cause and CVD mortality only) 4) Sensitivity analysis examining two modified LF combinations	Age, sex, history of hypertension, history of diabetes, perceived mental stress and regular employment (6)	Cross-product of dichotomous education level and healthy lifestyle score (continuous) in models for total CVD and all-cause mortality outcomes only	All-cause mortality: 0.11 CVD mortality: 0.23 (both for total population only)	1) No evidence of multiplicative interaction, with similar HRs for combinations of unhealthy LFs and both high and low SES 2) Single reference group analysis provides evidence for additive interaction for all-cause and CVD mortality: higher HRs in least healthy combination of LFs and lowest education groups 3) Survival curves suggest additive interaction: steeper mortality curve (highest mortality) for combination of unhealthy LFs in low education group 4) Sensitivity analysis: i) extended definition of healthy sleep and ii) dichotomous diet score (five components) in addition to extended sleep definition - consistent with findings from main analysis
Andersen 2018[44]	1) Cox-proportional hazard models for all-cause mortality for combinations of unhealthy LF categories, stratified by NDI quartiles 2) Cox-proportional hazard models for combinations of unhealthy LF categories, stratified by NDI quartiles using single reference (also stratified by sex)	Enrolment source, ethnicity, education, income, marital status, and insurance status (6)	Likelihood ratio tests, comparing main effects models with and without cross-product terms	All-cause mortality: 0.28 (men); 0.99 (women)	1) No evidence of multiplicative interaction with similar HRs for combinations of unhealthy LFs in both high and low SES 2) Single reference group analysis provides evidence for additive interaction in men and women for all-cause mortality: highest HRs in the least healthy combination of LFs and lowest SES (highest NDI) group
Foster 2018[19]	1) Cox-proportional hazard models for outcomes for combinations of unhealthy LF categories, stratified by SES quintiles (TDI, income, and education examined separately) 2) Cox-proportional hazard models for joint associations of combinations of unhealthy LF categories and SES measures (single reference group)	Age, sex, ethnicity, month of assessment, hypertension, systolic blood pressure, medication for hypercholesterolaemia or hypertension, and BMI (8)	1) Interaction term between combinations of unhealthy LFs and SES variables in models 2) Interaction sensitivity analyses (deprivation index): a) additional models with interaction term and i) dichotomous and ii) continuous combination of unhealthy LF variable b) Estimation of three measures of 'biological interaction': RERI, AP, and synergy index	Deprivation index All-cause and CVD-mortality: <0.0001 CVD incidence: 0.11 Income All-cause mortality: 0.001 CVD mortality: <0.0001 CVD incidence: 0.009 Education All-cause mortality: 0.002 CVD mortality: 0.047 CVD incidence: 0.051 (all for total population only)	1) Significant multiplicative interaction between combination of unhealthy LFs and deprivation/ education for all-cause and CVD mortality but not for CVD incidence. Significant multiplicative interaction between combinations of unhealthy LFs and income for all outcomes 2) Single reference analysis showed highest HRs for all-cause and CVD mortality in the least healthy combination of LFs and lowest SES groups 3) Interaction sensitivity results consistent with main findings with significant interaction across three measures of additive interaction

Study	Methods	Covariates (n)	Interaction tests between combinations of unhealthy LFs and SES	Main interaction results ($P_{interaction}$ or RERI)	Result summary
Choi 2022[45]	1) Cox-proportional hazard models for all-cause mortality for number of unhealthy LFs, stratified by high/low income group	Age, age squared, sex, education, race/ethnicity, acculturation, income assistance, health insurance, and marital status (9)	Unclear, but likely an interaction term between combinations of unhealthy LFs and income in models	<u>Primary outcomes</u> All-cause mortality: <0.05	Significant multiplicative interaction between combinations of unhealthy LFs and income for all-cause mortality. Mortality risk associated with each additional unhealthy LF was higher in higher income group.
Zhang 2021[46]	1) Cox-proportional hazard models for outcomes for combinations of unhealthy LF categories, stratified by SES category 2) Cox-proportional hazard models for outcomes joint associations of combinations of unhealthy LF categories and SES measures (single reference group) 3) Sensitivity analyses for models stratified by SES category by examining subgroups: male/female, white/non-white ethnicity, age </≥60 years 4) Sensitivity analyses of joint associations substituting individual-level latent class SES for: a) Each SES component used to generate latent class, separately b) Townsend index (area-level) with adjustment for latent class SES (UKB only) and *vice versa*	Age, sex, marital status (NHANES only), assessment centre (UKB only), self-reported race/ethnicity, acculturation score, BMI, hypertension, diabetes, CVD, cancer, lung disease (UKB only). (10-14)	1) Interaction term between combinations of unhealthy LFs and SES variables in models 2) Estimation of RERI	All-cause mortality: 0.85; RERI =0 (NHANES), <0.001; RERI >0 (UKB) CVD mortality: 0.002; RERI >0 (UKB) CVD incidence: 0.016; RERI >0 (UKB) <u>Secondary outcomes</u> Heart disease mortality: 0.29; RERI =0 (NHANES) Coronary heart disease mortality: 0.008; RERI >0 (UKB) Stroke mortality: 0.002; RERI >0 (UKB) Myocardial infarction incidence: 0.050; RERI >0 (UKB) Stroke incidence: 0.032; RERI >0 (UKB)	1) NHANES: no significant multiplicative (product term for interaction) or additive interaction (RERI) between combination of unhealthy LFs and SES for all-cause or heart disease mortality UKB: both significant multiplicative and additive interactions between combination of unhealthy LFs and SES for all-cause mortality, CVD mortality, CVD incidence, coronary heart disease mortality, and stroke mortality but not for myocardial infarction incidence or stroke incidence 2) Results for product term for interaction and RERI similar across sensitivity analyses (individual-level SES, individual/area-level SES mutual adjustment) 3) In both cohorts, joint association analysis showed highest HRs in the least healthy combination of LFs and lowest SES groups for all outcomes and across all sensitivity analyses 4) Subgroup analyses showed significant multiplicative and additive interactions between combination of unhealthy LFs and SES for most subgroups (sex/ethnicity/age) and primary outcomes in UKB but not in NHANES 5) Subgroup analyses of the joint associations of combination of unhealthy LFs and SES showed higher HRs in men *vs.* women and in younger *vs.* older adults for all-cause mortality in both cohorts, and in younger *vs.* older adults for CVD mortality in UKB

LFs, lifestyle factors; SES, socioeconomic status; $P_{interaction}$, p-value for interaction between combinations of unhealthy LFs and SES; RERI, relative excess risk due to interaction; HR, hazard ratio; NDI, Neighborhood deprivation index; TDI, Townsend deprivation index; BMI, body mass index; CVD, cardiovascular disease; 'Biological interaction', the degree of interaction between risk factors in terms of deviation from additivity in adverse health outcome rates[50]; AP, attributable proportion; UKB, UK Biobank; NHANES, US National Health and Nutrition Examination Survey.

HR (95% CIs)

Andersen 2016, African American women, Income, ≥/<$15,000/year — 2.08 (1.32-3.33) / 2.22 (1.67-3.03)

Andersen 2016, African American men, Income, ≥/<$15,000/year — 3.70 (2.22-6.25) / 2.00 (1.39-2.94)

Andersen 2016, White women, Income, ≥/<$15,000/year — 2.86 (1.28 -6.67) / 4.00 (2.22-7.14)

Andersen 2016, White men, Income, ≥/<$15,000/year — 4.17 (2.27-7.69) / 1.72 (1.00-3.03)

Eguchi 2017, women, Education (leaving age), ≥/<16 years — 1.82 (1.49-2.22) / 1.49 (1.25-1.79)

Eguchi 2017, men, Education (leaving age), ≥/<16 years — 1.82 (1.56-2.17) / 1.89 (1.52-2.38)

Eguchi 2017, women & men, Education (leaving age), ≥/<16 years — 1.79 (1.61-2.00) / 1.67 (1.47-1.89)

Andersen 2018, women, NDI, upper/lower quartiles — 0.68 (0.32-1.45) / 1.59 (1.32-1.91)

Andersen 2018, men, NDI, upper/lower quartiles — 1.43 (0.94-2.16) / 1.42 (1.23-1.65)

Foster 2018, women & men, TDI, upper/lower quintiles — 1.65 (1.25-2.19) / 2.47 (2.04-3.00)

Choi 2020, women & men, Income, high/low — 4.30 (CI not reported) / 3.45 (CI not reported)

Zhang 2021, NHANES, women & men, Latent class*, high/low categories — 1.76 (1.43-2.17) / 1.30 (1.13-1.50)

Zhang 2021, UKB, women & men, Latent class*, high/low categories — 1.17 (1.04-1.32) / 1.80 (1.69-1.93)

● Most advantaged
□ Least advantaged

Hazard ratio (95% confidence intervals)

Figure 2. Hazard ratios for the association between combinations of unhealthy LFs and all-cause mortality in the most and least advantaged SES groups by study and population. Comparison of HRs from SES stratified analyses for the associations between combinations of unhealthy LFs and all-cause mortality in the most and least advantaged SES groups (main comparator). Combinations of healthy LFs in the same SES strata (most/least advantaged) are the reference group. Legend indicates the study, population, SES measure, and definition for the most/least advantaged SES groups. LFs, lifestyle factors; SES, socioeconomic status; HR, hazard ratio; CI, confidence interval; NDI, Neighborhood Deprivation Index; TDI, Townsend Deprivation Index; NHANES, US National Health and Nutrition Examination Survey; UKB, UK Biobank; *Latent class analysis based on income, education, occupation/employment, and (for NHANES only) health insurance.

HR (95% CIs)

CVD mortality

Eguchi 2017, women, Education
2.56 (1.75-3.70)
2.27 (1.64-3.23)

Eguchi 2017, men, Education
2.17 (1.56-3.03)
4.00 (2.27-7.14)

Eguchi 2017, women & men, Education
1.96 (1.92-3.03)
2.78 (2.13-3.03)

Foster 2018, women & men, TDI
1.93 (1.16-3.20)
3.36 (2.36-4.76)

Zhang 2021, UKB, women & men, Latent class*
0.97 (0.74-1.29)
1.76 (1.53-2.04)

CVD incidence

Foster 2018, women & men, TDI
1.29 (1.10-1.52)
1.41 (1.25-1.60)

Zhang 2021, UKB, women & men, Latent class*
1.15 (0.96-1.38)
1.58 (1.39-1.79)

CHD mortality

Eguchi 2017, women, Education
2.27 (0.92-5.88)
2.63 (1.22-5.88)

Eguchi 2017, men, Education
3.23 (1.47-7.14)
3.23 (0.99-10.00)

Eguchi 2017, women & men, Education
2.70 (1.61-4.55)
2.94 (1.56-5.56)

Zhang 2021, UKB, women & men, Latent class*
0.91 (0.62-1.35)
1.85 (1.51-2.26)

Heart disease mortality

Zhang 2021, NHANES, women & men, Latent class*
1.42 (0.89-2.27)
1.32 (0.95-1.81)

MI incidence

Zhang 2021, UKB, women & men, Latent class*
1.11 (0.88-1.40)
1.58 (1.35-1.86)

Stroke mortality

Eguchi 2017, women, Education
2.44 (1.35-4.55)
2.00 (1.28-3.13)

Eguchi 2017, men, Education
2.13 (1.30-3.45)
3.70 (1.61-8.33)

Eguchi 2017, women & men, Education
2.44 (1.69-3.45)
2.33 (1.61-3.45)

Zhang 2021, UKB, women & men, Latent class*
0.73 (0.38-1.43)
2.09 (1.46-2.99)

Stroke incidence

Zhang 2021, UKB, women & men, Latent class*
1.26 (0.94-1.67)
1.54 (1.27-1.87)

Cancer mortality

Eguchi 2017, women, Education
1.28 (1.14-1.82)
0.63 (0.43-0.91)

Eguchi 2017, men, Education
1.67 (1.28-2.13)
1.28 (0.92-1.82)

Eguchi 2017, women & men, Education
2.00 (1.67-2.33)
1.61 (1.32-2.00)

0.2   0.4   1.0   2.0   4.0 6.0 8.0 10.0
Hazard ratio (95% confidence interval)

Figure 3. Hazard ratios for the association between combinations of unhealthy LFs and adverse health outcomes in the most and least advantaged SES groups by study and population. Comparison of HRs from SES stratified analyses for the associations between combinations of unhealthy LFs and adverse health outcomes in the most and least advantaged SES groups (main comparator). Combinations of healthy LFs in the same SES strata (most/least advantaged) are the reference group. Legend indicates the study, population, and SES measure. LFs, lifestyle factors; SES, socioeconomic status; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; NHANES, US National Health and Nutrition Examination Survey; UKB, UK Biobank.

in the other cohort (UKB)[46]. Sensitivity analysis results from one study of two cohorts that additionally stratified by ethnicity alone (White/Non-White) were mixed[46]. In the same study, sensitivity analysis stratified by age alone (≥60/<60 years old) suggested that all-cause mortality associated with combinations of unhealthy LFs was relatively higher for those <60 years old in the least advantaged groups in both cohorts[46]. Five main analyses from four cohorts examined the total population (not further stratified by sociodemographic variables) and the difference in all-cause mortality associated with unhealthy *versus* healthy LFs was greater in the most advantaged SES group in three cohorts (JCCS, NHIS, NHANES)[43,45,46] but greater in the least advantaged group in another cohort (UKB)[19,46]. Similarly mixed results were found with the sensitivity analyses (S8 Table, which can be found as *Extended data*)[37].

Results of tests for multiplicative interactions were also mixed (Table 2). A significant multiplicative interaction between the combination of LFs and SES was observed in four studies, but in opposing directions[19,42,45,46]. A significant multiplicative interaction was observed, with greater all-cause mortality associated with combinations of unhealthy LFs in the most advantaged group in the entire cohort of one study[45] but only in men in another study[42]. Whereas a significant multiplicative interaction was seen in two studies of UKB, where the difference in all-cause mortality associated with unhealthy *versus* healthy LFs was greater in the least advantaged group[19,46]. The multiplicative interaction observed in UKB was observed consistently across a set of interaction sensitivity analyses (Table 2)[19,46]. Two studies tested for and found significant additive interactions in the same cohort (UKB)[19,46] but one of these studies did not observe significant additive interactions in similar analysis of a second cohort (NHANES)[46]. Four studies of three cohorts examined combined associations of combinations of unhealthy LFs and less advantaged SES in eight analyses by comparing all groups to a single reference: the healthiest LF-most advantaged group[19,43,44,46]. In these analyses, HRs (95%CIs) for all-cause mortality for the least healthy-least advantaged group ranged from 1.43 (1.11–1.84) to 3.53 (3.01–4.14) (S9 Table, which can be found as *Extended data*)[37]. The highest all-cause mortality was observed in the least healthy-least advantaged groups in seven of eight of these analyses, suggesting an additive interaction between unhealthy LFs and less advantaged SES. For sensitivity, two studies examined additional measures of SES separately in single reference group analyses and consistently observed the highest all-cause mortality in the least healthy-least advantaged groups irrespective of SES measure[19,46]. Further evidence for an additive interaction came from the steeper Kaplan-Meier curves for an unhealthy combination of LFs in the least advantaged *versus* most advantaged group in one study[43].

CVD mortality. Three studies examined CVD mortality in two cohorts. Compared with healthy LFs, combinations of unhealthy LFs were consistently associated with higher CVD mortality[19,43,46]. In analyses stratified by SES alone, all three studies observed the difference in CVD mortality associated with unhealthy *versus* healthy LFs was greater in the least

advantaged SES group: HRs (95%CIs) in the least advantaged groups were 2.78 (2.13–3.03)[43], 3.36 (2.36–4.76)[19], and 1.76 (1.53–2.04)[46], respectively. Equivalent estimates in the most advantaged groups were 1.96 (1.92–3.03), 1.93 (1.16–3.20), and 0.97 (0.74–1.29) (Figure 3 and Table S8D Table, which can be found as *Extended data*). One of these studies also stratified analyses by sex and found the difference in CVD mortality associated with unhealthy *versus* healthy LFs was greater in the most advantaged group for men but in the least advantaged group for women[43]. However, the unhealthy *versus* healthy LFs CVD mortality for women was similar in the most and least advantaged groups. Similar results were found in sensitivity analyses (S8 Table, which can be found as *Extended data*)[37]. For LF-SES interactions for CVD mortality, one study provided evidence of an additive interaction through both single reference group analyses and steeper Kaplan-Meier survival curves[43]. In this study's single reference group analysis, the highest CVD mortality was associated with those in the least healthy-least advantaged group (S10 Table, which can be found as *Extended data*)[37,43]. However, the same study found no significant multiplicative interaction for CVD mortality (Table 2). By contrast, two other studies, both examining CVD mortality in UKB, reported a significant multiplicative interaction and in the single reference analysis, the least healthy-least advantaged group had markedly higher hazards than the least healthy-most advantaged group: 4.59 (3.33–6.32) *vs.* 2.01 (1.21–3.33)[19] and 2.65 (2.09–3.38) and 1.06 (0.80–1.39)[46], respectively (S10 Table, which can be found as *Extended data*)[37]. Both studies observed significant multiplicative interactions for CVD mortality consistently irrespective of SES measure and across interaction sensitivity analyses[19,46].

Other outcomes. Estimates for CVD incidence were provided by two studies of UKB and, in SES stratified analyses, compared with healthy LFs, combinations of unhealthy LFs were associated with higher CVD incidence[19,46]. The difference in CVD incidence associated with combinations of unhealthy *versus* healthy LFs was greater in the least advantaged groups in both studies (Figure 3 and Table S8E Table, which can be found as *Extended data*)). In combined single reference analysis, HRs (95%CIs) for the least healthy-most advantaged *versus* least healthy-least advantaged groups were: 1.30 (1.10–1.53) *versus* 1.75 (1.55–1.97)[19] and 1.18 (0.99–1.41) *versus* 2.09 (1.78–2.46)[46], respectively (S10 Table, which can be found as *Extended data*)[37]. Results from tests for SES-LF interactions for CVD incidence were mixed. Significant additive and multiplicative interactions were observed in one study (examining four LFs and latent class SES)[46] but not the other (examining nine LFs and area-based TDI)[19].

Two studies examined additional outcomes[43,46]. One of these performed SES-stratified analyses but did not report single reference group analyses or tests for interaction for these outcomes[43]. In this study's SES-stratified analyses, the difference in hazards associated with combinations of unhealthy *versus* healthy LFs for the total population was greater in the most advantaged group for mortality from stroke, and cancer but greater in the least advantaged group for CHD mortality (Figure 3

and S8F Table, which can be found as *Extended data*). Equivalent estimates from analyses additionally stratified by sex were similar, although, in men, the difference in hazards for stroke mortality was greater in the least advantaged group (Figure 3 and S8F Table, which can be found as *Extended data*). In SES-stratified analyses in the second study that examined additional outcomes in two cohorts, the difference in hazards associated with combinations of unhealthy *versus* healthy LFs for the total population was greater in the most advantaged group for mortality from 'heart disease' in NHANES but greater in the least advantaged group for coronary heart disease and stroke, cancer, and stroke and myocardial infarction incidence in UKB[46].

Discussion

Our review shows that the influence of SES on the association between a combination of unhealthy LFs and adverse health outcomes is unclear. There are several reasons for this. Firstly, few studies investigate this problem; only six studies met our eligibility criteria. Secondly, studies that do investigate this problem are heterogenous, varying by: cohort characteristics; lifestyle, SES, and covariate variables; outcomes assessed; and methodology by which SES influence was examined. Thirdly, where broadly similar estimates were compared directly (*i.e.*, *via* our main comparator), results were mixed: the difference in hazards associated with combinations of unhealthy *versus* healthy LFs was greater in the most advantaged SES group for some studies or cohorts and outcomes but in the least advantaged group for others. Fourthly, results for tests for multiplicative interactions between combinations of LFs and SES were conflicting. For example, for all-cause mortality, two studies found no evidence of multiplicative interaction[43,44]; two studies reported significant multiplicative interactions but observed a moderating influence of SES in opposing directions[19,42]; while a fifth study, of two cohorts, found significant multiplicative interactions in one cohort but not the other[46]. Finally, the quality of included studies varied, with only one scoring the highest possible quality score, so available study estimates may be biased. For example, a limitation to all studies examining SES measures is the difficulty of recruiting participants from less advantaged backgrounds, which introduces selection bias[51,52].

The heterogeneity and nature of the LF exposure variables examined by the included studies warrants further discussion. Firstly, each LF was measured or surveyed differently (e.g., diet assessed via a national dietary index comprising numerous survey items compared with diet assessed by a few specific food items; SES assess). Secondly, studies varied in their definitions of unhealthy (dichotomisation) for the same LF (e.g., unhealthy alcohol intake defined as >14/>7 weekly drinks for men/women vs. drinking daily or almost daily). Thirdly, dichotomising the LF exposure prior to creating the LF score or combination fails to capture the more complex dose-response and non-linear associations LFs have with adverse health-outcomes[53,54]. Fourthly, risk estimates associated with combinations of different LFs are difficult to compare where combinations from different studies lack shared LFs (*e.g.*, combination 1: smoking, alcohol, and physical inactivity *vs.* combination 2: sedentary time, unhealthy diet, and sleep duration). And fifthly, each LF will have differential contributions to the level of risk associated with the overall combination (*e.g.*, smoking is likely to drive the largest share of risk associated with CVD mortality)[55], thus making comparisons of estimates associated with unweighted combinations of different LFs hard to interpret. However, because unhealthy LFs are known to cluster among individuals, participants who report the unhealthiest LF combinations might be comparable even when different LFs are examined[4–8,56]. For example, among participants who report the unhealthiest combination of unhealthy LFs in 'study 1', there will be some participants with similar numbers and types of unhealthy LFs as those in 'study 2' who also report the unhealthiest combination even if study 2 examines fewer LFs because of clustering. This similarity or comparability is more likely where studies share more LF components (e.g., study 1: alcohol, unhealthy diet, and physical inactivity vs. study 2: alcohol, unhealthy diet, physical inactivity, and smoking). Although, in studies that examine more LFs or have more categories for LF analysis, those classified as the unhealthiest may represent a more extreme group. Nevertheless, , the aim of this review was to identify and appraise all studies that examined the effect of SES on the association between any LF combination and adverse health. Restricting the searches of this review to identify only those studies with the same or similar combinations of LFs would have yielded even fewer results and limited the synthesis. To explore the effect of specific LF combinations and of SES on the associations with adverse health outcomes, future research could attempt to identify the riskiest LF combinations, whether and how the riskiest combinations vary by SES, and whether and how SES effects the associations between specific combinations and adverse health outcomes. Further, there is currently a lack of guidance on how to live in health ways that considers LF combinations and there is no consensus definition for 'unhealthy lifestyle' overall. Numerous single LF specific guidelines exist, but these are often too complex to digest for most people and they often fail to account for interactions with other LFs or social contexts[57–59]. Therefore, as part of precision medicine, future research could explore the non-linear associations and interactions for a wide range of LFs to define 'unhealthy' levels for LFs within specific (or personalised) combinations and across SES the spectrum. These efforts could provide new targets for intervention and inform policies attempting to address unhealthy LFs in the least advantaged sections of society[60].

The range of SES measures used across studies highlights the myriad ways in which SES can be measured and ranked[11]. Although there is likely to be a high degree of correlation across SES measures, the impacts of different SES measures on the association between combinations of LFs and adverse health could be different[61]. For example, an individual-level measure (*e.g.*, age at last formal education) could have a weaker modifying effect on the association between combinations of LFs and adverse health than an area-based deprivation index if wider socioeconomic factors included or captured by the index (directly or indirectly) have a greater effect on the association. For instance, proximity and access to healthy food

or green spaces for PA could be more strongly associated with area-based SES indices than with individual-level SES measures[62]. Having few studies using the same SES measure limited the ability to draw conclusions on how the SES measure influences SES effects. For example, of the six studies that examined all-cause mortality, two use income, one uses education, two use area-based indices, and one uses a combination of income, education level, occupation/employment, and health insurance in a latent class analysis. Future reviews, with a greater number of included studies, could stratify and synthesise results by SES measure to investigate this further. Irrespective of SES heterogeneity, if an effect of SES was identified that was consistent across a broad range of SES measures this would strengthen the evidence for a general SES effect. Whereas if SES effects were consistently associated with one type of SES measurement (*e.g.*, income) and not others (*e.g.*, area-based indices) this could generate hypotheses and inform research that aims to explain underlying mechanisms of SES effects[61]. The aim of this review was to identify all available evidence and therefore studies were not excluded on the basis of LF and SES exposure variables despite the expected difficulties in comparability.

Notwithstanding study heterogeneity and the lack of data, the studies' assessments of the influence of SES on the association between a combination of unhealthy LFs and adverse health outcomes point broadly towards an additive influence of SES. Examining the combined effect of SES and combinations of unhealthy LFs by way of a single reference group (the healthiest LF-most advantaged group), four studies of five cohorts provide evidence for an additive interaction for multiple outcomes[19,43,44,46]. Two of these studies, both examining UKB, also observed significant results from formal tests for additive interactions as well as significant multiplicative interactions in same direction[19,46]. Together, this evidence does not strongly support a vulnerability hypothesis but it does provide some evidence against the so-called Blaxter hypothesis[63]. The Blaxter hypothesis suggests that detrimental effects of unhealthy lifestyles are masked by other adverse factors also associated with less advantaged SES (*e.g.*, insecure income, poor housing, more frequent adverse childhood experiences). If this hypothesis were correct, in analyses stratified by SES and in least advantaged SES groups, associations between combinations of LFs and adverse health would be similar whether the LFs were healthy or unhealthy (*i.e.*, a combination of unhealthy LFs would have little influence on a population with an already high risk due to other factors). However, in all studies, compared to those with healthy LFs, there were higher hazards for adverse health outcomes in those with a combination of unhealthy LFs irrespective of SES level. One study observed a multiplicative interaction (in men only), where the difference in hazards associated with a combination of unhealthy *versus* healthy LFs was greater in the most advantaged SES group, which could support the Blaxter hypothesis[42]. However, the authors did not report a single reference group analysis, which could help clarify the combined associations. Overall, the impression of an additive interaction between least advantaged SES and combinations of unhealthy LFs seen in four studies of five cohorts

and a multiplicative interaction in the same direction in two studies suggests that the detrimental effects of combinations of unhealthy LFs are not masked by other harmful factors associated with less advantaged SES but are at least in addition to, and potentially synergistic with, those factors. This finding, if borne out in future research, would indicate that less advantaged SES populations have the highest absolute risks associated with combinations of unhealthy LFs and would, therefore, support a strategy of focussing lifestyle resources on less advantaged SES populations where need is greatest.

Strengths and limitations

This review is strengthened by a rigorous pre-specified protocol[35]; a comprehensive search strategy including database, reference, citation, and grey literature searches[36]; and by reviewers working independently. Further, data synthesis follows SWiM guidelines and is fully transparent[41]. However, this review is limited by the small number of studies included and by the high level of heterogeneity between studies, which precluded meta-analysis. Therefore, the conclusions drawn here about whether and how SES influences the association between combinations of unhealthy LFs and adverse health may be altered by future research. Importantly, differential vulnerability to combinations of unhealthy LFs could be due to differential exposure that is not captured *via* questionnaires. For example, excess alcohol in less advantaged SES populations may be more extreme than excess alcohol in more advantaged groups[64]. Similarly, residual confounding, with unaccounted for differences between more and less advantaged populations, could also explain observed differential vulnerability. Our search terms were extensive and the databases we searched likely contained the vast majority of eligible articles[65]. Searching additional databases such as Scopus and Web of Science, which are noted for their use as citation indexes rather than primary sources[66], may have revealed additional eligible studies but this was beyond the time and human resources available for this project. Updating the searches could also identify newer studies, including studies that look at different health outcomes, such as specific cancers and studies from low- or middle-income countries[67,68]. It is unlikely that the addition of these studies would change the result around the heterogeneity of data but it could reveal more consistency in terms of SES effects. Our eligibility criteria may have been too restrictive resulting in few studies and retrospective studies may have yielded additional evidence. Generally, however, retrospective observational studies may have more biases than well-designed prospective ones. Future prospective studies, where data are updated during follow-up, could reduce potential misclassification bias by capturing participants' lifestyle changes. While the adverse health outcomes included here account for the vast majority of mortality and NCD burden[69], others, such as dementia and renal disease, are growing in prevalence and have similar lifestyle risk factors[70,71]. Our decision to extract the 'healthiest' vs. 'unhealthiest' in both the most and least advantaged groups as our main comparator may have limited our synthesis. Examining the effect of SES on associations between the extremes of lifestyle and adverse health outcomes may miss how SES might affect the relationships in more nuanced ways

as it relies on the assumption that SES effects will be seen at the extremes of lifestyle. However, we also extracted results for interactions between SES and LFs, which provided further evidence for whether and how SES effects associations between LFs and adverse health outcomes. As more studies examine associations between combinations of LFs and adverse health outcomes in more detail (e.g., by examining non-linear associations and using continuous rather than categorical or ordinal variables for LF combinations)[53,54], future reviews could examine how SES effects the shape of relationships between LFs and adverse health outcomes. The aim of this review was to identify and synthesise the evidence for SES modification of associations between LF combinations and adverse health outcomes, not to explain any identified effect modification. However, strong evidence for SES effect modification of such associations could prompt attempts to uncover underlying mechanisms, such as cumulative risks or accelerated biological ageing[25–27].

Conclusions

This is the first systematic review to examine if and how SES modifies associations between combinations of unhealthy LFs and adverse health outcomes. Prospective studies that examine this problem are few and heterogenous. The influence of SES on lifestyle-associated adverse health could be additive but remains unclear. New research using multiple datasets, a range of lifestyle and SES measures, and a comprehensive list of adverse health outcomes would improve understanding of SES influence on lifestyle risks and thereby inform lifestyle-related policy and interventions.

Data availability

Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Extended data
Figshare: 2022_12_08_SES_lifestyle_systematic_rv_SUPPORTING_INFORMATION.docx. https://doi.org/10.6084/m9.figshare.21701519[37].

Reporting guidelines
Figshare: PRISMA checklists for the abstract and main manuscript of 'The influence of socioeconomic status on the association between unhealthy lifestyle factors and adverse health outcomes: a systematic review'. https://doi.org/10.6084/m9.figshare.21770651[33] and https://doi.org/10.6084/m9.figshare.21770657[34].

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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Open Peer Review

Current Peer Review Status: ❓ ✅

Version 2

Reviewer Report 28 December 2023

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The rebuttal addressed most of my concerns and importantly told me that the authors thought about those issues. I accept the manuscript without any further changes.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nutrition, epidemiology, ageing

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 14 July 2023

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[2] CHRC, Universidade Nova de Lisboa, Lisbon, Portugal

I thank the authors for the big amount of work that went into searching, reviewing, analysing and drafting "The influence of socioeconomic status on the association between unhealthy lifestyle factors and adverse health outcomes: a systematic review". The paper is well-written and there is a careful presentation of the results. However, I have several concerns/comments that I will list, not by order of importance, but by order of appearance.

1. The title mentions "adverse health outcomes" but I think that a better description of what those outcomes are would be more informative. It could read "The influence of socioeconomic status on the association between unhealthy lifestyle factors and cardiovascular disease, cancer and mortality: a systematic review".

2. The search was conducted 1.5 years ago and although I am aware of the work involved in running it again I believe that, unless there is a very good reason not to, there should at the very least some mention in the discussion of the number of papers published that met your inclusion criteria in the past 1.5 years.

3. There are other databases that could have been searched as well. I believe the authors should justify why there was a decision not to search them, even if that decision was time constraints and believing that all the studies would be included in PubMed/EMBASE/CINAHL.

4. Abstract: It would be good to describe briefly which LFs were used or something from this phrase "i. combination of ≥3 LFs: studies that also included metabolic/intermediate factors (*e.g.*, blood pressure/body mass index (BMI)) as part of their combination of LFs were included so long as the combination also included ≥3 'behavioural' LFs (*e.g.*, smoking/PA/diet)."

5. The protocol mentions that all-cause mortality was the main outcome but I didn't seem to find any mention of it in this paper.

6. Introduction: The authors mention different possible explanations but I missed the authors hypothesis of how SES plays moderates the association between lifestyle and health outcomes, or mention which (or a blend of both) of the existing explanations is favoured by the authors.

7. Figure 2. Most of the HRs are between 1 and 3 but the ticks on the x axis are only every 1-point which doesn't let me, from the figure alone, see the estimates but only the direction and general magnitude. I suggest adding more ticks and having 1 decimal point instead of 2 (also remember its a log scale). And/or (and ideally) having the HRs and corresponding 95%CI on the plot for every row/analysis. I see that Choi 2020 did not provide confidence intervals or any measure of variability but that should be mentioned in the figure notes.

8. Supplementary tables should be mentioned along the text when needed .e.g. there is no mention on Table S8 when reporting on the results of the association between combinations of unhealthy LFs and all-cause mortality (figure 2). Also supplementary material are not annexes and table/figures/text should only be included in the paper when

these are mentioned.

9. Check if abbreviations are defined at their first appearance, .e.g NHANES in the abstract.

10. Discussion: There should be some mention about the possible selection bias in the recruitment of these studies, i.e. it is notoriously harder to recruit people from lower SES status.

11. Discussion: The authors mention how different combinations of LFs were used across studies but these were also measured differently. Please add that besides the difficulty of comparing different combinations of LFs, these were also often times measured in a very different way.

12. Discussion: Not using individual lifestyle such as smoking or alcohol and instead using lifestyle, combination, etc may have meant that some papers were not picked up. If this was the case or if the authors think this was unlikely, it should be mentioned

13. Discussion: "However, the level of evidence from retrospective design is lower" should be taken with caution because it oversimplifies the quality of evidence based on simply the study design. Adding something like "observational retrospective design may, in general, have more biases than a well-designed prospective observational study" would be better.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nutrition, epidemiology, ageing

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 28 Nov 2023
Hamish Foster

2nd Reviewer - Nuno Mendonça, CHRC, NOVA Medical School, Universidade Nova de

Lisboa, Lisboa, Portugal   I thank the authors for the big amount of work that went into searching, reviewing, analysing and drafting "The influence of socioeconomic status on the association between unhealthy lifestyle factors and adverse health outcomes: a systematic review". The paper is well-written and there is a careful presentation of the results. However, I have several concerns/comments that I will list, not by order of importance, but by order of appearance. **We thank the reviewer for their positive and helpful comments.**

1. The title mentions "adverse health outcomes" but I think that a better description of what those outcomes are would be more informative. It could read "The influence of socioeconomic status on the association between unhealthy lifestyle factors and cardiovascular disease, cancer and mortality: a systematic review".

We thank the reviewer for their suggestion. However, 'adverse health outcomes' is what we use in our protocol, and we justify the choice of selected outcomes (cardiovascular disease, cancer, and mortality) as being the main outcomes linked to 'lifestyle'. Also, it is a helpful phrase that we use a lot in the paper when referring to our outcomes. As a result, we have left the title as it was.

1. The search was conducted 1.5 years ago and although I am aware of the work involved in running it again I believe that, unless there is a very good reason not to, there should at the very least some mention in the discussion of the number of papers published that met your inclusion criteria in the past 1.5 years.

We appreciate this suggestion. We have responded to a similar point made by the 1st reviewers (Methods, Point 2) by adding the following the strengths and limitations section (lines 600-604): *'Updating the searches could also identify newer studies, including studies that look at different health outcomes, such as specific cancers and studies from low- or middle-income countries.67,68 It is unlikely that the addition of these studies would change the result around the heterogeneity of data but it could reveal more consistency in terms of SES effects.'*

1. There are other databases that could have been searched as well. I believe the authors should justify why there was a decision not to search them, even if that decision was time constraints and believing that all the studies would be included in PubMed/EMBASE/CINAHL.

As per our response to the first Reviewers' Point 1 (Methods) above - We agree that databases such as Scopus and Web of Science may cover additional articles not covered by the databases we selected. However, this project was limited in scope and time and therefore additional databases were felt to be beyond the resources available for this project. We have selected what we felt to be the most relevant databases. And have added the following to the strengths and limitation section (lines 596-600): *'Our search terms were extensive and the databases we searched likely contained the vast majority of eligible articles 65. Searching additional databases such as Scopus and Web of Science, which are noted for their use as citation indexes rather than primary sources, 66 may have revealed additional eligible studies but this was beyond the time and human resources available for this project.'*

1. Abstract: It would be good to describe briefly which LFs were used or something from this phrase "i. combination of ≥3 LFs: studies that also included metabolic/intermediate factors (*e.g.*, blood pressure/body mass index (BMI)) as part of their combination of LFs were included so long as the combination also included ≥3 'behavioural' LFs (*e.g.*, smoking/PA/diet)."

We thank the reviewer, and we agree this is helpful information for the abstract, which was omitted originally for reasons of word count, but we have added this in now. Similarly, we have also added examples for what we mean by SES in the abstract. The first sentence in the Methods section of the abstract now reads: 'Systematic review of studies that examine associations between combinations of >3 LFs *(eg.smoking/physical activity/diet)* **and health outcomes and report data on SES** *(eg.income/education/poverty-index)* **influences on associations.'**

1. The protocol mentions that all-cause mortality was the main outcome but I didn't seem to find any mention of it in this paper.

After running the searches and finding 6 studies that fit our criteria, we felt that there was no need to differentiate by main and secondary outcomes – only 3 studies examined outcomes other than all-cause mortality. Consequently, the largest section of our results (synthesised by outcomes) concerns all-cause mortality so we felt no need to highlight this as the 'main outcome' as this is superfluous when few other data exist pertaining to other outcomes.

1. Introduction: The authors mention different possible explanations but I missed the authors hypothesis of how SES plays moderates the association between lifestyle and health outcomes, or mention which (or a blend of both) of the existing explanations is favoured by the authors.

We thank the reviewer for this suggestion. However, our objective with this review was to examine whether and in what way SES influences associations between combinations of lifestyle factors and adverse health outcomes. Our aim was not to explore possible mechanisms, and as a group of authors, we are yet to form strong views on which explanatory mechanisms are most likely. The existence of plausible mechanisms for SES effects on these associations are pre-requisite to reviewing the literature for SES effects but understanding the mechanisms and their relative contributions will become much more relevant when the evidence is clear that there are indeed SES effects. Indeed, a review of possible mechanisms would be indicated if clear SES effects were found.   Please see our final sentences in the discussion which we feel respond directly to this comment (lines 624-628):   'The aim of this review was to identify and synthesise the evidence for SES modification of associations between LF combinations and adverse health outcomes, not to explain any identified effect modification. However, strong evidence for SES effect modification of such associations could prompt attempts to uncover underlying mechanisms, such as cumulative risks or accelerated biological ageing [25–27]**.'   Relatedly, we have added the following to the introduction to add clarity that we are discussing SES effects on lifestyle associations (line 35):   'Beyond differential exposure, further explanations for lifestyle-related health inequalities may involve interactions between LFs and SES; so-called 'differential vulnerability'** [17] **,** *where SES strengthens the association between lifestyle and adverse health outcomes***.'   And (lines 45-46)   'Mechanisms that explain differential lifestyle vulnerability** *or that explain how and why SES effects associations between lifestyle and adverse health outcomes* **are unclear but could include...'**

1. Figure 2. Most of the HRs are between 1 and 3 but the ticks on the x axis are only every 1-point which doesn't let me, from the figure alone, see the estimates but only the direction and general magnitude. I suggest adding more ticks and having 1 decimal point instead of 2 (also remember its a log scale). And/or (and ideally) having the HRs and corresponding 95%CI on the plot for every row/analysis. I see that Choi

> 2020 did not provide confidence intervals or any measure of variability but that should be mentioned in the figure notes.

We thank the reviewer for these suggestions. As per our response to the first reviewers, we have changed the horizontal axes of Figs 2 & 3 to the log scale. We have also altered the decimal place to 1. The figures are for general visualisation of the data to give an idea of direction and magnitude. However, we have added HRs and CIs to the figures to help the readers see the numerical estimates. We have also made it clear that Choi et al. did not provide CIs.

1. Supplementary tables should be mentioned along the text when needed .e.g. there is no mention on Table S8 when reporting on the results of the association between combinations of unhealthy LFs and all-cause mortality (figure 2). Also supplementary material are not annexes and table/figures/text should only be included in the paper when these are mentioned.

We thank the reviewer for this suggestion to add clarity. We have added mentions to the relevant supplementary Tables in the text instead of just referring to the Figures. In response to the second part of this comment regarding supplementary material and annexes, we are following the journal's instructions whereby supplementary material is submitted as 'extended data' and published on the publicly available repository of figshare.

1. Check if abbreviations are defined at their first appearance, .e.g NHANES in the abstract.

Thank you, this was due to the abstract word limit, but we have added that to the abstract now. We believe all other abbreviations in the manuscript are defined at first mention.

1. Discussion: There should be some mention about the possible selection bias in the recruitment of these studies, i.e. it is notoriously harder to recruit people from lower SES status

We agree this is an important caveat that links to all studies relating to SES and have added this to the discussion on study quality (lines 476-478): *'For example, a limitation to all studies examining SES measures is the difficulty of recruiting participants from less advantaged backgrounds, which introduces selection bias 51,52.'*

1. Discussion: The authors mention how different combinations of LFs were used across studies but these were also measured differently. Please add that besides the difficulty of comparing different combinations of LFs, these were also often times measured in a very different way.

We thank the reviewer for this point, which we address in our response the 1st reviewers who made a very similar point (Discussion point 2). This is the relevant addition we have made to the discussion section (lines 479-487): *'The heterogeneity and nature of the LF and SES exposure variables examined by the included studies warrants further discussion. Firstly, each LF was measured or surveyed differently (e.g., diet assessed via a national dietary index comprising numerous survey items compared with diet assessed by a few specific food items; SES assess). Secondly, studies varied in their definitions of unhealthy (dichotomisation) for the same LF (e.g., unhealthy alcohol intake defined as >14/>7 weekly drinks for men/women vs. drinking daily or almost daily). Thirdly, dichotomising the LF exposure prior to creating the LF score or combination fails to capture the more complex dose-response and non-linear associations LFs have with adverse health-outcomes 53,54.'*

1. Discussion: Not using individual lifestyle such as smoking or alcohol and instead using lifestyle, combination, etc may have meant that some papers were not picked up. If this was the case or if the authors think this was unlikely, it should be mentioned

We agree that omitting specific lifestyle factors may have meant some papers were picked up. However, the risk of omission we believe would be lowered by our searching terms such as 'behaviour', 'health factor', or 'modifiable factors' as well as 'lifestyle' and 'combination' in both the abstract and title. Crucially, our aim was to look at those papers which examined combinations of LFs rather than specific LFs and we feel that our search terms were wide enough to identify papers that looked at combinations of LFs. Further, including some of the specific LFs in the searches has the potential to explode the number of papers identified because the literature on each specific LF is large.

1. Discussion: "However, the level of evidence from retrospective design is lower" should be taken with caution because it oversimplifies the quality of evidence based on simply the study design. Adding something like "observational retrospective design may, in general, have more biases than a well-designed prospective observational study" would be better

We thank the reviewer for pointing out this sentence, which, we agree, oversimplifies the issue. The sentence now reads (lines 606-608): *Generally, however, retrospective observational studies may have more biases than well-designed prospective ones*.

Competing Interests: No competing interests were disclosed.

Reviewer Report 20 April 2023

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? **Sophie Jones**
Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK

Leandro Garcia (ID)
Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK

This systematic review aims to identify and appraise the available evidence on whether and how socioeconomic status modifies associations between combinations of lifestyle factors and adverse health outcomes. Overall, the paper is well-written and clearly defines the rationale and objectives for the systematic review. Methods followed the PRISMA guidelines and are described in sufficient detail. The review protocol was registered in PROSPERO. Only six papers met the inclusion criteria, but results are comprehensively and clearly presented, including the tables and figures. The conclusion was limited due to the high heterogeneity of measures for socioeconomic status, a combination of lifestyle factors and mixed findings from included studies. Please find major and

minor suggestions below.

MAJOR POINTS:
Methods
1. Comprehensive databases, such as Scopus and Web of Science, that cover potentially relevant journals not covered by the three databases selected, were not used in the search. Have the authors considered the addition of these and/or other databases to enlarge the search coverage? If so, why have other databases not been used?

2. The search was conducted more than one year ago. Do the authors have a good reason to believe that updating the search would not materially change the results and conclusions of the current review? If so, the authors could provide their reasons in the article. Otherwise –and assuming the authors do not have the resources to update the search at the moment- a caveat could be added in the limitations regarding the time elapsed since the search, referencing some of the relevant papers published recently.

Results
1. In the discussion, the authors highlight the possibility that different measures of SES (e.g., individual-level vs area-level) may yield different results. Can the authors clarify whether they considered stratifying results to investigate this?

2. Figures 2 and 3: given that different SES indicators were used across papers, and that potentially the modification effect can vary between different SES dimensions, it seems important to indicate in Figures 2 and 3 what SES stratifier was used by each analysis. E.g., presenting the SES stratifier below each author's name. When possible and relevant, authors can consider similarities and differences between results based on different SES stratifiers.

Discussion
1. "However, risk estimates associated with the healthiest and unhealthiest LF combinations where studies share similar LF components (e.g., combination 1: alcohol, unhealthy diet, and physical inactivity vs. combination 2: alcohol, unhealthy diet, physical inactivity, and smoking), are more comparable.": This statement is accurate only when the additional component(s) are known to have a significantly small contribution to the disease outcome in relation to the contribution of the shared components. In the example given by the authors, the contribution of smoking to mortality is likely to be significantly bigger than any of the other components, maybe significant even when the other components are combined. Hence, risk estimates of quasi-similar combinations cannot be assumed to be comparable in all (or even in most) cases.

2. Many of the lifestyle factors investigated are likely to have a dose-response association with the disease outcomes investigated. Hence, beyond the lack of shared lifestyle factors between studies, the lack of comparable thresholds used to classify (un)healthy behaviour across studies is an important limitation when summarizing the findings. It would be important that the authors acknowledge this, and elaborate on the implications for this and future research.

3. In the introduction, the authors highlight an "An important caveat..." as a justification for the use of the word lifestyle. However, we think there may be something missing about the consistency of the definition of "unhealthy lifestyle" amongst included studies and a

discussion about the implication of this on the findings. Could the authors address this somewhere in the discussion or as a limitation?

MINOR POINTS:

1. Aims: in "This systematic review aims to identify, describe, and synthesise the evidence for whether SES modifies associations between combinations of unhealthy LFs and adverse health outcomes", the authors might consider adding a parenthesis at the end specifying the outcomes investigated, for clarity. E.g., "adverse health outcomes (all-cause mortality, incidence and mortality from CVD or cancer)."

2. PECO criteria: the authors highlight the population as 'any general adult population'. Could the authors please clarify the age ranges they considered for this population?

3. Data extraction: could the authors please describe how exactly "[point] estimates [and confidence intervals] from studies where the unhealthiest group was the reference were transformed to make the 'healthiest' group the reference"?

4. Articles excluded if not in English: we understand that this is common practice in many reviews (albeit PRISMA recommends that articles are not excluded based on language only to avoid biases). However, given that (a) only two papers were not in English, (b) two more papers could be a valuable contribution to the review, given that only six could have been included, (c) these two papers are likely to come from low- or middle-income countries, increasing the diversity of the evidence based analysed, and (d) there are options available to get support with non-English articles (e.g., translation tools, colleagues who speak other languages than English, and Translators without Borders - https://translatorswithoutborders.org/), assessing the eligibility of these two papers based on the PECO criteria and including them in the review if relevant seems like a missed opportunity.

5. In Table 1, for the second to last study presented (Choi *et al.*, 2022), the lifestyle factors for "ii" appear as separate due to an additional return:

   "ii) weekly alcohol intake >14 drinks
   for men, >7 drinks for women …"

   Could the authors check, please?

6. Figures 2 and 3: the x-axis should be in logarithmic scale to ensure visual symmetry between values below and above 1 that indicate the same effect size (e.g., 0.5 and 2).

7. Figure 2: estimates for Choi 2020 do not have the confidence interval. Could author check if it is unintentionally missing?

8. Figure 3: the Eguchi 2017's analysis for non-CVD, non-cancer mortality seems to be outside the scope of the review, based on its objectives and PECO criteria. The authors should consider removing it from the article.

9. Table S1: some terms seem to be duplicated within searches #2 (see *risk reduction behaviour*[tiab]* and *health behaviour[tiab]* with and without asterisks) and #3 (see *health*

inequalities[tiab] and social-economic[tiab] with and without asterisk). This does not affect the results of the search but can be corrected for conciseness and clarity. Author might want to check whether the same occurred in Tables S2 and S3.

10. It seems Table S6 is cut short. Could the authors check, please?

OTHER POINTS:

Background and Discussion
1. The Background and Discussion sections would greatly benefit from the use of Sydemic Theory to substantiate the rationale for the study and discuss its findings.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health; Physical Activity; Systems Thinking.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 28 Nov 2023
Hamish Foster

Reviewer comments Authors' response **1st reviewers – Sophie Jones & Leandro Garcia, Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK**

This systematic review aims to identify and appraise the available evidence on whether and how socioeconomic status modifies associations between combinations of lifestyle factors and adverse health outcomes. Overall, the paper is well-written and clearly defines the rationale and objectives for the systematic review. Methods followed the PRISMA guidelines and are described in sufficient detail. The review protocol was registered in PROSPERO. Only six papers met the inclusion criteria, but results are comprehensively and clearly presented, including the tables and figures. The conclusion was limited due to the high heterogeneity of measures for socioeconomic status, a combination of lifestyle factors and mixed findings from included studies. Please find major and minor suggestions below. **We thank the**

reviewers for their positive comments on the quality of our article.

MAJOR POINTS

Methods

1. Comprehensive databases, such as Scopus and Web of Science, that cover potentially relevant journals not covered by the three databases selected, were not used in the search. Have the authors considered the addition of these and/or other databases to enlarge the search coverage? If so, why have other databases not been used? We agree with the reviewers that databases such as Scopus and Web of Science may cover additional articles not covered by the databases we selected. However, this project was limited in scope and time and therefore additional databases were felt to be beyond the resources available for this project. **We have selected what we felt to be the most relevant databases, in discussion with a subject-specific librarian. We have added this as a limitation to the strength and limitations section (lines 596-600):** *'Our search terms were extensive and the databases we searched likely contained the vast majority of eligible articles65. Searching additional databases such as Scopus and Web of Science, which are noted for their use as citation indexes rather than primary sources,66 may have revealed additional eligible studies but this was beyond the time and human resources available for this project.'*

2. The search was conducted more than one year ago. Do the authors have a good reason to believe that updating the search would not materially change the results and conclusions of the current review? If so, the authors could provide their reasons in the article. Otherwise –and assuming the authors do not have the resources to update the search at the moment- a caveat could be added in the limitations regarding the time elapsed since the search, referencing some of the relevant papers published recently. We thank the reviewers for this point. **We have added the following caveat to the strengths and limitations section (lines 600-604):** *'Updating the searches could also identify newer studies, including studies that look at different health outcomes, such as specific cancers and studies from low- or middle-income countries.67,68 It is unlikely that the addition of these studies would change the result around the heterogeneity of data but it could reveal more consistency in terms of SES effects.*

Results

1. In the discussion, the authors highlight the possibility that different measures of SES (e.g., individual-level vs area-level) may yield different results. Can the authors clarify whether they considered stratifying results to investigate this? We thank the reviewers for raising this point. As per our protocol, we planned on synthesising data by outcome, but we appreciate that identifying variation in SES effects by SES measure would be valuable. With few included studies we do not believe there is a clear indication for stratifying our results by SES measure but feel this would be an important consideration for future reviews that identify more studies. **We have added the following to the discussion (lines 542-543):** *'Future reviews, with a greater number of included studies, could stratify and synthesise results by SES measure to investigate this further.'*

2. Figures 2 and 3: given that different SES indicators were used across papers, and that potentially the modification effect can vary between different SES dimensions, it seems important to indicate in Figures 2 and 3 what SES stratifier was used by each analysis. E.g., presenting the SES stratifier below each author's name. When possible and relevant, authors can consider similarities and differences between results based on different SES stratifiers. **We agree that understanding which SES measure is being used is highly relevant and we thank the reviewer for suggesting adding this data into Figures 2 and 3. We have added the SES measure for each study below the author's name as well as the corresponding definitions for the most and least advantaged categories (Please see updated Figures 2 and 3). We have updated the legends for these figures accordingly.[HF1]   Without more studies that examine comparable SES measures it is difficult to draw conclusions on how the type of SES measure influences SES effects. For example, of the six studies that examine all-cause mortality, two use income, one uses education, two use area-based measures, and one uses latent class analysis (a combination) with 3 or 4 individual-level SES measures. We have highlighted this in the discussion section (lines 537-541):** *'Having few studies using the same SES measure limited the ability to draw conclusions on how the SES measure influences SES effects. For example, of the six studies that examined all-cause mortality, two use income, one uses education, two use area-based indices, and one uses a combination of income, education level, occupation/employment, and health insurance in a latent class analysis.'*

Discussion

1. "However, risk estimates associated with the healthiest and unhealthiest LF combinations where studies share similar LF components (e.g., combination 1: alcohol, unhealthy diet, and physical inactivity vs. combination 2: alcohol, unhealthy diet, physical inactivity, and smoking), are more comparable.": This statement is accurate only when the additional component(s) are known to have a significantly small contribution to the disease outcome in relation to the contribution of the shared components. In the example given by the authors, the contribution of smoking to mortality is likely to be significantly bigger than any of the other components, maybe significant even when the other components are combined. Hence, risk estimates of quasi-similar combinations cannot be assumed to be comparable in all (or even in most) cases. **We thank the reviewer for making this point. We agree that different combinations are not fully comparable for the reason they highlight and the effects of specific combinations remain relative. However, we believe there will be some comparability as unhealthy LFs tend to cluster among individuals.   As a result, we have added the following to the discussion section (Lines 494-526):** *'However, because unhealthy LFs are known to cluster among individuals, participants who report the unhealthiest LF combinations might be comparable even when different LFs are examined 4-8,56. For example, among participants who report the unhealthiest combination of unhealthy LFs in 'study 1', there will be some participants with similar numbers and types of unhealthy LFs as those in 'study 2' who also report the unhealthiest combination even if study 2 examines fewer LFs because of clustering. This similarity or comparability is more likely where studies share more LF components (e.g., study 1: alcohol, unhealthy diet, and physical inactivity vs. study 2: alcohol, unhealthy diet, physical inactivity, and smoking). Although, in studies that examine more LFs or have more*

categories for LF analysis, those classified as the unhealthiest may represent a more extreme group. Nevertheless, the aim of this review was to identify and appraise all studies that examined the effect of SES on the association between any LF combination and adverse health. Restricting the searches of this review to identify only those studies with the same or similar combinations of LFs would have yielded even fewer results and limited the synthesis. To explore the effect of specific LF combinations and of SES on the associations with adverse health outcomes, future research could attempt to identify the riskiest LF combinations, whether and how the riskiest combinations vary by SES, and whether and how SES effects the associations between specific combinations and adverse health outcomes. Further, there is currently a lack of guidance on how to live in health ways that considers LF combinations and there is no consensus definition for 'unhealthy lifestyle' overall. Numerous single LF specific guidelines exist, but these are often too complex to digest for most people and they often fail to account for interactions with other LFs or social contexts 57-59. Therefore, as part of precision medicine, future research could explore the non-linear associations and interactions for a wide range of LFs to define 'unhealthy' levels for LFs within specific (or personalised) combinations and across SES the spectrum. These efforts could provide...'

2. Many of the lifestyle factors investigated are likely to have a dose-response association with the disease outcomes investigated. Hence, beyond the lack of shared lifestyle factors between studies, the lack of comparable thresholds used to classify (un)healthy behaviour across studies is an important limitation when summarizing the findings. It would be important that the authors acknowledge this, and elaborate on the implications for this and future research. **We thank the reviewers for highlighting this important element of the heterogeneity of LFs examined.   We have expanded on this and its implications both in this study and future research in the discussion section (Lines 479-487):   *'The heterogeneity and nature of the LF and SES exposure variables examined by the included studies warrants further discussion. Firstly, each LF was measured or surveyed differently (e.g., diet assessed via a national dietary index comprising numerous survey items compared with diet assessed by a few specific food items; SES assess). Secondly, studies varied in their definitions of unhealthy (dichotomisation) for the same LF (e.g., unhealthy alcohol intake defined as >14/>7 weekly drinks for men/women vs. drinking daily or almost daily). Thirdly, dichotomising the LF exposure prior to creating the LF score or combination fails to capture the more complex dose-response and non-linear associations LFs have with adverse health-outcomes 53,54. Fourthly,...'***

3. In the introduction, the authors highlight an "An important caveat…" as a justification for the use of the word lifestyle. However, we think there may be something missing about the consistency of the definition of "unhealthy lifestyle" amongst included studies and a discussion about the implication of this on the findings. Could the authors address this somewhere in the discussion or as a limitation? **We thank the reviewer for raising this issue and we agree there is a difference between defining what unhealthy levels are for each single LF and defining what an 'unhealthy lifestyle overall' might be when considering a combination of LFs.   In the included studies, different numbers of categories were used for examining the associations with a combination of LFs (and then the effect of SES on those associations). The number of categories chosen was partly dependent on the number of LFs included (e.g., Eguchi 2017 et al. included 8 LFs**

but examined the associations between mortality and 5 lifestyle categories where participants were scored 0–3, 4, 5, 6, 7–8 based on how many LFs they had). However, the included studies did not actually define what 'unhealthy lifestyle' overall was, but rather, in our review, we extracted the estimates for the most extreme lifestyle categories (healthiest and unhealthiest) and we labelled these as 'healthy' and 'unhealthy', respectively. We appreciate this has implications for our main comparator where we selected estimates for the healthiest vs unhealthiest lifestyle overall in both the most and least advantaged SES groups. As a result, we have added the following to the limitations section (Lines 613-624): *'Our decision to extract the 'healthiest' vs. 'unhealthiest' in both the most and least advantaged groups as our main comparator may have limited our synthesis. Examining the effect of SES on associations between the extremes of lifestyle and adverse health outcomes may miss how SES might affect the relationships in more nuanced ways as it relies on the assumption that SES effects will be seen at the extremes of lifestyle. However, we also extracted results for interactions between SES and LFs, which provided further evidence for whether and how SES effects associations between LFs and adverse health outcomes. As more studies examine associations between combinations of LFs and adverse health outcomes in more detail (e.g., by examining non-linear associations and using continuous rather than categorical or ordinal variables for LF combinations) 53,54, future reviews could examine how SES effects the shape of relationships between LFs and adverse health outcomes.'* **As well as the above, we also wonder if there might be a lack of clarity here on our part. The section in the introduction starting, 'An important caveat...', may have been misleading. We only mean to highlight the word 'lifestyle' rather than the concept of 'unhealthy lifestyle overall'. This is because the negative connotations associated with the word lifestyle explained in the manuscript apply equally to single LFs or combinations of LFs (i.e., 'unhealthy lifestyle overall'). The word lifestyle is the problem and therefore we have removed 'unhealthy' from the relevant paragraph in the introduction to make this clearer. And, in view of the reviewers' point about defining 'unhealthy lifestyle' overall, we have added the following to the discussion (lines 517-521):** *'Further, there is currently a lack of guidance on how to live in health ways that considers LF combinations and there is no consensus definition for 'unhealthy lifestyle' overall. Numerous single LF specific guidelines exist, but these are often too complex to digest for most people and they often fail to account for interactions with other LFs or social contexts 57-59.'*

MINOR POINTS
1. Aims: in "This systematic review aims to identify, describe, and synthesise the evidence for whether SES modifies associations between combinations of unhealthy LFs and adverse health outcomes", the authors might consider adding a parenthesis at the end specifying the outcomes investigated, for clarity. E.g., "adverse health outcomes (all-cause mortality, incidence and mortality from CVD or cancer)."

Thank you. We have added this suggestion.
1. PECO criteria: the authors highlight the population as 'any general adult population'. Could the authors please clarify the age ranges they considered for this population?

We have added the following to our PECOS criteria: **'1) Population: any general adult population** *(age ≥18 years)...'*
1. Data extraction: could the authors please describe how exactly "[point] estimates [and confidence intervals] from studies where the unhealthiest group was the

reference were transformed to make the 'healthiest' group the reference"?

Thank you. We have added the following the relevant data extraction section (lines 135-140): *'This transformation was achieved by dividing: 1) all hazard ratios (HRs) by the HR of the healthiest category (the healthiest category HR then becomes 1.00), 2) all lower confidence intervals (CIs) by the lower CI of the healthiest category, and 3) all upper CIs by the upper CI of the healthiest category. This then requires swapping the upper and lower CIs because transformed lower CIs become upper CIs.'*

1. Articles excluded if not in English: we understand that this is common practice in many reviews (albeit PRISMA recommends that articles are not excluded based on language only to avoid biases). However, given that (a) only two papers were not in English, (b) two more papers could be a valuable contribution to the review, given that only six could have been included, (c) these two papers are likely to come from low- or middle-income countries, increasing the diversity of the evidence based analysed, and (d) there are options available to get support with non-English articles (e.g., translation tools, colleagues who speak other languages than English, and Translators without Borders - https://translatorswithoutborders.org/), assessing the eligibility of these two papers based on the PECO criteria and including them in the review if relevant seems like a missed opportunity.

We thank the reviewer for their suggestion of arranging translations for these 2 papers. We were not aware of freely available high quality translation tools but this is certainly something we can use in the future. We agree that adding more diverse studies would be of benefit. However, unfortunately, we currently do not have the human resources to investigate free and quality translation tools to then translate, review, and or synthesise these studies into our review.

1. In Table 1, for the second to last study presented (Choi *et al.*, 2022), the lifestyle factors for "ii" appear as separate due to an additional return:

   "ii) weekly alcohol intake >14 drinks
   for men, >7 drinks for women ..."

   Could the authors check, please?

Thank you. This was a formatting error, which we have corrected.

1. Figures 2 and 3: the x-axis should be in logarithmic scale to ensure visual symmetry between values below and above 1 that indicate the same effect size (e.g., 0.5 and 2).

We thank the reviewer for this suggestion. We have altered the x-axes to logarithmic scales. We hope this makes them more interpretable for readers.

1. Figure 2: estimates for Choi 2020 do not have the confidence interval. Could author check if it is unintentionally missing?

This is correct. Unfortunately, confidence intervals are not provided for all the results in their manuscript. Instead, whether or not it was significant (p<0.05) was indicated.

1. Figure 3: the Eguchi 2017's analysis for non-CVD, non-cancer mortality seems to be outside the scope of the review, based on its objectives and PECO criteria. The authors should consider removing it from the article.

The reviewer is correct, and we have removed that data and corresponding results from the figures and manuscript. We have made this clear in the results section (lines 175-176): *'The non-CVD and non-cancer results are not reported here as they are outside the scope of this review.'*

1. Table S1: some terms seem to be duplicated within searches #2 (see *risk reduction behaviour*[tiab]* and *health behaviour[tiab]* with and without asterisks) and #3 (see *health inequalities[tiab]* and social-economic[tiab] with and without asterisk). This does not affect the results of the search but can be corrected for conciseness and clarity. Author might want to check whether the same occurred in Tables S2 and S3.

We thank the reviewer for pointing this out. There was an error because of autocorrect to UK English. We had searched using both American and UK English spellings of the word 'behaviour' (behavior). We have now corrected #1 in Table S1 to show that. With this correction, there is no duplication with both UK and American English spelling searched for in MeSH terms and in title/abstracts separately. We do not see any duplication in #3. We have also checked Table S2 and S3 and there is no duplication.

1. It seems Table S6 is cut short. Could the authors check, please?

We have checked the original downloadable version from figshare and Table S6 is complete but it does go over 2 pages. Perhaps this was causing an issue for the reviewer but it appears correct when we have downloaded a new version as a reviewer or reader would. We have also ensured the new corrected version uploaded onto figshare is also complete. OTHER POINTS: Background and Discussion The Background and Discussion sections would greatly benefit from the use of Sydemic Theory to substantiate the rationale for the study and discuss its findings. We thank the reviewer for their suggestion. We agree Syndemic Theory could be a helpful theoretical tool to examine synergy and additive interactions between LFs and SES. However, applying Syndemic Theory to our study somewhat presupposes the presence of synergistic or additive interactions between LFs and SES. Whereas our aim was to examine for the presence of these interactions. If evidence for LF-SES interactions is strengthened then Syndemic Theory could be a useful theoretical lens with which to examine and or explain those interactions.
[HF1]Check

Competing Interests: No competing interests were disclosed.