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Review

The combined effects of healthy lifestyle behaviors on all cause mortality: A systematic review and meta-analysis

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ABSTRACT

Objective. Lifestyle factors are related to mortality. Although much is known about the impact of single factors, the current evidence about the combined effects of lifestyle behaviors on mortality has not yet been systematically compiled.

Method. We searched Medline, Embase, Global Health, and Somed up to February 2012. Prospective studies were selected if they reported the combined effects of at least three of five lifestyle factors (obesity, alcohol consumption, smoking, diet, and physical activity). The mean effect sizes that certain numbers of combined lifestyle factors have on mortality were compared to the group with the least number of healthy lifestyle factors by meta-analysis. Sensitivity analyses were conducted to explore the robustness of the results.

Results. 21 studies (18 cohorts) met the inclusion criteria of which 15 were included in the meta-analysis that comprised 531,804 people with a mean follow-up of 13.24 years. The relative risks decreased proportionate to a higher number of healthy lifestyle factors for all cause mortality. A combination of at least four healthy lifestyle factors is associated with a reduction of the all cause mortality risk by 66% (95% confidence interval 58%–73%).

Conclusion. Adherence to a healthy lifestyle is associated with a lower risk of mortality.

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Introduction

The risk of developing a major non-communicable disease, the leading cause of death in the world, is decisively affected by lifestyle choices (WHO, 2011a). Smoking, physical inactivity, unhealthy diet, obesity and other lifestyle behaviors are associated with the development of diseases such as cancer, heart disease, stroke, and diabetes (Lopez et al., 2006).

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In the United States, adherence to a healthy behavior in relation to the above factors decreased between 1988 and 2006: obesity in adults has increased from 28% to 36%, smoking rates have not changed, the consumption of five or more portions of fruit and vegetables a day has dropped from 42% to 26%, and the adherence to all five healthy habits decreased from 15% to 8% (King et al., 2009). The societal and monetary costs of the negative effects of these modifiable behaviors are huge (Scarborough et al., 2011). While many studies have investigated the effects of single lifestyle behaviors on health (Adams et al., 2006; Doll et al., 2000; Hung et al., 2004; Warburton et al., 2006), the minimization of the individual risk of disease might only be achieved by a combination of these behaviors. In the last decade, several cohorts have been examined for the combined effects of lifestyle factors on various outcomes.

Therefore we conducted a systematic review and a meta-analysis of prospective studies in order to quantitatively assess the association between the number of lifestyle habits (smoking, diet, physical activity, alcohol consumption, body mass index (BMI)) and all cause mortality.

Methods

Data Sources and Searches

We searched the following databases, from their onset up to February 2012, for studies that reported on the effects of single and combined health behaviors on morbidity or mortality: Embase, Global Health, Medline, and Somed. Three search themes were combined for this purpose. The themes covered the terms (1) *combined effects*, *combined**, *combination*, *integrated**, *joint effects*, *merged effects* and (2) *lifestyle*, *health factor*, *healthy lifestyle*, *healthy behaviors*, *low risk*, *protective factors*, *prevention guideline* and (3) *mortality*, *death*, *survival*, and *life expectancy*.

We adapted the terms used in the search process to the requirements of the individual databases and optimized each database search by testing different combinations. An example of a search history is shown in the supplement.

Study Selection

The inclusion criteria were that: (1) it was a longitudinal study with a minimum of 12 months of follow-up, (2) the participants were healthy at baseline; (3) the study reported relative risks or hazard ratios of the association between all cause mortality and the combination of at least three of the following lifestyle behaviors: not smoking, normal weight, healthy diet, appropriate physical exercise, moderate alcohol consumption. The study selection was performed by two researchers. Disagreement was resolved by consensus. A kappa statistic was calculated for measuring the agreement between the researchers. selection (Orwin, 1994).

Data Extraction and Quality Assessment

The following information was extracted: study name, authors, publication year, number of participants, years of follow-up, mean age and sex of participants, main outcome, effect size for single factors, effect size for combined factors, and adjusted confounders for single and combined behaviors. The reporting followed the MOOSE group's recommendations (Stroup et al., 2000). One study provided average effect sizes based on four (without alcohol) and five (with alcohol) lifestyle behaviors (van Dam et al., 2008). The effect sizes based on the maximum number of lifestyle behaviors (in this case five) were included in our analysis. In the event of missing data, the authors of the original studies were contacted and asked for details (effect sizes and confidence intervals (Iversen et al., 2010)).

The quality was assessed by analyzing the statistical adjustment for potential confounders with a particular focus on socio-economic markers, the complete description of the study population, and the detailed information regarding the measurement of healthy lifestyle behaviors.

Data Synthesis

According to our definition, a "healthy lifestyle" included the following parameters: non-smoking (currently not or never), optimal weight (BMI 18.5–25 kg/m^2), physically active (ca. 3.5 hours/week), a healthy diet (upper percentage of a healthy diet score including fruit and vegetable consumption), and the moderate consumption of alcohol (5–15 g/d for women and 5–30 g/d for men). Please note that the details in the parentheses represent approximations of the heterogeneous definitions of the underlying studies (see Table 1).

Statistical analyses

Studies were included in the meta-analysis if they provided effect sizes and confidence intervals for at least three lifestyle factors (in addition to the reference value). We standardized the data by calculating the effect sizes for varying numbers of healthy behaviors (dichotomously coded as "present" or "absent") as average of all available factor combinations, in comparison to the group with the minimum number of healthy behaviors.

The minimum number of healthy behaviors was 0 healthy behaviors in most studies, 0–1 in five (Hamer et al., 2011; Knoops et al., 2004; Kurth et al., 2006; McCullough et al., 2011; Zhang et al., 2011), and 0–2 healthy factors in one study (Tamakoshi et al., 2009). The effect of this heterogeneity was addressed by the sensitivity analysis. In consequence, the effects of the number of significant lifestyle factors on the risk of mortality or morbidity were analyzed and therefore not restricted to the effects of distinct patterns of healthy lifestyle.

The adjusted effect estimates were extracted from the original results as hazard ratios (HR) or relative risks (RR) that were assumed to approximate the same measure. Because the divergence between RR and HR increases in proportion to the length of the study and the magnitude of the effect size (Symons and Moore, 2002), we addressed a possible underestimation of the real effect by our calculation in the sensitivity analysis. We applied the natural logarithms of these values and calculated the standard errors based on 95% confidence intervals.

The effect sizes were pooled using DerSimonian and Laird random effect models if there were more than three studies, and study heterogeneity was high ($I^2>25$) (Higgins and Thompson, 2002). Otherwise fixed effect models were applied. A potential publication bias was assessed by visual inspection of funnel plots (Egger et al., 1997). Statistics were performed with RevMan 5.1 and SPSS.

We conducted sensitivity analyses by the combinatorial exclusion of studies in the meta-analysis in order to explore sources of heterogeneity in potential combinations of lifestyle factors. For this purpose, studies were grouped according to lifestyle factor combinations (e.g. all studies comprising moderate alcohol consumption as health behavior) or methodological aspects (e.g. 0 factors as reference level vs. 0–1 factors).

Results

Twenty one studies (18 cohorts) met the inclusion criteria (Byun et al., 2010; Chakravarty et al., 2012; Ford et al., 2009, 2011; Gopinath et al., 2010; Hamer et al., 2011; Haveman-Nies et al., 2002; Iversen et al., 2010; Khaw et al., 2008; King et al., 2007, 2011; Knoops et al., 2004; Kvaavik et al., 2010; Matheson et al., 2012; McCullough et al., 2011; Nechuta et al., 2010; Rhee et al., 2012; Tamakoshi et al., 2009; Tsubono et al., 2004; van Dam et al., 2008; van den Brandt, 2011) , of which 15 could be included in the meta-analysis (see Fig. 1). The kappa-value was k = 0.63.

Out of the 15 studies included in the meta-analysis, five had been conducted in the United States, seven in Europe, one in China and two in Japan. The cohorts comprised 531,804 participants and the studies' mean follow-up was 13.24 years (7.8–24). All studies covered at least three of the following five lifestyle factors: moderate consumption of alcohol, not being overweight or obese, not smoking, healthy diet, regular physical exercise (see Table 1). The weighted mean shares of subgroups with 0/ 1/ 2/ 3/≥4 healthy behaviors are 4% ± 1%, 16% ± 1%, 30% ± 2%, 29% ± 2%, 21% ± 1% for men and women combined.

The meta-analysis including 15 studies (Byun et al., 2010; Ford et al., 2009, 2011; Gopinath et al., 2010; Hamer et al., 2011; Iversen et al., 2010; Khaw et al., 2008; Knoops et al., 2004; Kvaavik et al., 2010; McCullough et al., 2011; Nechuta et al., 2010; Tamakoshi et al., 2009; Tsubono et

Table 1
Details of the studies included in the meta-analysis.

Ref.	Study characteristics	Definition of low/high risk lifestyle	Adjusted cofounders
van den Brandt (2011)	NLCS, n=120,852 (58,279 men, 62,573 women), age: 55–69, follow-up: up to 10 years	Not currently smoking, physically active (on average, 30 min/day), BMI: 18.5 to 25.0 kg/m2, having an aMED score of 5–9 points	Age, history of hypertension, education, energy intake
Byun et al. (2010)	ACLS; n=38,110 men (2642 deaths), age: 20–84, follow-up: 16 years	Not currently smoking, being physically active (no activities in the previous 3 months: physically inactive), exhibiting moderate to high CRF (top two-thirds of CRF), BMI: 18.5 to 25.0 kg/m2, moderate alcohol consumption (1–14 drinks per week)	Age, examination year, hypertension, diabetes, hypercholesterolemia
van Dam et al. (2008)	Nurses' health study, n=77,782 women (34–59), follow-up: 24 years	Never smoking, ≥30 min/day of at least moderate activity, diet in top 2 quintiles of the specified dietary score, BMI: 18.5 to 25 kg/m2, and moderate alcohol consumption (5 to 15 g alcohol/day)	Age, time period, alcohol consumption
Ford et al. (2009)	EPIC Potsdam study, n=23,153 (8965 men and 14,188 women), age: 35–65, follow-up: 7.8 years	Never smoking, engaging in physical activity for 3.5 h/week or more, BMI ≤30, and healthy dietary pattern (above the median of the summed z scores)	Sex, educational status, occupational status
Ford et al. (2011)	National Health and Nutrition Examination Survey III Mortality Study, n=16,958 (7928 men, 9030 women), age:17+, follow-up: up to 18 years	Never smoking, physical activity: moderately or vigorously active (≥3 times per week active with a metabolic equivalent level of ≥6 (7) for those aged ≥60 (≤60) years), diet: top 40% of the Healthy Eating Index, alcohol: men ≤60 drinks per month, but ≥0 drinks, women ≤30 drinks per month, but ≥0 drinks	Age, gender, race or ethnicity, education
Gopinath et al. (2010)	The Blue Mountains Eye Study, n=3654, age: 49+, follow-up: 15 years	Similar methods to define health behaviors as detailed by Kvaavik et al. (Physical activity measures included not only exercise during leisure time but also other activities. Poor physical activity was defined as less than 3 times per week.)	Age, sex, occupational prestige, BMI, blood pressure, different diseases
Hamer et al. (2011)	National Diet and Nutrition Survey (UK), n=1062 (539 men, 523 women), age: 65–99, follow-up: 9.2 years	Nonsmoking, moderate alcohol consumption (1–21 units for men, 1–14 units for women), regular moderate to vigorous physical activity, vitamin C in blood ≥50 mU	Age, sex, education, self-rated health, BMI
Iversen et al. (2010)	Royal College of General Practitioners' Oral Contraception Study, n=10,059 women, age: 56.1 (SD=0.5), follow-up: 11.8 years	Never smoking, physical activity >28 h per week (EPIC physical activity questionnaire), moderate alcohol consumption (<7 units of alcohol per week), normal BMI	Age, social class, parity, and history of serious illness
Khaw et al. (2008)	EPIC-Norfolk Prospective Population Study, n=20,244, age: 45–79, follow-up: 11 years	Not currently smoking; physical activity: not inactive (if sedentary occupation, ≥ half an hour of leisure time activity/day) ≥5 servings of fruit and vegetable/day (indicated by blood vitamin C ≥50 nmol/l), alcohol intake: ≥1 unit; ≤14 units (1 unit=8 g of alcohol)	Age, sex, BMI, social class
Knoops et al. (2004)	HALE Project - 2 cohorts: SENECA and FINEm n=1507 men; n=832 women (70–90); follow-up: 10 years	Not currently smoking, physical activity: Individuals with a score in the intermediate and the highest tertile on the Voorrips or Morris questionnaire , dietary intake: score of at least 4 on a modified version of the Mediterranean diet score, alcohol: ≥0 g of alcohol/day.	Other dietary and lifestyle factors, age, sex, number of years of education, body mass index, study
Kvaavik et al. (2010)	Health and Lifestyle Survey (HALS), n=4886, mean age=43.7 (16.3), follow-up: 20 years	Poor health behavior: being a current smoker, poor physical activity behavior: spending little or no time on exercise activities (<120 min during 1 week). Poor dietary behavior: having fruits and/or vegetables less than 3 times daily, drinking: ≥21 U (14 U) per week for men (women)	Age, sex, occupational social class, body mass index, blood pressure, hypertension, different diseases
McCullough et al. (2011)	Cancer Prevention Study-II Nutrition Cohort, n=11,1966 (50,727 men, 61,239 women) (16,982 deaths), age: 50–74, follow-up: 14 years	BMI: 18.5 to 25 kg/m2, physical activity: MET-hours/week less than 8.75 received a score of 0, 8.75 to <17.5 (=score of 1), >17.5 MET-hours (=score of 2), diet: 3–6 (7–9) on 9-point diet score were given a score of 1 (2), alcohol: nondrinkers = score of 1, women (men) with 1 drink/day (1 or 2 drinks/day) = score of 2.	Age, smoking status, education
Nechuta et al. (2010)	Shanghai Women's Health Study, n=71,243, age: 40–79, follow-up: 9.1 years	Calculation of lifestyle score: Model 1: BMI [18.5; 24.99], WHR (waist divided by hip circumference) Tertile 1, Exercise participation (MET hours/day) ≥2, Spouse never smokes, Fruit and vegetable daily intake (g) Tertile 3, ≥626.5 g/day	Age, education, occupation, income
Tamakoshi et al. (2009)	Japan Collaborative Cohort (JACC) Study, n=62,106 (27,582 men, 34,524 women); age: 40–79, follow-up: 12.5 years	Not currently smoking, drinking no more than 1 gou per occasion or not currently drinking, walking 1 h or more per day, sleeping 6.5 to 7.4 h per day, eating green-leafy vegetables almost daily, BMI: 18.5 to 24.9.	Age categories, education, stress, marital status, consumption of green-leafy vegetables, different diseases
Tsubono et al. (2004)	Miyagi Cohort Study, n=47,605 (25,279 men, 26,642 women), age: 40–64; follow-up: 11 years	Never smoking, physical activity: walking >1 h/day, BMI: 18.5–30, moderate alcohol consumption (<22,8 g/day)	Age, education, marital status, hypertension, different diseases, consumption of green vegetables and oranges

al., 2004; van Dam et al., 2008; van den Brandt, 2011) on the association between one, two, three, and four or more healthy lifestyle factors on all cause mortality compared to the minimum number of healthy lifestyle behaviors leads to the following relative risks: $RR_1=0.72$ (confidence interval 95% 0.65–0.8), $RR_2=0.58$ (CI 95% 0.49–0.67), $RR_3=0.46$ (CI 95% 0.38–0.55), and $RR_4=0.34$ (CI 95% 0.27–0.42), respectively. Fig. 2 shows the meta-analyses on the association between at least four healthy lifestyle factors and all cause mortality.

The studies' variation in terms of lifestyle definition and analysis may be reflected by the high statistical heterogeneity with $I^2 \geq 70\%$ for all meta-analyses. Therefore, studies were grouped according to methodological differences and then compared in the sensitivity analysis (see Supplement Table 1 for details). As one would expect, studies in which the number of healthy behaviors were compared to 0–1 healthy behaviors (Hamer et al., 2011; Knoops et al., 2004; McCullough et al., 2011; Tamakoshi et al., 2009) four or more healthy

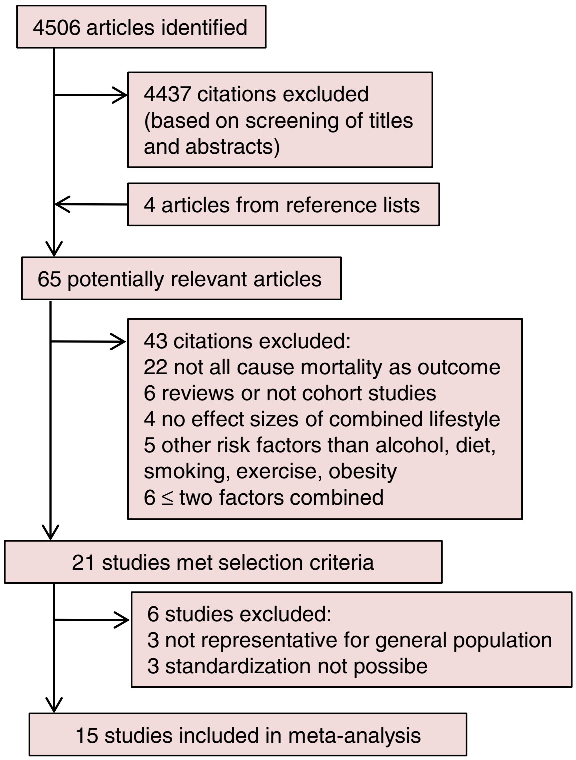


Fig. 1. Flow chart of the selection process.

factors showed a weaker effect (RR_4 = 0.5 (95% CI 0.41–0.62) than those compared to 0 factors (RR_4 = 0.29 (0.24–0.36)); however, there were neither significant differences for two or three factors nor for the trend. Studies which included BMI as a lifestyle behavior (Byun et al., 2010; Ford et al., 2009; McCullough et al., 2011; Nechuta et al., 2010; Tamakoshi et al., 2009; Tsubono et al., 2004; van Dam et al., 2008; van den Brandt, 2011) did not differ from those that did not for any number of healthy lifestyle factors (RR_4 = 0.31 (95% CI 0.24–0.41) vs. RR_4 = 0.36 (95% CI 0.27–0.48). Furthermore, the exclusion of single studies which did not include tobacco usage (McCullough et al., 2011), a healthy diet (Byun et al., 2010; Tsubono et al., 2004), or alcohol (Nechuta et al., 2010; van den Brandt, 2011) as a factor in the spectrum of lifestyle habits had no significant impact on the pooled effect sizes. A subgroup analysis for women (McCullough et al., 2011; Nechuta et al., 2010; Tamakoshi et al., 2009; van Dam et al., 2008; van den Brandt, 2011) and men (Byun et al., 2010; McCullough et al., 2011; Tamakoshi et al., 2009; van den Brandt, 2011) showed no gender differences (*women*: RR_4 = 0.46 (0.36–0.66); *men*: RR_4 = 0.49 (0.38–0.62)).

The funnel plots are displayed in the Supplementary Fig. 1. Based on visual analysis it can be seen that the plots of the different meta-analyses are quite different although they are based on the same studies. A conclusion on the absence of a publication bias cannot be drawn as none of them are symmetrical.

Discussion

This meta-analysis has quantitatively shown that the number of healthy lifestyle behaviors, which people adopt, is inversely related to the risk of all cause mortality. Compared with individuals who have an unhealthy lifestyle (smoking, no or excessive alcohol consumption, no physical exercise, unhealthy diet, obese), those with four or more healthy behaviors have an overall risk of mortality that is lower by 66%.

The present study is robust due to the very large sample sizes and long follow-ups of the underlying investigations. The multiple sensitivity analyses showed that effect sizes remained equal in subgroups of studies that were more homogenous in their definition of a healthy lifestyle or methodological aspects. All studies consistently found that the number of lifestyle behaviors adopted is associated with a decreased risk of mortality.

A meta-analysis of prospective studies might represent the most accurate source of evidence currently available because randomized controlled trials, in which multiple lifestyle factor are modified, are limited by low adherence (Ebrahim et al., 2011) and prohibitive costs.

However, the results should be viewed in the light of some limitations. First, there might be a selection bias, although we tried to minimize this source of bias by the double review process. Based on the visual inspection of all funnel plots we cannot rule out that a publication bias influences our results, although it is unlikely that large epidemiological studies remained unpublished due to their high costs and, usually, public funding source. Additionally, although all studies in the meta-analysis provided detailed information on the patient characteristics, the statistical analysis and how they measured a healthy lifestyle, a further potential bias is that they might not have adjusted for socio-economic status parameters as relevant confounders (Byun et al., 2010; van Dam et al., 2008) (see Suppl. Table 2).

Second, the measurement of the grading of healthy lifestyle by the number of behaviors is based on the application of dichotomized values of lifestyle factors (e.g. upper two quintiles of a diet score). These data imply a fluctuation margin that is not covered by the displayed confidence intervals. Another bias which may result in underestimation might arise from studies that compared numbers of healthy behaviors with 0–1 healthy behaviors instead of 0 healthy behaviors. Please note, however, that these inaccuracies work towards a more conservative estimate of the effects.

Third, there have been substantial heterogeneities between the studies derived in part from the different numbers and combinations of lifestyle factors in the studies. Our sensitivity analysis, however, showed that the pooled effect sizes for studies grouped according to (a) the inclusion of certain factors, (b) the number of lifestyle factors, and (c) the reference groups, do not significantly differ from the synoptic meta-analysis. Neither our analysis nor the underlying studies revealed significant differences in the association between certain factor combinations and the risk of mortality. This supports the meta-analytic approach and might suggest that the degree of a healthy lifestyle is more relevant for health than the distinct manifestation of certain behavioral patterns. This could be further examined by meta-analysis based on individual patient data.

Fourth, there is still no scientific consensus as to how to define a healthy behavior in relation to physical exercise or what nutritional components constitute a healthy diet. In consequence, the underlying studies also show differences in the cut-off points of how healthy behavior is defined for both factors. For instance, Ford et al. (2011) defined a healthy level of physical activity as being moderately or vigorously active or, in more detail, exercising at least three times per week with a metabolic equivalent level of at least six for those aged 60 years or above (Ford et al., 2011). Another group deemed those who spend at least 120 minutes on exercise activities per week to have a healthy level of physical activity (Kvaavik et al., 2010). In consequence, the meta-analysis incorporates some variability within such terms, consistent with the varability in the general recommendations on healthy diet and physical activity.

Another limitation which should be kept in mind is that approximately 20% of the studies included had been conducted in Asia and none in Africa and Australia: The meta-analysis is dominated by European and US-American cohorts. Some of these comprised participants with a high socio-economic status, such as the Aerobics Center Longitudinal Study (ACLS) or the Nurses' Health Study. Consequently, the average percentage of participants in the groups with 0, 1, 2, 3, ≥4 lifestyle habits may not represent the actual distribution of health behavior in the US- or other Western-country-populations (King et al., 2009; Reeves and Rafferty, 2005).

Seven studies were not integrated because they analyzed subgroups such as new adopters of a healthy lifestyle (King et al., 2007), people with a normal blood pressure, LDL cholesterol, and C-reactive protein (King et al., 2011), and obese people (Matheson et al., 2012). If, as in the Atherosclerosis Risk in Communities (ARIC) study, middle-aged people newly adopted a healthy lifestyle, there was a 40% reduction of all cause mortality within four years (King et al., 2007). Some studies were not included in the meta-analysis because the authors calculated health risk scores which included socio-economic surrogates and thus could not be compared with the other studies (Rhee et al., 2012) or because the analysis hampered an inclusion into the meta-analysis (Chakravarty et al., 2012). Two studies failed to provide confidence intervals or average effect sizes of numbers of healthy lifestyle behaviors on mortality (Chakravarty et al., 2012; Haveman-Nies et al., 2002) and could therefore not be included into to meta-analysis. In addition, some publications related to cohorts that were already covered by our meta-analysis through other studies. The Seneca cohort is included in the Hale Project (Knoops et al., 2004), but was separately interpreted taking a closer look at certain combinations of lifestyle behaviors (Haveman-Nies et al., 2002). Data from the US National Health and Nutrition Examination Survey III is included in the meta-analysis (Ford et al., 2011), but has also been analyzed with a focus on the lifestyle effects in different BMI-classes (Matheson et al., 2012) and people with normal blood pressure, LDL cholesterol and C-reactive protein (King et al., 2011).

Evidence for the effects of a healthy lifestyle is also provided by further studies which were not included in the systematic review as these studies (a) examined people who were not healthy at baseline, (b) used the incidence of a disease or disease-specific mortality as an outcome, and (c) defined a healthy lifestyle by other factors. For instance, a healthy lifestyle decreases the risk of mortality after stroke (Towfighi et al., 2011) and in people with diabetes type II (Nöthlings et al., 2010). Some studies measured a disease-specific mortality or

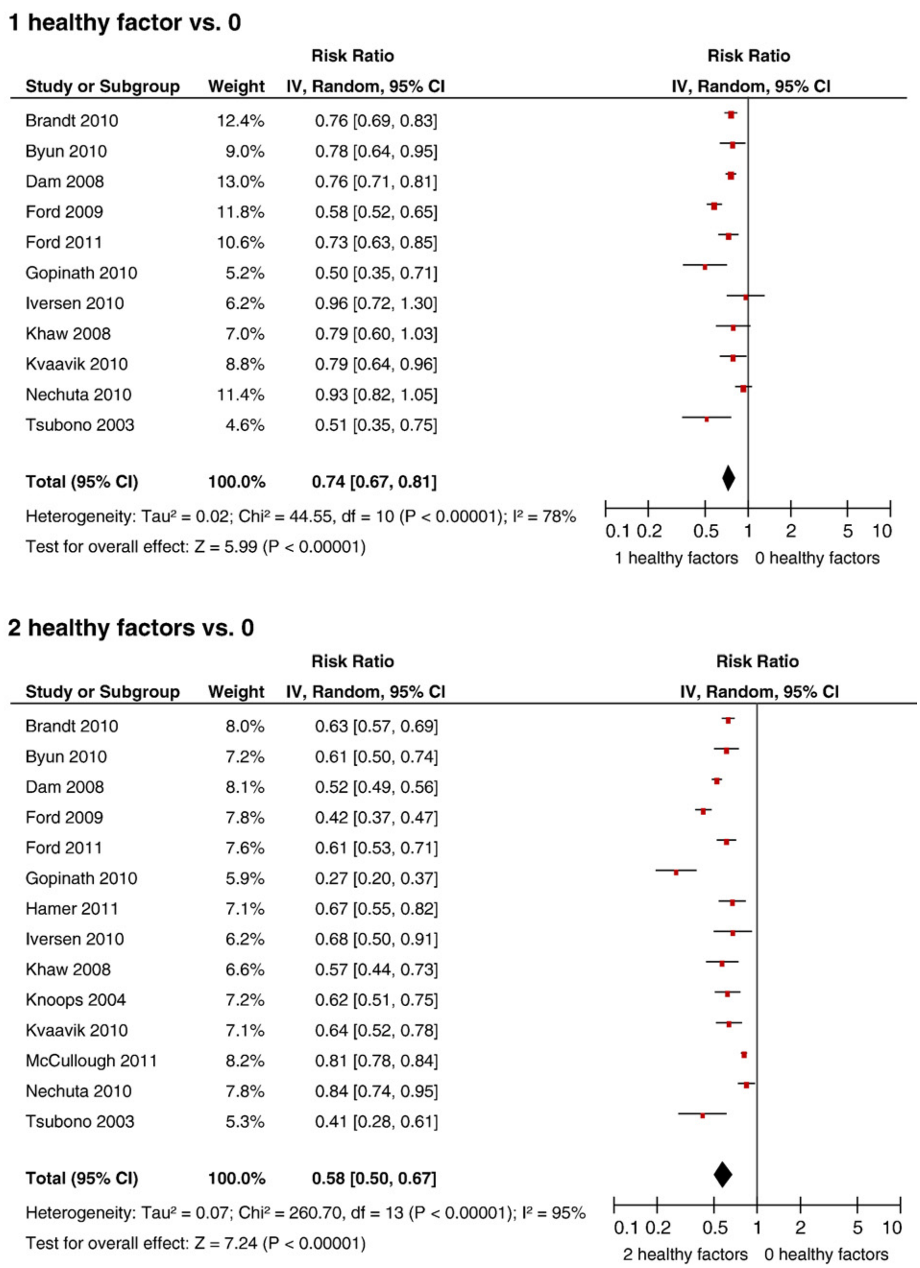
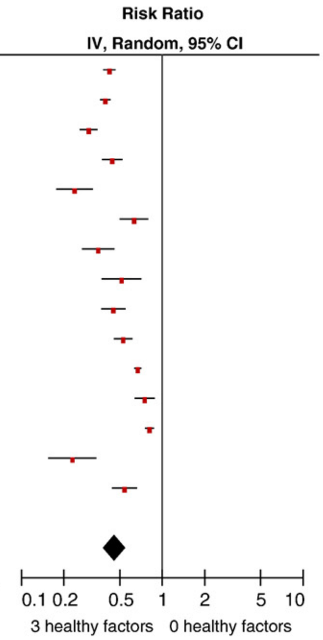


Fig. 2. Meta-analysis on the combined effects of 1 to ≥4 healthy lifestyles on all cause mortality compared to 0 factors (studies which referred to 0–1 factors are not included in the 1st meta-analysis). The studies are weighted by their inverse variances (IV). The model was a random effect meta-analysis (abbreviated as 'Random').

3 healthy factor svs. 0

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI
Brandt 2010	7.1%	0.42 [0.38, 0.46]
Byun 2010	7.2%	0.39 [0.37, 0.43]
Dam 2008	7.0%	0.30 [0.26, 0.34]
Ford 2009	6.9%	0.44 [0.38, 0.51]
Ford 2011	6.1%	0.24 [0.18, 0.32]
Gopinath 2010	6.5%	0.63 [0.50, 0.79]
Hamer 2011	6.3%	0.35 [0.27, 0.45]
Iversen 2010	5.9%	0.51 [0.37, 0.70]
Khaw 2008	6.7%	0.45 [0.37, 0.54]
Knoops 2004	6.9%	0.53 [0.46, 0.61]
Kvaavik 2010	7.2%	0.67 [0.64, 0.70]
McCullough 2011	6.9%	0.75 [0.64, 0.87]
Nechuta 2010	7.2%	0.81 [0.76, 0.86]
Tamakoshi 2009	5.5%	0.23 [0.16, 0.34]
Tsubono 2003	6.7%	0.54 [0.44, 0.66]
Total (95% CI)	**100.0%**	**0.46 [0.38, 0.55]**

Heterogeneity: Tau² = 0.12; Chi² = 496.32, df = 14 (P < 0.00001); I² = 97%
Test for overall effect: Z = 8.46 (P < 0.00001)



≥ 4 healthy factor svs. 0

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI
Brandt 2011	7.5%	0.30 [0.27, 0.33]
Byun 2010	7.4%	0.41 [0.36, 0.47]
Dam 2008	6.7%	0.27 [0.20, 0.36]
Ford 2009	7.0%	0.23 [0.18, 0.29]
Ford 2011	6.8%	0.37 [0.28, 0.49]
Gopinath 2010	5.0%	0.22 [0.12, 0.39]
Hamer 2011	6.8%	0.49 [0.37, 0.65]
Iversen 2010	4.5%	0.13 [0.07, 0.25]
Khaw 2008	6.9%	0.20 [0.16, 0.26]
Knoops 2004	7.1%	0.35 [0.28, 0.44]
Kvaavik 2010	6.3%	0.29 [0.20, 0.41]
McCullough 2011	7.6%	0.58 [0.54, 0.62]
Nechuta 2010	6.9%	0.57 [0.44, 0.74]
Tamakoshi 2009	7.3%	0.60 [0.50, 0.71]
Tsubono 2004	6.1%	0.16 [0.11, 0.24]
Total (95% CI)	**100.0%**	**0.32 [0.26, 0.40]**

Heterogeneity: Tau² = 0.16; Chi² = 250.72, df = 14 (P < 0.00001); I² = 94%
Test for overall effect: Z = 10.08 (P < 0.00001)

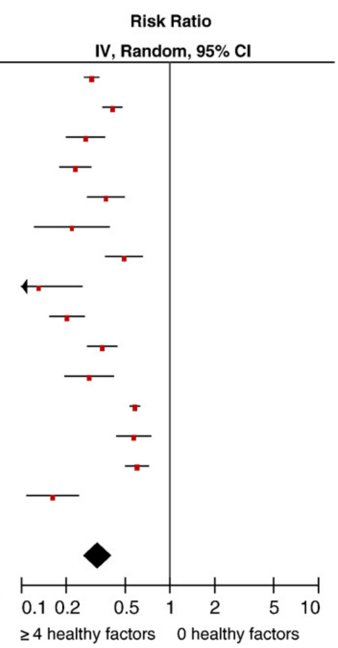


Fig 2. *(continued)*.

the incidence of a chronic disease. A combination of healthy lifestyle factors is associated with a lower cancer incidence and mortality, particularly in subtypes such as colorectal cancer (Kirkegaard et al., 2010) or pancreatic cancer (Jiao et al., 2009). It is related with a reduction of the risk of coronary heart disease (Chiuve et al., 2006), stroke (Chiuve et al., 2008), diabetes (Hu et al., 2001), and dementia (Gelber et al., 2012). This is also true in cases where other indicators of a healthy lifestyle have been selected such as, for example, the combination of hypercholesterolemia, hyperglycemia, smoking, and obesity, which has been shown to predict the mortality risk of cardiovascular diseases in a petroleum industry cohort (Tsai et al., 2009). What is the equivalent of the effect sizes in years and quality of additional lifetime? Adherence to a combination of healthy lifestyle factors increases the life expectancy at age 40 by approximately nine years (Tamakoshi et al., 2010), and more than triples the probability of survival to oldest-old age (Willcox et al., 2006) compared to low or non adherence.

The selected study of King et al. (2007) suggests an effect on mortality rates of a newly adopted healthy lifestyle within only four years, which supports the promotion of a healthy lifestyle throughout the lifetime (King et al., 2007).

Despite minor variations as described previously, the healthy lifestyle factors correspond roughly to the well known WHO criteria (WHO, 2011b) in which a weight balance in the range of 18.5–24.99 kg/m^2, a minimum of 150 min moderate to vigorous physical activity per week, healthy nutrition such as the Mediterranean diet or regular eating of fruit and vegetables, no consumption of tobacco, and moderate intake of alcohol are all behavioral components that increase the maintenance of health.

However, less than a fourth of the cohorts studied adhere to all factors. Hence, more than three quarters of the population have not really exhausted their potential to protect themselves from morbidity from these major life-style dependant diseases, and thus put strain on their lives, their economic circumstances and the public health sector. It is a major task for public health education to discover how to motivate the population to contribute to their own health protection by adopting healthy lifestyles. Considering this potential, prevention and education programs should be made a high priority in public funding of research and in policy.

Future qualitative research could be helpful to determine effective ways of promoting healthy lifestyle options for the public and how controlled trials with multiple lifestyle interventions should be shaped in order to overcome low adherence. For tailoring future prevention programs to genetically distinct individuals, it might be important to better understand the interplay of genetic risk factors and the human environment including the lifestyle. Such knowledge might also help motivate individuals to change habits and adopt such lifestyles. In general, before embarking on experimental testing of the effects of lifestyle changes in randomized trials we should aim to understand the factors that prevent people from adopting these lifestyles and the benefits they gain from their unhealthy lifestyles. These might encompass a wide range of socio-economic, cultural and personal determinants resulting in individually different capabilities in adopting a healthy lifestyle (Abel and Schori, 2009). If this is the case, then randomizing such people to groups with and with no change in the lifestyle within the context of a trial might result in a bias and hinder a true reflection of whether the lifestyle modification is beneficial or is not.

In conclusion, we found that a combination of lifestyle-related behaviors, such as not smoking, drinking alcohol in moderation, eating healthily, regular exercise, and maintaining an optimal weight, is associated with a reduction in mortality by 66%. Our meta-analysis provides strong support for the further promotion of a healthy lifestyle by governments, foundations, and the World Health Organization. If people accepted the responsibility for their own health, the worldwide costs and burden of disease could be greatly reduced.

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Conflict of interest statement

Neither of the authors have a conflict of interest.

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