Combined Impact of Lifestyle Factors on Prospective Change in Body Weight and Waist Circumference in Participants of the EPIC-PANACEA Study

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Combined Impact of Lifestyle Factors on Prospective Change in Body Weight and Waist Circumference in Participants of the EPIC-PANACEA Study

Anne M. May1,2*, Dora Romaguera3, Noémie Travier4, Ulf Ekelund5, Manuela M. Bergmann6, Rudolf Kaaks7, Birgit Teucher7, Annika Steffen8, Heiner Boeing6, Jytte Halkjaer8, Anne Tjonneland8, Marianne Uhre Jakobsen9, Kim Overvad9,10, Laureen Dartois11,12, Guy Fagherazzi11,12, Marie-Christine Boutron-Ruault11,12, J. Ramón Quirós13, Antonio Agudo4, Carlos Gonzalez4, María-José Sánchez14,15, Pilar Amiano15,16, Jose-Maria Huerta15,17, Eva Ardanaz15,18, Nicholas J. Wareham5, Francesca L. Crowe19, Androniki Naska20,21, Philipppos Orfanos20,21, Antonia Trichopoulou20,21, Domenico Palli22, Claudia Agnoli23, Rosario Tumino24, Paolo Vineis3,25, Salvatore Panico26, H. Bas Bueno-de-Mesquita2,27, Monique Verschuren1,2, Isabel Drake28, Emily Sonestedt28, Tonje Braaten29, Sabina Rinaldi30, Isabelle Romieu30, Nadia Slimani30, Teresa Norat3, Elio Riboli3, Petra H. M. Peeters1,3

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Abstract

Background: The evidence that individual dietary and lifestyle factors influence a person’s weight and waist circumference is well established; however their combined impact is less well documented. Therefore, we investigated the combined effect of physical activity, nutrition and smoking status on prospective gain in body weight and waist circumference.

Methods: We used data of the prospective EPIC-PANACEA study. Between 1992 and 2000, 325,537 participants (94,445 men and 231,092 women, aged between 25–70) were recruited from nine European countries. Participants were categorised into two groups (positive or negative health behaviours) for each of the following being physically active, adherent to a healthy (Mediterranean not including alcohol) diet, and never-smoking for a total score ranging from zero to three. Anthropometric measures were taken at baseline and were mainly self-reported after a medium follow-up time of 5 years.

Results: Mixed-effects linear regression models adjusted for age, educational level, alcohol consumption, baseline body mass index and follow-up time showed that men and women who reported to be physically active, never-smoking and adherent to the Mediterranean diet gained over a 5-year period 537 (95% CI −706, −368) and 200 (−478, −87) gram less weight and 0.95 (−1.27, −0.639) and 0.99 (−1.29, −0.69) cm less waist circumference, respectively, compared to participants with zero healthy behaviours.

Conclusion: The combination of positive health behaviours was associated with significantly lower weight and waist circumference gain.
Introduction

General and abdominal adiposity are related to mortality and many adverse health-related outcomes, such as diabetes, cardiovascular diseases, and several types of cancer [1–4]. Maintaining a healthy body weight is therefore desirable. The evidence that individual modifiable lifestyle behaviours, such as physical activity, smoking and diet influence a person’s weight is well established [5–8]. In previous studies, we have investigated the association of each individual lifestyle behaviour separately and subsequent changes of weight and waist circumference in a large cohort of European adults participating in the EPIC-PANACEA (European Prospective Investigation into Cancer-Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating out of home And obesity) project received funding from the Public Health Programme of the European Union (2005328). EPIC was financially supported by the European Commission: Public Health and Consumer Protection Directorate 1993–2004; Research Directorate-General 2005—; Ligue contre le Cancer, Société 3M, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center, Federal Ministry of Education and Research (Germany); Danish Cancer Society (Denmark); Health Research Institute Carlos III (RETICC RD06/0020) from the Spanish Ministry of Health, the participating regional governments and institutions (Spain); Cancer Research UK, Medical Research Council, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, the Welcome Trust (United Kingdom); Hellenic Health Foundation, Stavros Niarchos Foundation and Greek Ministry of Health and Social Solidarity (Greece); Italian Association for Research on Cancer, National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports, Dutch Ministry of Health, Dutch Prevention Funds, UK Research Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF) (The Netherlands); Swedish Cancer Society, Swedish Scientific Council, Regional Government of Skane (Sweden); Norwegian Cancer Society (Norway). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

et al. [29] showed that weight gain was lowest in the participants with positive changes of diet and physical activity.

The aim of the present study was to investigate the combined effect of physical activity, smoking status, and diet on future weight and waist circumference gain by combining these behaviours into a simple health behaviour score in the large EPIC-PANACEA study.

Methods

From 1992–2000, in the EPIC study more than 500,000 individuals aged between 25 and 70 years were recruited from 23 centres in 10 countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) [30,31]. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and from local institutions.

Of the total cohort of 519,931 participants, we excluded 22,196 individuals because of missing dietary and non-dietary questionnaires, extreme energy intake to energy expenditure ratio, pregnant women, and missing baseline weight or extreme anthropometry. Furthermore, we excluded participants with missing follow-up weight (n = 121,853; this included the cohorts of Turin and Ragusa (both Italy) and parts of cohorts from Norway and Naples (Italy)) or extreme anthropometry at follow-up (i.e., weight change<–5 or >5 kg/year over several years (n = 1,926) or BMI<16 kg/m² at follow-up (n = 140)). Information on smoking, physical activity or dietary variables was not available for 48,279 participants. Physical activity was mainly missing because centres in Norway and Umea (Sweden) used different questionnaires to assess physical activity. Therefore, the final study population comprised 325,537 participants from nine countries.

A total of 88,972 participants from Florence (Italy), Potsdam (Germany), Doetinchem (Netherlands) and Cambridge (United Kingdom) also provided data on waist circumference at baseline and follow-up.

Anthropometric Measures

Baseline body weight (kg) and height (cm) were measured according to standardised procedures without shoes [32], except for the centres of Oxford (UK) and France where self-reported anthropometric values at baseline were used. Baseline waist circumference (cm) was measured either at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest. Weight and waist measurements were corrected to account
for protocol differences between centres as previously described [32]. Briefly, for subjects who were dressed normally and were without shoes, 1.5 kg for weight and 2.0 cm for circumferences were subtracted from the original measurement, whereas for subjects in light clothing without shoes, 1 kg was subtracted from the weight.

At follow-up, weight and waist circumference were self-reported in all centres except in Cambridge (UK) and Doetinchem (Netherlands) where it was measured according to the baseline protocol. BMI was calculated as body weight (kg) divided by height squared (m²). For descriptive purposes, the accuracy of self-reported anthropometric measures was improved with the use of prediction equations derived from subjects with both measured and self-reported values (i.e., the Oxford correction equations) [33].

As follow-up times between first and second anthropometry assessment differed by centre (2–11 years), our main outcome was the 5-year change (i.e. [follow-up weight or waist circumference - baseline weight or waist circumference]/years of follow-up)*5).

Health Behaviour Score
We investigated the combined effect of three lifestyle factors, that is physical activity, diet (according to a Mediterranean diet that is associated to weight change [12]) and smoking using a pragmatic health behaviour score. All lifestyle factors were assessed at baseline. Smoking status was also assessed at follow-up in a subpopulation of 288,167 participants.

Habitual physical activity was self-reported using a standardized questionnaire and a validated 4-category index was derived by cross-classifying three questions referring to activities during the last year against classification of work activity [34]. For the current purpose, we dichotomised the index into inactive (sedentary job and no recreational activity) and active (any category with activity levels above the latter).

Usual food intakes were measured using country-specific validated dietary questionnaires [30]. The modified Mediterranean Diet Score (mMDS) [35,36], which is a variant of the original MDS [37] and has an applicability in both Mediterranean and non-Mediterranean countries, was constructed as described elsewhere [11,36,37] with the exception that alcohol consumption was not included in the score. The mMDS scored the consumption of 8 components of the Mediterranean diet (high fruit, vegetable, legumes, fish, cereals, unsaturated to saturated fat ratio, and low meat & meat products and dairy products). The score could take a value from 0 (minimal adherence) to 8 (maximal adherence), and was further categorized as low (0–4 points) and high (5–8 points) adherence to the mMDS, based on the median consumption of each of the indicated components observed in the present population.

Information on smoking status (never, former, current) at recruitment was assessed with standard questionnaires. For the current purpose, participants were grouped in two categories: ever smokers (current and former) and never smokers. In a subpopulation of 288,167 participants also information on smoking status at follow-up was available [14].

We constructed a simple pragmatic health behaviour score. Participants could get one point for each health behaviour, i.e., physically active, high adherence to the mMDS and never-smoking for a total score ranging from 0–3. Comparable scores were previously used and were associated with reduced risk of major chronic diseases [15,17–26].

Covariates
Total amount of daily consumed alcohol over the last 12 months was assessed by country-specific validated dietary questionnaires [30] and summarized as non-consumers, 1–6 g/day, 7–18 g/day, 19–30 g/day, 31–60 g/day, and >60 g/day (women) and 61–96 g/day and >96 g/day (men). Total energy intake was computed from the dietary questionnaire. The educational level (none, primary school, technical school, secondary school, and university degree) was used as a proxy for socioeconomic status. Information on the presence of chronic diseases (heart disease, stroke, diabetes mellitus, and cancer) before or at recruitment was assessed by questionnaire.

Statistical Analyses
Baseline characteristics of the study population are presented by health behaviour score and gender by using mean and standard deviation for continuous variables and percentages for categorical variables.

Associations between the health behaviour score and 5-year weight and waist circumference changes were modelled using sex-specific multilevel random mixed-effects linear regression, taking clustering of participants within countries and centres into account. Analyses were adjusted for age (years, continuous), follow-up time (years, continuous), baseline BMI (kg/m², continuous), education (categorical), total energy intake (kcal, continuous), and alcohol intake (categorical). The model with 5-year waist circumference change as the outcome was additionally adjusted for baseline waist circumference (cm, continuous) and in a second model also for BMI change (continuous) for estimation of the relationship between the health behaviour score and waist circumference change independently of changes of general obesity.

Plausible effect modification by age (<60 and ≥60 years of age), baseline BMI (<25, 25–30 and ≥30 kg/m²), and education were explored by adding a product term. Stratified analyses were conducted when the product term was significant.

Random-effect meta-analysis was used to assess whether there was heterogeneity among countries. Country specific estimates were calculated by using general linear models in countries with one centre only and multilevel mixed-effects models in countries with more than one centre.

Sensitivity analyses were performed by excluding participants with chronic diseases at baseline as well as participants who quit smoking during follow-up. Furthermore, we included never smoking as the health behaviour in the score. Since never smoking is a non-modifiable factor and current smokers can only revert to former smokers, we repeated our main analyses including smoking as non-current (1 point) and current (0 point) in the health score.

Results were computed using SAS 9.2. STATA 11 was used for the meta-analyses.

Results
In the current population, mean (standard deviation) 5-year weight gain was 0.71 (5.14) kg; when we applied the Oxford correction equations to improve the accuracy of the self-reported measurements, 5-year weight gain was 2.08 (5.07) kg. Five-year increase in waist circumference was 3.80 (6.42) cm (uncorrected) and 6.17 (6.40) cm (corrected). A total of 11.2% of men and 19.3% of women were scored to have all three health behaviours at study recruitment (Table 1). These men and women were on average younger, higher educated and had a lower alcohol intake, while their crude energy intake was higher in comparison to the participants who reported no health behaviours.
In most countries, the associations between the health behaviour score and anthropometry changes between countries was assessed using the meta-analysis approach (Appendix Figures S1, S2, S3, S4). For men, no heterogeneity was present (p for heterogeneity > 0.05). For women a significant degree of heterogeneity was found for the association with weight change. However, results were similar for women aged below or above 60 years (data not shown).

Heterogeneity in the association between the health behaviour score and anthropometry changes between countries was assessed using the meta-analysis approach (Appendix Figures S1, S2, S3, S4). For men, no heterogeneity was present (p for heterogeneity > 0.05). For women a significant degree of heterogeneity was found for the association with body weight and (I^2 = 60.7% (p = 0.002)) waist circumference change (I^2 = 62.0% (p = 0.033)).

For changes of weight and waist circumference, significant interactions were found between the health behaviour score and baseline BMI, except in women when waist circumference change was the outcome. Stratified analyses showed that the relationship between the score and weight change was stronger for people with normal weight (BMI < 25) and less obvious for obese people (BMI ≥ 30) (Table 4). The relationship with waist circumference change was more consistent for all BMI categories, with largest gain in obese women. No significant interactions between age or education and the health behaviour score were observed, except for younger and older women and weight change. However, results were similar for women aged below or above 60 years (data not shown).

Table 2 shows the independent effects of the individual health behaviours. Participants who were physically active, never-smoking, or highly adherent to the mMDS had on average a lower 5-year weight gain compared to people who were inactive, smoking or low adherent to the mMDS. However, relations were only significant for never-smoking and low mMDS adherent men or for physically active women. Five-year gain in waist circumference was lower for people who were physically active, never-smoking, and for women reporting high mMDS scores.

Table 3 shows the adjusted relationships between the health behaviour score and 5-year weight and waist circumference change. For each unit increase in the score, men and women gained significantly less weight and waist circumference (all p-values for trend < 0.0001). Compared to those with zero health behaviour, men who reported all three health behaviours gained 200 grams (0.986 cm (95% confidence interval: 0.68; 2.30 cm) less weight and 0.93 cm (2.37; 4.96) less waist circumference. Women with three health behaviours gained 200 grams (2.08; 4.37) less weight and 0.90 cm (2.37; 4.96) less waist circumference, respectively. Additional adjustment for simultaneous change of BMI in the model with waist circumference change as the outcome only slightly attenuated the results (0.69 cm (0.95; -0.42) and -0.60 cm (-0.93; -0.42) for men and women with three health behaviours versus zero, respectively (both p-values for trend < 0.0001)).
Table 2. Independent association between individual health behaviours and weight change (kg/5 y) and waist circumference change (cm/5 y) in EPIC-PANACEA participants.

<table>
<thead>
<tr>
<th></th>
<th>Weight change (kg/5 y)</th>
<th>Waist circumference change (cm/5 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ß 95% CI</td>
<td>ß 95% CI</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical active vs inactive</td>
<td>−0.073 (−0.158; 0.012)</td>
<td>−0.465 (−0.619; −0.311)</td>
</tr>
<tr>
<td>Never smoker vs ever smoker</td>
<td>−0.335 (−0.405; −0.266)</td>
<td>−0.469 (−0.589; −0.350)</td>
</tr>
<tr>
<td>High adherence to mMDS vs low adherence</td>
<td>−0.090 (−0.175; −0.005)</td>
<td>−0.047 (−0.093; 0.186)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical active vs inactive</td>
<td>−0.078 (−0.129; −0.026)</td>
<td>−0.276 (−0.419; −0.133)</td>
</tr>
<tr>
<td>Never smoker vs ever smoker</td>
<td>−0.018 (−0.061; 0.028)</td>
<td>−0.413 (−0.526; −0.306)</td>
</tr>
<tr>
<td>High adherence to mMDS vs low adherence</td>
<td>−0.031 (−0.078; 0.016)</td>
<td>−0.234 (−0.375; −0.102)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI – confidence interval, mMDS – modified Mediterranean Diet Score.

1 Linear mixed models adjusted for age, total energy intake, baseline body mass index, education, alcohol intake and follow-up time (men: n = 94,445; women n = 231,092). Individual health behaviours are also adjusted for each other.

2 Linear mixed models adjusted for age, total energy intake, baseline body mass index, baseline waist circumference, education, alcohol intake and follow-up time (men: n = 37,245; women n = 51,727). Individual health behaviours are also adjusted for each other.

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Score and anthropometry changes were inverse, with the exception for Cambridge and Oxford-Health Conscious (United Kingdom), and Greece where non-significant positive associations with weight change were observed.

Excluding participants with chronic diseases at baseline did not change the results (data not shown).

In 288,167 participants information on smoking habits at follow-up was available. Twenty-two percent of baseline smokers quit smoking during follow-up. Excluding these quitters from the analyses resulted in an attenuation of the effect of the health behaviour score on weight in men (three health behaviours versus zero: −298 grams (−0.483; −0.112) and a null effect in women (2 grams (−0.123; 0.127) (Table 5). Results for waist circumference change were also attenuated in men (0.70 cm (−1.02; −0.37)) and women (−0.75 cm (−1.06; −0.44)).

Sensitivity analyses including smoking as non-current (1 point) and current (0 point) in the health score yielded results comparable to our main analyses: Men and women who reported to be physically active, non-smoking and adherent to the Mediterranean Diet gained lesser weight and waist (men: −469 grams (95% CI: −674, −0.264) and women: −331 grams (−480, −182) and men: −0.93 cm (−1.27, −0.59) and women: −1.18 cm (−1.55, −0.83), respectively) compared to participants with no healthy behaviours.

**Discussion**

In the present large prospective study, the combination of positive health behaviours was associated with significantly lower weight gain and smaller increase in waist circumference in a dose-
response manner. Men and women who reported to be physically active, never-smoking and adherent to the Mediterranean Diet (mMDS) gained over a 5-year period on average 537 and 200 grams less weight and 0.95 and 0.99 cm less waist circumference, respectively, as compared to men and women who reported to be physically inactive, ever smokers and not adherent to the mMDS.

**Table 4.** Subgroup analysis stratified baseline body mass index for the association between the health behaviour score and weight change (kg/5 y) and waist circumference change in EPIC-PANACEA participants.

<table>
<thead>
<tr>
<th>Health behavior score</th>
<th>N</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 25 kg/m²</td>
<td>31,425</td>
<td>-0.176</td>
<td>(-0.380; 0.029)</td>
<td>-0.463</td>
<td>(-0.672; -0.255)</td>
<td>-0.669</td>
</tr>
<tr>
<td>BMI 25–30 kg/m²</td>
<td>47,558</td>
<td>0.034</td>
<td>(-0.157; 0.225)</td>
<td>-0.167</td>
<td>(-0.363; 0.029)</td>
<td>-0.368</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>15,396</td>
<td>-0.462</td>
<td>(-0.892; -0.031)</td>
<td>-0.504</td>
<td>(-0.947; -0.061)</td>
<td>-0.535</td>
</tr>
</tbody>
</table>

**Women**

| BMI < 25 kg/m²        | 13,739 | -0.197 | (-0.321; -0.072) | -0.232 | (-0.355; -0.110) | -0.210 | (-0.340; -0.079) | 0.028  |
| BMI 25–30 kg/m²       | 65,849 | 0.014  | (-0.190; 0.219)  | 0.026  | (-0.197; 0.249)  | 0.41   |
| BMI ≥ 30 kg/m²        | 29,382 | -0.350 | (-0.724; 0.024)  | -0.376 | (-0.744; -0.007) | -0.350 | (-0.757; 0.056) | 0.25   |

**WC change (cm/5 y)**

| Men                  | 13,340 | -0.507 | (-0.859; -0.156) | -0.904 | (-1.269; -0.539) | -1.078 | (-1.551; -0.605) | <0.0001 |
| BMI 25–30 kg/m²       | 18,984 | -0.434 | (-0.753; -0.154) | -0.660 | (-0.976; -0.345) | -0.913 | (-1.362; -0.465) | <0.0001 |
| BMI ≥ 30 kg/m²        | 4,888  | -0.640 | (-1.290; 0.009)  | -0.757 | (-1.453; -0.031) | -0.310 | (-1.509; 0.089) | 0.13   |

| Women                | 27,346 | -0.336 | (-0.659; -0.013) | -0.618 | (-0.940; -0.300) | -0.902 | (-1.280; -0.524) | <0.0001 |
| BMI 25–30 kg/m²       | 17,529 | -0.280 | (-0.733; 0.173)  | -0.615 | (-1.065; -0.166) | -0.735 | (-1.281; -0.189) | <0.0001 |
| BMI ≥ 30 kg/m²        | 6,806  | -0.960 | (-1.686; -0.233) | -1.573 | (-2.294; -0.851) | -2.091 | (-3.023; -1.159) | <0.0001 |

**Abbreviations:** CI – confidence interval, BMI – body mass index, WC – waist circumference.

1Linear mixed models adjusted for age, total energy intake, baseline body mass index, education, alcohol intake and follow-up time.

2Linear mixed models adjusted for age, total energy intake, baseline body mass index, baseline waist circumference, education, alcohol intake and follow-up time.

doi:10.1371/journal.pone.0050712.t004

**Table 5.** Sensitivity analyses: Association between the health behaviour score and weight change (kg/5 y) and waist circumference change (cm/5 y) excluding EPIC-PANACEA participants who quit smoking during follow-up.

<table>
<thead>
<tr>
<th>Health behaviour score</th>
<th>Weight change (kg/5 y)²</th>
<th>P for trend</th>
<th>Waist circumference (cm/5 y)²</th>
<th>P for trend</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Men</th>
<th>0.0004</th>
<th>0</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.103</td>
<td>(-0.253; 0.048)</td>
<td>-0.410</td>
</tr>
<tr>
<td>2</td>
<td>-0.159</td>
<td>(-0.313; -0.005)</td>
<td>-0.541</td>
</tr>
<tr>
<td>3</td>
<td>-0.298</td>
<td>(-0.483; -0.112)</td>
<td>-0.697</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
<th>0.06</th>
<th>0</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.070</td>
<td>(-0.188; 0.049)</td>
<td>-0.318</td>
</tr>
<tr>
<td>2</td>
<td>0.002</td>
<td>(-0.115; 0.118)</td>
<td>-0.505</td>
</tr>
<tr>
<td>3</td>
<td>0.002</td>
<td>(-0.123; 0.127)</td>
<td>-0.747</td>
</tr>
</tbody>
</table>

1Information about smoking status at follow-up was available for 288,167 participants (81,227 men and 206,940 women).

2Linear mixed models adjusted for age, total energy intake, baseline body mass index, education, alcohol intake and follow-up time (men: n = 81,227; women: n = 206,940).

3Linear mixed models adjusted for age, total energy intake, baseline body mass index, baseline waist circumference, education, alcohol intake and follow-up time (men: n = 36,949; women n = 51,221).

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Our results confirm findings from studies investigating individual relationships between physical activity, smoking and diet and changes in general and abdominal adiposity showing that each individual behaviour is related with changes in adiposity [10,12,13,27,29,38–40]. We extend these findings by reporting that combining these health behaviours leads to a lower increase in general and central adiposity than each single health behaviour. Bullo et al. [20] and Molenaar et al. [27] also investigated the effect of combined health behaviours and showed that reporting more health behaviours was cross-sectionally related to lower general and abdominal adiposity. However, the relationship with prospective changes was not investigated and the latter did not take diet into account.

In contrast to others [18–20] who investigated the association between combined health behaviours and body weight, we did not include moderate alcohol consumption as a health behaviour in our score. Although moderate alcohol consumption was shown to be associated to lower vascular risk [41], any use of alcohol is related to increased cancer risk [42]. Alcohol abuse causes many health-related harms [43]. Thus, in terms of public health, we prefer not to include alcohol as a potential beneficial behaviour and instead adjust for alcohol consumption in the analyses.

Combining the health behaviours in one score led to stronger associations compared to the associations of the individual behaviours with weight and waist circumference changes we reported earlier [10,12]. This is in line with Mouzaffarian et al. [29] who showed modest individual associations of diet and physical activity with weight changes and stronger associations in the aggregated analyses.

Recently in controlled intervention studies, it was reported that physical activity did not further affect weight loss in addition to a diet [44,45]. However, these trials measure only short-term effects, generally include a selected population (e.g. motivated to lose weight and to follow an intervention, only obese participants or health conscious participants). It might also be that the diet-exercise group compensates the extra activity with more sedentary time or a higher caloric intake. Results of a prospective cohort-study among free-living populations with long follow-up might provide results that rather reflect the real world, although residual confounding cannot be ruled out.

Strengths of the present study are the prospective design, the large sample of participants from 9 European countries and the use of validated and standardized questionnaires.

A limitation of our study was that in most of the centres weight and waist circumference at second assessment were self-reported and were therefore possibly underreported [46]. Generally, self-reported weight and waist circumference appear reasonably valid [47]. High correlations were reported between self-reported and measured weight and waist circumference in the present population as well (all Spearman correlations r\textgreater{}0.9, p\textless{}0.0001) [33]. Furthermore, we recently showed that self-reported waist circumference at follow-up could be used as a proxy for measured waist in regression analyses [40]. We also used a prediction equation to improve the accuracy of self-reported anthropometry and this resulted in values for weight and waist circumference gain comparable to levels observed in the two EPIC centres with measured weight both at baseline and follow-up. It seems unlikely that the significant association with the health behaviour score is explained by inaccuracies in anthropometry changes. Rather, our results may be attenuated due to random measurement error associated with self-reported lifestyle factors. We also cannot rule out residual confounding by poorly and/or unmeasured confounders.

Another limitation is that lifestyle assessment for creating the score was only done at baseline and possible behavioural changes during follow-up were not taken into account. In participants for whom we had information on smoking status during follow-up, quitting smoking was associated with weight gain compared to stable smokers [14]. Consequently, excluding participants who smoked at baseline and quit smoking during follow-up resulted in an attenuation of the beneficial effects on weight and waist circumference gain for combined positive health behaviours. Nevertheless, being physically active, adherent to the mMDS and never-smoking still had positive effects on weight gain in men and gain of waist circumference in men and women during a 5-year follow-up. Since quitting smoking seems to lead mainly to a short-term weight gain [13,14,29], the effect of excluding quitters might diminish with a longer follow-up time. Future studies are warranted investigating the combined effect of lifestyle factors on weight and waist circumference gain particularly considering (long-term) changes of all health behaviours.

We constructed a pragmatic simple health behaviour score by using dichotomous variables where 1 point was given for the presence of each of the positive health behaviours without weighting the individual strength of the relationship with anthropometry. A weighted approach might improve the estimation of the effects of the individual score, but the combined effect of reporting all three healthy behaviours would be similar. Nechuta et al. [23] showed that results using a more differentiated score were comparable to using the pragmatic score for the estimation of the association between combined lifestyles and mortality.

We developed a score including health behaviours that are presumable easy to achieve in the general population. We, for example, dichotomized physical activity into inactive (sedentary job and no recreational activity) and active (any category with activity levels above the latter). Therefore, a relatively high proportion of participants scored one or more points in our health behaviour score.

The choice of the components of our score was based on prior findings from EPIC-PANACEA. Therefore, we used the mMDS, which was associated with weight change [6,12], as the healthy diet component. One may argue that the Mediterranean Diet is a reflection of the traditional dietary pattern in Mediterranean countries rather than an a-priori healthy diet index based on scientific evidence. However, it has extensively been shown to be linked to a decreased risk of several chronic diseases and mortality [49]. Also others used the Mediterranean Diet in their health behaviour score and showed that the score was related to lower mortality risk [16,20]. It may well be possible that other healthy diets commonly used in Europe may also lead to similar favourable effects on weight and waist circumference gain.

Our results suggest that public health programs aiming at reducing the burden of obesity could benefit from targeting a cluster of behaviours. We show that combining health behaviours was associated to a lower gain in waist circumference – a valid marker of central adiposity [50] - independent of changes in BMI. Prevention of waist circumference gain is of potential importance because abdominal obesity, independent of general obesity, appears to be directly related to total mortality [2].

In conclusion, the combination of three positive health behaviours was associated with significantly lower 5-year weight and waist circumference gain compared with participants who scored to be inactive, smoking and low adherent to the Mediterranean Diet.
Supporting Information

Figure S1 Country/Centre-specific association between the health behaviour score (highest category, i.e. all three health behaviours) and 5-year weight change (kg) in men. Country or centre specific estimates were calculated using general linear models in centres and countries with one centre only, or multilevel mixed-effects linear regression models in countries with more than one centre, and were adjusted age, total energy intake, baseline body mass index, education, alcohol intake and follow-up time. The overall estimate was calculated using random effect meta-analyses. Because of differences in assessment of follow-up weight, and/or different follow-up times, the centres in Germany (Heidelberg, Potsdam), United Kingdom (Cambridge, Oxford-General population, Oxford-Health Conscious) and the Netherlands (Utrecht, Doetinchem, Amsterdam/Maastricht) were treated as separate cohorts. (TIF)

Figure S2 Country/Centre-specific association between the health behaviour score (highest category, i.e. all three health behaviours) and 5-year weight change (kg) in women. Country or centre specific estimates were calculated using general linear models in centres and countries with one centre only, or multilevel mixed-effects linear regression models in countries with more than one centre, and were adjusted age, total energy intake, baseline body mass index, education, alcohol intake and follow-up time. The overall estimate was calculated using random effect meta-analyses. Because of differences in assessment of follow-up weight, and/or different follow-up times, the centres in Germany (Heidelberg, Potsdam), United Kingdom (Cambridge, Oxford-General population, Oxford-Health Conscious) and the Netherlands (Utrecht, Doetinchem, Amsterdam/Maastricht) were treated as separate cohorts. (TIF)

Figure S3 Country/Centre-specific association between the health behaviour score (highest category, i.e. all three health behaviours) and 5-year waist circumference change (cm) in men. Country or centre specific estimates were calculated using general linear models in centres and countries with one centre only, or multilevel mixed-effects linear regression models in countries with more than one centre, and were adjusted age, total energy intake, baseline body mass index, baseline waist circumference, education, alcohol intake and follow-up time. The overall estimate was calculated using random effect meta-analyses. (TIF)

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Author Contributions

Conceived and designed the experiments: AMM DR NT UE MMB PHMP. Performed the experiments: AMM DR. Analyzed the data: AMM DR. Contributed reagents/materials/analysis tools: AMM DR NT UE MMB RK BT AS HB JH AR MU LD GF. Wrote the paper: AMM. Principal investigator of the EPIC-PANACEA project: PHMP. Overall coordinator of the EPIC study: ER. Approved the final version of the manuscript: AMM DR NT UE MMB RK BT AS HB JH AR MU LD GF. Combined Impact of Lifestyle on Anthropometry

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