**Supporting information**

**Additional file 1:**

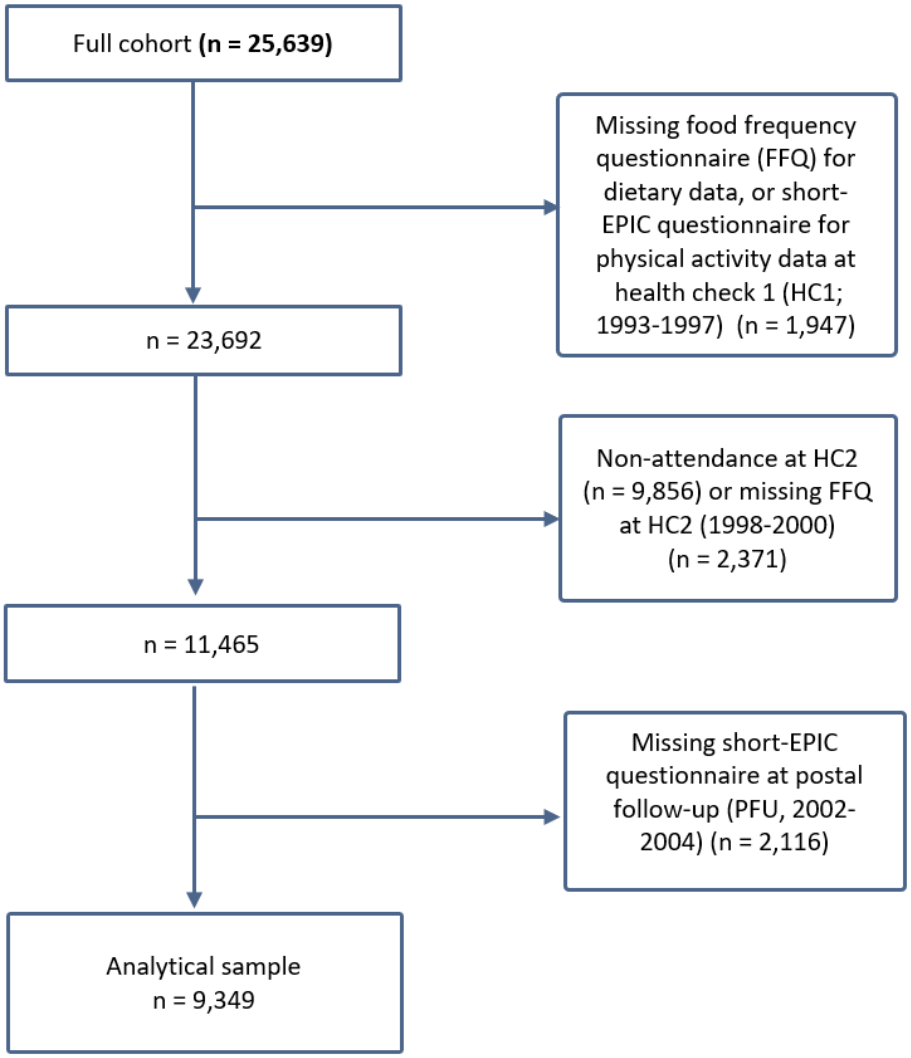



**Figure S1** - Flow diagram illustrating selection of the analytical sample in the EPIC-Norfolk Study.

**Table S1 - Comparison of baseline characteristics in the analytical sample according to all-cause mortality outcome at the end of follow-up in the EPIC-Norfolk Study**

| Characteristic | Alive (n=5,815) | Dead (n=3,534) | P-value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 54.4 (7.0) | 64.8 (7.1) | <0.001 |
| Women (%) | 63.3 | 50.9 | <0.001 |
| Education: GCSE/O level equivalent or below (%) | 38.8 | 46.6 | <0.001 |
| Occupation: Unemployed to semi-skilled work (%) | 14.6 | 17.1 | 0.001 |
| Occupation: Skilled workers (%) | 37.0 | 36.7 | 0.821 |
| Occupation: Managers & professionals (%) | 48.4 | 46.2 | 0.034 |
| **Metabolic risk factors** | | | |
| Body mass index (kg/m$^2$) | 25.6 (3.6) | 26.3 (3.8) | <0.001 |
| Systolic blood pressure (mmHg) | 131.0 (16.4) | 140.3 (18.2) | <0.001 |
| Diastolic blood pressure (mmHg) | 81.1 (10.5) | 84.5 (11.2) | <0.001 |
| Triglycerides (mmol/L) | 1.65 (1.03) | 1.88 (1.07) | <0.001 |
| Total Cholesterol (mmol/L) | 6.03 (1.12) | 6.34 (1.16) | <0.001 |
| HDL-Cholesterol (mmol/L) | 1.46 (0.44) | 1.39 (0.43) | <0.001 |
| LDL-Cholesterol (mmol/L) | 3.85 (1.01) | 4.11 (1.03) | <0.001 |
| **Self-reported comorbidities, medication, and family history** | | | |
| Diabetes mellitus (%) | 0.7 | 2.7 | <0.001 |
| Cardiovascular diseases (%) | 0 | 0.1 | 0.026 |
| Cancer (%) | 4.0 | 7.1 | <0.001 |
| Statins (%) | 0.6 | 1.2 | 0.002 |
| Anti-hypertensive drugs (%) | 9.2 | 21.7 | <0.001 |
| Family history of Diabetes Mellitus (%) | 14.0 | 12.9 | 0.128 |
| Family history of myocardial infarction (%) | 35.8 | 39.5 | <0.001 |
| **Health behaviours** | | | |
| MDS points | 8.63 (1.31) | 8.42 (1.27) | <0.001 |
| PAEE (kJ/kg/day) | 6.49 (4.58) | 5.31 (4.63) | <0.001 |
| Current smoker (%) | 7.3 | 8.9 | 0.005 |
| Former smoker (%) | 35.7 | 46.0 | <0.001 |
| Energy intake (kcal/day) | 2034.5 (582.8) | 2100.6 (581.4) | <0.001 |
| Alcohol (g/d) | 8.4 (11.7) | 8.7 (13.4) | 0.21 |

HDL=high density lipoprotein; LDL=low density lipoprotein; MDS=Mediterranean diet score; PAEE=physical activity energy expenditure.

**Table S2 - Comparison of baseline characteristics in the analytical sample and those excluded from analysis in the EPIC-Norfolk population.**

| Characteristic | Analytical sample (n= 9,349) | Excluded (n=16,287) | P-value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 58.3 (8.7) | 59.7 (9.6) | <0.001 |
| Women (%) | 58.6 | 52.5 | <0.001 |
| Education: GCSE/O level equivalent or below (%) | 41.7 | 50.2 | <0.001 |
| Occupation: Unemployed to semi-skilled work (%) | 15.5 | 20.6 | |
| Skilled workers (%) | 36.9 | 39.7 | <0.001 |
| Managers & Professionals (%) | 47.5 | 39.7 | |
| **Metabolic risk Factors** | | | |
| Body mass index (kg/m2) | 25.9 (3.7) | 26.6 (4.0) | <0.001 |
| Systolic blood pressure (mmHg) | 134.5 (17.7) | 136.5 (18.9) | <0.001 |
| Diastolic blood pressure (mmHg) | 82.2 (10.9) | 83.1 (11.5) | <0.001 |
| Triglycerides (mmol/L) | 1.73 (1.05) | 1.9 (1.32) | <0.001 |
| Total Cholesterol (mmol/L) | 6.15 (1.15) | 6.20 (1.18) | <0.001 |
| HDL-Cholesterol (mmol/L) | 1.43 (0.43) | 1.40 (0.43) | <0.001 |
| LDL-Cholesterol (mmol/L) | 3.95 (1.03) | 3.99 (1.04) | <0.001 |
| Prevalent diseases, medication, and family history | | | |
| Diabetes mellitus (%) | 1.4 | 2.8 | <0.001 |
| Cardiovascular diseases (%) | 0.1 | 7.0 | <0.001 |
| Cancer (%) | 5.1 | 5.7 | 0.055 |
| Statins (%) | 0.8 | 1.1 | 0.042 |
| Anti-hypertensive drugs (%) | 13.9 | 21.6 | <0.001 |
| Family history of diabetes mellitus (%) | 13.6 | 12.4 | 0.004 |
| Family history of myocardial infarction (%) | 37.2 | 35.9 | 0.038 |
| **Health behaviours** | | | |
| PAEE (kJ/kg/day) | 6.04 (4.64) | 5.13 (4.64) | <0.001 |
| MDS score | 8.55 (1.30) | 8.36 (1.32) | <0.001 |
| Current smoker (%) | 7.9 | 13.8 | <0.001 |
| Former smoker (%) | 39.6 | 43.3 | <0.001 |
| Energy intake (kcal/day) | 2059 (583) | 2036 (610) | 0.005 |
| Alcohol (g/d) | 8.5 (12.4) | 8.7 (13.3) | 0.378 |

HDL=high density lipoprotein; LDL=low density lipoprotein; PAEE=physical activity energy expenditure; MDS=Mediterranean diet score.
Data are presented as mean (SD) or %.

**Table S3 - Associations of mutually adjusted exposures with mortality outcomes in the EPIC-Norfolk Study (complete case analysis)†**

| | Exposures†† | Model 1<br>HR (95% CI) | Model 2<br>HR (95% CI) | Model 3<br>HR (95% CI) | Model 4<br>HR (95% CI) |
|---|---|---|---|---|---|
| No. of participants | | 9,349 | 9,276 | 8,483 | 7,461 |
| Time at risk | | 149,681 | 148,609 | 136,664 | 120,336 |
| **All-cause mortality** | | | | | |
| No. of death | | 3,534 | 3,496 | 3,105 | 2,729 |
| | Baseline PAEE | 0.87 (0.83 to 0.91)*** | 0.88 (0.84 to 0.92)*** | 0.90 (0.86 to 0.94)*** | 0.90 (0.85 to 0.94)*** |
| | ΔPAEE | 0.87 (0.83 to 0.91)*** | 0.88 (0.84 to 0.91)*** | 0.90 (0.86 to 0.94)*** | 0.89 (0.85 to 0.93)*** |
| | Baseline MDS | 0.92 (0.88 to 0.95)*** | 0.94 (0.90 to 0.97)** | 0.93 (0.89 to 0.97)** | 0.94 (0.90 to 0.99)** |
| | ΔMDS | 0.92 (0.88 to 0.95)*** | 0.93 (0.90 to 0.97)*** | 0.92 (0.89 to 0.96)*** | 0.91 (0.87 to 0.95)*** |
| **CVD mortality** | | | | | |
| No. of death | | 2,978 | 2,949 | 2,599 | 2,283 |
| | Baseline PAEE | 0.87 (0.83 to 0.91)*** | 0.88 (0.84 to 0.92)*** | 0.91 (0.87 to 0.96)*** | 0.91 (0.86 to 0.96)*** |
| | ΔPAEE | 0.87 (0.83 to 0.92)*** | 0.88 (0.84 to 0.92)*** | 0.91 (0.86 to 0.96)*** | 0.91 (0.86 to 0.96)*** |
| | Baseline MDS | 0.91 (0.87 to 0.95)*** | 0.93 (0.89 to 0.97)** | 0.91 (0.87 to 0.96)*** | 0.93 (0.88 to 0.97)** |
| | ΔMDS | 0.92 (0.88 to 0.96)*** | 0.93 (0.89 to 0.97)** | 0.92 (0.88 to 0.97)** | 0.91 (0.87 to 0.96)*** |
| **Cancer mortality** | | | | | |
| No. of death | | 1,794 | 1,771 | 1,591 | 1,407 |
| | Baseline PAEE | 0.89 (0.84 to 0.95)*** | 0.90 (0.85 to 0.96)** | 0.92 (0.86 to 0.98)** | 0.91 (0.85 to 0.97)** |
| | ΔPAEE | 0.88 (0.83 to 0.93)*** | 0.89 (0.84 to 0.94)*** | 0.90 (0.85 to 0.96)** | 0.90 (0.84 to 0.96)** |
| | Baseline MDS | 0.95 (0.90 to 1.00) | 0.97 (0.92 to 1.02) | 0.98 (0.92 to 1.04) | 0.98 (0.92 to 1.05) |
| | ΔMDS | 0.93 (0.88 to 0.98)** | 0.94 (0.89 to 0.99)* | 0.94 (0.89 to 1.00)* | 0.92 (0.86 to 0.98)** |

HR=Hazard ratio per SD difference in each exposure; CI=Confidence interval.

Covariates in Models:

Model 1: sex, age.

Model 2: variables in Model 1 + education, employment, and time updated variables for smoking.

Model 3: variables in Model 2 + family history of myocardial infarction, family history of diabetes mellitus, time updated variables for prevalent diabetes mellitus, prevalent cancer, prevalent cardiovascular diseases, and anti-hypertensive medication.

Model 4: variables in Model 3 + time updated variables for BMI, SBP, DBP, TG, LDL, HDL, and total energy intake.

† Level of statistical significance: p-value ≥ 0.05, unless indicated by asterisk.: * P-value < 0.05; ** P-value < 0.01; *** P-value < 0.001

†† SD increment in baseline PAEE equals to 4.64 kJ/kg/day, in ΔPAEE equals to 0.65 kJ/kg/day per year, in baseline MDS equals to 1.30 points, and in ΔMDS equals to 0.33 points per year

Number of participants with missing covariates: Smoking (at baseline): n=73, Smoking (at repeated assessment): n=71, Education level: n=4, Self-reported comorbidities: n=801, Family history of MI: n=5, BMI (at baseline): n=5, BMI (at repeated assessment): n=17, SBP (at baseline): n=18, SBP (at repeated assessment): n=16, DBP (at baseline): n=16, DBP (at repeated assessment): n=16, TG (at baseline): n=489, TG (at repeated assessment): n=489, LDL (at baseline): n=722, LDL (at repeated assessment): n=498, HDL (at baseline): n=722, HDL (at repeated assessment): n=496, Energy intake (at baseline): n=19, Energy intake (at repeated assessment): n=38

**Table S4 - Associations of mutually adjusted exposures with subtypes of CVD and cancer mortality outcomes in the EPIC-Norfolk Study†**

| Outcome | Exposures†† | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) | Model 4 HR (95% CI) |
|---|---|---|---|---|---|
| **IHD mortality (1,240 deaths)** | Baseline PAEE | 0.82 (0.76 to 0.88)*** | 0.83 (0.77 to 0.89)*** | 0.88 (0.82 to 0.95)** | 0.89 (0.83 to 0.96)** |
| | ΔPAEE | 0.85 (0.78 to 0.91)*** | 0.86 (0.79 to 0.92)*** | 0.88 (0.81 to 0.95)** | 0.88 (0.82 to 0.95)** |
| | Baseline MDS | 0.92 (0.87 to 0.98)* | 0.95 (0.89 to 1.01) | 0.94 (0.88 to 1.00) | 0.95 (0.89 to 1.02) |
| | ΔMDS | 0.90 (0.84 to 0.96)** | 0.91 (0.86 to 0.97)** | 0.92 (0.86 to 0.98)* | 0.91 (0.85 to 0.97)** |
| **Stroke mortality (976 deaths)** | Baseline PAEE | 0.88 (0.81 to 0.96)** | 0.89 (0.82 to 0.97)** | 0.92 (0.85 to 1.00)* | 0.91 (0.83 to 0.98)* |
| | ΔPAEE | 0.89 (0.82 to 0.97)** | 0.90 (0.83 to 0.98)* | 0.91 (0.84 to 0.99)* | 0.90 (0.83 to 0.98)* |
| | Baseline MDS | 0.87 (0.81 to 0.94)*** | 0.88 (0.82 to 0.95)** | 0.88 (0.82 to 0.95)** | 0.90 (0.84 to 0.98)* |
| | ΔMDS | 0.87 (0.80 to 0.93)*** | 0.87 (0.81 to 0.94)*** | 0.87 (0.81 to 0.94)*** | 0.87 (0.81 to 0.94)** |
| **Lung cancer mortality (169 deaths)** | Baseline PAEE | 0.68 (0.55 to 0.83)*** | 0.72 (0.58 to 0.88)** | 0.73 (0.59 to 0.90)** | 0.74 (0.60 to 0.90)** |
| | ΔPAEE | 0.79 (0.64 to 0.96)* | 0.82 (0.67 to 1.00) | 0.84 (0.68 to 1.03) | 0.84 (0.68 to 1.03) |
| | Baseline MDS | 0.87 (0.73 to 1.03) | 0.99 (0.83 to 1.18) | 0.97 (0.81 to 1.16) | 1.00 (0.83 to 1.20) |
| | ΔMDS | 0.87 (0.73 to 1.03) | 0.94 (0.79 to 1.11) | 0.92 (0.79 to 1.10) | 0.95 (0.79 to 1.13) |
| **Prostate cancer mortality (293 deaths)** | Baseline PAEE | 0.93 (0.81 to 1.07) | 0.93 (0.81 to 1.07) | 0.95 (0.83 to 1.10) | 0.92 (0.80 to 1.07) |
| | ΔPAEE | 1.03 (0.90 to 1.19) | 1.04 (0.91 to 1.19) | 1.08 (0.94 to 1.23) | 1.06 (0.92 to 1.22) |
| | Baseline MDS | 0.97 (0.88 to 1.11) | 0.98 (0.85 to 1.11) | 0.99 (0.87 to 1.13) | 1.01 (0.88 to 1.16) |
| | ΔMDS | 0.99 (0.87 to 1.14) | 0.99 (0.87 to 1.13) | 1.00 (0.88 to 1.15) | 1.02 (0.89 to 1.17) |

*Continue in next page*

**Table S4 (continued)**

| Outcome | Exposures†† | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) | Model 4 HR (95% CI) |
|---|---|---|---|---|---|
| **Breast cancer mortality (184 deaths)** | Baseline PAEE | 0.90 (0.74 to 1.09) | 0.90 (0.74 to 1.10) | 0.93 (0.76 to 1.13) | 0.90 (0.74 to 1.11) |
| | ΔPAEE | 0.96 (0.79 to 1.16) | 0.96 (0.79 to 1.16) | 1.00 (0.83 to 1.02) | 1.00 (0.83 to 1.21) |
| | Baseline MDS | 0.88 (0.75 to 1.05) | 0.89 (0.75 to 1.06) | 0.86 (0.72 to 1.03) | 0.88 (0.74 to 1.06) |
| | ΔMDS | 0.87 (0.74 to 1.02) | 0.87 (0.74 to 1.03) | 0.84 (0.71 to 1.00)* | 0.83 (0.70 to 0.98)* |
| **GI cancer mortality (352 deaths)** | Baseline PAEE | 0.90 (0.79 to 1.03) | 0.91 (0.80 to 1.04) | 0.93 (0.82 to 1.07) | 0.94 (0.82 to 1.08) |
| | ΔPAEE | 0.87 (0.76 to 1.00)* | 0.88 (0.77 to 1.00) | 0.91 (0.80 to 1.05) | 0.92 (0.80 to 1.06) |
| | Baseline MDS | 0.91 (0.81 to 1.03) | 0.93 (0.82 to 1.05) | 0.93 (0.82 to 1.05) | 0.91 (0.89 to 1.04) |
| | ΔMDS | 0.93 (0.82 to 1.05) | 0.94 (0.83 to 1.06) | 0.93 (0.82 to 1.05) | 0.90 (0.80 to 1.02) |

HR=Hazard ratio per SD difference in each exposure; CI=Confidence interval.
Covariates in Models:

Model 1: sex, age (only age for prostate and breast cancer mortality).

Model 2: variables in Model 1 + education, employment, and time updated variables for smoking.

Model 3: variables in Model 2 + family history of myocardial infarction, family history of diabetes mellitus, time updated variables for prevalent diabetes mellitus, prevalent cancer, prevalent cardiovascular diseases, and anti-hypertensive medication.

Model 4: variables in Model 3 + time updated variables for BMI, SBP, DBP, TG, LDL, HDL, and total energy intake.

† Level of statistical significance: p-value ≥ 0.05, unless indicated by asterisk.

* P-value < 0.05

** P-value < 0.01

*** P-value < 0.001

†† SD increment in baseline PAEE equals to 4.64 kJ/kg/day, in ΔPAEE equals to 0.65 kJ/kg/day per year, in baseline MDS equals to 1.30 points, and in ΔMDS equals to 0.33 points per year

**Table S5 - Tests of interaction between different combinations of the exposures for all-cause mortality outcome in the EPIC-Norfolk Study†**

| Interaction terms in the model | Multiplicative interaction†† | Additive interaction†† | | |
|---|---|---|---|---|
| | HR (95% CI) | RERI (95% CI) | AP (95% CI) | SI (95% CI) |
| a. Baseline PAEE × ΔPAEE | 0.97 (0.94 to 1.00) | -0.045 (-0.207, 0.116) | -0.055 (-0.247, 0.137) | 1.358 (0.336, 5.484) |
| b. Baseline MDS × ΔMDS | 0.99 (0.96 to 1.02) | 0.043 (-0.080, 0.167) | 0.052 (-0.097, 0.202) | 0.797 (0.445, 1.427) |
| c. Baseline PAEE × Baseline MDS | 1.00 (0.97 to 1.04) | -0.007 (-0.134, 0.120) | -0.008 (-0.147, 0.132) | 1.084 (0.236, 4.981) |
| d. ΔPAEE× ΔMDS | 1.02 (0.99 to 1.06) | 0.048 (-0.074, 0.171) | 0.055 (-0.086, 0.197) | 0.726 (0.364, 1.447) |
| | | Likelihood-ratio test (p-value)†† | | |
| a + b | | 0.144 | | |
| c + d | | 0.420 | | |
| a + b + c + d | | 0.248 | | |

HR, Hazard ratio; CI, Confidence interval RERI, the relative excess risk due to interaction; AP, the attributable proportion due to interaction; SI, the synergy index.

†Covariates in Model: sex, age, education, employment, family history of myocardial infarction, family history of diabetes mellitus, and time updated variables for smoking, prevalent diabetes mellitus, prevalent cancer, prevalent cardiovascular diseases, anti-hypertensive medication, BMI, SBP, DBP, TG, LDL, HDL, and total energy intake.

††Multiplicative interaction was tested by adding an interaction term between two exposures at a time and reporting the HR for that term from the regression model. Given all exposures are inversely related to mortality, an interaction HR of less than 1 indicates an amplification of the main effects. Additive interaction was assessed using the method previously described by Andersson T et al. (https://doi.org/10.1007/s10654-005-7835-x). When more than one interaction term was included in the model, a likelihood ratio test was used to compare the model with multiple interaction terms to a model without any interaction terms.

**Table S6 - Associations of mutually adjusted cumulative exposures with mortality outcomes in the EPIC-Norfolk Study†**

| Outcome | Exposures†† | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) | Model 4 HR (95% CI) |
|---|---|---|---|---|---|
| **All-cause mortality (3534 deaths)** | Cumulative PAEE | 0.89 (0.86 to 0.92)*** | 0.90 (0.87 to 0.93)*** | 0.92 (0.88 to 0.95)*** | 0.91 (0.88 to 0.95)*** |
| | Cumulative MDS | 0.92 (0.89 to 0.95)*** | 0.94 (0.91 to 0.97)** | 0.94 (0.91 to 0.97)*** | 0.95 (0.92 to 0.99)* |
| **CVD mortality (2,978 deaths)** | Cumulative PAEE | 0.89 (0.85 to 0.93)*** | 0.90 (0.86 to 0.94)*** | 0.93 (0.88 to 0.96)*** | 0.92 (0.89 to 0.96)*** |
| | Cumulative MDS | 0.91 (0.88 to 0.95)*** | 0.93 (0.90 to 0.97)*** | 0.93 (0.89 to 0.97)*** | 0.95 (0.91 to 0.98)** |
| **Cancer mortality (1,794 deaths)** | Cumulative PAEE | 0.91 (0.87 to 0.96)*** | 0.92 (0.87 to 0.97)** | 0.94 (0.89 to 0.99)* | 0.94 (0.89 to 0.99)* |
| | Cumulative MDS | 0.95 (0.90 to 0.99)* | 0.97 (0.92 to 1.02) | 0.97 (0.92 to 1.02) | 0.98 (0.93 to 1.03) |

HR=Hazard ratio per SD difference in each exposure; CI=Confidence interval.

Sample size = 9,349; person years = 149,681

Covariates in Models:

Model 1: sex, age.

Model 2: variables in Model 1 + education, employment, and time updated variables for smoking.

Model 3: variables in Model 2 + family history of myocardial infarction, family history of diabetes mellitus, time updated variables for prevalent diabetes mellitus, prevalent cancer, prevalent cardiovascular diseases, and anti-hypertensive medication.

Model 4: variables in Model 3 + time updated variables for BMI, SBP, DBP, TG, LDL, HDL, and total energy intake.

†Level of statistical significance: p-value ≥ 0.05, unless indicated by asterisk.

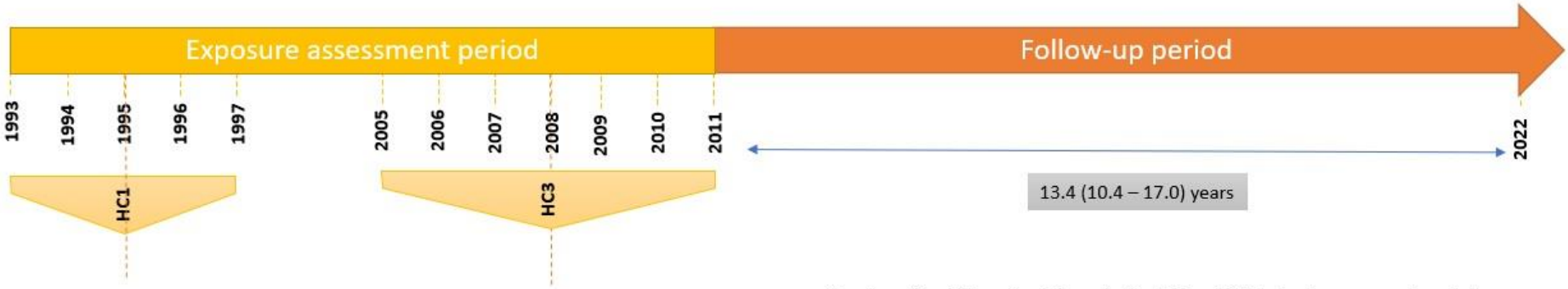
* P-value < 0.05

** P-value < 0.01

*** P-value < 0.001

†† SD increment in cumulative PAEE equals to 3.96 kJ/kg/day, and in cumulative MDS equals to 1.16 points,

Cumulative exposures are calculated by averaging MDS and PAEE at baseline and repeated assessments.




**Number of participants with available diet and PA data at assessment period**

| | HC1 : 1995 (1993-1997) | HC3 : 2008 (2005-2011) |
|---|---|---|
| Diet (FFQ) | 23,692 | 11,257 |
| PA (short-EPIC questionnaire) | 25,618 | 6,149 |

**Different combinations of available diet and PA variables across assessments**

| | |
|---|---|
| Repeated diet (HC1 and HC3) | 11,257 |
| Repeated PA (HC1 and HC3) | 5,910 |
| Repeated diet and repeated PA | 5,879 |

**Figure S2 - EPIC-Norfolk Study design and timeline, considering health check 3 as the end of assessment period.**
MDS=Mediterranean diet score; PAEE=physical activity energy expenditure; N/A= Not available; HC=health check; FFQ= food frequency questionnaire. Numbers in brackets above below arrow symbol indicate interquartile range of the years passed.

**Table S7 - Associations of mutually adjusted exposures with mortality in the EPIC-Norfolk Study, considering health check 3 as the end of the assessment period†**

| Outcome | Exposures†† | Model 1<br>HR (95% CI) | Model 2<br>HR (95% CI) | Model 3<br>HR (95% CI) | Model 4<br>HR (95% CI) |
|---|---|---|---|---|---|
| **All-cause mortality (1,726 deaths)** | Baseline PAEE | 0.89 (0.83 to 0.95)*** | 0.90 (0.84 to 0.96)** | 0.92 (0.86 to 0.98)* | 0.91 (0.85 to 0.98)** |
| | ΔPAEE | 0.89 (0.83 to 0.95)*** | 0.89 (0.85 to 0.96)** | 0.91 (0.85 to 0.98)** | 0.91 (0.85 to 0.98)** |
| | Baseline MDS | 0.95 (0.90 to 1.00) | 0.96 (0.91 to 1.01) | 0.96 (0.91 to 1.01) | 0.97 (0.92 to 1.03) |
| | ΔMDS | 0.95 (0.90 to 1.00) | 0.95 (0.90 to 1.00) | 0.96 (0.90 to 1.01) | 0.96 (0.91 to 1.01) |
| **CVD mortality (1,502 deaths)** | Baseline PAEE | 0.87 (0.81 to 0.94)*** | 0.88 (0.82 to 0.95)** | 0.91 (0.84 to 0.98)* | 0.91 (0.84 to 0.98)* |
| | ΔPAEE | 0.86 (0.80 to 0.93)*** | 0.87 (0.81 to 0.94)*** | 0.89 (0.83 to 0.96)** | 0.89 (0.83 to 0.96)** |
| | Baseline MDS | 0.96 (0.91 to 1.02) | 0.97 (0.92 to 1.03) | 0.97 (0.91 to 1.03) | 0.98 (0.93 to 1.04) |
| | ΔMDS | 0.95 (0.90 to 1.01) | 0.95 (0.90 to 1.01) | 0.96 (0.91 to 1.01) | 0.96 (0.91 to 1.02) |
| **Cancer mortality (912 deaths)** | Baseline PAEE | 0.89 (0.81 to 0.97)* | 0.90 (0.82 to 0.99)* | 0.92 (0.84 to 1.01) | 0.92 (0.83 to 1.01) |
| | ΔPAEE | 0.84 (0.77 to 0.93)*** | 0.85 (0.78 to 0.94)*** | 0.89 (0.81 to 0.97)* | 0.88 (0.80 to 0.97)* |
| | Baseline MDS | 0.98 (0.92 to 1.06) | 1.00 (0.93 to 1.08) | 1.01 (0.94 to 1.09) | 1.02 (0.95 to 1.11) |
| | ΔMDS | 0.95 (0.89 to 1.02) | 0.96 (0.89 to 1.03) | 0.97 (0.90 to 1.04) | 0.96 (0.90 to 1.03) |

HR=Hazard ratio per SD difference in each exposure; CI=Confidence interval.
Sample size = 5,878; person years = 69,456
Covariates in Models:

Model 1: sex, age.

Model 2: variables in Model 1 + education, employment, and time updated variables for smoking.

Model 3: variables in Model 2 + family history of myocardial infarction, family history of diabetes mellitus, time updated variables for prevalent diabetes mellitus, prevalent cancer, prevalent cardiovascular diseases, and anti-hypertensive medication.

Model 4: variables in Model 3 + time updated variables for BMI, SBP, DBP, TG, LDL, HDL, and total energy intake.

† Level of statistical significance: p-value ≥ 0.05, unless indicated by asterisk.

* P-value < 0.05

** P-value < 0.01

*** P-value < 0.001

†† SD increment in baseline PAEE equals to 4.64 kJ/kg/day, in ΔPAEE equals to 0.40 kJ/kg/day per year, in baseline MDS equals to 1.30 points, and in ΔMDS equals to 0.06 points per year.

**Table S8 - Associations of mutually adjusted exposures with mortality in the EPIC-Norfolk Study, excluding deaths that occurred within two years of the last measurement †**

| Outcome | Exposures†† | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) | Model 4 HR (95% CI) |
|---|---|---|---|---|---|
| **All-cause mortality (3,392 deaths)** | Baseline PAEE | 0.87 (0.83 to 0.91)*** | 0.88 (0.84 to 0.92)*** | 0.90 (0.86 to 0.94)*** | 0.90 (0.86 to 0.94)*** |
| | ΔPAEE | 0.88 (0.84 to 0.92)*** | 0.88 (0.85 to 0.92)*** | 0.90 (0.86 to 0.94)*** | 0.90 (0.86 to 0.94)*** |
| | Baseline MDS | 0.92 (0.89 to 0.96)*** | 0.94 (0.90 to 0.98)** | 0.94 (0.90 to 0.98)** | 0.95 (0.92 to 0.99)* |
| | ΔMDS | 0.92 (0.88 to 0.96)*** | 0.93 (0.90 to 0.97)*** | 0.93 (0.89 to 0.97)*** | 0.93 (0.89 to 0.97)*** |
| **CVD mortality (2,881 deaths)** | Baseline PAEE | 0.87 (0.83 to 0.91)*** | 0.88 (0.84 to 0.92)*** | 0.91 (0.87 to 0.96)*** | 0.91 (0.87 to 0.95)*** |
| | ΔPAEE | 0.88 (0.84 to 0.92)*** | 0.89 (0.85 to 0.93)*** | 0.91 (0.86 to 0.95)*** | 0.91 (0.87 to 0.95)*** |
| | Baseline MDS | 0.91 (0.88 to 0.95)*** | 0.93 (0.89 to 0.97)** | 0.93 (0.89 to 0.97)** | 0.95 (0.91 to 0.99)* |
| | ΔMDS | 0.92 (0.88 to 0.96)*** | 0.93 (0.89 to 0.97)*** | 0.93 (0.89 to 0.97)** | 0.93 (0.89 to 0.97)** |
| **Cancer mortality (1,712 deaths)** | Baseline PAEE | 0.89 (0.84 to 0.95)*** | 0.90 (0.85 to 0.96)** | 0.92 (0.87 to 0.98)* | 0.92 (0.87 to 0.98)** |
| | ΔPAEE | 0.89 (0.83 to 0.93)*** | 0.90 (0.84 to 0.95)*** | 0.92 (0.86 to 0.97)** | 0.91 (0.86 to 0.97)** |
| | Baseline MDS | 0.95 (0.90 to 1.00) | 0.98 (0.92 to 1.03) | 0.97 (0.92 to 1.03) | 0.99 (0.93 to 1.05) |
| | ΔMDS | 0.93 (0.88 to 0.98)** | 0.94 (0.89 to 1.00)* | 0.94 (0.89 to 1.00)* | 0.94 (0.89 to 0.99)* |

HR=Hazard ratio per SD difference in each exposure; CI=Confidence interval.
Sample size = 9,205; person years = 149,499
Covariates in Models:

Model 1: sex, age.

Model 2: variables in Model 1 + education, employment, and time updated variables for smoking.

Model 3: variables in Model 2 + family history of myocardial infarction, family history of diabetes mellitus, time updated variables for prevalent diabetes mellitus, prevalent cancer, prevalent cardiovascular diseases, and anti-hypertensive medication.

Model 4: variables in Model 3 + time updated variables for BMI, SBP, DBP, TG, LDL, HDL, and total energy intake.

† Level of statistical significance: p-value ≥ 0.05, unless indicated by asterisk.

* P-value < 0.05

** P-value < 0.01

*** P-value < 0.001

†† SD increment in baseline PAEE equals to 4.64 kJ/kg/day, in ΔPAEE equals to 0.65 kJ/kg/day per year, in baseline MDS equals to 1.30 points, and in ΔMDS equals to 0.33 points per year.

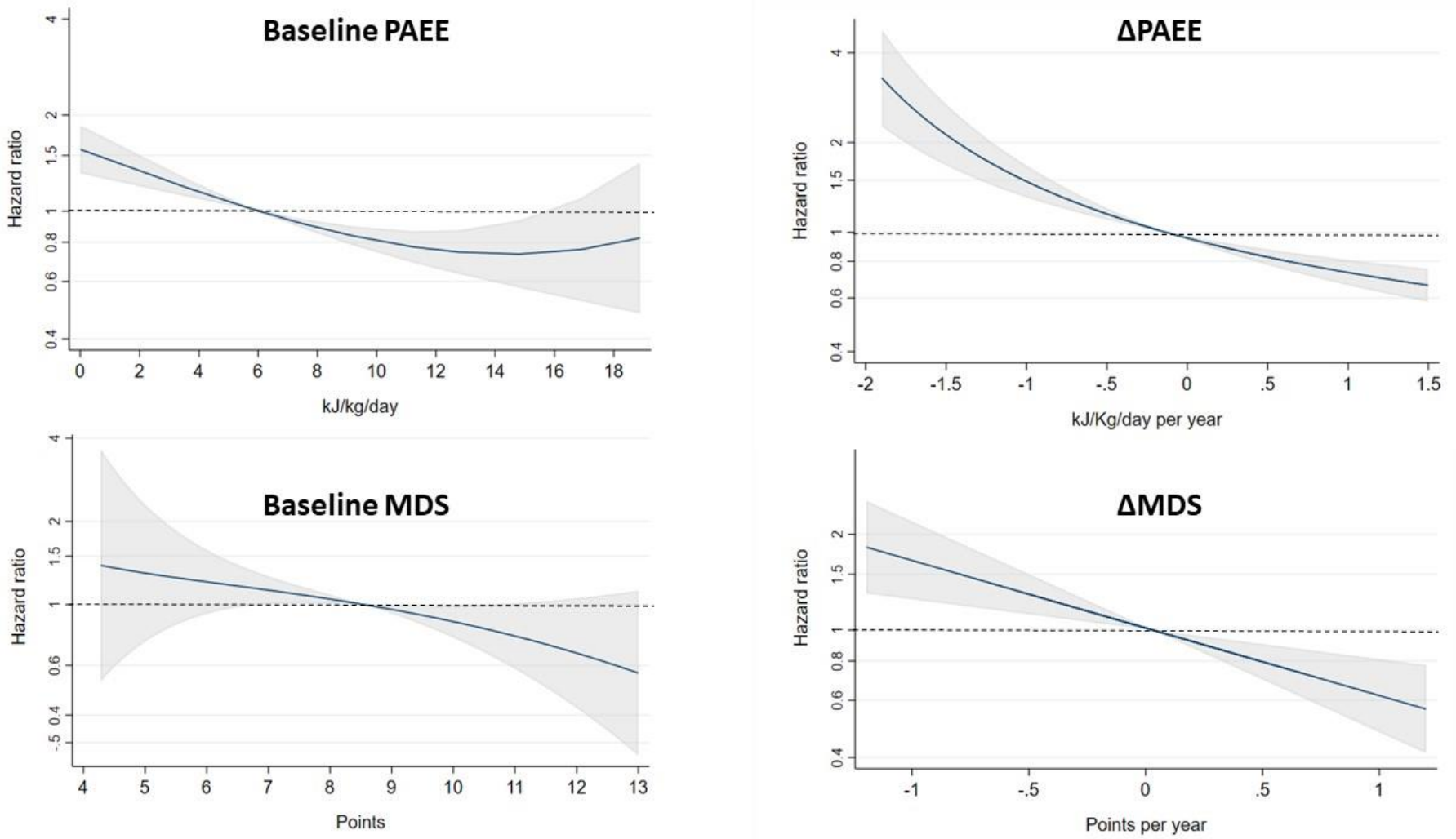



**Figure S3 - Dose-response relationship between PA and diet exposures and all-cause mortality fitted by using a Cox Proportional-Hazards with fractional polynomial in the EPIC-Norfolk Study.**

Model 4 was used for this analysis (see methods).

The 95% CI is depicted in the shaded regions.

MDS=Mediterranean diet score; PAEE=physical activity energy expenditure; ΔMDS=over time changes in MDS; ΔPAEE=over time changes in PAEE.

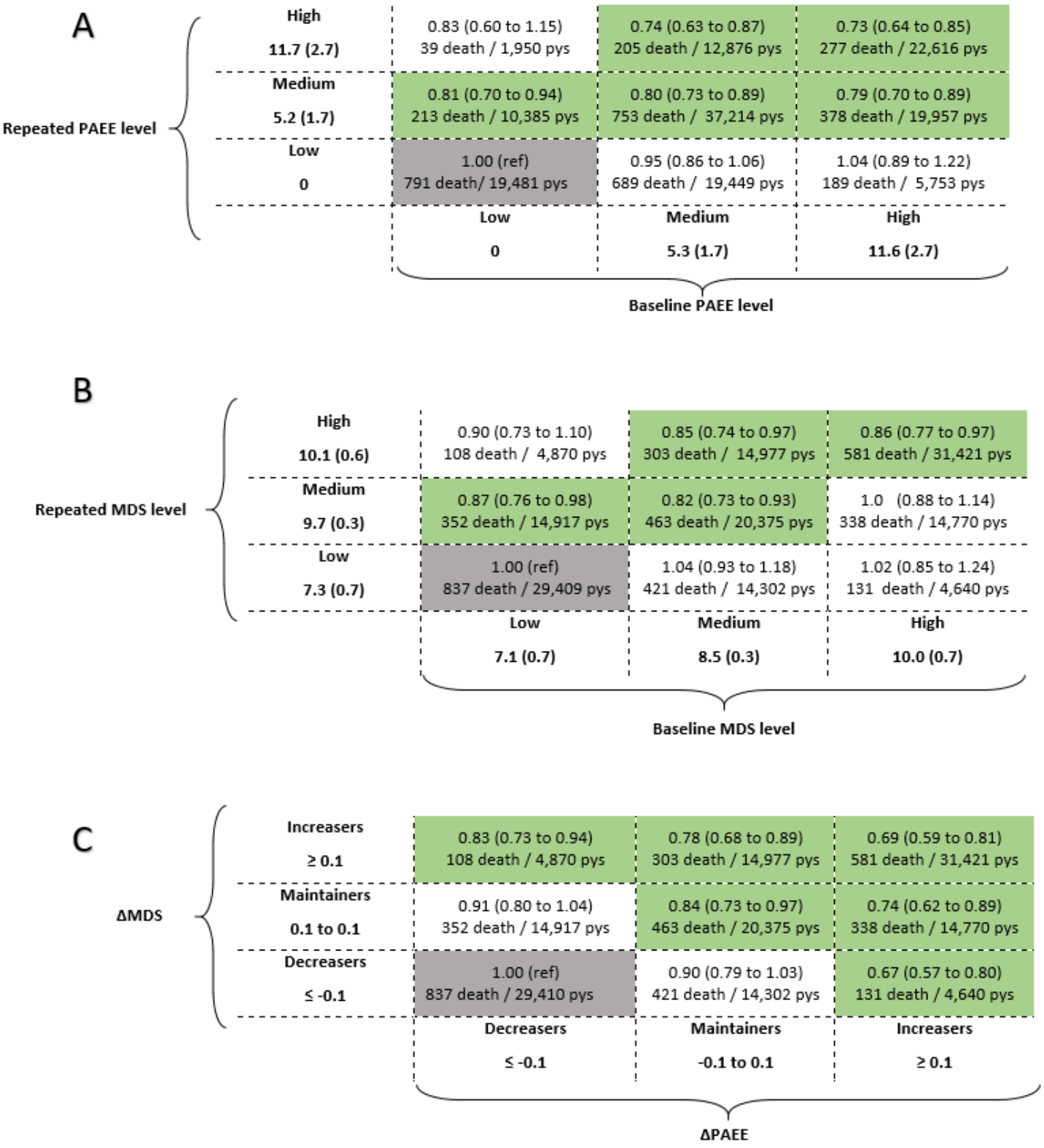



**Figure S4 - Associations of different trajectories of PA and diet with all-cause mortality in the EPIC-Norfolk Study, based on three-by-three levels of exposures**

Analyses are based on Model 4 (see methods). MDS=Mediterranean diet score; PAEE=physical activity energy expenditure; ΔMDS=over time changes in MDS; ΔPAEE=over time changes in PAEE.

A) Model mutually adjusted for baseline and repeated MDS. Cut offs for PAEE: Low PAEE = no PA reported, Medium PAEE = below 10 kJ/kg/day (WHO recommendations for additional health benefits), High PAEE = equal or above 10 kJ/kg/day.

B) Model mutually adjusted for baseline and repeated PAEE. Cut offs for MDS: Low MDS = 1st Tertile of MDS in population (< 8 points), Medium MDS 2nd Tertile of MDS in population (≥ 8 and ≤ 9.1 points), High MDS = 3rd Tertile of MDS in population (> 9.1 points).

C) Model mutually adjusted for baseline PAEE and baseline MDS. ΔPAEE is expressed in kJ/kg/day per year, ΔMDS is expressed in points per year.

**Table S9- Population impact by estimating the differences in total number of deaths that could have been potentially observed under two different counterfactual scenarios.**

| Trajectory Group (% of total sample)† | Scenario under observed exposures | | | Counterfactual scenario 1 Applying the adjusted mortality rate of G1 to all groups | | | Counterfactual scenario 2 Applying the adjusted mortality rate of G16 to all groups | | |
|---|---|---|---|---|---|---|---|---|---|
| | Crude deaths | Adjusted mortality rate‡ | Adjusted number of deaths | Number of deaths expected | Difference from the number of deaths observed | Percentage of contribution to total difference | Number of deaths expected | Difference from the number of deaths observed | Percentage of contribution to total difference |
| G1 (10.4%) | 522 | 3,095 | 433.9 | 433.9 | Ref | Ref | 369.8 | -64 | 19% |
| G2 (3.0%) | 101 | 2,943 | 120.5 | 125.2 | +5 | 2% | 106.7 | -14 | 4% |
| G3 (5.1%) | 219 | 2,852 | 198.0 | 210.7 | +13 | 5% | 179.5 | -18 | 5% |
| G4 (1.6%) | 44 | 2,119 | 50.7 | 68.2 | +18 | 6% | 58.1 | +7 | -2% |
| G5 (7.2%) | 357 | 3,443 | 327.3 | 302.9 | -24 | -9% | 258.3 | -69 | 20% |
| G6 (11.7%) | 330 | 2,762 | 449.5 | 490.0 | +41 | 15% | 417.8 | -32 | 9% |
| G7 (3.7%) | 150 | 2,813 | 144.1 | 154.9 | +11 | 4% | 132.1 | -12 | 3% |
| G8 (5.7%) | 134 | 2,606 | 207.6 | 236.7 | +29 | 11% | 201.8 | -6 | 2% |
| G9 (4.1%) | 199 | 3,260 | 177.3 | 170.6 | -7 | -2% | 145.4 | -32 | 9% |
| G10 (1.4%) | 44 | 3,042 | 55.7 | 56.4 | +1 | 0% | 48.1 | -8 | 2% |
| G11 (13.1%) | 475 | 2,775 | 499.5 | 542.7 | +43 | 16% | 462.5 | -37 | 11% |
| G12 (4.3%) | 114 | 2,461 | 150.2 | 179.2 | +29 | 11% | 152.7 | +3 | -1% |
| G13 (2.5%) | 129 | 3,472 | 115.2 | 106.0 | -9 | -3% | 90.4 | -25 | 7% |
| G14 (4.2%) | 119 | 2,774 | 163.3 | 177.4 | +14 | 5% | 151.2 | -12 | 3% |
| G15 (7.8%) | 295 | 2,831 | 305.4 | 326.6 | +21 | 8% | 278.5 | -27 | 8% |
| G16 (14.2%) | 302 | 2,514 | 506.3 | 594.0 | +88 | 32% | 506.3 | Ref | Ref |
| Sum | 3534 | | 3904 | 4175 | +271 (Standard Error: 127)§ | 100% | 3559 | -345 (Standard Error: 129)§ | 100% |
| **Percentage of difference in total deaths of counterfactual scenarios vs. observed adjusted deaths (95% CI)** | | | | | **+6.9% (0.6% to 13.3%)§** | | | **-8.8% (-15.3% to -2.4%)§** | |

†G = group. See figure 2 for the definition of each trajectory group.

‡Adjusted mortality rate is expressed as deaths per $10^5$ person-years and is based on covariates in the Model 4 (see methods).

§ Standard error of the count or percent points, estimated with a bootstrap technique.