## SUPPLEMENTARY TABLES

**Supplementary Table 1. Results of applications of joint models with shared random effects to measurements of LPC species and mortality data in the LLFS: Estimates of the association parameters for the random intercepts and random slopes of the metabolite in the survival sub-model.**

| Model | Metabolite | Variable | $\alpha_0$ ($\alpha_1$) | HR | 95% CI for HR | SD of Variable |
|---|---|---|---|---|---|---|
| int | LPC 0:0/16:0 | $b_{0i}$ | **−0.229** | **0.900** | **(0.845, 0.963)** | **0.461** |
| intslope | LPC 0:0/16:0 | $b_{0i}$ | **−0.403** | **0.828** | **(0.808, 0.948)** | **0.470** |
| intslope | LPC 0:0/16:0 | $b_{1i}$ | −6.115 | 0.990 | (0.969, 1.007) | 0.002 |
| int | LPC 0:0/16:1 | $b_{0i}$ | −0.010 | 0.996 | (0.931, 1.063) | 0.437 |
| intslope | LPC 0:0/16:1 | $b_{0i}$ | **−0.080** | **0.965** | **(0.817, 0.951)** | **0.445** |
| intslope | LPC 0:0/16:1 | $b_{1i}$ | −2.120 | 0.996 | (0.967, 1.008) | 0.002 |
| int | LPC 0:0/18:0 | $b_{0i}$ | −0.025 | 0.986 | (0.920, 1.053) | 0.572 |
| intslope | LPC 0:0/18:0 | $b_{0i}$ | −0.203 | 0.888 | (0.880, 1.036) | 0.585 |
| intslope | LPC 0:0/18:0 | $b_{1i}$ | −3.645 | 0.988 | (0.988, 1.010) | 0.003 |
| int | LPC 0:0/18:1 | $b_{0i}$ | **−0.148** | **0.931** | **(0.875, 0.996)** | **0.486** |
| intslope | LPC 0:0/18:1 | $b_{0i}$ | −0.333 | 0.849 | | 0.490 |
| intslope | LPC 0:0/18:1 | $b_{1i}$ | −16.596 | 0.989 | | 0.001 |
| int | LPC 0:0/18:2 | $b_{0i}$ | **−0.213** | **0.909** | **(0.849, 0.976)** | **0.447** |
| intslope | LPC 0:0/18:2 | $b_{0i}$ | −0.207 | 0.911 | | 0.450 |
| intslope | LPC 0:0/18:2 | $b_{1i}$ | −1.224 | 0.999 | | 0.001 |
| int | LPC 0:0/20:3 | $b_{0i}$ | −0.114 | 0.950 | (0.894, 1.010) | 0.455 |
| intslope | LPC 0:0/20:3 | $b_{0i}$ | −0.16 | 0.916 | | 0.547 |
| intslope | LPC 0:0/20:3 | $b_{1i}$ | −0.55 | 0.989 | | 0.020 |
| int | LPC 0:0/20:4 | $b_{0i}$ | **−0.158** | **0.922** | **(0.865, 0.984)** | **0.515** |
| intslope | LPC 0:0/20:4 | $b_{0i}$ | **−0.236** | **0.885** | **(0.847, 0.980)** | **0.519** |
| intslope | LPC 0:0/20:4 | $b_{1i}$ | −5.689 | 0.995 | (0.989, 1.001) | 0.001 |
| int | LPC 0:0/22:6 | $b_{0i}$ | **−0.179** | **0.91** | **(0.847, 0.969)** | **0.529** |
| intslope | LPC 0:0/22:6 | $b_{0i}$ | **−0.17** | **0.901** | **(0.822, 0.965)** | **0.610** |
| intslope | LPC 0:0/22:6 | $b_{1i}$ | −0.155 | 0.997 | (0.893, 1.076) | 0.022 |
| int | LPC 14:0/0:0 | $b_{0i}$ | **−0.225** | **0.922** | **(0.864, 0.979)** | **0.360** |
| intslope | LPC 14:0/0:0 | $b_{0i}$ | **−0.240** | **0.905** | **(0.846, 0.973)** | **0.416** |
| intslope | LPC 14:0/0:0 | $b_{1i}$ | −0.376 | 0.996 | (0.521, 1.173) | 0.012 |
| int | LPC 15:0/0:0 | $b_{0i}$ | **−0.436** | **0.786** | **(0.728, 0.840)** | **0.553** |
| intslope | LPC 15:0/0:0 | $b_{0i}$ | **−0.452** | **0.775** | **(0.726, 0.846)** | **0.563** |
| intslope | LPC 15:0/0:0 | $b_{1i}$ | −0.765 | 0.998 | (0.994, 1.004) | 0.002 |
| int | LPC 16:0/0:0 | $b_{0i}$ | **−0.230** | **0.889** | **(0.835, 0.947)** | **0.511** |
| intslope | LPC 16:0/0:0 | $b_{0i}$ | −0.369 | 0.825 | | 0.522 |
| intslope | LPC 16:0/0:0 | $b_{1i}$ | −3.785 | 0.990 | | 0.003 |
| int | LPC 16:1/0:0 | $b_{0i}$ | −0.034 | 0.985 | (0.920, 1.053) | 0.457 |
| intslope | LPC 16:1/0:0 | $b_{0i}$ | −0.249 | 0.890 | (0.891, 1.038) | 0.468 |
| intslope | LPC 16:1/0:0 | $b_{1i}$ | −4.560 | 0.988 | (0.982, 1.030) | 0.003 |
| int | LPC 17:0/0:0 | $b_{0i}$ | **−0.229** | **0.888** | **(0.832, 0.949)** | **0.518** |
| intslope | LPC 17:0/0:0 | $b_{0i}$ | −0.318 | 0.846 | | 0.524 |
| intslope | LPC 17:0/0:0 | $b_{1i}$ | −4.138 | 0.994 | | 0.002 |
| int | LPC 18:0/0:0 | $b_{0i}$ | 0.022 | 1.014 | (0.945, 1.080) | 0.620 |
| intslope | LPC 18:0/0:0 | $b_{0i}$ | 0.014 | 1.009 | (0.927, 1.070) | 0.625 |
| intslope | LPC 18:0/0:0 | $b_{1i}$ | 0.217 | 1.001 | (0.994, 1.013) | 0.005 |

| | | | | | | |
|---|---|---|---|---|---|---|
| int | LPC 18:1/0:0 | $b_{0i}$ | **−0.238** | **0.886** | **(0.831, 0.949)** | **0.506** |
| intslope | LPC 18:1/0:0 | $b_{0i}$ | **−0.430** | **0.801** | **(0.804, 0.944)** | **0.515** |
| intslope | LPC 18:1/0:0 | $b_{1i}$ | −5.637 | 0.988 | (0.985, 1.008) | 0.002 |
| int | LPC 18:2/0:0 | $b_{0i}$ | **−0.277** | **0.883** | **(0.825, 0.943)** | **0.450** |
| intslope | LPC 18:2/0:0 | $b_{0i}$ | **−0.276** | **0.883** | **(0.817, 0.942)** | **0.452** |
| intslope | LPC 18:2/0:0 | $b_{1i}$ | −1.238 | 0.999 | (0.995, 1.002) | 0.001 |
| int | LPC 18:3/0:0 | $b_{0i}$ | −0.144 | 0.953 | (0.886, 1.020) | 0.336 |
| intslope | LPC 18:3/0:0 | $b_{0i}$ | −0.148 | 0.950 | | 0.346 |
| intslope | LPC 18:3/0:0 | $b_{1i}$ | −0.640 | 0.998 | | 0.003 |
| int | LPC 20:2/0:0 | $b_{0i}$ | **−0.221** | **0.904** | **(0.849, 0.969)** | **0.458** |
| intslope | LPC 20:2/0:0 | $b_{0i}$ | **−0.227** | **0.900** | **(0.815, 0.960)** | **0.462** |
| intslope | LPC 20:2/0:0 | $b_{1i}$ | −1.342 | 0.999 | (0.988, 1.002) | 0.001 |
| int | LPC 20:3/0:0 | $b_{0i}$ | **−0.235** | **0.898** | **(0.842, 0.953)** | **0.458** |
| intslope | LPC 20:3/0:0 | $b_{0i}$ | **−0.248** | **0.891** | **(0.807, 0.947)** | **0.463** |
| intslope | LPC 20:3/0:0 | | −1.616 | 0.998 | (0.984, 1.000) | 0.001 |
| int | LPC 20:4/0:0 | $b_{0i}$ | **−0.190** | **0.912** | **(0.855, 0.974)** | **0.487** |
| intslope | LPC 20:4/0:0 | $b_{0i}$ | **−0.183** | **0.914** | **(0.822, 0.976)** | **0.488** |
| intslope | LPC 20:4/0:0 | $b_{1i}$ | −1.252 | 0.999 | (0.994, 1.005) | 0.001 |
| int | LPC 20:5/0:0 | $b_{0i}$ | **−0.230** | **0.896** | **(0.841, 0.957)** | **0.478** |
| intslope | LPC 20:5/0:0 | $b_{0i}$ | **−0.254** | **0.885** | **(0.830, 0.959)** | **0.483** |
| intslope | LPC 20:5/0:0 | $b_{1i}$ | −1.573 | 0.998 | (0.994, 1.004) | 0.001 |
| int | LPC 22:5/0:0 | $b_{0i}$ | **−0.215** | **0.892** | **(0.838, 0.955)** | **0.530** |
| intslope | LPC 22:5/0:0 | $b_{0i}$ | −0.291 | 0.856 | | 0.536 |
| intslope | LPC 22:5/0:0 | $b_{1i}$ | −4.164 | 0.994 | | 0.001 |
| int | LPC 22:6/0:0 | $b_{0i}$ | **−0.210** | **0.892** | **(0.830, 0.951)** | **0.546** |
| intslope | LPC 22:6/0:0 | $b_{0i}$ | **−0.210** | **0.892** | **(0.826, 0.951)** | **0.546** |
| intslope | LPC 22:6/0:0 | $b_{1i}$ | 0.369 | 1.000 | (0.999, 1.002) | 0.0004 |

Model – type of joint model (int – random intercept of LPC in survival sub-model, intslope – random intercept and slope of LPC in survival sub-model), see section Joint models: General specifications; Variable – $b_{0i}$: random intercept of the metabolite, $b_{1i}$: random slope of the metabolite; $\alpha_0$ ($\alpha_1$) – estimates of the regression parameters for $b_{0i}$ ($b_{1i}$) in respective models; HR – hazard ratios for an increase by a standard deviation of Variable; 95% CI for HR – respective 95% confidence intervals for HRs; SD of Variable – standard deviation of Variable. Highlighted in bold are cases where confidence intervals do not contain one. The JM were estimated using the R-package *joineR*. LPC values were transformed (see section Data). Note that for some LPCs, CIs are not available due to technical issues encountered in applications of the R-package *joineR*.

**Supplementary Table 2. Results of applications of the stochastic process model to measurements of LPC species and mortality data in the LLFS: Results of testing different null hypotheses on age patterns of the model's components.**

| LPC | H0 | | | | | | |
|---|---|---|---|---|---|---|---|
| | Qzero | QnoT | AnoT | F1noT | F0noT | ALzero | ALnoT |
| LPC 0:0/16:0 | 0.001 | 0.64 | 0.52 | <0.0001 | 0.87 | 0.88 | <0.0001 |
| LPC 0:0/16:1 | 0.010 | 1 | 0.83 | <0.0001 | 0.79 | 0.97 | <0.0001 |
| LPC 0:0/18:0 | 0.011 | 1 | 0.46 | 0.0002 | 0.22 | 0.59 | 0.0005 |
| LPC 0:0/18:1 | 0.049 | 1 | 1 | <0.0001 | 0.15 | 0.54 | <0.0001 |
| LPC 0:0/18:2 | 0.031 | 1 | 1 | <0.0001 | 0.13 | 0.055 | <0.0001 |
| LPC 0:0/20:3 | 0.005 | 0.48 | 1 | <0.0001 | 0.015 | 0.074 | <0.0001 |
| LPC 0:0/20:4 | 0.007 | 0.20 | 1 | <0.0001 | 0.013 | 0.018 | <0.0001 |
| LPC 0:0/22:6 | 0.005 | 0.34 | 0.37 | <0.0001 | 0.44 | 0.009 | <0.0001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| LPC 14:0/0:0 | <0.0001 | 0.25 | 0.08 | <0.0001 | 0.31 | 0.31 | <0.0001 |
| LPC 15:0/0:0 | <0.0001 | 0.0002 | 1 | <0.0001 | 0.0002 | <0.0001 | <0.0001 |
| LPC 16:0/0:0 | <0.0001 | 0.48 | 0.78 | <0.0001 | 0.45 | 0.53 | <0.0001 |
| LPC 16:1/0:0 | 0.003 | 1 | 0.48 | <0.0001 | 0.81 | 0.96 | <0.0001 |
| LPC 17:0/0:0 | 0.005 | 0.43 | 1 | <0.0001 | 0.63 | 0.37 | <0.0001 |
| LPC 18:0/0:0 | 0.033 | 1 | 1 | 0.040 | 0.14 | 0.37 | 0.040 |
| LPC 18:1/0:0 | 0.007 | 0.19 | 1 | <0.0001 | 0.23 | 0.44 | <0.0001 |
| LPC 18:2/0:0 | 0.008 | 0.11 | 1 | <0.0001 | 0.019 | 0.091 | <0.0001 |
| LPC 18:3/0:0 | 0.044 | 1 | 1 | <0.0001 | 0.16 | 0.082 | <0.0001 |
| LPC 20:2/0:0 | 0.002 | 1 | 1 | <0.0001 | 1 | 0.85 | <0.0001 |
| LPC 20:3/0:0 | 0.002 | 0.10 | 0.94 | <0.0001 | 0.09 | 0.34 | <0.0001 |
| LPC 20:4/0:0 | 0.004 | 0.20 | 1 | <0.0001 | 0.011 | 0.014 | <0.0001 |
| LPC 20:5/0:0 | 0.009 | 0.27 | 1 | <0.0001 | 0.39 | 0.012 | <0.0001 |
| LPC 22:5/0:0 | 0.0008 | 0.047 | 1 | <0.0001 | 0.005 | 0.014 | <0.0001 |
| LPC 22:6/0:0 | 0.007 | 1 | 1 | <0.0001 | 0.69 | 0.017 | <0.0001 |

Notes: The table shows results (p-values) of testing the following null hypotheses (H0) corresponding to one or more restrictions on parameters of SPM (see Stochastic process models: Specific parameterizations used in applications): H0: $Q(t,c) = 0$ (Qzero); H0: $Q(t,c) = Q(c)$ (QnoT); H0: $a(t,c) = a(c)$ (AnoT); H0: $f_1(t,c) = f_1(c)$ (F1noT); H0: $f_0(t,c) = f_0(c)$ (F0noT); H0: $f_1(t,c) = f_0(t,c)$, i.e., $AL(t,c) = 0$ (ALzero); H0: $f_1(t,c) = f_1(c)$ and $f_0(t,c) = f_0(c)$, i.e., $AL(t,c) = AL(c)$ (ALnoT).

**Supplementary Table 3. Results of applications of the stochastic process model to measurements of LPC species and mortality data in the LLFS: Results of testing different null hypotheses on sex-dependence of the model's components.**

| LPC | H0 | | | | | | |
|---|---|---|---|---|---|---|---|
| | MU0noC | QnoC | AnoC | BnoC | F1noC | F0noC | ALLnoC |
| LPC 0:0/16:0 | <0.0001 | 0.09 | 0.57 | 0.40 | 0.56 | 0.57 | <0.0001 |
| LPC 0:0/16:1 | <0.0001 | 0.037 | 0.18 | 0.75 | <0.0001 | 1 | <0.0001 |
| LPC 0:0/18:0 | <0.0001 | 0.10 | 0.59 | 0.58 | <0.0001 | 1 | <0.0001 |
| LPC 0:0/18:1 | <0.0001 | 0.53 | 0.61 | 0.63 | 0.63 | 1 | <0.0001 |
| LPC 0:0/18:2 | <0.0001 | 0.35 | 0.40 | 0.14 | <0.0001 | 1 | <0.0001 |
| LPC 0:0/20:3 | <0.0001 | 0.05 | 0.71 | 0.83 | 0.16 | 1 | <0.0001 |
| LPC 0:0/20:4 | <0.0001 | 0.06 | 0.35 | 0.87 | 0.007 | 1 | <0.0001 |
| LPC 0:0/22:6 | <0.0001 | 0.94 | 0.77 | 0.51 | 0.10 | 0.37 | <0.0001 |
| LPC 14:0/0:0 | <0.0001 | 0.008 | 0.16 | 0.74 | <0.0001 | 0.29 | <0.0001 |
| LPC 15:0/0:0 | <0.0001 | 0.13 | 0.12 | 0.40 | 0.001 | 0.16 | <0.0001 |
| LPC 16:0/0:0 | <0.0001 | 0.07 | 0.82 | 0.40 | 0.07 | 0.50 | <0.0001 |
| LPC 16:1/0:0 | <0.0001 | 0.011 | 0.18 | 0.33 | <0.0001 | 1 | <0.0001 |
| LPC 17:0/0:0 | <0.0001 | 0.29 | 0.39 | 0.66 | 0.0004 | 0.54 | <0.0001 |
| LPC 18:0/0:0 | <0.0001 | 0.11 | 0.85 | 0.32 | <0.0001 | 1 | <0.0001 |
| LPC 18:1/0:0 | <0.0001 | 0.08 | 0.85 | 0.96 | 0.83 | 0.65 | <0.0001 |
| LPC 18:2/0:0 | <0.0001 | 0.11 | 0.36 | 0.16 | <0.0001 | 0.50 | <0.0001 |
| LPC 18:3/0:0 | <0.0001 | 0.38 | 0.84 | 0.77 | 1 | 1 | <0.0001 |
| LPC 20:2/0:0 | <0.0001 | 0.025 | 0.37 | 0.66 | 0.46 | 1 | <0.0001 |
| LPC 20:3/0:0 | <0.0001 | 0.05 | 0.53 | 0.14 | 0.018 | 0.68 | <0.0001 |
| LPC 20:4/0:0 | <0.0001 | 0.041 | 0.72 | 0.46 | <0.0001 | 1 | <0.0001 |
| LPC 20:5/0:0 | <0.0001 | 0.39 | 0.31 | 0.37 | 0.018 | 0.36 | <0.0001 |
| LPC 22:5/0:0 | <0.0001 | 0.043 | 0.63 | 0.26 | <0.0001 | 0.81 | <0.0001 |
| LPC 22:6/0:0 | <0.0001 | 0.76 | 0.42 | 0.71 | 0.14 | 1 | <0.0001 |

The table shows results (*p*-values) of testing the following null hypotheses (H0) corresponding to one or more restrictions on parameters of SPM (see Stochastic process models: Specific parameterizations used in applications): H0: $\mu_0(t,c) = \mu_0(t)$ (MU0noC); H0: $Q(t,c) = Q(t)$ (QnoC); H0: $a(t,c) = a(t)$ (AnoC); H0: $b(t,c) = b(t)$ (BnoC); H0: $f_1(t,c) = f_1(t)$ (F1noC); H0: $f_0(t,c) = f_0(t)$ (F0noC); H0: $\mu_0(t,c) = \mu_0(t)$ and $Q(t,c) = Q(t)$ and $a(t,c) = a(t)$ and $b(t,c) = b(t)$ and $f_1(t,c) = f_1(c)$ and $f_0(t,c) = f_0(c)$ (ALLnoC). Here, $c$ denotes variable SexM in respective components. Note that there are other covariates in $\mu_0(t,c)$ (see Stochastic process models: Specific parameterizations used in applications), which still remain in the restricted models in MU0noC and ALLnoC; for brevity of notation, we do not show them in the formulae above.

**Supplementary Table 4. Results of applications of the stochastic process model to measurements of LPC species and mortality data in the LLFS: Estimates of parameters in different components of the model.**

| LPC | $\mu_0(t,c)$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $\ln a_{\mu_0}$ | $b_{\mu_0}$ | $\beta_{\mu_0}$ (SexM) | $\beta_{\mu_0}$ (IsDK) | $\beta_{\mu_0}$ (LowEduc) | $\beta_{\mu_0}$ (Smoke100) | $\beta_{\mu_0}$ (MedsLipid) | $\beta_{\mu_0}$ (MedsHtn) | $\beta_{\mu_0}$ (MedsNitro) |
| LPC 0:0/16:0 | −4.681 | 0.119 | 0.491 | 0.077 | −0.069 | 0.204 | −0.235 | −0.184 | 0.474 |
| LPC 0:0/16:1 | −4.721 | 0.118 | 0.499 | 0.082 | −0.063 | 0.202 | −0.225 | −0.184 | 0.468 |
| LPC 0:0/18:0 | −4.815 | 0.117 | 0.511 | 0.076 | −0.063 | 0.199 | −0.225 | −0.181 | 0.470 |
| LPC 0:0/18:1 | −4.928 | 0.117 | 0.476 | 0.070 | −0.062 | 0.205 | −0.221 | −0.182 | 0.459 |
| LPC 0:0/18:2 | −4.920 | 0.117 | 0.481 | 0.073 | −0.063 | 0.204 | −0.221 | −0.183 | 0.461 |
| LPC 0:0/20:3 | −4.688 | 0.117 | 0.498 | 0.081 | −0.064 | 0.209 | −0.228 | −0.187 | 0.469 |
| LPC 0:0/20:4 | −4.631 | 0.116 | 0.512 | 0.074 | −0.068 | 0.209 | −0.227 | −0.191 | 0.478 |
| LPC 0:0/22:6 | −4.833 | 0.119 | 0.470 | 0.071 | −0.062 | 0.205 | −0.217 | −0.178 | 0.462 |
| LPC 14:0/0:0 | −4.576 | 0.120 | 0.495 | 0.079 | −0.074 | 0.212 | −0.249 | −0.191 | 0.488 |
| LPC 15:0/0:0 | −3.580 | 0.127 | 0.560 | −0.020 | −0.117 | 0.225 | −0.384 | −0.244 | 0.629 |
| LPC 16:0/0:0 | −4.617 | 0.120 | 0.502 | 0.079 | −0.074 | 0.205 | −0.245 | −0.184 | 0.481 |
| LPC 16:1/0:0 | −4.707 | 0.118 | 0.502 | 0.082 | −0.066 | 0.201 | −0.227 | −0.184 | 0.470 |
| LPC 17:0/0:0 | −4.864 | 0.119 | 0.477 | 0.057 | −0.064 | 0.205 | −0.232 | −0.184 | 0.469 |
| LPC 18:0/0:0 | −4.825 | 0.117 | 0.513 | 0.072 | −0.061 | 0.200 | −0.226 | −0.182 | 0.470 |
| LPC 18:1/0:0 | −4.314 | 0.116 | 0.509 | 0.098 | −0.074 | 0.219 | −0.251 | −0.197 | 0.498 |
| LPC 18:2/0:0 | −4.282 | 0.116 | 0.509 | 0.064 | −0.071 | 0.215 | −0.272 | −0.203 | 0.501 |
| LPC 18:3/0:0 | −4.896 | 0.117 | 0.477 | 0.072 | −0.062 | 0.205 | −0.219 | −0.182 | 0.459 |
| LPC 20:2/0:0 | −4.758 | 0.118 | 0.503 | 0.071 | −0.065 | 0.203 | −0.233 | −0.184 | 0.470 |
| LPC 20:3/0:0 | −4.422 | 0.115 | 0.503 | 0.078 | −0.073 | 0.214 | −0.252 | −0.196 | 0.490 |
| LPC 20:4/0:0 | −4.559 | 0.117 | 0.514 | 0.073 | −0.070 | 0.210 | −0.225 | −0.188 | 0.477 |
| LPC 20:5/0:0 | −4.396 | 0.115 | 0.576 | 0.133 | −0.067 | 0.219 | −0.228 | −0.210 | 0.515 |
| LPC 22:5/0:0 | −4.404 | 0.116 | 0.542 | 0.086 | −0.070 | 0.209 | −0.242 | −0.205 | 0.503 |
| LPC 22:6/0:0 | −4.819 | 0.118 | 0.491 | 0.084 | −0.065 | 0.204 | −0.215 | −0.182 | 0.463 |

**Supplementary Table 4. (Continued)**

| LPC | $\mu_0(t,c)$ | | | | | | | | $Q(t,c)$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\beta_{\mu_0}$ (MedsDiab) | $\beta_{\mu_0}$ (APOE4) | $\beta_{\mu_0}$ (NoIntPA) | $\beta_{\mu_0}$ (SPPB) | $\beta_{\mu_0}$ (PREV6) | $\beta_{\mu_0}$ (BMI) | $\beta_{\mu_0}$ (PC1) | $\beta_{\mu_0}$ (PC2) | $a_Q$ | $b_Q$ | $\beta_Q$ |
| LPC 0:0/16:0 | 0.353 | 0.204 | 0.032 | −0.140 | 0.191 | −0.024 | −0.304 | −0.125 | 1.1E-03 | 4.8E-06 | −1.1E-03 |
| LPC 0:0/16:1 | 0.349 | 0.203 | 0.034 | −0.140 | 0.183 | −0.023 | −0.239 | −0.093 | 1.1E-03 | 3.3E-11 | −1.1E-03 |
| LPC 0:0/18:0 | 0.354 | 0.206 | 0.031 | −0.141 | 0.191 | −0.024 | −0.158 | −0.044 | 7.9E-04 | 6.2E-12 | −7.9E-04 |
| LPC 0:0/18:1 | 0.340 | 0.204 | 0.034 | −0.140 | 0.199 | −0.024 | −0.077 | 0.131 | 8.8E-05 | 2.4E-12 | −8.8E-05 |
| LPC 0:0/18:2 | 0.340 | 0.205 | 0.032 | −0.139 | 0.200 | −0.024 | −0.096 | 0.103 | 1.1E-04 | 6.2E-15 | −1.1E-04 |
| LPC 0:0/20:3 | 0.353 | 0.205 | 0.035 | −0.141 | 0.199 | −0.024 | −0.228 | −0.150 | 4.2E-04 | 1.2E-05 | −4.2E-04 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| LPC 0:0/20:4 | 0.357 | 0.211 | 0.040 | −0.145 | 0.215 | −0.025 | −0.241 | −0.123 | 5.7E-04 | 2.4E-05 | −5.7E-04 |
| LPC 0:0/22:6 | 0.354 | 0.214 | 0.031 | −0.139 | 0.193 | −0.024 | −0.201 | −0.050 | 2.0E-04 | -3.4E-06 | 2.0E-05 |
| LPC 14:0/0:0 | 0.364 | 0.219 | 0.038 | −0.142 | 0.210 | −0.027 | −0.340 | −0.319 | 1.3E-03 | 1.2E-05 | −1.3E-03 |
| LPC 15:0/0:0 | 0.424 | 0.286 | 0.013 | −0.168 | 0.181 | −0.046 | −0.799 | −0.869 | 1.2E-03 | 9.6E-05 | −1.1E-03 |
| LPC 16:0/0:0 | 0.356 | 0.205 | 0.031 | −0.141 | 0.185 | −0.025 | −0.372 | −0.160 | 1.3E-03 | 1.7E-05 | −1.3E-03 |
| LPC 16:1/0:0 | 0.348 | 0.200 | 0.033 | −0.140 | 0.185 | −0.023 | −0.245 | −0.131 | 1.2E-03 | 1.1E-11 | −1.2E-03 |
| LPC 17:0/0:0 | 0.347 | 0.207 | 0.036 | −0.140 | 0.190 | −0.024 | −0.178 | 0.058 | 4.0E-04 | 6.0E-06 | −4.0E-04 |
| LPC 18:0/0:0 | 0.353 | 0.206 | 0.031 | −0.142 | 0.195 | −0.024 | −0.124 | −0.007 | 5.8E-04 | 4.7E-12 | −5.8E-04 |
| LPC 18:1/0:0 | 0.349 | 0.205 | 0.039 | −0.148 | 0.201 | −0.030 | −0.389 | −0.237 | 6.9E-04 | 2.7E-05 | −6.9E-04 |
| LPC 18:2/0:0 | 0.348 | 0.210 | 0.044 | −0.149 | 0.219 | −0.030 | −0.377 | −0.311 | 6.6E-04 | 3.6E-05 | −6.6E-04 |
| LPC 18:3/0:0 | 0.343 | 0.204 | 0.031 | −0.139 | 0.198 | −0.024 | −0.102 | 0.087 | 9.9E-05 | 1.0E-12 | −9.9E-05 |
| LPC 20:2/0:0 | 0.342 | 0.201 | 0.030 | −0.140 | 0.193 | −0.024 | −0.219 | −0.057 | 1.0E-03 | 5.0E-12 | −1.0E-03 |
| LPC 20:3/0:0 | 0.362 | 0.202 | 0.047 | −0.149 | 0.215 | −0.028 | −0.313 | −0.216 | 5.6E-04 | 3.8E-05 | −5.6E-04 |
| LPC 20:4/0:0 | 0.363 | 0.208 | 0.035 | −0.145 | 0.210 | −0.025 | −0.304 | −0.198 | 5.4E-04 | 2.4E-05 | −5.4E-04 |
| LPC 20:5/0:0 | 0.348 | 0.207 | 0.041 | −0.153 | 0.203 | −0.032 | −0.318 | −0.105 | 3.6E-04 | 3.9E-05 | −3.6E-04 |
| LPC 22:5/0:0 | 0.351 | 0.209 | 0.043 | −0.150 | 0.219 | −0.029 | −0.286 | −0.293 | 7.0E-04 | 4.0E-05 | −7.0E-04 |
| LPC 22:6/0:0 | 0.347 | 0.205 | 0.030 | −0.139 | 0.195 | −0.024 | −0.185 | −0.016 | 2.2E-04 | 1.5E-11 | −2.2E-04 |

**Supplementary Table 4. (Continued)**

| LPC | $a(t,c)$ | | $Y(t_0,c)$ | $b(t,c)$ | | $f_1(t,c)$ | | | $f_0(t,c)$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $a_Y$ | $b_Y$ | $\beta_Y$ | $\sigma_0$ | $\sigma_1$ | $\beta_W$ | $a_{f_1}$ | $b_{f_1}$ | $\beta_{f_1}$ | $a_{f_0}$ | $b_{f_0}$ | $\beta_{f_0}$ |
| LPC 0:0/16:0 | −0.075 | 1.6E-04 | 2.0E-04 | 1.002 | 0.305 | 9.3E-03 | 0.237 | −0.012 | −0.018 | 0.200 | 0.005 | 2.4E+00 |
| LPC 0:0/16:1 | −0.077 | 5.4E-05 | 7.9E-03 | 0.982 | 0.326 | 3.7E-03 | 0.252 | −0.007 | −0.256 | 0.154 | −0.011 | −2.1E-01 |
| LPC 0:0/18:0 | −0.063 | 1.7E-05 | 2.9E-03 | 1.006 | 0.302 | −5.9E-03 | 0.170 | −0.004 | −0.146 | 0.298 | −0.050 | 4.9E-01 |
| LPC 0:0/18:1 | −0.063 | 4.9E-10 | −3.0E-03 | 0.987 | 0.314 | 5.5E-03 | 0.198 | −0.010 | −0.015 | 4.000 | −0.133 | −2.6E+00 |
| LPC 0:0/18:2 | −0.064 | 5.9E-13 | −5.1E-03 | 0.952 | 0.304 | 1.6E-02 | 0.233 | −0.017 | 0.188 | 4.000 | −0.133 | −2.4E+00 |
| LPC 0:0/20:3 | −0.075 | 7.6E-09 | 2.1E-03 | 0.991 | 0.317 | −2.4E-03 | 0.223 | −0.011 | −0.044 | −1.764 | 0.096 | −7.1E-06 |
| LPC 0:0/20:4 | −0.064 | 2.7E-10 | 5.2E-03 | 0.992 | 0.297 | −1.8E-03 | 0.181 | −0.012 | 0.086 | −1.240 | 0.087 | 4.5E-06 |
| LPC 0:0/22:6 | −0.052 | 7.5E-10 | −1.5E-03 | 0.989 | 0.284 | 6.8E-03 | 0.139 | −0.005 | −0.054 | 2.912 | −0.068 | −3.4E+00 |
| LPC 14:0/0:0 | −0.089 | 4.7E-04 | −4.9E-03 | 0.980 | 0.326 | −3.8E-03 | 0.343 | −0.013 | −0.184 | 0.242 | 0.026 | 1.8E+00 |
| LPC 15:0/0:0 | −0.057 | 4.8E-10 | −8.1E-03 | 0.986 | 0.276 | 8.3E-03 | 0.314 | −0.015 | −0.104 | 0.111 | 0.057 | 4.8E-01 |
| LPC 16:0/0:0 | −0.069 | 6.7E-05 | 1.3E-03 | 1.005 | 0.298 | 9.2E-03 | 0.246 | −0.011 | −0.057 | 0.088 | 0.020 | 1.1E+00 |
| LPC 16:1/0:0 | −0.077 | 1.8E-04 | 7.9E-03 | 0.984 | 0.316 | 1.3E-02 | 0.240 | −0.006 | −0.278 | −0.005 | 0.009 | −3.0E-01 |
| LPC 17:0/0:0 | −0.066 | 1.1E-10 | 1.8E-03 | 1.016 | 0.298 | −4.7E-03 | 0.163 | −0.005 | −0.115 | 1.579 | −0.033 | 1.5E+00 |
| LPC 18:0/0:0 | −0.049 | 2.9E-09 | −1.0E-03 | 0.996 | 0.299 | −1.1E-02 | 0.141 | −0.002 | −0.145 | 0.441 | −0.074 | 5.5E-01 |
| LPC 18:1/0:0 | −0.064 | 1.4E-10 | 1.1E-03 | 0.987 | 0.308 | 5.6E-04 | 0.232 | −0.012 | −0.007 | −0.532 | 0.068 | 4.6E-01 |
| LPC 18:2/0:0 | −0.065 | 1.4E-10 | −5.4E-03 | 0.953 | 0.301 | 1.5E-02 | 0.222 | −0.017 | 0.222 | −0.848 | 0.070 | 6.2E-01 |
| LPC 18:3/0:0 | −0.082 | 3.4E-10 | 1.2E-03 | 0.967 | 0.331 | −3.4E-03 | 0.250 | −0.013 | 0.000 | 4.000 | −0.133 | −2.2E+00 |
| LPC 20:2/0:0 | −0.071 | 1.8E-10 | 5.2E-03 | 1.011 | 0.314 | 5.0E-03 | 0.160 | −0.008 | −0.024 | 0.323 | 0.001 | −7.0E-02 |
| LPC 20:3/0:0 | −0.074 | 2.0E-05 | 3.7E-03 | 0.980 | 0.307 | 1.7E-02 | 0.242 | −0.015 | 0.074 | −0.970 | 0.076 | 3.8E-01 |
| LPC 20:4/0:0 | −0.060 | 3.7E-11 | 1.9E-03 | 0.994 | 0.288 | 7.6E-03 | 0.121 | −0.011 | 0.175 | −1.516 | 0.092 | 2.4E-06 |
| LPC 20:5/0:0 | −0.048 | 4.0E-11 | −5.0E-03 | 0.975 | 0.271 | 8.7E-03 | 0.241 | −0.013 | 0.075 | 0.420 | 0.060 | −8.0E-01 |
| LPC 22:5/0:0 | −0.065 | 5.4E-12 | 2.8E-03 | 0.983 | 0.301 | 1.2E-02 | 0.108 | −0.008 | 0.142 | −0.913 | 0.082 | −1.7E-01 |
| LPC 22:6/0:0 | −0.055 | 3.5E-11 | 4.3E-03 | 0.985 | 0.286 | 3.9E-03 | 0.120 | −0.006 | 0.049 | 2.632 | −0.058 | −1.8E+00 |

Notes: Columns $\beta_{\mu_0}(.)$ show coefficients for the variables in the baseline hazard rate ($\mu_0(t,c)$): SexM: sex (1 – male, 0 – female); IsDK: country (1 – Denmark, 0 – USA); LowEduc: low education (1 – below high school, 0 – otherwise); Smoke100: smoking (1 – smoked 100 cigarettes in lifetime, 0 - otherwise); MedsLipid: lipid-lowering medications (1 – taking, 0 – not taking); MedsHtn: hypertension medications (1 – taking, 0 – not taking); MedsNitro: angina medications (1 – taking, 0 – not taking); MedsDiab: diabetes mellitus medications (1 – taking,

0 – not taking); APOE4: *APOE* ε4 carrier status (1 – carrier, 0 – non-carrier); NoIntPA: no intense physical activity (PA) at baseline (1 – no intense PA, 0 – intense PA); SPPB: Short Physical Performance Battery (SPPB) total score at baseline; PREV6: prevalence of major diseases (heart disease, stroke, lung disease, cancer, hypertension, diabetes) at baseline (1: any of the diseases, 0 – none of the diseases); BMI: body mass index (BMI) at baseline; PC1, PC2: first two principal components computed from LLFS whole-genome sequencing data. In other components, respective $\beta$'s show coefficients for variable SexM. LPC values were transformed (see Data).

**Supplementary Table 5. Applications of joint models to measurements of LPC variants and mortality data in the LLFS: Estimates from familial bootstrap.**

| Metabolite | Median HR (Range) | | |
|---|---|---|---|
| | Total | Females | Males |
| LPC 0:0/16:0 | **0.830 (0.743, 0.934)** | **0.843 (0.723, 0.971)** | **0.813 (0.694, 0.968)** |
| LPC 0:0/16:1 | 0.961 (0.842, 1.079) | 0.989 (0.844, 1.134) | 0.935 (0.775, 1.074) |
| LPC 0:0/18:0 | 0.977 (0.896, 1.075) | 1.003 (0.868, 1.142) | 0.942 (0.817, 1.070) |
| LPC 0:0/18:1 | **0.884 (0.796, 0.994)** | 0.923 (0.790, 1.083) | **0.831 (0.685, 0.995)** |
| LPC 0:0/18:2 | **0.824 (0.718, 0.942)** | 0.910 (0.749, 1.090) | **0.735 (0.611, 0.897)** |
| LPC 0:0/20:3 | **0.852 (0.764, 0.973)** | **0.858 (0.735, 0.976)** | **0.836 (0.691, 0.993)** |
| LPC 0:0/20:4 | **0.860 (0.778, 0.962)** | **0.852 (0.747, 0.986)** | **0.867 (0.736, 0.981)** |
| LPC 0:0/22:6 | **0.842 (0.757, 0.921)** | **0.799 (0.677, 0.900)** | **0.869 (0.735, 0.986)** |
| LPC 14:0/0:0 | **0.828 (0.738, 0.947)** | **0.858 (0.723, 0.995)** | **0.801 (0.670, 0.982)** |
| LPC 15:0/0:0 | **0.713 (0.643, 0.778)** | **0.732 (0.638, 0.850)** | **0.690 (0.591, 0.772)** |
| LPC 16:0/0:0 | **0.831 (0.768, 0.915)** | **0.848 (0.732, 0.998)** | **0.815 (0.739, 0.934)** |
| LPC 16:1/0:0 | 0.951 (0.836, 1.056) | 0.981 (0.828, 1.135) | 0.924 (0.794, 1.044) |
| LPC 17:0/0:0 | **0.821 (0.737, 0.913]** | **0.828 (0.712, 0.955)** | **0.817 (0.705, 0.973)** |
| LPC 18:0/0:0 | 1.014 (0.913, 1.115) | 1.054 (0.931, 1.214) | 0.976 (0.831, 1.142) |
| LPC 18:1/0:0 | **0.820 (0.742, 0.924)** | 0.863 (0.731, 1.043) | **0.794 (0.666, 0.932)** |
| LPC 18:2/0:0 | **0.785 (0.678, 0.871)** | 0.870 (0.711, 1.049) | **0.707 (0.563, 0.838)** |
| LPC 18:3/0:0 | 0.888 (0.756, 1.025) | 0.987 (0.855, 1.240) | **0.780 (0.625, 0.985)** |
| LPC 20:2/0:0 | **0.820 (0.715, 0.910)** | 0.856 (0.765, 1.048) | **0.774 (0.659, 0.869)** |
| LPC 20:3/0:0 | **0.767 (0.680, 0.873)** | **0.798 (0.657, 0.950)** | **0.746 (0.603, 0.882)** |
| LPC 20:4/0:0 | **0.861 (0.764, 0.949)** | 0.897 (0.785, 1.049) | 0.808 (0.684, 1.004) |
| LPC 20:5/0:0 | **0.776 (0.696, 0.870)** | **0.742 (0.619, 0.864)** | **0.810 (0.698, 0.989)** |
| LPC 22:5/0:0 | **0.793 (0.714, 0.857)** | **0.781 (0.670, 0.883)** | **0.796 (0.680, 0.898)** |
| LPC 22:6/0:0 | **0.805 (0.733, 0.892)** | **0.759 (0.674, 0.912)** | **0.829 (0.731, 0.936)** |

Notes: The table reports medians of hazard ratios (HR) for a unit increase in the transformed metabolite values (ranges in parentheses) for the association parameters for the metabolites in the survival sub-model computed using the familial bootstrap method [18] in 100 bootstrap samples generated from the original sample. See main text (section Materials and Methods: Sensitivity analyses) for details. The joint models were estimated using the R-package *JM*. The cases where the range of HR does not contain one are highlighted in bold. The case where 95% confidence intervals (CI) for HR in the main calculations (Table 1) did not contain one but the HR range in the familial bootstrap included one is highlighted with a yellow background. The cases where 95% CI for HR in the main calculations (Table 1) contained one but the HR range in the familial bootstrap did not include one are highlighted with a grey background.

**Supplementary Table 6. Characteristics of the Long Life Family Study metabolomics sample (batch 6, released on October 25, 2023)**

| Characteristics | Field Center | | | | Total Sample |
|---|---|---|---|---|---|
| | BU | NY | PT | DK | |
| Number of families | 244 | 263 | 222 | 77 | 582 |
| Number of participants at any visit | 1,282 | 875 | 1,185 | 1,239 | 4,581 |
| Number of participants at visit 1 | 1,176 | 718 | 1,131 | 1,196 | 4,221 |

| | | | | | |
|---|---|---|---|---|---|
| Number of participants at visit 2 | 682 | 490 | 585 | 798 | 2,555 |
| Number of participants with genetic PCs | 1,270 | 847 | 1,174 | 1,229 | 4,520 |
| Number (%) of deceased participants | 435 (33.9%) | 358 (40.9%) | 477 (40.3%) | 388 (31.3%) | 1,658 (36.2%) |
| Follow-up period (years) (mean ± SD (range)) | 10.5 ± 4.8 (0.00, 18.22) | 10.1 ± 4.5 (0.00, 18.41) | 10.8 ± 4.8 (0.29, 18.50) | 11.7 ± 5.5 (0.00, 17.93) | 10.8 ± 5.0 (0.00, 18.50) |
| Age at baseline (mean ± SD (range)) | 69.5 ± 16.0 (32, 110) | 73.5 ± 16.1 (24, 108) | 71.2 ± 15.9 (36, 104) | 67.3 ± 14.3 (36, 104) | 70.0 ± 15.7 (24, 110) |
| Whites (%) | 99.2% | 98.3% | 99.6% | 99.0% | 99.1% |
| Females (%) | 55.5% | 54.6% | 55.9% | 54.3% | 55.1% |
| Low educated participants (below high school) (%) | 5.9% | 7.4% | 7.2% | 27.7% | 12.4% |
| Smokers (smoked >100 cigarettes in lifetime) (%) | 41.5% | 45.5% | 35.6% | 49.2% | 42.8% |
| *APOE* ε4 allele carriers (%) | 13.7% | 17.3% | 17.2% | 25.3% | 18.4% |
| Medication use: angina (%) | 32.1% | 30.4% | 32.8% | 23.5% | 29.6% |
| Medication use: anti-diabetic (%) | 6.8% | 7.5% | 9.1% | 5.5% | 7.2% |
| Medication use: anti-hypertensive (%) | 50.4% | 52.5% | 55.1% | 42.0% | 49.7% |
| Medication use: lipid-lowering (%) | 34.9% | 43.3% | 39.2% | 21.1% | 33.9% |
| No intense physical activity at baseline (%) | 64.2% | 56.9% | 62.3% | 74.0% | 65.0% |
| SPPB total score at baseline (mean ± SD (range)) | 10.0 ± 3.0 (0, 12) | 9.6 ± 3.0 (0, 12) | 9.8 ± 3.0 (1, 12) | 10.4 ± 2.8 (1, 12) | 10.0 ± 3.0 (0, 12) |
| Prevalence of major diseases at baseline (%) | 68.9% | 70.4% | 69.8% | 66.5% | 68.8% |
| BMI at baseline (mean ± SD (range)) | 27.5 ± 5.1 (16, 57) | 26.6 ± 4.2 (17, 41) | 27.7 ± 5.2 (17, 52) | 26.4 ± 4.2 (13, 54) | 27.1 ± 4.8 (13, 57) |

Notes: (a) Genetic PCs were computed from LLFS whole-genome sequencing data; (b) Number of missing data: race – 20, education – 10, smoking – 18, *APOE* – 257, angina medications – 273, anti-diabetic drugs – 273, anti-hypertensive drugs – 273, lipid-lowering drugs – 273, no intense physical activity at baseline – 449, SPPB total score at baseline – 179, prevalence of major diseases at baseline – 2, other variables listed in the table have no missing values; (c) The numbers shown in "Number of deceased participants" and "Follow-up period" correspond to the LLFS data release used in this paper (see Data). Abbreviations: BMI: body mass index; BU: Boston; DK: Denmark; NY: New York; PT: Pittsburgh; SD: standard deviation; SPPB: Short Physical Performance Battery.