

Table S1 Descriptive statistics of the study population.

| Characteristics   |               | Total<br>(N=377) | Female<br>(N=252) | Male<br>(N=125) | p-value†<br>(sex diff) |
|-------------------|---------------|------------------|-------------------|-----------------|------------------------|
| LTL (in kb)       | mean(SD)      | 5.73             | 5.80              | 5.61            | 0.006*                 |
| Fatigue score     | mean(SD)      | 5.33             | 5.27              | 5.45            | 0.187                  |
|                   | 0 N (%)       | 4 (1.1%)         | 4 (1.6%)          | 0 (0%)          |                        |
|                   | 1 N (%)       | 2 (0.5%)         | 2 (0.8%)          | 0 (0%)          |                        |
|                   | 2 N (%)       | 15 (4.0%)        | 10 (4.0%)         | 5 (4.0%)        |                        |
|                   | 3 N (%)       | 21 (5.6%)        | 15 (6.0%)         | 6 (4.8%)        |                        |
|                   | 4 N (%)       | 25 (6.6%)        | 16 (6.3%)         | 9 (7.2%)        |                        |
|                   | 5 N (%)       | 47 (12.5%)       | 34 (13.5%)        | 13 (10.4%)      |                        |
|                   | 6 N (%)       | 263 (69.8%)      | 171 (67.8%)       | 92 (73.6%)      |                        |
| Age               | mean(SD)      | 78.8             | 78.9              | 78.5            | 0.277                  |
| Zygosity          | MZ N(%)       | 174 (46.2%)      | 120 (47.6%)       | 54 (43.2%)      |                        |
|                   | DZ N(%)       | 203 (53.8%)      | 132 (52.4%)       | 71 (56.8%)      |                        |
| Smoking           | Never N (%)   | 137 (36.3%)      | 113 (44.8%)       | 24 (19.2%)      |                        |
|                   | Former N (%)  | 131 (34.7%)      | 74 (29.4%)        | 57 (45.6%)      |                        |
|                   | Current N (%) | 109 (28.9%)      | 65 (25.8%)        | 44 (35.2%)      |                        |
| BMI               | mean(SD)      | 24.07            | 23.58             | 25.05           | <0.001*                |
| Physical activity | mean(SD)      | 2.51             | 2.51              | 2.52            | 0.892                  |
|                   | 0 N (%)       | 53 (14.1%)       | 35 (13.9%)        | 18 (14.4%)      |                        |
|                   | 1 N (%)       | 8 (2.1%)         | 6 (2.4%)          | 2 (1.6%)        |                        |
|                   | 2 N (%)       | 139 (36.9%)      | 91 (36.1%)        | 48 (38.4%)      |                        |
|                   | 3 N (%)       | 47 (12.5%)       | 36 (14.3%)        | 11 (8.8%)       |                        |
|                   | 4 N (%)       | 130 (34.5%)      | 84 (33.3%)        | 46 (36.8%)      |                        |

| Characteristics continued. |          | Total (N=377) | Female (N=252) | Male (N=125) | p-value (sex diff) |
|----------------------------|----------|---------------|----------------|--------------|--------------------|
| Cognitive comp.            | mean(SD) | 1.50          | 1.70           | 1.09         | 0.058              |
| Depression sympt.          | mean(SD) | 20.9          | 20.9           | 20.9         | 0.932              |
| Rheumatic disease          | No N     | 247           | 150            | 97           |                    |
|                            | Yes N(%) | 130 (34.5%)   | 102 (40.5%)    | 28 (22.4%)   |                    |
| CVD                        | No N     | 238           | 153            | 85           |                    |
|                            | Yes N(%) | 139 (36.9%)   | 99 (39.3%)     | 40 (32.0%)   |                    |
| Cancer                     | No N     | 338           | 221            | 117          |                    |
|                            | Yes N(%) | 39 (10.3%)    | 31 (12.3%)     | 8 (6.4%)     |                    |
| Diabetes                   | No N     | 360           | 240            | 120          |                    |
|                            | Yes N(%) | 17 (4.5%)     | 12 (4.8%)      | 5 (4.0%)     |                    |

Table S2. The association between covariates and LTL respectively fatigue.

| Covariates                      | Association to LTL |                 |       |                     |                        |              | Association to fatigue |                 |        |                     |                        |                  |
|---------------------------------|--------------------|-----------------|-------|---------------------|------------------------|--------------|------------------------|-----------------|--------|---------------------|------------------------|------------------|
|                                 | Raw                |                 |       | Adjusted (sex, age) |                        |              | Raw                    |                 |        | Adjusted (sex, age) |                        |                  |
|                                 | Coef <sup>d</sup>  | CI (95%)        | p     | Coef <sup>d</sup>   | CI (95%)               | p            | Coef <sup>d</sup>      | CI (95%)        | p      | Coef <sup>d</sup>   | CI (95%)               | p                |
| Fatigue (Score 0 – 6)           | 0.029              | -0.008 – 0.065  | 0.121 | 0.027 <sup>ff</sup> | -0.009 – 0.063         | 0.140        |                        |                 |        |                     |                        |                  |
| Age                             | -0.021             | -0.039 – -0.003 | 0.023 | <b>-0.022</b>       | <b>-0.040 – -0.004</b> | <b>0.015</b> | -0.043                 | -0.078 – -0.008 | 0.017  | <b>-0.042</b>       | <b>-0.077 – -0.007</b> | <b>0.019</b>     |
| Sex                             | Ref                |                 |       | Ref                 |                        |              | Ref                    |                 |        | Ref                 |                        |                  |
| Female                          | 0.173              | 0.024 – 0.323   | 0.023 | <b>0.183</b>        | <b>0.035 – 0.331</b>   | <b>0.015</b> | -0.180                 | -0.466 – 0.107  | 0.219  | -0.161              | -0.444 – 0.122         | 0.264            |
| Zygoty                          | Ref                |                 |       | Ref                 |                        |              | Ref                    |                 |        | Ref                 |                        |                  |
| DZ                              | -0.062             | -0.205 – 0.081  | 0.394 | -0.083              | -0.225 – 0.016         | 0.251        | 0.001                  | -0.271 – 0.272  | 0.996  | -0.044              | -0.312 – 0.224         | 0.748            |
| Gel-effect                      | 0.010              | 0.001 – 0.019   | 0.023 | 0.005               | -0.007 – 0.016         | 0.415        |                        |                 |        |                     |                        |                  |
| Smoking                         | Ref                |                 |       | Ref                 |                        |              | Ref                    |                 |        | Ref                 |                        |                  |
| Former                          | -0.101             | -0.208 – 0.007  | 0.066 | -0.089              | -0.198 – 0.183         | 0.103        | -0.204                 | -0.507 – 0.098  | 0.185  | -0.274              | -0.580 – 0.032         | 0.079            |
| Current                         | -0.166             | -0.285 – -0.046 | 0.007 | <b>-0.163</b>       | <b>-0.283 – 0.043</b>  | <b>0.008</b> | -0.221                 | -0.541 – 0.099  | 0.176  | -0.310              | -0.633 – 0.013         | 0.060            |
| Physical activity (Score 0 – 4) | 0.043              | 0.008 – 0.077   | 0.016 | <b>0.038</b>        | <b>0.003 – 0.072</b>   | <b>0.034</b> | 0.341                  | 0.252 – 0.429   | <0.001 | <b>0.331</b>        | <b>0.241 – 0.420</b>   | <b>&lt;0.001</b> |
| BMI                             | -0.007             | -0.022 – 0.007  | 0.328 | -0.008              | -0.022 – 0.007         | 0.309        | -0.035                 | -0.072 – 0.001  | 0.060  | <b>-0.050</b>       | <b>-0.008 – -0.013</b> | <b>0.009</b>     |
| Cognitive function              | 0.020              | 0.004 – 0.035   | 0.014 | <b>0.017</b>        | <b>0.001 – 0.032</b>   | <b>0.037</b> | 0.047                  | 0.008 – 0.087   | 0.020  | <b>0.044</b>        | <b>0.004 – 0.083</b>   | <b>0.032</b>     |
| Depression symptomatology       | -0.015             | -0.026 – -0.003 | 0.012 | <b>-0.014</b>       | <b>-0.025 – -0.003</b> | <b>0.016</b> | -0.117                 | -0.145 – -0.090 | <0.001 | <b>-0.116</b>       | <b>-0.144 – -0.089</b> | <b>&lt;0.001</b> |
| Cancer                          | Ref                |                 |       | Ref                 |                        |              | Ref                    |                 |        | Ref                 |                        |                  |
| Yes                             | -0.042             | -0.182 – 0.098  | 0.557 | -0.051              | -0.190 – 0.088         | 0.475        | -0.287                 | -0.698 – 0.123  | 0.170  | -0.270              | -0.679 – 0.139         | 0.196            |
| CVD                             | Ref                |                 |       | Ref                 |                        |              | Ref                    |                 |        | Ref                 |                        |                  |
| Yes                             | -0.019             | -0.115 – 0.078  | 0.705 | -0.027              | -0.122 – 0.069         | 0.586        | -0.187                 | -0.451 – 0.078  | 0.167  | -0.186              | -0.448 – 0.077         | 0.166            |
| Diabetes                        | Ref                |                 |       | Ref                 |                        |              | Ref                    |                 |        | Ref                 |                        |                  |
| Yes                             | -0.007             | -0.229 – 0.215  | 0.952 | -0.010              | -0.231 – 0.210         | 0.926        | -0.114                 | -0.731 – 0.503  | 0.718  | -0.098              | -0.709 – 0.513         | 0.754            |
| Rheumatic                       | Ref                |                 |       | Ref                 |                        |              | Ref                    |                 |        | Ref                 |                        |                  |
| Yes                             | 0.028              | -0.066 – 0.123  | 0.561 | 0.012               | -0.082 – 0.107         | 0.800        | -0.440                 | -0.704 – -0.176 | 0.001  | <b>-0.437</b>       | <b>-0.702 – -0.172</b> | <b>&lt;0.001</b> |

Table S3. The association between LTL and fatigue.

| Population    |         | Model 1<br>Raw | Model 2<br>Age, sex | Model 3<br>Lifestyle | Model 4<br>Mental | Model 5<br>Somatic | Model 6<br>Full |
|---------------|---------|----------------|---------------------|----------------------|-------------------|--------------------|-----------------|
| All<br>N=377  | Coef    | 0.029          | 0.027               | 0.011                | 0.016             | 0.027              | 0.0001          |
|               | CI 95%  | -0.008 – 0.065 | -0.009 – 0.063      | -0.027 – 0.050       | -0.022 – 0.055    | -0.010 – 0.064     | -0.041 – 0.041  |
|               | p-value | 0.121          | 0.140               | 0.573                | 0.400             | 0.149              | 0.997           |
| <80y<br>N=257 | Coef    | 0.044          | 0.046               | 0.030                | 0.040             | 0.041              | 0.023           |
|               | CI 95%  | -0.005 – 0.093 | -0.003 – 0.095      | -0.022 – 0.081       | -0.015 – 0.096    | -0.009 – 0.092     | -0.035 – 0.081  |
|               | p-value | 0.078          | 0.067               | 0.261                | 0.157             | 0.110              | 0.442           |

Table S4. Intrapair analysis.

|              |         | All            | MZ             | DZ             |
|--------------|---------|----------------|----------------|----------------|
| All<br>N=148 | Coef    | 0.021          | 0.038          | 0.008          |
|              | CI 95%  | -0.024 – 0.066 | -0.026 – 0.102 | -0.056 – 0.072 |
|              | p-value | 0.357          | 0.239          | 0.807          |
| <80y<br>N=86 | Coef    | 0.052          | 0.062          | 0.043          |
|              | CI 95%  | -0.011 – 0.115 | -0.029 – 0.153 | -0.047 – 0.134 |
|              | p-value | 0.105          | 0.175          | 0.347          |