**SUPPLEMENTARY MATERIALS**

**Supplementary Table 1:** Comparison of model fit after stratifying by sex

**Supplementary Table 2:** Comparison of sample with missing data and sample with all data available.

**Supplementary Table 3:** Unadjusted and adjusted models testing direct, indirect, and total associations between accumulating affective symptoms from age 23 to 42 and midlife cognitive outcomes at age 50, mediated by 9 cardiometabolic risk biomarkers (included individually in model).

**Supplementary Table 4:** Mediation model additionally adjusted for cardiovascular medication use.

**Supplementary Figure 1:** Flow chart to show missing data.

**Supplementary Table 1:** Comparison of model fit after stratifying by sex.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Not stratified by sex** | **Stratified by sex** | **Difference** |
| X2 | 5.873 | 6.581 | 0.708 |
| df | 1 | 2 | 1 |
| *p* | .015 | .037 | >.05 |

\* Model fit does not significantly improve after stratifying by sex. Sex was therefore used as a covariate in models, rather than as a stratifying variable.

**Supplementary Table 2:** Comparison of sample with missing data and sample with all data available.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Missing data** |  | **Sample with all data available (N/Mean)** | **Sample with data missing (N/Mean)** | **Chi-square / T-test** |
| Immediate memory | | 6.65 (1.47) | 6.54 (1.49) | t (8129)=-3.38, *p*=.001 |
| Delayed memory | | 5.56 (1.79) | 5.39 (1.88) | t (7989.92)=-4.14, *p*<.001 |
| Verbal fluency | | 22.61 (6.37) | 22.28 (6.21) | t (8129)=-2.36, *p*=.02 |
| Information processing speed | | 335.08 (88.58) | 332.33 (87.49) | t (7979)=-1.39, *p*=.16 |
| Information processing accuracy | | 4.15 (3.87) | 4.46 (4.07) | t (7926.66)=3.45, *p*=.001 |
| Number of time points with affective symptoms from age 23 to 42 | 0 times | 3191 | 2563 | X2 (3)=34.71, *p*<.001 |
| 1 time | 369 | 412 |
| 2 times | 132 | 134 |
| 3 times | 38 | 67 |
| Cardiometabolic biomarkers (Z scores) | Total cholesterol | -0.03 (0.96) | 0.03 (1.03) | t (7818.64)=2.44, *p*=.02 |
| Glycated haemoglobin | -0.05 (0.92) | 0.04 (1.07) | t (7913.79)=3.91, *p*<.001 |
| Systolic blood pressure | -0.03 (1.00) | 0.02 (1.00\_ | t (9229)=2.53, *p*=.01 |
| Diastolic blood pressure | -0.04 (1.01) | 0.03 (0.99) | t (9228)=3.17, *p*=.002 |
| HDL cholesterol | -0.04 (0.99) | 0.03 (1.00) | t (7806)=2.99, *p*=.003 |
| Triglycerides | -0.04 (0.97) | 0.04 (1.03) | t (7789.28)=3.49, *p*<.001 |
| C-reactive protein | -0.05 (1.00) | 0.05 (1.00) | t (7460)=4.22, *p*<.001 |
| Resting heart rate | -0.05 (0.98) | 0.04 (1.01) | t (9230)=4.11, *p*<.001 |
| Fibrinogen | -0.10 (0.89) | 0.10 (1.09) | t (7529.24)=8.86, *p*<.001 |
| Composite cardiometabolic risk score | -0.43 (4.61) | 0.02 (4.69) | t (7145)=4.05, *p*<.001 |
| Affective symptoms at age 50 | | 1.34 (1.80) | 1.53 (1.97) | t (8073.84)=4.38, *p*<.001 |
| Sex | Male | 1821 | 2844 | X2 (1)=2.08, *p*=.15 |
| Female | 1909 | 2803 |
| Childhood cognition | | 47.07 (14.57) | 44.02 (15.96) | t (8080.78)=-9.02, *p*<.001 |
| Household socioeconomic position | Working | 1467 | 1771 | X2 (2)=18.07, *p*<.001 |
| Intermediate | 1416 | 1464 |
| Middle | 847 | 805 |
| Education | No academic qualification | 424 | 899 | X2 (2)=118.39, *p*<.001 |
| GCSE to A Level (or Scottish equivalent) | 2333 | 2448 |
| Higher education | 973 | 1118 |
| Cardiovascular medication | Yes | 254 | 503 | X2 (1)=13.00, *p*<.001 |
| No | 3460 | 5122 |

**Supplementary Table 3:** Unadjusted and adjusted models testing direct, indirect, and total associations between accumulating affective symptoms from age 23 to 42 and midlife cognitive outcomes at age 50, mediated by 9 cardiometabolic risk biomarkers (included individually in model).

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Immediate Memory β (SE), *p*** | | **Delayed Memory β (SE), *p*** | | **Verbal Fluency β (SE), *p*** | | **Processing Speed**  **β (SE), *p*** | | **Processing Accuracy β (SE), *p*** | |
| **Unadjusted** | **Adjusted\*** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| **Model fit:**  **Unadjusted:**  N=6899; X2 (1)=5.71, *p*=.02; CFI=1.00; TLI=0.98; RMSEA=0.03.  **Adjusted:**  N=6405; X2 (12)=33.29, *p*<.001; CFI=1.00; TLI=0.99; RMSEA=0.02. | | | | | | | | | | | |
| Direct | | -0.09 (0.01),  < .001 | -0.02 (0.02),  .20 | -0.08 (0.01),  < .001 | -0.02 (0.02),  .11 | -0.09 (0.01),  < .001 | 0.001 (0.02),  .95 | 0.01 (0.01),  .32 | 0.03 (0.02),  .06 | 0.05 (0.01),  < .001 | 0.03 (0.02),  .09 |
| Indirect | High-density lipoprotein cholesterol \*\* | -0.001 (0.001), .34 | 0.001 (0.001), .51 | -0.001 (0.001),  .41 | 0.003 (0.001),  .05 | -0.001 (0.001),  .27 | -0.001 (0.001),  .49 | -0.002 (0.001),  .06 | -0.001 (0.001),  .32 | 0.00 (0.001),  .57 | -0.001 (0.001),  .48 |
| Total cholesterol | 0.00 (0.00), .81 | 0.00 (0.00), .88 | 0.00 (0.00),  .87 | 0.00 (0.00),  .67 | 0.00 (0.00),  .75 | 0.00 (0.00),  .76 | 0.00 (0.00),  .98 | 0.00 (0.00),  .96 | 0.00 (0.00),  .73 | 0.00 (0.00),  .86 |
| Triglycerides | -0.001 (0.001), .12 | 0.00 (0.001), .73 | -0.001 (0.001),  .16 | 0.00 (0.001),  .83 | 0.00 (0.001),  .50 | 0.001 (0.001),  .32 | 0.00 (0.001),  .45 | 0.001 (0.001),  .37 | 0.00 (0.001),  .88 | 0.00 (0.001),  .87 |
| Glycosylated hemoglobin (HbA1c) | 0.00 (0.00), .44 | 0.00 (0.00), .72 | 0.00 (0.00),  .43 | 0.00 (0.00),  .62 | 0.00 (0.00),  .54 | 0.00 (0.00),  .73 | 0.00 (0.00),  .43 | 0.00 (0.00),  .63 | 0.00 (0.00),  .56 | 0.00 (0.00),  .69 |
| Systolic blood pressure \*\*\* | 0.003 (0.001), .04 | 0.00 (0.00), .88 | 0.003 (0.001),  .03 | 0.00 (0.00),  .88 | 0.002 (0.001),  .16 | 0.00 (0.00),  .88 | 0.002 (0.001),  .06 | 0.00 (0.00),  .88 | 0.00 (0.001),  .71 | 0.00 (0.00),  .89 |
| Diastolic blood pressure \*\*\* | -0.001 (0.001), .34 | 0.00 (0.001), .44 | 0.00 (0.00),  .96 | 0.00 (0.00),  .81 | 0.00 (0.00),  .75 | 0.00 (0.00),  .95 | 0.00 (0.00),  .95 | 0.00 (0.00),  .48 | 0.00 (0.00),  .51 | 0.00 (0.00),  .60 |
| C-Reactive protein (CRP) | -0.003 (0.002), .10 | -0.002 (0.001), .09 | -0.001 (0.002),  .40 | -0.001 (0.001),  .31 | -0.003 (0.0002),  .07 | 0.00 (0.001),  .59 | 0.001 (0.002),  .38 | 0.00 (0.001),  .57 | 0.001 (0.002),  .49 | 0.00 (0.001),  .70 |
| Resting heart rate\*\*\* | 0.00 (0.001),  .52 | -0.001 (0.001),  .36 | 0.001 (0.001),  .39 | 0.00 (0.001),  .85 | -0.001 (0.001),  .19 | 0.00 (0.001),  .99 | 0.00 (0.001),  .56 | -0.001 (0.001),  .17 | 0.00 (0.001),  .62 | 0.00 (0.001),  .90 |
| Fibrinogen | -0.003 (0.002),  .11 | -0.001 (0.001),  .14 | -0.004 (0.002),  .02 | -0.003 (0.001),  .03 | -0.002 (0.002),  .19 | 0.00 (0.001),  .57 | 0.002 (0.002),  .30 | 0.00 (0.001),  .90 | 0.00 (0.002),  .87 | 0.00 (0.001),  .67 |
| Total\*\*\*\* | | -0.09 (0.01),  < .001 | -0.05 (0.01),   .001 | -0.08 (0.01),  < .001 | -0.05 (0.01),  < .001 | -0.10 (0.01),  < .001 | -0.02 (0.01),  .19 | 0.02 (0.10),  .22 | 0.02 (0.01),  .15 | 0.05 (0.01),  < .001 | 0.04 (0.01),  .01 |
|  | | **Unadjusted** | **Fully Adjusted** | **Unadjusted** | **Fully Adjusted** | **Unadjusted** | **Fully Adjusted** | **Unadjusted** | **Fully Adjusted** | **Unadjusted** | **Fully Adjusted** |

\* Adjusted for sex, education, socioeconomic position, childhood cognition, affective symptoms at age 50.

\*\* Reverse scored.

\*\*\* Averaged across 3 measurements.

\*\*\*\* Total effects include direct effects of affective symptoms on cognitive outcomes and indirect effects through cardiometabolic biomarkers and affective symptoms at age 50.

**Supplementary Table 4:** Mediation model additionally adjusted for cardiovascular medication use.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Immediate Memory**  **β (SE), *p*\*** | **Delayed Memory**  **β (SE), *p*** | **Verbal Fluency**  **β (SE), *p*** | **Processing Speed**  **β (SE), *p*** | **Processing Accuracy**  **β (SE), *p*** |
| **Model fit:** N=6370; X2 (3)=12.12, *p*=.01; CFI=1.00; TLI=0.98; RMSEA=0.02. | | | | | |
| Direct | -0.02 (0.02), .15 | -0.03 (0.02), .08 | 0.00 (0.02), 1.00 | 0.03 (0.02), .06 | 0.03 (0.02), .10 |
| Indirect | -0.002 (0.001), .03 | -0.001 (0.001), .15 | -0.001 (0.001), .47 | 0.00 (0.001), .79 | -0.001 (0.001), .28 |
| Total\*\* | -0.05 (0.01), .001 | -0.05 (0.01),<.001 | -0.02 (0.01), .17 | 0.02 (0.01), .14 | 0.04 (0.01), .01 |

\* Models adjusted for sex, education, socioeconomic position, childhood cognition, affective symptoms at age 50, and cardiovascular medication use.

\*\* Total effects include direct effects of affective symptoms on cognitive outcomes and indirect effects through cardiometabolic biomarkers and affective symptoms at age 50.

**Supplementary Figure 1:** Flow chart to show missing data.

