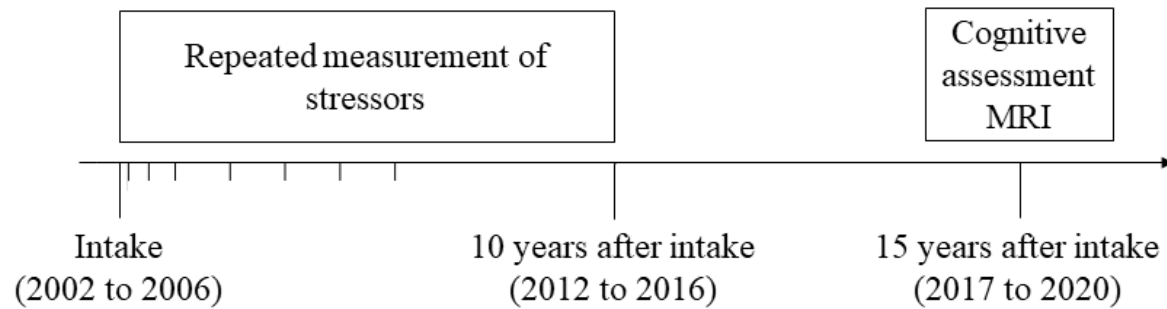


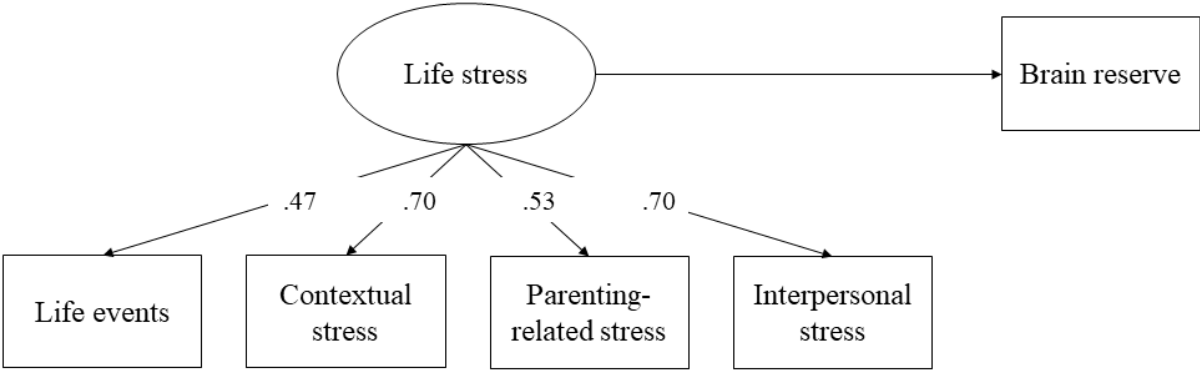
Supplementary Material

The Association of Life Stress with Subsequent Brain and Cognitive Reserve in Middle-Aged Women

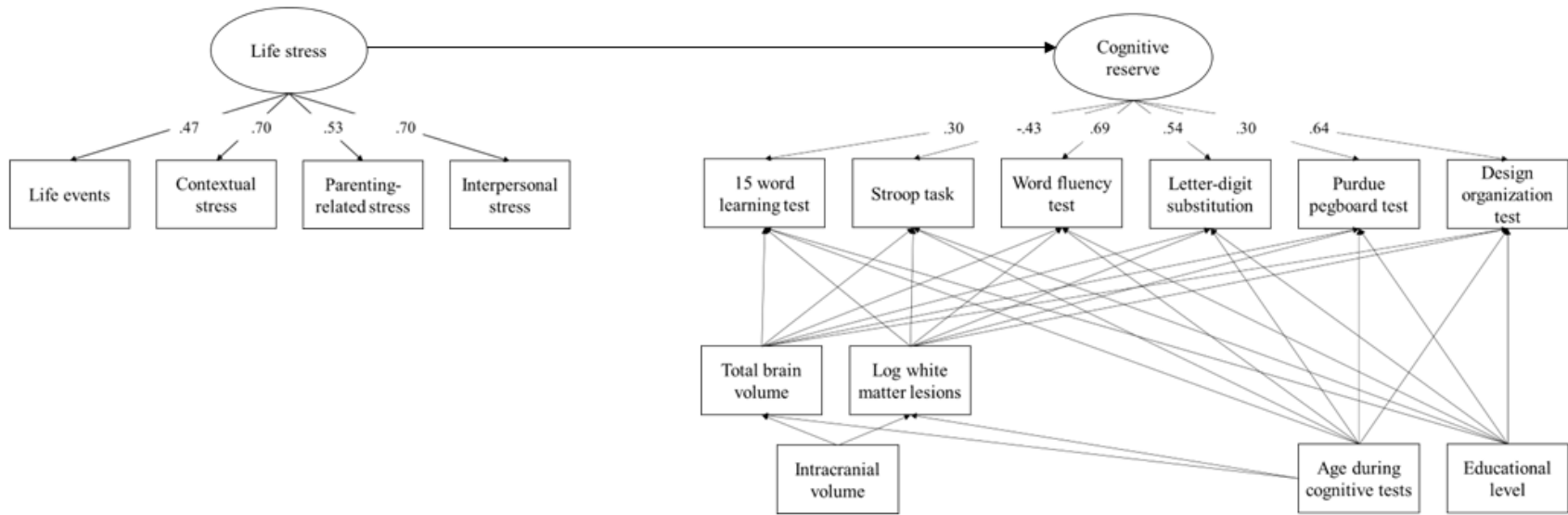
Supplementary Figure 1. Timeline of study assessments



Supplementary Figure 2. Structural equation model association life stress and brain reserve



Supplementary Figure 3. Structural equation model association life stress and cognitive reserve



Supplementary Table 1. Overview stressors per cumulative stress domain

| LIFE EVENTS | Question; <i>answer considered as risk</i> | Time point (after birth) | Reference |
|---|---|--------------------------|-----------|
| 1. Death of child or partner | Has one of your children or your partner died? <i>Yes.</i> Is the father/mother or other caretaker still alive? <i>No.</i> What is your marital status? <i>Widow.</i> | prenatal, 2 y, 5 y, 9 y | [1-3] |
| 2. Death of someone else | Has your father or mother (in-law) a brother or sister or a good friend died? <i>Yes.</i> Is your mother still alive? Is your father still alive? <i>No.</i> Have the following things occurred: Death of someone in close proximity. <i>Yes.</i> | prenatal, 3 y | [2, 3] |
| 3. Sickness in family or friends | Has your partner or other family member or one of your parents (in-law) been seriously ill? <i>Yes.</i> Are you nursing an ill or handicapped family member or friend who does not live in your home? <i>Yes.</i> Have the following things occurred: problems with physical/mental health of people in close proximity. <i>Yes.</i> Did a family member get seriously sick or did he/she have an accident? <i>Yes.</i> | prenatal, 3 y, 9 y | [1, 3, 4] |
| 4. Infertility | Is this pregnancy the result of infertility treatment? <i>Yes.</i> Have you had problems becoming pregnant again? <i>Yes.</i> | prenatal, 4 y | [2] |
| 5. Abortion | Have you had an abortion? <i>Yes.</i> | 9 y | [2] |
| 6. Miscarriage/ stillborn | Have you had: a miscarriage (before 16 weeks)? <i>Yes.</i> A stillborn (after 16 weeks)? <i>Yes (including ectopic pregnancies, molar pregnancies and vanishing twins).</i> | 9 y | [2] |
| 7. Victim of crime | Have you been a victim of robbery, theft, physical abuse or rape? <i>Yes.</i> Has the following occurred: Fire or burglary. <i>Yes.</i> | prenatal, 3 y | [3] |
| 8. Perceived discrimination | I have been taunted and insulted due to my ethnic background? <i>Yes.</i> I have been threatened or attacked due to my ethnic background? <i>Yes.</i> | prenatal | [5] |
| 9. Material deprivation during childhood mother | Does your family: have sufficient heating in house during cold weather; pay rent or mortgage without problems; have on average one hot meal per day; own or lease a car; own a washing machine; own a refrigerator; own a telephone; have holidays away from home 1 or more weeks per year. <i>If the family possessed 6/8 (75%) or less.</i> | prenatal | [6] |
| 10. Childhood abuse | Sexual abuse ≥ 10 , physical abuse ≥ 10 and/or emotional abuse ≥ 13 . | prenatal | [7, 8] |
| 11. Childhood neglect | CTQ: physical neglect ≥ 16 and/or emotional neglect ≥ 30 . | prenatal | [7, 8] |
| 12. Divorce own parents | Are your parents divorced or separated? <i>Yes.</i> | prenatal | [2] |

| | | | |
|----------------------------------|--|-------------------------------------|-----------|
| 13. Immigration | What is the country of your birth? <i>If not the Netherlands.</i> | prenatal | [2] |
| CONTEXTUAL STRESS | | | |
| 1. Chronic unemployment | Have you become unemployed? <i>Yes.</i> Which description most applies to you at this moment? <i>I am looking for work, I am disabled, I live off a social benefit allowance; I am a housewife; I am a school pupil/student</i> Has the following occurred: Unemployment. <i>Yes.</i> Did one of the parents involuntary become unemployed? <i>Yes. Risk should be present at each time point.</i> | prenatal, 12 mo, 2 y, 3 y, 5 y, 9 y | [1, 3, 9] |
| 2. Trouble paying | Have you experienced any difficulty in paying for food, rent, electricity bill and suchlike? <i>Yes.</i> | prenatal, 2 y, 3 y, 9 y | [2] |
| 3. Financial difficulties | Have you had any financial problems? <i>Yes.</i> Have the following things occurred: financial problem. <i>Yes.</i> Does your family have financial difficulties or did your family ever have them? <i>Yes.</i> | prenatal, 3 y, 9 y | [3, 4] |
| 4. Low household income | Indicate the net income of your household (per month). $\leq 10th$ percentile. | prenatal, 2 y, 3 y, 5 y, 9 y | [9] |
| 5. Chronic low household income* | "..." <i>low income at each time point</i> | All time points | [9] |
| 6. Work or study stress | Have you had problems with or at your work during the past year? <i>Yes.</i> Have you had problems at school or with your studies during the past year? <i>Yes.</i> Have the following things occurred: tension at the parent's work that has been felt at home. <i>Yes.</i> | prenatal, 3 y | [3, 4] |
| 7. Material deprivation | Does your family: have sufficient heating in house during cold weather; pay rent or mortgage without problems; have on average one hot meal per day; own or lease a car; own a washing machine; own a refrigerator; own a telephone; have holidays away from home 1 or more weeks per year. <i>If the family possessed 6/8 (75%) or less.</i> | Prenatal, 9 y | [6] |
| 8. Neighborhood problems | Have you had problems with the residential environment in your street or neighborhood? <i>Yes.</i> Are/were there problems in the neighborhood? (e.g., vandalism or insecurity) <i>Yes.</i> Have you often had problems with vandalism, grime, crime etc. in your neighborhood? <i>Yes.</i> | prenatal, 9 y | [1, 4, 9] |
| 9. Arrested by police | Have you ever been arrested by the police? <i>Yes.</i> | prenatal | [2] |
| PARENTING-RELATED STRESS | | | |
| 1. Parenting stress at 18 months | I have much more trouble raising children than I thought. <i>Yes</i> I often feel that I can't cope with things very well. <i>Yes.</i> | 18 mo | [10] |

| | | | |
|--|---|--------------------------------------|-------------|
| 2. Parenting stress at 8 years | Being a parent is more difficult than I thought. <i>Yes</i> I feel that I can't cope with raising children very well. <i>Yes</i> . | 8 y | [10] |
| 3. Unplanned pregnancy | Was this pregnancy planned? <i>No</i> . | prenatal | [2] |
| 4. Worried about pregnancy outcome | Pregnancy Outcome Questionnaire. <i>Weighted sum score > 30</i> . | prenatal | [11] |
| 5. Direct victimization of the child | Did someone ever use physical violence against your child (e.g., beating him/her up)? <i>Yes</i> . Did somebody almost use physical violence against your child? <i>Yes</i> . Did anybody make sexual comments or movements towards your child? <i>Yes</i> . Has your child experienced inappropriate sexual behavior? <i>Yes</i> . | 9 y | [1] |
| 6. Bad general health child | How would you describe your child's general health? <i>Bad or moderate</i> . How often is your child ill and does it use healthcare facilities? <i>Slightly more often, repeatedly, almost always</i> . How would you rate you child's health in the past 6 months? <i>Frequently sick or almost always sick</i> . | 6 mo, 12 mo, 2 y, 3 y, 4 y, 5 y, 9 y | [2, 12, 13] |
| 7. Hospitalization or accident of child (needs to be more than once) | Was your child admitted to the children's ward of a hospital in its first week? <i>Yes</i> . Has your child ever had an accident at or near home or with traffic that needed treatment by a GP, doctor at the emergency help or admittance to the hospital? <i>Yes</i> . How often has your child been admitted to the hospital in the last 6 months? <i>Once or more</i> Has your child been injured as the result of an accident and as a resulted needed a doctor or hospital visit? <i>Yes</i> . How often during the past year has your child gone into hospital? <i>At least once</i> . How often have you taken your child to the doctor/emergency room in the past year? <i>At least once</i> . For each broken bone that your child had, please indicate the extent of the trauma. <i>Average trauma or severe trauma</i> . Did your child get very sick or did he/she get an accident? <i>Yes</i> . | 2 mo, 6 mo, 12 mo, 2 y, 5 y, 9 y | [1, 2] |
| 8. Problems with child's physical health affect parent | Did you have less time for yourself in the last 4 weeks due to your child's physical health? <i>Yes</i> . Have you been worried in the last 4 weeks due your child's physical health? <i>Yes</i> . I worry more about my child's health than other parents do. <i>Yes</i> . | 12 mo, 2 y, 4 y, 5 y, 9 y | [12] |
| 9. Total problem behavior | Total problem score of the CBCL. <i>T-score above 63 at any of the time points</i> . | 18 mo, 3 y, 5 y, 9 y | [14, 15] |
| 10. Callous unemotional traits | Interpersonal Callousness questionnaire. <i>If 80th percentile or higher</i> . | 9 y | [16] |

| | | | |
|---|--|------------------------------------|---------|
| 11. Child's emotional and/or behavioral problems affect parents | Did you have less time for yourself in the last 4 weeks due to your child's emotional well-being or behavior? <i>Yes.</i> Have you been worried in the last 4 weeks due to your child's emotional well-being or behavior? <i>Yes.</i> | 12 mo; 2 y, 4 y, 5 y | [12] |
| 12. Child has conflicts | Does your child have ongoing conflicts with a family member or did your child ever have such a conflict? <i>Yes.</i> Does your child have long-lasting conflicts with someone outside the family or did they ever have those? <i>Yes.</i> | 9 y | [1] |
| 13. Child bullies or is victim of bullying | Has your child been bullied or has it bullied other children at least once a week? <i>Yes.</i> | 8 y | [2] |
| INTERPERSONAL STRESS | | | |
| 1. No partner | Do you currently have a partner? <i>No.</i> Do you have the same partner as during your Gen R pregnancy? <i>No, I have no partner.</i> | prenatal, 6 mo, 2 y, 3 y, 4 y, 5 y | [2] |
| 2. Divorce/separation | Have you had a divorce or broken off the relationship with your partner? <i>Yes.</i> What is your marital status? <i>Divorced.</i> Has the following occurred? Divorce. <i>Yes.</i> Are you and your partner divorced or separated? <i>Yes.</i> | prenatal, 2 y, 3 y, 5 y, 9 y | [1-3] |
| 3. Relationship problems | Has the following occurred? Problems with marriage relations. <i>Yes.</i> In the past year, have there been difficulties between you and your partner? <i>Yes.</i> | prenatal, 3 y | [3, 4] |
| 4. Family distress | Family distress, > 2.17 at least one of the time points. | prenatal, 5 y, 9 y | [17] |
| 5. Family conflicts | How would you describe the way the members of your family interact with each other? <i>Poor or average.</i> Do other family members have ongoing conflicts with each other (of did they ever have them)? <i>Yes.</i> | 12 mo, 2 y, 4 y, 5 y, 9 y | [1, 12] |
| 6. Difficulties with family, friends, or others | In the past year, have there been: difficulties in or with your contact with others? <i>Yes.</i> Difficulties between you and your parents or parents-in-law? <i>Yes.</i> Difficulties between you and one or more brothers/sisters? <i>Yes.</i> Problems with people who are or were your friends? <i>Yes.</i> Problems with one or more people from your neighborhood? <i>Yes.</i> Fighting with neighbors, friends or family? <i>Yes.</i> | prenatal, 3 y | [3, 4] |
| 7. Lack of social support | Social Support List, <i>weighted sum score</i> ≤ 26. | 6 mo | [18] |

* correlation item low household income and item chronic low household income is 0.52.

Supplementary Table 2. Overview countries of origin

| | <i>N</i> (%) | <i>N</i> (%) |
|-----------------------------------|--------------|--------------|
| Western | 943 (76.5) | |
| Dutch | | 860 (69.9) |
| Non-Dutch European | | 81 (6.6) |
| North-American | | 1 (0.1) |
| Oceanian | | 1 (0.1) |
| Non-Western | 288 (23.4) | |
| Surinamese | | 87 (7.1) |
| Indonesian | | 46 (3.7) |
| Turkish | | 37 (3.0) |
| Moroccan | | 33 (2.7) |
| Dutch Antillean | | 21 (2.7) |
| Cape Verdean | | 28 (2.3) |
| Asian (excl. Japan and Indonesia) | | 18 (1.5) |
| South/Central American | | 11 (0.9) |
| African | | 7 (0.6) |

Supplementary Table 3. Comparison of included sample to non-included sample

| | <u>Included</u> | <u>Excluded</u> | | | |
|---|-----------------|-----------------|------------------------|------------------------|----------|
| | <i>N</i> (%) | <i>N</i> (%) | <i>t</i> (<i>df</i>) | χ^2 (<i>df</i>) | <i>p</i> |
| <i>N</i> | 1,232 | 130 | | | |
| Age at follow up, y | 46.62 ± 4.45 | 46.2 ± 5.28 | 0.86 | 148.97 | 0.394 |
| Education level | 151 (12.3) | 28 (23.7) | 11.35 | 1 | 0.001 |
| Ethnicity | 943 (76.6) | 77 (63.6) | 9.31 | 1 | 0.002 |
| Marital status | 1099 (92.0) | 96 (86.5) | 3.25 | 1 | 0.071 |
| Household income | 970 (91.0) | 75 (81.5) | 7.59 | 1 | 0.006 |
| Clinically relevant depressive symptoms | 870 (86.2) | 68 (73.9) | 9.18 | 1 | 0.002 |

For continuous outcomes, the included sample was compared to the excluded sample using *t*-tests (presented as $M \pm SD$). For categorical outcomes, comparison was done using a χ^2 -squared test (presented as *N* (%)).

Supplementary Table 4. Correlation matrix

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
|---------|----------|----------|---------|----------|----------|----------|---------|----------|---------|----------|----------|----------|----------|----------|---------|----------|----------|
| 1 LE | 1*** | | | | | | | | | | | | | | | | |
| 2 CS | 0.33*** | 1*** | | | | | | | | | | | | | | | |
| 3 PS | 0.23*** | 0.34*** | 1*** | | | | | | | | | | | | | | |
| 4 IS | 0.36*** | 0.48*** | 0.38*** | 1*** | | | | | | | | | | | | | |
| 5 BR | -0.14*** | -0.12*** | -0.09* | -0.11** | 1*** | | | | | | | | | | | | |
| 6 TBV | -0.13*** | -0.12*** | -0.09* | -0.11** | 1.00*** | 1*** | | | | | | | | | | | |
| 7 WML | -0.01 | -0.02 | 0.00 | -0.03 | 0.31*** | 0.31*** | 1*** | | | | | | | | | | |
| 8 ICV | -0.19*** | -0.16*** | -0.09* | -0.13*** | 0.83*** | 0.83*** | 0.34*** | 1*** | | | | | | | | | |
| 9 CR | -0.16*** | -0.10** | -0.05 | -0.04 | 0.00 | 0.00 | 0.00 | 0.05 | 1*** | | | | | | | | |
| 10 LDST | -0.15*** | -0.15*** | -0.04 | -0.06 | 0.18*** | 0.18*** | -0.03 | 0.19*** | 0.81*** | 1*** | | | | | | | |
| 11 WFT | -0.15*** | -0.12*** | -0.07 | -0.11** | 0.17*** | 0.17*** | 0.01 | 0.18*** | 0.63*** | 0.46*** | 1*** | | | | | | |
| 12 WLT | -0.10* | -0.10** | -0.06 | -0.03 | 0.03 | 0.03 | -0.02 | 0.01 | 0.35*** | 0.22*** | 0.29*** | 1*** | | | | | |
| 13 PPB | -0.10* | -0.12** | -0.06 | -0.01 | 0.12*** | 0.12*** | -0.05 | .010** | 0.35*** | 0.31*** | 0.15*** | 0.11** | 1*** | | | | |
| 14 STR | 0.15*** | 0.15*** | 0.09* | 0.09** | -0.22*** | -0.22*** | -0.02 | -0.23*** | -0.5*** | -0.35*** | -0.33*** | -0.20*** | -0.12*** | 1*** | | | |
| 15 DOT | -0.19*** | -0.17*** | -0.07 | -0.09* | 0.28*** | 0.28*** | -0.02 | 0.30*** | 0.75*** | 0.57*** | 0.43*** | 0.25*** | 0.27*** | -0.43*** | 1*** | | |
| 16 Age | -0.02 | -0.23*** | -0.07 | -0.07* | 0.02 | 0.02 | 0.20*** | 0.12*** | 0.00 | -0.08** | 0.09** | 0.01 | -0.08* | -0.04 | -0.01 | 1*** | |
| 17 Edu1 | 0.04 | 0.06* | 0.04 | 0.05 | -0.10*** | -0.10*** | -0.03 | -0.11*** | 0.00 | -0.02 | -0.06* | -0.06* | 0.03 | 0.05 | -0.06 | -0.09*** | 1*** |
| 18 Edu2 | -0.12** | -0.24*** | -0.09* | -0.16*** | 0.19*** | 0.19*** | 0.04 | 0.22*** | 0.00 | 0.16*** | 0.20*** | 0.18*** | 0.04 | -0.19*** | 0.23*** | 0.22*** | -0.77*** |

1. LE, life events; 2. CS, contextual stress; 3. PS, parenting-related stress; 4. IS, interpersonal stress; 5. BR, brain reserve; 6. TBV, total brain volume; 7. WML, white matter lesions; 8. ICV, intracranial volume; 9. Age, age at scanning; 10. Edu1, intermediate education, yes; 11. Edu2, high education, yes; 12. LDST, letter digit substitution test; 13. WFT, word fluency test; 14. WLT, 15 word learning test; 15. PPT, Purdue pegboard test; 16. STR, Stroop task; 17. DOT, design organization test. CR, cognitive reserve. *significant at $p < 0.05$, **significant at $p < 0.01$, ***significant at $p < 0.001$.

Supplementary Table 5. The mutually adjusted association of cumulative stress domains with brain reserve and cognitive reserve

| | Brain reserve | | | Cognitive reserve | | |
|--------------------------|---------------|--------------|----------|-------------------|--------------|----------|
| | Adj. dif. | 95% CI | <i>p</i> | Adj. dif. | 95% CI | <i>p</i> |
| Life events | -0.05 | -0.11, 0.02 | 0.137 | -0.16 | -0.23, -0.09 | <0.001 |
| Contextual stress | -0.08 | -0.14, -0.01 | 0.033 | -0.10 | -0.20, -0.01 | 0.025 |
| Parenting-related stress | -0.08 | -0.15, -0.02 | 0.013 | -0.05 | -0.13, 0.03 | 0.207 |
| Interpersonal stress | -0.02 | -0.09, 0.05 | 0.579 | 0.05 | -0.04, 0.14 | 0.259 |

Adj. dif., standardized adjusted difference in the outcome per 1-SD increase in stress. Table shows one model output.

Supplementary Table 6. The association of life stress with brain reserve and cognitive reserve – analyses restricted to women without depressive symptoms

| | Brain reserve | | | Cognitive reserve | | |
|--------------------------------|---------------|--------------|----------|-------------------|--------------|----------|
| | Adj. dif. | 95% CI | <i>p</i> | Adj. dif. | 95% CI | <i>p</i> |
| <i>Singular models</i> | | | | | | |
| Life stress | -0.14 | -0.23, -0.06 | 0.001 | -0.22 | -0.33, -0.11 | <0.001 |
| Life events | -0.09 | -0.16, -0.02 | 0.009 | -0.20 | -0.28, -0.12 | <0.001 |
| Contextual stress | -0.09 | -0.16, -0.02 | 0.013 | -0.15 | -0.24, -0.06 | 0.002 |
| Parenting-related stress | -0.09 | -0.16, -0.02 | 0.008 | -0.14 | -0.23, -0.05 | 0.002 |
| Interpersonal stress | -0.08 | -0.15, -0.01 | 0.018 | -0.08 | -0.17, 0.00 | 0.056 |
| <i>Mutually adjusted model</i> | | | | | | |
| Life events | -0.06 | -0.13, 0.02 | 0.119 | -0.17 | -0.25, -0.08 | <0.001 |
| Contextual stress | -0.04 | -0.12, 0.04 | 0.374 | -0.09 | -0.20, 0.02 | 0.109 |
| Parenting-related stress | -0.06 | -0.13, 0.02 | 0.149 | -0.09 | -0.18, 0.01 | 0.087 |
| Interpersonal stress | -0.03 | -0.11, 0.05 | 0.456 | 0.03 | -0.08, 0.13 | 0.607 |

Adj. dif., standardized adjusted difference in the outcome per 1-SD increase in stress. For singular models: each row corresponds to one model output. For mutually adjusted model: all four rows correspond to one model output.

Supplementary Table 7. The association of life stress with brain reserve and cognitive reserve – analyses restricted to non-Western women

| | Brain reserve | | | Cognitive reserve | | |
|--------------------------------|---------------|--------------|----------|-------------------|--------------|----------|
| | Adj. dif. | 95% CI | <i>p</i> | Adj. dif. | 95% CI | <i>p</i> |
| <i>Singular models</i> | | | | | | |
| Life stress | -0.12 | -0.27, 0.03 | 0.122 | -0.10 | -0.29, 0.08 | 0.267 |
| Life events | -0.09 | -0.20, 0.03 | 0.163 | -0.11 | -0.23, 0.00 | 0.060 |
| Contextual stress | -0.05 | -0.18, 0.07 | 0.404 | -0.06 | -0.18, 0.06 | 0.308 |
| Parenting-related stress | -0.16 | -0.28, -0.04 | 0.009 | -0.14 | -0.26, -0.02 | 0.027 |
| Interpersonal stress | -0.03 | -0.15, 0.09 | 0.617 | 0.03 | -0.11, 0.16 | 0.696 |
| <i>Mutually adjusted model</i> | | | | | | |
| Life events | -0.05 | -0.18, 0.08 | 0.450 | -0.10 | -0.23, 0.03 | 0.134 |
| Contextual stress | 0.00 | -0.15, 0.15 | 0.999 | -0.04 | -0.18, 0.11 | 0.602 |
| Parenting-related stress | -0.17 | -0.31, -0.03 | 0.017 | -0.15 | -0.29, -0.01 | 0.030 |
| Interpersonal stress | 0.06 | -0.09, 0.20 | 0.437 | 0.14 | -0.02, 0.3 | 0.086 |

Adj. dif., standardized adjusted difference in the outcome per 1-SD increase in stress. For singular models: each row corresponds to one model output. For mutually adjusted model: all four rows correspond to one model output.

Supplementary Table 8. The association of life stress with brain reserve and cognitive reserve – analyses restricted to Western women

| | Brain reserve | | | Cognitive reserve | | |
|--------------------------------|---------------|--------------|----------|-------------------|--------------|----------|
| | Adj. dif. | 95% CI | <i>p</i> | Adj. dif. | 95% CI | <i>p</i> |
| <i>Singular models</i> | | | | | | |
| Life stress | -0.11 | -0.18, -0.03 | 0.004 | -0.08 | -0.18, 0.03 | 0.144 |
| Life events | -0.01 | -0.07, 0.05 | 0.764 | -0.10 | -0.19, -0.01 | 0.029 |
| Contextual stress | -0.08 | -0.14, -0.02 | 0.015 | -0.08 | -0.18, 0.02 | 0.133 |
| Parenting-related stress | -0.06 | -0.13, 0.00 | 0.045 | -0.01 | -0.10, 0.08 | 0.837 |
| Interpersonal stress | -0.07 | -0.13, -0.01 | 0.026 | -0.03 | -0.11, 0.06 | 0.497 |
| <i>Mutually adjusted model</i> | | | | | | |
| Life events | 0.02 | -0.05, 0.09 | 0.570 | -0.09 | -0.19, 0.00 | 0.057 |
| Contextual stress | -0.05 | -0.12, 0.02 | 0.175 | -0.07 | -0.19, 0.05 | 0.230 |
| Parenting-related stress | -0.04 | -0.11, 0.03 | 0.254 | 0.02 | -0.08, 0.12 | 0.689 |
| Interpersonal stress | -0.04 | -0.11, 0.03 | 0.268 | 0.01 | -0.09, 0.12 | 0.779 |

Adj. dif., standardized adjusted difference in the outcome per 1-SD increase in stress. For singular models: each row corresponds to one model output. For mutually adjusted model: all four rows correspond to one model output.

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