# Chapter 38 Aging and Psychological Stress

E. Zsoldos and K.P. Ebmeier

University of Oxford Department of Psychiatry, Warneford Hospital, Oxford, UK

Table 1

Overview of Primary and Secondary Markers of the Stress Response and Allostatic Load in the Whitehall II Study30

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Primary markers | Secondary markers | | |
|  |  |  | Framingham Stroke Risk Score31 | Metabolic syndrome (ATP III) | Allostatic load index |
| Cardiovascular | SBP |  | X | X | X |
|  | DBP |  |  | X | X |
|  | Prior CVD |  | X |  |  |
|  | Atrial fibrillation |  | X |  |  |
|  | Left ventricular hypertrophy |  | X |  | N/A |
|  | Hypertensive medication |  | X |  |  |
| Metabolic | Diabetes mellitus |  | X |  |  |
|  | Diabetes medication |  | X |  |  |
|  | Fasting glucose |  |  | X | X |
|  | Waist circumference |  |  | X |  |
|  | Weight |  |  |  | X |
|  | Fat mass |  |  |  | X |
|  | Percent body fat |  |  |  | X |
|  | Serum triglycerides |  |  | X | X |
|  | Low HDL cholesterol |  |  | X | X |
|  | High LDL cholesterol |  |  |  | X |
|  | Blood cholesterol |  |  |  | X |
|  | BMI |  |  |  | X |
|  | HbA1C |  |  |  | X |
| Immune | CRP | X |  |  | X |
|  | IL-6 | X |  |  | X |
| Other | Age |  | X |  |  |
|  | Cigarette smoking |  | X |  |  |
|  | Cortisol | X |  |  | X |
|  | TNF-α | N/A |  |  | N/A |

ATP III: Summary of the NCEP Adult Treatment Panel III Report (JAMA 2001, 285(19) 2486-97). SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; HbA1C, glycated hemoglobin; CRP, C-reactive protein; IL-6, interleukin-6, TNF-α, tumor necrosis factor-α.

Table 2

Selected Literature on Secondary Markers of the Stress Response and Allostatic Load

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Predictor/maker | Outcome/marker | Type | Association/outcome | Author | Journal |
| Low SES | CVD | Cross | Yes | Adler NE et al., 1993 | J Am Med Assoc 269, 3140-45 |
| Low SES | Increased prevalence of stressors in the home | Review | Yes | McEwen BS and Tucker P, 2011 | Am J Public Health 101, S131-139 |
| Cortisol response to laboratory induced stress | Incident high BP | Long | Yes | Hamer M et al., 2012 | J Clin Endocrinol Metab 97(1):E29-34 |
| High BP to psychological stress | Future BP | Long | Modest | Caroll D et al., 2001 | Psychosom Med 63(5):737-43 |
| Depression + age | Future BP | Long | Mixed, mostly due to age | Nabi H et al., 2011 | Hypertension 57(4):710-6 |
| High BP to stress task | Functional neural reactivity to stress task in brain areas that control CV system | Cross | Yes | Gianaros PJ et al., 2007 | Hypertension 49: 134-40 |
| Lifetime hypertension | Gray matter atrophy and white matter hyperintensities | Long | Yes | Allan CL et al., 2015 | Br J Psychiatry 206(4):308-15 |
| Job strain and low decision latitude | Risk of CHD | Long | Yes | Kuper H and Marmot M, 2003 | J Epidemiol Comm Health 57(2):147-53 |
| Job strain and SES | BP + stress ratings + happiness ratings | Cross | Yes | Steptoe A and Willemsen G, 2004 | J Hypertens 22(5):915-20 |
| Effort-reward imbalance | CHD + health | Long | Moderate | Kuper H et al., 2002 | Occup Environ Med 59(11): 777-84 |
| Effort-reward imbalance + job control | CHD | Long | Yes | Bosma H et al., 1998 | Am J Pub Health 88(1): 68-74 |
| Job insecurity | Incident CHD | Long | Yes | Ferrie JE et al., 2013 | Atheroscl 227(1):178-81 |
| Unfairness and job strain | Coronary events + mental and physical health | Long | Yes | De Vogli R et al., 2007 | J Epidemiol Comm Health 61(6):513-8 |
| Overtime work | Incident CHD | Long | Yes | Virtanen M et al., 2010 | Eur Heart J 31(14):1737-44 |
| Self-reported adverse effects of stress on health | CHD or MI risk | Long | Yes | Nabi H et al., 2013 | Eur Heart J 34(34):2697-705 |
| Cortisol secretion during the day | CVD mortality | Long | Yes | Kumari M et al., 2011 | J Clin Endocrinol Metab 96(5):1478-85 |
| Depression | Stroke and CVD | Long | Mixed (dose-response and reverse causation | Brunner EJ et al., 2014 | Eur J Prev Cardiol 21(3):340-6 |
| Cardiovascular risk and structural brain changes | Framingham CHD Risk Score | Cross | Yes + gender effects | Rondina JM et al., 2014 | Front Aging Neurosci 1(6):300-14 |
| Framingham Stroke Risk and CVD Risk Scores | Cognitive decline | Long | Yes | Dregan A et al., 2012 | Age and Ageing 42(3):338-45 |
| Framingham Stroke Risk and CVD Risk Scores + dementia risk score | Cognitive decline | Long | Framingham scores better predictors | Kaffashian S. et al., 2013 | Neurology 80(14):1300-6 |
| Framingham Stroke Risk Score | Gray matter decline + executive function decline | Long | Yes | Debette S et al., 2011 | Neurology 77(5): 461-68 |
| Framingham Stroke Risk Score in late-life depression | White matter integrity | Cross | Yes | Allan CL et al., 2012 | Int Psychogeriatr 24(4):524-31 |
| Organizational justice | Metabolic syndrome | Long | In men only | Gimeno D et al., 2010 | Occup Environ Med 67(4):256-62 |
| Job strain | Metabolic syndrome | Long | Yes | Chandola T et al., 2006 | BMJ 332(7540):521-5 |
| SES (employment grade) | Metabolic syndrome | Cross | Central obesity + plasma fibrinogen | Brunner EJ et al., 1997 | Diabetologia 40(11):1341-9 |
| SES (house hold wealth) | Metabolic syndrome | Cross | Yes | Perel P et al., 2006 | Diabetes care 29(12):2694-700 |
| Unfairness | Metabolic syndrome | Long | Yes, but reduced after adjusting for covariates | De Vogli R. et al., 2007 | J Psychosom Res 63(4):413-9 |
| Metabolic syndrome | Cardiovascular disease | Meta-analysis | Yes | Galassi A et al., 2006 | American J of Medicine 119(10):812-9 |
| Metabolic syndrome | Cardiovascular disease mortality | Long | In men only | Lakka H-M et al., 2002 | JAMA 288(21):2709-16 |
| Metabolic syndrome | Telomere shortening | Review | Yes | Epel ES, 2009 | Hormones 8(1):7-22 |
| Metabolic syndrome | Stroke + mortality rate | Cross | Yes | Isomaa B et al., 2001 | Diabetes Care 24(4):683-9 |
| Metabolic syndrome | Heart disease + physical functioning + mortality | Cross | Yes | Gardner AW et al., 2006 | J Vasc Surg 43(6):1191-6 |
| Cumulative metabolic syndrome | Poor cognition | Long | Yes | Akbaraly TN et al., 2010 | Diabetes care 33(1):84-9 |
| Metabolic syndrome | Onset of depressive symptoms | Long | Obesity + dyslipidemia | Akbaraly TN et al., 2009 | Diabetes care 32(3):499-504 |
| Job strain and caring for a relative | Allostatic load | Long | Yes | Dich N et al., 2015 | Psychosom Med [2015 May 15 Epub ahead of print] |
| Negative emotional response to stressful life events | Allostatic load | Long | Nonlinear | Dich N et al., 2014 | Psychoneuroendocrinol 49:54-61 |
| Allostatic load | Physical + cognitive decline | Long | Yes | Seeman TE et al., 1997 | Arch Intern Med 157(19): 2259-68 |
| Allostatic load | Physical + cognitive function | Long | AL better predictor than individual components | Karlamangla AS et al., 2002 | J Clin Epidemiol 55:696-710 |
| Allostatic load | CVD + mortality | Long | Yes | Seeman TE et al., 2001 | Proc Natl Acad Sci U S A 98(8): 4770-75 |
| Allostatic load | Physical + general health | Long | Yes | Read S and Grundy E, 2014 | Psychosom Med 76(7):490-496 |
| Allostatic load | Cognitive function | Cross | Yes | Karlamangla AS et al., 2014 | Neurobiol Aging 35(2):387-394 |
| Allostatic load | Mental health | Cross | AL better predictor than individual components | Bizik G et al., 2013 | Harv Rev Psychiatry 21(6):296-313 |
| Allostatic load reduction | Mortality risk decrease | Long | AL better predictor than individual components | Karlamangla AS et al., 2006 | Psychosom Med 68(3):500-7 |

AL, allostatic load; BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarct; SES, socioeconomic status.

Table 3

Structural and Functional Studies of the Brain in Allostatic Load and Overload

|  |  |  |  |
| --- | --- | --- | --- |
| Examined effect | Author | Journal | Notes |
| *Hippocampal/temporal lobe shrinkage* | | | |
| MCI and AD | de Leon MJ et al., 1997 | Neurobiol Aging 18, 1-11 |  |
| T2D | Gold SM et al., 2007  McEwen BS et al., 2007 | Diabetologia 50, 711-19  Physiol Rev 87, 873-904 | Besides its response to glucocorticoids, the hippocampus is an important target of metabolic hormones that have a variety of adaptive actions in the healthy brain, which is perturbed in metabolic disorders, such as T2D. The hippocampus has receptors for insulin-like growth factor-1 (IGF1), which mediates exercise-induced neurogenesis |
| Prolonged MDD | Sheline YI et al., 2003 | Biol Psychiatry 54, 338-52 |  |
| Autopsy on MDD-suicide | Stockmeier CA et al., 2004 | Biol Psychiatry 56, 640-50 | Most likely, due to glial cell loss + small soma size, which suggests shrinkage of dendritic trees in MDD |
| Postnatal depression | Lupien SJ et al., 2011 | Proc Natl Acad Sci 108, 14324-29 | Hippocampal volume *not* affected |
| Cushing's disease | Starkman MN et al., 1999 | Biol Psychiatry 46, 1595-02 |  |
| PTSD | Gurvits TV et al., 1996 | Biol Psychiatry 40, 1091-99 |  |
| Chronic stress | Gianaros PJ et al., 2007 | NeuroImage 35, 795-803 |  |
| Chronic inflammation | Marsland AL et al., 2008 | Biol Psychiatry 64, 484-90 |  |
| Lack of physical activity | Erickson KI et al., 2009 | Hippocampus 19, 1030-39 |  |
| Jet lag | Cho K, 2001 | Nat Neurosci 4, 567-68 |  |
| Low SES | Hanson JL et al., 2011 | PloS One 6, e18712 |  |
| *Amygdala hyperactivity and enlargement* | | | |
| MDD | Sheline YI et al., 2001  Frodl T et al., 2003 | Biol Psychiatry 50, 651-58  Biol Psychiatry 53, 338-44 | Hyperactivity  Enlargement |
| Anxiety | Drevets WC, 2000 | Biol Psychiatry 48, 813-29 | Hyperactivity |
| PTSD | Rao RP et al., 2012  Zohar J et al., 2011 | Biol Psychiatry 72, 466-75  Eur Neuropsychopharmacol 21, 796-809 | Corticosteroid treatment of PTSD (characterized by low cortisol levels) alleviate symptoms in patients and increases dendritic growth and spine density in *rat* amygdala |
| Postnatal depression | Lupien SJ et al., 2011 | Proc Natl Acad Sci 108, 14324-29 | Enlargement in offspring |
| CVD | Gianaros PJ et al., 2009 | Biol Psychiatry 65, 943-50 | Increased reactivity to angry + sad faces mediated by increased sympathetic activity |
| Traumatic event in healthy | Ganzel BL et al., 2008 | NeuroImage 40, 788-95 | Increased reactivity to angry + sad faces |
| Sleep deprivation | Yoo S-S et al., 2007 | Curr Biol 17, R877-78 | Increased reactivity to angry + sad faces |
| Upbringing in low SES environment | Gianaros PJ et al., 2008 | Soc Cogn Affect Neurosci 3, 91-96 | Increased reactivity to angry + sad faces |
| *Prefrontal cortex (PFC) impairment* | | | |
| Medial PFC | Liston C et al., 2006 | J Neurosci 26, 7870-74 | Shrinkage of dendrites and loss of spines through excitatory amino acids + glucocorticoids |
|  |  |  | Expansion of dendrites |
| Orbitofrontal cortex (OFC) | | | |
| Poor cognitive flexibility | Dias-Ferreira E et al., 2009  Liston C et al., 2006  Karatsoreos et al., 2011 | Science 325, 621-25  J Neurosci 26, 7080-74  Proc Natl Acad Sci 108, 1657-62 | Animal and human studies |
| Reduced functional connectivity | Liston C et al., 2009 | PNAS 106, 912-17 |  |
| Aging | Bloss EB et al., 2010 | Exp Neurol 210, 109-17 | Failure to reverse shrinkage of medial PFC neurons after chronic stress in *rats* |
| Low subjective SES | Gianaros PJ et al., 2007 | Soc Cogn Affect Neurosci 2, 161-73 | Reduction in PFC gray matter |

MCI, mild cognitive impairment; AD, Alzheimer’s disease; T2D, Type 2 diabetes; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SES, socioeconomic status; CVD, cardiovascular disease; PFC, prefrontal cortex; OFC, orbitofrontal cortex.

Adapted from Ref. 33.