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Linking Childhood Abuse and Hypertension: Sleep Disturbance and Inflammation as Mediators

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Abstract

The indirect association of childhood abuse with prevalent hypertension in adulthood through sleep disturbance and pro-inflammatory biomarkers was investigated in 589 community-dwelling, middle-aged adults. Participants completed the Childhood Trauma Questionnaire and self-reported current sleep disturbance and medical diagnoses including hypertension. Blood pressure was taken and blood samples were analyzed for C-reactive protein, interleukin-6, and fibrinogen.

Hypertension was present in 41.3% of the sample. In the full multiple mediation model, tested using structural equation modeling, all hypothesized pathways were significant (p 's < 0.05). Childhood abuse was significantly related to both body mass index and sleep disturbance, which, both in turn, were significantly associated with inflammation, which was subsequently associated with hypertension status. The model demonstrated good fit (χ^2 (122) = 352.0, p < 0.001, CFI = 0.918, RMSEA = 0.057) and the indirect effect of all mediators was significant (Indirect Effect: 0.02, 95% CI: 0.005–0.03, p = 0.001). Sleep disturbance, body mass, and inflammation may be independent, intermediate steps between childhood abuse and subsequent hypertension that may be amenable to biobehavioral interventions.

Keywords

Childhood abuse; hypertension; inflammation; body mass index; mediation; sleep disturbance; structural equation modeling

Empirical evidence as well as folk wisdom link childhood abuse to illness in later life. We examined potential mechanisms that underlie the relations between childhood abuse and hypertension. Abuse during childhood unfortunately is quite common among male and female children and adolescents. One large population study of mid-life women found that almost two thirds reported either physical or sexual abuse during childhood (Riley et al., 2010). A meta-analysis of the global prevalence of childhood sexual abuse ranged from 8% to 31% among girls and 3% to 17% among boys (Barth et al., 2013). A meta-analysis on

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childhood physical abuse indicated 22.6% report abuse worldwide (Stoltenborgh et al., 2013).

Childhood abuse is predictive of maladaptive health behaviors and poor cardiovascular health outcomes, namely hypertension (Afifi et al, 2013; Ekeberg, Anda, & Nordenberg, 1990; Felitti et al., 1998; Springer et al., 2007). Childhood abuse may be indirectly linked to hypertension through its robust associations with obesity, heightened immune system reactivity, and inflammation (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2015; Danese & Tan, 2013; Gouin et al., 2012; Matthews et al., 2014). Obesity has been prospectively associated with increased levels of inflammation (Rawson et al., 2003), and evidence suggests that inflammation serves as a mediator between obesity and cardiovascular outcomes (Wang & Nakayama, 2010). Further, findings from recent studies indicate that childhood abuse and other early-life stressors may be linked to inflammation through obesity (Bertone-Johnson, Whitcomb, Missmer, Karlson, & Rich-Edwards, 2012; Matthews et al., 2014; Raposa, Bower, Hammen, Najman, & Brennan, 2014). Increasing levels of pro-inflammatory factors such as interleukin-6 (IL-6) and C-reactive protein (CRP) are known to be involved in the full process of atherosclerosis that includes endothelial dysfunction and stiffening of the arteries (Kusche-Vihrog et al., 2011). Both of these physiological outcomes are leading predictors of incident hypertension (Ras et al., 2013). Thus far, the evidence points to chained linkages between childhood abuse and obesity followed by inflammation and incident hypertension.

Sleep disturbance may be a crucial, yet understudied mechanistic construct in the prediction of hypertension in the context of childhood abuse and the obesity-inflammatory pathway. Poor sleep is related to elevated levels of inflammation and circulating monocytes (Burgos et al., 2006; Floam et al., 2015; Irwin, 2015; Okun, Coussons-Read, & Hall, 2009) and increased risk for hypertension (Fernandez-Mendoza et al., 2012; Meng, Zheng, & Hui, 2013). However, inflammation has not been evaluated as a mediator between sleep disturbance and hypertension (Irwin, 2015). Further, interpersonal distress and childhood abuse are associated with poor sleep quality (Gregory et al., 2006; Gunn et al., 2014). One study found that poor sleep moderated the association between poor social relationships and levels of IL-6, such that individuals with the worst sleep and relationships had the highest levels of IL-6 (Friedman et al., 2005). Despite these strong associations, no studies have incorporated sleep disturbance as a mediator into a model of childhood abuse in prediction of hypertension with the addition of body mass and inflammation as predictive factors. Sleep disturbance is highly treatable and offers a modifiable target for intervention.

The present study had three aims: (1) to examine whether sleep disturbance and body mass index (BMI) mediated the relation between child abuse and inflammation, (2) to probe whether inflammation mediated the relation between sleep disturbance and prevalent hypertension, and (3) to test a model of childhood abuse on prevalent hypertension during middle adulthood through the parallel mechanisms of sleep disturbance and BMI followed by inflammation (Figure 1). In this model, we hypothesized that greater BMI and higher levels of sleep disturbance and inflammation would significantly mediate the association between childhood abuse and hypertension in middle adulthood after controlling for relevant covariates that may confound the relations of the constructs with hypertension. This study is

the first to test whether the biobehavioral links of body mass, sleep disturbance, and inflammatory processes constitute a mediational pathway by which child abuse is related to risk for hypertension.

Methods

From 2007 to 2012, 770 community-dwelling middle aged adults (40-65 years) representative of the middle-aged population in the Phoenix, Arizona metropolitan area were recruited to participate in a healthy aging study on physiological dysregulation and vulnerability to disease. All participants completed several questionnaires, including questionnaires on exposure to childhood abuse, sleep disturbance, medical history, current medication lists, and other information on sociodemographics and health behaviors. At a home health visit, participants underwent anthropometric measurement, and had blood drawn by a research phlebotomist to extract biomarkers of inflammation. For the present analysis, participants who refused the blood draw, or had missing or inadequate data were excluded from the analysis resulting in a sample size of 609 participants. A further 20 participants were excluded because data were missing for the primary study predictors and outcomes. Excluded participants did not differ from included participants in exposure to childhood abuse; however, excluded participants did report significantly higher levels on measures of sleep disturbance (except for sleep quality; described in Measures section below) than included participants (p 's < .05). The final sample size was 589. Overall, the sample was fairly split between males and females (47.0% vs. 53.0%, respectively), 53.6 years of age on average ($SD = 7.2$), and was evenly spread by education level (~ 25% at each education level: high school or less, some college, college degree, graduate degree). All procedures performed involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Measures

Childhood abuse—Childhood abuse was measured with the Childhood Trauma Questionnaire (CTQ) that measures physical, emotional, and sexual abuse. The CTQ uses a five-point rating scale anchored from “never true” to “very often true.” Items for each type of abuse were summed to yield three subscale scores. Sample items include: “people in my family hit me so hard that I left me with bruises or marks” (physical abuse), “people in my family said hurtful or insulting things to me” (emotional abuse), and “someone threatened to hurt me or tell lies about me unless I did something sexual with them” (sexual abuse). The CTQ has demonstrated robust validity and reliability properties (Bernstein et al., 1994). In the current sample, the internal consistency of the CTQ was 0.91. The internal consistency for the physical, emotional, and sexual abuse subscales were 0.88, 0.88, and 0.93, respectively.

Sleep disturbance—Sleep disturbance was measured using three instruments. Participants completed the sleep quality domain of the Pittsburgh Sleep Quality Index (Buysse et al., 1989) which is a single item that asks “How would you rate your sleep

quality overall?" with response options of "very good," "fairly good," "fairly bad," and "very bad." They completed a modified version of the Insomnia Severity Index (Morin, 1993) to assess difficulty falling and staying asleep, waking too early, level of satisfaction with their current sleep pattern, and how much their sleep pattern interfered with their daily functioning (range = 0-24; Cronbach's $\alpha = 0.85$). Lastly, they responded on a scale from "not at all" to "very much" to the item, "in general, I feel well-rested when I get up in the morning."

Pro-Inflammatory markers—Participants underwent a blood draw to assess levels of IL-6 (pg/ml), CRP(mg/L) and fibrinogen (mg/dL) levels. Blood samples were collected into Vacutainer tubes (Becton–Dickinson, Franklin Lakes, NJ) containing EDTA (IL-6, CRP) or sodium citrate (fibrinogen), held on ice, and centrifuged within 2 h of collection for 15 min at 1500g. Within two hours of collection of 10 ml of blood, the samples were centrifuged for 15 minutes at 1500g. Plasma was then aspirated, aliquoted, and frozen at -80°C until shipped for assay. All inflammatory marker values were determined by a Clinical Laboratory Improvement Amendments (CLIA) certified University of California at Los Angeles Medical Clinical Laboratory using standardized methodologies and reporting guidelines. Plasma levels of IL-6 were quantified using Quantikine High Sensitivity human IL-6 kits (R&D Systems, Inc., Minneapolis, MN), an enzyme-linked immunosorbent assay (ELISA) with an intra-assay coefficient of variation of 4% and inter-assay coefficient of variation of 10%. CRP was measured using the Dade Behring N *High Sensitivity* CRP turbidimetric immunoassay (Dade Behring Diagnostics, Marburg, Germany) on the BN ProSpec. Fibrinogen levels were determined by a commercial laboratory (Quest Diagnostics, Los Angeles, CA) through use of a clotting assay (Clauss, 1975) and reported in mg/dL.

Hypertension—The endpoint for analysis of the present study was prevalence of hypertension. Participants could meet criteria for hypertension in the following ways: 1) blood pressure assessment during the in-home visit; or 2) self-report of physician diagnosis of hypertension with objective verification. Blood pressure was assessed through use of an IBS Model SD-700A automated blood pressure monitor (IBS Corp, Waltham, MA) with a standard occluding cuff placed on the participant's non-dominant arm. Following five minutes of seated rest, blood pressure was assessed three times at two minute intervals. Hypertension was defined as either mean systolic blood pressure (average of three readings) of $\geq 140\text{mmHg}$, or mean diastolic blood pressure of $\geq 90\text{mmHg}$. Participant self-report of physician-diagnosed hypertension or high blood pressure was verified objectively with either documentation of hypertension medication use (i.e., the participant presented their medication to research staff at the in-home visit), or the participant's systolic or diastolic blood pressure was at pre-hypertension levels or above (i.e., systolic blood pressure: $\geq 120\text{mmHg}$; diastolic blood pressure: $\geq 80\text{mmHg}$).

Covariates—Participants provided information on sociodemographics (age, sex), highest level of education completed (high school degree or less; some college; college degree; graduate college degree), current smoking status (everyday, some days, not at all), alcohol use (never, monthly or less, 2-4 times per month, 2-3 times per week, 4+ times per week), physical activity as measured by the International Physical Activity Questionnaire

(IPAQ; Craig et al., 2003), body mass index (objectively-measured), anti-hypertension medication use (recorded at home health visit), and history of medical conditions. History of medical conditions was categorized as none, one, two, or 3 or more of the following set of conditions: coronary artery disease, congestive heart failure, myocardial infarction, cardiac arrhythmias, stroke, diabetes, and cancer. The M.I.N.I International Neuropsychiatric Interview was conducted by trained research team members with all participants to determine history of depression (Lecrubier et al., 1997).

All variables were assessed for missing data. Missing data (<5%) were handled with imputation. Differences between participants with and without reported hypertension were analyzed with one-way ANOVAs for continuous variables and Chi-square tests for categorical variables. Data distributions for IPAQ, BMI, CRP, IL-6, and fibrinogen were not normal, and natural logarithmic transformations were performed on each of these variables. Correlations between all the measured indicators were established. To test our hypotheses, we used structural equation modeling (SEM) to develop each of the models with AMOS (IBM Corp., SPSS, AMOS, version 22, Armonk, NY), using the maximum likelihood estimation procedure. We examined whether a latent variable reflecting childhood abuse was related to prevalence of hypertension, and whether these associations were mediated by latent variables reflecting current sleep disturbance and inflammation, and the observed variable of BMI. First, latent variables for childhood abuse, sleep disturbance, and inflammation were constructed by using observed scores described in each of the sections above dedicated to these constructs. Confirmatory factor analyses were performed to establish the measurement models of each of the latent variables. To identify these latent constructs, one indicator for each factor was set to 1.0. Next, we built and evaluated the structural models for study Aims 1-3. The final models that included hypertension as an outcome were tested while controlling for covariates (i.e., Aims 2 & 3). The models were constructed as simple mediation models followed by multiple mediation models using the *ab* product coefficient (indirect effect), where the *a* path refers to the relation between a predictor and a mediator and the *b* path refers to the relation between a mediator and an outcome (Preacher & Hayes, 2008). Residuals were allowed to covary (Preacher & Hayes, 2008). In the final model, the total, standardized indirect effect of all mediators was assessed using the bootstrapped bias-corrected percentile method. Adequacy of model fit was determined using several fit indices, including the chi square test of model fit, comparative fit index (CFI), and the root mean square error of approximation (RMSEA). Scores of 0.90 on the CFI and scores < 0.06 for RMSEA, were used as benchmarks to determine good model fit (Hu & Bentler, 1999).

Results

Of the total sample ($n = 589$), 243 (41.3%) had study-defined hypertension (i.e., blood pressure measurements meeting clinical level or self-reported, physician-diagnosed hypertension verified with current anti-hypertensive medication use or blood pressure levels meeting criteria for pre-hypertension or above). Of those, 152 (62.6%) were currently taking antihypertensive medications. The remaining 91 participants not taking antihypertensive medications, average systolic blood pressure was 127.0 ($SD = 14.5$), and average diastolic blood pressure was 87.4 ($SD = 7.7$). In the total sample, 76 participants (12.9%) were

current smokers. On average, the total sample was overweight (BMI: *Median* = 27.6, *IQR* = 23.8–31.9), and 19 participants (3.2%) met diagnostic criteria for depression. The distribution of medical conditions was as follows: none, *n* = 170 (28.9%); one, *n* = 173 (29.4%), two, *n* = 123 (20.9%); and three or more, *n* = 123 (20.9%). Presence of some degree of childhood physical, emotional, and sexual abuse was experienced by 45.8%, 77.6%, and 24.6% of the sample, respectively. Table 1 displays the sample characteristics by hypertension status. Participants with study-defined hypertension were more likely to be older, male, currently depressed, have less years of education, higher BMI, poorer sleep quality, greater insomnia severity, and heightened inflammatory biomarker levels.

In the first SEM analysis phase, we performed confirmatory factor analyses for each of the latent variables we constructed: childhood abuse, sleep disturbance, and inflammation. The factor loadings for each latent variable can be found in Table 2. All indicators loaded onto their intended latent construct and were statistically significant (all *p*'s < 0.01). The measurement model also demonstrated good fit ($\chi^2(24) = 25.6$, *p* = 0.37, CFI = 0.99, *RMSEA* = 0.01). Table 3 displays the correlations among the scores of the latent factors, predictors, and covariates for the total sample. Correlations among the latent factor scores revealed that childhood abuse was, as expected, significantly related to sleep disturbance (*r* = 0.36, *p* < 0.001), BMI (*r* = 0.10, *p* = 0.02), and inflammation (*r* = 0.19, *p* < 0.001), inflammation was significantly related to sleep disturbance (*r* = 0.15, *p* < 0.001) and BMI (*r* = 0.47, *p* < 0.001), but sleep disturbance and BMI were not significantly related (*r* = 0.07, *p* = 0.10). Lastly, hypertension status was significantly related to childhood abuse (*r* = .11, *p* = 0.008), sleep disturbance (*r* = .14, *p* = 0.001), BMI (*r* = .25, *p* < 0.001), and inflammation (*r* = .22, *p* < 0.001).

For Aim 1, we hypothesized that sleep disturbance and BMI would independently and simultaneously mediate the relation between childhood abuse and inflammation. In separate models, sleep disturbance (Standardized indirect effect: 0.05, 95%CI: 0.02, 0.08, *p* = 0.009), and BMI (Indirect effect: 0.05, 95%CI: 0.003, .10, *p* = 0.04) were significant mediators of the relation. When both mediators were added to the model the indirect effect of both sleep disturbance and BMI remained significant (Standardized indirect effect: 0.05, 95%CI: 0.02, 0.08, *p* = 0.009). Using the methods of Preacher and Hayes (2008), the mediators were contrasted to determine whether one was significantly stronger than the other, and results indicated there was no significant difference (Contrast Indirect Effect = −0.01, 95%CI: −0.06, 0.04).

For Aim 2, we investigated whether inflammation mediated the association between sleep disturbance and hypertension status after controlling for age, sex, education, smoking status, alcohol use, physical activity, depression status, number of medical conditions, and anti-inflammatory medication use. Inflammation significantly mediated the relation (Standardized indirect effect: .04, 95%CI: .02, .07, *p* = 0.006).

For Aim 3, we tested a model of the association between childhood abuse and hypertension status through the parallel mediation of both sleep disturbance and BMI sequentially followed by inflammation. In the final, adjusted model, the chi-square test was significant ($\chi^2(122) = 352.0$, *p* < 0.001), but the model fit was good overall, CFI = .918, *RMSEA* = .057

(90%CI = .050–.064), see Figure 2. Unstandardized regression weights for all pathways can be found in Table 4. Furthermore, the indirect effect of all mediators was significant (Standardized indirect effect: .02, 95%CI: .005–.03, $p = 0.001$). When examining each pathway individually, the results indicated that BMI and sleep disturbance both mediated the relation between childhood abuse and inflammation (Standardized indirect effect: 0.09, 95%CI: .03–.16, $p = 0.002$) as well as independently (BMI standardized indirect effect: .06, 95%CI .01–.11, $p = 0.03$; Sleep Disturbance standardized indirect effect: .04, 95%CI: .01–.08, $p = 0.005$). Inflammation also mediated the paths between sleep disturbance and hypertension (Standardized indirect effect: .02, 95%CI: .004–.04, $p = 0.004$), and the path between BMI and hypertension (Standardized indirect effect: .08, 95%CI: .04–.13, $p < .001$).

Discussion

The current study tested a multiple mediation model, linking childhood abuse, the mediators of sleep, body mass, and inflammation, and the outcome of hypertension status. The findings were consistent with a parallel and sequential mediation model of sleep disturbance and body mass followed by inflammation. Sleep disturbance, body mass, and inflammation were significant mediators of the relation between childhood abuse and prevalent hypertension in middle adulthood. Consistent with predictions and previous literature, body mass and sleep disturbance each independently mediated the association between childhood abuse and inflammation, and inflammation mediated the associations between sleep disturbance, body mass, and hypertension status. This mediation model was in accordance with previous literature that suggests that childhood abuse may simultaneously lead to abnormalities across multiple stress-sensitive biological systems including the sleep/wake and metabolic systems, that endure into adulthood (Danese et al., 2009).

Childhood is a vulnerable period for the development of the immune system. Acute and chronic stress due to childhood abuse may lead to immunological alterations that are detrimental to later health outcomes. Our results are consistent with previous findings of an association between childhood abuse and amplified, circulating levels of pro-inflammatory markers (Baumeister et al., 2015; Danese et al., 2009; Gouin et al., 2012). The biological underpinnings that explain these associations may be found in childhood abuse leading to a pro-inflammatory immune phenotype (Gouin et al., 2012) through alterations in the sleep/wake and metabolic systems, which may be characterized by an excessive inflammatory response by monocytes and macrophages (Miller, Chen, & Parker, 2011), resistance to mechanisms that inhibit inflammation (Miller et al., 2011), and alterations in neuroendocrine factors that promote production of pro-inflammatory markers (Fagundes, Glaser, & Kiecolt-Glaser, 2013). All together this inflammatory stew may incite early development of detrimental hemodynamic changes (Kusche-Vihrog et al., 2011). Future research should evaluate whether these pathways are related to hemodynamic changes among persons who report previous childhood abuse.

The present study is the first of its kind to evaluate sleep as a mediator in the relation between childhood abuse and hypertension in adulthood. Not only was it found to be a mediator in this relation but it was an upstream mediator to that of inflammation. There are many potential pathways that may link childhood abuse to greater risk for sleep disturbance

in adulthood, we have elucidated and provided evidence for only one. One pathway is through mental health disturbances. Chronic sleep disturbance is a common response to stress and anxiety, and is highly prevalent in pediatric stress-related disorders. Another potential pathway is stress from childhood abuse may trigger psychophysiological hyperarousal that may lead to neuroendocrine abnormalities (e.g., heightened norepinephrine levels, over-activity of the amygdala, underactivity of the medial prefrontal cortex) that dysregulate the sleep/wake cycle (e.g. nightmares, sleep deprivation; (Germain, Buysse, & Nofzinger, 2008)). Stress from childhood abuse may also lead to poor sleep behaviors as coping mechanisms that may preclude sleeping soundly such as sleeping at irregular times and locations to avoid victimization (Spilsbury, 2009). In turn, a dysregulated sleep/wake cycle may lead to greater circulating levels of pro-inflammatory biomarkers that affect hemodynamics. Indeed, case-control studies have shown that diagnosed insomnia was related to blunted nocturnal blood pressure dipping (Lanfranchi et al., 2009), impaired heart rate variability (Spiegelhalter et al., 2011), constant cardiac sympathetic hyperactivation at night (de Zambotti et al., 2013), and greater carotid intima media thickness (Nagai et al., 2013). Thus, neuroendocrine dysregulation, poor sleep behaviors, and mental health disturbances in response to childhood abuse likely lead to persistent sleep disturbances, which in turn incite an inflammatory response that affects vasculature functioning and structure. Longitudinal studies in cohorts who have experienced childhood abuse should be implemented to determine the sequence and magnitude of changes in neuroendocrine functioning, mental health, sleep behaviors, inflammation, and hemodynamics in comparison to persons not exposed to childhood abuse.

Activation of the stress system, mostly via heightened activity within the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, is the likely umbrella mediator that leads to nervous, immune, and endocrine/metabolic changes and links the association between childhood abuse and subsequent hypertension. Activation of the stress system is intimately related to sleep disturbance (de Zambotti et al., 2013) as well as a cascade of pro-inflammatory cytokine release in response to perceived threat and stress. Hyperactivation of the stress system may lead to these alterations simultaneously which will dispose these children to greater risk for hypertension in adulthood (Danese et al., 2009). However, childhood abuse may also exact a direct influence on early hemodynamics through activation of endothelial cells within the inner lining of the vessel wall. A recent study found that endothelin-1, a potent regulator of hemodynamics through vasoconstriction and pro-inflammatory activity, was elevated among adolescents and young adults who had adverse childhood experiences (Su et al., 2014). Systematic investigation of the indirect as well as the direct relations between childhood abuse and hemodynamic changes are both promising avenues of future research.

The present study has several strengths including it draws from a community-dwelling sample consisting of middle-aged adults who are at the prime age to be at risk for hypertension. The study also used a range of measures that were used to answer the study aims with a sophisticated structural equation modeling approach. This study was also the first to assess three major potential mediators, sleep disturbance, body mass, and inflammation, in the relation between childhood abuse and hypertension.

There are several limitations within this study that are noteworthy. First, the study was cross-sectional and therefore causal inferences about the direction of the pathways cannot be made. Second, the circulating levels of the inflammatory biomarkers may not represent values present in vascular regions associated with hypertension. Third, sleep disturbance was estimated with self-report rather than objective assessment of sleep quality and architecture. However, the sophistication of the structural equation modeling as an approach was able to aggregate these data into a strong latent construct. Fourth, the ability to control for potential confounding by family history of hypertension was not possible. However, previous literature suggests that the physiological and health consequences of childhood abuse occur regardless of family history for disease (Danese et al., 2009). Lastly, the generalizability of the results is somewhat limited by the high proportion of White participants and the study subsample was less likely to report sleep disturbances compared to the entire sample.

Sleep disturbance and body mass followed by elevated levels of pro-inflammatory markers appear to mediate the association between childhood abuse and hypertension in adulthood. Our findings suggest that multiple types of biobehavioral treatments including sleep, pharmaceutical, and lifestyle interventions may mitigate the cumulative effects of childhood abuse on the development of hypertension in adulthood. However, given the likely early development changes related to stress from childhood abuse, the most effective interventions would be psychosocial in nature with the family as the target population. Community-based interventions within communities most vulnerable to family conflict may have the most enduring effects on future health and quality of life for these children, and healthcare costs across the lifespan.

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References

- Afifi TO, Mota N, MacMillan HL, Sareen J. Harsh physical punishment in childhood and adults physical health. *Pediatrics*. 2013; 132:e333–e340. [PubMed: 23858428]
- Barth J, Bermetz L, Heim E, Trelle S, Tonia T. The current prevalence of child sexual abuse worldwide: a systematic review and meta-analysis. *International Journal of Public Health*. 2013; 58:469–483. [PubMed: 23178922]
- Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor- α . *Molecular psychiatry*. 2015 doi: 10.1038/mp.2015.67.
- Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, Ruggiero J. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry*. 1994; 151:1132–1136. [PubMed: 8037246]
- Bertone-Johnson ER, Whitcomb BW, Missmer SA, Karlson EW, Rich-Edwards JW. Inflammation and early-life abuse in women. *American journal of preventive medicine*. 2012; 43(6):611–620. [PubMed: 23159256]
- Burgos I, Richter L, Klein T, Fiebich B, Feige B, Lieb K. Increased nocturnal interleukin-6 excretion in patients with primary insomnia: a pilot study. *Brain, Behavior, & Immunity*. 2006; 20:246–253.
- Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatric Research*. 1989; 28:193–213.

- Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Oja P. International Physical Activity Questionnaire: 12-country reliability and validity. *Medicine & Science in Sports & Exercise*. 2003; 195(9131/03):3508–1381.
- Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, Caspi A. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatric & Adolescent Medicine*. 2009; 163:1135–1143.
- Danese A, Tan M. Childhood maltreatment and obesity: systematic review and meta-analysis. *Molecular psychiatry*. 2014; 19(5):544–554. [PubMed: 23689533]
- de Zambotti M, Covassin N, Sarlo M, De Min Tona G, Trinder J, Stegagno L. Nighttime cardiac sympathetic hyperactivation in young primary insomniacs. *Clinical Autonomic Research*. 2013; 23:49–56. [PubMed: 22975984]
- Ekeberg Ø, Kjeldsen SE, Leren P. Childhood traumas and psychosocial characteristics of 50-year-old men with essential hypertension. *Journal of Psychosomatic Research*. 1990; 34:643–649. [PubMed: 2135736]
- Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan. *Brain, Behavior, & Immunity*. 2013; 27C:8–12.
- Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine*. 1998; 14:245–258. [PubMed: 9635069]
- Fernandez-Mendoza J, Vgontzas AN, Liao D, Shaffer ML, Vela-Bueno A, Basta M, Bixler EO. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension*. 2012; 60:929–935. [PubMed: 22892811]
- Floam S, Simpson N, Nemeth E, Scott-Sutherland J, Gautam S, Haack M. Sleep characteristics as predictor variables of stress system markers in insomnia disorder. *Journal of Sleep Research*. 2015; 24:296–304. [PubMed: 25524529]
- Friedman EM, Hayney MS, Love GD, Urry HL, Rosenkranz MA, Davidson RJ, Ryff CD. Social relationships, sleep quality, and interleukin-6 in aging women. *Proceedings of the National Academy of Sciences*. 2005; 102:18757–18762.
- Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: Integrative review and neurobiological hypotheses. *Sleep Medicine Reviews*. 2008; 12:185–195. [PubMed: 17997114]
- Gouin J-P, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser JK. Childhood abuse and inflammatory responses to daily stressor. *Annals of Behavioral Medicine*. 2012; 44:287–292. [PubMed: 22714139]
- Gregory AM, Caspi A, Moffitt TE, Poulton E. Family conflict in childhood: A predictor of later insomnia. *Sleep*. 2006; 29:1063–1067. [PubMed: 16944675]
- Gunn HE, Troxel WM, Hall MH, Buysse DJ. Interpersonal distress is associated with sleep and arousal in insomnia and good sleepers. *Journal of Psychosomatic Research*. 2014; 76:242–248. [PubMed: 24529045]
- Hu LT, Bentlerd PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*. 1999; 6:1–55.
- Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. *Annual Review of Psychology*. 2015; 66:143–172.
- Kusche-Vihrog K, Urbanova K, Blanqué A, Wilhelmi M, Schillers H, Kliche K, Oberleithner H. C-reactive protein makes human endothelium stiff and tight. *Hypertension*. 2011; 57:231–237. [PubMed: 21149827]
- Lanfranchi PA, Pennestri MH, Fradette L, Dumont M, Morin CM, Montplaisir J. Nighttime blood pressure in normotensive subjects with chronic insomnia: implications for cardiovascular risk. *Sleep*. 2009; 32:760–766. [PubMed: 19544752]
- Leclercq Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, Dunbar GC. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structure interview: reliability and validity according to the CIDI. *European Psychiatry*. 1997; 12:224–231.

- Matthews KA, Change Y, Thurston RC, Bromberger JT. Child abuse is related to inflammation in mid-life women: role of obesity. *Brain, Behavior, & Immunity*. 2014; 36:29–34.
- McCaffery JM, Marsland AL, Strohacker K, Muldoon MF, Manuck SB. Factor structure underlying components of allostatic load. *PloS One*. 2012; 7:e47246. [PubMed: 23112812]
- Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. *Hypertension Research*. 2013; 36:985–995. [PubMed: 24005775]
- Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin*. 2011; 137:959–997. [PubMed: 21787044]
- Morin, CM. *Insomnia: psychological assessment and management*. Guilford Press; New York: 1993.
- Nagai M, Hoshida S, Nishikawa M, Shimada K, Kario K. Sleep duration and insomnia in the elderly: associations with blood pressure variability and carotid artery remodeling. *American Journal of Hypertension*. 2013; 26:981–989. [PubMed: 23723262]
- Okun ML, Coussons-Read M, Hall M. Disturbed sleep is associated with increased C-reactive protein in young women. *Brain, Behavior, & Immunity*. 2009; 23:351–354.
- Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavioral Research Methods*. 2008; 40:879–891.
- Raposa EB, Bower JE, Hammen CL, Najman JM, Brennan PA. A Developmental Pathway From Early Life Stress to Inflammation The Role of Negative Health Behaviors. *Psychological science*. 2014; 25(6):1268–1274. [PubMed: 24760142]
- Ras RT, Streppel MT, Draijer R, Zock PL. Flow-mediated dilation and cardiovascular risk prediction: A systematic review with meta-analysis. *International Journal of Cardiology*. 2013; 168:344–351. [PubMed: 23041097]
- Rawson ES, Freedson PS, Osganian SK, Matthews CE, Reed GE, Ockene IS. Body mass index, but not physical activity, is associated with C-reactive protein. *Medicine and science in sports and exercise*. 2003; 35(7):1160–1166. [PubMed: 12840637]
- Riley EH, Wright RJ, Jun HJ, Hibert EN, Rich-Edwards JW. Hypertension in adults survivors of child abuse: observations from the Nurses' Health Study II. *Journal of Epidemiology & Community Health*. 2010; 64:413–418. [PubMed: 20445210]
- Spiegelhalter K, Fuchs L, Ladwig J, Kyle SD, Nissen C, Voderholzer U, Riemann D. Heart rate and heart rate variability in subjectively reported insomnia. *Journal of Sleep Research*. 2011; 20:137–145. [PubMed: 20626615]
- Spilsbury JC. Sleep as a mediator in the pathway from violence-induced traumatic stress to poorer health and functioning: a review of the literature and proposed conceptual model. *Behavioral Sleep Medicine*. 2009; 7:223–244. [PubMed: 19787492]
- Springer KW, Sheridan J, Kuo D, Carne M. Long-term physical and mental health consequence of childhood physical abuse: results from a large population-based sample of men and women. *Child Abuse & Neglect*. 2007; 31:517–530. [PubMed: 17532465]
- Stoltenborgh M, Bakermans-Kranenburg J, van IJzendoorn MH, Alink LRA. Cultural-geographical differences in the occurrence of child physical abuse? A meta-analysis of global prevalence. *International Journal of Psychology*. 2013; 48:81–94. [PubMed: 23597008]
- Su S, Wang X, Kapuku GK, Treiber FA, Pollock DM, Harshfield GA, Pollock JS. Adverse childhood experiences are associated with detrimental hemodynamics and elevated circulating endothelin-1 in adolescents and young adults. *Hypertension*. 2014; 64:201–207. [PubMed: 24777980]
- Von Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. *Acta Haematol*. 1957; 17:237–246. [PubMed: 13434757]
- Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. *Mediators of Inflammation*. 2010; 2010 doi:10.1155/2010/535918.

Figure 1.
Hypothesized Mediation Model between Childhood Abuse and Hypertension through Sleep Disturbance, Body Mass, and Inflammation.

Figure 2.

Final Model, $\chi^2 (122) = 352.0$, $p < 0.001$, CFI = .918, RMSEA = .057 (90%CI = .050, .064).

All standardized regression coefficients significant at $p < .05$. For all mediators, higher values indicate higher levels of the construct.

Table 1

Characteristics of the study sample by hypertension prevalence.

Variable	Hypertensive <i>n</i> = 243		Non-hypertensive <i>n</i> = 346		<i>t/χ²</i>	<i>p</i>
	Mean (<i>n</i>)	SD (%)	Mean (<i>n</i>)	SD (%)		
Age (years)	54.7	7.1	52.9	7.2	−3.0	0.003
Male gender	140	57.6	137	39.6	18.6	<0.001
Education level					10.0	0.02
	HS or less	52	21.4	74	21.4	
	Some College	83	34.2	81	23.4	
	College Degree	5	23.5	90	26.0	
	Graduate Degree	51	21.0	101	29.2	
Smoking Status					0.1	0.74
	Not Smoking	213	87.7	300	86.7	
	Currently Smoking	30	12.3	46	13.3	
Alcohol Use					7.4	0.12
	Never	66	27.2	75	21.7	
	Monthly or less	67	27.6	81	23.4	
	2-4 times per month	50	20.6	80	23.1	
	2-3 times per week	24	9.9	56	16.2	
	4+ times per week	36	14.8	54	15.6	
Physical Activity ^a	3971.2	5701.9	5754.4	6649.0	9.2	0.003
Current Depression					3.9	0.049
	Yes	12	4.9	7	2.0	
	No	231	95.1	339	98.0	
Anti-Inflammatory Medications					18.0	<0.001
	Yes	94	38.7	78	22.5	
	No	149	61.3	268	77.5	
Medical Conditions					142.0	<0.001
	None	16	6.6	154	44.5	
	1	69	28.4	104	30.1	
	2	63	25.9	60	17.3	
	3+	95	39.1	28	8.1	
Systolic Blood Pressure (mmHg)	122.2	14.6	111.2	12.7	−9.4	<0.001
Diastolic Blood Pressure (mmHg)	82.0	10.7	73.6	14.6	−10.2	<0.001
BMI (kg/m ²) ^a	30.5	7.2	27.3	6.7	−6.0	<0.001
CTQ Physical Abuse	1.8	1.1	1.6	0.9	−2.3	0.02
CTQ Emotional Abuse	2.4	1.2	2.2	1.2	−2.2	0.03
CTQ Sexual Abuse	1.5	1.0	1.4	0.9	−0.9	0.40
Sleep Quality (PSQI domain)					14.7	0.002
	Very good	47	19.3	107	30.9	

Variable		Hypertensive <i>n</i> = 243		Non-hypertensive <i>n</i> = 346		<i>t/χ²</i>	<i>p</i>
		Mean (<i>n</i>)	SD (%)	Mean (<i>n</i>)	SD (%)		
Insomnia Severity (range: 0-20)	Fairly good	135	55.6	186	53.8	-2.6	0.009
	Fairly bad	45	18.5	41	11.8		
	Very bad	16	6.6	12	3.5		
		5.8	4.9	4.8	4.5		
	Well-Rested in the Morning?					6.1	0.19
	Not at all	25	10.3	22	6.4		
	A Little	28	11.5	48	13.9		
	Moderately	63	25.9	76	22.0		
	Quite a bit	77	31.7	110	31.8		
	Very Much	50	20.6	90	26.0		
CRP ^a		5.5	9.1	3.2	5.6	-5.4	<0.001
IL-6 ^a		2.7	3.1	2.1	4.4	-4.9	<0.001
Fibrinogen ^a		356.1	93.1	333.0	81.1	-3.2	0.001

^aAnalyses were conducted with log-normalized values of the dependent variables

Table 2

Factor loadings of measured predictors on their latent construct.

Indicator	Childhood Abuse	Sleep Disturbance	Inflammation
CTQ-Emotional	.904		
CTQ-Physical	.789		
CTQ-Sexual	.539		
Modified ISI		.875	
Sleep Quality		.833	
Well-Rested in the Morning		.743	
CRP			.847
IL-6			.670
Fibrinogen			.666

CRP = C-Reactive Protein; CTQ = Childhood Trauma Questionnaire; IL-6 = Interleukin 6; ISI = Insomnia Severity Index

Table 3

Correlations between all study predictors.

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	1.00												
2. Sex	.08*	1.00											
3. Education	.10*	-.01	1.00										
4. Smoking Status	.03	-.11*	.21*	1.00									
5. Alcohol Use	.01	.13*	.12*	-.04	1.00								
6. Physical Activity	-.06	.16*	-.03	-.04	.07	1.00							
7. Anti-inflammatories	.18*	.05	.02	-.02	-.02	-.04	1.00						
8. Current Depression	-.01	-.04	-.11*	-.06	-.13*	-.13*	.05	1.00					
9. No. Med Conditions	.25*	.001	-.08	-.03	-.14*	-.17*	.26*	.18*	1.00				
10. Childhood Abuse	-.03	-.10*	-.12*	-.11*	-.17*	-.01	.06	.21*	.14*	1.00			
11. BMI	-.01	.06	-.10*	.06	-.18*	-.05	.11*	.11*	.17*	.10*	1.00		
12. Sleep Disturbance	-.09*	-.11*	-.12*	-.05	-.14*	-.06	.04	.22*	.23*	.36*	.07	1.00	
13. Inflammation	.13*	-.12*	-.16*	-.12*	-.19*	-.08*	.06	.10*	.25*	.19*	.47*	.15*	1.00

BMI = body mass index

*
 $p < 0.05$

Table 4

Estimated unstandardized regression weights between all paths in the multiple mediation model

Pathways			Estimate	S.E.	P
Childhood Abuse	→	BMI	0.02	0.01	0.02
Childhood Abuse	→	Sleep Disturbance	1.41	0.19	<0.001
BMI	→	Inflammation	2.693	0.21	<0.001
Sleep Disturbance	→	Inflammation	0.03	0.01	0.01
Inflammation	→	Hypertension	0.07	0.02	<0.001
Age	→	Hypertension	−0.002	0.003	0.50
Sex	→	Hypertension	0.21	0.04	<0.001
Education	→	Hypertension	−0.01	0.01	0.21
Alcohol Use	→	Hypertension	−0.004	0.01	0.77
Smoking Status	→	Hypertension	0.06	0.03	0.02
Physical Activity	→	Hypertension	−0.01	0.01	0.19
Anti-Inflammatory Medication	→	Hypertension	0.05	0.04	0.23
No. Medical Conditions	→	Hypertension	0.19	0.02	<0.001
Current Depression	→	Hypertension	−0.05	0.10	0.65