

## THE ROLE OF STRESS IN PERIODONTAL DISEASE PROGRESSION IN OLDER ADULTS

**Christian R. Salazar, Ph.D, MPH**

Department of Epidemiology and Population Health, Albert Einstein College of Medicine  
Email: christian.salazar@einstein.yu.edu

### ABSTRACT

Periodontal disease is characterized by chronic inflammation of the gingiva (gum tissues) caused by infection with anaerobic bacteria. In older adults, progression of disease can lead to tooth loss, inadequate nutritional intake, and a higher risk of other chronic conditions such as cardiovascular disease and diabetes mellitus. As the proportion of older adults continues to grow over time and rates of tooth loss decline, prevalence and severity of periodontal disease will increase. While much is known about risk factors for disease onset, gaps remain in our understanding of factors that could influence disease progression. Over the past few decades, stress has been implicated as a contributory factor. This review critically examines the epidemiological and laboratory evidence and describes a conceptual framework that could help move the research forward.

### INTRODUCTION

Declines in fertility and increases in life expectancy have led to drastic shifts in the age distribution of the world's population, where the proportion of older individuals (aged 65 years or older) has risen steadily from 5.0% of the total population in 1950 to 7.5% in 2009, and is expected to more than double to 16% (1.5 billion persons) by 2050 (Lutz et al. 2008, United Nations. Dept. of Economic and Social Affairs. Population Division. 2010). Although more developed nations have relatively higher proportions of older adults, the growth is considerably more rapid in less developed regions (Bongaarts 2009). The fastest growing segment of the older population is the portion aged 80 years or over, where the growth rate is 4.0% per year.

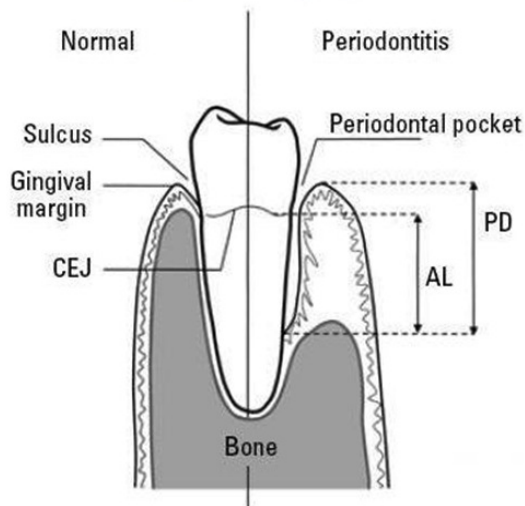
Paralleling this global upward trend is a steady increase in the number of older adults retaining their natural teeth. In the US, the proportion of adults over 65 years who are edentulous (missing all natural teeth) declined from 46% in the early 1970's to 27% by 2004 (Dye et al. 2007). A similar pattern of decline has been observed in other industrialized nations in Europe, Australia and Japan (Starr and Hall 2010). As rates of edentulism decline, the number of natural teeth potentially at risk for oral diseases rises; hence, there is widespread

concern that older adults may have an increasingly greater prevalence of periodontal diseases.

"Periodontal disease" is an umbrella term that includes gingivitis, an inflammation of the gingiva, and "periodontitis", a set of inflammatory conditions affecting the alveolar bone in the jaw and supporting soft tissues that help anchor teeth in place (Armitage 1999). The pathogenesis of periodontitis is complex but it is generally agreed that the initiating etiologic event involves infection with a group of predominantly gram-negative anaerobic bacteria that colonize the subgingival area (Pihlstrom et al. 2005). Progression of disease is dependent upon a complex inter-relationship between microbial activity and the host's inflammatory response to microbial challenge, which progressively leads to connective tissue degradation and alveolar bone loss. Differences in the clinical presentation of periodontitis reflect its complex multifactorial etiology, and these varying presentations have recently led to classification of the disease as either "chronic" or "aggressive" (Lang et al. 2005). Compared to chronic periodontitis, aggressive periodontitis is characterized by its relatively early onset, rapid progression, and familial aggregation.

### Measures of periodontal disease

Case definitions for periodontal disease are determined by an array of measures involving clinical signs and symptoms assessed predominantly with a periodontal probe (figure 1), and can vary from study to study. Periodontal probing depth, a commonly reported measure, is defined as the distance from the free gingival margin to the bottom of the pocket in millimeters (mm). Presence of gingival bleeding serves as another objective indicator for gingival inflammation associated with active disease (Greenstein et al. 1981).



**Figure 1. Measures of periodontal disease severity include: (a) clinical attachment loss (AL), the distance in millimeters between the cemento-enamel junction (CEJ) and bottom of the pocket, (b) periodontal probing depth (PD), the distance in millimeters between the gingival margin and the bottom of the pocket, (c) presence of gingival bleeding, (d) radiographically assessed alveolar bone loss**

Epidemiological studies additionally record clinical attachment level, which is the distance from the cemento-enamel junction to the bottom of the pocket, associated with gingival recession. In some studies, alveolar bone loss is radiographically assessed to determine extent of periodontal destruction (Armitage 2004). Differences in the number of clinical measures and thresholds used for defining disease can reduce the ability to compare prevalence rates across studies of older adult populations.

Furthermore, studies that measure disease from randomly selected quadrants in the mouth as opposed to full mouth underestimate the true prevalence and severity of disease (Hunt and Fann 1991, Kingman and Albandar 2002).

### **Periodontal disease in older adults**

While numerous cross-sectional and longitudinal studies have documented the prevalence and severity of periodontal disease in adults, data regarding disease progression in adults aged 65+ have been scarce, largely due to a low proportion of available subjects who have retained their natural dentition at older age and the difficulties associated with following older adults prospectively. Despite this, recent data from the 2009 and 2010 National Health and Nutrition Examination Survey (NHANES) showed that 64% of older adults have moderate or severe periodontitis, with severe levels confined to a small but substantial minority (Eke et al. 2012). The New England Elders Dental Study, which assessed the periodontal status of 554 adults aged 70+ years in the Northeast region of the US, similarly reported a prevalence of 66% with moderate periodontal pocketing, defined as at least one tooth with no more than a 4-6 mm pocket (Douglass et al. 1993, Fox et al. 1994). Similar rates of disease prevalence have been observed in other parts of the US (Phipps et al. 2009), and in other regions of the world (Gaio et al. 2012, Montero-Aguilar et al. 2012, Norderyd et al. 2012). Severe periodontitis, when defined as >6 mm pocket depth, is observed in only one fifth of adults aged 70+ years, but prevalence is estimated higher in the oldest old (85+ years) (Fox et al. 1994). Similar inferences can be drawn from studies of alveolar bone loss where only a minority of older adults is reported to have advanced bone loss (Renvert et al. 2011). Given these patterns of increasing prevalence and severity of periodontal disease with increasing age, one might conjecture that age is a risk factor. However, the general consensus today challenges that notion and argues that older adults experience a cumulative effect of

prolonged exposure to true risk factors of periodontal disease rather than a heightened susceptibility (Burt 1994).

## METHODS AND MATERIALS

### Search criteria

Peer-reviewed reports were collected from the publicly available database PubMed, which acquires citations from MEDLINE and other scientific data sources. Search terms for epidemiological reports included (a) “periodontal disease”, OR “periodontal inflammation”, OR “periodontitis”; AND (b) “stress”, OR “anxiety”, OR “life events”, “physical stress”, OR “emotional stress”, OR “psychological factors”. Additional terms were included to obtain articles from animal studies: “animal models”, OR “rats”, OR “mice”.

Original epidemiological research articles were included if: (a) at least one objective measure of periodontal disease was clinically assessed; (b) the study population included a minimum of 100 participants; and (c) the work was published in print or online between January 1, 1970 and November 30, 2012. Excluded were articles that did not control for established risk factors or markers for periodontal disease in multivariable models, namely smoking, sex, and age. Since further restriction of research articles to older adult populations would have yielded few articles after applying the inclusion and exclusion criteria, the search was not restricted by age.

Laboratory studies included original research articles in which (a) experimental treatments were administered to live animals; (b) animal tissues, cell systems or organ preparations were examined in the laboratory; and (c) the overarching objective of the study was to understand potential stress mechanism(s) involved in periodontal disease progression.

## RESULTS

### Stress and periodontal disease: Is there a link? *Associations between stress factors and*

*periodontal disease (see appendix table for summary)*

While established risk factors for chronic and aggressive periodontal disease include tobacco consumption, poorly controlled diabetes mellitus, and poor oral hygiene, variations in periodontal disease severity in older adults cannot be fully explained by these factors alone (Stabholz et al. 2010). It has been posited that factors leading to, or related to, stress may account for at least some of the remaining variability (Peruzzo et al. 2007, Rosania et al. 2009). Previous cross-sectional studies of middle-aged and older adult populations have reported strong dose-dependent positive associations between social and financial strain and severe periodontal disease (Moss et al. 1996, Genco et al. 1999, Ng and Leung 2006). Some studies showed that being widowed is a strong independent predictor of severe periodontitis in older adult populations (Hugoson et al. 2002, Chiou et al. 2010, Sabbah et al. 2011). However, the epidemiological evidence is less consistent when measures of stress symptoms, anxiety or depression are considered; some have reported a weak positive association (Croucher et al. 1997, Ng and Leung 2006) whereas others have not (Persson et al. 2003, Solis et al. 2004, Castro et al. 2006, Hilgert et al. 2006). This may be due in part to a lack of uniformity in the method for defining and quantifying these exposures. Definitions of depression and anxiety have ranged from subjective assessments of stressful situations, of which few were collected with validated questionnaires. Others had incorporated salivary cortisol as a physiological measure of stress. Single measures of salivary cortisol can exhibit wide intra-variability over a 24-hour period and lead to misclassification. Rather, stress could best be conceptualized as “part of a complex and dynamic system of positive and negative transactions between individuals and their environment, occurring universally in varying degrees, and exhibiting different effects upon individuals over their life course” (Selye 1976).

### *Animal studies*

Experimental studies involving rodent models have largely corroborated with epidemiological findings, suggesting that a biological mechanism is plausible. In a control trial, mice exposed to physical or emotional stressors such as cold temperatures and isolation demonstrated an inflammatory response to *Porphyromonas gingivalis*, a known pathogen that is etiologically linked to periodontitis (Shapira et al. 2000). Similarly, rats immobilized with flexible wire mesh – also known as restraint stress – exhibited a higher degree of alveolar bone loss than control rats after artificially subjecting them to periodontitis by tying ligatures around their molar teeth (Takada et al. 2004, Huang et al. 2011, Rivera et al. 2012). Rats exposed to restraint stress also produced higher levels of nitric oxide, an important mediator of the inflammatory response, and had increased levels of cortisol and adrenaline. Periodontal tissues of stressed rats also showed evidence of hypoxia, which promotes a favorable microenvironment for proliferation of anaerobic bacteria etiologically linked to periodontal disease. Notably, one study found a synergistic effect of nicotine exposure and restraint stress on periodontal disease progression (Benatti et al. 2003).

### **Suggested Pathways**

A number of pathways have been proposed to explain the stress-periodontal disease association (Genco et al. 1998, Rosania et al. 2009, Stabholz et al. 2010). In general, mechanisms have been grouped into 2 broad categories: (a) ‘health-impairing behaviors’ associated with stress, such as increases in tobacco and alcohol consumption, poor oral hygiene, and poor nutritional intake (Stabholz et al. 2010) ; and (b) ‘pathophysiological factors’ that lead to increases in stress hormones which can indirectly influence inflammatory and immunological profiles and increase the susceptibility to periodontal disease.

### *Health-impairing behaviors*

A number of health-impairing behaviors associated with stress are likely to influence periodontal health. Evidence suggests a positive bidirectional association between depression and smoking, particularly among young adults (Chaiton et al. 2009). As an established risk factor for periodontal disease, smoking may serve as a mediating factor between depression and periodontal disease progression. Smoking may also confound the positive association between alcohol consumption and periodontal disease observed in several epidemiological studies (Amaral Cda et al. 2009). Associations of other health-impairing behaviors such as poor oral hygiene and intake of fruits and vegetables with periodontitis show inconsistent findings, possibly due to confounding by other lifestyle factors (Sakki et al. 1995).

### *Pathophysiological factors*

In a highly coordinated response to physical and perceived stress, the brain activates the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic (SNS) and parasympathetic branches of the autonomic nervous system. The HPA axis releases glucocorticoids, a class of steroidal hormones important in stress-related pathology (Munck et al. 1984). Glucocorticoids exert a myriad of effects on the body ranging from immunosuppression to modification of cytokine and blood glucose levels (Sapolsky et al. 2000). In particular, increased levels of glucocorticoids alters inflammatory activity by suppressing inflammatory cytokine production, including interleukins (IL)-1, IL-2, IL-6, and tumor necrosis factors (Spencer RL et al. 2000). The SNS, in addition, releases catecholamines such as epinephrine and norepinephrine from the adrenal medulla. Catecholamines are monoamine hormones that regulate cardiovascular functioning and are involved in mobilizing and redistributing immune cells throughout the body often synergizing or antagonizing with the action of glucocorticoids (Dowdell K and Whitacre C 2000). Evidence from in-vitro studies have suggested that levels of epinephrine, norepinephrine, and cortisol might directly influence growth patterns of

single strains of periodontally-involved microorganisms (Roberts et al. 2002, Jentsch et al. 2013), although more work is necessary to evaluate whether these growth changes persist when the microorganisms are cultured collectively.

### **Allostasis: A conceptual framework**

While hormonal mediators of the stress response, i.e., glucocorticoids and catecholamines, have protective effects on the body in the short term, over-production can lead to pathophysiology and damage over the long term (McEwen and Seeman 1999). Chronic exposure to stress hormones from excessive cycles of response creates changing patterns of energy demand. To meet this challenge, a whole-body adaptation known as allostasis takes hold whereby physiological systems operate at new levels in order to maintain stability or homeostasis (Schulkin 2004). With allostasis, biological set points of physiological system parameters change to a new equilibrium, thereby increasing efficiency and allowing for the organism's continued survival during repeated challenge. Over time, however, cumulative damage to tissues and major organ systems result from this adaptation. This biological 'wear and tear' is referred to as allostatic load (McEwen 1998).

### *The allostatic load model*

Four types of allostatic physiological conditions can lead to allostatic load, illustrating the damaging effects that hormonal mediators of stress can have on the body and contribute to gradients of health. The first involves multiple hits from novel stressors, which, over time, result in over-exposure to stress hormones and eventual biological damage. The next three conditions involve a failure of the organism to adequately manage the hormonal stress response. In the first instance, there is a lack of habituation to repeated stressors of the same kind. In the second, the body experiences a delayed response due to an inability to properly shut down the stress system. Lastly, an inadequate physiological response in one

regulatory system, such as the HPA axis, leads to compensatory over-activity of other allostatic regulatory systems, which under normal circumstances are kept in balance by glucocorticoids and catecholamines.

Allostatic load differs from traditional approaches to measurement of disease risk. First, there is an emphasis on biological system interconnectedness rather than a reductionist approach that focuses on the role of only one aspect of the system. Second, allostatic load accounts for biological risk over the life course, consistent with the cumulative risk model proposed by Ben-Shlomo and Kuh (Ben-Shlomo and Kuh 2002). This life course approach predicts that individuals accumulate allostatic load at different rates over time; older adults would generally have higher levels of allostatic load than younger individuals (Crimmins et al. 2003). Differences in allostatic load scores in a given population would then reflect the myriad of prior exposures associated with stress that subsequently contribute to disease.

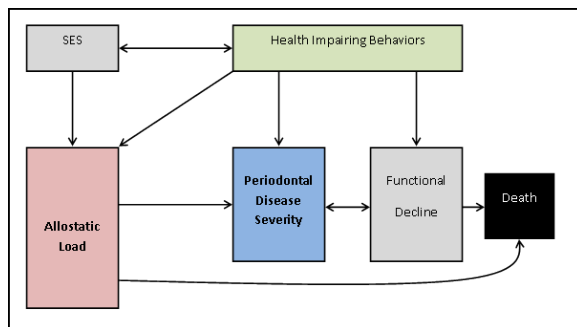
### *Operationalizing allostatic load*

Allostatic load has been operationalized using a variety of statistical approaches (Seplaki et al. 2005). Initial efforts involved a straightforward summative approach in which biomarkers of neuroendocrine, metabolic, inflammatory, and cardiovascular functioning were used to calculate an aggregate score, allowing for equal weighting of each contributing marker. However, this approach has received some criticism given that biomarkers biologically interact and likely contribute unequally to disease pathways. More complex scoring algorithms have been recently developed to expand the range of physiological measurements and account for unequal weighting, although no "gold standard" approach has yet been accepted. Nevertheless, even with a cruder summative scoring approach, cross-sectional and longitudinal studies of older adults have shown that allostatic load is a strong independent predictor of incident cardiovascular disease (Seeman et

al. 1997), declines in cognitive and physical functioning (Karlman et al. 2002, Wikby et al. 2005, Gruenewald et al. 2009, Karlman et al. 2013), and all-cause mortality (Seeman et al. 2004, Gruenewald et al. 2006, Karlman et al. 2006, Borrell et al. 2010).

### Allostatic load and periodontal disease: A life course approach

Using allostasis as a conceptual framework for disease risk over the life course, allostatic load could exert a direct effect on periodontal disease and may serve as a mediator for the relationship between social and health-impairing behaviors and periodontal disease severity (figure 2).



**Figure 2. Proposed pathways through which social and health-impairing behavioral factors might influence periodontal disease severity. Allostatic load could have a direct effect on periodontal disease severity and serve as a mediator for this relationship. (Abbreviation: SES= Socioeconomic status)**

### Associations between allostatic load and periodontal disease

In a cross-sectional study using NHANES (1998 – 1994) data, investigators reported, for the first time, a positive association between allostatic load, assessed with 7 biomarkers that spanned metabolic and inflammatory systems, and periodontitis in US adults (Sabbah et al. 2008). High levels of allostatic load independently predicted gingival inflammation, clinical attachment loss, and periodontal pocketing. In addition, allostatic load was also positively associated with ischemic heart disease, suggesting a common stress pathway for both

conditions. Recent findings using more current NHANES data (1999-2004) suggested similar associations (Borrell and Crawford 2009). Moving forward, longitudinal studies in other populations will be necessary to confirm these findings and to investigate the temporal directionality of the purported relationship.

### CONCLUSIONS

The older adult population is growing faster than any other age group worldwide. The prevalence and severity of periodontal disease among older adults are expected to rise globally as individuals experience longer life spans and retention of their natural teeth. Findings from epidemiological and animal studies suggest that stress can influence the progression of periodontal disease. One promising theoretical model that could offer insight from a life course perspective is allostatic load. Future studies will need to identify which set of biomarkers, or combination of biomarkers, are most useful in predicting periodontal disease. These findings could contribute immensely to our understanding of the role of stress and inflammation in relation to aging and offer avenues for intervention.

### Acknowledgements

I thank Drs. Pam Factor-Litvak and Douglas E Morse for a critical reading of the manuscript. The work was supported by NIH training grant T32-DE007255

## REFERENCES

- Amaral Cda, S., M. V. Vettore, and A. Leao. 2009. The relationship of alcohol dependence and alcohol consumption with periodontitis: a systematic review. *Journal of dentistry* **37**:643-651.
- Armitage, G. C. 1999. Development of a classification system for periodontal diseases and conditions. *Annals of periodontology / the American Academy of Periodontology* **4**:1-6.
- Armitage, G. C. 2004. The complete periodontal examination. *Periodontology 2000* **34**:22-33.
- Ben-Shlomo, Y. and D. Kuh. 2002. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *International journal of epidemiology* **31**:285-293.
- Benatti, B. B., G. R. Nogueira-Filho, M. C. Diniz, E. A. Sallum, A. W. Sallum, and F. H. Nociti, Jr. 2003. Stress may enhance nicotine effects on periodontal tissues. An in vivo study in rats. *Journal of periodontal research* **38**:351-353.
- Bongaarts, J. 2009. Human population growth and the demographic transition. *Philos Trans R Soc Lond B Biol Sci* **364**:2985-2990.
- Borrell, L. N. and N. D. Crawford. 2009. Social Disparities in Periodontitis among United States Adults: The effect of allostatic load. *J Epidemiol Community Health*.
- Borrell, L. N., F. J. Dallo, and N. Nguyen. 2010. Racial/ethnic disparities in all-cause mortality in U.S. adults: the effect of allostatic load. *Public health reports* **125**:810-816.
- Burt, B. A. 1994. Periodontitis and aging: reviewing recent evidence. *Journal of the American Dental Association* **125**:273-279.
- Castro, G. D., R. V. Oppermann, A. N. Haas, R. Winter, and J. C. Alchieri. 2006. Association between psychosocial factors and periodontitis: a case-control study. *Journal of clinical periodontology* **33**:109-114.
- Chaiton, M. O., J. E. Cohen, J. O'Loughlin, and J. Rehm. 2009. A systematic review of longitudinal studies on the association between depression and smoking in adolescents. *BMC public health* **9**:356.
- Chiou, L. J., Y. H. Yang, H. C. Hung, C. C. Tsai, T. Y. Shieh, Y. M. Wu, W. C. Wang, and T. C. Hsu. 2010. The association of psychosocial factors and smoking with periodontal health in a community population. *Journal of periodontal research* **45**:16-22.
- Crimmins, E. M., M. Johnston, M. Hayward, and T. Seeman. 2003. Age differences in allostatic load: an index of physiological dysregulation. *Experimental gerontology* **38**:731-734.
- Croucher, R., W. S. Marcenes, M. C. Torres, F. Hughes, and A. Sheiham. 1997. The relationship between life-events and periodontitis. A case-control study. *Journal of clinical periodontology* **24**:39-43.
- Douglass, C. W., A. M. Jette, C. H. Fox, S. L. Tennstedt, A. Joshi, H. A. Feldman, S. M. McGuire, and J. B. McKinlay. 1993. Oral health status of the elderly in New England. *Journal of gerontology* **48**:M39-46.
- Dowdell K and Whitacre C. 2000. *Coping with the environment: Neural and endocrine mechanisms*. Oxford University Press, New York.
- Dye, B. A., S. Tan, V. Smith, B. G. Lewis, L. K. Barker, G. Thornton-Evans, P. I. Eke, E. D. Beltran-Aguilar, A. M. Horowitz, and C. H. Li. 2007. Trends in oral health status: United States, 1988-1994 and 1999-2004. *Vital and health statistics. Series 11, Data from the national health survey*:1-92.
- Eke, P. I., B. A. Dye, L. Wei, G. O. Thornton-Evans, and R. J. Genco. 2012. Prevalence of periodontitis in adults in the United States:

2009 and 2010. *Journal of dental research* **91**:914-920.

Fox, C. H., A. M. Jette, S. M. McGuire, H. A. Feldman, and C. W. Douglass. 1994. Periodontal disease among New England elders. *Journal of periodontology* **65**:676-684.

Gaio, E. J., A. N. Haas, V. C. Carrard, R. V. Oppermann, J. Albandar, and C. Susin. 2012. Oral health status in elders from South Brazil: a population-based study. *Gerodontology* **29**:214-223.

Genco, R. J., A. W. Ho, S. G. Grossi, R. G. Dunford, and L. A. Tedesco. 1999. Relationship of stress, distress and inadequate coping behaviors to periodontal disease. *Journal of periodontology* **70**:711-723.

Genco, R. J., A. W. Ho, J. Kopman, S. G. Grossi, R. G. Dunford, and L. A. Tedesco. 1998. Models to evaluate the role of stress in periodontal disease. *Annals of periodontology / the American Academy of Periodontology* **3**:288-302.

Greenstein, G., J. Caton, and A. M. Polson. 1981. Histologic characteristics associated with bleeding after probing and visual signs of inflammation. *Journal of periodontology* **52**:420-425.

Gruenewald, T. L., T. E. Seeman, A. S. Karlamangla, and C. A. Sarkisian. 2009. Allostatic load and frailty in older adults. *Journal of the American Geriatrics Society* **57**:1525-1531.

Gruenewald, T. L., T. E. Seeman, C. D. Ryff, A. S. Karlamangla, and B. H. Singer. 2006. Combinations of biomarkers predictive of later life mortality. *Proc Natl Acad Sci U S A* **103**:14158-14163.

Hilgert, J. B., F. N. Hugo, D. R. Bandeira, and M. C. Bozzetti. 2006. Stress, cortisol, and periodontitis in a population aged 50 years and over. *Journal of dental research* **85**:324-328.

Huang, S., F. Lu, Z. Zhang, X. Yang, and Y. Chen. 2011. The role of psychologic stress-induced hypoxia-inducible factor-1alpha in rat experimental periodontitis. *Journal of periodontology* **82**:934-941.

Hugoson, A., B. Ljungquist, and T. Breivik. 2002. The relationship of some negative events and psychological factors to periodontal disease in an adult Swedish population 50 to 80 years of age. *Journal of clinical periodontology* **29**:247-253.

Hunt, R. J. and S. J. Fann. 1991. Effect of examining half the teeth in a partial periodontal recording of older adults. *Journal of dental research* **70**:1380-1385.

Jentsch, H. F., D. Marz, and M. Kruger. 2013. The effects of stress hormones on growth of selected periodontitis related bacteria. *Anaerobe*.

Karlamangla, A. S., D. Miller-Martinez, M. E. Lachman, P. A. Tun, B. K. Koretz, and T. E. Seeman. 2013. Biological correlates of adult cognition: Midlife in the United States (MIDUS). *Neurobiology of aging*.

Karlamangla, A. S., B. H. Singer, B. S. McEwen, J. W. Rowe, and T. E. Seeman. 2002. Allostatic load as a predictor of functional decline. *MacArthur studies of successful aging. Journal of clinical epidemiology* **55**:696-710.

Karlamangla, A. S., B. H. Singer, and T. E. Seeman. 2006. Reduction in allostatic load in older adults is associated with lower all-cause mortality risk: MacArthur studies of successful aging. *Psychosomatic medicine* **68**:500-507.

Kingman, A. and J. M. Albandar. 2002. Methodological aspects of epidemiological studies of periodontal diseases. *Periodontology 2000* **29**:11-30.

Lang, N. P., J. Lindhe, and U. van der Velden. 2005. Advances in the prevention of periodontitis. Group D consensus report of the



5th European Workshop in Periodontology. *Journal of clinical periodontology* **32 Suppl 6**:291-293.

Lutz, W., W. Sanderson, and S. Scherbov. 2008. The coming acceleration of global population ageing. *Nature* **451**:716-719.

McEwen, B. S. 1998. Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences* **840**:33-44.

McEwen, B. S. and T. Seeman. 1999. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences* **896**:30-47.

Montero-Aguilar, M., F. Munoz-Torres, A. R. Elias-Boneta, B. Dye, and K. J. Joshipura. 2012. High levels of periodontal disease among the older adult population in San Juan, Puerto Rico. *Community dental health* **29**:224-228.

Moss, M. E., J. D. Beck, B. H. Kaplan, S. Offenbacher, J. A. Weintraub, G. G. Koch, R. J. Genco, E. E. Machtei, and L. A. Tedesco. 1996. Exploratory case-control analysis of psychosocial factors and adult periodontitis. *Journal of periodontology* **67**:1060-1069.

Munck, A., P. M. Guyre, and N. J. Holbrook. 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocrine reviews* **5**:25-44.

Ng, S. K. and W. K. Leung. 2006. Oral health-related quality of life and periodontal status. *Community dentistry and oral epidemiology* **34**:114-122.

Norderyd, O., B. M. Henriksen, and H. Jansson. 2012. Periodontal disease in Norwegian old-age pensioners. *Gerodontology* **29**:4-8.

Persson, G. R., R. E. Persson, C. I. MacEntee, C. C. Wyatt, L. G. Hollender, and H. A. Kiyak. 2003. Periodontitis and perceived risk for periodontitis in elders with evidence of

depression. *Journal of clinical periodontology* **30**:691-696.

Peruzzo, D. C., B. B. Benatti, G. M. Ambrosano, G. R. Nogueira-Filho, E. A. Sallum, M. Z. Casati, and F. H. Nociti, Jr. 2007. A systematic review of stress and psychological factors as possible risk factors for periodontal disease. *Journal of periodontology* **78**:1491-1504.

Phipps, K. R., B. K. Chan, M. Jennings-Holt, N. C. Geurs, M. S. Reddy, C. E. Lewis, and E. S. Orwoll. 2009. Periodontal health of older men: the MrOS dental study. *Gerodontology* **26**:122-129.

Pihlstrom, B. L., B. S. Michalowicz, and N. W. Johnson. 2005. Periodontal diseases. *Lancet* **366**:1809-1820.

Renvert, S., J. Berglund, R. E. Persson, and G. R. Persson. 2011. Osteoporosis and periodontitis in older subjects participating in the Swedish National Survey on Aging and Care (SNAC-Blekinge). *Acta odontologica Scandinavica* **69**:201-207.

Rivera, C., F. Monsalve, I. Suazo, and J. Becerra. 2012. Stress increases periodontal inflammation. *Experimental and therapeutic medicine* **4**:883-888.

Roberts, A., J. B. Matthews, S. S. Socransky, P. P. Freestone, P. H. Williams, and I. L. Chapple. 2002. Stress and the periodontal diseases: effects of catecholamines on the growth of periodontal bacteria in vitro. *Oral microbiology and immunology* **17**:296-303.

Rosania, A. E., K. G. Low, C. M. McCormick, and D. A. Rosania. 2009. Stress, depression, cortisol, and periodontal disease. *Journal of periodontology* **80**:260-266.

Sabbah, W., G. Tsakos, T. Chandola, T. Newton, I. Kawachi, A. Sheiham, M. G. Marmot, and R. G. Watt. 2011. The relationship between social network, social support and periodontal disease among older Americans. *Journal of clinical periodontology* **38**:547-552.

- Sabbah, W., R. G. Watt, A. Sheiham, and G. Tsakos. 2008. Effects of allostatic load on the social gradient in ischaemic heart disease and periodontal disease: evidence from the Third National Health and Nutrition Examination Survey. *J Epidemiol Community Health* **62**:415-420.
- Sakki, T. K., M. L. Knuuttila, S. S. Vimpari, and M. S. Hartikainen. 1995. Association of lifestyle with periodontal health. *Community dentistry and oral epidemiology* **23**:155-158.
- Sapolsky, R. M., L. M. Romero, and A. U. Munck. 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine reviews* **21**:55-89.
- Schulkin, J. 2004. *Allostasis, homeostasis and the costs of physiological adaptation*. Cambridge University Press, New York.
- Seeman, T. E., E. Crimmins, M. H. Huang, B. Singer, A. Bucur, T. Gruenewald, L. F. Berkman, and D. B. Reuben. 2004. Cumulative biological risk and socio-economic differences in mortality: MacArthur studies of successful aging. *Social science & medicine* **58**:1985-1997.
- Seeman, T. E., B. H. Singer, J. W. Rowe, R. I. Horwitz, and B. S. McEwen. 1997. Price of adaptation--allostatic load and its health consequences. *MacArthur studies of successful aging*. *Archives of internal medicine* **157**:2259-2268.
- Selye, H. 1976. *Stress in health and disease*. Butterworths, Boston.
- Seplaki, C. L., N. Goldman, D. Glej, and M. Weinstein. 2005. A comparative analysis of measurement approaches for physiological dysregulation in an older population. *Experimental gerontology* **40**:438-449.
- Shapira, L., I. Frolov, A. Halabi, and D. Ben-Nathan. 2000. Experimental stress suppresses recruitment of macrophages but enhanced their *P. gingivalis* LPS-stimulated secretion of nitric oxide. *Journal of periodontology* **71**:476-481.
- Solis, A. C., R. F. Lotufo, C. M. Pannuti, E. C. Brunheiro, A. H. Marques, and F. Lotufo-Neto. 2004. Association of periodontal disease to anxiety and depression symptoms, and psychosocial stress factors. *Journal of clinical periodontology* **31**:633-638.
- Spencer RL, Kalman BA, and Dhabhar FS. 2000. *Coping with the environment: Neural and endocrine mechanisms*. Oxford University Press, New York.
- Stabholz, A., W. A. Soskolne, and L. Shapira. 2010. Genetic and environmental risk factors for chronic periodontitis and aggressive periodontitis. *Periodontology 2000* **53**:138-153.
- Starr, J. M. and R. Hall. 2010. Predictors and correlates of edentulism in healthy older people. *Current opinion in clinical nutrition and metabolic care* **13**:19-23.
- Takada, T., N. Yoshinari, S. Sugiishi, H. Kawase, T. Yamane, and T. Noguchi. 2004. Effect of restraint stress on the progression of experimental periodontitis in rats. *Journal of periodontology* **75**:306-315.
- United Nations. Dept. of Economic and Social Affairs. Population Division. 2010. *World population ageing 2009*. United Nations, Dept. of Economic and Social Affairs, Population Division, New York, N.Y.
- Wikby, A., F. Ferguson, R. Forsey, J. Thompson, J. Strindhall, S. Lofgren, B. O. Nilsson, J. Ernerudh, G. Pawelec, and B. Johansson. 2005. An immune risk phenotype, cognitive impairment, and survival in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans. *The journals of gerontology. Series A, Biological sciences and medical sciences* **60**:556-565.

**Appendix table.** Epidemiological studies evaluating the role of stress and psychological factors on periodontal disease

First author and year	Type of study	Periodontal disease measure	Population size (age range, y)	Geographical location	Principal Findings
Moss et al 1996	Case-control	AL and PD	71 cases, 77 controls (25 – 74)	USA	Role strain was positively associated with case status (OR=2.84, 1.08 – 7.46).
Genco et al 1999	Cross-sectional	AL and radiographs	1,426 (25 – 74)	USA	Financial strain was positively associated with AL (OR = 1.70, 1.09 – 2.65) and alveolar bone loss (OR=1.68, 1.20 – 2.37)
Hugoson et al 2002	Cross-sectional	PD	298 (50 – 80)	Sweden	Being widowed was positively associated with PD $\geq$ 4 mm as compared with being married, but was removed after controlling for age.
Sabbah et al 2011	Cross-sectional	AL, PD,	1,632 (60+)	USA	Being widowed was positively associated with AL $\geq$ 3 mm (adjusted OR=1.27, 1.03 – 1.58)
Chiou et al 2010	Cross-sectional	AL and PD	11,723 ( $\geq$ 18)	Taiwan	Psychosocial stress was positively associated with AL $\geq$ 6 mm (OR=1.69, 1.01 – 2.77)
Hilgert et al 2006	Cross-sectional	AL, PD, and BOP	235 (50 – 86)	Brazil	No association between stress and periodontal disease, but high levels of cortisol was positively associated with AL $\geq$ 4 mm (OR=6.9, 1.7 – 27.1), and PD $\geq$ 4 mm (OR=10.7, 1.9 – 54.1)
Solis et al 2004	Cross-sectional	AL and PD	153 (19 – 67)	Brazil	No association between depression, hopelessness, psychiatric symptoms and periodontitis
Persson et al 2003	Cross-sectional	PD and radiographs	701 (60 – 75)	USA	No association between depression and periodontitis

Castro et al 2006	Case-control	AL	165 (35 – 60)	Brazil	No association between life events, anxiety, and depression with periodontitis
Ng et al 2006	Cross-sectional	AL, PD, and BOP	1000 (25 – 64)	China	Factors that were positively associated with AL $\geq$ 4 mm were: depression (OR=1.62, 1.15 – 2.35) anxiety (OR=1.51, 1.09 – 2.72), job strain (OR=1.47, 1.21 – 2.01), and financial strain (OR=1.38, 1.13 – 1.71)
Croucher et al 1997	Case-control	PD	50 cases, 50 controls (18 – 60)	UK	Number of traumatic life events was positively associated with at least one tooth with PD $\geq$ 5 mm

---

**Abbreviations: PD= Periodontal probing depth, AL= Clinical attachment loss, BOP= Bleeding on probing, OR= Odds Ratio**