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# Association of periodontitis with subclinical atherosclerosis and peripheral arterial disease in Korean adults

# 한국 성인에서 치주병과 무증상동맥경화증 및 말초동맥경화증의 연관성

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ABSTRACT

# Association of periodontitis with subclinical atherosclerosis and peripheral arterial disease in Korean adults

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**Aim:**

This study aimed to evaluate the association of periodontal disease with the development of early atherosclerotic vascular disease in Korean adults.

**Materials and Methods:**

In this cross-sectional study, a total of 1,343 adults aged over 40 were recruited from a community-based cohort of Yangpyeong county, Korea, during the period of year 2010, 2012-2014. Only dentate individuals were included in the study. Subclinical atherosclerosis (SA) was defined as carotid intima-media thickness (cIMT)≥0.754mm,

as assessed bilaterally by B-mode ultrasound. Peripheral arterial disease (PAD) was defined as ankle-brachial index (ABI)≤1.0, as measured by Doppler. Periodontitis was assessed by measuring the radiographic alveolar bone loss (RABL) on a digital dental panorama and was classified into three groups: normal, moderate and severe periodontitis (two or more non-adjacent interproximal sites with RABL ≥4mm and 6mm, respectively). The associations of periodontitis with SA and PAD were evaluated by multivariable logistic regression analysis and analysis of covariance, adjusted for age, sex, education level, smoking, drinking, exercise, obesity, triglycerides, HDL, LDL, hs-CRP, diabetes and hypertension. Stratified analyses were performed to identify specific risk groups.

**Results:**

After controlling for confounders, severe periodontitis was associated with [adjusted odds ratio (aOR)= 1.50; 95% confidence interval (CI): 1.04-2.17] and PAD (aOR= 1.95; 95% CI: 1.01-3.75). The association of severe periodontitis with SA was highlighted in individuals aged over 65 years, females, never-smokers, drinkers and individuals without metabolic syndrome. The association of severe periodontitis with PAD was highlighted in individuals less than 65 years and never smokers. For increasing severity of periodontitis, the adjusted mean cIMT was increased (P=0.007) while that of ABI decreased (P=0.049).

**Conclusion:**

Our data showed that periodontitis is a substantially important risk factor on atherosclerotic vascular disease in Korean adults. Further research is indicated to elucidate the causality and the mechanism of this link.

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Keywords: Periodontitis, Subclinical atherosclerosis, Intima-media thickness, Peripheral arterial disease, Ankle-brachial index, Epidemiology.

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# Contents

## I. INTRODUCTION

Atherosclerotic vascular disease (ASVD) is a major public health burden on the global population (Barquera et al., 2015). As the leading cause of mortality worldwide, the two most prevalent ASVDs namely, ischemic heart disease and stroke, are responsible for more deaths than total cancers, accounting for 25.1% of all-cause mortality (WHO, 2014). Atherosclerosis is the major cause of these ASVDs, a condition characterized by thickening of the arterial wall due to chronic inflammation and lipid and metabolic alterations of vessel walls (Epstein and Ross, 1999). For the last few decades, growing evidence has implicated that a chronic low-grade inflammatory process of periodontal disease contributes to the pathogenesis of atherosclerosis and subsequently, ischemic heart disease (Lockhart et al., 2012) and stroke (Sim et al., 2008). Recently, a consensus report was published to conclude that the current state of the evidence supports a positive and significant association between periodontitis and ASVD (Tonetti et al., 2013).

Periodontal disease is a chronic inflammatory disease characterized by the destruction of the tooth-supporting connective tissues in response to subgingival infection with various periodontal pathogens, which ultimately leads to tooth loss and diminished masticatory function (Pihlstrom et al., 2005). The biological plausibility of periodontal inflammation-associated atherosclerotic process is supported by experimental studies on transient bacteremia and elevated inflammatory markers in patients with periodontitis. Periodonto-pathogenic bacteria such as Tennerella forsythensis, Porphyromonas gingivalis and Prevotella intermedia have been identified in atherosclerotic plaques (Haraszthy et al., 2000), as well as in human aortic and coronary endothelium (Deshpande et al., 1998). P. gingivalis, in particular, is implicated in cardiovascular

disease by direct invasion of endothelial cells and initiation of autophagic pathway in cardiovascular endothelial and smooth muscle cells (Dorn et al., 2001). Such a periodontal infection-mediated systemic bacteremia can induce upregulation of local and systemic cytokines and other inflammatory mediators (Han et al., 2012), which can subsequently lead to endothelial dysfunction and plaque formation (Haynes and Stanford, 2003, Reyes et al., 2013).

Epidemiological evidence on this link, however, is not yet conclusively established. Previous studies have presented inconsistent results on the association between periodontal disease and surrogate markers of atherosclerosis including such subclinical morphological changes as increased carotid intima-media thickness (cIMT) and low ankle-brachial index (ABI). Abnormally increased cIMT and a low ABI represent a state of subclinical atherosclerosis (SA) and peripheral arterial disease (PAD), respectively (Feinstein et al., 2002). Large cross-sectional studies conducted among Americans reported that increased cIMT is associated with periodontitis (Beck et al., 2001, Southerland et al., 2012) and periodontopathogenic bacterial dominance (Desvarieux et al., 2005). A cross-sectional study among Japanese (Hayashida et al., 2013) and a cohort study among Swedish (Söder et al., 2005) also reported that periodontitis is an independent predictor of an increased cIMT. On the other hand, case-control studies among Finnish (Ylöstalo et al., 2010) and Spanish (Lopez-Jornet et al., 2012) found no consistent association between periodontitis and cIMT. In Koreans, a recent cross-sectional study reported that periodontitis was not associated with increased cIMT (Jung et al., 2014). A few epidemiological studies explored the link between periodontitis and ABI-defined PAD. The Health Professionals Follow-up Study reported that periodontitis was associated with low ABI (Hung et al., 2003). A cross-sectional analysis of the NHANES data also showed a positive association between low ABI and periodontitis

(Lu et al., 2008). A Japanese study found an increased risk of ABI-defined PAD among periodontitis patients (Chen et al., 2008). However, in an Indian case-control study, the mean ABI was found to be rather higher among periodontitis cases compared to gingivitis cases (Shanker et al., 2013).

Hitherto, no study has reported on the association between periodontitis and the two markers of early ASVD, namely cIMT and ABI. In the lack of conclusive evidence on the association of periodontitis with early atherosclerosis development, the authors explored this potential link in Korean adults in the Korean Genome and Epidemiology Study (KoGES) Cardiovascular disease Association Study (CAVAS). Thus, the aim of this study was to test the hypothesis that periodontitis is associated with SA and PAD.

## II. MATERIALS AND METHODS

### Ethical consideration

This study was approved by the Institutional Review Board of Seoul National University, School of Dentistry (IRB No: S-D20100006, S-D20130005). All subjects provided written informed consent after receiving a full explanation of study details.

### Study design and subjects

We enrolled 1,854 subjects aged 40 years or more who participated in the KoGES_CAVAS in years 2010, 2012-2014 for an oral assessment conducted in Yangpyeong county, Korea. The KoGES_CAVAS is a community-based cohort which provides a health examination follow-up program for individuals aged 40 years or more,

directed by the Korea Centers for Disease Control and Prevention (KCDC). A detailed description of the sampling methods and survey contents is described in the cohort profile paper (Kim and Han, 2016). To overcome the limitations of multiyear study, a standardized protocol was employed to train all interviewers and examiners for questionnaires and examination procedure. Standardization training preceded each annual survey. Out of the 1,854 participants of the study, only dentate individuals with complete data sets were included in the analysis, which constituted a total of 1,343 individuals (501 males and 843 females) (Table 1).

**Assessment of ASVD risk markers**

The surrogate markers of atherosclerosis used for this study are cIMT and ABI, which are known as strong predictors of ASVD, such as stroke and myocardial infarction (Fowkes et al., 2008). The carotid artery was evaluated by using high-resolution B-mode ultrasound equipment (SonoAce-9900; Medison, Seoul, South Korea), equipped with a 7.5MHz linear array transducer. IMT was determined as the distance from the media-adventitia interface to the intima-lumen interface on the far wall in the longitudinal view. The captured ultrasonographic images were read by a single trained sonographer using Sigma Scan Pro 5.0 (SPSS Inc., Chicago, IL, USA). Between the carotid bulb origin and a point 10mm proximal to the common carotid artery (CCA), the maximal IMT value in a region free of plaque was determined as the maximal IMT of the left/right CCA. The average of the maximal IMT values of both CCA was used for analysis. SA was regarded as a binary variable with the threshold value set at cIMT $\geq$0.754mm, considering it as the critical value of increased cardiovascular risk in Koreans (Jeong et al., 2005). The sonographer was blinded of the periodontal status of

the participants. PAD was evaluated by using the ABI. The blood pressure in the upper and lower extremities was measured using a portable Doppler system Minidop Es-100Vx (Hadeco, Inc. Arima, Miyamae-ku, Kawasaki, Japan), applying the probe at the posterior tibial artery at an angle approximately 60° to the direction of blood flow. ABI was calculated separately by dividing the higher of the two systolic pressures in the ankle by the higher of the two systolic pressures in the arm. PAD was considered if the ABI was lower than 1.0, adopting the threshold value of increasing PAD-related mortality as suggested by the ABI Collaboration (Aboyans et al., 2012). Although individuals with a high ABI > 1.4 are also known to be at increased risk, these individuals were not separately considered in our study due to the very small number of cases. The threshold values for cIMT and ABI used to define SA and PAD in our study are lower than the conventionally used criteria of 1mm and 0.9. This was due to the very small number of SA and PAD cases when the conventional criteria were applied, as the study participants were predominantly healthy individuals. Thus, our definition of SA and PAD should be considered as an indicator of early vascular disease for the prevention and control of ASVD, rather than a diagnostic criteria for delineating cases for treatment.

**Assessment of periodontitis**

Periodontal status of the participants was assessed by dentists using panoramic radiographs taken by a digital panoramic tomography machine (Pax-Primo, Vatech Global, Seoul, Korea). The radiographic alveolar bone loss (RABL), defined as the vertical distance between the cemento-enamel junction (CEJ) and the deepest point of alveolar bone crest, was measured on the mesial and distal side of all teeth. When CEJ

was not clearly visible for technical reasons (overlapping teeth or prosthesis), arbitrary CEJ was applied by referring to the CEJ of the adjacent teeth. Training and calibration procedure preceded each annual survey. Classification of periodontitis status followed the Centers for Disease Control/ American Association of Periodontology (CDC/AAP) guidelines (Eke et al., 2012) for clinical attachment loss. For the purpose of this analysis, periodontal status was categorized into 3 groups: normal (no or mild periodontitis; RABL<4mm), moderate (RABL ≥ 4mm at two or more interproximal sites, not on the same tooth) and severe periodontitis (RABL ≥ 6mm at two or more interproximal sites, not on the same tooth).

**Assessment of potential confounders**

The authors considered the following as potential confounders on ASVD: age, sex, education level, smoking, drinking, exercise, central obesity, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), C-reactive protein (hs-CRP), diabetes mellitus and hypertension (Lockhart et al., 2012).

Information on demographics, smoking, alcohol intake, exercise, medical history, and medications was collected using a questionnaire administered by trained interviewers. Participants were categorized into two groups for age: 40-65 years and over 65; and education level: middle-school or lower and high-school or higher. Self-reported smoking status was dichotomized into never smokers or ever a smoker in lifetime. Self-reported alcohol consumption was similarly dichotomized into none or ever in lifetime. Past experience of smoking and alcohol-drinking was included due to the low prevalence of current smokers and alcohol-drinkers in our study sample. Information on

exercise was obtained by the question: 'do you regularly exercise for more than once a week?' and dichotomized into non-regular exercising and regular-exercising. Waist circumference was measured to the nearest 0.1cm at the midpoint between the lowest rib margin and the iliac crest during expiration. Central obesity was defined as waist circumference ≥90cm for males and ≥80cm for females (Lee et al., 2007). A standard mercury sphygmomanometer (Baumanometer, W.A. Baum, Copiague, NY) was used to measure the blood pressure on the participants' right arm in a seated position after at least five minutes of rest before the initial measurement. SBP and DBP were measured twice to the nearest 2mmHg at a five-minute interval and the average values were used. Hypertension was defined as having an average SBP ≥140mmHg or DBP ≥90mmHg or diagnosed or medicated for hypertension, based on the criteria suggested by the JNC7 report (Chobanian et al., 2003). Blood samples taken from the antecubital vein were collected from each subject during the morning after an 8-hour overnight fast, and all biochemical markers were evaluated. Triglycerides, high- and low-density lipoprotein cholesterol (HDL and LDL), hs-CRP and fasting plasma glucose (FPG) levels were analyzed on the same day using an ADVIA1650 Automatic Analyzer (Siemes, New York, NY, USA). Participants were dichotomized according to the threshold values of 150mg for triglycerides, 40mg/dL for males and 50mg/dL for females for HDL according to the IDF criteria (Alberti et al., 2006). The threshold values for high LDL and hs-CRP were 100mg/dL and 1mg/L, respectively, adopting the guideline of the American Heart Association (Pearson et al., 2002). Diabetes was defined as FPG over 126mg/dL or diagnosed or medicated for diabetes, according to the WHO criteria (WHO, 2006).

### Statistical analyses

In the analysis, the outcome variables were SA (cIMT≥0.754mm) and PAD (ABI≤1.0) and the main explanatory variable was periodontitis status. Summary statistics of the population characteristics were calculated as frequencies and proportions. Any statistically significant differences between the outcome groups, in terms of the socio-economic, behavioral and health-related factors, were examined using chi-square test. Multivariable logistic regression model was applied to evaluate the adjusted odds ratios (aOR) of the association of periodontitis with SA and PAD while adjusting for potential confounders. aORs and confidence intervals (CI) were calculated for each model. Stratified analyses were performed to identify specific risk groups for the following variables: age, sex, smoking, drinking and metabolic syndrome. The categorization of metabolic syndrome followed the aforementioned IDF criteria. Finally, the analysis of covariance was applied to examine the mean cIMT and ABI for each periodontitis group by adjusting for confounders. Any statistically significant differences among the three periodontitis groups were assessed by multiple comparison analysis of Bonferroni. For the analyses, statistical significance was set at p-values <0.05.

## III. RESULTS

### General characteristics of the subjects

Of the 1,343 participants included in the analysis, the prevalence of SA (IMT≥0.754mm) and PAD (ABI≤1.0) were 27.4% and 5.4%, respectively (Tables 1 and 2). Compared to the participants without SA, those with SA were significantly older, more males and had lower education level. Higher prevalence of severe periodontitis, high LDL, diabetes

and hypertension was also observed among individuals with SA. On the other hand, prevalence of non-regular exercise, high triglycerides, low HDL and high hs-CRP was significantly higher among those with PAD compared to those without PAD.

**Association of periodontitis with subclinical atherosclerosis and peripheral arterial disease**

Severe periodontitis was consistently associated with cIMT-defined SA after adjustment for various confounders (aOR=1.50; 95% CI: 1.04-2.17) (Table 3). In this model, older age, male sex, low HDL, high LDL and diabetes were positively associated with SA while higher education level showed preventive effect on SA. In addition, severe periodontitis was associated with PAD after adjustment for the confounders (aOR=1.95; 95% CI: 1.01-3.75) (Table 4). In this model, non-regular exercise and high hs-CRP were positively associated with PAD. The adjusted mean cIMT was significantly higher in individuals with severe periodontitis compared to periodontitis normal group (ANCOVA, p= 0.007) (Figure 1). For increasing severity of periodontitis, there was a decreasing trend in the adjusted mean ABI (ANCOVA, p= 0.049).

**Stratified association of periodontitis with subclinical atherosclerosis and peripheral arterial disease**

The link of periodontitis on SA was highlighted in females, individuals aged over 65 years, drinkers and in individuals without metabolic syndrome (Table 5). The link of periodontitis on PAD, on the other hand, was highlighted in individuals aged less than

65 years (Table 6). For both SA and PAD, the associations were stronger among never smokers.

## IV. DISCUSSION

The results of the present study demonstrated that periodontitis is associated with subclinical atherosclerosis and peripheral arterial disease among Korean adults, independent of the effects of such confounders as age, sex, education level, smoking, drinking, exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes and hypertension. To the best of our knowledge, this study presents the first evidence that periodontitis is associated with these two subclinical atherosclerotic conditions in Koreans.

Our study has some major strengths. First, the participants of this study were recruited from community-dwelling general population as opposed to hospital visitors which reduces the chance of introducing selection bias and enhances the generalizability of our results. Second, to corroborate the results with a higher level of evidence, the authors adopted the analogy criterion of the Bradford Hill's criteria (Hill, 1965) and employed two markers of early atherosclerosis lesions, cIMT and ABI, each of which represent the central and peripheral arterial stenosis.

Our results are consistent with previous studies showing an independent association of periodontitis with SA and PAD, which represent early atherosclerotic vascular changes. The biological mechanism by which periodontal disease contributes to the etiopathogenesis of atherosclerosis involves four pathways including: direct bacterial effects on platelets, autoimmune responses, invasion of bacteria in endothelial cells and systemic upregulation of pro-inflammatory mediators (Paquette and Genco, 2010).

Specific periodontal pathogens such as P.gingivalis can induce platelet aggregation (Herzberg and Meyer, 1996) and invade aortic and heart endothelial cells via fimbriae (Deshpande et al., 1998). Also, antibodies that cross-react with periodontal bacteria and human heat shock proteins have been identified, indicating autoimmune mechanisms for the etiopathogenesis (Hinode et al., 1998). In addition, periodontal infection results in a chronic low-grade bacteremia which induce both local and systemic upregulation of inflammatory cytokines such as interleukin (IL)-1, IL-12, IL-18 and tumor necrosis factor-alpha (TNF-a) that cause increase in adhesion molecules in the endothelium (Haynes and Stanford, 2003). The subsequent infiltration of chemo-attracted leukocytes into the vessel wall lead to endothelial dysfunction and formation of atherosclerotic plaques, which clinically manifests as the thickening of the carotid arterial wall and decreased patency of the extremity arteries at early stages of atherosclerotic lesion formation (Paquette and Genco, 2010). Our data showed that such an atherosclerotic vascular change was associated with severe periodontitis but not moderate periodontitis. Considering that periodontitis was defined by alveolar bone loss and not periodontal pocket depth, the severity of periodontitis proportionately represents the duration of periodontitis existence. Hence, it can be thought that a long duration of periodontitis existence has a larger extent of influence on atherogenesis than a short duration of periodontitis existence.

Our data showed that some known systemic health-related risk factors and behavioral risk factors were associated with SA and PAD. Diabetes, in particular, was identified as a significant predictor for SA. The production of reactive oxygen species and oxidative stress are increased in hyperglycemic state which can lead to a systemic inflammatory response, endothelial dysfunction and, in turn, atherosclerotic vascular pathology (Beckman et al., 2002). Abnormal levels of HDL and LDL, which are well-known risk

factors for both periodontitis and ASVD, were also found to be significant predictor for SA. Dyslipidemia is known to contribute directly to atherosclerotic disease. The uptake of plasma lipids into intima triggers lipid oxidation, endothelial activation and monocyte recruitment, which are initial processes of atherosclerosis development. LDL is known to be particularly atherogenic in that it stimulates the release of pro-inflammatory cytokines from macrophages after being and accelerates the atherogenic process (McQueen et al., 2008). Consistent with previous studies, lack of exercise and high hs-CRP were associated with higher prevalence of PAD. Chronic periodontitis results in upregulation of local and systemic inflammation cytokines which leads to increased production of the acute-phase reactant, hs-CRP (Abd et al., 2011). A high hs-CRP is known to play a direct role in the inflammatory responses linking periodontal inflammation and atherosclerosis as it can bind to LDL and lipid mediator platelet-activating factor and activate the complement system, leading to atherosclerotic lesion formation (Bisoendial et al., 2010).

The results of stratified analyses demonstrated that age and sex were important factors associated with the pathogenesis of atherosclerotic changes. In terms of age, the association of periodontitis with SA was highlighted in elders aged over 65 years. Increase in arterial wall thickness as observed in SA is a progressive and irreversible process and hence, the accumulation of the atherogenic effects of various contributors with aging could result in heightened association between periodontitis and SA in elders (Boesen et al., 2015). Also, our data showed that heightened influence of diabetes on SA could have attenuated the association between periodontitis and SA in individuals aged less than 65 years. Interestingly, the association of periodontitis with PAD was highlighted in comparatively younger age group, in individuals aged less than 65 years. Similar results were previously reported from the Health Professionals Follow-up study,

in which an increased association between periodontal disease and PAD was observed in adults aged below 60 years (Hung et al., 2003). ABI is an index that is dependent on the ratio between the ankle and brachial blood pressures, both of which can decrease with aging due to reduced arterial distensibility and elasticity (van der Heijden-Spek et al., 2000). The association between periodontitis and PAD could be masked in elders due to the age-influenced decrease in ABI and highlighted in comparatively younger individuals. In addition, the association of periodontitis with SA was highlighted in females suggesting that elderly females are at heightened risk of developing periodontitis and atherosclerotic lesions. A possible biological mechanism for this is that the post-menopausal drop in estrogen, which is involved in regulating lipid metabolism, leads to heightened lipid levels and higher risk of developing atherosclerosis and periodontitis among elderly females (Ylöstalo et al., 2010). The association of periodontitis with SA in male sex could be attenuated due to the heightened influence of abnormal lipid levels on SA. In addition, the association of periodontitis with SA and PAD were highlighted in never smokers, who had not been exposed to smoking-induced vascular changes. Tobacco smoking can reduce oxygen delivery to extremities by inducing vasocontriction and hypercoagulable state through increased levels of coagulants and pro-inflammatory state through upregulation of inflammatory mediators including IL-1, IL-6 and TNF-a (Teo et al., 2006). The absence of the association of periodontitis with SA and PAD among smokers could be due to the masking effect of smoking-related inflammatory effects on vasculature. The association of periodontitis with SA was also highlighted in drinkers and in those without metabolic syndrome. Alcohol drinking can provoke atherogenic and hemodynamic changes by inducing pro-inflammatory response, endothelial dysfunction, foam cell formation and stiffening of arterial wall (Shirpoor et al., 2012). The subsequent reduced peripheral blood flow and

oxygen delivery can also exacerbate periodontal degradation. The absence of significant association in individuals with metabolic syndrome could also be due to the masking effects of the its individual components of central obesity, abnormal lipid levels, hypertension and diabetes, each of which are strongly implicated in the pathogenesis of atherosclerosis (Ahluwalia et al., 2006).

Our study has some limitations. Owing to the limitations of the cross-sectional design of the survey, no inference on causality could be made. However, in order to aid the inference on temporal relationship between periodontitis and atherosclerosis, we assessed subclinical atherosclerotic vascular changes as the outcome which precedes the occurrence of clinically overt atherosclerotic disease. In our study, periodontitis was defined by the CDC/AAP criteria for clinical attachment loss using only the radiographic alveolar bone loss and neglecting the additional component of periodontal pocket depths (Eke et al., 2012). This could have underestimated our periodontitis cases as it does not account for the current state of periodontal inflammation but only includes cases with a history of periodontitis. This could have introduced a non-differential bias and could have diluted the estimated association (Rothman et al., 2008). Notwithstanding these limitations, the authors opine that the results of our study are reliable enough to test the hypothesis that periodontitis is associated with subclinical ASVD markers.

## V. CONCLUSIONS

Overall, periodontitis was a substantially important risk factor on ASVD among Korean adults. Dentists should take precaution for individuals with periodontitis to prevent or control for atherosclerosis. Likewise, physicians should provide care for individuals

with atherosclerosis to inform them of the possibility of periodontitis comorbidity. Meanwhile, considering that the prevention and control of the risk factors for both periodontitis and ASVD is possible, a future challenge could be to manage and reduce the common risk factors of both diseases in implementing policies and initiatives at a national and global level.

Table 1. Characteristics of the study participants by subclinical atherosclerosis (cIMT≥ 0.754mm). (*n*=1,343)

| Variable | *N* | Subclinical atherosclerosis | | |
|---|---|---|---|---|
| | | No (*n*=975) | Yes (*n*=368) | *p* Value[a] |
| Periodontitis, *n* (%) | | | | **0.004** |
| Normal | 494 | **371 (38.0)** | **123 (33.4)** | |
| Moderate | 620 | **458 (47.0)** | **162 (44.0)** | |
| Severe | 229 | **146 (15.0)** | **83 (22.6)** | |
| Age, *n* (%) | | | | **<0.0001** |
| 40-64 years | 655 | **562 (57.6)** | **93 (25.3)** | |
| ≥ 65 years | 688 | **413 (42.4)** | **275 (74.7)** | |
| Sex, *n* (%) | | | | **<0.0001** |
| Female | 842 | **655 (67.2)** | **187 (50.8)** | |
| Male | 501 | **302 (32.8)** | **181 (49.2)** | |
| Education level, *n* (%) | | | | **<0.0001** |
| ≤ Middle-school | 928 | **639 (65.5)** | **289 (78.5)** | |
| ≥ High-school | 415 | **336 (34.5)** | **79 (21.5)** | |
| Smoking, *n* (%) | | | | 0.868 |
| Never | 1182 | 859 (88.1) | 323 (87.8) | |
| Ever in lifetime | 161 | 116 (11.9) | 45 (12.2) | |
| Drinking, *n* (%) | | | | 0.943 |
| Never | 670 | 487 (49.9) | 183 (49.7) | |
| Ever in lifetime | 673 | 488 (50.1) | 185 (50.3) | |
| Regular exercise, *n* (%) | | | | 0.255 |
| Yes | 559 | 415 (42.6) | 144 (39.1) | |
| No | 784 | 560 (57.4) | 224 (60.9) | |
| Central obesity, *n* (%) | | | | 0.993 |
| No | 690 | 501 (51.4) | 189 (51.4) | |
| Yes | 653 | 474 (48.6) | 179 (48.6) | |
| Triglycerides, *n* (%) | | | | 0.454 |
| Normal | 847 | 609 (62.5) | 238 64.7) | |
| High | 496 | 366 (37.5) | 130 (35.3) | |
| HDL, *n* (%) | | | | 0.059 |
| Normal | 742 | 554 (56.8) | 188 (51.1) | |
| Low | 601 | 412 (43.2) | 180 (48.9) | |
| LDL, *n* (%) | | | | **0.035** |
| Normal | 480 | **365 (37.4)** | **115 (31.3)** | |
| High | 863 | **610 (62.6)** | **253 (68.8)** | |
| hs-CRP, *n* (%) | | | | 0.064 |
| Normal | 881 | 654 (67.1) | 227 (61.7) | |
| High | 462 | 321 (32.9) | 141 (38.3) | |
| Diabetes, *n* (%) | | | | **0.001** |
| No | 1139 | **847 (86.9)** | **292 (79.3)** | |
| Yes | 204 | **128 (13.1)** | **76 (20.7)** | |
| Hypertension, *n* (%) | | | | **<0.0001** |
| No | 722 | **558 (57.2)** | **164 (44.6)** | |
| Yes | 621 | **417 (42.8)** | **204 (55.4)** | |

[a]Obtained from chi-square test.

Bold denotes statistical significance at $p < 0.05$.

Table 2. Characteristics of the study participants peripheral arterial disease (ABI <1.0). (*n*=1,343)

| Variable | *N* | Peripheral arterial disease | | |
|---|---|---|---|---|
| | | No (*n*=1,271) | Yes (*n*=72) | *p* Value[a] |
| Periodontitis, *n* (%) | | | | **0.044** |
| Normal | 494 | **472 (37.1)** | **22 (30.6)** | |
| Moderate | 620 | **590 (46.4)** | **30 (41.7)** | |
| Severe | 229 | **209 (16.4)** | **20 (27.8)** | |
| Age, *n* (%) | | | | 0.215 |
| 40-64 years | 655 | 625 (49.2) | 30 (41.7) | |
| ≥ 65 years | 688 | 646 (50.8) | 42 (58.3) | |
| Sex, *n* (%) | | | | 0.775 |
| Female | 842 | 798 (62.8) | 44 (61.1) | |
| Male | 501 | 473 (37.2) | 28 (38.9) | |
| Education level, *n* (%) | | | | 0.101 |
| ≤ Middle-school | 928 | 872 (68.6) | 56 (77.8) | |
| ≥ High-school | 415 | 399 (31.4) | 16 (22.2) | |
| Smoking, *n* (%) | | | | 0.209 |
| Never | 1182 | 1122 (88.3) | 60 (83.3) | |
| Ever in lifetime | 161 | 149 (11.7) | 12 (16.7) | |
| Drinking, *n* (%) | | | | 0.323 |
| Never | 670 | 630 (49.6) | 40 (55.6) | |
| Ever in lifetime | 673 | 641 (50.4) | 32 (44.4) | |
| Regular exercise, *n* (%) | | | | **0.001** |
| Yes | 559 | **543 (42.7)** | **16 (22.2)** | |
| No | 784 | **728 (57.3)** | **56 (77.8)** | |
| Central obesity, *n* (%) | | | | 0.468 |
| No | 690 | 656 (51.6) | 34 (47.2) | |
| Yes | 653 | 615 (48.4) | 38 (52.8) | |
| Triglycerides, *n* (%) | | | | **0.035** |
| Normal | 847 | **810 (63.7)** | **37 (51.4)** | |
| High | 496 | **461 (36.3)** | **35 (48.6)** | |
| HDL, *n* (%) | | | | **0.032** |
| Normal | 742 | **711 (55.9)** | **31 (43.1)** | |
| Low | 601 | **560 (44.1)** | **41 (56.9)** | |
| LDL, *n* (%) | | | | 0.345 |
| Normal | 480 | 458 (36.0) | 22 (30.6) | |
| High | 863 | 813 (64.0) | 50 (69.4) | |
| hs-CRP, *n* (%) | | | | **0.019** |
| Normal | 881 | **843 (66.3)** | **38 (52.8)** | |
| High | 462 | **428 (33.7)** | **34 (47.2)** | |
| Diabetes, *n* (%) | | | | 0.486 |
| No | 1139 | 1080 (85.0) | 59 (81.9) | |
| Yes | 204 | 191 (15.0) | 13 (18.1) | |
| Hypertension, *n* (%) | | | | 0.253 |
| No | 722 | 688 (54.1) | 34 (47.2) | |
| Yes | 621 | 583 (45.9) | 38 (52.8) | |

[a]Obtained from chi-square test.

Bold denotes statistical significance at $p < 0.05$.

Table 3. Adjusted association of periodontitis with subclinical atherosclerosis (cIMT≥0.754mm). (*n*=1,343)

| Variable | *N* | Subclinical atherosclerosis | |
|---|---|---|---|
| | | Odds Ratio (95% CI) | *p* Value |
| Periodontitis | | | |
| Normal | 494 | 1 | |
| Moderate | 620 | 0.97 (0.72-1.31) | 0.850 |
| Severe | 229 | **1.50 (1.04-2.17)** | **0.032** |
| Age | | | |
| 40-64 years | 655 | 1 | |
| ≥ 65 years | 688 | **3.27 (2.43-4.39)** | **<0.0001** |
| Sex | | | |
| Female | 842 | 1 | |
| Male | 501 | **2.56 (1.83-3.58)** | **<0.0001** |
| Education level | | | |
| ≤ Middle-school | 928 | 1 | |
| ≥ High-school | 415 | **0.71 (0.51-0.99)** | **0.041** |
| Smoking | | | |
| Never | 1182 | 1 | |
| Ever in lifetime | 161 | 0.86 (0.56-1.32) | 0.490 |
| Drinking | | | |
| Never | 670 | 1 | |
| Ever in lifetime | 673 | 0.94 (0.71-1.24) | 0.663 |
| Regular exercise | | | |
| Yes | 559 | 1 | |
| No | 784 | 0.97 (0.74-1.26) | 0.800 |
| Central obesity | | | |
| No | 690 | 1 | |
| Yes | 653 | 1.15 (0.86-1.55) | 0.353 |
| Triglycerides | | | |
| Normal | 847 | 1 | |
| High | 496 | 0.83 (0.63-1.11) | 0.205 |
| HDL | | | |
| Normal | 742 | 1 | |
| Low | 601 | **1.46 (1.10-1.93)** | **0.008** |
| LDL | | | |
| Normal | 480 | 1 | |
| High | 863 | **1.61 (1.22-2.13)** | **0.001** |
| hs-CRP | | | |
| Normal | 881 | 1 | |
| High | 462 | 1.13 (0.86-1.48) | 0.371 |
| Diabetes | | | |
| No | 1139 | 1 | |
| Yes | 204 | **1.50 (1.06-2.11)** | **0.021** |
| Hypertension | | | |
| No | 722 | 1 | |
| Yes | 621 | 1.20 (0.92-1.57) | 0.188 |

Odds Ratios (95% Confidence Interval) are adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes and hypertension.

Bold denotes statistical significance at $p < 0.05$.

Table 4. Adjusted association of periodontitis with peripheral arterial disease (ABI <1.0). (*n*=1,343)

| Variable | *N* | Peripheral arterial disease | |
|---|---|---|---|
| | | Odds Ratio (95% CI) | *p* Value |
| Periodontitis | | | |
| Normal | 494 | 1 | |
| Moderate | 620 | 1.07 (0.60-1.91) | 0.821 |
| Severe | 229 | **1.95 (1.01-3.75)** | **0.047** |
| Age | | | |
| 40-64 years | 655 | 1 | |
| ≥ 65 years | 688 | 1.04 (0.60-1.80) | 0.885 |
| Sex | | | |
| Female | 842 | 1 | |
| Male | 501 | 1.14 (0.59-2.18) | 0.695 |
| Education level | | | |
| ≤ Middle-school | 928 | 1 | |
| ≥ High-school | 415 | 0.77 (0.41-1.44) | 0.412 |
| Smoking | | | |
| Never | 1182 | 1 | |
| Ever in lifetime | 161 | 1.40 (0.66-2.96) | 0.377 |
| Drinking | | | |
| Never | 670 | 1 | |
| Ever in lifetime | 673 | 0.80 (0.47-1.36) | 0.405 |
| Regular exercise | | | |
| Yes | 559 | 1 | |
| No | 784 | **2.48 (1.39-4.41)** | **0.002** |
| Central obesity | | | |
| No | 690 | 1 | |
| Yes | 653 | 1.00 (0.57-1.76) | 0.993 |
| Triglycerides | | | |
| Normal | 847 | 1 | |
| High | 496 | 1.53 (0.92-2.54) | 0.104 |
| HDL | | | |
| Normal | 742 | 1 | |
| Low | 601 | 1.57 (0.93-2.63) | 0.090 |
| LDL | | | |
| Normal | 480 | 1 | |
| High | 863 | 1.39 (0.82-2.37) | 0.226 |
| hs-CRP | | | |
| Normal | 881 | 1 | |
| High | 462 | **1.64 (1.00-2.70)** | **0.049** |
| Diabetes | | | |
| No | 1139 | 1 | |
| Yes | 204 | 1.04 (0.54-2.01) | 0.897 |
| Hypertension | | | |
| No | 722 | 1 | |
| Yes | 621 | 1.15 (0.69-1.93) | 0.590 |

Odds Ratios (95% Confidence Interval) are adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes and hypertension.

Bold denotes statistical significance at $p < 0.05$.

Table 5. Stratified adjusted association of periodontitis with subclinical atherosclerosis (cIMT≥0.754mm). (*n*=1,343).

| Stratum | *N* | Subclinical atherosclerosis | | |
|---|---|---|---|---|
| | | Odds ratio (95% Confidence Interval) | | |
| | | Normal | Moderate Periodontitis | Severe Periodontitis |
| Age | | | | |
| 40-64 years | 655 | 1 | 1.16 (0.69-1.95) | 1.06 (0.52-2.16) |
| ≥ 65 years | 688 | 1 | 0.88 (0.61-1.26) | **1.69 (1.07-2.65)** |
| Sex | | | | |
| Female | 842 | 1 | 1.10 (0.75-1.61) | **1.73 (1.05-2.86)** |
| Male | 501 | 1 | 0.79 (0.49-1.28) | 1.24 (0.70-2.19) |
| Smoking | | | | |
| Never smoker | 1182 | 1 | 0.99 (0.73-1.36) | **1.57 (1.05-2.33)** |
| Ever in lifetime | 161 | 1 | 0.78 (0.28-2.16) | 1.21 (0.40-3.67) |
| Drinking | | | | |
| Never | 670 | 1 | 0.95 (0.62-1.44) | 1.17 (0.69-1.99) |
| Ever in lifetime | 673 | 1 | 1.05 (0.68-1.61) | **2.05 (1.21-3.49)** |
| Metabolic syndrome | | | | |
| No | 900 | 1 | 1.01 (0.68-1.49) | **1.63 (1.03-2.59)** |
| Yes | 443 | 1 | 0.94 (0.58-1.53) | 1.30 (0.67-2.55) |

Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes and hypertension except the stratum. Bold denotes statistical significance at $p < 0.05$.

Table 6. Stratified adjusted association of periodontitis with peripheral arterial disease (ABI <1.0). (*n*=1,343).

| Stratum | *N* | Peripheral arterial disease | | |
|---|---|---|---|---|
| | | Odds ratio (95% Confidence Interval) | | |
| | | Normal | Moderate Periodontitis | Severe Periodontitis |
| Age | | | | |
| 40-64 years | 655 | 1 | 0.77 (0.31-1.91) | **2.82 (1.07-7.43)** |
| ≥ 65 years | 688 | 1 | 1.29 (0.59-2.78) | 1.75 (0.70-4.39) |
| Sex | | | | |
| Female | 842 | 1 | 0.98 (0.48-2.00) | 2.08 (0.92-4.68) |
| Male | 501 | 1 | 1.20 (0.40-3.63) | 1.89 (0.57-6.29) |
| Smoking | | | | |
| Never smoker | 1182 | 1 | 1.15 (0.62-2.16) | **2.16 (1.07-4.40)** |
| Ever in lifetime | 161 | 1 | 0.83 (0.14-4.99) | 0.87 (0.12-6.34) |
| Drinking | | | | |
| Never | 670 | 1 | 0.85 (0.39-1.82) | 1.71 (0.74-3.96) |
| Ever in lifetime | 673 | 1 | 1.68 (0.65-4.34) | 2.39 (0.81-7.08) |
| Metabolic syndrome | | | | |
| No | 900 | 1 | 1.00 (0.68-1.48) | **1.63 (1.02-2.58)** |
| Yes | 443 | 1 | 0.96 (0.60-1.55) | 1.37 (0.70-2.68) |

Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes and hypertension except the stratum. Bold denotes statistical significance at $p$ <0.05.

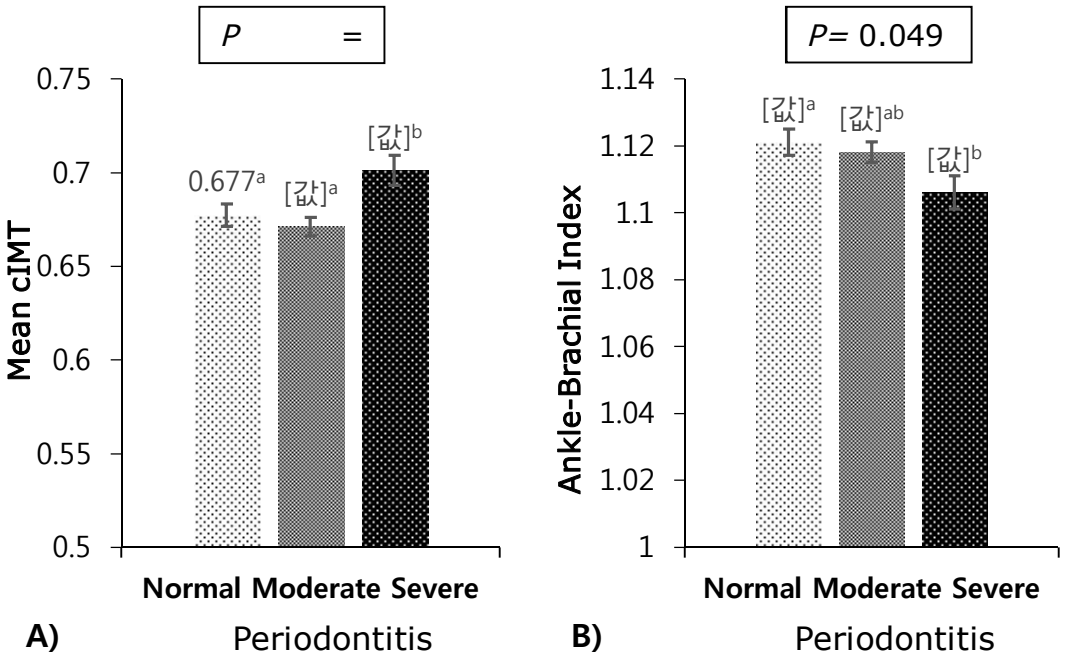


Figure 1. Adjusted relationship between periodontitis and atherosclerotic vascular disease risk indicators ($n$=1,343): A) mean carotid intima-media thickness (cIMT); B) ankle-brachial index. Each bar and error lines represent the mean ± standard error. Values are obtained from ANCOVA adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes and hypertension. Superscript denotes significantly different groups at $p$ <0.05 by multiple comparison analysis of Bonferroni.

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Supplement Table 1. Overview of studies on the association of periodontitis and cIMT-defined subclinical atherosclerosis (SA), sorted by the recency of publication.

| Publication | Country | Design | Sample size | SA definition | Findings | Adjusted for |
|---|---|---|---|---|---|---|
| Jung 2014 | Korea | Cross-sectional | 5,359 | Mean cIMT<br><br>Carotid plaque ≥1 | Periodontitis → cIMT no significant association (*p*= 0.94, 0.44, 0.64 for mild, moderate, severe periodontitis)<br><br>Periodontitis → carotid plaque presence, not significant (0.08, 0.11 for moderate, severe periodontitis) | Age, sex, BMI, smoking, pack-years, education, hypertension, diabetes, dyslipidemia, HDL, log-transformed TG, total cholesterol, plasma glucose, SBP. |
| Desvarieux 2013 | USA | Prospective cohort | 420 | Mean cIMT | 3-year change in mean cIMT across changes in periodontitis state (% sites >3mm PPD): 0.18, 0.16, 0.14, 0.07mm for worsening, stable, moderate and high periodontal disease improvement (Trend-*p* <0.001) | Age, sex, ethnicity, diabetes, smoking, education, BMI, SBP, LDL, HDL |
| Hayashida 2013 | Japan | Cross-sectional | 554 | cIMT≥1mm | 1 mm increase in mean PPD → SA (OR=1.40; 1.067-1.918, *P* =0.017)<br><br>1 mm increase in mean CAL→ SA (OR, 1.251; 1.032–1.516; *P* = 0.022) | Age, sex, number of present teeth, BMI, log-transformed TG, HDL, LDL, hemoglobin, A1c, SBP, smoking status, habitual drinking |
| Pinho 2013 | Portugal | Cross-sectional | 50 | cIMT≥1mm or<br><br>Carotid plaque ≥1 | Severe periodontitis was associated with SA (P=0.007) -higher percentage of severe periodontitis (33.3%) than non-SA controls (13.3%) | None |

| | | | | | | |
|---|---|---|---|---|---|---|
| Franek 2012 | Poland | Cross-sectional | 121 | cIMT≥0.8mm | Gingivitis or periodontitis → SA (OR:5.25; 1.1-25)<br><br>Significantly higher cIMT for increasing severity of periodontitis (0.67, 0.73, 0.81mm for healthy, gingivitis, periodontitis) | Age, sex, BMI, hemoglobin, LDL-cholesterol, CRP |
| Southerland 2012 | USA | Cross-sectional | 6,048 | cIMT≥1mm | Severe periodontitis → SA (OR= 1.3; 1.0-1.7)<br><br>Severe periodontitis → SA in diabetic individuals (OR= 2.2; 1.4-3.5) | Age, gender, race/field centre, BMI, smoking, income, education, HDL, LDL, TG, hypertension |
| Lopez-Jornet 2012 | Spain | Case-control | 50 | Mean cIMT<br><br>Carotid plaque | Periodontitis → .SA no significant association (*P*= 0.538, unadjusted)<br><br>Periodontitis → presence of carotid plaque (OR:5.23;1.65-16.51, *P* =0.037) | Age, sex, smoking, periodontitis, BMI, SBP, DBP, physical activity, CVD, glucose, TG, Cholesterol, LDL, HDL, CRP, leukocytes, hemoglobin, platelets |
| Ylostalo 2010 | Finland | Cross-sectional | 60 | Mean cIMT<br><br>Carotid plaque | Periodontitis (≥6mm PPD) → SA no significant association (regression co-efficient= -0.02; -0.15-0.12, *P*= 0.81)<br><br>Periodontitis (≥6mm PPD) → carotid plaque (RR= 1.0; 0.5-2.2) | Diabetes, sex |
| Cairo 2008 | Italy | Case-control | 90 | cIMT≥0.82mm | Periodontitis (Cal≥3mm) → IMT≥0.82mm OR=8.55 (2.38-39.81) | Age, gender, pack year, education, family history for CHD, regular physical activity, SBP, DBP, BMI, CRP, glucose, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | leukocytes, TG, total cholesterol, HDL, LDL, hemoglobin |
| Soder 2005 | Sweden | Prospective cohort | 113 | Mean cIMA<br><br>cIMT≥1mm | Periodontitis → cIMA (OR= 5.20; 1.73-15.67, *P*=0.003)<br><br>Periodontitis → cIMT (OR= 4.64; 1.64-13.10, *P*=0.004) | Age, gender, BMI, heredity for atherosclerosis, diabetes, hypertension, plasma cholesterol, smoking, education |
| Desvarieux 2005 | USA | Cross-sectional | 657 | Mean cIMT | Mean cIMT= 0.84mm, 0.85mm, 0.88mm (p=0.002) across tertiles of periodontally pathogenic bacterial dominance | Age, ethnicity, gender, education, BMI, smoking, DM, SBP, LDL, HDL, cholesterol |
| Desvarieux 2004 | USA | Cross-sectional | 1,710 | Mean cIMT<br><br>Carotid plaque | Mean cIMT= 0.80mm, 0.79mm, 0.82mm across tertiles of % CAL≥4mm (linear trend *P*=0.11)<br><br>Periodontitis → carotid plaque (OR=1.58; 1.00-2.51) in men only | Age, region, smoking, diabetes, SBP, high blood pressure, LDL, HDL, TG, education, BMI |
| Beck 2001 | USA | Cross-sectional | 6,017 | cIMT≥1mm | Severe periodontitis → SA (OR= 1.31; 1.03-1.66)<br><br>Moderate periodontitis → SA (OR= 1.40; 1.17-1.67) | Age, sex, diabetes, LDL, HDL, TG, hypertension, smoking, waist/hip ratio, education, race/center |

cIMT: carotid intima-media thickness; OR: odds ratio; RR= relative risk; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure; PPD: periodontal pocket depth; CAL: clinical attachment loss; CRP: C-reactive protein.

Supplement Table 2. Overview of studies on the association of periodontitis and ABI-defined peripheral arterial disease (PAD), sorted by the recency of publication.

| Publication | Country | Design | Sample size | PAD definition | Findings | Adjusted for |
|---|---|---|---|---|---|---|
| Sanker 2013 | India | Nested case-control | 814 | Mean ABI | Mean ABI= 1.04±0.004 in gingivitis group and 1.05±0.004 in periodontitis group (*P*=0.029) | None |
| Lu 2008 | USA | Cross-sectional | 3,585 | ABI <0.9 | Periodontitis (CAL≥3mm >33%) → PAD (OR= 2.13; 1.18-3.87, *P*=0.004) | Age, gender, race, poverty index, smoking, alcohol, physical activity, total cholesterol/HDL ratio, aspirin use, renal insufficiency, diabetes, hypertension, history of congestive heart failure |
| Chen 2008 | Japan | Case-control | 57 | ABI <0.7 | Periodontitis → PAD (OR=5.45; 1.57-18.89, *P*=0.007) | Age, gender, smoking, diabetes |
| Hung 2003 | USA | Prospective cohort | 45,136 | ABI <0.8 | Periodontitis → PAD (OR= 1.41; 1.21-1.77)<br><br>Stratified association highlighted in aspirin users, no diabetes, no hypertension, non-dentist, younger age, smoker groups | Age, smoking, alcohol drinking, BMI, physical activity, family history of myocardial infarction, multivitamin supplement, vitamin E use, history of hypertension, diabetes, hypercholesterolemia, profession |

ABI: ankle-brachial index; OR: Odds ratio; HDL: high-density lipoprotein; BMI: body mass index.

Supplement Table 3. Age-stratified adjusted association of periodontitis with subclinical atherosclerosis (cIMT≥0.754mm). (*n*=1,343).

| Variable | Subclinical atherosclerosis | | | |
|---|---|---|---|---|
| | 40-64 years (*n*=655) | | ≥ 65 years (*n*=688) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 1.16 (0.69-1.95) | 0.580 | 0.88 (0.61-1.26) | 0.477 |
| Severe | 1.06 (0.52-2.16) | 0.874 | **1.69 (1.07-2.65)** | **0.023** |
| Sex | | | | |
| Female | 1 | | 1 | |
| Male | **2.31 (1.31-4.07)** | **0.004** | 2.70 (1.75-4.17) | **<0.0001** |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | 0.74 (0.46-1.19) | 0.214 | 0.66 (0.41-1.07) | 0.091 |
| Smoking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.94 (0.48-1.84) | 0.858 | 0.81 (0.46-1.44) | 0.477 |
| Drinking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.88 (0.54-1.45) | 0.621 | 0.94 (0.67-1.33) | 0.729 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | 1.03 (0.65-1.63) | 0.905 | 0.94 (0.67-1.32) | 0.727 |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 1.38 (0.84-2.27) | 0.205 | 1.06 (0.73-1.56) | 0.753 |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 1.04 (0.64-1.70) | 0.866 | 0.78 (0.55-1.10) | 0.155 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | 1.09 (0.67-1.76) | 0.729 | **1.70 (1.20-2.42)** | **0.003** |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | 1.39 (0.84-2.29) | 0.203 | **1.73 (1.23-2.42)** | **0.002** |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.12 (0.69-1.81) | 0.661 | 1.10 (0.79-1.54) | 0.561 |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | **2.78 (1.56-4.93)** | **<0.0001** | 1.15 (0.76-1.76) | 0.514 |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 1.53 (0.95-2.47) | 0.079 | 1.06 (0.77-1.48) | 0.720 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 4. Age-stratified adjusted association of periodontitis with peripheral arterial disease (ABI <1.0). (*n*=1,343).

| Variable | Peripheral arterial disease | | | |
|---|---|---|---|---|
| | 40-64 years (*n*=655) | | ≥ 65 years (*n*=688) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 0.77 (0.31-1.91) | 0.571 | 1.29 (0.59-2.78) | 0.525 |
| Severe | **2.82 (1.07-7.43)** | **0.037** | 1.75 (0.70-4.39) | 0.235 |
| Sex | | | | |
| Female | 1 | | 1 | |
| Male | 0.68 (0.23-2.01) | 0.488 | 1.69 (0.70-4.07) | 0.245 |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | 1.22 (0.56-2.68) | 0.619 | 0.30 (0.07-1.33) | 0.113 |
| Smoking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 1.57 (0.48-5.15) | 0.459 | 1.47 (0.55-3.96) | 0.443 |
| Drinking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.95 (0.43-2.11) | 0.895 | 0.76 (0.37-1.56) | 0.454 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | **2.61 (1.12-6.06)** | **0.026** | **2.29 (1.02-5.15)** | **0.044** |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 1.09 (0.48-2.51) | 0.835 | 1.06 (0.48-2.36) | 0.879 |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 1.07 (0.47-2.44) | 0.878 | **2.07 (1.04-4.10)** | **0.037** |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | **2.29 (1.02-5.17)** | **0.045** | 1.19 (0.59-2.40) | 0.636 |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | 2.49 (0.91-6.78) | 0.075 | 1.01 (0.52-1.96) | 0.989 |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.08 (0.47-2.48) | 0.854 | **2.27 (1.17-4.40)** | **0.015** |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | 0.44 (0.10-2.01) | 0.286 | 1.34 (0.62-2.91) | 0.453 |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 1.12 (0.48-2.60) | 0.792 | 0.54 (1.25-0.62-2.53) | 0.535 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 5. Sex-stratified adjusted association of periodontitis with subclinical atherosclerosis (cIMT≥0.754mm). (*n*=1,343).

| Variable | Subclinical atherosclerosis | | | |
|---|---|---|---|---|
| | Female (*n*=842) | | Male (*n*=501) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 1.10 (0.75-1.61) | 0.632 | 0.79 (0.49-1.28) | 0.335 |
| Severe | **1.73 (1.05-2.86)** | **0.031** | 1.24 (0.70-2.19) | 0.462 |
| Age | | | | |
| 40-64 years | 1 | | 1 | |
| ≥ 65 years | **2.87 (1.92-4.28)** | **<0.0001** | **3.52 )2.24-5.54)** | **<0.0001** |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | 0.49 (0.28-0.85) | 0.011 | 0.89 (0.58-1.38) | 0.600 |
| Smoking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.63 (0.17-2.25) | 0.472 | 0.94 (0.59-1.51) | 0.811 |
| Drinking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.99 (0.68-1.43) | 0.948 | 0.92 (0.59-1.42) | 0.705 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | 0.94 (0.66-1.34) | 0.731 | 1.01 (0.66-1.53) | 0.973 |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 1.27 (0.85-1.89) | 0.245 | 0.94 (0.58-1.51) | 0.794 |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 0.86 (0.59-1.25) | 0.436 | 0.81 (0.52-1.25) | 0.337 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | 1.40 (0.97-2.01) | 0.074 | **1.62 (1.04-2.52)** | **0.033** |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | **1.49 (1.01-2.21)** | **0.047** | **1.78 (1.19-2.66)** | **0.005** |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.29 (0.90-1.86) | 0.165 | 0.92 (0.61-1.40) | 0.705 |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | **1.71 (1.07-2.71)** | **0.024** | 1.33 (0.79-2.24) | 0.278 |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 1.14 (0.78-1.65) | 0.501 | 1.26 (0.84-1.90) | 0.266 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular

exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 6. Sex-stratified adjusted association of periodontitis peripheral arterial disease (ABI <1.0). (*n*=1,343).

| Variable | Peripheral arterial disease | | | |
|---|---|---|---|---|
| | Female (*n*=842) | | Male (*n*=501) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 0.98 (0.48-2.00) | 0.960 | 1.20 (0.40-3.63) | 0.742 |
| Severe | 2.08 (0.92-4.68) | 0.078 | 1.89 (0.57-6.29) | 0.302 |
| Age | | | | |
| 40-64 years | 1 | | 1 | |
| ≥ 65 years | 0.79 (0.39-1.59) | 0.509 | 1.97 (0.73-5.32) | 0.182 |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | 0.70 (0.30-1.64) | 0.416 | 0.76 (0.28-2.05) | 0.592 |
| Smoking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.84 (0.11-6.57) | 0.870 | 1.80 (0.76-4.24) | 0.180 |
| Drinking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.73 (0.37-1.45) | 0.373 | 0.77 (0.32-1.90) | 0.575 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | **2.00 (1.00-4.00)** | **0.049** | **4.17 (1.35-12.82)** | **0.013** |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 0.86 (0.43-1.72) | 0.668 | 1.68 (0.69-4.12) | 0.254 |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 1.43 (0.75-2.74) | 0.280 | 1.89 (0.79-4.48) | 0.151 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | 1.86 (0.94-3.68) | 0.073 | 1.21 (0.51-2.87) | 0.666 |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | 1.23 (0.61-2.47) | 0.571 | 1.58 (0.67-3.70) | 0.295 |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.18 (0.61-2.29) | 0.616 | **2.90 (1.28-6.60)** | **0.011** |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | 1.89 (0.86-4.13) | 0.111 | 0.38 (0.10-1.45) | 0.157 |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 0.74 (0.37-1.46) | 0.378 | 2.33 (0.97-5.59) | 0.059 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular

exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 7. Stratified adjusted association of periodontitis with subclinical atherosclerosis (cIMT≥0.754mm) according to smoking status. (*n*=1,343).

| Variable | Subclinical atherosclerosis | | | |
|---|---|---|---|---|
| | Never smokers (*n*=1182) | | Ever smokers (*n*=161) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 0.99 (0.73-1.36) | 0.967 | 0.78 (0.28-2.16) | 0.636 |
| Severe | **1.57 (1.05-2.33)** | **0.028** | 1.21 (0.40-3.67) | 0.738 |
| Age | | | | |
| 40-64 years | 1 | | 1 | |
| ≥ 65 years | **3.24 (2.35-4.45)** | **<0.0001** | **3.03 (1.25-7.32)** | **0.014** |
| Sex | | | | |
| Female | 1 | | 1 | |
| Male | **2.51 (1.77-3.55)** | **<0.0001** | 4.03 (0.93-17.39) | 0.062 |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | **0.63 (0.44-0.91)** | **0.014** | 1.29 (0.55-3.04) | 0.565 |
| Drinking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 1.07 (0.80-1.44) | 0.662 | **0.41 (0.17-0.97)** | **0.043** |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | 0.95 (0.72-1.27) | 0.743 | 1.21 (0.50-2.90) | 0.675 |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 1.17 (0.85-1.62) | 0.329 | 0.85 (0.33-2.22) | 0.744 |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 0.86 (0.64-1.17) | 0.343 | 0.59 (0.24-1.43) | 0.244 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | **1.52 (1.13-2.05)** | **0.006** | 1.50 (0.58-3.89) | 0.409 |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | **1.62 (1.19-2.19)** | **0.002** | 1.80 (0.78-4.15) | 0.168 |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.17 (0.88-1.57) | 0.277 | 0.97 (0.43-2.22) | 0.948 |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | **1.71 (1.18-2.47)** | **0.005** | 0.65 (0.23-1.80) | 0.405 |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 1.17 (0.87-1.56) | 0.298 | 1.51 (0.66-3.45) | 0.327 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular

exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 8. Stratified adjusted association of periodontitis with peripheral arterial disease (ABI <1.0) according to smoking status. (*n*=1,343).

| Variable | Peripheral arterial disease | | | |
|---|---|---|---|---|
| | Never smokers (*n*=1182) | | Ever smokers (*n*=161) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 1.15 (0.62-2.16) | 0.654 | 0.83 (0.14-4.99) | 0.836 |
| Severe | **2.16 (1.0-4.40)** | **0.033** | 0.87 (0.12-6.34) | 0.892 |
| Age | | | | |
| 40-64 years | 1 | | 1 | |
| ≥ 65 years | 0.94 (0.52-1.68) | 0.824 | 2.15 (0.41-11.25) | 0.367 |
| Sex | | | | |
| Female | 1 | | 1 | |
| Male | 1.09 (0.55-2.17) | 0.798 | 1.24 (0.09-17.73) | 0.875 |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | 0.61 (0.29-1.26) | 0.180 | 2.54 (0.49-13.23) | 0.268 |
| Drinking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.70 (0.39-1.24) | 0.221 | 2.58 (0.40-16.82) | 0.322 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | **2.16 (1.18-3.97)** | **0.013** | **10.79 (1.16-99.97)** | **0.036** |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 0.91 (0.50-1.67) | 0.762 | 1.42 (0.29-7.04) | 0.670 |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 1.57 (0.90-2.73) | 0.114 | 0.80 (0.16-4.05) | 0.788 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | 1.54 (0.88-2.70) | 0.135 | 1.88 (0.39-9.11) | 0.435 |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | 1.07 (0.61-1.90) | 0.805 | 5.32 (0.98-28.76) | 0.052 |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.53 (0.89-2.64) | 0.123 | 2.63 (0.63-11.13) | 0.188 |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | 1.08 (0.52-2.23) | 0.846 | 0.92 (0.15-5.59) | 0.927 |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 0.95 (0.54-1.66) | 0.847 | 3.83 (0.88-16.67) | 0.073 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular

exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 9. Stratified adjusted association of periodontitis with subclinical atherosclerosis (cIMT≥0.754mm) according to alcohol drinking. (*n*=1,343).

| Variable | Subclinical atherosclerosis | | | |
|---|---|---|---|---|
| | Never drinkers (*n*=670) | | Ever drinkers (*n*=673) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 0.95 (0.62-1.44) | 0.792 | 1.05 (0.68-1.61) | 0.827 |
| Severe | 1.17 (0.69-1.99) | 0.567 | **2.05 (1.21-3.49)** | **0.008** |
| Age | | | | |
| 40-64 years | 1 | | 1 | |
| ≥ 65 years | **3.33 (2.16-5.14)** | **<0.0001** | **3.17 (2.09-4.80)** | **<0.0001** |
| Sex | | | | |
| Female | 1 | | 1 | |
| Male | **2.98 (1.76-5.04)** | **<0.0001** | **2.10 (1.34-3.30)** | **0.001** |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | **0.54 (0.32-0.91)** | **0.021** | 0.83 (0.54-1.30) | 0.418 |
| Smoking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 1.81 (0.87-3.76) | 0.115 | 0.58 (0.34-1.01) | 0.055 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | 0.87 (0.59-1.28) | 0.483 | 1.12 (0.76-1.65) | 0.569 |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | **1.81 (1.16-2.82)** | **0.009** | 0.74 (0.48-1.13) | 0.164 |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 0.76 (0.50-1.14) | 0.181 | 0.96 (0.64-1.43) | 0.834 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | 1.47 (0.99-2.19) | 0.057 | 1.48 (0.98-2.23) | 0.061 |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | **1.58 (1.04-2.41)** | **0.032** | **1.70 (1.15-2.51)** | **0.008** |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.21 (0.82-1.77) | 0.343 | 1.06 (0.71-1.57) | 0.777 |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | **1.81 (1.12-2.95)** | **0.017** | 1.18 (0.71-1.96) | 0.520 |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 0.95 (0.63-1.41) | 0.783 | **1.51 (1.02-2.22)** | **0.038** |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular

exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 10. Stratified adjusted association of periodontitis with peripheral arterial disease (ABI <1.0) according to alcohol drinking. (*n*=1,343).

| Variable | Peripheral arterial disease | | | |
|---|---|---|---|---|
| | Never drinkers (*n*=670) | | Ever drinkers (*n*=673) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 0.85 (0.39-1.82) | 0.669 | 1.68 (0.65-4.34) | 0.284 |
| Severe | 1.71 (0.74-3.96) | 0.214 | 2.39 (0.81-7.08) | 0.115 |
| Age | | | | |
| 40-64 years | 1 | | 1 | |
| ≥ 65 years | 1.13 (0.53-2.38) | 0.757 | 1.10 (0.48-2.51) | 0.823 |
| Sex | | | | |
| Female | 1 | | 1 | |
| Male | 1.09 (0.43-2.75) | 0.851 | 1.07 (0.40-2.84) | 0.896 |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | 0.97 (0.41-2.28) | 0.938 | 0.64 (0.25-1.68) | 0.365 |
| Smoking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 0.66 (0.14-3.23) | 0.611 | 2.20 (0.86-5.59) | 0.099 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | **2.89 (1.29-6.45)** | **0.010** | 2.11 (0.90-4.96) | 0.088 |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 0.96 (0.45-2.05) | 0.909 | 0.98 (0.41-2.32) | 0.958 |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 1.52 (0.77-3.02) | 0.230 | 1.55 (0.70-3.47) | 0.282 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | 1.11 (0.56-2.21) | 0.769 | **2.45 (1.10-5.48)** | **0.029** |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | 1.12 (0.55-2.31) | 0.755 | 1.82 (0.81-4.06) | 0.147 |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.44 (0.73-2.84) | 0.294 | 1.92 (0.91-4.07) | 0.087 |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | 1.65 (0.72-3.75) | 0.235 | 0.51 (0.16-1.63) | 0.257 |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 0.72 (0.35-1.46) | 0.359 | 2.01 (0.99-4.95) | 0.054 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular

exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 11. Stratified adjusted association of periodontitis with subclinical atherosclerosis (cIMT≥0.754mm) according to metabolic syndrome (MetS) presence. (*n*=1,343).

| Variable | Subclinical atherosclerosis | | | |
|---|---|---|---|---|
| | MetS negative (*n*=900) | | MetS positive (*n*=443) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 1.01 (0.68-1.49) | 0.974 | 0.94 (0.58-1.53) | 0.812 |
| Severe | **1.63 (1.03-2.59)** | **0.038** | 1.30 (0.67-2.55) | 0.438 |
| Age | | | | |
| 40-64 years | 1 | | 1 | |
| ≥ 65 years | **3.97 (2.71-5.82)** | **<0.0001** | **2.09 (1.27-3.45)** | **0.004** |
| Sex | | | | |
| Female | 1 | | 1 | |
| Male | **2.85 (1.89-4.30)** | **<0.0001** | 1.70 (0.89-3.23) | 0.106 |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | **0.65 (0.44-0.97)** | **0.033** | 0.96 (0.51-1.80) | 0.893 |
| Smoking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 1.06 (0.65-1.72) | 0.819 | **0.28 (0.08-0.92)** | **0.037** |
| Drinking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 1.07 (0.75-1.53) | 0.699 | 0.76 (0.48-1.21) | 0.246 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | 1.08 (0.76-1.53) | 0.662 | 0.74 (0.48-1.16) | 0.190 |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 1.25 (0.80-1.94) | 0.332 | - | - |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 0.91 (0.61-1.37) | 0.661 | 0.66 (0.42-1.03) | 0.069 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | **1.62 (1.11-2.34)** | **0.012** | 1.03 (0.63-1.70) | 0.903 |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | **1.62 (1.13-2.32)** | **0.009** | 1.57 (0.98-2.53) | 0.063 |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.11 (0.78-1.59) | 0.549 | 1.07 (0.69-1.65) | 0.777 |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | 1.06 (0.63-1.77) | 0.836 | **2.36 (1.44-3.84)** | **0.001** |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 1.40 (0.99-1.97) | 0.057 | 0.82 (0.50-1.36) | 0.444 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

Supplement Table 12. Stratified adjusted association of periodontitis with peripheral arterial disease (ABI <1.0) according to metabolic syndrome (MetS) presence. (*n*=1,343).

| Variable | Peripheral arterial disease | | | |
|---|---|---|---|---|
| | MetS negative (*n*=900) | | MetS positive (*n*=443) | |
| | aOR (95% CI)* | *P* | aOR (95% CI)* | *P* |
| Periodontitis | | | | |
| Normal | 1 | | 1 | |
| Moderate | 1.00 (0.68-1.48) | 0.991 | 0.96 (0.60-1.55) | 0.872 |
| Severe | **1.63 (1.02-2.58)** | **0.040** | 1.37 (0.70-2.68) | 0.359 |
| Age | | | | |
| 40-64 years | 1 | | 1 | |
| ≥ 65 years | **3.97 (2.71-5.82)** | **<0.0001** | **2.11 (1.28-3.47)** | **0.003** |
| Sex | | | | |
| Female | 1 | | 1 | |
| Male | **2.87 (1.90-4.33)** | **<0.0001** | 1.66 (0.87-3.15) | 0.122 |
| Education level | | | | |
| ≤ Middle-school | 1 | | 1 | |
| ≥ High-school | **0.64 (0.43-0.96)** | **0.029** | 0.96 (0.51-1.79) | 0.885 |
| Smoking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 1.06 (0.65-1.72) | 0.809 | **0.29 (0.09-0.95)** | **0.041** |
| Drinking | | | | |
| Never | 1 | | 1 | |
| Ever in lifetime | 1.07 (0.75-1.52) | 0.713 | 0.75 (0.47-1.19) | 0.225 |
| Regular exercise | | | | |
| Yes | 1 | | 1 | |
| No | 1.08 (0.76-1.53) | 0.665 | 0.75 (0.48-1.17) | 0.205 |
| Central obesity | | | | |
| No | 1 | | 1 | |
| Yes | 1.26 (0.81-1.97) | 0.297 | - | - |
| Triglycerides | | | | |
| Normal | 1 | | 1 | |
| High | 0.92 (0.62-1.38) | 0.686 | 0.65 (0.41-1.01) | 0.055 |
| HDL | | | | |
| Normal | 1 | | 1 | |
| Low | **1.62 (1.12-2.35)** | **0.011** | 1.01 (0.61-1.67) | 0.971 |
| LDL | | | | |
| Normal | 1 | | 1 | |
| High | **1.62 (1.13-2.32)** | **0.008** | 1.58 (0.98-2.54) | 0.060 |
| hs-CRP | | | | |
| Normal | 1 | | 1 | |
| High | 1.01 (0.98-1.03) | 0.709 | 0.97 (0.90-1.04) | 0.337 |
| Diabetes | | | | |
| No | 1 | | 1 | |
| Yes | 1.05 (0.63-1.75) | 0.864 | **2.42 (1.48-3.95)** | **<0.0001** |
| Hypertension | | | | |
| No | 1 | | 1 | |
| Yes | 1.39 (0.99-1.97) | 0.060 | 0.84 (0.51-1.39) | 0.491 |

aOR: adjusted odds ratio; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: heat shock C-reactive protein.

*Odds ratios are adjusted for age group, sex, education level, smoking, drinking, regular exercise, central obesity, triglycerides, HDL, LDL, hs-CRP, diabetes mellitus and hypertension except the stratum.

Bold denotes statistical significance at $p < 0.05$.

국문초록

# 한국 성인에서 치주병과 무증상동맥경화증 및 말초동맥경화증의 연관성

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**연구목적**

한국 성인에서 치주병과 무증상동맥경화증 및 말초동맥경화증 간의 연관성을 평가한다.

**연구대상 및 방법**

본 연구의 대상은 경기도 양평군에서 진행된 농촌코호트의 치주질환 기반조사에 해당하는 2010년, 2012-2014년도 검진참여자 1,854명 중 치아가 없거나 분석변수의 결측값을 가진 자를 제외한 40세 이상 성인 1,343명 (평균 연령 64세, 남자 501명, 여자 842명)이었다. 종속변수인 무증상동맥경화증은 고해상도 초음파 B-mode방식을 이용하여 측정한 양측 경동맥 내중막 두께가 평균 0.754 mm 이상인 경우로 평가되었다. 또 다른 종속변수인 말초동맥경화증은 도플러(Doppler)를 이용하여 측정한 발목 및 팔목의 수축기 혈압으로 산출한 발목상완지수가 1.0 미만인 경우로 평가되었다. 주요 설명변수인 치주병은 디지털 구강 파노라마방사선사진상의 치조골소실을 측정하여 미국치주학회의 치주병 평가기준에 따라 정상 (치주건강자 또는 저도치주병), 중등도치주병 (다른 치아 두 곳 이상에 4 mm 이상 치간부 치조골소실

이 존재), 고도치주병 (다른 치아 두 곳 이상에 6 mm 이상 치간부 치조골소실이 존재)으로 분류되었다. 치주병의 동맥경화성 혈관질환에 대한 연관성의 교란변수는 나이, 성별, 교육수준, 흡연력, 음주력, 운동량, 비만, 고혈압, 당뇨, 중성지방, 고밀도 지단백 콜레스테롤, 저밀도 지단백 콜레스테롤 및 C 반응성 단백 등이었고, 이들은 문진, 이화학적 검사 및 혈액 검사를 통해서 조사되었다. 치주병의 동맥경화성 혈관질환에 대한 교란변수가 보정된 연관성 추정에는, 다변수 로지스틱 회귀분석 및 공분산분석 등이 사용되었다. 치주병과 동맥경화성 혈관질환에 대한 연관성의 위험군 파악에는 연령군, 성별, 흡연력, 음주력 및 대사증후군별 층화분석이 시행되었다.

**결 과**

고도치주병은 무증상동맥경화증과 교란변수를 보정하였을 경우 연관성을 보였다(교차비= 1.50, 95% 신뢰구간 [CI]: 1.04-2.17). 층화분석 결과, 무증상동맥경화증과의 연관성은 65세 이상 고령군, 여성, 비흡연군, 음주군, 무대사증후군에서 더 높았다. 고도치주병은 말초동맥경화증과도 교란변수를 보정하였을 경우 연관성을 보였다(교차비= 1.95, 95% CI: 1.01-3.75). 층화분석 결과 말초동맥경화증과의 연관성은 65세 미만의 연령군, 비흡연군에서 더 높았다. 고도치주병군에서 치주병 정상군 보다 교란변수를 보정하였을 경우 경동맥 내중막 두께가 높았고 (0.701 mm 대 0.677 mm, P=0.007), 발목상완지수 (1.106 대 1.121, P=0.049)는 낮았다.

**결 론**

한국 성인에서 치주병은 동맥경화성 혈관질환에 대한 유의한 위험요인이었다. 향후 두 질환의 인과관계와 원인기전이 규명된다면, 치주병 및 동맥경화성 혈관질환의 공통 위험요인을 관리하여 두 질환의 동시적 예방이 가능할 것으로 검토되었다.

**주요어** : 치주병, 무증상동맥경화증, 경동맥 내중막 두께, 말초동맥경화증, 발목상완지수, 역학

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