



U.S. Department of Health and Human Services

# NIH News

National Institutes of Health

[The National Institute of Dental and  
Craniofacial Research \(NIDCR\)](#)

EMBARGOED FOR  
RELEASE  
Monday, February 7, 2005  
4:00 p.m. ET

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## Study Finds Direct Association Between Cardiovascular Disease and Periodontal Bacteria

Researchers report this week that older adults who have higher proportions of four periodontal-disease-causing bacteria inhabiting their mouths also tend to have thicker carotid arteries, a strong predictor of stroke and heart attack. The study, published in the current issue of the journal *Circulation*, was supported by four agencies of the National Institutes of Health.

According to the authors, these data mark the first report of a direct association between cardiovascular disease and bacteria involved in periodontal disease, inflammation of the gums that affects to varying degrees an estimated 200 million Americans. But the researchers say the findings are not proof that the bacteria cause cardiovascular disease, directly or indirectly.

“What was interesting to us was the specificity of the association,” said Moïse Desvarieux, M. D., Ph. D., the study’s lead author and an infectious disease epidemiologist at Columbia University’s Mailman School of Public Health and the University of Minnesota. “These same four bacteria were there, they were always there in the analysis, and the relationship seems to be pretty much, with one exception, limited to them.”

Desvarieux stressed that although the new data further illuminate a long-standing scientific issue, they shed little light on the broader public health question related to cardiovascular disease. The 657 people in the study had their oral bacteria and carotid thickness evaluated at the same point in time. So Desvarieux said, “It’s impossible to know which comes first, the periodontal disease or thickening of the carotid artery.” The answer to that question is fundamental to establishing causality — in this case, whether chronic inflammation or infection could have led to the atherosclerosis of the carotid arteries.

He and his colleagues noted that the public health information could come soon. “We will re-examine the participants in less than three years, and, at that point, we can better evaluate the progression of the atherosclerosis and, hopefully, begin to establish a time frame underlying the diseases,” said Ralph Sacco, M.D., M.S., associate chair of Neurology, professor of Neurology and Epidemiology, and the director of the Stroke and Critical Care Division of Columbia University College of Physicians and Surgeons. He also is an author on the paper.

The idea that oral bacteria shed from chronic gum infections, enter the circulatory system, and possibly contribute to diseases of the heart and other body organs once was widely accepted in medicine. The concept, known as the “focal infection theory,” fell out of fashion by the 1940s, then resurfaced four decades later with the publication of new data proposing a link.

Since then, a major sticking point in advancing the research has been simply how to pursue the hypothesis. Lacking the scientific tools to track oral bacteria in the body over several decades to determine if they directly trigger heart disease, most previous studies pursued indirect evidence. These included various measures of oral and cardiovascular health, which researchers then extrapolated to the influence of the oral pathogens. Conspicuously missing from the debate has been a large, well-designed study that in some way directly evaluates the role of the oral pathogens themselves.

To fill this void, the National Institute of Dental and Craniofacial Research launched the Oral Infections and Vascular Disease Epidemiology Study (INVEST), a multi-disciplinary endeavor whose principal investigator is Dr. Desvarieux. The study, which is the source of the paper published this week in *Circulation*, will monitor the oral and cardiovascular health of a large, racially mixed group of people. All enrollees in the study live in a northern section of Manhattan in New York City and are age 55 or older. Participants are also members of the Northern Manhattan Study (NOMAS), a prospective cohort study supported by NIH’s National Institute of Neurological Disorders and Stroke. Dr. Sacco is principal investigator of the companion NOMAS study.

“Although more than 600 bacteria have been shown to colonize the mouth, each person tends to carry different proportions of these microbes,” said Panos N. Papapanou, D.D.S., Ph.D., an author on the paper and professor and chair of the Section of Oral and Diagnostics Sciences and director of the Division of Periodontics at Columbia University School of Dental and Oral Surgery. He noted that only a subset of bacteria tend to be dominant in dental plaque.

“We wanted to know during the baseline examination of the participants whether it was true that the greater the proportion of so-called ‘bad’ bacteria in the mouth, the higher the likelihood of a thickened carotid artery,” added Papapanou, whose laboratory performed the periodontal microbiological analysis.

To get their answer, Desvarieux and colleagues collected on average seven dental plaque samples from a total of 657 older adults enrolled in INVEST who had not lost their teeth. The samples, taken from predetermined sites in the mouth, both diseased and healthy, were measured for 11 oral bacteria, including four bacteria widely regarded to be involved in causing periodontal disease: *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. The other seven bacteria served as controls, as their role in periodontal disease was either neutral or has not yet been established.

Then, to evaluate their cardiovascular health, the participants received a carotid intima-media thickness (IMT) measurement and provided a blood sample to determine their C-reactive protein levels. C-reactive protein has been reported to be elevated in people with periodontal disease, and recent studies found that testing for this protein may be predictive of developing heart disease.

Controlling for several risk factors that might skew their data — such as smoking and diabetes, both of which are independently associated with these conditions — the

scientists found the higher the levels of these periodontal-disease-causing bacteria, the more likely people were to have thicker carotid arteries. Interestingly, they noted no association between IMT, the periodontal pathogens, and C-reactive protein levels, suggesting the protein is involved in another cardiovascular disease pathway.

Next, the scientists wondered whether the broad association might be due to the four pathogens involved in causing periodontal disease, which combined accounted for only 23 percent of the bacteria in dental plaque. If so, the finding would provide added specificity to strengthen the case for the association.

“After re-analyzing the data, we found, with the exception of an oral bacterium called *Micromonas micros*, the relationship was limited to these four established oral pathogens,” said David Jacobs, Ph. D., another author and a professor in the Division of Epidemiology at the University of Minnesota School of Public Health.

“In other words, it was exactly what we hypothesized,” said Desvarieux.

However, he cautioned, “It now becomes crucial to follow the participants over time and see whether these baseline findings hold up and further translate into clinical disease.”

*The study was supported by the NIH’s National Institute of Dental and Craniofacial Research, the National Institute of Neurological Disorders and Stroke, National Heart, Lung, and Blood Institute, and National Center for Research Resources.*



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