



Let's put the mouth back into the body!

Speech by Prof. dr. Egija Zaura, Academic Centre for Dentistry Amsterdam, University of Amsterdam and Vrije Universiteit Amsterdam. This speech was delivered during the 392nd Dies Natalis celebration on Thursday, 11 January 2024.

It is my honor to stand here and speak from this lectern for the second time since my PhD defense in March 2002. Let me start with a fact I discovered recently, during my preparation for today's speech: the last time the Faculty of Dentistry was privileged to give a Dies speech was 28 years ago, in 1996, by prof. dr. Bob ten Cate, now emeritus professor with the Royal Netherlands Academy of Arts and Sciences (KNAW) and knight in the order of the Dutch Lion. A year later, in 1997, I exchanged work in a dental practice in Riga with becoming a PhD student at ACTA under Bob's supervision. Today the bar is set very high for me, since I am following up my mentor and dear friend 28 years after his lecture.

What do I mean with 'putting the mouth back into the body'? I hope to increase the awareness for the importance of a healthy mouth in a healthy body. I dare to say that our society, our government, our health care and health insurance system, our higher professional education system, and the research funding bodies have a blind spot regarding oral health. For example, dietary advices beneficial for metabolic health can be potentially detrimental for the oral health, such as the suggestion to use dried fruit as a snack in between meals advised by the Dutch Nutrition Centre. Not only dieticians, but also medical doctors can be ignorant on the effects that different medical conditions or interventions can have on one's oral health and vice versa. Instead of being seen as an integral part of health and wellbeing, oral health is marginalised and regarded as a niche for

which a full responsibility is left to a small group of specialised care professionals – dentists and dental hygienists.

Why should we care about putting the mouth back into the body? One's mouth has many functions. Most obvious one is the start of the digestive system where food is tasted, chewed, lubricated, predigested, and swallowed. The other major role for a mouth is being essential for communicating and for expressing emotions and affection. Think of talking, singing, smiling or kissing. There are multiple less obvious ways how a healthy functioning mouth contributes to our wellbeing. For instance, chewing is not only functional for food digestion but also activates our central nervous system. To enhance concentration, use of a chewing gum is commonly allowed during school exams. At an older age, mental health deteriorates faster in individuals with limited or disabled chewing function.

Having a healthy dentition allows not only to chew properly, but, especially in developed countries, where well-aligned and intact teeth have become a norm, healthy teeth and a pleasant smile can boost one's self-confidence in interacting with others. Studies indicate that besides positive psychological effects, smiling is associated with a faster recovery from a stressful situation and a reduction in pro-inflammatory cytokines⁽¹⁾. Laughter exercises and relaxes muscles, improves respiration, stimulates blood circulation, reduces stress hormones, enhances defence of the immune system, elevates pain threshold and tolerance and enhances mental functioning⁽²⁾.

Let me move to illustrating the role of a healthy mouth by using examples which are closer to my own research expertise - oral microbial ecology.

More than 3 billion years ago, anaerobic bacteria appeared as the first form of life on Earth. All other forms of life, including humans, have evolved in the presence of microbes. This has resulted in symbiosis or the mutually beneficial exchange of 'services': we provide a safe haven for microbial growth with a constant temperature and nutrient supply, and in turn our microbes perform crucial enzymatic reactions which our body is unable to run on its own. A well-known example of such symbiotic services is gut bacterial metabolism of complex food fibers, indigestible by our own cells. Less familiar are the special talents of our oral microbes.

My favourite example regards dietary pathway for nitric oxide (NO) formation. Our body depends on NO for many physiological functions, including regulation of cardiovascular function, metabolism, neurotransmission and immunity⁽³⁾. One way of increasing NO availability in our body is to use dietary nitrate, richly available in green leafy vegetables and beetroot. To obtain NO, dietary nitrate first needs to be reduced into nitrite. This is the step which our own cells are unable to perform, and we rely entirely on oral bacteria with nitrate reductase activity. When nitrate-rich food reaches our intestines, nitrate is absorbed into the bloodstream and via blood brought to salivary glands, where it is concentrated and released into saliva. This allows oral bacteria to metabolize nitrate into nitrite, which is then swallowed and reduced into NO at the low pH of stomach. The discovery of this health-promoting function of the oral microbes has led to a recent paradigm shift in oral microbiology: instead of attempting to kill as many oral microbes as possible, we now are looking for ways to enhance beneficial microbes and reduce the activity of less beneficial ones via microbiome modulation. The use of aggressive antimicrobial mouthwashes has been shown to lower nitrate reducing activity and to concomitantly increase blood pressure⁽⁴⁾. It has become clear that our body needs to be in a symbiotic balance instead in a fight with our microbes.

The opposite of a symbiotic balance is a state of dysbiosis, when proportions of certain commensal microbes and their functions are increased and those of others – diminished, making for the host more difficult to maintain its healthy state. In the oral cavity this may lead to diseases such as caries, periodontitis, and oral cancer.

Periodontitis is a chronic inflammatory disease in response to dysbiotic oral microbial community. It manifests itself as bleeding gums, bad breath, gum pockets around the teeth and irreversible bone loss, making teeth appear longer and becoming loose. Severe periodontitis is estimated to affect around 19% of the global adult population⁽⁵⁾. Risk factors for periodontitis are smoking, poor systemic health, genetic susceptibility, poor oral hygiene. Although hidden below the gum line, the inflammation can cover the area as large as one's hand palm. Imagine a wound of that size staying unnoticed! Our body cells do notice it and respond by sending armies of immune cells to this hot spot. Hereby it becomes a perpetuum mobile which will not stop unless treated. It is therefore not surprising to see correlations between periodontitis and chronic systemic conditions, such as diabetes, obesity, cardiovascular and cerebrovascular diseases, dementia, COPD, rheumatoid arthritis, pregnancy complications. These conditions have either common risk factors with periodontitis or are aggravated by chronic inflammation, or both.

Caries is the most prevalent human non-communicable disease, affecting over 35% of global population⁽⁶⁾. The main risk factor for caries is high and frequent sugar consumption, while healthy saliva, daily exposure to fluoride and good oral hygiene counteract caries risk considerably. Caries can occur at any age, once the protective factors are lost, for instance, due to reduced saliva flow as a side effect of certain medications. Socio-economic position (SEP) and cultural background greatly influence caries prevalence. In the Netherlands, in 2017, 49% of 5-year-old children from families at a low SEP had dental

caries versus 29% coming from high SEP families⁽⁷⁾. Sadly, in those low SEP families where mother had a migration background, 74% of the 5-year-olds had dental caries. Experiencing poor oral health while growing up affects healthy development of children, their sleep and wellbeing, their self-esteem and school performance, and may have a lifelong negative impact.

Another vulnerable group for oral health neglect are people at an old age. Previous decades of raised oral care standards have greatly improved oral health status for many current 70-year-olds. They now mostly retain their own dentition, or their teeth are replaced by dental implants. This greatly improves the quality of life, compared to having edentate mouth with ill-fitting dentures. The downside of this improved oral functioning is that increasingly more intensive care for maintaining oral health is required for older patients. Senescence of immune system, reduced saliva production due to aging and medication, cognitive decline, increased preference for sugar-containing snacks, impaired control over fine movements required for self-performed optimal oral hygiene – this all adds to an increased risk for oral and systemic diseases. Multimorbidity (several simultaneously occurring conditions) including those of oral diseases, interact and reinforce each other, becomes a fact rather than exception. Deterioration of oral health under such conditions occurs relatively fast and frequently remains unnoticed by care providers. Research on elderly entering residential home in the North of the Netherlands between 2002 and 2012 showed that 80% of them had oral health problems⁽⁸⁾. While research providing more recent data is lacking, personal communication with prof. Anita Visser, author of the previous study and gerodontologist at UMC Groningen, confirmed the situation in 2023 was even more shocking. Besides diabetes and cardiovascular diseases, poor oral health at older age is associated with more progressive rheumatoid arthritis, endocarditis, pneumonia, neurodegenerative diseases such as Alzheimer's and Parkinson's disease,

appetite loss, and avoidance of social contacts.

In summary, a healthy mouth is literally a mirror of one's overall health, and neglecting oral health will impact one's mental and physical wellbeing. Therefore, one's mouth should be seen as an integral part of the body and its health. This to me obvious conclusion still needs to reach the different societal, political, professional and educational stakeholders to solve the healthcare challenges we are facing.

Finally, I would like to share our success story where oral health in the context of overall health is taken seriously. Let's first go back in time, to the Dies Natalis celebration on January 8, 2020. During the reception I was approached by our own dean, who was inquired by the deans of the Faculty of Medicine and the Faculty of Science if ACTA would be willing to take the lead in proposing a new Research Priority Area on human microbiome. The deadline for submitting the preproposal for this interfaculty multidisciplinary research at the UvA call was in less than a month. At that moment, we had quite some contacts with the Faculty of Science (FNWI), the Faculty of Medicine (AUMC) and the Faculty of Social and Behavioural Sciences (FMG) regarding different microbiome projects and we decided to go for this challenge. Our proposal for the RPA on 'Personal Microbiome Health' was successful and our RPA started in January 2021. Although amidst the pandemics, together with researchers from the other three UvA faculties we managed to build a consortium with other academic and applied universities and many societal partners. We submitted our proposal "MetaHealth – health in a microbial, sociocultural and care context in the first 1000 days of life", focussing on oral and metabolic health in young children, to the Dutch National Research Agenda (NWA-ORC) call. Overweight and dental caries are commonly co-occurring conditions in children, especially from families at a low SEP. This impacts their health later in life and increases health inequalities. Our proposal got granted by the Dutch Research Council (NWO) and started

in January 2023⁽⁹⁾. On top of the 9 million euros awarded by the NWO, one million is contributed by our co-funding partners. With this project, we aim to acquire knowledge on the interplay between lifestyle, environment and microbiota in young children, especially those living in vulnerable conditions. We are learning how to provide care that fits the needs and the complex daily reality of the children and their families, and, based on this knowledge, we hope to co-create effective interventions for the prevention of overweight and tooth decay.

None of this would have been possible without the University of Amsterdam investing in our RPA which brought together bright minds from unrelated disciplines and made us to get to know each other's strengths and to learn to understand each other's language. With this I would like to thank the University of Amsterdam for being a driving force in kicking us, dental researchers, out of our comfort zone and enforcing us to go and embrace interdisciplinary research across the faculties. I see our MetaHealth programme just as the start. We have got a taste for new interdisciplinary initiatives in finding ways on how to put the mouth back into the body and make our healthcare system future proof.

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