

# Multimorbidity: a challenge and opportunity for the dental profession

Richard G. Watt\*<sup>1</sup> and Stefan Serban<sup>2</sup>

## Key points

This paper highlights the increasing importance of multimorbidity and presents an overview of its prevalence, impact and determinants.

The implications for the future training of oral health professionals, practice and delivery of dental care and dental research are considered.

The changing pattern of disease in society provides both challenges and opportunities ahead for the dental profession.

## Abstract

Multimorbidity (the coexistence of two or more chronic conditions) is common, is likely to be on the increase and has a major impact on quality of life, increased risk of mortality, and significant financial costs to the health and social care system. Multimorbidity is strongly associated with increasing age and is also directly linked to socioeconomic status. A substantial body of scientific evidence has shown an association between specific oral diseases and a range of other health conditions. Less is known, however, about the inter-relationships between oral diseases and multiple other health conditions. As multimorbidity is increasingly becoming the norm, rather than the exception, a profound shift is now needed in the training of oral health professionals, and the practice and delivery of dental care. A more integrated and coordinated approach to training and care is needed, which will require radical system-level reform and redesign of how health and dental services are commissioned, delivered and financed. Truly multidisciplinary teamwork requires system reform to facilitate effective joint working. The pattern of disease in society is changing and the dental profession needs to respond accordingly.

## Introduction

In recent decades, there has been a significant increase in life expectancy. In the UK, the proportion of the population aged 65 years and over has increased, from 15.9% in 1998 to 18.3% in 2018, and is projected to reach 24.2% by 2038.<sup>1</sup> This dramatic demographic transition presents both opportunities and challenges to society. With increasing numbers of the population now being in middle and older ages, many more people live with chronic long-term conditions such as cardiovascular diseases, cancers, chronic respiratory diseases, type 2 diabetes, and of course, dental caries, periodontal disease, tooth loss and a range of other oral conditions. In response to this demographic change, a significant shift

in focus is now beginning to take place in medicine, with increasing attention being placed on the issue of multimorbidity. The coexistence of two or more chronic conditions has profound future implications for medical training, clinical practice and research.<sup>2,3</sup> What is the relevance of multimorbidity to oral health and dentistry? This paper will present an overview of multimorbidity in terms of its meaning, impact and causes, and will highlight the implications of multimorbidity for future training of oral health professionals, practice of clinical dentistry and dental research.

## Defining multimorbidity

Of course, the coexistence of chronic conditions is not a new concept, but research and clinical practice have been hampered due to a lack of a consensus and precise definition of multimorbidity in the medical literature.<sup>4,5</sup> Various august bodies have recently defined multimorbidity in a range of subtly different ways. The World Health Organisation (WHO) defines multimorbidity as 'being affected by two or more chronic health conditions in the same individual'.<sup>6</sup> The National Institute for

Health and Care Excellence (NICE), in their clinical guidelines for optimising care for people with multimorbidity, described this as the presence of two or more chronic health conditions, including:

- Defined physical and mental health conditions
- Ongoing conditions such as learning disability
- Symptom complexes such as frailty and chronic pain
- Sensory impairment such as sight or hearing loss
- Alcohol and substance misuse.

The Academy of Medical Sciences in their recent report<sup>2</sup> came up with the following definition of multimorbidity as 'the coexistence of two or more chronic conditions each of which is either:

- A physical non-communicable disease of long duration such as cardiovascular disease or cancer
- A mental health condition of long duration such as mood disorder or dementia
- An infectious disease of long duration such as HIV or hepatitis C.

<sup>1</sup>Department of Epidemiology and Public Health, UCL, 1-19 Torrington Place, London, WC1E 6BT, UK; <sup>2</sup>School of Dentistry, University of Leeds, Clarendon Way, Leeds, LS2 9LU, UK.

\*Correspondence to: Richard Watt  
Email address: r.watt@ucl.ac.uk

Refereed Paper.

Accepted 16 June 2020

<https://doi.org/10.1038/s41415-020-2056-y>

None of these definitions explicitly include reference to oral conditions but clearly dental caries, periodontal diseases and many other conditions affecting the teeth and mouth are chronic, long-term, non-communicable diseases that affect a significant proportion of the adult and elderly population.<sup>7</sup>

Comorbidity and multimorbidity are neither synonymous nor mutually exclusive concepts – they provide two different perspectives through which to consider an individual with more than one health condition at the same time.<sup>8</sup> Comorbidity is the coexistence of other health conditions with an index condition that is the specific focus of attention. In contrast, multimorbidity is the coexistence of several health conditions, where none are considered an index condition that is the specific focus of attention. Multimorbidity is therefore a broader and more heterogeneous concept which can be used to describe a wide array of people experiencing a multitude of different combinations of conditions at the same time. The concept is also a more patient-centred concept, in that it also acknowledges that the impact of experiencing more than one chronic condition is influenced not only by health-related characteristics but also by the broader behavioural, socioeconomic, cultural and environmental context. The global COVID-19 pandemic acutely highlights the significance of multimorbidity, with severity and mortality risk greatly increased among those who have multiple underlying health conditions.<sup>9,10</sup>

## Prevalence and impact of multimorbidity

Despite differing definitions and measurement methods, the available evidence would suggest that multimorbidity is very common, is likely to be on the increase and has a major impact in terms of quality of life, increased risk of mortality and financial costs to the NHS.<sup>2</sup> Precise estimates of the prevalence of multimorbidity vary widely depending on the exact number of conditions included, whether highly prevalent conditions are considered and the age profile of the population involved. A recent study across several low-, middle- and high-income countries showed that the prevalence of multimorbidity across 12 health conditions including edentulism ranged from 34–62% in the 50–59-year-old age group and 50–92% in the 80+ years group.<sup>11</sup> Analysis by the Health Foundation estimated that 14 million people in England were living with two or more long-term health conditions.<sup>12</sup> Although in general the prevalence of multimorbidity is

strongly related to age,<sup>11,13</sup> it is not restricted to older people as many younger people are also affected by the coexistence of health conditions. In fact, in some populations, the absolute number of people affected by multimorbidity is greater among those under 65 years due to the population age structure.<sup>2</sup> The prevalence is also affected by broader socioeconomic factors – socially disadvantaged people experience multimorbidity at an earlier age than their more affluent contemporaries.<sup>12,14</sup> Data from longitudinal studies have highlighted that the prevalence of multimorbidity has increased in the last 20 years in many countries including the UK.<sup>2</sup> In a large UK study of 230,000 primary care patients over a four-year period, the prevalence of multimorbidity (coexistence of five or more conditions) quadrupled from 6% to 24%.<sup>15</sup> Multimorbidity is therefore increasingly becoming the norm, rather than the exception.

Extensive research has shown the negative impact of multimorbidity on peoples' lives and its broader societal effects. The coexistence of multiple chronic conditions is associated with reduced wellbeing and quality of life, and an increased risk of disability, functional decline and mortality.<sup>2</sup> People living with multiple conditions experience a greater treatment burden – the time and energy needed to access treatment from multiple providers of often uncoordinated care and complying with complex care plans involving multiple medications. The Health Foundation Report showed that patients with multimorbidities were prescribed on average 20.6 different medications compared to 5.6 medications for patients diagnosed with only one condition.<sup>12</sup> Carers and family members of people affected by multimorbidity also experience a range of negative health outcomes, including both mental and physical health conditions and increased mortality.<sup>2</sup> Finally, the economic burden of multimorbidity on the NHS and other healthcare systems is significant, with both an increased number of primary care visits and hospital admissions, both planned and unplanned.<sup>2,12</sup> Considering the burden that multimorbidities place on patients' quality of life, it is not surprising that oral healthcare and maintenance are not always a high priority in this group.<sup>16</sup>

## Determinants of multimorbidity

Several studies have shown, in different populations and diverse countries, a strong association between increasing age and higher rates of multimorbidity.<sup>2</sup> Indeed, multimorbidity

is typically the norm among many older people. However, multimorbidity is not unique to older people and there is evidence that the increasing prevalence of multimorbidity cannot be explained only by an ageing population.<sup>2</sup> Limited detailed research has, however, been conducted to uncover the underlying causes of multimorbidity and, as most of the previous studies have been cross-sectional in nature, it has been difficult to assess the direction of association between risk factors and multiple chronic conditions.

Some evidence suggests that multimorbidity is more common among women than men,<sup>17</sup> but it is unclear if this is due to the fact that women are more likely to attend health services and therefore have a condition diagnosed, or whether this is because women may suffer more adverse effects of poverty and income inequality and hence experience multiple health problems. Socioeconomic status is certainly strongly linked to higher rates of multimorbidity.<sup>12,17</sup> A Scottish study showed that people living in the most deprived neighbourhoods were almost twice as likely to have poor mental health and other conditions, and to experience the onset of multimorbidity 10–15 years earlier than those living in more affluent areas.<sup>18</sup>

Health-related behaviours such as smoking, alcohol consumption, poor nutrition and physical inactivity are identified as common risk factors for a range of chronic diseases<sup>19</sup> and are also associated with increased multimorbidity risk.<sup>2</sup> Behavioural risk factors including specific oral health-related behaviours such as tooth brushing and dental attendance have been shown to cluster together in certain patterns,<sup>20,21</sup> and these clusters are strongly associated with socioeconomic status and psychosocial factors.<sup>20,21,22</sup>

The available evidence suggests that the mechanisms underlying multimorbidity include shared biological (chronic inflammatory processes), behavioural, social and broader socioeconomic factors. More longitudinal studies are, however, needed to tease out the direction of the relationships between multimorbidity and potential risk factors, and to establish the causal mechanisms.

## Association between oral and general health

Over the last few decades, there have been an increasing number of studies exploring the nature and the direction of the associations between oral and general health. Most of the research to date has assessed comorbidity between a specific oral

disease and another specific systemic condition. Although there is no unified overarching theory to explain the potential association between a variety of oral and general health conditions, the associations are underpinned by shared biological mechanisms and by the wider social determinants of non-communicable diseases.<sup>18</sup> The strength of the evidence supporting these associations is varied from strong (diabetes) to weak (pregnancy outcomes).<sup>23,24,25</sup>

In terms of biological mechanisms, there are three main processes associated with periodontal pathogenesis that may play a role in the immune response associated with certain chronic conditions; namely infection, inflammation and adaptive immunity.<sup>26</sup> Over time, sustained localised inflammation in the periodontal tissue can trigger the initiation of a systemic inflammatory response that could contribute to the pathogenesis of certain systemic conditions with an inflammatory component, such as diabetes, cardiovascular disease and rheumatoid arthritis.<sup>27,28</sup>

Although the immune response to the presence of periodontal bacteria is genetically driven, wider risk factors may play a crucial role in how these traits are manifested.<sup>24</sup> The individual immune response is influenced by wider behavioural, environmental and societal risk factors, such as high-sugar diet, smoking and alcohol consumption, as well as societal factors such as socioeconomic status, psychosocial factors and access to care.<sup>18</sup>

To our knowledge, there are no robust longitudinal studies investigating the relationship between oral and general health in the context of multimorbidities, but there are several studies examining the associations between oral diseases and certain specific systemic conditions.<sup>29</sup>

Epidemiological data from systematic reviews of observational studies show that there is a bidirectional relationship between diabetes and periodontal disease. Systemically healthy people with periodontitis present poor glycaemic control and an increased risk for developing diabetes, while patients with diabetes and periodontitis present a higher prevalence of complications secondary to diabetes.<sup>25,30</sup> Two Cochrane reviews of randomised controlled trials reported a positive impact of non-surgical periodontal treatment on patients' short-term glycaemic control.<sup>31,32</sup> The clinical significance of this has been compared to adding an additional drug to the patient's treatment regime, but without the additional side effects associated with polypharmacy.<sup>25</sup>

Furthermore, the associations between periodontitis and cardiovascular disease have also been extensively investigated. Cardiovascular disease is often clustered with other systemic conditions in patients with multimorbidities, leading to increased mortality risk. The incidence of coronary heart disease, cerebrovascular disease and peripheral arterial disease has been associated with the prevalence and severity of periodontitis, independently of other risk factors.<sup>33,34</sup> Evidence supports the positive impact of periodontal treatment on surrogate cardiovascular outcomes such as decreased levels of systemic inflammatory markers and improved endothelial function in the short term,<sup>35</sup> but there is no evidence on the impact of periodontal treatment on long-term cardiovascular endpoints.<sup>36,37</sup>

Findings from observational studies and systematic reviews suggest that periodontal disease is also associated with the prevalence and severity of rheumatoid arthritis.<sup>38,39</sup> Additionally, patients with rheumatoid arthritis are more likely to be edentulous compared with healthy subjects.<sup>39</sup> A number of small, interventional studies suggest that non-surgical periodontal treatment could lead to a reduction of rheumatoid disease activity scores and of serum levels of inflammatory markers in the short term.<sup>40,41</sup> Patients with chronic kidney disease and periodontitis have a significantly increased mortality risk, independent of other risk factors, compared to patients without periodontitis.<sup>42</sup>

Emerging evidence from systematic reviews suggests an association between periodontitis and low birth weight.<sup>43,44</sup> It is unclear if periodontal treatment during pregnancy has an impact on preterm birth, but low-quality evidence suggests that periodontal treatment may reduce low birth weight.<sup>23</sup>

The findings of a number of systematic reviews suggest an association between periodontitis and chronic obstructive pulmonary disease (COPD).<sup>45,46</sup> Additionally, periodontitis severity has been associated with an increased mortality risk from pneumonia in the elderly.<sup>47</sup> The findings from a Cochrane review highlighted the beneficial role of using antibacterial mouthwash or gel in reducing the incidence of ventilator-associated pneumonia in critically ill patients.<sup>48</sup>

It is important to acknowledge the limitations of the existing literature on periodontal disease and other health conditions. Most of the interventional studies investigating the impact of periodontal treatment on various systemic outcomes were based on delivering non-surgical

periodontal treatment in secondary care settings and they shared a number of limitations, such as heterogeneity of definitions for periodontal disease and criteria for treatment success, short follow-up time and the use of surrogate outcomes.<sup>29,49</sup>

Besides periodontal disease, there are also other dental conditions that have been associated with systemic diseases. Data from systematic reviews exploring the associations between oral health and cognitive decline present conflicting results, likely due to methodological limitations.<sup>50</sup> There are some suggestions that poor oral health and severe tooth loss might be associated with increased risk of developing cognitive impairment and dementia.<sup>51</sup>

Most epidemiological studies on cancer prognosis have been focusing on cancers in isolation, but often cancers are associated with multimorbidity.<sup>52,53</sup> It is estimated that 82% of cancer patients present with at least one additional condition.<sup>12</sup> Head and neck cancers are no exception from this and are among the ten most prevalent forms of cancer in the UK, and have presented an increased incidence rate by nearly one-third in the last 20 years.<sup>54</sup>

When describing the bidirectional relationship between oral and general health, it is important to also consider how certain systemic conditions may affect oral health. This relationship can be supported through various mechanisms, both biological and behavioural. For example, poorly controlled diabetes has been associated with an increased risk of periodontal disease, and certain musculoskeletal conditions like osteoarthritis and rheumatoid arthritis may negatively impact on people's ability to maintain good oral health.<sup>25,55</sup> Data from systematic reviews and meta-analysis suggests that people with anxiety and depressive disorders present a greater risk of dental caries. The reasons for this could be multifactorial: decreased interest in maintaining good oral hygiene, an increased risk in smoking and consuming sugary foods and drinks, as well as the side effects of certain psychotropic medications that can cause dry mouth.<sup>56</sup>

### Implications of multimorbidity for oral health and dentistry

As multimorbidity is becoming the norm, rather than the exception, a profound shift is needed in the training of oral health professionals, the practice and delivery of dental care, and the focus of dental research.

### Training oral health professionals

Over the last 30 years, considerable efforts have been made to better integrate the training of oral health professionals within the wider healthcare educational system. However, in reality, much, if not most, of dental professional undergraduate, postgraduate and continuing professional development courses still continue to be delivered in an isolated and compartmentalised fashion, separated from the mainstream training of other health professionals. This siloed approach to professional education needs to radically change if the future oral health workforce is going to be equipped with the knowledge, skills and competencies needed to provide high-quality and integrated care to the ever-increasing numbers of patients with multiple health conditions.<sup>57</sup> Truly integrated models of education and training are needed which include a significant focus on multimorbidity (in terms of common social determinants, pathogenesis, treatment modalities and impact), and the best ways of addressing and supporting the (oral) health needs of patients with multiple conditions. Greater emphasis needs to be placed on training oral health professionals to be active and core members of multidisciplinary health teams working in primary care, community or hospital settings. Undergraduate and continuing professional development training also needs to equip oral health professionals with highly developed communication skills to enable them to communicate effectively with other health professionals, as well as with patients and their families living with complex health needs. It is also very important that core oral health input is included in the curriculum and assessment of medical, pharmacy and nursing students to ensure that they are better informed and equipped to deal with oral health problems, and when appropriate to refer patients to oral health professionals.<sup>58</sup>

### Clinical practice including prevention

A move towards greater horizontal service integration and the provision of coordinated care delivered by multidisciplinary teams (including oral health professionals working in primary, community and hospital settings) requires a radical system-level reform and redesign in how health and dental services are commissioned, remunerated and delivered. A Cochrane review of interventions treating multimorbidity highlighted that patient-level interventions such as educational support and patient self-management had little or no impact,

whereas ‘whole system’ and organisational-level interventions promoting integrated case management and the enhanced use of multidisciplinary teams (which specifically targeted particular combinations of conditions including depression and functional difficulties) had more promising results.<sup>59</sup> Innovative financing strategies need to be tested and adopted to create a stimulus and incentive to promote the coordination and integration of care for multimorbid patients across the health and social care system.<sup>60</sup> Integrated information systems also need to be created with unified electronic health records that capture all aspects of a patient’s care journey across primary, community, hospital and social care settings.

With increasing numbers of individuals in the general population living with multiple health conditions, oral health professionals working in general dental practice will have an absolutely fundamental role in providing care and treatment for these patients. As generalists, primary dental care teams will need to adopt a more holistic and systematic approach in how they undertake medical histories, diagnosis and treatment planning, and the provision of appropriate routine dental care for these patients. In multimorbid patients with more complex needs, primary dental care teams will need to liaise and refer these cases to appropriate specialists working in the community or hospital settings. Integrated care pathways are now being developed to improve the coordination of care. For example, in the United States and France, a periodontal assessment has been included in the national guidance for diabetes care.<sup>61,62</sup> In England, the Office of the Chief Dental Officer has recently published a guide to support commissioners to develop more integrated clinical pathways between the medical and dental care of diabetic patients.<sup>63</sup>

Multimorbidity also has important implications for the delivery of ongoing evidence-informed preventive care. It is particularly important that patients living with multiple health conditions receive effective preventive support from their oral health professional and are empowered to undertake appropriate self-care practices to maintain and improve their oral health status. Preventive resources such as *Delivering better oral health*<sup>64</sup> follow a common risk factor approach in advocating integrated preventive support, covering advice on diet, tobacco and alcohol use.<sup>19</sup> More detailed and comprehensive preventive support will also be needed for multimorbid patients experiencing

the complications of living with multiple conditions; for example, dry mouth linked to the use of polypharmacy.

### Research gaps

The Academy of Medical Sciences report on multimorbidity has highlighted a wide range of research gaps in this field<sup>2</sup> and the National Institute of Health Research has identified multimorbidity as a key research priority.<sup>65</sup> More longitudinal research is certainly needed to understand more comprehensively the underlying determinants and shared causal pathways between chronic conditions, including oral diseases. More interventional studies are also needed to evaluate interventions to prevent multimorbidity and to improve treatment outcomes. Rather than excluding participants with multiple conditions from clinical studies, as currently happens in most clinical trials, future studies should actively focus on their inclusion. Oral health outcomes need to be included in future multimorbidity studies to enable more research on how oral conditions cluster with other chronic conditions and the shared pathways.

### Conclusion

Multimorbidity is increasingly common and has a major impact on quality of life, mortality risk and costs to the NHS. This significant change in the pattern of disease in society has profound implications for the future training of oral health professionals, the practice and delivery of dental care, and dental research. The dental profession must respond to this challenge.

### References

- Office for National Statistics. Overview of the UK population: August 2019. 2019. Available at <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/august2019> (accessed April 2020)
- The Academy of Medical Sciences. Multimorbidity: a priority for global health research. 2018. Available at <https://acmedsci.ac.uk/file-download/82222577> (accessed April 2020).
- Whitty C J M, MacEwen C, Goddard A *et al*. Rising to the challenge of multimorbidity. *BMJ* 2020; **368**: l6964.
- Almirall J, Fortin M. The coexistence of terms to describe the presence of multiple concurrent diseases. *J Comorb* 2013; **3**: 4–9.
- Willadsen T G, Bebe A, Køster-Rasmussen R *et al*. The role of diseases, risk factors and symptoms in the definition of multimorbidity—a systematic review. *Scand J Prim Health Care* 2016; **34**: 112–121.
- World Health Organisation. Multimorbidity: Technical Series on Safer Primary Care. 2016. Available at <https://apps.who.int/iris/bitstream/handle/10665/252275/9789241511650-eng.pdf> (accessed April 2020).

7. Kassebaum N J, Smith A G C, Bernabe E *et al*. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990–2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. *J Dent Res* 2017; **96**: 380–387.
8. Radner H, Yoshida K, Smolen J S, Solomon D H. Multimorbidity and rheumatic conditions-enhancing the concept of comorbidity. *Nat Rev Rheumatol* 2014; **10**: 252–256.
9. Guan W J, Liang W H, Zhao Y *et al*. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J* 2020; **55**: 2000547.
10. Richardson S, Hirsch J S, Narasimhan M *et al*. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052–2059.
11. Garin N, Koyanagi A, Chatterji S *et al*. Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study. *J Gerontol A Biol Sci Med Sci* 2016; **71**: 205–214.
12. Stafford M, Steventon A, Thorlby R, Fisher R, Turton C, Deeny S. Briefing: Understanding the health care needs of people with multiple health conditions. 2018. Available at <https://www.health.org.uk/sites/default/files/upload/publications/2018/Understanding%20the%20health%20care%20needs%20of%20people%20with%20multiple%20health%20conditions.pdf> (accessed August 2020).
13. Salisbury C, Johnson L, Purdy S, Valderas J M, Montgomery A A. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract* 2011; DOI: 10.3399/bjgp11X548929.
14. Schiøtz M L, Stockmarr A, Host D, Glumer C, Frølich A. Social disparities in the prevalence of multimorbidity – a register-based population study. *BMC Public Health* 2017; **17**: 422.
15. Tran J, Norton R, Conrad N *et al*. Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: A population-based cohort study. *PLoS Med* 2018; DOI: 10.1371/journal.pmed.1002513.
16. Serban S, Dietrich T, Lopez-Oliva I *et al*. Attitudes towards Oral Health in Patients with Rheumatoid Arthritis: A Qualitative Study Nested within a Randomized Controlled Trial. *JDR Clin Trans Res* 2019; **4**: 360–370.
17. Violan C, Foguet-Boreu Q, Flores-Mateo G *et al*. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One* 2014; DOI: 10.1371/journal.pone.0102149.
18. Barnett K, Mercer S W, Norbury M *et al*. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; **380**: 37–43.
19. Watt R G, Sheiham A. Integrating the common risk factor approach into a social determinants framework. *Community Dent Oral Epidemiol* 2012; **40**: 289–296.
20. Singh A, Rouxel P, Watt R G, Tsakos G. Social inequalities in clustering of oral health related behaviours in a national sample of British adults. *Prev Med* 2013; **57**: 102–106.
21. Alzahrani S G, Watt R G, Sheiham A, Aresu M, Tsakos G. Patterns of clustering of six health-compromising behaviours in Saudi adolescents. *BMC Public Health* 2014; **14**: 1215.
22. Alzahrani S G, Sheiham A, Tsakos G, Watt R G. Psychosocial determinants of clustering health-compromising behaviours among Saudi male adolescents. *Int J Paediatr Adolesc Med* 2017; **4**: 26–32.
23. Iheozor-Ejiofor Z, Middleton P, Esposito M, Glenny A M. Treating periodontal disease for preventing adverse birth outcomes in pregnant women. *Cochrane Database Syst Rev* 2017; DOI: 10.1002/14651858.CD005297.pub3.
24. Chapple I L. Time to take periodontitis seriously. *BMJ* 2014; **348**: g2645.
25. Chapple I L, Genco R, working group 2 of the joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol* 2013; DOI: 10.1902/jop.2013.1340011.
26. Van Dyke T E, van Winkelhoff A J. Infection and inflammatory mechanisms. *J Clin Periodontol* 2013; DOI: 10.1111/jcpe.12088.
27. Cekici A, Kantarci A, Hasturk H, Van Dyke T E. Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontol* 2000 2014; **64**: 57–80.
28. Mankia K, Cheng Z, Do T *et al*. Prevalence of Periodontal Disease and Periodontopathic Bacteria in Anti-Cyclic Citrullinated Protein Antibody-Positive At-Risk Adults Without Arthritis. *JAMA Netw Open* 2019; DOI: 10.1001/jamanetworkopen.2019.5394.
29. Linden G J, Lyons A, Scannapieco F A. Periodontal systemic associations: review of the evidence. *J Clin Periodontol* 2013; DOI: 10.1902/jop.2013.1340010.
30. Graziani F, Gennai S, Solini A, Petrini M. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes An update of the EFP-AAP review. *J Clin Periodontol* 2018; **45**: 167–187.
31. Simpson T C, Weldon J C, Worthington H V *et al*. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. *Cochrane Database Syst Rev* 2015; DOI: 10.1002/14651858.CD004714.pub3.
32. Simpson T C, Needleman I, Wild S H, Moles D R, Mills E J. Treatment of periodontal disease for glycaemic control in people with diabetes. *Cochrane Database Syst Rev* 2010; DOI: 10.1002/14651858.CD004714.pub2.
33. Lockhart P B, Bolger A F, Papapanou P N *et al*. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation* 2012; **125**: 2520–2544.
34. Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. *J Clin Periodontol* 2013; DOI: 10.1111/jcpe.12062.
35. Tonetti MS, D’Aiuto F, Nibali L *et al*. Treatment of periodontitis and endothelial function. *N Engl J Med* 2007; **356**: 911–920.
36. Liu W, Cao Y, Dong L *et al*. Periodontal therapy for primary or secondary prevention of cardiovascular disease in people with periodontitis. *Cochrane Database Syst Rev* 2019; DOI: 10.1002/14651858.CD009197.pub4.
37. Li C, Lv Z, Shi Z *et al*. Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis. *Cochrane Database Syst Rev* 2017; DOI: 10.1002/14651858.CD009197.pub3.
38. Kaur S, White S, Bartold P M. Periodontal disease and rheumatoid arthritis: a systematic review. *J Dent Res* 2013; **92**: 399–408.
39. de Pablo P, Dietrich T, McAlindon T E. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. *J Rheumatol* 2008; **35**: 70–76.
40. Okada M, Kobayashi T, Ito S *et al*. Periodontal treatment decreases levels of antibodies to Porphyromonas gingivalis and citrulline in patients with rheumatoid arthritis and periodontitis. *J Periodontol* 2013; DOI: 10.1902/jop.2013.130079.
41. Lopez-Oliva I, Paropkari A D, Saraswat S *et al*. Dysbiotic Subgingival Microbial Communities in Periodontally Healthy Patients With Rheumatoid Arthritis. *Arthritis Rheumatol* 2018; **70**: 1008–1013.
42. Sharma P, Dietrich T, Ferro C J, Cockwell P, Chapple I L. Association between periodontitis and mortality in stages 3–5 chronic kidney disease: NHANES III and linked mortality study. *J Clin Periodontol* 2016; **43**: 104–113.
43. Ide M, Papapanou P N. Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes systematic review. *J Periodontol* 2013; DOI: 10.1902/jop.2013.134009.
44. Daalderop L A, Wieland B V, Tomsin K *et al*. Periodontal Disease and Pregnancy Outcomes: Overview of Systematic Reviews. *JDR Clin Trans Res* 2018; **3**: 10–27.
45. Zeng X T, Tu M L, Liu D Y *et al*. Periodontal disease and risk of chronic obstructive pulmonary disease: a meta-analysis of observational studies. *PLoS One* 2012; DOI: 10.1371/journal.pone.0046508.
46. Gomes-Filho I S, Cruz S S D, Trindade S C *et al*. Periodontitis and respiratory diseases: A systematic review with meta-analysis. *Oral Dis* 2020; **26**: 439–446.
47. Awano S, Ansal T, Takata Y *et al*. Oral health and mortality risk from pneumonia in the elderly. *J Dent Res* 2008; **87**: 334–339.
48. Hua F, Xie H, Worthington H V, Furness S, Zhang Q, Li C. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database Syst Rev* 2016; DOI: 10.1002/14651858.CD008367.pub3.
49. Borgnakke W S, Chapple I L, Genco R J *et al*. The multi-centre randomized controlled trial (RCT) published by the journal of the American Medical Association (JAMA) on the effect of periodontal therapy on glycated haemoglobin (HbA1c) has fundamental problems. *J Evid Based Dent Pract* 2014; **14**: 127–132.
50. Wu B, Fillenbaum G G, Plassman B L, Guo L. Association Between Oral Health and Cognitive Status: A Systematic Review. *J Am Geriatr Soc* 2016; **64**: 739–751.
51. Cerutti-Kopplin D, Feine J, Padilha D M *et al*. Tooth Loss Increases the Risk of Diminished Cognitive Function: A Systematic Review and Meta-analysis. *JDR Clin Trans Res* 2016; **1**: 10–19.
52. Sorensen H T. Multimorbidity and cancer outcomes: a for more research. *Clin Epidemiol* 2013; DOI: 10.2147/CLEP.S47149.
53. Yeh E T, Bickford C L. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009; **53**: 2231–2247.
54. Cancer Research UK. Head and neck cancers statistics. Available at <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers#heading-Zero> (accessed April 2020).
55. Kelsey J L, Lamster I B. Influence of musculoskeletal conditions on oral health among older adults. *Am J Public Health* 2008; **98**: 1177–1183.
56. Kiseley S, Sawyer E, Siskind D, Lalloo R. The oral health of people with anxiety and depressive disorders – a systematic review and meta-analysis. *J Affect Disord* 2016; **200**: 119–132.
57. Donoff B, McDonough J E, Riedy C A. Integrating oral and general health care. *N Engl J Med* 2014; **371**: 2247–2249.
58. Hein C, Schönwetter D J, Iacopino A M. Inclusion of oral-systemic health in predoctoral/undergraduate curricula of pharmacy, nursing, and medical schools around the world: a preliminary study. *J Dent Educ* 2011; **75**: 1187–1199.
59. Smith S M, Wallace E, O’Dowd T, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev* 2016 DOI: 10.1002/14651858.CD006560.pub3.
60. World Health Organisation. Universal health coverage (UHC). 2019. Available at [https://www.who.int/news-room/fact-sheets/detail/universal-health-coverage-\(uhc\)](https://www.who.int/news-room/fact-sheets/detail/universal-health-coverage-(uhc)) (accessed April 2020).
61. American Diabetes Association. 3. Comprehensive medical evaluation and assessment of comorbidities: standards of medical care in diabetes – 2018. *Diabetes Care* 2018; DOI: 10.2337/dc18-S003.
62. Haute Autorité de Santé. Guide parcours de soins: Diabète de type 2 de l’adulte. 2014. Available at [https://solidarites-sante.gouv.fr/IMG/pdf/guide\\_pds\\_diabete.pdf](https://solidarites-sante.gouv.fr/IMG/pdf/guide_pds_diabete.pdf) (accessed May 2020).
63. NHS England and NHS Improvement. Commissioning Standard: Dental Care for People with Diabetes. 2019. Available at <https://www.england.nhs.uk/wp-content/uploads/2019/08/commissioning-standard-dental-care-for-people.pdf> (accessed August 2020).
64. Public Health England. Delivering better oral health: an evidence-based toolkit for prevention (third edition). 2017. Available at [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/605266/Delivering\\_better\\_oral\\_health.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/605266/Delivering_better_oral_health.pdf) (accessed April 2020).
65. National Institute for Health Research, NHS England and NHS Improvement, The Academic Health Science Network. National Survey of Local Innovation and Research Needs of the NHS. 2019. Available at <https://www.ahsnetwork.com/wp-content/uploads/2019/07/National-survey-of-local-research-and-innovation-needs-of-the-NHS.pdf> (accessed April 2020).