

# Oral health and mental health

Dealing with this emerging interrelationship



A 10k magnification of the biofilm of bacteria at the gum line. The mix of bacteria in this biofilm is influential on Type 2 diabetes, hypertension, CVD, COPD, stroke, mild cognitive impairment and certain cancers. **New studies also indicate this biofilm is a significant risk factor in mental health.**

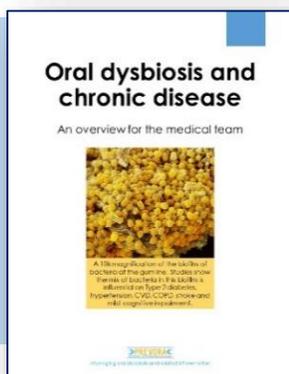


Managing oral dysbiosis and related inflammation

## Executive Summary

This report describes an emerging interrelationship between poor oral health and poor mental health. Key findings are:

- » There are, as yet, no randomized controlled intervention studies which demonstrate that improving oral health is an effective approach to improving mental health. Two pharmaceutical companies are pursuing this interrelationship with advanced clinical research. Moreover, numerous recent studies report oral health plays a significant role in mental health disorders.
- » The incidence, duration and severity of poor mental health in adults with poor oral health is higher than in healthy peers.
- » Poor oral health is a significant co-morbidity with poor mental health in adults.
- » Poor oral health can predict poor mental health.
- » Improving poor oral health in adults with poor mental health needs to address the fear and anxiety of surgical dental care, to reduce its costs significantly, and to open-up access. Surgical approaches to oral healthcare have created these barriers; these barriers can be overcome with a preventive model which focuses on pain-free management of the primary cause of poor oral health (oral dysbiosis).
- » **CHX Technologies (Toronto) and Cortexyme (San Francisco: CRTX on Nasdaq)** are developing new drugs to treat oral bacteria implicated in mental disorders and cognitive decline. CHX has an approved topical drug, Prevora, which significantly improves oral health for years and which has also shown anecdotally that it improves mild cognitive impairment for long periods. Prevora can be delivered in medical venues for improved access by adults with mental disorders, and reduces the cost of oral healthcare dramatically. Cortexyme has a drug which inhibits the release of an enzyme by an oral bacteria; it has shown in animal studies and a small Phase 1 study to improve memory function over 30 days. Both companies will report more results from their clinical studies in 2021.



An overview of the interrelationships between poor oral health and chronic disease is available at <https://chxtechnologies.com/wp-content/uploads/2020/01/Overview-of-oral-dysbiosis-and-chronic-diseases-Version-2-at-2020.pdf>



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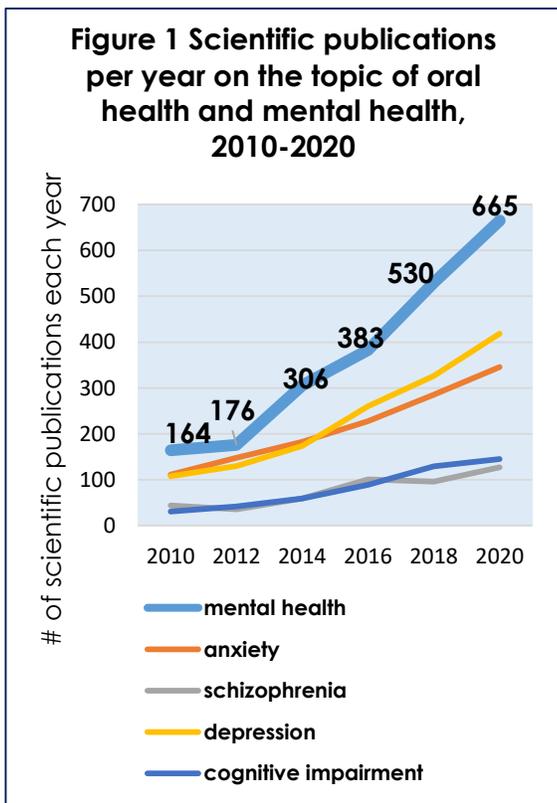
# An emerging interrelationship

Poor oral health, consisting of caries (tooth decay) and/or periodontal (gum) disease, is one of the most common chronic diseases during adulthood. It is also one of the most expensive and contributes significantly to overall medical spending.

Poor oral health has a bidirectional relationship with many chronic diseases such as diabetes and cognitive decline. It also contributes to the risks for instability of hypertension, COPD and arthritis. Readers are directed to the report shown opposite, which is available on the CHX Technologies website.

**This report evaluates the interrelationship which is emerging between poor oral health and poor mental health. For the purposes of this report, mental health includes forms of depression, anxiety, schizophrenia and cognitive impairment.**

For years, it has been documented that adults with poor mental health have a greater chance of poor oral health. In 1995, for example, a study reported that adults testing for depression, developed significantly more dental plaque/biofilm in 30 days than their peers without depression.<sup>1</sup> A more recent survey of adults with Bipolar Disorder (BD) and a control group reports those with BD had significantly more dental decay, a longer history of decay and more chronic oral inflammation.<sup>2</sup>



Source: PubMed

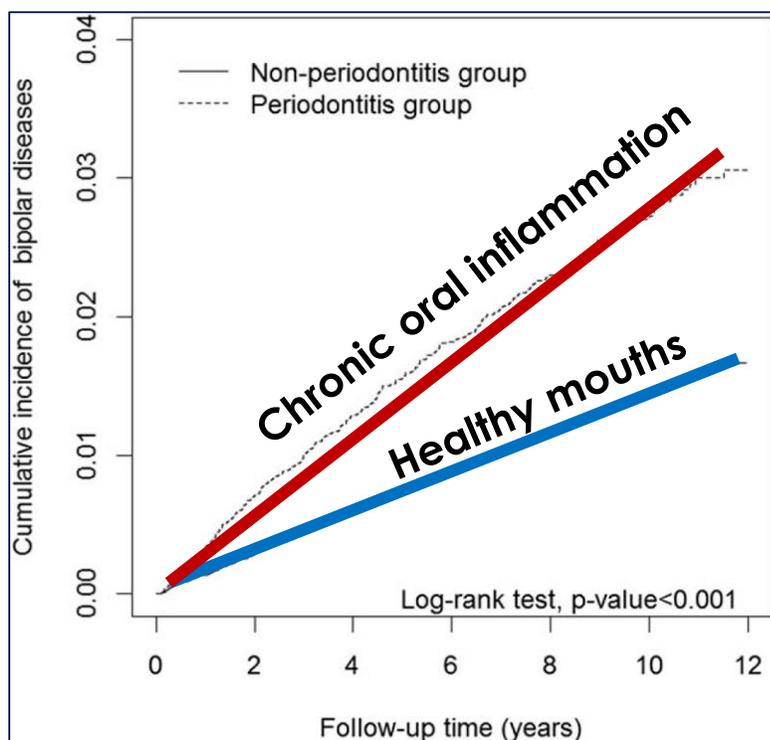
**But is there a reverse relationship whereby poor oral health contributes to poor mental health?** Importantly, the understanding of the interrelationship between mental health and oral health has expanded significantly in the past 5 years (Figure 1). **A review of the most recent studies finds that poor oral health and poor mental health may be bidirectional – meaning that improving oral health may be an effective strategy to improve mental health.**

<sup>1</sup> Kurer JRB et al. 1995. Psychological mood of regular dental attenders in relation to oral hygiene behavior and gingival health. J Clin Periodontol, 22: 52-55.

<sup>2</sup> Ofezer OG et al. 2018. Oral health among patients with Bipolar Disorder. Oral Health Prev Dent, 16(6): 509-516



# Poor oral health = higher incidence of poor mental health



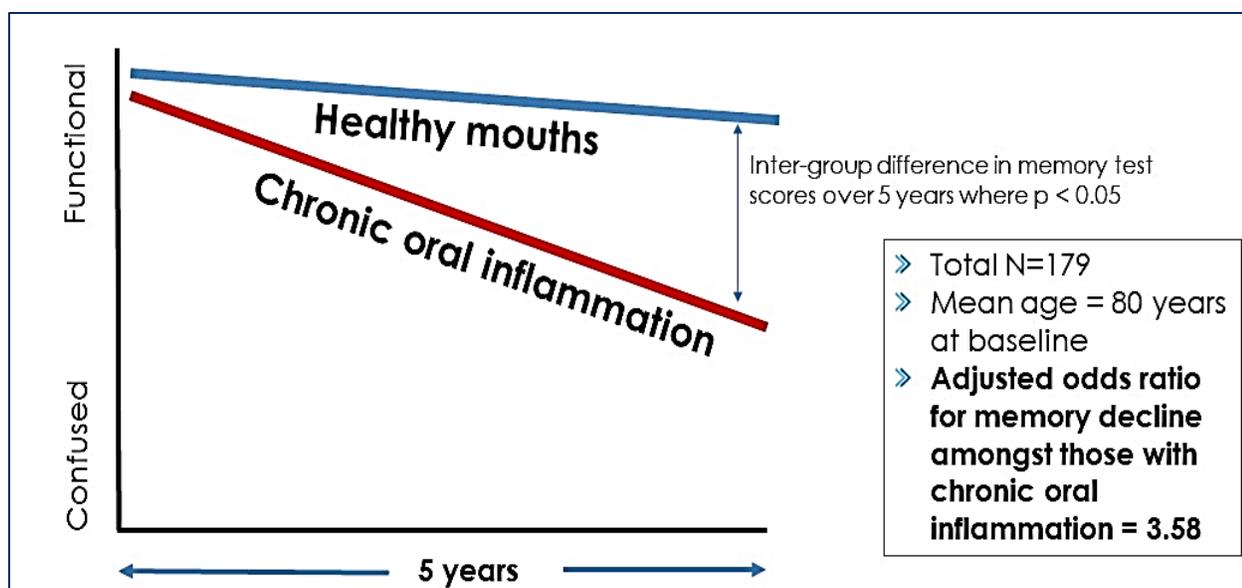
Source: Chang K-H et al. 2020. Association between periodontitis and bipolar disorder. *Medicine*, 99 (31), e21423

The contribution of oral health to mental health has yet to be defined via well controlled, prospective studies. At least two research-driven companies are working to fill this void – see page 8 of this report.

To encourage this controlled research, recent, long-term observational studies indicate that poor oral health (chronic oral inflammation) significantly increases the incidence of certain mental disorders -- bipolar disease (Figure 2) and memory loss (Figure 3).

**Figure 2** The growing incidence of bipolar diseases over time for those with poor oral health

**Figure 3** The relative decline over time of memory function for those with chronic oral inflammation over time



Source: Iwasaki M et al. 2019. Periodontitis, periodontal inflammation and mild cognitive impairment: a 5-year cohort study. *J Periodont Res.*, v.54, #3, 233-240

# Poor oral health coincides with depression in American seniors – which comes first?

Figure 4 Poor oral health in American seniors coincides with certain medical conditions, 2015-2016, where N>45,000	Level of significance using X <sup>2</sup>
<b>Depression</b>	<0.001
General health	
Energy levels	
Work limitations	
Appetite	
Diabetes	<0.05
Coronary heart disease	
Congestive heart failure	
Hypertension	
Asthma	
Liver condition	

Significant associations are reported between depression and poor oral health in a recent large population study of American seniors (Figure 4). Similar interrelationships are observed between poor oral health and several common chronic diseases in American seniors; some of these diseases may also be influential on mental health.

Another analysis of several studies on oral health and mental health found **adults with chronic oral inflammation are almost twice as likely to have depression as healthy peers<sup>3</sup> and four times as likely to experience more rapid cognitive decline.<sup>4</sup>**

Finally, a new study found the **severity of depression in seniors was significantly associated with worsening oral health. The number of missing teeth, the number of cavities and the extent of dry mouth defined the depth and duration of depression.<sup>5</sup>**

Source: Hung M et al. 2019. Oral health as a gateway to overall health and well-being: Surveillance of the geriatric population in the U.S. *Special Care Dentistry*, 39 (4): 354-361; see also <https://theconversation.com/depression-and-dementia-in-the-age-of-covid-19-two-sides-one-coin-146401>

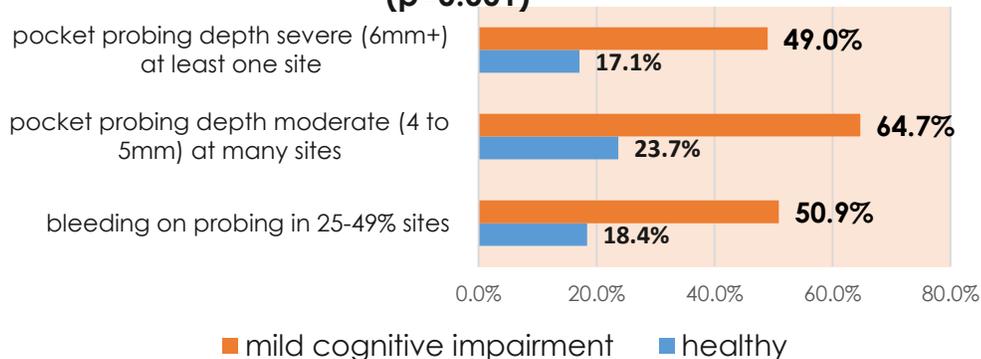
<sup>3</sup> Cademartori MG et al. 2018. Is depression associated with oral health outcomes in adults and elders? A systematic review and meta-analysis. *Clin Oral Investig*, 22(8): 2685-2702

<sup>4</sup> Refer to Figure 3.

<sup>5</sup> Skoskiewicz-Malinowska K et al. 2018. Oral health condition and occurrence of depression in the elderly. *Medicine*. 97 (41) e12490

# Poor oral health coincides with mild cognitive impairment

**Figure 5 Over 3 years, older Swedes with mild cognitive impairment experienced significantly more oral inflammation versus healthy peers (p=0.001)<sup>1</sup>**

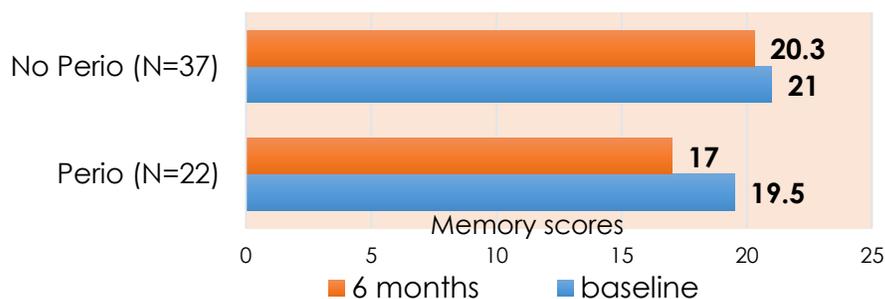


Early cognitive decline significantly contributes to poor oral health (Figure 5).

In turn, **poor oral health significantly coincides with memory loss** (Figure 6).

A Japanese study conducted over 5 years and involving 179 community-dwelling adults (mean age of 80 years), reports that compared to an absence of severe periodontal disease at the start of the study, **those with poor oral health had a much higher odds for mild cognitive impairment (MCI) over 5 years.** Likewise, **a larger degree of oral inflammation at baseline was also significantly predictive of MCI.**<sup>6</sup>

**Figure 6 Over 6 months, patients with mild cognitive impairment experience different rates of cognitive decline depending on oral inflammation (p <0.05)<sup>2</sup>**



Sources: Figure 5 Holmer J et al. 2018. Association between periodontitis and risk of Alzheimer's disease, mild cognitive impairment and subjective cognitive decline: A case-control study. J Clin Periodontol, October; Figure 6 Ide M et al. 2016. Periodontitis and cognitive decline in Alzheimer's Disease. PLOS One 11 (13).

<sup>6</sup> Iwasaki M et al. 2018. Periodontitis, periodontal inflammation, and mild cognitive impairment: A 5-year cohort study. J Periodont Res, October.

# Poor oral health – predictive of mental health problems

In these studies of older adults with complex needs, poor oral health forecasts mental disorders.

- » Anxiety and depressive tendencies for adults convalescing in two Japanese hospitals because of cardiovascular or orthopedic problems, were attributed to worsening oral hygiene. In particular, an extraordinary accumulation of plaque over a short period impacted patients reporting depression and anxiety.<sup>7</sup>
- » Among adults with Sjogren's syndrome, oral health and swallowing disorders were the most important predictors of anxiety. – so much so that investigators recommended rheumatologists focus on oral health managing Sjogren's.<sup>8</sup>
- » In the English Longitudinal Study on Aging, worsening oral health was associated with a significant increase in depressive symptoms over a 4-year period. These findings were adjusted for confounding factors of declining general health, activities of daily living and reduced social support.<sup>9</sup>

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<sup>7</sup> Hayashi K et al. 2019. Relationship between anxiety/depression and oral health-related quality of life in inpatients of convalescent hospitals. *Odontology*. 107 (2): 254-260

<sup>8</sup> Cui Y et al. 2018. Anxiety and depression in primary Sjogren's syndrome: a cross-sectional study. *BMC Psychiatry*, 18 #131

<sup>9</sup> Rouxel P et al. 2018. Oral health – a neglected aspect of subjective well being in later life. *J Gerontol B Psychol Sci Soc Sci*. 73 (3): 382-386

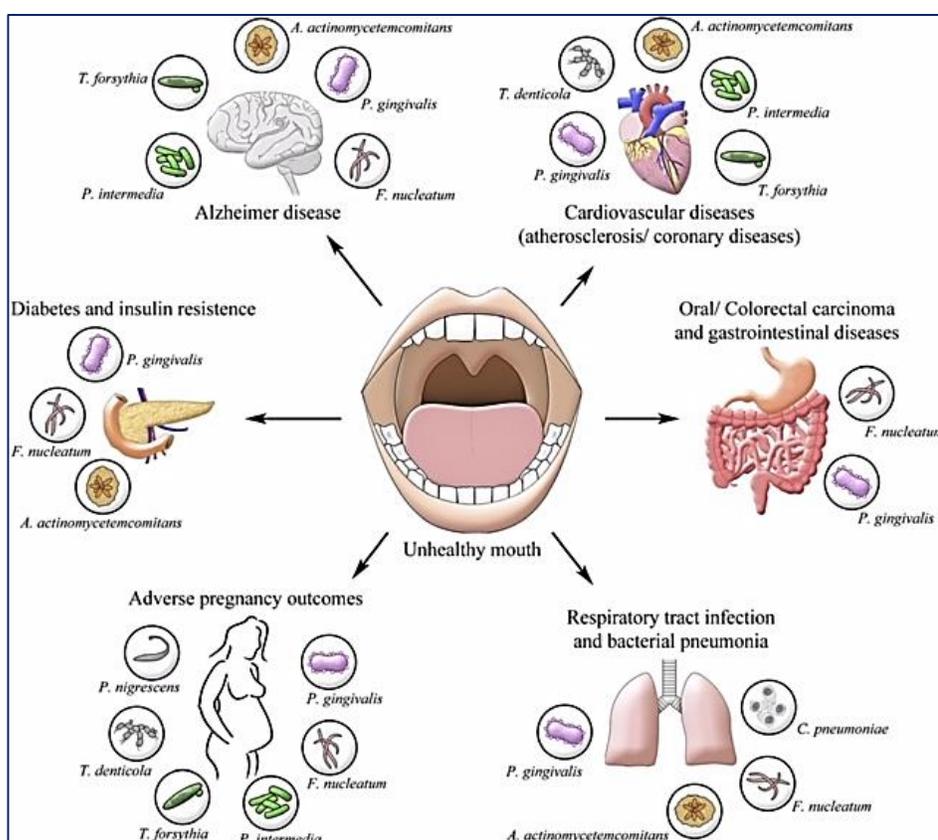


# Microbes cause poor oral health & possibly poor mental health

An imbalance in the mix of bacteria in the oral biofilm (the dental plaque) leads to the onset, advance or recurrence of oral diseases. This is a medical condition called oral dysbiosis.

During dysbiosis, certain "keystone" bacteria which are pathogenic and/or inflammatory, dominate the plaque (Figure 7). For caries, the keystone bacteria are *Streptococcus mutans* and *Scardovia wiggsiae*. For periodontal disease, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Fusobacteria nucleatum* and *Treponema denticola* are primarily involved.

These keystone oral bacteria are implicated in many chronic conditions (Figure 7).



Source: Bui FQ et al. 2019. Association between periodontal pathogens and systemic disease. Biomed J., 41, 1, 27-35

**Figure 7 The role of oral microbes in chronic diseases**

## Oral bacteria are implicated in poor mental health

The keystone pathogen called *Porphyromonas gingivalis* which originates at the gum line has recently been shown to:

- Induce depression-like behaviour in mice; treatment of this infection with systemic antibiotics ameliorated this behaviour.<sup>10</sup>
- Have a significant association with signs of depression (dysphoria and anhedonia) in older Americans<sup>11</sup>
- Increase the likelihood of the depressive phase of bipolar disease.<sup>12</sup>
- Impact memory & language scores in cognitive testing.<sup>13</sup>

Other oral microbes are also implicated, suggesting a broad spectrum antiseptic drug has merit.

<sup>10</sup> Wang Y-X et al. 2019. *Porphyromonas gingivalis* induces depression via downregulating p75<sup>NTR</sup>-mediated BDNF maturation in astrocytes. Brain, Behavior, and Immunity. 81, October: 523-534

<sup>11</sup> Postolache T et al. 2019. *Porphyromonas gingivalis* and cardinal symptoms of depression. Biological Psychiatry 85: S391

<sup>12</sup> Cunha FA et al. 2019. Periodontal condition and levels of bacteria associated with periodontitis in individuals with bipolar affective disorders: a case control study. J Periodont Res, 54(1): 63-73

<sup>13</sup> [https://www.cortexyme.com/wp-content/uploads/2020/07/AAIC\\_2020\\_COR388-A-novel-gingipain-inhibitor-decreases-ApoE-fragmentation-in-the-CNS-of-Alzheimers-disease-patients\\_Poster\\_070520.pdf](https://www.cortexyme.com/wp-content/uploads/2020/07/AAIC_2020_COR388-A-novel-gingipain-inhibitor-decreases-ApoE-fragmentation-in-the-CNS-of-Alzheimers-disease-patients_Poster_070520.pdf)

# Improving oral health for adults with mental disorders – the need to reduce dysbiosis, fear, cost & inconvenience

Dental fear, costs and difficulty of accessing professional dental care are the most frequently cited barriers to improving oral health for those with mental disorders. These barriers only grow with the severity and duration of mental illness and with age. They are also formidable.

- › Almost 7 in 10 adults with a mental disorder and with poor oral health fear the dentist; by contrast 14% of adults without mental problems but with poor oral health are anxious about dental care.<sup>14</sup>
- › Dental care is the most expensive healthcare service (American data). Those with mental disorders are commonly uninsured or underinsured.

These barriers are erected by the surgical model of oral healthcare. A painless, preventive model which focuses on managing the primary cause of poor oral health, oral dysbiosis, will significantly reduce fear, cost and inconvenience.

## New approaches to dealing with this emerging interrelationship

Two pharmaceutical companies are actively developing new methods for improving oral health as a way of managing the onset, duration and extent of mental disorders.

- › **CHX Technologies (Toronto)** has an approved, topical, broad spectrum antiseptic drug which restores symbiosis to the oral microbiome. Extensive clinical use of this drug, Prevora, has shown it significantly reduces chronic oral inflammation and dental decay for long periods in high risk adults. In doing so, Prevora has anecdotally also shown it improves mild cognitive impairment for years. CHX will implement an observational study of Prevora's ability to modify cognitive decline in 2021.
- › **Cortexyme (San Francisco, Nasdaq: CRTX)** has an investigational drug taken systemically to inhibit the release of enzymes by the oral bacteria *Porphyromonas gingivalis*. Data from animal studies and from a small Phase 1 study show memory function can improve over the short term with this drug. Cortexyme is in Phase 2/3 studies with results expected in 2021.

New approaches to dealing with this emerging interrelationship between poor oral health and poor mental health are underway.

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<sup>14</sup> Levin L et al. 2018. Demographic profile, oral health impact profile and dental anxiety scale in patients with chronic periodontitis: a case-control study. Int Dent J. 68(4): 269-278.





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