Exploring the relationships between periodontitis, high-risk oral human papillomavirus and social factors and their impact on oral health status in Indigenous South Australians

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Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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I acknowledge the support I have received for my research through the provision of Divisional scholarship by the University of Adelaide.

Signed:

Anna Ali (Candidature)

October 2022

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Keywords

Indigenous Australians

Periodontitis

Human papillomavirus

Oropharyngeal cancer

Social inequalities

Racism

Quantitative research

Qualitative research

List of abbreviations and acronyms

AAP: American academy of periodontology

ACCHO: Aboriginal Community Controlled Health Organisations

ACCHS: Aboriginal Community Controlled Health Services

APC: Annual percentage change

API: Approximal plaque index

BOP: Bleeding on probing

CAL: Clinical attachment loss

CDC: Centers for Disease Control and Prevention

CI: Confidence Intervals

GBI: Gingival bleeding index

GLOBOCAN: Global Cancer Observatory

GP: General primer

GRADE: Grading Of Recommendations, Assessment, Development And Evaluation

HPV: HumanPapillomavirus

Human Papillomavirus and Oropharyngeal Cancer among Indigenous Australians' (HPV-OPC

NHANES: National Health and Nutrition Examination Survey

NHMRC: National Health and Medical Research Council

NIH: National Heart, Lung and Blood Institut

OHIP-14: Oral Health Impact Profile

OHRQoL: Oral health related quality of life

OPSCCs: Oropharyngeal squamous cell carcinoma

OR: Odds ratio

PCR: polymerized chain reaction

PD: Pocket depth

PI: Plaque index

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PSR: Periodontal screening record

RR: Relative risk

SA: South Australia

SOC: Sense of coherence

WHO: World Health Organization

Thesis abstract

Aboriginal and Torres Strait Islander people (hereafter referred to as Indigenous people) have been living and practicing diverse cultures on the continent of Australia for more than 60,000 years. Yet following colonisation in the 1700s, Indigenous people have experienced continued oppression, marginalisation, and dispossession from land and culture, that manifests in unacceptably adverse health and wellbeing outcomes. This includes experiences of poor oral health, with high rates of dental caries, periodontitis, oral cancer and human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) in Indigenous Australians when compared with non-Indigenous Australians.

Indigenous people also access oral healthcare differently. They are less likely to visit a dentist for a routine dental check-ups and therefore less likely to receive preventive dental care, instead presenting more often with a dental health problem or established oral disease. Given the high burden of oral health conditions there is a strong need for strengthened efforts to promote preventive approaches related to oral health among Indigenous Australians. This includes a greater understanding of the etiological factors of emerging oral conditions such as HPV-positive OPSCC, which has high mortality rates because it is commonly discovered at a late stage. HPV vaccination programs remain an important OPSCC control strategy, however HPV vaccines provide little protection to individuals already exposed to HPV infection. This is why new approaches to screening are required to permit early detection, and management of OPSCC, particularly in high-risk populations.

One of the most consequential oral diseases for health and quality of life is periodontitis, which results in multiple tooth loss, edentulism and masticatory dysfunction, and disproportionately affects Indigenous people. Emerging data suggests a possible role for periodontitis as reservoir for latent oral HPV infection. Detection of periodontitis may thus identify individuals at increased risk of persistent infection and OPSCC, who may benefit from increased surveillance. The high burden of both periodontitis and HPV-positive OPSCC in Indigenous people indicates that Indigenous people may have great potential to benefit from improved screening for periodontitis and OPSCC; however, research is needed to confirm or refute a link between these conditions.

Given the high burden of oral disease, it is also important to understand the broader proximal and distal factors affecting oral disease and oral health related quality of life (OHRQoL).

Racism is known to negatively impact on the general health of an individual and there is emerging evidence that racism has adverse effects on oral health and OHRQoL. However, to date, the impact of racism on OHRQoL among Australian Indigenous people has not been studied systematically. It is important to understand this link further to determine the need to address racism in broader oral health promotion strategies.

Lastly, the inequities in oral health outcomes experienced by Indigenous people in Australia are thought to be underpinned by a complex interplay of social factors that reflect social disadvantage, poorer health literacy, a lack of awareness regarding oral health preventive programs, experiences of racism and limited availability of oral healthcare that is culturally relevant. To date, there has been limited in-depth investigation of barriers faced by Indigenous people with regard to seeking oral healthcare services, particularly preventive services. This area needs further exploration to understand experiences of oral healthcare and therefore opportunities to improve engagement with care and to reduce oral health inequities.

This thesis focuses on several key oral health areas that disproportionately affect Indigenous people and are understudied in this population. The thesis addresses key gaps in understanding about 1) the relationships between periodontitis, oral HPV and HPV-positive OPSCCs, 2) the relationships between self-reported periodontitis and oral high and low-risk HPV infection specifically among Indigenous people, 3) the influence of self-reported racism on OHRQoL among Indigenous people, and 4) factors that affect Indigeonus people seeking and accessing oral healthcare.

The aims of this thesis are to:

1. Examine the strength and quality of the overall evidence concerning the relationships between periodontitis, oral HPV infection and OPSCC;

2. Examine the association between self-reported periodontitis and oral high and low-risk HPV infection specifically among Indigenous South Australian adults;

3. Determine if self-reported racism is a risk factor for poor OHRQoL among Indigenous South Australian adults; and

4. Explore experiences of and the factors that influence Indigenous people's use of oral healthcare services.

Methods

1. A systematic review and meta-analysis was conducted capturing all published studies up to 12th February 2020 evaluating the association between periodontitis and separately, oral HPV infection and OPSCC.

2. Analysis of baseline and 12 month follow-up data collected as part of a prospective cohort study known as the 'Human papillomavirus and oropharyngeal cancer among Indigenous Australians' study, involving 1011 (at baseline) Indigenous South Australians (SA) aged 18+ years recruited between February 2018 and 2020. Detailed information on sociodemographic characteristics, health-related behaviours, and sexual history were collected at enrolment. Saliva samples were collected and tested for the presence of oral HPV DNA using the optimized general primer (GP) + PCR system. The primary outcomes were the prevalence of any high-risk oral HPV DNA and the prevalence of HPV 16 and/or 18, separately. Periodontitis was assessed using validated, self-reported periodontitis screening questions.

3. Analysis of data collected in the 'Human papillomavirus and oropharyngeal cancer among Indigenous Australians' study at enrolment that included social background, connection to culture and cultural values, utilization of dental services, and OHRQoL; the latter was captured using the Oral Health Impact Profile (OHIP-14). We defined the dependent variable 'poor OHRQoL' as the presence of one or more OHIP-14 items rated as 'very often' or 'fairly often'. Experiences of racism were also evaluated using the Measure of Indigenous Racism Experiences instrument. Interpersonal racism was classified into two categories ('no racism' vs. 'any racism in ≥ 1 setting') and three categories ('no racism', 'low racism', and 'high racism').

4. A qualitative study was undertaken with 19 Indigenous people living in different regions of South Australia including Adelaide, Port Augusta, Mount Gambier, Whyalla, Port Lincoln, and Port Pirie. Participants were identified through existing participation in the 'Human papillomavirus and oropharyngeal cancer among Indigenous Australians' study. Purposive sampling was undertaken to ensure variation in sample with respect to geographic location, gender and age group. The interviews were undertaken by an experienced Indigenous researcher, who was present in person with the participant, and a non-Indigenous researcher (Ph.D. candidate) who joined the interview remotely via video conferencing services. Interviews were transcribed, coded line-by-line and analysed using an inductive thematic approach to generate key themes, which were then checked and refined with the Indigenous researcher and the supervisory team. Theme development was informed by existing

frameworks concerning social and cultural determinants of oral health, including the framework by Patrick and colleagues (2006).

Results

1. The systematic review identified 13 studies; four case-control and nine cross-sectional. Of these, five studies could be included in the meta-analyses. There was no significant increase in the odds of high-risk oral HPV infection among individuals with confirmed periodontitis (odds ratio (OR): 4.71; 95% confidence interval (CI): 0.57–38.97). Individuals with periodontitis had a 3.65 (95% CI: 1.67–8.01) times higher odds of having any type of oral HPV infection compared with those without periodontitis. The overall body of evidence was rated as low to very low certainty. There were insufficient studies to robustly evaluate the relationship between periodontitis and HPV-positive OPSCC.

2. Among the 673 participants with sufficient data for analysis, 17.1% had self-reported periodontitis, 5.9% had any high-risk oral HPV and 2.1% had oral HPV 16 and/or 18. Among those who self-reported periodontitis, any high-risk oral HPV was detected among 17.5% participants and oral HPV 16 and/or 18 was detected in 21.4%. Logistic regression analyses revealed no significant association between self-reported periodontitis and either any high-risk oral HPV (adjusted OR: 1.10; 95% CI: 0.45–2.70) or oral HPV 16 and/or 18 (adjusted OR: 1.27; 95% CI: 0.32–5.03).

3. Among the 885 participants with sufficient data available for analysis, 50.2% reported poor OHRQoL and 52.1% reported experiencing any interpersonal racism in the previous 12 months. Relative to having no experiences of racism in the previous 12 months, those who experienced any racism (≥ 1 setting) were significantly more likely to report poor OHRQoL (adjusted OR: 1.43; CI:1.08–1.92). The odds of having poor OHRQoL among females experiencing racism were 1.74 times higher (95% CI: 1.07–2.81) than among males.

4. Thematic analyses identified individual, interpersonal, community and macro-level factors that influence Indigenous people to seek and access oral healthcare overall and preventive care specifically. Key obstacles to seeking care identified by participants included fear and shame, negative past experiences and oral health misconceptions at the individual level and personal stressors and racial discrimination at the interpersonal level. Accessibility of services and the degree of community-based services and support from community members were identified as important factors at the community level. At the macro level, complex processes relating to

financing and reimbursement for oral healthcare as well as workforce shortages were important impediments to use of oral healthcare services.

Conclusion

Findings of this thesis have demonstrated that there is an association between periodontitis and any HPV infection overall. However, the relationship with high-risk HPV is less clear, in part reflecting low certainty evidence. When studied specifically among Indigenous South Australians, the association between periodontitis and any or high-risk HPV could not be confirmed. This suggests that periodontitis may not be a useful marker to identify those at high-risk of OPSCC. Further research that includes a clinical diagnosis of periodontitis could help in clarifying the role of periodontitis in the acquisition and persistence of high-risk oral in communities with high disease prevalence.

This thesis has also demonstrated an association between racism and poor OHRQoL, suggesting the need for culturally sensitive strategies to overcome the experiences of racism among Indigenous Australians while seeking oral healthcare. In-depth analyses identified various individual, interpersonal, community and macro-level factors that affect oral healthcare seeking behaviour in this population. Collectively this indicates that strengthening preventive approaches to oral health for Indigenous people requires dedicated strategies to make oral healthcare more accessible and culturally sensitive. Sustained funding for oral healthcare and oral health literacy initiatives, co-design of services with Indigenous people and increasing the number of Indigenous people in the oral healthcare workforce are critical steps forward in this regard.

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Ali A, Rumbold AR, Kapellas K, Lassi ZS, Hedges J, Jamieson L. The impact of interpersonal racism on oral health related quality of life among Indigenous South Australians: a cross-sectional study. BMC oral health. 2021 Dec;21(1):1-1.

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Ali A, Hedges J, Jamieson L, Lassi ZS, Rumbold AR. Understanding Aboriginal people's experiences of dental care in South Australia, a qualitative study.

CHAPTER ONE: Introduction

1.1 Preamble

This chapter outlines the background of research that supports this thesis and summarises the burden of oral HPV infections, periodontitis, associated oropharyngeal cancer's social determinants and oral health related quality of life. When seeking oral healthcare, behaviours and barriers faced by Indigenous Australians are also discussesed. The chapter concludes by outlining the overarching aims and the structure of the thesis.

1.2 Overview

In Australia, 3.3% of the population are Indigenous comprising of Aboriginal and Torres Strait Island people. Indigenous Australians are people with unique languages, histories, and cultural traditions. In contemporary Australia, Indigenous Australians comprise of two distinct groups. Aboriginal Australians are the first peoples of mainland Australia and Tasmania, while Torres Strait Island peoples are the first peoples of islands located in the Torres Strait between Australia and Papua New Guinea (1). Indigenous people have lived in Australia for between 50,000 and 120,000 years. In 1788 when British coloniseres arrived in Australia there were 300,000 to 950,000 Aboriginal people living in Australia with 260 distinct languages and 500 dialects (2).

Indigenous Australians have 1.7 times higher the age-standardised death rate compared to non-Indigenous people from all causes (3). Further, the life expectancy of Indigenous Australians is approximately eight years less than non-Indigenous Australians (3). An excess of chronic non-communicable diseases such as cancers, diabetes, cardiovascular disease, ischaemic heart disease, chronic respiratory diseases, and poor mental health contribute to the high death rates and disease burden among Indigenous Australians (4, 5). The higher burden of chronic disease experienced by Indigenous Australians extends to poor oral health too. Indigenous Australians experience a high prevalence of oral diseases, including dental caries (tooth decay) (68%), periodontal (gum) disease (17%), tooth loss (15%) and head and neck cancers including oral cancers (27.9 new cases/100,000, 2009-2013) (6-8) (9). National Aboriginal and Torres Strait Islander Health Survey 2018-19 reported that a lesser percentage of Indigenous individuals visited a dentist in the past 12 months compared to non-Indigenous individuals (41.1% and

59.8%, respectively). Likewise, a lesser proportion of Indigenous individuals visited a dentist for general check-ups (50.4%) compared to non-Indigenous individuals (65.2%) (10).

Oral health is an integral component of the overall systemic health of individuals and, therefore, should be given the same importance as physical and mental health conditions when considering Indigenous health inequities. Despite the high burden of oral diseases, Indigenous oral health has traditionally been an understudied subject and has not been studied systematically (11, 12). Poor oral health conditions have a negative impact on the quality of life and has been associated with poor mental wellbeing. Pain from oral disease impacts an individuals' ability to eat and sleep well (13). Specifically in Indigenous populations, poor oral health has been associated with depression and suicidal thoughts (14), reinforcing the importance of incorporating a holistic approach when treating oral health conditions.

Many factors contribute to oral health disparities experienced by Indigenous Australians. These include a lack of awareness of preventive oral health interventions (15) as well as factors that reflect lesser access to oral healthcare as a result of living in remote or regional locations, financial costs and/or limited access to culturally targeted preventive strategies (15). Mistrust of the medical system compounded by the legacies of colonisation as well as overt experiences of racism may also prevent some Indigenous people from visiting oral healthcare professionals for a routine check-ups (15). This in turn can put the community at risk of limited awareness of oral conditions and increased risk of acquiring novel oral diseases that could be prevented through regular check-ups and targeted preventive strategies.

More broadly, poor social and emotional well-being related to the grief and trauma of colonisation, loss of family and kinship structures, land, and culture have also negatively influenced the health and quality of life of Indigenous Australians (16). Further, there are persistent social inequities experienced by Indigenous Australians including poorer access to education, financial security, adequate housing and transport, and social support (17). These social determinants have and continue to negatively affect oral health and health-related quality of life (17).

Thus, the poorer oral health experienced by Indigenous Australians, including the high rates of oral cancer-related morbidity and mortality cannot be addressed without considering the legacy of colonisation; including entrenched racism and vilification in and beyond the health system, as well as economic exclusion, and poverty. Through my Ph.D., I have tried to amalgamate the aforementioned concepts to understand the increasing oral health conditions among Indigenous

Australians. I have focussed on three main areas that reflect the oral disease burden in Indigenous peoples: (1) understanding the role of periodontitis in HPV-positive oropharyngeal squamous cell carcinoma (OPSCC); (2) exploring the impact of racism on the oral health related quality of life; and (3) asking Indigenous people about their experiences and needs of oral healthcare. The literature concerning each of these three areas is summarised below.

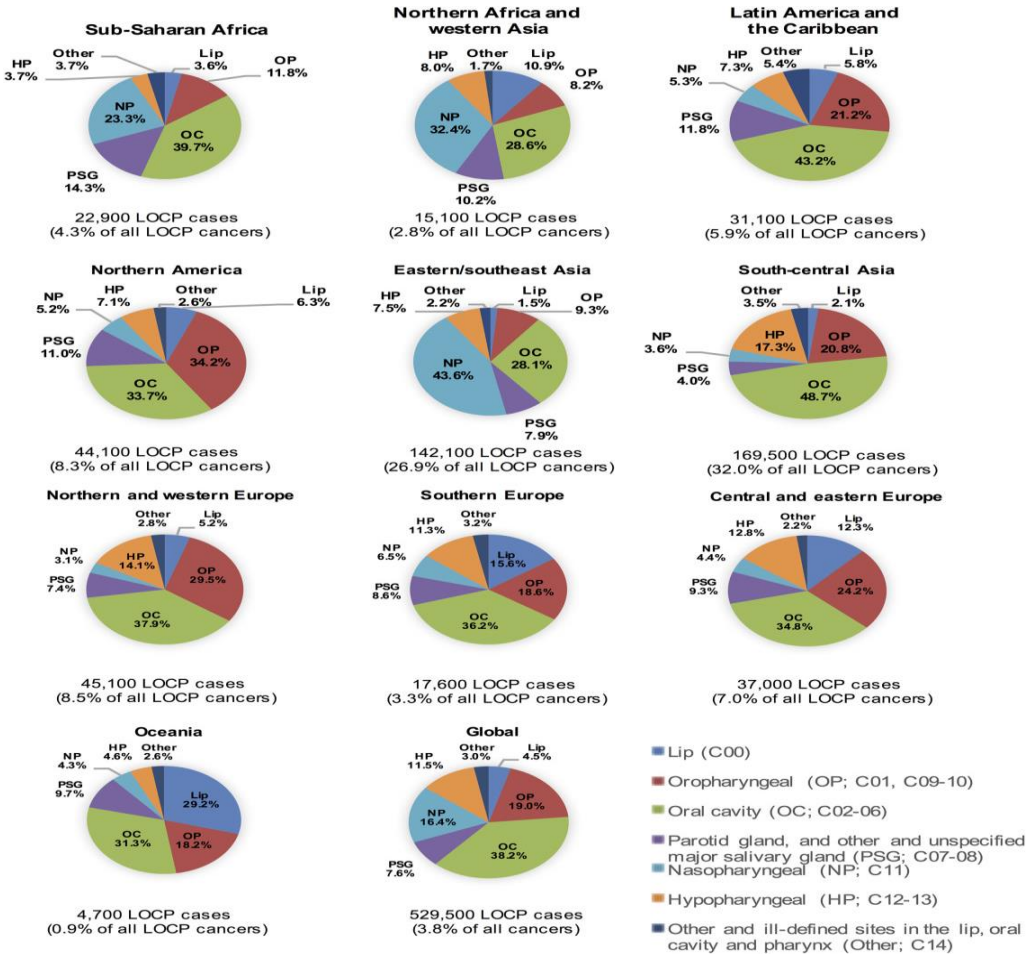
1.3 Oropharyngeal squamous cell carcinoma

The annual incidence of head and neck cancer is 400,000 cases worldwide, and it is considered the sixth most common cancer contributing 3.5% of all malignant tumours reported in western nations (18-20). Most head and neck cancers are squamous cell carcinomas (90%) with oral cavity squamous cell carcinoma being the most common head and neck carcinoma (21). However, in recent years, there has been a dramatic rise in the incidence of OPSCC (22).

The oral cavity includes the following anatomic structures: labial mucosa, buccal mucosa, the floor of the mouth, alveolar ridge and gingiva, anterior two-thirds of the tongue (anterior to the circumvallate papillae), hard palate, and retromolar trigone (23, 24). In contrast, the soft palate, base (or posterior one-third) of the tongue, palatine tonsils, palatoglossal folds, valleculae, and posterior pharyngeal wall constitute the oropharynx. The hard and soft palate junction separates the oral cavity from the oropharynx cavity from above, and the circumvallate palate separates them from below (23, 24).

According to the recent GLOBOCAN (Global Cancer Observatory) estimates of 2020 the age-standardized rate for lip/oral cavity cancers varies from 2.0/100,000 to 6.4/100,000 (25) . It is highest for the World Health Organization (WHO) South East Asia region, followed by the regions of Europe, Eastern Mediterranean, America, Africa, and the Western Pacific (Fig 1) (25-27). In comparison, the trends of other pharyngeal cancers vary from that of lip/oral cavity cancers; the age-standardized rate for other pharyngeal cancers ranges between 0.8/100,000 to 2.7/100,000. It is the highest for the WHO region of South East Asia, followed by Europe, the America, Eastern Mediterranean, Africa, and the Western Pacific region (Fig 1) (26, 27). The worldwide age-standardised mortality rate is 2.7 per 100,000 for lip/oral cavity cancer and 2.2 per 100,000 for other pharyngeal cancer (26).

Figure 1.3.1: The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012 (27)



1 Figure 1.3.1: The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012 [27]

1.4 Risk factors of oropharyngeal squamous cell carcinoma

Over the past few decades, increasing OPSCC incidences have been reported in many developed countries. The annual percentage change (APC) for OPSCC incidence in the US is 3.0% (between 1999 and 2012), in Canada is 2.7% (between 1992 and 2009), in Denmark is 3.5% (between 1978 and 2007), and in Australia is 1.2% for males and 0.8% for females (between 1982 and 2008) (28-32). The increasing trends reflect the shift in the dynamic risk factors. Tobacco and alcohol intake are traditional risk factors for these cancers; however, in recent decades, Human papillomavirus (HPV) has emerged as a major etiologic factor for OPSCC (33, 34). A dramatic increase in HPV-positive tumours accounts for rising OPSCC incidences in regions such as North America, Australia, and Europe. Whereas trends of HPV-negative OPSCC are largely consistent with tobacco use (34-36).

1.5 Oropharyngeal squamous cell carcinoma and human papillomavirus

Evidence from epidemiological studies, clinicopathological studies, and molecular studies have established a strong connection of HPV in a subset of head and neck squamous cell carcinoma (37-39). HPV is a small, non-enveloped DNA virus of the Papillomaviridae family. The potential oncogenic HPV can be divided into high-risk and low-risk groups. High-risk group includes HPV 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59 and low-risk group includes HPV 6, 11, 42, 43, 44 (40).

In the past, research on the oncogenic consequences of HPV has focused predominantly on cervical lesions. However, more recently, there has been recognition that the cervical membrane and oropharyngeal membrane contain the same epithelium cells and mucous membranes susceptible to infection with high-risk HPV strains (15, 41). Thus, the focus of HPV research has shifted towards studying the relationship between HPV and OPSCCs and understanding the impact of the HPV vaccine on preventing all HPV-related cancers and complications.

Most of the OPSCCs are HPV-positive, specifically the high-risk genotype HPV 16 and 18, accounts for 20-95% of HPV-positive OPSCCs (42-46). The risk profile of HPV-positive OPSCCs differs from that of HPV-negative OPSCCs; for example, HPV-positive tumours occur predominantly in white, relatively younger males with a median age of 54 years and individuals with high socioeconomic status. Studies have also reported a strong association of HPV-positive OPSCCs with an increased number of lifetime sexual or oral-sexual partners (47, 48). Moreover, HPV-positive tumours are less likely to arise in individuals with heavy tobacco and alcohol consumption (47).

Localization of high-risk HPV (HPV 16 and 18) within the nuclei of OPSCC cells is demonstrated in in-situ hybridization. In HPV-positive OPSCCs, high-risk HPV DNA is present in high copy numbers, and active transcription of the major viral oncoproteins E6 and E7 in the presence of high-risk HPV genomic DNA is frequently integrated into HPV-positive OPSCCs (42, 49-51). HPV-negative OPSCCs often lose 9p, 3p, and 17p chromosomes, and frequent mutation in p53 and p16 result in dysregulation of the cell cycle and genomic instability (52). On the other hand, there is no regular loss of chromosomes and decreased expression of p53 in HPV-positive OPSCCs. HPV-positive OPSCCs with positive HPV DNA/RNA and p16 overexpression have a better prognosis than HPV-negative OPSCCs (53,

54). HPV-positive OPSCC have 79% 5-year survival rates and 75% disease-free survival rates. The five-year local recurrence rate of HPV-positive OPSCC is 14%, compared to HPV-negative OPSCC (55).

Different mechanisms have been argued regarding the development of HPV within the oropharynx. However, to date, researchers have proposed few specific mechanisms explaining the acquisition, transmission, and persistence of oral HPV infection leading to OPSCC. For example, theories suggest that micro-trauma and exposure to basal epithelial cells lead to viral entry in the oropharynx. In addition, HPV-positive OPSCC within palatine and lingual tonsils are linked with the invasion of HPV in the tonsillar crypts that may serve as the reservoir for HPV (42, 49, 56). Also, the reticulated epithelium in these sites is attenuated with a discontinuous basement membrane, along with the immune-privileged sites such as deep crypts within the lymphoid tissue, favours persistent HPV infection and tumour invasion (42, 56).

1.6 Oropharyngeal squamous cell carcinoma, human papillomavirus, and periodontitis

An emerging hypothesis proposes that periodontitis may facilitate the persistence of HPV infection in the oral cavity. Periodontitis is estimated to affect up to 12% of the global population, and it is considered the sixth most prevalent oral condition (57). A relatively preventable chronic inflammatory disease of gums affects the gingiva's normal structures, periodontal ligament, and alveolar bone (58). It has a multifactorial origin, with the main etiological factor being the bacterial biofilm growing on tooth surfaces (59, 60). However, disease progression depends on local factors such as plaque and calculus and other generic factors such as host's immune system, genetics, environmental factors, underlying chronic disease, lifestyle factors, and social determinants (59).

Periodontitis is systemically related to a number of chronic conditions. Empirical research suggests an association between periodontitis and OPSCCs, with some studies reporting a 4-10 fold increased risk of OPSCCs among individuals with periodontitis (61). However, the mechanism behind this association is uncertain, and the role of local risk factors confounding the association between periodontitis and OPSCCs has not been robustly examined.

The periodontium serves as a reservoir for high-risk HPV infection. The exact pathophysiology is not known but it is suggested that diseased periodontium and oral high-risk HPV infection could influence basal cell and host cellular response system (62). In individuals with

compromised immunity, this inflammatory process could lead to formation of periodontal pockets and alveolar bone loss. Periodontal pockets serve as the continuous source of cytokines and further increases the exposure of oral cavity basal cells to inflammation. Imbalance in oral microbiota along with an inflammatory process may further accelerate tissue destruction and provide an opportunity to high-risk HPV infection to persist in the pockets and to colonize surrounding tissues. Untreated periodontal disease and pocketing modulate oncogenic expression (E6, E7) in HPV infected epithelial cells leads to oncogenic changes (62, 63).

It is therefore suggested that early detection and management of periodontitis and periodontal pockets could help in acquisition, colonization and persistence of high-risk HPV. It is documented that optimal survival after OPSCCs is less (56-75% depending on the specific site) as most are diagnosed in later life. OPSCC diagnosis relies on patient presentation and oral physical examination plus biopsy (64). Therefore, new approaches to screening and preventing development of life-threatening oral cancers are needed. In the case of HPV-positive OPSCC, it is difficult to identify a population at risk; as healthy individuals also carry HPV and there is no consensus on a standardized approach for oral HPV testing in terms of accuracy, feasibility and cost-effectiveness (65). The role of periodontitis in oral HPV infection and persistence could provide key evidence to guide recommendations about the utility of periodontitis screening to identify individuals at risk of HPV-positive OPSCC who may benefit from increased surveillance. My project has addressed this gap by examining the strength of the evidence and included a rigorous quality assessment by conducting a systematic review and meta-analysis. (See Chapter 3).

1.7 High-risk human papillomavirus and periodontitis OPSCC in Indigenous populations

Both incidence and mortality from OPSCCs are considerably higher in Indigenous Australians than in the non-Indigenous Australians (66). For example, among Australians living in Western Australia, Indigenous persons are diagnosed with oral cavity and oropharyngeal cancers at twice the rate of non-Indigenous persons (67). Data from South Australia indicated that head and neck cancers represent approximately 8% of cancer diagnoses in Indigenous South Australians compared to 2% of cancer in non-Indigenous South Australians (68). Despite the high burden of oral and oropharyngeal cancer among Indigenous Australians, Indigenous Australians are likely to be diagnosed with cancer at a later life stage. This further contributes

to the significantly lower 5-year survival rate from cancer compared to non-Indigenous Australians (68).

With respect to periodontitis, Indigenous Australians are more than twice as likely to have advanced periodontal disease than the non-Indigenous population (69). Recent data also confirms a high prevalence of oral HPV in this population (70). Despite this high prevalence of periodontitis and oral HPV, no previous study has examined the relationship between periodontitis and oral HPV in this high-risk group. Due to the high population prevalence of oral HPV infection, especially in the Indigenous population, routine testing of oral HPV is not recommended. Therefore, it is of foremost importance to study different markers that could identify high-risk populations. Previous studies have reported inconclusive findings, and most did not target marginalised communities (71). Previous studies varied in terms of participants' selection, study design, ascertainment of oral HPV and periodontitis. For example, four studies recruited oral cancer patients (65, 72-75), three studies recruited healthy individuals with no chronic conditions (76-78) while two included hospital patients or patients visiting a dentist (79, 80), three studies used survey data sets (74, 75, 81), one study recruited human immunodeficiency virus (HIV) positive patients (82) and one included women with HPV-positive gynaecological disease (83). Assessment and case definition of periodontitis and HPV also varied across the studies. Unique cultural heritage, a different lifestyle, high burden of oral conditions and non-optimal use of preventive dentistry may mean the Indigenous community is more vulnerable to acquiring such high-risk conditions. Therefore, my project evaluated this association by conducting a cross-sectional study among high-risk Indigenous South Australians while adjusting for certain sociodemographic, maladaptive and sexual behaviours (see Chapter 4).

1.8 Impact of social determinants on the oral health outcomes and oral health-related quality of life

Oral health-related quality of life (OHRQoL) is a relatively new but rapidly growing concept that has emerged over the past two decades to evaluate the physical, psychological, and social impact of oral conditions on an individual (84). Notably, the US Surgeon General reported that oral conditions could "undermine self-image and self-esteem, discourage normal social interaction, because other health problems, lead to chronic stress and depression, and incur a great financial cost. They may also interfere with vital functions such as breathing, food selection, eating, swallowing and speaking, and with activities of daily living such as work,

school, and family interactions" (85). Therefore, evaluating oral health-related quality of life is important to understand the multidimensional effect of functional factors, psychological factors, social factors, and experience of pain or discomfort related to an oral disease such as dental caries, periodontitis, and oral cancers (86).

OHRQoL assessment also helps identify and prioritize common oral health problems, facilitates communication, promotes early screening and decision-making, and ongoing monitoring (87). Indigenous Australians are known to experience a disproportionate burden of oral disease because of oral-health disparities (17, 88). These disparities are strongly associated with social, economic, cultural, and political inequities (89). A range of factors has been described as contributing to poor social and emotional well-being among Indigenous Australians. These include social determinants of health such as poor education, employment, income, housing, racism, and connection to culture (90).

Racism is recognised as an important social determinant of health. Racism is defined as – the inequitable distribution of opportunity, benefit, or resources across ethnic/racial groups expressed through attitudes, beliefs, behaviours, norms, and practice; and has been reported as being highly prevalent among Indigenous Australians (91). Racism is a major impediment to optimal Indigenous Australians' health and healthcare; it affects the individual's general health, and data is emerging on how it adversely affects oral health (14, 92). Details of these are described below.

Racism can cause chronic stress and create a distrust of healthcare providers, which negatively affects an individual's health (93). Racism can also act on institutional, personal, and internal levels to influence health outcomes (94). Racism could lead to unfair distribution of goods, services, and opportunities, leading to unfair and differential access to health-promoting resources (95). Moreover, implicit racial biases and racial stereotypes could influence healthcare providers' choice of management and treatment (96, 97). Racism could affect an individual's health by imposing psychological and physiological changes (98, 99).

As OHRQoL enables examination of the impact of oral health on psychological, functional, and social functioning and as the experience of racism also impose psychological and physiological health changes, it is not unlikely that racism could also negatively impose OHRQoL (98-100). Despite reporting the strong impact of racism on oral health (14, 89, 101), the impact of racism on OHRQoL is not well reported among Indigenous Australians. As the Indigenous population has higher rates of oral diseases and experiences more racism compared

to the non-Indigenous population, my project evaluated impacts of racism on OHRQoL by conducting a cross-sectional study among high-risk Indigenous South Australians to inform health and social policy to address racial discrimination and its resulting oral health inequalities (See Chapter 4).

1.9 Experiences of and the factors influencing Indigenous people's use of oral healthcare

Across the life span of Indigenous Australians, the basic requirements to support good oral health include adequate tooth brushing, avoiding sticky and sugary foods and beverages, adequate fluoride intake, visiting a dentist regularly, and avoiding tobacco and alcohol are lacking (102). Achieving these requirements requires adequate oral health literacy as well as access to timely and culturally relevant oral healthcare. Despite collective efforts to promote health equity in Australia, there is still a significant disparity related to oral health diseases among Indigenous and non-Indigenous Australians. Most oral health issues could be prevented by a supportive environment, availability, access to preventive care, providing financial support to access oral healthcare services, reinforcing the importance of oral health, disseminating accessible oral health information, and keeping the community up-to-date with new advancements in oral healthcare (14, 103). To achieve this, strategies are needed to address poor oral healthcare infrastructure, understaffed public services, language barriers, cultural inappropriateness and experiences of racism and prejudice that could negatively affect health-seeking behaviours and access to care by the Indigenous community (104-106).

To date, very few studies have assessed Indigenous peoples' dental care experiences in South Australia (106-108). Some of the qualitative studies focused on women and children's' unmet oral needs and oral health awareness (107, 108) while others highlighted most of the sociodemographic determinants impacting oral health of Indigenous communities (106). These studies highlighted the importance of involving Indigenous health workers in planning oral healthcare strategies and polices. My Ph.D. aims to build upon the findings of current studies and to gain insight into Indigenous peoples' experiences of oral healthcare and barriers that prevent them from seeking oral healthcare and explore the unmet needs of the Indigenous community living in South Australia.

Mainstream health services, particularly oral health services often fail to adequately meet the needs of Indigenous peoples (109) and therefore Aboriginal Community Controlled Health Services (ACCHS) were established to overcome the pitfalls of mainstream health services

(110). ACCHS are run by Indigenous health workers, and they catalyse health service provision and outcomes for Indigenous people (111, 112). However, involvement of Indigenous health workers in oral health preventive programs and promotions has been sporadic due to lack of training and the knowledge gap between Indigenous health workers and mainstream oral health services (113). Given the high burden of oral health diseases and various unmet needs of Indigenous communities, it is important that oral health models of care involve Indigenous health workers' perspectives and suggestions so that equitable service provision that aligns with Indigenous values could be planned.

Indigenous health researchers were involved during data collection and throughout guided my Ph.D. project.

1.10 Aims and objectives within this thesis

Initially, at the outset of my Ph.D., I wanted to undertake the following aims:

1. To examine the strength and quality of the evidence concerning periodontitis, oral HPV infection and OPSCC;
2. To assess the validity of a self-reported periodontal disease assessment against the current gold standard clinical assessment among Indigenous South Australian adults;
3. To examine the association between self-reported periodontitis and oral high and low-risk HPV infection among Indigenous South Australian adults; and
4. To conduct a national survey of oral health professionals to ascertain current awareness of HPV-related OPSCC and current practices surrounding OPSCC screening.

Aims 2 and 4 were revised in the month of March 2020 amid COVID-19 restrictions, and the Adelaide Graduate Research School approved the changes. Because of the COVID-19 circumstances, fieldwork that was essential for two aims of my Ph.D. were delayed and I was not able to conduct any dental examinations. The initial plan was to validate the self-reported questionnaire in the 12-month follow up of an existing cohort study of Indigenous South Australians and then use that questionnaire for assessing the status of periodontitis and possible associations with HPV in the subsequent 24-month follow up. However, as fieldwork had

ceased, I assessed periodontitis through self-reported questionnaires only (note this has been validated among non-indigenous Australians). In addition to delays in fieldwork, I was not able to undertake objective 4, which was to assess the knowledge of dentists related to periodontitis and oncogenic HPV, as many dental clinics had closed or offered only limited services due to coronavirus. Thus, my supervisors suggested it was not an appropriate time to be conducting a national survey to assess awareness among oral health professionals regarding HPV related OPSCCs. Therefore, I had to modify my Ph.D. aims and objectives and to incorporate changes in my proposal.

My revised aims were:
Aim 2: To examine if self-reported racism is a risk indicator of OHRQoL among Indigenous South Australian adults
Aim 4: To develop and validate a risk assessment tool to predict the presence of HPV associated with OPSCC.

In the month of August 2020, due to the growing pandemic and extended associated lockdowns, I had to modify my aims and objectives further. Fieldwork that was essential for the revised aim 4 was delayed until further notice; therefore, I was not able to develop and validate a risk assessment to predict the presence of oral HPV infection. My supervisors suggested having interviews via video conferencing with Indigenous adults to better understand their unmet needs related to oral health and their oral health-seeking behaviors. Therefore, I revised my aims once again and added some novel research areas to enrich my Ph.D. proposal.

The revision in the thesis included the following projects that incorporated quantitative and qualitative methodologies to provide in-depth and high-quality evidence.

1. To examine the strength and quality of the evidence concerning periodontitis, oral HPV infection and OPSCC;
2. To examine the association between self-reported periodontitis and oral high and low-risk HPV infection among Indigenous South Australian adults;
3. To examine if self-reported racism is a risk indicator of OHRQoL among Indigenous South Australian adults; and
4. To explore experiences of and the factors that influence Indigenous people's

use of oral healthcare.

1.11 Theoretical framework

It has been postulated that persistent infection with HPV can lead to oncological changes in the head and neck region. Studies have proposed that infected periodontal pockets and tissue within the oral cavity allow HPV infection to remain latent for many years and cause oncological changes in the surrounding tissues. Our current knowledge about the exact mechanisms and possible synergistic relationships between periodontitis, HPV infection, and OPSCC is still unclear. Current thinking revolves around two hypotheses: (1) periodontal tissue might serve as a reservoir for oral HPV infection, and (2) other chronic tissue inflammation might perpetuate an infection with oral HPV. We are using this model of biological plausibility to understand the association of periodontitis with persistent HPV infection as treatment of periodontitis could plausibly moderate the transmission and persistence of HPV infection, in turn reducing the risk of OPSCC.

With respect to the qualitative study framework formulated by Patrick and colleagues suggesting different level of barriers at individual, interpersonal, community and macro-level factors was used (114).

CHAPTER TWO: Methods

2.1 Preamble

This chapter outlines the different methodologies used for evaluating each aim. The analytical approaches are briefly explained.

2.2 Methods for Aim 1: Systematic review

The systematic review followed PRISMA guidelines for developing a review protocol and was registered with PROSPERO prior to commencement. Eligibility criteria included all observational studies (including cohort and case-control studies), including prospective and retrospective designs that reported an association between periodontitis and oral HPV infection among adults. Studies based on secondary evidence, such as systematic reviews, were excluded from the search.

We included all studies that assessed periodontitis clinically, radiographically, or through self-report. Information about relevant covariates (e.g., age, gender, smoking/alcohol use, oral cancer history) was extracted to assess potential confounding.

Our primary outcome was oral HPV infection, either any or persistent infection (as defined by the authors). We included all studies that assessed high-risk strains of HPV related to the oral cavity, including HPV 16 and HPV 18, either self-collected (e.g., oral swab or rinse) or by tissue biopsy and detected using polymerase chain reaction. Our secondary outcome was OPSCC.

A detailed search strategy was devised and used to search PubMed, EMBASE, Scopus, Web of Science, and Google Scholar. Titles and/or abstracts of studies retrieved using the search strategy and two review authors to identify studies that met the inclusion criteria screened those from additional sources independently. Two review team members retrieved the full text of these potentially eligible studies and independently assessed for eligibility. Any disagreement over the eligibility of particular studies was resolved through discussion with a third reviewer. A data extraction form was developed to assess study quality and evidence synthesis. The risk of bias was assessed using tools established by the National Heart, Lung and Blood Institute (NIH) (115) for observational and experimental studies. The quality of evidence for each outcome was assessed using the Grading Of Recommendations, Assessment, Development

And Evaluation (GRADE) approach (116), which results in an assessment of the quality of a body of evidence as one of four grades:

1. High quality: further research is unlikely to change our confidence in the estimate of effect.
2. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low quality: further research is very likely to impact our confidence in the estimate of effect and is likely to change the estimate.
4. Very low quality: we are very uncertain about the estimate.

A meta-analysis was undertaken to calculate a pooled odds ratio (OR) and 95% confidence interval (CI) using a random-effects model.

2.3 Methods for Aims 2 and 3: Cross-sectional studies

The two cross-sectional studies conducted in this thesis were part of a national project, 'Human Papillomavirus and Oropharyngeal Cancer among Indigenous Australians' (HPV-OPC), funded by the National Health and Medical Research Council (NHMRC). Led by the University of Adelaide, the project also involved researchers from the Menzies School of Health Research (Darwin), Aboriginal Health Council of South Australia (Adelaide), Yaitya Purruna Indigenous Health Unit (Adelaide), Aboriginal Health Division Women's and Children's Health Network (Adelaide), Pika Wiya Health Service Inc. (Port Augusta), Wardliparingga Aboriginal Research Unit, South Australian Health & Medical Research Institute (Adelaide), School of Health Sciences (University of South Australia, Adelaide), Griffith University (Gold Coast), Cancer Council of New South Wales (Sydney) and QIMR Berghofer Medical Research Institute (Brisbane) (117). An Indigenous Reference Group governed this study. All stages of the project were discussed with the Indigenous Reference Group, with suggestions from members being considered with equal weighting as those from the Investigator and Supervisors. The authors sincerely acknowledge and appreciate all that this Reference Group does. Strong community engagement of Indigenous researchers helped in smooth data collection, management and follow-ups of study participants.

At baseline, n=1011 Indigenous South Australian adults were recruited between March 2018 and February 2019 from Port Augusta, Whyalla, Port Lincoln, Port Pirie, Mount Gambier, Ceduna, and Adelaide. Census data indicates that approximately 22,000 Indigenous adults

reside in these areas. The investigators have a 13-year relationship with key Indigenous stakeholder groups in these locations, who were willing and excited to be part of the study. Recruitment strategies were based on those successfully implemented in the past, such as distributing flyers, giving presentations in the community, advertising in the local newspaper and radio channels, snowballing, and involving Indigenous community leaders and health professionals. The inclusion criteria of this project included being aged 18 years and above, identify as Aboriginal and/or Torres Strait Island people, and intending to live in South Australia (SA) for the next five years.

Briefly, this study involved testing the carriage of high-risk HPV strains in the mouth and oropharynx by collecting serial saliva samples at baseline and 12 and 24 months after recruitment. Along with assessing HPV strains, this study also aimed to collect information on sociodemographic characteristics and health-related behaviours, including tobacco and alcohol use. Information indicating oral health status and use of dental services was also collected, along with information on oral health-related quality of life. Information was additionally collected on aspects of cultural identity to assess the impact of social determinants including racism. At the planned 12-month follow-up, eight periodontitis screening questions previously validated among non-Indigenous Australians in the Australian National Survey of Adult Oral Health (2004-2006) were added to assess self-reported periodontitis in this cohort.

For Aim 2, self-reported periodontitis status was assessed, and any association of periodontitis with oral HPV infection was studied. Logistic regression analyses were undertaken to determine the association between self-reported periodontitis and oral HPV infection with adjustment for potential sociodemographic and behavioural confounders, with estimates presented as OR and 95% CI.

Likewise, for Aim 3, OHRQoL was captured using the Oral Health Impact Profile (OHIP-14) questionnaire (118). We defined the dependent variable ’poor OHRQoL’ as the presence of one or more OHIP-14 items rated as ‘very often’ or ‘fairly often.’ Experiences of racism were recorded using the Measure of Indigenous Racism Experiences instrument (119). Interpersonal racism was classified into two categories (‘no racism’ vs. ‘any racism in ≥ 1 setting’) and three categories (’no racism’, ’low racism’ (experienced in 1–3 settings), and ’high racism’ (experienced in 4–9 settings)). Logistic regression was used to examine associations between interpersonal racism, covariates, and OHRQoL, adjusting for potential confounding related to socioeconomic factors and access to dental services.

2.4 Methods for Aims 4: Qualitative Study

This qualitative study was also part of a more extensive study examining oral HPV infection among Indigenous South Australians. Participants aged 18 and above were included if they identified as Aboriginal and or Torres residing in SA, and were willing to give an interview. Participants' information was taken from the parent study. Selected participants from the parent study were offered to participate and these were sampled to give variation with respect to study site, gender and age group. Two interviewers (one Indigenous- J Hedges and one non-Indigenous- A Ali) with extensive experience working with Indigenous Australians conducted the interviews. The interviewers spent much time developing a rapport with the participant. Once the participant provided signed informed consent, the formal interview was conducted. The Indigenous interviewer was there in person with the study participant, while the non-Indigenous interviewer joined the participant remotely via video conferencing services. Thematic analysis of the transcription was planned. Themes representing the Indigenous community's rooted assumptions, beliefs, perceptions, and barriers that became the base of participants' perceptions of their own oral health and experiences with the oral health professionals along the life course were created. The framework, formulated by Patrick and colleagues was used to identify barriers at the individual (proximal), interpersonal (immediate), community (intermediate) and macro (distal) levels.

2.5 Funding and ethics

The project was funded by the National Health and Medical Research Council Grant funding - APP1120215. Ethics approval was obtained from the University of Adelaide Human Research Ethics Committee (H-2016-246) and the Aboriginal Health Council of South Australia (04-17-729).

CHAPTER THREE: A systematic review and meta-analysis of the association between periodontitis and oral high-risk human papillomavirus infection

3.1 Preamble

This chapter contains the first study of the thesis, which comprises a systematic review of 13 studies exploring the association between periodontitis, oral high-risk HPV and OPSCC. This review provides important foundational evidence for the other chapters in this thesis as the results reported a positive association between periodontitis and oral HPV infection. However, further studies are needed in vulnerable populations so that tailored and culturally safe preventive approaches can be planned.

This chapter has been published in the Journal of Public Health and is available in publication format in Appendix 3.

3.2 Statement of Authorship

Title of Paper	A systematic review and meta-analysis of the association between periodontitis and oral high-risk human papillomavirus infection
Publication Status	Published – 2020
Publication Details	**Ali A,** Lassi ZS, Kapellas K, Jamieson L, Rumbold AR. A systematic review and meta-analysis of the association between periodontitis and oral high-risk human papillomavirus infection. Journal of Public Health. 2020 Sep 11.

Principal Author

Name of Principal Author (Candidate)	Anna Ali
Contribution to the Paper	Acquiring data, knowledge, analysis, drafting
Overall Percentage (%)	70%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	**Date 29 June 2022**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Zohra S Lassi
Contribution to the Paper	Conceptualisation, acquiring data, analysis, drafting
Signature	**Date 29 June 2022**

Name of Co-Author	Kostas Kapellas
Contribution to the Paper	Conceptualisation, drafting
Signature	**Date 29 June 2022**

Name of Co-Author	Lisa Jamieson
Contribution to the Paper	Conception, knowledge, drafting
Signature	**Date 29 June 2022**

Name of Co-Author	Alice Rumbold
Contribution to the Paper	Supervised development of work, Conception, knowledge, drafting and editing
Signature	**Date 29 June 2022**

A systematic review and meta-analysis of the association between periodontitis and oral high-risk human papillomavirus infection

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3.3 Abstract

Background: The incidence of human papillomavirus (HPV)-related oropharyngeal squamous cell carcinomas (OPSCCs) is increasing globally. Common oral conditions such as periodontitis may contribute. We undertook a meta-analysis to quantify the association between periodontitis, oral HPV and OPSCCs.

Methods: Multiple electronic databases were searched until 12 February 2020. Studies conducted in males and/or females aged ≥ 18 years that examined periodontitis, periodontal procedures, oral HPV infection, and where possible, oral cancers, were eligible. Meta-analyses were conducted and the GRADE approach was used to examine the quality of evidence.

Results: Of 2709 studies identified, 13 met the eligibility criteria. Five studies could be included in the meta-analyses. There was no significant increase in the odds of high-risk oral HPV infection among individuals with confirmed periodontitis (odds ratio 4.71, 95% confidence interval 0.57–38.97). Individuals with periodontitis had a 3.65 times higher odds of having any type of oral HPV infection compared with those without periodontitis (95% confidence interval 1.67–8.01). The overall body of evidence was rated as low to very-low certainty.

Conclusion: Meta-analysis confirms there is a positive association between periodontitis and oral HPV infection, although the overall quality of this evidence is low. Evidence for an association between periodontitis and high-risk oral HPV infection is inconclusive.

Keywords: periodontitis, papillomaviridae, oropharyngeal squamous cell carcinoma

3.4 Introduction

Oropharyngeal squamous cell carcinomas (OPSCCs) include cancer in the oral cavity (throat, tonsils, tongue) and pharynx (120). Dental practitioners, as well as general health practitioners commonly diagnose OPSCCs. In the past, tobacco smoking and consumption of alcohol have been the major risk factors for OPSCCs, with other known risk factors including being male, older age, immunocompromised and/or infected with Candida or bacterial flora (121).

The past decade has witnessed a dramatic change in the epidemiology of OPSCCs, with a reduction in OPSCCs caused by tobacco and a steady increase of this cancer among younger age groups, primarily due to oncogenic human papillomavirus (HPV) infection (34, 122). Increases have been reported in many countries (34, 122, 123) and observed in both genders (124, 125). It is estimated that >80% of individuals will be exposed to HPV infection at some point in their lifetime. Oral HPV infection can occur by mouth-to-mouth contact, oral–genital contact and autoinoculation or mother-to-child transmission (126, 127). There are >100 different types of HPVs. Most are asymptomatic, clear rapidly and do not cause malignancies. Two common types, HPV 16 (80%) and 18 (3%) are found in OPSCCs (128, 129). Unlike HPV-negative OPSCCs, HPV-positive OPSCCs are associated with younger age, being male, sexual behaviour and number of sexual partners. Collectively, these factors increase the risk of cancer development by 3–5- fold (130, 131).

Little is known about the carcinogenic process from HPV infection to the development of OPSCCs. Most theories have been extrapolated from studies of cervical cancer, which is strongly associated with oncogenic HPV infection (129, 132).

An emerging hypothesis proposes that persistence of HPV infection in the oral cavity may be facilitated by periodontitis. Periodontitis is the sixth most prevalent oral condition estimated to affect up to 12% of the global population (58). It is a chronic inflammatory disease that affects normal structures of the gingiva, periodontal ligament and alveolar bone (58, 133).

Periodontitis is systemically related to a number of chronic conditions (61, 62). Empirical research suggests there could be an association between periodontitis and OPSCCs, with some studies reporting a 4–10-fold increased risk of OPSCCs among individuals with periodontitis (61). However, the mechanism behind this association is uncertain and the role of local risk factors confounding the association between periodontitis and OPSCCs is under study (61). The presence of high-risk HPV infection in both healthy and diseased periodontium has been reported (63). It has been proposed that the periodontium in closest proximity to the tongue and oropharynx may serve as reservoir for high-risk HPV infection, influencing both the basal cell and host cellular response system (134). To elaborate, among immunocompromised individuals permanent changes in the periodontium are caused by inflammatory responses against periodontal pathogens that result in the formation of pocketing and alveolar bone loss (58, 133). These pockets have the potential to become a constant source of inflammatory cytokines and to alter the local microbiota composition (135). Periodontal pocketing further increases the exposure of basal cells to inflammatory cytokines and microbiota that can accelerate tissue destruction and create conditions that promote colonization and persistence of oral HPV infection. Periodontitis may also modulate the proliferation of HPV and oncogenic expression (E6, E7) in HPV-infected epithelial cells (76, 135-138). It is plausible that periodontitis treatment could moderate the acquisition, transmission and persistence of oral HPV infection and, therefore, the risk of OPSCCs. For this reason, there are an increasing number of studies examining the relationship between periodontitis, oral HPV infection and oral malignancies; however, available studies report conflicting findings (139).

To date, there has been no meta-analysis nor assessment of the quality of this literature. We aimed to undertake a systematic review and meta-analysis to summarize the evidence and quantify the strength of the association between periodontitis and oral HPV infection, and to examine the association between periodontitis, oral HPV infection and OPSCCs. We also aimed to assess if treatment of periodontitis reduces prevalence of oral HPV infection, as this could potentially shed light on new pathways to HPV-related OPSCC prevention.

3.5 Methods

We reviewed all literature published up to 12 February 2020 to identify studies on periodontitis, oral HPV infection and OPSCCs. The review included full-text articles available on EMBASE, Scopus, PubMed, Web of Science, Google Scholar and the Cochrane Central Register of Controlled Trials (CENTRAL). A series of keywords were used to refine the search. The search

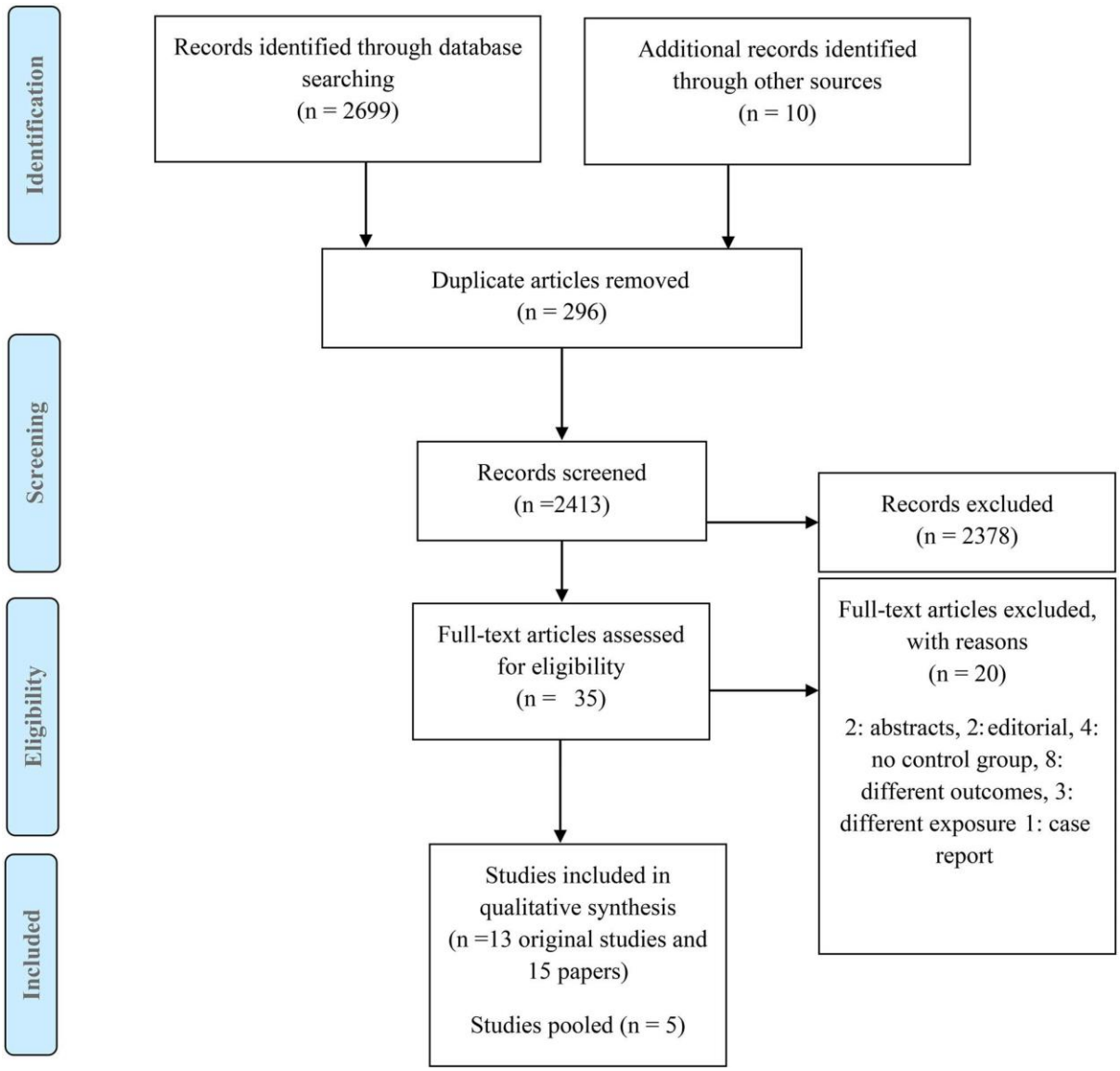
strategy included terms related to: individuals aged 18 years and above, having periodontal disease and being positive for an oral HPV infection (either on its own or as an HPV-positive OPSCC) (Supplementary Table S1). Additional studies were retrieved by manual searching of reference lists from the relevant systematic reviews found during the database search. The systematic review has registered on PROSPERO-CRD42019140645 (140).

Exposure definition: There are different ways of diagnosing periodontitis, with diagnosis depending on the number of teeth, sites examined and severity of disease. We included all studies that assessed periodontitis clinically, radiographically or through self-report (141-144). We also included articles reporting proxy measures of periodontitis to evaluate if any particular proxy measure is strongly linked with oral HPV infection.

Outcomes: The primary outcomes were the prevalence of any oral HPV infection (all types) and oral high-risk HPV infection (types 16 and 18), as determined by the study authors. We also examined the occurrence of OPSCCs as a secondary outcome. Common sites of HPV-related OPSCCs include the base of the tongue, tonsils and tonsillar crypts (145). Our primary comparison was the association between periodontitis and oral HPV infection. We also aimed to examine whether treatment of periodontitis influenced the prevalence of persistent oral HPV infection and development of OPSCCs. Surgical and non-surgical therapies for treating periodontitis such as scaling and root planing, flap surgery and bone and tissue grafts were included. Screening and data extraction Screening was undertaken using the Covidence online platform (146). Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two review authors (Ali A and ZL) to identify studies that potentially met the inclusion criteria. A data extraction form was developed for assessment of study quality and evidence synthesis. Missing data were requested from the study authors. The risk of bias in each study was assessed independently by two reviewers (Ali A and ZL) using the National Heart, Lung and Blood Institute quality assessment tool (115). The quality of the body of evidence concerning the outcomes was assessed using the GRADE approach (116). Meta-analysis was undertaken to calculate a pooled odds ratio (OR) with 95% confidence intervals (CI) and to generate a forest plot of the association between periodontitis and oral HPV infection. Where significant statistical heterogeneity was identified (Chi-square $P < 0.1$ and $I^2 > 50\%$), a random effects model was used. Separate meta-analyses were undertaken to examine the association between periodontitis and any HPV type, and high-risk HPV types, respectively.

We planned to undertake sensitivity analysis by study quality, and subgroup analysis based on study design (case– control, cross-sectional or cohort) as well as severity of periodontitis, proxy measures of periodontitis, age, gender, tobacco usage, smoker and non-smoker, alcohol consumption and sexual behaviours.

Figure 3.5.1: Flow chart of the study



1 Figure 3.5.1: Flow chart of the study

3.6 Results

The initial search identified 2709 studies. Of these, 35 were reviewed in full and 13 studies (15 separate articles) met the inclusion criteria (Fig. 3.5.1, Supplementary Table S2). Of the 13

studies, four were case–control and nine were cross-sectional in design. Of the case–control studies, two were from the USA (73, 135) and one each from Brazil (77) and India (79). Of the eligible cross-sectional studies, three were from the USA (81, 147, 148) and one each from Argentina (83), Australia (80), Austria (76), India (78), Norway (72) and Venezuela (82) (Table 3.6.1).

3.6.1 Periodontitis assessment

Among the case–control studies, two undertook a clinical assessment of periodontitis based on the American Academy of Periodontology (AAP) criteria (77, 79). One study used radiographic assessment (135) and one was based on self-reported periodontitis status (73). Of the cross-sectional studies, seven (76, 78, 80, 82, 83, 139, 148) had a clinical assessment and one (72) used radiographic assessment. One study used self-report together with clinical assessment of periodontitis and proxy measures of periodontitis such as the number of teeth lost and the presence of gum disease (147). In the cross-sectional studies, the prevalence of periodontitis ranged from 20 to 66% (Table 3.6.1). In the four case–control studies of OPSCCs, one39 reported 28% of oral cancer cases had gum disease and 43% had more than five missing teeth, whereas another (135) reported 86% of HPV-positive tumour patients had periodontitis. One study reported that 54% of cases had periodontitis (77), whereas one case–control study included 30 patients with periodontitis and 30 without (79).

Study quality: Quality was assessed to evaluate the internal validity of included studies. Of the four case–control studies, two studies (77, 79) were rated as overall 'fair' quality and the remainder were rated as 'good' (73, 135). Of the cross-sectional studies, three (78, 82, 83) were found to be 'fair' quality and six were rated as good (72, 76, 80, 81, 147, 148). The main methodological limitations in the studies rated as 'fair' related to insufficient information on: (i) sample size, (72, 76, 80, 81, 147, 148) (ii) eligibility criteria (77, 79) (iii) blinding of assessors (72, 76, 80, 81, 147, 148) (iv) exploration of cause and effect relationship (77, 79) and (v) control of confounding (72, 76, 80, 81, 147, 148) (Table 1, Supplementary Tables S3 and S4).

3.6.2 Primary outcome assessment

Ten studies reported high-risk HPV infection (types 16 and/or 18) (73, 77-80, 83, 135) two studies reported on high or low-risk HPV infection types (76, 81) whereas three

studies39,41,46 reported any type of HPV infection without giving further classification. The most common method for detecting HPV infection was DNA extraction along with polymerized chain reaction (PCR) (Table 3.6.1). In two case–control studies of OPSCC patients, high-risk HPV-positive OPSCC was reported in 44%36 and 70% (135) of patients, respectively. Another case–control study (79) reported half of the periodontal pocket samples were positive for high-risk HPV infection. In the remaining case–control study, none of the patients with chronic periodontitis had high-risk HPV infection (77). Among the cross-sectional studies, the prevalence of any type of HPV infection ranged from 8 to 21%, (76, 81, 82, 147, 148) whereas the prevalence of high-risk HPV infection was reported by five studies and ranged from 5 to 67% (72, 76, 80, 81, 83) .

Table 3.6.1: Baseline characteristics of included studies

Study and year	Sample size	Participants	Periodontitis	No periodontitis	Definition of periodontitis	Outcome		Prevalence of periodontitis	Prevalence of HPV	Quality *
						HPV	Definition			
Case-control studies										
Mazul et al. 2017(73)	Cases: 492 Control: 1396	Primary SCC of the oral cavity, pharynx, or larynx Age: 20 to 80 years	Oral health and gum disease	Healthy periodontium	Self-reported	High-risk HPV	CINtec Histology p16INK4a kit from tumour samples DNA extraction and PCR	Gum disease: 30.1% Tooth loss >5: 51.6% Tooth mobility: 35.1%	43.6% had HPV 16 positive cancer	Good
Shipilova et al. 2017[79, 149]	Cases: 30 Control: 30	Pocket and sulcus scraping from dental patients Age: 21-70	Localized chronic periodontitis	No attachment loss	AAP classification	E6, E7 mRNA	E6, 7-mRNA-in situ hybridization and flow cytometry	50.0%	Cases, 50.0% of pocket samples and 36.6% of sulcus samples showed presence of high-risk HPV E6/E7 mRNA	Fair
Horewicz et al. 2009[77]	Cases: 82 Control: 22	Gingival samples from medically fit individuals Age: 21-62 years	Chronic periodontitis and gingivitis	Healthy periodontium	AAP classification	HPV 16	DNA extraction and PCR	53.8%	Not found	Fair
Mine Tezal et al .2009[74, 135]	Cases: 21 Control: 9	Tumor samples from primary squamous cell carcinoma Age: >21 years	Periodontitis	Healthy periodontium	Radiographic assessment	HPV 16 and 18	DNA extraction and PCR	86.0% in HPV-positive	86.0% in HPV-positive	Good
Cross-sectional studies										
Torre et al. 2019 [76]	187	Brush smear from buccal mucosa from patients visiting clinic for 1st time Age: 23-46	Periodontitis	Healthy periodontium	API GBI	Low-risk and high-risk HPV	HPV DNA testing	API Mild: 44.9% Severe: 44.9% GBI Mild: 40.1% Severe: 8.6% Extracted teeth 1-3: 34.25 >3: 17.1%	20.9% any HPV 14.4% high-risk and 13.9% low risk	Good

Farran et al. 2019 [72]	90	Tumour samples from patient undergoing treatment for oropharynx Age: Not reported	Periodontitis	Healthy periodontium	Radiographic assessment	High-risk HPV	HPV DNA testing	Vertical BL: 3.3% Horizontal BL: 53.3% Apical Radiolucency ≥ 2: 15.5% Missing teeth >1: 78.8% Residual root ≥1: 20.0%	64.4% cancers were HPV +	Good
Ortiz et al. 2018[81]	740	Oral rinse samples from participants of San Juan Overweight Adults Longitudinal study Age: 40–65 years	Periodontitis	Healthy periodontium	CDC and AAP classification	Low-risk and High-risk HPV	DNA extraction and PCR	20.3% severe periodontitis	5.7% any HPV, HPV 16:7.1%	Good
Sun et al. 2016[80]	223	Oral rinse samples from patients attending The University of Queensland School of Dentistry Age: 18-90 years	Periodontitis	Healthy periodontium	Clinical examination for plaque, PSR, BOP and DMFT	HPV 16	DNA extraction and PCR	40.5%	4.5% oral HPV 16	Good
Wiener et al. 2015[148]	6004	Oral rinse samples form the participants of NHANES data Age: 30-69 years	Periodontitis	Healthy periodontium	CDC and AAP classification	HPV	PCR	40.3%	7.5% any HPV	Good
Jacob et al. 2014[78]	102	Gingival tissue samples from systemically healthy subjects Age: 15 -70 years	Periodontitis	Surgical crown lengthening for restorative purpose	Pocket depth of ≥5 mm who required flap surgery	HPV 16	DNA extraction and PCR	65.7%	Not found	Fair
Rossello et al. 2014 [83]	30	Non-menopausal women with HPV gynecological diseases Age: 18-50 years	Periodontitis	Healthy periodontium	PI, PD, CAL, BOP	High-risk HPV	PCR	Gingivitis: 40.0% Periodontitis: 36.7%	67.0% HPV 16 —30% from tongue tissues —13.3% from internal	Fair

									periodontal sites —16.7% from external periodontal sites	
Bui et al. 2013 (147)	3,439	Oral rinse samples form the participants of NHANES data Age: 30 years or older	Oral health, proxy of periodontitis	Good oral health	Self-reporting and oral health examination	Low-risk and High-risk HPV	PCR	27.8% poor oral health with 17.5% having gum disease	7.5% any HPV	Good
Escalona C et al. 2011 (82)	34	13 HIV + HAART + perio 7 HIV no HAART+ perio 7 Seronegative +chronic perio 7 Seronegative No perio Age: Not Reported	HIV + HAART+ Periodontitis	No periodontitis	PI, PD, CAL, GB	HPV	DNA extraction and PCR	-	-	Fair

Acronyms: SCC: squamous cell carcinoma, PCR: polymerized chain reaction, AAP: American academy of periodontology, API: Approximal plaque index, GBI: Gingival bleeding index CDC: Centers for Disease Control and Prevention PSR: Periodontal screening record, PI: Plaque index, PD: Pocket depth CAL: Clinical attachment loss, BOP: Bleeding on probing, NHANES: National Health and Nutrition Examination Survey

*For detailed quality assessment refer to table S3 and S4 in supplementary document

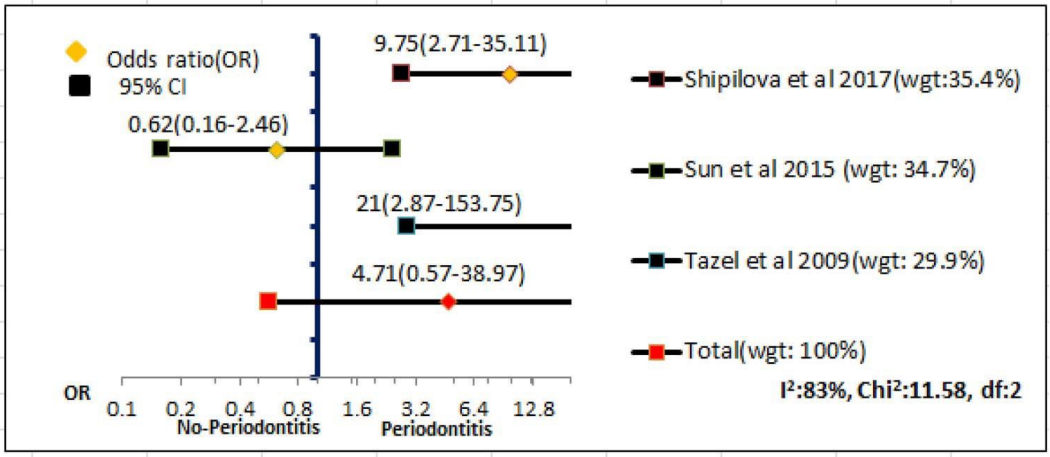
3.6.3 Secondary outcome assessment

Two case–control studies (73, 135) included participants with OPSCCs, detected HPV infection and measured clinical oral health. One cross-sectional study recruited patients who were undergoing treatment for OPSCCs and reported the survival outcome (72). Other cross-sectional studies did not report OPSCC as an outcome. None of the studies reported the effect of treatment of periodontitis on the prevalence/incidence of oral HPV infection.

3.6.4 Association of periodontitis and oral HPV infection

Seven studies (three case–controls and four cross-sectional) reported a positive association between periodontitis and any oral HPV infection (72, 73, 76, 79, 81, 135, 147). Of these, three case–control (73, 79, 135) studies also reported an association with high-risk HPV types and two cross-sectional studies (76, 81) reported an association with high-risk HPV and/or any HPV infection. Only five studies could be included in the meta-analysis (79, 80, 135, 139, 148). There was no clear increase in the odds of oral high-risk HPV infection among individuals with periodontitis (OR 4.71, 95% CI 0.57–38.97, three studies, n = 310) (Fig. 3.5.2).

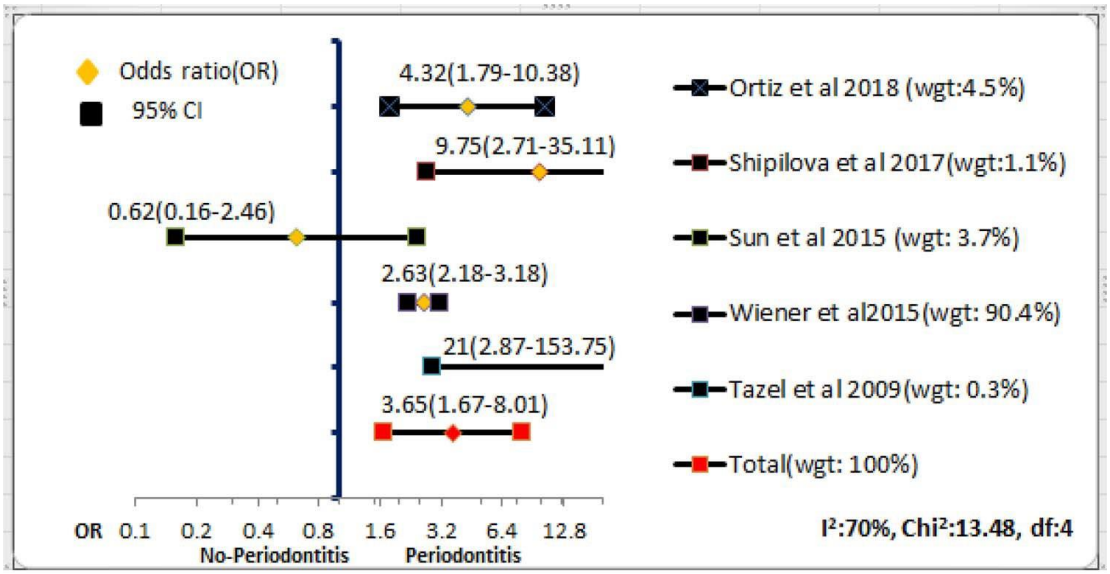
Figure 3.5.2 Meta-analysis of the association between confirmed periodontitis and oral high-risk HPV infection in case–control studies and cross-sectional studies (random effects).



The estimated pooled prevalence of high-risk HPV infection was 34% among those with periodontitis versus 13% in those with no periodontitis. There was a significant increase in the odds of any oral HPV infection among individuals with periodontitis (OR 3.65, 95% CI 1.67–8.01,

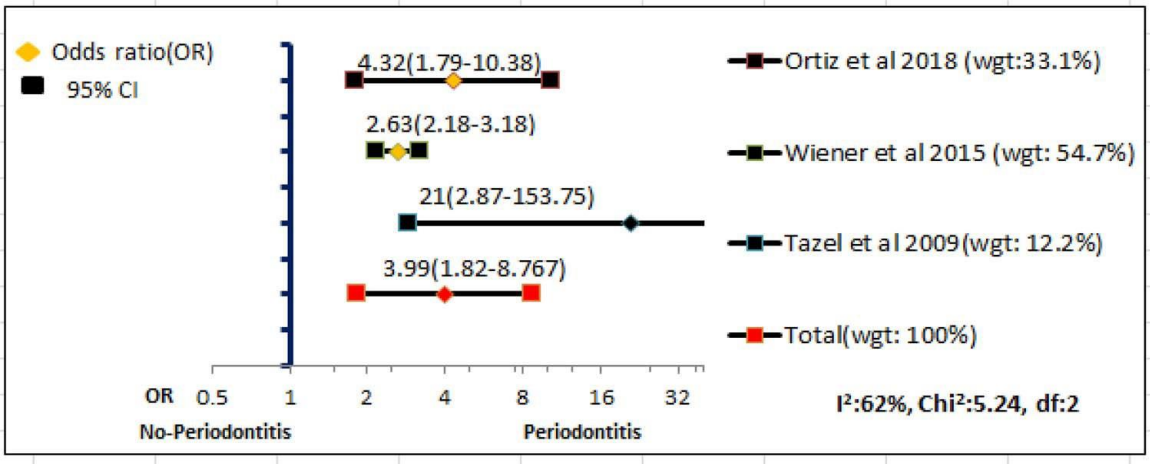
five studies, n = 7054) (Fig. 3.5.3). The estimated pooled prevalence of any type of HPV infection was 13.1% in those with periodontitis versus 5.4% in those without.

Figure 3.5.3 Meta-analysis of the association between confirmed periodontitis and any type of oral HPV infection in case–control and cross-sectional studies (random effects).



There was a significant increase in the odds of any oral HPV infection in individuals with periodontitis in the studies rated good quality (OR 3.99, 95% CI 1.82–8.76, three studies, n = 6774) (Fig. 3.5.4). The estimated pooled prevalence of any type of HPV infection was 12.6% among those rated periodontitis versus 5.1% among those without. However, significant heterogeneity was detected for all comparisons (I^2 = 83, 70 and 62%), respectively, and the overall body of evidence was rated low to very-low certainty using GRADE criteria (Supplementary Tables S5–S7).

Figure 3.5.4 Meta-analysis of the association between confirmed periodontitis and any type of oral HPV infection in case–control and cross-sectional studies rated as good quality.



3.6.5 Subgroup analyses

The planned subgroup analyses could not be undertaken due to insufficient and inconsistent reporting of factors across the included studies.

3.7 Discussion

This is the first meta-analysis of studies examining the relationship between periodontitis and oral HPV infection. Overall, findings from the meta-analysis suggest there may be a 3 to 4--fold increase in the risk of oral infection with any HPV type among individuals with confirmed periodontitis. The meta-analysis findings for high-risk HPV types were inconclusive, with no clear increase demonstrated due to very wide CIs that included a null effect. For both comparisons, there was limited certainty in the overall quality of the evidence. Among the eight studies that did not contribute data suitable for inclusion in the meta-analysis, three reported a positive association between the presence of periodontitis symptoms and high-risk HPV infection (72, 73, 76) in the order of 1.5–9 times higher risk, and a further study (147) found an association with any HPV type. The remaining studies reported no association. Overall, the inconsistent findings reported across available studies indicate the need for further high-quality research to clarify the relationship between periodontitis and oral HPV infection, particularly oncogenic subtypes.

We identified significant statistical heterogeneity in our comparisons concerning any oral HPV infection and high-risk HPV types. Possible reasons for heterogeneity include the differences in baseline characteristics of the sample, the small sample size of many included studies, differences in study design (case–control versus cross-sectional) as well as differences in the assessment of periodontitis and oral HPV status. For example, there were clear differences in baseline risk between included studies, reflected in wide variation in the prevalence of periodontitis (41–86%) and high-risk HPV infection (4.5–70%). Notably, the case–control studies included patients with confirmed OPSCC, whereas many of the cross-sectional studies were population based with some including patients visiting a dental clinic for the first time (76, 80). Comparisons were also limited by variation in the assessment of periodontitis that included clinical (76-83, 148, 149) self-reported (73, 147) and radiographical methods (72, 135, 138). Self-reporting of oral and gum health may be subject to recall and reporting bias that could lead to an over or underestimate of periodontitis.

There was also some variation in the HPV detection methods, and the sensitivity and specificity of detection techniques is known to vary (150, 151). Additionally, included studies sampled different oral sites to examine HPV status, including saliva, diseased gingival and periodontal tissue and tumour biopsies to examine oral HPV status. The use of tissue biopsies (77, 78) in assessing HPV status is a particular limitation as this is site-specific and a negative result does not exclude the presence of the virus in other epithelial sites (152). Overall, 8 of 13 studies were rated as good quality using established quality assessment tools (115). However, using the GRADE approach, which accounts for imprecision of findings, there was low to very-low certainty in the quality of the evidence. Arguably, the biggest limitation of the existing literature is the lack of longitudinal studies, which are required to assess temporality in acquisition of oral HPV infection. Therefore, while there is some evidence of an association between periodontitis and any oral HPV infection, the current body of literature cannot establish whether periodontitis preceded oral infection with HPV and therefore whether the association observed is causal. This should be a priority for future research.

This review also aimed to report the association of periodontitis and oral HPV infection with OPSCCs and the effect of treatment of periodontitis on the prevalence of oral HPV infection, but this could not be evaluated because of insufficient data. Similarly, subgroup analysis were not conducted because of inadequate reporting of subgroup characteristics. Nevertheless, the strong biological plausibility connecting poor oral healthcare and periodontitis with oral HPV infection (134-136) underscores the need to clarify these relationships. Should future research confirm a causal relationship between periodontitis and persistence of oral HPV infection, as periodontitis is highly modifiable, this offers another promising preventive strategy to reduce the burden of high-risk oral HPV infection and potentially OPSCC. This is particularly important as while HPV vaccination programs remain an important OPSCC control strategy, current vaccines offer little protection to individuals who have already been exposed to HPV (153). In addition, current diagnosis of OPSCC relies on patient presentation and oral physical examination plus biopsy. Most OPSCCs are thus diagnosed at a late stage, reflected in the less than optimal survival rates (range 56–75% depending on the specific site) (64). As a result, new approaches to screening are required to permit early detection and management. In the case of HPV-positive OPSCC, it is difficult to identity a population at risk; testing for oral HPV DNA is not recommended, given the ubiquitous exposure to HPV in the population, and the current inability to determine those with HPV

infections who will go on to develop malignant lesions. Confirmation of the role of periodontitis in oral HPV infection and persistence would provide key evidence to guide recommendations about the utility of periodontitis screening to identify individuals at risk of HPV-associated OPSCC, who may benefit from increased surveillance (for example, more frequent oral examinations).

Findings of the review should be considered with caution as the meta-analyses are based on observational studies, predominantly cross-sectional, which are prone to inherent biases. In addition, high heterogeneity was detected in all meta-analyses reflecting a lack of standardized protocols for assessment of periodontitis. There could also be potential biases due to inadequate adjustment for confounders such as age. The meta-analyses are based on a small number of studies that limits the ability to assess publication bias; therefore, small negative studies may be missing. Nevertheless, this review was conducted according to explicit and reproducible methodologies for synthesizing the findings of observational studies. A comprehensive search strategy was used, as were established tools to assess the quality of included studies and overall evidence.

3.8 Conclusion

Our review indicates there is low-certainty evidence of a positive association between periodontitis and any oral HPV infection. Evidence for an association between periodontitis and high-risk oral HPV infection is inconclusive. There was insufficient evidence to examine possible relationships between periodontitis, oral HPV infection and OPSCCs or the impact of periodontitis treatment.

3.9 Supplementary documents

Table S1: Logic grid:

PubMed

PERIODONTITS AND HPV

Periodontitis	**HPV**
"periodontitis"[MeSH Terms] OR periodont*[Text Word] OR “Periodontal Atrophy” [MeSH Terms] OR “Periodontal” [Text Word] OR “tooth loss” [MeSH Terms] OR “tooth loss” [Text Word] OR “tooth migration” [MeSH Terms] OR “tooth migration” [Text Word] “tooth mobility” [MeSH Terms] OR	HPV[Text Word] OR "papillomaviridae"[MeSH Terms] OR “human papillomavirus”[MeSH] OR “human papillomavirus”[Text Word] OR "human papillomavirus 16"[MeSH Terms] OR human papillomavirus 16 [Text Word] OR "human papillomavirus 18" [MeSH Terms] OR human

“tooth mobility” [Text Word] OR “chronic periodontitis” [MeSH Terms] OR “periodontal disease” [MeSH Terms] “marginal periodontium"[MeSH Terms] OR "periodontal ligament" [MeSH Terms] OR "gingiva"[MeSH Terms] OR gingiva* [Text Word] OR "oral health"[MeSH Terms] OR “oral health” [text word] OR "Periodontal Pocket"[MeSH Terms] OR "Root Planing"[MeSH Terms] OR "Subgingival Curettage"[MeSH Terms] OR "Periodontics"[MeSH Terms] OR "Periodontal Debridement"[MeSH Terms] OR “gum disease*”[Text Word] OR chronic*[Text Word]	papillomavirus 18 [Text Word] OR papillomavirus[Text Word]

Logic grid: Embase

Periodontitis	HPV
('periodontium':ti,ab,kw OR 'oral health':ti,ab,kw OR 'periodontitis':ti,ab,kw OR 'periodontal disease':ti,ab,kw OR 'tooth loss':ti,ab,kw OR 'tooth migration':ti,ab,kw OR 'tooth mobility':ti,ab,kw OR 'tooth movement':ti,ab,kw OR 'periodontal pockets':ti,ab,kw OR 'periodontal procedure':ti,ab,kw OR 'root planing':ti,ab,kw OR 'dental debridement':ti,ab,kw	('human papillomavirus type 16':ti,ab,kw OR 'human papillomavirus type 18':ti,ab,kw OR 'wart virus':ti,ab,kw OR 'oral human papillomavirus infection':ti,ab,kw OR 'hpv':ti,ab,kw)

Logic grid: Scopus

Periodontitis	HPV
TITLE-ABS-KEY (periodontitis) OR TITLE-ABS-KEY (Periodontal Atrophy) OR TITLE-ABS-KEY (tooth loss) OR TITLE-ABS-KEY (tooth migration) OR TITLE-ABS-KEY (tooth mobility) OR TITLE-ABS-KEY (chronic periodontitis) OR TITLE-ABS-KEY (periodontal disease) OR TITLE-ABS-KEY (tooth movement) OR TITLE-ABS-KEY (gingivitis) OR TITLE-ABS-KEY (alveolar bone loss) OR TITLE-ABS-KEY (periodontal pockets) OR TITLE-ABS-KEY (Root Planing) OR TITLE-ABS-KEY (Subgingival Curettage) OR TITLE-ABS-KEY (Periodontics) OR	TITLE-ABS-KEY (HPV) OR TITLE-ABS-KEY (papillomaviridae) OR TITLE-ABS-KEY (human papillomavirus) OR TITLE-ABS-KEY (human papillomavirus type 16) OR TITLE-ABS-KEY (human papillomavirus type 18)

TITLE-ABS-KEY (Periodontal Debridement) OR TITLE-ABS-KEY (Periodontal Procedure)	

Logic grid: Web of science

Periodontitis	HPV
TOPIC: (periodontitis OR oral health OR gingivitis OR Periodontal Atrophy OR chronic periodontitis OR periodontium OR Periodontal Pocket OR tooth migration OR tooth mobility OR tooth loss OR periodontal OR periodontal disease OR Root Planing OR Subgingival Curettage OR Periodontics OR Periodontal Debridement)	**TOPICS:** (HPV OR human papillomavirus OR human papillomavirus type 16 OR human papillomavirus type 18 OR Oral HPV OR wart virus)

Table S2: Reasons for exclusion

Printz C 2013	Letter to the editor
Gum disease and HPV up risk for cancer	
Rosenquist et al 2005	Abstract only
Farsi et al 2012	
Madinier et al 1992	No control group
Saglam et al 1996	
Parra and Slots 1996	
Hormia et al 2005	
Bui et al 2015	Case report
Bustos et al 2001	Different exposure
Gillison et al 2017	
Chaturvedi AK et al 2018	
McDaniel JT et al 2020	Outcomes of interest not reported
Contreras A et al 1996	
Contreras A et al 1999	
Contreras A et al 1999	
Contreras A et al 2000	

Saygun et al 2002	
Yapar et al 2003	

Table S3: Quality assessment by NIH scale for case-control studies

Study and year	Research question or objective clearly stated and appropriate	Study population clearly specified and defined	Sample size justification	Controls selected or recruited from the same or similar population that gave rise to the cases	Definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented	Cases clearly defined and differentiated from controls	If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible	Was there use of concurrent controls	Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case	Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants	Were the assessors of exposure/risk blinded to the case or control status of participants	Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis
Case-control												
Mazul et al. 2017(73)	Yes	Yes	NR	No	Yes	Yes	Yes	No	NR	Yes	NR	Yes
Shipilova et al. 2017(79, 149)	Yes	Yes	NR	Yes	Yes	Yes	No	No	NR	Yes	NR	NA
Horewicz et al. 2009(77)	Yes	Yes	NR	Yes	Yes	Yes	No	NR	NR	Yes	NR	NA
Mine Tezal et al .2009(74, 135)	Yes	Yes	NR	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	Yes

Table S4: Quality assessment by NIH scale for cross-sectional studies

Study and year	Search question or objective in this paper clearly stated	Study population clearly specified and defined	Participation rate of eligible persons at least 50%	Subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants	Sample size justification, power description, or variance and effect estimates provided	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed	Exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure,	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	Was the exposure(s) assessed more than once over time	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	Were the outcome assessors blinded to the exposure status of participants	Was loss to follow-up after baseline 20% or less	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and
Cross-sectional studies														
Torre et al. 2019 (76)	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	NA	Yes	NR	NR	Yes
Farran et al. 2019 (72)	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	NA	Yes	Yes	NR	Yes
Ortiz et al. 2018(81)	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	NA	Yes	NR	NR	Yes
Sun et al. 2016(80)	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes	YEs	NA	Yes	Yes	NR	NA
Wiener et al. 2015(148)	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	NA	Yes	NR	NR	Yes
Jacob et al. 2014(78)	Yes	Yes	Yes	yes	NR	Yes	NR	No	Yes	NA	Yes	NR	NA	NA
Rossello et al. 2014 (83)	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	NA	Yes	NR	NA	NA
Bui et al. 2013 (147)	Yes	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	NA	Yes	NR	NA	Yes
Escalona C et al. 2011 (82)	Yes	Yes	Yes	Yes	NR	Yes	NR	No	Yes	NA	Yes	NR	NA	NA

Table S5: GRADE estimation: periodontitis compared to no periodontitis for indicating at risk patients for high-risk HPV in case-control and cross-sectional studies

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no periodontitis	With periodontitis	Relative effect (95% CI)	Risk with no periodontitis	Risk difference with periodontitis
HPV											
310 (3 observational studies) (79, 80, 135)	serious [a]	serious [b]	not serious	serious [c]	all plausible residual confounding would reduce the demonstrated effect	⨁◯◯◯ VERY LOW	22/171 (12.9%)	47/139 (33.8%)	**OR 4.71** (0.57 to 38.97)	129 per 1,000	**282 more per 1,000** (from 51 fewer to 723 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Shipilova et al 2017 (79): Convenient sampling with very small sample size and unadjusted results were reported. Sun et al 2015 (80): Did not report adjusted results. Variation in the sample size and study design could also introduce the risk of bias. Moreover, periodontitis was assessed differently in the included studies, for example Tezal et al 2009 (135) measured it radiographically while Shipilova et al 2017 (79) used the AAP classification and Sun et al 2015 (80) used different parameters for the diagnosis of periodontitis.

b. Sun et al 2015 (80): Did not support the hypothesis and reported no association of HPV with periodontitis. The other two studies reported a positive association (79, 135).

c. Two studies (Shipilova et al 2017 and Sun et al 2015) (79, 80) reported unadjusted results and the sample size and number of events varied in all three studies (79, 80, 135).

Table S6: GRADE estimation: periodontitis compared to no periodontitis for indicating at risk patients for any type of HPV in case-control and cross-sectional studies

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no periodontitis	With periodontitis		Risk with no periodontitis	Risk difference with periodontitis
HPV											
7054 (5 observational studies) (79-81, 135, 148)	serious [a]	serious [b]	not serious	serious [c]	all plausible residual confounding would reduce the demonstrated effect	⨁⨁◯◯ LOW	217/4053 (5.4%)	392/3001 (13.1%)	**OR 3.65** (1.67 to 8.01)	54 per 1,000	**118 more per 1,000** (from 33 more to 258 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Shipilova et al 2017 (79): Very small convenience sample and unadjusted results are reported. Ortiz et al 2018 (81). : Recruited Hispanic adults' data from a longitudinal study and estimated risk based on any type of oral HPV infection. Sun et al 2015: Did not report adjusted results. Variation in the sample size and study design could also introduce risk of bias (80). Moreover, periodontitis was assessed differently in the included studies for example, Tezal et al 2007 (135) measured it radiographically, while Shipilova et al 2017 (79)and Wiener et al 2015 (148) used the AAP classification and Sun et al 2015 (80) used different parameters for the diagnosis of periodontitis.

b. Two cross-sectional studies by Sun et al 2015 and Wiener et al 2015 did not support the hypothesis and reported no association of HPV with periodontitis (80, 148). Ortiz et al reported an association with any type of oral HPV but not with high-risk and low-risk HPV (81).

c. Two studies (Shipilova et al 2017 and Sun et al 2015) (79, 80) reported unadjusted results only. Moreover, the sample size and number of events varied in all studies. Of five included studies three were cross-sectional and two were case-control and this variation in study design could impact the precision. Thus precision is questionable.

Table S7: GRADE estimation: periodontitis compared to no periodontitis for indicating at risk patients for any type of HPV in case-control and cross-sectional studies rated as good quality

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no periodontitis	With periodontitis		Risk with no periodontitis	Risk difference with periodontitis
HPV											
6774 (3 observational studies)(81, 135, 148)	serious [a]	serious [b]	not serious	serious [c]	all plausible residual confounding would reduce the demonstrated effect	⨁⨁◯◯ LOW	198/3892 (5.1%)	363/2882 (12.6%)	**OR 3.99** (1.82 to 8.76)	**Moderate**	
										53 per 1,000	**130 more per 1,000** (from 40 more to 277 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Ortiz et al 2018 (81): Recruited Hispanic adults' data from a longitudinal study and estimated risk based on any type of oral HPV status. Moreover, periodontitis was assessed differently in the included studies for example Tezal et al 2009 (135) measured it radiographically while Wiener et al 2015 (148) used the AAP classification.

b. Wiener et al 2015 (148) did not support the hypothesis and reported no association of HPV with periodontitis. Ortiz et al (148) reported the association with any type of oral HPV but not with high-risk and low-risk HPV. While Tazel et al reported the association with high-risk HPV (135).

c. Variation in the sample size and study design could also lead to imprecision.

CHAPTER FOUR: Association between self-reported periodontitis and high-risk oral human papillomavirus infection among Indigenous South Australians: a cross-sectional study

4.1 Preamble

This chapter contains the second study of the thesis, which comprises a cross-sectional study among Indigenous South Australians assessing the relationship between periodontits and high-risk oral HPV infection. This study could not find any significant associations, but given the high burden of both high-risk oral HPV and periodontitis in this population, targeted studies in such high-risk populations to identify individuals at risk of carrying high-risk oral HPV infection are warranted.

This chapter has been published in Plos One and is available in publication format in Appendix 4.

4.2 Statement of Authorship

Title of Paper	Association between self-reported periodontitis and high-risk oral human papillomavirus infection among Indigenous South Australians: A cross-sectional study
Publication Status	Published – 2022
Publication Details	**Ali A**, Rumbold AR, Kapellas K, Lassi ZS, Hedges J, Jamieson L. Association between self-reported periodontitis and high-risk oral human papillomavirus infection among Indigenous South Australians: A cross-sectional study. Plos One. 2022 Mar 24;17(3):e0265840.

Principal Author

Name of Principal Author (Candidate)	Anna Ali
Contribution to the Paper	Acquiring data, knowledge, analysis, drafting
Overall Percentage (%)	70%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature	**Date 29 June 2022**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Alice Rumbold
Contribution to the Paper	Supervised development of work, Conception, knowledge, drafting and editing

Signature	**Date 29 June 2022**

Name of Co-Author	Kostas Kapellas
Contribution to the Paper	Conceptualisation, drafting

Signature	**Date 29 June 2022**

Name of Co-Author	Zohra S Lassi
Contribution to the Paper	Conceptualisation, drafting and editing
Signature	**Date 29 June 2022**

Name of Co-Author	Joanne Hedges
Contribution to the Paper	Conception, data collection, knowledge, drafting and editing
Signature	**Date 29 June 2022**

Name of Co-Author	Lisa Jamieson
Contribution to the Paper	Supervised development of work, Conception, knowledge, drafting and editing
Signature	**Date 29 June 2022**

Association between self-reported periodontitis and high-risk oral human papillomavirus infection among Indigenous South Australians: a cross-sectional study

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4.3 Abstract

Background: The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing globally, reflecting an increase in human papillomavirus (HPV)-related lesions. Indigenous populations are disproportionately affected by OPSCCs. Currently, testing for oral HPV is not recommended as a screening tool to permit early detection of OPSCCs due to the high population prevalence of HPV infection. Periodontitis may be a marker of oral HPV infection, but previous research evaluating this association has been inconclusive. Here we report a large population-based study examining the association between high-risk oral HPV infection and periodontitis among Indigenous South Australians.

Methods: We utilised a large convenience sample of Indigenous South Australians aged 18+ years recruited between February 2018 and February 2020. Of the original cohort (n = 1011), 748 (73.9%) participants participated in the 12 month follow-up. Detailed information on sociodemographic characteristics, health-related behaviours, and sexual history were collected at enrolment. Saliva samples were collected at 12 months and tested for the presence of oral HPV DNA using the optimized general primer (GP) + PCR system. The primary outcomes were the prevalence of any high-risk oral HPV DNA, and separately, HPV 16 and/or 18. Periodontitis was assessed at follow-up by using validated self-reported periodontitis screening questions. Logistic regression analyses were undertaken to assess the association between self-reported periodontitis and oral HPV infection with adjustment for potential sociodemographic and behavioural confounders, with estimates presented as odds ratios (OR) and 95% confidence interval (CI).

Results: Data on 673 participants (89.9% of the follow-up cohort) were available. Participants ranged in age from 18 to 80 (mean age 42.2, SD 14.7) and 31.5% were male. Overall, 115 (17.1%) participants had self-reported periodontitis, 40 (5.9%) had any high-risk oral HPV and 14 (2.1%) had HPV 16 and/or 18. Any high-risk HPV was detected among seven (17.5%) participants and HPV 16 and/or 18 was detected in three (21.4%) who self-reported periodontitis. In the regression analyses no significant association was found between self-reported periodontitis and high-risk oral HPV (adjusted OR: 1.10; 95% CI: 0.45-2.70) or HPV 16 and/or 18 (adjusted OR: 1.27; 95% CI: 0.32-5.03).

Conclusion: This study did not find any association between self-reported periodontitis and high-risk oral HPV among Indigenous South Australians. Further targeted studies with standardized clinical measures of periodontal disease are needed to clarify the link between high-risk oral HPV and periodontal disease. If confirmed this would add further weight to the importance of recommendations about the utility of periodontitis screening to identify individuals at risk of carrying high-risk oral HPV, who may benefit from more intensive screening and ongoing monitoring.

Keywords
Periodontitis, Human papillomavirus, Indigenous population, First Nation

4.4 Introduction

The global prevalence of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is between 23.0-31.0% (128, 154), and there is evidence in many settings that the incidence of HPV-positive OPSCC is increasing (35). While known risk factors for OPSCCs include smoking and alcohol consumption (155), in the past decade there has been a dramatic change in the epidemiology of OPSCCs, with a reduction in OPSCCs caused by tobacco (reflecting reduced smoking rates), and a steady increase of this cancer in younger age groups, primarily due to oncogenic HPV infection (35, 156, 157).

Currently, screening for OPSCCs is done visually via an examination of the oral cavity to detect cancerous lesions. While screening has been shown to improve clinical outcomes only in those who are at risk of oral cancer (158, 159), many professional dental organisations recommend routine screening as part of a comprehensive oral examination (160). However, there remains considerable debate about the value of screening individuals without established risk factors,

namely, tobacco and heavy alcohol use (161). In the case of HPV-positive OPSCC, it is difficult to identity a specific population at risk, and testing for oral HPV DNA is not recommended due to the widespread exposure to HPV in the population, and current inability to reliably determine which individuals who are oral HPV-positive will go on to develop malignant lesions. This lack of understanding about the natural history of oral HPV infection and the carcinogenic process is a major impediment to improving early detection of HPV-positive OPSCC.

Nearly two decades ago, the presence of high-risk HPV in healthy and diseased periodontium was reported (63). Recent systematic reviews have reported a consistent association between periodontitis with any oral HPV infection, but the association with high-risk HPV is inconclusive (139, 71). Further, targeted research among populations at risk of OPSCCs is needed to understand the relationships between HPV, periodontitis and OPSCCs.

In Australia, 3.3% of the population are Indigenous, which includes Aboriginal and Torres Strait Islander peoples with unique languages, histories, and cultural traditions. Like many other health conditions, Indigenous Australians experience a disproportionate burden of poor oral health. Both incidence and mortality from OPSCCs are considerably higher in this group than in the Australian non-Indigenous population (162). Similarly, rates of periodontal disease are significantly higher among Indigenous communities compared to the non-Indigenous population, and the Indigenous population is more than twice as likely to have advanced periodontal disease (163). Recent data also confirms a high prevalence of oral HPV in this population (70).

There has been limited examination of the possible link between high-risk oral HPV and periodontitis among Indigenous Australians, despite the high burden of oral health conditions and OPSCCs in this population. If a link between oral HPV infection and periodontitis is confirmed, then this population may have great potential to benefit from improved screening for periodontitis and high-risk HPV infection. The aim of this study was to assess the association between periodontitis and high-risk oral HPV among Indigenous South Australians. We hypothesized that individuals with periodontitis would have higher prevalence of high-risk oral HPV compared to those with no periodontitis.

4.5 Methods

4.5.1 Study design and participants

We used a large convenience sample of Indigenous South Australians aged 18+ years recruited between February 2018 and February 2020 as part of a broader study investigating oral HPV and OPSCCs among Indigenous Australians (70, 117). Indigenous people living throughout South Australia were recruited and followed-up at 12 months. At baseline, data were obtained for 1011 participants and 748 were followed-up at 12 months. The current study utilises information collected at the baseline assessment and 12-month follow-up (Appendix 1 and 2). The study was supervised by an Indigenous Reference Group and trained Indigenous research officers collected the data from participants who were recruited through local Aboriginal Community Controlled Health Organisations (ACCHOs).

An Indigenous research officer explained the study aims and objectives to the participants and after obtaining written consent, participants were asked to share information related to their sociodemographic characteristics, health-related behaviors including tobacco and alcohol use, sexual history, self-reported oral and general health, HPV vaccination and answer questions about self-reported periodontitis. Each participant was requested to provide a saliva sample, through spitting and dribbling in a commercially available kit (Omnigene OM-501; DNA Genotek Inc, Canada) from which microbial DNA for genotyping was extracted.

4.5.2 Self-reported Data

Sociodemographic information collected at baseline included age, gender, geographic location, highest level of education completed and sexual history. Information on health-related behaviors including tobacco consumption, alcohol intake, and self-reported periodontitis were derived from the 12-month follow-up.

Age was dichotomised into individuals aged up to 40 years and 41 or older. Geographical location was categorised as metropolitan or non-metropolitan. The highest completed education level was dichotomised as up to and including high school or tertiary level. Smokers were categorised as a current regular smoker or non-smoker. Alcohol consumption included ex/current alcohol use or never consumes alcohol. Oral sex history was categorised as yes or no.

4.5.3 Laboratory Analysis

Saliva samples were collected using a commercially available kit (Omnigene OM-501; DNA

Genotek Inc., Canada), and analysed for HPV status using the optimized general primer (GP)+PCR system, which detects most mucosal HPV types and all high-risk HPV types. All HPV DNA positive samples were sequenced to confirm viral DNA sequences. Detail on the laboratory processes has been published elsewhere (70). For the current study, HPV status was taken from lab analysis at 12 months follow-up.

4.5.4 Exposure: Self-reported Periodontitis

At 12 month follow-up, self-reported periodontitis was assessed using eight periodontitis screening questions which have previously been validated among non-Indigenous Australians as part of the Australian National Survey of Adult Oral Health (2004-2006) administered via questionnaire (164). The eight questions ascertain self-reports of gum disease, bone loss, history of scaling/root planning, loose teeth, use of mouth wash and dental floss and overall gum health. In the previous validation studies, four questions were significantly associated with clinically assessed moderate and severe periodontitis, these included: 1) Do you think you have gum disease? 2) Have you ever been told that you have lost bone around your teeth? 3) Have you ever received scaling and root planing? and 4) Have you ever had any teeth become loose on their own, without an injury? Individuals with affirmative responses to all of these questions were classified as having periodontitis. Those responding 'no' to any of the above questions were categorised as not having periodontitis.

4.5.5 Key Outcome: High-risk HPV and HPV 16 and/or 18

There were two main outcomes: first, the presence of any high-risk oral HPV (Yes/No); and second, the presence of two specific subtypes, HPV 16 and/or 18 (Yes/No). Individuals were classified as having any high-risk HPV if they had a saliva sample positive for any one of the following HPV subtypes: 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and/or 70 in line with IARC classifications (166). For oral cancers, HPV 16 and HPV 18 are of primary concern and therefore these were studied separately.

4.5.6 Statistical Analysis

Descriptive analyses were undertaken to ascertain frequencies of all eight questions on self-reported periodontitis as well as the frequency of any high-risk oral HPV, and separately, any HPV 16 and/or 18 subtypes. Bivariate analyses were initially conducted to explore relationships between oral HPV status and sociodemographic status, health-related behaviours, sexual history characteristics and periodontitis. Logistic regression models were undertaken to examine the association between self-reported periodontitis and separately, high-risk oral HPV and HPV 16 and/or 18. Estimates are reported as an odds ratio (OR) with 95% confidence interval (CI). Models were adjusted for potential confounders reported in the literature (80, 81, 135) along with all the variables with $p \leq 0.25$ in the bivariate analyses. Two separate multivariate models were developed: Model A represents the association between self-reported periodontitis and any high-risk oral HPV (IARC classification) and Model B represents the association between self-reported periodontitis and HPV16 and/or 18 only. Both Model A and Model B included adjustment for age, gender, location, education, smoking, alcohol intake and history of oral sex. Model performance was evaluated by estimating model discrimination (c-statistic) and calibration. All analyses were conducted using STATA 15.

4.5.7 Ethics

This study was granted ethics approval from the University of Adelaide Human Research Ethics Committee and the Aboriginal Health Council of South Australia's Human Research Ethics Committee (H-2016-246). Interviewers (Indigenous and non-Indigenous) with extensive experience of working with Indigenous Australians conducted the surveys at each time point. Participant information sheets were shared with the participants in plain English language before commencing the survey. Participants provided written informed consent.

4.6 Results

Data on oral HPV status and periodontitis status were available for 673 participants (89.9% of the follow-up cohort) at the follow-up. Regarding sociodemographic characteristics, just over half were aged 40 years or younger (50.5%), more than two thirds were females (68.5%), living in non-metropolitan location (65.9%), and had attained a high school-level education (66.6%). Three quarters of participants were smokers (74.7%) and 91.2% had currently or previously consumed alcohol. Sixty five percent of participants reported a history of oral sex (Table 2).

Overall, 17.1% had self-reported periodontitis, 5.9% had any high-risk oral HPV and 2.1% had HPV 16 and/or 18. There was no difference in the prevalence of periodontitis with respect to age, gender, education, smoking status, alcohol intake, history of oral sex and HPV status (Table 4.6.1).

Table 4.6.1. Description of the study participants (N = 673)

Study variables	**Total** N = 673 (%)	**Periodontitis**	
		Yes n = 114(%)	**No** n = 547(%)
Age			
≤40	340 (50.5)	66 (19.4)	274 (80.6)
>40	333 (49.5)	49 (14.7)	284 (85.3)
Gender			
Male	212 (31.5)	34 (15.9)	179 (84.1)
Female	461 (68.5)	81 (17.7)	379 (82.3)
Location			
Non-metropolitan	444 (65.9)	74 (16.7)	370 (83.3)
Metropolitan	229 (34.1)	41 (17.9)	188 (82.1)
Completed education level¥			
High school or less	440 (66.6)	69 (15.7)	371 (84.3)
University or further	221 (33.4)	45 (20.4)	176 (79.6)
Tobacco smoking¥			
Yes	495 (74.7)	88 (17.8)	407 (82.2)
No	168 (25.3)	26 (15.5)	142 (84.5)
Alcohol intake			
Ex-drinker/Current	614 (91.2)	105 (17.1)	509 (82.9)
Never	59 (8.8)	10 (16.9)	49 (83.1)
History of oral sex¥			
Yes	388 (64.7)	75 (19.3)	313 (80.7)
No	211 (35.3)	28 (13.3)	183 (86.7)
Any high-risk HPV			
Yes	40 (5.9)	7 (17.5)	33 (82.5)
No	633 (94.1)	108 (17.1)	525 (82.9)
HPV 16 and/or 18			
Yes	14 (2.1)	3 (21.4)	11 (78.6)
No	659 (97.9)	112 (17.0)	547 (83.0)

¥ Missing values

In the bivariate analyses, being ≤40 years and living in metropolitan location were both significantly associated with the presence of any high-risk oral HPV (OR: 2.12; 95% CI: 1.08-4.19 and OR: 2.80; 95% CI: 1.47-5.36, respectively). Regarding HPV 16 and/or 18, there was a significant association between age and the presence of HPV 16 and/or 18 (OR: 3.67; 95% CI: 1.02-13.30).

In the unadjusted models, there was no significant increase in odds of either any high-risk oral HPV or HPV 16 and/or 18 among individuals with self-reported periodontitis (OR 1.03, 95% CI: 0.44-2.39 and OR 1.33, 95% CI: 0.37-4.85, respectively) (Table 4.6.2, 4.6.3).

Table 4.6.2. Bivariate association between sociodemographic and periodontitis with any high-risk oral HPV (N = 673)

Sociodemographic characteristics, sexual history and periodontal status	**Any high-risk oral HPV**		**Unadjusted OR**
	Yes n = 40 (%)	**No*** ** n = 633 (%)	**Yes** n = 40 (%)
Age			
≤40	27 (7.9)*	313 (92.2)	**2.12 (1.08-4.19)**
>40	13 (3.9)	320 (96.1)	Ref
Gender			
Male	13 (6.1)	199 (93.9)	1.05 (0.53-2.08)
Female	27 (5.9)	434 (94.1)	Ref
Location			
Non-metropolitan	17 (3.8)	427 (96.2)	Ref
Metropolitan	23 (10.0)*	206 (89.9)	**2.80 (1.47-5.36)**
Completed education level¥			
High school or less	24 (5.5)	416 (94.5)	Ref
University or further	15 (6.8)	206 (93.2)	1.26 (0.65-2.46)
Tobacco smoking¥			
Yes	28 (5.7)	467 (94.3)	0.94 (0.45-.99)
No	10 (5.9)	158 (94.1)	Ref
Alcohol intake			
Ex-drinker/Current	37 (6.0)	577 (93.9)	1.19 (0.36-4.01)
Never	3 (5.1)	56 (94.9)	Ref
History of oral sex¥			
Yes	29 (7.5)	359 (92.5)	2.05 (0.92-4.57)
No	8 (3.8)	203 (96.2)	Ref
Periodontitis			
Yes	7 (6.1)	108 (93.9)	1.03 (0.44-2.39)
No	33 (5.9)	525 (94.1)	Ref

*significant p value for chi square

*** includes those with no HPV detected and those with low risk subtypes

¥ Missing values

Table 4.6.3. Bivariate association between sociodemographic and periodontitis with HPV 16 and/or 18 (N = 673)

Sociodemographic characteristics, sexual history and periodontal status	**HPV 16 and/or 18**		**Unadjusted OR**
	Yes n = 14 (%)	**No**** ** n = 659 (%)	n = 14 (%)
Age			
≤40	11 (3.2)**	329 (96.8)	**3.67 (1.02-13.30)**
>40	3 (0.9)	330 (99.1)	Ref
Gender			
Male	5 (2.4)	207 (97.6)	1.20 (0.40-3.63)
Female	9 (1.9)	452 (98.1)	Ref
Location			
Non-metropolitan	6 (1.3)	438 (98.7)	2.64 (0.91-7.71)
Metropolitan	8 (3.5)	221 (96.5)	Ref
Education¥			
Primary/secondary	6 (1.4)	434 (98.6)	Ref
Higher	8 (3.6)	213 (96.4)	2.71 (0.93-7.92)
Regular smoker¥			
Yes	11 (1.8)	165 (98.2)	1.25 (0.34-4.53)
No	3 (2.2)	484 (97.8)	Ref
Alcohol intake			
Ex-drinker/Current	13 (2.1)	601 (97.9)	1.25 (0.16-9.76)

Never	1 (1.7)	58 (98.3)	Ref
History of oral sex¥			
Yes	10 (2.6)	378 (97.4)	2.76 (0.60-12.74)
No	2 (0.9)	209 (99.1)	Ref
Periodontitis			
Yes	3 (2.6)	112 (97.4)	1.33 (0.37-4.85)
No	11 (1.9)	547 (98.1)	Ref

**significant p value for fisher exact
**** includes those with no HPV detected, those with low risk types and those with high-risk subtypes other than 16 and 18
¥ Missing values

The findings were unchanged in the models that included adjustment for age, gender, location, education, smoking status, alcohol intake and history of oral sex (Table 4.6.4). Both adjusted models had moderate discrimination (C-statistic of 0.72 and 0.81 respectively) and good model calibration (Supplementary document: Figure S1).

Table 4.6.4. Adjusted association between periodontitis and any high-risk oral HPV and HPV 16 and/or 18

Exposure	**Any high-risk oral HPV (Model A)**	**HPV 16 and/or 18 (Model B)**
Periodontitis		
Yes	1.10 (0.45-2.70)*	1.27 (0.32-5.03)*
No	Ref	Ref
AUC	72.8	81.4
Hosmer-Lemshow chi^2 (p value)	10.35 (0.24)	12.14 (0.14)

*adjusted for age, gender, location, education, smoking and alcohol intake, and history of oral sex

4.7 Discussion

To the best of our knowledge, this is the first study to evaluate the association between high-risk oral HPV and periodontitis among Indigenous South Australians. Overall, 5.9% of participants had any high-risk oral HPV (IARC classification), while HPV 16 and/or 18 subtypes were detected among 2.1%. Our estimates of any type of high-risk oral HPV are lower than estimates reported among non-Indigenous Australians (80) and other international cohorts (81) but comparable to the prevalence seen in the baseline laboratory findings of the same cohort (166). Similarly, less than one-fifth of participants had self-reported periodontitis, which is lower than the prevalence reported in studies with clinical assessments of periodontitis among Indigenous Australians (167), but comparable to the prevalences reported in the most recent national survey of oral health among Australian adults (168).

Our study did not find any significant association between self-reported periodontitis and the presence of any high-risk oral HPV or the specific HPV 16 and/or 18 subtypes. This is in contrast to a previous study among Hispanic individuals, which found a significant correlation between oral HPV and periodontitis; however, that study focused on any type of HPV and did not report high-risk subtypes alone (81). A prospective study conducted in Austria among 187 adults reported a significant association between oral HPV and poor oral health. Poor oral health was defined as patients with approximal plaque index (proportion of plaque-covered interproximal spaces), gingival bleeding index (proportion of bleeding sites) of more than 40%, and lifetime number of extracted teeth (76). In both these studies, a clinical assessment was done to detect periodontitis, plaque, and gingivitis, which could have resulted in a more robust ascertainment of periodontitis than our study (76, 81). On the other hand, a US study utilising NHANES data did not find any association between clinically detected periodontitis and oral HPV infection (148). Studies from India and Brazil have also failed to report any significant association between HPV and periodontitis (77, 78). A recent systematic review examining the association of periodontitis and oral HPV reported no association of periodontitis with high-risk oral HPV but a positive association with any type of oral HPV, although the quality of evidence was low (71).

The conflicting results of the published literature are likely due to methodological differences in the detection and definition of periodontitis, as some studies have used radiographic assessment, whereas others are based on a clinical assessment or self-reported (71). Furthermore, differences in the ascertainment of HPV status may also explain the conflicting findings, with studies using gingival samples (76-78) and an oral rinse (81) for detecting HPV. The sensitivity and specificity of HPV detection techniques are known to vary, with no current Food and Drug Administration-approved tests to detect HPV DNA or mRNA in saliva (169). In the current study, we used a saliva sample as it is non-invasive, easy to administer, and can detect the presence of a virus in all the surrounding epithelial sites (168). In addition, variation in sample sizes and differences in baseline characteristics of participants may further explain differences in the findings of existing studies (71).

Several possible mechanisms could relate periodontitis with oral HPV persistence. Periodontitis results from an inflammatory response of the pathogens that leads to pocketing, alveolar bone loss, and subsequent tooth loss (170, 171). It has been suggested that periodontal pockets provide the perfect environment for HPV to persist in the oral cavity (63, 74).

Continuous release of cytokines exacerbates the inflammation process, which can lead to tissue damage and modulate the proliferation of HPV (135, 138). Thus, it is important to recognize that it is possible that direct effects of oral microbes, as well as the stimulation of a chronic inflammation process, could underpin an association between periodontitis and HPV.

The apparent biological plausibility underpins the need for future targeted studies using validated clinical data on periodontitis to clarify the relationship between periodontitis and high-risk oral HPV. This information is essential, as it would allow screening and ongoing monitoring of individuals with periodontitis to reduce the persistence of oral HPV, which may reduce the risk of HPV-positive OSCCs, particularly in high-risk groups such as Indigenous Australians. Moreover, the detection of high-risk oral HPV in Indigenous adults in our study reinforces the continued need for dental counselling on the importance of good oral hygiene and also the importance of HPV vaccination among Indigenous peoples, given the known efficacy of vaccination against oral HPV infection (172).

It is also recommended that dentists should advise patients about the risk of HPV and promote public awareness of oral health and HPV-related risks of cancer. As the current diagnosis of OSCCs relies on patient presentation and oral physical examination plus biopsy, most OSCCs are diagnosed at a late stage, reflected in less than optimal survival rates. As a result, new approaches to screening are required to permit early detection and management. Implementation of screening for OPSCCs as part of routine dental care should be considered. This is particularly pertinent for Indigenous peoples, who experience both a higher incidence and lower survival rates from OSCCs than non-Indigenous Australians.

Several limitations should be considered when interpreting the findings of this study. First, participants were not representative of the Australian Indigenous population; therefore, findings may not be generalizable. Second, the cross-sectional nature of data collection limits the examination of temporality and possible causal relationships. Third, a self-reported questionnaire was used to collect information from sociodemographic variables and to assess periodontitis, and could be subject to recall bias. Fourth, clinical assessment of periodontitis was impossible due to travel restrictions and clinical consultations during the COVID-19 pandemic. Therefore, a non-validated self-reported tool was the best available assessment. Strict criteria were used to define periodontitis by including questions that have been shown to have high sensitivity and specificity for detecting periodontitis among non-Indigenous Australians. As a result, it is possible that our criteria only identified participants with moderate

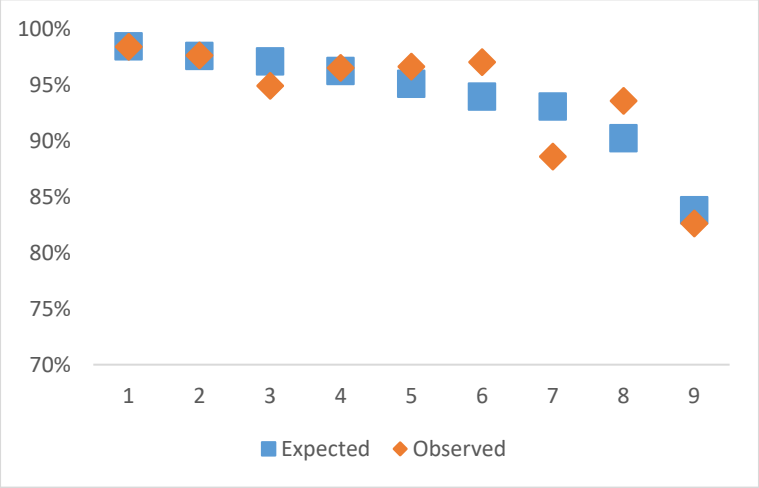
to severe periodontitis, which may explain our null findings. Nevertheless, clinical and radiographical assessments of periodontitis are costly, time-consuming, and often not feasible in large population-based studies. Further exploration and validation of self-reported measures of periodontal disease is an important area of future research to permit lower-cost population assessment of periodontitis. Finally, the types of HPV found in the mouth are almost entirely sexually transmitted. Several sexual behaviours could affect the transmission of HPV in the mouth, for example number of sexual partners, unprotected sex, and age at first sex (173). However, in the current study, we only adjusted for history of any oral sex, as this is one of the main routes of acquiring an oral HPV infection. While this study has incorporated all the important confounding variables as well as sensitive risk behavioural data, the possibility of residual confounding cannot be excluded.

4.8 Conclusion

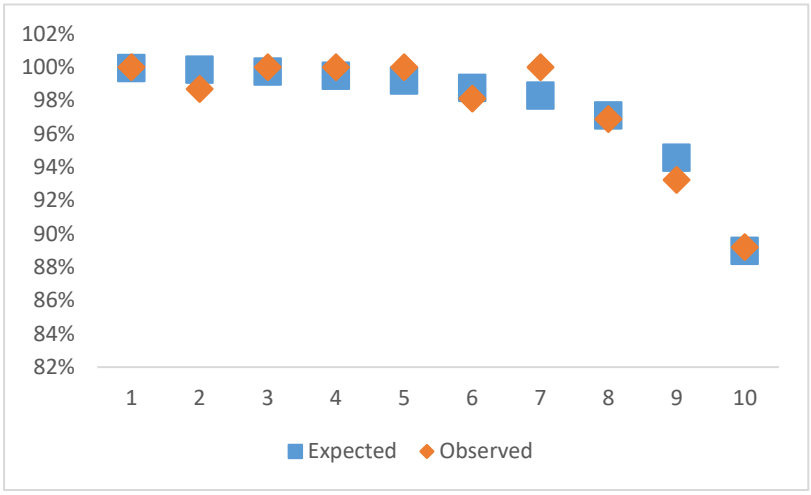
This study did not find any association between self-reported periodontitis and high-risk oral HPV among Indigenous South Australians. Further studies using the clinical diagnosis of periodontitis are needed to evaluate the role of periodontitis in the acquisition and persistence of high-risk oral HPV, as this may help identify individuals at high-risk of oncogenic HPV and thus OPSCC.

4.9 Supplementary document

S1 Fig: Goodness of fit: *Model A*



Model B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CHAPTER FIVE: The impact of interpersonal racism on oral health related quality of life among Indigenous South Australians; a cross-sectional study

5.1 Preamble

This chapter contains the third study of the thesis, which comprises a cross-sectional study among Indigenous South Australians assessing the relationship between interpersonal racism and OHRQoL. This study reported a negative impact of interpersonal racism on OHRQoL among Indigenous South Australians, suggesting the need for implementation of culturally appropriate strategies to address racism affecting oral health and OHRQoL of marginalized communities.

This chapter has been published in BMC Oral Health and is available in publication format in Appendix 5

5.2 Statement of Authorship

Title of Paper	The impact of interpersonal racism on oral health related quality of life among Indigenous South Australians: a cross-sectional study
Publication Status	Published – 2021
Publication Details	**Ali A**, Rumbold AR, Kapellas K, Lassi ZS, Hedges J, Jamieson L. The impact of interpersonal racism on oral health related quality of life among Indigenous South Australians: a cross-sectional study. BMC oral health. 2021 Dec;21(1):1-1.

Principal Author

Name of Principal Author (Candidate)	Anna Ali
Contribution to the Paper	Acquiring data, knowledge, analysis, drafting
Overall Percentage (%)	70%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	**Date 29 June 2022**

Co-author Contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate (as detailed above);
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution

Name of Co-Author	Alice Rumbold
Contribution to the Paper	Supervised development of work, conception, knowledge, drafting and editing
Signature	**Date 29 June 2022**

Name of Co-Author	Kostas Kapellas
Contribution to the Paper	Conceptualisation, drafting

Signature	**Date 29 June 2022**

Name of Co-Author	Zohra S Lassi
Contribution to the Paper	Conceptualisation, drafting and editing
Signature	**Date 29 June 2022**

Name of Co-Author	Joanne Hedges
Contribution to the Paper	Conception, data collection, knowledge, drafting and editing
Signature	**Date 29 June 2022**

Name of Co-Author	Lisa Jamieson
Contribution to the Paper	Supervised development of work, conception, knowledge, drafting and editing
Signature	**Date 29 June 2022**

The impact of interpersonal racism on oral health related quality of life among Indigenous South Australians; a cross-sectional study

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5.3 Abstract

Background: Interpersonal racism has had a profound impact on Indigenous populations globally, manifesting as negative experiences and discrimination at an individual, institutional and systemic level. Interpersonal racism has been shown to negatively influence a range of health outcomes but has received limited attention in the context of oral health. The aim of this paper was to examine the effects of experiences of interpersonal racism on oral health-related quality of life (OHRQoL) among Indigenous South Australians.

Methods: Data were sourced from a large convenience sample of Indigenous South Australian adults between Feb 2018 and Jan 2019. Questionnaires were used to collect data on socio-demographic characteristics, cultural values, utilization of dental services, and other related factors. OHRQoL was captured using the Oral Health Impact Profile (OHIP-14). We defined dependent variable "poor OHRQoL" as one or more OHIP-14 items rated 'very often' or 'fairly often. Experiences of racism were recorded using the Measure of Indigenous Racism Experiences instrument. Interpersonal racism was classified into two categories ('no racism' vs 'any racism in ≥1 setting') and three categories ("no racism", "low racism" (1-3 settings), and "high racism" (4-9 settings)). Logistic regression was used to examine associations between interpersonal racism, covariates and OHRQoL, adjusting for potential confounders related to socioeconomic factors.

Results: Data were available from 885 participants (88.7% of the total cohort). Approximately 52.1% reported experiencing any interpersonal racism in the previous 12 months, one-third

(31.6%) were classified as experiencing low racism, and one-fifth (20.5%) experienced high racism. Poor OHRQoL was reported by half the participants (50.2%). Relative to no experiences of racism in the previous 12 months, those who experienced any racism (≥1 setting) were significantly more likely to report poor OHRQoL (OR: 1.43; 95% CI 1.08-1.92), after adjusting for age, education, health-card, car ownership, self-reported oral health, dental visit, visiting dental for problem, not going to dentist because of cost, and having no family support. This was particularly seen among females, where, relative to males the odds of poor OHRQoL among females experiencing racism were 1.74 (95% CI 1.07-2.81).

Conclusion: Our findings indicate that the experience of interpersonal racism has a negative impact on OHRQoL among Indigenous Australians. The association persisted after adjusting for confounding factors. Identifying this link adds weight to the importance of addressing OHRQoL among South Australian's Indigenous population by implementing culturally sensitive strategies to address interpersonal racism.

Keywords: Oral health related quality of life, Racism, Indigenous Australians, Aboriginals, Torres Strait Islanders

5.4 Introduction

Racism has been defined as anything "that which maintains or exacerbates inequality of opportunity among ethno-racial groups" (91). Racism can have a profound impact on society through exclusion and marginalisation of certain ethnic or minority groups and promotion of concepts of inferiority in the worldview of the society as a whole (174-176). At an individual level, numerous studies demonstrate that racism can have a deleterious effect on health. This has been most studied in the context of adverse mental health outcomes and health behaviours (89, 177, 178). The effects of racism on health may occur via several pathways including chronic stress and distrust of healthcare providers, which may reduce healthcare seeking behaviours and use of preventive services, (93).

In a healthcare setting, racial discrimination is considered to be an individual's appraisal of unfair treatment related to differences in race, appearance and ethnicity (179). Theories explaining racism as a contributor to health inequalities argue that racism can act on three levels (institutionalized, personal, and internalized) to influence health outcomes (180). For example, institutional racism arising from unfair distribution of goods, services, and opportunities could

lead to unfair differential opportunities and access to health-promoting resources (95). It could also influence healthcare providers' decision making, treatment strategies and communication, through the development of implicit racial bias and explicit racial stereotypes (96, 97). Another pathway through which racism can impact on health outcomes is via psychological stress. Racism may act as a stressor that, in turn, results in psychological harm (e.g. distress), and physiological changes (e.g. increased blood pressure, pulse rate, nervousness, nausea), whilst simultaneously causing changes in health seeking behaviours (98, 99, 181). All factors may cumulatively provoke involuntary responses, such as anxiety or increased vigilance and voluntary coping responses including disengagement from situations or environments that negatively stereotype individuals, including healthcare settings (182).

The most disadvantaged social groups disproportionately feel the impacts of racism. This includes many Indigenous peoples, who have been profoundly affected by the ongoing effects of systemic and interpersonal racism (177, 183, 184). Indigenous Australians, those who identify as being of Aboriginal and/or Torres Strait people descent (185), are the oldest continuing civilization, dating back more than 65,000 years (186). Following European colonisation of Australia in the late 1700s, population numbers of Indigenous Australians rapidly declined due to extensive dispossession of land, massacres and relocation of people into religious missions (187). The effects of these practices are still felt today, and manifest in much higher rates of social, economic and health disadvantage in many Indigenous communities. This includes experiences of marginalisation and racism, which have been reported at interpersonal, institutional and broader structural levels (188). Indeed there is increasing recognition that both historic and contemporary racism contributes to longstanding inequalities in health, income, housing, and education between Indigenous and non-Indigenous Australians (189). Notably, while racism is experienced by Indigenous men and women, the effects of racism are gendered, exemplified by experiences of family violence and homelessness disproportionately affecting Indigenous women (190).

Poor oral health is a major concern for Indigenous Australians, who experience very high rates of untreated dental disease including dental caries, gum disease, tooth loss and tooth ache than non-Indigenous Australians (191). Study conducted during 2014-2015 among Indigenous Australians reported more females compared to males reported higher rates of oral conditions such as dental caries, utilization of dentures, and pain/discomfort in teeth/mouth (13). Poor oral health can have a significant impact on overall health as well as quality of life, affecting the ability to eat, speak and sleep, as well as confidence with social and professional interactions.

As a result, poor oral health can influence productivity in the workplace and negatively influence social and emotional well-being (100).

Oral health related quality of life (OHRQoL) is an important measure of the impact of oral conditions on health-related well-being (100). OHRQoL encompasses a range of factors such as access/utilization of health services, caregiver characteristics, and socio-demographic characteristics that could influence oral health (100). The broad and complex multidimensional construct of OHRQoL enables the examination of the impact of oral health on psychological, functional, and social functioning (100). As experiences of racism can also affect psychological and physiological well-being of an individual, it is plausible that racism could influence OHRQoL. However, this has received limited research attention, only one study conducted in Canada among pregnant Canadian Aboriginal women, reported high impact of racism on OHRQoL (89). We have previously shown that racism experienced by Indigenous Australians is associated with poorer oral health behaviours such as tooth brushing and use of dental services (92, 192, 193). Both are likely to affect OHRQoL, however, to date no study has examined the possible effects of racism on OHRQoL among Indigenous Australians.

The main aim of this study was to explore the association between self-reported interpersonal racism and OHRQoL among Indigenous South Australians, adjusting for potential confounding by socioeconomic factors. Our goal was to examine these relationships in a population with high levels of untreated dental disease to understand the widespread impacts of racism to further inform health and social policy to address racial and oral health inequalities.

5.5 Methods

5.5.1 Study design and participants

This paper is a part of a larger study investigating Human Papillomavirus and Oropharyngeal Squamous Cell Carcinoma (OPSCC) among Indigenous Australians (117). An Indigenous Reference Group governs the study, with data collected by trained Indigenous research officers. Data for this paper are drawn from the baseline data collection (appendix 1 and 2) which includes a large convenience sample of Indigenous South Australians recruited between February 2018 and Jan 2019.

5.5.2 Self-reported variables

Socio-demographic characteristics included age, gender, geographic location, education, income/welfare, ownership of a means-tested government healthcare card, number of people in household the previous night, and car ownership. Health-related behaviors included tobacco and alcohol use. Information indicating oral health and use of dental services was also collected. This included self-rated oral health (excellent, good, fair and poor), last dental visit (less than a year ago or more than a year ago), dental cost (not attending due to cost, difficulty in paying a $100 AUD dental bill), and reason for last dental visit (problem vs check-up).

Information was also collected on aspects of cultural identity, by asking the following questions which were assessed on a Likert scale: 1) Do you know a lot about your Aboriginal/Torres Strait Islander culture? 2) Do you identify with a tribal group, a language group or clan? 3) To you, is being Aboriginal/Torres Strait Islander the most important thing or important but not the only thing or want to know more or something you don't think about? 4) Do you feel like you know a lot about white fella ways? 5) Do you have a strong family who help each other?

5.5.4 Outcome: Oral health related quality of life (OHRQoL)

To evaluate OHRQoL, the short form of the oral health impact profile – OHIP-14 was used (118). This contains 14 items relating to the frequency with which oral conditions adversely affect quality of life. OHIP is assessed on a five-point ordinal scale with responses: very often (4), often (3), occasionally (2), hardly ever (1), and never (0). The first four items ask participants how often in the last year had they experienced "toothache or pain in the mouth", "bleeding gums when brushing", "chronic dry mouth", and "chronic bad breath". The following three items evaluated the frequency with which problems with teeth, dentures or gums produced varying levels of psychological discomfort (uncomfortable at work, school or in social situations), functional limitation (not able to eat some foods or had to eat them slowly), and social disability (missed work, school or took time away from normal activities) (Appendix 1). This tool has been validated among Indigenous and non-Indigenous Australians (194). We defined dependent variable "poor OHRQoL" as one or more OHIP-14 items rated 'very often' or 'fairly often (195).

5.5.5 Primary exposure: Experience of racism

Interpersonal racism was assessed using an adapted version of the Measure of Indigenous Racism Experiences (MIRE) instrument across nine settings (196). This version was shorter than the original (196), and was concerned with whether participants experienced unfair treatment due to their race in those nine settings over the last 12 months. Participants were asked: "In the last twelve months, have you felt that you have been treated unfairly in any of the following ways because you are Aboriginal?" The settings included: employment, domestic, educational/academic, recreational/leisure, law (enforcement), healthcare, government service provision, other service provision, public, any other situation (re-categorised according to the other settings where relevant). Response options were 'yes' or 'no'. Experience of racism was computed as a summary score; range 0 to 9 (92). The summary score was dichotomised into two ways. First, the experience of "any racism" (reported in one or more setting) vs no racism; and second, experience of "low racism" (reported in 1-3 settings), "high racism" (reported in 4-9 settings), and no racism.

5.5.6 Statistical Analysis

Normality of all continuous variables was assessed. Variables that were not normally distributed were re-coded as a categorical variable. Collinearity was assessed with no variables needing to be excluded due to weak associations. Frequency and percentage of categorical variables, and mean and standard deviation of continuous variables were reported. Variables conceptually associated with OHRQoL and racism were explored as potential confounders in the analyses after evaluating recent empirical evidence. Previous literature has shown strong associations between socio-demographics variables, health related behaviors and use of dental services with OHRQoL and interpersonal racism among Indigenous Australians (92, 100, 196). For example, study conducted among indigenous Australians in 2009 reported significant association of socio-demographics variables such as age, healthcare-card, smoking, alcohol with poor OHRQoL. With respect to dental service and oral health; problem-based dental attendance, avoiding dental care because of cost, difficulty paying a $100 dental bill were also significantly associated with poor OHRQoL (196). Likewise study conducted on Indigenous pregnant women reported strong association of healthcare card, having not gone to the dentist because of cost during the last year, having difficulty paying a $100 dental bill and fair or poor self-rated general health with racism (92).

Bivariate associations between socio-demographics, cultural identity variables, dental services and oral health related covariates and OHRQoL (OHIP-14) and experience of racism, ('no racism' vs 'any racism in ≥1 setting(s)') and 'no racism' vs 'low' and 'high' racism were tested for statistical significance using logistic regression. All variables with borderline statistical significance ($p<0.25$) were considered as a potential confounder or interaction variable. The association between self-reported interpersonal racism and OHRQoL is reported as an odds ratio (OR) with 95% confidence interval (CI). Multivariable binary logistic regression models were used to produce covariate adjusted OR and 95% CIs. To select the final variables, we included all candidate variables (socio-demographics, cultural identity variables, dental services and oral health related) in the model and then applied purposeful backward elimination as described by Hosmer and Lemeshow (198, 199), until the model contained only variables significant at $p <0.05$. Potential interactions were explored between the variables racism (any versus no racism), gender, and age.

Four different models were generated. Model 1 represents the crude association between racism and OHRQoL. Model 2 represents the association between 'no racism' vs any racism with OHRQoL after adjusting for education, healthcare-card, car ownership, self-reported oral health, last dental visit, reason for dental visit, not attending a dentist due to cost, family support and age with significance set at $p <0.05$. Models 3 and 4 examine the association between 'no racism' vs 'any racism' with OHRQoL with further adjustments to model 2. Namely, Model 3 adjusts for model 2 and gender. Model 4 is adjusted with variables of model 2 and an interaction term between the variables racism ('no racism vs 'any racism') and gender. Model performance was evaluated by estimating model discrimination (c-statistic) and calibration. All analyses were conducted using STATA 15.

5.6 Results

Of the total 1,011 participants, data from 885 (87.5 %) participants were available on racism. Just under one-third (31.6%) experienced low racism in 1-3 settings in the past 12 months, while one-fifth (20.5%) experienced high racism in 4-9 settings. The most frequent setting where participants reported racism was law enforcement (31.7%) followed by public settings (24.8%) and government service settings (22.0%) (Table 5.6.1).

Table 5.6.1: Frequency of nine MIRE items[1] used in current study (n=885)

Nine MIRE items[1]	**Frequency (%)**	**95%CI**
Employment	161(19.2)	15.70-20.89
Domestic	118(13.8)	11.16-15.75
Educational/Academic	143(17.0)	13.79-18.75
Recreational/leisure	139(16.2)	13.37-18.27
Law (enforcement)	271(31.7)	27.60-33.78
Healthcare	151(17.4)	14.64-19.71
Government service provision	191(22.0)	18.91-24.44
Other service provision	154(17.8)	14.96-20.06
Public settings	216(24.8)	21.61-27.38
Interpersonal racism		
No Racism	424(47.9)	44.57-51.26
Low Racism (1-3 setting)	280(31.6)	28.58-34.82
High Racism (4-9 settings)	181(20.5)	17.84-23.36
Any Racism (≥1setting)	461(52.09)	48.74-55.43

[1]Participants were asked: "In the last twelve months, have you felt that you have been treated unfairly in any of the following ways because you are Aboriginal?" The settings were: 1, Applying for work or when at work; 2, At home, by neighbors or at somebody else's house; 3, At school, university, training course, or other educational setting; 4, While doing any sporting, recreational or leisure activities; 5, By the police, security people, lawyers or in a court of law; 6, By doctors, dentists, nurses or other staff at hospitals, dental clinics or doctor's surgeries; 7, By staff of government agencies; 8, When seeking any other services; 9, By members of the general public; 10, Any other situation (re-categorized according to the other 9 settings where relevant)

Regarding the socio-demographic characteristics of study participants, more than half were aged 40 years or younger (55.8%), two-thirds were female (67.0%), and had attained a high school-level education (68.0%), whilst 74.9% were on welfare and held a healthcare card (78.3%). The majority of study participants had never smoked (57.7%). (Table 5.6.2).

More than one third had a lot (36.5%) and a fair bit (39.4%) of knowledge of being Aboriginal. More than two-thirds (69.5%) identified themselves with the tribal group. For more than half of the participants, being Aboriginal was the most important thing (55.6%) and for 31.2% it was important but not the only thing. More than one third reported that they knew a lot (42.8%) and had fair bit (40.1%) of knowledge about white fellas (Western). Around two thirds (61.6%) of participants reported they always had the strong family support.

Regarding oral health, half (50.3%) the participants reported poor OHRQoL (OHIP-14 scores very often and often) (5.6.2). Just over half of all participants reported their last dental visit was more than a year ago (53.4%) and that was for some oral problems (61.8%). Around one third reported they avoided dental care because of high cost (32.3%) and 44.7% reported they would have difficulty paying a $100 AUD dental bill. Two thirds rated their oral health as excellent/good (5.6.4).

In bivariate analysis, poor OHRQoL, represented by a high OHIP score, was associated with age >40 years, government welfare, possession of health card, ownership of car, and current or past smoker (5.6.2). Poor OHRQoL was additionally associated with not having strong family support (OR 1.70; 95% CI 1.18-2.57) (5.6.3). In terms of self-rated oral health and dental service utilisation, poor OHRQoL was significantly associated with consultation with a dental problem (OR 2.50; 95% CI 1.90-3.31), avoiding a dental visit because of the associated cost (OR 1.88; 95% CI 1.41-2.50), difficulty in paying a $100 AUD dental bill (OR 1.69; 95% CI 1.21-2.17), and fair or poor self-rated oral health (OR 3.43; 95% CI 2.55-4.62) (5.6.4).

There was a positive bivariate association between poor OHRQoL and low racism (OR 1.59; 95% CI 1.17-2.15) and high racism (OR 1.73; 95% CI 1.22-1.46) relative to those who reported no racism. The association between poor OHRQoL and low racism (1-3 settings) persisted after adjusting for education, having a health insurance card, car ownership, self-reported oral health, dental visit, cost associated with dental visit, family support, and age (OR 1.45; 95% CI 1.04-2.03) (5.6.5 and 5.6.6).

A bivariate association between poor OHRQoL and racism was also present when racism was categorised as “any racism” (≥1 settings’) compared with no racism (OR 1.64; 95% CI 1.25-2.14) (5.6.5). The experience of any racism persisted as a risk factor for poor OHRQoL after adjusting for education, having a health insurance card, car ownership, and self-reported oral health, and dental visit, costs associated with dental visit, family support, and age. The association was strengthened when gender was added as a covariate (AOR 1.48; 95% CI 1.09-1.98). An interaction term (any racism*gender) was added in multivariate models and a significant interaction between being female with racism was found. The odds of poor OHRQoL were 1.74 times (95% CI 1.07-2.81) higher among females experiencing any racism compared to males experiencing no racism. (5.6.6). All four-risk adjustment models had moderate discrimination (C-statistic of 0.72) and closely approximated the observed risk suggesting good model calibration (Supplemental Figure S2).

Table 5.6.2: Univariate, bivariate and multivariate associations between socio-demographic variables with OHRQoL and interpersonal racism (n=885)

Socio-demographics and related variables	**Total Frequency (%)**	**OHRQoL**		**Interpersonal racism**			**Poor OHIP**
		Good (n=440)	**Poor (n=445)**	**No Racism (n=424)**	**Low Racism (n=280)**	**High Racism (n=181)**	**Unadjusted OR**
Age in years							
</=40	494(55.8)	265(53.6)	229(46.4)	237(48.0)	174(35.2)	83(16.8)	Ref
>40	391(44.2)	175(44.8)	216(55.2)[a]	187(47.8)	106(27.1)	98(25.1)	1.43(1.09-1.86)[b]
Gender							
Female	593(67.0)	286(48.2)	307(51.8)	310(52.3)	169(28.5)	114(19.2)	Ref
Male	292(33.0)	154(52.7)	138(47.3)	114(39.0)	111(38.0)	67(22.9)	0.84(0.63-1.11)[b]
Education							
Further or university	283(32.0)	153(54.1)	130(45.9)	117(41.3)	99(35.0)	67(23.7)	Ref
High school or less	602(68.0)	287(47.7)	315(52.3)	307(51.0)	181(30.1)	114(18.9)	1.29(0.97-1.71)[b]
Income*							
Job	221(25.1)	126(57.0)	95(43.0)	101(45.7)	71(32.1)	49(22.2)	Ref
Welfare /Other	659(74.9)	313(47.5)	346(52.5)[a]	322(48.9)	207(31.4)	130(19.7)	1.47(1.08-1.99)[b]
Healthcare card							
No	192(21.7)	110(57.3)	82(42.7)	89(46.4)	64(33.3)	39(20.2)	Ref
Yes	693(78.3)	330(47.6)	363(52.4)[a]	335(48.3)	216(31.2)	142(20.6)	1.45(1.07-2.04)[b]
No. of people who stayed in house last night							
</=4	518(58.5)	260(50.2)	258(49.8)	253(48.8)	152(29.3)	113(21.8)	Ref
>4	367(41.5)	180(49.0)	187(51.0)	171(46.6)	128(34.9)	68(18.5)	1.05(0.80-1.37)

Car ownership							
Yes	490(55.4)	261(45.3)	229(46.7)	226(46.1)	160(32.7)	104(21.2)	Ref
No	395(44.6)	179(45.3)	216(54.7)[a]	198(50.1)	120(30.4)	77(19.5)	1.38(1.05-1.80)[b]
Tobacco smoking*							
Never/don't know	253(29.0)	146(57.7)	107(42.3)	146(57.7)	64(25.3)	43(17.0)	Ref
Currently/previous	620(71.0)	287(46.3)	216(54.7)[a]	273(44.0)	212(34.2)	135(21.8)	1.58(1.18-2.13)[b]
Alcohol intake*							
Never	317(36.5)	151(47.6)	166(52.4)	165(52.1)	90(28.4)	62(19.6)	Ref
Currently/previous	551(63.5)	278(50.5)	273(49.5)	249(45.2)	186(33.8)	116(21.1)	0.89(0.68-1.18)

*indicates missing data
a: Poor OHIP vs Good OHIP: p value for chi^2 :</=0.05
b: Poor OHIP vs Good OHIP: p value for univariate logistic regression:</=0.25

Table 5.6.3: Univariate, bivariate and multivariate associations between cultural identity variables with OHRQoL and interpersonal racism (n=885)

Cultural identity and related variables	Total Frequency (%)	OHRQoL		Interpersonal Racism			Poor OHRQoL
		Good (n=440)	Poor (n=445)	No Racism (n=424)	Low Racism (n=280)	High Racism (n=181)	Unadjusted OR
Know a lot about your Aboriginal/Torres Strait Islander culture*							
Little bit/Not much	212(24.1)	104(49.1)	108(50.9)	121(57.1)	60(28.3)	31(14.6)	Ref
A lot/Fair bit	669(75.9)	335(50.1)	334(49.9)	302(45.1)	219(32.7)	148(22.1)	1.04(0.76-1.42) [b]
Do you identify with a tribal group, a language group or clan?*							
No	148(16.9)	69(46.6)	79(53.4)	87(58.8)	39(26.4)	22(14.9)	Ref
Don't know	114(13.0)	55(48.2)	59(51.8)	62(54.4)	30(26.3)	22(19.3)	
Yes	615(70.1)	313(50.9)	302(49.1)	272(44.2)	207(33.7)	136(22.1)	0.86(0.64-1.15)
To you, is being Aboriginal/Torres Strait Islander*							
Something you don't know enough about and want to know more about/Something you don't think about	115(13.1)	51(44.3)	64(55.7)	66(57.4)	30(26.1)	19(16.5)	Ref
The most important thing/Important, but not the only thing	766(86.9)	386(50.4)	380(49.6)	356(46.5)	249(32.5)	161(21.0)	0.78(0.53-1.16)[b]
Know a lot about white fella ways*							
Little bit/Not much	150(17.0)	74(49.3)	76(50.7)	89(59.3)	40(26.7)	21(14.0)	Ref
A lot/Fair bit	733(83.0)	364(49.7)	369(50.3)	334(45.6)	239(32.6)	160(21.8)	0.99(0.69-1.40)
Have a strong family who help each other							
Always/Most times	748(84.5)	387(51.7)	361(48.3)	370(49.5)	229(30.6)	149(19.9)	Ref
Sometimes/ Not really	137(15.5)	53(38.7)	84(61.3)[a]	54(39.4)	51(37.2)	32(23.4)	1.70(1.18-2.57) [b]

*indicates missing data

a: Poor OHRQoL vs Good OHRQoL: p value for chi^2 :</=0.05
b: Poor OHRQoL vs Good OHRQoL: p value for univariate logistic regression:</=0.25

Table 5.6.4: Univariate, bivariate and multivariate associations between dental service utilisation and OHRQoL and interpersonal racism (n=885)

Dental services and oral health related quality of life	Total Frequency (%)	OHRQoL		Interpersonal Racism			Poor OHRQoL
		Good (n=440)	Poor (n=445)	No Racism (n=424)	Low Racism (n=280)	High Racism (n=181)	Unadjusted OR
Last dental service							
Less than a year ago	412(46.6)	196(47.6)	216(52.4)	196(47.6)	141(34.2)	75(18.2)	Ref
More than a year ago	473(53.4)	244(51.6)	229(48.4)	228(48.2)	139(29.4)	106(22.4)	0.85(0.65-1.11)[b]
Reason for last visit to dentist*							
Check up	338(38.2)	215(63.6)	123(36.4)	190(56.2)	95(28.1)	53(15.7)	Ref
Problem	547(61.8)	225(41.1)	322(58.9)[a]	234(42.8)	185(33.8)	128(23.4)	2.50(1.90-3.31)[b]
Avoid dental care because of cost							
No	599(67.7)	328(54.8)	271(45.2)	297(49.6)	183(30.6)	119(19.9)	Ref
Yes	286(32.3)	112(39.2)	174(60.8)[a]	127(44.4)	97(33.9)	62(21.7)	1.88(1.41-2.50)[b]
Difficult to pay a AUD100 dental bill*							
None, Hardly any, a little	484(55.3)	265(54.8)	219(45.2)	251(51.9)	155(32.0)	78(16.1)	Ref
A lot	392(44.7)	170(43.4)	222(56.6)[a]	168(42.9)	124(31.6)	100(25.5)	1.69(1.21-2.17)[b]
Self-rated oral health							
Excellent, very good, or good	589(66.6)	351(59.6)	238(40.4)	305(51.8)	183(31.1)	101(17.1)	Ref
Fair or poor	296(33.4)	89(30.1)	207(69.9)[a]	119(40.2)	97(32.8)	80(27.0)	3.43(2.55-4.62)[b]

*indicates missing data

a: Poor OHRQoL vs Good OHRQoL: p value for chi^2 :</=0.05

b: Poor OHRQoL vs Good OHRQoL: p value for univariate logistic regression:</=0.25

Table 5.6.5: Univariate association between interpersonal racism and poor OHRQoL (n=885)

Interpersonal Racism	**Total Frequency (%)**	**OHRQoL**		**Poor OHRQoL**
		Good (n=508)	**Poor (n=503)**	**Unadjusted OR**
Interpersonal Racism				
None	424(47.9)	238(56.1)	186(43.9)	Ref
Low	280(31.6)	125(44.6)	155(55.4)	1.59(1.17-2.15)
High	181(20.2)	77(42.5)	104(57.5)[a]	1.73(1.22-.46)
Interpersonal Racism				
None	424(47.9)	238(56.1)	186(43.9)	Ref
Any	461(52.1)	202(43.8)	259(56.2)[a]	1.64(1.25-2.14)
Interpersonal Racism*Gender				
None: Male	114(26.8)	67(58.8)	47(41.2)	Ref
None: Female	310(73.1)	171(55.2)	139(44.8)	1.15(0.75-1.79)
Any: Male	178(38.6)	87(48.9)	91(178)	1.49(0.92-2.39)
Any: Female	283(61.3	115(40.6)	168(59.4)[a]	2.08(1.33-3.23)
Interpersonal Racism*Age				
None: <40	237(55.9)	140(59.1)	97(40.9)	Ref
None:>40	187(44.1)	98(52.4)	89(47.6)	1.31(0.89-1.92)
Any: <40	257(55.7)	125(48.6)	132(51.4)[a]	1.52(1.06-2.17)
Any:>40	204(44.2)	77(37.7)	127(62.3)[a]	2.38(1.62-3.49)

a: Poor OHRQoL vs Good OHRQoL: p value for chi^2 :</=0.05

Table 5.6.7: Multivariate models examining the association between interpersonal racism and poor OHRQoL (n=885)

	Model 1	**Model 2**	**Model 3**	**Model 4**
LR chi^2	143.54	143.51	144.98	145.10
Pseudo R^2	0.1170	0.1170	0.1182	0.1183
Log likelihood	-541.650	-541.066	-540.93	-540.87
Area under curve (AUC)	72.6%	72.6%	72.7%	72.7%
Hosmer and Lemeshow chi^2	8.78(p value: 0.360)	9.29 (p value: 0.318)	8.74(p value: 0.364)	8.35 (p value: 0.400)
Low Racism High Racism None	1.45(95%CI:1.04-2.03) 1.40(95%CI: 0.95-2.06) Ref			
AOR of Any Racism and poor OHRQoL		1.43(95%CI :1.08-1.92)	1.48(95%CI :1.09-1.98)	
No Racism Female Any Racism Male **Any Racism Female** No Racism Male				1.14(95%CI: 0.71-1.82) 1.37(95%CI: 0.82-2.30) 1.74(95%CI: 1.07-2.81) Ref

Model 1: Adjusted for education, health-card, car, self-reported oral health, dental visit, visiting dental for problem, not going to dentist because of cost, no family support and age

Model 2: Adjusted for education, health-card, car, self-reported oral health, dental visit, visiting dental for problem, not going to dentist because of cost, no family support and age.

Model 3: Adjusted for education, health-card, car, self-reported oral health, dental visit, visiting dental for problem, not going to dentist because of cost, no family support and age+ forcing other variable like gender

Model 4: Adjusted for education, health-card, car, self-reported oral health, dental visit, visiting dental for problem, not going to dentist because of cost, no family support and age +added the interaction term (gender*racism)

5.7 Discussion

In this study, we found that individuals who reported interpersonal racism were more likely to have poor oral health quality of life. The association was strongest among those who reported experiences of interpersonal racism in four or more settings (classified as high racism), and among women. The associations held after adjusting for sociodemographic and cultural identity characteristics including age, education, and other oral health related variables.

Previous research conducted among Indigenous populations has found strong associations between interpersonal racism and different aspects of oral health such as increased early childhood caries, less frequent tooth brushing and less frequent visits to dental services particularly among pregnant women (89, 92, 199). However, the association between interpersonal racism and OHRQoL has received limited attention. Interpersonal racism may impact OHRQoL via several pathways. Experiences of interpersonal racism may cause cognitive, emotional and physical signs of stress contributing to poor mental and psychosocial well-being (200). Further, these experiences could negatively impact adaptive behaviours (regularly tooth brushing even when feeling anxious or stressed) and promote certain maladaptive behaviours (increased tobacco smoking and alcohol consumption) (200). The feeling of inferiority induced by experiencing interpersonal racism, especially across multiple settings, could lead to dental fear and anxiety, which may in turn lead to avoidance of services and deterioration in dental status (201). It has been argued that those who enter this vicious cycle, visit the dentist only when necessary (because of an existing problem) and not for general routine check-ups and preventive care. This is also evident by our findings that more than half of the individuals who faced any kind of interpersonal racism were going to consult the dentist because of an existing problem and not for the routine check-up.

Experiences of interpersonal racism could also impact on an individual's sense of coherence (SOC). This has been proposed to underpin positive health-related behaviours as high levels of SOC have been associated with improved physical and psychological health (202). Studies have reported positive associations between SOC and the frequency of dental check-ups, positive oral health-related behaviours and OHRQoL among non-Indigenous populations (203-206). The same mechanism could be present and possibly amplified among Indigenous populations, who in general experience high levels of stress and social disadvantage and reduced access to dental and other health services (207). Thus, participants experiencing interpersonal racism may have a lower SOC that might consequently lead to poorer OHRQoL.

Cultural sensitive strategies that encompass Indigenous population's understanding of SOC are needed to plan such interventions, as it may be an important concept to target in dental health promotion strategies among Indigenous individuals.

We found that although the frequency of interpersonal racism was higher in males, the association between interpersonal racism and OHRQoL was strongest among females. Previous studies have reported that racism negatively impacts females by affecting their daily activities such as a commute in public transport, grocery shopping and other related things which may compound the existing social inequalities faced by Indigenous women (92, 208). Our findings add weight to this evidence demonstrating that interpersonal racism may significantly deteriorate OHRQoL among women. We speculate that this may be linked to a higher proportion of psychological distress among Indigenous females, which has been consistently reported in national health surveys of Aboriginal and Torres Strait Islander peoples (10). Thus, experiences of racisms and possible negative effects of psychological well-being may be compounded by the disproportionately higher levels of distress experienced by Indigenous women effects. Further research that explores the possible mediating or modifying effects of psychological distress and gender in the relationships between interpersonal racism and poor oral health is warranted. Further studies are needed to examine in detail the underlying mechanism by which interpersonal racism can impact OHRQoL specifically among women. In light of past studies, it has been postulated that emotional and psychological well-being are important determinants of oral health and OHRQoL and given that Indigenous women are more vulnerable to interpersonal racism and had higher impact on OHRQoL, we recommend future research should be targeted particularly to this group.

The assessment of interpersonal racism in this study involved nine items, which gave us the flexibility to assess the frequency of interpersonal racism experienced in different situations (1-3 places or 4-9 places). We found that the poorest OHRQoL was observed among those who reported higher levels of interpersonal racism (e.g. in 4-9 settings). Increased odds of poor OHRQoL were also observed in those whom reported lower levels of interpersonal racism, but to a lesser degree. The adjusted odds for poor OHRQoL were comparable to those reporting low and high racism. This is similar to the strength of associations reported between interpersonal racism and general and oral health issues (89, 92, 210).

This is the first study to examine the association between interpersonal racism and OHRQoL among a large sample of Indigenous Australians. Established, validated instruments were used

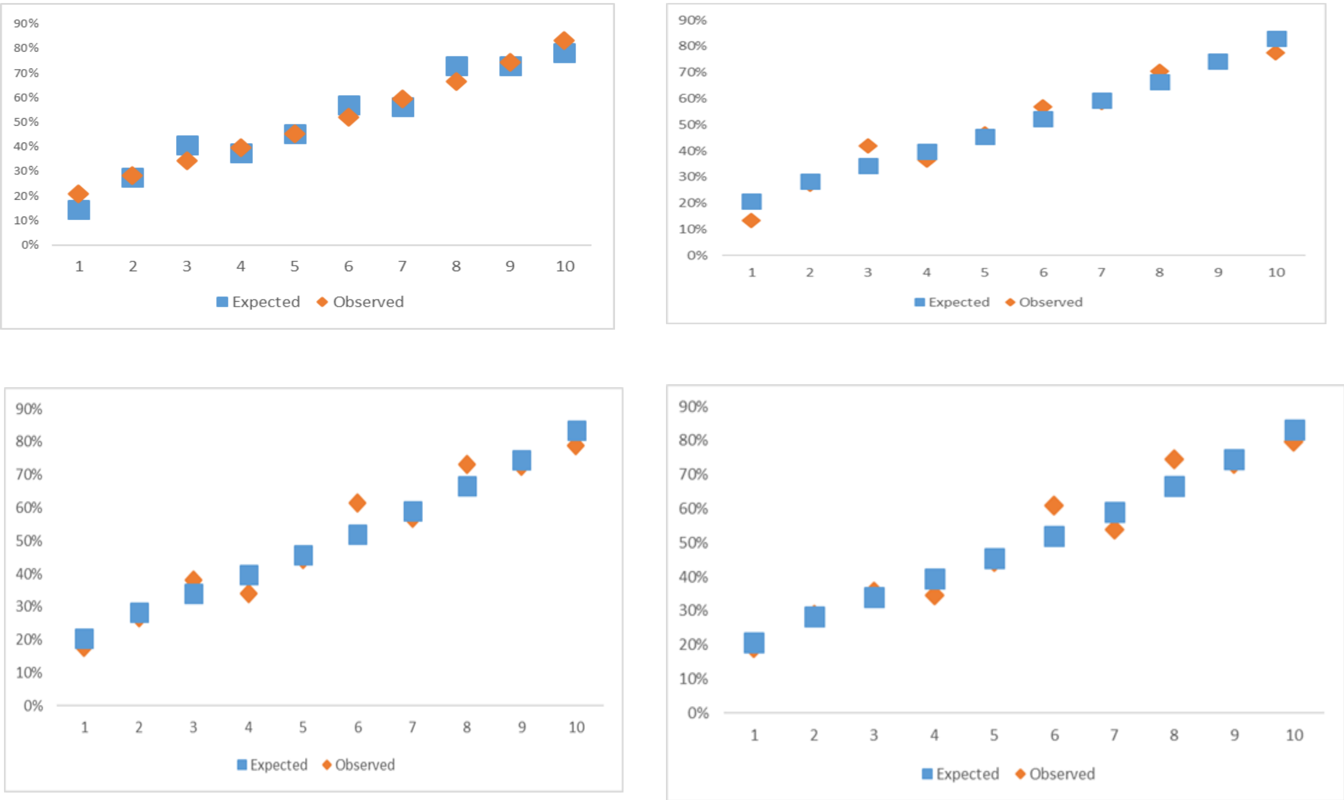
to capture both experiences of interpersonal racism and OHRQoL. Other strengths include use of Indigenous staff and a reference group guided the research. Our study findings should, however, be interpreted carefully as several limitations exist. First, participants were not representative of the entire Australian Aboriginal and Torres Strait Islander population, thus findings may not be generalizable. Second, the cross-sectional nature of data collection limits examination of temporality, and any causal assumptions. Third, a self-reported questionnaire was used to collect information on most of the variables therefore subject to recall and desirability bias. In addition, data on interpersonal racism was missing for 12% of the cohort. This may lead to a conservative bias, as it is possible that fears of disclosing experiences of interpersonal racism will have led some to avoid answering this question in the study. Thus, further studies, particularly with other Indigenous populations, are required to confirm these findings.

5.8 Conclusion

In this cross-sectional study, we identified a positive association between interpersonal racism and poor OHRQoL. The strength of the association was higher for females, but still present in males. The positive associations remained after adjustment for potential confounding factors. Targeting the broader societal, cultural and historical determinants that influence interpersonal racism in Australia warrants an urgent implementation of microsocial policies that may buffer the experiences of interpersonal racism among Indigenous Australians. These microsocial policies should target empowerment of Indigenous communities in oral health promotion decision, improving SOC and societal level policies (culturally sound and safe) should be implemented to reduce interpersonal racism. This may, in turn, result in improved OHRQoL to support Indigenous Australians to be able to live lives free of dental pain and enjoying the full benefits of optimal oral health.

5.9 Supplementary documents

Figure S2: Model 1-4: Goodness of fit:



CHAPTER SIX: Understanding the experiences of oral healthcare among Indigenous people living in South Australia

6.1 Preamble

This chapter contains the fourth study of the thesis, which comprises a qualitative study among Indigenous South Australians that assessed experiences of oral healthcare services and barriers faced while seeking preventive oral healthcare. This study identified barriers at individual, interpersonal, community and macro levels, indicating the need for comprehensive strategies at all levels for improving access to oral healthcare among Indigenous South Australians. Several enablers were also identified, focused on the role of grandparents, community members and community resources.

6.2 Abstract

Objective: To understand the experiences of oral healthcare and the individual and broader factors that influence use of oral healthcare services among Indigenous people living in South Australia.

Methods: This qualitative study was part of a larger study examining oral human papillomavirus (HPV) infection among Indigenous South Australians. A total of 19 interviews were conducted with Indigenous male and female participants. Emerging themes were identified using an inductive approach with line-by-line coding of interview transcripts using NVivo 12 software (QSR International Pty Ltd. Version 12.6.1). The analyses were informed by theoretical frameworks developed to examine oral health inequities, with themes organised under the following categories: individual (proximal), interpersonal (immediate), community (intermediate) and macro (distal).

Results: At the individual level, major themes concerning barriers to use of health services included: fear and shame, negative past experiences and oral health misconceptions. At the interpersonal level, personal stressors and racial discrimination were identified as key influences on use of services, whereas at the community-level, accessibility of services and the degree of community-based services and support from community members were identified as important factors. At the macro level, complex processes relating to financing and

reimbursement for oral healthcare as well as workforce shortages were important impediments to use of oral healthcare services.

Discussion: There is an urgent need for a greater focus on oral health promotion in Indigenous communities to reduce shame and stigma surrounding oral health issues. Improvements in oral healthcare services are also needed, that address discrimination and factors that limit the accessibility of services, in conjunction with broader strategies that address the current size and cultural competence of the oral health workforce in Australia.

6.3 Introduction

Reducing health inequalities is a priority of the Australian Government, demonstrated in the national Close the Gap campaign (211). Oral health is a key indicator of general health and has important impacts on health-related quality of life and wellbeing (212, 213). Across the life span, the basic requirements to support good oral health include regular tooth brushing, the avoidance of sticky and sugary foods, an optimal intake of fluoride, visiting a dentist regularly, and avoiding tobacco and alcohol (102). More broadly, many oral health issues can be prevented by providing a supportive home environment, by providing regular access to preventive dental healthcare and financial support to attend oral healthcare, and through continued efforts to raise community awareness of oral health promotion principles and practices (14, 103).

Social disadvantage can negatively influence many of the factors supporting good oral health, resulting in oral health inequities (107). This is observed among Indigenous people who experience a higher prevalence of dental caries, periodontitis and oral cancer than non-Indigenous Australians (211). Yet despite this higher burden of oral diseases, Indigenous people are around 20% less likely to visit a dentist and less likely to receive preventive dental care (214).

Existing research identifies the importance of addressing the social determinants of poor oral health (104-106), yet there has been limited exploration of the experiences of Indigenous people regarding access to oral healthcare. Of the few available studies undertaken, a consistent finding is that Indigenous people experience difficulty accessing current services, for a variety of reasons including costs and cultural inappropriateness, and previous negative experiences (106-108). Here we build on this literature to undertake an in-depth exploration of the

individual, interpersonal, community and macro-level factors that influence oral healthcare seeking and use of oral health scare services among Indigenous people living in South Australia.

6.4 Methods

This qualitative study was part of a larger study examining oral human papillomavirus (HPV) infection among Indigenous South Australians described elsewhere (117). Ethics approval for the qualitative study was received from the University of Adelaide (Approval Number: H-2016-246) and the Aboriginal Health Research Ethics Committee (AHREC14-18-865). Two interviewers (one Indigenous (J Hedges) and one non-Indigenous researcher (A Ali)) with extensive experience of working with Indigenous Australians conducted the interviews. The Indigenous researcher was present with the participants while the other interviewer joined remotely via video conferencing services (215). Participant information sheets were shared with the participants in plain English language before the interview commenced. The interviewer spent a lot of time developing a rapport with the participants. This was over the course of several days prior to the formal interview and occurred either over the telephone or at an Aboriginal Community Controlled Health Organisation. The interview was conducted once a signed informed consent was obtained.

6.4.1 Setting

A total of 19 interviews were conducted with participants from different regions of South Australia including Adelaide, Port Augusta, Mount Gambier, Whyalla, Port Lincoln, and Port Pierre. Adelaide is South Australia's cosmopolitan coastal capital with over one million population. Port Augusta, Mount Gambier, Whyalla, Port Lincoln, and Port Pirie are regional areas with an average of 223 to 650 kilometres distance from the Adelaide (216, 217). Three participants were from Port Augusta (male: 2, female: 1), four from Mount Gambier (male: 3, female: 1), five from Whyalla (male: 1, female: 4), four from Port Lincoln (male: 1, female: 3), two from Port Pirie (female: 2) and one female from Adelaide.

6.4.2 Sampling Strategy

Participants aged 18 years and above were included if they identified as Aboriginal and/or Torres Strait Island people residing in South Australia and were willing to give an interview. Participant's information was taken from the parent study. Selected participants were offered to participate in the study and they were sampled to give variation with respect to study site, gender and age.

6.4.3 Data collection technique

Interviews were conducted via video conferencing services (Zoom) and were audio or video recorded with the participant's consent. The length of the interview ranged from 30 to 45 minutes. Zoom is a video/audio conferencing tool and has user-specific authentication, real-time encryption of meetings, and has the ability to backup recordings to online remote server networks ("the cloud") or local drives, which can then be shared securely for collaboration. All interviews were audio or video recorded and consent for recording was taken separately from participants. All interviews were conducted as per participants' availability and at their preferred location. The study questionnaire was designed by the research team and was shared and refined with the senior Indigenous Research Officer on the parent study. The questionnaire aimed to capture experiences and barriers related to access and utilisation of oral healthcare services, health behaviours including oral hygiene practices, interpersonal factors such as social stressors and broader macro-social factors that influence social inequalities (Appendix 2). All interviews were transcribed and analysed in NVivo 12.

6.4.4 Analysis

Braun and Clarke's framework for reflexive thematic analysis guided the analytic process (219). Instead of a structured codebook, an inductive theme approach was used and line-by-line coding was undertaken with NVivo 12 software (QSR International Pty Ltd. Version 12.6.1). Initial codes were developed around the participants perceptions about their oral health, experiences of care, and broader social and cultural factors occurring in their lives. For iterative thematic development, similar codes were then grouped. The analyses then drew on the framework, formulated by Patrick and colleagues (114), that was developed to better understand the determinants of oral health inequalities. The authors identify key influences reflecting, proximal/individual level factors (e.g. personal oral health hygiene practices etc.),

immediate/interpersonal factors (e.g. social stressors, family environment etc.), intermediate/community factors (e.g. access to oral healthcare, cultural factors regarding the importance of oral health, community education etc.) and distal/macro level factors (e.g. the organisation of oral health services, regulation of the sugar content of food etc.). Emerging themes identified were consequently organised according to these four categories of influential factors.

Coding and initial identification of emerging themes was undertaken by one researcher (A Ali), and themes were further refined through discussion with co-authors (A Rumbold and J Hedges). Critically, the study's Senior Indigenous Research Officer (J Hedges) was involved in all stages in providing insights in the interpretation of the findings based on her first-hand cultural knowledge and lived experience. To maintain confidentiality and privacy pseudonyms are used instead of participant's actual names.

6.5 Results

Of the total 19 participants, 12 were females and 7 were males. The age of participants ranged between 19 to 60 years. Four individuals were living in Aboriginal hostels (accommodation for Indigenous Australians who need to be away from home to access education, employment, health and other services), two individuals were living alone, and the remainder were living with family.

6.5.1 Individual level factors:

At the individual level, three main themes emerged: fear and shame, negative past experiences and oral health misconceptions.

6.5.1.1 Fear and shame:

Participants commonly expressed fear and shame about visiting a dentist. This reflected a fear of being judged, particularly about the state of their teeth and a perception that they would receive different treatment to a non-Indigenous person accessing oral healthcare. Some participants spoke about a fear of pain associated with dental treatments:

"Because you see they all have fear. They think that dentist will put something in the gums and it's painful. I think that's it because they are sensitive about their mouth." (Participant: 5, Male, 55 years)

Participants also spoke of embarrassment and stigma due to missing teeth and avoiding oral healthcare services due to feeling ashamed of unhealthy behaviours related to eating, smoking and/or alcohol use:

"they [Aboriginal individuals] don't want the dentist to see what they are eating and how their teeth and gums look like." (Participant: 1, Female, 50 years)

6.5.1.2 Negative past experiences

A history of negative experiences with dentists and other oral healthcare providers was consistently identified as a barrier to using services. In some instances participants recalled negatives experiences as a child using the school dental program, whereas others spoke of more recent experiences:

"No, no conversation, I don't know why they pulled out my front tooth. And it was front tooth, imagine. So that was embarrassing for me to walk around like that. I wish we would had the mask thing then. You know. We should be treated like another human being, not just like a sheep be pushed in and get it done." (Participant: 19, Female, 40 years)

6.5.1.3 Oral health misconceptions

While there was generally good knowledge of the effects of sugar, alcohol and smoking on oral health female participants frequently reported oral health deterioration during pregnancy and breast-feeding, and expressed misinformation that this was due to foetal demands on calcium and/or was a normal part of pregnancy:

Participant: "I lost my teeth, during my last pregnancy, because she took all the calcium for me"
Interviewer: Did you see a dentist during pregnancy?
Participant: No, There's not enough communication out there because nobody told us that we can go to the dentist like this" (Participant: 10, Female, 60 years)

6.5.2 Interpersonal or immediate level factors:

At the interpersonal level, personal stressors and racial discrimination were identified as key barriers. Conversely, grandparents were consistently identified as important enablers for oral hygiene practices for children and encouraged use of oral healthcare services.

6.5.2.1 Personal stressors

Personal stressors were frequently reported by participants as affecting their oral health and whether they sought oral healthcare services. Female participants in particular identified the demands of family responsibilities and a lack of social support as impacting on their ability to care and prioritise their oral health:

"When I was young I used to work hard for my family. I was so busy working that I could not look after my own teeth. I would say I had pretty smile. I used to love that smile." (Participant: 12, Male, 60 years)

On the other hand, grandparents were consistently reported by participants as having an important role in promoting oral health by reinforcing the importance of brushing and healthy eating:

"For my granddaughter, she is now 2 years old, I started brushing her teeth when she started walking at 1 year. I even paid for her tooth brush." (Participant: 1, Female, 50 years)

Some participants, who were grandparents, reported singing brush time songs to their grandchildren and often took responsibility for taking their children to dental visits.

Four female participants shared their personal experiences of experiencing family violence and reflected on the impact this had on their oral health. For some, this meant that oral health was not considered a priority, whereas others reported that the family member responsible for the violence prevented them from visiting a dentist:

> *"When I was first knocked out by my husband some of my teeth fell out and my family told me to get it fixed. But my husband was around so I said no I can't go now. My husband knocked me out several times and one day I said enough!! He [ex-husband] is not around anymore. I am free now." (Participant: 9, Female, 32 years)*

6.5.2.3 Racial discrimination

Racial discrimination was identified as one of the major factors that prevented male and female participants from visiting a dentist. Participants shared their experiences of experiencing racial discrimination in various settings and across the life course:

> *"Yeah, I have a bad experience with white people and I have experienced it every day, this is not from just the dentist but with any white fella. In school, while growing up, we have always heard racist comments". (Participant: 9, Female, 32 years)*

Participants also spoke about specific instances of discrimination during a visit to an oral healthcare provider. Participants expressed feeling spoken to in a "nasty way" and feeling that the dentist "doesn't want to deal with me". For some, experiences of discrimination prevented them from visiting a dentist altogether:

> *"It [discrimination] happens, a lot. People who say that racism is not that bad... You got to be of a different colour to experience it… that feeling of being discriminated against stuck to me and I never went to the dentist again.*

I pulled my teeth by myself. The way they treat and looked at us, it's better to do it by ourselves." (Participant: 8, Male, 40 years)

Participants identified "cultural difference" with "white fella dentists" as a reason for the discrimination, yet also reported positive experiences with seeing dentists from other nationalities outside of Australia:

"Like he [non-white non-Indigenous dentist] greeted and welcomed me and you feel like sitting in there, whereas on the other hand at the white dentist you feel that you don't belong there and you are in a different place." (Participant: 16, Female, 38 years)

6.5.3 Community or intermediate level factors:

At the community level, a range of barriers to accessibility was reported. These included lack of information about prevention and treatment options, limited time and lack of privacy, lack of local services and long waiting times.

Participants also identified the role of community members in promoting oral health, community education programs and the school dental programs as key enablers to use of oral healthcare services.

6.5.3.1 Accessibility to dental services

6.5.3.1.1 Lack of information about preventive and treatment options

With respect to approachability of oral healthcare services, participants expressed that they did not have enough information on existing available oral healthcare services, including appropriate preventive and available treatment options. In particular, there was a perception that Indigenous people only visit the dentist with an established oral health problem, often when the issue become severe rather than for routine check-ups:

"And then you know I'm not really in the system and I sort of look at myself and do the right things for my body, but not in terms of my teeth. Just didn't have that information on and all that." (Participant: 3, Male, 45 years)

There was a lack of awareness among some participants that oral health treatments often required multiple visits to the services, with some expressing the expectation that their oral health issues were not dealt with in one visit.

6.5.3.1.2 Limited time and privacy

Participants expressed a number of concerns about the acceptability of oral healthcare services. Their concerns centred on the limited time available in the consultation, which left them feeling like procedures were rushed with limited explanation and with an inadequate discussion of an overall treatment plan:

"You can tell by their body language, the way they [dentist] treat, put water in your mouth, the drilling. You can tell that they are rushing. They're in hurry. Not communicating what they going to do. You need to have the patience to listen to your patients but they will just ignore by saying yeah yeah….yeah. It's like they're rushing. They're in hurry, do this, and do that. You should have the patience to look into people's mouths, but dentists are like yeah yeah you know." (Participant: 4, Male, 49 years)

Participants want services that spend time with patients and had welcoming environment for Indigenous people, with one participant commenting:

"But that can only happen if we receive the same respect. If it's in and out only then why would we go." (Participant: 11, Female, 32 years)

Other concern reported by participants included a lack of privacy during the treatments. Most reported that there were no separate rooms available and that they could see and hear other patients in situations of distress, which made the participants more nervous, as well as hear confidential information being discussed.

6.5.3.1.3 Lack of local services and long waiting times

Problems related to availability of dental facilities and accommodation were commonly reported by participants. Participants living in rural and remote area indicated that for tooth extraction and other surgical procedures there are not enough facilities in their regions necessitating travel to Adelaide. Participants reported not being able to attend appointments in Adelaide due to a lack of transport options, appointment cancellations and last minute changes to appointment times. Participants spoke of the requirement to have an escort (e.g., when patients require general anaesthetics) and viewed this as important, yet this was also identified as a barrier for those that do not live close to the facility due to the require the escort to travel:

> *"I was supposed to go last week, but I just don't have someone to escort me because I was required to be put to sleep for my procedure and I needed an escort... I found this at the last minute, and so I didn't end up going to the appointment. And also where I was staying at hostel none of them could accompany me." (Participant: 2, Female, 42 years)*

Long waiting period for appointments was another point of concern for some participants, who spoke about needing to call the dental facility several times to even book an appointment:

> *"They [dentist] all are the same. Long waiting period and you need to see them straight away." (Participant: 6, Female, 50 years)*

6.5.3.1.4 Cross-cultural communication difficulties, poor pain management and inconsistent care

Participants reported on a range of issues related to the quality of the oral healthcare provided, including cultural inappropriateness and communication styles, as well as the control of pain and other clinical issues. Foremost, many participants reported that either themselves of members of their family or local community had difficulty understanding what the dentist is explaining to them. This related to the use of technical terms and pre-and post-operative instructions were usually not clear. In addition, issues related to a lack of interpreters and/or Indigenous healthcare workers available to attend dental visit were also raised:

"You know many Aboriginal people do not speak English …You can't have a personal interpreter every day standing in a room to interpret instructions... I wish them to have a recorder so we can listen afterward and ask someone to translate for us... Something like that recorder is a good idea to have." (Participant: 15, Female, 38 years)

The other concern participants verbalised was regarding the inefficiency of dentists to control their pain. Most reported that dentists were not sensitive enough to understand when the patients do complain about pain:

"Once I went for my teeth. They put six needles and there's only two teeth which they need to pull out and I still felt and I was in so much pain I cried you know. He (dentist) couldn't relieve my pain. I couldn't breathe you know." (Participant: 6, Female, 50 years)

Some participants also shared experiences of inconsistent care including incorrect tooth extraction, mishandling of instruments, and an extraction of teeth that could have been saved. For some, they felt that the dental appointment was not able to address the oral health issue that concerned them the most. Participants also wanted continuity of care provider but were not able to access this:

"When you go back to the one dentist and you see another dentist person, as they say you cannot always see the same person. And when you visit another dentist and tell them what's wrong, they put blame on previous dentist for example they took a wrong tooth out and things like that you know." (Participant: 7, Male, 53 years)

6.5.3.2 Community-based services and support

Participants reported mixed experiences about community-based services such as school dental programs. Most considered the school programs were an important service that enabled them

to access dentists regularly, particularly as the service was offered, free of charge. For some, quarterly or six-monthly dental visits were mandatory by schools. Participants also spoke about other school-based oral health awareness programs running in schools, for example getting students to brush their teeth after lunchtime, encouraging use of mouthwash, and giving out toothbrush and toothpaste free, and the importance of these for motivating children to build oral health habits from a very early age:

> *"In the past, it was in school where kids were asked to wash their face and clean their teeth. They used to play one song to encourage them. They watched all the kids doing same so they all were motivated." (Participant: 17, Female, age 57)*

However, for some, negative experiences with the school program had enduring effects on their willingness to use oral healthcare services later in life:

> *"I would have been then about 10 years. We had a horrible dentist there [school] to see, and he would say to us that you don't look after your teeth and you have too much sugar and coke in your diet, which was certainly not the case in my family. We haven't had coke while growing up. But yeah he would always make you feel embarrassed. I used to walk out crying and I still get really emotional going to the dentist." (Participant: 14, Female, age 54)*

In addition to community-based services, the role of community members in encouraging oral healthcare and use of services was identified by many participants. In particular, female participants who had previously worked in the health sector reported that it is their role to encourage community members to seek help and provide support for oral health to other community members:

> *"I'll go, I'll go knock on their door and say let's go. I will ask them what you need help with your teeth. Come on let's go and do this, you know. There's help out there just need that encouragement. Because I just go in and talk to them as a family." (Participant: 13, Female, age 59)*

6.5.4 Macro or distal level barriers

At the macro level, key impediments to use of oral healthcare services included the complex processes of financing and reimbursement and oral healthcare workforce shortages.

6.5.4.1 Complex processes of financing and reimbursement

In Australia, individuals are eligible for free dental healthcare if they are residents and receive government benefits. However, most participants were not aware of the dental benefit of their healthcare card:

> *"Centrelink has resources or not, I don't know. What they just do is they just used to put pressure on you to find jobs and search for jobs and never explain us any benefits." (Participant: 6, Female, age 50)*

In addition, participants reported difficulty-providing evidence to be able to receive free dental care when they had an urgent oral health issue. Failure to have the required documentation to access immediate care and not having a healthcare card at the appointment resulted in them being ineligible to access the public dental health services. Many participants believed that there should be some flexibility if they are unable to bring all the valid documents to the appointment, particularly if English is not their first language and assistance is not available:

> *"As soon as you get into the clinic, and they ask what's wrong? I don't know what's wrong, I'm not a dentist, you are a dentist you tell me what is wrong. They [Dental staff] take the yellow paper [Concession form] and asked us not to come again as we can't use that paper again in the same clinic and this put us off." (Participant: 5, Male, 55 years)*

6.5.4.2 Workforce shortages

For those participants with dental care services available in their community, most spoke about shortage of dentists, which resulted in delays in getting appointments and reduced the likelihood of going to the dentist for routine, preventive check ups:

"They're understaffed. I do not know their capacity, you know. You would be lucky if they will see you in every six months You walk in and ask for that I need an appointment now. They will tell you to wait for six months they couldn't do it straight away." (Participant: 18, Male, 19 years)

All participants spoke about appreciating the role of Indigenous healthcare workers in supporting oral health. Participants believed that having an Indigenous representative gives them confidence in conveying their problems to the dentist. Participants reported feeling safe in those facilities where there are Indigenous workers. Participants also shared a desire to have Indigenous dentists and reported that young Indigenous students should be encouraged to become dentists:

"Provide us an Aboriginal dentist here, or some health worker … and I wouldn't be ashamed of going to an Aboriginal dentist." (Participant: 8, Male, 50 years)

In addition to increasing the number of Indigenous dentists and oral healthcare workers, participants identified opportunities to improve the cultural competence of the current workforce, including communication styles as described earlier under the theme of accessibility to services.

Table 6.5.1: Summary of factors that influence Indigenous people's use of oral healthcare (n=19)

Level	Theme and subtheme	Supporting quotes
Individual/proximal factors	Fear and shame • Fear of being judged	*"We want treatment where there is no judging about us drinking alcohol and having rotten teeth." (Participant: 1, Female, 50 years)*
	• Perception of receiving different treatment	*"One time, they took, they actually took a lady in while I was sitting there waiting to be called in. They took a woman in for me, knowing that I was on time for my appointment and they told me to wait. Something like this happens to me, every time in my dental appointments so when you get treated like that you just shy away from going and getting attention and things like that keep happening." (Participant: 14, Female, 54 years)*

	• Fear of dental treatments • Shame about unhealthy behaviours • Stigma from tooth loss	*"Once I went for my teeth. They put six needles and there's only two teeth which they need to pull out and I still felt and I was in so much pain I cried you know. He (dentist) couldn't relieve my pain. I couldn't breathe you know." (Participant: 6, Female, 50 years)* *"They don't want dentist to see what they are eating and how their teeth and gums look like." (Participant: 1, Female, 50 years)* *"I've only got four missing. Sometimes I feel shame to smile and I try to cover it a lot while I talk. But I'm trying to get that fixed." (Participant: 8, Male, 50 years)*
	Negative past experiences	*"No, no conversation, I don't know why they pulled out my front tooth. And it was front tooth, imagine. So that was embarrassing for me to walk around like that. I wish we would had the mask thing then. You know. We should be treated like another human being, not just like a sheep be pushed in and get it done" (Participant: 19, Female, 40 years)*
	Oral health misconceptions	*Participant: "I lost my teeth, during my last pregnancy, because she took all the calcium for me." Participant: 13, Female, 59 years)* *Interviewer: Did you see a dentist during pregnancy?* *Participant: No, There's not enough communication out there because nobody told us that we can go to the dentist like this" Participant: 10, Female, 60 years)*
Interpersonal factors	Personal stressors • Family responsibilities and lack of support • Family violence	*"When I was young I used to work hard for my family. I was so busy working that I could not look after my own teeth. I would say I had pretty smile. I used to love that smile." (Participant: 12, Male, 60 years)* *"When I was first knocked out by my husband some of my teeth fell out and my family told me to get it fixed. But my husband was around so I said no I can't go now. My husband knocked me out several times and one day I said enough!! He [ex-husband] is not around anymore. I am free now." (Participant: 9, Female, 32 years)*

	Racial discrimination	*"It [discrimination] happens, a lot. People who say that racism is not that bad... You got to be of a different colour to experience it… that feeling of being discriminated against stuck to me and I never went to the dentist again. I pulled my teeth by myself. The way they treat and looked at us, it's better to do it by ourselves." (Participant: 8, Male, 40 years)*
Community/intermediate factors	Accessibility of services • Lack of information about preventive and treatment options	*"You know I'm not really in the system and I sort of look at myself and do the right things for my body, but not in terms of my teeth. Just didn't have that information." (Participant: 3, Male, 45 years)*
	• Limited time and privacy	*"You can tell by their body language, the way they [dentist] treat, put water in your mouth, the drilling. You can tell that they are rushing. They are in hurry. Not communicating what they going to do. You need to have the patience to listen to your patients but they will just ignore by saying yeah yeah….yeah. It is like they're rushing. They are in hurry, do this, and do that. You should have the patience to look into people's mouths, but dentists are like yeah yeah you know." (Participant: 4, Male, 49 years)*
	• Lack of local services and long waiting times	*"I was supposed to go last week, but I just don't have someone to escort me because I was required to be put to sleep for my procedure and I needed an escort... I found this at the last minute, and so I did not end up going to the appointment. And also where I was staying at hostel none of them could accompany me." (Participant: 2, Female, 42 years)*
		"You know many Aboriginal people do not speak English …You can't have a personal interpreter every day

	• Cross-cultural communication difficulties, poor pain management and inconsistent care	*standing in a room to interpret instructions... I wish them to have a recorder so we can listen afterward and ask someone to translate for us... Something like that recorder is a good idea to have." (Participant: 15, Female, 38 years)*
	Community-based services and support	*"In the past, it was in school where kids were asked to wash their face and clean their teeth. They used to play one song to encourage them. They watched all the kids doing same so they all were motivated." (Participant: 17, Female, age 57)* *"I'll go, I'll go knock on their door and say let's go. I will ask them what you need help with your teeth. Come on let us go and do this, you know. There is help out there just need that encouragement. Because I just go in and talk to them as a family." (Participant: 13, Female, age 59)*
Macro/distal factors	Complex processes of financing and reimbursement	*"Centrelink has resources or not, I don't know. What they just do is they just used to put pressure on you to find jobs and search for jobs and never explain us any benefits. (Participant: 6, Female, age 50)*
	Workforce shortages	*"They're understaffed. I do not know their capacity, you know. You would be lucky if they will see you in every six months You walk in and ask for that I need an appointment now. They will tell you to wait for six months they couldn't do it straight away" (Participant: 5, Male, 55 years)*

6.6 Discussion

Through this qualitative study, we explored experiences and factors that influence Indigenous participants use of oral healthcare services. Individual, interpersonal, community and macro-level factors were identified. Fear and shame, negative past experiences and oral health misconceptions were identified as key factors influencing use of oral healthcare at the individual level. While personal stressors and racial discrimination were identified at the interpersonal level, whereas at the community level, accessibility of services and the degree of community-based services and support from community members were highlighted. Lastly, complex finance and reimbursement processes and shortages of oral health staff were main barriers to use of oral healthcare services.

Fear of being judged, a perception of receiving different treatment, fear of dental treatment and shame about unhealthy behaviours have been identified in previous research as barriers to oral healthcare and are further reinforced by the findings of the current study (106, 219, 220). More broadly, they reflect the ongoing impacts of colonisation and transgenerational trauma that have contributed to distrust and fear of the healthcare system, which has not been designed, with the needs of Indigenous communities in mind. Western expectations and protocols are pervasive in existing oral healthcare services, yet the findings of this study indicate the need for services to be more inclusive and flexible when treating Indigenous people, especially those living in remote areas. Open ended, two-way welcoming communication and services are critical to build trust and empowerment about oral health among Indigenous people. In addition inclusion of Indigenous healthcare workers and community members in the development of oral healthcare services is also likely to assist in mitigating fear and shame (221, 222).

Many participants reported cultural insensitiveness, lack of respect, discrimination, and racism within existing services as major barriers to seeking dental care, suggesting the current system may be undermining rather than promoting oral health in this population (223). Thus, there is a need for the current oral healthcare workforce, which is predominantly non-Indigenous, to adopt anti-racism and other strategies that address the range of complex structural and social factors that are often ignored yet play a key role in decisions about oral health among Indigenous people (219). A contributing factor to negative stereotyping is a lack of cultural knowledge (224, 225). Cultural competency awareness interventions and cultural awareness training have been found to improve relationships between healthcare providers and culturally diverse clients (226). However, research has found that current cultural awareness training about Indigenous people has limited impact on health professionals' abilities to provide culturally safe care (227). Therefore, revised cultural education models are needed to improve the delivery of culturally safe oral care to the Indigenous Australians. This includes training that is ongoing, engaging and specific to the region where the oral healthcare providers are working. In addition, non-Indigenous healthcare workers need to accustom themselves to the lived experiences of Indigenous Australians in order to develop and strengthen connections and relationships with Indigenous patients (228). Encouraging yarning with clients is an important way to build connections to understand the actual cause of the oral health conditions and tailor care accordingly. This approach would also help to reduce frustration expressed by participants that their consultations are rushed.

The findings of this study also demonstrated that among participants there was often limited knowledge of the benefits of early intervention, of regular dental visits and of available public dental service. Participants' experiences of visits to oral healthcare providers also suggested there is a strong focus on compliance with certain behaviours but with limited information sharing. Participants also emphasized the need for ongoing community-level programs and education. They reinforced the significance of involving community leaders and Indigenous healthcare workers in the planning of oral health programs for strengthening the integration of culture in these programs. Previous studies have highlighted the potential of Indigenous healthcare workers not only in planning and execution of oral health programs but in providing support services for Indigenous clients (229, 230). Thus continuing to build the Indigenous oral healthcare workforce is critical.

Participants also discussed lack of local services, shortage of oral healthcare staff, poor accessibility, limited consultation time and long waiting period. As previously reported in the literature there is a significant need for mobile dental clinics in remote Indigenous communities (231, 232). Mobile dental clinics can help facilitate visual publicity and awareness about oral healthcare and for some, it may be perceived as a safer option than the conventional indoor dental clinic environment (233). Studies have also reported the potential of community consultation and yarning in breaking down the barriers and facilitating a strong community engagement (234). Mobile dental clinics may help in reaching out to communities and have the potential to facilitate a deeper level of engagement by being more welcoming, open and approachable (233).

Regular dental visits are an important and cost-effective method for preventing the occurrence of oral health problems and for suppressing the progression of dental disease by intervening at earlier stages (231). Previous research suggests negative experience including the behaviour and attitudes of dentists, and competing health problems can negatively impact on regular dentist attendance (224-227). In the current study, we also found that negative past experiences were major barriers to regularly attending. Few participants reported attending for routine check-ups, instead most reported that they visited the dentist when they are in pain only. In addition, participants identified lack of proper pain management during their treatment as one of the reasons they avoided visiting a dentist. Previous studies (106, 235) have reported fear of dental treatment and pain associated with dental injections as common concerns about visiting dentists. However, no other studies involving Indigenous people have reported a lack of pain

management as a barrier to oral healthcare. Oral pain management is poorly studied and should be explored in further research to understand the optimal ways to manage oral pain among Indigenous people.

The negative effects of domestic violence on oral health is a key finding of this study that has not been reported previously. Several female participants reported that domestic violence was a reason for having missing teeth, and this affected their willingness and ability to use oral healthcare services. This again highlights the need for flexibility in the provision of oral healthcare services, such as walk in clinics, and non-judgemental care, to reduce feelings of shame. More generally, female participants in this study commented that their oral health declined not only with their age but also with their circumstances, such as limited family support, and household responsibilities which they named as impudent to taking care of their own oral health. Some female participants also reported that their pregnancy had negatively impacted their oral health. There were common misconceptions regarding the reasons for poor oral health during pregnancy, suggesting that oral health education and management during and after pregnancy may be neglected. Female participants also reported that during pregnancy they were not referred for oral health check-ups and were sometimes asked to wait to have a dental procedure after delivery of the baby. Previous studies have reported the positive outcome of oral healthcare during antenatal care, simultaneously representing an opportunity to support oral health of the woman and the next generation (236-238). Midwives can have an important role in promoting oral healthcare during pregnancy yet a lack of resources, time and financial constraints, and barriers to referring on to dentists continue to hinder implementation into routine antenatal care (239). Currently, it remains unclear to what extent oral health promotion is incorporated into antenatal care in Australia.

In line with the findings of a previously published study (240) many participants reflected on their experiences of school dental program, and in general, participants' emphasized that despite not all experiences being positive they acknowledged the importance of school-based programs and services. However, previous research has demonstrated that once children surpass the age criteria for school programs their oral health can deteriorate as parents/caregivers cannot always afford fees for dental consultations (241). In the current study, some participants reported deterioration of their oral health during the teenage years. In addition, participants who were parents and grandparents reported that school programs helped in sustaining the oral health behaviours of themselves and the children under their care. In line

with the findings of the previously published study (240), this emphasizes the benefits of extended family including grandparents in promoting oral health in Indigenous communities.

6.6.1 Strength and limitations

This study contributes to a growing body of research reporting the experiences, perceptions, and barriers of Indigenous Australians related to oral health in South Australia. The qualitative nature of the study allowed participants to share personal stories and personal perspectives that in turn helped in highlighting the multi-faceted circumstances and challenges that the community faced while seeking oral health treatment. Previous qualitative studies have recruited participants from either urban (241) or rural locations (235), one study aimed to study Indigenous health workers' perceptions (219), while others focused on barriers related to women (107) and children (220, 240) oral health-seeking behaviours. However, this qualitative study examined experiences of both males and females, young and old participants from urban and rural areas of South Australia. Another strength is the use of videoconferencing application for conducting audio and/or video interviews as this provided the safe space and time for participants to engage in conversations. Within this cohort, videoconferencing interviews were conducted for the first time. Participants liked the idea of connectivity and the success of interviewing through this medium in this community has provided the opportunity to connect with the remote participants in future projects. This project is also unique in terms of a non-white, international immigrant interviewing along with the Indigenous interviewer. This helped participants to share their stories in a comfortable zone without being judged. Participants felt and expressed several times their connection with the interviewers and therefore despite being hesitant at the beginning of interview, all shared their stories open heartedly. With respect to the barriers accessing oral health, previous studies have reported barriers related to communication, finance, education, and socio-cultural factors but in a study participants also opened up about social barriers that are not previously associated with oral health inequity, for example, domestic violence (106, 219, 220, 240). The unique relationship that builds between interviewers and the participants allowed all to self-reflect on their own shortcomings and what these might bring to the research exchange. Participants not only shared the negative aspects but also appreciated the gradual change they are witnessing in oral healthcare. Limitations include representation of participants being potentially biased, as selected participants were

draw from those participating in the larger cohort. In addition, the findings may not be generalisable to Indigenous people living outside of South Australia.

6.6.2 Recommendations

This project has highlighted Indigenous voices and documented their perspectives. Culturally sensitive oral health programs and interventions should be formulated targeting the needs of the local community. Our findings also validate that targeted strategies should promote connection to culture and positivity towards Indigenous Australians as this can assist in buffering the effects of discrimination, prejudice, and racism. Programs targeting Indigenous oral health should involve Indigenous healthcare workers and community leaders from the planning until the execution phase. Mandatory training of dentists is essential to build understanding of the unique cultures of Indigenous people and communities in Australia. Moreover, such a system should be implemented where practicing in remote areas is encouraged. A functional and robust system for complaints and follow-ups is also needed. Finally, it is important to not only reinforce the importance of oral health but information related to healthcare benefits, oral health benefits particular to the community should be shared in great detail. School oral health programs are an important sector-wide initiative that can help in preventing oral health diseases and for promoting oral health discussions for achieving long-term management and sustainability in Indigenous communities of rural and urban areas. Despite having current evidence-based guidelines regarding oral health practices during pregnancy, female participants reported common misinformation around dental visits during pregnancy. Therefore, mandating oral health promotion and education for pregnant women, midwives, Indigenous health workers, and oral health professionals is recommended for dealing with misconceptions around oral health management during pregnancy.

6.7 Conclusion

Findings of this study identify a number of opportunities to improve the oral healthcare system to meet the needs of Indigenous people. Improving the cultural competence of the workforce is critical, this requires anti-racism strategies including cultural awareness training and workforce development strategies to recruit train and retain Indigenous people in the oral healthcare workforce. Improving communication about oral health, including preventive health

and pain management is also needed, as are oral health promotion strategies that address shame and stigma surrounding poor oral health and negative past healthcare experiences. These must include adoption of holistic concepts of oral and general health that build on cultural knowledge and strengths, including the positive role of extended family in promoting oral health and the unique skills of Indigenous healthcare workers as cultural brokers.

CHAPTER SEVEN: Discussion & conclusion

This thesis has contributed important evidence and built awareness of the under-explored area of Indigenous oral health and OHRQoL. A critical aspect of the thesis has been the privilege of gaining perspectives from Indigenous people throughout each component of research. Their involvement was demonstrated by the contribution of Indigenous researchers in the formulation of the research aims and objectives, as co-researchers in the collection and interpretation of both qualitative and quantitative data, and as co-authors in the publication and wider dissemination of study findings. In addition, this thesis would not have been possible without the many Indigenous participants who generously gave their time to participate in the longitudinal study and the qualitative interviews. I would particularly like to acknowledge the individuals who participated in the interview sessions, whose invaluable insights were imperative to chapters three to six, and towards my overall Ph.D. experience. It was a privilege to connect with these participants and to gain insight into their oral health experiences and needs.

Novel, high-quality evidence from this thesis addresses key gaps in understanding oral health conditions and OHRQoL among Indigenous Australians. This has improved the understanding of pressing oral health conditions, experiences and unmet needs regarding oral health and health-seeking behaviour, and the important modifiable social factors that influence the high burden of oral conditions and OHRQoL. The findings from this thesis provide evidence that can help integrate community needs and voices into strategies to improve oral health conditions and provide guidance for future research focused on developing preventive strategies.

This final chapter provides an overview of the key findings from each project, a discussion linking these findings, the strengths and limitations of the body of evidence, and recommendations for moving forward.

7.1 Relationship between periodontitis and oral HPV infection

The first aim of this thesis was to evaluate the association between periodontitis, oral HPV infection and OPSCCs; the second aim was to evaluate this association among Indigenous South Australians.

These two studies were undertaken to understand whether the presence of periodontitis could be used reliably to identify individuals who may benefit from increased surveillance for oral cancers, particularly among Indigenous Australians who experience unacceptably high rates of oral cancers and oral disease.

Chapter 3 collated and synthesised evidence concerning the association of periodontitis with oral HPV infection. The synthesis of 13 studies (72-74, 76, 78-81, 83, 135, 147-149) suggested a positive association between periodontitis and any oral HPV infection, yet this was based on overall, low certainty evidence. A positive association between periodontitis and high-risk HPV was not established. The meta-analysis was able to be performed using data from five observational studies (79-81, 135, 148); these were predominantly cross-sectional studies with inherent biases, including issues of temporality, difficulty in establishing cause and effect relationships, variation in baseline characteristics of participants, and biases with respect to residual confounding. Therefore, any conclusion should be interpreted with caution. In addition, the included studies were very heterogeneous with respect to participant characteristics, and assessment of periodontitis and oral HPV varied in the studies. None of the studies was longitudinal in nature; therefore, temporality has not been proven. Therefore, despite positive findings in existing studies, it is impossible to establish a causal relationship between periodontitis and oral HPV infection, necessitating the need for longitudinal studies.

Building on the findings of the meta-analysis, a cross-sectional study was conducted with 673 Indigenous adults living in South Australia. No significant association was found between periodontitis and either any HPV or high-risk HPV infection in the statistical models which included adjustment for potential confounding due to age, gender, location, education, smoking and alcohol intake, and history of oral sex. It is possible that the null finding reflects the assessment of periodontitis, which was based on self-reported rather than a clinical assessment (which was not possible due to COVID-19 restrictions), which may have led to under-estimate periodontitis as the questions are more likely to capture severe disease. However, it is also possible that the characteristics of participants are different from participants in previous research, which to date, has not involved Indigenous Australians. As Indigenous people experience unique barriers to accessing high-quality oral healthcare, it is important to conduct future studies with more robust methodologies for assessing the relationship between periodontitis and oral HPV infection among Indigenous Australians to determine whether further investment is needed to enhance surveillance and monitoring of OPSCCs.

Future studies should be longitudinal to aid in the assessment of potential causality, adopt a clinical assessment of periodontitis, and collect detailed information about possible confounding factors, including the history of HPV vaccination and several other sexual behaviours that could affect the transmission of HPV infection to the mouth.

While HPV vaccination programs remain an essential preventive strategy for OPSCCs (and other cancers), the rate of course completion of HPV vaccination is lower among Indigenous Australians, reducing the effectiveness of these vaccines (242). Therefore, there is a continued need to develop novel approaches for detecting individuals at high-risk of OPSCCs. A greater understanding of the role of periodontitis in HPV-positive OPSCCs would assist in early detection and long-term monitoring. However, it would also allow the dentist to create awareness regarding different preventive measures related to HPV-positive OPSCCs and the importance of maintaining good oral hygiene.

7.2 Strong impact of racism on OHRQoL

The third aim of this thesis was to evaluate the relationship between interpersonal racism and OHRQoL. Assessing the impact of racism on oral health and OHRQoL provides critical evidence to inform strategies to make the current oral healthcare system more culturally responsive. This evidence is also important for raising awareness of racism among oral healthcare providers and the need for more respectful forms of communication with Indigenous patients.

Chapter 4 described a study evaluating the impact of racism on OHRQoL. This is the first study that has assessed this relationship among Indigenous Australians. While previous studies have reported a negative impact of racism on oral health conditions and practices (89, 92, 200), the potential impact on OHRQoL has received little attention. This study found a negative impact of racism on OHRQoL after controlling for a range of potential confounders related to socioeconomic factors and access to dental services. The association was more prominent among females than males, with a disproportionately higher level of distress also noted among Indigenous women (199, 208). The findings indicate the need for culturally responsive approaches that include considerations of gender to improve oral healthcare for Indigenous Australians.

There is clear evidence that culturally responsive oral healthcare programs are possible when Indigenous people are involved in the development and implementation of programs and when programs respond to community needs and acknowledge the underlying sociocultural factors that impact oral health outcomes (243, 244). Research has also shown that acknowledgment and support of traditional practices, such as the use of cradles to pacify fussy infants instead of baby bottles containing sugary drinks, and yarning, can improve oral health in First Nations populations overseas (245).

Concerning culturally responsive programs that are gender-sensitive, previous research suggests that pregnancy is an important time to enhance oral health, with positive effects for not only mothers but also their infants. Training Indigenous health workers to provide basic oral health promotion advice during antenatal consultations can improve oral health literacy among Indigenous women. Literature also demonstrates the favourable impact of culturally appropriate interventions on oral health literacy during pregnancy. These approaches include Indigenous health workers yarning with Indigenous women about their oral health, oral health screening undertaken by Indigenous health workers, providing assistance in different referral options, and escorting patients to dental facilities (246-248).

When focussing specifically on OHRQoL, there is limited evidence about strategies that may improve OHRQoL of Indigenous men and women beyond providing culturally responsive oral healthcare. Existing research outside of Indigenous populations has focussed on disease management interventions. For example, two studies from Brazil reported a positive impact of periodontal therapy (e.g. supragingival and subgingival scaling and polishing with oral hygiene instruction) on OHRQoL of non-Indigenous Brazilians (249, 250). A further study conducted among Brazilian disadvantaged school students reported a positive impact of a school-based intervention designed to enhance an individual's sense of coherence on OHRQoL (251). This was achieved through different sessions and games, which stimulated schoolchildren to think positively about their health; they learned some ways to improve their oral health, became self-confident, and were able to plan some goals for their lives. Whether psychosocial interventions have the potential to enhance OHRQoL among Indigenous people is unclear. Yet, the positive impact found in existing research (252) suggests that such interventions, designed with community members and targeted to the needs of the community, could positively impact OHRQoL among Indigenous people. This warrants further exploration and robust evaluation.

7.3 Experiences and use of oral healthcare services

Chapter five builds on the findings of the two cross-sectional studies by providing in-depth evidence about experiences of oral healthcare among Indigenous people in South Australia. The high prevalence of oral conditions and the negative impact of racism on oral health and OHRQoL seen in previous chapters reinforced the need to gain insight into the oral health needs of Indigenous people and common impediments to effective oral health management and treatment.

The analyses were informed by framework suggested by Patrick et al. (114). The findings indicated a range of influential factors operating at the individual (proximal) level, interpersonal (immediate) level, community (intermediate) level and macro (distal) level. At the individual level, fear and shame, negative past experiences and oral health misconceptions were identified as key factors that prevented participants from seeking oral healthcare. At the interpersonal level, personal stressors and racial discrimination were identified as key barriers, whereas at the community-level, accessibility of services and the degree of community-based services and support from community members were they key barriers. At the macro level, complex processes relating to financing and reimbursement for oral healthcare as well as workforce shortages were key obstacles for the Indigenous participants to seek oral healthcare services. Some of the factors for e.g. fear and shame, fear of dental treatment, cultural insensitiveness, lack of respect, discrimination, and racism have been reported previously and are further reinforced by the current study (106, 219, 220, 240).

Some of the specific novel barriers highlighted in this study were the impact of domestic violence on oral health and the impact of domestic responsibilities on oral healthcare seeking behaviour. Participants spoke about family pressure and responsibilities that keep them occupied with limited time to visit a dentist. Some important misconceptions were also identified about the safety of dental procedures during pregnancy. Female participants also spoke about being unable to access referrals to oral healthcare providers during pregnancy and a lack of information about oral health provided during antenatal visits. Addressing the misconceptions and improving the provision of oral healthcare information during pregnancy are highly modifiable factors and highlight the antenatal period as an important target for oral health preventive strategies.

Previous research has focused specifically on the oral health of Indigenous women during pregnancy. A systematic review of nine studies identify a range of socioeconomic and psychosocial factors that affect oral health-seeking behaviour during this time (247). These include education, geographical setting, income, level of social support, and perceived personal control. Further, several intervention studies have demonstrated the positive impacts of antenatal education about oral health on knowledge, beliefs, attitudes, self-efficacy and oral hygiene, and health-seeking behaviours (252). Despite these positive findings, there appears to be a gap in translating these interventions into practice for Indigenous women during pregnancy. As per the national pregnancy guidelines, all women are advised to have oral health check-ups and treatment if required. During antenatal visits, midwives, obstetricians, Indigenous health workers and multicultural health workers are advised to discuss oral health with women (253). However, it is unclear how consistently oral health information is provided as standard care for Indigenous women who are pregnant. It is known that Indigenous women visit antenatal clinics less frequently and later in pregnancy than non-Indigenous pregnant women (254, 255), which may limit the opportunities to discuss oral health issues.

Despite some limitations of the school dentistry program, participants acknowledged the importance of such initiatives and reported some long-term positive impacts on their own oral health and that of future generations. Participants reinforced that support from the community, elderly Indigenous persons, and Indigenous healthcare workers are a source of positive reinforcement for themselves and their children to look after their oral health. This was also documented in a previous study with Indigenous South Australians that explored current barriers impeding parental efforts to establish oral health and nutrition practices among children (240).

With respect to oral health treatment options, in our study, participants felt that they were not given proper pain management following a dental procedure and felt there was room to improve oral consultations in terms of discussing comprehensive treatment plans, explaining the pros and cons of different treatment options and specifying clear pre and post-procedure instructions. Previous studies (106, 235) have reported the fear of dental treatment and injections among Indigenous people, but issues raised in the current study such as the level of pain management in terms of proper anaesthesia, prescribing and giving detailed post-operative medication and instruction, and lack of post-procedure follow-ups have not been comprehensively studied among Indigenous people. Previous research in other areas of health have highlighted inequities in the management of pain among Indigenous people but not in

relation to oral pain management (256). Therefore, the findings of this study also point to the need for improved oral healthcare not only culturally but also clinically, with a detailed plan for oral pain management and long-term monitoring to determine if medications are appropriate for managing oral pain.

Finally, the qualitative study has provided a snapshot of current oral healthcare-seeking behaviours and barriers faced by the Indigenous people. The findings demonstrate that oral health is considered an important aspect of health and wellbeing; however, multiple barriers, both structural (e.g., finances, process of reimbursement, issues of accessibility, supply of dentist and dental units) and interpersonal (e.g., personal stressors and racial discrimination) limit the uptake of oral health services. The findings highlight the need for further investment in Indigenous communities to prioritise oral healthcare and improve oral health literacy to mitigate the disproportionately high levels of severe pain from untreated oral disease, financial constraints to accessing services, and difficulty accessing preventive oral healthcare that is culturally relevant.

7.4 Strengths and limitations

The strengths and limitations of each individual project are discussed in corresponding chapters (Chapters two-six). The strengths and limitations detailed here relate to the thesis overall, including data sources and methodological considerations.

In this thesis, different research methods were used to generate high-quality evidence; for example, robust methodological approaches were used to synthesise evidence that informed questions that were then tested in a large prospective study. The qualitative method was used to provide in-depth information about oral healthcare experiences of Indigenous people. Combining these methods produced rich, high-quality data for formulating future strategies for the community.

Notably, half of my candidature was undertaken during the emergence of COVID-19, which caused a number of delays and challenges with respect to data collection. However, a novel approach was identified for conducting in-depth interviews remotely. For example, Zoom video conferencing service was used to provide a safe space and time for participants to engage in conversations. To ensure cultural safety, the interviews were conducted with an experienced Aboriginal researcher acting as a cultural broker who helped create an environment where

participants felt comfortable sharing their stories without being judged. The success of this method is reflected as participants shared not only their oral healthcare experiences but also experiences of cultural insensitivity, a lack of respect, as well as discrimination, and racism while seeking oral healthcare.

Further, participants reported that they liked the idea of enhanced connectivity to metropolitan areas using Zoom. The success of interviewing through this medium in this community has provided the opportunity to engage with remote participants in future projects.

Overall, the findings of the thesis should take into account the following limitations. First, this thesis is limited to Indigenous people in South Australia; therefore, the findings may not be generalisable to the experiences of other Indigenous people around Australia who have diverse cultures and practices. Second, temporality and cause-and-effect relationships could not be established because of the cross-sectional nature of the studies evaluating the association of periodontitis, high-risk HPV infection, racism and OHRQoL. Third, due to restrictions on face-to-face visits due to the COVID-19 outbreak, a self-reported periodontitis questionnaire was used in the study described in chapter three instead of conducting a clinical examination. The tool utilised is validated in non-Indigenous populations but has not been validated for use with Indigenous people, which may have reduced the ability to ascertain periodontitis accurately. Questions with high sensitivity and specificity for detecting periodontitis among non-Indigenous Australians were used to identify individuals with periodontitis. Therefore, it is possible that only participants with moderate to severe periodontitis were identified and with participants with less severe periodontitis perhaps being missed. However, using a self-reported tool is beneficial in other ways, as clinical and radiographical assessments are costly, time-consuming, and often not feasible in large population-based studies.

Nevertheless, the rate of periodontitis identified through this questionnaire was similar to that reported in the previous National Study of Adult Oral Health 2017–18, indicating that the questionnaire could be useful in evaluating such conditions in places difficult to access, such as remote and rural settings in different geographical locations. Validation of the tool is and should be a priority for future research to permit lower-cost population assessment of periodontitis. Further, although this study was based in South Australia only, using the survey rather than a clinical evaluation, allowed the data collectors to extend the coverage of study participants and recruit participants from different regional and remote areas of South Australia. Lastly, despite collecting information on most of the confounding factors and

controlling for most of the confounder factors through statistical analysis, the possibility of residual confounding cannot be excluded in both cross-sectional studies (Chapters 3 and 4).

7.5 Implications for policy and practice

This thesis has identified that Indigenous people continue to face an increased burden of oral health conditions and suboptimal oral healthcare. This high burden of oral disease coupled with experiences of racism and social risk factors contributes to poorer OHRQoL.

Collectively, this thesis provides several relevant recommendations for developing oral health policies for improving oral health and OHRQoL among Indigenous people. The current National Oral Health Plan 2015-2024 (257) identified Aboriginal and Torres Strait Island people as a priority population that needs the "development of integrated models of care that incorporate oral health education, prevention and screening with other primary care services". Chapter 3 explored whether periodontitis is associated with oral HPV infection, to understand whether periodontitis could be a valuable marker for enhanced screening. Yet the findings did not support an association. Further studies using a clinical assessment of periodontitis are needed. This chapter recommended the importance of novel prevention and screening strategies for continuous surveillance required for preventing the occurrence and progression of HPV-positive OPSCCs.

In addition, an important recommendation in the National Oral Health Plan is to "Increase the representation and engagement of Aboriginal and Torres Strait Island people in the oral health workforce". The findings of chapter six strongly align with this recommendation and identified the need for more Indigenous people trained as dentists and other representatives in the oral health workforce to encourage the Indigenous community to visit the dentist more frequently and regularly and enhance the cultural safety of oral healthcare.

The National Oral Health Plan indicated the importance of cultural competency in clinical management; findings of the cross-sectional study and qualitative study implicated the same. Chapter 5 reported the negative impact of racism on OHRQoL. Participants reported facing racism in different settings including in healthcare. Interpersonal racism affected dental visiting patterns; most participants visited the dentist only when necessary and not for general preventive care. These findings suggested the need for culturally sensitive approaches to improve oral health among Indigenous people. In addition, chapter six highlighted that one of

the main reasons for not visiting the dental clinic was cultural inappropriateness; therefore, it is crucial that clinical facilities and management should be culturally competent so that community members can visit the dentist without any hesitation and shame.

In line with the National Oral Health Plan for enhancement of programs to recruit and retain oral health students and professionals in regional and remote areas, the findings of the qualitative study implied the same by highlighting the need to recruit more dentists in regional and remote areas to address the issue of accessibility and availability of oral health practitioners.

Hence oral health promotion efforts are needed particularly in South Australia's regional areas. Programs that allow breaking down of barriers, empowering the community, and eliminate discrimination are required. In the qualitative study, female participants reported the negative impact of family responsibilities and domestic violence on oral healthcare seeking, highlighting the importance of broader social policies that address family and community wellbeing for oral health. The findings also reiterate the need for continued focus on the social determinants of health and how community empowerment strategies that address family violence and promote wellbeing are critical to promote oral health. It is important that interventions and educational programs for women should be separate, and oral health management during childbearing age and pregnancy should be implemented. A key recommendation emerging from this thesis is to involve Indigenous health workers at all levels of future research and policy related to oral health so that oral health services are culturally aligned and fulfil the need of Indigenous patients. The National Oral Health Plan indicated that to reduce the inequalities in oral health outcomes experienced by Indigenous community, the involvement of Indigenous health workers and community leaders should be encouraged. This is strongly supported by the evidence in this thesis.

There is evidence of successful past culturally appropriate and targeted oral health programs for Indigenous people. For example, the Aboriginal Health Program introduced in 2005 in South Australia reported that from 2005 to 2015, Indigenous Australians accessing mainstream dental care increased from 60 to 4800 people (258). This program involved targeted strategies encouraging the Indigenous community to visit dental facilities more frequently. Those strategies included free general oral check-ups, no waiting lists, encouragement of teenagers to visit the dentist, clearer referral pathways to ensure oral health access for Indigenous children and provision of oral health resources to the community. In New South Wales, oral health

promotion programs co-designed with local Indigenous communities have significantly improved oral health outcomes for Indigenous people (259, 260). In addition, oral health interventions involving trained local Indigenous people to deliver oral health promotion programs have also reported sustained improved outcomes for the Indigenous community (259-262). Several studies reported the successful delivery of oral health services in the Indigenous community that were culturally safe and involved training of Indigenous people in the delivery of oral health interventions (263-265). To date, several successful individual oral health projects (246, 259-267) involved Indigenous health workers, engaged local stakeholders, and were culturally appropriate but further advocacy and research to drive mandatory system-wide changes are still lacking.

7.6 Future research recommendations

Priorities for future research include:

1) Undertake collaborative research with Indigenous communities outside of SA that focuses on oral diseases and provides communities with a platform to articulate their specific needs regarding oral healthcare.
2) Use Indigenous research methodologies such as yarning and deep listening to further understand the context and depth of the community's oral health-related problems.
3) Further in-depth research to explore how oral healthcare can be further adapted to meet the specific needs of Indigenous women and men. Understanding the best ways to deliver oral healthcare antenatally and evaluating the role of midwives and Indigenous health workers in discussing and promoting oral healthcare during pregnancy are of key importance.
4) Understanding the best ways to manage oral pain among Indigenous people.

7.7 Conclusion

The research in this thesis supports the present evidence that Indigenous people face an increased burden of oral health conditions and negatively impacted social determinants on oral

health and oral health-related quality of life. Strategies are needed to enhance education about the importance of HPV vaccination, the risks of HPV infection, and healthy oral health practices among Indigenous communities. Along with these, education on safe sexual practices should be reinforced in the community. Awareness about emerging diseases, their negative consequences, and preventive measures should be shared with the community. Routine oral health check-ups and vigilant monitoring of any oral health condition are recommended to identify high-risk individuals.

To improve the quality of oral health of the Indigenous community, strategies must involve community leaders and create specific oral health roles for Indigenous health workers. Specific funding, national-level programs, and co-design of oral health services are needed to strengthen sustainability and to raise awareness among Indigenous communities.

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Appendices

Appendix 1: Cross-sectional studies questionnaires

Appendix 2: Qualitative study questionnaire

Appendix 3: Ali A, Lassi ZS, Kapellas K, Jamieson L, Rumbold AR. A systematic review and meta-analysis of the association between periodontitis and oral high-risk human papillomavirus infection. Journal of Public Health. 2021 Dec;43(4):e610-9.

Appendix 4: Ali A, Rumbold AR, Kapellas K, Lassi ZS, Hedges J, Jamieson L. Association between self-reported periodontitis and high-risk oral human papillomavirus infection among Indigenous South Australians: A cross-sectional study. Plos One. 2022 Mar 24;17(3):e0265840.

Appendix 5: Ali A, Rumbold AR, Kapellas K, Lassi ZS, Hedges J, Jamieson L. The impact of interpersonal racism on oral health related quality of life among Indigenous South Australians: a cross-sectional study. BMC oral health. 2021 Dec;21(1):1-1