The Role of Psychosocial Factors in Oral Health and Related Major Chronic Conditions

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics
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Abstract

Psychosocial factors may be a common pathway that increases the susceptibility to co-occurring oral health conditions and other non-communicable chronic conditions. This thesis aimed to investigate the role of psychosocial stress in the co-occurrence of oral health conditions and systemic chronic conditions. First, a scoping review was conducted which found psychosocial stress to be positively associated with both oral and other chronic diseases. Next, a cluster analysis of oral health and multimorbidity profiles was conducted which showed middle-aged and older Canadians to have varying health profiles based on their oral health and multimorbidity status. We also found that individuals with inadequate oral health and multimorbidity to be more likely to report experiencing psychological distress or adverse childhood experiences. Further research can be directed to better understand the contribution of factors of psychosocial stress to the co-occurrence of oral health and multimorbidity in Canadians over the life-course.

Keywords

oral health, multimorbidity, psychosocial factors, psychological distress, adverse childhood experiences, aging, CLSA, Canada
Summary for Lay Audience

As the number of adults aged 65 and older in our population continues to grow, the prevalence of oral disease and multimorbidity, or the co-existence of two or more chronic conditions, is also projected to increase, highlighting the importance of understanding the risk factors that contribute to the co-occurrence of these conditions around aging. Psychosocial stress has been shown to increase the risk of both oral diseases and other chronic conditions such as heart diseases and diabetes. However, the relationship between psychosocial stress and the co-occurrence of oral health conditions and multimorbidity is less understood. The overall aim of this thesis was to explore the role of psychosocial stress in the co-occurrence of oral health conditions and multimorbidity. The first study was a scoping review which compiled findings from 30 studies examining indicators of psychosocial stress and their relationship with oral and systemic diseases. Indicators of psychosocial stress included perceived stress, emotional distress, lifestyle conditions, childhood adversity, and the stress hormone cortisol. We found that high stress was associated with both oral and non-oral diseases. The majority of studies (70%) included only one systemic disease, and only one study investigated the role of childhood adversity. The second study used data from the Canadian Longitudinal Study on Aging (CLSA)—a Canada-wide, on-going cohort study of adults aged 45-85 years at the time of recruitment. In this cluster analysis, we identified five distinct groups of individuals based on their oral health and multimorbidity status. We found that individuals with poor oral health and/or high rates of multimorbidity were more likely to report experiencing psychological distress or adverse childhood experiences compared to participants with good oral health and low rates of multimorbidity. Further research is needed to fully understand how stress contributes to the co-occurrence of oral health conditions and multimorbidity among Canadians to help develop better strategies to prevent these health issues and promote overall well-being.
Co-Authorship Statement

This thesis includes two integrated articles, which have been or will be submitted for publication to a peer-reviewed journal. The co-authorship details for each article are presented below.

**Chapter 3:** Hensel A, Nicholson K, Anderson KK, & Gomaa N. The Role of Psychosocial Stress in the Oral-Systemic Health Connection: A Scoping Review.

Abby Hensel was involved in the conception and design of the study, study screening, extraction of data, data analysis, interpretation of data, and writing the first and subsequent drafts of the paper. Dr. Noha Gomaa was involved in the conception and design of the study, interpretation of data, writing drafts of the paper, and critical revision of the article. All authors critically reviewed the manuscript and provided feedback.


Abby Hensel was involved in the conception and design of the studying, data acquisition and curation, coding and statistical analysis of data, and writing the first and subsequent drafts of the paper. Steve Lee was involved in the statistical analysis of data. Drs. Kathryn Nicholson and Kelly K. Anderson were involved in the design of the study, interpretation of results, and in the critical revision of the article. Dr. Noha Gomaa was involved in the conception and design of the study, data acquisition, interpretation of results, writing drafts of the paper, and in the critical revision of the article.
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List of Abbreviations

ACE – Adverse Childhood Experiences

ACTH – Adrenocorticotropic Hormone

AIC – Akaike Information Criterion

APA – American Psychological Association

AVP – Arginine Vasopressin

BDNF – Brain-Derived Neurotrophic Factor

BIC – Bayesian Information Criterion

BMI – Body Mass Index

CAL – Clinical Attachment Loss

CATI – Computer Assisted Telephone Interviews

CEVQ – Childhood Experience of Violence Questionnaire

CI – Confidence Interval

CLSA – Canadian Longitudinal Study on Aging

COPD – Chronic Obstructive Pulmonary Disease

CRH – Corticotropin Releasing Hormone

CRP – C-Reactive Protein

DAG – Directed Acyclic Graph

DASS – Depression Anxiety and Stress Scale

DMFT – Decayed, Missing, and Filled Teeth
DSP – Derogatis Stress Profile

DT – Distress Thermometer

GCF – Gingival Crevicular Fluid

HPA – Hypothalamic-Pituitary-Adrenal

IgA – Immunoglobulin A

IgG – Immunoglobulin G

IL-6 – Interleukin-6

LCA – Latent Class Analysis

LES – Life Events Scale

MeSH – Medical Subject Heading

OHM – Oral Health and Multimorbidity

OR – Odds Ratio

PHAC – Public Health Agency of Canada

PRISMA-ScR – Preferred Reporting Items for Systematic Review and Meta-Analysis

Extension for Scoping Reviews

PSS – Perceived Stress Scale

REB – Research Ethics Board
Chapter 1

1 Background

1.1 The Oral-Systemic Health Connection

The relationship between oral health and other chronic conditions, commonly referred to as the oral-systemic health connection, has been an area of increased interest and investigation in both clinical and oral health policy circles (1). A large body of literature demonstrates that both groups of diseases are linked through biological mechanisms. For example, periodontal disease – which is the most common inflammatory condition affecting the tooth-supporting structures and a major cause of tooth loss – is known for its association with an array of chronic conditions including heart disease, diabetes, osteoporosis, and possibly adverse pregnancy outcomes, although the strength of the evidence on these associations varies (2–7). Previous studies have also shown the number of functional teeth to predict mortality and cognitive health in older adults (8,9). These associations have consistently been attributed to underlying inflammatory mechanisms. Periodontal disease is often initiated by an uncontrolled host-inflammatory response to a slow and constant bacterial colonization (10–12). Pathogens trigger leukocytes of the innate immune system to release pro-inflammatory mediators, such as cytokines, that play an essential role in the progression of chronic periodontitis (13). These pathogens activate the immune system, contributing to an exacerbated progression of inflammation (12,13). As the immune response continues, damage occurs to both soft and hard periodontal tissues such as the tooth-supporting bone, gums and periodontal ligaments (12,13). Prolonged disruption to the oral microbiome may trigger innate immune pathways (14,15). Thus, failure to resolve the inflammatory response sustains the release of pro-inflammatory mediators and triggers pathogenic processes that may extend to other locations, eventually contributing to systemic inflammation (12). Periodontal pathogens can be dislodged directly to induce and promote systemic inflammation either by exacerbating firsthand toxin release or by the dislodgment of microbial products into the bloodstream (12,13). Several oral pathogens, such as *P. gingivalis* and *A. actinomycetemcomitans*, may contribute to the risk of heart disease and myocardial infarction (16,17). Similarly, these
processes have been linked to the risk of diabetes and other conditions with an inflammatory basis (18).

1.1.1 Multimorbidity and Oral-Systemic Health

With a larger proportion of individuals now being in middle and older ages, many more people live with chronic long-term conditions such as heart diseases, cancers, diabetes, periodontal disease, and tooth loss, with the prevalence and co-occurrence of these conditions increasing as individuals age (19,20). In response to an age-related demographic shift in the population and the number of older individuals presenting with multiple chronic conditions, increased attention is now being placed on the issue of multimorbidity. Multimorbidity refers to the co-existence of two or more chronic diseases or health conditions simultaneously in an individual (21). Extensive research has shown the negative impact of multimorbidity on individuals’ lives and its broader societal effects. The co-occurrence of multiple chronic conditions is associated with reduced well-being and quality of life, as well as an increased risk of disability, functional decline, and mortality (22).

Among the various health conditions associated with multimorbidity, oral diseases have recently gained attention in relation to their co-occurrence with multimorbidity. Individuals with multimorbidity often experience compromised immune function, medication side effects, and limited physical capabilities, which can contribute to an increased risk of developing oral health conditions such as dental caries and periodontal disease. Conversely, oral disease can also worsen existing systemic conditions in individuals with multimorbidity. However, our understanding of the association between oral disease and multimorbidity, their co-occurrence, and their shared risk factors and pathways is limited (23,24).

1.2 Models and Pathways Explaining the Oral-Systemic Health Connection

1.2.1 Biomedical Model and Biological Factors

Explanations of the oral-systemic health connection that are solely inflammatory-focused largely follow the biomedical model. The biomedical model is one of the most dominant
in the Western literature and focuses on health purely in terms of biological factors (25). Specifically, it is characterized by attributing illness to physical disruptions (25–27). For example, an infection is explained with pathogenic processes, a metabolic disorder with a genetic mutation, a psychiatric disorder with an imbalance of neurotransmitters, and so on (25).

Under the biomedical model, disease is always reducible to a physical or biological disruption (26). It is focused on aspects which are viewed as analyzable into separate parts. This is a mechanistic view of biology in which parts are not changed by the context and therefore can be studied in isolation. Another notion that is attributed to the biomedical model is the specific understanding of ‘health’ as being merely the absence of physical signs of disease (28,29). The biomedical model focuses on specific findings that are interpreted as causal factors of a disease or disorder that need to be eliminated by medical interventions. As a result, “curing” a disease is exclusively a task for medical professionals and medical technology, whereas an individual with the disease is a receiver of such cures (25).

The biomedical model has been extensively used to explain the oral-systemic disease connection and has dominated discussions in this area, starting with the focal infection theory to contemporary studies employing multi-omics. However, there are several limitations to the biomedical model (30). The main criticism is that illness is a condition of the whole person, and treating independent organs or systems in isolation might alleviate some symptoms without solving the source or “root cause” of the problem (25,31,32). This has become increasingly evident with the rising prevalence of chronic illnesses and metabolic disorders such as diabetes (33), obesity (34), and heart disease (35). Another criticism of the biomedical model is that it objectifies individuals and reduces them to an object of illness or passive target of therapy, rather than as an active part in the healing process (36). Finally, this health model fails to account for the various conditions under which an illness occurs in the absence of physical or biological signs of dysfunction (25). For example, under the biomedical model, burnout may be translated into depression, effectively reducing a complex psychosocial phenomenon to a medically accepted symptom (37). However, the problem arises when burnout is then treated medically as if it
were depression instead of being treating independently. The failure of the biomedical model in fully explaining the oral-systemic health connection is further highlighted by evidence that clinical and chair-side oral health interventions that aim to alleviate periodontal diseases do not necessarily, on their own, alleviate the risk of associated systemic health conditions (38,39). Thus, other models that incorporate more than just the physical manifestations of a disease are essential to further investigate the oral-systemic health connection.

1.2.2 Biopsychosocial Model

To address the limitations and criticisms of the biomedical model, George Engel (1977) proposed a new model in the 1970s to better understand the various factors involved in health and disease (40). The biopsychosocial model is commonly used to explain how biological (e.g., viruses, bacteria, etc.), psychological (e.g., stress, coping strategies, health behaviours, etc.), and social (e.g., race/ethnicity, level of education, employment, etc.) factors work to influence and shape health across the lifespan (41). It embraces the advances of modern medicine while also highlighting that many conditions cannot be explained by detecting changes at the cellular or molecular levels (41–44).

Social and psychosocial exposures have long been postulated as common risk factors and pathways to oral and systemic health conditions (45). The biopsychosocial model helps in conceptualizing the role of social and psychosocial factors and their role in altering biological factors involved in oral and systemic health conditions (41). It is therefore considered a more comprehensive approach to understanding health. According to the American Psychological Association (APA), a psychosocial stressor refers to “a life situation that creates an unusual or intense level of stress that may contribute to the development or aggravation of mental disorder, illness, or maladaptive behaviour” (46). Previous research has demonstrated that stress may change the internal homeostatic state of an individual. The hypothalamic-pituitary-adrenal (HPA) axis constitutes one of the major endocrine systems that maintains homeostasis when an organism is challenged or stressed (47,48). During acute stress, the HPA axis is activated through the secretion of corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) by the parvocellular neurons of the paraventricular nucleus of the hypothalamus (49,50). These
neuropeptides activate the synthesis and release of adrenocorticotropic hormone (ACTH) from the pituitary (47–50). ACTH secretion then stimulates the adrenal cortex to synthesize glucocorticoids, such as cortisol, which helps regulate inflammatory responses and lymphocytic activity (47–50).

Although short-term elevations in glucocorticoids can reduce inflammation and mobilize immune components, when expressed over the long-term during chronic stress, glucocorticoids may reduce immunocompetency through the inhibition of immunoglobulin A (IgA), immunoglobulin G (IgG), and neutrophil function (51). IgA antibodies reduce the initial colonization of periodontal organisms, and IgG antibodies may make periodontal pathogens more vulnerable to phagocytosis by neutrophils (51). There is also evidence that longer-term elevations in cortisol may be associated with chronic inflammation because the glucocorticoid loses its ability to inhibit inflammatory responses initiated by the immune system (52). Therefore, depressed immunity and chronically elevated cortisol may result in inflammation and more destructive periodontitis (51,52).

It is widely accepted that chronic stress may cause a homeostatic shift in the diurnal rhythm of cortisol and stress-induced cortisol levels, increasing the sensitivity of the HPA axis (53). More specifically, chronic stress may cause dysregulation of corticosteroid receptors, directly resulting in increased vulnerability to oral and non-oral diseases (53,54). In particular, prolonged exposure to chronic stress has been accepted as a driver for the pathogenesis and exacerbation of numerous physical diseases over the lifespan, including periodontitis, heart disease, and diabetes (53–58). However, it is important to note that while the biopsychosocial model has had considerable impact in explaining inflammatory diseases, it has also been the object of controversies and criticism. One problem with this model is that it may be vague in the formulation of a method for collecting the relevant biopsychosocial information (59). Another critique of this model is that it may be difficult to implement into clinical practice (59). That said, it remains an important model that provides significant insight into disease initiation and progression through an ecological lens.
1.2.3 Psychosocial Stress, Agential Factors, and Coping Strategies

As discussed above, the biopsychosocial model accentuates the role of psychosocial stress in health outcomes. In addition to altering physiological responses, psychosocial stress may also be linked to agential factors and health behaviours as well as coping strategies, all of which have been shown to contribute to oral and systemic health (60,61). For example, a recent study has shown that health-harming behaviours, such as smoking, alcohol consumption, and less frequent tooth-brushing, co-occur among adolescents (62). Psychosocial stress has also been shown to impact stress-coping mechanisms or to dysregulate central autonomic functions involved (63,64). The latter has been shown to link social adversity and associated behavioural tendencies to an altered structure and function of stress-regulating regions such as the hippocampus (65). These findings suggest that the possible impact of stress on health behaviours and consequential oral and systemic health conditions may be regulated centrally (44,66).

Similar findings can also be observed in coping strategies that play a critical role in mitigating the relationship between stress, behaviours, and health. For example, inadequate coping skills have been shown to exacerbate the association between periodontal disease and diabetes (67), as well as stress and heart disease (68,69). Smoking, poor oral hygiene, and lack of physical activity, have also been associated with the stress-health relationship and directly linked to health risks (70). Evidence on the oral-systemic health connection suggests that enhancing individual behaviours, including oral hygiene practices, and the reduction of common risk factors, such as smoking and alcohol consumption, may mitigate the effects of psychosocial stress and may prevent and/or improve related systemic health outcomes (e.g., diabetes, heart disease, etc.) (71,72). Such agential factors have been argued to be supported by the social environment, social networks, and experiences of an individual, and may be explained by underlying central biological mechanisms (e.g., hippocampal value, HPA dysregulation, etc.) involved in the regulation of behavioural and agential factors related to stress (44,73).
1.2.4 Exposure to Psychosocial Stress in Early Life

The impact of social and psychosocial exposures on health outcomes may be influenced by the magnitude and the timing at which the exposure occurs over the lifespan (66). The life-course model envisions current health to be shaped by earlier exposures to physical, environmental, and psychosocial factors that mold biological outcomes (74). According to the developmental theory of the life-course perspective (life-span development), which focuses on the role of critical and sensitive periods in shaping health overtime, adverse childhood experiences (ACEs) such as growing up in poverty and/or experiencing neglect or abuse may alter the regulation of the HPA axis and increase the risk for health problems that manifest later in life (74–77). Although responses to an adverse environment may initially appear adaptive, prolonged dysregulation of physiologic stress mechanisms can persist into adulthood and older age (74,78).

A growing body of research has investigated the long-term effects of ACEs on the oral and general health of individuals. For example, adults who report ACEs have been shown to have worse oral health outcomes than those who did not report ACEs (79). ACEs such as abuse in its various forms (physical, psychological, emotional abuse and/or sexual) and neglect have been shown to be associated with oral health problems including tooth loss, dental pain, and periodontal diseases (79). Early life stress has also been shown to increase the risk of diabetes (80), ischemic heart disease (81), stroke (81), and hypertension (82). Some studies have also demonstrated that there is a graded dose-response relationship between ACEs and health outcomes in which the risk of diseases increases as the number of ACEs which an individual has experienced rises (83). Despite this, limited research has explored the association between ACEs and the co-occurrence of oral and systemic diseases.

To this end, we recognize that psychosocial stress may play a pivotal role in the disease process, with a magnitude of effect that can vary according to the timing of the exposure. To date, there has been little empirical evidence on the extent to which psychosocial stress at different timepoints (i.e., early in life versus later in adulthood) can contribute to the oral-systemic health connection. Thus, investigating psychosocial stress across the life-course is important in identifying risk factors for the oral-systemic disease connection.
1.3 The Role of Aging

Intrinsic processes, such as those related to aging, may also impact the extent to which psychosocial factors influence oral and systemic health. Aging is a complex biological process that occurs in an intricate biological and physiological setting. As we age, we progressively accumulate disease risk, thereby increasing the susceptibility for both oral and systemic diseases (84). Many extensively studied diseases, such as atherosclerosis, metabolic syndrome, neurodegeneration, autoimmune diseases, and cancer, have an age-associated occurrence and prevalence (85–90). This has given rise to the notion that aging may be a major risk factor for these diseases and that “inflammaging” may be a main contributor. Inflammaging refers to the chronic low-grade state of inflammation due to aging in the absence of overt infection, which has been postulated as a mechanism that can underlie both morbidity and mortality in older adults (91). Recent epidemiological studies have suggested that a state of mild inflammation, revealed by elevated levels of inflammatory biomarkers such as C-reactive protein and interleukin-6, are predictive of several aging phenotypes such as changes in body composition, immune senescence, disruption of metabolic homeostasis, and neuronal degeneration (92).

The accumulation of molecular and cellular damage over time contributes to an increase in the risk of chronic oral and systemic health conditions with age. The higher prevalence of periodontitis in older adults, relative to middle-aged or younger adults, can be a manifestation of inflammaging. Similarly, a higher proportion of older adults have multiple chronic inflammatory conditions compared to their younger counterparts. For example, approximately 24% of older American adults have at least one chronic condition, whereas 64% experience multiple co-occurring chronic conditions, such as periodontal disease, heart disease, dementia, or diabetes (24,93).

1.4 Thesis Rationale and Objectives

Previous research indicates that psychosocial stress may be a common risk factor to oral-systemic disease, and that oral and systemic conditions may frequently co-occur in individuals. Extensive research has been conducted on the contribution of psychosocial stress to oral disease as well as to systemic conditions. However, the role that psychosocial
stress play in the co-occurrence of oral disease and multimorbidity is less understood. With the growing population of adults aged 65 years and older, there is a rising prevalence of oral disease and multimorbidity, and therefore a need to identify possible risk factors to the co-occurrence of oral-systemic disease to help inform preventive measures.

1.4.1 Study Objectives

The overall objective of this thesis was to explore the relationship between oral health and multimorbidity among middle-aged and older adults, and to determine the extent to which psychosocial stress may contribute to the oral-systemic health connection. This was achieved through a scoping review of the prior literature (Chapter 2) to summarize the current state of knowledge on psychosocial stress as a common risk factor to oral and systemic disease in adults. Additionally, an analysis of national cohort data from the Canadian Longitudinal Study on Aging (CLSA) was conducted (Chapter 3) to identify how oral health and multimorbidity cluster together in middle-aged and older Canadians and investigate the extent to which identified disease clusters were associated with psychological distress and/or ACEs. To meet these objectives, our thesis aimed to answer the following questions:

1) To what extent do indicators of psychosocial stress contribute to oral and systemic diseases? (Chapter 2)

2) How do inadequate oral health and multimorbidity profiles cluster together in middle-aged and older Canadians? (Chapter 3)

3) To what extent do ACEs and psychological distress associate with clusters of oral health and multimorbidity? (Chapter 3)

We hypothesized that individuals with co-occurring poor oral health and multimorbidity would have higher levels of psychological distress and ACEs, whereas adults with poor oral health and low rates of multimorbidity, good oral health and high rates of multimorbidity, or good oral health and low rates of multimorbidity, would report lower levels of psychosocial stress. We anticipate that findings from this study will facilitate a better understanding of how oral and systemic disease co-occur. This information will
assist in identifying common pathways and risk factors for oral-systemic disease and will help inform preventive strategies for middle-aged and older Canadians.
Chapter 2

2 The Role of Psychosocial Stress in the Oral-Systemic Disease Connection: A Scoping Review

2.1 Abstract

Background: The association between chronic oral diseases and other major systemic health conditions, commonly referred to as the oral-systemic health connection, has been extensively studied. However, the pathways linking both groups of diseases are not well understood. Evidence suggests that psychosocial stress contributes to an increased susceptibility to chronic oral and non-oral diseases. The aim of this review is to summarize the current state of knowledge on the impact of psychosocial stress to the chronic oral and systemic diseases. Methods: A literature search was conducted using four databases (CINAHL, Embase, Medline, and PsycINFO) in addition to searching reference lists of original and review articles. A combination of keywords and search terms related to psychosocial stress, systemic disease, and oral conditions were used. Studies were eligible for inclusion if they included human adults (aged 18 years and older). Only English-language articles were considered. Results: A total of thirty articles (thirteen cross-sectional, eleven case-control, five cohort studies, one clinical trial) were included in the analysis. Periodontal disease was most commonly studied in relation to depression, diabetes, and heart disease. Psychosocial stress was measured using a range of psychometric and biologic indicators, including perceived life stress, emotional distress, individual and lifestyle behaviour, childhood adversity, and cortisol. In total, twenty-seven studies found a positive association between measures of psychosocial stress and oral-systemic health. Conclusion: Psychosocial stress contributes to both oral and non-oral diseases and their co-occurrence. Future longitudinal studies that use large and diverse population-based samples will be helpful to further understand the contribution of psychosocial stress to the oral-systemic disease connection.

Keywords: Psychological stress, oral disease, systemic disease, chronic disease, psychosocial factors, cortisol
2.2 Introduction

The oral-systemic health connection, which refers to the link between oral and other health conditions, has traditionally been a topic of particular importance for oral health policy and clinical practice (1). The oral cavity is at the intersection of medicine and dentistry and provides insight into general health (84,94). Various systemic diseases and related medications can impact the oral cavity, and oral pathologic conditions can likewise have a systemic impact. It has been estimated that more than 100 systemic diseases and upward of 500 medications have oral manifestations, which are typically more prevalent in the older population (94).

While there is a continued growing interest in the links between oral and systemic health, these connections are indeed an old observation. For example, the focal infection theory was defined more than a century ago by W.D. Miller as “a chronic, usually low-grade, infection that develops insidiously and progresses slowly and that can produce local and systemic symptoms” (95), suggesting the human mouth as a focus of infection. Miller theorized that oral microorganisms and/or their products are able to access other areas and organs that are adjacent to or distant from the mouth (96). The focal infection theory was primarily based on observations that linked oral sepsis and dental extractions with endocarditis. However, in recent years, the area of oral-systemic health research has considerably intensified and evolved, and there is now a plethora of evidence that demonstrates that both groups of diseases are linked socially and biologically, although the causal biological links remain in question. For example, periodontal disease, defined as the inflammation of tooth-supporting structures including the gums, ligaments and bone, has been consistently associated with atherosclerosis, heart disease, diabetes, osteoporosis, and other conditions (2–7). Meanwhile, the number of functional teeth has been postulated as a predictor of mortality and cognitive health in older adults (8,9). These are only examples of a growing body of literature linking oral health, mostly tooth loss and periodontal disease, with various health conditions, particularly in middle-aged and older adults.

In addition to the burden of oral-systemic disease on individuals, particularly older adults, the oral-systemic health connection also impacts societies and healthcare systems (24). Oral and systemic diseases have a significant socio-economic impact in terms of healthcare
costs, absence from work or school, and individuals’ daily lives and self-esteem (1,97). Furthermore, the lack of quality healthcare, barriers to costs of care, and lack of insurance are all factors that can prevent people from seeking medical and dental treatment (98). Thus, in order to identify those at risk of oral and systemic diseases and to inform early prevention and intervention, it is necessary to understand the risk factors and pathways that contribute to both oral and non-oral health conditions and their co-occurrence. Several pathways have been postulated, such as biological/biomedical (e.g., inflammation) and behavioural ones (e.g., smoking, lifestyle factors, oral hygiene habits). Additionally, adverse social exposures such as precarious living conditions and lack of affordability have been postulated to play a role in oral and systemic health conditions through the psychosocial stress pathway, although this remains understudied.

Despite the plethora of evidence on the contribution of psychosocial stress to each of chronic oral health and systemic conditions, little is known on whether it contributes to their co-occurrence, and possible underlying mechanisms. To answer these questions, we conducted a scoping review that aimed to identify the current knowledge on the role of psychosocial stress in co-occurring oral and systemic disease.

2.3 Methods

This scoping review was conducted to identify and describe the prior evidence on the contribution of psychosocial stress to the co-occurrence of oral-systemic disease in adults. A scoping review methodology was selected to examine the extent of the literature available, summarize the findings, and identify knowledge gaps (99). Searches and data extraction were conducted following the PRISMA-ScR (Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews) checklist (100).

2.3.1 Search Strategy

A systematic search of the literature was done using the following electronic databases: CINAHL, Embase, Medline, and PsycINFO in March 2022, and updated in March 2023. As each database has its own unique indexing terms, individual search strategies were developed for each database. The search strategy for each database is shown in Table 2.1. A combination of keywords and search terms using Boolean operators, truncation, phrase
searching, and MeSH terms related to: (i) psychosocial stress (e.g., psychological stress, adverse childhood experiences, life stress, etc.), (ii) oral health conditions (e.g., periodontal disease, dental caries, oral health, etc.), and (iii) systemic disease (included groups of chronic conditions consistent with the most recent definition of multimorbidity according to the Public Health Agency of Canada (PHAC) (101)) were used in the search strategy. Systemic condition search terms included arthritis, asthma, cancer, COPD, dementia, diabetes, heart disease, stroke. The search included all relevant published and unpublished literature available in the English language with no restriction on study design or article type. The reference lists and bibliographies of all included studies were hand searched for further references.
Table 2.1: Keyword search strategies for CINAHL, Embase, MEDLINE, and PsycINFO. For each database, keywords in each category were grouped together with “OR”, while the categories were grouped together with “AND”.

<table>
<thead>
<tr>
<th>Database</th>
<th>Search strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CINAHL</td>
<td>(“oral health” OR “periodontal diseases” OR “periodontitis” OR “dental caries” OR “mouth diseases” OR “tooth loss” OR “tooth diseases”) AND (“chronic disease” OR “arthritis” OR “asthma” OR “cancer” OR “pulmonary disease, chronic obstructive” OR “dementia” OR “diabetes mellitus” OR “heart diseases” OR “mental disorders” OR “stroke”) AND (“stress, psychological” OR “psychological distress” OR “adverse childhood experiences” OR “biological markers” OR “hydrocortisone” OR “adrenocorticotropic hormone” OR “brain-derived neurotrophic factor”))</td>
</tr>
<tr>
<td>Embase</td>
<td>(“periodontal disease” OR “mouth disease” OR “periodontitis” OR “dental caries” OR “tooth disease”) AND (“chronic disease” OR “arthritis” OR “asthma” OR “chronic obstructive lung disease” OR “dementia” OR “diabetes mellitus” OR “heart disease” OR “mental disease” OR “cerebrovascular accident”) AND (“mental stress” OR “emotional stress” OR “childhood adversity” OR “childhood trauma” OR “early life stress” OR “life stress” OR “biological marker” OR “hydrocortisone” OR “corticotropin releasing factor” OR “brain-derived neurotrophic factor”))</td>
</tr>
<tr>
<td>Medline</td>
<td>(“oral health” OR “periodontal diseases” OR “periodontitis” OR “dental caries” OR “mouth diseases” OR “tooth loss” OR “tooth diseases”) AND (“arthritis” OR “asthma” OR “pulmonary disease, chronic obstructive” OR “dementia” OR “diabetes mellitus” OR “heart diseases” OR “mental disorders” OR “chronic disease” OR “stroke”) AND (“stress, psychological” OR “psychological distress” OR “adverse childhood experiences” OR “biomarkers” OR “hydrocortisone” OR “adrenocorticotropic hormone” OR “brain-derived neurotrophic factor”))</td>
</tr>
<tr>
<td>PsycINFO</td>
<td>(“oral health” OR “dental disorders” OR “dental health”) AND (“chronic illness” OR “arthritis” OR “asthma” OR “chronic obstructive pulmonary disease” OR “dementia” OR “diabetes mellitus” OR “heart disorders” OR “mental disorders” OR “cerebrovascular accidents”) AND (“psychological stress” OR “childhood adversity” OR “psychosocial factors” OR “biologic markers” OR “hydrocortisone” OR “corticotropin releasing factor” OR “brain-derived neurotrophic factor”))</td>
</tr>
</tbody>
</table>
2.3.2 Eligibility Criteria, Article Selection, and Data Extraction

Titles and abstracts were reviewed using the following inclusion criteria: human empirical studies of adults (aged 18 years and above), psychosocial stress as an exposure measure, and outcome measures of both oral and systemic disease. Other criteria for inclusion were: (a) population-based observational studies; (b) peer-reviewed publication to assure a minimal threshold for quality of the studies; (c) no geographical restrictions were placed so as to allow for a global perspective; (d) studies published in the English language. Literature relating to animal studies, only inflammatory biomarkers of stress, children (0-17 years), and COVID-19 as a systemic condition were removed through the process of title/abstract screening. The reference lists and bibliographies of relevant systematic reviews, meta-analyses, case-reports, overviews, and commentaries were scanned to identify relevant studies; however, the reviews themselves were excluded.

Search results were extracted to Endnote and duplicates of identified records were removed and screened before the eligibility test during title/abstract/full-text assessment. One author (A.H.) conducted the screening process for relevance to the topic based on titles, abstracts, and full text. To ensure reviewer consistency, the first 50 articles were re-screened for inclusion after all other articles. Records that passed the initial screening had their full text downloaded and key information extraction to assess for inclusion. Items extracted as key information included: author(s) and year of publication; study design; study focus/aim; country of origin; sample size and demographics; exposure variable(s); outcome variables; and key findings. Results are reported in a narrative format, and no critical appraisal of individual studies was conducted, consistent with the scoping review approach (100).

2.4 Results

A total of 778 articles were identified and underwent titles/abstract screening for relevance. After screening by title and abstract, 556 articles were excluded, with the most common reason of either not including both oral and systemic conditions, or including inflammatory biomarkers of stress. After evaluating the full text of 65 articles, a total of 30 studies met the inclusion criteria for the current review (Fig. 2.1).
**Figure 2.1:** PRISMA flow diagram depicting the article selection process.

1. **Total articles identified by search in five databases** *(n = 778)*

2. **Duplicates removed** *(n = 210)*

3. **Articles remaining after duplicates removed** *(n = 568)*

4. **Articles identified through grey literature and reference lists** *(n = 53)*

5. **Screened by title and abstract** *(n = 621)*

6. **Records excluded based on exclusion criteria** *(n = 556)*

7. **Articles remaining, reviewed full text for eligibility** *(n = 65)*

8. **Records excluded based on exclusion criteria** *(n = 35)*

9. **Records included in scoping review** *(n = 30)*
2.4.1 Characteristics of Included Studies

Of the thirty articles included in this review, twenty-three studies used a psychometric measure of stress (Table 2.2) (102–124), ten studies measured stress biologically via cortisol (Table 2.3) (113,115,116,125–131), and three studies assessed stress both psychometrically and biologically (113,115,116). In total, the studies in this review involved 50,292 individuals, where the weighted mean age of participants was 60.0 (range 17-92) and 45.9% were female (range 16-100%). With regard to study design, thirteen used a cross-sectional design, eleven used a case-control design, five used a cohort design, and one was a clinical trial including baseline data comparing darapladib, a selective oral inhibitor of lipoprotein-associated phospholipase A2, with placebo in patients with coronary heart disease (123). There was also variation in geographical location, with ten studies conducted in Europe, six in North America, five in the Middle-East, five in Asia, two in South America, one in New Zealand, and one was a multi-country study (123).
Table 2.2: Summary of studies using psychometric assessments for the role of psychosocial stress in the oral-systemic health connection.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>% female</th>
<th>Mean Age/Range (y)</th>
<th>Measure of Stress</th>
<th>Oral Condition</th>
<th>Systemic Disease</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed et al. (2017)</td>
<td>Cross-sectional</td>
<td>Saudi Arabia</td>
<td>438</td>
<td>100%</td>
<td>30 ± 5.4</td>
<td>Perceived stress (Arabic version PSS-10)</td>
<td>Self-reported dry mouth, gingivitis, dental caries, dental pain</td>
<td>Self-reported hypertension, chronic disease</td>
<td>High stress associated with chronic and oral disease</td>
</tr>
<tr>
<td>Albright et al. (2013)</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>88</td>
<td>52%</td>
<td>68.8</td>
<td>Experience of life stress (interview)</td>
<td>Poor oral health</td>
<td>Dental interview/exam</td>
<td>Diabetes (BMI)</td>
</tr>
<tr>
<td>Bensley et al. (2011)</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>672</td>
<td>51%</td>
<td>48</td>
<td>Perceived life stress (PSS-10)</td>
<td>Self-reported periodontal disease</td>
<td>Clinical metabolic syndrome</td>
<td>Psychosocial stress is associated with number of chronic conditions and periodontal disease</td>
</tr>
<tr>
<td>Carreiras-Miguez et al. (2022)</td>
<td>Case-control</td>
<td>Spain</td>
<td>148</td>
<td>NR</td>
<td>45.7 ± 12; 48.9 ± 7.9</td>
<td>Perceived stress (short Spanish version PSS-14)</td>
<td>Self-reported dry mouth</td>
<td>Depression (Zung Depression Scale)</td>
<td>Depressed individuals had higher PSS and loneliness scores and higher prevalence of dry mouth than controls</td>
</tr>
<tr>
<td>Chen et al. (2022)</td>
<td>Cross-sectional</td>
<td>Taiwan</td>
<td>1,232</td>
<td>56%</td>
<td>66 ± 10</td>
<td>Perceived stress (PSS-14), psychological well-being (5-item WHO Well-Being Index)</td>
<td>Self-reported dental problems (yes, no)</td>
<td>Self-reported multimorbidity (two or more chronic conditions), depression (CES-D)</td>
<td>Low psychological well-being associated with higher prevalence multimorbidity, depression, dental problems, and perceived stress</td>
</tr>
<tr>
<td>Cinar &amp; Schou (2014)</td>
<td>Prospective intervention cohort</td>
<td>Turkey</td>
<td>186</td>
<td>NR</td>
<td>30-65</td>
<td>Perceived stress (self-reported single question), health coaching intervention</td>
<td>Tooth loss, CAL (clinical assessment)</td>
<td>Diabetes (HBA1C levels)</td>
<td>CAL and diabetes was associated with the higher stress control group</td>
</tr>
<tr>
<td>Dumitrescu et al. (2009)</td>
<td>Cross-sectional</td>
<td>Romania</td>
<td>161</td>
<td>44%</td>
<td>53.9</td>
<td>Perceived stress (self-reported single question)</td>
<td>Self-reported dental caries, gingivitis, bleeding gums</td>
<td>Self-reported depression or anxiety, diagnosed chronic renal failure</td>
<td>Increased risk for anxiety, depression, stress, and impaired dental/gingival health among renal dialysis patients</td>
</tr>
</tbody>
</table>

PSS: Perceived Stress Scale; BMI: body mass index; WHO: World Health Organization; CES-D: Center for Epidemiologic Studies Depression Scale; NR: not reported.
Table 2.2 con’t: Summary of studies using psychometric assessments for the role of psychosocial stress in the oral-systemic health connection

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
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<th>% female</th>
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<th>Oral Condition</th>
<th>Systemic Disease</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iskander &amp; Samin (2022)</td>
<td>Retrospective cohort</td>
<td>Canada</td>
<td>94</td>
<td>73%</td>
<td>62.2</td>
<td>Perceived stress (self-reported)</td>
<td>Diagnosed OLP</td>
<td>Diagnosed diabetes, hypertension, thyroid disorders</td>
<td>Thyroid disease, diabetes, and psychological stress may play a role in the development of OLP</td>
</tr>
<tr>
<td>Kjellström et al. (2017)</td>
<td>Case-control</td>
<td>Sweden</td>
<td>1610</td>
<td>19%</td>
<td>62 ± 8</td>
<td>Psychosocial stress (self-reported questionnaire)</td>
<td>Periodontitis (clinical examination and x-ray of bone loss)</td>
<td>Depression (MADRS), myocardial infarction (patients hospitalized for first MI)</td>
<td>Patients with a first MI had higher psychosocial stress and greater risk for depression and periodontitis</td>
</tr>
<tr>
<td>Kurushima et al. (2019)</td>
<td>Cross-sectional</td>
<td>United Kingdom</td>
<td>4244</td>
<td>100%</td>
<td>57.6</td>
<td>Self-reported anxiety/stress</td>
<td>Self-reported bleeding gums, periodontitis</td>
<td>Self-reported depression, coronary heart disease, hypertension</td>
<td>Anxiety and stress related to higher prevalence of depression and periodontal disease</td>
</tr>
<tr>
<td>Monteiro da Silva et al. (1996)</td>
<td>Case-control</td>
<td>United Kingdom</td>
<td>150</td>
<td>66%</td>
<td>40.6</td>
<td>Perceived stress (PSS)</td>
<td>Periodontitis (clinical examination)</td>
<td>Depression (HADS)</td>
<td>Greater perceived stress and depression in patients with rapidly progressive periodontitis</td>
</tr>
<tr>
<td>Rajhans et al. (2017)</td>
<td>Case-control</td>
<td>India</td>
<td>60</td>
<td>NR</td>
<td>35-50</td>
<td>Perceived life stress (PSS)</td>
<td>Chronic periodontitis (clinical examination of PI GI, PD, CAL)</td>
<td>Diabetes (blood samples)</td>
<td>Higher perceived stress in patients with both periodontitis and diabetes compared to healthy controls</td>
</tr>
<tr>
<td>Rezazadeh et al. (2021)</td>
<td>Case-control</td>
<td>Iran</td>
<td>38</td>
<td>16%</td>
<td>52</td>
<td>Perceived stress (DASS-21)</td>
<td>BMS (VAS)</td>
<td>Depression, anxiety (DASS-21), sleep disorder (PSQI)</td>
<td>Higher prevalence of stress, anxiety, depression, and sleep disorders in patients with BMS</td>
</tr>
<tr>
<td>Rosania et al. (2009)</td>
<td>Cross-sectional</td>
<td>USA &amp; Canada</td>
<td>45</td>
<td>69%</td>
<td>45-82</td>
<td>Chronic stress (DSP)</td>
<td>Periodontal disease, tooth loss, CAL (clinical examination)</td>
<td>Depression (CES-D)</td>
<td>Chronic stress and cortisol correlated with greater CAL, tooth loss, and periodontal disease; depression associated with greater tooth loss</td>
</tr>
<tr>
<td>Shah et al. (2009)</td>
<td>Case-control</td>
<td>India</td>
<td>60</td>
<td>57%</td>
<td>40.1 ± 12.6</td>
<td>Perceived stress (DASS)</td>
<td>OLP (VAS)</td>
<td>Depression, anxiety (DASS)</td>
<td>Higher depression, perceived stress scores, and cortisol levels in OLP patients compared to controls</td>
</tr>
</tbody>
</table>

PSS: Perceived Stress Scale; CES-D: Center for Epidemiologic Studies Depression Scale; CAL: clinical attachment loss; VAS: Visual Analog Scale; BMS: Burning Mouth Syndrome; OLP: Oral Lichen Planus; MADRS: Montgomery–Åsberg Depression Rating Scale; MI: myocardial infarction; PI: approximal plaque index; HADS: Hospital Anxiety and Depression Scale; GI: gingival index; PD: probing depth; DASS: Depression, Anxiety, and Stress Scale; DSP: Derogatis Stress Profile;
Table 2.2 cont’d: Summary of studies using psychometric assessments for the role of psychosocial stress in the oral-systemic health connection

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>% female</th>
<th>Mean Age/Range (y)</th>
<th>Measure of Stress</th>
<th>Oral Condition</th>
<th>Systemic Disease</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solis et al. (2004)</td>
<td>Cross-sectional</td>
<td>Brazil</td>
<td>160</td>
<td>62%</td>
<td>35.7 ± 10.3</td>
<td>Psychological stress (LES)</td>
<td>Periodontitis (PD, CAL, PI, GI)</td>
<td>Depression (BDI)</td>
<td>No association between depression, hopelessness, and established periodontitis</td>
</tr>
<tr>
<td>Di Stasio et al. (2018)</td>
<td>Case-control</td>
<td>Italy</td>
<td>49</td>
<td>87%</td>
<td>62</td>
<td>Emotional distress (Distress Thermometer)</td>
<td>BMS (VAS)</td>
<td>Depression (HAM-D)</td>
<td>Depression and emotional distress correlated with BMS</td>
</tr>
<tr>
<td>Klages et al. (2005)</td>
<td>Cross-sectional</td>
<td>Germany</td>
<td>140</td>
<td>66%</td>
<td>40.7</td>
<td>Negative life events (sf-LES 15 item)</td>
<td>PI, SBI</td>
<td>Depression (SCL-90-R)</td>
<td>Preoccupation with adverse events and depression may play a role in gingival inflammation</td>
</tr>
<tr>
<td>Lim et al. (2023)</td>
<td>Prospective cohort</td>
<td>USA</td>
<td>1,021</td>
<td>96%</td>
<td>29</td>
<td>Emotional distress (self-reported)</td>
<td>Dental caries (clinical examination)</td>
<td>Self-reported heart condition, endocarditis, diabetes, epilepsy, heart attack</td>
<td>Emotional distress and chronic health conditions increased risk of developing dental caries</td>
</tr>
</tbody>
</table>

**Emotional distress**

**Living conditions and lifestyle behaviours**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>% female</th>
<th>Mean Age/Range (y)</th>
<th>Measure of Stress</th>
<th>Oral Condition</th>
<th>Systemic Disease</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negishi et al. (2004)</td>
<td>Cross-sectional</td>
<td>Japan</td>
<td>57</td>
<td>16%</td>
<td>17-79</td>
<td>Lifestyle (smoking, drinking, diet, distress, sleep disorders; self-reported)</td>
<td>PD, alveolar bone loss (clinical examination)</td>
<td>Diabetes (HBA1C)</td>
<td>Drinking habits, anger, high levels of HbA1c associated with high alveolar bone loss and probing depth greater than 6mm in diabetic patients</td>
</tr>
<tr>
<td>Parbhakar et al. (2022)</td>
<td>Cross-sectional</td>
<td>Canada</td>
<td>23,131</td>
<td>51%</td>
<td>35+</td>
<td>Living conditions (e.g., job status, sense of belonging), individual behaviour (e.g., smoking, alcohol)</td>
<td>Self-reported oral health</td>
<td>Self-reported arthritis, hypertension, COPD, diabetes, heart disease, stroke</td>
<td>Living conditions and individuals behaviours attenuate the association between oral and systemic diseases</td>
</tr>
<tr>
<td>Vedin et al. (2015)</td>
<td>RCT</td>
<td>Global</td>
<td>15,828</td>
<td>19%</td>
<td>65</td>
<td>Lifestyle (education, stress, alcohol, physical activity; self-reported)</td>
<td>Self-reported tooth loss, bleeding gums</td>
<td>Coronary heart disease (prior MI or prior coronary revascularization)</td>
<td>Lifestyle stress associated with increased odds of tooth loss and bleeding gums in coronary heart disease patients</td>
</tr>
</tbody>
</table>

CAL: clinical attachment loss; VAS: Visual Analog Scale; BMS: Burning Mouth Syndrome; HAM-D: Hamilton Depression Rating Scale; OLP: MI: myocardial infarction; LES: Life Events Scale; PI: approximal plaque index; SBI: sulcus bleeding index; SCL-90-R: Symptom Checklist-90-Revised; GI: gingival index; PD: probing depth; COPD: chronic obstructive pulmonary disease; BDI: Beck Depression Inventory; RCT: randomized controlled trial; NR: not reported
Table 2.2 con’t: Summary of studies using psychometric assessments for the role of psychosocial stress in the oral-systemic health connection

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>% female</th>
<th>Mean Age/Age Range (y)</th>
<th>Measure of Stress</th>
<th>Oral Condition</th>
<th>Systemic Disease</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood adversity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poulton et al., 2002</td>
<td>Cohort</td>
<td>New Zealand</td>
<td>980</td>
<td>48%</td>
<td>26</td>
<td>Socioeconomic disadvantage in childhood</td>
<td>Gingival bleeding, CAL, periodontal disease, dental caries (clinical assessment)</td>
<td>Cardiovascular health, depression (clinical diagnosis based on DSM-IV criteria)</td>
<td>Children with low socioeconomic status had increased incidence of poor cardiovascular health and oral health conditions</td>
</tr>
</tbody>
</table>

CAL: clinical attachment loss
Table 2.3: Summary of studies using biological assessments of psychosocial stress (i.e., cortisol) in the oral-systemic health connection.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>% female</th>
<th>Mean Age/Range (y)</th>
<th>Measure of Stress</th>
<th>Oral Condition</th>
<th>Systemic Disease</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albahli et al., 2021</td>
<td>Case-control</td>
<td>Saudi Arabia</td>
<td>40</td>
<td>13%</td>
<td>39.1 ± 12.1; 38.3 ± 11.6</td>
<td>Salivary cortisol</td>
<td>Periodontal disease (clinical examination of GI, PI, PD, CAL)</td>
<td>Schizophrenia (clinical diagnosis)</td>
<td>Higher periodontal parameters and lower cortisol in schizophrenic patients</td>
</tr>
<tr>
<td>Hugo et al., 2006</td>
<td>Cross-sectional</td>
<td>Brazil</td>
<td>230</td>
<td>84%</td>
<td>61.6 ± 8.2</td>
<td>Salivary cortisol</td>
<td>PI, gingival bleeding index (clinical examination)</td>
<td>Depression (BDI), diabetes (clinical diagnosis)</td>
<td>Salivary cortisol, high perceived stress, and diabetes were associated with high plaque index and high gingival bleeding index</td>
</tr>
<tr>
<td>Johannsen et al., 2006</td>
<td>Case-control</td>
<td>Sweden</td>
<td>72</td>
<td>100%</td>
<td>42 ± 9.3; 54.5 ± 2.9</td>
<td>Cortisol, inflammatory biomarkers</td>
<td>Periodontal disease (clinical examination)</td>
<td>Depression (clinical diagnosis)</td>
<td>Women with stress-related depression and exhaustion had more plaque accumulation, gingival inflammation, and increased levels of IL-6 and cortisol in GCF</td>
</tr>
<tr>
<td>Johannsen et al., 2007</td>
<td>Case-control</td>
<td>Sweden</td>
<td>49</td>
<td>100%</td>
<td>48.5 ± 6.9; 54.5 ± 2.9</td>
<td>Serum cortisol, inflammatory biomarkers</td>
<td>Periodontal disease (clinical examination)</td>
<td>Depression (clinical diagnosis)</td>
<td>Depressed women had more severe periodontitis and higher concentrations of IL-6 in GCF</td>
</tr>
<tr>
<td>Kurer et al., 1995</td>
<td>Cohort</td>
<td>United Kingdom</td>
<td>51</td>
<td>NR</td>
<td>20-50</td>
<td>Salivary cortisol</td>
<td>PI, gingivitis (clinical examination)</td>
<td>Depression (HADS)</td>
<td>Cortisol was not associated with plaque and gingivitis</td>
</tr>
<tr>
<td>Rajhans et al., 2017</td>
<td>Case-control</td>
<td>India</td>
<td>60</td>
<td>NR</td>
<td>35-50</td>
<td>Serum cortisol</td>
<td>Chronic periodontitis (clinical examination of PI GI, PD, CAL)</td>
<td>Diabetes (blood samples)</td>
<td>Clinical attachment levels and mean cortisol levels were highest in patients with both periodontitis and diabetes</td>
</tr>
<tr>
<td>Rosania et al., 2009</td>
<td>Cross-sectional</td>
<td>USA &amp; Canada</td>
<td>45</td>
<td>69%</td>
<td>45-82</td>
<td>Salivary cortisol</td>
<td>Periodontal disease, tooth loss, CAL (clinical examination)</td>
<td>Depression (CES-D)</td>
<td>Chronic stress and cortisol correlated with greater CAL, tooth loss, and periodontal disease; depression associated with greater tooth loss</td>
</tr>
<tr>
<td>Salehi et al., 2019</td>
<td>Case-control</td>
<td>Iran</td>
<td>132</td>
<td>77.3%</td>
<td>54±5.7; 48±8.7; 43±11.9</td>
<td>Salivary cortisol</td>
<td>DMFT (clinical examination)</td>
<td>Diabetes (clinical diagnosis)</td>
<td>Salivary cortisol and DMFT was higher in diabetic patients; salivary cortisol was associated with DMFT index</td>
</tr>
</tbody>
</table>

GI: gingival index; PD: probing depth; PI: approximal plaque index; CAL: clinical attachment loss; BDI: Beck Depression Inventory; GCF: gingival crevicular fluid; HADS: Hospital Anxiety and Depression Scale; CES-D: Center for Epidemiologic Studies Depression Scale; DMFT: decayed, missing, and filled teeth; NR: not reported.
Table 2.3 con’t: Summary of studies using biological assessments of psychosocial stress (i.e., cortisol) in the oral-systemic health connection.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Sample Size</th>
<th>% female</th>
<th>Mean Age/Range (y)</th>
<th>Measure of Stress</th>
<th>Oral Condition</th>
<th>Systemic Disease</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al., 2009</td>
<td>Case-control</td>
<td>India</td>
<td>60</td>
<td>57%</td>
<td>40.1 ± 12.6</td>
<td>Salivary cortisol</td>
<td>OLP (VAS)</td>
<td>Depression, anxiety (DASS)</td>
<td>Higher prevalence of depression, higher perceived stress scores, and higher cortisol levels in OLP patients compared to controls</td>
</tr>
<tr>
<td>Yang et al., 2022</td>
<td>Cross-sectional</td>
<td>China</td>
<td>106</td>
<td>38%</td>
<td>75.3 ± 6.6</td>
<td>Cortisol, inflammatory biomarkers</td>
<td>Dental caries, periodontal disease, self-reported oral health (clinical examination and self-reported)</td>
<td>Alzheimer's disease (clinical diagnosis)</td>
<td>Stress biomarkers and oral health indicators were poorer in individuals with Alzheimer's disease compared to those with subjective cognitive decline or mild cognitive impairment</td>
</tr>
</tbody>
</table>

OLP: oral lichen planus; DASS: Depression, Anxiety, and Stress Scale;
2.4.2 Oral-Systemic Disease Connection

Periodontal disease was the most common oral health outcome measured, included in 53% of all included studies. The majority of studies recorded oral disease using clinical examinations or diagnosis of participants (67%), while the remaining studies assessed oral health using self-report questionnaires. Clinically assessed outcomes included periodontal disease, dental caries, tooth loss, clinical attachment loss, oral lichen planus, burning mouth syndrome, and poor oral health. Self-reported outcomes included self-reported oral health, dental problems, and self-reported dental pain. Other oral health conditions that were assessed via self-report questionnaires included periodontal disease, tooth loss, dental caries, and bleeding gums.

Mental health conditions, such as anxiety, depression, and schizophrenia, as well as diabetes, and heart diseases, including coronary heart disease, myocardial infarction, and stroke, were the most common systemic diseases studied, comprising 57%, 23%, and 27% of eligible studies, respectively. Other systemic diseases included hypertension, arthritis, chronic renal failure, thyroid disorders, sleep disorders, chronic obstructive pulmonary disorders (COPD), and Alzheimer’s disease. Nine articles studied more than one systemic disease outcome (106,108–111,114,120,122,126). Physical measures, such as BMI, blood samples, clinical exams, and angiographs, were used to assess 38% of systemic disease outcomes, while self-report questionnaires, standardized assessment scales, and interviews were used in 62% of studies.

Periodontal disease was more commonly studied in relation to depression and heart disease. Heart disease was also studied with bleeding gums, dental caries, self-reported oral health, and tooth loss. Diabetes was studied in relation to self-reported oral health, periodontal disease, oral lichen planus, clinical attachment loss, dental caries, tooth loss, and poor oral health. Aside from periodontal disease, depression was assessed with bleeding gums, oral lichen planus, dental caries, dry mouth, and self-reported dental problems. Both articles on burning mouth syndrome studied the condition in relation to depression (114,118). Regarding oral-systemic health, five studies used only self-report questionnaires to assess both oral and systemic health outcomes, ten used only clinical examinations, and fifteen
used a combination of self-report questionnaires and clinical exams to assess oral and systemic health outcomes.

2.4.3 Psychosocial Stress and the Oral-Systemic Disease Connection

Twenty-three articles identified in this review measured stress psychometrically and its association with oral-systemic health (102–124). Psychometric psychosocial stress variables fell into four main categories: “perceived life stress”, “emotional distress”, “lifestyle or individual behaviour”, and “childhood adversity”. Of the articles that assessed perceived life stress, six studies used Cohen’s Perceived Stress Scale (PSS), two used the Depression, Anxiety and Stress Scale (DASS), and one used the Derogatis Stress Profile (DSP). The remaining six “perceived stress” studies interviewed participants, either in person or using questionnaires, with questions pertaining to experiencing life stress (e.g., “Have you ever been told by a doctor or other health professional that you had an anxiety or stress disorder?”). Emotional distress was assessed using the Life Events Scale (LES), the Distress Thermometer (DT), and self-report questionnaire. Lifestyle or individual behaviour was assessed using questionnaires focused on living conditions and behaviours and included questions focused on smoking, alcohol consumption, diet, distress, financial stress, etc. Finally, childhood adversity was assessed in a cohort study using socioeconomic disadvantage in childhood (124).

Fifteen articles concluded that perceived life stress was higher in individuals with both oral and systemic disease outcomes. In pregnant women, high perceived stress was associated with chronic disease and oral disease (102). Higher prevalence of depression, perceived stress, and anxiety were found in both oral lichen planus (116), burning mouth syndrome (114), and periodontal disease (111,112,115,117). Perceived stress was also found to be higher in individuals with both periodontal disease and diabetes when compared to healthy controls (107,113). Participants with heart disease experienced greater psychosocial stress and demonstrated increased risk for periodontitis (104,110,111), as did those with chronic renal failure (108). Self-reported measures, such as dry mouth (105) and dental problems (106), were also associated with high perceived stress and chronic disease such as
depression and multimorbidity. However, one study found no evidence for an association between psychological stress, depression, and periodontitis (114).

Three studies found that emotional distress was associated with a higher risk of oral disease and chronic disease. Depression and emotional distress were correlated with the occurrence of burning mouth syndrome (118) and gingival inflammation (119), while individuals with emotional distress and heart disease had a higher risk of developing dental caries (120).

Poor living conditions, such as low income and food insecurity, increased the odds of the co-occurrence of oral-systemic disease (122), and negative lifestyle was associated with poor gingival health in diabetic patients (121) and increased the odds of tooth loss in coronary heart disease patients (123).

Only one study explored the association between childhood adversity and adult health (124). As part of a longitudinal cohort, health and behaviour of participants was assessed from birth until 26 years old. In this study, researchers found that children who grew up in low socioeconomic status families were at greater risk of having poor cardiovascular health, depression, and periodontal disease in adulthood. No studies using an ACEs score in association with oral-systemic health outcomes were identified.

2.4.4 Biomarkers of Psychosocial Stress and the Oral-Systemic Disease Connection

Biomarkers of psychosocial stress were used in ten studies, with eight studies finding a positive association between stress and oral-systemic health (113,115,116,125–131). Psychosocial stress was measured biologically using cortisol extracted from saliva samples and/or gingival crevicular fluid. Although other biomarkers of psychosocial stress were included in the search strategy, namely ACTH and brain-derived neurotrophic factor (BDNF), no studies assessing their association to oral-systemic health were identified.

Salivary and serum cortisol were most often studied in individuals with depression. High GCF cortisol was associated with more severe plaque accumulation, gingival inflammation, and periodontitis in women with depression (127,128). Similarly, cortisol was also correlated with greater clinical attachment loss, tooth loss, and periodontal disease
in individuals with depression (115). In people with oral lichen planus, there was a higher prevalence of depression, perceived stress, and higher levels of cortisol relative to healthy controls (116). However, one study concluded that cortisol was not associated with plaque or gingivitis in people with depression (129).

Cortisol was also associated with greater incidence of oral conditions and diabetes. One study found that salivary cortisol and diabetes were associated with high plaque and bleeding index (126), while another concluded that clinical attachment loss and mean cortisol levels were highest in individuals with both periodontitis and diabetes (113). A third article reported that salivary cortisol and DMFT (decayed, missing, and filled teeth) scores were higher in diabetic patients, and also found an association between salivary cortisol and the DMFT index (130).

The role of cortisol in periodontal disease severity among people with schizophrenia was not supported; although there were significantly higher values of periodontal disease parameters in people with schizophrenia, cortisol levels were much lower in cases compared to healthy controls (125). However, in individuals with Alzheimer’s disease, higher cortisol levels and poorer oral health indicators were present compared to those with subjective cognitive decline or mild cognitive impairment (131).

2.5 Discussion

The aim of this scoping review was to identify the current state of knowledge of the contribution of psychosocial stress to the oral-systemic health connection in the adult population. This review included a total of thirty original research articles from the past thirty years and focused on a range of both psychometric and biological measures of psychosocial stress. Among the psychometric indicators of stress were perceived life stress, emotional distress, living conditions and lifestyle factors, and childhood adversity, in addition to biological measures of psychosocial stress using cortisol. The findings of the present review demonstrate an overall positive association between indicators of psychosocial stress and oral-systemic health, where higher levels of psychosocial stress were associated with greater risk of oral-systemic disease.
Previous research has identified stress as a premorbid factor associated with many risk factors for chronic disease (132). Stress can stem from external events, such as major stressful life events or minor daily stressors, or from one’s own perception of those experiences (133). Coping skills and resiliency usually help in managing emotions and altering the relationship between the individual and the stressor, which is helpful in reducing the biological impact of future stressors (133–135). As well, early childhood adversity can increase vulnerability to a maladaptive stress response that imprints onto the immature brain and persists into adulthood (136). For example, children exposed to chronic stress experience a higher prevalence of systemic illnesses as adults, including heart disease (137) and autoimmune diseases (138). Despite the evidence on the crucial role of exposures in childhood on the risk of chronic disease later in life, we identified only one study that investigated the impact of childhood adversity on oral health in relation to cardiovascular health and depression, thereby indicating a clear knowledge gap in this area.

We found the majority of studies included in this review assessed psychosocial stress psychometrically in adults. Exposure to psychosocial stress through various factors, including precarious social and living conditions in adulthood, can have a significant toll on biological mechanisms that are known to contribute to increased risk for oral and systemic health conditions. Our findings agree with other studies investigating the role of psychosocial stress in health outcomes. For example, low job control has been linked to an increased risk of all-cause and coronary heart disease mortality (139). Similarly, other factors, such as life satisfaction and social isolation, have been associated with a higher risk of stroke and transient ischemic attacks (140). On the contrary, social support has been found to be protective against dental pain (141), while individuals with greater perceived stress are more likely to report poor oral health (142).

In addition to psychometric measures of psychosocial stress, this review also investigated the association of the stress hormone cortisol as a biologic indicator of psychosocial stress with oral-systemic health. It is well established that higher levels of serum cortisol may be associated with psychosocial factors due to activation of the HPA axis (143–145). In addition to short-term adaptive changes, cortisol is also involved in other long-term stress-related changes such as shaping and regulating a number of physiological processes,
including immune responsiveness. While it is normal for cortisol levels to fluctuate and remain elevated at specific times of the day (e.g., in the morning), when cortisol levels are persistently high throughout the day, this can be reflective of a the HPA axis hyperactivity (144,145). In this review, we found 80% of the studies investigating the role of cortisol to support the association with oral and systemic health. Examining other biomarkers that may be sensitive to the stress response can also provide new insight into the role of psychosocial stress in the development and progression of oral-systemic disease.

2.5.1 Strengths and Limitations

The present study included thirty observational studies from several countries reporting data of more than 50,000 participants with numerous psychometric and biological measures of psychosocial stress. Our review is the first to assess the role of psychosocial stress in oral and systemic disease conditions on a large scale while using both psychometric and biological measures of stress. This was done by following a systematic method for retrieving and analyzing the studies included in this scoping review.

We acknowledge several limitations of this work as well. Namely, the choice of a scoping review methodology may have contributed to not finding additional studies examining biomarkers of psychosocial stress in relation to oral-systemic disease. A scoping review may miss important studies since it does not aim to assess all literature systematically. For instance, we used the search terms “cortisol” and “biomarkers” regarding biological markers of psychosocial stress; however, including additional search terms, such as “glucocorticoids” for example, may have yielded additional results. Furthermore, the quality of the included studies was not formally assessed in this scoping review – as the methodology does not require it – but it is a limitation that may affect the results. However, all articles were published by peer-reviewed journals and, as such, are expected to be of a good standard. Finally, although a scoping review cannot state how much psychosocial stress is related to oral-systemic disease, this type of review enables us to obtain insight into how oral-systemic disease may be related to psychosocial stress, with the data being interpreted in a qualitative way.
2.5.2 Gaps in Prior Research and Future Directions

This review was limited by the study design, small sample sizes, and other methodological limitations of the included studies. Although a variety of psychometric measures were assessed, such as perceived life stress and emotional distress, studies focused only on cortisol as a biological measure of psychosocial stress. Thus, future research should include other biological measures of psychosocial stress, such as ACTH or BDNF, in relation to oral-systemic disease. Furthermore, while a third of the included articles focused on the association of cortisol with oral-systemic health, sample sizes were small, potentially limiting the interpretability and generalizability of findings. Additionally, the measurement of the relationship between oral and systemic conditions was inconsistent; while some studies directly assessed the relationship between oral and systemic disease, others examined the effect of stress on oral and systemic conditions independently. Therefore, future research should aim to use standardized measures and established definitions of oral-systemic health. Finally, while childhood adversity was included in this review as a psychometric measure of stress, only one study investigated its relationship with oral-systemic health without the use of a standardized ACEs measure. Future research should further explore the role of childhood adversity in relation to the oral-systemic disease connection, and whether the timing of exposure over the lifespan can play a role in the magnitude of the association.

2.6 Conclusion

As an increasing proportion of the global population grows older, a rising number of adults have been presenting with multiple co-occurring chronic conditions, including oral and systemic disease. Findings from the current scoping review suggest that there is an association between psychosocial stress and oral-systemic disease, as measured by psychometric and biological indicators. It is important to understand the magnitude and epidemiology of how oral and systemic diseases co-occur in individuals and to identify common pathways and risk factors to the oral-systemic disease connection, with the ultimate aim of informing and improving preventative strategies.
Chapter 3

3 The Roles of Adverse Childhood Experiences and Psychological Distress in Oral Health and Multimorbidity: A Cluster Analysis of the Canadian Longitudinal Study on Aging

3.1 Abstract

**Objective:** To (i) identify clusters of individuals who share a similar pattern of disease based on their oral health and multimorbidity (OHM) profiles, and (ii) investigate the extent to which adverse childhood experiences (ACEs) and psychological distress contribute to any clustering patterns. **Methods:** We accessed data of 30,097 Canadian adults, aged 45-85 years old, from the comprehensive cohort of the Canadian Longitudinal Study on Aging (CLSA), which is an ongoing Canada-wide cohort study. Using latent class analysis, we identified clusters of oral health and multimorbidity (defined as having two or more chronic conditions) based on participant responses to a series of questionnaires related to oral health and chronic condition status. The optimal number of clusters was determined based on measures of model fit and interpretability. We examined associations between OHM clusters and both psychological distress and ACEs using a series of multinomial regression models adjusting for age, sex, health behaviours (smoking status, alcohol consumption, sugar consumption, sleep quality), and socioeconomic status (household income, education, home ownership). **Results:** We identified five OHM clusters: poor oral health and high multimorbidity (3.9%), good oral health and low multimorbidity (49.9%), good oral health and high multimorbidity (19.9%), poor oral health and low multimorbidity (8.8%), and moderate OHM (17.5%). On average, participants in the poor OHM cluster were older, had a lower education level, and reported lower total household income. This cluster of participants were also more likely to be daily smokers and/or regular consumers of alcohol. Both psychological distress (OR=1.14, 95% CI: 1.13, 1.16) and ACEs (OR=2.21, 95% CI: 1.91, 2.57) were associated with higher odds of being in the poor OHM cluster compared to the good OHM cluster, after adjusting for covariates. **Conclusion:** Middle-aged and older Canadians show different health profiles based on their oral health and multimorbidity status. Psychological distress and ACEs may
contribute to the clustering of participants. Future research can explore the role of the social determinants of health, and subsequent psychosocial stress, in the relationship between oral health and multimorbidity over the life-course.

**Keywords:** Oral health, multimorbidity, psychosocial factors, psychological distress, adverse childhood experiences, latent class analysis, aging, CLSA, Canada
3.2 Introduction

Oral diseases are among the most common health conditions in the population, affecting more than 3.5 billion people globally (146,147). The burden of oral diseases increases with age, especially for conditions such as dental caries, periodontal disease, edentulism, and dry mouth (148,149). In addition to impacting quality of life, oral conditions are strongly linked to major health conditions such as heart disease (150) and diabetes (151) and have been shown to contribute to direct and indirect costs for individuals and healthcare systems, making oral diseases a prominent public health concern (152).

Multimorbidity refers to the co-existence of two or more chronic diseases or medical conditions simultaneously in an individual (21). With an increasing proportion of the population aged 65 and older, as well as increased survival rates, a growing number of adults have been presenting with multiple co-occurring chronic conditions (19,20,24). Thus, multimorbidity in the aging population represents one of the greatest challenges for health systems. In several countries, the prevalence of multimorbidity in the older adult population and its impact on healthcare spending have led to initiatives to tackle this problem, investigate potential risk factors, and explore mitigating strategies to improve health and function (20,21).

As the prevalence of both oral disease and multimorbidity increase in the population, placing further emphasis on understanding the connection between oral health and other non-communicable diseases (known as the oral-systemic health connection) is of upmost importance. This has been an area of interest for a long time in both clinical and oral health policy circles. The associations between oral disease and other chronic conditions have been reported in previous studies and there continues to be emerging evidence that oral health plays a role in some chronic diseases (11,153). For example, periodontal pathogens have been shown to contribute to the link between periodontal disease and atherosclerotic cardiovascular disease (154). Chronic periodontitis and the oral microbiome have also been linked to the onset, progression, and exacerbation of respiratory diseases such as chronic obstructive pulmonary disease (COPD) (155). A bidirectional relationship between periodontal disease and diabetes has also been identified (7). However, despite the evidence on the co-occurrence of oral diseases and other chronic health conditions, there
is limited research on the relationship between oral health and multimorbidity, their shared risk factors, and common pathways.

Previous research has suggested that both oral and other chronic diseases are not merely the product of cellular and molecular cascades, but rather the result of an interplay between social and biological factors (66,156). For example, in a study assessing the link between psychological stress and oral health, poor socioeconomic factors were found to exacerbate the association between current stress and poor oral health (142). Similarly, indicators of social and economic capital, including social relationships, household income, dental insurance, and home ownership, were found to modify the association between perceived life stress and inadequate oral health, where individuals with high perceived stress and low economic capital had greater risk of reporting inadequate oral health (157). Socioeconomic position was also found to attenuate the association between markers of systemic inflammation and periodontal disease in American adults (158). Health behaviours have also been strongly implicated in the development of oral disease and multimorbidity. For example, disrupted sleep and poor sleep quality were shown to be linked to the increased odds of multimorbidity in a cohort of middle-aged and older Canadians (159), while malnutrition was linked to increased tooth loss in older Sri Lankan adults (160). Smoking and alcohol consumption are strongly related to oral diseases and to several chronic diseases, such as heart disease (161–163), as well as multimorbidity (164,165).

Importantly, psychosocial and psychological factors have been extensively investigated in relation to chronic oral and systemic conditions, including multimorbidity. Impacts of psychosocial stress can accumulate over a lifetime, alter health trajectories across the life course, and be transferred across generations (166,167). Oral diseases share similar psychosocial determinants and risk factors with many chronic diseases, including heart disease, cancer, chronic obstructive pulmonary disease, diabetes, dementia, and stroke (168). For example, isolation, loneliness, marital status, and social relationships have all been established as being common to both groups of health conditions (169–172). Several studies have also shown that acute and chronic exposure to psychosocial and psychological stressors may be associated with an increased risk of oral disease and multimorbidity in children and adults (133,173).
Psychological distress is prevalent in older adults (174). Psychological distress is known to contribute to disruptions of daily life and can have a negative impact on quality of life and health-related behaviours, including dietary patterns and oral hygiene behaviours, thereby contributing to poor oral and chronic health conditions (174,175). Psychological distress has been linked to oral diseases and multimorbidity in several populations. For example, the risk of chronic periodontitis has been shown to be higher in those with psychological distress than those without (176). Similarly, a higher risk of chronic conditions in association with psychological distress has been reported in population-based studies in adults (177,178).

It is important to note that the impact of stressful exposures on health outcomes may be further influenced by the magnitude and timing during which the exposure occurs over the lifespan (66,179,180). The life course model suggests that health in later life is shaped by earlier exposures to physical, environmental, and psychosocial factors that mold biological outcomes (74). A growing body of research has adopted the life course perspective, emphasizing the importance of early life and childhood exposures. This can be exemplified by findings of individuals with adverse childhood experiences (ACEs) (e.g., childhood maltreatment, exposure to domestic violence, etc.) exhibiting a greater risk of health problems as adults and ultimately a greater risk of premature mortality than those who were not exposed (181,182). Several studies have linked ACEs to poor health later in life including chronic obstructive pulmonary disease (183,184), heart disease (182,185), periodontal disease (79), and multimorbidity (186,187). Thus, individuals reporting ACEs may be more susceptible to disease development through both differences in physiological development and adoption and persistence of health-damaging behaviours. Indeed, childhood exposure to chronic stress has been shown to contribute to changes in neurodevelopment, endocrinal, and immune system problems, that eventually can lead to impaired cognitive, social, and emotional functions, and physiological dysfunction (188,189).

Given this collective evidence, we hypothesize that oral health conditions and multimorbidity cluster together and are associated with ACEs and psychological distress. Therefore, our objectives were to identify clusters of individuals who share a similar
pattern of disease based on their oral health and multimorbidity (OHM) profiles, and then determine whether psychosocial or psychological factors are linked to any observed clustering patterns. Specifically, we had the following three aims: 1) to identify and characterize clusters of OHM in a population-based sample of middle-aged and older Canadians; 2) to measure the extent to which OHM clusters are associated with ACEs; and 3) to measure the extent to which OHM clusters are associated with psychological distress.

3.3 Methods

3.3.1 Sample Overview

This study used baseline and first follow-up data from the Canadian Longitudinal Study on Aging (CLSA). CLSA is a nation-wide on-going cohort study, with 51,338 participants from all 10 Canadian provinces aged 45-85 years old at the time of recruitment (2011-2015). These participants will be followed every three years until 2033 or until death or loss to follow-up (190). All study participants provided data on the demographic, biological, medical, psychosocial, economic, lifestyle, and behavioural factors through either a computer-assisted telephone interview or an in-person home interview. Of the 51,338 participants, a subset of 30,097 participants (Comprehensive cohort) living within 25-50 km distance from one of eleven data collection sites located across seven provinces were invited to complete detailed physical assessments and to provide blood and urine samples. From this cohort, we assessed a sample of 25,411 participants who had complete data for outcome variables. In this study, we used a combination of baseline and first follow-up data from the Comprehensive cohort due to our variables of interest. A detailed description of CLSA recruitment and data collection have been previously described (190).

3.3.2 Measures

3.3.2.1 Independent Variables

*Adverse childhood experiences (ACEs)*

The ACEs questionnaire (CEX) was administered in the first follow-up wave of the comprehensive cohort. Questions pertaining to ACEs were adapted from the Childhood Experience of Violence Questionnaire (CEVQ) (194) and the National Longitudinal Study
of Adolescent to Adult Health Wave III questionnaire (195). ACEs were broadly characterized in the CLSA as (i) childhood maltreatment, including: physical, sexual, and emotional abuse; neglect; and witnessing intimate partner violence in the household prior to age of 16, and (ii) other adverse events experienced prior to age 18, including: parental death or serious illness; parental divorce or separation; and mental or psychiatric illness of a family member.

Frequency and severity of exposure to childhood abuse, neglect and intimate partner violence were assessed on an ordinal scale (never, 1–2 times, 3–5 times, 6–10 times or more than 10 times) and subsequently dichotomized as presence or absence of exposure based on the CEVQ instructions (196). Physical abuse was present if the participant reported being slapped on the face, head or ears, or hit or spanked with something hard 3 or more times; being pushed, grabbed or shoved, or having something thrown to hurt 3 or more times; or being kicked, bit or punched, or choked, burned or physically attacked in some other way 1 or more times.

Sexual abuse was present if the participant reported being threatened, touched or forced into unwanted sexual activity 1 or more times. Emotional abuse was present if the participant reported parents or guardians swearing, saying hurtful or insulting things that made the participant feel unloved or unwanted 3 or more times. Participants were classified as being neglected if they reported their parents or guardians not having taken care of their basic needs. Childhood exposure to intimate partner violence was present if the participant reported seeing or hearing parents or guardians say hurtful things to each other 6 or more times, or seeing or hearing parents or guardians hit each other 3 or more times.

Other forms of ACEs including “parental divorce or separation,” “parental death” or “living with a family member with mental health problems” were assessed dichotomously. A cumulative ACEs score was created by summing the number of individual ACEs that participants have experienced and ranged from 0 to 8. We further dichotomized ACEs score as “high” (ACEs score>=4) and “low” (ACEs scores<=3).
Psychological distress

Psychological distress was assessed using the K10 questionnaire at baseline and included 17 questions from the Kessler Psychological Distress Scale (191–193). The scale is designed to assess non-specific psychological distress, with questions focusing on anxiety and depressive symptoms in the previous 30 days (e.g., “How often did you feel nervous?”; “How often did you feel hopeless?”; “How often did you feel depressed?”) and recorded on a 5-point Likert scale (none of the time; a little of the time; some of the time; most of the time; all of the time). We used the continuous K10 scores to assess psychological distress.

3.3.2.2 Dependent Variables

Oral health

Participants in the comprehensive cohort provided information at baseline about their oral health status through “the maintaining contact” telephone interviews. The oral health (ORH) questionnaire was based on the Canadian Community Health Survey 2.1, which incorporated subjective indicators of oral health status developed by Locker (199). For oral health questions recorded on a Likert scale, responses were transformed to a binary format to improve the interpretability of oral health and multimorbidity classes in the latent class analysis. The following four oral health variables were included in our assessment of oral health conditions:

- Self-reported oral health status was measured using single-item Likert responses to the question “In general, would you say the health of your mouth is excellent, very good, good, fair, or poor?”. We further dichotomized self-reported oral health as “good” (excellent, very good, good) and “poor” (fair, poor).

- Edentulism, which is the state of having no natural teeth or being toothless, was measured using the question “Do you have one or more of your natural teeth?”. We reverse coded this question to reflect the variable edentulism as “yes” (has no natural teeth) and “no” (has one or more natural teeth).
• Denture/false teeth use was measured as a proxy for having missing teeth using the question “Do you wear dentures (full or partial) or false teeth?”. Denture/false teeth use was reported as a binary variable, “yes” (uses dentures/false teeth) and “no” (does not use dentures/false teeth).

• Oral health problems included several questions on whether participants experienced several oral health conditions including discomfort during eating, avoidance of specific foods, xerostomia (mouth dryness), toothache, gingival bleeding, and halitosis (bad breath). We combined these conditions and dichotomized them as oral health problems “yes” (i.e., has an oral health problem) and “no” (i.e., does not have an oral health problem).

Multimorbidity

We assessed multimorbidity using the chronic condition (CCC) questionnaire in the comprehensive baseline cohort and operationalized it using the public health definition of multimorbidity as defined by the Public Health Agency of Canada (PHAC) (101). Chronic conditions in the public health definition of multimorbidity included: Alzheimer’s disease and related dementias, anxiety or mood disorders, arthritis, asthma, cancer, chronic obstructive pulmonary disease, diabetes, heart disease, and stroke. We then grouped all variables into a derived binary variable coded as “no multimorbidity” (zero or one chronic condition) or “multimorbidity” (two or more chronic conditions).

3.3.2.3 Covariates

A directed acyclic graph (DAG) was constructed using the DAGitty 3.0 software informed by a priori knowledge of the literature to identify potential confounders (Fig. 1). We included three categories of covariates in this study, including demographic factors (age, sex assigned at birth, race/ethnicity, country of birth, marital status), socioeconomic factors (total annual household income, highest level of education attained, home ownership), and health behavioural factors (smoking, alcohol consumption, sugar consumption, sleep quality). The details of how each of the covariates were measured and operationalized are described in Appendix 3A.
Figure 3.1: Directed acyclic graph (DAG) illustrating the causal effect of psychosocial stress on oral disease and multimorbidity.
3.3.3 Statistical Analysis

3.3.3.1 Descriptive Statistics

We performed descriptive analyses to understand the characteristics of the study sample (n=25,411) across three age categories (45-54, 55-64, 65+) and stratified by sex. Weighted means and standard deviations were reported for continuous variables, and weighted percentages were reported for categorical variables. Weighted prevalence estimates and corresponding 95% confidence intervals of multimorbidity (two or more chronic conditions) were calculated using inflation weights, stratified by age and sex.

3.3.3.2 Latent Class Analysis and Model Selection

Latent class analysis (LCA) was used to describe the distribution of health outcomes in the sample and categorize participants according to their oral health and multimorbidity status (OHM). LCA uses maximum likelihood estimation to categorize individuals into each latent class, i.e., to each cluster of participants, thereby classifying individuals into unobserved classes according to their responses to a number of observed and measured categorical variables. In order to understand the ideal number of latent classes or clusters that best represents our data, we compared different latent class models with different number of classes. Five binary observed outcome variables (self-reported oral health, edentulism, denture/false teeth use, oral health problem, multimorbidity) described in the methods section were used in the models. We fit 2-, 3-, 4-, 5-, 6-, and 7-class models to the data. AIC and BIC were used as performance criteria to identify the ideal model.

The model fit statistics are presented in Table 3.1. The 5-class model was selected based on model fit criteria and clinical interpretability. For each participant, the maximum class membership probability of each class was reported. We assigned the class with the greatest membership probability for each participant which represented their overall oral health and multimorbidity status. We used the poLCA package in R statistical software for all LCA (R Core Team, 2022).
**Table 3.1:** Model fit statistics for 2- to 7-class models for oral health and multimorbidity status.

<table>
<thead>
<tr>
<th>Number of classes</th>
<th>AIC</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
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<td>116474.6</td>
</tr>
<tr>
<td>3</td>
<td>114688.7</td>
<td>114827.1</td>
</tr>
<tr>
<td>4</td>
<td>114671.7</td>
<td>114859</td>
</tr>
<tr>
<td>5</td>
<td>114593.6</td>
<td>114829.7</td>
</tr>
<tr>
<td>6</td>
<td>114604.1</td>
<td>114889.1</td>
</tr>
<tr>
<td>7</td>
<td>114613.9</td>
<td>114947.7</td>
</tr>
</tbody>
</table>
3.3.3.3 Multinomial Logistic Regression Analyses

Multinomial logistic regression was used to assess the associations between psychological distress, ACEs, and the outcome of OHM class. Block-wise regression, which is a method of building models by adding variables, was used to add four blocks/categories of covariates to each unadjusted model. Table 3.2 demonstrates the list of variables we used for the psychological distress and ACEs logistic regression models. Good OHM status class was set as the reference outcome category, and the odds (OR) of falling in other classes versus the reference category was estimated using different exposure variables in the model. These models were analyzed for the outcome variable – OHM classes – with psychological distress as the main independent variable for the first series of regressions, and ACEs as the main independent variable for the second series of regressions. Results are reported in odds ratios (OR) and 95% confidence intervals (CI). Analyses were conducted using Stata/BE 17.0 (College Station, Texas).

3.3.4 Ethical Considerations

This study was approved by the Research Ethics Board (REB) of Western University (Project ID: 120939) and closely followed the Data and Biospecimen Access Policy and Guiding Principles specified by CLSA. Appendices 3B and 3C provide the ethical approval letter and CLSA access agreement, respectively.
Table 3.2: Four regression models fitted separately for each outcome variable, where ACEs is the main independent variable for the first series of regressions, psychological distress is the main independent variable for the second series of regressions, and oral health-multimorbidity clusters are the dependent variables in all models.

<table>
<thead>
<tr>
<th>Model number</th>
<th>Independent variables</th>
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<td>Unadjusted</td>
</tr>
<tr>
<td>Model 2</td>
<td>Age, sex, race/ethnicity, marital status</td>
</tr>
<tr>
<td>Model 3</td>
<td>Age, sex, race/ethnicity, marital status, smoking status, alcohol consumption, sugar consumption, sleep quality</td>
</tr>
<tr>
<td>Model 4</td>
<td>Age, sex, race/ethnicity, marital status, smoking status, alcohol consumption, sugar consumption, sleep quality, total household income, education, home ownership</td>
</tr>
</tbody>
</table>
3.4 Results

3.4.1 Characteristics of Study Sample

Our study sample (n=25,411) using data from the Comprehensive Cohort of the CLSA represented 3,202,142 Canadians. The weighted mean age (±sd) for this sample was 59.6 (±10.2) years old, with 51.9% (n=13,191) being female. The majority of participants had a post-secondary degree (70.5%), owned a home (82.8%), and were married or living with a partner (74.8%). A total of 94.0% of participants reported their race/ethnicity to be White, and 80.9% reported being born in Canada. Table 3.3 summarizes the sociodemographic characteristics of the participants in this sample and provides a descriptive summary of oral health and multimorbidity variables, stratified by age and sex (n=25,411).

3.4.2 Oral Health and Multimorbidity Clusters

LCA was used to classify participants into unobserved clusters based on four measured oral health conditions and multimorbidity status (two or more chronic conditions). Figure 3.2 presents the likelihood of reporting “favourable OHM” for each variable/question in each class. Results from the LCA models suggest that 50% of participants had a lower probability of reporting poor OHM, whereas the other 50% clustered into one of four OHM groups. A summary of these descriptive statistics by each cluster is presented in Table 3.4. Based on the patterns of responses to different questions, classes are described below.

*Class 1: Poor oral health and high multimorbidity*

Class 1 was the smallest latent group with the poor OHM status and included 887 individuals (3.9% of the weighted sample). Individuals in this group had a 14.6% probability of having poor self-reported oral health, 54.7% probability of being edentulous, and 64.2% probability of experiencing multimorbidity. Participants in this class were also more likely to wear dentures or have false teeth (98.9%) and report an oral health problem such as toothache or bleeding gums (99.9%).
Class 2: Good oral health and low multimorbidity

Class 2 was the largest latent group comprising 12,387 (49.9%) of participants. Individuals in this group had a 1.0% probability of being edentulous and having poor self-reported oral health, an 8.4% probability of wearing dentures and/or false teeth, and a 34.7% probability of having other oral health problems such as burning mouth or bad breath in the past 12 months. Class 2 members also had the lowest probability of having multimorbidity (<1.0%).

Class 3: Good oral health and high multimorbidity

Class 3 included 5,685 individuals, representing 19.9% of the weighted sample. Individuals in this group, which was the second largest latent group, had a 57.7% probability of multimorbidity and a 1.0% probability of being edentulous. These participants also had a 1.0% probability of using dentures/false teeth, a 45.0% probability of having an oral health problem, and the lowest probability of reporting poor self-reported oral health (0%).

Class 4: Poor oral health and low multimorbidity

Class 4 represents 8.8% of the weighted sample (n=2,380). Members in this class had a 1.4% probability of having poor self-reported oral health, a 33.8% probability of being edentulous, and the lowest probability of having an oral health problem (29.3%). Individuals in this latent class had a 95.1% probability of wearing dentures or false teeth and a 43.2% probability of having multimorbidity.

Class 5: Moderate oral health and moderate multimorbidity

Class 5 included 4,072 participants, representing 17.5% of the weighted sample. Individuals in this latent class had moderate levels of oral disease (i.e., neither good nor poor), with a 29.6% probability of wearing dentures or false teeth, a 22.6% probability of reporting poor self-reported oral health, a 1.2% probability of being edentulous, and a 96.0% probability of having an oral health problem. Class 5 participants also had a moderate probability of having multimorbidity (48.8%).
3.4.3 ACEs and OHM Class Membership

In crude models, high ACEs score was associated with 2.26 (95% CI: 1.97, 2.59) higher odds of being in the poor OHM class compared to the good OHM class (reference category) (Table 3.5). This association remained after sequentially adjusting for covariates. Similar results were observed with the association between ACEs and the odds of being in the moderate OHM class, compared to the class with the good OHM status. Finally, ACEs was associated with a higher odds of being in the good oral health and high rates of multimorbidity class and in the poor oral health and low rates of multimorbidity class, compared to the reference OHM health class, across unadjusted and adjusted models.

3.4.4 Psychological Distress and OHM Class Membership

Crude multinomial logistic regression models to estimate the extent to which psychological distress was associated with OHM clustering showed psychological distress to be associated with a 1.13 (95% CI: 1.12, 1.14) higher odds of being in the poor OHM class compared to the good OHM class (reference class) (Table 3.6). This association remained significant in subsequent models that adjusted for age, sex, socioeconomic (household income, education, and home ownership), and behavioural (smoking status and alcohol consumption) factors. Psychological distress was associated with lower odds of being in the poor oral health and low rates of multimorbidity class in unadjusted models (OR=0.98, 95% CI: 0.96, 0.99). However, psychological distress was not associated with being in the poor oral health and low rates of multimorbidity class in subsequent adjusted models. Among unadjusted and adjusted models, psychological distress was associated with a higher odds of participants being in the good oral health and high rates of multimorbidity class, as well as the moderate OHM class, compared to being in the class with the good OHM status.
### Table 3.3: Characteristics of the study sample stratified by age and sex, CLSA Baseline Comprehensive Cohort (n=25,411), 2011.

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<thead>
<tr>
<th></th>
<th>Female</th>
<th></th>
<th>Male</th>
<th></th>
<th></th>
<th>Overall</th>
</tr>
</thead>
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<td>55-64</td>
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<td>n=3,102</td>
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<td>Age (years)</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
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<td>Mean (SD)</td>
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<tr>
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<td>9.3</td>
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<td>$20,000 and &lt;$50,000</td>
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<td>23.0</td>
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<td>$50,000 and &lt;$100,000</td>
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<td>4.4</td>
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</table>

*Note: Weighted percentages are shown.*
Table 3.3 con’t: Characteristics of the study sample stratified by age and sex, CLSA Baseline Comprehensive Cohort (n=25,411), 2011.

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<th></th>
<th>Male</th>
<th></th>
<th></th>
<th></th>
<th>Overall</th>
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<td>n=3,454</td>
<td>n=4,423</td>
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<tr>
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<tr>
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<tr>
<td>No (Edentulous)</td>
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*Note: Weighted percentages are shown.*
Table 3.3 con’t: Characteristics of the study sample stratified by age and sex, CLSA Baseline Comprehensive Cohort (n=25,411), 2011.

<table>
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<tr>
<th>Characteristic</th>
<th>Female</th>
<th>Male</th>
<th>Overall</th>
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<td></td>
<td>45-54</td>
<td>55-64</td>
<td>65+</td>
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<tr>
<td></td>
<td>n=3,454</td>
<td>n=4,423</td>
<td>n=5,314</td>
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<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
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<tr>
<td>Denture/false teeth use</td>
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<td>Yes</td>
<td>12.7</td>
<td>25.1</td>
<td>52.9</td>
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<tr>
<td>No</td>
<td>87.3</td>
<td>74.9</td>
<td>47.1</td>
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<td>Oral health problem</td>
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<td>70.1</td>
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<tr>
<td>No</td>
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<td>29.9</td>
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<td>&lt;0.1</td>
<td>&lt;0.1</td>
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<tr>
<td>Chronic conditions</td>
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<tr>
<td>Alzheimer’s disease or related dementias</td>
<td>&lt;0.1</td>
<td>0.4</td>
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<td>Anxiety and/or mood disorders</td>
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<td>35.2</td>
<td>26.0</td>
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<tr>
<td>Asthma</td>
<td>18.7</td>
<td>19.1</td>
<td>17.5</td>
</tr>
<tr>
<td>Arthritis (including osteoarthritis and rheumatoid arthritis)</td>
<td>31.8</td>
<td>54.1</td>
<td>61.2</td>
</tr>
<tr>
<td>Cancer</td>
<td>9.8</td>
<td>18.4</td>
<td>25.6</td>
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<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>5.5</td>
<td>9.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14.8</td>
<td>21.2</td>
<td>21.9</td>
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<tr>
<td>Heart disease</td>
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</tr>
<tr>
<td>Stroke (including transient ischemic attack)</td>
<td>2.4</td>
<td>4.0</td>
<td>9.9</td>
</tr>
<tr>
<td>Prevalence of multimorbidity (95% confidence interval)</td>
<td>23.6 (22.2 - 25.0)</td>
<td>37.2 (35.8 - 38.6)</td>
<td>47.8 (46.4 - 49.1)</td>
</tr>
</tbody>
</table>

Note: Weighted percentages are shown.
**Figure 3.2**: Heatmap visualizing the probability of individuals in each class to report favourable oral health and multimorbidity.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oral Health-Multimorbidity Classes</th>
<th>Probability</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Class 1: Poor OH High MM</td>
<td></td>
</tr>
<tr>
<td>Self-reported oral health</td>
<td>Class 2: Good OH Low MM</td>
<td></td>
</tr>
<tr>
<td>Edentulism</td>
<td>Class 3: Good OH High MM</td>
<td></td>
</tr>
<tr>
<td>Denture/false teeth use</td>
<td>Class 4: Poor OH Low MM</td>
<td></td>
</tr>
<tr>
<td>Oral health condition</td>
<td>Class 5: Moderate OHM</td>
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</tr>
<tr>
<td>Multimorbidity</td>
<td></td>
<td>0.0-0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1-0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2-0.3</td>
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<tr>
<td></td>
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<td>0.3-0.4</td>
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<tr>
<td></td>
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<td>0.4-0.5</td>
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<td>0.6-0.7</td>
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<td></td>
<td></td>
<td>0.7-0.8</td>
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<tr>
<td></td>
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<td>0.8-0.9</td>
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<tr>
<td></td>
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<td>0.9-1.0</td>
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</table>

**OHM**: oral health and multimorbidity; **OH**: oral health; **MM**: multimorbidity
Table 3.4: Descriptive statistics of oral health-multimorbidity classes (N=25,411).

<table>
<thead>
<tr>
<th>Class 1 (Poor OH and high MM)</th>
<th>Class 2 (Good OH and low MM)</th>
<th>Class 3 (Good OH and high MM)</th>
<th>Class 4 (Poor OH and low MM)</th>
<th>Class 5 (Moderate OH and MM)</th>
<th>Overall</th>
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</thead>
<tbody>
<tr>
<td>N=887 (%)</td>
<td>N=12,387 (%)</td>
<td>N=5,685 (%)</td>
<td>N=2,380 (%)</td>
<td>N=4,072 (%)</td>
<td>N=25,411 (%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>69.8 (0.03)</td>
<td>56.3 (0.01)</td>
<td>60.6 (0.01)</td>
<td>67.1 (0.02)</td>
<td>61.9 (0.01)</td>
</tr>
<tr>
<td>Ethnicity</td>
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<tr>
<td>White</td>
<td>96.9</td>
<td>94.1</td>
<td>95.2</td>
<td>95</td>
<td>91.5</td>
</tr>
<tr>
<td>Non-white</td>
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<td>4.8</td>
<td>4.7</td>
<td>8.1</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.3</td>
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<td>Country of birth</td>
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<td>Canada</td>
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<td>80.7</td>
<td>79.7</td>
<td>81.5</td>
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<td>Other</td>
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<tr>
<td>Education</td>
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<td></td>
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<tr>
<td>Less than secondary</td>
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<td>4.1</td>
<td>8</td>
<td>17.5</td>
<td>14.6</td>
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<td>Secondary</td>
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<td>10.6</td>
<td>10.9</td>
<td>14.5</td>
<td>12.3</td>
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<tr>
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<td>8.9</td>
<td>10.9</td>
<td>9.1</td>
<td>8.3</td>
</tr>
<tr>
<td>Post-secondary degree</td>
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<td>76.4</td>
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<td>64.7</td>
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<td>0.2</td>
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<td>7.9</td>
<td>8.3</td>
<td>11.7</td>
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<td>Married/Living with partner</td>
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<td>74.7</td>
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<td>Widowed/Divorced/Separated</td>
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<tr>
<td>Total household income</td>
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<td>&lt;$20,000</td>
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<td>≥$20,000 and &lt;$50,000</td>
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<tr>
<td>≥$50,000 and &lt;$100,000</td>
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<td>5.7</td>
<td>7.1</td>
<td>7.1</td>
<td>6.8</td>
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</table>

Note: Weighted percentages are shown.
OH: oral health; MM: multimorbidity
Table 3.4 con’t: Descriptive statistics of oral health-multimorbidity classes (N=25,411).

<table>
<thead>
<tr>
<th></th>
<th>Class 1 (Poor OH and high MM)</th>
<th>Class 2 (Good OH and low MM)</th>
<th>Class 3 (Good OH and high MM)</th>
<th>Class 4 (Poor OH and low MM)</th>
<th>Class 5 (Moderate OH and MM)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=887 (%)</td>
<td>N=12,387 (%)</td>
<td>N=5,685 (%)</td>
<td>N=2,380 (%)</td>
<td>N=4,072 (%)</td>
<td>N=25,411 (%)</td>
</tr>
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<td><strong>Home ownership</strong></td>
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<td>70.2</td>
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<td>20.8</td>
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<td>2.3</td>
<td>2.6</td>
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</tr>
<tr>
<td>Satisfied</td>
<td>57.5</td>
<td>59.7</td>
<td>51.1</td>
<td>70.4</td>
<td>53.3</td>
<td>57.7</td>
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<tr>
<td>Neutral</td>
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<td>18.9</td>
<td>16.1</td>
<td>25.1</td>
<td>18.5</td>
<td>15.2</td>
</tr>
<tr>
<td>Missing</td>
<td>0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td><strong>ACEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;=4)</td>
<td>36.8</td>
<td>19.5</td>
<td>29.7</td>
<td>23.5</td>
<td>31.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Low (&lt;=3)</td>
<td>63.2</td>
<td>80.5</td>
<td>70.3</td>
<td>76.5</td>
<td>68.2</td>
<td>75.3</td>
</tr>
<tr>
<td><strong>Psychological distress (K10)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>70.7</td>
<td>89.7</td>
<td>79</td>
<td>90.8</td>
<td>72.6</td>
<td>83.9</td>
</tr>
<tr>
<td>Mild</td>
<td>14.1</td>
<td>6.2</td>
<td>11.3</td>
<td>5.1</td>
<td>15</td>
<td>8.9</td>
</tr>
<tr>
<td>Moderate</td>
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<td>2.2</td>
<td>5.3</td>
<td>1.4</td>
<td>5.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Severe</td>
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<td>1.1</td>
<td>2.9</td>
<td>0.8</td>
<td>5.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Missing</td>
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<td>0.8</td>
<td>1.6</td>
<td>1.9</td>
<td>1.7</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Note: Weighted percentages are shown.
OH: oral health; MM: multimorbidity
### Table 3.5: Multinomial regression models reporting odds ratios for the associations between ACEs and oral health and multimorbidity classes.

<table>
<thead>
<tr>
<th></th>
<th>Good oral health and low multimorbidity (class 2)</th>
<th>Good oral health and high multimorbidity (class 3)</th>
<th>Poor oral health and low multimorbidity (class 4)</th>
<th>Moderate oral health and multimorbidity (class 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1*</td>
<td>Model 2**</td>
<td>Model 3***</td>
<td>Model 4****</td>
</tr>
<tr>
<td>Good oral health and low multimorbidity (class 2)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Good oral health and high multimorbidity (class 3)</td>
<td>1.69 [1.57, 1.82]</td>
<td>1.81 [1.68, 1.95]</td>
<td>1.82 [1.68, 1.97]</td>
<td>1.75 [1.62, 1.89]</td>
</tr>
<tr>
<td>Poor oral health and low multimorbidity (class 4)</td>
<td>1.06 [0.95, 1.18]</td>
<td>1.27 [1.13, 1.42]</td>
<td>1.23 [1.09, 1.38]</td>
<td>1.12 [1.00, 1.27]</td>
</tr>
<tr>
<td>Moderate oral health and multimorbidity (class 5)</td>
<td>1.83 [1.69, 1.98]</td>
<td>2.03 [1.87, 2.19]</td>
<td>1.93 [1.77, 2.09]</td>
<td>1.74 [1.59, 1.89]</td>
</tr>
<tr>
<td>Poor oral health and high multimorbidity (class 1)</td>
<td>2.26 [1.97, 2.59]</td>
<td>2.75 [2.38, 3.17]</td>
<td>2.48 [2.14, 2.88]</td>
<td>2.21 [1.91, 2.57]</td>
</tr>
</tbody>
</table>

Reference group: Class 2 (good oral health and low multimorbidity)
*Crude association between ACEs and oral health-multimorbidity classification
**Estimation adjusted for age, sex, race/ethnicity, marital status
***Estimation adjusted for age, sex, race/ethnicity, marital status, smoking status, alcohol consumption, sugar consumption, sleep quality
****Estimation adjusted for age, sex, race/ethnicity, marital status, smoking status, alcohol consumption, sugar consumption, sleep quality, total household income, education, homeownership
Table 3.6: Multinomial regression models reporting odds ratios for the associations between later-life psychological distress and oral health-multimorbidity classes.

<table>
<thead>
<tr>
<th>Good oral health and low multimorbidity (class 2)</th>
<th>Model 1*</th>
<th>Model 2**</th>
<th>Model 3***</th>
<th>Model 4****</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Good oral health and high multimorbidity (class 3)</th>
<th>1.08 [1.07, 1.09]</th>
<th>1.10 [1.09, 1.11]</th>
<th>1.10 [1.09, 1.11]</th>
<th>1.09 [1.08, 1.10]</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Poor oral health and low multimorbidity (class 4)</th>
<th>0.98 [0.96, 0.99]</th>
<th>1.01 [1.00, 1.03]</th>
<th>1.01 [1.00, 1.02]</th>
<th>0.99 [0.98, 1.01]</th>
</tr>
</thead>
</table>

|--------------------------------------------------|------------------|------------------|------------------|------------------|

<table>
<thead>
<tr>
<th>Poor oral health and high multimorbidity (class 1)</th>
<th>1.13 [1.12, 1.14]</th>
<th>1.18 [1.16, 1.19]</th>
<th>1.17 [1.15, 1.18]</th>
<th>1.15 [1.13, 1.16]</th>
</tr>
</thead>
</table>

Reference group: Class 2 (good oral health and low multimorbidity)

*Crude association between psychological distress and oral health-multimorbidity classification

**Estimation adjusted for age, sex, race/ethnicity, marital status

***Estimation adjusted for age, sex, race/ethnicity, marital status, smoking status, alcohol consumption, sugar consumption, sleep quality

****Estimation adjusted for age, sex, race/ethnicity, marital status, smoking status, alcohol consumption, sugar consumption, sleep quality, total household income, education, homeownership
3.5 Discussion

In this study, we used LCA to identify OHM clusters in a large, national sample of Canadian middle-aged and older adults. We also assessed the association between the identified clusters and psychological distress and ACEs. Our results suggest the existence of five distinct classes of individuals who differed with respect to their OHM profiles. Furthermore, we found that older adults in any of the classes that included individuals with poor OHM were more likely to experience psychological distress, and more likely to report higher ACEs. The identified latent class structure, therefore, may have important implications for identifying subgroups of older adults whose experience of psychosocial or psychological stress may increase their risk of developing multiple co-occurring chronic diseases, complications from unmanaged illnesses, and/or adverse health outcomes.

Our results demonstrating distinct clusters of oral health and multimorbidity among an aging population are supported by previous studies demonstrating increasing prevalence of oral diseases and multimorbidity in the population, particularly among aging adults. For example, a study exploring the prevalence and patterns of multimorbidity in Canada found that the prevalence of multimorbidity increased from 3.1% among adults 20-34 years old to 31.3% among adults 65 years and older (200). Aging often increases risk factors for chronic disease, such as cognitive and functional impairment, reduced mobility, and frailty (201). Furthermore, these chronic conditions are directly associated with compromised oral health (202). Studies exploring the differences in the distribution of oral health indicators among older adults with and without multimorbidity observed a significantly higher prevalence of inadequate oral health, such as edentulism, among multimorbid participants (21,203).

In addition to identifying clusters of OHM, we found that ACEs and psychological distress were associated with patterns of OHM clustering, even after controlling for behavioural and socioeconomic factors. We acknowledge that some of the variables adjusted for in our models, particularly the behavioural factors, could be mediators of the association between psychological distress or ACEs and OHM. Our results show that psychological distress was associated with an increased odds of being in all poor oral health and/or high rates of multimorbidity classes compared to the good OHM class. Similarly, ACEs exposure
increased the odds of membership in all OHM classes, relative to the good OHM class, with the highest odds being for participants in the poor oral health and high multimorbidity class. Our findings are consistent with previous literature linking psychosocial and psychological stress to an increased risk of oral and chronic health conditions later in life. For example, Canadian adults with moderate to severe psychological distress are at a higher risk of multiple chronic conditions, relative to their unexposed counterparts (204). More recently, we have shown that psychosocial stress is associated with poor oral health in a representative sample of Ontario adults, with the magnitude of the association being largest in an older population (157). Previous studies have also shown that among American adults aged 50 years and older, ACEs such as childhood trauma and abuse contributed to higher odds of total tooth loss in later life (205). Similarly, findings from a 30-year follow-up study showed that child abuse and neglect affected adult health status by increasing the risk for diabetes, lung disease, and oral health problems (206).

By and large, there are two main pathways that can explain the observed associations between psychosocial and psychological stress and OHM clustering, namely the biological and behavioural pathways. Both pathways are generally intertwined and can be best described through the biopsychosocial model which is commonly employed to explain how biological, psychological, and social factors work synergistically to influence and shape health outcomes across the lifespan. Here, psychosocial stressors, such as ACEs, may provoke the dysregulation of the central nervous system and contribute to alterations of the stress response that can persist into adulthood (207,208). When experiencing psychosocial or psychological stress, adaptive biochemical responses occur, which include the increased activation of the hypothalamus-pituitary-adrenal (HPA) axis and the secretion of adrenocortical hormones, primarily cortisol (47,48,209). These responses may help an individual to cope with an acute stressor but may be detrimental when stressful experiences are extreme or chronic as evident by studies on allostatic load (210,211). Long-term elevation of cortisol suppresses both the immune and inflammatory responses of an individual and may alter development of the HPA axis early or later in life, increasing the risk of developing chronic conditions (212). On the other hand, the behavioural pathway proposes that psychosocial stress could affect health through agential and health-related
behaviours, such as smoking, drinking, and obesity, all of which are risk factors for OHM (213).

An important finding of our study is the magnitude of the association between each of psychological distress and ACEs and OHM clustering. We found ACEs to have a larger magnitude of the effect with OHM clustering than adult psychological distress. Although we did not assess the impact of each of the ACEs or adult psychological distress longitudinally, our findings emphasize the importance of early exposures on oral health and multimorbidity. This agrees with life course epidemiology research demonstrating the timing of the stressful exposure to be critical to the developing health problems later in life (179). The argument is that early stress induced by ACEs may have greater impairment on later-life health through biological embedding, where early stress may alter neurological responses and damage immune systems (78,205). In the context of oral health and its relationship to major systemic health conditions, immune system dysregulation due to stress has been shown to increase susceptibility to oral health problems, including dental caries and periodontal disease, likely through alterations in HPA axis function, subsequent cortisol increases, pro-inflammatory responses, and microbiome dysbiosis (43,66,74,209).

Our findings have important implications for public health policy. As life expectancy continues to rise globally, the burden of multimorbidity and oral disease are also projected to increase. The observed latent class structure in this study, in which individuals cluster based on their oral health and multimorbidity profiles, suggests that assessing both oral and non-oral health outcomes is necessary for improving disease prevention strategies. On the other hand, our findings may be suggestive that policies focusing exclusively on the endpoints of the co-occurrence of chronic conditions may be insufficient for improving overall health due to the additional contributing factors that occur over the life-course, such as the impact of psychosocial stress. Although our study did not specifically compare the magnitude of the outcomes in association with the timing of exposure, our results contribute to knowledge on the importance of prevention in early life and the focus on psychosocial factors across the life-course.
3.5.1 Strengths and Limitations

There has been an increased interest in the association between oral health and multimorbidity recently. However, how oral health and multimorbidity cluster in the population, particularly in older adults who typically bear the highest burden of disease, is largely unstudied. Among the strengths of our current work is the use of a large, national cohort as well as the application of advanced analytical methods such as LCA to understand how oral health and multimorbidity co-occur in Canada’s aging population. Furthermore, we used historical and current proxies of psychosocial stress to assess the potential impact of the timing of exposure on disease clustering later in life.

Nevertheless, there are limitations to our analyses that require caution when interpreting the results. ACEs were measured through the retrospective self-report of events that happened between 30 and 70 years previously, depending on the age of the participants when undergoing the study. While most questions concerned specific events, such as abuse or parental death, questions on neglect focused on less objective events, such as whether the participant felt unloved. Therefore, these questions may be subject to greater recall bias. Finally, our measure of multimorbidity relied on self-reported chronic health conditions; however, these questionnaires are commonly used in large cohort studies and have shown acceptable reliability and validity (214). It is also important to note that the Kessler Psychological Distress Scale, which was used to assess psychological distress as an exposure variable, is intended to provide a global measure of distress based on questions related to anxiety and depression and is therefore often used as a brief screening tool to assess and inform potential anxiety and/or depression diagnosis. As the definition of multimorbidity also included anxiety and/or mood disorders as a chronic condition according to PHAC, assessing psychological distress and its association with OHM class membership may have been impacted by the assessment of mood disorders in both the K10 questionnaire and OHM class membership variable. However, to address this issue, we performed exploratory analyses to assess the correlation between psychological distress and multimorbidity (Appendix 3D). We found only a weak correlation between both variables, thereby increasing confidence in the interpretation of our findings.
3.5.2 Future Research Directions

This study provides useful information about the clustering of a large sample of aging Canadians regarding their oral health and multimorbidity. We showed that middle-aged and older adults tend to form distinct clusters in terms of their self-reported oral health and chronic systemic conditions. Future studies may adopt a life-course approach to explore the OHM association and the different contributing factors to this relationship across the lifespan, such as ACEs, as well as the underlying biological mechanisms (43,66). Additionally, future research may use methods, such as pathway analyses, to further explore these relationships.

3.6 Conclusion

We demonstrate that the health profiles of aging Canadians vary according to their oral health and multimorbidity statuses. The role of psychosocial stress in the clustering patterns of oral health and multimorbidity that we observed in this study highlights the need for future research on the timing and magnitude of stressful exposures over the life-course and how they may relate to disease clustering patterns. Indeed, further investigation into the contribution of oral health to multimorbidity, and the key role of the social determinants of health as common risk factors, will continue to be of relevance to tackle health problems of the aging population.
Chapter 4

4 Synthesis and Conclusion

This chapter aims to synthesize and contextualize the findings from Chapters 2 and 3 of this thesis to the larger body of literature. Together, these two studies build a greater understanding of the potential risk factors and pathways to the oral-systemic health connection. The research contributions and limitations of our studies will be noted. Finally, we will discuss clinical implications and direction for future studies in this area.

4.1 Summary of Studies

The overall aim of this thesis was to explore the extent to which psychosocial stress factors contribute to the oral-systemic health connection using two independent studies. First, we conducted a scoping review to synthesize existing literature on the role of psychosocial stress in the co-occurrence of oral and systemic disease (Chapter 2). This provided context for our subsequent study, in which we used data from the CLSA to explore the roles of ACEs and psychological distress in the clustering of oral disease and multimorbidity (Chapter 3).

Our scoping review included studies that examined indicators of psychosocial stress in relation to oral-systemic disease. All thirty articles that were included in this review examined a range of psychometric and biological measures of psychosocial stress. Psychometric measures included perceived life stress, emotional distress, lifestyle or behavioural factors, and childhood adversity. Cortisol was the only biological measure of psychosocial stress identified in this review. Periodontal disease, depression, diabetes, and heart disease were the most common oral and systemic conditions studied. Overall, twenty-seven studies found a positive association between psychosocial stress and the association between oral and other chronic conditions (systemic diseases).

Our clustering analysis of CLSA cohort data identified five distinct clusters of individuals based on their oral health and multimorbidity profiles. Approximately 50% of the weighted sample population belonged to the cluster characterized by good oral health and low multimorbidity, while the remaining sample population grouped into one of the following
four clusters: 1) poor oral health and high multimorbidity (3.9%), 2) good oral health and high multimorbidity (19.9%), 3) poor oral health and low multimorbidity (8.8%), and 4) moderate oral health and multimorbidity (17.5%). We also found that ACEs exposure increased the odds of membership in the poor oral health and high multimorbidity cluster (OR=2.21, 95% CI: 1.91, 2.57) compared to the good oral health and low multimorbidity group (reference class), adjusting for all covariates. Similarly, psychological distress increased the odds of being in the poor oral health and high multimorbidity group (OR=1.13, 95% CI: 1.12, 1.14) compared to the reference group of good oral health and low multimorbidity.

4.2 Synthesis

In this section, we compare findings from our two studies and discuss these findings in the context of the existing literature.

In our quantitative analysis (Chapter 3), we found that psychological distress and ACEs increased the odds of poor oral health and/or high multimorbidity class membership. These results agree with our findings from the scoping review (Chapter 2), in which the majority of included articles found a positive association between indicators of psychosocial stress and oral and systemic diseases. Prior research indicates that social determinants of health, including psychosocial factors, increase the likelihood of experiencing oral and/or other chronic conditions (168,215), and that both groups of diseases often co-occur (216) and are further exacerbated by aging. Taken together, our study findings suggest that psychosocial stress plays a role in the co-occurrence of oral and systemic disease in middle-aged and older adults. Our two studies also had similar findings with regards to psychosocial stress and oral disease and multimorbidity. We found that eight of nine articles in our scoping review that investigated more than one chronic condition found a positive association between psychosocial stress, oral disease, and multiple systemic disease outcomes. These findings agree with our cross-sectional CLSA analysis, suggesting that psychosocial stress also contributes to the co-occurrence of oral health conditions and multimorbidity.
Few studies have explored the clustering patterns of multimorbidity or oral health conditions. These have used cluster analyses to explore the role of the social determinants of health in patterns of oral or general health-related behaviour (217–219), but not in the clustering of the conditions themselves. Clusters of multimorbidity have also been identified in previous studies (220–222); however, oral health conditions were not included in these analyses. To our knowledge, only a handful of studies have explored the clustering patterns of multimorbidity and oral conditions together. For example, an article conducted by Larvin et al. (23) used a clustering analysis approach to explore the relationship between multimorbidity and oral health; however, in this study, multimorbidity clusters were explored in the context of individuals with periodontitis, with no “good oral health” comparison group. Our quantitative analysis included all individuals in the sample, regardless of oral health status, thus providing a thorough interpretation of how both oral disease and multimorbidity may cluster in individuals. Moreover, while our scoping review identified studies exploring the role of psychosocial stress in oral-systemic disease, there is limited evidence on the extent to which psychosocial stress may impact the co-occurrence of oral disease and specifically multimorbidity. However, this discrepancy is less surprising as studies on multimorbidity have become of more prominence only in recent years, particularly as the population of adults aged 65 years and older is growing and multimorbidity is becoming a more common observation (24,200). Our study findings are therefore novel and important to the larger body of literature investigating the role of social determinants of health in disease outcomes around aging.

4.3 Research Contributions

The chapters of this thesis add to the body of literature on how oral health co-occurs with systemic conditions, as well as the role of psychosocial stress in this relationship. Specifically, we conducted a scoping review to explore the role of psychosocial stress in the oral-systemic disease connection (Chapter 2). This review clarified and summarized findings from the larger body of literature and contributed to understanding how psychosocial stress factors may contribute to oral and systemic disease. To our knowledge, our study using data from the CLSA is the first to explore how oral health and multimorbidity cluster in the Canadian population, particularly in middle-aged and older
adults who bear a higher burden of disease, and how psychosocial stress factors may contribute to this clustering pattern at varying life stages (Chapter 3). Regarding oral-systemic disease, prior literature has focused on the co-occurrence between oral disease and systemic disease, with our study findings filling the gap of how oral disease co-occurs with multimorbidity. Furthermore, while previous research has focused on how psychosocial stress is associated with oral and systemic diseases separately, our results highlight the contribution of psychosocial in the co-occurrence of oral-systemic disease as well as oral health conditions and multimorbidity.

4.4 Strengths

Our scoping review included thirty observational studies from several countries reporting data of more than 50,000 participants with numerous psychometric and biological measures of psychosocial stress. Our review is also the first to assess the role of psychosocial stress in the co-occurrence of oral and systemic disease conditions on a large scale while using both psychometric and biological measures of stress.

Among the strengths of our quantitative work is the use of data from the CLSA, which is a large, population-based cohort study that provides comprehensive information on the health of aging Canadians. A primary strength of this study is the large sample size of the CLSA, which provides high power and precision to our statistical analyses. Moreover, we used LCA as a novel analysis to better understand the clustering of a Canadian sample based on their oral health and multimorbidity status. This approach allowed us to assess the potential impact of the timing of stress exposures, namely ACEs and psychological distress, on disease clustering later in life.

4.5 Limitations

Our scoping review has some limitations. First, the scoping review methodology may have contributed to not finding additional studies examining biomarkers of psychosocial stress other than cortisol. A systematic approach or the inclusion of additional search terms may address this limitation in future studies. Second, the quality of the included studies was not formally assessed in this scoping review, and is a limitation that may affect any conclusion.
drawn from the results. However, all articles were published by peer-reviewed journals and are expected to be of good, scientific standard. Finally, due to the qualitative nature of this review, we are unable to assess how much psychosocial stress factors are related to oral-systemic disease.

In our cohort analysis, the assessment of ACEs may have been impacted by recall bias as ACEs were measured through the retrospective self-report of events that happened between 30 and 70 years previously, depending on the age of the participants undergoing the study. This bias is not unique to our study; rather, nearly all studies exploring the impact of ACEs on adult health outcomes encounter the risk of recall bias (223). Mental dispositions may bias retrospective ACEs assessment toward underestimating or overestimating the impact of adversity on life outcomes, such as disease (224). Using objectively measured life outcomes, such as standardized assessment tools, can help to mitigate the potential recall bias resulting from retrospective ACEs measures (223). Due to the CLSA questionnaires that we included in our study being largely based on standardized measures (190), we were able to utilize objectively measured oral and systemic disease outcomes, thereby aiding in mitigating the risk of recall bias. However, cautious interpretation of the association between ACEs and oral health and multimorbidity clustering must still be considered.

Additionally, a limitation of our CLSA cohort analysis stems from the assessment of psychological distress as an exposure variable to oral health and multimorbidity cluster membership. The Kessler Psychological Distress Scale, which was used to assess psychological distress in this study, is intended to provide a global measure of distress based on questions relating to anxiety and depression (192). Furthermore, this scale is often used as a brief screening tool to assess and inform potential anxiety and/or depression diagnosis (193). However, our definition of multimorbidity (as defined by PHAC (101)) also included anxiety and/or mood disorders as a chronic condition. While we conducted exploratory sensitivity analyses to assess the correlation between these variables (Appendix 3D), assessing psychological distress and its association with oral health and multimorbidity cluster membership could have been impacted by the assessment of anxiety and mood disorders in both the K10 questionnaire and the multimorbidity variable, which was ultimately included in clustering analysis.
4.6 Clinical Implications

Both of the studies included in this thesis highlight the importance of the contribution of social determinants of health to chronic disease outcomes in the middle-aged and older adult population. With an increasing number of older individuals in the population living with multiple health conditions, including oral and systemic conditions, a profound shift in identifying and addressing common risk factors is clinically imperative. Our findings suggest that policies focusing exclusively on the health outcomes of the co-occurrence of chronic conditions may be insufficient for improving overall health due to the additional contributing factors that occur over the life-course, such as the impact of psychosocial stress. Current preventative resources are beginning to follow a common risk factor approach in advocating integrated preventative support (24). However, more detailed and comprehensive preventative support will also be needed for multimorbid patients experiencing the complications of living with multiple conditions, including the onset of oral conditions due to the use of polypharmacy (i.e., dry mouth) or side effects from systemic conditions (i.e., lack of mobility leading to poor oral hygiene). Additionally, our study findings showcase the importance of adopting a life-course perspective to prevention and intervention strategies. This will be critical to addressing the disease burden in the population. Intervening on psychosocial risk factors at an early age may allow for the prevention or delay of disease progression later in life, thereby reducing disease burden in older age, both to the individual and the healthcare system as a whole (225). Furthermore, healthcare systems and providers should consider expanding intervention strategies to include trauma-informed practices that, while addressing poor health outcomes, also help to improve quality of life and mental well-being among older adults who experienced ACEs or are currently experiencing psychosocial stress.

4.7 Future Studies

Future research is required to further assess the role of psychosocial stress and other social determinants of health in oral-systemic disease patterns, particularly in the context of adults aged 65 years and older. Impacts of social determinants of health can be accumulated over the life-course, alter health trajectories across the lifespan, and be transferred across generations (168). Identifying common risk factors to oral-systemic disease that occur over
the life-course, such as ACEs, may allow for better prevention and intervention strategies to be implemented early and across the lifespan, ultimately working to lower the disease burden on individuals as well as the healthcare system.

Chronic stress exposures have been shown to result in biological alterations of the stress pathways, such as the HPA axis, the autonomic nervous system, and the immune system (145). In particular, psychosocial stress impacts the HPA axis, impacting biomarkers involved in the stress response such as cortisol, ACTH, and BDNF (145). However, our scoping review only identified cortisol as a biological indicator of psychosocial stress in relation with oral-systemic disease. Therefore, in an effort to be thorough in the investigation of the role of psychosocial stress in oral-systemic disease, additional biological measures of stress should be explored in future studies.

Previous research has also hypothesized the role of psychosocial stress in biological aging as a risk factor for disease (226). Aging is the single most important risk factor for diseases that are currently the leading causes of morbidity and mortality (226). Studies suggest that biological age may be influenced by multiple factors, including exposure to psychosocial stress (227). Clinical and epidemiological studies have found that accelerated epigenetic age, in which epigenetic or biological age is “older” than chronological age, may be an indicator of risk for several health problems among adults such as cancer, cardiovascular disease, asthma, and periodontal disease (227–230). However, there is limited research on the contribution of psychosocial stress to epigenetic aging and its impact on later oral-systemic disease outcomes. Future research may therefore investigate the relationship between biological age and later oral-systemic disease, and how psychosocial stress may impact this association.

4.8 Conclusions

The primary objective of this thesis was to investigate the role of psychosocial stress in the oral-systemic health connection. Our scoping review identified thirty studies, of which twenty-seven found a positive association between psychosocial stress and the presence of oral-systemic disease outcomes. However, these findings were largely limited to samples that investigated only one oral disease and one systemic disease, with only a third of
included articles investigating multiple diseases. Our subsequent analysis of a national cohort found that individuals cluster together based on their oral health and multimorbidity profiles. Approximately half of the sample population presenting with good oral health and low multimorbidity, while the remaining half of the sample population clustered into four groups of poor oral health and/or high multimorbidity outcomes. We also found that psychological distress and ACEs increased the odds of membership in poor oral health and/or high multimorbidity clusters compared to membership in the good oral health and low multimorbidity cluster. Overall, this thesis contributes evidence on the role of psychosocial stress in the oral-systemic disease connection, and further contextualizes this contribution in middle-aged and older Canadians. The findings from this thesis highlight the importance of understanding the role of social determinants of health as common risk factors to oral-systemic disease in the aging population and serves to inform the inclusion of psychosocial factors in disease prevention strategies.
References


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Appendices

Appendix 3A: Description of covariates.

a) Demographic factors

*Age and sex:* The study participants reported their age (in years) and their sex as a binary variable (male/female). We further categorized age into three groups: 45-54 years, 55-64 years, 65+ years.

*Ethnicity:* Participant ethnicity was recorded in 15 categories. Due to the small number of individuals in each category, we dichotomized participants to “white” and “non-white”. This dichotomization has been described in previous studies using CLSA data (Nicholson et al. 2020).

*Country of birth:* Participant country of birth was recorded in 20 categories. Due to the small number of individuals in each category, we dichotomized participants to “Canada” and “other”.

*Marital status:* Participants reported their marital status using six response categories, which we further categorized into three groups: single, married/living with partner, and widowed/divorced/separated.

b) Socioeconomic factors

*Total household income:* Total household income from all sources before taxes and deductions in the past 12 months was reported in one question using multiple response categories, including “less than $20,000”, “$20,000 to less than $50,000”, “$50,000 to less than $100,000”, “$100,000 to less than $150,000”, and “$150,000 or more”.

*Education:* Highest attained education level of participants was recorded using the follow response categories: “less than secondary school education”, “secondary school education”, “some post-secondary education”, and “post-secondary degree/diploma”.

*Home ownership:* We used home ownership as a wealth indicator using the following CLSA question: “Do you (or your spouse/partner) own or rent your dwelling?”. The
corresponding response categories included: “owns dwelling”, “rents dwelling”, and “other”.

c) Behavioural factors

**Smoking:** We categorized smoking into 3 categories including “current daily smokers”, “current occasional smokers”, and “current non-smokers”.

**Alcohol consumption:** We categorized alcohol consumption into four categories including “daily drinkers”, “regular drinkers”, “occasional drinkers”, and “non-drinkers”, where a “daily drinker” is someone who drinks almost every day, a “regular drinker” is someone who drinks at least once a month, an “occasional drinker” drinks less than once a month, and a “non-drinker” is someone who has not drank in the past 12 months.

**Sugar consumption:** We operationalized sugar consumption using the following three questions:
1. “How often do you usually eat ice cream, ice milk, frozen yogurt, milk-based desserts (puddings, …)?”
2. “How often do you usually eat cakes, pies, doughnuts, pastries, cookies, muffins…?”
3. “How often do you usually eat chocolate bars?”

To define sugar consumption, we created a binary variable by dichotomizing responses to the survey questions (never, daily, weekly, monthly, yearly) as “high” (daily, weekly) and “low” (monthly, yearly, never).

**Sleep quality:** Sleep quality was operationalized using the response to the question “How satisfied or dissatisfied are you with your current sleep pattern?”, which originally included five Likert responses (very dissatisfied, dissatisfied, neutral, satisfied, and very satisfied). We dichotomized sleep quality as “satisfied” (satisfied, very satisfied) and “dissatisfied” (dissatisfied, very dissatisfied).

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1 Sugar consumption was derived from the Short Diet Questionnaire (SDQ). The development, testing and validation of the SDQ were carried out among NuAge study participants as part of the Canadian Longitudinal Study on Aging (CLSA) Phase II validation studies, CIHR 2006-2008. The NuAge study was supported by the Canadian Institutes for Health Research (CIHR), Grant number MOP-62842, and the Quebec Network for Research on Aging, a network funded by the Fonds de Recherche du Québec-Santé.

2 Shatenstein B., & Payette H. Evaluation of the relative validity of the Short Diet Questionnaire for assessing usual consumption frequencies of selected nutrients and foods. Nutrients. 2015;7(8):6362-6374
Appendix 3B: Western REB study approval letter.

Date: 19 May 2022

To: Dr Noha Gomaa

Project ID: 120939

Study Title: Psychosocial stress and epigenetic aging as common pathways to oral diseases and multimorbidity

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 14 June 2022

Date Approval Issued: 19 May 2022

REB Approval Expiry Date: 19 May 2023

Dear Dr Noha Gomaa,

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study.

Documents Approved:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Document Type</th>
<th>Document Date</th>
<th>Document Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>April12_2022_Data Checklist 2203064 version 1</td>
<td>Other Data Collection Instruments</td>
<td>12/Apr/2022</td>
<td>1</td>
</tr>
<tr>
<td>revised_REB_Gomaa_CLSA_proposal_biopsychosocial pathway_2022/May13</td>
<td>Protocol</td>
<td>13/May/2022</td>
<td>2</td>
</tr>
</tbody>
</table>

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Device Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000946.

Please do not hesitate to contact us if you have any questions. Sincerely,

Ms. Jhanninee Subendran, Ethics Officer on behalf of Dr. Roberta Berard, HSREB Vice Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Appendix 3C: CLSA Access Agreement

CLSA Access Agreement

This agreement is entered into this Aug. 22 2022 (the “Effective Date”), at Hamilton, Ontario.

McMaster University, a University incorporated by special act of the Province of Ontario, Canada, with a main address at 1280 Main Street West, McMaster Innovation Park, Suite 309/A, Hamilton, Ontario, Canada, L8S 4K1 (“McMaster”) is the host institution of the Canadian Longitudinal Study on Aging (“CLSA”).

AND

The University of Western Ontario, with a main address at 1151 Richmond St, London, Ontario, Canada N6A 3K7 (“Approved User Institution”)

WHEREAS:

A. Dr. Parminder Raina (McMaster University) is the Lead Investigator for the CLSA funded by a grant from the Canadian Institutes of Health Research (CIHR) and is responsible for the academic obligations under this Agreement.

B. Dr. Noha Gomaa (the “Approved User”) is an Assistant Professor at the Institution, where he/she carries or wishes to carry out a project entitled “Psychosocial stress and epigenetic aging as common pathways to oral disease and multimorbidity”, for which access to CLSA samples or data (or both) will be required.

C. The document titled “CLSA Data and Biospecimen Access Policy and Guiding Principles” attached, as Schedule A is an integral part of this agreement. All obligations contained therein are part of this agreement.

The parties hereto agree as follows:

1. Definitions

“Agreement” means this CLSA Access Agreement.

“DSAC” means the CLSA’s Data and Sample Access Committee.

“Project” means the CLSA Data and/or Biospecimen Request Application described in Schedule B attached hereto.

“Transferred Materials,” means the CLSA data, Metabolon Data, Regeneron Data and/or the biospecimens described in Schedule B attached hereto.

“Metabolon Data” means the metabolite biomarker signature data generated by Metabolon Inc. for CLSA described in Schedule B attached hereto.

“Regeneron Data” means the genomic data generated by the Regeneron Genetics Center for CLSA described in Schedule B attached hereto.

2. Sample and Data Security.

2.1 Security measures specified in Schedule C attached hereto will apply to all Transferred Materials. The Approved User and Institution undertakes to respect these security measures during the Project and afterwards, during storage of Transferred Materials where necessary.

2.2 The Approved User and Institution shall agree to the audit of their research facility by McMaster to ensure the security and confidentiality of Transferred Materials. These audits may be conducted with reasonable notice. Any discrepancies between the security measures specified in Schedule C and what is found at the Approved User and Institution’s research facility will have to be corrected within sixty (60) days notice by McMaster. McMaster will support the costs associated with these audits.

2.3 Transferred Materials, including any copies thereof, may only be used for the Project described in Schedule B and may not be disclosed, transmitted or shipped to anyone except employees working directly with the Approved User and Institution or co-investigators including co-applicants or other personnel from other institution(s), indicated in the Project who will require direct access to the CLSA Data and who agree to be bound by the terms of this Agreement or to persons expressly designated in
writing by McMaster. The Approved User shall retain control of the Transferred Material at all times. It is the responsibility of the Approved User and Institution to inform the staff and co-investigators, including co-applicants and other personnel at other third-party institution(s) entering into contact with the Transferred Materials of the obligations contained in the CLSA Data and Biospecimen Access Policy and Guiding Principles and this Agreement. As such, co-applicants and other personnel at other third-party institution(s) must submit a signed Schedule F attached hereto. Transfer of any CLSA biospecimens outside Canada is strictly prohibited. Data access will only be provided to institutional email addresses.

4 Any Metabolon Data provided hereunder may not be used in research sponsored by for-profit entities and/or transferred to any for-profit entities.

5 Any Regeneron Data provided hereunder may not be used in research sponsored by for-profit entities and/or transferred to any for-profit entities.

Return of Derived Data. The Approved User undertakes to return to McMaster the results of the Project analyses as specified in Schedule D attached hereto within the timeframe and conditions specified therein.

Fees. The Institution shall pay to McMaster the access fees and transportation fees specified in Schedule E attached hereto within forty-five (45) days after receipt of the invoice.

Representations and Warranties of the Approved User and the Institution

1 The Approved User and the Institution represent and warrant that the Project has received ethical approval from the Institution’s research ethics committee or, if no such committee exists within the Institution, from a recognized research ethics committee for the duration of the Project. All documents in the Approved User’s possession concerning ethical approval of the Project, including any subsequent amendments/renewals that may be applicable, have been provided to McMaster.

2 The Approved User and the Institution represent that they have read and took note of their obligations under the CLSA Data and Biospecimen Access Policy and Guiding Principles attached hereto as Schedule A.


7. Exclusive Access: No exclusive access will be granted to any portion of the Transferred Materials. McMaster may grant access to the Transferred Materials to others and may use it for its own internal purposes.

8. Publications: Copies of all proposed publications using Transferred Materials from McMaster must be submitted to McMaster for review at least 15 working days prior to submission. This review will be limited to ensuring that participants cannot be identified in such publications, that results are presented in a scientifically accurate manner to prevent the stigmatization of participants and of the communities they belong to. Users are required to follow the process and conditions contained in the CLSA publication and promotion policy, which can be found on the CLSA Website: [https://www.elsa-elev.ca](https://www.elsa-elev.ca). For additional clarity, pursuant to clause 13.1, the Approved User’s right to publish shall end upon termination of this Agreement.

9. Archives and Peer Review. Approved User will be permitted to archive the Transferred Material for the period of time required for peer review and audit purposes but not to exceed 1 year following the termination of this Agreement. Once this period of time has elapsed, the Approved User undertakes to destroy all Transferred Materials and all copies thereof in his/her possession or his/her control. When requested by McMaster, the Approved User shall certify in writing that the Transferred Material and all copies thereof were destroyed (Schedule C).

10. Reporting Obligations: Approved Users shall comply with the following reporting obligations: i) a Final Report is to be submitted 60 days following the end date of this agreement; and ii) notify McMaster without delay for: a) incidents affecting the confidentiality of participants; b) incidents affecting the security or integrity of data/samples; c) suspension or lapse of any relevant authorizations (e.g. Ethics approval), professional qualifications, funding or approvals.

11. Undertakings and Liability

11.1 The Institution and Approved User acknowledges that the biological samples contained in the Transferred Material may carry viruses, latent viral genomes, and other infectious agents. The Approved User undertakes to treat all such biological samples
as if they are not free of contamination, and to ensure that all such biological samples are handled only by trained personnel under laboratory conditions that afford adequate biohazard containment. By accepting delivery of these biological samples, the Institution and Approved User assume full responsibility and risk for their safe and appropriate use, handling, storage, and/or disposal.

11.2 To the extent permitted by law, the Approved User and the Institution assume all liability or damages arising from the use, storage or disposal of the Transferred Material and further agrees to defend, indemnify and hold harmless McMaster and its agents and employees from any unauthorized use of or disclosure or transfer of the Metabolon Data or Regeneron Data pursuant to Section 2.4 and all liabilities, damages, demands, expenses and losses arising out of the acceptance, use for any purpose, handling or storage and/or disposal of the Transferred Materials or their by-products or modified or unmodified derivatives and in respect of all matters associated with the research results arising from the use of the Transferred Materials by the Approved User, the Institution or its employees, except when such claims are the result of the gross negligence or willful misconduct of McMaster.

12. Default of Approved User or Institution. Failure to comply with the terms of this Agreement may result, in addition to termination of this agreement pursuant to Section 13.2, in the disqualification of the Approved User or the Institution (or both) from receiving any additional data or biological samples from McMaster. McMaster reserves the right to institute and to take appropriate proceedings at law (or in equity, where applicable) against the Approved User or the Institution (or both) in connection with breaches of this Agreement.

13. Termination

13.1 This Agreement will terminate two years after the end date of the Project unless the parties agree in writing to renew it or to terminate it earlier upon thirty (30) days written notice to the other party. Upon termination of the Agreement, the Approved Users will destroy all Transferred Materials in his or her possession. Following termination of the Agreement, Approved User’s right to publish pursuant to Section 8 hereunder shall end.

13.2 McMaster may terminate this Agreement if the Approved User or the Institution are in default of any of the provisions of this Agreement and this default has not been remedied within sixty (60) days of written notice sent by McMaster to the Approved User or the Institution in respect of this default. Upon termination of this Agreement pursuant to this Section 13.2, the Approved User will return all Transferred Material in his or her possession to McMaster or destroy them and all copies thereof in possession or control of the Approved User or the Institution according to the instructions provided by McMaster. The Approved User will provide McMaster with a certificate attesting to such destruction, executed by him/her and an authorized representative of the Institution (Schedule C). In the event the Approved User is found to be in breach of this Agreement and such breach has not been remedied in accordance with this Section 13.2, the Approved User will not be entitled to publish the results of any Project except with the written agreement of McMaster.

14. No Warranties. The Transferred Materials accessed or delivered pursuant to this agreement are understood to be experimental in nature and are provided "as is". McMaster makes no representations and extends no warranties of any kind; either expressed or implied whatsoever in respect of the Transferred Materials. There are no express or implied warranties of merchantability, utility, efficacy, safety, identity, composition, non-toxicity and accuracy or fitness for a particular purpose or that the use thereof will not infringe any patent or other proprietary rights of any third party.

15. Notices. Any notice to be given by either party to the other shall be sent to the following:

<table>
<thead>
<tr>
<th>For McMaster: CLSA Management Contact:</th>
<th>For Legal Matters:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Parminder Raina, PhD</td>
<td>Executive Director, McMaster Industry Liaison Office</td>
</tr>
<tr>
<td>Lead Principal Investigator</td>
<td>MIP - Rm. 305</td>
</tr>
<tr>
<td>Canadian Longitudinal Study on Aging</td>
<td>175 Longwood Rd S, Hamilton, ON L8P 0A1</td>
</tr>
<tr>
<td>McMaster University</td>
<td>Tel: [xxx]xxx-xxxx</td>
</tr>
<tr>
<td>175 Longwood Rd. S. Suite 309A</td>
<td>Fax: [xxx]xxx-xxxx</td>
</tr>
<tr>
<td>Hamilton, ON L8P 0A1</td>
<td>Email: [<a href="mailto:mcmaster@mcmaster.ca">mcmaster@mcmaster.ca</a>]</td>
</tr>
<tr>
<td>Tel: [xxx]xxx-xxxx</td>
<td>If for Institution (add contact details)</td>
</tr>
<tr>
<td>Email: [<a href="mailto:mcmaster@mcmaster.ca">mcmaster@mcmaster.ca</a>]</td>
<td>Nancy McCready</td>
</tr>
<tr>
<td></td>
<td>Contract Coordinator</td>
</tr>
<tr>
<td>If for Approved User:</td>
<td>1391 Western Road, SS 5150</td>
</tr>
<tr>
<td>Dr. Noha Gomaa, PhD</td>
<td>London, Ontario</td>
</tr>
<tr>
<td>Assistant Professor</td>
<td>N6G 1C</td>
</tr>
<tr>
<td>Western University</td>
<td>Tel: [xxx]xxx-xxxx</td>
</tr>
<tr>
<td>Dental Sciences Building,</td>
<td>Fax: [xxx]xxx-xxxx</td>
</tr>
<tr>
<td>Western University,</td>
<td>Email: [<a href="mailto:xxy@www.com">xxy@www.com</a>]</td>
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<tr>
<td>London, ON N6A 5C</td>
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</table>

16.1 This Agreement and the attached Schedules represent the entire understanding between the parties related to the Transferred Materials and the Project and supersedes any previous understandings, commitments or agreements, whether written or oral. If any provision of this Agreement is wholly or partially unenforceable for any reason, all other provisions will continue in full force and effect.

16.2 This Agreement is governed by and will be construed in accordance with the laws of the Province of Ontario, without regard to conflicts of laws principles.

16.3 The following provisions will survive termination of this Agreement: 5, 9, 10, 11, 12, 14, and 15.

16.4 This Agreement shall not be amended, modified, varied, or supplemented except in writing signed by each of the parties.

16.5 No party shall use, or authorize others to use, the name, symbols, or marks of another party hereto or IN WITNESS WHEREOF, the parties hereto have signed this Agreement.

---

**MCMASTER UNIVERSITY**

Name: Gay Yuyitung, PhD
Title: Executive Director, MILO
Date:

**Dr. Parminder Raina**

Name: Parminder Raina, PhD
Title: Lead Investigator, CLSA
Date:

The Institution, through its authorized representative who has signed below, acknowledges that it is bound by this Agreement.

**INSTITUTION**

Name: Caroline Calmettes
Title: Director, Contracts & Agreements
Date:

**APPROVED USER**

Name: Noha Gomaa, PhD
Title: Assistant Professor
Date:
Schedule A:

Canadian Longitudinal Study on Aging (CLSA)

Data and Biospecimen Access
Policy and Guiding Principles
1. DEFINITIONS

1.1. **Applicant:** An investigator affiliated with a public research organization based in Canada or elsewhere who is applying to access data/biospecimens collected as part of the CLSA.

1.2. **CLSA Bioanalysis and Biorepository Centre (BBC):** the centre that stores the biological samples from CLSA participants and houses a research laboratory dedicated to undertaking detailed standardized biospecimen analysis of specialized biomarkers.

1.3. **CLSA Access Agreement:** An agreement developed by the CLSA and the lead investigator’s institution which contractually binds the parties involved in accessing CLSA data/biospecimens. An executed Access Agreement is necessary to obtain access to data/biospecimens from the CLSA.

1.4. **Lead Institution:** McMaster University, where the National Coordinating Centre (NCC) is located.

1.5. **Canadian Institutes of Health Research (CIHR) Advisory Committee on Ethical, Legal, and Social Issues (ELSI) for the CLSA:** An independent advisory body under the governance of the Canadian Institutes of Health Research set in place specifically to address the various ELSI needs of the CLSA (hereafter “CIHR ELSI Advisory Committee”).

1.6. **CLSA Biomarker, Genetic and Epigenetics Centres:** The centres where specified analyses for biomarkers are carried out on CLSA biospecimens to ensure standardized results.

1.7. **CLSA Statistical Analysis Centre (SAC):** The centre where data verification and preparation is carried out. The SAC also prepares alphanumeric datasets for users.

1.8. **CLSA Scientific Management Team (SMT):** The executive management body within CLSA.

1.9. **Custodian:** As per agreements between McMaster University (Lead Institution) and all CLSA Sites across Canada, McMaster University is deemed the legal custodian of the CLSA data and biospecimens, regardless of where the CLSA data and biospecimens were collected.

1.10. **Data and Biospecimen Access Committee (DSAC):** A committee with the mandate to review data and biospecimen access applications to the CLSA. The DSAC makes recommendations for approval/rejection of access requests to the SMT.

1.11. **Research:** Any systematic inquiry into the dimensions of adult development, health and aging using CLSA data and/or biospecimens.

1.12. **Study Results:** All analyses, including the results of laboratory testing, obtained from the analysis, manipulation, or testing of CLSA data and/or biospecimens.

1.13. **Users:** Applicants who have received the necessary approvals to access CLSA data and/or biospecimens.

2. DATA AND BIOSPECIMEN ACCESS POLICIES AND PRINCIPLES

2.1. **Introduction**

The Canadian Longitudinal Study on Aging (CLSA) is a scientific research program and research platform. Over the course of the conduct of the CLSA, a rich resource of data and biospecimens collected from study participants will be assembled. All participants in the CLSA have provided signed informed consent that includes the stipulation that the data and biospecimens collected from them will be treated according to strict security and confidentiality standards. In addition, CLSA participants are also informed that data and biospecimens collected from them will be made available to researchers under a set of conditions that respect the CLSA consent with particular attention to security and confidentiality of the data and biospecimens. Data and biospecimen access in large-scale longitudinal studies is complex. Governance of access to the CLSA data must balance the interests of the CLSA, the custodian, Users and study participants.
The CLSA has implemented policies and procedures that create a fair and transparent process to access its data and biospecimens. The CLSA has developed principles to guide access to, and the use of, the CLSA data and biospecimens and these are described in this document. These principles, policies, and procedures apply to the access to all CLSA data and biospecimens for research purposes. All researchers, including CLSA investigators that are requesting access to data and/or biospecimens for research are required to follow the CLSA Data and Biospecimen Access Policies and Guiding Principles.

The CLSA includes as part of its governance structure the DSAC; the body responsible for the review of applications for access to, and use of, data and biospecimens, collected as part of the CLSA. The DSAC is composed of voting members selected from the research community (in Canada and overseas) in addition to an ex officio CLSA investigator and an ex officio observer from CIHR. The Committee functions in accordance with the CLSA policies, guidelines, and procedures for data and biospecimen access.

2.2. Guiding Principles

Access to, and use of, CLSA data and biospecimens are governed by the following principles:

- The rights, privacy and consent of participants must be protected and respected at all times (see CLSA Privacy Policy at www.elsa-elev.ca).
- The confidentiality and the security of CLSA data and biospecimens must be safeguarded at all times.
- CLSA data and biospecimens are resources that will be used optimally to support research to benefit all Canadians.
- CLSA data and biospecimens will be made available for use in a timely and responsible manner taking into account the need to assure data validity and biospecimen integrity.
- CLSA biospecimens constitute a finite resource and procedures will be put in place to ensure that this resource is used optimally, according to the long-term research goals of CLSA, and in keeping with the informed consent.
- CLSA data and biospecimens will only be released to researchers once ethics approval for the research project has been obtained from the appropriate Research Ethics Board (REB) and the CLSA Access Agreement between the CLSA Custodian and the Applicant’s institution has been executed. In addition, the biospecimens will only be released once evidence of funding to analyze the biospecimens is received.
- To meet data quality standards set by the CLSA documentation pertaining to biospecimen handling and analysis will be required. This includes standard operating procedures (SOP), lot-to-lot comparisons, quality control information and a temperature record.
- Exclusive access rights to CLSA data and biospecimens will not be granted to any Applicant for any Research.
- All Applicants will be required to follow the Access Procedures.
- Approved Applicants (Users) may be required to return derived variables and/or results to the CLSA within a timeframe specified in the CLSA Access Agreement noted above.
- Data and biospecimen management for access purposes will be cost neutral to the CLSA. The CLSA has a fixed charge for each biospecimen regardless of biospecimen type and a fixed cost for data regardless of number of participants or variables requested. These costs include administration, IT, retrieval, and shipping of consumables; the cost for shipping of biospecimens is additional and will vary depending on shipping location.
- The CLSA SMT team will have access to CLSA data and biospecimens for operational activities required for developing, managing and achieving overall success of the CLSA Platform. These are for example: to conduct methodological analyses for the purposes of enhancing the design of the CLSA; enabling the development of communication materials to promote the CLSA Platform; and, facilitating partnerships in order to support long-term sustainability of the CLSA. The CLSA SMT is the decision
making body for such operational activities and the CLSA will report on these activities to CIHR annually.

2.3. Limits on the Use of CLSA Data and Biospecimens

CLSA data and biospecimens can only be used by investigators affiliated with a public sector research organization\(^1\). Research projects must have received REB approval prior to the release of CLSA data and/or biospecimens.

In circumstances where CLSA links participant data and biospecimens to third party data holdings (e.g. provincial healthcare databases) the release of these data will be managed taking into account the terms and conditions of the third party data holdings, and thus may be subject to certain jurisdictional limitations with respect to the transfer and use of the linked data.

An important goal of the CLSA is to make the data and biospecimens available in a timely fashion for Research after data quality control and biospecimen integrity analyses are completed. If a User wishes to use CLSA data and/or biospecimens already received for a purpose other than the original purpose, then he/she must submit a new application to the DSAC. Any other change to the original application will require an amendment to the application and CLSA Access Agreement (as appropriate). CLSA Users are not permitted to share the data or biospecimens provided to them to others other than individuals identified as Users in the CLSA Access Agreement.

2.4. Access to CLSA Biospecimens

The Canadian Longitudinal Study on Aging (CLSA) collects blood and urine samples from consenting participants and stores the biospecimens in a Biorepository at McMaster University for future use. Biospecimens collected as part of the CLSA are valuable and finite resources. The CLSA SMT has the authority and the duty to responsibly manage biospecimens and to make sure the best possible scientific value is derived from these biospecimens. To achieve this objective, CLSA SMT and the DSAC will ensure that approved applications to use this resource will be of the highest scientific quality that will result in reliable, valid, informative and novel sets of biomarkers to advance the health and well-being of Canadians.

The CLSA is a longitudinal platform and the proposed use of the biospecimens should maximize the strength of this type of platform. The CLSA also requires the Users to return all the derived biomarker variables to the CLSA platform for use by other researchers. The intake of applications to access biospecimens will be once a year. The release of biospecimens to the user will require confirmation of funding to access and analyze the biospecimens. The CLSA’s Biospecimen Access Guidelines can be found on the CLSA website at: [https://www.clsa-cls.ca](https://www.clsa-cls.ca).

2.5. Intellectual Property

The CLSA and its Lead Institution do not claim any ownership of, or exploitation rights to, any intellectual property resulting from the Users’ research conducted with CLSA data/biospecimens.\(^2\) Indeed, given the public nature of the CLSA research platform, it aims to promote a wide and accessible distribution of knowledge developed using this resource and achieves maximum public benefit. Thus, CLSA data and biospecimen Users are strongly encouraged to make their results (including research tools) rapidly and widely available to the scientific community.

Regarding genetic inventions, CLSA Users are strongly encouraged to follow the “Guidelines for the Licensing of Genetic Inventions” developed by the Organization for Economic Co-operation and Development (OECD) when licensing their intellectual property (presently found at: [http://www.oecd.org/dataoecd/39/38/36198812.pdf](http://www.oecd.org/dataoecd/39/38/36198812.pdf)).

\(^1\)Alphanumeric data is available to all public sector investigators nationally and internationally. However, currently there is no provision to transfer biospecimens to applicants outside of Canada.

\(^2\)Note that where the Applicant in question is an investigator from McMaster University, he/she will still be bound by the university’s intellectual property policies. This is independent of the CLSA intellectual property policy.
2.6. Financial Considerations
The CLSA is a publicly funded research project and platform; access fees will be based on a cost recovery model and will be determined by the SMT.

2.7. Access Requests
Data and Biospecimen Access Application processes and procedures can be found on the CLSA website at https://www.clsa-clev.ca.

2.8. Dissemination of Access Requests
To ensure transparency, and to ensure that participants are able to provide informed consent and withdraw if so desired, and to promote public awareness, the CLSA will provide information to study participants, to Applicants/Users and to the public on the general nature of research projects using CLSA data and/or biospecimens. Summary results from completed studies that use CLSA data and/or biospecimens will also be available in lay language. These will be provided by the researchers and will be posted on the CLSA website and in participant newsletters.

2.9. Obligations of Approved CLSA Data and Biospecimen Users

1.1. Research Quality
Users have a responsibility to enhance the value of the CLSA data by conducting high quality ethical research and sharing their findings in a timely manner to support dissemination and uptake. Formal scientific peer and ethical review of research proposals are important aspects of assuring quality and feasibility.

Safeguards will be maintained to ensure the anonymity and confidentiality of participants’ data and biospecimens. Data and/or biospecimens provided to researchers from the CLSA will not contain any information that identifies any particular participant (i.e. they will be “de-identified” and coded). It is the obligation of the Users not to attempt to identify participants, and to use the data provided in a secure location to protect the privacy and confidentiality of the CLSA participants as per the CLSA Access Agreement as well as the CLSA consent form and Tri Council policies.

Return of Derived Variables

Data
As part of the conditions of the CLSA Access Agreement (as noted in Section 2) Users may be required to return to the CLSA derived variables for inclusion in the CLSA database for use by other researchers. In addition Users may be asked to return derived variables if such variables are identified in annual progress reports or manuscripts emanating from use of the CLSA data/biospecimens. In either case, Users will be asked to provide the code/syntax along with explanatory documentation to allow other researchers to understand the derivation and potential use of these derived variables. Users returning derived variables to the CLSA will work closely with the CLSA Statistical Analysis Centre.

1.2. Biospecimens
All data arising from research using CLSA biospecimens will be returned to the CLSA with exclusive use by the researcher who obtained funding for and produced the analyses lasting for a period of one year after which the data will be made available to all researchers.

2.10. Return of participants personal results from analyses conducted by Users
As a general policy, the CLSA will not return to participants their personal results from analyses conducted by Users. Nevertheless, given the duration of CLSA and the impossibility of foreseeing the nature of research projects that will be conducted using the CLSA data and biospecimens, Users shall be aware of the possibility
that the CLSA may return validated results back to CLSA participants where such information is determined to be critical for the care of the participant. The decision regarding this return, whether and what to return will be taken by the SMT in consultation with the CIHR ELSI Advisory Committee and the relevant research ethics boards. Any situation in which personal results of analyses are returned to CLSA participants will be managed by the CLSA.

2.11. Public Disclosure and Proprietary Interests

The need to protect proprietary interests (e.g. patents) or pre-publication results may result in corresponding constraints on public disclosure of research results. In such situations, and where the time period during which results must be returned to CLSA is not sufficient, the User may request an extension.

2.12. Publications arising from Data and Biospecimen Access

Copies of all proposed publications using CLSA data and/or biospecimens must be submitted to the National Coordinating Centre at McMaster University for review by the CLSA Publication Review Committee at least 15 working days prior to submission. This review will be limited to ensuring that participants cannot be identified in such publications, appropriate acknowledgement has been given (see below), and that results are presented in accordance with the objectives stated in the CLSA Access Agreement. Users should review the CLSA publication policy prior to preparing manuscripts (The CLSA publication policy can be found on the CLSA Website: https://www.clsa-elcv.ca).

2.13. CLSA Acknowledgement in Publications

Full acknowledgement of the source of CLSA data and biospecimens must be included in any publications that arise from access to, and use of, the CLSA data and biospecimens. This acknowledgement must reference the sources of funding for the CLSA and its data platform and the core CLSA team responsible for the creation and implementation of the platform. Additional acknowledgements may apply if linked data have been used. All publications must include at a minimum the following acknowledgment for sources of funding:

“This research was made possible using the data/biospecimens collected by the Canadian Longitudinal Study on Aging (CLSA) [Data set version #]. Funding for the Canadian Longitudinal Study on Aging (CLSA) is provided by the Government of Canada through the Canadian Institutes of Health Research (CIHR) under grant reference: LSA 94473 and the Canada Foundation for Innovation”. The specific wording of the acknowledgements will be operationalized in the CLSA Access Agreement.
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Schedule B – Approved CLSA Data Request Application
## CLSA Data and Biospecimen Request Application

**Demande d’accès aux données et aux échantillons de l’ÉLCV**

### Application Part 1 of 3: General Project Information /
**Partie 1 de 3 : Renseignements généraux**

#### A1. Applicant Information / **Renseignements sur le demandeur**

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**Complete this section if this is a Graduate student application /
**Remplir cette section si la demande est faite par un étudiant des cycles supérieurs**

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A2. Project Team / Équipe de projet

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<tr>
<td>Kathryn Nicholson</td>
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<td>Kelly Anderson</td>
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CLSA DataBiospecimen App  v2_2020Aug28  Page 2 of 10
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|------------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
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|            |                                                                                                                             | No / Non                                                                              |
|            |                                                                                                                             | Yes / Oui                                                                             |
|            |                                                                                                                             | No / Non                                                                              |
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|            |                                                                                                                             | No / Non                                                                              |
A3. Project Timeline / Échéancier du projet
Anticipated start date / Date prévue de début : 2022-10-01
Proposed project duration / Durée proposée du projet : 2 years

A4. Project Description / Description du projet

Project Title / Titre du projet :
Psychosocial stress and epigenetic aging as common pathways to oral disease and multimorbidity

Lay Summary / Résumé non scientifique
Please provide a lay language summary of your project (maximum 150 words) suitable for posting on the CLSA website if your application is approved. Please ensure that the lay summary provides a stand-alone, informative description of your project.

Veuillez fournir un résumé non scientifique de votre projet (150 mots maximum) pouvant être publié sur le site Web de l’ELCV si votre demande est approuvée. Assurez-vous de fournir un résumé détaillé et complet de votre projet.

Previous studies show that good oral health is key for general health, suggesting that oral diseases can co-occur with other major health problems, such as diabetes, heart disease or Alzheimer’s disease. Stressful life experiences have been suggested to contribute to poor health through triggering the stress response resulting in alteration of biological processes including accelerating the aging process, in which one’s apparent age is older than their actual chronological age. Whether stressful experiences and biological aging contribute to oral diseases and other general health conditions in older Canadians is unknown. Therefore, our proposed study aims to investigate whether general health conditions and oral diseases can co-occur in the same individuals, and whether stressful experiences and biological aging can contribute to the co-occurrence of these conditions.

Word Count / Nombre de mots 125

Keywords / Mots clés
Please provide 3-5 keywords describing your project. / Veuillez fournir 3 à 5 mots clés décrivant votre projet.

multimorbidity, oral health, clustering, stress, psychosocial factors, epigenetics
Detailed description / Description détaillée

Please provide a description of the proposed project.

Background

Multimorbidity, defined as the coexistence of two or more chronic diseases or medical conditions in an individual, has been identified as a major public health concern [1-3]. With an increasing proportion of the population aged 65 and older and increased overall survival, a growing number of adults have been presenting with multiple coexisting chronic conditions [1-3]. Multimorbidity is known to be strongly associated with several sociodemographic factors such as increasing age and poor socioeconomic conditions [2]. For example, studies have shown that lower levels of income and education increase the risk for multimorbidity, resulting in health inequalities [2]. Along with having a significant negative impact on the quality of life of older individuals, multimorbidity is known to increase the risk of disability and mortality among older adults, ultimately increasing healthcare utilization and costs and increasing the economic burden on the healthcare system [1-3].

In addition to the rising prevalence of multimorbidity, oral diseases such as dental caries, periodontal diseases, and tooth loss are also prevalent in older individuals [1,4-6] and are known for their association with many other systemic diseases such as cardiovascular disease and diabetes [4-6]. Recent studies using the Canadian Longitudinal Study on Aging have shown that poor oral health in older Canadian adults is associated with frailty [7]. More recently, studies have assessed clustering patterns of oral and systemic health conditions, suggesting similar patterns of clustering between periodontal disease and multimorbidity, as well as oral conditions and coronary heart disease [8].

An inflammatory mechanism has been consistently postulated to link oral and non-oral health conditions. Particularly, the process of inflammaging — the chronic low-grade state of inflammation that develops with advanced age — may be a common biological pathway to both oral diseases and related morbidities [9]. However, whether inflammaging plays a role in the onset of oral diseases and multimorbidity in the older population and whether there are common risk factors that can contribute to inflammaging remains underexplored.

The biopsychosocial pathway to aging postulated as common risk factors to oral diseases and related morbidity conditions [10,11]. These have been shown to become biologically embedded through triggering the biological stress responses and activating the hypothalamic-pituitary adrenal axis which in turn can result in a cascade of inflammatory responses that contribute to increasing the risk of several health conditions including cardiovascular disease, diabetes, obesity, periodontal diseases, and tooth loss [10,11]. Understanding the common biopsychosocial pathways to oral and related morbidities in the older population can help us inform the development of common prevention and intervention strategies.

One of the mechanisms postulated to stem from the impact of psychosocial stress over time is the acceleration of biological aging, which constitutes the difference between an individual’s chronological age and apparent age [12,13]. Traditionally, telomere lengths were used to measure biological aging [14]. For example, previous studies have linked poor oral and non-oral health conditions to shortened telomeres [15]. More recently developed DNA methylation-based epigenetic clocks appear to provide a more accurate measure of biological age [16,17]. Epigenetic clocks are built from a set of DNA methylation markers that correlate with chronologic age and can be used to predict obesity, cancer, neurological disorders, and all-cause mortality [10,17]. Furthermore, epigenetic clocks derived from cells of the immune system have been postulated as candidate biomarkers for the inflammaging process.
Study objectives

The main objective of this study is to identify clusters that share a similar pattern based on their oral disease and multimorbidity profiles, while investigating whether biopsychosocial factors can contribute to these clustering patterns.

Specifically, we first aim to identify clusters among older Canadians that share a similar pattern based on oral disease and multimorbidity. We will describe the identified clusters based on sociodemographic variables. We will further investigate the extent to which the identified clusters are associated with psychosocial factors and biological aging factors, as measured by the epigenetic clock. Our specific aims are:

1. To identify and characterize clusters of oral disease and multimorbidity in a community sample of middle-aged and elderly Canadians;
2. To investigate the extent to which these clusters are associated with psychosocial stress factors, adjusted for confounders;
3. To investigate the extent to which these clusters are associated with epigenetic aging, adjusted for confounders.
Methods

Study Sample
We will use data from the CLSA comprehensive component (baseline and follow-up), which includes the 30,000 participants submitted to physical and complementary exams at 11 data collection sites. For the first and second objectives of this study, we will use data collected from the full comprehensive cohort. For the third objective, we will use data from the subsample of participants (n=1750) for whom epigenetic data is available.

Variables
Multimorbidity: will be assessed using the chronic condition (CCT/CCC) questionnaire in the comprehensive cohort (baseline and follow-up data) and operationalized using a primary care definition and public health definition, as well as a cut-point of two or more chronic conditions. Chronic conditions in the primary care definition of multimorbidity include: anxiety or depression, asthma or chronic obstructive pulmonary disease, cancer, cardiovascular disease, chronic hepatitis, chronic musculoskeletal problem, chronic urinary problem, colon problem, dementia or Alzheimer’s disease, diabetes, heart failure, hypertension, kidney disease or failure, obesity, osteoarthritis or rheumatoid arthritis, osteoporosis, stomach problems, stroke or transient ischemic attack, and thyroid disorder. For the primary care definition of multimorbidity, hypertension will be determined using self-report, medication, or blood pressure measurements, and obesity will be determined using body mass index (BMI). Chronic conditions in the public health definition of multimorbidity include: Alzheimer’s disease and related dementias, anxiety or mood disorders, arthritis, asthma, cancer, chronic obstructive pulmonary disease, diabetes, heart disease, and stroke. All these variables will be grouped into a derived binary variable coded as absent multimorbidity (=0) or present multimorbidity (=1).

Oral disease: This will be operationalized based on the following oral health variables collected for the comprehensive cohort: (1) self-reported oral health status (1 question, 5-point Likert scale); (2) presence of natural teeth (1 yes/no question) and (3) eventual use of dentures (1 yes/no question); (4) comfort during eating (1 question, 5-point Likert scale); (5) avoidance of specific foods (1 question, 5 point Likert scale); (6) occurrence of specific symptoms (20 yes/no questions, including xerostomia, toothache, gingival bleeding and halitosis); and (7) oral hygiene (1 question, daily frequency of oral hygiene). All these variables will be grouped into a derived binary variable coded as absent oral disease (=0) or present oral disease (=1).

Psychosocial stress: will be assessed and dichotomized using the following questionnaires and variables from the comprehensive cohort (baseline and follow-up): psychological distress (K10), social inequality (SEQ), childhood maltreatment and health across the lifespan (CEX), loneliness scale (LON), satisfaction with life scale (SLS), social networks (SN), social support (SSA), and social participation (SPA).

The epigenetic age variables: these will be assessed and operationalized using epigenetic age-related measures in the comprehensive CLSA cohort including age acceleration difference (dAA) (calculated as the difference between chronological age and epigenetic age), age acceleration residual (dAA), extrinsic epigenetic age acceleration (EEAA), and extrinsic epigenetic age acceleration (IEAA).

Other variables: Analyses will consider data on diverse variables that may act as confounders in the association between epigenetic aging and clusters of oral disease and multimorbidity. These will include age, sex, socioeconomic status (SES) (as defined by income (INC), wealth (WEA), education (ED), and home ownership (OWN)), and behavioural factors such as smoking status (SMK) and alcohol use (ALC).
Data analysis

Preliminarily, we will check the distribution of each variable for outliers. Descriptive statistics will be used to determine the prevalence of oral diseases and multimorbidity in the sample across three age groups (45-54y; 55-64y; 65+*) and stratified by sex. Results will be expressed as means and standard deviations for continuous variables (the four epigenetic age variables) and proportions for categorical variables (oral disease, multimorbidity, etc.). Prevalence estimates and corresponding 95% confidence intervals of oral disease will be determined using the total number of participants with at least one oral health condition (as described above) over the denominator consisting of all adult patients in the sample population, stratified by sex. Prevalence estimates and corresponding 95% confidence intervals of multimorbidity will be determined using the total number of participants with at least two chronic conditions over the denominator consisting of all adult patients in the sample population, stratified by sex.

For the first objective "to identify clusters of oral diseases and multimorbidity", we will use latent cluster analysis. Four classes will be defined based on the binary contracts (absent/present) categories of each of oral disease and multimorbidity. These are derived from the oral health questions on oral disease, and the presence of two or more chronic conditions for multimorbidity. Latent class analysis (LCA) uses maximum likelihood estimation to categorize individuals into each latent class, i.e., to each cluster of participants, thereby classifying individuals into unobserved classes according to their responses to a number of observed and measured categorical variables. For each participant the probability of being a member of each class is reported. An advantage of latent class analysis is that it is a model-based approach, making it more flexible than other clustering analysis approaches, and where the choice of a cluster criterion is less arbitrary. In this study, we will use maximum probability to assign each participant to one class of the latent variables. To identify the model with the best fit, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) will be used.

For the second objective "to investigate the extent to which these clusters are associated with psychosocial stress factors", multinominal logistic regression models will be applied to assess the extent of the association between cluster membership and each of the binary psychosocial stress variables (psychological distress, social inequality, childhood maltreatment and health across the lifespan, loneliness scale, satisfaction with life, social networks, social support, and social participation), adjusted for age, sex, SES, smoking, and alcohol consumption.

For the third objective, "to investigate the extent to which these clusters are associated with epigenetic aging", the subsample for which epigenetic data is available (n=1750), will be used to assess the clustering of oral disease and multimorbidity, and then multinominal logistic regression models will be applied to assess the extent of the association between cluster membership and each of the epigenetic variables (dAA, rAA, EEAA and IEAA), adjusted for confounders.

We consider that there may be a chance that the clusters may not be clinically interpretable. In this case, we will model the joint probability of oral disease and multimorbidity through multivariate logistic regression models, adjusted for potential confounders. We will then use blockwise method to assess the contribution of the psychosocial and epigenetic variables to these models, and whether they explain any association between oral diseases and multimorbidity.
A5. Scientific Review / Évaluation scientifique du projet

Peer Reviewed Funding / Financement évalué par les pairs

☑ Yes / Oui  ☒ No / Non  ☐ Requested / Demandé

Please provide name of funding agency. /  Veuillez fournir le nom de l’organisme de financement.

A6. Ethics Approval / Approbation éthique

Has this project received ethics approval? / Ce projet a-t-il reçu une approbation éthique?

☑ Yes / Oui

☐ No / Non

☐ Exempt / Exemption
CLSA Application: Data Checklist
Application Part 2

Demande de l’ÉLCV : Sélection des données
Partie 2 de la demande

Primary Applicant Information / Informations sur le demandeur principal

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☐ Tracking Cohort (Telephone Interview) / Cohorte de surveillance (Entrevue téléphonique) (TRM)

☑ Comprehensive Cohort (In-home Interview & DCS visit) / Cohorte globale (Entrevue à domicile et au site) (COM)

Application number of the related CLSA approved project / Le numéro de demande du projet connexe approuvé par l’ÉLCV: N/A

CORE CLSA DATA / DONNÉES DE BASE DE L’ÉLCV

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| 1er suivi | Follow-up 2 /  
| 2e suivi |
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| (Hematology and  
| Chemistry) /  
| Biomarqueurs sanguins  
| (hématologie et chimie) | | | |
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| Epigenetics /  
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Comments / Commentaires
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Comments / Commentaires

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<th>Follow-up 2 / <em>2e suivi</em></th>
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<td>CSD / <em>SDR</em></td>
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Justification / *Justification*
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<th>Data module / Module de données</th>
<th>CLSA / ÉLCV</th>
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<tr>
<td>COVID-19 Seroprevalence Study Data / Données du l’étude sur la séroprévalence de la COVID-19 (N= 19,334)</td>
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Comments / Commentaires
Schedule C – Specific security measures

Definitions

Information:
- Any CLSA data and samples obtained from the CLSA pursuant to this Agreement, with or without name or other identifying information, and any aggregation of responses that could directly or indirectly identify an individual person, business, or organization.

Authorized Person:
- Person who is the PI(s) on the approved project.

Identified Person:
- Authorized Person and all others listed as Co-investigators/Collaborators or staff on the approved project.

Transportable media:
- All types of transportable storage media on which data can be saved, including laptops, CD-ROMs, flash memory sticks, and removable hard disk.

Visitor:
- Person, other than an Authorized Person, who has been invited into the secure area by an Authorized Person, as permitted by the Institution’s access policies.

Security Requirements

The Institution must ensure that adequate protection is in place to provide for the security of the Information. The security requirements described below are the minimum requirements that must be met by the Institution.

Physical Access

1. The Information must be accessed only from within a secure location that allows access only to Authorized and Identified Persons. The secure location can be within a series of buildings, one entire building, an entire floor within a building, or a single room. Once the perimeter of the secure location is defined, the procedures apply to all areas within the perimeter. Where a series of buildings are involved, a secure perimeter must be defined for each building.

2. Access to the Information is limited to Authorized and Identified Persons. The manager responsible for ensuring that the Institution’s requirements are met must maintain an auditable trail, listing the Identified Persons, the specific Information to be accessed, the period for which this access is granted, the purpose for the access, and where applicable, that the Person meets any special requirements for access.

3. Visitors may have access to the secure area. However, under no circumstances may visitors be provided access to the Information.

IT Storage and Transmission

4. All computers with access to the Information must employ logical access controls (passwords) at the device and network level.

5. Where the Information is held on laptops, CD-ROMs, flash memory sticks or other transportable media of any type, passwords and full encryption must be used. This applies equally to backups of the Information stored on transportable media.

6. The Information cannot be electronically transmitted, except as described in points 7 and 8. This includes the transmittal of the Information by facsimile or by e-mail.
7. Servers storing and transmitting unencrypted data, where used, must be located in a secure, controlled-access area, preferably in the same area where the Information is accessed. If located in a separate area, controls must be in place to ensure that only Identified Persons can access the server. Unless the Information is encrypted continuously while outside the secure area, conduit must be used for all cabling and all cross-connect areas must be physically secured.

8. Network firewalls and access rules must be in place to prevent access to the Information, other than to Identified Persons. Information may be stored on and transmitted over networks not meeting these requirements, provided that it is encrypted, except when in use by an Identified Person. Alternatively, the Information may be stored on a stand-alone computer with no external connections, or on a closed network. When a network transmits information that leaves a secure area (for example, when a series of buildings house employees within a single organization), the data must be encrypted whenever it is outside the secure area.

Physical Storage

9. When not in use, transportable media containing the Information must be stored in secure containers. This applies equally to backups of the Information.

10. The Information shall not be removed from the secure area (as described in point 1, above) in any format (e.g., laptops, printouts, flash memory sticks, transportable media of any type, etc.), except as described in points 7 and 8 above.

11. When not in use, printed documents containing the Information must always be stored in secure containers.

Information Copying and Retention & Record Management

12. Copies and extracts of the Information may only be made for the purposes of carrying out work as covered by this Agreement. When no longer needed, any such copies or extracts must be destroyed in a secure manner (as per points 13 and 14 below).

13. Paper documents containing the Information must be destroyed (shredded) in a secure manner before disposal. Destruction must occur within the secure area.

14. All electronic storage media used in the processing of the Information, including all back-up and transportable media must be sanitized or destroyed on completion of their use. Destruction must occur within the secure area.

15. These security requirements must be communicated regularly to all Identified Persons and be available for reference, as required.
Schedule D - Return of Derived Variables

Canadian Longitudinal Study on Aging (CLSA)
Policy on the Return of Derived Variables

In accordance with the Canadian Longitudinal Study on Aging’s Data and Sample Access Policy and Guiding Principles and your signed CLSA Access Agreement, you may be asked to return to the CLSA Derived Variables that you created as part of your research.

What are Derived Variables?
Derived Variables (DV) include new data-fields (apart from simple recoding) constructed by you whilst undertaking your research project using CLSA raw alphanumeric data, biomarker data, or a combination of both. A separate policy governs the return of biomarker data obtained from biospecimens to the CLSA.

Why might I be asked to return Derived Variables to the CLSA?
The objectives in asking for the DVs and documentation are that, in keeping with the CLSA as a research platform, CLSA can:

(i) expand and enhance the utility of the CLSA platform;
(ii) make your DVs available for use by other approved users;
(iii) make your methods for constructing DVs available to other researchers so that analyses can be replicated.

How do I report on Derived Variables?
In accordance with the CLSA’s Data and Sample Access Policy and Guiding Principles and your signed CLSA Access Agreement, you will be asked to submit a Final Report at the end of your project. In this Report, you will be asked to describe any DVs you have created.

When do I return Derived Variables?
Once the CLSA has reviewed the Final Report and determined that the DVs would be of utility to the CLSA platform, the Statistical Analysis Centre (SAC) will send you a document with guidelines on the Return of Derived Variables to the CLSA by Approved Users, including details on what needs to be returned and how to transfer files to the CLSA. Researchers will be asked to return DVs within 6 months of the date of the first publication using the DV.

How will my Derived Variables be used by CLSA?
The DVs will be made available with acknowledgement of the provenance. The CLSA will not audit your DVs and is not responsible for its accuracy or validity. The CLSA will review the documentation and algorithms you provide to ensure that sufficient explanatory documentation has been provided. Derived variable fields and accompanying documentation may be made available for use by other approved users, and may be included in our Data Preview Portal (http://clsa-elcv.ca/).

Researchers who have any questions concerning the process or content for the return of DVs should contact the CLSA Statistical Analysis Centre via access@clsa-elcv.ca.
Schedule E – Fees

Fees Waived for Abby Hensel MSc Trainee
Schedule F: Project Team

All Co-Applicants and Other Personnel listed below are indicated in the application Schedule B, as well as any changes to co-applicants/other personnel required since the initial submission of Schedule B and requiring direct access to the CLSA Data. Each of these Co-Applicants must sign Schedule F to agree to comply with the conditions outlined in Articles 2.1 and 2.3 (excerpts below) of this CLSA Access Agreement also located at (https://elsa-elev.ca/doc/1042). All others should be listed but will not require a signature if they will not have direct access to the data.

Sample and Data Security.

Security measures specified in Schedule C attached hereto will apply to all Transferred Materials. The Approved User and institution undertakes to respect these security measures during the Project and afterwards, during storage of Transferred Materials where necessary.

Transferred Materials, including any copies thereof, may only be used for the Project described in Schedule B and may not be disclosed, transmitted or shipped to anyone except employees working directly with the Approved User or co-investigators including co-applicants or other personnel from other not-for-profit institution(s), indicated in the Project who will require direct access to the CLSA Data and who agree to be bound by the terms of this Agreement or to persons expressly designated in writing by McMaster. The Approved User shall retain control of the Transferred Material at all times. It is the responsibility of the Approved User’s Institution to inform the staff and co-investigators, including co-applicants and other personnel at other third-party institution(s) entering into contact with the Transferred Materials of the obligations contained in the Data and Biospecimen Access Policy and Guiding Principles and this Agreement. As such, co-applicants and other personnel at other third-party institution(s) must submit a signed Schedule F attached hereto. The transfer of any CLSA Data to any for-profit entities is strictly prohibited. Transfer of any CLSA biospecimens outside Canada is strictly prohibited. Data access will only be provided to institutional email addresses.

Co-Applicants and Other Personnel

Please list all co-applicants including students and any other personnel who will be involved in the project (eg: advisor, statistician, research assistant, etc.).

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation &amp; institutional email address</th>
<th>Academic Position and Role on Project</th>
<th>Signature</th>
</tr>
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<tbody>
<tr>
<td>Abby Hensel</td>
<td>Masters Student, Epidemiology Western University</td>
<td>Trainee</td>
<td>[Hidden]</td>
</tr>
<tr>
<td>Kathryn Nicholson</td>
<td>Adjunct Assistant Professor Western University</td>
<td>Co-applicant</td>
<td>[Hidden]</td>
</tr>
<tr>
<td>Kelly Anderson</td>
<td>Associate Professor and Graduate Program Chair, Epidemiology Western University</td>
<td>Co-supervisor</td>
<td>[Hidden]</td>
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<tr>
<td>Name</td>
<td>Affiliation &amp; institutional email address</td>
<td>Academic Position and Role on Project</td>
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</tr>
<tr>
<td>Steve Lee</td>
<td>Research Assistant, Epidemiology Western University</td>
<td>Collaborator</td>
<td></td>
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</table>
Appendix 3D: Exploratory analyses between psychological distress, mood disorders, and multimorbidity.

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<tr>
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<th>No Multimorbidity</th>
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<tr>
<td></td>
<td>No Mood Disorder</td>
<td>Mood Disorder</td>
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<tr>
<td><strong>Low K10 Score (10-29)</strong></td>
<td>13,812</td>
<td>1,960</td>
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<tr>
<td><strong>High K10 Score (30-50)</strong></td>
<td>345</td>
<td>354</td>
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<tr>
<td><strong>Total</strong></td>
<td>14,157</td>
<td>2,314</td>
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To assess the level of association between K10 scores, mood disorders, and multimorbidity, correlations were conducted, first between K10 scores and multimorbidity and then between K10 scores and mood disorder frequency. The correlation between K10 scores and multimorbidity was 0.18, while the correlation between K10 scores and mood disorder frequency was 0.33.

In summary, among those with multimorbidity (n=8,940), 55% did not have an anxiety/mood disorder while 45% did have an anxiety/mood disorder that contributed to their multimorbidity. Conversely, about 64% of people with an anxiety/mood disorder also reported having multimorbidity, while the remaining 36% with an anxiety/mood disorder did not have multimorbidity.

When stratified by multimorbidity status, among those had a mood disorder and multimorbidity, 19% reported having high psychological distress compared to 15% among those had a mood disorder and no multimorbidity.
Curriculum Vitae

Name: Abby Hensel

Post-secondary Education and Degrees:

University of Windsor
Windsor, Ontario, Canada
2016-2020 B.Sc.

University of Windsor
Windsor, Ontario, Canada
2020-2021 M.Sc.

The University of Western Ontario
London, Ontario, Canada
2021-2023 M.Sc.

Honours and Awards:
Western Graduate Research Scholarship
2021

CIHR Canadian Graduate Scholarship
Master’s Program
2022

Related Work Experience
Graduate Teaching Assistant
University of Windsor
2020-2021

Content Development Specialist – Externship
Statistics Canada
2022

Graduate Fellowship
The University of Western Ontario
2023

Publications:

