Longitudinal associations between periodontitis and glycated haemoglobin

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Abstract

Context: The plausibility of a bidirectional link between periodontitis and type 2 diabetes has recently been acknowledged. However, little is known of the relationship between the two conditions at an earlier stage in the dysglycaemia continuum.

Objective: To describe the natural histories of periodontitis and dysglycaemia over 12 years through the third and fourth decades of life, to identify predictors of both conditions, and to explore the bidirectional relationship between them.

Methods: This study used data from the Dunedin Multidisciplinary Health and Development Study (DMHDS), a long-running prospective study of a birth cohort, and the utilisation of advanced statistical techniques to analyse these data. Both periodontal and glycated haemoglobin (HbA1c) data were gathered during the age-26, age-32 and age-38 assessments. Group-based trajectory analysis (GBTM) was used to assign Study members to trajectories of (a) periodontal experience (using mean % of sites with 4+mm attachment loss) and (b) dysglycaemia experience (using mean HbA1c). Generalisations of the model allowed the statistical linking of baseline characteristics to group membership probability, and identified effect modifiers associated with deviations from the group trajectory.

Results: Prevalence, extent and severity of periodontitis, and mean HbA1c, all increased with age, as did the prevalence of prediabetes, type 2 diabetes and dysglycaemia. Both periodontitis and dysglycaemia were highly prevalent by age 38, and health status at 26 predicted health status at 38. Four periodontal trajectory groups were identified: “Very low” 54.0%, “Low” 31.3%, “Medium” 11.3%, and “High” 3.5% (with mean % of sites with 4+mm attachment loss at age 38 of 0.0%, 2.9%, 19.6% and 64.4% respectively). Periodontal status, male sex, smoking, marijuana use, low SES, high plaque score and episodic use of dental services at age 26 were found to be predictors of poorer periodontal status 12 years later. Three HbA1c trajectory groups were identified: “Low” 11.0%; “Medium” 54.0%; and “High” 35.0% (with mean HbA1c at age 38 of 29.9 mmol/mol, 34.2 mmol/mol and 38.5 mmol/mol respectively). HbA1c levels, male sex, smoking, high waist circumference and high waist-height ratio at age 26 were predictors of dysglycaemia 12 years later. The influence of dysglycaemia at age 38 on the extent of periodontitis was found to be minimal and inconsistent, and periodontitis was found to have no influence on HbA1c at any age.

Conclusions: Trajectories of both periodontitis and HbA1c begin relatively early in adulthood with a greater risk of poor outcomes being established in the middle of the third decade of life. Periodontal and glycaemic health status at 38 were predicted by periodontal and glycaemic health status respectively at 26. Both conditions were highly prevalent by age 38. No relationship was found between periodontitis and dysglycaemia at this stage in the life course. The findings reinforce the importance of smoking and central adiposity as risk factors for poor health outcomes; they establish that health status at 26 has an influence 12 years later; and recommend that planning for the future burden of disease, early cardiometabolic screening, smoking reduction policies, and measures to tackle the obesogenic environment should be prioritised.

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“The good life is one inspired by love and guided by knowledge” (Bertrand Russell, 1925)

Abbreviations used in this thesis

ACR	Albumin/creatinine ratio
ADA	American Diabetes Association
AGE	Advanced glycation end product
AHA/NHLB	American Heart Association/National Heart, Lung, and Blood Institute
AIC	Akaike information criterion
AL	Attachment loss
ANCOVA	Analysis of covariance
AvePP	Average posterior probability
BIC	Bayesian information criterion
BMI	Body Mass Index
BOP	Bleeding on probing
CI	Confidence Intervals
CPITN or CPI	Community periodontal index of treatment needs
CVD	Cardiovascular Disease
DMHDS	Dunedin Multidisciplinary Health & Development Study
DPTT	Diabetes and Periodontal Therapy Trial
ECG	Electrocardiogram
ESRD	End-stage renal disease
FPG	Fasting plasma glucose test
GBTM	Group based trajectory modeling
GCF	Gingival crevicular fluid
GFR	Glomerular filtration rate
GR	Gingival recession
GST	Goods and Services Tax
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model of assessment – insulin resistance
HPLC	High performance liquid chromatography
hs-CRP	High-sensitivity C-reactive protein
IFCC	International Federation of Clinical Chemistry
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL-1β	Interleukin 1 beta
Il-6	Interleukin-6
IL-8	Interleukin-8

LDL	Low-density lipoprotein
LMM	Linear mixed effects models
MAR	Missing at random
MeS	Metabolic syndrome
MET	Metabolic Equivalent Hours
ML	Maximum likelihood estimation
MMP	Matrix metalloproteinases
NCEP, ATP III	National Cholesterol Education Program Adult Treatment Panel III
NGSP	National Glycohemoglobin Standardization Program
NGT	Normal glucose tolerance
NHANES	National Health and Nutrition Examination Survey
NIDR	National Institute of Dental Research
NZSEI	New Zealand Socio-Economic Index
NZSSD	New Zealand Society for the Study of Diabetes
OGTT	Oral glucose tolerance test
OR	Odds Ratio
PD	Pocket depth
PGE2	Prostaglandin E2
PISA	Periodontal inflamed surface area
PURE	Prospective Urban Rural Epidemiology study
RCT	Randomised Controlled Trial
SD	Standard Deviation
SES	Socioeconomic status
SHIP	Study of Health in Pomerania
SI	Sisteme Internationale
SSBs	Sugar sweetened beverages
TNF-α	tumour necrosis factor-alpha
WC	Waist circumference
WHO	World Health Organisation
ZDF	Zucker fatty rat with diabetes
ZFR	Zucker fatty rat
ZIP	Zero-inflated Poisson

Contents

1 Introduction and literature review

1.1 Introduction

Reports of the association between periodontal and systemic health date back to the late 19th century (Miller, 1891; Williams, 1928), and the evidence linking the two has accumulated since then, particularly over the past two decades. Associations have been suggested between periodontal disease and a range of disorders including diabetes mellitus (and its complications), cardiovascular disease (CVD), pre-term birth, low birth-weight, respiratory disorders and rheumatoid arthritis (Cullinan et al., 2009; D'Aiuto et al., 2005; Kuo et al., 2008; Linden et al., 2013). However, the evidence is particularly strong for periodontal-diabetes mellitus and periodontal-cardiovascular disease associations (Kuo et al., 2008).

Diabetes mellitus is a clinically and genetically heterogeneous group of metabolic diseases of multiple aetiology characterized by chronic hyperglycaemia (an abnormal elevation in blood glucose levels) with disturbances of carbohydrate, fat and protein metabolism resulting from defective insulin secretion whereby not enough insulin is produced, insulin resistance whereby cells do not respond to the insulin that is produced, or both (World Health Organization, 1999). Reduced insulin levels and/or insulin resistance prevent the conversion of glucose into glycogen, with resultant hyperglycaemia. In many cases, prediabetes (dysglycaemia or abnormal glucose metabolism) may be an undetected feature for some time before diabetes becomes evident.

1.1.1 Diabetes prevalence and burden of disease

The World Health Organisation estimates 346 million people (approximately 5%) worldwide had diabetes in 2011 (World Health Organization, 2011c). In the United States, 25.8 million (8.3%) of the total population had diabetes in 2010 (Centers for Disease Control and Prevention, 2011). This figure included seven million with undiagnosed diabetes. Adults accounted for the vast majority of cases with 25.6 million (11.5%) of the population age 20 and over with diabetes. About 1.9 million people age 20 years or older were newly diagnosed with diabetes in 2010 (Centers for Disease Control and Prevention, 2011). Some 68,905 people died of diabetes-related complications in the US in 2010 (Murphy et al.,

2012). In New Zealand, it is estimated that the number of people diagnosed with diabetes exceeded 200,000 (4.6% of total population) people in 2010, with approximately another 100,000 people with undiagnosed diabetes (Ministry of Health, 2010b).

The prevalence of prediabetes is not as clear as it is a largely asymptomatic condition that does not present early, and may go undetected for years. In any case, in the years 2005−2008, it was estimated some 35% of U.S. adults aged 20 years or older had prediabetes, and half of those age 65 years or older had prediabetes (Centers for Disease Control and Prevention, 2011). If this percentage is applied to the entire U.S. population in 2010, it yields an estimated 79.0 million Americans aged 20 years or older with prediabetes (Centers for Disease Control and Prevention, 2011). If this is added to the 25.6 million age 20 years or older with diabetes, the total number of adults with dysglycaemia is about 104.6 million (about a third of the total population, or almost half the adult population). The situation is no better in New Zealand; a recent study found the prevalence of prediabetes to be 25.5% for the total NZ population over the age of 15 (Coppell et al., 2013). Of particular concern is the increasing number of adolescents with prediabetes (Cali and Caprio, 2008). Studies examining trends among U.S. adolescents found the prevalence of adolescents with prediabetes or diabetes (mostly prediabetes) to have increased markedly from 9.0% to 23.0% between 1999 and 2008 (May et al., 2012); another study found the prevalence of prediabetes to be 16.1% in 2006 in this age group (Li et al., 2009).

Treatment of type 2 diabetes consists of management of hyperglycaemia and prevention of secondary conditions. These include microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) complications, and result in organ and tissue damage, increased morbidity and mortality (Stratton et al., 2000). Research suggests that individuals with diabetes with sustained hyperglycaemia suffer more severe diabetic complications than those with better glycaemic control (Daneman, 2006; Stratton et al., 2000); and those with diabetes who benefit from early intensive treatment of hyperglycaemia will experience a reduced risk of complications in the long-term (Callaghan et al., 2012; Genuth, 2006). Nor are complications exclusively predicted by the presence or absence of diabetes as such with prediabetes being found to be a risk factor for endothelial dysfunction[1], increased arterial

[1] Endothelial dysfunction is an early sign of atherosclerosis (Landmesser and Drexler, 2005).

stiffness[2], and future cardiovascular events (DeFronzo and Abdul-Ghani, 2011; Shin et al., 2011; Su et al., 2008).

The morbidity and mortality associated with diabetes is substantial. Diabetes mellitus is the seventh leading cause of death in the United States in 2010 (Murphy et al., 2012). Globally diabetes is the fifth leading cause of death (Roglic et al., 2005). However, diabetes is likely to be underestimated as a cause of death as individuals with type 2 diabetes do not necessarily have the disease entered on their death certificate (Cheng et al., 2008; Will et al., 2001).

The burden of diabetes and its complications, and the rate of death attributable to diabetes is increasing globally, mainly in developing countries (Dalal et al., 2011; Hossain et al., 2007; Misra and Khurana, 2008; Ueshima et al., 2008). The prevalence of diabetes is predicted to be 366 million worldwide by 2030 (Wild et al., 2004); this may well prove to be an underestimate. The International Diabetes Federation predicts the prevalence to be 522 million by 2030 (The International Diabetes Federation's Diabetes Atlas.). The present economic cost of diabetes, and its secondary conditions, on individuals, communities and health care systems is already substantial (Centers for Disease Control and Prevention, 2011). This cost is projected to rise significantly in the future, with consequential suffering, reduced productivity, and increased use of scarce resources (American Diabetes Society, 2008; Davis et al., 2006; Fradkin and Rodgers, 2008; Huang et al., 2009). The management of diabetes, the effective management of its risk factors, and the prevention of its complications, is a major public health issue.

[2] Increased arterial stiffness is associated with atherosclerosis (Hamilton et al., 2007; Herrington et al., 2004).

1.1.2 Diabetes, tests for diabetes, and diabetic states

Normally, the classification of diabetes is based upon its pathophysiology. While some authors have proposed changes to this categorisation, the customary classification is outlined here (Wilkin, 2007).

1.1.2.1 Diabetes

Type 1 diabetes results from a T-cell-mediated autoimmune destruction of the insulin-producing β-cells of the islets of Langerhans in the pancreas, usually leading to absolute insulin deficiency (American Diabetes Association, 2011). The lack of insulin production in patients with type 1 diabetes makes the use of exogenous insulin necessary to prevent the development of hyperglycaemia and life-threatening ketoacidosis. The incidence of type 1 diabetes reaches a peak at puberty, and has been thought to decline rapidly thereafter. However, it occurs in older people too with some researchers reporting a peak before puberty, and again during or after the fifth decade (Haller et al., 2005; Karjalainen et al., 1989; Thunander et al., 2008).

Type 2 diabetes is characterized by insulin resistance which is the impairment of the responsiveness of body tissues to endogenously produced insulin. In the early stages, insulin levels may be raised as more insulin is produced to compensate for insulin resistance. This may be followed by a decrease in insulin secretion due to the sustained increase in secretory demand with many individuals eventually requiring insulin therapy to manage their condition (although some capacity for some insulin production remains). Hyperglycaemia has a gradual onset, and is generally asymptomatic initially. At this early stage, it may be reversed by dietary measures (at least in the short term), weight loss, exercise, bariatric surgery and medication (American Diabetes Association, 2010; Lim et al., 2011; Umpierre et al., 2011). Type 2 diabetes accounts for between 90-95% of those with diabetes (American Diabetes Association, 2011).

Gestational diabetes is another type of diabetes which develops only during pregnancy, and is a risk factor for later development of Type 2. Rarer forms include diabetes due to genetic defects of the β-cell, genetic defects in insulin action, pancreatic disease, endocrinopathies, drug- or chemical-induced diabetes and infections.

1.1.2.2 Tests for diagnosis of diabetes

Diabetes is characterized by persistent hyperglycaemia, and diagnosis generally involves one of the following tests.

Fasting plasma glucose (FPG) test

This test measures blood glucose in a person who has had no caloric intake for at least eight hours prior to the test. It is most reliable when done in the morning. The FPG test is convenient (apart from the necessity of fasting) and low cost. However, it will miss some diabetes or prediabetes that can be found with the oral glucose tolerance test (OGTT). Impaired fasting glucose (IFG) is defined as a fasting plasma glucose level of 5.6 mmol/l - 6.9 mmol/l. IFG indicates prediabetes, and increases the risk of developing type 2 diabetes. A FPG above 6.9 mmol/l indicates diabetes (Table 1.1).

Oral glucose tolerance test (OGTT)

An OGTT measures the body's ability to metabolize glucose. The patient is instructed to have no caloric intake for at least eight hours prior to the test. A liquid containing 75 grams of glucose dissolved in water is drunk, and blood levels are checked two hours later. While the OGTT is more sensitive than the FPG test for diagnosing prediabetes it is less convenient, it costs more, is time-consuming, and is less reproducible. These limitations make the OGTT inappropriate for use in epidemiological research. If the blood glucose level is 7.8 mmol/l - 11.0 mmol/l two hours after drinking the liquid, the patient has a form of prediabetes called impaired glucose tolerance (IGT). Having IGT, like having IFG, means an individual has an increased risk of developing type 2 diabetes. Above 11.0 mmol/l, a diagnosis of diabetes is made (Table 1.1).

Glycated haemoglobin (HbA1c)

HbA1c is a reliable measure of glycaemic levels over time as it measures the average plasma glucose concentration over the previous four weeks to three months. It is convenient as fasting is not required and the OGTT's two-hour wait is not necessary. It captures chronic hyperglycaemia much better than FPG and OGTT as it is not influenced by transient episodes of illness or stress. HbA1c is reported in two different units: the National Glycohemoglobin Standardization Program (NGSP) reference system (%) and the International Federation of Clinical Chemistry (IFCC) reference system (mmol/mol). According to the NGSP system, prediabetes is implied when HbA1c levels of 5.7% – 6.4%,

and diabetes is 6.5% and above (Table 1.1). Measured by the IFCC system, prediabetes is HbA1c levels of 39 mmol/mol – 47 mmol/mol, and diabetes at 48 mmol/mol and above (American Diabetes Association, 2012). The HbA1c measures, as well as the dysglycaemia category cut-points used, are discussed in more detail in the Methods section.

Table 1.1. Tests for diagnosis of prediabetes and diabetes

	Normoglycaemia	**Prediabetes**	**Diabetes**
FPG[1]	<5.6 mmol/l	5.6 mmol/l -6.9 mmol/l (IFG[2])	≥7.0 mmol/l
OGTT[3]	<7.8 mmol/l	7.8 mmol/l - 11.0 mmol/l (IGT[4])	≥11.1 mmol/l
HbA1c[5]			
ADA values[6]			
NGSP[7]	<5.7%	5.7% – 6.4%	≥6.5%
IFCC[8]	<39 mmol/mol	39 mmol/mol – 47 mmol/mol	≥48 mmol/mol
NZ values[9]			
IFCC[7]	<40 mmol/mol	40 mmol/mol – 49 mmol/mol	≥50 mmol/mol

[1]Fasting Plasma Glucose test. Fasting is defined as no caloric intake for at least 8 hours.
[2]Impaired Fasting Glucose.
[3]Two-hour plasma glucose Oral Glucose Tolerance Test using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
[4]Impaired Glucose Tolerance.
[5]Glycated Haemoglobin.
[6]Anerican Dental Association values.
[7]Assayed using the National Glycohemoglobin Standardization Program (NGSP) reference system.
[8]Assayed using the International Federation of Clinical Chemistry (IFCC) reference system.
[9]New Zealand Society for the Study of Diabetes values.

1.1.2.3 Diabetic states

Prediabetes

Prediabetes is a condition in which individuals have glycaemia levels that are considered higher than normal, but not high enough to be classified as diabetes (Table 1.1). Individuals with prediabetes are considered to be at greater risk of developing type 2 diabetes in the future (American Diabetes Association, 2011; de Vegt et al., 2001; Inoue et al., 2008); moreover, prediabetes may be an independent risk factor for CVD (Hanna-Moussa et al., 2009). Prediabetes can be IFG or IGT (or both), depending on which test was used. If the

FPG test is used for diagnosis, it will be referred to as impaired fasting glucose (IFG). If the OGTT test is used, it's called impaired glucose tolerance (IGT). Or it may be diagnosed using HbA1c levels.

The American Diabetes Association (ADA) recently recommended a range of 39 mmol/mol – 47 mmol/mol for prediabetes (American Diabetes Association, 2011); previously, the recommended lower cut-off point was 42 mmol/mol (2009). This value of 39 mmol/mol, compared with other cut points, has been found to have a good combination of sensitivity and specificity to identify cases of prediabetes (American Diabetes Association, 2011; Cheng et al., 2011; Choi et al., 2011a). Furthermore, it was found to be cost-effective to target preventive interventions from the 39 mmol/mol point and above (Zhuo et al., 2012). However, the importance of regarding the range of HbA1c values from normal through various levels of dysglycaemia as a continuum of risk must be emphasised, and the practice of defining cut-off points for normoglycaemia, prediabetes and diabetes should be seen as somewhat arbitrary. Risk does not suddenly increase as an individual moves from one category to the next. Rather there is a gradual rise in CVD risk as glycaemia increases, and a gradual rise in type 2 diabetes risk as glycaemia increases across the spectrum of prediabetes towards the diabetes threshold. Most recently, the New Zealand Society for the Study of Diabetes (NZSSD) has recommended a range of 41 mmol/mol – 49 mmol/mol for prediabetes (Braatvedt et al., 2012; New Zealand Society for the Study of Diabetes, 2011). This pragmatic approach recognises that the values "40 and below" for minimal risk, and "50 and above" for high risk, are more likely than other values to be easily remembered by patients (Table 1.1).

Individuals with prediabetes who lose weight using dietary, physical activity, or behavioural interventions have a consequent decrease in the risk for progression to type 2 diabetes (Norris et al., 2005). Prediabetes is associated with obesity (particularly abdominal obesity), high serum triglycerides, low HDL cholesterol, and hypertension. These are the components of metabolic syndrome.

Metabolic Syndrome

Metabolic syndrome (MeS) may be best seen as a clustering of certain cardiometabolic risk factors rather than a "syndrome" as such as its causes are not well understood, and no clear basis exists for the algorithm that defines it (Kahn, 2007; Mann, 2012). Although its clinical

utility is questioned, it does help to define a cluster of disorders that often occur together, and put individuals at higher risk of CVD and type 2 diabetes (Alberti et al., 2009; Gami et al., 2007). Insulin resistance has been suggested as a possible linking factor (World Health Organization, 1999). Some authorities suggest that these disorders are multiplicative – together they pose a higher risk over and above that posed by the individual disorders; others argue that "the whole is not greater than the sum of the parts" (Kahn, 2006). In addition, its diagnostic criteria are disputed with different diagnostic criteria proposed by different organisations (Table 1.2).

The first formal definition of metabolic syndrome was published by the World Health Organisation (WHO) in 1999 (World Health Organization, 1999); this definition required insulin resistance as a component. This was followed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP, ATP III) criteria in 2001 (National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002). This definition did not require evidence of insulin resistance. Two more definitions followed, one from the International Diabetes Federation (IDF) (Alberti et al., 2005), and the other from the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLB) (Grundy et al., 2004; Grundy et al., 2005). These differed with respect to waist circumference (Table 1.2).

Debate continues as to whether MeS represents a specific syndrome or simply a cluster of factors that increases risk, and precisely what those factors should be (Kassi et al., 2011). The feasibility of using HbA1c as a component of MeS is being examined (Ong et al., 2010). Management of the component conditions (weight loss coupled with lifestyle changes and/or medication to lower hypertension, improve lipid profiles, and reduce hyperglycaemia will reduce this risk (Grundy et al., 2004). The prevalence of MeS depends on which definition is used, but it is clear that the prevalence is high. For example, depending on the population studied, and the criteria used, estimates range from 4.6% to 29.4% in the U.S (Ford, 2004); and in India from 8.0% to 46.0% (Cameron et al., 2004). Furthermore, it is likely the prevalence is increasing (Ford et al., 2004).

Table 1.2. Diagnostic criteria for metabolic syndrome proposed by different organisations (essential components shaded)

	WHO	**NCEP, ATP III**	**IDF**	**AHA/NHLB**
	Insulin resistance or dysglycaemia is an essential component plus any 2 of the others	Three or more of any components	Abdominal obesity is an essential component plus any 2 of the others	Three or more of any components
Insulin resistance or dysglycaemia	Type 2 diabetes, IFG or IGT or impaired disposal of glucose under hyperinsulinemic, euglycemic conditions.	Fasting glucose ≥ 6.1 mmol/L	Fasting glucose ≥ 5.6 mmol/L	Fasting glucose ≥ 5.6 mmol/L
Abdominal Obesity	W/H >0.9 (M) W/H >0.85 (F) And/or BMI >30 kg/m2	Waist >102 cm (M) Waist >88 cm (F)	Europeans ≥94 cm (M) ≥80 cm (F) South Asians/Chinese ≥90 cm (M) ≥80 cm (F)	Waist >102 cm (M) Waist >88 cm (F)
Elevated triglycerides	≥1.7 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L	≥1.7 mmol/L Or drug treatment for elevated triglycerides
Low HDL	<0.9 mmol/L (M), <1.0 mmol/L (F)	<1.0 mmol/L (M), <1.3 mmol/L (F)	<1.03 mmol/L (M), <1.29 mmol/L (F)	<1.03 mmol/L (M), <1.3 mmol/L (F) Or drug treatment for low HDL
Hypertension	≥ 140/90 mmHg	≥130/85 mmHg Or drug treatment for hypertension	≥130/85 mmHg Or drug treatment for hypertension	≥130/85 mmHg Or drug treatment for hypertension
Other components	Microalbuminuria			

Note: IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; W/H, Waist/hip ratio; BMI, Body mass index; M, Male; F, Female; HDL, High-density lipoprotein.

1.1.3 Periodontitis

Periodontal diseases are a group of diseases characterized by inflammation of the surrounding and supporting structures of the teeth: the gingiva, periodontal ligament, cementum, and alveolar bone. While the term periodontal disease includes localized juvenile periodontitis, pericoronitis, acute necrotising gingivitis and acute periodontitis, it is generally used for the most common form – chronic periodontitis. This highly prevalent, chronic inflammatory disease results in the formation of soft tissue pockets between the gingiva and the tooth, loss of connective tissue and eventual bone destruction, and is a major cause of tooth loss in adults.

1.1.3.1 Periodontitis prevalence and burden of disease

Estimates of the prevalence and incidence of periodontitis are complicated by a lack of standardisation and agreement in establishing criteria for the diagnosis of the condition (Hugoson and Norderyd, 2008; Leroy et al., 2010; Page and Eke, 2007). In addition, different indices have been used to record clinical assessment of periodontitis including the community periodontal index of treatment needs (CPITN or CPI), Russell's periodontal index, clinical attachment loss (AL) and pocket depth (PD), and radiographic examination (Savage et al., 2009). Examinations may be full-mouth or part-mouth, and recordings may be made for between one to six sites per tooth. So comparisons between countries, and between studies, are problematic.

The Study of Health in Pomerania (SHIP) is an East German prospective cohort study which accessed the prevalence of periodontitis in adults age 20-81 years using PD and AL between 1997-2001 (Hensel et al., 2003). In this population, 89.7% had one or more sites with 3mm or more AL, 71.4% had one or more sites with 4mm or more AL, 54.0% had one or more sites with 5mm or more AL, and 39.1% had one or more sites with 6mm or more AL (Holtfreter et al., 2009). The 2009 New Zealand Oral Health Survey found 49.9% of adults age 18 and over had one or more sites with 4mm or more AL, 27.5% had one or more sites with 5mm or more AL, and 13.4% had one or more sites with 6mm or more AL (Ministry of Health, 2010a). This is a markedly lower prevalence than was observed in the SHIP study, but it does tally well with the findings from the 2004-06 Australian National Survey of Adult Oral Health in which the percentage of the Australian population age 15 and over with AL of 4mm or more was 42.5% (AIHW Dental Statistics and Research Unit, 2007). In the U.S. 2009-2010 National Health and Nutrition Examination Survey (NHANES), over 63.0% of adults age 30 and over

had one or more sites with 4mm or more AL, and 43.4% had one or more sites with 5mm or more AL (Eke et al., 2012). In each of these surveys, prevalence increased with age with older age groups experiencing more severe disease.

The future burden of periodontitis is clear when the consequence of ageing populations having greater expectations of retaining a functional dentition for life is considered (Kassebaum et al., 2014; Shearer et al., 2011). The combination of increases in life expectancy, effective population-based oral health strategies in most developed countries over the past 40 years, a trend of decreasing edentulism, and advances in restorative dentistry means that more elderly people are now retaining teeth which would have been previously lost to dental caries. Essentially, *more* teeth are at risk of periodontal disease *for longer* (Shearer et al., 2011). Although periodontitis is largely painless, individuals with advanced disease may suffer the discomfort of loose teeth, difficulties with mastication, sensitivity, halitosis, and unaesthetic appearance; indeed, periodontitis may have a direct effect on quality of life (Cunha-Cruz et al., 2007; Jansson et al., 2014; Needleman et al., 2004). However, the greatest burden of periodontal disease may be only now becoming apparent as evidence mounts for associations between periodontal disease and inflammatory-driven systemic disease (Cullinan et al., 2009; D'Aiuto et al., 2005; Kuo et al., 2008; Yoon et al., 2012). The relationship with type 2 diabetes is particularly strong (Kuo et al., 2008; Lakschevitz et al., 2011; Lalla and Papapanou, 2011; Mealey, 2006; Mealey and Oates, 2006; Preshaw and Bissett, 2013; Taylor, 2001); and the possible bidirectional link between periodontal disease and diabetes mellitus suggests that a higher prevalence of periodontal disease in a population may adversely affect its overall health, with consequential suffering, costs, and use of scarce resources.

1.1.3.2 Periodontitis aetiology and risk factors

Periodontitis is a chronic inflammatory disease that stems from a complex polymicrobial infection, leading to tissue destruction as a consequence of the interaction between pathogenic dental plaque microorganisms and the host defences in susceptible individuals (Sanz and van Winkelhoff, 2011). The microorganisms involved are primarily gram-negative anaerobic bacteria, predominantly *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, although *Prevotella intermedia*, *Tannerella forsythia* and *Treponema denticola* (amongst others) are also implicated (Dumitrescu and Ohara, 2010; Van der Velden et al., 2006). While some harm to the periodontium is caused by direct infection via a range of

cellular or toxic processes, it is believed that most of the tissue injury in periodontitis is due to an autoimmune mechanism whereby the host's inflammatory response to the bacterial challenge causes the destruction of the periodontium. As plaque accumulates, and the bacterial load increases, bacterial enzymes and metabolic end products trigger an exaggerated inflammatory response leading to production of high levels of the pro-inflammatory cytokines, interleukin 1 beta (IL-1β), interleukin-6 (IL-6), interferon-gamma-γ, and tumour necrosis factor alpha (TNF-α), the chemokine interleukin-8 (IL-8), prostaglandin E2 (PGE2), and other pro-inflammatory agents; these initiate connective tissue breakdown and loss of bone. Overproduction of these cytokines continues, and along with the action of a family of enzymes called matrix metalloproteinases (MMP), leads to further breakdown of extracellular matrix proteins, and alveolar bone loss.

In addition to pathogenic microorganisms in the biofilm, a range of risk factors contribute to the cause of chronic periodontitis. Important non-modifiable risk factors include age, gender, ethnicity, family history and genetic and other heritable factors. The most important modifiable risk factors are smoking (including cannabis use), oral hygiene status expressed in terms of supragingival plaque accumulation and subgingival calculus, and diabetes (Gelskey, 1999; Löe, 1993; Mealey and Ocampo, 2007; Preshaw et al., 2012; Shearer et al., 2011; Thomson et al., 2007; Thomson et al., 2008; Torrungruang et al., 2005). Other putative factors include subgingival presence of *A. actinomycetemcomitans* and *P. gingivalis*, stress, socioeconomic status (SES), education, use of dental services, the presence of chronic disease characterised by underlying systemic inflammation (CVD, hypertension, adverse birth outcomes), and obesity (Chaffee and Weston, 2010; Dye, 2012; Kuo et al., 2008; Modeer et al., 2011; Peruzzo et al., 2007; Thomson et al., 2004; Torrungruang et al., 2005; Torrungruang et al., 2009).

1.1.4 Summary

This brief prologue has introduced diabetes and periodontitis – two very common, chronic conditions – and has mentioned associations between them. The literature review that follows is in eight parts. First is an overview of how the concept of links between diabetes and periodontitis evolved over the past 135 years. This is followed by a short synopsis of some of the literature concerning diabetes and glycaemic control as a risk factor for periodontitis. A

detailed review of the research to date investigating periodontitis as a risk factor for dysglycaemia (or poor glycaemic control in those with diabetes) forms the main part of the literature review. This is complemented by an outline of trials using animal models, and by a review of the literature on associations between periodontitis and diabetes complications, the effect of periodontal treatment on glycaemic control, and associations between periodontitis and metabolic syndrome.

1.2 Literature Review

1.2.1 Background

Recognition of the links between diabetes and periodontitis is not new. In 1928, JB Williams described “diabetic periodontoclasia”, his term for the oral manifestations of diabetes mellitus (Williams, 1928). He referred to academic publications which recorded the condition as far back as 1888, and observed that the statement “teeth became loose in diabetes” first appeared in the Encyclopedia Britannica in 1877 (Williams, 1928). Hirschfeld expanded on the theory in 1934 by reporting on five cases of oral manifestations of type 2 diabetes (Hirschfeld, 1934).

At the same time, there was also an understanding that periodontitis could influence the management of diabetes. The American dentist, Willoughby D. Miller, was likely the first to suggest that “pyorrhea alveolaris” (chronic periodontitis) should be regarded as detrimental to systemic health, maintaining that the “evil results of allowing this disease to gain the upper hand” may result in “fever, loss of appetite, stiffness, severe disturbances of the alimentary canal, insomnia …” (Miller, 1891). Miller’s seminal paper led to the focal infection theory, a phrase coined by Frank Billings in 1912 (Billings, 1912). This theory was further disseminated by Billings in the Lane lectures at the Stanford University Medical School in September, 1915 where he made mention of the oral cavity, and pyorrhea alveolaris in particular, as foci of infection (Billings, 1917) as outlined in (Focal Infection. The Lane Medical Lectures, 1917). What followed was an enthusiastic increase in the number of dental extractions (often without evidence of infection) in an attempt to cure a variety of poorly understood disorders (Gibbons RV, 1998; Haden RL, 1936). However, this was not accompanied by a consequent decline in disease, and the theory gradually fell out of favour (Reimann and Havens, 1940). The exception to this trend was the recommendations made by the American Heart Association for the prevention of infective endocarditis in individuals with congenital heart disease or post-rheumatic fever valve damage (Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis and American Heart Association, 1960).

Nevertheless, the notion that periodontitis may have systemic effects was presented again in 1960 when Williams and Mahan found reductions in insulin requirements in individuals

with type 1 diabetes following periodontal therapy (Williams and Mahan, 1960). The non-randomly selected sample comprised only nine people however, and no control was used.

The publication of two Finnish case-control studies in 1989 suggesting periodontitis to be associated with elevated levels of von Willebrand antigen[3] levels and cerebral infarction began a resurgence of interest in oral-systemic associations (Mattila et al., 1989; Syrjänen et al., 1989). Both studies used the same small sample of 40 people, and randomly selected controls. Miller et al. conducted a pilot study to examine the effect of periodontal therapy on HbA1c in nine Texan patients; an association was found between periodontal bleeding improvements and glycaemic control improvements (Miller et al., 1992). Indeed, Papapanou was prompted to remark in his 1996 review article that we cannot predict to what extent "the old concept of focal infections" will be reactivated in periodontal research, and that the mouth "belongs to and interacts with the human body" (Papapanou, 1996). The time had come for a re-evaluation of the role the oral cavity plays in systemic health.

1.2.2 Diabetes as a risk factor for periodontitis

Concurrently, research into the effect of diabetes on the periodontium continued, and following decades of research (much of it longitudinal), it is now thoroughly documented that those with poorly controlled diabetes are at greater risk of periodontitis than those without diabetes. In recent years, numerous review articles have summarised the abundant evidence for this association (Azarpazhooh and Tenenbaum, 2012; Bascones-Martinez et al., 2011; Cullinan et al., 2009; D'Aiuto et al., 2005; Grossi and Genco, 1998; Kandelman et al., 2008; Khader et al., 2006; Kuo et al., 2008; Lakschevitz et al., 2011; Lalla and Papapanou, 2011; Löe, 1993; Mealey, 2006; Mealey and Oates, 2006; Mealey and Ocampo, 2007; Papapanou, 1996; Preshaw et al., 2012; Salvi et al., 2008; Taylor, 2001; Williams et al., 2008) (Chapple et al., 2013). Indeed, Löe asserted periodontitis should be regarded as the "sixth complication of diabetes mellitus" (Löe, 1993).

Evidence-based medicine places systematic reviews and meta-analyses at the pinnacle of the evidence hierarchy (Greenhalgh, 1997). Prospective studies are essential for assessing temporality. Khader and associates' comprehensive meta-analysis of heterogeneous studies published between 1970 and 2003 was based on 18 cross-sectional studies, three prospective

[3] Elevated von Willebrand antigen levels are commonly observed in association with endothelial cell damage, and may predict adverse clinical outcomes and mortality after myocardial infarction (Spiel et al., 2008).

observational studies, and baseline data from two clinical trials (Khader et al., 2006). Studies on both Type 1 and Type 2 diabetes were included. While those with diabetes and healthy individuals were found to experience the same extent of periodontitis, individuals with diabetes suffered more severe disease (as measured by PD and AL), and had worse oral hygiene. No pattern of less favourable bleeding on probing (BOP) score, plaque index and pocketing measures was found according to glycaemic control. There were three prospective studies included in this meta-analysis (Firatli, 1997; Pohjamo et al., 1995; Tervonen and Karjalainen, 1997). However, one study described as prospective reported periodontal data from one time point only (the longitudinal aspect of the study examined use of dental services) and so would be better categorised as cross-sectional (Pohjamo et al., 1995). A 1997 Turkish paper reported a significantly higher AL in children and adolescents with Type 1 diabetes over five years compared to healthy controls, and a positive correlation between AL and duration of diabetes (Firatli, 1997). The study did have a large rate of attrition over the five years, and therefore its representativeness must be questioned. The third prospective study was a Finnish pilot study involved individuals with Type 1 diabetes; the response to periodontal therapy for well-controlled, variable-controlled, and poorly-controlled individuals was examined (Tervonen and Karjalainen, 1997). It was found that those with poorly-controlled type 1 diabetes and those with multiple diabetic complications had a higher risk of periodontal disease than those with well-controlled and variable-controlled diabetes. Those with poorly-controlled diabetes had more severe periodontitis to start with, and showed least improvement after therapy over the long term.

Taylor's 2001 systematic review appraised 45 studies involving individuals with either Type 1 or Type 2 diabetes, and a range of age groups from children through to the elderly (Taylor, 2001). All except three studies reported greater prevalence, extent or severity of one or more periodontal measures in those with diabetes than those without diabetes; these three studies were all cross-sectional (Benveniste et al., 1967; Goteiner et al., 1986; Hove and Stallard, 1970). There were seven prospective studies reviewed; four found those with diabetes to suffer greater severity or greater extent of attachment loss than healthy individuals (Cohen et al., 1970; Firatli, 1997; Novaes et al., 1996; Tervonen and Karjalainen, 1997); and three found those with diabetes to experience a higher incidence of radiographic alveolar bone loss than healthy individuals (Nelson RG et al., 1990; Taylor et al., 1998a; Taylor et al., 1998b). Of these prospective studies, the findings for four were limited by small sample

sizes (Cohen et al., 1970; Firatli, 1997; Novaes et al., 1996; Tervonen and Karjalainen, 1997), and case definitions for periodontitis varied between studies.

A dose-response relationship between exposure and outcome is indicative of the strength of an association, and may suggest causality. Taylor's review also evaluated nine prospective studies which examined the relationship between poorer glycaemic control and poorer periodontal status (Ainamo et al., 1990; Firatli, 1997; Karjalainen and Knuuttila, 1996; Novaes et al., 1996; Seppälä et al., 1993; Seppälä and Ainamo, 1994; Taylor et al., 1998a; Tervonen and Karjalainen, 1997). However, a relationship between poorer glycaemic control and periodontal status is not specifically mentioned in the Firatli paper (only between duration of type 1 diabetes and periodontal status), so this one must be discounted (Firatli, 1997). As outlined above, a Danish study examined the healing of periodontal pockets following therapy, and found those with poorly-controlled type 1 diabetes were at greater risk of periodontitis than those with well-controlled diabetes (Tervonen and Karjalainen, 1997). Novaes reported differences in AL between those with type 2 diabetes and those without, and differences in both PD and AL in the participants with type 2 diabetes according to glycaemic control (Novaes et al., 1996). The Pima Indians of the Gila River Indian Community in Arizona have been participants in studies of the aetiology of type 2 diabetes since 1965 (Knowler WC et al., 1978; The National Institute of Diabetes and Digestive and Kidney Diseases.). A 1998 paper noted an association between poorer glycaemic control and an increased risk of alveolar bone loss over a couple of years in a sample drawn from the Pima Indian community (Taylor et al., 1998a). The Ainamo et al. paper essentially describes two case studies featuring rapid periodontal destruction over time associated with poor glycaemic control (Ainamo et al., 1990). Two Finnish studies found poor glycaemic control to be related to gingivitis, BOP, attachment loss and alveolar bone loss; however, they did suffer a poor retention rate, and no adjustment for confounders was done (Seppälä et al., 1993; Seppälä and Ainamo, 1994). Karjalainen and Knuuttila examined children and adolescents with Type 1 diabetes, and found gingival bleeding to be associated with glycaemic control (Karjalainen and Knuuttila, 1996). Generally, these prospective studies do suggest a dose-response relationship between poorer glycaemic control and poorer periodontal status.

Gingival bleeding has long been observed in young people with type 1 diabetes. In fact, periodontal destruction in children with type 1 diabetes (as measured by AL) may begin at a

younger age than previously assumed (Lalla et al., 2006; Lalla et al., 2007). Children with Type 1 diabetes between ages six and eleven were found to have a significantly greater risk of AL of 2+mm or more on 1+ sites on 2+ teeth compared with healthy controls (Lalla et al., 2007). This risk was independent of confounding factors age, gender, ethnicity, plaque index and use of dental services. However, duration of diabetes and HbA1c were not found to be related to AL (Lalla et al., 2006).

Despite shortcomings in individual studies, the absolute weight of evidence linking diabetes and periodontitis is convincing. By the end of the 20th century, it was generally accepted that those with poorly controlled diabetes were at greater risk of periodontitis than those with well-controlled diabetes and healthy individuals. That this risk is related to metabolic control and disease duration had also been established. More recently, investigators have instead focussed on investigating the mechanisms whereby diabetes impacts on periodontitis. Research has been conducted into associations between diabetes, periodontitis and IL-1β (Engebretson et al., 2004), IL-1β and IL-6 (Duarte et al., 2007), collagenase activity in gingival crevicular fluid (GCF) (Safkan-Seppala et al., 2006), IL-1β, IL-8 and matrix metalloproteinases[4] (Salvi et al., 2010), a variant IL-1 genotype, AGEs (Takeda et al., 2006), adiponectin and resistin (Saito et al., 2008), PGE_2, IL-1β, and TNF-α (Salvi et al., 1998), TNF-α (Engebretson et al., 2007; Genco et al., 2005; Nishimura et al., 2003; Pacios et al., 2012; Takano et al., 2010), and oxidative stress (Bullon et al., 2009).

1.2.3 Periodontitis as a risk factor for dysglycaemia

Interest in periodontitis as a risk factor for poor glycaemic control has been rekindled in the past twenty years with the acknowledgement of the plausibility of a bidirectional link between the two conditions. The associations between background low-grade systemic inflammation and dysglycaemia are well recognised (Pitsavos et al., 2007; Wellen and Hotamisligil, 2005). The chronic inflammation of periodontitis may influence glycaemic control in susceptible individuals via pro-inflammatory mediators interleukin 1 beta (IL-1β), interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α), and other pro-inflammatory agents. Subsequently, this glycaemia can lead to a further deterioration in periodontal status which then increases the risk of worsening glycaemia, and so on. Each condition potentially

[4] MMPs are proteolytic enzymes involved in normal extracellular matrix remodeling, but have also been implicated in impaired wound healing, tumour progression, and destructive conditions (Salvi et al., 2010)

worsens the other, and a detrimental sequence ensues. Of particular importance in elucidating these relationships are the small number of longitudinal studies that specifically looked at the influence of periodontitis as a risk factor for type 2 diabetes, prediabetes and glycaemic control (Collin et al., 1998; Demmer et al., 2008; Demmer et al., 2010; Ide et al., 2011; Morita et al., 2012; Saito et al., 2004; Taylor et al., 1996).

The first of these was a longitudinal examination was carried out by Taylor and colleagues in 1996 using a sample from the Pima Indians study (Taylor et al., 1996). They found severe periodontitis at baseline to be associated with an increased risk for poorer glycaemic control within a couple of years as measured by HbA1c; this finding was independent of baseline type 2 diabetes severity (measured using OGTT) and baseline HbA1c (Taylor et al., 1996). Baseline periodontitis was measured both by clinically assessed attachment loss, and by radiographic evidence of bone loss (different sample sizes for each). Their findings also suggested the effect of baseline severe periodontitis on poor glycaemic control risk decreased as age increased, and baseline smoker status increased risk. A range of putative confounders and effect modifiers were assessed at baseline (age, sex, smoking status, alcohol consumption, prevalence of retinopathy, systolic blood pressure, diabetes severity and duration, insulin use, hypoglycaemic use, and abnormality on resting ECG). Other potential confounders not included were lifestyle factors such as diet, and general attitude/health behaviours in managing type 2 diabetes and oral health. The sample sizes were relatively small, and healthy individuals were not included. The HbA1c variable was dichotomised which introduces the potential for misclassification, as well as the loss of information (Altman and Royston, 2006). However, this study is important in that it implies a temporal association between periodontitis and poorer glycaemic control.

Taylor's study was followed two years later by a Finnish study which classified periodontal condition (as measured by alveolar bone loss and pocket depth) in 25 patients with Type 2 diabetes and 40 healthy controls into three categories: "Good condition", "Moderate periodontitis" or "Advanced periodontitis" (Collin et al., 1998). Individuals with diabetes and advanced periodontitis were found to have experienced an increase in HbA1c over two or three years, whereas individuals with diabetes and moderate periodontitis or a healthy periodontium experienced a decrease. This study had significant limitations. As for the Pima Indians study above, there was the potential for misclassification and loss of information with the categorisation of the continuous variables. The convenience sample was small, and

the findings were not generalizable to other populations. Multivariate analyses were not performed, so spurious associations could not be excluded. The periodontal examination was at one point in time only; as periodontal status at baseline was unknown, so too was the direction of the association.

Recently, a systematic review of observational studies concluded a small body of evidence suggests periodontitis may have an adverse effect on glycaemic control (Borgnakke et al., 2013). Nevertheless, it did also assert that the research to date is scant, periodontal and metabolic outcome parameters varied widely between studies, and there is a need for prospective observational studies of long duration.

While some researchers have examined the impact of periodontitis on those with type 2 diabetes, others have considered whether periodontitis also affects glycaemia in healthy individuals and those with prediabetes. The Hisayama study is a population-based prospective study examining the morbidity and mortality of cardiovascular disease and its risk factors in the town of Hisayama in southern Japan. Full community surveys of the residents aged 40 years and over have been done since 1961. Saito and associates carried out a retrospective cohort study on 591 Hisayama study participants in 1998, and found a fifth of those with NGT (as measured by OGTT) in 1988 had progressed to IGT or type 2 diabetes over the ten-year period; increased risk of progression was associated with greater pocket depth (Saito et al., 2004). In addition, analyses found each additional millimetre in mean pocket depth in 1998 corresponded to a 0.13% increase in HbA1c between 1988 and 1998. IGT correlates age, sex, BMI, exercise frequency, alcohol consumption and smoking were included in the multivariate analysis, but metabolic biomarkers and hypertension were not. No such associations were found for attachment loss, the authors suggesting attachment loss may be associated with a lower bacterial load than deep pocketing. While OGTT and HbA1c data were collected at two points, periodontal status was assessed at one point only (in 1998). The possibility that periodontal status measured then was quite different from periodontal status in 1988 cannot be excluded. Participation rates were very low, particularly for the periodontal assessments, so the findings are not generalizable to the source population.

However, the following year, Saito et al. reported no associations between IGT (as measured by OGTT) and either deep pocketing or severe attachment loss (Saito et al.,

2005). This was in contrast to their previous study whereby deep pockets were closely related to both current glucose tolerance status and the development of IGT (Saito et al., 2004). Again the sample was derived from the Hisayama study, but this later study differed in that only women were examined, the study was cross-sectional, and covariates plaque index and occupation along with either BMI, body fat or waist-hip ratio were controlled for in the multivariate analyses. The participants were grouped into quintiles according to their two periodontal measurements: mean pocket depth and mean attachment loss. However, these quintiles were further grouped into two categories (the most severe quintile as group 1, and the other four together as group 2) effectively resulting in loss of information, and under-utilisation of the data. The HbA1c levels were not included in the multivariate analyses; this is a pity as HbA1c data was collected, and it would have been of interest to see if this measure of chronic glucose exposure was more useful regarding the presence of dysglycaemia than the OGTT.

Saito and co-workers again investigated associations between periodontitis and IGT in a survey of defence force men (Saito et al., 2006). This time periodontitis was measured by alveolar bone loss determined by panoramic radiograph, and an association was found between this and prevalence of IGT as measured by OGTT. A second analysis found no association between alveolar bone loss and type 2 diabetes (although this may have been due to Type 2 error as the sample size in this analysis was small). Clearly, temporality was not shown as the study was cross-sectional, and the findings not generalizable as the participants were all men aged 50-55 from the Japanese Self-Defence Force. Another consideration is that radiographic evidence of alveolar bone loss may reflect resolved periodontitis rather than current disease; no measurement of pocket depth or bleeding was done in this study.

It is appropriate to mention here a novel classification of periodontitis, the periodontal inflamed surface area (PISA) which has recently been developed in an attempt to quantify the *area* of inflamed periodontal tissue, and thus reflect the inflammatory burden generated by periodontitis (Nesse et al., 2008). PISA reflects the surface area of bleeding pocket epithelium in mm^2. While PISA may not precisely measure the amount of inflamed tissue, it is likely the most accurate tool available at this time. Interestingly, researchers found a dose-response relationship between PISA and HbA1c in participants with type 2 diabetes (Nesse et al., 2009). This was important as such a relationship may indicate a causal relationship

between PISA and HbA1c. The findings were independent of sex, oral hygiene, BMI, SES and duration of diabetes. Unfortunately, the study was cross-sectional only, had a small convenience sample, and most of the participants were women. So temporality could not be established, and the findings were not generalizable to a wider population. Moreover, the participants all had Type 2 diabetes; it would be worthwhile to investigate if such a dose-response relationship was also seen in healthy individuals and those with prediabetes.

Healthy participants in the NHANES I study formed the basis of a longitudinal study investigating associations between periodontitis and incident Type 2 diabetes (Demmer et al., 2008). Some 9296 individuals had a baseline periodontal examination between 1971 and 1976, and a follow up examination between 1982 and 1992. Diabetic status was assessed on both occasions, but periodontal status at baseline only. An association between baseline periodontitis and incident diabetes 6 - 21 years later was found. This association was independent of age, sex, ethnicity, SES, education, BMI, skinfold measurements, physical activity, cholesterol, hypertension, smoking, and 24-hour dietary record, and the large sample was reasonably representative of the US population aged 25-74 years. Unfortunately, diabetic status was measured either by death certificate (in the case of the follow up), diagnosis of type 2 diabetes from a health facility, or self-reported physician diagnosis requiring medication. The latter category excluded those with diabetes treated by lifestyle modification. Without an objective measure of glycaemia, the potential for misclassification of diabetic status is evident, particularly those with undiagnosed type 2 diabetes being categorised as healthy. However, an attempt to minimise this bias was made by excluding participants who reported incident diabetes within one year of baseline from analyses. In addition, a subgroup analysis restricted to incident diabetes occurring ten or more years after baseline left the findings essentially unchanged. Russell's Periodontal index which was used to classify periodontitis is no longer considered valid as it assumes gradually progressive disease, measures pocket depth only (and not as a continuous measure), and ignores attachment loss (Dhingra and Vandana, 2011; Dye, 2012; Russell, 1956). Furthermore, one of the analyses used missing teeth as a surrogate for periodontitis. While this is not a reasonable assumption as many teeth would have been lost to caries, to some extent it is supported by research linking tooth loss and cardiovascular disease (Desvarieux et al., 2003). The authors speculated on tooth loss acting both as a *consequence* of periodontitis and as a *preventive* measure for future periodontal risk due to bacterial exposure, and tooth loss occurring early in life might confer some protection. This is a very

valid point, and relates well to the concept of PISA (Nesse et al., 2008; Nesse et al., 2009). Other interesting ideas proposed included a possible threshold level of periodontitis above which risk of incident diabetes increases markedly, and the notion that common genetic/family history susceptibility underlies both periodontitis and type 2 diabetes.

Demmer and colleagues addressed many of the limitations of their 2008 paper with a longitudinal analysis of periodontal and HbA1c data from the Study of Health in Pomerania (SHIP), an East German prospective cohort study (Hensel et al., 2003; John et al., 2001). They found periodontitis (as measured by attachment loss and pocket depth) at baseline in healthy participants to be associated with HbA1c progression five years later whereby those with more severe periodontitis at baseline experienced greater increases in HbA1c (Demmer et al., 2010). Furthermore, those with baseline periodontitis that had deteriorated over that time experienced the greatest increase of all. The latter associations were true for worsening attachment loss, but not for worsening pocket depth. Participants who were edentulous at baseline experienced increases in HbA1c of the same order as the most severe periodontitis category. Diabetic status at baseline was assessed by HbA1c measurement, self-reported or physician prevalent type 2 diabetes. Periodontal status and HbA1c were both assessed twice – at baseline and at follow up five years later. Importantly, temporality was established in that periodontitis preceded the change in HbA1c; type 2 diabetes was eliminated as a contributor to baseline periodontitis as only healthy individuals were included. Confounders controlled for were age, sex, education, region, BMI, waist-hip ratio, smoking, hypertension, triglycerides, fibrinogen, C-reactive protein, white blood cell count, and family history of type 2 diabetes. Interaction models were done for fibrinogen, C-reactive protein, and white blood cell count, and found effect modification between periodontal status and C-reactive protein only. The original sample of 7,008 was representative; however, the low participation rate (68.8%) for baseline raises doubts about the study's generalizability. In addition, the follow up rate of 83.6% of the baseline sample was further reduced by exclusions due to missing data. In effect, analyses were carried out on 2793 individuals (71.8% of the baseline participants, and only 39.9% of the original randomly chosen sample). An analysis of how the non-participants differed from those who did take part would have been of interest. The finding that individuals who were edentulous at baseline experienced increases in HbA1c of the same order as the most severe periodontitis category led the authors to further speculate on the role tooth loss plays as it appears to contradict the notion of PISA (Nesse et al., 2008; Nesse et al., 2009). It is possible that

infection-induced systemic damage is not entirely reversible, or systemic inflammation due to periodontitis may not fully subside after extraction (Desvarieux et al., 2003).

A pilot study in a Minnesota School of Dentistry clinic investigated whether healthy individuals with periodontitis had higher HbA1c compared with healthy (no diabetes) controls without periodontitis (Wolff et al., 2009). While the study did find periodontitis prevalence to be associated with a slightly higher HbA1c, it had some significant shortcomings. It was cross-sectional, and so offered a low level of evidence. The convenience sample was not representative of the clinic population, much less a wider population. Some controls had received periodontal treatment in the past (more than six months prior to the study) and the possibility that systemic damage due to past periodontitis was still having an impact at the time of the study could not be excluded (Desvarieux et al., 2003). Periodontal status was not assessed by clinical examination; instead existing clinical and radiographic records were used. Obviously, this introduces the potential for serious error as the examiners (it is not known how many examiners were involved) were not calibrated. The study examined HbA1c levels in people with "undiagnosed diabetes" as opposed to healthy individuals. It's difficult to see the value of this as some participants had elevated HbA1c, and indeed had undiagnosed type 2 diabetes. These individuals should have excluded from the analyses as it would have been more useful to involve healthy individuals only. Correlates included in the multivariate analysis were limited to age, gender, BMI and smoking. A point-of-care device (A1cNow) was used to measure HbA1c. Some researchers reported a good correlation between A1cNow and laboratory values (Arrendale et al., 2008; Chang et al., 2010). However, others did not (Lenters-Westra and Slingerland, 2010). The worst correlation between A1cNow and laboratory values was seen for HbA1c values below 7.0% (Arrendale et al., 2008). Therefore, the instrument wasn't particularly accurate for the range of HbA1c values in this paper (5.66% ± 0.56% for cases, and 5.51% ± 0.44% for controls). A1cNow is designed to be used in a clinical setting and for patient self-monitoring, not for epidemiological research. Due to the study's serious limitations, its findings do not carry much weight.

A Japanese study carried out between 2005-2006 on associations between periodontal status and HbA1c in healthy individuals contributed little more than the Minnesota study as it too was cross-sectional, and it's unclear how the sample was selected (Hayashida et al., 2009). A relationship was found between the two variables, with a range of confounders (age,

gender, BMI, smoking, alcohol, and exercise) controlled for. The community periodontal index (CPI) score was used to record periodontal status. The shortcomings of the CPI are well known. It does not measure attachment loss, and its validity has been questioned (Leroy et al., 2010; Lewis et al., 1994). Statistical analysis was done using ANCOVA for HbA1c and a 3-category periodontal variable ("Healthy", "Mild/moderate" and "Severe") but no post-hoc comparisons were done to clarify which of the categories differed.

An analysis of data from the NHANES III found a dose-response relationship between periodontitis (measured by AL and PD) and IFG (Choi et al., 2011b). The associations remained for both IFG and type 2 diabetes following adjustments for a comprehensive range of covariates. The study was cross-sectional only, and a partial mouth examination was used to assess periodontitis. Zadik et al. also examined links between periodontitis (measured by radiographic alveolar bone loss) and IFG in healthy individuals, finding cross-sectional associations between the two (Zadik et al., 2010). However, the sample was not representative, and no multivariate analysis was done.

In addition to the 2005 Saito paper, a couple of other recent studies also found no relationship between IGT and periodontitis. A Japanese case-control study measured alveolar bone loss using panoramic radiographs, and found type 2 diabetes, but not IGT, to be associated with alveolar bone loss (Marugame et al., 2003). Interestingly, this is the opposite of what Saito et al. found (Saito et al., 2005). A non-representative, middle-aged, male-only sample was used. Prevalence of bone loss was high, with the "severe alveolar bone loss" cases making up three-quarters of the sample. The authors suggested possible reasons for the lack of association between IGT and periodontitis. Only IGT individuals with a propensity to progress to type 2 diabetes develop alveolar bone loss. Or the dysglycaemia in those with IGT has been of short duration, and thus had not had time to impact on the alveolar bone (severe alveolar bone loss being a feature of advanced periodontitis). Furthermore, as radiographic evidence of alveolar bone loss may reflect past disease rather than current, the precise nature of the associations (or lack thereof) is unclear. It is also possible there may have been insufficient statistical power in the study to detect an association between IGT and periodontitis.

In Japan, employees who are regularly employed by a company undergo mandatory annual medical tests. As a result Japanese researchers have access to limited (the data is collected

for health insurance, rather than research, purposes) longitudinal data on both periodontitis and diabetes. Ide and associates found no overall independent association between periodontitis and incident type 2 diabetes over a seven year period in a large sample of Japanese civil servants, although an association was found between moderate periodontitis and incident diabetes in women (Ide et al., 2011). Because both individuals with confirmed and undiagnosed type 2 diabetes were excluded at the baseline stage, temporality was established (that is, periodontitis preceded incident diabetes). Confounders controlled for were age, sex, smoking, BMI, triglycerides, hypertension, HDL, y-glutamyl transpeptidase. The study had some limitations. The sample was not representative of the Japanese population, periodontal data was collected at baseline only (so a substantial improvement in periodontal health over the study period could not be excluded), and the CPI score was used to record periodontal status. The weak points of the CPI have been outlined above. Most of the continuous variables were dichotomised resulting in significant loss of information (Altman and Royston, 2006). Fasting plasma glucose (FPG) was used to diagnose incident diabetes; although considered the gold standard for diagnosis, this test is subject to several limitations (Sacks, 2011). The study participant had to have been fasting at the time the blood sample was taken, and a lack of reproducibility could have been a problem. While no method of measurement is perfect, some organizations are recommending that HbA1c be used for screening and diagnosis of type 2 diabetes (American Diabetes Association, 2011; 2009).

Another Japanese paper outlined two studies using two separate samples (Morita et al., 2012). It seems the samples were derived from the same population of Japanese civil servants as used by Ide and colleagues, although this is not clear. Study 1 involved HbA1c and periodontal data being gathered at baseline with periodontal data gathered again about 5 years later. Individuals with periodontitis at baseline were excluded, and the associations between baseline HbA1c and incident periodontitis were examined. Study 2 involved HbA1c and periodontal data being gathered at baseline with HbA1c data gathered again about 5 years later. In this case, individuals with type 2 diabetes at baseline were excluded, and the associations between baseline periodontitis and HbA1c elevation were examined. Both studies had large sample sizes (5,856 and 6,125 participants respectively). Associations were found between higher HbA1c at baseline and the risk of having developed periodontitis five years later, and between periodontitis at baseline and the risk of elevated HbA1c five years later. Confounders controlled for were age, sex, BMI, alcohol

consumption and smoking; metabolic biomarkers and hypertension were not. The use of the CPI score to record periodontal status was a limitation. The findings were not generalizable even to the civil servant population from which the sample was derived much less to the general Japanese population. There was some confusion with respect to terminology with the study variously referred to as a "prospective cohort analysis" and "a "case-control cohort study". Despite these limitations, this important paper suggests a bi-directional relationship between periodontitis and elevated HbA1c.

Three other cross-sectional studies should be mentioned as they demonstrate the conflicting results that are seen in periodontal and prediabetes research. Lamster and colleagues found that those with newly identified prediabetes experienced a level of periodontitis (as measured by the extent of teeth with 5mm+ pocket depth) between that experienced by normoglycaemic individuals and those with type 2 diabetes (Lamster et al., 2014). These findings were limited by the cross-sectional design, a lack of generalisability, the use of a point-of-care device to record HbA1c levels, and the fact that attachment loss data were not recorded. Nonetheless, these findings do strengthen the concept that periodontal disease may be an early indicator of dysglycaemia. Conversely, a SHIP-Trend study found no association between prediabetes and the extent of teeth with 4mm+ AL or mean probing depth (Kowall et al., 2015). Incidentally, the SHIP-Trend study did find mean AL to be associated with poorly-controlled type 2 diabetes, but not with well-controlled diabetes. This was a large population-based study, and adjustment was made for a comprehensive of range of confounders. However, it was limited by its cross-sectional design, a poor response rate, and that the periodontal examination was half-mouth only. Another cross-sectional study using data from the Continuous NHANES 2009-2010 survey found associations between severe periodontitis and IGT, but not IFG; and no associations between moderate periodontitis and either IGT or IFG (Arora et al., 2014).

On a practical note, some authors propose that dentists and other oral health-care professionals may have a role to play in identifying individuals with undiagnosed diabetes or prediabetes thus enabling early treatment of hyperglycaemia, and the minimisation of future diabetic complications (Lalla et al., 2011). It is suggested that greater collaboration between dental and medical professionals is required so that periodontitis and diabetes can be managed in a timely fashion (Iacopino, 2009).

In conclusion, the possibility of periodontitis being a risk factor for dysglycaemia must be acknowledged. Some studies have suggested a temporal relationship whereby periodontitis preceded dysglycaemia or deterioration in glycated hemoglobin (HbA1c) levels (Demmer et al., 2010; Morita et al., 2012; Taylor et al., 1996). It is clear that there has been little research to date in this field, and the need for long-running prospective observational studies is evident.

1.2.4 Animal studies

For ethical and pragmatic reasons, periodontitis or diabetes cannot be experimentally induced in humans. Nor can some confounding factors be easily accounted for in human studies. To resolve these difficulties, two recent studies used animal models to research the relationship between induced periodontitis and prediabetes, and periodontitis and insulin resistance (Pontes Andersen et al., 2007; Watanabe et al., 2008). Zucker rats are an animal model for research on obesity, prediabetes and hypertension, and there are two types: the lean Zucker rat, and the characteristically obese Zucker fatty rat (ZFR). The former study induced periodontitis in half the ZFRs and in half their lean littermates, using the periodontitis-free ZFRs and the periodontitis-free leans as controls (Pontes Andersen et al., 2007). After four weeks, they found periodontitis to be associated with a worsening of prediabetes in ZFRs; it was also associated with glycaemic dysfunction in the lean rats, but not to the same extent. In addition, the ZFRs with prediabetes and periodontitis were found to have more severe alveolar bone loss than the healthy leans with periodontitis. Therefore, periodontitis worsened prediabetes, and prediabetes worsened periodontitis, indicating a bi-directional link between the two conditions in these animals. A very similar study design was followed by the Illinois study, although a substrain of ZFR, Zucker fatty rats (ZDF) with diabetes was used (Watanabe et al., 2008). ZDFs with induced periodontitis who were also fed a high-fat diet suffered earlier and more severe insulin resistance than high-fat diet ZDFs without periodontitis, or low-fat diet ZDFs with or with our periodontitis. The authors suggest the influence of periodontitis on insulin resistance may be most evident when insulin action or secretion is already compromised, as would be when a high-fat diet is consumed (Watanabe et al., 2008).

1.2.5 Periodontitis and diabetes complications

Poor glycaemic control, sustained over the long term, has been closely linked to macrovascular (cardiovascular, cerebrovascular, and peripheral vascular disease) and microvascular (retinopathy, nephropathy, and neuropathy) complications (Daneman, 2006; Diabetes Control and Complications Trial Research Group, 1993; 1994; Stratton et al., 2000). With the growing accumulation of evidence for periodontitis as a risk factor for poor glycaemic control it is plausible that periodontitis has an influence on diabetes complications. Two longitudinal studies using data from the Pima Indians study examined the relationship between periodontitis and overt nephropathy and end-stage renal disease (Shultis et al., 2007); and between periodontitis and mortality due to cardiorenal (a grouping of ischaemic heart disease or diabetic nephropathy or both) complications (Saremi et al., 2005).

The Shultis et al. study followed 529 participants without baseline nephropathy, as measured by the albumin/creatinine ratio[5] (ACR) and the glomerular filtration rate[6] (GFR). Periodontitis was assessed by the number of teeth, and alveolar bone loss determined by radiograph. Over a median follow-up period of 9.4 years, 193 people developed macroalbuminuria, and 68 developed end-stage renal disease (ESRD) over a median follow-up of 14.9 years. It was found that moderate or severe periodontitis, or edentulism, predicted both overt nephropathy and ESRD in a dose-dependent manner, after adjustment for common risk factors age, sex, diabetes duration, BMI and smoking, but not glycaemic control (Shultis et al., 2007).

In addition to the above risk factors, the comprehensive Saremi et al. analysis also adjusted for glycaemic control (as measured by either HbA1c or FPG), macroalbuminuria, cholesterol, hypertension and electrocardiograph abnormalities (Saremi et al., 2005). In the sample of 628 people, 204 died over the median follow-up period of 11 years. It was reported the death rate from cardiorenal complications in participants with severe periodontitis (as measured by attachment loss, and alveolar bone loss determined by radiograph) was 3.5 times as high in those with no, mild or moderate periodontitis. Unfortunately, this is somewhat unclear as while the text reports this finding as “3.5 times as high”, the abstract reports it as “3.2 times the risk”. Nonetheless (and while association

[5] The albumin/creatinine ratio is a measure of macroalbuminuria, a marker for nephropathy
[6] The glomerular filtration rate is a measure of kidney function

does not infer causality, and unmeasured common risk factors cannot be excluded) these intriguing findings do suggest the possibility of periodontitis severity having an independent effect on diabetes complications prevalence.

1.2.6 Effect of periodontal treatment on glycaemic control

Complementing the observational studies on the bidirectional link between periodontitis and glycaemic control, there has been a number of intervention trials on the effect of periodontal treatment on glycaemia. While most of this research has been in recent years, Williams and Mahan's 1960 study which found reduced insulin requirements in individuals with type 1 diabetes following periodontal therapy was an early investigation of this effect (Williams and Mahan, 1960). In the past few years, meta-analyses have been undertaken on trials conducted since 1992 (Darre et al., 2008; Janket et al., 2005; Simpson et al., 2010; Teeuw et al., 2010). Most recent was the thorough Cochrane review which concluded there was some evidence of glycaemic control improvement following periodontal treatment (Simpson et al., 2010).

The Pima Indian community again contributed to periodontal research in the 1997 Grossi et al. study (Grossi et al., 1997). Participants with Type 2 diabetes were randomised into five different groups which each received mechanical therapy combined with different antimicrobial therapies (the control group received a placebo only); at 3 months post-treatment all five groups showed an improvement in periodontal health with the three groups receiving systemic doxycycline also experiencing significant reductions in HbA1c.

Al-Mubarak and colleagues examined the effect of sub-gingival water irrigation as an adjunct to mechanical therapy in people with Type 1 or Type 2 diabetes (Al-Mubarak et al., 2002). They found no significant difference in HbA1c between the groups after 12 weeks (although there was a non-significant reduction in the test group), despite the treatment group showing a significant improvement in some periodontal parameters and systemic inflammatory markers. However, it is possible that the change in HbA1c was attenuated by the inclusion of those with Type 1 diabetes. Type 2 diabetes is thought to be inflammatory in nature, whereas Type 1 is believed to be an autoimmune condition, and thus less reactive to a reduction in the inflammatory burden (although they will still have deterioration in

glycaemic control when they get an inflammatory condition). Furthermore, glycaemia in Type 1 diabetes is generally tightly controlled by frequent monitoring and insulin administration.

Rodrigues et al. found significant reductions in HbA1c in individuals with Type 2 diabetes three months after mechanical therapy for both the treatment group who had systemic antimicrobial adjunctive therapy (amoxicillin/clavulanic), and the control group who had mechanical therapy only (Rodrigues et al., 2003). Interestingly, the control group showed a more favourable response then the treatment group. Furthermore, those with the most poorly controlled diabetes at baseline showed the greatest response of all.

Two years later, Kiran and associates reported a significant reduction in HbA1c in the treatment group (mechanical therapy) three months post-therapy, whereas the control group (no treatment) showed a slight increase in HbA1c (Kiran et al., 2005). In accordance with Kiran et al., another trial found HbA1c levels to decrease significantly in a treatment group which had full mouth mechanical therapy compared with a control group which had supragingival plaque and calculus removal only (Koromantzos et al., 2011).

On the other hand, a RCT involving participants with poorly-controlled type 2 diabetes found no significant benefit (although a trend was seen) for mechanical therapy with chlorhexidine and systemic doxycycline compared to a "health care as usual or no treatment' control after four months (Jones et al., 2007). It is possible this nonsignificant finding was due to pre-notification of participants' normal doctor (thus informing the doctor their patient was poorly controlled which may have resulted in more aggressive treatment of glycaemic control, and biasing the results towards the null).

In 2007, Yun et al. reported on a RCT which evaluated the effect of mechanical therapy plus systemic doxycycline versus a control group receiving systemic doxycycline only (Yun et al., 2007). Both the treatment and control group showed significant reductions in HbA1c; however, there was no significant difference between the two groups. A more recent trial found that mechanical therapy followed by adjunctive sub-antimicrobial-dose doxycycline taken for three months resulted in a 0.9% reduction in HbA1c (Engebretson and Hey-Hadavi, 2011). This was a much more favourable response than for a group taking

antimicrobial-dose doxycycline for two weeks following mechanical therapy (0.3% change), and a placebo control who had mechanical therapy only (no change).

There has been some debate as to what actually constitutes periodontal treatment, and whether extractions and endodontic treatment should be included along with mechanical therapy (scaling and root curettage or planing), systemic or local antimicrobial therapy, periodontal surgery and oral hygiene instruction (Friedlander, 2010a; b). The effect of the most radical form of treatment, the extraction of periodontally compromised teeth, in addition to scaling, root curettage, and oral hygiene instruction was examined in a trial in 2001 (Stewart et al., 2001). A marked improvement in HbA1c was found in the treatment group. However, these findings were limited by the small sample size, selection bias, and non-randomisation (the treatment group was matched to historical controls). More recently, Khader et al. reported a marked reduction in HbA1c in individuals with Type 2 type 2 diabetes following full-mouth tooth extraction (Khader et al., 2010). The mean reduction in the treatment group was 1.23% at three months, and 1.37% at six months. This compared to a mean reduction of 0.28% at both three and six months in the control group who were not treated. These studies suggest the extraction of the worst periodontally involved teeth may be a valid treatment option for those with Type 2 diabetes.

Other investigators have considered the effect of periodontal treatment on systemic inflammatory markers which are thought to play a role in the bidirectional link between periodontitis and glycaemia. Katagiri and associates found that mechanical therapy combined with topical administration of minocycline in periodontal pockets reduced HbA1c levels in individuals with type 2 diabetes only when hs-CRP levels were also reduced (Katagiri et al., 2009). This may partly explain the inconsistent effects of periodontal therapy on glycaemia. Those individuals who experienced the greatest reductions in HbA1c also had the greatest inflammatory burden at baseline (as assessed by BOP), and may have been more likely to benefit from antimicrobial treatment. A study found periodontal treatment (mechanical therapy and oral hygiene instruction) significantly reduced the level of serum TNF-α in those with well-controlled and poorly-controlled type 2 diabetes, and in healthy individuals (Dag et al., 2009). However, only the well-controlled diabetes group achieved significant reductions in HbA1c suggesting that careful glycaemic control may be necessary to optimise the effect of periodontal therapy. A recent RCT found the serum

levels of hs-CRP, TNF-α, IL-6, FPG, HbA1c, fasting insulin and HOMA-IR[7] were reduced, and serum levels of adiponectin were slightly increased, in a periodontal treatment group compared to an untreated control group (Sun et al., 2011). The participants had poorly controlled Type 2 diabetes, and treatment involved mechanical therapy and oral hygiene instruction, periodontal surgery, extractions and systemic antimicrobial medication.

More recently, the United States Diabetes and Periodontal Therapy Trial (DPTT) published findings from a 6-month randomised clinical trial to determine if periodontal treatment reduced HbA1c levels in individuals with Type 2 diabetes with a diagnosis of moderate to advanced periodontitis (Engebretson et al., 2013). Periodontal treatment was confined to scaling/root planing, oral hygiene instruction and chlorhexidine oral rinse. Enrolment into the trial was terminated early due to futility. Within 6 months the treatment group had a 0.17% increase in mean HbA1c while the control group had a 0.11% increase in mean HbA1c. This was despite an improvement in the periodontal parameters in the treatment group compared with the control group. The authors concluded non-surgical periodontal treatment did not improve glycaemic control in this sample. This study provoked quite a strong response from other researchers who did not agree with its conclusions (Borgnakke et al., 2014). They were concerned the non-surgical periodontal treatment provided had failed to control the periodontal infection and associated inflammation (there was minimal reduction in bleeding on probing following treatment), and that baseline glycaemic control in the treatment group was generally good (meaning a substantial improvement could not be expected). In addition, the treatment group had a high mean BMI (mean 34.7 kg/m^2). There is some evidence that the inflammatory state associated with obesity would overwhelm any reduction in inflammation associated with periodontal treatment. In other words, periodontal treatment may have an attenuated effect on HbA1c levels in those individuals with Type 2 diabetes who are also obese (Offenbacher et al., 2009; Zhu and Nikolajczyk, 2014).

While controlled trials give some insight into the relationship between periodontal therapy and glycaemia the findings of many have been limited by small sample sizes, lack of power, lack of randomisation and bias. Conflicting findings may be attributed to differences in sample sizes and makeup, in methodology, and in periodontal therapy provided. This is a

[7] HOMA-IR. Homeostasis model of assessment – insulin resistance. An empirical mathematical formula based on fasting plasma glucose and fasting plasma insulin levels that was developed as a surrogate measurement of in vivo insulin sensitivity (National Diabetes Education Initiative.). It is used to quantify insulin resistance.

field that is currently attracting a great deal of interest, and the need for carefully conducted trials with large sample sizes is a priority (Engebretson and Kocher, 2013).

1.2.7 Periodontitis and metabolic syndrome

The studies outlined so far suggest the possibility that periodontitis may have an effect on diabetes status, prediabetes or HbA1c levels. Some researchers have focussed instead on the associations between periodontitis and metabolic syndrome (of which prediabetes is a component). Most of this research has been cross-sectional (Chen et al., 2011; D'Aiuto et al., 2008; Han et al., 2010; Khader et al., 2008; Morita et al., 2009; Shimazaki et al., 2007; Timonen et al., 2010). Associations were found between MeS and periodontitis in each of these studies. Generally, the greater the number of MeS components, the more severe the periodontitis, or the stronger the association between the two conditions. Five studies demonstrated a significant association between the dysglycaemia component of MeS and periodontitis (D'Aiuto et al., 2008; Han et al., 2010; Khader et al., 2008; Morita et al., 2009; Shimazaki et al., 2007); one study found no association (Timonen et al., 2010); and one reported unadjusted associations only between periodontitis and individual MeS components (Chen et al., 2011). The findings of two studies were limited by the use of the CPI score to record periodontal status (Han et al., 2010; Morita et al., 2009). Many of the samples were not representative of the general population (Chen et al., 2011; Han et al., 2010; Khader et al., 2008; Morita et al., 2009; Timonen et al., 2010); one was (D'Aiuto et al., 2008); and one sample was female only (Shimazaki et al., 2007). All adjusted for some confounding factors. The different studies used different case definitions to categorise periodontal status, and the cross-sectional design of these studies meant temporality could not be implied.

Nibali et al. compared some MeS markers (serum triglycerides, HDL and glucose levels) and inflammatory markers (total and differential leukocyte counts) in people with and without severe periodontitis (Nibali et al., 2007). They found those with severe periodontitis (cases) had higher serum glucose levels and leukocyte counts, and worse dyslipidaemia profiles, when compared with those without severe periodontitis (controls). The study was described as “case-control”. While a control (people without severe periodontitis) was used, both the blood sampling and periodontal examinations were carried out at the same point in time, so this study may be better described as cross-sectional. Case-control study designs

generally involve “working backwards in time” to determine exposure information. In any case, no conjectures relating to temporality can be raised by this study.

Morita and associates carried out a prospective cohort study over four years to examine the impact of periodontitis on the development of MeS (Morita et al., 2010). Periodontal status (as measured by CPI score) at baseline was found to predict the number of MeS components four years later. These associations were independent of age, gender, smoking, exercise and eating habits and weight. Individuals with any of the MeS components at baseline were excluded, so a temporal relationship between the two conditions was demonstrated with periodontitis preceding conversion to one or more MeS components. Unfortunately, the follow-up periodontal data were not presented, and it is possible participants’ periodontal status had changed over the four years. With respect to conversion to individual components, periodontitis predicted hypertension and dyslipidaemia, but not obesity or hyperglycaemia. The participants in this study were derived from the 2009 study sample (Morita et al., 2009); and the later study had the same shortcomings of lack of generalizability and use of the CPI score (Morita et al., 2010).

1.2.8 Two-way links between dysglycaemia and periodontitis

This literature review has shown there is firm support for the notion that chronic hyperglycaemia in type 2 diabetes contributes to periodontitis; that periodontitis can negatively influence glycaemic control which, in turn, leads to a further periodontal deterioration. It is plausible that each condition exacerbates the other. In the words of Grossi and Genco, it is a “self-feeding” system of “catabolic response and tissue destruction” (Grossi and Genco, 1998).

Attempts to further clarify the bidirectional relationship between type 2 diabetes and periodontitis should consider at what stage in the dysglycaemia continuum this relationship begins. For example, is there a bidirectional link between prediabetes and periodontitis? The possibility that an individual with prediabetes has an increased risk of periodontitis, and subsequently this periodontitis increases the risk the prediabetes will eventually progress to type 2 diabetes, is an intriguing one. It is also one with profound public health implications, yet has received scant attention to date.

This review has highlighted some other gaps in the research to date. The revised American Diabetes Association recommendation for lower HbA1c cut-off points for prediabetes and type 2 diabetes (and the rationale behind this) reflects the fact that people with lower levels of dysglycaemia are at risk of poor cardiometabolic outcomes. Therefore prevalence and incidence data for these populations are a priority. There is an urgent necessity to track the evolution of early dysglycaemia as it progresses to further disease (or to resolution), and determine the factors that contribute to the eventual outcome. Studies have examined dysglycaemia in children and adolescents; however, there is little research following populations from young adulthood onwards in early middle age – a crucial time for preventive intervention.

1.2.9 Research objectives

The study will use data from the Dunedin Multidisciplinary Health and Development Study (DMHDS) to explore the two-way relationship between periodontal disease and glycaemia over twelve years. The DMHDS is a longitudinal epidemiological study of a birth cohort with a large, representative sample size, and an excellent retention rate. Data have been gathered through the life course with both glycaemic and periodontal data collected at ages 26, 32 and 38. Data have also been collected over the years on a wide range of potential risk, ameliorating, exacerbating and confounding factors.

The thesis has the following objectives:

- Glycaemia data (HbA1c assays) collected during assessments at ages 26, 32, and 38 will be used to assess the incidence, prevalence and natural history of dysglycaemia (encompassing both prediabetes and type 2 diabetes) in the cohort. With three time points, trajectories can be identified by trajectory analysis. Associations with other variables would be identified.
- Periodontal data (combined AL) collected during assessments at ages 26, 32, and 38 will be used to assess the incidence, prevalence and natural history of periodontitis in the cohort. With three time points, trajectories can be identified by trajectory analysis. Associations with other variables would be identified.
- HbA1c levels/dysglycaemia will be examined as a risk factor for periodontal disease from age 26 through to age 38.

- Periodontal disease will be examined as a risk factor for HbA1c levels/dysglycaemia from age 26 through to age 38.

Two hypotheses will be tested (1) that dysglycaemia is a risk factor for periodontal disease from age 26 through to age 38; and (2) that periodontal disease is a risk factor for dysglycaemia from age 26 through to age 38.

In view of the prevalence of both periodontal disease and type 2 diabetes (and the burden of diabetes complications), research to investigate these two-way relationships is crucial. The DMHDS is particularly well placed to elucidate the bidirectional links and complex associations between periodontal disease and dysglycaemia, and will provide a unique opportunity to explore the temporal relationship between them. This study is both essential and timely, and may contribute to the future management of prediabetes, diabetes, and diabetic complications. If this is the case, the public health significance will be substantial.

2 Methods

2.1 The participants

This study used data collected during the age-26, age-32 and age-38 assessments of the Dunedin Multidisciplinary Health and Development Study (DMHDS), and the utilisation of novel and advanced statistical techniques to analyse these data. The DMHDS is a longitudinal health and behavioural epidemiological study of a birth cohort of 1,037 children born in Dunedin, the major city of the province of Otago in the South Island of New Zealand, between 1 April 1972 and 31 March 1973. A total of 1661 children were born at the Queen Mary Hospital, the only maternity hospital in Dunedin, between these dates. Perinatal, demographic and anthropometric data were collected for these children at birth. By age three, twelve children had died, and 510 were no longer living in Otago. The 1037 children represent 91% of the 1139 eligible (still living in Otago at age three) children born between these dates (McGee and Silva, 1982). In terms of prenatal, birth and neonatal characteristics, the 102 (9%) who declined participation at age three did not differ from those who did enrol in the longitudinal study (Poulton et al., 2015; Silva and McGee, 1984). Nor did they differ from the 522 who were either deceased, or no longer living in Otago (McGee and Silva, 1982). The children were assessed at the DMHDS research Unit for the first time within a month of their third birthday, and subsequently at ages 5, 7, 9, 11, 13, 15, 18, 21, 26, 32 and 38 years, thus spanning the life course from birth to adulthood (Poulton et al., 2015). The original cohort was made up of 1013 singletons and 24 twins. The sample at age three consisted of 535 (51.6%) boys and 502 (48.4%) girls. Of these children, 1000 were still alive in 2015. The 7.5% who self-identified as Maori matches the ethnic make-up of the South Island of New Zealand (Poulton et al., 2015). Ethics approval for each assessment phase was granted by the Otago Research Ethics Committee, and study members gave informed consent before participating.

Great importance is placed on the retention of study members. A total of 980, 972 and 961 individuals participated in the age 26, age 32 and age 38 assessments respectively; this exceptionally high retention rate represents over 95% of the surviving cohort.

At each assessment, Study members come to the DMHDS Unit for a full day of examinations and interviews (a few study members were interviewed by unit staff elsewhere). Potential barriers to Study members' participation were reduced by the Study Unit covering members' costs (travel from anywhere in the world, accommodation, child care and car parking). In addition, participants could choose their preferred assessment day. The Study has a large, representative sample size enabling statistical estimations with good power with data collected over the years on a comprehensive range of physical, mental and psychosocial factors.

2.2 Measurement of exposure and outcome variables

The age 26 assessments were carried out in 1998-99, the age 32 assessments in 2003-2005, and the age 38 assessments in 2010-2012. Periodontal data and glycaemic data (along with data on a range of potential risk and confounding factors) were collected at each assessment.

2.2.1 Periodontal measurements

Periodontal examinations were conducted at ages 26, 32 and 38, with half-mouth examinations at age 26 but full-mouth examinations at ages 32 and 38. Calibrated examiners carried out the periodontal examinations at each assessment. Third molars and implants were not included in the periodontal examinations. If a tooth was absent, the reason for its absence was determined (by asking the study member) and the age at which the tooth was lost was recorded.

2.2.1.1 Age 26

Three calibrated examiners carried out periodontal examinations on 918 of the 980 Study members who attended the age 26 assessment. Of the 980, two Study members were edentulous, 45 either declined to have an oral examination or could not attend for one, and 15 were excluded due to a history of cardiac valvular abnormalities or rheumatic fever. The examiners assessed 85%, 10% and 5% respectively of the Study members. Due to time limitations, periodontal measurements were made in two quadrants; the upper right and lower left quadrants for those whose Study ID number was odd, and the upper left and lower right for those whose Study ID number was even. The mix of odd and even numbers was approximately even. Three sites (mesio-buccal, buccal and disto-lingual) per tooth were examined. A NIDR probe (the Hu-Friedy PCP-2) was used; this has 6 alternating 2mm bands and a rounded tip. Midbuccal measurements for molars were made at the midpoint of the mesial root, and measurements were rounded down to the nearest whole millimeter. Two measures were recorded: gingival recession (GR; the distance in millimetres from the gingival margin to the cemento-enamel junction) and probing depth (PD; the distance from the gingival margin to the tip of the probe). Gingival recession was recorded as a negative where the gingival margin was situated more than 1mm coronally to the cemento-enamel junction (as would be the case in gingival hyperplasia). The attachment loss (AL) for each site was computed by summing the GR and PD measurements.

Gingival bleeding on probing was assessed for each tooth by observing the presence or absence of bleeding at each of the three probing sites. If bleeding was observed 10 seconds after probing, then "bleeding on probing" (BOP) was recorded for that tooth. From this, the percentage of teeth which bled on probing was computed for each Study member.

A modified version of the simplified oral hygiene index was used to quantify plaque accumulation (Greene and Vermillion, 1964). Six index teeth were scored according to the amount of plaque detectable with an explorer. No detectable plaque scored 0, plaque covering no more than the cervical third of the tooth scored 1, plaque covering more than the cervical third of the tooth but no more than two-thirds scored 2, and plaque covering more than two-thirds of the tooth scored 3. The overall plaque score was the sum of the scores divided by the number of teeth scored. In addition, Study members were categorised according to their plaque score at all three ages 26, 32 and 38: score 0 to 0.5 "Very low"; score >0.5 to 1.0 "Low"; score >1.0 to 1.5 "Moderate"; and score >1.5 "High".

2.2.1.2 Age 32

The Phase 32 assessments commenced in November 2003 and ran until the middle of 2005. During this time, 972 current study members (almost 96% of the surviving 1015) were assessed. At this assessment, three Study members were edentulous, 34 either declined to have an oral examination or could not attend for one, and 17 were excluded due to a history of cardiac valvular abnormalities or rheumatic fever. The remaining 918 participants had a periodontal examination in which the clinical procedures were the same as at age 26, except that a full-mouth examination was possible this time; three sites per tooth were examined in all four quadrants. Measures for gingival bleeding on probing, and plaque score, were also recorded. This time, two calibrated examiners were used, and they examined 53% and 47% of Study members respectively. The second examiner was the same one who had carried out 85% of the examinations at age 26.

2.2.1.3 Age 38

At age 38, the clinical procedures were identical to the age 32 assessment. Three calibrated examiners were used; they examined 58%, 39% and 3% of Study members respectively (the former two had undertaken the age 32 examinations). By this time, seven Study members were edentulous. Some 54 Study members either declined to have an oral examination or

could not attend for one, or they had a history of cardiac valvular abnormalities or rheumatic fever. The remaining 900 participants had a full-mouth periodontal examination in which the clinical procedures were exactly the same as at age 32.

2.2.1.4 Periodontal prevalence case definition, extent and severity

At each age, three different case definitions for the prevalence of periodontal disease were determined by identifying Study members with 1+ sites with 4+mm AL, with 2+ sites with 4+mm AL, and with 1+ sites with 5+mm AL (Thomson et al., 2007). Two different measures of the extent of periodontal disease were obtained by computing the percentage of sites with 4+mm AL, or 5+mm AL, for each participant. Finally, severity of periodontal disease was estimated by calculating mean AL. Half-mouth data was used at all ages for analyses to enable longitudinal comparisons.

2.2.1.5 Periodontal examiner reliability

Replicate examinations were not carried out at age 26 due to time constraints (participants undergo a very busy assessment day with the dental examinations being carried out at the end of the day) so examiner reliability data were not available for the age 26 assessment.

Replicate examinations were conducted on a separate sample of 16 adults on four occasions during the age 32 data collection phase, giving data for 1,423 measured sites (Thomson et al., 2006). Intra-examiner reliability coefficients for absolute agreement of the site-level periodontal measurements pooled for the two examiners (with individual examiner intra-examiner reliability coefficients in parentheses) were 0.93 (0.94, 0.89) for mean GR, 0.68 (0.46, 0.83) for mean PD, and 0.69 (0.66, 0.86) for mean AL. Cohen's kappa coefficient (a measure of inter-examiner agreement) for the prevalence of 1+ sites with 4+ mm AL was 0.5 (0.7, 0.8). Of the 1,423 replicated pairs of measurements for AL, only 0.4% differed by 3+ mm (99.6% were within ±2 mm). Accordingly, intra- and inter-examiner reliability at age 32 was acceptable (Goodson, 1986).

As at age 32, replicate examinations were conducted on a separate sample of adults during the age-38 assessment; these gave data for 672 periodontal sites measured by the three examiners twice each. Intra-examiner reliability coefficients for absolute agreement of the site-level periodontal measurements were pooled for the three examiners (with individual

examiner intra-examiner reliability coefficients in parentheses). These were found to be 0.95 (0.99, 0.92, 0.94) for GR; 0.73 (0.73, 0.69, 0.80) for PD; and 0.71 (0.71, 0.68, 0.79) for AL; and 0.75 (0.99, 0.74, 0.97) for the prevalence of 1+ sites with 4+mm AL (Zeng et al., 2014). When intra-examiner reliability was pooled for all three examiners, only 2.6% of measurements differed by >1 mm, and no measurements differed by >2 mm. This indicates high intra-examiner reliability as 1 mm within and among examiners is considered to be normal measurement error for GR, PD, and AL (Goodson, 1986). In a similar manner, inter-examiner reliability at age-38 was also high. Of all the sites assessed for AL, each of the examiners differed from the other examiners by 1+mm in no more than 5.4% of measurements, and by 2+mm in no more than 0.8% of measurements (Zeng et al., 2014). Thus intra- and interexaminer reliability was high, and was similar to that reported in other studies (Goodson, 1986).

2.2.2 Glycated haemoglobin

Glycated haemoglobin (HbA1c) was measured during assessments at ages 26, 32, and 38 in order to quantify chronic glycaemia. Not all Study members consented to venepuncture. To ensure the validity of the data, HbA1c assays were not carried out on pregnant women (33 women at age 26, 31 at age 32 and 9 at age 38); HbA1c levels vary significantly during pregnancy (Nielsen et al., 2004). In addition, there were four individuals with Type 1 diabetes in the cohort; these individuals were excluded from all analyses. In total, HbA1c data was available for 836 Study members at age 26, 858 at age 32 and 891 at age 38.

Venepuncture was conducted by a registered nurse between 16:15 and 16.45 at each assessment. The blood samples collected at age 26 were processed and aliquoted, then stored at -80º Celsius controlled temperature. Age 26 HbA1c was then assayed in 2002 using ion-exchange high performance liquid chromatography (HPLC) on a BioRad Variant II (Bio-Rad, Hercules, California). HbA1c was measured at 32 and 38 using ion-exchange HPLC on a BioRad Variant II and a BioRad Variant II Turbo (Bio-Rad, Hercules, California) respectively.

HbA1c is presently reported in two different units: the older National Glycohemoglobin Standardization Program (NGSP) units, whereby HbA1c is expressed as a % of total haemoglobin; and the International Federation of Clinical Chemistry (IFCC) reference system, where it is expressed in SI (Sisteme Internationale) units (mmol/mol). The age 38 data were reported in both units at the time of measurement; the age 26 and 32 data were converted to the IFCC SI units using the master equation IFCC-HbA1c (mmol/mol) = [NGSP-HbA1c (%) - 2.15]*10.929.

The prevalence of diabetes and prediabetes was defined according to the American Diabetes Association (ADA) guidelines, whereby prediabetes was defined as 39 to 47 mmol/mol HbA1c, and diabetes as ≥48 mmol/mol HbA1c (American Diabetes Association, 2011). Dysglycaemia (defined as ≥39 mmol/mol HbA1c) encompasses both of these.

2.3 Measurement of risk variables

A range of potential risk and confounding factors were assessed at each assessment age. These include sociodemographic factors, health- and oral health-related behaviours, and anthropometric factors.

2.3.1 Socioeconomic status

Measures of socioeconomic status (SES) were obtained for each Study member. Childhood SES is an established risk factor for poorer health outcomes in adulthood (Poulton et al., 2002; Thomson et al., 2004). In the DMHDS childhood SES was measured on the basis of the parents' occupational status (the average of the highest SES level of either parent) assessed repeatedly from Study members' birth to age 15. SES at ages 26, 32 and 38 was obtained from each Study member according to their own occupation. The childhood and age 26 measures used the Elley-Irving 1985 scale which applied a six-category grouping of occupations (Elley and Irving, 1985; Poulton et al., 2002). However, this scale did not classify students, the unemployed, retired people or homemakers. The age 32 measure used the New Zealand Socio-Economic Index (NZSEI) which was developed to replace the Elley-Irving scale. This scale applies a six-interval, occupationally-based classification of socioeconomic status which also allowed classification of those individuals outside the labour market (Davis et al., 1997; Davis et al., 2003). As an example, a doctor scores "1" and a labourer scores "6" on both scales. Study members with a score of "1" or "2" were allocated to the "High" SES group; those with a score of "3" or "4" were assigned to the "Medium" SES group; and those with a score of "5" or "6" were assigned to the "Low" SES group. An updated version of the scale (NZSEI-06) was similarly used to categorise Study members in "High", "Medium" and "Low" SES groups at age 38 (Milne et al., 2013). A comparison between NZSEI-06 and the earlier NZSEI showed that both scales classified individuals from the 2006 Census similarly, but not identically (Milne et al., 2013).

2.3.2 Smoking

Associations between tobacco smoking and periodontal disease are well documented (Gelskey, 1999; Thomson et al., 2007; Zeng et al., 2014); links between cannabis use and periodontal disease have been found more recently (Thomson et al., 2008; Zeng et al., 2014). Study members were questioned on their smoking history at ages 26, 32 and 38. Current smokers were those who gave a positive response to the question "Have you

smoked every day for one month or more of the previous 12 months?". Current and ex-smokers were also asked about the number of cigarettes smoked per day and the number of years at this level of consumption. These data were used to compute "pack-years to age 26", "pack-years to age 32" and "pack-years to age 38" for each individual; this represents the number of packs of cigarettes smoked per day multiplied by the number of years smoked at that rate. Pack-years may be regarded as a measure of cumulative smoking risk, and "10 pack-years" could be interpreted variously as a pack a day for 10 years, or half a pack a day for 20 years, or two packs a day for five years.

2.3.3 Cannabis use

Cannabis smoking was assessed at all three ages. Frequency of cannabis use was determined by asking participants how many times in the previous year they had smoked cannabis. Those who reported no cannabis use in the previous year were assigned to the "no cannabis use group"; the remainder were categorised as "less than weekly" or "weekly or more" according to their answer to the frequency question. A further category of "regular users" comprised those who typically used cannabis 4+ times weekly in the previous year.

2.3.4 Alcohol use

Research suggests a U-shaped dose-response relationship between alcohol consumption and type 2 diabetes; moderate consumption may be protective for type 2 diabetes but the opposite is true for heavier consumption (Baliunas et al., 2009). Study members were asked the following at ages 26, 32 and 38: 1) how many weeks in the past year they'd used alcohol; 2) how many drinks (standard units) they'd usually have Monday to Thursday; and 3) how many drinks (standard units) they'd usually have Friday to Sunday. The latter two questions were used to calculate the total number of alcohol units consumed per week at each of the three ages.

2.3.5 Physical activity

There is convincing evidence of a reduced risk of Type 2 diabetes associated with regular physical activity (World Health Organization, 2003). In the DMHDS, exercise frequency was assessed at ages 32 and 38; comparable data were not available for exercise at age 26. Exercise activities included occupational and household tasks, and sport/leisure activities. The mean number of hours during weekdays and weekends for all forms of exercise –

moderate, hard and extreme – was recorded at ages 32 and 38. Moderate exercise involved activities such as gardening, brisk walking and golf. Hard exercise comprised building, chopping wood and running ≥8 km/hour. Extreme exercise included firefighting, karate and cross-country skiing at a vigorous pace. These exercise data were converted to Metabolic Equivalent Hours (MET) whereby one hour of moderate activity was equivalent to four MET, one hour of hard activity was equivalent to seven MET and one hour of extreme activity was equivalent to 10 MET (Ainsworth et al., 2011). The total MET hours per week was computed by summing MET hours from each activity type. A MET is defined as the ratio of the energy expenditure of a given activity to the energy expenditure at rest (Moore et al., 2012). Thus the greater the energy expenditure of the activity, and the longer its duration, the higher the MET will be. It provides a mechanism for quantifying exercise activity across different individuals with different levels and durations of activity.

2.3.6 Use of dental services

Non-routine use of dental services is a known risk factor for poorer oral health (Thomson et al., 2010). Data on use of dental services was collected at ages 26, 32 and 38. Study members were asked whether they usually visited the dentist for a check-up or visited only to have a problem addressed (episodic attender), and the length of time since their previous visit was recorded (Thomson et al., 2010). A routine attender was determined to be one who (1) usually visited for a check-up, and (2) had attended within the previous year.

2.3.7 Anthropometric measures

Anthropometric parameters assessed at ages 26, 32, and 38 included height, weight, waist circumference (WC) and hip girth. These were assessed by anthropometrist-trained health professionals, with participants in the standing position, head and eyes directed forward and arms hanging by the sides. Height was measured on a portable stadiometer in bare feet to the nearest 1 mm, with feet together and standing as tall as possible. Body weight was recorded using calibrated scales in light clothing to the nearest 0.1 of a kilogram. Individual body mass index (BMI) was computed using the formula: BMI = weight in kg/(height in meters)^2. WC was recorded by measuring girth to the nearest 1 mm at the skin, using a steel tape calibrated in centimetres with millimetre gradations. It was taken at the level of the noticeable waist narrowing located approximately halfway between the costal border and the iliac crest; it was measured at the time of greatest expiration, and with instructions to

relax the diaphragm. Hip girth was taken as the perimeter at the level of the greatest protuberance and at about the symphysion pubic level anteriorly. Measurements were taken twice and the mean of two readings calculated. Waist-hip ratio and waist-height ratio were recorded as the ratio of the WC to that of the hips, and to that of the person's height respectively.

In addition to these outcome covariates being used as continuous variables, BMI, WC, waist-hip ratio and waist-height ratio were also dichotomised according to established guidelines for greater risk of cardiometabolic complications. The WHO classifies BMI 30+ as obese (National Health and Medical Research Council, 2013; National Institutes of Health, 1998; World Health Organisation, 2006). Guidelines for waist circumference differ according to sex, ethnicity, country and the organisation proposing the guideline, but women and men are generally considered to be at much higher risk at 880+mm and 1020+mm respectively (National Health and Medical Research Council, 2013; National Institutes of Health, 1998). Abdominal obesity is defined as a waist-hip ratio of more than 0.85 for females, and more than 0.90 for males (World Health Organisation., 2008). A waist-height ratio of 0.50+ is generally regarded as being of higher risk for both sexes (Ashwell et al., 2012; Browning et al., 2010; Hsieh et al., 2003). Thus, the covariates were dichotomised as per the table below (Table 2.1).

Table 2.1. Cut-off points for high risk anthropometric covariates and high risk group by sex.

Covariate	**High risk group**	**Cut-off point**
BMI	High BMI group	30+
Waist circumference	High WC group	880+mm (women) 1020+mm (men)
Waist-Hip ratio	High waist-hip group	0.85+ (women) 0.90+ (men)
Waist-Height ratio	High waist-height group	0.50+

2.4 Statistical analysis

2.4.1 Descriptive and bivariate analyses

Analyses began with an attrition analysis followed by a description of the cohort at ages 26, 32 and 38. This was followed by both cross-sectional bivariate analyses at each age, and longitudinal bivariate analyses for data at 26 and 32; 26 and 38; and 32 and 38. Chi-square tests and Fisher's exact tests were used to examine the statistical significance of associations observed between categorical variables. Mann-Whitney U tests and Kruskal-Wallis tests were used to test the statistical significance of associations between independent variables and continuous dependent variables. Spearman's rho correlations were used to explore relationships between continuous independent and dependent variables. Statistical tests were two-tailed and the threshold for statistical significance was set at $p<0.05$. All descriptive and bivariate analyses were conducted using either SPSS version 20 (SPSS Inc. Chicago, Illinois) or Stata IC 12.0 for Windows (StataCorp 2011, *Stata Statistical Software: Release 12*, College Station, Tx, USA).

2.4.2 Longitudinal analyses

The defining feature of longitudinal studies such as the DMHDS (that involve repeated measurements of the same variables for each participant over a period of time) is precisely what makes their analyses so complex. While there have been extensive methodological developments for the analysis of such data in recent years it remains a challenging undertaking. There is no "perfect" method of carrying out analyses with each of the various statistical methods available having their limitations (Tu et al., 2013). Problems that may be encountered include large variations in the response profile among individuals (some are intrinsically high responders, others are low responders); missing data; lack of statistical independence between observations on the same individuals at different times; non-homogeneity of variance; and measurement error (Diggle et al., 2002). Ignoring these matters will generally result in biased estimates, and may result in inaccurate conclusions (Fitzmaurice et al., 2004). Since different methods have different strengths and weaknesses, a combination of diverse techniques may be a valid approach to unravel the complexities observed in longitudinal research and draw more reliable conclusions from the information-rich data (Tu et al., 2013).

First, group based trajectory modeling (GBTM) was used to describe the natural history of the outcomes of interest, to explore the impact of risk factors on them and investigate their influence on each other. A second analysis of the longitudinal data was carried out using linear mixed effect modeling which integrates both fixed and random effects. The aim of this was to provide a methodological complement to the GBTM analysis, to provide analytical triangulation and so give the thesis findings more rigour. Thus, the complex relationship between periodontal disease and glycaemia was investigated in two different ways.

2.4.2.1 Group based trajectory modeling (GBTM)

A primary aim of this research was to describe the natural history of two outcomes: periodontal condition (as measured by extent of 4+mm AL); and glycaemia (as measured by HbA1c) over 12 years. The evolution of an outcome over time is its developmental trajectory, and it was hypothesised that there were groups of individuals within the cohort that follow distinctive developmental trajectories that were not identifiable prior to analysis (Nagin, 1999). GBTM was used to identify latent trajectory groups for both periodontal experience and HbA1c levels from age 26 to 38 (Nagin, 2005).

GBTM is a specialised application of finite mixture modeling and involves a procedure which gathers individuals into meaningful subgroups that show statistically similar trajectories. It provides a statistical method to identify (rather than assuming a priori) groups of distinctive trajectories which are summarised by a finite set of different polynomial functions of age or time, as determined by maximum likelihood estimation (Nagin, 1999; 2005). The maximisation is performed using a general quasi-Newton procedure (Jones and Nagin, 2012). Rather than prescribing the existence of trajectories of a specific form ex ante on the basis of an individual trait or traits, the method allows the trajectories to emerge from the data itself. This offers an alternative to the limitations of using assignment rules based on inherently subjective categorisation criteria; it determines the form and number of groups that best fit the data; and it provides a metric for evaluating the precision of group assignments (Nagin, 1999). GBTM predicts the trajectory of each group, the form of each trajectory, estimates the probability for each individual of group membership and assigns them to the group for which they have the highest probability.

GBTM handles missing data by fitting the model using maximum likelihood estimation. This will generate asymptotically unbiased parameter estimates assuming the data are missing at random (Nagin and Odgers, 2010). Data are considered to be missing at random (MAR) if the "missingness" is not related to the measured outcome. For both the periodontal and HbA1c GBTM, there were potentially three data points for each participant – at 26, 32 and 38. It was decided to include those who had data collected at two or more ages, and exclude those with fewer than two.

Trajectory groups are latent strata; that is, they are groups of individuals following approximately the same developmental course. Individuals do not actually *belong* to trajectory groups; rather, they are assigned a *probability* of group membership. Groups should not be reified (that is, should not be regarded as concrete or real). The cohort naturally follows a continuous rather than a discrete distribution; the model should then be regarded as a convenient statistical device, rather than a state of being, for summarizing trajectories in distinctive regions of the distribution (Nagin and Odgers, 2010). The number of trajectory groups is not immutable, and individuals do not follow the group-level trajectory in lock step (Nagin and Tremblay, 2005).

Generalisations of the GBTM model were used to (1) link baseline characteristics to the probability of group membership, and (2) to identify effect modifiers associated with deviations from the group trajectory (Nagin, 2005; Nagin and Odgers, 2010). GBTM analyses were undertaken using Stata IC 12.0 for Windows (StataCorp 2011, *Stata Statistical Software: Release 12*, College Station, Tx, USA).

While GBTM has been used extensively in delinquency trajectory research, it has only recently been used in oral health research (Broadbent et al., 2008; Thomson et al., 2013). Several developmental trajectory modeling techniques—including linear modeling, latent class growth–analysis, linear mixed modeling and group-based trajectory modeling (Gebregziabher et al., 2010; Heianza et al., 2012; Helgeson et al., 2010; Hilliard et al., 2013; Luyckx and Seiffge-Krenke, 2009; Wang et al., 2011)—have been used to track HbA1c over time. However, that research has focused on either populations with type 1 diabetes (Helgeson et al., 2010; Hilliard et al., 2013; Luyckx and Seiffge-Krenke, 2009; Wang et al., 2011), or on older populations with type 2 diabetes (Gebregziabher et al., 2010; Heianza et al., 2012). To date, GBTM has not been used to track HbA1c in initially healthy populations

from young adulthood onwards into early middle age, a potentially important time for intervention aimed at preventing progression to type 2 diabetes.

The GBTM was undertaken using a Stata Plugin for estimating group-based trajectory models (Jones and Nagin, 2013; Jones and Nagin, 2012). The Plugin generates parameter estimates which allow the calculation of a) the probability of group membership[8]; b) the predicted trajectory for each group[9]; and c) the posterior probabilities of group membership[10].

Mean HbA1c was modelled using the censored normal distribution (Jones and Nagin, 2013). Censors were set at values that were well beyond the range of any data values (minimum HbA1c = 10mmol/mol and maximum HbA1c = 150mmol/mol). Periodontal experience (as measured by the extent of 4+mm AL) was modelled using the zero-inflated Poisson distribution. We used the Bayesian information criterion (BIC)[11] as the criterion for model selection. However, this was moderated by (a) a preference for a useful parsimonious model which fitted the data well; (b) close correspondence between each group's estimated probability and the proportion of Study members classified to that group according to the maximum posterior probability assignment rule; (c) an average posterior probability (AvePP) value >0.7 for each group; (d) adequate sample numbers in each group; (e) reasonably narrow confidence intervals; and (f) the odds of correct classification based on the posterior probabilities of group membership >5 for each group (Nagin and Odgers, 2010). There is more information on these criteria and diagnostics, and how they were computed and interpreted, in the Results chapter (Section 3.5). Wald tests were used to test whether the model parameter estimates (intercepts and slopes) differed between trajectory groups.

Once GBTM groups were determined, bivariate associations between trajectory groups and covariates were tested for statistical significance using Chi-square tests for proportions, and

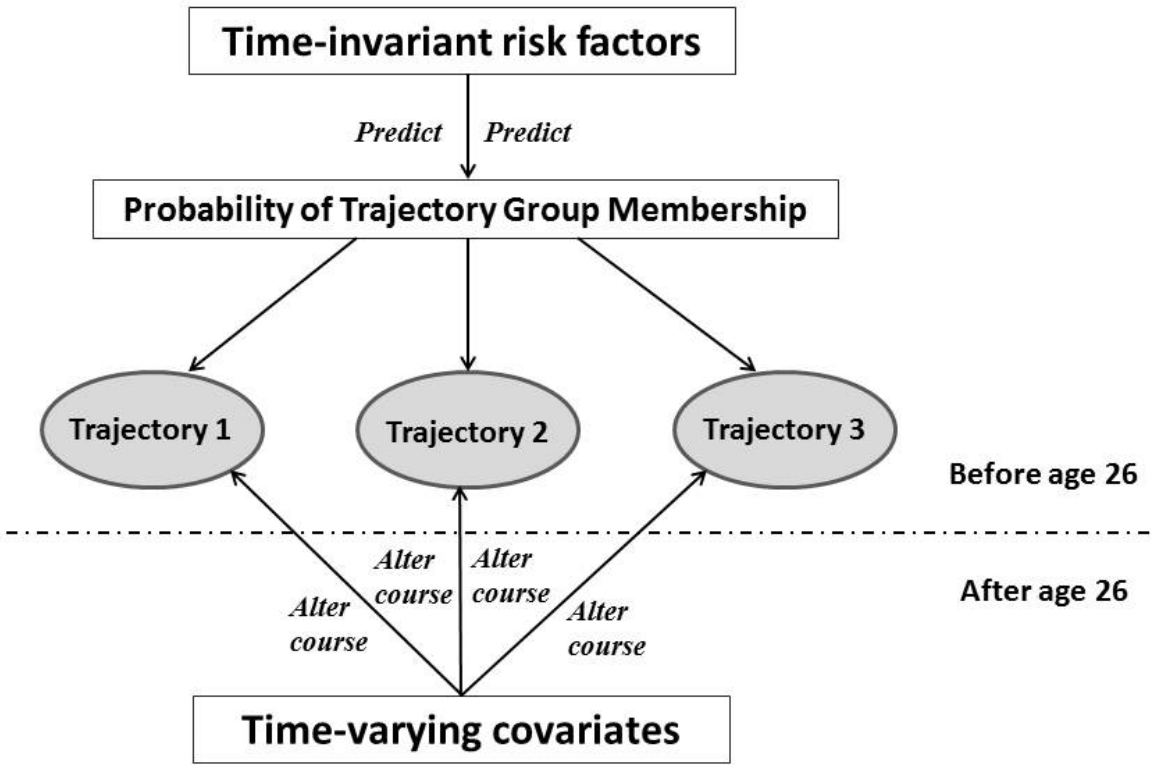
[8] The proportion of the population that belongs to each group.
[9] The capture of the essential features of a complex reality by a finite number of trajectory groups, each of a specific form, whether zero-order, linear, quadratic, cubic or higher.
[10] The collective measurement of each individual's probability of belonging to each trajectory group.
[11] The BIC (Bayesian information criterion) was introduced as an alternative to the Akaike information criterion (AIC) in 1978 (Schwarz, 1978). The two criteria are closely related, are both model selection criteria, and feature the same goodness-of-fit term. Generally the BIC penalises free parameters more strongly than does the AIC, so the BIC favours more parsimonious models. The model with the highest (least negative) value of BIC and AIC is preferred.

Kruskal-Wallis tests for means. Statistical tests were two-tailed and the threshold for statistical significance was set at $p<0.05$.

Two generalisations of the GBTM model were applied (Fig 2.1). The first was used to link baseline (at age 26 or earlier) or *time-invariant* individual characteristics and risk factors to the probability of group membership (Nagin, 2005; Nagin and Odgers, 2010). The association between each of these baseline characteristics and the probability of group membership was estimated simultaneously with the estimation of the trajectories themselves (Nagin, 2005). In GBTM, where there are more than two trajectory groups, associations are examined by specifying the probability of trajectory group membership to follow a multinomial logit model. The coefficients produced can be interpreted in terms of odds ratio (obtained by exponentiating the multinomial logit coefficients). Wald tests were used to test the equality of the time-invariant factors estimates across the trajectories.

The second generalisation applied added effect modifiers or *time-varying covariates* to the trajectories themselves (Fig 2.1). This examined whether events that occurred during the course of the trajectory altered its course (Nagin, 2005; Nagin and Odgers, 2010). For this generalisation the coefficients produced are interpreted in terms of how much higher or lower a trajectory is for each unit increase in the time varying covariate.

Fig 2.1. GBTM generalisations



(Adapted from (Nagin, 2005))

2.4.2.2 Linear Mixed Modelling

Linear mixed effects models (LMM) account for two common features of longitudinal data: non-independence of the observations and non-homogeneity of variance. First, longitudinal observations in the same participant over time are correlated. A response on one occasion predicts the likely value of the response on the next occasion, so the repeated measures cannot be regarded as independent from each other. Second, the variance of the response often changes over time. The lack of statistical independence and non-homogeneity of variance violate the assumptions of generalised linear modeling and other standard analytical techniques. LMM provides a technique for the analysis of longitudinal continuous data in which the residuals are normally distributed but may not have constant variance or be independent (West et al., 2014). LMM adjusts for the non-independence of the repeated observations within one individual by estimating the differences among all the individuals. The term "mixed" indicates that the model contains both (a) fixed effects (population characteristics assumed to be common to all individuals) and (b) random effects (characteristics that are specific to a particular individual). An added advantage is that cases with some missing values can be included in LMM analyses, thus minimising selection bias. In this thesis, LMM was used to quantify associations between continuous dependent variables (mean HbA1c and mean AL) and predictor variables while estimating covariance parameters to account for correlated observations.

Naïve regression model

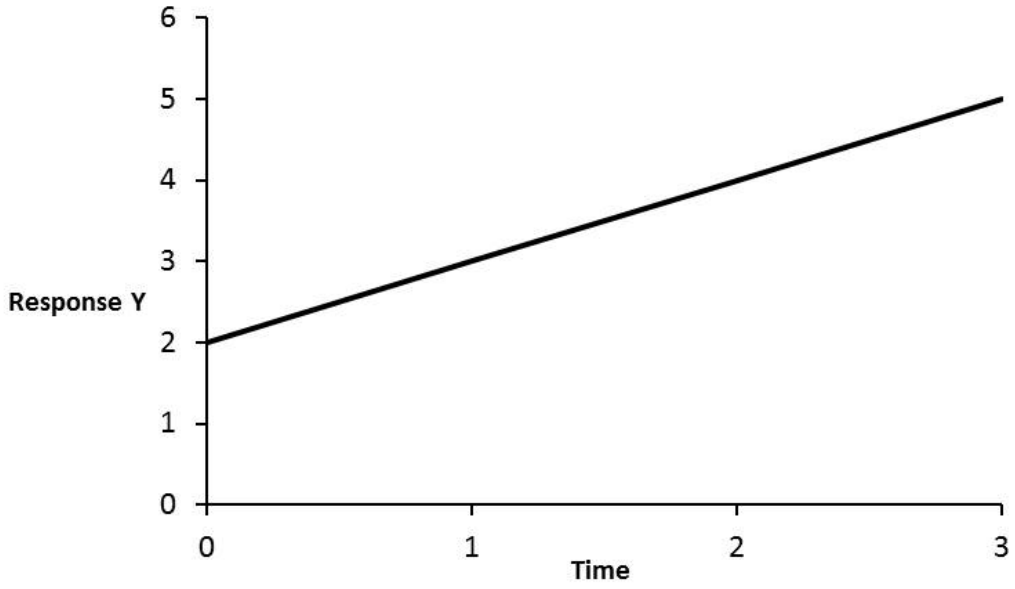
Assume that we are interested in the relationship between response variable Y and time-dependent variable X (could be age, years or hours etc). Consider first the simple 'standard' or 'naïve' regression model which ignores correlations between observations (Fig 2.2).

$$Y_{it} = \beta_0 + \beta_1 X_{it} + \varepsilon_{it}$$

where Y_{it} = response variable for individual i at time t; β_0 = intercept (value of Y when time = 0); β_1 = regression coefficient (slope) for X; X_{it} = time-dependent variable for individual i at time t; and ε = error or residual for individual i at time t.

The intercept β_0 and the regression coefficient β_1 form the "fixed" part of the model, and the difference between the observed response and the fixed part is the residual or "random" part of the model ε.

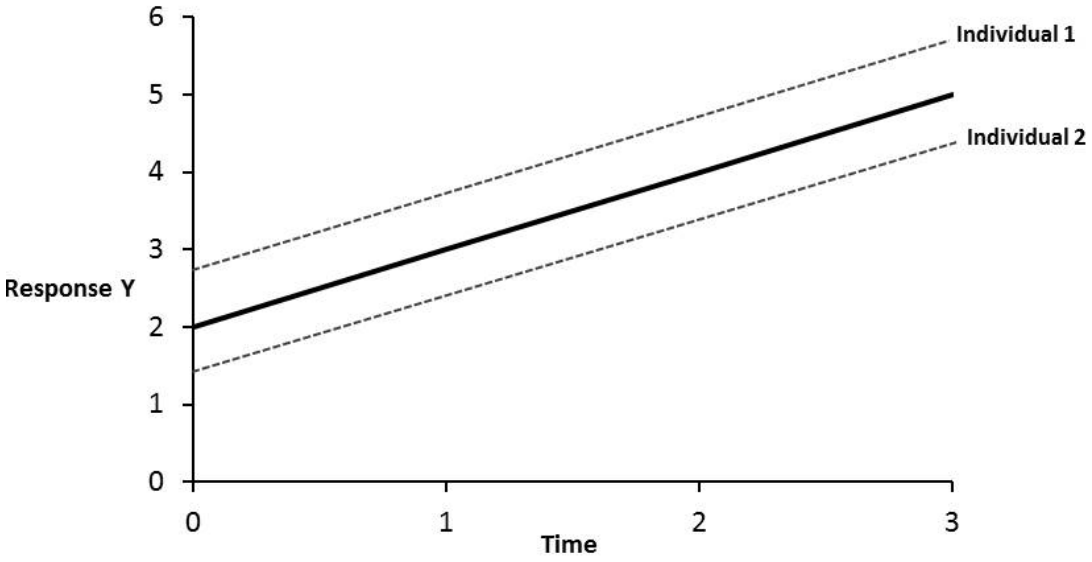
Fig 2.2. Naïve regression model.



Random intercepts models

Some individuals will have higher values than the mean response profile in the population (marginal mean) and some will have lower (Fig 2.3). The solid line denotes the marginal mean, and the broken lines denote the conditional (or subject-specific) response trajectories of two individuals, say 1 and 2. The intercept for individual 1 is higher than the marginal mean, and the intercept for individual 2 is lower than the marginal mean.

Fig 2.3. Marginal mean intercept and conditional intercepts.



The model could incorporate a correction using dummy variables for these two individuals whereby different intercepts are estimated for each.

$$Y_{it} = \beta_0 + \beta_1 X_{it} + \beta_2(\text{individual}_1) + \beta_3(\text{individual}_2) + \varepsilon_{it}$$

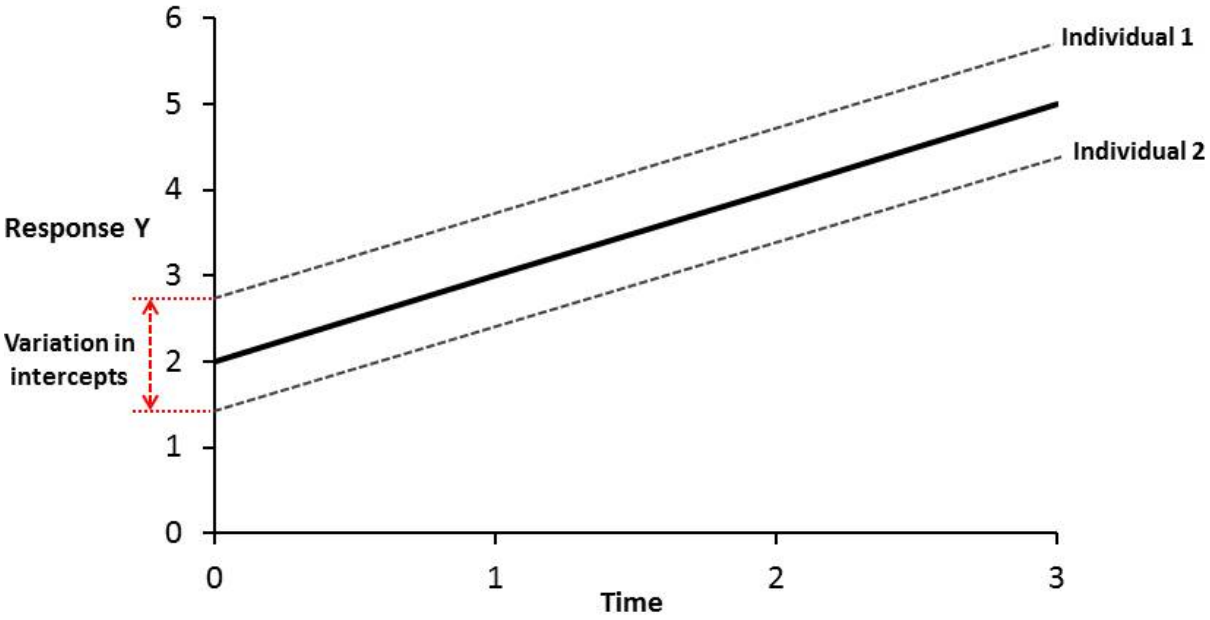
where Y_{it} = response variable for individual i at time t; β_0 = intercept (value of Y when time = 0); β_1 = regression coefficient (slope) for X; X_{it} = time-dependent variable for individual i at time t; β_2 = regression coefficient for dummy variable for individual 1; individual_1 = dummy variable representing individual 1; β_3 = regression coefficient for dummy variable for individual 2; individual_2 = dummy variable representing individual 2; and ε_{it} = error or residual for individual i at time t.

Estimating individual intercepts in this way for larger sample sizes is obviously impractical as the greater the number of individuals, the greater the number of dummy variables and consequent complexity involved. Instead, the random intercepts model provides an efficient, elegant and parsimonious method to incorporate individual intercepts into the model by estimating the variance of the intercepts, rather than estimating the separate intercepts themselves. The model assumes that there is a normal distribution of individual intercepts, and the variance of that distribution is estimated (Twisk, 2006). One variance parameter replaces all the parameters required for each individual. This random intercepts model is the simplest form of a LMM (Fig 2.4).

$$Y_{it} = \beta_{0i} + \beta_1 X_{it} + \varepsilon_{it}$$

where Y_{it} = response variable for individual i at time t; β_{0i} = random intercept; β_1 = regression coefficient (slope) for X; X_{it} = time-dependent variable for individual i at time t; and ε_{it} = error or residual for individual i at time t.

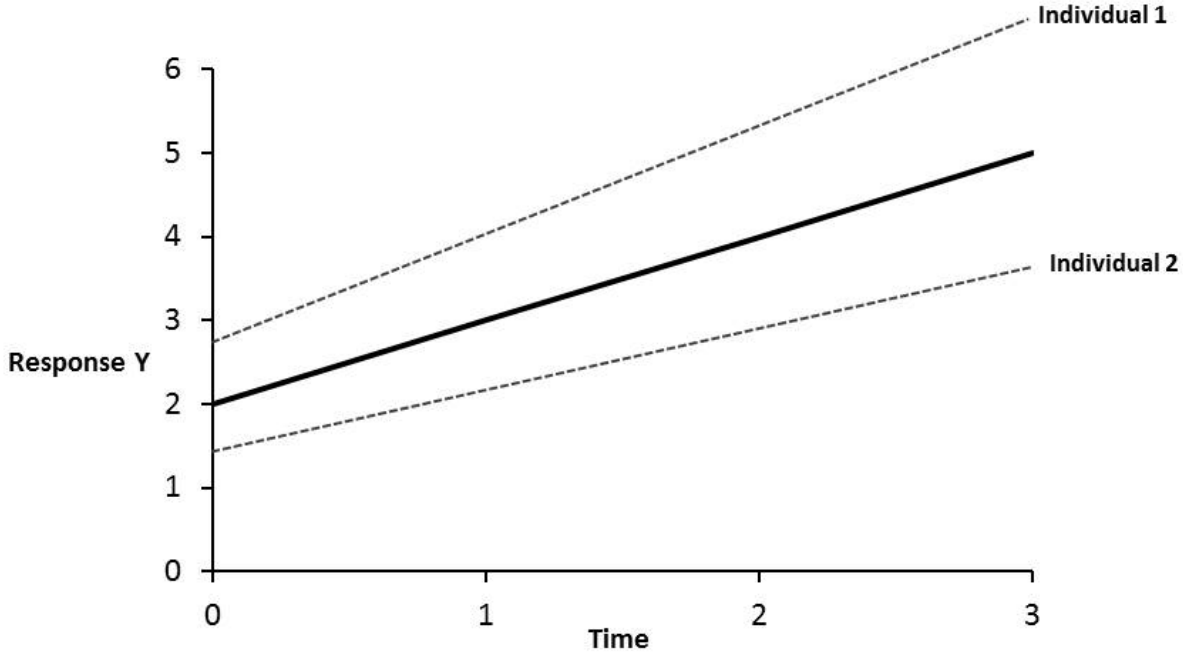
Fig 2.4. Random intercepts model



Random intercepts and slope models

Random intercepts and slope models expand on the random intercepts models by allowing each individual's value of the outcome variable to follow a unique trajectory over time. While the random intercepts model allows the intercepts to differ between individuals, their regression coefficients (slopes) are all the same. Different individual regression coefficients as well as intercepts are a common characteristic of longitudinal studies; in other words, there is an interaction between the individual and the time-dependent covariate X (Fig 2.5).

Fig 2.5. Interaction between individuals and the time-dependent covariate.



The model could correct for the different regression coefficients for these two individuals by incorporating dummy variables with interaction terms into the model.

$$Y_{it} = \beta_{0i} + \beta_1 X_{it} + \beta_2(\text{individual}_1 * X) + \beta_3(\text{individual}_2 * X) + \varepsilon_{it}$$

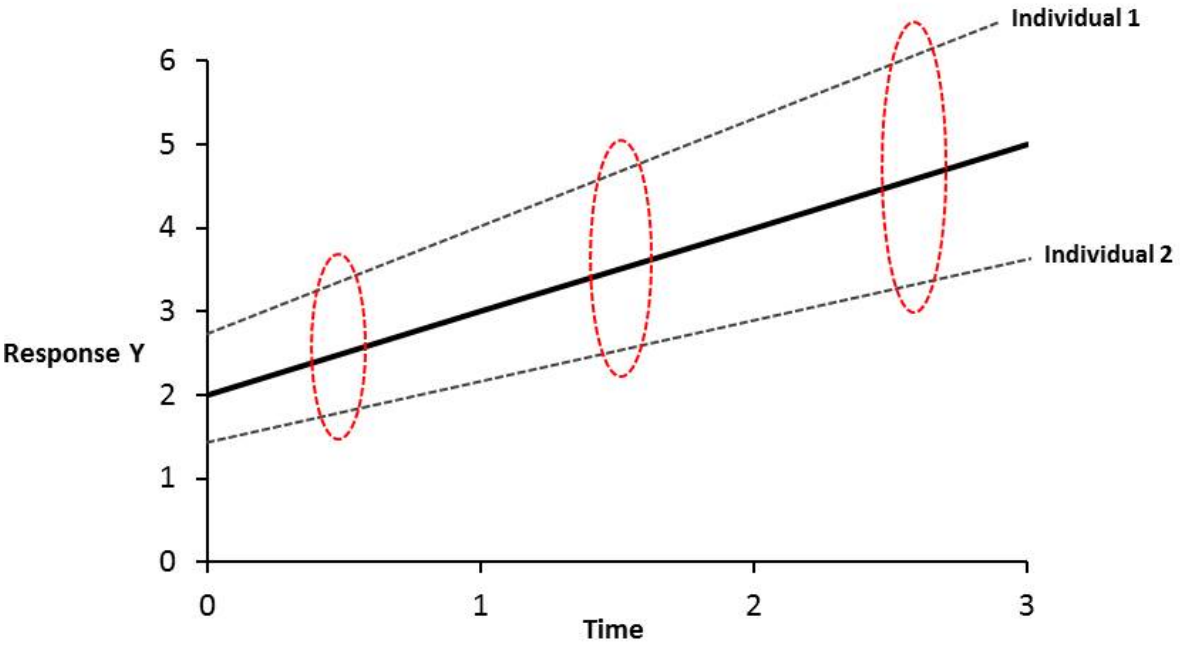
where Y_{it} = response variable for individual i at time t; β_{0i} = random intercept; β_1 = regression coefficient (slope) for X; X_{it} = time-dependent variable for individual i at time t; β_2 = regression coefficient for the interaction between the dummy variable for individual 1 and X; β_3 = regression coefficient for the interaction between the dummy variable for individual 2 and X; and ε_{it} = error or residual for individual i at time t.

As for the random intercepts model, this method becomes impractical for larger sample sizes and the parsimonious solution is as for the random intercepts model. A normal distribution is drawn around the regression coefficients, the variance of that distribution is estimated, and this variance parameter is added to the model (Fig 2.6)

$$Y_{it} = \beta_{0i} + \beta_{1i}X_{it} + \varepsilon_{it}$$

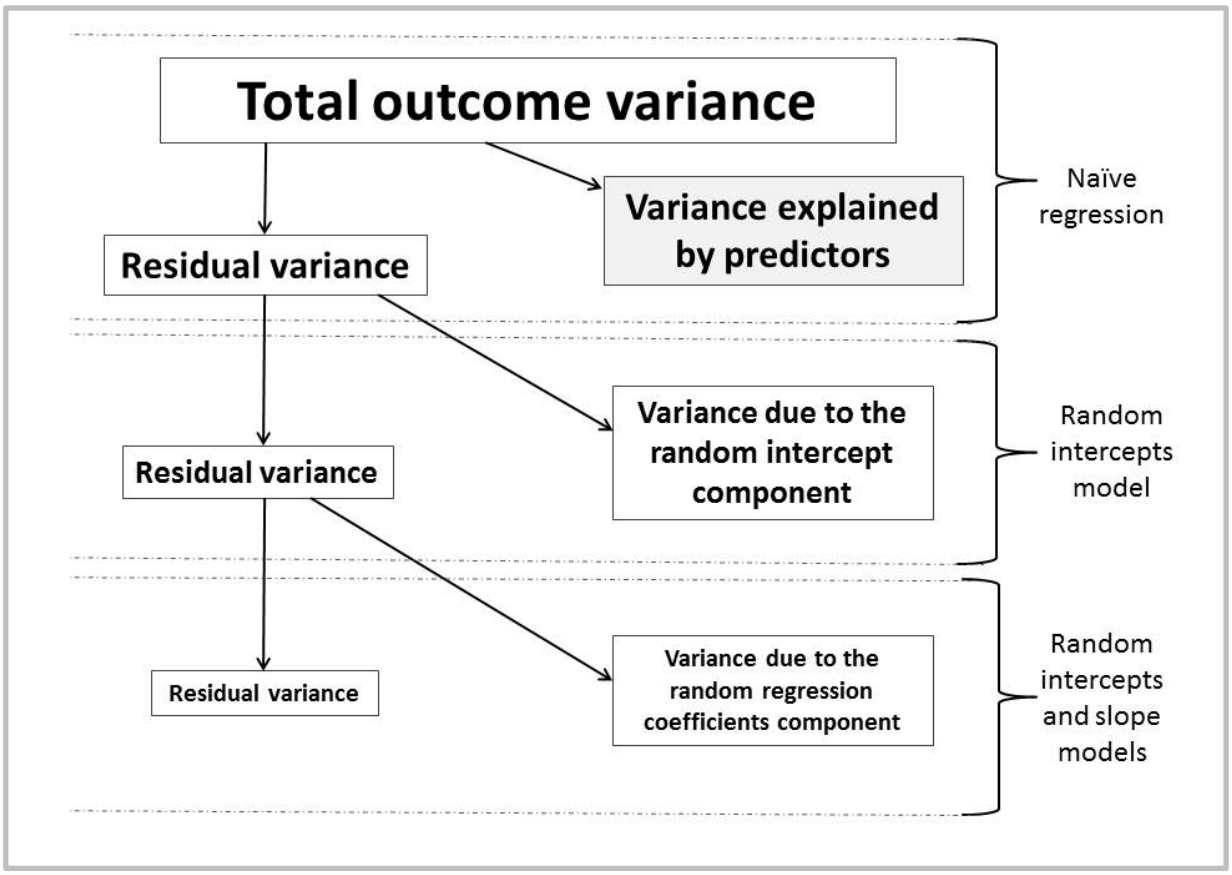
where Y_{it} = response variable for individual i at time t; β_{0i} = random intercept; β_{1i} = random regression coefficient (slope) for X; X_{it} = time-dependent variable for individual i at time t; and ε_{it} = error or residual for individual i at time t.

Fig 2.6. Random intercepts and slope models



Essentially, a LMM can control for the effect of individual variation. It gives structure to the residual or "random" part of the model by dividing it into (a) variance due to the random intercept component, (b) variance due to the random regression coefficients component, and (c) remaining residual variance (Fig 2.7).

Fig 2.7. Components of the residual part of the model.

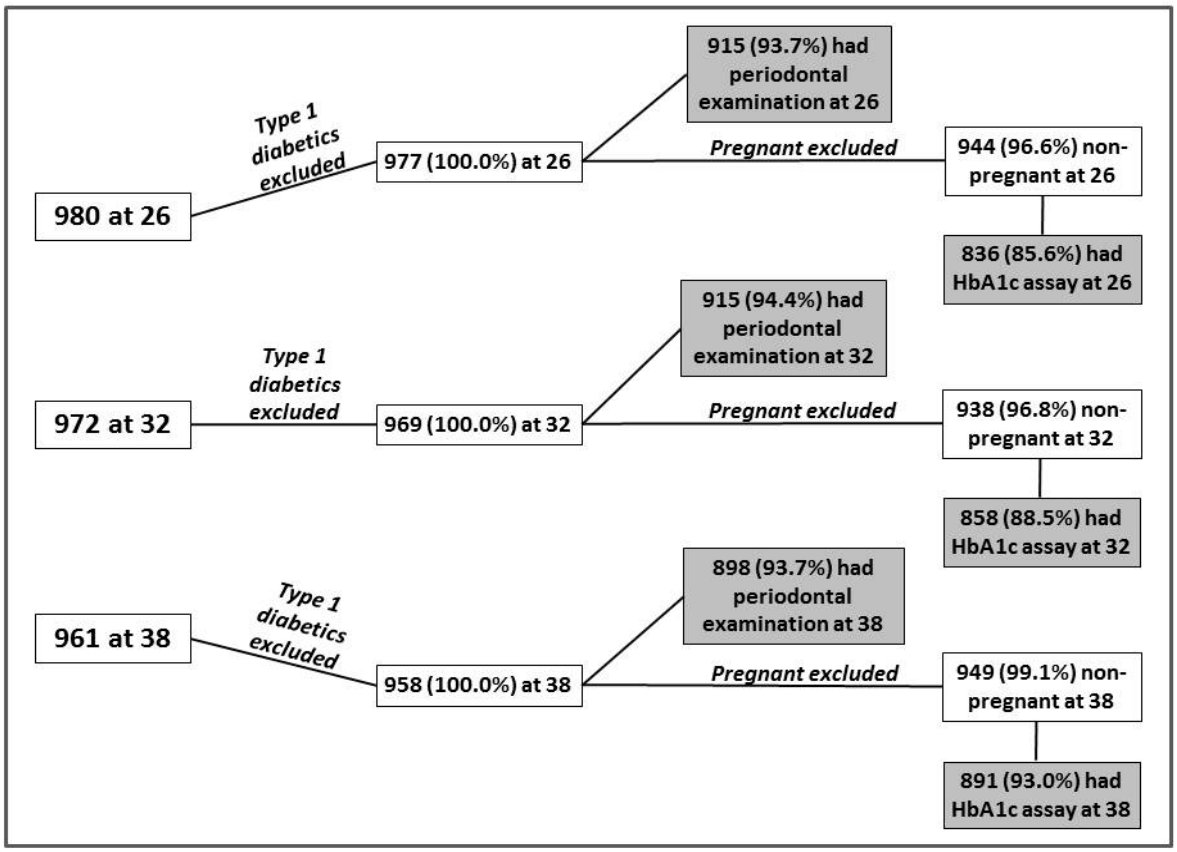


3 Results

3.1 Attrition analysis

A total of 980, 972 and 961 individuals participated in the age 26, age 32 and age 38 assessments respectively (Fig 3.1). These represented 96.2%, 95.8% and 95.8% respectively of the surviving cohorts at each age. There were three Study members with Type 1 diabetes in the cohort at the age 26 and age 32 assessments. By the age 38 assessment, one of these people was deceased, but another person had been diagnosed with Type 1 diabetes between the age 32 and age 38 assessments. Thus, there was a total of three excluded from analyses at each of the three ages, resulting in 977, 969 and 958 participants respectively being included in these analyses (Fig 3.1).

Fig 3.1. Attrition flowchart



Of these, 915 (93.7%) had a periodontal examination at age 26, 915 (94.4%) at age 32 and 898 (93.7%) at age 38. A further 33 (3.4%) at 26, 31 (3.2%) at 32 and 9 (0.9%) at 38 were excluded from HbA1c assays and anthropometric measurements due to pregnancy. Of the remaining participants, 836 (85.6%), 858 (88.5%) and 891 (93.0%) had HbA1c assays at ages 26, 32 and 38 respectively.

With respect to the GBTM, there were potentially three data points for each study member – at 26, 32 and 38. It was decided to include those who had data collected at two or more ages, and exclude those with less than two (Figs 3.2 and 3.3). In total, 924 and 893 Study members were included in the periodontal and HbA1c GBTM analysis respectively.

While those excluded from the GBTM represent a small proportion of the original cohort, it is important to determine whether they differ from those included. The two groups were compared on the basis of sex, childhood SES, SES at 26, 32 and 38, and smoking. There were proportionately fewer individuals of low childhood SES, low SES at 26 and 32, and smokers at 32 included in the periodontal GBTM (Table 3.1). No differences were found between those included in, and those excluded from, the HbA1c GBTM (Table 3.1).

Fig 3.2. Inclusion in the periodontal GBTM

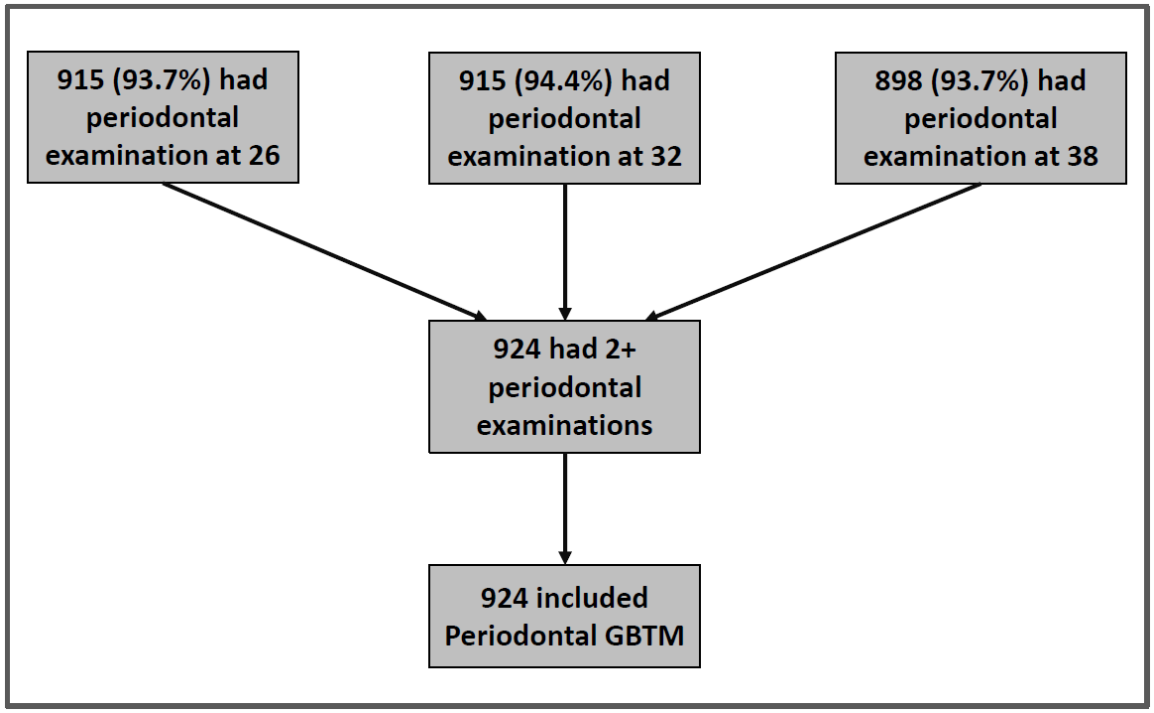


Fig 3.3. Inclusion in the HbA1c GBTM

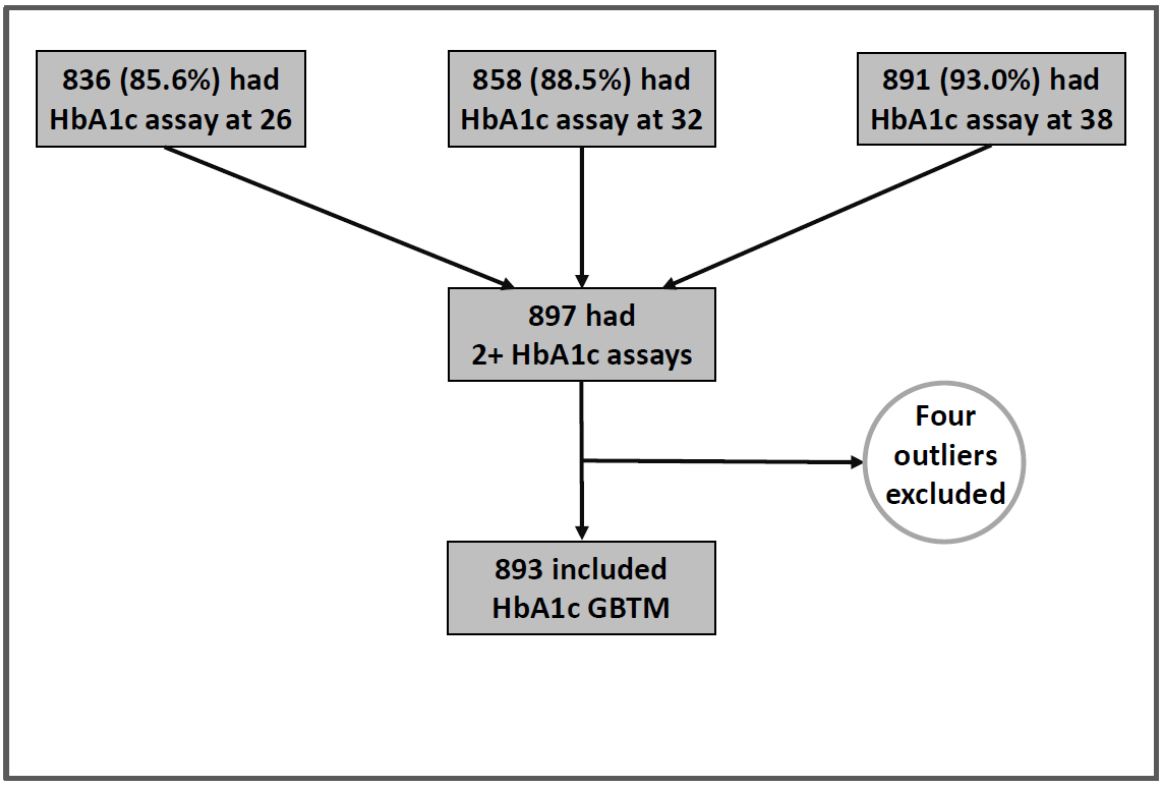


Table 3.1. Attrition analyses.

	Periodontal GBTM		HbA1c GBTM	
	Included	**Not included**	**Included**	**Not included**
	N = 924	N = 113	N = 893	N = 144
Male (N=535, 51.6%)	469 (50.8)	66 (58.4)	457 (51.2)	78 (54.2)
Maori (N=73, 7.5%)	68 (7.4)	5 (8.6)	67 (7.5)	5 (6.8)
Low childhood SES group (N=215, 20.9%)	181 (19.7)	34 (30.4)[a]	178 (20.0)	37 (25.9)
Low SES group at age 26 (N=258, 27.6%)	228 (26.0)	30 (50.0)[b]	228 (26.9)	30 (34.5)
Low SES group at age 32 (N=301, 31.0%)	278 (30.2)	23 (46.0)[c]	272 (30.5)	29 (36.3)
Low SES group at age 38 (N=187, 19.6%)	175 (19.4)	12 (24.5)	169 (19.3)	18 (23.1)
Smoker at 26 (N=392, 39.5%)	364 (39.5)	28 (48.3)	356 (40.0)	36 (40.4)
Smoker at 32 (N=327, 33.6%)	303 (32.9)	24 (48.0)[c]	300 (33.6)	27 (33.8)
Smoker at 38 (N=253, 26.4%)	234 (25.8)	19 (37.3)	232 (26.4)	21 (26.6)

[a]$p<0.01$; chi-square test. [b]$p<0.001$; chi-square test. [c]$p<0.01$; chi-square test.

3.2 Description of the sample at ages 26, 32 and 38

The DMHDS cohort at age three consisted of 535 (51.6%) boys and 502 (48.4%) girls. The prevalence of males had dropped slightly by ages 26 and 32, and again by 38 (Table 3.2). The percentage of Study members self-identifying as Maori remained constant over the 12 years. A similar proportion of female Study members were pregnant at 26 and 32 with the proportion dropping sharply by age 38.

A total of 1031 Study members had childhood SES – based on the mean of parents' occupational status – recorded over the years between birth and age 15 (Table 3.2). SES was also assessed at ages 26, 32 and 38. Different prevalences of low, medium and high SES were seen as the cohort aged, and became more affluent (these disparities also reflected the use of different measurement scales).

The prevalence of smoking declined from four out of ten of the sample reporting smoking every day for a month or more in the previous year at 26 to just over a quarter at 38 (Table 3.2). The mean number of cumulative pack years doubled between these ages. Marijuana use declined from half of the sample at age 26 to a quarter at 38 while the proportion of regular users (four or more times per week) dropped by almost a third.

As the cohort aged, there was an increase in the mean number of alcoholic drinks consumed during the week, and a decrease in the mean number during the weekend (Table 3.2). However, the mean total number of drinks per week remained the same over the twelve years. The mean number of hours for all forms of exercise – moderate, hard and extreme – increased between ages 32 and 38. The mean number of MET hours per week increased markedly between ages 32 and 38. Comparable data were not available for exercise at age 26.

Table 3.2. Demographic characteristics, socio-economic status, smoking status, marijuana and alcohol use, and exercise frequency at ages 26, 32 and 38.

	Age 26 N = 977	Age 32 N = 968	Age 38 N = 958
Male (%)	498 (51.0)	493 (50.9)	483 (50.4)
Maori[1] (%)	72 (7.4)	71 (7.4)	70 (7.4)
Pregnant (%)	33 (3.4)	31 (3.2)	9 (0.9)
Childhood SES[2] (%)			
Low	201 (20.7)	197 (20.5)	193 (20.3)
Medium	614 (63.2)	611 (63.4)	604 (63.4)
High	157 (16.2)	155 (16.1)	156 (16.4)
SES group[3] (%)			
Low	258 (27.7)	300 (31.0)	186 (19.6)
Medium	493 (52.8)	502 (51.9)	481 (50.6)
High	182 (19.5)	165 (17.1)	283 (29.8)
Smoking			
Current smoker[4] (%)	392 (40.2)	327 (33.8)	253 (26.5)
Mean cumulative pack years[5] (SD)	3.1 (4.4)	4.8 (6.6)	6.2 (8.7)
Frequency of marijuana use[6] (%)			
None	485 (49.8)	605 (62.8)	700 (74.1)
Less than weekly	326 (33.5)	221 (22.9)	146 (15.4)
Weekly or more	162 (16.6)	138 (14.3)	99 (10.5)
Regular user (4+ times weekly)	83 (8.7)	85 (8.8)	58 (6.1)
Alcohol use[7] (SD)			
Mean number of weeks had alcohol	33.1 (19.2)	33.1 (19.7)	33.9 (20.1)
Mean number of drinks Monday-Thursday	3.2 (7.0)	3.7 (7.6)	4.4 (8.3)
Mean number of drinks Friday-Sunday	9.1 (10.3)	7.9 (9.6)	7.8 (10.1)
Mean number of drinks per week	12.3 (15.1)	11.6 (15.3)	12.2 (16.8)
Exercise[8] (SD)			
Mean hours moderate – weekdays	-	5.2 (8.3)	5.5 (9.4)
Mean hours moderate – weekends	-	1.6 (2.5)	1.8 (2.8)
Mean total hours moderate	-	6.8 (9.6)	7.4 (10.6)
Mean hours hard – weekdays	-	1.1 (4.5)	2.7 (7.3)
Mean hours hard – weekends	-	0.3 (1.2)	0.7 (1.9)
Mean total hours hard	-	1.5 (5.1)	3.4 (8.2)
Mean hours extreme – weekdays	-	0.0 (0.3)	0.3 (2.0)
Mean hours extreme – weekends	-	0.0 (0.3)	0.1 (0.5)
Mean total hours extreme	-	0.0 (0.4)	0.4 (2.2)
Mean total MET hours per week	-	37.7 (52.0)	56.8 (74.5)

Percentages may not total 100% due to rounding. Not all participants responded to all items.
[1]N = 975 at 26, 959 at 32, and 946 at 38.
[2]N = 972 at 26, 963 at 32, and 953 at 38.
[3]N = 933 at 26, 967 at 32, and 950 at 38.
[4]N = 976 at 26, and 954 at 38
[5]N = 976 at 26, 967 at 32, and 950 at 38.
[6]N = 973 at 26 (958 at 26 for 'Regular Users' variable), 964 at 32, and 945 at 38.
[7]N = 973 at 26, 960 at 32, and 947 at 38.
[8]N = 959 at 32, and 955 at 38.

Periodontal status worsened with age (Table 3.3). Half-mouth measures were available for all three ages 26, 32 and 38 with full-mouth measures for ages 32 and 38 only. The mean number of periodontally-examined sites decreased with age, prevalence and extent increased, and a clear gradient was seen in these parameters across the ages. No such clear pattern was seen with severity of disease, although mean AL was higher at age 38 than at 26 or 32. Looking at the half-mouth measures, prevalence increased by almost half, almost three-fold and over four-fold for 1+ sites with 4+mm AL, 2+ sites with 4+mm AL and 1+ sites with 5+mm AL respectively between ages 26 and 38. Mean extent showed a similar striking increase. Generally, the greatest deterioration in periodontal status was between the ages 32 and 38. Conversely, other periodontal measures improved. The mean % of sites showing BOP reduced by a quarter, the mean plaque score reduced by a third, and the proportion of Study members in the "moderate" or "high" plaque score groups decreased markedly over the twelve years. The prevalence of routine and episodic use of dental services changed little over the 12 years.

Table 3.3. Prevalence, extent and severity of periodontal disease, bleeding on probing, plaque score and plaque score group, and dental attendance patterns, at ages 26, 32 and 38.

	Age 26 N = 915	**Age 32 N = 915**	**Age 38 N =898**
Full-mouth			
Mean number of sites assessed (SD)	-	79.8 (6.3)	78.4 (8.5)
Prevalence of periodontitis			
1+ sites with 4+mm AL (%)	-	272 (29.7)	394 (43.9)
2+ sites with 4+mm AL (%)	-	183 (20.0)	286 (31.8)
1+ sites with 5+mm AL (%)	-	112 (12.2)	206 (22.9)
Extent			
Mean % of sites with 4+mm AL (SD)	-	2.1 (6.1)	5.1 (13.3)
Mean % of sites with 5+mm AL (SD)	-	0.6 (2.8)	2.4 (9.7)
Severity			
Mean AL (SD)		1.4 (0.4)	1.6 (0.7)
Mean % of sites with BOP (SD)	-	8.5 (7.2)	7.4 (7.5)
Mean plaque score[1] (SD)	-	0.8 (0.5)	0.6 (0.5)
Half-mouth			
Mean number of sites assessed (SD)	40.4 (2.6)	39.8 (3.3)	39.2 (4.4)
Prevalence of periodontitis			
1+ sites with 4+mm AL (%)	173 (18.9)	206 (22.5)	313 (34.9)
2+ sites with 4+mm AL (%)	77 (8.4)	119 (13.0)	207 (23.1)
1+ sites with 5+mm AL (%)	35 (3.8)	77 (8.4)	160 (17.8)
Extent			
Mean % of sites with 4+mm AL (SD)	1.1 (3.3)	2.1 (6.5)	5.1 (13.4)
Mean % of sites with 5+mm AL (SD)	0.2 (1.2)	0.6 (3.1)	2.4 (9.7)
Severity			
Mean AL (SD)	1.5 (0.3)	1.4 (0.4)	1.6 (0.8)
Mean % of sites with BOP (SD)	9.9 (8.6)	8.3 (7.7)	7.4 (8.0)
Mean plaque score[1] (SD)	0.9 (0.5)	0.8 (0.5)	0.6 (0.5)
Plaque score group			
Very low (%)	312 (33.8)	409 (44.2)	502 (55.4)
Low (%)	335 (36.3)	293 (31.6)	244 (26.9)
Moderate (%)	189 (20.5)	136 (14.7)	93 (10.2)
High (%)	87 (9.4)	88 (9.5)	68 (7.5)
Dental attendance patterns			
Routine attender[2] (%)	286 (31.3)	295 (32.4)	306 (34.1)
Episodic attender[3] (%)	492 (53.8)	486 (53.2)	505 (56.2)

SD; Standard Deviation. AL; Combined Attachment Loss, BOP; Bleeding on probing

[1]N = 923 at 26, 926 at 32 and 907 at 38 (some participants who were excluded from a full periodontal examination agreed to have their plaque scores recorded).

[2]N = 913 at 26, 910 at 32 and 897 at 38.

[3]N = 914 at 32.

Mean HbA1c increased with age, as did the prevalence of prediabetes, type 2 diabetes and dysglycaemia (Table 3.4). There was an overall relative increase of 16.0% in mean HbA1c between 26 and 38, with the greatest increase between ages 26 and 32 (11.1% between ages 26 and 32 and 4.4% between 32 and 38). Of those who had HbA1c levels assayed at both 26 and 38, some 724 (93.2%) experienced a rise in HbA1c between these ages, and 54 (6.8%) experienced a drop. Of those 54 individuals whose HbA1c dropped, the mean drop was 1.3 mmol/mol (SD = 1.3) between 26 and 38, the median was 1.3 mmol/mol and the range was 0.1 mmol/mol – 6.6 mmol/mol. Of those 724 individuals whose HbA1c rose, the mean rise was 5.4 mmol/mol (SD = 5.1), the median was 4.9 mmol/mol and the range was 0.1 mmol/mol – 92.9 mmol/mol.

The anthropometric measures all increased between ages 26 and 38; there were increases of 9.0%, 8.8%, 7.9%, 7.5% and 6.4% (respectively) for mean weight, mean BMI, mean WC, mean waist-hip ratio and mean waist-height ratio between ages 26 and 38 (Table 3.4). Generally, the greatest increases were between ages 26 and 32, with smaller increases between ages 32 and 38. Likewise, the proportion of Study members in the high risk anthropometric groups increased steadily over the twelve years, more than doubling in the case of the high BMI group and high waist-height groups, almost tripling in the case of the high WC group, and increasing more than five-fold in the case of the high waist-hip group (Table 3.4)

Table 3.4. Mean HbA1c levels, prevalence of prediabetes, type 2 diabetes and dysglycaemia, mean anthropometric measures, and anthropometric high risk groups at ages 26, 32 and 38.

	Age 26 N = 944	**Age 32 N = 937**	**Age 38 N =949**
Mean HbA1c in mmol (SD)[1]	30.7 (3.1)	34.0 (3.6)	35.5 (5.5)
Prediabetes (%)[1]	2 (0.2)	31 (3.6)	155 (17.4)
Diabetes (%)[1]	0 (0.0)	1 (0.1)	6 (0.6)
Dysglycaemia (%)[1]	2 (0.2)	32 (3.7)	161 (18.1)
Anthropometric measures (SD)			
Mean weight in kg[2] (SD)	74.1 (14.8)	78.2 (16.6)	80.8 (17.4)
Mean BMI[3] (SD)	25.0 (4.4)	26.2 (5.0)	27.2 (5.3)
Mean waist circumference in mm[4] (SD)	801.4 (99.6)	844.5 (114.0)	864.1 (126.4)
Mean waist-hip ratio[5] (SD)	0.80 (0.07)	0.83 (0.07)	0.85 (0.08)
Mean waist-height ratio[4] (SD)	0.47 (0.06)	0.49 (0.06)	0.50 (0.07)
High BMI group[3] (%)	110 (11.8)	164 (15.9)	227 (24.4)
High WC group[4] (%)	63 (6.8)	144 (15.5)	191 (18.5)
High waist-hip group[5] (%)	60 (6.5)	198 (21.4)	316 (34.1)
High waist-height group[4] (%)	208 (20.1)	346 (37.3)	422 (45.3)

SD; Standard Deviation.
Prediabetes; 39mmol/mol – 47mmol/mol. Diabetes; 48+mmol/mol). Dysglycaemia; 39+mmol/mol
[1]N = 836 at 26, 858 at 32, and 891 at 38.
[2]N = 936 at 26, 926 at 32, and 936 at 38.
[3]N = 936 at 26, 926 at 32, and 931 at 38.
[4]N = 924 at 26, 927 at 32, and 932 at 38.
[5]N = 924 at 26, 927 at 32, and 928 at 38.

3.3 Cross-sectional associations at ages 26, 32 and 38

3.3.1 Periodontal experience – covariate associations

The cross-sectional bivariate associations between periodontal experience and periodontal covariates were explored using chi-square tests for categorical variables, Mann-Whitney U tests for categorical and continuous variables, and Spearman's correlation coefficient for continuous variables.

3.3.1.1 Age 26

Statistically significant associations were found between all three periodontal disease prevalence case definitions and low childhood SES, smoking status, mean pack years, regular marijuana use and mean plaque score (Table 3.5). While an association was found between low SES at age 26 and 1+ sites with 4+mm AL, no associations were found with the more severe prevalence case definitions. Those with 1+ or 2+ sites with 4+mm AL were more likely to be in the "high" plaque score group; the opposite was the case for those in "very low" plaque score group. Those with 1+ sites with 4+mm AL or 1+ sites with 5+mm AL were more likely to be episodic attenders while those with 1+ or 2+ sites with 4+mm AL were less likely to be routine attenders.

Statistically significant associations were found between extent of periodontal disease (as measured by the mean % of sites with 4+mm AL) and low childhood SES, SES at 26, smoking status, mean pack years, regular marijuana use, mean plaque score, plaque score group and use of dental services (Table 3.6). More extensive disease (as measured by the mean % of sites with 5+mm AL) was associated with low childhood SES, smoking status, mean pack years, weekly+ and regular marijuana use, mean plaque score and episodic use of dental services. The severity of periodontal disease was associated with all the demographic, smoking and oral health care covariates. The correlations between continuous variables were all positive; both extent and severity of disease at age 26 were positively associated with mean pack years and with mean plaque score. The correlations ranged in value from 0.072 to 0.362 (representing shared variances of 0.5% and 13.1% respectively).

Table 3.5. Age 26 periodontitis prevalence (half-mouth measures) by demographic, smoking and oral health care variables. Column percentages or standard deviation in parentheses. N = 915.

	Periodontitis prevalence (half-mouth) at 26					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=742	Yes N=173	No N=838	Yes N=77	No N=880	Yes N=35
Demographic characteristics						
Male (N=466, 50.9%)	368 (49.6)	98 (56.6)	425 (50.7)	41 (53.2)	443 (50.3)	23 (65.7)
Low childhood SES[1] (N=180, 19.8%)	124 (16.8)	56 (32.7)[a]	154 (18.4)	26 (34.7)[b]	164 (18.7)	16 (47.1)[a]
Low SES at age 26 (N=233, 26.8%)	181 (25.3)	52 (33.5)[c]	210 (26.0)	23 (35.9)	221 (26.2)	12 (42.9)
Smoking at age 26						
Current smoker (N=363, 39.7%)	274 (36.9)	89 (51.4)[b]	315 (37.6)	48 (62.3)[a]	342 (38.9)	21 (60.0)[c]
Mean pack years (SD)	2.7 (4.1)	4.6 (5.0)[d]	2.8 (4.1)	6.0 (5.4)[d]	2.9 (4.2)	6.6 (5.5)[d]
Marijuana weekly or more (N=158, 17.3%)	123 (16.6)	35 (20.2)	138 (16.5)	20 (26.0)	145 (16.5)	13 (37.1)[b]
Regular Marijuana user[2] (N=82, 9.1%)	59 (8.0)	23 (13.5)[c]	69 (8.3)	13 (17.1)[c]	72 (8.3)	10 (28.6)[a]
Oral health care at age 26						
Mean plaque score (SD)	0.8 (0.5)	1.1 (0.6)[d]	0.8 (0.5)	1.1 (0.6)[d]	0.9 (0.5)	1.1 (0.6)[e]
Plaque score group						
Very low (N=305, 33.5%)	268 (36.2)	37 (21.9)	292 (34.9)	13 (17.6)	298 (33.9)	7 (22.6)
Low (N=333, 36.6%)	279 (37.7)	54 (32.0)	307 (36.7)	26 (35.1)	324 (36.9)	9 (29.0)
Moderate (N=185, 20.3%)	135 (18.2)	50 (29.6)	164 (19.6)	21 (28.4)	177 (20.1)	8 (25.8)
High (N=87, 9.6%)	59 (8.0)	28 (16.6)[a]	73 (8.7)	14 (18.9)[b]	80 (9.1)	7 (22.6)
Routine attender (N=286, 31.3%)	248 (33.5)	38 (22.1)[f]	271 (32.4)	15 (19.7)[c]	280 (31.9)	6 (17.1)
Episodic attender (N=492, 53.8%)	383 (51.6)	109 (63.0)[f]	442 (52.7)	50 (64.9)	466 (53.0)	26 (74.3)[c]

[a]p<0.001; chi-square test. [b]p<0.005; chi-square test. [c]p<0.05; chi-square test. [d]p<0.001; Mann-Whitney U test. [e]p<0.05; Mann-Whitney U test. [f]p<0.01; chi-square test. SES; Socioeconomic status. [1]Low SES birth to age 15. [2]Uses marijuana 4+ times a week.

Table 3.6. Age 26 periodontitis extent and severity (half-mouth measures) by demographic, smoking and oral health care variables, and correlations with mean pack years. Standard deviation in parentheses. N = 918.

	Periodontitis extent and severity (half-mouth) at 26 (SD)		
	Mean % of sites with 4+mm AL	Mean % of sites with 5+mm AL	Mean AL
Demographic characteristics			
Male			
No (N=449, 49.1%)	0.9 (2.9)	0.2 (1.4)	1.5 (0.3)
Yes (N=466, 50.9%)	1.2 (3.6)	0.2 (1.0)	1.5 (0.3)[a]
Low childhood SES			
No (N=731, 80.2%)	0.8 (2.8)	0.1 (0.7)	1.6 (0.3)
Yes (N=180, 19.8%)	2.0 (4.6)[a]	0.5 (2.3)[a]	1.6 (0.4)[b]
Low SES at age 26			
No (N=638, 73.2%)	0.8 (2.8)	0.1 (1.3)	1.5 (0.3)
Yes (N=233, 26.8%)	1.3 (3.7)[c]	0.2 (0.8)	1.5 (0.3)[d]
Smoking at age 26			
Current smoker			
No (N=552, 60.3%)	0.7 (2.6)	0.1 (1.3)	1.5 (0.3)
Yes (N=363, 39.7%)	1.5 (4.0)[a]	0.2 (1.0)[c]	1.6 (0.4)[a]
Mean pack years*	0.173[e]	0.140[e]	0.219[e]
Marijuana weekly or more			
No (N=754, 82.7%)	0.9 (3.0)	0.1 (1.2)	1.5 (0.3)
Yes (N=158, 17.3%)	1.6 (4.4)	0.3 (1.2)[d]	1.6 (0.3)[b]
Regular Marijuana user			
No (N=821, 90.9%)	1.0 (3.1)	0.2 (1.2)	1.5 (0.3)
Yes (N=82, 9.1%)	1.9 (4.4)[c]	0.5 (1.4)[a]	1.6 (0.3)[a]
Oral health care at age 26			
Mean plaque score*	0.173[e]	0.072[f]	0.362[e]
Plaque score group			
Very low (N=305, 33.5%)	0.7 (2.9)	0.2 (1.7)	1.4 (0.3)
Low (N=333, 36.6%)	0.9 (2.5)	0.1 (0.6)	1.5 (0.3)
Moderate (N=185, 20.3%)	1.6 (4.4)	0.2 (0.9)	1.6 (0.3)
High (N=87, 9.6%)	1.7 (3.8)[g]	0.3 (1.2)	1.7 (0.3)[g]
Routine attender			
No (N=627, 68.7%)	1.2 (3.5)	0.2 (1.4)	1.5 (0.3)
Yes (N=286, 31.3%)	0.6 (2.7)[d]	0.1 (0.6)	1.4 (0.3)[a]
Episodic attender			
No (N=423, 46.2%)	0.8 (3.2)	0.1 (1.5)	1.4 (0.3)
Yes (N=492, 53.8%)	1.2 (3.3)[b]	0.2 (0.9)[c]	1.5 (0.3)[a]

*Spearman correlation coefficient. [a]p<0.001; Mann-Whitney U test. [b]p<0.01; Mann-Whitney U test. [c]p<0.05; Mann-Whitney U test. [d]p<0.005; Mann-Whitney U test. [e]p<0.001; Spearman's rho correlation. [f]p<0.05; Spearman's rho correlation. [g]p<0.001; Kruskal Wallis test.

3.3.1.2 Age 32

Statistically significant associations were found between all three periodontal disease prevalence case definitions and low childhood SES, low SES at 32, smoking status, mean pack years, marijuana use weekly or more, regular marijuana use, and mean plaque score (Table 3.7). Those with any of the three prevalence case definitions were more likely to be in the "high" plaque score group and to be episodic attenders, and less likely to be in the "low" plaque score group and to be routine attenders.

Statistically significant associations were found between extent of periodontal disease (as measured by the mean % of sites with 4+mm or 5+mm AL) and low childhood SES, low SES at 32, smoking status, mean pack years, marijuana use weekly or more, regular marijuana use, mean plaque score, plaque score group and use of dental services (Table 3.8). Severity of periodontal disease was associated with all the demographic, smoking and oral health care covariates. The correlations between continuous variables were all positive; both the extent and severity of disease at age 32 were positively associated with mean pack years and with mean plaque score. The correlations ranged in value from 0.073 to 0.349 (representing shared variances of 0.5% and 12.2% respectively).

Table 3.7. Age 32 periodontitis prevalence (half-mouth measures) by demographic, smoking and oral health care variables. Column percentages or standard deviation in parentheses. N = 915.

	Periodontitis prevalence (half-mouth) at 32					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=709	Yes N=206	No N=796	Yes N=119	No N=838	Yes N=77
Demographic characteristics						
Male (N=468, 51.1%)	353 (49.8)	115 (55.8)	405 (50.9)	63 (52.9)	425 (50.7)	43 (55.8)
Low childhood SES[1] (N=180, 19.8%)	116 (16.5)	64 (31.1)[a]	135 (17.1)	45 (37.8)[a]	153 (18.4)	27 (35.1)[b]
Low SES at age 32 (N=277, 30.3%)	182 (25.7)	95 (46.3)[a]	221 (27.8)	56 (47.1)[a]	238 (28.4)	39 (50.6)[a]
Smoking at age 32						
Current smoker (N=305, 33.3%)	182 (25.7)	123 (59.7)[a]	220 (27.6)	85 (71.4)[a]	252 (30.1)	53 (68.8)[a]
Mean pack years (SD)	3.6 (5.5)	9.0 (7.8)[c]	3.9 (5.9)	10.5 (7.6)[c]	4.3 (6.3)	10.1 (7.0)[c]
Marijuana weekly or more (N=133, 14.6%)	72 (10.2)	61 (29.8)[a]	95 (12.0)	38 (31.9)[a]	108 (12.9)	25 (32.5)[a]
Regular Marijuana user[2] (N=81, 8.9%)	42 (5.9)	39 (19.0)[a]	60 (7.6)	21 (17.6)[b]	67 (8.0)	14 (18.2)[d]
Oral health care at age 32						
Mean plaque score (SD)	0.7 (0.5)	1.0 (0.7)[c]	0.7 (0.5)	1.0 (0.7)[c]	0.7 (0.5)	1.0 (0.7)[e]
Plaque score group						
Very low (N=403, 44.2%)	332 (47.0)	71 (34.6)	362 (45.6)	41 (34.7)	374 (44.7)	29 (38.2)
Low (N=287, 31.5%)	233 (33.0)	54 (26.3)	261 (32.9)	26 (22.0)	267 (31.9)	20 (26.3)
Moderate (N=134, 14.7%)	99 (14.0)	35 (17.1)	113 (14.2)	21 (17.8)	123 (14.7)	11 (14.5)
High (N=88, 9.6%)	43 (6.1)	45 (22.0)[a]	58 (7.3)	30 (25.4)[a]	72 (8.6)	16 (21.1)[d]
Routine attender (N=295, 32.4%)	252 (35.7)	43 (21.0)[a]	275 (34.7)	20 (16.9)[a]	281 (33.7)	14 (18.2)[d]
Episodic attender (N=486, 53.1%)	349 (49.2)	137 (66.8)[a]	397 (49.9)	89 (75.4)[a]	429 (51.3)	57 (74.0)[a]

[a]p<0.001; chi-square test. [b]p<0.005; chi-square test. [c]p<0.001; Mann-Whitney U test. [d]p<0.01; chi-square test. [e]p<0.05; Mann-Whitney U test.

Table 3.8. Age 32 periodontitis extent and severity (half-mouth measures) by demographic, smoking and oral health care variables, and correlations with mean pack years. Standard deviation in parentheses. N = 915.

	Periodontitis extent and severity (half-mouth) at 32 (SD)		
	Mean % of sites with 4+mm AL	Mean % of sites with 5+mm AL	Mean AL
Demographic characteristics			
Male			
No (N=447, 48.9%)	2.0 (6.6)	0.6 (2.9)	1.3 (0.4)
Yes (N=468, 51.1%)	2.1 (6.4)	0.7 (3.3)	1.5 (0.4)[a]
Low childhood SES[1]			
No (N=730, 80.2%)	1.6 (5.4)	0.4 (2.7)	1.4 (0.4)
Yes (N=180, 19.8%)	4.2 (9.6)[a]	1.3 (4.5)[a]	1.6 (0.5)[a]
Low SES at age 32			
No (N=637, 69.7%)	1.4 (4.6)	0.3 (1.7)	1.4 (0.4)
Yes (N=277, 30.3%)	3.7 (9.4)[a]	1.1 (5.0)[a]	1.6 (0.6)[a]
Smoking at age 32			
Current smoker			
No (N=610, 66.7%)	0.8 (3.6)	0.2 (1.8)	1.3 (0.3)
Yes (N=305, 33.3%)	4.5 (9.7)[a]	1.2 (4.7)[a]	1.6 (0.6)[a]
Mean pack years*	0.349[b]	0.248[b]	0.306[b]
Marijuana weekly or more			
No (N=780, 85.4%)	1.4 (4.6)	0.4 (1.9)	1.4 (0.4)
Yes (N=133, 14.6%)	5.9 (12.4)[a]	1.8 (6.7)[a]	1.7 (0.6)[a]
Regular Marijuana user[2]			
No (N=832, 91.1%)	1.7 (5.1)	0.4 (2.0)	1.4 (0.4)
Yes (N=81, 8.9%)	6.0 (14.1)[a]	2.2 (8.3)[c]	1.8 (0.7)[a]
Oral health care at age 32			
Mean plaque score*	0.177[b]	0.073[d]	0.333[b]
Plaque score group			
Very low (N=403, 44.2%)	1.5 (4.8)	0.4 (1.7)	1.3 (0.4)
Low (N=287, 31.5%)	1.3 (3.9)	0.3 (1.2)	1.4 (0.3)
Moderate (N=134, 14.7%)	2.2 (6.4)	0.5 (2.7)	1.5 (0.4)
High (N=88, 9.6%)	6.3 (12.0)[e]	2.0 (7.4)[f]	1.9 (0.6)[e]
Routine attender			
No (N=615, 67.6%)	2.5 (7.4)	0.7 (3.6)	1.5 (0.5)
Yes (N=295, 32.3%)	1.1 (4.2)[a]	0.3 (1.7)[g]	1.3 (0.3)[a]
Episodic attender			
No (N=428, 46.8%)	1.1 (4.0)	0.3 (1.6)	1.3 (0.3)
Yes (N=486, 53.2%)	2.9 (8.1)[a]	0.8 (4.0)[a]	1.5 (0.5)[a]

*Spearman correlation coefficient. [a]p<0.001; Mann-Whitney U test. [b]p<0.001; Spearman's rho correlation. [c]p<0.005; Mann-Whitney U test. [d]p<0.05; Spearman's rho correlation. [e]p<0.001; Kruskal Wallis test. [f]p<0.001; Kruskal Wallis test. [g]p<0.01; Mann-Whitney U test.

3.3.1.3 Age 38

The association between sex and periodontal disease prevalence became apparent by age 38 whereby Study members with any of the three prevalence case definitions were more likely to be male (Table 3.9). Statistically significant associations were also found between all three periodontal disease prevalence case definitions and low childhood SES, low SES at 38, smoking status, mean pack years, marijuana use weekly or more, regular marijuana use, and mean plaque score. Those with any of the three prevalence case definitions were more likely to be in the "high" plaque score group and to be episodic attenders, and less likely to be in the "low" plaque score group and to be routine attenders.

Statistically significant associations were found between extent of periodontal disease (as measured by the mean % of sites with 4+mm or 5+mm AL) and all the demographic, smoking and oral health care covariates (Table 3.10). Severity of periodontal disease was also associated with all covariates. By age 38, correlations between continuous variables were stronger than in previous years; both extent and severity of disease at age 38 were positively associated with mean pack years and mean plaque score. The correlations ranged in value from 0.224 to 0.425 (representing shared variances of 5.0% and 18.0% respectively).

Table 3.9. Age 38 periodontitis prevalence (half-mouth measures) by demographic, smoking and oral health care variables. Column percentages or standard deviation in parentheses. N = 898.

	Periodontitis prevalence (half-mouth) at 38					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=585	Yes N=313	No N=691	Yes N=207	No N=738	Yes N=160
Demographic characteristics						
Male (N=452, 50.3%)	265 (45.3)	187 (59.7)[a]	325 (47.0)	127 (61.4)[a]	356 (48.2)	96 (60.0)[b]
Low childhood SES[1] (N=171, 19.1%)	83 (14.3)	88 (28.2)[a]	105 (15.3)	66 (32.0)[a]	121 (16.5)	50 (31.2)[a]
Low SES at age 38 (N=166, 18.5%)	62 (10.6)	104 (33.4)[a]	86 (12.5)	80 (38.8)[a]	105 (14.3)	61 (38.4)[a]
Smoking at age 38						
Current smoker (N=230, 25.7%)	92 (15.8)	138 (44.1)[a]	120 (17.4)	110 (53.1)[a]	148 (20.1)	82 (51.2)[a]
Mean pack years (SD)	3.6 (6.3)	10.2 (10.2)[c]	3.9 (6.6)	12.5 (10.6)[c]	4.5 (7.3)	12.4 (10.6)[c]
Marijuana weekly or more (N=92, 10.3%)	35 (6.0)	57 (18.3)[a]	42 (6.1)	50 (24.3)[a]	52 (7.1)	40 (25.2)[a]
Regular Marijuana user[2] (N=52, 5.8%)	18 (3.1)	34 (10.9)[a]	22 (3.2)	30 (14.6)[a]	26 (3.5)	26 (16.4)[a]
Oral health care at age 38						
Mean plaque score (SD)	0.5 (0.4)	0.8 (0.6)[c]	0.6 (0.4)	0.9 (0.7)[c]	0.6 (0.5)	0.9 (0.7)[c]
Plaque score group						
Very low (N=496, 55.7%)	376 (64.5)	120 (39.1)	425 (61.9)	71 (35.0)	442 (60.2)	54 (34.6)
Low (N=239, 26.9%)	147 (25.2)	92 (30.0)	176 (25.6)	63 (31.0)	188 (25.6)	51 (32.7)
Moderate (N=90, 10.1%)	39 (6.7)	51 (16.6)	56 (8.2)	34 (16.7)	65 (8.9)	25 (16.0)
High (N=65, 7.3%)	21 (3.6)	44 (14.3)[a]	30 (4.4)	35 (17.2)[a]	39 (5.3)	26 (16.7)[a]
Routine attender (N=306, 34.1%)	232 (39.7)	75 (23.6)[a]	263 (38.1)	44 (20.8)[a]	274 (37.2)	32 (20.0)[a]
Episodic attender (N=505, 56.2%)	283 (48.4)	222 (70.9)[a]	352 (50.9)	153 (73.9)[a]	382 (51.8)	123 (76.9)[a]

[a]p<0.001; chi-square test. [b]p<0.01; chi-square test. [c]p<0.001; Mann-Whitney U test.

Table 3.10. Age 38 periodontitis extent and severity (half-mouth measures) by demographic, smoking and oral health care variables, and correlations with mean pack years. Standard deviation in parentheses. N = 898.

	Periodontitis extent and severity (half-mouth) at 38 (SD)		
	Mean % of sites with 4+mm AL	Mean % of sites with 5+mm AL	Mean AL
Demographic characteristics			
Male			
No (N=446, 49.7%)	3.8 (10.9)	1.7 (7.7)	1.5 (0.7)
Yes (N=452, 50.3%)	6.4 (15.4)[a]	3.0 (11.2)[b]	1.7 (0.8)[a]
Low childhood SES[1]			
No (N=722, 80.9%)	3.9 (11.2)	1.7 (7.8)	1.5 (0.7)
Yes (N=171, 19.1%)	10.3 (19.6)[a]	5.4 (14.9)[a]	1.9 (1.0)[a]
Low SES at age 38			
No (N=729, 81.5%)	3.2 (9.8)	1.3 (6.6)	1.5 (0.6)
Yes (N=166, 18.5%)	13.4 (21.6)[a]	6.8 (17.0)[a]	2.1 (1.1)[a]
Smoking at age 38			
Current smoker			
No (N=666, 74.3%)	2.3 (6.7)	0.8 (4.2)	1.4 (0.4)
Yes (N=230, 25.6%)	13.4 (21.9)[a]	7.0 (17.0)[a]	2.1 (1.1)[a]
Mean pack years*	0.391[b]	0.325[c]	0.425[c]
Marijuana weekly or more			
No (N=803, 89.7%)	3.5 (9.6)	1.4 (6.1)	1.5 (0.6)
Yes (N=92, 10.3%)	18.3 (26.6)[a]	10.1 (22.4)[a]	2.3 (1.5)[a]
Regular Marijuana user[2]			
No (N=848, 94.2%)	3.9 (10.4)	1.6 (6.6)	1.5 (0.6)
Yes (N=52, 5.8%)	23.4 (29.9)[a]	14.1 (26.8)[a]	2.6 (1.7)[a]
Oral health care at age 38			
Mean plaque score*	0.274[c]	0.224[c]	0.339[c]
Plaque score group			
Very low (N=496, 55.7%)	2.3 (6.4)	0.8 (3.2)	1.4 (0.4)
Low (N=239, 26.9%)	4.9 (10.9)	1.9 (6.7)	1.6 (0.6)
Moderate (N=90, 10.1%)	8.0 (14.4)	3.2 (9.6)	1.9 (0.8)
High (N=65, 7.3%)	19.9 (29.0)[d]	11.4 (22.3)[d]	2.5 (1.3)[d]
Routine attender			
No (N=591, 65.9%)	6.7 (15.6)	3.2 (11.5)	1.7 (0.9)
Yes (N=306, 34.1%)	2.0 (5.7)[a]	0.7 (3.6)[a]	1.4 (0.4)[a]
Episodic attender			
No (N=393, 43.8%)	1.9 (5.4)	0.6 (3.2)	1.4 (0.4)
Yes (N=505, 56.2%)	7.7 (16.8)[a]	3.7 (12.4)[a]	1.8 (0.9)[a]

*Spearman correlation coefficient. [a]p<0.001; Mann-Whitney U test. [b]p<0.01; Mann-Whitney U test. [c]p<0.001; Spearman's rho correlation. [d]p<0.001; Kruskal Wallis test.

3.3.2 Glycated haemoglobin – covariate associations

The cross-sectional bivariate associations between the prevalence of prediabetes, diabetes or dysglycaemia and mean HbA1c and their covariates were explored using chi-square tests for categorical variables (or Fisher's exact test where sample sizes were small); Mann-Whitney U tests for categorical and continuous variables; and Spearman's correlation coefficient for continuous variables.

3.3.2.1 Prediabetes, diabetes or dysglycaemia at ages 26, 32 and 38

As there were only two individuals with dysglycaemia at age 26 (both had prediabetes, none had diabetes) it was not appropriate to conduct statistical testing on associations between the prevalence of prediabetes, diabetes or dysglycaemia at 26 and demographic covariates, alcohol use or anthropometric covariates (Table 3.11).

By age 32, only one Study member had diabetes and 31 had prediabetes (Table 3.12). Statistical testing was not conducted for associations between diabetes at 32 and demographic covariates, alcohol use or anthropometric covariates due to insufficient sample size in the category for diabetes at age 32. Associations were seen between prediabetes/dysglycaemia and the mean number of weeks alcohol was consumed. Study members with prediabetes or dysglycaemia were more likely to have higher scores on most anthropometric measures as well as being in the high risk groups for these measures.

Statistically significant associations were found between prediabetes/dysglycaemia and sex, low SES at 38, smoking, mean scores and high score groups for anthropometric measures (Table 3.13). Those with diabetes at 38 reported significantly lower consumption of alcohol than healthy participants (whether measured by the mean number of weeks alcohol was consumed or the mean number of drinks a week). Those with dysglycaemia reported a lower mean number of weeks in which alcohol was consumed than normoglycaemic participants. Those with prediabetes, diabetes or dysglycaemia were more likely to have higher mean scores on all anthropometric measures as well as being in the high risk groups for these measures (with the exception of waist-hip ratio in those with diabetes).

Table 3.11**.** Prevalence of prediabetes, diabetes and dysglycaemia by demographic characteristics, alcohol use and anthropological measures at 26. Percentages or standard deviation in parentheses. N = 836.

	Prevalence at 26					
	Prediabetes*		Diabetes*		Dysglycaemia*	
	No N=834	Yes N=2	No N=836	Yes N=0	No N=834	Yes N=2
Demographic characteristics						
Male (N=447, 53.5%)	446 (53.5)	1 (50.0)	447 (53.5)	0 (0.0)	446 (53.5)	1 (50.0)
Low childhood SES[1] (N=163, 19.6%)	162 (19.5)	1 (50.0)	163 (19.6)	0 (0.0)	162 (19.5)	1 (50.0)
Low SES at age 26 (N=217, 27.1%)	216 (27.1)	1 (50.0)	217 (27.1)	0 (0.0)	216 (27.1)	1 (50.0)
Smoking						
Smoker at 26 (N=327, 39.1%)	326 (39.1)	1 (50.0)	327 (39.1)	0 (0.0)	326 (39.1)	1 (50.0)
Alcohol use						
Mean number of weeks had alcohol (SD)	34.1 (18.7)	27.0 (35.4)	34.1 (18.8)	-	34.1 (18.7)	27.0 (35.4)
Mean number of drinks a week (SD)	12.6 (15.1)	8.5 (5.0)	12.6 (15.1)	-	12.6 (15.1)	8.5 (5.0)
Anthropometric measures						
Mean weight kg (SD)	74.5 (14.7)	88.9 (1.9)	74.5 (14.7)	-	74.5 (14.7)	88.9 (1.9)
Mean BMI (SD)	25.1 (4.4)	30.7 (3.8)	25.1 (4.4)	-	25.1 (4.4)	30.7 (3.8)
Mean waist circumference mm (SD)	803.3 (99.7)	913.0 (4.2)	803.6 (99.7)	-	803.3 (99.7)	913.0 (4.2)
Mean waist-hip ratio (SD)	0.80 (0.07)	0.82 (0.12)	0.80 (0.07)	-	0.80 (0.07)	0.82 (0.12)
Mean waist-height ratio (SD)	0.47 (0.05)	0.54 (0.04)	0.47 (0.05)	-	0.47 (0.05)	0.54 (0.04)
High BMI group (N=98, 11.8%)	97 (11.7)	1 (50.0)	98 (11.8)	0 (0.0)	97 (11.7)	1 (50.0)
High WC group (N=58, 7.0%)	57 (6.9)	1 (50.0)	58 (7.0)	0 (0.0)	57 (6.9)	1 (50.0)
High waist-hip group (N=55, 6.7%)	54 (6.5)	1 (50.0)	55 (6.7)	0 (0.0)	54 (6.5)	1 (50.0)
High waist-height group (N=190, 23.0%)	188 (22.8)	2 (100.0)	190 (23.0)	0 (0.0)	188 (22.8)	2 (100.0)

*Statistical testing not conducted due to insufficient sample sizes in the categories for prediabetes, diabetes, and dysglycaemia at age 26.

Table 3.12. Prevalence of prediabetes, diabetes and dysglycaemia by demographic characteristics, alcohol use, exercise (MET hours) and anthropological measures at 32. Percentages or standard deviation in parentheses. N = 858.

	Prevalence at 32					
	Prediabetes		Diabetes*		Dysglycaemia	
	No N=827	Yes N=31	No N=857	Yes N=1	No N=826	Yes N=32
Demographic characteristics						
Male (N=453, 52.8%)	434 (52.5)	19 (61.3)	452 (52.7)	1 (100.0)	433 (52.4)	20 (62.5)
Low childhood SES[1] (N=170, 19.9%)	162 (19.7)	8 (25.8)	170 (20.0)	0 (0.0)	162 (19.7)	8 (25.0)
Low SES at age 32 (N=267, 31.2%)	256 (31.0)	11 (35.5)	267 (31.2)	0 (0.0)	256 (31.0)	11 (34.4)
Smoking						
Smoker at 32 (N=294, 34.3%)	282 (34.1)	12 (38.7)	294 (34.3)	0 (0.0)	282 (34.1)	12 (37.5)
Alcohol use						
Mean number of weeks had alcohol (SD)	34.0 (19.6)	24.5 (21.0)[a]	33.7 (19.7)	8.0 (0.0)	34.0 (19.6)	24.0 (20.9)[b]
Mean number of drinks a week (SD)	11.7 (15.2)	9.9 (15.1)	11.6 (15.2)	6.0 (0.0)	11.7 (15.2)	9.8 (14.8)
Exercise						
Mean hours moderate weekly (SD)	6.8 (9.6)	6.2 (6.8)	6.8 (9.5)	1.5 (0.0)	6.9 (9.6)	6.0 (6.7)
Mean hours hard weekly (SD)	1.6 (5.3)	0.9 (2.3)	1.5 (5.3)	0.0 (0.0)	1.6 (5.3)	0.9 (2.3)
Mean MET hours weekly (SD)	38.7 (53.6)	31.4 (29.7)	38.5 (52.9)	6.0 (0.0)	38.8 (53.6)	30.6 (29.6)
Anthropometric measures						
Mean weight kg (SD)	77.6 (16.0)	90.5 (25.3)[b]	78.0 (16.5)	120.0 (0.0)	77.5 (15.9)	91.4 (25.5)[c]
Mean BMI (SD)	26.0 (4.7)	30.2 (8.0)[c]	26.1 (4.9)	35.0 (0.0)	26.0 (4.7)	30.3 (7.9)[c]
Mean waist circumference mm (SD)	840.8 (109.7)	924.9 (165.7)[b]	843.5 (112.9)	1097.5 (0.0)	840.5 (109.4)	930.3 (165.8)[c]
Mean waist-hip ratio (SD)	0.83 (0.07)	0.86 (0.08)	0.83 (0.07)	0.95 (0.0)	0.83 (0.07)	0.86 (0.08)[a]
Mean waist-height ratio (SD)	0.49 (0.06)	0.53 (0.09)[b]	0.49 (0.06)	0.59 (0.0)	0.49 (0.06)	0.54 (0.09)[c]
High BMI group (N=147, 17.2%)	135 (16.3)	12 (38.7)[d]	146 (17.1)	1 (100.0)	134 (16.2)	13 (40.6)[e]
High WC group (N=130, 15.2%)	119 (14.4)	11 (35.5)[e]	129 (15.1)	1 (100.0)	118 (14.3)	12 (37.5)[e]
High waist-hip group (N=179, 20.9%)	168 (20.3)	11 (35.5)[f]	179 (20.8)	1 (100.0)	167 (20.2)	12 (37.5)[f]
High waist-height group (N=320, 37.3%)	303 (36.7)	17 (54.8)[f]	319 (37.3)	1 (100.0)	302 (36.6)	18 (56.3)[f]

*Statistical testing not conducted due to insufficient sample size in the category for diabetes at age 32. [a]$p<0.05$; Mann-Whitney U test. [b]$p<0.01$; Mann-Whitney U test. [c]$p<0.005$; Mann-Whitney U test. [d]$p<0.005$; chi-square test. [e]$p<0.005$; Fisher's exact test. [f]$p<0.05$; chi-square test.

Table 3.13. Prevalence of prediabetes, diabetes and dysglycaemia by demographics, alcohol use, exercise (MET hours) and anthropological measures at 38. Percentages or standard deviation in parentheses. N = 891.

	Prevalence at 38					
	Prediabetes		Diabetes		Dysglycaemia	
	No N=736	Yes N=155	No N=885	Yes N=6	No N=730	Yes N=161
Demographic characteristics						
Male (N=449, 50.4%)	350 (47.6)	99 (63.9)[a]	445 (50.3)	4 (66.7)	346 (47.4)	103 (64.0)[a]
Low childhood SES[1] (N=173, 19.5%)	138 (18.8)	35 (22.9)	171 (19.4)	2 (33.3)	136 (18.7)	37 (23.3)
Low SES at age 38 (N=170, 19.2%)	121 (16.5)	49 (31.8)[a]	169 (19.2)	1 (16.7)	120 (16.5)	50 (31.2)[a]
Smoking						
Smoker at 38 (N=237, 26.6%)	176 (23.9)	61 (39.4)[a]	236 (26.7)	1 (16.7)	175 (24.0)	62 (38.5)[a]
Alcohol use						
Mean number of weeks had alcohol (SD)	34.6 (19.9)	31.4 (21.0)	34.3 (20.0)	4.3 (5.3)[b]	34.9 (19.7)	30.4 (21.2)[c]
Mean number of drinks a week (SD)	11.8 (15.6)	14.2 (22.0)	12.3 (16.9)	2.7 (3.2)[c]	11.9 (15.6)	13.8 (21.7)
Exercise						
Mean hours moderate weekly (SD)	6.9 (9.9)	8.4 (11.2)	7.2 (10.1)	3.8 (5.4)	6.9 (9.9)	8.2 (11.1)
Mean hours hard weekly (SD)	3.2 (7.7)	4.9 (11.1)	3.5 (8.4)	0.3 (0.8)	3.3 (7.7)	4.7 (10.9)
Mean MET hours weekly (SD)	54.3 (70.6)	70.2 (91.4)	57.3 (75.0)	17.7 (26.9)[c]	54.6 (70.7)	68.3 (90.3)
Anthropometric measures						
Mean weight kg (SD)	79.6 (16.6)	85.8 (19.1)[d]	80.5 (16.9)	113.7 (22.2)[b]	79.4 (16.2)	86.9 (19.8)[d]
Mean BMI (SD)	26.9 (5.1)	28.5 (5.7)[b]	27.1 (5.2)	38.0 (8.5)[b]	26.8 (5.0)	28.9 (6.1)[d]
Mean waist circumference mm (SD)	854.8 (120.3)	905.6 (138.3)[d]	861.8 (122.9)	1130.9 (162.1)[d]	852.5 (117.4)	914.1 (145.2)[d]
Mean waist-hip ratio (SD)	0.85 (0.08)	0.88 (0.08)[d]	0.85 (0.08)	0.95 (0.11)[c]	0.85 (0.08)	0.89 (0.08)[d]
Mean waist-height ratio (SD)	0.50 (0.07)	0.52 (0.08)[d]	0.50 (0.07)	0.65 (0.10)[b]	0.50 (0.07)	0.53 (0.08)[d]
High BMI group (N=214, 24.1%)	161 (21.9)	53 (34.4)[e]	209 (23.7)	5 (83.3)[f]	156 (21.4)	58 (36.3)[a]
High WC group (N=179, 20.2%)	134 (18.3)	45 (29.2)[e]	174 (19.7)	5 (83.3)[f]	129 (17.7)	50 (31.3)[a]
High waist-hip group (N=304, 34.4%)	227 (31.1)	77 (50.0)[a]	301 (34.2)	3 (60.0)	224 (30.9)	80 (50.3)[a]
High waist-height group (N=403, 45.4%)	319 (43.5)	84 (54.5)[g]	397 (45.0)	6 (100.0)[h]	313 (43.0)	90 (56.3)[e]

[a]$p<0.001$; chi-square test. [b]$p<0.005$; Mann-Whitney U test. [c]$p<0.05$; Mann-Whitney U test. [d]$p<0.001$; Mann-Whitney U test. [e]$p<0.005$; chi-square test.
[f]$p<0.005$; Fisher's exact test. [g]$p<0.05$; chi-square test. [h]$p<0.01$; Fisher's exact test.

3.3.2.2 Mean HbA1c at ages 26, 32 and 38

Statistically significant associations were found between HbA1c and sex and mean waist circumference at ages 32 and 38 (Table 3.14). Associations between HbA1c and smoking, mean waist-hip ratio, high BMI risk group, high WC risk group and high waist-height risk group were seen at all three ages while associations between HbA1c and the mean number of weeks alcohol was consumed, mean weight, mean BMI and mean waist-height ratio were found at age 38 only. The mean number of weeks alcohol was consumed at age 38 was negatively correlated with mean HbA1c at this age. Correlations with anthropological measures were positive. The correlations ranged in value from -0.102 to 0.216 (representing shared variances of 1.0% and 4.7% respectively). Low childhood SES was associated with mean HbA1c at age 26 only while there were cross-sectional associations between mean HbA1c and low SES and high waist-hip risk group at ages 26 and 38.

Table 3.14. Mean HbA1c by demographic characteristics, smoking and anthropological high risk groups, and correlations between mean HbA1c and alcohol use, exercise (MET hours) and anthropological measures. Standard deviation in parentheses. N = 836.

	Mean HbA1c (SD)		
	Age 26 N = 836	Age 32 N = 858	Age 38 N = 891
Demographic characteristics			
Sex			
Female	30.4 (3.1)	33.7 (3.2)	34.7 (4.1)
Male	30.8 (3.1)	34.2 (3.8)[a]	36.2 (6.5)[b]
Low childhood SES[1]			
No	30.5 (3.1)	33.9 (3.7)	35.3 (5.2)
Yes	31.4 (3.0)[c]	34.5 (3.0)	36.2 (6.8)
Low SES			
No	30.5 (3.1)	33.9 (3.6)	35.2 (5.4)
Yes	31.0 (3.3)[d]	34.1 (3.4)	36.5 (6.1)[c]
Smoking			
Current smoker			
No	30.3 (3.1)	33.7 (3.7)	35.1 (5.5)
Yes	31.3 (3.1)[b]	34.5 (3.2)[b]	36.6 (5.3)[b]
Alcohol use			
Mean number of weeks had alcohol*	-0.047	-0.022	-0.102[e]
Mean number of drinks a week*	-0.028	-0.001	-0.030
Exercise			
Mean hours moderate weekly*	-	0.061	0.038
Mean hours hard weekly*	-	-0.023	-0.018
Mean MET hours weekly*	-	0.049	0.033
Anthropometric measures			
Mean weight*	0.043	0.064	0.173[f]
Mean BMI*	0.012	0.031	0.128[f]
Mean waist circumference*	0.053	0.071[g]	0.183[f]
Mean waist-hip ratio*	0.083[g]	0.098[e]	0.216[f]
Mean waist-height ratio*	0.027	0.048	0.148[f]
High BMI group			
No	30.6 (3.1)	33.8 (3.3)	35.0 (4.9)
Yes	31.4 (3.4)[c]	35.0 (4.6)[a]	37.0 (6.9)[b]
High WC group			
No	30.6 (3.1)	33.8 (3.3)	35.2 (4.8)
Yes	31.9 (3.1)[d]	35.1 (4.8)[a]	36.8 (7.6)[d]
High waist-hip group			
No	30.6 (3.1)	33.8 (3.3)	34.9 (3.6)
Yes	31.6 (3.3)[c]	34.5 (4.4)	36.5 (7.0)[b]
High waist-height group			
No	30.5 (3.0)	33.7 (3.2)	34.9 (3.4)
Yes	31.2 (3.3)[a]	34.4 (4.0)[c]	36.2 (7.2)[d]

*Spearman correlation coefficient. [a]p<0.01; Mann-Whitney U test. [b]p<0.001; Mann-Whitney U test. [c]p<0.005; Mann-Whitney U test. [d]p<0.05; Mann-Whitney U test. [e]p<0.005; Spearman's rho correlation. [f]p<0.001; Spearman's rho correlation. [g]p<0.05; Spearman's rho correlation.

3.3.3 Glycated haemoglobin – Periodontal associations

The cross-sectional bivariate associations between periodontal experience (prevalence, extent and severity of periodontitis) and the prevalence of prediabetes, diabetes or dysglycaemia and mean HbA1c were explored using chi-square tests for categorical variables (or Fisher's exact test where sample sizes were small); Mann-Whitney U tests for categorical and continuous variables; and Spearman's correlation coefficient for continuous variables.

3.3.3.1 Age 26

Statistical testing was not conducted for associations between the prevalence of prediabetes, diabetes, and dysglycaemia at age 26 and periodontal experience at 26 due to insufficient sample sizes in the categories for prediabetes, diabetes, and dysglycaemia at age 26 (Table 3.15). Statistically significant associations were found between mean HbA1c and the prevalence of all three periodontal case definitions (Tables 3.15). Those with 1+ or 2+ sites with 4+mm AL or 1+ sites with 5+mm AL had a higher mean HbA1c at 26 than those without. The extent of periodontal disease at age 26 was positively associated with mean HbA1c (Table 3.16). The correlations ranged in value from 0.097 to 0.120 (representing shared variances of 0.9% and 1.4% respectively).

Table 3.15. Mean HbA1c, and prevalence of prediabetes, diabetes and dysglycaemia at 26 by periodontitis prevalence (half-mouth measures) at 26. Column percentages or standard deviation in parentheses. N = 802.

	Periodontitis prevalence (half-mouth) at 26					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=651	Yes N=151	No N=735	Yes N=67	No N=769	Yes N=33
HbA1c at 26						
Mean HbA1c (SD)	30.6 (3.1)	31.3 (3.3)[a]	30.6 (3.1)	31.5 (3.5)[b]	30.6 (3.1)	32.6 (3.2)[c]
Prediabetes (N=2, 0.2%)[*]	2 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)
Diabetes (N=0, 0.0%)[*]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysglycaemia (N=2, 0.2%)[*]	2 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)

[*]Statistical testing not conducted due to insufficient sample sizes in the categories for prediabetes, diabetes, and dysglycaemia at age 26.
[a]$p<0.01$; Mann-Whitney U test. [b]$p<0.05$; Mann-Whitney U test. [c]$p<0.005$; Mann-Whitney U test.

Table 3.16. Correlations between mean HbA1c at 26 and periodontitis extent and severity (half-mouth measures) at 26, and prevalence of prediabetes, diabetes and dysglycaemia at 26 by periodontitis extent and severity (half-mouth measures) at 26. Standard deviation in parentheses. N = 802.

	Periodontitis extent and severity (half-mouth) at 26		
	Mean % of sites with 4+mm AL (SD)	Mean % of sites with 5+mm AL (SD)	Mean AL (SD)
HbA1c at 26			
Mean HbA1c[§]	0.097[a]	0.120[b]	0.065
Prediabetes[*]			
No (N=800, 99.8%)	1.1 (3.4)	0.2 (1.3)	1.49 (0.32)
Yes (N=2, 0.2%)	0.0 (0.0)	0.0 (0.0)	1.60 (0.07)
Diabetes[*]			
No (N=802, 100.0%)	1.1 (3.4)	0.2 (1.3)	1.49 (0.32)
Yes (N=0, 0.0%)	-	-	-
Dysglycaemia[*]			
No (N=800, 99.8%)	1.1 (3.4)	0.2 (1.3)	1.49 (0.32)
Yes (N=2, 0.2%)	0.0 (0.0)	0.0 (0.0)	1.60 (0.07)

[§]Spearman correlation coefficient. [a]$p<0.01$; Spearman's rho correlation. [b]$p<0.005$; Spearman's rho correlation.
[*]Statistical testing not conducted due to insufficient sample sizes in the categories for prediabetes, diabetes, and dysglycaemia at age 26.

3.3.3.2 Age 32

By age 32, one Study member had type 2 diabetes, 30 had prediabetes, and 31 had dysglycaemia (Table 3.17). Statistical testing was not conducted for associations between the prevalence diabetes at age 32 and periodontal experience at 32 due to insufficient sample sizes in the category for diabetes at age 32. Statistically significant associations were found between mean HbA1c and the prevalence of all three periodontal case definitions at age 32 (Table 3.17). Those with 1+ or 2+ sites with 4+mm AL or 1+ sites with 5+mm AL had a higher mean HbA1c at this age than those without. The extent of periodontal disease at 32 was positively associated with mean HbA1c (Table 3.18). The correlations ranged in value from 0.080 to 0.113 (representing shared variances of 0.6% and 1.3% respectively). The extent of periodontal disease at 32 (as defined by the mean % of sites with 4+mm AL) was associated with prediabetes whereby those with prediabetes experienced more extensive disease than those without (Table 3.18).

Table 3.17. Mean HbA1c, and prevalence of prediabetes, diabetes and dysglycaemia at 32 by periodontitis prevalence (half-mouth measures) at 32. Column percentages or standard deviation in parentheses. N = 824.

	Periodontitis prevalence (half-mouth) at 32					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=636	Yes N=188	No N=719	Yes N=105	No N=753	Yes N=71
HbA1c at 32						
Mean HbA1c (SD)	33.8 (3.5)	34.7 (3.3)[a]	33.9 (3.5)	34.8 (3.2)[b]	33.9 (3.5)	34.9 (3.4)[c]
Prediabetes (N=30, 3.6%)	19 (3.0)	11 (5.9)	23 (3.2)	7 (6.7)	25 (3.3)	5 (7.0)
Diabetes (N=1, 0.1%)[*]	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)
Dysglycaemia (N=31, 3.8%)	20 (3.1)	11 (5.9)	24 (3.3)	7 (6.7)	26 (3.5)	5 (7.0)

[a]$p<0.005$; Mann-Whitney U test. [b]$p<0.01$; Mann-Whitney U test. [c]$p<0.05$; Mann-Whitney U test.
[*]Statistical testing not conducted due to insufficient sample size in the category for diabetes at age 32.

Table 3.18. Correlations between mean HbA1c at 32 and periodontitis extent and severity (half-mouth measures) at 32, and prevalence of prediabetes, diabetes and dysglycaemia at 32 by periodontitis extent and severity (half-mouth measures) at 32. Standard deviation in parentheses. N = 824.

	Periodontitis extent and severity (half-mouth) at 32		
	Mean % of sites with 4+mm AL (SD)	Mean % of sites with 5+mm AL (SD)	Mean AL (SD)
HbA1c at 32			
Mean HbA1c[§]	0.113[a]	0.080[b]	0.051
Prediabetes			
No (N=794, 96.4%)	1.9 (6.2)	0.5 (2.8)	1.41 (0.43)
Yes (N=30, 3.6%)	5.7 (14.3)[c]	2.5 (9.4)	1.58 (0.76)
Diabetes[*]			
No (N=823, 99.9%)	2.1 (6.7)	0.6 (3.3)	1.42 (0.44)
Yes (N=1, 0.1%)	0.0 (0.0)	0.0 (0.0)	1.38 (0.00)
Dysglycaemia			
No (N=793, 96.2%)	1.9 (6.2)	0.5 (2.8)	1.41 (0.43)
Yes (N=31, 3.8%)	5.5 (14.1)	2.4 (9.2)	1.58 (0.75)

[§]Spearman correlation coefficient. [a]$p<0.005$; Spearman's rho correlation. [b]$p<0.05$; Spearman's rho correlation.
[c]$p<0.05$; Mann-Whitney U test.
[*]Statistical testing not conducted due to insufficient sample size in the category for diabetes at age 32.

3.3.3.3 Age 38

Although there were six individuals with Type 2 diabetes by age 38, only four of them had a periodontal examination (Table 3.19). Statistically significant associations were found between the prevalence of periodontal disease at 38 and the prevalence of prediabetes and dysglycaemia whereby those with 2+ sites with 4+mm AL had a greater prevalence of both prediabetes and dysglycaemia (Table 3.19). The extent of periodontal disease at 32 (as defined by the mean % of sites with 4+mm AL) and mean AL were positively associated with mean HbA1c. The correlations ranged in value from 0.070 to 0.071 (representing shared variances of 0.5% and 0.5% respectively). Study members with prediabetes had a higher extent of 4+mm AL, and higher a mean AL, than those without diabetes; and those with dysglycaemia had a higher mean AL than those without dysglycaemia (Table 3.20)

Table 3.19. Mean HbA1c, and prevalence of prediabetes, diabetes and dysglycaemia at 38 by periodontitis prevalence (half-mouth measures) at 38. Column percentages or standard deviation in parentheses. N = 849.

	Periodontitis prevalence (half-mouth) at 38					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=553	Yes N=296	No N=653	Yes N=196	No N=696	Yes N=153
HbA1c at 38						
Mean HbA1c (SD)	35.1 (4.3)	35.9 (6.3)	35.2 (4.1)	36.1 (7.4)	35.3 (4.2)	36.0 (8.0)
Prediabetes (N=148, 17.4%)	88 (15.9)	60 (20.3)	104 (15.9)	44 (22.4)[a]	116 (16.7)	32 (20.9)
Diabetes (N=4, 0.5%)	3 (0.5)	1 (0.3)	3 (0.5)	1 (0.5)	3 (0.4)	1 (0.7)
Dysglycaemia (N=152, 17.9%)	91 (16.5)	61 (20.6)	107 (16.4)	45 (23.0)[a]	119 (17.1)	33 (21.6)

[a]$p<0.05$; chi-square test

.

Table 3.20. Correlations between mean HbA1c at 38 and periodontitis extent and severity (half-mouth measures) at 38, and prevalence of prediabetes, diabetes and dysglycaemia at 38 by periodontitis extent and severity (half-mouth measures) at 38. Standard deviation in parentheses. N = 849.

	Periodontitis extent and severity (half-mouth) at 38		
	Mean % of sites with 4+mm AL (SD)	Mean % of sites with 5+mm AL (SD)	Mean AL (SD)
HbA1c at 38			
Mean HbA1c*	0.070[a]	0.026	0.071[a]
Prediabetes			
No (N=701, 82.6%)	4.5 (11.9)	2.0 (8.4)	1.56 (0.68)
Yes (N=148, 17.4%)	8.1 (18.7)[b]	4.4 (14.4)	1.80 (1.02)[c]
Diabetes			
No (N=845, 99.5%)	5.1 (13.4)	2.4 (9.8)	1.61 (0.76)
Yes (N=4, 0.5%)	5.8 (11.7)	4.2 (8.3)	1.59 (0.68)
Dysglycaemia			
No (N=697, 82.1%)	4.5 (11.9)	2.0 (8.4)	1.56 (0.68)
Yes (N=152, 17.9%)	8.0 (18.6)	4.4 (14.3)	1.80 (1.01)[c]

*Spearman correlation coefficient. [a]$p<0.05$; Spearman's rho correlation. [b]$p<0.05$; Mann-Whitney U test. [c]$p<0.005$; Mann-Whitney U test.

3.4 Longitudinal bivariate associations

3.4.1 Periodontal - Glycated haemoglobin associations

3.4.1.1 Periodontal experience at 26 - Glycated haemoglobin at 32

Due to there being no individuals in the category for diabetes at age 32 statistical testing was not carried out for associations between diabetes at age 32 and periodontal experience at 26. No associations were found between periodontitis prevalence, extent or severity at age 26 and mean HbA1c, and prevalence of prediabetes and dysglycaemia at 32 (Tables 3.21 and 3.22)

Table 3.21**.** Mean HbA1c, and prevalence of prediabetes, diabetes and dysglycaemia at 32 by periodontitis prevalence (half-mouth measures) at 26. Column percentages or standard deviation in parentheses. N = 811.

	Periodontitis prevalence (half-mouth) at 26					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=656	Yes N=155	No N=744	Yes N=67	No N=780	Yes N=31
HbA1c at 32						
Mean HbA1c (SD)	33.9 (3.4)	34.1 (3.0)	33.9 (3.3)	34.3 (2.8)	33.9 (3.3)	34.8 (2.9)
Prediabetes (N=29, 3.6%)	25 (3.8)	4 (2.6)	27 (3.6)	2 (3.0)	7 (3.5)	2 (6.5)
Diabetes (N=0, 0.0%)*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysglycaemia (N=29, 3.6%)	25 (3.8)	4 (2.6)	27 (3.6)	2 (3.0)	7 (3.5)	2 (6.5)

*Statistical testing not conducted due to no individuals in the category for diabetes at age 26.

Table 3.22. Correlations between mean HbA1c at 32 and periodontitis extent and severity (half-mouth measures) at 26, and prevalence of prediabetes, diabetes and dysglycaemia at 32 by periodontitis extent and severity (half-mouth measures) at 26. Standard deviation in parentheses. N = 811.

	Periodontitis extent and severity (half-mouth) at 26		
	Mean % of sites with 4+mm AL (SD)	Mean % of sites with 5+mm AL (SD)	Mean AL (SD)
HbA1c at 32			
Mean HbA1c[§]	0.028	0.053	0.043
Prediabetes			
No (N=782, 96.4%)	1.0 (2.8)	0.1 (0.9)	1.50 (0.31)
Yes (N=29, 3.6%)	2.6 (9.1)	1.1 (4.8)	1.54 (0.47)
Diabetes[*]			
No (N=811, 100.0%)	1.1 (3.3)	0.2 (1.3)	1.50 (0.32)
Yes (N=0, 0.0%)	-	-	-
Dysglycaemia			
No (N=782, 96.4%)	1.0 (2.8)	0.1 (0.9)	1.50 (0.31)
Yes (N=29, 3.6%)	2.6 (9.1)	1.1 (4.8)	1.54 (0.47)

[§]Spearman correlation coefficient.
[*]Statistical testing not conducted due to no individuals in the category for diabetes at age 26.

3.4.1.2 Periodontal experience at 26 - Glycated haemoglobin at 38

Statistically significant associations were found between the prevalence of periodontal disease at 26 and mean HbA1c at 38 whereby those with 1+ sites with 5+mm AL at 26 had a higher mean HbA1c at 38 than those without 1+ sites with 5+mm AL (Table 3.23). The extent of periodontal disease at 26 (as defined by the mean % of sites with 5+mm AL) was positively associated with mean HbA1c at 38 (Table 3.24). The correlation 0.080 represented a shared variance of 0.6%. Study members who had prediabetes at 38 had a higher mean AL at 26 than those who did not (Table 3.24).

Table 3.23. Mean HbA1c, and prevalence of prediabetes, diabetes and dysglycaemia at 38 by periodontitis prevalence (half-mouth measures) at 26. Column percentages or standard deviation in parentheses. N = 839.

	Periodontitis prevalence (half-mouth) at 26					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=685	Yes N=154	No N=771	Yes N=68	No N=809	Yes N=30
HbA1c at 38						
Mean HbA1c (SD)	35.5 (6.0)	35.6 (3.3)	35.5 (5.7)	36.0 (3.5)	35.5 (5.7)	36.8 (3.1)[a]
Prediabetes (N=145, 17.3%)	116 (16.9)	29 (18.8)	132 (17.1)	13 (19.1)	139 (17.2)	6 (20.0)
Diabetes (N=6, 0.7%)	6 (0.9)	0 (0.0)	6 (0.8)	0 (0.0)	6 (0.7)	0 (0.0)
Dysglycaemia (N=151, 18.0%)	122 (17.8)	29 (18.8)	138 (17.9)	13 (19.1)	145 (17.9)	6 (20.0)

[a]p<0.05; Mann-Whitney U test

Table 3.24. Correlations between mean HbA1c at 38 and periodontitis extent and severity (half-mouth measures) at 26, and prevalence of prediabetes, diabetes and dysglycaemia at 38 by periodontitis extent and severity (half-mouth measures) at 26. Standard deviation in parentheses. N = 839.

	Periodontitis extent and severity (half-mouth) at 26		
	Mean % of sites with 4+mm AL (SD)	Mean % of sites with 5+mm AL (SD)	Mean AL (SD)
HbA1c at 38			
Mean HbA1c*	0.052	0.080[a]	0.057
Prediabetes			
No (N=694, 82.7%)	1.0 (2.9)	0.1 (0.7)	1.48 (0.31)
Yes (N=145, 17.3%)	1.4 (4.7)	0.3 (2.2)	1.54 (0.36)[b]
Diabetes			
No (N=833, 99.3%)	1.0 (3.4)	0.2 (1.1)	1.49 (0.32)
Yes (N=6, 0.7%)	0.0 (0.0)	0.0 (0.0)	1.35 (0.15)
Dysglycaemia			
No (N=688, 82.0%)	1.0 (2.9)	0.1 (0.7)	1.48 (0.31)
Yes (N=151, 18.0%)	1.3 (3.3)	0.3 (2.2)	1.54 (0.35)

*Spearman correlation coefficient. [a]p<0.05; Spearman's rho correlation. [b]p<0.05; Mann-Whitney U test.

3.4.1.3 Periodontal experience at 32 - Glycated haemoglobin at 38

Statistically significant associations were found between the prevalence of periodontal disease at 32 and mean HbA1c at 38, whereby those with 1+ sites with 4+mm AL at 32 had a higher mean HbA1c at 38 than those without 1+ sites with 4+mm AL (Table 3.25). In addition, those with 1+ sites with 4+mm AL at 32 had a greater prevalence of dysglycaemia at 38 than those who were periodontally healthy at 32. The extent of periodontal disease (as defined by the mean % of sites with 4+mm AL) and mean AL at 32 were positively associated with mean HbA1c at 38 (Table 3.26). The correlations ranged in value from 0.072 to 0.080 (representing shared variances of 0.5% and 0.6% respectively). Participants with prediabetes or dysglycaemia at 38 had a higher mean % of sites with 4+mm AL and a higher mean AL at 32 than normoglycaemic participants (Table 3.26).

Table 3.25. Mean HbA1c, and prevalence of prediabetes, diabetes and dysglycaemia at 38 by periodontitis prevalence (half-mouth measures) at 32. Column percentages or standard deviation in parentheses. N = 844.

	Periodontitis prevalence (half-mouth) at 32					
	1+ sites with 4+mm AL		2+ sites with 4+mm AL		1+ sites with 5+mm AL	
	No N=657	Yes N=187	No N=734	Yes N=110	No N=772	Yes N=72
HbA1c at 38						
Mean HbA1c (SD)	35.1 (3.9)	36.8 (9.3)[a]	35.4 (5.6)	36.1 (5.5)	35.4 (4.8)	36.6 (11.0)
Prediabetes (N=145, 17.2%)	104 (15.8)	41 (21.9)	121 (16.5)	24 (21.8)	133 (17.2)	12 (16.7)
Diabetes (N=6, 0.7%)	3 (0.5)	3 (1.6)	5 (0.7)	1 (0.9)	5 (0.6)	1 (1.4)
Dysglycaemia (N=151, 17.9%)	107 (16.3)	44 (23.5)[b]	126 (17.2)	25 (22.7)	138 (17.9)	13 (18.1)

[a]$p<0.05$; Mann-Whitney U test. [b]$p<0.05$; chi-square test.

Table 3.26. Correlations between mean HbA1c at 38 and periodontitis extent and severity (half-mouth measures) at 32, and prevalence of prediabetes, diabetes and dysglycaemia at 38 by periodontitis extent and severity (half-mouth measures) at 32. Standard deviation in parentheses. N = 844.

	Periodontitis extent and severity (half-mouth) at 32		
	Mean % of sites with 4+mm AL (SD)	Mean % of sites with 5+mm AL (SD)	Mean AL (SD)
HbA1c at 38			
Mean HbA1c*	0.080[a]	0.014	0.072[a]
Prediabetes			
No (N=699, 82.8%)	1.8 (5.8)	0.5 (2.6)	1.39 (0.41)
Yes (N=145, 17.2%)	3.1 (8.5)[b]	0.9 (4.9)	1.50 (0.53)[b]
Diabetes			
No (N=838, 99.3%)	2.0 (6.4)	0.6 (3.1)	1.41 (0.44)
Yes (N=6, 0.7%)	1.8 (2.2)	0.5 (1.1)	1.58 (0.25)
Dysglycaemia			
No (N=693, 82.1%)	1.8 (5.8)	0.5 (2.6)	1.39 (0.41)
Yes (N=151, 17.9%)	3.0 (8.4)[b]	0.9 (4.8)	1.50 (0.52)[b]

*Spearman correlation coefficient. [a]$p<0.05$; Spearman's rho correlation. [b]$p<0.05$; Mann-Whitney U test.

3.4.2 Glycated haemoglobin – Periodontal experience associations

3.4.2.1 Glycated haemoglobin at 26 - Periodontal experience at 32

Statistically significant associations were found between the prevalence of periodontal disease at 32 and mean HbA1c at 26 whereby those with 1+ or 2+ sites with 4+mm AL at 32 had a higher mean HbA1c at 26 than those without (Table 3.27). In addition, positive correlations were found between mean HbA1c at 26 and the extent of periodontal disease (as defined by the mean % of sites with 4+mm AL) and mean AL at 32. The correlations ranged in value from 0.041 to 0.141 (representing shared variances of 0.2% and 2.0% respectively). Statistical testing was not conducted for associations between the prevalence of diabetes at 26 and periodontal experience at 32 due to insufficient sample size in the category for diabetes at age 26 (Table 3.28). No associations were seen between the prevalence of prediabetes or dysglycaemia at 26 and periodontal experience at 32 (Table 3.28).

Table 3.27. Periodontitis prevalence (half-mouth measures) at 32 by mean HbA1c at 26, and correlations between mean HbA1c at 26 and periodontitis extent and severity (half-mouth measures) at 32. Standard deviation in parentheses. N =788.

	Mean HbA1c at 26 (SD)
Periodontitis prevalence at 32	
1+ sites with 4+mm AL	
No (N = 620, 78.7%)	30.5 (3.1)
Yes (N = 168, 21.3%)	31.5 (3.1)[a]
2+ sites with 4+mm AL	
No (N = 692, 87.8%)	30.6 (3.1)
Yes (N = 96, 12.2%)	31.5 (3.0)[b]
1+ sites with 5+mm AL	
No (N=725, 92.0%)	30.7 (3.1)
Yes (N=63, 8.0%)	31.0 (3.1)
Periodontitis extent at 32	
Mean % of sites with 4+mm AL*	0.141[c]
Mean % of sites with 5+mm AL*	0.041
Periodontitis severity at 32	
Mean AL*	0.109[d]

*Spearman correlation coefficient. [a]p<0.001; Mann-Whitney U test. [b]p<0.005; Mann-Whitney U test. [c]p<0.001; Spearman's rho correlation. [c]p<0.001; Spearman's rho correlation.

Table 3.28. Periodontitis prevalence, extent and severity at 32 (half-mouth measures) by prevalence of prediabetes, diabetes and dysglycaemia at 26. Column percentages or standard deviation in parentheses. N = 788.

	Prediabetes at 26*		**Diabetes at 26***		**Dysglycaemia at 26***	
	No N=786	Yes N=2	No N=788	Yes N=0	No N=786	Yes N=2
Periodontitis prevalence at 32						
1+ sites with 4+mm AL (N=168, 21.3%)	167 (21.2)	1 (50.0)	168 (21.3)	-	167 (21.2)	1 (50.0)
2+ sites with 4+mm AL (N=96, 12.2%)	96 (12.2)	0 (0.0)	96 (12.2)	-	96 (12.2)	0 (0.0)
1+ sites with 5+mm AL (N=63, 8.0%)	63 (8.0)	0 (0.0)	63 (8.0)	-	63 (8.0)	0 (0.0)
Periodontitis extent at 32						
Mean % of sites with 4+mm AL (SD)	1.9 (5.8)	1.3 (1.8)	1.8 (5.8)	-	1.9 (5.8)	1.3 (1.8)
Mean % of sites with 5+mm AL (SD)	0.5 (2.8)	0 (0.0)	0.5 (2.8)	-	0.5 (2.8)	0 (0.0)
Periodontitis severity at 32						
Mean AL (SD)	1.41 (0.43)	1.47 (0.09)	1.41 (0.43)	-	1.41 (0.43)	1.47 (0.09)

*Statistical testing not conducted due to insufficient sample sizes in the categories for prediabetes, diabetes, and dysglycaemia at age 26.

3.4.2.2 Glycated haemoglobin at 26 - Periodontal experience at 38

Statistically significant associations were found between the prevalence of periodontal disease at 38 and mean HbA1c at 26 whereby those with 2+ sites with 4+mm AL at 38 had a higher mean HbA1c at 26 than those without (Table 3.29). In addition, positive correlations were found between mean HbA1c at 26 and the extent of periodontal disease (as defined by the mean % of sites with 4+mm AL) and mean AL at 38. The correlations ranged in value from 0.062 to 0.093 (representing shared variances of 0.4% and 0.9% respectively).

Statistical testing was not conducted for the prevalence of prediabetes, diabetes or dysglycaemia at 26 and periodontal experience at 38 due to insufficient sample sizes in the categories for prediabetes, diabetes, and dysglycaemia at age 26 (Table 3.30).

Table 3.29. Periodontitis prevalence (half-mouth measures) at 38 by mean HbA1c at 26, and correlations between mean HbA1c at 26 and periodontitis extent and severity (half-mouth measures) at 38. Standard deviation in parentheses. N = 773.

	Mean HbA1c at 26 (SD)
Periodontitis prevalence at 38	
1+ sites with 4+mm AL	
No (N = 506, 65.5%)	30.5 (3.1)
Yes (N = 267, 34.5%)	30.9 (3.1)
2+ sites with 4+mm AL	
No (N = 597, 77.2%)	30.5 (3.0)
Yes (N = 176, 22.8%)	31.2 (3.2)[a]
1+ sites with 5+mm AL	
No (N=640, 82.8%)	30.6 (3.1)
Yes (N=133, 17.2%)	31.0 (3.1)
Periodontitis extent at 38	
Mean % of sites with 4+mm AL*	0.092[b]
Mean % of sites with 5+mm AL*	0.062
Periodontitis severity at 38	
Mean AL*	0.093[c]

*Spearman correlation coefficient. [a]p<0.01; Mann-Whitney U test. [b]p<0.05; Spearman's rho correlation. [c]p<0.01; Spearman's rho correlation

Table 3.30. Periodontitis prevalence, extent and severity at 38 (half-mouth measures) by prevalence of prediabetes, diabetes and dysglycaemia at 26. Column percentages or standard deviation in parentheses. N = 773.

	Prediabetes at 26*		**Diabetes at 26***		**Dysglycaemia at 26***	
	No N=771	Yes N=2	No N=773	Yes N=0	No N=771	Yes N=2
Periodontitis prevalence at 38						
1+ sites with 4+mm AL (N=267, 34.5%)	266 (34.5)	1 (50.0)	267 (34.5)	-	266 (34.5)	1 (50.0)
2+ sites with 4+mm AL (N=176, 22.8%)	175 (22.7)	1 (50.0)	176 (22.8)	-	175 (22.7)	1 (50.0)
1+ sites with 5+mm AL (N=133, 17.2%)	133 (17.3)	0 (0.0)	133 (17.2)	-	133 (17.3)	0 (0.0)
Periodontitis extent at 38						
Mean % of sites with 4+mm AL (SD)	5.0 (13.3)	3.8 (5.4)	5.0 (13.3)	-	5.0 (13.3)	3.8 (5.4)
Mean % of sites with 5+mm AL (SD)	2.3 (9.6)	0 (0.0)	2.3 (9.6)	-	2.3 (9.6)	0 (0.0)
Periodontitis severity at 38						
Mean AL (SD)	1.60 (0.74)	1.47 (0.43)	1.60 (0.74)	-	1.60 (0.74)	1.47 (0.43)

*Statistical testing not conducted due to insufficient sample sizes in the categories for prediabetes, diabetes, and dysglycaemia at age 26.

3.4.2.3 Glycated haemoglobin at 32 - Periodontal experience at 38

No associations were seen between periodontal experience at 38 and mean HbA1c at 32 (Table 3.31). Statistical testing was not conducted for associations between periodontal experience at 38 and the prevalence of diabetes at 32 due to insufficient sample size in the category for diabetes at age 32 (Table 3.32). No associations were seen between periodontal experience at 38 and the prevalence of prediabetes or dysglycaemia at 32 (Table 3.32).

Table 3.31. Periodontitis prevalence (half-mouth measures) at 38 by mean HbA1c at 32, and correlations between mean HbA1c at 32 and periodontitis extent and severity (half-mouth measures) at 38. Standard deviation in parentheses. N = 799.

	Mean HbA1c at 32 (SD)
Periodontitis prevalence at 38	
1+ sites with 4+mm AL	
No (N = 521, 65.2%)	33.8 (3.4)
Yes (N = 278, 34.8%)	34.2 (3.8)
2+ sites with 4+mm AL	
No (N = 614, 76.8%)	33.8 (3.3)
Yes (N = 185, 23.2%)	34.5 (4.2)
1+ sites with 5+mm AL	
No (N=657, 82.2%)	33.9 (3.6)
Yes (N=142, 17.8%)	34.1 (3.4)
Periodontitis extent at 38	
Mean % of sites with 4+mm AL*	0.054
Mean % of sites with 5+mm AL*	0.044
Periodontitis severity at 38	
Mean AL*	0.038

*Spearman correlation coefficient.

Table 3.32. Periodontitis prevalence, extent and severity (half-mouth measures) at 38 by prevalence of prediabetes, diabetes and dysglycaemia at 32. Column percentages or standard deviation in parentheses. N = 799.

	Prediabetes at 32		**Diabetes at 32***		**Dysglycaemia at 32**	
	No N=773	Yes N=26	No N=798	Yes N=1	No N=772	Yes N=27
Periodontitis prevalence at 38						
1+ sites with 4+mm AL (N=278, 34.8%)	267 (34.5)	11 (42.3)	277 (34.7)	1 (100.0)	266 (34.5)	12 (44.4)
2+ sites with 4+mm AL (N=185, 23.2%)	176 (22.8)	9 (34.6)	184 (23.1)	1 (100.0)	175 (22.7)	10 (37.0)
1+ sites with 5+mm AL (N=142, 17.8%)	135 (17.5)	7 (26.9)	142 (17.8)	0 (0.0)	135 (17.5)	7 (25.9)
Periodontitis extent at 32						
Mean % of sites with 4+mm AL (SD)	5.0 (13.1)	8.5 (20.3)	5.1 (13.4)	4.8 (0.0)	5.0 (13.1)	8.4 (19.9)
Mean % of sites with 5+mm AL (SD)	2.2 (8.9)	5.7 (19.8)	2.3 (9.5)	0 (0.0)	2.2 (8.9)	5.5 (19.5)
Periodontitis severity at 32						
Mean AL (SD)	1.60 (0.71)	1.89 (1.46)	1.61 (0.75)	1.60 (0.0)	1.60 (0.71)	1.88 (1.43)

*Statistical testing not conducted due to insufficient sample size in the category for diabetes at age 32.

3.5 Group based trajectory modeling analyses

3.5.1 Identification of periodontal GBTM groups

The identification of periodontal GBTM groups included 924 Study members who had two or more periodontal assessments over the 12 years. The zero-inflated Poisson (ZIP) model was used to model the extent of periodontal disease (as measured by the mean % sites with 4+mm AL).

GBTM began with the choice of the number of groups to include in the model. There were a large number of participants with zero % sites with 4+mm AL at each of the three ages. To accommodate this group, the models in the search included one group that was specified to follow a zero-order trajectory (that is, constant over the twelve years). It was hypothesised the other groups would follow a quadratic trajectory (although lower order trajectories were also tested).

GBTM analyses using the mean % sites with 4+mm AL measures at ages 26, 32 and 38 started with 2-group models, testing zero-order, linear and quadratic specifications for the trajectory shapes (Table 3.33). Extra groups were added (3-, 4- and 5-groups) until the best fitting model was established. Some of the 5-group models had an insufficient number of people in one group, and would not allow the calculation of standard errors for the coefficients due to the variance matrix being non-symmetric or highly singular. A 5-group model with one zero-order and four quadratic trajectories (0 2 2 2 2) was found to have the highest (least negative) BIC whether calculated for the total number of participants or total number of observations (Table 3.33). However, the 4-group model with one zero-order and three quadratic trajectories (0 2 2 2) was found to capture the essential features of the data in a more parsimonious, comprehensible and analytically tractable manner, and therefore this was the model chosen.

Table 3.33. BIC for periodontal GBTM according to number of groups and trajectory shapes

Number of groups	Trajectory shapes[1]	BIC[2] (N = 924)	BIC[3] (N = 2685)
2	0 0	-8309.26	-8310.86
2	0 1	-6971.86	-6974.00
2	0 2	-6975.05	-6977.71
3	0 0 0	-7195.13	-7197.80
3	0 1 1	-5728.34	-5732.07
3	0 1 2	-5731.19	-5735.46
3	0 2 1	-5680.38	-5684.65
3	0 2 2	-5680.44	-5685.24
4	0 0 0 0	-7201.96	-5205.70
4	0 1 1 1	-4992.66	-4997.99
4	0 1 1 2	-4994.76	-5000.63
4	0 1 2 2	-4991.18	-4997.58
4	0 2 2 2	**-4968.20**	**-4975.13**
5	0 1 1 1 1*	-5002.90	-5009.83
5	0 1 1 1 2*	-5005.01	-5012.47
5	0 1 1 2 2*	-5072.31	-5080.31
5	0 1 2 2 2	-4978.44	-4986.98
5	0 2 2 2 2	**-4698.66**	**-4707.73**

[1]Trajectory shapes; 0 = zero-order; 1 = linear; 2 = quadratic.
[2]BIC = Bayesian information criterion (for the total number of participants)
[3]BIC = Bayesian information criterion (for the total number of observations)
*Variance matrix is nonsymmetric or highly singular. The regression results display coefficient estimates but no standard errors for any of the coefficients. It is generally due to one or more of the groups having a very small proportion of the observations.

The model had an adequate proportion and sample number in each group: “Very low” 54.0%, “Low” 31.3%, “Medium” 11.3%, and “High” 3.5% (Figure 3.4). The matrix of the observed and predicted values showed that the model fitted the data well and confidence intervals were narrow for each group (Table 3.34). The average posterior probability (AvePP) value was 0.98 or more for each group, well above the recommended minimum AvePP value of 0.70 (Table 3.35). The odds of correct classification based on the posterior probabilities of group membership were well over 5.0 for all four groups, indicating the model had good assignment accuracy (Table 3.35). Finally, there was very close correspondence between each group’s estimated probability and the proportion of Study members assigned to it according to the maximum posterior probability assignment rule (Table 3.36)

Fig 3.4. Periodontal trajectory groups

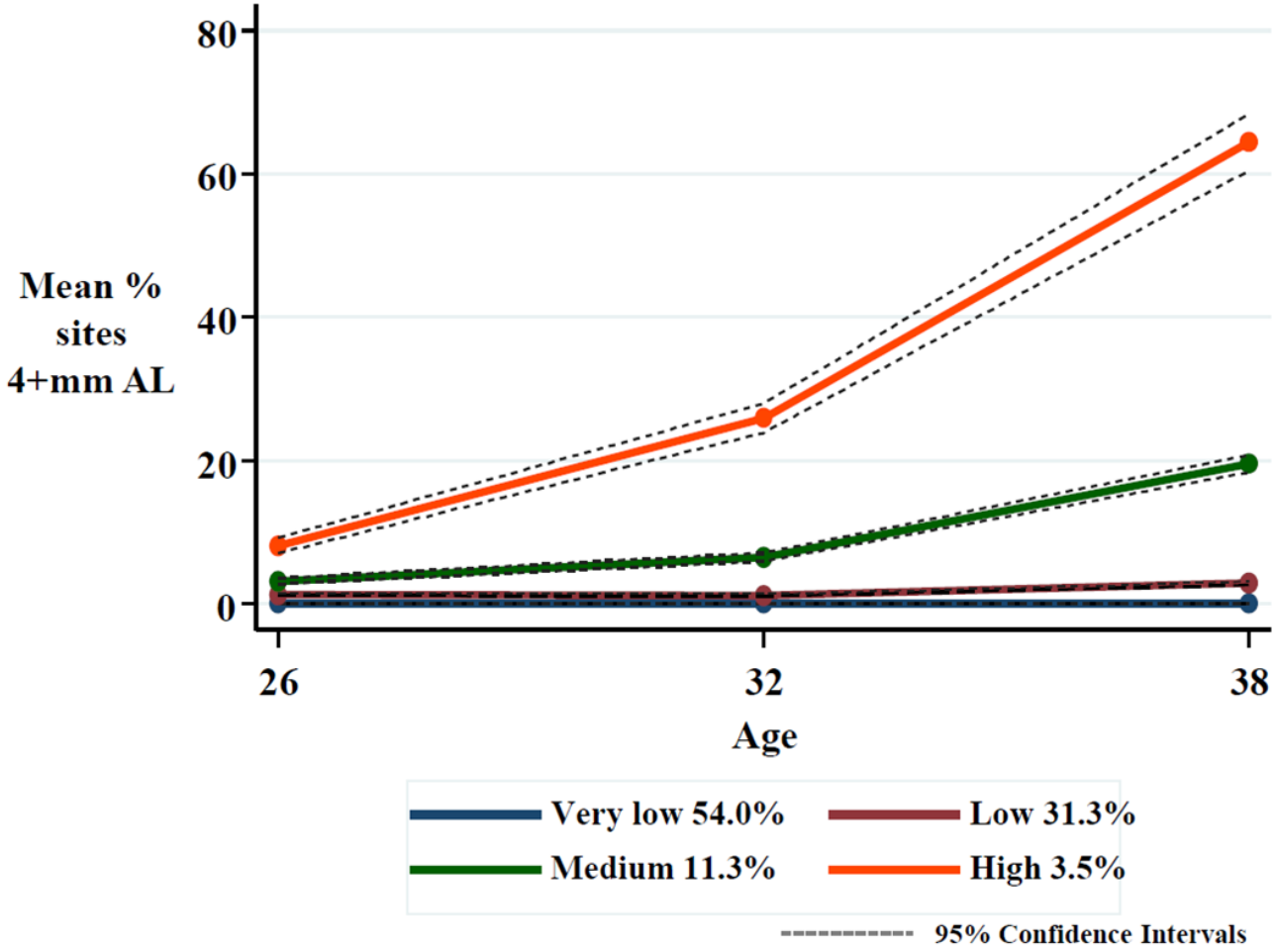


Table 3.34. Matrix of the observed and predicted values for periodontal (mean % sites with 4+mm AL) GBTM groups

	Periodontal trajectory group			
	Very low	**Low**	**Medium**	**High**
Age 26				
Observed values	0.00	1.30	3.18	8.15
Predicted values (95% CI)	0.00 (0.00, 0.00)	1.30 (1.15, 1.45)	3.18 (2.78, 3.59)	8.15 (7.06, 9.23)
Age 32				
Observed values	0.00	1.23	6.54	25.92
Predicted values (95% CI)	0.00 (0.00, 0.00)	1.23 (1.10, 1.37)	6.54 (5.94, 7.14)	25.92 (23.87, 27.96)
Age 38				
Observed values	0.00	2.89	19.56	64.39
Predicted values (95% CI)	0.00 (0.00, 0.00)	2.89 (2.66, 3.13)	19.56 (18.35, 20.77)	64.39 (60.45, 68.33)

Table 3.35. Average posterior probability (AvePP) value and odds of correct classification for periodontal (mean % sites with 4+mm AL) GBTM groups

	Mean % sites with 4+mm AL			
	Trajectory group			
	Very low	**Low**	**Medium**	**High**
Average posterior probability value	0.99	0.99	0.98	0.98
Odds of correct classification	85.2	215.7	385.8	1633.3

Table 3.36. Periodontal trajectory groups' estimated probability and the proportion of Study members classified to each group according to the maximum posterior probability assignment rule

Group	**Estimated group probability**	**Proportion assigned to group according to the maximum posterior probability assignment rule**
Very low	53.8	54.0
Low	31.5	31.3
Medium	11.3	11.3
High	3.4	3.5

3.5.2 Natural history of periodontal disease

The "Very low" group experienced no disease (at least as measured by the extent of sites with 4+mm AL). The "Low" group experienced minimal disease over the 12 years going from a mean % of 1.3 sites with 4+mm AL at 26, dropping slightly to a mean % of 1.2 sites at 32 before rising to a mean % of 2.9 sites at 38 (Figure 3.4). The "Medium" group showed a rise between 26 and 32 going from a mean % of 3.2 sites to a mean % of 6.5 sites before rising sharply to a mean % of 19.6 sites with 4+mm AL at 38. The "High" group showed the greatest increase of all, going from a mean % of 8.2 sites with 4+mm AL to a mean % of 25.9 at 32 followed by a very marked increase to a mean % of 64.4 sites with 4+mm AL at 38. The four trajectory groups had statistically significantly different mean % sites with 4+mm AL at all ages (Table 3.34). The "Very low" group included participants with zero % sites with 4+mm AL at all three ages, and thus had no changes over the twelve years. The "Low" group had no difference in the mean % sites with 4+mm AL between ages 26 and 32, but a significant difference was seen between ages 32 and 38. Both the "Medium" and "High" groups had different mean % sites with 4+mm AL between 26 and 32, and between 32 and 38.

Wald tests found the intercepts of all four groups to be significantly different from one other ($\chi^2 = 49.0$, $p < 0.001$). This was also true of the three groups with linear functions ($\chi^2 = 57.9$, $p < 0.001$), and quadratic functions ($\chi^2 = 50.2$, $p < 0.001$). The "Very low" group had neither linear nor quadratic functions, and therefore had no slope.

The prevalence of low SES, prevalence of periodontal disease, current smoking, regular marijuana use, high plaque score and episodic use of dental services at all three ages showed a clear upward gradient across the four groups from "Very low" to "High" (Tables 3.37 and 3.38). The gradient for male sex was less clear across the groups although the prevalence for the "High" group was one-third higher again than for the "Very low" group. A very clear upward gradient was seen across the groups from "Very low" to "High" for the mean % sites with 1+ sites AL at 26, 32 and 38. At all three ages, Study members in the "High" periodontal trajectory group had a higher mean HbA1c than those in the "Very low" and "Low" groups with a clear upward gradient across the groups at ages 26 and 32, and a less clear gradient at 38. The prevalence of dysglycaemia at 32 and 38 showed a clear upward gradient across the four groups from "Very low" to "High" (although the association at 32 did not reach statistical significance).

Table 3.37. Periodontal trajectory group by demographic characteristics, periodontal and HbA1c variables. Percentages or standard deviation in parentheses. N = 924.

	Periodontal trajectory group			
	Very low (N=499)	Low (N=289)	Medium (N=104)	High (N=32)
Demographic characteristics				
Male (N=469, 50.8%)	223 (44.7)	169 (58.5)	58 (55.8)	19 (59.4)[a]
Low SES at 26 (N=228, 26.0%)	96 (19.7)	81 (30.0)	37 (40.7)	14 (51.9)[b]
Low SES at 32 (N=278, 30.2%)	117 (23.5)	95 (33.1)	47 (45.2)	19 (61.3)[b]
Low SES at 38 (N=175, 19.4%)	51 (10.4)	62 (22.2)	44 (43.1)	18 (56.3)[b]
Periodontal measures				
1+ sites with 4+mm AL at 26 (N=168, 18.7%)	0 (0.0)	97 (34.3)	51 (53.7)	20 (62.5)[c]
1+ sites with 4+mm AL at 32 (N=200, 22.1%)	0 (0.0)	96 (33.8)	74 (72.6)	30 (96.8)[c]
1+ sites with 4+mm AL at 38 (N=307, 34.9%)	0 (0.0)	182 (66.7)	98 (98.0)	27 (100.0)[c]
2+ sites with 4+mm AL at 26 (N=73, 8.1%)	0 (0.0)	27 (9.5)	33 (34.7)	13 (40.6)[c]
2+ sites with 4+mm AL at 32 (N=114, 12.6%)	0 (0.0)	31 (10.9)	53 (52.0)	30 (96.8)[c]
2+ sites with 4+mm AL at 38 (N=203, 23.1%)	0 (0.0)	80 (29.3)	96 (96.0)	27 (100.0)[c]
Mean % sites with 1+ sites with 4+mm AL at 26 (SD)	0 (0.0)	1.3 (2.3)	3.3 (4.4)	8.0 (10.8)[d]
Mean % sites with 1+ sites with 4+mm AL at 32 (SD)	0 (0.0)	1.3 (2.0)	6.5 (7.1)	26.0 (17.6)[d]
Mean % sites with 1+ sites with 4+mm AL at 38 (SD)	0 (0.0)	2.9 (2.9)	19.5 (10.3)	63.9 (23.2)[d]
HbA1c measures				
HbA1c at 26 (SD)	30.4 (3.1)	30.7 (3.1)	31.7 (3.0)	31.9 (3.0)[d]
HbA1c at 32 (SD)	33.7 (3.6)	34.2 (3.9)	34.5 (3.2)	35.6 (2.7)[e]
HbA1c at 38 (SD)	35.0 (4.1)	35.9 (5.9)	36.6 (9.8)	36.1 (3.9)[f]
Dysglycaemia at 26 (N=2, 0.3%)	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
Dysglycaemia at 32 (N=30, 3.6%)	14 (3.2)	9 (3.5)	5 (5.4)	2 (7.1)
Dysglycaemia at 38 (N=153, 17.9%)	73 (15.7)	47 (17.7)	23 (24.0)	10 (33.3)[g]

[a]$p<0.005$; chi-square test. [b]$p<0.001$; chi-square test. [c]$p<0.001$; Fisher's exact test. [d]$p<0.001$; Kruskal–Wallis test. [e]$p<0.01$; Kruskal–Wallis test. [f]$p<0.05$; Kruskal–Wallis test. [g]$p<0.05$; chi-square test.

Table 3.38. Periodontal trajectory group by smoking and oral health care and variables. Percentages in parentheses. N = 924.

	Periodontal trajectory group			
	Very low (N=499)	Low (N=289)	Medium (N=104)	High (N=32)
Smoking				
Current smoker at 26 (N=364, 39.5%)	139 (27.9)	123 (42.6)	75 (73.5)	27 (84.4)[a]
Current smoker at 32 (N=303, 32.9%)	100 (20.0)	107 (37.2)	70 (67.3)	26 (83.9)[a]
Current smoker at 38 (N=234, 25.8%)	66 (13.5)	85 (30.3)	62 (60.2)	21 (65.6)[a]
Regular Marijuana user[1] at 26 (N=75, 8.3%)	18 (3.7)	27 (9.5)	20 (19.6)	10 (31.3)[a]
Regular Marijuana user[1] at 32 (N=80, 8.7%)	21 (4.2)	26 (9.1)	23 (22.1)	10 (32.3)[a]
Regular Marijuana user[1] at 38 (N=53, 5.9%)	15 (3.1)	11 (3.9)	16 (15.5)	11 (34.4)[a]
Oral health care				
High plaque score group at 26 (N=83, 9.2%)	25 (5.1)	36 (12.7)	13 (13.7)	9 (29.0)[a]
High plaque score group at 32 (N=84, 9.3%)	22 (4.5)	27 (9.5)	20 (19.8)	15 (50.0)[a]
High plaque score group at 38 (N=62, 7.1%)	17 (3.5)	21 (7.7)	15 (15.3)	9 (36.0)[a]
Episodic attender at 26 (N=484, 53.1%)	235 (47.7)	152 (53.2)	69 (69.7)	28 (87.5)[a]
Episodic attender at 32 (N=484, 52.7%)	225 (45.3)	158 (55.1)	73 (70.9)	28 (90.3)[a]
Episodic attender at 38 (N=512, 56.5%)	233 (47.5)	173 (61.6)	77 (74.8)	29 (90.6)[a]

[a]$p<0.001$; chi-square test.

3.5.2.1 Time-invariant predictors of periodontal group membership

The first generalisation of the GBTM model linked time-invariant (baseline) individual characteristics and risk factors to the probability of periodontal group membership with the associations between each of these baseline characteristics and the probability of group membership being estimated simultaneously with the estimation of the trajectories themselves (Table 3.39).

Model 1 examined associations with the baseline demographic factors sex and SES at 26. Being male, and being of low SES at 26, increased the odds ratio (OR) of being in a trajectory group other than the "Very low" reference group (Table 3.39). The addition of these factors to the model raised the BIC from -4968.20 for the 'empty' model to -4444.39.

Model 2 added tobacco smoking and regular marijuana use at 26 to Model 1 (Table 3.39). The OR for males of being in the "High" trajectory group was reduced slightly and was no longer statistically significant. The OR for those of low SES at 26 of being in a trajectory group other than the "Very low" was reduced, and the OR for the "Low" group was no longer statistically significant. Strong associations were seen between smoking at 26 and the OR of being in the "Low", "Medium" and "High" groups, and a very clear upward gradient was seen across the groups from "Very low" to "High". Associations were also seen for being a regular marijuana user at 26 and RR of Medium" and "High" group membership. The addition of the baseline smoking factors again raised the BIC.

Model 3 added oral health care factors, high plaque score group and episodic attendance, to Model 2 (Table 3.39). In this model, the OR for those of low SES at 26 of being in the "Medium" group, and the OR for regular marijuana users of being in the "High" group, were no longer statistically significant. However, strong associations were still seen between smoking at 26 and the odds of being in the "Low", "Medium" and "High" groups, with a very clear upward gradient seen across the groups. Study members in the high plaque score group had a higher OR of being in the "Low" and "Medium" groups while those who were episodic attenders had a higher OR of being in the "High" group only. It is worth noting that, in the "High" trajectory group, there were only seven individuals who were regular marijuana users and six who were in the high plaque score group, so a lack of statistical power *may* have led to

a Type 2 error for this group. The addition of the baseline oral health care factors raised the BIC to -4277.73.

Wald tests were conducted to test the equality of the time-invariant factors' estimates across the trajectories. Only smoking showed a differential effect on the trajectory groups ($\chi^2 = 18.6$, $p < 0.001$). The "Low" and "Medium" groups differed from each other ($\chi^2 = 13.5$, $p < 0.001$) as did the "Low" and "High" groups ($\chi^2 = 6.9$, $p < 0.01$). The effect of smoking at 26 on the "Medium" and "High" groups did not differ.

Table 3.39. Adjusted odds ratios for periodontal trajectory group membership

	Periodontal trajectory group membership OR (CI)				
	Very Low	**Low**	**Medium**	**High**	**BIC**
Model 1					
Male	1.00	**1.88 (1.38, 2.56)**	**1.78 (1.10, 2.87)**	**2.53 (1.07, 5.98)**	-4444.39
Low SES at 26	1.00	**1.63 (1.14, 2.32)**	**2.67 (1.64, 4.37)**	**4.46 (2.02, 9.86)**	
Model 2					
Male	1.00	**1.83 (1.33, 2.52)**	**1.78 (1.07, 2.96)**	2.30 (0.94, 5.64)	
Low SES at 26	1.00	1.40 (0.97, 2.03)	**1.78 (1.06, 3.00)**	**2.70 (1.18, 6.18)**	-4368.53
Current smoker at 26	1.00	**1.71 (1.22, 2.41)**	**5.62 (3.32, 9.54)**	**9.39 (3.27, 26.95)**	
Regular Marijuana user[1] at 26	1.00	1.78 (0.91, 3.49)	**2.88 (1.33, 6.25)**	**3.92 (1.40, 10.97)**	
Model 3					
Male	1.00	**1.67 (1.21, 2.32)**	**1.72 (1.00, 2.94)**	2.26 (0.85, 6.00)	
Low SES at 26	1.00	1.40 (0.96, 2.04)	1.67 (0.97, 2.87)	**2.86 (1.23, 6.69)**	
Current smoker at 26	1.00	**1.66 (1.17, 2.36)**	**4.89 (2.82, 8.49)**	**7.29 (2.43, 21.82)**	-4277.73
Regular Marijuana user[1] at 26	1.00	1.75 (0.88, 3.48)	**2.86 (1.30, 6.28)**	2.62 (0.90, 7.67)	
High plaque score group at 26	1.00	**2.04 (1.13, 3.66)**	**2.24 (1.01, 4.96)**	2.34 (0.78, 7.00)	
Episodic attender at 26	1.00	0.96 (0.69, 1.33)	1.27 (0.74, 2.18)	**5.03 (1.24, 20.37)**	

CI; confidence intervals. BIC; Bayesian information criterion (for the total number of participants).
Reference categories: female (for male); high SES at 26 (for low SES at 26); not current smoker at 26 (for current smoker at 26); not regular marijuana user at 26 (for regular marijuana user at 26); low plaque score group at 26 (for high plaque score group at 26); and non-episodic attender at 26 (for episodic attender at 26).
Statistically significant associations in **bold** type.

3.5.2.2 Effect of time-varying covariates (effect modifiers)

The second generalisation of the GBTM model added the time-varying covariate dysglycaemia to the trajectories themselves, in order to examine whether dysglycaemia at 32 and 38 altered the course of the "Low", "Medium" and "High" trajectories (Table 3.40). It was not appropriate to generate coefficients and confidence intervals for the "Very low" trajectory due to its very large negative intercept (as a result of this trajectory being made up of participants with zero % sites with 4+mm AL). All the coefficients were positive, indicating that having dysglycaemia at 32 and 38 was associated with an upward shift of the trajectories. However, these associations were statistically significant for the "High" trajectory only. The addition of dysglycaemia case status to the model raised the BIC to -3939.61. This represented an improvement of 26.1% over the unadjusted model.

A detailed examination of the predicted values for each of the trajectories confirmed this upward shift associated with dysglycaemia for the "Low", "Medium" and "High" trajectories at ages 32 and 38 (Table 3.41). However, overlapping confidence intervals for most of the parameters demonstrated that the associations were statistically significant for the "High" trajectory at age 38 only. The marked upward shift in the "High" trajectory at age 38 (fully adjusted model) can be seen graphically (Fig 3.5.).

Table 3.40. Coefficients for shift in periodontal trajectory per unit change for dysglycaemia at 32 and 38

	Periodontal trajectory group			
	Low	Medium	High	BIC
Shift in trajectory				
Unadjusted model[1]	0.116 (-0.086, 0.319)	0.080 (-0.062, 0.222)	**0.178 (0.073, 0.283)**	-4532.52
Model 3[2]	0.052 (-0.195, 0.230)	0.128 (-0.035, 0.291)	**0.195 (0.089, 0.300)**	-3939.61

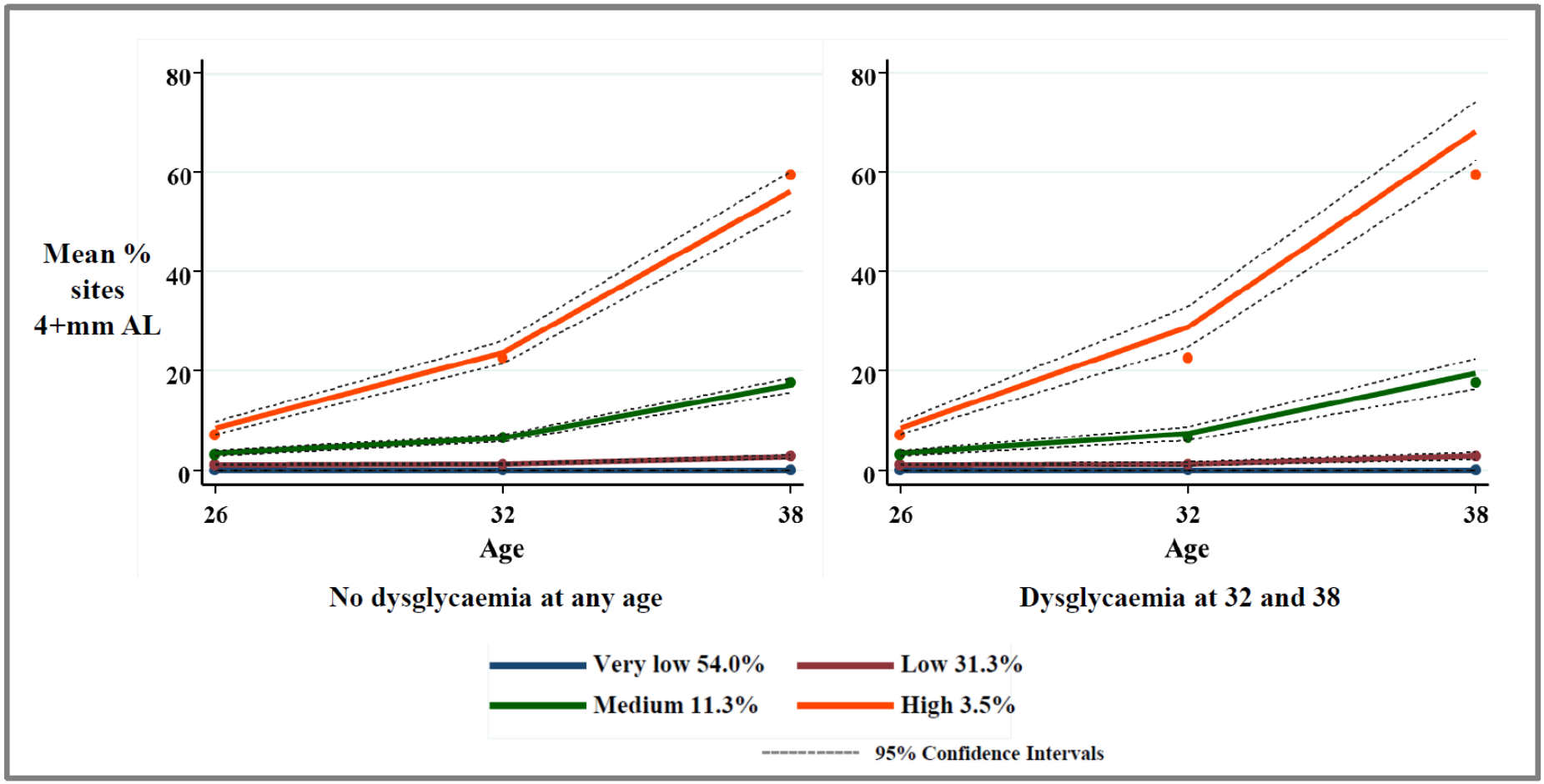
[1]Unadjusted model includes time-varying covariates only.
[2]Model 3 includes both time-invariant covariates (sex, SES at 26, smoking at 26, marijuana use at 26, high plaque score group membership at 26, and use of dental services at 26) and time-varying covariates.
Statistically significant coefficients shown in **bold** type.

Table 3.41. Predicted values for periodontal (mean % sites with 4+mm AL) GBTM groups with and without dysglycaemia at 32 and 38. Confidence intervals in parentheses.

	Periodontal trajectory group			
	Very low	**Low**	**Medium**	**High**
Age 26				
Fully adjusted model (Model 3)				
No dysglycaemia at 32 and 38	0.00 (0.00, 0.00)	1.16 (1.01, 1.31)	3.40 (2.87, 3.93)	8.52 (7.27, 9.77)
Dysglycaemia at 32 and 38	0.00 (0.00, 0.00)	1.16 (1.01, 1.31)	3.40 (2.87, 3.93)	8.52 (7.27, 9.77)
Age 32				
Fully adjusted model (Model 3)				
No dysglycaemia at 32 and 38	0.00 (0.00, 0.00)	1.27 (1.11, 1.44)	6.47 (5.77, 7.17)	23.79 (21.52, 26.05)
Dysglycaemia at 32 and 38	0.00 (0.00, 0.00)	1.34 (0.97, 1.71)	7.35 (5.99, 8.71)	28.89 (24.81, 32.98)
Age 38				
Fully adjusted model (Model 3)				
No dysglycaemia at 32 and 38	0.00 (0.00, 0.00)	2.74 (2.43, 3.06)	17.09 (15.64, 18.53)	**56.23 (52.29, 60.17)**
Dysglycaemia at 32 and 38	0.00 (0.00, 0.00)	2.89 (2.19, 3.59)	19.41 (16.37, 22.45)	**68.30 (62.35, 74.26)**

Significantly different trajectories shown in **bold** type.

Fig 3.5. Periodontal GBTM trajectories for (a) no prevalence of and (b) prevalence of dysglycaemia at 32 and 38.



3.5.3 Identification of HbA1c GBTM groups

Identification of HbA1c GBTM groups began with 897 Study members who had two or more HbA1c assays over the 12 years. The four most extreme outliers were also removed because they gave rise to an analytically intractable 4-person group. The censored normal model was used to model mean HbA1c, with censors set at minimum 10mmol/mol and maximum 150mmol/mol.

The HbA1c GBTM proceeded in a similar way to the periodontal GBTM, beginning with the choice of the number of groups to include in the model (Table 3.42). Although the (1 2 2) model had a slightly higher BIC than the (2 2 2) model, the latter fitted the data better. Both the 4-group and the 5-group models gave rise to one or more groups with a very small proportion of the observations (ten or less individuals). Thus the 3-group model with three quadratic trajectories (2 2 2) was chosen.

Table 3.42. BIC for HbA1c GBTM according to number of groups and trajectory shapes.

Number of groups	Trajectory shapes[1]	BIC[2] (N = 896)	BIC[3] (N = 2520)
2	0 0	-7205.68	-7207.75
2	0 1	-6912.80	-6915.38
2	0 2	-6898.46	-6901.56
2	1 1	-6781.01	-6784.11
2	1 2	-6839.65	-6843.26
2	2 2	-6828.91	-6833.05
3	0 0 0	-6879.95	-6883.05
3	0 1 1	-6371.67	-6375.80
3	0 1 2	-6360.70	-6365.34
3	0 2 2	-6335.71	-6340.88
3	1 1 1	-6346.80	-6351.45
3	1 1 2	-6338.70	-6343.86
3	1 2 1	-6314.04	-6319.21
3	1 2 2	-6311.06	-6316.74
3	2 1 0	-6382.19	-6386.84
3	2 1 1	-6342.69	-6347.85
3	2 1 2	-6337.07	-6342.75
3	2 2 1	-6313.65	-6319.33
3	2 2 2	**-6311.47**	**-6317.67**
4	0 0 0 0*	-6882.62	-6878.49
5	0 0 0 0 0*	-6890.45	-6885.29

[1]Trajectory shapes; 0 = zero-order; 1 = linear; 2 = quadratic.
[2]BIC = Bayesian information criterion (for the total number of participants)
[3]BIC = Bayesian information criterion (for the total number of observations)
*One or more of the groups had a very small proportion of the observations.

The model had an adequate proportion and sample number in each group: “Low” 11.0%, “Medium” 54.0%, and “High” 35.0% (Figure 3.6). The matrix of the observed and predicted values showed that the model fitted the data well and confidence intervals were narrow for each group (Table 3.43). The average posterior probability (AvePP) value was 0.84 or more for each group; well above the recommended minimum AvePP value of 0.70 (Table 3.44). The odds of correct classification based on the posterior probabilities of group membership were over 5.0 for all three groups, indicating the model had good assignment accuracy (Table 3.44). Finally, there was very close correspondence between each group’s estimated probability and the proportion of Study members assigned to it according to the maximum posterior probability assignment rule (Table 3.45).

Fig 3.6. HbA1c trajectory groups

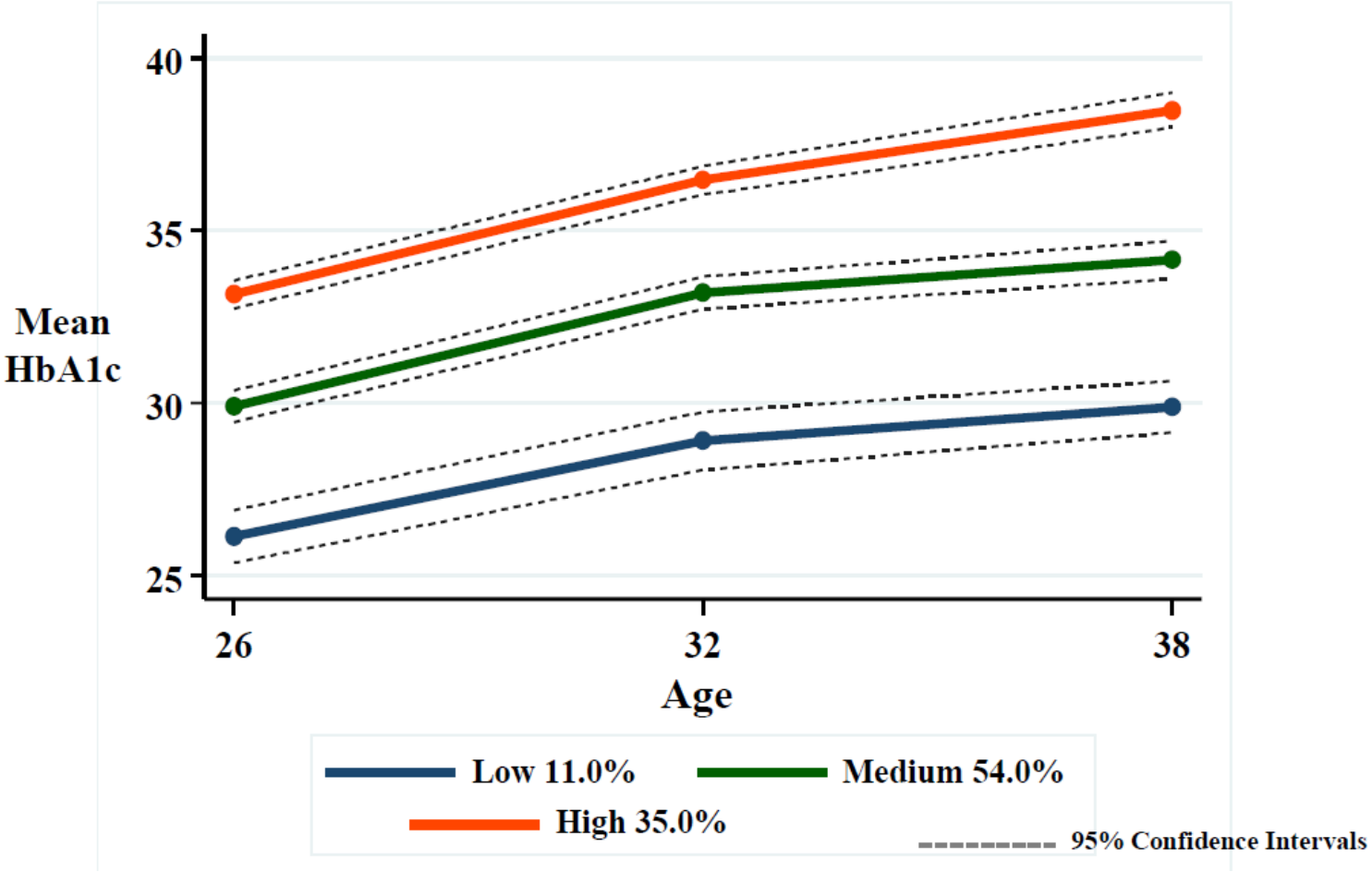


Table 3.43. Matrix of the observed and predicted values for mean HbA1c GBTM groups

	HbA1c trajectory group		
	Low	**Medium**	**High**
Age 26			
Observed values	26.13	29.91	33.14
Predicted values (95% CI)	26.13 (25.37, 26.89)	29.91 (29.45, 30.36)	33.14 (32.73, 33.55)
Age 32			
Observed values	28.90	33.20	36.45
Predicted values (95% CI)	28.90 (28.06, 29.74)	33.20 (32.73, 33.66)	36.45 (36.04, 36.87)
Age 38			
Observed values	29.89	34.15	38.49
Predicted values (95% CI)	29.89 (29.14, 30.63)	34.15 (33.59, 34.70)	38.49 (37.98, 38.99)

Table 3.44. Average posterior probability (AvePP) value and odds of correct classification for HbA1c GBTM groups

	HbA1c trajectory group		
	Low	**Medium**	**High**
Average posterior probability value	0.84	0.86	0.87
Odds of correct classification	43.3	5.2	12.6

Table 3.45. HbA1c trajectory groups' estimated probability and the proportion of Study members classified to each group according to the maximum posterior probability assignment rule

Group	**Estimated group probability**	**Proportion assigned to group according to the maximum posterior probability assignment rule**
Low	11.3	11.0
Medium	52.5	54.0
High	36.1	35.0

3.5.4 Natural history of glycated haemoglobin

The three groups had statistically significantly different mean HbA1c at age 26 (as evidenced by non-overlapping confidence intervals at age 26), and followed similar rising trajectories to age 32, with increases in mean HbA1c of 2.8 mmol/mol, 3.3 mmol/mol and 3.3 mmol/mol for the "Low", "Medium", and "High" groups respectively over the six years (Table matrix and Fig). While the trajectories for all three groups rose less steeply between ages 32 and 38, the "High" group followed a steeper trajectory than the other two groups with increases in mean HbA1c of 1.0 mmol/mol, 1.0 mmol/mol and 2.0 mmol/mol for the "Low", "Medium", and "High" groups respectively. Overall, the "Low" group had a 4.4% increase, the "Medium" group had a 4.2% increase and the "High" group had a 6.1% increase over the twelve years from 26 to 38. While the differences between the mean HbA1c values at 26 and 32 were statistically significant for all three groups, the differences between 32 and 38 were significant for the "High" group only.

Wald tests found that the intercepts ($\chi^2 = 4.8$, $p < 0.05$) and the quadratic functions ($\chi^2 = 4.4$, $p < 0.05$) of the "Medium" and "High" trajectory groups differed from each other. No differences were found between the intercepts or the slopes of the "Low" and "Medium" groups or the "Low" and "High" groups.

Low SES at 26 and 38, mean HbA1c at all three ages, dysglycaemia at 32 and 38, and having 1+ sites with 4+mm AL at 32 showed a clear upward gradient across the three groups from "Low" to "High" (Table). The gradient for males was less clear across the groups, although there were a higher proportion of males in the "High" group than in the "Low" group. Mean weight, mean WC, mean waist-hip ratio and mean waist-height ratio (at age 38 only) followed a similar pattern, with those in "High" group experiencing higher mean values at all three ages than those in the "Low" group (Table). The change over time was similar for the high risk anthropometric groups, although statistical significance was not reached at all ages.

Table 3.46. HbA1c trajectory group by demographic, HbA1c and periodontal variables. Percentages or standard deviation in parentheses. N = 893

	HbA1c trajectory group		
	Low (N=98)	Medium (N=482)	High (N=313)
Demographic characteristics			
Male (N=457, 51.2%)	47 (48.0)	226 (46.9)	184 (58.8)[a]
Low SES at 26 (N=228, 26.9%)	20 (20.8)	110 (24.4)	98 (32.5)[b]
Low SES at 32 (N=272, 30.5%)	24 (24.5)	155 (32.2)	93 (29.9)
Low SES at 38 (N=169, 19.3%)	8 (8.2)	85 (18.0)	76 (24.9)[a]
HbA1c measures			
HbA1c at 26 (SD)	25.9 (1.9)	29.9 (2.1)	33.4 (2.1)[c]
HbA1c at 32 (SD)	28.6 (2.2)	33.2 (2.1)	36.7 (2.2)[c]
HbA1c at 38 (SD)	29.6 (2.1)	34.1 (2.3)	38.7 (2.7)[c]
Dysglycaemia at 26 (N=2, 0.3%)	0 (0.0)	0 (0.0)	2 (0.7)
Dysglycaemia at 32 (N=27, 3.2%)	0 (0.0)	1 (0.2)	26 (8.9)[d]
Dysglycaemia at 38 (N=149, 17.5%)	0 (0.0)	5 (1.1)	144 (48.3)[d]
Periodontal measures			
1+ sites with 4+mm AL at 26 (N=157, 18.5%)	11 (12.0)	82 (17.8)	64 (21.6)
1+ sites with 4+mm AL at 32 (N=187, 21.9%)	12 (13.6)	97 (20.8)	78 (26.1)[b]
1+ sites with 4+mm AL at 38 (N=291, 34.6%)	28 (29.8)	156 (34.5)	107 (36.3)
2+ sites with 4+mm AL at 26 (N=69, 8.1%)	3 (3.3)	36 (7.8)	30 (10.1)
2+ sites with 4+mm AL at 32 (N=107, 12.5%)	6 (6.8)	57 (12.2)	44 (14.7)
2+ sites with 4+mm AL at 38 (N=192, 22.8%)	17 (18.1)	100 (22.1)	75 (25.4)
Mean % sites with 4+mm AL at 26 (SD)	0.5 (2.0)	1.0 (3.1)	1.3 (3.9)
Mean % sites with 4+mm AL at 32 (SD)	0.9 (2.7)	1.9 (6.4)	2.5 (7.0)[e]
Mean % sites with 4+mm AL at 38 (SD)	2.6 (6.4)	4.7 (12.5)	6.4 (16.0)
Smoking			
Smoker at 26 (N=356, 40.0%)	23 (23.7)	189 (39.3)	144 (46.2)[f]
Smoker at 32 (N=300, 33.6%)	22 (22.5)	157 (32.6)	121 (38.8)[g]
Smoker at 38 (N=232, 26.4%)	11 (11.2)	117 (24.7)	104 (34.0)[f]

[a]$p<0.005$; chi-square test. [b]$p<0.05$; chi-square test. [c]$p<0.001$; Kruskal–Wallis test. [d]$p<0.001$; Fisher's exact test. [e]$p<0.05$; Kruskal–Wallis test. [f]$p<0.001$; chi-square test. [g]$p<0.01$; chi-square test.

Table 3.47. HbA1c trajectory group by anthropometric variables. Percentages or standard deviation in parentheses. N = 893.

	HbA1c trajectory group		
	Low (N=98)	Medium (N=482)	High (N=313)
Anthropometric measures			
Mean weight in kg at 26 (SD)	73.7 (11.3)	72.8 (13.5)	76.2 (16.1)[a]
Mean weight in kg at 32 (SD)	77.2 (13.6)	76.4 (15.2)	81.0 (18.6)[b]
Mean weight in kg at 38 (SD)	79.7 (13.8)	78.9 (16.1)	83.7 (19.2)[b]
Mean BMI at 26 (SD)	24.8 (3.4)	24.7 (3.9)	25.5 (4.9)
Mean BMI at 32 (SD)	25.6 (4.0)	25.8 (4.5)	26.8 (5.5)
Mean BMI at 38 (SD)	26.7 (4.4)	26.7 (4.9)	27.9 (5.9)
Mean WC in mm at 26 (SD)	795.6 (81.6)	792.0 (91.6)	817.7 (106.4)[b]
Mean WC in mm at 32 (SD)	833.9 (99.8)	834.4 (105.8)	863.0 (123.1)[b]
Mean WC in mm at 38 (SD)	851.8 (103.6)	850.7 (118.2)	885.8 (140.0)[c]
Mean waist-hip ratio at 26 (SD)	0.79 (0.07)	0.79 (0.07)	0.81 (0.07)[d]
Mean waist-hip ratio at 32 (SD)	0.82 (0.08)	0.83 (0.07)	0.84 (0.07)[a]
Mean waist-hip ratio at 38 (SD)	0.84 (0.08)	0.85 (0.08)	0.87 (0.08)[d]
Mean waist-height ratio at 26 (SD)	0.46 (0.05)	0.46 (0.05)	0.47 (0.06)
Mean waist-height ratio at 32 (SD)	0.48 (0.05)	0.49 (0.06)	0.50 (0.07)
Mean waist-height ratio at 38 (SD)	0.49 (0.06)	0.50 (0.07)	0.51 (0.08)[a]
High BMI group at 26 (N=98, 11.4%)	9 (9.6)	47 (10.0)	42 (14.0)
High BMI group at 32 (N=151, 17.5%)	10 (10.8)	70 (14.9)	71 (23.4)[e]
High BMI group at 38 (N=207, 23.9%)	18 (18.4)	95 (20.5)	94 (30.9)[e]
High WC group at 26 (N=56, 6.6%)	3 (3.2)	24 (5.2)	29 (9.9)[f]
High WC group at 32 (N=132, 15.3%)	7 (7.5)	66 (14.0)	59 (19.5)[g]
High WC group at 38 (N=176, 20.3%)	17 (17.4)	82 (17.7)	77 (25.3)[h]
High waist-hip group at 26 (N=54, 6.3%)	5 (5.3)	22 (4.7)	27 (9.18)
High waist-hip group at 32 (N=183, 21.2%)	19 (20.4)	93 (19.8)	71 (23.5)
High waist-hip group at 38 (N=294, 34.1%)	28 (28.9)	145 (31.4)	121 (39.8)[h]
High waist-height group at 26 (N=190, 22.3%)	14 (14.9)	91 (19.5)	85 (28.9)[e]
High waist-height group at 32 (N=327, 37.8%)	30 (32.3)	169 (35.9)	128 (42.4)
High waist-height group at 38 (N=391, 45.2%)	41 (41.8)	196 (42.2)	154 (50.7)

[a]p<0.05; Kruskal–Wallis test. [b]p<0.01; Kruskal–Wallis test. [c]p<0.005; Kruskal–Wallis test. [d]p<0.001; Kruskal–Wallis test. [e]p<0.005; chi-square test. [f]p<0.05; Fisher's exact test. [g]p<0.001; Fisher's exact test. [h]p<0.05; chi-square test.

High BMI group; 30+. High WC group; women 880+mm, men 1020+mm. High waist-hip ratio group; women 0.85+, men 0.90+. High waist-height ratio group; 0.50+.

3.5.4.1 Time-invariant predictors of HbA1c group membership

As previously described, a generalisation of the GBTM model linked time-invariant (baseline) individual characteristics and risk factors to the probability of periodontal group membership with the associations between each of these baseline characteristics and the probability of group membership being estimated simultaneously with the estimation of the trajectories themselves (Table 3.48).

Model 1 examined associations between baseline demographic factors sex and SES at 26, and smoking at 26. Being a smoker at 26 increased the odds of being in the "Medium" or "High" trajectory group (Table 3.48). Being male increased the odds of being in the "High" trajectory group. The addition of these factors to the model raised the BIC from -6317.67 for the 'empty' model to -6025.06.

To examine the individual effects of anthropometric risk factors, Models 2 (a), 2(b), 2(c) and 2(d) added high BMI group, high WC group, high waist-hip group and high waist-height group membership (respectively) to Model 1 (Table 3.48). Both high WC group and high waist-height membership increased the odds of being in the "High" trajectory, and the inclusion of either of these two high risk groups increased the BIC (to -5852.70 and -5853.31 respectively). Smoking at 26 continued to increase the odds of belonging to the "Medium" or "High" trajectory group, whereas being male was associated with being in the "High" group only. Wald tests were conducted to test the equality of the time-invariant factors estimates across the trajectories. The effect of sex, smoking, and high WC group membership differed for the "Medium" and "High" trajectories in the high WC group model ($\chi^2 = 12.0$, $p < 0.001$ for sex; $\chi^2 = 6.5$, $p < 0.05$ for smoking; and $\chi^2 = 7.1$, $p < 0.01$ for high WC group membership). The effect of sex, smoking and high waist-height group membership differed for the "Medium" and "High" trajectories in the high waist-height group model ($\chi^2 = 9.7$, $p < 0.005$ for sex; $\chi^2 = 7.7$, $p < 0.01$ for smoking; and $\chi^2 = 7.5$, $p < 0.01$ for high waist-height group membership).

Finally, it was considered whether the addition of high BMI group membership improved the model. Models 3(a) and 3(b) added high BMI group membership to the high WC group and high waist-height group models (Table 3.49). This addition did not improve the models. Instead, it lowered the BIC to -5856.89 and -5856.54 respectively. This may have been due to

the BIC generally favouring more parsimonious models. However, the AIC (which does not penalise as much as the BIC for more complex models) also showed deterioration with the addition of high BMI group membership (from -5803.32 to -5805.13 for the high WC group model, and from -5803.00 to -5804.78 for the waist-height group model).

Table 3.48. Adjusted odds ratio (OR) for HbA1c trajectory group membership

	HbA1c trajectory group membership OR (CI)			
	Low	**Medium**	**High**	**BIC**
Model 1				
Male	1.00	0.99 (0.57, 1.75)	**1.78 (1.02, 3.12)**	-6025.06
Low SES at 26	1.00	1.00 (0.52, 1.92)	1.22 (0.65, 2.30)	
Smoker at 26	1.00	**1.95 (1.03, 3.69)**	**3.21 (1.73, 5.96)**	
Model 2 (a)				
Male	1.00	0.99 (0.56, 1.76)	**1.91 (1.08, 3.38)**	-5906.20
Low SES at 26	1.00	1.13 (0.57, 2.24)	1.33 (0.70, 2.55)	
Smoker at 26	1.00	**1.91 (1.02, 3.60)**	**3.25 (1.76, 6.01)**	
High BMI group at 26	1.00	1.05 (0.41, 2.68)	1.91 (0.79, 4.58)	
Model 2 (b)				
Male	1.00	1.07 (0.61, 1.86)	**2.27 (1.27, 4.03)**	-5850.38
Low SES at 26	1.00	1.11 (0.57, 2.17)	1.30 (0.69, 2.47)	
Smoker at 26	1.00	**1.90 (1.03, 3.49)**	**3.25 (1.78, 5.94)**	
High WC group at 26	1.00	1.80 (0.37, 8.72)	**5.32 (1.21, 23.34)**	
Model 2 (c)				
Male	1.00	1.03 (0.58, 1.81)	**1.80 (1.02, 3.18)**	-5853.48
Low SES at 26	1.00	1.15 (0.58, 2.28)	1.34 (0.70, 2.57)	
Smoker at 26	1.00	**1.89 (1.00, 3.56)**	**3.20 (1.73, 5.93)**	
High waist-hip group at 26	1.00	0.77 (0.22, 2.62)	1.80 (0.60, 5.34)	
Model 2 (d)				
Male	1.00	1.00 (0.57, 1.75)	**1.92 (1.09, 3.40)**	-5850.06
Low SES at 26	1.00	1.12 (0.57, 2.20)	1.26 (0.66, 3.42)	
Smoker at 26	1.00	**1.93 (1.03, 3.60)**	**3.46 (1.87, 6.40)**	
High waist-height group at 26	1.00	1.31 (0.63, 2.72)	**2.51 (1.26, 5.01)**	

CI; confidence intervals. BIC; Bayesian information criterion (for the total number of participants).
Reference categories: female (for male); high SES at 26 (for low SES at 26); non-smoker at 26 (for smoker at 26); not in high BMI group at 26 (for high BMI group at 26); not in high WC group at 26 (for high WC group at 26); not in high waist-hip group at 26 (for high waist-hip group at 26); and not in high waist-height group at 26 (for high waist-height group at 26). Statistically significant associations in **bold** type.

Table 3.49. Adjusted odds ratio (OR) for HbA1c trajectory group membership

	HbA1c trajectory group membership OR (CI)			
	Low	**Medium**	**High**	**BIC**
Model 3 (a)				
Male	1.00	1.07 (0.62, 1.87)	**2.27 (1.28, 4.04)**	-5856.89
Low SES at 26	1.00	1.11 (0.57, 2.17)	1.29 (0.68, 2.45)	
Smoker at 26	1.00	**1.89 (1.03, 3.48)**	**3.24 (1.78, 5.92)**	
High WC group at 26	1.00	2.23 (0.37, 13.54)	**5.53 (1.01, 30.25)**	
High BMI group at 26	1.00	0.77 (0.28, 2.12)	0.96 (0.35, 2.58)	
Model 3 (b)				
Male	1.00	0.98 (0.56, 1.73)	**1.90 (1.07, 3.39)**	-5856.54
Low SES at 26	1.00	1.11 (0.57, 2.19)	1.26 (0.66, 2.41)	
Smoker at 26	1.00	**1.93 (1.03, 3.60)**	**3.44 (1.86, 6.37)**	
High waist-height group at 26	1.00	1.58 (0.60, 4.14)	**2.76 (1.10, 6.93)**	
High BMI group at 26	1.00	0.69 (0.20, 2.30)	0.83 (0.26, 2.61)	

CI; confidence intervals. BIC; Bayesian information criterion (for the total number of participants).
Reference categories: female (for male); high SES at 26 (for low SES at 26); non-smoker at 26 (for smoker at 26); not in high BMI group at 26 (for high BMI group at 26); not in high WC group at 26 (for high WC group at 26); not in high waist-hip group at 26 (for high waist-hip group at 26); and not in high waist-height group at 26 (for high waist-height group at 26). Statistically significant associations in **bold** type.

3.5.4.2 Effect of time-varying covariates (effect modifiers)

The second generalisation of the GBTM model added the time-varying covariate periodontitis (as measured by prevalence of 1+ sites with 4+mm AL) to the trajectories themselves to examine whether periodontitis at 32 and 38 altered the course of the "Low", "Medium" and "High" trajectories (Table 3.50). This was carried out for Model 2(d), the high waist-height group model. All of the coefficients were positive, indicating that having periodontitis at 32 and 38 was associated with an upward shift of the trajectories. However, these associations were statistically significant for the "High" trajectory only. The addition of periodontitis case status to the model raised the BIC to -5628.83. These values represented an improvement of 12.2% over the completely unadjusted (no time-invariant or time-varying covariates) model.

A detailed examination of the predicted values for each of the trajectories confirmed this upward shift associated with periodontitis for the "Low", "Medium" and "High" trajectories at ages 32 and 38 (Table 3.51). However, overlapping confidence intervals were seen for all of the parameters, indicating that none of the associations were statistically significant. While the upward shift in the trajectories (fully adjusted model) can be seen graphically, the overlapping confidence intervals are also evident (Fig 3.7).

As a sensitivity analysis, this generalisation was also carried out for a more rigorous periodontitis case definition, 2+ sites with 4+mm AL. The findings were almost identical to those for 1+ sites with 4+mm AL analysis (data not shown).

Table 3.50. Coefficients for shift in HbA1c trajectory per unit change for prevalence of 1+ sites with 4+mm AL at 32 and 38

	HbA1c trajectory group			
	Low	Medium	High	BIC
Shift in trajectory				
Unadjusted model[1]	0.787 (-0.253, 1.827)	0.245 (-0.146, 0.636)	**0.596 (0.211, 0.982)**	-6055.00
High waist-height group model[2]	0.495 (-0.577, 1.568)	0.238 (-0.178, 0.653)	**0.562 (0.152, 0.971)**	-5628.83

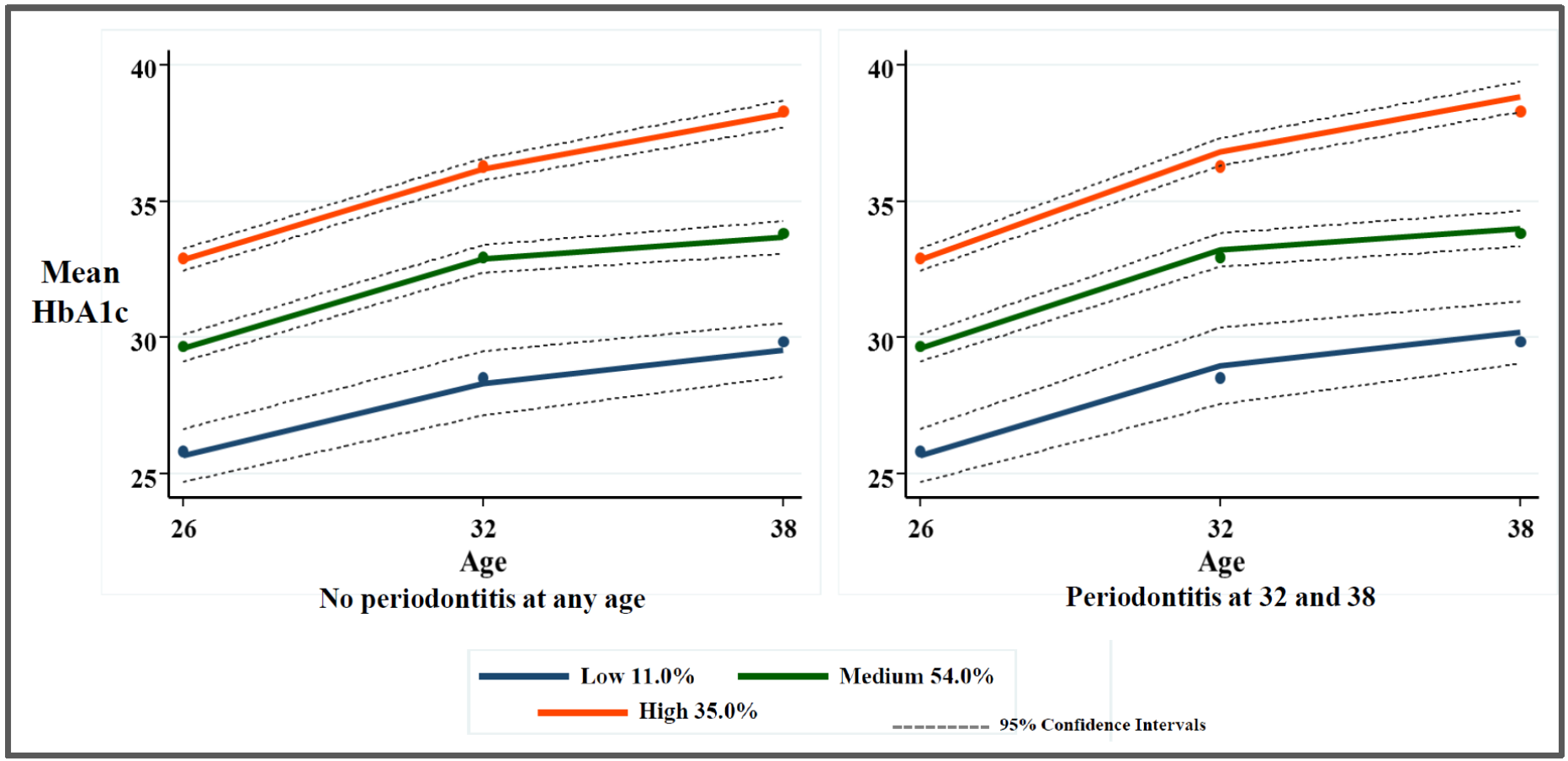
[1]Unadjusted model includes time-varying covariates only.
[2]The high waist-height group model includes both time-invariant covariates (sex, SES at 26, smoking at 26 and membership of the high waist-height group at 26) and time-varying covariates.
Statistically significant coefficients shown in **bold** type.

Table 3.51. Predicted values for HbA1c GBTM groups with and without periodontitis at 32 and 38. Confidence intervals in parentheses.

	HbA1c trajectory group		
	Low	**Medium**	**High**
Age 26			
Fully adjusted model			
No periodontitis at 32 and 38	25.62 (24.62, 26.61)	29.58 (29.09, 30.07)	32.84 (32.44, 33.24)
Periodontitis at 32 and 38	25.62 (24.62, 26.61)	29.58 (29.09, 30.07)	32.84 (32.44, 33.24)
Age 32			
Fully adjusted model			
No periodontitis at 32 and 38	28.25 (27.05, 29.44)	32.85 (32.34, 33.36)	36.15 (35.75, 36.55)
Periodontitis at 32 and 38	28.74 (27.30, 30.18)	33.08 (32.48, 33.69)	36.71 (36.22, 37.20)
Age 38			
Fully adjusted model			
No periodontitis at 32 and 38	29.52 (28.52, 30.51)	33.64 (33.04, 34.24)	38.17 (37.68, 38.67)
Periodontitis at 32 and 38	30.01 (28.84, 31.18)	33.88 (33.24, 34.52)	38.73 (38.20, 39.27)

Fully adjusted model includes time-invariant covariates sex, SES at 26, smoking at 26 and membership of the high waist-height group, and time-varying covariate prevalence of periodontitis (as measured by prevalence of 1+ sites with 4+mm AL) at 32 and 38.

Fig 3.7. HbA1c GBTM trajectories for (a) no periodontitis and (b) periodontitis at 32 and 38.

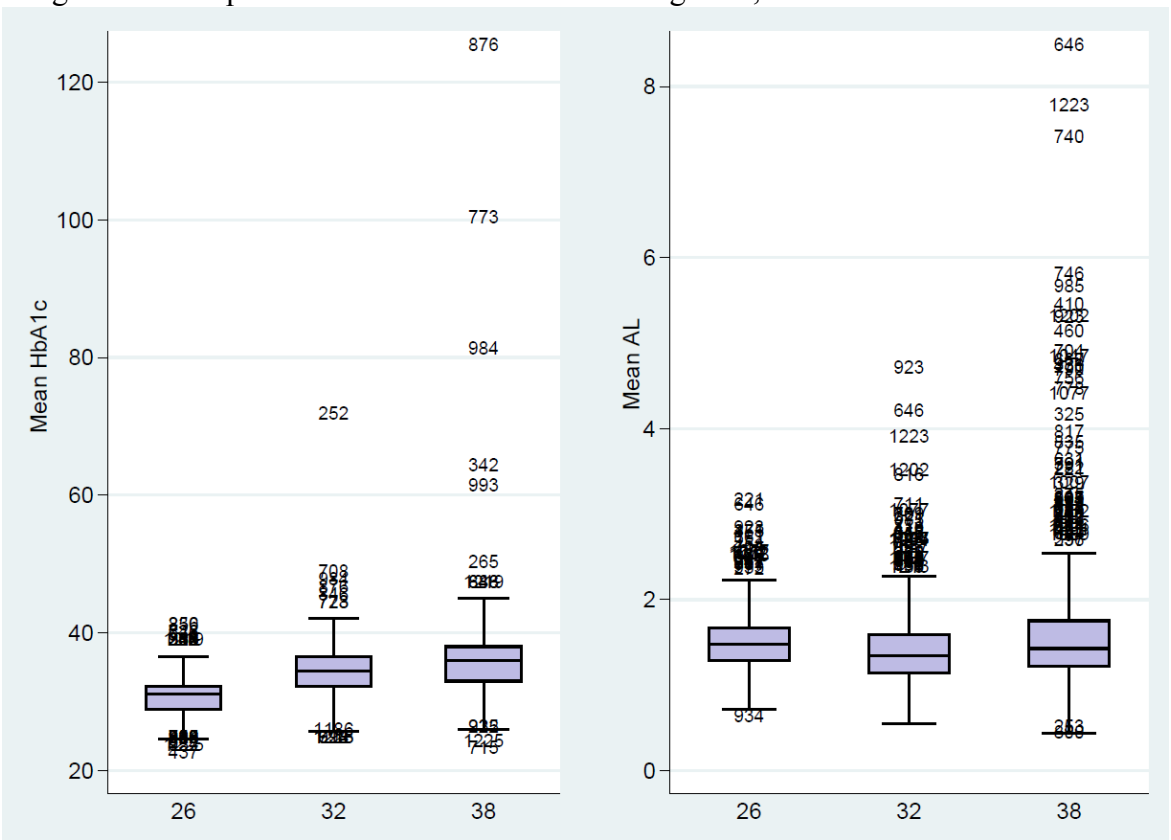


3.6 Linear Mixed Models

A linear mixed model (LMM) was used to model (a) the HbA1c trajectory over time and (b) the mean AL trajectory over time, with age considered as the time variable. Analysis began with a closer examination of these two variables using boxplots and random draw scatterplots.

The boxplots graphically depict information about the distributions of HbA1c and mean AL at ages 26, 32 and 38 (Figure 3.8). The median value (the solid line across the inside of each box) for HbA1c increased over the twelve years, with the greatest increase between ages 26 and 32. The boxes represent the interquartile range (values from the 25th to the 75th percentile) and contain 50% of participants. The whiskers (the lines extending vertically from the boxes) indicate the upper and lower quartiles. The whiskers end at the most extreme values that are within 1.5 box lengths from the edge of the box, with outliers lying beyond that. There are outliers at both low and high values at each age, with extreme high value outliers at ages 32 and 38.

Figure 3.8. Boxplots for HbA1c and mean AL at ages 26, 32 and 38.

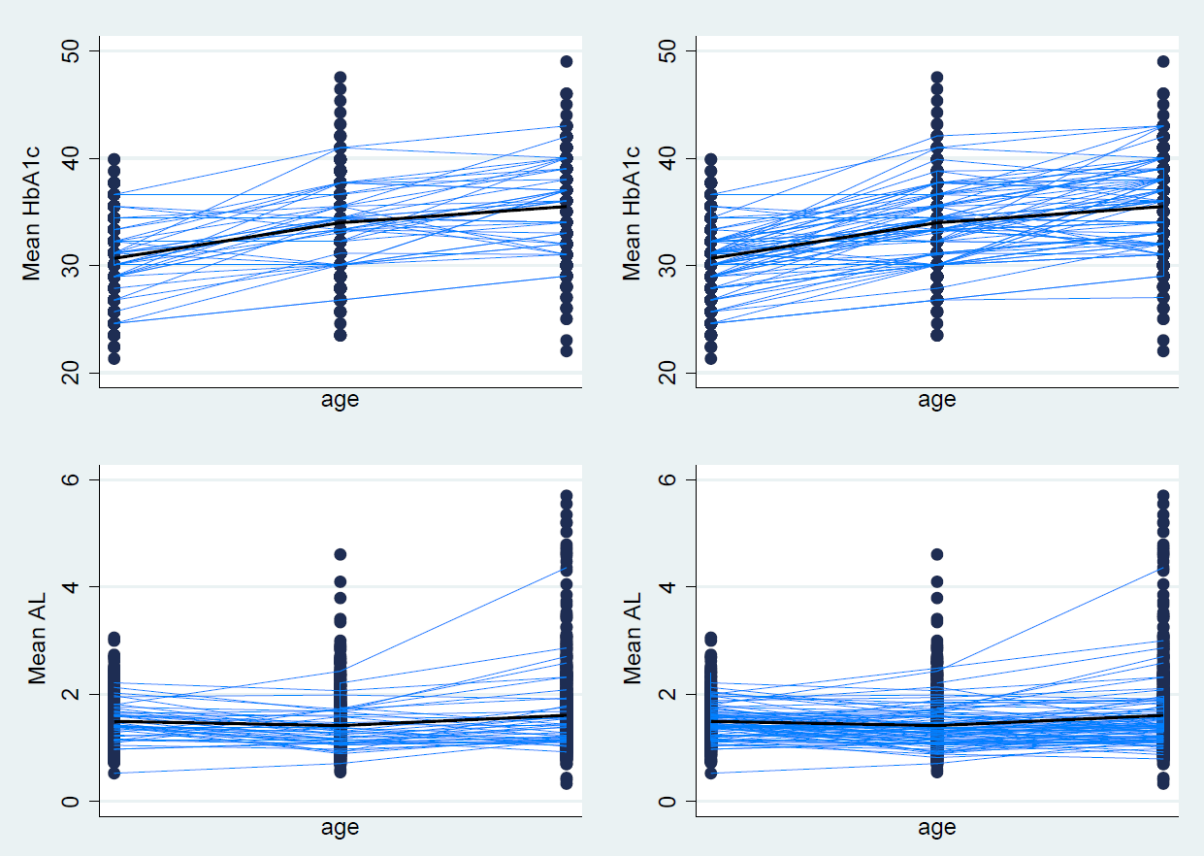


The median value for mean AL decreased between ages 26 and 32, rising slightly again between 32 and 38 (Figure 3.8). There were one and two low value outliers at ages 26 and 38 respectively,

no low value outliers at age 32, many high value outliers at all three ages, and extreme high value outliers at ages 32 and 38.

Random draw scatter plots of HbA1c and mean AL over time provide a quick glance into how the variables developed over the twelve years from 26 to 38 (Figure 3.9). These indicate that there are indeed different intercepts and slopes for different participants.

Figure 3.9. Random draw scatter plots for HbA1c and mean AL at ages 26, 32 and 38.



3.6.1 Linear Mixed Model for mean AL

The results of a simple 'standard' or 'naïve' regression model for associations between mean AL and covariates mean HbA1c and age are shown in Table 3.53. The fixed effects part of the model gives estimates for β_0 (the intercept for AL when HbA1c = 0 and age = 26) and coefficients for mean HbA1c and age 32 and 38, along with their associated standard errors. Mean AL and ages 32 and 38 had statistically significant coefficients of 0.01, -0.11 and 0.06, respectively. The coefficient 0.01 represents the increase in the predicted value of AL for each 1 mmol/mol increase in mean HbA1c, if age remains constant; the coefficient -0.11 represents the decrease in the predicted value of AL for the six-year difference in age from 26 to 32, if HbA1c remains constant; and the coefficient 0.06 represents the increase in the predicted value of AL for the twelve-year difference in age from 26 to 38, if HbA1c remains constant. The random effects part of the model gives estimates for the total variance in HbA1c not explained by explanatory variables AL and age, that is, the Variance (Residual) estimate and its standard error. However, this model does not account for correlations between observations; it does not have a random intercept and therefore essentially ignores the longitudinal nature of the data. The table also shows the model information criteria: the log-likelihood of model, the AIC and the BIC.

Model 2 shows the results of a LMM analysis which adds a random intercept to the model (Table 3.53). The -xtmixed- default maximum likelihood (ML) estimation approach was used to estimate both fixed effects and random effects. The coefficient for mean HbA1c was unchanged. The variance component has now been divided into two parts: one part is related to the random variance around the intercept (0.16); the other is the remaining variance (0.14) not explained by the explanatory variables or the intercept variance. The model information criteria indicated that this model is a better fit than Model 1. The log-likelihood, AIC and BIC were all improved by adding a random intercept to the model.

In Model 3, a random slope was added to the random intercept model (Table 3.53). The coefficient for mean HbA1c was further reduced, and was no longer statistically significant. The variance component has been given more structure. It is now made up of four parts: the variance of the slope 0.00; the variance around the intercept 0.04; the covariance between the random intercept and the random slope 0.01; and the remaining variance 0.06 not explained by the explanatory variables or the other variances. The estimate for the covariance between the random intercept and the random slope gives information about the relationship between random intercept

and slope. It is positive, which indicates that the participants with a high intercept also have a high slope. The log-likelihood, AIC and BIC for Model 3 showed an improvement over those of Model 2.

The fully adjusted LMM with random intercept and slope models (Model 4) is presented in Table 3.54. This model added the covariates smoking, sex, SES, plaque score group, and use of dental services to the model. In addition, a range of interactions between age and other predictors were included. In this fully adjusted model, the coefficient for mean HbA1c was unchanged, and was not statistically significant. The coefficients for age, male sex, plaque score group, and use of dental services were all significant as were interactions between age and use of marijuana weekly or more, age and smoking, age and male, age 32 and routine use of dental services, and age 38 and SES. The variance component part of the model was similar to the unadjusted Model 3, but the values for the model information criteria all showed an improvement, indicating the fully adjusted model to be a better fit than the unadjusted one.

Table 3.53. Linear mixed models for mean AL without explanatory variables other than mean HbA1c and age.

	Model 1 Naïve Model			**Model 2 Random Intercept model**			**Model 3 Random Intercept & slope model**		
Fixed effect parameters	Estimate	SE	95% CI	Estimate	SE	95% CI	Estimate	SE	95% CI
β_0 (Intercept)	1.15	0.08	(0.99, 1.32)	1.30	0.09	(1.13, 1.47)	1.41	0.07	(1.27, 1.55)
Mean HbA1c	**0.01**	0.00	(0.00, 0.02)	**0.01**	0.00	(0.00, 0.01)	0.00	0.00	(-0.00, 0.01)
Age									
32	**-0.11**	0.03	(-0.17, -0.06)	**-0.11**	0.01	(-0.14, -0.08)	**-0.09**	0.01	(-0.12, -0.06)
38	**0.06**	0.03	(0.00, 0.12)	**0.08**	0.02	(0.03, 0.13)	**0.11**	0.02	(0.06, 0.16)
Random effect parameters	Estimate	SE	95% CI	Estimate	SE	95% CI	Estimate	SE	95% CI
Variance (Age)	-	-	-	-	-	-	0.00	0.00	(0.00, 0.00)
Variance (Intercept)	-	-	-	0.16	0.02	(0.12, 0.21)	0.04	0.01	(0.03, 0.06)
Covariance (Age, Intercept)	-	-	-	-	-	-	0.01	0.00	(0.00, 0.01)
Variance (Residual)	0.29	0.01	(0.27, 0.30)	0.14	0.02	(0.10, 0.18)	0.06	0.01	(0.05, 0.07)
Model Information Criteria	Estimate			Estimate			Estimate		
Log-likelihood of model	-1959.54			-1669.28			-1231.03		
AIC	3929.09			3350.57			2478.06		
BIC	3958.16			3385.45			2524.57		

Statistically significant parameters in **bold** type. SE; standard error of the estimate. CI; confidence interval.

Table 3.54. Adjusted Linear mixed model for mean AL

	Model 4 Random Intercept & slope model		
Fixed effect parameters	Estimate	SE	95% CI
β_0 (Intercept)	1.38	0.07	(1.23, 1.52)
Mean HbA1c	0.00	0.00	(-0.00, 0.01)
Age 32[1]	**-0.15**	0.03	(-0.21, -0.08)
Age 38[1]	**0.14**	0.06	(0.01, 0.26)
Smoker[2]	0.02	0.02	(-0.02, 0.06)
Male[3]	**0.07**	0.02	(0.03, 0.11)
Marijuana Use[4]			
Less than weekly	0.01	0.02	(-0.03, 0.05)
Weekly or more	-0.01	0.03	(-0.07, 0.04)
SES[5]			
Medium	-0.01	0.02	(-0.05, 0.03)
High	-0.01	0.03	(-0.06, 0.04)
Plaque score group[6]			
Low (%)	**0.08**	0.01	(0.05, 0.11)
Moderate (%)	**0.15**	0.02	(0.11, 0.19)
High (%)	**0.21**	0.03	(0.15, 0.27)
Routine attender[7]	**-0.09**	0.02	(-0.13, -0.05)
Interactions			
Age 32* Marijuana less than weekly[8]	-0.01	0.03	(-0.07, 0.05)
Age 32* Marijuana weekly or more [8]	**0.15**	0.04	(0.07, 0.23)
Age 38* Marijuana less than weekly[8]	0.01	0.05	(-0.08, 0.10)
Age 38* Marijuana weekly or more [8]	**0.27**	0.09	(0.08, 0.45)
Age 32*Smoker[9]	**0.10**	0.03	(0.04, 0.16)
Age 38*Smoker[9]	**0.31**	0.05	(0.21, 0.42)
Age 32*Male[10]	**0.05**	0.02	(0.00, 0.09)
Age 38*Male[10]	**0.09**	0.03	(0.02, 0.16)
Age 32*Routine[11]	**0.07**	0.03	(0.02, 0.12)
Age 38*Routine[11]	-0.02	0.03	(-0.08, 0.04)
Age 32*Medium SES[12]	-0.03	0.03	(-0.09, 0.03)
Age 32*High SES[12]	0.03	0.04	(-0.10, 0.05)
Age 38*Medium SES[12]	**-0.18**	0.06	(-0.30, -0.06)
Age 38*High SES[12]	**-0.18**	0.06	(-0.31, -0.05)
Random effect parameters	Estimate	SE	95% CI
Variance (Age)	0.00	0.00	(0.00, 0.00)
Variance (Intercept)	0.03	0.01	(0.02, 0.05)
Covariance (Age, Intercept)	0.00	0.00	(0.00, 0.00)
Variance (Residual)	0.06	0.00	(0.05, 0.07)
Model Information Criteria	Estimate		
Log-likelihood of model	-922.32		
AIC	1908.63		
BIC	2093.83		

SE; standard error of the estimate. CI; confidence interval. Statistically significant coefficients in **bold** type. Reference categories: [1]Age 26, [2]Non-smoker, [3]Female, [4]No marijuana use, [5]Low SES, [6]Very low plaque score group, [7]Non-routine attender, [8]Age 26 + No marijuana use, [9]Age 26 + non-smoker, [10]Age 26 + female, [11]Age 26 + Non-routine attender, [12]Age 26 + low SES.

3.6.2 Linear Mixed Model for mean HbA1c

Results of a simple 'standard' or 'naïve' regression model for associations between mean HbA1c and covariates mean AL and age are shown in Table 3.51. The fixed effects part of the model gives estimates for β_0 (the intercept for HbA1c when AL = 0 and age = 26) and coefficients for mean AL and age 32 and 38, along with their associated standard errors. Mean AL and age 32 and 38 had statistically significant coefficients of 0.63, 3.40 and 4.65 respectively. The coefficient 0.63 represents the increase in the predicted value of HbA1c for each 1% point increase in AL, if age remains constant; the coefficient 3.40 represents the increase in the predicted value of HbA1c for the six-year difference in age from 26 to 32, if AL remains constant; and the coefficient 4.65 represents the increase in the predicted value of HbA1c for the twelve-year difference in age from 26 to 38, if AL remains constant. The random effects part of the model gives estimates for the total variance in mean HbA1c not explained by explanatory variables mean AL and age, that is, the Variance (Residual) estimate and its standard error. However, this model does not account for correlations between observations; it does not have a random intercept and therefore essentially ignores the longitudinal nature of the data.

The Table also shows the model information criteria: the log-likelihood of model, the AIC and the BIC (Table 3.51). As outlined in the Methods section, these criteria in themselves are not meaningful. Rather, they are used to compare competing nested models with the model, with the lowest (or least negative in the case of negative values) AIC or BIC being the "best" model among all models specified for the data at hand.

Model 2 shows the results of a LMM analysis which adds a random intercept to the model (Table 3.51). The -xtmixed- default maximum likelihood (ML) estimation approach was used to estimate both fixed effects and random effects. The coefficient for mean AL was reduced. The variance component has been divided into two parts: one part is related to the random variance around the intercept, the other is the remaining variance not explained by the explanatory variables or the intercept variance. The model information criteria indicated this model is a better fit than Model 1. The log-likelihood, AIC and BIC were all improved by adding a random intercept to the model.

In Model 3, a random slope was added to the random intercept model (Table 3.51). The coefficient for mean AL was further reduced and was no longer statistically significant. The variance component has been given more structure. It is now made up of four parts: the variance of the slope 0.07; the variance around the intercept 4.76; the covariance between the random intercept and the random slope 0.08; and the remaining variance 5.78 not explained by the explanatory variables or the other variances. The estimate for the covariance between the random intercept and the random slope gives information about the relationship between random intercept and slope. It is positive which indicates the participants with a high intercept also have a high slope. The log-likelihood, AIC and BIC for Model 3 showed an improvement over those for Model 2.

Table 3.51. Linear mixed models for Mean HbA1c without explanatory variables other than mean AL and age.

	Model 1 Naïve Model			**Model 2 Random Intercept model**			**Model 3 Random Intercept & slope model**		
Fixed effect parameters	Estimate	SE	95% CI	Estimate	SE	95% CI	Estimate	SE	95% CI
β_0 (Intercept)	29.74	0.26	(29.22, 30.26)	30.07	0.31	(29.46, 30.68)	30.18	0.29	(29.61, 30.75)
Mean AL	**0.63**	0.15	(0.33, 0.92)	**0.42**	0.19	(0.03, 0.80)	0.35	0.18	(-0.01, 0.70)
Age									
32	**3.40**	0.20	(3.00, 3.79)	**3.36**	0.10	(3.15, 3.56)	**3.34**	0.10	(3.14, 3.54)
38	**4.65**	0.20	(4.26, 5.04)	**4.68**	0.16	(4.37, 4.99)	**4.71**	0.16	(4.40, 5.02)
Random effect parameters	Estimate	SE	95% CI	Estimate	SE	95% CI	Estimate	SE	95% CI
Variance (Age)	-	-	-	-	-	-	0.07	0.05	(0.02, 0.31)
Variance (Intercept)	-	-	-	7.47	0.63	(6.33, 8.81)	4.76	0.98	(3.18, 7.12)
Covariance (Age, Intercept)	-	-	-	-	-	-	0.08	0.06	(-0.05, 0.20)
Variance (Residual)	15.97	0.45	(15.12, 16.89)	8.42	3.00	(4.19, 16.94)	5.78	1.23	(3.82, 8.79)
Model Information Criteria	Estimate			Estimate			Estimate		
Log-likelihood of model	-6940.69			-6706.83			-6592.36		
AIC	13891.39			13425.65			13200.71		
BIC	13920.39			13460.54			13247.22		

Statistically significant parameters in **bold** type. SE; standard error of the estimate. CI; confidence interval.

The fully adjusted LMM with random intercept and slope models (Model 4) is presented in Table 3.52. This model added smoking, BMI, SES and sex covariates to the model. In addition, sex*age interactions were included. The presence of a significant interaction indicates that the effect of one predictor variable (such as age) on the response variable (mean HbA1c) is different at different values of the other predictor variable (such as sex).

In this fully adjusted model, the coefficient for mean AL was further reduced and was not statistically significant (Table 3.52). The coefficients for smoking, marijuana use weekly or more, BMI, and age 32 and 38 were all statistically significant. In addition, the male*age-38 interaction indicated that the association between mean HbA1c and age 38 was significantly stronger for males than for females. The variance component part of the model was similar to the unadjusted Model 3, but the values for the model information criteria all showed an improvement indicating the fully adjusted model to be a better fit than the unadjusted.

Table 3.52. Adjusted linear mixed model for mean HbA1c

	Model 4 Random Intercept & slope model		
Fixed effect parameters	Estimate	SE	95% CI
β_0 (Intercept)	27.67	0.62	(26.46, 28.88)
Mean AL	0.09	0.18	(-0.27, 0.45)
Smoker[1]	**0.71**	0.17	(0.37, 1.05)
Marijuana Use[2]			
Less than weekly	-0.21	0.24	(-0.67, 0.26)
Weekly or more	**0.46**	0.23	(0.01, 0.91)
BMI	**0.10**	0.02	(0.05, 0.14)
SES[3]			
Medium	0.01	0.14	(-0.26, 0.29)
High	-0.17	0.20	(-0.56, 0.23)
Male[4]	0.35	0.22	(-0.08, 0.78)
Age 32[5]	**3.22**	0.17	(2.89, 3.55)
Age 38[5]	**4.19**	0.20	(3.80, 4.58)
Interactions			
Male*Age 32[6]	0.04	0.21	(-0.37, 0.45)
Male*Age 38[6]	**0.89**	0.32	(0.26, 1.51)
Random effect parameters	Estimate	SE	95% CI
Variance (Age)	0.07	0.05	(0.02, 0.32)
Variance (Intercept)	4.57	1.01	(2.96, 7.05)
Covariance (Age, Intercept)	0.06	0.06	(-0.07, 0.18)
Variance (Residual)	5.73	1.26	(3.72, 8.83)
Model Information Criteria	Estimate		
Log-likelihood of model	-6410.60		
AIC	12857.20		
BIC	12961.41		

SE; standard error of the estimate. CI; confidence interval. Statistically significant coefficients in **bold** type.
Reference categories: [1]Non-smoker, [2]No marijuana use, [3]Low SES, [4]female, [5]age 26, [6]female + age 26.

3.7 Summary of results

The following is a brief summary of the main points of the results chapter.

1) Attrition analysis

Proportionately fewer individuals of low childhood SES, low SES at 26 and 32, and smokers at 32 were included in the periodontal GBTM.

There were no differences between those included in, and those excluded from, the HbA1c GBTM.

2) Description of the sample

The proportion who smoked declined over the 12 years.

Periodontal status worsened with age.

Mean HbA1c increased with age, as did the prevalence of prediabetes, type 2 diabetes and dysglycaemia.

The anthropometric measures all increased between ages 26 and 38.

3) Cross-sectional associations

Cross-sectional associations were found between periodontal status and covariates SES, smoking (both tobacco and marijuana), and oral health care at all three ages (associations generally became stronger with age).

Cross-sectional associations were found between HbA1c and covariates smoking and anthropometric measures at most ages (associations generally became stronger with age).

Some cross-sectional associations found between periodontal status and HbA1c at each age.

4) Longitudinal associations

No longitudinal associations were found between periodontitis at 26 and HbA1c at 32.

Some longitudinal associations were found between periodontitis at 26 and HbA1c at 38.

Some longitudinal associations were found between periodontitis at 32 and HbA1c at 38.

Some longitudinal associations were found between HbA1c at 26 and periodontitis at 32.

Some longitudinal associations were found between HbA1c at 26 and periodontitis at 38.

No longitudinal associations were found between HbA1c at 32 and periodontitis at 38.

5) Group based trajectory modeling

Periodontal GBTM

Periodontal GBTM identified a 4-group trajectory model.

Associations were found between periodontal trajectory group and male sex, low SES, current smoking, regular marijuana use, high plaque score group, and episodic use of dental services. Odds ratios for these variables showed an upward gradient across the trajectory groups from "Very low" to "High"

Dysglycaemia at 32 and 38 was associated with an upward shift in the periodontal trajectories. These associations were statistically significant for the "High" trajectory at age 38 only.

HbA1c GBTM

HbA1c GBTM identified a 3-group trajectory model.

Associations were found between HbA1c trajectory group and male sex, smoking at 26, high WC group at 26 and high waist-height group at 26. Odds ratios for these variables showed an upward gradient across the trajectory groups from "Low" to "High"

Periodontitis at 32 and 38 was associated with an upward shift in the HbA1c trajectories. However, none of the associations were statistically significant.

6) Linear mixed models

Mean AL LLM

Associations were found between mean AL and age, male sex, plaque score group, and use of dental services.

No association was found with mean HbA1c.

There were interaction effects between age*use of marijuana weekly or more, age*smoking, age*male sex, age 32* routine use of dental services, and age 38* SES.

Mean HbA1c LLM

Associations were found between mean HbA1c and smoking, marijuana use weekly or more, BMI and age.

No association was found with mean AL.

There was an interaction effect between age 38*sex.

4 Discussion

The Dunedin Multidisciplinary Health and Development Study data have provided a unique opportunity to explore the putative bidirectional relationship between periodontal disease and dysglycaemia in an initially healthy population over 12 years from early adulthood into early middle age. The natural histories of both of these widespread chronic conditions were tracked using group based trajectory modeling, covariates for both conditions were identified, and a gradual decline in health status over the time period was noted. Both conditions were highly prevalent by age 38, and it was found that health status at 26 predicted health status at 38. Some unadjusted cross-sectional and longitudinal associations were found between the two conditions. However, when fully-adjusted GBTM models were fitted, the influence of dysglycaemia on periodontitis was found to be minimal, and periodontitis was found to have no influence on HbA1c. A supplementary analysis using linear mixed effect modeling confirmed what the GBTM had found – there was no real relationship between the two conditions at this stage in the life course.

4.1 Strengths and limitations

The strengths of this study include the large sample size and the very high retention rate (over 95% of the surviving cohort) for all three assessments. This is due to the loyalty, commitment and goodwill of the Study members and their families, the mutual trust and respect between Study members and researchers, and a long history of confidentiality and non-intervention. Barriers to participation were minimised and Study members felt a sense of pride when they saw DMHDS research outputs in the media. The retention rates are exceptional for a longitudinal study, especially after 32 years, with many other longitudinal studies worldwide reporting much higher drop-out rates.

The use of a birth cohort, and the high retention rate, means that the sample is representative of its source population (the South Island of New Zealand). The issue of whether the findings can be generalized to the whole New Zealand population, and to other populations (particularly the United States) must be considered. A 2006 paper provided broad support for the generalisability of findings from the Dunedin Study whereby Study members were

similar to their age matched peers in two nationally representative surveys on most of the health measures compared (Poulton et al., 2006). With respect to the periodontal data, this has been addressed by another paper using data from this sample (Thomson et al., 2006). It was concluded that findings from the DMHDS can be generalised to these populations. The prevalence of dysglycaemia in the cohort is consistent with data from the U.S. (Marcinkevage et al., 2013) and the U.K. (Wilmot et al., 2013), and it is therefore likely that the findings are generalisable to these populations.

The Dunedin Study is also the longest-running longitudinal observational study of oral health in the world, and no other longitudinal study presents such a wealth of objective oral health data. Likewise, the collection of objective HbA1c and anthropometric data over such a lengthy period in this age group is exceptional. It is believed no other study has both periodontal and HbA1c data in an initially healthy cohort in this age group. It follows that this opportunity to concurrently track the natural histories of both periodontitis and dysglycaemia from young adulthood towards mid-life is unique.

The use of GBTM to identify latent HbA1c trajectory groups is a further strength of this study. The principal advantage of GBTM over other trajectory modeling techniques is that it does not assume *a priori* the existence of trajectories of a specific form. Rather, it allows distinctive latent developmental trajectories to emerge from the data (Nagin, 2005). It facilitates the examination of factors that may determine trajectory group membership, and it enables the dissemination and communication of complex findings in a form which is readily understood by non-technical audiences, public health funders, politicians, general practitioners and the public.

The study had some limitations that must be recognised. One is the under-representativeness of Māori people in the cohort with respect to the total New Zealand Maori (14.9% in the 2013 census) population. However, the proportion (7.5%) who self-identified as Maori at age 26 in the Dunedin Study does match the proportion of Maori in the South Island. Pacific groups are also under-represented in the cohort. As both type 2 diabetes and periodontal disease disproportionately affect Pacific adults this may have led to an attenuation of the findings (Ministry of Health, 2010a; 2012).

The DMHDS data are right-censored. Data to age 38 have been gathered, but we have no information yet as to what will happen beyond this age. In other words, our observations are incomplete. It is likely that future periodontitis and dysglycaemia states will be more prevalent, extensive and severe than those recorded at 38, but we do not know for sure how they will develop over the years ahead.

The ideal protocol for periodontal studies is the full-mouth examination of six sites per tooth (Papapanou, 2012; Savage et al., 2009). Although full-mouth periodontal examinations were carried out at ages 32 and 38, it was necessary to convert these to half-mouth data to allow longitudinal comparisons with the age 26 data. In addition, recordings were made from three sites only per tooth. These two factors have likely led to an underestimation of the prevalence of periodontitis, and possibly an attenuation of the strength of the associations between periodontitis prevalence and other parameters (although there is no way to know for sure). However, with respect to the sites per tooth, research has shown that of the three random half-mouth protocols in general use, the one used in the DMHDS (three-site mesio-buccal, mid-buccal, and disto-lingual) produced less bias than the others (Susin et al., 2005).

Self-report data were used to provide information on reasons for tooth loss, SES, tobacco and cannabis smoking status, alcohol use, physical activity and use of dental services; the issue of the reliability and validity of this self-report data must be addressed. With respect to tooth loss, the Florida Dental Care Study data found a telephone interview to be an effective method for gathering tooth count information at nominal and ordinal levels (Gilbert et al., 1997). A Harvard School of Dental Medicine study found that asking participants the question “How many natural teeth do you have in your mouth now?” could accurately report their actual number of teeth, with a slight tendency towards underreporting (Pitiphat et al., 2002). Meanwhile, a study using data from the 2007 to 2009 Canadian Health Measures Survey concluded accurate estimates of the prevalence of cigarette smoking can be derived from self-reported smoking status data (Wong et al., 2012). Interview/examiner-based assessments, as used in the Dunedin study, are more likely to yield valid data than “self-completed” data. Furthermore, Study members are familiar with interviews, are aware of the importance of accurate responses, and there is a long history of mutual trust and respect between participants and researchers.

Another potential limitation was the comparability of the data over the three ages. While it is common practice for long-term studies to freeze blood or serum, the issue of the comparability of frozen and fresh samples must be addressed. A recent study found a high correlation between HbA1c data from fresh, frozen and refrozen samples, particularly at lower (<42mmol/mol) values of HbA1c (Liotta et al., 2013). At age 26, only two Study members were found to have ≥41 mmol/mol HbA1c. These individuals both had Type 1 diabetes, and were excluded from the current analyses. The remaining age 26 sample were all below 41 mmol/mol HbA1c, and so categorised as "low level". We therefore concluded that the frozen HbA1c assays at age 26, and the fresh HbA1c assays at ages 32 and 38 were comparable.

4.2 The findings of this study

The findings of this study can be summarised as: (1) a gradual decline in health status was seen between ages 26 and 38; (2) health status at age 38 was associated with health status at 26; (3) predictors of periodontal disease experience included male sex, smoking, marijuana use, SES, plaque score and episodic use of dental services at age 26; (4) predictors of dysglycaemia included male sex, smoking, higher waist circumference and higher waist-height ratio at age 26; and (5) no association was found between periodontitis and dysglycaemia in the fully-adjusted models.

4.2.1 A gradual decline in health status

The period from the mid-twenties to the end of the fourth decade of life generally signifies a time when people settle down, obtain a steady job or start a career, perhaps buy property, have a mortgage, begin to raise a family, and become a productive part of the society in which they live. It can also represent a time when a gradual decline in health status is seen in many individuals, setting the stage for poorer health in later years. The DMHDS cohort showed an overall deterioration in periodontal, glycated haemoglobin and anthropometric measures over the 12 years of the study. This section considers that deterioration, and compares the DMHDS data with those from other studies in similar age groups.

By whatever measure was used (prevalence, extent or severity), periodontal status worsened with time, with the greatest deterioration seen between ages 32 and 38. This was despite a reduction in the proportion of sites with bleeding on probing, a reduction in mean plaque score, a reduction in the proportion of Study members in the “moderate” or “high” plaque score groups, and an increase in the proportion of them in the “very low” plaque score group between ages 26 and 38. In addition, the prevalence of risky health behaviours—cigarette smoking and marijuana use—dropped over the years (although the mean pack years increased, reflecting the cumulative effects of smoking in the cohort). This overall deterioration was also despite almost half the cohort following the “Very low” periodontitis trajectory with zero % sites with 4+mm AL at each of the three ages. Moreover, the “Low” trajectory group experienced only slight worsening in periodontal status over the 12 years. The greatest burden of declining periodontal health was concentrated in the 14.8% of the cohort who were in in the “Medium” and “High” groups.

A comparison of DMHDS periodontal disease data with data from other studies is difficult due to differences in study design, age groups examined, and methods of disease detection, measurement and categorisation (Savage et al., 2009). However, those that are comparable found prevalence estimates for 1+ sites with 4+mm AL that were generally consistent with those seen in the Dunedin Study. The Australian National Survey of Adult Oral Health 2004-2006 reported that 48.8% of adults age 35-54 years had 1+sites with 4+mm AL, while the SHIP study found that 26.8% of participants age 20-29, and 61.5% of participants age 30-39 had 1+sites with 4+mm AL (Holtfreter et al., 2009; Slade et al., 2007). Although the SHIP study's prevalence of 61.5% for ages 30-39 was markedly higher than the DMHDS full-mouth prevalence of 43.9% at age 38, the prevalence of 26.8% for the age 20-29 group was consistent with the DMHDS full-mouth prevalence of 29.7% at age 32. The most recent NHANES periodontal data showed a 32.4% prevalence of 1+sites with 4+mm AL in the 30-34 age group, and 53.5% in the 35-49 age group (Eke et al., 2012). The findings of the 2009 New Zealand Oral Health Survey are consistent with the current study's findings: the prevalence of 1+sites with 4+mm AL was 35.3% for the 25-34 age group; and 44.0% for the 35-44 age group (Ministry of Health, 2010a). In particular, the consistency with the New Zealand Oral Health Survey gives confidence in the generalisability of the findings to the whole New Zealand population.

A recent meta-analysis of 72 studies from 37 countries found that periodontitis prevalence increases gradually with age, showing a steep increase between the third and fourth decades of life, and plateauing from age 40 onwards (Kassebaum et al., 2014). However, this meta-analysis consisted mostly of cross-sectional studies. A previous Dunedin Study paper tracked periodontal changes from 26 to 38 using GBTM (Thomson et al., 2013). In that paper the sample was made up of those participants with data at all three assessment points, and thus was a smaller sample size (N = 831). Nonetheless, the periodontitis prevalences, trajectory groups' proportions and trajectory forms were similar to those of this study. In addition, the 2013 paper found strong associations between trajectory group and tobacco smoking at all assessments between ages 15 and 38.

Mean HbA1c also increased steadily with age, with the great majority of Study members experiencing a rise in HbA1c level over the 12 years, and a small proportion (6.8%) experiencing a small reduction. The finding that mean HbA1c increased with age is not surprising, because this phenomenon has been seen elsewhere (Hashimoto et al., 1995; Pani

et al., 2008; Yang et al., 1997). However, most other studies focusing on HbA1c and age have examined older populations, and the magnitude of the change (an increase of 16.0% between 26 and 38) in this relatively young age group is noteworthy. What is remarkable is that most of this change happened at a very young age indeed, between 26 and 32, with lesser change seen between 32 and 38.

The prevalence of dysglycaemia rose over this time from a negligible proportion to almost one in five Study members by age 38. This high prevalence is of great concern. While few Study members were actually diabetic by age 38, those categorised as dysglycaemic are at great risk of developing type 2 diabetes within a decade (Ackermann et al., 2011). The findings are consistent with those of a recent New Zealand study which found the prevalence of prediabetes to be 25.5% for the total NZ population over the age of 15, with a prediabetes prevalence of 18.9% for the 25-44 age group (Coppell et al., 2013). What the present study adds is that three distinctive patterns of glycaemia experience were able to be identified from age 26 through to age 38. This provided a different perspective on the natural history of dysglycaemia; rather than defining thresholds for normoglycaemia, prediabetes and diabetes, this study instead characterised its natural history in terms of a subpopulation's development trajectory.

Reflecting the deterioration in periodontal and glycaemic health, the anthropometric measures all increased between ages 26 and 38. Overall, the Study members became heavier and their mean waist circumference increased over the years spanning young adulthood into early middle age. Similar changes in this age group been comprehensively demonstrated in previous studies (Colditz et al., 1995; Jacobsen et al., 2001; Liu et al., 2012; Ostbye et al., 2011). As with mean HbA1c and the prevalence of dysglycaemia, the greatest increases in the anthropometric measures were mostly between ages 26 and 32, with smaller changes between 32 and 38. Likewise, the proportion of those considered to be at greater risk of cardiometabolic complications also increased over the 12 years. The anthropometric risk group rates at age 38 were alarming; almost a quarter were categorised as obese; almost a fifth had a dangerously large waist circumference; over a third had a waist-hip ratio that classified them as having abdominal obesity; and almost half the cohort had a waist-height ratio that would be considered to put them at risk.

These anthropometric findings are not unusual. In New Zealand, the 2012/13 New Zealand Health Survey found that 27.5% of participants in the 25-34 age group were obese, as were 34.1% in the 35-44 age group (Ministry of Health, 2013). Considering that the Health Survey sample had a higher proportion of Maori and Pacific groups (with those being at greater risk of being obese) than the DMHDS sample, the findings of the two studies are consistent. The 2011-2012 nationally representative National Health and Nutrition Examination Survey (NHANES) reported the prevalence of obesity to be 30.3% for US adults in the 20–39 age group. Similar findings were reported in the U.K. (Moody, 2014), where 26.0% of men and 26.3% of women in the 25-34 age group were categorised as obese. The latter survey found 21.0% of men and 33.0% of women in the age 25-34 age group to be in the waist circumference high-risk group; this was higher than the proportion seen at age 38 in the Dunedin Study.

4.2.2 Health at age 38 was associated with health 12 years earlier

This analysis of the Dunedin Study longitudinal data using GBTM clearly demonstrated that the risk of being in an unfavourable trajectory by age 38 was associated with health status at age 26. These findings correspond well with the life course approach to chronic disease epidemiology whereby later life outcomes are influenced by physical and social exposures during gestation, childhood, adolescence, and young adulthood (Kuh and Ben-Shlomo, 2004). In theory, factors operating early in the life course of an individual may contribute to the risk of periodontitis or dysglycaemia many years later. Thus, health status at 26 may be regarded as an early warning of this cumulative disadvantage – years before more advanced disease becomes apparent.

A higher risk of being in an unfavourable periodontal trajectory by 38 was associated with a greater extent of disease 12 years earlier. The extent of periodontitis at age 26, as defined by % sites with 4+mm AL, was significantly different for the four trajectories (0.00%, 1.30%, 3.18% and 8.15% at 26 for the “Very low”, “Low”, “Medium” and “High” trajectory groups respectively). This implies that susceptibility to periodontal disease may be well established by early adulthood.

HbA1c levels at age 26 may have an important role in identifying those most at risk for dysglycaemia 12 years later. The three HbA1c trajectories did not start from the same age 26 HbA1c level and then diverge; rather, they were distinguishable at age 26 (25.9 mmol/mol, 29.9 mmol/mol and 33.4 mmol/mol for the "Low", "Medium" and "High" trajectory groups respectively). Although these three starting levels are all within a normoglycaemic range, the risk of being in an unfavourable trajectory by age 38 was associated with the higher initial HbA1c level 12 years earlier. These findings suggest that: the path towards dysglycaemia can be identified much sooner than previously assumed; the roots of cardiometabolic disease may be established early in life; and the implications of this for our understanding of its natural history are important. Accordingly, the therapeutic and preventive implications are significant.

4.2.3 Predictors of periodontal disease

The use of the GBTM model generalisations allowed the linkage of baseline characteristics to the probability of group membership (Nagin, 2005; Nagin and Odgers, 2010). It was found that males, smokers, marijuana users, those of low SES, those who had poor oral hygiene, and those who were episodic users of dental services had the greatest odds of belonging to the two least favourable periodontal trajectory groups. The associations found between periodontal trajectory group and sex, tobacco smoking and low SES were consistent with the 2009-2010 National Health and Nutrition Examination Survey (NHANES) periodontal findings, where periodontitis experience was more prevalent and extensive in men, poorer and less-educated adults, and current smokers (Eke et al., 2012).

4.2.3.1 Sex

Disparities in the burden of periodontal disease by sex have been acknowledged (Albandar, 2002; Eke et al., 2012; Shiau and Reynolds, 2010a). The prevalence of periodontitis was found to be significantly higher in males than in females in the German SHIP-0 sample (Zhan et al., 2014). It is unclear whether sex differences in periodontal prevalence are due to male sex being a marker for riskier oral health habits (smoking, marijuana use, poor oral hygiene, episodic use of dental services) or whether there is an intrinsic susceptibility to—and a plausible biologic basis for—the greater prevalence of periodontitis in males, or both (Shiau and Reynolds, 2010b). The present study found male sex to be a predictor of "Low",

"Medium" and "High" periodontal trajectory membership when the model adjusted for low SES only. When other predictors were added to the model (smoking, marijuana use) the association between male sex and the "High" periodontal trajectory group disappeared, but it remained for the "Low" and "Medium" groups. It is possible that a lack of statistical power (due to the small sample size of the high periodontal trajectory group) may have led to a Type 2 error for this group.

4.2.3.2 Smoking

Smoking has long been recognised as a risk factor for periodontal disease, although the precise biological mechanisms of that effect are unclear (Bergstrom, 2006; Genco and Borgnakke, 2013; Jansson and Lavstedt, 2002; Johannsen et al., 2014; Palmer et al., 2005; Thomson et al., 2007; Tonetti, 1998; Warnakulasuriya et al., 2010; Zeng et al., 2014). What is clear is: the consistency of findings across many studies in different populations, countries and age groups; the strength and the biological gradient of the association; the temporal sequence of smoking and periodontal disease; and its biologic plausibility (Genco and Borgnakke, 2013). This study adds to the weight of evidence, with strong associations and clear gradients between smoking at baseline and the odds of membership in the "Low", "Medium" and "High" periodontal trajectory groups. The linear mixed model for mean AL found an interaction between smoking and age, whereby the association between smoking and mean AL became stronger over time.

4.2.3.3 Marijuana use

The GBTM found marijuana use was associated with membership of the periodontal "Medium" trajectory group, but not the "High" trajectory group (as with the associations between male sex and the "High" trajectory group, this may have been due to Type 2 error). The linear mixed model for mean AL found an interaction between marijuana use and age, whereby the association between marijuana use weekly (or more) and mean AL became stronger over time. There were only two other papers found that examined marijuana use as a risk factor for chronic periodontitis in humans. Thomson et al found marijuana use to be a risk factor for attachment loss at age 32 while a Chilean paper found the opposite to be true for adolescents (Lopez and Baelum, 2009; Thomson et al., 2008). However, a recent animal study did find an association between marijuana exposure and alveolar bone loss in rats

(Nogueira-Filho et al., 2011). Further research into these associations in diverse settings is required.

4.2.3.4 Low SES

That low SES is a risk factor for poorer health has been comprehensively established (Kuh et al., 2002; Poulton et al., 2002; Power et al., 2005; Wadsworth, 1997). With respect to periodontal health, a Dunedin Study paper found longitudinal associations between low childhood SES and a greater prevalence and extent of periodontitis at age 26, and Morita et al. reported a significant social gradient by job classification in periodontal status in a Japanese sample (Morita et al., 2007; Thomson et al., 2004). A SHIP study found longitudinal associations between education and income levels and the progression of periodontitis over a five-year period (Buchwald et al., 2013). A recent British paper using data from the 2009 UK Adult Health Survey suggested that income inequalities in periodontal disease were mediated by education and smoking (Steele et al., 2015). The current study found a clear gradient across the periodontal trajectory groups although only the association with the "High" trajectory group membership was statistically significant. The pathways between low SES and periodontitis risk are undoubtedly complex. For example, it is possible education is a proxy for oral health behaviours (oral hygiene practices, use of dental services, dietary factors). The low-SES–periodontitis link is one that requires further investigation.

4.2.3.5 Plaque score

The role of dental plaque in the initiation and progression of destructive periodontitis is currently unclear. Systematic reviews have concluded that there are insufficient well-designed randomised controlled trials to reach conclusions on the beneficial effects of repeated oral hygiene instruction in the prevention or control of periodontitis (Hujoel et al., 2005; Pastagia et al., 2006). Of course, it does not follow that oral hygiene instruction will necessarily result in a reduction in dental plaque. In this respect, two recent reviews are of interest. Both examined the role of professional mechanical plaque removal (PMPR) by dental professionals on a regular basis in the prevention of periodontitis (Needleman et al., 2015; Trombelli et al., 2015). Trombelli et al found that study participants who regularly complied with the PMPR programme had minimal variations in plaque scores in contrast to irregular compliers who showed a substantial increase (Trombelli et al., 2015). Meanwhile,

Needleman et al found low to moderate strength of evidence that PMPR, especially if combined with oral hygiene instructions, produced generally greater reductions in plaque than no treatment (Needleman et al., 2015).

The DMHDS paper on marijuana use reported the prevalence of destructive periodontal disease to be inconsistently related to dental plaque, and found no association between dental plaque and incident destructive periodontal disease (Thomson et al., 2008). In this instance, plaque score was measured cross-sectionally. Another Dunedin Study paper which recorded plaque longitudinally demonstrated clear gradients in more prevalent and extensive periodontitis across dental plaque trajectory groups from high to low (Broadbent et al., 2011). The present study's findings on plaque score group were inconclusive. Bivariate analyses found a clear gradient across the periodontal trajectory groups for membership of the high plaque score group at 26, 32 and 38. However, the fully adjusted model found that membership of the high plaque score group at 26 was associated with membership of the "Low" and "Medium" periodontal trajectory groups but not the "High" trajectory group. Clearly, more research is needed on the role of plaque in the initiation and progression of periodontitis.

4.2.3.6 Episodic use of dental services

In contrast, the fully adjusted model found that those categorised as episodic users of dental services at age 26 had greater odds of belonging to the "High" periodontal trajectory group, but not the "Medium" or "Low" groups. DMHDS data have been used to examine associations between dental visiting patterns and dental caries and missing teeth (Crocombe et al., 2012; Thomson et al., 2010). However few studies have reported on associations between dental visiting patterns and periodontal status, and the findings from those which have done so have been inconclusive (Davenport et al., 2003).

It is clear that adults vary widely in their susceptibility to periodontitis, and only a subset will suffer from severe periodontitis (Genco and Borgnakke, 2013). The early identification of those who are at greatest risk of progression to destructive disease would be advantageous. However, this is not straightforward. The initiation and progression of destructive chronic periodontitis involves a complex interplay of genetic and epigenetic factors, psychosocial and behavioural influences, and environmental exposures. This study

has provided a novel perspective to the identification of this group by the use of GBTM to (1) identify those at greatest risk of poor periodontal health, and (2) identify early adulthood predictors of that risk.

4.2.4 Predictors of dysglycaemia

As with the periodontal data, the use of the GBTM model generalisations allowed the linkage of baseline characteristics to the probability of HbA1c group membership (Nagin, 2005; Nagin and Odgers, 2010). While any attempt to categorise glycaemic risk must be regarded as somewhat arbitrary, GBTM differs from the conventional practice of defining thresholds for normoglycaemia, prediabetes and diabetes; essentially, those are stages in the natural history of dysglycaemia rather than separate diseases. GBTM instead characterises risk in terms of a subpopulation's developmental trajectory, and so provides a different perspective on identifying those most at risk. It was found that being male, or being a member of the high WC group or the high waist-height group at 26, was associated with membership of the HbA1c "High" trajectory group, and that being a smoker at 26 was associated with membership of either the HbA1c "Medium" or "High" trajectory group. Males, smokers, and those who had an unhealthily large WC or waist-height ratio, had the greatest odds of belonging to the "High" HbA1c trajectory group. Conversely, females, non-smokers, and those with a healthy WC or waist-height ratio had the greatest odds of following a favourable trajectory from age 26 to 38.

4.2.4.1 Sex

Little research on sex differences in HbA1c levels has been carried out, so it is difficult to compare findings between this study and others. The ongoing Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study reported no sex differences in baseline HbA1c; however, the sample comprised older individuals with Type 2 diabetes (Bethel et al., 2015). A comparable sample in a US study yielded similar findings; no sex differences in HbA1c were seen (Strom Williams et al., 2014). Finally, the 2005–2008 National Health and Nutrition Examination Surveys (NHANES) reported no sex differences in prediabetes prevalence as defined by HbA1c ≥39 mmol/mol (James et al., 2011). No research examining sex differences in HbA1c levels in the third and fourth decades was identified. Accordingly, it is believed this study is the first to demonstrate a longitudinal

association between male sex at 26 and the odds of following an unfavourable HbA1c trajectory subsequently.

4.2.4.2 Smoking

This study confirms previous research on smoking as an independent and modifiable risk factor for dysglycaemia. It found the odds for a smoker at 26 of belonging to the "Medium" HbA1c trajectory group to be almost double those for a non-smoker, and the odds for a smoker at 26 of belonging to the "High" HbA1c trajectory group to be over three times those for a non-smoker. These strong associations are consistent with the EPIC-Norfolk study, which reported strong cross-sectional associations between smoking and HbA1c in a large population-based sample (Sargeant et al., 2001). A dose-response relationship was seen between HbA1c and both the number of cigarettes smoked daily and cumulative smoking exposure as measured by pack-years. They are also comparable to 1999-2008 NHANES data demonstrating associations between HbA1c and self-reported smoking and blood cotinine[12] levels (Clair et al., 2011). Those studies were both cross-sectional, so a temporal relationship could not be determined.

A longitudinal dose-response association was found between smoking exposure and reported diagnosis of Type 2 diabetes in the male Physicians' Health Study (Manson et al., 2000). Likewise, a cohort study of male Japanese steel workers over eight years found a longitudinal dose-response association between smoking exposure and dysglycaemia as defined as HbA1c ≥43 mmol/mol or taking anti-diabetic medication (Teratani et al., 2012). A US study found a longitudinal dose-response association between smoking exposure and the transition from normoglycaemia to IFG (Rafalson et al., 2009). The participants in all of these longitudinal studies were middle-aged or older; the longitudinal study in which HbA1c was used as an outcome did not include females, and the longitudinal study which did include females did not use HbA1c as an outcome. Finally, a comprehensive meta-analysis of prospective studies by Willi et al. found evidence for a longitudinal association between smoking and IFG, OGTT and Type 2 diabetes (Willi et al., 2007). Unfortunately, no studies with HbA1c as an outcome were included in that meta-analysis. Consequently, while smoking is well established as a risk factor for dysglycaemia (as measured by IFG, OGTT, or diabetes incidence in the middle aged and older people), the influence of smoking

[12]A nicotine metabolite

on HbA1c levels in younger populations has not been investigated. Thus, it is believed that the current study is the first to demonstrate a longitudinal association between smoking and HbA1c levels over the third and fourth decades of life in a representative and initially healthy population.

4.2.4.3 Anthropometric measures

Generally, the anthropometric parameters followed a pattern whereby those in the "High" HbA1c trajectory group had higher mean values at all three ages than those in the "Low" group, with the same being true of the anthropometric dichotomous variables. This is not surprising, and is in agreement with current research. There is convincing evidence that excessive body weight and central adiposity are risk factors for dysglycaemia (World Health Organization, 2003). However, debate continues as to which characteristic is most closely linked to that risk (Ashwell et al., 2012; Feng et al., 2012; Janssen et al., 2004; Lee et al., 2008; Truswell, 2012; Tulloch-Reid et al., 2003; Vazquez et al., 2007).

Weight gain in adulthood should be considered to be a predictor of cardiometabolic risk (Colditz et al., 1995). A recent meta-analysis found weight gain (particularly between ages 18 and 24 years rather than 25 years and older) was associated with a greater risk of later developing Type 2 diabetes (Kodama et al., 2014).

The BMI was originally developed as the "Quetelet Index" in 1832. This index, with minor variations, continues to be widely used today as an expression of the link between excess relative weight and morbidity (Eknoyan, 2008; Narayan et al., 2007; Tulloch-Reid et al., 2003). It is associated with general obesity; height and weight are easy to measure; and it is considered to be a good predictor of type 2 diabetes risk (Tulloch-Reid et al., 2003). However, it does not distinguish fat from muscle, or take account of body fat distribution.

WC correlates with central adiposity – a known risk factor for type 2 diabetes (Feng et al., 2012; Janssen et al., 2004; Onat et al., 2004; Pouliot et al., 1994). It is simple and inexpensive to measure, and predicts diabetes risk better than BMI (Feng et al., 2012; Janssen et al., 2004), but it does not take differences in height into account (Browning et al., 2010). In addition, there are different thresholds for males and females, and for different ethnic groups.

Waist-hip ratio is currently used less often. It attempts to quantify relative distribution of fat (individuals with more abdominal fat are at greater cardiometabolic risk than those who carry more weight around the hips). However, research is divided on the utility of the waist-hip ratio in predicting type 2 diabetes risk (Liu et al., 2011; Vazquez et al., 2007). Weight change does not generally lead to a pronounced change in this ratio, since both waist and hip measurements can increase/decrease with weight gain/loss. In addition, it requires two measurements which are both more prone to measurement error than either weight or height measurement. In one study, BMI, WC and waist-hip ratio were all found to have similar associations with type 2 diabetes (Vazquez et al., 2007). Another found that, while BMI, WC and waist-height ratio were all found to be associated with fasting plasma glucose, waist-hip ratio was not (Liu et al., 2011).

Waist-height ratio has become more popular in recent years. Like WC, it correlates well with central adiposity, it is the same for imperial or metric scales, and only a tape measure is required. Unlike WC, it accounts for different heights. This minimises the requirement to have different thresholds for the different sexes and ethnic groups, with a "one size fits all" value of 0.5 (Browning et al., 2010; Hsieh et al., 2003). One study found that BMI, WC and waist-height ratio similarly predict metabolic risk (Liu et al., 2011); others found waist-height ratio to be a better screening tool for risk than either BMI or WC (Ashwell et al., 2012; Browning et al., 2010; Savva et al., 2013). However, a recent meta-analysis found that waist-height ratio was better than BMI and waist-hip ratio in predicting incident diabetes, but no better than WC alone (Kodama et al., 2012).

The findings of the present study add to the body of research regarding anthropometric measures, and are consistent with studies reporting associations between the central adiposity measures, WC and waist-height ratio, and cardiometabolic risk (Ashwell et al., 2012; Browning et al., 2010; Feng et al., 2012; Janssen et al., 2004; Kodama et al., 2012; Lam et al., 2015; Liu et al., 2011; Savva et al., 2013). In agreement with these papers, this study found associations between both WC and waist-height ratio and membership of the HbA1c "High" trajectory group.

Some researchers have found a combination of waist-height ratio and BMI to be the best predictor of risk (Lam et al., 2015). This study found that not to be the case in the DMHDS cohort. Membership of the high WC group predicted HbA1c "High" trajectory group

membership better than the combination of high WC group membership and high BMI group membership, and membership of the high waist-height ratio group predicted HbA1c "High" trajectory group membership better than the combination of high waist-height ratio group membership and high BMI group membership. However, it is possible that a combination of measures may prove to be a better predictor of risk as the cohort ages.

The odds ratio for the high WC group membership was greater than for the high waist-height ratio group membership. However, the wide 95% confidence intervals for the high WC group may indicate a degree of imprecision for the finding; the number in the high WC group at 26 was small (N=29). The narrower 95% confidence intervals for the high waist-height ratio group indicate greater precision for this finding.

It is believed there has been only one other prospective study (Ware et al., 2014) examining waist-height ratio using HbA1c as an outcome measure. This study used South African data from the Prospective Urban Rural Epidemiology (PURE) study. Baseline measurements were taken in 2005 (N=1519, mean age 51.2 years for men, 50.7 years for women), and the follow-up was five years later in 2010. It found associations between waist-height ratio at baseline and HbA1c levels five years later. A lack of generalisability to the source population was a serious limitation for this study. The overall retention rate was 60.4% over the five years, but excluding 308 participants who had dysglycaemia at baseline from the prospective analysis for HbA1c resulted in an actual retention rate of only 40.0%. Accordingly, it is believed that the present study is the first to report longitudinal associations between waist-height ratio and HbA1c in a representative cohort (with the added advantages of a long observation period over the third and fourth decades of life, and an excellent retention rate).

4.2.5 No relationship between periodontitis and dysglycaemia

The use of the GBTM model generalisations allowed the identification of effect modifiers associated with deviations from the group trajectory (Nagin, 2005; Nagin and Odgers, 2010). In this way, the influence of HbA1c on the periodontitis trajectories, and the influence of periodontitis on the HbA1c trajectories, in the fourth decade of life were explored.

Having dysglycaemia at age 38 was associated with an upward shift of the "High" periodontal trajectory. Dysglycaemia which occurred during the course of the "High" trajectory altered the direction of that trajectory, and set it on a steeper upward path than it would have followed if that condition had not occurred. The shift was from a mean 56.2% sites with 4+mm AL at 38 (no dysglycaemia at 38) to a mean 68.3% sites with 4+mm AL (dysglycaemia at 38). This represents a 21.5% relative increase in the mean % sites with 4+mm AL for dysglycaemia at 38 over no dysglycaemia at 38. However, these GBTM findings were not replicated in the linear mixed model analysis, which found no relationship between HbA1c and the mean % sites with 4+mm AL.

This difference in findings between GBTM and LMM may have been because the extent of periodontal experience (mean % sites with 4+mm AL) was used in the GBTM analysis while the severity of periodontal experience (mean AL) was used in the LMM analysis. Or it may have been due to the fundamental differences in the way the two methods handle the data. GBTM gathers individuals into subgroups that show statistically similar trajectories with individuals being assigned a probability of group membership (Nagin, 2005). Covariates are handled in two ways; baseline covariates can be linked to the probability of group membership, and events that occur during the course of the trajectory can be examined for their impact on the trajectories' paths. Linear mixed modeling assumes all individuals follow the same basic developmental pattern with random variation around that pattern; it takes the hierarchical nature of the data into account; and it allows for the simultaneous estimation of the influence of covariates at tooth and person level (Tu et al., 2013; Zeng et al., 2014). It is likely that the dissimilarity in the GBTM and LMM findings is due to a combination of the methodological differences and the different variables used.

Having periodontitis during the fourth decade of life was not found to have any influence on the HbA1c trajectory groups; a non-statistically significant minimal difference in mean HbA1c was seen between those with periodontitis at ages 32 and 38, and those without periodontitis at these ages. This finding was repeated in the linear mixed model analysis, which found no relationship between the mean % sites with 4+mm AL and HbA1c.

Most researchers agree that individuals with poorly controlled diabetes have a greater risk of destructive periodontitis (Azarpazhooh and Tenenbaum, 2012; Bascones-Martinez et al., 2011; Cullinan et al., 2009; D'Aiuto et al., 2005; Grossi and Genco, 1998; Kandelman et al.,

2008; Khader et al., 2006; Kuo et al., 2008; Lakschevitz et al., 2011; Lalla and Papapanou, 2011; Löe, 1993; Mealey, 2006; Mealey and Oates, 2006; Mealey and Ocampo, 2007; Papapanou, 1996; Preshaw et al., 2012; Salvi et al., 2008; Taylor, 2001; Williams et al., 2008). There is also substantial evidence that a bidirectional relationship exists between periodontitis and type 2 diabetes; the chronic inflammation of periodontitis may influence glycaemic control in susceptible individuals, with each condition potentially exacerbating the other. However, research to date has reported conflicting findings, with some studies suggesting that periodontitis may influence HbA1c levels, IGT, glycaemic control in those with type 2 diabetes or diabetes risk (Borgnakke et al., 2013; Choi et al., 2011b; Demmer et al., 2008; Demmer et al., 2010; Grossi and Genco, 1998; Ide et al., 2011; Lamster et al., 2014; Morita et al., 2012; Nesse et al., 2009; Saito et al., 2004; Saito et al., 2006; Taylor et al., 1996; Zadik et al., 2010), and others finding no associations (Marugame et al., 2003; Saito et al., 2005). The corollary of a bidirectional relationship between periodontitis and diabetes is that treatment of periodontal disease in those with poorly-controlled diabetes may improve their glycaemic control. Once again, the evidence is conflicting but mostly positive (Borgnakke et al., 2014; Darre et al., 2008; Engebretson and Hey-Hadavi, 2011; Grossi et al., 1997; Khader et al., 2010; Kiran et al., 2005; Koromantzos et al., 2011; Simpson et al., 2010; Teeuw et al., 2010). However, others have found no effect (Engebretson et al., 2013; Janket et al., 2005; Jones et al., 2007; Yun et al., 2007).

Most research has been carried out on participants who already had type 2 diabetes (or the study had diabetes incidence as an outcome), on middle-aged or older people, on children and adolescents with Type 1 diabetes, or on population-based samples with the full range of adult age groups. There has been little research on an initially healthy sample and concentrating specifically on early dysglycaemia/prediabetes as a predictor for periodontitis, or on periodontitis as a predictor for early dysglycaemia/prediabetes. Thus, comparisons between the present study and others are difficult. The three studies by Saito and colleagues on Japanese samples had inconsistent findings: a greater risk of progression to IGT with greater periodontal probing depth (Saito et al., 2004); no associations between IGT and either deep pocketing or severe attachment loss in a female-only sub-sample of the previous study (Saito et al., 2005); and associations between alveolar bone loss and IGT in a different sample (Saito et al., 2006). A 2010 SHIP paper found periodontitis at baseline in healthy individuals to be associated with HbA1c progression five years later (Demmer et al., 2010). Choi et al. found a dose-response relationship between periodontitis and IFG in a NHANES

III sample (Choi et al., 2011b). Another study found associations between higher HbA1c at baseline and the risk of developing periodontitis five years later, and between periodontitis at baseline and the risk of higher HbA1c five years later (Morita et al., 2012). Lamster et al. found that participants with previously unidentified prediabetes demonstrated periodontitis experience at a level between those observed for normoglycaemic participants and participants with type 2 diabetes (Lamster et al., 2014). In contrast, a recent SHIP-Trend study found no association between prediabetes and the extent of teeth with 4mm+ AL or mean probing depth (Kowall et al., 2015). Meanwhile, the Continuous NHANES 2009-2010 survey found associations between severe periodontitis and IGT, but not IFG, and no associations between moderate periodontitis and either IGT or IFG (Arora et al., 2014). Of these studies, only three were longitudinal. One was retrospective (Saito et al., 2004) and two were prospective (Demmer et al., 2010; Morita et al., 2012). For each of these longitudinal studies, participation/retention rates were poor, so the findings were not generalisable to the source populations.

Therefore, it is believed the current study is the first to examine the longitudinal bidirectional associations between periodontitis and dysglycaemia, as measured by HbA1c, at an early stage in the glycaemia continuum. Some unadjusted cross-sectional and longitudinal associations were found between the two conditions over 12 years. However, in the fully adjusted models, the influence of dysglycaemia at age 38 on periodontitis was found to be minimal, and having periodontitis at age 32 or 38 had no influence on HbA1c levels. In addition, a supplementary analysis using linear mixed effect modeling confirmed no associations between mean AL and mean HbA1c over the twelve years. It must therefore be acknowledged that there was no real relationship between the two conditions at this stage in the life course.

Why was no relationship found between the two conditions in this study while some of the other studies did find associations? There is no way of knowing for sure, but it is possible to speculate. First, the age groups in the other studies were both older and (with the exception of the 2006 Saito et al paper) had a wider range of ages. The Saito studies had participants aged 40 years and older (Saito et al., 2004; Saito et al., 2005) and 50-55 years (Saito et al., 2006). Both the SHIP and the NHANES III samples were 20 years and older (Choi et al., 2011b; Demmer et al., 2010). The Morita et al sample was aged 30-69 years; the Columbia University study sample was age 40 and over if Caucasian, and age 30 and over if non-

Caucasian or Hispanic; the Continuous NHANES 2009-2010 sample was ages 30-80; and the SHIP-Trend sample was ages 20-82 (Arora et al., 2014; Kowall et al., 2015; Lamster et al., 2014; Morita et al., 2012).

The current study focused on the 12 years between ages 26 and 38; this is a time of life when the foundations of poor health are being laid down, but it may also be a developmental epoch in which it is just too early to see clear bidirectional associations between periodontitis and dysglycaemia. While the prevalence of both conditions was high in the Dunedin cohort by age 38, the experience of neither was very severe. This study investigated dysglycaemia as a predictor of periodontitis at an earlier stage in the life course than had much previous research, and in an initially healthy cohort (there were only two individuals with prediabetes at age 26). Therefore, it is not surprising that dysglycaemia was found to exert only minimal influence on periodontitis in the fourth decade. That this influence was exerted on those already at risk of poorer periodontal outcomes (those in the "High" periodontal trajectory) supports the concept that developmental history not only modifies the response to impacts, but may also define the magnitude of that response (Elder, 1998). Disadvantage may accumulate throughout life, with those most disadvantaged diverging further from those less disadvantaged with each subsequent challenge. Likewise, much of the research into the influence of periodontal disease on dysglycaemia/glycaemic control has been carried out on participants with diabetes, and has been in older populations. The present study examined the influence of periodontitis at a much earlier stage in the life course – and found no effect. Since both periodontitis and dysglycaemia generally worsen with time, it is possible that such associations may develop as the cohort ages (Hashimoto et al., 1995; Kassebaum et al., 2014; Pani et al., 2008; Yang et al., 1997).

Second, different studies have used different definitions of dysglycaemia. Most papers used IGT as an indicator of dysglycaemia (Choi et al., 2011b; Kowall et al., 2015; Saito et al., 2004; Saito et al., 2005; Saito et al., 2006); changes in mean HbA1c were used in two studies (Demmer et al., 2010) (Morita et al., 2012); and HbA1c levels recorded by a point-of-care device were used in one (Lamster et al., 2014). Another study found that whether there were associations or not depended on how dysglycaemia was assessed: either by IGT or IFG (Arora et al., 2014). The present study used both mean HbA1c and dysglycaemia as defined by ≥39 mmol/mol HbA1c (American Diabetes Association, 2011). While no method of measurement is perfect, research indicates (and many organisations are

recommending) that HbA1c be used for screening and diagnosis of diabetes (American Diabetes Association, 2014; Hare et al., 2012; Santos-Rey et al., 2010; The International Expert Committee, 2009; World Health Organization, 2011b).

Third, there was even more variation among studies in how periodontitis experience was defined. Globally, there is a lack of standardisation and agreement in establishing criteria for the diagnosis of the condition, so comparisons among studies are problematic (Hugoson and Norderyd, 2008; Leroy et al., 2010; Page and Eke, 2007). Within the studies examining the bidirectional associations between periodontitis and diabetes, periodontitis was variously assessed by the Community Periodontal Index of Treatment Need (CPITN or CPI) (Morita et al., 2012), clinical attachment loss (AL) and pocket depth (Arora et al., 2014; Choi et al., 2011b; Demmer et al., 2010; Kowall et al., 2015; Saito et al., 2004; Saito et al., 2005), pocket depth only (Lamster et al., 2014), and by alveolar bone loss determined using radiography (Saito et al., 2006). Most periodontal examinations (including the age-26 data in the present study) were half-mouth only (Choi et al., 2011b; Demmer et al., 2010; Kowall et al., 2015; Saito et al., 2004; Saito et al., 2005); full-mouth recordings were made in only two studies, and they were both cross-sectional (Arora et al., 2014; Lamster et al., 2014). For the current study, it was necessary to convert the age 32 and 38 measures to half-mouth data in order to allow longitudinal comparisons with the age 26 data. Furthermore, AL data were gathered from only three sites per tooth, whereas some of the other studies had recordings from four or six sites per tooth. Together, these may have led to an underestimation of the prevalence of periodontitis, and possibly a reduction in the strength of the associations between periodontitis prevalence and other parameters.

4.3 Implications of the findings

This section discusses the theory, research, practice and policy implications of the findings of this study, and makes recommendations based on the findings. The findings of this study contribute substantially to our understanding of two very common disorders, periodontitis and dysglycaemia, and fill a gap in the *theory* of how they develop during the third and fourth decades. They underline the need for future *research* onwards into the fifth decade of life to further understand their evolution, their associations with one other, and with their covariates. Clinicians require clear, down-to-earth, valid and evidence-based guidelines on how best to assess an individual's risk within clinical *practice*. The findings reinforce the importance of smoking and central adiposity as risk factors for poor health outcomes, and suggest these risk factors may have an impact from an early age. The formulation of effective public health *policy* requires comprehensive and objective information on the magnitude of health problems and their likely future trends. In this way, governments can make the decisions now for investment in necessary health research, health workforce development and physical infrastructure requirements, as well as planning for the most appropriate and efficient treatment and preventive interventions. The findings of this study imply that planning for the future burden of disease, smoking reduction policies and interventions, and measures to tackle our obesogenic environment should be included in the main priorities.

4.3.1 Planning for the future burden of disease

Non-communicable diseases including cardiovascular diseases, chronic respiratory diseases, cancer, diabetes, autoimmune disorders, and oral diseases exact a huge disease burden worldwide (World Health Organization, 2011a). These diseases have reached epidemic proportions, and their prevalence is projected to increase, particularly in developing countries (Abegunde et al., 2007; Nikolic et al., 2011). The current study has found a high prevalence of both periodontal disease and dysglycaemia by the end of the fourth decade. The burden of both these conditions in the decades ahead has implications for both workforce planning and the cost of healthcare in the future.

4.3.1.1 Future burden of periodontal disease

The future burden of periodontitis is evident when the decline in edentulism, increases in life expectancy, and advances in restorative dentistry mean that higher retention of teeth in the middle-aged and older people is inevitable. Teeth that in past years would have been lost to dentures are now being retained, resulting in more teeth being at risk of periodontitis for a longer period (Shearer et al., 2011). The current study has found periodontal disease to be already both highly prevalent and extensive by the end of the fourth decade. By age 38, almost half the Dunedin cohort had 1+ sites with 4+mm AL; a third had 2+ sites with 4+mm AL, and there was a mean 5.1% of sites with 4+mm AL. It is probable that few Study members will become edentulous in the future; the prevalence of edentulism in New Zealand has dropped steadily since 1976 (Ministry of Health, 2010a). In Australia, projections for the prevalence of edentulism vary (depending on the assumptions made in the models) between 2.7% and 3.1% for the year 2021; and between 0.4% and 1.0% for the year 2041 (AIHW Dental Statistics and Research Unit, 2007). Thus, there will likely be a substantial future burden of periodontal disease in this cohort.

Globally, the proportion of people who would expect to keep their teeth for life is increasing, and many will not have access to comprehensive and ongoing periodontal care.
In later years, many will face the irritation and pain of loose teeth, reduced functional capacity, sensitivity, halitosis, unaesthetic appearance, and associated loss of self-esteem. Most worrying, the extraction of teeth may not ultimately be avoided. Rather, it may be delayed until well into old age, and the future workforce will have to meet the challenge of difficult tooth extractions in a medically-compromised and frail elderly population.

Future workforce planning needs to consider and provide for the oral health needs of older people. Geriatric dentistry is often seen to be less attractive than other aspects of general dental practice (Antoun et al., 2008). The inclusion of a geriatric care module within the undergraduate programme, continuing dental education for existing practitioners, and a post-graduate degree in gerodontology may go some way towards addressing this issue (Thomson and Ma, 2014). In addition to tackling the issue of geriatric care (and to attempt to avoid some of the problems outlined above), the future of the periodontal care workforce will also need to be addressed to facilitate timely and accessible care for the projected rise in the dentate population with periodontitis. This includes assessing the most appropriate mix

of specialist periodontists, dental hygienists and oral health therapists to best manage all aspects of periodontal care.

4.3.1.2 Future burden of dysglycaemia

The prevalence of dysglycaemia in the Dunedin cohort is of great concern. While few Study members had type 2 diabetes at age 38, almost one in five were categorised as having prediabetes by that age, and those individuals are at great risk of developing type 2 diabetes within a decade (Ackermann et al., 2011). Ackermann et al. calculated the probability of developing type 2 diabetes within 7.5 years for individuals with ≥39 mmol/mol HbA1c to be 41%. It may be assumed the incidence and prevalence of type 2 diabetes in New Zealand will rise markedly in the coming years.

Globally, the prevalence of type 2 diabetes has risen over recent years and is projected to rise substantially in the future (Boyle et al., 2010; The International Diabetes Federation's Diabetes Atlas.; Webber et al., 2014; Wild et al., 2004). The burden and economic cost of diabetes and its complications are already significant (Centers for Disease Control and Prevention, 2011). However, this cost is forecast to rise substantially in the future, with consequential morbidity, mortality, suffering, reduced productivity, and increased use of scarce healthcare resources (American Diabetes Society, 2008; Davis et al., 2006; Fradkin and Rodgers, 2008; Huang et al., 2009).

Policy makers will have to understand and plan for these costs over the next decades. For example, the diabetes-related healthcare costs are expected to increase from $113 billion in 2009 to $336 billion in 2034 (Huang et al., 2009). Policy makers also need to urgently fund and implement effective preventive interventions to try to minimise future increases in type 2 diabetes prevalence. Likewise, future diabetes care workforce needs (including endocrinologists, diabetes nurses and educators, dieticians, podiatrists, bariatric and renal specialists, ophthalmologists and more) must be assessed, planned, and trained.

4.3.2 Early identification of those at risk

Almost 20 years ago, Burt outlined a three-tiered approach to prevention involving: (1) population strategies aimed at the whole population; (2) targeted strategies are aimed at

sections of the population considered to be most at risk; and (3) individually targeted strategies aimed at the high-risk individual (Burt, 1998). Individuals differ widely in their vulnerability to non-communicable diseases, which are driven by a complex range of interconnected risk factors including genetic and familial factors, sociodemographic influences, economic factors, and modifiable lifestyle choices. Premature death and suffering could be greatly reduced, and economic and social burdens lessened, by the early identification and timely treatment of those most at risk. It makes sense to attempt to target those at highest risk of disease for intensive preventive measures; these can be very effective in reducing disease prevalence and severity (Axelsson et al., 1991; Löe, 2000; Stamm et al., 1991). The cost of early prevention is generally cost-effective compared to the cost of later treatment, and allows for the most effective use of healthcare resources. However, the identification of those groups most at risk is not necessarily straightforward.

This study has provided a novel perspective to the identification of those most at risk of two non-communicable diseases—destructive chronic periodontitis and type 2 diabetes—by characterising risk in terms of a subpopulation's development trajectory. In the DMHDS cohort, periodontal and glycaemic health status at 38 was predicted by periodontal and glycaemic health status respectively at 26. The study has not only added to the body of evidence for the role of the classic risk factors of smoking and obesity, but it has also suggested that they may contribute to disease risk at an earlier stage in life than previously presumed. These findings should provide clinicians and public health policy makers with a good theoretical basis for developing effective screening and intervention programmes earlier in life rather than later – which often can be just too late.

4.3.3 Smoking reduction programmes must be a priority

Cigarette smoking was first linked to poor health outcomes 65 years ago (Doll and Bradford Hill, 1950). Since then, the volume of research demonstrating the association between smoking and a host of diseases has been overwhelming, and it leaves little doubt that smoking is one of the most hazardous modifiable risk factors known.

This study has demonstrated that smoking at age 26 as a risk factor for the poorest periodontal outcomes 12 years later, and as a risk factor for the change from

normoglycaemia along the continuum to dysglycaemia. To date, smoking as a risk factor for type 2 diabetes has not received a great deal of publicity. It is believed this is the first time an association between smoking during the third decade and dysglycaemia 12 years later has been demonstrated, and it provides smokers with another reason to quit. In the DMHDS cohort, periodontitis and dysglycaemia share smoking as their strongest and most consistent risk factor. It is becoming increasingly obvious that an evidence-based approach to the primary prevention of these two conditions should include smoking prevention and cessation, and this realisation reconfirms the need for a common risk factor approach (Sheiham and Watt, 2000). This concept suggests that the control of a small number of risk factors may have a substantial and cost-effective impact on a large number of disease outcomes (Sheiham and Watt, 2000). This calls for greater collaboration between oral healthcare providers, diabetologists, cardiologists, oncologists and primary care providers in lobbying for more legislation and funding aimed at reducing smoking prevalence.

Legislation could include more restrictions on where smoking is permitted, tax and price measures to reduce tobacco consumption, the introduction of standardised packaging of tobacco products, and the introduction of tobacco retail licensing and registration, whereby tobacco retailers and wholesalers must obtain a license to sell tobacco products. Currently, the minimum legal age for buying cigarettes and other tobacco products in New Zealand is 18. Recently, the Californian State Senate approved a bill that would raise the minimum legal age from 18 to 21. It is estimated such a measure would likely prevent or delay initiation of tobacco use by adolescents and young adults, and substantially reduce smoking prevalence (IOM (Institute of Medicine), 2015). Should New Zealand also consider such a measure?

Additional measures to reduce smoking prevalence could include funding for further social marketing campaigns, general medical and dental practitioners paid to provide ongoing cessation counselling, and increased funding for the Quitline nicotine replacement therapy programme.

4.3.4 Central adiposity measures as predictors of dysglycaemia

There is convincing evidence that excessive body weight and central adiposity are risk factors for dysglycaemia (World Health Organization, 2003). However, the question as to which measure is most closely linked to that risk has not been resolved (Ashwell et al., 2012; Browning et al., 2010; Feng et al., 2012; Janssen et al., 2004; Kodama et al., 2012; Lee et al., 2008; Liu et al., 2011; Truswell, 2012; Tulloch-Reid et al., 2003; Vazquez et al., 2007). Clinicians and epidemiologists would welcome clear guidance on which measure (preferably a quick and easy one with minimal potential for error) will most reliably predict risk in their patients and study participants.

This study confirms the two central adiposity measures WC and waist-height ratio to be valid clinical predictors for future dysglycaemia risk. These findings have implications for both clinical and public health practitioners; they underline the importance of the central adiposity measures (WC and waist-height ratio) for patients, and reinforce the "keep your waist circumference to less than half your height" public health message. It will be of interest to busy clinicians that the addition of BMI did not enhance the predictive utility of these measures of central adiposity in this cohort. Moreover, the findings suggest that routine screening using WC and waist-height ratio from the middle of the third decade may help to identify those most at risk of unfavourable future outcomes. It may be appropriate to encourage primary care providers and clinicians to do this. While the use of waist-height ratio to assess cardiometabolic risk is relatively recent, the findings of this study indicate its use should be encouraged. Currently, the New Zealand Guidelines Group recommends the use of BMI and WC for cardiovascular risk assessment and type 2 diabetes screening (New Zealand Guidelines Group, 2012). It is proposed that waist-height ratio should also be recommended in future guidelines.

The high prevalence of obesity by age 38 in the Dunedin cohort (and the sharp increase between ages 26 and 38) adds to the widespread concern about the rising prevalence of obesity globally, and underlines the need for effective and comprehensive public health programmes to reduce obesity prevalence and its consequences. There is a need to move away from victim blaming and instead focus on public health interventions that change the obesogenic environment. Instead of blaming individuals for eating too much and exercising too little, we should be advocating for legislation and policies that make "the healthy choice

the easy choice" (Ashe et al., 2011; Koelen and Lindstrom, 2005). Measures proposed include a tax on unhealthy foods, removing GST on fruit and vegetables, introduction of a traffic light nutrition labelling system, legislating for only healthy food to be available in schools, limiting the sale and advertising of sugar sweetened beverages (SSBs), implementing SSB-free policies in workplaces and public institutions, ensuring all New Zealand families have enough income to buy healthy food, and removing barriers to physical activity. These policies may go some way towards addressing the very complex underlying issues that contribute to the obesity epidemic.

4.3.5 No relationship between periodontitis and dysglycaemia

This study found no substantial relationship between periodontitis and dysglycaemia during the fourth decade of life. This "negative finding" adds to the theoretical understanding of how these two conditions interrelate, and it gives rise to new hypotheses. For example, it is possible that one condition may need to reach a particular threshold of severity to impact on the other. There are important implications for future research. It is essential to continue to track the natural history of both conditions in order to understand how they develop and interact over the next decades of life. The DMHDS cohort is in a unique position to continue to track trajectories of periodontitis and HbA1c onward into middle age. Data from the middle of the fifth decade should be available from 2018, and they will facilitate the further elucidation of the bidirectional links, complex associations and temporal relationship between periodontal disease and dysglycaemia as the cohort ages. Building on the foundations of the present study, the further examination of the longitudinal associations between these two conditions and their covariates—and their associations with each other—should inform future public health policy and clinical practice.

4.4 Negative findings and the research journey

"I can now rejoice even in the falsification of a cherished theory, because even this is a scientific success" (Eccles, 1989).

It is probable that every researcher begins a project in the hope that his/her findings will substantially contribute to the sum of knowledge. Generally, those findings are envisaged as being positive, and it is usually disappointing when this turns out to be not the case. Often, negative findings tend not to be greeted with the same enthusiasm by journal editors and the press as positive findings are. The most newsworthy findings have the greatest chance of being published.

I have now been through the experience of having a negative finding for a major component of my thesis (the finding that there was no relationship between periodontitis and dysglycaemia in the fourth decade) and I have, of course, experienced feelings of disappointment and frustration. However, I am reassured by the words of Karl Popper "Every genuine test of a theory is an attempt to falsify it or to refute it" (Popper, 2014). In this, I have succeeded. I understand that knowing what is not true is as important as knowing what is. Negative findings do contribute to the sum of knowledge. What is important is that they are recognised as such. The proportion of negative findings papers that have been published has dropped in recent years from 29.8% in 1990 to 14.1% in 2007 (Fanelli, 2011). This positive findings bias is something that must be reversed. Negative results should be shared with the broader academic community. Failure to report them is a barrier to knowledge and understanding, and it distorts the scientific literature.

The concept of a PhD thesis as a "research journey" has been used so often that it is in danger of becoming clichéd. Even so, it is a reasonable way of visualising the process of beginning a research project and seeing it through to the end. However, the journey is not a straightforward process of travelling directly from beginning to end. There are many stops and starts along the way. It is iterative; often, one returns to an earlier stage in the journey, travels it again, and finds something different each time. There are interruptions, distractions, false starts, blind alleys, and plenty of pitfalls along the way. Some days, the destination seems too far away, and the journey too long. But as the journey now draws to

an end, the words of Henry Miller come to mind: “One’s destination is never a place, but rather a new way of looking at things” (Miller, 1957). I believe that the journey to this particular destination has given me the opportunity to look at the world anew.

4.5 Summary and conclusions

This study has tracked the natural history of two conditions—periodontitis and dysglycaemia—from the middle of the third decade to the end of the fourth decade of life. It provides strong evidence for a gradual decline in health status during this time, and found that both conditions were highly prevalent by age 38. It found that: (a) periodontal status, male sex, smoking, marijuana use, low SES, high plaque score and episodic use of dental services at age 26 were predictors of periodontal status 12 years later; and (b) glycated haemoglobin levels, male sex, smoking, high waist circumference and high waist-height ratio at age 26 were predictors of dysglycaemia 12 years later. No relationship was found between periodontitis and dysglycaemia at this stage in the life course. The findings contribute substantially to our understanding of the two conditions and fill a gap in the theory as to how they develop during the third and fourth decades. The findings reinforce the importance of smoking and central adiposity as risk factors for poor health outcomes, and suggest that these factors may have an impact from an early age. The replication of these findings by other researchers in diverse settings is welcomed. Given the high prevalence of both conditions at this relatively early stage in life, it is suggested that planning for the future burden of disease, earlier routine cardiometabolic screening, smoking reduction policies and interventions, and measures to tackle the obesogenic environment should be considered as important priorities for future public health policy.

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