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An investigation of risk factors for the later development of Type 2 Diabetes Mellitus, using HbA1c as a measure of glycaemia in a group of Auckland school children.

A thesis presented in partial fulfilment of the requirements for the degree of

Master of Science
in
Nutrition and Dietetics

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Abstract

Background: A glycated haemoglobin (HbA1c) test is recommended in diagnosing type 2 diabetes mellitus (T2DM) and to identify prediabetics. This test is advocated over other methods due to ease of application and processing. Few studies have examined associations between HbA1c levels and T2DM risk factors (RFs) in children.

Aim and hypotheses: To investigate the relationship between HbA1c levels and selected RFs associated with T2DM risk in a group of Auckland children. It is hypothesized that ethnicity and waist circumference (WC) will be reliable indicators of later T2DM risk. Body fat percentage (%BF) will likely be positively correlated with HbA1c level.

Study design: A cross-sectional study involving children aged 8-11 years from six Auckland primary schools. Physical measures included weight, height, WC and %BF. A finger-prick blood test was collected for HbA1c levels. Ethnicity, gender, age, usual beverage intake and physical activity (PA) behaviours were assessed by self-completed questionnaires. Stepwise multiple linear regression analysis was used to explore which independent variables best predicted variance in HbA1c level.

Results: When children (n=451, 10.4$\pm$0.6 years) were classified by glycaemic status, 71 children (15.7%) had HbA1c levels indicative of prediabetes. This was greatest in Pacific (n=29) and South Asian (n=13) children. Maori and Pacific children had higher BMI than European children ($p<0.0001$). For HbA1c, Pacific and South Asian children had higher levels than European ($p<0.0001$), as did Maori children ($p<0.05$). Asian children exhibited high %BF for a low BMI. In regression analysis to explain the variance in HbA1c, WC was the most significant predictor for South Asian, Pacific and Asian children.

Conclusion: Ethnicity and adiposity (both central and overall) are key RF for T2DM risk. Waist circumference, waist-to-height ratio (WtHR) and BMI may all be used as measures in screening for T2DM risk. Glycated haemoglobin was a useful screening tool alongside RFs and not dependent on obesity.

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List of Abbreviations

2hPG:	2-hour plasma glucose
ADA:	American Diabetes Association
BIA:	Bioelectrical impedance analysis
BF:	Body fat
BP:	Blood pressure
BMI:	Body mass index
CHD:	Coronary heart disease
CVD:	Cardiovascular disease
FPG:	Fasting plasma glucose
GI:	Glycaemic index
HbA1c:	Glycated haemoglobin
HDL-C:	High-density lipoprotein cholesterol
IGT:	Impaired glucose tolerance
IR:	Insulin resistance
LDL-C:	Low-density lipoprotein cholesterol
MetS:	Metabolic Syndrome
NHS:	Nurse's Health Study
NZ:	New Zealand
NZSSD:	New Zealand Society for the Study of Diabetes
OGTT:	Oral glucose tolerance test
PA:	Physical activity
PoC	Point of care
RF:	Risk factor
SES:	Socioeconomic status
SSB:	Sugar-sweetened beverage
T1DM:	Type 1 diabetes mellitus
T2DM:	Type 2 diabetes mellitus
WC:	Waist circumference
WHO:	World Health Organisation
WHtR:	Waist-to-height ratio
WHR:	Waist-to-hip ratio

Chapter One

1.0 Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterised by hyperglycaemia due to dysfunction of insulin secretion, insulin action or a combination of both (American Diabetes Association, 2010). The long-term consequences of having T2DM are varied and diabetes-related complications may include retinopathy, nephropathy, neuropathy or comorbidities such as hypertension, hyperlipidaemia and increased risk of cardiovascular disease (CVD) (American Diabetes Association, 2010; Dabelea et al., 2017; Pinhas-Hamiel & Zeitler, 2004).

Type 2 diabetes mellitus has previously been considered a disease of adulthood but in recent times the prevalence amongst children and adolescents has increased (Chen, Magliano, & Zimmet, 2012; Dabelea et al., 2014; Zimmet, Magliano, Herman, & Shaw, 2013), with minority populations and low socioeconomic status groups disproportionately affected (Imperatore et al., 2012; Khanolkar et al., 2016; Wang & Beydoun, 2007). Globally the prevalence of diabetes in 2015 was estimated to be 415 million (uncertainty interval: 340–536 million) people aged 20-79 years (Ogurtsova et al., 2017). This is predicted to rise to 642 million (uncertainty interval: 521–829 million) people aged 20-79 years by 2040 (Ogurtsova et al., 2017). Estimates for T2DM prevalence in those aged <20 years in the United States are forecasted to increase from 0.27/1000 to 0.75/1000 representing a +178% increase from 2010 to 2050, especially among minority youth (Imperatore et al., 2012).

Less is known of the T2DM epidemiology in children and adolescents when compared to adults, however the causes are considered to be more environment-related than purely genetic and associated with the concurrent childhood obesity epidemic (Arslanian, 2002; Imperatore et al., 2012; Pinhas-Hamiel & Zeitler, 2000). The increased prevalence of obesity amongst minority populations (Imperatore et al., 2012; Pinhas-Hamiel & Zeitler, 2005) and exposure to maternal diabetes or obesity in utero (Dabelea et al., 2008) are thought to be other related factors. With higher rates of obesity, there is a raised awareness of T2DM in children and adolescents, which is also thought to

be a contributing factor to the increased prevalence in T2DM (Pinhas-Hamiel & Zeitler, 2000; Pinhas-Hamiel & Zeitler, 2005).

Early-onset T2DM is associated with a longer duration of exposure to hyperglycaemia (Pinhas-Hamiel & Zeitler, 2005), and the earlier progression of complications at a younger age impacting on quality of life, life expectancy and healthcare costs (Fagot-Campagna et al., 2000; Imperatore et al., 2012). This highlights the importance of early identification of risk factors (RFs) and the screening of at-risk children and adolescents.

There are numerous RFs for T2DM and the disease itself is a RF for CVD, which is one of the leading causes of mortality in New Zealand (NZ) (Ministry of Health, 2015). Screening for T2DM is undertaken as part of a CVD risk assessment with family history RFs including the presence of diabetes, coronary heart disease (CHD) or ischaemic stroke in first-degree relatives, or individual RFs such as being a smoker, obese, having hypertension, high cholesterol or impaired renal function (New Zealand Guidelines Group, 2009). Current NZ CVD screening guidelines do not extend to those aged under 25 years, however the New Zealand Society for the Study of Diabetes (NZSSD), suggests opportunistic screening in obese children and young adults if there is a family history of early-onset T2DM or a high-risk ethnic group (New Zealand Society for the Study of Diabetes, 2011).

There are also non-clinical RFs for T2DM which include socioeconomic status (Maty, Lynch, Raghunathan, & Kaplan, 2008; Wang & Beydoun, 2007), a shift to “obesogenic” environments that promote an imbalance between energy intake and energy expenditure (Spruijt-Metz, 2011), physical inactivity (International Diabetes Federation, 2015; Steyn et al., 2004) and puberty (Goran, Ball, & Cruz, 2003).

A glycated haemoglobin (HbA1c) test is the recommended screening method used in the diagnosis of T2DM, and may also be used as an opportunistic screening tool for prediabetes, an intermediary state of glycaemia above normal but below that of T2DM (Sequeira & Poppitt, 2017). The test is advocated over the fasting plasma glucose (FPG) method as it eliminates the requirement for fasting, there is lower biological variability and it is relatively easy to process samples (New Zealand Society for the Study of Diabetes, 2011; World Health Organisation, 2011). Used alongside an initial risk assessment screening tool,

an HbA1c test would provide an opportunity to readily assess and identify at-risk individuals. Such screening amongst at-risk groups, presents as an opportunity for early detection of risk and the implementation of lifestyle modification interventions, which may mitigate the risk of future diabetes onset and related complications.

1.1 Purpose of the study

The prevalence of T2DM continues to increase and in recent times, the age of onset has fallen with T2DM now increasingly occurring in children and adolescents, particularly amongst high-risk groups. The increased incidence is thought to be related in part to the obesity epidemic with changes in dietary intakes and physical activity (PA) levels compared to earlier generations.

Type 2 diabetes mellitus is a progressive disease with potential long-term complications if not managed. This reinforces the need to proactively and effectively identify at-risk children and adolescents to deliver interventions to either reverse or slow the effects, whilst also managing the healthcare and economic burden of the disease.

Whilst HbA1c is a recognised tool for diagnosing T2DM, it can also be utilised as an opportunistic screening tool for prediabetes. Disease related complications may already be present at diagnosis so timely interventions may prove effective in preventing the disease. The current study seeks to investigate RFs for the later development of T2DM, using HbA1c levels as a measure of glycaemia in a group of Auckland school children.

1.2 Aim

To investigate the relationship between HbA1c level as a measure of glycaemic control, and other recognised RFs for the later development of T2DM in a group of Auckland school children.

1.2.1 Objectives

To determine body composition, ethnicity, demographic characteristics and PA levels in a group of Auckland school children, exploring their relevance and association with glycaemic control as measured by HbA1c level, to assess later risk of T2DM.

1.2.2 Hypotheses

- That ethnicity and waist measures (waist circumference (WC) and waist-to-height ratio (WtHR)) will be reliable indicators of later risk of T2DM, as measured by current HbA1c status.
- That body fat percentage will be positively correlated with HbA1c level.

1.3 Thesis structure

This thesis is structured into four chapters.

Chapter one

The focus of chapter one is to contextualise the study including the research aim and the significance of the research.

Chapter two

A review of the literature is presented. This includes identifying and assessing the current evidence concerning RFs for T2DM alongside measures for diagnosing the condition.

Chapter three

This section is compiled as a complete presentation of the research study as a manuscript prepared for submission to a peer-reviewed journal. Included are the study methods, key results and discussion of the findings, conclusions and recommendations for future research.

Chapter four

This chapter concludes the thesis providing the main study findings as well as strengths and limitations of the current study and recommendations for future research.

1.4 Researcher's contributions

Researchers	Contribution to Thesis
Donna Lawgun	Designed questionnaires, supported with ethics application, preparation of database, analysed data, interpreted results and author of thesis
Dr Pamela von Hurst	Primary supervisor, conceptualised and principal investigator of the research, compiled the study team, developed ethics application, obtained funding for the research, supervised development of questionnaires, gave feedback and approved final thesis.
Dr Cheryl Gammon	Co-supervisor, metabolic markers, statistics, gave feedback on thesis. Obtained funding for HbA1c cartridges.
Dr Cath Conlon	Paediatric nutrition.
Dr Kathryn Beck	Physical activity.
Owen Mugridge	Research manager. Development of standard operating procedures, training and coordination of data collection team and phlebotomist.
Maya Carryer	Registered teacher delivered educational module
The following supported with participant testing and data collection: David Alsford, Dr Kathryn Beck, Maya Carryer, Dr Cath Conlon, Mia David, Maryam Delshad, Jasmine Foote, Dr Cheryl Gammon, Dr Pam von Hurst, Donna Lawgun, Tara Lemmon, Owen Mugridge, Sanaz Naghizadeh, Emma Smirk, Emma Ternouth, Alex Tava and PC Tong.	

Chapter Two

2.0 Literature review

2.1 Diabetes prevalence

Globally, the prevalence of combined overweight and obesity increased by 27.5% in adults and by 47.1% in children during the period 1980-2013 (World Health Organisation, 2015a). The increased prevalence is deemed an obesity epidemic and has affected all age groups, ethnicities and genders in both developing and developed countries (World Health Organisation, 2015a). Correspondingly, type 2 diabetes mellitus (T2DM), a chronic disease previously seen only in the middle-aged and elderly (Alberti et al., 2004; Daniels et al., 2005) and strongly believed to be a by-product of obesity (Han, Lawlor, & Kimm, 2010; Hu, Manson, et al., 2001; Ludwig & Ebbeling, 2001), has now become increasingly prevalent in children and adolescents (Chen et al., 2012; Dabelea et al., 2014; Zimmet et al., 2013). The prevalence of T2DM is rising globally and it was estimated that 415 million (uncertainty interval: 340–536 million) people aged 20-79 years were living with diabetes in 2015 and that this would rise to 642 million (uncertainty interval: 521–829 million) people by 2040 (Ogurtsova et al., 2017). Estimates for T2DM prevalence in those aged <20 years in the United States are forecasted to increase from 0.27/1000 to 0.75/1000 representing a +178% increase from 2010 to 2050, especially among minority youth (Imperatore et al., 2012). Additionally in 2015, 16.2% of live births (20.9 million), were linked with hyperglycaemia in pregnancy with 85% of these cases attributable to gestational diabetes (Ogurtsova et al., 2017). This presents as a RF for health risks and later development of T2DM in both mother and child (American Diabetes Association, 2014). In New Zealand a virtual diabetes register of those accessing diabetes health services estimates prevalence at 241,463 people (or 5% of the population) in 2016 and this figure has increased from 144,747 in 2006 (Ministry of Health, 2017).

2.2 Type 2 diabetes mellitus

2.2.1 Definition and aetiology

Type 2 diabetes mellitus is a metabolic disorder involving insulin resistance (IR) with accompanying insulin deficiency or insulin secretory dysfunction (American Diabetes Association, 2010). Less is known of the T2DM epidemiology in children and adolescents when compared to adults, however the causes are considered to be more environment-related than purely genetic and associated with the concurrent childhood obesity epidemic (Arslanian, 2002; Imperatore et al., 2012; Pinhas-Hamiel & Zeitler, 2000). Table 2.1 from Alberti et al, (2004) details the characteristics that differentiate the presentation of type 1 diabetes mellitus (T1DM) and T2DM in young people. Type 1 diabetes mellitus is an autoimmune disorder. The incidence rates for this condition peak by the mid-teens (Katsarou et al., 2017), and it is usually associated with weight loss. The treatment for T1DM is ultimately insulin. In contrast, T2DM is strongly associated with being obese (American Diabetes Association, 2010; Hussain, Claussen, Ramachandran, & Williams, 2007; Meisinger, Döring, Thorand, Heier, & Löwel, 2006; Wang, Rimm, Stampfer, Willett, & Hu, 2005), with diagnosis tending to occur in children and adolescents recording a BMI >30kg/m^2, which is indicative of obesity by adult standards (Daniels et al., 2005). First-line treatment is diet and exercise and an oral hypolgycemic may be appropriate (American Diabetes Association, 2000).

Table 2.1 Differentiation of type 1 and 2 diabetes mellitus in young people (Alberti et al., 2004)

	Type 1 diabetes	**Type 2 diabetes**
Onset	Acute - symptomatic	Slow - often asymptomatic
Clinical picture	Weight loss	Obese
	Polyuria	Strong family history of T2DM
	Polydipsia	Ethnicity - high-prevalence populations

	Type 1 diabetes	Type 2 diabetes
	Polyphagia	Acanthosis nigricans
		Poly-cystic ovary syndrome
Ketosis	Almost always present	Usually absent
Insulin	C-peptide negative	C-peptide positive
Antibodies	ICA positive	ICA negative
	Anti-GAD positive	Anti-GAD negative
	ICA 512 positive	ICA 512 negative
First-line therapy	Insulin invariably	Oral hypoglycemic agents
Associated autoimmune diseases	Yes	No

Source: The International Diabetes Federation Consensus Workshop (2004). Type 2 diabetes in the young: The evolving epidemic.

2.2.2 Comorbidities and implications arising from early-onset T2DM

In addition to T2DM itself, the longer-term consequences of the condition are varied and related complications may include retinopathy, nephropathy, neuropathy or comorbidities such as hypertension, hyperlipidaemia and increased risk of cardiovascular disease (CVD) (American Diabetes Association, 2010; Dabelea et al., 2017; Pinhas-Hamiel & Zeitler, 2004).

Whilst the aetiology and medical management of diabetes in adults is well studied, less is known of the associated complications arising from youth-onset diabetes and whether the outcomes are equal to that of usual onset in adulthood, given the relatively recent emergence in younger people (Al-Saeed et al., 2016; American Diabetes Association, 2000; Dabelea et al., 2017; Daniels et al., 2005). Recent studies suggest young-onset T2DM has a higher occurrence of complications and comorbidities than those with T1DM (Amutha et al., 2017; Dabelea et al., 2017; Eppens et al., 2006), or in those diagnosed at usual onset (Al-Saeed et al., 2016). An earlier onset of the disease is also associated with complications at a younger age, including a greater risk of renal

and nerve disorders and a higher standardised rate of mortality (Al-Saeed et al., 2016). With obesity a common presenting factor (Dabelea et al., 2017; Mayer-Davis et al., 2017), this further compounds poor outcomes with a predisposition to related comorbidities including hypertension, hyperlipidaemia and non-alcoholic fatty liver disease, all of which contribute to increased CVD risk (Pinhas-Hamiel & Zeitler, 2004).

2.3 A public health issue

With the increasing prevalence of diabetes in youth and the longer-term repercussions throughout life, obesity and T2DM are serious public health issues. They require early screening, preventative and self-management measures to minimise the economic, social and personal costs of T2DM and related complications throughout life.

Total global health spending attributed to diabetes was estimated at US$673 billion for 2015 and expected to increase to US$802 billion by 2040 (Ogurtsova et al., 2017). This equates to around 12% of all global healthcare spend towards diabetes (Ogurtsova et al., 2017).

This literature review will seek to review the effect of selected RFs on the development of T2DM in children. These include obesity, puberty, ethnicity, socioeconomic status (SES), genetic and hereditary aspects, PA and dietary factors. The role of the glycated haemoglobin (HbA1c) test as a screening tool will also be discussed.

2.4 Risk factors for the development of type 2 diabetes mellitus

In addition to being overweight or obese, RFs for the development of T2DM in children include a family history of T2DM (American Diabetes Association, 2000; Morrison, Friedman, Wang, & Glueck, 2008), belonging to an ethnic minority population (Goran et al., 2003; Pinhas-Hamiel & Zeitler, 2005), the onset of puberty (American Diabetes Association, 2000; Goran et al., 2003) and a cluster of features including IR or associated conditions including hypertension and dyslipidaemia, all of which contribute to metabolic syndrome (MetS) (Franks et al., 2007; Morrison et al., 2008).

Table 2.2 is reproduced from the American Diabetes Association (ADA) (2014) and details criteria and RFs used to test for T2DM or prediabetes in asymptomatic children (aged <18 years).

Table 2.2. Criteria for testing for T2DM or prediabetes in asymptomatic children[a]

Criteria
• Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
Plus any two of the following risk factors:
• Family history of type 2 diabetes in first- or second-degree relative
• Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
• Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)
• Maternal history of diabetes or GDM during the child's gestation
Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age
Frequency of testing: every 3 years

[a] Persons aged ≤18 years.
Source: Classification and diagnosis of Diabetes. (2014) (American Diabetes Association, 2014)

Table 2.3 is reproduced from the NZ Guidelines Group (2012) and details criteria for T2DM screening in children in NZ. Current NZ guidelines for screening children and young people do not detail RFs such as a maternal history of diabetes during gestation or specify an age for initiating screening as per other guidelines such as the ADA criteria (American Diabetes Association, 2014)

Table 2.3. Type 2 diabetes mellitus screening recommendations for children and young people in NZ

Obese children and young adults. (BMI > 30kg/m2 or BMI > 27kg/m2 for Indo-Asian* peoples)	The NZSSD recommends screening if: • there is a family history of early onset type 2 diabetes mellitus; or • they are of Maori, Pacific or Indo-Asian* ethnicity
* Indo-Asian Indian, including Fijian Indian, Sri Lankan, Afghani, Bangladeshi, Nepalese, Pakistani, Tibetan.	

Source New Zealand Primary Care Handbook. (2012) (New Zealand Guidelines Group, 2012)

Being overweight is considered the most critical RF for T2DM (American Diabetes Association, 2000; Hu, van Dam, & Liu, 2001; Hussain et al., 2007) as evidenced by as many as 85% of children either overweight or obese when diagnosed (American Diabetes Association, 2000). It is however observed that RFs appear to have an additive effect for T2DM and CVD (American Diabetes Association, 2000; Berenson et al., 1998; Goran et al., 2003), meaning the more RFs present, the greater the risk of disease.

2.4.1 Obesity

Overweight and obesity refers to an atypical or excessive fat accumulation that may impair health (World Health Organisation, 2015b). The association of being overweight or obese and the risk of developing diabetes (A. E. Field et al., 2001; Goran et al., 2003; Meisinger et al., 2006; Steinberger & Daniels, 2003; Wang et al., 2005) or CVD (A. E. Field et al., 2001; Goran et al., 2003; Hubert, Feinleib, McNamara, & Castelli, 1983; McGill et al., 2002; Steinberger & Daniels, 2003) has been well documented. Of the known RFs for the development of T2DM, obesity is considered a critical RF (American Diabetes Association, 2000; Hu, Manson, et al., 2001; Hussain et al., 2007; Wang et al., 2005). Figure 2.1 reproduced from Visshcer & Seidell (2011) illustrates the contribution of obesity to other morbidities including T2DM and CVD, both of which lead to mortality or disability as well as the direct and additive effects, such as T2DM hastening CVD development.

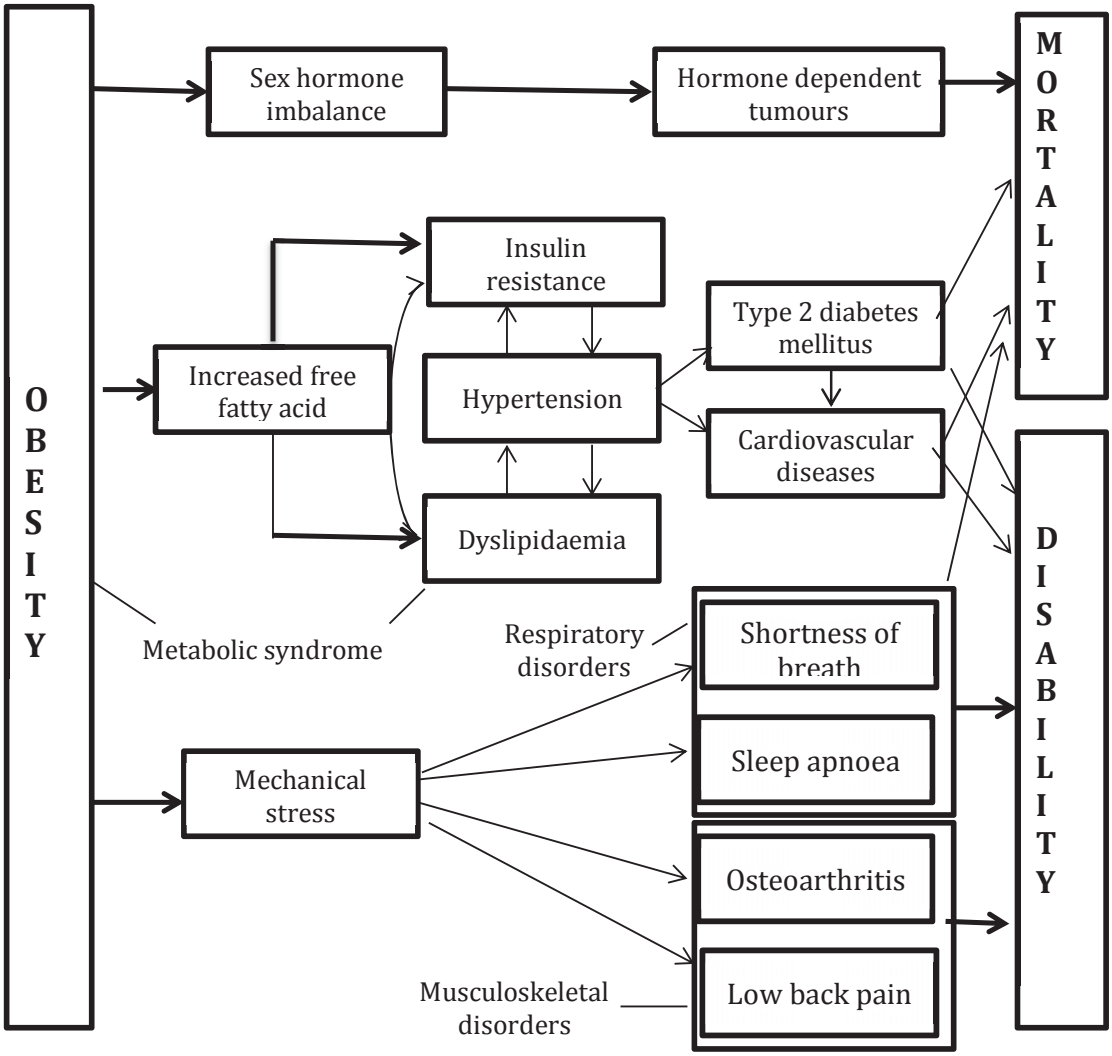

Figure 2.1. Public health impact of obesity. Sourced from (Visscher & Seidell, 2001) with permission from. Annual Review of Public Health, Volume 22. © Annual Reviews (www.annualreviews.org).

Obesity is also a contributing RF for MetS, a precursor to T2DM and CVD, which has been observed in children and adolescents (Goran et al., 2003; Moran et al., 1999; Srinivasan, Myers, & Berenson, 2002; Steinberger & Daniels, 2003). The combined prospective Lipid Research Clinic, Princeton Prevalence Study, and the 25 to 30 year Princeton Follow-up Study, identified that the presence of MetS in childhood, a family presence of T2DM, age at follow-up and changes in age-specific BMI percentile were all significant indicators of MetS in adulthood (Morrison et al., 2008). This illustrates how such morbidities can continue to track through life with obesity at a young age

observed later in adulthood (Freedman et al., 2005; Guo & Chumlea, 1999). This highlights the need to control obesity to help prevent later chronic diseases with interventions such as diabetes screening programs (Fagot-Campagna et al., 2000; Pinhas-Hamiel & Zeitler, 2005) or healthy lifestyle programs focussing on weight management, a healthy diet and physical activity (PA) (Steyn et al., 2004)

Body mass index (BMI) calculated as weight in kilograms divided by height in metres squared (kg/m^2) is an index commonly applied in adults to classify overweight and obesity (World Health Organisation, 2015b). A BMI of $25kg/m^2$ or greater indicates overweight and a BMI of $30kg/m^2$ or greater, obesity (Refer Table 2.4). The measure provides an indirect gauge of adiposity in children and is commonly used, as it is relatively easy to ascertain and correlates with body composition (Rolland-Cachera, 2011). There are various references and cut-offs in use, including the World Health Organisation (WHO) age-specific BMI cut-offs, the Centres for Disease Control and Prevention Growth Charts for children aged 2-18 years and the International Obesity Task Force (IOTF) childhood BMI cut-offs. The IOTF cut-offs were initially based on the equivalent adult BMI cut-offs, but have since been amended to enable BMI to be expressed as centile or SD scores as per other cut-offs, thus enabling comparisons between different cut-offs or studies (Cole & Lobstein, 2012). Additionally, there are different terminologies in use for levels of adiposity, which makes it difficult to assess the prevalence of obesity, with various references applied (Rolland-Cachera, 2011). Table 2.5 details BMI classifications for some of the different models in use.

Table 2.4. The international classification of adult underweight, overweight and obesity according to BMI (World Health Organisation, 2006a)

Classification	**BMI(kg/m^2)**	
	Principal cut-off points	**Additional cut-off points**
Underweight	**<18.50**	**<18.50**
Severe thinness	<16.00	<16.00
Moderate thinness	16.00 - 16.99	16.00 - 16.99
Mild thinness	17.00 - 18.49	17.00 - 18.49
Normal range	**18.50 - 24.99**	**18.50 - 22.99**
		23.00 - 24.99
Overweight	**≥25.00**	**≥25.00**
Pre-obese	25.00 - 29.99	25.00 - 27.49
		27.50 - 29.99
Obese	**≥30.00**	**≥30.00**
Obese class I	30.00 - 34.99	30.00 - 32.49
		32.50 - 34.99
Obese class II	35.00 - 39.99	35.00 - 37.49
		37.50 - 39.99
Obese class III	≥40.00	≥40.00

Source BMI Classification (World Health Organisation, 2006a)

The precision of BMI to gauge excess weight in children varies considerably according to the level of body fatness (Freedman & Sherry, 2009). Body mass index provides a good measure of adiposity in relatively fat children, but less so in relatively thin children (Freedman & Sherry, 2009). The index can be useful for comparing mean relative weights between populations, however its use is limited in individuals, as the relationship between fat-free mass, height and percentage body fat (%BF) changes throughout childhood due to periods of growth, such as with puberty (Cole, Freeman, & Preece, 1995; Wells, 2000). Body mass index does not provide a measure of anatomical distribution of fat (Khoury, Manlhiot, & McCrindle, 2013), so different children may record the same BMI, but have different body compositions with regards to fat-free mass and %BF (Wells, 2000).

Table 2.5. BMI classifications for thinness, overweight and obesity according to different definitions (Rolland-Cachera, 2011)

	Low BMI	High BMI		
Classification	< Level -1	Level +1 to +2	> Level +2	> Level +1
WHO Adults (World Health Organisation, 1995)	BMI<18.5 "Grades 1+2+3 thinness"	25≤BMI<30 "Grade 1 OW" or OW excluding obesity"	BMI≥30 "Grade 2 OW" or "Obesity"	BMI≥25 "Grades 1+2 OW" or "OW"
Cole et al (Cole, Bellizzi, Flegal, & Dietz, 2000) and IOTF (Cole, Flegal, Nicholls, & Jackson, 2007)	BMI<C-18.5[a] "Grades 1+2+3 thinness"	C-25≤BMI<C-30 [a] "OW excluding obesity"	BMI≥C-30 [a] "Obesity"	BMI≥C-25 [a] "OW" (including obesity)
WHO<5 years (World Health Organisation, 2006b)	BMI<-2SDS "Thinness" [b]	+1 SDS<BMI≤+2SDS "At risk of OW excluding OW"	BMI≥C-30 "OW" [c]	BMI≥C-25 "At risk of OW" (including OW)
WHO 5-19 years (Onis et al., 2007)	BMI<-2SDS "Thinness" [b]	+1 SDS<BMI≤+2SDS "OW excluding obesity"	BMI>+2SDS "Obesity" [d]	BMI.+1SDS "OW" (including obesity)
US CDC (Kuczmarski et al., 2000)	BMI<5th centile "Underweight"	85th≤BMI<95th centile "OW"	BMI≥95th centile "Obesity"	BMI>85th centile "OW + obesity"

BMI: Body mass index; OW: Overweight; SDS: Standard Deviation Score; [a] C-18.5; C-25 and C-30 correspond to centiles that match BMI 18.5, 25 and 30 at the age of 18 y; [b] Thinness includes "severe thinness" (< -3SDS); [c] Overweight includes "obesity" (>3SDS); [d] Obesity includes "severe obesity" (>3SDS).

Source: Childhood obesity: current definitions and recommendations for their use. Adapted from (Rolland-Cachera, 2011) with permission from the International Journal of Pediatric Obesity, Volume 6. © Taylor and Francis. (www.tandfonline.com)

Differences in BMI and %BF in children have also been observed between multi-ethnic groups (Duncan, Duncan, & Schofield, 2010; Freedman et al., 2008; Hudda et al., 2017; Liu et al., 2011; Rush, Puniani, Valencia, Davies, & Plank, 2003; Rush, Scragg, Schaaf, Juranovich, & Plank, 2008). Specifically, there is evidence that the relationship between BMI, %BF and health risks for Asian populations differs to that of Europeans, with higher risks for T2DM at BMI scores less than the cut-off point for overweight ($\geq$25 kg/m^2), due to a higher %BF at lower BMI (World Health Organisation, 2004). In contrast, Pacific people record the highest rates of obesity globally with a lower proportion of fat mass to lean mass than Europeans, yet register a higher prevalence of diabetes (World Health Organisation, 2004). Whilst the variance in Asian populations has been observed, it was not deemed possible to derive separate BMI cut-off points for all Asian populations, given variances amongst sub-groups within this grouping, however additional cut-offs were added to the continuum as reference points for public health action (World Health Organisation, 2004). The IOTF BMI cut-offs also reflect these unofficial Asian cut-offs (World Obesity Federation, 2015).

Table 2.6 summarises six studies that have explored the associations between BMI, body fatness and race/ethnicity. Three of these studies were conducted in NZ, whilst the remainder were from other countries. These studies demonstrate differences in the accuracy of measuring overweight in participants of different ethnic backgrounds, owing to different phenotypes to that of Europeans, on which the reference measures tend to be based. Recurring observations include that Maori and Pacific Island children tend to display higher levels of obesity, yet less fat mass at the equivalent BMI to European children (Duncan et al., 2010; Rush et al., 2003; Rush et al., 2008). In contrast, Asian children averaged higher %BF than European children at equivalent BMI-for-age (Freedman et al., 2008; Hudda et al., 2017). Differences within Asian ethnic groups were also observed with the relationship between %BF and BMI dependent on ethnicity (Liu et al., 2011). These studies suggest that applying the standard BMI cut-offs may miss-classify selected ethnic groups.

Table 2.6. Summary of studies investigating the accuracy of BMI and body fat measures across different races/ethnicities.

Study objective	Study reference	Study design	Body composition measure	Relevant findings
Explore ethnic-specific BMI criteria for standardising overweight and obesity in a multi-ethnic population of female children and adolescents	(Duncan et al., 2010)	Cross-sectional study of 1,676 females aged 5-16 years from Auckland, NZ. Range of ethnicities including 680 European, 355 Pacific Island, 216 Māori, 243 East Asian, and 182 South Asian.	BMI Bioelectrical impedance analysis for % BF	Pacific Island girls averaged the highest BMI cut-off points for overweight and obesity and greater than the IOTF cut-offs. The same thresholds for overweight and obesity were too low for South Asian girls. Certain ethnic groups likely miss-classified applying IOTF cut-offs due to different ethnic phenotypes to that of Europeans.
Determine whether differences in body fatness between different races/ ethnicities vary by BMI-for-age and whether the accuracy of the overweight measure using Centres for Disease Control measure varies by ethnicity	(Freedman et al., 2008)	Cross-sectional study of 1,196 participants aged 5-18 years and of different races (white, black, Asian, Hispanic) from America.	BMI Dual-energy X-ray absorptiometry for %BF	At equivalent BMI-for-age, black children had less BF than white children and Asian girls had slightly higher BF than white children. This varied by BMI-for-age with excess BF in Asians pronounced in thin children. The capacity for the overweight classification to identify girls with excess body fatness varied by race/ethnicity.

Study objective	Study reference	Study design	Body composition measure	Relevant findings
Quantify BMI adjustments needed for UK children of black and South Asian backgrounds for a better association with body fat.	(Hudda et al., 2017)	Four cross-sectional studies pooled. Participants were children aged 4-15 years in the UK. Ethnicities included White European, South Asian and Black African origin.	Deuterium dilution method to measure total body water; and indirectly fat mass. Fat mass calculated as the difference between body weight and fat free mass.	BMI underestimated BF in South Asians and overestimated BF in Black Africans. Suggestion that ethnic-specific adjustments, including increasing BMI in South Asians and reducing BMI in Black Africans would improve the accuracy of BF assessment in these groups.
Determine the relationship and variability between BF and BMI. Explore the development of adiposity independent of change in body size	(Rush et al., 2008)	Sub-sample from 2002 Children's Nutrition Survey. 643 children of Maori, Pacific and European descent.	Bio-electrical impedance for %BF	For the same BMI, Pacific and Maori girls have less fat and more fat free mass than European girls. No observable differences seen in boys across these ethnic groups. Within sample, Māori and Pacific children on average have higher BMI than European children. Percentage BF generally higher in Pacific children compared to the other children along with measures of central adiposity.

Study objective	Study reference	Study design	Body composition measure	Relevant findings
Explore differences in the relationship between BMI and %BF among Asian children from different backgrounds.	(Liu et al., 2011)	Cross sectional study. Participants from five countries including East, West and South-East Asian countries. 1,039 participants aged 8-10 years.	Total body water using Deuterium dilution method. Fat mass calculated as the difference between body weight and fat free mass	Relationship between %BF (as measured from total body water) and BMI was dependent on ethnicity. At equivalent BMI levels, Filipino boys recorded lower %BF than Malay and Thai boys. Thai girls had significantly higher %BF than Chinese, Malay and Filipino children.
Compare %BF for stated BMI in New Zealand European, Maori and Pacific Island children.	(Rush et al., 2003)	Cross sectional study. Maori, Pacific Island and European children aged 5-14 years.	Total body water using Deuterium dilution method. Fat mass calculated. Bioelectrical impedance analysis. BMI	At the same BMI, Maori and Pacific girls averaged lower %BF than their European counterparts. This relationship was not observed with boys as %BF not significantly influenced by BMI. Suggestions that BMI obesity thresholds be raised for Maori and Pacific girls in the studied age range.

In addition to fat mass, the location of fat deposition is important with visceral fat identified as an independent predictor for T2DM (Boyko, Fujimoto, Leonetti, & Newell-Morris, 2000; Goran et al., 2003; Hu & Malik, 2010; Kissebah, 1996; Meisinger et al., 2006; Ohlson et al., 1985). Visceral fat deposition has been linked with reduced peripheral insulin sensitivity and thought to add to hepatic IR (Gastaldelli et al., 2002) or hyperinsulinemia (Freedman et al., 1987).

A WHO Expert Consultation report found that increases in waist circumference (WC) or waist-to-hip ratio (WHR) were linked with increased metabolic disease with the association observed across diverse ethnic groups (World Health Organisation, 2008). Practically it was observed that WC may be favoured over BMI and WHR measures due to ease and accuracy of obtaining a WC measure, however it was desirable to still collect BMI to enable joint use of the measures (World Health Organisation, 2008). There was insufficient evidence on waist-to-height ratio (WtHR) to make a recommendation on its use (World Health Organisation, 2008).

Central adiposity measures including WC and WtHR have been identified as better predictors of CVD disease risk, than BMI in children (Khoury et al., 2013; Savva et al., 2000). In studies comparing BMI, WC and WHR, visceral fat as measured by WC, presents as a more effective predictor for T2DM than total BF in obese children and adolescents (Goran et al., 2003). Similarly in adults, WC is a more robust predictor of T2DM risk than WHR (Wang et al., 2005; Wei, Gaskill, Haffner, & Stern, 1997). This is because WC specifically gauges abdominal obesity and has stronger associations with T2DM risk than WHR or BMI (Wei et al., 1997). A relative risk analysis of the relation of body fat distribution in adults, identified that when fat was centred in the upper body segment, the risk increased three-fold compared to obesity alone (Kissebah et al., 1982).

Waist to height ratio has been identified as being a more robust indicator of metabolic risk than BMI, WC, WHR or skinfold measures in different ethnic populations, genders and age groups (Hsieh & Yoshinaga, 1995a, 1995b; Savva et al., 2000). Aside from being more sensitive than BMI for early indication of health risks, WHtR is considered cheaper and easier to conduct with only a tape measure needed, rather than requiring scales and equal boundary values (WHtR=0.5) are applied for different genders and ethnic

groups (Ashwell & Hsieh, 2005). There is evidence that WHtR can be used to assess metabolic risk in children (Kahn, Imperatore, & Cheng, 2005; Savva et al., 2000), and thus the same boundary measure may be applied across children and adults (Ashwell & Hsieh, 2005).

Abdominal fat was associated with adverse levels of triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and insulin in the Bolagusa Heart study with 5-17 year old participants (Freedman, Serdula, Srinivasan, & Berenson, 1999). With WC serving as both a measure of obesity and fat distribution, and correlating with lipid levels, it could also be utilised to identify those at risk of high concentrations of lipids and other obesity-related RFs (Freedman et al., 1999).

In another study, WC was identified as the strongest and most significant modifiable predictor of diabetes in 5-9 year old participants, and with almost the same cumulative predictive strength as the other metabolic, anthropometric and vascular factors (Franks et al., 2007). Amongst 10-14 year old participants, the strongest independent modifiable predictors were 2-hour plasma glucose (2hPG) following an oral glucose tolerance test (OGTT), BMI and HbA1c and in 15-19 year olds, 2hPG, WC and HbA1c (Franks et al., 2007). When all participants were combined (age range 5-19 years), the independent modifiable predictors were BMI, FPG, 2hPG, and HDL cholesterol (Franks et al., 2007). This suggests that whilst obesity is a suitable measure for assessing risk of T2DM in younger children, obesity and hyperglycaemia provide a stronger predictor of risk in adolescents (Franks et al., 2007). The modifiable predictor is affected or dependent on age, likely owing to the effects of puberty.

In the long running epidemiological Nurse's Health Study (NHS) with adult females and the Health Professionals Follow Up Study with adult men, the risk of developing diabetes, heart disease, hypertension and stroke increased with the degree of overweight (A. E. Field et al., 2001). Amongst both cohorts, those registering a BMI of 35kg/m^2 or greater were approximately 20 times more likely to develop diabetes (relative risk [RR], 17.0; 95% confidence interval [CI], 14.2-20.5 for women; RR, 23.4; 95% CI, 19.4-33.2 for men), than their peer equivalents with BMI in the normal range (18.5-24.9kg/m^2) (A. E. Field et al., 2001). Those who were overweight but not obese, were more than three-times

as likely to develop diabetes than their peers with BMIs in the normal range, during 10 years of follow up (A. E. Field et al., 2001).

Importantly lifestyle modifications such as weight loss in overweight or obese participants have been shown to lead to a decrease in insulin concentration and improvements in insulin sensitivity (X.-R. Pan et al., 1997; Rocchini, Katch, Schork, & Kelch, 1987), thus reducing the risk of developing T2DM and CVD (Steinberger & Daniels, 2003).

2.4.2 Puberty

The onset of puberty is a RF for T2DM in children and adolescents (American Diabetes Association, 2000; Arslanian, 2002; Goran et al., 2003). The mean age of T2DM diagnosis in children and adolescents tends to align with puberty at around 12- 14 years (Fagot-Campagna et al., 2000; Pinhas-Hamiel et al., 1996; Reinehr, 2005; Rosenbloom, Silverstein, Amemiya, Zeitler, & Klingensmith, 2009). The association with puberty is attributed to a transient resistance to the action of insulin, which triggers an increased production of the hormone resulting in hyperinsulinemia (Arslanian, 2002; Moran et al., 1999; Steinberger & Daniels, 2003).

During puberty both genders develop increased total fat mass, however the percentage of total BF increases in girls and decreases in boys (Hergenroeder & Klish, 1990), as lean tissue increases substantially more in males, so their fat mass contributes proportionally less to their total body weight (Travers, Jeffers, Bloch, Hill, & Eckel, 1995). Whilst the peak of IR occurs at Tanner stage 3 across both genders, girls record higher levels of IR than boys at all Tanner stages of maturity (Burke et al., 1986; Moran et al., 1999). It is thought that this may be the initiator for a range of disorders in later life (Haffner et al., 1992), including obesity, T2DM, hypertension, dyslipidaemia and CVD RFs (Moran et al., 1999). This may explain differences in risk between genders (Burke et al., 1986), with a higher prevalence of T2DM amongst females to males, with ratios of 1.6:1 to 3:1 reported (Dabelea, Pettitt, Jones, & Arslanian, 1999).

There are differing hypotheses on the contributing cause for transient IR in puberty, with suggestion the mediator of insulin sensitivity is increased BF and BMI (Travers et al., 1995), or that insulin sensitivity is independent of BF levels given body fatness increases pre, during and post puberty, whilst insulin

sensitivity decreases during puberty and resolves post puberty (Moran et al., 1999). The rationale for the latter hypothesis is that an increase in growth hormone secretion is a causal factor of IR in puberty (American Diabetes Association, 2000; Reinehr, 2005), with growth hormone secretion and IR declining almost to Tanner 1 levels (Moran et al., 1999), at the conclusion of puberty (American Diabetes Association, 2000; Daniels et al., 2005; Reinehr, 2005).

In the Bogalusa Heart study, fasting glucose levels peaked around 12-14 years, before levelling off in boys and declining in older girls, which was likely attributed to the earlier progression of puberty in girls (Burke et al., 1986). Insulin levels were significantly higher in girls increasing up until 13 years of age, peaking just before the pubertal growth spurt (Burke et al., 1986). Whilst pubertal IR coincides with changes in body composition and hormone levels with increases in lean body mass and fat mass (Moran et al., 1999), IR may also occur during puberty without changes in BMI (Cook, Hoffman, Stene, & Hansen, 1993). This indicates that there are factors other than changes in body composition that contribute to the onset of IR in puberty (Moran et al., 1999).

2.4.3 Ethnic or minority population bias

Whilst T1DM has been observed to occur in proportion to socioeconomic distribution (Rosenbloom et al., 2009), T2DM disproportionately affects those of lower socioeconomic status (SES) (Rosenbloom et al., 2009; Wang & Beydoun, 2007), or of certain minority race or ethnic groups (Dabelea et al., 2014; Fagot-Campagna et al., 2000; Pinhas-Hamiel & Zeitler, 2005). This bias is evident in NZ with a higher prevalence of diabetes amongst Maori and Pacific populations (Pinhas-Hamiel & Zeitler, 2005), with adjusted rate ratios of 1.97 and 3.11 times that of non-Maori or non-Pacific populations respectively (Ministry of Health, 2016b). Studies show a corresponding prevalence of T2DM across such populations, with high obesity and T2DM prevalence across NZ Maori (McGrath, Parker, & Dawson, 1999), Pacific Island populations (Coppell et al., 2013), Pima Indians of Arizona (Knowler, Pettitt, Savage, & Bennett, 1981; Pinhas-Hamiel & Zeitler, 2005), First Nation people in Canada, black or Hispanic populations in America and Aborigines in Australia (Pinhas-Hamiel & Zeitler, 2005). This differing prevalence amongst different minority ethnicities is

likely attributable to a heredity component (Florez, 2008), in addition to social or environmental factors (Dabelea et al., 2014; Fagot-Campagna et al., 2000; Pinhas-Hamiel & Zeitler, 2005).

In a study, African American children had lower insulin sensitivity and higher acute insulin responses than white non-diabetic children after adjustments for total BF mass and hours per week of activity and vigorous activity (Ku, Gower, Hunter, & Goran, 2000). This suggests racial differences in insulin action occur as a result of factors other than anthropometry, cardiovascular function and PA (Ku et al., 2000). In the Princeton Follow-up Study, MetS in childhood, age at follow up, being of black race and parental diabetes were identified as predictors for T2DM (Morrison et al., 2008), indicating the influence of ethnicity or being of a minority population which could be attributable to genetic and/or environmental factors.

2.4.4 Socioeconomic status

Socioeconomic status is a consistent predictor of disease and mortality risk (N. E Adler et al., 1994; N. E. Adler, Boyce, Chesney, Folkman, & Syme, 1993). A social gradient exists whereby mortality shows an inverse relationship with SES (N. E Adler et al., 1994; Marmot, Ryff, Bumpass, Shipley, & Marks, 1997) and those with the lowest SES, experience the worst health. This holds true throughout the life course (Lu & Halfon, 2003) for obesity (Everson, Maty, Lynch, & Kaplan, 2002; Wang & Beydoun, 2007), or related comorbidities including T2DM (Connolly, Unwin, Sherriff, Bilous, & Kelly, 2000; Everson et al., 2002). A common mechanism attributed to the increased health risk is unhealthy behaviours, whereby disadvantage may constrain access to affordable nutritious foods, the ability to exercise or stress from economic uncertainty may lead to undesirable actions such as smoking or alcohol consumption (Lynch, Kaplan, & Salonen, 1997; Wang & Beydoun, 2007).

A systematic review and meta-analysis examining T2DM and SES reported that compared with high educational attainment, occupation and income, those with poorer attainment or status in these areas had an association with an increased risk of T2DM (Agardh, Allebeck, Hallqvist, Moradi, & Sidorchuk, 2011). Whilst it is generally observed that a deprived SES, increases the risk of children developing obesity or related disorders including T2DM, the evidence remains

contradictory (Parsons, Power, Logan, & Summerbell, 1999; Sobal & Stunkard, 1989; Spencer, Thanh, & Louise, 2013). A systematic review found no proof of association between SES and childhood adiposity, however there was a relationship between poor SES in early life and increased adiposity in adulthood (Parsons et al., 1999). Studies examining the association were large however few studies investigated confounding by other factors such as parental fatness (Parsons et al., 1999). It is likely that there could be other independent factors that may contribute, as suggested by the Barker hypothesis, whereby a smaller size at birth is related to increased risk of CHD, diabetes, hypertension and stroke in adulthood, due to physiological adaptations (de Boo & Harding, 2006).

A retrospective, cross-sectional study of 74,500 children aged three years identified that children in the most deprived groups, were three times more likely to be obese, than those in the least deprived groups (Armstrong, Dorosty, Reilly, & Emmett, 2003). Whilst this was a study concerning obesity and not T2DM, obesity is a RF for T2DM and other chronic diseases.

2.4.5 Genetics, heredity and environmental factors

Type 2 diabetes mellitus is often linked with a strong genetic predisposition, more so than T1DM, however the genetics of T2DM are multi-faceted and not clearly understood (American Diabetes Association, 2010). Evidence suggests that populations seemingly predisposed to T2DM such as the Pima Indians and urbanised Pacific Island populations have a genetic susceptibility (Knowler et al., 1981; Zimmet, 1982). The disease may also be influenced by environmental factors such as PA and energy balance (Dabelea et al., 2000; Goran et al., 2003), with a continuum of interaction between genetic and environmental factors (Zimmet, 1982). This means that two members of the same family may develop T2DM independent of genetic causes, due to common environmental influences, alongside the high prevalence of the disease (Steyn et al., 2004).

A strong familial component has been observed globally across geographies, ethnicities and cultures, with associations between the prevalence of T2DM in adults and the eventual advent of the disorder in adolescents (Dabelea et al., 2000; Gregg, Sattar, & Ali, 2016; Pettitt et al., 1988; Pinhas-Hamiel & Zeitler, 2005). Of those affected, 45-80% have at least one parent with diabetes and

the presence of the disease is likely to occur over several generations (American Diabetes Association, 2000). The prevalence amongst offspring is greatest when both parents experience diabetes onset at an early age, with the risk decreasing if only one or neither parent is affected, or the onset occurred at a later age (Dabelea et al., 1999).

2.4.5.1 Risk from intrauterine exposure

Intrauterine exposure to diabetes carries a higher risk for the development of obesity and diabetes in offspring than that attributable to genetic factors (Dabelea et al., 2000). It is also associated with a greater risk of offspring being obese at a younger age and developing T2DM, than older siblings born before the mother was recognised as having developed diabetes (Dabelea et al., 2000; Pettitt et al., 1988; Pettitt, Baird, Aleck, Bennett, & Knowler, 1983). Whilst both offspring will possess the same risk of inheriting the genes rendering them susceptible to T2DM, the difference in risk is attributable to the intrauterine exposure to diabetes (Dabelea et al., 2000). Offspring with a mother who developed T2DM during pregnancy in a Pima Indian population recorded a higher prevalence of T2DM (45%) at age 20-24 years, compared to offspring of non-diabetic women (1.4%), or offspring of pre-diabetic women (8.6%) (Pettitt et al., 1988). This association was independent of other RFs including maternal obesity, the offspring's birth weight, age of diabetes onset in parents and later obesity (Pettitt et al., 1988).

2.4.6 Physical activity

Being sedentary is a modifiable RF for T2DM with PA conferring a reduced risk of chronic diseases including T2DM and CVD, when compared to sedentary individuals (Bassuk & Manson, 2005; Hu, Li, Colditz, Willett, & Manson, 2003; Kriska et al., 2003; Tremblay et al., 2011). The mechanisms by which PA may assist in preventing or deferring the occurrence and progression of T2DM include weight loss and improved insulin sensitivity, glycaemic control, BP or lipid profiles (Bassuk & Manson, 2005; Colberg et al., 2010).

Significant associations have been observed between PA and both insulin sensitivity and acute insulin response, with more active children recording lower insulin secretion and stronger insulin sensitivity, irrespective of body

composition and ethnicity (Ku et al., 2000). Whilst a cross-sectional observation with a small sample, this indicates that PA has an advantageous effect on insulin secretion and function and therefore a possible reduction in risk of metabolic-related disease (Ku et al., 2000). The beneficial effect of PA has been observed in studies with adolescents and adults (Hu et al., 2003; X.-R. Pan et al., 1997; Tremblay et al., 2011). The Da Qing IGT and Diabetes Study randomised men or women with impaired glucose tolerance to one of three groups including dietary changes only, exercise only or a combination of the two (X.-R. Pan et al., 1997). After adjustments, a proportional hazards analysis found that the exercise only intervention resulted in a 46% reduction in risk of developing diabetes ($p<0.0005$), followed by diet and exercise 42% ($p<0.005$) and diet only 31%, ($p<0.03$) (X.-R. Pan et al., 1997). The NHS indicated watching television was positively associated with risk of obesity and T2DM, whilst brisk walking for one hour a day was associated with a 24% reduction in obesity and a 12% reduction in diabetes (Hu et al., 2003).

A systematic review of studies involving youth (5-17 years), identified that sedentary behaviour (primarily increased television watching), for more than two hours per day, was associated with negative indicators including BMI (Tremblay et al., 2011). Sedentary behaviour was associated with increased risks for metabolic syndrome and CVD across 11 studies, however it was cautioned that the studies should be viewed objectively, as only a small proportion of youth have measurable RFs for these diseases (Tremblay et al., 2011).

In a randomized-controlled school-based trial, children who received an intervention to reduce television viewing recorded statistically significant relative decreases in anthropometric measures, including BMI, WC and WHR (Robinson, 1999). There were no statistically significant variances between the groups for changes in energy dense food intake or moderate to vigorous PA (Robinson, 1999), thus suggesting the negative effects of sedentary behaviour.

2.4.7 Dietary factors

The dietary choices people make will impact on their health, growth and development and lifestyle behaviours, such as PA levels will modify this result, with either a beneficial or detrimental effect (World Health Organisation & Food and Agriculture Organisation, 2003). Environmental factors have influenced

dietary intake and behaviours with increasing industrialisation, urbanisation and technological advances, which has seen diets become more high-fat and energy-dense, whilst lifestyles have become more sedentary (World Health Organisation & Food and Agriculture Organisation, 2003) resulting in an energy imbalance. The effect of rapid cultural, dietary and environmental changes with acculturation from traditional diets to a westernised diet has been observed with the Pima Indians in Arizona (P. H. Bennett, 1999), Japanese (Kitagawa, Owada, Urakami, & Yamauchi, 1998) and Pacific Island populations living in westernised environments (Zimmet, 1979). Whilst some of these populations are believed to be genetically predisposed towards diabetes, lifestyle factors including dietary changes and reduced PA are modifiable factors that may contribute to unlocking an increased susceptibility to T2DM (Kitagawa et al., 1998; Pinhas-Hamiel & Zeitler, 2005; Steyn et al., 2004; Zimmet, 1982).

Diet has been attributed to the development of diabetes in two ways; the first through a high calorie intake and low PA leading to obesity; and the second relates to the quality or composition of the diet (Zimmet, 1982). Dietary studies have examined fats and carbohydrates (Hu, van Dam, et al., 2001), glycaemic load and fibre (Schulze, Liu, et al., 2004) and dietary sugars (Ebbeling et al., 2006; James, Thomas, Cavan, & Kerr, 2004; Schulze, Manson, et al., 2004; Te Morenga, Mallard, & Mann, 2013) in relation to weight gain and the incidence of obesity and T2DM. The findings of many studies are inconclusive with regards to the effects of specific nutrients, however the majority of studies advocate achieving and maintaining an ideal body weight through balancing energy intake and PA levels to minimise risk (Alberti, Zimmet, & Shaw, 2007; Hu, van Dam, et al., 2001). In the NHS cohort, lifestyle factors including, a diet high in fibre and polyunsaturated fats and low in saturated fats and glycaemic load, regular PA, not smoking and a moderate alcohol intake were associated with an approximately 90% lower incidence of T2DM (Hu, Manson, et al., 2001). The Da Qing IGT and Diabetes study showed that dietary changes can be an effective means to reducing diabetes risk with dietary and /or PA interventions associated with reductions of 31-46% in the risk of developing diabetes (X.-R. Pan et al., 1997).

2.4.7.1 Dietary sugars from sugar sweetened beverages

The role of dietary sugars and specifically sugar-sweetened beverages (SSBs) is topical given mounting evidence that a high intake of free sugars contributes to weight gain (World Health Organisation, 2015c). A regular intake of SSBs has been linked with weight gain and a resulting risk of overweight and obesity, MetS and T2DM (Hu & Malik, 2010; Malik, Popkin, Bray, Després, Willett, et al., 2010). These beverages are believed to contribute to weight gain owing to their high energy content, the large volumes consumed and incomplete total energy compensation at later meals (Hu & Malik, 2010; Ludwig, Peterson, & Gortmaker, 2001; Malik, Schulze, & Hu, 2006; Mattes, 1996).

The glycaemic index (GI) is a system for classifying carbohydrate-containing foods according to their glycaemic response following ingestion (Ludwig, 2002). A low GI diet results in lower post-prandial glucose and insulin levels, whilst a high GI diet encourages lipogenesis and contributes to increased fat cell size (Morris & Zemel, 1999). As a result, a regular intake of high GI foods including SSBs has been associated with adverse lipid levels and inflammation (Ludwig, 2002; Malik, Popkin, Bray, Després, & Hu, 2010), thus increasing the risk for obesity, T2DM and CHD (Ludwig, 2002). In the NHS cohort, a regular intake of SSBs was associated with a greater risk of CHD in women, even after adjusting for dietary and lifestyle factors (Fung et al., 2009). Adjustments for BMI and energy intake tempered the result, suggesting that excess calorie intake and overweight or obesity, formed part of the association (Fung et al., 2009). This resonates with a meta-analysis which observed associations between SSB intake and risk of MetS and T2DM (Malik, Popkin, Bray, Després, Willett, et al., 2010). The risk may be attributed to excess calories contributing to weight gain as well as high intakes of rapidly absorbed sugars, which result in a high dietary glycaemic load (Malik, Popkin, Bray, Després, Willett, et al., 2010). It may also contribute to glucose intolerance and IR, particularly amongst those already susceptible, such as the overweight or obese (Schulze, Liu, et al., 2004).

The consumption of SSB has also been associated with obesity in children (James & Kerr, 2005; Ludwig et al., 2001). For each additional serving of SSB, BMI and frequency of obesity increased after adjusting for anthropometric, demographic and lifestyle variables including diet (Ludwig et al., 2001). A

baseline intake of SSB was also independently associated with alterations in BMI for each daily serve (Ludwig et al., 2001).

2.5 Glycated haemoglobin as a screening indicator

2.5.1 Importance of early detection and diagnosis

Unlike T1DM, T2DM may go undetected in the early stages due to its asymptomatic nature (C. M. Bennett, Guo, & Dharmage, 2007). Around one-in-four people with diabetes in the United States has diabetes, but is not aware as they have not been formally diagnosed (Centers for Disease Control and Prevention, 2014). A similar figure has been estimated for New Zealander's (Diabetes New Zealand, 2015). As a result, there can be a four-to-seven year lag between onset and diagnosis, by which time clinically significant complications may have developed (Harris, Klein, Welborn, & Knuiman, 1992). In T2DM patients aged around 21 years and with a mean 7.9 years diabetes duration, almost three in four (72%) had at least one diabetes-related complication or comorbidity (Dabelea et al., 2017). This signals the importance of early T2DM diagnosis to help reduce long-term complications (C. M. Bennett et al., 2007; World Health Organisation, 1998).

2.5.2 Use of glycated haemoglobin in diagnosis or screening for T2DM

Glycated haemoglobin (HbA1c) provides an average measure of blood glucose levels over a three month period (American Diabetes Association, 2010) and is recognised and recommended as a test for diagnosing T2DM (American Diabetes Association, 2010; C. M. Bennett et al., 2007; Drury, 2012; New Zealand Society for the Study of Diabetes, 2011; Saudek et al., 2008; The International Expert Committee, 2009).

In NZ an HbA1c value of 41-49mmol/mol (5.9-6.6%) is indicative of prediabetes, whilst a value of <40mmol/mol (5.8%) suggests low risk (Table 2.7) (New Zealand Society for the Study of Diabetes, 2011). There are however different cut-offs used internationally, such as the ADA guidelines which have a prediabetes value of 39-46mmol/mol (5.7-6.4%) (American Diabetes Association, 2014).

Table 2.7. Reporting and interpreting glycated haemoglobin (HbA1c) results

HbA1c value mmol/mol and (%)	Comment
40 or less (<5.8%)	Virtually excludes diabetes. No need to repeat until next scheduled CVD risk assessment
41 – 49 (5.9-6.6%)	Abnormal glucose tolerance Recommend diet/lifestyle changes and assess/manage all CV risk factors Repeat annually unless symptomatic in interim
50 or greater (>6.7%)	Supports diagnosis of diabetes (in asymptomatic people must be confirmed on a second sample after an interval) Recommend diet/lifestyle changes and assess/manage CV risk factors Start regular retinal, microalbuminuria, renal function and foot screening

Source (New Zealand Society for the Study of Diabetes, 2016)

Diagnosis of T2DM for an asymptomatic individual using HbA1c requires an abnormal HbA1c result be further validated with a further HbA1c test or plasma glucose test result within an abnormal range for confirmation (World Health Organisation, 2011).

Advantages of using HbA1c include greater correlations between HbA1c levels and retinopathy, than FPG and retinopathy (Tapp et al., 2008), no requirement for fasting (C. M. Bennett et al., 2007), a longer-term read of glycaemia than plasma glucose (Saudek et al., 2008), and less analytical variability than FPG and the OGTT methods (New Zealand Society for the Study of Diabetes, 2011). There are some limitations of the HbA1c test due to non-glycaemic factors or certain conditions impacting red cell turnover (The International Expert Committee, 2009), however these can be minimised by confirming with a plasma glucose specific test if warranted (Saudek et al., 2008; The International Expert Committee, 2009).

The development of portable point of care (PoC) testing devices such as the Roche Cobas b 101, have been validated and deliver comparable outcomes to venous results on reference laboratory platforms (Allan & Taylor, 2014). Being

portable, these devices can be used in community settings and the finger prick test method is a less invasive option, particularly for children.

In order to assess HbA1c results, measures of sensitivity and specificity are calculated. Sensitivity refers to individuals at or higher than a specified cut-off point who have diabetes, whilst specificity refers to those with an HbA1c level under the cut-off, who do not have diabetes (C. M. Bennett et al., 2007). In a systematic review of screening tools to detect T2DM, HbA1c registered marginally lower sensitivity but higher specificity than the FPG test in detecting diabetes, however neither test was reliable in determining impaired glucose tolerance (IGT) (C. M. Bennett et al., 2007). As the HbA1c test diagnosed fewer at risk individuals than the impaired FPG test, but similar predictive properties for progression to diabetes, it is suggested that the two tests could be used in a paired manner for enhanced diagnostic sensitivity (Heianza et al., 2011; Ko et al., 1998; Tanaka et al., 2001).

HbA1c testing has been shown to provide a useful marker in the diagnosis of T2DM in studies with adults (Jesudason, Dunstan, Leong, & Wittert, 2003; Ko et al., 1998; Tanaka et al., 2001), as well as being a cost-effective screening tool that can be administered in advance of an OGTT (Ko et al., 1998; Tavintharan, Chew, & Heng, 2000). Fewer studies have been conducted with children or adolescent participants. However in a 1965-2007 longitudinal study with 2,095 children and adolescents, HbA1c level was found to be a good predictor of future diabetes across various ages and genders, with similar or better predictive values than FPG and 2hPG testing, with the exception of adult women (Vijayakumar, Nelson, Hanson, Knowler, & Sinha, 2016). The participants were stratified by glycaemic status and for both adults and children, those with a higher HbA1c level at baseline had a higher incidence of diabetes, compared to those in the lowest HbA1c category (Vijayakumar et al., 2016). This study also stratified by ADA recommended RFs and when participants were overweight plus met two additional RFs (with one being from a high risk ethnic group), the sensitivity was ~13% and specificity ~99% in predicting the 10 year incidence of diabetes, when applying ADA criteria of >39mmol/mol (>5.7%) for prediabetes (Vijayakumar et al., 2016).

Earlier studies assessed the HbA1c test alongside other methods in obese youth, finding HbA1c to be useful for screening purposes (Shah, Kublaoui,

Oden, & White, 2009). The joint use of HbA1c and FPG tests in screening for prediabetes and to identify those who may require a follow up OGTT was also advocated (Brar, Mengwall, Franklin, & Fierman, 2014).

2.6 Limitations and areas requiring further investigation

A recurring limitation for many of the identified RFs for T2DM is the absence of information for paediatric populations compared to adults, given the relatively recent emergence of the disease in the younger group. There are some challenges in working with paediatric populations, such as being able to assess anthropometry accurately with variable growth patterns in childhood and adolescence, and discrepancies over the most appropriate assessment measure. Whilst BMI is widely used, it is reported to be limited in its application across different ethnic groups and the inability to differentiate between fat and fat free mass. Waist circumference is regarded as an effective measure, as it can assess obesity as well as central adiposity, which is an independent RF for T2DM.

With regards to the effect of puberty as a RF, the contributing mechanism for transient IR in puberty is not well understood and neither is the impact of the resulting hyperinsulinemia in later life, particularly for females who appear to have an increased T2DM risk.

With a limited understanding of the influence of individual dietary factors on IR and T2DM, much of the evidence-based advice is focussed on promoting healthy lifestyles and behaviours through balanced energy intake, weight management and PA, particularly in the overweight and obese. Further studies are required to understand factors that can be modified in order to implement screening programs using an HbA1c test alongside other known RFs to screen and manage the incidence of obesity and T2DM.

2.7 Conclusions

The prevalence of T2DM continues to increase. The disease is a result of many interactions including genetic and environmental, however the rapid increases across different geographic regions, cultures and ethnicities, suggests the increase is likely attributable more so to environmental behaviours.

Whilst once considered a disease of the middle-aged, T2DM is now becoming increasingly present in paediatric and adolescent populations. Accordingly, there is a wealth of knowledge concerning RFs and guidelines for the management of obesity or T2DM in adults, but less is known of the pathophysiology, treatment and longer-term consequences, when onset occurs at a younger age. If the primary cause in younger people is attributed to modifiable behaviours, screening and prevention programs should be put in place early to reduce the occurrence and accompanying complications of the disease, in an effort to manage the personal and public health burden.

Chapter Three

3.0 Research study manuscript prepared for Pediatrics Journal

3.1 Abstract

Background: A glycated haemoglobin (HbA1c) test is recommended in diagnosing type 2 diabetes mellitus (T2DM) and to identify prediabetics. This test is advocated over other methods due to ease of application and processing. Few studies have examined associations between HbA1c levels and T2DM risk factors (RFs) in children.

Aim and hypotheses: To investigate the relationship between HbA1c levels and selected RFs associated with T2DM risk in a group of Auckland children. It is hypothesized that ethnicity and waist circumference (WC) will be reliable indicators of later T2DM risk. Body fat percentage (%BF) will likely be positively correlated with HbA1c level.

Study design: A cross-sectional study involving children aged 8-11 years from six Auckland primary schools. Physical measures included weight, height, WC and %BF. A finger-prick blood test was collected for HbA1c levels. Ethnicity, gender, age, usual beverage intake and physical activity (PA) behaviours were assessed by self-completed questionnaires. Stepwise multiple linear regression analysis was used to explore which independent variables best predicted variance in HbA1c level.

Results: When children (n=451, 10.4$\pm$0.6 years) were classified by glycaemic status, 71 children (15.7%) had HbA1c levels indicative of prediabetes. This was greatest in Pacific (n=29) and South Asian (n=13) children. Maori and Pacific children had higher BMI than European children ($p<0.0001$). For HbA1c, Pacific and South Asian children had higher levels than European ($p<0.0001$), as did Maori children ($p<0.05$). Asian children exhibited high %BF for a low BMI. In regression analysis to explain the variance in HbA1c, WC was the most significant predictor for South Asian, Pacific and Asian children.

Conclusion: Ethnicity and adiposity (both central and overall) are key RF for T2DM risk. Waist circumference, waist-to-height ratio (WtHR) and BMI may all be used as measures in screening for T2DM risk. Glycated haemoglobin was a useful screening tool alongside RFs and not dependent on obesity.

3.2 Introduction

Type 2 diabetes mellitus, a metabolic disorder with long-lasting comorbidities was previously considered a disease of adulthood (Alberti et al., 2004; Daniels et al., 2005). However with almost one-in-six children overweight or obese (Organisation for Economic Co-operation and Development, 2017), T2DM is increasingly occurring in children and adolescents (Al-Saeed et al., 2016; Alberti et al., 2004; Daniels et al., 2005; Pinhas-Hamiel & Zeitler, 2005). Until recently, less was known of the associated risks and disease outcomes from early-onset diabetes (Wong, Constantino, & Yue, 2014). In teenagers and young adults with early-onset diabetes, the prevalence of complications and comorbidities has been observed to be higher in those with T2DM compared with T1DM (type 1 diabetes mellitus) (Amutha et al., 2017; Dabelea et al., 2017; Wong et al., 2014). Those with early-onset T2DM also appear to have greater risk of macrovascular complications compared with age-matched controls (Hillier & Pedula, 2003), likely resulting in morbidity or premature mortality at a much younger stage of life. As a result, adults with early-onset diabetes will further contribute to a significant personal health and economic burden, due to early-onset, longer duration of the disease and the likely occurrence of related complications at a younger age (Ebbeling, Pawlak, & Ludwig, 2002; Hannon, Rao, & Arslanian, 2005; Imperatore et al., 2012).

The aetiology of T2DM in adults is multi-factorial and entails both genetic and environmental causes (Chen et al., 2012; Dabelea et al., 2011; Reinehr, 2013), however the increased prevalence is deemed to have occurred too rapidly to be attributed solely to genetic influences (American Diabetes Association, 2000). Being overweight or obese is considered a critical environmental risk factor (RF) for the development of T2DM (Hu, Manson, et al., 2001; Zheng, Manson, Yuan, & et al., 2017).

A glycated haemoglobin test is a recommended diagnostic test used in the diagnosis of T2DM (World Health Organisation, 2011), and may also be used as an opportunistic screening tool for prediabetes in those who present with RFs (New Zealand Society for the Study of Diabetes, 2011). The wider availability of PoC meters to measure HbA1c levels provides the opportunity to

reach a greater proportion of at risk individuals, through screening in community settings (Allan & Taylor, 2014).

The recognised RFs used to assess T2DM in children or adolescents include being obese, a family history of early onset T2DM or being of a high risk ethnic group (American Diabetes Association, 2014; New Zealand Guidelines Group, 2012). Other RFs associated with T2DM include diet, physical activity (PA) or gestational diabetes mellitus (International Diabetes Federation, 2015). The mostly commonly applied measure of obesity is body mass index (BMI), but alternative measures such as waist circumference (WC) or waist-to-height (WtHR) which provide an indication of central obesity, have also been identified as being an independent RF for T2DM (Bassali, Waller, Gower, Allison, & Davis, 2010; Savva et al., 2000).

The aim of this study is to investigate the relationship between HbA1c levels as a measure of glycaemia, and a number of recognised RF that are associated with the later development of T2DM in a group of Auckland school children. Being able to identify at risk children early, could provide the opportunity to implement lifestyle modifications, which might delay the progression to T2DM.

3.2 Methods

3.2.1 Participants

The study was a cross-sectional study conducted between August and September in 2016 and 2017 using a subset of participants from a wider study. Schools spanning a range of decile levels (a measure of socioeconomic status) and ethnicities were approached to participate to ensure a diverse sample with oversampling of certain ethnic minority groups (Maori, Pacific Island and South Asian), known to be at higher risk of T2DM. This was to allow ethnic-specific analysis. Inclusion criteria was all students in Years five and six. There were no exclusion criteria applied. Schools that agreed to participate were provided with written study protocol information for the school, parents and children. This detailed the intent of the study, anthropometric test procedures and included a link for a short video, to explain the data collection procedures to the children. Informed written consent was obtained from the parent and child, alongside an option to decline the finger prick blood test, but still participate in the broader

Bone Study of which this study was a subset of. The study was approved by the Massey University Human Ethics Committee: Southern A, Application 16/42.

3.2.2 Measures

Measurements were collected during the school day by the study team in a designated room at the children's school. Height was recorded with a portable stadiometer (Seca 213) without shoes with the reading to the nearest 0.1cm and two measurements taken. Percentage body fat (%BF) was assessed with the Biospace InBody 230 Bio-electric Impedance Analyser (BIA) with the whole body %BF used. The use of BIA has been validated against dual-energy X-ray absorptiometry for %BF in adults (von Hurst et al., 2014) but not in children. The statistical methods for the development of prediction equations based on body composition parameters have been described elsewhere (Guo, Chumlea, & Cockram, 1996). Weight was recorded to the nearest 0.1kg without shoes and in light clothing using the BIA. Body mass index was calculated as weight (kg)/height^2 (m). Waist circumference (WC) was measured in duplicate using the landmarks for waist measurements (Gibson, 2005) with a Lufkin W606PM pocket tape positioned around the body over light clothing whilst standing and recorded to the nearest 0.1cm. Exact age at time of measurement was determined from the date of birth and date of measurement. Age and gender specific BMI was ascertained using the International BMI cut-offs (also referred to as the International Obesity Taskforce (IOTF) cutoffs), applying the equivalent BMI values at 18 years and linking to child centiles (Cole et al., 2000; Cole & Lobstein, 2012; H. Pan & Cole, 2012). A trained phlebotomist collected a finger prick blood sample for HbA1c assessment (Roche Cobas b 101) and only one measure was taken.

3.2.3 Questionnaires

Physical activity was quantitatively assessed with duration and frequency of activity undertaken as well as whether the child walked to school and the time taken to enable an estimation of activity recorded in minutes. Demographic information collected included age, gender (coded as male = 1, female = 2),

date of birth (with exact age calculated using the day of data collection) and ethnicity (whereby each ethnic group was assigned a code).

3.2.4 Statistical analysis

Data was analysed using the IBM SPSS statistical program, Version 24.0 software (IBM Corporation, New York, USA).

Data is displayed as proportions for categorical variables and as mean values and standard deviation for continuous variables. Differences between groups as defined by American Diabetes Association (ADA) diabetes criteria (American Diabetes Association, 2014), were tested with Mann-Whitney and Independent t-tests.

Dependent variables (body composition, age, HbA1c and physical activity) were analysed by two-way ANOVA tests applying gender and ethnicity as the grouping variables, followed by Tukey's post-hoc analysis. Pearson's correlation coefficient was used to evaluate associations between the aforementioned dependent variables.

Multiple linear regression analysis using the stepwise method was used to assess the influence of dependent variables including anthropometric, PA, ethnicity and beverage intake behaviours on HbA1c level as the dependent variable. Results with p values <0.05 were considered significant. For variables that showed statistically significant differences between groups, effect size was calculated to provide an objective measure of the importance of the effect by using the partial ETA squared value. An effect size value of 0.10 indicated a small effect, 0.3 a medium effect and a value greater than 0.5, a large effect (A. P. Field, 2013) Ethnic groups were assigned a dummy variable to enable comparisons between groups (dummy coded as European = 0, Maori = 2, Pacific Island = 3, South Asian = 4, Asian = 5, South East Asian = 6 and Other = 7).

3.3 Results

Of the 741 children who were eligible to participate, 685 consented to take part (participation rate 92.4%). Finger prick blood samples and anthropometric measurements were obtained from 452 children for the HbA1c study. Figure 3.1 details the study characteristics from recruitment through to the final number of participants. One European female child was identified as an outlier due to T1DM (HbA1c 51mmol/mol, [6.8%]) and excluded from the HbA1c dataset

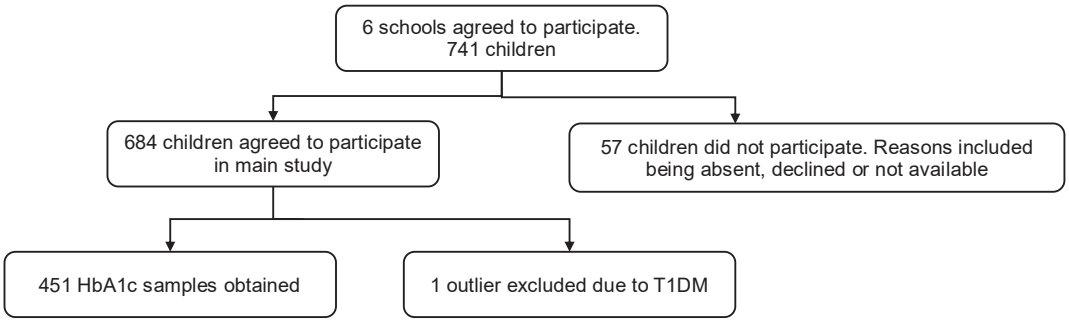

Figure 3.1. Diagram showing study characteristics from recruitment stage to final study group

There were significant differences for age, height, weight and WC, with those in the HbA1c group being older, taller, heavier and having greater WC than those who did not provide an HbA1c sample. There were no significant differences in gender, ethnicity, BMI, %BF or PA (Supplementary Table 1).

Participant demographics, anthropometric variables, HbA1c and PA levels are presented below (Table 3.1) for total HbA1c group and stratified into normoglycaemic (HbA1c ≤39mmol/mol [<5.7%]) and prediabetic (HbA1c >39mmol/mol [>5.7%]) (American Diabetes Association, 2014). The predominant ethnic group was European (35.7%) and the other proportions reflect the over-sampling of ethnic groups recognised to be at increased risk of T2DM. The South Asian group (10%) includes those of Indian, Pakistani, Sri Lankan and Bangladeshi descent. Asian (9.5%) refers to Chinese, Taiwanese, Korean or Japanese participants. The South East Asian group (4.5%) includes participants from Indonesia, Thailand, Singapore, Malaysia, Philippines and Laos. Finally the *Other* ethnic group (3.6%) comprised a diverse range of

ethnicities such as Middle East, Latin American and African. Due to the wide diversity and small size of this group, this group has been omitted from subsequent ethnic group analysis following this table.

A greater proportion of Maori, Pacific Island and South Asian children had HbA1c levels indicative of prediabetes. In contrast European and Asian children were predominantly within the normoglycaemic range. There was a greater proportion of overweight or obese participants in the prediabetic group, compared to the normoglycaemic group. The prediabetic group displayed significantly greater mean height, weight, BMI, WC, WtHR, HbA1c levels and %BF than the normoglyacemic group.

Table 3.2 presents physical characteristics, HbA1c level and PA stratified by ethnic group. Two-way ANOVA indicated no statistically significant interaction between the effects of gender and ethnicity for each of the variables. There was no significant main effect for ethnicity and age. There were however, significant medium to large effects observed between the ethnic groups for height, weight, BMI, WC, WtHR, %BF, HbA1c level. There were no significant main effects of gender on any of the variables. In post-hoc analysis there was no significant difference in age between the ethnic groups ($P>0.05$). For all other variables, the differences between Pacific Island and European children were significant ($p<0.001$). There were also significant differences between Maori and European children for weight, BMI, WC, WtHR, %BF ($p<0.001$) and HbA1c ($p<0.05$)

Table 3.1. Participant demographic, anthropometric, HbA1c and physical activity levels for total group and stratified by glycaemic status.

	Total group n=451	Normo-glycaemic[e] n=380	Prediabetic[f] n=71
	n (%)	n (%)	n (%)
Gender			
Male	204 (45.2)	173 (45.5)	31 (43.7)
Female	247 (54.8)	207 (54.5)	40 (56.3)
Ethnicity			
European	158 (35.7)	148 (39.8)	10 (14.3)
Maori	56 (12.7)	46 (12.4)	10 (14.3)
Pacific Island	106 (24.0)	77 (20.7)	29 (41.4)
South Asian[a]	44 (10.0)	31 (8.3)	13 (18.6)
Asian[b]	42 (9.5	40 (10.8)	2 (2.9)
South East Asian[c]	20 (4.5)	17 (4.6)	3 (4.3)
Other[d]	16 (3.6)	13 (3.5)	3 (4.3)
BMI (IOTF cut-offs)			
Thin 16-18.5kg/m^2	33 (7.4)	31 (8.2)	2 (2.8)
Normal 18.5-25kg/m^2	294 (65.6)	264 (69.7)	30 (43.5)
Overweight 25-29.9kg/m^2	74 (16.5)	57 (15.0)	17 (24.6)
Obese >30kg/m^2	47 (10.5)	27 (7.1)	20 (29.0)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	10.40 (0.63)	10.39 (0.63)	10.48 (0.60)
Height (m)	1.44 (0.8)	1.44 (0.8)	1.46 (0.80)[g]
Weight (kg)	39.7 (11.3)	38.4 (10.2)	46.9 (14.2)[h]
BMI (kg/m^2)	18.8 (4.0)	18.3 (3.5)	21.7 (5.0)[h]
Waist circumference (cm)	63.1 (10.8)	61.6 (9.7)	71.3 (12.9)[h]
Waist-to-height ratio	.44 (0.07)	.43 (0.06)	.49 (0.08)[h]
HbA1c (mmol/mol)	36 (3)	35 (2)	40 (2)[h]
Body fat (%)	22.9 (9.3)	21.7 (8.4)	30.1 (10.7)[h]
Physical activity (hours)	3.6 (2.4)	3.75 (2.3)	3.07 (2.7)

BMI Body mass index. IOTF, International Obesity Task Force; HbA1c, glycated haemoglobin; SD, standard deviation; [a]Indian, Pakistani, Sri Lankan, Bangladeshi; [b]Chinese, Taiwanese,

Korean, Japanese; [c]Indonesian, Thai, Singaporean, Malaysian, Filipino, Lao; [d]Middle Eastern, Latin American, African; [e]glycaemic levels <39mmol/mol (<5.7%) as per American Diabetes Association criteria (American Diabetes Association, 2014); [f]glycaemic levels >39mmol/mol (>5.7%) as per American Diabetes Association criteria (American Diabetes Association, 2014); [g]Statistically significant difference from normoglycaemia P<0.05, [h]Statistically significant difference from normoglycaemic P<0.001

Table 3.3 details the proportion of participants with an HbA1c level in the prediabetic range (ADA criteria of HbA1c >39mmol/mol [>5.7%]), by ethnicity and anthropometric risk variables: IOTF BMI grade, WC percentile and %BF. In total 71 participants (15.7%) had an HbA1c level that was in the prediabetic range. Applying IOTF BMI cut-off criteria, 32 participants (7.1%), had a normal BMI but an at-risk HbA1c level. For WC percentile, 54 participants (12%), had a WC within the healthy range (Fryar, Gu, & Ogden, 2012), but an HbA1c level in the prediabetic range. For %BF, 24 participants (5.3%), were within normal %BF ranges (applying children's standards) (BioSpace InBody, 2017), but had an at-risk HbA1c level. The South Asian group had the highest percentage of participants within normal ranges for each of the anthropometric variables, but with HbA1c levels in the prediabetic range.

Results of the regression analysis examining the independent variables are presented in Supplementary Tables 2-4 with Table 3.4 displaying the final model. In this analysis, HbA1c level was the dependent variable and WC, BMI, PA and ethnicity were the independent variables. WC and South Asian, Pacific Island and Asian groups were significant determinants for HbA1c level, whereas BMI, PA level, Maori and South East Asian groups did not prove to be significant predictors, and were excluded from the model. In regression analysis, all things being equal, the average value of HbA1c is 2.785 units (mmol/mol) higher for the South Asian children than for Europeans (the reference ethnic group). For Pacific Island children, the average value of HbA1c was 1.202 units higher than the reference group and for Asian children, the average value was 1.073 units higher. For WC, all things being equal, a 10cm increase in WC is associated with an average increase of 0.9 units of HbA1c.

Table 3.2. Anthropometric characteristics, HbA1c levels and physical activity stratified by ethnic group.

	Ethnicity						P value[d]	
	European n=158	Maori n=56	Pacific Island n=104	South Asian[a] n=43	Asian[b] n=42	South East Asian[c] n=20		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Gender	Ethnicity
Age (years)	10.4 (.62)	10.4 (.76)	10.5 (.62)	10.4 (.60)	10.4 (0.57)	10.3 (0.58)	.043	.271
Height (cm)	143 (7)	147 (9)	147 (8)[f]	142 (7)	143 (8)	139 (6)	.012	.0001
Weight (kgs)	35.5 (7.0)	45.7 (14.1)[f]	47.4 (13.3)[f]	36.7 (9.7)	35.9 (7.4)	32.6 (5.0)	.348	.0001
BMI (kg/m^2)	17.2 (2.5)	20.8 (4.7)[f]	21.5 (4.8)[f]	18.0 (3.7)	17.4 (2.4)	16.8 (1.8)	.981	.0001
Waist (cm)	59.3 (7.4)	68.7 (12.6)[f]	69.9 (10.9)[f]	62.5 (10.9)	57.0 (8.9)	56.0 (7.1)	.300	.0001
Waist-to height-ratio	0.41 (0.05)	0.47 (0.07)[f]	0.47 (0.06)[f]	0.44 (0.07)	0.40 (0.06)	0.40 (0.05)	0.37	.0001
Body fat (%)	19.2 (6.8)	25.5 (10.2)[f]	27.9 (10.5)[f]	24.2 (9.7)	21.3 (7.1)	18.5 (5.9)	.470	.0001
HbA1c (mmol/mol)	34 (3)	36 (3)[e]	37 (3)[f]	37 (4)[f]	35 (2)	35 (3)	.554	.0001
PA (hours)	4.44 (2.5)	4.19 (3.0)	2.86 (1.6)[f]	3.27 (2.0)	3.10 (1.9)[e]	2.27 (2.0)[e]	.359	.0001

BMI, Body mass index; HbA1c, glycated haemoglobin; PA, physical activity; SD, standard deviation. [a]Indian, Pakistani, Sri Lankan, Bangladeshi; [b]Chinese, Taiwanese, Korean, Japanese; [c]Indonesian, Thai, Singaporean, Malaysian, Filipino, Lao; [d]Statistical significance of effect by two-way ANOVA; [e]Mean difference is significant (P<0.05) compared to European children; [f]Mean difference is significant (P<0.001) compared to European children.

Table 3.3. Proportion of participants with HbA1c level in prediabetic range (>39mmol/mol [>5.7%]) by ethnicity and anthropometric risk variable with cut-offs.

	Ethnicity											
	European n=158		Maori n=56		Pacific Island n=104		South Asian[a] n=43		Asian[b] n=42		South East Asian[c] n=20	
	%	n	%	n	%	n	%	n	%	n	%	n
IOTF BMI grade[d]												
Thinness grade 2	0.6	1	-	-	-	-	-	-	-	-	-	-
Thinness grade 1	-	-	-	-	-	-	2.3	1	-	-	-	-
Normal	3.8	6	8.9	5	6.7	7	16.3	7	2.4	1	10.0	2
Overweight	0.6	1	3.6	2	7.7	8	7.0	3	2.4	1	5.0	1
Obesity	1.3	2	5.4	3	11.5	12	4.7	2	-	-	-	-
Total at risk by IOTF BMI grade	6.3	10	17.9	10	26.0	27	30.2	13	4.8	2	15.0	3
WC percentile[e]												
<85th	4.5	7	14.8	8	19.2	20	23.3	10	4.8	2	15.0	3
85th-95th	0.6	1	-	-	3.8	4	4.7	2	-	-	-	-
>95th	0.6	1	1.9	1	2.9	3	2.3	1	-	-	-	-
Total at risk by WC percentile	5.7	9	16.7	9	25.9	27	30.3	13	4.8	2	15.0	3
% body fat range[f]												
Low or normal body fat	3.8	6	7.1	4	5.7	6	9.1	4	2.4	1	15.0	3
Above normal range (obese)	2.5	4	10.7	6	19.8	21	20.5	9	2.4	1	-	-
Total at risk by % body fat	6.3	10	17.9	10	25.5	27	29.5	13	4.8	2	15.0	3

HbA1c, glycated haemoglobin; IOTF BMI grade. International Obesity Task Force Body Mass Index grade; WC, waist circumference; [a]Indian, Pakistani, Sri Lankan, Bangladeshi; [b]Chinese, Taiwanese, Korean, Japanese; [c]Indonesian, Thai, Singaporean, Malaysian, Filipino, Lao [d]IOTF BMI grade (Cole & Lobstein, 2012) [e]Waist circumference percentiles by sex and age for children and adolescents aged 2-19 years (Fryar et al., 2012) [f]% body fat normal ranges, children's standards applied (BioSpace InBody, 2017).

Table 3.4. Regression model for explaining the variance of HbA1c. (n=402)

Model	Coefficient (β)	Standard error β	Adjusted R^2	P-value
(Constant)	29.130	0.855		
Waist circumference	0.090	0.014	0.119[d]	
South Asian	2.785	0.478	0.169[c]	
Pacific Island	1.202	0.356	0.186[b]	
Asian	1.073	0.462	0.195[a]	0.001

Stepwise method. [a]F(4, 401) = 25.286, [b]F(3, 401) = 31.571, [c]F(2, 401) = 41.886, [d]F(1, 401) = 55.406

3.4 Discussion

Stratifying by ethnicity, Pacific Island, Maori and South Asian children had higher mean HbA1c levels compared to European children. These children also recorded higher mean measures for BMI, WC, WtHR and %BF alongside lower average PA levels. However, where regression analysis indicates that for South Asian and Pacific children, that WC, WtHR, BMI and %BF accounted for some of the variance in HbA1c levels compared to European children, the same was not seen for Maori children, with none of the variables significant predictors in the variance of HbA1c level. A difference between these groups was in PA levels with Maori children undertaking more PA, however the difference in activity level was significant between Pacific Island and European children only. Another observation was that on average, Asian children recorded comparable anthropometric measures to European children with no significant differences observed, except for lower PA levels. However there were subtle differences evident and compared to European children, the Asian children had higher average %BF at lower BMI. The South Asian children also displayed this profile but South East Asian children did not. This observation is consistent with studies that have shown Asians have a higher BF% at a lower BMI compared to Europeans (Deurenberg, Deurenberg-Yap, & Guricci, 2002; Tillin et al., 2015), and may have an increased %BF distributed predominantly in the abdominal region, despite not appearing obese by other weight criteria (American Diabetes Association, 2010). Differences between Asian sub-groups have been observed elsewhere (Deurenberg et al., 2002; World Health Organisation, 2004). Accordingly, in regression analysis, WC and WtHR were also

contributing factors for variance in HbA1c for the Asian children. This effect was not seen for the South East Asian children and this could be due to low statistical power with smaller numbers in this group, or other variables not assessed.

These findings highlight the differing interactions between ethnic groups, for different anthropometric RFs and the resulting variance in predicting HbA1c level. Specifically, for South Asian and Pacific children, each of the examined anthropometric variables accounted for variance in HbA1c level compared to European children. For Asian and South East Asian children, the variance in HbA1c level was most notable for measures of central adiposity and for these latter groups, waist measures may provide a better marker of cardiometabolic disease risk (Browning, Hsieh, & Ashwell, 2010; Jayawardana, Ranasinghe, Sheriff, Matthews, & Katulanda, 2013). This is significant for later risk of T2DM, given central adiposity has a greater association with IR and T2DM, than overall body fatness (Radzevičienė & Ostrauskas, 2013).

That each of the examined anthropometric variables accounted for variance in HbA1c for Pacific Island children compared to European children is consistent with studies finding that this group has the highest rates of obesity when compared to Maori and European children (Duncan, Duncan, & Schofield, 2009; Goulding et al., 2007; Ministry of Health, 2016a; Tyrrell et al., 2001). Pacific people are also known to have a high prevalence of T2DM (Liese et al., 2006) including the highest prevalence of undiagnosed T2DM in NZ (Coppell et al., 2013). With increasing numbers of T2DM occurring in minority ethnic groups such as Maori and Pacific children, there is a need to target at-risk groups with healthy lifestyle interventions in order to prevent or delay onset and reduce the resulting health burden on both the individual and health system.

Physical activity is recognised as being key in preventing T2DM (Colberg et al., 2010; Lebovitz, 2006). It was observed that Pacific Island children exercised significantly less than the European and Maori children. Whilst PA did not account for variance in HbA1c in any of the regression models, this may be attributable in part to the method of data collection with a self-completed questionnaire used to estimate time spent engaging in physical activities (including walking to school). This meant that the accuracy of the data was dependent on the literacy and willingness of those providing it. Additionally,

with the study conducted over the winter period, seasonality may have had an effect.. The use of accelerometers for energy expenditure, would provide a more accurate assessment. Other possible limitations in this analysis include that SES which is a significant predictor of body composition in childhood (Spencer et al., 2013), was not assessed and neither was family history of T2DM which is a recognised RF (American Diabetes Association, 2014).

As far as explaining variance of HbA1c, the regression models that examined the WC and WtHR variables were the best predictors. The differences between these models and those including the BMI and %BF variables were marginal, although the last two models displayed less of an effect in accounting for differences across the ethnic groups. The results of this study align with findings that both central and overall adiposity are associated with T2DM and that a high BMI, WC and WtHR are all predictors of T2DM risk (Browning et al., 2010; Radzevičienė & Ostrauskas, 2013). A systematic review of cross-sectional and prospective studies indicates that evidence supports WtHR and WC as stronger predictors than BMI and after adjustments, waist measures predicted outcomes independent of BMI (Browning et al., 2010). A meta-analysis examining for cardiometabolic RFs identified that indices of abdominal obesity were better indicators than BMI, with WtHR particularly preferable to BMI (Lee, Huxley, Wildman, & Woodward, 2008). However whilst differences in measures exist they are deemed to be minor, and of little clinical relevance and based on available data, with no overall measure advocated over others (Lee et al., 2008). Elsewhere the joint use of BMI and waist measures is advocated due to the additive effect of RFs (Katzmarzyk et al., 2004; Meisinger et al., 2006). Such an approach may be beneficial with Asian populations recording lower BMI but higher %BF in the abdominal region.

Percentage BF was positively correlated with HbA1c levels and this held true across all ethnic groups. Differences in %BF were observed between groups with a higher proportion of Pacific Island, Maori and South Asian participants possessing higher mean %BF and HbA1c levels and stronger correlations than their European or South East Asian peers. This difference in %BF measures between ethnicities has been observed elsewhere (Deurenberg et al., 2002; Rush et al., 2003). The use of BIA to obtain a measure of %BF is advantageous as it allows for the differentiation between fat mass and lean

muscle mass, whilst BMI does not (Rush et al., 2003). A limitation of assessing %BF however is that it is not a simple measure and requires trained personnel or specialized equipment to measure.

A further limitation of the current study was that no assessment was made of pubertal stage, which may have differed between the different ethnic groups and influenced anthropometric measures or HbA1c levels due to hormonal changes associated with puberty (Goran & Gower, 2001; Moran et al., 1999; Travers et al., 1995).

We identified 71 participants (15.7%) with HbA1c levels >5.7% (39mmol/mol) which is indicative of prediabetes as per ADA guidelines (American Diabetes Association, 2014). This was evident across all ethnic groups, however the greatest prevalence was observed in South Asian (29.5%), Pacific (27.4%) and Maori children (17.9%). This is in contrast to European (6.3%) and Asian children (4.8%). As expected, being overweight or obese was a contributing RF for an elevated HbA1c level, however there were also participants within normal cut-off ranges for BMI (46% of normal or thin BMI), WC (79% within <85th percentile) and %BF (36% of low or normal body fat), who registered Hba1c levels indicative of prediabetes. Thus being overweight or obese as assessed by a range of anthropometric cut-offs was not a requirement for predicting an elevated HbA1c level. With the exception of the Pacific and Maori groups, more than half of those with an HbA1c level in the prediabetic range had a normal BMI. This aligns with the stance that overweight and obesity are not finite cut-offs and it is possible to be on a trajectory to obesity, even when within a normal BMI-for-age range (World Health Organisation, 2016). These findings pose a question around the suitability of universal cut-offs for different ethnic groups. A further question concerns whether HbA1c level is a suitable measure of risk in children approaching adolescence or whether the cut-offs are appropriate for paediatric groups, as the data upon which the diagnosis criteria were formed are based on adults (Nowicka et al., 2011). There is less evidence on the use of HbA1c level as an indicator of risk in paediatric populations, however it has shown similar predictive value to the FPG and OGTT tests in a prospective study (Vijayakumar et al., 2016).

To the best of our knowledge, this study is unique in assessing a range of RFs associated with the later development of T2DM, alongside the use of an HbA1c test as a measure of glycaemia in a paediatric population of mixed ethnicities.

The current study builds upon the exploration of the use of HbA1c testing in paediatric populations by examining in a multi-ethnic group randomly selected with regards to body composition status. This study illustrates the value of using an HbA1c test or similar clinical measure as a screening tool alongside other recognised RF and including in those who are not obese. There are some caveats however, as it is recognised that ethnic groups have differing sensitivity and specificity to HbA1c (C. M. Bennett et al., 2007).

Whilst studies have identified merits in the various anthropometric measures, it would appear that BMI, WC and WtHR can all be useful indicators of prediabetes risk. The use of a clinical measure such as HbA1c alongside identified RFs provides an opportunity for further validation of risk.

Key strengths of the current study include a large paediatric cohort with a mix of ethnic groups. The cohort was not pre-screened to focus on obese participants only as previous studies have, and revealed potential risk present in children displaying normal anthropometric measures when stratified by HbA1c level. The use of a portable point of care (PoC) machine to collect HbA1c samples alongside anthropometric measurements provided a clinical measure to further assess risk.

Limitations of the present study include that accurate assessments were not made to further support the validation of an HbA1c test or T2DM risk, such as the use of OGTT or FPG tests, however they would not be practical in this setting. Additionally as the relationship between HbA1c levels and other known risk factors was being assessed for T2DM risk only and not a diagnosis, only one HbA1c sample was collected. The study was a cross-sectional study from a group of Auckland school children, so the findings are observational only and cannot be interpreted as being representative of the broader population. The current study primarily focussed on anthropometric measures and ethnicity alongside HbA1c however it is acknowledged that there are other factors which may impact on risk such as stage of puberty, family history and overall activity expenditure and dietary intake that were not assessed. Finally further

investigations are required to determine appropriate HbA1c level cut-offs for paediatric groups, which may include variability for age, puberty and ethnicity.

3.5 Conclusion

In conclusion, this study confirms that both central and overall adiposity are associated with T2DM and that WC, WtHR and BMI measures may all be used in the screening for later T2DM risk. There were differences observed in the prediction of HbA1c level across the anthropometric measures with waist measures showing slightly greater prediction in HbA1c variance across the groups, however the differences between the anthropometric measures were marginal.

Differences between ethnic groups were observed with Pacific Island, Maori and South Asian minority groups experiencing higher anthropometric measures alongside poorer glycaemic control. Compared to European children, Asian and South Asian children displayed higher average %BF at lower BMI. This likely materialised as increased BF in the abdominal region as identified in regression analysis with waist measures predicting variance in HbA1c for these ethnic groups. This was not evident for the South East Asian group and this may have been attributable to statistical power or other unidentified factors.

As expected, overweight or obesity was a contributing RF towards an elevated HbA1c level. However when stratified by anthropometric measures, there were participants who were within normal cut-off ranges for BMI, WC and %BF. With the exception of the Pacific and Maori groups, more than half of those with an HbA1c level in the prediabetic range had a normal BMI. In this instance, the use of HbA1c as a clinical measure alongside other RFs served to enhance the assessment of later T2DM risk by using a glycaemic measure that did not discriminate on physical adiposity status. This is key as overweight or obesity measures are not finite cut-offs and risk may still be present even if within a normal BMI range.

As this study was cross-sectional, further prospective studies are needed to further examine the use of HbA1c as a clinical measure alongside other RFs or testing methods for further validation, in order to assess future T2DM risk in paediatric populations.

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Supplementary Tables

Supplementary Table 1. Participant demographic, anthropometric, HbA1c and physical activity levels for total group, HbA1c group and non-HbA1c group.

	Total group n=685	HbA1c group n=451	No HbA1c n=234
	n (%)	n (%)	n (%)
Gender			
Male	309 (45.1)	204 (45.2)	105 (44.9)
Female	376 (54.9)	247 (54.8)	129 (55.1)
Ethnicity			
European	260 (38.9)	158 (35.7)	102 (45.1)
Maori	74 (11.1)	56 (12.7)	18 (8.0)
Pacific Island	144 (21.6)	106 (24.0)	38 (16.8)
South Asian[a]	70 (10.5)	44 (10.0)	26(11.5)
Asian[b]	65 (9.7	42 (9.5	23 (10.2)
South East Asian[c]	25 (3.7)	20 (4.5)	5 (2.2)
Other[d]	30 (4.5)	16 (3.6)	14 (6.2)
BMI (IOTF cut-offs)			
Thin 16-18.5kg/m^2	54 (7.9)	33 (7.4)	21 (9.0)
Normal 18.5-25kg/m^2	455 (66.8)	294 (65.6)	161 (69.1)
Overweight 25-29.9kg/m^2	108 (15.9)	74 (16.5)	34 (14.6)
Obese >30kg/m^2	64 (9.4)	47 (10.5)	17 (7.3)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	10.34 (0.62)	10.40 (0.63)	10.22 (0.58)[h]
Height (m)	1.43 (0.8)	1.44 (0.8)	1.42 (0.8)[h]
Weight (kg)	38.8 (11.2)	39.7 (11.3)	37.3 (10.8)[g]
BMI (kg/m^2)	18.7 (3.9)	18.8 (4.0)	18.3 (3.8)
Waist circumference (cm)	62.1 (10.8)	63.1 (10.8)	60.1 (10.6)[g]
Waist-to-height ratio	.43 (0.07)	.44 (0.07)	.42 (0.07)
Body fat (%)	22.8 (9.3)	22.9 (9.3)	22.5 (9.0)
Physical activity (hours)	3.6 (2.3)	3.6 (2.4)	3.5 (2.3)

BMI Body mass index. IOTF, International Obesity Task Force; HbA1c, glycated haemoglobin; SD, standard deviation; [a]Indian, Pakistani, Sri Lankan, Bangladeshi; [b]Chinese, Taiwanese,

Korean, Japanese; [c]Indonesian, Thai, Singaporean, Malaysian, Filipino, Lao; [d]Middle Eastern, Latin American, African; [g]Statistically significant difference from HbA1c group P<0.05, [h]Statistically significant difference from HbA1c group P<0.001

Supplementary Table 2. Stepwise multiple regression analysis models for explaining the variance of HbA1c. Independent variables were WtHR, PA and ethnic groups. (n=402)

Model	Coefficient (β)	Standard error β	Adjusted R^2	P-value
(Constant)	28.848	0.964		
Waist-to-height	13.633	2.217	0.108[d]	
South Asian	2.714	0.482	0.153[c]	
Pacific Island	1.340	0.355	0.175[b]	
Asian	1.047	0.466	0.184[a]	0.001

Stepwise method. [a]F(4, 401) = 23.55, [b]F(3, 401) = 29.42, [c]F(2, 401) = 37.2, [d]F(1, 401) = 49.5

Supplementary Table 3. Stepwise multiple regression analysis models for explaining the variance of HbA1c. Independent variables were BMI, PA and ethnic groups. (n=408)

Model	Coefficient (β)	Standard error β	Adjusted R^2	P-value
(Constant)	30.673	0.688		
BMI	0.229	0.037	0.106[c]	
South Asian	2.755	0.477	0.163[b]	
Pacific Island	1.011	0.356	0.177[a]	0.001

BMI, body mass index; Stepwise method. [a]F(3, 404) = 30.27, [b]F(2, 405) = 40.68, [c]F(1, 406) = 49.37

Supplementary Table 4. Stepwise multiple regression analysis models for explaining the variance of HbA1c. Independent variables were %BF, PA and ethnicity. (n=408)

Model	Coefficient (β)	Standard error β	Adjusted R^2	P-value
(Constant)	32.810	0.370		
% BF	0.095	0.016	0.113[c]	
South Asian	2.471	0.480	0.154[b]	
Pacific Island	1.158	0.350	0.174[a]	0.001

%BF, percentage body fat; Stepwise method. [a]F(3, 404) = 29.62, [b]F(2, 405) = 38.02, [c]F(1, 406) = 52.78

Chapter Four

4 Conclusions

4.1 Research problem and aims of the research study

Type 2 diabetes mellitus, a metabolic disorder with long-lasting comorbidities was previously considered a disease of adulthood (Alberti et al., 2004; Daniels et al., 2005). With almost one-in-six children now overweight or obese (Organisation for Economic Co-operation and Development, 2017), T2DM is increasingly occurring in children and adolescents (Al-Saeed et al., 2016; Alberti et al., 2004; Daniels et al., 2005; Pinhas-Hamiel & Zeitler, 2005). An increased prevalence of early-onset diabetes will further contribute to be a significant personal health and economic burden, due to a longer duration of the disease and the likely occurrence of related complications at a younger age (Ebbeling et al., 2002; Hannon et al., 2005; Imperatore et al., 2012).

The aim of this study was to investigate the relationship between HbA1c level as a measure of glycaemia, and a number of recognised RF that are associated with the later development of T2DM. Being able to identify at-risk individuals early, could provide the opportunity to implement lifestyle modifications, which might delay the progression to T2DM.

4.2 The main findings of the research study

In stratifying by ethnic group, differences were evident with Pacific Island, Maori and South Asian children recording higher mean anthropometric measures and lower PA levels. This culminated in higher mean HbA1c levels compared to European children. These combined findings illustrate the differing interactions or effects of ethnicity on anthropometry (Fryar et al., 2012) and differing levels of glycaemic control across ethnic groups (Khanolkar et al., 2016). They also reinforce that minority populations are disproportionately affected in risk for T2DM (Arslanian, 2002; Imperatore et al., 2012).

Differences were observed between European and Asian groups and between Asian sub-groups. As observed elsewhere, South Asian and Asian groups

recorded higher average %BF at lower BMI compared to European children (Deurenberg et al., 2002; Duncan et al., 2009; World Health Organisation, 2004).

The current study found that WC and WtHR accounted for variance in HbA1c for more ethnic groups in regression analysis, than did the BMI or %BF measures. However the differences across the measures were marginal. This aligns with data from a systematic review (Browning et al., 2010) and meta analysis (Lee et al., 2008), that found that WC or WtHR measures perform slightly better than BMI, given the effect of abdominal obesity on risk, however they are minor and of little clinical relevance. Elsewhere studies advocate the joint use of BMI and waist measures, given the additive effect of RFs (Katzmarzyk et al., 2004; Meisinger et al., 2006; Radzevičienė & Ostrauskas, 2013). The use of a clinical measure such as HbA1c alongside identified RFs provides an opportunity for further validation of overall risk.

An interesting observation was that when stratifying the data by HbA1c level, of those within a prediabetic range, 46% of the participants had a thin or normal BMI. This suggests that cut-offs are subject to variation by ethnic group and that the anthropometric measure should be evaluated alongside other recognised RF as part of an overall risk assessment. Furthermore, it has previously been indicated, that overweight and obesity are not finite cut-offs and there is still a risk for obesity even when within normal BMI ranges (World Health Organisation, 2016).

4.3 Strengths

By conducting the study in a number of schools across the Auckland region, we were able to access large numbers of children, as well as oversampling of ethnic groups known to be at increased risk of T2DM.

The use of the portable PoC machine for HbA1c level assessment was convenient in its portability, alongside the fact that it does not require fasting. It also gives a more accurate indication of current risk in regards to blood glucose levels, with the results reflecting the average level of glycaemia over eight to twelve weeks.

With the relatively recent emergence of T2DM in children and adolescents, HbA1c testing has not been used as extensively in these groups. Additionally,

as our cohort was not recruited on any specific weight status, we were able to assess a range of body types, whilst paediatric studies utilising HbA1c as a measure, have tended to focus on overweight or obese subjects only. The observation that even those of normal weight registered elevated HbA1c levels indicative of prediabetes, was a strength of this approach.

Through collecting a range of anthropometric measures, we were able to assess and evaluate each to determine any differences with the observation that overall they performed comparably in regression analysis.

4.4 Limitations

The current study was a cross-sectional study from a group of Auckland school children so the findings are observational only and cannot be taken as representative of the broader population.

The study protocol involved taking children out of class to complete the measurements, and having the children and parents or caregivers complete, PA and demographic questionnaires, which included ethnic group. This meant that the accuracy of the data collected was dependent on the literacy and willingness of those providing it. A variety of measures including detailed food diaries, use of accelerometers and trained interviewers could overcome some of the issues, however these must be balanced with time, cost and participant burden.

The findings of the present study are limited to an assessment of the studied RFs only with a focus on anthropometric measures and ethnicity with HbA1c level as a glycaemic measure to assess later risk of T2DM. It is acknowledged that there are other factors, which may impact on risk, such as stage of puberty, family history and overall activity expenditure and dietary intake that were not considered or accurately assessed. We also did not test HbA1c against other testing methods, such as the OGTT or FPG tests, however this would not have been practical in the school setting.

Further investigations are required to determine appropriate HbA1c level cut-offs for paediatric groups, which may also include greater variability for different age ranges given the effects of puberty, and ethnic-specific cut-offs.

4.5 Application/implications of the research findings

The findings of the study suggest that an HbA1c test can be utilised in paediatric groups, as a simple tool for the screening of later risk of T2DM alongside the assessment of other recognised RFs.

For assessments of overweight or obesity, the use of BMI is not always appropriate particularly in multi-ethnic groups such as Asian's who tend to have higher levels of body fatness at a lower BMI or increased central adiposity. These findings would appear to support the application of ethnic specific BMI cut-offs or the use of an alternative measure of obesity such as WC or WtHR. Additionally whilst being overweight or obese is deemed a critical RF, it was not a requirement in contributing to an elevated HbA1c level and so a range of RFs in addition to obesity measures, should be considered.

4.6 Recommendations for future research

With ethnic differences in body composition observed, there is some evidence that universal BMI thresholds do not take into account differing body fat levels in children from different ethnic backgrounds for the same BMI. The application of ethnic-specific BMI cut-offs with differing obesity thresholds, would provide a more accurate representation of overweight and obesity in multiethnic groups.

There are many variables identified as RFs for the later development of T2DM and even differing screening criteria such as the ADA and NZ guidelines. Further understanding of the role or interaction of RFs may aid in determining the most appropriate criteria for detecting future T2DM risk. That BMI, WC, WtHR and %BF delivered comparable outcomes suggests that they could be used jointly where there is uncertainty in one measure or the presence of additional RFs that warrant the use of another measure such as abdominal obesity.

Longer-term prospective studies are recommended encompassing a range of ethnicities to further assess the relationship of HbA1c levels in childhood and the later risk of developing T2DM alongside other recognised RFs. These studies would ideally include participants of a normal weight as well as overweight and obese participants to further understand the role of weight and body fatness in T2DM risk in paediatric and adolescent populations.

Finally whilst there is some evidence to support the use of HbA1c testing in assessing future T2DM risk, further longitudinal studies would further validate the predictive value of the test compared to other testing methods.

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Appendices

Appendix A Study information sheet

MASSEY UNIVERSITY

The Children's Bone Study

INFORMATION SHEET FOR PARENTS

Thank you for your interest in the children's bone study. This sheet gives information on the conduct and organisation of this study, including confidentiality and data protection. It is important that you read this and are happy with the information given before agreeing to take part in the study.

Why is this research important?
Anecdotal evidence suggests that a greater number of primary school children are having more broken bones than their grandparents did. We want to find out the relationships between history of broken bones, bone mineral density, dietary intake of nutrients related to bone health, beverage choices and preferences, physical activity, sun exposure behaviours and body composition of children living in Auckland.

Who are we looking for?
We are inviting around 600+ children who are enrolled in Year 5 or 6 in Auckland primary schools and who do not have any gastrointestinal disorders or bone disease to take part in this study. Each child and at least one of the child's parents/guardians need to be able to read and comprehend English to a sufficient level that they can understand the information provided about the study and make an informed decision about whether or not they wish to participate.

What is going to happen?
Initially, the children will have a science lesson, facilitated by our specialist science teacher, on the topic of bone health. Classroom sessions will be arranged at times to suit teachers and teaching schedules, and will be designed to link with curriculum. They will also answer a short questionnaire about different types of drinks. All data collection from the children will take place in school. Further information will be sought from you, parents or caregivers, through two questionnaires, which your child will bring home, along with a consent form.

One questionnaire will have questions about your child such as: Gender, date of birth, ethnicity, and information about any broken bones your child has had. Also history of sun exposure/sun protection practices, physical activity and type of sports your child plays. The second questionnaire is a food frequency questionnaire to find out about your child's milk/dairy product consumption, other beverage choices, and other dietary sources of calcium. These questionnaires will take approximately twenty (20) minutes to complete. You will only need to complete these questionnaires once.

All data collection from the children will take place in school. The children will have measurements made to determine their body composition (level of muscle and fat), and a finger prick blood spot to measure vitamin D levels. We will also measure the bone

density of their heel bone using the quantitative ultra sound (QUS), and their blood pressure.
All the children in the class will be shown a short video which will explain all the things that will happen during the study. Your child will have the opportunity to ask both his/her teacher and the specialist teacher who is part of the study team, any questions about the study.

If you and your child decide against participating in the study, your child will still be involved in all the classroom activities associated with the study. There is no obligation to be part of the study.

Height and waist measurement
We will ask your child to remove his/her shoes due to measuring his/her height. Standing height using a stadiometer, and waist circumference using a measuring tape will be measured for each child.

Blood pressure
We will measure your child blood pressure with automated blood pressure monitor.

BIA (above left)
Bio-electric impedance analysis is a method for measuring body composition. This machine is used to tell us how much fat and muscle mass your child has on his/her body. This test will take only a few minutes and won't hurt at all. We will ask your child to remove her/his shoes and socks, Stand on the machine's scale. Then hold the two handles for a few seconds (as in the picture). A very tiny electrical current passes through the body, but you cannot feel anything.

Quantitative Ultra Sound (QUS – above right)
Quantitative ultrasound is a radiation-free technique for providing a proxy for bone mineral density by determining how rapidly sound travels through the bone. We will ask your child to bare one of his/her legs (no shoes or socks) and then put his/her heel into the machine for less than one minute.

Finger prick blood spot
We will ask children to wash their hands with warm water. Then they will asked to shake their hand and choose a finger for finger prick. Then we will prick the finger with a lancet and collect a full drop of blood.

Who will see the information about your child?
All information about your child will be stored in a locked filing cabinet accessed by the research team only. No names or any other informationthat could be used to identify your child will be used in any publication.

We are required to keep any data that may be medically relevant for your child in the future for ten years. All electronic data will be stored password-protected on the University's secure server. For the first 5 years we will store any paper copies of data in a locked filing cabinet within a locked office. For the remainder of the time, data will be stored in a secure archive in boxes labelled by barcode only. This data will be accessible by nominated staff only. After the mandatory storage time has passed, all data filed on paper will be shredded and electronic data will be deleted from our computer records and databases.

Would your child like to take part?
If "YES"
If your child would like to take part in this study and you are happy for them to do so, please sign the attached consent form and ask your child to return it to their teacher.

If "NO"
If you do not want your child to participate or your child does not want to take part in this study then you do not need to do anything. Your child will still take part in the special science lesson, but we will not collect any data from, or about, your child.

What are the benefits and risks of taking part in this study?

- You will receive a brief report summarising the main findings of the project via mail or email.
- The principal benefit of taking part in this study is that you will contribute to a study and our understanding of bone mineral density, dietary intake of nutrients related to bone health, beverage choices and preferences, physical activity, sun exposure behaviours and body composition of children.
- It is not envisaged that there will be any discomforts or risks to the participants as a result of participation, other than the minor discomfort of the finger prick blood test.
- If you have any specific requirements including cultural requirements or concerns about the project, or about being a participant, please contact a member of the research team to discuss.

Who is funding the research?
This is funded by a grant from the Massey University Research Fund.

What are my rights and the rights of my child?
We respect your rights and your child's rights to:

- refuse to answer any particular question or take part in any testing (finger prick blood spot, QUS or BIA)
- withdraw from the study at any time
- ask further questions about the study that occur to you during your participation
- provide information on the understanding that it is completely confidential to the researchers. All information is collected confidentially, and it will not be possible to identify you or your child in any reports that are prepared from the study
- be given access to a summary of the findings from the study when it is concluded.

Compensation for Injury
In the unlikely event that physical injury results from your child's participation in this study, you should visit a treatment provider to make a claim to ACC as soon as possible. ACC cover and entitlements are not automatic and your claim will be assessed by ACC in accordance with the Compensation Act 2001. If your claim is accepted, ACC must inform you of your entitlements, and must help you access those entitlements. Entitlements may include, but not be limited to, treatment costs, travel costs for rehabilitation, loss of earnings, and/or lump sum for permanent impairment. Compensation for mental trauma may also be included, but only if this is incurred as a result of physical injury.

If your ACC claim is not accepted you should immediately contact the researcher. The researcher will initiate processes to ensure you receive compensation equivalent to that to which you would have been entitled had ACC accepted your claim from Massey University.

If you have any questions please contact Dr Pamela von Hurst who will be happy to discuss the project in more detail.

Contact details:

Dr Pamela von Hurst
School of Food and Nutrition, College of Health
Massey University
Email P.R.vonHurst@massey.ac.nz
Phone (09) 213 6657

This project has been reviewed and approved by the Massey University Human Ethics Committee: Southern A, Application 16/42 If you have any concerns about the conduct of this research, please contact Mr Jeremy Hubbard, Chairperson, Massey University Human Ethics Committee: Southern A, telephone 64 9 414 0800 x 63487.
email humanethicsoutha@massey.ac.nz.

Appendix B Parent and child consent forms

The children's bone study

PARENT AND CHILD CONSENT FORM

Parent to complete this section:

I have read the Information Sheet and have had the details of the study explained to me. My questions have been answered to my satisfaction, and I understand that I may ask further questions at any time.

☐ I agree for my child to participate in this study including the finger prick blood spot under the conditions set out in the Information Sheet.

☐ I agree for my child to participate in this study but not the finger prick blood spot under the conditions set out in the Information Sheet.

Signature: ..... **Date:** .....

Full Name (printed) .....

Child's Full Name .....

Child's date of birth .....

Any allergies and/or medication .....

Child to complete this section:

☐ I agree to participate in this study including the finger prick blood spot under the conditions set out in the Information Sheet.

☐ I agree to participate in this study but not the finger prick blood spot under the conditions set out in the Information Sheet.

Signature: ..... **Date:** .....

Appendix C Ethnicity, fracture history and physical activity questionnaire

Date .....

The Children's Bone Study

To be completed by parent or guardian

Thank you for participating in this study, if you have any questions please feel free to discuss them with the researcher.

Principal Investigator:
Dr Pamela von Hurst, School of Food and Nutrition, Massey University
Email: p.r.vonhurst@massey.ac.nz

All information you provide will remain strictly confidential

Participant Demographics

First Name of your child

.....

Family Name of your child

.....

Date of birth of your child

.....

Address

.....

.....

Phone (home)

.....

Phone (mobile)

.....

Email

.....

Which ethnic group or groups does your child belong to? (Please √ all that apply)

New Zealand European	□	
Maori	□	
Pacific	□	Please specify_____
South Asian/ Indian	□	
Chinese	□	
Korean	□	
Southeast Asian	□	Please specify_____
Other ethnicity	□	Please specify_____

How would you describe your child's skin colour? (Please ☑ one)

☐	Fair	Easily burns in the sun, doesn't tan
☐	Medium	Can burn, but tans after some sun exposure
☐	Olive	Rarely gets sunburnt, becomes quite tanned in summer
☐	Brown	Light to medium brown, very rarely gets sunburnt
☐	Dark	Very dark brown, never gets sunburnt

Is your child taking any medication or supplements? Please list

.....

.....

.....

Does your child have any chronic illness (for example, asthma) or food allergy? Please list.

.....

.....

.....

Participant fracture history

Has your child ever been diagnosed with any bone fracture (broken bone)?
□ Yes (Please put the details in the table)

□ No (go to next page)

Which bone? For instance: upper right arm, lower left leg	**Age when it happened**	**How did it happen? For instance: Fell out of a tree, fell off skateboard, was doing a cartwheel**
1.		
2.		
3.		
4.		
5.		
6.		

Does your child have brothers and/or sisters who have also had a bone fracture?
□ Yes □ No or □ No siblings

If yes, please note the details below:

Gender of sibling	**Age when fractured**	**Location of fracture**

A large part of how strong our bones are is determined by our genes. Therefore, family history provides important information about the health of your child's bones.
Do any other family members have a history of broken bones or osteoporosis?

Relationship to child	**Broken bones**	**Any diagnosis? At what age? (Osteopenia/osteoporosis)**
Mother		

Father		
Maternal grandmother		
Maternal grandfather		
Paternal grandmother		
Maternal grandfather		

Sunlight exposure

How many hours each day does your child usually spend outside in summer?
During school time.....
During weekends and holidays.....

Which part of his/her body is usually exposed to the sunlight?
□ Only face

□ Only arms

□ Face and arms

□ Only legs

□ Arms and legs

□ Face, arms, and legs

Does he/she use sunscreen cream?
□ Yes - all year round □ Yes - only in summer

□ No (go to next page)

If "Yes" how often does he/she use it?
□ Always

□ Some times

□ Rarely

□ Never

To which part of his/her body does he/she apply sunscreen?

□ Only face
□ Only arms
□ Face and arms
□ Only legs
□ Arms and legs
□ Face, arms, and legs

Physical activity levels

Does your child walk to school?
□ Yes - approximately how far, or how long does the walk take?
……
□ No

Does your child play sport or some other kind of physical activity, like dance?
□ Yes
□ No
What kind of activity?
……
……
How many times each week does he/she do this activity?
……
……
How many hours is he/she active for each time?
……
……

Anything else you would like to tell us about your child?

……
……
……

Thank you for your participation.

Appendix D Data collection form

StudyID:
School:
Date:

Name			
Date of Birth			
Age			
Gender (circle)	Male	Female	
Last drank (mins ago)			
		Complete above this line only	
Height (cm)			
Weight (kg)			
Waist circumference (cm)			
BIA Body Fat %			Remove watches, rings, bracelets and necklaces
QUS T-Score			
QUS Stiffness			
QUS BMD			
Blood Pressure			
Ave Heart Rate (bpm)			
Blood Spot complete			
HbA1c			
Notes			

Appendix E Supplementary Table 1 explaining variances between total group, HbA1c group and no HbA1c group

	Total group n=685	HbA1c group n=451	No HbA1c n=234
	n (%)	n (%)	n (%)
Gender			
Male	309 (45.1)	204 (45.2)	105 (44.9)
Female	376 (54.9)	247 (54.8)	129 (55.1)
Ethnicity			
European	260 (38.9)	158 (35.7)	102 (45.1)
Maori	74 (11.1)	56 (12.7)	18 (8.0)
Pacific Island	144 (21.6)	106 (24.0)	38 (16.8)
South Asian[a]	70 (10.5)	44 (10.0)	26(11.5)
Asian[b]	65 (9.7	42 (9.5	23 (10.2)
South East Asian[c]	25 (3.7)	20 (4.5)	5 (2.2)
Other[d]	30 (4.5)	16 (3.6)	14 (6.2)
BMI (IOTF cut-offs)			
Thin 16-18.5kg/m^2	54 (7.9)	33 (7.4)	21 (9.0)
Normal 18.5-25kg/m^2	455 (66.8)	294 (65.6)	161 (69.1)
Overweight 25-29.9kg/m^2	108 (15.9)	74 (16.5)	34 (14.6)
Obese >30kg/m^2	64 (9.4)	47 (10.5)	17 (7.3)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	10.34 (0.62)	10.40 (0.63)	10.22 (0.58)[h]
Height (m)	1.43 (0.8)	1.44 (0.8)	1.42 (0.8)[h]
Weight (kg)	38.8 (11.2)	39.7 (11.3)	37.3 (10.8)[g]
BMI (kg/m^2)	18.7 (3.9)	18.8 (4.0)	18.3 (3.8)
Waist circumference (cm)	62.1 (10.8)	63.1 (10.8)	60.1 (10.6)[g]
Waist-to-height ratio	.43 (0.07)	.44 (0.07)	.42 (0.07)
Body fat (%)	22.8 (9.3)	22.9 (9.3)	22.5 (9.0)
Physical activity (hours)	3.6 (2.3)	3.6 (2.4)	3.5 (2.3)

BMI Body mass index. IOTF, International Obesity Task Force; HbA1c, glycated haemoglobin; SD, standard deviation; [a]Indian, Pakistani, Sri Lankan, Bangladeshi; [b]Chinese, Taiwanese, Korean, Japanese; [c]Indonesian, Thai, Singaporean, Malaysian, Filipino, Lao; [d]Middle Eastern,

Latin American, African; [g]Statistically significant difference from total group P<0.05, [h]Statistically significant difference from total group P<0.0001

Appendix F Supplementary regression analysis models

Supplementary Table 2. Stepwise multiple regression analysis models for explaining the variance of HbA1c. Independent variables were WtHR, PA and ethnic groups. (n=402)

Model	Coefficient (β)	Standard error β	Adjusted R^2	P-value
(Constant)	28.848	0.964		
WtHR	13.633	2.217	0.108[d]	
South Asian	2.714	0.482	0.153[c]	
Pacific Island	1.340	0.355	0.175[b]	
Asian	1.047	0.466	0.184[a]	0.001

WtHR, Waist-to-height; Stepwise method. [a]F(4, 401) = 23.55, [b]F(3, 401) = 29.42, [c]F(2, 401) = 37.2, [d]F(1, 401) = 49.5

Supplementary Table 3. Stepwise multiple regression analysis models for explaining the variance of HbA1c. Independent variables were BMI, PA and ethnic groups. (n=408)

Model	Coefficient (β)	Standard error β	Adjusted R^2	P-value
(Constant)	30.673	0.688		
BMI	0.229	0.037	0.106[c]	
South Asian	2.755	0.477	0.163[b]	
Pacific Island	1.011	0.356	0.177[a]	0.001

BMI, body mass index; Stepwise method. [a]F(3, 404) = 30.27, [b]F(2, 405) = 40.68, [c]F(1, 406) = 49.37

Supplementary Table 4. Stepwise multiple regression analysis models for explaining the variance of HbA1c. Independent variables were %BF, PA and ethnicity. (n=408)

Model	Coefficient (β)	Standard error β	Adjusted R^2	P-value
(Constant)	32.810	0.370		
% BF	0.095	0.016	0.113[c]	
South Asian	2.471	0.480	0.154[b]	
Pacific Island	1.158	0.350	0.174[a]	0.001

%BF, percentage body fat; Stepwise method. [a]F(3, 404) = 29.62, [b]F(2, 405) = 38.02, [c]F(1, 406) = 52.78