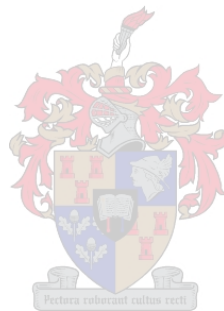# The prevalence of metabolic syndrome and presumed non-alcoholic fatty liver disease in obese children at Tygerberg Hospital.

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Thesis presented in partial fulfillment of the requirements for the Degree of Masters of Medicine in the Faculty of Health Sciences, at Stellenbosch University

Supervisor: Prof. E Zöllner

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Abstract

Introduction: The prevalence of obesity in children and adolescents is increasing worldwide, including in low and middle income countries (LMIC). Childhood obesity is also associated with conditions like metabolic syndrome (MS) and non-alcoholic fatty liver disease (NAFLD).This study looks at the prevalence of these complications and the factors that predict for them in obese children. Finally the effectiveness of the interventions implemented is assessed.

Methods: This is a retrospective cohort study with cross-sectional elements performed at Tygerberg Children's Hospital. Obese and morbidly obese children (under 18years) attending the endocrinology clinic over a 7year period (2008 to 2014) were included in the study. Demographic data, severity of obesity and data on possible predictive factors for MS and NAFLD were collected.

Results: Obese (n=18) and morbidly obese (n=65) children were studied. MS occurred in 45.5 % of the study population. MS was significantly more common in the morbidly obese group (p = <0.001). Possible NAFLD occurred in 63% with no significant difference in incidence between obese and morbidly obese children. No factors predicted the presence of MS or NAFLD in this group of obese children. Factors predicting a decrease in BMI SDS were: BMI at presentation (p = 0.01), duration of follow-up (p = 0.01) and age at presentation (p = 0.08).

Conclusion: MS and NAFLD are as prevalent in obese children seen at Tygerberg Children's Hospital as demonstrated internationally. The follow-up BMI findings suggest that in order to successfully manage childhood obesity in our setting, long-term follow up and early intervention is required. Weight loss after dietary and lifestyle advice occurs more often in patients with a higher BMI.

Afrikaanse abstrak

Inleiding: Die voorkoms van obesiteit in kinders en tieners is wêreldwydaan die toeneem, insluitende in die lae-en middel-inkomste lande. Obesiteit in kinders word geassosieer met toestande soos metaboliese sindroom en nie-alkoholiese vetterige lewersiekte. Hierdie studie kyk na die voorkoms van die komplikasies en die faktore wat hierdie komplikasies sal voorspel in vetsugtige kinders. Ten slotte word die doeltreffendheid van die intervensies wat geïmplementeer word beoordeel.

Metodes: Dit is 'n terugwerkende kohort studie met deursnee-elemente wat by Tygerberg hospitaal gedoen is. Vetsugtige kinders (onder 18 jaar) wat die endokrinologie kliniek bygewoon het oor 'n tydperk van 7 jaar (2008-2014) is ingesluit in die studie. Demografiese data, graad van vetsug en data oor moontlike voorspellende faktore vir metaboliese sindroom en nie-alkoholiese vetterige lewer siekte is ingesamel.

Resultate: Vetsugtige (n = 18) en morbied vetsugtige (n = 65) kinders is bestudeer. Metaboliese sindroom is gevind in 45.5% van die studiepopulasie en is aansienlik meer algemeen in die morbied vetsugtige groep (p = <0.001). Moontlike nie-alkoholiese vetterige lewersiekteis gevind in 63% met geen beduidende verskil in voorkoms tussen vetsugtige en morbied vetsugtige kinders nie. Voorspellende faktore vir 'n suksesvolle uitkoms na intervensie was: liggaamsmassa-indeks by eerste besoek (p = 0.01), tydperk van opvolg (p = 0.01) en ouderdom by eerste besoek (p = 0.08). Geen voorspellende faktore vir die ontwikkeling van metaboliese sindroom of nie-alkoholiese vetterige lewersiekte is in die groep vetsugtige kinders gedemonstreer nie.

Gevolgtrekking: Metaboliese sindroom en nie-alkoholiese vetterige lewer siekte is net so algemeen in vetsugtigekinders gesien by die Tygerberg hospitaal as wat internasionaal gedemonstreer word. Die bevindings dui daarop dat om vetsugtige kinders suksesvol te behandel daar vroeë intervensie moet plaasvind en dat hulle vir lang termyn opgevolg moet word. Kinders met 'n hoër liggaamsmassa-indeks was meer geneig tot 'n suksessvolle uitkoms na intervensie.

Acknowledgements

I would like to thank my supervisor, Prof. Zöllner for the support and guidance with this MMed study.

A special thank you to Prof. Gie for his input in this MMed and my medical career.

This would not be possible without the help from Tonya Esterhuizen at the University of Stellenbosch's Biostatistics department.

Dedications

I dedicate this to my parents who worked hard and sacrificed a lot to give me the opportunity to study medicine and do what I love.

Also to my wife who spent many nights alone while I was working and supported me through difficult times and numerous exams.

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List of Abbreviations

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

BMI: Body mass index

BMI SDS: Body mass index standard deviation score

BP: Blood pressure

CRP: C-reactive protein

CT: Computerised tomography

ECM: Enterprise Content Management

GGT: Gamma-glutamyl transferase

HDL-C: High-density lipoprotein cholesterol

ICD10: The International Statistical Classification of Diseases and Related Health Problems, 10th Revision

LDL-C: Low-density lipoprotein cholesterol

LFTs: Liver function tests

LMIC: Low and middle income countries

MRI: Magnetic resonance imaging

MS: Metabolic syndrome

NAFLD: Non-alcoholic fatty liver disease

NCEP: National Cholesterol Education Program

NHANES: The National Health and Nutrition Examination Survey

PWS: Prader-Willi syndrome

SD: Standard deviation

UK: United Kingdom

USA: United States of America

WC: Waist circumference

WHO: World Health Organisation

Definitions

Adolescents: Girls between 11 and 18 years and boys between 12 and 18 years

Body mass index (BMI): Individual's weight (in kilograms) divided by the length or height (in meters) squared

Hypertension: A systemic blood pressure above the 95th percentile for systolic or diastolic as per National High Blood Pressure Education Program (Using updated values from NHANES III – Appendix 2)

Morbid Obesity: BMI of the patient above 99,6th percentile (2 ⅔ standard deviations) on UK BMI chart (Appendix 1)

Obesity: BMI of the patient above the 98th percentile (2 standard deviations) on UK BMI chart (Appendix 1)

Presumed non-alcoholic fatty liver disease (NAFLD): An elevation above the normal range (as provided by the NHLS laboratory) of at least one of the liver associated enzymes AST, ALT or GGT in obese patients without another cause for liver disease

Screen time: Amount of time per day spent on non-academic activities using an electronic device with a screen e.g. television, computer, tablet, cellphone.

Sedentary lifestyle: A lifestyle with no or irregular physical activity that does not increase energy expenditure substantially above the resting level and includes activities such as sleeping, sitting, lying down, and watching television, and other forms of screen-based entertainment

Type 2 Diabetes: In this study: An obese child with a fasting glucose >7mmol/l and/or random glucose >11,1mmol/l and/or >11,1mmol/l 2hrs after meal or glucose tolerance test

Waist circumference (WC): A WC above the 90th percentile for gender and age is increased as interpreted in accordance with the values from the NHANES III study. The landmark for taking the waist circumference is the high point of the iliac crest in a standing position. (Appendix 3)

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Chapter 1: Introduction

The prevalence of obesity in children and adolescents is increasing worldwide. In Africa the number of children who are overweight or obese has nearly doubled since 1990, increasing from 5.4 million to 10.3 million in 2016. [29] Childhood obesity is associated with significant health problems like insulin resistance and obstructive sleep apnoea and is an early risk factor for increased morbidity and mortality in adults. [11] As the prevalence of obesity increases, so too does the prevalence of the metabolic syndrome (MS). MS prevalence ranges from 18 to 50% in obese paediatric patients. [12]

Non-alcoholicfatty liver disease (NAFLD) is becoming the most common cause of liver disease in children and adolescents. [8] NAFLD is strongly associated with obesity and the MS and is seen as the hepatic manifestation thereof. [19] NAFLD can lead to liver inflammation, fibrosis, cirrhosis and even death.

This study looks at the prevalence of MS and NAFLD in obese children and adolescents seen at Tygerberg Children's Hospital. So far, little data is available for this or any other population group living in a low and middle income country (LMIC). This study also assesses the predictive factors for MS and NAFLD as well as the effectiveness of the interventions to manage obesity in this population.

Chapter 2: Literature Review

South Africa is a country with challenges unique to low and middle income countries (LMIC). In LMIC infectious diseases complicated by HIV and malnutrition are the main causes of mortality and morbidity. In most LMIC faced with a large burden of poverty under nutrition is common, especially amongst children and adolescents. But over the last decades the prevalence of obesity is increasing dramatically especially in the middle and high income groups living in LMIC leading to a dual burden of disease caused by malnutrition. The increase in obesity has been ascribed to the ongoing economic and lifestyle changes in our country. [1]

Childhood obesity is a growing problem globally. Obesity was recently officially classified as a disease by the American Medical Association. In essence due to lifestyle and diet, obesity has become one of the most important public health problems worldwide. In modern times lifestyles are more sedentary. Add to that a high refined carbohydrate and saturated fat diet and an increase in weight and fat tissue is inevitable. Obesity related healthcare, already a large health burden, is set to increase in the future. Comparing the data from the USA's National Health Examination Survey (NHANES) 2009 to 2010 with the earlier data from the 1999 to 2000 survey, an increase in the percentage of overweight children was demonstrated. There was a 5% increase in prevalence of overweight children aged 12 to 19 years, a 4% increase in ages 6 to 11 years and a 3.2% increase in ages 2 to 5 years. [2,3] Globally the same trend has been observed. Even preschool children (under 5 years) have shown a marked increase in obesity over the 20 years from 1990 to 2010 of about 60%. [3] It was estimated that 6.7% of children were overweight or obese in 2010 compared to 4.2% in 1990. [3] Recent estimations put the global number of obese preschool children at approximately 43 million. This estimation was based on cross-sectional surveys performed on 144 countries using the 2006 World Health Organization (WHO) child growth charts. Using these charts, children with a BMI for age >2 Standard deviations (SD) above the mean, were regarded as overweight and >3 SD were obese. [3]

There are limited data concerning childhood obesity available from LMIC where the prevalence of obesity is lower but increasing at a more rapid rate than in high income countries. In a study, specifically looking at preschool children (<5 years age), Southern Africa ranked second amongst developing nations in the United Nations when looking at the prevalence of overweight children (defined as >2 SD weight-for-age). [4] In this study 6.7% of preschool children were classified as overweight. The prevalence was not evenly distributed amongst Southern African countries as data from South Africa was overrepresented and largely responsible for this high proportion. The highest prevalence was seen in North Africa mainly due to the data from Algeria, Egypt and Morocco. [4] A study, performed in 2006, looking at 10195 primary school children in 5 provinces in South Africa, 14% boys and 17.9% girls were found to be overweight. Body mass index (BMI) was measured according to the Cole et al BMI chart of 2000. Cole determined cut-off points for BMI for overweight and obesity among children. This was developed from a sample of 192727 international subjects. This data was used to predict the BMI at different ages that would result in an overweight (BMI 25 kg/m^2) or obese (BMI 30 kg/m^2) subject at theage of 18 years. This was done in an effort to standardise measurements and allow international comparisons. [5] In a recent systematic review of 10 sub-Saharan countries ranging from upper middle to low income countries the prevalence of overweight or obesity ranged from 0.9 to 36.5% in girls and 0.4 to 21.0% in boys ages 5 to 18 years. Overweight or obesity was strongly associated with socio-economic status with children from the highest socio-economic status groups having a 5.28 (95% CI 2.62-10.66) greater risk of being overweight or obese. [24] The high prevalence of overweight and obesity is not isolated to LMIC in sub-Saharan Africa. Studies from India demonstrated similar data. In the Indian study the prevalence of overweight and obesity was 19.3% which had increased from 16.3% over 5 years in children 1 to 18 years. [25]

Obesity can be divided into primary (simple) or secondary obesity. Primary obesity is by definition not explained by any known genetic or metabolic defect and typically has increased height and accelerated bone maturation. Secondary obesity can be caused by endocrine or genetic abnormalities and typically these patients have a short stature and delayed bone maturity. [6] In order to diagnose obesity, the body composition must be determined. Indirect measures to assess excess adipose tissue are used. In the

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clinical setting anthropometry and skin fold thickness is commonly used as they are inexpensive and readily available. Direct means of measuring adipose tissue are not readily available and are expensive. Hydrodensitometry is regarded as the gold standard. Direct measures such as bioimpedence analysis, dual energy x-ray absorptiometry, computer tomography (CT) and magnetic resonance scanning (MRI) are also able to estimate adiposity but are mostly used in research settings. [6,7] The only methods that can accurately assess intra-abdominal fat are CT and MRI. The most commonly used anthropometry based method is the body mass index (BMI). BMI has been proven an appropriate way to measure adiposity and correlates well to the percentage body fat. BMI is less effective in thin and/or athletic children where differences in BMI are largely due to fat-free mass. [7]The BMI correlation with body fat is not precise as BMI cannot distinguish between body fatness, muscle mass and skeletal mass. Other ways of assessing obesity are weight for age and weight for length charts. These measurements are not accurate as they do not take body composition and fat distribution into account.

The classification using BMI was based on the UK charts as compiled by Cole et al in 1995. A measurement above the 98th centile (or 2 SD) is obese and above the 99,6[th] centile is morbidly obese (Appendix 1). These BMI classifications can be confusing at times as USA versions have different nomenclature and definitions. The same patient that is classified as obese in the UK and at our clinic will be labeled as 'overweight' in the USA. There is also no absolute cut-off for BMI in paediatrics as fat mass changes with age. The adult BMI classification (obese being BMI $\geq 30kg/m^2$) can therefore not be directly applied to children. BMI is low in infancy, rises and peaks at about 1year age, falls in early childhood and rises again after 8 years. This is referred to as the obesity rebound. [21] In this study we made use of the standard deviation (BMI SDS) score when following and comparing BMI trends.

Physical measurements such as waist circumference (WC) and waist to hip ratio can also be used in assessing obesity. WC is a marker for intra-abdominal fat and is tightly correlated with hepatic triglyceride content, elevated ALT, liver inflammation and fibrosis indicating non-alcoholic fatty liver disease. [8] WC also indicates higher relative risk for developing obesity associated complications like type 2 diabetes, dyslipidaemia, hypertension and cardiovascular disease. This has been proven in

adults and children (dyslipidaemia and hypertension) [9]. In a paediatric study increased waist circumference and increased abdominal adipose tissue was related to a higher incidence of NAFLD. [10]

In adults there are commonly used standardised criteria for defining and diagnosing metabolic syndrome (MS). The difficulty with making the diagnosis of MS in children is that there is no consensus on the diagnostic criteria that should be used. Another problem is that not all general paeditricians are aware of the existence of this entity. A commonly used definition is the National Cholesterol Education Program (Adult treatment panel [ATP] III). In 2007, the International Diabetes Federation (IDF) attempted a definition of paediatric metabolic syndrome using age-specific diagnostic criteria. In practice at our endocrinology clinic at Tygerberg Children's Hospital we use the National Cholesterol Education Program (NCEP) criteria for adolescents to diagnose MS.

Current NCEP criteria define the MS as the presence of any three of the following five traits:

- Abdominal obesity, defined as a waist circumference ≥90th percentile

- Serum triglycerides ≥1,2 mmol/L

- Serum HDL cholesterol <1 mmol/L

- Blood pressure ≥90th percentile for age and length

- Fasting plasma glucose (FPG) ≥5,6 mmol/L

MS increases the risk of cardiovascular and various other complications. [11] Although MS is associated with obesity, this does not mean that it is a causative association as MS can also occur in lean children and adults. [11] Associations among blood pressure, obesity, and impaired glucose tolerance have been described since the 1920's. The associated occurrences of these conditions led to the recognition of them as a syndrome, Metabolic Syndrome, in 1988. Widespread recognition of this syndrome followed. It was assumed at that time and later verified that the syndrome can be modified by changes in body weight and physical activity. [12] Among obese children, the prevalence of the MS is high and increases with worsening obesity. A 2004 USA based study of 439 obese, 31 overweight, and 20 normal-weight children

and adolescents (between 4 and 20 years) showed that MSwas present in 39% and 50% of the moderately and severely obese subjects respectively. None of the overweight or normal weight children in this study had MS. [13] In a longitudinal study performed by the National Heart, Lung and Blood Institute it was demonstrated that obesity and increasing visceral fat were risk factors for developing childhood MS. The Growth and Health Study enrolled girls aged 9 and 10 years (n=1192) from USA and followed them for 10 years from 1988 to 1998. MS (defined by Adult treatment panel III criteria) was present in 0.2% at baseline. At ages 18 to 19 years of age MS was present in 3.5% of black and 2.4% of white girls. For every increase of 1 cm in waist circumference the risk of developing metabolic syndrome increased by 7.4%. [14]

The complications of MS and obesity are multiple. Two of the main complications are insulin resistance leading to type 2 diabetes and cardiovascular disease. Other obesity associated complications include: polycystic ovarian syndrome with infertility, gynaecomastia, growth acceleration, pseudo-Cushing's, pseudotumorcerebri, obstructive sleep apnoea, cholelithiasis and orthopaedic related disorders like Blount's disease and slipped capital femoral epiphysis.

NAFLD is not part of the MS definition but is considered the hepatic manifestation thereof.The pathophysiology is not completely understood. A combination of genetic and environmental factors is likely responsible for the development of NAFLD. Insulin resistance plays a role in the processes leading to increased free fatty acid and triglyceride accumulation in the hepatocytes. The gold standard for making the diagnosis is a liver biopsy. NAFLD presents with a wide variety of pathologies. The pathology can range from simple fatty accumulation in the liver to non-alcoholic steatohepatitis which has been associated with liver fibrosis and cirrhosis in childhood and adolescences. [19,26] Although the exact cause of NAFLD is unknown, it is associated with obesity. As obesity increases throughout the world, so NAFLD is increasing. In obese children NAFLD prevalence as high as 70 to 80% has been reported. [27] The exact prevalence is however not known and there is a paucity of data from LMIC concerning this disease.

Although the diagnosis is confirmed with liver biopsy, this is not feasible or indicated in the majority of cases. Various non-invasive diagnostic criteria have been explored which include analysis of liver enzymes and anti-inflammatory cytokine release analysis as well as imaging. Imaging modalities include liver ultrasound, CT and MRI scanning. All these tests have their limitations with varying degrees of sensitivity and specificity. CT (sensitivity 82%; specificity 100%) and MRI (sensitivity 100% and specificity 90.4%) are not feasible due to availability and cost. [18] Ultrasound is readily used but is operator-dependent and lacks the ability to objectively quantifying liver steatosis. Ultrasound detects steatosis with high sensitivity only if more that 30% of hepatocytes are involved. [23] A 2008 study shows that a computerized calculated hepatorenal index could objectively quantify liver steatosis in cases where as little as 5% of hepatocytes were affected. Depending on the percentage of steatosis the sensitivity ranged from 90% to 100% with specificity between 90% and 93%. [23] This is not available at our institution. Transient elastography (Fibroscan), which measures liver stiffness non-invasively, is used in identifying advanced fibrosis in patients with hepatitis B and hepatitis C. Recent studies show high sensitivity and specificity for identifying fibrosis in NAFLD, but it has a high failure rate in individuals with a higher BMI and is not specific to the cause of the fibrosis. [15] This is also not readily available at our institution.

The diagnosis of NAFLD according to the American guidelines requires that

- there is hepatic steatosis by imaging or histology,

- there is no significant alcohol consumption,

- there are no competing aetiologies for hepatic steatosis, and

- there are no co-existing causes for chronic liver disease.

Scoring systems like The NAFLD Fibrosis Score has been proposed in an attempt to more accurately diagnose advanced NAFLD non-invasively. It is based on six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio). The score has a 67% sensitivity and 97% specificity for predicting advanced liver fibrosis and a 90% sensitivity and 60% specificity in excluding advanced fibrosis. [15] In our setting a screening test that is readily available, easy to perform and cost effective must be used. In our clinic any raised serum liver enzyme levels above normal

cut-off values (ALT, AST and/or GGT), in the absence of any other cause for liver damage, is seen as possible NAFLD.

Serum alanine aminotransferase (ALT) has been studied as a screening for NALFD. [8] An Italian study in 2007 of 268 obese children looked at predictors of NAFLD. ALT was found to be the most specific when compared to aspartate aminotransferase (AST), gamma-glutamyl-transferase (GGT), cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, uric acid, glucose, glucose during oral glucose tolerance testing, insulin, insulin during oral glucose tolerance testing, insulin resistance as estimated by homeostasis model assessment (HOMA) or C-reactive protein (CRP) as a single measurement. The specificity of ALT was 81% at levels more than 30 U/L (95% CI 0.67 – 0.77) and 89% if more than 40 U/L (95% CI 0.6 – 0.7). Sensitivity ranged from 41 to 64% at the same corresponding levels. [16] The analyzer used in the study was not stated. A 2013 study from Hawaii, using patients aged 1-19 years being seen at their endocrinology clinic for suspected metabolic syndrome, used ALT as a screening parameter for liver disease in MS. 68% boys and 57% girls were found to havean elevated ALT. In this study lower cut-off limits were used (25.8 U/L for boys and 22.1U/L for girls). [17]

The degree of ALT elevation however does not correlate with the presence or severity of histological findings of NAFLD. ALT cut-off values have also been debated. The Screening ALT for Elevation in Today's Youth (SAFETY) study done in America in 2010 took results from 43 different USA hospitals with a total of 982 children aged 1-17 years after excluding all children with liver disease, obesity and those using potential hepatotoxic medications. This study found ALT cut-off values are set too high for the reliable detection of paediatric chronic liver disease and NAFLD. In the National Health and Nutrition Examination Survey (NHANES) study, the 95th percentile levels for ALT in healthy weight, metabolically normal, liver disease–free boys were 25.8 U/L and girls 22.1 U/L. [18] NAFLD has widespread implications for healthcare. NALFD is currently the most common cause of chronic liver disease in childhood and adolescence in the USA.   As obesity in the paediatric age group increases, NAFLD has become increasingly prevalent. [19] The question however remains if a similar situation exists in our clinic.

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In addition to physical health concerns, obesity in childhood can also lead to social as well as psychological problems. These include low self-esteem, depression, bullying, social isolation and discrimination.

Simple obesity and with it MS is an almost entirely preventable disease. When MS is present, lifestyle modification alone can be a very effective intervention. [28] The emphasis is on behavioural change, a calorie-controlled diet and increased physical activity. Should comorbid conditions be present, then they must be treated appropriately. Pharmacological intervention might be needed to control hypertension or type 2 diabetes. Surgical interventions e.g. gastric binding or bypass might be required in extreme cases.

Probably the most feasible option in our setting is a conservative approach of diet and exercise to obtain and maintain optimal weight. The importance of weight management to prevent progression of MS and its complications were demonstrated by the Coronary Artery Risk Development in Young Adults (CARDIA) study. In this observational study of 5115 young adults (ages 18 to 30 years), increasing BMI over 15 years was associated with progression of MS components compared with young adults who maintained stable BMI over the study period, regardless of baseline BMI. [20] A 2012 systematic review on the effectiveness of lifestyle modifications in childhood obesity looked at data from 1975 to 2010. 38 Studies were included. The results support the importance of lifestyle interventions as acritical part of treatment of childhood obesity. Weight loss was greater when the duration of treatment was longer (>6 months). Lifestyle interventions produced significant weight loss compared with no treatment control groups when looking at BMI ($-1.25kg/m^2$, 95% confidence interval [CI] -2.18 to -0.32; p = 0.008) and the BMI Z-score (-0.10, 95% CI-0.18 to -0.02; p = 0.01). Lifestyle interventions also produced significant improvement in triglyceride (p = 0.0003) and LDL-C (p = <0.0001), but not HDL-C (p = 0.22). It is not clear whether the effects were due to the weight loss alone or attributable to the otheraspects of lifestyle intervention. Comparing outcomes is difficult as there are various strategies of implementing dietary and activity changes. [28]

It is clear from the literature that childhood obesity is increasing in both highly developed countries as well as in LMIC. As the prevalence of obesity is increasing so

are MS and NAFLD. The increase in these complications associated with obesity has tremendous health implications in LMIC, where the health budgets are constrained by the economy. Early recognition and prevention of obesity and its complications are required. To date, there is minimal data available on childhood obesity and MS with regards to the population in the Western Cape. This includes children attending our clinic at Tygerberg Children's Hospital. It is important to establish the prevalence of MS and NAFLD in obese children in our setting and to determine whether dietary and lifestyle advice are effective in controlling obesity and thus its complications.

Chapter 3: Aim of the investigation

3.1 Research justification:

From the literature review it is clear that the prevalence of obesity in children and adolescents is rising throughout the world. The situation in low and middle income countries (LMIC) is no different than in other parts of the world and even children less than 5 years of age are becoming more obese. Obesity in children is associated with numerous well known complications including systemic hypertension, asthma, insulin resistance and dyslipidaemia resulting in increased morbidity and use of health facilities. [13] In contrast to adult patients the metabolic syndrome (MS) is less well recognised in children and adolescents. The MS as diagnosed by clinical findings and laboratory results is in turn associated with non-alcoholic fatty liver disease (NAFLD). As obesity and the MS have increased in children worldwide so has the prevalence of NAFLD. NAFLD is now estimated to be the most common cause of chronic liver disease in children and adolescents. If not correctly managed NAFLD causes long-term liver disease including liver fibrosis and cirrhosis. The impact that NAFLD has on health services in LMIC has not been estimated as there is a paucity of data concerning this disease. This study serves as a baseline study for our clinic at Tygerberg Children's Hospital. It documents the prevalence of MS and NAFLD in obese clinic patients from the population we serve. It also measures the success of current management. This data can then be used to compare future interventions. Identifying factors which predict a drop in BMI could lead to modification of management practices and local guidelines.

3.2 Research hypotheses:

1. MS and NAFLD are common in obese children attending the paediatric endocrinology clinic at Tygerberg Children's Hospital, Western Cape, South Africa.

2. Lack of weight loss following dietary and lifestyle advice is predicted by a higher initial BMI, poor social circumstances and low income, number of caregivers and duration of follow-up.

3.3 Research question:

What is the prevalence of the MS and NAFLD in obese children attending the paediatric endocrine clinic in a tertiary hospital in the Western Cape, South Africa and what is the effect on BMI of management strategies in the same clinic?

3.4 Primary research objectives:

1. To determine the prevalence of the MS in obese children attending the endocrine clinic in Tygerberg Children's hospital.

2. To determine the prevalence of possible NAFLD in obese children attending the endocrine clinic in Tygerberg Children's hospital.

3. To determine the change in BMI in response to dietary and lifestyle advice.

3.5 Secondary objectives:

1. To determine the prevalence of the MS in obese children and adolescents in different age bands(<2 years; 2 to 5 years; 5 to 18 years).

2. To determine the prevalence of NAFLD in obese children and adolescents in different age bands(<2 years; 2 to 5 years; 5 to 18 years).

3. To determine factors that predicts the presence of the MS.

4. To determine factors that predicts the presence of possible NAFLD.

5. To determine factors that predict a drop in BMI SDS.

Chapter 4: Methodology

4.1 Setting:

The study was carried out at the Tygerberg Children's Hospital. The hospital is a tertiary care hospital situated in the Western Cape serving a population of approximately 1.5 million people. Of the children living in the Western Cape 10% live below the absolute poverty line. The majority of the children referred to the hospital come from impoverished communities. The hospital admits approximately 12000 children per annum (2014) and 630 children were seen in the endocrinology outpatient service (2014).

4.2 Study Design:

Retrospective cohort study.

4.3 Time frame:

7 year period from January 2008 to December 2014.

4.4 Study population:

Children and adolescents younger than 18 years of age attending the endocrinology clinic at the Tygerberg Children's Hospital were screened to see if they met the inclusion criteria of the study. ICD10 codes E66.0, E66.8 and E66.9 were used to identify the patients.

4.4.1: Inclusion Criteria:

All patients identified from the paediatric endocrine clinic who were confirmed to be obese (BMI above 98th percentile or 2 standard deviations on UK BMI chart)) or morbidly obese (BMI above 99,6th percentile or 2 ⅔ standard deviations on UK BMI chart) were included in the study.

4.4.2 Exclusion Criteria:

The following patients were excluded:

- Prader-Willi syndrome (PWS)

- other genetic conditions associated with obesity

- untreated hypopituitarism

- when the medical records of the patient could not be retrieved.

4.5 Data collection:

The data collected include the demographic data and relevant measurements: weight, height, BMI, and waist circumference (WC). Medical data included systemic blood pressure, data on co-morbid diseases and relevant special investigations. Relevant special investigations included serum enzymes indicative of liver disease (AST,ALT,GGT), serum triglyceride levels, blood glucose levels including fasting serum glucose and results of an oral glucose tolerance test if performed. Body mass index standard deviation score (BMI SDS) was calculated at the first and last clinic visit of the collection period. BMI SDS was calculated using a UK based website. (http://www.phsim.man.ac.uk)

4.6 Case definitions used:

4.6.1 Obesity: BMI of the patient above the 98th percentile (>2 SD) on UK BMI chart (Appendix 1).

4.6.2: Morbid Obesity: BMI of the patient above 99,6[th] percentile (>2 ⅔SD) on UK BMI chart (Appendix 1).

4.6.3: Metabolic syndrome (MS): Using NCEP criteria for adolescents, MS is defined in the presence of any three of the following:

- Abdominal obesity, defined as a WC ≥90th percentile for age

- Serum triglycerides ≥1,2 mmol/L

- Serum HDL cholesterol <1 mmol/L

- Blood pressure ≥90th percentile for age and length

- Fasting plasma glucose (FPG) ≥5,6 mmol/L

4.6.4 Non-alcoholic fatty liver disease (NAFLD): Is diagnosed in the presence of obesity if one or more liver enzyme levels are elevated. Enzymes used were AST, ALT and GGT and levels were according to the NHLS laboratory's normal limits for age using the Siemens Advia 1800 analyser.

4.7 Interventions:

Patients were counselled on lifestyle at the clinic. This included exercise, diet and limiting screen time. They were also seen by the dietician with advice on appropriate portions and a balanced meal.

4.8 Data Management:

The hospital's patient database was searched for all pediatric patients with a diagnosis and ICD-10 code (E66.0, E66.8, E66.9) for obesity or morbid obesity. The data sources were the medical records department, the clinic's record system and the hospital's Enterprise Content Management (ECM) system. Data was captured on a case recording form (Appendix 4). Each case was allocated a unique case number which was used to protect the patient's identity. The data was then transferred to an Excel spreadsheet for analysis.

4.9 Data Analysis:

Data analysis was done in collaboration with the Biostatistics Department at the University of Stellenbosch. Stata version 14 was used to analyse the all the data. A p-value <0.05 was considered as statistically significant. The outcome of prevalence of MS is described as a proportion and 95% confidence interval. Predictors of MS were assessed in bivariate analysis using independent samples t-tests and Pearson's chi square tests. Multivariable logistic regression analysis was used to assess the independent effects of the predictors. In order to assess the effect of the intervention, to account for differing time of follow up, rates of change was computed for each individual by dividing the change in their standard deviation score over time by the time period of observation. Rates were modelled using a Poisson regression analysis to

assess the effects of predictors such as number of siblings, income and other socio-demographic risk factors.

4.10 Ethical considerations:

Ethical approval was obtained from the Committee for Human Research at the University of Stellenbosch. Reference number S15/03/056. (Appendix 5)

4.11 Limitations:

A retrospective study like this relies on adequate documentation and clinical records by the attending medical doctors. The most important limitation was the lack of data. This ranged from the necessary blood testing not being done to physical measurements not being taken e.g. waist circumference. This is due to the lack of a standard clinical information form or protocol to guide doctors in training who rotate through the clinic.

Not all 3 liver enzymes were done on all the patients therefore patients with possible NAFLD might have been missed.

Another limitation with every retrospective study is that it assumed that measurements were taken correctly e.g. blood pressure being measured with the correctly sized cuff.

Tanner staging was not recorded. For this study puberty was defined by age. Assessment of pubertal onset by age is less accurate as there is considerable variation in the onset of puberty.

The patients included are only those seen in our hospital clinic. These patients are only from our drainage area which is a low income community. The findings of this study may therefore not be generalised to the population as a whole or to the more affluent strata of the society.

Chapter 5: Results

Based on the ICD10 codes, 134 patients were found in the hospital database. Of these, 44 were found not to match the study definition for obesity. Of the remaining 90, 7 were excluded from the study as one patient had Prader-Willi Syndrome (PWS) and 6 were diagnosed with untreated hypopituitarism. The remaining 83 were included in the study. (See diagram 1)

Of the 83 obese children 39 (47%) did not have all the parameters measured for diagnosing or excluding metabolic syndrome (MS). The remaining 44 obese and morbidly obese children were used to examine the relationship of obesity and MS. Of the 83 obese and morbidly obese patients included in the study, 15 (18%) did not have a waist circumference (WC) recorded, 2 patients did not have a WC greater than 90th percentile and 22 (26.5%) did not have liver functions performed. This then left 44 patients that were obese or morbidly obese with a recorded WC who also had liver functions done.

Of the 83 obese and morbidly obese patients in the study 46 (55.4%) had at least one of the liver enzymes done. Of these 29 (63%) were abnormal. Of the 29 with abnormal LFT's 4 were obese and 25 morbidly obese. These patients were the study sample used to investigate the relationship between obesity and NAFLD. (See diagram 2)

25 patients were preschool children of which 12 were under the age of 2 years. The average age was 7.7 years (8 months to 16 years 3 months). Patient demographics are shown in Table 1.

On presentation the meanBMI SDS was 3.39 with the median being 3.1. Figure 1 demonstrates the distribution of the BMI SDS at presentation. Table 2 illustrates the severity of obesity by age.

Diagram 1: Flow diagram of patients studied to determine the relationship between obesity and metabolic syndrome

n = 134 patients with Obese/Morbid obese ICD10 code

44 patients with wrong diagnosis or not obese by definition

n = 90 patients

Excluded 7 patients: 1 with PWS and 6 with untreated hypopituitarism

n = 83 patients used in study

39 patients did not have all the parameters to diagnose MS

n = 44 patients

n = 20 patients with MS

n = 24 patients without MS

n = 9 patients with abnormal LFTs

30

Diagram 2: Flow diagram of patients included in the study to determine the relationship between obesity and non-alcoholic fatty liver disease
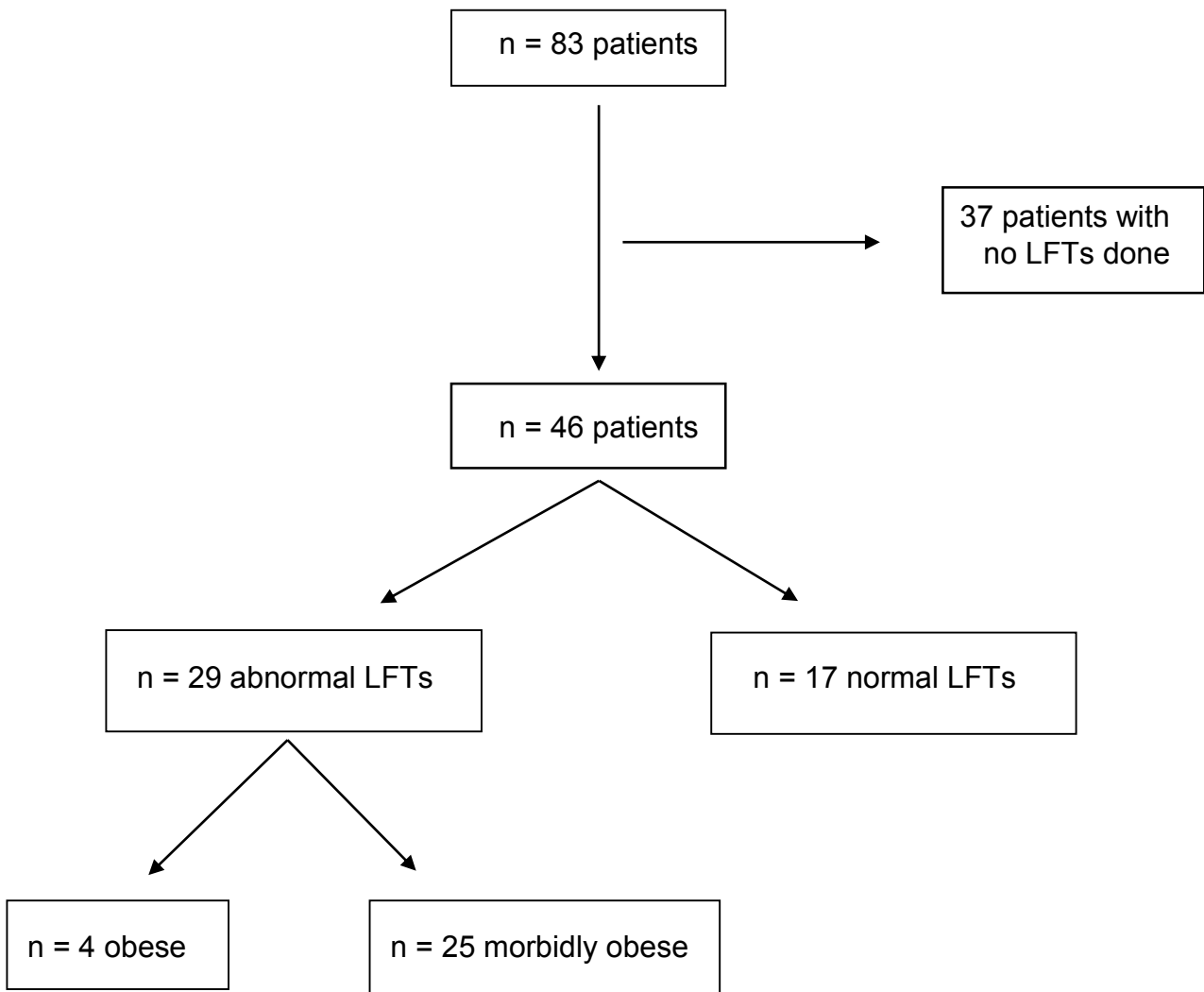
Table 1: Demographics of enrolled patients

Patients (n=83)		n	% of total patients
Age	<2 years	12	14.5
	2-5 years	14	16.8
	5-18 years*	57	68.7
Gender	Female	34	41.0
	Male	49	59.0
Severity	Morbidly obese	65	78.3
	Obese	18	21.7
Race	Coloured	59	71.1
	White	13	15.7
	Black	10	12.0
	Indian	1	1.2

*Adolescents made up 18.1% (n=15) of all patients; Adolescents were defined by age: girls 11 to 18 years (n=5) and boys 12 to 18 years (n=10).
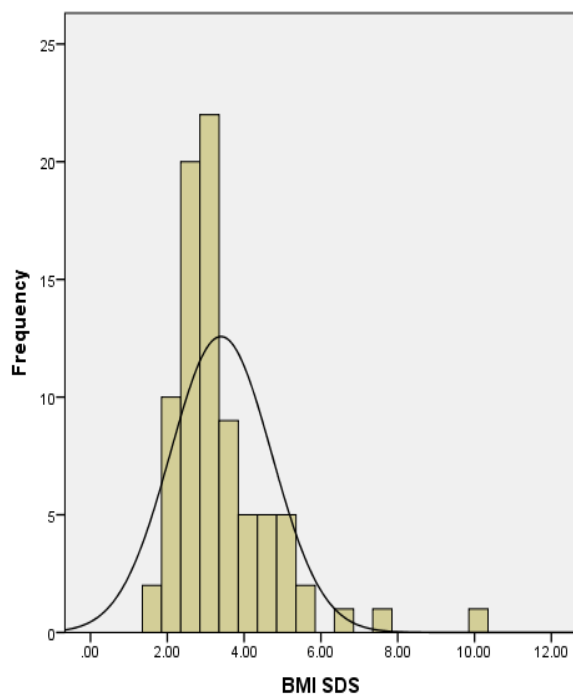
Fig 1: Distribution of BMI SDS at presentation

There were 44 children with obesity and morbid obesity who had all the parameters measured to diagnose or exclude MS. The mean age of this population was 7.5 years(range = 8 months to 16 years 3 months). Of these 44 children who met the criteria 20 (45.5%) had MS of which 14 were obese and 30 morbidly obese. MS was present in 4 (28.5%) of obese and 16 (53.3%) of the morbidly obese patients (p = <0.001). Of the 10 adolescents, where all the parameters were available, 5 (50%) had MS and they were all morbidly obese. All the patients (n = 20) with MS had a WC above the 90th percentile. Table 3 shows the prevalence of MS by age and severity of obesity.

Table 2: Severity of obesity by age

Age	Obese n = (%)	Morbidly obese n = (%)	Total n = (%)
<2 years	2 (2.4)	10 (12)	12 (14.4)
2-5 years	2 (2.4)	12 (14.5)	14 (16.9)
6-18 years*	14 (16.9)	43 (51.8)	57 (68.7)
Total	18 (21.7)	65 (78.3)	83 (100)

*Adolescent group: obese n=3 and morbidly obese n=12

Table 3: Distribution of MS[1] by age and severity of obesity

Age	Obese n = (%)	Morbidly obese n = (%)	Total n = (%)
<2 years	0 (0)	3 (15)	3 (15)
2-5 years	1 (5)	2 (10)	3 (15)
6-18 years[2]	3 (15)	11(55)	14 (70)
Total	4 (20)	16 (80)	20 (100)

1 = Metabolic syndrome; 2 = Adolescent group: 5 with MS were all morbidly obese

Predictive factors for Metabolic Syndrome

Household income median showed a difference of R1473 between the group with MS (R3625) and those without MS (R2125). Even though the MS group has about a 70% higher income, both groups still fall in the lower income class. There was no significant difference of MS when comparing the different income groups (p = 0.51).

There was no significant difference found when comparing single to multiple caregivers (p = 0.45). No significant difference was found in screen time between children with MS and those without MS with the median being 3 hours (range = 1 – 8 hours) per day (p = 1.0). MS group had a median BMI SDS of 3.45 at presentation with the non-MS group median being 3.0. The BMI SDS at presentation was higher in the group with MS but was not found to be statistically significant (p = 0.12). Residential area played no role in predicting for MS. The majority of our patients come from low income communities and the patients included came from all parts of our drainage area.

Table 4: Putative predictive factors for MS

Variable	p-value
Household income	0.51
Number of caregivers	0.45
Screen time	1.0
Initial BMI SDS	0.12

The prevalence of NAFLD in obese children

Of the 83 patients included, 46 (55%) had liver function testing done. The 46 patients consisted of 7 obese and 39 morbidly obese children. Of these 46 patients 29 (63%) had abnormal liver function results. 4 out of the 7 obese (57.1%) and 25 of the 39 morbidly obese (64.1%) children had abnormal LFT's. There is no significant difference between the two groups. (p = 0.72)

Table 5: Obesity and possible NAFLD by age

Age	n	Severity of obesity	Normal LFTs	Possible NAFLD
<2 years	8	Obese	0	1
		Morbidly obese	2	5
2-5 years	5	Obese	0	0
		Morbidly obese	1	4
6-18 years*	33	Obese	3	3
		Morbidly obese	11	16

*Possible NAFLD in 5 adolescents: 2 obese and 3 morbidly obese

Predictive factors for possible NAFLD

Of the 83 patients included in the study 29 had possible NAFLD.There was no significant difference between the possible NAFLD group and the group with normal LFTs regarding hypertension (p = 0.65) and dyslipidaemia (p = 0.45). Insulin resistance, assessed as abnormal high fasting glucose, could not be demonstrated possibly due to limited number of patients that had the test done.

Waist circumference (WC) however did show a relationship with possible NAFLD but was also not statistically significant. 68 (82%) of the 83 patients in the study had a WCrecorded. Of these 66 (97%) were above the 90th percentile.

Only 44 of the 66 patients with a WC >90th percentile had LFT results available and of these 28 (63%) had abnormal LFTs and thus possible NAFLD.

Of the 29 patients in the study with possible NAFLD 26 (89%) had a WC>90th percentile.

44 patients that had all necessary parameters measured in order to make the diagnosis of MS. 9 patients (45%) with MS had possible NAFLD and 15 patients (62%) without MS had possible NAFLD. There was no significant difference between the two groups (p = 0.31).

Relationship between MS and possible NAFLD

Of the 29 patients with deranged liver enzymes 4 (14%) were obese and 25 (86%) morbidly obese. Possible NAFLD occurred in 57% of obese and 66% of morbidly obese patients suggesting that there may not be a significant relationship between the severity of obesity and NAFLD. This relationship was not formally evaluated in this study. Of the 29 patients with possible NAFLD only 9 (31%) were diagnosed to have MS (Table 6). This difference is not statistically significant (p = 0.3).

Table 6: MS and possible NAFLD by age

Age	MS with possible NAFLD n = (%)	MS without possible NAFLD n = (%)	Total n = (%)
<2 years	2 (10)	1 (5)	3 (15)
2-5 years	0 (0)	3 (15)	3 (15)
6-18 years*	7 (35)	7 (35)	14 (70)
Total	9 (45)	11 (55)	20 (100)

* 3 adolescents with MS had possible NAFLD

Effectiveness of intervention

Changes in the BMI SDS of the 83 patients in this study were as follows: 48 (57.8%) decreased, 12 (14.5%) increased and 23 (27.7%) remained unchanged. Factors predicting a favourable outcome following interventions to manage the patient's obesity was investigated (Table 7). Figure 2 shows age at booking visit compared to changes in BMI SDS as an interval plot depicting 95% confidence intervals. The younger patients showed a decrease in BMI SDS which was clinically significantly different when compared to the older group of patients that showed an increase in their BMI SDS. The variable 'age of first visit' was approaching significance (p = 0.08). The duration of follow-up was significant (p = 0.01). A longer follow-up duration showed improved outcome with decrease in BMI SDS. Follow-up duration ranged from 3 months to 6.42 years (mean = 1.5 years). Figure 3 shows duration of follow-up compared to changes in BMI SDS depicted in a box-and-whisker plot. BMI SDS at presentation was also significant (p = 0.01). The initial BMI SDS was higher in the group that showed a decrease in BMI SDS. The mean BMI SDS in the group that showed a decrease in BMI SDS was 3.3. This was significantly higher than the mean BMI SDS of 2.8 found in the study group where the BMI SDS increased or remained unchanged.

Household income (p = 0.71), screen time (p = 0.77), caregiver (p = 0.94), number of siblings (p = 0.14), number of dietician visits (p = 0.17), presence of MS (p = 0.05) and the number of times the patient was seen by the paediatric endocrinologist when compared to the paediatric registrar was not related to the effectiveness of the interventions to reduce BMI SDS (p = 0.16).

Table 7: Factors predicting a decrease in BMI SDS

Variable	p-value
Household income	0.71
Number of caregivers	0.94
Number of siblings	0.14
Screen time	0.77
Seen by endocrinologist vs registrar	0.16
Number of dietician visits	0.17
Metabolic syndrome	0.05
Initial BMI SDS	0.01*
Age of first visit	0.08
Duration of follow-up	0.01*

*Significant
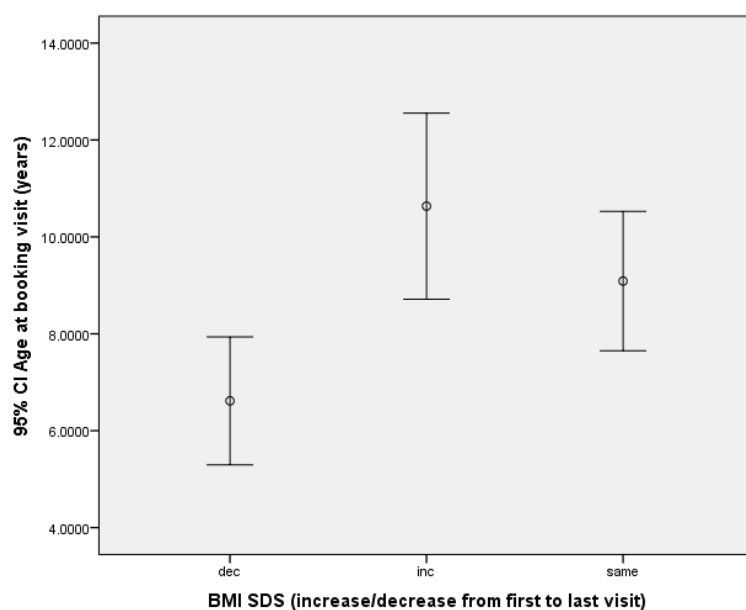
Fig. 2: Effectiveness of intervention – Age at booking versus BMI SDS change
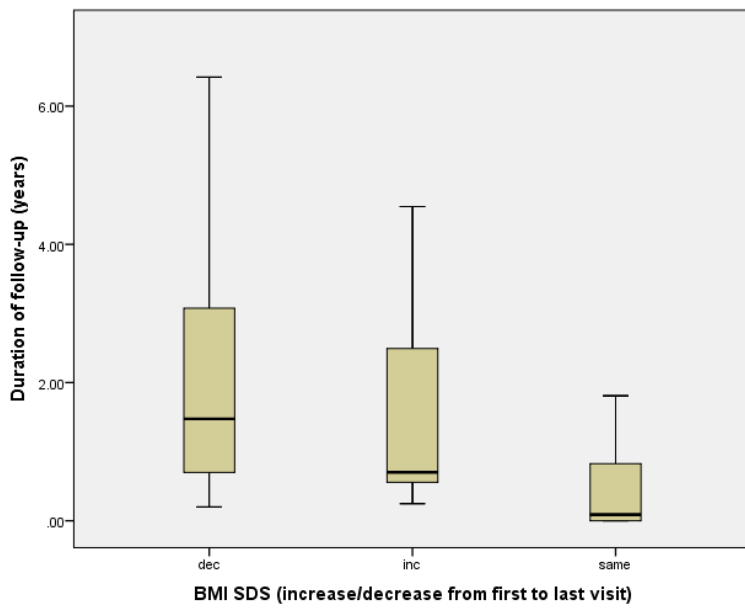
Fig. 3: Effectiveness of intervention – Follow-up duration versus BMI SDS change

Table 8: Relationship between duration of follow-up and BMI SDS change

Duration of follow-up	BMI SDS decrease n = (%)	BMI SDS increase n = (%)	BMI SDS unchanged n = (%)
<6 months	8 (16.7)	2 (16.6)	15 (65.2)
6 months – 1 year	10 (20.8)	5 (41.7)	7 (30.5)
>1 year	30 (62.5)	5 (41.7)	1(4.3)
Total	48 (100)	12 (100)	23 (100)

Chapter 6: Discussion

There are a number of studies reporting the prevalence of obesity in LMIC which varies from 6.7% to 19.3%. [4,5,25] The trend in LMIC is following the trends previously reported in high income countries but the rate of increase in obesity is currently higher in LMIC while the rates of increase in obesity seem to be plateauing in developed countries. [25] In spite of these many reports on the rising prevalence of obesity in children in LMIC there are few reports of the prevalence of MS and NAFLD occurring in these populations.MS and NAFLD are strongly associated with obesity and these entities have been widely reported in the obese population of high income countries. This study only looked at obese patients in a hospital setting. In the study group used 21.7% were obese and 78.3% morbidly obese. This difference is likely due to our clinic being a referral unit and morbid obesity is more likely to be referred.

MS occurred in 28.5% of obese and 53.3% of morbidly obese children and it was significantly more common in children with morbid obesity (p<0.001). This is in keeping with international data. A USA based study demonstrated MS prevalence in 38.7% of obese and 49.7% of morbidly obese children and adolescence aged 4 to 20 years. The USA study also found that each half-unit increase in the Z score for the BMI was associated with a significant increase in the risk of the MS (odds ratio, 1.55; 95 percent confidence interval, 1.16 to 2.08). [13] This study thus confirms that MS occurs in obese children in our setting.

Possible NAFLD occurred in 63% of the patients in our study. This is in keeping with international results from the USA where the prevalence of NAFLD was found to be 60% in obese and 90% in morbidly obese adults at autopsy. [19] There was no significant difference in the prevalence of NAFLD demonstrated between the obese (57.1%) and morbidly obese (64.1%) children and adolescents in our study. In patients with MS 45% had possible NAFLD. The true prevalence of paediatric NAFLD in the community is not known. International studies also using transaminase as diagnosis for possible NAFLD found a prevalence of 29% in obese children, but when using lower cut-off limits for ALT (from the SAFETY study) the prevalence of possible NAFLD increased to 63%. [17,19] Some studies in developed countries i.e. USA have reported

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prevalence of possible NAFLD as high as 70% to 80% in obese children. [27] In the current study the correlation was higher when comparing possible NAFLD with obesity and an increased WC than it was comparing possible NAFLD with MS. Of the patients with possible NAFLD 89% had a WC>90th percentile. Of the patients with possible NAFLD 14% were obese and 86% morbidly obese. Only 31% of patients with possible NAFLD also had MS.

Confirming NAFLD by liver biopsy is not feasible in either developed or developing countries. For this reason, non-invasive diagnostic screening tests have been proposed and are widely used, indicating possible NAFLD. As with MS, it is worrying that NAFLD has not been widely reported from LMIC. The implications for health service delivery in these resource limited countries have not been considered. The development of non-invasive tests with high specificity and sensitivity for NAFLD would be important. In our setting cost and availability are limiting factors. Ultrasound techniques such as the hepatorenal index together with the use of liver function testing might be a viable option in the future and should be studied in our setting. [23]

In most studies MS and NAFLD are not considered in young children. In this study 3 out of 9 (33%) of the children younger than 2 years of age fulfilled the criteria allowing for the diagnosis of MS to be made. Similarly in this age group 5 out of 7 (71%) met the criteria of possible NAFLD. This might indicate that these complications occur in younger children in our setting. This worrying observation needs further investigation and demonstrates the need for early intervention in young children who are obese and referral where indicated.

Factors predicting the presence of MS and NAFLD were assessed. Demonstrating predictive factors can help with improving and planning future interventions. In this study we were unable to confirm any suspected risk factors that predicted the presence of MS. A higher BMI SDS at presentation was found in the group with MS but was not statistically significant. This might be due to the small sample size. Similarly, we were unable to demonstrate risk factors that predicted for NAFLD. This is also likely due to the small sample size especially in the younger age range. MS was not found to be a

predictor of possible NAFLD but of note is that of the patients with a WC>90th percentile, 63% had possible NAFLD.

This study did demonstrate duration of follow-up and initial BMI to be significant predictive factors for weight loss following lifestyle intervention. This is in keeping with international data from Australia and the UK that the outcome is better when obese children are followed up for more than 6 months after implementation of the management interventions [28]. In our study 83.3% of patients that were followed up for >1 year showed a decrease in BMI SDS as compared to 38.2% who followed up for<1 year.

The age of presentation was approaching significance when comparing the group that demonstrated a change in BMI compared to the unchanged and increased BMI groups. But if only the 'increase in BMI SDS' group is compared to the 'decrease in BMI' group there is a significant difference between the groups as shown in Figure 2. This study suggests that there is an increased chance of success in the patients that present at <8 years of age. If the patient presented for the first time over the age of 8 years they either maintain or even increase their BMI SDS.

There were certain factors for predicting a favorable outcome following intervention that were expected to be significant, but in the current study were not. The small number of patients in the study was most likely the reason for this. Another reason for screen time not being significant could be due to patients underestimating the actual time spent using electronic devices. Income is confounded by the fact that all the patients come from the same socio-economic class. The number of dietician visits and number of times seen by the endocrinologist were also not found to be statistically significant but can be explained. Almost all the patients were seen by a dietician at least once and got the necessary education. Dietary input would most likely also have been given by the doctor. These patients were all also seen at least once by the endocrinologist and/or got discussed with him on most visits if seen by a doctor in training. The endocrinologist would then assist the doctor in decision making and management of the patients. This likely contributes to the finding of no significance of

these factors. Decrease in BMI SDS was more likely with a higher initial BMI and this was statistically significant.

Chapter 7: Conclusion

The prevalence of MS and NAFLD in this study is in keeping with international data suggesting that these complications of obesity are as common in our setting as reported worldwide. MS was more common in morbidly obese children. Even children < 2 years met the criteria of MS and possible NAFLD. Prevalence of possible NAFLD using elevated liver enzymes as a screening tool was similar to international data suggesting that we can continue using this practice. Lower cut-off limits might need to be implemented. Although not reaching significance, possible NAFLD seemed to be more closely associated with obesity and increased waist circumference than with MS. Children referred and treated before 8 years and followed-up for >1 year are more likely to show a decrease in BMI. With the increasing numbers of obese children it is impossible to treat all these patients in a tertiary clinic. They should ideally be treated at their local health institutions. It is time consuming and a multidisciplinary approach is needed. This is not feasible for many parts of our drainage area at present.

Recommendation:

All children and adolescent patients who are obese should be screened for MS and NAFLD. Early referral and a prolonged management period are needed in order to achieve decrease in BMI SDS. A bigger study to investigate whether WC is a suitable screening tool for NAFLD in our setting is needed. As liver enzymes are not specific for NAFLD, additional methods to detect NAFLD like ultrasound and hepatorenal index should also be used. A large community based study to establish true prevalence of MS and NAFLD in obese children of the community should be done. This study can also be used to establish predictive factors for both entities. How obesity is managed at primary and secondary level should be reviewed and efforts to prevent the scourge of obesity, and with that MS and NAFLD, should be improved.

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Appendixes
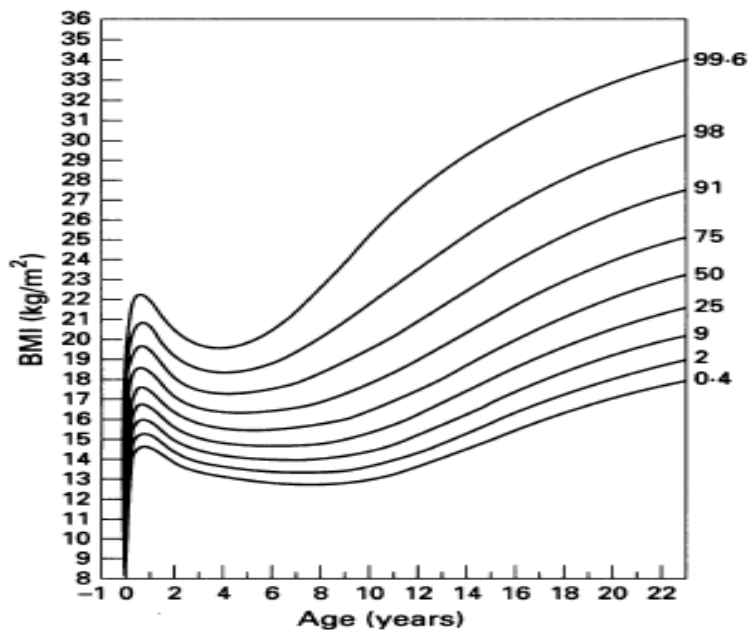
Appendix 1

BMI percentile charts

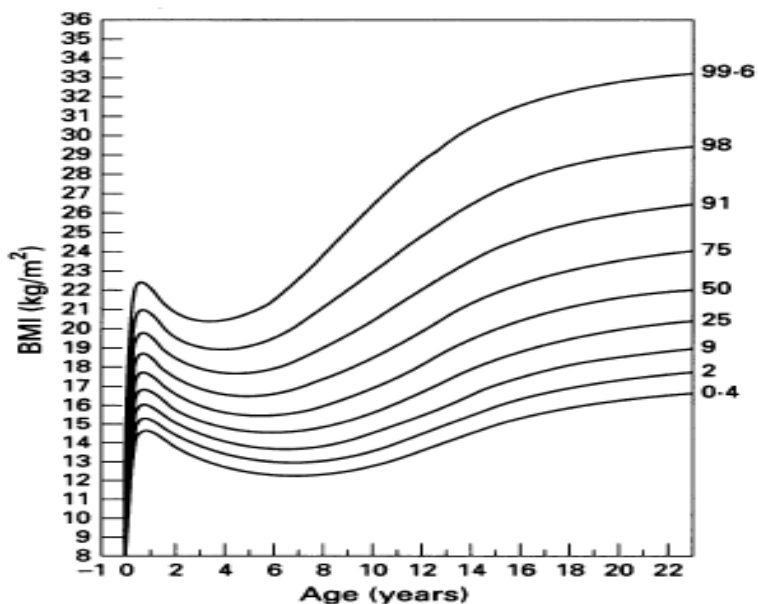*Figure 1   Nine centiles for BMI in British boys 1990. The centiles are spaced two thirds of an SD score apart.*

Figure 2   Nine centiles for BMI in British girls 1990. The centiles are spaced two thirds of an SD score apart.

Appendix 2

Bloodpressure tables

TABLE 3. BP Levels for Boys by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

TABLE 4.   BP Levels for Girls by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

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Appendix 3

Waist circumference table as for NHANES III

Table IV. Estimated value for percentile regression for all children and adolescents combined, according to sex

	Percentile for boys					Percentile for girls				
	10th	25th	50th	75th	90th	10th	25th	50th	75th	90th
Intercept	39.7	41.3	43.0	43.6	44.0	40.7	41.7	43.2	44.7	46.1
Slope	1.7	1.9	2.0	2.6	3.4	1.6	1.7	2.0	2.4	3.1
Age (y)										
2	43.2	45.0	47.1	48.8	50.8	43.8	45.0	47.1	49.5	52.2
3	44.9	46.9	49.1	51.3	54.2	45.4	46.7	49.1	51.9	55.3
4	46.6	48.7	51.1	53.9	57.6	46.9	48.4	51.1	54.3	58.3
5	48.4	50.6	53.2	56.4	61.0	48.5	50.1	53.0	56.7	61.4
6	50.1	52.4	55.2	59.0	64.4	50.1	51.8	55.0	59.1	64.4
7	51.8	54.3	57.2	61.5	67.8	51.6	53.5	56.9	61.5	67.5
8	53.5	56.1	59.3	64.1	71.2	53.2	55.2	58.9	63.9	70.5
9	55.3	58.0	61.3	66.6	74.6	54.8	56.9	60.8	66.3	73.6
10	57.0	59.8	63.3	69.2	78.0	56.3	58.6	62.8	68.7	76.6
11	58.7	61.7	65.4	71.7	81.4	57.9	60.3	64.8	71.1	79.7
12	60.5	63.5	67.4	74.3	84.8	59.5	62.0	66.7	73.5	82.7
13	62.2	65.4	69.5	76.8	88.2	61.0	63.7	68.7	75.9	85.8
14	63.9	67.2	71.5	79.4	91.6	62.6	65.4	70.6	78.3	88.8
15	65.6	69.1	73.5	81.9	95.0	64.2	67.1	72.6	80.7	91.9
16	67.4	70.9	75.6	84.5	98.4	65.7	68.8	74.6	83.1	94.9
17	69.1	72.8	77.6	87.0	101.8	67.3	70.5	76.5	85.5	98.0
18	70.8	74.6	79.6	89.6	105.2	68.9	72.2	78.5	87.9	101.0

Appendix 4

Case recording form

1. Patient name and folder number

2. Patient case number

3. Date of birth (DD/MM/YEAR); Age

4. Gender (M/F)

5. Race (W/C/B/O)

6. Height (m)

7. Weight (kg)

8. BMI

9. BMI SDS

10. BMI (Increase/Decrease)

11. Waist circumference (cm)

12. Blood pressure (mm Hg)

13. Triglycerides (mmol/L)

14. HDL (mmol/L)

15. Fasting glucose (mmol/L)

16. ALT (U/l)

17. AST (U/l)

18. GGT (U/l)

19. Metabolic syndrome (Y/N)

20. NAFLD (Y/N)

21. Dietician (Y/N)
    – no of visits

22. Endocrinologist (Y/N)
    -no of visits

23. Duration of follow-up

24. No of visits to tertiary centre

Appendix 5

<u>Ethics Approval</u>

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Approval Notice
Response to Modifications- (New Application)

07-Jul-2015
Hough, Wayne W

Ethics Reference #: S15/03/056
Title: The prevalence of metabolic syndrome and fatty liver disease in obese children at Tygerberg Hospital.

Dear Dr Wayne Hough,

The Response to Modifications - *(New Application)* received on 22-May-2015, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **07-Jul-2015** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **07-Jul-2015 -07-Jul-2016**

Please remember to use your **protocol number** (S15/03/056) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 219389207.

Included Documents:
CV E Zollner
Declaration E Zollner
MOD_Protocol
Declaration W Hough

Checklist

MOD_Cover letter_Response to modifications

Protocol

Protocol Synopsis

CV W Hough

Application form

Sincerely,

Mertrude Davids
HREC Coordinator
Health Research Ethics Committee 2