THE CONTRIBUTION OF LIFESTYLE TO THE RISK OF TYPE 2 DIABETES MELLITUS IN AFRICANS IN TRANSITION IN THE NORTH WEST PROVINCE

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I dedicate this study to my late father, Daan Meyer, for always believing in me
and to my husband, Gert, for his support and patience.

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SUMMARY

Objectives:

The comprehensive objective of this study was to investigate the lifestyle-related risk factors for type 2 diabetes mellitus in a sample of "apparently healthy" Africans of the North West Province of South Africa to consequently provide information for suitable prevention programmes. The hypothesis tested was that with urbanisation changes in lifestyle will increase risk factors for type 2 diabetes in Africans.

The first objective was to determine the impact of urbanisation on the risk markers of glucose intolerance and type 2 diabetes and to investigate the influence of changes in lifestyle during urbanisation.

The second objective was to characterise the occurrence and levels of the known risk factors for glucose intolerance and type 2 diabetes in the sample population.

The third objective was to describe the unique characteristics of subjects that were identified with type 2 diabetes (fasting blood glucose concentration >7.1 mmol/l) at a relatively young age (<45 years).

Background and motivation:

South Africa is currently experiencing an urbanisation process coupled with westernisation that is characterised by changes in economical status, lifestyle and eating patterns. Worldwide this process is associated with an alarming increase in the incidence of diabetes mellitus and other lifestyle associated diseases (Hakeem *et al.*, 1999). According to Steyn (1995) 28.5% of all deaths in South Africa can be attributed to chronic diseases of lifestyle and according to Mollentze *et al.* (1993) South Africa is on the verge of a diabetes mellitus epidemic.

The natural development of type 2 diabetes includes changes in glucose tolerance and insulin secretion (Bradley, 1991; Lebovitz, 1999). A degree of genetic predisposition and a wide variety of environmental factors are the common causes of most forms of type 2 diabetes (De Fronzo *et al*, 1997; Morwessel, 1998). Risk factors for type 2 diabetes include insulin resistance, obesity, fat distribution, changes in nutrient intakes, a decrease in physical activity levels and stress (Lebovitz, 1999). All the associated mechanisms are, however, not clear yet. It is possible that all population groups do not have the same risk factors. Therefore, it is important to study different ethnic and population groups.

The treatment of lifestyle associated diseases such as type 2 diabetes places a tremendous financial and labour burden on the already overburdened medical and health services. More information on the development and progress of these diseases and the risk factors associated with them, may result in better prevention. This may decrease the burden on the health services and increase the quality of life of potential patients.

Study design:

A cross sectional epidemiologic study design with a convenience - but representative sample of 1854 "apparently healthy" volunteers, 15 years and older, were used to investigate the risk factors of glucose intolerance and type 2 diabetes.

Methods:

This study was done as part of the THUSA (Transition and Health during Urbanisation of South Africans) project, with permission from the Ethics Committee of the PU vir CHO and in collaboration with the North West Department of Health. A representative sample of 1854 black residents of the North West Province voluntarily participated in the project, after giving informed consent. Pregnant and lactating women and subjects known to suffer from any disease or using chronic medication were excluded. These subjects were grouped according to age, gender and stratum (level of westernisation). The strata included rural people, farm workers, "squatters", urban middle class and urban upper class. All the participants underwent a glucose tolerance test. A glucose load of 50g was used. Fasting and two-hour post-load venous blood samples were taken. Serum was prepared for the determination of glucose and insulin concentrations. Glucose was determined enzymatically with the *DAX Profile* method and insulin with the *IBL I25-insulin RIA* method. The clinical profile, blood pressure, nutritional status, anthropometry, demographic information, medical history, smoking habit and alcohol use of the subjects were determined by skilled field workers and researchers, using standardised methods and tested questionnaires.

The data were computerised and cleaned. Statistical analyses were performed using SPSS software and the Excel programme. Means and standard deviations were calculated and associations and relationships between risk factors and -markers were determined. Significant differences and correlations between continuous variables were calculated. Partial correlations were done to determine associations between the variables and fasting blood glucose, fasting insulin and two-hour glucose levels. Univariate analyses were used to calculate the effect of stratum on the markers of type 2 diabetes (serum glucose and -insulin levels), before and after controlling for lifestyle factors (age, smoking habit, body

mass index, waist-to-hip ratio and physical activity). The effect of stratum on these lifestyle factors was further determined with multivariate analyses.

The values from the glucose tolerance test were used to divide the subjects who participated in 1996 in a normal glucose tolerance group, or in one of two glucose intolerant groups. The World Health Organisation criteria were used. The first glucose intolerant group consisted of subjects that would have been diagnosed as glucose intolerant according to the World Health Organisation. The second glucose intolerant group consisted of those subjects that had at least one value during the glucose tolerance test that fell within the limits of type 2 diabetes.

Results:

In general the results showed that these black subjects did not have the same patterns of risk factors or -markers for type 2 diabetes than other population groups. It further seemed that the risk factors or -markers differed between males and females. The effect of stratum (level of urbanisation) on the markers of type 2 diabetes was dependent on lifestyle factors (age, smoking habit, body mass index, waist-to-hip ratio and physical activity). In the men, physical activity was an important factor, while age, the smoking habit, waist-to-hip ratio and especially fasting insulin levels were important in females. The effect of stratum on the two-hour glucose level seemed to be dependent upon all the lifestyle factors that were tested for the males, but not for the females. This is not in accordance with the general accepted notion that changes in lifestyle during modernisation (westernisation) are, to a large extent, responsible for the development of type 2 diabetes.

Type 2 diabetes mellitus was also observed in individuals younger than 45 years, especially in lean males. An analysis of the results showed that in females this phenomenon was probably the result of overweight. In the males it was not the result of overweight, but probably of an iron overload (in this case it is probably diabetes secondary to hemochromatosis and not type 2 diabetes). These findings have to be investigated in future studies and young, lean, black males with hyperglycaemia have to be tested for iron overload. Eating a typical Western diet, rich in saturated fats and animal protein did not emerge as a risk factor, probably because even the most westernised subjects, followed a prudent diet. A low intake of several micronutrients showed significant associations with glucose intolerance, suggesting that forms of malnutrition may be an important factor in these subjects.

Conclusion:

It was concluded that in these subjects, urbanisation and consequently westernisation, had a significant impact on the risk markers of glucose intolerance and type 2 diabetes, which were sometimes but not always, connected to the changes in certain lifestyle-related risk factors. The observed differences in the risk factors between males and females, as well as the role of iron overload in certain males, have important applications for the development of preventive and screening programmes, as well as for the diagnosis and treatment of type 2 diabetes in this population group.

OPSOMMING

Doelstellings:

Die omvattende doel van hierdie studie was om die lewensstyl-verwante risikofaktore vir tipe 2 diabetes mellitus in die "oënskynlik gesonde" swart proefpersone van die Noord-Wes Provinsie van Suid-Afrika te interstice, om sodoende inligting vir geskikte voorkomingsprogramme te verskaf. Die hipotese is gestel dat veranderinge in lewensstyl tydens verstedeliking die riskofaktore vir tipe 2 diabetes in die swart bevolking sal laat toeneem

Die eerste doelwit was om die impak van verstedeliking op die risikomerkers van glukose-intoleransie en tipe 2 diabetes te bepaal, en om die invloed van veranderinge in lewensstyl tydens verstedeliking te ondersoek.

Die tweede doelwit was om die voorkoms en vlakke van die bekende risikofaktore vir glukose-intoleransie en tipe 2 diabetes in die steekproef-populasie te karakteriseer.

Die derde doelwit was om die unieke eienskappe van proefpersone wat op 'n relatiewe jong ouderdom (< 45 jaar) met tipe 2 diabetes (vastende bloedglukose konsentrsie > 7.1 mmol/L) geïdentifiseer is, te beskryf.

Agtergrond en motivering:

Suid - Afrika beleef tans 'n verstedelikings- met gepaardgaande verwestering, wat deur veranderinge in ekonomiese status, lewenswyse en eetpatrone gekenmerk word. Hierdie proses word wêreldwyd met 'n kommerwekkende toename in die voorkoms van diabetes mellitus en ander lewensstyl-verwante siektes geassosieer (Hakeem et al., 1999) Volgens Steyn (1995) kan 28.5% van alle sterftes in Suid Afrika aan chroniese siektes van lewenstyl toegeskryf word en volgens Mollentze *et al.* (1993) is Suid Afrika waarskynlik op die randjie van 'n diabetes mellitus epidemie.

Die natuurlike ontwikkeling van tipe 2 diabetes sluit veranderinge in glukosetoleransie en insuliensekresie in (Bradley, 1991; Lebovitz, 1999). 'n Mate van genetiese predisposisie en 'n wye verskeidenheid omgewingsfaktore is die gesamentlike oorsaak van die meeste vorme van tipe 2 diabetes (De Fronzo *et al.*, 1997; Morwessel, 1998). Risikofaktore vir tipe 2 diabetes sluit insulienweerstand, obesiteit, vetverspreiding, verandering in nutriëntinnames, verlaging in fisiese aktiwiteitsvlakke en stres in (Lebovitz, 1999). Die betrokke meganismes is egter nog nie almal duidelik nie. Dit is moontlik dat alle

bevolkingsgroepe nie dieselfde risikofaktore het nie. Daarom is dit belangrik om verskillende etniese- en bevolkingsgroepe te bestudeer.

Die behandeling van lewensstyl-verwante siektes soos tipe 2 diabetes plaas 'n geweldige finansiële- en arbeidslas op die reeds oorlaaide mediese- en gesondheidsdienste. Meer inligting oor die ontstaan en verloop van hierdie siektes en die risikofaktore wat daarby betrokke is, mag beter voorkoming tot gevolg hê, en kan die las op gesondheidsdienste aansienlik verminder en die lewenskwaliteit van potensiële pasiënte verhoog.

Studie-ontwerp:
'n Dwars-deursnit epidemiologiese studie-ontwerp met 'n gerieflikheids - maar verteenwoordige steekproef van 1854 "oënskynlik gesonde"vrywilligers, 15 jaar en ouer, is gebruik om die risikofaktore van glukose-intoleransie en tipe 2 diabetes te ondersoek.

Metodes:
Die studie is gedoen as deel van die THUSA (Transition and Health during Urbanisation of South Africans) projek, met toestemming van die Etiekkomitee van die PU vir CHO en in samewerking met die Noord-Wes Departement van Gesondheid. 'n Verteenwoordigende monster van 1854 "oënskynlik gesonde"swart inwoners van die Noord-Wes Provinsie het vrywillig, na ingeligde toestemming, aan die projek deelgeneem. Swanger en lakterende vroue, siek persone of dié wat chroniese medikasie gebruik het is uitgesluit.Hierdie proefpersone is gegroepeer volgens ouderdom, geslag en stratum (vlak van verwestering). Die strata het plattelandse inwoners, plaaswerkers, "plakkers", stedelike middelklas en stedelike hoëklas ingesluit. Al die deelnemers het 'n glukose toleransietoets ondergaan. ' n Glukoselading van 50g is gebruik. Daar is vastende en twee-uur na-beladings veneuse bloedmonsters getrek. Serum is berei vir die bepaling van glukose en insulien konsentrasies. Glukose is ensiematies met behulp van die *DAX Profile*-metode bepaal, en insulien met behulp van 'n *IBL I25-insulin RIA* metode. Die kliniese profiel, bloeddruk, voedingstatus, antropometrie, demografiese inligting, mediese geskiedenis, rookgewoonte en alkohol gebruik van die proefpersone is met behulp van gestandaardiseerde metodes en getoetsde vraelyste deur opgeleide veldwerkers en navorsers bepaal.

Die data is gerekenariseer en ontfout. Die SSPS sagteware en die Excel program is gebruik vir die statistiese verwerkings. Gemiddelde en standaard afwykings is bereken en assosiasies en verbande tussen risikofaktore en -merkers is bepaal. Betekenisvolle verskille en korrelasies tussen kontinue veranderlikes is bereken. Parsiële korrelasies is gedoen om die verbande tussen die veranderlikes en vastende bloedglukose, vastende insulien en twee-

uur glukosevlakke te bepaal. Enkelvoudige analises is gebruik om die effek van stratum op die merkers van tipe 2 diabetes (serumglukose en insulienvlakke) te bereken voor en nadat daar gekontroleer is vir lewensstylfaktore (ouderdom, rook gewoonte, liggaamsmassa-indeks, middel-tot-heup verhouding en fisiese aktiwiteit). Die effek van stratum op hierdie lewensstyl faktore is verder met meervoudige analises bepaal.

Op grond van die waardes wat tydens die glukose toleransietoets verkry is, is die proefpersone wat in 1996 deelgeneem het, ingedeel in 'n normale glukose toleransie groep, of in een van twee glukose intolerante groepe. Die Wêreld Gesondheidsorganisasie se kriteria is gebruik. Die eerste glukose intolerante groep het bestaan uit proefpersone wat volgens die Wêreld Gesondhiedsorganisasie as glukose-intolerant gediagnoseer sou word. Die tweede glukose-intolerante groep het bestaan uit proefpersone waarvan een van die glukose waardes binne die grense vir tipe 2 diabetes geval het.

Resultate:
Oor die algemeen het die resultate getoon dat hierdie swart proefpersone nie diesefde patrone van risikofaktore of -merkers vir tipe 2 diabetes het as ander bevolkingsgroepe nie. Dit het verder geblyk dat die risikofaktore of -merkers vir mans en vrouens verskil. Die effek van stratum(vlak van verwestering) op die merkers vir tipe 2 diabetes was afhanklik van lewensstylfaktore (ouderdom, rookgewoonte, liggaamsmassa-indeks, middel-tot-heup verhouding en fisiese aktiwiteit). In die geval van die mans was fisiese aktiwiteit 'n belangrike faktor, terwyl ouderdom, die rookgewoonte, middel-tot-heup verhouding en veral vastende insulienvlakke by vrouens belangrik kon wees. In die geval van die mans, het die effek van stratum op die twee-uur glukose vlak geblyk om afhanklik te wees van al die lewensstyl faktore wat getoets was. Dieselfde was nie die geval by die vrouens nie. Dit is teenstrydig met die algemene aanvaarde siening dat die verandering in lewensstyl tydens modernisering (verwestering) tot 'n groot mate vir die onwikkeling van tipe 2 diabetes verantwoordelik is.

Tipe 2 diabetes mellitus is ook by individue jonger as 45 jaar waargeneem, veral by maer mans. 'n Ontleding van die resultate het getoon dat hierdie verskynsel in die geval van vrouens waarskynlik die gevolg was van oorgewig. In die geval van mans was dit nie die gevolg van oorgewig nie, maar word dit waarskynlik deur 'n ysteroorbelading veroorsaak (in hierdie geval is dit waarskynlik diabetes sekondêr tot hemochromatose en nie tipe 2 diabetes nie). Hierdie bevindings moet in toekomstige studies verder ondersoek word, en jong, maer, swart mans met hiperglukemie, moet ook vir ysteroorbelading getoets word. Die volg van 'n tipiese Westerse diëet, ryk aan versadigde vette en dierlike proteien het nie as 'n riskofaktor tevoorskyn getree nie, waarskynlik omdat selfs die mees verwesterde

proefpersone, 'n omsigtige diëet met lae vetinnames gevolg het. ' n Lae inname van verskeie mikronutriente het betekenisvolle assosiasies met glukose intoleransie getoon, wat suggereer dat vorme van wanvoeding 'n belangrike faktor in hierdie proefpersone mag wees.

Gevolgtrekking:

Die gevolgtrekking is gemaak dat verstedeliking en gevolglik verwestering, in hierdie proefpersone'n betekenisvolle impak op die risikomerkers van glukose intoleransie en tipe 2 diabetes het, wat meestal maar nie altyd nie, met die verandering in sommige lewensstyl-geassosieerde risikofaktore verband hou. Die waargenome verskille in die risikofaktore tussen mans en vroue, asook die rol van ysteroorbelading in sommige mans, het belangrike toepassings vir die onwikkeling van voorkomings en siftingsprogramme, asook vir die diagnosering en behandeling van tipe 2 diabetes in hierdie bevolkingsgroep.

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aa	amino acids
ADA	American Diabetes Association
ADM	atypical diabetes mellitus
ADSA	Association for Dietetics in South Africa
AIDS	Acquired Immunity Deficiency Syndrome
ALP	alanine phosphatase
ALT	alanine amino transferase
AST	aspartate amino transferase
BMI	body mass index
CHD	coronary heart disease

CHO	**carbohydrates**
CK	**creatine kinase**
Cu	**copper**
CVD	**cardiovascular disease**
DM	**Diabetes mellitus**
DM1	**type 1 diabetes mellitus**
DM2	**type 2 diabetes mellitus**
FBG	**fibrinogen**
Fe	**iron**
FFA	**free fatty acids**
GDM	**gestational diabetes mellitus**
GI	**glycaemic index**
GIP	**glucose dependent insulinotrophic peptide**
GIT	**glucose intolerance**
GIT1 group	**glucose intolerance group 1**
GIT2 group	**glucose intolerance group 2**
GTT	**glucose tolerance test**
HDL	**high density lipoprotein**
HPLC	**high pressure liquid chromatography**
HT	**hypertension**
IFG	**impaired fasting glucose**
Ir	**insulin receptor**
IR	**insulin resistance**
K	**potassium**
Kg	**kilogram**
KJ	**kilojoules**
LDH	**lactic dehydrogenase**
LDL	**low density lipoprotein**
Mg	**magnesium**

MIDD	**maternally inherited diabetes and deafness**
Mn	**manganese**
MODY	**maturity onset diabetes of the young**
MPC	**macromolecular protein complex**
MUFA	**monounsaturated fatty acids**
Na	**sodium**
NGT	**normal glucose tolerance**
ODF	**older females with glucose intolerance group 2**
ODM	**older males with glucose intolerance group 2**
OGF	**older females with glucose intolerance group 1**
OGM	**older males with glucose intolerance group 1**
ONF	**older normal females**
ONM	**older normal males**
P	**phosphate**
PAI-1	**platelet activation inhibitor - 1**
PS-ratio	**polyunsaturated - saturated fat ratio**
PUFAS	**polyunsaturated fatty acids**
RDA	**recommended dietary allowances**
RIA	**radioimmunoassy**
SD	**standard deviation**
TC	**total cholesterol**
TG	**triglycerides**
THUSA	**Transition and health during Urbanisation of South Africans**
TIBC	**total iron binding capacity**
TK	**tyrosine kinase**
TRSFA	**trans fatty acids**
UP	**University of Pretoria**
USA	**United States of America**
VLDL	**very low density lipoprotein**

WHO	**World Health Organisation**
YDF	**young females with glucose intolerance group 2**
YDM	**young males with glucose intolerance group 2**
YGF	**young females with glucose intolerance group 1**
YGM	**young males with glucose intolerance group 1**
YNF	**young normal females**
YNM	**young normal males**
Zn	**zinc**

CHAPTER 1
INTRODUCTION

1.1 Background and motivation

Diabetes mellitus (DM) is a complex syndrome characterized by a relative or absolute deficiency of insulin or its functions, leading to hyperglycaemia (WHO Study group, 1985; Lebovitz, 1999). Information regarding the occurrence of DM in Africa is scarce (Krolewski & Warram 1985) but Walker *et al.* (1994) reported that the incidence of type 2 diabetes and other chronic diseases are increasing among adult Africans. According to some researchers, the prevalence of type 2 diabetes in urbanised Africans in South Africa is increasing and may reach epidemic proportions in the near future (Naik, 1992; Levitt *et al.*, 1993). Recent studies indicate that the prevalence of type 2 diabetes in the African population is approximately 4% in the rural population and between 6 and 8% in the urban population (Omar *et al.*, 1993). Studies show a prevalence of between 5 and 7% in Indians, and of 8.7% in coloureds (Steyn *et al.*, 1985; Fritz, 1995). One study reported that DM is already one of the major causes for hospitalisation in African women in South Kwa Zulu-Natal (Walker *et al.*, 1994).

South Africa is not the only country experiencing an increase in the prevalence of type 2 diabetes. The disease affects large numbers of people in a wide range of ethnic groups of all social and economic levels throughout the world (Zimmet *et al.*, 1997; Raman-Kutty *et al.*, 1999; Middelkoop *et al.*, 1999; Okada *et al.*, 2000). At least 100 million people worldwide suffer from type 2 diabetes, and by the year 2010, an estimated 215 million people will have the disease (Zimmet *et al.*, 1997). The incidence of DM varies across the world and also differs between communities living in the same location (Jenkins & Jenkins, 1994; Jaber *et al.*, 1995). Exceptionally high rates of type 2 diabetes have been documented in populations who have changed from a traditional to a modern lifestyle (Jenkins & Jenkins, 1994; Zimmet *et al.*, 1997). The condition is affecting as many as 5 - 10% of persons in both Japan and Western countries and the incidence in Japan is increasing (WHO Study group, 1985; Suehiro *et al.*, 1995). Type 2 diabetes affects an estimated 12% of 40- to 74-year-old people in the United States of America (USA) (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). DM and its associated risk factors are considered major public health problems in the USA (Pfeifer *et al.*, 1996; White & Nanan, 1999). DM is among the five leading causes of death by disease in most countries, but these statistics may be greatly under represented (Exempt *et al.*, 1997).

Apart from the health impact, the economic cost of diabetes and its complications is enormous, both for health care and loss of productivity to society (Zimmet *et al.*, 1997). Over the next

decade, following the initial phase of the type 2 diabetes epidemic, macrovascular and microvascular complications will emerge as a major threat to future public health throughout the world with huge economic and social costs (Zimmet *et al.*, 1997). Thus, DM is an increasing problem worldwide and it places an increasing load on health and medical facilities. Knowledge of the epidemiology of type 2 diabetes is essential for the national planning and development of preventive and healthcare programmes (Pfeifer et al., 1996).

Several risk factors for the development of type 2 diabetes have been identified, including age, obesity, increased energy intake, physical inactivity, insulin resistance (IR), glucose intolerance (GIT), and impairment of β-cell function (Kahn, 1985; Mollentze *et al.*,1992; Jenkins & Jenkins, 1994; Lindquist *et al.*, 2000). Clearly, environmental factors play an important role in the development of DM, but the role of genetic predisposition cannot be ignored. GIT is probably an intermediate state between normal glucose tolerance and type 2 diabetes (Mollentze *et al*, 1992). Conditions, for example IR, preceding type 2 diabetes which that are involved in its pathogenesis most likely occur during this stage (Naik, 1992; Lebovitz, 1999).

In the past many diseases occurring frequently in Western populations were seldom found in African populations South of the Sahara (Trowell, 1978). Although these diseases have partly unknown and multi factorial aetiologies, some of them have clearly defined risk factors. These risk factors generally occur in association with a Western diet coupled with a sedentary lifestyle (Trowell, 1978). Mollentze *et al.* (1992) found the incidence of type 2 diabetes in a semi-urbanised African population to be 5.1%. Taylor *et al.* (1991) found similar results in a group of urbanised Africans in Johannesburg where 6.6% of the population had either DM or GIT . According to Gresse and Vorster (1992) there are also indications that an increasing number of urbanised Africans are visiting the diabetic clinics in South African hospitals. Albertse (1988) found the incidence of diabetes in rural African women visibly lower compared to their urbanised counterparts. Environmental factors inherent in modern Western civilization encompassing urbanisation and changes in lifestyle and dietary habits have been incriminated as largely responsible for the differences observed (Naik, 1992; Singh *et al.*, 1999). There is clear evidence that a reasonably affluent lifestyle is a prerequisite for high levels of type 2 diabetes (Barker, 1995). Probably even more variability in population frequency rates will appear as new populations increase in affluence (Barker, 1995).

Type 2 diabetes is one of the chronic diseases that can be prevented by changes in lifestyle and diet, if high risk groups can be identified (Jenkins *et al.*, 1980; Shaheen & Flemming, 1987). By decreasing body weight both IR and hyperinsulinaemia are decreased or removed and the disease can be controlled (Carmena, 1990; Connel & Thomas-Doberson, 1991). The current diabetic diet has a nutrient composition similar to the diet of the rural African population of South-Africa (Jenkins *et al.*, 1980; Silvis *et al.*, 1989). This diet (high in fibre, low in fat) has a low glycaemic

index (GI) resulting in slower absorption of carbohydrates (CHO) and thus a lower blood glucose response (Mann, 1997). It also protects against chronic diseases and obesity, is economical and easy to follow. It seems to be the optimal treatment, as well as an optimal tool to prevent development of diabetes in Africans (Silvis *et al.*, 1989). The change from this prudent diet to the diet of affluence associated with urbanisation and Westernisation contributes to changes in the metabolism which may play a role in the development of chronic diseases. It is hypothesised that the urbanite does not adapt very well to the modern concentrated high CHO foods such as sugar and white flour (James, 1997a; Sprietsma, 1999). The increasing consumption of fat decreases CHO tolerance (Mann, 1997) and can thus act as a risk factor for the development of diabetes.

1.2 The problem and hypothesis

In South Africa, urbanisation of the African population seems to result in an increase in type 2 diabetes. More knowledge is needed about the role of diet and other lifestyle factors involved in the aetiology of type 2 diabetes in the African population. This should lead to the development of better prevention strategies and improved understanding about the value of especially diet, in the treatment of type 2 diabetes in the African population. The hypothesis tested in this study is that with urbanisation (westernisation, acculturation, modernisation) changes in the lifestyle of Africans will increase their risk factors for type 2 diabetes.

1.3 Objectives

The main objective of this study was to shed more light on environmental (not genetic) risk factors that may play a role in the development of GIT and type 2 diabetes in the African population of the North West Province in South Africa. The results of this study might help to establish preventative policies concerning eating patterns and lifestyle that can result in a decrease in the development of type 2 diabetes and GIT during urbanisation.

Specific objectives of the study were formulated as follows:

- To determine the effect of urbanisation on the markers for GIT and type 2 diabetes (fasting serum insulin and –glucose and two hour serum glucose) and to get an indication of the lifestyle factors which influence the effect of urbanisation;
- To examine the relationships between established lifestyle risk factors such as age, smoking habit, BMI, waist-to-hip ratio and physical activity, and the risk markers of GIT and type 2 diabetes in this population;
- To compare risk factors for type 2 diabetes in this population with those reported for other populations;

- To identify unique characteristics and factors in this population that may be used in the planning of relevant preventative and intervention strategies and programmes to address the problem of increasing diabetes mellitus;

To realise these objectives:

- a representative sample of apparently healthy African males and females aged 15-64 from all socio-economic and urbanisation strata of the African population of the North West Province of South Africa was drawn and
- an oral glucose tolerance test was performed on these subjects in order to identify those with abnormal glucose tolerance (GIT) and diabetes mellitus.

1.4 Structure of the thesis

The structure of this theses is as follows: In the literature survey, Chapter 2, DM and the risk factors associated with the disease are discussed. The study design and experimental methods are given in Chapter 3. In Chapter 4 the effect of urbanisation on the risk markers of GIT and type 2 diabetes, and the lifestyle factors influencing this effect are investigated and discussed. This chapter includes data from the total study population, and the fasting state was quantified and controlled for. In Chapter 5 the results of the analysis of the relationships between known lifestyle-related risk factors and different levels of GIT are given and discussed. In this part of the study data from all the subjects recruited and examined in 1996 were analysed. The 1996 part of the study was an exploratory exercise to test the protocol and to determine the most important factors involved in the development of GIT and type 2 diabetes in this study population. The glucose tolerance tests on these subjects were done by the researcher. Because some of the subjects did not report to the test site in a fasting state subjects were not classified as diabetic but as glucose intolerant using the "fasting" glucose level as a random glucose value. In Chapter 6 the characteristics of young subjects (<45 years) who were identified with a fasting blood glucose level >7.1 mmol/l are compared to a matched control group. A true fasting glucose value was one of the inclusion criteria when diabetic subjects were identified, and control subjects selected. Chapter 7 comprises a brief joint discussion, the conclusions and suggestions for future studies.

CHAPTER 2
LITERATURE SURVEY

2.1 Introduction

The main application of the results of this study, lies in the field of the early recognition of Africans in transition at risk of developing type 2 diabetes. The literature review therefore concentrates on type 2 diabetes with emphasis on possible risk factors for the development of the disease.

In remote rural areas of South Africa, type 2 diabetes remained very uncommon for decades. Today it is a common disorder in all South African population groups (Seedat *et al.*1988). The incidence of type 2 diabetes in the African population in South Africa has doubled over the past twenty years. This increase has been mainly in urbanised Africans (Walker & Walker, 1991). Urbanisation and Westernisation are characterised by many changes in the lives of new urbanites, with an important impact on health (Malan *et al.*, 1992, Malan *et al.*, 1992a). Some of these are changes in technology, culture, economy and eating patterns, as well as disruption in traditional family structures (Motala, 1995; Sprietsma, 1999). These changes result in stress and increase the risk for the development of chronic diseases such as type 2 diabetes (Motala, 1995, Yach, 1995). Westernisation is associated with the other risk factors for type 2 diabetes, including obesity, a Western diet, low physical activity and age (Motala, 1995). These risk factors against the background of urbanisation will be briefly reviewed in this chapter.

2.2 Diabetes mellitus

2.2.1 Definition and classification

Several terms are used in the literature to describe the two major types of diabetes. Mostly the term insulin dependent diabetes mellitus or type 1 diabetes is used for the type of diabetes with an onset typically at an early age and dependence on exogenous insulin for survival. The term non-insulin dependent diabetes mellitus or type 2 diabetes is used for the type of diabetes with an onset typically at a later age and is usually not dependent on exogenous insulin for survival. Although all these terms are extensively used in the literature, the terms insulin dependent and

non- insulin dependent diabetes mellitus may cause confusion since some patients with insulin dependent diabetes mellitus may have periods during which little or no exogenous insulin is needed, while some patients with non-insulin dependent diabetes may need exogenous insulin as the disease progress to sustain normoglycaemia. For this reason the terms type 1 diabetes and type 2 diabetes are used in this study.

In this thesis the term glucose intolerance (GIT) is used to describe the metabolic condition intermediate between normal glucose tolerance and type 2 diabetes. In some literature the term impaired glucose tolerance is used to describe this condition, while GIT is used to describe both impaired glucose tolerance and type2 .

Diabetes mellitus (DM) is a collection of heterogenic, metabolic diseases with different underlying causes and multiple hormonal abnormalities, that often results in negative health outcomes (Bradley, 1991; Goetsch *et al.*, 1993; Zhang *et al.*, 1996; The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998; Morwessel, 1998). It can be viewed as a complex disorder of the CHO metabolism characterised by glucose overproduction and underutilisation and is associated with a deficiency of insulin or insulin function (Meehan *et al.*, 1993; Yki-Jarvinsen, 1994; Vaag *et al.*, 1995; Ionescu-Tirgoviste, 1998). Relative insufficiency of insulin will result in hyperglycaemia (Bradley, 1991; Ionescu-Tirgoviste, 1998). When the blood glucose levels exceed 11.1 mmol/l, glucose is excreted in the urine, resulting in polyuria, dehydration and thirst that are common symptoms of untreated DM. The disease is also characterized by an increased catabolism of fats and proteins (WHO study group, 1985; WHO, 1997).

At present, DM is classified into several subtypes, which are listed in Table 2.1 (Maassen & Kadowaki, 1996; WHO, 1997; The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998; Ionescu-Tirgoviste, 1998; Wood, 1998; Weyer *et al.*, 1999). This classification includes stages that may be part of the natural history of DM in which there are no present abnormalities of the CHO metabolism. These include previous and potential abnormalities of glucose tolerance. (The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998; Colman *et al.*, 1999). Glucose intolerance (GIT) and impaired fasting glucose (IFG) are stages in the development of diabetes, where the blood glucose levels are no longer within normal limits. Type 1 and type 2 diabetes, gestational diabetes (GDM) and the other specific types of diabetes are true diabetic conditions. The ratio of type 2 diabetes to type 1

diabetes is 4:1 (The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998; Lebovitz, 1999).

An understanding of glucose homeostasis, the secretion of insulin and the role of insulin in maintaining a normal blood glucose level is crucial to understand the mechanisms involved in the development of type 2 diabetes and to relate risk factors to the development of the disease. Therefore, the glucose homeostasis is briefly reviewed below.

Table 2.1: The different classes of diabetes mellitus

1. Potential abnormality of glucose tolerance		
2. Previous abnormality of glucose tolerance		
3. Impaired fasting glucose		
4. Glucose intolerance		
5. Type 1 diabetes	a).	Immune mediated
	b).	Idiopathic
6. Type 2 diabetes	a).	Obese
	b).	Non-obese
	c).	Maturity onset diabetes of the young (MODY)
7. Malnutrition related diabetes		
8. Gestational diabetes		
9. Other specific types	a).	Genetic defects of beta-cell functions
	b).	Genetic defects in insulin action
	c).	Diseases of the exocrine pancreas
	d).	Endocrinopathies
	e).	Drug- or chemical-induced
	f).	Infections
	g).	Uncommon forms of immune-mediated diabetes
	h).	Other genetic syndromes sometimes sometimes associated with diabetes
	i).	Diabetes associated with haematochromatosis

(Maassen & Kadowaki, 1996; The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998; Ionescu-Tirgoviste, 1998; Weyer *et al*, 1999; Colman *et al.*, 1999)

2.2.2 Glucose homeostasis and the function of insulin

The final products of carbohydrate (CHO) digestion, mostly D-glucose and to a lesser extent G-galactose and D-fructose, is rapidly absorbed and transported to the liver via the portal vein

(Nuttal, 1988; Pitout, 1992; Wright, 1993; Scholtka *et al.*, 1999; Gromova & Gruzdkov, 1999). Figure 2.1 shows the mechanism for the absorption of CHO's from the small intestine.

The majority of the fructose and galactose are converted to glucose in the liver (Zilva *et al.*, 1988; Nuttal, 1988). Some glucose passes through the liver and causes an increase in the systemic glucose concentration which stimulates the β-cells of the pancreas to secrete insulin (Zilva *et al.*, 1988; Lawrence *et al.*, 1993; Svoboda *et al.*, 1999; Haymond & Sunehag, 1999). Insulin stimulates glucose uptake in insulin sensitive tissues, principally by recruiting GLUT-4 (the glucose transporter molecule) from an intracellular pool to the plasma membrane (Mayor *et al.*, 1992; Hamann *et al.*, 1995; Coderre *et al.*, 1996; Holman, 1999; Giorgino *et al.*, 2000). This results in a decrease in the plasma glucose levels (Steiner *et al.*, 1980; Lawrence *et al.*, 1993; Tolekova & Popov, 1999). Therefore, the defence against postprandial hyperglycaemia depends on appropriate timing and quantity of the insulin response to each meal (Unger, 1981).

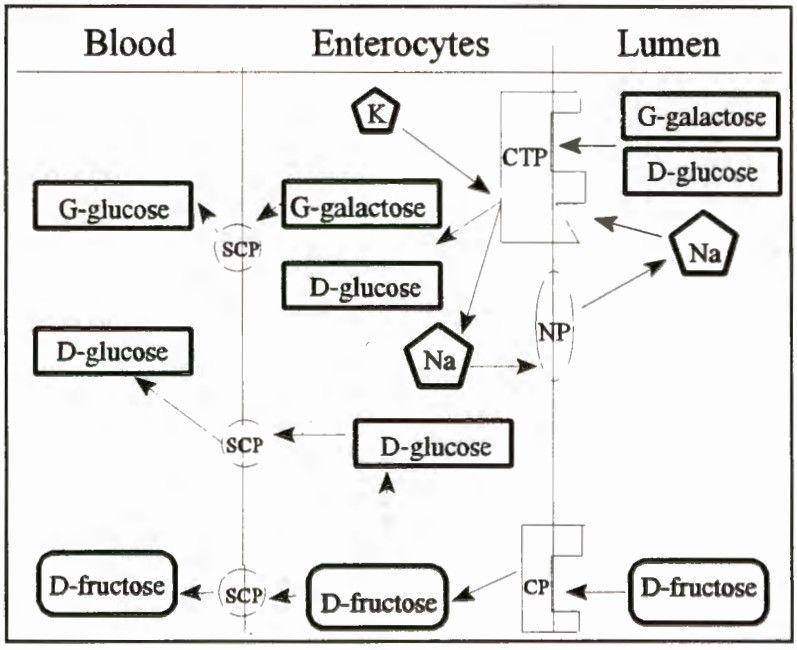

Figure 2.1: The absorption of carbohydrates from the small intestine. (G-galactose = levo-galactose; D-glucose = dekstro-glucose; D-fructose = dekstro-fructose; CTP = co-transporter protein; NP = sodium pump; SCP = specific carrier protein; CP = carrier protein for D-fructose) (Nuttal, 1988; Pitout, 1992; Wright, 1993; Scholtka *et al.*, 1999; Gromova & Gruzdkov, 1999)

Hypoglycaemia will cause an increase in the secretion of glucose counter regulatory hormones, including glucagon, adrenaline, noradrenaline, growth hormone, and cortisol, which will result in an increase in the plasma glucose level (Surwitt *et al.*, 1992; Yanagudi, 1992; Goetsch *et al.*,

1993; Svoboda *et al.*, 1999; Haymond & Sunehag, 1999). During periods of instant and intense muscular activity and stress, glucose homeostasis is also maintained with the help of the central nervous system (Unger, 1981; Surwitt *et al.*, 1992).

Insulin is secreted in response to hyperglycaemia (Prior *et al.*, 1964; Wilkens, 1993; Ling *et al.*, 1998; Haymond & Sunehag, 1999). The mechanism of insulin secretion is represented in figure 2.2 (Bressler and Johnson, 1997). Open ATP-modulated K^+ channels maintain polarization of the plasma membrane in the basal state. Voltage-dependent Ca^{2+} channels are closed. When glucose enters the beta-cell, its metabolism increases ATP production, resulting in closure of the K^+ channels. The increase in intracellular K^+ causes depolarisation of the plasma membrane and the voltage-dependent Ca^{2+} channels open, allowing Ca^{2+} to enter the cell. The increase in systolic Ca^{2+} stimulates the secretion of insulin (Thomas *et al.*, 1995; Aguilar-Brywn *et al.*, 1995; Bressler &Johnson, 1997; Aspinwall *et al.*, 1999). Under basal conditions insulin circulates as a monomer in a free state at a concentration of approximately 1U/hour in peripheral venous serum (Prior *et al.*, 1964), with additional meal related surges of perhaps 3-5 U/hour (Prior *et al.*, 1964). About half of the secreted insulin is removed from the blood by the liver (Prior *et al.*, 1964). It is destroyed by glutathione-insulin-trans-hydrogenase, which degrades the disulphide linkages. The breakdown products of insulin are excreted by the kidneys (Prior *et al.*, 1964).

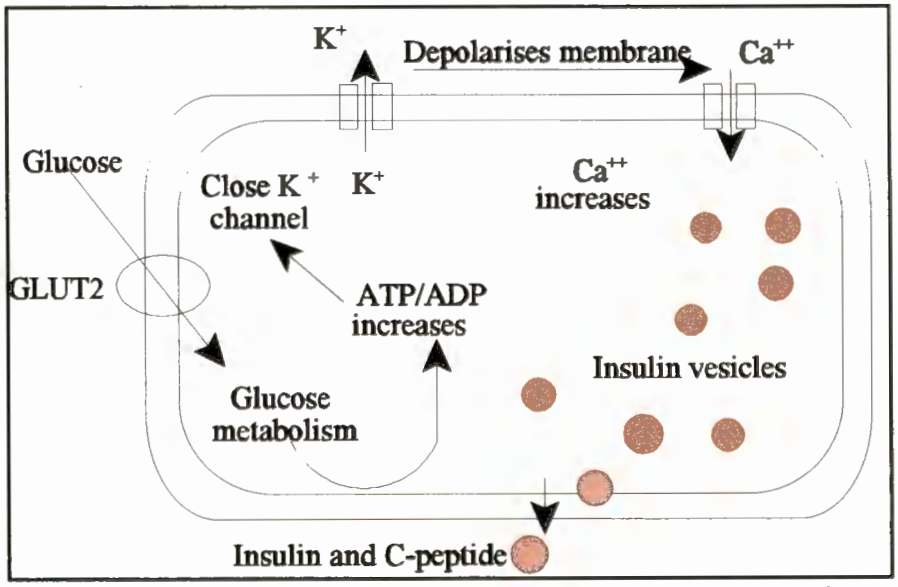

Figure 2.2: The mechanism of insulin secretion (adapted from Bressler & Johnson, 1997)

The factors that regulate insulin secretion are listed in figure 2.3 (Prior *et al.*, 1964; Powis *et al.*, 1994; Sharp, 1996; Bressler & Johnson, 1997; Rutter, 1999; Kloss *et al.*, 1999 Porksen *et al.*, 2000). The normal β-cells increase both the rate of insulin biosynthesis and release when it is

stimulated (Setlzer *et al.*, 1967; Mulder *et al.*, 1996; Rutter, 1999; Kloss *et al.*, 1999). The numerous long-term and short term effects of insulin are listed in figure 2.3 (Dardevet *et al.*, 1991; Pillay & Makgoba, 1991; Panidis *et al.*, 1995; Bressler & Johnson, 1997; Ceresa & Pessin, 1998).

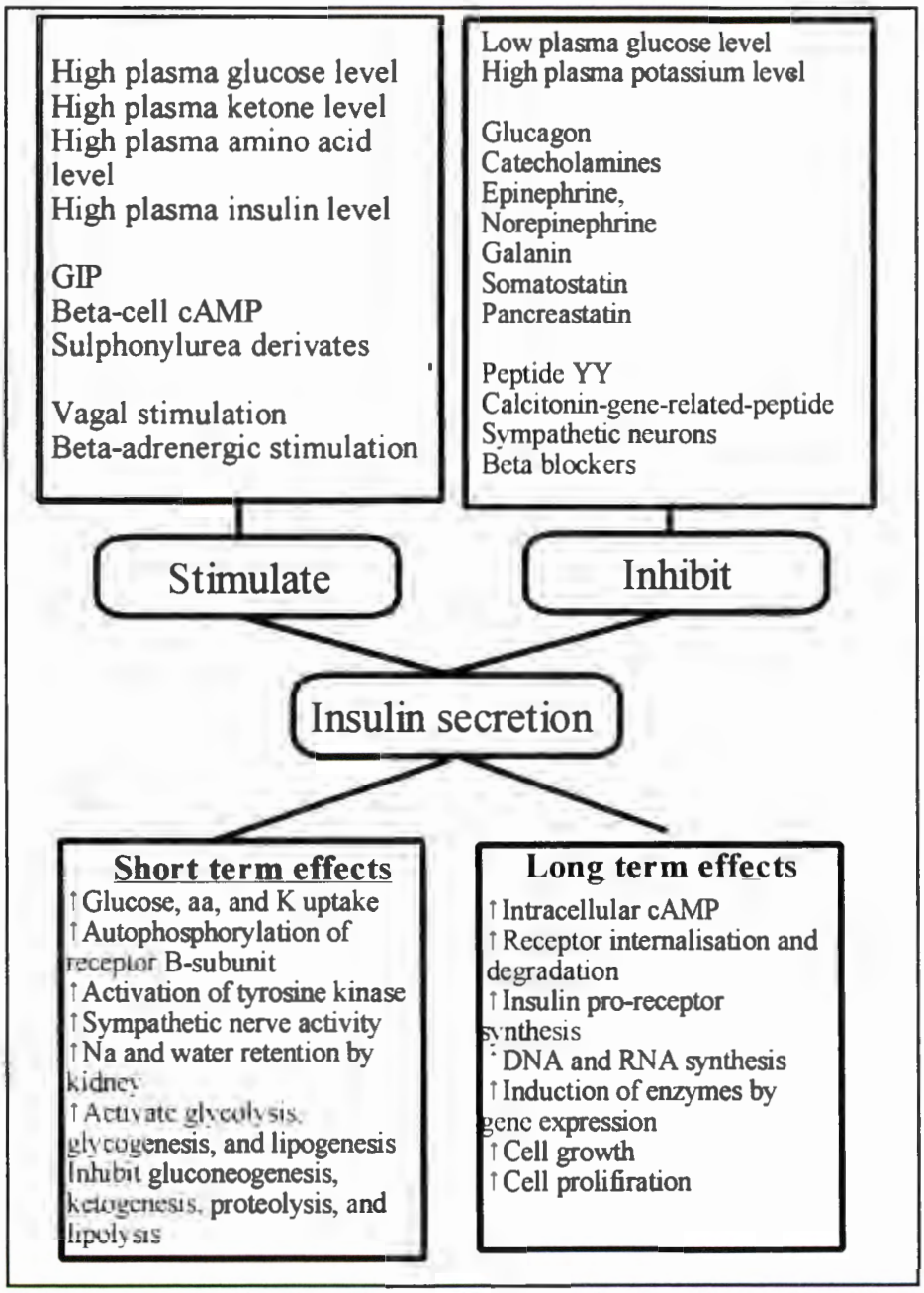

Figure 2.3: Factors controlling insulin secretion and the functions of insulin. (aa=amino acids; GIP=glucose dependent insulinotrophic peptide; K=potassium; Na=sodium; ↑=increase) (Dardevet *et al.*, 1991; Pillay & Makgoba, 1991; Powis *et al.*, 1994; Panidis *et al.*, 1995; Sharp, 1996; Bressler & Johnson, 1997; Ceresa & Pessin, 1998; Rutter, 1999; Kloss *et al.*, 1999; Porksen *et al.*, 2000)

The mature insulin receptor can be seen in figure 2.4 (Pillay & Makgoba, 1991; Dardevet *et al.*, 1991; Bonini *et al.*, 1995). The binding sites for insulin are situated on the α-subunits which are located outside the cell (Bhathena, 1987; Dardevet *et al.*, 1991). The β-subunits are transmembrane proteins, have intrinsic insulin stimulated tyrosine kinase activity and probably mediate the intracellular effects of insulin (Kasuga *et al.*, 1982; Bhathena, 1987; Bonini *et al.*, 1995). The majority of insulin receptors are in the plasma membrane and entry of insulin into the cell is not required for the biological action of insulin (Bhathena, 1987; Di-Guglielmo *et al.*, 1998). If the insulin-receptor complex is internalised, it can bind to receptors on intracellular organelles (Bhathena, 1987; Di-Guglielmo *et al.*, 1998).

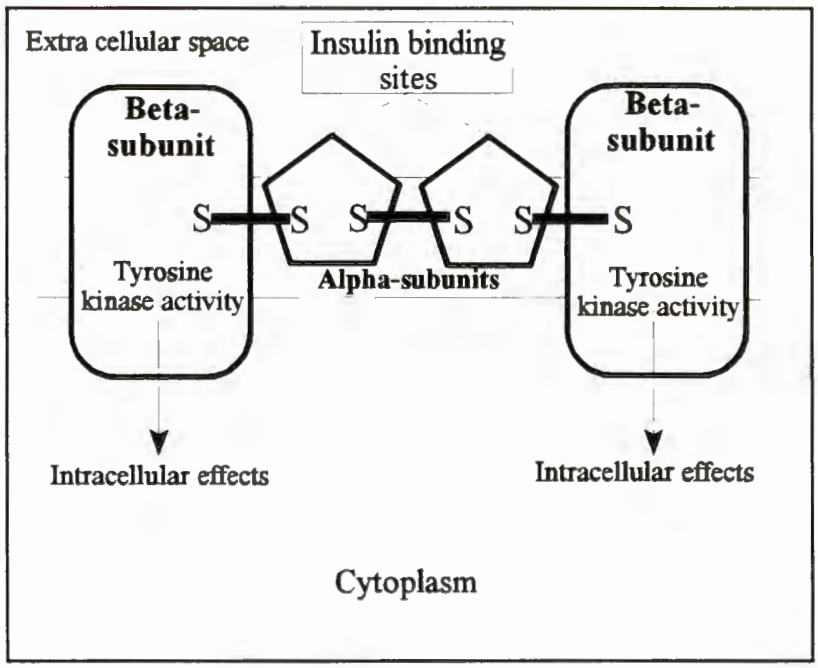

Figure 2.4: A schematic representation of the insulin receptor. (S--S = disulphide linkages) (Pillay & Makgoba, 1991; Dardevet *et al.*, 1991; Bonini *et al.*, 1995)

The magnitude of the biological effect of insulin depends mainly on the nature of the insulin molecule, on the binding process and on postreceptor events (Bhathena, 1987). The binding of insulin results in an intra molecular rearrangement of the α-subunits. This results in the activation of the tyrosine kinase activity on the β-subunits, leading to auto-phosphorylation of the insulin receptor on key tyrosine residues and activation of the receptor towards phosphorylating other substrates through a second messenger system (Dardevet *et al.*, 1991; Srinivas *et al.*, 1993; Bonini *et al.*, 1995; Sauvage *et al.*, 2000). The events linking this auto-phosphorylation reaction with the eventual cellular effects of insulin are somewhat obscure and the second messenger or

messengers have not been identified yet (Yu & Czech, 1984; Bhathena, 1987; Srinivas *et al.*, 1993; Goldstein *et al.*, 2000). Potential signals involved in the acute response to insulin include insulin receptor substrate-1, G-proteins; Ca^{2+}-signals, cytosolic and inravesicular pH, and activation of protein kinase-C (Klip *et al.*, 1993; Sauvage *et al.*, 2000; Yamashita *et al.*, 2000; Ueno *et al.*, 2000; Lee *et al.*, 2000).

The binding of insulin to its receptor is governed by several factors, including the specificity of insulin for its receptor, the affinity of the receptor for insulin, changes in receptor number, spare receptors, saturation and reversibility of the binding (Bhathena, 1987). Changes in any of these factors will result in changes in the binding and thus in the biological function of insulin. The above-mentioned factors can be changed by substances such as hormones, nutrients, trace minerals and enzymes (Bhathena, 1987; Bressler & Johnson, 1997). There is a positive correlation between fluidity of a membrane and insulin binding brought about by dietary lipids (Bhathena, 1987). Acute exercise increases the insulin receptor number, while aging appears to decrease insulin receptors (Bhathena, 1987).

The net number of cell surface insulin receptors are determined by both insulin concentration and the duration of exposure to insulin (down and up-regulation) and the duration of exposure to insulin by at least four mechanisms: 1) altering the rate of receptor degradation 2) receptor redistribution from the cell surface 3) extracellular shedding of receptors 4) regulating *de novo* receptor synthesis and/or maturation through effects on receptor transcription, translation and/or maturation (Marshall *et al.*, 1984; Bhathena, 1987; Pillay & Makgoba, 1991; Dardevet *et al.*, 1991; Bonini *et al.*, 1995). By regulating the number of cell surface insulin receptors, insulin also regulates insulin sensitivity of the cells (Marshall *et al.*, 1984).

2.2.3 Type 2 diabetes mellitus

Type 2 diabetic patients represent about 85% of all DM patients in developed countries (Chen *et al.*, 1992; Bressler & Johnson, 1997; Zimmet *et al.*, 1997). It has reached epidemic proportions in many developing nations and disadvantaged groups in developed countries (Zimmet *et al.*, 1997). Several factors including genetic, environmental and metabolic factors play a role in the development of the disease (Froguel *et al.*, 1993; Goetsch *et al.*, 1993; Jaber *et al.*, 1995; Bressler & Johnson, 1997; Meneilly & Elliot, 1999; Carvalho *et al.*, 1999). These factors will be discussed in section 2.2.7. The onset of type 2 diabetes usually occurs after the age of 40, is most common after the age of 55 years, but may develop in young individuals (Bressler & Johnson, 1997; Rosenbloom *et al.*, 1999).

Type 2 diabetics usually do not need insulin treatment to survive (The Expert Committee on the Classification and Diagnosis of Diabetes Mellitus, 1998). In Western societies 60 - 80% of all type 2 diabetics are obese (Kolterman *et al.*, 1981; Bogardus *et al.*, 1985; Kahn, 1985; Bressler & Johnson, 1997). Nonobese type 2 diabetic patients may have an abdominal fat distribution (Kissebha *et al.*, 1982; Moller *et al.*, 2000). The disease is not HLA related and there is no evidence of auto-immune manifestation (Naik, 1992; The Expert Committee on the Classification and Diagnosis of Diabetes Mellitus, 1998). Glucose may be present in the urine under certain metabolic conditions (Naik, 1992). Although type 2 diabetics are not prone to develop ketosis and hyperglycaemic comas, they may develop these conditions under certain circumstances such as severe stress due to infections or trauma (Butkiewicz *et al.*, 1995; The Expert Committee on the Classification and Diagnosis of Diabetes Mellitus, 1998). There is no absolute insulin deficiency and insulin is often abundant, but the body tissues are often insulin resistant (IR) (Unger, 1981; Rizza *et al.*, 1981; Olefsky *et al.*, 1982; Lebovitz, 1999). Thus, type 2 diabetic patients do possess some homeostatic control over their blood glucose concentration. The disease frequently presents with minimal or no symptoms (Bradley, 1991; Chen *et al.*, 1992; The Expert Committee on the Classification and Diagnosis of Diabetes Mellitus, 1998). Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications (Andersson & Svaardsudd, 1995; Yuan *et al.*, 1999)

The aetiology of type 2 diabetes is complex, as can be seen in figure 2.5 (Mayor *et al.*, 1992; Polonsky *et al.*, 1996; Lebovitz *et al.*, 1999). The disease has different aetiologies depending on genetic susceptibility, environmental and behavioural factors involved in a specific individual or population group.

Type 2 diabetes develops as a consequence of interplay between beta-cell dysfunction, peripheral IR, impaired CHO utilisation, and elevated hepatic glucose production (Yki-Jarvinen, 1995; Vaag *et al.*, 1995; Picarel-Blanchot *et al.*, 1996; Bressler & Johnson, 1997; Lebovitz, 1999). It is not certain which of these are the primary abnormality and which are secondary to glucose toxicity (Vaag *et al.*, 1995; Picarel-Blanchot *et al.*, 1996; Bressler & Johnson, 1997; Perry *et al.*, 1999). Experiments in rats suggest a primary role for liver and beta cell defects in the etiology of type 2 diabetes (Picarel-Blanchot et al., 1996). In the early stages of the disease, treatment with diet, drugs and insulin may reverse impaired beta-cell function, leading to increased insulin secretion. (Wing *et al.*, 1994). Sometimes both α- and β-cells are resistant to the inhibiting effect of insulin resulting in the hyper-secretion of both insulin and glucagon (Unger, 1981). It seems as if hyperglycaemia and hyperinsulinaemia may act independently (and additively) via different regulatory effects on the glucose transport system (Mayor *et al.*, 1992).

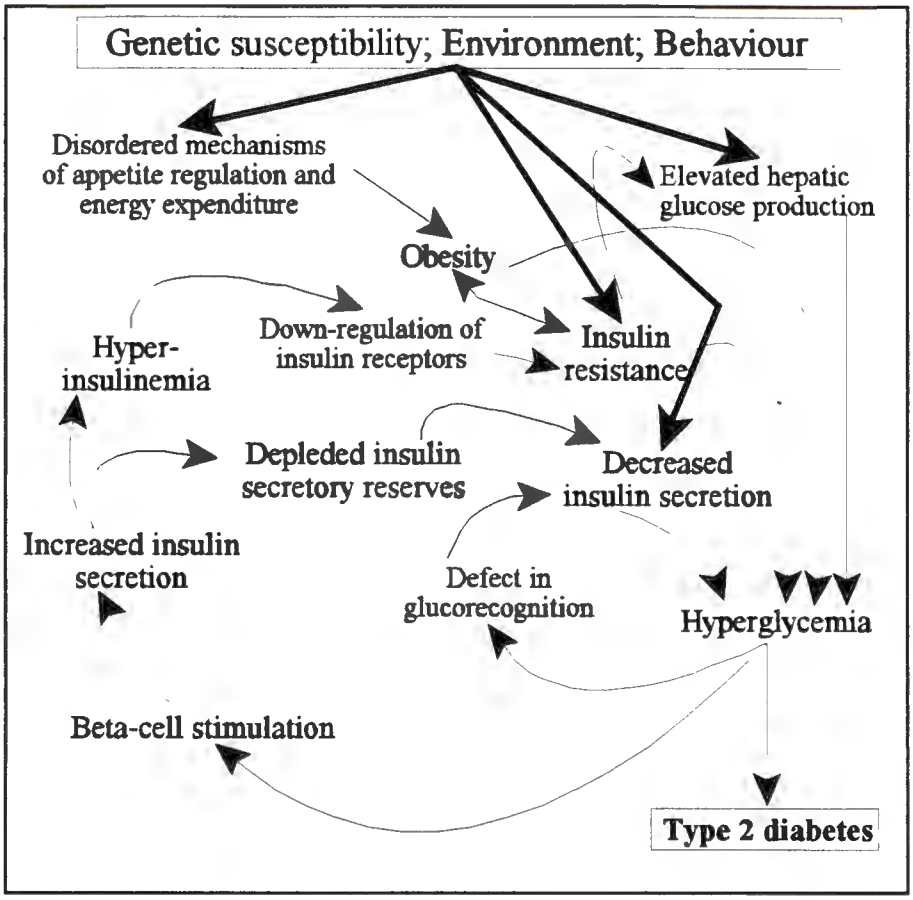

Figure 2.5: Possible mechanisms for the development of type 2 diabetes. It is clear that several possible mechanisms exist and that the interaction between the different factors involved in the etiology of the disease make it difficult to determine the primary defect (Mayor *et al.*, 1992; Polonsky *et al.*, 1996; Lebovitz *et al.*, 1999; Perry *et al.*, 1999; Meneilly & Elliot, 1999; Moller *et al.*, 2000)

Eighty percent of patients with type 2 diabetes are not dependant on exogenous insulin for the prevention of ketonuria (Bradley, 1991). In obese type 2 diabetics it is often possible to reduce the CHO intake to within a range in which endogenous insulin can cope and the disease can then be managed by diet alone (Bradley, 1991). In nonobese type 2 diabetes there is likely to be insufficient utilization of CHO (Bradley, 1991; Lebovitz, 1999).

2.2.4 Diagnosis of diabetes mellitus

There are three ways to diagnose diabetes (McCance *et al.*, 1997; The Expert Committee on the Classification and Diagnosis of Diabetes Mellitus, 1998). On a subsequent day each diagnosis must be confirmed by any of the three methods given in Table 2.2. The plasma glucose values reported in Table 2.2 are those currently used by the American Diabetic Association, and by the WHO (WHO, 1985; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). For epidemiological studies, estimates of diabetes prevalence and incidence

should be based on a fasting plasma glucose concentration of ≥ 7.0 mmol/l (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). This approach will lead to slightly lower estimates for prevalence than would be obtained from the combined use of the fasting plasma glucose concentration and the oral glucose tolerance test (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998).

Table 2.2: The criteria for the diagnosis of diabetes mellitus, gestational diabetes, glucose intolerance and impaired fasting glucose

Type of diabetes	Tests used	Plasma glucose concentrations
Impaired fasting glucose	1. Fasting plasma glucose	1. Fasting -≥ 6.1-<7.0 mmol/l (ADA)
Glucose intolerance	1. Oral glucose tolerance test	1. 2hr. - ≥7.8 - <11.1 mmol/l (ADA) Fasting - 6-7.1mmol/l (WHO) 2hr - 5-11.1 mmol/l (WHO)
Gestational diabetes	1. Screening test (a 50g glucose load) followed by 2. Diagnostic test (a 100g glucose load)	1. 1hr. - ≥7.8 mmol/l (ADA) 2. Fasting - ≥5.8 mmol/l (ADA) 1hr. - ≥6.0 mmol/l (ADA) 2hr. - ≥9.2 mmol/l (ADA) 3hr. - ≥8.1 mmol/l (ADA)
All other types of diabetes mellitus	Any of the following on two occasions: 1. Symptoms and casual plasma glucose 2. Fasting plasma glucose 3. Oral glucose tolerance test (75 g glucose load)	1. Casual - ≥11.1 mmol/l (ADA) 2. Fasting - ≥7.0 mmol/l (ADA) >7.1 mmol/l (WHO) 3. 2hr. - ≥11.1 mmol/l (ADA) >11.1 mmol/l (WHO)

(The World Health Organisation (WHO), 1985; WOH, 1997; American Diabetes Association (ADA), 1998; Pauvilai *et al.*, 1999). Fasting glucose should be measured at least eight hours after the last meal

The most recent criteria used by the American Diabetic Association (ADA) have been revised in 1997. It has been shown that GIT predicts the progression to type 2 diabetes better than impaired fasting glucose (IFG) (Shaw *et al.*, 1999; Forengo *et al.*, 1999; Ollerton *et al.*, 1999; Gniuli *et al.*, 1999). Thus, screening by the criteria for IFG alone will identify fewer individuals who subsequently progress to type 2 diabetes than screening with the oral glucose tolerance test (Shaw *et al.*, 1999; Ollerton *et al.*, 1999; Gniuli *et al.*, 1999). For this reason the criteria proposed by ADA for IFG have been widely criticised (Florkowski &Thompson, 1999; Fornengo *et al.*, 1999; Ollerton *et al.*, 1999; Gniuli *et al.*, 1999).

Fasting blood glucose is easier and more economic to determine than two-hour post load blood glucose and there is very little difference between the two values although the two-hour post load

value is favoured in many studies (McCance *et al.*, 1997; Shaw *et al.*, 1999; Forengo *et al.*, 1999; Ollerton *et al.*, 1999; Gniuli *et al.*, 1999). Fasting plasma glucose is probably the best single test for the diagnoses of diabetes because of its simplicity, low cost, reproducibility and world wide availability (McCance *et al.*, 1997).

In children DM can be diagnosed if the classic symptoms of diabetes are present and if the child has a random plasma glucose value of more than 11.1 mmol/l. An oral glucose tolerance test is not required for the diagnosis, but if it is administered it should be done twice and under the same standard conditions as for adults (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). Thus, in the case of children the emphasis for the diagnosis of DM is placed on the fasting glucose concentration.

There are factors other than DM that will elevate fasting blood glucose concentration or impair glucose tolerance and these must be considered before diagnosing a person as having diabetes (National Diabetes Data Group, 1979; The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). These factors include a variety of metabolic disturbances associated with stress such as illness, trauma, pregnancy, endocrinopathies and certain drugs that induce hyperglycaemia (National Diabetes Data Group, 1979; The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). Physical inactivity or a CHO intake of less than 150 g/day for several days before the oral glucose tolerance test as well as administration of the test in the afternoon, can produce an abnormal glucose tolerance (National Diabetes Data Group, 1979). If a person is less than ten hours fasting, plasma glucose values can be elevated and fasting more than sixteen hours can impair glucose tolerance (National Diabetes Data Group, 1979). There are intra-personal variations in the glucose tolerance test of any person, but average plasma glucose levels in a number of individuals should be constant (National Diabetes Data Group, 1979; The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998).

2.2.5 Long-term complications of diabetes mellitus.

Individuals with type 2 diabetes have an age-specific mortality rate of twice that of the non-diabetic population (Zimmet *et al.*, 1997). This is due to the widespread pattern of tissue damage associated with the disease. Type 2 diabetes is associated with both acute and long-term complications. The acute complications include hypoglycaemia, ketoacidosis and hyperglycaemic nonketotic coma, infections and gangrene (Lebovitz, 1999). The long-term complications (shown

in figure 2.6) may precede the diagnosis of type 2 diabetes in older subjects and it is unusual for a diabetic to be free of complications 20 years after the onset of type 2 diabetes (Bradley, 1991; Ruigomez & Garcia-Rodriguez, 1998). The complications seem to be directly related to hyperglycaemia (glucotoxicity) and poor glycaemic control (Klein, 1995; Andersson & Svärdsudd, 1995; Reichard, *et al.*, 1996; Meigs *et al.*, 2000).

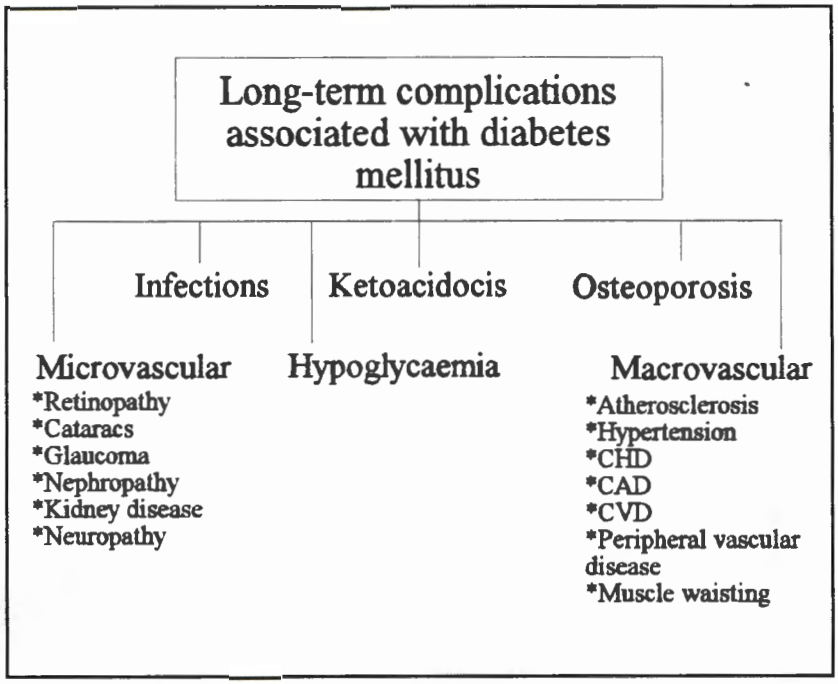

Figure 2.6. The long-term complications associated with diabetes mellitus (Bradley, 1991; Klein, 1995; Andersson & Svärdsudd, 1995; Reichard *et al.*, 1996; Zimmet *et al.*, 1997; Ruigomez & Garcia-Rodriguez, 1998; The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998; Lebovitz, 1999; Meigs *et al.*, 2000)

Microvascular complications are caused by damage to the vascular beds in different tissues. It appears that different degrees of hyperglycaemia may be required to damage vascular beds in different tissues (Nuttal, 1988; Bradley, 1991; Chen *et al.*, 1992). Attempts to avoid the microvascular complications are therefore directed mainly at improving blood glucose control (Bradley, 1991; The Expert committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). It is also important to control hypertension in diabetic patients to prevent these microvascular complications from developing (American Diabetes Association, 1998)

Patients with DM have an increased risk for developing macrovascular diseases such as coronary heart disease (CHD), peripheral vascular and cerebrovascular disease (McCormack *et al.*, 1996; Jorneskog *et al.*, 1996; Zimmet *et al.*, 1997; Bressler & Johnson, 1997; Gumbiner *et al.*, 1998;

Meigs *et al.*, 2000). The atherosclerosis associated with diabetes is a diffuse process, leading to the development of diffuse arterial diseases, such as an increase in ischemic heart disease, stroke, and peripheral vascular disease (Uusitopa *et al.*, 1997). Hypertension, abnormalities of lipoprotein metabolism, dislipidaemia, and periodontal disease are often found in people with diabetes (Nuttal, 1988; Carmena, 1990; Bradley, 1991; Gumbiner *et al.*, 1998; Meigs *et al.*, 2000). According to Krolewski and Warram (1985), Krolewski and co-workers (1991) and Bressler and Johnson (1997), the cardiovascular changes associated with poorly controlled diabetes (hyperglycaemia) include hyperlipidaemia leading to the development of atherosclerosis, arteriosclerosis and eventually gangrene of the toes. Hypertriglyceridaemia is the most common lipid abnormality found in type 2 diabetics, possibly due to an increase in the hepatic synthesis of very low density lipoprotein (VLDL) caused by hyperinsulinaemia (Carmena, 1990; Lampman & Schteingart, 1991; Gumbiner *et al.*, 1998). Many type 2 diabetics have a moderate elevation in levels of LDL cholesterol and have low HDL cholesterol concentrations (Nuttal, 1988; ADA, 1998c; Gumbiner *et al.*, 1998). The decrease in the HDL levels can be attributed to IR and it can be normalised with the correction of hypertriglyceridaemia and better diabetic control (Carmena, 1990).

Alteration of the clotting system in diabetic patients may have a potential role in the development of macro and macrovascular complications (Jorneskog *et al.*, 1996; Mansfield & Grant, 1995; Gabazza *et al.*, 1996). The mechanism by which fibrinogen acts is unclear, but it may play a role in the pathogenesis of vascular complications, as the structural element in a clot is derived from fibrinogen (Jorneskog *et al.*, 1996). Insulin may stimulate the production of plasminogen activator inhibitor-1, which could contribute to thrombus formation by inhibiting fibrinolysis (Stern, 1997). An increased clotting potential of fibrinogen levels may result in a more rigid fibrin gel structure, which might be more thrombogenic (Jorneskog *et al.*, 1996). The alteration of the fibrin gel structure seems to start early after the onset of diabetes (Jorneskog *et al.*, 1996). It has been suggested that hyperglycaemia plays an important role in the alteration of the fibrin gel structure in diabetic patients (Jorneskog *et al.*, 1996).

2.2.6 Epidemiology of diabetes mellitus

2.2.6.1 Global patterns

There are only crude estimates of the total number of people with diabetes at a national, regional, or global level (Zimmet *et al.*, 1997). However, DM is one of the most common chronic diseases, with an estimated prevalence of 100 million people world wide (Zimmet *et al.*, 1997; Goetsch *et*

al., 1993). Type 2 diabetes is a common disease in affluent societies affecting about 5 - 10% of the population over the age of 40 years (Cooper *et al.*, 1984; Harris *et al.*, 1987). In the past 40 years the prevalence of type 2 diabetes among many indigenous populations over the world has changed from a rare occurrence to an epidemic (Stuart *et al.*, 1994; Raman-Kutty *et al.*, 1999; Middelkoop *et al.*, 1999).

Table 2.3: The prevalence of type 2 diabetes in several population groups

Population group	Prevalence	Reference
USA – European	6.2%	Stuart *et al.*, 1994; Jaber et al., 1995
USA - Cubans	9.3%	Stuart *et al.*, 1994; Jaber et al., 1995
African Americans	10.2%	Stuart *et al.*, 1994; Jaber et al., 1995
Mexican Americans	13%	Stuart *et al.*, 1994; Jaber et al., 1995
USA - Puerto Ricans	13.4%	Stuart *et al.*, 1994; Jaber et al., 1995
USA - Pima Indians	50%	Stuart *et al.*, 1994; Jaber et al., 1995
Jamaica - rural Jamaicans	8.5%	Mbanja *et al.*, 1999
Manchester - urban Jamaicans	14.6%	Mbanja *et al.*, 1999
Europeans	1-3%	Carmena, 1990
Singapore - urban Chinese	7.8%	Tan *et al.*, 1999
Singapore - urban Malayans	10.1%	Tan *et al.*, 1999
Singapore - urban Indians	12.2%	Tan *et al.*, 1999
Pakistan - rural Indians	10.2%	Shera *et al.*, 1999
Kerala - urban Indians	16.3%	Raman-Kutty *et al.*, 1999
Melanesians - rural Fiji	1.5%	Bradley, 1991
Nauruans - urban	25-30%	Bradley, 1991
Tokelau	2.3-6.1%	Bradley, 1991
Papua New Guinea - rural	0%	Bradley, 1991; Zimmet *et al.*, 1997
Some Asian populations	30-50%	Carmena, 1990; Jaber *et al.*, 1995
Camaroon - rural Africans	0.8%	Mbanja *et al.*, 1999
Camaroon - urban Africans	2.0%	Mbanja *et al.*, 1999
South Africa - Indians	10%	Seedat *et al.*, 1988
South Africa - whites	4%	Seedat *et al.*, 1988
South Africa - coloureds	8%	Seedat *et al.*, 1988
South Africa - urban Africans	4.2%	Seedat *et al.*, 1988

The world wide prevalence of type 2 diabetes varies dramatically between different population groups and even within the same population group as a function of geographical variation, as is shown in Table 2.3 (Jaber *et al.*, 1995; Raman-Kutty *et al.*, 1999). This is due to the heterogeneity

of the disease as well as a combination of differences in genetic susceptibility and social and environmental risk factors such as change in diet, obesity, physical inactivity, and possibly factors relating to intrauterine development (Naik, 1992; Jaber *et al.*, 1995; Zimmet *et al.*, 1997; Bradley, 1991; Raman-Kutty *et al.*, 1999; Middelkoop *et al.*, 1999; Okada *et al.*, 2000).

Type 2 diabetes is common in some Indian subcontinent communities, and in Asian Indians living in the United Kingdom, Singapore, South Africa, Fiji, and Tanzania (Bradley, 1991; Zimmet *et al.*, 1997; Raman-Kutty *et al.*, 1999; Shera *et al.*, 1999). Mauritius has among the highest diabetes prevalence and diabetes-related mortality in the world, and demonstrates the potential public health catastrophe resulting from type 2 diabetes (Zimmet *et al.*, 1997). Since the ethnic composition of more than two thirds of the global community mirrors that of Mauritius the same may occur in many other countries (Zimmet *et al.*, 1997). However, in some population groups living in rural areas, such as the rural Africans in Tanzania, and Chinese in mainland China, the prevalence of DM is as low as 2% or even lower (Zimmet *et al.*, 1997). The age standardized diabetes prevalence in rural Camaroon is 0.8% compared to the 2.0% in urban Camaroon (Mbanja *et al.*, 1999).

2.2.6.2 The increasing prevalence of diabetes mellitus in South Africa

The estimated prevalence of type 2 diabetes for Africa was 4.7 million cases over the age of 20 in an estimated population of 698 million in 1994 (McCarty & Zimmet, 1994). However, epidemiologic studies are only available from very few countries and many of the older studies did not employ the screening methods recommended by the WHO (Krolewski & Warram, 1985; de Courten *et al.*, 1997). Recent reports indicated that the prevalence of type 2 diabetes is increasing in urban Africans (de Courten *et al.*, 1997).

All South African populations are affected by type 2 diabetes (Table 2.4) (Seedat *et al.*, 1988). The prevalence is still low in some rural populations, but the incidence is increasing among Africans (Zimmet, 1982; Motala, 1995). The increasing number of African patients attending diabetes clinics in several large hospitals throughout South Africa, indicates an increase in either the diagnosis or the incidence of the disease (Gresse & Vorster, 1992).

GIT is an increasing phenomenon is South African whites, Indians and urbanised Africans (Motala, 1995). It is a possible indicator of the early stage of a type 2 diabetes epidemic in South Africa (Motala, 1995). Studies on elderly rural Africans during 1965, 1966, and 1990 revealed a rising prevalence of DM (Walker & Walker, 1991). The prevalence of DM in a semi-rural population

in Qua-Qua was found to be 5.1% and that for GIT 11.5%, adjusted to the world standard population (Mollentze *et al.*, 1992).

2.3 Risk factors/markers/associates of type 2 diabetes mellitus

2.3.1 Risk factors: definition

Fletcher and co-workers (1987) define risk factors as factors that are associated with an increased risk of becoming diseased. Risk factors are used to predict the occurrence of diseases. People who are currently without a disease, but who are exposed to certain risk factors, have a greater risk to acquire the disease than those not exposed to the risk factors. The presence of a risk factor does not mean that an individual will get the disease, it only means that the person has a greater risk of getting the disease than a person in whom the risk factor is absent. Risk factors may be environmental, (such as toxins, infectious agents, and drugs), social (such as disruption of family, daily routines and culture), behavioural (including smoking and inactivity), or inherited. A risk factor which marks a disease outcome indirectly, by virtue of an association with some other determinants of disease is called a marker. Being a marker implies that removing the risk factor will not remove the excess risk associated with it. Thus it is a valuable tool for screening people at high risk of developing a disease, but once a high risk group has been identified, it is of no value in the prevention or treatment of the disease. If a risk factor is also a cause of disease, its removal can be used to prevent disease whether or not the mechanism by which the disease takes place, is known.

It is generally accepted that a wide range of environmental and behavioural risk factors interact with a degree of genetic predisposition to result in the development of type 2 diabetes (Kadowaki *et al.*, 1994; Maassen & Kadowaki, 1996; Morwessel, 1998; Lebovitz, 1999; Lindquist *et al.*, 2000) as can be seen in figure 2.7. In most cases, however, it is not the genetic and environmental risk factors that cause type 2 diabetes, but the metabolic derangement that they give rise to. The metabolic "abnormalities" can thus be called metabolic risk factors since any person presenting these risk factors, has an increased risk for the development of type 2 diabetes. The metabolic risk factors are not the same in all potential diabetics, but depend on the genetic predisposition and on the environmental risk factors influencing the individual.

In the following sections all three classes of risk factors (genetic, environmental, and metabolic) will be discussed with regard to their contribution to the development of type 2 diabetes. For the sake of this discussion, environmental risk factors will include any risk factor that is neither genetic nor metabolic. Environmental risk factors will therefore include risk factors associated with social factors and behaviour as well as factors associated with the physical environment.

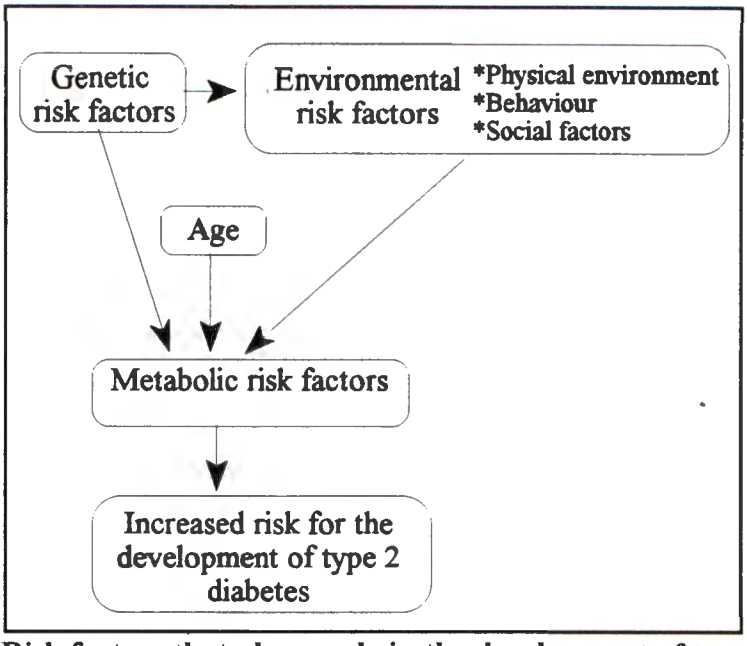

Figure 2.7: Risk factors that play a role in the development of type 2 diabetes (Kadowaki *et al.*, 1994; Maassen & Kadowaki, 1996; Morwessel, 1998; Lebovitz, 1999; Lindquist *et al.*, 2000)

2.3.2 Age as a risk factor for developing DM

Aging is inherent to human nature and thus cannot be discussed under either genetic or environmental risk factors. Nevertheless, aging plays an important role as a risk factor for type 2 diabetes and it is viewed by some as one of the most important, if not the most important risk factor for type 2 diabetes (McCance *et al.*, 1997; Peters & Davidson, 1997, 1151) (figure 2.7). It seems as if the two hour postload glucose levels increase more with age than the fasting blood glucose levels. It is estimated that fasting glucose levels increase by 0.055 mmol/l per decade, while the one hour to two hour postload glucose levels increase by 0.3-0.7 mmol/l per decade (Davidson, 1979; Jackson, 1990; Peters & Davidson, 1997, 1153).

The IR and hyperinsulinaemia associated with puberty can increase the risk for type 2 diabetes, especially in genetically predisposed individuals. Thus, during and after puberty the risk for developing type 2 diabetes may increase. Over the past 20 years, there has been evidence of an emerging epidemic of type 2 diabetes and atypical diabetes mellitus (ADM) (an autosomal dominant condition) among the youth in minority communities such as African American populations (Rosenbloom *et al.*, 1999). Maturity onset diabetes of the young (MODY) is rarely seen and only in Europeans (Rosenbloom *et al.*, 1999). The increase in the postprandial blood glucose levels with aging may be greater in females than in males (Jackson, 1990; Peters & Davidson, 1997, 1154). The age of onset of type 2 diabetes also differs in different population groups. Generally it can be said that ethnic populations such as Pima Indians and Africans tend

to develop type 2 diabetes at an earlier age than Europeans. According to Abbott and Foley (Abbott & Foley, 1987) this is evident as early as in prepubertal children.

There is a spectrum of glucose abnormalities in the elderly ranging from the "youthful" glucose tolerance seen in the highly trained older person to the usual raise of postprandial glucose levels associated with aging to true GIT and type 2 diabetes depending on the diet, physical activity, degree of obesity, body fat distribution, decreased relative insulin secretion, peripheral IR and the use of drugs that impair glucose tolerance. A genetic factor is probably also important in the age-related deterioration of GIT to diabetes (Peters & Davidson, 1997, 1153).

The possible mechanisms for the GIT of aging are shown in figure 2.8. The GIT of aging appears to be due to an increase in peripheral IR (Meneilly *et al.*, 1987; Fukagawa *et al.*, 1988; Khan *et al.*, 2000). Although the exact mechanism remains unknown, it is probably associated with postreceptor defects in insulin action (Fink *et al.*, 1986; Meneilly *et al.*, 1987; Pacini *et al.*, 1988; Khan *et al.*, 2000).

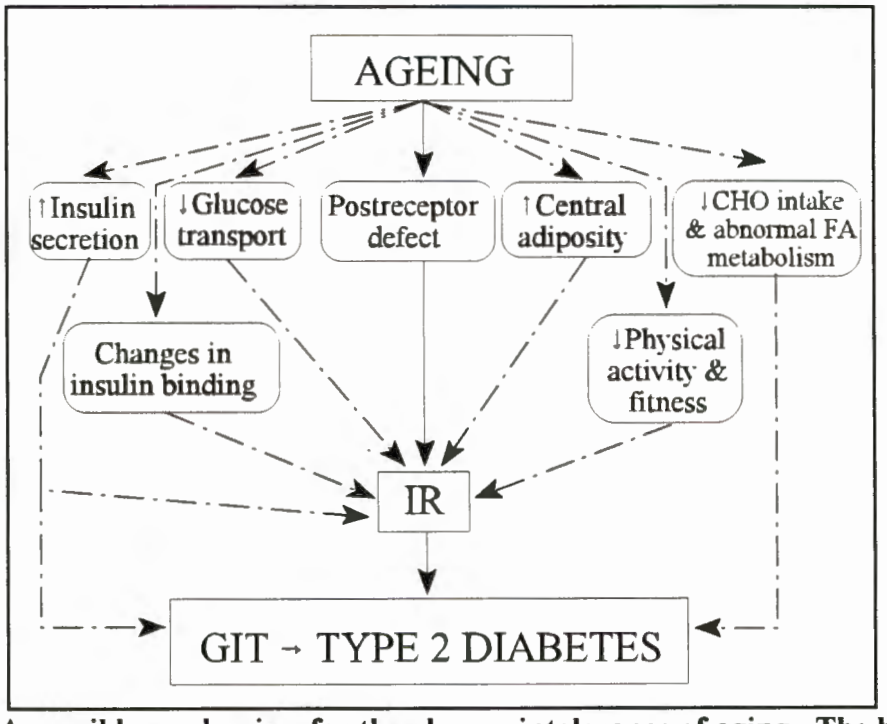

Figure 2.8: A possible mechanism for the glucose intolerance of aging. The broken lines indicate a small or uncertain contribution to glucose intolerance and the solid lines indicate an important contribution to glucose intolerance (↑ = increase; ↓ = decrease; CHO = carbohydrate; FA = fatty acid; IR = insulin resistance; GIT = glucose intolerance) (Davidson, 1979; Fink *et al.*, 1986; Meneilly *et al.*, 1987; Pacini *et al.*, 1988; Fukagawa *et al.*, 1988; Jackson, 1990; McCance *et al.*, 1997; Peters & Davidson, 1997, 1151; Khan *et al.*, 2000)

A decrease in insulin mediated glucose transport in the elderly contributes to the impairment of insulin action (Fink *et al.*, 1984a; Peters & Davidson, 1997, 1156; Khan *et al.*, 2000). The absorption of glucose and non-insulin mediated glucose transport probably do not alter with aging and therefore do not play a role in the IR and GIT of aging (Tonio *et al.*, 1989; Kahn *et al.*, 1992; Peters & Davidson, 1997,1157). Slight abnormalities in hepatic glucose production and suppression by insulin do not explain the GIT seen with aging (Jackson *et al.*, 1988; Peters & Davidson, 1997, 1157).

Lean body mass decreases with age, but changes in glucose tolerance with aging cannot be explained by changes in lean body mass (Fink *et al.*, 1986; Fukagawa *et al.*, 1988). Abdominal adiposity increases with age and may underlie part of the IR associated with aging (Kahn *et al.*, 1992; Peters & Davidson, 1997, 1157). Decreased carbohydrate (CHO) intake in older people does not seem to be a major cause of the GIT of aging (Shimokata, *et al.*, 1991). Changes in the degree of physical fitness and physical activity cannot entirely explain the IR noted in the elderly (Kahn *et al.*, 1992; Dela *et al.*, 1993; Peters & Davidson, 1157, 1997). Abnormalities of the fatty acid metabolism may contribute to the development of GIT and type 2 diabetes, but do not play a major role in the GIT of aging (Fraze *et al.*, 1985; Meneilly *et al.*, 1987).

2.3.3 Genetic risk factors

2.3.3.1 Defective molecules resulting from mutations on genes

Type 2 diabetes has a strong genetic basis (Morwessel, 1998; Nilsson, 1999). Besides mutations on specific genes, there are other genetic risk factors for the development of type 2 diabetes. These are all based on the genotype of an individual and include factors such as a family history of DM, belonging to a specific ethnic group and being of a specific gender. Genetically-influenced efficient metabolisms may also play a role in the development of type 2 diabetes (McGarvey, 1995; Nilsson, 1999).

The specific genetics of type 2 diabetes remains an enigma (Alcolado &Alcolado, 1991; Morwessel, 1998). Only 10% of the genes contributing susceptibility to type 2 diabetes are known, and they are primarily associated with uncommon subtypes of the disorder (Morwessel, 1998). Many patients have a positive family history (Alcolado & Alcolado, 1991; Morwessel, 1998). There is strong evidence, from high concordance rates in monozygotic twins, indicating the presence of pronounced predisposing genetic factors (Alcolado & Alcolado, 1991; Groop *et al.*, 1993; Walston *et al.*, 1995; Maassen & Kadowaki, 1996). However, most forms of the disease

do not have a simple Mendelian pattern of inheritance (Walston *et al.*, 1995; Zimmet *et al.*, 1997; Morwessel, 1998).

Controversy exists as to whether the genetic defect in type 2 diabetes lies within the insulin secretory pathway or the tissue response to insulin (Baroni *et al.*, 1992; Morwessel, 1998). Various candidate genes have been studied, but linkage of type 2 diabetes with these genes has been mostly negative (Zimmet, 1995; Morwessel, 1998). Current knowledge suggests that type 2 diabetes is a polygenic disorder in which different phenotypes are due to a combination of different mutations in several autosomal transmitted gene variants and to environmental influences (Knowler *et al.*, 1991; Baroni *et al.*, 1992; McCarthy *et al.*, 1994; Maassen & Kadowaki, 1996; Nillson, 1999). Candidate sites for genetic defects in IR and type 2 diabetes are listed in Table 2.4. IR has been indicated as a major risk factor for type 2 diabetes and therefore the genetic defects in IR have been included in the table.

Table 2.4: Susceptibility genes involved with type 2 diabetes

Susceptibility gene	Results	Reference
Insulin receptor gene on chromosome 19	Numerous mutations are associated with this gene.	Knowler *et al.*, 1991; Baroni *et al.*, 1992; McCarthy *et al.*, 1994; Maassen & Kadowaki, 1996; Morwessel, 1998
GLUT 1 gene	A good candidate gene. Discrepancies between population groups are probably due to racial differences.	Li *et al.*, 1988; Tuomilheto-Wolf *et al.*, 1989; Baroni *et al.*, 1992; Morwessel, 1998
GLUT 2 gene on chromosome 3q26	A good candidate gene. Discrepancies between population groups are probably due to racial differences.	Li et al., 1988; Tuomilheto-Wolf *et al.*, 1989; Baroni *et al.*, 1992; Morwessel, 1998
GLUT 4 gene	Numerous mutations are associated with this gene.	Knowler *et al.*, 1991; Baroni *et al.*, 1992; McCarthy *et al.*, 1994; Maassen & Kadowaki, 1996; Morwessel, 1998
Insulin signal transduction pathway genes	Possibly linked to type 2 diabetes via its link with IR.	Taylor *et al.*, 1988
Insulin regulated genes.	Involved in peripheral utilization of glucose or suppression of hepatic glucose production.	Taylor *et al.*, 1988
IRS-1 gene	Polymorphisms in this gene are linked with type 2 diabetes, obesity and IR in Caucasians.	Imai *et al.*, 1994; Hitman *et al.*, 1995; Clausen *et al.*, 1995; Ura *et al.*, 1996; Carvalho *et al.*, 1999
Glycogen synthase gene on chromosome 19	Linked with type 2 diabetes, obesity and IR in Caucasians.	Groop *et al.*, 1993; Kadowaki *et al.*, 1993
Beta-3- adrenergic receptor genes	Linked with type 2 diabetes, obesity and IR in Caucasians.	Clement *et al.*, 1995; Kadowaki *et al.*, 1995; Walston *et al.*, 1995; Fujisawa *et al.*, 1996
Glucagon receptor gene on chromosome 17	Linked with type 2 diabetes, but does not always indicate the occurrence of the disease. Causes a decreased affinity of glucagon for its receptor.	Clement *et al.*, 1995;
Glycogen gene on chromosome q25.5	Link with type 2 diabetes not proved yet.	Barbetti *et al.*, 1996
Glucokinase gene	Linked with type 2 diabetes. Prevalence is low in Japanese.	Hattersley *et al.*, 1992; Kadowaki *et al.*, 1994.

(IR = insulin resistance)

Maternal effects in the transmission of DM suggest the involvement of a genetic factor encoded by mitochondrial DNA (Valle *et al.*, 1997, 131). True genetic maternal autosomal inheritance may result if maternally derived genes are passed on to offspring in preference to paternal genes (as in the mitochondrial myopathies) or if maternal genes are preferentially switched on during ontogeny (Alcolado & Alcolado, 1991). It has been suggested that oxidative phosphorylation in the mitochondria has a crucial role in the secretion of insulin (Kadowaki *et al.*, 1993; Defronzo *et al.*, 1997, 647). Thus any mutation in mitochondrial DNA that will influence oxidative phosphorylation will affect insulin secretion. A new subclass of DM, maternally inherited diabetes and deafness (MIDD), associated with secondary loss of hearing is linked with specific mutations in the mitochondrial DNA (Defronzo *et al.*, 1997, 647; Valle *et al.*, 1997, 131). These forms of diabetes, represent less than 2% of all cases of type 2 diabetes (Maassen & Kadowaki, 1996). The effect of the environment on the expression of MIDD is unknown, but it seems to be a primarily genetic form of the disease.

Very little data are available on the genetics of type 2 diabetes in South Africans, especially in Indian and African populations (Levitt & Mollentze, 1995). A positive correlation with HLA B15 was shown in young South African Indians of North Indian origin and an increased frequency (statistically insignificant) of HLA Bw61 was found in type 2 diabetic Indians as a group (Omar *et al.*, 1985). The frequency of HLA A2 in Xhosas with type 2 diabetes was also found to be insignificantly increased (Levitt & Mollentze, 1995). No significant alteration in HLA-A or HLA-B antigen frequencies was found in type 2 diabetic Africans in Johannesburg (Shires *et al.*, 1983).

2.3.3.2 The thrifty genotype hypothesis

A thrifty genotype hypothesis was first suggested in 1962 by J.V. Neel, who revised it in 1982 (Neel, 1962; Rotter, 1982; Maher & Keen, 1985; Brewis *et al.*, 1995; Lebovitz, 1999). According to Neel, the thrifty genotype allowed storage of calories as fat in times of plenty and provided an energy buffer for times of food scarcity (Neel, 1962; O'Dea, 1995; Shetty & Tedstone, 1997; Lebovitz, 1999). Individuals with the thrifty genotype might have been healthier, survived longer, and had more offspring (McGarvey, 1995; Joffe & Zimmet, 1998). With westernisation the behavioural traits which were so important to the survival of hunter-gatherers in combination with the thrifty metabolism produce a vicious cycle of weight gain and worsening IR resulting in obesity and type 2 diabetes in individuals with the susceptibility to pancreatic beta-cell incompetency (McCance *et al.*, 1994; O'Dea, 1995; Swinburn, 1995; McGarvey, 1995; Joffe & Zimmet, 1998; Lebovitz, 1999).

The mechanisms that have been suggested to explain the association between type 2 diabetes and the thrifty genotype (Swinburn, 1995; Joffe & Zimmet, 1998), can be seen in figure 2.9 and different views are summarised in Table 2.5. Neel himself is of the opinion that type 2 diabetes is a heterogeneous disease and that the thrifty genotype hypothesis may be merely one aspect of the aetiology of the disease. (Barker, 1995). The conceptual structure or the thrifty genotype seems to fit well with the rapid and massive weight gain in Polynesians and Micronesians. However, the linkage of type 2 diabetes to a feast and famine history fits only some populations and there are some researchers who question its validity and with good reason (Joffe & Zimmet, 1998). For example, it is possible that Polynesians became bulky and muscular not to survive famishes, but to survive episodes of extreme low temperatures to which their ancestors would have been exposed (Houghton, 1995; Brewis *et al.*,1995) .

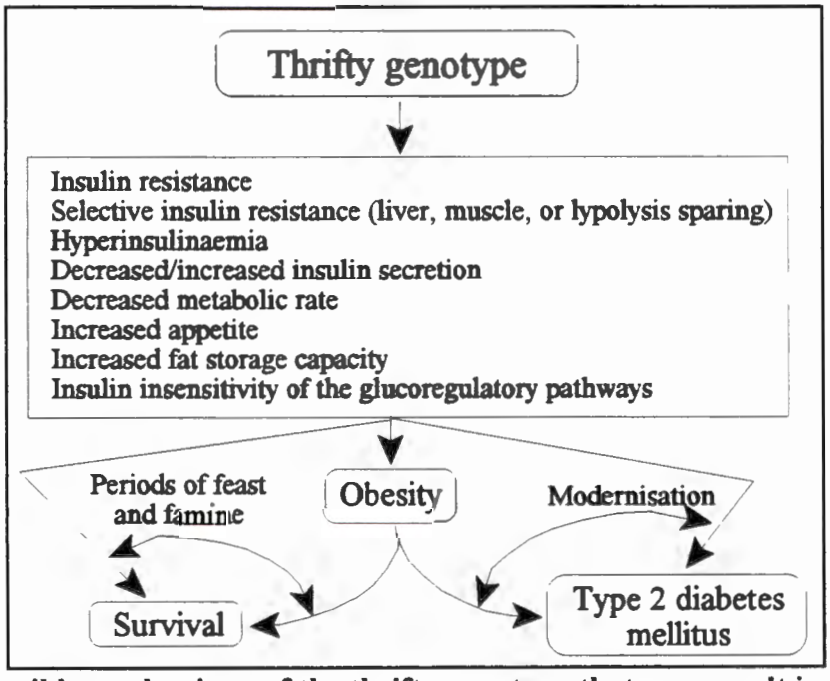

Figure 2.9: Possible mechanisms of the thrifty genotype that may result in type 2 diabetes (Swinburn, 1995; Joffe & Zimmet, 1998; Lebovitz, 1999)

The Thrifty genotype hypothesis certainly has a place in explaining the increasing prevalence of type 2 diabetes in certain ethnic groups. Furthermore it is also important to remember that this hypothesis does not only single out genetic susceptibility to disease as a culprit but it also stresses the importance of environmental inputs both in the past and the present. The genetic contribution to type 2 diabetes does not seem to be the same in all population groups and thus the thrifty genotype may play a smaller role in some population groups than in others.

Table 2.5: Views on the thrifty genotype hypothesis

Support or object	Race	Study design or argument	Reference
Support	Native Americans, Pacific islanders	Thrifty genotype may be virtually pan-species, with a small number of populations recently experiencing selection for a nonthrifty genotype.	Brewis *et al.*, 1995
Support	Pacific populations	The thrifty genotype hypothesis is alive but there is no agreed description of the mechanisms of the hypothesis. It still emphasises the genetic basis for type 2 diabetes.	Swinburn, 1995; Joffe & Zimmet, 1998
Support		The thrifty genotype and thrifty phenotype hypotheses may coexist. The author is in favour of the thrifty genotype acting alone or in conjunction with other mechanisms to increase the risk for type 2 diabetes.	O'Dea, 1995
Support	Non-European populations	Favour the existence of a thrifty genotype in non-European populations, and offers an explanation of the absence of the thrifty genotype in European populations	Allen & Cheer, 1995; Joffe & Zimmet, 1998; Chukwuma & Tuomilehto, 1998
Support		The author support the thrifty genotype and believe it to be an explanation for modern man's craving for sugar, salt and fat.	Scott, 1992
Question	Samoans	Question whether the increase in overweight found with increasing modernisation is due to genetic susceptibility. If this is true the thrifty genotype hypothesis holds water.	McGarvey, 1995
Object	Pacific populations	Question the concept of a thrifty genotype for the Pacific population, because the evolutionary background differs from that used in the explanation of the thrifty genotype.	Houghton, 1995
Object	Pacific populations	The author doubts that the association between an increase in body fat and type 2 diabetes is strong enough to prove that obesity will result in type 2 diabetes. But he is in favour of a genetic basis to type 2 diabetes.	Baker, 1995
Object	American-Indian population	The study provides evidence for the association between selective survival of small babies, genetically susceptible to insulin resistance and high prevalence of type 2 diabetes.	McCance *et al.*, 1994

2.3.4 Family history

The genetic contribution to a disease can be evaluated by the degree of familial clustering of the disease (Luo *et al.*, 1995). The risk of type 2 diabetes within a family will depend on the severity of the disorder in the proband, the number of family members affected, and the contribution from environmental factors (Baroni *et al.*, 1992).

First degree relatives of diabetic patients are at high risk to develop type 2 diabetes (Vaag *et al.*, 1992; Barbetti *et al.*, 1996; Morwessel, 1998). The familial risk to develop diabetes is shown in Table 2.6. Having a parent with diabetes seems to be a greater risk than having a sibling with diabetes (Alcolado & Alcolado, 1991). The risk of type 2 diabetes is about 20-40% in children with one diabetic parent and it has been suggested that abnormalities in the glucose metabolism occur at an earlier age in individuals with two diabetic parents (Alcolado & Alcolado, 1991; Groop *et al.*, 1993; Froguel *et al.*, 1993). According to Alcolado and Alcolado, (1991) having a mother with type 2 diabetes seems to place a person at higher risk to develop the disease. This may be due to the inheritance of mitochondrial DNA mutations, or the influence of intrauterine nutrition on the developing fetus. MIDD has already been discussed and it seems that almost all children from a

mother with this mutation are carriers of the mutant gene (Maassen & Kadowaki, 1996). However, only about 60% of the carriers will develop MIDD (Maassen & Kadowaki, 1996).

Table 2.6: Family history as a risk factor for the development of type 2 diabetes

Percentage inheritance	Race	Reference
80% positive family history.	South African Indians	Omar & Asmal, 1983a
75% positive family history.	South African Indians.	Asmal *et al.*, 1981
67% obese type 2 diabetics and 31% obese nondiabetics had positive family history	Indians (Natal, SA)	Omar *et al.*, 1994
40% nonobese type 2 diabetics had a positive family history	Indians (Natal, SA)	Omar *et al.*, 1994
37% had positive family history	Africans (SA)	Omar & Asmal, 1983a
55% had positive family history (9 subjects)	Africans (SA)	Asmal *et al.*, 1981
No association	Africans (Cape Town, SA)	Levitt *et al.*, 1993
26% had a positive family history	Caucasians (UK)	Alcolado & Alcolado, 1991
Family history of type 2 diabetes associated with IR in normoglycaemic subjects	Caucasians	Laws *et al.*, 1989
Only one parent implicated in 53% of diabetics (38.5% mothers and 14.5% fathers)	Caucasians	Alcolado & Alcolado, 1991
In 3% of diabetics with a positive family history both parents have diabetes	Caucasians	Alcolado & Alcolado, 1991
90% of second twins develop diabetes (monozygotic twins)	Caucasians	Groop *et al.*, 1993; Simmons, 1995
40% of second twins develop diabetes (monozygotic twins)	Caucasians	Groop *et al.*, 1993; Simmons, 1995

It has been shown that normoglycaemic first degree relatives of patients with GIT or type 2 diabetes, are insulin resistant compared to individuals without a family history of type 2 diabetes (Laws, *et al,* 1989). These individuals are at higher risk to develop type 2 diabetes. An individual with a first degree family member with diabetes due to a mutation on the glycogen synthase gene also has a good chance to develop diabetes (Groop *et al.*, 1993; Morwessel, 1998).

Type 2 diabetes has a concordance rate approaching 40% in monozygotic twins (Alcolado & Alcolado, 1991; Simmons, 1995; Maassen & Kadowaki, 1996). Monozygotic twins share both genomic sequence and intrauterine environment. Having a diabetic monozygotic twin places one at increased risk of developing type 2 diabetes either through sharing the same intra-uterine environment or through sharing the same genomic sequence.

It seems as if family history of type 2 diabetes differs in different population groups, probably due to the genetic heterogeneity of the disease in first degree relatives (Levitt & Mollentze, 1995). Omar and co-workers (1994) found that obese diabetic subjects had a stronger family history of a first

degree relative with type 2 diabetes than nonobese diabetic subjects and that both obese and nonobese diabetics had a stronger family history of a first degree relative with type 2 diabetes than obese non diabetic subjects. In South Africa it seems that the African population has a low frequency of family history (Omar *et al.*, 1994). One study on African diabetics has shown the family history to be 55%, however this study only included nine subjects (Omar *et al.*, 1994). This does not necessarily implicate a low genetic contribution in Africans. It is possible that the environmental changes associated with the modernisation of Africans, result in the development of type 2 diabetes in genetic susceptible individuals, who would not have developed the disease in the absence of these risk factors

2.3.5 Ethnic group

Ethnic group is not a strict biological indicator, but rather a social category. Differences between ethnic groups are not absolute and are generally not reflected by the presence or absence of a particular trait, but rather whether it occurs more or less frequently in a specific ethnic group (Rutledge, 1994). There is a wide variation in the prevalence of type 2 diabetes among different ethnic groups and even within the same ethnic group as a function of geographic variation (Jaber *et al.*, 1995; Simmons, 1995; Osei *et al.*, 1997; Mbanya *et al.*, 1999). Data supporting the differences in prevalence of diabetes between different ethnic groups are summarized in Table 2.7. Figure 2.10 explains the influence of mutations and other factors on the ethnic differences in the prevalence of type 2 diabetes.

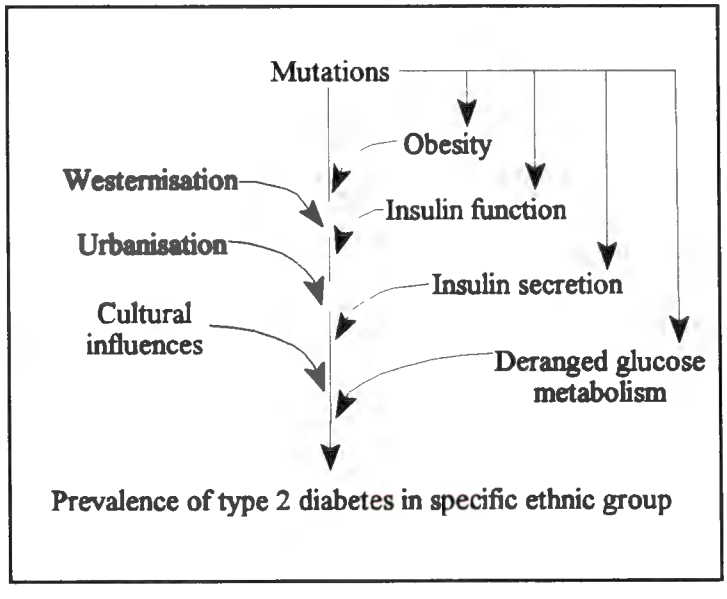

Figure 2.10: The effect of mutation and other factors on the ethnic differences in the prevalence of type 2 diabetes (Baroni *et al.*, 1992; McCarthy *et al.*, 1994; Walton *et al.*, 1995; Stern, 1995; Luo *et al.*, 1995; Mbanya, 1999)

Table 2.7: Differences in the prevalence of type 2 diabetes in different ethnic groups

Race	Location	Prevalence	Reference
Caucasians	United States	8 - 10%	Walston *et al.*, 1995
Caucasians	United States	6.2%	Jaber *et al.*, 1995; Schwartz *et al.*, 1995
Caucasians	New Zealand	4%	Ostbye *et al.*, 1989
Polynesians	Rural Fiji	1.5%	Ostbye *et al.*, 1989
Nauruans (Micronesians)	Urban	41.3%	Simmons, 1995;
Nauruans	Urban Pacific region	30%	Ostbye *et al.*, 1989
Tokelauan men	Urban	2.3%	Ostbye *et al.*, 1989
Tokelauan women	Urban	6.1%	Ostbye *et al.*, 1989
Maori men	New Zealand	12%	Jaber *et al.*, 1995
Maori women	New Zealand	12.5%	Jaber *et al.*, 1995
Arabs	Arab countries	3% - 5%	Jaber *et al.*, 1995
Cubans	United States	9.3%	Jaber *et al.*, 1995
African Americans	United States	10.2%	Jaber *et al.*, 1995
Mexican Americans	United States	13%	Jaber *et al.*, 1995; Schwartz *et al.*, 1995
Puerto Ricans	United States	13.4%	Jaber *et al.*, 1995
Pima Indians	United States	50%	Jaber *et al.*, 1995
Tunisians	Rural Tunisia	1.2%	Simmons, 1995
Tanzanians	Rural Tanzania	1.2%	Simmons, 1995
Indians (Asians)	Rural	2.7%	Simmons, 1995
Indians (Asians)	Fiji - urban	22%	Simmons, 1995
Indians (Asians)	India - urban	16.3%	Raman-Kutty, 1999
Hindu Indians (Asians)	Mauritius	12.4%	Maassen & Kadowaki, 1996
Muslim Indians (Asians)	Mauritius	13.3%	Maassen & Kadowaki, 1996
Creoles	Mauritius	10.4%	Maassen & Kadowaki, 1996
Chinese	Mauritius	11.9%	Maassen & Kadowaki, 1996
Africans	Cameroon - rural	0.8%	Mbanya *et al.*, 1999
Africans	Cameroon - urban	2.0%	Mbanya *et al.*, 1999
Africans	Jamaica	8.5%	Mbanya *et al.*, 1999
Africans	Manchester (Brittan)	14.6%	Mbanya *et al.*, 1999
Chinese	Rural China	1.6%	Simmons, 1995;
Chinese	Mauritius (urban)	13.1%	Simmons, 1995

Since genetic susceptibility seems to account for less than 10% of type 2 diabetes in a variety of ethnic groups (McCarthy *et al.*, 1994), it is possible that ethnic differences do not have a very strong genetic base. All genetic mutations do not have the same prevalence in all ethnic groups and certain mutations may be absent in some groups while being very strongly linked with type 2 diabetes in other groups (Baroni *et al.*, 1992; Walston *et al.*, 1995; Stern, 1995; Luo *et al.*, 1995). The prevalence of some genetic mutations may even vary within an ethic group (Luo *et al.*, 1995).

There may be other, nongenetic differences in the prevalence of type 2 diabetes. Recently there has been an extraordinary increase in type 2 diabetes in a variety of ethnic groups of non-European origin (Reaven, 1993; Osei *et al.*, 1997; Rosenbloom, 1999). The diagnosis of type 2 diabetes is usually made after the age of 50 years in Europeans, but at a much younger age in these populations (Valle *et al.*, 1997, 132; Rosenbloom, 1999). Modernisation-associated changes in diet, life style and weight (and the rate of these changes) may impose sufficient environmental stress on the genetically predisposed metabolism for type 2 diabetes to develop (Brewis *et al.*, 1995; McGarvey, 1995; Barker, 1995; Chukwuma & Tuomilehto, 1998). It may also be responsible for the higher prevalence and the earlier onset of type 2 diabetes in these populations (McGarvey, 1995; Baker, 1995; Chukwuma & Tuomilehto, 1998).

The ethnic differences in the prevalence of type 2 diabetes may also be due to differences in β-cell function, hepatic glucose overproduction, hyperinsulinaemia, IR, and body weight (McKeigue *et al.*, 1991; Haffner *et al.*, 1997). Scientists believe that some populations with a high prevalence of type 2 diabetes, may possess hereditary insulin insensitivity, hyperinsulinaemia and bimodality of the two-hour post load plasma glucose levels (Reichard *et al.*, 1996; McCance *et al.*, 1997; Haffner *et al.*, 1997; Reaven, 1998). There are differences in insulin sensitivity, insulin level, hepatic insulin extraction and basal glucose production between young non-diabetic African and white Americans (irrespective of family history of DM) (Osei *et al.*, 1992).

Ethnic differences in the prevalence of type 2 diabetes are, in some cases, attributable to a given degree or type of obesity (Bose, 1992; Swinburn *et al.*, 1995; McAnulty & Scragg, 1995; Osei *et al.*, 1997). Obesity is known to be one of the three most important risk factors in European populations, but not in all other ethnic groups (Suehiro *et al.*, 1995; Valle *et al.*, 1997, 133). Upper body obesity seems to be less detrimental for African than for European women of similar adiposity with regard to risk for developing type 2 diabetes. (Conway *et al.*, 1995). At this stage there is controversy about the contribution of obesity to the development of diabetes in populations who have always been heavy or obese, even in their rural settings (Suehiro *et al.*, 1995).

Socioeconomic status may also contribute to the ethnical differences in the prevalence of type 2 diabetes (Osei *et al.*, 1997). The relationship between income and diet has an important culture specific component (Popkin, 1993). It is known that an affluent or Western diet contributes to the development of type 2 diabetes. The extent to which ethnic-related food choices contribute to the development of type 2 diabetes in specific populations is unfortunately not known.

2.3.6 Gender

The relative prevalence of type 2 diabetes in males and females varies inconsistently in epidemiological studies (Eriksson *et al.*, 1992; Bruno *et al.*, 1992; de Courten *et al.*, 1997, 147; Valle *et al.*, 1997, 132; Raman-Kutty *et al.*, 1999; Shera *et al.*, 1999). In Europeans, DM is more prevalent in females, than in males (Despres *et al.*, 1995; Schwartz *et al.*, 1995; Conway *et al.*, 1995; Osei *et al.*, 1997). In some communities there seem to be a trend towards a male excess in prevalence in higher socioeconomic groups (Stern *et al.*,1984; Wingard *et al.*, 1990). In Finland and in some Italian populations the age-specific prevalence of known diabetes is higher in males up to the age of 60 years, but in older groups the prevalence is higher in females (Eriksson *et al.*, 1992; Muggeo *et al.*, 1995; Garacini *et al.*, 1995). In many tropical countries there is a male predominance of type 2 diabetes, probably due to the fact that females are less likely to seek medical attention (Mohan & Alberti, 1997, 174). Comparisons of population-based studies in USA adults with type 2 diabetes, subdivided by ethnic background, do not show any consistent gender preference (Zimmet, 1989; King & Rewers, 1993).

The possible mechanisms for gender differences in the prevalence of type 2 diabetes are listed in figure 2.11. Much, if not all, the differences in the gender ratio of diabetes can be explained by male/female differences in the relative frequency of obesity and physical activity in different cultures and ethnic groups (de Courten *et al.*, p147, 1997). The higher prevalence of type 2 diabetes in women may be due to the greater measure of obesity found in women or to the sedentary life style of women (Ostbye *et al.*, 1989). A given excess of body fat in men could be associated with greater metabolic disturbances than in women with similar excess body fat (Despres *et al.*, 1995). Thus although a woman has a greater chance of becoming obese, the excess body fat does not seem to cause as much metabolic derangement as in men.

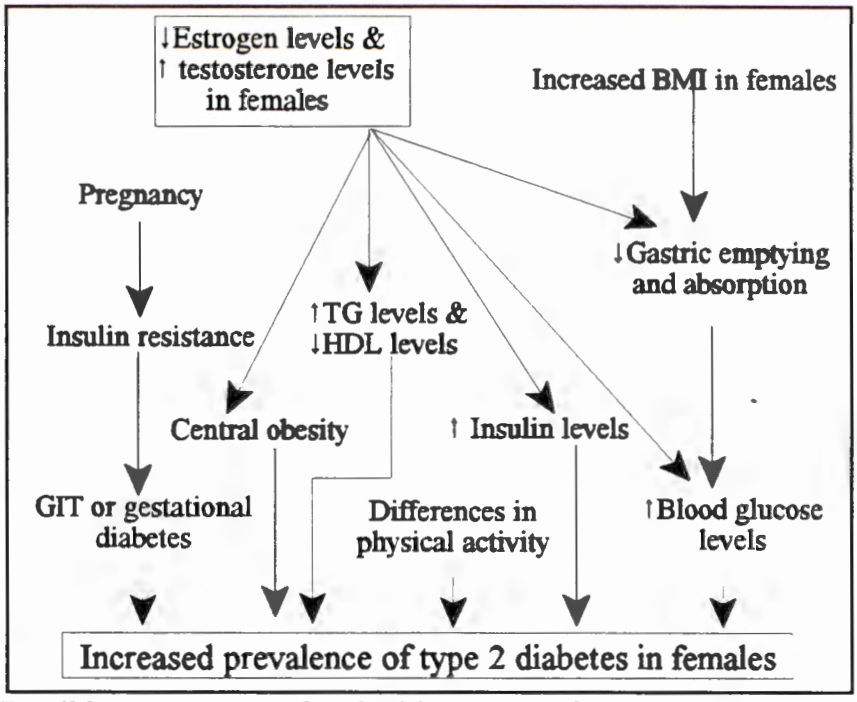

Figure 2.11: Possible explanations for the higher prevalence of type 2 diabetes in females compared to males (de Courten *et al.*, 1997, 147; Ostbye *et al.*, 1989; Despres *et al.*, 1995; Stern, 1997, 270; Haffner *et al.*, 1989; Wild *et al.*, 1990; Haffner *et al.*, 1993; Haffner *et al.*, 1992; Hamann *et al.*, 1995; Schwartz *et al.*, 1995)

A role for sex hormones is also implied. Central obesity, higher triglyceride and low HDL levels are more commonly found in males than in females (Stern, 1997, 270). Androgenisation (associated with testosterone) in premenopausal females has been shown to correlate with central obesity, increased glucose and insulin concentrations, hypertriglyceridaemia and low HDL levels, which are all risk factors for the development of type 2 diabetes (Haffner *et al.*, 1989; Wild *et al.*, 1990). It also predicts future DM in premenopausal and postmenopausal females (Haffner *et al.*, 1992; Haffner *et al.*, 1993). Similar metabolic abnormalities have been described for females with polycystic ovarian disease, who are known to be androgenised (Wild *et al.*, 1990). In males most of the above associations are either not present or in the opposite direction (Stern, 1997, 270). In prospective studies of males, low total testosterone is a risk factor for future diabetes (Stern, 1997, 270). Estrogens may have a protective effect on the development of diabetes (Hamann *et al.*, 1995). In premenopausal women (or postmenopausal women receiving hormone therapy) it seems as if estrogen and progesterone somehow decrease gastric emptying and thus also the absorption rate of digestive products (Schwartz *et al.*, 1995). This results in lower postprandial blood glucose levels (Schwartz *et al.*, 1995), which may "protect" against the development of DM.

2.3.7 Increased gastric emptying and absorption rate

The regulation of gastric emptying is a complex process, depending on several factors that are listed in figure 2.12 (Hutston *et al.*, 1989; Schwartz *et al.*, 1995; Calbet & MacLean, 1997; Guidobono, 1998; Young & Denaro, 1998). Low pH and temperature, as well as high osmolarity, viscosity, fat and fibre content and caloric density delay gastric emptying (Brener *et al.*, 1983; Lin *et al.*, 1990; Lin *et al.*, 1993; Maerz *et al.*, 1994). The differences in the gastric emptying rates in different ethnic groups, suggest that the rate of gastric emptying is genetically determined. Estrogen and progesterone may be responsible for the decreased gastric emptying rate in females, but difference in body size may also play a role in that the males, with their larger bodies, will empty and absorb a specific meal faster than females (Schwartz *et al.*, 1995). Higher BMI is also associated with rapid gastric emptying and thus rapid small bowel absorption (Schwartz *et al.*, 1995).

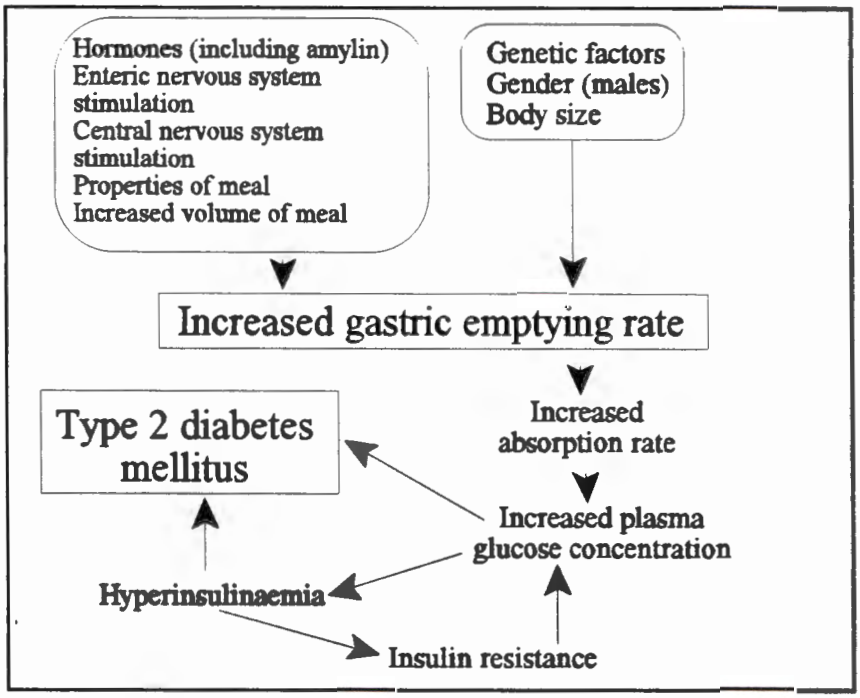

Figure 2.12: The factors influencing gastric emptying rate and how this may increase the risk for developing type 2 diabetes (Hutston *et al.*, 1989; Schwartz *et al.*, 1995; Calbet & MacLean, 1997; Guidobono, 1998; Young & Denaro, 1998)

An increased gastric emptying rate contributes to an increased rate of nutrient absorption (Schwartz *et al.*, 1995; Guidobono, 1998; Young & Denaro, 1998). This in turn will lead to greater elevation of postprandial glucose levels, which may result in compensatory hyperinsulinaemia and decrease of glucose transport (Schwartz *et al.*, 1995). Both these conditions will contribute to hyperglycaemia and increase the risk for type 2 diabetes (Schwartz *et al.*, 1995).

This hypothesis has been extensively tested in Mexican-Americans, but it may also play a role in

other populations. Schwartz and co-workers (1995) have shown that patients with recently diagnosed type 2 diabetes have a more rapid gastric emptying rate of glucose solutions than matched non-diabetic subjects. The fact that diabetes has been diagnosed only recently in this population rules out a possible effect of diabetes on gastric emptying. Rapid gastric emptying of quickly absorbable highly processed foods in the Western diet will increase an individual's risk of developing diabetes, especially if the individual has a genetically determined increased gastric emptying rate to start with (Schwartz *et al.*, 1995). An increased gastric emptying rate alone is probably not responsible for the increased prevalence of type 2 diabetes in certain populations.

2.3.8 Environmental risk factors

2.3.8.1 Introduction

There is strong evidence for the role of environmental risk factors in the unmasking of type 2 diabetes in genetically susceptible individuals (Zimmet, 1995; Zimmet *et al.*, 1997). These risk factors are summarised in figure 2.13. For the purpose of this study, environmental risk factors have been divided into fetal and early postnatal environmental factors and environmental factors associated with later life. It is important to note that, in this study, environmental factors are defined as any risk factors that are neither genetic nor metabolic.

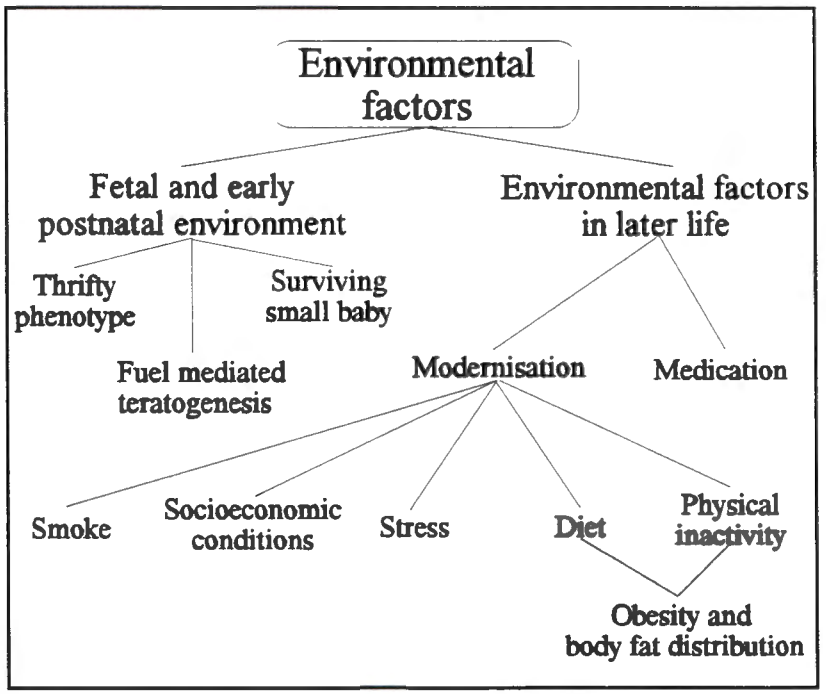

Figure 2.13: The environmental risk factors, that play a role in the development of type 2 diabetes (Alcolado & Alcolado, 1991; Zimmet, 1995; Zimmet *et al.*, 1997; Lebovitz, 1999; Nilsson, 1999; Buchanan & Kjos, 1999; Linquist *et al.*, 2000; Hanley, *et al.*, 2000)

2.3.8.2 Fetal and early life environmental factors

Recent studies suggested that intra-uterine and early postnatal environment may play a role in the transmission of type 2 diabetes (Alcolado & Alcolado, 1991; Lebovitz, 1999; Nilsson, 1999). This may complicate the interpretation of genetic studies (Alcolado & Alcolado, 1991). For instance, concordance rates of type 2 diabetes in identical twins may not be justifiable as identical twins share a common early nutritional environment (Gorman & Bowman, 1988). There are at least three hypotheses for the role of environmental factors during fetal development and early life.

(i) The thrifty phenotype hypothesis

Hales and Barker developed the thrifty phenotype hypothesis (Barker hypothesis) as an alternative to the thrifty genotype hypothesis (Hales & Barker, 1992). It states that type 2 diabetes is mainly the result of fetal and early postnatal environmental factors and that genetic factors play little or no role in its development (McCance *et al.*, 1994; O'Dea, 1995; Lebovitz, 1999; Nilsson, 1999; Ozanne & Hales, 1999). Nutritional deprivation will cause the foetus to divert nutrients to critical organs, such as the brain, at the expense of other organs such as the pancreas, liver and muscle (Hales & Barker, 1992; Simmons, 1995; Ozanne & Hales, 1999). This could have a permanent effect on the metabolic activity of these organs, predisposing the individual to glucose intolerance (GIT) and type 2 diabetes (Simmons, 1995; Fall *et al.*, 1995; Ozanne *et al.*, 1996; Zimmet *et al.*, 1997; Nilsson, 1999). Therefore, babies with a low birth weight (and weight at one year) are at higher risk for developing type 2 diabetes than babies with a normal birth weight (Hales *et al.*, 1991; McCance *et al.*, 1994; Terauchi *et al.*, 2000).

There are four possible mechanisms responsible for the association between intra-uterine under nutrition and the development of diabetes and GIT later in life (McCance *et al.*, 1994). These are impaired development of pancreatic beta-cells (Hales & Barker, 1992; Wilkens, 1993), acquired IR (Hales & Barker, 1992; Phillips *et al.*, 1994; O'Dea, 1995; Ozanne & Hales, 1999; Lebovitz, 1999), limited development of adipocytes, and the tendency to develop abdominal obesity (Stern, 1995).

It is difficult to prove the thrifty phenotype hypothesis, since both the nutritional status of the mother during pregnancy and the glucose tolerance status of the offspring as an adult are needed. The nutritional status of mothers during pregnancy is not always available and thus longitudinal studies with a long time-span are needed. For this reason many studies in this field are done in animals, such as rats and sheep, that reach "adulthood" faster than humans. The results obtained from these studies are very valuable but it cannot be extrapolated to humans. It is therefore necessary to test these results in humans. Studies proving or contradicting the thrifty phenotype hypothesis are listed in Table 2.8.

Table 2.8: Literature supporting and contradicting the thrifty phenotype hypothesis

Population group	Gender	Age	Method	Study outcome	Reference
American Indians (at least half Pima)	Males & Females	20 -39 years	Singleton pregnancies. Diabetic status of the mother is not known. Birth weight available. Two hour postload glucose values obtained.	Low and high birth weight associated with increased prevalence of type 2 diabetes. Development of type 2 diabetes was mostly associated with normal birth weight. Support the surviving small baby or the fuel mediated teratogenesis hypothesis.	Wilkins, 1993; McCance *et al.*, 1994
Wistar rats	Males	Young and Adult	Genetically similar control and test groups. Glucose transport determined by isolated muscle strip technique	Programming of muscle insulin sensitivity can occur during fetal life. Protein deficiency in fetal and early life results in decreased capacity to modulate glucose transport. Support the thrifty phenotype hypothesis.	Ozanne *et al.*, 1996
Caucasians United Kingdom	Males	59-70 years	Singleton babies. An oral glucose tolerance test Samples at time 0, 30, & 120 min	Found a strong link between reduced growth in early life and GIT or type 2 diabetes. Support the thrifty phenotype hypothesis.	Hales *et al.*, 1991
Study done in the United kingdom	Males	18 - 25 years	Birth weight &other obstetric data were known. Oral glucose tolerance tests with samples taken at 30 minutes.	Association between low birth weight and 30 minute postload glucose levels, was possibly due to a decrease in the number and/or size of the beta-cell component. Independent of gestational age, current body mass, height and social class. Support the thrifty phenotype hypothesis.	Robinson *et al.*, 1992
Study done in the United Kingdom	Males	About 51 - 64 years.	Obstetric data known. Adult anthropometry, social history, smoking habits and the alcohol intake known. No glucose status obtained.	A tendency towards central obesity may be a persisting response to adverse conditions and growth failure in fetal life. Central obesity is a risk factor for type 2 diabetes . The results were independent of adult height, smoking, alcohol consumption, social class and age. Support the thrifty phenotype.	Law *et al.*, 1992
Rats				Undernourishment for 7 generations in rats needs 3 generations of nutritional rehabilitation to recover.	Harding. 1995
Humans				Under nutrition in early pregnancy causes an increased rate of obesity in offspring.	Harding, 1995
Humans				Baby girls exposed to under nutrition in early gestation during the Dutch famine gave birth to small babies.	Harding, 1995

(ii) The surviving small baby theory

The thrifty phenotype hypothesis fails to take into account the high mortality rate amongst small babies. As an alternative McCance and co-workers (1994) proposed the surviving small baby genotype. They are of the opinion that the inverse relationship between birth weight and GIT in adult life will disappear if the small babies, who do not survive, are taken into account. McCance *et al.* (1994) suggested that the increasing prevalence of type 2 diabetes among subjects with low birth weight could reflect the selective survival of low birth weight infants who are genetically susceptible to develop type 2 diabetes. According to these researchers IR is associated with both low and high birth weights and thus the genetic predisposition to IR may represent the mechanism which facilitates such selective survival advantage that leads to a high prevalence of type 2 diabetes over many generations (figure 2.14) (McCance *et al.*, 1994). Several characteristics related to IR, besides DM and GIT, are found more often in subjects with low birth weights. These include abnormal insulin concentration, high blood pressure, and central obesity (McCance *et al.*, 1994).

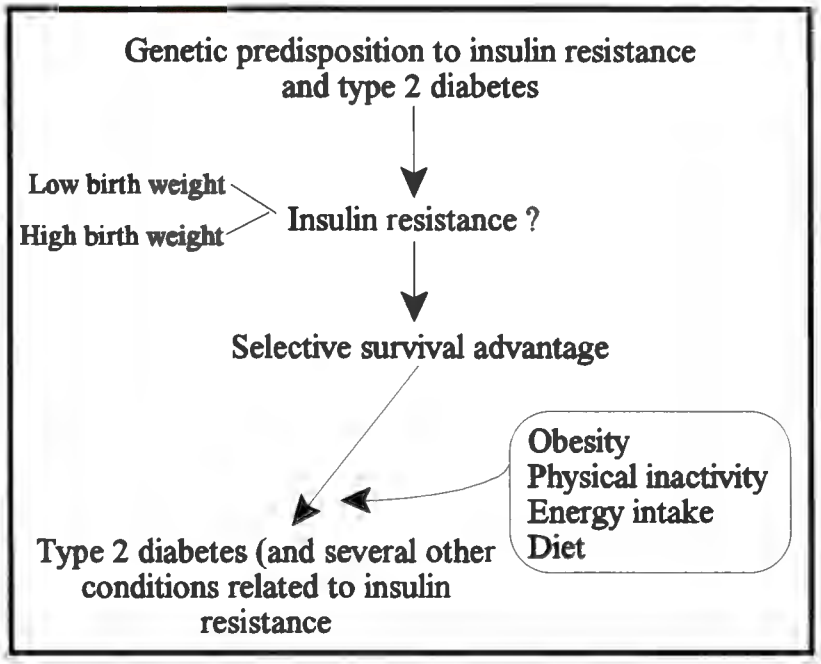

Figure 2.14: A possible mechanism explaining the surviving small baby hypothesis (McCance *et al.*, 1994)

It is difficult to prove the surviving small baby hypothesis due to the fact that the small babies who do not survive to develop type 2 diabetes mellitus cannot be investigated to determine their glucose tolerance status. Nevertheless, McCance and co-workers (1994) offered a mechanism that must be considered when investigating the effect of fetal and early environment on the development of type 2 diabetes.

(iii) Fuel mediated teratogenesis

The thrifty phenotype hypothesis fails to explain the increased prevalence of type 2 diabetes in large babies. The association between maternal diabetes, macrosomia and the high prevalence of type 2 diabetes in the offspring of diabetic parents have led to the development of the fuel mediated teratogenesis hypothesis (Simmons, 1995). This hypothesis proposes that exposure to high concentrations of glucose and other metabolic fuels in late gestation causes beta-cell hyperplasia, as can be seen in the macrosomic fetus, increasing the risk for type 2 diabetes (Simmons, 1995).

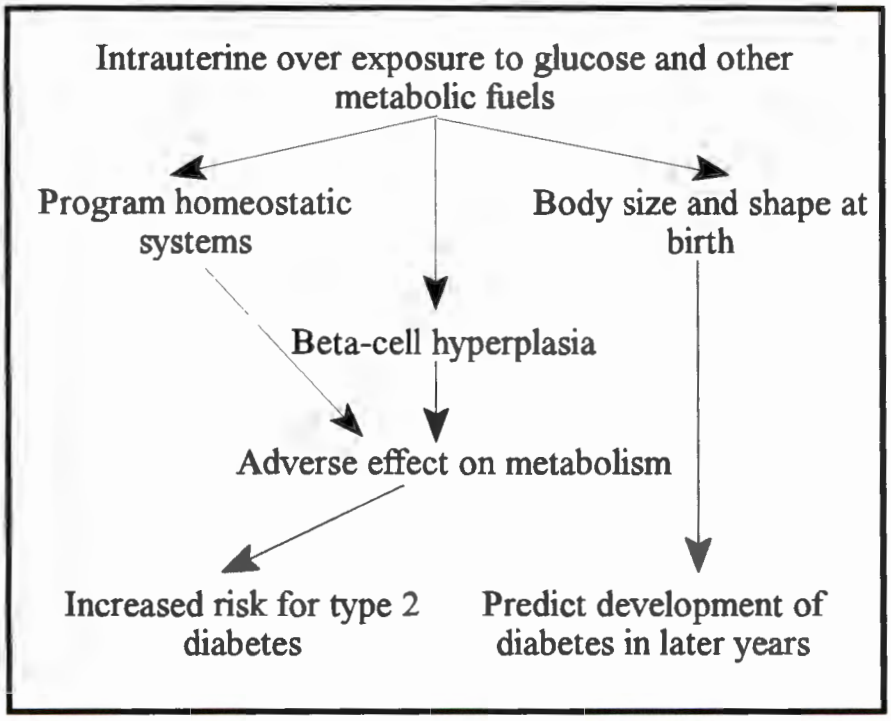

Figure 2.15: Possible mechanisms whereby the fuel mediated teratogenesis can predispose to the development of type 2 diabetes (Alcolado & Alcolado, 1991; Simmons, 1995; Harding, 1995)

Harding (1995) hypothesized that intra-uterine nutrition determines both birth phenotype and the programming of a number of key homeostatic systems in a way which predisposes to diseases such as type 2 diabetes (Harding, 1995). Thus, body size and shape at birth are strong predictors of the subsequent risk of developing type 2 diabetes. These effects of the phenotype at birth are independent of other known risk factors and it grows stronger with increasing age (Harding, 1995). It is important to remember that birth phenotype *per se* does not cause an increase in the risk to develop type 2 diabetes, but it is associated with an effect on the metabolism giving rise to a greater risk to develop the disease in adulthood. The possible mechanisms whereby the fuel mediated

teratogenesis can predispose to the development of type 2 diabetes, are shown in figure 2.15, and the results of studies which examined this hypothesis are summarised in Table 2.9

Table 2.9: Summary of studies proving the fuel teratogenesis hypothesis

Support or object to hypothesis	Population group	Study design or argument	Reference
Support	Rats.	Intrauterine hyperglycaemia results in type 2 diabetes persisting for at least 4 generations without a genetic predisposition.	Harding, 1995; Simmons, 1995
Support	Pima Indians	Offspring of women with GIT have a greater chance to develop type 2 diabetes than offspring of women with a normal glucose tolerance.	Wardzala, 1980; Alcolado & Alcolado, 1991; Cushman & Simmons, 1995
Support	Pima Indians	The development of type 2 diabetes was more common in offspring of women who developed type 2 diabetes during rather than after pregnancy.	Simmons, 1995
Support	European, Maori, Pacific island populations in Auckland.	Women with type 2 diabetes and previous gestational diabetes have an increased risk of having a diabetic offspring than the normal maternal risk.	Simmons *et al.*, 1995
Support		The study provides evidence that gestational diabetes predisposes to the development of type 2 diabetes in the offspring.	Hales & Barker, 1992
Oppose	Pima Indians hyperglycaemia	Most diabetic Pima Indians had birth weights in the normal range.	McCance *et al.*, 1994
Oppose		It was found that the largest babies in the study were the least likely to develop type 2 diabetes.	Robinson *et al.*, 1992

(GIT = glucose intolerance)

2.3.8.3 Environmental factors in later life

(i) Modernisation

Urbanisation can be defined as urban growth due to the migration of an increasing number of people from the rural areas to the cities and, to a lesser extent, from smaller to larger cities (Popkin, 1993). In the world history urbanisation is closely related to technological progress (Wilson, 1994). As a society becomes richer it spends a greater proportion of its income on things other than food. These things are generally produced in towns and hence there is a steady pressure taking people into towns (Wilson, 1994). Urbanisation in developing countries is often associated with poor housing and sanitation, chemical pollution, a breakdown of the social network in the family and community, a change in lifestyle and a change in the eating pattern (Telela & Mofara, 1994; Gross, 1995). Urbanisation is also a characteristic manifestation of cultural evolution taking place in almost all countries and communities independent of their economic, cultural, political or environmental

situations (Gross, 1995). Thus, urbanisation can be defined as a change in environment from rural to city.

Acculturation and Westernization on the other hand, are not so much changes in the environment as changes in the lifestyle. Acculturation means a change in the cultural rituals, language, social laws and eating patterns of an individual. Westernization can be seen as a form of acculturation whereby the person exchange his or her traditional lifestyle towards a typical Western lifestyle. In the context of this study this means that Africans would exchange traditional life in a tribe, in a rural area for life in a city, often as an individual. The term Westernization will therefore be the best of the two terms to use in this study.

Urbanization will necessarily lead to a degree of Westernization or acculturation which may differ from person to person and also from one town or city to the next. Urbanization takes relatively little time - a person simply moves from one place to another, but acculturation takes longer. It can take place over many years. For instance, a person who moved to the city may only succumb to a total Western diet over a period of time, although some changes in the diet will be necessary from the beginning because all the foods from the rural diet may not be available in the city.

Transition is the term used for the process of urbanisation and the associated acculturation. It includes all the changes taking place in such a person's life both during the move to the city and the process of acculturation.

Modernisation includes both transition and the degree of urbanisation and Westernisation brought to rural parts of the country during the past few years. These changes include the availability of water, electricity, shops, shopping centres, roads and motor vehicles as a mode of transport. The lifestyles of people living in rural areas changed as a result of the above-mentioned factors, without these individuals moving to towns or cities. Nevertheless, these lifestyle changes will have profound effects on the health of rural dwellers. Modernisation is therefore the term often used in this study.

The gap between the demands of a traditional rural community and those of a Western economy and lifestyle is enormous and will affect all facets of daily life (Malan *et al.*, 1992; Malan, 1995; Galloway, 1995). Factors that influence health including education, technology, culture, politics and economics are undergoing profound transition during the urbanisation process (Yach, 1995). Food and health services are more available in the city compared to the rural areas, but it is not always accessible to all households (Gross, 1995). As social class increase, the prevalence of unhealthy lifestyles will increase until education, income and occupation combine to reduce these behaviours (Yach, 1995).

Modernisation is characterised by increased life expectancy, due to lower morbidity and mortality from infectious diseases, and an increase in chronic diseases (Malan *et al.*, 1992; Popkin, 1993; Pollock, 1995; Shetty, 1997; Chucwuma & Tuomilehto, 1998). The WHO predicted that when the life expectancy of a community reaches 60 years, chronic diseases of lifestyle including type 2 diabetes will become major causes of death (Steyn, 1994). In 1985 the life expectancy of African females was already 61 years and that for African males 55 years (Steyn, 1994). The acquisition of risk for the development of chronic diseases seems to depend on the acculturation rate (Shetty, 1997; Chucwuma & Tuomilehto, 1998). Urban exposure has been identified as a significant independent risk factor for the prevalence of type 2 diabetes among Africans (Levitt *et al.*, 1993).

In 1988 hypertension, atherosclerosis and diabetes together with certain cancers were responsible for 24.5% of all deaths reported in South Africa (Steyn, 1994). The chronic diseases of lifestyle were between the top twenty causes of death in South Africa in 1990 (tobacco induced cancer - 2.5%; chronic obstructive lung disease, emphysema and bronchitis - 2.5%; cerebrovascular disease and stroke - 7.2%; ischemic heart diseases, atherosclerosis and heart attack - 8.7%; renal disease, end stage diabetes, osteoporosis and cirrhosis - 2.4%; Nutrition induced cancers - 1.2%) (Steyn, 1994; Bradshaw *et al.*, 1995). The absence of type 2 diabetes from this list may be explained by the fact that it is generally underestimated when a single cause of death is coded, and because diabetic patients more often die of the complications associated with the disease than of diabetes *per se* (Bradshaw *et al.*, 1995). It appears that the risk factors for chronic diseases of lifestyle are increasing in peri-urban and rural areas, indicating the prevalence of the diseases will increase in the future (Bradshaw *et al.*, 1995). The African population is currently experiencing the three to four-year incubation period of the chronic diseases and therefore these diseases may, at present, not seem very prominent in the mortality pattern of this population (Steyn, 1994). Chronic diseases of lifestyle will become more common in the developed sector of the South African population (Steyn, 1994). Several authors have reported on the increased prevalence of type 2 diabetes following modernisation (Shetty, 1997). Examples of the effect of modernisation on different populations are shown in Table 2.10

Table 2.10: The effect of modernisation on the prevalence of type 2 diabetes in different population groups

Population group	Effect of modernisation	Reference
Taiwanese in Taipei city	Prevalence of type 2 diabetes in the population older than 39 increased from 5.05% in 1970 to 8.17% in 1986.	Chen *et al.*, 1992
Africans in Africa	Urbanisation is associated with increased risk for the development of type 2 diabetes.	Levitt *et al.*, 1993
Africans in the rest of the world	Urbanisation is associated with increased risk for the development of type 2 diabetes	Mbanya et al., 1999
Indians in India	An increased prevalence of type 2 diabetes in urban compared to rural areas.	Singh *et al.*, 1995; Ramachandran *et al.*, 1999
Indian migrants to other countries	An increased prevalence of type 2 diabetes in migrants compared to Indians living on the Indian subcontinent.	Simmons *et al.*, 1989; McKeigue *et al.*, 1991; Bose, 1992
Polynesian migrants to New Zealand	Increased prevalence of type 2 diabetes two to three years after migration.	Maling *et al.*, 1995
Tokelauan migrants to New Zealand	Increased type 2 diabetes prevalence are probably linked to lifestyle and diet changes associated with modernisation.	Ostbye *et al.*, 1989

The ancestors of Africans were hunter-gatherers in the distant past, like the Bushmen today (Walker *et al.*, 1994). During the last century their lifestyle changed to one of pastoralism and dependency on subsistence (Walker *et al.*, 1994). More recently their lifestyle changed even more and today many Africans work on farms or in towns and cities (Walker *et al.*, 1994; Wilson, 1994; Galloway, 1995). In 1990 about 35.5% of the population in Africa lived in urban areas (Bourne *et al.*, 1993). In South Africa approximately 50% of the African population are living in urban areas and it is estimated that the urban African population will increase by 1 million per annum in the next 10 years causing an overburdening of particularly health services, and housing in the urban areas (Telela & Mofara, 1994; Galloway, 1995; Von Schirnding & Dada, 1995). In 2010, an estimated 70% of the population in South Africa will live in urban areas (Bourne *et al.*, 1993; Mollentze *et al.*, 1993), affecting mainly the African population. But modernisation has also moved to the rural areas. In the last half of the century transport and access to villages have improved and most villages now have a store, a clinic, a school, improved water supply and transport to towns (Walker *et al.*, 1994).

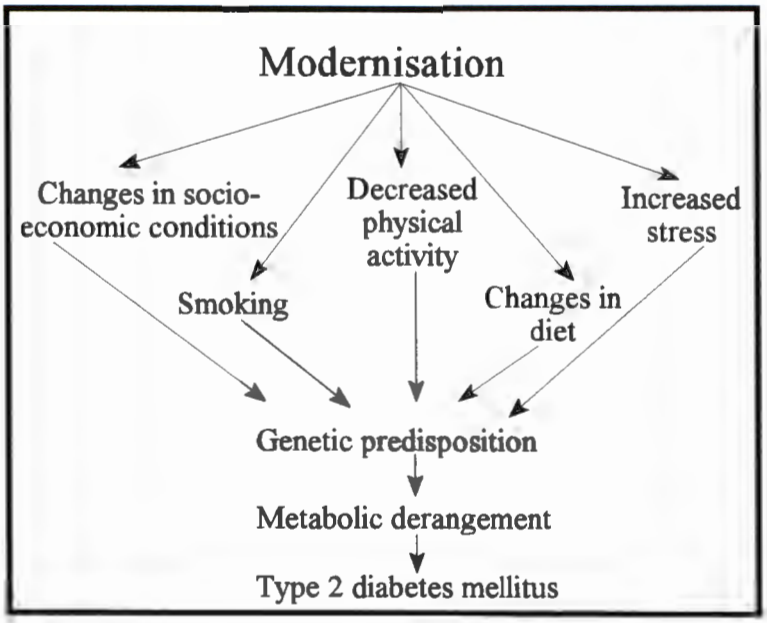

Figure 2.16: The relationship between genetic susceptibility and environmental risk factors associated with modernisation, in the development of type 2 diabetes (Malan *et al.*, 1992; Popkin, 1993; Steyn, 1994; Pollock, 1995; Shetty, 1997; Chucwuma & Tuomilehto, 1998; Chukwuma & Tuomilehto, 1998)

One possible explanation of the association between modernisation and type 2 diabetes is that there may be a genetic susceptibility to type 2 diabetes in certain populations, which is unmasked by environmental factors associated with modernisation (the thrifty genotype) as can be seen in figure 2.16 (Bose, 1992; Maling *et al.*, 1995; Shetty, 1997; Chukwuma & Tuomilehto, 1998). But differences in diet and lifestyle may be more important than genetic factors in the pathogenesis of type 2 diabetes among urbanites than among the rural population (Singh *et al.*, 1995). It seems that less rapid changes in diet and increased physical activity may cause better adaptation to a Western type of lifestyle and less risk of developing chronic diseases such as type 2 diabetes (Singh *et al.*, 1995).

Another explanation for the increased prevalence of type 2 diabetes may be that modernisation results in a decrease in mortality due to communicable diseases. This will result in more people reaching an age where type 2 diabetes is likely to occur (Pollock, 1995; Chucwuma & Tuomilehto, 1998). If this is the case, it is possible that the risk factors for type 2 diabetes have always been present in a population, even prior to urbanisation, but few individuals ever reached the age where the disease usually develops. This will be very difficult to prove and it is highly unlikely to be the case, since the prevalence of type 2 diabetes in the surviving population has been low.

Thus it is not modernisation *per se* that increases the risk for type 2 diabetes but rather the factors or changes associated with it, including smoking, stress, changes in socioeconomic conditions, changes in diet and decreased physical activity. These factors will be discussed in the following section.

(ii) Smoking

There is evidence that neuroendocrine abnormalities associated with smoking result in central obesity and insulin resistance (IR), which are both risk factors for the development of type 2 diabetes (Bjorntorp, 1997, 621; Mikhailidis *et al.*, 1998). It has been shown that although BMI is lower in smokers than in nonsmoker, smokers have significantly higher waist to hip ratios than nonsmoker (Jeffery *et al.*, 1989; Grievink *et al.*, 1995). Some studies also reported higher waist to hip ratios among smokers when age and total body fatness was considered (Troisi *et al.*, 1990; Grievink *et al.*, 1995). It is also possible that decreased physical activity due to the adverse effects of smoking on the cardiovascular and pulmonary systems are responsible for the impairment in insulin sensitivity (De Fronzo *et al.*, 1997, 683). Smoking may therefore increase the risk for type 2 diabetes by increasing the waist to hip ratio and IR. These possible mechanisms can be seen in figure 2.17. Smoking also has adverse effects on some of the complications associated with diabetes (Reichard & Rosenqvist, 1989; Reichard *et al.*, 1991; Mikhailidis *et al.*, 1998).

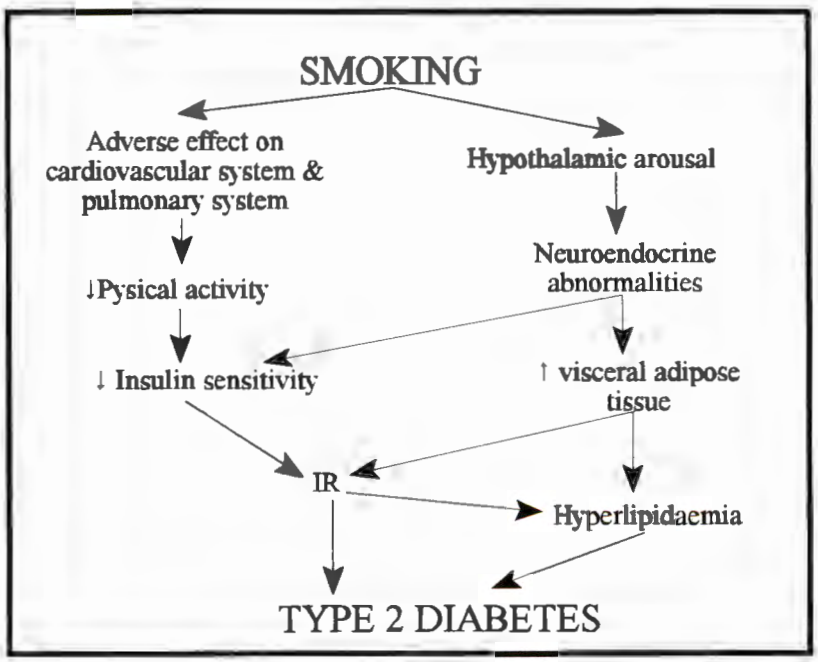

Figure 2.17: Possible mechanisms for the role of smoking in the development of type 2 diabetes (Reichard & Rosenqvist, 1989; Jeffery *et al.*, 1989; Troisi *et al.*, 1990; Reichard *et al.*, 1991; Grievink *et al.*, 1995; Bjorntorp, 1997, 621; Mikhailidis *et al.*, 1998)

(iii) Socioeconomic conditions

Shetty (1997) pointed out that nonbiological factors such as socialisation, civic-cohesion, "groupishness", aspiration, family structure, cultural factors, social-cohesion, psychological determinants and family structure are important determinants of chronic disease risk. These may also be common factors that link ethnic variations with socioeconomic differentials in the prevalence of chronic disease within a population.

(iv)Stress

It seems as if stress can precipitate diabetes onset and disrupt diabetes control (Peyrot *et al.*, 1999). However, no direct evidence of the role of stress in type 2 diabetes has so far been proved (Bradley, 1991). Urbanisation in Africa exposes many Africans to a process of social and cultural disruption leading to an increased level of stress (Malan *et al.*, 1992; Kruger *et al.*, 1994a; Peyrot *et al.*, 1999). Available evidence suggests that especially the females are affected, since they have no more hours to spend, and no higher proportion of their income to devote to others (Emmet *et al.*, 1994).

Stress-related factors may exert their effects by dietary and other behavioural changes, or by neuroendocrine mechanisms which are independent of behavioural factors (Bjorntorp, 1997, 621). Most scientists seem to favour the neuroendocrine mechanisms, which can be attributed to the fight or flight response (Surwitt *et al.*, 1992). This includes sympathetic discharge and elevation in circulating levels of catecholamines, glucocorticoids and growth hormone, resulting in elevated blood glucose levels (Bjorntorp, 1997, 621; De Fronzo *et al.*, 1997, 685). Over a period of time hyperglycaemia can impair the pancreas's ability to respond to a glucose stimulus via IR (Ostbye *et al.*, 1989; Bjorntorp, 1997, 621). Thus glucose toxicity that results from chronic intermittent stress-induced elevations in blood glucose may worsen already compromised pancreatic secretory ability (Ostbye *et al.*, 1989), leading to the progression of type 2 diabetes (Ostbye *et al.*, 1989). This mechanism is shown in figure 2.18.

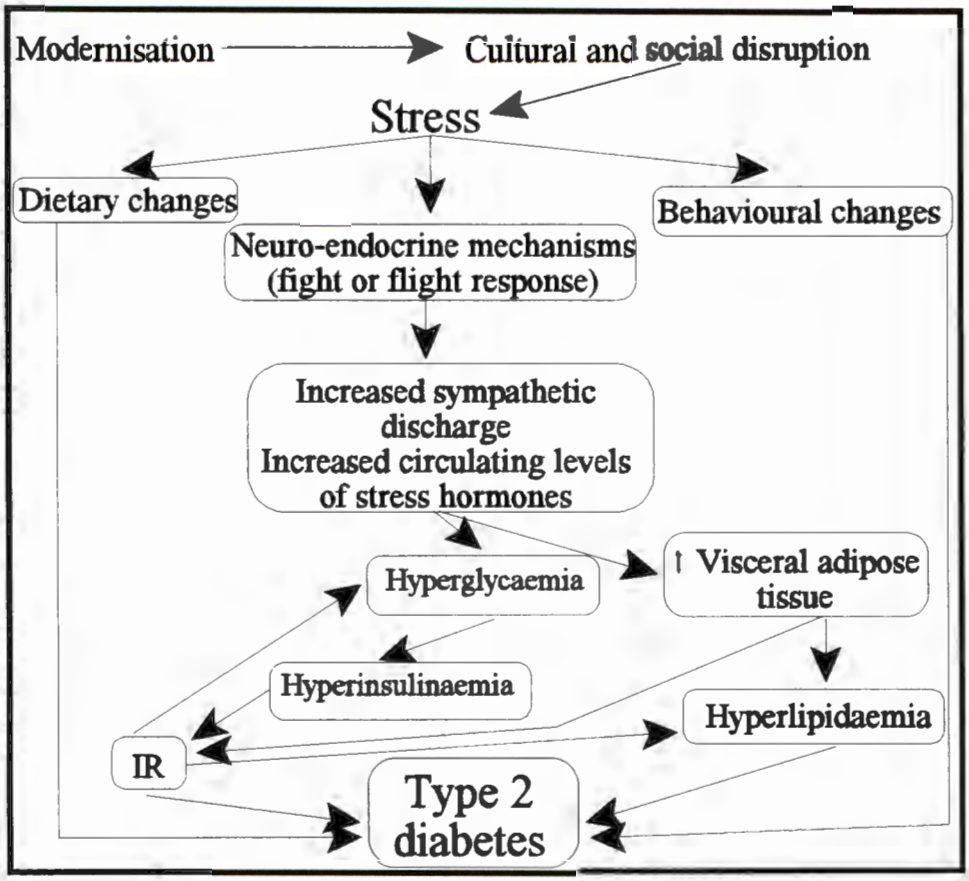

Figure 2.18: Possible mechanisms linking stress to the development of type 2 diabetes (IR= insulin resistance) (Ostbye *et al.*, 1989; Surwitt *et al.*, 1992; Malan *et al.*, 1992; Kruger *et al.*, 1994a; Emmet *et al.*, 1994; Bjorntorp, 1997,621; de Fronzo *et al.*, 1997,685)

Individuals with type 2 diabetes may be particularly sensitive to stressful environmental stimulation, due to increased adrenergic sensitivity in the pancreas (and perhaps other sites as well), which could result in increased insulin release (Surwitt *et al.*, 1992). Exaggerated glycaemic reactivity to behavioural stress also appears to be characteristic of at least some individuals who are predisposed to develop type 2 diabetes (Surwitt *et al.*, 1992). It appears as though the diabetes-prone Pima Indians have a specific glucoregulatory defect that becomes apparent during stress (Surwitt *et al.*, 1992). Other stimuli such as dietary fat and simple carbohydrates (CHO's) may also contribute more to the development of type 2 diabetes through this adrenergic mechanism (Surwitt *et al.*, 1992). The effects of stress in obese animals are more pronounced compared to lean animals (Surwitt *et al.*, 1992). Thus, the combined effects of increased obesity and stress associated with modernisation may result in the development of type 2 diabetes in subjects with a susceptibility for the disease. It seems to be highly unlikely that the stress associated with modernisation alone can precipitate in type 2 diabetes in the absence of other risk factors.

(v) Diet as a risk factor for the development of type 2 diabetes

Migrants to urban areas tend to adopt a Western dietary pattern (Popkin, 1993; Solomons & Rainer, 1995; Shetty, 1997; Drewnowski & Popkin, 1997; Kromhout & Bloemberg, 1997; Gaskin, 1999). The effects of a more regular diet due to modernisation are very complex, but it is followed by large increases in diet-related chronic diseases, including type 2 diabetes (Pollock, 1995; Shetty, 1997; Drewnowski & Popkin, 1997; Kromhout & Bloemberg, 1997). The effect of modernisation on the diet and the resultant increase in type 2 diabetes are shown in figure 2.19. It will also lead to the development of obesity, thereby further increasing the risk for type 2 diabetes (Ostbye *et al.*, 1989). Diet not only influences health, but is itself influenced by numerous factors (Brunner, 1997).

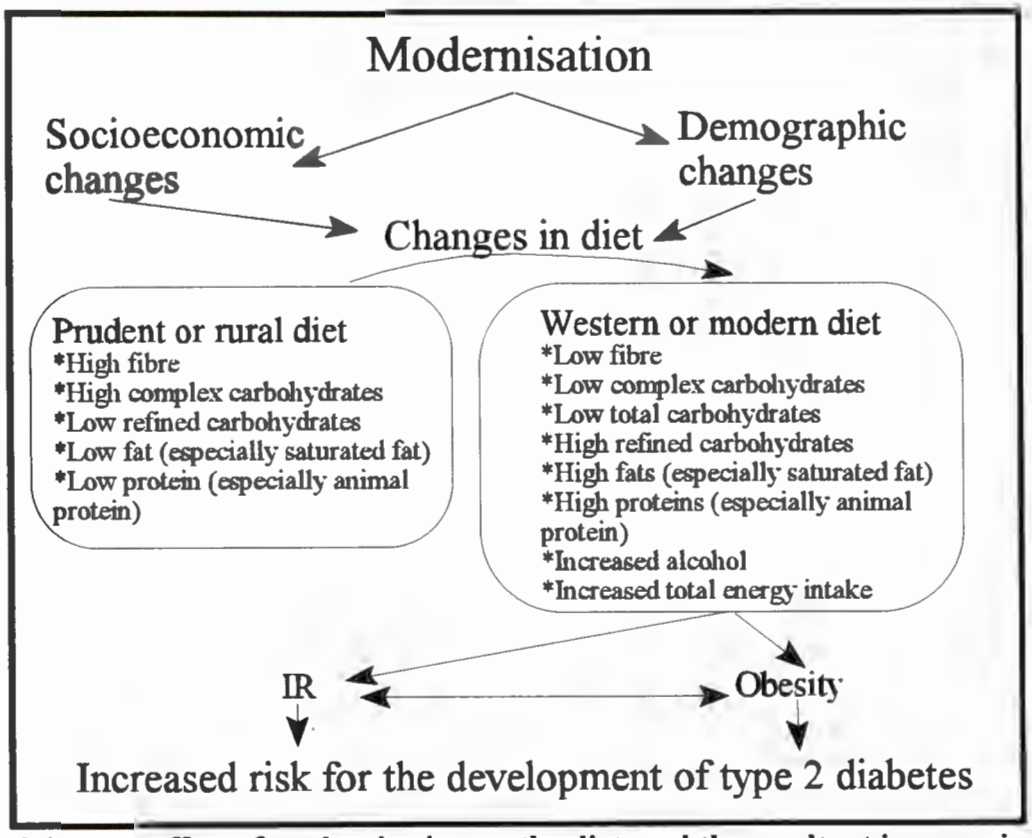

Figure 2.19: The effect of modernisation on the diet, and the resultant increase in type 2 diabetes (Ostbye *et al.*, 1989; Popkin, 1993; Solomons & Rainer, 1995; Pollock, 1995; Shetty, 1997; Drewnowski & Popkin, 1997; Kromhout & Bloemberg, 1997; Brunner, 1997; Gaskin, 1999; Sprietsma, 1999)

The Western diet is associated with high intakes of animal proteins, fat (especially saturated fat), cholesterol, sugar, processed products, and refined foods (Pitout, 1992; Shetty, 1997; Drewnowski & Popkin, 1997; Sprietsma, 1999). These are all more available in the urban environment than in

the rural settlement (Pollock, 1995; Drewnowski & Popkin, 1997). Furthermore, the Western diet is associated with low intakes of fibre, complex carbohydrates, and polyunsaturated fats. Fat and animal protein intake increase and carbohydrate intake decreases as the length of urban exposure increases (Bourne, 1995; Sprietsma, 1999).

Several aspects of the western diet are implicated in the etiology of type 2 diabetes as can be seen in figure 2.20. These factors will be discussed briefly.

The role of dietary fibre

Type 2 diabetes is associated with a diet low in dietary fibre (Schneeman, 1986). Evidence suggests that dietary fibre has a protective role in the prevention of type 2 diabetes, because it modulates and slows down the absorption rate of a meal, and is, therefore, associated with a reduced glucose and insulin response (Schneeman, 1986; Vorster, 1994; Mann, 1997). The activity of the digestive enzymes in the small intestine could also be diminished in the presence of certain types of dietary fibre (Schneeman, 1986).

Some studies provide indirect support for this hypothesis (Mann, 1997). Countries with high intakes of fibre have low rates of diabetes and the reduced mortality rates for diabetes during and after the second world war parallelled the increased intake of dietary fibre during that period (Mann, 1997). Vegetarian men have a lower prevalence and incidence of type 2 diabetes compared to non vegetarian men, independent of obesity and physical activity (Snowdown, 1988). Diabetes risk is also lower in Seventh day Adventists who are vegetarians, than in those who are not strict vegetarians (Mann, 1997). These fibre rich diets are typically lower in fat (especially saturated fat) and protein levels than low fibre diets and also differ in micronutrient composition (Schneeman, 1986; Mann, 1997). Thus, there are confounding factors influencing the association between a fibre rich vegetarian diet and protection against type 2 diabetes. Although at least one study found no association between fibre intake and the risk of type 2 diabetes, the overall weight of evidence suggests that individuals who consume diets rich in soluble dietary fibre are at reduced risk of developing diabetes (Mann, 1997).

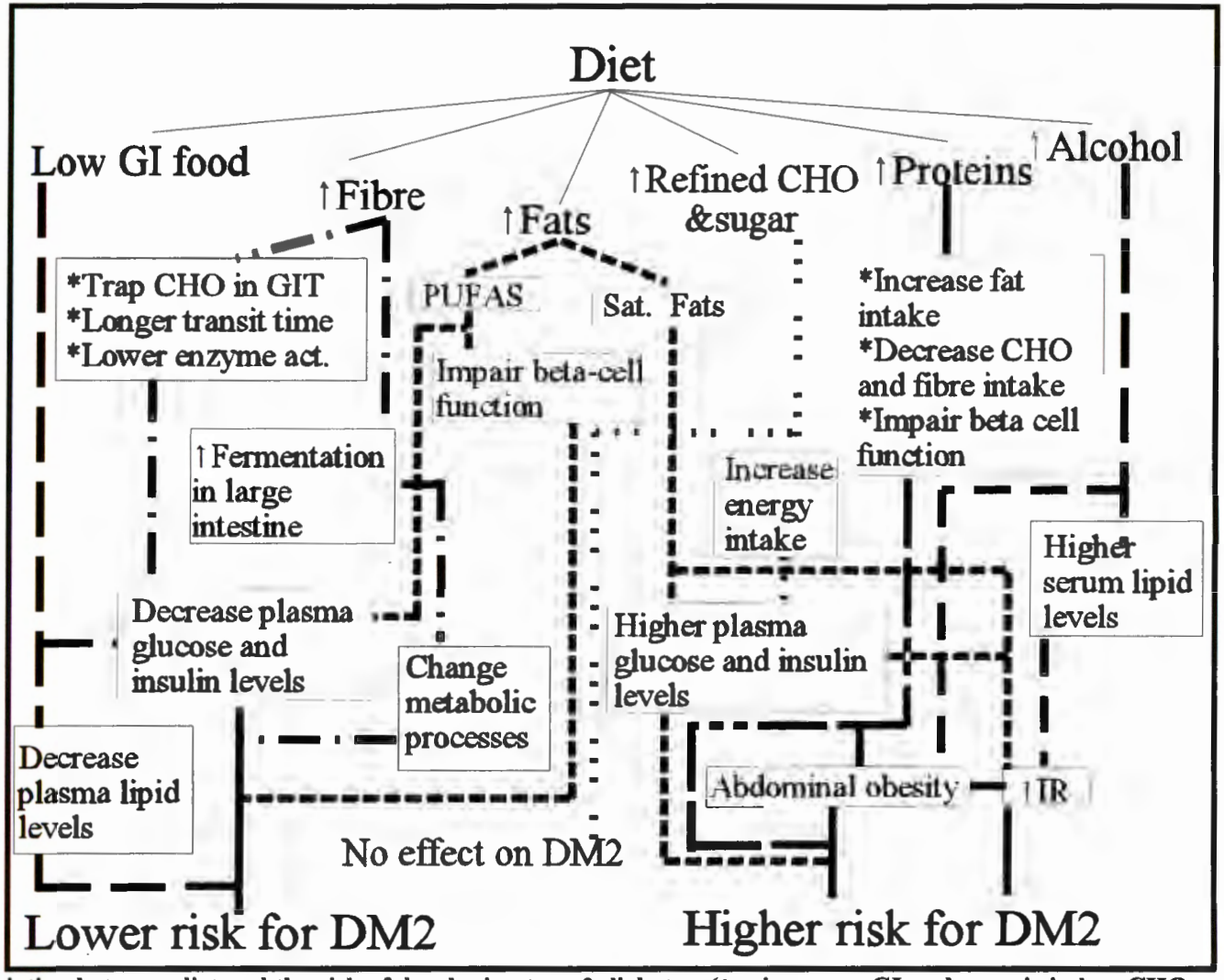

Figure 2.20: The association between diet and the risk of developing type 2 diabetes (↑ = increase; GI = glycaemic index; CHO = carbohydrates; GIT = gastrointestinal tract; act. = activity; PUFAS = polyunsaturated fatty acids; Sat. Fats = saturated fatty acids; IR = insulin resistance) (Shneeman, 1986; Wolever *et al.*, 1991; Maron *et al.*, 1991; Vorster, 1994; Wolever *et al.*, 1994; Dachicourt, *et al.*, 1996; Mann, 1997)

The role of low glycaemic index foods

Low glycaemic index (GI) foods may protect against the development of type 2 diabetes, independent of energy intake and BMI, and are inversely related with the risk of glucose intolerance (GIT) (Mann, 1997). Reduction of the overall glycaemic impact of the diet by incorporating foods with low GI's, with no changes in macronutrients or dietary fibre, decreases postprandial blood glucose and insulin responses and improves overall blood glucose and lipid concentrations in normal and diabetic subjects (Wolever *et al.*, 1991; Wolever *et al.*, 1994; Seewi *et al.*, 1999). Although Mann (1997) found no association between carbohydrate or fibre intake and the risk of type 2 diabetes, the overall weight of evidence suggests that individuals who consume diets with a low GI may be at reduced risk of developing type 2 diabetes (Mann, 1997).

The role of refined carbohydrates and sugar

More than 40 studies have examined the role of sugar in the aetiology of type 2 diabetes with about half suggesting a positive association and a comparable number suggesting no association (Mann, 1997). Carefully controlled studies in type 2 diabetics provide evidence to suggest that sucrose is not an important contributing factor in the aetiology of type 2 diabetes (Mann, 1997).

The role of dietary fats

Several prospective studies found an association between fat intake and subsequent risk for the development of type 2 diabetes (Mann, 1997). Countries with increased fat and decreased CHO intakes have higher prevalences of type 2 diabetes and obesity compared to countries with decreased fat and increased CHO intakes (Maron *et al.*, 1991; Mann, 1997). One study found no association between fat intake and risk of type 2 diabetes (Mann, 1997). However, diets which are high in CHO's are likely to be low in fat so that it may be impossible to disentangle the consequences of increased intakes of the fat and low intakes of CHO's (Mann, 1997).

Not only the amount, but also the type of dietary fat may be relevant, saturated fatty acids may increase the risk for type 2 diabetes, while polyunsaturated fatty acids are negatively related to postprandial glucose levels (Mann, 1997) and to insulin sensitivity or function (Maron *et al.*, 1991; Dachicourt *et al.*, 1996; Mann, 1997). Hepatic handling of insulin may be modulated by habitual fat intake and on a high fat diet, insulin secretion may increase to suppress hepatic glucose production resulting in IR (Cruickshank *et al.*, 1991; Maron *et al.*, 1991; Mann, 1997). N-3 polyunsaturated fatty acids may also have an important role in the development of type 2 diabetes, habitual fish eaters were shown to have a 50% lower risk of developing GIT compared with those who are not regular fish eaters (Mann, 1997). Furthermore addition of N-3 polyunsaturated fatty acids to the diet of healthy volunteers resulted in a significant increase in insulin sensitivity, and replacement of linoleic acid by saturated fatty acids resulted in an increase in blood glucose levels and insulin requirements (Mann, 1997). N-3 polyunsaturated fatty acids have an influence on the

production of eicosanoids which in turn may have an appreciable effect on pancreatic beta-cell function (Mann, 1997). Dietary fat and particularly saturated fatty acids, may play a role in the development of obesity, influencing risk of type 2 diabetes (Romieu *et al.*, 1988; Dreon *et al.*, 1988).

The role of proteins

There are no firm epidemiological data concerning the role of protein intake in the etiology of type 2 diabetes (Mann, 1997). The strong positive associations between animal protein and saturated fatty acids, and vegetable protein and dietary fibre make it almost impossible to disentangle separate effects in epidemiological studies (Mann, 1997). Some amino acids such as arginine, leucine and phenylalanine, have been shown to influence beta-cell function (Mann, 1997). Although populations living traditionally rural seem to be protected from diabetes, severe deprivation of proteins and energy may result in type 2 diabetes (Mann, 1997).

The role of alcohol

The pattern of alcohol use increases with Westernisation (Ostbye *et al.*, 1989), and lately increased consumption of alcohol was noted even in rural parts. Alcohol intake has been shown to be associated with increased abdominal adiposity (Troisi *et al.*, 1990) and serum lipid levels (Gaziano *et al.*, 1993), and thus it is one of the dietary factors thought to contribute to obesity and hence to IR (Lee *et al.*, 1995). In a French prospective study abnormal liver function tests, used as an indicator of alcohol excess, were an independent predictors of 4 year diabetes risk in middle aged men (Mann, 1997). In the Rancho Bernardo study increasing intakes of alcohol in obese men were associated with an increased risk of diabetes (Mann, 1997). However, a light to moderate intake of alcohol is associated with enhanced insulin sensitivity (Mann, 1997). In another study it was found that among men with a BMI $\geq$22.1 kg/m^2, moderate alcohol consumption was associated with a reduced risk of type 2 diabetes, but among men with a BMI $\leq$22.1 kg/m^2, heavy alcohol consumption was associated with an increased risk of type 2 diabetes (Tsumura *et al.*, 1999)

The effect of iron overload

Iron participates in a wide range of biochemical pathways that govern cellular metabolism, but iron absorption is regulated via poorly understood mechanisms to maintain body iron stores at optimum levels while keeping the risk of iron toxicity to a minimum (Ryan & Aust, 1992). The liver is the major iron storage organ and therefore a close association exists between iron and liver disorders (Tandon, *et al.*, 2000)There is no effective physiological mechanism for the excretion of excess body iron, hence increased ingestion or absorption of iron would increase body iron stores and hepatic injury (Halliday & Powell, 1992).

Diabetes mellitus occurs in over 75% of patients with hemochromatosis (Del Prato & Tiengo 1997, 194). Concomitant liver cirrhosis can affect the glucose metabolism, but can not fully account for the diabetic condition (Del Prato & Tiengo, 1997, 194). In patients with hemochromatosis diabetes is an early complication and it often precedes the clinical recognition of hemochromatosis by about 1 year (Saddi & Feingold, 1974). It is rarely associated with obesity and affects males ten times more frequently than females (Del Prato & Tiengo, 1997, 194). Diabetes and hemochromatosis have independent genetic transmission and the diabetes results from the interaction of a diabetic genetic predisposition and pancreas infiltration by excess iron (Del Prato & Tiengo, 1997, 194). Iron infiltration or destruction may be considered an environmental factor capable of unmasking the diabetic predisposition. It is associated with low levels of insulin, reflecting a primary defect in beta-cell function. IR is common, probably due to the coexisting hepatic cirrhosis (Del Prato & Tiengo, 1997, 194). Two recent studies on African pedigrees provided evidence that in some individuals exposed to increased dietary iron, a genetic defect allows an elevation in serum ferritin and in transferrin saturation and a decrease in unsaturated iron binding (Gorduek, *et al.*, 1992; Moyo, *et al.*, 1998).

It has been shown that iron overload may be associated with the metabolic syndrome in some individuals (Ferrannini, 2000). The mechanisms underlying the association of iron overload, liver damage, or both with the metabolic syndrome have not been identified. Defects in both insulin action and secretion are common among patients with familial hemochromatosis. Also genetic hemochromatosis is more frequent among diabetic patients than in the non-diabetic population (Ferrannini, 2000). Thus genetic linkage may exist between hemochromatosis and diabetes, and this may explain the co-occurrence of iron overload and the metabolic syndrome. At the physiological level, hepatic iron overload, with hepatic steatosis may interfere with insulin extraction in the liver, and thereby contribute to peripheral hyperinsulinaemia with the attendant downregulation of insulin receptors and hence, insulin action (Del Prato, et al., 1994). In this proposed sequence, central obesity would be the dominant feature of the metabolic syndrome (Ferrannini, 2000). Alternatively insulin resistance may lead to liver steatosis from unrestrained lipolysis and increased delivery of non-esterified fatty acids to the liver (Reaven, 1995). Transferrin receptors, insulin-regulatable glucose transporters, and insulin-like growth factor II receptors have been shown to co-localise in microsomal membranes in cultured adipocytes, and insulin causes the simultaneous translocation of all three proteins to the coll membrane (Tanner & Lienhard, 1989). Thus, one of insulin's primary actions, namely to stimulate glucose transport, may be inherently coupled with the redistribution of transferrin receptors to the cell surface, where they mediate uptake of extracellular iron (Ferrannini, 2000). If the effect of insulin on transferrin receptors was also present in hepatocytes or reticuloendothelial cells, it could be tempting to speculate that the hyperinsulinaemia

of the metabolic syndrome may be directly responsible for the accumulation of iron in the liver (Ferrannini, 2000). Another explanation involves inflammation, since the metabolic syndrome is an atherogenic state, widespread activation of inflammatory cytokines in the subendothelial space increases transcription of ferritin mRNA in macrophages; these cells may subsequently transfer ferritin to hepatocytes (Ferrannini, 2000).

Secondary hemochromatosis DM is not genetically linked, but associated with a massive iron overload (Isaakson *et al.*, 1961; Köppel & Int'Veld, 1997, 304). According to Köppel & Int'Veld, (1997, 304), in this type of diabetes insulin secretion may only be moderately impaired, but hyperglucagonaemia is almost universally encountered. Iron infiltration of the pancreas is often found in rural male Africans. Many African males ingest more than 100mg of iron per day in the form of alcoholic drinks which are brewed in iron containers. In such individuals the prevalence of DM is ten times higher than in African males who do not consume such alcoholic beverages. Iron deposits are restricted to the beta-cells (Rahier *et al.*, 1987) and are associated with a loss of insulin granules. This suggests that an iron overload of the beta-cells affects insulin biosynthesis thereby resulting in the development of DM. As beta-cell destruction does not occur in this type of diabetes, it differs from type 1 diabetes. The mechanism of how the iron interferes with beta-cell function and why it does not affect the other cells in the pancreas remain to be explained.

In experimental studies on small animals, the addition of iron salts to the diet has been shown to cause excessive iron deposition. The spleen is most affected, followed by the liver and the kidney, but with only traces in the pancreas. However, in the studies made on rats, the diets used has a much higher iron concentration than that found in African diets . The pattern of distribution of iron in the animals was found to be similar to that observed chemically and histopathologically in siderosis in Africans (Walker & Segal, 1999). It is not clear why iron deposits in the pancreas were so low and how this impacts on the development of diabetes due to iron overload in Africans, but it may be due to the fact that Africans may have a genetic predisposition for iron overload.

(vi) Physical activity

The effects of physical activity on blood glucose are still controversial (Gautier *et al.*, 1995; Mourier *et al.*, 1997). Physical activity increases energy expenditure, which plays an important role in the development of obesity (Pollock, 1995) and in the prediction of future weight gain (Ravussin, 1995). It has been shown that males with a high level of spontaneous activity are less likely to gain weight (Zurlo *et al.*, 1992). It is possible that exercise exerts a positive effect on blood glucose levels through its effects on obesity. This may explain the protective role of exercise in the

prevention and treatment of type 2 diabetes. It may also explain why decreased physical activity is associated with an increase in the prevalence of type 2 diabetes.

Physical activity levels decrease as the level of modernisation increases, as is shown in figure 2.21. This is caused by mechanisation in transport and place of employment (Jenkins & Jenkins, 1994). According to Pollock (1995) energy expenditure has changed with new activities and the day's length extended by electricity, but have not necessarily been reduced. Furthermore, in some populations the decrease in energy expenditure may be less than in others (Pollock, 1995), or it may take on more intense forms, such as participation in sport (Pollock, 1995).

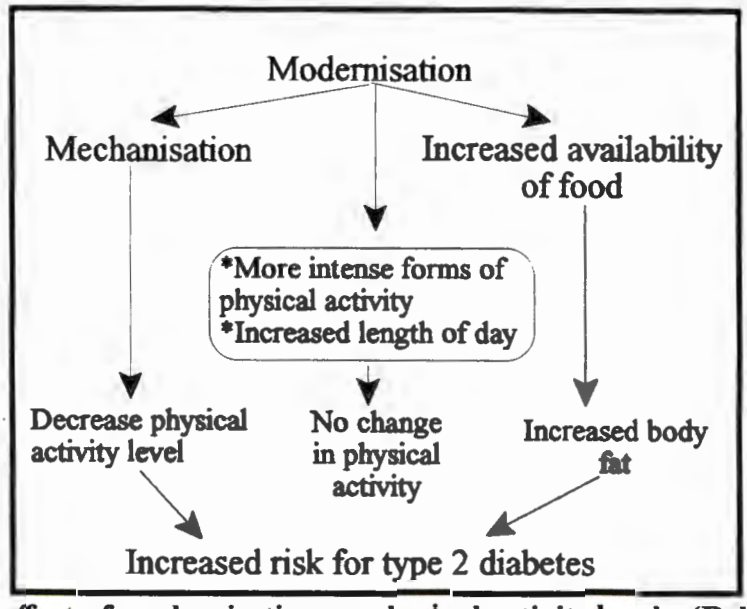

Figure 2.21: The effect of modernisation on physical activity levels (Rebuffs-Scribe *et al.*, 1990, Zurlo *et al.*, 1992; Fried *et al.*, 1993; Jenkins & Jenkins, 1994; Ravussin, 1995; Pollock, 1995; Gautier *et al.*, 1995; Mourier *et al.*, 1997)

The possible mechanisms whereby physical activity affects type 2 diabetes are shown in figure 2.22. Exercise leads to increased muscular glucose intake, which in turn increases insulin sensitivity and decreases IR (Mourier *et al.*, 1997; ADA, 1998a). It also decreases fat-mass accumulation (Mourier *et al.*, 1997; ADA, 1998a). This may be the result of increased lipolysis in omental and mesenteric adipocytes in response to catecholamines, released during exercise (especially high intensity exercise) (Rebuffs-Scribe *et al.*, 1990, Fried *et al.*, 1993, Maurier *et al.*, 1997). The decrease in visceral adipose tissue as a result of lipolysis may then decrease IR (Maurier *et al.*, 1997).

The factors that contribute to the increment in insulin sensitivity after physical training include: increases in glucose transport and storage, membrane GLUT4 proteins, muscle GLUT4 content and

nonoxidative glucose disposal (Dela *et al.*, 1993, Ebeling *et al.*, 1993). Thus, physical activity may exert its effect on the glucose metabolism through increased obesity and decreased absorption of glucose, due to decreased insulin sensitivity and increased IR.

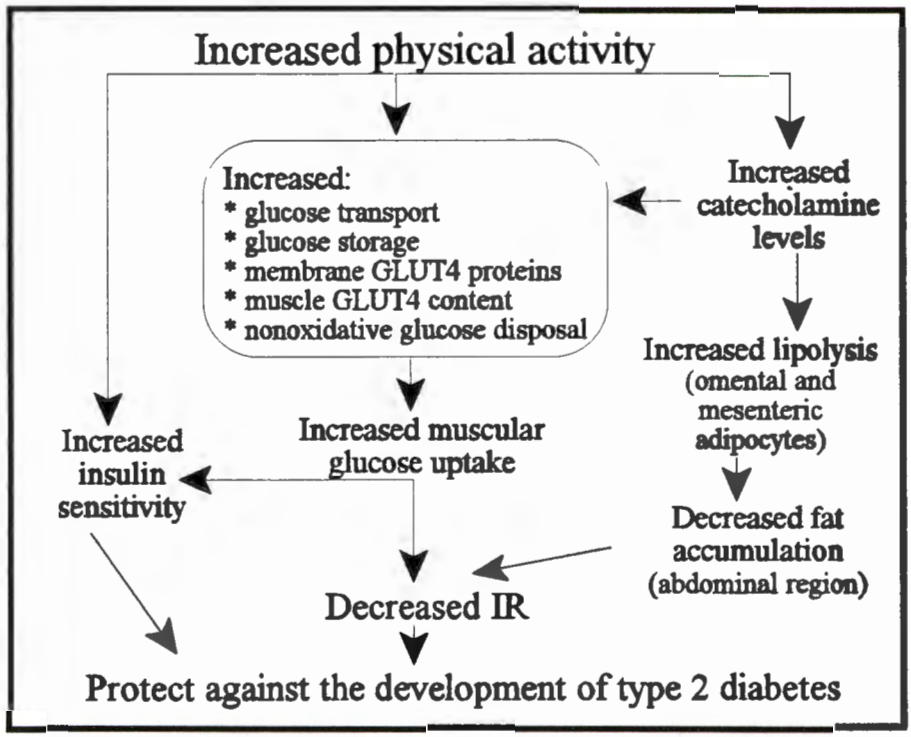

Figure 2.22: The effects of physical activity on type 2 diabetes mellitus: possible mechanisms (Rebuffs-Scribe *et al.*, 1990, Fried *et al.*, 1993, Dela *et al.*, 1993, Ebeling *et al.*, 1993; Maurier *et al.*, 1997; ADA, 1998a)

(vii) Obesity

Most researchers define obesity as an inappropriate fat or energy balance (Prentice, 1992), or excessive body weight (Kruger *et al.*, 1994b). It can also be defined as a body mass index (BMI) greater than 25 Kg/m^2 for men and 27 Kg/m^2 for women (National Diabetes Data Group, 1979; WHO, 1995). The prevalence of obesity varies along racial lines and is greatly influenced by gender and age (Rutledge, 1994). It is more prevalent in minority populations and it is also relatively common in Europe especially among women in South and East Europe (Kumanyika, 1993; Conway et al., 1995; Seidell, 1995). Female obesity of adult onset is observed universally in all socioeconomic groups. There is an independent relationship between BMI and the development of type 2 diabetes (Perry *et al.*, 1995; Shaper *et al.*, 1997; Williams *et al.*, 1998). Obesity is present in 50-80% of the individuals in various type 2 diabetes populations and approximately 75% of obese individuals will develop the disease (Roder *et al.*, 1999; Kennedy, 1999). It seems that the relative risk of type 2 diabetes increases progressively from a BMI >20 Kg/m^2, especially in industrialised societies (Shaper *et al.*, 1997; Sjostrom, 1997; Brunner, 1997; Mourier *et al.*, 1997).

There is a high prevalence of obesity in South Africa especially in women, and more so in African women, even when controlling for socioeconomic status (Steyn *et al.*, 1991; Kruger *et al.*, 1994b; Rutledge, 1994; McGarvey, 1995). The high prevalence of obesity in Africans may be explained by the fact that the African community has a more tolerant social climate for obesity (Walker *et al.*, 1991; Kruger *et al.*, 1994b). They view it not as a health problem, but rather as a normal and attractive state, associated with health and prosperity, whereas lean people are believed to be ill and poor (Kruger *et al.*, 1994). Although the results from studies concerning the risk of obesity for type 2 diabetes in South Africa are contradicting, obesity has been implicated as a risk factor in the development of type 2 diabetes in all population groups (Michael, *et al.* 1971; Levitt & Mollentze, 1995). It does not seem to play a very important role in the development of type 2 diabetes in the Indian population (Omar *et al.*, 1985a; Omar *et al.*, 1994; Levitt & Mollentze, 1995).

Obesity has been shown to be an important risk factor for type 2 diabetes in urban Africans and African females (Levitt & Mollentze, 1995). In a study done in the Free State, it was found that a BMI of 25 Kg/m^2 or more was associated with (GIT) in the urban, but not in the partly rural population (Levitt & Mollentze, 1995). But Walker and co-workers (1991) found no differences in the prevalence of hyperglycaemia or hyperlipidaemia between obese and nonobese Africans. Studies on African Americans suggested that Africans have lower caloric requirements and more efficient energy utilization than Europeans of the same body weight (the thrifty genotype hypothesis) (Bourne *et al.*, 1993). This may explain why Africans, who are faced with excessive energy availability after modernisation, develop type 2 diabetes.

There is a strong association between obesity, type 2 diabetes and IR, but the nature of this relationship and the contribution of obesity to the development of type 2 diabetes and to the IR of the disease remains controversial (Pories *et al.*, 1992; Ludvik *et al.*, 1995; Swinburn, 1995; Roder *et al.*, 1999). Many type 2 diabetics are at least moderately obese and although this may be inherited as a separate genetic trait, it often precedes the development of type 2 diabetes and it seems to have a delayed value to predict the onset of type 2 diabetes about five years prior to the onset of the disease (Nuttal, 1988; Levitt & Mollentze, 1995). In Table 2.11 studies, which examined different hypotheses concerning the relationship between obesity and development of type 2 diabetes, are summarised.

Table 2.11: Research supporting the different hypotheses concerning obesity as a risk factor for the development of type 2 diabetes

Hypotheses supported	Results of the studies	References
Obesity *per se* does not cause DM2.	Tests done on Asians living in Britain.	Simmons *et al.*, 1989; McKeigue, *et al*, 1991
Obesity *per se* does not cause DM2.	Tests done on South island populations. Only weak association between obesity and DM2.	Barker, 1995
Obesity causes DM2.	In native Americans obesity almost always leads to DM2.	Stuart *et al.*, 1994
Obesity causes DM2.	In migrants and non migrants in Tokelau, obesity leads to DM2.	Ostbye *et al.*, 1989
Obesity causes DM2.	In African women with a prevalence of obesity > 50%, have high rates of DM2.	Otten *et al.*, 1984
Obesity causes DM2.	A significant amount of overweight adolescents develop DM2 or GIT in adulthood. Makes no statement on the role of IR.	Must *et al.*, 1992; Le Stunff & Bougneres, 1996
Obesity causes DM2.	Makes no statement on the role of IR. Compared lean, moderately obese and severely obese females.	Hartz *et al.*, 1983
Obesity is not the only cause of DM2.	Indians older than 40 years, with obesity, a family history of diabetes, female sex, and urban origin have an increased risk for type 2 diabetes.	Zargar *et al.*, 2000
Obesity is not the only cause of DM2.	Increased secretory demand from obesity-associated IR cannot explain elevated intact proinsulin and disproportionate hyperproinsulinemia in type 2 diabetes.	Roder *et al.*, 1999
Obesity is not the only cause of DM2.	Obesity is only weakly associated with DM2 in Pima Indians without a family history of DM2.	Ostbye *et al.*, 1989
Obesity is not the only cause of DM2.	The high prevalence of obesity in Mexican Americans does not completely account for the high prevalence of DM2.	Schwartz *et al.*, 1995
Question the role of IR in causing DM2 in obese individuals.	Relationship between obesity and IR were found to be not very tight.	Swinburn *et al.*, 1991
Question the role of IR in causing DM2 in obese individuals.	Several studies, but IR were calculated using different methods.	Firth *et al.*, 1987; Ludvik *et al.*, 1995
IR does not cause both obesity and DM2.	IR calculated using a different method.	Swinburn, 1995
There is a significant correlation between obesity, IR and DM2.	IR calculated using a different method.	Ludvik *et al.*, 1995
IR plays a role in the development of DM2 in obese individuals.	IR is associated with both obesity and DM2. Weight gain results in increased IR and weight loss in decreased IR.	Swinburn, 1995
IR plays a role in the development of DM2 in obese individuals.	Compared obese with a normal glucose tolerance and with DM2 to lean controls. Euglycemic clamp method was used.	Burnstein *et al.*, 1995

Hypotheses supported	Results of the studies	References
IR does play a role in the development of DM2 in obese individuals.	Compared obese and lean children with normal glucose tolerance. Glucose infusion test with and without lactate infusion were used.	Le Stunff & Bougneres, 1996
IR does play a role in the development of DM2 in obese individuals.	Compared female obese pre adolescents, adolescents and adults. Euglycemic insulin clamp and hyperglycaemic clamp methods were used.	Webber *et al.*, 1994.
IR does play a role in the development of DM2 in obese individuals. DM2 also lead to IR.	In lean DM2 subjects, IR is the result of diabetes. In obese DM2 subjects 60-75% of the IR is the result of diabetes and the remainder of obesity.	Ludvik *et al.*, 1995
IR does play a role in the development of DM2 in obese individuals. IR may be caused by a defect in the beta cell action.	Compared lean and obese subjects with normal glucose tolerance and with DM2. Oral and intra venous glucose tolerance tests were performed.	Seltzer *et al.*, 1967
IR does play a role in the development of DM2 in obese individuals. IR may be caused by a decrease in GLUT4 expression.	Decreased GLUT4 expression was only proved in adipose tissue but not in muscle tissue. Tests done on rats.	Kahn, 1992; Kahn *et al.*, 1992; Coderre *et al.*, 1996
IR does play a role in the development of DM2 in obese individuals. DM2 may also increase the IR.	Only proved in adipose and liver tissue and not in muscle. IR in obesity may be due to decreased binding, and in diabetes it may also be the result of a postreceptor defect.	Bhathena, 1987

(GIT = glucose intolerance; DM2 = type 2 diabetes; IR = insulin resistance)

At this stage it seems as if obesity is neither a prerequisite nor does it guarantee the development of type 2 diabetes but the WHO expert committee on diabetes (1980) and several other researchers concluded that it is the most powerful risk factor for the development of type 2 diabetes (Knowler *et al.*, 1991; Bosse, 1992). Most researchers agree that IR plays a role in the development of type 2 diabetes in obese individuals, it may however not be the only factor playing a role and different factors may play more or less important roles in different populations and under different circumstances. There is also disagreement about the causes of the IR associated with obesity and why this IR will result in type 2 diabetes.

viii) Body fat distribution

Type 2 diabetes is strongly and independently associated with waist-hip ratio, which can be used as an indication of body fat distribution (McGinnis & Ballard-Barbash, 1991; Märin *et al.*, 1992; Bosse, 1992; Jarret, 1993; Sekikawa *et al.*, 1999). Upper body fat predominance seems to be a

greater risk factor for the development of type 2 diabetes than lower body fat predominance or total body fatness (Bosse, 1992; O'Dea, 1994; Mourier *et al.*, 1997; Moller *et al.*, 2000). Insulin sensitivity and hyperinsulinaemia, associated with GIT, correlate with fat cell size rather than with the number of fat cells or total body fat (Bosse, 1992). Waist circumference has recently been claimed to be a better measure of risk for type 2 diabetes than waist-hip ratio (Despres *et al.*, 1995). Waist circumference implicates abdominal adiposity particularly in visceral adipose tissues (Seidell *et al.*, 1992; Mourier *et al.*, 1997). Research suggests that even in the early stages of obesity, abdominal visceral obesity and not subcutaneous fat is the most important determinant of the glucose metabolism (Caprio *et al.*, 1995). The waist-hip ratio does not discriminate between these two locations of fat and this may explain some of the discrepancies found in literature. Upper body fat distribution is mostly associated with men and postmenopausal women and thus excess body fat in men would be associated with greater metabolic disturbances than in women (Märin *et al.*, 1992; Lemieux *et al.*, 1993; Despres *et al.*, 1995; Weidner, *et al.*, 1995).

Most of the evidence for the association between central obesity and type 2 diabetes, comes from studies on European populations (Seidell *et al.*, 1991), but data on the effect of race on these factors are limited (Conway *et al.*, 1995). The best documented difference between body composition in African and European populations is an increase in the density of the fat-free mass in Africans because of the heavier and denser skeletal mass (Ortiz *et al.*, 1992; Conway *et al.*, 1995). African women are particularly affected by central obesity and obesity related conditions such as type 2 diabetes (Otten *et al.*, 1984; Zillikens & Conway, 1990; Conway *et al.*, 1995). However, according to Conway *et al.* (1995) and Kruger *et al.* (1994b) upper body obesity, independent of total body fatness is less detrimental for African women than for European women. Conway *et al.*(1995) demonstrated that African women have less visceral fat than European women of comparable BMI.

Both IR and abdominal obesity are found in first degree family members of type 2 diabetics (Eriksson *et al.*, 1989). This indicates a role for a genetic factor (or factors) in the association between central obesity and type 2 diabetes. There are several putative candidates for this genetic factor, including the ob-gene, tumour necrosis factor alpha and the β_3-adrenergic gene (Emorine *et al.*, 1989; Hotamisligil *et al.*, 1993; Zhang *et al.*, 1994). The role of the β_3-adrenergic gene in the development of type 2 diabetes via central obesity is explained in figure 2.23. It is also possible that

both central obesity and type 2 diabetes are inherited as separate genetic traits, which would mean that central obesity does not necessarily play a role in the development of type 2 diabetes (Hartz *et al.*, 1983). Yet another possibility is that both type 2 diabetes and central obesity may reflect an underlying hormonal imbalance (Hartz *et al.*, 1983).

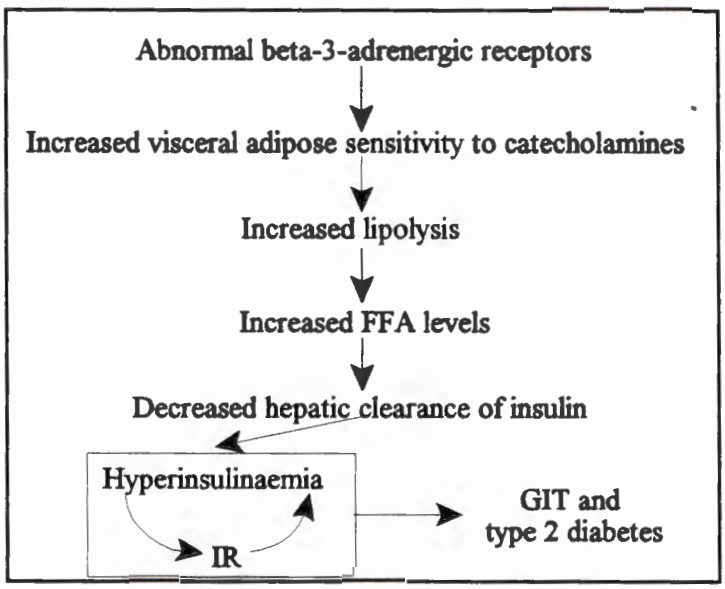

Figure 2.23: The influence of an abnormality in the β_3-adrenergic receptor on the abdominal adipocytes to increase the risk of developing type 2 diabetes (FFA = free fatty acids; IR = insulin resistance; GIT = glucose intolerance) (Emorine *et al.*, 1989; Hotamisligil *et al.*, 1993; Zhang *et al.*, 1994)

Most of the hypotheses explaining the role of abdominal obesity in the development of type 2 diabetes implicate the properties of the abdominal adipocytes as can be seen in figure 2.24. There are intrinsic differences in fat cells which may influence metabolic function throughout the body such as that abdominal adipocytes are more insulin resistant than femoral adipocytes (Kissebah *et al.*, 1982; Wahrenberg *et al.*, 1989; Caprio *et al.*, 1995).

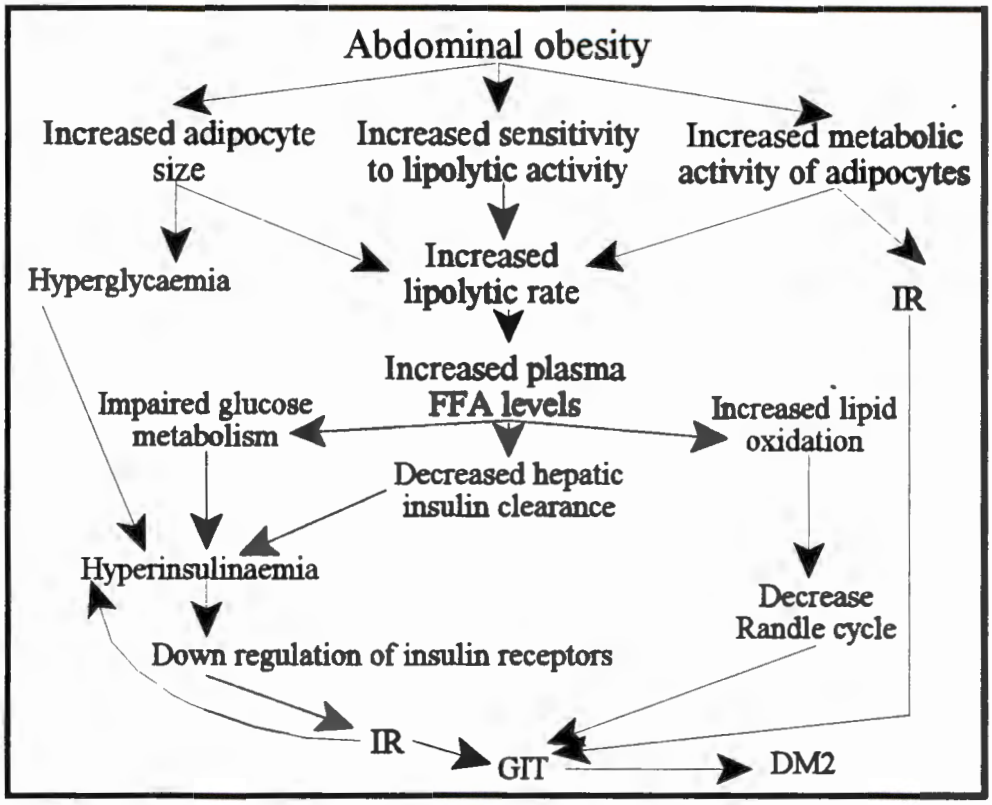

Figure 2.24: Possible hypotheses explaining how abdominal obesity increases the risk for the development of type 2 diabetes (Kissebah *et al.*, 1982; Pieris *et al.*, 1986; Wahrenberg *et al.*, 1989; Strombiad & Bjorntorp, 1993; Caprio *et al.*, 1995; Kaplan, 1998)

Abdominal adipocytes are larger than femoral adipocytes, they have an increased metabolic activity compared to femoral adipocytes, and are more sensitive to lipolytic hormones (Pieris *et al.*, 1986; Caprio *et al.*, 1995). This will result in increased plasma levels of free fatty acids in the portal circulation exposing the liver and peripheral tissues to elevated levels of free fatty acids, which in turn could impair glucose metabolism (Caprio *et al.*, 1995; Kaplan, 1998). The resultant hyperglycaemia and compensatory hyperinsulinaemia will cause IR. Increased delivery of free fatty acids into the portal system may also reduce the hepatic clearance of insulin (Strombiad & Bjorntorp, 1993; Kaplan, 1998). The peripheral hyperinsulinaemia could lead to secondary IR by down-regulating insulin receptors (Caprio *et al.*, 1995). Increased levels of free fatty acids could also, through an increased rate of lipid oxidation, decrease oxidation and utilization by the Randle cycle (Caprio *et al.*, 1995). Other factors, not yet identified, may also play a role in the association between visceral obesity and IR (Caprio *et al.*, 1995). Table 2.12 lists the literature that support the association between body fat distribution and type 2 diabetes.

Table 2.12: Hypotheses supporting the association between body fat distribution and increased risk for the development of type 2 diabetes

Hypotheses supported	Study results	References
Abdominal obesity increases the risk for DM2.	Abdominal adipocytes are larger than femoral adipocytes.	Hartz *et al.*, 1983.
Abdominal obesity increases the risk for DM2.	Women with type 2 diabetes tend to have an upper body fat distribution.	Moller *et al.*, 2000
Abdominal obesity increases the risk for DM2.	Body fat distribution plays an important role for developing type 2 diabetes independent of obesity.	Sekikawa *et al.*, 1999
Abdominal obesity increases the risk for DM2 via increased IR.	Abdominal adipocytes are larger and more insulin resistant than femoral adipocytes.	Hartz *et al.*, 1983
Abdominal obesity increases the risk for DM2 via increased IR.	Abdominal adipocytes are more responsive to insulin and norepinephrine.	Hartz *et al.*, 1983.
Abdominal obesity increases the risk for DM2 via increased IR.	Defect in beta$_3$-adrenergic receptor gene implicated as cause for abdominal obesity. Compared non-diabetic and diabetic subjects.	Widén *et al.*, 1995
Abdominal obesity increases the risk for DM2 via increased IR.	Decreased testosterone levels in males implicated as cause for abdominal obesity.	Marin *et al.*, 1992.
Abdominal obesity increases the risk for DM2 via increased IR and hyperinsulinaemia. The latter is caused by increased free fatty acid levels.	Visceral fat is IR and sensitive to lipolytic hormones compared to femoral fat. Compared obese and nonobese adolescent girls and lean adult females.	Caprio *et al.*, 1995.
Nature and distribution of body fat may increase the risk for DM2.	Abdominal adipocytes are larger and more responsive to insulin.	Kissebah *et al.*, 1982.
Brown adipose tissue deficiency may increase the risk for DM2 and GIT via IR resulting from receptor and postreceptor defects.	Study done in rats. Intra peritoneal glucose and insulin tolerance tests and receptor studies were done.	Hamann *et al.*, 1995.

DM2 = type 2 diabetes mellitus; IR = insulin resistance; GIT = glucose intolerance

2.3.9 Metabolic risk factors

2.3.9.1 Introduction

Environmental and genetic risk factors result in certain metabolic risk factors. These metabolic risk factors will cause the serious derangement in the carbohydrate (CHO) metabolism which may progress into type 2 diabetes (Haffner *et al.*, 1997). Several metabolic risk factors for the development of type 2 diabetes have already been identified, but the biochemic sequence of changes involved in the transition of the metabolic abnormalities to type 2 diabetes are still unknown (Lillioja *et al.*, 1993; Bressler & Johnson, 1997). The most important metabolic risk factors for the development of type 2 diabetes are shown in figure 2.25. These risk factors are briefly discussed in the following sections.

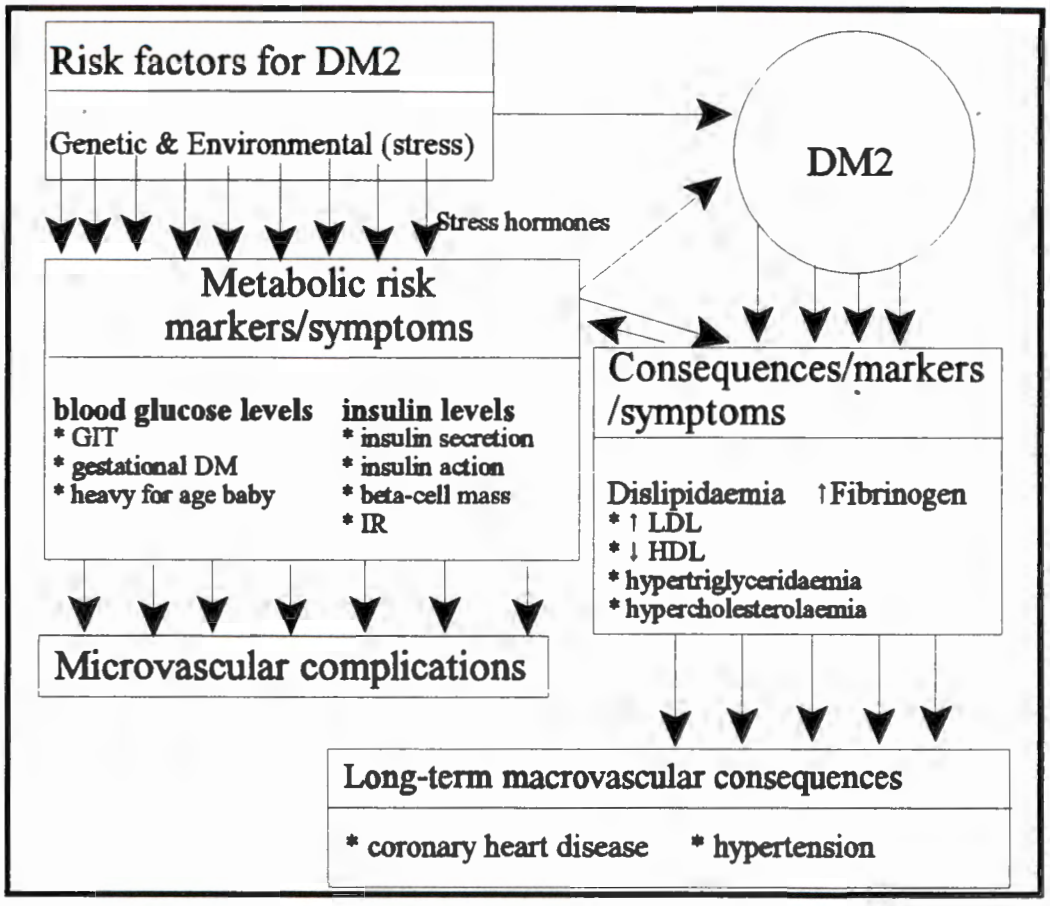

Figure 2.25: Metabolic risk factors and markers for the development of type 2 diabetes (DM2 = type 2 diabetes mellitus; DM = diabetes mellitus; GIT = glucose intolerance; IR = insulin resistance; LDL= low density lipoprotein; HDL = high density lipoprotein; ↓ = decrease; ↑ = increase) (Lillioja *et al.*, 1993; Bressler & Johnson, 1997; Haffner *et al.*, 1997; ADA, 1998c; Barnard *et al.*, 1998; Haffner *et al.*, 1999; Yuan *et al.*, 1999; Perry *et al.*, 1999; Moller *et al.*, 2000; Meigs *et al.*, 2000)

2.3.9.2 Glucose tolerance status

Continuous hyperglycaemia may eventually result in glucose intolerance (GIT) which in turn will result in worsening of the initial hyperglycaemia. Individuals with GIT are at increased risk to develop type 2 diabetes (Mitrakou *et al.*, 1992; Levitt & Mollentze, 1995). The progression from GIT to type 2 diabetes is a slow process. Many individuals with GIT are normoglycaemic in their daily lives and GIT is only noticed when the body is challenged with a large CHO- load, such as during a glucose tolerance test (Levitt & Mollentze, 1995). The mechanisms responsible for the progression of GIT to type 2 diabetes are still controversial. Table 2.13 shows the genetic and environmental risk factors that may act through the hypoglycaemia-GIT mechanism.

Table 2.13: Genetic and environmental risk factors that may act through the hyperglycaemia-glucose intolerance mechanism

Genetic risk factors	Environmental risk factors
Belonging to a specific ethnic group	Poor fetal and postnatal nutrition
Being a female	Diet: increased energy intake increased intake of refined CHO's increased intake of lipids
Having an increased gastric emptying and absorption rate	Modernisation
	Stress
	Obesity
	Abdominal obesity
	The use of certain drugs

(CHO's = carbohydrates)
(Wallberg-Hendriksson, 1987; Dohm *et al.*, 1988; Mitrakou *et al.*, 1992; Levitt & Mollentze, 1995; Hamann *et al.*, 1995; Ryan *et al.*, 1995; Bressler & Johnsson, 1997)

2.3.9.3 Insulin-related metabolic risk factors

Both insulin resistance (IR) and decreased insulin secretion have been shown to predict the development of type 2 diabetes (Ryan *et al.*, 1995; Haffner *et al.*, 1997; Perry *et al.*, 1999;). There is controversy about the role and importance of each of these two risk factors in the development of type 2 diabetes, as can be seen in Table 2.14 (Haffner *et al.*, 1997). The presence of either IR or decreased insulin secretion as a strong risk factor in a population does not imply that other risk factors have no influence in the development of type 2 diabetes in that population (Haffner *et al.*, 1997). For instance, low insulin sensitivity was associated with a 30-fold higher relative risk for type 2 diabetes, whereas high fasting insulin was associated with a 15-fold higher relative risk of type 2 diabetes in Pima Indians (Haffner *et al.*, 1997). It seems as if IR is the stronger predictor of type 2 diabetes in high-risk populations, which are generally obese and IR (Haffner *et al.*, 1997). Decreased insulin secretion seems to be the stronger predictor of type 2 diabetes in low-risk populations (Haffner *et al.*, 1997). Figure 2.26 shows the insulin-related risk factors for type 2 diabetes. The relationships between defective beta-cell function (Seltzer *et al.*, 1967; Ryan *et al.*, 1995; Haffner *et al.*, 1997; Haeften *et al.*, 1998), hyperinsulinaemia (Simmons, 1995; Ryan *et al.*, 1995; Nabulsi *et al.*, 1995; Schwartz *et al.*, 1995; Perry *et al.*, 1999; Kekäläinen *et al.*, 1999), and IR (O'Dea, 1994; Widén *et al.*, 1995; Ryan *et al.*, 1995; Castillo *et al.*, 1995; ADA, 1998d; Barnard *et al.*, 1998) with the development of type 2 diabetes have been reviewed extensively in the literature and will not be discussed here since it lies outside the scope of this epidemiologic study.

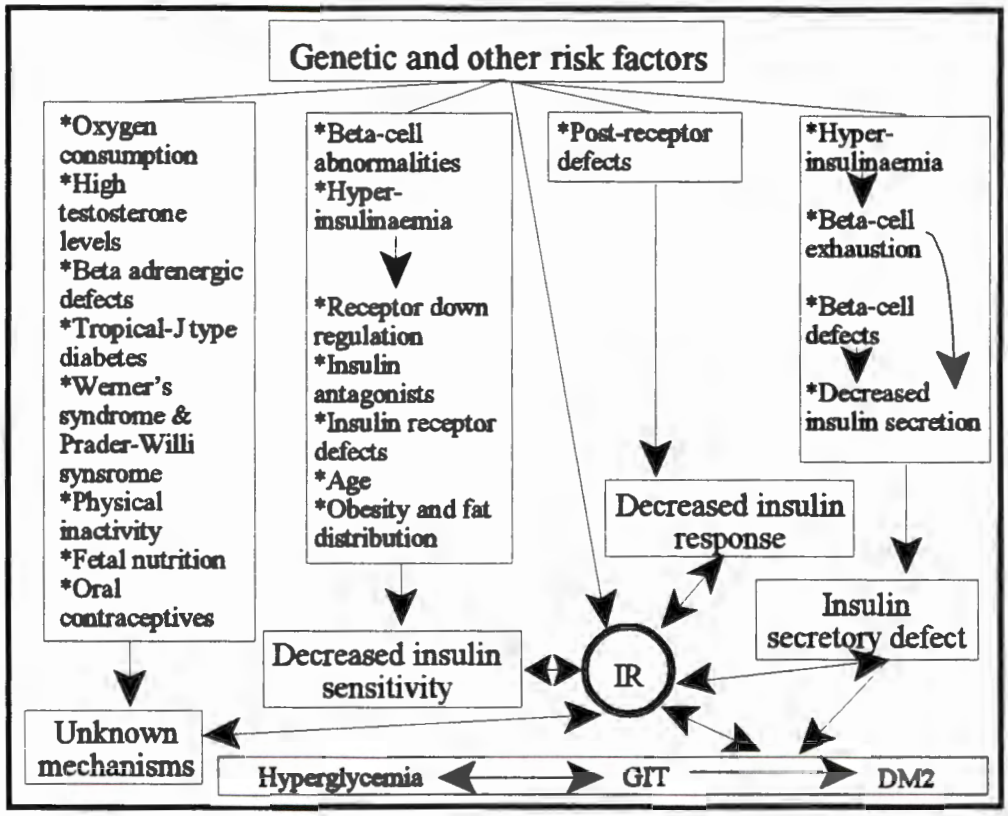

Figure 2.26: Insulin related risk factors that increase the risk for the development of type 2 diabetes and some of the complicated interrelations between them (IR = insulin resistance; GIT = glucose intolerance; DM2 = type 2 diabetes mellitus) (Castillo *et al.*, 1995; Widén *et al.*, 1995; Nabulsi *et al.*, 1995; Ryan *et al.*, 1995; Haffner *et al.*, 1997; Haeften *et al.*, 1998; ADA, 1998d; Barnard *et al.*, 1998; Perry *et al.*, 1999; Kekäläinen *et al.*, 1999)

Table 2.14: The role of insulin secretory defects and insulin resistance in the development of type 2 diabetes

Primary insulin related risk factor	Study population and results	Reference
IR and decreased insulin secretion	Mexican Americans	Haffner, *et al.*, 1997.
IR and decreased insulin secretion	Swedish	Haffner *et al.*, 1997
Decreased insulin secretion; IR also plays a role	Caucasians, both defects present before onset of CHO metabolic defects	Ryan *et al.*, 1995
IR; decreased insulin secretion only plays a contributory role	Pima Indians	Lillioja *et al.*, 1993
IR	High risk populations, usually insulin resistant and obese	Haffner *et al.*, 1997
IR	European men - Onset of type 2 diabetes is characterised by the early development of IR with compensatory hyperinsulinaemia.	Perry *et al.*, 1999
IR	Children with 2 diabetic parents - normal insulin secretion	Martin *et al.*, 1992
IR	IR and hyperinsulinaemia (due to diet and obesity) occur before the onset of type 2 diabetes	Barnard *et al.*, 1998
Decreased insulin secretion	Low risk populations have a decreased insulin secretion.	Haffner *et al.*, 1997
Decreased insulin secretion	Normal glucose tolerant first-degree relatives of type 2 diabetic subjects have a decreased second-phase insulin release.	Haeften *et al.*, 1998
Defective insulin secretion	First degree relatives of type 2 diabetics - mainly disordered pulsatile insulin secretion	Ryan *et al.*, 1995
Decreased first phase insulin secretion	Found to be an early defect of type 2 diabetes	Polonsky *et al.*, 1988

(IR = insulin resistance; CHO = carbohydrate)

2.3.9.4 Elevated stress hormone levels

Cortisol, growth hormone, catecholamines, testosterone and prolactin, are secreted in response to stress (Malan *et al.*, 1992). Cortisol levels, which can be regarded as an indication of anticipation stress, usually increase before the onset of the stressful event (Malan *et al.*, 1992). Prolactin and growth hormone levels are secreted during stress (Malan *et al.*, 1992). Acute stress stimulates testosterone secretion while chronic stress inhibits it (Ursin *et al.*, 1978; McGrady, 1984).

Growth hormone, cortisol and the catecholamines act as insulin antagonists, and adrenalin is known to impair tissue insulin sensitivity (Bhathena *et al.*, 1989; Surwitt *et al.*, 1992). Increased levels of growth hormone and corticosteroids decrease insulin binding, and thus also results in

decreased insulin sensitivity (Bhathena *et al.*, 1989). If an individual is continuously subjected to stress (as happens during modernisation), it would lead to increased levels of these stress hormones (except in the case of testosterone). This may interfere with the functioning of insulin, and result in insulin resistance (IR), hyperinsulinaemia and eventually to hyperglycaemia, glucose intolerance (GIT) and type 2 diabetes (figure 2.27). Trauma, especially in childhood years, may result in a permanent increase in the baseline cortisol levels (Mason, 1975). Malan *et al.*, (1992) found that urban Africans have higher baseline cortisol levels than their rural counterparts, and suggested the possibility of a permanent increase of the hormone, as a result if the trauma of urbanisation. Stress hormones may also increase the risk for type 2 diabetes through the development of hypertension (HT), which is another risk factor for type 2 diabetes (Malan *et al.*, 1992), as can be seen in figure 2.27 (solid lines).

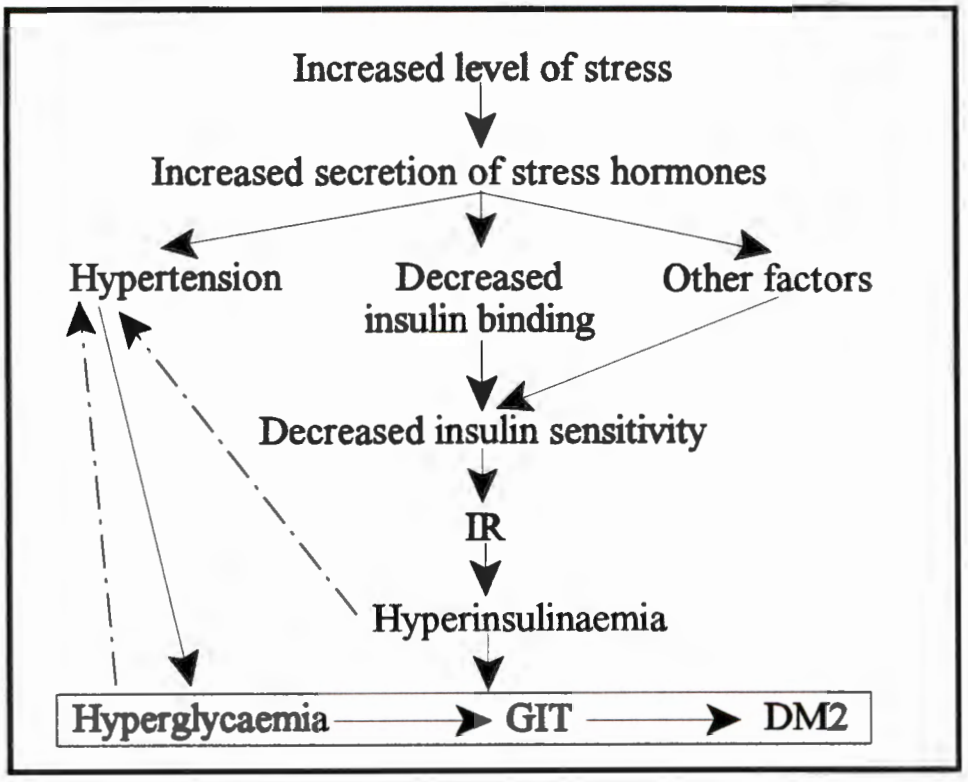

Figure 2.27: Mechanisms whereby elevated levels of stress hormones may progress into the development of type 2 diabetes. The broken lines show that hyperinsulinaemia and hyperglycaemia may in turn result in hypertension and in this way a snow ball effect is created, which increases the risk for type 2 diabetes even more (IR = insulin resistance; GIT = glucose intolerance; DM2 = type 2 diabetes) (Mason, 1975; Bhathena *et al.*, 1989; Malan *et al.*, 1992; Surwitt *et al.*, 1992)

Any environmental risk factor, which causes an increase in the level of stress hormones, may act through this metabolic mechanism to increase the risk for the development of type 2 diabetes. These include socioeconomic conditions, modernisation, stress and fetal and early life nutrition.

2.3.9.5 The metabolic syndrome as a risk factor for type 2 diabetes

The metabolic syndrome is a cluster of metabolic disturbances associated with a state of IR (Despres *et al.*, 1995; Beck-Nielsen, 1999). Several synonyms have arisen for the term, including insulin resistance syndrome, obesity-insulin resistance syndrome, Reaven's syndrome, syndrome X and the deadly quartet. Several conditions, which are frequently associated with the metabolic syndrome, are listed in figure 2.28 (Caprio *et al.*, 1995; Widèn *et al.*, 1995; Brunner, 1997; Kaplan, 1998; Watts & Dimmitt, 1999; Byrne *et al.*, 1999; Williams, 1999; Carroll *et al.*, 2000; Okada *et al.*, 2000). These conditions have very complex relationships with each other and it is important to realise that conditions at the same "level" may also influence each other, and that there is no specific number of levels in the etiology of the diseases associated with the metabolic syndrome.

Factors associated with Westernisation, such as poor lifestyle (figure 2.28), and psycho social demands (figure 2.28) play an important role in the development of the metabolic syndrome (Bjorntorp, 1987; Haffner *et al.*, 1988a; Lee *et al.*, 1995; Brunner, 1997). It also seems as if the rate at which Westernisation takes place, influences the development of the metabolic syndrome (Singh *et al.*, 1995). There are several examples of the association between the metabolic syndrome and type 2 diabetes. Many of the characteristics of the metabolic syndrome are associated with IR and this may in part explain the strong association of the metabolic syndrome with type 2 diabetes. (Reaven, 1988; Despres *et al.*, 1995; Widèn *et al.*, 1995; Austin & Selby, 1995; Wassef, 1999; Byrne *et al.*, 1999; Beck-Nielsen, 1999; Williams, 1999).

Reaven suggested that IR associated with compensatory hyperinsulinaemia potentially leading to GIT and type 2 diabetes is characteristic of the metabolic syndrome (Reaven, 1988). Therefore the metabolic syndrome would contribute to increase the risk of type 2 diabetes and GIT (Despres *et al.*, 1995). According to the WHO a person with type 2 diabetes or GIT has the metabolic syndrome if two of the criteria listed below are fulfilled. A person with normal glucose tolerance has the metabolic syndrome if he/she fulfils two of the criteria in addition to being insulin resistant. The criteria are hypertension, dislipidaemia, obesity and/or high waist-to-hip ratio and

microalbuminuria (Alberti & Zimmet, 1998). Applying this definition it has been found that in the population from the Botnia study in Finland and Sweden (Groop *et al.*, 1996)about 10% of subjects with a normal glucose tolerance, 40% of subjects with GIT and 70% of subjects with type 2 diabetes would have the metabolic syndrome (Groop, 2000). This shows that the metabolic syndrome is already present in subjects before the development of type 2 diabetes and therefore it can be classified as a marker for the disease. IR clusters in families and is influenced by both genetic and environmental factors (Groop, 2000). One of the factors that may link the metabolic syndrome (and IR) with the development of type 2 diabetes is obesity and more importantly an abdominal distribution of body fat. Both total body fat and abdominal obesity can be partly attributed to genetic factors (Bouchard, *et al.*, 1988, 1996; Samaras, *et al.*, 1997). First-degree relatives of patients with type 2 diabetes have an increased waist-to-hip ratio (without a significant increase in total body fat) compared with their spouses without a family history of type 2 diabetes (Groop *et al.*, 1996). Redistribution of body fat to the abdominal region is seen at completely normal glucose tolerance (Groop, 2000). The inheritance of type 2 diabetes seems to favour fat accumulation in the intra-abdominal region. Intra-abdominal fat is metabolically very active, with a high rate of free fatty acid turnover. Intra-abdominal free fatty acid metabolism is relatively resistant to the effect of insulin in persons with abdominal obesity (Lönnqvist *et al.*, 1995). Instead, the $beta_3$-adrenergic receptor of visceral fat is sensitive to stimulation by catecholamines (Krief *et al.* 1993). This, in turn, will ensure a large supply of free fatty acids to the portal vein for further transport to the liver and other tissues such as muscle. In contrast, lipolysis in subcutaneous fat is more sensitive to the inhibitory effect of insulin, which will favour re-esterification of free fatty acids to triglycerides (Reynisdotter *et al.* 1994). The strong association between IR and abdominal obesity suggests that abdominal obesity may be at least partly responsible for the association between type 2 diabetes and the metabolic syndrome.

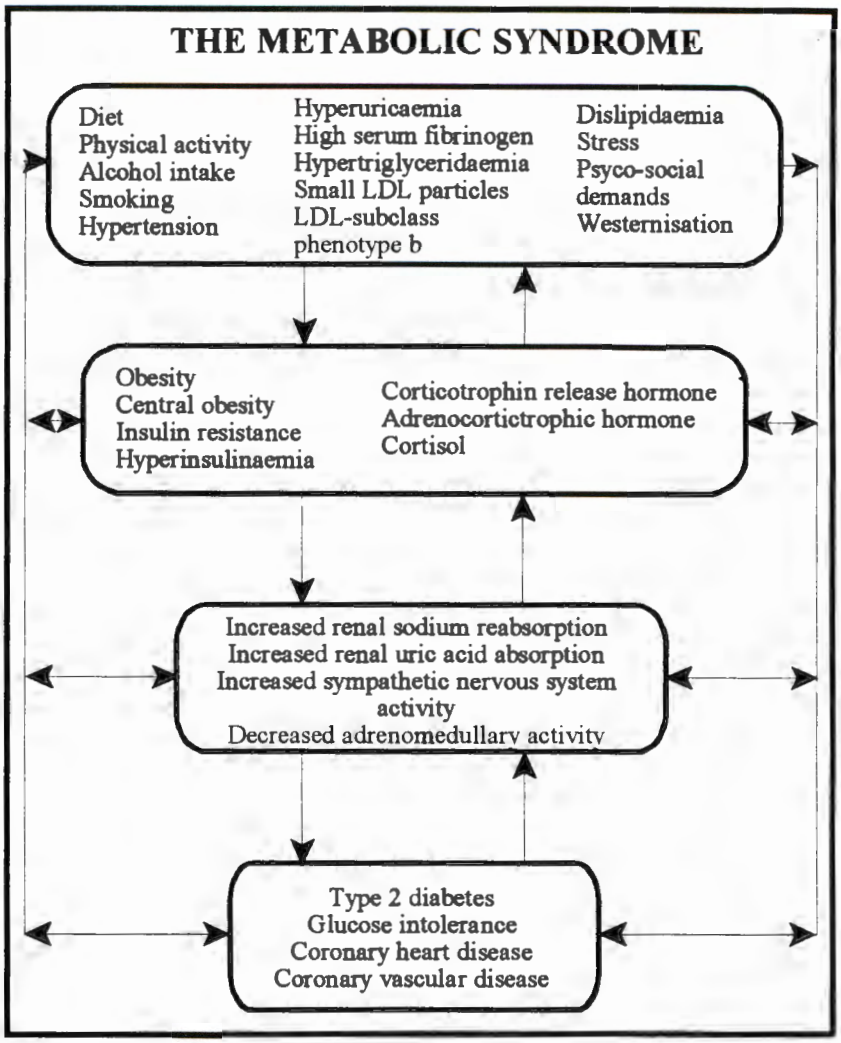

Figure 2.28: The relationships between conditions frequently associated with the metabolic syndrome. Note that conditions can influence each other both at the same level and at different levels of the diagram (Austin & Selby, 1995; Widèn *et al.*, 1995; Brunner, 1997; Kaplan, 1998; Watts & Dimmitt, 1999; Byrne *et al.*, 1999; Williams, 1999; Wassef, 1999; Beck-Nielsen, 1999; Carroll *et al.*, 2000; Okada *et al.*, 2000)

2.5 Conclusion

From the above it is clear that the development of type 2 diabetes is influenced by several risk factors which have complicated and sometimes confusing interrelationships, both with each other and with the development of the disease. The effects of modernisation on populations in transition are also complicated, affecting all aspects in the lives of these people. It is clear that the stressful effects of modernisation increase the risk for type 2 diabetes in susceptible populations, in a direct and/or indirect way. Therefore the modernisation is associated with an increase in the prevalence of chronic diseases of lifestyle, such as type 2 diabetes. However, all populations may not react in the same way to these stressors or changes. The question is whether the African population

in South Africa experiences the transition from a rural to an urban lifestyle, as stressful as has been described for other populations. It is also important to know whether the stressful effects associated with modernisation has the same physiological influence on the African population as on other populations in transition. This study investigated the effect of modernisation on the glucose tolerance status of the African population, and tried to describe the profile of young African diabetic subjects. The hypothesis tested was that the changes in lifestyle and behaviour associated with urbanisation, will result in an increase in the risk of type 2 diabetes in a sample of "apparently healthy" Africans in the North West Province of South Africa.

CHAPTER 3
METHODS

3.1 Design

This study formed part of the 'THUSA' project, during which fieldwork was done from 1996-1998. It was designed as a cross-sectional population-based study to compare known risk factors for type 2 diabetes mellitus in apparently healthy Africans of the North West Province at different levels of urbanisation. A representative sample of 1854 apparently healthy individuals from the African population was recruited from 37 randomly selected different sites and stratified for gender, age and stratum (level of urbanisation). The total sample was used to determine the effect of urbanisation on the markers for GIT and type 2 diabetes (blood insulin and glucose levels), before and after adjusting for certain lifestyle factors (age, smoking habit, BMI, waist-to-hip ratio and physical activity). The effect of urbanisation on the lifestyle factors was also investigated. These results and a short discussion are given in Chapter 4. The 1996 phase of the project was used as an exploratory study to investigate the glucose tolerance situation and to characterise subjects with two different levels of glucose intolerance (GIT). It therefore includes information on the 728 subjects included in the 1996 phase of the project, and not all 1854 subjects. The results and a short discussion of this exploratory study are given in Chapter 5. Data from the total 1854 subjects were used in the third part of the study, to further characterise young African diabetic subjects who were identified in the study. In a nested case-control study, diabetic subjects younger than 45 years were compared with a matched control group from the total study population. The two groups were matched for age, gender, body mass index (BMI), stratum and education. The results form this part of the study are given in Chapter 6. Because the THUSA study was designed to measure the impact of urbanisation on the risk factors of chronic diseases of lifestyle, data from this study will reflect neither the prevalence nor the incidence of any disease. The data will, however, give information of risk factor prevalence in "apparently healthy" subjects and levels in those individuals identified with GIT and type 2 diabetes.

3.2 Selection of subjects

3.2.1 Number of subjects

Seven hundred and twenty-eight apparently healthy volunteers participated in the exploratory study, which was done during 1996. At the end of 1998, 1854 subjects were included in the study. Eleven diabetic subjects younger than 45 years and eleven matched controls from the total 1854 subjects were included in the third part of this study (Chapter 6).

3.2.2 Age ranges

Type 2 diabetes is a disease of adulthood, but it may start developing in childhood. Haffner and co-workers (1988a) pointed out that the risk factors for type 2 diabetes are present many years before it actually develops. Therefore, it was decided to include subjects from 15 to 65 years of age in the sample. Older persons were not included because of the pronounced effect of age on type 2 diabetes. Subjects were grouped into five age groups (15-24.9; 25-34.9; 35-44.9; 45-54.9 and 55-65 years).

3.2.3 Randomisation

Because of several logistic reasons, selection of a total randomised sample of Africans in the North West was not possible. With the help of the Biostatistic Consultation Services of the PU vir CHE, a model was designed to recruit a representative sample. The Province was divided into four quarters. Five centres in each quarter were randomly chosen. Subjects were recruited from different sites in or around each centre. The requirements for each centre were that a temporary field laboratory could be set up centrally for all sites, and that suitable accommodation for a team of 20 or more researchers was available. Furthermore, the five centres within each quarter of the Province should have given access to subjects from different strata or levels of urbanisation. Figure 3.1 shows a map of the North West Province.

3.2.4 Criteria for defining the strata

3.2.4.1 Stratum I: Rural people

Usually, rural includes subjects living in pastoral or agricultural circumstances. In this study, rural Africans were defined as people who lived under the authority of a traditional tribal head (chief, captain or headman) in and around traditional African villages. These villages were often without running water and electricity.

3.2.4.2 Stratum II: Farm workers

These subjects worked on commercial farms, mostly owned by white farmers. They lived in brick houses clustered together on each farm. Running water and electricity were available at some but not all the farms.

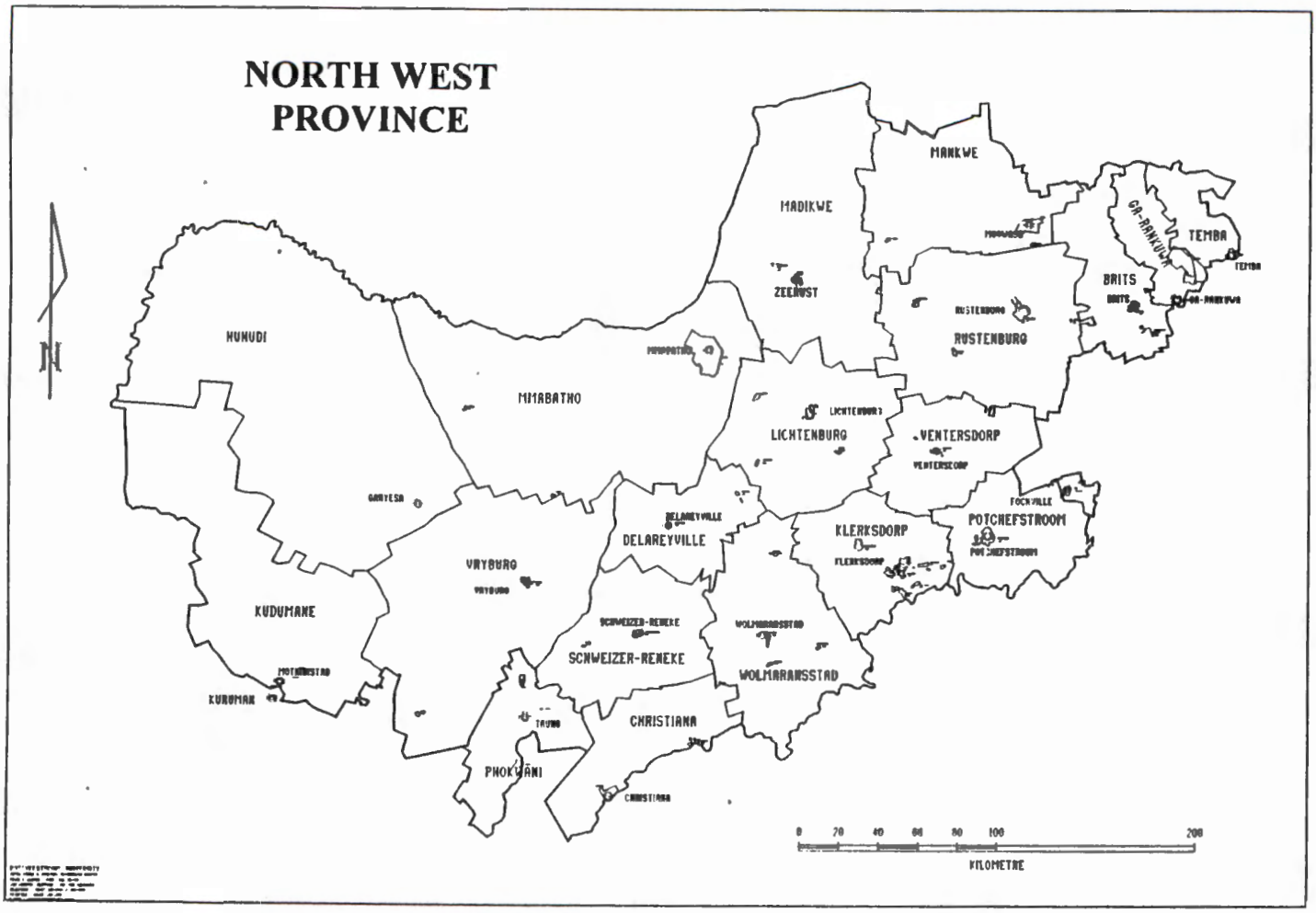

Figure 3.1: A map of the North West Province

3.2.4.3 Stratum III: Squatters

These subjects were from the informal housing areas (squatter camps) near larger towns and lived in temporary houses made from corrugated iron and other materials known as Makuku's. Electricity and communal water taps were only available in some of these areas.

3.2.4.4 Stratum IV: Urban "middle class"

These subjects were from established townships or locations found adjacent to all towns and cities in South Africa. The subjects own the brick houses they lived in and most had running water and electricity.

3.2.4.5 Stratum V: Urban "upper class"

Subjects for this stratum were recruited from professional people, including nurses, teachers,

doctors, government workers, and politicians. They lived either in the established townships or in formerly "white" residential areas in towns and cities. Some lived in affluent circumstances in the traditional rural villages where they worked as teachers, nurses, etc.

3.2.5 Exclusion criteria

The following subjects were excluded from the study:

- Pregnant and lactating women
- Subjects known to suffer from any infectious or noncommunicable disease
- Subjects using any form of chronic medication (many hypertensive subjects and diabetics were excluded because of this criterium)
- Subjects younger than 15 and older that 65 years (identification documents were used to obtain the correct age)
- Inebriated subjects
- Subjects suffering from epilepsy and mental diseases or defects

3.3 Ethical considerations

The study was approved by the Ethics Committee of the Potchefstroom University for Christian Higher Education (project number HHK 4M5-95). Subjects signed an informed consent form giving permission to draw blood samples. In many instances, especially in strata one to three, subjects were illiterate and signed with a cross. Parents of legal guardians signed the consent forms of all participants younger than 21 years. At the completion of the study in 1998, ethics permission to test anonymously for HIV infection was obtained from the same Ethics Committee.

3.4 Organisational procedures

After a site or centre has been chosen, the necessary permission to do the study was obtained from the relevant authorities (tribal chief, mayor, clinic head, hospital matron, secondary school headmaster, or employer of subjects). Two researchers visited the area and identified a suitable person, from the Department of Health Regional Offices or the Tribal Office, to help with the organisation of the field visits and recruitment of subjects. The local organiser in each centre helped to identify the sites around the centre where subjects were recruited and studied. This person also arranged a meeting between the researchers and the community leaders during which the objectives and methods of the study were explained and questions were answered. The local organiser further arranged that the subjects voluntarily fasted for eight to twelve hours prior to

the test and that they bring their identification documents on the day of the study. Each local organiser received detailed written instructions (addendum 1) and copies of a brochure, motivating and explaining the study to assist in the recruitment of subjects (addendum 2). The local organiser advised the researchers on reimbursement of subjects. It was clearly stated that subjects will not be paid to participate, except those subjects who had to keep a seven day weighed dietary record and collect 24 hour urine for the dietary validation study. These subjects also received a packet of dry beans, donated by the Dry Bean Producers Organisation. In one rural area (four sites) subjects were given clothing, donated by an international relief organisation and in another eight sites subjects received a packet of fruit after completion of the study.

To avoid recruitment of ill subjects, subjects were not recruited from hospital or community clinic attendees. During the field study, a temporary field laboratory was established in each centre for the processing of samples and measurements of haematocrit and haemoglobin. The researchers stayed at the chosen centre and travelled daily to each site with the necessary equipment and ice to keep the samples at 4° C. If the site was too far from the centre to process the samples within 3-6 hours, centrifuges, and generators (where necessary) were taken to the site to process the samples in the field.

On the morning of each field visit, the study was explained in detail to all subjects intending to participate, in their home language. Subjects were then asked to sign the informed consent form (addendum 3). Each subject then received a "green card" (addendum 4) with their name and subject number, which had to be filled in (or ticked off) by the researchers at each of the following "stations" where information, measurements and samples were collected:

Station 1: Demographic questionnaire (addendum 5)
Station 2: Dietary questionnaires (addendum 6 and addendum 11)
Station 3: Anthropometric measurements (addendum 10)
Station 4: Clinical signs of malnutrition, blood pressure, oral temperature and blood samples (addendum 4)
Station 5: Urine sample
Station 6: Two hour glucose tolerance tests (addendum 4)
Station 7: Reproductive, contraception and parity questionnaire (only women, addendum 7)
Station 8: Cardiovascular reactivity (stress test)
Station 9: Physical activity questionnaire (addendum 9)
Station 10: Attitude towards weight control (addendum 11)

During the1998 fieldwork, information on mental health was collected by specially trained field workers, using structured psychology questionnaires. A station where bone stiffness was measured was also included.

After completion a feedback form was completed for each subject, advising them to see a doctor or go to the clinic if any abnormalities were revealed in the field tests (addendum 8). Subjects were also advised on lifestyle and dietary changes that would improve their health and decrease their risk for chronic diseases of lifestyle.

3.5 Demographic, medical, reproductive and socioeconomic information

During individual interviews with each subject a questionnaire (addendum 5) was used to obtain the following information:

- age
- medical history
- family history of noncommunicable diseases
- smoking habits
- alcohol intake
- household composition
- household income
- education level
- living circumstances (type of house, toilet facilities, etc.)

Subjects were asked what type of cigarettes or tobacco they smoke, or what type of snuff they use. They were also asked to report the amounts of cigarettes, tobacco, or snuff they use and the duration of use. In the case of cigarettes this information was used to calculate "pack years" ([n = cigarettes smoked per day /20] x [n = years smoking]). In the case of tobacco and snuff, the amount used by the subject was reported in grams per week. Subjects were asked to report the type, amount, and frequency of alcohol used. This information was used to calculate the alcohol intake in grams per day, based on the alcohol content of reported alcoholic beverages.

3.6 Dietary information

A food frequency questionnaire was developed specifically for the THUSA study (MacIntyre, 1998). The types of foods usually eaten by Africans of the North West Province were assessed

in a pilot study. The food frequency questionnaire was based on results of the pilot study and was validated by comparing reported intakes of a sub-sample of women (n=100) with seven days weighed records and 24 hour urinary nitrogen excretions. Books of photographs of three different portion sizes of the foods most frequently eaten, were developed. Five Setswana speaking field workers were trained to use these books, food models, food containers and package materials, as well as household utensils to measure habitual intakes during individual interviews with each subject with the food frequency questionnaire. The questionnaire also included questions to evaluate level of acculturation, meal frequency, alcohol intakes, snacking habits and where meals are usually eaten. The reported food intakes were coded by an experienced dietitian and analysed with a computer programme based on the South African Food Composition Tables.

3.7 Anthropometric measurements

Weight was measured to the nearest 0.5 Kg with a portable bathroom balance (Precision Health Scale, A & D Company, Japan). Subjects took off their shoes and wore only light indoor clothing. Height was measured to the nearest 0.5 mm using a plastic anthropometer (Invicta, IP 1465, UK). Subjects were barefoot or wore only socks. Waist and hip circumferences were measured with an un stretchable measuring tape around the smallest and widest parts of the waist and hips respectively. The triceps and subscapular skinfolds were measured in triplicate with a skinfold calliper (John Bull, British Indicators, Ltd.). Mean values for the skinfold measurements were calculated and reported.

Body mass indexes (BMI's) were calculated using the following formula: weight (Kg)/height^2 (m). Several criteria are available for the interpretation of the BMI data. In this study the WHO and American criteria were used to distinguish between normal weight, overweight, and obese subjects (Table 3.1; Must *et al.*, 1992). However, because the American criteria excluded subjects between the ages of 16-19.9 and 44.1-65 years, the WHO criteria were favoured.

Table 3.1: The body mass index criteria used to distinguish between normal weight, overweight, and obese subjects

Criteria	BMI	Weight status
WHO	20-24.9 (male and female)	Normal weight
WHO	25-29.9 (male and female)	Overweight
WHO	≥30 (male and female)	Obese
American	> 27.3 (females aged 20-44 years)	Obese
American	> 27.8 (males aged 20-44 years)	Obese

Waist-to-hip ratios were calculated and used to distinguish between upper and lower body distribution of body fat. A waist-to-hip ratio of >0.95 for males and >0.80 for females were taken to be an indication of distribution of body fat towards the abdomen (upper body fat distribution) (Must *et al.*, 1991).

3.8 Clinical examination

A specially trained nursing sister examined the thyroid, hair, skin, tongue and eyes of subjects for any signs of malnutrition. She also took oral temperatures and blood pressures, while subjects were seated for at least 10 minutes. A sphygmomanometer (Tycos®; USA) with adjustable cuffs of different sizes were used. Systolic and diastolic blood pressures were recorded as the first and the fifth Korotkoff sounds. The lowest blood pressure recording of the two or more measurements was used. Hypertension was diagnosed as a systolic blood pressure >140 mmHg and a diastolic blood pressure >90 mmHg. Subjects who were diagnosed with hypertension were referred to a medical doctor or their local clinic.

3.9 Glucose tolerance test (GTT)

The researcher was responsible for the glucose tolerance tests during the 1996 phase of the THUSA project. She also assisted in the recruitment of subjects, anthropometric measurements, blood pressure measurements and processing of blood samples in the field. She further analysed the serum samples to assess glucose and insulin concentrations, and with the help of a statistician, analysed the data for this thesis.

According to The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, (1998) the oral glucose tolerance test should have a standard 75g CHO dose for nonpregnant adults and 1.75g CHO/Kg ideal body weight for children not to exceed 75 g. It should be performed in the morning after at least three days of unrestricted diet and physical activity and after an eight to sixteen-hour fast. Subjects may drink water during the fasting period. Subjects should not smoke and should remain seated for the duration of the test. A fasting blood sample should be collected before the ingestion of the glucose load. The glucose load should be ingested in five minutes or less.

A two-hour glucose tolerance test (GTT) was performed on each subject after fasting blood samples were taken. Because subjects aged 15 years and older were included, and because of logistic considerations which argued against giving a 1.75 g/Kg load it was decided to use a load

of 50 g glucose (Alpha® Glucose Powder; Allied Pharmaceuticals) dissolved in 200 ml water per subject. Subjects were instructed to drink the glucose solution within five minutes. A second blood sample was taken 120 minutes after ingestion of the glucose load. Blood samples were put on ice until it started to clot. Serum was prepared from the blood samples and stored at -20^{0}C and after 1- 4 days at -84^{0}C for the determination of serum glucose and serum insulin levels. Capillary blood glucose concentrations were obtained by a finger prick before and after 120 minutes of the test, in order to give immediate feedback to subjects. A glucometer (Ames Glucometer®Gx; Miles USA) and glucose strips (Glucostix®, Bayer Diagnostics; Ames USA) were used.

Certain practical problems were experienced during the GTT. The first blood samples were not always true fasting samples, due to the fact that some subjects did not report to the test site after an eight to twelve-hour fast as they were instructed (193 males and 233 females were definitely fasting. The fasting state of the remaining subjects are not certain.) In as many cases as possible the second blood samples were taken after exactly 120 minutes. However, in some instances the second sample was taken 15 min earlier.

Table 3.2 Diagnostic criteria for type 2 diabetes glucose intolerance (GIT) and normal glucose tolerance

Glucose tolerance status	Diagnostic criteria
Normal glucose tolerance	Fasting blood glucose concentration: <6.0 mmol/l 120 minute postload blood glucose concentration <5 mmol/l
Glucose intolerance (GIT1 in the exploratory study)	Fasting blood glucose concentration:6.0-7.1 mmol/l 120 minute postload blood glucose concentration ≥5.0-11.0 mmol/l
Type 2 diabetes (GIT2 in the exploratory study)	Fasting blood glucose concentrations > 7.1 mmol/l 120 minute postload blood glucose concentration ≥11.1 mmol/l

(WHO criteria were used (WHO, 1985; WHO, 1997))

For the purpose of this study, the study population was divided into two age groups, young subjects (younger than 45 years) and older subjects (45 years or older). The diagnostic criteria of type 2 diabetes, GIT and normal glucose tolerance given by the World Health Organisation (WHO, 1985; WHO, 1997) were used. These criteria are given in Table 3.2. Any newly diagnosed diabetic subjects were referred to a doctor for retesting, diagnosis and treatment. Subjects were divided into 3 groups on the basis of their glucose tolerance status. Subjects with a normal glucose tolerance according to the World Health Organisation were classified as the

normal group, and subjects who were GIT according to the World Health Organisation were classified as the glucose intolerance -1 (GIT1) group. Because the fasting state in some subjects was suspected (self-reporting of fasting), and because some of the second blood samples (120 minute post load) were taken 15 min earlier than 120 minutes, those subjects with fasting or 120 min postload glucose levels ≥11.1 mol./l were referred to as the glucose intolerance-2 (GIT2) group in the exploratory study. In the nested case-control study only diabetic subjects who were really fasting and whose postload glucose levels were determined exactly 120 minutes after ingestion of the glucose were used. These subjects are called the diabetic group.

3.10 Blood samples

Blood samples were drawn from the *vena cephalica* using a sterile butterfly infusion set (Johnson & Johnson, 21G, 19 mm) and syringes. For the preparation of serum, 50 ml of blood was allowed to clot in glass tubes (on ice), centrifuged at 3000 rpm for 15 minutes (the centrifuge used in this study (Hettich 16R Tuttlingen, Germany) is equipped with a cooling system). For each subject 30 x 1 ml aliquots were frozen at -20°C for 1 - 4 days and then at -84°C in the laboratory until the biochemical analyses were performed. Citrated blood samples (0.5 ml 1 mol./l citrate, pH 4.5 - 4.8, and 4.5 ml venous blood) were centrifuged in plastic tubes at 3000 rpm for 10 minutes. The citrated plasmas were divided into five aliquots, stored at -20°C for 1 - 4 days and then at -84°C in the laboratory until the biochemical analyses were performed. Five ml of blood was transferred to EDTA glass tubes. Haematocrit and haemoglobin were determined on EDTA blood. Blood cells and EDTA plasma were separated by centrifugation at 300 rpm for 10 minutes. Aliquots of plasma and cells were stored separately, at -20°C for 1 - 4 days and then at -84°C in the laboratory until the biochemical analyses were performed.

The butterfly system was kept viable with a solution of 3 units heparin per 5 ml saline for drawing the120 minute sample. More than 2 ml of blood was discarded before drawing the 120 min blood sample to get rid of the heparin and saline solution.

3.11 Biochemical analyses

Tables 3.3, 3.4, 3.5 and 3.6 give the different variables determined and methods used in the analyses of the blood, serum and plasma samples. The normal ranges for adults with the appropriate references are also given in these tables.

Table 3.3: Variables that were determined from whole blood

Variable	Method and supplier of reagents	Normal range
Haematocrit	Capillary tube (Marinfield Germany) and centrifuge (Hettich, D-78532 Tuttlingen, Germany)	Men: 39-49%; Women: 33-44% (Murphy, 1996, 294)
Haemoglobin	Colorimetric (Boehringer Mannheim)	Men: 13-18 g/dl; Women: 11.5-15.5 g/dl (Murphy, 1996, 294)

Table 3.4: Variables that were determined from plasma

Variable and unit	Method and supplier of reagents	Normal range
Fibrin content of fibrin networks	Method of Ratnoff & Menzies (1981) (Veldman, 1996)	
Fibrinogen concentration	Method of Clauss (1957)(Veldman, 1996)	180-250 mg/dl (Veldman, 1996)
Macromolecular protein complex (MPC)	Method of Ratnof & Menzies (1981); Method of Clauss (1957) (Veldman, 1996)	200-400 mg/dl (Veldman, 1996)

Table 3.5: Variables that were determined from serum. All the variables were determined with the DAX Profile (discrete analyser "Technikon DAX 48")

Variable	Normal range as supplied by Chemical Pathology UP	Variable	Normal range as supplied by Chemical Pathology UP
Sodium	137-144 mol./l	Bilirubin : D	4-30 µmol/l
Potassium	3.6-4.7 mol./l	alkaline phosphatase (ALP)	38-120 IU/l
Chloride	98-108 mol./l	gamma-glutamyl transferase (GGT.)	8-32 IU/l
CO_2-content	23-29 mol./l	alanine amino-transferase (ALT)	6-32 IU/l
Anion gap	7-14 mol./l	aspartate amino transferase (AST)	9-34 IU/l
Urea	3.6-7.8 mol./l	Lactic dehydrogenase (LD)	90-180 IU/l
Urate	0.13-0.47 mol./l	creatine kinase (CK)	45-165 IU/l
Creatinine	81-114 mol./l	Total cholesterol	3.40-5.40 mol./l
Phosphate	0.6-1.4 mol./l	Triglyceride	<2 mol./l
Calcium	2.20-2.60 mol./l	HDL-cholesterol	>1 mol./l
Magnesium	0.70-0.89 mol./l	LDL-cholesterol	<3.5 mol./l
Total protein	66-79 g/l	Osmolarity	275-295 mol./l
Albumin	39-50 g/l	Glucose	3.5-6.2 mol./l
Globulin	18-36g/l	Amylase	34-126 g/l
Bilirubin : T	4-30 µmol/l	Transferrin	2-3.2 g/l
Glucose	3.5-5.3 mmol/l	Vitamin A	30-60 µg/dl

UP=University of Pretoria

Table 3.6: Variables that were determined from serum

Variable	Method and supplier of reagents	Normal range as supplied by Chemical Pathology PU
Pyridoxal phosphate (PLP)	HPLC (Ubbink, *et al.*, 1985)	20-80 mol./l
Vitamin E	HPLC and immunological (Becton Dickson, Orangeburg, New York)	8 mg α-TE
Vitamin B_{12}	Radio assay (Becton Dickson, Orangeburg, New York)	118-716 pmol/l
Homocysteine	Derivatised with ammonium 7-fluoro-benzo-2 oxa-1,3 diazole-4-sulfonate ([SBD-F] Wako, Neuss, Germany) according to the method of Araki and Sako (Araki & Sako, 1989)	2.4µmol/l
Red cell folate	Radio assay (Becton Dickson, Orangeburg, New York)	>272 µmol/l
Folic acid	Radio assay (Becton Dickson, Orangeburg, New York)	2-10ng/ml
Ferritin	Immunoradiometric assay (Ferritin Man Solid Phase Component System, Becton Dickenson and company Orangeburg, New York), using an Auto Gamma 500C counting system from United Technologies Packard, USA.	>8.5 µmol/l
Iron	Spectrophotometrically with Technicon RA-1000 automated system, using a colorimetric method without deproteinisation (Boehringer Mannheim, Mannheim, Germany)	10-30 µmol/l
Total iron binding capacity (TIBC)	Saturate trans. ferritin with iron and precipitated uncomplexed iron with magnesium carbonate (Boeringer Mannheim). Determine TIBC spectrophotometrically with Technicon RA-1000 automated system, using a colorimetric method without deproteinisation (Boehringer Mannheim, Mannheim, Germany)	
Insulin	IBL ^{125}I-insulin-RIA (coated tube) Cat.-No.: IC 13021	72-179 pmol/l

UP=University of Pretoria; HPLC=high-pressure liquid chromatography; RIA=radioimmunoassay

3.12 Statistical analyses

The data were computerised and cleaned. To address the specific objectives, the data were analysed in three steps. In the first step, using the SPSS-package, means, medians, standard deviations, standard errors and 95% confidence intervals were calculated. Data that were not

normally distributed were logarithmically transformed and nonparametric tests used to test for significant differences between groups and effects of urbanisation. Of the first 889 subjects, complete data on all measured variables were available for only 728 subjects. Univariate analysis of variance (ANOVA), the post hoc test of least significant differences (LSD), multivariate regression analysis, stepwise regression models and Spearman rank-order correlations with adjustments for confounding factors were used to examine the influence of level of urbanisation and the relationships between measured variables. Data collection of the THUSA study was done in 1996 and 1998. To test if the two sets of data could be combined total reported energy intakes of women in the 1996 and 1998 data sets were compared. The mean intake of the 1996 group was 7973.7 kJ and the 1998 group 7997.1kJ and it was judged that the two sets of data could be combined.

Data from the total population were used to determine the effect of urbanisation on the markers of GIT and type 2 diabetes (fasting serum glucose and insulin levels and postload glucose levels) before and after adjusting for certain lifestyle factors (age, smoking habit, BMI, waist-to-hip ratio and physical activity). After adjusting for all these lifestyle factors together, they were also adjusted for separately and in a "step wise" fashion, adding one factor at a time. The effect of urbanisation on these lifestyle factors was also determined. The same statistical analyses were done to determine the effect of HIV infection on the markers of GIT and type 2 diabetes and on the lifestyle factors. No significant effects of HIV infection were found and it is therefore not reported in this study.

In the second step, the following statistical analyses were done on the 1996 data, using the Excel programme:

- Means, standard deviations, and standard errors of all the variables were determined for the continuous variables.
- Chi-square tests of association to determine associations or relationships between categorical variables such as glucose tolerance groups, age groups, gender, stratum, family history of chronic diseases of lifestyle, BMI groups and HIV infection status. A p-value <0.05 indicated a significant association between two variables.
- Spearman's rho to determine correlations between categorical variables such as glucose tolerance status, stratum, BMI groups, waist circumference >1M, and family history of chronic diseases of lifestyle. A correlation was significant if the p-value was <0.05.
- Pearson correlation coefficients to determine significant correlations between all the

continuous variables and both fasting and postload glucose levels. A correlation was significant if the p-value was <0.05.

- T-tests to determine significant differences for all continuous variables between the normal glucose tolerance groups and the GIT2 groups.
- Partial correlation coefficients were used to determine significant differences between normal glucose tolerance groups and GIT2 groups, when controlling for gender and age.

In the third step data from the entire study population (1854 subjects) were used. All newly diagnosed diabetic subjects who were 45 years or younger were selected using the criteria given in Table 3.2. A control subject was selected, by the computer, for each of the diabetic subjects, matched for gender, age, BMI, stratum, and education level. The diabetic subjects in this group were definitely fasting and the postload blood samples were drawn at exactly 120 min after ingestion of the glucose load. Therefore, this group was termed the diabetic group. The following statistical analyses were done on this data using SPSS software:

- Means, standard, deviations and standard errors of all continuous variables were calculated for all subject groups.
- T-tests to determine significant differences for all continuous variables between the diabetic and control groups.
- Partial correlations controlling for age, gender, BMI and energy intake to determine associations between the variables and fasting blood glucose levels.

The results of the three sets of analyses, addressing the three stated objectives, are reported in Chapters 4,5 and 6 respectively.

CHAPTER 4
RESULTS AND DISCUSSION: THE EFFECT OF URBANISATION ON TYPE 2 DIABETES

4.1 Introduction

In this chapter the effect of urbanisation on the risk factors or markers (where a causal relationship with type 2 diabetes has not been proved) for the development of type 2 diabetes (baseline serum insulin, baseline serum glucose and two hour serum glucose levels) was tested in males and females separately. The dependence of this effect on lifestyle and other factors such as age, smoking, body mass index (BMI), waist-to-hip ratio and physical activity were also examined by adjusting for these variables in correlations between level of urbanisation and risk factors of type 2 diabetes. The nature of the modernisation process, of which urbanisation is part, is complex and it involves several lifestyle factors including smoking, stress, diet, physical activity, obesity and body fat distribution. Modernisation, and the factors linking it to type 2 diabetes were discussed in Chapter 2 (2.3.8.3) as an environmental risk factor for type 2 diabetes. In this chapter the results of the effects of urbanisation on the risk factors of type 2 diabetes in the total THUSA population are presented and discussed.

4.2 Results

4.2.1 Introduction

Table 4.1 shows the age, BMI and waist-to-hip ratio for the males and the females in each stratum. The number of subjects per group is also included in this table. Because age were used to stratify the THUSA results, the data in this table is age adjusted. These results show that in all strata, the males are lean, but the females are overweight. In all the strata both the males and females had waist-to-hip ratios indicative of lower body fat distribution (>0.90 for the males and >0.80 for the females).

Table 4.1: Mean age, body mass index, waist-to-hip ratio and number of males and females in each stratum

Stratum	Gender	Number of subjects	Mean age	Mean BMI	Mean W:H
Rural people	Males	200	41.3	20.8	0.84
Farm workers		117	35.8	21.0	0.83
Squatters		137	35.9	20.4	0.84
Urban middle class		237	37.0	21.3	0.85
Urban Upper class		86	29.4	23.0	0.84
Total male group		777	37.4	20.7	0.84
Rural people	Females	252	39.8	25.6	0.77
Farm workers		209	37.4	26.3	0.77
Squatters		218	36.5	26.9	0.76
Urban middle class		236	39.0	28.1	0.77
Urban upper class		172	31.7	28.1	0.75
Total female group		1087	37.0	26.9	0.76

Baseline serum insulin, baseline serum glucose and two hour serum glucose levels are markers of type 2 diabetes and glucose intolerance (GIT). The effects of urbanisation on these markers, as found by univariate analyses, are shown in Tables 4.2 and 4.3. Co-variate analyses were used to determine whether the effect of urbanisation on each of the markers was dependent on age, smoking, body mass index (BMI), waist-to-hip ratio and physical activity level and results are shown in Tables 4.4 and 4.5. The results for all three markers of type 2 diabetes and GIT are reported. After controlling for all these factors together, they were also controlled for separately. These results were only significant for the baseline serum glucose levels and therefore, are not reported for baseline serum insulin or two-hour serum glucose. The fasting state of the subjects and the insulin level were also controlled for. Although the subjects were requested to fast for 8-12 hours, not all complied with this criterium. Using the information supplied on the recruitment form, a "new" variable for fasting was created, assigning a value for "fasting", "had a drink" and "had something to eat" of 1, 2 and 3. The factors were also controlled for in a step-wise way adding one factor to the previous factors at a time. No significant results were found using this procedure. The effects of stratum on the possible confounders, age, the smoking habit, BMI, waist-to-hip ratio and physical activity was then determined and are shown in Table 4.6.

4.2.2 The effect of stratum on baseline serum insulin

Table 4.2 shows that stratum had a significant effect on baseline serum insulin levels. Complete data for 1163 subjects was available and are included in this table. The univariate analysis showed that the effect of stratum on insulin levels in males was highly significant (p=0.007) and even more significant in females (p=0.000). However, after controlling for age, the smoking habit, BMI, waist-to-hip ratio and physical activity, the effect of stratum on baseline serum insulin levels was no longer significant, for either the males (p=0.473) or the females (p=0.550). The effect of stratum on baseline serum insulin levels was therefore dependent on the above factors. The large sizes of the rural and urban middle class and the small size of the upper urban females could have influenced these results.

Table 4.2: The effect of stratum on baseline (t_0) insulin, before and after controlling for lifestyle factors

Stratum	Males			Females		
	Mean µU/ml	±SD	n	Mean µU/ml	±SD	n
Rural people	21.0 [ab] (17.4)	1.9 (2.2)	144	22.6 [efg] (23.5)	1.5 (1.8)	212
Farm workers	17.4 [cd] (17.9)	3.0 (3.3)	57	19.2 [hij] (20.1)	2.1 (2.3)	110
Squatters	29.1 [ac] (24.2)	2.6 (2.5)	76	30.0 [eh] (25.9)	2.2 (2.9)	106
Urban middle class	23.7 (19.3)	1.8 (1.8)	159	29.2 [fh] (24.2)	1.6 (1.9)	191
Urban upper class	17.4 [b,d] (18.3)	3.0 (6.9)	53	32.0 [gi] (23.1)	3.0 (10.4)	55

The estimated marginal means and standard deviations are given in brackets
n = number of subjects per group
Alphabet letters indicate significant differences on the unadjusted data – (univariate model)
a, b = ($p \leq 0.05$)
c, d, e, f, g = ($p \leq 0.01$)
h, i, j = ($p \leq 0.001$)

4.2.3 The effect of stratum on baseline serum glucose

According to Table 4.3 the effect of stratum on the baseline serum glucose levels was dependent on age, the smoking habit, BMI, waist-to-hip ratio, and physical activity in some, but not all cases. Complete data were available for 1717 subjects and are included in the table. The univariate analysis showed that the effect of stratum on baseline glucose levels was highly significant for males (p=0.000) but not significant for females (p=0.061). After controlling for the factors mentioned above the analysis showed that the effect of stratum on baseline glucose was significant

for males (p=0.006) and highly significant for females (p=0.000). There were no significant differences between baseline glucose levels in either the farm workers or the urban middle class and any other strata before controlling for the lifestyle factors. After controlling for the lifestyle factors significant differences emerged between these two strata and the urban upper class. This could be due to the fact that changes in one or more of these factors masked the significant relationship.

Table 4.3: The effect of stratum on baseline (t_0) serum glucose before and after controlling for lifestyle factors

Stratum	Males			Females		
	Mean (mmol/l)	±SD	n	Mean (mmol/l)	±SD	n
Rural people	5.0 $^{a^* a b c}$ (4.6)	0.1 (0.1)	193	4.9 $^{c^* d}$ (4.8)	0.1 (0.1)	287
Farm workers	4.7 $^{b^* a}$ (4.9)	0.1 (0.1)	117	4.8 ^{e} (4.9)	0.2 (0.1)	146
Squatters	4.9 $^{c^* b}$ (5.0)	0.1 (0.1)	136	5.1 $^{f^* f}$ (4.9)	0.1 (0.1)	172
Urban middle class	4.9 $^{d^* c}$ (4.9)	0.1 (0.1)	223	4.7 ^{g} (4.8)	0.1 (0.1)	285
Urban upper class	4.2 $^{a^* b^* c^* d^*}$ (4.7)	0.2 (0.2)	61	4.4 $^{e^* f^* d e f g}$ (8.8)	0.2 (0.6)	97

The estimated marginal means and standard deviations are given in brackets;
n = number of subjects per group
Alphabet letters indicate significant differences on the unadjusted data – (univariate model)
Alphabet letters with a "*" indicate significant differences on the data adjusted for age(38.5 years for males; 38.9 years for females), the smoking habit (1.4 pack years for males; 1.9 pack years for females), BMI (20.7 for males; 26.8 for females), waist-to-hip ratio (0.85 for males; 0.77 for females) and physical activity level (3.6 for males; 2.8 for females) – (co-variate analysis).
e*, a = ($p \leq 0.05$)
b*, f* = ($p \leq 0.01$)
a*, c*, d*, b, c, d, e, f, g = ($p \leq 0.001$)

According to Table 4.4 it seems that in many cases where the relationship between the baseline glucose levels of two strata was not significant, the relationship was dependent upon the lifestyle factors as well as the baseline state and insulin level. However, where there were significant differences between the baseline glucose levels of two groups all these factors were not present. In the males these significant differences were only dependent on physical activity level and fasting state. In the females they were dependent on insulin in both instances and in one case on age, the smoking habit, and waist-to-hip ratio. These results support the notion that the risk factors for type 2 diabetes and GIT differ in males and females. In both males and females the effect of urbanisation in the urban upper class was dependent on a different set of factors than in the other

strata. This suggests that in the urban upper class other factors may influence the effect of stratum on baseline glucose levels.

Table 4.4: Lifestyle factors which influenced the effect of stratum on baseline glucose levels

Significant difference between baseline glucose in:		Males	Females
Rural *	**Farm**	age, smoking habit, BMI, WH, activity, fasting state, insulin	age, smoking habit, BMI, WH, activity, fasting state, insulin
	Squatters	age, smoking habit, BMI, WH, insulin	age, smoking habit, BMI, WH, activity, fasting state, insulin
	Urban	age, smoking habit, BMI, WH, insulin	age, smoking habit, BMI, WH, activity, fasting state, insulin
	Upper *	activity, fasting state	age, smoking habit, WH, insulin
Farm *	**Squatters**	age, smoking habit, BMI, WH, activity, fasting state, insulin	age, smoking habit, BMI, WH, activity, fasting state, insulin
	Urban	age, smoking habit, BMI, WH, activity, fasting state, insulin	age, smoking habit, BMI, WH, insulin
	Upper *	activity, fasting state	age, smoking habit, BMI, WH, activity, fasting state, insulin
Squatters *	**Urban**	age, smoking habit, BMI, WH, activity, fasting state, insulin	age, smoking habit, BMI, WH, activity, fasting state, insulin
	Upper *	activity, fasting state	insulin
Urban *	**Upper ***	activity, fasting state	age, smoking habit, BMI, WH, insulin

Rural = rural people, Farm = farm workers, Urban = urban middle class; Upper = urban upper class, BMI = body mass index, WH = waist-to-hip ratio, activity = physical activity

*** indicates a significant difference between the baseline glucose levels of two groups before adjusting for lifestyle factors – (univariate analysis)**

Estimated marginal means after adjusted for age(38.5 years for males; 38.9 years for females), the smoking habit (1.4 pack years for males; 1.9 pack years for females), BMI (20.7 for males; 26.8 for females), waist-to-hip ratio (0.85 for males; 0.77 for females) and physical activity level (3.6 for males; 2.8 for females) – (co-variate analysis)

4.2.4 The effect of stratum on the two-hour serum glucose levels

Table 4.5 shows that in the males the effect of stratum on the two-hour glucose level was dependent on lifestyle factors. In the females this effect was not dependent on the lifestyle factors (except in the urban upper class). The univariate analysis showed that the effect of stratum on the two hour glucose levels was highly significant for males and females ($p=0.000$ in both cases) before controlling for lifestyle factors. After controlling for lifestyle factors the effect of stratum on the two hour glucose levels was not significant for the males ($p=0.936$), but significant for females ($p= 0.002$). This also supports the notion that the risk factors for type 2 diabetes are different in males and females.

Table 4.5: The effect of stratum on the two hour serum glucose levels before and after controlling for lifestyle factors

Stratum	Males			Females		
	Mean (mmol/l)	±SD	n	Mean (mmol/l)	±SD	n
Rural people	5.7 [a b c] (5.3)	0.2 (0.2)	178	6.3 [h a*] (5.8)	0.1 (0.1)	264
Farm workers	6.2 [d e] (5.5)	0.2 (0.2)	108	6.6 [i a* b* c*] (6.7)	0.2 (0.2)	130
Squatters	4.8 [a d g] (5.4)	0.2 (0.2)	89	5.5 [h i j k b*] (5.6)	0.2 (0.2)	141
Urban middle class	5.0 [b e f] (5.2)	0.2 (0.2)	187	6.2 [j l c*] (6.0)	0.1 (0.2)	268
Urban upper class	6.6 [c f g] (5.4)	0.2 (0.6)	71	6.8 [k l] (6.6)	0.2 (0.8)	96

The estimated marginal means and standard deviations are given in brackets;
n = number of subjects per group
Alphabet letters indicate significant differences on the unadjusted data – (univariate model)
Alphabet letters with a "*" indicate significant differences on the data adjusted for age(39.6 years for males;39.8 years for females), the smoking habit (1.4 pack years for males; 1.9 pack years for females), BMI (20.9 for males; 26.7 for females), waist-to-hip ratio (0.86 for males; 0.77 for females) and physical activity (3.4 for males; 2.7 for females) – (co-variate analysis)
a, b, c, j, k, l, c* = ($p \leq 0.01$)
d, e, f, g, h, i, a*, b* = ($p \leq 0.001$)

4.2.5 The effect of stratum on lifestyle factors

There were no significant differences in smoking habit between the different strata, and results of smoking are therefore, not reported here. Table 4.6 shows that in females the effect of stratum was only significant on activity level. The multivariate analysis also showed that the effect of stratum on physical activity level was highly significant (p=0.000) for females. The fact that BMI and waist-to-hip ratio differed significantly between strata for the males but not the females may be due to the occurrence of obesity in the females in all strata (as can be seen from the mean BMI for females in Table 4.6). As a group the males were lean, but BMI increased with urbanisation. The effect of stratum on physical activity in both the males and females suggests that differences in physical activity occur during urbanisation and may play a role in the development of type 2 diabetes. According to the multivariate analysis the effect of stratum on the lifestyle factors was significant for males (age - p=0.002; BMI - p=0.015; waist-to-hip ratio - p=0.22; physical activity - p=0.000). Thus, the effect of stratum on physical activity was highly significant for both the males and the females, supporting the notion that changes in physical activity during urbanisation may be important in the development of type 2 diabetes and GIT. The results of in this table was

calculated for 234 males and 136 females and this difference in the sizes of the two groups could have influenced the results.

Table 4.6: The effect of stratum on lifestyle factors

Stratum	Variable	Males			Females		
		Mean	±SD	n	Mean	±SD	n
Rural	BMI	20.4 [a]	0.5	57	25.9	0.9	51
Farm		19.5 [b]	0.7	22	25.8	1.3	25
Squatters		19.4 [cd]	0.5	54	25.3	1.2	26
Urban		20.7 [ce]	0.4	94	27.5	1.1	34
Upper		23.7 [abde]	1.3	7	-	-	-
Rural	WH	0.87 [f]	0.01	57	0.80	0.01	51
Farm		0.85	0.15	22	0.80	0.02	25
Squatters		0.84 [fg]	0.01	54	0.77	0.02	26
Urban		0.87 [g]	0.01	94	0.78	0.01	34
Upper		0.88	0.03	7	-	-	-
Rural	activity	2.7 [nijk]	0.2	57	2.3 [op]	0.1	51
Farm		3.8 [nl]	0.3	22	2.9 [oq]	0.1	25
Squatters		3.7 [imp]	0.2	54	2.6 [pr]	0.1	26
Urban		3.6 [jn]	0.2	94	2.4 [qr]	0.1	34
Upper		5.3 [klmn]	0.6	7	-	-	-

n = number of subjects per group
Rural = rural people, Farm = farm workers, Urban = urban middle class; Upper = urban upper class, BMI = body mass index, WH = waist-to-hip ratio, activity = physical activity
Alphabet letters indicate a significant difference for a specific lifestyle factor in two strata -univariate analysis
a, c, e, l, m, r = $p \leq 0.05$
b, d, f, g, n, i, n = $p \leq 0.01$
j, k, o, p, q = $p \leq 0.001$

4.3 Discussion

To address the question whether stratum or level of urbanisation, influences risk factors or markers of type 2 diabetes, significant differences in these markers between strata were examined. Significant differences were interpreted that there are relationships between urbanisation and risk factors of type 2 diabetes. The results reported above suggest that: 1). The effect of stratum on serum insulin levels was dependent on the lifestyle factors that were measured. 2). The effect of stratum on the baseline serum glucose levels was dependent on physical activity level and fasting state in the males and on age, the smoking habit, waist-to-hip ratio and especially baseline insulin levels in the females. 3). The effect of stratum on the two-hour glucose level seemed to be dependent upon all the lifestyle factors that were tested for the males, but not for the females. 4). The overall results suggest that the risk factors for the development of type 2 diabetes were

different in males and females. Other not-measured risk factors may also play a role in the development of type 2 diabetes. Obesity, which is one of the most important risk factors for the development of type 2 diabetes, was not indicated as a high priority risk factor in this study group. However, waist-to-hip ratio in the females had a significant influence on the effect of stratum on diabetes risk factors, indicting the existence of "healthy" and "unhealthy obesity" in this population. The fact that the baseline glucose and insulin levels in rural men were higher than in the urban upper class is intriguing especially in the light of the increased BMI in the urban upper class. The results of this study did indicate that body weight is not an important risk factor for the development of type 2 diabetes in the study population. And it is therefore possible that the rural males may have other contributing factors responsible for the higher baseline serum glucose and insulin levels, that is absent in the urban upper class. Another possibility is that because heath services is more available in urban areas, some people with high fasting glucose levels are diagnosed at an early stage and receive treatment either for hyperglycaemia or for another disease and are therefore not included in this study. This would have resulted in a "healthier" subject group for the urban upper class than for the rural subjects. Since the amount of subjects not included in the study due to use of chronic medication, is not known it is not possible to test whether this was indeed the case in the THUSA study. However this phenomenon deserves attention in future research projects. It seems that the African population shares the same risk factors than other populations (McKeigue *et al.*, 1991; Osei *et al.*, 1992; Conway *et al.*, 1995; Haffner *et al.*, 1997), but that the order of importance of the risk factors may not be the same. This could be due to the effect of urbanisation, where an individual is confronted with several risk factors for type 2 diabetes at the same time.

The fact that the upper urban men and women had the lowest mean (unadjusted) fasting glucose level, but the highest two-hour glucose value is intriguing. As mentioned, there were different "levels" of fasting in these subjects and the results reported above indicated that many lifestyle factors influenced serum glucose. It is, however, note worthy that a particular set of circumstances or influences resulted in lower baseline glucose values but higher glucose values two hours after ingestion of glucose. Differences between strata of the drink and/or snack ("something light") taken and the resultant second meal effect (Wolever, 1990) could possibly explain these findings. However, lack of data prevents a conclusion regarding this observation.

CHAPTER 5
RESULTS AND DISCUSSION: RELATIONSHIPS BETWEEN LIFESTYLE-RELATED RISK FACTORS OF DIABETES AND GLUCOSE INTOLERANCE IN THE THUSA POPULATION

5.1 Introduction

In this part of the study data from all the subjects recruited and examined in 1996 (n = 728) were analysed. This part of the study was an exploratory exercise to identify the most important risk factors for the development of type 2 diabetes in this population. The glucose tolerance tests on these subjects were done by the researcher. This data were analysed during 1997 to assess whether the protocol of the THUSA study should be changed in the 1998 field work. During 1998 the fasting state of each subject was noted. In the 1996 study this was only done for some of the subjects, therefore subjects were not classified as diabetic, but as glucose intolerant using a random, and not a fasting glucose level.

5.2 General information of study population

The total study group consisted of 728 subjects (1996 phase of the THUSA study), of which 40.5% (295) were male and 59.5% (433) female. Figure 5.1 shows the percentages of males and females in each age group of the total sample. Figure 5.2 shows the percentages of males and females in each stratum in the total study population.

More females than males were included in the study due to the fact that a large percentage of the males were working and were therefore not able to participate in certain sites. The first age group (15-24.9 years) included mainly school children and therefore equal numbers of males and females were included. For the second and the third age groups (25-34.9 and 35-44.9 years respectively), almost twice as many females were studied compared to the males, especially in the rural areas, squatter camps, and urban middle class. The older men (45-54.9 and 55-65 years) were more readily available to participate, since many of them were workless or retired. In the oldest age group (55-65 years) fewer subjects were studied, probably due to the fact that many subjects aged 55 years or older were excluded because they suffered from some chronic disease, and/or were using chronic medication.

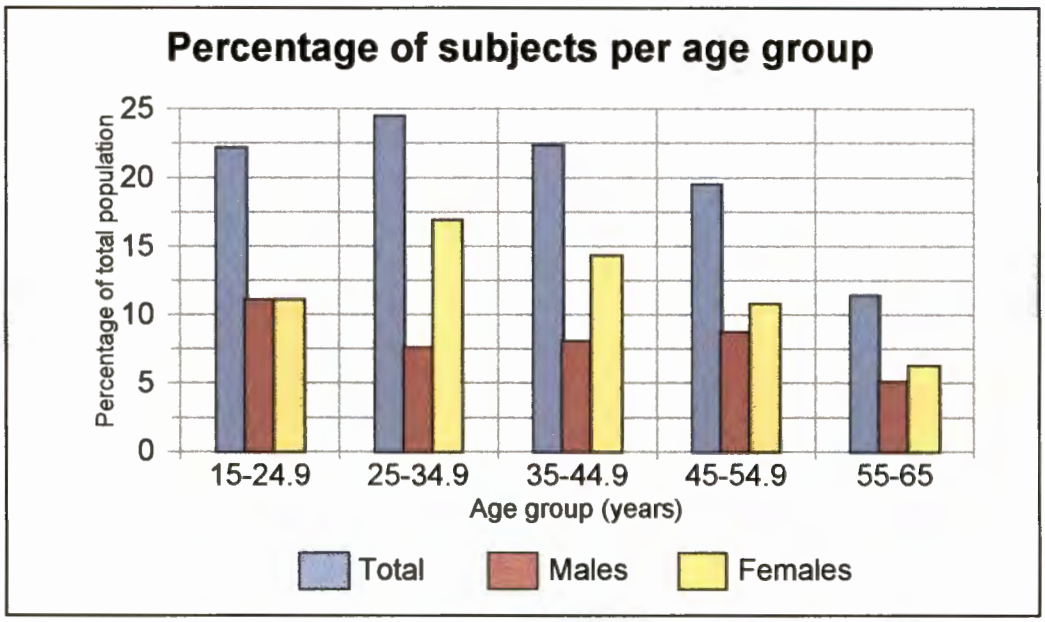

Figure 5.1: The percentage of the total sample, males, and females that fall into each age group (Total = total sample)

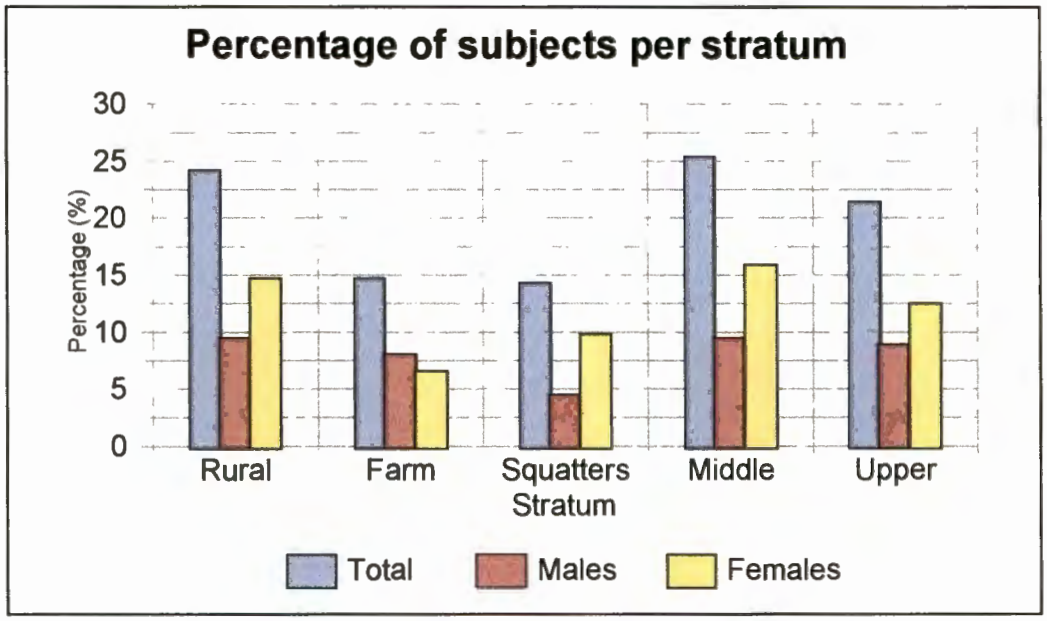

Figure 5.2: The percentage of the total sample, males and females in each stratum (Rural = rural people; Farm = farm workers; Middle = urban middle class; Upper = urban upper class; total = total sample)

Figure 5.2 shows that more females than males were tested in all strata except the farm worker's stratum. Farm workers were mainly males and on most farms more males than females were available for testing.

5.3 Grouping of subjects

For the purpose of this analysis the study population was divided into males and females of two age groups of 15-44.9 years and 45-65 years, resulting in the following four groups:

- Females, <45 years (young females)
- Females, 45 years and older (older females)
- Males, <45 years (young males)
- Males, 45 years and older (older males)

The standard deviations and means for all the variables tested were calculated for these four groups. These results mainly concern differences between males and females and are therefore not given in this chapter.

The above four groups were further divided into three each according to the glucose tolerance status, using the criteria given in section 3.10, Table 3.2. The resulting twelve groups are given in Table5.1.

Table 5.1: Grouping of subjects into age, gender and glucose tolerance status groups

Group	Criteria (serum glucose concentration)	Females	Males
young NGT	Fasting <7.1 mmol/l; 120 min postload <7.7 mmol/l	n = 213	n = 157
young GIT1	120 min postload ≥7.7 mmol/l but <11.1 mmol/l	n = 75	n = 28
young GIT2	Fasting >7.1 mmol/l; 120 min postload ≥11.1 mmol/l	n =20	n = 10
older NGT	Fasting <7.1 mmol/l; 120 min postload <7.7 mmol/l	n = 73	n = 71
older GIT1	120 min postload ≥7.7 mmol/l but <11.1 mmol/l	n = 30	n =17
older GIT2	Fasting >7.1 mmol/l; 120 min postload ≥11.1 mmol/l	n = 22	n = 12

(young = <45 years; older = 45 years or older; NGT = normal glucose tolerance; GIT1 = glucose intolerant group 1; GIT2 = glucose intolerant group 2; n = number of subjects)

The means and standard deviations for all the variables tested were calculated for these twelve groups, but the results mainly concern differences between males and females and therefore only the means and standard deviations for selected variables are listed in tables in this chapter.

5.4 Demographic information

5.4.1 Age

Table 5.2 shows the means and standard deviations for age in the twelve age and gender groups. It is well known that the risk to develop type 2 diabetes increases with advancing age (McCance, *et al.*, 1997). Table 5.2 shows that the mean ages of the young and older females increased as the

glucose tolerance status worsened. The same trend was not present in either the young or the older males. There were, however, no significant differences in the mean ages of any of these groups.

Table 5.3 and figure 5.3 show the number and percentage of subjects with normal glucose tolerance, GIT1 and GIT2 in each age group in the total sample. The same information for the females is shown in Table 5.4 and figure5.4 and for males in Table 5.5 and figure 5.5. The negative effect of aging on the glucose tolerance of the study population can be seen in figures 5.3, 5.4, and 5.5. Figure 5.3 shows that the higher percentage of subjects with GIT2 with aging was accompanied by a lower percentage with normal glucose tolerance. However, when the males and females were separated it became clear that the effect of aging on glucose tolerance was more pronounced in the females than in the males (figures 5.4 and 5.5). This was especially true in the 55-65 year age group. In all three groups there was much higher percentages of subjects with glucose intolerance (GIT) in the 35-44.9 year age group than in the 25-34.9 year age group. The results further indicated that the biggest increase in the percentage of subjects with GIT2 was between the 35-44.9 year and the 45-54.9 year age group. This suggested that normal glucose tolerance worsened to GIT in subjects older than 35 years and that GIT may have progressed to type 2 diabetes especially afer the age of 45 years. For this reason the split of the sample at the age of 45 years into a young group (15-44.9 years) and an older group (45-65 years) was justified.

Table 5.2: Descriptive statistics of age

Group	Variable	Females		Males	
		mean	SD	mean	SD
<45 years, NGT	age (years)	29.4	±7.9	28.0	±8.2
<45 years, GIT1	age (years)	32.2	±8.5	30.9	±10.3
<45 years, GIT2	age (years)	32.2	±8.6	26.9	±7.8
≥45 years, NGT	age (years)	52.2	±5.7	52.9	±6.2
≥45 years, GIT1	age (years)	53.2	±6.5	53.1	±7.1
≥45 years, GIT2	age (years)	53.3	±6.0	52.2	±5.3

(SD = standard deviation; NGT = normal glucose tolerance; GIT1 = glucose intolerance group 1; GIT2 = glucose intolerance group 2)

The higher percentage of subjects with GIT2 in the 15-24.9 year age group compared to the 25-34 year and 35-44.9 year old subjects is not in accordance with the effect of aging on glucose

tolerance. However, Table 5.5 and figure 5.5 show that it could have been as a result of the high percentage of GIT2 in the 15-24.9 year age group in the males.

GIT1 seemed to increase with age in the first 3 age groups. In the total sample, the highest percentage of subjects with GIT1 was found in the 35-44.9 year age group. In the total sample and in the females the higher percentage of subjects with normal glucose tolerance in the 45-54.9 year age group compared to the 35-44.9 year and the 55-65 year age groups were unexpected. According to the literature the detrimental effect of age on glucose tolerance is one of the three most important risk factors for the development of type 2 diabetes. Thus, a continuous decrease in normal glucose tolerance with aging was expected. This was clearly not found. However, it must be taken into account that this study only reported newly diagnosed cases of type 2 diabetes (GIT2). The high number of subjects with GIT2 in the 45-54.9 year age group suggests that many individuals developed the disease between these ages. It is therefore possible that many individuals have already been diagnosed with type 2 diabetes prior to this study, and were therefore excluded.

Table 5.3: The number and percentage of subjects with normal glucose tolerance, GIT1, and GIT2, in each age group in the total population

Age groups (years)		NGT	GIT1	GIT2	Row total
15-24.9	Count	128	23	11	**162**
	Row Pct	79.0	14.2	6.8	**22.2**
	Col Pct	24.9	15.3	17.2	
25-34.9	Count	138	30	10	**178**
	Row Pct	77.5	16.9	5.6	**24.5**
	Col Pct	26.8	20.0	15.6	
35-44.9	Count	104	50	9	**163**
	Row Pct	63.8	30.7	5.5	**22.4**
	Col Pct	20.2	33.3	14.1	
45-54.9	Count	96	26	20	**142**
	Row Pct	67.6	18.3	14.1	**19.5**
	Col Pct	18.7	17.3	31.3	
55-65	Count	48	21	14	**83**
	Row Pct	57.8	25.3	16.9	**11.4**
	Col Pct	9.3	14.0	21.9	
Column total	**Count**	**514**	**150**	**64**	**728**
	Col Pct	**70.6**	**20.6**	**8.8**	**100**

(NGT = normal glucose tolerance; GIT1= glucose intolerant group 1; GIT2 = glucose intolerant group 2; Row Pct = row percentage; Col Pct = column percentage)

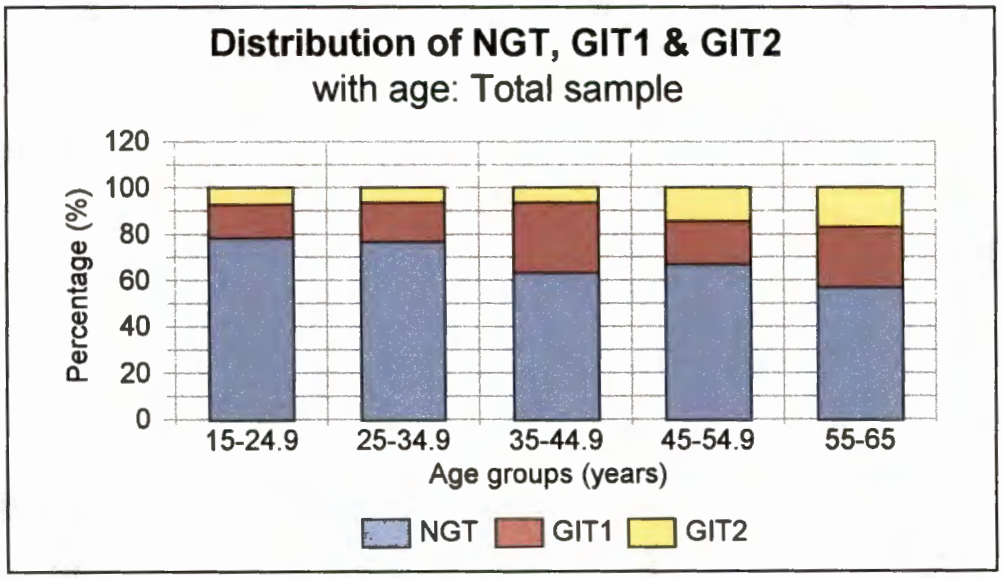

Figure 5.3: The distribution of normal glucose tolerance, GIT1 and GIT2 in the total sample in each age group (NGT = normal glucose tolerance; GIT1 = glucose intolerant group 1; GIT2 = glucose intolerant group 2)

Table 5.4: The distribution of normal glucose tolerance, GIT1 and GIT2, in each age group in the females

Age groups (years)		NGT	GIT1	GIT2	Row total
15-24.9	Count	62	14	5	**81**
	Row Pct	76.5	17.3	6.2	**18.7**
	Col Pct	21.7	13.3	11.9	
25-34.9	Count	91	24	8	**123**
	Row Pct	74.0	19.5	6.5	**28.4**
	Col Pct	31.8	22.9	19.0	
35-44.9	Count	60	37	7	**104**
	Row Pct	57.7	35.6	6.7	**24.0**
	Col Pct	21.0	35.2	16.7	
45-54.9	Count	51	16	12	**79**
	Row Pct	64.6	20.3	15.2	**18.2**
	Col Pct	17.8	15.2	28.6	
55-65	Count	22	14	10	**46**
	Row Pct	47.8	30.4	21.7	**10.6**
	Col Pct	7.7	13.3	23.8	
Column total	**Count**	**286**	**105**	**42**	**433**
	Col Pct	**66.1**	**24.2**	**9.7**	**100.0**

(NGT = normal glucose tolerance; GIT1 = glucose intolerant group 2; GIT2 = glucose intolerant group 2; Row Pct = row percentage; Col Pct = column percentage)

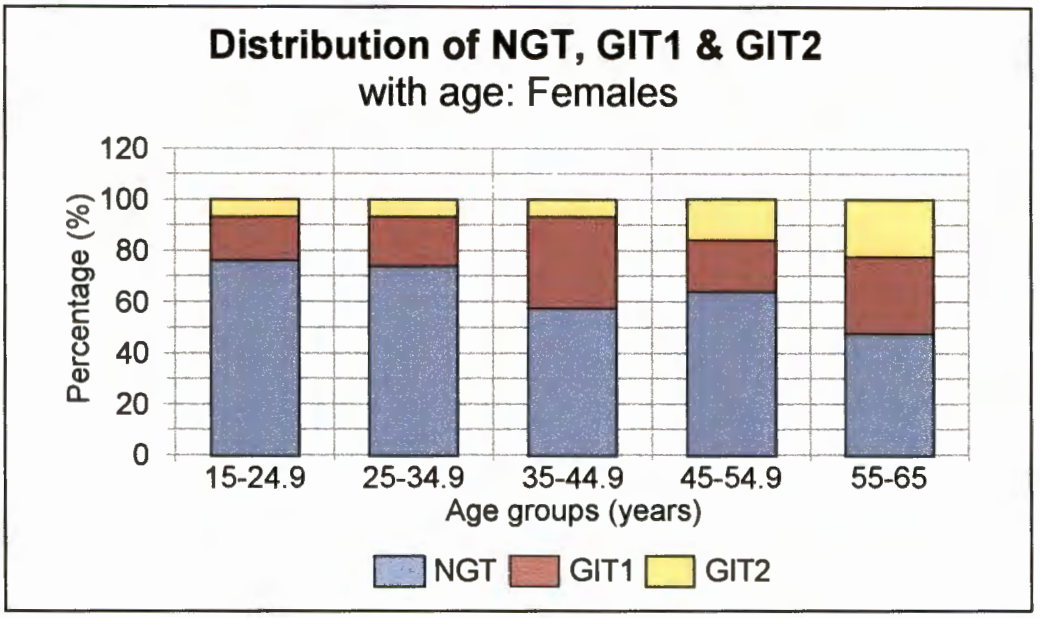

Figure 5.4: The distribution of normal glucose tolerance, GIT1 and GIT2 in females in each age group (NGT = normal glucose tolerance; GIT1 = glucose intolerant group 1; GIT2 = glucose intolerant group 2)

Table 5.5: The distribution of normal glucose tolerance, GIT1, and GIT2 in each age group, in the males

Age groups (years)		NGT	GIT1	GIT2	Row total
15-24.9	Count	66	9	6	**81**
	Row Pct	81.5	11.1	7.4	**27.5**
	Col Pct	28.9	20.0	27.3	
25-34.9	Count	47	6	2	**59**
	Row Pct	85.5	10.9	3.6	**20.0**
	Col Pct	20.6	13.3	9.1	
35-44.9	Count	44	13	2	**59**
	Row Pct	74.6	22.0	3.4	**20.0**
	Col Pct	19.3	28.9	9.1	
45-54.9	Count	45	10	8	**63**
	Row Pct	71.4	15.9	12.7	**21.4**
	Col Pct	19.7	22.2	36.4	
55-65	Count	26	7	4	**37**
	Row Pct	70.3	18.9	10.8	**12.5**
	Col Pct	00.4	15.6	18.2	
Column total	**Count**	**228**	**45**	**22**	**295**
	Col Pct	**77.3**	**15.3**	**7.5**	**100.0**

(NGT = normal glucose tolerance; GIT1 = glucose intolerant group 1; GIT2 = glucose intolerant group 2; Row Pct = row percentage; Col Pct = column percentage)

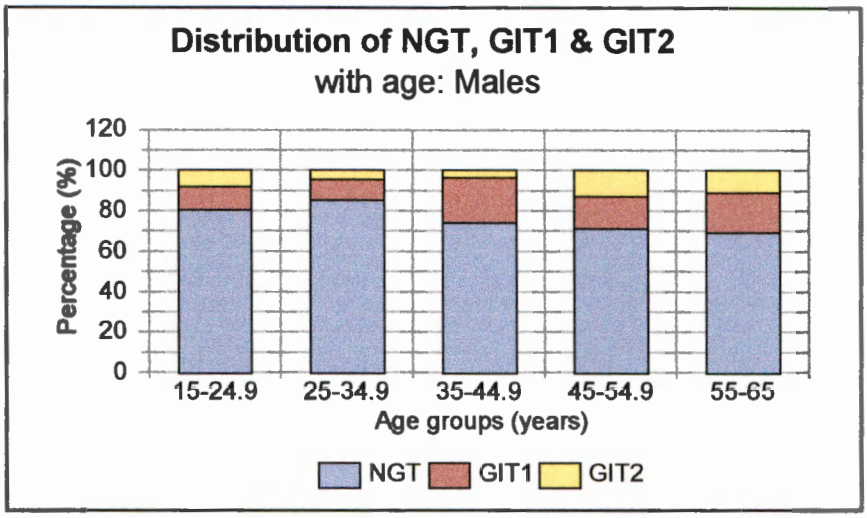

Figure 5.5: The distribution of normal glucose tolerance, GIT1 and GIT2 in the males, in each age group (NGT = normal glucose tolerance; GIT1 = glucose intolerance group 2; GIT2 = glucose intolerance group 2)

Pearson correlations showed that there were a significant association between age and glucose tolerance status in the total sample (p=0.00), and in females (p=0.00), but not in the males (p=0.25). In the light of these results the separation of the study population into males and females is justified.

5.4.2 Gender

Type 2 diabetes is often more prevalent in females than in males (Schwartz, *et al.*, 1995; Conway *et al.*, 1995; Despres, *et al.*, 1995; Osei, *et al.*, 1997). According to the literature, gender, age and obesity are the three most important risk factors for the development of type 2 diabetes. In this population type 2 diabetes was also more prevalent in females than in males. Tables 5.4 and 5.5 and figures 5.4 and 5.5 show that for every age group, except the 15-24.9 year group, the females had a larger percentage GIT2 subjects than the males. In total, 9.7% of all females and 7.5% of all males fell into the GIT2 group. The females also had a higher percentage of GIT1 subjects for every age group compared to the males. In total, 24.2% of all females and 15.3 % of all males fell into the GIT1 group. In total, 77.3% of all males and 66.1% of all females had a normal glucose tolerance. According to the Pearson Chi-square there was a significant relationship between glucose tolerance status and gender (p=0.004).

Thus, in this sample GIT1 and GIT2 were higher in the females than in the males, and normal glucose tolerance was therefore higher in the males. The results also suggested that the risk

factors for the development of type 2 diabetes were not the same in the male and female population.

5.4.3 Stratum

The prevalence of type 2 diabetes increases as third world populations adopt a Western lifestyle (Reaven, 1993; Osei, *et al.*, 1997). This has lead scientists to believe that Westernisation or modernisation increases the risk for the development of type 2 diabetes. Table 5.6 shows the percentage of males and females in both the young and older age groups with normal glucose tolerance, GIT1 and GIT2, in every stratum.

Table 5.6: The percentage of males and females in both the young and the older age groups, with normal glucose tolerance, GIT1 and GIT2 in every stratum

Group	Stratum	Females NGT	Females GIT1	Females GIT2	Males NGT	Males GIT1	Males GIT2
<45 years	Rural people	66.2% (43)	27.7% (18)	6.2% (4)	78.6% (33)	11.9% (5)	9.5% (4)
	Farm workers	72.5% (21)	24.1% (7)	3.4% (1)	65.6% (21)	28.1% (9)	6.2% (2)
	Squatters	84.0% (42)	10.0% (5)	6.0% (3)	95.2% (20)	0.0% (0)	4.8% (1)
	Urban middle class	67.1% (55)	22.0% (18)	11.0% (9)	85.7% (36)	14.3% (6)	0.0% (0)
	Urban upper class	63.4% (52)	32.9% (27)	3.6% (3)	81.0% (47)	13.8% (8)	5.2% (3)
≥45 years	Rural people	50.0% (21)	28.6% (12)	21.4% (9)	66.7% (18)	22.2% (6)	11.1% (3)
	Farm workers	57.8% (11)	21.1% (4)	21.1% (4)	63.0% (17)	22.2% (6)	14.8% (4)
	Squatters	71.4% (15)	14.3% (3)	14.3% (3)	83.3% (10)	16.7% (2)	0.0% (0)
	Urban middle class	61.8% (21)	23.5% (8)	14.7% (5)	81.5% (12)	11.0% (3)	7.4% (2)
	Urban upper class	55.6% (5)	3.3% (3)	11.1% (1)	57.1% (4)	0.0% (0)	42.9% (3)

(NGT=normal glucose tolerance; GIT1= glucose intolerant group 1; GIT2 = glucose intolerant group 2) The number of subjects in each category is given in brackets.

The high percentages of subjects in the GIT1 groups may be explained by the fact that all the subjects were not in a fasting state. In general there was no specific trend in the incidence of GIT 2 as subjects became more Westernised. In the older women the rates of GIT2 were lower in the most modernised strata (urban middle and upper classes), than in the rural strata. The high incidence of GIT2 in the older males (42.9%) in the urban upper class was probably the result of the small number of subjects included in this group (only 7 subjects), and may not reflect the true incidence of GIT2 in this population. In two of the groups there were no GIT2 subjects. In the

case of the older male squatters, the absence of GIT2 subjects might have been the result of the small number of subjects included in this group (12 subjects). In the case of the young urban middle class males, 21 subjects were included in the group and the absence of GIT2 in this group might have indicated true low incidence of GIT2 in this group. The high rates of GIT2 in the rural population may be the result of lower diagnosis of the disease in the rural areas, where individuals often have to travel long distances to hospitals or clinics. On the other hand the lower rates of GIT2 in the urban population may be the result of the higher diagnosis of the disease in towns and cities where clinics and hospitals are within easy reach of residents.

From Table 5.6 it can be seen that the rate of GIT2 was higher in the older than in the younger females and males in every stratum. The exception was in the squatters, where no older GIT2 males were diagnosed. In the older males there was a significant correlation between stratum and fasting glucose level (Spearman's rho - p=0.000). Thus it seemed as if stratum might have had an influence on the development of GIT 2 in the males, but not in the females. This observation might be explained by the differences in effects of urbanisation on body mass index (BMI) of males and females.

5.4.4 Family history of chronic diseases

A family history of type 2 diabetes, type 1 diabetes and other chronic diseases, such as hypertension (HT), coronary heart disease (CHD), and stroke are known to be risk factors for the development of type 2 diabetes (Groop, *et al.*, 1993; Alcolado &Alcolado, 1991; Froguel, *et al.*, 1993; Levitt & Mollentze, 1995). In this study family history of these diseases was assessed by a questionnaire where subjects had to indicate which diseases, if any, were present in their families. The results gained in this way may not reflect the true incidences of these chronic diseases in family members. Medical services for Africans in rural South Africa were poor before 1994. This could have resulted in under diagnosis of chronic diseases. Another problem is that in cases such as type 2 diabetes, where death or disability results more from the complications associated with the disease than the disease *per se* , type 2 diabetes and type 1 diabetes were and still are not listed as causes of death. Therefore, the reported prevalence of these chronic diseases in family members of the subjects could be low.

Table 5.7: Family history of chronic diseases in the study population per glucose tolerance groups

Chronic disease		♀ NGT	♀ GIT1	♀ GIT2	row total	♂ NGT	♂ GIT1	♂ GIT2	row total
No family history of DM2	count	225	98	34	**387**	214	40	19	**273**
	row %	65.9	25.3	8.8	**89.4**	78.4	14.7	7.0	**92.5**
	col %	89.2	93.3	81.0		93.9	88.9	86.4	
Family history of DM2	count	31	7	8	**46**	14	5	3	**22**
	row %	67.4	15.2	17.4	**10.6**	63.6	22.7	13.6	**7.5**
	col %	10.8	6.7	19.0		6.1	11.1	13.6	
Column total	**count**	**286**	**105**	**42**	**433**	**228**	**45**	**22**	**295**
	col%	**66.1**	**24.2**	**9.7**	**100**	**77.3**	**15.3**	**75**	**100**
No family history of DM1	count	272	99	39	**410**	219	44	21	**284**
	row %	66.3	24.1	9.5	**94.7**	77.1	15.5	7.4	**96.3**
	col %	95.1	94.3	92.9		96.1	97.8	95.5	
Family history of DM1	count	14	6	3	**23**	9	1	1	**11**
	row %	60.9	26.1	13.0	**5.3**	81.8	9.1	9.1	**3.7**
	col %	4.9	5.7	7.1		3.9	2.2	4.5	
Column total	**count**	**286**	**105**	**42**	**433**	**228**	**45**	**22**	**295**
	col%	**66.1**	**24.2**	**9.7**	**100**	**77.3**	**15.3**	**7.5**	**100**
No family history of CHD	count	245	91	33	**369**	198	41	19	**258**
	row %	66.4	24.7	8.9	**85.2**	76.7	15.9	7.4	**87.5**
	col %	85.7	86.7	78.6		86.8	91.1	86.4	
Family history of CHD	count	41	14	9	**64**	30	4	3	**37**
	row %	64.1	21.9	14.1	**14.8**	81.1	10.8	8.1	**12.5**
	col %	14.3	13.3	21.1		13.2	8.9	13.6	
Column total	**count**	**286**	**105**	**42**	**433**	**228**	**45**	**22**	**295**
	col%	**66.1**	**24.2**	**9.7**	**100**	**77.3**	**15.3**	**7.5**	**100**
No family history of HT	count	174	53	30	**257**	167	35	16	**216**
	row %	67.7	20.6	11.7	**59.4**	76.4	16.2	7.4	**73.2**
	col %	60.8	50.5	71.4		72.4	77.8	72.7	
Family history of HT	count	112	52	12	**176**	63	10	6	**79**
	row %	63.6	29.5	6.8	**40.6**	79.7	12.7	7.6	**26.8**
	col %	39.2	49.5	28.6		27.6	22.2	27.3	
Column total	**count**	**286**	**105**	**42**	**433**	**228**	**45**	**22**	**295**
	col%	**66.1**	**24.2**	**9.7**	**100**	**77.3**	**15.3**	**7.5**	**100**
No family history of stroke	count	245	97	36	**378**	210	44	22	**276**
	row %	64.8	25.7	9.5	**87.3**	76.1	15.9	8.0	**93.6**
	col %	85.7	92.4	85.7		92.1	97.8	100	
Family history of stroke	count	41	8	6	**55**	18	1	0	**19**
	row %	74.5	14.5	10.9	**12.7**	94.7	5.3	0.0	**6.4**
	col %	14.3	7.6	14.3		7.9	2.2	0.0	
Column total	**count**	**286**	**105**	**42**	**433**	**228**	**45**	**22**	**295**
	col%	**66.1**	**24.2**	**9.7**	**100**	**77.3**	**15.3**	**7.5**	**100**

(col=column; ♀=female; ♂=male; NGT=normal glucose tolerance; GIT=glucose intolerant group 1; GIT2 = glucose intolerant group 2; DM2 = type 2 diabetes; DM1=type 1 diabetes; CHD=coronary heart disease; HT=hypertension)

The percentages of the male and female population who reported a family history of these chronic diseases are listed in Table 5.7. A higher percentage of female GIT2 than male GIT2 subjects reported a family history of all the chronic diseases listed in Table 5.7. Table 5.8 gives a list of the significant associations and correlations for a family history of chronic diseases. A significant association between a family history of HT and diabetes status in female subjects (p=0.044), was observed. There were also significant correlations between a family history of type 2 diabetes and

the 120 min postload glucose levels in the young males (p=0.022), and older females (p=0.050). Furthermore, a significant correlation between a family history of stroke and the 120 min postload glucose levels (p=0.026) in the older females was seen. These results suggest that the risk factors for the development of GIT could also have a familial component in this population and that they may be different in the females and males.

Table 5.8: Significant associations and correlations for family history of chronic diseases

Groups	r-value
Significant association between glucose tolerance status and family history of hypertension in females.	+-association *
Significant correlation between family history of type 2 diabetes in young males and the 120 min post load glucose levels.	0.16 *
Significant correlation between family history of type 2 diabetes and 120 min postload glucose levels in older females.	-0.18 *
Significant correlation between family history of stroke and 120 min postload glucose levels in older females.	-0.20 *

***=Correlation significant at the 0.05 level**
(NGT=normal glucose tolerant; DM2=type 2 diabetes)

5.4.5 Smoking

Table 5.9 describes the relationships between smoking habit and status with the glucose tolerance status. Cigarette smoking was measured in pack years ([n_1 = cigarettes smoked per day/20] x [n_2 = years smoking]) and other use of tobacco was measured in gram tobacco per week. The reported use of tobacco includes the use of snuff.

According to the literature smoking is a risk factor for the development of type 2 diabetes. In this study the smoking habit was defined in two ways. In the first place each subject had to indicate whether he or she smoked or not (indicated by the term smoking in the results). In the second place the amount and duration of cigarette smoking were noted and packet years calculated or in the case of tobacco the amount of tobacco used per week was noted (g tobacco/week). From Table 5.9 it can be seen that the young female GIT2 subjects reported a higher use of cigarettes than the NGT and the GIT1 groups (0.96, 0.18, and 0.09 respectively). The older GIT2 females reported a higher use of tobacco than the NGT and the GIT1 groups (11.74, 5.32, and 8.23 g tobacco/week). These differences were however not significant. The older GIT2 males reported a significantly higher use of tobacco than the NGT group (but not the GIT1 group). This is an indication that smoking could be an important risk factor for type 2 diabetes in males. Thus, in

the older population the use of tobacco could have increased the risk for type 2 diabetes, while cigarette smoking could have increased the risk for type 2 diabetes in young females.

Although the results on smoking in this study population is very interesting and unique, the focus of this study was to analyse the factors contributing to the development of type 2 diabetes and GIT or that can be used as risk markers for these diseases. Since smoking does not seem to be one of the important risk factors for this population (especially the females) at this stage, these results were not further studied or discussed. However, it is important to look into this matter in future studies. If the smoking habit of this population increases further, it is possible that smoking may play a more important role in the development of type 2 diabetes and GIT in this study population.

Table 5.9: Descriptive statistics for smoking

Group	Variable	Females < 45 years		Males < 45 years		Females ≥45 years		Males ≥45 years	
		mean	±SD	mean	±SD	mean	±SD	mean	±SD
NGT	smoking (packet years)	0.2	1.5	1.5	3.9	0.8	4.6	4.0	10.8
	smoking (g tobacco/week)	4.4	13.3	7.4	21.3	5.3	11.5	2.6	22.6
GIT1	smoking (packet years)	0.1	0.6	0.7	2.2	0.01	0.04	*0.4	1.0
	smoking (g tobacco/week)	1.9	5.6	10.6	23.7	8.2	20.6	23.0	33.5
GIT2	smoking (packet years)	1.0	3.0	0.9	1.9	0.6	2.2	*0	0.0
	smoking (g tobacco/week)	3.1	8.2	5.8	18.4	11.7	26.2	14.6	32.4

***Significant difference between two groups (p-value <0.05)**
(SD = standard deviation; NGT = normal glucose tolerant; GIT1 = glucose intolerant group 1; GIT2= glucose intolerant group 2)

Table 5.10: Smoking and glucose tolerance status in the male and female subjects

		Females			Males		
Smoking		NGT	GIT1	GIT2	NGT	GIT1	GIT2
Subjects <45 years							
No	count	155	59	12	75	12	5
	row%	48.7	18.6	3.8	23.6	3.8	1.6
	col%	72.8	78.7	60.0	47.8	42.9	50.0
Yes	count	58	16	8	82	16	5
	row%	31.4	8.6	4.3	44.3	8.6	2.7
	col%	27.2	21.3	40.0	52.2	57.1	50.0
Subjects ≥45 years							
No	count	38	17	9	24	5	8
	row%	37.6	16.8	8.9	23.8	5.0	7.9
	col%	52.1	56.7	40.9	33.8	29.4	66.7
Yes	count	35	13	13	47	12	4
	row%	28.2	10.5	10.5	37.9	9.7	3.2
	col%	47.9	43.3	59.1	66.2	70.6	33.3

(NGT=normal glucose tolerance; GIT1=glucose intolerant group 1; GIT2 = glucose intolerant group 2; col=column)

From Table 5.10 it can be seen that 40% of all young female diabetics and 50% of all young male diabetics smoked, while 59.1% of all older female diabetics and 33.3% of all older male diabetics smoked. The older GIT2 females were the only group with a higher percentage of smokers than nonsmokers. However, this did not take the amount of smoking into account. These females did not necessarily smoke more than the other groups, there were only more individuals that smoked.

5.4.6. Alcohol intake

Table 5.11 gives the means and standard deviations for the reported alcohol intake in this sample. Increased alcohol intakes are associated with an increased risk for type 2 diabetes (Mann, 1997). Table 5.11 shows that in the young females and older males the GIT2 groups reported lower mean alcohol intakes than the NGT groups. The older female and young male GIT2 groups reported higher alcohol intakes than the NGT groups.

Table 5.11: Descriptive statistics of alcohol intakes

Group	Variable	Females <45 years		Males < 45 years		Females <45 years		Males < 45 years	
		mean	± SD	mean	±SD	mean	± SD	mean	±SD
NGT	g alcohol/week	86.7	53.0	229.3	315.7	73.4	80.0	165.8	160.0
GIT1	g alcohol/week	119.4	236.1	218.0	233.5	39.3	28.8	198.4	116.7
GIT2	g alcohol/week	63.2	58.1	314.9	367.4	191.2	218.6	133.0	115.0

(SD = standard deviation; NGT = normal glucose tolerant; GIT1 = glucose intolerant group 1; GIT2= glucose intolerant group 2)

Table 5.12 shows that there was a significant correlation between the use of alcohol and the 120 min postload glucose levels in older GIT1 females. The absence of significant correlations or differences in the use of alcohol between NGT and GIT2 groups suggest that alcohol was not the major risk factor for the development of type 2 diabetes in this population. In older males other factors probably overrode any alcohol effects. However, in the older females, alcohol seemed to play a significant role.

Table 5.12: Significant correlations for the use of alcohol

Group	r-value
Significant correlation between alcohol intakes (g alcohol/week) and 120 min postload glucose in older GIT1 females	0.86 *

***=Correlation significant at the 0.05 level**
(GIT1 = glucose intolerant group 1)

5.5 Anthropometry

5.5.1 Weight, height and body mass index (BMI)

Table 5.13 consists of the means and standard deviations of the weight, height and BMI of the study sample. Obesity is one of the most important risk factors for the development of type 2 diabetes (Perry, *et al.*, 1995; Shaper, *et al.*, 1997). According to Table 5.13 the mean weight and BMI of the young females and the older males increased as the glucose tolerance status worsened, while the mean BMI of the young males and the older females did not change markedly. This suggests that weight could be a more important risk factor for the development of type 2 diabetes in young females and older males than in older females and young males. The results clearly indicate that in young males, GIT 2 developed in lean subjects. In the older females all groups had a mean BMI indicative of overweight.

Table 5.13: Descriptive statistics of weight, height and body mass index

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	weight (Kg)	65.7	16.2	61.8	14.7	67.6	19.1	62.5	16.43
	height (m)	1.6	0.1	1.7	0.1	1.6	0.1	1.7	0.1
	BMI (Kg/m^2)	26.5	6.6	21.4	4.9	27.4	7.5	22.2	5.1
GIT1	weight (Kg)	68.5	16.8	59.2	11.7	71.4	19.0	59.6	11.2
	height (m)	1.6	0.1	1.7	0.1	1.6	0.1	1.7	0.1
	BMI (Kg/m^2)	27.4	6.5	21.1	3.8	29.6	7.6	21.1	3.3
GIT2	weight (Kg)	69.6	18.6	59.4	7.0	65.9	17.3	65.9	13.9
	height (m)	1.6	0.06	1.7	0.04	1.6	0.1	1.7	0.1
	BMI (Kg/m^2)	27.5	6.8	21.0	2.3	27.2	7.3	23.7	5.8

There was a significant difference for BMI between the males and females of the total population (p=0.000) (SD=standard deviation; NGT=normal glucose tolerance; GIT1 = glucose intolerant group 1; GIT2 = glucose intolerant group 2; BMI = body mass index)

Table 5.14 shows the significant correlations for the anthropometric variables. Although, there was a significant correlation (p=0.013) between weight and the 120 min glucose levels in young GIT1 males, the absence of such correlations in the NGT and GIT2 groups suggests that weight was not the most important risk factor for the development of GIT2, but that it may have had an effect on glucose levels. The absence of significant differences in the weight between NGT and GIT2 groups also suggested that weight *per se* was not the most important risk factor for the development of GIT2 in this population. There were no significant differences in height between any of the groups. This suggested that height *per se* was not an important risk factor for the

development of GIT2 in this population. Height may be indicative of early malnutrition in stunted individuals. The thrifty phenotype hypothesis (Hales & Barker, 1992) states that the risk of chronic diseases of lifestyle is increased in such individuals. In this sample, no such effect was visible. The females were significantly more obese than the males ($p = 0.00$)

Table 5.14: Significant correlations for the body mass index (BMI)

Groups	r-value
Significant correlation between body weight and the 120 min glucose levels in young GIT1 males	-0.46 *

***=Significant difference at the 0.01 level**
(GIT1= glucose intolerant group 1)

Table 5.15: The percentage of subjects in each group that were lean, normal weight, overweight and obese according to WHO criteria

Age group	Weight group		Females				Males			
			NGT	GIT1	GIT2	Row total	NGT	GIT1	GIT2	Row total
<45 years	Lean	count	29	7	3	3913	65	13	4	8243
		row%	74.4	17.9	7.7		79.3	15.8	4.9	
		col%	13.7	8.8	15.0		41.9	46.4	40.0	
	Normal weight	count	80	21	6	107	68	10	5	83
		row%	74.8	19.6	5.6	34.3	81.9	12.0	6.0	43.0
		col%	37.8	26.2	30.0		43.9	35.7	50.0	
	Over-weight	count	48	30	5	83	17	4	1	22
		row%	57.8	36.1	6.0	26.6	77.3	18.2	4.5	11.4
		col%	22.6	37.5	25.0		11.0	14.3	10.0	
	Obese	count	55	22	6	83	5	1	0	6
		row%	66.3	26.5	7.2	26.6	83.3	16.7	0.0	3.1
		col%	25.9	27.5	30.0		3.2	3.6	0.0	
	Column total	count	212	80	20	312	155	28	10	193
		col%	67.9	25.6	6.4	100	80.3	14.5	5.2	100
≥45 years	Lean	count	10	2	4	1613	29	8	4	4141
		row%	62.5	12.5	25.0		70.7	19.5	9.8	
		col%	14.1	6.9	19.0		47.0	47.0	33.3	
	Normal weight	count	18	5	3	26	24	8	3	35
		row%	69.2	19.2	11.5	215	68.6	22.8	8.6	35.0
		col%	25.4	17.2	14.3		33.8	47.0	25.0	
	Over-weight	count	19	11	7	37	12	1	4	17
		row%	51.4	29.7	18.9	30.6	70.6	5.9	23.5	17.0
		col%	26.8	37.9	33.3		16.0	5.9	33.3	
	Obese	count	24	11	7	42	6	0	1	7
		row%	57.1	26.2	16.7	34.7	85.7	0.0	14.3	7.0
		col%	33.8	37.9	33.3		8.4	0.0	8.3	
	Column total	count	71	29	21	121	71	17	12	100
		col%	58.7	24.0	17.4	100	71.0	17.0	12.0	100

(NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2; col=column; tot=total)

If the sample is divided into lean, normal weight, overweight and obese subjects according to the WHO criteria (WHO, 1995), the effect of BMI on glucose tolerance can be seen (Table 5.15 and

figures 5.6 and 5.7). A higher percentage of young GIT2 females were overweight or obese compared to the young GIT2 males. In fact there were no obese young GIT2 males. If the overweight and obese subjects are combined, 55% of the young GIT2 females and only 10% of the young GIT2 males fell into this group. These differences were, however, not significant. This is in accordance with the mean values for BMI of young GIT2 males (Table 5.15). Older GIT2 females also had a high percentage of obese and overweight subjects, 66.6% compared to the 41.6% of the older males

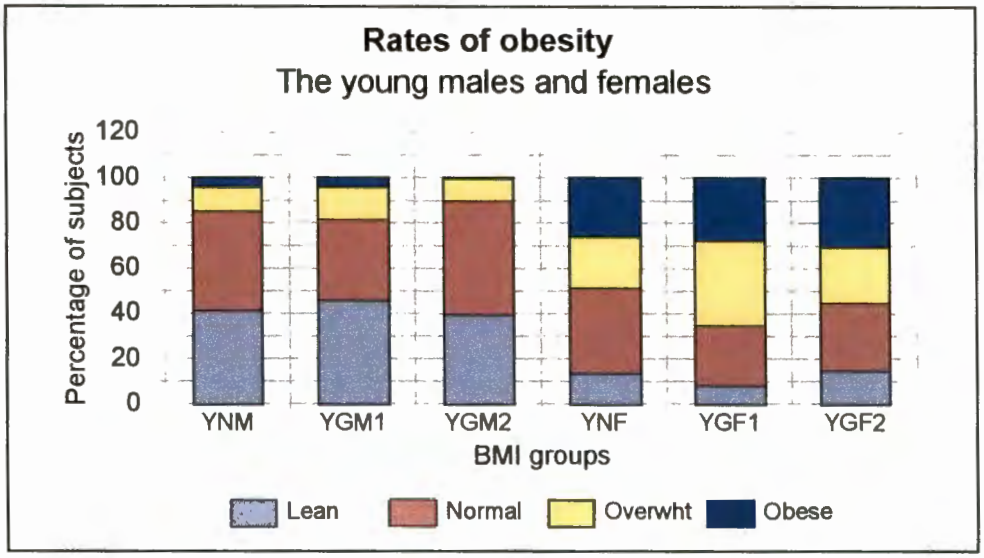

Figure 5.6: The rates of obesity in the young males and females. (BMI=body mass index; YNM=young males with normal glucose tolerance; YGM1=young males with glucose intolerance group 1; YGM2=young males with glucose intolerance group 2; YNF=young females with normal glucose tolerance; YGF1=young females with glucose intolerance group 1; YGF2=young females with glucose intolerance group 2; Normal=normal weight; Overwht=over weight)

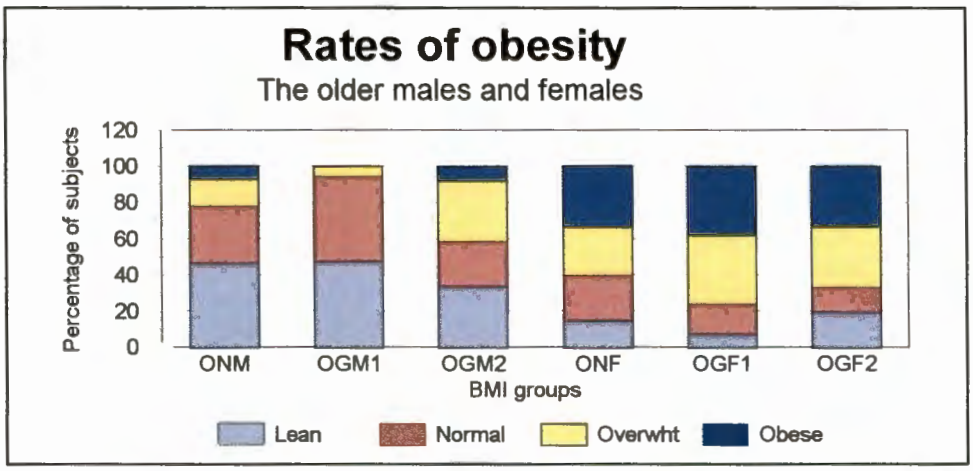

Figure 5.7: The rates of obesity in the older males and females. (BMI=body mass index; ONM=older males with normal glucose tolerance; OGM1=older males with glucose intolerance group 1; OGM2=older males with glucose intolerance group 2; ONF=older females with normal glucose tolerance; OGF1=older females with glucose intolerance group 1; OGF2=older females with glucose intolerance group 2; Normal=normal weight; Overwht=over weight)

5.5.2 Waist circumference and waist-hip ratio

Table 5.16 gives the means and standard deviations of the waist circumference and waist-hip-ratio of the sample. According to the literature waist-hip ratio may be a stronger risk factor than BMI for the development of type 2 diabetes (Lampman & Schteingart, 1991; Martin, *et al.*, 1992; Jarret, 1993). The higher the waist-hip ratio which depicts an android versus a gynoid body build, the greater the risk for the development of type 2 diabetes (McGinnis & Barash 1991; Bosse 1992). The normal glucose tolerance subjects had a significantly lower waist-hip ratio than the GIT2 subjects ($p=0.004$), even after controlling for gender, age and total energy intake ($p<0.001$). From Table 5.16 it can be seen that in all three glucose tolerance status groups, males had significantly ($p=0.000$) higher mean waist-hip ratios than females. In the young females and the older males mean waist-hip ratios increased as the glucose tolerance worsened.

Table 5.16: Descriptive statistics of waist circumference and waist-hip ratios

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	waist (cm)	75.8	12.3	74.0	8.9	81.8	14.4	79.7	12.7
	waist-hip ratio	a#0.74	0.1	a0.82	0.04	$_{d}$0.79	0.1	$_{d}$*0.87	0.1
GIT1	waist (cm)	78.2	12.4	73.4	10.9	83.6	12.8	77.8	9.6
	waist-hip ratio	b0.76	0.1	b0.80	0.1	e0.80	0.1	e0.87	0.1
GIT2	waist (cm)	82.9	17.9	72.7	9.1	79.0	14.6	85.7	11.6
	waist-hip ratio	c#0.79	0.1	c0.82	0.1	$_{f}$0.79	0.1	$_{f}$*0.90	0.04

***=Significant difference: $p<0.05$**
a; b; c; d; e; f; #=Significant difference: $p<0.001$
Significant difference for waist-hip ratio between the NGT and GIT2 groups in the total population ($p<0.01$), even after controlling for gender, age and energy intake ($p<0.001$)
(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

The sample population was divided into android and gynoid groups. A waist-hip ratio of >0.8 for females and >0.95 for males were taken to be indicative of an android body fat distribution (Must, *et al.*, 1991). As shown in Table 5.17 and figures 5.8 and 5.9, no young males had android obesity. Only 30.0% of the young GIT2 females and 33.3% of the older GIT2 females had android obesity, while only 16.7% of the older males had android obesity. Thus, in all groups the percentage subjects with android obesity were less than those with gynoid obesity. Both the young and the older GIT2 females had a higher percentage of subjects with android obesity than the males. In the young females with android obesity 11.1% fell into the GIT2 group, while 5.6% of the young females with gynoid obesity fell into the GIT2 group. In the older males with android obesity 18.2% were in the GIT2 group, while 11.0% of the older males with gynoid

obesity were in this group. In the young males and older females with android obesity, the percentage of diabetic subjects was larger than for the gynoid obese groups (0.0% and 4.7% for the young males and 14.0% and 19.7 % for the older females).

Table 5.17: The percentage of the male and female population with android and gynoid obesity

Age group	Waist-hip ratio		Females				Males			
			NGT	GIT1	GIT2	Row total	NGT	GIT1	GIT2	Row total
<45 years	Android	count	31	17	6	5418	0	0	0	0
		row%	57.4	31.5	11.0		0.0	0.0	0.0	
		col%	14.8	23.0	30.0		0.0	0.0	0.0	
	Gynoid	count	179	57	14	250	173	28	10	211
		row%	71.6	22.8	5.6	82.2	82.0	13.3	4.7	100
		col%	85.2	77.0	70.0		100	100	100	
	Column total	count	210	74	20	304	173	28	10	211
		col%	69.1	24.3	6.6	100	82.0	13.3	4.7	100
≥45 years	Android	count	31	12	7	5041	4	3	2	99
		row%	62.0	24.0	14.0		44.4	33.3	22.2	
		col%	43.7	41.4	33.3		5.6	17.6	16.7	
	Gynoid	count	40	17	14	71	67	14	10	91
		row%	56.3	23.9	19.7	58.7	73.6	15.4	11.0	91.0
		col%	56.3	58.6	66.7		94.4	82.3	83.3	
	Column total	count	71	29	21	121	71	17	12	100
		col%	58.7	24.0	17.4	100	71.0	17.0	12.0	100

(NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2; col=column)

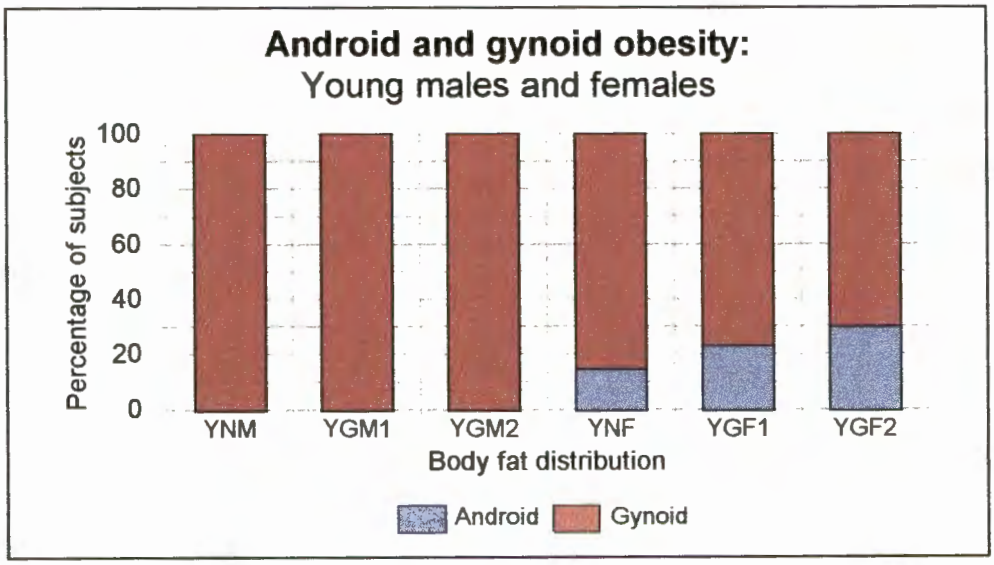

Figure 5.8: Android and gynoid obesity in the young males and females. (YNM=young males with normal glucose tolerance; YGM1=young males with glucose intolerance group 1; YGM2=young males with glucose intolerance group 2; YNF=young females with normal glucose tolerance; YGF1=young females with glucose intolerance group 1; YGF2=young females with glucose intolerance group 2; Android=android obesity; Gynoid=gynoid obesity)

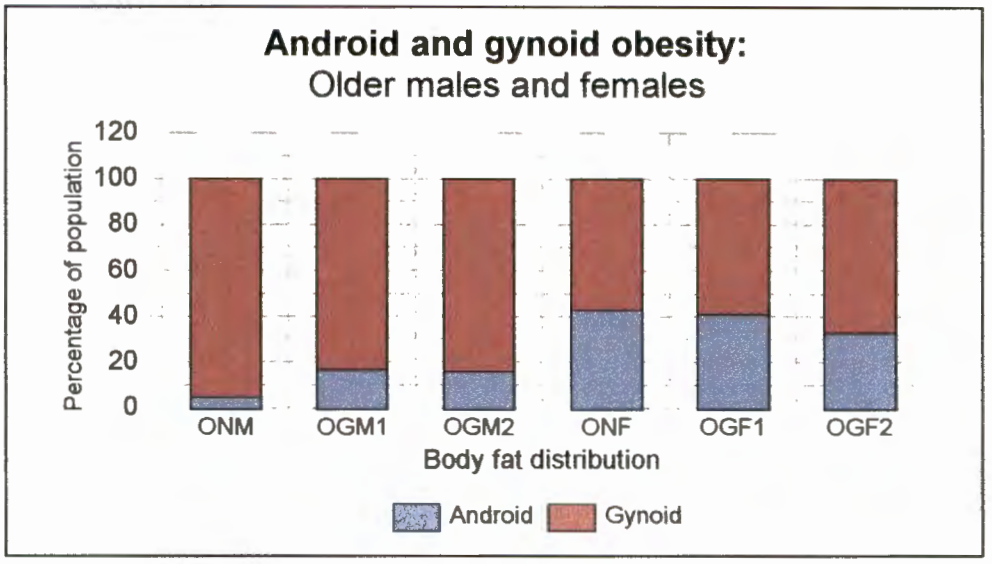

Figure 5.9: Android and gynoid obesity in the older males and females. (ONM=older males with normal glucose tolerance; OGM=older males with glucose intolerance group 1; ODM=older males with glucose intolerance group 2; ONF=older females with normal glucose tolerance; OGF=older females with glucose intolerance group 1; ODF=older females with glucose intolerance group 2; Android=android obesity; Gynoid=gynoid obesity)

Table 5.18: Significant correlations for waist circumference and waist-hip ratios

Variables and group	r-value
Significant correlation between waist-hip ratios and the 120 min postload glucose levels for the young females.	**0.136
Significant correlation between waist-hip ratios and the 120 min postload glucose levels for the older GIT1 males	*-0.497
Significant correlation between a waist circumference of more than 1 m and fasting glucose levels for the young females.	*-0.112

***=Correlation significant at the 0.05 level**

****=Correlation significant at the 0.01 level**

(GIT1 = glucose intolerant group 1)l

In recent years, researchers showed that waist circumference, especially a waist circumference of more than one metre, may be a better indication of disease risk that either BMI or waist-hip ratio (however this marker has not been verified in the Tswana population) (Despres, *et al.*, 1995). In Table 5.16 it can be seen that the older males and females had higher mean waist circumferences than the young males and females. There were no significant differences between the waist circumference of the NGT and the GIT2 groups, indicating that waist circumference was not an important marker of risk for the development of type 2 diabetes in this population.

The percentage of the subjects in each group of the population with a waist circumference of more than one metre is listed in Table 5.19. It can be seen that 10.0% of all young GIT2 females had a waist circumference of more than one metre, while none of the young GIT2 males had a waist circumference of more than one metre. The significant correlation between a waist circumference of more than one metre and fasting glucose levels suggests that waist circumference influenced glucose levels. However, the low percentage of GIT2 subjects with a waist circumference of more than one metre, suggests that gross obesity was not necessary for development of GIT2 in this population.

Table 5.19: The percentage of the population in each group with a waist circumference of more than one metre

Age group	Waist circumference		Females				Males			
			NGT	GIT1	GIT2	Row total	NGT	GIT1	GIT2	Row total
<45 years	>1 m	count	6	5	2	134.3	2	0	0	21
		row%	46.2	38.5	15.4		100.0	0.00	0.00	
		col%	2.8	6.7	10.0		1.3	0.00	0.00	
	<1 m	count	205	70	18	293	153	28	10	191
		row%	70.0	23.9	6.1	95.8	80.1	14.7	5.2	99.0
		col%	97.2	93.3	90.0		98.7	100.0	100.0	
	Column total	**count**	**211**	**75**	**20**	**306**	**155**	**28**	**10**	**193**
		col%	**69.0**	**24.5**	**6.5**	**100.0**	**80.3**	**14.5**	**5.2**	**100**
≥45 years	>1 m	count	7	3	3	1311	5	0	1	66
		row%	53.8	23.1	23.1		83.3	0.00	16.7	
		col%	9.0	10.3	14.3		7.0	0.00	8.3	
	<1 m	count	64	26	18	108	66	17	11	94
		row%	59	24.1	16.7	89.3	70.2	18.1	11.7	94.0
		col%	90.1	89.7	85.7		93.0	100.0	91.7	
	Column total	**count**	**71**	**29**	**21**	**121**	**71**	**17**	**12**	**100**
		col%	**58.7**	**24.0**	**17.4**	**100.0**	**71.0**	**17.0**	**12.0**	**100**

(col=column; NGT=normal glucose tolerance; GIT1 glucose intolerance group 1; GIT2 = glucose intolerance group 2)

5.5.3 Subscapular and triceps skinfolds

Table 5.20 gives the means and standard deviations of the subscapular and triceps skinfolds for this sample population. Both these skinfolds were selected because they may reflect upper body (android) obesity better than waist-hip ratio.

From Table 5.20 it can be seen that the young and the older females had higher subscapular and triceps skinfolds than the males. The older subjects also had higher subscapular and triceps skinfolds than the young subjects. The subscapular skinfolds increased as glucose tolerance status

worsened in the young males and females. In the older females the subscapular skinfold was similar in the NGT and GIT2 groups. In the older males the GIT2 group had the highest subscapular skinfold, but the GIT1 and not the NGT group had the lowest subscapular skinfold. The triceps skinfold in the young males increased as the glucose tolerance status worsened, but in the older males the triceps skinfold decreased as the glucose tolerance status worsened. In the young females the NGT group had the lowest triceps skinfold, but the GIT1 and not the GIT2 groups had the highest skinfold. In the older females the GIT2 group had the lowest triceps skinfold, but the GIT1 group and not the NGT group had the highest triceps skinfold. Thus the older GIT2 females had lower subscapular and triceps skinfolds than the younger females.

Table 5.20: Descriptive statistics of subscapular and triceps skinfolds

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	sub-scapular skinfold (mm)	21.1	12.0	9.8	5.3	23.8	13.0	11.5	7.5
	triceps skinfold (mm)	20.7	9.3	7.7	4.8	22.7	10.1	8.2	6.4
GIT1	sub-scapular skinfold (mm)	24.5	14.2	10.4	6.5	30.1	14.8	10.3	5.3
	triceps skinfold (mm)	23.9	11.0	9.1	5.6	26.7	9.5	9.4	6.1
GIT2	sub-scapular skinfold (mm)	25.2	14.8	11.1	6.0	23.3	13.0	16.1	8.1
	triceps skinfold (mm)	21.8	9.8	9.8	5.8	21.9	10.6	11.6	8.0

There was a significant difference between subscapular skinfold of the NGT and GIT2 groups of the total population (p=0.019)
(SD=standard deviation; NGT=normal glucose tolerance; GIT1= glucose intolerance group 1; GIT2= glucose intolerance group 2)

Table 5.21 shows that there were significant correlations between subscapular skinfold and 120 min postload glucose levels for the young females and the older NGT males and between subscapular skinfold and fasting glucose levels for the older males as a group and the older GIT1 males. There were also significant correlations between triceps skinfold and 120 minute postload glucose levels for young females, young males and young NGT males, and between triceps skinfold and fasting glucose levels in older males. There was not a significant difference between either subscapular or triceps skinfold and glucose levels for the older females. In general in the young subjects skinfold correlated with the 120 min postload glucose levels and in the older subjects it correlated with fasting glucose levels. The NGT subjects had a significantly smaller subscapular skinfold (p=0.019) than the GIT2 population. This suggests that subscapular skinfold could be a good marker for the development of glucose intolerance. It also seems that triceps skinfolds are not such good markers as subscapular skinfold.

Table 5.21: Significant correlations for subscapular and triceps skinfolds

Variables and group	r-value
Between subscapular skinfold and 120 min postload glucose level for young females.	*0.119
Between subscapular skinfold and fasting glucose level for older males.	*0.199
Between subscapular skinfold and 120 min postload glucose level for young NGT males.	*0.166
Between subscapular skinfold and fasting glucose level for older GIT1 males	*0.527
Between triceps skinfold and 120 min postload glucose level for young females.	*0.120
Between triceps skinfold and 120 min postload glucose level for young males.	*0.18
Between triceps skinfold and fasting glucose level for older males.	*0.196
Between triceps skinfold and 120 min postload glucose level for young NGT males.	*0.173

***=Correlation significant at the 0.05 level**

(NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1)

5.6 Blood pressure

High blood pressure (hypertension) is a known risk factor for the development of type 2 diabetes, as well as a complication of the disease (Nuttal, 1988; Engelgau, *et al.*, 1995; Stern, 1995). Table 5.22 shows the means and standard deviations for systolic and diastolic blood pressure in this sample.

The sample included only newly diagnosed type 2 diabetics (some subjects in the GIT2 group). According to Table 5.22 the mean systolic and diastolic blood pressures of the older subjects were, as expected, higher than that of the young subjects and means of systolic pressures were above the levels of hypertension. The systolic and diastolic blood pressures of the young females and males increased as the glucose tolerance status worsened. However, these differences were not significant, suggesting that the systolic and diastolic blood pressures were not important markers for the development of GIT or its complications in this study population.

Table 5.22: Descriptive statistics for systolic and diastolic blood pressure

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	SBP (mmHg)	119.5	18.7	122.8	14.2	140.5	28.3	130.4	17.5
	DBP (mmHg)	73.7	12.3	75.6	11.2	87.9	15.2	82.5	11.2
GIT1	SBP (mmHg)	122.5	19.4	119.1	12.1	146.1	30.6	131.5	23.2
	DBP (mmHg)	77.6	15.1	74.8	11.9	90.2	14.3	81.5	17.5
GIT2	SBP (mmHg)	125.2	14.3	123.5	9.4	135	12.2	139.6	25.5
	DBP (mmHg)	79.5	10.9	75.0	10.5	85.0	10.3	85.0	11.7

(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2; SBP=systolic blood pressure; DBP=diastolic blood pressure)

5.7 Dietary intakes

5.7.1 Total energy intake (KJ)

Table 5.23 shows the means and standard deviations for total energy intakes. A Western diet is known to be one of the risk factors for the development of type 2 diabetes (Mann, 1997), and it is also associated with an increased energy intake (Ostbye, *et al.*, 1989). The results of this study are in contradiction with this concept. The males had a significantly higher total energy intake than the females in both the young and the older groups (Table 4.23). Table 5.23 shows that the reported total energy intake in the young and older females decreased as the glucose tolerance status worsened. No such trends were present in the young and older males, but the GIT2 men also had the lowest energy intake (6800 KJ for the young males and 7764 KJ for the older males).

Table 5.23: Descriptive statistics for energy intakes in the glucose tolerance status groups

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	Kilojoules (KJ)	8373	2921.5	9881	3565.0	7560	2620.1	8881	3409.9
GIT1	Kilojoules (KJ)	7861	3253.2	10227	4292.8	7104	2742.4	9222	3215.3
GIT2	Kilojoules (KJ)	7595	3213.0	8044	2616.8	6800	2318.2	7764	2615.8

There was a significant difference for total energy intakes between the NGT and GIT2 groups in the total sample ($p=0.004$) even after controlling for gender and age ($p<0.05$)
(SD=standard deviation; NGT=normal glucose tolerance; GIT1= glucose intolerance group 1; GIT2=glucose intolerance group 2)

There was a significant negative correlation between energy intake and fasting glucose levels for older females ($p=0.001$). There was also a significant difference for the energy intake between NGT and GIT2 groups in the total sample ($p=0.004$) indicating that energy intake in the GIT2 groups were significantly lower than in the NGT groups, after controlling for age and gender. This negative correlation between energy intake and glucose intolerance (GIT) is in line with the observation that in this population, young lean men developed diabetes, and that not energy intakes, but inactivity was found to be the main determinant of obesity in these subjects (Kruger, 2000).

Table 54.24: Significant correlations for total energy intakes

Variable and group	r-value
Between total energy intake and fasting glucose levels in older females.	*-0.274

***=Correlation significant at the 0.001 level**

5.7.2 Protein intakes

Table 5.25 shows the means and standard deviations for a protein intake. The role of protein intake in the development of type 2 diabetes is controversial (Mann, 1997), but some scientists believe increased intakes of proteins may lead to an increased risk for the development of type 2 diabetes. Table 5.25 and 5.26 show that the males had a significantly higher total protein intake than the females, and that the older subjects had a lower protein intake than the younger subjects. Table 5.25 shows that in the young and older females the intake of total proteins and plant proteins decreased as glucose tolerance status worsened. In the young males total protein, plant protein and animal protein intakes decreased as glucose tolerance status worsened. For the older males the plant protein intake also decreased as the glucose tolerance status worsened, but the GIT2 group had the lowest intake of both total and animal proteins.

According to Table 5.26 there was a significant negative correlation between the total protein intake and fasting glucose for the older females ($p=0.026$). There was also a significant negative difference for total protein intakes between the NGT and GIT2 groups in the total population ($p=0.009$) after controlling for age and gender ($p<0.05$), but not after controlling for total energy intakes. Therefore, these significant differences are due to the difference in total energy intake in the NGT and the GIT2 groups. This suggests that lower total protein intakes could have played a role in the development of GIT2 in this population.

Table 5.26 further shows that there was a significant negative correlation between plant proteins and fasting glucose for older females ($p=0.000$) and the older NGT females ($p=0.019$). There was also a significant difference for the intake of plant proteins between the NGT and GIT2 groups in the total population ($p=0.002$) after controlling for age and gender ($p<0.01$), but not after controlling for total energy intakes. This is due to the significant difference in total energy intake between the NGT and GIT2 groups. These results suggest that lower plant protein intake could have played a role in the development of GIT2 in this sample or that high plant protein intake is protective. The males had a significantly higher intake of plant proteins than the females ($p=0.000$). The significant difference in plant protein intake between the older male NGT and GIT2 groups ($p=0.038$) suggests that lower plant protein intake could also have played a role in the development of GIT2 in the males. The absence of significant differences in plant protein intakes between female NGT and GIT2 groups, suggests that decreased plant protein intake could have been a risk factor for GIT2 in the older males, but not the females or the young males, or that the groups were too small. There also was a significant negative correlation between animal

protein intake and 120 min postload glucose levels for young GIT1 males (p=0.027). This indicated that lower intake of animal protein in the young GIT1 males resulted in higher glucose levels.

Table 5.25: Descriptive statistics for the protein intakes

Group	Variable	Females <45 years		Males <45 years		Females		Males	
		mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	total proteins (g)	65.0	23.1	77.2	26.7	59.6	21.3	66.7	27.1
	plant proteins (g)	29.9	12.2	36.2	16.8	29.4	13.5	*34.2	15.1
	animal proteins (g)	34.9	18.1	40.9	17.7	30.1	14.1	32.4	17.9
GIT1	total proteins (g)	62.7	21.4	76.1	31.4	55.5	20.3	73.8	25.9
	plant proteins (g)	27.5	13.6	35.3	16.0	27.4	12.9	32.6	17.3
	animal proteins (g)	35.2	13.7	40.6	26.1	28.1	13.7	41.0	15.0
GIT2	total proteins (g)	61.2	30.9	61.4	22.0	54.6	16.5	58.6	23.5
	plant proteins (g)	27.4	11.3	24.3	9.3	23.6	10.8	*27.8	11.3
	animal proteins (g)	33.6	21.6	37.1	16.4	31.0	12.2	30.8	15.1

***=Differ significantly from each other (p=0.038)**
There was a significant difference for total protein intakes between the NGT and GIT2 groups in the total sample (p=0.009) even after controlling for age and gender (p<0.05)
There was a significant difference for plant protein intakes between the NGT and GIT2 groups in the total sample (0.002) even after controlling for age and gender (p<0.01)
(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.26: Significant correlations for protein intakes

Variable and group	r-value
Total protein intake and fasting glucose in older females.	*-0.193
Plant protein and fasting glucose level for older females.	***-0.330
Plant protein and fasting glucose in older NGT females.	*-0.278
Animal protein and 120 min postload glucose level in young GIT1males.	*-0.426

***=Correlation significant at the 0.05 level**
*****=Correlation significant at the 0.001 level**

5.7.3 Fat intakes

Table 5.27 gives the means and standard deviations for the intakes of total and specific lipids. High intakes of fat increase the risk for type 2 diabetes (Mann, 1997). From Table 5.27 and 5.28 it can be seen that total fat, saturated fat, monounsaturated fat, polyunsaturated fat and cholesterol intakes were higher in males than in females (p=0.002 for total fat; p=0.013 for

saturated fat; p=0.002 for monounsaturated fat) and higher in the young population than in the older population. However, in all groups the mean percentage of energy contributed by fat was less than 30% and the female groups had the higher values.

Table 5.27 shows that total fat intake decreased as glucose tolerance status worsened in the young female, young male and older female groups. In the older males no trend was present but the GIT2 group had the lowest total fat intake. Saturated fat intakes increased as glucose tolerance status worsened in the older females. Monounsaturated fat intakes decreased as glucose tolerance status worsened in the older females, and the young males. Polyunsaturated fat intakes decreased as glucose tolerance status worsened in the young females, young males and older females. The only significant difference observed was the lower P/S ratio in the diet of the older GIT2 females compared to the older NGT groups. Cholesterol intakes showed no trends, but were the lowest in the GIT2 subjects of the older male and young female groups.

Table 5.28 shows that there were significant negative correlations between total fat intake and fasting glucose levels in older females (p=0.026). There also was a significant difference for total fat intakes between NGT and GIT2 groups in the total sample (p=0.024), but not after controlling for age, gender and total energy intake. Therefore, this association is probably related to the observed relationship between energy intake and risk of diabetes.

There were no significant correlations or differences for saturated fat between NGT and GIT2 groups. There were significant negative correlations between monounsaturated fat intakes and fasting glucose in older females (p=0.047). The significant difference for monounsaturated fat between the NGT and the GIT2 groups in the total sample (p=0.023) disappeared after controlling for age, gender and total energy intake, indicating that it was probably due to the observed relationship between energy intake and risk of diabetes.

There was a significant difference for polyunsaturated fat intakes between the NGT and GIT2 groups in the total sample (p=0.013), even after controlling for age and gender ($p<0.05$), but not after controlling for total energy intakes. There were significant correlations between polyunsaturated fat intake and fasting glucose levels in the older females (p=0.004), and in the older NGT females (p=0.034), but this could be due to the lower fat intakes reported by the GIT2 group. These results suggest a minor role for low polyunsaturated fat intake in the development of type 2 diabetes in the females of this study population.

Table 5.27: Descriptive statistics for the lipid intakes in the glucose tolerance status groups

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	total fat (g) (% energy contributed by fat)	61.5 (27.9)	27.7	70.0 (26.9)	28.6	50.6 (25.4)	21.9	53.56 (22.9)	26.7
	saturated fat (g)	19.9	10.1	22.2	9.3	15.8	7.5	17.1	8.8
	monounsaturated fat (g)	21.6	10.3	25.0	11.1	17.6	7.8	18.9	9.9
	polyunsaturated fat (g)	13.8	6.7	16.1	7.9	12.0	5.9	13.0	7.2
	cholesterol (g)	294.0	193.3	373.7	233.2	243.5	139.5	304.3	227.7
	PS ratio (g)	0.8	0.3	0.8	0.4	*0.8	0.3	0.8	0.4
GIT1	total fat (g) (% energy contributed by fat)	60.9 (29.4)	24.7	68.5 (25.5)	39.2	48.3 (25.8)	22.4	63.6 (26.2)	26.9
	saturated fat (g)	19.7	8.7	23.1	13.91	16.2	8.6	21.2	9.5
	monounsaturated fat (g)	21.7	9.1	24.1	14.1	16.7	8.5	22.0	10.1
	polyunsaturated fat (g)	13.6	6.1	15.1	9.0	11.3	4.8	14.6	8.7
	cholesterol (mg)	318.6	187.3	347.0	243.7	278.9	168.3	388.9	213.8
	PS ratio (g)	0.7	0.3	0.7	0.4	0.8	0.3	0.7	0.4
GIT2	total fat (g) (% energy contributed by fat)	59.4 (29.7)	35.5	51.6 (24.4)	18.7	46.5 (26.0)	21.0	50.0 (24.5)	25.7
	saturated fat (g)	19.2	11.6	16.0	5.0	17.1	7.8	16.9	8.6
	monounsaturated fat (g)	21.6	14.1	18.1	7.1	15.5	7.0	17.2	8.7
	polyunsaturated fat (g)	12.8	7.2	11.8	5.6	10.1	7.1	11.7	7.0
	cholesterol (mg)	292.3	214.6	353.7	209.8	265.5	168.7	281.1	192.3
	PS ratio (g)	0.7	0.2	0.7	0.2	*0.6	0.4	0.7	0.3

***=Significant difference (p=0.026)**

There was a significant difference for total fat intakes between the NGT and GIT2 groups in the total sample (p=0.024)

There was a significant difference for monounsaturated fat intakes between the NGT and GIT2 groups in the total sample (p=0.023)

There was a significant difference for polyunsaturated fat intakes between the NGT and GIT2 groups in the total sample (p=0.023) even after controlling for age and gender (p<0.05)

There was a significant difference for PS ratio between the NGT and GIT2 groups in the total sample after controlling for age, gender and total energy intake (p<0.05)

(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.28: Significant correlations for the fat intakes

Variables and group	r-value
Total fat intake and fasting glucose in older females.	*-0.192
Monounsaturated fat intake and fasting glucose in older females.	*-0.172
Polyunsaturated fat and fasting glucose in older females.	**-0.249
Polyunsaturated fat and fasting glucose in older NGT females.	*-0.251
Polyunsaturated fat and fasting glucose in the total population **after controlling for age and gender**	**-0.124
Polyunsaturated fat and fasting glucose in the total population **after controlling for age, gender and total energy intake**	*-0.115
PS-ratio and fasting glucose for older females.	*-0.179
PS-ratio and fasting glucose for the total population **after controlling for age and gender**	**-0.146
PS-ratio and fasting glucose for the total population **after controlling for age, gender and total energy intake**	*-0.094

***=Correlation significant at the 0.05 level**
****=Correlation significant at the 0.01 level**
(PS-ratio=polyunsaturated fat-saturated fat ratio; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1)

According to Table 5.27 and 5.28 there were no significant differences for the polyunsaturated/saturated fat ratio (PS-ratio) between males and females. Table 5.27 shows that the PS-ratio decreased as glucose tolerance status worsened in all four of the age and-gender groups. The NGT group had a significantly higher PS-ratio than the GIT2 group for the total sample (0.041) and the older females (p=0.026). The significant difference in the total sample persisted after controlling for age, gender and total energy intake ($p<0.05$). There was a significant negative correlation between fasting glucose and PS-ratio after controlling for age, gender and total energy intake ($p<0.01$). There was also a significant negative correlation between the PS-ratio and the fasting glucose levels for older females (p=0.039).

5.7.4 Fatty acids

5.7.4.1 Saturated fatty acids

Table 5.29 consists of the means and standard deviations of the saturated fatty acid intakes, and Table 5.30 shows that there were several significant correlations between fasting glucose levels and saturated fatty acid intakes. The absence of significant differences for most saturated fatty acids between the NGT and the GIT2 groups suggest that although these molecules influenced the glucose levels, it might not have played an important role in the development of type 2 diabetes in this study population. The GIT2 group had significantly lower (p=0.036) intakes of palmitic acid (C16-0) than the NGT. However, this significant difference did not persist after controlling for age, gender and total energy intake, probably due to the observed association between energy intake and glucose tolerance.

Table 5.29: Descriptive statistics for saturated fatty acid intakes

Group	Variable	Female <45 years		Male <45 years		Female ≥45 years		Males ≥45 years	
	(g)	mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD(±)
NGT	C4-0	0.2	0.2	0.3	0.2	0.3	0.2	0.3	0.2
	C6-0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	C10-0	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	C12-0	0.6	1.1	0.6	0.6	0.3	0.2	0.3	0.3
	C16-0	10.8	5.2	12.4	5.4	8.8	4.0	9.4	4.9
	C20-0	0.1	0.01	0.2	0.1	0.1	0.1	0.1	0.1
	C22-0	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2
GIT1	C4-0	0.2	0.2	0.3	0.2	0.2	0.2	0.4	0.5
	C6-0	0.1	0.1	0.2	0.1	0.1	0.2	0.2	0.3
	C10-0	0.2	0.2	0.3	0.2	0.2	0.2	0.3	0.3
	C12-0	0.7	0.2	1.0	1.7	0.8	1.8	0.4	0.3
	C16-0	10.6	4.4	12.4	7.6	8.4	4.2	11.6	4.8
	C20-0	0.1	0.1	0.2	0.1	0.1	0.1	0.2	0.2
	C22-0	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.3
GIT2	C4-0	0.2	0.2	0.3	0.2	0.4	0.3	0.3	0.2
	C6-0	0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.1
	C10-0	0.2	0.1	0.2	0.1	0.3	0.3	0.2	0.2
	C12-0	0.5	0.6	0.3	0.2	1.0	1.8	0.7	1.0
	C16-0	10.4	6.4	9.1	2.8	8.4	3.5	8.8	4.0
	C20-0	0.1	0.1	0.1	0.1	0.09	0.07	0.1	0.1
	C22-0	0.2	0.2	0.2	0.2	0.1	0.1	0.2	0.1

There was a significant difference for the C16-0 intake between the GIT2 and the NGT groups in the total population (p=0.036)

(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.30: Significant correlations for saturated fatty acids.

Variable and group	r-value
C4-0 and fasting glucose young males.	*0.185
C6-0 and fasting glucose in young males.	*0.159
C10-0 and fasting glucose in young males.	*0.136
C12-0 and fasting glucose in young females.	*-0.114
C20-0 and fasting glucose in older females.	*-0.215
C22-0 and fasting glucose in older females.	*-0.181

***=Correlation is significant at the 0.05 level**

5.7.4.2 Monounsaturated fatty acid intakes

Table 5.31 gives the means and standard deviations of the monounsaturated fatty acid (MUFA) intakes. Table 5.32 shows that there were several significant correlations between fasting glucose levels and C14-1, C18-1, and C20-1. These correlations were positive for males and negative for females. The absence of significant differences for these fatty acids between the NGT and GIT2 groups suggests that although these fatty acids might have influenced the glucose levels, they might not have played an important role in the development of GIT2 in this population. The significant difference for C18-1 between the GIT2 and the NGT groups in the total population after controlling for age and gender, did not persist after controlling for energy intakes.

Table 5.31: Descriptive statistics for monounsaturated fatty acid intakes in the glucose tolerance status groups

Group	Variable	Female <45 years		Male <45 years		Female ≥45 years		Male ≥45 years	
	(g)	mean	SD (±)	mean	SD (±)	mean	SD(±)	mean	SD(±)
NGT	C14-1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	C18-1	19.7	9.40	22.8	10.2	16.2	7.2	17.4	9.0
	C20-1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	10.0
GIT1	C14-1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.2
	C18-1	19.7	8.5	21.8	12.7	15.3	7.8	20.2	9.3
	C20-1	0.1	0.1	0.2	0.1	0.1	0.1	0.2	0.2
GIT2	C14-1	0.1	0.1	0.1	0.1	0.1	1.0	0.1	0.03
	C18-1	19.1	12.8	16.6	6.6	14.0	6.5	15.6	7.8
	C20-1	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1

There was a significant difference for C18-1 between the NGT and GIT2 groups in the total population (p=0.013) even after controlling for age and gender (p<0.05)
(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.32: Significant correlations for monounsaturated fatty acid intakes

Group	r-value
C14-1 and fasting glucose in young males.	*0.171
C18-1 and fasting glucose in older females.	*-0.182
C20-1 and fasting glucose in older females.	*-0.200

***=Correlation significant at the 0.05 level**

5.7.4.3 Polyunsaturated fatty acid intakes

Table 5.33 consists of the means and standard deviations of the polyunsaturated fatty acid (PUFA) intakes. Table 5.34 shows that there were several significant correlations between fasting glucose levels and linoleic acid (C18-2), C18-4, Dihommo-γ-linolenic acid (C20-3), and docosahexaenoic acid (C22-6). There also was a significant correlation between fasting glucose and oleic acid after controlling for age, gender and energy intake ($p<0.01$). Once again the correlations were negative for the females and positive for the males. The significant difference for oleic acid, and linolenic acid (C18-3) between the GIT2 and the NGT groups in the total population suggested that low intakes of these fatty acids may play a role in the development of type 2 diabetes in this population. However the significant difference for oleic acid persisted after controlling for age and gender ($p<0.05$), but disappeared after controlling for total energy intakes. The significant difference for linoleic acid disappeared after controlling for age, gender and total energy intakes. This is probably due to the observed association between energy intake and glucose tolerance.

Table 5.33: Descriptive statistics for polyunsaturated fatty acid intakes

Group	Variable	Female <45 years		Male <45 years		Female ≥45 years		Male ≥45 years	
	(g)	mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	C18-2	12.8	6.42	14.9	7.62	11.2	5.67	12.1	6.85
	C18-3	0.5	0.22	0.6	0.25	0.4	0.18	0.5	0.22
	C18-4	0.01	0.013	0.01	0.024	0.01	0.015	0.01	0.012
	C20-3	0.004	0.01	0.01	0.002	0.01	0.02	0.004	0.01
	C22-6	0.1	0.12	0.2	0.21	0.1	0.14	0.1	0.12
GIT1	C18-2	12.5	5.87	14.1	8.54	10.5	4.59	13.6	8.46
	C18-3	0.5	0.19	0.6	0.34	0.4	0.20	0.5	0.2
	C18-4	0.01	0.01	0.01	0.01	0.003	0.01	0.01	0.01
	C20-3	0.003	0.01	0.01	0.01	0.004	0.01	0.01	0.01
	C22-6	0.1	0.11	0.1	0.1	0.1	0.06	0.1	0.11
GIT2	C18-2	11.6	6.69	10.9	5.39	9.3	6.85	10.7	6.54
	C18-3	0.5	0.27	0.4	0.13	0.4	0.15	0.4	0.16
	C18-4	0.003	0.006	0.01	0.01	0.01	0.01	0.01	0.02
	C20-3	0.01	0.03	0.01	0.03	0.003	0.01	0.01	0.01
	C22-6	0.1	0.09	0.2	0.11	0.1	0.10	0.1	0.14

There was a significant difference for C18-2 as well as C18-3 between the NGT and GIT2 groups in the total population ($p<0.05$), and for C18-2 after controlling for age and gender ($p<0.05$)
(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.34: Significant correlations for polyunsaturated fatty acids.

Group	r-value
C18-2 and fasting glucose in older females.	**-0.252
C18-2 and fasting glucose in the total population **after controlling for age and gender**	**-0.131
C18-2 and fasting glucose in the total population **after controlling for age, gender and energy intake**	**-0.123
C18-4 and fasting glucose in young males.	*0.137
C20-3 and fasting glucose in older males.	**0.317
C22-6 and fasting glucose in young males.	*0.138

***=Correlation is significant at the 0.05 level**
****=Correlation is significant at the 0.01 level**

5.7.4.4 Trans fatty acids

Table 5.35 consists of the means and standard deviations for the trans fatty acids. The trans fatty acid intake of all four age and gender groups were less in the GIT2 groups than in the NGT groups. The significant correlations between trans fatty acids and fasting glucose shown in Table 5.36 indicate that trans fatty acid intakes might have influenced the glucose levels in the males. There was a significant difference between trans fatty acid intakes of the NGT and GIT2 groups in the older females.

Table 5.35: Descriptive statistics for the trans fatty acid intakes

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
	(g)	mean	SD (±)	mean	SD(±)	mean	SD (±)	mean	SD (±)
NGT	trans fatty acids	2.3	1.6	*2.4	1.7	#2.0	1.4	***1.9	1.3
GIT1	trans fatty acids	2.4	1.6	*2.2	1.5	#1.7	1.4	2.0	1.0
GIT2	trans fatty acids	2.0	2.0	1.6	1.1	1.4	0.8	1.7	1.1

***=Significant correlation with fasting glucose (p≤.05)**
****=Significant correlation with fasting glucose (p ≤0.001)**
 # = Significant difference (p=0.022)
(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.36: Significant differences for trans fatty acid intakes

Group	r-value
TRSFA and fasting glucose in young GIT1 males.	*-0.456
TRSFA and fasting glucose in young NGT males.	*0.162
TRSFA and fasting glucose in older NGT males.	***0.832

***=Correlation significant at the 0.05 level**
****=Correlation significant at the 0.001 level**
(TRSFA=trans fatty acid; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1)

5.7.5 Carbohydrate and fibre intake

Table 5.37 shows the means and standard deviations for the carbohydrate (CHO) fibre, and sugar intakes. According to Tables 5.37 and Table 5.38 the males had a significant higher intake of total CHO than the females (p=0.000). The younger subjects also had a higher intake of total CHO than the older subjects. In all four age-and gender groups the GIT2 group had a lower CHO intake than the NGT group, and the difference was significant for the total sample (p=0.001), even after controlling for age and gender (p<0.05), but not after controlling for total energy intakes. There were significant correlations between total CHO intake and fasting glucose levels in older females (p=0.001) and in older GIT1males (p=0.022).

Table 5.37: Descriptive statistics for carbohydrate and fibre intakes

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		mean	SD (±)	mean	SD (±)	mean	SD (±)	mean	SD (±)
NGT	total carbohydrates (g)	294.0	116.9	336.9	144.0	276.3	108.4	321.3	123.6
	fibre (g)	16.6	7.3	19.4	10.0	16.0	7.8	17.2	8.5
	added sugar (g)	52.1	47.2	49.9	43.8	44.6	37.1	45.8	36.4
GIT1	total carbohydrates (g)	267.16	136.2	341.8	155.3	260.2	111.5	293.1	115.8
	fibre (g)	17.59	8.4	18.5	9.1	15.2	7.7	16.7	9.1
	added sugar (g)	50.4	54.1	52.2	56.8	40.1	32.8	42.2	21.0
GIT2	total carbohydrates (g)	255.2	94.4	265.7	94.6	242.8	92.0	278.1	98.0
	fibre (g)	16.36	8.9	13.3	5.7	12.4	5.7	14.4	7.8
	added sugar (g)	43.36	33.6	55.5	53.1	44.4	27.9	42.4	35.2

There was a significant difference for total carbohydrate intakes between the NGT and GIT2 groups in the total sample (p=0.001) even after controlling for age and gender (p<0.05)
There was a significant difference for fibre intakes between the NGT and GIT2 groups in the total sample (p=0.009) even after controlling for age and gender (p<0.05)
(SD=standard deviation; NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Tables 5.37 and 5.38 show that there were significant differences between the mean fibre intakes of the males and females (p=0.002), and between young NGT males and females (p=0.002). In all four age and gender groups the GIT2 subjects had a lower mean fibre intake than the NGT groups. There was a significant difference for fibre intakes between the NGT and GIT2 groups in the total sample (p=0.009) even after controlling for age and gender (p<0.05), but not after controlling for total energy intakes. There was a significant correlation between fibre intakes and

the fasting glucose levels after controlling for age and gender ($p<0.05$). There was also a significant correlation between fibre intake and fasting glucose in the older females ($p=0.001$) and in older NGT females ($p=0.008$). There were no significant differences or correlations for added sugar intakes.

Table 5.38: Significant correlations for carbohydrate and fibre intakes

Variables and group	r-value
Total CHO intake and fasting glucose in older females.	***-0.278
Total CHO intake and fasting glucose in older NGT males.	*0.650
Fibre intake and fasting glucose in older females.	***-0.289
Fibre intake and fasting glucose in older NGT females.	**-0.313
Fibre intake and fasting glucose in the total population **after controlling for age and gender**	*-0.094

***=Correlation significant at the 0.05 level**
****=Correlation significant at the 0.01 level**
******=Correlation significant at the 0.001 level**
(CHO=carbohydrates; NGT=normal glucose tolerance group)

5.7.6 Mineral and trace element intakes

Table 5.39 consists of the means and standard deviations for the mineral intakes. In all four age and gender groups the GIT2 subjects had lower mean intakes of Fe, Mg, and K. These lower intakes are probably related to the lower energy and therefore total food intake of the GIT2 subjects. Without controlling for energy intakes no conclusion about the possible role of minerals in the development of glucose intolerance (GIT) can be made.

According to Table 5.40 the Fe, P, and Cu intakes of the NGT and GIT2 groups did not differ significantly. However, there were several significant negative correlations between the intakes of these minerals and fasting blood glucose levels. There were significant differences for Mg, K and Zn intakes between the NGT and GIT2 groups in the total sample, supported by significant negative correlations between Mg, K and Zn and fasting glucose levels in older females and young males. The significant difference for Mg persisted after controlling for gender and age, but all significant differences disappeared after controlling for energy intakes. A significant difference for Na intakes between the NGT and the GIT2 groups in the total sample and the older females was observed, but disappeared after controlling for age, gender and energy intake. As mentioned above, these relationships are influenced by the total energy, and thus food intakes.

Table 5.39: Descriptive statistics of the mineral intakes

Group	Mineral (mg)	Female <45 years		Male <45 years		Female ≥ 45 years		Male ≥45 years	
		means	SD (±)	means	SD (±)	means	SD (±)	means	SD (±)
NGT	Mn	2.2	1.2	2.8	1.8	**2.0	1.1	2.5	1.5
	Fe	9.0	4.0	9.8	4.0	8.8	5.4	8.4	4.1
	Mg	306.4	127.8	362.0	163.1	303.2	126.3	366.5	160.5
	P	1039.7	387.1	1263.1	467.7	987.3	358.8	1170.3	490.3
	K	2172.9	798.1	2454.4	876.0	214.3	788.7	2266.1	848.9
	Na	1389.7	697.9	1607.9	870.4	#1174.3	107.2	**1091.5	608.6
	Zn	9.2	3.9	##10.6	4.2	8.4	3.6	9.0	4.1
	Cu	1.1	0.5	1.3	0.6	1.1	0.6	1.1	0.5
GIT1	Mn	2.3	1.4	2.8	1.4	2.0	1.3	2.9	2.2
	Fe	9.1	3.7	9.9	4.5	7.7	3.1	9.8	6.2
	Mg	290.4	130.3	385.3	74.1	275.0	119.0	384.2	205.2
	P	1007.7	390.4	1305.1	570.1	930.1	392.0	1335.8	519.5
	K	2248.5	831.9	2563.9	1187.0	1957.0	790.8	2541.8	947.9
	Na	1459.4	749.0	1514.0	1017.5	1063.9	560.2	1337.7	771.0
	Zn	9.2	3.5	10.3	4.3	7.8	3.2	10.1	4.5
	Cu	1.2	0.5	1.3	0.6	1.0	0.5	1.2	0.7
GIT2	Mn	2.0	1.1	2.1	1.4	1.7	1.0	1.9	1.1
	Fe	8.6	4.5	7.5	2.6	*7.5	3.1	7.6	4.5
	Mg	274.3	120.9	320.1	137.3	277.0	123.6	294.3	116.9
	P	961.0	449.0	1076.6	387.6	996.0	383.8	1017.9	368.6
	K	2078.0	1027.9	2137.0	587.1	1979.7	674.8	1943.3	596.0
	Na	1393.7	971.3	1260.0	489.9	#799.0	418.2	1039.6	724.3
	Zn	8.9	5.0	##7.8	2.7	8.0	2.6	7.8	4.1
	Cu	1.2	0.7	0.9	0.4	0.9	0.3	1.0	0.5

***=Significant correlation with fasting glucose levels ($p \leq 0.05$)**

****=Significant correlation with fasting glucose levels ($p \leq 0.01$)**

There was a significant difference for Mn, Mg, K, Na, and Zn between the NGT and GIT2 groups in the total population ($p \leq 0.05$)

The significant difference for Mg persisted after controlling for age and gender ($p<0.05$)

 # = significant difference ($p \leq 0.05$)

= significant difference ($p \leq 0.05$)

(SD=standard deviations; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.40: Significant correlations for the mineral intakes.

Variables and group	r-value
Mn and fasting glucose in older females.	**-0.265
Mn and fasting glucose in older NGT females.	*-0.283
Fe and fasting glucose level for older females.	**-0.234
Fe and fasting glucose level for older GIT2 females	*-0.50 2
Mg and fasting glucose level for older females.	**-0.266
P and fasting glucose level for older females.	*-0.199
K and fasting glucose level for older females.	**-0.257
Na and fasting glucose level for older females.	*-0.206
Na and fasting glucose level for older GIT2 males.	**0.743
Zn and fasting glucose for older females.	*-0.175
Cu and fasting glucose levels for older females.	**-0.243

***=Correlation significant at the 0.05 level**
****=Correlation significant at the 0.01 level**
(NGT=normal glucose tolerance group; GIT2=glucose intolerance group 2)

5.7.7 Vitamin intakes

According to Table 5.41 it can be seen that in all groups the GIT2 subjects had lower mean intakes of vitamin B1, vitamin B6, vitamin E and nicotinamide than the NGT subjects. The young GIT2 females and the older GIT2 males had a higher intake of folic acid than the NGT groups, while the young GIT2 males and the older GIT2 females had lower intakes of folic acid than the NGT groups.

From Table 5.42 it can be seen that there were significant correlations for vitamin B6, vitamin C, and folic acid with fasting glucose levels, but these differences were no longer significant after controlling for age, gender and total energy intake. There were significant correlations between vitamin B1 and fasting glucose as well as a significant difference for vitamin B1 between the NGT and the GIT2 groups in the young males. There were also significant negative correlations of vitamin E and nicotinamide with fasting glucose levels. Both vitamin E and nicotinamide differed significantly between the NGT and GIT2 groups in the total sample. Nicotinamide had a significantly negative correlation with fasting glucose in the total sample after controlling for age and gender. Although no clear and consistent patterns of relationships between vitamin intakes and GIT were found, the results suggest vitamin intakes, and therefore the adequacy and quality of the diet may play a role in the development of GIT and type 2 diabetes.

Table 5.41: Descriptive statistics for the vitamin intakes

Group	Vitamin	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		means	SD (±)	means	SD (±)	means	SD (±)	means	SD (±)
NGT	vitamin A (µg/TE)	883.2	766.0	753.8	688.4	1034.1	1063.2	705.4	626.7
	vitamin B1 (mg)	1.1	0.5	#1.3	0.5	1.1	0.5	1.2	0.5
	vitamin B6 (mg)	1.2	0.6	1.3	0.6	1.0	0.5	1.0	0.5
	vitamin B12 (µg)	6.1	6.1	5.7	5.8	6.4	7.8	5.4	5.3
	vitamin C (mg)	47.7	53.2	43.3	37.5	40.4	39.9	36.9	67.8
	vitamin E (mgα-TE)	9.9	5.9	11.7	6.8	9.0	5.5	10.1	7.5
	Nicotinamide (mg)	14.6	6.2	17.3	7.3	12.9	5.6	15.8	7.4
	Folic acid (µg)	201.1	90.4	230.1	100.1	*203.0	78.3	215.6	93.2
	Pantothenic acid (mg)	3.8	1.5	4.6	1.8	3.5	1.3	4.1	1.9
GIT1	vitamin A (µg/TE)	1078.8	880.8	829.6	755.8	852.9	723.0	1069.0	809.4
	vitamin B1 (mg)	1.1	0.4	1.3	0.5	1.0	0.4	1.2	0.7
	vitamin B6 (mg)	1.2	0.5	1.4	1.0	0.9	0.4	1.3	0.6
	vitamin B12 (µg)	6.4	5.2	6.4	6.9	6.4	6.8	6.8	4.2
	vitamin C (mg)	62.6	53.8	*63.8	67.6	37.6	34.6	35.8	30.5
	vitamin E (mgα-TE)	10.7	6.4	11.1	6.3	8.3	3.9	11.3	5.7
	Nicotinamide (mg)	13.9	5.8	17.3	10.0	11.6	5.5	16.2	10.0
	Folic acid (µg)	227.2	92.3	238.6	128.3	189.1	79.1	273.6	176.4
	Pantothenic acid (mg)	3.9	1.5	4.8	2.5	3.5	1.5	5.0	2.0
GIT2	vitamin A (µg/TE)	921.7	992.3	772.3	492.8	696.2	573.7	798.8	918.3
	vitamin B1 (mg)	1.1	0.5	#0.9	0.4	1.0	0.4	*1.0	0.5
	vitamin B6 (mg)	1.2	0.7	1.1	0.4	0.8	0.3	0.9	0.4
	vitamin B12 (µg)	6.9	9.2	4.5	2.4	5.1	4.8	5.1	3.2
	vitamin C (mg)	60.4	63.9	34.6	30.2	29.2	22.9	31.8	30.4
	vitamin E (mgα-TE)	8.5	5.5	9.6	4.8	7.5	6.0	8.7	5.4
	Nicotinamide (mg)	13.7	7.3	14.7	7.4	10.8	4.7	12.5	6.3
	Folic acid (µg)	218.3	144.5	213.9	89.6	178.0	68.8	171.7	85.7
	Pantothenic acid (mg)	3.9	2.2	4.1	1.5	3.4	1.2	3.6	1.5

*** = Significant correlation with fasting glucose ($p \leq 0.05$)**

 # = Significant difference ($p \leq 0.05$)

There was a significant difference for vitamin E* and nicotinamide between NGT and GIT2 groups in the total population (*=$p \leq 0.05$; **=$p \leq 0.01$)**

(SD=standard deviation; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.42: Significant correlations for the vitamin intakes

Variables and group	r-value
vitamin B1 and fasting glucose level in older females.	**-0.255
vitamin B1 and fasting glucose in older GIT2 males.	*0.619
vitamin B6 and fasting glucose in older females.	*-0.188
vitamin C and fasting glucose level in young GIT1 males.	*-0.439
vitamin E and fasting glucose level in older females.	*-0.186
nicotinamide and fasting glucose level in older females.	**-0.243
nicotinamide and fasting glucose level in the total population **after controlling for age and gender**	*-0.092
nicotinamide and fasting glucose level in the total population **after controlling for age, gender and energy intake**	*-0.092
Folic acid and fasting glucose levels in older females.	*-0.202
folic acid and fasting glucose levels in older NGT females.	*-0.257

***= Correlation significant at the 0.05 level**
****=Correlation significant at the 0.01 level**
(NGT = normal glucose tolerance group; GIT1 = glucose intolerance group 1; GIT2 = glucose intolerance group 2)

5.8 Blood biochemistry

5.8.1 Glucose and insulin levels

Table 5.43 gives of the means and standard deviations for the blood glucose and insulin levels. Since the GIT2 group only included newly diagnosed type 2 diabetic subjects who did not use any drugs for the treatment of the condition it was expected that the blood insulin levels would be lower in the GIT2 groups than in the NGT groups and that the insulin levels in the GIT1 groups may have been higher than both the NGT and the GIT2 groups reflecting insulin resistance (IR). This was not the case in any of the groups.

As expected, because of selection of the groups the fasting and the 120 min postload glucose levels differed significantly between the NGT and the GIT2 groups of the total sample population and all four of the age and gender groups. Table 5.45 further shows that relatively few significant correlations were found between insulin and glucose levels. This could be an indication that not all the subjects were fasting.

Table 5.43: Descriptive statistics for blood glucose and fasting insulin levels

Group	Variable	Female <45 years		Male <45 years		Female ≥45 years		Male ≥45 years	
		mean	SD (±)	mean	SD(±)	mean	SD(±)	mean	SD(±)
NGT	glucose 1 (mmol/l)	[a]4.9	1.9	[e]5.0	1.9	[b]5.2	1.8	4.9	2.3
	glucose 2 (mmol/l)	[c]5.0	1.7	[f]5.0	1.6	[d]5.2	1.6	[g]4.4	1.8
	insulin (µU/l)	30.4	18.0	33.8	24.5	25.6	14.1	28.9	31.5
GIT1	glucose 1 (mmol/l)	5.7	1.9	5.9	1.8	5.7	1.7	5.1	2.4
	glucose 2 (mmol/l)	8.7	0.8	8.8	0.9	9.1	0.8	9.2	1.1
	insulin (µU/l)	31.9	25.9	25.4	18.8	27.6	10.5	[e]24.3	19.5
GIT2	glucose 1 (mmol/l)	[a]7.8	4.2	[e]7.6	4.9	[b]7.7	2.8	9.0	4.9
	glucose 2 (mmol/l)	[c]10.8	3.3	[f]11.2	3.3	[d]12.2	2.1	[g]11.5	2.2
	insulin (µU/l)	33.7	23.0	22.3	8.7	25.6	11.2	37.5	12.5

There were significant differences for fasting and postload glucose levels between NGT and GIT2 groups in the total sample ($p \leq 0.001$)
Symbols indicate a significant difference between two variables.
a, c , f , g = Significant difference ($p \leq 0.001$)
e = Significant difference ($p \leq 0.05$)
b, d, = Significant difference ($p \leq 0.01$)

Table 5.44: Means and standard deviations for insulin and glucose levels of males and females in the total population

Variable	Females		Males	
	mean	SD (±)	means	SD(±)
Fasting glucose (mmol/l)	*5.4	2.2	*5.2	2.4
Postload glucose (mmol/l)	#6.6	2.8	#5.9	2.7
Insulin µU/L	29.7 (24.9)	18.7	30.0 (23.2)	23.8

The medians for the insulin levels are given in brackets below the mean values.
***=Differ significantly ($p<0.001$); #=differ significantly ($p<0.001$)**
(SD=standard deviation)

Table 5.45: Significant correlations for blood glucose and insulin levels

Group	r-value
Insulin levels and 120 min postload glucose levels in young males.	*-0191
Insulin levels and fasting glucose levels in older GIT1 males.	*0.828

***=Correlation significant at the 0.05 level**
(GIT1=glucose intolerance group 1)

According to the literature (Immuno Biological Laboratories, 1997) the normal values for fasting insulin are 10-25 µU/L. Table 5.46 shows the percentage of subjects with normal, low and high insulin levels. What was most interesting was that 53% of all subjects with GIT2 had high insulin levels, while 41.0% had normal insulin levels. It was expected that the GIT2 subjects would be relatively insulin deficient, but this does not seem to have been the case. The interpretation of

these results is unfortunately hampered by the fact that all subjects were not in a fasting state when the glucose tolerance test was done. However, the general trend is that despite significant increases in fasting and postload glucose levels between NGT and GIT2 groups, no significant differences in insulin were observed. This suggests that the same "amount" of insulin could not maintain a normal fasting glucose level, indicating insulin resistance. The fact that insulin concentrations did not change shows that this is probably an early phase of insulin resistance – without affecting pancreatic insulin secretion.

Table 5.46: The percentage of subjects with low, normal and high insulin levels in each glucose tolerance status group

Insulin level		NGT	GIT1	GIT2	Row total
I<10	count	13	4	2	**19**
	row %	68	21.1	10.5	**5.2**
	column %	5.3	5.1	5.1	
I normal	count	114	38	16	**168**
	row%	67.9	22.6	9.5	**46.2**
	column %	46.3	48.1	41.0	
I>25	count	119	37	21	**177**
	row%	67.2	20.9	11.9	**48.6**
	column %	48.4	46.8	53.8	
column total	**count**	**246**	**79**	**39**	**364**
	column %	**67**	**21.7**	**10.7**	**100.0**

(NGT=normal glucose tolerance; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2; I<10= insulin level lower than 10 µU/L; I normal= insulin levels between 10 and 25 µU/L; I>25= insulin level higher than 25 µU/L)

5.8.2 The blood iron status

Table 5.47 gives the means and standard deviations for the iron status. According to this Table serum iron and percentage saturation of ferritin were lower in GIT2 groups compared to NGT groups in the young females, older females and older males, but higher in young males. Ferritin concentrations were lower in GIT2 groups than in NGT groups in the young and older females and higher in the young and older males. The serum total iron binding capacities (TIBC) were lower in the GIT2 groups than in the NGT groups in the young females and older males and lower in the young males and the older females. Thus, in general variables indicative of iron status decreased as glucose tolerance deteriorated in young females, older females and older males. In

young males deterioration of the glucose tolerance was associated with an increase in the variables indicative of iron status.

Table 5.47: Descriptive statistics of the iron status

Group	Variable	Female <45 years		Male <45 years		Female ≥45 years		Male ≥45 years	
		means	SD (±)	means	SD (±)	means	SD(±)	means	SD(±)
NGT	serum iron (µmol/l)	16.6	7.2	19.7	7.8	16.4	8.8	18.2	7.1
	serum ferritin (µmol/l)	73.2	90.9	153.1	187.6	*220.6	323.5	342.8	371.3
	% saturation	23.1	10.9	29.4	11.9	25.8	15.4	29.2	12.6
	serum total iron binding capacity (%)	73.2	12.0	69.4	15.5	#65.4	10.7	64.5	13.2
	haematocrit (%)	41.6	4.6	46.5	4.0	42.0	4.4	44.7	3.9
	haemoglobin (g/dl)	11.9	1.4	13.2	1.1	11.9	1.5	12.9	1.4
GIT1	serum iron (µmol/l)	15.4	7.1	17.5	6.9	13.1	4.9	20.5	9.3
	serum ferritin (µmol/l)	84.0	180.2	146.1	106.1	114.6	100.2	351.3	266.5
	% saturation	21.5	10.9	27.3	11.3	21.0	9.3	35.4	14.7
	serum total iron binding capacity (%)	74.8	14.1	66.4	12.3	65.7	15.7	59.8	9.2
	haematocrit %	41.5	4.1	45.6	5.7	39.7	4.6	45.3	3.8
	haemoglobin (g/dl)	11.7	1.3	12.8	2.2	11.6	1.4	13.2	1.2
GIT2	serum iron (µmol/l)	15.8	7.5	22.2	8.8	14.5	5.7	15.9	6.4
	serum ferritin (µmol/l)	70.0	8.8	231.0	197.1	*98.3	86.6	382.5	332.0
	% saturation	23.0	11.5	32.1	11.7	21.2	9.9	25.5	10.1
	serum total iron binding capacity (%)	70.0	8.8	69.6	8.6	#72.2	9.0	64.0	16.8
	haematocrit (%)	42.5	4.6	46.4	5.5	41.6	4.0	44.2	6.1
	haemoglobin (g/dl)	12.0	1.2	12.9	2.0	11.5	1.3	12.5	1.9

***, #: = Differ significantly ($p<0.05$)**
(SD=standard deviation; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2; % saturation=% saturation of ferritin)

Table 5.47 shows that there was a significant negative correlation between serum iron concentration and 120 min postload glucose in young females. This correlation could have been accidental, especially in the light of the near absence of significant differences between NGT and GIT2 groups. There were no significant differences between NGT and GIT2 groups in the total population. The only two significant differences between NGT and GIT2 groups were for serum TIBC and serum ferritin concentration in older females. Since ferritin is an indication of the total body iron stores, it would be expected that changes in ferritin concentrations would result in changes in serum TIBC. Haemoglobin correlated negatively with fasting glucose in the young males.

Table 5.48: Significant correlations for iron status

Group	r-value
Serum iron concentration and 120 min postload glucose level in young females.	*-0.119
Serum haemoglobin and fasting glucose level in the young males.	*-0.133

***=Correlation significant at the 0.05 level**
(% saturation=% saturation of ferritin; STIBC=serum total iron binding capacity)

5.8.3 Blood vitamin levels

Table 5.49 gives the means and standard deviations for the serum vitamin A and serum vitamin E concentrations. Vitamin B6 and folic acid were only determined in a random sub-sample of subjects and therefore the means and standard deviations for these two vitamins are not given here.

Table 5.49: Descriptive statistics of the blood vitamin levels

Group	Vitamin	Female <45 years		Male <45 years		Female ≥45 years		Male ≥45 years	
		means	SD(±)	means	SD(±)	means	SD(±)	means	SD(±)
NGT	vitamin A (µg/dl)	42.2	13.6	46.3	14.1	47.5	17.6	48.8	17.0
	vitamin E (mmol/l)	7.5	3.1	7.9	2.5	#8.4	2.9	##8.1	2.8
GIT1	vitamin A (µg/dl)	44.6	17.5	48.1	14.1	48.1	19.0	52.5	15.9
	vitamin E (mmol/l)	8.7	3.1	8.0	2.5	10.1	2.7	8.1	2.8
GIT2	vitamin A (µg/dl)	40.4	12.2	50.7	19.8	#49.7	16.9	##51.1	16.6
	vitamin E (mmol/l)	9.1	4.1	8.1	4.1	10.6	3.5	7.6	3.4

There were significant differences for serum vitamin E between the NGT and GIT2 groups in the total sample* ($p \leq 0.05$), in the older females # ($p \leq 0.01$) and in the older males ## ($p \leq 0.05$)
(SD=standard deviation; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

According to Table 5.49, in the young females, young males and older females, the vitamin E intake increased as the glucose tolerance status worsened, while it decreased in the older males. The vitamin A levels in young males, older females and older males increased as the glucose tolerance status worsened, while it decreased in the young females.

In the literature no associations between any of these vitamins and either type 2 diabetes or glucose tolerance are mentioned. The three significant correlations between glucose and vitamin E (Table 5.50) together with the three significant differences for vitamin E between NGT and GIT2 groups, suggested that there may have been a relationship between vitamin E status and type 2 diabetes in this study population. However, vitamin E did not differ significantly between the NGT and GIT2 groups after controlling for age, gender and energy intake. Therefore, these associations could also have been the result of the observed association between energy intake and glucose tolerance.

Table 5.50: Significant correlations for serum vitamin E levels

Group	r-value
Serum vitamin E and 120 min postload glucose level in young females.	*0.129
Serum vitamin E and fasting glucose level in older females.	*0.186
Serum vitamin E and 120 min postload level in older females	*0.200

***=Correlation significant at the 0.05 level**

5.8.4 Serum electrolyte levels

Table 5.51 shows the means and standard deviations of the serum electrolyte levels. The differences in the mean serum electrolyte levels between NGT and GIT2 groups were very small. Sodium is linked with the development of type 2 diabetes through its effect on the blood vessels and its relationship with IR. There is also an association between blood and probably also intracellular potassium levels and beta-cell function (hypokalemia interfere with insulin secretion). Table 5.52 shows that there were no significant differences in the sodium levels between NGT and GIT2 groups in this study population, furthermore there were no significant correlations between sodium and either fasting or 120 min postload glucose levels. There were significant differences for serum phosphate levels between the NGT and GIT2 groups in the older females and the young males. Table 5.52 shows that there were significant correlations between serum magnesium and fasting glucose in both the older and young males.

Table 5.51: Descriptive statistics of the serum electrolytes

Group	Electrolyte (mmol/l)	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		means	SD(±)	means	SD(±)	means	SD(±)	means	SD(±)
NGT	potassium	4.0	0.4	4.1	0.4	4.1	0.5	4.3	0.5
	chloride	105.0	2.5	103.8	2.5	103.1	3.4	103.6	2.9
	phosphate	1.1	0.2	##1.1	0.2	#1.1	0.2	1.1	0.2
	calcium	2.3	0.1	2.4	0.1	2.3	0.1	2.3	0.1
	magnesium	0.9	0.1	0.9	0.1	0.9	0.1	0.9	0.1
	sodium	137.2	2.8	137.6	3.6	137.2	2.8	138.1	2.5
GIT1	potassium	4.2	1.3	4.3	0.6	3.9	0.5	4.2	0.5
	chloride	104.3	2.3	104.4	3.3	102.0	3.7	102.7	3.0
	phosphate	1.1	0.2	1.2	0.2	1.2	0.2	1.2	0.2
	calcium	2.3	0.1	2.3	0.1	2.3	0.1	2.3	0.2
	magnesium	0.9	0.1	0.9	0.1	0.9	0.1	0.9	0.1
	sodium	137.3	2.5	132.7	24.9	137.5	3.4	137.5	1.9
GIT2	potassium	3.9	0.3	4.1	0.3	4.1	0.5	4.2	0.5
	chloride	104.2	3.6	103.6	1.7	102.5	3.7	103.3	4.1
	phosphate	1.1	0.2	##1.3	0.2	#1.3	0.2	1.1	0.2
	calcium	2.3	0.1	2.4	0.1	2.3	0.1	2.3	0.1
	magnesium	0.8	0.1	0.9	0.1	0.9	0.1	0.9	0.1
	sodium	136.3	2.5	138.0	2.3	136.9	3.7	136.3	1.7

 # = Significant difference ($p \leq 0.05$)
= Significant difference ($p \leq 0.01$)
(SD=standard deviation; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.52: Significant correlations for the serum electrolyte levels

Variables and group	r-value
Serum magnesium and fasting glucose level in young males.	*0.157

***=Correlation significant at the 0.05 level**

5.8.5 Serum concentrations of excretory products

Table 5.53 shows the means and standard deviations of certain excretory products. It seems as if there are no trends of differences in the levels of any of the excretory products between the NGT and GIT2 groups. The differences in the mean levels of these products between the NGT and GIT2 groups were relatively small, but most of the excretory products were lower in the GIT2 groups than in the NGT groups. Table 5.54 shows the significant correlations for the serum concentrations of these excretory products.

Table 5.53: Descriptive statistics of the serum concentrations of excretory products

Group	Excretory product (mmol/l)	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		means	SD(±)	means	SD(±)	means	SD(±)	means	SD(±)
NGT	carbon dioxide	20.7	2.2	23.0	2.2	22.1	2.4	23.5 #	2.6
	urea	3.6	1.1	4.1	1.2	3.6	1.1	6.9	25.1
	urate	0.3	0.2	0.4	0.1	0.3	0.1	0.4	0.1
	creatine	73.3	10.7	85.5	13.2	76.2	11.9	85.2	14.2
GIT1	carbon dioxide	20.8	1.8	21.5	2.1	23.0	2.4	23.4	2.7
	urea	3.8	1.2	4.2	1.3	4.0	1.4	4.0	1.7
	urate	0.3	0.1	0.3	0.1	0.4	0.1	0.4	0.1
	creatine	73.9	11.3	85.2	13.0	77.6	14.0	87.6	16.0
GIT2	carbon dioxide	21.0	2.3	22.3	2.7	23.0	2.4	21.5 #	1.9
	urea	3.6	1.0	3.9	1.2	3.8	1.5	4.4	2.2
	urate	0.3	0.1	0.4	0.1	0.3	0.1	0.3	0.1
	creatine	72.1	10.0	80.6	7.1	70.6	13.2	91.7*	17.1

*** = Significant correlation with fasting glucose ($p \leq 0.05$)**
 # = Significant difference ($p \leq 0.05$)
(SD=standard deviation; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.54: Significant correlations for excretory products

Variables and group	r-value
Serum urea and fasting glucose level in older females.	0.193 *
Serum creatine and fasting glucose level in older males.	0.212 *

***=Correlation significant at the 0.05 level**

5.8.6 Serum protein levels

Table 5.55 shows the means and standard deviations for the serum protein levels. The GIT2 groups had lower levels of all the serum proteins than the NGT groups. The only exception was serum albumin in the young males, where the GIT2 group had a slightly, but not significantly higher mean level than the NGT group. Serum albumin is often used as an indicator of nutritional status. If under nutrition plays a role in the development of type 2 diabetes - especially in the young males - one would have expected a lower albumin concentration in GIT1 and GIT2 subjects, which was not the case in this study population.

Table 5.56 shows the significant correlations for the serum proteins. This table shows significant negative correlations for both serum proteins and albumin with 120 min postload glucose levels. The absence of significant correlations and differences for these factors in other groups suggested that these significant correlations may have been by chance.

Table 5.55: Descriptive statistics of the serum protein levels

Group	Protein (g/l)	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		means	SD(±)	means	SD(±)	means	SD(±)	means	SD(±)
NGT	total proteins	76.1	6.8	75.8	5.8	75.8	6.4	74.5	4.9
	albumin	44.3	3.9	46.8	3.4	43.1	3.8	43.5	3.9
GIT1	total proteins	74.8	9.8	74.2	5.3	74.4	6.3	74.7	5.8
	albumin	44.3	4.8	44.7	3.7	42.6	4.9	44.6	4.9
GIT2	total proteins	74.0	5.4	75.7	4.9	74.5	6.3	71.3	6.2
	albumin	44.1	3.6	47.8	3.4	42.8	2.7	41.8	5.1

(SD= standard deviation; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

Table 5.56: Significant correlations for the serum protein levels

Group	r-value
Total serum protein and 120 min postload glucose levels in older males.	*-0.206
Total serum protein and 120 min postload glucose levels in older NGT males.	**-0.355
Serum albumin and 120 min postload glucose level in older GIT1 females.	*-0.474

***=Correlation significant at the 0.05 level**
****=Correlation significant at the 0.01 level**
(NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1)

5.8.7 Serum levels of certain enzymes

Table 5.57 shows the means and standard deviations for the serum levels of certain enzymes. This table shows that there are no trends for differences in the serum enzyme levels between the NGT and GIT2 subjects. It can be seen that the serum levels of alanine phosphatase (ALP) were higher for GIT2 subjects in all groups compared to the NGT subjects and this difference is significant for the young females ($p<0.05$).

Table 5.58 shows the significant correlations for these enzymes. In the literature only one of these enzymes is linked to diabetes mellitus (DM) (Kumar & Clark, 1996). Aspartate amino transferase

levels decreases in uncontrolled DM with acidosis (Kumar & Clark, 1996). There were no significant differences between the NGT and GIT2 groups for aspartate amino transferase in this study population. There was a significant difference between the ALP levels in NGT and GIT2 subjects in the young females. It is possible that the blood glucose had an effect on the enzyme rather than the reverse, or an unknown factor could have influenced both serum glucose and ALP.

Table 5.57: Descriptive statistics of the serum levels of certain liver enzymes

Group	Enzyme	Female <45 years		Male <45 years		Female ≥45 years		Male ≥45 years	
	(IU/l)	means	SD(±)	means	SD(±)	means	SD(±)	means	SD(±)
NGT	ALP	#64.8	20.5	84.8	52.9	76.3	24.5	70.7	21.8
	ALT	9.1	6.5	12.2	8.1	11.0	7.9	##11.3	5.9
	AST	18.3	12.2	22.0	9.0	19.5	12.9	22.7	9.8
	LDH	123.6	33.9	123.3	28.9	136.9	35.6	119.8	31.5
	CK	123.7	153.4	245.5	300.2	112.5	69.7	198.8	263.6
GIT1	ALP	66.6	31.4	62.9	27.5	75.8	30.2	78.0	33.1
	ALT	14.7	28.4	14.0	14.4	9.0	4.8	14.1	12.5
	AST	19.5	14.6	22.5	14.1	17.6	4.2	28.7	23.6
	LDH	126.4	31.0	124.5	22.6	142.1	31.4	116.9	31.2
	CK	123.4	76.3	156.8	118.9	173.1	221.2	199.0	187.1
GIT2	ALP	#79.0	28.6	105.2	73.1	68.8	14.6	77.2	20.5
	ALT	9.2	7.7	9.7	3.7	10.2	4.0	##20.9	26.1
	AST	16.0	7.1	22.2	5.2	18.8	5.1	30.0	26.8
	LDH	121.5	27.4	125.1	16.5	136.9	29.1	117.9	25.9
	CK	109.3	58.4	228.9	176.6	117.8	56.0	131.0	59.1

 # = Significant difference ($p \leq 0.05$)
= Significant difference ($p \leq 0.01$)
(SD=standard deviation; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 1; GIT2= glucose intolerance group 2; ALP=alanine phosphatase; ALT=alanine amino transferase; AST=aspartate amino transferase; LDH=lactic dehydrogenase; CK=creatine kinase)

Table 5.58: Significant correlations for the serum levels of certain liver enzymes

Variables and group	r-value
Serum alanine phosphatase and fasting glucose in older females.	*-0.180
Serum alanine phosphatase and fasting glucose level in older NGT females.	*-0.277
Serum lactic dehydrogenase and fasting glucose level in older GIT1 males.	**0.647
Serum creatine kinase and fasting glucose level in young GIT1 males.	*0.451

***=Correlation significant at the 0.05 level**
****=Correlation significant at the 0.01 level**

5.8.8 Serum lipid levels

Table 5.59 gives the means and standard deviations of the serum lipid levels. High levels of LDL and triglycerides and low levels of HDL are associated with type 2 diabetes (see literature survey). These factors may be markers or consequences of the disease rather than risk factors, because it usually develops concurrently with GIT. The total cholesterol levels were higher in the GIT2 subjects in all the groups compared to the NGT subjects. It can also be seen that in the young females and older males the GIT2 subjects had lower HDL and higher LDL levels than the NGT subjects, as would be expected. However, the young GIT2 males had higher HDL and lower LDL levels than the young NGT males. The older GIT2 females had higher levels of both HDL and LDL than the older NGT females. Triglycerides were higher in the GIT2 groups than in the NGT groups, except in the young males where the GIT2 subjects had a lower mean triglyceride level than the NGT subjects.

Table 5.59: Descriptive statistics of the serum lipid levels

Group	Serum lipid (mmol/l)	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
		means	SD(±)	means	SD(±)	means	SD(±)	means	SD(±)
NGT	TC	4.1	0.9	4.0	1.1	4.7	1.2	4.5	1.0
	HDL	1.2	0.3	1.2	0.4	1.3	0.4	#1.3	0.4
	LDL	2.4	0.9	2.3	1.1	3.0	1.2	2.7	1.0
	TG	1.1	0.7	1.2	0.9	1.7	1.0	1.7	0.9
GIT1	TC	4.4	1.0	4.1	0.7	5.4	1.1	4.8	1.1
	HDL	1.2	0.3	1.3	0.4	1.2	0.3	1.6	0.6
	LDL	2.7	0.9	2.4	0.8	3.7	1.0	2.7	1.0
	TG	1.3	0.8	1.2	0.5	1.7	0.6	1.3	0.5
GIT2	TC	4.4	1.1	4.0	1.3	5.1	0.9	4.6	1.0
	HDL	1.1	0.3	1.3	0.5	1.4	0.4	#1.0	0.3
	LDL	2.8	1.0	2.2	1.0	3.3	0.8	3.1	1.1
	TG	1.4	0.8	1.1	0.8	1.8	0.9	2.1	1.1

There were significant differences for serum TC* , serum TG* and serum LDL cholesterol between the NGT and GIT2 groups in the total population (*=p<0.05; **=p<0.01)**
There was a significant difference for LDL cholesterol between the NGT and GIT2 groups in the total sample after controlling for age and gender (p<0.05) and age gender and energy intake (p<0.05)
 # = Significant difference (p≤0.05)
(SD=standard deviation; NGT=normal glucose tolerance group; GIT1= glucose intolerance group 1; GIT2=glucose intolerance group 2; TC=total cholesterol; HDL=high density lipoprotein; LDL=low density lipoproteins; TG=triglycerides)

Table 5.60 shows the significant differences for the serum lipid concentrations. There were significant differences for total cholesterol, LDL-cholesterol and triglycerides between the NGT

and GIT2 subjects of the total population and a significant difference for HDL-cholesterol between the NGT and GIT2 subjects of the older males only. The differences for total cholesterol and triglyceride levels were not significant after controlling for age, gender and energy intake. After controlling for age, gender and energy intake the differences in LDL-cholesterol levels were still significant between the NGT and GIT1 group, indicating that LDL-cholesterol is significantly higher in the GIT2 group. HDL-cholesterol also correlated with fasting glucose in the older males. This could be by chance, but there were a negative correlation and low levels of HDL-cholesterol is known to be associated with type 2 diabetes and other chronic diseases. LDL-cholesterol correlated with fasting glucose in the young females and the older GIT2 males. Triglycerides also correlated with fasting glucose in the young females, older males and older GIT1 females. High levels of LDL-cholesterol and triglycerides are known to be associated with type 2 diabetes. From these results it seemed as if high levels of total cholesterol, LDL-cholesterol and triglycerides may have been more important in the development of type 2 diabetes than low levels of HDL-cholesterol.

Table 5.60: Significant correlations for the serum lipid levels

Variables and group	r-value
Serum HDL and fasting glucose level in older males.	**-0.238
Serum LDL and fasting glucose level in young females.	*0.130
Serum LDL and fasting glucose level in older GIT2 males.	*0.707
Serum TG and fasting glucose level in young females.	*0.108
Serum TG and fasting glucose level in older males.	*0.215
Serum TG and fasting glucose level in older GIT1 females.	*0.484

***=Correlation significant at the 0.05 level**
****=Correlation significant at the 0.01 level**
(HDL=high density lipoprotein; LDL=low density lipoprotein; TG=triglycerides)

5.8.9 Factors that are involved in blood clotting

Table 5.61 gives the means and standard deviations of plasma fibrinogen, determined with the method of Clauss, and a macromolecular protein complex (MPC) which is thought to be a risk marker for thrombosis (Lipinsky, 1994)

Table 5.62 gives the significant correlations for these clotting factors. Although there were no significant differences of these factors between the NGT and GIT2 groups, several significant correlations were found. Fibrinogen correlates with fasting glucose in the young females as a group, older males as a group, and older GIT1 males. Macro molecular protein complex

correlates with fasting glucose in the older males and the older GIT2 males. It seems as if these clotting factors could be associated with type 2 diabetes in this sample, which is in agreement with a large body of literature on the abnormal haemostatic profile of type 2 diabetic patients.

Table 5.61: Descriptive statistics of some factors that are involved in blood clotting

Group	Variable	Females <45 years		Males <45 years		Females ≥45 years		Males ≥45 years	
	(mg/dl)	means	SD(±)	means	SD(±)	means	SD(±)	means	SD(±)
NGT	FBG	3.7	0.9	3.2	0.8	4.0	1.0	3.6	1.1
	MPC	2.4	1.4	2.0	1.4	2.3	1.4	2.8	1.7
GIT1	FBG	3.7	0.9	3.2	0.9	4.0	0.8	4	1.3
	MPC	2.3	1.6	1.8	1.6	2.1	1.7	1.8	1.6
GIT2	FBG	3.5	0.9	2.8	0.7	3.6	0.9	4	1.9
	MPC	2.1	1.4	1.7	1.0	2.1	2.4	3.1	2.7

(SD=standard deviation; NGT=normal glucose tolerance group; GIT1=glucose intolerance group 2; GIT2=glucose intolerance group 2; FBG=fibrinogen; MPC=macromolecular protein complex)

Table 5.62: Significant correlations for some of the clotting factors

Variables and group	r-value
Plasma fibrinogen and fasting glucose level in young females.	*0.112
Plasma fibrinogen and fasting glucose level in the older males.	***0.351
Plasm fibrinogen and fasting glucose level in the older GIT1 males.	*0.554
Plasma fibrinogen and fasting glucose level in the older GIT2 males.	**0.750
Plasma macromolecular protein complex and fasting glucose levels in older males.	**0.298
Plasma macromolecular protein complex and fasting glucose levels in older GIT2 males.	*0.763

***=Correlation significant at the 0.05 level**
****=Correlation significant at the 0.01 level**
*****=Correlation significant at the 0.001 level**
(GIT1=glucose intolerance group 1; GIT2=glucose intolerance group 2)

5.9 Discussion

5.9.1 Risk factors for glucose intolerance

This part of the study had certain limitations and the results should be interpreted in the light of these limitations. Some of the variables such as dietary intakes, smoking habit and family history of chronic diseases were reported by the subjects and are therefore subject to bias. The fasting state of some of the subjects was in doubt. This may have influenced some of the results and for that reason the population has been divided into NGT, GIT1 and GIT2 (not diabetic) subjects on the bases of their glucose tolerance status.

The objective of this part of the study was to investigate all the known risk factors for type 2 diabetes to determine whether or not they were important in the development of GIT in this sample. From the results it is possible to list the risk factors or markers for GIT and type 2 diabetes for this study sample (Table 5.63). Some of the well-known risk factors and markers for type 2 diabetes do not seem to play an important role in the development of GIT in these subjects. But, several factors that are not listed as risk factors of type 2 diabetes in the literature were shown to be associated with GIT in this study population.

The risk factors and markers for GIT that emerged in this population sample, being significantly higher in the GIT groups than in the NGT, were age (in females), waist-to-hip ratio, the smoking habit in males, hyperglycaemia and hyperlipidaemia. Females had higher GIT rates than males.

*** Waist-to-hip ratio**

The significant difference between the waist-hip ratio for the NGT and the GIT2 groups for the total population, older males and younger females shows that waist-to-hip ratio was a strong marker of risk for GIT in this sample. Therefore, waist-hip ratio may not be an ideal or only marker for type 2 diabetes in this population, but it seems to be a better marker than a waist circumference and BMI in this population.

*** The smoking habit**

Smoking is known to be a risk factor for the development of type 2 diabetes. It was an important risk factor for type 2 diabetes in males, but not in females, probably because fewer females smoked.

*** Hyperglycaemia**

When interpreting the blood glucose levels it is important to keep in mind that the fasting state of some of the subjects was in doubt. This could explain why insulin levels did not differ consistently between NGT and GIT2 groups. The absence of significant differences for insulin levels between the NGT and the GIT2 groups is however, in accordance with the suggestion that diabetic subjects (especially females) still have the ability to secrete insulin, and that IR resulted in the observed increased blood glucose levels. Based on the mean glucose and insulin levels (Table 5.46) these subjects may have an early phase of IR.

*** Dislipidaemia**

Dislipidaemia is a marker for type 2 diabetes (Stern, 1995). In this population the GIT2 group had significantly higher serum total cholesterol and triglyceride levels than the NGT group, but

the significance disappeared after controlling for age and gender and for energy intakes. The significant difference for LDL-cholesterol between the NGT and the GIT2 groups in the total population was still significant after controlling for age, gender and energy intake, suggesting that a high LDL-cholesterol level is a marker for the development of GIT and type 2 diabetes in this population.

Table 5.63: Risk factors that differed significantly between the normal glucose tolerance group and the glucose intolerance group 2

Risk factor or marker	
High waist-hip ratio * #	Low C18-3 intakes
High subscapular skinfold	Low Mn intakes
Low total energy intake *	Low Mg intakes *
Low total protein intake *	Low K intakes
Low plant protein intake *	Low Na intakes
Low total fat intake	Low Zn intakes
Low monounsaturated fat intake	Low Vitamin E intakes
Low polyunsaturated fat intake *	Low nicotinamide intake *
Low PS-ratio * #	High fasting glucose levels
Low total a carbohydrate intake *	High 120 min post load glucose levels
Low fibre intake *	High serum vitamin E levels
Low C16-0 intake	High serum total cholesterol levels
Low C18-1 intake *	High serum LDL-cholesterol levels * #
Low C18-2 intake *	High serum triglyceride levels

* = Difference still significant after controlling for age and gender
# = Difference still significant after controlling for age, gender and energy intake

5.9.2 Established risk factors and markers not significant in this study population

Table 5.64 gives a list of the established risk factors or markers for type 2 diabetes that did not seem to play an important role in the development of GIT.

Table 5.64: Risk factors or markers that are commonly associated with the development of type 2 diabetes, but that did not seem to play a role in this sample

Risk factors or markers	
age (in males)	Western diet
high body mass index	high refined carbohydrate (added sugar) intakes
high waist circumference	high saturated fat intakes
high triceps skinfold	high animal protein intakes
hypertension	high cholesterol intakes
family history of type 2 diabetes	high or very low serum insulin levels
family history of other chronic diseases	fibrinogen low serum HDL levels
high alcohol intake	

Gender, age and obesity (BMI) are listed as the most important risk factors for the development of type 2 diabetes. In this sample age played a role only in the females, and BMI and waist circumference (strong indicators of obesity) did not differ significantly between the GIT2 and NGT groups.

*** Age in the males**

In this sample there was a stronger association between age and GIT in the females than in the males. No indication in literature could be found that aging is a less important risk factor in males than in females. An unexpectedly high percentage of the GIT2 population were below the age of 45. This is in accordance with recent reports of increasing numbers of young subjects developing type 2 diabetes (Rosenbloom, *et al.*, 1999). This finding led to the nested case control study of diabetic subjects below the age of 45 using the complete set of data from the THUSA study (Chapter 6).

*** Body mass index, waist circumference and triceps skinfold**

Waist circumference, especially a waist circumference of more than one metre may be a better indication of disease risk than either BMI or waist-hip ratio (Despres, *et al.*, 1995). Triceps skinfold is an indicator of android fat distribution and therefore it is a marker of type 2 diabetes risk. In this study sample BMI, waist circumference and triceps skinfold did not differ significantly between the NGT and GIT2 groups, suggesting that they are not significant for the development of type 2 diabetes. This is supported by the lean young males in the GIT2 group and the large percentage of obese or overweight females in the NGT group. This suggests that black obese females will not develop type 2 diabetes as easily as in other populations. Waist-hip ratio, however, seemed to be a risk factor, indicating that central distribution of body fat may play a role, rather than total body obesity.

*** Hypertension**

Although the hypertension (HT) rates in Africans with urbanisation are high (Rutledge, 1994), the absence of significant differences between the systolic and diastolic blood pressure in the young females and males suggest that in the THUSA population HT is not necessarily linked with GIT and type 2 diabetes, indicating different aetiological factors in the development of HT and GIT.

*** Family history of type 2 diabetes and other chronic diseases of lifestyle**

Family history of type 2 diabetes, one of the most important risk factors was not significant in this sample, probably because reported family history was measured, making the data subject to bias.

*** Alcohol intake and consuming a Western diet**

Alcohol consumption has been implicated as a possible independent risk factor for type 2 diabetes through its effect on glucose tolerance and on the pancreas (Courten, *et al.*, 1997). The reported consumption of alcohol in this sample did not differ significantly between the NGT and the GIT2 groups. As stated before reported information may be subject to bias. Alcohol consumption could have played a role in individual cases. In the older females it seems to have played a significant role, but in the older males BMI was perhaps a stronger risk factor than alcohol intake. Consuming a Western diet is known to be a risk factor for the development of type 2 diabetes (Shetty, 1997). In this study sample there were no significant differences between the NGT and GIT2 groups for animal protein, saturated fatty acid or cholesterol intakes. However, even the most urbanised group, had mean fat, protein and carbohydrate intakes indicative of the prudent diet (MacIntyre, 1998). These subjects may therefore not be a suitable group to examine the influence of the Western diet.

*** Serum insulin, fibrinogen and high density lipoprotein levels**

The absence of significant differences for serum insulin levels between the NGT and GIT2 groups and of correlations between insulin and glucose levels should be seen in the light that all the subjects were not fasting. Therefore, no conclusion can be made about the effect of insulin in the development of type 2 diabetes in this population. In both the young and the older females it seemed as if IR was present in the GIT2 groups and that the pancreas was still able to secrete insulin, suggesting a receptor or a postreceptor defect rather than insulin insufficiency as the factor playing a role in the development of type 2 diabetes. In the young males insulin deficiency seems to have been responsible for the GIT rather than IR. Increased fibrinogen may be a marker for GIT and type 2 diabetes (Nabulsi, *et al.*, 1995). In this study sample fibrinogen does not seem to be associated with GIT. Low serum HDL level is known to be associated with type 2 diabetes (Nuttal, 1988). In this study population there was no significant difference for HDL between the NGT and GIT2 groups.

5.9.3 "Unexpected" factors in this study population

Table 5.65 gives a list of the "unexpected" factors associated with GIT in this study population. None of these factors differed significantly between the NGT and GIT2 groups after controlling for age, gender and energy intake. However, some differed significantly after controlling for only age and gender.

Some of the factors listed in this table may influence the development of a process that is associated with the development of type 2 diabetes (such as IR), and thus, only play an indirect role in the development of the disease. Each of these "unexpected" risk factors should be investigated, to determine their possible roles in the development of type 2 diabetes.

Table 5.65: "Unexpected" risk factors or markers associated with GIT and type 2 diabetes in this population

Risk factor or marker	
subscapular skinfold	low Mn intakes
low total energy intake *	low Mg intakes *
low total protein intake *	low K intakes
low total fat intakes	low Zn intakes
low total carbohydrate intake *	low Na intakes
low C16-0 intakes	low vitamin E intakes
low C18-1 intake *	low nicotinamide intake *
low C18-2 intake *	high serum vitamin E levels
low C18-3 intake	

*=risk factor was significant after controlling for age and gender

* Subscapular skinfold

Subscapular skinfold measure is related to intra-abdominal fat and the fact that it differed significantly between the NGT and GIT2 groups, even after corrections for age and gender, may indicate that intra-abdominal fat rather than total body fat is an important risk factor for the development of type 2 diabetes in this sample. This is in accordance with waist-hip ratio as an important risk factor.

* Low total energy and nutrient intakes

Low total energy and protein and intakes, suggest a possibility of a Tropical J-type diabetes. This is in accordance with the low intakes of fats, CHO's, and some fatty acids as well as low intakes of some electrolytes (Mn, Mg, K, Zn, and Na) and vitamin E. However, the significant difference for all the above nutrient intakes between the NGT and the GIT2 groups disappeared after

controlling for energy intake, suggesting that the lower intakes can be explained by the lower energy intake of the GIT2 group compared to the NGT group. The dietary intakes were reported by the subjects, and are therefore subject to bias. This may explain the lower energy intakes in the overweight GIT2 subjects. However, differences in activity levels may also explain why overweight GIT2 subjects had a lower energy intake compared to NGT subjects. Serum albumin levels were not significantly different between the groups, indicating that protein status did not play a role in the development of GIT in these subjects.

*** High serum vitamin E levels**

In the literature low levels of vitamin E has been found in diabetic subjects (Ceriello & Giugliano, 1997). It is hypothesized that glucose creates free radicals that result in lower levels of antioxidants such as vitamin E (Cereillo & Giugliano, 1997; Tuomiltho & Rostenyte, 1997). Therefore, the higher serum vitamin E level of the GIT2 subjects is intriguing. They could reflect increased fat intakes which were not measured by the dietary intake method.

The findings of this part of the study will be discussed further in chapter 7.

CHAPTER 6
RESULTS AND DISCUSSION: CHARACTERISTICS OF YOUNG (<45 years) SUBJECTS WHO WERE IDENTIFIED WITH DIABETES

6.1 Introduction

The observation from results reported in Chapter 5 that the metabolic profile and possibly risk factors of the younger male group differed from the younger females and older males and females, motivated this part of the study. All subjects below the age of 45 with a fasting blood glucose level of >7.1 mmol/l or a 120 min postload blood glucose level of ≥11.1 mmol/l were selected from the total subject group (1996-1998 subjects). Only truly fasting subjects were included in this group and it is called the diabetic (DM2) group. Of the total group of 1854 subjects only 426 (23%) were definitely in a fasting state. Only eleven of these truly fasting subjects were diagnosed with type 2 diabetes. Therefore, this group consisted of eleven subjects. A control subject was selected for each of these DM2 subjects, matched for age, gender, body mass index (BMI) and stratum (level of urbanisation). The subjects in the control group had normal blood glucose levels. The control group and DM2 groups were compared with regard to risk factors or markers for type 2 diabetes. These factors were then divided into factors that were the same and those that differed significantly in between the two groups.

Because this study was part of the multi disciplinary THUSA project, several variables were determined that are thought not to be directly associated with type 2 diabetes or glucose intolerance (GIT). These variables, which did not differ significantly between the DM2 and the control groups are listed in Table 6.1.

6.2 Known risk factors or markers that did not differ

6.2.1 Factors (variables) used to match the control and DM2 subjects

Table 6.2 gives the means and standard deviations of age and BMI for the DM2 and the control groups. There were seven female and four male type 2 diabetics identified with the strict criteria used. Due to the small sizes males and females were not separated. Two subjects in each group were farm workers, six were living in squatter camps and three were from the urban middle class. No diabetic subjects were found in the rural and urban upper class strata.

Table 6.1: Variables determined in the study that did not differ significantly between the type 2 diabetes and control groups and that have no proven direct association with type 2 diabetes

Anthropometry	Dietary intakes	Blood biochemistry	Other
iliac-crest skinfold	calcium	potassium	HIV-infection
supra spinal skinfold	magnesium	phosphate	basal metabolic rate
thigh skinfold	phosphate	calcium	
calf skinfold	potassium	magnesium	
arm circumference (relaxed)	zinc	proteins	
arm circumference (tensed)	copper	globulin	
maximum forearm circumference	all saturated fatty acids	Conjugated bilirubin	
thigh circumference	all monounsaturated fatty acids	D-bilirubin	
mid-thigh circumference	all polyunsaturated fatty acids	T-bilirubin	
calf circumference	essential amino acids	osmolarity	
humerus circumference	vitamin intakes	anion gap	
wrist circumference		urea	
femur circumference		uric acid	
ankle circumference		creatine	
sum of 7 skinfolds		carbon dioxide	
mass		haematocrit	
stature		haemoglobin	
skeletal mass			

The higher mean age of the DM2 subjects, was the result of matching for several variables besides age. In order to find a matching control for stratum and BMI a control subject of the exact age was not available in all instances. The nearest 5-year age span was then selected. However, the mean ages of the two groups did not differ significantly and all other variables were controlled for age and gender.

The mean BMI's of the two groups were the same. However, all the males had a BMI of between 17.7 Kg/m^2 and 21.7 Kg/m^2, indicating that the young males who developed type 2 diabetes were lean, or underweight. The females had BMI's between 18.2 Kg/m^2 and 34.5 Kg/m^2. Six of the female subject-pairs had BMI's >25 Kg/m^2.

Table 6.2: The means and standard deviations of age and body mass index for the diabetic and control groups

Variable	Control group	DM2 group	Normal range
	means (±SD)	means (±SD)	
age (years)	33.4 (7.4)	38.3 (7.4)	-
BMI (Kg/m^2)	25.7 (5.3)	25.7 (5.9)	20-25

(DM2=diabetes; SD=standard deviation; BMI=body mass index)

6.2.2 Other variables that did not differ between the two groups

6.2.2.1 Family history of diabetes and other chronic diseases of lifestyle

The family history of diabetes and other chronic diseases of lifestyle were reported by the subjects and are therefore subject to bias. The results showed that there were no significant correlations between the fasting glucose level and reported family history of diabetes and other chronic diseases of lifestyle in these subjects.

6.2.2.2 Smoking

Table 6.3 gives the means and standard deviations for smoking in the two groups. Smoking is known to be one of the risk factors for type 2 diabetes (Bjorntorp, 1997, 621). No difference in smoking (pack years) was observed between controls and the DM2 group.

Table 6.3: The means and standard deviations for smoking, physical activity and blood pressure in the type 2 diabetes and control groups

Variable	Control group	DM2 group	Normal range
	means (±SD)	means (±SD)	
Smoking (pack years)	1.6(0.5)	1.5 (0.5)	-
Physical activity	3.9 (2.0)	2.4 (0.7)	-
Systolic blood pressure (mmHg)	127.3 (22.5)	130.1 (17.4)	120-140
Diastolic blood pressure (mmHg)	83.6 (11.6)	80.3 (12.8)	80-90

(DM2=diabetes; SD=standard deviation)

6.2.2.3 Physical activity

Table 6.3 gives the means and standard deviations for the physical activity score of the two groups. A decrease in physical activity (often associated with modernisation) is known to be one of the risk factors for type 2 diabetes (Jenkins & Jenkins, 1994; Maurier, *et al.*, 1997). The DM2

group did not have significantly lower levels of physical activity than the control group, although from Table 6.3 it can be seen that the physical activity level of the DM2 group was slightly lower than for the control group.

6.2.2.4 Blood pressure

Hypertension is both a marker of type 2 diabetes and a complication of the condition (Engelgau, *et al.*, 1995; Stern, 1995). From Table 6.3 it can be seen that the DM2 group had a higher systolic, but a lower diastolic blood pressure than the control group. These differences were not significant and the mean systolic and diastolic blood pressure for both groups were not high enough to indicate hypertension. However, as can be seen from the standard deviations, some subjects in both groups were hypertensive.

6.2.2.5 Anthropometry

Table 6.4 gives the means and standard deviations for the anthropometric measurements of the two groups. A large waist circumference (>1m) is associated with the development of type 2 diabetes (Despres, *et al.*, 1995), but in this study the DM2 group did not have a significantly higher waist circumference than the control group. Large triceps, subscapular and abdominal skinfolds are indicative of an abdominal fat distribution, a marker of type 2 diabetes. These skinfolds were not significantly higher in the DM2 group than in the control group. In fact, the DM2 group had a lower triceps skinfold than the control group.

Table 6.4: The means and standard deviations for the anthropometric measurements in the type 2 diabetes and control groups

Variable	Control group	DM2 group
	means (±SD)	means (±SD)
Waist circumference (cm)	76.2 (8.8)	81.6 (11.1)
Triceps skinfold (mm)	17.4 (9.3)	15.1 (9.8)
Subscapular skinfold (mm)	16.2 (7.8)	18.4 (12.7)
Abdominal skinfold (mm)	17.0 (11.3)	26.0 (15.7)

(DM2=diabetes; SD=standard deviation)

6.2.2.6 Dietary intakes

Table 6.5 gives the means and standard deviations for the dietary intakes. A Western diet is one of the risk factors for type 2 diabetes (Shetty, 1997). This diet is characterised by a high energy

intake, high refined carbohydrates (CHO's), fat, and animal protein intakes and by lower intakes of complex CHO's and fibre. However, the DM2 group had a lower total energy intake (with or without energy from alcohol) than the control group. The DM2 group also reported a lower intake of alcohol, total protein, plant protein and animal protein than the control group. Both groups had a lower percentage food energy from proteins than the suggested by the Recommended Dietary Intakes (RDA).

Table 6.5: The means and standard deviations for the dietary intakes in the type 2 diabetes and control groups

Variable	Control group	DM2 group	Normal ranges
	means (±SD)	means (±SD)	
Total energy intake including alcohol (KJ)	9905 (4215)	8276 (3560)	females - 9211 males - 12142
Food energy intake (excluding alcohol) (KJ)	9648 (4034)	8084 (3572)	
Total protein intake (g)	67.4 (24.6)	57.1 (19.4)	females - 46-50 males - 58-63
Percent food energy from proteins (%)	11.5 (1.7)	11.6 (2.0)	20
Plant proteins (g)	45.5 (22.5)	34.4 (17.0)	-
Animal proteins (g)	21.8 (7.3)	22.6 (10.2)	-
Percent food energy from fat (%)	24.9 (7.1)	20.1 (3.3)	≤ 30
Saturated fat (g)	17.4 (6.7)	12.7 (3.9)	≤ 10
Polyunsaturated fat (g)	18.1 (7.7)	12.3 (7.7)	≤ 10
Cholesterol (g)	288.1 (165.5)	274.4 (170.9)	
Total carbohydrates (g)	372.7 (181.4)	334.5 (172.0)	
Percent food energy from carbohydrates (%)	65.3 (8.9)	70.3 (1.6)	55
Fibre (g)	22.2 (10.5)	17.6 (8.8)	30
Added sugar (g)	56.9 (32.8)	54.8 (45.7)	-
Alcohol (g)	8.6 (11.9)	6.5 (16.4)	-

Normal ranges from Subcommittee on the Tenth Edition of the RDA's, 1989; (DM2=diabetes; SD=standard deviation)

Both groups also derived a lower percentage of food energy from fat than the upper limit of 30% recommended for the prudent diet (James, 19). In the DM2 group a lower percentage of energy was derived from fats than in the control group. The DM2 group also reported a lower intake of saturated fat, polyunsaturated fat and cholesterol than the control group.

The DM2 group had a lower intake of total CHO's and added sugar than the control group, but

when the CHO intake is reported as a percentage of the energy intake, the DM2 group had a higher percentage than the control group. A low fibre intake is also associated with a Western diet and in this study the DM2 group had a lower fibre intake than the control group. Both groups reported lower fibre intakes than the recommended 20-30g per day (James, 1997).

The differences reported above are not significant and both groups clearly followed a prudent diet regarding macro nutrient composition. In total, however, they do suggest that the DM2 group may have followed a "healthier" diet than the control group. This is supported by the slightly, but not significantly, higher blood vitamin levels in the DM2 group compared to the control group (Table 6.6).

Table 6.6: The means and standard deviations for the blood vitamin levels of the type 2 diabetes subjects and control groups

Vitamin	Control group	DM2 group	Normal range
	mean (±SD)	mean (±SD)	
vitamin A (µg/dl)	43.8 (12.8)	44.8 (12.5)	30-60 µg/dl
vitamin E (mg α-TE)	9.2 (3.7)	9.6 (2.9)	8 mg α-TE

(DM2=diabetes; SD=standard deviation)

6.2.2.7 Serum lipid levels

Table 6.7 gives the means and standard deviations for the serum lipid levels. High serum levels of cholesterol and LDL-cholesterol and low serum levels of HDL-cholesterol are known to be complications associated with type 2 diabetes (Stern, 1995; Bressler & Johnson, 1997), but it may also be present before the onset of the disease (Stern, 1995). Therefore, it can be considered as a marker for the development of type 2 diabetes. Despite a lower total energy intake and a lower total fat intake, the DM2 group had higher levels of total cholesterol, triglycerides and LDL-cholesterol than the control group, but these differences were not significant. All four variables were within the normal ranges in both groups.

The total cholesterol, LDL-cholesterol and triglyceride levels of the DM2 group correlated significantly with the fasting blood glucose levels, even after correlating for age, gender, energy intake and BMI. Table 6.8 shows that these correlations were highly significant for triglyceride levels, indicating that although the blood lipid levels did not differ between the two groups, in the DM2 group there is an association between the blood lipid levels and the fasting glucose levels. It seems as if especially triglycerides and therefore also the triglyceride: HDL-ratio is associated

with the blood glucose levels. These correlations should be interpreted with care since the group was so small.

Table 6.7: The means and standard deviations for the blood lipids and insulin levels in the type 2 diabetes and control groups

Variable	Control group	DM2 group	Normal ranges
	means (±SD)	means (±SD)	
Total cholesterol (mmol/l)	4.0 (0.9)	4.7 (1.1)#	3.4-5.4
High density lipoprotein cholesterol (mmol/l)	1.1 (0.3)	1.2 (0.2)	>1.0
Low density lipoprotein cholesterol (mmol/l)	2.5 (0.9)	3.2 (1.2)#	<3.5
Triglyceride (mmol/l)	0.9 (0.3)	1.5 (0.9)#	0.3 - 1.5
Triglyceride : HDL ratio	0.8 (0.3)	1.4 (0.9)#	-
Serum insulin (µU/l)	18.9 (9.8)	60.4 (72.3)	10-25

Normal ranges supplied by UP Pathology Department; #= significant correlation with fasting glucose after correlating for age, gender, energy intake and body mass index
(DM2=diabetes; SD=standard deviation; HDL=high density lipoprotein cholesterol)

Table 6.8: Significant correlations between blood lipids and fasting glucose levels in the type 2 diabetes subjects

Correlated for	Total cholesterol	LDL-cholesterol	Triglycerides	Triglyceride: HDL ratio
	r-value	r-value	r-value	r-value
age	0.756*	0.692 *	0.861 ***	0.796 **
gender	0.792 **	0.706 *	0.868 ***	0.758 **
energy intake	0.743 *	0.675 *	0.858 ***	0.770 **
body mass index	0.773 **	0.692 *	0.831 **	0.742 *

***=correlation significant at the 0.05 level; **=correlation significant at the 0.01 level; ***=correlation significant at the 0.001 level; (LDL=low density lipoprotein; HDL=high density lipoprotein)**

6.2.2.8 Serum insulin levels

The mean serum insulin levels of the two groups are given in table 6.7. Although the DM2 group had a higher mean serum insulin level than the control group, this difference was not significant. This is probably due to the small sample size and the large standard deviation in the DM2 group.

6.3 Variables that differed significantly between the two groups

6.3.1 Fasting glucose levels

Since the subjects were divided into DM2 and control groups on the basis of the fasting glucose level (and the postload glucose level), the significant difference (Table 6.9) in fasting glucose levels was expected.

6.3.2 The waist-to-hip ratio

The DM2 group had a significantly higher mean waist hip ratio than the control group. A high waist-hip ratio is an indication of an android fat distribution, which is one of the risk factors for type 2 diabetes. From Table 6.9 it can be seen that the waist-to-hip ratio for the control group is indicative of a gynoid fat distribution for both males and females. In the case of the DM2 group the mean ratio is indicative of an android fat distribution for females, but not for males. Since the group only included three males (with BMI's <24 Kg/m^2), this result shows that the females in this group also had an android distribution of body fat.

Table 6.9: Means and standard deviations of some variables that differed significantly between the type 2 diabetes and control groups

Variable	Control group	DM2 group	Normal range
	mean (±SD)	mean (±SD)	
fasting glucose (mmol/l)*	4.5 (0.6)	13.4 (10.1)	<7.1
waist-hip ratio *	0.75 (0.11)	0.84 (0.06)	for android distribution: females >8.0 males >0.95
total fat intake (g) *	62.6 (25.9)	42.3 (14.4)	-
monounsaturated fat intake (g) *	21.8 (11.0)	13.2 (3.6)	-
serum chloride(mmol/l) **	105.5 (2.5)	101.3 (3.7)	69-106
fibrinogen (g/L) *	3.1 (0.8)	4.3 (1.2)	2.5-3.0

***=significant difference ($p< 0.05$) between the Control and the DM2 groups**
****=significant difference ($p<0.01$) between the Control and the DM2 groups**
(SD=standard deviation; DM2=diabetic)

6.3.3 The total fat intake and monounsaturated fat intake

According to Table 6.9 the DM2 group had significantly lower intakes of total fat and monounsaturated fat. This is in accordance with the dietary results reported in section 6.2.2.6. These results were influenced by the lower energy intake of the DM2 group. In both cases the significance of the difference disappeared after controlling for energy intakes.

6.3.4 Serum chloride

In the literature there is no mention of an association between serum chloride level and the development of type 2 diabetes. In this study the DM2 group had a significantly lower mean serum chloride level than the control group. The mean serum chloride levels of both groups were within normal ranges. The clinical implication of this significant difference for serum chloride levels is not clear.

6.3.5 Plasma fibrinogen

The DM2 group had a significantly higher mean fibrinogen level than the control group, as can be seen in Table 6.9. Both groups had higher fibrinogen levels than the normal range.

6.3.6 Iron status

Table 6.10 gives the means and standard deviations for the variables associated with the iron status of the subjects. From the table it is clear that the DM2 group had a considerably higher serum ferritin level than the control group, despite the fact that the iron intakes, serum iron, total iron binding capacity (TIBC) and percentage saturation of the two groups hardly differed.

The ferritin levels of the two groups did not differ significantly. This may be due to the large variety in serum ferritin levels between individuals in a group (Table 6.11). From this table it can be seen that the serum ferritin levels of the control group are all within normal ranges, but the serum ferritin levels of the DM2 group vary between 32 and 1020. All the DM2 males were lean and in all four cases the serum ferritin levels exceeded 200. All the DM2 females had serum ferritin levels within normal ranges. Increased ferritin levels can be due to an increase in acute phase proteins or to an iron overload. Fibrinogen is also an acute phase protein, and should be increased if ferritin is increased. Table 6.11 shows that fibrinogen was not excessively increased in the four lean diabetic males. Increases in acute phase proteins are associated with decreased levels of albumin. Table 6.11 shows that this is not the case for these four subjects. There were no significant correlations between fibrinogen and ferritin or albumin, or between ferritin and albumin. Thus, it seems as if the increase in ferritin in the four lean male diabetics was not due to an increase in acute phase proteins.

Table 6.10: Means and standard deviations for the variables associated with the iron status of the type 2 diabetes and control groups

Variable	Control group	DM2 group	Normal range
	mean (±SD)	mean (±SD)	
Iron intake* (mg)	10.8 (5.8)	7.9 (2.9)	
Serum iron (μmol/l)	16.9 (5.3)	16.7 (6.0)	10-30
Total iron binding capacity (μmol/l)	67.1 (8.8)	67.6 (12.7)	Males: 54-72 Females: 54-63
Percentage saturation (%)	25.6 (8.2)	25.8 (12.1)	
Serum ferritin (μmol/l)	39.3 (31.6)	275.6 (378.4)	<200

(DM2=type 2 diabetes; SD=standard deviation)

*** = reported intake from food sources**

From table 6.11 it can be seen that the fasting serum insulin levels were only available for two of the four subjects with high ferritin levels. In both cases the insulin levels are higher than normal, however the fasting serum glucose levels of these two subject are only slightly higher than normal. This indicated that the pancreas was still able to secrete insulin and that the diabetes could be associated with liver damage since an iron overload is associated with liver damage. In Table 6.12 the liver enzymes of these two groups are given and in Table 6.13 the serum levels of the liver enzymes are given for the individual subjects. From table 6.12 it can be seen that all the liver enzymes except lactate dehydrogenase (LDH), are higher for the DM2 group than for the control group, but the difference is only significant in the case of AST. T his suggests that certain subjects in the DM2 group may have some degree of liver damage due to the iron overload. However, from table 6.13 it is clear that the first four diabetic subjects, who had high serum ferritin levels, did not have liver damage. Two diabetic subjects (numbers 9 and 10) had high GGT levels, indicating high alcohol intakes. Subjects 9 and 11 had a high AST level indicating liver damage. Thus it seems that in subject 9 the diabetes is due to a high alcohol intake.

Table 6.11: Serum ferritin, albumin and fibrinogen levels and general information on the individual subjects of this study

Group	Number	Gender	BMI (Kg/m^2)	Ferritin (µmol/l)	Albumin (g/l)	Fibrinogen (mg/dl)	Insulin (µU/l)	Glucose 1 (mmol/l)
DM2	1	male	20	509	36.7	4.3	-	4.0
	2	male	18	1020	44.7	5.3	-	8.0
	3	male	17	253	39.0	5.8	19.5	6.2
	4	male	24	938	41.2	2.0	104.5	6.4
	5	female	29	32	42.4	4.8	66.9	28.2
	6	female	28	141	44.1	3.1	26.3	34.6
	7	female	24	33	41.3	4.6	18.7	18.3
	8	female	29	14	42.5	5.9	-	6.5
	9	female	34	48	46.8	4.3	220.4	6.2
	10	female	26	25	44.5	3.1	15.4	14.8
	11	female	34	19	39.6	3.8	11.3	14.7
Control	12	male	19	13	40.1	3.8	8.2	4.8
	13	male	22	57	47.2	-	12.3	4.1
	14	male	18	96	52.7	3.4	-	4.3
	15	male	24	34	43.1	3.3	-	4.4
	16	female	29	29	39.1	2.2	17.4	3.8
	17	female	27	61	44.2	3.7	16.6	3.6
	18	female	31	7	40.8	-	14.2	4.9
	19	female	32	5	40.8	2.8	-	4.5
	20	female	27	88	41.7	2.0	18.0	4.6
	21	female	21	20	39.2	2.6	22.3	4.2
	22	female	34	23	39.1	2.4	40.6	5.9

(DM2=type 2 diabetic group; BMI=body mass index; W:H=waist-hip ratio)

Table 6.12: The means and standard deviations for the liver enzymes of the type 2 diabetes and control groups

Enzyme	Control group	DM2 group	Normal range
	mean (±SD)	mean (±SD)	
Alkaline phosphatase	71.0 (20.1)	89.8 (25.8)	38-120 IU/L
Gamma-glutamyl transferase	26.2 (16.1)	33.5 (21.6)	8-32 IU/L
Alanine amino transferase *	7.9 (2.3)	15.3 (8.1)	6-32 IU/L
Aspartate amino transferase	17.9 (4.7)	42.4 (81.8)	9-34 IU/L
Lactate dehydrogenase	143.4 (20.8)	139.0 (34.6)	90-180 IU/L
Creatine kinase	95.8 (12.1)	78.4 (32.6)	45-165 IU/L

***= significant difference between the control and the DM2 groups (p>0.05)**
(DM2=type 2 diabetes; SD=standard deviation)

Table 6.13: The serum levels of liver enzymes of the individual subjects in this study

Group	Number	ALP (IU/l)	GGT (IU/l)	ALT (IU/l)	AST (IU/l)	LD (IU/l)
DM2	1	57.1	25.3	5.4	24.3	182.0
	2	43.7	16.5	5.4	14.7	179.7
	3	100.2	29.4	6.0	10.3	113.9
	4	65.0	32.3	19.0	15.5	122.6
	5	85.1	16.0	5.5	18.5	122.0
	6	51.6	26.4	4.7	14.2	167.6
	7	119.8	16.2	16.5	13.3	140.2
	8	48.8	11.4	11.0	14.6	92.2
	9	79.3	92.4	31.3	288.4	132.5
	10	85.2	54.4	10.2	14.2	126.7
	11	67.0	11.0	11.0	28.0	184.0
Control	12	101.7	12.8	5.8	18.2	148.8
	13	104.1	44.0	11.0	23.2	124.8
	14	80.8	49.8	8.0	15.8	117.8
	15	84.3	20.7	9.2	21.6	133.5
	16	97.8	21.9	13.2	21.6	130.0
	17	68.8	9.3	7.6	16.0	158.0
	18	97.8	29.6	21.7	27.9	214.6
	19	92.0	27.1	10.8	12.2	108.5
	20	96.1	43.6	24.1	25.8	178.3
	21	48.1	28.8	8.5	12.1	136.7
	22	134.2	39.1	9.1	12.8	133.7

DM2 = type 2 diabetes; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; ALT = alanine amino transferase; AST = aspartate amino transferase; LD = lactate dehydrogenase

6.4 Discussion

6.4.1 Introduction

The objective of the nested case-control study was to characterise the younger subjects (<45 years) who were identified as type 2 diabetics. The diabetic subjects were matched for gender, age, stratum, and BMI. More females than males were diagnosed. Type 2 diabetes developed in young lean males, but also in young lean females. However, not all the females were lean. According to the literature, diabetes in young subjects may be due to genetic factors and/or obesity (Rosenbloom, *et al.*, 1999). In African Americans type 2 diabetes in the young is associated with obesity, but in this study population it seems as if obesity played a role in only some females.

6.4.2 Factors that did not differ significantly

Some of the known risk factors for the development of type 2 diabetes did not differ significantly between the DM2 and the control groups. This may be due to the small sample size. Another explanation may be that these risk factors are not important in this sample, especially in the light of the possibility of diabetes due to an iron overload and possible liver damage in some subjects. In certain cases the data were reported by the subjects and are, therefore, subject to bias. This includes smoking, physical activity level and diet. The fact that the controls were matched for age, gender and stratum, could probably have influenced some of the factors discussed below.

*** Smoking**

Smoking did not differ significantly between the DM2 group and the control group. The females as a group smoked less than the males.

*** Physical activity**

Physical activity was not significantly lower in the DM2 group than in the control group. This could be explained by the fact that the controls were matched for age, gender and stratum, factors that probably influenced activity levels.

*** Blood pressure**

Blood pressure of the diabetic subjects would be expected to be higher than in the nondiabetic subjects. Both hypertension (HT) and type 2 diabetes increase with age. Therefore, the young age of the subjects could explain why HT had not yet developed in these subjects. Selection criteria of all subjects could have been responsible. Only "apparently healthy" subjects without known HT or diabetes were recruited.

*** Anthropometry**

The DM2 group did not have a significantly higher waist circumference, triceps skinfold, subscapular skinfold and abdominal skinfold than the control group due to the fact that one of the criteria used to match the control subjects was BMI. The waist-hip-ratio differed significantly ($p<0.05$) between the two groups, indicating that android fat distribution was a marker for the development of type 2 diabetes in these subjects.

*** Diet**

The total energy intake for both the control and the DM2 groups was within the normal ranges. It seems as if the two groups followed similar diets, suggesting that diet was not an important risk factor for the development of type 2 diabetes in this study population. The higher blood vitamin levels in the DM2 group suggest that the diabetic group had a "healthier" diet than the control group, (except for reported lower fibre intakes). A high fibre intake may have a protective role against the development of the disease. However, a low fibre intake, against the background of the lower fat intakes of the DM2 group, was probably not an important risk factor. The low intake of total fats may also explain why the blood cholesterol, HDL-cholesterol and LDL-cholesterol levels did not differ significantly in these two groups.

*** Blood lipids**

The absence of significant differences for triglyceride, LDL-cholesterol and total cholesterol levels between the control and DM2 groups support the theory that lipid abnormalities develop as a complication of type 2 diabetes and that it is not a strong marker for the development of the disease. Low HDL-cholesterol levels are associated with type 2 diabetes. In these subjects the higher HDL-cholesterol levels in the DM2 group, although not significant may also be explained by the fact that the diabetic subjects were newly diagnosed, and that complications were only starting to develop.

The triglyceride-HDL ratio is used as a marker for the metabolic syndrome. Since the DM2 group and the control group did not have significantly different triglyceride-HDL ratios, type 2 diabetes may not be associated with the metabolic syndrome in these subjects.

*** Serum insulin levels**

The higher serum insulin levels in the DM2 group compared to the control group, although not significant, shows that in the DM2 subjects the pancreas was still able to secrete insulin, and that IR was probably present. This can be explained by the fact that only newly diagnosed diabetic subjects were included in this study. It seems as if the pancreatic beta-cells in these subjects were not totally exhausted and still capable of secreting insulin. The higher insulin in the DM2 subjects

could reflect insulin resistance, indicating that these DM2 subjects were either at an early stage of the disease, or that they had secondary diabetes.

6.4.3 Factors that differed significantly between the two groups

* Fasting blood glucose

Fasting blood glucose level was the main criterium used to divide the study population into diabetic and control groups and therefore differed significantly.

* The waist-to-hip ratio

The significantly higher waist-hip ratio of the DM2 group indicates that android distribution of body fat was a marker for the development of type 2 diabetes in these subjects. Other indicators of android fat distribution such as the subscapular skinfold, triceps skinfold, abdominal skinfold and waist circumference did not differ significantly between the two groups, and it may be that in this study population these skinfolds and waist circumference are not good indicators of an android fat distribution. The waist-hip ratio for the control was indicative of a gynoid fat distribution. In the DM2 group there were four males and two females with a BMI of <25 Kg/m^2. In these individuals fat distribution, rather than total body fat was thus a better marker for type 2 diabetes.

* The total fat and monounsaturated fat intake

Although total fat and monounsaturated fat intakes were significantly lower in the DM2 group than in the control group, the significance disappeared after controlling for energy intakes. The DM2 group also did not have a significantly lower percentage of energy from fats. These results confirmed that macronutrient intakes were probably not related to the development of diabetes in these subjects.

* Fibrinogen levels and the iron status of the two groups

A high plasma fibrinogen level has been observed in many studies on diabetic patients (reviewed by Vorster *et al.*, 1999). It is also associated with the metabolic syndrome (Vorster, *et al.*, 1998). Several studies have shown that Africans (Vorster *et al.*, 1997) and Afro-Americans (Folsom, 1992) have higher fibrinogens than other racial groups. In this study the control and DM2 groups both had fibrinogen levels above the normal ranges. Fibrinogen and ferritin are both acute phase proteins and increase in response to trauma, infection, necrosis, tumours or other inflammatory events. They also play a part in nonspecific defence mechanisms and in immunopathological processes (Kumar, *et al.*, 1996, 132). If fibrinogen increased because it is an acute-phase protein,

ferritin levels should also be elevated. In this study the ferritin levels of the DM2 group were higher than that of the control group, but this difference was not significant. It is unlikely that the high fibrinogen observed was due to an acute phase response, because oral temperatures of the subjects were normal. Furthermore, increases in the acute phase protein levels are associated with a decrease in the albumin levels, because during infection there is a diversion of protein synthesis away from somatic and circulating proteins such as albumin towards acute phase proteins (Kumar, *et al.*, 1996, 132). In this study the albumin levels of the DM2 group were not significantly lower than in the control group (42.5 and 42.0 g/L respectively).

The difference in the mean serum ferritin levels of the control and the DM2 groups were not significant. Extremely high ferritin levels were observed in the four young males in the diabetic group. The increase in ferritin may be an indication of an iron overload (Kumar & Clark, 1996). The dietary information shows that the DM2 group had lower iron intakes than the control group, but the measurement of the iron intake in this study only included the food eaten by the subjects and not the method of preparation or the cooking utensils that were used. It has been known that many rural male Africans ingest more than 100mg of iron/day in beer which is brewed in iron containers (Isaacson, *et al.*, 1961; Klöppel & In"t Veld, 1997, 304). In these individuals the prevalence of diabetes is ten times more than in African males who do not consume alcoholic beverages (Isaacson, *et al.*, 1961). This may be due to iron deposits in the beta-cells that interferes with the biosynthesis of insulin.

This type of diabetes is associated with hemochromatosis characterised by increased serum iron levels, reduction in total iron binding capacity and transferritin saturation of >60%. None of these characteristics were found in this study. This suggests that the diabetes in these subjects may not be associated with hemochromatosis. In hemochromatosis liver biochemistry may be normal. In this study the DM2 group had normal levels for all the tested liver enzymes, except for increased aspartate amino transferase which differed significantly from the control group. This is indicative of liver damage. The DM2 group also had higher levels of alkaline phosphatase, gamma-glutamyl transferase, alanine amino transferase and aspartate amino transferase than the control group. Although these differences were not significant, it may have clinical importance in that it suggests that these subjects may be beginning to show the signs of liver damage. The individual levels of the liver enzymes for these subject showed that the four subjects with the high ferritin levels did not have liver damage. In these cases the diabetes could be due to an early phase pancreatic damage. The fasting serum insulin and glucose levels suggested that these subjects could have IR. The IR could be the result of insulin receptor down regulation or to other unknown factors. In at least one

of the diabetic subjects (number 9) the diabetes seems to have been the result of a high alcohol intake.

If the increased ferritin levels in these lean males were not the result of an increase in the ingestion of iron these subject may have a genetic defect in the mechanisms that control the absorption or storage of iron in the body. The results of this study indicated that hyperglycaemia in some young African males are associated with high serum ferritin levels.

CHAPTER 7
COMBINED DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

7.1 Limitations of the study

Certain problems occurred during the performance of the study. Although the subjects were instructed to arrive fasting at the test site, not all subject were in a fasting state. It was soon realised that in the culture of these African subjects, "fasting" means no large meal should be consumed. Having tea or any other drink or even a snack such as a fruit or a cookie is not regarded as a meal. Therefore, attempts were made to emphasise that *nothing* should be drank or eaten for 8-12 hours preceding the test. With recruitment of subjects details about the fasting period were noted. Therefore, in the analysis of the results of the total sample (see Chapter 4) the fasting state could be categorised as 1, 2 or 3 and controlled for. However, for the first 728 subjects, these details were not available. Another problem that was related to the subjects was that in the first phase of the study some subjects had to leave the test site before the 120 minute glucose tolerance test was completed, and in these cases the postload blood sample was drawn 15 minutes before 120 minutes after ingestion of the glucose load. Due to these limitations it was not possible to diagnose diabetic subjects from the first phase of the study. Therefore the study group was divided into normal glucose tolerance (NGT), glucose intolerance group 1 (GIT1) and glucose intolerance group 2 (GIT2). Only subjects who were truly fasting and whose postload blood samples were drawn at precisely 120 minutes were included in the nested case-control study. It was possible to diagnose diabetic subjects, and to select a control subject to match each diabetic subject for age, gender, body mass index (BMI) and the stratum in this study (Chapter 6).

Insulin levels were not determined for all the subjects in the case-control study and because the fasting state of many subjects in the exploratory study was doubtful, it was not possible to calculate insulin resistance (IR) in these subjects. It is therefore also not possible to make any conclusions about the ability of the pancreas to secrete insulin or about the ability of the body to respond to the insulin in the blood.

Certain information was gathered from each subject with the aid of questionnaires. The results are therefore subject to bias. If both practicality of the method and reliability of the results are taken into account, questionnaires are the best method to gather this information from the subjects. Great care was taken to ensure that these questionnaires were validated in this population group and completed as accurately as possible. In many cases, such as for the dietary questionnaire, subjects were interviewed in a language of their choice, and in the case of the other questionnaires a translator was always available to ensure that the subjects really understood the questions. Nevertheless, the results on family history, dietary intakes, physical activity, smoking and the consumption of alcohol are "soft data" and subject to bias.

The fact that this was not a total random sample could be interpreted as a limitation. The study was, however, not designed to measure incidence or prevalence of type 2 diabetes or its risk factors, but to determine the influence of urbanisation on these risk factors and their associates in "apparently healthy" individuals. This design permits conclusions on how the changes in the lifestyle that are associated with urbanisation or westernisation or modernisation influence the risk factors and markers of type 2 diabetes mellitus. The unique way in which subjects were recruited to participate in the study could also have influenced the risk factors that were found to be associated with GIT and type 2 diabetes. Another possible limitation of the study is the small amount of individuals in each stratum and category.

7.2 Discussion

The first objective of this study was to examine the impact of urbanisation on the risk markers of GIT and type 2 diabetes mellitus and to investigate the influence of changes in the lifestyle during urbanisation. The results indicated that in both men and women the 120 minute mean serum glucose levels of subjects from the upper urban stratum and from the farm workers were significantly higher than those for the other strata. The results further showed that the effect of urbanisation on the risk markers of GIT and type 2 diabetes was modulated by certain lifestyle factors and that these lifestyle factors were not the same for males and females. Thus, changes in certain lifestyle factors that occur during urbanisation have a negative effect on the glucose tolerance contributing to the development of GIT and ultimately type 2 diabetes.

The second objective of this study was to characterise the occurrence and levels of the known risk factors for GIT and type 2 diabetes in the sample population. According to the results the pattern of risk factors for GIT and type 2 diabetes in this sample population differed from other populations. The pattern of risk factors was also not the same for the males and females in this sample. This could be due to healthy obesity in the females, the absence of obesity in the males and the fact that even the most urban subjects did not follow a Western diet (less and 30% of the total energy intake were derived from fats). Malnutrition regarding certain micronutrients may also explain these results.

The third objective of this study was to describe the unique characteristics of subjects that were identified with type 2 diabetes at a relatively young age (<45 years). The results indicated that in the young males the diabetes or glucose intolerance was probably the result of an iron overload, in which case they do not have type 2 diabetes but glucose intolerance due to an iron overload. In the young females the diabetes was probably the result of obesity. The relative absence of obesity in the males could explain why obesity did not present as a risk marker for type 2 diabetes in young males. Another important finding of this study is that young African diabetics do not seem to have developed the cardiovascular complications associated with diabetes at this early stage. However, the results suggest that these complications may already be present in their early stages. For instance, fibrinogen is a risk factor for the development of stroke, coronary heart disease and other cardiovascular complications. Therefore, the higher fibrinogen levels of the diabetic subjects may indicate that these subjects are more susceptible to these conditions than the normal population. This is supported by the lipoprotein profile of the diabetic subjects.

The results from this study showed that the risk factors for type 2 diabetes differ for males and females. Age was shown to have a more pronounced effect on the development of type 2 diabetes and glucose intolerance (GIT) in females than in males. In Chapter 4 it was shown that in the males physical activity influenced the effect of urbanisation on the development of type 2 diabetes. Physical activity does not seem to be important for the females. However the females as a group were obese and it has been shown that in this study population there is a strong relationship between obesity and a decrease in physical activity (Kruger, 1999). Waist-to-hip ratio seems to be important in the females (Chapters 4 and 5), and in the older males (Chapter 5). This could be explained by the fact that very few of the young males were obese or overweight. Although the urban subjects are following a more Westernised diet, at this point in time (despite obesity)

it is still a prudent diet. The macronutrient does not seem to play an important role in the development of type 2 diabetes or GIT at this stage, but some deficiencies in micronutrients may affect the development of these conditions. Kruger (1999) showed that obesity in this study population was related to physical activity rather than to the diet. The effect of smoking is not clear. The results from Chapter 4 showed that smoking affected the effect of urbanisation on type 2 diabetes and glucose intolerance (GIT) in females, but not in males. The results from Chapter 5 showed that smoking had a more pronounced effect on the development of GIT in males than in females. More research in this field is necessary. Both Chapters 4 and 5 indicated that the pattern of risk factors in this African study population differs from that of other populations, as reviewed in Chapter 2.

7.3 Conclusions

From the results it can be concluded that:

* The effect of urbanisation or modernisation on the development of type 2 diabetes is dependent upon interrelationships between genetics and certain lifestyle factors and their effects, such as age, smoking habit, BMI, physical activity level, and waist-to-hip ratio. The Western diet associated with urbanisation is expected to increase the risk for the development of type 2 diabetes and GIT. In this study the increases in fat and animal protein intakes with urbanisation are indicative of westernisation of the diet. However, the diet still fell within the limits of the prudent diet (< 30% of energy as fat). With urbanisation fibre and micronutrient intakes improved, suggesting an actual improvement in the diet of these subjects. In rural areas obese females consumed more than enough energy, but not enough micronutrients. Thus, in this study population there are two powers in the diet that have opposite effects on the risk for type 2 diabetes. The macronutrients have a moderate negative effect on the risk for diabetes while the improvement in fibre and micronutrient intakes have a protective effect on the risk for diabetes. The two balance each other, masking the effect of diet and urbanisation on the development of type 2 diabetes and GIT in this study sample. The increase in BMI is the result of the balance between energy intake and expenditure (physical activity). Although reported energy intakes did not increase, physical activity decreased with urbanisation. This may explain why BMI was not a strong risk marker for these conditions in this population.

* All of the known risk factors for type 2 diabetes did not contribute to the development of the disease during urbanisation in an equal way. There were strong indications that the risk factors for males and females were different. During modernisation physical activity level seemed to be important in males, while insulin levels seem to have a stronger influence in females together with other risk factors such as age, smoking habit and waist-to-hip ratio. It can be expected that with increasing urbanisation the prevalence of GIT and type 2 diabetes in the African population will increase due to lifestyle-related changes during the urbanisation process.

* Diabetes secondary to liver damage does still occur in African males, even at a young age (<45 years). Obese females can be expected to develop type 2 diabetes at a young age (<45 years). This is important in the light of the high levels of obesity in African females.

7.4 Recommendations

7.4.1 Further research

Further studies in this field are important to help identify high risk individuals for type 2 diabetes in this population. From the preceding discussion it appears that future research on type 2 diabetes in Africans should:

- Investigate the effect of urbanisation on the development of GIT and type 2 diabetes in males and females separately, with special emphasis on the effect of lifestyle-related factors on this relationship.
- Determine the most important risk factors or markers for the development of GIT and type 2 diabetes in Africans, keeping in mind that males and females may not have the same risk factors or markers.
- The interesting results on iron overload in a subgroup of young males diabetics should be further investigated in future research projects.
- Determine the iron intake not only form foods eaten, but also from the method of preparation and the utensils used.
- Investigate possible associations between type 2 diabetes and iron metabolism and intakes in the African population, especially in young, lean diabetic males.

- It is necessary to determine if a decrease in the iron intake in lean male diabetic subjects with increased ferritin levels will result in a decrease of the ferritin levels and if this will result in a reversal or improvement in the glucose intolerance (GIT) that is associated with diabetes. In this study damage to the liver and pancreas should also be determined.
- Investigate the observation that many obese females did not develop type 2 diabetes, and the possible role of healthy obesity in this population.

7.4.2 Applications of the research

The results of this study indicated that:

- When screening for type 2 diabetes, the risk profile of the males and females may be different.
- In the development of preventive programmes, special attention has to be given to the different risk factors or markers for males and females. Thus, a preventive approach that will be very successful for females, may not have good results for males and *vice versa*.
- In lifestyle-related treatment modalities of type 2 diabetes it may also prove useful to develop different programmes for males and females, each concentrating on the specific risk factors that are of great importance in the development of the disease.
- Health workers and other medical professionals need to test the serum ferritin levels in young, lean males who develop type 2 diabetes. The iron intake of these individuals should also be determined taking into account not only the iron present in the food, but also iron transferred to the food by cooking methods or utensils.

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Addendum 1

Potchefstroomse Universiteit
vir Christelike Hoër Onderwys

The THUSA project:

information for participating clinic sisters

Dear Sister

Thank you for being willing to help us in organising this very important project. We are sure that the project will contribute to improved health of all the people of the North West Province.

The aim of the project is to get enough information regarding level of urbanisation, eating patterns, life-style and certain health indicators, to plan appropriate health and nutrition intervention strategies.

For the baseline survey, which will be done from February 1996 to March 1997, we need 2500 subjects who must be representative of the African population of the North West. These subjects will be drawn in matched groups from randomly selected traditional rural areas, from farms, from squatter camps, from urban towns and cities and also from professional people. Therefore, 500 subjects from 5 different levels of urbanisation. To control for seasonal influences, we will examine only a quarter of each group (± 128 subjects) during a specific visit. A visit will be from a Monday morning 08:00 to Friday afternoon 12:00. During each visit, we would like to get subjects from 4 different areas or points (around a clinic for example). Therefore, 32 subjects from four different places in your area. In total, the 128 subjects measured during our visit to your area, must include:

- 64 men, aged 15-65
- 64 women, aged 15-65

We would appreciate it if the ages are evenly distributed, as follows:

12 or 13 men or women in each 10 year span: 15-25; 25-35; 35-45; 45-55; 55-65.

What do we need from you?

1 To help us to set up the survey in your area. We will visit you for final arrangements at least two weeks before the field visit (survey) date. You must please help to identify the places where we can get subjects to participate.

2 We would need 2 or 3 rooms either in a clinic, hospital, school or other building to work in. If possible, also ± 5 tables and 10 chairs.

- A nurse or another leader in the community to help with the motivation and recruitment of healthy subjects. In other words, to explain the project to the subjects in their mother-tongue and to get signed informed consent to take a blood sample. To ask subjects to bring their ID with them.

- A nurse (one or more) to help with the taking of the blood samples. We will show the nurse exactly how the sample should be taken. We will centrifuge the sample and do all other measurements ourselves.

- Please note, we **will not test for HIV or AIDS.** Sterilised disposable needles, syringes and gloves will be used.

- Additional subjects for every diabetic and people suffering from diseases will have to be recruited.

- If possible, a nurse to assist with the blood pressure measurements.

- We have motivated for funds to pay an honorarium to all helpers. If these funds realise, we plan to pay R10 per hour per helper.

We will visit your area on the following dates:

..... for preliminary talks and arrangements of main visit

..... for actual survey

- While in your area, we will be staying at .....

- Please call (0148) 299 2481 or 299 2469 for further information.

Kind regards

PROF HH VORSTER

Potchefstroomse Universiteit
vir Christelike Hoër Onderwys

The THUSA project:

information for participating subjects

- **What is the THUSA project?**

THUSA stands for Transition, Health and Urbanisation of South Africans. In the project the effects of a change in eating patterns and life-style on health during the movement from rural to urban areas will be monitored. The main aim is to plan appropriate interventions that will ensure good health for all. During the baseline survey from February 1996 to March 1997, health indicators and eating patterns of Africans living in remote rural areas, on farms, in squatter camps and established towns and cities in the North West Province will be measured.

- **Why is the project so important?**

In all developing countries, the transition from rural to urban life-styles has been characterised by an increase in the diseases of overnutrition such as obesity, diabetes, high blood pressure, stroke, heart disease and certain forms of cancer. We know that it is possible to alleviate **hunger** and **undernutrition** and at the same time to **prevent** overnutrition, if people are helped to make the right food choices.

In this project we want to analyse the situation in the North West so that our Department of Health and Developmental Social Welfare will know which strategies to follow to ensure optimal nutrition and health for all. Therefore, by participating in this project, you will help all the people of the North West.

- **What will be measured in the project?**

  - Eating and drinking habits - food and nutrient intakes
  - Socio-economic background
  - Medical history
  - Activity levels
  - Smoking habits
  - Weight, height, waist, hip and arm measurements
  - Clinical signs of malnutrition (appearance of hair, skin, eyes, thyroid)
  - Blood sample: markers of nutritional status and disease. Please note, **NO** HIV or AIDS testing
  - Urine sample: excretion of minerals
  - Blood pressures
  - Diabetes

- **Who may participate?**

  Healthy Africans living in the North West Province who are between 15 and 65 years of age. People will be asked to participate and may refuse. Therefore, only **volunteers** will be asked to sign the informed consent form to participate.

- **What are the benefits for you?**

  Many health and nutritional status indicators of yourself will be measured. You will receive feedback during which a member of the investigation team will explain your health risk to you. You will receive dietary advice and will be referred to your clinic or doctor if necessary

- **What do we expect from you?**

  - Please bring your ID; we need to know your birth date.
  - We will appreciate it if you will report fasting on the day of your participation. It means that for 10 - 12 hours before your blood sample is taken, you must not eat or drink anything but pure water.
  - You will be asked to sign a form giving consent to participate in the project.
  - We will ask you a number of questions regarding your health, age, income, family, smoking and drinking habits, etc.
  - Then you will receive a **number** for the project.
  - You will be weighed and measured.
  - We will take your blood pressure to determine stroke risk.
  - You will be asked to give us a urine sample
  - We will then take a blood sample with a thin, sterilised butterfly needle and a number of small sterile syringes.
  - Your temperature will be taken (orally).
  - Your finger will be pricked twice to measure blood sugar. You will also be asked to drink a sugar cool drink.
  - You will be questioned in detail about your eating habits.
  - Every third person will be asked to participate in a blood pressure project.
  - You will receive journals to read while you wait!
  - If you have any questions about the project, please do not hesitate to ask any one of the field workers.

Thank you for your participation!

ESTé VORSTER

Addendum 2

THUSA PROJECT : PU FOR CHE
RECRUITMENT AND INFORMED CONSENT FORM

Title of the project: Nutritional and health status of Africans in transition

Name: ..... No.....

Address: .....

Tel no:.....

Age: .....

Are you pregnant? .....

Are you lactating? .....

Do you suffer from diabetes? hypertension? Other disease?.....

When did you have your last meal?

.....

or anything but water to drink? .....

Addendum 3

INFORMED CONSENT

I, the undersigned .....
(full names in print), have read the details of the project or, have listened to the oral explanation thereof, and declare that I understand it. I have had the opportunity to discuss relevant aspects with the researcher and declare that I voluntarily participate in the project. I hereby give consent to participate in the project.

.....
Signature of volunteer

Witnesses

....

Signed at ..... on .....

For subjects under the age of 21, signed consent of a parent or legal guardian is necessary.

I, ... (full names) the parent/legal guardian of the person named above, hereby consent that he/she may participate in the THUSA project.

Signature ..... Date .....

Relationship .....

Addendum 4

Potchefstroomse Universiteit vir Christelike Hoër Onderwys

THE THUSA PROJECT

Subject name:_____ No:_____ S:_____

		CHECK / CONTROL
STATION 1	RECRUITMENT DEMOGRAPHIC QUESTIONNAIRE	
STATION 2	CLINICAL EXAMINATION Blood pressure	
	Oral temperature	
	Thyroid	
	Hair	
	Skin	
	Eyes	
	Blood sample YES NO	
STATION 3	ANTHROPOMETRY	
STATION 4	DIETARY QUESTIONNAIRE	
STATION 5	URINE SAMPLE	
STATION 6	GLUCOSE TOLERANCE	t_0 = t_{120} =
STATION 7	STRESS TESTS	
STATION 8	FOOD SECURITY QUESTIONNAIRE	
STATION 9	PHYSICAL ACTIVITY QUESTIONNAIRE	
STATION 10	ATTITUDE QUESTIONNAIRE (WOMEN ONLY)	
STATION 1	BACK TO CHECK / CONTROL	_____ SIGNATURE
LUNCH		
STATION 11	PSYCHOLOGICAL TESTS	

Addendum 5

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Subject number			
Date	D	M	Y
Place			
Interviewer			

Home address _____

_____

_____

_____

Sex	Male	1
	Female	2

Age				
Date of birth	D	M	Y	

First Language	Tswana	1
	Afr	2
	Eng	3
	Xhosa	4
	Zulu	5
	Other	6

Second Language	Tswana	1
	Afr	2
	Eng	3
	Xhosa	4
	Zulu	5
	Other	6

What is your marital status?	Never married	1
	Married	2
	Divorced	3
	Widowed	4

Do you suffer from:			
	High blood	Yes	1
		No	2
	Diabetes	Yes	1
		No	2
	CHD	Yes	1
		No	2
	Stroke	Yes	1
		No	2

Does anyone in your family suffer from:			
	High blood	Yes	1
		No	2
	Diabetes	Yes	1
		No	2
	CHD	Yes	1
		No	2
	Stroke	Yes	1
		No	2

Do you take medicine regularly?			
		Yes	1
		No	2
If yes - what do you take?			

Do you snuff?			
		Yes	1
		No	2
Do you smoke?		Yes	1
		No	2
If no - have you smoked regularly before?		Yes	1
		No	2
If yes - what do you smoke?		Cigarettes	1
		Tobacco/pipe	2
		Other	3
If other - describe			
How much do you smoke?	per day		
	per week		
For how long have you been smoking (years)			
Calculate pack years			

What is your highest qualification?	None	1
	< St.6	2
	St. 6-8	3
	St. 6-8 + trade	4
	St. 9-10	5
	St. 9-10 + trade	6
	St. 9-10 + academic	7

What is your occupation?	

Do you have a job at the moment?	Yes	1
	No	2

If yes - what kind of job?	

On which days of the week do you work?	Irregular (piece work)	1
	Part time (1-4 days)	2
	Full time (5-6 days)	3

How much money do you earn? Is it between...	R0-100	
	R101-500	
	R501-1000	
	R1000-2000	
	R2000-3000	
	R3000+	

What is the source of this income?	

Do you receive any additional pensions?	Yes	1
	No	2

How much pension do you receive per month? _____

Interviewer - *Re-evaluate final income category*	R0-100	1
	R101-500	2
	R501-1000	3
	R1000-2000	4
	R2000-3000	5
	R3000+	6

Who else contributes money to your household? How much?

Yes	1
No	2

_____

_____

_____

_____

Who else contributes other resources eg. food, sharing work/chors to your household? - specify!

_____
_____
_____
_____

Yes	1
No	2

Does any member of your household have the right to use any property as his/her own?	Yes	1
	No	2

What type of property?	

How do you use it?	

Please name the members of your household

Member	Age	Education	Present job

What type of house do you live in?	Traditional	1
	Mokuku	2
	Brick house	3
	Other	4
Specify other		

Do you share a toilet with other households?	Yes	1
	No	2

What type of toilet do you have?	Communal	1
	None	2
	Bucket system	3
	Outside longdrop	4
	Outside chemical	5
	Outside water flush	6
	Inside water flush	7

Where do you get your drinking water from?	Fountain, river	1
	Communal tap	2
	Tap on premises	3
	Tap in house	4
	Other	5
If other specify		

Do you have access to electricity inside your house?	Yes	1
	No	2

What type of stove do you have?	None	1
	Coal/wood	2
	Gas or parrafin	3
	Electric	4

What type of fridge do you have?	None	1
	Parraffin	2
	Gas	3
	Electric	4

How long have you been living here? (years)	

Where did you live before coming here?	Rural area	1
	Farm	2
	Squatter camp	3
	Township	4

Addendum 6

Subject number_____ **Interviewer**_____

QUANTITATIVE FOOD FREQUENCY QUESTIONNAIRE

INTRODUCTION:

Greeting

Thank you for giving up your time to participate in this study. I hope you are enjoying it so far. Here we want to find out what people living in this area eat and drink. This information is important to know as it will tell us if people are eating enough and if they are healthy.

Please think carefully about the food and drink you have consumed during the past four weeks. I will now go through a list of foods and drinks with you and I would like you to tell me:

- if you eat the food
- how the food is prepared
- how much of the food you eat at a time
- how many times a day you eat it and if you do not eat it every day, how many times a week or a month you eat it.

To help you to describe the amount of a food you eat, I will show you pictures of different amounts of the food. Please say which picture is the closest to the amount you eat, or if it is smaller, between sizes or bigger than the pictures.

THERE ARE NO RIGHT OR WRONG ANSWERS.

EVERYTHING YOU TELL ME IS CONFIDENTIAL. ONLY YOUR SUBJECT NUMBER APPEARS ON THE FORM.

IS THERE ANYTHING YOU WANT TO ASK NOW?

ARE YOU WILLING TO GO ON WITH THE QUESTIONS?

INSTRUCTION

Circle the subject's answer. Fill in the amount and times eaten in the appropriate columns.

I shall now ask you about the type and the amount of food you have been eating in the last few months. Please tell if you eat the food, how much you eat and how often you eat it. We shall start with maize meal porridge.

Do you eat maize meal porridge? YES 1 NO 2

If YES, what type do you have at home now?

Brand name_____

Don't know_____2

Grind self_____3

If brand name given, do you usually use this brand YES 1 NO 2 DON'T KNOW 3

Where do you get your maize-meal from? (May answer more than one)

Shop ☐ 1

Employer ☐ 2

Harvest and grind self ☐ 3

Other - specify _____ ☐ 4

Don't know ☐ 5

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
Maize-meal porridge	Stiff (pap)						e4225 4250	
Maize-meal porridge	Soft (slappap)						e4225 4250	
Maize-meal porridge	Crumbly (phutu)						e4225 4250	
Ting								
Mabella Coarse Fine Rice	Stiff						4082	
Mabella	Soft						4082	
Oats							4032	

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
Breakfast cereals	Brand names of cereals at home now: (5) Don't know							

Do you pour milk on your porridge or cereal? YES 1 NO 2

If YES, what type of milk (whole fresh. sour, 1%, fat free, milk blend.)_____

INSTRUCTION: Show subject examples.

If YES, how much milk?								

Do you pour sugar on your cereal/porridge/mabella YES 1 NO 2

If YES, how much sugar?							9012	
Samp	Bought Self ground						4077 4073	
Samp and beans							A014	

Are the amounts of samp and beans the same as in the picture? YES NO

If no, do you use more beans than in the picture or less? MORE LESS

Samp and peanuts							A013	

Are the amounts of samp and peanuts the same as in the picture? YES NO

If no, do you use more peanuts than in the picture or less? MORE LESS

Rice	White Brown Maize rice						4040 4134 4043	
Pastas	Macaroni Spaghetti Other:						4062	

You are being very helpful. Can I now ask you about meat?

CHICKEN, MEAT, FISH

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
Chicken	Boiled						1521	
	Fried: in batter/crumbs Not coated						1634 1520	
	Roasted/grilled						1520	
Do you eat chicken skin	ALWAYS 1	SOMETIMES 2	NEVER 3					
Chicken bones stew							A003	
Chicken feet							A004 1689	
Chicken offal							1610	
Red meat:	How do you like meat? With fat Fat trimmed							
Red meat	Fried							
	Stewed						A001	
	Mince with tomato and onion						1585	
Beef Offal	Intestines: boiled, nothing added						1616	
	Stewed with vegetables							
	Liver						1515	
	Kidney						1518	
	Other specify:							
What vegetables are usually put into meat stews?								
Wors / sausage	Fried						1526	
Bacon							1501	
Cold meats	Polony						1514	
	Ham						1564	
	Viennas						1531	
	Other - specify							
Canned meat	Bully beef						1535	
	Other specify:							
Meat pie	Bought						1548	
Hamburger	Bought						A015	

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
Dried beans/peas/ lentils (10)	Soup Salad						3033 3508	
Soya products eg. Toppers	Brands at home now (5) Don't know_____ **Show examples**						3527	
Pilchards in tomato/chilli/ brine	Whole						2557	
	Mashed with fried onion						A005	
Fried fish	With batter/crumbs						2509	
	Without batter/crumbs						2523	
Other canned fish	Tuna						2547	
	Pickled fish Other:						2562	
Fish cakes	Fried						2531	
Eggs	Boiled/poached Scrambled Fried						1001 1025 1003	

WE NOW COME TO VEGETABLES AND FRUIT

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
Cabbage	How do you cook cabbage?							
	Boiled, nothing added						8066	
	Boiled with potato and onion and fat						A006	
	Fried, nothing added						A007	
	Boiled, then fried with potato, onion						A006	
	Other: Don't know							

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
Spinach/morogo/ other green leafy	How do you cook spinach?							
	Boiled, nothing added						**8071**	
	Boiled fat added						**8209**	
	Boiled with onion/tomato and fat						**A011**	
	- onion, tomato & potato							
	- with peanuts							
	Other: Don't know							
Tomato and onion 'gravy'	Home made - with fat - without fat						**A012** **A016**	
	Canned						**8221**	
Pumpkin	How do you cook pumpkin?							
	Cooked in fat & sugar						**A010**	
	Boiled, little sugar and fat						**A009**	
	Other: Don't know							
Carrots	How do you cook carrots?							
	Boiled, sugar & fat						**8129**	
	With potato/onion						**A008**	
	Raw, salad						**8015**	
	Chakalaka							
	Other: Don't know							
Mealies/Sweet corn	How do you eat mealies?							
	On cob						**8033**	
	Off cobb - creamed sweet corn - whole kernel						**8034** **8261**	
Beetroot salad	Home made Bought						**8005**	

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
otatoes	How do you cook potatoes?							
	Boiled/baked with skin						8046	
	- without skin						8045	
	Mashed						8187	
	Roasted						8189	
	French fries						8048	
	Salad Other:						8236	
weet potatoes	How do you cook sweet potatoes?							
	Boiled/baked with skin						8057	
	- without skin						8214	
	Mashed							
	Other: Don't know							
lad vegetables	Raw tomato						8059	
	Lettuce						8031	
	Cucumber						8025	
ther vegetables, ecify:								

RUIT:

o you like fruit? YES NO

pples/Pears	Fresh Canned pears						7001 7054	
nanas							7009	
ranges/naartjie							7031	
rapes							7020	
eaches	Fresh Canned						7036 7038	
pricots	Fresh Canned						7003 7004	
angoes	Fresh						7026	

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
ıavas	Fresh Canned						**7021** **7023**	
subject eats canned fruit: Do you have custard with canned fruit:			YES 1		NO 2			
ıstard	Home made Ultramel						**0004**	
'ild fuit/berries	Specify type						**7070**	
ried fruit	Types:							
ther fruit								

READ AND BREAD SPREADS

read/Bread rolls	White						**4001**	
	Brown						**4002**	
	Whole wheat						**4003**	
o you spread anything on the bread?			ALWAYS 1		SOMETIMES 2		NEVER 3	
largarine	What brand do you have at home now? _____ Don't know_____ **Show examples**							
eanut butter							**6509**	
m/syrup/honey							**9008**	
larmite/Fray entos							**9501**	
ish/meat paste							**1512**	

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
Cheese	Type:						**0010**	
Achaar							**A017**	
Other spreads:	Specify							
Dumpling							**4001**	
Vetkoek							**4057**	
Provita, crackers, etc.								
Mayonnaise/salad dressing	Number of spoons_____/ number in family						**6573**	

DRINKS:

Tea							**9514**	
Coffee							**9513**	
Sugar/cup tea or coffee							**9012**	
Milk/cup tea or coffee	What type of milk do you use in tea and coffee?							
	Fresh/long life whole						**0006**	
	Fresh/long life 2%						**0069**	
	Fresh/long life fat free						**0072**	
	Whole milk powder Brand_____						**0009**	
	Skimmed milk powder Brand_____						**0008**	
	Milk blend Brand_____						**0068**	
	Whitener Brand_____						**0039**	
	Condensed milk						**0002**	
	Evaporated milk						**0003**	
	None							
Milk as such	What type of milk do you drink as such?							

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
	Fresh/long life whole						0006	
	Sour / Maas						0006	
Milk drinks Brand	Nestle_____ Milo_____ Flavoured milk_____ Other_____						0023	
Yoghurt	Drinking yoghurt Thick yoghurt						0044 0020	
Squash	SweetO SixO Oros/Lecol with sugar - artificial sweetener Kool Aid Other						9013 9013 9002 9013 9002	
Fruit juice	Fresh/Liquifruit/Ceres						0535	
	Tropica Show examples						0089	
Fizzy drinks Coke, Fanta	Sweetened Diet						9001 9013	
Mageu/Motogo							9562	
Home brew							9516	
Tlokwe							9516	
Beer							9506	
Spirits							9510	
Wine red							9508	
Wine white							9518	
Other specify								

SNACKS AND SWEETS:

Potato crisps							8049	
Peanuts	Raw Roasted						6001 6007	
Cheese curls: Niknaks etc							4076	
Raisins							7022	

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		
Peanuts and raisins							6007 7022	
Chocolates	Name						9024	
Candies	Sugus, gums, hard sweets						9009	
Sweets	Toffees, fudge, caramels						9014	
Biscuits	Type							
Cakes & tarts	Type							
Scones							4029	
Rusks							4160	
Savouries	Sausage rolls Samoosas Biscuits eg bacon kips Other:						1534 4196 4162	
Jelly							9004	
Baked pudding							4181	
Instant pudding							4066	
Ice cream Sorbet							6507 6516	
Other Specify:								

SAUCES / GRAVIES / CONDIMENTS

Tomato Sauce Worcester sauce							9505	
Chutney							9524	
Pickles							8176	
Packet soups							4069	
Others:								

WILD BIRDS, ANIMALS OR INSECTS (hunted in rural areas or on farms)

Wild fruit								

MISCELLANEOUS: Please mention any other foods used more than once/two weeks which we have not talked about:

FOOD	DESCRIPTION	Amount	TIMES EATEN				CODE	AMOUNT/DAY
			Per day	Per week	Per month	Seldom/ Never		

SALT USE:

What type of salt do you use?_____

The next few questions are to find out if you use salt. where you use it and how much you use?

Do you add salt to food while it is being cooked?

Always 1	Sometimes 2	Never 3	Don't know 4

Do you add salt to your food after it has been cooked?

Always 1	Sometimes 2	Never 3

Do you like salty foods eg. salted peanuts. crisps?

Very much 1	Like 2	Not al all 3

Do you use any of the following:

	Name of product	Amount/day
Vitamins/vitamins & minerals		
Tonics		
Health foods		
Body building preparations		
Dietary fibre supplement		
Other: specify		

THANK YOU FOR YOUR COOPERATION AND PATIENCE

GOOD-BYE!

Addendum 7

Potchefstroom University
for Christian Higher Education

QUESTIONNAIRE 3 **THUSA PROJECT**

NO .....

ALL THE INFORMATION OF THIS QUESTIONNAIRE IS CONFIDENTIAL

1. Are you using any form of contraceptive? No- 1/Yes - 2 [ ]

2. If yes, state type [ ]
   1. IUD
   2. Condoms
   3. Other
   4. Pill
   5. Injection

   If 4 or 5 state product name.....

3. At what age did you start using contraceptives? [ ]
   Duration of use? [ ]

4. Has your method of contraceptive changed during this time? [ ]
   No – 1/yes – 2

5. If yes, how and when .....
   .....
   .....
   .....
   .....

6. At what age did you experience your first menstruation? [ ]
   1. < 12
   2. 13-16
   3. > 17

7. What is the date of the first day of your last menstruation?
   day ..... month .....

8. How many days between menstruation? .....
   Phase at present

9. How old were you when your first child was born? ☐
   1. < 24
   2. 25-29
   3. > 30

10. Have you experienced your menopause? No – 1/Yes – 2 ☐

11. If yes, at what age? ☐
   1. Pre
   2. < 50
   3. > 50

12. Have you had a hysterectomy? No – 1/Yes – 2 ☐

13. If yes, at what age? ☐
   1. < 24
   2. 25-29
   3. > 30

14. How many children do you have? ☐

15. What are the ages of your youngest and oldest? Youngest ☐
   Oldest ☐

16. How many of your children were breast fed? ☐

17. How long did you breast fed each child?
   1. ..... 7. .....
   2. ..... 8. .....
   3. ..... 9. .....
   4. ..... 10. ....
   5. ..... 11. ....
   6. ..... 12. ....

18. Have you had any previous problems with your breasts?
   No – 1/Yes – 2 ☐

19. If yes, state what. .....
   .....
   .....
   .....

20. Do you have a family history of breast problems?
   No – 1/Yes – 2 ☐

Addendum 8

Potchefstroom University
for Christian Higher Education

The THUSA project

Feedback to participants

Dear Participant

No. .....

Name: .....

Your tests have shown that

- Everything measured were normal, no signs of disease .....
- You must see your clinic or doctor to check for:
  - goitre .....
  - high blood pressure .....
  - blood sugar (diabetes) .....
  - anaemia .....
  - heart disease .....
- You must try to loose weight .....
- You must include more of the following foods in your diet .....

.....

.....

.....

Thank you for participating in this project.

Addendum 9

PU vir CHO, POTCHEFSTROOM

THUSA STUDY: Physical activity questionnaire

Date: Place: Interviewer:

The information on this questionnaire is confidential

1.	Subject number						(1-4)
2.	Gender	Male	1	Female	2		(5)
3.	What is your main occupation?.....						
	Low level: office work, housework, scholar				1		
	Middle level: factory work, carpentry, farming, hospital nurse, plumber				2		(6)
	High level ("sweat work"): construction work, digging, manual labour				3		
4.	At work I sit	1. never	2. seldom	3. sometimes	4.often	5.always	(7)
5.	At work I stand	1. never	2. seldom	3. sometimes	4.often	5.always	(8)
6.	At work I walk	1. never	2. seldom	3. sometimes	4.often	5.always	(9)
7.	At work I lift heavy loads	1. never	2. seldom	3. sometimes	4.often	5.always	(10)
8.	At work I am tired	1.never	2.seldom	3. sometimes	4.often	5.always	(11)
9.	At work I sweat	1.never	2.seldom	3. sometimes	4.often	5.always	(12)
10.	If you work away from home, how do you get to work/school?				walk	1	
					cycle	2	(13)
					car/taxi	3	
11.	How long does it take you to walk/cycle to work/school? (or to the taxi rank/ bus stop/ train station)				0-15 min	1	
					16-30 min	2	
					31-60 min	3	
					1-2 hours	4	(14)
12.	If you walk or cycle to work/school, what is your usual pace? (or to taxi rank/bus stop/ train station)				casual strolling	1	
					fairly brisk	2	
					brisk/fast	3	(15)
13.	Do you climb stairs often?				yes	1	
					no	2	(16)
14.	If yes, how many flights of stairs do you climb each day? (1 flight = 10 steps)						(17)
15.	How many days per week do you climb steps?						(18)
16.	Do you play sport?				yes	1	
					no	2	(19)
17.	Which sport do you play most frequently?	low level: bowling, golf, billiards				1	0.76*[1]
		middle level: tennis, athletics, cycling				2	1.26
		high level: soccer, rugby, netball, boxing				3	1.76(20)
18.	How many hours per week do you practice?<1/ 1-2/ 2-3/ 3-4/ >4 (Write appropriate code in space) 0.5, 1.5, 2.5, 3.5, 4.5*[2]					.	(21-23)
19.	How many months per year ? <1/ 1-3/ 4-6/ 7-9/ >9 (Write appropriate code in space) 0.04, 0.17, 0.42, 0.67, 0.92*[3]				.		(24-26)

*[1] intensity code of sport, *[2] time code for sport, *[3] proportion of year

20.	If you play a second sport, which is it?	low level: bowling, golf, billiards				1	0.76*[1]
		middle level: tennis, athletics, cycling				2	1.26
		high level: soccer, rugby, netball, boxing				3	1.76(27)
21.	How many hours per week do you practice?	<1/ 1-2/ 2-3/ 3-4/ >4 0.5, 1.5, 2.5, 3.5, 4.5*[2]				.	(28-30)
22.	How many months per year?	<1/ 1-3/ 4-6/ 7-9/ >9 0.04, 0.17, 0.42, 0.67, 0.92*[3]			.		(31-33)
23.	During leisure time I watch TV/ do sitting activities (read, needle-work, play cards)	1.never	2.sel-dom	3.some-times	4.often	5.al-ways	(34)
24.	During leisure time I walk/ do standing activities (gardening, housework)	1.never	2.sel-dom	3.some-times	4.often	5.al-ways	(35)
25.	Other leisure-time activities:..... (leisure-time = time off from work/. school)		2.sel-dom	3.some-times	4.often	5.al-ways	(36)

Definitions and explanation of the questionnaire (interviewer's notes)

Item 1: Write in the subject number as on the name label provided at the recruitment station.
Item 2: Circle gender: male or female
Item 3. Occupation: paid job or unpaid duties for most of the day; including school, housework, childminding
Write in the occupation stated and circle 1,2 or 3 (low level, middle level or high level)

Item 4-9:	never:	⊕:	never, almost never
	seldom:	⊕	one-quarter of the workday or workweek
	sometimes:	⊕	half the workday or workweek
	often:	⊕	three-quarters of the workday or workweek
	always:	⊕	almost all the time

Item 13: If the subject does not climb stairs, go on to question 16.
Item 16: If the subject does not play sport, go on to question 23.
Item 17: Circle 1/2/3
Item 18 and 21: Write time code in space, note decimal point
Item 19 and 22: Write code in space, note decimal point
Item 20: Circle 1/2/3

Item 23-25:	never:	⊕	never, almost never
	seldom:	⊕	one-quarter of off-time, 1-2 days per week
	sometimes:	⊕	half my off-time, 3-4 days per week
	often:	⊕	three-quarters of my off-time, 5-6 days per week
	always:	⊕	almost all the time, mostly 7 days per week

Item 23: sitting activities: watch TV, listen radio, reading, writing, knitting, needlework, playing cards, visiting friends
Item 24: standing activities: gardening, walking with friends, cleaning, cooking, doing laundry, ironing, dishwashing after work at your own home
Item 25: other leisure-time activities: name any other leisure-time activities that you do and how often you do these activities.
NB: *leisure-time* is time after work, school, or housework is finished

Addendum 10

THUSA STUDY – SOUTH AFRICA 1998
ANTHROPOMETRY

Subject ID#

Gender (1 = M, 2 = F)

Projection box + constant

		.	

Skinfolds

Triceps			.				.					.		
Subscapular			.				.					.		
Iliac Crest			.				.					.		
Supraspinale			.				.					.		
Abdominal			.				.					.		
Front Thigh			.				.					.		
Medial Calf			.				.					.		

Girths

Arm - Relaxed			.				.					.		
Arm - Fully flexed/Tensed			.				.					.		
Forearm - Maximum			.				.					.		
Waist - Minimum			.				.					.		
Hip (Gluteal) - Maximum			.				.					.		
Thigh - 1cm below gluteal fold			.				.					.		
Thigh - Mid trio-tib lat			.				.					.		
Calf - Maximum			.				.					.		

Breadths

Humerus (cm)			.				.							
Wrist (cm)			.				.					.		
Femur (cm)			.				.					.		
Ankle (cm)			.				.					.		

Other

Mass (kg)				.	
Stature - Stretched (cm)				.	

Addendum 11

STUDIENOMMER _____ DEEL I

INSTRUKSIE: Skryf die proefpersoon se antwoord in die blokke langs die vraag OF omkring die nommer langs die proefpersoon se antwoord.

VOORBEELD:

1. Hoeveel maaltye het jy gister geëet? Gister=Maan1 Dins2 Woens3 Don4 Vry5 Sat6 Son7				
2.1.1 Omtrent hoe laat het jy jou eerste maaltyd geëet?				
2.1.2 Waar het jy die maaltyd geëet? Huis Werk Ander spesifiseer_____ Nie van toepassing				

Beantwoord asseblief die volgende vrae:

1. Hoeveel maaltye het jy gister geëet? Gister=Maan1 Dins2 Woens3 Don4 Vry5 Sat6 Son7				
2.1.1 Omtrent hoe laat het jy jou eerste maaltyd geëet?				
2.1.2 Waar het jy die maaltyd geëet? Huis Werk Ander spesifiseer_____ Nie van toepassing				1 2 3 4
2.2.1 Omtrent hoe laat het jy jou tweede maaltyd geëet?				
2.2.2 Waar het jy die maaltyd geëet? Huis Werk Ander spesifiseer_____ Nie van toepassing				1 2 3 4
2.3.1 Omtrent hoe laat het jy jou derde maaltyd geëet?				
2.3.2 Waar het jy die maaltyd geëet? Huis Werk Ander spesifiseer_____ Nie van toepassing				1 2 3 4
2.4.1 Omtrent hoe laat het jy jou vierde maaltyd geëet?				

2.3.2 Waar het jy die maaltyd geëet? Huis Werk Ander spesifiseer_____ Nie van toepassing					1 2 3 4
2.5 Eet jy hierdie hoeveelheid maaltye op meeste weeksdae?	JA 1			NEE 2	
INDIEN NEE: 2.5.1 Hoeveel maaltye eet jy gewoonlik per weeksdag?					
2.6 Eet jy jou maaltye op meeste weeksdae op omtrent dieselfde tye as bo?	JA 1			NEE 2	
INDIEN NEE:					
2.6.1 Omtrent hoe laat eet jy jou eerste maaltyd gewoonlik?					
2.6.2 Waar eet jy die maaltyd gewoonlik? Huis Werk Ander spesifiseer_____ Nie van toepassing					1 2 3 4
2.6.3 Omtrent hoe laat eet jy gewoonlik jou tweede maaltyd?					
2.6.4 Waar eet jy gewoonlik die maaltyd? Huis Werk Ander spesifiseer_____ Nie van toepassing					1 2 3 4
2.6.5 Omtrent hoe laat eet jy jou derde maaltyd?					
2.6.6 Waar eet jy die maaltyd gewoonlik? Huis Werk Ander spesifiseer_____ Nie van toepassing					1 2 3 4
2.6.7 Omtrent hoe laat eet jy gewoonlik jou ander maaltye?					
2.6.8 Waar eet jy gewoonlik die maaltye? Huis Werk Ander spesifiseer_____ Nie van toepassing					1 2 3 4

3. Het jy gister enigiets geëet of gedrink voor, tussen of na maaltye ?					J 1	N 2
3.1 **INDIEN JA:** Wat het jy geëet of gedrink en waar en wanneer het jy dit geëet of gedrink?						
Tipe voedsel:	Wanneer? (vroeg oggend , oggend, middag, aand)	Waar?				
INSTRUKSIE: Indien proefpersoon JA op vraag 3 geantwoord het, vra 3.2, indien NEE, VRA 3.3						
3.2 Eet of drink jy enigiets voor, tussen of na maaltye op meeste dae?			JA 1		NEE 2	
3.3 Alhoewel jy niks tussen maaltye gister geeet het, eet of drink jy gewoonlik iets tussen maaltye?			JA 1		NEE 2	
3.3.1 Indien JA, wat eet of drink jy gewoonlik tussen maaltye, en waar en wanneer eet jy dit?						
Tipe voedsel	Waar?	Wanneer?				

4

. Hoe word kos gewoonlik in jou gesin bedien?

Moeder bedien almal op individuele borde	1
Elke bedien hom/haarself om individuele borde	2
Vader bedien almal op individuele borde	3
Volwassenes bedien vir hulself, en skep vir kinders in	4
Almal eet uit 'n gemeenskaplike skottel	5
Volwassenes en kinders eet uit aparte gemeenskaplike skottels	6
Volwassesnes eet uit borde, kinders eet uit 'n gemeenskaplike bord	7

Ander Beskryf bv woon alleen of in 'n koshuis	8

5. Hoe dikwels eet jy by restaurante, 'steak houses', Wimpy, kafees, 'fast-food' winkels, wegneem plekke, padkafees?	
Daagliks	1
Weekliks	2
Maandeliks	3
Selde	4
Nooit	5

5.1 INDIEN DAAGLIKS, WEEKLIKS OF MAANDELIKS, Waar eet jy en wat eet jy gewoonlik?					
Plek (Naam en beskrywing)	VOEDSEL GEËET				

STUDIENOMMER_____ DEEL II

INSTRUKSIE: Omkring die proefpersoon se antwoord. Vul die hoeveelheid en hoeveel keer geëet in gegewe kolomme in.

Ek gaan jou nou uitvra oor die tipe en die hoeveelheid voedsel wat jy eet. Sê asseblief of jy die voedsel eet, hoeveel jy eet en hoe gereeld jy dit eet. Ons gaan begin met mieliemeel pap.

Vir kantoor gebruik

VOEDSEL	BESKRYWING	HOEVEEL-HEID	HOEVEEL KEER GEËET Per dag	Per week	Per maand	Selde	Nooit	KODE	HVHD/DAG
Eet jy mieliemeel pap? JA 1 NEE 2 Indien JA, watter tipe het jy op die oomblik by die huis? Naam van produk_____1 Weet nie_____2 Maal self_____3 Indien die naam van die produk gegee is: Gebruik jy gewoonlik die produk? JA 1 NEE 2 WEET NIE 3 Waar kry jy jou mieliemeel vandaan? (Mag meer as een antwoord gee) Winkel 1 Werkgewer 2 Oes en maal self 3 Ander - spesifeer 4 Weet nie 5									
Mieliemeel pap	Styf (pap)							e4225 4250	
Mieliemeel pap	Slap							e4225 4250	
Gooi jy melk oor jou slappap? JA 1 NEE 2 INDIEN JA, watter tipe melk (volroom vars, suur,vetvry, 2%, melk mengsel)_____ INSTRUKSIE: Wys die proefpersone die voorbeelde									
INDIEN JA, hoeveel melk?									
Gooi jy suiker oor jou pap? JA 1 NEE 2									
Indien JA, hoeveel suiker?								9012	
'Ting'									
Mabella: tipe: Grof Fyn Rys	Styf							4082	
Gooi jy melk oor jou mabellapap? JA 1 NEE 2 INDIEN JA, watter tipe melk (volroom vars, suur,vetvry, 2%, melk mengsel)_____ INSTRUKSIE: Wys die proefpersone die voorbeelde									
INDIEN JA, hoeveel melk?									
Gooi jy suiker oor jou mabellapap? JA 1 NEE 2									
Indien JA, hoeveel suiker?								9012	
Hawermout								4032	
Gooi jy melk oor jou hawermoutpap? JA 1 NEE 2 INDIEN JA, watter tipe melk (volroom vars, suur,vetvry, 2%, melk mengsel)_____ INSTRUKSIE: Wys die proefpersone die voorbeelde									
INDIEN JA, hoeveel melk?									
Gooi jy suiker oor jou hawerpap? JA 1 NEE 2									

VOEDSEL	BESKRYWING	HOEVEEL-HEID	HOEVEEL KEER GEEET Per dag	Per week	Per maand	Selde	Nooit	KODE	HVHD/DAG
Indien JA, hoeveel suiker?								9012	
Ontbyt graankos	Handelsnaam van graankosse tans in die huis: Weet nie__								
Gooi jy melk oor jou ontbytgraan? JA 1 NEE 2 INDIEN JA, watter tipe melk (volroom vars, suur,vetvry, 2%, melk mengsel)_____ INSTRUKSIE: Wys die proefpersone die voorbeelde									
INDIEN JA, hoeveel melk?									
Gooi jy suiker oor jou ontbytgraan? JA 1 NEE 2									
Indien JA, hoeveel suiker?								9012	
Stampmielies	Gekoop Self gemaal Met vet Sonder vet							4077 4073	
Stampmielies met droë boontjies								A014	
Is die hoeveelheid stampmielies en bone dieselfde as op die foto? JA 1 NEE 2 Indien NEE, gebruik jy meer bone as op die foto of minder? MEER 1 MINDER 2									
Stampmielies met grondboontjies								A013	
Is die hoeveelheid stampmielies en grondboontjies dieselfde as op die foto? JA 1 NEE 2 Indien NEE, gebruik jy meer grondboontjies as op die foto of minder? MEER 1 MINDER 2									
Rys	Wit Bruin Mielierys							4040 4134 4043	
Pastas	Macaroni Spaghetti Ander:							4062	
Jy is baie behulpsaam. Kan ek jou nou uitvra oor vleis? HOENDER, ROOIVLEIS EN VIS Hoeveel keer in die week eet jy rooivleis, hoender , vis of soya produkte? _____ Eet jy hoender? JA 1 NEE 2 INDIEN JA, Waar kry jy jou hoender vandaan? (Mag meer as een antwoord gee) Winkel/supermark/spaza 1 Werkgewer 2 Slag eie 3 Geskenke 4 Ander spesifiseer 5 Eet nie hoender nie 6									
Hoender:	Hoe maak jy hoender gaar?								
	Gekook, niks bygevoeg							1521	
	Gebraai: in deeg/krummels								
	sonder deeg/krummels							1520	
	Gerooster								

VOEDSEL	BESKRYWING	HOEVEEL-HEID	HOEVEEL KEER GEËET Per dag	Per week	Per maand	Selde	Nooit	KODE	HVHD/DAG
	Bredie Watter groente sit jy gewoonlik by?							A002	
Eet jy die hoender se vel?			Altyd 1	Soms 2	Nooit 3				
Hoenderbeen-bredie								A003	
Hoenderpote	Met vel Sonder vel							A004 1609	
Hoender afval	Hoe maak jy dit gaar?							1610	
Waar kry jy jou rooivleis vandaan? (Mag meer as een antwoord)								Winkel/supermark/'spaza' 1 Werkgewer 2 Slag eie 3 Geskenke 4 Ander spesifiseer: 5 Eet nie rooivleis 6	
Rooivleis	Hoe hou jy van vleis? Met vet Sonder vet								
Beesvleis	Hoe maak jy beesvleis gaar?								
	Gebraai met been								
	Gebraai sonder been								
	Gestowe met been							A001	
	Gestowe sonder been							A001	
	Gerooster met been								
	Gerooster sonder been								
	Gemaal							1571	
Skaapvleis	Hoe maak jy skaapvleis gaar?								
	Gebraai met been								
	Gebraai sonder been								
	Gestowe met been							1511	
	Gestowe sonder been							1511	
	Gerooster met been								
	Gerooster sonder been								
	Gemaal							1571	
Varkvleis	Hoe maak jy varkvleis gaar?								
	Gebraai met been								
	Gebraai sonder been								
	Gestowe met been								
	Gestowe sonder been								

VOEDSEL	BESKRYWING	HOEVEEL-HEID	HOEVEEL KEER GEEET Per dag	Per week	Per maand	Selde	Nooit	KODE	HVHD/DAG
	Gerooster met been								
	Gerooster sonder been								
	Gemaal							1598	
Afval	Derms: gekook, niks bygevoeg								
	Gestowe met groente								
	Maag							1546	
	Hart							1565	
	Longe								
	Lewer							1515	
	Niertjies							1518	
Watter groente word gewoonlik by die bredies bygevoeg?									
Wors	Gebraai Gerooster							1526	
Spekvleis								1501	
Koue vleis	Polonie							1514	
	Ham							1564	
	Weenseworsies							1531	
	Ander - spesifiseer								
Vleispastei	Tuisgemaak Gekoop							1548	
Blikkies vleis	'Bully beef' Ander Wys voorbeelde							1535	
Hamburger	Tuisgemaak Gekoop							A015	
Droë bone/ertjies/ lensies	Hoe maak jy dit gaar?								
Sojaprodukte bv Toppers	Handelsname van sojaprodukte wat gebruik word: Weet nie___ Wys voorbeelde							3527	
Sardyne in tamatie/chilli sous	Heel							2503	
	Fyngemaak met gebraaide uie							A005	
Gebraaide vis	Met deeg/krummels Sonder deeg/krummels							2509 2523	
Ander ingemaakte vis	Tuna Gepekelde vis Ander:							2547	

VOEDSEL	BESKRYWING	HOEVEEL-HEID	HOEVEEL KEER GEEET Per dag	Per week	Per maand	Selde Nooit	KODE	HVHD/DAG
Viskoekies	Tuisgemaak Bevrore (gevries) Gekoop						2531	
Eiers	Gekook/ geposjeer Roereier Gebraai						1001 1003	

ONS KOM NOU BY GROENTE EN VRUGTE

Waar kry jy jou groente vandaan? (Mag meer as een antwoord)

Eie groente tuin	1
Werkgewer/ werkgewer se plaas	2
Eie plaas	3
Winkel/Supermark/ groentewinkel	4
Smous	5
Veld (bv morogo)	6
Geskenke	7
Ander spesifiseer	8

Hoeveel keer in die week eet jy groente? _____

VOEDSEL	BESKRYWING	Hoeveel-heid	HOEVEEL KEER GEEET Per dag	Per week	Per maand	Selde Nooit	KODE	HVD/DAG
Kool	Hoe maak jy kool gaar?							
	Gekook, niks bygevoeg						8066	
	Gekook met aartappel, ui en vet						A006	
	Gebraai, niks bygevoeg						A007	
	Gekook dan gebraai met aartappel en uie						A005	
	ander: Weet nie:							
Spinasie/ morogo/ ander groen blaargroente	Hoe maak jy spinasie gaar?							
	Gekook, niks bygevoeg						8071	
	Gekook, vet bygevoeg							
	Gekook met uie, tamatie en vet						A011	
	Gekook met uie,tamatie en aartappel							
	Gekook met grondboontjies							
	Ander: Weet nie:							

VOEDSEL	BESKRYWING	Hoeveelheid	HOEVEEL KEER GEEET Per dag	Per week	Per maand	Selde Nooit	KODE	HVD/DAG
Tamatie en uie sous	Tuisgemaak met vet -sonder vet Ingemaak {Is dit die hoeveelheid pap wat jy eet? Hoeveel meer of minder? }						A012 A016 8221	
Pampoen	Hoe kook jy pampoen?							
	Gaargemaak in vet en suiker						A010	
	Gekook, bietjie suiker en vet						A009	
	Ander_____ Weet nie_____							
Wortels	Hoe kook jy wortels?							
	Gekook met suiker en vet						8129	
	- met aartappel en uie						A008	
	Rou, slaai						8015	
	Ander_____ Weet nie_____							
Mielies/ suikermielies	Hoe eet jy mielies? Aan stronk met vet - sonder vet						8033	
	Van die stronk af met vet sonder vet						8261	
Beetslaai	Tuisgemaak Gekoop						8005	
Aartappels	Hoe maak jy aartappels gaar?							
	Gekook/gebak met skil						8046	
	- sonder skil						8045	
	Fyngedruk							
	Gebraai						8189	
	Skyfies						8048	
	Slaai Ander spesifiseer: Weet nie						8226	
Patats	Hoe maak jy patats gaar?							
	Gekook/gebak met skil sonder skil						8057 8214	
	Fyngedruk met vet en suiker							
	Ander spesifiseer: Weet nie___							

VOEDSEL	BESKRYWING	Hoeveelheid	HOEVEEL KEER GEËET Per dag	Per week	Per maand	Selde	Nooit	KODE	HVD/DAG
Slaai groente	Rou tamatie,							8059	
	Blaarslaai							8031	
	Komkommer							8025	
Ander groente	Spesifiseer:								

VRUGTE

Hou jy van vrugte? JA 1 NEE 2

Hoeveel keer in 'n week of in 'n maand eet jy vrugte? _____

Waar kry jy jou vrugte vandaan?

Eie vrugte bome	1
Werkgewer/werkgewer se plaas	2
Eie plaas	3
Winkel/supermark/groentewinkel	4
Smous	5
Veld	6
Geskenke	7
Ander spesifiseer	8

VOEDSEL	BESKRYWING	Hoeveelheid	HOEVEEL KEER GEËET Per dag	Per week	Per maand	Selde	Nooit	KODE	HVD/DAG
Appels/Pere	Vars Geblikte pere							7001 7054	
Piesangs								7009	
Lemoene / naartjies								7031	
Druiwe								7020	
Perskes	Vars Geblikte perskes							7036 7038	
Appelkose	Vars Geblikte perskes							7003 7004	
Mango's	Vars							7026	
Koejawels	Vars Geblikte koejawels							7021 7023	
Indien proefpersoon geblikte vrugte eet: Eet jy vla saam met die geblikte vrugte? ALTYD 1 SOMS 2 NOOIT 3									
Vla	Tuisgemaak Langlewe (Ultramel)							0004	
Wildevrugte/ bessies	Stamvrugte Noem-noem Klappers Maroelas Nastergals Ander -spesifiseer							7070	

VOEDSEL	BESKRYWING	Hoeveel-heid	HOEVEEL KEER GEËET Per dag	Per week	Per Selde maand	Nooit	KODE	HVD/DAG
Gedroogte vrugte	Tipes:							
Ander vrugte:								
BROOD EN BROODSMERE								
Brood Broodrolle	Wit						4001	
	Bruin						4002	
	Volgraan						4003	
Smeer jy enigiets op die brood? Altyd 1 Soms 2 Nooit 3 Indien ALTYD of SOMS, wat smeer jy op?								
Margarien	Wat is die handelsnaam van die margarien wat jy tans gebruik? _____ Weet nie __ Wys voorbeelde							
Botter	Wat is die handelsnaam van die botter wat jy tans gebruik? _____ Tuisgemaak Weet nie ___						6502	
Grondboontjie botter							6509	
Konfyt/stroop/ heuning							9008	
Marmite/Fray Bentos ens							9501	
Vis/vleis smeer							1512	
Kaas	Tipe:							
Atjar							A017	
Polonie							1514	
Ander smere:	Spesifiseer:							
Kluitjie							4001	
Vetkoek							4057	
Provita, kraak-beskuitjies								
VETTE: Watter vette gebruik jy en waarmee saam gebruik jy dit?								

VOEDSEL	BESKRYWING	Hoeveelheid	HOEVEEL KEER GEEET Per dag	Per week	Per maand	Selde Nooit	KODE	HVD/DAG
Margarien	Waar gebruik op brood met groente Hoeveelheid lepels ___per nommer gesinslede_____ ander-spesifiseer							
Botter	Waar gebruik: op brood met groente ander-spesifiseer Hoeveelheid lepels ___per nommer gesinslede_____							
Holsum /plantvette	Waar gebruik: Hoeveelheid lepels ___per nommer gesinslede____						6508	
Olie	Waar gebruik: Hoeveelheid lepels ___per nommer gesinslede____						6510	
Uitgebraaide vet	Waar gebruik: Hoeveelheid lepels ___per nommer gesinslede____							
Gemengde vet (makhuru)	Waar gebruik: Hoeveelheid lepels ___per nommer gesinslede____							
Niervet	Waar gebruik: Hoeveelheid lepels ___per nommer gesinslede____						6520	
Mayonnaise/ slaaisous	Hoeveelheid lepels ___per nommer gesinslede____						6573	
Room	Vars/Langlewe/ geblik 'Orley whip'	-					6503	
DRANKE:								
Tee							9514	
Suiker/koppie tee							9012	
Melk/koppie tee	Watter tipe melk gebruik jy in jou tee?							
	Vars/langlewe volroom						0006	
	Vars/langlewe 2%							
	Vars/langlewe vetvry						0072	
	Volroommelkpoeier naam_____						0009	

VOEDSEL	BESKRYWING	Hoeveelheid	HOEVEEL KEER GEËET Per dag	Per week	Per maand	Selde Nooit	KODE	HVD/DAG
	Afgeroomde melkpoeier naam_____						0008	
	Melkmengsel naam_____						0068	
	Verromer naam_____						0039	
	Gekondenseerde melk						0002	
	Ingedampte melk						0003	
	Geen							
Koffie							1513	
Suiker/koppie koffie							9012	
Melk/koppie koffie	Watter tipe melk gebruik jy in jou koffie? Vars/langlewe volroom						0006	
	Vars/langlewe 2%							
	Vars/langlewe vetvry						0072	
	Volroommelkpoeier naam_____						0009	
	Afgeroomde melkpoeier naam_____						0008	
	Melkmengsel naam_____						0068	
	Verromer naam_____						0039	
	Gekondenseerde melk						0002	
	Ingedamptemelk						0003	
	Geen							
Melk as sulks	Vars/langlewe volroom						0006	
	Vars/langlewe 2%							
	Vars/langlewe vetvry						0072	
	Suurmelk(maas)						0006	
	Volroommelkpoeier naam_____						0009	
	Afgeroomde melkpoeier naam_____						0008	
	Melkmengsel naam_____						0068	
	Gekondenseerde melk						0002	
	Ingedampte melk						0003	
Melkdranke	Nestle Milo Ander:							
Yoghurt	Drink yoghurt Dik yoghurt						0044 0020	

VOEDSEL	BESKRYWING	Hoeveelheid	HOEVEEL KEER GEËET Per dag	Per week	Per Selde maand	Nooit	KODE	HVD/DAG
Kwas	Sweeto						9013	
	SixO						9013	
	Oros/Lecol-met suiker						9002	
	- nagemaakte versoeter						9013	
	Kool Aid						9002	
	Ander:							
	Wys voorbeelde	-						
Vrugtesap Spesifiseer tipes:	Vars/ Liquifruit/Ceres							
	Tropica							
	Konsentrate bv Halls							
	Nektars							
	Handelsname:_____ Wys voorbeelde							
Gaskoeldranke bv Coke, Fanta	Versoet Dieet						9001 9013	
Mageu /Motogo								
Tuisgemaak							9516	
Tlokwe							9516	
Bier							9506	
Spirituliee							9510	
Rooiwyn							9508	
Witwyn							9518	
Likeur							9517	
Ander: spesifiseer								
PEUSELHAPPIES EN LEKKERGOED:								
Aartappelskyfies							8049	
Grondboontjies	Rou Gebraaide Gesout Sonder sout						6001 6007	
Kaaskrulle Niknaks ens							4076	
Rosyntjies							7022	
Grondboontjies en rosyntjies								
Sjokolade	Naam							
Suikerlekkers	Sugas, gommetjies						9009	
Lekkers	Toffies, Karamels						9014	

VOEDSEL	BESKRYWING	Hoeveelheid	HOEVEEL KEER GEËET Per dag	Per week	Per Selde maand	Nooit	KODE	HVD/DAG
Beskuitjies	Tipe							
Koeke en terte	Tipe							
Skons							4029	
Beskuit							4160	
Southappies	Vleisrolletjies Samoosas Beskuitjies bv Bacon kips Ander spesifiseer:						1534 4196 4162	
POEDINGS:								
Ingemaakte vrugte	Tipe:							
Jellie							9004	
Vla	Tuisgemaak Langlewe (Ultramel)						0004	
Gebakte poeding							4181	
Kitspoeding							4066	
Roomys Sorbet							6507 6516	
Ander spesifiseer:								
SOUSE / GEURMIDDELS:								
Atjar							A017	
Tamatiesous Worcestersous							9505	
Blatjang							9524	
Piekels							8176	
Pakkies sop							4069	
Ander:								
INSEKTE:								
Sprinkane								
Mopani wurms								
Ander:								
WILDE VORLS OP DIKTE (Gejag in landelike gebiede of op plase)								

VOEDSEL	BESKRYWING	Hoeveel-heid	HOEVEEL KEER GEËET Per dag	Per week	Per maand	Selde	Nooit	KODE	HVD/DAG
ALLERLEI: Noem asseblief enige ander voedsel wat meer as een/twee keer per week geeet word waaroor ons nie gepraat het nie.									

SOUT GEBRUIK :
Die volgende paar vrae is om uit te vind of jy sout gebruik, waar jy dit gebruik en hoeveel gebruik.

Voeg jy sout by kos terwyl dit gaargemaak word?

Altyd 1	Soms 2	Nooit 3	Weet nie 4

Voeg jy sout by kos nadat dit gaargemaak is?

Altyd 1	Soms 2	Nooit 3

Hou jy van souterige kosse soos gesoute grondboontjies, aartappelskyfies ens?

Baie lief daarvoor 1	Hou daarvan 2	Hou nie baie daarvan,eet dit soms 3	Eet dit nooit 4

BÊRE VAN VOEDSEL:

Bêre jy voedsel van een maaltyd om tydens 'n volgende maaltyd te eet?

Altyd 1	Soms 2	Nooit 3

Indien ALTYD of SOMS, watter voedsel bêre jy?
Eet jy hierdie oorskiet kosse koud of maak jy dit warm?

VOEDSEL	Her-verhit	Koud

Gebruik jy enige van die volgende?

	Naam van produk	Hoeveelheid /dag
Vitamiene/vitamiene & minerale		
Tonikums		
Gesondheidskosse		
Liggaamsbou-preparate		
Dieetvesel supplement		
Ander: spesifiseer		

DANKIE VIR U SAMEWERKING EN GEDULD!

TOTSIENS!