# CHAPTER 7: RESULTS AND DISCUSSION

## CLUSTERING OF RISK FACTORS FOR THE METABOLIC SYNDROME

### 7.1 Introduction

The first question addressed in this chapter is whether clustering of risk factors (with or without insulin resistance) exists in this sample of Africans. The second question is, if clustering does exit, is it possible to identify one or more risk marker to predict the presence of insulin resistance and eventually the metabolic syndrome, as defined in Chapter 1 of this thesis, in these subjects?

The metabolic syndrome is a constellation of metabolic abnormalities all characterized by hyperinsulinaemia and insulin resistance (Reaven, 1988; Kaplan, 1989; Vague & Raccah, 1992; Zimmet *et al.*, 1997; Haffner, 1997). These abnormalities are manifested by the clustering of risk factors of the chronic diseases of lifestyle in one person (as discussed in Chapter 2).

Epidemiological evidence pointed out that identifying patients with the metabolic syndrome by a clinical marker might be possible, i.e. central obesity, and a biological marker, i.e. hyperinsulinemia (Fontbone and Eschwège, 1991). According to these researchers, the metabolic syndrome is partly reversible through proper actions to prevent the clinical and biological risk factors of the metabolic syndrome in populations.

To investigate whether the clustering of risk factors occurred in this population (with or without insulin resistance), the frequencies of risk factors above normal ranges in every subject were calculated and expressed as a percentage of the population. The risk factors examined, with their cut points for raised values, are listed in Table 7.1. These cut points are internationally accepted. The relevance of these cut points for this particular population remains to be determined, and they were therefore accepted as the best data available.

As indicated in Chapter 6 there were some subtle, but consistent shifts towards increased values in the risk factors measured, from the high insulin sensitivity quartile towards the low insulin sensitivity (IS) quartile. Whether these shifts are biologically important in this population are doubtful since the values measured, even in the highest insulin sensitivity quartile, were

predominantly still within low to normal ranges. Trying to quantify the importance of these shifts and identify one or more risk factors (of the chronic diseases of lifestyle) to serve as a predictor for the development of insulin resistance in this population, odds ratios have been calculated. Every risk marker that related to insulin sensitivity in the previous chapters (Chapters 5 and 6) was divided into quartiles for each gender separately. The values in the upper quartile of each risk factor were then evaluated against insulin resistance as implicated by the lowest IS quartile by means of cross tabulation. Linear regression and logistic regression analyses were performed to derive estimates of risk (odds ratio).

**Table 7.1 Traditional risk factors/markers for the metabolic syndrome**

| Risk factors | Cutoff values for abnormal range | Reference |
|---|---|---|
| **Serum TC** | > 5,5 mmol/L | Rossouw *et al.*, 1988 |
| **Serum Tg:HDL-C ratio** | > 2.3 | HDL-C < 1 (Berger en Marais, 1987)<br>TG > 2.3 (The Study group of the European Atherosclerosis Society, 1987). |
| **Fasting serum insulin** | < 10 $\mu$U/L and > 25 $\mu$U/L | Immuno Biological Laboratories, 1995 (Chapter 3) |
| **Fasting serum glucose** | > 7.1 mmol/L | WHO (1997) |
| **Body mass index (BMI)** | > 30 kg/m$^2$ | WHO (1995) |
| **Waist to hip ratio** | > 0.85 | Kaplan (1989) |
| **Systolic blood pressure** | > 140 mmHg | WHO (1999) |
| **Diastolic blood pressure** | > 95 mmHg | WHO (1999) |

Refer abbreviations to LIST OF ABBREVIATIONS

The same cutoff values for abnormal ranges were used for both genders. No official different cutoff values between men and women exist.

To identify one or more risk factor or marker in the development of the metabolic syndrome in this study population, the subjects with two and more risk factors (Table 7.1) were identified and a combined variable was created for each subject. Every risk factor that related to insulin sensitivity in the previous chapters (Chapters 5 and 6) was again divided into quartiles for each gender separately. The values in the upper quartile of the risk factor were then evaluated against the "combined" variable by means of cross tabulation. Odds ratios were calculated. Logistic regressions were used to identify the lifestyle factor/s with the largest impact on the development

of insulin resistance and the metabolic syndrome.

## 7.2 Results

The results on the number of subjects who were at risk to develop insulin resistance or the metabolic syndrome, the clustering effect of the risk factors in subjects and the influence of urbanisation are given. This is followed by a risk estimation of suggested risk factors to serve as possible predictors for the developing of insulin resistance and/or the metabolic syndrome.

### 7.2.1 Results on elevated traditional risk factors of the metabolic syndrome

The frequencies of risk factors above the cutoff values (Table 7.1) are tabulated in Table 7.2.

**Table 7.2 A summary of the percentage of evaluated risk factors for the metabolic syndrome**

| | | PERCENTAGE MEN n=193 * | PERCENTAGE WOMEN n=233* |
|---|---|---|---|
| RISK FACTORS ABOVE CUT POINTS FOR NORMALITY: | Serum TC | 5.7 | 12.9 |
| | TG / HDL-C ratio | 2.1 | 4.7 |
| | Fasting serum insulin | 14 | 19.7 |
| | Fasting serum glucose | 3.6 | 3.4 |
| | BMI | 1.6 | 29.2 |
| | WHR | 35.2 | 13.3 |
| | Diastolic blood pressure | 7.3 | 10.3 |
| | Systolic blood pressure | 25.4 | 24.9 |

* Percentage subjects above the cut points given in Table 7.1

**Abbreviations refer to LIST OF ABBREVIATIONS**

Table 7.2 shows that more women than men had values above the cut points for the selected variables, except for WHR and systolic blood pressure.

The results of a stepwise linear regression analysis to indicate the influence of all variables associated with insulin sensitivity (chapters 5 and 6) as well as the traditional risk markers

of the metabolic syndrome are shown in Table 7.3 for the men and Table 7.4 for the women respectively.

**Table 7.3 Stepwise regression analysis for the men**

| **Model summary** | **Adjusted R square** | **R** | **Sig** |
|---|---|---|---|
| Model 3 | 0.127 | 0.4 | 0.002 |
| **Predictors in model 3** | **Standardised coefficients - Beta** | **t-value** | **Sig** |
| Triceps skinfold (mm) | -0.19 | -1.8 | 0.076 |
| Serum calcium (mmol/L) | -0.25 | -2.5 | 0.015 |
| Serum uric acid (mmol/L) | -0.23 | -2.1 | 0.036 |

**Variables excluded from the model:** S-LD; S-TG; S-HDL-C; S-LDL-C; S-TC; DBP;Body mass; Alcohol consumption; S-% Fe saturation; S-ferritin; S-Glucose $T_{120}$
**Dependent variable:** Insulin sensitivity index.
**Referred abbreviations to LIST OF ABBREVIATIONS**

Table 7.3 reveals that from all the variables associated with insulin sensitivity in the men of this studied population, an increased triceps skinfold thickness, serum calcium levels and serum uric acid values had the largest lowering impact on insulin sensitivity.

**Table 7.4 Stepwise regression analysis for the women**

| **Model summary** | **Adjusted R square** | **R** | **Sig** |
|---|---|---|---|
| Model 4 | 0.21 | 0.5 | 0 |
| **Predictors in model 4** | **Standardised coefficients - Beta** | **t-value** | **Sig** |
| Serum calcium (mmol/L) | -0.28 | -4 | 0 |
| Body mass (kg) | -0.32 | -4.4 | 0 |
| Age (years) | 0.28 | 3.8 | 0 |
| Serum urea (mmol/L) | -0.14 | -2 | 0.047 |

**Variables excluded from the model:** S-TG; S-HDL-C; S-LDL-C; SBP; DBP; BMI; Alcohol consumption;; S-ferritin; Pl-Fibrinogen; Hip-maximum; S-uric acid; Total food energy intake (minus alcohol)
**Dependent variable:** Insulin sensitivity index
**Referred abbreviations to LIST OF ABBREVIATIONS**

Table 7.4 shows that from all the variables associated with insulin sensitivity in the women of this studied population, a younger age, an increased body mass, serum calcium levels

and serum urea values had the largest lowering effect on insulin sensitivity.

### 7.2.2 Risk estimation of risk markers for insulin sensitivity

Although only "apparently healthy" subjects participated in this study, the above results and the results from the previous chapters (Chapters 5 and 6) gave an indication that there were subjects in this studied population who were at risk to develop insulin resistance. Tables 7.5 and 7.6 show the odds ratio of risk factors associated with a low insulin sensitivity [insulin resistance (IR)] in these men and women, based on a comparison of subjects in the lowest insulin sensitivity quartile to those in the other three quartiles.

**Table 7.5 Risk estimation of risk factors associated with IR for the men**

| Risk marker | Upper quartile | Odds ratio | 95% CI |
|---|---|---|---|
| Total serum cholesterol | >4.4 mmol/L | 1.399 | 0.6 - 3.4 |
| Serum Ferritin | 163.4 μg/L | 1.25 | 0.5 - 3.1 |
| Serum Glucose $T_{120}$ | >6.1 mmol/L | 1.093 | 0.4 - 3.4 |
| Serum calcium | > 2.4 mmol/L | 1.014 | 0.4 - 2.5 |
| Diastolic blood pressure | 82 mmHg | 1.399 | 0.5 - 3.8 |

CI = Confidence intervals

Table 7.5 shows that the men with a total serum cholesterol above 4.4 mmol/L had a 40% increased risk to be insulin resistant than those men with lower total cholesterol levels in the other three insulin sensitivity quartiles. Similarly, the men with serum ferritin levels above 163 μg/L had a 25% increased risk, those with a two hour serum glucose levels above 6.1 mmol/L a 9% increased risk, those with serum calcium levels above 2.4 mmol/L an 1% increased risk and those men with a diastolic blood pressure above 82 mmHg , a 40% increased risk for insulin resistance.

Table 7.6 reveals that the women with a plasma fibrinogen level above 4.3 g/L had a 34% greater risk for insulin resistance compared to those with lower plasma fibrinogen levels in the other three IS quartiles. Similarly, the women with a serum ferritin level above 75.3

$\mu$g/L had a 24% increased risk, those with a serum triglyceride level above 1.2 mmol/L had a 15% increased risk, those with LDL-C: HDL-C ratio above 3.3 mmol/L had a 47% increased risk, those with a serum uric acid above 0.28 mmol/L had a 14% increased risk and those with a triceps skinfold thickness above 25mm had a 92% greater estimated risk to be insulin resistant.

**Table 7.6 Risk estimation of risk factors associated with IR for the women**

| Risk marker | Upper quartile | Odds ratio | 95% CI |
|---|---|---|---|
| Plasma Fibrinogen | >4.3 g/L | 1.338 | 0.6 - 3.1 |
| Serum Ferritin | 75.3 $\mu$g/L | 1.24 | 0.6 - 2.8 |
| Serum triglycerides | 1.2 mmol/L | 1.145 | 0.5 - 2.7 |
| Serum LDL-C:HDL-C ratio | 3.3 | 1.469 | 0.6 - 3.5 |
| Serum uric acid | 0.28 mmol/L | 1.137 | 0.5 - 2.5 |
| Triceps skinfold | 25 mm | 1.92 | 0.5 - 6.8 |

**CI = Confidence intervals**

It is, however, important to note that although the odds ratios suggested a certain percentage of increased risk, none of these increases can be considered with any statistical confidence to be significant, as the confidence intervals included 1.0 for all variables. These results should therefore be interpreted with care.

### 7.2.3 Clustering of risk factors with insulin resistance as underlying common factor

To investigate the metabolic syndrome, the presence of one to eight risk factors per subject were calculated (Table 7.7). The highest clustering was six factors that occurred in one woman from the upper urban stratum. As indicated in Table 7.7, clustering of up to five risk factors per subject occurred in both men and women although the percentage within the sexes as well as in the total group of subjects for the clustering of three and more risk factors were low.

**Table 7.7 The clustering of risk factors of the metabolic syndrome**

| | | | PERCENTAGE MEN n=193 | PERCENTAGE WOMEN n=233 |
|---|---|---|---|---|
| CLUSTERING OF RISK FACTORS: | No risk factor | | 41.5 | 42.5 |
| | risk factor: n = 1 | | 34.2 | 25.8 |
| | risk factor : n = 2 | | 15 | 16.7 |
| | risk factor: n = 3 | | 7.3 | 7.7 |
| | risk factor: n = 4 | | 1.6 | 5.6 |
| | risk factor : n = 5 | | 0.5 | 1.3 |
| | risk factor: n =6 | | none | 0.4 |
| FREQUENCY OF IR AND THE CLUSTERING OF RISK FACTORS | > 2 risk factors | IR | 12.1 | 20.5 |
| | | IS | 9.1 | 4.5 |

IS = INSULIN SENSITIVE (IS-index men > 191.5; women >158.95)

IR = INSULIN RESISTANCE (IS-index men <= 113; women <=87.7)

The role that insulin resistance plays in the clustering of risk factors is also revealed in Table 7.7. This table shows that 12% men and 20.5% women with a cluster of more than two risk factors were insulin resistant. Only 9.1% men and 4.5% women with a cluster of more than two risk factors were insulin sensitive. Figure 7.1 shows these results in more detail. From this figure it can be seen that more men and women with no risk factors were more insulin sensitive than resistant. It also reveals that more women with more than two risk factors were insulin resistant. In the men, those with more than three risk factors were more insulin resistant than the rest.

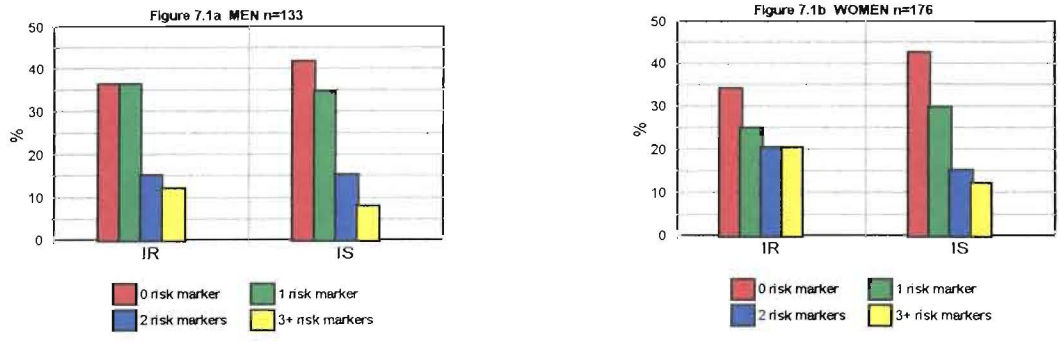



**Figure 7.1 Illustration of the influence of insulin resistance on the clustering of risk factors in men and women**

### 7.2.4 Prediction of the metabolic syndrome (clustering of risk factors)

Tables 7.8 and 7.9 give the results of the odds ratio estimations to suggest which risk factor might be a good indicator to predict the clustering of risk factors in an individual.

Tables 7.8 and 7.9 reveal that a total serum cholesterol level above 4.4 mmol/L in men and 4.8 mmol/L in women might be a major predictor for the clustering of risk factors in the development of the metabolic syndrome. These results should also be interpreted with care due to the large ranges of the confidence intervals in both genders.

**Table 7.8 Predictive value of risk markers for the metabolic syndrome for the men (clusters of more than two risk factors)**

| Risk marker | Upper quartile | Odds ratio | 95% CI |
|---|---|---|---|
| Total serum cholesterol | > 4.4 mmol/L | 10.553 | 3.5 - 31.6 |
| Plasma Fibrinogen | > 3.5 g/L | 1.167 | 0.4 - 3.7 |
| Serum Glucose $T_{120}$ | > 6.1 mmol/L | 2.02 | 0.4 - 9.5 |
| Serum HDL-C | < 0.92 mmol/L | 2.82 | 0.6 - 12.7 |
| Serum calcium | > 2.4 mmol/L | 1.167 | 0.4 - 3.8 |
| Insulin sensitivity index | < 113 | 1.55 | 0.4 - 5.5 |

**CI = confidence intervals**

**Table 7.9 Predictive value of risk markers for the metabolic syndrome for the women (clusters of more than two risk factors)**

| Risk marker | Upper quartile | Odds ratio | 95% CI |
|---|---|---|---|
| serum insulin | > 23.6$\mu$U/L | 1.41 | 0.5 - 4.0 |
| Total serum cholesterol | > 4.8 mmol/L | 11.22 | 4.4 - 28.5 |
| Insulin sensitivity index | < 87.7 | 1.85 | 0.8 - 4.5 |

**CI = confidence intervals**

Other predictors for the development of the metabolic syndrome in these men were a plasma fibrinogen level above 3.5 g/L (17%), two hour glucose levels above 6.1 mmol/L (100%), a serum HDL-C of less than 0.92 mmol/L (182%), a serum calcium level above

2.4 mmol/L (17%) and an insulin sensitivity index of less than 113 (55%). In the women other predictors were fasting serum insulin levels above 23.6 $\mu$U/L (41%) and an insulin sensitivity index less than 87.7 (85%).

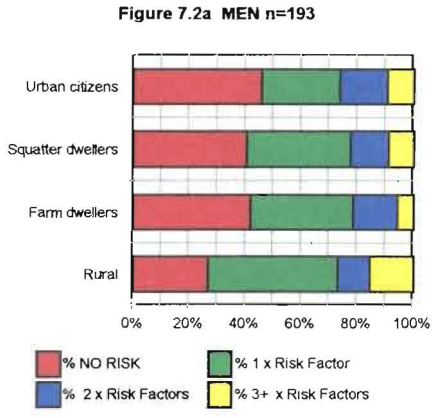
### 7.2.5 The influence of urbanisation on the development of the metabolic syndrome

The effect of urbanisation on the clustering of risk factors is shown in Table 7.10. Because of small numbers, the rural and farm dwellers (stratum 1 and 2) and the three urban strata (3,4 and 5) were combined. From this table it is clear that there was no definite pattern in the occurrence of the clustering of risk factors within the different levels of urbanisation. The highest percentage of men with one, three and four risk factors occurred in the rural settlements. The highest occurrence of three and more risk factors clustering in a women was in the upper urban class. Less clustering of risk factors occurred in the men living on farms (maximum of three factors). Men from the upper class (46.1%) and women from the urban class (53.6%) had the highest percentage of no risk factors per person. In both men and women the clustering of 5 risk factors (1 man and 2 women) was found in the upper urbanised level as well as in one women living on a farm. A cluster of six factors was only present in one women in the upper stratum.

**Table 7.10 The influence of urbanisation on the clustering of risk factors**

| | | # | Percentage MEN/stratum n=193 | percentage WOMEN/stratum n=233 |
|---|---|---|---|---|
| URBANISATION AND THE | No risk factor | S1 + S2<br>S3, S4, S5 | 33.3<br>43.9 | 39.1<br>44.5 |
| CLUSTERING OF RISK | risk factor n =1 | S1 + S2<br>S3, S4, S5 | 42.2<br>31.8 | 34.5<br>20.5 |
| FACTORS | risk factor n= 2 | S1 + S2<br>S3, S4, S5 | 13.3<br>15.5 | 13.8<br>18.5 |
| | risk factor n = 3 | S1 + S2<br>S3, S4, S5 | 8.9<br>6.8 | 6.9<br>8.2 |
| | risk factor n= 4 | S1 + S2<br>S3, S4, S5 | 2.2<br>1.4 | 4.6<br>6.2 |
| | risk factor n= 5 | S1 + S2<br>S3, S4, S5 | none<br>0.7 | 1.1<br>1.4 |
| | risk factor n=6 | S1 + S2<br>S3, S4, S5 | none<br>none | none<br>0.7 |

# S1 + S2 = rural plus farm dwellers; men n=45; women n=87
S3 + S4 + S5= squatters plus urban plus upper urban citizens; men n=148; women n=146



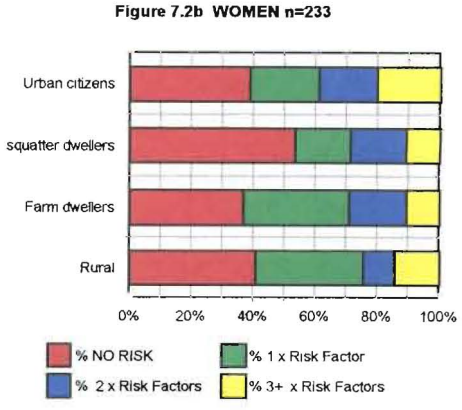




**Figure 7.2a and b Illustration of the influence of urbanisation on the clustering of risk factors (Table 7.8)**

### 7.2.6 Risk estimation of the influence of lifestyle factors on insulin resistance and the metabolic syndrome

To decide which lifestyle factor had the largest influence on insulin sensitivity in these men and women, log linear regressions were performed and the results are tabulated in Table 7.11. The factors that were used in this model include urbanisation, the smoking habit, alcohol consumption and energy intake, HIV infection, total household income, education level, and the level of physical activity.

In the men it seems as if education plays a role in the development of insulin resistance. The men with the higher education levels seem to be more likely to be insulin sensitive. Total food energy intake (excluding alcohol consumption) seems to be a risk in the women who are more insulin resistant. This finding is according to the results reported by O'Dea (1991). When Australian Aborigines make the transition from their traditional lifestyle to a westernised lifestyle, the latter was characterised by reduced physical activity and an energy dense diet that promoted obesity and maximised insulin resistance (O'Dea, 1991). The rural women in this study and those living on farms seemed to be more insulin sensitive.

Table 7.12 reveals that a total household income between R1 000 - R2 000 per month is protective against the clustering of risk factors in the men. It also reveals that the food energy intake (excluding alcohol consumption) of these men was protective against the clustering of risk factors. This is contradictory to expectations. This contradiction can most probably be explained by the fact that although these men had much higher reported energy intakes than the women, they were much leaner and were more physically active than the women. Their meal composition also differed from that of the women (they consumed meals with a lower polyunsaturated:saturated fat ratio and higher in carbohydrate content - data not shown).

**Table 7.11 Significant influences of lifestyle factors on the development of insulin resistance in this population**

| Gender | Lifestyle marker | Odds ratio | Sig | 95% CI |
|---|---|---|---|---|
| Men | Education (st. 9-10 with/without trade) | 8.9 | 0.03 | 1.3 - 61.0 |
| | Education (st. 9-10 / higher education) | 7.6 | 0.04 | 1.2 - 52.0 |
| Women | urbanisation (rural) | 4.5 | 0.02 | 1.3 - 15.5 |
| | urbanisation (farm dwellers) | 3.1 | 0.04 | 1.1 - 9.4 |
| | Food energy intake | 0.9999 | 0.5 | 0.99- 1.00 |

**Variables in model:** total household income, education level, level of urbanisation, the smoking habit, alcohol consumption, physical activity level, food energy intake (without alcohol) and HIV status.
**CI** = confidence intervals; **sig**=significance

Physical inactivity seems to be the lifestyle factor to predict the metabolic syndrome in these women. Table 7.12 reveals that physical activity was protective against the clustering of risk factors in these women.

**Table 7.12 Significant influences of lifestyle factors on the clustering of risk factors in the development of the metabolic syndrome in this population**

| Gender | Lifestyle marker | Odds ratio | Sig | 95% CI |
|---|---|---|---|---|
| male | Income R1001-R2000 | 24.5 | 0.04 | 1.1 - 530.9 |
| | Food energy intake | 1.0004 | 0.01 | 1.0 - 1.1 |
| Female | Physical activity | 3.8 | 0.02 | 1.3 - 11.6 |

**Variables in model:** total household income, education level, level of urbanisation, the smoking habit, alcohol consumption, physical activity level, food energy intake (without alcohol) and HIV status.
**CI** = confidence intervals; **sig**=significance

## 7.3 Discussion

Insulin resistance was present in the studied population. The clustering of risk factors also occurred, although no definite pattern between the different insulin sensitivity quartiles could be observed. However, the clustering of two or more factors tended to be predominant in the lowest insulin sensitivity quartile for both gender groups, although the percentage of men per insulin quartile was low. Results from the Paris Prospective Study suggest that clustering of mild abnormalities is probably present long before a susceptible patient develops frank hyperglycemia or CHD (Fontbone and Eschwège, 1991).

From the results in Table 7.2 it can be assumed that the presence of an increased BMI (29.2%), followed by systolic hypertension (24.9%), and increased fasting serum insulin (20%) were the main traditional risk factors for the development of the metabolic syndrome in the women. However, the results in Table 7.4 reveal that an elevated serum calcium, body mass and serum urea were the main indicators for a decreased insulin sensitivity in these women. In men a high WHR (35.2%) followed by systolic hypertension (25.4%) were the main traditional risk factors. However, the results in Table 7.3 reveal that an increased triceps skinfold and elevated serum calcium and uric acid were the main indicators for a decrease in insulin sensitivity in these men. Risk estimations of all the possible risk markers (traditional and other) showed that a total serum cholesterol above 4.4 mmol/L followed by a serum ferritin level greater than 163.4 $\mu$g/L in the men, and a LDL-C:HDL-C ratio above 3.3 mmol/L followed by a plasma fibrinogen level above 4.3 g/L in the women, could be the biological markers for insulin resistance in this population. A triceps skinfold thicker than 25mm could be a possible anthropometric marker for the metabolic syndrome to develop in women. In the studied population no such marker was found for the men. However, it should be taken into account that the real statistical significance of these risk estimations are low, due to the large confidence intervals. If the sample size was larger, the interpretation of these results would probably be easier. Thus, these results should be taken only as an indication of possible risk markers for the metabolic syndrome in this population and should be investigated further.

Table 7.4 also reveals that it was the younger women in this study who tended to be most insulin resistant (lowest insulin sensitivity). This finding supports the statement of Kohrt (2000) that age-related decreases of insulin sensitivity (increases in insulin resistance) are due to other factors and that aging *per se* has little to do with it. In this study we expect the younger women to be longer exposed to a westernised lifestyle than the older women. From our data there is, however, no justification for this suggestion.

Urbanisation seems to be a factor in the development of insulin resistance in these men and women. The rural and farm living women tended to be more insulin sensitive (Table 7.11 and 4.8).

The presence of one risk factor was found in more than a quarter of these (34.2% in men and 25.8% in women) "apparently healthy" subjects (Table 7.7). Mollentze *et al.* (1995) also reported a frequent occurrence of one risk factor in Africans from the Free State. They reported a lower incidence of risk factors in rural men/women than in urban men/women. The lower incidence of risk factors in the women of that study was striking (Mollentze *et al.*, 1995). The THUSA-study demonstrates a higher incidence of risk markers in the rural men/women than in the urban men/women without a striking difference in incidence of risk markers between genders (Table 7.10). Unfortunately, not all the same risk factors were measured in the two studies, but trends can be followed and compared.

Risk estimations for the clustering of risk factors revealed that total serum cholesterol may be a predictor at lower than normally accepted levels, although large variations occurred between subjects in both genders. In the men a two hour serum glucose level above 6.1 mmol/L might also be a good predictor of the metabolic syndrome. In the women fasting serum insulin levels greater than 23.6 $\mu$U/L might also indicate the development of the metabolic syndrome. Again these results should be interpreted with care because of the insufficient evidence for statistically significance and should be used only as an indication for possible risk factor clustering.

Clustering of risk factors was present. A cluster of up to five risk factors in the men and six in the women was found in this population. However, the incidence of clustering was low. The same tendency was reported in the Africans of the Free State (Mollentze *et al.*, 1995) and the black population of the Cape Peninsula (Steyn *et al.*, 1991).

Insulin resistance was present in only 28% of the men who showed clustering of risk factors and in 34% of the women. In both genders insulin resistance predicted the metabolic syndrome (49% in men and 68% in women), indicating that insulin resistance might account for less than a half of the clustering of risk factors for some of the chronic diseases of lifestyle in this population. These results indicate that the clustering of risk factors for the "metabolic syndrome" was not essentially related to insulin resistance in this population.

The influence of urbanisation on the development of the metabolic syndrome is not clear The presence of risk factors as well as their clustering effect were observed in all categories of urbanisation in this study population and even higher in the rural than urban groups. It seems as if "contamination" between the different urbanised groups occurred. This tendency of "urbanised" or western influences on lifestyle in rural settings was also reported by Mollentze *et al.* (1995) and Gelderblom and Kok (1994). The findings of Vorster *et al.* (2000) that the psychological and nutritional status of the urbanised THUSA-subjects were "better" than the rural and farm living subjects probably also play an important role in the development of risk for chronic diseases of lifestyle.

Although the predictive value of plasma fibrinogen as a marker for insulin resistance in the women and a marker for the clustering of risk factors in the men should also be interpreted with care due to the large confidence intervals, it should not totally be ignored. Recent studies have shown fibrinogen to be an independent risk factor in the development of CHD (Kannel *et al.*, 1987; Assmann *et al.*, 1993; De la Serna, 1994) while others classify it as a "new" factor or characteristic of the metabolic syndrome (Imperatore *et al.*, 1998; Brun *et al.*, 1998). Yudkin (2000) reported that the release of TNF-α, a proinflammatory cytokine that has inhibitory actions on insulin signalling as a result from effects on phosphorylation of the insulin receptor substrate-1, is increased in overweight subjects. But no significant release of TNF-α from subcutaneous adipose tissue could be shown from their research. However, they found a 3-4-fold higher concentration of interleukin-6 in adipose tissue. Yudkin (2000) proposed that obesity may induce both insulin resistance and endothelial dysfunction through the high release of the interleukin-6 cytokine. Interleukin-6 is the major stimulant for fibrinogen synthesis and secretion (Bini and Kurdryk, 1992). As mentioned, the women in this study were predominantly obese while the men were not. It is therefore suggested that the involvement of interleukin-6, as mentioned above, should be further investigated in this population.

## 7.4 Conclusion

It can be concluded that low clustering of the traditional risk factors for the chronic diseases of lifestyle exists in these "apparently healthy" subjects and that insulin resistance only accounts for approximately 50% of these clusters. From the results of this study (Chapters 4 and 7) it is difficult to conclude that more risk factors cluster in subjects living in the urban than in the rural areas. However, the highest insulin sensitivity was found in the rural and farm living men and women and the lowest insulin sensitivity was found in the squatter men and urban women, indicating that the development of insulin resistance is associated with urbanisation.

Despite the outspoken presence of overweight and obesity in these women, the clustering of risk factors for the chronic diseases of lifestyle is still very low. The presence of insulin resistance as well as its role in the clustering were limited. Despite the fact that the percentage of men with no risk factors (41.5%) did not differ from the women (42.5%; Table 7.5), little obesity occurred in these men. This might be an indication of different mechanisms involved in the developing of the metabolic syndrome in the men and women in this population. Results in Tables 7.11 and 7.12 suggest that the low reported food energy intake of these men protected against the clustering of risk factors, but that the large reported amount of food energy intake in the women predicts inulin resistance. This may also be an indication that food energy intake *per se* is not a factor in the development of the metabolic syndrome, but that the composition of the energy intake might be the factor predicting the metabolic syndrome and/or insulin resistance. Another explanation for this finding could be the fact that "overnutrition" as indicated by a mean BMI of 26.9 $kg/m^2$ was present in the women, while undernutrition (mean BMI of 20.5 $kg/m^2$) was more prevalent in the men. An increase in energy intake would represent further overnutrition in women, while in men it would result in more adequate or optimal nutrition.

There are also indications that certain lifestyle factors such as the level of urbanisation in the women and the level of education in the men might predict the development of insulin resistance and that the level of physical activity in the women might predict the metabolic syndrome in this population. Since urbanisation, insulin resistance, physical activity, food energy consumption, and obesity relate to each other, and the level of education as well as the monthly income guide lifestyle, it is suggested that a follow-up of this study should be done in a few years time.