Overweight and fat distribution
Associations with aspects of morbidity

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Proefschrift
Ter verkrijging van de graad van
doctor in de landbouwwetenschappen,
op gezag van de rector magnificus,
dr. C. C. Oosterlee,
in het openbaar te verdedigen
op vrijdag 3 oktober 1986
des namiddags te vier uur in de aula
van de Landbouwuniversiteit te
Wageningen

Aan mijn ouders en Ellen

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STELLINGEN

1. Bij herziening van het advies inzake adipositas van de gezondheidsraad (1984) verdienen de volgende punten extra aandacht in de aanbevelingen:
   - Het belang van preventieve maatregelen voor overgewicht.
   - Het belang van de vetverdeling in de relatie overgewicht en morbiditeit.
   - Leeftijdsspecifieke grenswaarden voor overgewicht.

2. De weegschaal is een belangrijk instrument voor de huisarts, een meetlint is mogelijk nog belangrijker.

3. De verschillen in psychosociale problematiek rond overgewicht tussen mannen en vrouwen geven aan dat 'gewichtsbeleving' een onderwerp is wat dringend emancipatie behoeft.

4. De vetzuursamenstelling van vetweefsel uit het omentum zal eerder veranderingen in de vetzuursamenstelling van de voeding reflecteren dan die van vetweefsel uit het femorale en gluteale gebied.

5. Het feit dat bij het ouder worden relatief meer vet in de buikholte wordt opgeslagen en de opvatting dat juist dit intra-abdominale vetweefsel ongunstige eigenschappen heeft zijn in tegenspraak met de bevinding dat het gezondheidsrisico bij een bepaalde mate van overgewicht afneemt bij toenemende leeftijd.

6. Correlations on the aggregate level of nations do not prove anything; their only purpose in research is to stimulate the generation of hypotheses

   F. de Waard. Nutrition and Cancer 1986;8:5-8.

7. Het zou in ieders belang zijn wanneer de adviezen van de Gezondheidsraad, hoe deskundig ze ook opgesteld mogen zijn, vóór publicatie aan multidisciplinaire panels zouden worden voorgelegd.

8. Het algemeen gebruik van multipele regressie vergelijkingen bij studies naar de determinanten van hart- en vaatziekten waarbij, naast een maat voor obesitas, ook de andere bekende risicofactoren voor de eindpunten worden betrokken, geven een sterke onderschatting van het gezondheidsrisico behorend bij een bepaalde mate van overgewicht.

9. Het verouderen van een populatie gaat gepaard met een toenemende heterogeniteit van fysiologische variabelen. Het opstellen van voedingsrichtlijnen voor ouderen zal gebaseerd moeten zijn op deze heterogeniteit.

10. And then there is significance - a word that is probably the single greatest intellectual pathogen in both biological and statistical domains today.

Feinstein A.R.'Clinical epidemiology'.Philadelphia, W.B. Saunders 1981.

11. The issues of preventive medicine have little to do with science, relative risks, and risk factors. They could be more profitably debated within the framework to which they belong - ethics, politics, and vested interests.

Skrabanek P. Lancet 1986;i:143-4.

12. Een 'population strategy' en een 'high risk strategy' voor het gunstig beïnvloeden van risicofactoren zijn geen elkaar uitsluitende alternatieven maar dienen beiden tegelijkertijd te worden toegepast.

zie ook: Lewis B, Mann J.I., Mancini M. Lancet 1986;i:956-9.

13. Het schrijven van een onderzoeksvoorstel zou opgenomen moeten zijn als onderdeel van een verplicht onderwijselement in het studiecurriculum 'Voeding van de mens'.

14. Diegenen die van vermageren een afval-race maken lopen een grote kans als eersten aan te komen.

Stellingen behorend bij het proefschrift van Jaap C. Seidell.
Overweight and fat distribution - associations with aspects of morbidity.
Wageningen, 3 oktober 1986.

CONTENTS

VOORWOORD

In dit proefschrift worden enkele onderzoeken beschreven naar de associaties tussen overgewicht en parameters van de gezondheidstoestand. Hoewel de Vakgroep Humane Voeding van de Landbouw Hogeschool te Wageningen de thuisbasis was voor de onderzoeken, werd het grootste deel van het werk uitgevoerd in samenwerking met het Centraal Bureau voor de Statistiek, het Nijmeegs Universitair Huisartsen Instituut en het Instituut voor Radiodiagnostiek van de Katholieke Universiteit te Nijmegen.
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OVERWEIGHT AND FAT DISTRIBUTION - ASSOCIATIONS WITH ASPECTS OF MORBIDITY

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ABSTRACT

This thesis reports on the association between estimates of the amount and distribution of fat mass with aspects of morbidity in Dutch adults. A literature review on the current insights into these associations is included. The results of several cross-sectional and retrospective cohort studies are presented. The prevalence of severe overweight, defined as a Body Mass Index (BMI=kg/m^2) higher than 30 kg/m^2, is about 6% in women and 4% in men, while about 34% of the men and 24% of the women are moderately overweight (BMI 25-30 kg/m^2). Among overweight persons, especially when severely overweight, the prevalence and incidence of various chronic disorders and use of aspects of medical care was higher than in non-overweight persons. For gout and arteriosclerotic disease, overweight appeared to be a risk factor at lower levels of BMI in men than in women. The incidence was particularly high in men with an initial BMI between 27-30 kg/m^2. The association between BMI and subjective health was more pronounced in women than in men. This was true for certain somatic as well as psychosomatic complaints.
Fat distribution, as measured with the waist-hip circumference ratio or waist-thigh circumference ratio, was shown to be related to the prevalence of certain chronic disorders in men and women. These associations were independent of age and BMI. A study in which Computed Tomography scans, taken at the level of the L4 vertebra, were related to anthropometric measurements, revealed that correlations of circumference ratios with the amount of intra-abdominal fat were higher than with subcutaneous abdominal fat.

It is concluded that overweight is related to aspects of morbidity but that it may be particularly relevant to include fat distribution measurements in the evaluation of health risks in overweight subjects.

CHAPTER 1

OBESITY AND FAT DISTRIBUTION IN RELATION TO HEALTH - CURRENT INSIGHTS AND RECOMMENDATIONS

J.C. Seidell, P. Deurenberg, J.G.A.J. Hautvast

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GENERAL INTRODUCTION

Obesity research has received much attention during the past decades, during which new evidence for aetiologic and prognostic aspects of obesity and underlying mechanisms has been accumulating. The recommendations for prevention and therapy, however, have not changed dramatically. In February 1985, a consensus panel at the National Institute of Health in Bethesda, Maryland, discussed the available knowledge on the health consequences of obesity and formulated recommendations for the treatment of obesity. Some aspects of the evidence that formed the basis for these recommendations are discussed in the first part of this review.

The consensus panel concluded that recent evidence strongly suggests that the regional distribution of body fat is an important determinant for the occurrence of clinical correlates of obesity such as cardiovascular disease, stroke and diabetes. The current knowledge of the assessment and consequences of types of fat distribution is discussed in the second part of this review. It can be expected that, in the near future, measures of fat distribution will be included in recommendations for the diagnosis and treatment of human obesity.

1. OBESITY, CURRENT RECOMMENDATIONS

1.1. Definition and assessment of overweight and obesity; agreement on an international standard

Bray [25] has pointed out that it is important to distinguish between overweight and obesity. Overweight is defined as an increase in body weight above some arbitrary standard defined in relation to health. Obesity is defined as an abnormally high proportion of body fat. The term 'abnormal' indicates that obesity corresponds to the upper end of range of the body fat percentages observed in a particular population. Overweight and obesity can be distinguished only if the amount of body fat can be measured. The methods for assessing body fat can be divided into direct and indirect methods. These methods have recently been well reviewed by Garrow [51]. Table 1 gives a summary of methods currently in use. They are of varying accuracy and it is difficult to pinpoint one of the indirect methods as the most valid one.

Table 1. Quantitative methods for the determination of body fat in human (adapted from Bray 1985) [25]

1) Direct carcass analyis
2) Body density and body volume (by under water weighing; plethysmography)
3) Isotope or chemical dilution
   - Amount of body fat, by measuring the distribution of cyclopropane or Krypton
   - Amount of lean body mass, by measurement of Potassium (40 K) in the body
   - Amount of body water, by measuring the distribution of tritiated water (3H2O) or antipyrine
4) Anthropometric measurements
   - Height and weight tables or indices (sometimes including measures of frame size)
   - Skinfold thickness (usually triceps, biceps, supra-iliac, subscapular skinfolds)
   - Circumference measurements (now often used for the assessment of body fat distribution, usually thigh, hips and waist circumferences)
5) Electrical conductivity of the body
   - Total body electrical conductivity (TOBEC)
   - Bioelectric impedance
6) Imaging techniques
   - Ultra-sound waves
   - Computerized tomography (CT) or nuclear magnetic resonance (NMR)

The difficulty of validating the methods has recently been discussed by Garrow [51]. A new method of determining body fat content, which allows specification of body fat distribution over different body fat depots is computed tomography. This method will be discussed in more detail in section 2.1.3 of this review. This method can probably be regarded as the best indirect method available, but it involves radiation of subjects. Nuclear Magnetic Resonance imaging (NMR) may be a good alternative to computed tomography [43] but this requires further investigation.

Currently, weight-height indices are the most widely used measures of adiposity and overweight. They have the advantage of easy calculation and can be used in epidemiologic studies on large groups of individuals. They suffer, however, from misclassification bias. Weight-height indices are constructed on the basis of three criteria.

a) Zero correlation with body height.
b) High correlation with body fatness.
c) Correlation with mortality.

These criteria will now be discussed.

a) On the basis of the criterion of no correlation with height, Benn [11] proposed weight/height^p as an obesity index, in which p is a population-specific value, obtained by minimizing the correlation of the index with height [11]. Garrow argued that a disadvantage of this index is that it can be applied to individuals only after the correct value for p has been determined in the appropriate population [51]. Another disadvantage is that results from different populations are difficult to compare and to interpret [49]. Quetelet [81] observed in 1869 that inidividuals' weights were roughly proportional to height squared. Since then the index weight/height^2 has been shown to satisfy the criterion of low correlation with height. Use of a fixed p value (i.e. 2) does not have the disadvantages of the Benn Index.
b) Although the correlation of Quetelet's Index, or the 'Body Mass Index', with the percentage of body fat (as determined by, for instance, under-water weighing) is generally found not to be very high (around 0.7 - 0.8), other indices rarely show higher correlations [49]. Garrow and Webster [51a] critically examined the relation of Quetelet's index to body fat and demonstrated that three standard methods (under water weighing, water dilution or potassium counting), yield considerably different results and, in addition, showed that Quetelet's Index should not be related to percentage body fat, because it is a measure of the amount of fat (kg). Indices which take measures of frame size into account, show no meaningful improvement in estimating body fatness in young adults [10, 86]. The importance of frame size in other age groups requires further investigation [90].
c) On the basis of analysis of existing mortality data, Garrow [50] proposed a classification of obesity on the basis of Quetelet's Index (Table 2).

Table 2. Garrow's classification of obesity in categories of Body Mass Index or Quetelet's Index (kg/m^2) [50]

	BMI (kg/m^2)	Interpretation of BMI in category
	< 20	Underweight
Grade 0 obesity	20 - 24.9	Acceptable weight
Grade 1 obesity	25 - 29.9	Moderate overweight
Grade 2 obesity	30 - 39.9	Severe overweight, obese
Grade 3 obesity	$\geq$ 40	Morbidly obese

Some investigators have preferred to use 27 kg/m^2 as a cut-off point for obesity in men [65, 98]. As Quetelet's Index has been shown to be somewhat inferior to Benn's Index with 1.5 as value for p in women, some investigators have used $weight/height^{1.5}$ for women [97]. To make comparisons between men and women more easy they transformed the different indices into standard scores. The advantages of this approach remain to be proven.
Sofar, Quetelet's Index has been accepted by expert committees as the most useful measure of obesity when only height and weight data are available [29, 53, 87, 91]. Other indices as Broca's index or the ponderal index are now generally considered to be less suitable indices of body fatness.

1.2. Prevalence of overweight and obesity in industrial countries

Table 3. Prevalence of moderate and severe overweight (obesity) in some industrialized countries (in percentages)

Quetelet's Index (kg/m^2)	United Kingdom men	United Kingdom women	The Netherlands men	The Netherlands women	United States men	United States women	Australia men	Australia women
moderate overweight; 25 - 29.9	34	24	34	24	31	24	34	24
severe overweight: $\geq$30	6	8	4	6	12	12	7	7

In the four countries shown in table 3, moderate overweight appears to be more common in men than in women. In European countries, obesity is slightly more common in women than in men. Obesity appears to be more prevalent in the United States in both men and women than in any of the other industrial countries in the table

1.3. Body fatness and mortality - epidemiological evidence

1.3.1. Epidemiological evidence

One of the most comprehensive reviews on obesity and mortality was published by Simopoulos and Van Itallie in 1984 [90]. Their review is based on the conclusions of a workshop on body weight, health and longevity held in Bethesda, Maryland, in 1982. They reviewed a number of large population studies in which a relationship between overweight and mortality had been demonstrated. Some characteristics of these studies, to which we add a recently published population study from Norway [107], are shown in table 4.

It is typical for all these studies that large populations had to be followed up for at least 10 years before any effect of body weight on mortality was detectable. Björntorp [15] has proposed that the delayed effect may be explained by the possibility that excess mortality (especially from cardiovascular disease) is present mainly in a subgroup of the obese population. Lumping all types of obesity into one category may cause statistical dilution of an effect of body fatness on mortality in a subpopulation of the obese. Another feature of the studies summarized in table 4 is the J-shaped relation between Body Mass Index and mortality. Excess mortality at both ends of the range of Body Mass Index are evaluated in section 1.3.2.

Smoking appears to be an important confounding factor in the relationship between body fatness and mortality, and needs to be taken into account assessing the risk of overweight and obesity.

The available epidemiological evidence has led to the conclusion that 'overweight persons (i.e. persons whose weights are above average) tend to die younger than average weight persons, particularly those who are overweight at younger ages' [90]. Similar conclusions were drawn by the Royal College of Physicians in 1983 [87].

It remains to be determined, however, whether persons who are moderately overweight but not obese might benefit from weight reduction when there is no indication of abnormalities (e.g. hypertension, impaired glucose tolerance,

Table 4. Some aspects of studies demonstrating a relationship between an obesity index and mortality (adapted from Simopoulos and Van Itallie [90]

n	Type of studies	Mathematical relation	Weight with minimum mortality	Sex and age difference of relation BMI and mortality	Average/ max follow-up(yrs)	Remarks on study population	Follow-up after which an increased risk became apparent(yrs
	<u>Life insurance statistics</u>						
4.2 million	- Build Study 1979	J-shaped	weight below average	more apparent in men age 15-39 than in age 40 - 69	6.6/22	Policy-holders, mainly male, middle-class, of apparently good health	± 10
	- Provident mutual life study	?	weight below average	only men	? /34	Male policy holders	± 16
	<u>Prospective studies</u>						
750000	- American Cancer Society	J-shaped	10-20% below of average weight (non-smokers)		6 /14	Predominantly middle class healthy volunteers self-reported data	?
5209	- Framingham Heart Study	J-shaped	± 20% below average weight (non-smokers)	effect in men decreased with age	- /26	Residents of Framingham	± 10
3983	- Manitoba Study	?	below average	most apparent in men 20-40 yrs	- /26	Male pilots	16
1.2 million	- Norway	J-shaped	BMI's* between 23 and 27 kg/m^2 for males and females	flatter curve for women minimum increase	10 /15	General population	?
?	- Britain	J-shaped (after adjustment of weight change in adult hood	around a BMI* of 23 kg/m^2		- /10	Middle aged men	?

* BMI = Body Mass Index (weight/height^2 in kg/m^2)

hyperuricaemia or hyperlipoproteinemia) and no evidence of clinical illness or a genetic predisposition for such illness. This point has been stressed by Berger et al [12] and Andres [2] who have since been frequently misquoted as being proponents of the view that overweight subjects should not be treated unless they are really obese (BMI > 30 kg/m^2).

The main problem of overweight subjects is that they are at risk of becoming obese, and for prevention purposes this group requires attention [50, 59]. More important is the finding that fat distribution, even in very moderate degrees of overweight, seems to have a substantial impact on health risk. A re-evaluation of existing evidence might lead to new diagnostic criteria for estimating the risk of overweight and obese individuals (See section 2 for more details).

Another factor that needs to be taken into account in the evaluation of overweight individuals is their age, as it has been shown that weight at minimum mortality increases with age [2]. In fact the NIH consensus development conference concluded from the Framingham and American Cancer Societies study that the increase in mortality with relative weight is steeper for those under 50 years of age, suggesting increased desirability of treatment in younger age groups.

1.3.2. Causes of death in overweight and underweight individuals

As discussed in the previous section, it has been shown that mortality rates are increased at both ends of the distribution of the Body Mass Index. The main causes of death in the underweight and the overweight part of the population are dissimilar. Waaler [107] identified lung diseases (including lung cancer, tuberculosis and obstructive lung disease) and stomach cancer as typical causes of death of underweight individuals. It must be noted, however, that no adjustments had been made for possible confounding effects of smoking. Cardiovascular disease, cerebrovascular disease and diabetes were found to be characteristic causes of death in overweight subjects. Similar conclusions have been drawn from other investigations, where increased cancer incidence was observed in underweight subjects and increased cardiovascular risk was apparent in overweight subjects [9, 46]. Such illness might also be the cause of underweight.

From a Norwegian study [107] it was calculated that obesity is responsible for 4% of all deaths in women and 5% in men. This is of the same order as for lung cancer in men and breast cancer in women.

Lew and Garfinkel [74] in their much cited analysis of the American Cancer

Society Study found that men with weights more than 40% above the average were at increased risk of cancer of the colon, rectum and prostate. In obese women, increased risk for cancer of the gallbladder, breast, cervix (especially post-menopausal), endometrium, uterus and ovarium was found (especially in lower socio-economic groups). More evidence for increased risk of cancer at particular sites in both underweight and overweight subjects shows that it is impossible to give an optimal weight for cancer risk, especially since nutritional factors may be important in the association of body weight and cancer risk [46]. Garn proposed that low serum and tissue levels of vitamins (particularly vitamin A) and low cholesterol levels might explain the increased mortality risk in the underweight part of the population.

Cardiovascular mortality

Apart from the possible statistical dilution effect due to the failure to take the heterogeneity of human obesity into account, sophisticated analyses may blurr the picture. It has been proposed [65] that obesity is not a major risk factor for cardiovascular disease since it proved not to be a risk factor independently of other risk factors, such as elevated blood pressure, ECG abnormalities, cholesterol and glucose tolerance. The mechanism by which obesity could lead to premature cardiovascular death probably involves these risk factors and it is not fully clear how a statistically independent effect of Body Mass Index on cardiovascular disease should be interpreted [87].

Brunzell [27] has argued that, since cardiovascular disease risk is particularly elevated in young adults, genetic factors may play a major role in the association. This hypothesis has to be investigated further.

Hubert et al [60] in a 26 year of follow-up study of 5209 men and women, concluded that Metropolitan relative weight at baseline examination was an independent predictor of angina pectoris and other coronary disease in men and women. In women it was also a predictor of stroke, congestive failure and coronary and cardiovascular death. In this relation adjustments were made for age, cholesterol, systolic blood pressure, smoking, left ventricular hypertrophy and glucose tolerance. As discussed above, there is no obvious underlying mechanism for the independent relationship is not directly at hand. The data of the Framingham study [60] also revealed that weight gain in young adult years conveyed an increased risk of cardiovascular disease in men and women, that could not be attributed to initial weight or to risk factors that may result from weight gain.

From this important study it was concluded that intervention in obesity is an advisable goal in the primary prevention of cardiovascular disease.

1.4. Obesity and morbidity

From an extensive review of the literature, Berger et al [13] concluded that the associations of obesity with several chronic disorders are well established, but that the evidence for other claimed associations is not always conclusive. A listing of the disorders found, or claimed, to be associated with overweight is shown in table 5.

Table 5. Diseases and metabolic abnormalities proven or claimed to be related to obesity (adapted from Berger et al 1985 [13]

Diseases related to obesity (well documented evidence)	Diseases related to obesity (not well documented evidence)
hypertension	gall stones
hyperlipoproteinaemia	kidney stones
gout	musculo-skeletal disorders
diabetes mellitis	hernia
glucose intolerance	pulmonary insufficiency
cardiovascular disease	alveolar hypoventilation
	venous stasis
	haemmorrhoids
	severe impairment of self-image
	susceptibility to psychoneuroses
	impairment of sexual and reproductive functions
	risk of endometrial and breast cancers

An important problem with the diseases that are not firmly related to obesity, shown in table 5, is that they are difficult to study in prospective studies. Several variables, associated with environment and life style, may confound the relation. Available evidence is based mainly on self-reported data or case-control studies in selected populations. As will be discussed in the next section, fat distribution may complicate the detection of existing associations. Furthermore, slimming efforts might contribute to the onset of diseases such as gallstone disease and may thus lead to spurious associations with overweight.

Clearly, the relation of body weight to morbidity is a very complex field to study. The NIH consensus panel, discussing this subject, placed considerable weight on evidence from the two National Health and Nutrition Surveys (NHANES) conducted by the National Center for Health Statistics (NCHS) in the USA. The NHANES II (1976 - 1980) study revealed strong associations of hypertension, hypercholesterolemia and diabetes with BMI values at or above 27.8 for men and 27.3 for women (the 85th percentile level in the USA), especially in young adults (ages 20 - 44).

Recommendations for weight reduction, based on increased risk of morbidity and mortality with overweight, were made for the following circumstances (adapted from [29]).

(i) Excess body weight of 20 percent or more. This corresponds to a BMI above 26.4 for men and 25.8 for women (1959 Metropolitan tables), or above 27.2 for men and 26.9 for women (1983 Metropolitan tables). For extreme obesity, risks are much greater, including a risk of dangerous cardiopulmonary conditions.

(ii) Family history or risk factors for maturity onset (Type-II) diabetes.

(iii) High blood pressure.

(iv) Hypertriglyceridemia or hypercholesterolemia.

(v) Coronary disease (or atherosclerosis).

(vi) Gout.

(vii) Functional impairment due to heart disease, chronic obstructive pulmonary disease, or osteoarthritis (spine, hips and knees, which bear weight).

(viii) History of childhood obesity.

Diagnostic and cardiopulmonary fitness assessments should involve the physician, and programs of weight reduction should bring in other health professionals as well.

One of the research areas stressed by the panel as being an important area for future study was research on determinants of body fat distribution, and on the mechanisms of its adverse effects.

We may conclude that, although some associations remain to be clarified, obese or overweight individuals who have musculoskeletal or respiratory complaints, elevated blood pressure, hyperlipoproteinemia, diabetes type II, or glucose tolerance can be expected to benefit from weight reduction [16, 59].

2. FAT DISTRIBUTION; A NEW DIMENSION IN OBESITY RESEARCH

2.1. Introduction

In the previous section some recommendations made by the consensus panel of the NIH in Bethesda, Maryland in 1985 were cited. From the reports of the panel it was clear that throughout the discussions the topic of fat distribution was a recurrent theme. Similarly, at many important international congresses on obesity research (e.g. the International Congress on Obesity in New York in 1984 and the International Symposium on the Metabolic Consequences of Obesity in Marseille in 1985) increasing attention has been paid to the classification of types of body fat distribution and its relations to disease. Although the importance of a distinction between central and peripheral types of fat distribution was stressed by Vague in the early fourties, the subject of human fat distribution has been a somewhat neglected subject in obesity research until recent years.

Investigators from many countries (especially Sweden, France and the United States) are now clarifying the metabolic basis for the observed relations between different types of fat distribution and various clinical associates of obesity.

Table 6 shows a summary of some of the relationships established between a fat distribution type, in which fat is predominantly stored in the abdominal region, and various diseases.

Table 6. Diseases or metabolic abnormalities shown to be related to abdominal fat distribution

Men		Women	
Prospective studies	Only in cross-sectional studies	Prospective studies	Only in cross-sectional studies
- ischemic heart disease	- arthrosis	- myocardial infarction	- hypertension
- stroke	- hypertension	- angina pectoris	- glucose intolerance
- diabetes	- glucose intolerance	- stroke	- hyperinsulemia
	- hyperinsulemia		- menstrual abnormalities

unclear: gout, gallstones, kidney stones

In the next section of this review we will first discuss some of the methods used for the classification of types of fat distribution, and then consider the functional characteristics of fat stored in different regions of the body. Finally, the relations, summarized in table 6, will be discussed in some detail.

2.1. An overview of methods used for the classification of types of fat distribution

2.1.1. Subcutaneous fat patterning

Jean Vague can be regarded as one of the pioneers in research on body fat distribution. He introduced, in the early fourties, the concepts of android and gynoid types of fat distribution [101]. For classification purposes he developed an Index of Masculine Differentiation (IMD) based on the average of the nape to sacrum skinfold ratio (corrected for the total thickness of the fat in the two regions) and the 'Brachio/Femoral Adipo Musculo Ratio' (B/F AMR). THE B/F AMR was calculated from skinfolds at the proximal parts of the arm and thigh and circumferences of the limbs at the same level [103]. Relatively high values of the IMD were typically found in men (android fat distribution) while lower values were found to be characteristic in women (gynoid fat distribution). Vague's observations of associations of these types of fat distribution with specific disorders and metabolic abnormalities stimulated research in this area. Other methods used for the description of subcutaneous fat patterns include Z-score pattern profiles [45], ratios of skinfolds such as triceps/subscapular ratios [42], and the ratio of sum of trunk skinfolds to the sum of skinfolds on extremities [36, 23, 30]. Principal components analysis of subcutaneous fat sites has also been used in the study of human fat patterning, and the usefulness of this approach has recently been confirmed [34, 79]. Joos et al [62] used discriminant analysis of skinfold thicknessess in order to distinguish diabetics from non diabetics. It was shown that in men a contrast of subscapular with waist and leg skinfolds and in women of subscapular and leg (calf) skinfolds provided the best basis for the classification of subjects into diabetics and non-diabetics.

In obesity research these methods have certain drawbacks, since skinfold thickness measurements in obese subjects are often difficult to measure and have poor reproducibility [26].

Another drawback is that measurement of the distribution of subcutaneous fat alone fails to take the intra-abdominal fat depot into account.

2.1.2. Circumference ratios for describing fat distribution patterns

Methods of describing more than the subcutaneous fat pattern alone involve, for instance, somatotyping. In such methods, that were frequently used in the fifties and sixties of this century, classification of typical forms of body build is made by trained raters. Craig and Bayer [31] used photographs and outlines of obese women and classified them into categories ranging from hyperfeminine to hypofeminine. Damon et al [32] classified Framingham males according to the typology of Sheldon and related different types of body build to health.

Ashwell et al [6] redeveloped the concepts of gynoid and android fat distribution and rated pictures of obese women as android and gynoid. Discriminant analysis was used to construct a Fat Distribution score (FD-score) based on body dimension measurements. With this score a similar classification of obese subjects into types of fat distribution was obtained compared to the classification based on the photographs and the classification system that was developed by Vague. The score of Ashwell et al was calculated from the ratio of waist diameter to thigh diameter [6]. Later they proved that this 'Fat Distribution score' was highly correlated with the ratio of waist to thigh circumferences [7].

In Sweden, collaborators in research on fat cell metabolism and metabolic complications found that the waist circumference was highly correlated with metabolic complications. As the waist circumference was closely dependent on the size of the individual, the ratio of the waist to hips circumference was used in the analyses in order to correct for body size [68]. In an epidemiological study of 15532 obese women in a slimming organization in the USA, the ratio of reported waist girth and hips girth was used as an index of body fat distribution as 'it was similar to the index reported by Aswell et al, and the Index proposed by Vague' [57]. Evans et al [38] later confirmed that the simplest method for describing fat distribution (i.e. waist/hips circumference ratio) was at the same time the most useful one with respect to metabolic complications [38]. Later, this ratio of waist to hips circumference was found to be a strong predictor of mortality in men and women [73, 72]. Waist/thigh ratio is probably an equally useful measure of fat distribution [16, 88] although in practice subjects may be more reluctant to have their thigh circumference measured than their hips circumference.

The waist/hips and waist/thigh circumference ratios does measure the predominance of fat storage in either the abdominal region or, respectively, the gluteal and femoral region. The abdominal fat depot indicated by the magnitude of the waist circumference includes both the subcutaneous fat depot and the intra-abdominal fat depot. These fat depots have different morphological and metabolic characteristics, and it may be important to distinguish the two in studies of metabolic complications, morbidity and mortality. Computed tomography has been found to be a useful tool for estimating the amount of abdominal fat stored internally and subcutaneously.

2.1.3. Computed tomography in fat distribution research

In 1982, Borkan et al [21] published the results of an investigation which demonstrated the value of CT scanning in assessing abdominal fat content. Data from 8 male patients revealed that a single scan at the level of the umbilicus provided the most useful information on intra-abdominal and subcutaneous abdominal fat. Dixon [35] compared CT-scans of 25 men and 25 women at this level (which corresponds in most cases to the level of the L4 vertebra) and observed that men had significantly more fat within the abdominal cavity. The total amount of body fat in this region was found to be similar in men and women, but in women a greater proportion of the fat was stored subcutaneously. Grauer et al [55] studied 50 adult males and 62 adult females and assessed fat distribution at several other vertebral levels (L1, L3 and L5). They confirmed that the proportion of subcutaneous fat is greater in women than in men but found that total fat volume in women was higher than in men. Similar results were obtained from obese subjects [100]. Borkan et al [22] showed that total fat mass in men did not differ between middle aged (mean age 46 years) and older men (mean age 69 years), but that the proportion of subcutaneous abdominal fat was lower and, correspondingly, the proportion of intra-abdominal fat was higher in the older men. Aswell et al [8] studied in 28 women the relationships between the circumference ratios described above and the ratio of subcutaneous abdominal fat to subcutaneous fat at the umbilicus (L4) level. There was a significant correlation between the waist/hips circumference ratio and the proportion of intra-abdominal fat. These correlations remained significant after adjustments for age and degree of obesity. The authors suggest that the observed relationship between a high waist/hips ratio and metabolic complications might, at least in women, reflect a relatively large amount of intra-abdominal fat.

If this is proven to be the case, it might provide a further explanation for the higher risks that men have for metabolic complications, compared to women, at the same degree of obesity [68]. On the other hand, there is a discrepancy between the observed internalization of fat with increasing age and the decrease in morbidity risk of obesity with advancing age. Further research is needed to clarify this apparent paradox. Figures 1 and 2 illustrate the use of computed tomography performed on two male patients. The patient in figure 2 is older and fatter than the patient in figure 1. The larger amount of body fat in the abdominal region in patient 2 is clearly predominantly stored as intra-abdominal fat.

Figures 1 and 2:
Computed tomographic scans at L4 level in two male patients.

Figure 1. Age: 33 years; BMI: 21.1 kg/m^2; Surface of intra-abdominal body fat: 30 cm^2; Surface of subcutaneous body fat: 124 cm^2.

Figure 2. Age: 55 years; BMI: 26.5 kg/m^2; Surface of intra-abdominal body fat: 157 cm^2; Surface of subcutaneous body fat: 179 cm^2.

2.2. Functional characteristics of fat stored in different regions

2.2.1. Morphology of adipocytes in different regions

It has been known for a long time that women have more body fat than men [77]. Sjöström et al [92] showed, in a study of 11 male and 12 female students, whose weights were within the normal range, that women had more subcutaneous body fat than men and that this difference could be attributed to a larger fat cell number in women than in men. This was demonstrated for the epigastric, hypogastric and femoral region but not for the gluteal region. In the gluteal region the difference in subcutaneous fat thickness between men and women was due to larger fat cell size in women. Krotkiewski et al [67] found that non-obese middle aged women had more body fat than non- obese young women, owing mainly to the larger fat cells in the older women, particularly in the abdominal region. This finding indicated that fat cells of the abdominal region are more responsive to nutritional or hormonal factors than fat cells from other regions. When Krotkiewski et al [68] extended their studies to a large population (n = 930) of obese individuals they found that fat cell weight in obese men was similar in all four studied regions but fat cell number was found to be highest in the abdominal region. In obese women, as in women of normal weight, fat cell size and fat cell weight were highest in the gluteal region.

Thus, the typical characteristics of fat cell morphology and fat distribution in men and women of normal weight remains present in obesity. It was shown that in the obese, the increasing amount of body fat leads to an increased fat cell size, up to a critical value of 0.7 - 0.8 ug per cell. After this increase, a more rapid increase of fat cell number was observed in all regions. This finding challenged the hypothesis (which was hotly debated some years ago) that fat cell number is a characteristic determined early in life and predisposing fat infants to lifelong obesity. This hypothesis has now been generally rejected [56, 63]. The differences between men and women with regard to fat cell morphology and fat distribution may be, according to Björntorp [14], explained by the specific control of femoral-gluteal fat cells by female sex hormones.

The role of hormonal regulation of body fat distribution and fat cell size was further elucidated by work of Rebuffé-Scrive et al [83] who found that fat cells were larger in both abdominal and femoral regions in lactating women than in pregnant and non-pregnant women. Lipo-protein Lipase (LPL) activity was higher in the femoral than in the abdominal region in non-pregnant and pregnant women. Thus, fat is preferentially stored in the femoral region under normal conditions

and in pregnancy in women. During lactation, however, LPL activity was markedly reduced in the femoral region while there was no change in the abdominal region. Basal and catecholamine stimulated lipolysis were found to be more active in the abdominal region (as had also been observed in other studies [5, 76, 69]).
During lactation, in contrast to other conditions, lipolysis increased in the femoral regions. These findings led to the hypothesis that the characteristic female fat storage in the gluteal and femoral fat depots have a function for the storage of triglycerides that can be used to provide the extra energy needed for lactation. This can probably be regarded as an adaptation that was advantageous in pre-industrial civilizations but is no longer of much great physiological importance and is, ironically, the cause of cosmetic concern in women living in populations where food is abundant in all seasons.
It has been reported that in the post-menopausal state women become more similar to men with regard to regional differences in fat cell morphology, and may be influenced by the use of estrogen medication [14, 15]. Other findings which support the hypothesis of hormonal regulation of body fat distribution were published by Evans et al [39]. They studied adipocyte morphology and metabolic profiles in 80 healthy pre-menopausal white women with body weights ranging from normal to markedly obese. They reported that increasing androgenicity (reflected in decreased plasma - sex hormone binding globulin and an increased percentage of free testosterone) was correlated with increasing waist-hips circumference ratio and an increase in fat cell size in the abdominal but not in the femoral region.
Although the details of the mechanisms involved remain to be elucidated, evidence so far strongly suggests that specific endocrine regulation of abdominal and femoral adipocytes explains at least some of the differences between men and women and between types of body fat distribution with regard to the regional variation in morphology and distribution of adipocytes.

2.2.2. Additional factors that may influence regional differences in fat cell distribution and metabolism

2.2.2.1. Weight reduction and fasting

As has been discussed in the previous sections, the abdominal fat depot appears to be a more labile depot of triglycerides. It might therefore be expected that weight reduction would lead to a reduction in cell size, particularly in the abdominal region. This hypothesis is supported by findings of Arner et al [4], who observed that, in 25 obese middle aged women, fat cell volume decreased in the abdominal but not in the femoral region during one week of fasting. LPL activity decreased, and lipolytic activity increased, in the femoral region as result of fasting, but these effects were found to be much more pronounced in the abdominal region. Similar observations were made by Smith et al [94] who studied seriously obese patients before and after jejuno-ileal by-pass. Fat patterns would therefore be likely to be altered after substantial weight reduction. Many studies in the past, however, have been unable to confirm this. For example, Edwards [37] observed in 1950 that in women who lost more than 12.7 kg there was a basic fat pattern that remained stable over a broad weight range. Garn [45] studied 13 men during controlled weight loss and found that the relative fat pattern remained constant. Craig and Bayer [31] re-examined 50 women 2-10 years after conspicious weight loss or gain, and concluded on the basis of outlines that whether weight was lost or gained the distribution of fat and the androgynic pattern remained the same. Vague in 1974 reported that in a study of 13 obese males, 28 obese females and 21 lean females during weight loss or gain the adipomuscular ratios in individuals were more or less characteristic and were inclined to reappear whatever weight variations were imposed on the subject [105]. Ashwell et al [6] found no correlation of their 'Fat Distribution Score' with weight loss and proposed that fat distribution was relatively constant and possibly genetically determined. The work of Börjeson [20] in 1976 on monozygotic and dizygotic twins suggested that fat distribution might indeed have an important genetic component. A recent investigation of weight loss in 187 severely obese women by Lanska et al [69] demonstrated that the ratio of waist to hips girth was not a useful prognostic indicator of weight change for these women with, it should be noted, refractory severe obesity. The assumption that obesity is more catching in the abdominal region and that femoral regions are more resistant to slimming [3] may be unwarranted [52]. On the other hand, Albrink and Meigs showed, in 1964, that in 419 male factory workers, skinfold thickness of the trunk was correlated with the amount of weight gained since age twenty five, but forearm skinfold thickness showed no such correlation [1]. They hypothesized that forearm skinfold thickness reflected innate lifelong obesity, while skinfold thickness of the trunk reflected, at least in part, obesity acquired during adult life. Genetically determined fat storage capacity in different regions may become apparent only in later life under the influences of environmental factors. This hypothesis, that fat in the extremities is increased in inherited but not in acquired obesity, is strengthened by the report of Strendberg (quoted by Wells [108]) of a full thickness skin graft from the abdominal wall to the hand of a slim young girl. As an adult this girl acquired excess weight about the girth and the skin graft of the hand also became obese, although the neighboring forearm adipose tissue did not increase in size. The result, a grotesque boxing glove appearance to the hand, suggests that there is a greater potential for abdominal fat to expand than for fat of the extremities. Thus, environmental influences may be necessary for the expression of genetic factors that determine fat distribution. If this is indeed the case, weight gain in the 'innate' obese should not influence fat distribution, but in those with adult onset obesity it should do so. The conflicting results described above could be due to differences in the aetiology of the obese subjects that were studied. Another feature of the studies described above is that they considered only subcutaneous fat patterning before and after weight loss, and may have failed to take alterations in the intra-abdominal fat depot into account. As was discussed in the previous section, this depot, of all the major fat depots, is the most labile pool of triglycerides. Studies in which subjects with a clear abdominal fat distribution are compared to those with fat storage predominantly in gluteal and femoral depots, before and after controlled weight reduction, are needed to clarify this issue. Although it will be difficult to identify them without misclassification, individuals who are genetically predisposed towards obesity should be separated from those with no family history of obesity at all. In such studies, not only should subcutaneous fat distribution be studied; variation in the amount of fat within the abdominal cavity should also be included. Studies of Bouchard et al [24] suggest that about 60% of the subcutaneous fat pattern might be explained by genetic and environmental factors, which are both equally important. The important implications for the treatment of abdominal obesity mean that priority should be given to studies of the effects of weight reduction by various methods on fat distribution and associated risk factors.

2.2.2.2. Age, degree of obesity, age of onset of obesity, parity

Studies of subcutaneous fat patterns have revealed that, with increasing age, fat shifts from the extremities towards the trunk [47, 48, 93]. Aswell et al [6] showed that older, fatter women are more likely to have a central type of fat distribution. This was confirmed in a study by Seidell et al [88] in which Body Mass Index explained 15.9% of the variation in the waist-thigh ratio of overweight women, and age explained 9.0%. In overweight men, age was significantly correlated with the waist-thigh ratio (r2 = 16.5%), and to a small but significant extent, social class was negatively correlated with the waist-thigh ratio (r^2 = 3.3%).

Data from a large cross sectional survey in the United States (52953 women who participated in a TOPS, 'Take Off Pounds Sensibly', programme) revealed similar results [70]. In this study, in which self-reported waist and hip girths were used, the waist to hip circumference ratio increased with age and body weight. These effects could not be accounted for on the basis of parity, menopausal status or obesity history. Obesity history was defined as the greatest percent over 'Ideal Body Weight' attained during the teenage years. The study has the advantage of a large number of subjects, but the information was obtained from a rather selective population and might be biased by self-reporting of the data. In the study of Seidell el al [88], self-reported weight history revealed that women belonging to the upper tertile of waist thigh ratio had a later onset of obesity than those in the lower tertile of the ratio. In men, no such an effect of onset of obesity was found. Such findings have led investigators to hypothesize that obesity, acquired early in life would lead to generalized obesity with expansion of all fat depots, while in adult onset obesity this expansion would be confined to the abdominal region. As fatness in children is associated with early maturation, one might expect long-term differences in the fat distribution of early- and late-maturing individuals [44]. The effect of maturation on body fat distribution has been studied by Frisancho and Flegel [44] who examined the data from the National Health and Nutrition Examination Survey I in the United States (NHANES I). Percentage trunk fat (defined as subscapular skinfold devided by the sum of the triceps and the subscapular skinfold) was found to be related to bone age (in children) and age of menarche (in adult women). Their results suggested that early maturation from 7 years onwards (except for males aged 13 to 16 years) is associated with larger triceps and subscapular skinfold thickness. This was more evident in the subscapular skinfold. The authors concluded that advanced maturation is associated with an accentuation of the centripetal (abdominal) distribution of fat during adolescence and adulthood. They suggested that environmental influences may bring about the expression of genetic factors that determine fat distribution. Their paper was critisized by Deutch and Mueller [34] who argued that in females the difference ascribed to maturity was likely to be a secondary effect of the correlation between percentage trunk fat and body fatness. In contrast to Frisancho and Flegel, they found that, using principal component analysis of subcutaneous fat distribution in adolesence and young adults, obesity in adolescence and young adulthood was associated with fat concentrated in the upper part of the trunk. This effect was independent of maturity, which was found to be a significant correlate of the trunk/extremity patterning component but not of the upper/lower trunk-fat component (in males). Only long term prospective studies, in which both body weight development and fat distribution are followed, can clearly give the answer to the question whether fat distribution is related to the onset of obesity, menopausal status, and/or parity.

2.2.2.3. Regional differences in fatty acid and glucose metabolism in adipocytes.

It is difficult to study cells from the intra-abdominal fat depot. Those who have studied these cells, obtained them from the omentum major of patients undergoing abdominal surgery. Omental fat cells were found to differ from subcutaneous fat cells in their lipolytic response. It has been demonstrated that omental fat cells are more responsive to the lipolytic effect of epinephrine and nor-epinephrine [54]. Bolinder et al [18] showed that in non-obese adult men and women, omental fat was less responsive to the antilipolytic effect of insulin than subcutaneous abdominal fat. They demonstrated that the difference could be explained by differences in insulin receptor affinity, and by a difference in insulin action at the post-receptor level. It can be expected, therefore, that in vivo relatively large amounts of free fatty acids will be released from abdominal adipocytes into the bloodstream. From the intra-abdominal fat depot the free fatty acids will drain directly into the portal vein, so the liver will be exposed to an increased concentration of free fatty acids. From the subcutaneous fat depot the released free fatty acids will go into the systemic circulation. Figure 3 shows a tentative overview of the possible consequences of the release of large amounts of free fatty acids (FFA) by the abdominal depots (adapted from Björntorp 14, 15).

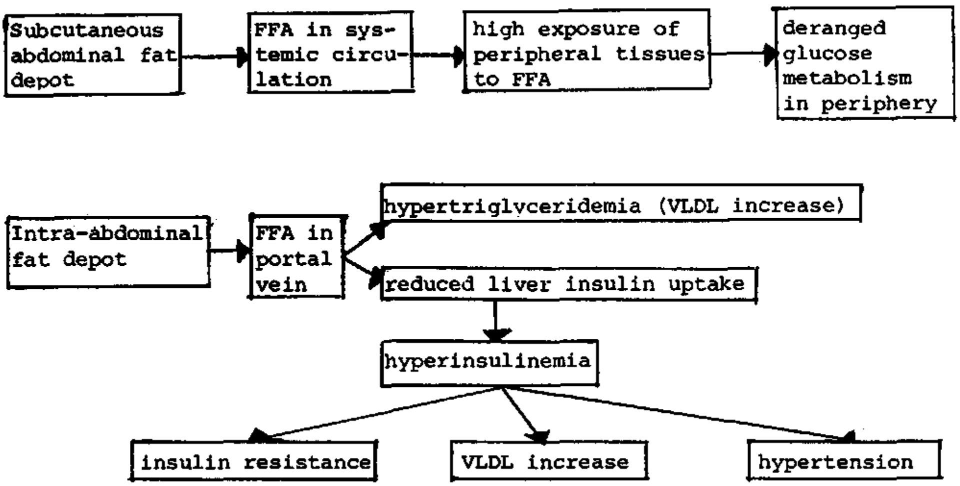

Figure 3. Schematic representation of the (hypothetical) mechanisms by which increased fat mass may lead to metabolic complications. (Adapted from Björntorp (15).

The relation between predominance of trunk fat (as opposed to fat on the extremities) and plasma triglycerides was shown by Albrink and Meigs in 1964 [1], and has since been confirmed several times [40, 64]. As discussed in the previous section, Albrink and Meigs found a correlation of trunk fat (but not forearm fat) with weight gain since age twenty-five. In men with slender forearms, triglyceride concentration increased significantly with abdominal skinfold thickness. In men with fat forearms no such correlation was found. Albrink and Meigs suggested that this finding, and the fact that mean triglyceride levels in innately thin men (with slender forearms) who became obese later in life were higher than in the innately fat men (with fat forearms), may have been the result of overloading of existing adipose cells. Després et al [33] in a study on 234 women and 238 men of 18 - 50 years of age, confirmed that abdominal and subscapular fat depots are more closely associated with serum lipids than other fat depots, particularly in men. The abdominal and subscapular skinfolds were found to be positively correlated with serum trigliccerides and total cholesterol, negatively with HDL-cholesterol, and most strongly with the ratio of HDL-cholesterol to total cholesterol. This regional trend remained significant after correction for concomitant variables such as age, cigarette smoking, habitual energy intake and energy expenditure, maximal aerobic power and alcohol consumption. Such associations were less clear in women who, although they were fatter than the men in the study, had lower triglyceride and total cholesterol concentrations and higher values of the HDL cholesterol/total cholesterol ratio than the men. More recently other parts of the mechanism described in figure 3 have been proven. Thiébaud et al [99] demonstrated that increased plasma FFA levels in 25 healthy young volunteers, established by means of intralipid infusion, impaired the ability of insulin to stimulate glucose oxidation and storage. This inhibitory effect of elevated FFA levels on glucose storage contributed more to the impairment of glucose tolerance than the defect in glucose oxidation. They found no effect of FFA on baseline insulin levels. Smith has recently cited evidence [95] that perfusion with a high free fatty acid concentration in the rat, reduced insulin clearance. Decreased hepatic insulin removal is an important cause of hyperinsulinemia in obesity, especially in diabetics [19]. High FFA in the portal vein might thus, as suggested in figure 3, be responsible for hyperinsulinemia. Although more evidence is needed to understand the mechanisms described in figure 3, this field of research is developing rapidly, and it can be expected that within a few years the true cascade of events will be established. One question of particular importance is which of the two abdominal fat depots (intra-abdominal or subcutaneous) causes the metabolic aberrations associated with a central fat distribution.

2.3. Clinical correlates of human fat distribution

The hypothetical mechanisms shown in figure 3 provide a possible explanation for the findings of epidemiological and clinical research revealing an association between abdominal obesity and disorders such as ischemic heart disease, diabetes mellitus (type II), hypertension, and stroke. The evidence for these associations will now be discussed in more detail.

2.3.1. Ischemic heart disease

Jean Vague was probably the first to report a relationship between fat located in the upper part of the body and ischemic heart disease (characteristic in his android type of obesity). He called fat mass located in the upper part of the body, 'diabetogenic' and 'atherogenic' fat mass [101, 102, 103, 104, 105]. In 1959 he and his co-workers published a study on 82 obese men and 158 obese women [106]. They compared subjects with clinical symptoms of atherosclerotic disease to those without evidence of such disease. It was found that between the groups there were no differences in age and total fat mass, but that the B/F AMR was significantly higher in the men and women with symptoms of atherosclerotic disease. They proposed, on the basis of preliminary evidence, that minor hypercorticism, that would accompany android obesity, could, in part, be responsible for the progression of obesity towards atherosclerosis. His retrospective evidence in a rather selective population has long remained unrecognized. Damon et al [32] found that in Framingham males cases of coronary heart disease were 'fatter, more muscular and stockier' than others . The relationships were not very clear and it is difficult to translate body build into terms of fat distribution.

Only recently have clear relationships between abdominal fat distribution and several cardiovascular endpoints been established in large prospective studies. In Göteborg, in Sweden, investigators included waist and hips circumference measurements in their set of anthropometric baseline data, when they started their long-term follow up studies of males and females. A thirteen-year follow-up of 54-year old men born in 1913 revealed that a significant association between the waist to hips circumference ratio and the occurrence of ischemic heart disease. In fact, it proved to be the most powerful predictor for these endpoints, of all the anthropometric variables studied (including Body Mass Index) [73].

The waist to hips ratio predicted ischemic heart disease independently of

measures of obesity, but not when risk factors like smoking, systolic blood pressure and serum cholesterol were taken into account. What is remarkable is that the risk for ischemic heart disease was highest in men in the highest tertile of waist to hips ratio and in the lowest tertile of Body Mass Index. These findings were confirmed in the Paris prospective heart study [36]. In this study circumferences had not been measured at baseline examination, but an index of fat distribution was constructed on the basis of skinfolds at several sites. The ratio of the sum of skinfolds on the trunk to the sum of skinfolds on the extremities proved to be an independent predictor of cardiovascular endpoints in a 10-year follow up of middle-aged men. Lapidus et al [72] showed that in a 12-year follow up of women aged 38 - 60 years, similar associations were found to be even more pronounced than in men. The waist/hips ratio was associated with the incidence of myocardial infarction and angina pectoris even when age, body mass index, smoking habits, serum cholesterol and triglycerides, and systolic blood pressure were taken into account. One drawback of these studies is that subsequent events are linked only to measurements at baseline examination: changes in body weight and fat distribution during follow-up cannot be taken into account. Such an approach would involve frequent re-examinations, which are impossible in practice. The study of Larson et al raise the question why relatively lean men with high waist/hips ratios, have the highest risk for developing coronary heart disease.
Studies on eight non-obese women with familial partial lipodystrophy [85], which is characterized by fat storage predominantly as subcutaneous abdominal fat, and a patient with Werner's syndrome [96], showed that even in non-obese individuals an increased ratio of central to peripheral fat is associated with metabolic complications.

2.3.2. Diabetes Mellitus, glucose intolerance and hyperinsulinemia

Diabetes Mellitus type II was the first disorder found to be associated with abdominal, upper body and/or android types of fat distribution was. Vague observed that in obese patients increasing severity of diabetes was accompanied by an increase in B/F AMR [106]. Lister and Tanner [75] compared 'acutely' diabetic patients with 'non-acute' diabetics and found that the non-acute diabetics were more endomorphic than those whose diabetes had appeared during early life. Endomorphy is characterized by roundness of the body contour, a tendency to obesity, a smooth skin with fine hair, and short tapering limbs with small hands and feet. It is clear that these persons, who can be regarded as typical type II diabetics, would also have a high waist to thigh circumference ratio. Other workers have compared skinfold measurements of diabetics and non-diabetics and concluded that diabetics have relatively larger skinfolds on the trunk than on the extremities [42, 62]. Kissebah et al [66] later confirmed the findings of Vague but, in subsequent research, preferred the use of waist to hips ratio for measuring fat distribution. In a series of experiments on about 90 women Kissebah and his co-workers examined the mechanisms underlying the relation between fat distribution and diabetes [38, 39, 40, 41]. They concluded from their experiments that diminished skeletal muscle insulin sensitivity with impaired glucose storage capacity contributes to the insulin resistance and, in turn, to the associated glucose intolerance and hyperinsulinemia of upper body segment obesity (or abdominal obesity). This effect may be the result of a reduction in insulin receptor number which could, in turn, be secondary to persistently elevated fasting plasma insulin levels [38, 39, 40, 41].

The mechanism described above is based on correlations between many variables involved in the complex glucose-insulin regulatory system, and has still to be experimentally validated.

Recently, Smith [95] cited evidence suggesting that high Free Fatty Acid (FFA) concentrations, which were found to be associated with abdominal fat distribution (see figure 3), cause a decrease in insulin clearance which could lead to hyperinsulinemia. Lipolysis activity may, therefore, be the key factor in the relation between abdominal obesity and diabetes.

Thus, although the epidemiological evidence for such a relation is fairly strong and consistent, the mechanism behind the causal relationship between an abdominal type of fat distribution and diabetes appears to be very complex.

The epidemiological evidence comes from cross-sectional surveys [58] in which the prevalence of self-reported diabetes increased with waist/hips circumference ratio. This relation was independent of the degree of obesity.

Ohlsen et al [80] showed that, in their prospective study of middle-aged men, the incidence of diabetes was associated with waist/hips circumference ratios at baseline examination.

In obese non-diabetic and otherwise apparently healthy subjects, the relation between glucose intolerance and hyperinsulinemia and the waist to hips circumference has also been demonstrated [64].

2.3.3. Hypertension

Vague noted in 1956 [102] that android obese persons had a tendency to develop hypertension. In recent clinical and epidemiological studies this has been confirmed [58, 39, 17, 88]. It should be noted that Krotkiewski [68] found that body fat in obese women and fat cell size in obese men were, in stepwise regression analysis, more important than the waist/thigh circumference ratio. Hartz et al [58], in their large study on TOPS members, compared obese women in the upper quartile of waist/hips circumference ratio with women in the lowest quartile of the ratio. They found a relative risk of 1.74, adjusted for effects of age and relative weight. Relative risk for women in the upper quartile of relative weight, compared with that of those in the lowest quartile was 4.01 adjusted for age and waist to hips ratio. The effects of body fat distribution and excess fat mass thus seem to be independent. It is not yet clear how this association of body fat distribution can be explained. The hyperinsulinemia, that is found to be associated with abdominal obesity (figure 1), might be involved in the mechanism. It is well known that hyperinsulinemia causes sodium retention and acts on the sympathic nervous system. Effects of hormonal factors on both fat distribution and blood pressure cannot be excluded.
Since hypertension is a risk factor for cardiovascular disease and cerebrovascular accidents, the observed relation between abdominal fat distribution and hypertension may in part explain the epidemiological findings in which central fat distribution has been found to be associated with cardiovascular disease and stroke.

2.3.4. Other clinical correlates of body fat distribution

Although Vague and his co-workers played an important role in stimulating research on body fat distribution, some of their evidence was poorly documented. In his much cited paper in 1956, Vague [102] stated that android obesity was associated with gout, uric acid crystals and gallstones. Gynoid obesity, on the other hand, was associated with direct mechanical complications (respiratory and circulation problems). These findings were based on 'observations on thousands of patients' but no data were presented. Vague proposed that these associations were possibly related to hormonal differences that caused both fat patterns and the complications.
Hartz et al [58] argued that if Vague's hypothesis was true the associations of body fat distribution with menstrual abnormalities would be even more

pronounced than with other disorders. They studied the relationship between the waist to hip ratio and reported menstrual abnormalities (irregular cycles, oligomenorrhea and hirsutism) in 11791 women aged 20 - 39 years. They confirmed that such an association existed, but that it was no stronger than those with diabetes, hypertension or gallbladder disease [58].
Therefore Hartz et al proposed another mechanism by which body fat distribution influences synthesis of estradione from plasma androstenedione. Adipose tissue seems indeed to influence this conversion [59, 78]. Whether adipose tissue in different regions behave differently in this respect needs to be investigated.
As mentioned above, Hartz et al observed a relation of fat distribution with gallbladder disease. It was suggested that cholesterol metabolism may be involved in this relation.
In a Dutch study it has been found that arthrosis in obese men is more prevalent in those with a high waist/thigh ratio than in those with a low waist/thigh ratio [88]. Silberberg, in a review of the relation between arthrosis and obesity, concluded that arthrosis is more closely associated with abnormalities in fat metabolism than with weight-induced wear and tear [89]. In fact, after adjustment for fat distribution, Seidell et al [88] found a negative association between Body Mass Index and arthrosis. For the interpretation of this finding it should be noted into account that this study involved obese men only. The same study revealed that a low waist/hips ratio or waist/thigh ratio was associated with a high prevalence of varicose veins [88]. This is in agreement with findings by Vague who proposed that 'venous insufficiency' was one of the characteristics of gynoid obesity [102].
Whether this relation indicates that when fat is stored predominantly in the thigh or hips region blood flow in peripheral tissues of these areas is impaired remains to be proven.

2.4. General conclusions

The consistency of the relationships described in the previous section leads to the conclusion that predominance of fat stored in the abdominal region is hazardous to health. Thus previous research in which excess fat has been treated as a simple entity must be interpreted with caution. The implications of these findings for the diagnosis and treatment of obese individuals have been summarized by Björntorp [15]. He proposes that abdominal obesity (a waist hips ratio greater than 1.0 in men and greater than 0.8 in women) is dangerous and should be diagnosed early and examined for associated risk factors on wide indications (plasma insulin and lipids, glucose tolerance, blood pressure). Future research should focus on manipulating fat distribution, and on evaluation of the effects of this manipulation on morbidity and mortality.

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CHAPTER 2

ASSOCIATIONS OF MODERATE AND SEVERE OVERWEIGHT WITH SELF-REPORTED ILLNESS AND MEDICAL CARE IN DUTCH ADULTS

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ABSTRACT

Data on height, weight, illness, medical care consumption, and demographic variables for 19,126 Dutch adults aged 20 years or older were obtained from three annual Health Interview Surveys. Data on severely (Body Mass Index 30.0 - 40.0 kg/m^2) and moderately (BMI 25.0 - 29.9 kg/m^2) overweight subjects were compared with those on non-overweight persons (BMI 20.0 - 24.9 kg/m^2), taking into account effect of sex, age, and educational level. In men, severe overweight was associated with hypertension, especially in men under 50 years of age. In women, severe overweight was associated with hypertension, diabetes, varicose veins, asthma/bronchitis, and hemorrhoids. Increased utilization of medical care and medications were also associated with severe overweight. For moderately overweight subjects, these associations were less clear or absent.

INTRODUCTION

Obesity is considered to be one of the most prevalent medical and public health problems in affluent societies[1-3] although this assumption has been criticized.[4,5] The importance of obesity as a public health problem has been reviewed recently in the reports of expert committees on overweight and obesity in England,[6] and the USA,[2] and in The Netherlands[7]. These reports recommend the use of the Body Mass Index (BMI or Quetelet's Index in kg/m^2) as a crude indicator of the body's fat content. From data available from several relatively small surveys, it can be estimated that a large proportion of the Dutch adult population is at least moderately overweight (BMI > 25 kg/m^2).[7,9,10] It is important to know if overweight in different degrees of severity is associated with a higher prevalence of chronic disorders or other health complaints,

related in turn to an increased use of medical services and medicines, than could be expected in subjects with a BMI within the desirable range. Evaluation of the risks could be helpful in deciding whether to direct public health programs at reduction of body weight throughout the population, or whether the effort should be concentrated on the severely overweight.
In this study, the associations of BMI (calculated from self-reported height and weight) with reported chronic illness and aspects of medical consumption were investigated, using data on a representative population of 19,126 Dutch adults.

METHODS

Subjects

Subjects were interviewees in the annual Continuous Dutch Health Interview Surveys. Each year since 1981, the Dutch Central Bureau of Statistics (CBS) has approached a representative sample of the total non-institutionalized population in The Netherlands. The study described here excluded those without Dutch nationality and those under 20 years of age. Subjects whose BMI exceeded 40 kg/m^2 were excluded (0.8% of the total study population). Close inspection of their data aroused strong suspicions about the validity of the reported weight (e.g., weight expressed in pounds instead of kilograms). The remaining population of the surveys of 1981, 1982, and 1983 comprised 9,369 men and 9,757 women. Individuals with a BMI below the desirable range (i.e. < 20 kg/m^2) were excluded from the comparison of severely and moderately overweight with non-overweight since they are known to have increased risk of morbidity.[11,12,13]

The average non-response rates for these surveys were about 33 per cent. About 22 per cent refused to participate, 8 per cent were not at home and 3 per cent were unable to answer because of medical, linguistic, or other reasons. More details of non-responders are described elsewhere.[14,15]

Sampling, Variables

Sampling was done in two steps. In the first step, a representative sample of all municipalities in The Netherlands was taken. In the second step, a sample of households out of every sampled municipality was taken. Trained interviewers visited these households throughout the year, asked the questions to the members of the household, and noted the answers in a prestructured questionnaire. Further details have been described elsewhere.[16]

In constructing the variables used in analysis, age was categorized into intervals of 20-34, 35-49, 50-64, and 65 years or older. Education served as an indicator of socio-economic status: low level = primary school and some occupational training; middle level = secondary school; high level = university and other tertiary institutions. Body Mass Index (or Quetelet's Index) was calculated from self-reported height (without shoes) and weight (without clothes), dividing weight in kilograms by the square of the height in meters. Three categories of BMI were distinguished, using the classification of Garrow.[8]

- BMI = 20.0 - 24.9 kg/m^2 (Desirable range or grade 0 obesity).
- BMI = 25.0 - 29.9 kg/m^2 (Moderate overweight or grade I obesity).
- BMI = 30.0 - 40.0 kg/m^2 (Severe overweight or grade II obesity).

Subjects were asked whether they suffered from long-standing illnesses, handicaps, or the consequences of accidents listed on a card with 19 items. Each person could mention up to four illnesses.

Subjects were asked the reasons for up to six consultations with the general practitioner and, in a separate question, with medical specialists, in the three months (two months in the 1983 survey) preceding the interview. Consultations by telephone (except those for making appointments) were included. Treatments by medical specialists during hospitalization were excluded, but outpatient clinical treatments (e.g., first aid and x-ray) were included.

Subjects were asked about any hospitalization (for more than one day and one night) in the year preceding the interview. Subjects were asked about any medicines prescribed by a physician in the 14 days preceding the interview (excluding oral contraceptives), and in a separate question about the use of medicines without a presciption (a description of chronic disorders and categories of medical care is given in Appendix I en II).

Analysis

Data from the 1981 survey were used to make a preliminary selection of the medical consumption variables apparently associated with overweight in analysis of contingency tables. The strengths of the associations were evaluated with the extended version of the Mantel-Haenszel chi-square statistic for contingency tables.[17] When age-specific or stratum-specific estimates of risk were different from one ($p < 0.10$), the dependent variable (disease or medical consumption) was selected for further study.

In a stepwise forward multivariate logistic regression analysis (using the package program BMDPLR),[18] dummy variables were used for categories of BMI, age, and educational level and interaction terms (BMI x age and BMI x education). The

three categorized independent variables and the interaction terms were added ($p < 0.10$) or removed ($p > 0.15$) in p value order. The dependent dichotomous variable was presence or absence of a particular disease or reason for medical care or use of a type of medicine.
Using the coefficients of regression on BMI categories, odds ratios were calculated adjusted for the other variables in the model, comparing severe and moderate overweight to non-overweight. We calculated 95 per cent confidence intervals for the odds ratios, using the standard errors of, and the correlations between, the multiple logistic regression coefficients, according to the procedure described by Lemeshow and Hosmer.[19]
The same procedure of logistic regression analysis was followed for the selected dependent variables, using the data from the combined surveys. The data presented below were calculated from the combined surveys unless stated otherwise.

RESULTS

According to the criteria used in this study, about 4 per cent of adult men and 6 per cent of adult women in The Netherlands are severely overweight. The prevalence of moderate overweight can be estimated as 34 per cent in men and 24 per cent in women. In tables 1 and 2, some characteristics of the study population are shown for the combined surveys. The prevalence of severe and moderate overweight is inversely related to educational level.

Table 1. Mean weight, height, body mass index (BMI) of the study population, by sex, combined surveys 1981-83

	men n = 9369		women n = 9757	
Characteristics	Mean	Sd	Mean	Sd
Weight (kg)	76,5	10,0	65,0	10,4
Height (cm)	177,3	7,7	166,1	6,4
BMI (kg/m^2)	24,3	2,9	23,6	3,7
Age (years)	43,9	16,5	44,9	17,0

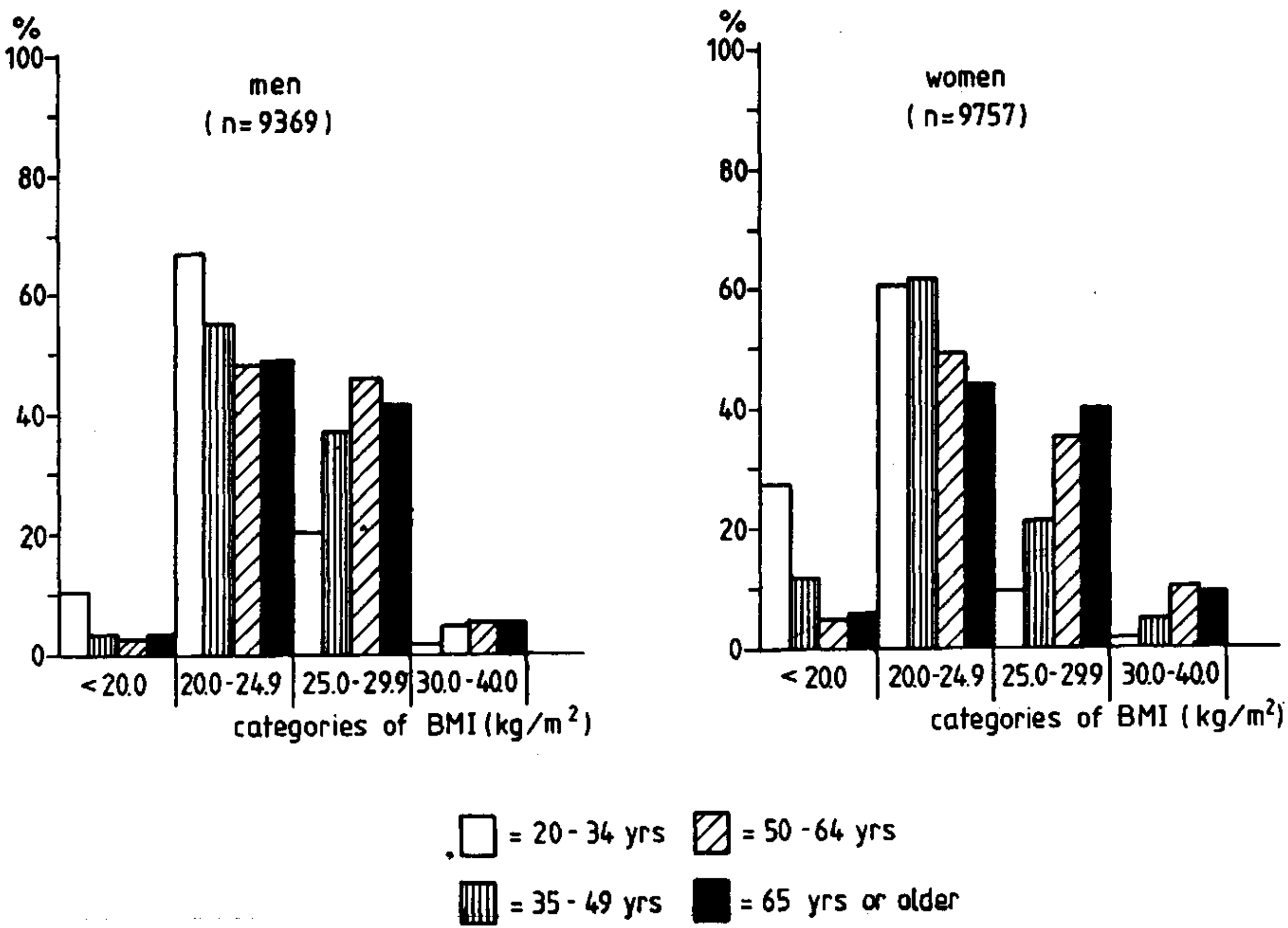

FIGURE 1 - Percentages of Men and Women in Categories of Body Mass Index (BMI) for Different Age Groups (data from combined surveys).

Table 2. Distribution of educational levels within different categories of body mass index (BMI), according to sex

BMI (kg/m^2)	n	Low level	Middle level	High level
Men				
20.0–24.9	5214	46.3%	36.4%	17.3%
25.0–29.9	3275	62.5%	27.5%	10.0%
30.0–40.0	368	70.9%	22.0%	7.1%
TOTAL	8857			
Women				
20.0–24.9	5349	62.1%	27.0%	10.9%
25.0–29.9	2379	81.1%	14.1%	4.8%
30.0–40.0	581	80.0%	17.1%	2.8%
TOTAL	8309			

Figure 1 shows the age group-specific distributions of BMI categories for each sex. For subjects younger than 65 years, the prevalence of moderate and severe overweight increases with age.

Results of the stepwise logistic regression analysis, using the data of the combined surveys, are presented in Tables 3 and 4. Table 3 shows the variables included in the logistic model. Only the models in which BMI appeared are presented. Interactions are evaluated on a multiplicative scale. Table 4 shows the odds ratios (with 95 per cent confidence intervals) for moderately and severely overweight compared to non-overweight subjects.

Table 3. Variables included in a forward stepwise multiple logistic regression model*

Variables	Gender	Dependent variable description	Number of cases	Variables included in the model (+				
				BMI	age	education	BMIx age	BMIx educati
Chronical illnessess	men	hypertension	281 (3,2%)	+	+	–	+	–
		diabetes	116 (1.3%)	+	+	–	–	–
	women	hypertension	474 (5.7%)	+	+	–	–	–
		diabetes	152 (1.8%)	+	+	+	–	–
		varicose veins	197 (2.4%)	+	+	+	–	–
		asthma	218 (2.6%)	+	+	–	–	–
		haemorrhoids	123 (1.5%)	+	–	–	–	–
		at least 1 illness	2519 (30.3%)	+	+	–	–	–
Reason for consulting general practitioner**	men	trunk/extremities	310 (3.4%)	+	+	–	–	–
	women	cardiovascular complaints	339 (4.1%)	+	+	+	–	–
		routine handlings	818 (9.8%)	+	+	–	–	–
Reason for consulting medical specialist**	men	trunk/extremities	127 (1.4%)	+	–	+	–	–
		back/joints/muscles	147 (1.7%)	+	+	+	–	+
	women	at least 1 consultation	1900 (22.9%)	+	+	+	–	–
Hospitalization***	women	at least 1 hospitalization	736 (8.9%)	–	–	–	–	–

* Only models that included BMI are presented

** During three months preceding the interview

*** In one year preceding the interview

Table 4. Odds ratios (OR) adjusted for age and educational level and 95% confidence intervals (CI) for moderately[1] and severely[1] overweight subjects vs subjects not overweight

			Odds ratios (OR) and 95% confidence intervals (CI) of:			
			Moderately overweight[1]		Severely overweight[1]	
Variables	Gender	Dependent variable	OR	CI	OR	CI
Chronic illness	men	hypertension	1.64	1.27-2.13	2.48	1.57-3.90
		diabetes	0.61	0.71-0.92	1.39	0.70-2.76
	women	hypertension	1.84	1.55-2.19	2.63	1.96-3.53
		diabetes	1.39	0.95-2.03	3.34	2.13-5.22
		varicose veins	1.53	1.21-1.94	3.06	2.03-4.62
		asthma/bronchitis	1.07	0.78-1.47	1.80	1.18-2.76
		haemorrhoids	0.75	0.47-1.17	2.28	1.37-3.80
		at least 1 illness	1.15	1.03-1.28	1.72	1.43-2.06
Reason for consulting general practitionar*	men	trunk/extremities	1.24	0.97-1.59	2.17	1.38-3.43
	women	cardiovascular	1.32	1.03-1.68	1.93	1.36-2.73
		routine matters	1.18	1.01-1.40	1.68	1.31-2.14
Reason for consulting medical specialist*	men	trunk/extremities	1.50	1.04-2.17	2.27	1.14-4.50
		back/joints/muscles	1.38	0.97-1.96	2.17	1.14-4.09
	women	at least 1 consultation	0.91	0.82-1.02	1.51	1.28-1.78
Hospitalization**	women	at least 1 consultation	1.14	0.98-1.33	1.72	1.38-2.16

* Consultations in three months preceding the interview (detailed description of dependent variables available in Appendix II)

** Hospitalization in one year preceding the interview (details in Appendix II)

1 Moderate overweight: BMI 25.0-29.9 kg/m^2; Severe overweight: BMI 30.0-40.0 kg/m^2. The reference category is BMI 20.0-24.9 kg/m^2

Source: data obtained from Central Bureau of Statistics Health Interview Surveys 1981-83 (n = 17166)

Compared to non-overweight women, severely overweight women reported that they suffered from hypertension, diabetes, varicose veins, asthma/bronchitis and haemorrhoids more often, and consulted their general practitioner about cardiovascular complaints or routine matters, and medical specialists for all reasons combined. They had also been hospitalized more often in the year preceding the interview.

Severely overweight men reported having hypertension more often than did non-overweight men, and they also had consulted their general practitioner or medical specialist more often about complaints of the trunk or extremities. In addition, they were also more likely to have consulted a medical specialist about joint, back, or muscle complaints. Level of education appeared to modify this latter association: Table 5 shows that this association was most evident in men with an intermediate level of education.

Age appeared to modify the relation between overweight and hypertension for men; the magnitude and strength of this association decreases with age and is not evident at age 65 and over.

Table 5. Odds ratios in strata of effect-modifying variables (interaction terms of the variable with BMI included in the regression model

			Stratum-specific Odds Ratios (95% Confidence Intervals)			
			Moderately Overweight*		Severely Overweight*	
Dependent variable	Interaction term in Regression Model	Stratum effect Modifier	OR	95% CI	OR	95% CI
Hypertension (men)	BMI x Age	20 - 34 yrs	4.17	1.94-8.95	6.94	1.85-26.09
		35 - 49 yrs	2.23	1.30-3.83	5.48	2.67-11.28
		50 - 64 yrs	1.15	0.79-1.66	1.75	0.89- 3.42
		65+ yrs	1.67	0.99-2.83	1.09	0.32- 3.72
Consulting Medical Specialist for back/joint/muscles (men)	BMI x Education	Low	1.38	0.92-2.08	1.30	0.55- 3.07
		Middle	1.12	0.50-2.52	7.28	3.03-17.51
		High	2.16	0.82-5.73	3.97	0.57-28.87

* Moderately overweight: BMI 25.0 - 29.9 kg kg/m^2; severely overweight: BMI 30.0 - 40.0 kg/m^2; the reference category was BMI 20.0 - 24.9 kg/m^2

Table 6. Odds ratios, adjusted for effects of age and educational level, for the use of prescribed and unprescribed drugs according to sex in different categories of Body Mass Index, in 14 days preceding interview

Type of medicines	Number of cases (% population)	Odds ratios (OR) and 95% confidence intervals (CI)			
		Moderately overweight*		Severely overweight	
		OR	CI	OR	CI
Men					
For stomach and intestinal complaints (unprescribed)	17 (0.6%)	2.92	1.73-4.92	2.96	1.00-8.85
Women					
Diuretics (prescribed)	76 (2.7%)	2.00	1.52-2.65	4.57	3.30-6.34
For cardiovascular/circulation problems (including hypertension; (prescribed)	147 (5.3%)	1.78	1.46-2.15	2.69	2.07-3.50
Sleeping pill, sedatives, tranquilizers (prescribed)	125 (4.5%)	1.20	0.97-1.48	2.00	1.50-2.65
For stomach and intestinal complaints; for women under age 50** (prescribed)	29 (1.1%)	7.18	2.79-18.5	no use for severely overweight women	

* Moderatele overweight: BMI 25.0 - 29.0 kg/m^2; severely overweight: BMI 30.0 - 40.0 kg/m^2;
Reference category: BMI 20.0 - 24.9 kg/m^2

** Age modified the association with overweight

For moderate overweight the associations observed between severe overweight and the various complaints were weaker or absent (table 4). Compared to non-overwight women, moderately overweight women, reported hypertension and varicose veins more often and consultations with their general practitioner about cardiovascular complaints and routine matters slightly more often. Moderately overweight men under 50 years of age reported more hypertension than non-overweight men, (table 5) and consulted a medical specialist more often for complaints of trunk and extremities. Table 6 shows the odds ratios for severely and moderately overweight compared to non-overweight men and women. Severely and moderately overweight men reported more use of non-prescription medicines for stomach and intestinal complaints than non-overweight men. Moderately and severely overweight women reported more use of prescribed diuretics, sleeping pills or sedatives, and medicines used to treat cardiovascular and circulation disorders than non-overweight women. Moderately overweight women under age 50 used medicines for stomach and intestinal complaints more often than non-overweight women.

DISCUSSION

Based on the self-reported data from the cross-sectional surveys, it can be concluded that severe overweight, especially in women, is accompanied by an excess of chronic disorders and increased use of medical care. Moderate overweight is far more common than severe overweight and, although it is not a strong risk factor on an individual level, it may have substantial impact on the prevalence of some chronic disorders and the demand on health care facilities. The associations between body fatness and hypertension and diabetes mentioned are well documented in numerous studies.[6,7] Data from large prospective studies, like the Framingham study, do not confirm our observation that obesity and hypertension are associated only in men under 50 years of age.[20] Varicose veins are more common in overweight women than in those who are not overweight.[21,22] Results from a recent study on fat distribution indicate that while hypertension, diabetes, and arthrosis were more prevalent in obese subjects with an abdominal type of fat distribution, varicose veins were more common in obese women whose fat was predominantly stored around hips and thighs.[23]

The associations of severe overweight with haemmorhoids and asthma/bronchitis in women are less clearly established in the literature, although it is well known that respiratory function is often impaired in obese subjects.[24-26]

Reduced physical activity, resulting from chronic illness, might have contributed to the excess of weight. Therefore, associations found in this study do not necessarily imply causal relations.

Comparing self-reported data of the health status of overweight and not overweight subjects may be biased. Undiagnosed illness might be more common in those who are not overweight[27]; while on the other hand, taking medication (e.g., anti-hypertensive) might lead to underestimation of risk. Although it has been found that people tend to report their height and weight in the direction of culturally desirable values (i.e., slim women, tall men), investigators generally agree that for large groups, self-reported data are sufficiently accurate and do not substantially affect conclusions.[28-32] Any bias introduced by the underreporting of weight would probably be toward the null hypothesis. The true prevalence of moderate and severe overweight in The Netherlands might be somewhat underestimated in this study.

Overweight, in this study, was also found to be associated with medical care not necessarily resulting from the associations with chronic disorders described above.

More than 70 per cent of Dutch adults are publicly insured for medical care and are not permitted to contact a specialist directly.[34] The finding that severely and moderately overweight men more often consulted a medical specialist for some combinations of complaints (Table 4) implies that these complaints generally were considered serious enough by their general practitionar, who usually provides primary medical care, for referral to a specialist. For women, it was shown that severe overweight was accompanied by higher use of medical care at all levels. It is not surprising that overweight women were found to use more diuretics and medicines used to treat cardiovascular disorders (including hypertension) since these drugs are often prescribed for women in The Netherlands. The finding that severely overweight women use sleeping pills or sedatives more often than women who are not overweight may be the consequence of either the social stigma that obesity carries in affluent societies,[36] or that stress factors may have lead to eating habits that, in turn, caused weight gain.[37,38]

In the Netherlands, it was recently recommended that treatment is indicated in everyone who is severely overweight and in those who are moderately overweight accompanied by increased levels on risk factors, or who suffer from chronic disorders.[7] The findings of this study support these recommendations. Once severe overweight is established, however, it is very difficult to treat successfully in the long term. The prevention of weight gain, especially in young adults, seems a matter deserving attention. The general practitionar, who plays an important role as a family physician and who provides continuous primary care to patients, might be in an excellent position to identify and treat those who are at risk of becoming severely overweight. Prospective studies should be carried out to investigate the possible benefits of such an approach.

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Appendix I

List of chronical illnessess or handicaps shown to subjects in the C.B.S. Health Interview Survey. Subjects could state the presence of maximal 4 different items

Description of complaints

1. Asthma, chronical bronchitis or nasal cavity inflammation
2. Heart disease or functional disturbances of the heart
3. High blood pressure
4. Stroke
5. Varicose veins
6. Haemmorrhoids
7. Peptic ulcer or other chronic stomach complaints
8. Chronic intestinal complaints
9. Gallstones, gallbladder or liver disease
10. Rupture
11. Renal calculus, chronical inflammation of the bladder
12. Prostate complaints (men), prolapse (women)
13. Diabetes mellitus
14. Thyroid dysfunction
15. Rheumatism, joint disease, slipped disc
16. Epilepsy, migraine, skin disease
17. Cancerous tumours or growth
18. Consequences of accident
19. Other chronical disorders

Appendix II

Classifications of illnesses, complaints or actions which were characteristic for a reported consultation of a general practitionar or medical specialist in 3 months preceeding the interview or hospitalization in 1 year preceeding the interview

	Group description	Abbreviation (these were used in the text)
1	Childhood diseases	Childhood disease
2	Common cold, flue, infalammations of throat, tonsils, cavity of jaw, frontal sinus, nasal cavity	Common infections/ inflammations
3	Chronical bronchitis, asthma, respiratory illness thighness of chest, coughing, hay-fever, pneumonia, pulmonary affection	Respiratory
4	Heart disease, stroke, hypertension, hypotension, anemia, varicose veins, heammorroids, sore leg	Cardiovascular
5	Toothache	Toothache
6	Peptic ulcer, duodenum ulcer, stomach complaints indigestion, intestinal complaints, diarrhea, constipation, gastroenteritis, liver and gallbladder disease, appendicitis	Internal organs/ digestive tract
7	Renal calculus, nephritis, cystitis, menstrual abnormalities, fleshy growths, menopausal complaints	Urogenital
8	Pregnancy, miscarriage, delivery, anticonceptiva, sterilization	Reproduction/ fertility
9	Disorders of the thyroid gland, diabetes, overweight	Metabolic disorders
10	Cancer	Cancer
11	Complaints or diseases concerning ears, eys, speech	Ears/eyes
12	Allergy, eczema or skin disease	Allergy/skin
13	Backache for various reasons, myelitis, rheumatoid complaints, arthrosis, sprain, aching muscles	Back/joint/muscles
14	Fracturse, injuries, concussion of the brain, contusions, burns, intoxications	Accidents
15	Insomnia, fatigue, vertigo, headaches, migraine, nerves	Nervous/stress

16	Complaints of neck, shoulder, extremities, chest, ribs, hips	Trunk/extremities
17	Pains not in categories above, itchings, fever	Pain
18	Injections, blood pressure control, recipies, general examinations, referrals	Routine
19	Operations	Operations

Appendix III

Categories of medicines used in the Dutch Health Interview Surveys (prescribed, and not prescribed)

a. Pain relievers and medicines used to treat fever (e.g. aspirin)
b. Medicines used to treat coughs, common cold, flue, angina etc
c. Medicines like vitamins, minerals and tonics
d. Medicines used to treat disordes of the heart, circulation and raised blood pressure
e. Diuretics
f. Medicines used to treat constipation
g. Medicines used to treat stomach- and intestinal complaints and indigestion
h. Sleeping drugs, sedatives and transquilizers
i. Antibiotics (like pencillin) and sulphonamides
j. Medicines used to treat skin disorders (including eczema, itchings, dandruff)
k. Medicines used to treat rheumatism and arthritis
l. Medicines used to treat allergy
m. Medicines used to treat bronchial astma
n. Medicines not described above

CHAPTER 3

UTILIZATION OF PRIMARY HEALTH CARE OF OVERWEIGHT AND NON-OVERWEIGHT SUBJECTS - A SIX YEAR FOLLOW-UP STUDY

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ABSTRACT

In this study, 315 adult men and 562 adult women from four general practises in The Netherlands were followed for six years in a continuous morbidity registration. Follow-up began in the year they were registered as overweight by their general practitioner. The incidence of new spells of illness in this overweight group was compared with that in a control group of 438 men and 618 women who, for each calendar year of start of follow-up were matched to the overweight group according to the general practise they were in, and their sex and age. It was shown that new spells of illness that are not life-threatening or longterm, were more frequently registered in the overweight group. This difference was also apparent after stratification for sex, age, and social class. Specific afflictions that were registered more often in the overweight group were common cold and influenza, psychoneurotic complaints, skin problems, myalgia and lumbago, distortions (in men and women), menstrual abnormalities (in women), and minor injuries (in men).
Comparing screening data from 1978 with the overweight and hypertension status as given in the morbidity register, just prior to the screening, indicated that the sensitivity of the registration of overweight and of hypertension increases with age (with the exception of overweight in women). Using the screening data, it can be inferred that overweight indicates a risk of hypertension, and this risk is greater the younger that obesity is confirmed. Odds ratios calculated the registration data indicated that these data may be biased: however, no consistent pattern of the strength and direction of this bias was seen in different age and sex groups. It was concluded that overweight patients in general practises do show more new spells of illness than those who are not known to be overweight by the general practitioners.

INTRODUCTION

The relationship between overweight and the incidence of various chronic disorders is well known from review studies [1] and has recently been confirmed in The Netherlands [2]. The association of overweight with less severe and more common afflictions is less well known. Self-reported data from overweight persons indicated that they visited general practitioners and medical specialists more frequently for specific reasons [3,4]. Self-reported data might suffer from misclassification bias and subjects can only be asked about previous medical care that covers a short period of time, because it has been shown they soon forget [5]. In order to study medical care and overweight more objectively we studied the incidence of afflictions in a retrospective cohort study comparing registered overweight subjects with subjects that had never been registered as overweight.

It has been suggested that such data might also be biased by general practitioners who have a tendency to register as overweight those subjects who have a higher morbidity. In addition, in overweight subjects who receive medical care more often and more specifically it may be more likely that certain disorders will be detected than in non-overweight subjects [6]. Therefore, we paid special attention to the validity of the registration of hypertension and overweight and to the possibility of differential misclassification of these conditions by the general practitioners.

Our study also indicates the extra workload for general practitioners that can be attributed to their overweight patients.

POPULATION AND METHODS

Morbidity registration

The continuous morbidity registration of the Department of General Practise of the University of Nijmegen was started in 1967 in two practises, and was augmented by two others in 1971. These general practices comprise about 12,000 patients and are located in a big industrial town, a small town, urbanized countryside and a rural area. In these four practises, all diagnoses and referrals are registered daily, according to the E-list, which is an adapted version of the International Classification of Diseases [7] used in The Netherlands. A distinction is made between new spells of illness and diagnoses and contacts with patients because of an illness that has previously been recorded. This enabled us to restrict our study to new spells of illness only. In this paper the results of analysing all definite new diagnoses over a period of 6 years retrospective follow-up are presented. Total morbidity was divided into three groups of severity as classified by the Department of General Practise [8]: highest level of severity = potentially life-threatening, or long-term illness; middle level of severity = temporarily threatening; lower level of severity = generally not threatening. The groups of illness studied in this paper are described in Appendices I and II.

Population

The overweight group comprised all patients who, at an age between 20 and 50 years, had been diagnosed by their general practitioner as being overweight. The criterion for overweight was a Body Mass index (BMI= weight divided by height squared) exceeding about 26 kg/m^2 (for women) or 27 kg/m^2 (for men). Weight and height was measured by the general practitioner (either at routine examination or at the initiative of the patient or the general practitioner). These weights and heights were not entered in the morbidity registration.
For each calendar year of start of follow-up, a control group that had never been registered as overweight in the period 1967 - 1984 was selected from the total population. These persons were randomly assigned to starting years of follow-up in the period 1967 - 1978, followed by a frequency matching procedure done according to general practise, sex and age at start of follow-up (in 5-year age groups). Some characteristics of the study population are shown in table 1.

Estimate of information bias

In 1977/1978 patients were screened for cardiovascular risk factors in three of the four practices that participate in the morbidity registration. Eighty percent of all patients aged between 20 and 50 years were weighed (without shoes and wearing indoor clothing only) and their height and blood pressure were measured. Blood pressure was measured using a sphygmomanometer, as commonly used in general practices [9] with the subject sitting, after 15 minutes' rest. Diastolic pressure was read at the disappearance of sounds (Korotkov phase V). The average of two readings, taken 15 minutes apart, was used for classification of hypertension (cut-off point 100 mm Hg, which corresponds to the criterion used in the morbidity registration). Details of the screening have been given elsewhere [10]. Subjects whose diastolic pressure was below the cut-off point for hypertension, but whose records showed they were receiving anti-hypertension medication were classified as hypertensives in the screening data. At the screening examination BMI was used to identify overweight subjects (cut-off points: 26 kg/m^2 for women, 27 kg/m^2 for men).

Statistical methods

Category-specific and adjusted risk ratios and odds ratios (comparing overweight with non-overweight subjects) were calculated and their confidence intervals estimated using Taylor series approximation for variance, as described elsewhere [11]. The numbers of afflictions were compared using the Wilcoxon rank-order test of unpaired samples [12]. P values (two-sided) were taken to be significant when smaller than 0.05.

RESULTS

Table 1 shows the distribution of subjects in the overweight and the control group over categories of social class and of age. In the overweight group the distribution is shifted towards the lower social classes.

Table 1. Distribution of the study population over categories of social class (according to profession of the head of the household) and over categories of age (at start of follow-up)

Social class	Women		Men	
	Overweight n(%)	Non-overweight n(%)	Overweight n(%)	Non-overweight n(%)
low	359(63.9)	296(47.9)	202(64.1)	208(47.5)
middle	174(31.0)	255(41.3)	100(31.8)	177(40.4)
high	29(5.1)	67(10.8)	13(4.1)	53(12.1)
	562(100)	618(100)	315(100)	438(100)
Age				
20 - 29	140(24.9)	163(26.4)	68(21.2)	91(20.8)
30 - 39	183(32.6)	208(33.6)	113(35.2)	160(36.5)
40 - 50	239(42.5)	247(40.0)	140(43.6)	187(42.7)
	562(100)	618(100)	321(100)	438(100)

Table 2. Relative risks, adjusted for age and social class, for at least one new spell of illness being registered; overweight persons versus not overweight persons

Ilnness (codes)	Women RR(95% confidence interval)	Registered as exhibiting illness		Men RR(95% confidence interval)	Registered as exhibiting illness	
		Overweight %	Control %		Overweight %	Control %
Common cold & influenza (240-3, 245)	1.16(1.09 - 1.24)*	79.2	68.2	1.16(1.06 - 1.26)*	78.1	63.9
Anemia (111)	0.80(0.52 - 1.22)	7.7	6.7	- - -	-	-
Psychoneurosis (135)	1.09(1.01 - 1.18)*	66.2	60.4	1.40(1.22 - 1.61)*	64.1	43.2
Otitis externa (182)	1.44(0.94 - 2.22)	8.3	5.4	1.52(0.84 - 2.76)	6.7	4.6
Cystitis acuta (313)	1.17(0.94 - 1.45)	25.0	21.1	1.83(0.88 - 3.82)	5.1	2.7
Menstrual disorders (325, 327-9)	1.36(1.13 - 1.63)*	31.7	22.4	- - -	-	-
Skin problems (370,372,377,381)	1.33(1.12 - 1.59)*	34.5	25.3	1.27(1.01 - 1.59)*	32.7	25.1
Myalgia, lumbago (407, 408)	1.13(1.01 - 1.27)*	53.3	47.1	1.39(1.22 - 1.57)*	65.7	49.8
Distortions (480)	1.54(1.08 - 2.21)*	12.1	7.5	1.51(1.02 - 2.24)*	14.6	8.9
Minor injuries (495)	1.14(0.95 - 1.37)	31.0	27.6	1.27(1.08 - 1.48)*	50.5	42.0

* $p < 0.05$

In table 2 the relative risks for the incidence of one or more diagnoses of new spells of illness during the six years of follow-up are shown for the overweight group vis-à-vis the non-overweight group. Although for most of the diseases shown in the table the risks are only moderately elevated, the high rates of incidence do indicate considerably more cases of such illnesses in the overweight group.

The percentages of persons who manifested at least one new illness during the six years of follow-up, as shown in table 3, show that almost everyone in the study population was seen by the general practitioner at least once. This tendency was more pronounced in the overweight group (especially in the lower and middle social classes).

Table 3. Percentage of persons experiencing at least one illness in the course of six years follow-up in a morbidity registration, stratified according to social class. Adjusted for age. Illnesses classified by severity as described in Appendix II)

		Women		Men	
Severity of illness	Social class	Overweight %	Non overweight %	Overweight %	Non overweight %
low	low	97.4	92.9*	97.5	92.8
	middle	90.3	83.5**	95.0	81.3**
	high	80.5	85.1	84.6	75.5
middle	low	95.6	88.5*	92.3	87.5*
	middle	92.5	83.9**	95.0	76.8**
	high	72.4	80.6	84.6	71.7
high	low	17.0	15.6	15.3	17.8
	middle	16.7	12.6	20.0	10.7*
	high	20.5	14.9	7.7	15.1

* $p < 0.10$ (Non overweight compared to overweight)

** $p < 0.05$ (Non overweight compared to overweight)

The total number of complaints in the six-year period, as reflected in the average number of afflictions reported per person, was higher for new spells of illness in the overweight group than in the not-overweight group (except for the most severe illnesses). Illnesses of lower and middle level of severity show a higher average number of afflictions in women than in men and a decrease in incidence with increasing social status.

Table 4. Average number of afflictions per person during six years of follow-up in a morbidity registration, stratified by social class. Weighted averages of age groups. Illnesses classified by severity (see Appendix II)

		Women		Men	
Severity of illness	Social class	Overweight	Non overweight	Overweight	Non overweight
low	low	8.3	7.0*	6.9	5.3**
	middle	7.8	5.7**	4.4	3.8
	high	6.4	4.6	3.7	3.0
middle	low	6.4	4.6**	5.9	4.4*
	middle	4.6	3.7**	4.2	3.0**
	high	3.4	3.6	3.6	2.0
high	low	0.2	0.2	0.2	0.2
	middle	0.2	0.1	0.2	0.2
	high	0.3	0.2	0.1	0.1

* $p < 0.10$ (Non overweight compared to overweight)
** $p < 0.05$ (Non overweight compared to overweight)

Note

Average is total number of registrations in a sex/age/social class category, divided by the number of subjects in that category. Differences between groups were tested using the Wilcoxon rank test

Table 5. Sensitivity and specificity of the registration of overweight and hypertension in three general practises (Data from a screening in 1978 and from the morbidity register just prior to the screening)

Disorder	Sex	Age	n	% with hypertension at screening	Sensitivity %	Specificity %
Hypertension	Men	20 - 29	343	1.8	16.7	98.5
		30 - 39	333	7.2	29.2	96.8
		40 - 50	363	13.0	66.0	93.7
		20 - 50	1039	7.4	50.6	96.4
	Women	20 - 29	349	4.3	33.3	99.4
		30 - 39	350	3.7	76.9	96.4
		40 - 50	397	17.6	89.9	95.4
		20 - 50	1086	9.0	74.5	97.3
Overweight	Men	20 - 29	343	12.9	59.1	95.3
		30 - 39	333	27.9	68.8	94.2
		40 - 50	363	31.4	77.2	88.0
		20 - 50	1039	24.2	70.9	92.6
	Women	20 - 29	349	9.17	93.8	89.9
		30 - 39	350	18.00	92.1	87.7
		40 - 50	397	39.04	87.7	85.5
		20 - 50	1086	23.02	89.6	87.9

Note (for Table 5):

Sensitivity = percentage of those with the disorder at the screening that had been registered as having that disorder.

Specificity = percentage of those without the disorder at the screening and who had not been registered as having that disorder.

Persons who at the time of the screening were undergoing treatment for hypertension were regarded as hypertensive regardless of their blood pressure

Results from a screening in three practises in 1978 show that the prevalence of both hypertension and overweight increase with age. The percentage of subjects as hypertensive at the screening who had been registered in the morbidity register because of overweight increased with age. The accuracy of the registration of hypertension appeared to be much better for women than for men. The same was true for the registration of overweight, registered was greater than the percentage of correctly registered hypertensives (table 5).

Calculations of the odds ratios for the presence of hypertension in overweight subjects compared with non-overweight subjects (using the screening data) indicated that the strength of the correlation between overweight and hypertension decreases with age. The odds ratios calculated from the registration data showed that this trend was less clear in men, while in women, an increase in odds ratios with age was observed. Our results show that using the registration data to calculate the correlation between overweight and hypertension would results in underestimate for women aged 20 - 29 years and an overestimate for men aged 40 - 50 years.

Table 6. Odds ratios for presence or absence of hypertension in overweight subjects compared with non-overweight subjects. Calculations using data from morbidity register and data from a screening in 1978

	Women				Men			
	Registration		Screening		Registration		Screening	
Age	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
20 - 29	1.88	0.36-9.92	7.90	2.61-23.91	8.05	1.57-41.37	7.3	1.76-30.45
30 - 39	2.34	0.94-5.84	1.82	0.55- 5.99	2.36	1.16- 8.40	4.94	2.08-11.73
40 - 50	3.94	2.27-6.82	2.93	1.71- 4.98	2.73	1.50- 4.99	1.28	0.67- 2.49
20 - 50	3.28	2.09-5.16	4.52	2.96- 6.90	3.11	1.90- 5.08	2.89	1.81- 4.64

DISCUSSION AND CONCLUSIONS

In this study it was shown that patients from four general practises who were registered as being overweight by their general practitioner displayed more new spells of illness during six years of follow-up than patients who were not registered as overweight. These differences were also apparent within age and social class groups. The registration in these four practises is continually monitored and evaluated and is done according to standardized criteria. It is therefore very likely that these differences are real. Nevertheless, it is not possible to infer a causal relationship between overweight and the incidence of common illness. Personal characteristics not measured in this study could be responsible for both overweight and illness.
Some of the associations between overweight and illness that were observed in this study (Table 2) have been observed before. The association between overweight and musculo-skeletal disorders [3,13,14], skin afflictions [15], distortions and minor injuries [16,17] and menstrual abnormalities [18,19] have been reported. The association between overweight and psychoneurotic complaints is often cited but is difficult to interpret. It is known that being overweight may cause much distress, especially in women [20,21,22]. This has been confirmed in the Netherlands, where it has been shown that adult overweight women reported that they used sleeping pills, sedatives or tranquilizers more often than non-overweight women did [3]. Young overweight adult women reported having headaches and nervous breakdowns more often than non-overweight women [4]. On the other hand, it is known that mood and certain mental states may contribute to the onset of overweight [23,24]. Our finding that this relationship was more pronounced in men than in women is not confirmed in the literature. It must be noted, however, that most research on overweight in relation to psychosocial problems has been carried out in women. Huygen and his colleagues [25] demonstrated that subjects with recurrent psychosocial complaints visited their general practitioner more often but were also more often overweight. Overweight, psychoneurotic complaints and other illnesses may thus be interrelated and it is not possible to interpret the associations between these in terms of causality . Franks and his colleagues [6] have pointed out a problem that may arise from the use of data derived from diagnoses. They found that frequency of visits to the general practitioner and percentage with psychosocial complaints differed between obese patients according to whether their obesity had been diagnosed. In their study it was clear that the registered obese and the not registered obese groups differed in age (men and women) and social class (men). In our data, age

and social class were shown to be important associates of registered morbidity and might therefore explain, at least partly, the findings of Franks and his colleagues. A related argument was put forward by Garrow [26], who proposed that practitioners may examine overweight subjects more thoroughly for disorders they suspect to be related to overweight than they examine subjects who are not overweight. One disorder most likely to be affected by such information bias is hypertension. From our comparison of data from a screening and data from the morbidity register just prior to the screening it was evident that there was misclassification of overweight and hypertension, but no consistent pattern through the age and sex groups could be found. The accuracy of the registration of hypertension and overweight increased with age, and thereby with the prevalence of hypertension and overweight, and was more accurate in women than in men. This finding probably reflects that with increasing age patients receive more routine examinations (including blood pressure measurements) and contact their physician more often. The same is true for women compared to men. Comparing the odds ratios calculated from the screening data to those calculated from the register data revealed that in some age groups the association between overweight and hypertension is somewhat underestimated and in others somewhat overestimated. Conclusions based on the registration data would differ from the screening data in women aged 20-29 years and in men aged 40-50 years. In the other sex and age groups the associations were quite similar. Information bias due to differential misclassification of hypertension in overweight and non-overweight groups is present only to a limited extent. Of course these comparisons are only a crude way to detect a consistent bias and are based on data measured on one particular occasion. It is very likely that, due to this screening in 1977-1978 the accuracy of the registration of both hypertension and overweight in the morbidity registration has improved considerably. In addition, hypertension is one of the disorders that is most likely to suffer from bias, and it is even less likely that a similar bias is present in other associations observed in this study such as the association between overweight and common cold and influenza, an association that is probably not anticipated by general practitioners.

It remains to be established whether the associations observed in this study are caused by overweight or whether overweight subjects are merely more hypochondriacal than non-overweight subjects. Further evidence for a causal relationship may be obtained from studies in which the effects of prevention and treatment of overweight in general practises on the use of medical care are studied. Such evidence may contribute to an eventual reduction of utilization of primary health care in practises in which physicians pay much attention to the reduction of the prevalence of overweight among their patients.

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Appendix I. Description of codes and groups of codes used in analysis

Code	Description
111	Iron deficiency anemia and other hypochronic anemia, excl. anaemia in pregnancy.
135	Emotional disorders with or without somatic symptoms (or reactions),('Nervous-functional complaints'), incl. nervous reactions, psychogenic reactions, functional reactions, hypochondriasis, neurasthenia, overwork.
182	Otitis externa, excl. that as a result of perforation.
240	Coryza, common cold, incl. rhinitis, sore throat without temerature, excl. allergic rhinitis and glue ear.
241	Febrile common cold and influenza-like illness, influenza, pharyngitis.
242	Tonsillitis, including lymphadenitis colly, tonsillar abcess, excl. acute lymphadenitis.
243	Sinusitis, acute.
245	Epidemic influenza.
313	Urinary infection, acute (acute cystitis), excl. pyelitis and acute pyelonephritis.
325	Dysmenorrhoea, excluding premenstrual symptoms.
327	Irregular menstruation, incl. amenorrhoea not during pregnancy and less than 4 months, excl. amenorrhoea more than 4 months.
328	Menorraghia.
329	Menopausal and climacterial symptoms.
381	Dermatitis, incl. diaper rash, intertrigo, allergic eczema, contact dermatitis, varicose eczema, nickel eczema, rhagades, seborrhoeic dermatitis in adults, dermatitis due to the sun. Excl. dermatitis due to occupation or drugs, urticaria, insect bites, pigmented naevus, scabies, erysipelas, dystrichotic eczema, strophulus, sun burn, allergic sun reaction, herpetic dermatitis.
370	Furuncle, carbuncle (boil).
377	Skin infections: pyoderma, folliculitis, secondary impetigo of the skin, excl. dermatophytosis, pilonidal sinus.
372	Cellulitis and abscesses without lynphadenitis, incl. sebaceous cyst, pompholyx, sweat gland disease, para-anal abscess, erysipeloïd, excl. cellulitis of finger and toe and non-infected cellulitis.
407	Acute lumbago, excl. prolapsed intervertebral disc., sciatica.

408 Fibrositis, incl. myositis, myalgia, tenditis around shoulder, stiff neck, low back pain, overstrained muscle; excl. tenosynovitis.

480 Sprains and strains, incl. effusion after injury.

495 Small superficial injuries or contusions, blisters, excl. non-traumatic epistaxis.

* Illnesses looked at but too few for analysis: infectious diseases, allergies, thyroid disfunction, metabolic disturbances, diseases of blood and bloodforming organs, psychiatric diseases, addiction, illnesses of nervous system and senses, digestive tract complaints

** Chronic diseases studied with longer follow-up: neoplasmata, diabetes mellitus, gout, cardiovascular disease, arthrosis

Appendix II. Morbidity subdivided into levels of severity

Level of severity	Complaint	Codes of complaints in E-list
lower	skin infections	021
	anemia	111
	psychoneurotic complaints	135
	otitis externa	102
	varicose veins	224
	hemorrhoids	225
	common cold without fever	240
	gastroenteritis	289
	cystitis acuta	313
	menstrual disorders	325–9
	eczema	379–81
	acne vulgaris	385
	minor injuries	495
middle	herpes simplex	014
	diabetes mellitis	091
	gout	093
	common cold with fever, influenza	241–5
	bronchitis	247–8
	prolapsed uterus	324
	skin disorders	370
	psoriasis	382
	skeletal problems	406–8
	distortions	480
higher	all malignant tumors	050–69
	cerebrovascular accident	155
	coronary heart disease	211–3
	vascular complaints	221–3
	all fractures (excluding wrist and collar bone)	410–77

CHAPTER 4

OVERWEIGHT AND CHRONIC ILLNESS - A RETROSPECTIVE COHORT STUDY, WITH A FOLLOW-UP OF 6 - 17 YEARS, IN MEN AND WOMEN OF INITIALLY 20 - 50 YEARS OF AGE

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ABSTRACT

A retrospective cohort-study with a follow-up of 6 - 17 years was carried out in four general practices in The Netherlands in the period 1967 - 1983. In total 317 overweight men and 565 overweight women were followed in a continuous morbidity registration, starting in the year they were diagnosed as overweight (at age 20 - 50 years). Incidence of illnesses in this group was compared to that in a control group (444 men and 627 women without registered overweight), matched on sex, age and calendar-year at start of follow-up.
The incidence of registered morbidity in the overweight group was higher for diabetes, gout, arteriosclerotic disease, arthrosis for men and women, and also for varicose veins for women. Increasing BMI at start of follow-up was associated with increased risk for most illnesses under study. For gout and arteriosclerotic disease in men, overweight appeared to be a risk factor at lower levels of BMI than in women.

INTRODUCTION

Recent reports of expert committees have stressed that overweight and obesity are important health hazards in affluent societies [1,2,3]. Many prospective studies have shown that the overweight and the obese tend to have shorter life spans [3], and an excess risk for morbidity. From the reports or reviews on the risks of overweight it is clear that obesity is considered to be a risk factor for many illnesses, but that these risks have rarely been studied in terms of Body Mass Index (BMI in kg/m^2) in a follow-up situation of long duration. In this study a retrospective cohort analysis was carried out, using a continuous morbidity registration with standardized criteria for diagnoses of diseases in four general practices. The incidence in subjects, registered as overweight during a follow-up period of 6-17 years, was compared to that in a control group without registered overweight. With the use of weight and height data of overweight subjects, measured by the general practitioners, an impression of the risks in different categories of BMI could be evaluated.

METHODS

For this study, information was obtained from the Continuous Morbidity Registration of the Department of General Practice of the University of Nijmegen. In four practices, all diagnoses are registered on a day to day basis. These morbidity data can be linked to a computerized continuous registration of the patient files (which includes up-to-date information on demographic variables). Two practices started the registration in 1967, two others joined in 1971. The total population of the four practices together comprises about 12,000 patients and is considered to be representative of the Dutch population, with respect to the distribution of age and sex. One practice is situated in an industrial town (approximately 180,000 inhabitants), one in a middle sized mixed industrial/rural town (approximately 10,000 inhabitants) and the two other practices are situated in rural areas. Diagnoses are registered according to the E-list [4], which is a version of the 'International Statistical Classification of Diseases and Causes of Death' adapted for use in The Netherlands. A description of the diagnostic criteria for diseases studied in this paper can be found in the Appendix. Two groups of patients, an overweight group and a non-overweight group, were retrospectively followed up. The overweight group comprised of all patients who were registered as overweight by their general practitioners in the period 1967 - 1978. The threshold criteria for diagnosis of overweight (relative weight > 115%) corresponds to a BMI between 25.0 - 26.0 kg/m^2 (for women) or between 26.0 - 27.0 kg/m^2 (for men). Overweight was only registered when initial diagnosed overweight persisted in the subsequent year. Overweight subjects were followed-up in the morbidity registration, starting in the year their overweight status appeared for the fast time in the registration (t_0 for these persons).
The overweight population was restricted to patients for whom overweight was registered for the first time between ages 20 - 50 years, and who could be followed for at least 6 years in the registration.
Data on height and weight were obtained from individual patient records. Due to omissions of general practitioners on their patient records or records missing was performed with regard to age at start of follow-up (in 5 year age groups),

sex and general practice. The ratio of the cell frequencies in the 576 (6*2*4*12) cells of the control group compared to the cell frequencies of the overweight group was always between 1.0 and 1.5 (average 1.3). To obtain a valid control group, information on non-overweight status in the morbidity registration throughout the complete observation period 1967 - 1983 was used. Therefore, theoratically, the control group could not be contaminated with non overweight subjects who subsequently became overweight.
Both the overweight and the control group were restricted, before matching, to persons still present in the general practices. They were sent a questionnaire (response: 70%; details are described elsewhere) [7a]. Those who were candidates for the study population, but died before the end of the observation period were first analysed separately and were later added to the study population. Social class was defined as the profession of the head of the household and rated as low (unskilled and skilled workers); middle (lower and middle employees) or high (high employees).

Statistical analysis
Since length of follow-up differed between individuals, statistical techniques for analysing survival data were applied to study the incidence of registrations of chronic diseases for the overweight and the control group [8]. Using these techniques it was possible to use information on the complete observation period of up to 17 years (1967 - 1983). Endpoints in the analysis were either the first occurrence of the particular disease under study or the end of the observation period (1/1/1984). Only persons who were, according to the registration, free of the disease under study at the time the follow-up started, were used for follow-up.
Analysis was performed for men and women separately, and for age groups (based on age at start of follow-up) separately as well as for all ages together. Kaplan-Meier estimates of the 'disease-free' proportion of the population were calculated for each year of follow-up, using the SAS-program PHGLM [9]. The logrank statistic [10] was used to test differences, on a year-to-year basis, between cumulative incidences of the diseases under study of the overweight and the control groups. The proportional hazards model of Cox [11] was applied to estimate the risk of overweight and to control for potentially confounding effects of sex, age, social class and practice, using dummy variables for categorically scaled variables. Relative risks were calculated as the ratio of the incidence densities (incidence divided by number of person years observed) in the overweight and the control group. It appeared that 32 men

(11.9%) and 23 women (5.9%) belonging to the control group could now be considered overweight. Analyses were repeated deleting these 'false negative' subjects from the control group. Endpoints were first registrations of the following chronic disorders: angina pectoris or myocardial infarction; gout, diabetes mellitus, varicose veins; arthrosis; stroke; chronical bronchitis and myodegeneratio cordis. No relation between overweight and the latter three diseases was found. Results of the analyses of these diseases are omitted.

RESULTS

In Table 1 some characteristics of the study population are shown. The differences between the overweight and the control group in distribution over the social classes reflect an inverse relationship between level of profession and body fatness.

Table 1a. Age and number of years of follow-up of the study population

	Men				Women			
	Overweight group		Control group		Overweight group		Control group	
	mean	SD	mean	SD	mean	SD	mean	SD
Age at start of follow-up	37.6	8.0	37.4	8.1	36.8	8.6	36.1	8.7
Years of follow-up	10.6	3.1	10.4	3.0	12.0	3.1	11.3	3.1

Table 1b. Distribution of persons in the study population over social classes

Social class	n	%	n	%	n	%	n	%
low	203	64.0	210	47.3	361	63.9	297	47.7
middle	101	31.9	179	40.3	175	31.0	260	41.5
high	13	4.1	55	12.4	29	5.1	70	11.2
	317	100.0	444	100.0	565	100.0	627	100.0

BMI's at start of follow-up could be calculated for 83.3% of overweight men and 88.3% of overweight women. Mean BMI of overweight men (28.7 kg/m^2; SD 2.0) was lower ($p < 0.05$) than the mean BMI of overweight women (29.3 kg/m^2; SD 3.4). BMI's of the overweight incident cases were calculated. The distributions over categories of BMI for the overweight cases of various diseases and of all overweight persons are shown in Table 2.
Table 2 indicates that, for women, there is an increase in risk for all diseases shown, except for gout, with higher levels of body fatness. The proportion of female cases is clearly elevated, compared to the control group, and compared to lower levels of BMI, when the BMI is higher than 30.0 kg/m^2. A similar trend is seen for diabetes and arthrosis in men. The incidence of gout and arteriosclerotic disease, however, was particularly high for overweight men in the BMI category 27.0 - 29.9 kg/m^2.

In Table 3 the logrank statistics for differences in the cumulative proportions of persons with the disease under study between the overweight and control groups are given (for age groups separately and all ages combined). Differences were greater for age groups above 30 years.

Adding the persons who died in the period 1967 - 1983 to the study population in the retrospective cohort analysis did not alter any of the conclusions drawn from the analysis excluding deaths. Cox's regression model was used to control for the potential confounding effects of social class or general practice. Neither social class nor differences in practice nor adding the small group of deceased persons to the study population, significantly influenced the relationship between overweight and the incidence of registered diseases. To give an impression of the BMI's of the subjects in the overweight and the control groups the BMI's based on self-reported height and weights at the end of the observation period (spring 1984) are shown (Table 4).

Table 2. Distribution over categories of BMI of overweight persons and of overweight incident cases for diseases

BMI category	men: all men	men: number of incident cases (n) and % within BMI category: diabetes mellitus	gout	atherosclerotic disease*	arthrosis	women: all women	women: number of incident cases (n) and % within BMI category: diabetes mellitus	gout	atheros-clerotic disease*	arthrosis	varicose veins
	n	n (%)	n (%)	n (%)	n (%)	n	n (%)	n (%)	n (%)	n (%)	n (%)
< 27.0	32	-	-	1 (3.1)	5 (15.6)	118	-	-	1 (0.8)	7 (5.9)	8 (6.8)
27.0 - 29.9	163	3 (1.8)	6 (3.7)	14 (8.6)	20 (12.3)	225	5 (2.2)	3 (1.3)	3 (1.3)	26 (11.6)	34 (15.1)
30.0 - 39.9	69	4 (5.8)	- (-)	1 (1.4)	11 (15.9)	146	6 (4.1)	1 (0.7)	11 (7.5)	27 (18.5)	31 (21.2)
> 40.0	-	-	-	-	-	10	-	-	1 (10.0)	1 (10.0)	3 (30.0)
Unknown	53	5	1	3	5	66	6	-	5	13	18
Total	317	12 (3.8)	7 (2.2)	19 (6.0)	41 (12.9)	565	17 (3.0)	4 (0.7)	21 (3.7)	73 (12.9)	94 (16.6)
Control group	444	3 (0.7)	1 (0.2)	6 (1.4)	31 (7.0)	627	3 (0.5)	- (-)	4 (0.6)	56 (8.9)	76 (12.1)
Deceased	13	- (-)	- (-)	6 (46.1)**	1 (7.7)	11	- (-)	1 (9.1)	1 (9.1)	3 (27.3)	1 (9.1)

* Myocardial infarction or angina pectoris

** Four of these cases had a BMI at start of follow-up between 27.0 - 29.9 kg/m^2; two a BMI between 30.0 - 39.9 kg/m^2

Table 3. Relative Risks and logrank statistics for testing differences in incidence between overweight and control group during 17 years of follow-up in a continuous morbidity registration

Illness	sex	age at t_0	disease free population overweight: control	number of incident cases overweight: control observed	expected	Relative Risk	p-value for logra statisti
Diabetes	men	20 – 29	64 : 93	1 : 0	0.4 : 0.6	–	0.24
		30 – 39	113 : 161	5 : 1	2.5 : 3.3	7.1	0.036**
		40 – 50	139 : 187	6 : 2	3.4 : 4.6	4.0	0.063*
		20 – 50	316 : 441	12 : 3	6.2 : 8.7	5.6	0.003**
	women	20 – 29	140 : 168	1 : 1	0.9 : 1.1	1.2	0.91
		30 – 39	182 : 210	3 : 1	2.0 : 2.0	3.5	0.32
		40 – 50	237 : 247	13 : 1	7.1 : 6.9	13.5	0.002**
		20 – 50	559 : 625	17 : 3	9.9 : 10.2	6.3	0.001**
Arteriosclerotic disease	men	20 – 29	64 : 93	0 : 0	– : –	–	–
		30 – 39	112 : 162	4 : 1	2.1 : 3.0	5.8	0.076*
		40 – 50	136 : 185	15 : 5	8.3 : 11.7	4.1	0.002**
		20 – 50	312 : 440	19 : 6	10.3 : 14.7	4.5	0.0004**
	women	20 – 29	140 : 168	0 : 0	– : –	–	–
		30 – 39	183 : 210	5 : 0	2.4 : 2.7	–	0.017**
		40 – 50	240 : 248	16 : 4	10.1 : 9.9	5.8	0.008**
		20 – 50	563 : 626	21 : 4	12.2 : 12.8	5.8	0.0005**
Arthrosis	men	20 – 29	64 : 93	5 : 3	3.3 : 4.7	(2.4)	0.23
		30 – 39	113 : 160	11 : 5	6.6 : 9.5	(3.1)	0.024**
		40 – 50	139 : 187	25 : 23	19.9 : 28.5	1.5	0.14
		20 – 50	316 : 440	41 : 31	29.7 : 42.3	1.8	0.007**
	women	20 – 29	140 : 168	2 : 3	2.4 : 2.7	0.8	0.76
		30 – 39	183 : 210	19 : 9	13.8 : 14.2	2.4	0.049**
		40 – 50	238 : 248	52 : 44	47.7 : 48.3	1.2	0.38
		20 – 50	561 : 626	73 : 56	62.6 : 66.4	1.5	0.066*
Gout	men	20 – 29	64 : 93	3 : 0	1.4 : 1.6	–	0.057*
		30 – 39	113 : 163	1 : 0	0.4 : 0.6	–	0.23
		40 – 50	149 : 187	3 : 1	1.7 : 2.3	3.8	0.19
		20 – 50	317 : 444	7 : 1	3.4 : 4.6	9.5	0.010**
	women	20 – 29	138 : 168	0 : 0	0 : 0	–	–
		30 – 39	183 : 210	2 : 0	1.0 : 1.0	–	0.15
		40 – 50	241 : 248	2 : 0	1.0 : 1.0	–	0.17
		20 – 50	562 : 626	4 : 0	2.0 : 2.0	–	0.046**
Varicose veins	women	20 – 29	135 : 167	17 : 17	15.5 : 18.5	1.2	0.60
		30 – 39	176 : 202	30 : 24	25.0 : 29.0	1.2	0.18
		40 – 50	230 : 257	47 : 35	40.4 : 41.6	1.5	0.15
		20 – 50	541 : 626	94 : 76	80.2 : 89.8	1.4	0.034**

* $p < 0.10$

** $p < 0.05$

Table 4. Distribution over categories of BMI based on self-reported weight and height in 1984*

BMI category (kg/m^2)	Overweight group				Control group			
	men		women		men		women	
	n	(%)	n	(%)	n	(%)	n	(%)
< 25.0	27	(14.8)	55	(14.8)	181	(67.3)	313	(80.5)
25.0-26.9	48	(26.4)	96	(25.9)	56	(20.8)	53	(13.6)
27.0-29.9	64	(35.2)	117	(31.6)	30	(11.2)	17	(4.4)
≥ 30.0	43	(23.6)	102	(27.6)	2	(0.7)	6	(1.5)
	182	(100.0)	370	(100.0)	269	(100.0)	389	(100.0)
Unknown	135		192		175		238	
Total	317		562		444		627	

* Actual measured weight (without clothes) and height (without shoes) were requested. 70% returned the questionnaire, of these 95.2% gave both weight and height

Table 4 shows that about 15% of the overweight population can no longer be considered overweight (BMI < 25.0 kg/m^2). This may have been the result of weight reducing efforts resulting in, at least temporarily, normal weight or the consequence of chronic illness. An effect of ageing or of underreporting of weight cannot be excluded. In the control group, 12% of the men and 6% of the women have a BMI > 27 kg $/m^2$. These persons can be considered as false negative control subjects, who have never been registered by their general practitioner as overweight in the morbidity registration. As these unproper control subjects might influence estimates of relative risk as presented in table 2, analysis were repeated after deleting these persons from the control group. Table 5 shows the relative risks and p-values of the logrank statistics after removal of these subjects.

Table 5. Relative risks calculated as the ratio of incidence densities of some chronic illnesses in the overweight group and in the control group, after exclusion of subjects in the control group who, according to self reported data, had a BMI > 27.0 kg/m^2 in the spring of 1984

Illness	Sex	Relative Risk	p-value for logrank statistic
Diabetes Mellitis	men	5.2	0.004
	women	5.6	0.002
Arteriosclerotic Disease	men	4.2	0.0009
	women	5.1	0.0008
Arthrosis	men	1.9	0.006
	women	1.3	0.10
Gout	men	9.0	0.013
	women	-	0.05
Varicose veins	women	1.4	0.04

DISCUSSION

This study demonstrates that overweight patients in general practice are at higher risk for developing arteriosclerotic disease, diabetes mellitus, arthrosis, gout and varicose veins (the latter only for women). It should be noted that the overweight group and the control group differed in frequency of illness at the beginning of the study, because persons in the overweight group, but not in the control group, were selected at the start of follow-up on the basis of a visit to the general practitioner (on which occasion their overweight status was diagnosed.

Many investigators have studied the associations between overweight and disease. Most of these studies, however, have cross-sectional or case-control designs. Causal inference from these studies is often problematic, especially when diseases such as arthrosis, gout, varicose veins and non-fatal

arteriosclerotic disease are under study, because these diseases might contribute to weight change. This could lead to misleading associations. The prospective studies that have been undertaken have generally considered causes of death. Only very few investigators have studied the incidence of disease in relation to overweight [12]. In this study, cases of particular diseases under study at the start of follow-up were excluded, so time-relationships between the onset of overweight and the onset of diseases are likely. For overweight cases, the weight change between the start of the follow-up and the end of the observation-period were analyzed. There is no indication that any of the diseases under study caused significant weight gain or weight loss.
As in every other observational study in which overweight is the independent variable, the time between the start of follow-up and the occurrence of disease should be interpreted with caution, because the exact 'exposure time', i.e. the age of onset of overweight is rarely known. In this study, the use of a continuous morbidity registration implies that, especially in the first years of the registration, many overweight persons had been overweight for a considerable number of years before the start of follow-up. This exposure-time, which is not accounted for in the analysis, probably increases with increasing age at the start of follow-up. This might explain, not only the increasing incidence of chronical illness with advancing age, but also the stronger associations of illness with overweight in the older age groups. The finding in Table 4 that more men than women from the control group can be considered overweight, probably reflects the selective attention of general practitioners with regard to overweight in women. Comparing the results from Table 3 with those in Table 5 suggests that the inclusion of the false negative controls introduced a slight bias away from the null. This could mean that undiagnosed overweight subjects have relatively lower incidence of illnesses compared to diagnosed overweight subjects. Such selection bias has been reported in general practices in the United States [13]. The relationships with chronic illnesses demonstrated in this study are discussed below.

Arteriosclerotic disease

Both myocardial infarction and angina pectoris are common manifestations of arteriosclerotic disease, the most common cause of death in The Netherlands [14]. Both have one underlying functional abnormality: ischemia or insufficient oxygen supply to the tissues of the heart. In long-term follow-up studies, overweight has been associated with arteriosclerotic disease in multivariate analysis as an independent predictor [15]. A large proportion of cases with clinical manifestations of arteriosclerotic disease do survive, probably with severe impairment of their quality of life. This study shows that arteriosclerotic disease, including and excluding fatal cases, is clearly related to overweight. An important finding is that a pronounced increase in risk in men was observed at lower levels of BMI in men than in women. This may be due to sex differences in fat distribution, which are related to hypertension [16,17] and cardiovascular mortality [18]. It must be noted that body weight is clearly related to major risk factors for cardiovascular disease like serum cholesterol level and blood pressure. Adjustments for these factors are likely to yield lower estimates of the relative risks associated with overweight, as has been demonstrated in the Framingham Heart Study [12]. No baseline data of these possible confounding factors were present in the morbidity registration on which we based our analysis, nor were measures of fat distribution. These limitations should be kept in mind in the interpretation of our results.

Diabetes mellitus

Many studies, prospective [19,20] as well as cross-sectional [21,22,23], have demonstrated the association between overweight and diabetes (Type II). This study confirms that there is an increase in risk with higher levels of BMI.

Gout

In the Framingham study it was shown that the risk for gout in men increased appreciably only when weights exceeded 130% of the appropriate weight for height [24]. Although gout was not a common disorder in this study, it is striking that virtually all cases belonged to the overweight population. Most of the cases of gout had a BMI, at the start of follow-up in the category 27.0 - 29.9 kg/m^2, which is clearly lower than 130% of the appropriate weight, as found in the Framingham study.

Arthrosis

The Royal College of Physicians has emphasized the possibility that the association between overweight and arthrosis might be the result of reduced physical activity, leading to weight gain [1]. Comparing the BMI's of cases of arthrosis at the start of follow-up with BMI's based on weights measured by the general practitioner an average of 11 years later, revealed that only 18% were in a higher category of BMI than at the start of follow-up. From Tables 4 and 5 it can be seen that an increase in risk for arthrosis becomes apparent when the

BMI is 27.0 or higher and that 30 - 39 year old overweight women were particularly at risk for developing arthrosis. The individual patient records were studied for the affected sites of arthrosis. In about 35% of the cases in both the overweight and the control group, the affected sites were weight-bearing joints (knees and hips). Also for other sites, no difference was found between the overweight and the control group. The fact that arthrosis associated with overweight is not restricted to weight bearing joints has been observed in previous studies [25].

Varicose veins

Varicose veins were much more common in women than in men. It has been observed that women with varicose veins are heavier than controls of the same age [26,27]. Results from the Basle study [28] demonstrated that parity is an important risk factor for varicose veins in women.
In our population, parity in the overweight group (nulliparous: 6%, one pregnancy: 10%, two pregnancies: 33%, three pregnancies: 23%, four or more pregnancies: 28%) was very similar to parity in the control group (nulliparous: 7%, one pregnancy: 9%), (two pregnancies: 31%, three pregnancies 25%, four or more pregnancies: 28%). Comparing incidence of varicose veins between the overweight and control group in categories of parity showed no confounding effect of parity on the estimates of relative risk.

In the analysis no adjustments could be made for the possible confounding effect of smoking, underweight or type of fat distribution. Since smokers are generally less obese than non-smokers, and also have higher morbidity, taking smoking into account would probably yield higher estimates of relative risk. Fat distribution, was only assessed in a subpopulation of the overweight subjects in two general practices. The waist: thigh circumference ratio was shown to be related to arthrosis in men, hypertension in men and women, diabetes or gout in women, and varicose veins in women. These associations were independent of the degree of overweight [17].

CONCLUSIONS

Overweight leads to an increased frequency of chronic illnesses, registered in general practice. For men, this elevated risk was apparent at lower levels of BMI than for women. This is in agreement with findings of studies on fat distribution, which have shown that, for the same degree of overweight, men are

at higher risk of various disorders than women [29].
At present, overweight in general practice is a condition for which relatively more women are treated than men. However overweight as a health hazard in men should not be neglected. This study does not allow for detecting a dose-response relationship, but it is apparent from Table 2 that overweight in men is associated with chronic illness at lower levels of BMI than in women. The diseases that were found to be associated with overweight might lead to important functional limitations and diminished subjective health. It should be emphasized that selection bias might have influenced the results of the analysis and that the elevated risks associated with overweight might at least partly be attributed to confounding effects of factors like serum cholesterol and blood pressure. Levels of these risk factors for arteriosclerotic disease usually tend to normalize and conditions like diabetes mellitus, gout and arthrosis are likely to improve when a substantial weight reduction is achieved and maintained [30].
Thus, treatment of those who are already overweight and, perhaps more importantly, prevention of overweight in those who are at risk, deserves attention in general practice. The general practitioner is able to monitor weight changes on a regular basis. When persons, especially young adults, who are already moderately overweight (BMI > 25 kg/m^2) gain weight, attention should be paid to their nutritional habits and other aspects of their lifestyles, in order to prevent them from becoming severely overweight, which would increase their chances of developing a chronic disease.

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APPENDIX

Diagnostic criteria for chronic diseases in the continuous morbidity registration.

Diabetes mellitus

A single blood-glucoselevel > 10 mmol/l was used as the criterion. In doubtful cases, this was confirmed by an abnormal Oral Glucose Tolerance Test according to WHO criteria.

Gout

Gout was registered when the usual clinical symptoms were observed, if necessary confirmed by laboratory investigation.

Arthrosis

Arthrosis deformans was registered when there were clear clinical signs of arthrosis (e.g., pain, stiffness and inflammation), confirmed by an X-ray.

Varicose veins

Varicose veins of lower limbs were registered when clearly visible varicose veins were presented, observed either at routine examination or following specific complaints from the patient.

Myocardial infarction

Myocardial infarction was registered when a clinical suspection of a myocardial infarction could be confirmed by an abnormal ECG and/or by measurements of the concentrations of the enzymes CPK, SGOT, LDH (exceptions were made for patients who died before such investigations were possible).

Angina pectoris

Angina pectoris was diagnosed when a clinical examination provided sufficient evidence for angina pectoris (not necessarily confirmed by laboratory - or ECG - test).

CHAPTER 5

THE RELATION BETWEEN OVERWEIGHT AND SUBJECTIVE HEALTH - WITH ATTENTION TO THE EFFECTS OF AGE, SOCIAL CLASS, SLIMMING BEHAVIOR AND SMOKING HABITS ON THIS RELATION

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ABSTRACT

Subjective health status was assessed, in relation to overweight, by administering a list of 51 health complaints to adult men and women who were either chronically overweight as defined by Body Mass Index (BMI) or not overweight, in a continuous morbidity registration in four general practices during the period 1967 - 1983. Responses were received from 455 men (182 overweight) and 790 women (386 overweight), age 26 - 66 years. Response rate (71%) and age distribution (mean age 48) were equal in overweight and non-overweight groups of both sexes. BMI was correlated with the total number of complaints in women (r = 0.15) but not in men (r = 0.07). Multiple regression analysis revealed, however, that age was an effect modifier in this relation, there being a negative association between BMI and subjective health in younger men and a positive association in older men, whereas, in women, the association between BMI and subjective health was much more pronounced at younger ages than at older ages. In addition, current smoking habits and social class (in men and women) and reported slimming behavior (in women) had an independent relation to the total number of health complaints. BMI was also related to specific complaints and groups of complaints, particularly in women.

INTRODUCTION

Overweight is a risk factor for the development of various diseases[1,2] and is very common in affluent countries including The Netherlands. We have shown that overweight is accompanied by an excess of both objectively registered morbidity and subjective reported illness, increased use of medical care for particular reasons, and the use of certain drugs[3]. The subjective health status of overweight persons could be mediated through the association between overweight and morbidity. On the other hand, in the absence of illness, overweight per se may be related to a diminished feeling of well being. Deviations from a cultural ideal of slimmness may be involved in such a relation[4,5] as well as functional limitations due to excess weight.

The association of overweight with states of mental health has been the subject of many studies, but the association with subjective health complaints has been a somewhat neglected subject. Research in the U.S.A.[6] indicated that overweight was related to functional limitations, pain, worry and restricted activities. In Sweden, associations between overweight and indices of health were found to be less pronounced in middle aged men than in women[7,8].

In this study we investigated the association between the Body Mass Index (BMI = weight/height^2) and responses to a list of 51 subjective health complaints. The relations of BMI with the total number of complaints as well as with groups of complaints were studied, adjusting for the possible confounding effects of slimming behavior, smoking habits, age, and social class.

METHODS

Sample characteristics

The data presented in this paper were obtained from a questionnaire that was administered in the spring of 1984 to members of a study population that had been followed-up in a continuous morbidity registration[9]. For the overweight group, persons were selected on the basis of diagnosis of overweight at age 20 - 50 years by general practitioners from four general practices in a mixed rural/urban area. The control group comprised a random sample of adults who had never been diagnosed as overweight; this group was matched to the overweight group in age, sex, practice and calendar-year at start of follow-up. Details of the follow-up study and sampling methods have been described elsewhere[9].

The total population in the four general practices comprises about 12.000 individuals, and is representative for the Dutch population with respect to the distribution of age and sex. All persons sampled were Caucasian and of Dutch nationality.

Persons whose addresses were known (93%) were sent a questionnaire, which was returned by 1241 persons (71% response). The response was not selective with regard to overweight status, sex, age or social class. Table 1 shows some characteristics of the study group.

Description of measures

1. Overweight was diagnosed in the period 1967 - 1978 by general practitioners according to criteria that correspond to a Body Mass Index (BMI = weight/height^2) of at least 26.0 kg/m^2 (for women) or 27.0 kg/m^2 (for men). Height and weight were measured by the general practioners at the time of the diagnosis of overweight. On average, this was 12 years prior to the administration of the questionnaire (range 6 - 17 years). As part of the follow-up questionnaire in 1984, subjects were asked to weigh themselves in the morning without shoes and clothes and measure their actual height without shoes. Virtually all subjects indicated, when asked in the questionnaire, that they had been able to follow these instructions for weighing themselves and measuring height. In addition, self-reported heights and weights were found to be accurate when compared to measured heights and weights in a sample of 305 of the overweight subjects [25]. Unless otherwise specified, BMI when used in this paper refers to current BMI.
2. Social class was defined as lower (unskilled and skilled manual workers), middle (lower employees) or upper (higher employees), according to the profession of the head of the household.
3. Smoking behavior was classified from questionnaire into four categories (never smoked, stopped smoking, smoking less than 10 cigarettes per day, and 10 cigarettes or more per day). In multiple regression analyses dummy variables for the categories "stopped smoking", and "smoking" were used, while "never smoked" was the reference category.
4. Slimming behavior was classified into five categories ("never", "seldom", "regularly", "often", or "(almost) always", trying to reduce weight). In the multiple regression analyses, "regularly" and "often" slimming were combined into one category. Dummy variables were used, with "never slimming" as the reference category.
5. Subjective health was measured by rated health on a 7-point scale and by the answers to a list of 53 health complaints[10]. This list is often used in The Netherlands to assess subjective health status[11]. Appendix I gives a short description of some single items and, items and clusters identified using factor analysis[12]. All items were dichotomous; two items ("do you feel too thin?" and "do you feel overweight?") were excluded from the analysis since these items could seriously confound the relation between overweight and the total number of complaints. The square root of the total number of complaints (from the remaining 51 items) had a close approximation to the normal distribution and showed the clearest linear relationship with BMI and other

variables; it was therefore used in the analysis as an index for general subjective health. In logistic regression, scores on subscales were considered as well as some single items. These items were selected when, in analysis of contingency tables, after adjustments for sex, social class in the period 1967 - 1978 and age, the answers on these items were differed between the overweight and the control group at a probability level of 0.05.

6. Statistical methods. Multiple linear and logistic regression analyses were performed with the use of the statistical package programs BMDP2R and BMDPLR[13]. Presence of interaction was assessed by adding cross-product terms of variables to a model that contained all the main effects. When the F-to-enter of an interaction term had a probability value less than 0.10, the cross-product term was included in the straight regression analysis whose results are presented in the tables. The dependent variable in multiple linear regression (table 4) was the square root of the total number of complaints. Independent variables were BMI, age (and a cross-product term of BMI and age, reflecting statistical interaction of BMI and age in the analysis), social class, smoking habits and slimming behavior. For categories of smoking habits and slimming behavior, dummy variables were used (using never-smoking and never-slimming as reference categories). In multiple logistic regression (table 6) the same independent variables were used. The dependent variable was dichotomous: presence or absence of a complaint (single items) or presence or absence of at least one complaint (groups of items).

RESULTS

Table 1 shows the distribution of subjects in BMI categories and categories of possible confounding variables. At the time of the study, about 27% of the originally registered overweight women and 41% of the originally registered overweight men could not be considered overweight any longer, while about 6% of the women and 12% of the men in the control group would be considered overweight, according to the same criteria used earlier by their general practitioners. In Table 1, current overweight is inversely related to social class; age and smoking more than women; subjects in the overweight groups reported slimming more often than those in the control group, this being more pronounced in women than in men. Subjective health, rated on a 7-point scale, was highly correlated with the square root of the number of complaints (men: $r = 0.61$, 95% CI = 0.55 - 0.66; women: $r = 0.65$, 95% CI = 0.61 - 0.69)

Table 1. Body Mass Index, social class, age, smoking habits, and slimming behaviour of those responding to the questionnaire, classified according to overweight status (registered in 1967 - 1978) and sex

	Women				Men			
	Overweight		Control		Overweight		Control	
	n	%	n	%	n	%	n	%
A. Body Mass Index (kg/m^2)								
< 25.0	55	14.8	313	80.5	27	14.8	181	67.3
25.0-26.9	96	25.9	53	13.6	48	26.4	56	20.8
27.0-29.9	117	31.6	17	4.4	64	35.2	30	11.2
> 30.0	102	27.6	6	1.5	43	23.6	2	0.7
unknown	16	-	15	-	0	-	4	-
B. Social Class								
Lower	248	64.2	186	46.1	117	64.3	124	45.4
Middle	118	30.6	177	43.8	59	32.4	117	42.9
Upper	20	5.2	41	10.1	6	3.3	32	11.7
C. Age (years)								
26-39	82	21.2	87	21.5	35	19.2	62	22.7
40-49	98	25.4	131	32.4	64	35.2	78	28.6
50-66	205	53.1	184	45.5	74	40.7	130	47.6
D. Smoking habits								
never smoked	163	42.2	156	38.6	22	12.1	40	14.7
stopped smoking	85	22.0	99	24.5	59	32.4	79	28.9
smoking < 10 cigs/day	43	11.1	59	14.6	41	22.5	46	16.8
smoking > 10 cigs/day	95	24.6	90	22.3	60	32.0	108	39.6
E. Slimming behaviour								
never	52	13.6	207	51.6	55	31.1	190	69.6
seldom	83	21.8	108	26.9	59	33.3	55	20.1
regular	119	31.2	56	14.0	34	19.2	16	5.9
often	48	12.6	12	3.0	15	8.5	0	0.0
(almost) always	79	20.7	18	4.5	14	7.9	12	4.4
unknown	5	-	3	-	5	-	0	-
Total	386	100	404	100	182	100	273	100

In women BMI was correlated with the number of complaints ($r = 0.15$; 95% CI: 0.08 - 0.21), but in men the correlation was very slight ($r = 0.07$; 95% CI: -0.03 - 0.17). In table 2 the average of the square root of the total number of complaints in various categories of BMI are shown. It can be seen that in all categories of BMI more complaints were reported in the overweight group than in the control group. Overweight status in this table was based on the classification by the general practitioners. In subsequent analysis we did not use the general practitioner classification as this would probably would have led to an overestimation of the association between current overweight and current subjective health.

Table 2. Square root of the total number of complaints per category of current Body Mass Index by overweight status based on the diagnosis of their general practitioners 6-17 years earlier

	Women		Men	
	Overweight mean	Control mean	Overweight mean	Control mean
A. Body Mass Index (kg/m^2)				
< 25.0	3.3	3.0	3.1	2.8
25.0 - 26.9	3.2	2.9	3.3	2.5
27.0 - 29.9	3.4	2.8	3.2	2.8
≥ 30.0	3.5	3.0	3.2	3.0

The average number of complaints in categories of other variables that were used in this study are shown in Table 3. The number of complaints generally increased with age, with heavier smoking (in men and women) and with more frequent slimming in women. A clear inverse relation between social class and the number of complaints was found in men and women.

As the variables in table 3 are known to be related to both overweight and to subjective health we performed a multiple regression analysis in which all these variables were taken into account. In the evaluation of the data a clear interaction between age and BMI was observed in both men and women. Therefore this interaction was included in the multiple regression model. The results are presented in table 4.

Table 3. Square root of the total number of complaints according to current BMI, social class, age, smoking habits, and slimming behavior for men and women

	Women n = 790	Men n = 451
Body Mass Index (kg/m^2)	mean	mean
< 25.0	3.0	2.8
25.0 - 26.9	3.1	2.9
27.0 - 29.9	3.3	3.1
> 30.0	3.5	3.1
Social class		
Low	3.3	3.1
Middle	3.0	2.6
High	2.7	2.4
Age (years)		
26 - 39	3.0	2.7
40 - 49	3.2	2.9
50 - 66	3.3	3.0
Smoking habits		
never smoked	3.0	2.7
stopped smoking	3.2	2.6
smoking < 10 cigs/day	3.1	3.0
smoking > 10 cigs/day	3.4	3.1
Slimming behavior		
Never	2.9	2.9
Seldom	3.0	2.8
Regular	3.3	2.8
Often	3.4	3.9
(Almost) always	3.5	2.9

Table 4. Relation of BMI, age, social class, smoking habits, and slimming behavior to the square root of the total number of complaints (51 items). Results of multiple linear regression analysis

Sex	Variable	Regression coefficient	Standard Error of regr.coeff.
Women	BMI (kg/m2)	0.022	0.014
	Age (years)	0.078*	0.032
	BMI x (Age-48)+	-0.002*	0.001
	Social class	-0.272*	0.081
	Smoking‡	0.326*	0.117
	Ex-smoking‡	0.278*	0.131
	Slimming (seldom)§	0.233*	0.118
	Slimming (often/regular)§	0.352	0.220
	Slimming (almost always)§	0.438*	0.179
	Total $R^2 * 100 = 7.6$		
Men	BMI (kg/m2)	0.020	0.021
	Age (years)	-0.092*	0.051
	BMI x (Age-48)+	0.004*	0.002
	Social class	-0.344*	0.099
	Smoking‡	0.376*	0.189
	Ex-smoking‡	-0.199	0.207
	Slimming (seldom)§	-0.003	0.145
	Slimming (often/regular)§	0.832*	0.422
	Slimming (almost always)§	0.228	0.284
	Total $R^2 * 100 = 10$		

Notes: * $p < 0.05$

+ Cross-product term of BMI and age indicating statistical interaction between BMI and age in their association with subjective health (48 years is the average age in men and women)

‡ Dummy variables for categories of smoking habits ("never smoked" is the reference category)

§ Dummy variables for categories of slimming habits ("never slimming" is the reference category

The results in Table 4 are in agreement with the simple analysis in that social class was found to be negatively related to subjective health, that smokers had

more health complaints than those who reported they never smoked. Men who stopped smoking had less complaints and women who stopped had more complaints than those who never smoked. In most categories of slimming frequency the number of complaints was higher than in the category of "never slimming" also after adjustment for BMI and the other variables and this was more pronounced in women than in men. The presence of an interaction term in multiple regression in table 4 complicates the interpretation of the regression coefficients of BMI and age. For interpretation purposes we calculated the predicted average number of complaints according to the regression models in table 4 for different values of BMI and age (corrected for the transformation of the predicted square root values to actual number of complaints).
The results are shown in Table 5. In men, a higher BMI was associated with more health complaints at the age of 55 but with less complaints at 35. In women a higher BMI was associated with more complaints at the age of 35 but not at the age of 55. An increase in number of complaints with age was clearer in overweight men than in lean men, and clearer in lean women than in overweight women.

Table 5. Average number of complaints, predicted by regression coefficients of the regression model from table 4, at two different ages and for two different levels of Body Mass Index

Sex	Age	Body Mass Index	
		23 kg/m^2	28 kg/m^2
Women	35 years	9.6	11.1
	55 years	12.3	12.4
Men	35 years	9.2	8.3
	55 years	9.8	11.3

Note: estimates corrected for transforming the predicted square root of complaints to the average number of complaints (by adding the residual variance of the number of complaints in the square root scale)

As the BMI might be related to specific complaints but not to others, we studied the relation of BMI to absence or presence of specific complaints and absences or presence of at least one complaint out of groups of complaints. The complaints that were found to be related to BMI, independent of age, social class, and smoking habits are shown in Table 6.

Table 6. Groups of complaints (clusters) and single complaints related to the Body Mass Index, adjusting for age, social class, slimming behavior, and smoking habits. Results from multiple logistic regression analysis

Sex	Description of complaints	No. of items in cluster	% reporting 1 complaints from cluster	Partial logistic regression coefficient of BMI b	SE(b)
Women	Stomach/digestion	5	30.6	0.0422	0.0194
	Skeleto/muscular	5	67.2	0.0703	0.0244
	Nervousness	4	48.3	0.0570	0.0196
	Tiredness	5	50.0	0.0432	0.0194
	Nose/throat	3	22.6	0.0371	0.0208
	Shortness of breath	1	18.0	0.115	0.0228
	Pain chest/heart	1	13.8	0.0390	0.0230
	Often having mishaps	1	6.8	0.115	0.0309
	Tight in chest	1	12.4	0.0584	0.0250
Men	Stomach/digestion	5	27.5	0.0760	0.0344
	Skeleto/muscular	5	59.3	0.0767	0.0359
	Shortness of breath	1	12.8	0.0898	0.0368

Note: all regression coefficients significantly different from zero ($p < 0.05$). The dependent variable in the analysis was dichotomous: presence or absence of a particular complaint (single items) or presence or absence of at least one complaint out of a group (cluster) of complaints

Complaints of the digestive tract, the skeleto-muscular system and shortness of breath were associated with BMI in men and women. In addition, in women an association was found between BMI and complaints of nervousness, tiredness, nose and throat, pain in the chest and heart region, often having mishaps, and often feeling tight in the chest. Slimming behavior was independently related to complaints of tiredness and often having mishaps (not shown in the tables).

DISCUSSION

Our data show that increased Body Mass Index is associated with more subjective health complaints but that age is an effect modifier in this association. In men a positive association could be demonstrated in older ages and a negative association in younger ages. In women, on the other hand, the positive correlation between BMI and number of complaints diminished with age. In most studies that have reported an association between overweight and subjective health a possible interaction between age and BMI was not taken into account[6,7,8].

The effect modification of age in men cannot be easily explained. It may be that a long period of overweight is needed before an effect of overweight on subjective health becomes apparent in men. The reason why in younger women a much stronger relation between overweight and complaints was found than in older women may be that younger women worry more and are more concerned about being overweight, hence, exhibit more health complaints. Some of the specific health complaints associated with BMI are psychosomatic (e.g. nervousness, tiredness, often having mishaps). In these relations no significant interaction was observed but it must be noted that in logistic analysis, interaction is evaluated on a multiplicative scale whereas in multiple linear regression analysis interaction is assessed on an additive scale[14].

In our study it was not possible to determine whether psychosomatic complaints were the cause or the result of overweight[15,16]. The effects of the stigma of obesity, especially in women, have been reviewed recently[4,5] and it has been suggested that society's discrimination against the obese and the pressures for thinness are enough to account for many psychological complaints in the overweight[17]. On the other hand, it has been shown that psychosocial problems may contribute to weight gain[18] and that weight changes are accompanied by changes in mood[19,20]. In women, a higher frequency of slimming behavior was related to more health complaints, independently of the degree of overweight; only 15% of the women, however, reported that health reasons were important as motives for slimming, whereas the reasons 'problems with clothes' and 'my figure' were each endorsed by 65% of the women who had ever tried to lose weight. Therefore, it is not likely that the relation between slimming and subjective health complaints can be explained by the fact that most women try to lose weight because of health problems. Perhaps slimming behavior in itself is associated with increased distress. When we stratified the overweight group (as classified by the general practitioners) into persons who shifted out of the

overweight category (based current BMI) and those who remained in the overweight category it was surprising to find that these two groups had an equal average number of complaints and both groups had more complaints than the group that had remained non-overweight. Thus, successful slimming cannot account for improved subjective health status. Only 10% or less of the variance in the number of complaints could be explained by all the variables in the regression analysis (Table 4). Thus there must be other unmeasured determinants, that account for the unexplained part of the variance.
Although subjects received instructions for measuring heights and weights, the use of self-reported measurements has its limitations. For example, even when all subjects would have followed the instructions carefully, insystematic errors may have occurred because of the poor quality of some home weighing-scales.
We may conclude that the association of overweight and poorer subjective health status differs between men and women and that this association is dependent on age. In younger women, this association is probably related to an increased concern of these women about their weight or figure. In this particular age group it may be important to investigate whether the 'legitimization' of being overweight (as suggested by Stewart and her colleagues[6]) may have a positive effect on subjective health. In case of increased health risk it remains necessary to treat those who are overweight. Public health measures should be directed towards the prevention of overweight and increasing awareness about the health risks associated with overweight when accompanied by an abdominal fat distribution[22], a family history of cardiovascular disease or diabetes, elevated levels of risk factors for cardiovascular disease[23] and in those cases when subjects suffer from afflictions that may benefit from weight reduction[21]. In our opinion, public health measures should, besides informing the public about the health hazards of overweight, pay attention to the unwarranted social pressures for thinness especially in those in whom overweight is predominantly a cosmetic problem[24].

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Appendix I

A. Description of clusters of complaints (identified using factor analysis (Philipsen et al. 1983)

Name of cluster	Item	Women	Men
- Stomach/digestion	1. Does your stomach often feel full and bloated?	+	+
	2. Do you often have pains in the stomach region?	+	+
	3. Do you often have an upset stomach?		+
	4. Do you often have stomach complaints?		
	5. Do you often have indigestion?	+	+
- Skeleto-muscular	1. Do you often have unpleasantly cold fingers, hands or feet?		
	2. Do your bones or muscles often ache?	+	+
	3. Are you bothered by weak or aching feet?	+	
	4. Are you often troubled by backache?	+	+
	5. Do your arms and legs often go dead or tingle?		+
- Nervousness	1. Do you often get upset?		
	2. Do you often feel nervous?	+	
	3. Are you often irritable?	+	
	4. Do your hands often shake?		
- Tiredness	1. Do you often feel tired	+	
	2. Do you often feel sleepish or sluggish?	+	
	3. Do you often feel listless?	+	
	4. Do you generally get up feeling tired and not rested in the morning?		
	5. Do you feel tired sooner than you think is normal?	+	

- Nose and throat	1. Are you regularly bothered by coughing?	+	
	2. Do you often have to clear your throat?	+	
	3. Is your nose often blocked?	+	

B. Other complaints, for which the answers were found to differ between the overweight and control groups ($p < 0.05$, after adjustment for social class). Only complaints that are not included in the clusters of complaints listed above are presented.

- Complaint	1. Do you get short of breath easily ?	+	+
	2. Do you fall asleep easily and do you sleep well?	+	
	3. Do you sometimes sweat heavily even when it is not hot?	+	
	4. Do you often have little mishaps ?	+	
	5. Do you often feel tight in the chest?	+	

+ = Stratified analysis (with adjustment for social class) revealed a difference between overweight and control group ($p < 0.05$)(using the chi-squared test of Mantel Haenszel[14])

Note: clusters (factors) identified when, after rotation, the factor loading of the items on only one of the factores was at least 0.40. More information about the cluster analysis is available on request to the authors.

CHAPTER 6

FAT DISTRIBUTION OF OVERWEIGHT PERSONS IN RELATION TO MORBIDITY AND SUBJECTIVE HEALTH

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ABSTRACT

The association between fat distribution, morbidity and subjective health was studied in 95 overweight adult men and 210 overweight adult women. Retrospective morbidity data were taken from a continuous morbidity registration made by general practitioners over a period of maximally 17 years. In addition information about subjective health and weight history was obtained from a self-administered questionnaire. Anthropometric measurements were taken and, on the basis of waist-hip and waist-thigh circumference ratios, subjects were classified into upper body segment obesity, intermediate obesity, and lower body segment obesity.

It was found that, adjusted for age and body mass index, a high waist-thigh circumference ratio was a risk factor for hypertension and for gout or diabetes in women and arthrosis in men. A low waist-thigh ratio was associated with a high prevalence of varicose veins in women.

The associations of waist-hips circumference ratio with morbidity were less pronounced, with the exception of hypertension for men. Information from the questionnaire revealed that persons with upper body segment obesity (especially men) felt less healthy and had more health complaints. These findings were more pronounced for subjects younger than 50 years of age than for those of 50 years and older.

The weight histories suggest that women with lower body segment obesity had a longer history of obesity than women with upper body segment obesity. This was not found in men. It is concluded that classification of obesity on the basis of circumference ratios is useful for the evaluation of health hazards of overweight subjects.

INTRODUCTION

The distribution of fat over the body is important in the association of obesity and some metabolic disturbances in lipid and carbohydrate metabolism.
A relative predominance of fat in the upper part of the body, or, more specifically, in the abdominal region, is related to metabolic disturbances as well as to the prevalence of various disorders, such as diabetes mellitus[9,15,16,18,21,29,31] hypertension[3,16,18,21] gallbladder disease[16] and menstrual disorders[16]. Fat distribution has also been shown to be an important predictor of death due to cardiovascular disease or stroke, and of deaths from all causes in men[22] and women[21a].
Useful measures for the classification of different types of fat distribution in epidemiological studies include the circumference ratio of waist and hips[7,15,18,21,22] and the ratio of waist and thigh diameters[1].
Both waist-hips and waist-thigh circumference ratios were used in this study to describe the fat distribution in a group of overweight Dutch men and women. The aim of the study was to determine whether associations of fat distribution with disease could be confirmed or established, and whether fat distribution was related to subjective well-being and weight history. The results of the study confirm that fat distribution is an important indicator for both registered disorders and subjective health status (the latter especially in men).

SUBJECTS AND METHODS

Subjects

Subjects were patients of two general practices taking part in the Continuous Morbidity Registration at the Department of General Practice of the University of Nijmegen. Persons who had been diagnosed, by the general practitioner as 'obese' (criterium: Broca Index > 115%) at an age between 20 and 50 years, and were still obese at the time of this investigation, received a mailed questionnaire. Those who completed the questionnaire, from which information about subjective health and weight history was obtained, were asked to participate in an anthropometric study. 548 Persons were sent a questionnaire, 401 (73%) returned the questionnaire and, of these, 305 (56%; 95 men, 210 women) agreed to participate in the anthropometric study.

Measurements

The subjects were measured either at home or in the doctor's office by a trained assistant. Height in standing position (to the nearest 0.1 cm) and weight (to the nearest 0.5 kg, on a calibrated balance) were measured of subjects without shoes, wearing only underwear or light indoor clothing. Measurements of the circumferences of subjects were taken in a standing position, breathing normally. The minimal circumference of the waist, the maximal hips circumferences and the highest horizontal circumference of the left upper thigh were measured (to the nearest 0.1 cm) using a metal tape measure.

Calculations

The ratios of waist to thigh circumference ratio (waist-thigh ratio) and waist to hips circumference (waist-hips ratio) were calculated. Waist-hips ratio has been shown to be a useful measure for classification of fat distribution in relation to metabolic associates of obesity[2,7,15,18,21,22]. There were indications from the literature that the waist-thigh ratio could be at least an equally good indicator of fat distribution[1]. Therefore both circumference ratios were used in the analysis. As in other studies, Upper Body Segment Obesity (UBSO) was defined as the upper tertile of the circumference ratios, when these were used as categorically scaled variables, and Lower Body Segment Obesity (LBSO) as the lower tertile of the ratios[9,22].

Body Mass Index (BMI in kg/m^2) was calculated using weight and height as measured by the general practitioners at the time of which obesity was diagnosed (t_0) and using weight and height at time of the anthropometric study in 1984. In analysis, with categorically scaled variables, two classes of obesity were distinguished, according to the classification of Garrow[13]: BMI 25.0 - 29.9 (Grade I or moderate obesity) and BMI > 30.0 (Grade II or severe obesity).

Morbidity analysis

For all persons that took part in the study, we were informed about the diagnoses made by the general practitioners during the previous 17 years (i.e. since the start of the Continuous Morbidity Registration) of any of the following chronic disorders: diabetes mellitus, gout, angina pectoris, hypertension, varicose veins, non-fatal ischaemic heart disease, arthrosis, eczema and prolaps uteri.

The diagnoses were made using a classification system based on the International Classification of Diseases (ICD version 6) using standardized procedures[24] a short description of diagnostic criteria is included in Appendix I. The prevalence of some possibly relevant disorders for this study was too low for analysis e.g. cancer, stroke, gallstones, myodegeneratio cordis and periferal arterial heart disease.

Combinations of some disorders were also studied (e.g. diabetes and/or gout, and a combination of serious disorders: diabetes, gout, angina pectoris, ischaemic heart disease and arthrosis).

Questionnaire

The subjects were asked to rate their subjective health status on a 7-point scale (1 = very good, 7 = very bad). The questionnaire included a list of 53 items (subjective health complaints) often used to measure subjective health in epidemiologic surveys in The Netherlands[4]. For this paper, a 39-item abbreviation was used, in analysis since these items had been published in English[26]. The total number of complaints on this 39-item list was calculated for each subject. The distribution of these cumulative scores was markedly skewed to the left. The square root was approximately normally distributed and was therefore used in analysis. Subscores of some clusters of complaints were calculated. These clusters had been indentified using factor analysis on data from large epidemiologic surveys[25].

Information about weight history, about smoking habits and about slimming frequency was also obtained from the questionnaire. Age and socio-economic status, based on the profession of the head of the household, were registered in the morbidity registration[24].

Statistical methods morbidity analysis

In a forward stepwise multiple logistic regression analysis, using the computer package programme BMPLR[5], the following continuous variables were candidates for inclusion in the logistic model as independent variables: age, BMI, circumference ratios and, categorically scaled, socio-economic status (lower, middle, upper class)[24].

Analysis using age (< 50; > 50 years in 1984), BMI (< 30; > 30 kg/m^2 in 1984) and circumference values (lower, middle and upper tertile) as categorically scaled variables produced comparable results. The latter procedure yielded multiple regression coefficients intervals of the odds ratios according to Lemeshow and Hosmen (1984)[23] capaing the upper tertile of the circumference ratios to the lower tertile. Analysis were performed separately for men and women and for the two circumference ratios.

Questionnaire analysis

For the analysis of the information obtained from the questionnaire, t-tests or chi-squared tests were performed to compare subjects in the upper tertile (upper body segment obesity) with those in the lower tertile (lower body segment obesity) of the waist-thigh ratio. Multiple linear regression analyses were performed using the program BMDPLR[5].

RESULTS

Some characteristics of the study population are given in Table 1.

Table 1. Mean and standard deviation of age and some anthropometric measurements of the study population

		Women (n=210)		Men (n=95)	
		Mean	S.D.	Mean	S.D.
Age	years	49.9	9.7	49.2	9.2
Weight	kg	78.7	11.9	90.3	11.8
Height	cm	163.4	6.1	177.4	6.1
BMI	kg/m^2	29.5	4.1	28.7	3.1
Waist-circumference	cm	89.6	9.7	101.6	8.8
Hips-circumference	cm	109.9	10.0	105.0	5.8
Thigh-circumference	cm	60.1	5.0	59.2	4.0
Waist-hips ratio		0.82	0.05	0.97	0.06
Waist-thigh ratio		1.42	0.16	1.72	0.15

In Table 2 the classification of men and women in types of fat distribution (upper body segment obesity, intermediate obesity or lower body segment obesity) is shown. When classifying according to both waist-hips ratios and waist-thigh ratios no exactly equal groups could be formed (especially in the case of the waist-hips ratio distribution). Therefore only approximations of the tertiles of the ratios were used. The ratios were highly correlated ($r = 0.76$; $p < 0.001$) and only a few subjects appear in different extreme tertiles of the different ratios.

Table 2. Number of subjects in various classes of waist-hips circumference ratio and waist-thigh circumference ratio*

Women					
Waist-thigh ratio		Waist-hips ratio			
		< 0.78 (LBSO)**	0.79 - 0.84 (Intermediate)	> 0.85 (UBSO)	all women
< 1.34	(LBSO)**	45	24	2	71
1.35 - 1.49	(Intermediate)	9	44	14	67
> 1.50	(UBSO)	3	19	49	71
all women		57	87	65	209

Men					
Waist-thigh ratio		Waist-hips ratio			
		<0.94 (LBSO)**	0.95 - 0.99 (Intermediate)	> 1.00 (UBSO)	all men
< 1.65	(LBSO)**	26	4	2	32
1.66 - 1.78	(Intermediate)	4	15	13	32
> 1.79	(UBSO)	1	8	22	31
all men		31	27	37	95

* Cut-off values were set to obtain approximate tertiles of the distribution of the circumference ratios. Because of the distribution of the circumference ratios exactly equal groups could not be formed

** LBSO (Lower Body Segment Obesity) was defined as the category with low values of the circumference ratios. Intermediate was defined as the middle category of the circumference ratios.
UBSO (Upper body segment obesity) was defined as the category with high values of the circumference ratios

From Table 3 it can be seen that women with upper body segment obesity were heavier at the time of investigation (1984) than at time of diagnosis of obesity (t_0). Upper body segment obese women gained 2.7 ± 7.6 kg (mean $\pm$ standard deviation). There was no significant change of weight in subjects in any of the other categories of waist-thigh ratio.

Table 3. Age and Body Mass Index (BMI) of the study population at time of investigation (1984) and at time of diagnosis (t_0) in different classes of fat distribution

Number of subjects	LBSO** Mean	SD	Intermediate Mean	SD	UBSO** Mean	SD
Women						
Number of subjects	71		67		71	
Age at t_0	34.03	8.91	38.27	9.08	41.04	8.41
Age in 1984	46.24	9.65	50.49	9.83	53.15	8.51
BMI at t_0	28.15	2.04	29.15	3.56	29.74	3.23***
BMI in 1984	27.84	2.99	29.20	3.75	31.05	4.34***
Men						
Number of subjects	32		32		31	
Age at t_0	35.52	8.69	37.83	7.54	41.04	6.95
Age in 1984	45.34	9.65	48.59	7.74	53.65	8.32
BMI at t_0	28.43	1.54	28.76	1.38	29.60	2.70
BMI in 1984	27.74	2.31	28.77	2.49	29.46	4.02

* t_0 = 1967 - 1983. Subjects were selected on the grounds that they had been diagnosed by their general practitionar at age 20 - 50 years

** LBSO (Lower Body Segment Obesity), Intermediate and UBSO (Upper Body Segment Obesity) were defined as the lower, middle and upper tertile of waist-thigh ratio respectively (see Table 1)

*** Difference in BMI between time t_0 and 1984 statistically significant, ($p < 0.05$)

The independent variables included in the stepwise logistic regression analysis, the multiple logistic regression coefficients and their standard errors, using age, BMI and circumference ratios as continuous variables are shown in Table 4. The number of cases for each disorder or combination of disorders is also given.

The results shown in Table 4 were essentially the same when categorically scaled variables for age, BMI and circumference ratios were used.
The odds' ratios (shown in Table 5, with their confidence intervals) are estimates of relative risk for having a disorder for subjects with upper body segment obesity compared to persons with lower body segment obesity. The odds

able 4. Multiple regression coefficients obtained in stepwise multivariate logistic regression analysis, using disorders as dependent variables and BMI, age and circumferences ratios as independent continuous variables

ender	Dependent variable (Disorder)	Circum-ference ratio	Regression coefficients						Number of cases
			constant	circum-ference	age	BMI	SES high/low	SES middle/low	
omen	Hypertension	WT	- 9.45	2.46	0.10	-	-	-	62
		WH	- 8.28	-	0.10	0.07	-	-	62
	Gout or diabetes	WT	- 9.43	4.58	-	-	-	-	13
		WH	- 15.80	11.50	-	0.12	-	-	13
	Arthrosis	WT/WH*	- 8.10	-	0.12	-	-	-	36
	Varicose veins	WT	1.19	- 2.70	0.03	-	-	-	55
		WH	4.26	- 6.44	-	-	-	-	55
	Angina pectoris or myocardial infarction	WT/WH*	- 8.88	-	0.12	0.83	-	-	13
	Prolaps uteri	WT/WH*	- 8.64	-	0.13	-	1.25	- 0.97	22
	Serious disorders combined**	WT/WH*	- 10.90	-	0.12	0.11	-	-	50
en	Hypertension	WT	- 8.17	3.96	-	-	0.87	0.97	16
		WH	- 12.60	19.10	-	- 0.26	0.51	0.39	16
	Arthrosis	WT	- 8.86	7.49	-	- 0.25	-	-	12
		WH	- 7.50	-	0.12	-	1.56	- 1.25	12
	Angina pectoris or myocardial infarction	WT/WH	- 8.11	-	0.11	-	-	-	8
	Serious disorders	WT	- 3.54	5.86	-	- 0.27	-	-	26
	combined**	WH	- 4.79	-	0.08	-	-	-	26
	Serious disorder or	WT	- 3.06	4.67	-	- 0.20	-	-	32
	hypertension	WH	- 3.21	-	0.05	-	-	-	32

* Neither WT nor WH were included in the stepwise regression analysis and therefore produced the same

* One or more of the following disorders: gout, diabetes, arthrosis, angina pectoris, myocardial infarction, prolaps uter

ll regression coefficients were statistically significant from zero (b/SE(b) greater than 2) ratios are derived from regression coefficients of the categorically scaled circumference ratios and are adjusted for other variables in the model. The results indicate a higher prevalence of hypertension, gout or diabetes in women in the upper tertile of the waist-thigh ratio then in women in the lower tertile, and a lower prevalence of varicose veins in women in the upper tertile of both circumference ratios.

Table 5. Odds ratios and 95% Confidence intervals of Odds ratios for disorders, comparing the upper tertile to the lower tertile of the circumference ratios of waist-hips and waist-thigh

	Circum-ference Ratio	Disorder	Odds ratio	95% Confidence Interval of the Odds Ratio
Women	WT	Hypertension	2.44	1.09 - 5.56
		Gout or diabetes	4.68	2.10 - 10.44
		Varicose Veins	0.37	0.27 - 0.60
	WH	Gout or diabetes	2.66	0.68 - 10.38
		Varicose Veins	0.40	0.16 - 0.86
Men	WT	Hypertension	3.69	1.74 - 5.64
		Arthrosis	11.88	1.38 - 35.40
		Serious disorders[1]	5.58	2.86 - 10.89
	WH	Hypertension	54.98	4.02 -752.00*

Note:

[1] Serious disorders: one or more of the following disorders: angina pectoris, Ischemic heart disease, gout, diabetes, arthrosis

- Odds adjusted for other variables in the logistic regression model
- WT = waist-thigh ratio
  WH = waist-hips ratio

* The magnitude of the odds ratio and its wide confidence interval can be explained by the large number of variables in the model (4) while there were only 16 male cases of hypertension

For men, a high prevalence of arthrosis, or of at least one serious disorder, was found in the upper tertile of the waist-thigh ratio. Using the waist-hips ratio as indicator of fat distribution, hypertension was more frequent in subjects in the upper tertile of both ratios.

Upper body segment obese men and women, as defined as the upper tertile of the waist-thigh ratio, reported a lower subjective health status than lower body segment obese men and women ($p < 0.05$). When stratified into two age groups ($<$ 50 years; $\geq$ 50 years), this difference disappeared in the group of women of 50 years and older.

The means and standard deviation of the square root of the number of complaints are given in Table 6. Without taking age into account, a statistically significant difference was found between the results for upper body segment obese men and lower body segment obese men. When subjects were stratified into two age groups, a significant difference ($p < 0.05$) was found only for men younger than 50 years of age.

Table 6. Crude and age-specific estimates of the square root* of the total number of health complaints on a list of 39 complaints (mean and standard deviations) in men and women with UBSO and LBSO**

	age	n	LBSO** mean score* st.dev.	n	UBSO** mean score st.dev.	p-value for difference in mean score
Women	< 50 yrs	42	2.88 - 0.83	17	3.37 - 1.05	0.1314
	$\geq$ 50 yrs	19	2.94 - 1.26	44	3.02 - 1.39	0.8873
	all ages	61	2.90 - 0.97	61	3.11 - 1.31	0.2384
Men	< 50 yrs	17	2.25 - 1.32	6	3.63 - 0.80	0.0214
	$\geq$ 50 yrs	11	2.48 - 1.01	16	3.08 - 1.13	0.2184
	all ages	28	2.34 - 1.19	22	3.23 - 1.06	0.0124

* Square root was taken because its distribution was approximately normal (a higher value indicates more health complaints)

** LBSO and UBSO Lower and Upper Body Segment Obesity, defined as the lower and upper tertile of the waist-thigh distribution, respectively

Multiple linear regression was performed, with the square root of the total number of complaints as a continuous dependent variable and the waist-thigh ratio, age, BMI in 1984 (all three continuous), socio-economic status, slimming frequency, and smoking habits (all three as categorical variables) as independent variables.

For men, 12.0% of the variance was explained by the full model, with the waist-thigh ratio as the only significant independent variable (r^2 = 6.7%). For women 10.2% of the variance in the number of complaints was explained by all six variables in the model, with slimming frequency as the only significant independent variable (r^2 = 5.6%).

When clusters of organ-specific complaints were analysed, upper body segment obese men were found to suffer more from heart and chest pains, complaints of bones and extremities and shortness of breath than lower body segment obese men. These differences were still significant ($p < 0.05$) also when adjusted for age. For men younger than 50 years, stomach complaints and indigestion were also significantly more frequent in upper body segment obese subjects ($p < 0.05$) (see Appendix II for a listing of the items of the clusters of complaints).

A multiple lineair regression was performed with waist-thigh ratio as a continuous dependent variable and six independent variables: age, BMI at t_0, BMI in 1984 as continuous variables, and smoking habits, slimming frequency and socio-economic status as categorically scaled variables. For men the full model explained 30.1% of the variation in the waist-thigh ratio. The single variables with significant predictive power were age (r^2 = 16.5%) and socio-economic status (r^2 = 3.3%). For women the full model explained 22.0% of the variation in the waist-thigh ratio, with the BMI in 1984 (r^2 = 15.9%) and age (r^2 = 9.0%) as significant predictors. A high waist-thigh ratio (upper body segment obesity) is thus associated with older age in men and with older age and higher degree of obesity in women.

Women with upper body segment obesity reported less often that they had been "too fat" at birth ($p < 0.05$), in childhood or in adolescence ($p < 0.10$) than lower body segment obese women. Men did not consider themselves to have been overweight before 20 years of age. When the subjects were asked about the maximal weight they remembered from actual measurements during six age intervals 15 - 19, 20 - 29, 30 - 39, 40 - 49, 50 - 59, 60 years or older) the average BMI in all age intervals, except 15 - 19 and 20 - 29 years, was found to be higher for women with upper body segment obesity than for women with lower body segment obesity. The average BMI of men with upper body segment obesity was significantly lower than that of men with lower body segment obesity in the age interval 20 - 29 years. In other age intervals there was no difference between the average BMI of upper and lower body segment obese men. No differences were found between upper body segment obese subjects and lower body segment obese subjects in slimming frequency, smoking habits or socio-economic status.

DISCUSSION

The study population was a group of obese subjects in two general practices in two medium sized mixed rural/industrial towns in The Netherlands (near Nijmegen). The population was probably not representative for the entire obese population in The Netherlands but within the population of obese subjects of the practices the study population was not selected on the basis of BMI and morbidity. Nevertheless, extrapolation to other overweight populations should be done with caution.

Obesity had been diagnosed by the general practitionars within the last 5 - 17 years before this study. From the weight histories in the questionnaire it was clear that the subjects included in the study population had been obese at least since the time of diagnosis of obesity.

There is evidence that fat distribution is a relatively permanent charactistic of subjects, even when there are major weight changes[1,6,12,14,30]. It was considered appropriate therefore, to link present fat distribution to the retrospective morbidity data.

Upper body segment obesity and lower body segment obesity were arbitrarily defined as the upper tertile and lower tertile of the circumference ratios, an approach used also by other investigators[9,22]. Both circumference ratios probably measure approximately the same concept: the fat stored in the abdominal region relative to that in the gluteal (hips) and femoral (thighs) regions. Both gluteal and femoral regions probably have similar physiological characteristics[2].

The results from the morbidity analysis confirm that fat distribution, as measured by circumference ratios, is associated with the prevalence of some chronic disorders in seriously or moderately obese subjects. The associations of a relatively central deposition of fat with diabetes, glucose tolerance and hyperinsulinemia are well known[9,10,11,15,16,17,18,25,29,31]. The possible mechanisms of this relationship have recently been studied by Evans et al.[8,9,10]. Diabetes was significantly related to the waist-thigh ratio for women in unvariate analysis but not after adjustments for age and BMI. Both diabetes and gout are known to be the result of metabolic aberrations associated with obesity[19,28] and Vague reported that all of his gout-afflicted subjects were hyperandroïd[29].

Diabetes (11 female cases) and gout (2 female cases) were not very common in the study population but the combination was independently related to fat distribution.

We found a strong association between hypertension and both the waist-hips ratio for men, and a more moderate association between hypertension and the waist-thigh ratio for both men and women. Other studies have also found that fat distribution, independently of degree of obesity, is related to hypertension[3,15,16,18,21,29]. Since hypertension is a risk factor for cardiovascular disease and stroke, this observed relation may partly explain the findings from Gothenburg[21a,22] in which it was demonstrated that, for men, the waist-hips ratio is a prognostic factor for death from cardiovascular disease or stroke and for death of all causes.

We are not aware of any study reporting an association between fat distribution and arthrosis. It is tempting to suggest that the association observed here indicates that metabolic disturbance may play a greater role than weight induced wear and tear in the etiology of arthrosis. In fact, after adjustment for the waist thigh ratio, a negative multiple regression coefficient for BMI was found (Table 4). Silberberg[27] has reviewed numerous studies on the association of obesity and arthrosis, and has concluded that there is no reason to assume a direct causal relationship between joint disease and the mechanical overload caused by obesity. An injurious metabolic effect of fat or components of fat on weight bearing as well as non-weight bearing joints was hypothesized[27]. It could be important to note that an association between fat distribution and blood lipids levels has been observed[8,9,21]. Univariate analysis revealed that fat distribution in women was associated with arthrosis (results not shown) but this association disappeared when adjustments for BMI and age were made. The reason for this sex difference in risk is not clear, although it should be noted that in general men have higher circumference ratios than women (Table 2).

The negative association between circumference ratios and varicose veins has not been reported in any other studies on fat distribution and disease, although it has been suggested by Vague that insufficient venous circulation is one of the characteristics of gynoid obesity[29]. Upper body segment obesity and android obesity are thought to overlap considerably as are lower body segment obesity and gynoid obesity[1,21].

The analysis of the information obtained from the questionnaire revealed that, for men also other disorders, not measured in the morbidity registration, were associated with fat distribution. A high waist-thigh ratio was associated with stomach complaints and indigestion, heart and chest pains, skeletal complaints, problems in the extremities, and shortness of breath.

For women a relative predominance of fat storage in the abdominal region (upper body segment obesity) was associated with degree of obesity, and probably also with a relatively late onset of obesity. This is in agreement with the results of studies demonstrating the relation between adult onset of obesity or adult weight gain and various metabolic associates of obesity. These relations are essentially the same as those found between fat distribution and metabolic aberrations.

We may conclude that in the evaluation of the risk profile of moderately and seriously obese subjects it is important to assess their fat distribution. Circumference ratios may be useful for this purpose. They are easy to measure and can be applied in epidemiologic research as well as in general practice. The waist-thigh ratio could be considered, as well as the waist-hips ratio, because the former ratio might be at least equally sensitive as an indicator of chronic disorders as the latter ratio. Further research, preferably large-prospective studies, should relate the incidence of disorders not only to baseline fat distribution and BMI but also to changes in these characteristics, to take into account individuals' weight history and family history of obesity and morbidity. The effects of weight reduction on both fat distribution and health should also be carefully studied.

Until more precise criteria are developed, the tertiles of the waist-thigh ratio and waist-hips ratio can be used as a rough measure for classification into extreme types of fat distribution.

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Appendix I

Diagnostic criteria for chronic diseases in the continuous morbidity registration.

Hypertension

Hypertension was registrated when diastolic blood pressure (measured in lying position) was higher than 100 mm Hg at at least three different occasions.

Diabetes mellitus

A single blood glucose-level > 10 mmol/l was used as the criterion. In doubt (6-10 mmol/l) confirmed by glucose tolerance test.

Gout

Gout was registered when several clinical symptoms clearly indicated gout (e.g. pain and swelling in a large toe, unilateral arthritis in feet or toes, hyperuricarmia, manifestation or suspection of tophus, presence of urale crystals in joints etc.)

Arthrosis

Arthrosis deformans was registered when there were clear clinical signs of arthrosis (like pain, stiffness and inflammation) were found, in most cases confirmed by an X-ray.

Varicose veins

Varicose veins of lower limbs were registered when clearly visible varicose veins were presented, observed either at routine examination or following specific complaints of the patient.

Myocardial infarction

Myocardial infarction was registered when a clinical suspection of a myocardial infarction could be verified by abnormal ECG and/or of concentrations of enzymes CPK, SGOT, LDH (exceptions were made for patients who died before such investigations were possible).

Angina pectoris

Angina pectoris was diagnosed when a clinical examination provided sufficient evidence for angina pectoris (not necessarily confirmed by laboratory - or ECG - test).

Appendix II

Clusters of complaints taken from a list of 53 health complaints[4,25]. Subjects were asked to circle 'yes' or 'no' for each item

- Digestive tract complaints
  - Does your stomach feel full and bloated?
  - Do you often have pains in the stomach region?
  - Do you often have stomach trouble?
  - Do you have unspecific stomach complaints?
  - Do you often have indigestion?

- Skeletal complaints
  - Do you regularly have unpleasant cold fingers, hands or feet?
  - Do your bones or muscles often ache?
  - Are you bothered by weak or aching feet?
  - Are you often troubled by backache?
  - Do your arms and legs often go dead or tingle?

- Heart and chest complaints
  - Do you often have pains in the chest or heart region?
  - Do you often have palpitations of the heart or throbbing in your heart region?
  - Do you have feel thight in the chest?

- Short of breath
  - Do you get short of breath easily?

CHAPTER 7

ASSESSMENT OF INTRA-ABDOMINAL AND SUBCUTANEOUS ABDOMINAL FAT - RELATION ANTHROPOMETRY AND COMPUTED TOMOGRAPHY

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ABSTRACT

The ability to distinguish between intra-abdominal and subcutaneous abdominal fat may be important in epidemiologic and clinical research. In this study anthropometric measurements were taken from 71 men and 34 women presenting for routine computed tomography (CT). Areas of abdominal fat were calculated from CT scans made at the level of the L4 vertebra. The amounts of intra-abdominal and subcutaneous abdominal fat could be accurately predicted from several circumferences, skinfold measurements, body mass index and age (R^2 ranged from 0.79 to 0.84). In addition, it was found that the area of intra-abdominal fat on the CT scan was related to the waist/hip circumference ratio (r = 0.75 in men, r = 0.55 in women) and to the waist/thigh circumference ratio (r = 0.55 in men, r = 0.70 in women). The correlations of the circumference ratios with the areas of subcutaneous fat were invariably lower.

INTRODUCTION

It is now generally recognized that fat distribution, as ascertained from the ratio of waist circumference to hip circumference, is an important prognostic indicator of the occurrence of metabolic abnormalities, diabetes mellitus (type II), hypertension, cardiovascular disease, stroke and death in men and women (1). This relationship might depend on the increased accumulation of intra-abdominal fat (2). It has been shown that subcutaneous fat is less responsive than omental adipose tissue to the lipolytic effects of epinephrine and nor-epinephrine (3) and to the antilipolytic effect of insulin (4). Free fatty acids are therefore released at a rapid rate and drain directly into the portal vein. Long-term exposure of the liver to high concentrations of fatty acids may result in metabolic derangements (5,6).

Ashwell et al (7) recently compared information from computed tomography scans made at the level of the umbilicus with circumference ratios of 28 adult women and showed that these circumference ratios were related to the amount of intra-abdominal fat and the ratio of intra-abdominal fat to subcutaneous abdominal fat.
Kissebah and his collegues (8) showed that in women, the latter ratio correlates strongly ($r = 0.8$ approximately) with increased glucose response to oral glucose challenge and to insulin levels.
In our study of these relationships we included both men and women. Furthermore, we measured circumferences at more levels and included skinfold measurements taken at the level of the umbilicus. We developed multiple regression models to predict the amount and proportions of intra-abdominal fat and subcutaneous abdominal fat from these simple data on anthropometry and age. Although extrapolation of the resulting regression equations to other populations must be done with great caution they provide insight into the independent contribution of the independent variables to the variation in fat areas on the CT scans.

PATIENTS AND METHODS

Patients

We studied patients who, during a period of three months, were referred to the Radiodiagnostic Institute of the University Hospital in Nijmegen for a CT scan of the abdomen. They comprised in-patients as well as out-patients and, in most cases, they came for diagnosis or therapeutic evaluation of cancer or other malignancies. We excluded patients under the age of 19 and all those whose CT scans revealed abnormal features that could influence the measurements of fat or anthropometric measurements. Thus, patients with large local abnormalities, enlarged liver or spleen, and those with a stoma at the level at which the measurements were taken were excluded. Menopausal status was assessed, and in one case where this was uncertain because of illness and therapy, a woman was excluded. The final population comprised 71 males and 34 females. The procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the Institute of Radiodiagnostics.

Computed Tomography

The CT scanning was done with a Siemens Somatom DR3 (Siemens UB Med, Henkestrasse 127, 8520 Erlangen GFR). Radiographic factors were 125 KV and 350 mAs. With a lateral computed radiograph indexed to the scanner table position,

the CT-scan through the the fourth lumbar vertebra (L4 was obtained. The resulting scan was of a layer 8 mm thick .The L4 level corresponds to the umbilicus level, at which waist circumference is usually measured (7,9). As described in other studies (10) the amount of fat at the umbilicus level is representative of the total abdominal fat and it has been suggested that you can best distinguish the sexes on the basis of fat at the umbilicus (11). The data from the scans were analysed using a histogram-based volumetric analysis technique by which tissue area on a CT scan image can be measured using a certain range of Hounsfield Units (10,12). We determined the range for measurements of fat to be -150 to -50 Hounsfield units, which is in accordance with ranges described in similar studies (7,9,10).
We used a range of -700 to 3071 Hounsfield units (thereby excluding small amounts of air present on the scan) for the total area of the cross-section. The area of intra-abdominal fat was discerned from the area of subcutaneous fat by tracing a line with a light pen cursor through the m. rectus abdominus, m. obliquus internus, m. quadratus lumbarum and the long back muscles. The total area of fat within this line was defined as the intra-abdominal fat. The amount of subcutaneous fat was ascertained as the difference between the total area of fat shown on the scan and the area of intra-abdominal fat. This method has been proved to be very accurate and reproducible as has been reviewed by Grauer et al(12). The ratio of intra-abdominal fat to subcutaneous abdominal fat was calculated. Fat percentage was calculated as the ratio of total area of fat to total area of the cross-section.

Anthropometric measurements

All patients were asked a series of questions. Their responses together with the patient files and the evaluation of the radiologists, provided information about current health status and past illness, type of treatment or use of drugs, menopausal status, long-term bedrest, weight changes in the year preceding the examination, and age.
We measured the height to the nearest 0.1 cm and body weight to the nearest 0.5 kg on a calibrated weighing scale of the subjects when they were not wearing shoes and were clad only in underwear or light indoor clothing. Body Mass Index (BMI in kg/m 2) was calculated as weight divided by height squared.
Circumferences were measured at the following levels, using a plastic tape measure: smallest circumference at the waist, waist at the umbilicus level, widest hip circumference, hips at the level of the anterior superior iliac spine of the iliac crest, and thigh circumference at the highest level.

Most results presented in this paper were obtained using the ratio of waist circumference: hip circumference (WHR) and the ratio of the waist circumference: thigh circumference (WTR) based on waist at the umbilicus level, hips at the iliac crest and the highest thigh circumference.
Two skinfold measurements (Harpender skinfold caliper, CMS Weighing Equipment Ltd, London) were taken on the horizontal line from the umbilicus to the mid-axillary line: one horizontally, at one-third of the distance from the umbilicus (para-umbilicalis), and the other obliquely, on the mid-axillary line itself (which in most cases corresponds with the supra-iliac skinfold). All measurements were taken with the subject standing upright and breathing lightly.

Statistical analysis
The relations between anthropometric measurements, weight changes in the preceding year, menopausal status, and age, and of various fat areas and proportions of fat areas as obtained from the CT scans were analysed by calculating product-moment correlation coefficients and by using multiple linear regression analysis (13). Comparing untransformed variables with log transformations and square root transformations of the variables revealed that the square roots of all the CT scan measurements gave a much better approximation to the normal distribution and to linear relations in the regression analysis. Therefore, in our statistical analysis we used the square roots of these variables.

RESULTS

Table 1 shows some characteristics of the sample. On average, in this study the Body Mass Index (BMI) of the women was higher than that of the men but, nevertheless, in women the ratios of waist circumference to hip circumference and waist circumference to thigh circumference were lower. When the WHR based on minimum waist girth and maximum hip girth was used, the difference between men and women was even more pronounced (average ratio for men: 0.93, for women: 0.87). CT-scan measurements at the level of the L4 show that, on average, women had a larger total area of body fat than men: this could largely be attributed to differences in amounts of subcutaneous fat and was also reflected in the proportions of intra-abdominal fat in men and women.

Table 1. Details of 71 men and 34 women attending for computed tomography

	Men mean	SD	range	Women mean	SD	range
Age (years)	51.5	17.2	19 - 85	52.4	13.4	19 - 72
Body Mass Index (kg/m^2)	23.4	3.1	17.8 - 31.6	26.0	5.0	19.4 - 38.3
Waist:hip ratio	0.96	0.05	0.80 - 1.10	0.94	0.08	0.79 - 1.09
Waist:thigh ratio	1.75	0.18	1.41 - 2.10	1.68	0.22	1.28 - 2.08
CT scan data:						
Total area of fat (cm^2)	220.2	112.9	24.2 - 487.1	347.9	169.5	90.8 - 691.0
Area of intra-abdominal fat (cm^2)	89.9	53.0	12.7 - 247.0	91.8	52.7	18.8 - 221.0
Area of subcutaneous fat (cm^2)	130.3	70.9	11.4 - 319.1	256.2	129.9	71.5 - 567.5
Ratio of intra-abdominal to subcutaneous fat	0.77	0.39	0.11 - 2.42	0.38	0.19	0.08 - 1.04

In Tables 2 and 3 the correlations between some of the relevant variables are presented. In men and in women the WHR correlated positively with the total area of fat, area of intra-abdominal fat and area of subcutaneous fat. In women, but not in men, the WHR is correlated with the ratio of intra-abdominal fat to subcutaneous fat. In women, the correlations between the WTR and areas of fat are consistently higher than those between the WHR and areas of fat. In men, the reverse is true, the correlations of the WHR with areas of fat being higher than those of the WTR with the exception of the correlations with the ratio of intra-abdominal fat and subcutaneous fat.

In most epidemiologic studies the effects of fat distribution are estimated after adjusting for BMI and age. Table 4 shows the significance of the partial correlations of WHR and WTR with the areas of fat, adjusted for age and BMI. The partial correlations with intra-abdominal fat were invariably higher than those with subcutaneous fat. The statistical association between WHR in men and areas of fat was similar to that of WTR in women and areas of fat. The same holds for the WTR in men and the WHR in women.

Table 2. Correlation matrix of variables in men

	1	2	3	4	5	6	7	8	9	10
1. Age	1.00									
2. Body Mass Index (weight/height^2)	0.15	1.00								
3. Waist: hip ratio	0.24*	0.68**	1.00							
4. Waist: thigh ratio	0.76**	0.14	0.47**	1.00						
5. Total area of fat (CT scan)	0.33*	0.81**	0.76**	0.35*	1.00					
6. Total area of intra-abdominal fat (CT scan)	0.54**	0.75**	0.75**	0.55**	0.90**	1.00				
7. Area of subcutaneous fat (CT scan)	0.14	0.76**	0.68**	0.16	0.95**	0.72**	1.00			
8. Ratio of intra-abdominal to subcutaneous fat	0.53**	0.02	0.13	0.56**	-0.03	0.37**	-0.33*	1.00		
9. Ratio of total fat to total body area	0.29*	0.67**	0.66**	0.29*	0.96**	0.83**	0.93**	-0.10	1.00	
10. Sum skinfolds (para-umbilical and supra-iliac)	-0.09	0.70**	0.59**	0.05	0.77**	0.57**	0.83**	-0.33*	0.73**	1.00

Table 3. Correlation matrix of variables in women

	1	2	3	4	5	6	7	8	9	10
1. Age	1.00									
2. Body Mass Index (weight/height^2)	0.51*	1.00								
3. Waist: hip ratio	0.40*	0.47*	1.00							
4. Waist: thigh ratio	0.60**	0.55**	0.77**	1.00						
5. Total area of fat (CT scan)	0.54**	0.91**	0.47*	0.65**	1.00					
6. Area of intra-abdominal fat (CT scan)	0.62**	0.82**	0.55**	0.70**	0.86**	1.00				
7. Area of subcutaneous fat (CT scan)	0.46*	0.87**	0.39*	0.57**	0.98**	0.73**	1.00)			
8. Ratio of intra-abdominal to subcutaneous fat	0.42*	0.16	0.34*	0.42*	0.14	0.61**	-0.07	1.00		
9. Ratio of total fat to total body area	0.47*	0.78**	0.47*	0.63**	0.95**	0.78**	0.94**	0.08	1.00	
10. Sum of skinfolds (para-umbilical and supra-iliac)	0.43*	0.83**	0.73**	0.56**	0.89**	0.73**	0.88**	0.05	0.36	1.00

* < 0.05; ** < 0.001

Table 4. T-values for the partial correlation coefficients of waist:hip ratio and waist:thigh ratio with fat areas on the umbilical CT scan; adjusted for age and BMI

Dependent variable	Men Waist:hip	Men Waist:thigh	Women Waist:hip	Women Waist:thigh
Area of total fat	4.33**	1.79	0.53	2.73*
Area of intra-abdominal fat	4.86**	3.38*	1.66	2.63*
Area of subcutaneous fat	2.96*	0.66	0.22	1.66
Ratio of intra-abdominal to subcutaneous fat	0.64	2.10*	1.41	1.48
Percentage fat	3.17*	0.94	0.97	2.32*

p-values: * < 0.05 ; ** < 0.001

In Tables 5 and 6 the results of stepwise multiple regression analysis arepresented, using the areas of fat calculated from the CT scans as dependent variables and anthropometric data and age as independent variables. Most (79.4% to 90.5%) of the variance in total area of fat as well as in areas of with the results from table 4, the results in Tables 5 and 6 show that,in men, the WHR is a better index of characteristics of the areas of fat than the WTR, whereas in women the WTR is the more appropriate index. Note that, in women, menopausal state was more closely associated with the area of intra-abdominal fat than age. Menopausal state had no relation with total fat or subcutaneous fat.To learn more about why the WHR and WTR behaved differently in the statistical analysis we repeated the analysis using separate circumference measurements rather than ratios of circumferences.

In men, the hip circumference, after adjustment for all the other variables, correlated negatively with the intra-abdominal and subcutaneous areas of fat on the CT scan, whereas waist and thigh circumferences had positive partial correlation coefficients. In women, the thigh circumference had a negative partial correlation coefficient with both fat areas, whereas the hip circumference correlated positively with total and subcutaneous fat and negatively with intra-abdominal fat. Waist, in women, remained positively correlated with both areas of fat.

Table 5. Multiple regression models linking fat measurements taken from CT scans to anthropometric variables and age

Men Dependent variable	Independent variable	Regression coefficients	Standard error of regr. coeff.	Total R^2 x 100 (adjusted)
Total area of fat (cm^2)	BMI	0.404	0.108	
	Skinfolds	1.480	0.243	84.6%
	WHR	34.122	10.284	
	Age	0.060	0.012	
	Intercept: - 39.953			
Area of intra-abdominal fat (cm^2): I	BMI	0.350	0.084	
	Skinfolds	0.405	0.189	81.9%
	WHR	33.118	8.032	
	Age	0.068	0.009	
	Intercept: - 37.322			
Area of subcutaneous fat (cm^2): S	BMI	0.157	0.108*	
	Skinfolds	1.630	0.227	79.4%
	WHR	29.159	11.397	
	Age	0.051	0.018	
	WTR	-10.694	5.060	
	Intercept: - 18.798			
Ratio of I:S	BMI	0.029	0.009	
	Skinfolds	- 0.109	0.021	49.3%
	WTR	1.583	0.272	
	Intercept: - 1.323			

Table 6. Multiple regression models linking fat measurements taken from CT scans (at the level of the umbilicus) to anthropometric variables and age

Women Dependent variable	Independent variable	Regression coefficients	Standard error of regr. coeff.	Total R^2 x 100 (adjusted)
Total area of fat (cm^2)	BMI	0.508	0.097	
	Skinfolds	1.044	0.297	90.5%
	WTR	9.958	3.871	
	Intercept: -15.282			
Area of intra-abdominal fat (cm^2): I	BMI	0.367	0.061	
	WTR	10.911	3.660	79.5%
	Menopausal state (1 = post; 0 = pre)	0.994	0.497	
	Intercept: -15.083			
Area of subcutaneous fat (cm^2): S	BMI	0.373	0.105	
	Skinfolds	1.301	0.313	84.2%
	Intercept: - 3.327			
Ratio of I:S	Skinfolds	-0.036	0.017	
	WTR	0.870	0.369	31.7%
	Age	0.0026	0.0019*	
	Intercept: - 0.4105			

Note (table 5 & 6) the square roots were taken of the dependent variables and of waist:hip ratio (WHR), waist:thigh ratio (WTR) and sum of skinfolds (Skinfolds); variables were selected by means of stepwise multiple regression analysis (p value for F-to-enter less than 0.10); other candidates for regression were: height, weight change in the year preceding the examination and all cross-products of variables of the independent variables

* All other regression coefficients statistically significant different from zero (p < 0.05)

DISCUSSION

WHR and WTR are often used in epidemiologic and clinical investigations as indices of fat distribution. The results of our study indicate that WHR and WTR in men and women are associated more closely with intra-abdominal fat than with subcutaneous abdominal fat at the level of the fourth lumbar vertebra.
We also demonstrated (Tables 5 and 6) that amounts of intra-abdominal and subcutaneous fat can be predicted accurately by means of easy-to-measure anthropometric variables and age. These predictions may be important in future research because they enable the specific effects of these fat depots on morbidity and mortality to be estimated. Recently, Sjöström et al. (11) presented preliminary results that indicate that even higher correlations of anthropometric variables with total volume of visceral adipose tissue may be obtained by assessing the total cross-sectional body area by means of transverse and sagittal diameters of the body (in men, corrected for subcutaneous fat). Although their approach was different, the aim of their study was similar to ours. Therefore it will be important to compare the results when all details of their study become available.
As can be seen from Table 1, men have a greater proportion of intra-abdominal fat than women. This may partly explain why, when equally obese, men have a greater risk for cardiovascular disease than women. This difference between men and women agrees with results from other studies (9,12) and probably reflects the importance of hormones and/or genetic influences on fat distribution in the abdomen.
Borkan et al. (14) suggested that in men, age is an important determinant for the proportion of intra-abdominal fat. This observation is confirmed by our data, as we found that, in men, age correlated with the amount of intra-abdominal fat ($r = 0.54$) but not with the amount of subcutaneous fat ($r = 0.14$). In women this was less clear (Table 3).
Our results confirm the findings reported by Ashwell et al. (7) whose study of the CT scans of 28 women showed that circumference ratios were related more strongly to intra-abdominal fat than to subcutaneous fat. We have now shown that this is also true in men. We were unable to confirm, however, that after adjustments for age and BMI, circumference ratios are correlated negatively with subcutaneous fat. Although our study was similar to the study done by Ashwell et al, we used WHR based on waist girth at the level of the umbilicus rather than the minimum waist circumference, and the hip circumference at the level of the anterior iliac crest rather than the widest hip circumference. We repeated our

analysis using the same ratios as Aswell and her collegues but, in contrast to their findings we found even poorer correlations with the ratio of intra-abdominal fat and subcutaneous fat, both in men and in women. Note that WHRs calculated from the different circumferences correlated strongly in men (r = 0.90) but less well in women (r = 0.77). This indicates that, especially in women, it is important to standardize these measurements.

The results presented in Tables 5 and 6 indicate that the WHR and WTR differ between men and women as indices of fat distribution. WHR in men resembles WTR in women in the statistical analysis whereas WTR in men resembles WHR in women. The negative partial correlation coefficients for area of abdominal fat and the hip circumference in men and the thigh circumference in women indicate that these circumferences provide additional information on non-fat tissue, i.e. that at a given waist and thigh circumference a larger hip circumference indicates, in men, a higher proportion of lean body mass in the abdomen, whereas in women with a given waist and hips circumference, a larger thigh circumference indicates more lean body mass in the abdomen.

Analysis of residuals indicated that there were no deviations from linearity in the multiple regression analyses presented in Tables 5 and 6. When the data were stratified into 10-year age groups and categories of BMI, the analysis revealed similar associations throughout the range of age and BMI.

It should be noted that, as we described in the Patients and Methods section, the sample of people we studied cannot be regarded as representative of the total population of the same age range. We carefully excluded all patients in whom illness could have distorted our measurements. We cannot be certain, however, that illness or therapy did not influence the amount or distribution of fat in the abdomen. Altered menopausal status and weight loss are the most likely causes for such changes. We repeated the analysis, including weight change in the year preceding the examination but we found no independent relation of this variable with any of the dependent variables we used. Thus, although the size of areas of fat on the CT scan may have been influenced by factors that we did not measure, it seems likely that any such factor would have produced corresponding changes in circumferences, skinfolds and weight.

Summarizing our results, we can confirm that, in our study population, in both men and women, the WHR and WTR are related more strongly to the amount of intra-abdominal fat than to the amount of subcutaneous abdominal fat. This finding might be important for explaining the consistent relations between WHR and WTR and metabolic aberrations, manifest illness and death.

The regression models we present in this paper are based on observations on men and women covering a wide range of age and degree of obesity. Given the fairly restricted number of subjects, especially in women, the extrapolation of the regression models to other populations must be done with great caution. The multiple regression analysis shows, however, that, in the studied groups, the variation in the fat areas on the CT scans are explained to a high degree by the simple anthropometric variables, age, and menopausal state. In addition, the multiple regression models provide information about the independent contributions of each of the independent variables to the explanation of the variance of intra-abdominal and subcutaneous abdominal fat areas on the CT scans at the L4 level.

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GENERAL DISCUSSION

This thesis reports on the associations between overweight and several aspects of morbidity. The last two chapters provide some insight in the role of fat distribution in these associations. In the studies described in this thesis overweight and obesity (or severe overweight) are defined in terms of the Body Mass Index (BMI = weight/height^2). Although it is known that in individuals the BMI can be an unreliable estimate of body fatness, in epidemiologic research it is considered to be the most satisfactory measure of obesity (1,2,3). The most serious misclassification of obesity status on the basis of the BMI occurs in the very old, the very muscular and those who have not reached the end of puberty (4). The treshold levels of BMI for the definition of (moderate) overweight and obesity (or severe overweight) are still arbitrary although it is now generally agreed that when the BMI exceeds 30 kg/m^2 a person is obese with clearly associated increased risks for premature death, cardiovascular disease, diabetes mellitus and several other more or less serious metabolic abberations. Most of these associations were confirmed by the results of the studies presented in this thesis. Below a BMI of 30 kg/m^2 increased morbidity risks are less clear and probably confined to subgroups: those with an abdominal type of fat distribution, those who were already overweight as young adults, and those who have a family history of chronic disorders or increased levels on cardiovascular risk factors.
From cross-sectional studies (Chapters 2 and 5) as well as from longitudinal studies (Chapters 3 and 4) it is not directly possible to make inferences about the causal relationships between overweight and morbidity. For some of the observed associations (e.g. those of BMI with hypertension, cardiovascular disease, diabetes mellitus, arthrosis, menstrual abnormalities) there is now much evidence from the literature that the disorders are the result of increased body fatness. An important aspect of the evidence, with implications for the treatment of overweight is, that when overweight persons succeed in losing weight, blood pressure, glucose tolerance and levels of blood lipids generally tend to normalize. Overweight subjects who suffer from joint disorders, menstrual abnormalities, shortness of breath etc. normally find relief of their symptoms when they lose weight(5). In some overweight subjects, especially in women, mental state improves when they succeed in maintaining substantial weight loss. Although the benefits of reducing weight are clear, it must be noted that slimming in itself may cause unwanted side effects. For instance, it has been argued that slimming will increase the lithogenity of the bile, thereby

increasing the risk of gallstones. Unsuccessful slimming attempts may lead to increased depression. Thus, slimming should, ideally, be supervised by medical professionalists.

The association of BMI and psychosomatic complaints is an example of the complex interrelations between the two variables. It may be that psychosomatic complaints are the result of being overweight but some psychological studies have shown that psycho-social problems may contribute to weight gain(6). In addition, the possibility that personal characteristics cause overweight as well as psycho-somatic complaints cannot be excluded. In the population from four general practices, described in Chapters 3 - 6 it was found that especially women were much concerned about their weight and that in those who considered themselves overweight, cosmetic problems dominated and were far more important than concerns about health(7). When looking at the registers of general physicians one would tend to conclude that overweight is predominantly a problem in women. In Chapter 4, however, it was shown that in men an increased risk for cardiovascular disease becomes apparent at lower levels of BMI than in women. Thus, as Garrow has stated (8), many people do not correctly appreciate the hazards of obesity. Some people, who do not need to, worry about their weight. Others, who do need to worry about their weight, do not.

The finding that men seem to be more vulnerable to the effects of obesity on cardiovascular disease risk factors than women can, at least partly, be explained by sex differences in fat distribution (9). This brings us to the topic of fat distribution which is the subject of Chapters 6 and 7. It has been shown in these and other studies (reviewed in Chapter 1) that the waist/hip circumference ratio and the waist/thigh circumference ratio are convenient indicators of fat distribution. The results presented in Chapter 6 confirm that these circumference ratios are, independent of the degree of overweight and age, related to the prevalence of certain disorders. The finding that, in women, a high waist/thigh ratio was associated with a reported onset of overweight at later age than in those with a low waist/thigh ratio might give an indication of one aspect of fat distribution that has received little attention (Fig). Levels of sex-hormones that change with ageing are probably the most likely explanation for this observation.

Hormonal factors are probably of primary importance in determining an individual's fat distribution. The typical female adipose tissue in the femoral-gluteal region is thought to have a specific female function: energy storage for lactation purposes (10). The influence of menopausal state, the administration of sex hormones and the levels of sex-hormones in obese women

with different types of fat distribution (11) demonstrate the importance of hormonal influences. The finding that an abdominal type of fat distribution is associated with complicating disorders is shown unanimously in numerous studies. Yet it remains to be proven that these associations are independent of hormonal factors. Probably, sex hormones have both a direct effect on glucose and lipid metabolism as well as an indirect effect via their relation to fat distribution (11). The association of menopausal state with intra-abdominal fat but not with subcutaneous abdominal fat (described in Chapter 7) indicates that a high waist thigh ratio in post-menopausal women may be more deletorious to health than in pre-menopausal women. This, however, requires further investigation.
Circumference measurements should be incorporated in the set of anthropometric measurements in any epidemiologic and clinical research. Studies in which the independent effects of both intra-abdominal and subcutaneous abdominal amounts of fat to metabolic disorders and clinical illness can be established are urgently needed. Such studies would be important for further characterization of subgroups of overweight subjects that have increased health risks. The effects of treatment in these subgroups should be studied carefully in well controlled intervention studies with long follow-up. Detailed classification, on the basis of the fat distribution over and within the body of overweight subjects will be important for the diagnosis and treatment of overweight and obesity.

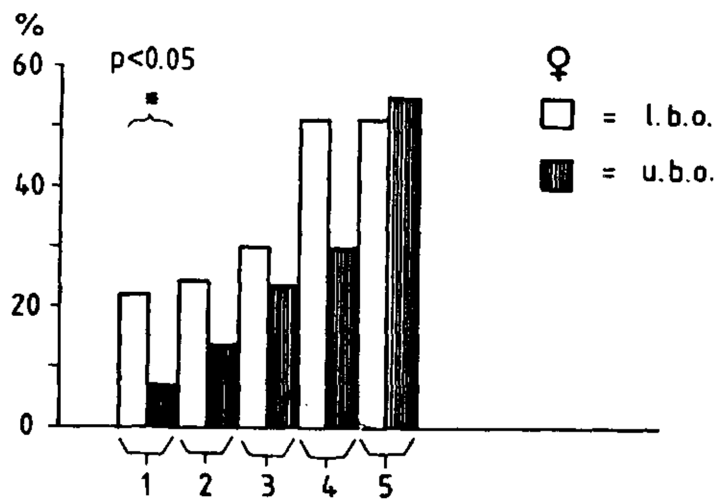

FIGURE - Percentage of women who indicated to have been 'too fat' at different stages of life.
1= at birth; 2= childhood (<12 yrs); 3= adolescence (12-20 yrs); 4= young adult (20-30 yrs); 5= after 30 years of age.
l.b.o. = lower tertile of waist-thigh circumference ratio
u.b.o. = upper tertile of waist-thigh circumference ratio
(Chapter 6)

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SAMENVATTING

In dit proefschrift worden onderzoeken beschreven naar de verbanden tussen overgewicht en vetverdeling enerzijds en aspecten van gezondheid anderzijds. De ideale proefopzet om deze verbanden te onderzoeken is met behulp van prospectieve cohort studies waarin grote aantallen individuen, liefst van enkele generaties, vanaf hun geboorte tot hun dood zouden moeten worden gevolgd. Gedurende de observatieperiode zou van de onderzoekspopulatie zowel de gewichtsontwikkeling, de vetverdeling alswel het optreden van ziekten en het subjectief welbevinden moeten worden bijgehouden. In zo'n ideale onderzoeksopzet zouden ook sociale kenmerken, familiaire kenmerken en leefgewoonten moeten worden betrokken en de niveaus van risicofactoren voor chronische aandoeningen herhaaldelijk moeten worden bepaald.
De in dit proefschrift beschreven onderzoeken zijn, in het licht van de hierboven geschetste onderzoeksopzet, noodzakelijkerwijs zeer beperkt en hierdoor kunnen slechts enkele aspecten van de verbanden tussen overgewicht en vetverdeling en de objectieve en subjectieve gezondheidstoestand worden belicht.

Er zijn goede redenen om deze verbanden te onderzoeken. Niet alleen komt overgewicht veel voor in landen zoals Nederland met een geïndustrialiseerde samenleving maar er zijn tevens veel aanwijzingen dat de prevalentie van overgewicht in die landen toeneemt. Bovendien maakt een groot deel van de Nederlandse volwassenen zich, om uiteenlopende redenen, zorgen over het lichaamsgewicht. Op de vraag of deze zorgen, vanuit gezondheidskundig oogpunt, terecht zijn kan dit proefschrift geen direct antwoord geven. De beschreven onderzoeken geven, op zijn best, een schatting van het relatieve risico dat personen met een bepaalde mate van overgewicht of een bepaalde vetverdeling hebben ten opzichte van personen zonder overgewicht of met een 'gunstige' vetverdeling. Het relatieve risico geeft een indruk van de verhouding van kansen op het hebben of krijgen van bepaalde aandoeningen in de groepen die worden vergeleken.
Of een individu zich zorgen zou moeten maken over een verhoogde kans op het krijgen van een aandoening is een zuiver persoonlijke aangelegenheid. Of een samenleving zich daarover zorgen maakt is een politieke en ethische kwestie.

In hoofdstuk 1 wordt een overzicht gegeven van de huidige inzichten in de verbanden tussen overgewicht, vetverdeling en het optreden van stoornissen in het metabolisme en, eventueel daaruit voortkomende, aandoeningen.

In hoofdstuk 2 wordt een indruk gegeven van de prevalentie van matig (QI 25 - 30 kg/m^2) en ernstig (QI > 30 kg/m^2) overgewicht bij Nederlandse volwassenen, gebaseerd op de gewichten en lengtes zoals ongeveer 19000 Nederlanders, ouder dan 20 jaar, ze opgaven aan enquetrices van het C.B.S. Bepaalde aandoeningen werden vaker genoemd door personen met overgewicht dan door personen zonder overgewicht (o.m. hypertensie, suikerziekte, spataderen, asthma/brochitis en aambeien bij vrouwen, hypertensie bij mannen). Ook bleken personen met overgewicht, om sommige redenen, vaker bij de huisarts of een specialist te komen en werden bepaalde medicijnen vaker gebruikt.
Deze verschillen waren vooral duidelijk wanneer personen met ernstig overgewicht werden vergeleken met personen zonder overgewicht; bij personen met matig overgewicht waren de verschillen veel minder groot en maar in enkele gevallen statistisch significant.
Hoofdstukken 3 tot en met 6 hebben betrekking op een retrospectief cohort onderzoek dat werd verricht met behulp van de gegevens verzameld in de Continue Morbiditeits Registratie van het Nijmeegs Universitair Huisartsen Instituut. Alle personen bij wie overgewicht door de huisartsen werd geregistreerd van 20 tot 50-jarige leeftijd in de periode 1967 - 1978 en die nog bereikbaar waren in 1983, werden vergeleken met een groep personen bij wie nooit overgewicht was vastgesteld. De groepen waren, wat betreft leeftijd, geslacht en huisartsenpraktijk, zo goed mogelijk aan elkaar gelijk gemaakt.
Alle personen waren 6 jaar te volgen in de Continue Morbiditeits Registratie. Het bleek dat, gedurende die 6 jaar, zowel de mannen als vrouwen met overgewicht meer verkoudheid/griep, nerveus-functionele klachten, huidproblemen, myalgie en lumbago en distorsies voorkwamen dan in de groep zonder overgewicht. Bij vrouwen was dat bovendien ook nog het geval voor menstruatiestoornissen, en bij mannen voor kleine ongevallen (Hoofdstuk 3). De follow-up werd uitgebreid tot maximaal 17 jaren (Hoofdstuk 4) en de incidenties van verschillende chronische aandoeningen werden bestudeerd en vergeleken met behulp van 'survival-analyse' technieken. De incidentie van diabetes mellitus, jicht, myocard infarct/angina pectoris en artrose was hoger in de groep met overgewicht (zowel bij mannen als bij vrouwen). Bij de vrouwen was dit het geval voor spataderen. De incidentie van hypertensie was ook verhoogd in de groep met overgewicht (niet beschreven in dit proefschrift[1]).
In 1983 werd de personen uit de gevolgde cohorten een vragenlijst gestuurd. Deze werd ingevuld teruggestuurd door 71%.
Enkele analyses van deze enquete zijn vermeld in hoofdstuk 5. Veel andere gegevens zijn elders gepubliceerd[2]. In de vragenlijst was onder meer een lijst

opgenomen van 51 klachten (de zgn. VOEG-lijst van Dirken) en tevens werd gevraagd naar het huidige gewicht, de lengte, rookgewoonten en de frequentie van vermageren. De somscore van de 51 klachten bleek gecorreleerd aan de QI bij vrouwen maar niet bij mannen. In multipele lineaire regressie bleek echter dat leeftijd een interactie vertoonde met de QI in hun relatie met de klachtenscore. Bij jonge mannen was er een negatief verband tussen de QI en de klachtenscore, bij oudere mannen een positief verband. Bij vrouwen bleek de associatie tussen de QI en de klachtenscore veel duidelijker bij jonge vrouwen dan bij oudere vrouwen.

De QI bleek, in multipele logistische regressie analyse, ook gerelateerd aan afzonderlijke klachten of groepjes van klachten. Bij mannen en vrouwen waren deze klachten: klachten aan het maagdarm kanaal, spier- en gewrichtsklachten en kortademigheid en bij vrouwen: nervositeit, moeheid, neus- en keelklachten, pijn in de hart- en borststreek, benauwdheid op de borst en het vaak hebben van kleine ongevalletjes.

In Hoofdstuk 6 is een onderzoek beschreven waarbij bij 305 personen uit de groep met overgewicht de vetverdeling werd bepaald aan de hand van de middel/heup omtrek verhouding (middel/heup ratio) en de middel/dij omtrek verhouding (middel/dij ratio). De middel/dij ratio bleek, ook na correctie voor leeftijd en QI, positief geassocieerd met de prevalentie van hypertensie bij mannen en vrouwen, jicht of diabetes bij vrouwen, arthrose bij mannen en negatief geassocieerd met de prevalentie van spataderen bij vrouwen. De associaties van de middel/heup ratio met deze aandoeningen bleken minder sterk (met uitzondering van hypertensie bij mannen). De klachtenscore (zie hoofdstuk 5) bleek bij mannen positief gecorreleerd met de middel/dij ratio. Groepen van klachten die geassocieerd waren met de middel/dij ratio waren: pijn in de hart- en borststreek, gewrichtsklachten en kortademigheid. Vrouwen met een hoge middel/dij ratio gaven aan pas op oudere leeftijd 'te dik' te zijn geworden dan de vrouwen met een lage middel/dij ratio. Dit werd bevestigd door hun gerapporteerde gewichtsontwikkeling.

Hoofdstuk 7 beschrijft een onderzoek waarbij met behulp van 'Computed Tomography' de relatie werd onderzocht tussen de omtrekverhoudingen en de hoeveelheid en de verhouding van intra-abdominaal vet en subcutaan abdominaal vet ter hoogte van de L4 (meestal op navelhoogte). Het bleek dat de correlaties tussen de omtrekverhoudingen en de hoeveelheid intra-abdominaal vet significant waren, ook na correctie voor de leeftijd en de QI. De correlaties tussen de omtrekverhoudingen en de hoeveelheid subcutaan vet waren steeds lager. Er bleken opvallende verschillen te bestaan tussen mannen en vrouwen. Bij mannen was relatief een veel groter deel van het abdominale vet in de buikholte opgeslagen. Dit aandeel nam toe met de leeftijd en, bij vrouwen, na de menopauze.

De voornaamste conclusies van de onderzoeken zijn dat ernstig overgewicht, en in mindere mate ook matig overgewicht, samengaan met meer morbiditeit en met verminderd subjectief welbevinden. Vanuit gezondheidskundig oogpunt zou men bij de evaluatie van personen met zowel matig als ernstig overgewicht rekening moeten houden met de vetverdeling.

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SUMMARY

This thesis reports on the association between overweight and fat distribution with aspects of morbidity in Dutch adults.
The ideal study design for investigating these associations would have been to carry out a large prospective cohort study in which a large number of individuals, preferably from several generations, could be followed up from birth to death. Throughout the observation period the development of weight and fat distribution would have to be registered as well as the occurrence of all diseases and level and change of well-being. Such an ideal study would involve measures of familiarity, elements of life-style and the levels of known risk factors for disease.
It should be noted that the studies described in this thesis are, compared to the described study design, severely limited and it may very well be that associations observed in the studies can be, at least in part, explained by variables that have not been measured in the studies.
There are several good reasons for studying the associations between overweight and aspects of health. Not only is the prevalence of overweight in industrial societies, like in The Netherlands, considered to be high but, moreover, there are many indications that the prevalence of overweight has been increasing over the past decades. In addition, a large proportion of Dutch adults are, because of various reasons, concerned about their weight. Whether or not this concern is justified on medical grounds is not the direct subject of this thesis. The investigations presented here can, at best, give an estimation of the relative risks for certain disorders comparing several degrees of overweight. Whether or not an individual worries about a certain increase in health risks is a personal matter. Societies concern about overweight and its possible consequences is a political and ethical matter. It is not the task of epidemiologists to tell individuals and gouvernments how to feel and act.
Chapter 1 of this thesis is a literature review, giving an overview of current insights in the associations between overweight, fat distribution and the occurrence of metabolic disturbances and, possibly resulting, complicating disorders.
Chapter 2 gives the prevalence of moderate overweight (BMI 25 - 30 kg/m^2) and severe overweight (BMI > 30 kg/m^2) in 19,000 Dutch adults (self-reported data). It could be shown that, after adjustments for age and educational level, certain chronic disorders were reported more often in overweight subjects than in subjects without overweight (i.e. hypertension, diabetes mellitus, varicose

veins, asthma/bronchitis and hemorroids in women, hypertension in men). In addition, it appeared that more of the overweight subjects consulted their general practitioner or a medical specialist for particular reasons and a higher use of several medicins than those who were not overweight. These differences were more pronounced when comparing severely overweight subjects to non-overwight subjects and less clear or absent for moderately overweight subjects.

Chapters 3 - 6 consider retrospective cohort studies that were performed on data collected in a continuous morbidity registration in four general practices (source: Department of General Practice, University of Nijmegen). All subjects who were registered as overweight at the age of 20 - 50 years in the period 1967 - 1978 were followed in the registration. The morbidity data were compared to those in a control group frequency matched on age, sex, general practice and duration of follow-up. All subjects were selected on the basis that they could be followed for at least 6 years. During these six years (Chapter 3) it was shown that more overweight men and women were seen by their GP's for common cold & influenza, psychosocial problems, skin afflictions, myalgy and lumbago, distortions, menstrual abnormalities (women only), and small injuries (men only) than men and women in the non-overweight group. The follow-up period was extended to maximal 17 years (Chapter 4) and the incidences of several chronic diseases were compared between the overweight and the non-overweight group with the use of 'survival analysis' techniques. The incidence of diabetes mellitus, gout, arteriosclerotic disease, artrosis, varicose veins (women only), and hypertension (presented elsewhere[1]) was increased in the overweight group. In Chapter 5 some results are presented of the relation between BMI and complaints listed in a questionnaire that was administered to the study population (spring 1984). The response rate was 71%. Many other results were reported elsewhere[2]. The questionnaire included, besides the list of 51 subjective health complaints, questions about current weight and height, smoking habits and slimming frequency. In multiple linear regression analysis the sum of complaints was correlated with the BMI in women (especially young women), positively in older men and negatively in younger men. In addition, it could be shown that, in multiple logistic regression analysis, the presence of particular complaints or groups of complaints was related to the BMI (in men and women: digestive tract complaints, muscle and joint complaints, shortness of breath; in women only: nervousness, tiredness, nose- and throat complaints, pain in the heart- or chest region, tightness at the chest and often having little mishaps).

In Chapter 6, a study is described relating the fat distribution (in 310 subjects of the overweight study group) to registered morbidity. The waist/hip circumference ratio (WHR) and waist/thigh circumference ratio (WTR) were taken as measures of fat distribution. The WTR was, after adjustments for age and BMI, positively related to the prevalence of hypertension (in men and women), gout or diabetes (in women), artrosis (in men), and negatively related to the prevalence of varicose veins in women. The associations of the WHR with these disorders were equal or less strong (with the exception of hypertension in men). The total number of subjective health complaints (see also Chapter 5) was positively related with the WTR in men. Women with a high WTR reported to have been 'too fat' at older ages than women with a low WTR. This was confirmed by their weight history. In Chapter 7, the relation of circumference ratios to fat areas on Computed Tomography scans at the L4 level was studied. It was found that the correlation of the circumference ratios were higher with the amount of intra-abdominal fat than with subcutaneous abdominal fat. There were pronounced differences in the abdominal fat distribution between men and women. In men, a relatively larger proportion of fat was stored in the abdominal cavity. This proportion increased with age and, in women, after menopause.

It is concluded that, from a medical point of view, it is necessary to include measures of fat distribution in the evaluation of overweight and obese subjects.

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CURRICULUM VITAE

Jacob Caesar Seidell werd op 3 november 1957 geboren te Weert. Het Atheneum-B diploma werd behaald in 1976 aan het Eckart College te Eindhoven. In hetzelfde jaar werd zijn studie aan de Landbouwhogeschool te Wageningen aangevangen. Tijdens zijn praktijktijd deed hij onderzoek op het 'Dunn Clinical Nutrition Centre' te Cambridge, Engeland. In juli 1983 slaagde hij voor het doctoraal examen (met lof) met als hoofdvakken Humane Voeding en Toxicologie. Per 1 september 1983 trad hij in dienst bij de Vakgroep Humane Voeding te Wageningen als wetenschappelijk assistent alwaar, met financiële steun van het Praeventiefonds, het in dit proefschrift beschreven onderzoek werd verricht. Per 1 januari 1987 zal hij, met behulp van een stipendium van ZWO, gedurende een jaar verder onderzoek naar aspecten van vetverdeling verrichten aan de Universiteit van Göteborg te Zweden.