ESTHER ALETTA MOLENAAR

Obesity Matters: Findings in the Utrecht Health Project and the Framingham Heart Study

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Utrecht, Universiteit Utrecht, Faculteit Geneeskunde

Thesis University Utrecht - with a summary in Dutch
Proefschrift Universiteit Utrecht – met een samenvatting in het Nederlands
ISBN 978-90-393-4896-3

Cover: Marjo Starink
Photograph: Bob en Nel Molenaar
Lay-out: Irma Hornman, Studio Cursief
Print: Gildeprint Drukkerijen BV, Enschede, the Netherlands

Obesity Matters: Findings in the Utrecht Health Project and the Framingham Heart Study

Over Gewicht: Resultaten uit het Leidsche Rijn Gezondheidsproject en de Framingham Heart Study

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. J.C. Stoof,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 30 september 2008 des ochtends te 10.30 uur

door

ESTHER ALETTA MOLENAAR

geboren op 24 juli 1979 te Zwolle

Promotor:
Prof. dr. D.E. Grobbee

Co-promotoren:
Dr. M.E. Numans
Dr. E.J.C. van Ameijden

The studies described in this thesis were funded by a grant from the Ministry of Health, Welfare and Sport (grant number 76064), the Netherlands Organization for Scientific Research (grant number R96-262), and the Netherlands Heart Foundation (grant number 2006R026)

Financial support by the Netherlands Heart Foundation and the Julius Center for Health Sciences and Primary Care for the publication of this thesis is gratefully acknowledged. Additional financial support was kindly provided by AstraZeneca BV, Bristol-Myers Squibb BV, Genzyme BV, Pfizer BV, Sanofi-Aventis Netherlands BV and Schering-Plough BV.

MANUSCRIPTS BASES ON THE STUDIES PRESENTED IN THIS THESIS

CHAPTER 2

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CHAPTER 3

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CHAPTER 6

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CHAPTER 1

General Introduction

OVERWEIGHT AND OBESITY: A GROWING PUBLIC HEALTH ISSUE

Worldwide, the prevalence of overweight and obesity rapidly increased the last two decades.[1] Overweight and obesity have become a major public health concern[1] and are one of the most discussed health issues of the 21st century.[2] The phenomenon has been referred to as a global epidemic, globesity and a pandemic.[1,3] Overweight and obesity are now so common that they are replacing the more traditional public health concerns such as undernutrition and infectious diseases as some of the most substantial contributors to the disease burden in most parts of the world.[1,4] For the first time in history, the number of overweight and obese people worldwide has overtaken the number of malnourished people.[5]

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.[6] The body mass index (BMI) is a simple index of weight-for-height that provides the most useful population-level measure of excess body weight. It is calculated as weight in kilograms divided by the square of height in meters (kg/m^2). According to the World Health Organization (WHO) classification scheme a BMI equal to or more than 25 is defined as overweight, and a BMI equal to or more than 30 as obesity (Table 1).[1] Globally there are approximately 1.6 billion overweight adults and at least 400 million obese adults.[6]

Table 1 The WHO classification of adult weight status according to BMI[1]

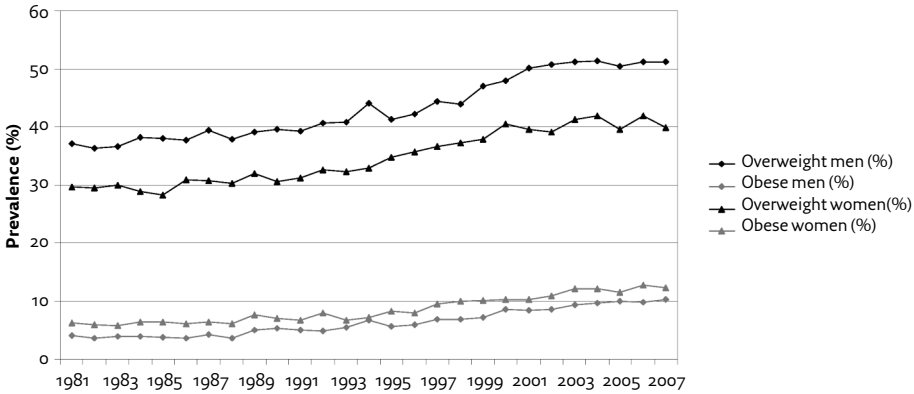
Classification	BMI (kg/m^2)	Risk of comorbidities
Normal weight	18.5-24.9	Average
Overweight	≥25.0	
Moderate overweight	25.0-29.9	Increased
Obesity (severe overweight)	≥30.0	
Obese Class I	30.0-34.9	Moderate
Obese Class II	35.0-39.9	Severe
Obese Class III	≥40.0	Very severe

Overweight and obesity are major risk factors for a number of chronic diseases such as cardiovascular disease (CVD), diabetes, musculoskeletal disorders[7] and certain cancers,[8] and they pose a progressively increasing risk as BMI increases.[7]

OVERWEIGHT AND OBESITY IN THE NETHERLANDS

In the Netherlands, as in many other countries, there has been a rise in the number of overweight and obese individuals. Based on self-reported data, the prevalence of overweight among Dutch adult men increased from 37% in 1981 to 51% in 2007, and among Dutch adult women from 30% in 1981 to 40% in 2007 (Figure 1).[9] During the same time period, the obesity prevalence among adults more than doubled.[9]

Figure 1 Trends for prevalence of overweight (BMI≥25) and obesity (BMI≥30) in men and women in the Netherlands 1981–2007, based on self-reported data.[9]



Compared to other European countries, the occurrence of moderate overweight in the Netherlands (41% in men, 28% in women) is in the middle range, while the occurrence of obesity is relative low (10% in men, 12% in women).[10] The proportion of European adults who are moderate overweight ranges from 23% in French women to 53% in German men, and the proportion obese adults ranges from less than 10% in Italian women to more than 25% in Czech women.[10] In the United States, the prevalence of obesity is even higher. One out of every three American adults is obese.[11]

On an annual basis, approximately 40,000 incident cases of adult CVD, diabetes and cancer in the Netherlands can be attributed to overweight and obesity,[12] making them leading contributors to reduced quality of life.[13] The direct health costs of overweight and obesity are estimated to be €0.5 billion annually, while the indirect cost (due to absenteeism, loss of productivity, benefits and social costs) are estimated at €2 billion.[14] Evidently, overweight and obesity pose serious health consequences that are costly to the individual and society.

GENERAL OBJECTIVE

The research described in this thesis focuses on overweight and obesity in the general adult population. Despite numerous population-wide prevention efforts, the prevalence of overweight and obesity continues to rise.[1] Therefore, early identification and treatment of overweight and obesity and their associated co-morbidities are becoming increasingly important to minimize the risk of complications. This urges for more targeted approaches directed at overweight and obese adults and adults at high risk to become overweight or obese to complement public health strategies, and emphasizes the role of the health care system. As in many Western countries most health care contacts occur in the primary care setting,[15] primary care physicians are particularly well-positioned to reach a large proportion of the overweight and obese adult population.[16] However, research to demonstrate efficacy of interventions for overweight adults that are integrated in routine primary care is scarce.

The main objective of this thesis was to examine the burden and treatment of adult overweight, obesity and their associated co-morbidities using data from two large ongoing population-based prospective cohort studies, the Utrecht Health Project and the Framingham Heart Study. The first study combines routinely collected information from primary care with additional collected basline data and allowed us to simultaneously explore various methods to use data from this setting for early identification and treatment of high-risk subgroups. Using data from the PROVE-IT TIMI 22 trial, we took our examination one step further by studying the potential benefit of treating risk factors in overweight patients with coronary artery disease.

THE UTRECHT HEALTH PROJECT

The Utrecht Health Project (UHP, or in Dutch "Leidsche Rijn Gezondheidsproject") started in 2000 in Leidsche Rijn, a newly developed residential area part of the city of Utrecht, the Netherlands.[17] By 2025, this area is expected to house approximately 80,000 inhabitants. The UHP infrastructure is solidly embedded in the academic Julius primary health care centers in Leidsche Rijn. The objective of the UHP is to study determinants of health and disease and answer research questions on the effects and costs of health care. All new inhabitants are invited to participate in the UHP when they register with their new primary care physician. At baseline a standardized health assessment is performed, which serves as the starting point for the UHP research database as well as for the primary care electronic medical records. The participants are followed up by means of continuously collected data from routine health care. By July 2008, 10,000 inhabitants in the area had given informed consent to participate in the UHP, reflecting a response of over 50%, and participation is steadily increasing.

THE FRAMINGHAM HEART STUDY

The Original Cohort of the Framingham Heart Study (FHS) began in 1948 with the recruitment and examination of 5209 inhabitants from Framingham, Massachusetts, United States.[18] At that time little was known about the underlying causes of CVD, while it had become the leading cause of death in the United States. The objective of the FHS was to identify factors and characteristics that contribute to CVD. Since the start of the study, health examinations have followed approximately every 2 years. In 1971, 5124 men and women were enrolled into the Offspring cohort, including the children and spouses of the children of the original cohort, to participate in similar examinations.[19] Thirty-one years later, the Third Generation Cohort was added, consisting of 4095 participants who had at least one parent in the Offspring Cohort.[20] Over the years the FHS has contributed to the identification of many major risk factors (a term largely coined by the FHS) for CVD and has expanded research in other areas.

OUTLINE OF THIS THESIS

This thesis is structured as follows. *Chapter 2* describes the association between overweight and physical and mental health conditions, and health-related quality of life. The burden as well as rates of treatment and control of CVD risk factors in normal weight, overweight and obese individuals is reported in *Chapter 3*. In *Chapter 4* we assessed the influence of BMI on the impact of intensive versus moderate lipid-lowering statin therapy on cardiovascular outcomes in patients with acute coronary syndrome. In *Chapter 5* we examined the association of lifestyle factors (diet, physical activity, alcohol consumption and smoking) with abdominal subcutaneous and visceral adiposity. The results of a randomized clinical trial on the efficacy of a multidisciplinary weight management program in primary care are presented in *Chapter 6*. The study reports on the effect of nutritional counseling by a dietician in comparison to nutritional plus exercise counseling by a dietician and a physiotherapist on body weight and waist circumference in an adult overweight population. In *Chapter 7* we assessed the value of biometrical data on hypertension and diabetes complementary to self-reported questionnaire information for estimating the prevalence of the overweight-related CVD risk factors. In *Chapter 8* we reflect on certain methodological aspects of the use of routine health care data for epidemiologic and public health research. The findings of the different studies described in this thesis are summarized in *Chapter 9*.

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CHAPTER 2

Substantial Comorbidity in Dutch Overweight Adults: Findings in the Utrecht Health Project

ABSTRACT

BACKGROUND The prevalence of overweight and obesity is rapidly increasing worldwide. We sought to determine the association between overweight, physical and mental health conditions and health-related quality of life in an adult community population upon entering a new primary care practice.

METHODS A cross-sectional study was performed using baseline data of 4825 participants (mean age 39 years, 55% women) of the Utrecht Health Project, a dynamic population study in primary care, to determine and compare the prevalence of health conditions and quality of life among individuals with normal weight (body mass index (BMI) 18.5-<25), overweight (BMI 25-<30) and obesity (BMI ≥30). Normal weight was used as reference category.

RESULTS Overweight individuals were approximately twice as likely to have cardiovascular risk factors and had a 20% to 60% increased risk of back pain, osteoarthritis, migraine, dyspepsia and respiratory symptoms as compared to normal weight individuals. Obese individuals were nearly twice to four times more likely to have these conditions and were additionally at increased risk of pulmonary diseases, a heart attack, arthritis and wheezing (range of odds ratios (ORS): 1.9-3.3). Somatization and a reduced physical well-being were more common among both overweight (ORS: 1.2-1.5) and obese (ORS: 1.7-3.7) individuals, whereas only obese individuals demonstrated a 30% to 50% increased risk of mental health conditions and a reduced mental well-being.

CONCLUSION Overweight and obesity are associated with a broad range of physical and mental health conditions and a reduced health-related quality of life. Measurement of BMI upon entering a primary care practice is relatively simple and may be a useful contribution to identify risk groups.

INTRODUCTION

Worldwide, the prevalence of overweight is rising to epidemic proportions at an alarming rate. Also in the Netherlands, the proportion of overweight adults rapidly increased the last decades. While approximately one-third of the Dutch adult population was moderate or severe overweight in 1981, currently almost half of the population meet the criteria for overweight.[1] Overweight is associated with an increased risk of many diseases and health conditions.[2-5] Because of its high prevalence and high risk of comorbidity, excess weight is recognized as a major threat to public health.

Thus far only one large study investigated the relation between overweight, health conditions and health-related quality of life in the Netherlands.[3] Therefore, knowledge on the relation between overweight and health in the Dutch population is limited. In addition, few studies have comprehensively investigated the relation between overweight, physical as well as mental health conditions and health-related quality of life. Lastly, it is not common practice to systematically register the BMI and other basic patient characteristics upon entering a new primary care practice in the Netherlands. However, within the Utrecht Health Project (UHP), a dynamic population study solidly embedded in primary care, these baseline data are collected by means of a extended intake procedure and enable to gain insight into the individuals' health status in the phase preceding an indicated health care contact.[6] For present study we used these data to examine the association between overweight, physical and mental health conditions and health-related quality of life in an adult community population.

METHODS

Sample

The present study used data from the UHP, a dynamic population study in primary care conducted in a newly developed residential area in the Netherlands (i.e. Leidsche Rijn).[6] Residents are invited to participate in the UHP

when they register with their new primary care physician. After informed consent is obtained, information regarding the participants' health status and disease history is recorded during an extended intake procedure resulting in a so-called 'Individual Health Profile' (IHP). The data that are captured in the IHP (Table 1) are the starting point for the UHP research database as well as for the primary care (electronic) medical records.

Table 1 The Individual Health Profile (IHP)

Medical history
Chronic disorders
Operations
Infectious diseases, allergies
Medication
Risk factors
Questionnaires
Social and economic status (education, occupation)
Health (disease, medication)
Physical problems
Lifestyle factors (alcohol, smoking, physical activity)
Use of healthcare (physician, dentist, physiotherapist, specialist, hospital)
Accidents
Rand SF-36 (health-related quality of life)
SCL-90 (symptoms of psychopathology)
WHO/Rose (peripheral arterial disease)
VVZ Dyspepsia (abdominal complaints)
Biometry, risk factors and biochemistry
Age, gender
Height
Weight
Blood pressure
Serum glucose
Serum cholesterol, HDL-cholesterol
ECG
Spirometry (without provocation)

Abbrevations: SF-36, Short-Form 36 Item Health Survey; SCL, Sympton Checklist; WHO, World Health Organization; VVZ, Veldhuyzen van Zanten; HDL, high-density lipoprotein; ECG, electrocardiography

The UHP started to recruit participants in 2000 and since then the response has been steadily increasing. By July 2008 there were 9927 participants reflecting a response of over 50%. The Medical Ethics commission of the University Medical Center Utrecht has approved the UHP. For present analysis, intake data were available on 4946 adult participants 18 years and older collected between March 2000 and January 2005. We excluded participants who met the World Health Organization (WHO) criteria for underweight[7] (n=66), pregnant women (n=33) and participants with missing data on weight and/or height (n=22), resulting in 4825 eligible participants.

Overweight and obesity

Height and weight were measured with the participant wearing light clothing and no footwear. Moderate overweight (BMI 25-<30) will be simply referred to as overweight throughout the rest of the paper. Thus, normal weight, overweight and obesity were respectively defined as BMI 18.5-<25, BMI 25-<30 and BMI ≥30.

Health measures

The health conditions and the health related quality of life were categorized in five groups and were assessed using the following definitions:

— Cardiovascular risk factors
  The presence of diabetes was defined as fasting venous glucose levels >6.9 mmol/l, fasting capillary glucose levels >6.0 mmol/l, or non-fasting glucose levels >11.0 mmol/l.[8] Hypertension was based on the average of two consecutive readings at a single session and defined as a systolic blood pressure ≥140 mm Hg.[9] Participants with fasting serum cholesterol levels ≥6.5 mmol/l were defined as having hypercholesterolemia.[9] The data were respectively corrected for the use of antidiabetics, antihypertensives, and cholesterol-lowering medication.
— Previously physician-diagnosed medical conditions
  The presence of physician-diagnosed medical conditions were based on self-reported affirmative answers to the question 'Have you had any of the following conditions anywhere during the past twelve months, that have (ever) been diagnosed by a physician or specialist; asthma/chronic bronchitis, heart attack, stroke, cancer, persistent back complaints/hernia, arthritis, osteoarthritis, migraine or depression/stressed?'
— Health conditions
  Current health conditions included dyspepsia, peripheral arterial disease, shortness of breath and wheezing. Dyspepsia was assessed using the

questionnaire of Veldhuyzen van Zanten et al.[10] A total score >17 indicated the presence of relevant gastric disturbances. The WHO/Rose criteria were used to detect peripheral arterial disease.[11] Shortness of breath and wheezing were respectively based on self-reported answers to the questions 'Are you ever short of breath?' and 'Do you ever experience wheezing?'.

— Symptoms of psychopathology
The extent to which participants experienced psychological complaints during the preceding weeks were determined using the scores on the subscales of the psychiatric Symptom CheckList (SCL-90): agoraphobia, anxiety, depression, somatization, insufficiency, distrust and interpersonal sensitivity, hostility, sleep difficulties, and the total score on psychoneuroticism.[12] The sex-specific mean subscale scores for the Dutch population were used as cut-off points for above average subscale scores.[12]

— Health related quality of life
Health related quality of life was assessed by means of the standardized score on the subscales of the RAND SF-36 questionnaire: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, vitality, mental health, pain and general health.[13] A standardized score on the subscale below 66.7 was used as cut-off point for a reduced well-being on that particular scale.[3]

Demographics
Self-reported data in the questionnaire provided for information on gender, age, country of origin, and educational level of the participants.

Statistical Analysis
Multivariate logistic regression analysis was used to examine the associations between overweight and obesity and a variety of health measures, using normal weight (BMI 18.5-<25) as reference category. The health measures were the dependent variables. All analyses were adjusted for gender and age. Results are presented as odds ratio (OR) with the corresponding 95% confidence interval (CI). A two-tailed $p<0.05$ was considered as statistically significant. In secondary analyses we assessed the presence of interactions for the associations between overweight and obesity and the health measures with gender and age, considering a two-tailed $p<0.01$ as statistically significant. All analyses were performed using SPSS (version 14.0).

RESULTS

The mean (±standard deviation) age of the study sample was 39±13 years and more than half (54.6%) of the participants were female (Table 2). The majority (78.6%) was of Dutch origin, over one-third completed higher vocational or university education, and approximately one-quarter of the population (24.3%) were current smokers. Over one-third of the participants (36.8%) were overweight and 12.8% met the criteria for obesity. The prevalence of the health conditions (Table 3) and the mean score on symptoms of psychopathology (SCL-90) and subscales of health related quality of life (RAND SF-36) in our study sample were in a similar range as in the general Dutch population.[12-14] Since we did not observe interaction, with the exception for hypercholesterolemia, the results are not stratified by sex or age.

Table 2 General characteristics of the total study sample and by BMI-category*

	Total N=4825	Normal Weight (BMI 18.5-< 25) N= 2401	Overweight (25 ≤ BMI <30) N=1800	Obesity (BMI ≥30) N=624
Women (%)	2633 (54.6)	1450 (60.4)	812 (45.1)	371 (59.5)
Age (yrs)	39±13	37±11	42±13	43±13
Dutch origin (%)	3656 (78.6)	1861 (80.1)	1350 (77.7)	445 (74.9)
Higher education (%)†	1657 (36.7)	982 (43.5)	561 (33.2)	114 (20.2)
Current smoker (%)	1121 (24.3)	597 (26.0)	399 (23.1)	125 (21.1)

Abbrevations: BMI, Body Mass Index

** Data are shown as n (percent) for dichotomous variables and mean ± standard deviation for continuous variables*

† Higher vocational or university education

Cardiovascular risk factors, diagnosed medical conditions, and health conditions

Overweight participants were approximately twice as likely to have diabetes (OR =2.1; 95% CI 1.3-3.2), hypertension (OR =1.7; 95% CI 1.4-2.0), and hypercholesterolemia (OR =1.7; 95% CI 1.4-2.0) than normal weight participants (Table 3). In addition overweight participants had a 20% to 60% increased risk (range of ORs: 1.2-1.6) of physician diagnosed back complaints, osteoarthritis, migraine and several health conditions including dyspepsia,

Table 3 Overall crude prevalence (%) and age- and sex-adjusted odds ratios (95% CI) for cardiovascular risk factors, physician-diagnosed medical conditions, and health conditions by BMI-category, using normal weight as reference

	Prevalence (%)	OR (95% CI)		
	Total	Normal Weight (BMI 18.5-<25)	Overweight (BMI 25-<30)	Obesity (BMI ≥30)
Cardiovascular risk factors				
Diabetes	3.4	1	2.1 (1.3-3.2)	3.7 (2.3-6.0)
Hypertension	21.3	1	1.7 (1.4-2.0)	3.9 (3.1-4.8)
Hypercholesterolemia	15.2	1	1.7 (1.4-2.0)	1.7 (1.3-2.3)*
Diagnosed conditions†				
Asthma/bronchitis	9.7	1	1.0 (0.8-1.2)	2.0 (1.5-2.6)
Heart attack‡	1.2	1	1.8 (0.9-3.5)	3.3 (1.6-7.1)
Back complaints	11.4	1	1.4 (1.1-1.7)	1.8 (1.3-2.3)
Arthritis	3.6	1	1.2 (0.9-1.8)	1.9 (1.2-2.9)
Osteoarthritis	8.0	1	1.6 (1.2-2.1)	2.4 (1.7-3.3)
Migraine	10.8	1	1.5 (1.2-1.8)	1.4 (1.0-1.8)
Depression/stressed	13.0	1	1.1 (0.9-1.4)	1.6 (1.2-2.0)
Health conditions†				
Dyspepsia	7.6	1	1.3 (1.0-1.7)	2.3 (1.7-3.1)
Shortness of breath	32.7	1	1.3 (1.1-1.4)	2.3 (1.9-2.8)
Wheezing	19.3	1	1.2 (1.0-1.4)	1.9 (1.5-2.3)

Abbreviations: OR, odds ratio; CI, Confidence Interval; BMI, Body Mass Index

** Significant negative age-interaction (p-value =0.002)*

† No significant relationships were found for stroke, cancer and peripheral arterial disease

‡ Interpret with caution as the prevalence is low

shortness of breath and wheezing. Obese individuals were nearly twice to four times more likely to have these conditions, with the exception of hypercholesterolemia and migraine, than normal weight participants. Moreover, obese participants were one-and-a-half to over three times more likely to have physician-diagnosed pulmonary disease (OR=2.0; 95% CI 1.5-2.6), experienced a heart attack (OR=3.3; 95% CI 1.6-7.1), arthritis (OR=1.9; 95% CI 1.2-2.9), to be depressed or stressed (OR=1.6; 95% CI 1.2-2.0), and to wheeze (OR=1.9; 95% CI 1.5-2.3) than normal weight participants. The

strength of the association between obesity and hypercholesterolemia decreased with increasing age (p-value for age-interaction=0.002).

Symptoms of psychopathology

Overweight as well as obese participants were more likely to have somatic complaints (OR=1.2; 95% CI 1.1-1.4 and OR=1.7; 95% CI 1.4-2.0 respectively) than normal weight participants (Table 4). Obese participants additionally demonstrated a 30% to 50% increased risk of agoraphobia, depression,

Table 4 Mean (±standard deviation) score and age- and sex-adjusted odds ratios (95% CI) for symptoms of psychopathology and reduced health-related quality of life by BMI-category, using normal weight as reference

	Score	OR (95% CI)		
	Total	Normal Weight (BMI 18.5-<25)	Overweight (BMI 25-<30)	Obesity (BMI ≥30)
Symptoms of psychopathology (SCL-90)*				
Agoraphobia	7.6±1.9	1	1.2 (1.0-1.4)	1.5 (1.2-1.9)
Depression	21.0±7.3	1	1.1 (0.9-1.2)	1.3 (1.0-1.5)
Somatization	16.6±5.3	1	1.2 (1.1-1.4)	1.7 (1.4-2.0)
Distrust/Interpersonal sens.	22.1±6.5	1	1.0 (0.9-1.2)	1.4 (1.1-1.7)
Hostility	7.1±2.1	1	1.1 (1.0-1.3)	1.3 (1.0-1.6)
Psychoneuroticism	113.8±30.5	1	1.1 (1.0-1.3)	1.4 (1.1-1.7)
Reduced quality of life (RAND SF-36)				
Physical functioning	89.2±16.9	1	1.5 (1.2-2.0)	3.7 (2.9-4.9)
Social functioning	86.0±20.2	1	1.0 (0.9-1.2)	1.5 (1.2-1.9)
Role limitations-physical	81.6±33.4	1	1.3 (1.1-1.5)	1.9 (1.6-2.4)
Role limitations-emotional	87.2±29.6	1	1.0 (0.9-1.2)	1.4 (1.1-1.7)
Mental health	76.7±16.1	1	1.0 (0.9-1.2)	1.4 (1.1-1.7)
Vitality	60.2±18.9	1	1.0 (0.9-1.2)	1.6 (1.3-2.0)
Pain	82.5±21.6	1	1.5 (1.2-1.8)	2.1 (1.7-2.6)
General health	75.1±21.4	1	1.3 (1.1-1.5)	2.1 (1.7-2.5)

Abbreviations: OR, odds ratio; CI, Confidence Interval; BMI, Body Mass Index, Interpersonal sens, interpersonal sensitivity

** No significant relationships were found for anxiety, insufficiency and sleep difficulties*

distrust and interpersonal sensitivity, hostility and psychoneuroticism, while no significant associations were observed for overweight participants.

Health related quality of life

Overweight participants had a 30% to 50% increased risk of a reduced health related quality of life regarding physical functioning (OR=1.5; 95% CI 1.2-2.0), role limitations due to physical problems (OR=1.3; 95% CI 1.1-1.5), pain (OR=1.5; 95% CI 1.2-1.8), and general health (OR=1.3; 95% CI 1.1-1.5) than those with a normal weight (Table 4). Obese participants were even more likely to have a reduced quality of life in these areas, particularly in the area of physical functioning (OR=3.7; 95% CI 2.9-4.9). Additionally, obese participants had a 40% to 60% increased risk of a reduced quality of life regarding social functioning, role limitations due to emotional problems, mental health and vitality than normal weight participants.

DISCUSSION

In the present study, in a large population based adult cohort upon entering a new primary care practice, the vast majority of health conditions were substantially more common among overweight and obese individuals than among normal weight individuals. We observed a clear gradient with increasing BMI-category.

There are certain limitations that need to be addressed before discussing the results. As present study used cross-sectional data, no evidence of temporal association or causality can be given. Another limitation was the relative low mean age of the study sample that resulted in relatively low prevalences of heart attack, stroke, cancer and peripheral arterial disease. Therefore, the findings with regard to these conditions need to be interpreted with caution.

Strengths of our study include the use of objective measurements of height, weight and cardiovascular risk factors. Self-reported height and weight leads to an underestimation of overweight and obesity prevalence.[15,16] Moreover, we have previously demonstrated in our own study population that sole reliance on self-reported hypertension and diabetes may lead to an underestimation of the prevalence rates of these conditions and potentially bias the results.[17] Additional strengths of present study are the use of validated questionnaires and the possibility to comprehensively investigate a wide range of health conditions.

Consistent with findings from previous studies, we also observed the strongest association with the CVD risk factors hypertension and diabetes in our relatively young population. Excess fat is a well-known risk factor for hypertension and diabetes.[3,5] The relationship between overweight and obesity and dyspepsia is more ambiguous and previous population-based studies have yielded contradictory results.[18-20] In accordance with the findings of most recent studies, we observed a strong positive association between dyspepsia and overweight and obesity.[18,20] Additionally, our results confirm the findings from previous studies by demonstrating an increased likelihood of arthritis, osteoarthritis, pulmonary diseases and back pain among overweight and obese individuals.[3,5,21-23]

In line with above mentioned observations and findings from previous studies,[3,24-29] overweight as well as obese individuals were more likely to have somatic complaints and a reduced well-being in physically oriented domains, although the effect was more pronounced in the obesity category. We observed an increased risk of psychological complaints and a reduced mental well-being in obese individuals only. Earlier population-based studies on overweight, psychological complaints[24-29] and mental well-being[26,30,31] demonstrate conflicting results. Nevertheless, our findings suggest it is important to consider mental health conditions in obese individuals.

Physicians are likely to frequently encounter overweight and obese patients because of the high prevalence of excess weight. Our findings confirm and extend the results of a previous Dutch study:[3] overweight and obesity are associated with substantial comorbidity. Although the risk of comorbidity and mental health conditions increases with higher levels of BMI, overweight already confers an increased health risk. Moreover, as the proportion of overweight individuals is higher than the proportion of individuals with obesity, the first group may pose a bigger threat to public health. Therefore, physicians should consider a wide range of health conditions in both overweight and obese individuals.

Our study illustrates that relatively simple procedures, such as the measurement of BMI, as part of a health assessment at intake in a primary care practice can provide valuable information. The BMI is not frequently registered in Dutch primary care medical records. To illustrate, in only 10.4% of the adults not participating in the UHP but who are registered with a general practitioner in Leidsche Rijn, we were able to find the BMI in the medical record. Adding information on BMI to the medical record may contribute to the early identification of individuals with a high risk of comorbidity.

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CHAPTER 3

Burden and Rates of Treatment and Control of Cardiovascular Disease Risk Factors in Obesity: the Framingham Heart Study

ABSTRACT

BACKGROUND Obesity is associated with an increased risk for cardiovascular disease (CVD). We sought to determine rates of treatment and control of CVD risk factors among normal weight, overweight and obese individuals in a community-based cohort.

METHODS Participants free of CVD (n=6801; mean age 49 years; 54% women) from the Framingham Offspring and Third Generation cohorts who attended the seventh Offspring examination (1998-2001) or first Third Generation (2002-2005) examination were studied.

RESULTS Obese participants with hypertension were more likely to receive antihypertensive treatment (62.3%) than normal weight (58.7%) or overweight individuals (59.0%; p=0.002), but no differences in hypertension control across BMI subgroups among participants with hypertension were observed (36.7% [normal weight], 37.3% [overweight], and 39.4% [obese]; p=0.48). Rates of lipid-lowering treatment were higher among obese participants with elevated LDL cholesterol (39.5%) compared with normal weight (34.2%) or overweight participants (36.4%; p=0.02), but control rates among those with elevated LDL cholesterol did not differ across BMI categories (26.7% [normal weight], 26.0% [overweight], and 29.2% [obese]; p=0.11). There were no differences in diabetes treatment among participants with diabetes across BMI groups (69.2% [normal weight], 50.0% [overweight], 55.0% [obese]; p=0.54), but obese participants with diabetes were less likely to have fasting blood glucose <126 mg/dL (15.7%) than normal weight (30.4%) or overweight participants (20.7%; p=0.02).

CONCLUSION These findings emphasize the suboptimal rates of treatment and control of CVD risk factors among overweight and obese individuals.

INTRODUCTION

Obesity affects more than one-third of the adult population in the United States. Excess weight is associated with multiple cardiovascular disease (CVD) risk factors, including hypertension, dyslipidemia, diabetes, and the metabolic syndrome.

Although the incidence and mortality of CVD have declined markedly during the past decades, some studies suggest that the increasing prevalence of obesity and diabetes may have slowed this rate of decline.[1] In addition, recent data suggests that the prevalence of chronic kidney disease is increasing, in part due to the increasing rates of diabetes.[2] Unfortunately, the efficacy of current therapies for obesity including lifestyle and pharmacologic interventions, is limited.[3] While bariatric surgery is an effective method of weight loss among severely obese individuals, eligibility criteria limit its use to only the most significantly affected patients.

Given the current limitations of effective weight loss therapies, minimizing the risk of complications of obesity and diabetes due to CVD risk factors is essential. Few studies have focused on a comprehensive approach to CVD risk factor burden, treatment, and control among obese individuals. Therefore, the aim of this study is to examine the burden of CVD risk factors as well as rates of treatment and control among normal weight, overweight and obese individuals in an unselected population-based cohort. As abdominal fat accumulation is strongly associated with metabolic and CVD risk factors, and as recent guidelines have emphasized the importance of measuring waist circumference as part of clinical cardiovascular risk assessment, we also studied individuals with and without abdominal obesity.

METHODS

Study sample

The Framingham Heart Study is a population-based prospective cohort study that commenced in 1948, and consists of 5209 men and women in the

original cohort. In 1971, 5124 men and women were enrolled into the Framingham Heart Study Offspring cohort, including the children and spouses of the children of the original cohort. Starting in 2002, 4095 participants who had at least one parent in the Offspring cohort, were enrolled into the Framingham Heart Third Generation Study. Approximately every 4 years Offspring participants underwent examinations; the design and methodology of the Offspring and Third Generation cohort have been previously described.[4,5]

For the current study, the study sample consisted of Offspring and Third Generation participants who attended the seventh (1998-2001) and first (2002-2005) examination cycle, respectively.

Of 7634 participants (3539 Offspring, 4095 Third Generation participants) eligible participants, we excluded those with prevalent CVD (n=463), body mass index (BMI) <18.5 kg/m^2 or incomplete BMI data (n=196), type 1 diabetes (n=15), missing waist circumference values (n=105) and missing covariate data (n=54), resulting in 6801 eligible participants.

The study protocol was approved by the institutional review boards of the Boston University Medical Center. All subjects provided written informed consent.

Measurements and definitions

Height and weight were directly measured using a standardized protocol. BMI was calculated by dividing weight in kilograms by the square of the height in meters. General obesity was defined according to the World Health Organization/National Institutes of Health classification scheme. Waist circumference was measured at the level of the umbilicus. Abdominal obesity was defined as a waist circumference ≥88 cm (women) and 102 cm (men).

CVD risk factor assessment

Assessment of CVD risk factors (including fasting blood testing) was based on measurements obtained during a single examination. Hypertension was defined as systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg (based on the average of 2 readings), or current use of antihypertensive medication for hypertension. Serum cholesterol levels were measured in a fasting state. Participants with elevated low-density lipoprotein cholesterol (LDL-C) levels according to their CVD risk level as classified by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) algorithm, or those receiving lipid-lowering agents

were defined as having elevated LDL-C levels. Type 2 diabetes was defined as a fasting blood glucose level of ≥126 mg/dL (7.0 mmol/L) or current use of insulin and/or hypoglycemic treatment for diabetes. High-performance liquid chromatography was used to measure hemoglobin A_{1C} levels with an assay coefficient of variation <2.5%.

Treatment and control of CVD risk factors

To determine rates of treatment, the number of participants receiving medication for each individual condition was divided by the number of all participants with the condition. Rates of control were determined by dividing the number of participants classified as controlled by the total number of individuals with the condition. Control of hypertension was defined as either a blood pressure <140/90 mm Hg or 130/80 mm Hg for participants with diabetes.[6] Control of LDL-C levels was determined using participant's specified treatment goal according to the NCEP ATPIII algorithm. Diabetes control rates were assessed by dividing the number of individuals with fasting blood glucose <126 mg/dL by the number of all participants with diabetes. A hemoglobin A_{1C} level of <7.0% was additionally used to calculate rates of glycemic control in the Offspring cohort only.

Statistical analysis

Prevalence and rates of treatment and control of CVD risk factors were compared among individuals in the three BMI categories. For each risk factor, the age-sex adjusted proportion of participants with the condition that were treated and controlled was calculated; 95% confidence intervals (95% CI) were abstracted from the logistic regression models. In all analyses, the global p-values were obtained from models using the generalized estimation equation (GEE) to account for familial correlation, except for analyses where sample sizes were too small to permit the GEE. In this case, ANOVA p-values were calculated. Low high-density lipoprotein cholesterol (HDL-C) levels were defined as <50 mg/dL (1.29 mmol/L) in women and <40 mg/dL (1.03 mmol/L) in men or current use of lipid-lowering agents. Rates of dual control of hypertension and elevated LDL-C levels and triple control of hypertension, elevated LDL-C and fasting blood glucose were calculated and compared across the three BMI categories.

The following secondary analyses were performed. Participants were stratified by abdominal obesity. In addition, general obesity was further categorized in Stage I (BMI 30-<35 kg/m^2) and Stage II or higher (BMI ≥35 kg/m^2) obesity; the latter is indicated in the text simply as Stage II obesity.

Participants were also stratified by age (<50 years or ≥50 years) and sex.

Statistical analyses were performed using SAS statistical software, version 8. Two-tailed $p<0.05$ and $p<0.01$ were considered statistically significant for primary and secondary analyses, respectively.

RESULTS

Overall, 36.1% of the study participants (mean±SD age 49±13 years; 54% women) were normal weight, 38.2% were overweight, and 25.7% were obese; 47.7% had abdominal obesity. The characteristics of the study participants are displayed in Table 1.

Table 1 Characteristics of study participants within different BMI categories. Data shown as mean ± standard deviation for continuous variables, and n (percent) for dichotomous variables

	BMI 18.5-<25 N=2458	BMI 25-<30 N=2596	BMI ≥30 N=1747	p-value*
Age, years	46 ± 14	50 ± 13	51 ± 13	<0.001
Female (%)	1727 (70.3)	1093 (42.1)	866 (49.6)	<0.001
Systolic blood pressure, mm Hg	115 ± 16	122 ± 16	127 ± 16	<0.001
Diastolic blood pressure, mm Hg	71 ± 9	76 ± 9	79 ± 9	<0.001
Fasting blood glucose, mg/dL	91 ± 12	98 ± 17	107 ± 29	<0.001
Total cholesterol, mg/dL	187 ± 34	199 ± 37	198 ± 35	<0.001
LDL cholesterol, mg/dL	107 ± 31	122 ± 32	120 ± 31	<0.001
HDL cholesterol, mg/dL	61 ± 17	52 ± 15	48 ± 14	<0.001
Triglycerides, median [25/75 percentiles], mg/dL	78 [58, 109]	109 [76, 161]	131 [93, 184]	<0.001
BMI, kg/m^2	22.5 ± 1.6	27.3 ± 1.4	34.6 ± 4.5	<0.001
Waist circumference, cm	82.6 ± 7.6	96.6 ± 7.2	113.7 ± 12.0	<0.001
Current smoker (%)	407 (16.6)	386 (14.9)	247 (14.1)	0.14

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein

SI conversion factors: To convert glucose to mmol/L, multiply mg/dL values by 0.0555; total, LDL and HDL cholesterol to mmol/L, multiply mg/dL values by 0.0259; triglycerides to mmol/L, multiply mg/dL values by 0.0113

** Global GEE age- and sex-adjusted p-value, except for age which is sex-adjusted and sex, which is age-adjusted*

Hypertension

The prevalence of hypertension increased significantly with increasing BMI category (p<0.001, Table 2). Among those with hypertension, obese participants were more likely to be treated (62.3%) than normal weight (58.7%) or overweight participants (59.0%; p=0.002). However, control rates were uniformly poor and did not differ by BMI category (36.7% [normal weight], 37.3% [overweight], and 39.4% [obese]; p=0.48).

Elevated LDL Cholesterol

Elevated LDL-C increased with increasing BMI categories (p<0.001, Table 2). Obese participants with elevated LDL-C were more likely to be treated with lipid lowering agents (39.5%) than normal weight (34.2%) or overweight

Table 2 Age- and sex-adjusted rates of hypertension, elevated levels of low lipoprotein cholesterol, type 2 diabetes, treatment and control among BMI categories

	% of Participants (95% CI)			
	BMI 18.5-<25 N=2458	BMI 25-<30 N=2596	BMI ≥30 N=1747	p-value*
Hypertension				
Prevalence	11.5 (10.2-12.9)	22.8 (21.0-24.8)	37.6 (34.5-40.7)	<0.001
Treatment	58.7 (49.8-67.1)	59.0 (52.8-65.0)	62.3 (56.1-68.2)	0.002
Control	36.7 (30.3-43.5)	37.3 (32.7-41.9)	39.4 (34.9-44.0)	0.48
Elevated LDL-C				
Prevalence	12.7 (11.3-14.2)	28.2 (26.2-30.4)	35.1 (32.2-38.2)	<0.001
Treatment	34.2 (28.2-40.6)	36.4 (32.3-40.6)	39.5 (34.9-44.4)	0.02
Control	26.7 (21.5-32.4)	26.0 (22.6-29.7)	29.2 (25.3-33.4)	0.11
Diabetes				
Prevalence	1.4 (0.9-1.9)	4.1 (3.4-5.0)	11.9 (10.3-13.6)	<0.001
Treatment	69.2 (38.6-90.9)	50.0 (35.2-64.8)	55.0 (44.7-65.0)	0.54
Hb A1c <7.0% †	50.0 (18.7-81.3)	58.8 (40.7-75.4)	47.7 (35.3-59.4)	0.26
FPG <126 mg/dL	30.4 (13.2-52.9)	20.7 (12.8-30.7)	15.7 (10.8-21.7)	0.02

Abbreviations: CI, confidence interval; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; Hb A1c, Hemoglobin A_{1C} level; FPG, fasting plasma glucose

SI conversion factor: To convert fasting plasma glucose to mmol/L, multiply mg/dL values by 0.0555

** Global GEE p-value*

† Data only available for Offspring cohort

(36.4%) participants (p=0.02). Less than one third of the participants were controlled and rates of control did not differ by BMI category (p=0.11).

Type 2 diabetes

Despite higher prevalence rates of diabetes with increasing BMI (p<0.001, Table 2), there were no differences in hypoglycemic treatment (69.2% [normal weight], 50.0% [overweight], 55.0% [obese]; p=0.54), or differences in prevalence of optimal hemoglobin A_{1C} levels across BMI categories in the Offspring cohort (50.0% [normal weight], 58.8% [overweight], 47.7% [obese]; p=0.26) among participants with diabetes. Obese participants were less likely to have fasting blood glucose <126 mg/dL (15.7%) than normal weight (30.4%) or overweight (20.7%) participants (p=0.02).

Combinations of risk factors

The number of CVD risk factors among BMI categories is displayed in Appendix Figure 1; only 6.0% of obese participants had no CVD risk factors. Dual control of hypertension and elevated LDL-C was uniformly low and did not differ by BMI category (19.1% (95% CI; 12.6%-27.0%) [normal weight], 12.1% (95% CI; 9.0%-15.8%) [overweight], and 16.0% (95% CI; 12.7%-19.8%) [obese]; p=0.94). Rates of triple control of hypertension, LDL-C and diabetes were low and showed no differences by BMI category (p=0.15): none of the normal weight participants with hypertension, elevated LDL-C and diabetes (n=17) achieved optimal triple control (0%; 95% CI 0%-0%), only 3 out of 52 overweight participants (5.9%; 95% CI 1.2%-16.2%), and only 2 out of 131 obese individuals achieved optimal triple control (1.6%; 95% CI 0.2%-5.5%).

Secondary analyses

When results were stratified by abdominal obesity, findings were not materially different (Appendix Table 1).

In analyses stratified by age, among older participants, obese individuals with hypertension were more likely to receive antihypertensive treatment (74.1%) than those with normal weight (67.4%) and overweight (67.5%; p=0.006, Appendix Table 2), whereas hypertension treatment rates among participants younger than 50 years were uniformly lower and similar across BMI categories (p=0.26). Age-stratified analyses of hypoglycemic treatment demonstrated that in participants <50 years of age, obese individuals with diabetes were less likely to receive treatment (39.3%) than overweight individuals with diabetes (50.0%; p=0.006, Appendix Table 2).

In sex-specific analyses, obese men were more likely to receive anti-hyper-

tensive treatment (56.9%) than normal weight men (50.9%) or overweight men (53.5%; p=0.006, Appendix Table 3), whereas treatment rates among women were uniformly the same across BMI categories (p=0.15). A similar pattern of sex differences was observed for lipid-lowering treatment and control of elevated LDL-C (Appendix Table 3). Sex-specific analyses of elevated glucose control demonstrated that among women, obese individuals with diabetes were less likely to have fasting blood glucose <126 mg/dL (12.8%) as compared to normal weight (30.8%) or overweight (32.3%) individuals (p<0.001, Appendix Table 3), whereas the rates among men were uniformly the same across BMI categories.

When the obesity category was further broken down into Stage I vs. Stage II obesity, no difference in treatment or control of hypertension (Figure 1A), elevated LDL-C (Figure 1B) and diabetes (Figure 1C) was observed despite higher prevalence of hypertension and diabetes among participants with Stage II obesity.

DISCUSSION

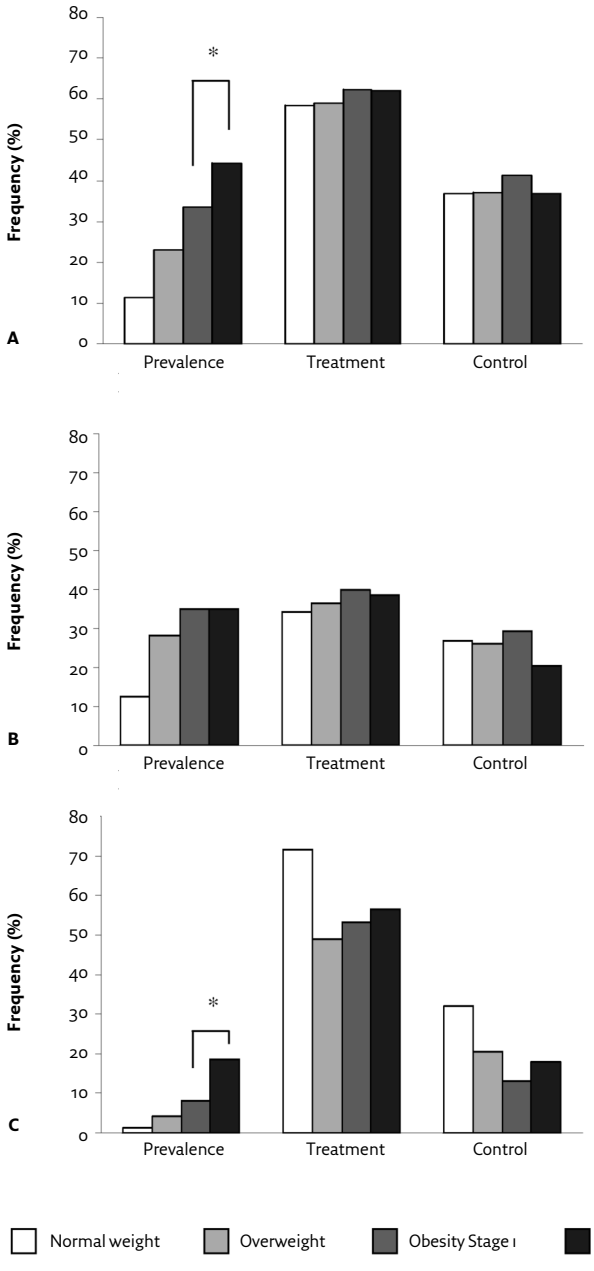
Principal findings

Despite the higher burden of CVD risk factors among participants with obesity from the Framingham Heart Study, rates of treatment and control of CVD risk factors are suboptimal among overweight and obese individuals. Among participants with obesity, only four in ten with hypertension achieved recommended blood pressure levels, less than one third with elevated LDL-C had optimal control of elevated LDL-C and only one in six participants with diabetes achieved fasting blood glucose <126 mg/dL. Dual and triple control of CVD risk factors were uniformly poor across all BMI categories.

Hypertension

High blood pressure is associated with an increased risk of mortality and morbidity from stroke, coronary heart disease and congestive heart failure[7] and is more frequent in obese individuals than in lean individuals.[8] Obese participants were more likely to receive antihypertensive treatment but were not more likely to achieve control. Overall, potential reasons for poor blood pressure may include unrecognized hypertension, poor adherence to medication regimen[9] and failure to initiate or intensify therapy when indicated.[10] In addition, the pathophysiology of obesity-related hypertension

Figure 1 Prevalence and rates of treatment and control of hypertension (Panel A), elevated levels of low-density lipoprotein cholesterol (Panel B), and type 2 diabetes (Panel C) among normal weight, overweight, obese Stage I, and obese Stage II participants. GEE p-values represent obesity Stage I vs. obesity Stage II adjusted for age and sex



may differ from hypertension among non-obese individuals because of the presence of excess adipose tissue. Potential mechanisms that link adipose tissue to hypertension include alterations in the renin-angiotensin system, activation of the sympathetic nervous system, insulin resistance, sodium and volume retention and renal dysfunction.[11] These mechanisms may have important implications for the effectiveness of antihypertensive therapy in obese individuals. Clinical trial data has shown that beta-blockers alone,[12] or in combination with doxazosin,[13] more effectively lower blood pressure in obese than in lean hypertensive individuals. Clinical trials have consistently shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are associated with reductions in the risk of new-onset type 2 diabetes,[14] and there is growing evidence that drugs blocking the renin-angiotensin system may be beneficial in the management of hypertension in obese individuals.[15] Current treatment guidelines do not provide specific recommendations for obese individuals regarding blood pressure targets and a particular treatment. This may be due to lack of randomized clinical trials that have focused specifically on this question.

Elevated LDL Cholesterol

Obese participants with elevated LDL-C were more likely to receive lipid-lowering therapy but rates of control of LDL-C among affected individuals did not differ across BMI categories. Among all participants with elevated LDL-C, levels were well controlled in less than one-third.

High levels of LDL-C are an important modifiable risk factor in the development of CVD. Many primary and secondary prevention trials have demonstrated the efficacy and safety of statins in reducing CVD risk. Therefore, it is surprising that LDL control was so poor among obese participants. There are several potential reasons for this. The current National Cholesterol Education Program guidelines do not specifically target obesity as a high-risk condition warranting lower LDL targets for lipid lowering. In addition, few clinical trials have studied the efficacy of statins in BMI subgroups on intermediate markers of CVD demonstrating increased benefit among obese individuals as compared to non-obese individuals or consistent effects across subgroups. Lastly, clinical trials studying the efficacy of statins on cardiovascular outcomes in BMI subgroups are lacking.

Type 2 diabetes

The prevalence of diabetes has increased substantially over the last several decades,[16] probably because of increases in obesity, and the prevalence of

obesity among individuals with diabetes increased by 50% between 1970 and 1989.[17] Rates of CVD associated with type 2 diabetes are high,[18] and recent increases in chronic kidney disease may be due in part to increases in obesity and diabetes.[2]

Despite these facts, we observed similarly low rates of treatment and control of hemoglobin A_{1c} levels across BMI subgroups. There may be several potential reasons for the observed poor glycemic control. First, diabetes may be unrecognized and therefore untreated. Second, clinical trial data demonstrating CVD event reduction in the setting of optimal glycemic control is lacking. However, improved blood glucose control reduces the risk of chronic kidney disease and diabetic retinopathy.[19] Third, patients may not be complying with treatment regimens, including diet and exercise recommendations. Undesirable side effects due to antidiabetic agents, in particular weight gain in the setting of insulin treatment, may limit treatment adherence as well. Last, clinical trials suggest that diabetes is more difficult to control among obese individuals.[20]

We have shown that material differences in treatment of diabetes do not exist across BMI categories and that obese individuals are less likely to achieve optimal fasting blood glucose levels. The majority of diabetes occurs in obese individuals. Our results highlight the vast numbers of untreated and uncontrolled diabetes in this subgroup.

Control of combinations of risk factors

Rates of dual and triple control of CVD risk factors were uniformly poor across BMI categories in our study sample. Clustering of metabolic abnormalities contributes cumulatively to CVD risk and complicates treatment.[21] This data emphasizes the importance of a treatment regimen aimed at multiple risk factors.

Clinical implications and future research

The suboptimal rates of diabetes treatment and control of CVD risk factors in obese participants in the current study are of particular concern, given the increasing rates of overweight and obesity among U.S. adults. Without substantial improvements in CVD risk factor treatment and control rates among obese individuals, the medical and financial burden of CVD events may grow substantially in the next several decades. There is a paucity of clinical trial data specifically testing interventions in obese subgroups to determine whether more intensive risk factor management or obesity-specific treatment and control guidelines would result in decreased CVD

outcomes. Additionally, there is a need for more effective pharmacotherapy for obesity.

Strengths and limitations

Strengths of our study include the examination of a large, population-based sample of women and men with a broad age spectrum and standardized assessment of anthropometric measures and CVD risk factors and treatment. Several limitations should be acknowledged. We used guidelines for treatment that were not necessarily in place at the time of data collection. However, the aim of current study was to characterize the burden of CVD risk factors using the most contemporary data available. The data collection period spanned from 1998 to 2005 and rates of treatment or control of CVD risk factors may have changed during this period. Participants of the Offspring cohort were followed for several years and may have benefited with respect to risk factor reduction as the findings of each examination are reviewed and letters are sent to the physician. However, our rates of treatment and control of CVD risk factors are similar to data from national surveys,[22] suggesting that the rates of treatment and control mirror national data. Further, the data in the present study from the Third Generation cohort represent their first examination, minimizing this concern. The Framingham Heart Study Offspring and Third Generation cohort participants are primarily white, therefore the generalizability of our findings to other racial groups may be limited. Lastly, we did not examine the reasons for low rates of treatment and control.

Conclusion

Rates of treatment and control of CVD risk factors are suboptimal among overweight and obese individuals in the Framingham Heart Study.

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Appendix Table 1 Age- and sex-adjusted rates of hypertension, elevated levels of low-density lipoprotein cholesterol, type 2 diabetes, treatment and control among waist circumference categories

	% of Participants (95% CI)		p-value*
	WC <88 OR 102 N=3558	WC ≥88 OR 102 N=3243	
Hypertension			
Prevalence	13.5 (12.3-14.8)	33.0 (31.0-35.1)	<0.001
Treatment	54.2 (47.6-60.6)	63.9 (59.0-68.5)	0.009
Control	36.7 (31.7-41.9)	38.6 (35.2-42.2)	0.78
Elevated LDL-C			
Prevalence	16.3 (15.0-17.7)	33.0 (31.0-35.1)	<0.001
Treatment	33.7 (29.4-38.3)	39.2 (35.6-42.8)	0.05
Control	24.5 (20.8-28.4)	29.0 (26.0-32.1)	0.09
Diabetes			
Prevalence	1.8 (1.3-2.2)	8.9 (7.9-10.0)	<0.001
Treatment	62.5 (40.6-81.2)	53.3 (44.6-61.9)	0.19
Hb A1c <7% †	55.6 (30.8-78.5)	50.5 (40.3-60.7)	0.75
FPG <126 mg/dL	25.5 (13.9-40.4)	16.9 (12.5-22.2)	0.08

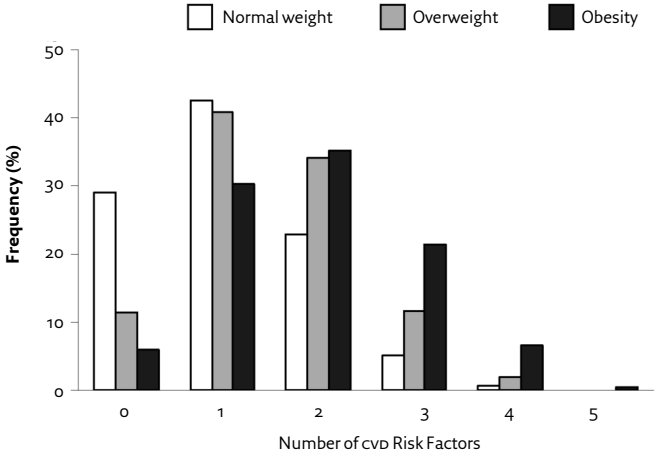
Abbreviations: CI, confidence interval; WC, waist circumference; LDL-C, low-density lipoprotein cholesterol; Hb A1c, Hemoglobin A_{1c} level; fpg, fasting plasma glucose

SI conversion factor: To convert fasting plasma glucose to mmol/L, multiply mg/dL values by 0.0555

** Global GEE p-value*

† Data only available for Offspring cohort

Appendix Figure 1 Percentage of participants with 0 to 5 risk factors for cardiovascular disease (CVD) stratified by body mass index category. Risk factors for CVD include hypertension, elevated levels of low-density lipoprotein cholesterol, type 2 diabetes, low levels of high-density lipoprotein cholesterol, and smoking.



Appendix Table 2 Sex-adjusted rates of hypertension, elevated levels of low lipoprotein cholesterol, type 2 diabetes, treatment and control among BMI categories, stratified by age

		% of Participants (95% CI)			
		BMI 18.5-<25 N=1548	BMI 25-<30 N=1327	BMI ≥30 N=828	p-value*
<50 year	Hypertension				
	Prevalence	4.7 (3.7-5.9)	12.3 (10.4-14.3)	27.4 (23.9-31.2)	<0.001
	Treatment	40.5 (25.6-56.7)	43.3 (33.3-53.8)	45.9 (36.9-55.2)	0.26
	Control	28.6 (16.6-43.3)	33.9 (25.4-43.2)	30.8 (23.8-38.6)	0.99
	Elevated LDL-C				
	Prevalence	6.0 (4.9-7.4)	17.0 (14.8-19.3)	24.3 (21.0-28.0)	<0.001
	Treatment	23.2 (13.9-34.9)	36.4 (29.0-44.2)	30.6 (23.2-39.8)	0.48
	Control	18.4 (10.5-29.0)	29.1 (22.5-36.3)	25.5 (18.9-33.0)	0.34
	Diabetes				
	Prevalence	†	1.4 (0.8-2.2)	5.6 (4.1-7.5)	<0.001 ‡
	Treatment	†	50.0 (11.8-88.2)	39.3 (21.5-59.4)	0.006 ‡
	FPG <126 mg/dL	†	36.4 (10.9-69.2)	15.4 (5.9-30.5)	0.02 ‡
50+ year	Hypertension				
	Prevalence	26.2 (22.9-29.8)	39.7 (36.1-43.4)	54.1 (49.0-59.1)	<0.001
	Treatment	67.4 (56.8-76.8)	67.5 (59.7-74.6)	74.1 (66.0-81.2)	0.006
	Control	37.9 (30.5-45.6)	37.8 (32.5-43.3)	42.5 (36.9-48.3)	0.69
	Elevated LDL-C				
	Prevalence	27.6 (24.1-31.2)	45.7 (41.9-49.5)	51.5 (46.5-56.4)	<0.001
	Treatment	38.5 (31.1-46.2)	36.1 (31.2-41.3)	44.0 (38.1-50.0)	0.03
	Control	29.7 (23.3-36.7)	24.5 (20.5-28.8)	30.6 (25.7-35.7)	0.18
	Diabetes				
	Prevalence	3.2 (2.1-4.6)	7.2 (5.8-8.8)	18.4 (15.7-21.4)	<0.001
	Treatment	61.5 (31.6-86.1)	48.8 (32.9-64.9)	58.9 (46.8-70.3)	0.43
	FPG <126 mg/dL	27.3 (10.7-50.2)	17.3 (9.6-28.2)	15.8 (10.3-22.7)	0.26

Abbreviations: CI, confidence interval; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; Hb A1c, Hemoglobin A_{1c} level; FPG, fasting plasma glucose

SI conversion factor: To convert fasting plasma glucose to mmol/L, multiply mg/dL values by 0.0555

** Global GEE p-value*

† Among participants younger than 50 years of age with a BMI 18.5-<25, there were only 5 individuals with type 2 diabetes. Of those, 5 received hypoglycemic treatment and 3 had FPG <126 mg/dL

‡ Interpret p-value with caution as there are only small number in the cells of participants younger than 50 years of age with a BMI 18.5-<25

Appendix Table 3 Age-adjusted rates of hypertension, elevated levels of low-density lipoprotein cholesterol, type 2 diabetes, treatment and control among BMI categories, stratified by sex

		% of Participants (95% CI)			
		BMI 18.5-<25 N=1727	BMI 25-<30 N=1093	BMI ≥30 N=866	p-value*
Women	Hypertension				
	Prevalence	10.1 (8.6-11.7)	20.8 (18.0-23.8)	34.7 (30.6-39.1)	<0.001
	Treatment	64.0 (52.1-74.8)	67.4 (56.8-76.8)	68.4 (59.1-76.8)	0.15
	Control	37.9 (29.6-46.7)	38.3 (31.1-45.9)	41.0 (34.4-47.9)	0.83
	Elevated LDL-C				
	Prevalence	10.4 (8.9-12.0)	22.8 (20.0-25.8)	30.2 (26.4-34.2)	<0.001
	Treatment	39.0 (30.4-48.2)	39.1 (31.7-46.8)	40.7 (33.4-48.3)	0.53
	Control	33.1 (25.3-41.7)	30.3 (23.9-37.2)	31.1 (24.9-37.9)	0.74
	Diabetes				
	Prevalence	1.2 (0.8-1.9)	3.5 (2.5-4.8)	12.0 (9.8-14.5)	<0.001
	Treatment	62.5 (24.5-91.5)	62.5 (35.4-84.8)	57.5 (42.2-71.7)	0.51 †
	FPG <126 mg/dL	30.8 (9.1-61.4)	32.3 (16.7-51.4)	12.8 (6.8-21.2)	<0.001
Men	Hypertension				
	Prevalence	14.8 (12.1-17.9)	24.4 (21.9-27.1)	40.3 (35.9-44.8)	<0.001
	Treatment	50.9 (37.3-64.4)	53.5 (45.7-61.1)	56.9 (48.4-65.0)	0.006
	Control	33.3 (23.4-44.5)	36.1 (30.3-42.1)	36.8-(30.8-43.2)	0.30
	Elevated LDL-C				
	Prevalence	18.6 (15.5-22.1)	32.9 (29.9-36.0)	41.1 (36.6-45.8)	<0.001
	Treatment	28.3 (20.2-37.6)	34.9 (30.0-40.0)	38.9 (32.8-45.3)	0.009
	Control	18.5 (12.2-26.2)	23.9 (19.9-28.2)	27.9 (22.8-33.4)	0.009
	Diabetes				
	Prevalence	1.7 (0.9-2.9)	4.5 (3.5-5.7)	11.8 (9.6-14.3)	<0.001
	Treatment	80.0 (28.4-99.5)	43.8 (26.4-62.3)	52.8 (38.6-66.7)	0.90
	FPG <126 mg/dL	40.0 (12.2-73.8)	14.3 (6.4-26.2)	17.8 (10.5-27.3)	0.40

Abbreviations: CI, confidence interval; BMI, body mass index; ldl-c, low-density lipoprotein cholesterol; Hb A1c, Hemoglobin A_{1c} level; FPG, fasting plasma glucose

SI conversion factor: To convert fasting plasma glucose to mmol/L, multiply mg/dL values by 0.0555

** Global GEE p-value*

† Global ANOVA p-value

CHAPTER 4

Intensive Lipid-lowering Therapy Provides Increased Benefit in Acute Coronary Syndrome Patients with Overweight: a PROVE IT-TIMI 22 *Analysis*

ABSTRACT

BACKGROUND Excess weight may influence the impact of intensive vs. moderate statin therapy in patients with acute coronary syndrome (ACS). The benefit of different statin regimens on cardiovascular outcomes in normal weight and overweight patients has not been well studied.

METHODS The PROVE-IT TIMI 22 trial compared intensive (atorvastatin 80 mg) and moderate statin therapy (pravastatin 40 mg) in patients stabilized from ACS. We used cox proportional hazard models to assess the effect of intensive vs. moderate therapy in normal weight (body mass index (BMI) 18.5-<25 kg/m^2; n=757) and overweight or obese (BMI ≥25 kg/m^2; n=3223) patients. The primary end point was a composite of death, myocardial infarction (MI), unstable angina, revascularization and stroke.

RESULTS The primary end point was significantly reduced with intensive vs. moderate therapy in overweight or obese patients (21.5% vs. 26.3%, hazard ratio (HR) =0.81, 95% CI 0.70-0.93; p=0.004), while no reductions were observed in normal weight patients (26.7% vs. 25.2%, HR=1.02, 95% CI 0.77-1.35; p=0.88) during 2 years of follow-up (test for interaction p=0.14). With intensive therapy, the number needed to treat (NNT) among overweight patients to prevent one event was twenty-one, compared to twenty-eight in the overall trial. The effects were consistent among overweight and obese subgroups as well as across secondary clinical endpoints.

CONCLUSION Compared to normal weight patients with ACS, overweight and obese patients appear to derive an increased benefit from intensive statin therapy on cardiovascular outcomes. In view of the increasing burden of obesity and its cardiovascular risk these observations merit further investigation.

INTRODUCTION

The prevalence of overweight has reached epidemic proportions in developed countries and is rapidly increasing in developing countries as well.[1] More than half of the adults in the United States are overweight or obese.[2] Obesity is a well-known risk factor for the development[3] and progression of coronary artery disease (CAD),[4] in part due to the strong relation between excess weight and atherogenic dyslipidemia.[5] Key features of atherogenic dyslipidemia include raised triglycerides, reduced HDL cholesterol, and increased numbers of small, dense LDL particles but not necessarily elevated LDL cholesterol (LDL-C).[6] In addition, inflammatory mechanisms may contribute to an increased risk of CAD in overweight individuals.[7]

Data from several large, randomized trials have established the efficacy and safety of statins in reducing LDL-C and cardiovascular risk.[8-10] In addition, the increased clinical benefit of intensive lipid-lowering therapy in patients with stable CAD[11,12] and acute coronary syndrome (ACS)[13-15] has been demonstrated. Importantly, several lines of evidence indicate that statins have direct anti-inflammatory properties that extend beyond their lipid lowering effects.[16,17] This suggests that overweight individuals in particular may benefit from high-dose statin therapy. Moreover, we have recently demonstrated that despite higher rates of lipid-lowering therapy among obese individuals in the community with elevated LDL-C as compared to normal or overweight individuals, the rates of control of LDL-C did not differ.[18] These results suggest it may be more difficult to achieve LDL-C treatment goals with a standard statin regimen in obese individuals and an intensive regimen may provide increased benefit. However, to date it is not clear whether intensive therapy confers increased clinical benefit among overweight individuals.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) Thrombolysis in Myocardial Infarction (TIMI) 22 trial demonstrated a greater protection against cardiovascular complications in ACS patients with intensive versus moderate statin therapy.[13] We analyzed data from PROVE-IT TIMI 22 to assess the influence of body mass index (BMI) on the impact of intensive vs. moderate statin therapy on cardiovascular outcomes in patients with ACS.

METHODS

This is a subgroup analysis based on data from PROVE-IT TIMI 22, a randomized trial that compared the effects of an intensive lipid-lowering statin regimen (atorvastatin 80 mg) with a moderate statin regimen (pravastatin 40 mg) on the protection against recurrent coronary events among patients with ACS. Details of the overall PROVE-IT TIMI 22 trial design[19] and principal findings have been previously described.[13] In brief, between November 2000 and December 2001, 4162 patients stabilized following ACS were enrolled at 349 sites in eight countries and were followed for 18 to 36 months, with an average follow-up of 24 months. Eligible patients were randomly assigned in a 1:1 ratio to receive 40 mg of pravastatin or 80 mg of atorvastatin daily. Follow-up visits took place at 30 days, 4 months, and every 4 months thereafter until the final visit. Plasma samples for analysis of lipid profiles and high-sensitivity C-reactive protein (hsCRP) were obtained at randomization, after 30 days, and after 4, 8 and 16 months of treatment.

Patient population

Patients were eligible for the study if they had been hospitalized for an acute myocardial infarction or high-risk unstable angina in the preceding 10 days, had a total cholesterol level of 240 mg/dl or less, and a stable condition at the time of enrollment. Exclusion criteria included current statin therapy at a dose of 80 mg/day, or current lipid-lowering therapy with fibric acid derivatives or niacin. For the purpose of this analysis, patients with a BMI <18.5 kg/m^2 or missing data for height and/or weight (n=182) were excluded, resulting in 3980 eligible patients.

Anthropometry

Height and weight were measured at baseline. BMI was calculated by dividing weight in kilograms by the square of the height in meters. There was no stratification of randomization based on BMI.

Biochemical parameters

For this analysis, the achieved levels of LDL-C and hsCRP with statin therapy were defined as the levels at 30 days. This provides an adequate time period to observe the effects of statin therapy on both LDL-C and hsCRP in the absence of any residual ischemic influences.

Clinical endpoints

The primary endpoint was death from any cause, myocardial infarction (MI), unstable angina requiring rehospitalization, revascularization (occurring at least 30 days following randomization), or stroke assessed from randomization through follow-up. Secondary endpoints included death from coronary heart disease, nonfatal MI, or revascularization (at least 30 days post randomization). All clinical endpoints presented were adjudicated by an independent clinical events committee blind to treatment assignment.

Data analysis

All analyses were based on the intention-to treat principle. Patients were categorized in two BMI subgroups according to the World Health Organization/National Institutes of Health classification scheme:[20] normal weight (BMI 18.5-<25 kg/m^2) and overweight or obese (BMI ≥25 kg/m^2), the combination of overweight and obese is simply indicated as overweight for this analysis. Baseline characteristics of the patients in the BMI subgroups were compared using the chi-square test and Wilcoxon rank sum test, as appropriate.

Cox proportional hazard models were used for the analysis of the clinical endpoints comparing intensive with moderate statin therapy, with randomized treatment as the covariate and stratification according to BMI subgroup. Estimates of the hazard ratios (HR) and corresponding 95 percent confidence intervals (95% CI) are presented. In addition, for both treatments the number of patients who need to be treated to prevent endpoint events (NNT) were calculated, stratified by BMI category. To investigate whether statin therapy and overweight interact on the risk of clinical endpoints, hazard ratios with 95% CI were calculated for the combination of the two treatments (i.e. 80 mg Atorvastatin and 40 mg Pravastatin) with the two BMI subgroups. In secondary analyses, the overweight subgroup was further categorized in moderate overweight (BMI 25-<30 kg/m^2), and severe overweight or obesity (BMI ≥30 kg/m^2). All analyses were conducted using STATA/SE 9.2 (College Station, TX, USA).

RESULTS

Baseline characteristics

Overall, 19% of the patients were normal weight and 81% were overweight, including 39% who were obese. Compared with normal weight patients,

Table 1 Baseline characteristics of the patients

	BMI 18.5-<25		BMI ≥25	
	Atorvastatin 80 mg	**Pravastatin 40 mg**	**Atorvastatin 80 mg**	**Pravastatin 40 mg**
	N=383	**N=374**	**N=1623**	**N=1600**
Age, years	60.5±12.1	60.3±11.8	57.4±10.8	57.9±11.0
Female sex (%)	25.3	26.2	20.8	20.6
White race (%)	91.4	90.4	90.8	90.6
Current smoker (%)	46.0	46.5	34.1	34.8
BMI, kg/m²	22.9±1.5	23.1±1.5	31.2±5.2	31.0±5.2
Diabetes mellitus (%)	9.7	8.6	19.8	19.9
Hypertension (%)	42.8	36.1	53.7	51.9
Peripheral vascular disease (%)	7.6	8.3	4.4	6.1
Prior MI (%)	15.9	20.9	18.1	18.8
Percutaneous coronary intervention before index event (%)	13.3	15.5	16.0	16.1
Coronary bypass surgery before index event (%)	11.2	9.9	11.4	11.1
Index event (%)				
Unstable angina	25.6	21.1	29.7	31.3
MI without ST-segment elevation	30.0	38.8	36.7	36.8
MI with ST-segment elevation	44.4	40.1	33.6	31.9
Medications before ACS event (%)				
Statins	21.2	21.1	26.4	25.9
Fibrates	1.0	0.8	1.0	1.8
Beta-blockers	21.7	22.2	24.7	25.3
Calcium channel blockers	13.6	12.9	17.8	17.5
Angiotensin receptor blocker	3.7	4.0	6.5	5.5
Aspirin	30.3	34.0	35.9	35.5
Insulin	1.8	1.3	3.6	4.3
Oral hypoglycemic agents	6.8	5.9	14.8	15.7
Lipid values (median (IQR))				
Total cholesterol, mg/dL	177 (154, 199)	177 (158, 201)	181 (162, 205)	180 (159, 203)
LDL cholesterol, mg/dL	104 (86, 125)	106 (87, 127)	106 (89, 128)	106 (88, 127)
LDL cholesterol, mg/dL	40 (34, 48)	41 (35, 49)	38 (32, 45)	38 (32, 45)
Triglycerides, mg/dL	135 (104, 171)	134 (101, 181)	164 (124, 221)	159 (120, 214)
hsCRP, mg/L (median (IQR))	10.6 (4.3, 26.7)	11.9 (4.2, 29.3)	12.5 (4.9, 28.8)	12.3 (5.5, 29.4)
apoB, mg/L (median (IQR))	97 (83, 115)	98 (83, 114)	102 (89, 118)	103 (88, 117)

overweight patients were younger, less often female, had more often diabetes and hypertension, but less frequently peripheral vascular disease, and smoked less often (Table 1). The index event in overweight patients was more often highrisk unstable angina, myocardial infarction without electrocardiographic evidence of ST-segment elevation, and less often myocardial infarction with ST-elevation than in normal weight patients. The use of medications prior to ACS was higher in overweight patients. Median baseline LDL-C levels were similar in patients with and without overweight. The median HDL-C levels were lower in overweight patients than normal weight patients, whereas the median triglyceride, hsCRP and APOB levels were higher in overweight patients at baseline.

Achieved LDL-C, high-sensitivity c-reative protein

In overweight patients, median LDL-C levels were reduced to 56 mg/dL (interquartile range 44, 71) with intensive statin therapy, compared to 89 mg/dL (72, 107) with moderate therapy by 30 days ($p<0.0001$, Table 2). This represents a fall of 47% and 18% in baseline LDL-C respectively (Figure 1). Similar absolute and relative reductions in median LDL-C with intensive versus moderate therapy were obtained in normal weight patients.

Median hsCRP levels fell to 1.7 mg/dL (interquartile range 0.8, 3.8) with intensive therapy, and to 2.4 mg/dL (1.2, 4.9) with moderate therapy ($p<0.0001$) in overweight patients (Table 2), representing a fall of 83% and 78% respectively (Figure 1). The median hsCRP levels achieved were slightly lower in normal weight patients with intensive as well as moderate therapy (1.3 mg/dL [0.5, 2.9] vs. 1.8 [0.8, 3.9], $p=0.0007$). This corresponds to an 88% and 85% reduction in baseline hsCRP respectively.

Clinical endpoints

In patients with overweight, the event rate of the primary endpoint after two years of follow-up was 21.5% with intensive statin therapy and 26.3% with moderate therapy, representing a 19% reduction in the hazard ratio (HR) in favor of intensive statin therapy (HR= 0.81, 95% CI 0.70-0.93, $p=0.004$;

Belonging to table 1

Abbreviations: BMI, body mass index; MI, myocardial infarction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity c-reactive protein; APOB, apolipoprotein b.

SI conversion factors: To convert cholesterol to mmol/L, multiply mg/dL values by 0.02586. To convert triglycerides to mmol/L, multiply mg/dL values by 0.01129.

Table 2 Effect of statin treatment on lipoprotein, triglycerides and high-sensitivity c-reactive protein levels*

	Atorvastatin 80 mg	Pravastin 40 mg	p-value
LDL-C, mg/dL			
BMI 18.5-<25			
Baseline	104 (86, 125)	106 (87, 127)	0.72
Achieved	58 (45, 74)	87 (72, 107)	<0.0001
BMI≥25			
Baseline	106 (89, 128)	106 (88, 127)	0.41
Achieved	56 (44, 71)	89 (72, 107)	<0.0001
HDL-C, mg/dL			
BMI 18.5-<25			
Baseline	40 (34, 48)	41 (35, 49)	0.26
Achieved	41 (34, 48)	44 (37, 52)	0.0001
BMI≥25			
Baseline	38 (32, 45)	38 (32, 45)	0.53
Achieved	37 (31, 44)	40 (33, 47)	<0.0001
TG, mg/dL			
BMI 18.5-<25			
Baseline	135 (104, 171)	134 (101, 181)	0.84
Achieved	95 (72, 122)	119 (89, 175)	<0.0001
BMI≥25			
Baseline	164 (124, 221)	159 (120, 214)	0.051
Achieved	114 (85, 158)	143 (105, 208)	<0.0001
hsCRP, mg/L			
BMI 18.5-<25			
Baseline	10.6 (4.3, 26.7)	11.9 (4.2, 29.3)	0.64
Achieved	1.3 (0.5, 2.9)	1.8 (0.8, 3.9)	0.0007
BMI≥25			
Baseline	12.5 (4.9, 28.8)	12.3 (5.5, 29.4)	0.33
Achieved	1.7 (0.8, 3.8)	2.4 (1.2, 4.9)	<0.0001

** Values are expressed as median (IQR); achieved level is the level by 30 days.*

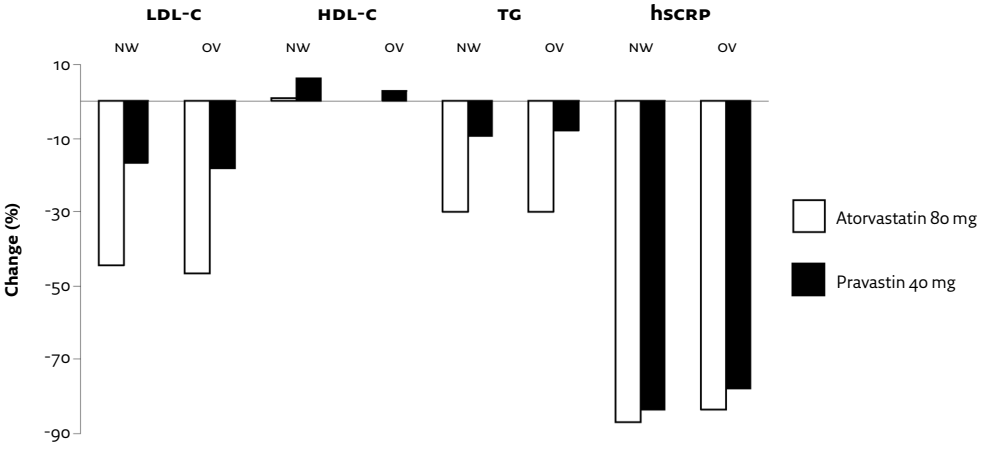
Abbreviations: LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; TG, triglycerides; hsCRP, high-sensitivity C-reactive protein; BMI, body mass index

Figure 2). With intensive therapy, the NNT among overweight patients to prevent one event was twenty-one. In contrast, the two-year event rate of the primary endpoint in normal weight patients were similar for the intensive and moderate statin regimen (26.7% vs. 25.2%, HR=1.02, 95% CI 0.77-1.35; p=0.88). However, a formal test for the interaction between overweight and statin therapy was not statistically significant (p=0.14). The secondary endpoint of death from coronary heart disease, nonfatal MI, or revascularization demonstrated a similar pattern with a reduced risk in overweight patients treated with a high-dose versus a moderate-dose statin (19.2% vs. 22.5%, HR=0.83, 95% CI 0.71-0.97; p=0.017), but no reductions among normal weight patients (22.6% vs. 20.7%, HR=1.08, 95% CI 0.79-1.47; p=0.63).

Secondary analyses

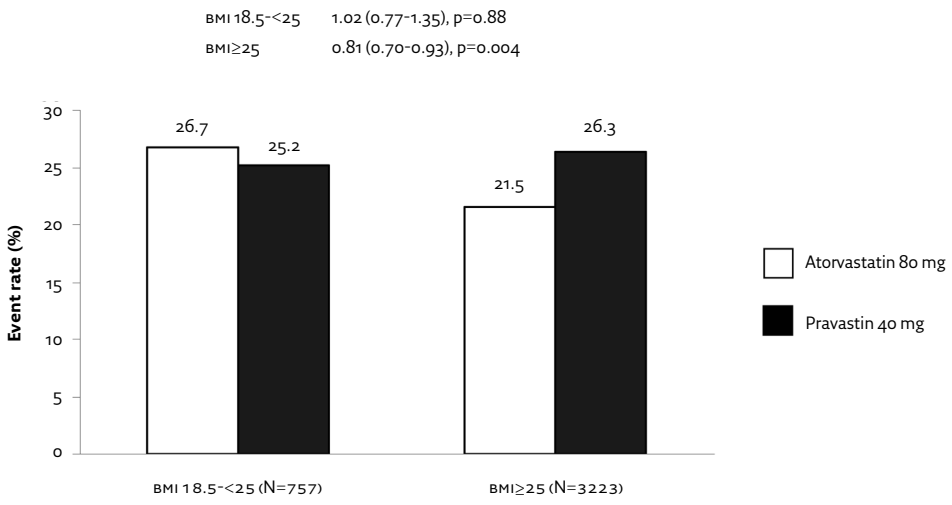
When the overweight category was further broken down, the benefit of intensive versus moderate statin therapy was consistent among patients with moderate overweight (21.6% vs. 27.6%, HR=0.77, 95% CI 0.64-0.94; p=0.011, p for interaction=0.11) and those with obesity (21.3% vs. 24.8%, HR=0.85, 95% CI 0.69-1.05; p=0.13, p for interaction=0.31).

Figure 1 Percentage change in lipoprotein, triglycerides and high-sensitivity C-reactive protein levels after 30 days in normal weight and overweight ACS patients treated with intensive vs. standard statin therapy.



Abbreviations: LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; TG, triglycerides; hsCRP, high-sensitivity C-reactive protein; NW, normal weight; OV, overweight

Figure 2 Kaplan Meier estimates of the primary end point by 2 years in normal weight and overweight ACS patients treated with intensive vs. standard statin therapy. Primary endpoint was a composite of death, MI, unstable angina, revascularization and stroke. p=0.14 for overweight and treatment interaction.



DISCUSSION

In this analysis of the PROVE-IT TIMI 22 trial, an intensive statin regimen with high-dose atorvastatin compared with a moderate regimen with pravastatin resulted in greater reductions of baseline LDL-C and hsCRP to a similar degree in both overweight and normal weight patients with recent ACS. Among overweight patients, intensive therapy resulted in a lower risk of death and cardiovascular complications than did moderate therapy, whereas no significant reduction was apparent among normal weight patients. While statistical interaction did not reach formal significance levels, overweight patients appeared to derive a larger absolute benefit from intensive therapy. It was estimated that one acute cardiac event was prevented for every twenty-one patients with overweight treated with a high-dose statin for two years, compared to twenty-eight patients in the overall trial. In normal weight patients, no reduction was observed with an intensive statin regimen.

Some aspects of the present study need to be addressed to interpret our findings. First, the analysis of BMI subgroups was not pre-specified in the

study protocol. Second, BMI was only assessed at baseline while body weight may have changed during the follow-up period. Despite the large number of subjects in the trial for a post-ACS population, the relative small number of patients with normal weight may have limited the power to detect a significant interaction in the response to the intensive therapy between overweight and normal weight patients. Nevertheless, the high prevalence of overweight among the ACS population in our analysis (81%) was in a similar range as contemporary studies (71-73 %).[21,22]

Despite the markedly high prevalence of overweight[2] and its strong association with CAD,[3,4] little is known about the efficacy of statins on cardiovascular outcomes in overweight patients with ACS. The present analysis of PROVE-IT TIMI 22 trial data is the first to address this issue. The consistently larger treatment effects among overweight subgroups and across secondary clinical endpoints strengthens the idea that overweight patients derive more benefit from intensive therapy. Further analyses of other secondary prevention, as well as primary prevention, statin trials are needed to confirm whether, and to what extent, intensive statin therapy is superior to moderate therapy in terms of cardiovascular risk reduction in the large group of overweight patients.

Results from trials examining the benefit of statins on intermediate markers of CAD across different BMI subgroups have been published. The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, a randomized controlled trial of 502 patients 30 to 75 years of age with CAD, showed that obese individuals derived more benefit as compared to non-obese individuals from an intensive lipid-lowering strategy with atorvastatin on progression of coronary atherosclerosis as measured by intravascular ultrasound.[23] A recent randomized controlled trial of 984 middle-aged individuals with low Framingham risk scores and evidence of subclinical atherosclerosis demonstrated that 40 mg rosuvastatin therapy reduced the rate of progression of carotid intima-media thickness over 2 years with consistent results across BMI groups.[24]

The finding that intensive therapy versus moderate therapy resulted in similar reductions of baseline LDL-C among overweight and normal weight patients is consistent with observations from a meta-analysis of 5 lipid-lowering trials in hypercholesterolemic patients that found similar effects of 10 mg rosuvastatin on plasma lipids among obese patients and the overall population.[25] In the REVERSAL study, obese patients had lower relative reductions in LDL-C with intensive therapy compared to non-obese patients.[23] These data combined could imply that the same level and change

in serum lipids has a larger vascular impact in the presence of obesity. Alternatively, the data may support the importance of nonlipid-lowering properties ('pleiotropic effects') of intensive statin therapy[26] and suggest that statins may modulate the inflammatory state that characterizes overweight patients.

In conclusion, compared to normal weight patients stabilized from ACS, intensive statin therapy appears to provide an increased clinical benefit in overweight or obese patients. Our findings lend support to the view that a more aggressive statin regimen may play an important role in the strategy to prevent recurrent coronary events in the presence of overweight.

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CHAPTER 5

Association of Lifestyle Factors with Abdominal Subcutaneous and Visceral Adiposity: the Framingham Heart Study

ABSTRACT

BACKGROUND Abdominal adiposity, particularly visceral adipose tissue (VAT), is strongly associated with cardiometabolic risk. The relationship between lifestyle factors and abdominal subcutaneous adipose tissue (SAT) and VAT has not been well studied in a community-based setting.

METHODS Cross-sectional associations between lifestyle factors (dietary quality, physical activity, smoking and alcohol consumption) and SAT and VAT volumes, were examined in 2926 Framingham Heart Study participants (48.6% women, age 50±10 years).

RESULTS Diet consistent with the 2005 Dietary Guidelines for Americans and greater physical activity were inversely associated with SAT and VAT (p-value<0.0001 to 0.002). In men, former smoking was associated with higher SAT (2743±56 cm^3) as compared to current (2629±88 cm^3) or never smokers (2538±44 cm^3; p=0.02). Both former and current smoking was associated with higher VAT (p=0.03 [women]; p=0.005 [men]). Women with high amounts of alcohol intake (>7 drinks/week) had lower SAT (2869±106 cm^3) than those who consumed less (3184±44 cm^3, p=0.006); significant differences in VAT were not observed (p=0.18). In men, high amounts of alcohol intake (>14 drinks/week) were associated with higher VAT (2272±59 cm^3) compared to ≤14 drinks/week (2139±25 cm^3, p=0.04), whereas SAT did not differ (p=0.91). An increasing number of healthy lifestyle factors was associated with lower SAT and VAT volumes (all p-values<0.003).

CONCLUSION A healthy diet and physical activity are associated with lower SAT and VAT volumes. However, both smoking and high alcohol intake are differentially associated with higher VAT volumes. Further research to uncover the putative mechanisms is warranted.

INTRODUCTION

Abdominal adiposity is strongly associated with metabolic and cardiovascular (CVD) risk.[1,2] Visceral adipose tissue (VAT) in particular may be a pathogenic fat compartment.[3] Numerous studies have demonstrated that central obesity is associated with lifestyle factors.[4-8] However, the majority of these studies used waist circumference as a proxy for abdominal obesity, which does not allow to differentiate between subcutaneous adipose tissue (SAT) and VAT. As VAT is more strongly associated with metabolic risk factors than SAT,[1] it is important to identify whether VAT is more correlated with lifestyle factors. This may provide more understanding of the relationship between a healthy lifestyle and VAT and the contribution of individual lifestyle factors to cardiometabolic risk.

Thus, the aim of the present study is to examine the relation between lifestyle factors (dietary quality, physical activity, smoking and alcohol consumption) and SAT and VAT volumes, as assessed by multidetector computed tomography (MDCT), in a large population-based cohort of women and men free of CVD.

METHODS

Study sample

Participants for this study were part of the Framingham Heart Study MDCT Study, a sub-study of the population-based Framingham Heart Offspring and Third Generation Study. Starting in 1948, 5209 men and women were enrolled in the original cohort of the Framingham Heart Study. In 1971, the offspring and spouses of the offspring of the original cohort enrolled in the Framingham Offspring Study. Selection criteria and study design have been described previously.[9] Beginning in 2002, 4095 adults who had at least one parent in the Offspring cohort, were enrolled into the Framingham Heart Third Generation Study and underwent standard clinic examinations.[10] The examination included a physician interview, a physical examination, and

laboratory tests. The study sample for the current study consisted of women and men from the Offspring and Third Generation Study cohorts who participated in the MDCT study. The study protocol was approved by the institutional review boards of the Boston University Medical Center and Massachusetts General Hospital. All subjects provided written informed consent prior to study participation.

In total, 1418 Offspring and 2111 Third Generation participants underwent MDCT measurements of coronary and aortic calcium between June 2002 to April 2005; subcutaneous and visceral fat measures were ascertained secondarily after study completion. Inclusion criteria's have been previously described.[11] Of the total of 3529 participants imaged, 3394 had interpretable CT measures, 3370 of those had both SAT and VAT measured, 3164 of those were free of CVD, 3142 of those attended the contemporaneous examination, and 3141 of those had at least one of the lifestyle factor variables. Of these 3141 participants, 2926 had a complete covariate profile. Data on dietary intake was only available in a subset of the Offspring cohort (n=925 participants).

Abdominal adipose tissue measurement

Imaging of the chest and abdomen was performed using a 8-slice MDCT (LightSpeed Ultra, General Electric, Milwaukee, WI) as previously described.[12] Briefly, 25 contiguous five mm thick slices (120 kVp, 400 mA, gantry rotation time 500 ms, table feed 3:1) were obtained covering 125 mm above the level of S1. Volumes of SAT and VAT were assessed (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA) as previously described. Briefly, fat pixels were identified (image display window width -195 to -45 Hounsfield Units (HU); window center of -120 HU) and the abdominal muscular wall was manually traced to separate the visceral from the subcutaneous compartment.[12] Inter-reader reproducibility was high, with inter-class correlations of 0.992 for VAT and 0.997 for SAT.[12]

Lifestyle factors and covariate assessment

Lifestyle factors and covariates were measured at the contemporaneous examination cycles.

Diet. Dietary intake was assessed using a semi-quantitative food frequency questionnaire consisting of 126 items developed by Willet et al.[13] Subsequently, the recently validated 2005 Dietary Guidelines Adherence Index (DGAI)[6] was used as a summary measure of adherence to the 2005 Dietary Guidelines for Americans.[14] Briefly, the DGAI consists of a total of 20

items. Eleven index items assess adherence to energy-specific food intake recommendations and nine assess adherence to healthy choice nutrient intake recommendations. Each item is scored from a minimum of zero to a maximum of one, with a maximum score of 20 points.

Physical activity. Habitual physical activity was assessed using a structured questionnaire. Subsequently the average daily number of hours at different levels of activity (sleep, sedentary, slight, moderate, and heavy activity) was determined. A physical activity index (PAI) score was calculated by summing the reported numbers for each level of activity, weighted by their estimated metabolic expenditure, as previously described.[15] The PAI ranges from a minimum score of 24, indicating 24 hours of sleeping, to a maximum score of 120, indicating 24 hours of heavy physical activity.[15]

Smoking. Participants were questioned in detail about current and prior cigarette smoking habits and were considered to be current smokers if they reported smoking at least one cigarette per day for the last year, former smokers if they were not smoking at present but had previously smoked as much as one cigarette per day for as long as a year, and never smokers if they smoked neither at present nor in the past. In addition, cumulative exposure pack-years of smoking was calculated by multiplying the number of cigarettes smoked per day by number of years smoked. One pack-year was equivalent to one cigarette pack per day for 1 year.

Alcohol consumption. Information on the amount of alcohol consumption was obtained from a physician-administered questionnaire in which participants were asked to report on the average number of drinks per week over the previous year. Based on current alcohol guidelines,[14] women consuming ≤7 drinks/week and men consuming ≤14 drinks/week were defined as light-to-moderate drinkers; participants exceeding these cutoff points were defined as high alcohol consumers.

Healthy lifestyle factors. Healthy lifestyle habits were defined as the upper quartile of the PAI, abstinence from smoking and moderate alcohol consumption (1-≤7 drinks/week for women, 1-≤14 drinks/week for men).[14] Quartiles were selected for ease of data presentation.

Covariates. Women were considered to be menopausal if their periods had stopped for at least one year. Information on hormone replacement therapy was obtained from the physician-administered questionnaire. Information on education was obtained by asking the participants to report on their highest educational level attained.

Statistical Analysis

SAT and VAT were normally distributed. In addition, the lifestyle factors - with the exception of pack years of smoking - were normally distributed. Multivariable linear regression was used to assess the significance of covariate-adjusted cross-sectional relations between the continuous lifestyle factors (DGAI and PAI) and SAT and VAT. We estimated the covariate-adjusted mean volume of SAT and VAT associated with a 1 standard deviation (SD) higher DGAI and PAI. For the categorical lifestyle factors (smoking and alcohol), least square means were calculated to assess the relative amounts of SAT and VAT in current, former and never smokers and by categories of alcohol consumption; ANOVA p-values are presented. All models were adjusted for age, menopause, hormone replacement therapy, education, alcohol, and smoking. All analyses were sex-specific given our prior observation that relations between metabolic risk factors and VAT were stronger in women than in men.[11] Tests for the significance of the difference between the beta coefficients of the lifestyle factors in the models with SAT vs. the models with VAT as outcome (in which SAT and VAT were first standardized to a mean of 0 and a SD of 1) were performed in situations where SAT and VAT were both associated with the individual lifestyle factor. To determine the relation between the number of healthy lifestyle factors and SAT and VAT, age-adjusted mean volumes of SAT and VAT associated with practicing 0, 1, 2 or 3 healthy lifestyle habits were calculated; age-adjusted p-values for trend were calculated as well.

Secondary analyses were performed. Pack years of smoking was log transformed. The covariate-adjusted mean volume of SAT and VAT associated with a 1 SD higher log pack years of smoking was estimated, separately for current and former smokers. Alcohol consumption was redefined and further subdivided into the following six groups of average alcoholic drinks per week: none, <1, 1-<4, 4-7, >7-14 and >14 drinks/week. ANOVA p-values and p-values for quadratic trends to test for a U-shape relation were calculated. Physical activity was included as an additional covariate in all models. The above multivariable regressions and least square means were repeated using the general estimating equation procedure to account for familial correlations in the study sample. Interactions for the associations between the individual lifestyle factors and SAT and VAT with age (equal or above/below the median age of 50 years) and BMI (<25, 25-<30, ≥30 kg/m^2) were tested in multivariable adjusted models.

SAS version 8.0 was used to perform all computations;[16] a two-tailed p-value<0.05 and <0.01 were considered significant for primary and secondary analyses, respectively.

RESULTS

The study sample consisted of 1421 women and 1505 men with a mean age of 50±10 years (Table 1), with the exception of the dietary analysis which was limited to only 925 participants.

SAT, VAT and Dietary Quality

In women, a 1-SD higher DGAI was significantly associated with lower SAT (232 cm^3 lower, p=0.002) and lower VAT (139 cm^3 lower, p=0.001, Table 2). Similar results were obtained in men. The difference between the magnitude of the association between DGAI and VAT vs. SAT was not significant (p=0.19 for women, p=0.78 for men).

SAT, VAT and Physical Activity

A 1-SD higher PAI was inversely associated with SAT in both women (-253 cm^3, p<0.0001) and men (-128 cm^3, p=0.0001, Table 2), although the association was more pronounced in women (p-value for sex-interaction=0.0002). For VAT, similar results were obtained (-100 cm^3, p<0.0001 for women; -85 cm^3, p=0.0006 for men), although the sex-interaction did not reach statistical significance (p=0.05). No difference was observed in the strength of the association of PAI with SAT vs. VAT (p=0.21 for women, p=0.27 for men).

SAT, VAT and Smoking

In women, former smokers tended to have the highest mean (± 1 standard error) SAT (3247±63 cm^3) as compared to current (2976±117 cm^3) or never smokers (3081±60 cm^3, p=0.06, Table 3). Similar results were observed in men, with a significant difference observed among the three groups (p=0.02). Mean VAT was higher in current smokers (1393±59 cm^3 [women], 2188±66 cm^3 [men]) and former smokers (1348±32 cm^3 [women], 2262±42 cm^3 [men]) as compared to those who never smoked (1250±30 cm^3 [women], 2086±33 cm^3 [men]) in both women (p=0.03) and men (p=0.005).

SAT, VAT and Alcohol Consumption

In women, participants with light-to-moderate alcohol intake had higher mean SAT (3184±44 cm^3) as compared to those with high alcohol intake (2869±106 cm^3, p=0.006), whereas there was no difference in mean VAT (p=0.18, Table 3). In contrast, SAT did not differ according to alcohol intake in men (p=0.91), while men with light-to-moderate alcohol intake had lower mean VAT (2139±25 cm^3) as compared to high alcohol consumers (2272±59 cm^3, p=0.04).

Table 1 Characteristics of study participants. Data shown as mean±standard deviation for continuous variables, and percent for dichotomous and categorical variables

	Women (n=1421)	Men (n=1505)
Age (years)	51±9	48±10
Body mass index (kg/m^2)	27.0±5.9	28.3±4.5
Waist circumference (cm)	93±15	100±12
Post-menopausal (%)	46.2	-
Hormone-replacement therapy (%)	22.9	-
Education (%)		
≤11th grade	0.8	1.6
High school or equivalent degree	22.8	17.9
College Grade/Trade school	33.2	27.0
College Grade/Post Grad	43.1	53.4
DGAI score*	10.0±2.6	8.5±2.6
PAI score†	37±6	38±8
Smoking (%)		
Current	12.3	13.0
Former	41.6	34.2
Never	46.1	52.8
Smoking (pack years)		
Current	26	28
Former	13	19
Alcohol (drinks/week, %)		
0	29.7	19.3
<1	9.9	4.7
1-<4	28.8	19.8
4-7	16.8	20.1
>7-14	11.3	20.7
≥14	3.6	15.4
SAT (cm^3)	3137±1548	2620±1212
VAT (cm^3)	1308±813	2160±969

Abbreviations: DGAI, Dietary Guidelines for Americans Adherence Index; PAI, Physical Activity Index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue

** Data only available for Offspring cohort (n=925), scores range from 0-20 points,*

† Scores range from 24-120 points

Table 2 Sex-specific multivariable-adjusted* mean difference (95% CI) in volumes of SAT and VAT (cm^3) per 1 SD increment in DGAI and PAI

	Women		Men		
	MV Adjusted Residual Effect Size	p-value†	MV Adjusted Residual Effect Size	p-value†	p-value for sex-interaction
DGAI ‡					
SAT	-232 (-375, -88)	0.002	-217 (-339, -95)	0.0006	0.87
VAT	-139 (-222, -57)	0.001	-243 (-353, -132)	<0.0001	0.14
PAI					
SAT	-253 (-333, -173)	<0.0001	-128 (-193, -63)	0.0001	0.0002
VAT	-100 (-140, -60)	<0.0001	- 85 (-133, -37)	0.0006	0.05

Abbreviations: CI, Confidence Interval; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; SD, standard deviation; MV, multivariable; DGAI, Dietary Guidelines for Americans Adherence Index; PAI, Physical Activity Index

**Adjusted for age, menopause (women only), hormone replacement therapy (women only), smoking, alcohol and education*

† ANOVA p-value

‡ Data only available for Offspring cohort (n=925)

SAT, VAT and Number of Healthy Lifestyle Factors

In both women and men, practicing a higher number of healthy lifestyle habits was significantly associated with lower mean SAT (p<0.0001 [women], p<0.001 [men]) and VAT (p<0.0001, Figure 1A; 1B).

Secondary analysis

Among women former smokers, higher log-pack-years of smoking was associated with higher SAT (225 cm^3 higher, p=0.001) and VAT (95 cm^3 higher, p=0.007). The association of pack-years of smoking with VAT was even stronger among former smokers in men (228 cm^3 higher, p<0.0001; p-value for sex-interaction=0.04). Among current smokers, no association was observed between pack years of smoking and either SAT (p=0.35 [women], p=0.13 [men]) or VAT (p=0.98 [women], p=0.48 [men]). The difference in the magnitude of the association between pack years of smoking and VAT vs. SAT was not significant in former (p=0.64 [women], p=0.52 [men]) or current smokers (p=0.63 [women], p=0.48 [men]).

When the amount of alcohol consumed was further broken down into six categories, women demonstrated significant differences in SAT (p<0.0001) as well as VAT (p=0.002, Appendix Figure 1A) across alcohol categories, with

Table 3 Sex-specific multivariable adjusted* least squares mean volumes of SAT and VAT (cm^3) by smoking and alcohol categories

		Women		Men		
		Least Squares Mean ± SE	p-value †	Least Squares Mean ± SE	p-value †	p-value for sex-interaction
Smoking	SAT					
	Current	2976±117	0.06	2629±88	0.02	0.46
	Former	3247±63		2743±56		
	Never	3081±60		2538±44		
	VAT					
	Current	1393±59	0.03	2188±66	0.005	0.10
	Former	1348±32		2262±42		
	Never	1250±30		2086±33		
Alcohol (Drinks/ week)	SAT					
	Light/Mod‡	3184±44	0.006	2622±34	0.91	0.02
	High	2869±106		2612±80		
	VAT					
	Light/Mod‡	1320±22	0.18	2139±25	0.04	0.01
	High	1243±53		2272±59		

Abbreviations: SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; SE, standard error; Mod, moderate

**Adjusted for age, menopause (women only), hormone replacement therapy (women only), smoking, alcohol and education*

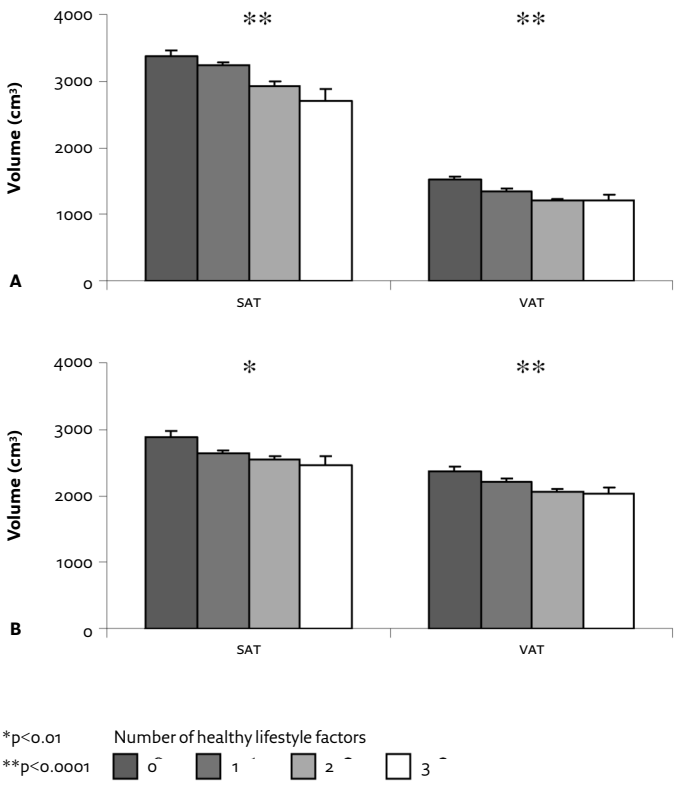
† Global p-value

‡ Light-to-moderate alcohol consumption (≤7 drinks/week for women and ≤14 drinks/week for men)

higher mean SAT and VAT in the extreme categories of alcohol intake, whereas differences in men were not significant (p=0.66 for SAT; p=0.37 for VAT, Appendix Figure 1B). None of the tests for a U-shape relation between alcohol consumption and SAT and VAT were significant.

The additional inclusion of physical activity as a covariate did not materially change the associations between the lifestyle factors and SAT and VAT (data not shown). When the general estimating equation procedure was used to repeat the analyses, the results did not substantially differ from the findings reported above (data not shown). Significant effect modification of BMI on the association between DGAI and SAT, and PAI and VAT was

Figure 1 Age-adjusted mean (± 1 standard error) volumes of SAT and VAT in women (Panel 1A) and men (Panel 1B) associated with practicing 0, 1, 2 or 3 healthy lifestyle habits. Age-adjusted p-values for trend are presented.



observed (Appendix Table 1). The strongest association between DGAI and SAT was in overweight individuals, whereas the strongest association between PAI and VAT was observed in normal weight individuals.

DISCUSSION

In a large cross-sectional population-based study, our findings were four-fold. First, a diet consistent with recommended dietary guidelines and a greater physical activity were equally associated with lower amounts of SAT

and VAT. Secondly, both current and former smokers had higher levels of VAT. Third, men who consumed higher amounts of alcohol had higher VAT. Lastly, an increasing number of healthy lifestyle factors overall was associated with lower SAT and VAT volumes.

Diet

In the present study, a diet consistent with the 2005 Dietary Guidelines for Americans was equally associated with lower volumes of SAT and VAT. While our findings are concordant with prior cross-sectional and prospective studies that documented similar findings using conventional measures of adiposity,[6,17] we extend the current literature by demonstrating an equivalent association between dietary quality and SAT and VAT on a population-based level.

The present findings are supported by some small randomized clinical trials and metabolic studies (n=32-78) that have focused on the effects of diet-induced weight loss on different abdominal fat compartments.[18-21] The results of these trials demonstrated similar relative reductions in VAT and SAT in overweight and obese individuals after consumption of a very low energy diet for 3 to 6 months. However, other studies have demonstrated a greater relative reduction in VAT as compared to SAT.[22,23] Given that VAT is a more pathogenic compartment, more research is needed to determine whether different dietary components, in addition to total energy intake, are differentially associated with SAT and VAT volumes in order to gain more insight into the contribution of specific nutrients to cardiometabolic risk.

Physical activity

A higher level of physical activity was equally associated with lower SAT and VAT volumes in both sexes, extending the results from prior relatively small cross-sectional studies (n=137-450) in men[24,25] and older individuals[26] to a large population-based study of both women and men. Results from prospective studies have consistently demonstrated that greater physical activity is associated with less weight gain,[27,28] lower abdominal adiposity[7,27,29] and less increase in abdominal girth over time.[30] In addition, several small randomized controlled trials (n=14-52) demonstrated a greater relative reduction in VAT as compared to SAT,[22,31,32] whereas results from three recent, relatively larger trials (n=102-175) suggest equal relative reductions in SAT and VAT.[33-35] The latter studies are concordant with our findings that SAT and VAT are equally associated with physical activity.

The reductions in SAT and VAT induced by physical activity may occur

with concomitant weight loss,[22,33] although results from several exercise studies demonstrated that reductions may also occur in the absence of weight loss.[22,36] These findings suggest that physical activity may affect SAT and VAT through a mechanism above and beyond reductions in body weight and therefore may have a positive impact on metabolic risk factors. Further research should be pursued to assess whether different types of physical activity are differentially associated with SAT and VAT to gain more insight in the magnitude of the effect of different types of physical activity on cardiometabolic risk.

Smoking

Despite the abundance of data showing that current smokers have a lower BMI when compared to former and never smokers,[4,37]data from the present study show that smokers have more VAT. These findings are supported by the work of others who have shown that higher waist circumference and waist-hip ratio are present in current smokers.[8,38] Further, a recent study of 450 Japanese men with an extremely high smoking prevalence of nearly two-thirds of the sample demonstrated more VAT but less SAT among heavier smokers.[25] Our findings extend the results of this study by demonstrating associations between smoking and larger amounts of VAT in a large population-based study of both women and men; accounting for multiple potential covariates; and generalizing these findings to a study sample with a lower prevalence of smoking.

Smoking may affect VAT by reducing the bioavailability of endogenous estrogen,[39] and increasing the production of adrenal androgens in women[40] and men.[41] Estrogens are implicated in the pathogenesis of adiposity, as postmenopausal women tend to have increased visceral abdominal adipose tissue compared to pre-menopausal women.[42]

Alcohol

The present study is notable for higher levels of VAT among men who consume higher amounts of alcohol. In a small study of 18 healthy 38-year old women,[43] VAT was positively correlated with higher amounts of daily alcohol intake. In a study of 450 Japanese men with high levels of smoking, men consuming alcohol had significantly more VAT than alcohol abstainers.[25] Habitual high alcohol intake may cause fatty liver,[44] which can result in hepatic insulin resistance[45] and subsequent weight gain.[46]

Strengths and limitations

Strengths of our study include the examination of the association between several lifestyle factors and radiographically assessed adipose tissue compartments; the statistical power provided by the use of a large population-based sample of women and men; the ability to adjust for several potential confounders; and the assessment of SAT and VAT volumes using a highly reproducible method.

Some notable limitations of our study include the cross-sectional design, which does not allow us to make causal inferences between lifestyle factors and SAT and VAT. The study sample is primarily white; therefore the results may not be generalizable to other ethnicities.

Conclusion

A healthy diet and physical activity are equally associated with lower SAT and VAT volumes. However, both smoking and high alcohol intake are differentially associated with higher VAT volumes. Further research to uncover the putative mechanisms is warranted.

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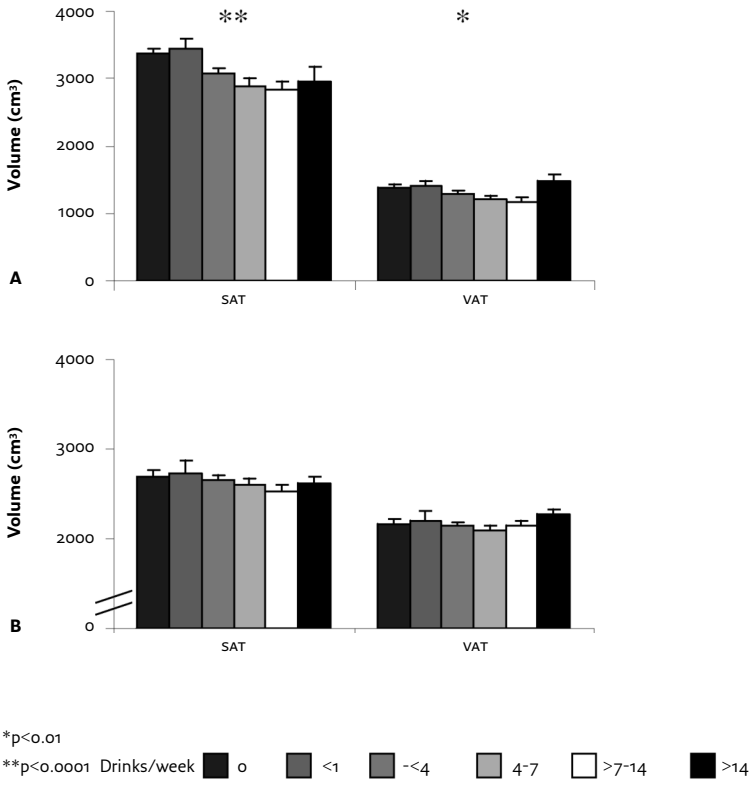
Appendix Figure 1 Mean volumes of SAT and VAT in women (Panel 1A) and men (Panel 1B) associated with different categories of alcohol intake expressed as drinks per week. ANOVA p-values for the difference across alcohol categories are presented.



Appendix Table 1 Interactions with age and BMI for the associations between volumes of SAT or VAT and the lifestyle factors*

		Average mean SAT or VAT (cm^3)	p-value for interaction †
DGAI			
SAT			
	BMI<25	-39 (-129, 50)	0.001
	BMI 25-<30	-80 (-157, -5)	
	BMI≥30	14 (-133, 161)	
PAI			
VAT			
	BMI<25	-37 (-65, -8)	<0.001
	BMI 25-<30	-15 (-49, 19)	
	BMI≥30	-16 (-71, 39)	

Abbreviations: BMI, Body Mass Index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; DGAI Dietary Guidelines for Americans Adherence Index; PAI, Physical Activity Index

** No significant interactions with age were found. No significant interactions with BMI were found for the association between DGAI and VAT, PAI and SAT, smoking and SAT or VAT, and alcohol and SAT or VAT*

† Adjusted for age, sex, menopause and HRT

CHAPTER 6

Effect of Nutritional Counseling and Nutritional Plus Exercise Counseling in Overweight Adults: a Randomized Trial in Primary Care

ABSTRACT

BACKGROUND Most trials involving lifestyle interventions for the management of overweight are performed in academic medical centers and not incorporated in daily health care. We compared the effects of nutritional counseling with nutritional plus exercise counseling on body weight and waist circumference in overweight adults in a primary care setting.

METHODS One hundred thirty-four overweight adults (body mass index (BMI) from 28 to 35) were randomly assigned to individual counseling sessions by a dietician (D) or counseling sessions by a dietician plus physiotherapist (D+E) during 6 months with one follow-up session at 12 months. Outcomes were assessed at baseline, 6, and 12 months. Difference in changes of outcome measures between groups were analyzed using generalized estimating equations. A total of 110 participants (82%) completed 6 months of study, 101 (75%) completed 12 months.

RESULTS Weight reduced from baseline to 6 months in D (-2.2 [-3.1 to -1.4] kg) and D+E (-3.0 [-4.0 to -2.0] kg) and was sustained at 12 months (-2.0 [-3.1 to -1.4] kg and -3.1 [-4.5 to -1.6] kg respectively). The reduction in weight did not significantly differ between D and D+E (p=0.48). In both groups waist circumference decreased from baseline to 6 months (-2.1 [-3.3 to -0.8] cm for D; -3.7 [-5.1 to -2.3] cm for D+E), and was sustained at 12 months (-2.1 [-3.5 to -0.7] cm and -4.2 [-6.0 to -2.5] cm respectively). Participants in D+E tended to decrease their waist circumference more than those in D (p=0.14).

CONCLUSION Nutritional counseling by a dietician resulted in modest reductions in body weight and waist circumference in overweight adults, that were sustained up to 12 months. Adding exercise counseling by a physiotherapist did not significantly enhance the effect on weight. Exercise counseling may, however, further improve waist circumference.

INTRODUCTION

Overweight and obesity pose one of the most serious public health challenges of the 21st century, both in developed and developing countries.[1] Worldwide, the occurrence of overweight and obesity increased markedly during the last quarter century.[1] Overweight, especially obesity, is associated with various health problems,[2] disability[3] and impaired quality of life.[4]

The expanding obesity epidemic and the adverse health risks of obesity have urged several Western countries to develop evidence-based clinical guidelines for prevention and management of obesity.[5-7] These guidelines emphasize the role of primary care physicians in identifying and treating obesity. In Australia, Canada and several European countries such as the United Kingdom and the Netherlands, primary care physicians serve as gatekeepers and the vast majority of inhabitants is enlisted in a primary care practice during lifetime. Primary care physicians are well-positioned to reach a large proportion of the general population[8] and routine consultations provide opportunities to initiate weight management interventions. Given the time-limited nature of primary care visits and lack of primary care physicians' training in diet and exercise counseling,[9] referral of patients to a multidisciplinary weight management program appears to be the most attractive strategy for obesity management in routine primary care.

Data from randomized controlled trials have consistently demonstrated that energy-restricted diets are more effective in facilitating weight loss than exercise.[6,10] In addition, programs including both diet and exercise produce greater weight loss than diet alone in overweight and obese individuals after one year of follow-up.[6,10,11] However, the majority of the trials involving lifestyle interventions for the management of obesity were performed in academic medical centers and not incorporated in daily health care. Therefore, the generalizability of the results to routine clinical practice is unknown. Translational studies are needed to determine whether the weight losses achieved in tightly controlled clinical trials can be achieved in real practice settings.[12]

We conducted a 12-month randomized clinical trial in a primary care set-

ting to evaluate the efficacy of nutritional counseling by a dietician compared with multidisciplinary nutritional plus exercise counseling by a dietician and physiotherapist on weight loss in an adult overweight population. As abdominal obesity is particularly associated with adverse health risks,[13] changes in waist circumference were taken as a secondary outcome. The secondary aim of the study was to compare both interventions with usual care.

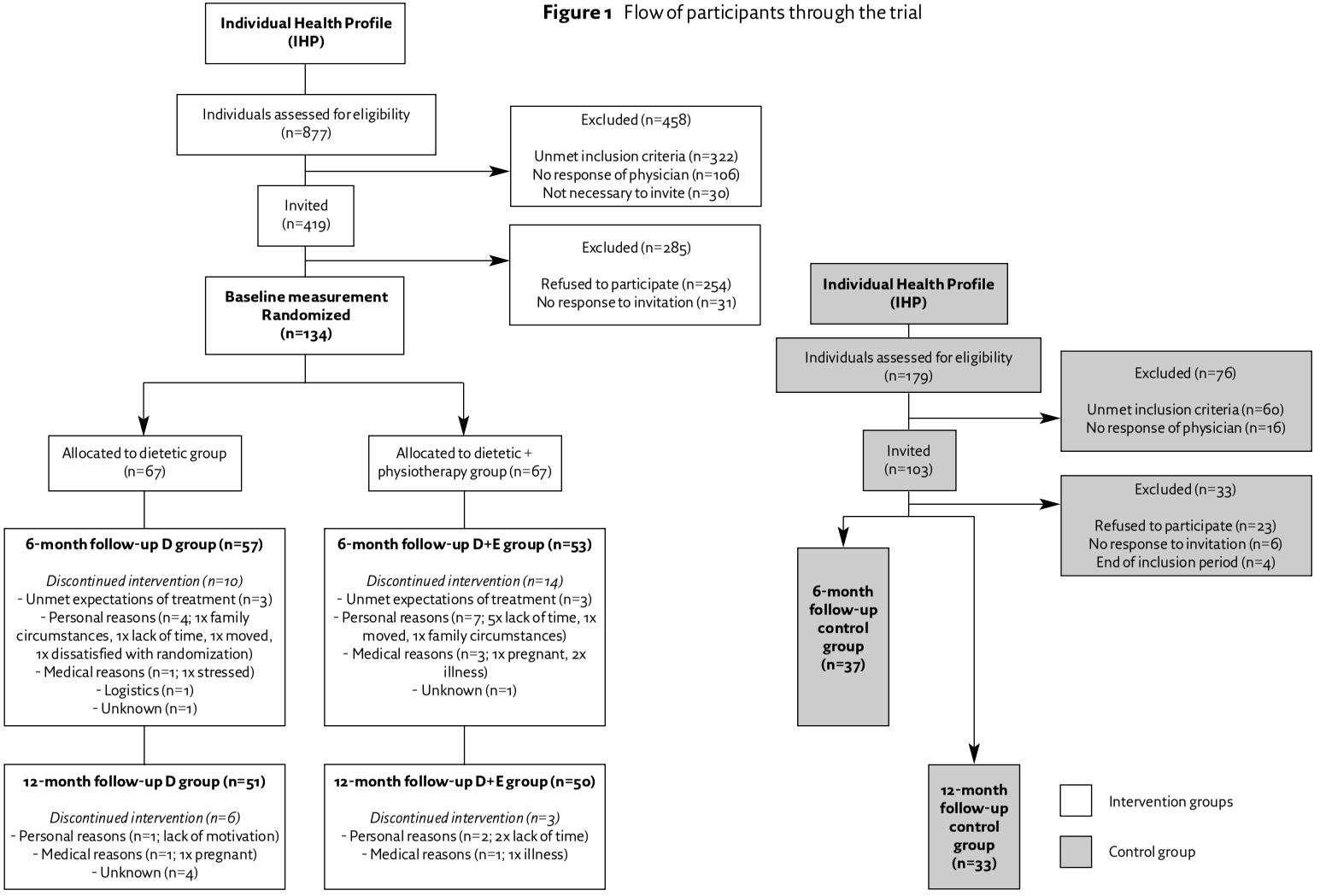
METHODS

Participants and study design

For the current trial participants were recruited from the Utrecht Health Project (UHP), an ongoing prospective cohort study, that started in 2000 in Leidsche Rijn, a newly residential area west of the city of Utrecht, the Netherlands. Details of the UHP have been described previously.[14] In brief, the UHP is a research infrastructure solidly embedded in primary care that enables answering questions about disease occurrence and its determinants, as well as studying the effects of health care policies and quality by using routine health care data. All new inhabitants are invited by their primary care physician to participate in the UHP. After informed consent is obtained, an Individual Health Profile (IHP) is produced for each participant that captures information on the participants' health status and medical history at entry of the study. For the current study IHP entry data were used to select men and non-pregnant women aged 18 to 65 years with a body mass index (BMI) from 28 to 35 kg/m^2. Subsequently, the primary care physicians were asked to exclude participants that were unable to speak Dutch, already treated for their overweight by a dietician and/or physiotherapist, as well as participants who had diagnosed mental health problems (i.e. depression, schizophrenia, anxiety disorder, binge eating disorder, bulimia nervosa) or known plans to move out of the residential area shortly. The remaining eligible participants were invited to participate in the trial by a letter from their primary care physician.

Participant recruitment took place between February 2006 and October 2006. Of the 419 invited individuals, 254 declined to participate and 31 did not respond to the invitation letter (Figure 1). After informed consent was obtained, the 134 remaining participants were randomly assigned to the nutritional counseling group, further referred to as Diet (D) group, or nutritional plus exercise counseling group, further referred to as Diet + Exercise (D+E) group, using computerized randomization. Measurements started in

Figure 1 Flow of participants through the trial



March 2006 and the follow-up measurements ended in January 2008. The mean follow-up was 13.7±1.1 months.

An untreated control group was selected from new participants of the UHP that fulfilled the above described in- and exclusion criteria of the trial. The dates of entry to the UHP of the control group were matched to the dates of the baseline measurement of the intervention participants. Controls were recruited between October 2006 and April 2007. Of the 103 invited individuals, 23 declined to participate, 6 did not respond to the invitation letter, and 4 responded after the recruitment period ended (Figure 1), resulting in 70 controls.

The trial was approved by the Ethics Committee of the University Medical Center Utrecht, the Netherlands, and all participants provided written informed consent.

Nutritional counseling

All randomized participants were provided with a referral letter from their primary care physician to attend seven individual face-to-face counseling sessions with a dietician during 6 months (with session 4 and 7 fixed at respectively 3 and 6 months after the first session) and one follow-up session at 12 months. At the first session, the dietician measured the weight and waist circumference of the participants and discussed the presence of cardiovascular risk factors, medication use and medical history of the participants. The dietician went through a 3-day food record (2 week-days and 1 weekend-day) that the participants were asked to complete beforehand and bring to the counseling appointment. Participants were informed about the significant health gains that can be achieved with relatively small long-lasting weight loss of about 5 to 10%, and in order to establish realistic expectations it was emphasized that successful weight loss and maintenance require gradual changes in lifestyle that can be continued over time. In cooperation with the participants, individualized, attainable goals for a healthy diet (based on the guidelines from the Health Council of the Netherlands) and effective caloric intake reduction were set and a strategy was developed to gradually achieve a moderate, sustainable weight reduction, taking dietary history and habitual diet routines into account. At subsequent sessions the dietician provided support, dietary advice and encouraged the participants to achieve or maintain their goals. Barriers encountered since the last session were recorded and, if necessary, the goals were reset and the strategy to achieve weight loss was adjusted in cooperation with the participants. The weight and waist circumference of the participants were

measured at each counseling session and additionally at the 6 and 12 month session a 3-day food record was completed. The duration of the initial session was assumed to be approximately 40 minutes and later sessions approximately 20 minutes.

Nutritional plus exercise counseling

Participants randomized to the D+E group were additionally provided with a referral letter from their primary care physician to attend six individual face-to-face counseling sessions with a physiotherapist during 6 months (with session 4 and 6 fixed at respectively 3 and 6 months after the first session) and one follow-up session at 12 months. At the first session, the physiotherapist went through a physical activity questionnaire known as the SQUASH (short questionnaire to asses health enhancing physical activity)[15] that the participants were asked to complete beforehand and bring to the counseling appointment. Under the supervision of the physiotherapist the participants performed the Astrand submaximal cycle test to determine their maximal oxygen uptake as a measure of cardiorespiratory fitness.[16] In cooperation with the participants individualized, attainable goals for an increase in daily physical activity were set and a strategy was developed to gradually achieve a moderate, sustainable weight reduction and improve cardiorespiratory fitness, taking habitual physical activity, fitness and personal preferences into account. The physiotherapist provided advice on exercise and building physical activity into daily life and informed the participants about possibilities for voluntary exercise (swimming, fitness/aerobics and running) at reduced costs as part of the intervention. At subsequent sessions the physiotherapist provided support, physical activity advice and encouraged the participants to achieve or maintain their goals. Barriers encountered since the last session were recorded and, if necessary, the goals were reset and the strategy was adjusted in cooperation with the participants. At the 6 and 12 month counseling session the participants were asked to perform another Astrand submaximal cycle test. The duration of the initial counseling session was assumed to be approximately 45-60 minutes and later sessions approximately 30 minutes.

Adherence to the intervention

The dieticians and physiotherapists recorded attendance of the participant at each session and documented all relevant information in an internet-accessible central database. The counseling sessions were additionally registered in the electronic medical record.

Attrition

Twenty-four participants (18 percent) did not complete the six-month intensive intervention period and an additional nine participants (7 percent) dropped out during the six-month follow-up period (Figure 1). Participants dropped out of the study because of personal reasons (n=14), unmet expectations of the counseling sessions (n=6), medical reasons (n=6), unknown reasons (n=6) or logistic problems (n=1). Baseline characteristics of participants that completed the study and those who dropped out did not differ, except that completers were older than participants who discontinued the study (44 years, SD=10 vs. 40 years, SD=8).

Control group

Participants in the control group received usual care and were not invited to receive structured nutritional or exercise counseling by a dietician or physiotherapist.

Outcome measures

Outcome measures were assessed at baseline, at 6 months and at 12 months by research nurses of the UHP. Height and weight were measured without shoes and heavy clothing to the nearest 0.1 cm and 0.1 kg. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was recorded at the midpoint of the lowest rib and the top of the hipbone (often located at the umbilicus level) to the nearest 0.5 cm.

The intake measurements of the UHP (the Individual Health Profile) of the control group served as their baseline measurement of the trial (Figure 1). Changes in waist circumference were not measured in the control group, since this was not part of the IHP routine yet. For reasons of feasibility, outcomes at 6 months were assessed in about half of the participants of the control group (n=37), while outcomes at 12 months were assessed in the remaining half of the control group (n=33).

Statistical analysis

Data were analyzed using a modified intention-to-treat approach, which included all participants that had at least one follow-up measurement. Continuous variables are presented as means with standard deviation (SD) and categorical variables as percentages. First, crude changes in outcome measures were compared between intervention groups (D+E vs. D) using linear regression analysis. Subsequently, generalized estimating equations (GEE) were applied with an autoregressive heterogeneous covariance

structure to take the correlation into account between repeated outcome measures within participants. Variables in the GEE models included intervention assignment, time (0, 6 and 12 months) and the interaction between intervention and time. In addition, the proportion of participants who achieved over 5 percent of weight loss at 6 and 12 months were calculated. Differences in proportion of weight loss over 5% between the D and D+E group were expressed as relative risks (RR) with corresponding 95% confidence interval (CI). In secondary analyses we compared changes in weight between intervention and control groups with GEE analysis similarly as described for the two intervention groups. Analyses were conducted using SPSS version 14.0 and R version 2.3.

RESULTS

Overall, 58% of the participants in the intervention groups were men with a mean age of 43±9 years and a mean BMI of 31.0±1.9 kg/m^2 (Table 1). Baseline characteristics of D and D+E were comparable.

In the control group, 63% were men with a mean age of 41±11 years and a mean BMI of 30.2±1.9 kg/m^2 (Table 2). The intervention and control group were well matched with regard to the baseline characteristics, except that participants in the intervention groups had a higher BMI.

Adherence to the intervention

Eighty-eight percent of the participants in the D group and 89 percent of those in the D+E group visited the dietician (D 4.5±2.1 sessions; D+E 4.1±2.0 sessions). Exclusion of dropouts resulted in a mean number of attended dietician sessions of respectively 5.0±1.9 and 4.4±1.9 for the D and D+E group. Eighty-seven percent of the D+E group visited the physiotherapist (5.0±2.1 sessions, without dropouts 5.6±1.9 sessions).

Difference in outcome measures between intervention groups

Crude changes in weight are presented in Table 3. Taking into account the correlated observations, weight decreased significantly from baseline to 6 months in D (-2.2 95% CI [-3.1 to -1.4] kg) and D+E (-3.0 [-4.0 to -2.0] kg; Table 4). The achieved weight loss at 6 months was maintained at 12 months in both intervention groups (-2.0 [-3.1 to -1.4] kg for D; -3.1 [-4.5 to -1.6] kg for D+E). The reduction of body weight in D+E was slightly higher than in D at 6 months (-0.8 [-2.1 to 0.6] kg) and at 12 months (-1.1 [-2.9 to 0.8] kg), though

Table 1 Baseline Characteristics of the Diet and Diet+Exercise groups*

	D Group N=67	D+E Group N=67
Gender		
Women	28 (42)	28 (42)
Men	39 (58)	39 (58)
Age, years	43±9	43±10
Country of origin		
Netherlands	52 (78)	50 (77)
Other	15 (22)	15 (23)
Education		
Low	9 (14)	10 (16)
Middle	31 (47)	29 (46)
High	26 (39)	24 (38)
Smoking		
Current	8 (12)	12 (18)
Never	31 (47)	34 (51)
Ever	27 (41)	21 (31)
Weight, kg	96.9±13.0	94.0±10.7
Height, cm	175.8±11.3	174.6±9.8
BMI, kg/m^2	31.3±2.0	30.8±1.9
Waist circumference, cm	103.7±8.6	104.1±7.1

Abbreviations: D, diet; D+E, diet + exercise; BMI, body mass index

** Data are presented as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables*

not statistically significant (overall p-value for interaction in GEE model =0.48). The interindividual variation in weight change was large (Figure 2).

Twenty-eight percent (95% CI; 16 to 40%) of the participants in the D+E group lost over 5 percent of their baseline weight at 6 months, while the proportion of participants in the D group was 16 percent (6 to 25%). The corresponding RR of losing over 5% weight in D+E vs. D was 1.8 (95% CI; 0.9 to 3.8). At 12 months, the proportion of participants who achieved over 5 percent of weight loss in the D+E and D groups were respectively 32 percent (19 to 45%) and 20 percent (9 to 31%), with a corresponding RR of 1.6 (0.8 to 3.2).

Table 2 Baseline characteristics of Intervention and Control groups*

	Total I Group N=134	Total C Group N=70
Gender		
Women	56 (42)	26 (37)
Men	78 (58)	44 (63)
Age, years	43±9	41±11
Country of origin		
Netherlands	102 (77)	59 (87)
Other	30 (23)	9 (13)
Education		
Low	19 (15)	16 (25)
Middle	60 (47)	23 (35)
High	50 (39)	26 (40)
Smoking		
Current	20 (15)	9 (13)
Never	65 (49)	31 (46)
Ever	48 (36)	28 (41)
Weight, kg	95.5±12.0	94.4±11.2
Height, cm	175.2±10.6	176.6±9.4
BMI, kg/m^2	31.0±1.9	30.2±1.9

Abbreviations: I, intervention (either D or D+E); C, control; BMI, body mass index

** Data are presented as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables*

Crude changes in waist circumference are presented in Table 3. Taking into account the correlated observations, the waist circumference decreased significantly from baseline to 6 months in both intervention groups (-2.1 [-3.3 to -0.8] cm for D; -3.7 [-5.1 to -2.3] cm for D+E) and was sustained up to 12 months (-2.1 [-3.5 to -0.7] cm and -4.2 [-6.0 to -2.5] cm respectively; Table 4). The reduction in waist circumference tended to be larger in participants in the D+E group compared to those in the D group at 6 months (-1.6 [-3.5 to 0.2] cm) and 12 months (-2.2 [-4.4 to 0.06] cm; overall p-value for interaction in GEE model=0.14).

Table 3 Changes in baseline weight and waist circumference for the Diet and Diet+Exercise groups at 6 and 12 months*

	Month	D Group mean (95% CI)	D+E Group mean (95% CI)	Additional Effect † mean (95% CI)
Weight, kg	6	-2.3 (-3.2 to -1.3)	-3.0 (-4.0 to -2.0)	-0.7 (-2.1 to 0.6)
	12	-2.3 (-3.7 to -1.0)	-3.2 (-4.5 to -1.8)	-0.8 (-2.7 to 1.0)
Waist, cm	6	-1.9 (-3.2 to -0.5)	-3.8 (-5.2 to -2.4)	-1.9 (-3.8 to -0.05)‡
	12	-2.3 (-4.0 to -0.7)	-4.3 (-6.0 to -2.7)	-2.0 (-4.3 to 0.3)

Abbreviations: D, diet; D+E, diet+ exercise; CI, confidence interval

** 95% CI are estimated with linear regression analysis*

† Additional effect is defined as change in D group - change in D+E group

‡ Statistically significant difference between change in D and D+E group

Table 4 Changes in baseline weight and waist circumference for the Diet and Diet+Exercise groups at 6 and 12 months*

	Month	D Group Mean (95% CI)	D+E Group mean (95% CI)	Additional Effect † mean (95% CI)	p-value for interaction‡
Weight, kg	6	-2.2 (-3.1 to -1.4)	-3.0 (-4.0 to -2.0)	-0.8 (-2.1 to 0.6)	0.48
	12	-2.0 (-3.1 to -1.4)	-3.1 (-4.5 to -1.6)	-1.1 (-2.9 to 0.8)	
Waist, cm	6	-2.1 (-3.3 to -0.8)	-3.7 (-5.1 to -2.3)	-1.6 (-3.5 to 0.2)	0.14
	12	-2.1 (-3.5 to -0.7)	-4.2 (-6.0 to -2.5)	-2.2 (-4.4 to 0.06)	

Abbreviations: D, diet; D+E, diet+ exercise; CI, confidence interval

** 95% CI are estimated with generalized estimating equations analysis*

† Additional effect is defined as change in D group - change in D+E group

*‡ Interaction: time*intervention*

Difference in outcome measures between intervention and control groups
Participants in the D and D+E group lost statistically significant more weight than those in the control group at 6 months (-2.7 [-4.2 to -1.1] kg and -3.5 [-5.1 to -1.8] kg respectively; Figure 3). Differences in weight loss from baseline to 12 months were smaller (-1.3 [-4.0 to 1.4] kg for D; -2.4 [-5.2 to 0.5] kg for D+E).

Figure 2 Body weight of individual participants at baseline and six months, and boxplots of change in baseline weight at six months, for the Diet and Diet+Exercise groups

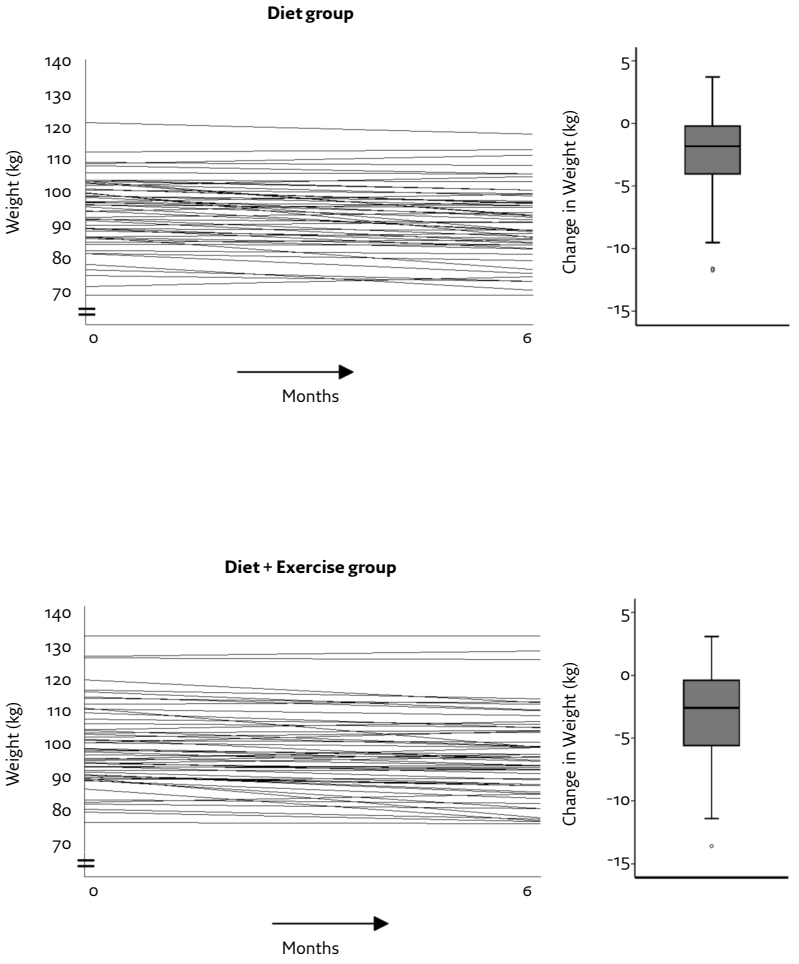
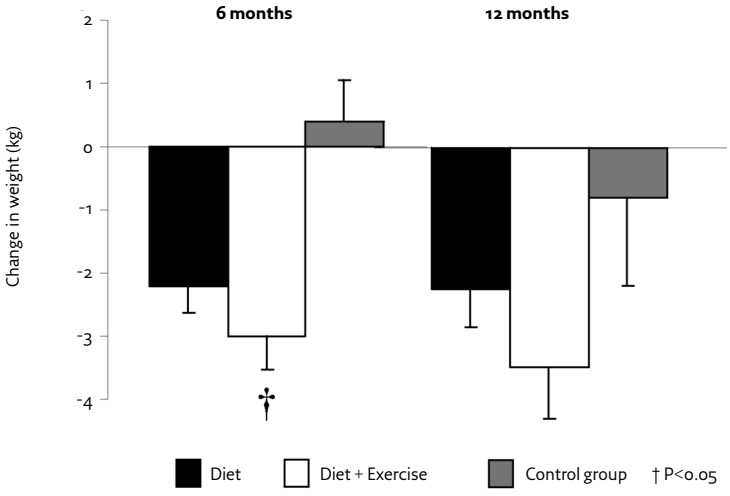


Figure 3 Change in baseline weight for the Control and Intervention groups at 6 and 12 months*



* Results are estimated with generalized estimating equations analysis

DISCUSSION

In the present randomized clinical trial, conducted in a primary care setting, we found that nutritional counseling by a dietician during 6 months resulted in modest but significant reductions in body weight and waist circumference in overweight adults. The effects were sustained up to 12 months. Adding exercise counseling by a physiotherapist did not significantly enhance the effect on weight, although a small additional beneficial effect on waist circumference may be present.

Strengths of our study include the randomized clinical trial design, performance of the trial in a real primary care setting, and the use of few exclusion criteria allowing for translation of the results to everyday clinical practice. Also, the approach was multidisciplinary with tailor-made counseling sessions. Furthermore, the research infrastructure of the UHP[14] allowed the controls to be unaware of the program until they received the invitation to participate in the trial several months after entry to the UHP. Knowledge of the trial and its aim beforehand could otherwise have biased the results.

Some limitations of our study deserve to be mentioned. Although the

involved dieticians and physiotherapists were provided with a working framework, they did not receive a detailed protocol nor was the intervention based on a theory of behavior change. Instead, the dieticians and physiotherapists worked according to usual standards that reflected real practice. While it was our intention to evaluate usual care, it may potentially limit the generalization of the results to foreign clinical settings. In addition, the attrition rate in our study (25% at 12 months) may potentially bias the results. However, participants who discontinued were evenly distributed among the intervention groups, and the characteristics of those who discontinued and who remained did not differ except that the latter were older. Furthermore, the effect size we found reflects what can be expected when conducting a weight management program in real life. For completeness, we imputed the missing outcome values multiple times to examine whether the missings could have introduced bias in our study.[17] Re-analyses on the imputed datasets resulted in somewhat smaller effect estimates with wider confidence intervals i.e. attenuated intervention effects compared to the complete case analyses. The direction of the effect was the same. Further, the number of participants in the control group was limited for logistic reasons. A last limitation is that the control group was not randomly selected. This design was chosen because the primary comparison was between the two weight reduction strategies and to allow the controls to be unaware of the weight management program until they received an invitation for participation in the trial. This minimizes non-specific effects of trial participation (i.e. the Hawthorne effect).

Participants in our intervention groups lost on average about 2 kg (diet only group) to 3 kg (diet plus exercise group) of their baseline weight during the 6-month counseling period, that was sustained up to 12 months. This effect is about two-fold less than that of meta-analyses by Avenell[18] and Anderson[19], but is of similar magnitude as the result of a recent systematic review on the effectiveness of weight-loss interventions for adults with prediabetes.[20] The relatively small reductions in weight in our study may be partly explained by the fact that participants did not sought weight loss on their own initiative but were approached by their primary care physicians. Furthermore, the participants did not necessarily have comorbidities. Therefore some participants may not have recognized the need and benefits of weight reduction themselves and still have been in the (pre)contemplation stage of change.[21] In addition, no severe energy restriction or (very) low calorie diets were prescribed, which often result in greater short-term weight loss but more marked drop-out.

Before discussing our findings in light of previous studies that compared the effects of diet plus exercise with diet alone, the following issues need consideration. As the dieticians also provided advice on enhancing physical activity as part of routine care, a ceiling effect may partly explain the lack of additional benefits in our study. Furthermore, long-term effects might be different. Nutritional plus exercise counseling may be superior in the long-term. Extensive evidence emphasizes the important role of exercise in long-term weight and waist maintenance.[22,23] Importantly, our results do not imply that exercise counseling alone is ineffective. We can only conclude that exercise counseling does not add to the beneficial effect of dietary counseling because we did not use a full factorial design.

Our study demonstrates that counseling sessions by a physiotherapist do not significantly add to the beneficial effect of counseling by a dietician on weight. While a recent meta-analysis of fourteen trials with a follow-up between 3 and 12 months demonstrated greater weight reductions in the exercise and diet group compared with the diet only group (-1.1 [-1.5 to -0.6] kg),[10] the magnitude of the pooled effect was similar to the difference in weight reduction between intervention groups at 12 months that we observed (-1.1 [-2.9 to 0.8] kg). However, our results indicate that exercise counseling may potentially provide additional beneficial effects on waist circumference. Emerging evidence suggests that physical activity is associated with a preferential reduction in abdominal adipose tissue, even with minimal or no changes in body weight.[24,25] This is important as abdominal obesity in particular conveys an increased health risk.[13] Further, it is essential to note that increased regular exercise can improve cardiorespiratory fitness, which is associated with reduced morbidity and mortality independent of changes in weight and abdominal adiposity.[26-28]

We evaluated our tailor made weight management program at a group level but we observed substantial differences in efficacy between participants. Therefore, future research should examine predictors of successful treatment to further customize the intervention. Importantly, the cost-effectiveness should also be assessed.

In summary, nutritional counseling by a dietician resulted in modest reductions of weight and waist circumference in overweight adults in a primary care setting, that were sustained up to 12 months. Adding exercise counseling by a physiotherapist did not significantly enhance the effect, but may have additional beneficial effects on waist circumference.

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CHAPTER 7

Comparison of Routine Care Self-reported and Biometrical Data on Hypertension and Diabetes: Results of the Utrecht Health Project

ABSTRACT

BACKGROUND Information on the prevalence of diseases is commonly gathered by questionnaires. Although the method is relatively inexpensive and efficient opposed to physical examinations, the validity of the information collected is often questioned. The objective of this study was to assess the value of biometrical data complementary to self-reported questionnaire information for estimating the prevalence of hypertension and diabetes in the population at large and to examine factors that affect the accuracy of self-reporting.

METHODS Baseline data of 4950 adult participants of the Utrecht Health Project, a community-based prospective cohort study, were used to calculate sensitivity and specificity of self-reported hypertension and diabetes with the results of blood pressure measurements and blood glucose levels, corrected for current medication use, as the reference standard. Multivariate logistic regression analysis was performed to determine which participants' characteristics independently predicted the accuracy of self-reports.

RESULTS Overall sensitivity was 34.5% for self-reported data on hypertension and 58.9% for diabetes, while overall specificity was high for both conditions (96.4% and 99.4%, respectively). The agreement between self-reported and biometrical data was higher for diabetes than for hypertension and varied per subgroup.

CONCLUSION The use of self-reported data to estimate the prevalence of hypertension and diabetes may lead to underestimated prevalence estimates and biased associations with risk factors due to differential misclassification. Adding biometrical measurements to self-reported questionnaire information will assure the validity of the data. The magnitude of the additional value of biometrical data depends on the condition studied and the characteristics of the population under investigation.

INTRODUCTION

In public health surveys information on the prevalence of diseases in the population at large is commonly gathered by questionnaires.[1] Although the method is relatively inexpensive and efficient opposed to physical examinations and anthropometrics, the validity of the information collected is often questioned as it may be threatened by random and systematic errors.[2,3] The accuracy of self-reported data on medical history depends amongst others on the subjects' knowledge and understanding of the relevant information, ability to recall it, and willingness to report it.[4] Furthermore, diseases may not (yet) have been diagnosed.[5] The rate of incorrect reporting and therefore misclassification can be significant and can vary by disease, population and by the severity of the disease.[5-10]

Hypertension and diabetes are two major chronic conditions that contribute considerably to the global burden of disease.[11,12] Accurate information about the prevalence of these conditions is essential for health care planners, policy makers and health professionals. Several studies have tried to assess the accuracy of self-reported questionnaire information on hypertension and/or diabetes but the majority of these studies was based on relatively small samples and/or restricted to certain subgroups, notably the elderly.[1-5,7-9,13-19] Limited information is available on the accuracy of self-reported data in large community-based samples.[3]

The present study utilized baseline data of a comprehensive cohort study that starts with an extended intake procedure in primary care. The value of biometrical data, as extracted from the extended intake procedure, was assessed complementary to self-reported questionnaire information for estimating the prevalence of hypertension and diabetes. This approach allowed for an evaluation of the accuracy of reported data in a large community-wide population taken from primary care practices. In addition factors were examined that affect sensitivity and specificity of self-reported disease information in subgroups to identify possible differential misclassification.

METHODS

Study population

The present study used baseline data from the Utrecht Health Project (UHP). Details of the study have been published previously.[20] In summary, the UHP is a prospective cohort study conducted in a newly developed residential area in the Netherlands (i.e. Leidsche Rijn). All new residents of the area are invited by their new primary care physician to participate in the UHP. At baseline an Individual Health Profile (IHP) is made by means of an extended intake procedure for the new primary care physician. This procedure includes information from the following three sources: (1) data on past medical history and use of medication obtained from the previous primary care physician and the pharmacist; (2) answers to a self-administered postal health questionnaire; and (3) results from a physical examination by research nurses, laboratory tests and diagnostic tests. The health questionnaire is completed before the physical examination takes place.

The Medical Ethics commission of the University Medical Center Utrecht in The Netherlands has approved the UHP. The UHP started to recruit participants in 2001 and since then response has been steadily increasing. By January 2005 13128 inhabitants were invited of whom 6755 gave informed consent (response 51.4%). Baseline data were complete for 6304 (48%) participants of whom 4950 were aged 18 years and over. The present analysis was based on the information of the first 4950 adult participants of the UHP.

Data

The self-reported information on hypertension was based on the question 'Have you had a high blood pressure during the past twelve months, that has (ever) been diagnosed by a primary care physician or specialist?' The self-reported information on diabetes was based on the question 'Have you had diabetes during the past twelve months, that has (ever) been diagnosed by a primary care physician or specialist?'

Blood pressure was measured twice on a single occasion as part of the IHP. The average of the two blood pressure readings was used to determine blood pressure levels. In agreement with current guidelines of the Dutch College of General Practitioners, hypertension was defined as a systolic blood pressure ≥140 mmHg (if age <60 years) or ≥160 mmHg (if age ≥60 years) and/or a diastolic blood pressure ≥90 mmHg (all ages) and current use of antihypertensive drugs for the indication of hypertension.[21]

In addition, glucose levels were determined as part of the IHP. In agreement with current diabetes guidelines of the Dutch College of General Practitioners, diabetes was defined as fasting venous glucose levels >6.9 mmol/l or fasting capillary glucose levels >6.0 mmol/l or non-fasting venous glucose levels >11.0 mmol/l and current use of antidiabetic drug.[22]

When pharmaceutical data were incomplete, self-reported information on current use of antihypertensive drugs for the indication of hypertension or current use of antidiabetic drugs was checked and used. An overview of the methods used to classify whether participants were having hypertension and/or diabetes is given in Table 1. Biometrical measurements corrected for current medication use are further referred to as biometrical measurements/data.

Table 1 Overview of classification method of participants with hypertension and/or diabetes based on different data sources

Biometrical data*	Current medication use†	Classified hypertensive and/or diabetic
+	+	+
+	-	+
-	+	+
-	-	-

** Hypertension: blood pressure ≥140/90 mmHg (18-59 years), blood pressure ≥160/90 mmHg (60 years and older) Diabetes: fasting venous glucose levels >6.9 mmol/l, fasting capillary glucose levels >6.0 mmol/l, non-fasting glucose levels >11.0 mmol/l*

† Current use of antihypertensive drugs for the indication of hypertension and current use of antidiabetic medication based on pharmaceutical records and self-reported information

Self-reported data in the questionnaire provided for the majority of the information on the participant characteristics. According to Dutch standards, ethnicity was based on the country of birth of the participant and both parents. Educational level was used as measure of social economic status (SES) since it is considered the most stable indicator of SES throughout adulthood.[23] The variable referred to the highest education level completed, with the respondent choosing one of the eight categories in the questionnaire. History of cardiovascular disease (CVD) was based on the question

'Have you had serious heart complaints or a stroke for the past twelve months, that has (ever) been diagnosed by a primary care physician or specialist?' Participants having both hypertension and diabetes, based on the biometrical data, were defined as having a combination of the conditions. Height and weight were measured as part of the IHP to the nearest 0.1 cm and 0.5 kg. Overweight was defined as a body mass index ≥25 kg/m^2. The presence of depressive symptoms was assessed by means of the score on the SCL-90.[24] A score ≥25 was considered high and used as indicator for the presence of depressive symptoms.[25] Utilization of health care was a summary measure of contact with the primary care physician or visit to a specialist the past 2 months or hospitalization the past 12 months. Contact with the primary care physician also included telephone calls with the primary care physician or the assistant and could refer to the former or current primary care physician.

Data analysis

Age was classified in five categories: 18-29, 30-39, 40-49, 50-59 and 60+. Ethnicity was dichotomized as Dutch and non-Dutch. Socioeconomic status was grouped into three standard hierarchic levels: low (no formal education, lower secondary education or intermediate secondary education), middle (higher secondary education) and high (higher vocational or university education).

To assess the difference in prevalence estimates by data collection method, the prevalence of hypertension and diabetes was calculated based on self-reported information as well as on results from biometrical measurements. To assess the accuracy of the self-reported data, sensitivity and specificity were calculated with the results of the biometrical measurements as the reference standard for a diagnosis of hypertension or diabetes. Sensitivity was defined as the percentage of participants with a diagnosis, based on the biometrical data, who reported to have the condition in the questionnaire. Specificity was defined as the percentage of participants without a diagnosis, who reported not to have the condition in the questionnaire.

Sensitivity and specificity estimates were calculated across different subgroups. Pearson's chi-square tests were used to assess differences in sensitivity and specificity between subgroups. If one of the cells had a count less than five, Fisher's exact tests were employed.

To determine which participant characteristics independently predicted the accuracy of self-reports, multivariate logistic regression analysis with backwards-variable selection was performed with above-mentioned varia-

bles as independent factors, considering the dichotomous variable of correct self-reporting as the dependent variable. The analyses were done separately for the participants with a diagnosis and those without a diagnosis, to study sensitivity and specificity respectively. Participants with missing or unknown data on a particular variable were excluded from that analysis only. All analyses were performed with the SPSS package (version 12.0).

RESULTS

General characteristics

More than half (55.1%) of the participants were female, the majority aged 30 to 39 years with a mean age of 39±13 years. The vast majority was of Dutch origin, rather well educated and had no history of CVD or a combination of hypertension and diabetes. Half of the participants were overweight and in nearly a fifth of the participants depressive symptoms were present. Sixty-three percent of the study population had recently been in contact with health care (Table 2).

Prevalence

The prevalence of hypertension and diabetes based on the biometrical data was 22.9% (95% confidence interval (CI) 21.7- 24.1) and 3.6% (95% CI 3.0-4.1) respectively. Self-reported data underestimated the prevalence of hypertension more than two-fold. The prevalence of diabetes based on the self-reported data lead to an underestimation of 40% compared to the reference standard (Table 3).

Sensitivity

Almost two third of the participants with confirmed hypertension misclassified themselves as not having hypertension and only a third reported correctly on their condition (overall sensitivity 34.5%; 95% CI 31.7-37.4, Table 3). The degree of accurate reporting differed between subgroups (Table 4). It was almost four times more likely for participants who had recently used health care to report hypertension accurately compared with those who had not (odds ratio (OR) =3.85; 95% CI 2.70-5.47). The likelihood of correct reporting increased as age increased (OR=1.42; 95% CI 1.28-1.57) and females were almost twice more likely to accurately report hypertension when present than men (OR= 1.96; 95% CI 1.45-2.66). In addition, participants with a history of CVD (OR=2.57; 95% CI 1.08-6.13) overweight

Table 2 General characteristics of study population

	N	%
Gender	4950	
Male	2221	44.9
Female	2729	55.1
Age	4950	
18-29	1029	20.8
30-39	2206	44.6
40-49	781	15.8
50-59	509	10.3
60+	425	8.6
Ethnicity	4770	
Dutch	3747	78.6
Non-Dutch	1023	21.4
Education	4622	
Low	920	19.9
Middle	1995	43.2
High	1707	36.9
History of CVD	4698	
No	4622	98.4
Yes	76	1.6
Combination of hypertension and diabetes	4399	
No	4308	97.9
Yes	91	2.1
Overweight	4923	
No	2485	50.5
Yes	2438	49.5
Use of health care	4651	
No	1724	37.1
Yes	2927	62.9
Depressive symptoms	4703	
No	3842	81.7
Yes	861	18.3

(OR=1.45; 95% CI 1.05-2.01), or depressive symptoms (OR=1.57; 95% CI 1.09-2.27) were more likely to correctly classify themselves as having a diagnosis of hypertension than those without. Among the participants with depressive symptoms, men were more likely to accurately report hypertension than women.

The overall sensitivity for self-reported diabetes was higher than for hypertension. More than half of the participants with diabetes, according to the biometrical measurement, reported the condition correctly (overall sensitivity 58.9%; 95% CI 51.1-66.8, Table 3). The degree of accurate reporting differed between subgroups (Table 4). There were not enough diabetic participants (N=151) to allow multivariate analyses but crude analyses showed that, as for hypertension, accurate reporting was more common among recent health care users (OR_{crude}=3.98; 95% CI 1.44-11.05). On the other hand, females were twice less likely to report diabetes when present (OR_{crude}= 0.48; 95% CI 0.25-0.92).

Specificity

The overall specificity for self-reported hypertension was high. Of those with normal blood pressure measurements, 96.4% (95% CI 95.7-97.0) classified themselves correctly whereas 3.6% erroneously indicated that they were having hypertension (Table 3). Women (OR=0.61; 95% CI 0.40-0.92), elderly persons (OR=0.69; 95% CI 0.61-0.79), participants with a history of CVD (OR=0.13; 95% CI 0.06-0.27), and recent health care users (OR=0.39; 95% CI 0.23-0.65) were less likely to correctly report the absence of hypertension (Table 4).

Table 3 Comparison of self-reported and biometrical data on hypertension and diabetes in the total study population

	Biometrical measurement			
	Hypertension (N=4679)		Diabetes (N=4237)	
Self-report	**Yes**	**No**	**Yes**	**No**
Yes	370	131	89	23
No	701	3477	62	4063
Prevalence self-report % (95% CI)	10.7 (9.8-11.6)		2.6 (2.2-3.1)	
Prevalence biometrical measurement % (95% CI)	22.9 (21.7-24.1)		3.6 (3.0-4.1)	
Sensitivity of self-report % (95% CI)	34.5 (31.7-37.4)		58.9 (51.1-66.8)	
Specificity of self-report % (95% CI)	96.4 (95.7-97.0)		99.4 (99.2-99.7)	

Table 4 Sensitivity and specificity of self-reported data compared with biometrical data*

	Hypertension				Diabetes			
	Sens (%) (95% CI) N=1071	OR (95% CI)	Spec (%) (95% CI) N=3608	OR (95% CI)	Sens (%) (95% CI) N=151	OR § (95% CI)	Spec (%) (95% CI) N=4086	OR (95% CI)
Gender								
Male	25.3 (21.9-28.7)	1	97.1 (96.1-97.9)	1	67.1 (55.8-77.1)		99.6 (99.2-99.8)	
Female	48.3 (43.5-53.0)	1.96 (1.45-2.66)†	95.9 (94.9-96.6)	0.61 (0.40-0.92)‡	49.3 (37.0-61.6)		99.3 (98.9-99.6)	
Age (years)								
19-29	15.6 (9.1-22.0)		98.5 (97.4-99.2)		66.7 (22.3-95.7)		99.9 (99.4-100)	
30-39	23.3 (18.7-28.0)		96.8 (95.8-97.5)		61.1 (35.7-82.7)		99.7 (99.3-99.9)	
40-49	32.7 (26.1-39.2)		96.9 (95.0-98.2)		52.6 (28.9-75.6)		99.4 (98.4-99.8)	
50-59	45.8 (39.3-52.3)		90.8 (86.6-94.0)		56.5 (41.1-71.1)		98.3 (96.6-99.3)	
60+	52.1 (45.4-58.9)		90.0 (85.0-93.8)		61.3 (48.1-73.4)		98.5 (96.5-99.5)	
Ethnicity								
Dutch	33.7 (30.5-36.8)		96.5 (95.7-97.1)		55.0 (45.7-64.4)		99.6 (99.3-99.8)	
Non-Dutch	38.7 (31.8-45.5)		96.1 (94.6-97.4)		68.3 (51.9-81.9)		99.0 (98.0-99.5)	

Table 4 Continued

	Hypertension				Diabetes			
	Sens (%) (95% CI) N=1071	OR (95% CI)	Spec (%) (95% CI) N=3608	OR (95% CI)	Sens (%) (95% CI) N=151	OR § (95% CI)	Spec (%) (95% CI) N=4086	OR (95% CI)
Education								
Low	44.6 (39.0-50.3)		93.6 (91.3-95.4)		54.0 (40.9-66.6)		98.5 (97.4-99.3)	
Middle	33.4 (29.1-37.7)		96.0 (94.9-97.0)		63.2 (49.3-75.6)		99.5 (99.1-99.8)	
High	23.3 (18.2-28.4)		98.1 (97.2-98.7)		62.5 (40.6-81.2)		99.8 (99.4-100)	
History of CVD								
No	33.0 (30.1-50.3)	1	96.8 (96.1-97.3)	1	56.6 (48.3-64.9)		99.6 (99.3-99.7)	1
Yes	71.4 (51.3-86.8)	2.57 (1.08-6.13)‡	70.8 (55.9-83.1)	0.13 (0.06-0.27)†	80.0 (44.4-97.5)		91.1 (80.4-97.0)	0.06 (0.02-0.16)†
Combination of HTN and DM								
No	33.4 (30.3-36.5)				61.9 (48.8-73.9)			
Yes	56.8 (45.8-67.3)				56.8 (45.8-67.3)			

Abbreviations: Sens, sensitivity; Spec, specificity; OR, odds ratio; CI, confidence interval; HTN, hypertension; DM, diabetes mellitus

** Sensitivity and specificity and 95% CI of self-reported hypertension and diabetes and estimated adjusted ORs and 95% CI for logistic models of the probability that a participant with hypertension respectively a participant without hypertension or diabetes provides accurate self-reported data compared to biometrical data*

Chi-square † p<0.001 ‡ p<0.05

§ There were not enough diabetic participants to allow multivariate analyses

Table 4 Continued

	Hypertension				Diabetes			
	Sens (%) (95% CI) N=1071	OR (95% CI)	Spec (%) (95% CI) N=3608	OR (95% CI)	Sens (%) (95% CI) N=151	OR § (95% CI)	Spec (%) (95% CI) N=4086	OR (95% CI)
Use of health care								
No	13.9 (10.4-17.4)	1	98.6 (97.8-99.1)	1	30.0 (11.9-54.3)		99.8 (99.4-100)	
Yes	46.7 (42.9-50.5)	3.85 (2.70-5.47)†	95.2 (94.2-96.1)	0.39 (0.23-0.65)†	63.1 (54.8-71.4)		99.3 (98.8-99.6)	
Overweight								
No	28.7 (23.7-33.6)	1	97.3 (96.5-98.0)		65.7 (47.8-80.9)		99.7 (99.3-99.9)	
Yes	37.2 (33.7-40.7)	1.45 (1.05-2.01)‡	95.1 (94.0-96.1)		56.9 (47.0-65.1)		99.2 (98.7-99.5)	
Depressive symptoms								
No	31.0 (27.9-34.1)	1	96.9 (96.2-97.5)		57.8 (48.8-66.7)		99.7 (99.4-99.8)	1
Yes	50.3 (43.1-57.5)	1.57 (1.63-3.11)‡	94.4 (92.3-96.0)		64.7 (46.5-80.3)		98.5 (97.3-99.2)	0.26 (0.11-0.63)‡

Abbreviations: Sens, sensitivity; Spec, specificity; OR, odds ratio; CI, confidence interval; HTN, hypertension; DM, diabetes mellitus

** Sensitivity and specificity and 95% CI of self-reported hypertension and diabetes and estimated adjusted ORs and 95% CI for logistic models of the probability that a participant with hypertension respectively a participant without hypertension or diabetes provides accurate self-reported data compared to biometrical data*

Chi-square † p<0.001 ‡ p<0.05

§ There were not enough diabetic participants to allow multivariate analyses

Self-reported diabetes had a higher specificity than hypertension. Of all participants without diabetes 99.4% (95% CI 99.2-99.7) accurately reported absence of the disease (table 3). A history of CVD (OR=0.06; 95% CI 0.02-0.16) and depressive symptoms (OR=0.26; 95% CI 0.11-0.63) were found to be independent predictors for accurate reporting (Table 4).

DISCUSSION

The present analysis of self-reported and biometrical data on hypertension and diabetes obtained in a large community-based cohort taken from primary practices shows a sensitivity of 34.5% for self-reported data on hypertension and a sensitivity of 58.9% for diabetes. Specificity was high for both conditions. Thus, few participants without the condition erroneously report hypertension or diabetes in a questionnaire, but 65% of the cases of hypertension and about 40% of the cases of diabetes will be missed. The agreement between self-reported and biometrical data was higher for diabetes than for hypertension and varied across subgroups. Gender, age, recent use of health care and a history of CVD were found to be the strongest independent predictors of the accuracy of self-reported data on hypertension and diabetes.

There are certain limitations to be addressed to appreciate the findings in this study. First, due to the limited availability of pharmaceutical data, information on current medication use was based on pharmaceutical as well as self-reported data to minimize underascertainment of medication use. Although Klungel et al.[26] reported a close agreement for data on current prescription medication use between both information sources, recall sensitivity was higher for questions about medication used for a specific indication than for open-ended questions as applied in the current study. Incomplete information on medication use may therefore account for misclassification of participants whose biometrical data were normalized due to medication use (the supposedly false positives). In our judgment, this potential bias will be small and not influence our main conclusions

Second, the reliance on two measurements taken during a single physical examination instead of on multiple measurements over longer time intervals may have lead to biased estimates of the prevalence of disease.[13] In the case of blood pressure measurements presence of white coat hypertension could induce an overestimation of the prevalence of hypertension and a concomitant underestimation of the sensitivity of the self-report.[4] In addition,

primary care physicians may use higher cut-off values for the diagnosis of hypertension, classifying patients with hypertension according to the guidelines as not having hypertension.[5,13] When hypertension was defined as a systolic blood pressure of ≥160 mmHg, and/or a diastolic blood pressure of ≥95 mmHg for all age categories, the sensitivity of self-reported hypertension in this study increased from 34.5% to 54.7% whereas the specificity decreased slightly from 96.4% to 95.1%. This shows the strong influence of the criteria for hypertension on the sensitivity of self-reported data.

The study was done in a rather homogeneous (78.6% Dutch, 80.1% middle or high educated) population. Although the sample reflects the demographic composition of the inhabitants of the residential area studied, generalization to other, more heterogeneous, populations is uncertain.

Finally, due to a limited number of diabetic participants there was limited power to study the influence of participants' characteristics on the sensitivity of the self-reported data on diabetes.

With regard to the validity of self-reported data, previous studies have also demonstrated that self-reported questionnaires are insensitive instruments that often underestimate the real prevalence rate of hypertension and diabetes.[18,19] However, the sensitivity in this study (34.5% for self-reported hypertension and 58.9% for diabetes) was poor compared to the estimates in other studies that used biometrical data as reference. In these studies the sensitivity for hypertension ranged from the lowest value of 43% to the highest value of 82% and for diabetes it ranged from 66.7% to 85.2%.[4,6,13,14,17,19,27-29] When medical records were used as reference data even higher sensitivities were found.[2,7,8,18] This can partly be explained by the fact that undiagnosed subjects will remain hidden when this methodology is used. In addition, most validation studies on older populations showed higher estimates, which can be explained by more accurate reporting by elderly who have the condition, as in the present study, and the more severe stage of the conditions in this subpopulation. As expected, the specificity in this study was markedly high for both conditions (96.4% for hypertension and 99.4% for diabetes), which is consistent with the findings of previous studies that used biometrical data as reference. In the literature, specificity for hypertension ranged from 80% to 95.3% and from 95.2% to 99% for diabetes.[4,13-15,19,28,29]

Overall, we found self-reported data on hypertension and diabetes were more specific than sensitive. Therefore an underestimation of prevalence estimates and an attenuation of associations with risk factors can be expected. For example, given the sensitivity and specificity estimates

obtained in this study and the assumption of non-differential misclassification, a true relative risk (RR) of 2.0 will result in an observed RR of 1.46 for hypertension and 1.94 for diabetes.

Our study supports the view that self-reporting of diabetes has a better validity than that of hypertension.[13,14,19] It has been postulated that conditions with more clear diagnostic criteria, like diabetes, are more likely to be reported accurately than conditions, like hypertension, that have less unambiguous criteria and are less disabling during daily life.[5] However, as these silent conditions may be major risk factors for chronic diseases it is important for the primary care physician to assess the condition in an early stage and make sure the subject receives appropriate treatment and is aware of the condition.

Our findings show that certain subgroups are more likely to accurately self-report hypertension. Recent health care users, older participants, females, and those with a history of CVD, overweight or depressive symptoms were more likely to correctly self-report their hypertensive state. Previous studies have also found higher sensitivity of self-reported hypertension among the first four mentioned subgroups.[4,8,13,17,18,27-29] Possible explanations may be the increased exposure to monitoring programs and a higher health consciousness among these subgroups.[4] The few studies that investigated the influence of depressive symptoms showed variable results.[16,19] This could partly be due to the use of different criteria for the presence of depression.

The observed misclassification between subgroups in this study indicates differential misclassification which may have serious consequences from an etiological point of view, namely biased associations with risk factors. For example, the RR for hypertension associated with overweight will be overestimated given the higher sensitivity of self-reported hypertension among overweight participants in this study. The observed differential misclassification may also have possible consequences for the overall sensitivity and specificity estimates generated by present study, due to overrepresentation of some subgroups. However, as some of the overrepresented subgroups seem to increase the likelihood of accurate reporting on hypertension and diabetes (recent health care users), whereas others seem to decrease the accuracy (young of age, well educated), we expect the effect on the overall estimates to be small.

In conclusion, the results from the current study support the view that adding biometrical data to self-reported questionnaire information for monitoring the prevalence of diabetes and hypertension does markedly

improve the accuracy of detecting populations at risk due to hypertension or diabetes. As the accuracy of self-reporting varied between condition and subgroups (implying systematic errors), the magnitude of the additional value would depend on the condition studied and the characteristics of the population under investigation. Conditions that have more pronounced symptoms that affect the daily life of the individual and are better defined may be more likely to be reported correctly. However, in general, when self-reports are the sole source of information used this will lead to an underestimation of the prevalence rates of hypertension and diabetes and biased associations with risk factors due to differential misclassification. Therefore it is recommended to include biometrical measurements in order to assure the validity of the data and to reduce misclassification at the individual level.

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CHAPTER 8

Discussion

Can We Rely on Routine Care Data for Epidemiologic and Public Health Research?

One of the reasons to start this series of studies was to gain experience in the use of data from the recently established Utrecht Health Project (UHP) and explore its possibilities for research.[1] The UHP has the particular feature that it combines data captured during a standardized baseline health assessment at intake in the primary care practice with follow-up data collected from routine primary health care medical registration. In developing this infrastructure, the view was that in the end the dataset could compete with traditional cohort studies for causal research, as well as with prespecified trial populations established for intervention studies. Because the UHP is anchored in primary care and monitors each individuals health in detail, it might be used for diagnostic and prognostic research more easily than traditional cohorts. Routine health care data essentially should resemble data from population-based cohort studies as both are derived from large unselected groups of individuals that are followed over time. They may only differ in that the membership of a traditional cohort is fixed, while individuals in a routine care setting may enter and leave the population because they move out of the area or change their health care provider. In the latter situation, the population may change and is therefore more formally termed dynamic population.[2]

Routine health care data can offer a valuable resource for epidemiologic and public health research, and the increasing availability of coded and anonymized extractions of computerized routine health care databases greatly facilitates research opportunities. One might wonder whether studies based on routine health care data can, partly, replace costly and time consuming traditional cohort studies in epidemiologic and public health research. In this chapter we address this issue and discuss whether and to what extent we can rely on routine care data for research. We start with a definition of routine health care for the purpose of this discussion, and the types of research to which we refer to as epidemiologic and public health research. Subsequently we discuss whether routine care data in its current state can compete with cohort studies. We close the chapter discussing what

aspects of routine care data can be improved for research purposes and how this can be achieved.

ROUTINE HEALTH CARE AND TYPES OF RESEARCH

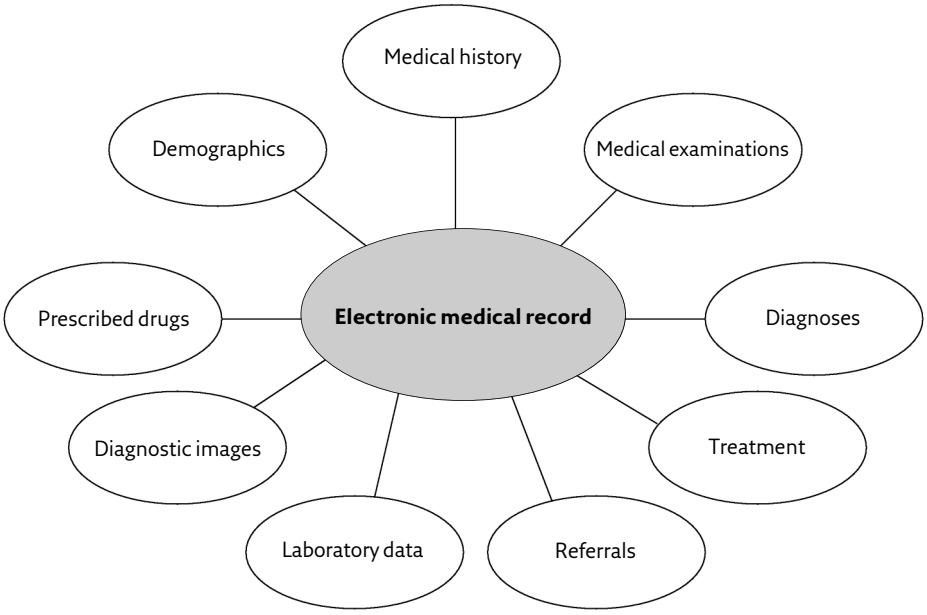
For the purpose of this discussion we define routine health care as comprehensive preventive and curative care with a central role for primary care. Health care related services that are registered in primary care medical records such as pharmaceutical care, youth health care and population screening are included in our definition. We focus on health care in countries that provide health care coverage for all of their inhabitants, where the vast majority of inhabitants is enlisted with a single primary care practice, and where the primary care physician has a gatekeeper function.[3] This is clearly the case in the Netherlands, Scandinavia and the United Kingdom. In these countries, most contacts between the public and health care take place in the primary care setting. For example, approximately three-quarters of the Dutch population consult their primary care physician over the course of a year and 96% of the reasons of individuals to visit the primary care physician are managed solely within primary care practice.[4] Consequently, primary care data in these countries are population-based, and not derived from a selected subset of the population.

Routine care data offer a resource to causal as well as descriptive research. The data can be used to establish determinants of health and disease, the effects of health care policy, health care utilization, and to monitor health and disease. For simplicity, we capture these types of research in the term epidemiologic and public health research.

CURRENT STATE OF ROUTINE CARE DATA

In recent years medical care has increasingly abandoned conventional handwritten medical records and started implementing records in a digital format i.e. electronic medical records.[5,6] Electronic medical records facilitate storage, sorting and retrieval of patient information, and enhance data accessibility and accuracy. In primary care these records include data on medical history, symptoms, diagnoses, additional investigations, treatment, prescribed drugs and referrals to secondary and tertiary care (Figure 1).

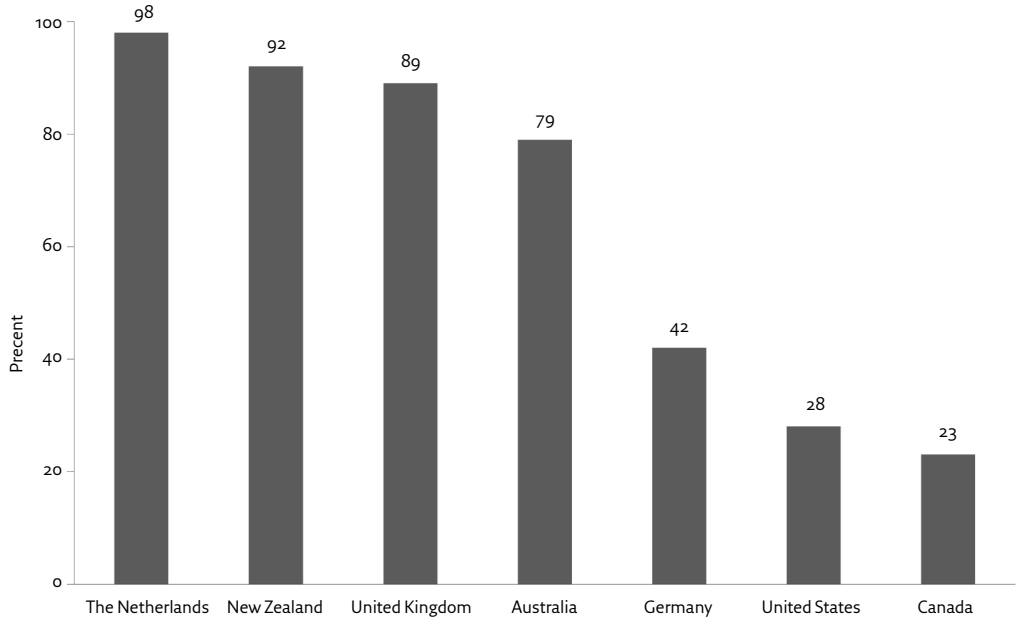
Figure 1 Types of data stored in an electronic medical record



The Netherlands and the United Kingdom, in particular, have a high level of computerized primary care practices (Figure 2),[7] but other countries are catching up.[8] While the main aim of the electronic medical record is to improve the quality of patient care and patient safety, it also makes large volumes of health care data more accessible than ever. Taken together with the equal access to health care, and the longitudinal continuity of care it may appear reasonable to suggest that studies based on routine care data can replace traditional cohort studies. However, despite the potential value of currently available routine care data, there are several issues concerning data completeness and quality that need consideration.

First, information on basic patient characteristics, such as social circumstances, ethnic status, subjective diagnoses (e.g. depression) and lifestyle parameters (e.g. smoking) is often lacking. Typically, electronic data systems used by primary care physicians leave ample room to their users to omit data if not deemed relevant. Consequently, information on potential confounders, which is especially relevant for causal research, is limited.[2] In addition, although routine health care data are suitable as a source for well

Figure 2 Primary care physicians' use of electronic medical records in 2006 [7]



described diseases, they are insufficient for studying diseases or conditions that are relatively often managed without the need to consult a physician or are only presented with delay.

Second, the completeness of medical records may be variable. Routine health care data are likely to be incomplete and, importantly, the missing data do not tend to occur at random but are often related to patient characteristics.[2] For example, patients with severe symptoms may already be referred for additional tests before full completion of the patient history and physical examination, while patients with mild or no symptoms may have incomplete additional test information because the physician already ruled out the disease. This may lead to biased results in descriptive research.[9] However, the recognized importance of integrating prevention in health care is likely to result in more complete documentation of test results in a larger group of individuals at an earlier stage.

Third, physicians and assistants may classify patients incorrectly, which is likely to happen in busy routine care. Also, variations in coding between health care staff may exist due to clinical experience and differences in knowledge.

Last, errors in data entry can occur and data can be difficult to retrieve or even lost when health care computer systems or coding systems change.

WHAT CAN BE IMPROVED?

As described in previous paragraph, current routine health care data do not inherently meet the quality standards to compete with cohort studies. This leaves two options: forget about routine care data and create new, separate cohorts to address the research questions, or upgrade the available routine care data. The latter strategy has been followed in the UHP.[1] Routine health care data can be upgraded for research either by improving the quality and completeness of the data or by collecting additional information.

Routine care data can be optimized by providing training in computerized recording and coding for health care staff to encourage specific, consistent and uniform terminology. Data quality can also be improved by introducing more powerful queries for data retrieval to minimize reliance on coding by health care staff.[10] Another option is to add quality checks for completeness and plausibility during data entry to help identify missing data and ensure that data values are within valid ranges. For example, when the physician does not enter the systolic blood pressure or enters a value outside the logical range of 60 to 280 mmHg, a warning message may appear on the screen. An approach to deal with missing data beyond routine care is to address the issue in the statistical analysis. Multiple imputation is a sophisticated statistical technique that predicts logical values for the missing data based on as many as other known patient characteristics.[11,12]

Routine health care data can also be upgraded for research by adding extra information. In the UHP, routine care data are optimized by adding data on patient characteristics of the whole population that are captured during a standardized health assessment at intake in the primary care practice.[1] This strategy can be extended by repeating health assessments at certain time intervals.

Ideally, relatively simple, objective measurements such as the body mass index (BMI) or ankle-arm index are integrated in routine health care. This improves the value of routine care data for research by generating data on established measures, in our example for overweight[13] and generalized atherosclerosis.[14] Simultaneously, this will allow physicians to identify high-risk patients and offers the opportunity to initiate interventions. However, some measures may prove to be too invasive (for example imaging of the

abdomen to assess the amount of subcutaneous and visceral fat), or too time-consuming (for example a 150-item food frequency questionnaire) to be obtained in a routine care setting. Therefore, "add-on" procedures to routine health care, or traditional cohort studies may still be needed to answer research questions that require specific and detailed information that can not be easily obtained in routine care.

The choice to invest in new data collection or upgrade available routine care data is based on cost-effectiveness considerations. Although initiation of a traditional cohort is time consuming and expensive, it is important to realize beforehand that optimization of routine health care data by developing a research infrastructure such as the UHP is also expensive, requires continuous funding and involves complex data management.

IN CONCLUSION

While routine care data offer a valuable resource for epidemiologic and public health research, it is unrealistic to think that they can fully replace the traditional cohort study and capture all information that is needed to answer current and future research questions in epidemiology and public health. However, before embarking on yet another cohort study it is important to consider the option of using available routine care data or supplementing existing routine care data with additional information. The "best of both worlds" may be combined by adding data from a standardized health assessment, either at baseline or at repeated time intervals, to routine health care data.

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CHAPTER 9

Summary

Samenvatting

Dankwoord

Curriculum Vitae

Overweight and obesity have reached epidemic proportions globally. Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. The body mass index (BMI, body weight in kilograms divided by height in meters squared = kg/m^2) is a useful measure of excess body weight at a population level. A BMI equal to or more than 25 is defined as overweight and a BMI equal to or more than 30 as severe overweight or obesity. Overweight and obese individuals are at increased risk for many diseases and health conditions including hypertension, diabetes, dyslipidemia, cardiovascular disease (CVD), osteoarthritis and certain types of cancer. Despite population-based prevention efforts the prevalence of overweight and obesity is increasing, stressing the importance of early identification and treatment of overweight and obesity and their associated co-morbidities to minimize the risk of complications.

The work presented in this thesis focused on the burden and treatment of overweight, obesity and their associated co-morbidities in the general adult population. For all but one study we used data from two large ongoing population-based prospective cohort studies, the Utrecht Health Project (in Dutch; 'Leidsche Rijn Gezondheidsproject') and the Framingham Heart Study. The Utrecht Health Project combines data captured during a standardized baseline health assessment at intake in the primary care practice, resulting in a so-called 'Individual Health Profile', with follow-up data collected from routine health care.

Few studies have comprehensively investigated the relation between overweight, physical as well as mental health conditions and quality of life in an adult community population. In *Chapter 2* we used baseline data from the Utrecht Health Project to compare the prevalence of a broad range of health conditions, psychological complaints and health-related quality of life among 4825 individuals with normal weight, overweight and obesity. The vast majority of the physical health conditions were substantially more common among overweight and obese individuals than among those

with normal weight, and we observed a clear gradient with increasing BMI-category. Somatization and a reduced physical well-being were more common among both overweight and obese individuals, whereas an increased risk of psychological complaints and a reduced mental well-being were confined to obese individuals. Our results suggest that physicians should consider a wide range of health conditions in overweight and obese individuals. Measurement of BMI, as part of a health assessment at intake in a primary care practice therefore might be an easy procedure to start being informed on many health risks.

To help understand the potential increased burden of CVD due to obesity, it is important to comprehend the current burden of CVD risk factors among obese individuals. *Chapter 3* describes the rates of treatment and control of CVD risk factors among 6801 normal weight, overweight and obese participants of the Framingham Heart Study that were free of CVD. Obese individuals with hypertension were more likely to receive antihypertensive treatment, but hypertension control across BMI subgroups among individuals with hypertension did not differ. Only four out of ten obese individuals with hypertension had recommended blood pressure levels. Likewise, obese individuals with elevated LDL cholesterol (LDL-C) levels were more likely to be treated with lipid-lowering agents than normal weight or overweight individuals, but the rate of control did not differ by BMI category. Less than one third of the obese individuals with elevated LDL-C had optimal control of elevated LDL-C. There were no differences in hypoglycemic treatment among individuals with diabetes across BMI groups, but obese individuals with diabetes were less likely to have well controlled fasting blood glucose than normal weight or overweight individuals. Only one in six obese individuals with diabetes had optimal fasting blood glucose levels. Dual and triple control of CVD risk factors were uniformly poor across all BMI categories. These findings emphasize the suboptimal rates of treatment and control of CVD risk factors among overweight and obese individuals.

In Chapter 3 we demonstrated that despite higher rates of lipid-lowering therapy among obese individuals with elevated LDL-C than normal or overweight individuals, the rates of control of LDL-C did not differ. These results suggest that it may be more difficult to achieve LDL-C treatment goals with a standard statin regimen in obese individuals. An intensive regimen may provide increased benefit in this subgroup. In *Chapter 4* we assessed the influence of BMI on the impact of intensive versus moderate lipid-lowering

statin therapy on cardiovascular outcomes in patients with acute coronary syndrome using data from the PROVE IT-TIMI 22 trial. Among overweight patients, intensive therapy resulted in a 19% lower risk of death and cardiovascular complications than did moderate therapy (hazard ratio=0.81, 95% CI 0.70-0.93), whereas no increased clinical benefit was apparent among normal weight patients (hazard ratio=1.02, 95% CI 0.77-1.35). Although the difference in response to the intensive statin regimen between overweight and normal weight patients did not reach statistical significance, overweight patients appeared to derive a larger absolute benefit from intensive therapy. Our findings lend support to the view that a more aggressive statin regimen may play an important role in the strategy to prevent recurrent coronary events in the presence of overweight.

Excessive body fat, in particular abdominal adiposity, is strongly associated with cardiometabolic risk. Visceral adipose tissue (VAT) may be a more pathogenic abdominal fat compartment than subcutaneous adipose tissue (SAT). Numerous studies have demonstrated that central obesity is associated with lifestyle factors using waist circumference as a proxy for abdominal adiposity. However, waist circumference does not allow to differentiate between SAT and VAT. To provide more understanding of the relationship between a healthy lifestyle and VAT and the contribution of individual lifestyle factors to cardiometabolic risk, we examined the association between lifestyle factors (diet, physical activity, alcohol consumption and smoking) and SAT and VAT volumes in *Chapter 5*. SAT and VAT volumes were assessed in 2926 participants of the Framingham Heart Study, using multidetector computed tomography. A diet consistent with recommended dietary guidelines and a higher level of physical activity were equally associated with lower amounts of SAT and VAT, whereas both former and current smoking and high alcohol intake were differentially associated with higher VAT. Practicing a higher number of healthy lifestyle factors was associated with lower SAT and VAT volumes.

The majority of the trials involving lifestyle interventions for the management of overweight are performed in academic medical centers and are not incorporated in daily health care. Therefore, the generalizability of the results to routine clinical practice is unknown. We conducted a 12-month randomized clinical trial in primary care to evaluate the efficacy of nutritional counseling with multidisciplinary nutritional plus exercise counseling on body weight and waist circumference in overweight adults. Participants

were recruited from the Utrecht Health Project. One hundred thirty-four overweight adults (BMI 28 to 35) were randomly assigned to individual counseling sessions by a dietician or counseling sessions by a dietician plus a physiotherapist during 6 months with one follow-up session at 12 months. *Chapter 6* describes the results of this trial. Participants who received nutritional counseling by a dietician demonstrated modest reductions in body weight (-2.2 [-3.1 to -1.4] kg) and waist circumference (-2.1 [-3.3 to -0.8] cm) at 6 months. The effects were sustained up to 12 months. Participants who received multidisciplinary counseling by a dietician plus a physiotherapist showed slightly higher reductions in body weight, although not statistically significant, and tended to have a larger decrease in waist circumference. Our findings suggest that exercise counseling does not significantly add to the beneficial effect of nutritional counseling on body weight, but may have a small additional beneficial effect on waist circumference in overweight adults.

Hypertension and diabetes are two major CVD risk factors that are closely associated with overweight. Accurate information about the prevalence of these risk factors is essential for health care planners, policy makers and health professionals. In *Chapter 7* we used baseline data from the Utrecht Health Project to assess the value of biometrical data on hypertension and diabetes complementary to self-reported questionnaire information and to examine factors that affect the accuracy of self-reporting. Overall sensitivity was 34.5% for self-reported data on hypertension and 58.9% for diabetes, while overall specificity was high for both conditions (96.4% and 99.4% respectively). Thus, few participants without the condition erroneously report hypertension or diabetes in a questionnaire, but two out of three individuals with hypertension and about 40% of the individuals with diabetes will be missed. In addition, the agreement between self-reported and biometrical data varied across subgroups. Gender, age, recent use of health care and a history of CVD were found to be the strongest independent predictors of the accuracy of self-reported hypertension and diabetes. Therefore, the use of self-reported data to estimate the prevalence of hypertension and diabetes may lead to underestimated prevalence estimates and biased associations with risk factors. Adding biometrical measurements to self-reported questionnaire information will assure the validity of the data.

The Utrecht Health Project has the particular feature that it combines data captured during a standardized baseline health assessment at intake in the

primary care practice with follow-up data collected from routine primary health care medical registration. In developing this infrastructure the view was that in the end the dataset could compete with traditional cohort studies. *Chapter 8* deals with certain methodological aspects of the use of routine health care data for epidemiologic and public health research. We discuss whether studies with routine care data in its current state can, partly, replace costly and time consuming traditional cohort studies, what aspects can be improved for research purposes and how this can be achieved.

CHAPTER 9

Wereldwijd hebben overgewicht en obesitas (ernstig overgewicht) epidemische vormen aangenomen. Overgewicht en obesitas worden gedefinieerd als een abnormale of buitensporige ophoping van vet dat de gezondheid kan beïnvloeden. De body mass index (BMI, het lichaamsgewicht in kilogrammen gedeeld door de lengte in meters in het kwadraat = kg/m^2), is een bruikbare maat voor het vaststellen van overgewicht en obesitas in de algemene volwassen bevolking. Bij een BMI van 25 of meer is er sprake van overgewicht. Een BMI tussen de 25 en 30 wijst op matig overgewicht, terwijl een BMI van 30 of meer op ernstig overgewicht ofwel obesitas wijst. Mensen met overgewicht hebben een verhoogde kans op tal van aandoeningen en ziekten zoals een hoge bloeddruk (hypertensie), suikerziekte (diabetes), verstoring van de vetwaarden in het bloed (dyslipidemie), hart- en vaatziekten (HVZ), gewrichtsaandoeningen en bepaalde vormen van kanker. Ondanks preventieve maatregelen gericht op de algemene volwassen bevolking neemt het aantal mensen met overgewicht toe. Deze trend benadrukt het belang van vroege identificatie en behandeling van overgewicht en obesitas en de daarmee samenhangende aandoeningen en ziekten zodat het risico op complicaties beperkt blijft.

De studies beschreven in dit proefschrift richten zich op de ziektelast en behandeling van overgewicht, obesitas en daarmee samenhangende aandoeningen en ziekten in de algemene volwassen bevolking. Met uitzondering van één studie maakten we gebruik van gegevens van twee grootschalige populatiegebaseerde prospectieve cohort onderzoeken, het Leidsche Rijn Gezondheidsproject (in het Engels; 'Utrecht Health Project') en de Framingham Heart Study. Binnen het Leidsche Rijn Gezondheidsproject worden gegevens van een gestandaardiseerde check-up bij inschrijving in een nieuwe huisartsenpraktijk, die in een 'Individueel Gezondheidsprofiel' resulteert, eens per drie maanden aangevuld met follow-up gegevens uit de registratie van de huisarts.

Weinig studies hebben het verband tussen overgewicht en zowel lichamelijke en psychische gezondheidsproblemen als ook kwaliteit van leven in een algemene volwassen populatie onderzocht. In *Hoofdstuk 2* gebruikten we intakegegevens van het Leidsche Rijn Gezondheidsproject om de prevalentie van een breed scala aan aandoeningen, gezondheidsklachten en gezondheidsgerelateerde kwaliteit van leven bij 4825 mensen met normaal gewicht, matig overgewicht en obesitas in kaart te brengen en te vergelijken. In vergelijking met mensen met een normaal gewicht kwam de meerderheid van de aandoeningen beduidend vaker voor bij mensen met matig overgewicht, en nog vaker bij mensen met obesitas. Psychische klachten en een verminderde gezondheidsgerelateerde kwaliteit van leven beperkten zich bij mensen met matig overgewicht tot lichamelijke aspecten, terwijl obese mensen zowel op lichamelijke als psychische aspecten verschilden van mensen met een normaal gewicht. Onze resultaten suggereren dat huisartsen, zowel bij mensen met matig overgewicht als met ernstig overgewicht, alert moeten zijn op verschillende aandoeningen. Het vaststellen van de BMI als onderdeel van een check-up bij inschrijving in een nieuwe huisartsenpraktijk zou een nuttige bijdrage kunnen leveren aan het vroegtijdig identificeren van mensen met een verhoogd risico op gezondheidsproblemen.

Obesitas verhoogt de kans op HVZ, een van de belangrijkste oorzaken van sterfte in Nederland en de rest van de Westerse wereld. Om inzicht te krijgen in de mogelijke toename van de ziektelast van HVZ door obesitas, is het van belang de huidige ziektelast van risicofactoren voor HVZ bij mensen met obesitas vast te stellen. In *Hoofdstuk 3* worden de prevalentie, medicamenteuze behandeling en controle (ofwel goede instelling: het bereiken van de aanbevolen streefwaarden) van risicofactoren voor HVZ bij 6801 deelnemers van de Framingham Heart Study met een normaal gewicht, matig overgewicht en obesitas beschreven. De prevalentie van verhoogde bloeddruk, verhoogde bloedvetwaarden en suikerziekte was hoger bij mensen met obesitas vergeleken met mensen met een normaal gewicht of matig overgewicht. Obese mensen met een verhoogde bloeddruk ontvingen vaker antihypertensiva, maar ze waren niet vaker beter ingesteld dan mensen met een normaal gewicht of matig overgewicht. Slechts vier op de tien obese mensen met een verhoogde bloeddruk hadden een bloeddruk onder de streefwaarde. Evenzo was de mate van vetverlagende behandeling bij obese mensen met verhoogde bloedvetwaarden hoger vergeleken met mensen met normaal gewicht of matig overgewicht. De mate van controle van verhoogde bloedvetten verschilde echter niet tussen de drie BMI categorieën. Minder dan een derde van

de obese mensen met verhoogde bloedvetwaarden waren goed ingesteld. Er werden geen verschillen in de mate van behandeling van suikerziekte tussen de drie BMI categorieën waargenomen, terwijl het minder waarschijnlijk was voor obese mensen om nuchter bloedglucose onder de streefwaarde te hebben. Slechts een op de zes obese mensen met suikerziekte hadden optimale nuchtere bloedglucosewaarden. Deze bevindingen benadrukken dat de mate van medicamenteuze behandeling en controle van risicofactoren voor HVZ bij obese mensen suboptimaal is.

In Hoofdstuk 3 hebben we laten zien dat het percentage mensen met verhoogde bloedvetwaarden dat goed ingesteld was niet verschilde tussen de drie BMI categorieën, terwijl een groter percentage van de obese mensen medicamenteus behandeld werd. Deze resultaten suggereren dat het voor obese mensen wellicht moeilijker is om de streefwaarden voor bloedvetten te bereiken met een normale vetverlagende behandeling. In *Hoofdstuk 4* hebben we de invloed van BMI op het effect van een intensieve vetverlagende behandeling op complicaties van HVZ en sterfte vergeleken met een standaard vetverlagende behandeling bij patiënten met acuut coronair syndroom. We maakten hiervoor gebruik van gegevens van een gerandomiseerd klinisch onderzoek, PROVE IT-TIMI 22. Bij patiënten met overgewicht resulteerde de intensieve behandeling in een 19% lager risico op complicaties van HVZ en sterfte vergeleken met de standaard behandeling (hazard ratio=0.81, 95% betrouwbaarheidsinterval 0.70-0.93), terwijl er geen positief effect bij patiënten met een normaal gewicht werd waargenomen (hazard ratio=1.02, 95% betrouwbaarheidsinterval 0.77-1.35). Hoewel het verschil in respons op de intensieve vetverlagende behandeling tussen patiënten met een normaal gewicht en overgewicht niet statistisch significant was, lijken patiënten met overgewicht meer baat te hebben bij een intensieve behandeling. Deze resultaten ondersteunen de hypothese dat een meer agressieve vetverlagende behandeling bij mensen met overgewicht een belangrijke rol zou kunnen spelen bij het voorkómen van een nieuwe uiting van coronaire hartziekten.

Met name vetophoping bij de buik brengt gezondheidsrisico's met zich mee. Visceraal buikvet (vet rondom de organen in de buikholte) is waarschijnlijk schadelijker voor de gezondheid dan subcutaan buikvet (onderhuids vet). Veel studies hebben het verband tussen vetophoping in de buik en leefstijlfactoren aangetoond. Deze studies gebruikten echter de tailleomvang als benadering voor buikvetophoping waardoor het niet mogelijk is om onderscheid tussen visceraal en subcutaan buikvet te maken. Om de samenhang

tussen een gezonde leefstijl en visceraal buikvet, en de bijdrage van leefstijlfactoren aan het risico op HVZ, beter te begrijpen hebben wij in *Hoofdstuk 5* het verband tussen leefstijlfactoren (voeding, lichamelijke activiteit, alcoholgebruik en roken) en visceraal en subcutaan buikvet bij 2926 deelnemers van de Framingham Heart Study onderzocht. De hoeveelheid visceraal en subcutaan buikvet werd vastgesteld aan de hand van computer tomografie. Een dieet in overeenstemming met de voedingsrichtlijnen en een grotere lichamelijke activiteit waren evenredig geassocieerd met lagere hoeveelheden van visceraal en subcutaan buikvet. Huidig roken, ex-roken en een hoog alcoholgebruik waren daarentegen geassocieerd met grotere hoeveelheden visceraal buikvet. Deelnemers die er meer gezonde leefstijlfactoren op na hielden, hadden lagere hoeveelheden visceraal en subcutaan buikvet.

De meerderheid van de gerandomiseerde klinische onderzoeken naar leefstijlinterventies bij mensen met overgewicht worden in academische centra uitgevoerd en niet in de eerstelijnszorg. Het in daarom onbekend of de resultaten van deze onderzoeken naar de dagelijkse huisartsenpraktijk vertaald kunnen worden. Wij voerden een 12 maanden durende gerandomiseerd klinisch onderzoek in de eerstelijnszorg uit om het effect van een behandeling door een diëtist op lichaamsgewicht en tailleomvang van volwassenen met overgewicht te vergelijken met het effect van een combinatie van behandeling door een diëtist en een fysiotherapeut. Deelnemers werden uit het Leidsche Rijn Gezondheidsproject gerekruteerd. Honderdvierendertig volwassenen (BMI 28 tot 35) werden op basis van toeval toegewezen aan individuele voedingsbegeleiding door een diëtist of aan begeleiding op het gebied van voeding plus beweging door zowel een diëtist als een fysiotherapeut gedurende 6 maanden met één vervolgconsult na nog een half jaar. In *Hoofdstuk 6* worden de resultaten van dit onderzoek beschreven. Deelnemers die door een diëtist begeleid werden, bereikten een bescheiden afname in gewicht (-2.2 [-3.1 tot -1.4] kg) en tailleomvang (-2.1 [-3.3 tot -0.8] cm) na 6 maanden. Deze effecten bleven behouden tot 12 maanden. Deelnemers die zowel door een diëtist als een fysiotherapeut begeleid werden, hadden een iets sterkere daling van het lichaamsgewicht, hoewel het verschil niet statistisch significant was, en neigden naar een sterkere daling van de tailleomvang. Onze resultaten suggereren dat het toevoegen van bewegingsbegeleiding aan voedingsbegeleiding geen significante meerwaarde heeft op lichaamsgewicht van volwassenen met overgewicht, maar een kleine toegevoegde waarde op de tailleomvang zou kunnen hebben.

Verhoogde bloeddruk en suikerziekte zijn twee belangrijke risicofactoren voor HVZ die nauw met overgewicht samenhangen. Voor planners en (beleids)medewerkers in de gezondheidszorg is het belangrijk om over juiste informatie met betrekking tot de prevalentie van deze risicofactoren te beschikken. In *Hoofdstuk 7* gebruikten we intakegegevens van het Leidsche Rijn Gezondheidsproject om de validiteit van zelfgerapporteerde verhoogde bloeddruk en suikerziekte na te gaan, eventuele groepsverschillen met betrekking tot zelfrapportage te onderscheiden en de toegevoegde waarde van biometrie vast te stellen. De sensitiviteit van zelfgerapporteerde verhoogde bloeddruk en suikerziekte was respectievelijk 34.5% en 58.9%, terwijl beide aandoeningen een hoge specificiteit toonden (96.4% en 99.4% respectievelijk). Met andere woorden, weinig deelnemers zonder de aandoening rapporteren onterecht een verhoogde bloeddruk of suikerziekte, terwijl twee van de drie mensen met een verhoogde bloeddruk en ongeveer 40% van de mensen met suikerziekte onterecht als ziektevrij geclassificeerd zullen worden. Bovendien verschilde de overeenstemming tussen zelfrapportage en biometrie tussen subgroepen. Geslacht, leeftijd, recente zorgconsumptie en een ziektegeschiedenis op het gebied van hart en bloedvaten bleken de sterkste onafhankelijke voorspellers van juist gerapporteerde verhoogde bloeddruk en suikerziekte. We concludeerden dat het gebruik van zelfgerapporteerde gegevens in een algemene volwassen populatie tot een onderschatting van de prevalentie van hypertensie en diabetes en tot systematische fouten kan leiden. Het toevoegen van biometrie als aanvulling op zelfgerapporteerde gegevens zal de validiteit van de gegevens verhogen.

Een bijzonder kenmerk van het Leidsche Rijn Gezondheidsproject is dat gegevens van een gestandaardiseerde check-up bij inschrijving in de nieuwe huisartsenpraktijk aangevuld worden met follow-up gegevens uit de medische registratie van de dagelijkse eerstelijnszorg. Bij het ontwikkelen van deze infrastructuur werd beoogd dat de gegevensverzameling uiteindelijk de competitie zou kunnen aangaan met traditionele cohort studies. *Hoofdstuk 8* richt zich op enkele methodologische aspecten van het gebruik van gegevens uit de dagelijkse gezondheidszorg voor onderzoek op het gebied van epidemiologie en algemene gezondheidszorg. We bediscussiëren of studies met gezondheidszorggegevens in hun huidige staat de dure en tijdrovende traditionele cohort studies (gedeeltelijk) kunnen vervangen, welke aspecten ten aanzien van onderzoeksdoeleinden verbeterd kunnen worden en hoe dit bereikt kan worden.

CHAPTER 9

Eindelijk begin ik aan het laatst geschreven, maar vaak eerst gelezen deel van mijn proefschrift: het dankwoord. Ik moet mezelf nog even goed in mijn arm knijpen want de afgelopen jaren heb ik me wel eens afgevraagd of ik ooit op dit punt zou belanden. Het is uiteindelijk toch gelukt en dat was zeker geen eenmansactie.

Beste Rick, ik had het genoegen regelmatig met je te overleggen en ik heb heel veel van je geleerd. Ik ben je erg dankbaar voor alle tijd die je in me geïnvesteerd hebt en voor je vertrouwen in me, ook in mindere tijden. Dat je me de mogelijkheid gaf een half jaar onderzoek bij de Framingham Heart Study te doen, was een schot in de roos. Ik heb enorm geluk gehad met een promotor als jij. Ik wens je een heel mooie tijd in Australië toe!

Beste Mattijs, de afgelopen vijf jaar heb ik heel wat uurtjes tegenover je aan je bureau gezeten. Je stond altijd voor me klaar, was belangstellend en had geduld als ik weer eens mijn waslijst met vragen afliep. Met je optimisme en enthousiasme heb je me vele malen weten op te beuren. Ik heb genoten van je mooie anekdotes en levendige mailtjes. Daarnaast was jouw inbreng als huisarts onmisbaar en heb je me veel geholpen met het inkorten en verbeteren van teksten. Bedankt voor alles!

Beste Erik, tijdens overleg zette je me vaak aan het denken met kritische vragen en je zorgde ervoor dat ik niet in details verzandde maar de grote lijn in de gaten hield. Je statistische kennis en bijdrage vanuit de public health hoek kwamen goed van pas. Jouw lijfspreuk 'Whatever can go wrong, will go wrong' (Murphy's law), zal ik niet snel vergeten.

Beste Yvonne, op de valreep heb ik nog met je samen mogen werken en dat was een groot genoegen. Bedankt voor je geweldige hulp bij de data-analyse en kritische blik op ons artikel.

Dear Caroline, you taught me new things every time we met. Thank you for being the best mentor I could have imagined during my research fellowship

in Framingham. Dan, I am very grateful that you gave me the opportunity to work at the Framingham Heart Study. It was a privilege to work with such inspiring researchers. Arend, bedankt voor je hulp bij het leggen van het eerste contact met Framingham. Je hebt destijds een onuitwisbare indruk bij de Framingham onderzoekers achtergelaten.

Shih-Jen, thank you for all your hard work and the pleasant meetings. I enjoyed working with you very much. Joe, we only met once in person, but we had many conference calls to discuss our paper. Thank you for the pleasant discussions and all your efforts. All co-authors, thank you for your valuable comments on the papers.

Dear Stephen, thank you for allowing me to get involved in such an interesting project. I look forward to continue to work on our project.

De leden van de leescommissie, Prof. Dr. Backx, Prof. Dr. Rutten, Prof. Dr. Seidell, Prof. Dr. Stolk en Dr. Visseren, hartelijk dank voor het evalueren van dit manuscript.

Zonder de bereidheid van de duizenden inwoners van Leidsche Rijn en Framingham om aan respectievelijk het Leidsche Rijn Gezondheids Project en de Framingham Heart Study deel te nemen, waren er geen data geweest en had het onderzoek dat in dit proefschrift beschreven staat nooit uitgevoerd kunnen worden. Ik ben jullie erg dankbaar.

I would like to thank the thousands of inhabitants of Leidsche Rijn and Framingham for their willingness to participate in respectively the Utrecht Health Project and the Framingham Heart Study. Without your efforts we would not have been able to perform the research described in this thesis.

De deelnemers van het Gewichtsprogramma Leidsche Rijn wil ik in het bijzonder bedanken voor hun inzet tijdens de interventie en de bereidheid om herhaaldelijk naar het gezondheidscentrum te komen voor een meting.

De medewerking van de huisartsen en doktersassistenten in Leidsche Rijn was essentieel tijdens de inclusieperiode van het Gewichtsprogramma. Allemaal ontzettend bedankt voor jullie kostbare tijd. Zonder diëtisten en fysiotherapeuten was het programma nooit van de grond gekomen. Jullie inbreng, inzet en enthousiasme waren van grote waarde en ik ben jullie allemaal heel erg dankbaar. Beste Rob, bedankt voor je toestemming voor het opzetten en uitvoeren van het onderzoek in 'jouw' Julius gezondheidscentra in Leidsche Rijn. Lieve LRGP dames, Khodeza, Mirjam, Marjon, Janet, Jaqcueline, Simo-

ne, jullie hadden het al zo druk met de gebruikelijke werkzaamheden en toen kwam ik er ook nog 'even' tussendoor met extra onderzoeksprojecten. Het was niet altijd gemakkelijk maar uiteindelijk is het toch gelukt om het onderzoek goed af te ronden. Heel erg bedankt voor jullie hulp! Carla, Gerard en Wesley, dankzij jullie konden wij de deelnemers de mogelijkheid bieden om tegen een gereduceerd tarief te sporten. Bedankt voor het creëren van deze mogelijkheid. Peter, bedankt voor je advies en hulp tijdens het opzetten van het onderzoek. Erika en Evelyn, jullie wil ik graag bedanken voor het meedenken over respectievelijk de voedings- en bewegingsvragenlijsten.

Beste datamanagers, jullie hulp was onmisbaar! Hanneke en Nicole, we hebben samen heel wat dataselecties, etiketten en uitnodigingsbrieven gemaakt en jullie hebben mij van heel wat databestanden voorzien. Heel erg bedankt voor jullie inzet en het actieve meedenken. Lara, ik heb ontzettend veel aan je gehad. Je was altijd behulpzaam, nauwkeurig en snel. Ik weet zeker dat ze je nu al missen op het Julius. Alexander, Jan Willem, Joost, Marinus, Robert en Rutger, jullie ook bedankt voor alle hulp en nuttige adviezen.

Beste Peter, Edwin, Ingeborg, bij jullie kon ik terecht als ik er zelf echt niet meer uit kwam. Bedankt voor jullie statistische adviezen. Mieke, Vera en René van SALTRO, bedankt voor de prettige samenwerking. José, ik stel het erg op prijs dat je onze bloedmonsters ook onder je hoede nam. Ronald en Eefje, jullie hebben onder het luistergenot van Hollandse meezingers honderden formulieren voor mij gescand en ze waren altijd klaar voor ik het wist.

Toen ik begon, was overgewicht bij volwassenen niet de hoofdmoot van mijn promotie maar hield ik mij ook bezig met onderzoek naar kinderen met astma. Hoewel we van opname van de resultaten van dat onderzoeksproject in dit proefschrift moesten afzien, wil ik toch alle gezinnen die bereid waren om aan het project deel te nemen, heel erg bedanken. Daarnaast ben ik grote dank verschuldigd aan de mensen die me geholpen hebben bij het opzetten en uitvoeren van het onderzoek; Gea, Marieke en alle anderen van het IRAS, Ingrid en Vivienne van farmacie, Corien, Francoise en Tina van het LRGP, en Ingrid en Marijke van de GG&GD. Gea, jou wil ik extra bedanken voor je onvermoeibare en enthousiaste inzet, zelfs vanuit het hoge Noorden.

Beste Jacoba, Iris, Anouk, Danja, Janneke en Stephen, tijdens jullie stages hebben jullie, hoop ik, veel geleerd en onderzoekservaring opgedaan, maar ik heb er minstens zoveel van opgestoken. Bedankt voor jullie belangrijke bij-

drage aan metingen, data-analyses en voor de gezelligheid die jullie meebrachten.

Beste Giene, bedankt voor je hartelijkheid, betrokkenheid en hulp als ik voor de zoveelste keer bij je aanklopte. Dear Esta, without your efforts to arrange my visa at such short notice I would have never got in the U.S. in the first place. Beste Gerard, bij jou een declaratie indienen was altijd goed voor een gezellig praatje. Beste secretaresses en medewerkers van de helpdesk, ik heb jullie hulp, ondersteuning en uitleg altijd erg gewaardeerd.

Beste Irma en Marjo, omzettend bedankt voor jullie hulp bij de vormgeving van het binnenwerk en het omslag van mijn proefschrift! Ik ben erg blij met het resultaat.

Lieve (ex-)kamergenootjes, Anne, Carline, Diane, Femke, Ingrid, Manja, Maud, Sjors, Soner, Yvonne en Wijnand, zonder jullie was het allemaal een stuk minder gezellig geweest, op het werk maar ook daarbuiten. Anne, 'leuk dat je er bent'! Carlientje, wat een perfecte timing! Met iemand de laatste promotiefase ingaan, kan ik iedereen aanraden. We hebben elkaar door de laatste weken heen gesleept. Leuk dat ik je op het laatst toch nog een stuk beter heb leren kennen. Dientje, jij bent altijd de relaxedheid zelve en ik heb daar als roomie lekker van meegenoten. Soner, nu jij ook je manuscript hebt ingeleverd moeten we binnenkort maar weer eens voor het betere werk gaan en lekker gaan meppen op de squashbaan. Yvie, ook al ben je inmiddels drie jaar bij het Julius weg, je bent nog steeds in the picture en wat mij betreft houden we dat zo. Wijnand, bedankt voor je oneindige hulp als ik in de clinch lag met mijn pc. Of het nu op het Julius of in Lombok was, jij was altijd bereid om langs te komen.

Onder het motto 'hoe meer zielen, hoe meer vreugd' kon ik mijn hart ophalen aan het grote aantal promovendi en aan de mensen die na hun promotie op het Julius bleven werken. Lieve Alike, Anne, Audrey, Beate, Kristel, Marjolein, Mirjam, Nadine, Nicky, Rolf en alle andere collega-onderzoekers, bedankt voor alle gezellige PROTESTEN, uitjes, lunches en kletspraatjes op de gang. Mirjam, ik wil jou daarnaast in het bijzonder bedanken voor je inhoudelijke hulp. Je weet dingen heel goed uit te leggen en hebt mij vaak op weg geholpen.

Lieve GG&GD collega's, jullie verwenden mij ook met aangenaam gezelschap. Sabine, vanaf dag één was er een klik. Je bent een ontzettende lieve,

trouwe vriendin met een optimistische kijk op het leven en niet onbelangrijk, altijd in voor een feestje. Wat wil een mens nog meer? Katrien, in een heftige periode in je leven werd ik je kamergenoot. Ondanks alles had je een enorm positieve instelling en maakte je er wat moois van. Bedankt voor alle gezelligheid! Dorie, hoewel we maar heel even kamergenoten zijn geweest, ben je niet snel te vergeten. Bedankt voor je mooie verhalen vanuit het Verre Oosten waarbij ik even weg kon dromen vanachter mijn bureau. Addi, Annnemarie, Hanneke's, Jaap, Jessica, Karin, Teresa en alle andere collega's, heel erg bedankt voor de leuke tijd op de GG&GD.

Dear Dimitra, Billy and Kempe, thanks for all the fun during drinks, dinners, nights-out, roofdeck parties and for being my Bostonian family! Dear Nina, thanks for being such a good friend during my stay in the U.S. Lieve Moniek en Welmoed, jullie waren een gezellig stukje Nederland in Amerika en met jullie kon ik af en toe lekker de echte toerist uithangen.

Lieve Daniël, Jacomien, Sanne, Suzanne, Jaap en andere (ex-)Zwollywood-vrienden, jullie zorgen al meer dan de helft van mijn leven voor de nodige ontspanning. Daan, we hebben soms heel wat te overbruggen, maar vinden elkaar ook vaak genoeg in het midden. Ik ben blij dat we nog altijd zulk goed contact hebben. Jac, de stand van de sterren was het begin en de rest volgt vanzelf! Het is altijd een feest om jou te zien. Sanne, goed dat je terug bent! Het is tijd om de schade in te halen. Suus en Jaap, jullie laten mij zien wat voor moois er nog allemaal kan komen. Lieve vrienden uit Utrecht, bedankt voor alle gezellige avonden! Lieve Gari, no more ideal balit but nevertheless it is always nice to meet up.

Lieve paranimfen, Maud en Martijn, ik vraag me af of jullie beseffen wat voor belangrijke rol jullie de afgelopen jaren hebben gespeeld. Maud, je was, en bent nog steeds, de beste kamergenoot die ik me kon wensen! Altijd vrolijk, relaxed en in voor alles. Jij hebt mijn kwaliteit van leven significant verhoogd en ik hoop dat je dat nog lang blijft doen! Tinez, wat was ik blij toen ik tussen die promoverende meiden jou aantrof. De afgelopen jaren hebben we heel wat gelachen, gehuild (dat was ik vooral), gekletst, gegeten en gedronken. En niet te vergeten, gemaild. Heel veel gemaild. Je bent een waardevolle vriend en ik kan je niet genoeg bedanken voor je steun, gezelligheid, zorgzaamheid, relativeringsvermogen en alle pakjes Bubblicious.

Lieve Bob, Nel en Judith, jullie betekenen onbeschrijfelijk veel voor mij. Juut, mijn lieve kleine wijze zusje, bedankt dat je er altijd voor me bent en mij een andere kant van het leven laat zien. En niet te vergeten, dat je mijn hele manuscript hebt nagekeken terwijl de inhoud mijlenver van je afstaat. Ik kan nog heel veel van je leren en zou je voor geen goud willen missen! Lieve papa en mama, het is moeilijk om me tot een paar regels te beperken maar een ding is zeker, I'm a lucky girl! Bedankt voor jullie luisterende oren, bemoedigende woorden, de tientallen grappige, ontroerende en lieve kaarten die ik op mijn deurmat vond en nog zo veel meer. Ik ben heel trots op jullie en ga vooral door met waar jullie zo goed in zijn; genieten van het leven!

Utrecht, augustus 2008

CHAPTER 9

The author of this thesis, Esther Aletta Molenaar, was born on July 24th 1979, in Zwolle, the Netherlands. In 1996 she graduated from the HAVO (higher general secondary education) at the Meander College in Zwolle and continued with the VWO (pre-university education). She gained her VWO diploma in 1998. In that same year she commenced her training in Health Sciences at Maastricht University. As part of her master course Biological Health Sciences, she conducted two research projects at the department of Human Biology, faculty of Health Sciences at Maastricht University, and one research project at the Smart Foods Centre, University of Wollongong, Australia. The first project focused on cholesterol metabolism and the expression of the LDL-receptor (supervised by Dr. J. Plat), the second project was on the effects of fish oil on fasting and postprandial lipid and glucose (supervised by Prof. Dr. R.P. Mensink and Dr. A. Jellema), and the third project aimed at evaluating the food intake of older Australians participating in a resistance exercise training program (supervised by Prof. Dr. L.C. Tapsell and Prof. Dr. W.H.M. Saris). In June 2003 she obtained her Master of Science degree in Biological Health Science (with distinction). In August 2003 she started working on the PhD research described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht and the Municipal Health Service Utrecht, under supervision of Prof. Dr. D.E. Grobbee, Dr. M.E. Numans and Dr. E.J.C. van Ameijden. She obtained her Master of Science degree in Epidemiology at the Netherlands Institute for Health Sciences, Erasmus University Rotterdam in June 2005. From February 2007 till August 2007, she conducted research at the Framingham Heart Study, Framingham, Massachusetts, USA under supervision of Dr. C.S. Fox, which resulted in two articles that are part of this thesis.