

Characteristics of US adults with the metabolic syndrome and therapeutic implications

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Background: The third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program defines clinical criteria for diagnosis of the metabolic syndrome, which increases cardiovascular risk and is a target for therapy.

Aim: We analysed the third National Health and Nutrition Examination Survey (NHANES III; 1988–94) to determine how many US adults meet these criteria and are recommended for lipid-modifying drug therapy by ATP III.

Methods: NHANES III data were used to estimate the number of individuals with the metabolic syndrome and the number recommended for treatment by ATP III, based on 1990 census data.

Results: An estimated 36.3 million (23%) US adults have the metabolic syndrome. Of these, 84% met the criterion for obesity, 76% for blood pressure, 75% for HDL-C, 74% for triglycerides and 41% for glucose. Most (54%) are in the higher risk categories of ATP III, yet only 39% overall are recommended for drug therapy by ATP III cutpoints; of these, most will achieve LDL-C targets with reductions of 35–40%. Of the 15.3 million individuals with the metabolic syndrome and triglycerides ≥ 2.26 mmol/l (200 mg/dl), non-HDL-C is above ATP III recommendations in 11.6 million.

Conclusions: Of the large number of Americans with the metabolic syndrome, ATP III recommends drug therapy for only a minority, because LDL-C typically is not substantially elevated. Instead, high triglycerides and low HDL-C are more common; clinical trial data are needed to determine whether optimal therapy should focus on reductions in LDL-C or on comprehensive improvements to the lipid profile.

Keywords: drug therapy, metabolic syndrome, treatment guidelines

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Introduction

The guidelines of the third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program [1] recommend identification and treatment of individuals

with the metabolic syndrome (table 1), a constellation of risk factors [abdominal obesity, elevated blood pressure and triglycerides, low high-density lipoprotein cholesterol (HDL-C) and impaired fasting glucose] that increases coronary heart disease (CHD) risk by an estimated two

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Table 1 Clinical identification of the metabolic syndrome [1]

Risk factor	Defining level
Abdominal obesity (waist circumference)	
Men	>102 cm (40 in)
Women	>88 cm (35 in)
Triglycerides	≥1.69 mmol/l (150 mg/dl)
High-density lipoprotein cholesterol	
Men	<1.03 mmol/l (40 mg/dl)
Women	<1.29 mmol/l (50 mg/dl)
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥6.1 mmol/l (110 mg/dl)

to six times [2] and therefore warrants aggressive therapy. A prior observational study showed that individuals with the metabolic syndrome (using an older definition) have a three- to sixfold increase in cardiovascular disease morbidity and mortality [3]. A recent analysis of participants in the Atherosclerosis Risk in Communities study shows an association between prevalent or incident CHD and the metabolic syndrome as defined in the ATP III guidelines [4]. Finally, in a large cross-sectional study, risk factors commonly associated with the metabolic syndrome (increased systolic blood pressure, fasting and postchallenge plasma glucose, plasma triglycerides and total cholesterol/HDL-C ratio and decreased HDL-C) were associated with increased risk for CHD [5].

In the United States, the presence of these risk factors, alone or in combination, is widespread; an estimated 20% of US adults have body mass index ≥ 30 kg/m² [6], 24% have blood pressure $\geq 140/90$ mmHg [7], 7% have fasting glucose of 6.1–6.9 mmol/l (110–125 mg/dl) [8], approximately 33% of men and 20% of women have HDL-C < 1.03 mmol/l (40 mg/dl) [9] and 24% have previously been estimated to have the metabolic syndrome [10]. The purpose of this study was to determine how many American adults who have the metabolic syndrome would be considered to be at high risk for CHD by the ATP III guidelines and how many would be recommended for lipid-modifying drug therapy.

Methods

Third National Health and Nutrition Examination Survey

Detailed survey design and methods of third National Health and Nutrition Examination Survey (NHANES III; 1988–94) [11], including the methods for obtaining lipid values and other risk factors characteristic of the metabolic syndrome [12], have already been published.

Briefly, NHANES III was conducted by the National Center for Health Statistics in two phases, 1988–91 and 1991–94; data from both phases were analysed in this study. Of the 18 825 adults aged 20 years and older who completed the household questionnaire, physical examinations (including blood sample and blood pressure measurement) were performed in 17 030 (95%). Of these, 8476 were randomly assigned to a 12-h morning fasting blood sample; after exclusion of individuals in this morning subgroup who had fasted less than 9 h, who had triglyceride > 4.52 mmol/l (400 mg/dl, which would have prevented calculation of LDL-C) or haemophilia, and for whom information on LDL-C or other CHD risk factors was not available, the remaining 6768 individuals were included in this analysis.

Risk Factor Assessment

Serum total cholesterol, HDL-C and triglyceride concentrations were measured in a single venous blood sample at the Johns Hopkins University Lipid Research Clinical Laboratory (Baltimore, MD, USA), which was standardized according to the criteria of the Centers for Disease Control/National Heart, Lung and Blood Institute Lipid Standardization Programs [13]. LDL-C concentration was calculated in individuals with triglyceride levels ≤ 4.52 mmol/l (400 mg/dl) according to the equation developed by Friedewald [14] (all units mg/dl): LDL-C = total cholesterol – [HDL-C + (triglyceride/5)].

Plasma glucose was measured after an overnight fast of 9–24 h. Samples were analysed in the Diabetes Diagnostic Laboratory of the University of Missouri.

Blood pressure was measured according to the American Heart Association standardized protocol [15]. The average of three measurements obtained at the participant's home and three obtained at the mobile examination centre is used in this analysis.

Waist circumference was measured at the high point of the iliac crest, at minimal respiration, to the nearest 0.1 cm [16].

History of diabetes and hypertension, cigarette smoking status and family history of heart attack were determined by response to the household questionnaire.

The metabolic syndrome was defined by the presence of at least three of the criteria on table 1.

Risk Stratification

ATP III defines as the highest-risk category individuals with CHD or a CHD risk equivalent: clinical non-coronary atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid

artery disease), diabetes and multiple risk factors estimated to confer a 10-year CHD risk >20%. Using the available NHANES III data, CHD was defined as a self-reported history of heart attack or a positive score for angina on the Rose questionnaire, and peripheral arterial disease was defined as a positive score for intermittent claudication on the Rose questionnaire; abdominal aortic aneurysm and carotid artery disease were not assessed in NHANES III. Individuals were classified as diabetic if fasting plasma glucose was ≥ 7.0 mmol/l (126 mg/dl) or if they had ever been told by a doctor that they had diabetes and were taking insulin or oral diabetes medication. Estimation of 10-year CHD risk in individuals with multiple risk factors was calculated by Framingham point scores as described below.

For primary prevention, ATP III first dichotomizes individuals by whether they have two or more or less than two of the following CHD risk factors: cigarette smoking, hypertension (blood pressure $\geq 140/90$ mmHg or on antihypertensive medication), low HDL-C [< 1.03 mmol/l (40 mg/dl)], family history of premature CHD (CHD in male first-degree relative < 55 years and female first-degree relative < 65 years) and age (≥ 45 years in men and ≥ 55 years in women); presence of high HDL-C [≥ 1.55 mmol/l (60 mg/dl)] decreases the number of risk factors by one. Based on the data collected in NHANES III, family history of premature CHD was defined as a heart attack before the age of 50 in a first-degree relative (parent, sibling or offspring) of either sex; the other risk factors were defined as in ATP III. The total number of risk factors was counted for each individual by adding one point for each risk factor present and subtracting one point from the total score if high HDL-C was present.

For individuals with two or more risk factors, ATP III further refines risk assessment by estimation of 10-year CHD risk, determined by Framingham point

scores. This analysis follows the charts included in the ATP III guidelines [1]. Individuals with 10-year risk >20% are considered to have a CHD risk equivalent and are categorized with individuals with known CHD. Individuals with 10-year CHD risk $\leq 20\%$ are dichotomized by whether estimated 10-year risk is 10–20 or $< 10\%$.

Recommendations for Therapy

The primary target of therapy in the ATP III guidelines is LDL-C, which determines the need for and intensity of therapy (table 2). ATP III defines the metabolic syndrome (table 1) as a secondary target of therapy. In individuals with triglyceride ≥ 2.26 mmol/l (200 mg/dl), non-HDL-C is also a secondary target of therapy. Non-HDL-C, which represents the combined cholesterol in LDL and triglyceride-rich lipoproteins, is calculated by subtracting HDL-C from total cholesterol.

Data Analysis

Sampling weights reflecting the survey design were used to produce national estimates [17]; the weighted total was 154.8 million Americans aged 20 or older as of October 1991, the midpoint of NHANES III. All statistical analyses were performed with SAS version 8.1 and SUDAAN release 8.0 and were based on 1990 US census data.

Results

An estimated 36.3 million (23.4%) US adults aged ≥ 20 years have the metabolic syndrome (table 3). Of them, almost an equal percentage are men and women. A lower percentage of non-Hispanic blacks (19.4%) have the metabolic syndrome than that of non-Hispanic whites (24.0%), Mexican Americans (24.2%) or individuals of other races (23.0%). Among the 28.8 million

Table 2 Low-density lipoprotein cholesterol goals and cutpoints for therapeutic lifestyle changes and drug therapy in different risk categories [1]

Risk category	LDL-C (mg/dl)		Non-HDL-C (mg/dl)	
	Goal	Initiation level for TLC	Consideration level for drug therapy	Goal
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥ 100	≥ 130 (100–129: drug optional)	<130
Two or more risk factors* (10-year risk $\leq 20\%$)	<130	≥ 130	10% year risk 10–20%: ≥ 130 ; 10-year risk <10%: ≥ 160	<160
0–1 risk factors*	<160	≥ 160	≥ 190 (160–189: LDL-lowering drug optional)	<190

CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TLC = therapeutic lifestyle changes.

*Cigarette smoking, hypertension (blood pressure $\geq 140/90$ mmHg or on antihypertensive medication), low HDL-C [< 1.03 mmol/l (40 mg/dl)], family history of premature coronary heart disease (male first-degree relative aged < 55 years; female first-degree relative aged < 65 years), age (men ≥ 45 years; women ≥ 55 years); HDL-C ≥ 1.55 mmol/l (60 mg/dl) is a negative risk factor, decreasing by one the total number of risk factors.

Table 3 Characteristics of individuals with the metabolic syndrome in National Health and Nutrition Examination Survey III

Characteristic	Millions (% of individuals with the metabolic syndrome)
Sex	
Male	16.8 (46.3)
Female	19.5 (53.7)
Diagnostic criteria	
Abdominal obesity	30.3 (83.5)
Men	12.7 (75.6*)
Women	17.6 (90.4*)
Blood pressure	27.6 (76.1)
High-density lipoprotein cholesterol	27.4 (75.5)
Men	12.3 (73.2*)
Women	15.1 (77.6*)
Triglyceride	26.9 (74.3)
Glucose	14.8 (40.8)
110–125 mg/dl	7.4 (20.3)
≥126 mg/dl or diabetes†	7.5 (20.6)

*Per cent within each sex.

†As diagnosed by a doctor or requiring insulin or oral diabetes medication.

non-diabetics with the metabolic syndrome (79.3% of all adults with the metabolic syndrome), individuals are widely distributed across all age ranges; 4.0 million are younger than 35 years and 7.7 million are 65 years or older, including 2.8 million aged 75 years or older (figure 1). Most individuals with the metabolic syndrome are in the higher risk categories of ATP III (figure 2), and prevalence of the metabolic syndrome within each risk category increases with increasing risk (table 4).

LDL-C is above ATP III target levels in 22.8 million (63.0%) individuals with the metabolic syndrome (table 4), who would therefore be recommended for diet therapy to lower LDL-C; 16.7 million of these are non-diabetics. By the drug-initiation cutpoints in ATP III, drug therapy is recommended for only 14.2 million (39.2%) individuals with the metabolic syndrome (figure 3), and addition of individuals for whom drug

therapy is optional increases the number to 19.8 million (54.6%).

LDL-C is typically not substantially elevated in individuals with the metabolic syndrome (figure 4) [mean 3.60 mmol/l (139.3 mg/dl) and median 3.52 mmol/l (136.0 mg/dl)], and most individuals would achieve ATP III targets for LDL-C with reductions of 35–40% (figure 5), which can be obtained with statin therapy. Diet and exercise may provide an additional 5% reduction in LDL-C and therefore enable more individuals to reach therapeutic goals. Among non-diabetic individuals with the metabolic syndrome, 79.3% would reach LDL-C goals with a 35% reduction and 84.7% with a 40% reduction. An additional 5% LDL-C reduction with

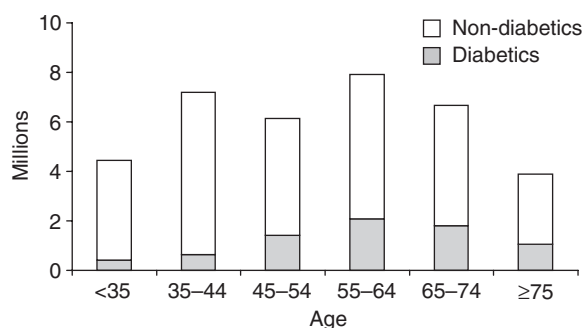


Fig. 1 Distribution of diabetic and non-diabetic US adults with the metabolic syndrome by age.

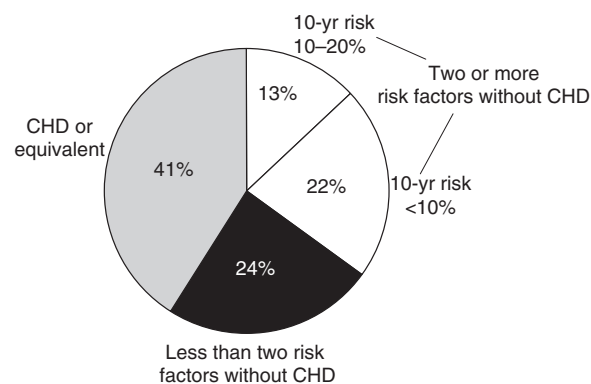


Fig. 2 Per cent of individuals with the metabolic syndrome by Adult Treatment Panel III risk categories. CHD, coronary heart disease.

Table 4 Risk category distribution and therapy recommendations for individuals with the metabolic syndrome

	Millions (%)				Overall
	CHD or equivalent	Two or more RFs,* 10–20% 10-year risk	Two or more RFs,* <10% 10-year risk	Less than two RFs*	
Total in risk category	27.6	11.4	20.4	95.5	154.8
Metabolic syndrome	14.9/27.6 (54.1)	4.8/11.4 (41.8)	7.9/20.4 (38.9)	8.6/95.5 (9.0)	36.3/154.8 (23.4)
Diet therapy for LDL-C†	12.8/14.9 (86.0)	3.2/4.8 (66.3)	5.0/7.9 (63.1)	1.8/8.6 (21.3)	22.8/36.3 (63.0)
Drug therapy for LDL-C‡					
By cutpoints	8.4/14.9 (56.7)	3.2/4.8 (66.3)	2.0/7.9 (24.9)	0.6/8.6 (7.3)	14.2/36.3 (39.2)
By cutpoints + optional	12.8/14.9 (86.0)	3.2/4.8 (66.3)	2.0/7.9 (24.9)	1.8/8.6 (21.3)	19.8/36.3 (54.6)
Therapy for non-HDL-C‡	5.7/14.9 (38.3)	1.6/4.8 (33.3)	2.8/7.9 (35.4)	1.5/8.6 (17.4)	11.6/36.3 (31.9)

CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; RF, risk factors.

*Cigarette smoking, hypertension (blood pressure $\geq 140/90$ mmHg or on antihypertensive medication), low HDL-C [< 1.03 mmol/l (40 mg/dl)], family history of premature coronary heart disease (male first-degree relative aged < 55 years; female first-degree relative aged < 65 years), age (men ≥ 45 years; women ≥ 55 years); HDL-C ≥ 1.55 mmol/l (60 mg/dl) is a negative risk factor, decreasing by one the total number of risk factors.

†ATP III recommends diet therapy if LDL-C is ≥ 2.59 mmol/l (100 mg/dl) and drug therapy if LDL-C is ≥ 3.36 mmol/l (130 mg/dl), with the option of initiating drug therapy if LDL-C is 100–129 mg/dl. In individuals without CHD or equivalent who have two or more risk factors, ATP III recommends diet therapy if LDL-C is ≥ 3.36 mmol/l (130 mg/dl); drug therapy is recommended if 10-year risk is 10–20% and LDL-C is ≥ 3.36 mmol/l (130 mg/dl) or if 10-year risk is $< 10\%$ and LDL-C is ≥ 4.14 mmol/l (160 mg/dl). In patients without CHD or equivalent who have less than two risk factors, ATP III recommends diet therapy if LDL-C is ≥ 4.14 mmol/l (160 mg/dl) and drug therapy if LDL-C is ≥ 4.91 mmol/l (190 mg/dl), with the option of initiating drug therapy if LDL-C is 4.14–4.90 mmol/l (160–189 mg/dl).

‡In individuals with triglyceride ≥ 2.26 mmol/l (200 mg/dl) and non-HDL-C ≥ 3.36 mmol/l (130 mg/dl) in individuals with CHD or CHD risk equivalent, ≥ 4.14 mmol/l (160 mg/dl) in individuals without CHD who have two or more risk factors, and ≥ 4.91 mmol/l (190 mg/dl) in individuals without CHD who have less than two risk factors.

diet would increase the percentages to 84.7 and 89.6% respectively.

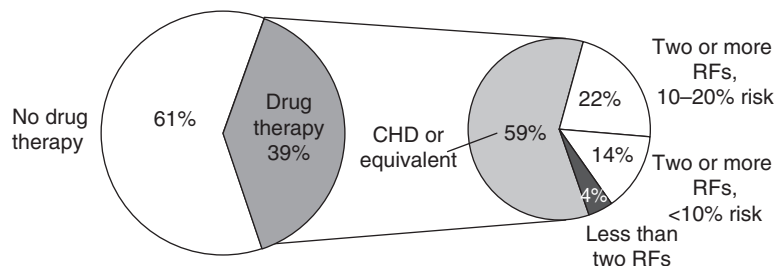
While LDL-C often is not substantially elevated in individuals with the metabolic syndrome, elevated triglyceride and low HDL-C are common dyslipidaemias in this population, present in 74 and 76% respectively; mean triglyceride was 2.19 mmol/l [194.1 mg/dl; median 2.07 mmol/l (183.3 mg/dl)], and mean HDL-C was 0.97 mmol/l [37.4 mg/dl; median 0.93 mmol/l (35.9 mg/dl)] in men and 1.17 mmol/l [45.4 mg/dl; median 1.10 mmol/l (42.6 mg/dl)] in women. Among individuals with the metabolic syndrome, mean non-HDL-C was 4.61 mmol/l (178.1 mg/dl) and median non-HDL-C was 4.54 mmol/l (175.4 mg/dl) (figure 6). Non-HDL-C is a secondary target for therapy in the 15.3 million individuals with the metabolic syndrome and triglycerides ≥ 2.26 mmol/l

(200 mg/dl) (42.2% of those with the metabolic syndrome). Of these, 11.6 million (75.7%) have non-HDL-C above the levels recommended by ATP III (table 4). Of the 12.1 million non-diabetics with the metabolic syndrome and triglycerides ≥ 2.26 mmol/l (200 mg/dl), 8.7 million (71.9%) have non-HDL-C above the levels recommended by ATP III.

Discussion

In this analysis of NHANES III data, we show that the ATP III definition of the metabolic syndrome describes a large number of Americans, yet because LDL-C typically is not substantially elevated, the guidelines recommend drug therapy for only a minority. Instead, high triglycerides and low HDL-C are more common dyslipidaemias

Fig. 3 Per cent of individuals with the metabolic syndrome recommended for drug therapy by Adult Treatment Panel III cutpoints. CHD, coronary heart disease; RF, risk factors.



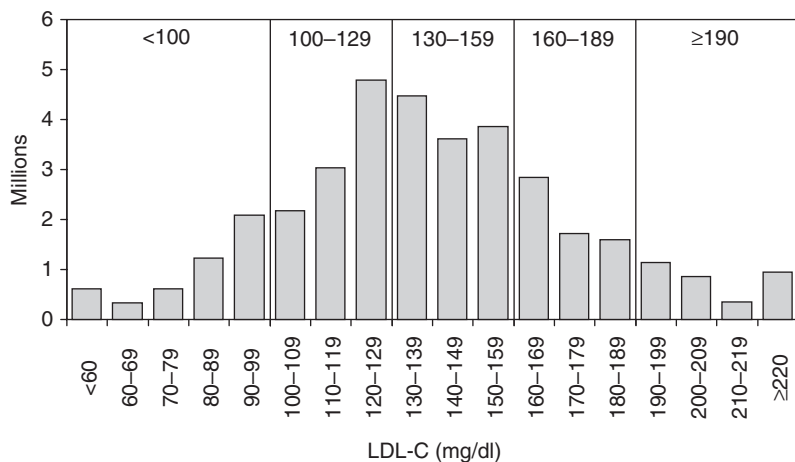


Fig. 4 Distribution of low-density lipoprotein cholesterol (LDL-C) levels in US adults with the metabolic syndrome.

in this growing patient population, and these lipid abnormalities as well as elevated blood pressure and waist circumference are found in more individuals with the metabolic syndrome than is elevated glucose. Two-fifths of patients with the metabolic syndrome have CHD or a CHD risk equivalent, and more than half of all US adults with CHD or equivalent have the metabolic syndrome.

Of the estimated 36.3 million individuals with the metabolic syndrome, the majority are middle aged, but approximately 3–4 million non-diabetics with the metabolic syndrome are younger (aged < 35 years) or older (aged ≥ 75 years) and are therefore traditionally less likely to be treated with lipid-lowering therapy.

In the Framingham Offspring Study, clusters of three or more metabolic risk factors (lowest quintile of HDL-C, highest quintiles of body mass index, systolic blood pressure, triglycerides, glucose and serum cholesterol) significantly increased risk for CHD events over 16-year follow-up by 2.4 times in men and 5.9 times in women [2]. In the Botnia study, conducted in families with type 2 diabetes in Finland and Sweden, cardiovascular mortality was 12.0% in subjects with the metabolic

syndrome as defined by the World Health Organization (two or more of the following: obesity, hypertension, dyslipidaemia and microalbuminuria), significantly higher than the 2.2% found in subjects without the metabolic syndrome [3]. In an analysis of 999 asymptomatic individuals enrolled in the Prospective Army Coronary Calcium study, subjects with the metabolic syndrome as defined in the ATP III guidelines (n = 89) were significantly more likely to have a positive coronary artery calcification score on electron beam-computed tomography than were subjects without the metabolic syndrome (24.7 vs. 16.5%), and the percentage of subjects with positive calcification scores increased significantly with the number of components of the metabolic syndrome that were present [18].

The metabolic syndrome is associated with insulin resistance, which may be the fundamental defect underlying this constellation of risk factors [19]. Several studies have demonstrated that the components of the metabolic syndrome cluster in individuals [20,21], with obesity as a central component [22]. The influence of obesity on CHD risk with this syndrome may be mediated by proinflammatory and prothrombotic states [23]; however, diagnosis and therapy (beyond aspirin) for these conditions have not yet been defined.

Although a large number of US adults are identified as having the metabolic syndrome on the basis of this analysis of NHANES III, this number may be an underestimation because of the NHANES study design and available data. A previous estimate of prevalence of the metabolic syndrome based on NHANES III data reported a similar prevalence (23.7%, age adjusted) but applied this rate to 2000 census data to suggest that a larger number of individuals have the metabolic syndrome [10]; in the present analysis, 1990 census data were

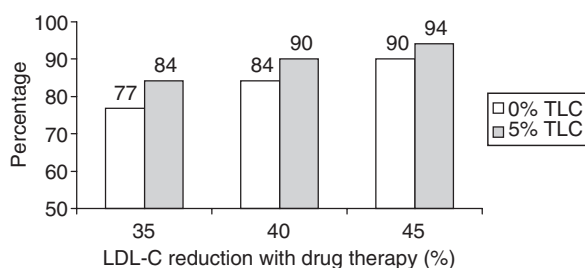


Fig. 5 Per cent of individuals with the metabolic syndrome reaching low-density lipoprotein cholesterol (LDL-C) goal with drug therapy and therapeutic lifestyle changes (TLC).

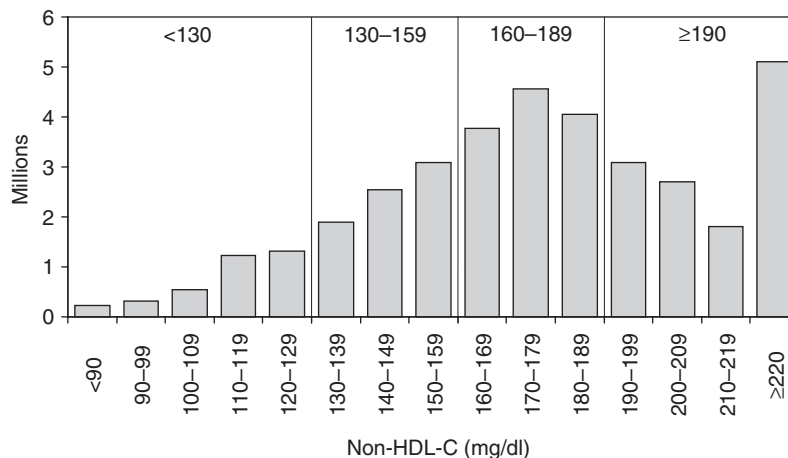


Fig. 6 Distribution of non-high-density lipoprotein cholesterol (non-HDL-C) levels in US adults with the metabolic syndrome.

used as a more valid reflection of the US population at the time NHANES III was conducted (1988–94). Individuals who were unable to give a fasting blood sample, including diabetics on insulin, were excluded from the analysis, as were individuals with a triglyceride level > 4.52 mmol/l (400 mg/dl), of whom a large proportion likely had the metabolic syndrome. Also, our analysis does not take into account the increasing epidemic of diabetes and obesity in the years since NHANES III was conducted [6]; the estimated 8.8 million diabetics in NHANES III is far less than the most recent national estimate of 17 million [24], and only 7.5 million diabetics were identified in this analysis as having the metabolic syndrome, indicating that not all diabetics meet these diagnostic criteria. Conversely, this analysis also showed that the metabolic syndrome (or insulin resistance) is present in a large number of individuals without diabetes or impaired fasting glucose.

The previous analysis [10] also failed to distinguish between diabetics and non-diabetics and used as the criterion for impaired fasting glucose all values ≥ 6.1 mmol/l (110 mg/dl), instead of 6.1–6.9 mmol/l (110–125 mg/dl) as recommended in the ATP III full report. While the guidelines provide for aggressive therapy in individuals with diabetes, including these patients in the highest-risk category of CHD equivalent and recommending the lowest targets for both LDL-C and non-HDL-C, the treatment of non-diabetics with the metabolic syndrome is less clear; most are not recommended for drug therapy by the ATP III cutpoints, yet this large number of individuals is at increased CHD risk because of this constellation of risk factors.

Most individuals with the metabolic syndrome are in the higher risk categories defined by ATP III; 41% have CHD or CHD risk equivalents and 35% do not have CHD

but do have multiple risk factors. Of the total estimated number of individuals with CHD or CHD risk equivalents, most (54%) have the metabolic syndrome as defined by ATP III. However, using the LDL-C drug-initiation cutpoints in ATP III, drug therapy is recommended for only 57% of individuals with the metabolic syndrome and CHD or CHD risk equivalents, and for only 36% of individuals with the metabolic syndrome who do not have CHD but do have multiple risk factors. The presence of the metabolic syndrome enhances CHD risk at any given LDL-C level [1]; because of the high CHD risk of these patients, aggressive intervention may be warranted. In the Heart Protection Study, conducted in more than 20 000 men and women with CHD or other non-coronary atherosclerosis, diabetes or treated hypertension, lipid-lowering therapy with simvastatin 40 mg/d reduced vascular events at 5 years regardless of baseline LDL-C, including among patients whose LDL-C was < 3.0 mmol/l (116 mg/dl) at baseline [25]. In the Lescol Intervention Prevention Study, conducted in 1677 men and women after percutaneous coronary intervention, lipid-lowering therapy with fluvastatin 80 mg/d reduced major adverse cardiac events at 4 years in patients whose LDL-C was below the median of 3.4 mmol/l (132 mg/dl) at baseline [26]. In the Veterans Affairs High-Density Lipoprotein Intervention Trial, lipid-lowering therapy with gemfibrozil reduced CHD events in high-risk patients with low LDL-C [mean 2.9 mmol/l (111 mg/dl)] [27], particularly in those with aspects of the metabolic syndrome [28].

Diet and exercise are first-line therapy for all individuals with the metabolic syndrome [1,29], even if LDL-C levels would not be considered elevated by the ATP III guidelines [1]. Recent studies have shown that these interventions can prevent the onset of type 2 diabetes

mellitus [30,31]. These therapeutic lifestyle changes are safe and effective and may target the underlying pathophysiology of the metabolic syndrome, but many individuals are unable to reach or maintain recommended goals of therapy with lifestyle interventions alone. Pharmacologic therapy, including antihypertensive, antidiabetic and lipid-regulating medications, may be required to treat the metabolic abnormalities associated with the metabolic syndrome. Because of the increased risk for cardiovascular disease associated with the metabolic syndrome [2,3], aggressive treatment of the component abnormalities is essential.

Most individuals with the metabolic syndrome (almost 61%) are not recommended for drug therapy by the LDL-C cutpoints for drug initiation in the ATP III guidelines. LDL-C is often not substantially elevated in individuals with the metabolic syndrome; in this analysis, mean LDL-C was 3.6 mmol/l (139 mg/dl) and median LDL-C was 3.5 mmol/l (136 mg/dl). With moderate LDL-C lowering of 35–40%, most of the 14.2 million individuals recommended for lipid-lowering drug therapy will reach LDL-C goals recommended by ATP III.

Instead of elevated LDL-C, more common dyslipidaemias among individuals with the metabolic syndrome are elevated triglycerides [≥ 1.69 mmol/l (150 mg/dl) in 74%] and low HDL-C [< 1.03 mmol/l (40 mg/dl) in 51%]. The current guidelines do not recommend routine measurement of LDL particle size or apolipoprotein B-100 level, which may be abnormal in many of these patients; instead, non-HDL-C level is targeted for therapy. Non-HDL-C [mean 4.60 mmol/l (178 mg/dl) and median 4.53 mmol/l (175 mg/dl) in all individuals with the metabolic syndrome] is an important secondary target for the 15 million individuals who have the metabolic syndrome and triglycerides ≥ 2.26 mmol/l (200 mg/dl). Non-HDL-C is above the levels recommended by ATP III in most (76%) of these individuals, identifying a large number of individuals that should be targeted for therapy. ATP III does not provide specific guidelines on when to initiate drug therapy for elevated non-HDL-C if LDL-C is below the level for drug initiation. More intensive therapy, including combination lipid-lowering therapy and aggressive lifestyle changes, may be required to achieve target levels for both LDL-C and non-HDL-C in many individuals. This population may also benefit from increasing the level of HDL-C, although a specific goal of therapy has yet to be established.

Clinical trial evidence in patients with elevated triglycerides and/or low HDL-C supports the use of fibrates or statins to reduce risk for CHD events. *Post hoc* analyses of the Helsinki Heart Study [32] and the Bezafibrate Infarction Prevention (BIP) study [33] both demon-

strated that patients with lipid profiles characteristic of the metabolic syndrome [LDL-C/HDL-C ratio > 5 and triglyceride level > 2.31 mmol/l (205 mg/dl) in Helsinki; HDL-C < 0.91 mmol/l (35 mg/dl) and triglycerides ≥ 2.26 mmol/l (200 mg/dl) in BIP] had increased risk for CHD events and increased benefit with fibrate therapy. Statin therapy was also shown to provide greater benefit in patients in the lowest quartile for HDL-C [< 1.00 mmol/l (39 mg/dl)] and the highest quartile for triglycerides [> 1.80 mmol/l (159 mg/dl)] in a *post hoc* analysis of the Scandinavian Simvastatin Survival Study, in which all patients also had elevated LDL-C; placebo patients with this lipid profile had the highest CHD event rate [34].

Combination therapy was studied in the HDL-Atherosclerosis Treatment Study, in which mean triglyceride was 2.40 mmol/l (213 mg/dl) and mean HDL-C was 0.80 mmol/l (31 mg/dl) at baseline; simvastatin plus niacin significantly reduced the risk for a composite cardiovascular endpoint by 90% compared with placebo and resulted in regression of atherosclerosis as measured by angiography [35]. Subgroup analysis of the 77 patients (48%) with the metabolic syndrome [three or more of the following: triglycerides ≥ 1.69 mmol/l (150 mg/dl), HDL-C < 1.03 mmol/l (40 mg/dl) in men or < 1.29 mmol/l (50 mg/dl) in women, treated hypertension or blood pressure $\geq 130/85$ mmHg, fasting glucose ≥ 6.1 mmol/l (110 mg/dl)] indicated that placebo patients with the metabolic syndrome had the highest cardiovascular event rate (30%, compared with 14% in placebo patients without the metabolic syndrome) and the most CHD progression (4.1% increase in per cent diameter stenosis, compared with 1.4% increase in placebo patients without the metabolic syndrome); simvastatin plus niacin reduced cardiovascular events by 40% and significantly reduced CHD progression by 90% [36].

Clinical trials of lipid-modifying therapy are needed in this high-risk population with the metabolic syndrome to determine whether the benefits of combination therapy outweigh the potential risks, particularly of myopathy, which have been associated with combination therapy with a statin. Although statins are considered to have a class effect on inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and all of them lower LDL-C levels by varying degrees, the rate of reported fatal rhabdomyolysis ranged from 0 per million prescriptions with fluvastatin to 0.04 per million with pravastatin and atorvastatin up to 3.16 per million with cerivastatin [37]. Most of the evidence on combining a statin with a fibrate has been with gemfibrozil; it is possible that the incidence is lower with fenofibrate. Additional studies are needed to determine

whether differences in statin or fibrate pharmacology may lead to clinically significant differences in the risks of combination therapy. The identification of 36.3 million American adults with the metabolic syndrome as defined by the ATP III diagnostic criteria confirms the magnitude of the problem, and the growing epidemics of obesity, diabetes and insulin resistance will continue to increase this patient population. CHD prevention in these high-risk patients should include diagnosis and treatment of not only elevated LDL-C but also elevated non-HDL-C and low HDL-C levels, as well as the other lipid and non-lipid risk factors associated with the metabolic syndrome.

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