

## Autonomic nervous cardiovascular regulation in borderline hypertension

S. Julius, M. Esler

*Am J Cardiol.* 1975;36:685-696

---

In this article from 1975, the authors review the evidence for the hypothesis that most of the observed abnormalities in borderline hypertension can be explained by neurogenic mechanisms. This theory states that increased autonomic drive to the heart, vasculature, kidneys, and other organs results in hypertension. The authors believe that people with borderline hypertension make good subjects for research into the pathophysiology of hypertension. This is because unlike subjects with established hypertension they do not have secondary changes due to hypertension, which may bias research.

The authors begin by presenting the biochemical evidence for overactivity of the sympathetic nervous system in borderline hypertension. Norepinephrine levels have been demonstrated to be elevated in blood and urine in some patients with hypertension. Results are less conclusive in those with borderline hypertension. It has also been reported that patients with borderline hypertension have increased catecholamine responsiveness to stimuli, such as mental stress, that affect the sympathetic nervous system.

Next they turn their attention to the cardiovascular system. Patients with established hypertension have increased peripheral resistance with a normal cardiac output. In contrast, some patients with borderline hypertension have been found to have an increased cardiac output (termed hyperkinetic borderline hypertension). The authors' studies suggest that the autonomic nervous system may have a role in this increase in cardiac output.

Subjects with hyperkinetic borderline hypertension were injected with propranolol and atropine to block the effect of the autonomic nervous system: as a result, the increase in cardiac output was abolished. Both heart rate and stroke volume returned to normal, suggesting that both components of cardiac output were under neurogenic control. Peripheral resistance is normal in hyperkinetic borderline hypertension, but this can be seen as inappropriate because the expected response to increased cardiac output is a decrease in peripheral resistance. In addition, in patients with borderline hypertension, there is a diminished

response to stimuli such as exercise and plasma volume expansion, which normally decrease peripheral resistance. Subjects with borderline hypertension and normal cardiac output have increased peripheral vascular resistance at rest. The authors demonstrated that in up to 30% of patients this may be determined neurogenically as the increase was abolished by the injection of an  $\alpha$ -blocker.

The role of renin is discussed. It is noted that plasma renin activity has been shown to be elevated in some patients with borderline hypertension and that some patients show an excessive increase in renin with postural change. This may be related to increased sympathetic tone as renal sympathetic nerves have a role in renin release. Possible mechanisms to account for the autonomic changes are discussed. These include defective reuptake of norepinephrine or increased responsiveness of target organs to a normal level of stimulation. There is also some evidence of vascular hyperreactivity in borderline hypertension and this may play a part in end organ hyperresponsiveness. The authors consider the integrative areas of the medulla oblongata in the brain to control the abnormal autoregulation. They believe the parasympathetic system to be involved, too, as evidenced by the effect of atropine in reducing cardiac output in borderline hypertension. They suggest that arterial baroreceptors could be reset to allow higher resting sympathetic tone, although this hypothesis has not been tested.

Thus, this paper provided a comprehensive review of the role of the sympathetic nervous system in borderline hypertension.

---

1975

Soviet dissident Andrei Sakharov wins  
the Nobel Peace Prize;

Archbishop Oliver Plunkett becomes the first

Irish-born saint in 7 centuries; and

Soviet spaceprobe Venera 9 lands on Venus



## Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR)

E. Ferrannini, A. Natali, P. Bell, P. Cavallo-Perin, N. Lalic, G. Mingrone

*J Clin Invest.* 1997;100:1166-1173

Insulin resistance is commonly recognized to occur in obesity and, when associated with other abnormalities, may be termed the insulin resistance syndrome. This study estimated the prevalence of insulin resistance in obesity using the database of the European Group for the Study of Insulin Resistance (EGIR). The database includes data from over 1000 healthy white men and women between 18 and 85 years old. Insulin resistance was measured in all patients using the euglycemic insulin clamp technique (the gold standard). This measures insulin sensitivity by infusing a constant amount of insulin and measuring how much intravenous glucose is required to maintain euglycemia. Insulin sensitivity is measured as glucose disposal rate (M). In addition, insulin secretion rates were calculated.

Data were contributed from 20 research centers in 9 different European countries. Each center contributed between 21 and 122 clamp studies in healthy patients with normal glucose tolerance, blood pressure less than 160/95 mm Hg, and no other cardiac, renal liver, or endocrine disease. This was the largest study to assess insulin resistance in healthy subjects.

A body mass index (BMI, kg/m<sup>2</sup>) greater than 25 was found in 47% of subjects in the study. The obese were older than the lean and had higher waist and hip circumferences, waist-to-hip ratio, fasting plasma glucose, fasting and steady state insulin concentration, and posthepatic plasma insulin clearance rates. The obese were more insulin-resistant, using all indices of insulin sensitivity. The average difference in insulin sensitivity was 24% to 34% when based on body weight, but fell to 15% to 25% according to indices based on fat-free mass. Differing definitions of obesity and insulin resistance resulted in ratios of insulin resistance in obese vs lean subjects in the range of 2.3 to 3.3. If insulin resistance was defined as the bottom 10% of M values in the lean group, then the frequency of insulin resistance was 19% in subjects with a BMI <30, 34% in subjects with a BMI <35, and 60% in subjects with a BMI >35. Insulin sensitivity (based on fat-free mass) decreased linearly with increasing BMI.

Using the upper 10% of fasting plasma insulin concentrations in the lean group, the frequency of hyperinsulinemia increased with BMI from 32% in those with a BMI <30, to 57% in those with a BMI <35, and to 77% in those with a BMI >35. Insulin hypersecretion also increased with BMI, from 28% in those with a BMI <30, to 49% in those with a BMI <35, and to 80% in those with a BMI >35.

In summary, the study highlighted the large variability in insulin sensitivity even in lean subjects. Obesity led to a highly significant decrease in insulin sensitivity. The prevalence of insulin resistance in the obese subjects was surprisingly low (although the study excluded subjects with hypertension, diabetes, or impaired glucose tolerance, and therefore may have selected an insulin-sensitive obese population). In addition, insulin hypersecretion was found to be more frequent than insulin resistance in the obese. Insulin resistance is difficult to measure, and the euglycemic clamp is still the best method available. This study was a masterpiece of organization, and allowed the clamp technique to be used in a large trial.

---

### 1997

---

Scotland votes for a separate Parliament for the first time since 1707, while retaining ties with the British monarchy and the National government;  
Mother Teresa, founder of the Order of Missionaries of Charity and Nobel Peace prizewinner, dies, aged 87, in the odor of sanctity;  
and Patrick Rafter of Australia wins the US Open tennis championship, defeating Greg Rudsecki in the final

## State-of-the-art lecture. Obesity-induced hypertension: new concepts from the emerging biology of obesity

A. L. Mark, M. Correia, D. A. Morgan, R. A. Schaffer, W. G. Haynes

Haynes. 1999;33(1 pt 2):537-541

**M**ark et al, in this article, challenge the view that obesity-induced hypertension is secondary to insulin resistance and hyperinsulinemia. The authors propose that advances in the understanding of the genetic and neurobiological mechanisms of obesity will provide insight into obesity and hypertension. They present the evidence for the sympathetic and cardiovascular actions of leptin and melanocortin receptor agonists.

**Leptin.** Leptin increases sympathetic nervous system (SNS) activity to brown adipose tissue and to the kidneys, adrenals, and hind limbs in rats. These actions are thought to be independent of the action of insulin because they occur in the absence of changes in insulin and glucose. Leptin may also have depressor activity, although the predominant effect seems to be pressor. In chronic administration, leptin causes increased arterial pressure in rats. This effect is seen despite an increase in insulin sensitivity, suggesting that insulin resistance is not the mediator. Decreased renal blood flow and increased renal vascular resistance and heart rate were seen, consistent with increased sympathetic activity. Conversely, natriuresis was not seen. Transgenic mice that overexpress leptin have hypertension. Obese *ob* mice with genetic leptin deficiency have significantly lower blood pressure on a low salt diet than lean controls. Similar findings are reported with leptin-resistant rats. Therefore, obesity is not universally related to hypertension, and these genetic models show that leptin deficiency or resistance can result in decreased arterial pressure despite the presence of obesity.

**Melanocortin-4 receptors.** The agouti yellow obesity syndrome in mice is linked to a mutation in the agouti gene leading to an overexpression of the agouti protein. This protein binds to melanocortin-1 receptors and prevents alpha-melanocyte stimulating hormone ( $\alpha$ -MSH) from stimulating melanin synthesis (hence the yellow hair). It also blocks  $\alpha$ -MSH effects on hypothalamic melanocortin-4 receptors, which are involved in feeding regulation, thus resulting in obesity. The authors have found that stimulation of melanocortin-4 receptors by a receptor antagonist

increases sympathetic nerve activity to brown adipose tissue and the kidney in rats, without any change in blood pressure. Agouti obese mice were found to have significantly higher arterial pressure than lean controls despite having less severe obesity than *ob* mice. Therefore, blood pressure effects of obesity may be critically dependent on the mechanism inducing the obesity.

**Genetic factors.** The authors also present evidence that genetic factors may modify the blood pressure response to obesity. The hypertensive response to obesity is less in Pima Indians, Hispanic-Americans, and African-Americans, compared with whites. Blood pressure is normal in 40% of obese people, suggesting modifying genes may have a substantial influence of phenotypic expression of obesity. Finally, findings in *ob* mice, Zucker obese rats, and Koletsky obese rats, suggest that the different genetic background of the rats influences the effect of leptin resistance on blood pressure.

In summary, the article suggests a role for leptin in obesity-induced hypertension and provides some possible underlying mechanisms (sympathetic, vascular, and renal). It also demonstrates the importance of the cause of obesity and how genetic factors may influence the blood pressure response to obesity.

---

1999

An international team of scientists trace the HIV virus to a chimpanzee subspecies;  
NATO authorizes military action if Serbia does not agree to begin talks with ethnic Albanian leaders;  
and Brazil devalues its currency by 8% following declines in its stock market and the resignation of the country's Central Bank president



## Adrenergic and reflex abnormalities in obesity-related hypertension

G. Grassi, G. Seravalle, R. Dell'Oro, C. Turri, G. B. Bolla, G. Mancia

*Hypertension*. 2000;36:538-542

Sympathetic overactivity as assessed by norepinephrine spillover and microneurographic recording of muscle sympathetic nervous activity (MSNA) has been shown to be present in normotensive overweight subjects. Similar increases have been shown in lean subjects with hypertension. The aim of this study was to determine whether these effects were additive.

A total of 57 subjects with age-range from 22 to 50 years were studied. They were divided into 4 groups, controls, obese, hypertensive, and obese hypertensive. They were classified as normotensive if blood pressure was less than 140/90 mm Hg, obese if BMI was greater than 27 kg/m<sup>2</sup> and lean if BMI was less than 25 kg/m<sup>2</sup>. In each subject measurements of blood pressure, plasma norepinephrine, and MSNA were made. In addition, baroreceptor modulation of MSNA and heart rate was assessed following the intravenous administration of two vasoactive compounds, phenylephrine and nitroprusside. Phenylephrine should induce an increase in blood pressure and an accompanying drop in heart rate and MSNA. Conversely, nitroprusside causes a decrease in blood pressure and hence the opposite effect, an increase in MSNA and heart rate. MSNA was found to be greater in obese normotensive and lean hypertensive groups. A further increase was noted in the obese hypertensive group. Plasma norepinephrine showed a similar trend, but the between-group differences were not statistically significant. In multiple regression analysis, MSNA was related to BMI and blood pressure. Reflex heart rate responses to phenylephrine and nitroprusside were less in the obese normotensive and the lean hypertensive groups compared with normals. A further reduction was seen in the obese hypertensives. In lean hypertensives, reflex sympathetic responses were preserved, but they were reduced in obese subjects and more reduced in the obese hypertensives.

These results, therefore, confirmed that MSNA was greater in obese and hypertensive individuals. In addition, it showed an additive effect on MSNA in the presence of both conditions. The authors speculate that the observed reduction in baroreceptor reflex modulation may play a role in sym-

pathetic overactivity in the obese and hypertensive. They keep their options open by suggesting other possible mechanisms such as cardiac hypertrophy, reduced insulin sensitivity, ischemic involvement of the chemoreceptors, and reduced renin, leptin, and endothelin secretion. They suggest there may be a link between sympathetic activation in the obese hypertensive and sudden death. They also suggest that their results would favor the use of drugs that act upon the central and peripheral sympathetic nervous system in patients with obesity and hypertension.

In summary, this paper provides experimental evidence for sympathetic overactivity in humans with obesity and hypertension. Additionally, it demonstrates that having both obesity and hypertension is associated with a further increase in sympathetic activity.

---

### 2000

---

Yugoslavian President Slobodan Milosevic is overthrown after several hundred thousand protesters swarm Belgrade and take over Parliament and the state-run television station; the New York Yankees defeat the Mets to win the 26th baseball world series; and Polish President Aleksander Kwasniewski is reelected with 55% of the vote

## Impact of overweight on the risk of developing common chronic diseases during a 10-year period

A. E. Field, E. H. Coakley, A. Must, J. L. Spadano, N. Laird, W. H. Dietz, E. Rimm, G. A. Colditz

*Arch Intern Med.* 2001;161:1581-1586

---

**A** comparison of the 10-year risk of developing chronic diseases such as high cholesterol level, hypertension, gallstones, type 2 diabetes, heart disease, stroke, and colon cancer in overweight and normal weight adults was carried out in 77 690 women from the Nurses' Health Study (mean age 52.9 years) and 46 060 men from the Health Professionals Follow-up study (mean age 54.5 years). They were predominately white (>93%) and 14.8% of women and 8.2% of men had a body mass index (BMI, kg/m<sup>2</sup>) greater than 30 when measured in 1986.

It was the first study to use the US dietary guidelines and World Health Organization definition of overweight, which is a BMI equal to or greater than 25. The previously used US definition had been a BMI of greater than 27.3 for women and 27.8 for men. This change in cutoff led to an increased prevalence of overweight and also to confusion about whether what was previously taken to be a healthy weight was actually associated with increased morbidity.

The study found that the risk of developing diabetes, gallstones, hypertension, heart disease, and stroke increased with severity of overweight. In addition, the risk of developing more than one illness increased with weight. Those with a BMI of more than 35 were about 20 times more likely to develop diabetes than those with a BMI in the normal range.

Adults with a BMI between 25 and 29.9 were found to be at significantly greater risk of developing many common diseases. They were 3 times more likely to develop diabetes over 10 years and were also more likely to develop gallstones, hypertension, high cholesterol, and heart disease than those with a BMI of less than 25. Men with a BMI between 25 and 29.9 also had an increased risk of stroke.

There was also an increased risk of developing common diseases at the heavier end of the normal range. The risk of developing an outcome was significantly higher in those with a BMI between 22 and 24.9 compared with those with a BMI between 18.5 and 21.9. If the reference group for

comparison was restricted to those with a BMI between 18.5 and 21.9, then the risks associated with higher BMIs (equal to or greater than 25) also increased. For example, there was a 17-fold increase in the risk of diabetes in a woman with a BMI of 35 compared with women with a BMI between 18.5 to 24.9, but this increased to a 30-fold risk if the reference group was those with a BMI between 18.5 and 21.9.

In summary, this study clearly demonstrated the risks of increasing BMI. It also demonstrated the risk of having a BMI between 25 and 30 and that even a BMI at the heavier end of the normal range was associated with additional risk of common diseases. Being overweight is bad news!

---

### 2001

---

David Trimble, the First Minister of the Northern Ireland Assembly, steps down in protest against delays in IRA weapons decommissioning; Belgian surgeon Jacques Rogge is elected the eighth president of the International Olympic Committee; and Australian Ian Thorpe breaks his own world record and anchors Australia's 400-m relay team to win gold at the FINA World Swimming Championships



## Sympathetic nervous system and insulin resistance: from obesity to diabetes

M. Esler, M. Rumantir, G. Wiesner, D. Kaye, J. Hastings, G. Lambert

*Am J Hypertens.* 2001;14(11 pt 2):304S-309S

**H**ighlighting the role of obesity in the development of hypertension, insulin resistance, and diabetes in reference to the sympathetic nervous system (SNS), this article reviews studies that have quantified SNS function by measuring rates of sympathetic nerve firing (clinical micro-neurography) and measuring organ-specific norepinephrine (NE) spillover into plasma.

Studies have shown that obese normotensive people have a normal whole-body NE spillover rate, but increased NE spillover in the kidneys, suggesting increased SNS activation of the kidney. There is also evidence of increased SNS activation in skeletal muscle from microneurography, which shows increased nerve firing in the vasculature of skeletal muscle. Interestingly, obese people with normal blood pressure have been shown to have subnormal cardiac NE spillover. Obese people with hypertension also show increased SNS activation in the kidney and skeletal muscle. However, cardiac NE spillover is almost double that of the obese normotensives and 25% higher than that of healthy volunteers, and this may partly explain the development of hypertension.

The question as to how SNS activity is stimulated in obesity is discussed. Landsberg's hypothesis suggests that SNS overactivity is a mechanism to help stabilize body weight in overeating by stimulating thermogenesis. However, this increase in SNS activity also affects the kidneys, heart, and blood vessels, increasing the blood pressure. Increased insulin secretion is seen as the mediator. An alternative explanation is that SNS activation is driven by leptin. Intravenous infusion of leptin into rats causes activation of SNS activity of the renal and hind limb vasculature without affecting heart rate (a similar pattern of SNS activation to that seen in obese humans). However, the authors have found that, in humans, leptin levels are not related to measurement of SNS activity.

How this increase in SNS activity leads to hypertension is discussed. The renal sympathetic nerves have been demonstrated to be important in the development of hypertension

in animal models. The underlying mechanism is thought to be through stimulation of renin release and reabsorption of sodium in the renal tubule. However, renal SNS overactivity is present in both normotensive and hypertensive obese humans. No predisposing or genetic factors have been identified yet that explain this.

Obesity and hypertension are often associated with hyperlipidemia and insulin resistance. The authors suggest that insulin resistance may be secondary to SNS overactivity. Vasoconstriction decreases muscle blood flow and hence decreases glucose uptake by muscle, resulting in insulin resistance. A similar mechanism is proposed to explain the lipid abnormalities seen in obesity, with vasoconstriction leading to decreased chylomicron clearance.

Whether SNS activation in hypertension has implications for the treatment of hypertension is discussed. Exercise and diet are known to reduce SNS activity and are suggested as first-line therapy in the obese. Some drugs cause reduction in SNS firing, eg, the imidazoline-binding agent rilmenidine. Other drugs, such as diuretics and some calcium channel blockers, cause reflex SNS activation. Drugs that favor vascular resistance tend to improve insulin sensitivity and, theoretically, this may make these drugs particularly useful in the management of obesity-related hypertension and insulin resistance.

---

### 2001

---

George Harrison, lead guitarist with the Beatles, dies of cancer, aged 58; an American jetliner bound for Santo Domingo plunges into the Queens neighborhood in New York just after takeoff; and the head of Hamas, Mahmoud Abu Hunud, is killed in an Israeli helicopter attack in Jerusalem

## Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey

E. S. Ford, W. H. Giles, W. H. Dietz

JAMA. 2002;287:356-359

---

Similar to the paper by Park et al (2003) from the *Archives of Internal Medicine* (see review), this brief report seeks to establish the prevalence of the metabolic syndrome as defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III). It uses the same diagnostic criteria for the metabolic syndrome in a population of subjects recruited into the Third National Health and Nutrition Examination Survey between 1988 and 1994. However, it includes a slightly smaller sample, 8814 participants instead of 12 861.

The results are comparable. Among male subjects, Mexican-Americans and whites had a higher prevalence of abdominal obesity and dyslipidemia, and African-American males had a higher prevalence of hypertension. Mexican-American males had the highest rates of hyperglycemia. Among women Mexican-Americans and African-Americans had the highest prevalence of abdominal obesity. African-American women had the highest prevalence of hypertension. Mexican-American women had the highest prevalence of hyperglycemia and dyslipidemia. The prevalence of the metabolic syndrome was 21.8% unadjusted and 23.7% age-adjusted. The prevalence increased with age and was similar in men and women.

The authors comment on the high prevalence of the metabolic syndrome in American adults. They also comment that these figures probably underestimate current prevalence, as they are based on statistics from 1988 to 1994. They feel there is an urgent need to direct efforts towards controlling the epidemic of obesity and inactivity, and that the results may have implications for health care costs in the future.

---

2002

---

“Wall Street Journal” reporter Daniel Pearle is kidnapped in Pakistan while investigating Muslim fundamentalist groups, and murdered; the master of horror Stephen King announces that he will retire when his present contract expires; and on 1st January 2003, the Europeans start using their new currency, the Euro (€)



## Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome

B. Balkau, M. A. Charles, T. Drivsholm, K. Borch-Johnsen, N. Wareham, J. S. Yudkin, R. Morris, I. Zavaroni, R. van Dam, E. Feskens, et al; European Group For The Study Of Insulin Resistance (EGIR)

*Diabetes Metab.* 2002;28:364-376

The World Health Organization (WHO) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus defined the metabolic syndrome in 1999. The European Group for the Study of Insulin Resistance (EGIR) proposed an alternative definition called the insulin resistance syndrome. The two definitions aim to describe the same condition and recognize its importance in the development of diabetes and cardiovascular disease. However the criteria for diagnosis differ. The WHO definition applies to people with or without diabetes and requires either an objective measure of insulin resistance using the hyperinsulinemic euglycemic clamp or evidence of impaired glucose regulation and 2 or more of raised blood pressure, central obesity, microalbuminuria, and raised triglycerides with low HDL cholesterol. By contrast, the EGIR definition applies only to the nondiabetic population and uses a surrogate marker of insulin resistance, hyperinsulinemia, as the core feature. In addition, patients must have 2 or more of hyperglycemia, hypertension, dyslipidemia (high triglyceride, low HDL), and central obesity. EGIR includes treatment for hypertension and dyslipidemia in the definition. To classify obesity, the WHO uses the waist-hip ratio and the body mass index (BMI), whereas EGIR uses the waist circumference only. The purpose of this paper was to compare the frequency of the syndrome in different European populations using the WHO and EGIR definitions.

Data were contributed from 8 different studies between 1981 and 1997 in 7 different European countries. In total, 8200 men and 9363 women were studied. Because none of the studies give any data on insulin resistance measured using the clamp technique as specified by the WHO criteria, the authors have used fasting insulin as a surrogate measure. Overall, the prevalence of abnormalities as defined by either the WHO or the EGIR method varied markedly between different studies depending on the population studied. Abnormalities were more frequent in males than females and increased with age. The overall prevalence of the syndrome as defined by the WHO increased with age from 14% and 4% in men and women under 40, respectively to 23% and 13% in men and women between 40 and 55, re-

spectively, and to 41% and 26% in men and women over 55, respectively. By comparison with EGIR, the frequency of impaired glucose regulation was higher in the WHO definition, which used the oral glucose tolerance test (OGTT) rather than fasting glucose. Using the WHO definition, more than 50% of people over 55 had raised blood pressure. The frequency of hypertension was higher in the EGIR definition, which included people on antihypertensive medication. Central obesity was more common in men using the WHO definition. In contrast, obesity was more common in women with the EGIR definition. Overall, the WHO syndrome was more frequent than the EGIR syndrome, but the difference was less marked in women compared with men. This was mainly due to the differing definition of obesity.

The authors suggest that the definition of obesity needs to be refined.

To summarize, this article concludes that the frequency of the metabolic syndrome varies depending on how the metabolic syndrome is defined. It also varies depending upon the population studied and how measurements such as insulin level and waist measurement are made. Ongoing studies will hopefully demonstrate the usefulness of diagnosing the metabolic syndrome and which diagnostic criteria have the greatest prognostic implications.

### 2002

Forty countries endorse the “Kimberley Process,” which prevents the trading of illegally mined diamonds from Africa on the international market; three Israelis and nine Kenyans die in a suicide attack on an Israeli-owned seaside hotel in Mombasa; and the 16th Congress of the Chinese Communist Party names Hu Jintao as Jiang Zemin’s successor to lead the country

## The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men

H. M. Lakka, D. E. Laaksonen, T. A. Lakka, L. K. Niskanen, E. Kumpusalo, J. Tuomilehto, J. T. Salonen

JAMA. 2002;288:2709-2716

Lakka and colleagues, in this article, assessed the association of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) and the World Health Organization (WHO) with cardiovascular and overall mortality during an 11-year follow-up in a population of middle-aged Finnish men with no diabetes or cardiovascular disease at baseline. The NCEP definition differs from the WHO definition, as it does not include hyperinsulinemia, uses waist circumference as the measure of obesity rather than waist-hip ratio and body mass index (BMI) used in the WHO definition, and has slightly less generous cut-offs for blood pressure and high-density lipoprotein (HDL) cholesterol.

Data were analyzed for 1209 men. The WHO definition of the metabolic syndrome was modified to not include microalbuminuria and to have a lower definition of hypertension than the original proposal.

Deaths were ascertained by computer linkage to the Finnish National Death Registry using the Finnish social security number with no patients lost to follow-up. The median follow-up was 11.6 years. There were 109 deaths during follow-up: 46 were due to cardiovascular disease (CVD), of which 27 were due to coronary heart disease (CHD). The prevalence of the metabolic syndrome at baseline was quite low, 9% to 14%, depending on the definition used.

Factors associated with CVD, CHD, and all-cause mortality were blood pressure, BMI, waist circumference, smoking, and alcohol intake. Blood glucose and insulin levels were associated with CVD and all-cause mortality, but dyslipidemia was not.

The Kaplan-Meier estimate of overall survival at 13.7 years of men with vs without the metabolic syndrome was 79% vs 90% using the NCEP criteria with a waist cutoff of 102 cm, 83% vs 90% for the NCEP criteria using a waist cutoff of 94cm, 84% vs 90% for the WHO definition based on the waist-hip ratio, and 83% vs 90% for the WHO definition with a waist cutoff of 94 cm.

The metabolic syndrome was associated with a 2.4 to 3.4 times higher mortality from CHD and this was increased by taking into account other conventional risk factors. In subjects with the metabolic syndrome, age-adjusted mortality from CVD was 2.5 to 2.8 times higher, although using the NCEP criteria this association did not reach statistical significance. Men with the WHO criteria had a 1.9 to 2.1 higher overall mortality, but using the NCEP criteria this association only tended toward statistical significance. The association between metabolic syndrome and cardiovascular mortality remained when patients with fasting hyperglycemia were excluded.

In summary, this study demonstrated in a prospective population-based cohort study that the metabolic syndrome was associated with increased total and cardiovascular mortality. This was independent of other risk factors such as smoking, low-density lipoprotein (LDL) cholesterol levels, and fasting hyperglycemia. The impact on overall mortality from the metabolic syndrome was mainly mediated through increased CHD deaths with a contribution from CVD deaths. The NCEP definition was better at predicting mortality rate if the waist cutoff of 102 cm was used, but the WHO definition more consistently predicted cardiovascular and overall mortality.

---

### 2002

---

Opposition leader Mwai Kibaki is elected president of Kenya; opponents of Venezuelan president Hugo Chavez launch a nationwide strike against his government, demanding a referendum on his presidency; and Israeli prime minister Ariel Sharon accepts a US-sponsored peace plan that includes the formation of a Palestinian state on the condition that Yasir Arafat is removed from power



## The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994

Y. W. Park, S. Zhu, L. Palaniappan, S. Heshka, M. R. Carnethon, S. B. Heymsfield

*Arch Intern Med.* 2003;163:427-436

Using the Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP III) guidelines for diagnosis of the metabolic syndrome, this paper aimed to examine the prevalence of the metabolic syndrome by ethnicity, age, body mass index (BMI), socioeconomic status, and lifestyle factors. The criteria used are 3 or more of abdominal obesity (using waist circumference), high triglyceride, low high-density lipoprotein (HDL) cholesterol, high blood pressure, and high fasting plasma glucose. These were chosen since they are easily measurable in clinical practice. An initial study had indicated that the prevalence of the metabolic syndrome was 21.8% unadjusted and 23.7% age-adjusted.

Data were collected from the Third National Health and Nutrition Examination Survey, which was conducted in two 3-year phases from 1988 to 1991 and from 1991 to 1994 in 89 centers across the USA. A total of 12 861 individuals from a variety of ethnic backgrounds had the required anthropometric measurements and were included in this study. All participants were 20 years or older.

The overall percentage of the metabolic syndrome in US adults was 22.8% for men and 22.6% for women. It was 13.9%, 20.8% and 24.3% for black, Mexican-American, and white men, respectively. It was 20.9%, 22.9%, and 27.2% for black, white, and Mexican-American women, respectively. For men and women, the prevalence of the metabolic syndrome increased sharply after the third decade and peaked in men between 50 and 70 years old and in women between 60 and 80 years old. A steep increase in the prevalence of the metabolic syndrome was noted in overweight people (BMI 25-30 kg/m<sup>2</sup>). The prevalence was 4.6%, 22.4%, and 59.6% in normal weight, overweight, and obese men and the corresponding prevalence rates for women were 6.2%, 28.1%, and 50%, respectively.

Some patterns emerged when looking at components of the metabolic syndrome. Black men had higher blood pressure, lower waist measurements, and less dyslipidemia. Mexican-American women had more dyslipidemia. Black

women had higher blood pressure and white women had lower waist measurements in the younger age groups. Multiple regression analysis showed that current smokers were significantly more likely to have the metabolic syndrome. Other factors associated with the metabolic syndrome were low household income, no alcohol consumption, high carbohydrate intake, and physical inactivity.

Thus, this large study confirmed that the metabolic syndrome was widespread among American adults. The prevalence rates varied among different ethnic groups, age-groups, and with factors such as cigarette smoking, activity levels, and carbohydrate intake. Interestingly, black men had the lowest prevalence, although they have the highest coronary heart disease mortality of any group. The authors question the validity of the metabolic syndrome diagnostic criteria when applied across different age, sex, and ethnic groups.

---

### 2003

---

The Yugoslavian Parliament votes to rename the country Serbia and Montenegro, a move aimed at reflecting Montenegro's drive for independence; the space shuttle "Columbia" breaks up as it reenters the Earth's atmosphere, killing all seven crewmembers; and architect Daniel Liebeskind's design is selected for the rebuilding of the site of the Twin Towers in New York, featuring a recessed memorial to the 9/11 victims and a 1776-foot tower