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PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA

To request monthly issues go to Rjames6556@aol.com

This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* MARCH 2009

Mortality Was Lowest At BMI Of 22.5 To 25.

3-1 BODY-MASS INDEX AND CAUSE-SPECIFIC MORTALITY IN 900 000 ADULTS

A Collaborative Analysis of 57 Prospective Studies.

This study analyzed baseline BMI vs mortality in over 890 000 participants. (At baseline, 61% male; mean age 46; range 35-89; mean BMI 25). None had a history of heart disease or stroke

The analyses were adjusted for age, sex, and smoking. Omitted the first 5 years of follow-up, leaving over 66 500 deaths of known cause during a mean of 8 years following the omitted 5 years.

In both sexes mortality was lowest at BMI of 22.5 to 25.

Mortality increased for each 5 kg/m2 increase in BMI: Overall mortality 40%; Ischemic heart disease 40%; Stroke 40%; Neoplastic disease 10%; Respiratory disease (chiefly COPD) 20%.

In the upper range (BMI 25-40) BMI was also strongly and positively associated with mortality due to diabetes, non-neoplastic kidney disease, and non-neoplastic liver disease (chiefly cirrhosis)

Absolute excess mortality in males *each year:*

For those with a BMI 35-40 (vs 22.5-25) excess mortality was about 5 per 1000

For those with a BMI 40 and above, excess mortality was about 13 per 1000

In the present decade, about 29% of vascular deaths and 8% of neoplastic deaths in late middle-age could be attributable to having a BMI greater than 25.

Median survival at age 60:

For people who reach a BMI of 25-27, life was shortened by 0-1 years

For BMI 28-30, by 1-2 years

For BMI 30-35, by 2-4 years

For BMI 40-45, by 8-10 years.

Below 22.5 mortality rose as BMI fell. (Inverse relationship) The inverse relationship was mainly because of respiratory disease and lung cancer. It was much stronger for smokers than for non-smokers.

Much of the mortality risk in the low BMI subjects could be non-causal (ie,, not due to low BMI per se, but to the cause of the low BMI. If so, the real optimum BMI might be somewhat lower than 22.5 to 25.

Association of other risk factors with increasing BMI: BP; Lipids; Diabetes;

Smoking:

The absolute excess risks for higher BMI and smoking were roughly additive.

Although both smokers and non-smokers follow the same BMI mortality trajectory, the

difference in mortality between the two is striking. In those with a BMI 22,5 – 25, yearly all-cause mortality per 1000 was about 8 in non-smokers, and 15 in smokers.

The inverse associations with COPD, lung cancer, and upper aerodigestive cancers was much steeper in smokers. Smoking can cause weight loss. Thus there would be substantially more smokers in the lower BMI categories.

Effective interventions for weight loss lower BP, favorably affect lipoprotein particles, and increase insulin sensitivity. "At least some of the major aspects of obesity are therefore reversible."

In adult life, it may be easier to avoid substantial weight gain than to lose that weight once it has been gained. By avoiding a further increase in BMI from 28 to 32, a typical person in early middle-age would gain about 2 years of life expectancy. By avoiding an increase from 24 to 32, a young adult would on average gain about 3 extra years of life.

Conclusion: BMI is a strong predictor of overall mortality, both above and below BMI of 22.5 -25 (the apparent optimum). The excess of mortality below 22.5 is due mainly to smoking.

This remarkable study should be required reading for all primary care physicians and patients.

Smoking + obesity is a deadly combination.

It is easier to calculate BMI than measure waist and hip circumference and calculate the ratio.

The article is long and complex. It was difficult to abstract.

Read the full abstract.

The Gap Between The Standards Set In CVD Prevention Guidelines And Clinical Practice Continues.

3-2 CARDIOVASCULAR PREVENTION GUIDELINES IN DAILY PRACTICE

Guidelines in Europe give high priority to prevention of CVD in clinical practice. Lifestyle preventive measures include: stopping smoking; making healthy food choices; and becoming physically active.

The evidence for CVD prevention and rehabilitation programs that address lifestyles is compelling. Yet access to such programs in Europe is limited.

This article describes three cross sectional surveys in 8 European countries 1997-2007. It asked whether preventive lifestyle measures had improved over the years, and whether the recommendations were followed in practice.

All three surveys identified consecutive hospitalized patients (men and women; mean age 60). All had a recent occurrence of acute CVD. All were interviewed one year later to determine if lifestyle preventive measures had been implemented over time.

Results (total of 8 countries):

Total change (%) over 3 surveys:	1995-1996	1999-2000	2006-2007
Smoking	20	21	18
Overweight and obesity	77	80	83
Obesity	25	33	38
Raised BP	58	58	61
Raised cholesterol	94	77	46
Diabetes	13	20	28

The results should be a cause for concern to all health policy makers, physicians, and other health-care professionals.

Unhealthy lifestyles draw attention to the need for a social strategy for CVD prevention.

It is difficult for patients to change behavior despite the development to a life-threatening disease. Sustained professional support is required to encourage lifestyle change. Drug treatment is not enough.

European health-care systems are dominated by acute care, medical technology, devices, and pharmacological treatment. All patients with CVD would benefit from access to comprehensive cardiovascular prevention and rehabilitation programs. To salvage the acutely ischemic myocardium without addressing the underlying lifestyle causes is futile. “We need to invest in prevention.”

This is discouraging. If people with a life-threatening wake-up call do not or cannot change lifestyles, how can we expect those with no history of CVD to improve their lifestyles?

Physicians must remain dedicated to education of their patients and to relentless promotion of healthy lifestyles in the general population.

An important step: Physicians must act as role models. “Physician, heal thyself!”

Social interventions have begun. New York City has taken steps to limit trans fats and salt consumption, and encouraging publication of caloric content of foods in restaurants. Schools are limiting access to soft drinks and encouraging healthy foods in cafeterias.

Nutrition facts published on food packaging are helpful. People should be encouraged to read and understand them.

Change will not be easy. It will be slow. I have hopes.

"Aspirin Continues To Be Underused"

3-3 ASPIRIN FOR PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASE

Some fundamental questions about prophylactic use of aspirin remain unanswered. Two key questions are:

1) What is the optimum dose for treatment of established cardiovascular disease (secondary prevention)?
2) In whom and when should aspirin be used for prevention of cardiovascular events in persons with no history of cardiovascular disease (primary prevention)?

The large Antithrombotic Trialists' Collaboration meta-analysis (**ATC**; 2002) of patients at high risk found that antiplatelet therapy (chiefly aspirin) reduced the risk of serious vascular events by 1/4; non-fatal MI by 1/3; non-fatal stroke by ¼; and vascular mortality by 1/6. (*Secondary prevention.)*

The combined evidence from aspirin trials is compelling, and has led to the universal recommendation of aspirin as standard therapy in patients with established vascular disease.

The benefit of aspirin is no greater with high doses than with low doses (75-150 mg). Higher doses do not lead to improved efficiency, and may be associated with more bleeding.

In this issue of Annals, the US Preventive Services Task Force (**USPSTF**) updates its recommendations for aspirin in *primary* prevention of coronary heart disease

USPSTF encourages use of aspirin:

1) For men age 45 to 79 when the potential benefit of a reduction in MI outweighs the potential harm of GI hemorrhage.
2) For women age 55 to 79 when the potential benefit in reduction of stroke outweighs the potential harm of GI hemorrhage.

The USPSTF guidelines do *not* recommend aspirin for men under age 45, or for women under age 55.

It could be argued that aspirin should be used in all individuals, men and women, who have a reasonable risk of a major cardiovascular event.

A valuable feature of USPSTF is the recommendation to share decision-making with the patient, discussing the benefits and risks, and individualizing decisions to the specific patient or situation.

"Aspirin continues to be underused, and the incorporation of the USPSTF's recommendations into daily practice will increase the use of aspirin and, in turn, prevent many thousands of cardiovascular events every year."

The Women's Health Study (WHS; 2005) was somewhat contrary. It randomized aspirin 100 mg every other day vs placebo for a mean of 10 years in over 39 000 women age 45 and older (mean age 55). Unexpectedly, aspirin did not reduce risk of myocardial infarction or death. The risk of ischemic stroke declined by 24%, with a non-significant increase in risk of hemorrhagic stroke.

The editorial comments on some debatable aspects of the trial.

As usual, decisions to use aspirin depend on agreement between clinicians and patients who are fully informed about benefits and harms.

For details about the ATC and the Women's study go to Google:

PMID: 11786451 PMID: 15753114

Red Meat Associated with Increases in Total, Cancer, and CVD Mortality

3-4 MEAT INTAKE AND MORTALITY: A Prospective Study of Over Half a Million People

This study assessed the relation between red, white, and processed meat on the risk of total mortality and cause-specific mortality. It included about half a million men and women enrolled in the National Institutes of Health—AARP Diet and Health Study.

Recruited individuals age 50 to 71 for 6 states and two metropolitan areas. After exclusions, the analytic cohort included 322 265 men and 223 390 women.

At baseline, all completed a 124-item questionnaire on demographic and lifestyle characteristics, including dietary habits.

Meat intakes based on quintiles of red meat intake in men:

	Q1	Q5
Red meat g/1000 kcal	10	68
White meat g/1000 kcal	37	31
Processed meat g/kcal	5	19

Intakes was similar in women.

During 10 years of follow-up, there were 47 976 male deaths, and 23 276 female deaths.

Mortality in men (Hazard ratios—adjusted):

A. Red meat intake	Q1	Q5
All deaths	1.00	1,31
Cancer deaths	1.00	1.22
CVD deaths	1.00	1.27
B. White meat intake		
All deaths	1.00	0.92

Cancer deaths	1.00	0.84
CVD deaths	1.00	1.05
C. Processed meat		
All deaths	1.00	1.16
Cancer deaths	1.00	1.12
CVD deaths	1.00	1.09

Mortality in women was similar.

"We found modest increases in risk for total mortality, as well as cancer and CVD mortality, with higher intakes of red and processed meat."

In contrast, higher white meat consumption was associated with a small *decrease* in total and cancer mortality.

CONCLUSION: Higher red and processed meat intakes were associated with modest increases in total, cancer, and cardiovascular mortality. High white meat intake was associated with a small *decease* in total and cancer mortality.

I believe primary care clinicians may reasonably advise patients about these dietary restrictions.

It joins other important beneficial life-style modifications.

Primary care clinicians should adopt healthy lifestyles themselves.

Healthy Life-Style Behaviors Lower Risk Of Stroke.

3-5 COMBINED EFFECT OF HEALTH BEHAVIORS AND RISK OF FIRST EVER STROKE IN 20 040 MEN AND WOMEN OVER 11 YEARS' FOLLOW-UP

This study examined the potential magnitude of combined lifestyle behaviors on the incidence of stroke in men and women age 40-79 over a 12 year period.

Created a health behavior score:	Points
Non-smoker	1
Physically active or non-sedentary occupation	1
Alcohol 1 to 14 drinks per week	1
Fruit and vegetable intake 5 or more/ day	1

Total score ranging from 0 to 4. (Highest score the healthiest.)

Determined incident cases of stroke

Incidence of stroke decreased in a linear fashion with every point increase in score.

Absolute risks for incident stroke (%)

Behavior score	0	5.8
	1	6.1
	2	4.0
	3	2.4
	4	1.7

Conclusion: Relatively modest and achievable health behaviors in combination (non-smoking, physically active, moderate alcohol intake, and eating fruits and vegetables) can produce a substantial reduction in risk of stroke.

Favorable lifestyle behaviors reduce risk of hypertension, diabetes, and coronary heart disease, as well as stroke.

Leading patients to adopt healthy lifestyles is an opportunity and challenge for primary care.

If we could get the general population of the US to adopt a healthy lifestyle, I believe our problems with financing good health care for all would disappear.

Getting one patient to stop smoking might be equivalent to avoiding one coronary by-pass.

"The Key Question Is Not Whether PSA Screening Is Effective, But Whether It Does More Good Than Harm."

3-6 SCREENING FOR PROSTATE CANCER: The Controversy That Refuses to Die

In the US, most men over age 50 have had a prostate-specific antigen (**PSA**) test despite the absence of evidence from large, randomized trials of a net benefit. About 95% of urologists and 78% of primary care physicians age 50 and over report that they have had a PSA test themselves.

And indeed, US death rates from prostate cancer (**PC**) have fallen about 4% per year since 1992. "Perhaps the answer to the PSA controversy is already staring us in the face."

At the same time, practice guidelines cite unproven benefits of PSA screening, as well as the known side effects, which largely reflect the high risks of overdiagnosis and overtreatment that screening engenders.

This issue of NEJM reports two large studies:

The first trial reported *no* mortality benefit from combined screening with PSA and digital rectal examination (**DRE**) during a median follow-up of 10 years.

The second trial reported that PSA screening without DRE, at a median follow-up of 9 years, was associated with an absolute reduction of about 7 PC deaths per 10 000 men screened.

Where do we stand?

Serial PSA screening has, at best, a modest effect of PC mortality during the first decade of follow-up. This benefit comes at the cost of substantial overdiagnosis and overtreatment.

"It is important to remember that the key question is not whether PSA screening is effective, but whether it does more good than harm."

Compared with breast cancer screening, which also has modest effectiveness, PSA screening leads to a much higher risk of overdiagnosis and overtreatment.

"The implications of the trade-offs reflected in these data, like beauty, will be in the eye of the beholder." "Further analysis will be needed from these trials, as well as from others, if the PSA controversy is to sleep the big sleep."

A shared decision-making approach to PSA screening, as recommended by most guidelines, seems more appropriate than ever.

The editorialist seems unenthusiastic about screening with PSA He may be leaning toward DRE

But, why are PC deaths down over the past 17 years?

The bloom has been coming off PSA. We have progressed from enthusiasm, to concern, to doubt.

The articles give a rough guide the help the patients to make a shared-decision about screening:

If you are asymptomatic, PSA screening will reduce your chances of dying from PC to 1 in 1000 over the next 10 years.

Screening will increase your chances of receiving a biopsy by 4 in 10.

It will increase your chances of receiving a radical prostatectomy to 3 in 100.

Radical therapy will reduce your chances of death from PC in the next 10 years by about 1 in 50.

Serious adverse effects follow radical surgery.

ABSTRACTS MARCH 2009

Mortality Was Lowest At BMI Of 22.5 To 25.

3-1 BODY-MASS INDEX AND CAUSE-SPECIFIC MORTALITY IN 900 000 ADULTS

A Collaborative Analysis of 57 Prospective Studies.

Raised BMI is an established risk factor for several causes of death: ischemic heart disease; stroke; and cancers of the large intestine, endometrium, kidney, and postmenopausal breast.

The main associations of BMI with overall and cause-specific mortality can best be assessed by a long-term prospective follow-up of large numbers of people.

The Prospective Studies Collaboration included 57 studies relating BMI to cause-specific mortality.

STUDY

1. Analyzed baseline BMI vs mortality in over 890 000 participants. (At baseline, 61% male; mean age 46; range 35-89; mean BMI 25). None had a history of heart disease or stroke. Information about BP, total cholesterol, smoking, and diabetes was available for most.
2. The analyses were adjusted for age, sex, and smoking. Omitted the first 5 years of follow-up, leaving over 66 500 deaths of known cause during a mean of 8 years following the omitted 5 years.
3. Mean age at death was 67.
4. Obtained information about underlying causes of death.

RESULTS

1. In both sexes mortality was lowest at BMI of 22.5 to 25.
2. Mortality for *each* 5 kg/m^2 BMI higher than 25:
    - A. Overall mortality: Increased by about 30%
        - The absolute excess risks for higher BMI and smoking were roughly additive
        - The proportional increase was greater in ages 35-59, but was still associated with almost a 30% higher mortality at age 70-79
    - B. Ischemic heart disease mortality: Increased by about 40%.
        - The positive association with BMI was largely accounted for by increases in BP, lipoprotein particles, and diabetes
    - C. Stroke mortality: Increased by about 40%.
        - The association was much stronger in middle than in older age
        - BMI was associated positively with ischemic, hemorrhagic, and total stroke, largely

accounted for by effects of BMI on BP

D. Neoplastic disease mortality: Increased by about: 10%.

The association was much weaker than for vascular disease

E. Respiratory disease mortality: Increased by about 20%

F. Remaining causes of mortality:

In the upper range (BMI 25-40) BMI was strongly and positively associated with mortality due to diabetes, non-neoplastic kidney disease, and non-neoplastic liver disease (chiefly cirrhosis)

3. These positive associations with BMI could have resulted from the effects of adiposity on BP, diabetes, lipids, and on non-alcoholic fatty liver disease.

4. Absolute excess mortality in males *each year:*

For those with a BMI 35-40 (vs 22.5-25) excess mortality was about 5 per 1000

For those with a BMI 40 and above, excess mortality was about 13 per 1000

5. In the present decade, about 29% of vascular deaths and 8% of neoplastic deaths in late middle-age could be attributable to having a BMI greater than 25.

6. Median survival at age 60:

For people who reach a BMI of 25-27, life was shortened by 0-1 years

For BMI 28-30, by 1-2 years

For BMI 30-35, by 2-4 years

For BMI 40-45, by 8-10 years.

7. Mortality in subjects with BMI *under* 22.5 (15-22.4):

Below 22.5 mortality rose as BMI fell. (Inverse relationship)

The inverse relationship was mainly because of respiratory disease and lung cancer.

It was much stronger for smokers than for non-smokers.

Upper aerodigestive cancer: Cancers of the mouth, pharynx, and larynx, and esophagus increased as BMI fell.

Respiratory disease rose as BMI fell, mainly due to COPD. COPD mortality was 4 times higher for each 5 kg/m2 decrease in BMI, mainly due to smoking.

Much of the mortality risk in the low BMI subjects could be non-causal (ie,, not due to low BMI per se, but to the cause of the low BMI. If so, the real optimum BMI might be somewhat lower than 22.5 to 25.

In the 15-22 range, there was no evidence of a positive association between BMI and mortality

from stroke.

8. Association of other risk factors with BMI:

BP: On average, across all ages, every 5 kg/m^2 increase in BMI was associated with at least a 5 mmHg higher systolic and a 4 mmHg higher diastolic.

Lipids: Each 5 kg/m^2 increase was associated with a 0.5 mmol/L higher non-HDL cholesterol and a higher non-HDL / HDL ratio.

Diabetes: BMI > 30 was strongly associated with diabetes, with prevalences rising more than 5-fold over the range 30-50.

Alcohol: BMI was lower in regular alcohol users. The presence of drinking (especially in females) tended to be higher in those with a low BMI.

Smoking:

The absolute excess risks for higher BMI and smoking were roughly additive.

Although both smokers and non-smokers follow the same BMI mortality trajectory, the difference in mortality between the two is striking. In those with a BMI 22.5 – 25, yearly all-cause mortality per 1000 was about 8 in non-smokers, and 15 in smokers.

In the lower BMI range, the inverse associations with COPD, lung cancer, and upper aerodigestive cancers was much steeper in smokers.

Smoking can cause weight loss. Thus there would be substantially more smokers in the lower BMI categories.

DISCUSSION

1. "In this collaborative analysis of data from almost 900 000 adults in 57 prospective studies, overall mortality was lowest at about 22.5-25 kg/m^2 in both sexes, and at all ages."
2. Both in current cigarette smokers and life-long non-smokers, overall mortality was lowest at BMI 22.5 – 25 kg/m^2
3. Above 25, *each* 5 kg/m^2 higher BMI was associated with about 30% higher all-cause mortality.
4. Below 22.5, as BMI fell, mortality rose. (Inverse relation)

The inverse association was predominantly due to smoking-related respiratory disease and ischemic heart disease.

5. BMI is strongly associated with waist circumference. In the EPIC prospective study, of 360 000

adults, the two variables had about an 85% correlation. Each has a similar association with mortality. Either measurement can be used to help assess the causal relevance of obesity to mortality. Each could add to the other. Neither, however, directly measures visceral fat. (*This study did not measure central obesity.*)

6. Both BMI and waist circumference are closely correlated with aspects of adiposity that directly affect BP, lipoprotein particles, and diabetes.
7. Effective interventions for weight loss lower BP, favorably affect lipoprotein particles, and increase insulin sensitivity. "At least some of the major aspects of obesity are therefore reversible."
8. In adult life, it may be easier to avoid substantial weight gain than to lose that weight once it has been gained. By avoiding a further increase in BMI from 28 to 32, a typical person in early middle-age would gain about 2 years of life expectancy. By avoiding an increase from 24 to 32, a young adult would on average gain about 3 extra years of life.

CONCLUSION

BMI is a strong predictor of overall mortality, both above and below BMI of 22.5 -25 (the apparent optimum).

The excess of mortality below 22.5 is due mainly to smoking.

Lancet March 28, 2009; 373: 1083-96 Analysis by the Prospective Studies Collaboration, Clinical Trial Service Unit and Epidemiological Services Unit, University of Oxford, UK

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The Gap Between The Standards Set In CVD Prevention Guidelines And Clinical Practice Continues.

3-2 CARDIOVASCULAR PREVENTION GUIDELINES IN DAILY PRACTICE

Management of patients with established cardiovascular disease (**CVD**) should aim to reduce the risk of future atherosclerotic events, improve quality of life, and lengthen survival.

Guidelines in Europe give high priority to prevention of CVD in clinical practice. Lifestyle preventive measures include: stopping smoking; making healthy food choices; and becoming physically active.

The evidence for CVD prevention and rehabilitation programs that address lifestyles is compelling. Yet access to such programs in Europe is limited.

This article describes three cross sectional surveys in 8 European countries: 1995-1996; 1999-2000; and 2006-2007. It asked whether preventive lifestyle measures had improved over the years, and whether the recommendations were followed in practice.

STUDY

1. All three surveys identified consecutive hospitalized patients (men and women; n = over 3000 in the first survey; over 2900 in the second; and over 2300 in the third). Mean age was 60. All had a recent occurrence of acute CVD. All were interviewed one year later to determine if lifestyle preventive measures had been implemented over time.
2. Results (total of 8 countries):

Total change (%) over 3 surveys:	1995-1996	1999-2000	2006-2007
Smoking	20	21	18
Overweight and obesity	77	80	83
Obesity	25	33	38
Raised BP	58	58	61
Raised cholesterol	94	77	46
Diabetes	13	20	28

3. Smoking prevalence increased in women under age 50.
4. The proportion of subjects taking lipid-modifying drugs increased 7-fold. However, in survey 3, 43% had not achieved the recommended target (<175 mg/dL).
5. Therapeutic control of diabetes remained poor.

DISCUSSION

1. The gap between the standards set in CVD prevention guidelines and clinical practice continues.
2. The results should be a cause for concern to all health policy makers, physicians, and other health-care professionals.
3. The adverse lifestyle trends, especially the increase in smoking in younger female patients and the substantial increase in obesity indicate the need for better preventive programs.
4. Successful weight reduction needs sustained personal and family motivation and long-term professional support.
5. BP control did not improve despite large increases in prescriptions for all classes of

anti-hypertension drugs. This might be due to the increase in obesity, inadequate up-titration of dose, and poor patient compliance.

6. In contrast to BP, lipid concentrations have improved substantially, largely due to increased use of statins.
7. Good glycemic control prevents microvascular complications of diabetes if implemented soon after diagnosis. It also reduces risk of cardiovascular disease. The reported increase in diabetes reflects the rise in obesity. Undetected diabetes is a particular concern.
8. Unhealthy lifestyles draw attention to the need for a social strategy for CVD prevention.
9. It is difficult for patients to change behavior despite the development to a life-threatening disease. Sustained professional support is required to encourage lifestyle change. Drug treatment is not enough.
10. European health-care systems are dominated by acute care, medical technology, devices, and pharmacological treatment. All patients with CVD would benefit from access to comprehensive cardiovascular prevention and rehabilitation programs. To salvage the acutely ischemic myocardium without addressing the underlying lifestyle causes is futile. "We need to invest in prevention."

Lancet March 14, 2009; 373: 929-40 Original investigation by EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events), first author Kamelia Kotseva, National Heart and lung Institute, Imperial College, London, UK

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"Aspirin Continues To Be Underused"

3-3 ASPIRIN FOR PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASE

Millions of persons worldwide take aspirin on a daily basis for the prevention and treatment of cardiovascular disease. Aspirin inhibits platelets by irreversibly inactivating cyclo-oxygenase, thereby blocking generation of thromboxane, a potent vasoconstrictor and platelet agonist.

Some fundamental questions about prophylactic use of aspirin remain unanswered. Two key questions are:

1) What is the optimum dose for treatment of established cardiovascular disease (secondary prevention)?
2) In whom and when should aspirin be used for prevention of cardiovascular events in persons with no history of cardiovascular disease (primary prevention)?

The large Antithrombotic Trialists' Collaboration meta-analysis (**ATC**; 2002) of patients at high risk found that antiplatelet therapy (chiefly aspirin) reduced the risk of serious vascular events by 1/4; non-fatal MI by 1/3; non-fatal stroke by ¼; and vascular mortality by 1/6.

Absolute reductions in risk ranged between 2 and 9 per 100 treated. The absolute benefits substantially outweighed the risks of bleeding.[1]

The dose of aspirin has varied in trials from as high as 1500 mg daily to as low as 50 mg. In order to clarify the optimum dose, an ATC overview compared trials of different doses vs placebo. They found that the relative benefit of aspirin was no greater with high doses than with low doses (75-150 mg).

The combined evidence from aspirin trials is compelling, and has led to the universal recommendation of aspirin as standard therapy in patients with established vascular disease.

Other large trials demonstrated that, in acute coronary syndromes, bleeding risks increased with increasing doses without any concomitant improvement in efficacy.

"These data seem to support the use of lower doses of aspirin."

Higher doses of aspirin do not lead to improved efficacy, and may be associated with more bleeding.

The Women's Health Study (**WHS;** 2005) was a randomized, double-blind trial of aspirin 100 mg every other day vs placebo for a mean of 10 years in over 39 000 women age 45 and older (mean age 55). *Unexpectedly*, aspirin did *not* reduce risk of myocardial infarction or death. The risk of ischemic stroke declined by 24%, with a non-significant increase in risk of hemorrhagic stroke.

In this issue of Annals, the US Preventive Services Task Force (**USPSTF**) updates its recommendations for aspirin in *primary* prevention of coronary heart disease. The recommendations were based on five randomized trials, only two of which enrolled women. The new recommendations attempt to incorporate the results of the WHS and a new sex-based meta-analysis of aspirin trials.

On the basis of these new data, the USPSTF now encourages use of aspirin:

1) For men age 45 to 79 when the potential benefit of a reduction in MI outweighs the potential harm of GI hemorrhage.
2) For women age 55 to 79 when the potential benefit in reduction of stroke outweighs the potential harm of GI hemorrhage.

The USPSTF guidelines do *not* recommend aspirin for men underage 45, or for women under age 55.

Is it reasonable to recommend the same drug for the prevention of one type of event in men and another in women? Although the data support this in the case of aspirin, the concept is still debatable. It could be argued that the WHS enrolled a relatively low-risk population, which had too few cardiovascular events to detect a true difference if it existed. Only 10% of women in the trial were over

age 65. In this group, the WHS demonstrated a clear 26% reduction in MI. Even in this low-risk population of women, stroke was more common than MI, making an argument for use of aspirin for stroke prevention. If aspirin is used to prevent one type of event (stroke) the patient will also derive any benefit that aspirin may provide.

It could be argued that aspirin should be used in all individuals, men and women, who have a reasonable risk of a major cardiovascular event.

A key issue for primary care is when to recommend *against* taking aspirin. If the harm of bleeding outweighs the risk of cardiovascular events, recommend against aspirin. This assumes however, that patients place the same value on avoiding a bleeding event as they do on avoiding a stroke. Some would rather avoid a stroke than avoid a bleeding event.

A valuable feature of USPSTF is the recommendation to share decision-making with the patient, discussing the benefits and risks, and individualizing decisions to the specific patient or situation.

Patients with a relatively high risk of intracranial bleeding should not receive aspirin.

"Aspirin continues to be underused, and the incorporation of the USPSTF's recommendations into daily practice will increase the use of aspirin and, in turn, prevent many thousands of cardiovascular events every year."

Annals Int Med March 17, 2009; 150: 414-416 Editorial by Shamir R Mehta, McMaster University, Hamilton, Ontario, Canada**.**

1 Details abstracted from PubMed Go to Google: PMID: 11786451

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Red Meat Associated with Increases in Total, Cancer, and CVD Mortality

3-4 MEAT INTAKE AND MORTALITY: A Prospective Study of Over Half a Million People

High intake of red or processed meat may increase the risk of death..

This study assessed the relation between red, white, and processed meat on the risk of total mortality and cause-specific mortality. It included about half a million men and women enrolled in the National Institutes of Health—AARP Diet and Health Study.

STUDY

1. Recruited individuals age 50 to 71 for 6 states and two metropolitan areas. After exclusions, the analytic cohort included 322 265 men and 223 390 women. Follow-up = 10 years.
2. At baseline, all completed a 124-item questionnaire on demographic and lifestyle characteristics,

including dietary habits. The food frequency questionnaire asked about the usual consumption of foods and drinks, and portion sizes over the past 12 months.

3. Red meat intake was calculated from the frequency of consumption and portion size of all types of beef and pork, including bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, sausage, steak, and meats in foods such as pizza, chili, lasagna, and stew.
4. White meat, included chicken, turkey, fish, canned tuna, and low-fat sausages and low-fat hot dogs made from poultry.
5. Processed meats included bacon, red meat sausage, luncheon meats, cold cuts, ham, and regular hot dogs,
6. Divided meat intake into quintiles, and estimated hazard ratios with the lowest quintile as the referent category.
7. Followed cohorts from baseline (beginning in 1995) through 2005.
8. Determined total mortality, and deaths due to cancer and cardiovascular disease.

RESULTS

1. Meat intake based on quintiles of red meat intake in men:

	Q1	Q2	Q3	Q4	Q5
Red meat g/1000 kcal	10	21	31	43	68
White meat g/1000 kcal	37	32	31	30	31
Processed meat g/kcal	5	8	10	13	19

2. Red meat intake by quintiles in women:

	Q1	Q2	Q3	Q4	Q5
Red meat g/1000 kcal	9	21	31	43	66
White meat g/1000 kcal	37	35	35	35	35
Processed meat g/kcal	4	6	9	11	16

3. During 10 years of follow-up, there were 47 976 male deaths, and 23 276 female deaths.
4. Mortality in men (Hazard ratios—adjusted):

A. Red meat intake	Q1	Q2	Q3	Q4	Q5
All deaths	1.00	1.06	1.14	1.21	1,31
Cancer deaths	1.00	1.05	1.13	1.18	1.22
CVD deaths	1.00	0.99	1.08	1.18	1.27
B. White meat intake					
All deaths	1.00	0.92	0.90	0.96	0.92

Cancer deaths	1.00	0.91	0.87	0.85	0.84
CVD deaths	1.00	0.96	0.96	0.99	1.05
C. Processed meat					
All deaths	1.00	1.01	1.07	1.12	1.16
Cancer deaths	1.00	1.07	1.11	1.14	1.12
CVD deaths	1.00	0.92	0.99	1.02	1.09

4. Adjusted hazard ratios were broadly similar in women.
5. The investigators calculated the population-attributable risks representing the percentage of deaths that could be prevented if individuals decreased their red meat consumption to the levels in the first quintile:

	Men	Women
Overall mortality	11%	16%
CVD mortality	11%	21%

DISCUSSION

1. The principle strength of the study was the large size of the cohort.
2. "We found modest increases in risk for total mortality, as well as cancer and CVD mortality, with higher intakes of red and processed meat."
3. In contrast, higher white meat consumption was associated with a small *decrease* in total and cancer mortality.
4. Within smoking subgroups (never, former, current) there were consistent results for red, white and processed meat intakes. In addition to exposure to N-nitroso compounds from processed meats, smokers inhale carcinogenic chemicals.
5. Meat is a source of several multisite carcinogens, which are formed during high-temperature cooking , as well as N-nitroso compounds. Iron in red meat may increase oxidative damage and increase formation of N-nitroso compounds. Meat is a major source of saturated fat, which has been positively associated with breast and colorectal cancers.
6. In relation to CVD, elevated BP has been positively associated with higher intakes of red and processed meats. Adverse effects on lipid concentrations have been associated with red meat intake. Substitution of red meats with fish improves the lipid profile.
8. Cancer societies recommend reduction of red and processed meats.

CONCLUSION

Higher red and processed meat intakes were associated with modest increases in total, cancer, and cardiovascular mortality.

High white meat intake was associated with a small *decrease* in total and cancer mortality.

Archives Intern Med March 23, 2009; 169: 562-71 Original investigation, first author Rashmi Sinha, National Cancer Institute and National Institutes of Health, Rockville MD

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Healthy Life-Style Behaviors Lower Risk Of Stroke.

3-5 COMBINED EFFECT OF HEALTH BEHAVIORS AND RISK OF FIRST EVER STROKE IN 20 040 MEN AND WOMEN OVER 11 YEARS' FOLLOW-UP

Lifestyle behaviors influence the risk of cardiovascular disease, including stroke.

This study examined the potential magnitude of combined lifestyle behaviors on the incidence of stroke in men and women age 40-79.

STUDY

1. This prospective community-dwelling population study entered (in 1993-97) and followed over 20 000 subjects (age 40-79). The cohort was compatible with national population samples. None had a history of stroke or myocardial infarction.
2. Created a health behavior score:

	Points
Non-smoker	1
Physically active or non-sedentary occupation	1
Alcohol 1 to 14 drinks per week	1
Fruit and vegetable intake 5 or more/ day	1

3. Total score ranging from 0 to 4. (Highest score, the healthiest.)
4. Determined incident cases of stroke
5. Follow-up to 2007. Average = 12 years.

RESULTS

1. There were a total of 599 strokes over follow-up; 168 were fatal.
2. Subjects who smoked, were physically inactive, consumed no alcohol or more than 14 units

weekly, and those who ate fewer than 5 fruits and vegetables daily (score = 0) were at a significantly higher risk of stroke.

3. Relative risk of stroke in various categories:

Health behavior score		0	4
Men		1.5	1.0 (referent)
Women		3.5	
Age	< 65	4.5	
	> 65	1.5	
BMI	< 25	2.8	
	25-30	1.3	
	>30	4.6	
Social class			
	Non-manual	3.2	
	Manual	1.6	

4. Incidence of stroke decreased in a linear fashion with every point increase in score:

Absolute risks for incident stroke (%)

Behavior score	
0	5.8
1	6.1
2	4.0
3	2.4
4	1.7

DISCUSSION

1. Modifiable lifestyle behaviors were associated with a substantially lower risk of subsequent stroke.
2. The lifestyle behaviors examined in this study are potentially achievable in the general population. These findings are of relevance to middle aged and older people.

CONCLUSION

Relatively modest and achievable health behaviors in combination (non-smoking, physically active, moderate alcohol intake, and eating fruits and vegetables) can produce a substantial reduction in risk of stroke.

BMJ March 14, 2009; 339: by the European Prospective Investigation on Cancer—Norfolk cohort (EPIC—Norfolk) first author Phyo K Myint, University of East Anglia, Norwich. UK

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"The Key Question Is Not Whether PSA Screening Is Effective, But Whether It Does More Good Than Harm."

3-6 SCREENING FOR PROSTATE CANCER: The Controversy That Refuses to Die

In the US, most men over age 50 have had a prostate-specific antigen (**PSA**) test despite the absence of evidence from large, randomized trials of a net benefit. About 95% of urologists and 78% of primary care physicians age 50 and over report that they have had a PSA test themselves.

And indeed, US death rates from prostate cancer (**PC**) have fallen about 4% per year since 1992. "Perhaps the answer to the PSA controversy is already staring us in the face."

At the same time, practice guidelines cite unproven benefits of PSA screening, as well as the known side effects, which largely reflect the high risks of overdiagnosis and overtreatment that screening engenders.

This issue of NEJM reports two large studies:

1) Mortality Results from a Randomized Prostate-Cancer Screening Trial.[1] (*In the USA*)

2) Screening and Prostate-Cancer Mortality in a Randomized European Study [2]

The first trial reported no mortality benefit from combined screening with PSA and digital rectal examination (**DRE**) during a median follow-up of 11 years.

The second trial reported that PSA screening without DRE was associated with an absolute reduction of about 7 PC deaths per 10 000 men screened at a median follow-up of 9 years,

Why are these results being published now? Neither set of findings seems definitive. There is neither a clear declaration of futility in the first study, nor an unanimous net benefit in the second study. Both studies are ongoing. Both decisions to publish now can be criticized as premature, leaving clinicians and patients to deal with the ambiguity.

The European trial:

Actually a collection of trials from different countries with different eligibility criteria, randomization schemes, and strategies for screening and follow-up. The study was based on a predefined core group of men age 55-69 at entry. Biopsies were generally recommended for subjects with a PSA over 3.0 ng/mL. Adjudication of the causes of death were made by committees whose members were unaware of the study group assignments. They were aware of treatments. This point is

important, since previous research has suggested that the cause of death is less likely to be attributed to PC among men receiving attempted curative treatment. Misattribution might create a bias toward screening.

The 7 in 10 000 chance of reduction in PC mortality after 9 years, if real and not the result of bias, must be weighed against the additional interventions and burdens. The 73 000 men in the screening group underwent more that 17 000 biopsies. Men in the screening group had a substantially higher cumulative risk of receiving the diagnosis of PC. Diagnosis led to more treatment (radical prostatectomy (277 per 10 000 screened men vs 100 per 10 000 controls) or radiation (220 vs 123 per 10 000).

Side effects would be proportionally higher in the men who were tested vs those not tested.

The European results also reemphasize the need for caution in screening men over age 69.

“To the extent that the diagnosis and treatment of prostate cancer in the screening group differed from those in the control group, it becomes difficult to dissect out the benefit attributable to screening versus improved treatment once prostate cancer is suspected or diagnosed.”

The trial notes that 1410 men would need to be offered screening, and an additional 48 would be treated to prevent one PC death during 10 years.

The U.S. trial:

Was smaller and less mature than the European, with 174 PC deaths vs 540 in the European trial. The screening protocol was homogeneous across sites, with an enrollment of men age 55-74, an annual PSA test for 6 years, and DRE every year for 4 years.

Subjects in the screening group who had a suspicious DRE, or a PSA over 4.0 ng/mL, received a recommendation for further evaluation. This strategy helped to ensure that any difference in outcome was attributable to screening, rather than management.

Although the 10-year trial has shown no significant effect on PC mortality to date, the relatively low number of endpoints begets a wide confidence interval. Contamination of the control group was high, with about half the control subjects undergoing PSA testing.

Although the trial may not have the power as yet to detect a similarly modest benefit of screening, its power is more than adequate to detect important harm through overdiagnosis.

“Ongoing results from both of these trials may necessitate rethinking about the role of DRE in cancer screening.”

Where do we stand?

Serial PSA screening has, at best, a modest effect of PC mortality during the first decade of follow-up. This benefit comes at the cost of substantial overdiagnosis and overtreatment.

Compared with breast cancer screening, which also has modest effectiveness, PSA screening leads to a much higher risk of overdiagnosis and overtreatment.

"It is important to remember that the key question is not whether PSA screening is effective, but whether it does more good than harm."

"The implications of the trade-offs reflected in these data, like beauty, will be in the eye of the beholder." "Further analysis will be needed from these trials, as well as from others, if the PSA controversy is to sleep the big sleep."

A shared decision-making approach to PSA screening, as recommended by most guidelines, seems more appropriate than ever.

"Both groups deserve high praise for their persistence and perseverance. To manage such monstrous trials is a Herculean task, made no easier when so many observers think the results are self-evident."

NEJM March 26, 2009; 360: 1351-54 Editorial by Michael J Barry, Massachusetts General Hospital, and Harvard Medical School, Boston MASS

1 The U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLOC), first author Gerald L Androle, Washington University School of Medicine, St Louis, MO

2 The European Randomized Study of Screening for Prostate Cancer (ERSPC) , first author Fritz H Schroeder, Erasmus Medical Center, Rotterdam, the Netherlands.

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