Open Access: free full text available online
For the full versions of these articles see bmj.com

Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study

Antonia Trichopoulou,[1] Christina Bamia,[1] Dimitrios Trichopoulos[2]

[1]Department of Hygiene, Epidemiology and Medical Statistics, University of Athens, Medical School, 115 27 Athens, Greece

[2]Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA

Correspondence to:
D Trichopoulos
dtrichop@hsph.harvard.edu

Cite this as: *BMJ* 2009;338:b2337
doi:10.1136/bmj.b2337

ABSTRACT

Objective To investigate the relative importance of the individual components of the Mediterranean diet in generating the inverse association of increased adherence to this diet and overall mortality.

Design Prospective cohort study.

Setting Greek segment of the European Prospective Investigation into Cancer and nutrition (EPIC).

Participants 23 349 men and women, not previously diagnosed with cancer, coronary heart disease, or diabetes, with documented survival status until June 2008 and complete information on nutritional variables and important covariates at enrolment.

Main outcome measure All cause mortality.

Results After a mean follow-up of 8.5 years, 652 deaths from any cause had occurred among 12 694 participants with Mediterranean diet scores 0-4 and 423 among 10 655 participants with scores of 5 or more. Controlling for potential confounders, higher adherence to a Mediterranean diet was associated with a statistically significant reduction in total mortality (adjusted mortality ratio per two unit increase in score 0.864, 95% confidence interval 0.802 to 0.932). The contributions of the individual components of the Mediterranean diet to this association were moderate ethanol consumption 23.5%, low consumption of meat and meat products 16.6%, high vegetable consumption 16.2%, high fruit and nut consumption 11.2%, high monounsaturated to saturated lipid ratio 10.6%, and high legume consumption 9.7%. The contributions of high cereal consumption and low dairy consumption were minimal, whereas high fish and seafood consumption was associated with a non-significant increase in mortality ratio.

Conclusion The dominant components of the Mediterranean diet score as a predictor of lower mortality are moderate consumption of ethanol, low consumption of meat and meat products, and high consumption of vegetables, fruits and nuts, olive oil, and legumes. Minimal contributions were found for cereals and dairy products, possibly because they are heterogeneous categories of foods with differential health effects, and for fish and seafood, the intake of which is low in this population.

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2009;338:b2337

INTRODUCTION

The Mediterranean diet was introduced to the scientific community as a health protecting diet by the classic studies of Ancel Keys and colleagues.[1] In 1995 a simple score to assess adherence to the Mediterranean diet was introduced,[2] and this score (or variants of it) has been used to evaluate the relation of the Mediterranean diet to overall mortality and specific health outcomes.[3-5] Most of these studies have focused on overall survival. A recent meta-analysis summarised the results of nine cohort studies that evaluated the relation between adherence to the Mediterranean diet and overall mortality.[6] An inverse association was noted in all these studies. However, no attempt has been made to investigate the relative importance of the individual components of the Mediterranean diet.

We evaluated the contribution of the nine widely accepted components of the Mediterranean diet in the inverse association of this diet with all cause mortality in a population based cohort in Greece.

METHODS

European Prospective Investigation into Cancer and nutrition—The study population consisted of the participants in the Greek segment of the European Prospective Investigation into Cancer and nutrition (EPIC). Between 1994 and 1997 28 572 healthy men and women aged 20-86 years were recruited from the general population throughout the country.

Data on diet—Dietary intakes during the year preceding enrolment were assessed with the use of a validated food frequency questionnaire.[7] For each participant, grams per day of intake of various food groups and nutrients, as well as total energy intake, were calculated. We focused on nine nutritional variables: vegetables, legumes, fruits and nuts, dairy products, cereals, meat and meat products, fish and seafood, monounsaturated to saturated lipid ratio, and ethanol.

Mediterranean diet score—We assessed the conformity to the traditional Mediterranean diet with a 10 unit scale based on the nine nutritional variables.[8] We assigned values of 0 or 1 to each component by using the sex specific medians in the studied population as cut-offs. We assigned a value of 0 to people whose consumption was below the median values of components

Table 1 | Mutually adjusted mortality ratios associated with intake of components of Mediterranean diet

Dietary variable	Mortality ratio* (95% CI)	P value
Vegetables:		
<Median	Reference	
≥Median	0.901 (0.775 to 1.048)	0.177
Legumes:		
<Median	Reference	
≥Median	0.942 (0.825 to 1.076)	0.379
Fruits and nuts:		
<Median	Reference	
≥Median	0.931 (0.816 to 1.061)	0.284
Cereals:		
<Median	Reference	
≥Median	0.989 (0.862 to 1.133)	0.869
Fish and seafood		
<Median	Reference	
≥Median	1.078 (0.950 to 1.224)	0.243
Monounsaturated/ saturated lipids (ratio):		
<Median	Reference	
≥Median	0.908 (0.792 to 1.042)	0.171
Dairy products:		
<Median	Reference	
≥Median	1.069 (0.931 to 1.227)	0.345
Meat and meat products:		
<Median	Reference	
≥Median	1.148 (0.992 to 1.329)	0.063
Ethanol intake†:		
Moderate	Reference	
Low intake	1.193 (1.032 to 1.380)	0.017
High intake	1.470 (1.132 to 1.907)	0.004

*Adjusted for sex, age (<45, 45-54, 55-64, ≥65, categorically), education (none/elementary school degree, secondary or technical school degree, university degree or higher, categorically), smoking status (never, former, and current at enrolment with cigarettes per day 1-10, 11-20, 21-30, 31-40, ≥41 ordered), waist:hip ratio (sex specific fifths, ordered), body mass index (sex specific fifths, ordered), MET score (fifths, ordered), and total energy intake (fifths, ordered).
†Low: <10 g/day for men, <5 g/day for women; moderate: men ≥10 g/day and ≤50 g/day, women ≥5 g/day and ≤25 g/day; high: >50 g/day for men, >25 g/day for women.

with a presumably beneficial effect (vegetables, legumes, fruits and nuts, fish and seafood, cereals, and monounsaturated to saturated lipid ratio) and a value of 1 to people with consumption equal to or above the median. In contrast, we assigned a value of 1 to people with below the median consumption of components without a beneficial effect (meat and meat products and dairy products) and a value of 0 to those whose consumption of these components was equal to or above the corresponding median. For ethanol, we gave value of 1 to men who consumed quantities from 10 g (or one unit) a day to less than 50 g (or six units) a day and a value of 0 otherwise; the corresponding cut-offs for women were 5 g a day and 25 g a day. The total Mediterranean diet score can take values from 0 (minimal conformity to the traditional Mediterranean diet) to 9 (maximal conformity to the traditional Mediterranean diet).

Lifestyle, anthropometric, dietary, and medical history data—We produced an index of daily physical activity and collected data on smoking status, body mass index, waist to hip ratio, and previous diagnoses of cancer, diabetes mellitus, myocardial infarction, and angina pectoris.

Study participants and follow-up—Greek EPIC participants were actively followed up until June 2008. Of the initial 28 572 participants, 1073 (4%) did not respond and were excluded from further analysis. Of the remaining 27 499 participants, 4150 had either a previous diagnosis of coronary heart disease, cancer, or diabetes or missing data and were excluded from analyses. Thus, the final sample consisted of 23 349 participants. The mean length of follow-up was 8.5 years.

Statistical analysis—We used proportional hazards (Cox) regression models to analyse survival data. We estimated the association of a two unit increase in the Mediterranean diet score with all cause mortality. We also evaluated the relative importance of each of the components of the scale by subtracting alternately one component at a time from the original score. In another analysis, we successively removed from the Mediterranean diet score each of the components in descending order of importance to evaluate the impact on the mortality ratio of the sequential removal of the component factors. Lastly, we evaluated the association with mortality of the joint action of each two by two combination of the individual components of the Mediterranean diet score. In all analyses, we controlled for sex, age at enrolment, education, smoking status, MET-hours (metabolic equivalent of task), total energy intake, waist to hip ratio, and body mass index.

RESULTS

The 23 349 study participants were followed up for 199 726 person years, during which period 1075 deaths occurred. Medians and interquartile ranges of the daily intakes of food groups that are characteristic of the traditional Mediterranean diet show high consumption of vegetables, legumes, fruits, and monounsaturated lipids.

After a mean follow-up of 8.5 years, 652 deaths from any cause had occurred among 12 694 participants with Mediterranean diet scores 0-4 and 423 among 10 655 participants with scores 5 or more. Table 1 shows associations of the nine components of the Mediterranean diet with mortality through mutually adjusted ratios contrasting high with low consumption. Compared with moderate intake of ethanol, both low and high intakes were associated with excess mortality to a statistically significant degree. Among the presumed beneficial components of the Mediterranean diet score, high consumption of all but fish and seafood was inversely associated with mortality, although none of these associations was statistically significant. For fish and seafood, the mortality ratio for consumption above or equal to the median compared with consumption below the median was 1.078 (95% confidence interval 0.950 to 1.224; P=0.243). With respect to meat and meat products and dairy products, as

Table 2 | Mortality ratios associated with two unit increment* in Mediterranean diet score (MDS) and after alternate subtraction of each of its dietary components

Dietary variable	Mortality ratio† (95% CI)	P value	Reduction in apparent effect (%)‡
MDS overall	0.864 (0.802 to 0.932)	<0.001	0
MDS minus vegetables	0.886 (0.822 to 0.955)	0.002	16.2
MDS minus legumes	0.877 (0.815 to 0.944)	<0.001	9.7
MDS minus fruit and nuts	0.879 (0.818 to 0.946)	0.001	11.2
MDS minus cereals	0.872 (0.814 to 0.935)	<0.001	6.1
MDS minus monounsaturated/saturated lipids (ratio)	0.878 (0.806 to 0.957)	0.003	10.6
MDS minus dairy products	0.870 (0.806 to 0.939)	<0.001	4.5
MDS minus meat and meat products	0.887 (0.825 to 0.953)	0.001	16.6
MDS minus ethanol	0.896 (0.835 to 0.962)	0.002	23.5

*Originally estimated logarithms of mortality ratios were multiplied by 9/10 and then exponentiated to correct for nine point scale.
†Adjusted for sex, age (<45, 45-54, 55-64, ≥65, categorically), education (none/elementary school degree, secondary or technical school degree, university degree or higher, categorically), smoking status (never, former, and current at enrolment with cigarettes per day 1-10, 11-20, 21-30, 31-40, ≥41 ordered), waist:hip ratio (sex specific fifths, ordered), body mass index (sex specific fifths, ordered), MET score (fifths, ordered), total energy intake (fifths, ordered), and corresponding subtracted components (<median intake, ≥ median intake).
‡Estimated from original numbers.

expected we found positive associations, which for meat and meat products approached statistical significance (P=0.06).

Table 2 shows the mortality ratio associated with a two unit increment in the Mediterranean diet score, as well as how this ratio changes with alternate exclusion of each of the nine components of the score. The benefit is expected to decrease after the alternate exclusion from the score of each of the nine components.

We also assessed changes in the mortality ratios associated with a two unit increment in the Mediterranean diet score, after successive removal of each of its components, ranked according to the magnitude of effect in the model in which the nine components were mutually adjusted (see bmj.com). As expected, the mortality ratio gradually approaches the null value of 1 after removal firstly of ethanol, then of meat and meat products, then of vegetables, then of fruits and nuts, then of the lipid ratio, and finally of legumes.

We also examined the consequences of the joint presence of any two by two combinations of eight (fish and seafood excluded) components of the Mediterranean diet score. Of the 28 possible two by two combinations, we found clear additive or super-additive associations of the joint presence of any two components in 13 instances (in none of these instances was there a statistically significant interaction in the multiplicative scale implicit in the Cox regression). Moderate ethanol consumption, high lipid ratio, and low intake of meat and meat products were each present five times in the 26 (2×13) possible entries, whereas high intakes of vegetable, fruits, and legumes were each represented three times. We interpret these findings as suggesting that moderate ethanol intake, low intake of meat and meat products, high lipid ratio, and high intake of plant foods are driving the association of high Mediterranean diet score with low mortality.

DISCUSSION

Main findings

Closer adherence to the traditional Mediterranean diet, as indicated by the Mediterranean diet score, is associated with lower overall mortality. Specifically, increased adherence to the Mediterranean diet score by two units was associated with a statistically significant 14% lower overall mortality.

The contribution to the association of adherence to the Mediterranean diet score with lower mortality was larger for moderate consumption of ethanol (24%), followed by low consumption of meat and meat products (17%) and high consumption of vegetables (16%); high consumption of fruits and nuts, high monounsaturated to saturated lipid ratio, and high consumption of legumes each contributed about 10-11%. The contributions of high consumption of cereals and low consumption of dairy products were minimal at about 5%. In these data, high consumption of fish and seafood was associated with a non-significant increase in mortality ratio after adjustment for potential confounders. The inverse association of the Mediterranean diet score with mortality ceased to exist after successive removal of the components referring to ethanol, meat and meat products, vegetables, fruits and nuts, lipid ratio, and legumes—in other words, in these data the components referring to dairy products, cereals, and fish and seafood were largely inconsequential.

This conclusion needs to be qualified, however. Recollection of habitual intake of alcoholic beverages is probably better than that of habitual intake of the foods, and the corresponding non-differential misclassification is likely to be less evident for alcohol than for the other components. Cereals, as generally reported, are a mix of the wholegrain cereals and other varieties, and milk and dairy products are also a mix of low fat and full fat products. Lastly, consumption of fish and seafood by the participants in this study was generally quite low.

Advantages of Mediterranean diet score

Certain questions need to be considered in view of these results. Why do Mediterranean diet scores tend to generate fairly consistent results with respect to health benefits, whereas studies focusing on the component foods or food groups are often contradictory? Why do Mediterranean diet scores in Mediterranean countries seem to be more strongly inversely related to adverse health outcomes than Mediterranean-like scores in non-Mediterranean countries? With respect to the first question, chance, non-differential misclassification, and residual confounding may have more important consequences when a single food is evaluated rather than a multi-component, unidimensional score, for several reasons.[8 9] With respect to the second question, the Mediterranean diet scores in Mediterranean countries assess the impact of large quantities of fruits and nuts, vegetables, legumes, and olive oil, which are consumed by many people in Mediterranean countries but by relatively few people in non-Mediterranean countries.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Several prospective cohort studies have consistently indicated that conformity to the traditional Mediterranean diet is associated with longevity

No study has investigated the relative importance of individual components of the Mediterranean diet score in the generation of this association

WHAT THIS STUDY ADDS

The contribution of the nine components to the apparent protective effect of the score assessing adherence to traditional Mediterranean diet is approximately additive

The dominant components of the Mediterranean diet score as a predictor of lower mortality are moderate consumption of alcohol, low consumption of meat and meat products, and high consumption of vegetables, fruits and nuts, olive oil, and legumes

Strengths and limitations of study

Advantages of this study are its prospective nature, its reliance on a population based sample in a typical Mediterranean country, and the use of a validated dietary questionnaire. A limitation is that diet was assessed many years before the occurrence of the outcome, allowing for unavoidable intervening changes in dietary habits. Power constraints did not allow us to look for multiple disease specific associations. We were unable to evaluate in a meaningful way multiplicative interactions, again because of power constraints. Moreover, when the mortality ratio varies by at most around 1.5, the excess risk from an additive or multiplicative joint action of two factors is fairly similar. Thus, the results of our study do not refute the possibility of synergistic effects among foods and nutrients in the Mediterranean diet.

Contributors: See bmj.com.
Funding: This study was supported by the Europe against Cancer Program of the European Commission, the Greek Ministries of Health and Education, and a grant to the Hellenic Health Foundation by the Stavros Niarchos Foundation. The study sponsors did not have any role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication. Researchers were independent from funders.
Competing interests: None declared.
Ethical approval: All volunteers signed informed consent forms, and the study protocol was approved by ethics committees at the International Agency for Research on Cancer (Lyon, France) and the University of Athens, Medical School.

1 Keys A. *Seven countries: a multivariate analysis of death and coronary heart disease*. Cambridge, MA: Harvard University Press, 1980.
2 Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, Polychronopoulos E, et al. Diet and overall survival in the elderly. *BMJ* 1995;311:1457-60.
3 Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease, and vascular mediation. *Arch Neurol* 2006;63:1709-17.
4 Martínez-González MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, Basterra-Gortari FJ, Beunza JJ, Vazquez Z, et al. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. *BMJ* 2008;336:1348-51.
5 Benetou V, Trichopoulou A, Orfanos P, Naska A, Lagiou P, Boffetta P, et al. Conformity to traditional Mediterranean diet and cancer incidence: the Greek EPIC cohort. *Br J Cancer* 2008;99:191-5.
6 Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008;337:a1344.
7 Katsouyianni K, Rimm EB, Gnardellis C, Trichopoulos D, Polychronopoulos E, Trichopoulou A. Reproducibility and relative validity of an extensive semi-quantitative food frequency questionnaire using dietary records and chemical markers among Greek school teachers. *Int J Epidemiol* 1997;26(suppl 1):S118-27.
8 Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;348:2599-608.
9 Jacques PF, Tucker KL. Are dietary patterns useful for understanding the role of diet in chronic disease? *Am J Clin Nutr* 2001;73:1-2.

Accepted: 6 February 2009

Imaging strategies for detection of urgent conditions in patients with acute abdominal pain: diagnostic accuracy study

Wytze Laméris,[1,2] Adrienne van Randen,[2,1] H Wouter van Es,[3] Johannes P M van Heesewijk,[3] Bert van Ramshorst,[4] Wim H Bouma,[5] Wim ten Hove,[6] Maarten S van Leeuwen,[7] Esteban M van Keulen,[8] Marcel G W Dijkgraaf,[9] Patrick M M Bossuyt,[9] Marja A Boermeester,[1] Jaap Stoker,[2] on behalf of the OPTIMA study group

EDITORIAL by Dixon and Watson

[1]Department of Surgery, Academic Medical Center, Amsterdam, Netherlands
[2]Department of Radiology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam
[3]Department of Radiology, St Antonius Hospital, Nieuwegein, Netherlands

ABSTRACT

Objective To identify an optimal imaging strategy for the accurate detection of urgent conditions in patients with acute abdominal pain.
Design Fully paired multicentre diagnostic accuracy study with prospective data collection.
Setting Emergency departments of two university hospitals and four large teaching hospitals in the Netherlands.
Participants 1021 patients with non-traumatic abdominal pain of ›2 hours' and ‹5 days' duration. Exclusion criteria were discharge from the emergency department with no imaging considered warranted by the treating physician, pregnancy, and haemorrhagic shock.
Intervention All patients had plain radiographs (upright chest and supine abdominal), ultrasonography, and computed tomography (CT) after clinical and laboratory examination. A panel of experienced physicians assigned a final diagnosis after six months and classified the condition as urgent or non-urgent.
Main outcome measures Sensitivity and specificity for urgent conditions, percentage of missed cases and false positives, and exposure to radiation for single imaging strategies, conditional imaging strategies (CT after initial

[4]Department of Surgery, St Antonius Hospital, Nieuwegein
[5]Department of Surgery, Gelre Hospitals, Apeldoorn, Netherlands
[6]Department of Radiology, Gelre Hospitals, Apeldoorn
[7]Department of Radiology, University Medical Center Utrecht, Utrecht, Netherlands
[8]Department of Radiology, Tergooi Hospitals, Hilversum, Netherlands
[9]Department of Clinical Epidemiology, Biostatistics, and Bioinformatics, Academic Medical Center, Amsterdam
Correspondence to: J Stoker
j.stoker@amc.uva.nl

Cite this as: *BMJ* 2009;338:b2431

ultrasonography), and strategies driven by body mass index and age or by location of pain.

Results 661 (65%) patients had a final diagnosis classified as urgent. The initial clinical diagnosis resulted in many false positive urgent diagnoses, which were significantly reduced after ultrasonography or CT. CT detected more urgent diagnoses than did ultrasonography: sensitivity was 89% (95% confidence interval 87% to 92%) for CT and 70% (67% to 74%) for ultrasonography (P<0.001). A conditional strategy with CT only after negative or inconclusive ultrasonography yielded the highest sensitivity, missing only 6% of urgent cases. With this strategy, only 49% (46% to 52%) of patients would have CT. Alternative strategies guided by body mass index, age, or location of the pain would all result in a loss of sensitivity.

Conclusion Although CT is the most sensitive imaging investigation for detecting urgent conditions in patients with abdominal pain, using ultrasonography first and CT only in those with negative or inconclusive ultrasonography results in the best sensitivity and lowers exposure to radiation.

INTRODUCTION

Decision making in patients with acute abdominal pain on the basis of clinical and laboratory evaluation alone can result in unnecessary interventions or in delayed treatment of urgent conditions. Several forms of imaging, of which ultrasonography and computed tomography (CT) are the most often used, can assist in clinical decision making. Imaging has been shown to have a positive effect on the accuracy of the clinical diagnosis,[1 2] to lead to changes in decisions about management,[3 4] and to increase the level of diagnostic certainty in patients with acute abdominal pain.[5 6]

Diagnostic imaging in the emergency department has been responsible for an increase in hospital costs,[7 8] and CT has been a growing source of exposure to radiation in adult patients.[9] This calls for a rational, evidence based approach to imaging in patients with abdominal pain. Unfortunately, many of the studies on imaging for acute abdominal pain have evaluated investigations in isolation, and several show methodological shortcomings. We evaluated the added value of plain radiographs, ultrasonography, and computed tomography after clinical evaluation for making urgent diagnoses in patients presenting with abdominal pain.

METHODS

We collected data prospectively within a multicentre, fully paired diagnostic accuracy study.[10] Eligible patients were adults (≥18 years) presenting at the emergency department with non-traumatic abdominal pain of more than two hours' and less than five days' duration. We excluded patients in haemorrhagic shock and pregnant women. Six hospitals in the Netherlands participated: two university hospitals and four large teaching hospitals.

Diagnostic protocol and observer experience

A diagnosis based on clinical evaluation and laboratory investigation was recorded for each patient. Thereafter, patients were investigated with a full structured imaging protocol, including upright chest and supine abdominal plain radiography, abdominal ultrasonography, and CT. After the physician in the emergency department had assessed the plain radiographs, a new diagnosis was recorded. Ultrasonography and CT were each read without disclosure of any results of the other investigation.

Final diagnosis

We followed all included patients for at least six months. We collected data on clinical, laboratory, and surgical findings; pathology results; imaging reports; and outcomes of treatment. An expert panel formed of two gastrointestinal surgeons and an abdominal radiologist assigned a final diagnosis. We defined urgent diagnoses as conditions needing treatment within 24 hours.

Diagnostic strategies

We compared the diagnostic accuracy of the following single imaging strategies with the panel based final diagnosis as the reference standard: (1) diagnosis after clinical evaluation, (2) clinical diagnosis plus plain radiographs, (3) ultrasonography in all patients, and (4) CT in all patients. We investigated the following conditional ultrasonography and CT strategies: (5) ultrasonography first in all patients and CT in those with a negative or inconclusive ultrasonography and (6) ultrasonography in all patients and CT only in patients with inconclusive ultrasonography.

We investigated imaging strategies driven by patients' characteristics, in which only selected patients would have initial ultrasonography, with CT after a negative or inconclusive ultrasonography, whereas all others would have initial CT. For initial ultrasonography in these strategies, we selected (7) younger patients (<45 years), for whom exposure to ionising radiation is most hazardous, and (8) non-obese patients (body mass index <30 kg/m^2), in whom ultrasonography is more likely to be diagnostic. In another strategy (9) both younger and non-obese patients would have initial ultrasonography.

We investigated strategies in which the selection of ultrasonography or CT was driven by the abdominal quadrant in which the pain was predominantly located. In strategy (10) the choice of investigation was based on the American College of Radiology guidelines, which recommend ultrasonography for pain in the right upper quadrant and computed tomography for pain in the other quadrants and for diffuse abdominal pain.[11-14] In an alternative pain location driven strategy (11) patients with pain in the right upper quadrant or right lower quadrant would have initial ultrasonography and all others would have initial CT.

Diagnostic accuracy and use of imaging for each imaging strategy. Values are percentages (95% confidence intervals); numbers

Imaging strategies	Sensitivity (true positives)	Specificity (true negatives)	Missed urgent diagnoses (false negatives)	False positives*	CT use	US use
1) Clinical diagnosis	88 (86 to 91); 582	41 (36 to 46); 147	12 (79)	27; 213/795	0	0
Single imaging strategies						
2) Clinical diagnosis after plain radiographs	88 (86 to 91); 583	43 (38 to 48); 154	12 (78)	26; 206/789	0	0
3) Ultrasonography in all patients	70 (67 to 74); 465	85 (81 to 88); 305	30 (196)	11; 55/520	0	100; 1021
4) Computed tomography in all patients	89 (87 to 92); 591	77 (72 to 81); 276	11 (70)	12; 84/675	100; 1021	0
Conditional strategies						
5) US in all patients; CT if US negative†	94 (92 to 96); 620	68 (64 to 73); 246	6 (41)	16; 114/734	49 (46 to 52); 501	100; 1021
6) US in all patients; CT if US inconclusive	85 (82 to 88); 563	76 (71 to 80); 272	15 (98)	14; 88/651	27 (24 to 29); 271	100; 1021
Strategies driven by patients' characteristics						
7) If age <45 then US and CT if US negative†; if age ≥45 then CT	90 (87 to 92); 593	72 (67 to 76); 258	10 (68)	15; 102/695	78 (76 to 81); 800	47 (44 to 50); 484
8) If BMI <30 then US and CT if US negative†; if BMI ≥30 then CT	91 (88 to 93); 599	71 (67 to 76); 257	9 (62)	15; 103/702	56 (53 to 59); 570	85 (82 to 87); 864
9) If BMI <30 or age <45 then US and CT if US negative†; CT in all other patients	90 (87 to 92); 593	72 (68 to 77); 260	10 (68)	14; 100/693	81 (78 to 83); 825	42 (39 to 45); 426
Strategies driven by location of pain						
10) If tenderness RUQ then US; if tenderness RLQ, LUQ, or LLQ then CT; if diffuse tenderness then CT; CT in all other patients	89 (87 to 92); 591	78 (73 to 82); 279	11 (70)	12; 81/672	95 (93 to 96); 970	5 (4 to 7); 51
11) If tenderness RUQ or RLQ then US; if tenderness LLQ or LUQ then CT; if diffuse tenderness then CT; CT in all other patients	84 (81 to 87); 555	79 (75 to 83); 285	16 (106)	12; 75/630	65 (62 to 68); 660	35 (32 to 38); 361

BMI=body mass index; CT=computed tomography; LLQ=left lower quadrant; LUQ=left upper quadrant; RLQ=right lower quadrant; RUQ=right upper quadrant; US=ultrasonography.
*Calculated as false positives/all positives.
†Including inconclusive ultrasonography.

Data analysis

We calculated sensitivity and specificity for detecting urgent conditions for each of the 11 diagnostic strategies. We calculated the percentage of missed cases and the percentage of false positives. We plotted the accuracy of all strategies in a receiver operating characteristics space.

We compared sensitivities and specificities between single imaging strategies. We compared the clinical diagnosis and the most accurate single test strategy with the multi-investigation strategies. We evaluated the gain in accuracy in strategies from combining two forms of imaging relative to the most accurate single test strategy.[15] We calculated the percentage of patients who had ultrasonography and the percentage who were exposed to CT related ionising radiation for each strategy.

RESULTS

Inclusion started in March 2005, and 1101 patients were included over the following 21 months. Of the patients approached, 2% (4/188) refused to participate. Data collection could not be completed for 80 patients. The mean age of the remaining 1021 patients was 47 (range 19-94) years; 55% (565) were female. Most (75%; 766) patients had been referred to the emergency department by a general practitioner.

Surgical residents evaluated 74% (757) of patients, and emergency medicine residents evaluated the other 26% (264). The ultrasonography was done by a radiological resident in 57% (582) of patients and by a staff radiologist in 43% (439). CT was evaluated by a radiological resident supervised by a radiologist in 29% (299) of cases and directly by a radiologist in 71% (722). The expert panel assigned an urgent diagnosis to 661 (65%) patients. Acute appendicitis was the most common final diagnosis, followed by acute diverticulitis (see bmj.com).

Diagnostic accuracy

The table shows the accuracy results for each strategy. The figure shows these results plotted in a receiver operating characteristics space. The clinical diagnosis with or without plain radiographs had a high sensitivity but lacked specificity for urgent cases. Compared with the clinical diagnosis, the use of ultrasonography in all patients (ultrasonography strategy) reduced the number of false positive urgent diagnoses, but 30% of urgent conditions would still be missed. Ultrasonography as a single test was inferior to CT as a single test (CT strategy) for the detection of urgent conditions, as the sensitivity was significantly higher for CT (89%) than for ultrasonography (70%, $P<0.001$). The sensitivities of both strategies were not significantly higher than with clinical evaluation alone; only specificities were significantly improved.

The sensitivity of 65% (95% confidence interval 58% to 72%) for ultrasonography done by residents without supervision was significantly lower than sensitivity of 74% (69% to 74%) for ultrasonography by radiologists ($P=0.03$). The sensitivity was 69% (82% to 91%) for ultrasonography done by residents under supervision,

which was not significantly lower than for ultrasonography done by radiologists (P=0.20). The specificity for urgent conditions did not differ significantly between radiologists and supervised or unsupervised residents (P=0.70).

Application of CT after a negative or inconclusive ultrasonography result (strategy 5) had a higher sensitivity than the clinical diagnosis without imaging: 94% versus 88% (P<0.001). This conditional strategy would result in a significantly lower number of missed urgent conditions compared with CT only: 6% versus 11%, with a higher sensitivity (P<0.001) but a lower specificity (P<0.001). An alternative conditional strategy with CT only after inconclusive ultrasonography (strategy 6) would further reduce use of CT (27% of patients) but would increase the proportion of missed urgent conditions from 6% to 15%.

Nine per cent of urgent conditions would be missed with a strategy in which imaging is based on body mass index (strategy 8) compared with 10% for the strategies based on age (strategy 7) or on both age and body mass index (strategy 9). The diagnostic accuracy of the strategy reflecting the American College of Radiology guidelines (10) was comparable to that of the CT only strategy. The use of ultrasonography for both pain in the right upper quadrant and pain in the right lower quadrant (strategy 11) would lead to 16% missed urgent conditions.

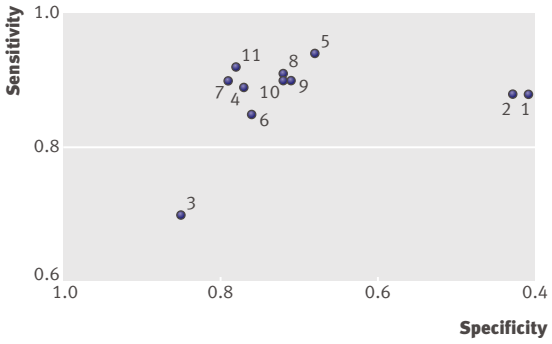
Exposure to radiation

CT related exposure to radiation would vary between 56% and 81% for the strategies driven by patients' characteristics and between 65% and 95% for the strategies driven by location of pain (table). The second lowest use of CT (49%) would be achieved with the conditional CT strategy.

DISCUSSION

In this study, relying on the clinical diagnosis would have led to a high number of false positive urgent diagnoses, whereas the use of ultrasonography as the only imaging investigation would have given an unacceptably high number of missed urgent conditions. The use of computed tomography conditional on a negative or inconclusive ultrasonography result had the highest sensitivity for urgent conditions and would result in the lowest overall exposure to radiation. Use of imaging driven by patients' characteristics or location of pain would have led to a loss in accuracy compared with the conditional CT strategy.

We acknowledge several potential limitations of this analysis. The study design allowed us to make comparisons without doing a randomised clinical trial with 11 groups, but no direct evaluation of the effects of imaging on patients' management and outcome was possible. This study had a pre-imaging selection of patients. Patients discharged from the emergency department without imaging were not included. This selection resulted in a relatively high prevalence of urgent conditions. Although we used a multimember panel, other clinical groups might classify the urgency of conditions and individual cases in a slightly different way.



Diagnostic performance of all imaging strategies presented in receiver operating characteristics space (see bmj.com for more information); strategy 5 is ultrasonography in all patients with computed tomography if ultrasonography is negative or inconclusive

A high sensitivity for urgent conditions is clinically important, as patients with an urgent diagnosis being discharged home and left untreated is undesirable. False positive urgent diagnoses, on the other hand, could lead to overtreatment. The gain in diagnostic performance of the conditional CT strategy compared with the CT only strategy represents a trade-off between a gain in sensitivity and a loss in specificity. No disproportionate decrease in specificity accompanied the 5% increase in sensitivity when switching from a general to a conditional CT strategy.

We showed that the sensitivity of ultrasonography depended on observers' experience. Ultrasonography by residents without supervision resulted in a higher number of missed urgent conditions. In clinical practice, secondary CT will more often be needed after ultrasonography done by unsupervised residents than after ultrasonography done by radiologists. The performance of CT is known to be less dependent on observers' experience in patients with acute abdominal pain.

This multicentre study closely mimicked daily practice; a large number of residents and radiological observers, with varying levels of experience, participated. The multicentre setting included university and teaching hospitals. We believe that our results reflect the performance of imaging strategies in daily practice.

The lifetime risk of radiation induced fatal cancer is age dependent. In general, consensus exists that the information obtained with diagnostic CT outweighs the risk associated with radiation. In the future, magnetic resonance imaging may be valuable for making a diagnosis in acute abdominal pain.[16]

In conclusion, we recommend use of ultrasonography as the initial investigation in the diagnostic investigation of patients presenting with acute abdominal pain, with CT after negative or inconclusive ultrasonography.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Ultrasound and computed tomography increase the accuracy of the clinical diagnosis, increase diagnostic certainty, and influence management decisions in patients with acute abdominal pain

WHAT THIS STUDY ADDS

As a single imaging strategy, computed tomography is better overall than ultrasonography in detecting urgent conditions

A conditional computed tomography strategy, with ultrasonography in all patients and computed tomography only after negative or inconclusive ultrasonography, gives the highest sensitivity for detecting urgent conditions

With this conditional computed tomography strategy, only half of patients would require computed tomography

Contributors: See bmj.com.
Funding: The Dutch Organization for Health Research and Development (ZonMw), Health Care Efficiency Research programme, funded the study (ZonMw grant number: 945-04-308). ZonMw approved the study protocol after consulting national and international independent reviewers. The collection, analysis, and interpretation of data; writing of the article; and decision to submit were left to the authors' discretion and were not influenced by ZonMw.
Competing interests: None declared.
Ethical approval: The independent medical ethics committee of the Academic Medical Center Amsterdam approved the final study protocol. The medical ethics committees of the other five hospitals also gave their approval after assessing the local feasibility of the study.

1 Walsh PF, Crawford D, Crossling FT, Sutherland GR, Negrette JJ, Shand J. The value of immediate ultrasound in acute abdominal conditions: a critical appraisal. *Clin Radiol* 1990;42:47-9.
2 Allemann F, Cassina P, Rothlin M, Largiader F. Ultrasound scans done by surgeons for patients with acute abdominal pain: a prospective study. *Eur J Surg* 1999;165:966-70.
3 Rosen MP, Siewert B, Sands DZ, Bromberg R, Edlow J, Raptopoulos V. Value of abdominal CT in the emergency department for patients with abdominal pain. *Eur Radiol* 2003;13:418-24.
4 Esses D, Birnbaum A, Bijur P, Shah S, Gleyzer A, Gallagher EJ. Ability of CT to alter decision making in elderly patients with acute abdominal pain. *Am J Emerg Med* 2004;22:270-2.
5 Bassler D, Snoey ER, Kim J. Goal-directed abdominal ultrasonography: impact on real-time decision making in the emergency department. *J Emerg Med* 2003;24:375-8.
6 Sala E, Watson CJ, Beadsmoore C, Groot-Wassink T, Fanshawe TR, Smith JC, et al. A randomized, controlled trial of routine early abdominal computed tomography in patients presenting with non-specific acute abdominal pain. *Clin Radiol* 2007;62:961-9.
7 Broder J, Warshauer DM. Increasing utilization of computed tomography in the adult emergency department, 2000-2005. *Emerg Radiol* 2006;13:25-30.
8 Mitka M. Costly surge in diagnostic imaging spurs debate. *JAMA* 2005;293:665-7.
9 Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007;357:2277-84.
10 Lameris W, van Randen A, Dijkgraaf MG, Bossuyt PM, Stoker J, Boermeester MA. Optimization of diagnostic imaging use in patients with acute abdominal pain (OPTIMA): design and rationale. *BMC Emerg Med* 2007;7:9.
11 Balfe DM, Levine MS, Ralls PW, Bree RL, DiSantis DJ, Glick SN, et al. Evaluation of left lower quadrant pain. American College of Radiology: ACR appropriateness criteria. *Radiology* 2000;215(suppl):167-71.
12 Bree RL, Ralls PW, Balfe DM, DiSantis DJ, Glick SN, Levine MS, et al. Evaluation of patients with acute right upper quadrant pain. American College of Radiology: ACR appropriateness criteria. *Radiology* 2000;215(suppl):153-7.
13 Ralls PW, Balfe DM, Bree RL, DiSantis DJ, Glick SN, Levine MS, et al. Evaluation of acute right lower quadrant pain. American College of Radiology: ACR appropriateness criteria. *Radiology* 2000;215(suppl):159-66.
14 Saini S, Ralls PW, Balfe DM, Bree RL, DiSantis DJ, Glick SN, et al. Suspected abdominal abscess. American College of Radiology: ACR appropriateness criteria. *Radiology* 2000;215(suppl):173-9.
15 Macaskill P, Walter SD, Irwig L, Franco EL. Assessing the gain in diagnostic performance when combining two diagnostic tests. *Stat Med* 2002;21:2527-46.
16 Stoker J. Magnetic resonance imaging and the acute abdomen. *Br J Surg* 2008;95:1193-4.

Accepted: 13 March 2009

Different

When I came in the examining room, he was sitting in bed. Even though I was confident with my white shirt and red bow-tie, I sensed a strange feeling. I checked his medical file in order to understand why my resident had asked me to see the patient, admitted to the hepatology unit the previous day for investigations.

I read that he had schizophrenia. The psychiatric disorder was written in bold characters; my odd sensation considerably increased. At this time, I was a young and untrained student, who had never been so close to "madness" before. I forgot all my lessons about mental illness, I was frightened.

I looked at my stethoscope and felt a little bit reassured: I decided then to overcome my fear and examined him. He was peaceful and looked "normal" with his green shirt. Then I asked questions about his medical background. He answered my questions with strange words or expressions, such as "mumlady" for mummy, "his father had no child." I was sitting next to him but far away from his mind. He looked at me for the first time and asked why he should give me a piece of his "live." I answered that he was to have some examinations including a liver biopsy. I tried to explain to him the difference between liver and live, without any success.

When I performed a physical examination he asked if I could hear "her" with my stethoscope. "Her?" I asked.

"Yes, my conscience. I don't want you to take her away with your biopsy-chiatrist."

In the middle of the examination, he put his clothes on, and went into the adjacent bathroom, not paying any attention to what I was doing. I felt alone. Although he was not entirely with me during the examination, I felt abandoned. I did not know why I sensed that I had to go after him.

He was standing in the cramped bathroom, in front of the mirror. He was touching his face. He was frightened. I tried to take his hand, to reassure him. I thought I was responsible for his state of panic. He stepped back and pushed me. A nurse came in and administrated an antipsychotic injection.

That day, his medications were increased. I had no more contact with this patient, except for the biopsy (could we call that a contact?). Three days later, I learnt that he had killed himself. Even though my resident told me that the patient was really sick and reluctant to take antipsychotic drugs, I always wondered if our drugs were not too strong and had provoked his voices, leading him to try to reach "her."

I have tried ever since to keep this experience in mind and to take into account the differences of schizophrenic patients and to tolerate non-dangerous variations of normality.

Alexis Descatha occupational and emergency physician, occupational health unit, Raymond Poincare University Hospital, Garches, France
alexis.descatha@rpc.aphp.fr

I thank Olivia Laborde to her help in improving the English of this manuscript.
Patient consent not required (patient dead, anonymised, or hypothetical).
Cite this as: *BMJ* 2009;338:b1929

pico

Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study

Sonia Hernández-Díaz,[1] Sengwee Toh,[1] Sven Cnattingius[2]

[1]Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115, USA

[2]Department of Medical Epidemiology and Biostatistics and Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, S-171 77 Stockholm, Sweden

Correspondence to: S Hernández-Díaz **shernan@hsph.harvard.edu**

Cite this as: *BMJ* 2009;338:b2255
doi: 10.1136/bmj.b2255

STUDY QUESTION Is pre-eclampsia more common in first pregnancies solely because fewer affected women, who presumably have a higher risk of recurrence, go on to have subsequent pregnancies?

SUMMARY ANSWER No, the lower overall risk of pre-eclampsia among parous women is not explained by fewer pregnancies among women who experienced pre-eclampsia in a previous gestation. Having pre-eclampsia in one pregnancy is a strong predictor for recurrence of pre-eclampsia in future gestations but a poor predictor of subsequent pregnancy.

Participants and setting

A cohort of 763 795 women who had their first births in Sweden, 1987-2004.

Design, size, and duration

We used data from the Swedish Medical Birth Register, a population based registry that includes more than 98% of all births in Sweden. Starting with the first antenatal visit, information is prospectively collected on maternal demographic data, reproductive history, pregnancy, and birth characteristics. The diagnoses are recorded at hospital discharge.

Main results and the role of chance

The risk of pre-eclampsia was 4.1% in the first pregnancy and 1.7% in later pregnancies overall. The risk for multiparous women without a history of pre-eclampsia was around 1%. The risk of recurrence was around 15% for women who had pre-eclampsia in one previous pregnancy and around 30% when two consecutive previous pregnancies were affected. Recurrence was higher for pre-eclampsia associated with very preterm delivery. The estimated risk of pre-eclampsia in parous women did not change with standardisation for pregnancy rates. The proportion of women who went on to have a further pregnancy was 4-5% lower after having a pregnancy with any pre-eclampsia and over 10% lower if pre-eclampsia was associated with very preterm delivery. Findings are consistent with the existence of two distinct conditions: a severe recurrent early onset type affected by chronic factors, genetic or environmental, and a milder sporadic form affected by transient factors.

Bias, confounding, and other reasons for caution

We used pre-eclampsia associated with delivery before 34 gestational weeks as a proxy for early onset and severity. Further research is needed to characterise the different disorders under the classification of gestational hypertension and proteinuria. Meanwhile, when advising women who developed pre-eclampsia in their first pregnancy and are contemplating a second pregnancy, we cannot say that their risk is low because pre-eclampsia is a "disease of nulliparity," particularly if they had an early onset event.

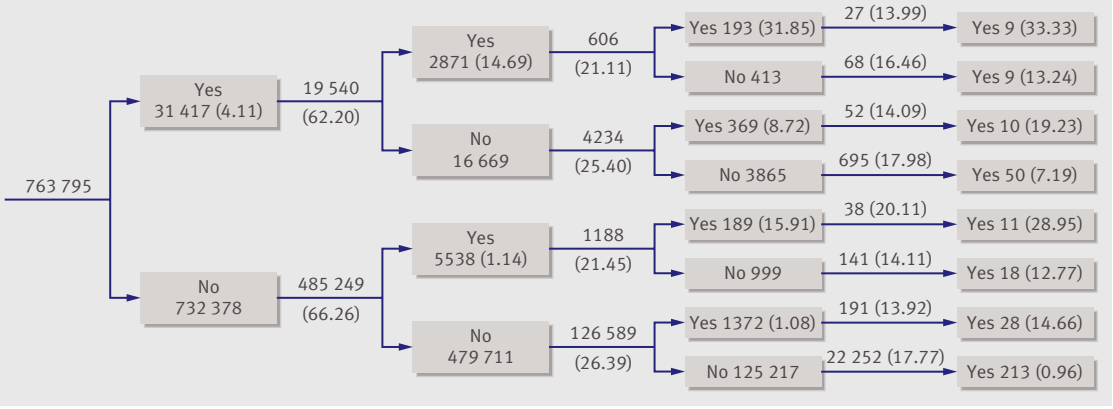
Generalisability to other populations

These findings are generalisable to populations with a similar distribution of risk factors for pre-eclampsia.

Study funding/potential competing interests

This research received no specific grant from any agency in the public, commercial, or not-for-profit sectors.

RISK OF PRE-ECLAMPSIA IN GIVEN PREGNANCY BY PREGNANCY ORDER AND HISTORY OF PRE-ECLAMPSIA, SWEDISH MEDICAL BIRTH REGISTER, 1987-2004



This is a summary of a paper that was published on bmj.com. Cite this article as: *BMJ* 2009;338:b2255

pico

Kidney function and risk of cardiovascular disease and mortality in women: a prospective cohort study

Tobias Kurth,[1234] Paul E de Jong,[5] Nancy R Cook,[12] Julie E Buring,[12678] Paul M Ridker[1267]

EDITORIAL by Weiner and Rifkin

[1]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston MA, USA
[2]Department of Epidemiology, Harvard School of Public Health, Boston MA
[3]INSERM Unit 708—Neuroepidemiology, Paris, France
[4]Faculty of Medicine, University Pierre et Marie Curie, Paris, France
[5]Department of Internal Medicine, University Medical Center Groningen, Groningen, the Netherlands
[6]Center for Cardiovascular Disease Prevention, Department of Medicine, Brigham and Women's Hospital
[7]Donald W Reynolds Center for Cardiovascular Research, Department of Medicine, Brigham and Women's Hospital
[8]Department of Ambulatory Care and Prevention, Harvard Medical School

Correspondence to:
T Kurth, INSERM Unit 708—Neuroepidemiology, Hôpital de la Pitié-Salpêtrière, 47 boulevard de l'Hôpital, 75651 Paris Cedex 13, France
tkurth@rics.bwh.harvard.edu

Cite this as: *BMJ* 2009;338:b2392
doi: 10.1136/bmj.b2392

STUDY QUESTION What is the association between kidney function and incident cardiovascular disease and mortality among apparently healthy women?

SUMMARY ANSWER Mild to moderate kidney impairment is not associated with increased risk of incident cardiovascular disease or mortality. Impaired kidney function (glomerular filtration rate <60 ml/min/1.73 m^2) was only associated with an increased risk of cardiovascular disease death but not other cardiovascular or mortality outcomes.

Participants and setting

We included female health professionals who participated in the US based Women's Health Study, who were aged ≥45 and who were free of cardiovascular disease and other major disease, including symptomatic kidney disease.

Design, size, and duration

This was a prospective cohort study among 27 939 women that started in 1992-5 when a blood sample was taken. Glomerular filtration rate (GFR) was estimated with the abbreviated Modification of Diet in Renal Disease Study equation: 1315 (4.7%) women had impaired kidney function (GFR <60 ml/min/1.73 m^2). During a follow-up of 12 years, 1199 women had a confirmed first cardiovascular event, and 856 died (179 from cardiovascular disease). We used a multivariable adjusted time-to-event modelling approach.

Main results and the role of chance

Compared with women with GFR ≥90 ml/min/1.73 m^2, the adjusted hazard ratios for any first cardiovascular disease were 0.95 (95% CI 0.83 to 1.08), 0.84 (0.70 to 1.00), and 1.00 (0.79 to 1.27) among women with GFR of 75-89.9, 60-74.9, and <60 ml/min/1.73 m^2, respectively. The equivalent hazard ratios for all-cause mortality were 0.93 (0.79 to 1.09), 1.03 (0.85 to 1.26), and 1.09 (0.83 to 1.45). Similar null findings were observed for myocardial infarction, stroke, coronary revascularisation, and non-cardiovascular death. However, an increased risk of death from cardiovascular disease was found among women with GFR <60 ml/min/1.73 m^2 (hazard ratio 1.68 (1.02 to 2.79)).

Bias, confounding, and other reasons for caution

GFR was assessed only at baseline, so changes over time could not be evaluated. We used a prediction equation to estimate GFR. However, when we repeated the analysis using blood creatinine concentration as measure for kidney function, we found similar associations. We controlled for major cardiovascular risk factors on our models, but, since our study is observational, residual confounding remains possible. Despite the large cohort size, the number of outcome events in GFR categories was limited, resulting in increased uncertainty of our estimates.

Generalisability to other populations

All participants were female health professionals, and most were white, which may limit generalisability to other populations. Specifically, in men and in black people an association between impaired kidney function and cardiovascular disease or mortality seems more apparent.

Study funding/potential competing interests

The Women's Health Study is supported by grants from the National Heart, Lung, and Blood Institute and the National Cancer Institute. The research for this work was supported by grants from the Donald W Reynolds Foundation, the Leducq Foundation, and the Doris Duke Charitable Foundation. The authors have no potential competing interest but give a complete disclosure in the full paper on bmj.com.

ADJUSTED HAZARD RATIOS (95% CI) FOR CARDIOVASCULAR EVENTS AND MORTALITY BY KIDNEY FUNCTION

Event	Estimated glomerular filtration rate (ml/min/1.73 m^2)			
	<60 (n=1315)	60-74 (n=3572)	75-89 (n=8073)	≥90 (n=14 979)
Any cardiovascular event* (n=1199)	1.00 (0.79 to 1.27)	0.84 (0.70 to 1.00)	0.95 (0.83 to 1.08)	1.00
All-cause mortality (n=856)	1.09 (0.83 to 1.45)	1.03 (0.85 to 1.26)	0.93 (0.79 to 1.09)	1.00
Cardiovascular disease death (n=179)	1.68 (1.02 to 2.79)	1.18 (0.77 to 1.79)	0.87 (0.60 to 1.27)	1.00

**The first of any of non-fatal stroke, non-fatal myocardial infarction, coronary revascularisation procedure (including bypass surgery or percutaneous coronary angioplasty), or death from a cardiovascular cause*

This is a summary of a paper that was published on bmj.com as *BMJ* 2009;338:b2392

pico

The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials

J J Brugts,[1] T Yetgin,[1] S E Hoeks,[1] A M Gotto,[2] J Shepherd,[3] R G J Westendorp,[4] A J M de Craen,[4] R H Knopp,[5] H Nakamura,[6] P Ridker,[7] R van Domburg,[1] J W Deckers[1]

[1]Department of Cardiology, Erasmus MC Thoraxcenter, 3015 GD, Rotterdam, Netherlands
[2]Weill Medical College of Cornell University, NY, USA
[3]University of Glasgow, Scotland
[4]Department of Gerontology and Geriatrics, Leiden University Medical Center, Netherlands
[5]Department of Medicine and Northwest Lipid Research Clinic, WA, USA
[6]Mitsukoshi Health and Welfare Foundation, Tokyo, Japan
[7]Brigham and Women's Hospital, Boston, MA, USA

Correspondence to: J J Brugts
j.brugts@erasmusmc.nl

Cite this as: *BMJ* 2009;338:b2376
doi: 10.1136/bmj.b2376

This is a summary of a paper that was published on bmj.com as *BMJ* 2009;338:2376

STUDY QUESTION What are the treatment benefits of statins and do they apply to people without established cardiovascular disease but with cardiovascular risk factors?

SUMMARY ANSWER Statin use in patients without established cardiovascular disease but with cardiovascular risk factors is associated with significantly improved survival and large reductions in the risk of major cardiovascular events.

Selection criteria for studies

We carried out a meta-analysis of randomised clinical trials identified through a search of the Cochrane controlled trials register, Embase, and Medline that investigated the clinical effects of statins compared with a placebo or control group with follow-up of at least one year, at least 80% or more participants without established cardiovascular disease, and outcome data on mortality and major cardiovascular disease events.

Primary outcome

Risk reduction in all cause mortality.

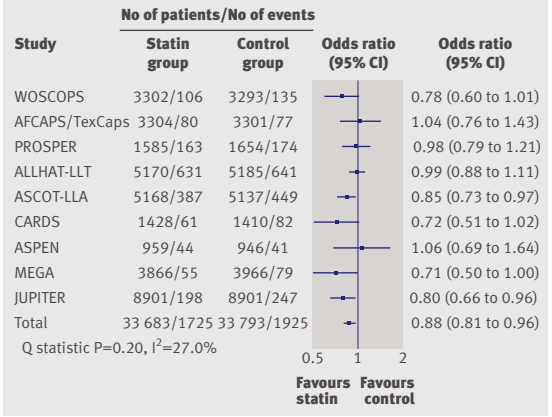
Main results and the role of chance

Ten studies were included, totalling 70 388 participants. The mean follow-up was 4.1 years. Statin therapy significantly reduced the risk of all cause mortality (odds ratio 0.88, 95% confidence interval 0.81 to 0.96), major coronary events (0.70, 0.61 to 0.81), and major cerebrovascular events (0.81, 0.71 to 0.93).

Bias, confounding, and other reasons for caution

No funnel plot asymmetry was visualised for the main end points, and P values using the Egger regression test were greater than 0.10 for all the major end points (all cause mortality: intercept −0.8, 95% confidence interval −3.1 to 1.5; P value 0.42). Using the Q statistics and the I^2 index we found no significant heterogeneity of the treatment effect in defined subgroups according to age, sex, or diabetes status.

EFFECT OF STATINS *v* CONTROL ON ALL CAUSE MORTALITY IN PEOPLE FREE OF CARDIOVASCULAR DISEASE BUT WITH RISK FACTORS



Study funding/potential competing interests

This study received no funding. AMG, JS, RGJW, HN, RHK, and PR have declared financial links with pharmaceutical companies (Abbott, Aegerion, Arisaph, Astra-Zeneca, Bristol-Myers Squibb, DuPont, Genentech, ISIS, Kowa, Martek, Merck, and Merck/Schering-Plough, Novartis, Pfizer, Roche, Sankyo, Sanofi-Aventis, and Vascular Biogenics), funding institutions (National Heart, Lung, and Blood Institute, National Cancer Institute, Donald W Reynolds Foundation, and Leducq Foundation), and patents (held by Brigham and Women's Hospital) (see online version for details).

What types of article does the *BMJ* consider?

We are delighted to receive articles for publication—from doctors and others—on the clinical, scientific, social, political, and economic factors affecting health. We give priority to articles that will help doctors to make better decisions. Please see our advice to authors at http://resources.bmj.com/bmj/authors, and if you would like to submit an article do so via our online editorial office at http://submit.bmj.com.

All original research articles are submitted, although we may invite submission (without promising acceptance) if we come across research being presented at conferences, if we see it in abstract form, or if the authors make an inquiry about the suitability of their work before submission.

We are also pleased to consider submitted articles for sections which carry a mix of commissioned and submitted articles—editorials, analysis, clinical review, practice, fillers, and Career Focus. Please follow the specific advice on each of these article types (see http://resources.bmj.com/bmj/authors/types-of-article) before submitting your article. Some types of article—news, features, observations, head to head, views and reviews—are commissioned by the editors.