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LITERATURE REVIEW

Body-Mass Index and Mortality in a Prospective Cohort of US Adults

Keith Clark

Reference: Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW. Body-mass index and mortality in a prospective cohort of US adults. *N Engl J Med.* 1999;341:1097–1105.

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Key words: Body mass index, mortality, United States, obesity, underweight, adult.

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This article reported a study of the relationship of body-mass index (BMI) to mortality using data from the American Cancer Society's Cancer Prevention Study II. The magnitude of the cohort is quite significant. This was a prospective study of more than 1 million adults in the United States. It is rare that such a large volume of information is available from any source, public or private.

This study tried to avoid the problems where other studies of BMI and mortality have been criticized. These problems include failing to identify smokers and those with a history of disease as possible confounding factors. Failure to exclude or identify these groups have been cited as a potential fatal flaw in the observation in other studies of the so-called ''J-shaped'' mortality curve, where the most lean subjects have increased mortality.

Subjects from the American Cancer Society Cancer Prevention Study II were used for the cohort. About 1.2 million subjects have been enrolled since 1982 and followed through 1996. The average age at enrollment was 57 years, and all enrollees were at least 30 years old. About 1 million subjects qualified for this study.

METHODS

The cohort was subdivided in multiple categories using the following definitions:

1. By BMI, where BMI = (weight in kilograms)/(height in meters)^2, or in English units, (weight in pounds $\times$ 703)/(height in inches)^2. These included the following categories: $<$18.5; 18.5 to 20.4; 20.5 to 21.9; 22 to 23.4; 23.5 to 24.9; 25.0 to 26.4; 26.5 to

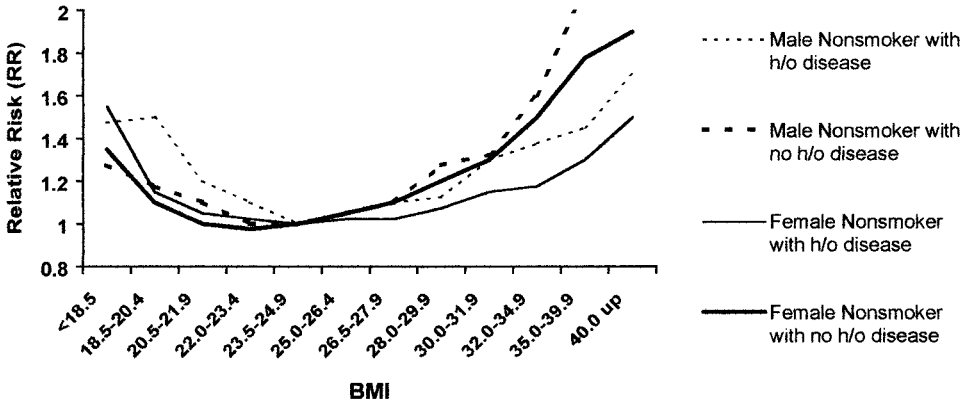

Figure 1. *Relative risk and body-mass index of male and female nonsmokers.*

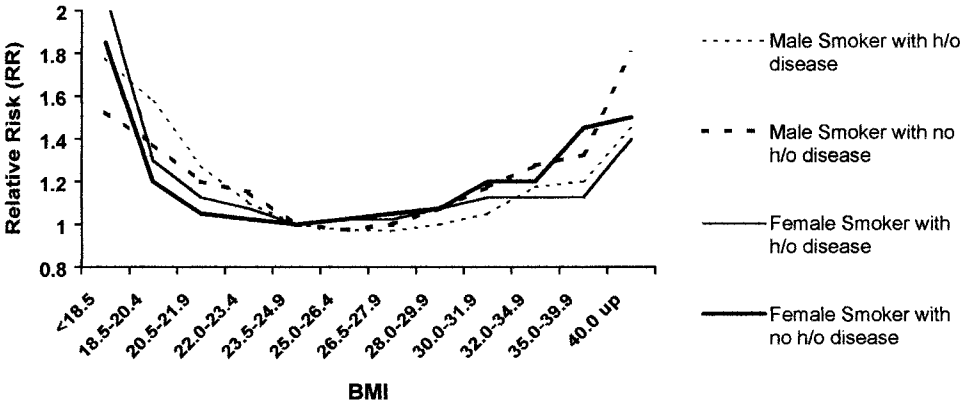

Figure 2. *Relative risk and body-mass index of male and female smokers.*

27.9; 28.0 to 29.9; 30.0 to 31.9; 32.0 to 34.9; 35.0 to 39.9; and 40.0 or higher.

2. Nonsmoker versus smoker (current smoker or a history of smoking).
3. With or without history of disease, including cancer, heart disease, stroke, respiratory disease, any current illness, or recent weight loss (defined as 10 pounds in the prior year).
4. Age in years, grouped in the following categories: 30–64 years; 65–74 years; and 75 years and up.
5. Race (white and black entrants only).

Statistical analysis used age-adjusted death rates. For each group the death rate was standardized to a reference category: BMI 23.5 to 24.9. This gives BMI values of 23.5 to 24.9 a relative risk (RR) of 1.0, and all other subgroups are reported as the RR compared with their reference group.

RESULTS

The lowest mortality for healthy nonsmokers was observed in men with a BMI of 23.5 to 24.9 and in women with a BMI of 22.0 to 23.4. Increases in mortality were modest at BMIs just below or above these ranges (Figure 1).

BMI has a curvilinear relationship with mortality. Mortality increased with increased BMI in all subcohorts and was affected by sex, history of smoking, history of disease, and age.

Cancer as the cause of death was not increased at the leanest BMI, whereas cardiovascular disease and all other causes were.

In the most obese, the RR of death was increased the most in healthy nonsmokers (men and women) and the least in smokers with a history of disease. The opposite was observed in the leanest subjects, in which smokers with

a history of disease had the greatest increase in RR.

Higher mortality was observed with an increased BMI in all age groups of healthy men and women, but this (the RR) diminished with an increase in age.

DISCUSSION

The first figure in this article has separate graphs for men and women and their RR of death with history of smoking and history of disease. I have changed the graphs to smokers and nonsmokers in an effort to more easily compare men and women (Figures 1 and 2). Other studies have observed that women better tolerate obesity than males. In contrast, in Figure 1, the mortality observed in obese male and female nonsmokers with no history of disease is very similar.

This study's data show that obesity results in less of an increase in the RR of mortality in those with a history of disease (Figures 1 and 2) compared with those with no history of disease. I will remind the reader that this is not absolute risk and that the reference group (where RR = 1.0) is not the same for the groups being compared. For example, smokers with a history of disease and a high BMI are being compared with smokers with a history of disease and a BMI of 23.5 to 24.9.

I found this review article difficult to write. One reason is that the authors used several variables to study the relationship between BMI and mortality. So although this is an impressive study by the sheer size of the cohort, it was not possible for the authors to present all the results.

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LITERATURE REVIEW

Completed Suicide Among Older Patients in Primary Care Practices: A Controlled Study

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Reference: Conwell Y, Lyness J, Duberstein P, et al. Completed suicide among older patients in primary care practices: a controlled study. *J Am Geriatr Soc.* 2000;48:23–29.

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Key words: Suicide, primary care, depression, affective disorder.

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Suicide is a devastating event, no matter the age of the victim. Older patients are the fastest-growing segment of our population. The suicide rate in late life is higher than any other point in history and has risen to 65 of 100,000 in white men aged 85 years old or older.

Previous studies have shown that a large proportion of suicide victims had visited a primary care (PC) provider within the final days or weeks of their lives. For older patients, 70% have seen their doctors within 30 days of completed suicide (SC).

This study attempted to determine whether physical and psychiatric illness, functional status, and medical history distinguish older PC patients who completed suicide from those who did not. The 2 study groups were patients who had SC and older patients from PC clinics.

COMPLETED SUICIDE

Between 1988 and 1994, the eligible victims were those who were 60 years or more old, SC in 1 county and had been seen by their PC doctor within the previous 30 days. A ''psychological'' autopsy was completed with family and friends. Additional information was obtained from medical records and phone interviews with the PC doctor. This group was compared with a random selection of patients from a number of PC clinics.

DEMOGRAPHICS AND PSYCHIATRIC ILLNESS

Of the SC group, 71% were men, a finding consistent with other studies; one third lived alone, and almost half had 12 years or more of education. The prevalence of psychiatric illness was significantly higher in the SC group.

Psychopathology Prevalance		
Disorder	Completed Suicide	Primary Care
Mood disorders	76%	25%
Major affective disorders	62%	11%
Past suicide attempt	19%	4%

The Table summarizes the psychopathology prevalence.

Measures of psychiatric illness and symptom severity significantly distinguished the 2 groups. The increased prevalence of mood and affective disorders were seen in the SC group. Over 90% of the SC group had received psychiatric care, either inpatient or outpatient (the study did not delineate), yet only 14% were under the care of a psychiatrist at the time of suicide. Alcohol and substance abuse were infrequent in both groups (14% SC; 3% PC).

PHYSICAL HEALTH AND FUNCTIONAL STATUS

There were significant differences in the measurements of the physical health and functional status of the 2 groups. Assessments were performed using the following scales: Cumulative Illness Rating Scale, Global Assessment of Functioning, Karnosky Performance Status Scale, Instrumental Activities of Daily Living, and Physical Self-Maintenance Scale.

All 5 assessment tools were statistically significant, showing marked impaired performance in the SC group. For example, the GAF mean was 44 in the SC group, which exemplifies serious impairments in this patient population.

This study continues to add observations to the understanding of older patients who are at increased risk of suicide. The study is limited in that the numbers are relatively small. The SC group is obviously retrospective, and the assessments performed are secondhand. I would prefer following PC patients prospectively with numbers assessment tools in an attempt to stratify suicide risk.

The older male patient who is depressed often appears to avoid adequate evaluation and treatment of his psychiatric condition. Depression is certainly a significant comorbid factor in the patient with lower physical performance or a higher burden of disease severity. Standard physical and emotional assessment tools should be studied prospectively in order to determine an accurate predictive value for suicide risk of the elderly.

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LITERATURE REVIEW

Prospective Evaluation of Unexplained Chronic Liver Transaminase Abnormalities in Asymptomatic and Symptomatic Patients

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Reference: Daniel S, Ben-Menchem T, Vasudevan G, Ma C, Blumenkehl M. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. *Am J Gastroenterol.* 1999;94:3010–3014.

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Key words: Liver functions, transaminase, liver biopsy.

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Elevated transaminase levels on blood chemistry testing are a frequent finding in the life of an insurance medical director as he or she evaluates applicants. With few dollars with which to order further testing, the delineation of which elevations are ominous and which are not can be quite vexing. In this study, over 1100 patients were evaluated prospectively to determine, by transcutaneous liver biopsy if necessary, the etiology of the elevation.

METHODS

A prospective study of 1124 adults who were referred for chronically elevated (>6 months) serum transaminases was undertaken. A comprehensive history and physical was performed and blood testing was carried out for the following tests: complete blood count, protime, albumin, cholesterol, triglycerides, TSH, AST, ALT, alkaline phosphatase, GGT, bilirubin, hepatitis B surface antigen, hepatitis B surface and core antibody, hepatitis C antibody, ANA, antimitochondrial antibody, anti–smooth muscle antibody, serum protein electrophoresis, alpha-1 antitrypsin, ceruloplasmin, iron, iron-binding capacity, ferritin, and angiotensin-converting enzyme.

Patients were excluded from consideration for a liver biopsy for the following reasons: the patient had a hepatic mass; findings were suggestive of sarcoid; the patient consumed 20 g or more of alcohol a day; the patient had a history of intravenous drug use; the patient had a history of the use of hepatotoxic drugs; the patient was positive for HIV infection; the patient had a history of malignancy; or the patient was positive for the blood tests described above.

FINDINGS

The use of these exclusion criteria eliminated 1043 patients, and thus only 81 were deemed ''unexplained'' and underwent percutaneous liver biopsy.

In the 81 patients who underwent liver biopsy, the following results were found: 8 (9%) had normal biopsies; 41 (50%) had steatosis; 26 (32%) had steatohepatitis; 4 (5%) had fibrosis; and 2 (2%) had cirrhosis.

Interestingly, there was no difference in the incidence in any of the above conditions whether the patient was symptomatic or not. There was also no difference if the patient had obesity, hyperlipidemia, or diabetes.

DISCUSSION

The results of this study have shown that with a history, physical examination, and battery of blood tests, one can usually (93%) determine the etiology of transaminase elevation without resorting to liver biopsy. However, in those cases in which no factor is found, the majority of elevations would result from fatty infiltration of the liver. There may also be some fibrosis, and in a rare percentage, frank cirrhosis.

The findings of this study are somewhat reassuring to the medical director in that in the majority of cases, unexplained transaminase elevation is from a benign cause. The findings of steatohepatitis, fibrosis, and cirrhosis, although relatively rare, are still noteworthy.

This study utilized much more intensive blood testing than is available to the average insurance applicant. The exclusion criteria results were not published in the article. I believe that those numbers might have been useful as well to see if expansion of ''normal'' reflex testing parameters off elevated transaminase levels might be warranted.

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LITERATURE REVIEW

Fasting Blood Glucose: An Underestimated Risk Factor for Cardiovascular Death

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Reference: Bjornholt J, Erikssen G, Aaser E, et al. Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care.* 1999;22:45–49.

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Key words: Coronary artery disease, mortality, fasting glucose.

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It has been well established that diabetes is associated with an increased risk of total mortality from coronary heart disease and stroke. There is a similar association noted with nondiabetic subjects with glucose intolerance, but the strength of this association has not been settled. There have been few studies that have corrected for the established coronary heart disease risk factors such as smoking, blood lipids, blood pressure, age, body-mass index, and physical fitness and these outcomes.

This 22-year follow-up study of healthy men by Bjornholt et al assesses the possible relationship between fasting glucose level and cardiovascular death and corrects for a number of confounding, accepted coronary risk factors. In Oslo, Norway, in 1972, apparently healthy men aged 40–59 years were invited to participate in a cardiovascular screening survey; 2014 men fulfilled the inclusion/exclusion criteria and agreed to participate. For this current study and review of the data, only those men with fasting blood glucose levels ≤ 110 mg/dL were included in the analysis. The baseline examination of this cohort was done between August 1972 and March 1975. A comprehensive health questionnaire was completed by the subjects, and a complete clinical examination was performed. Blood was drawn after a 12-hour overnight fast and 8 hours of abstaining from smoking.

The association between fasting blood glucose levels and mortality from both cardiovascular and noncardiovascular causes was assessed by mortality relating to blood glucose quartiles. The association between time until death was corrected for possible differences in age. Other selected variables were

evaluated by means of a proportional hazards model. The introduced variables were selected from previous knowledge of their associations with cardiovascular disease mortality. The results were presented as relative risk (RR).

Mortality data were obtained from Statistics Norway, which records all deaths in Norway.

RESULTS

During the 22 years of follow-up, the results revealed noncardiovascular mortality rates were independent of fasting blood glucose. Near-identical cardiovascular and noncardiovascular mortality rates were observed in the 3 lowest quartiles (blood glucose <85 mg/dL), but in quartile IV (blood glucose >85 mg/dL), cardiovascular morality was significantly higher (RR = 1.4, P = .0014, 95% confidence interval = 1.04–1.8). The associations remained after adjustment for all variables in the model: age, systolic and diastolic blood pressure, resting heart rate, smoking, cholesterol, triglycerides, body-mass index, physical fitness (J/kg), and FEV1.

DISCUSSION

This study demonstrated an increase in cardiovascular mortality at a much lower fasting blood glucose than was previously realized as carrying increased risk. A receiver operating characteristic analysis was done that optimized the sum of the sensitivity and specificity. This suggested the threshold value for increased risk is as low as 88 mg/dL. By comparing the subjects above and below this value, the RR of cardiovascular-related mortality is 1.5 (95% confidence interval = 1.2–2.0) for those with a blood glucose of 88 mg/dL or more. This association appears primarily to occur among men aged 40–49 years. Additionally, the subjects with blood glucose in the upper normal range show a clustering of other unfavorable cardiovascular risk traits, such as elevated blood pressure, increased blood lipids, and higher resting heart rate. This recognition of the risk for cardiovascular disease represented by fasting blood glucose well within previously accepted normal ranges may be significant in our risk assessment process.

In the insurance industry, we are now trying to find those clients that represent the better than standard risk: the preferred and the superpreferred. This study may be a starting point for discussions about reevaluating the criteria we use to assign clients to the better than standard classifications.