Attachment E

Summary of OSH Scientific Issues for Internal Review Committee regarding *Actual Causes of Death in the United States, 2000*

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Summary of OSH Scientific Issues for Internal Review Committee regarding *Actual Causes of Death in the United States, 2000*

- Accuracy of Estimates
- Comparability of Estimates
- Description of Methods

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Accuracy of Estimates

- Problems using Simple All-Cause Attributable Risk Methodology to Estimate Deaths Due to Lifestyle Causes
- Impact of Effect Modification (e.g., Age)
- Importance of Confounding Interactions

Lessons Learned from Tobacco Use Estimates

- Tobacco-related Estimates use Cause-Specific Risks stratified by Age and Sex
- High Causality Standard for Causes included
- Potential Confounding Evaluated for All Included Causes of Death
- Methodology used for Tobacco Use Audited by GAO in Spring 2003

Scientific Issues Noted

- Tobacco-related Estimates use Cause-Specific Risks stratified by Age and Sex
  - Relative Risks for Obesity also decline with age
  - All-cause Methodology can incorrectly include non-causal deaths (e.g., higher motor vehicle deaths in smokers)
- Potential Confounding Needs to be Evaluated
  - Multi-factorial Aspects of Coronary Heart Disease Deaths
  - Example of Liver Cancer Deaths due to Smoking and Alcohol Use
- Technically Incorrect All-Cause Methodology would Estimate over 650,000 Annual Tobacco-Related Deaths

Comparability of Estimates

- Methodology and Rigor Varied Widely
- "Apples to Oranges" Problem
- Impact of Different Sources of Prevalence Data Not Considered

Description of Methods

- Limited Description of Methodology Used for Nine Areas Provided
- Appropriateness of Using Obesity as Proxy for Poor Diet and Physical Inactivity Not Justified
- Limitations Noted More Fully in 1993 Paper

Recommendations

- Use More Comparable Methodology for All Estimates in Nine Areas
- As much as possible use:
  - Cause-Specific Risk Methodology
  - Age and Sex Stratification
  - Carefully Evaluate Confounding & Interactions
- Directly Make Estimate for Poor Diet and Physical Inactivity

Calculation of overweight-attributable deaths in the 2004 JAMA Actual causes of death paper

Katherine M. Flegal, Ph.D.

Centers for Disease Control and Prevention
National Center for Health Statistics

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Allison et al, 1999

- Allison, JAMA 1999 calculated deaths attributable to overweight and obesity in 1991,
  - using relative risks from six cohort studies
  - combined with overweight and obesity prevalence from NHANES III
  - and with mortality statistics for 1991.

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JAMA 2004 Actual causes of death paper states that the procedure used was the same as that reported by Allison

" We used the same procedure reported by Allison et al to estimate annual overweight-attributable deaths", p. 1239

Actual causes of death paper, 2004

- Actual causes of death, JAMA 2004 calculated deaths attributable to overweight and obesity in 2000
  - using the same relative risks from the same six cohort studies as Allison
  - combined with overweight and obesity prevalence from NHANES 1999-2000
  - and with mortality statistics for 2000.

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Issues

- Calculations of overweight-attributable deaths done erroneously in Causes paper
- Causes formula does not quite match Allison formula
- NHANES I relative risks from Allison paper used in Causes paper are not reproducible
- Allison/ Causes approach does not properly account for confounding or effect modification

Actual causes of death paper: formula and notation

"We used the following formula to calculate attributable fractions for each disease: [(P0+(Pi*Ri)) − 1]/[P0+(Pi*Ri)], in which P0 is the percentage of individuals in the United States not engaging in the risk behavior, Pi is the percentage engaging in separate categories of the risk behavior, and Ri is the RR of death for each separate category relative to [P0]." pp 1238-1239

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Actual causes of death paper: formula to calculate overweight-attributable deaths

$[(P0 + (\sum Pi*Ri) - 1) / (P0 + \sum Pi*Ri)] * \text{Number of deaths}$

For NHANES 99-00, P0=.3712 (proportion with BMI <25)

Number of deaths (ages 18+ in 2000)=2,356,064

Substituting:

$[(.3712 + (\sum Pi*Ri) - 1) / (.3712 + \sum Pi*Ri)] * 2356064$

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Expected versus actual calculations of overweight-attributable deaths

Expected:

$$[(.3712 + (\sum P_i * R_i) - 1) / (.3712 + \sum P_i * R_i)] * 2356064$$

.3712=P0 from NHANES 99-00

2356064= Number of deaths in 2000

Expected versus actual calculations of overweight-attributable deaths

Expected:

$[(.3712 + (\sum Pi*Ri) - 1) / (.3712 + \sum Pi*Ri)] * 2356064$

.3712=P0 from NHANES 99-00

2356064= Number of deaths in 2000

Actually used:

$[(.4610 + (\sum Pi*Ri) - 1) / (.4610 + \sum Pi*Ri)] * 2110687$

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Expected versus actual calculations of overweight-attributable deaths

Expected:

$[(.3712 + (\sum Pi*Ri) - 1) / (.3712 + \sum Pi*Ri)] * 2356064$

.3712=P0 from NHANES 99-00

2356064= Number of deaths in 2000

Actually used:

$[(.4610 + (\sum Pi*Ri) - 1) / (.4610 + \sum Pi*Ri)] * 2110687$

.4610 = P0 from NHANES III based on Allison article

2110687= Number of deaths in 1991, from Allison article

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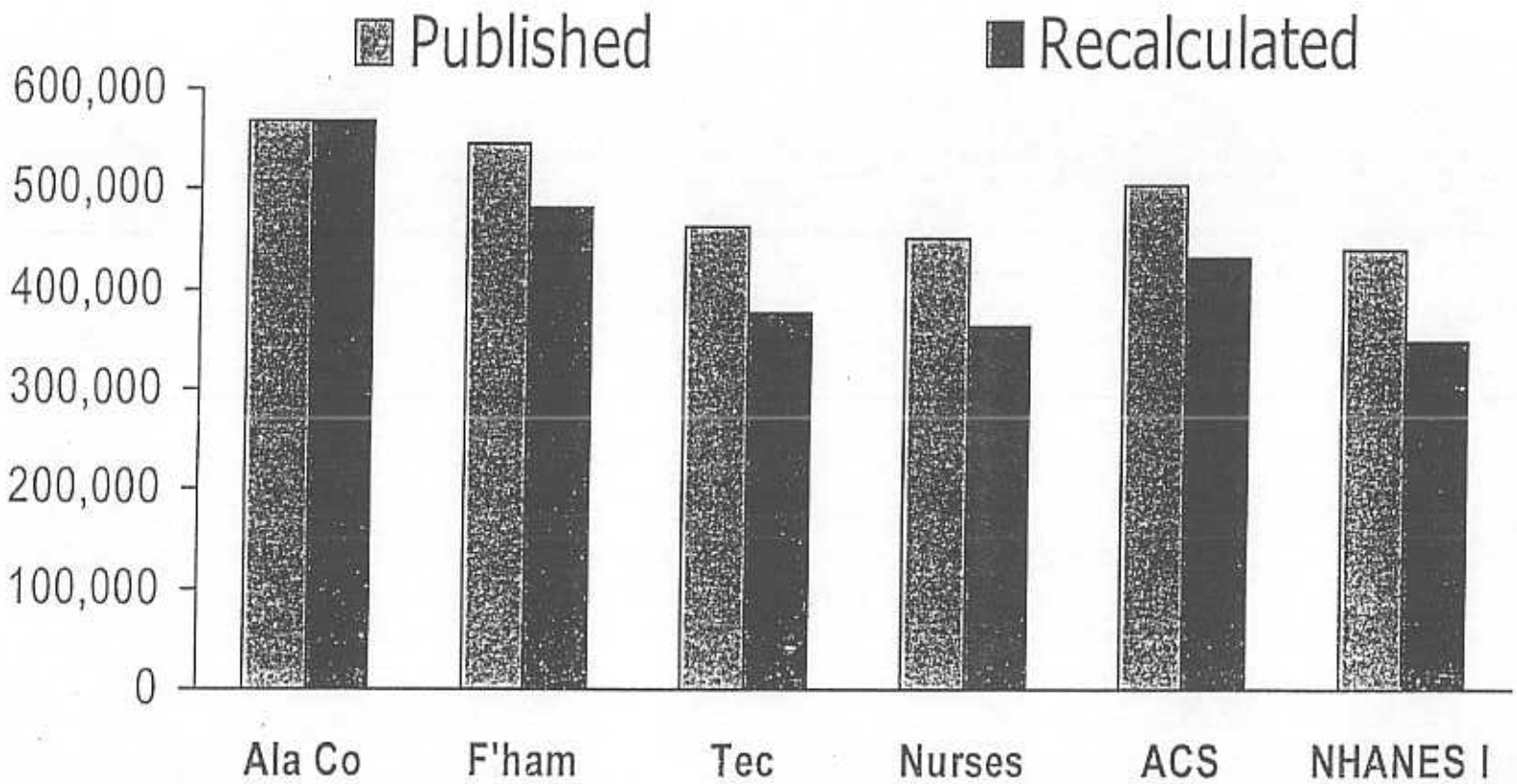
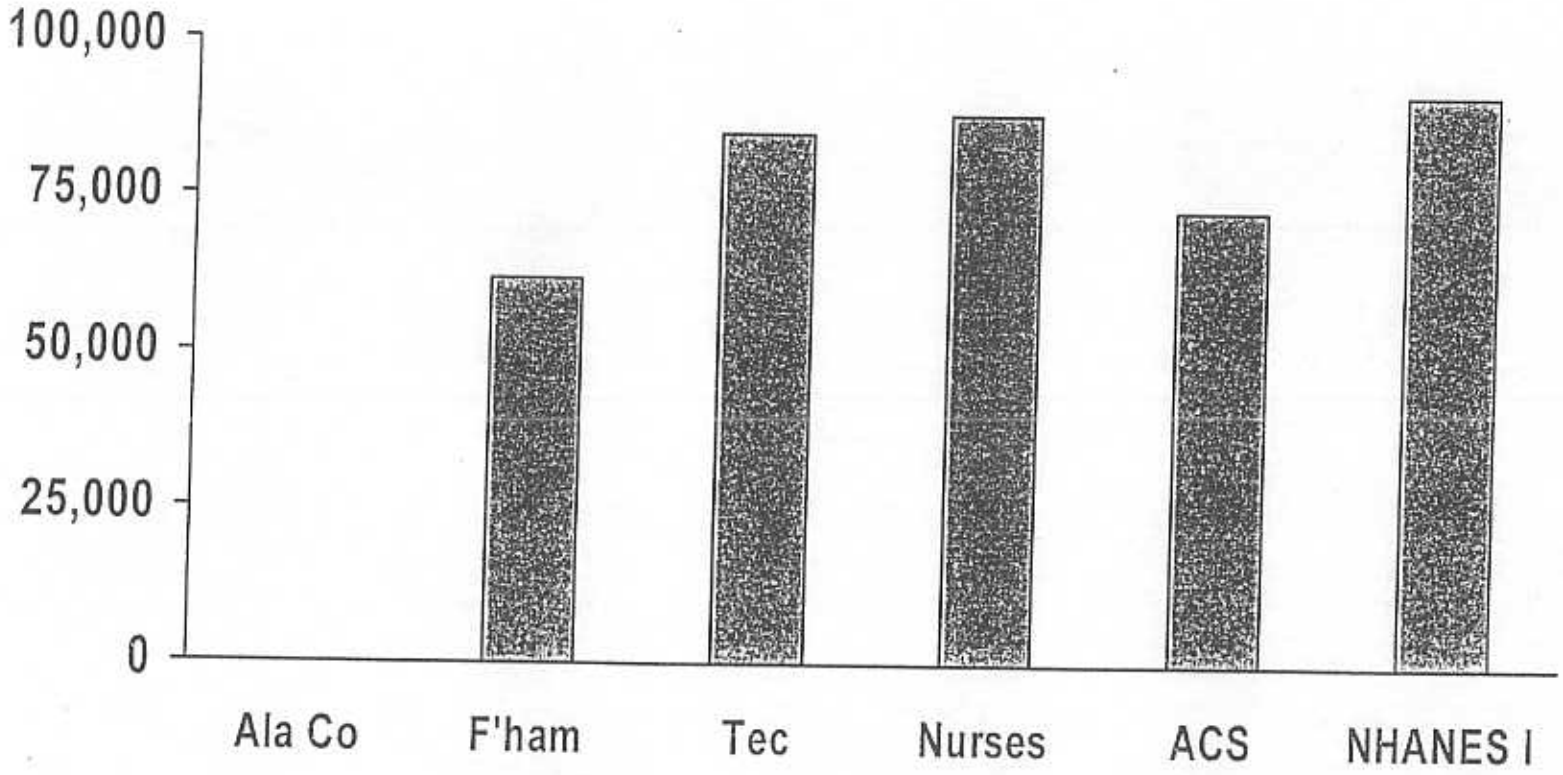
Published and recalculated numbers of overweight-attributable deaths



Difference (published – recalculated)



Issues

- **Calculations of overweight-attributable deaths done erroneously in Causes paper**
- Causes formula does not quite match Allison formula
- **NHANES I relative risks from Allison paper used in Causes paper are not reproducible**
- **Allison/ Causes approach does not properly account for confounding or effect modification**

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Actual causes of death paper formula to calculate overweight-attributable deaths

$$(P0 + (\sum Pi*Ri) - 1) / (P0 + \sum Pi*Ri)$$

Allison formula:

$$(P'0 + P''0 + (\sum Pi*Ri) - 1) / (P'0 + P''0*R''0 + \sum Pi*Ri)$$

where P'0=reference category (BMI 23-<25)

P''0=lowest BMI category (BMI < 23)

R''0=relative risk associated with lowest BMI category

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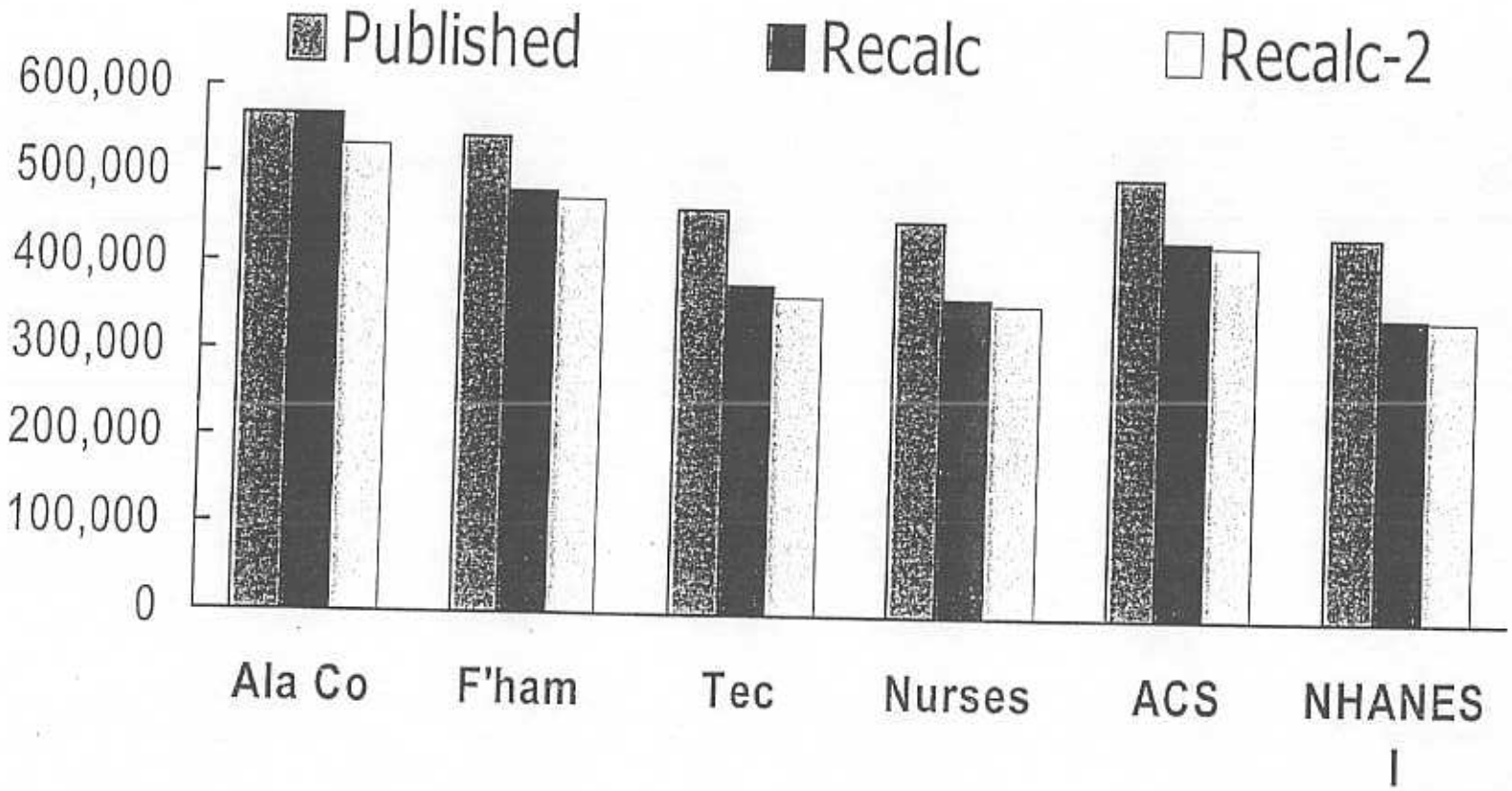
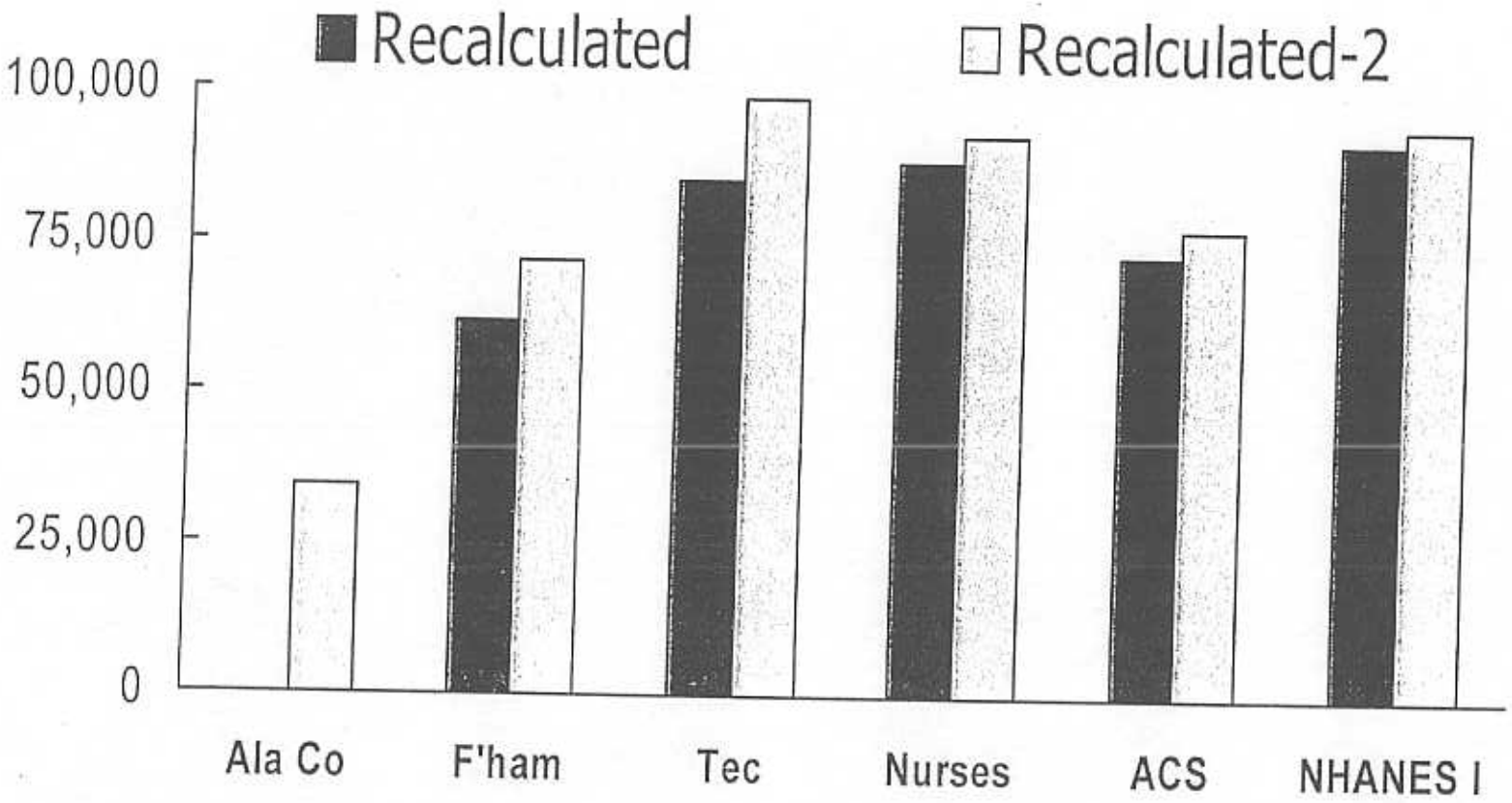
Published and recalculated numbers of overweight-attributable deaths



Difference (published – recalculated)



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Issues

- Calculations of overweight-attributable deaths done erroneously in Causes paper
- Causes formula does not quite match Allison formula
- NHANES I relative risks from Allison paper are not reproducible
- Allison/ Causes approach does not properly account for confounding or effect modification

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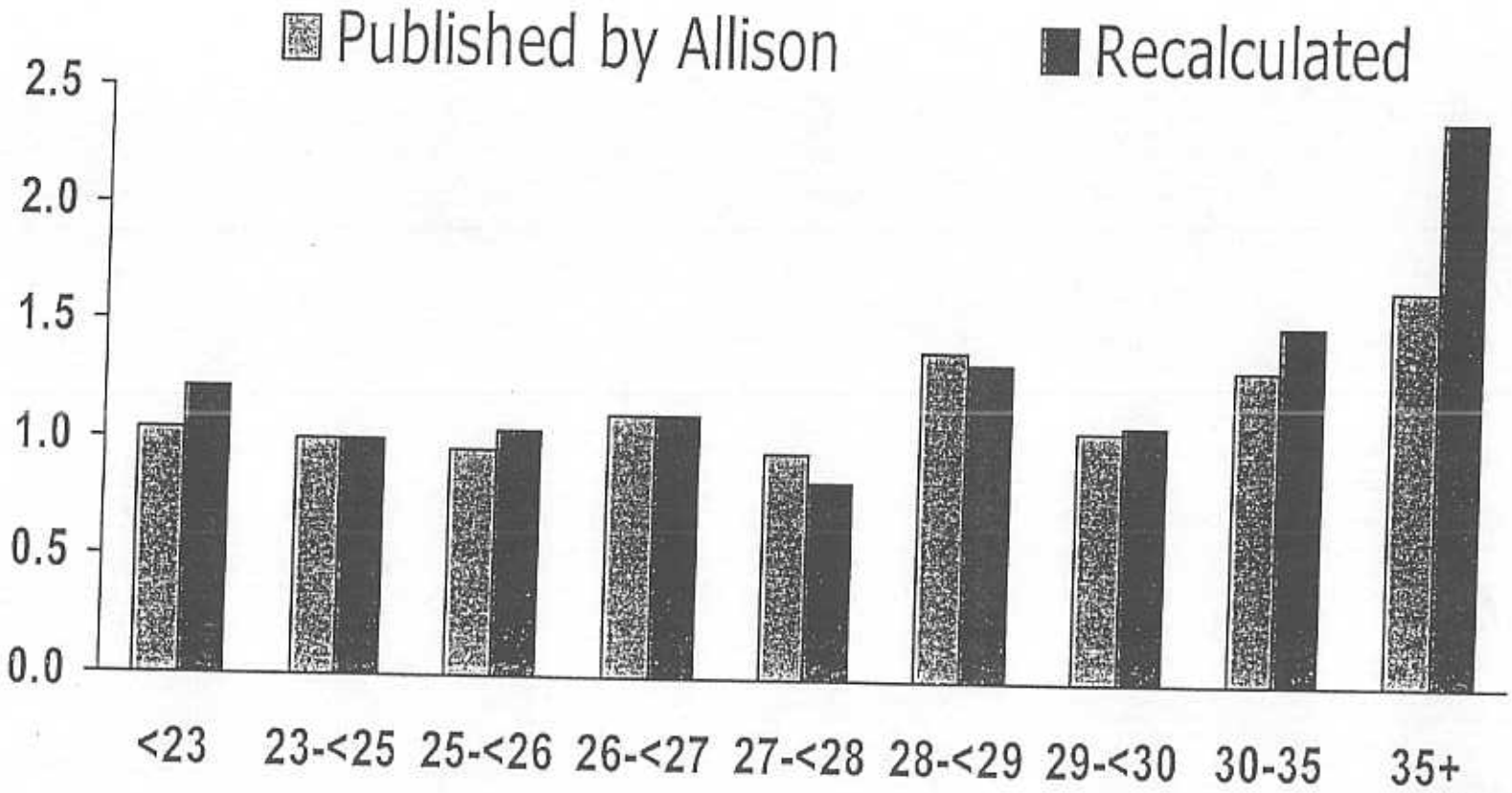
Adjusted relative risks from NHANES I



SOURCE: NHANES I, 1971-1974

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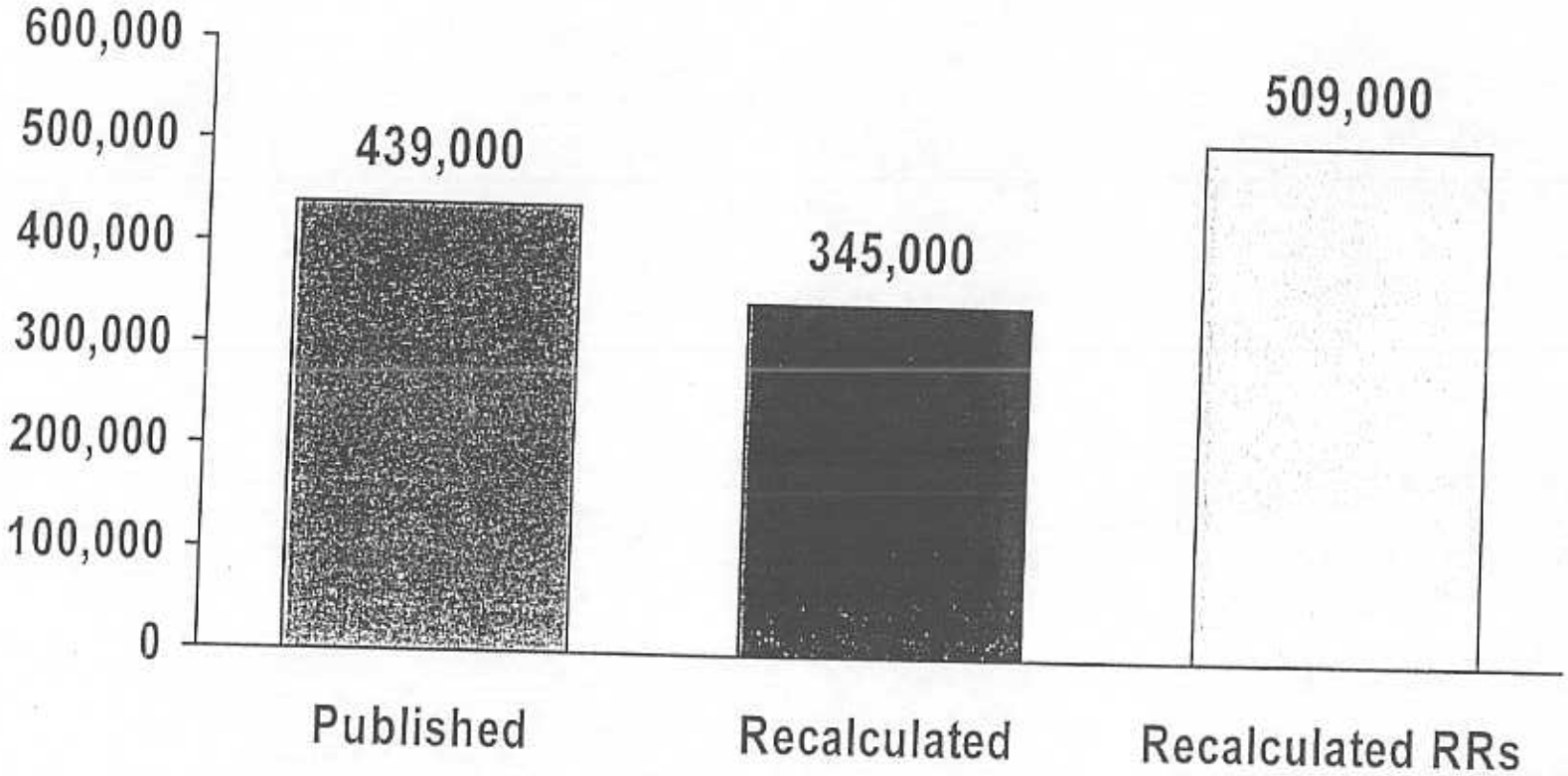
Overweight-attributable deaths for NHANES I



SOURCE: NHANES I, 1971-75

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Issues

- Calculations of overweight-attributable deaths done erroneously in Causes paper
- Causes formula does not quite match Allison formula
- NHANES I relative risks from Allison paper used in Causes paper are not reproducible
- Allison/ Causes approach does not properly account for confounding or effect modification

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Adjustment for confounding

- The relative risk estimates calculated by Allison et al and used in the Actual Causes of death paper are adjusted for confounding by age, sex and smoking.
- However, the attributable fraction formula used by Allison et al and approximately in the Causes paper is only appropriate for unadjusted relative risks.
- This information is readily available in review articles in the statistical and epidemiologic literature

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Rockhill et al, 1998

- 1998, Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions, Am J Pub Hlth

"..Errors in estimation are common. Probably the most common error is the use of adjusted relative risks in formula 3 [equivalent to Allison formula]. The magnitude of the bias resulting from this error will depend on the degree of confounding." P. 16

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Benichou, 2001

- 2001, Benichou J, , A review of adjusted estimators of attributable risk, Stat Med

"Another natural approach based on using equation (2) [equivalent to Allison formula] and plugging in a common adjusted relative risk estimate...has been advocated but it too has been shown to yield inconsistent estimates. and accordingly, severe bias was exhibited in simulations..." p. 200

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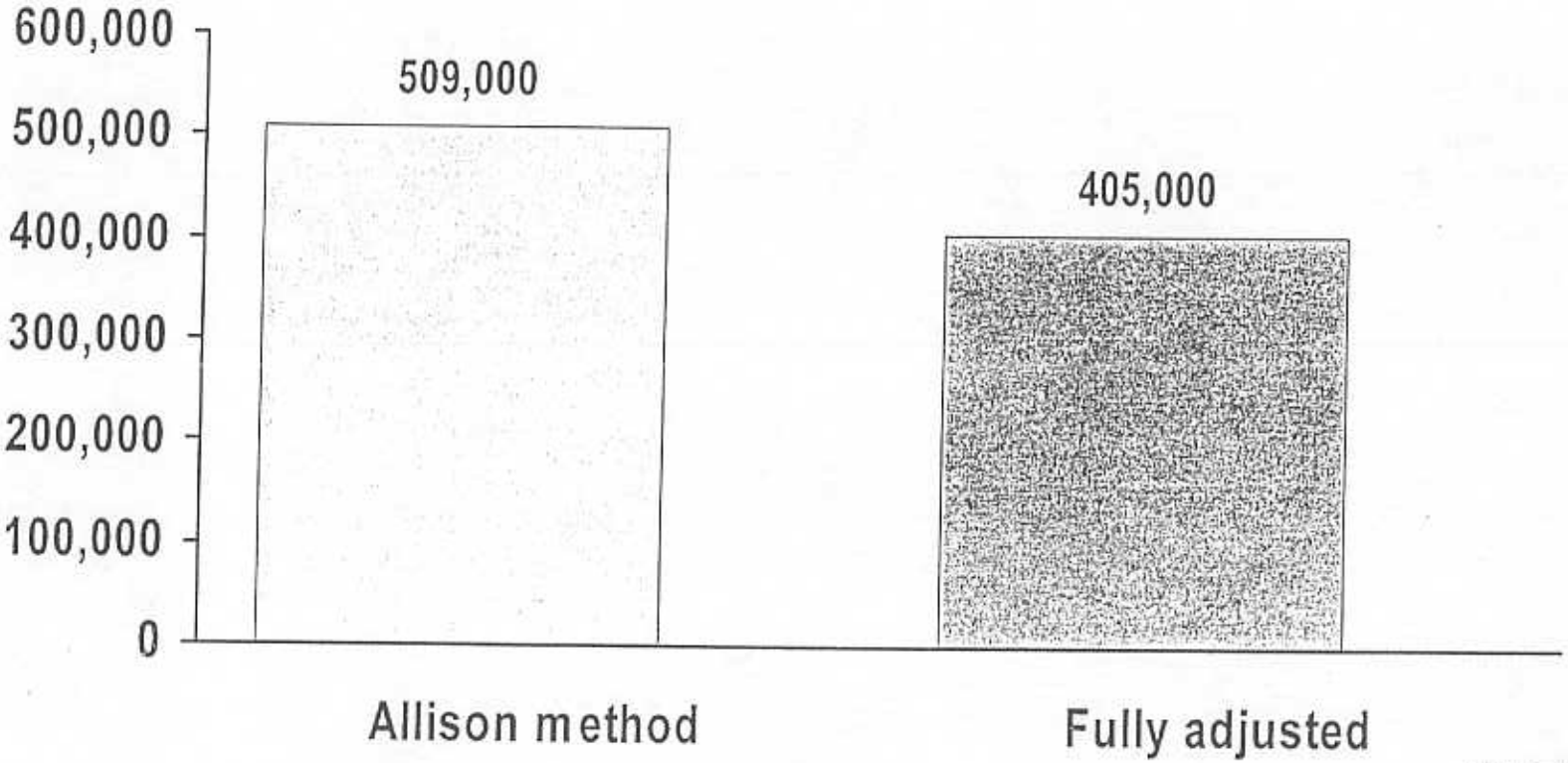
Estimated bias from incomplete adjustment for confounding is about 25%



SOURCE: NHANES I, 1971-75

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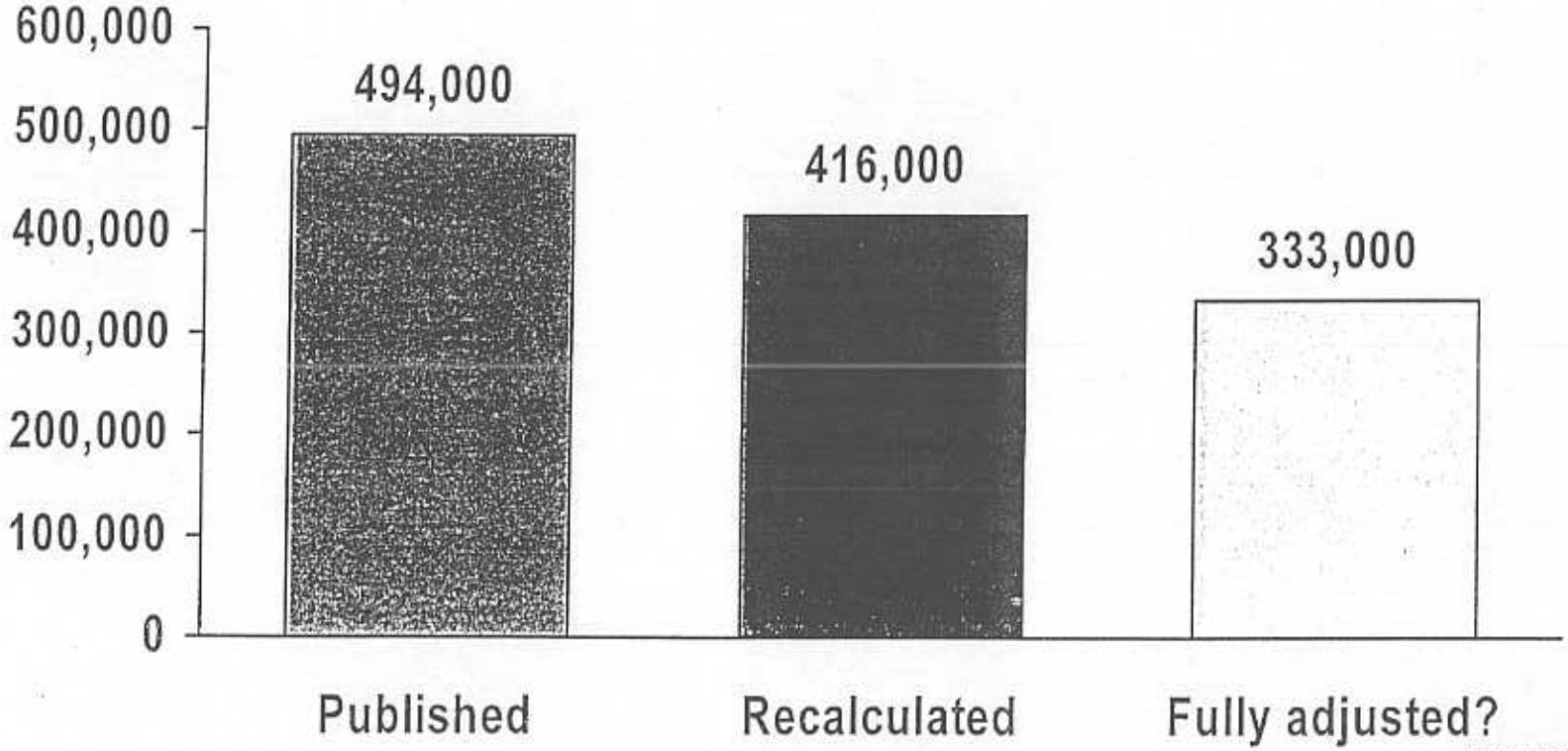
Mean overweight-attributable deaths over six cohorts



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Summary

- Calculations of overweight-attributable deaths were done erroneously in Causes paper, and as a result, the published numbers do not match the methods described in the paper, are not replicable, and are too high by about 80,000 deaths on average
- The approach that was used does not properly account for confounding or effect modification, probably leading to additional bias upwards.

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Table sent to DFW on 9/3/2004:

Utilizing the methodology provide by Ali Mokdad, I attempted to replicated the numbers published in the paper by Mokdad et al. In the second column are the estimates published by Mokdad et al, the next column includes my estimates followed by the percent agreement.
Results from the Internal Review of the Mokdad et al. Estimates of Deaths Attributable to Selected Conditions.

Characteristic	Published By Mokdad et al.	Internal Review	Percent Agreement
Smoking	435,000	433,787	99%
Poor Diet and Physical Inactivity	400,000	400,000	100%
Alcohol	85,000	87,000	98%
Microbial Agents	97313	97313	100%
Toxic Agents	55,000	55,277	100%
Motor Vehicle	43354	43354	100%
Fire Arms	28663	28752	100%
Sexual Behavior	14578	14478	100%
	5357	5357	100%
	4200	4200	100%
Overall	20000 (18k-25k)	24035	83%
Illicit Drug Use	17000	17103	99%

Differences are likely due to updates to CDC wonder mortality data files and rounding of prevalence estimates and relative risks.

Based on hardcopy of spreadsheets
sent to DFW on 9/14/04

Cohort	Published	"Replicate"	|Diff|	% Agrmt		Diff
Alameda	567,683	695,683	128,000	77.5		+128,000
Framghm.	543,981	535,763	8,218	98.5		-8,218
Tecumseh	462,005	461,605	400	99.9		-400
ACS I	451,708	401,878	49,830	89.0		-49,830
Nurses	504,602	465,887	38,715	92.3		-38,715
NHANES I	439,548	374,938	64,610	85.3		-64,610
Mean	494,921	*Mean*	48,296		*Mean*	+ 5,629

Correct % Agreement = (1.00 - (48,296/ 494,921))*100% **= 90.2%**

Conclusion:

The attempt by a CDC scientist to replicate the results for obesity reported in the JAMA article did not achieve 100% agreement.

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An Examination of Key Assumptions used in the 2004 JAMA *Actual Causes of Death* Paper

David F. Williamson, Ph.D.

Division of Diabetes Translation
National Center for Chronic Disease Prevention and Health Promotion
Coordinating Center for Health Promotion
Centers for Disease Control and Prevention

Key Assumptions

(all found on p. 1240, col 2):

1. Compared to overweight, diet has a minor additional impact on mortality due to "lack of certain essential nutrients".
2. The impact of physical inactivity on mortality is "accounted for" by overweight.
3. Overweight accounts for 96% (15,000/400,000) of all excess deaths from poor diet and physical inactivity.

p. 1240 JAMA, March 10, 2004—Vol 291, No. 10

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Assumption 1:

"Diet may have a minor additional effect on mortality mainly from lack of certain essential nutrients.[21,22]"

(p. 1240 JAMA, March 10, 2004—Vol 291, No. 10)

Result of search for the following words:
"essential nutrients", "micronutrients",

- essential nutrients: **No occurrences.**
- micronutrients: **2 occurrences in text.**

22. Peto J. Cancer epidemiology in the last century and the next decade. *Nature.* 2001;411:390-395.

22. Peto J. Cancer epidemiology in the last century and the next decade. *Nature.* 2001;411:390-395.

"Radical changes in national dietary habits would not be easy to achieve even if there were a consensus on which foods are relevant. Dietary supplements such as vitamins or other micronutrients seem an attractive alternative, but they may not have the same effects as the foods that contain them, and some may even be harmful[13]". (p. 391)

"The American panel[15] concluded that various cancers were likely to be reduced by foods containing adequate amounts of carotenoids, vitamins C and E and selenium, but neither they nor the British panel[13] recommended that these micronutrients should be taken as supplements". (p. 391)

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22. Peto J. Cancer epidemiology in the last century and the next decade. *Nature.* 2001;411:390-395.

"Doll and Peto[10] conclude that about a third of British cancer deaths might eventually prove to be avoidable by dietary change but only those due to obesity are definitely avoidable. In contrast, an American expert panel[15] recently concluded that about a third of cancers worldwide would probably be prevented by adoption of their quantitative recommendations on daily consumption of various foods. Another British report made qualitatively similar recommendations but stated that current evidence is insufficient to determine optimal quantities[13]" (p. 390).

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22. Peto J. Cancer epidemiology in the last century and the next decade. *Nature.* 2001;411:390-395.

Table 2 US Cancer deaths that would be avoided by eliminating known risks

Cause	Deaths (%) avoided after removing preceding causes	
	Current smokers*	Non-smokers
Smoking	60	—
Known infections†	2	5
Alcohol‡	0.4	1
Sunlight	0.4	1
Air pollution§	0.4	1
Occupation‖	0.4	1
Lack of exercise¶	0.4	1
Diet#		
Overweight (BMI >25 kg m^{-2})	4	10
Other dietary factors	4–12?	10–30?
Presently unavoidable**	About a quarter	At least half

Assumption 1 (cont'd):

"Diet may have a minor additional effect on mortality mainly from lack of certain essential nutrients.[21,22]"

(p. 1240 JAMA, March 10, 2004—Vol 291, No. 10)

21. Hu FB, Willet WC. Optimal diets for prevention of coronary heart disease. *JAMA.* 2002;288:2569-2578.

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Results of search for the following words:
"essential nutrients", "micronutrients",

- essential nutrients: **No occurrences.**
- (micro)nutrients: **5 occurrences in text.**

21. Hu FB, Willet WC. Optimal diets for prevention of coronary heart disease. *JAMA.* 2002;288:2569-2578.

21. Hu FB, Willet WC. Optimal diets for prevention of coronary heart disease. *JAMA.* 2002;288:2569-2578.

- "In the past 2 decades, understanding of the nutrients and foods likely to promote cardiac health has gown substantially owing to studies of the molecular mechanisms of atherosclerosis and the metabolic effects of various nutrients and foods..." (p. 2569)
- "Thus, carbohydrate-containing foods should not be judged simply by their GI values; the amount of carbohydrates, fiber, and other nutrients are also important." (p. 2573)
- "...the low GI of foods with a high level of fiber and numerous micronutrients in whole grains may also contribute to the benefits.[85]" (p. 2573)
- "Although prevailing dietary guidelines emphasize target intake of specific macronutrients (eg, not exceeding 30% of energy from fat),[71] such numerical criteria are not based on solid scientific evidence, and the public finds it difficult to make dietary changes based on such criteria." (p. 2575)

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21. Hu FB, Willet WC. Optimal diets for prevention of coronary heart disease. *JAMA.* 2002;288:2569-2578.

From the Abstract:

- "Compelling evidence ... indicates that at least 3 dietary strategies are effective in preventing CHD: substitute nonhydrogrenated unsaturated fats for saturated and trans-fats; increase consumption of omega-3 fatty acids from fish, fish oil supplements, or plant sources; and consume a diet high in fruits, vegetables, nuts, and whole grains and low in refined grain products... Many issues remain unsetttled, including... the effect of individual phytochemicals, antioxidant vitamins, and minerals."
- "Such diets, together with regular physical activity, avoidance of smoking, and maintenance of a healthy body weight, may prevent the majority of cardiovascular disease in Western populations."

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Assumption 2:

"Overweight would account for the major impact of poor diet and physical inactivity on mortality".[20]

(p. 1240 JAMA, March 10, 2004—Vol 291, No. 10)

20. Blair SN, Nichaman MZ. The public health problem of increasing prevalence rates of obesity and what should be done about it. *Mayo Clin Proc.* 2002;77:109-113.

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Blair et al. respond:

To the Editor:

"To compute the fraction of mortality attributed to specific behaviors relating to poor diet and overweight, Dr Mokdad and colleagues[1] estimated the annual deaths due to overweight. We do not understand the authors' conclusion that the "major impact of poor diet and physical inactivity" would be mediated by overweight, *and we are puzzled by why they cited one of our articles[2] to support this assertion..."*

Steven N. Blair, PED
sblair@cooperinst.org
Michael J. LaMonte, PhD, MPH
Milton Z. Nichaman, MD, ScD
The Cooper Institute
Dallas, Tex

p. 2942 JAMA, June 23/30, 2004—Vol 291, No. 24

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Results of search for the following words:
"death", "fatal", "mortality"

- death: **No occurrence in text.**
- fatal: **No occurrence in text.**
- mortality: **1 occurrence in the text.**

(20. Blair SN, Nichaman MZ. The public health problem of increasing prevalence rates
of obesity and what should be done about it. Mayo Clin Proc. 2002;77: 109-113.)

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The word mortality appears only once in the text, on page 111:

Chakravarthy et al,[16] in this issue of the *Proceedings*, present a compelling case for the importance of physical inactivity as a cause of many chronic health conditions. Human beings did not evolve to live in an environment where food is available everywhere at low cost and where physical activity has been engineered out of daily life. Regardless of the specific contributions of inactivity to the prevalence of obesity, physicians should aggressively promote activity to their patients. The benefits of activity go well beyond the effect on weight control or on other conventional risk factors for chronic health conditions. We find that a fit and active way of live reduces mortality risk in virtually all subgroups—the middle-aged and the elderly, women and men, the fat and the thin, and those with hypertension and those with normal blood pressure.[17-20]

(20. Blair SN, Nichaman MZ. The public health problem of increasing prevalence rates of obesity and what should be done about it. Mayo Clin Proc. 2002;77: 109-113.)

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Assumption 3

"Thus, we believe a more accurate and conservative estimate for overweight mortality in 2000 such as 385000, which is the rounded average of 2000 and 1991 estimates (494921 and 280184)... (ll 3-6)

We estimate that poor diet and physical inactivity will

cause an additional 15000 deaths a year, although this too may be conservative. (ll 19-21)

[No reference is given to support this statement]

We estimate that 400000 deaths were attributable to poor diet and physical inactivity..." (ll 26-27)

p. 1240 JAMA, March 10, 2004—Vol 291, No. 10

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Summary

- The authors of the *JAMA 2004 Actual Causes of Death* paper cited references that either did not support (refs 21,22) or contradicted (ref 20), the stated assumptions in the paper that the impact of diet and physical inactivity is accounted for by overweight.
- The authors provided no reference to support their stated assumption that 15,000 deaths out of 400,000 were caused by diet or physical inactivity.
- The authors of the *JAMA 2004 Actual Causes of Death* paper did not provide adequate support from the literature for three key assumptions that are necessary to conclude that overweight, rather than diet and physical inactivity, is the true cause of excess mortality in the U.S. population.

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Actual causes of death paper: Issues

Deb Galuska
Division of Nutrition and Physical Activity

Issues

- Direct comparison of number of deaths attributed to poor diet and physical inactivity in Mokdad et al. paper with numbers estimated from McGinnis and Foege paper
- Use of obesity as a proxy for poor diet and physical inactivity
  - Other causes for obesity
  - Independent effect of poor diet and physical inactivity on mortality
- Unclear how additional number of deaths attributed to diet and physical activity calculated
- Inability to replicate numbers in the paper

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Issues

- Direct comparison of number of deaths attributed to poor diet and physical inactivity in Mokdad et al. paper with numbers estimated from McGinnis and Foege paper
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"We estimate that approximate that 400,000 deaths were attributable to poor diet and physical inactivity, an increase of one third from 300,000 deaths estimated by McGinnis and Foege, and the largest increase among all actual causes of death" (p. 1240)

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Comparison of methodologies

McGinnis

- Estimates % of deaths attributed to diet and physical activity for a variety of diseases (i.e. cancer, diabetes, CVD) based on review articles and other literature
- Calculates range and uses lower end of range
- Does not directly account for any lag time between exposure and death
- Rounds to nearest 100,000

Mokdad

- # of deaths attributed by overweight and obesity + 15,000 additional deaths
- Accounts for lag time between weight status and death
- Does not round

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Potential independent effects of diet and physical activity

- Diet
  - Cachexia
  - Saturated fat (vs. polyunsaturated fats) and CVD events
- Physical activity
  - Review by Blair et al

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Other causes for obesity and overweight

- Medication use
- Some diseases
  - Endocrine disorders
  - Single gene disorders

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Calculation of additional deaths from diet and physical activity

- Estimate of 15,000 total
- 4242 deaths from nutritional deficiencies (p. 1240)
- Assumptions used to estimate remaining 10,758 not provided

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Issues

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