Epidemiological Studies of Chronic Disease: Maladjustment of Observed Mortality Rates

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Abstract: Age adjustment of observed mortality and morbidity rates is not a substitute for age-specific analysis. Measures of association between potential causal factors and adjusted mortality rates are functions of the particular adjustment procedure and the choice of reference population.

We exhibit here the wide variation in simple correlation statistics that occurs with eight adjustment methods and three reference populations. We then generalize these results to the multivariate situation showing an example in which there is coherent structure for the associations between predictors and mortality. This is contrasted with another example in which no such meaningful pattern exists. Studies are cited that could have been improved by greater attention to the underlying structure of age-adjusted rates.

Age adjustment of total observed rates yields meaningless numbers that are useful for *comparative* purposes only. Total observed rates have substantive meaning but provide useful etiological clues primarily when supported by analyses of appropriate age-specific data. (*Am J Public Health* 70:142–150, 1980.)

It has long been known that adjustment of observed mortality data for age is appropriate for comparative epidemiological studies. However, recently a trend has developed toward adjusting epidemiological data for age, and perhaps for other characteristics such as sex and race, in a routine manner prior to analysis and without giving consideration to the ultimate aims of the studies. The inadvisability of routine adjustment for age has been recognized for many years. Hill, writing in 1939, is very clear:

> "The standardized death rate is . . . a fiction. . . . It is not the total death-rate that actually exists in an area but the rate the area would have if, while retaining its own rates of ages, it had instead of its real population one of some particular chosen type. The fiction is useful because . . . it enables summary comparisons to be made . . . free from the distortions which arise from age and sex differences in the existing populations. The object throughout is, therefore, comparison; a standardized death rate alone has no meaning."[1]

Yerushalmy,[2] Kitagawa,[3] Chiazze,[4] and Fleiss[5] have taken similar positions. Yerushalmy[2] presented examples of several different kinds of distortion that can arise through uncritical age adjustment. Nevertheless, it is recognized that situations arise in which it is desirable to use a single summary figure for a population's mortality rate.[6]

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The type of analysis, and thus the treatment of mortality rates in a study, must depend upon the purpose of the research. In this paper we discuss studies that seek etiological clues from statistical associations. We propose to show that use of age-adjustment in such studies can be counterproductive, and that, if used, it should be supported by examination of observed and age-specific rates.

Effects of Age Adjustment on Statistical Association

Appendix Table 1 summarizes the computations for eight methods (four rates and four indices) of age adjustment. The four age-adjusted rates are measured in the same units as are the initial age-specific rates, e.g., in deaths per 10^5 of population. The four indices are ratios of rates and as such are pure numbers.

Let us hypothesize a chronic disease, mallard de mer,* an affliction of the central nervous system affecting equilibrium, that formerly has been found only among avian species. The disease has now been discovered among humans exposed to domesticated birds, usually ducks, that are visited by wild mallards (*Anas platyrhynchos*), with death often a consequence of extended contact. Suppose that for several rural areas data were collected that included degree of contact of the population with domestic ducks and that regression techniques showed that 95 per cent of the variance in observed mortality rate from mallard de mer was associated

*Apologies to Walt Kelly.

TABLE 1—Age Structure and Age-specific Rates for Areas under Study: Mallard de Mer Data

Area		1		2		3		4		5	
Exposure = c		2		4		9		7		6	
Age Class	Number of Years w_i	p_i	a_i	p_i	a_i	p_i	a_i	p_i	a_i	p_i	a_i
0–24.99	25	0.3	10	0.5	30	0.2	20	0.2	20	0.1	20
25–39.99	15	0.4	10	0.2	30	0.3	40	0.2	30	0.2	30
40–69.99	30	0.2	50	0.2	50	0.2	70	0.3	70	0.4	50
70–99.99	30	0.1	80	0.1	80	0.3	90	0.3	70	0.3	70

*For notation, see footnote to Table 4.

with the exposure factor. Then the field program would have emitted a clear signal: "Examine the biological relationships between exposure to domestic ducks and mallard de mer," and laboratory research would be started on the proper route.

This clue might have been missed if age-adjustment techniques had been used. Assume that, in five rural areas over a long period of time, degree of human contact with domestic ducks has been reasonably stable. In a recent year, age-specific mortality rates, a_i, per 100,000 of population were computed for mallard de mer in each area (Table 1). The age structures of the population vary considerably with area. In Areas 3 and 4 the populations are distributed fairly evenly across all age strata as might be characteristic of a mature area with a stable economy, excellent sanitation, effective medical care, and little growth in population. In Areas 1 and 2 a heavy concentration occurs in the younger age strata as might be encountered in a region of rapid economic growth, while Area 5 holds the greatest proportion of older people as would be expected in a rural area with considerable out-migration. Also, as with most chronic disease, the age-specific rates for mallard de mer increase with age in all cases. Area 1 shows the lowest rates among the young; Area 3 the highest among the old. Epidemiological data on mallard de mer are scarce, but the incidence is increasing dramatically so that analysis of the available data is imperative.

The data indicate a moderate relationship of mortality from mallard de mer with exposure to domestic ducks for adults only between 25 and 70 years of age. This seems reasonable since the workers who care for the ducks are mostly adults, and exposure does, in fact, differ by age group. Although substantial differences in population structure among the areas and in the age-specific rates in themselves make the use of summary measures questionable, let us review what occurs when summary measures are applied to the data.

To illustrate the dependence of regression and correlation statistics upon the reference population as well as upon the choice of adjustment method, Table 2 shows, in column 1, a reference population with the age structure of Area 5, but with lower age-specific rates. These rates recommended it to the investigators who felt that the specific rates in some instances might have been inflated in the data collection process. Table 2 also includes two alternative reference populations. Reference population 2 has the structure of a developing area while reference population 3 might be a retirement area.

The eight age-adjusted mortality rates are shown in Table 3 for each of the five areas and all three reference populations; their computation follows the procedures shown in Appendix Table 1. Table 3 also shows the measure of exposure c, the standard mortality rates (A) for mallard de mer for the reference populations, and the observed rate (a) for each area.

In Table 3, the eight age-adjusted figures for each reference population are presented in two groups. The first consists of those whose units are deaths per 10^5 population, the second group consists of indices, which by their nature are

TABLE 2—Age Structure and Age-specific Rates of Reference Populations: Mallard de Mer Data

		Reference Population 1		2		3	
Age Class	Number of Years, w_i	P_i	A_i	P_i	A_i	P_i	A_i
0–24.99	25	0.1	10	0.4	30	0.1	10
25–39.99	15	0.2	10	0.3	40	0.2	20
40–69.99	30	0.4	20	0.2	70	0.2	40
70–99.99	30	0.3	40	0.1	80	0.5	60
A			23		46		43

*For notation, see footnote to Table 4.

TABLE 3—Mortality Rates and Indices: Mallard de Mer Data*

Data Category	Area 1	2	3	4	5
Exposure to domestic ducks (c)	2	4	9	7	6
Observed mortality rate (a)	25	39	57	52	49
Reference population #1					
Standard Mortality Rate (A)	23	23	23	23	23
Age-adjusted rates					
a_D (direct)	47.00	53.00	65.00	57.00	49.00
a_I (indirect)	38.3333	59.80	62.4285	54.3636	49.00
a_C (c.m.r.)	36.00	46.00	61.00	54.50	49.00
a_E (Yule)	43.00	51.00	59.00	51.50	45.50
Age-adjusted indices					
a_X (c.m.f.)	2.0435	2.3043	2.8261	2.4783	2.1304
a_Y (s.m.f.)	1.6667	2.60	2.7143	2.3636	2.1304
a_M (Yerushalmy)	1.75	2.55	2.825	2.525	2.225
a_Z (r.m.i.)	1.40	2.80	2.975	2.575	2.325
Reference Population #2					
Standard Mortality Rate (A)	46	46	46	46	46
Age-adjusted rates					
a_D (direct)	25.00	39.00	43.00	38.00	34.00
a_I (indirect)	24.4681	39.8667	46.8214	40.5424	35.7778
a_C (c.m.r.)	25.00	39.00	50.00	45.00	41.50
a_E (Yule)	43.00	51.00	59.00	51.50	45.50
Age-adjusted indices					
a_X (c.m.f.)	0.5435	0.8478	0.9348	0.8261	0.7391
a_Y (s.m.f.)	0.5319	0.8667	1.0179	0.8814	0.7778
a_M (Yerushalmy)	0.6351	0.8768	0.9542	0.8417	0.7560
a_Z (r.m.i.)	0.4429	0.8929	0.9708	0.8458	0.7649
Reference Population #3					
Standard Mortality Rate (A)	43	43	43	43	43
Age-adjusted rates					
a_D (direct)	53.00	59.00	69.00	57.00	53.00
a_I (indirect)	43.00	72.9130	72.0882	62.1111	54.0256
a_C (c.m.r.)	39.00	49.00	63.00	54.50	51.00
a_E (Yule)	43.00	51.00	59.00	51.50	45.50
Age-adjusted indices					
a_X (c.m.f.)	1.2326	1.3721	1.6047	1.3256	1.2326
a_Y (s.m.f.)	1.00	1.6957	1.6765	1.4444	1.2564
a_M (Yerushalmy)	1.10	1.75	1.7757	1.60	1.45
a_Z (r.m.i.)	0.8833	2.1833	1.80	1.575	1.35

*For notation, see footnote to Table 4.

of a lower order of magnitude. For a given reference population, the range from high to low among an area's rates can be quite similar from one age-adjustment method to another, but variability among the areas is considerably affected by the age-adjustment procedure selected. The indices are similarly affected. It is important to see how differences of this magnitude can affect measures of association.

Table 3 demonstrates that the different age-adjusted rates also vary according to the particular reference population employed. Only Yule's method,[7] which does not use a reference population, shows no change. A different reference population can result in a different ranking of the rates and indices from smallest to largest within an area. For each reference population the adjusted rates or indices from each area tend to be within a characteristic range.

Table 4 shows linear regression equations associating the measure of exposure, c, with the observed mortality rate and with each of the eight age-adjusted figures for each reference population. These were calculated from Table 3 (the first equation computed directly from rows one and two, the second equation from rows one and four, etc.). Also given are the coefficients of determination and correlation, r^2 and r. We shall concentrate our attention upon r^2, the proportion of the variance in the mortality rate in question that is explained by the difference in exposure to domestic ducks. While the observed coefficient of determination, 0.953, is somewhat higher than the age-specific coefficients of determination (not shown here), the age-adjusted coefficients of determination vary across much of the admissible range (0.173 to 0.975). The coefficient of determination for the commonly used indirect method varies from 0.362 to 0.767, depending on the reference population selected. The indirect rate and the relative mortality index reduce the observed r^2 of 0.953 to 0.362 or below, using the third reference population (A = 43), but show an r^2 of approximately 0.5 using the first reference population (A = 23), and an r^2 of 0.64 or more using the second reference population (A = 46). As a consequence of their proportionality, a_D and a_X will always have

TABLE 4—Linear Relationships: Mallard de Mer Data*

Dependent Variable	Regression Equation	r^2	r
a (observed)	a = 4.582c + 18.739	0.953	0.976
Reference Population #1, A = 23			
Age-adjusted rates			
a_D (direct)	a_D = 2.274 c + 41.466	0.737	0.859
a_I (indirect)	a_I = 2.544 c + 38.538	0.514	0.717
a_C (c.m.r.)	a_C = 3.428 c + 30.103	0.975	0.988
a_E (Yule)	a_E = 1.866 c + 39.548	0.663	0.814
Age-adjusted indices			
a_X (c.m.f.)	a_X = 0.099 c + 1.803	0.737	0.859
a_Y (s.m.f.)	a_Y = 0.111 c + 1.676	0.514	0.717
a_M (Yerushalmy)	a_M = 0.125 c + 1.675	0.682	0.826
a_Z (r.m.i.)	a_Z = 0.176 c + 1.431	0.591	0.769
Reference Population #2, A = 46			
Age-adjusted rates			
a_D (direct)	a_D = 2.075 c + 24.178	0.673	0.821
a_I (indirect)	a_I = 2.685 c + 22.461	0.767	0.876
a_C (c.m.r.)	a_C = 3.329 c + 21.459	0.916	0.957
a_E (Yule)	a_E = 1.866 c + 39.548	0.663	0.814
Age-adjusted indices			
a_X (c.m.f.)	a_X = 0.045 c + 0.526	0.673	0.821
a_Y (s.m.f.)	a_Y = 0.058 c + 0.488	0.767	0.876
a_M (Yerushalmy)	a_M = 0.035 c + 0.614	0.615	0.784
a_Z (r.m.i.)	a_Z = 0.061 c + 0.444	0.640	0.800
Reference Population #3, A = 43			
Age-adjusted rates			
a_D (direct)	a_D = 1.726 c + 48.534	0.503	0.709
a_I (indirect)	a_I = 2.815 c + 45.062	0.362	0.602
a_C (c.m.r.)	a_C = 3.154 c + 33.637	0.956	0.978
a_E (Yule)	a_E = 1.866 c + 39.548	0.663	0.814
Age-adjusted indices			
a_X (c.m.f.)	a_X = 0.040 c + 1.129	0.503	0.709
a_Y (s.m.f.)	a_Y = 0.065 c + 1.048	0.362	0.602
a_M (Yerushalmy)	a_M = 0.072 c + 1.133	0.494	0.703
a_Z (r.m.i.)	a_Z = 0.075 c + 1.138	0.173	0.417

*Notation:
i = index for age strata in all populations, i = 1, . . . , N.
w_i = number of years in the i^{th} age stratum.
a_i = specific rate for the i^{th} stratum in the population under study.
A_i = specific rate for the i^{th} stratum in the reference population.
a = observed rate for the population under study.
A = observed rate for the reference population.
p_i = proportion of the population under study in the i^{th} stratum.
P_i = proportion of the reference population in the i^{th} stratum.

We note that $a = \sum_{i=1}^{N} a_i p_i$, and $A = \sum_{i=1}^{N} A_i P_i$.

the same r^2 as will a_I and a_Y. It is clear than an investigator can obtain almost any degree of relationship desired by careful choice of age-adjustment method and reference population.

There is no assurance that any one age-adjustment method is superior to any other method in the sense of minimizing deviations from observed r^2. One can assemble examples in which any one of the methods reduces a substantial observed r^2 to insignificance, or in which any one of them seriously inflates a near zero observed r^2. This latter situation is perhaps the most serious since the effect of age adjustment here is to create false clues rather than to obliterate existing clues.

We have performed the necessary routine calculations with data for various age distributions in other hypothetical cases and in actual cases. Even when age distributions are much less extreme than those used here, considerable differences in correlation and regression statistics arise from the choice of adjustment method, and from selection of the reference population.

Some Research Examples of the Effect of Age Adjustment on Linear Relationships

In exploratory studies previously reported,[8-10] Hickey, et al, averaged mean annual air pollutant concentrations and water hardness data, 1957-1964, involving one to six annual measurements, to estimate mean regional values for 38 Standard Metropolitan Statistical Areas (SMSAs) of the United States. Means of annual mortality rates for a number of chronic diseases, 1959-1961, were the dependent variables regressed upon the natural logarithms of mean annual air pollutant concentrations as the independent variables. Coefficients of multiple determination were computed, and standard tests of significance run for coefficients of determina-

TABLE 5—Matrix of Correlation Coefficients for Observed, Age-Adjusted, and Age-Specific Mortality Rates per 10^5 Persons for Lung Cancer for White Males, 38 SMSAs, 1959–1961, vs Several Environmental Chemical Variables*

	Correlation Coefficients							
	Age Cohorts							
Predictors*	35-44	45-54	55-64	65-74	75-84	≥ 85	All, Adjusted‡	All, Observed
Cd	+0.03	−0.14	−0.15	+0.05	−0.15	+0.09	−0.11	−0.03
Cr	+0.28	+0.08	+0.06	+0.23	−0.20	−0.24	+0.10	+0.19
Cu	−0.27	−0.21	−0.26	−0.22	−0.08	−0.12	−0.30	−0.34
Fe	+0.28	−0.01	−0.04	+0.14	−0.25	−0.26	0.00	+0.01
Pb	−0.01	−0.12	−0.22	−0.08	−0.06	−0.03	−0.17	−0.05
Mn	+0.45	+0.11	+0.01	+0.09	−0.14	−0.25	+0.06	+0.04
Ni	−0.07	−0.02	+0.14	+0.27	−0.26	+0.21	+0.12	+0.35
Sn	+0.11	+0.13	−0.01	+0.19	−0.20	+0.17	+0.08	+0.07
Ti	+0.23	−0.27	−0.32	−0.06	−0.14	−0.28	−0.25	−0.34
V	+0.10	+0.07	+0.21	+0.29	0.00	+0.17	+0.25	+0.44
Zn	+0.18	0.00	−0.18	+0.11	−0.18	+0.08	−0.05	+0.10
NO_2	+0.05	+0.19	+0.35	+0.34	−0.39	+0.27	+0.27	+0.52
SO_2	−0.05	−0.19	−0.21	+0.09	+0.05	+0.05	−0.09	+0.28
$SO_4^=$	+0.35	+0.16	+0.23	+0.27	−0.06	+0.04	+0.27	+0.52
WH	−0.17	+0.07	+0.07	+0.16	+0.15	−0.05	+0.13	−0.09
As	+0.12	−0.12	−0.13	−0.25	−0.42	+0.01	−0.27	−0.11

*Chemical data used are in natural logarithms of atmospheric concentrations in $\mu g/m^3$ of air. WH is drinking water hardness in ppm of $CaCO_3$ equivalent.
‡Direct method of adjustment.

tion and regression coefficients. Parallel analyses were also performed using as dependent variables the mortality rates for the same diseases adjusted with the direct method for age, sex and race by Duffy and Carroll.[11] In some cases age-specific rates were also analyzed. We are here concerned with the effects of "adjustment" on the linear relationship existing among these various variables.

Simple correlation coefficients were computed relating the natural logarithms (ln) of chemical concentrations employed in these studies to observed mortality rates from various chronic diseases. These were supported by recalculations based on the standardized rates for age, sex and race given by Duffy and Carroll[11] using the direct method. Many substantial differences occurred between coefficients within these pairs.

Tables 5, 6, and 7 contrast the results of multivariate analyses relating the natural logarithms of mean annual concentrations of environmental chemicals with mortality rates for lung cancer and arteriosclerotic heart disease. Specific rates for white male age cohorts and total white male mortality rates, with or without age adjustment,[11] were used. Tables 5 and 6 give bivariate correlation coefficients by age cohorts as well as for total observed and age-adjusted rates. The age cohorts for those less than 35 years of age were omitted since the numbers of deaths in these groups were small. In all regression analyses R^2 was corrected for sample size. An optimal subset selection regression algorithm[12] was used throughout.

As an example of how regression equations in Table 7 should be read, consider the second row, "Direct Adjusted." When the adjusted lung cancer mortality rate data were regressed upon the logarithms, ln, of the concentrations of the 12 chemicals listed as column headings, only one-half of these chemicals made significant contributions to variance reduction. The resulting regression equation may be expressed as:

$$\text{Lung Cancer Mortality Rate (Adj.)} = 23.001 - 2.5754 \ln c(SO_2) + 5.6238 \ln c(NO_2) - 5.1766 \ln c(Ti) + 5.0954 \ln c(Mn) + 1.7477 \ln c(V) - 2.2248 \ln c(As)$$

These six variables explained 48.5 per cent of the variance in adjusted lung cancer mortality rate for 38 urban regions.

We have chosen the two sets of regression equations to illustrate one situation in which the statistical analyses appear to present an interesting set of clues to the laboratory scientist and another situation in which a casual examination of total rates could provide misleading implications.

The analysis of white male mortality rates for lung cancer (ICD Nos. 162-163) given in Table 7 shows a rather strong relationship between some chemical pollutants and that rate. Analysis based on direct adjusted rates shows a much weaker relationship involving a somewhat different set of chemicals. Even more important is the fact that analysis of age-specific rates indicated even weaker relationships and stresses different chemicals for different age cohorts. In particular, among environmental chemicals that other investigators have related to lung cancer mortality, no strong case is shown here for identification of SO_2, $SO_4^=$, or NO_2 as worthy of further study. The pollutant that occurs most frequently is titanium and this has not been commonly cited as related etiologically to lung cancer mortality. We conclude that our analysis has not provided the kinds of statistical clues that we were seeking; and that the use of total mortality rates—observed or adjusted—could be misleading.

TABLE 6—Matrix of Correlation Coefficients for Observed, Age-Adjusted, and Age Specific Mortality Rates per 10^5 Persons for Arteriosclerotic Heart Disease for White Males, 37 SMSAs, 1959–1961, vs Several Environmental Chemical Variables*

	Correlation Coefficients							
	Age Cohorts							
Predictors	35–44	45–54	55–64	65–74	75–84	≥85	All, Adjusted‡	All, Observed
Cd	−0.18	−0.29	−0.32	+0.09	−0.06	+0.07	−0.17	−0.03
Cr	+0.35	+0.14	−0.06	−0.06	+0.08	−0.05	+0.04	+0.13
Cu	−0.18	−0.37	−0.34	−0.15	−0.22	−0.24	−0.32	−0.26
Fe	+0.10	−0.02	−0.19	−0.15	−0.15	−0.23	−0.17	−0.08
Pb	−0.01	−0.05	−0.22	−0.19	−0.11	−0.13	−0.14	0.00
Mn	+0.17	+0.05	−0.13	−0.12	−0.03	−0.15	−0.07	−0.04
Ni	−0.04	−0.09	+0.08	+0.02	+0.32	+0.38	+0.23	+0.35
Sn	−0.04	−0.11	−0.15	0.00	−0.06	+0.05	−0.06	−0.04
Ti	+0.04	−0.07	−0.29	−0.18	−0.30	−0.39	−0.30	−0.29
V	+0.23	+0.29	+0.38	+0.16	+0.49	+0.50	+0.51	+0.50
Zn	−0.09	−0.16	−0.36	+0.07	−0.08	+0.02	−0.15	+0.05
NO_2	−0.26	−0.17	−0.10	+0.04	+0.19	+0.31	+0.08	+0.34
SO_2	+0.24	+0.20	+0.22	+0.27	+0.47	+0.40	+0.41	+0.54
$SO_4^=$	+0.31	+0.30	+0.27	+0.26	+0.52	+0.42	+0.47	+0.51
WH	−0.07	−0.24	−0.16	−0.09	−0.22	−0.27	−0.26	−0.38
As	−0.34	−0.29	−0.35	−0.10	−0.13	0.00	−0.22	+0.02

*Chemical Data used are in natural logarithms of atmospheric concentrations in $\mu g/m^3$ of air. WH is drinking water hardness in ppm of $CaCO_3$ equivalent.
‡Direct method of adjustment.

In contrast, the analyses of white male mortality rates from arterioscleriotic heart disease (ICD No. 420) are quite consistent. The equations based on total observed and on direct age-adjusted rates explain about the same proportion of total variance in the dependent variable. The same set of predictor variables was selected. The signs and even the magnitudes of the regression coefficients agree. In addition, all predictors selected in these equations recur repeatedly in the age-cohort equations with exactly the same sign patterns and a coherent progression of magnitudes. Futhermore the coefficients of determination are quite stable across age-cohorts and agree well with those derived from the total rates analyses. We have concluded that SO_2 and $SO_4^=$ are indicated as tentative contributors to AHD mortality. Other investigators have also implicated these chemicals.

Rather generally, the changes in R^2 caused by adjustment are what would be expected after the mallard de mer illustration. In many cases, adjustment will strengthen the relationship between certain variables and amortality rate and weaken its relationship to others so that some of the changes will cancel each other. What may seem surprising is the occasional strong effect of adjustment upon the particular set of predictor variables selected in view of the fact that multicollinearity is not a severe problem here. In any case, different methods of adjustment might have yielded entirely different sets of environmental clues. Thus an investigator who can access various sets of etiological clues, depending on the choice of adjustment method and reference population, may mask one or more substantive factors, in addition to introducing irrevelant factors.

Some Examples of Disease Etiology Studies

We have selected a few published examples of the use of rates adjusted for age and other variables in studies of statistical association intended to elucidate disease etiologies. It is not our intent to denigrate anyone's research, but rather to propose a simple way in which results could be made more informative and potentially more useful in preventive medicine.

Winkelstein, et al, recently reported on correlations among incidence rates for selected cancers in seven metropolitan areas and two states. The abstract states:

> "It was hypothesized that cancers which varied together across the nine survey communities might have common etiologic factors . . . The most notable findings were the high correlations between the incidence rates for the three gastrointestinal sites (stomach, colon, and rectum) and bladder cancer in both men and women and the high correlation between three female sexual sites (breast, corpus, and ovary). . . . These associations suggest possible common etiologic agents, despite the fact that the individual secular trends for some of these cancers differ."[13]

Incidence rates for 1960–1971, available from the Third National Cancer Survey for relatively homogeneous, i.e., race- and sex-specific populations, were used. Unfortunately, the available age-specific rates for whites were pooled in an unspecified manner using the 1950 US population as a reference standard for obtaining total age-adjusted incidence rates. Correlation coefficients were then computed using these age-adjusted rates. Characteristic race and sex differences were observed in the occurrence of many can-

TABLE 7—Regression Analyses for Two Disease Categories Using Environmental Chemical Concentration and Mortality Rates for White Males

	Regression coefficients for Chemicals*													
	Constant	SO_2	$SO_4^=$	NO_2	Cu	Ti	Ni	Fe	Mn	V	Pb	As	Sn	R^2
38 SMSAs, Lung Cancer (ICD Nos. 162, 163)														
Total Observed	−66.047		7.9367**	8.7535	−4.8893	−8.1913		6.5535				−1.2353		0.758
Direct Adjusted	23.001	−2.5754*		5.6238		−5.1766			5.0954	1.7477		−2.2248		0.485
Age-Specific														
35–44	−11.549		5.105		−2.931	2.027	−2.345							0.464
45–54	37.237	−7.6979				−21.836		14.453	5.7855	3.3279				0.339
55–64	89.603	−18.821				−49.971		46.751		9.4577				0.492
65–74	−87.711			75.318					24.449	8.313	−33.613	−19.555		0.465
75–84	148.49											−14.113		0.155
≥85	118.85					−56.026							46.775	0.144
	Constant	SO_2	$SO_4^=$	NO_2	Cu	Ti	Ni	Fe	Mn	V	Pb	As	Zn	R^2
37 SMSAs, Arteriosclerotic Heart Disease (ICD No. 420)														
Total Observed	−163.18	42.217*	74.310**		− 57.245								− 26.037	0.535
Direct Adjusted	65.228	20.930	56.608		− 36.645								− 26.969	0.593
Age-Specific														
35–44	101.43		25.741	−20.743								− 4.8603		0.413
45–54	− 74.741		80.685		− 31.370		−53.337			13.226		−10.672		0.530
55–64	337.20	35.889	98.821		− 69.074								− 72.993	0.498
65–74	371.72	113.27	251.961		−179.86								−125.01	0.539
75–84	179.13	251.25	664.87		−336.73								−286.40	0.555
≥85	6631.1					−963.98				403.93				0.370

*Based on the standard t-test, all regression coefficients shown in this table are significant at the $\alpha \leq 0.05$ level of significance.

**Chemical terms in the regression equations are all expressed as natural logarithms of concentrations of the chemicals selected by the algorithm. For example, the $SO_4^=$ term for total observed AHD mortality rate is properly + 74.310 ln c($SO_4^=$), with sulfate concentration, c($SO_4^=$), expressed as $\mu g/m^3$ of air.

cers, especially those of the stomach and bladder. It is regrettable that correlations were not also computed using original, observed age-sex-race-specific incidence rates, thus facilitating alternative considerations and hypotheses in identification of common etiologic factors.

Yano, et al, reported associations involving the drinking of coffee and alcoholic beverages in relation to risk of coronary heart disease (CHD) among Japanese men in Hawaii.[14] CHD risk, related to coffee and alcohol consumption, was estimated from direct age-adjusted incidence rates. The extent of the effect of age adjustment is not evident from information given. However, the report used age-adjusted rates to relate coffee and alcohol drinking habits to CHD, finding a strong *negative* association between alcohol intake (mainly beer) and CHD risk and a positive association between coffee intake and CHD risk.

It would have been desirable to report relationships involving both the observed and age-specific rates in the same manner as was done for age-adjusted rates. One can hypothesize that any effects of coffee and alcoholic beverage drinking on CHD risk will accumulate over time. Thus one might expect age-specific rates, particularly in the upper age brackets, to show even stronger relationships between usage of these popular products and CHD mortality rate than would age-adjusted rates. If this is the case, why diminish the associations by age adjustment?

In 1970, Stocks reported on relationships between the consumption of coffee, tea, cigarettes, and solid fuel and death rates for several categories of cancer.[15] Data for 20 countries, compiled by Segi, Kurihara and Mitsuyama,[16] were used. All rates were age-adjusted, although the adjustment method was not specified, and white and non-white populations in the United States were combined. Stocks examined differences in mean death rates for several categories of cancer between countries with above and below median consumption of the environmental variables. He found significant ($p < 0.01$) associations between per capita consumption of solid fuel and age-adjusted mortality rate for cancer of the bladder for both males and females, for breast cancer for females, and for cancer of the lung and bronchus for males. He also found significant positive correlations of per capita coffee consumption with age-adjusted mortality rate for cancer of the prostate and pancreas and for leukemia in males, and for cancer of the ovary in females. If Stocks' mortality rates had not been adjusted for age, would the set of clues have been different?

In a somewhat comparable study, Palotas reported briefly on correlations for 16 countries between apparent per capita consumption of coffee and mortality rate for arteriosclerotic and degenerative heart disease for the 1965–1966 period.[17] For the 16 countries, $r = +0.763$ ($p < 0.01$). For countries grossly similar in diet and climate, the association strengthened. Thus, for Belgium, Netherlands, Norway, Finland, Denmark and Sweden, $r = +0.990$ ($p < 0.005$), and for Italy, Greece, Japan, Portugal, and Israel, $r = +0.974$ ($p < 0.01$). Although information given was scant,[17] the mortality rate data used were presumably observed rates; nothing was said about adjustment.

Discussion

The object of age adjustment of mortality rates is meaningful comparison of representative rates from different populations.[1] As we have demonstrated, its use in epidemiological studies of association may lead to distortion, to suppression or elimination of clues of potential etiological importance, and to introduction of misleading clues in studies of association aimed at etiological explanation. Careful consideration of the logical basis of age-adjustment in terms of the disease under study and the question to be answered is essential whenever it is employed. In such studies of association, age-adjustment is no substitute for age-specific analyses—particularly when the goal is determination of chronic disease etiology whose development takes place over a long period of time.

It should always be remembered that the use of total rates unsupported by age-specific analyses may be dangerous. Where age-adjusted rates are used to any important degree in influencing public policy and regulatory matters, such as in the designation of "causes" of human morbidity and mortality, the process is unacceptable if false clues can be designated. Since age-adjusted mortality rates are heavily dependent upon both the adjustment method selected and the reference population employed, the simple fact is that in "correcting for age" one may be unwittingly introducing false clues or erasing clues pointing to biological and/or environmental factors that operate in a cumulative fashion over time.

We recommend that investigators report both total observed rates and age-specific rates, analyzing them in parallel with any adjusted rates in studies of statistical association. It should also be recognized that perfect age adjustments would be likely to destroy any evidence of biochemical causative factors whose effects accumulate slowly over time. Furthermore, it is desirable for investigators to explain both the functional basis for differences in their studies using adjusted and observed rates, and the rationale for their selection of a particular adjustment procedure.

REFERENCES

1. Hill AB: Principles of medical statistics. London, 1939, The Lancet, Ltd., *e.g.*, p. 158.
2. Yerushalmy J: A mortality index for use in place of the age-adjusted death rate. Am J Public Health 41:907–922, 1951.
3. Kitagawa EM: Standardized comparisons in population research. Demography 1:296–315, 1964.
4. Chiazze L, Jr: Indexes of mortality. 5. Discussion. Human Biol 38:320–322, 1966.
5. Fleiss JL: Statistical methods for rates and proportions. New York, 1973, John Wiley and Sons, chapter 13.
6. Kleinman JC: Age-adjusted mortality indices for small areas: Applications to health planning. Am J Public Health 67:834–840, 1977.
7. Yule GU: On some points relating to vital statistics, more especially statistics of occupational mortality. J Roy Stat Soc 97, part 1:1–84, 1934.
8. Hickey RJ, Boyce DE, Harner EB and Clelland RC: Ecological statistical studies concerning environmental pollution and chronic disease. IEEE Trans Geosci Electronics GE-8:186–202, 1970.
9. Hickey RJ, Boyce DE, Harner EB and Clelland RC: Exploratory ecological studies of variables related to chronic disease mortality rates. Philadelphia, 1971, University of Pennsylvania, Available as NTIS No. PB-246,383; Springfield, VA, 1975, National Technical Information Service, US Dept of Commerce.
10. Hickey RJ, Boyce DE, Clelland RC, et al: Demographic and chemical variables related to chronic disease mortality in man. Philadelphia, 1976, Department of Statistics, The Wharton School, University of Pennsylvania; Technical Report No. 15.
11. Duffy EA and Carroll RC: United States Metropolitan Mortality, 1959–1961; PHS Pub. No. 999-AP-39, Cincinnati, OH, 1967, National Center for Air Pollution Control, US Public Health Service.
12. Boyce DE, Farhi A and Weischedel R: Optimal subset selection: multiple regression, interdependence and optimal network algorithms. Lecture notes in economics and mathematical systems 103. New York, 1974, Springer-Verlag.
13. Winkelstein W., Jr, Sacks ST, Ernster VL and Selvin S: Correlations of incidence rates for selected cancers in nine areas of the third national cancer survey. Am J Epidem 105:407–419, 1977.
14. Yano K, Rhoads GG and Kagan A: Coffee, alcohol and risk of coronary heart disease in Japanese Americans. N Eng J Med 297:405–409, 1977.
15. Stocks P: Cancer mortality in relation to national consumption of cigarettes, solid fuel, tea and coffee. Brit J Cancer 24:215–225, 1970.
16. Segi M, Kurihara M and Matsuyama T: Cancer Mortality for Selected Sites in 24 Countries, No. 5. Sendai, Japan, 1969, Department of Public Health, Tohoku University.
17. Palotas G: Coffee and myocardial infarction. N Engl J Med 289:978, 1973.

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APPENDIX TABLE 1—Eight Methods for Age Standardization*

Rates		Indices		
Name	Formula	Name	Formula	Specific Rates**
Direct[1]	$a_D = \sum_{i=1}^{N} a_i P_i$	Comparative mortality figure (c.m.f.)[5]	$a_X = a_D/A$	Yes
Indirect[1]	$a_I = A\,a \Big/ \sum_{i=1}^{N} A_i p_i$	Standard mortality figure (s.m.f.)[5]	$a_Y = a_I/A$	No
Yule[7]	$a_E = \sum_{i=1}^{N} w_i a_i \Big/ \sum_{i=1}^{N} w_i$	Yerushalmy[2]	$a_M = \sum_{i=1}^{N} (w_i a_i/A_i) \Big/ \sum_{i=1}^{N} w_i$	Yes Yes
Comparative mortality rate (c.m.r.)[5]	$a_C = {}^1/_2(a + a_D)$			Yes
		Relative mortality index (r.m.i.)[5]	$a_Z = \sum_{i=1}^{N} (a_i p_i/A_i)$	Yes

*Notation:
i = index for age strata in all populations, $i = 1, \ldots, N$.
w_i = number of years in the i^{th} age stratum.
a_i = specific rate for the i^{th} stratum in the population under study.
A_i = specific rate for the i^{th} stratum in the reference population.
a = observed rate for the population under study.
A = observed rate for the reference population.
p_i = proportion of the population under study in the i^{th} stratum.
P_i = proportion of the reference population in the i^{th} stratum.

We note that $a = \sum_{i=1}^{N} a_i p_i$, and $A = \sum_{i=1}^{N} A_i P_i$.

**Specific rates for the population under study needed in the calculation.

Applications Being Accepted for 15th Graduate Summer Session in Epidemiology

The 15th graduate summer session in Epidemiology will take place at the University of Minnesota June 22 to July 12, 1980. Sponsored by the Epidemiology section of the American Public Health Association, the Association of Teachers of Preventive Medicine, and the American College of Preventive Medicine, the session will be presented through the University of Minneapolis School of Public Health, Health Sciences Center and the Nolte Center for Continuing Education. The course is accredited (Category I) for the AMA Physicians' Recognition Award.

Course work for this program includes Fundamentals of Epidemiology, Fundamentas of Biostatistics, Epidemiology of Cancer, Epidemiology of Cardiovascular Diseases, Hospital Epidemiology, Occupational Epidemiology and Infection Control, Advanced Statistical Methods in Epidemiology, Clinical Trials, Epidemiology of Injuries, and two courses in infectious disease: Surveillance and Control of Communicable Disease, and Advanced Infectious Disease Epidemiology.

Tuition for the three-week session is $435. Special rates for food and lodging in dormitories have been arranged. The course will be limited to 300 students; application deadline is May 1, 1980. Further information and application forms may be obtained by writing to Dr. Leonard M. Schuman, Director, Graduate Summer Session in Epidemiology, University of Minnesota School of Public Health, 1-117 Health Science Unit A, 515 Delaware Street, SE, Minneapolis, MN 55455.