ORIGINAL ARTICLE

Random effects regression models for trends in standardised mortality ratios

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ABSTRACT

Objectives Standardised mortality ratios (SMRs) play an important role in the epidemiological literature, particularly in evaluations of occupational hazards. While some authors have argued that comparisons of SMRs should be avoided, many investigators find such analyses appealing particularly when data are sparse. For example, calendar period-specific SMRs often are examined to identify emerging problems or to assess whether a hazard that impacted death rates in the past has abated. However, because the distribution of people with respect to age usually changes as calendar time advances, comparisons of SMRs across calendar periods can produce misleading results.

Methods We propose a random effects model to reduce the potential bias arising from comparisons of SMRs. This approach is illustrated using data from a study of workers employed at the Department of Energy's Oak Ridge National Laboratory.

Results When there is homogeneity across strata of covariates in the ratio of death rates in the target population to that in the reference population, the proposed model yields results equivalent to those obtained by a classical analysis of SMRs. However, as evidence against such homogeneity increases, the model yields a random effects version of SMRs for which patterns will conform better to those obtained from an internal analysis of rate ratios.

Conclusions The proposed random effects model can reduce potential bias arising in the comparisons of SMRs.

What this paper adds

- ▸ Calendar period-specific standardised mortality ratios (SMRs) often are examined to identify emerging problems.
- ▸ When age-specific mortality ratios are not equal and the cohort's age-structure changes with time, spurious time trends may be observed.
- ▸ We propose a regression approach to reduce this type of bias in the comparisons of SMRs.

INTRODUCTION

Standardised mortality ratios (SMRs) play an important role in the epidemiological literature, particularly in the evaluations of occupational and environmental hazards. The SMR represents the ratio of the number of deaths observed in the study cohort to the number expected if the cohort had experienced the death rates of the reference population.[1–3] Adjustment for potential confounding in the comparison of the study and reference populations is achieved by stratification on factors such as age, sex and calendar period.

Some authors have argued that comparisons of SMRs should be avoided entirely.[4] Nonetheless, many investigators find analyses of trends in SMRs appealing, particularly when the outcome of interest is rare and the data for the subgroups under comparison are sparse.[5–11] For example, calendar period-specific SMRs often are examined to identify emerging problems or to assess whether a hazard that impacted death rates in the past has abated.[5–11] However, when age-specific mortality ratios are not equal and the cohort's age-structure changes with time, calendar period-specific SMRs for all ages combined change due to differences in age-structure even when age-specific mortality ratios are constant over calendar time.

An investigator can examine whether age-specific mortality ratios are homogenous. However, assessment of homogeneity of age-specific mortality ratios often is difficult because of the instability of stratum-specific results. In principle, one could employ a statistical test of homogeneity of the age-specific mortality ratios, but such tests tend to be underpowered to detect meaningful departures from homogeneity and are seldom used for this purpose.

In the current paper, we propose a random effects regression approach to reduce this type of bias in the comparisons of SMRs and to provide a quantitative metric that signals when such bias is likely. The proposed model yields results equivalent to those obtained by the classical analysis of SMRs (and trends therein) when there is homogeneity across strata of confounding factors in the ratio of death rates in the target population to those in the reference population. In such situations, the ratio of SMRs is an unbiased estimator of the rate ratio comparison and provides a more precise estimator than a directly adjusted rate ratio.[1] However, as evidence against such homogeneity increases, the model we propose employs a random effects approach to summarising stratum-specific mortality ratios. Moreover, if there is marked heterogeneity in stratum-specific ratios one can readily describe stratum-specific trends using our model. This approach is motivated by an update of follow-up of a large cohort of workers employed at the US Department of Energy's Oak Ridge National Laboratory; in previous analyses of Oak Ridge facility workers substantial attention was given to comparisons of SMRs over time.[12 13]

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METHODS

Consider a study in which deaths have been ascertained for a cohort over an extended period of follow-up and an investigator is interested in analysis of death rates. Let I denote the stratifying factors other than the factor of primary interest (eg, suppose I indexes strata defined by categories of age and sex), and let J denote the factor of primary interest which is also a factor upon which the reference rates have been stratified (eg, let J index calendar period). The person-time and deaths in the stratum defined by the cross-classification of i and j are denoted n_{ij} and d_{ij}, yielding an estimator of the rate, λ_{ij}.

Standardised mortality ratio

Denote by λ'_{ij} the death rates in a reference population. A model to compare SMRs over calendar time may take the form

$$\log\left(\frac{d_{ij}}{n_{ij}\times\lambda'_{ij}}\right)=\mu+x_j\delta_j, \tag{1}$$

where x_j denotes indicator variables indexing the explanatory factor of primary interest, calendar period. The expression on the left side of equation 1 is the log of the ratio of observed to expected deaths. The quantity $\exp(\mu)$ yields the classical summary SMR for the group indexed by $x_j=0$.

Some authors have argued that this type of comparison of SMRs should be avoided since each calendar period's SMR is weighted to the age-distribution of person-time in that group.[4] If the cohort's age-structure changes over calendar time, and age-specific mortality ratios are not homogenous, then calendar period-specific SMRs will change due to differences in age-structure. An investigator can examine whether stratum-specific mortality ratios are homogenous by fitting a model that allows for such variation:

$$\log\left(\frac{d_{ij}}{n_{ij}\times\lambda'_{ij}}\right)=\mu_i+x_j\delta'_j, \tag{2}$$

where the quantity $\exp(\mu_i)$ represents the ratio of observed to expected deaths in the ith stratum of the study population when $x_j=0$. We assume that product terms between the confounders i and the factor of primary interest j are not needed, such that the stratum-specific ratios in one subgroup of j relative to another can be usefully characterised by the summary parameter, δ'_j.

If the assumption $\mu_1=\mu_2=\ldots=\mu_I=\mu$ holds then equation 1 yields an estimated coefficient, δ_j, that is identical to the parameter, δ'_j, obtained under equation 2, and will tend to have greater precision, reflecting the smaller number of parameters estimated. Unfortunately, assessment of homogeneity of age-specific mortality ratios often is difficult because of the instability of stratum-specific results, and equation 2 yields a large number of age-sex-specific mortality ratios rather than a single summary SMR for a calendar period.

Random effects regression model

Suppose that we consider equation 2 as our 'saturated' model (one that allows μ_i to vary freely across strata i) and equation 1 as our 'reduced' model. A random effects regression model allows us to 'shrink' the saturated model (equation 2) towards our reduced model (equation 1) for the effects of strata i; the degree of shrinkage depends upon the observed data,

$$\log\left(\frac{d_{ij}}{n_{ij}\times\lambda'_{ij}}\right)=\mu'_i+x_j\delta''_j, \tag{3}$$

where

$$\mu'_i=\mu'+\eta_i$$

$$\eta_i\sim N(0,\sigma^2).$$

The parameters δ''_j in equation 3 summarise the relationship between SMRs in subgroups indexed by j. The estimated coefficient σ^2 summarises the degree of heterogeneity in mortality ratios across the strata i. As $\sigma^2\to0$, implying $\mu_1\to\mu_2\to\ldots\to\mu_I\to\mu$, the estimated coefficients for the calendar period effects obtained under equations 1– 3 will be approximately equivalent (ie, $\delta''_j\approx\delta'_j\approx\delta_j$). For reference, we use the term homogeneity to refer to settings in which σ^2 is equal to zero, moderate heterogeneity to refer to settings in which $0<\sigma^2\le0.25$ and substantial heterogeneity in age-specific ratios to refer to settings in which $0.25<\sigma^2$. The estimated parameter μ' represents the mean of the stratum-specific log mortality ratios; therefore, $\exp(\mu')$ represents the geometric mean of these stratum-specific mortality ratios. When there is heterogeneity in the mortality ratio across age-strata which the investigator wishes to summarise by a single ratio measure, the geometric mean of these ratios is an attractive summary measure because it equals the geometric mean of the observed numbers of deaths in each stratum divided by the geometric mean of the expected numbers. We refer to this quantity as a random effects summary SMR to distinguish it from the classical summary SMR obtained under equation 1, $\exp(\mu)$, which is derived under the assumption that the stratum-specific SMRs are constant (a fixed effect).

The proposed model (equation 3) employs random effects to summarise stratum-specific mortality ratios, and yields SMRs, and estimated ratios of SMRs for contrasts drawn between levels of J. These values are equivalent to patterns observed in analysis of classical SMRs if there is homogeneity in mortality ratios across strata of potential confounders, i. However, relative to the coefficient δ_j obtained under equation 1, the coefficient δ''_j provides a summary of the relationship between mortality ratios in subgroups defined by calendar period that is less liable to confounding that may arise, for example, when age-specific mortality ratios are not equal and the cohort's age-structure changes with calendar time.

Implementation

A tabulation of person-time, deaths and reference death rates (based on state or national rates), for strata indexed by categories of attained age, sex, race and calendar period, is readily-produced and exported by statistical packages for analysis of SMRs, such as the publicly available LTAS.NET.[14] In the online supplementary appendix 1 we describe the fitting of a log-linear Poisson regression model to such data tabulations to estimate calendar period-specific SMRs (equation 2). We also describe the fitting of the proposed model (equation 3). Both models are fitted using the NLMIXED procedure in the SAS (V.9.2) statistical package. The SAS code focuses on application of these models to analysis of calendar time trends in SMRs. In the online supplementary information we extend this model to scenarios in which SMRs are compared between subgroups defined by a factor that is extrinsic to the set of factors defining reference rates, as when SMRs are compared between groups of people defined by work areas, pay codes or job categories.

Wald-type 95% CIs for estimated SMRs are computed using this sample code (see online supplementary appendix 1). The online supplementary appendix 1 also provides sample code using SAS PROC MCMC to obtain exact posterior intervals for estimated SMRs which may be desirable when the number of observed deaths is small (eg, less than six).

Simulation example

Simulations are used to illustrate this approach. Let I index categories of age and J index categories of calendar time. Deaths were generated conforming to the model $d_{ij} \sim \text{Poisson}(n_{ij}\lambda'_{ij}\exp(\mu_i+x_j\delta_j))$ where n_{ij} are specified by the number of person years observed among white males employed at Oak Ridge National Laboratory (table 1) between 1943-and 1999 by age (in 15 5-year age groups) and calendar period (in 5-year groups), λ'_{ij} are respiratory cancer death rates for US white males by age (in 5-year groups) and calendar period (in 5-year intervals from 1940–1944 through 1999), and x_j are binary indicator variables for calendar periods (1943–1949, 1950–1959, …, 1990–1999). Data were simulated specifying that $\delta_j = 0$ so that there was no true variation with calendar period in death rates in the simulated data. Simulations were conducted with μ_i={0, 0,…,0, 0}, {−0.7, −0.6, … 0.6, 0.7} or {−1.4, −1.2, …, 1.2, 1.4} for j=1, 2,…,15 to illustrate the impact on estimates of calendar period-specific SMRs of homogeneity, moderate heterogeneity or substantial heterogeneity in age-specific ratios. Simulations were conducted over 1000 iterations and the mean of the calendar period-specific SMRs and associated upper and lower CIs were derived under standard and random effects regression models (see online supplementary appendix 1).

When μ_i={0, 0,…,0, 0}, implying homogeneity in mortality ratios across age strata, the standard SMR analysis (figure 1A) and the random effects model (figure 1B) yield essentially equivalent results both in terms of calendar period-specific SMRs and associated CIs. The average estimated parameter, $\sigma^2=1\times10^{-6}$ (95% CI not obtained), indicates homogeneity of stratum-specific rate ratios. When there was moderate heterogeneity in age-specific mortality ratios (ie, μ_i={−0.7, −0.6, … 0.6, 0.7}), a standard analysis yields estimated SMRs that vary by calendar period (despite the data being generated under a model in which death rate ratios did not vary with calendar time) (figure 1C). The variation in calendar period-specific SMRs is an artefact and occurs because the age-specific distribution of person-time varied across calendar period (table 1) and there was heterogeneity across age strata of mortality in the target population relative to that in the reference population. The random effects model yields estimates of (random effects) SMRs that do not vary noticeably over calendar periods (figure 1D). The estimated coefficients summarising the ratio of death rates by calendar period conform to the simulation conditions (ie, no trend in SMR over calendar period). The average estimated heterogeneity parameter, σ^2, obtained from the random effects model was 0.18 (95% CI 0.08 to 0.41) indicating moderate heterogeneity of stratum-specific rates and that a comparison of standard SMRs across calendar periods is liable to bias. The CIs for the calendar period-specific (random effects) SMRs are wider than those obtained using the classical method. When there was substantial heterogeneity in age-specific rate ratios (ie, μ_i={−1.4, −1.2, …, 1.2, 1.4}), a classical analysis again yields estimated SMRs that vary by calendar period despite the data being generated under a model in which death rate ratios did not vary with calendar time (figure 1E). Again, the variation in calendar period-specific SMRs is an artefact and occurs because the age-specific distribution of person-time varied across calendar period and there was heterogeneity in age-specific rate ratios. The random effects model yields estimates of (random effects) SMRs that do not vary over time (figure 2F), with substantially wider CIs than obtained under the classical SMR. The average estimated heterogeneity parameter, σ^2, obtained from the random effects model was 0.74 (95% CI 0.33 to 1.65) indicating substantial heterogeneity of stratum-specific rates and that a comparison of standard summary SMRs across calendar period is liable to bias.

Table 1 Distribution of person-years by age and calendar period

Calendar period age group	1940–1949	1950–1959	1960–1969	1970–1979	1980–1989	1990–1999
15–<25	43.38	27.27	20.08	11.42	1.81	0.00
25–<35	35.33	34.35	22.36	18.74	12.17	2.06
35–<45	15.15	24.63	28.03	20.60	19.88	13.79
45–<55	5.10	10.17	19.75	25.55	21.66	22.40
55–<65	0.96	3.05	7.55	17.10	25.55	23.65
65–<75	0.08	0.51	1.95	5.51	15.14	25.07
75–<85		0.03	0.26	1.02	3.47	11.60
85+			0.01	0.07	0.31	1.42

White male Oak Ridge National Laboratory workers hired between 1943 and 1985.

Empirical example

We enumerated a cohort of employees hired at Oak Ridge National Laboratory between 1943 and 1984 who worked 30 or more days, for whom there was complete information on dates of birth and hire. Vital status was ascertained through 31 December 2008 and information on underlying cause of death was coded to the International Classification of Diseases. Our analysis focuses on deaths due to all cancer, accidents, and symptoms and ill-defined conditions; the latter outcome was of interest because prior analyses have reported notably elevated SMRs for Oak Ridge facility workers, particularly in more recent years of follow-up.[15 16] The LTAS-NET computer program was used to create a tabulation of person-time and deaths classified by sex, race (white vs other), 5-year intervals of attained age and calendar time, with reference rates based on data for the US population.[14 17] Standard and random effects Poisson regression models were fit to estimate SMRs by categories of calendar time.

SMRs for deaths due to accidents were significantly below unity for each calendar period and were nearest to unity during the period 2000–2008 (figure 2A). Employing the proposed random effects model yielded random effects estimates of SMRs that were below unity for all calendar periods, but were nearest to unity during the earliest period (1943–1959) and most below unity during the most recent periods (1990–1999 and 2000–2008) (figure 2B). The parameter, σ^2, estimated from the random effects model was 0.16 (95% CI 0.05 to 0.48) indicating moderate heterogeneity of stratum-specific mortality ratios and suggesting that secular trends in standard summary SMRs are liable to bias.

SMRs for deaths due to symptoms and ill-defined conditions were above unity for each calendar period, and were significantly elevated during the periods 1940–1959, 1970–1979, 1980–1989 and 1990–1999 (figure 2C). Employing the proposed model yielded a random effects estimate of the SMR that was below unity for the most recent calendar period (2000–2008), was somewhat further from unity for the first two calendar periods, and somewhat closer to unity for the periods 1970–1979, 1980–1989 and 1990–1999 (figure 2D). The CIs for calendar period-specific SMRs are substantially wider for the

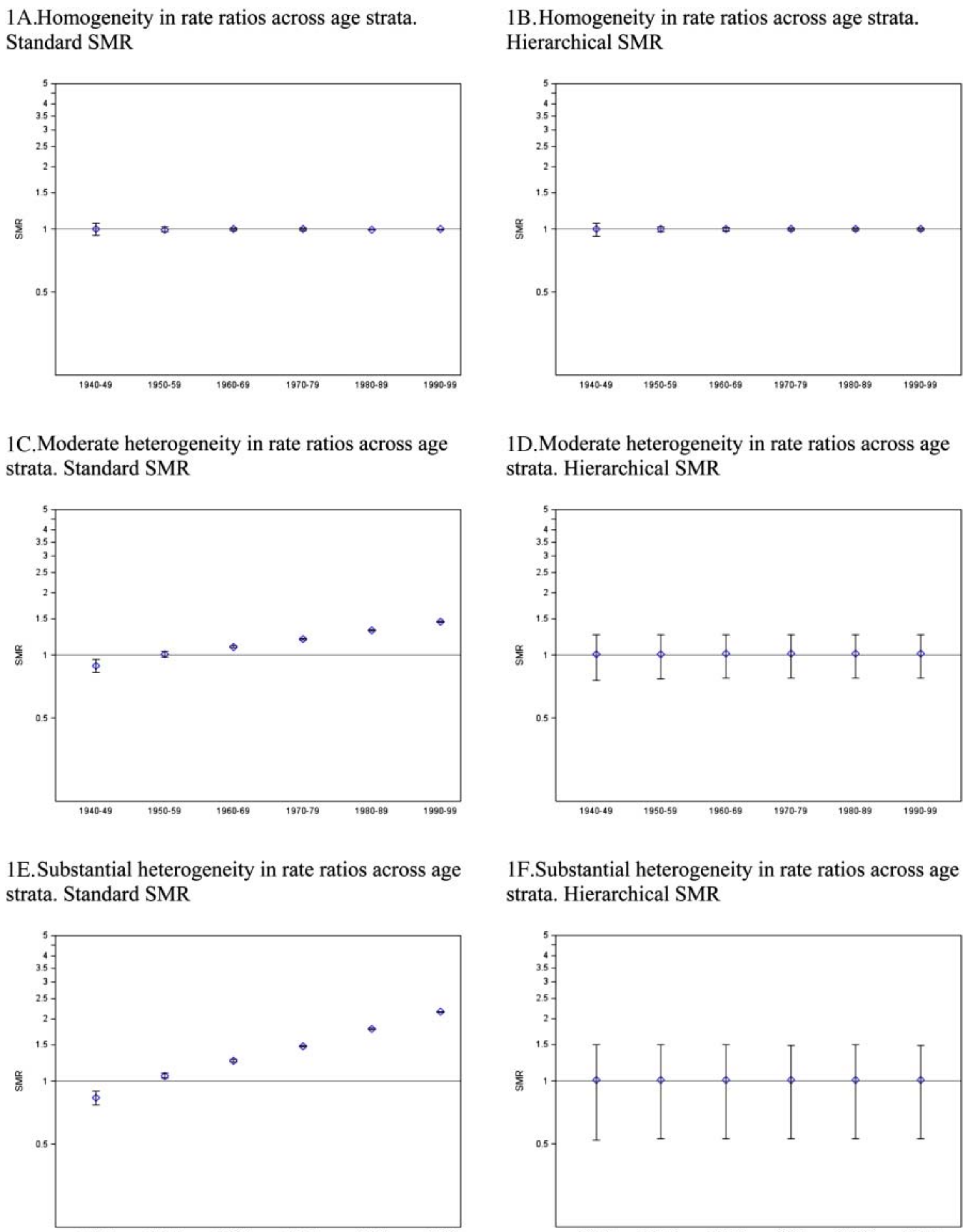

Figure 1 Simulated data. There is no calendar period variation in the rate ratio. (A) Homogeneity in rate ratios across age strata. Standardised mortality ratio (SMR). (B) Homogeneity in rate ratios across age strata. Hierarchical SMR. (C) Moderate heterogeneity in rate ratios across age strata. Standard SMR. (D) Moderate heterogeneity in rate ratios across age strata. Hierarchical SMR. (E) Substantial heterogeneity in rate ratios across age strata. Standard SMR. (F) Substantial heterogeneity in rate ratios across age strata. Hierarchical SMR. This figure is only reproduced in colour in the online version.

random effects model, reflecting the fact that the gain in precision yielded by the standard SMR only should be conferred if the simplifying assumption of a common SMR holds. The parameter, σ^2, estimated from the random effects model was 0.30 (95% CI 0.10 to 0.92) indicating substantial heterogeneity of stratum-specific mortality ratios and suggesting that secular trends in standard summary SMRs are liable to bias.

In contrast, for the analysis of all cancers, the parameter, σ^2, estimated from the random effects model was 0.04 (95% CI 0.02 to 0.10) indicating very modest heterogeneity of stratum-

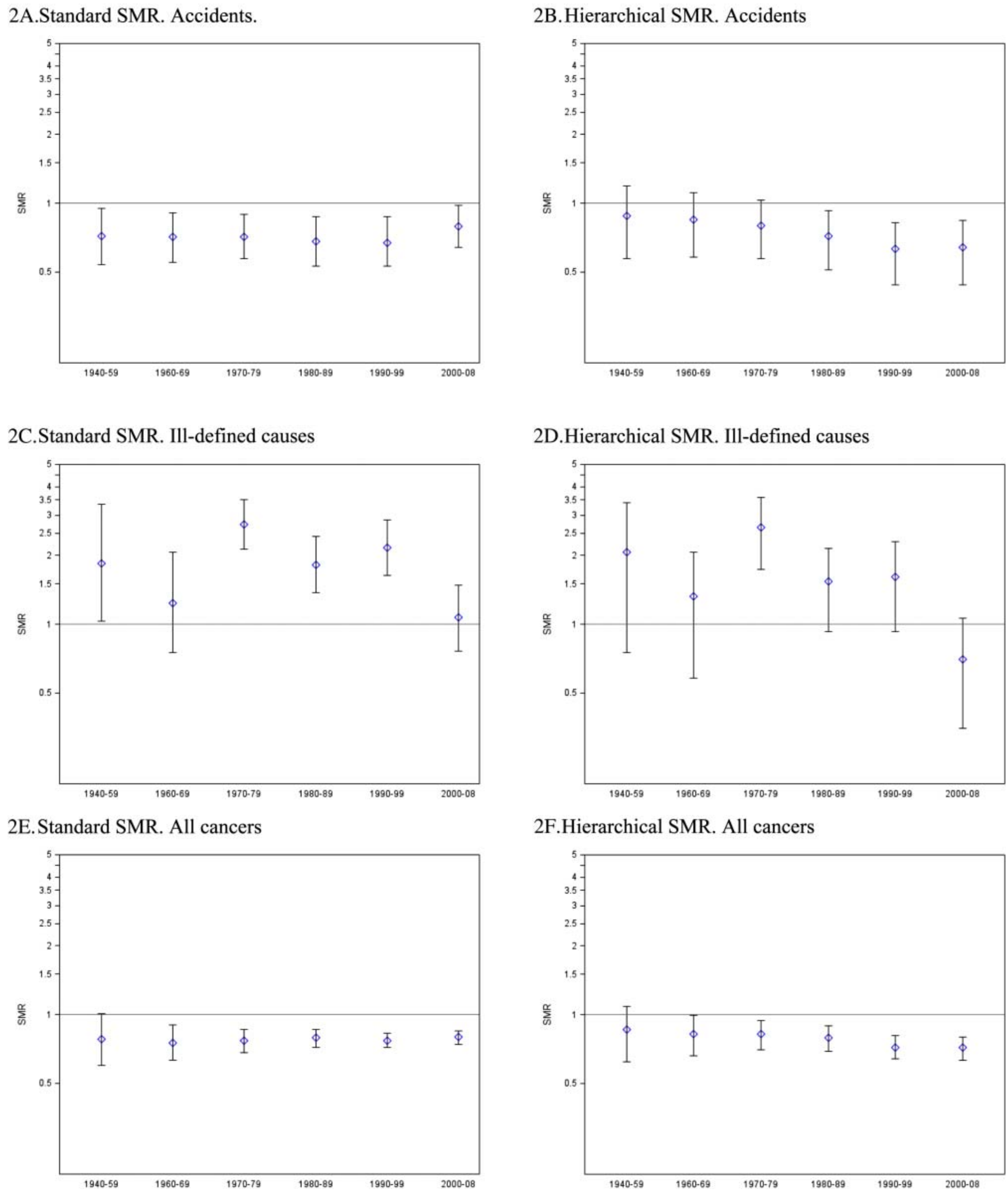

Figure 2 Cause-specific standardised mortality ratios (SMRs) by calendar period. Oak Ridge National Laboratory workers hired between 1943 and 1985 and followed through 2008. (A) Standard SMR. Accidents. (B) Hierarchical SMR. Accidents. (C) Standard SMR. Ill-defined causes. (D) Hierarchical SMR. Ill-defined causes. (E) Standard SMR. All cancers. (F) Hierarchical SMR. All cancers. This figure is only reproduced in colour in the online version.

specific rates (in fact, quite close to homogeneity). SMRs for deaths due to cancer were below unity for each 10-year calendar period (figure 2E) and employing a random effects model yields similar estimates of random effects SMRs with slightly wider CIs (figure 2F).

DISCUSSION

The SMR is a simple and widely-used measure in occupational and environmental epidemiology. However, a direct comparison of SMRs between subgroups of a study cohort may be distorted because each subgroup's SMR is weighted to the distribution of that group's person-time, and these weights are not necessarily comparable.

Previously described 'correction' procedures for comparison of SMRs for two groups have been infrequently used; one reason may be that these 'corrected' SMRs are no longer meaningful by themselves and should only be used for comparisons between the two groups.[18] In contrast, our proposed approach yields a random effects version of the SMR that will tend to conform closely to the classical SMR when stratum-specific mortality ratios are homogenous. Although the necessary conditions for validly comparing SMRs between exposure groups may not hold exactly, the conditions are often approximated such that a comparison of SMRs will suffer little distortion due to the lack of mutual standardisation.[19] As illustrated in our simulations, when stratum-specific ratios are nearly constant across strata our random effects model yields an SMR that will converge towards the classical SMR with little cost in terms of precision (ie, the cost of estimation of the single additional parameter, σ^2). If one cannot be confident that the bias due to comparing SMRs directly is negligible, our approach can be used to signal bias due to violation of the assumption of homogeneity of the mortality ratio across strata. In the framework of the proposed random effects model in the current paper, a test of homogeneity across strata of covariates would be framed as a test of $\sigma^2=0$ vs $\sigma^2>0$.[20]

In this paper, we consider the situation in which an investigator wishes to compare mortality ratios between groups defined by a factor that is within the set of stratifying factors which define the reference rates, specifically a comparison of SMRs between calendar periods. As illustrated in table 1 for our motivating example, the distribution of person-time with respect to age tends to vary markedly across calendar periods, thereby creating a setting where a comparison of SMRs between calendar periods is vulnerable to bias. In the online supplementary information, we consider the situation in which an investigator wishes to compare death rates between groups defined by a factor that is not within the set of stratifying factors which define the reference rates.

The SMR yields an estimate of the number of deaths that would be observed if the exposed cohort had not been exposed. In the current paper we do not address issues of confounding bias that may arise due to non-comparability of the index population (ie, the study cohort) and the reference population, sometimes referred to as a healthy worker effect. This is, however, an example of residual confounding that is not unique to SMR analyses, but rather is common in observational studies. The fact that the ratio of death rates in the target population to the reference population varies with age poses a challenge as to how to summarise the data when examining calendar time trends. The classical SMR suffers the problem that differences in age-specific mortality ratios cause confounding in secular trends in SMRs even when age-specific mortality ratios are constant over time and trends therein diverge from those in directly adjusted rates.

The random effects SMRs obtained from our proposed model will be approximately equivalent in magnitude and precision to classical (fixed effect) SMRs if there is homogeneity in stratum-specific mortality ratios. However, when there is heterogeneity in stratum-specific ratios the proposed model will signal this departure (by the parameter, $\sigma^2>0$) and will yield a summary random effects SMR. Given heterogeneity in ratios between strata an investigator could derive a summary SMR under a fixed effect model or under a random effects model. Under the fixed effect model we assume that there is one true SMR which is common for all strata. Under the random effects model we allow that the true mortality ratio could vary from stratum to stratum (eg, the mortality ratio might be higher if people are older than if they are younger). The random effects model estimates the mean and variance of this distribution of stratum-specific mortality ratios; large strata may yield more precise estimates than small strata, but each stratum is estimating a different ratio, and each serves as a sample from the population distribution of mortality ratios that we wish to estimate. Our proposed model estimates the random effects version of the summary of the stratum-specific mortality ratios. In comparison with previous log-linear models for SMRs (such as equation 1) the proposed random effects SMR will be less likely to yield erroneous conclusions regarding trends in SMRs over calendar time that are simply a consequence of changes in distribution of person-time with respect to covariates, such as age, and the random effects summary of stratum-specific mortality ratios is less likely to be dominated by large strata than the classical SMR. By summarising stratum-specific mortality ratios using the proposed model, investigators may retain the use of SMRs (and insights that they may afford) while minimising the potential for misleading results regarding time trends.

Contributors DBR developed the research question, worked on the statistical problems, conducted the empirical data analysis and simulations, and produced the initial draft of the manuscript. SRC helped refine the analytic strategy and contributed to writing of the manuscript. HC helped refine the simulations and empirical data analysis and contributed to writing of the manuscript.

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