This is a non-final version of an article published in final form in:
Moreno-Betancur M, Latouche A, Menvielle G, Kunst AE, Rey G. Relative index of inequality and slope index of inequality: A structured regression framework for estimation. *Epidemiology* 2015; 26(4):518-527 (click citation to access journal website)

Relative index of inequality and slope index of inequality: A structured regression framework for estimation

Margarita Moreno-Betancur[1,2,3,*], Aurélien Latouche[4], Gwenn Menvielle[5,6], Anton E Kunst[7], Grégoire Rey[1]

Inserm CépiDc, Le Kremlin-Bicêtre, France
[2]Inserm Centre for research in Epidemiology and Population Health, U1018, Biostatistics, F-94807, Villejuif, France
[3]Univ Paris-Sud, UMRS 1018, F-94807, Villejuif, France
[4]Conservatoire national des arts et métiers, France
[5]Inserm, UMR_S 1136, Pierre Louis Institute of Epidemiology and Public Health, F-75013, Paris, France
[6]Sorbonne Universités, UPMC Univ Paris 06, UMR_S 1136, Pierre Louis Institute of Epidemiology and Public Health, F-75013, Paris, France
[7]Department of Public Health, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

***Corresponding author:** Dr Margarita Moreno-Betancur, Inserm CépiDc, 80 rue du Général Leclerc, 94276 Le Kremlin-Bicêtre Cedex, France. Tel : +33149591911, Fax : +33145591930 margarita.moreno@inserm.fr

Running head: Estimation of the relative and slope indices of inequality

Conflicts of Interest and Source of Funding: This work was supported by a doctoral grant from Université Paris-Sud, a research grant from Institut National du Cancer (INCa, 2012-1-PL SHS-05-INSERM 11-1) and Cancéropôle Ile-de-France. Conflicts of interest: None declared.

ABSTRACT

Background: The relative index of inequality (RII) and the slope index of inequality (SII) are the two major indices used in epidemiological studies for the measurement of socioeconomic inequalities in health. Yet, the current definitions of these indices are not adapted to their main purpose, which is to provide summary measures of the linear association between socioeconomic status and health in a way that enables valid between-population comparisons. The lack of appropriate definitions has dissuaded the application of suitable regression methods for estimating the SII.

Methods: We suggest formally defining the RII and SII as so-called *least false parameters*, or more precisely, as the parameters that provide the best approximation of the relation between socioeconomic status and the health outcome by log-linear and linear models, respectively. From this standpoint, we establish a structured regression framework for inference on these indices. Guidelines for implementation of the methods, including R and SAS codes, are provided.

Results: The new definitions yield appropriate summary measures of the linear association across the entire socioeconomic scale, suitable for comparative studies in epidemiology. Our regression-based approach for estimation of the SII contributes to an advancement of the current methodology, which mainly consists of a heuristic formula relying on restrictive assumptions. A study of the educational inequalities in all-cause and cause-specific mortality in France is used for illustration.

Conclusion: The proposed definitions and methods should guide the use and estimation of these indices in future studies.

BACKGROUND

Following the World Health Organization's call for the reduction of socioeconomic inequalities in health,[1] there has been much debate about the meaning and measurement of these inequalities.[2–4] One possibility is to consider inequalities that arise as a monotonic association between an ordered socioeconomic indicator, such as education level or income bracket, and a health outcome, e.g. increasing health with increasing status. Several methods have been proposed for measuring such *socioeconomic gradients* with health outcomes that quantify the occurrence of an event (e.g. the hazard rate or incidence rate).[4–7] Simple measures comparing two socioeconomic groups are insightful (e.g. incidence rate ratios/differences), but not comparable across populations having different distributions of the socioeconomic indicator due to the implied differences in the relative position of each group in the population. More sophisticated measures are necessary for such comparisons.

The relative index of inequality (RII) and the slope index of inequality (SII)[6,8] are the two major measures used in epidemiological studies for comparisons, and quantify the socioeconomic gradient in relative and absolute terms, respectively, thus providing complementary information. The key to the validity of cross-population comparisons with these indices is the use of the socioeconomic rank x, defined as the proportion of the population with higher socioeconomic status, as the measure of exposure to an adverse socioeconomic position. Of note, a few authors use a reversed scale (the proportion with a *lower* socioeconomic status), thus measuring exposure to an advantageous position. The socioeconomic rank is a measure of the relative socioeconomic position of the individual in the population, thus making valid comparisons possible across populations defined for instance by geographical location, time-period or birth cohort. More broadly, these indices facilitate comparisons through the production of one single, comprehensive metric, for example when comparing socioeconomic inequalities in mortality by cause of death within one population.

Following Mackenbach and Kunst's[6] milestone work, the RII is usually defined in analogy to a relative risk as $\mathrm{RII}_1 = h(1)/h(0)$, where $h(x)$ is the health outcome quantifying event occurrence (e.g. the hazard rate or incidence rate) as a function of the socioeconomic rank x, and

0 and 1 are the positions of the hypothetical best-placed and worst-placed persons, respectively. Note that we use the term "relative risk" in a broad sense as discussed by Greenland et al.[9] This definition of the RII is appealing because all the tools available for relative risk estimation may be used, e.g. confounder adjustment is easier than for the earlier definition proposed by Pamuk,[8] who first coined the terms RII and SII, and other related indices.[5,6,10] The SII is defined as $\mathrm{SII}_1 = h(1) - h(0)$ in analogy to an "excess risk", where this term is also used in a broad sense to designate a difference in health outcomes. Models for estimating excess risks are far less well known,[11] possibly explaining the seldom use of absolute measures in studies that present the Mackenbach-Kunst RII.[12] Studies that do present SII estimates for event occurrence outcomes usually use (possibly weighted) least squares regression on incidence rates,[13] or a heuristic formula expressing the SII in terms of the RII.[14–19] It is now widely acknowledged that Poisson regression should be used for modeling incidence rates. The heuristic formula is easy to use and has undeniably contributed to an increased reporting of the SII, for which estimation methods were lacking. However, the formula relies on some restrictive assumptions that may not be tenable (see details in Appendix B).

The above definitions have further found appeal because they seem to facilitate the communication of findings, these indices often being described as relative and excess risks between two hypothetical extremes. However, what these indices are intended to measure (and what epidemiologists usually estimate, at least for the RII) are not the actual relative and excess risks comparing the hypothetical extremes of the scale as implied by these definitions, but the linear association across the entire socioeconomic scale in order to summarize information in a way that enables valid comparisons. The lack of coherence between the purpose and definition of these indices has further dissuaded the use of appropriate estimation methods.

This work contributes to the existing literature in two aspects. First, we propose new definitions for the RII and SII that are adapted to the actual purpose of these indices and yield a concrete interpretation that may be used to communicate findings to a wider audience. In addition to making the purpose and interpretation of these indices more transparent, this new conceptualization facilitates estimation because it entails the measurement of solely the linear aspect of the association between the socioeconomic rank and the health outcome. Second, we

provide a structured regression framework for estimation of the RII and SII in cohort studies grounded on this rationale. The proposed methodology arises from the analogies of the indices with relative and excess risks, which are preserved with the new definitions. As discussed further below, the same reasoning can be applied to other study designs (e.g. cross-sectional studies), although the health outcomes, and thus the regression models used for estimation, will then be different. While for the RII the proposed methods coincide with those used currently in the literature, for the SII these methods constitute an alternative to the aforementioned current approaches. Some general guidelines for estimation are also provided. A study of the educational gradients in all-cause and cause-specific mortality in France is used for illustration. In the eAppendix we provide R (R Foundation for Statistical Computing, Vienna) and SAS (SAS Institute Inc., Cary) codes for implementing the proposed methods.

METHODS

New definitions

The purpose of the RII and SII is to quantify, in relative and absolute terms respectively, the linear association between the socioeconomic rank x and the chosen health outcome y. For instance, as discussed by Rothman et al.[20], in a cohort study the choice of health outcome (e.g. hazard rate or incidence rate) will depend on the type of data available (individual time-to-event data or event data aggregated by socioeconomic group) and the study design (fixed or varying entry and follow-up times).

Intuitively, a suitable measure of this linear association is given by the slope estimated when fitting a regression line to the set of pairs (x, y) observed under appropriate distributional assumptions. The estimated slope provides a summary measure of the linear aspect of the association even when the relation between x and y is manifestly not linear. Our definitions of the RII and SII are based on this idea of fitting a regression line to the data that possibly does not reflect the true shape of the association between x and y. Before giving the formal definitions, two important remarks are necessary concerning estimation in such "outside-the-model" conditions. Firstly, the estimated regression parameter vector no longer corresponds to an estimate of a true population parameter, i.e. a parameter of the "true" model underlying the

data. It is, however, an estimate of a useful quantity called the *least false parameter,*[21,22] which may be thought of as the parameter vector that minimizes a distance function between the data and the model, and is thus the parameter value that yields the best approximation of the data by the posited model (here a regression line). Secondly, "model-robust" approaches are necessary to obtain standard errors and perform inferences.

We use the ideas above to define the RII and SII, remarking that a logarithmic link between exposure and outcome will yield a measure interpretable in relative terms, and an identity link will yield a measure interpretable in absolute terms. Formally, to define the RII, we consider log-linear models of the form $f_\beta(x) = y_0 \exp(\beta x)$, indexed by parameter β, with $y_0 > 0$ being a nuisance parameter. Setting $y = f_\beta(x)$, the socioeconomic gradient may be characterized by the factor $\exp(\beta)$, which indicates the magnitude of the linear association between x and y in relative terms, and its direction: above 1 if the association between x and y is positive and below 1 if it is negative. We define $\mathrm{RII} \coloneqq \exp(\beta^*)$ where β^* is the least false parameter, that is, the parameter that yields the best approximation of the association between x and y by a log-linear model. For the SII, we consider linear models of the form $g_\alpha(x) = y_0 + \alpha x$. The indexing parameter is α and $y_0 > 0$ is a nuisance parameter. Setting $y = g_\alpha(x)$, the socioeconomic gradient is characterized by the term α, indicating the magnitude and direction of the linear association in absolute terms: the further α is from zero, the stronger the association, and the sign of α indicates the direction. We define $\mathrm{SII} \coloneqq \alpha^*$, where α^* is the least false parameter, that is, the parameter providing the best approximation of the association between x and y by a linear model.

The definitions of the RII and SII as least false parameters entail the use of log-linear and linear models to estimate these indices, respectively, regardless of the shape of the observed relation between x and y. This new conceptualization thus guarantees that the RII and SII summarize, in one single figure, the linear association across the entire socioeconomic scale, which is the actual purpose of these indices.

To obtain estimates of the RII and SII, suitable distributional assumptions need to be made, and these will depend on which health outcome is chosen. With the new definitions, the analogies

with relative and excess risks are preserved because $\mathrm{RII} = f_{\beta^*}(1)/f_{\beta^*}(0)$ and $\mathrm{SII} = g_{\alpha^*}(1) - g_{\alpha^*}(0)$, which means that we can rely on regression models already available for relative and excess risk estimation. The models available for the health outcomes most often used in cohort studies are reviewed in the next section. Model-robust approaches to obtain standard errors, construct confidence intervals and perform tests in each case are detailed in Appendix A. The models of relevance with other health outcomes and study designs (e.g. cross-sectional studies) are briefly discussed in the concluding remarks.

With the previous definitions, the indices were expressed as the true relative and excess risks comparing the extremes of the scale, i.e. $\mathrm{RII}_1 = h(1)/h(0)$ and $\mathrm{SII}_1 = h(1) - h(0)$, where h is the true relation between x and y. Although the resulting interpretation is appealing, the function h may not be linear, which is why these formal definitions were not adapted to the intended purpose of the indices. With the new definitions, the identities $\mathrm{RII} = f_{\beta^*}(1)/f_{\beta^*}(0)$ and $\mathrm{SII} = g_{\alpha^*}(1) - g_{\alpha^*}(0)$ hold for $f_{\beta^*}$and g_{α^*}, but are not assumed to hold for the true relation h linking x and y. Hence, with the new definitions the indices cannot be directly described as measures of the true relative and excess risks comparing the extremes of the scale. That is, the RII and SII are not true population parameters but simply summary measures of the linear association across the entire scale. In particular, these indices are not true causal parameters in studies where association can be endowed with a causal interpretation. The concept of the least false parameter thus contrasts with regression-based measures in the classical epidemiological setting, where regression models are built to reflect the true exposure-outcome association, e.g. an epidemiologist will try to model a non-linear tendency such as the U-shaped association between alcohol consumption and mortality.[23] With the new definitions of the RII and SII we are therefore outside the classical setting.

An alternative concrete and useful interpretation can however be given to the resulting indices: The RII and SII are the expected relative and excess risks comparing the hypothetical extremes of the scale under the log-linear and linear models, respectively, that best approximate the relation between socioeconomic status and health.

Regression models for estimation

Like relative and excess risks, the RII and SII may be estimated using regression models that assume, respectively, multiplicative and additive effects of the exposure on the outcome. Next we review the available models for the health outcomes most often used in cohort studies, distinguishing two scenarios according to the nature of the available data as this determines which health outcome can or should be chosen.[20] Table 1 provides a summary.

Individual time-to-event data

For each person $i = 1, \dots, N$ in the study, the observed outcome data consist of a time-to-event T_i, possibly subject to right-censoring, and an indicator δ_i of whether T_i is right-censored ($\delta_i = 0$) or not ($\delta_i = 1$). The *hazard rate* $\lambda(t)$, defined as the rate at which events occur over an infinitesimal exposure time among the individuals at risk just before time t, is the preferred health outcome in this situation. Usually, the individual rank x_i cannot be precisely known or fully measured, and only the socioeconomic group G_i is observed (e.g. the education level or the income bracket). Thus, we approximate the rank of each person in the k^{th} socioeconomic group, where $k = 1, \dots, K$, by the rank $x_{(k)}$ defined as the percentage of the population in strictly lower groups plus half of the percentage of the population in group k.

The RII can be estimated by means of a Cox model,[24] which specifies a log-linear relation between the hazard rate and the exposure: $\lambda(t|G = k) = \beta_0(t) \exp\{\beta x_{(k)}\}$. Here, $\beta_0(t)$ is the baseline hazard which is left unspecified. The estimate of the RII is given by $\widehat{\text{RII}} = \exp(\hat{\beta})$, where $\hat{\beta}$ is usually obtained by partial maximum likelihood. The SII can be estimated by fitting an additive model for the hazard rate:[25,26] $\lambda(t|G = k) = \alpha_0(t) + \alpha x_{(k)}$, where the baseline hazard $\alpha_0(t)$ is unspecified. The estimate of the SII is given by $\widehat{\text{SII}} = \hat{\alpha}$, where $\hat{\alpha}$ may be obtained with the approach of Lin and Ying,[33] and has the same units as hazard rates, which are events per unit of time (e.g. events per 1 person-year if the failure time is measured in years).

Event data aggregated by socioeconomic group

For socioeconomic group k, we observe the number of events, n_k, and the person-time at risk, m_k. The *incidence rate* (also known as *incidence density*), which is a common epidemiological measure of disease occurrence suitable for studies with varying entry and follow-up times among

subjects, can be used as the health outcome. The crude incidence rate in group k is given by $r_k = n_k/m_k$. The exposure variable is the rank $x_{(k)}$.

The RII can be estimated by fitting a multiplicative Poisson model, assuming that n_k is Poisson distributed, with mean satisfying $E(n_k) = m_k \exp\{\beta_0 + \beta x_{(k)}\} = \exp\{\log(m_k) + \beta_0 + \beta x_{(k)}\}$. The estimate of the RII is given by $\widehat{\mathrm{RII}} = \exp(\hat{\beta})$, where $\hat{\beta}$ is obtained by maximum likelihood. The SII can be estimated by fitting an additive Poisson model, assuming that n_k is Poisson distributed with mean satisfying a linear model:[27] $E(n_k) = m_k\{\alpha_0 + \alpha x_{(k)}\} = \alpha_0 m_k + \alpha\{m_k x_{(k)}\}$. The estimate of the SII is given by $\widehat{\mathrm{SII}} = \hat{\alpha}$, where $\hat{\alpha}$ is obtained by maximum likelihood, and is expressed in events per unit of time. The review by Atkinson et al.[11] about Poisson models can be consulted for further details.

(Table 1 here)

Guidelines for model-building

Covariate adjustment

In order to achieve a better comparability of these indices with regards to the factor of primary interest (i.e. socioeconomic group), the regression models used for estimation should be adjusted by certain covariates whose distributions may vary across populations. Covariates are adjusted for as usual in relative and excess risk models, and this does not perturb the definitions and interpretations of the RII and SII. To adjust for age with hazard models (Cox or additive), it is often appropriate to take age as the time-scale.[28] To adjust for age with Poisson models, the event count and person-year calculations within each age-group should account for the fact that an individual changes age-group during follow-up.[29]

Age-standardized SII

When estimating the SII, simply adjusting for age may not be enough to obtain a truly comparable measure, particularly in mortality studies. To explain this, note that, for a fixed RII, the magnitude of the SII depends on the level of health in the population because it is an absolute measure. Thus, in mortality studies, we may expect a strong interaction between the socioeconomic rank and

age because the relation between age and mortality is of an undisputable exponential nature.[30] That is, we may expect higher SIIs within older age-groups, and accordingly this is what we observed in our illustrative example. In such scenarios, the SII estimate obtained from a single model neglecting this interaction will depend on the age-structure of the population, and is thus unsuitable for comparing populations with different age-structures.

To overcome this issue, we propose using *age-standardized SIIs*, that is, weighted sums of estimated age-group-specific SIIs with the weights corresponding to the relative sizes of the age-groups in a reference population. To estimate age-group-specific SIIs based on hazard rates, we recommend fitting a separate additive hazards model within each age-group, with age as the time-scale to tightly control for age. Thus, for age-group $s = 1, \dots, S$, the model has the form

$$\lambda(t|G = k) = \alpha_{0s}(t) + \alpha_s x_{(k)} \quad (1)$$

where the time-scale of t is the age. An alternative to estimate age-group-specific SIIs based on hazard rates would be to fit a single additive hazards model with time-on-study as the time variable, and the age-group, the rank $x_{(k)}$ and their interaction as predictors. With incidence rates, age-group-specific SIIs can be obtained with an additive Poisson model stratified by age-group and allowing for different coefficients for the predictor $x_{(k)}$ across age-groups. That is, assuming that the number of events n_{ks} in socioeconomic group k and age-group s is Poisson distributed with mean satisfying:

$$E(n_{ks}) = \alpha_{0s} m_{ks} + \alpha_s \{m_{ks} x_{(k)}\}, \quad (2)$$

where m_{ks} is the person-time at risk in socioeconomic group k and age-group s.

The age-group-specific SIIs are $\alpha_1, \dots, \alpha_S$ in both (1) and (2). Given the proportion w_s of the population in age-group s in a reference population, and estimates $\hat{\alpha}_1, \dots, \hat{\alpha}_S$, the age-standardized SII is estimated as $\widehat{\mathrm{SII}}_{age} = \sum_{s=1}^{S} w_s \hat{\alpha}_s$. Of course, a logical intermediate step would be to report the estimated age-group-specific SIIs $\hat{\alpha}_1, \dots, \hat{\alpha}_S$, which could be used to perform comparisons by age-group.

Competing risks

The RII and SII may be used to measure socioeconomic gradients in cause-specific event rates, for example in cause-specific mortality (e.g. cancer mortality, cardiovascular disease mortality). With individual time-to-event data, the health outcome is the *cause-specific hazard rate*, denoted by $\lambda^j(t)$ for cause $j = 1, \dots, J$, which is the instantaneous rate of cause j events in the presence of competing causes.[31] Cox and additive hazards models for the cause-specific hazard may be used to estimate the RII and SII, respectively, by censoring individuals with other-cause events at the time of their event. With aggregated data, we may consider the *cause-specific incidence rate,*[32] given for cause j and group k by $r_k^j = n_k^j / m_k^j$, where n_k^j is the number of cause j events, and m_k^j is the person-time at risk calculated by censoring other-cause events at the time of event. Multiplicative and additive Poisson models for the cause-specific incidence rate may be used to estimate the RII and SII, respectively.

The all-cause and cause-specific hazard/incidence rates satisfy $\lambda(t) = \sum_j \lambda^j(t)$ and $r_k = \sum_j r_k^j$. Hence, $\widehat{\mathrm{SII}} \approx \sum_j \widehat{\mathrm{SII}}^j$, where $\widehat{\mathrm{SII}}$ and $\widehat{\mathrm{SII}}^j, j = 1, \dots, J$, are estimates of the all-cause and cause-specific SIIs obtained either from hazard or incidence rates. An interesting measure is thus the percentage of the all-cause SII attributable to a given cause j.[33]

Determining the group-specific ranks $x_{(k)}$

In many studies, separate estimations of the RII and SII for well-defined subpopulations are prescribed (e.g. men and women). In such cases, a set of ranks $x_{(k)}$, $k = 1, \dots, K$, should be derived for each subpopulation by considering only the distribution of the socioeconomic indicator within it. A more subtle question is whether the ranks $x_{(k)}$ should be derived by age-group or birth cohort. There may be reasons to do so, as the relative position at the social hierarchy is determined especially vis-a-vis people of the same generation. With this approach, the RII and SII would be measures of the mean socioeconomic gradient across age-groups or birth cohorts. Such indices may be particularly pertinent when the distribution of the socioeconomic indicator is substantially different across the different subgroups.

ILLUSTRATIVE EXAMPLE

We reanalyzed the data of a previous study[34] consisting of a permanent cross-sectionally representative 1% sample of the French population started in 1968 by the French National Institute of Statistics and Economic Studies (Insee).[35] For the sampled individuals, information on education level in the form of a four-category variable was available from exhaustive population censuses that took place in 1982, 1990 and 1999. The categories were: incomplete elementary education; completed elementary education; general and vocational qualifications with no other degree; and high school diploma or higher. We assessed the evolution of relative and absolute educational gradients in all-cause and cause-specific mortality among 30-84 year-olds in France. We estimated RIIs and age-standardized SIIs separately for each of three periods (1982-1988, 1990-1996 and 1999-2005), using the methodology proposed. In addition, to examine temporal changes, we pooled the data from the first and last period to obtain estimates and confidence intervals for the ratio of the RIIs and the difference in the age-standardized SIIs of these two periods (see details in Appendix A). With such individual time-to-event data, the preferred health outcome is the (cause-specific) hazard rate and we thus used Cox and additive hazards models for estimation. However, for illustration purposes, we aggregated these data and also considered the (cause-specific) incidence rate as outcome, thus obtaining alternative estimates from Poisson regression models. We used the European IARC 1976 population for standardization.[36]

All-cause mortality

Figure 1 shows (log) RII estimates for all-cause mortality in men and women. Figure 2 shows the corresponding age-standardized SIIs. Qualitatively, both health outcomes reflected similar time-trends for both indices, with men displaying larger RIIs and SIIs than women. According to the hazard-based analysis, there was an increase in the RII for men from 1.98 to 2.25 (RII ratio = 1.14 [95% confidence interval = 1.04; 1.25]), and for women from 1.81 to 2.01 (RII ratio = 1.01 [0.90; 1.14]). On the other hand, the SII decreased for both sexes, going from 1213 to 1008 deaths per 100 000 person-years in men (SII difference = -204 [-352; -57]), and from 530 to 438 deaths per 100 000 person-years in women (SII difference = -91 [-182; -1]).

(Figure 1 here)

(Figure 2 here)

Cause-specific mortality

Table 2 shows RII estimates for cause-specific mortality in men and women in each period, and RII ratio estimates comparing the first and last period. Overall, cause-specific hazard and incidence rates reflected similar time-trends. Relative inequalities in men are higher than for women for cancer and external causes, and lower for cardiovascular disease. In men, substantial changes over time were observed for example for cancer and cardiovascular disease, with RIIs increasing from 1.76 to 1.91 (RII ratio = 1.21 [1.04; 1.42]) and from 1.65 to 2.36 (RII ratio = 1.43 [1.19; 1.71]), respectively, according to the hazard-based analysis. In women, we observed substantial increases in the RIIs of cardiovascular disease and other cause mortality, which went respectively from 1.98 to 2.97 (RII ratio = 1.43 [1.14; 1.79]) and from 2.40 to 3.07 (RII ratio = 1.29 [1.03; 1.61]) according to the hazard-based analysis. For both sexes, the highest relative inequalities were those associated with other-cause mortality.

(Table 2 here)

Table 3 shows age-standardized cause-specific SIIs and SII difference estimates comparing the first and last period. Cause-specific hazard and incidence rates reflected similar time-trends, with absolute inequalities being higher for men than for women for each cause-of-death group. Substantial changes in the SII over time were observed for example for other-cause mortality in men, which decreased from 470 to 338 deaths per 100 000 person-years (SII difference = -132 [-206; -59]), and for cardiovascular diseases in women, which decreased from 223 to 177 deaths per 100 000 person-years (SII difference = -46 [-95; 3]), according to the hazard-based analysis. These results are contrasted in Figures 3 and 4 with those obtained with the aforementioned heuristic formula, which is further discussed in Appendix B. Compared to regression-based estimates, the formula-based estimates obtained for these data generally yielded similar trends across causes of death and time-periods, although absolute SII differences across these were less marked and some relative SII differences changed.

(Figure 3 here)

(Figure 4 here)

Table 3 also shows the percentage contributions of the cause-specific SIIs to the all-cause SII per period (column "%"). The biggest contributors to absolute inequalities are cancer and other-cause mortality in men, and cardiovascular and other-cause mortality in women, with the percentage contributions having remained relatively stable throughout all periods.

(Table 3 here)

CONCLUDING REMARKS

The main purpose of the RII and SII is to summarize, in relative and absolute terms, the linear association between socioeconomic status and health across the entire socioeconomic scale in a way that enables valid cross-population comparisons. The previous formal definitions of these indices expressed these as the ratio or difference between the outcomes at the hypothetical extremes of the scale and were thus not in accordance with this purpose. New definitions were thus required, and we have provided these by identifying parameters that summarize the linear association across the entire socioeconomic scale: the least false parameters in log-linear and linear models. In addition to bringing coherence between the definition and purpose of these indices, the clear identification of the relevant target parameters dictates the methods that are appropriate for estimation. In particular, we have identified suitable regression methods for estimating the SII in cohort studies that had never been used before. An important consequence of the new definitions is that the fit of the log-linear or linear models to the data does not matter when estimating these indices. The previous definitions did raise the issue of goodness of fit[7,34] and thus led to methodological proposals that distanced from the main purpose of these indices, such as the work of Sergeant and Firth.[27] This illustrates the importance of carefully defining the target parameter of interest in accordance with the purpose of the study, before moving on to identifying an appropriate estimation method. Often the process is done in reverse (first estimate using common/easy methods, and then attempt to interpret the estimate), and this leads to confusion regarding what we aim to measure.

A practical implication of the new definitions is that two regression models must be fitted for estimation, one for each index. In order to produce comparable measures, both models should be correctly adjusted for the same covariates, taking into account the particularities inherent to

each type of model. For instance, the socioeconomic rank-age interaction mentioned earlier is likely to be strong in linear models for mortality outcomes, which is why age-standardization is required for the SII, while this interaction is usually much lower in log-linear models. The use of two estimation models has another consequence: the two indices could in some cases yield different rankings when comparing two populations of equal mean health. Although counterintuitive, this should not be perceived as a disadvantage as the cases where this occurs likely reflect a complex reality that should be explored in detail anyway. In contrast, the previous definitions concerned the true relation h between x and y, implying the construction of only one model, the predictions of which need to be used to derive at least one of the indices. This has other practical drawbacks: different values of a prediction-derived index are then yielded for each value of the vector of adjusting covariates, and the use of semi-parametric models (e.g. Cox or additive hazard) is precluded because part of the outcome distribution, required for prediction, is left unspecified.

Here we have discussed the previous definition of the RII given by Mackenbach and Kunst and proposed an alternative conceptualisation. Of note, the earlier RII definition proposed by Pamuk,[8] is derived from SII_1, which measures the excess risk relative to the highest position ($x = 0$), and is taken to a relative form by using as reference the mean health of the population. Hence, this index mixes two different reference points, making it, in our view, somewhat harder to understand or communicate. In particular, Pamuk's RII cannot be alternatively conceptualized as a least false parameter, at least not in a straightforward way.

In this work we have proposed regression methods for estimating these indices in cohort studies, and particularly with event rate outcomes which are often the most suitable health outcomes in such studies. In the rare situations where the entry and follow-up times are fixed for all individuals, one may use the prevalence/risk as health outcome. In that case, Poisson regression can be used as described for incidence rates, replacing the person-years by the number at risk at the beginning of the study. It is important to note that Poisson regression should be used only in studies where the event is rare. Binomial regression can be used instead with common events, and also for estimating these indices in cross-sectional studies of e.g. health survey data with the prevalence rate as health outcome.[37] As before, a log link should be used for RII estimation and

an identity link for SII estimation. Software packages are available for fitting such models (see references in the eAppendix).

Harper et al.,[38] as other authors,[39,40] rightly point out the need to clearly identify the value judgments underlying inequality indices. Concerning the RII and SII, an important remark is that with these indices, it is not the socioeconomic group itself that is important, but its relative size and position in the population, measured through the socioeconomic rank x. This is crucial for the comparability of these measures, but is an intrinsic value judgement. Also, in estimating these indices, covariate adjustment is used to isolate the association between socioeconomic rank and health from for example gender or age effects that are not the factors of interest and that are not direct or indirect consequences of socioeconomic conditions. The choice of covariates adjusted for to achieve this carries an implicit value judgement, particularly because it depends on the covariates available.

A final remark concerns the type of inequalities measured by these indices, regardless of the definition adopted. Consider the example presented by Wagstaff et al.[5] of a study with three socioeconomic groups, where the extreme groups had similar health status and the middle group had a markedly higher health status than the other groups, the RII and SII were close to 1 and 0, respectively. This is consequent with the fact that there is no linear association. Of course, one may argue that in this scenario there are "socioeconomic inequalities" of another kind. Other indices like the Index of Dissimilarity[6] are available for measuring "socioeconomic inequalities" defined differently, that is, not as gradients. In that sense, we consider the terms "relative index of inequality" and "slope index of inequality", coined by Pamuk,[8] to be unfortunate because they do not wholly convey the particular type of "socioeconomic inequalities" measured by these indices. However, we will continue to use these terms for consistency with the already extensive literature using the RII and SII.

SUPPLEMENTARY MATERIALS

In the eAppendix we provide R (R Foundation for Statistical Computing, Vienna) and SAS (SAS Institute Inc., Cary) codes for implementing the proposed methods. Simulated data sets to run these codes are also provided in the eAppendix.

REFERENCES

1. World Health Organization. *Targets for Health for All*. Copenhagen: WHO; 1985.

2. Braveman P, Krieger N, Lynch J. Health inequalities and social inequalities in health. *Bull. World Health Organ.* 2000;78(2):232-235.

3. Murray CJL, Gakidou EE, Frenk J. Health inequalities and social group differences: what should we measure ? *Bull. World Health Organ.* 1999;77(7):537-544.

4. Regidor E. Measures of health inequalities: part 1. *J. Epidemiol. Community Health* 2004;58(10):858-61. doi:10.1136/jech.2003.015347.

5. Wagstaff A, Paci P, van Doorslaer E. On the measurement of inequalities in health. *Soc. Sci. Med.* 1991;33(5):545-57.

6. Mackenbach J, Kunst A. Measuring the magnitude of socio-economic inequalities in health: an overview of available measures illustrated with two examples from Europe. *Soc. Sci. Med.* 1997;44(6):757-771.

7. Regidor E. Measures of health inequalities: part 2. *J. Epidemiol. Community Health* 2004;58(11):900-3. doi:10.1136/jech.2004.023036.

8. Pamuk ER. Social class inequality in mortality from 1921 to 1972 in England and Wales. *Popul. Stud. (NY).* 1985;39(1):17-31. doi:10.1080/0032472031000141256.

9. Greenland S, Rothman K, Lash T. Measures of Effect and Measures of Association. In: Rothman K, Greenland S, Lash T, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:51-70.

10. Kakwani N, Wagstaff A, Doorslaer E Van. Socioeconomic inequalities in health: Measurement, computation, and statistical inference. *J. Econom.* 1997;77:87-103.

11. Atkinson E, Crowson C, Pedersen R, Therneau T. *Poisson Models for Person-Years and Expected Rates*.; 2008. Available at: http://www.mayo.edu/research/documents/biostat-81pdf/DOC-10026981. Accessed November 28, 2012.

12. King NB, Harper S, Young ME. Use of relative and absolute effect measures in reporting health inequalities: structured review. *BMJ* 2012;345:5774-5774. doi:10.1136/bmj.e5774.

13. World Health Organization. *Handbook on Health Inequality Monitoring with a Special Focus on Low- and Middle-Income Countries*. Geneva: WHO; 2013.

14. Menvielle G, Leclerc A, Chastang J-F, Luce D. Socioeconomic inequalities in cause specific mortality among older people in France. *BMC Public Health* 2010;10(260):1-9. doi:10.1186/1471-2458-10-260.

15. Mackenbach JP, Stirbu I, Roskam A-JR, et al. Socioeconomic inequalities in health in 22 European countries. *N. Engl. J. Med.* 2008;359(23):2468-2481. doi:10.1056/NEJMc081414.

16. Ezendam NPM, Stirbu I, Leinsalu M, et al. Educational inequalities in cancer mortality differ greatly between countries around the Baltic Sea. *Eur. J. Cancer* 2008;44(3):454-64. doi:10.1016/j.ejca.2007.11.015.

17. Puigpinós R, Borrell C, Antunes JLF, et al. Trends in socioeconomic inequalities in cancer mortality in Barcelona: 1992-2003. *BMC Public Health* 2009;9(35):1-9. doi:10.1186/1471-2458-9-35.

18. Van der Heyden JH a, Schaap MM, Kunst a E, et al. Socioeconomic inequalities in lung cancer mortality in 16 European populations. *Lung Cancer* 2009;63(3):322-30. doi:10.1016/j.lungcan.2008.06.006.

19. Stickley A, Leinsalu M, Kunst AE, et al. Socioeconomic inequalities in homicide mortality: a population-based comparative study of 12 European countries. *Eur. J. Epidemiol.* 2012;27(11):877-84. doi:10.1007/s10654-012-9717-3.

20. Rothman K, Greenland S. Cohort Studies. In: Rothman K, Greenland S, Lash T, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:100-110.

21. Hjort NL. On Inference in Parametric Survival Data Models. *Int. Stat. Rev.* 1992;60(3):355-387.

22. Maldonado G, Greenland S. Interpreting model coefficients when the true model form is unknown. *Epidemiology* 1993;4(4):310-8.

23. Bergmann MM, Rehm J, Klipstein-Grobusch K, et al. The association of pattern of lifetime alcohol use and cause of death in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Int. J. Epidemiol.* 2013;42(6):1772-90. doi:10.1093/ije/dyt154.

24. Cox DR. Regression models and life-tables. *J. R. Stat. Soc. Ser. B* 1972;34(2):187-220.

25. McKeague IW, Sasieni PD. A partly parametric additive risk model. *Biometrika* 1994;81(3):501-514.

26. Lin DY, Ying ZL. Semiparametric analysis of the additive risk model. *Biometrika* 1994;81(1):61-71.

27. Sergeant JC, Firth D. Relative index of inequality: definition, estimation, and inference. *Biostatistics* 2006;7(2):213-24. doi:10.1093/biostatistics/kxj002.

28. Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat. Med.* 2004;23(24):3803-20. doi:10.1002/sim.2098.

29. Breslow N, Day N. *Statistical Methods in Cancer Research. Vol. 1. The Analysis of Case-Control Studies.* Distributed for IARC by WHO, Geneva, Switzerland; 1980:42-81.

30. Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philos. Trans. R. Soc. London* 1825;115(1825):513-583.

31. Prentice RL, Kalbfleisch JD, Peterson A V., Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics* 1978;34(4):541-554. doi:10.2307/2530374.

32. Grambauer N, Schumacher M, Dettenkofer M, Beyersmann J. Incidence densities in a competing events analysis. *Am. J. Epidemiol.* 2010;172(9):1077-84. doi:10.1093/aje/kwq246.

33. Fawcett J, Blakely T. Cancer is overtaking cardiovascular disease as the main driver of socioeconomic inequalities in mortality: New Zealand (1981-99). *J. Epidemiol. Community Health* 2007;61(1):59-66. doi:10.1136/jech.2005.044016.

34. Menvielle G, Chastang JF, Luce D, Leclerc A. Temporal trends in socioeconomic inequality in mortality in France between 1968 and 1996. Study of educational differences by cause of death. *Rev. Epidemiol. Sante Publique* 2007;55:e1-e8. doi:10.1016/j.respe.2006.10.003.

35. Couet C. INSEE's Permanent Demographic Sample (EDP). *Courr. des Stat. English Ser.* 2007;13:29-38.

36. Waterhouse J, Muir C, Correa P, Powell J, eds. *Cancer Incidence in Five Continents*. Lyon: IARC; 1976:3; 456.

37. Barros AJD, Hirakata VN. Alternatives for logistic regression in cross-sectional studies : an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med. Res. Methodol.* 2003;3:21.

38. Harper S, King N, Meersman S, Reichman M, Breen N, Lynch J. Implicit value judgments in the measurement of health inequalities. *Milbank Q.* 2010;88(1):4-29. doi:10.1111/j.1468-0009.2008.00538.x.

39. Allanson P, Petrie D. Understanding the vertical equity judgements underpinning health inequality measures. *Health Econ.* 2013. doi:10.1002/hec.

40. Kjellsson G, Gerdtham U. On correcting the concentration index for binary variables. *J. Health Econ.* 2013;32(3):659-670. doi:10.1016/j.jhealeco.2012.10.012.

41. Lin D, Wei L. The robust inference for the Cox proportional hazards model. *J. Am. Stat. Assoc.* 1989;84(408):1074-1078.

42. Martinussen T, Scheike TH. *Dynamic Regression Models for Survival Data*. New York: Springer; 2006.

43. O'Donnell O, van Doorslaer E, Wagstaff A, Lindelow M. *Analyzing Health Equity Using Household Survey Data*.; 2008.

44. Davison AC, Hinkley D V. *Bootstrap Methods and Their Applications*. Cambridge: Cambridge University Press; 1997.

45. Hayes LJ, Berry G. Sampling variability of the Kunst-Mackenbach relative index of inequality. *J. Epidemiol. Community Health* 2002;56(10):762-5.

APPENDIX A – Standard errors, confidence intervals and tests

The standard error (SE) of a least false parameter estimator is derived from so-called model-robust approaches, that do not rely on the assumption that the model is correctly specified.[21,22] For the Cox and additive hazards models, robust SE estimators have been proposed.[41,42] An alternative with individual time-to-event data is a non-parametric bootstrap procedure, where the individual independent observations are resampled with replacement.[21] For Poisson regression, SEs that account for overdispersion may be considered. In obtaining SEs, one may also need to account for a possible positive autocorrelation arising from the use of the rank variable,[10,43] although several socioeconomic groups would be required to precisely estimate the correlation structure. Under asymptotic conditions, robust SEs may be used to construct robust confidence intervals and tests as usual by taking the normal distribution as reference.

SEs for age-standardized SIIs need to account for the correlation between age-specific SIIs. The non-parametric bootstrap will yield robust SEs accounting for this correlation for the age-standardized SII derived from (1). If the age-standardized SII is derived from (2) or from a single additive hazards model, appropriate robust SEs may be obtained with the delta-method using the age-group-specific estimates and their robust variance-covariance matrix estimated when fitting the model.

Model-robust SEs should also be used when examining temporal changes in these indices, for example when estimating confidence intervals for the ratio of or difference in the indices of two periods. For this purpose, robust SE estimators and bootstrap procedures adapted for correlated data may be required. For instance, in our illustrative example, SEs for estimates of the ratio of or difference in the indices of the first and last periods based on the hazard rate had to account for the correlation between the individual time-to-event data of individuals who belonged to both cohorts. Thus, for the RII, we fitted a single Cox model for the data of these two periods with age as timescale and including the period, the socioeconomic rank and a socioeconomic rank-period product term as predictors. A robust SE estimator accounting for the aforementioned correlations was used to construct confidence intervals for the product term coefficient, which gives an estimate of the ratio of the RIIs of the two periods. For the SII, the SE for the difference in the age-standardized SIIs in the two periods was obtained from a nonparametric bootstrap procedure adapted for correlated data, in which the individuals present in either cohort were resampled with replacement before performing the period-specific estimations.[44]

APPENDIX B – A detailed study of the heuristic formula

Derivation of the formula

Kunst et al.[15,16] derived a formula for the SII in terms of the RII and the average health outcome in the study population, $\bar{y}$. This formula has already been used in several studies[14–19] and is given by:

$$\mathrm{SII}_1 = \frac{2\bar{y}(\mathrm{RII}_1 - 1)}{\mathrm{RII}_1 + 1}. \qquad (3)$$

Formula (3), which we refer to as the "heuristic formula", is derived under the previous definitions of the RII and SII, $\mathrm{RII}_1 = h(1)/h(0)$ and $\mathrm{SII}_1 = h(1) - h(0)$ where h is the true function linking x and y, and relies on the assumption that h is a linear function, i.e. $h(x) = \alpha_0 + \alpha x$.[33] To derive the formula, it is assumed that the linear relation passes through the mean of y, which is $\bar{y}$, and the mean of x, which is $1/2$ by construction. Thus, $\bar{y} = \alpha_0 + \alpha/2$. Since $\mathrm{SII}_1 = \alpha$, the identity $2\alpha_0 = 2\bar{y} - \mathrm{SII}_1$ holds. From this and the definition of RII_1 we have,

$$\mathrm{RII}_1 = \frac{h(1)}{h(0)} = \frac{\alpha_0 + \mathrm{SII}_1}{\alpha_0} = \frac{2\bar{y} + \mathrm{SII}_1}{2\bar{y} - \mathrm{SII}_1}. \quad (4)$$

Rearranging terms gives formula (3). Of note, the results of Hayes and Berry[45] on the sampling variability of the RII are based on formula (4), but inversed because they used a reversed socioeconomic scale (i.e. 0=poor and 1=rich).

Note that the derivation of the heuristic formula (3) does not extend in a straightforward way to the scenario in which a vector Z of covariates is adjusted for (i.e. $\alpha_0 = \alpha_0(Z)$) because $\bar{y}$ will then depend on the distribution of Z, and thus the identity derived from its calculation will no longer hold. In practice, an age-standardized version of $\bar{y}$ is used to circumvent this problem for age, and of course this approach could be applied to any other covariate. The derivation does not extend either to the scenario in which the baseline outcome α_0 depends on time (i.e. $\alpha_0 = \alpha_0(t)$), as is usually the case when the health outcome is the hazard rate. Indeed, the derivation requires that the baseline outcome α_0, and thus the health outcome for a given x, be constant over time to ensure that $\bar{y}$ is constant over time too. Otherwise, $\bar{y}$ depends on time and the formula implies a time-dependent SII. In practice, the incidence rate, which is a sort of time-averaged measure of $\bar{y}$ when y is the hazard rate, is used to circumvent this problem.

Limits of the formula

The heuristic formula (3) is practical in the sense that fitting an additional model for the SII can be avoided. However, its derivation relies on the previous definitions of the RII and SII, RII_1 and SII_1, which, as discussed in the main text, are not adapted to the purpose of these indices. More importantly, the heuristic formula relies on the assumption that the true model is a linear model

and derived estimates may be biased for SII_1 if this assumption is violated. Of course, confidence intervals and p-values derived from biased estimates will also be biased. In fact, even if the linear model holds, the formula may still yield a biased estimation of SII_1 (which in that case coincides with SII, i.e. with our least false parameter definition) if the RII plugged-in is estimated as usual from a multiplicative Poisson model or a Cox model. Indeed, the heuristic formula applies to $\mathrm{RII}_1 = h(1)/h(0)$ under the linear model, that is, the RII of the previous definition given by the ratio of health between the worst-off and best-off, these outcomes being derived from the linear model. But RII_1 does not coincide with the index derived from a log-linear model, which is the RII from our definition, RII. Actually, RII_1 will generally be larger ($\mathrm{RII}_1 \geq \mathrm{RII}$). For a fixed mean health outcome $\bar{y}$, the formula is an increasing function of the RII. Hence, applying the formula to RII leads to underestimate $\mathrm{SII}_1 = \mathrm{SII}$. The bias increases as the RII increases because RII_1 and RII diverge as deviations from the mean health increase. In the following, we investigate the bias of the heuristic formula as compared to the proposed regression approaches. Of note, the formula is no longer useful if one seeks to apply it to RII_1 instead because the linear model required for estimating RII_1 directly yields an estimate of $\mathrm{SII}_1 = \mathrm{SII}$.

Bias assessment

We performed a small-scale simulation study where we considered estimation of the SII from health outcomes across four socioeconomic groups. The sizes of the groups, from the highest to the lowest level, were 10%, 20%, 30% and 40%. We performed Monte Carlo simulations based on two data generation models, one for aggregated data and one for time-to-event data. We considered the case where the true model is linear, so that the proposed and previous definitions of the SII (least false parameter and $h(1) - h(0)$) coincide, i.e. $\mathrm{SII}_1 = \mathrm{SII}$. This way, the study of bias was independent of the definition adopted. Thus, to generate aggregated data, we assumed an additive Poisson model for the incidence rates with conditional mean satisfying $E(n_k) = \alpha_{01} + \alpha x_{(k)}$ (i.e. $m_k = 1$ for all k). For individual time-to-event data, we assumed an additive model for the hazard rates with a Weibull baseline hazard function, i.e. $\lambda(t|x) = \alpha_{02}\alpha_{03}t^{\alpha_{03}-1} + \alpha x$. For the latter, data sets of size $N = 500$ were generated on which around 50% uniform censoring was superimposed. Thus, in both cases a linear model held and the SII was given by

parameter α regardless of the definition of the SII adopted (least false parameter or $h(1) - h(0)$). The baseline parameter α_{01} in the additive Poisson model represents the incidence rate per 100 000 person-years when $x = 0$. In the additive hazards model, α_{02} is a scale parameter fixed at 100 in all simulations, and α_{03} is a shape parameter such that the hazard rate increases with time when $\alpha_{03} > 1$.

In each case, we generated data for four different populations (A through D) with an SII fixed at 100 per 100 000 person-years, but different values of the baseline parameters such that the expected RII fluctuated between 2 and 10. The SII in each population was estimated by either fitting regression models as described in the previous sections ($\widehat{\mathrm{SII}}_M$) or by using the heuristic formula (3) ($\widehat{\mathrm{SII}}_F$). The estimate of the RII used in the formula, $\widehat{\mathrm{RII}}$, was obtained from a multiplicative Poisson model or a Cox model, depending on the nature of the data generated (aggregated or individual time-to-event). For each data generation model, population and estimation approach, the mean SII estimate across 1000 datasets was computed.

Table A1 shows the results obtained. For both generation models, the regression-based estimates were unbiased as expected. On the other hand, as expected, the formula-based estimates were biased in all cases even though the true model was linear, with a bias that increased with the underlying RII. The extent of the bias was similar with aggregated data and individual time-to-event data. Similar biases in the formula-based estimates were observed in additional simulations (results omitted), in which the true model was multiplicative and the proposed least-false parameter definition of the SII was adopted, so that the regression-based estimates were the reference to assess bias.

(Table A1 here)

Practical implications

In the simulation study, the heuristic formula (3) always resulted in a downward bias, and the extent of the bias depended on the underlying generation model and RII. In practice, such a downward bias will result in the absolute differences in the SIIs across populations being less marked when using the formula. If the magnitude of the bias is the same across populations, then

relative SII differences will remain the same. Otherwise, relative SII differences may change, but qualitative conclusions may still remain unchanged as the direction of the bias is the same. This was illustrated in Figures 3 and 4 for the French data analyzed in the main text. Qualitative conclusions could change in situations where the extent of the bias in each population is very different, e.g. when the RIIs or the true models underlying the populations compared greatly differ. This situation is probably uncommon. Therefore, the qualitative conclusions from previous studies using the formula will likely remain unchanged as observed for the French data. It would nevertheless be desirable to assess this in cross-country comparisons.

Conclusion

As mentioned before, the heuristic formula (3) provided a helpful tool for SII estimation when appropriate methods were lacking and even inaccessible. Indeed, software for fitting additive Poisson or additive hazard models were unstable or unavailable until very recently. The methods proposed in this paper represent an advancement of the methodology in that they guarantee unbiased estimates under less restrictive assumptions, and respond to the recent availability of these regression methods in mainstream statistical software. Even though the qualitative conclusions yielded by the formula and regression-based approaches may be similar, it is undoubtedly preferable to use unbiased approaches for estimation.

FIGURES

Figure 1 (Log) RII estimates and 95% confidence intervals for all-cause mortality in men and women based on two different health outcomes: the hazard rate and the incidence rate.

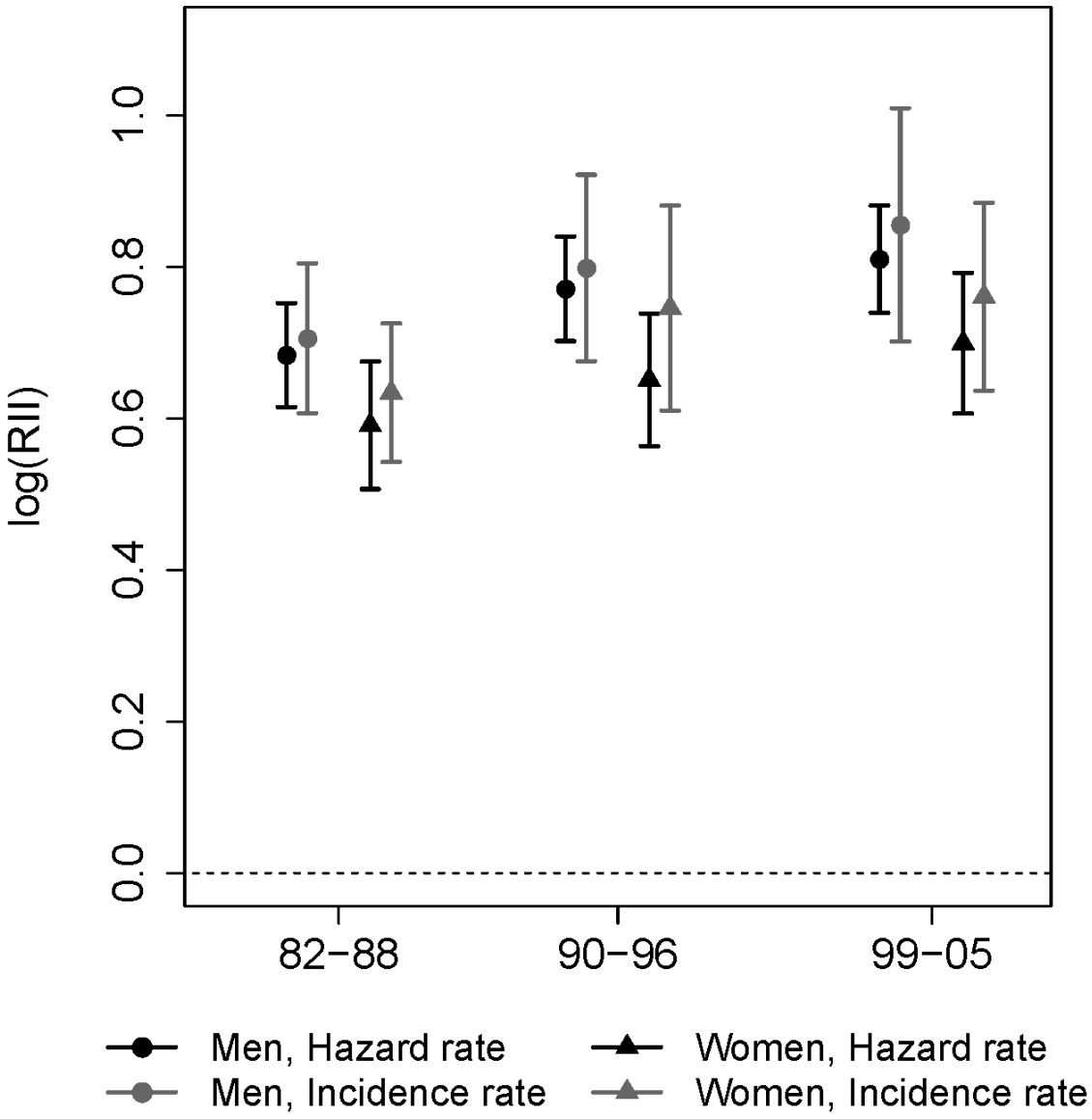


Figure 2 Age-standardized SII estimates and 95% confidence intervals for all-cause mortality in men and women based on two different health outcomes: the hazard rate and the incidence rate.

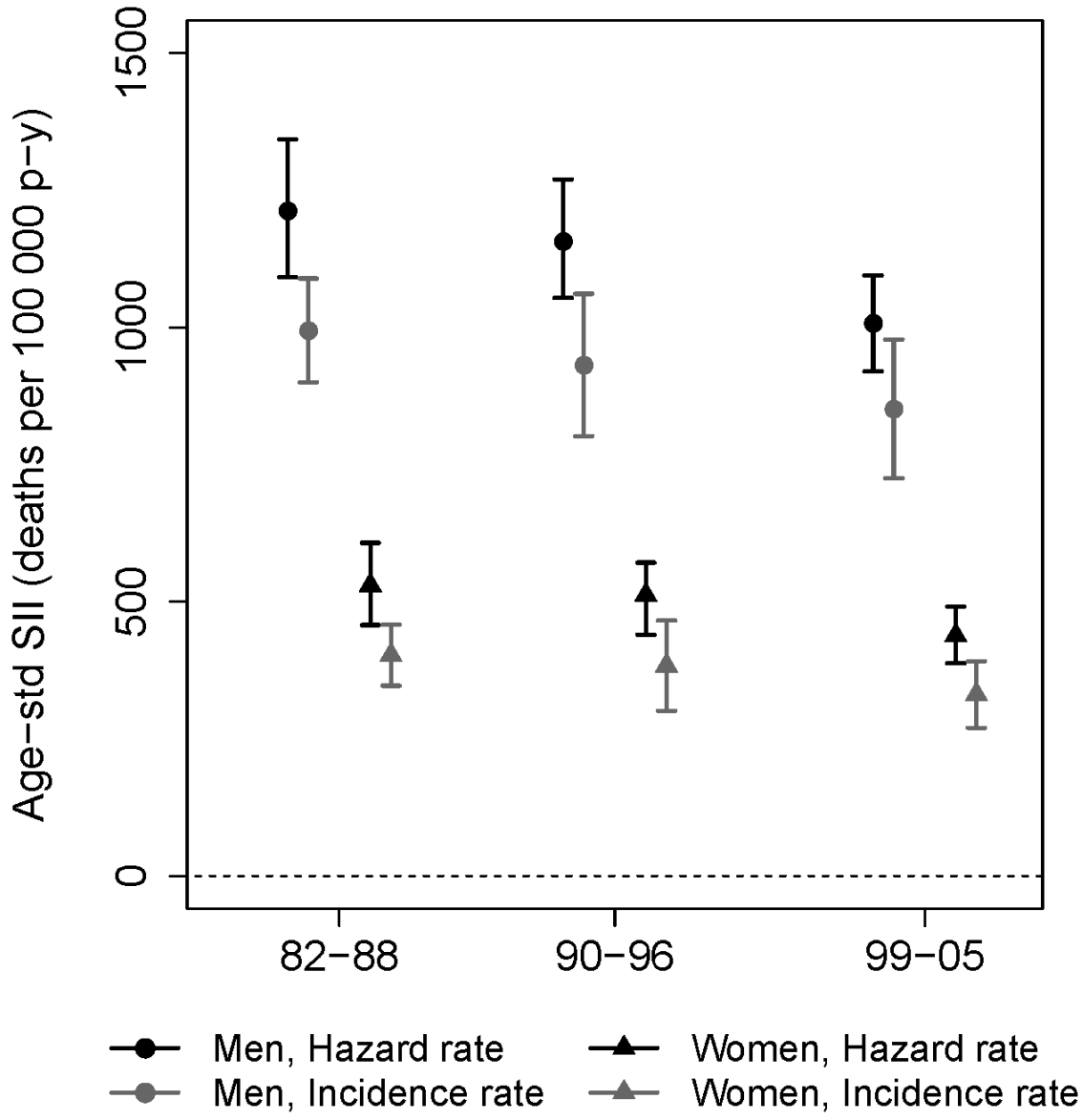


Figure 3 Age-standardized SII estimates for cause-specific mortality in men obtained with (A) additive hazards regression models and (B) the heuristic formula.

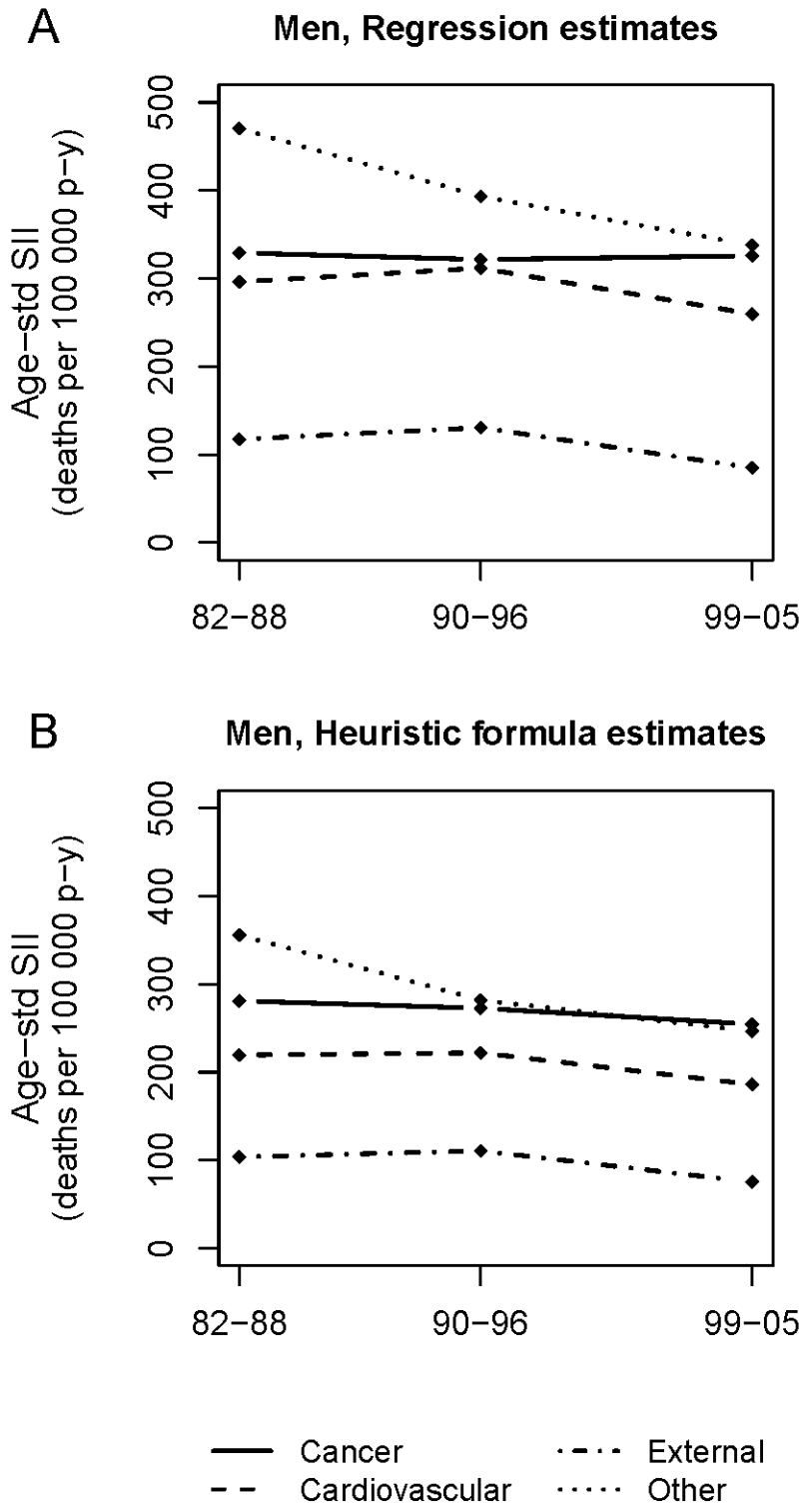
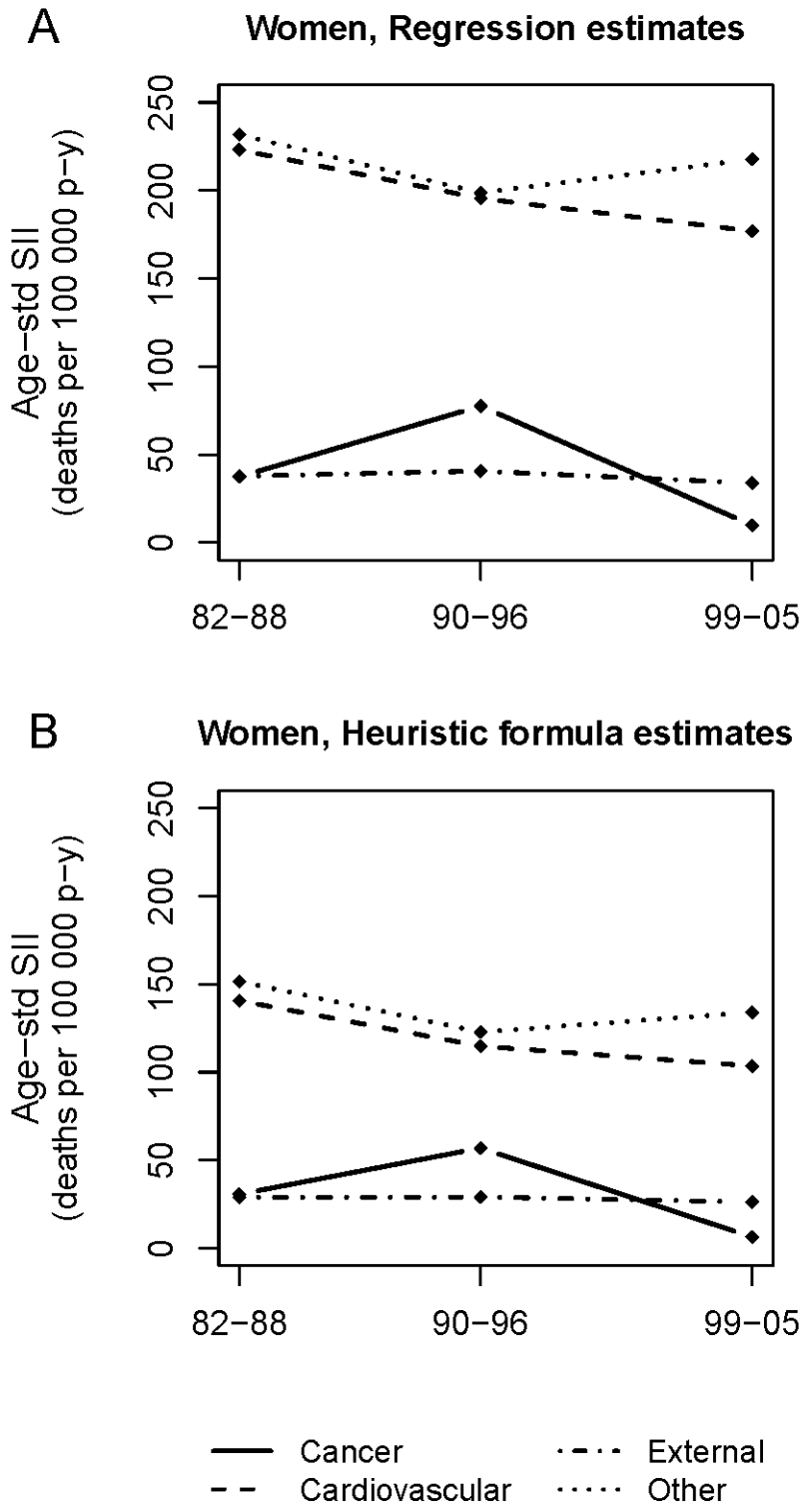


Figure 4 Age-standardized SII estimates for cause-specific mortality in women obtained with (A) additive hazards regression models and (B) the heuristic formula.



TABLES

Table 1 Regression models for estimation of the RII and SII with event rate outcomes

Available data	Health outcome	Estimation	
		RII	SII
Individual time-to-event data	Single event: Hazard rate	Cox model	Additive hazards model
	Competing risks: Cause-specific hazard rate		
Event data aggregated by socio-economic group	Single event: Incidence rate	Multiplicative Poisson model	Additive Poisson model
	Competing risks: Cause-specific incidence rate		

Table 2 RII estimates and 95% confidence intervals (CI) obtained with cause-specific hazard and incidence rates for each period and major cause-of-death groups. Estimates of RII ratios comparing the first and last periods are also provided.

		1982-1988[a]		1990-1996[a]		1999-2005[a]		Change (first to last period)[b]	
		RII	**CI**	**RII**	**CI**	**RII**	**CI**	**RII ratio**	**CI**
Men									
Cancer	Hazard rate	1.76	(1.56; 1.98)	1.81	(1.62; 2.02)	1.91	(1.71; 2.14)	1.21	(1.04; 1.42)
	Incidence rate	1.83	(1.59; 2.10)	1.82	(1.53; 2.17)	1.98	(1.67; 2.34)	1.20	(0.95; 1.51)
Cardiovascular	Hazard rate	1.65	(1.47; 1.86)	1.99	(1.76; 2.26)	2.36	(2.04; 2.72)	1.43	(1.19; 1.71)
	Incidence rate	1.71	(1.48; 1.98)	2.08	(1.71; 2.52)	2.40	(1.93; 2.98)	1.40	(1.09; 1.79)
External	Hazard rate	2.40	(1.89; 3.05)	2.89	(2.30; 3.64)	2.50	(1.96; 3.19)	0.97	(0.70; 1.34)
	Incidence rate	2.37	(1.85; 3.03)	2.97	(2.24; 3.92)	2.63	(1.84; 3.77)	1.03	(0.70; 1.50)
Other	Hazard rate	2.71	(2.36; 3.11)	2.81	(2.43; 3.25)	2.62	(2.29; 3.01)	0.96	(0.80; 1.16)
	Incidence rate	2.70	(2.29; 3.19)	2.97	(2.42; 3.63)	2.89	(2.38; 3.52)	1.06	(0.83; 1.34)
Women									
Cancer	Hazard rate	1.16	(0.99; 1.37)	1.32	(1.13; 1.54)	1.04	(0.89; 1.20)	0.87	(0.70; 1.07)
	Incidence rate	1.16	(0.99; 1.37)	1.41	(1.21; 1.65)	1.03	(0.89; 1.20)	0.86	(0.70; 1.07)
Cardiovascular	Hazard rate	1.98	(1.73; 2.27)	2.27	(1.95; 2.65)	2.97	(2.46; 3.58)	1.43	(1.14; 1.79)
	Incidence rate	2.15	(1.84; 2.52)	2.54	(2.07; 3.12)	3.39	(2.60; 4.42)	1.43	(1.04; 1.96)
External	Hazard rate	1.83	(1.32; 2.54)	1.95	(1.41; 2.70)	2.33	(1.62; 3.36)	1.02	(0.65; 1.60)
	Incidence rate	1.85	(1.31; 2.62)	2.14	(1.46; 3.15)	2.71	(1.84; 4.00)	1.08	(0.67; 1.76)
Other	Hazard rate	2.40	(2.04; 2.82)	2.41	(2.03; 2.85)	3.07	(2.58; 3.65)	1.29	(1.03; 1.61)
	Incidence rate	2.69	(2.13; 3.40)	2.92	(2.30; 3.72)	3.79	(3.05; 4.72)	1.39	(1.02; 1.89)

[a] Results for each period obtained from a separate multiplicative model.

[b] Results obtained from pooled data of the first and last period using a multiplicative model with a product term for the socioeconomic rank and period (see Appendix A for details).

Table 3 Age-standardized SII estimates in deaths per 100 000 person-years, 95% confidence intervals (CI) and percentage (%) contribution to the all-cause SII, obtained with cause-specific hazard and incidence rates for each period and major cause-of-death groups. Estimates of age-standardized SII differences comparing the first and last periods are also provided.

		1982-1988[a]			1990-1996[a]			1999-2005[a]			Change (first to last period)[b]	
		SII	CI	%	SII	CI	%	SII	CI	%	SII diff.	CI
Men												
Cancer	Hazard rate	329	(262; 404)	27.1	322	(254; 390)	27.8	326	(272; 381)	32.3	-3	(-87; 81)
	Incidence rate	306	(250; 362)	31.0	279	(201; 356)	30.3	287	(236; 338)	33.8	-19	(-96; 59)
Cardiovascular	Hazard rate	296	(228; 363)	24.4	312	(257; 366)	26.9	260	(212; 303)	25.8	-36	(-114; 41)
	Incidence rate	231	(179; 284)	23.4	243	(203; 284)	26.4	189	(146; 233)	22.3	-42	(-116; 32)
External	Hazard rate	117	(84; 147)	9.7	131	(104; 160)	11.3	85	(60; 108)	8.4	-32	(-74; 9)
	Incidence rate	102	(73; 132)	10.3	113	(78; 148)	12.3	92	(58; 126)	10.8	-11	(-57; 36)
Other	Hazard rate	470	(403; 539)	38.8	393	(340; 437)	33.9	338	(290; 379)	33.5	-132	(-206; -59)
	Incidence rate	348	(301; 395)	35.3	286	(227; 345)	31.1	281	(233; 328)	33.1	-67	(-134; -1)
Women												
Cancer	Hazard rate	37	(-1; 77)	7.0	78	(43; 118)	15.2	10	(-26; 43)	2.3	-28	(-83; 28)
	Incidence rate	27	(-6; 61)	6.7	69	(35; 103)	18.4	15	(-14; 45)	4.7	-12	(-57; 33)
Cardiovascular	Hazard rate	223	(184; 267)	42.1	196	(162; 231)	38.1	177	(150; 206)	40.3	-46	(-95; 3)
	Incidence rate	169	(140; 197)	41.7	133	(107; 158)	35.4	111	(86; 135)	34.5	-58	(-96; -20)
External	Hazard rate	38	(20; 57)	7.2	41	(22; 57)	8.0	34	(18; 47)	7.7	-4	(-27; 19)
	Incidence rate	28	(11; 45)	6.9	35	(18; 52)	9.3	34	(21; 48)	10.6	6	(-15; 28)
Other	Hazard rate	232	(194; 268)	43.8	199	(166; 234)	38.7	218	(185; 249)	49.7	-14	(-62; 34)
	Incidence rate	181	(148; 214)	44.7	139	(101; 178)	37.0	162	(136; 187)	50.3	-19	(-61; 22)

[a] Results for each period obtained from a separate additive model.

[b] Results obtained from pooled data of the first and last period; for the hazard rate, using a non-parametric bootstrap procedure; for the incidence rate, using an additive model with a product term for the socioeconomic rank, age-group and period (see Appendix A for details).

Table A1 Simulation study results: Expected values of regression-based estimators ($\widehat{\mathbf{SII}}_{\mathbf{M}}$) and formula-based SII estimators ($\widehat{\mathbf{SII}}_{\mathbf{F}}$).

	Population	Baseline parameter[a]	True SII	Mean $\widehat{\mathbf{RII}}$	Mean $\widehat{\mathbf{SII}}_{\mathbf{M}}$	Mean $\widehat{\mathbf{SII}}_{\mathbf{F}}$
Additive Poisson model	A	75	100	2	100	90
	B	30	100	4	100	82
	C	10	100	8	100	73
	D	5	100	10	100	69
Additive hazards model	A	1	100	2	100	97
	B	1.25	100	4	100	89
	C	1.65	100	8	100	79
	D	2	100	10	100	76

[a]Refers to α_{01} for the additive Poisson model and α_{03} for the additive hazards model. Parameter α_{02} for the latter was fixed at 100 for all populations.