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Abstract

Whether the effect of a risk factor on mortality rises or falls with age has important relevancies to life-course theory and public health policy. Many studies report that the hazard ratio of dying associated with a risk factor declines over age. Risk factors found to conform to this pattern include those that are socioeconomic, behavioral, and physiological in nature. In this paper, we show that the putative declining effect of a risk factor over age is a function of interpreting an interaction between a risk factor and age on a multiplicative scale. Drawing from well-known principles on statistical interaction, we show that interpretations on the additive scale often lead to different set of conclusions about the nature of the interaction. Namely, we show that on an additive scale the excess death risks posed by many major risk factors tends to increase with age. Studies have not generally recognized this additive interpretation. We discuss how the prevailing pattern of increasing susceptibilities by age has critical underpinnings for cumulative disadvantage processes and public health interventions. Data from the U.S. National Health Interview Survey were used to provide empirical support.

Keywords: Mortality, life-course, socioeconomic disparities, statistical interaction, aging

INTRODUCTION

Researchers are often interested in how a risk factor's effect on mortality changes with age because the pattern has direct relevancies to life-course theories, public health practice, and demographic modeling. Life-course theories such as cumulative disadvantage make specific predictions about how the health effects of a social risk factor such as one's educational attainment changes as a function of age. From a public health perspective, beliefs that the effect of obesity on death risks is small at older ages relative to younger ages may, for example, lead to clinical or public health complacency in targeting obesity among older adults. Demographers are often interested in estimates of a risk factor's population attributable risk fraction and its effect on life expectancy. These indicators are influenced by the magnitude of the effect of a risk factor at different ages and whether a statistical model from which they are often derived allow for variation in the effects by age.

The finding that a risk factor's association with mortality is age-dependent is normally characterized as an interaction effect between the risk factor and age. Namely, the magnitude of the effect of the risk factor on mortality changes with age. Many studies, examining a wide array of risk factors, report that the hazard ratio of death associated with a risk factor declines with age. The risk factors that have been shown to conform to this pattern include those that are social, physiological, and behavioral in nature (Calle et al. 1999; Flanders et al. 2003; Marmot and Shipley 1996; Martelin 1994; Mehta and Preston 2012; Prospective Studies Collaboration 2009; Sairenchi et al. 2005; Stevens et al. 1998).

The explanations for the observed decline usually pertain to the peculiarities of the risk factor under investigation. For example, the smaller hazard ratio of death associated with obesity at older compared to younger ages has been attributed to the protective nature of caloric reserves in old age (Janssen and Mark 2007). That the deleterious effect of low education appears to diminish with age has been attributed to biases arising from an inadequate accounting of cohort changes in the importance of education (Lauderdale 2001; Lynch 2003). The pattern has also been explained by a reduction in socioeconomic differences in exposure to risk factors at older ages and universal biological frailty (House et al. 2005; Zheng et al. 2016). Selective mortality or "survival of the fittest," on the other hand, is a non-specific mechanism that can be applied to many types of risk factors (Vaupel and Yashin 1985).

This paper has two objectives. The first is to highlight the importance of mathematical scale to interpreting risk factor by age interactions. Like any statistical interaction, risk factor by age interactions can be interpreted on an additive or multiplicative scale. We develop the formal logic of the two scales in the context of risk factor by age interactions. We describe how the choice of scale has critical implications for theory development and argue that many life-course studies have not recognized the importance of scale to conclusions drawn from their findings. The second objective is to provide an empirical analysis of risk factor by age interactions drawing from a set of major risk factors for mortality often studied in demography and epidemiology. We show that these risk factors conform to a general pattern—the strength of their association with mortality tends to increase with age. This prevailing pattern of increasing risks by age across multiple major risk factors for mortality has not been identified previously. We go on to argue that the pattern has critical underpinnings for life-course theory, public health allocation, and clinical practice.

BACKGROUND

Additive and Multiplicative Interactions

Statistical interactions usually refer to "the interdependence between the effects of two or more factors" (Rothman et al. 1980, p. 467). Identifying whether risk factors have dependent or independent effects from each other requires that one choose a scale to assess the dependency. The most common scales are additive and multiplicative. The logic of multiplicative and additive scales has been described previously (for recent descriptions, see VanderWeele and Knol (2014) and Mehta and Preston (2016)). We provide an overview of the logic in the context of risk factor by age interactions. We consider age to be a risk factor that embodies all pertinent biological and non-biological variables not captured by any other risk factor under consideration.

We motivate our discussion using the example of the effects of smoking and age on mortality. Table 1 shows a cross-classification table of age and smoking. For simplicity, smoking and age are treated as dichotomous (smoker/nonsmoker, young/old). Let μ_{00} be the mortality rate among young non-smokers and μ_{11} the mortality rate among old smokers. If smoking and age were interacting in an additive way, the excess death rate associated with an old smoker is simply the sum of the individual effects of age and smoking (Table 1a). Formally:

$$\mu_{11}^{A} = (\mu_{10} - \mu_{00}) + (\mu_{01} - \mu_{00}) + \mu_{00} \quad [1]$$

The term $(\mu_{10} - \mu_{00})$ is the excess death rate associated with getting older and $(\mu_{01} - \mu_{00})$ is the excess death rate associated with smoking. The super-script A denotes the additive prediction for μ_{11}. A strictly additive relationship necessarily implies that the excess death rate associated with smoking is the same for the young and old and the excess death rate associated with getting older is the same for smokers and non-smokers. The epidemiologic measure of "rate difference" is naturally suited to assess additivity and any departures from it.

If the two risk factors are operating in a strictly multiplicative way, μ_{11} would be the product of the hazard ratios associated with each risk factor and the baseline hazard (Table 1b). We define HR_{01}= μ_{01}/μ_{00} to be the hazard ratio (HR) for smoking among the young and HR_{10}= μ_{10}/μ_{00} to be the hazard ratio for age among non-smokers. Under strict multiplicativity, we would expect:

$$\mu_{11}^{M} = HR_{01} * HR_{10} * \mu_{00} \quad [2]$$

The super-script M denotes the multiplicative prediction for μ_{11}. Strict multiplicativity implies constancy of the HRs for each risk factor across levels of the other risk factor (e.g., HR_{01}=HR_{11}= μ_{01}/μ_{00}=μ_{11}/μ_{10}). A departure from multiplicativity would occur if the HR for a risk factor differed across levels of the other risk factor. Thus, ratio measures such as the HR, relative risk, or odds ratio are naturally suited to assess multiplicativity and any departures from it.

It is important to note that the multiplicative prediction will necessarily result in a higher value than the additive prediction (i.e., $\mu_{11}^{M} > \mu_{11}^{A}$) as long as each risk factor increased the risk of the outcome (Mehta and Preston 2016). If we find that the HR for a risk factor is smaller at old compared to young ages, we would state that the risk factor and age are interacting sub-multiplicatively (because the observed $\mu_{11}$is less than μ_{11}^{M}). In this case, the relationship on an additive scale is ambiguous. The relationship could by supper-additive ($\mu_{11} > \mu_{11}^{A}$), additive ($\mu_{11} = \mu_{11}^{A}$), or sub-additive ($\mu_{11} < \mu_{11}^{A}$). Each of these descriptors is consistent with sub-multiplicativity.

Table 2 provides an illustration from a published analysis of smoking and mortality in the United States in which the effects of smoking were allowed to vary with age (Mehta and Preston 2012). Table 2 shows that the HRs of death for smoking decline by age (row C), while its rate

difference increases by age (row D). We can term the relation between smoking and age accurately as sub-multiplicative or supper-additive depending on one's scale of reference. Older smokers suffer an incrementally higher death risk associated with their smoking compared to younger smokers in an additive sense. Such an interpretation is missed if one solely focuses on the multiplicative relation shown in row C.

Common Approaches to Modelling Risk Factor by Age Interactions in Mortality Studies

In multivariate studies of mortality, researchers often model the logarithm of the risk of death as a linear function of explanatory variables. These models include proportional hazards models, discrete-time logit models, and Poisson models. By design, such log-linear specifications force risk factors to operate multiplicatively because additivity on a logarithmic scale implies multiplicativity on the untransformed scale. For example, in a log-linear hazard model with obesity and smoking as predictors, the hazard associated with an obese smoker is the product of some baseline hazard λ, the HR associated with obesity, and the HR associated with smoking.

In testing for risk factor by age interactions, we often include in the model a product term of the risk factor and age variables. An HR that deviates from 1.00 on this product term is interpreted as a signal that there is a statistical interaction between the risk factor and age. This interpretation is implicitly based on the multiplicative scale since we are assessing HRs. Negative coefficients (i.e., HRs<1.00) on the product term are interpreted as a signal that the effect of the risk factor declines by age. Explanations for a "declining effect" are then sought. A negative coefficient on the "interaction term", however, only implies that the relation of the risk factor and age is sub-multiplicative. Without further investigation, it is not apparent if age and the risk factor are operating in a sub-additive, additive, or super-additive fashion. That is, it is not clear whether older individuals suffer less, equally, or more from the dangers of the risk factor compared to younger individuals.

Relevancy of Scale to Public Health Practice and Social Theory

Additive interpretations of interactions have long been recognized to be more relevant to public health policy and clinical decisions than multiplicative interpretations (Blot and Day 1979; Mehta and Preston 2016; Rothman et al. 1980; VanderWeele and Knol 2014). This preference is

due to the fact that the relationship on an additive scale unambiguously directs us to which set of individuals would improve the most from an effective intervention. Also pertinent to policy is the joint distribution of the risk factors in a population, but this distribution does not by itself inform how the effects of risk factors interact with each other.

The additive interpretation is also relevant to the development of social theories of aging and health disparities. A prominent hypothesis in sociology labeled cumulative disadvantage posits that the effect of education on health will increase with age because health-promoting "[r]esources associated with education cumulate through life" (Ross and Wu 1996, p. 106). Dupre (2007) makes the useful distinction of interpreting outcomes based on prevalence differently than incident outcomes. Disparities in the prevalence of disease at a specific age encapsulate differences in incidence, recovery, and case-fatality at earlier ages. Therefore, modeling incident outcomes provides a cleaner approach to testing the hypothesis. A key prediction of cumulative disadvantage would be that the effect of education on death or incident disease will grow stronger with age. However, there has been no guidance on whether the effect should be evaluated on the multiplicative or additive scale.

A hypothesis counter to the cumulative disadvantage is known as the "age-as-leveler." It posits that the effect of socioeconomic status tends to be strongest at middle age and then the effect recedes in old age (House et al. 1990, 1994). Rationale for "leveling" have included mortality selection, convergence in behaviors across social groups at old age, and the equalizing nature of old-aged social benefits (Benzeval et al. 2011; de Mheen et al. 2001; House et al. 1990). Studies seeking evidence to test the competing hypotheses have largely interpreted findings from log-linear models and as such implicitly on the multiplicative scale (Beckett 2000; de Mheen et al. 2001; Dupre 2007; Hoffmann 2011; Knesebeck et al. 2003; Lauderdale 2001; Lynch 2003). The "age-as-lever" has frequently been given empirical support based on evidence that the HR for socioeconomic variables decline by age. An interpretation based on the additive or rate difference scale may lead to different conclusions.

Beyond social theory, choice of scale is relevant to the age dependency in the effects of biologic risk factors. Obesity is a notable example. Whether the mortality risks associated with obesity rise or fall with age has elicited much attention (Hanley 2017; Masters et al. 2013; Zheng and Dirlam 2016). Studies of large epidemiological cohorts have reported that the relative risks of death from obesity decline with age (Flegal et al. 2005; Prospective Studies Collaboration

2009; Stevens et al. 1998). The smaller relative risk in old age has been attributed to the biasing effects of disease-induced weight loss and the protective aspects of excess caloric reserves in old age. Such an interpretation may lead one to conclude that obesity as a risk factor should not be targeted as aggressively among older individuals compared to younger individuals. Whether older individuals compared to younger individuals suffer less from the death risks associated with obesity in an additive sense has, to our knowledge, not been critically evaluated.

Empirical Analysis

In order to better understand the nature of interactions between risk factors and age, we examined eight risk factors for mortality drawn from key domains often studied by researchers. These were socio-demographic (male, black, low education), behavioral (cigarette smoker), self-assessed (poor rating on a general health scale), and biologic (obesity, diabetes, hypertension). We assessed the interaction of each risk factor with age on the multiplicative and additive scales. By arraying multiple risk factors from different domains in one setting, we were positioned to observe general patterns about the nature of interactions between age and major risk factors for mortality.

METHODS

Data

Data were from the IPUMS National Health Interview Survey (NHIS) database (https://ihis.ipums.org/ihis/) (Lynn et al. 2016). The IPUMS NHIS database contains harmonized variables and mortality linkages from the NHIS. NHIS is an annual cross-sectional study of non-institutionalized U.S. residents. Individual records in the NHIS have been prospectively linked to the National Death Index by the National Center for Health Statistics. Our analysis was based on individuals in the "sample adult files" of the 1997-2009 NHIS surveys. At the time of our study, mortality information at quarter-year intervals was available through December 31, 2011. We focused on individuals who were ages 40-84 at the time of the NHIS survey (n=224,914). We eliminated observations that had missing information on any of the risk factors (n=13,027) or had incomplete information to be included in the mortality study (additional 9,320 respondents). Our analytic sample consisted of 202,567 unique individuals who contributed 1,646,097 person-years of follow-up and 28,388 deaths.

Measures

Binary variables for the presence of each risk factor were constructed based on respondent reports. Blacks were those who reported black/African American on a question asking about racial background. Low education was defined as completing 12 or less years of schooling. Cigarette smokers were those who reported currently smoking cigarettes. Obesity was a body mass index of 30 kg/m^2 or more calculated from reports of height and weight. Poor self-rated health was a report of "poor" or "very poor" on a five-point scale of general health. Hypertension and diabetes were based on reports of having ever been diagnosed with the condition by a health profession.

Analytic Approach

The usual approach to investigating risk factor by age interactions is to interact a risk factor with age that is measured in single years within a log-linear model. We begin with this common approach. Specifically, we estimate a generalized linear model on a person-year file with a log-link and Poisson distribution. The model takes the form:

$$\ln(\mu) = \gamma_0 + \gamma_1 * Age + \gamma_2 * Risk + \gamma_3 * Age * Risk \qquad [3]$$

where μ is the hazard of death in person-year units, Age is in units of years, and $Risk$ is the binary risk factor status. Risk factors were examined separately. Age was centered at age 65 and, therefore, e^{γ_2} is the HR associated with the risk factor at age 65. The HR for the "interaction term", e^{γ_3}, indicates the multiplicative change in the hazard ratio per each year of age. An estimated e^{γ_3} of less than 1.00 would indicate sub-multiplicativity, e^{γ_3}=1.00 would indicate multiplicativity, and an e^{γ_3}>1.00 would indicate super-multiplicativity. To obtain the interaction effect on the additive scale, we predicted from the model the rate difference associated with the risk factor at each individual age between age 40 and 89. Age in the analysis represented age at exposure (sometimes referred to as "age at follow-up").

A second model used 10-year age categories instead of continuous age:

$$\ln(\mu) = \gamma_0 + \sum_{a=50,10}^{80}(\gamma_{1a} * AgeCat_a) + \gamma_2 * Risk + \sum_{a=50,10}^{80}(\gamma_{3a} * AgeCat_a * Risk) \qquad [4]$$

The age category 40-9 was the omitted age category. An advantage of this model over the original model is that it allows for a more flexible form of the risk factor by age interaction. Specifically, the hazard ratio for the risk factor is not constrained to change over age by a fixed proportion. From this model, we computed hazard ratios and rate differences for the risk factor at each 10-year age category between ages 40 and 89. The large sample size contained in the NHIS facilitates stable estimates within 10-year age categories.

We additionally report results from models that included controls for multiple socio-demographic characteristics, time in study, and calendar year. Life-course studies benefit from a birth cohort perspective as this perspective allows us to observe processes associated with aging directly. Analyses by birth cohorts are also presented.

RESULTS

Table 3 presents the distribution of each of the risk factors. Male (44%) and low education (51%) were the most prevalent risk factors. Diabetes (11%) and poor self-rated health (5%) were the least prevalent.

Table 4 show results from equation (3), the specification with continuous age. The main effect is the HR pertinent to the risk factor at age 65. The interaction effect is the proportionate change in the HR for the risk factor for each year of age. The HRs for the interaction effect were all less than 1.00 indicating that the HR for the risk factor declines with age (Panel A). We have characterized this relationship as sub-multiplicative. Sub-multiplicativity implies that the direction of the interaction on an additive scale is ambiguous. The effect of a risk factor could rise, fall, or remain the same with increasing age. The predicted rate difference at each age is plotted in Figure 1. Up until age 80, the rate difference for each risk factor rises with age. This pattern implies a super-additive relationship between the risk factor and age. After age 80, the pattern is more varied with four risk factors (black, high school, obese, and hypertension) displaying a declining slope. Panel B of Table 4 shows results for models with controls for socio-demographic characteristics, time in study, and calendar year. Results from these models were highly similar to that of the original models.

Figures 2 and 3 plot the HRs and predicted rate differences from equation (4), the more flexible specification with categorical age. These figures highlight clearly the opposing pattern on the two scales. Focusing on HRs, the dominant pattern is that of declining HRs over age as

was observed in Table 4. On the additive or rate difference scale, the dominant pattern is that of an increasing association. We would characterize the dominant patterns shown in Figures 2 and 3 as supper-additive. Only a few deviations from supper-additivity were observed and these were at the oldest ages. On the additive scale, the rate difference for obesity begins to decline after ages 60-9 and the rate difference for blacks is smaller at ages 80-9 compared to ages 70-9.

Figure 4 provides results from an analysis following three birth cohorts (1920-9, 1930-9, and 1940-9). Because cohort analyses are strengthened by long observation windows, we included data going back to 1986 (we used NHIS surveys 1986-2009). This inclusion restricted the number of risk factors that were regularly collected in the NHIS. For the cohort analysis, we evaluated male, black, low education, and poor self-rated health, which were collected annually in the NHIS. Each cohort was observed over three 10-year age spans beginning at ages 40-9 (1940-9 cohort), 50-9 (1930-9 cohort), and 60-9 (1920-9 cohort). The cohort pattern accords with our main result that HRs tend to decline over age and rate differences tend to increase over age.

DISCUSSION

Whether the effect of a risk factor changes with age is often of interest to researchers. Many studies conclude that the effect of a risk factor declines with age. Explanations for this pattern are then sought. We show that claims of a declining effect are often implicitly based on interpreting the interaction between a risk factor and age on a multiplicative scale. Drawing from well-known principles on statistical interaction, we show that an opposite conclusion is often reached if the interaction is interpreted on an additive scale. On the additive scale, the prevailing pattern is that of increasing susceptibilities by age. Namely, the excess death risks associated with risk factors tend to increase with age. The generalizability of this pattern across major risk factors for mortality, to our knowledge, has not been recognized previously. The fact that a consistent pattern is observed from following actual birth cohorts increases the confidence that our main conclusions pertain to processes occurring within birth cohorts.

The nature of risk factor by age interactions will be a net result of many processes, some of them off-setting the effects of others. Mortality selection is a prominent explanation for observed declines in the effect of a risk factor over age (Beckett 2000; Fenelon 2013; Lynch 2003; Sautter et al. 2012; Vaupel et al. 1979; Zajacova et al. 2009). Our results do not argue that mortality selection is not operational, but that it is likely one force out of many. What our results

do argue for is that theories or conclusions should consider additive-based interpretations. Theories such as cumulative disadvantage make explicit predictions for how the effect of a risk factor should change over the life-course. However, there has been little guidance on whether one should interpret changes in the effect on an additive or multiplicative scale. We contend that the additive interpretation is valuable because it directly identifies the magnitude of excess risk associated with a risk factor across levels of another risk factor. Similarly, conclusions on the declining effect of a risk factor over age based solely on HRs are premature (Sairenchi et al. 2005; Wang 2015). Such conclusions risk misguiding public health policies and clinical practice.

Our empirical findings generate a number of interesting research questions that could be pursued in more detailed analysis of each risk factor. The fundamental issue concerns the dominant finding of supper-additivity. Why do the excess risks associated with risk factors often rise with age? Underlying processes will depend on the peculiarities of each risk factor, but the empirical regularity across major risk factors also suggests that general explanations could be at play.

Risk factors such as race/ethnicity and one's educational attainment are factors that persist throughout life and are ascribed (e.g., race) or commonly achieved (e.g., educational attainment) early in life. The effect of being black or having low education today may be higher than it was in the past because it is operating on a system already damaged from being a member of a socially disadvantaged group throughout life. Such an explanation is also consistent with cumulative disadvantage processes, although it does not require "[r]esources associated with education [to] cumulate through life." (Ross and Wu 1996, p. 106) All it requires is that some damage done in the past makes the body more susceptible to being socially disadvantaged in the present. Such a process would in turn be consistent with policies favoring improvement in circumstances of younger individuals with the goal of preventing physiological damage that can make the body more susceptible to insults later in life.

Interpreting the pattern for risk factors that are dynamic in nature or acquired later in life require additional considerations. Diabetes and hypertension are diseases that usually appear during middle or late adulthood. For a given age, those with the risk factor will reflect those recently acquiring the disease and those who acquired it an earlier age. Prior studies document that the excess risk associated with a disease positively correlates with the length of life lived with the disease (Fox et al. 2004; Niiranen et al. 2017; Zoungas et al. 2014). One explanation for

the pattern we observed is that it reflects the effects of duration with a disease (conditional on age being positively correlated with disease duration). Older individuals are also more likely to have combinations of diseases compared to younger individuals (Stenholm et al. 2015) and the excess risk associated with any one disease may be enhanced by the presence of other diseases operating on the same body system. Models that test these various explanations could provide additional insights into the general pattern of increasing risks by age.

The rate difference associated with current smoking was observed to rise at an increasing rate over age. Age and duration of smoking positively correlate among current smokers because few U.S. smokers pick up the habit after age 30 (Holford et al. 2014). It has been difficult, therefore, in U.S. samples to separate the age-pattern of the effects of current smoking from the effects of smoking duration (Flanders et al. 2003). The pattern that we observe is broadly consistent with prior work indicating that the effect of an additional year of smoking duration on lung cancer mortality increases the longer one has smoked (Doll and Peto 1978; Flanders et al. 2003).

Similar to smoking, the excess death risks associated with being male rose at an increasing rate over age. This pattern is consistent with findings reported in Wisser and Vaupel (2014), which studied absolute male-female mortality differences for 10-year birth cohorts born in Sweden, France, and England and Wales since 1860. Wisser and Vaupel (2014) found that excess male mortality rose exponentially over age from age 40 for cohorts born since 1900. They postulated that the pattern represented a synergistic interaction between age and risky behaviors: the effect of risky behaviors, which males are more likely to engage in, rises with age.

Deviations from the prevailing pattern of super-additivity may signal statistical biases. We noted two exceptions to the prevailing pattern. Beginning at age 60, obesity and age appear to operate sub-additively. Reverse causal processes associated with disease-induced weight loss may become increasingly important with age producing an artefactual decline (Mehta 2015; Stokes and Preston 2016). It is plausible, however, that the smaller association at the oldest age is real and reflective of the protective properties of nutritional or caloric reserves in frailer populations. Nonetheless, our findings suggest that the excess risks of obesity as measured under additivity increase until nearly age 80. The clear implication for public health and clinical practice is that obesity should be treated among most older adults.

The hazard associated with being black dropped after ages 70-79. This finding appears in line with the well-documented racial crossover of black-white mortality differences (Fenelon 2013), although we did not observe an actual cross-over. High levels of age misreporting among older blacks in cohorts born during the beginning of the 20th century and earlier have been postulated to result in an underestimation of black mortality and contribute to the crossover (Elo and Preston 1994; Hussey and Elo 1997). The 80-9 age group in our sample covered cohorts born during 1902-1931 and we found a relatively small excess risk associated with being black in this group as assessed on the additive scale. Differential selective mortality by race at younger ages has also been hypothesized to explain the crossover (Fenelon 2013).

Log-linear models have useful statistical properties for the modelling of binary outcomes or time-dependent processes. The imposed relationship of multiplicativity among risk factors in log-linear models, however, is often not acknowledged by researchers (Mehta and Preston 2016; Richardson and Kaufman 2009). Inclusion of product terms among predictor variables can relax the assumption of strict multiplicativity and help test for departures from multiplicativity. Researchers can also recover the rate or risk difference to assess the additive interpretation of interactions by predicting the outcome from the model as we did in our study. Formal tests for assessing interactions on the additive scale in log-linear models are available and have been described in the epidemiological literature (Hosmer and Lemeshow 1992; Li and Chambless 2007; VanderWeele and Knol 2014). One such test is the "relative excess risk due to interaction" (RERI), which has recently been described in detail and in an accessible fashion by VanderWeele and Knol (2014).

We did not aim to develop causal models for each of the risk factors examined. Doing so would require a careful assessment of confounding for each risk factor and an estimation of individualized models suited to the context each risk factor is operating within. Our findings were, nonetheless, robust to a basic set of controls for socio-demographic characteristics, calendar year, and time in study. We aimed, rather, to identify whether there are empirical regularities in risk factor by age interactions across many major risk factors for mortality drawn from distinct domains. Our findings suggest that there are important regularities that have bearings for the interpretation of life-course studies. The conceptual framework of additivity and multiplicativity are also not restricted to death or binary exposures, but any categorical or continuous set of variables. We used binary exposures mainly to aid our exposition of the relevant mathematical and interpretive issues.

In sum, many prior studies examining the age-dependency of the effects of risk factors on mortality draw conclusions based on the multiplicative scale. We believe that this choice is often made implicitly without recognition that a contradictory pattern can emerge when interpretations are made on the additive scale. We show empirically that this contradictory pattern, namely that of increasing susceptibilities with age, appears to be a prevailing pattern across major risk factors for mortality.

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Table 1. Additive and multiplicative interactions in a hypothetical case of the effects of smoking and age on death risks

(a) Additive Interaction

	Old Age	Young Age
Smoker	$\mu_{11}^{A} = (\mu_{10} - \mu_{00}) + (\mu_{01} - \mu_{00}) + \mu_{00}$	μ_{01}
Non-Smoker	μ_{10}	μ_{00}

(b) Multiplicative Interaction

	Old Age	Young Age
Smoker	$\mu_{11}^{M} = HR_{01} * HR_{10} * \mu_{00}$	μ_{01}
Non-Smoker	μ_{10}	μ_{00}

Note: μ is the rate of death and HR is the hazard ratio. The superscripts A and M denote the additive and multiplicative predictions, respectively.

Table 2. Example of declining hazard ratios and increasing additive (excess) risks of death by age

Estimate	Age 65	Age 75
Hazard of death among current smokers (per 1,000)	24.39	60.56
Hazard of death among never smokers (per 1,000)	8.48	24.72
Hazard ratio of death from smoking	2.88	2.45
Excess risk of death from smoking (per 1,000)	15.92	35.83

Note: Estimates obtained from Model 1 of Table 2 in Mehta and Preston (Mehta and Preston 2012). Data were from a combined sample of men and women in the 1987-2003 U.S. National Health Interview Surveys (excluding 1989 and 1996) with mortality linkage through December 31, 2006.

Table 3. Descriptive characteristics of analytic sample, 1997-2009 U.S. National Health Interview Survey

Characteristic	Percentage (unless noted otherwise)
Age (mean, years)	56.2
Male	44.4
Black	14.0
HS graduate or less	50.7
Obese (body mass index≥30 kg/m^2)	26.7
Current smoker	21.1
Poor self-rated health	5.1
Diabetes	11.3
Hypertension	38.6
	Number
Sample size	202,567
Person-years	1,646,097
Deaths	28,388

Note: Ages 40-84 at time of survey. Death linkages are through December 31, 2011. Age is age at follow-up year. Other characteristics pertain to time at survey.

Table 4. Hazard ratios for risk factors and interaction of risk factors with continuous age, 1997-2009 U.S. National Health Interview Survey

Characteristic	Panel A		Panel B	
	Main Effect	Interaction Effect	Main Effect	Interaction Effect
Male	1.583***	0.997**	1.636***	0.996***
Black	1.501***	0.984***	1.478***	0.984***
HS graduate or less	1.539***	0.987***	1.528***	0.989***
Obese	1.156***	0.993***	1.126***	0.995***
Current smoker	2.380***	0.990***	2.199***	0.992***
Poor self-rated health	3.996***	0.967***	3.650***	0.971***
Diabetes	2.353***	0.978***	2.208***	0.981***
Hypertension	1.611***	0.983***	1.547***	0.987***

Note: Estimates from equation (3) in paper. Main effect pertains to age 65. Panel A are from models that only include the risk factor and age. Panel B includes adjustments for socio-demographic characteristics, time in study, and calendar year of exposure. *** p<.001; ** p<.01

Figure 1. Rate difference (per 1,000 person-years) for each risk factor estimated from continuous age model in Table 3 (Panel A)

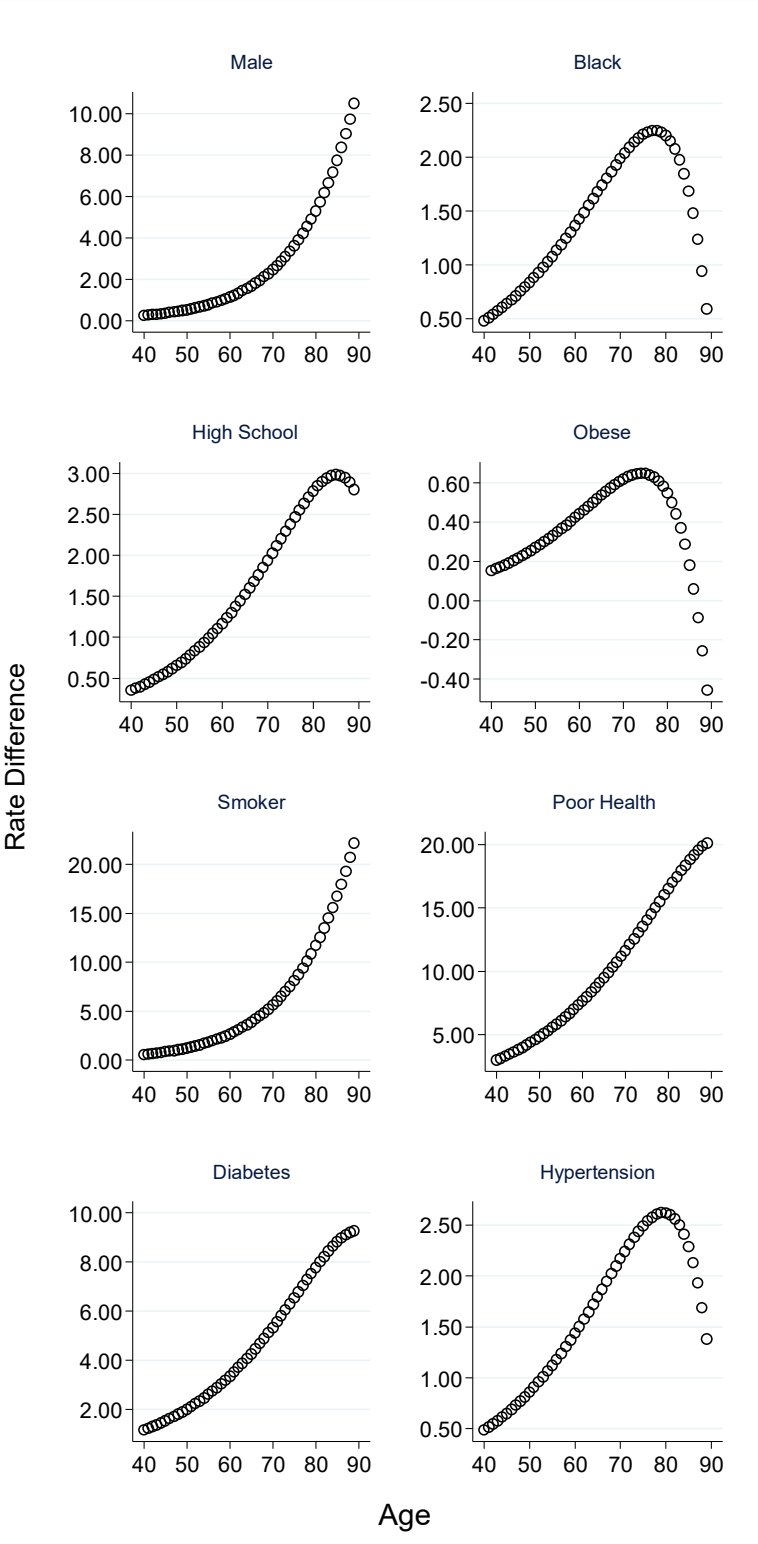


Figure 2. Hazard ratios and rate differences (per 1,000 person-years) by 10-year age group for socio-demographic characteristics, obesity, and smoking based on categorical age model.

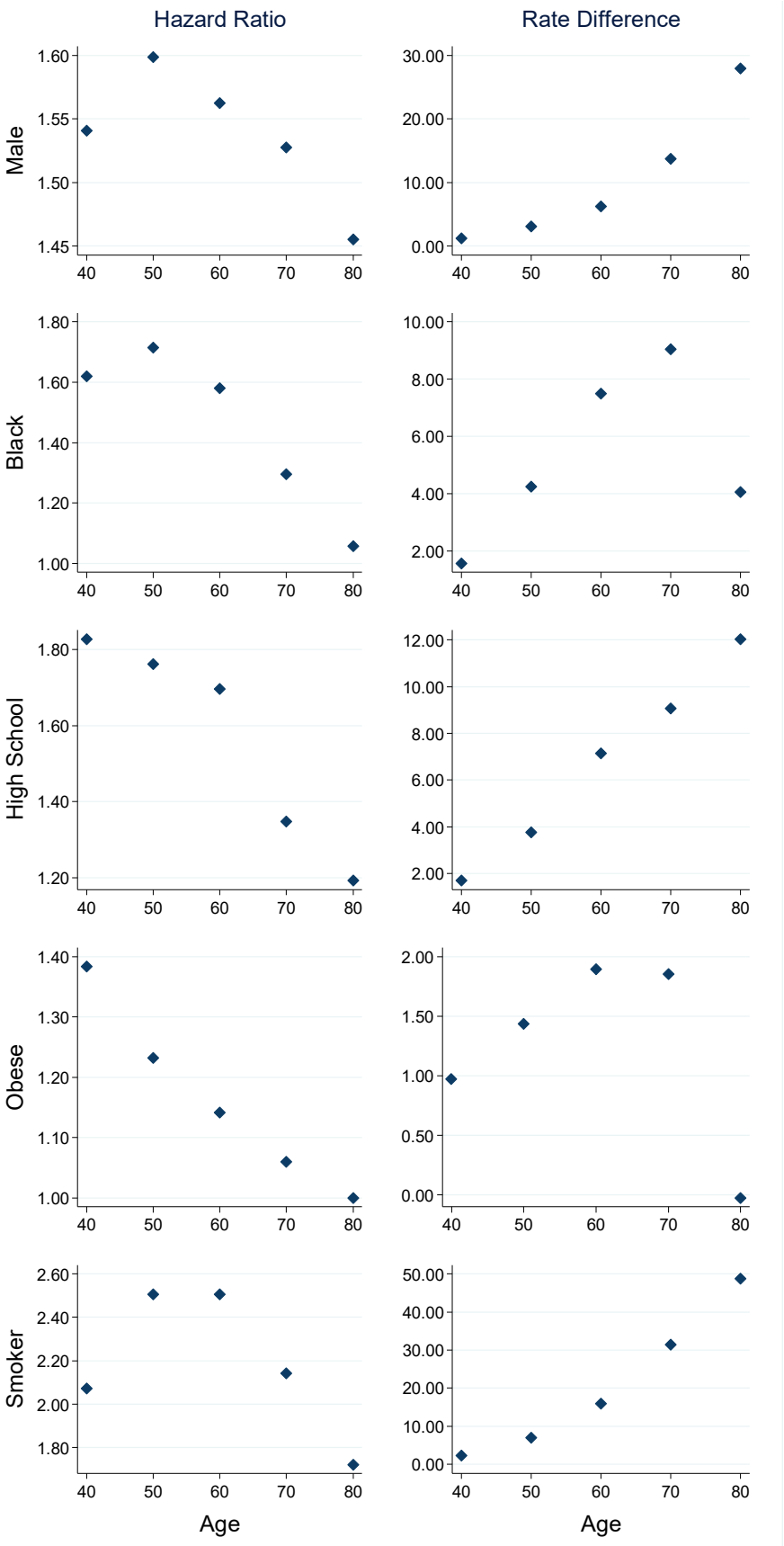


Figure 3. Hazard ratios and rate differences (per 1,000 person-years) by 10-year age group for poor health, diabetes, and hypertension based on categorical age model.

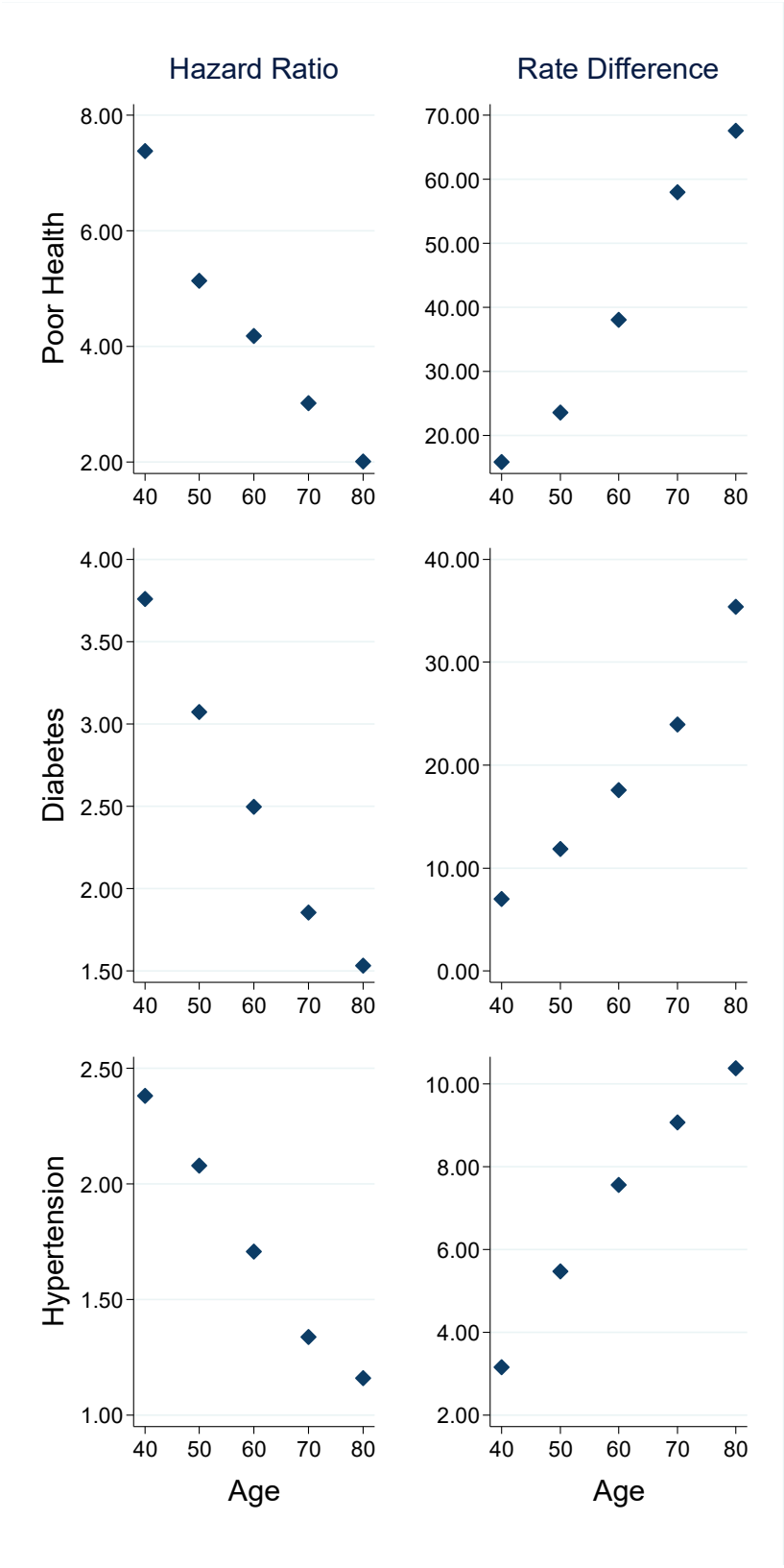
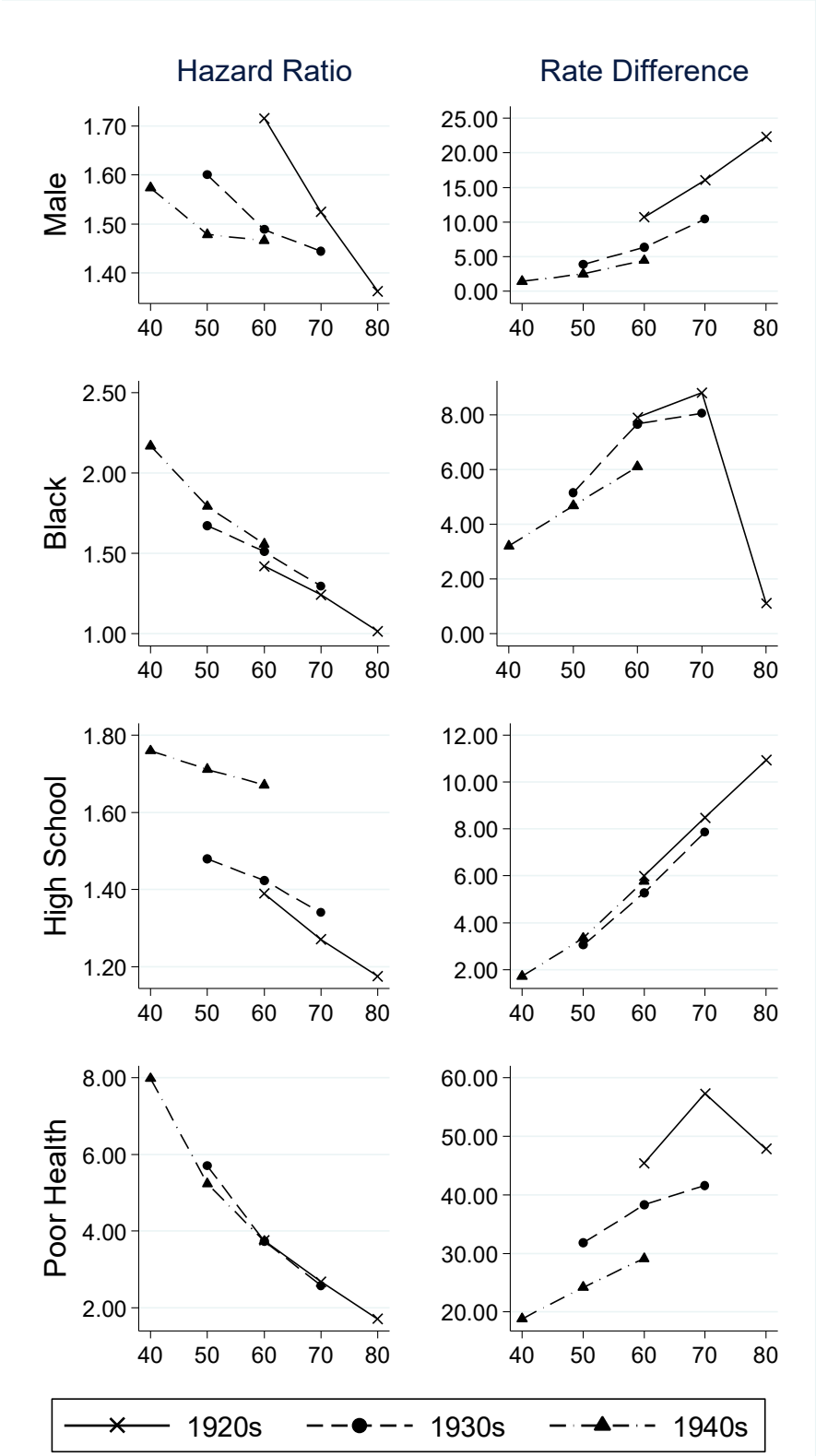


Figure 4. Hazard ratios and rate differences (per 1,000 person-years) by 10-year age group for cohorts born during 1920-9, 193-9, and 1940-9.



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