Smoking and Ischemic Heart Disease Disparities Between Studies, Genders, Times, and Socioeconomic Strata

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Abstract Large, unexplained, but possibly related dispar-
ities exist between heart disease risks observed in differing
genders, educational levels, times, and studies. Such heart
disease disparities might be related to cumulative tobacco
smoke damage (smoke load) disparities that are overlooked
in standard assessments of point smoking status. So, I
reviewed possible relationships between smoke load and
heart disease levels across genders, educational strata,
years, and leading studies. Smoker heart disease risk
assessments in the Nurses Health Study (Nurses), Cancer
Prevention Study-II (CPS-II), and British Doctors studies
were compared and related to their likely selection and
misclassification biases. Relationships between smoke
loads and United States (US) education- and gender-
related heart disease mortality disparities were qualitatively
assessed using lung cancer rates as a smoke load proxy. The
high heart disease mortality risks observed in smoking
Nurses in 1980–2004 and in less educated US women in
2001 were qualitatively associated with their higher smoke
loads and lower selection and exposure misclassification
biases than in the CPS-II and Doctors studies. Smoking-
attributable heart disease death tolls and disparities extrap-
olated from mortality ratios from the CPS-II and Doctors
studies may be substantial underestimates. Such studies
appear to have compared convenience samples of light
smokers to lighter smokers instead of comparing represen-
tative smokers to the unexposed. Further efforts to
minimize smoke exposures and better quantify cumulative
smoking-attributable burdens are needed.

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Introduction

Large, deadly, unexplained, but possibly related disparities
exist between heart disease risks observed in less versus
more educated groups, 1993 versus 2001, women versus
men [14], and different studies and definitions of "smok-
ing" [18, 33]. Thus, while at age 25–64 years, female heart
disease age-standardized mortality rates per 100,000 (rates)
fell in most groups, they inexplicably rose in the lowest
education (<12 years) US White women from 84 in 1993 to
98 per 100,000 in 2001 [14]. That 2001 rate was twice the
United States (US) male and six times the White female
heart disease mortality rates seen in the most educated (16+
years of education) in 2001 [14]. Also, unexplained are
disparities between the female smoker age-adjusted ische-
mic heart disease (IHD) mortality ratios of 3.3 (95%
confidence interval (CI) 2.9–3.8) in Nurses Health Study
(Nurse) smokers versus 1.6 (CI 1.4–1.7) in the Cancer
Prevention Study-II (CPS-II) from which official US and
global smoking-attributable heart disease mortality esti-
mates are extrapolated [18, 33]. Lastly, relationships
between smoking and US male/female mortality rate
disparities in 2001 that were reversed for lung cancer and
trending toward reversal for heart disease in the highly
educated are unexplained [14].

Given the large unexplained decreases in gender-
related and increases in education or smoking-related
heart disease mortality disparities noted above, a closer
review of the possible sources of such disparities seems
merited. So, I overviewed possible oversights in past
assessments of relationships of smoking to heart disease

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mortality disparities between genders, socioeconomic strata, times, and major cohorts.

Methods

I contrasted methods and their relationships to IHD mortality ratios in four leading cohort studies. The studies selected were: (1) the Nurses Health Study (NHS) 1980–2004 follow-up due to its recency, methodologic strengths, and high mortality ratios in smokers; (2) CPS-II [33] since it has been extrapolated into recent estimates of 443,000 annual US [1] and up to one billion global twenty-first century smoking-attributable deaths [37]; and the British (3) male and (4) female Doctors Studies, since they seem to be earlier, smaller, British versions of the methods in CPS-II [9–11, 33].

The NHS began with about 122,000 healthy, married US female nurses ages 30 to 55 years from 11 states in 1976 [18], though only the 1980–2004 data were used in the recent analyses I discuss (Tables 1 and 2). The NHS is relatively unique among large cohort studies in recency, use of biennial exposure reassessment, juried cause of death assignment, and fixing of smoking status for analysis purposes at the biennial assessment prior to the diagnosis of vascular, neoplastic, or respiratory disease. Those

methods help to minimize exposure and outcome (detection) misclassification biases and confounding by nonfatal diseases, respectively [18].

The CPS-II is the very large US cohort on which most US and global smoking-attributable mortality estimates are based. It began in 1982 with about 480,000 women ages 45+years in cancer society member acquaintance households [33]. The CPS-II cohort both used a definition of "never smoker" that misclassifies smokers as "never smokers"[7] and has subsequently been shown to have disproportionately high education, life expectancy, and probable smoking cessation rates and thus probably low smoke exposures relative to the US population [31, 32].

The British male and female Doctors Studies are the longest (1951–2001 and 1951–1972, respectively) early large cohort studies of smoking effects. Since true "non-smokers" were thought to be nonexistent at the time, less regular smokers (those denying smoking at least one cigarette daily for 365 days consecutively) were termed never smokers at least near the initiation of the study in 1951 [7, 8].

Possible selection and misclassification biases in the CPS-II, NHS, and Doctors studies were evaluated by reviewing their methods including timing, enrollment criteria, exclusions, smoking prevalence, age, "never" and "current" smoker definitions, and means of cause of death

Table 1 Background information on the Nurses, CPS-II, and British Doctors studies

	Study			
	Nurses Health [18]	Cancer Prevention Study-II (CPS-II) [33]	British Doctors Males [10]	British Doctors Females [9]
Analytic cohort nos.	About 100,000	711,000, about 2/3 women	34,440, about 2/3 of eligible male doctors	6,194
Enrollment	1976, but Kenfield excluded 1976–1980 data	Fall, 1982	1951	1951
End of follow-up	2004 for Kenfield hazard ratios [18]; 2002/2003 for mortality rates [28]	12/31/1988	2001	1972
Enrollment criteria	Initially healthy, female married registered nurses from 11 states	Friends, neighbors, and acquaintances of American Cancer Society volunteers	British male physicians	British female physicians
Exclusions	1976–1980 data and the unmarried, or diseased [18]	Pipe, cigar, or unclassifiable smokers	Users of any tobacco except cigarettes	Users of any tobacco except cigarettes
Initial current/ ever smoking prevalence	28%/54.3%	Age adjusted in White women, 20%/42%	~80%/83%	–/50%
Exposure reassessment	Biennial until disease diagnosed [18]	None in the 6 years analyzed	Every 6–13 years	Every 6–9 years
Outcome assessment	Juried by experts with terminal care records for 94% of deaths	Death certificate	Death certificate unless lung cancer	Death certificate unless lung cancer
Ages analyzed	34–84 years	35+years	~20+years	~20+years
URL/link	http://jama.ama-assn.org/cgi/content/short/299/17/2037	http://cancercontrol.cancer.gov/TCRB/monographs/8/index.html	http://www.bmj.com/cgi/content/abstract/bmj.38142.554479.AEv1	http://www.ncbi.nlm.nih.gov/pubmed/7417764?dopt=Citation

Table 2 Selection and misclassification biases and smoker mortality ratios in the Nurses, CPS-II, and British Doctors studies

	Study		
	Nurses Health [18]	Cancer Prevention Study-II (CPS-II) [33]	British Male and Female Doctors [9, 10]
Selection bias: studied "smoker"/ national population [18, 29] lung cancer (lung) and all-cause mortality rate ratios	2-fold lung cancer (=$10 \times 22/100$) [18, 29, 34] and 0.87- and 0.89-fold all-cause mortality rate ratios at ages 50–54 and 55–59 years rising to 1.19 at ages 70–74 years [28, 29]	1.49-fold lung cancer and 0.61-fold all-cause mortality rate ratios in women ages 35+years standardized to the 1980 US population (2009) [33]. Per Peto, Thun, and colleagues "...death rates among the nonsmokers and the smokers in the CPS-II study cannot be generalised even to the US" [25]	Healthy volunteer US doctors had about half the average US White male death rate in the 1980s [30]
Never smokers denied that they ever smoked:	"...regularly"	"...cigarettes at least 1 a day for one year's time."	At least 1 cigarette daily for a year
Misclassified "never" smokers had misreported [35], passive, insensible [3], or:	Intermittent (never "regularly") smoking	Intermittent (never 365+ consecutive days) smoking	Intermittent (never 365+ consecutive days) smoking
Definition of a current smoker:	Smoked at biennium baseline or diagnosis of vascular, respiratory, or neoplastic disease	Smoked cigarettes at study initiation	Smoked cigarettes at an approximate decennial baseline
Misclassified "current" smokers:	Quit transiently or up to almost 2 years	Quit transiently or up to almost 6 years	Quit transiently or up to almost 11 years
Age adjusted "current"/"never" smoker IHD mortality ratio	3.34 (CI 2.94–3.80) multiply adjusted 3.91 (CI 3.41–4.48)	1.9 (CI 1.8–2.0) in males and 1.8 (CI 1.7–2.0) in females versus 1.7 (CI 1.6–1.8) in males and 1.6 (CI 1.4–1.7) in females adjusted to the 1980 US population	1.6 in males and 2 in females directly standardized to male physician age groups

assignment (Table 1) and biases and/or mortality rate ratios versus the general population (Table 2). Table 2 helps to quantify selection bias possibly due to the disproportionate selection of light "smokers" by comparing lung cancer or all cause mortality rates in the cohort or similar groups to the general population. One would expect representative smokers to have far higher mortality rates than average Americans, about ¾ of whom deny current smoking. Table 2 helps to overview exposure misclassification bias by comparing definitions of "smoking" in the cohort to the types of smoke exposure overlooked by each definition of "smoker." Given the selection and exposure misclassification biases in those studies (Tables 1 and 2), other more representative exposure/outcome associations seem to be needed. So, I qualitatively contrasted 1993 and 2001 US female heart disease and lung cancer mortality rates and smoking prevalence across educational strata [2, 14] since such mortality rates were more current and widely used than other (income, class, deprivation, …) socioeconomic stratifications in the USA, lung cancer rates are a good proxy for cumulative tobacco smoke damage (smoke load) [19–22, 26], and US data had been used in the Nurses and CPS-II analyses [18, 33].

Results

The studies reviewed addressed distinct populations, times, and other background differences (Table 1); definitions of "never" and "current" smoking with attendant differences in exposure misclassification (Table 2); and smoker IHD mortality ratios (Table 2). Still, each study exhibited selection bias with narrow, skewed eligibility criteria (Table 1), low participant fractions (<3%), and/or low mortality rates, compared to the general population (Table 2). Selection bias was substantial in Nurses. Nurse "smokers" had little (1.19-fold at ages 70–74) to no (0.87-fold at ages 50–54) more premature mortality than nationally representative women yet thrice the all-cause mortality rate of Nurse never smokers (Table 2) [18, 28]. Selection bias was even clearer and stronger in CPS-II women age 35+years, where "never" and "current" smokers had lung cancer death rates 87% and −49%, respectively, and all-cause death rates 65% and 39%, respectively, below all US female averages for the 1983–1988 period [29, 33]. Prominent epidemiologists Peto, Thun, and Lopez wrote this about CPS-II: "…death rates among the nonsmokers and the smokers in the CPS-II study cannot be generalised even to the US, let alone to other populations. For example, the probability that a 35-year-old man will die before 70 is 34% at US 1985 death rates, but only 13% and 32% at the non-smoker and smoker death rates in years 3–6 of CPS-II." [25].

Heart disease and lung cancer mortality rates by education stratum and year in White US women at working ages are shown in Fig. 1. The data are for decedents from 43 states who were age 25–64 years with recorded years of education [14]. Smoke load (lung cancer rate in red and graphed on the y-1 axis) and heart disease rate levels (graphed on the right (y-2) axis) generally were closely proportional to each other across education and time strata and both rose proportionately in the least educated, were stable in high school graduates, and fell in the most educated (Fig. 1).

Figure 2 contrasts male and female smoke loads, as reflected in lung cancer rates, by the same year–education strata as in Fig. 1. Smoke load changes from 1993 to 2001 ranged from a 22% increase in the least educated women to 1%, 17%, and 34% decreases in the least educated men and

Fig. 1 United States White female lung cancer and heart disease mortality rates by year and years of education, ages 25–64 years
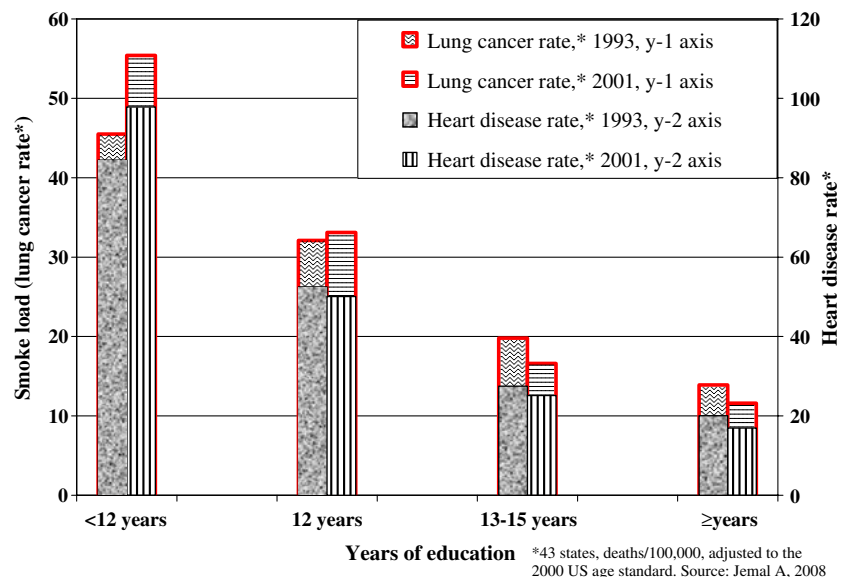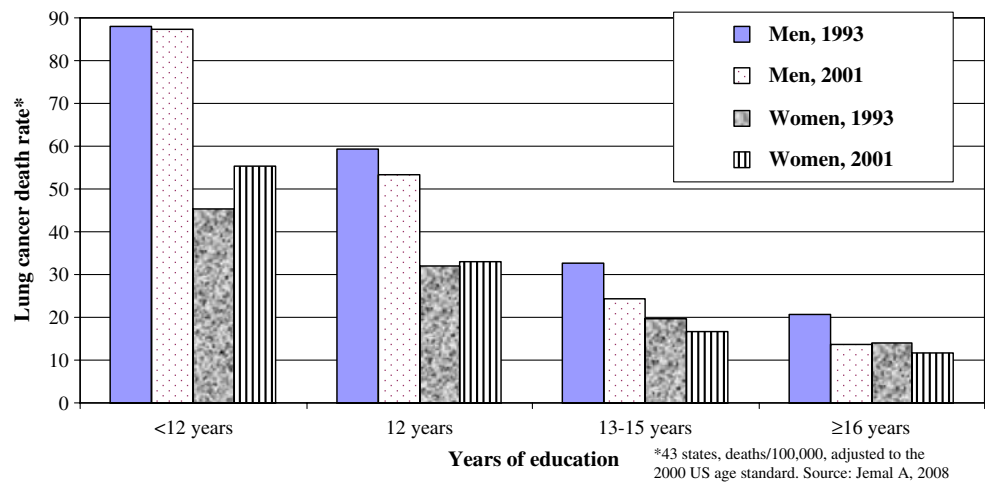
Fig. 2 United States White lung cancer mortality rates by gender–year–years of education, ages 25–64 years

the most educated women and men, respectively. By 2001, the male/female lung cancer mortality rate ratios were 1.18 and 0.98 in those with 16+ versus 17+years of education, respectively, and the heart disease rate ratio with 16+years of education was 3, down from 4 in 1993 as their male heart disease mortality rate fell 21 deaths/100,000, seven times their female rate decline (Fig. 3).

Discussion

This study found large heart disease mortality disparities, large smoke load disparities, and suggestive qualitative relationships between higher smoke loads and higher heart disease mortality levels across education levels, times, genders, and studies. Thus, the highest female heart disease and lung cancer rates and rate increases from 1993 to 2001 all occurred in the least educated females (Fig. 1), a group underrepresented in CPS-II [33], while the greatest drops

all occurred in the most educated men (Figs. 2 and 3), a group overrepresented in CPS-II [33]. As expected, reduced selection and misclassification biases in Nurses appear to have resulted in greater disparities between Nurse than CPS-II female "current" versus "never" smoker exposures and death rates. That is suggested by Nurse "smoker" mortality ratios that are higher than in CPS-II women for lung cancer or all-causes versus national averages (Table 2) or for all-causes versus "never" smokers (age-adjusted all-cause mortality ratios of 2.77 (CI 2.65–2.90) in Nurses versus 1.9 (CI 1.9–2.0) in CPS-II women). In other words, the improved definitions of "smoker" and more representative "smokers" in Nurses are associated with about 4-fold higher "smoker" IHD mortality excesses (2.3 (age adjusted) to 2.9 (multiply adjusted) in Nurses versus 0.6 to 0.8 in CPS-II women where excess risk equals IHD mortality ratios from Table 2, minus 1, the risk in the unexposed).

This study has several strengths. First, suggestions of higher smoking-related heart disease mortality burdens with

Fig. 3 United States White heart disease mortality rates by gender–year–years of education, ages 25–64 years
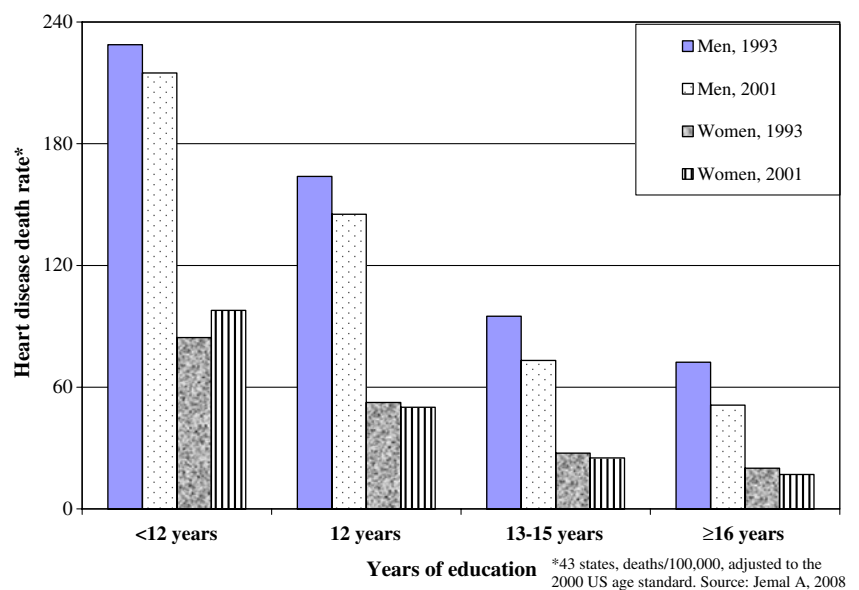
the higher quality cohort study methods in Nurses [18] corroborate the seemingly strong relationship between female smoke load and heart disease mortality rates across educational disparities (Fig. 1). Second, the general population lung cancer/heart disease rate associations (Fig. 1) qualitatively support suggestions that improved measurement of smoking will help account for more mortality disparities. Lung cancer rates are preferred as smoke load measures since they integrate several important aspects of exposure existence, duration, and level that are overlooked by self-reported point smoking status. For example, mortality is strongly related to forgotten [35], secondhand, insensible [3], and durational [27] aspects of exposure that are ignored in assessments of self-reported current active smoking. Second, the 1980–2004 Nurse [18] and 2001 national information studied is far more recent and less prone to selection, misclassification, and detection biases than are the 1982–1988 CPS-II and 1951–1972 female doctors data [35].

This review has weaknesses. Only three of the most prominent studies were discussed in depth, and all of them had some selection bias (Table 2). Despite their reduced misclassification bias compared to CPS-II, Nurses still had probably significant misclassification biases from secondhand and insensible smoking [3] and possibly from forgetfulness [35], never "regularly" smoking, or cessation periods between biennial reports of active smoking. Besides smoke load, other exposures could have differed between the studies. However, adjustment for numerous self-reported IHD risk factors raised the Nurse "smoker" IHD mortality hazard ratio from 3.34 to 3.91, widening the disparity between Nurse versus female CPS-II or Doctor mortality ratios [18]. The qualitative lung cancer/IHD mortality rate association across education levels (Fig. 1) exclude about seven states, are ecologic, and are based on proxy-reported decedent education levels and intercensal persons-at-risk estimates [14]. Lastly, little mention was made of the importance of smoking-related female lung cancer and other non-heart disease deaths. Yet, lung cancer alone killed nearly twice as many US women as breast cancer in 2005 [29], was increasingly disparate across education strata (Fig. 2), and appears to be persisting more in educated women than men (Fig. 2). Also, the Kenfield reanalysis of Nurses data linked smoking to both considerably greater mortality ratios and ranges of diseases than are included in official smoking-attributable mortality estimates [18].

Both this and several prior studies imply that heart disease mortality rate disparities might be largely linked to smoke load disparities and official estimates of death tolls from smoking may deserve to be raised substantially. A similar prior review of differing lung cancer risks found the differences to be largely due to differing smoke exposures [35]. Previous underestimation of strong relationships between smoking and heart disease mortality disparities are suggested by (1) the heightened IHD risk estimates in

Nurses when exposure misclassification and selection biases were reduced (Table 2), (2) persistent selection and misclassification biases in the Nurses study albeit smaller biases than in CPS-II, (3) close proportionality between the female smoke load and heart disease mortality levels over time and education in Fig. 1, and (4) prior papers. Jousilahti noted both that nonparticipants in a high (84%) participation rate survey had twice the tobacco-related disease mortality rate of participants [17] and that smoker mortality relative risks fell considerably with even two added years of cessation-related misclassification of "current" smoking [16]. Taylor and Thun showed substantial effects of possible CPS-II misclassification of ex-smoking years as "smoking" years [32]. Wacholder et al. [36] Boffetta et al. [4] and Marshall et al. [23, 24] each have noted that study risk estimates are very sensitive to misclassification of exposure as occurred even in Nurses (Table 2) [3]. Recent papers by Jha et al. [15] and Gruer et al. [12] have suggested apparent dominant roles of smoking in socioeconomic mortality disparities.

This study has several implications. First, reducing active, secondhand, and insensible [3] smoking in all and especially the less educated (Fig. 2) and reducing bias in studies assessing or adjusting for smoking effects seem merited [23, 24, 36]. Second, as others have noted, development and use of better smoke load biochemical markers or sentinel health event smoke load bio-indices like lung cancer rates with juried cause of death assessments may be useful [13]. Third, increasing the numbers of studies which publish the absolute smoke loads and heart disease mortality rates in their exposed and control populations might allow both construction of smoke load/heart disease mortality rate dose–response curves across studies and assessment of which parts of that curve were best represented in individual cohorts.

Further research is needed to help better quantify and communicate smoke load risks to women and men. Communicating with women may be especially pressing since smoking prevalence, smoke loads, and/or heart disease mortality rates were falling faster in men of working age, thus rapidly trending toward female lung cancer and heart disease death rates exceeding men in the most educated, some northern states [6] and some northern European nations [37].

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