



Invited Commentary

Invited Commentary: The Search for Preventable Causes of Cardiovascular Disease—Whither Work?

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The incidence and mortality of the major cardiovascular disorders vary sharply by occupation, but this is usually attributed to broad socioeconomic factors; the contributions of physical and psychosocial stressors at work remain obscure or controversial. Review of the ongoing studies of cardiovascular disease in the United States in this issue of the *Journal* demonstrates that few have either collected sufficient occupational data or used these data in published analyses to address this issue. There are compelling reasons to study this issue, starting with the sheer magnitude of the occupational gradient and disease prevalence. If only 5%–15% prove causally linked to preventable factors, an enormous disease-control opportunity would present itself. Moreover, the most suspect work factors—job stress, fine particulate dust, heat, noise, and shiftwork—are highly prevalent in the US workforce. Thankfully, there is evidence that many of the large ongoing studies are moving toward enhancing their occupational data and using what they have already collected. However, because of the complexity of studying these relations, the better solution is not retrofitting but designing studies in the future that combine de novo the conceptual frameworks and technical skills of occupational and social epidemiologists with those of more biologically focused investigators.

cardiovascular diseases; epidemiologic methods; occupational groups; socioeconomic factors

Abbreviation: CVD, cardiovascular disease.

Although it has been appreciated for decades that rates of and mortality from cardiovascular disease (CVD) in developed countries vary sharply by occupation, with variation top to bottom in the same range as the largest risk factors including smoking, hypertension, diabetes, or cholesterol (1–3), we know far less in 2009 about work as a preventable cause of ischemic heart disease or stroke than about its role in lung disease and cancer. As both vivid illustration and consequence of that fact, no single current clinical practice or prevention guideline in the United States for either disorder includes even mention of a work factor. In this regard, the review of work as a covariate in the major ongoing studies of cardiovascular epidemiology by MacDonald et al. in this issue of the *Journal* (4) provides both a partial explanation for why so little is known and a sobering look at what we can expect to know in the foreseeable future if present study directions remain unchanged. With the strong push to explore

early biomarkers of disease, host genetic predisposition, and their interactions with established CVD risks, the prospects for filling this knowledge gap appear low.

The stakes, on the other hand, are very high. Although it may indeed turn out, as some believe, that occupation portends CVD only as a marker for other social factors, such as material well-being or education, or confers risk through non-job-connected social pathways, such as societal status or access to material benefits including income, pension, and, in the United States, health care, there is at least a priori reason for concern about workplace exposures to physical and chemical hazards and psychosocial stressors, including those introduced by job insecurity, family-work conflicts, and complex and expanding work shifts. If no more than 15% of cardiovascular disease were proved attributable to 1 or more of these factors, a figure comparable to the current best estimates of the contribution of work hazards to chronic

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respiratory disease (5), an enormous opportunity would present itself. Even at 5% attributable risk, as currently the best estimate for the contribution of work hazards to all cancer death (6, 7), the value of prevention focused on the (relatively small) subpopulations that assume such risks could be considerable. Moreover, for both respiratory disease and cancer, not just ecologic attribution but specific causes of excess risk have been elucidated, rendering straightforward the pathway to preventive practice. Although existing empirical data for CVD are, by comparison, fragmentary, an estimate somewhere between these figures would not be far-fetched and may be too low. For example, on the psychosocial side, work strain—high job demand, low control and reward, and poor social support—appears to explain a higher portion of the variation in CVD incidence between the lowest and highest job grades among civil servants in the Whitehall II study (8). Other European studies have corroborated this finding (9), although not all (10), and controversy limits acceptance. On the physical hazard side, daunting published estimates of the impact on CVD rates attributable to fine particles (particulate matter with an aerodynamic diameter of $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$)) in ambient pollution—at concentrations 1–3 orders of magnitude lower than those allowed in the workplace air (11, 12)—should chasten those who discount a role for physical factors just because strong gradients in risk exist in the absence of such factors, as in the Whitehall population. In addition to fine dust, noise, shift work, and heat are among other prevalent hazards of concern in relation to CVD risk (13–15). These exposures remain very widespread in lower tiers of employment. Although it is often presumed by non-occupational epidemiologists that only office and like service jobs remain in our postdeveloped society, almost 25% of the US workforce is still employed in manufacturing, construction, mining, or farming, and another estimated 25% have exposure to physical, chemical, and biologic work hazards in service-sector jobs in transportation, health care, food handling, and uniformed services, including the military (16).

The demonstration by MacDonald et al. (4) that opportunities to explore such possibilities are not being exploited in major ongoing studies of CVD, however, should not be blithely attributed to lack of interest in these hypotheses or simple errors of omission. Both theoretical and practical limitations abound, as they acknowledge. On the theoretical side, the conceptual relation between work and health, as recently elaborated by Lipscomb et al. (17), is extraordinarily complex and dictates that meaningful estimation of even the most salient work factors requires data collection and/or access to existing data over several domains, since most of the putative social determinants of CVD are highly collinear with the workplace hazards. The burden for the investigator not experienced with strategies to assess occupational factors is further complicated by the extraordinarily strong forces of selection operating in the workplace setting: Exposures are rarely randomly assigned, either at initial job placement or subsequently, as workers and their employers choose and select for all intents and purposes continuously over a work career. For example, in most large workplaces, employees with evidence of heart disease or any of its precursors, such as hypertension or diabetes, are routinely excluded from work around heat, rendering heat exposure

virtually impossible to study as a potential causal factor itself, although it's a credible one. Remaining in the active workforce is also in part conditioned by health status, resulting in a reverse-causal pathway in which outcome determines exposure and leading to paradoxical dose-response relations unless care is taken in study design (18). In addition to strategies such as scrupulous truncation of exposure at the case date of leaving work in case-control studies and lagging exposures to account for unhealthy survivor effects, there has been some uptake of more sophisticated methods to manage selection, based on explicit estimates of the effect of counterfactual exposure assignments using marginal structural models and G-estimation where sufficient longitudinal data are available (19, 20).

From a practical standpoint, collecting useful data about physical and psychosocial stressors is often difficult, even where there are a will to do so and adequate funding. Where study subjects are drawn from a broad population, about the best that can be realized is self-report about job hazards, physical and psychosocial, or estimates of these derived from job title and industry, based on expert opinion or published translational matrices (21). Collection of objective data, let alone quantitative exposure information, is prohibitive unless study subjects are drawn from a single or very small number of workplaces (as Whitehall). Such single (large, geographically dispersed) workforce studies are attractive in this regard and may offer the potential for collection of *existing, objectively obtained* data on physical hazards, as well as sociodemographic factors, even behavioral and psychosocial parameters in some companies. In the ideal design, these can be directly linked to health claims or other outcome data, such as routine surveillance of blood pressure at work (3). On the other hand, such studies suffer potentially from lack of generalizability, one of the concerns about Whitehall. The ramifications of these theoretical and practical limitations have been discussed for years within occupational epidemiology (22), but they are not necessarily part of standard chronic disease epidemiology training or practice.

Practitioners of occupational and environmental epidemiology may be far less attuned, on the other hand, to managing confounding created by social forces lurking outside the workplace gate, surely responsible for some, if not most, of the social gradients in CVD no matter what is eventually established about the causative roles of the workplace physical and psychosocial environment. As has been painfully and repeatedly proved, legal structures notwithstanding, racial and more subtle social discrimination weighs heavily on employment decisions, no doubt part of the explanation of why taller men earn more than shorter ones and why thinner women earn more than heavier ones (23, 24). For this reason, it is likely that, even in the same workplace, those more heavily exposed to noxious agents may differ—endogenously—from those less exposed, to a degree that could severely confound associations with health, even after adjustment for easily measurable social indicators, such as years of schooling or income category. As an illustration, such confounding is likely the best explanation for 2 recent, very high-profile reports linking environmental chemical exposures to CVD risk. In the first, a Women's Health Initiative analysis showed that levels of differential ambient particulate matter with an

aerodynamic diameter of $\leq 2.5 \mu\text{m}$, after adjustment for standard socioeconomic status predictors, explained a gradient in CVD mortality severalfold steeper than previous estimates (12), but this proved true only for differences in exposure *within*—but not *between*—the study metropolitan areas, suggesting that people choosing less rather than more polluted neighborhoods might differ in other, unmeasured ways. Likewise, an analysis of data from the National Health and Nutrition Examination Survey (NHANES) showed a strong association between the highly controversial endocrine-disrupting chemical bisphenol A measured in urine and self-reported CVD *after controlling for the very strong effects of race, income, gender, and education* (25). However, because canned food is the major source of bisphenol A in adult blood, the result seems likely distorted by unmeasured dietary and behavioral differences even within similar social strata. Social epidemiologists and economists have shown more willingness to measure such factors when feasible, as well as to exploit strategies to better manage unmeasurable endogenous differences, including the use of propensity scores and the application of instrumental variables wherever possible.

Bottom line? The complexity of CVD etiology in our society and the certain historic and transnational evidence that it is almost all preventable compel us to reconsider the way we approach the search for preventable causes such as work factors. As MacDonald et al. rightly, if less than explicitly, propose, research teams must incorporate measures of work exposures beyond adjustments for social class. Gratifyingly, in both the detailed presentation of the trajectories of some of the larger collaborative studies ongoing and the anecdotal discussion that follows, there is evidence that such “add-ons” are already occurring. For example, investigators in the Coronary Artery Risk Development in Young Adults (CARDIA) Study have recently incorporated collected job data to demonstrate an association between biomarkers of inflammation, likely predictive of later disease, and periods of unemployment, although the model is far from strong enough to demonstrate a causal pathway (26). It is likely that further efforts will be spawned as a consequence of the timely report by MacDonald et al.

That is all to the good, but the longer-term solution rests not in retrofitting these longstanding efforts but in evolving a new approach to collaborative designs, in which the biologic sophistication and cutting edge tools of traditional CVD research teams combine—from the inception—with groups better able to conceptualize and measure social constructs of relevance and more experienced at measuring workplace exposures hypothesized to cause disease. Such collaborators in social and occupational epidemiology are, respectively, also in the best position to manage the daunting complexity of social and behavioral factors as likely confounds and the never-ceasing selection pressures certain to vitiate every inference unless harnessed in the design phase. Ideally, statistical analyses should reflect the strategies deemed by the respective specialists as best able to overcome practical limitations, all driven by an explicit, mutually accepted, and compelling conceptual framework about how work and CVD might be interrelated. The increased friendliness of software for performing multilevel models, allowing the elucidation of effects that may often be nonlinear and/or con-

textual, makes this lofty collaborative ambition the more feasible if, sadly, the antiquated organizational structures of our academic departments and research funding agencies do not.

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