DESCRIPTION OF A LARGE-SCALE STUDY DESIGN TO ASSESS WORK-STRESS-DISEASE ASSOCIATIONS FOR CARDIOVASCULAR DISEASE

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Abstract
We claim that a new level of studies is needed to answer a series of important questions about the expanding global chronic disease burden for cardiovascular disease (CVD) and for related conditions such as diabetes, metabolic syndrome, and obesity. These require a new study design structure, related to a new level of theory that goes beyond the current single-factor, a-theoretic epidemiological studies. This new platform for the design of large-scale Work/Stress/Disease studies would assess CVD-related disease mechanisms in a more general and dynamic form, based on the use of new tools for measuring autonomic functions in an occupational stress context and a new theory of disease causation. A sample outline is presented for such a study, based on Stress-Disequilibrium Theory (SDT) hypotheses, building on analytic tools developed for the assessment of stress-related exhaustion effects and chronic disease risks from Heart Rate Variability (HRV) research studies. The goal is to assess the associations between social organizational risks, particularly at work, and hypertension, metabolic syndrome, and diabetes II. The study design is multi-stage, spanning across several levels of disease-related de-regulation, and addressing co-morbidity of the conditions themselves. The study design is meant to span across a broad social population at all levels and would probably be multi-site, involving several countries, to yield the larger sample increased power for finding associations for work — physiological effects.

Key words:
Stress, Cardiovascular disease, Low control, Growth and regeneration, Large-scale study design

SECTION I. JUSTIFICATION FOR A LARGE STUDY IDEA BASED ON MAJOR UNRESOLVED QUESTIONS

There is increasing evidence around the world of a growing chronic disease problem: for example: cardiovascular diseases (CVD) are the leading cause of death in the US [1,2] and other industrialized countries, and are fast becoming the major cause of mortality in rapidly industrializing societies such as China. In the US CVD risk factors and related conditions for persons over age 20 are estimated to have prevalence of 34%, 33%, and 34% for hypertension,
Therefore, we could claim, a bit provocatively, that what is now needed is a new stress model of “how absolute low social control, in major socio-economic institutions, causes chronic disease”, as the third explanation for the inverse social gradient in health. In fact, there is much evidence that shows CVD, MD and MSD are related to low control in our modern social organizations. For example, after reviewing 46 studies Belkic et al., concluded that low workplace control and high job demands were a major risk factor for CVD, a connection now acknowledged by the American Heart Association [5,13,14]. Bongers et al. find a similar picture for the upper extremity MSD risk factors in a review of 28 studies: identifying mental work load, low workplace control, and lack of workplace support as significant causes [15]. In addition to this, in a review of 68 studies of mental strain and depression, van der Doef and Maes found, and in 11 longitudinal studies of job strain and depression [16] also found, associations between low workplace control and high mental work demands [17]. We could further note that there is evidence of both increases in and emerging congruence of these psychosocial working conditions risks in workplaces around the world highlighting both the potential for increasing future prevalence and the global nature of the burden — an unsurprising concomitant of our globalized economy and communication [18].

While we cannot assert to have concluded discussion with such comments, we do claim that even such a brief review makes it clear that at least Four Major Questions exist in relation to this disease burden, and that answers to them probably need radically new approaches — to effectively change these trends before such disease burdens become overwhelming difficulties for modern societies:

Question I. There is increasing prevalence — why, and how large? How big are the benefits of prevention?

Question II. Co-morbidity: Why?

There is substantial co-morbidity among the conditions such as hypertension, diabetes II, metabolic syndrome, general CVD, and also depression, and obesity. General observations of this co-morbidity, since the work of Syme and Syme and Berkman have noted that individuals at risk for one of these diseases are often at risk for one of the
DESIGN OF LARGE-SCALE WORK STRESS CVD STUDY

Question III. Job strain and/or low social control are associated strongly with disease — Why?
Question IV: Why is it taking so long to understand the specific operating physiological risk mechanisms?

SECTION II. ADDRESSING THE LIMITATIONS IN OUR CURRENT RESEARCH

The answer to the last question — why is it taking so long to understand the physiological mechanisms responsible for the development of these diseases — could have to do with the complexity of the multi-causal explanations. The typical presented list of risk factors for CVD (or MD or MSD) is long, with factors at many levels — physiological and social [21–23].

We can summarize our suspicions about why the progress has been so slow via the following critique of the existing literature that addresses the combination of questions relating to “work-stress-disease.” Many highly related physiological parameters are powerfully linked to stress response and stress theories imply an integrated function among them. However, while the “stress theories” themselves tend to provide integrated explanations, our research traditions have lagged behind in this integration.

Partial models
We have a deluge of micro-level findings with fragmentary, unspecified linkages to integrated physiological/social theory. Obviously, the “work-stress-disease” hypotheses vary substantially across studies. But even in the studies with similar approach the hypotheses themselves are usually fragmentary predictions — with indeterminate implications in the context of a long chain of dynamically-integrated systemic relationships, given that unmeasured context factors could indeed differ. Thus, only a few links in putative causal physiological chains are measured, and findings from one study may assess a population with levels on some of the unmeasured factors dramatically different than the unmeasured factors in another study. Measures have differing etiological status with respect to disease progression. Stress effects may be considered to be biologically detectable lesions in patients with already compromised circulatory systems, or behavioral indications of exhausted response capability of “healthy” working people that is only “disease threat” if continued without respite for long periods. More comprehensive coverage and specification is needed.

A number of studies have examined patho-physiological stress responses. However, generally these studies do not include an ordering hypothesis of several links in the exposure-disease chain. A recent review on psycho-physiological biomarkers of workplace stressors distinguished results from studies on plasma catecholamines, separate studies on heart rate variability and yet other studies on post-morning cortisol [24]. Most studies fail to include various levels of physiological deregulation. One exception to this is a study from Whitehall II in which the prospective relation between stress and CHD was examined while, in addition, indirect mechanisms (behavioral risk factors and metabolic syndrome) and direct physiological pathways through both autonomic activation and neuroendocrine systems were looked at [25].

Partial measures
There are often numerous measures of personal preventions based on personal lifestyle, but no data on work conditions or social organization, or economic burdens on subjects. Moreover, there are often limited data on other social risk factors from a subject’s social, cultural, class, industrial sector or globalization context.

Studies examining the measures of autonomic dysfunction in response to stress usually focus on one particular stress exposure. A more comprehensive assessment of low social control in several major socio-economic domains is lacking. A number of studies have examined work-related stress in relation to heart rate variability [26–31]. Only rarely some studies have additionally investigated the social co-risk factors such as social network and social support or social economic risks [32–34]. There are many diverse choices of factors to be included across studies — in addition to absence/presence of the
above factors. The logical status in the statistical analytic models using the same measures may differ between studies; measures being variously used as independent, dependent, intervening or effect modifying variables. Health status may predict return to work possibility, or features of the work may contribute to health status.

There are un-standardized measurement protocols at all levels of analysis. Many forms of “psychosocial job stress” assessment are used. Autonomic dysfunction outcomes have been related to stress measures in both the job strain model [29,32,34] and the effort-reward imbalance model [26,33]. On rare occasions both these models were simultaneously examined in relation to heart rate variability [30]. Many bio-monitoring technologies have multiple parameters that can affect measurement accuracy which are left to vary across studies. Several studies have examined the associations between work stress and heart rate variability based on 5- or 3-minute ECG recordings [25,28,32,33,35], while other studies included measures from 24-hour ambulatory monitoring [26,27,29–31,34]. The results obtained from short-term ECG recordings are difficult to compare with the findings based on 24-hour monitoring because the interpretation of heart rate variability measures depends fundamentally on the length of the recording period according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [36]. Another important issue is that stress response profiles should be looked at for different sociological periods such as work vs. rest or awake vs. sleep time [26,29,30,34].

The most standardized elements of the study exist in the context of CVD studies where some outcomes, such as coronary heart disease (CHD) and strokes of several classifications are routinely classified in internationally consistent manner.

**Partial populations**

Populations differ dramatically across studies. A study of CVD-patient population of advanced age may be compared to a random population study of healthy subjects, or studies in a manufacturing department in one industry may be compared to randomly selected subjects from a national pool. On the whole, the measurement of physiological biomarkers of work stress tends to be limited to small focused studies rather than large scale epidemiological cohorts [24]. Studies including 24-hour ECG recordings are particularly based on rather small selected samples of less than 200 subjects [26,27,29,34], although recently a few studies have been published with findings based on ambulatory ECG monitoring in samples of approximately 600 persons [31,37]. A lot of variation exists in the occupational profile of the study samples. While some studies included workers with a wide variety of occupational titles [29,31,33,34], other studies were based on homogeneous occupational samples [26–28,35]. As for the gender distribution, a large number of studies investigating stress and heart rate variability included only male subjects [26,27,29,31,32,35], while some other studies were based on mixed gender samples [25,30,33,34] or a strictly female sample [27].

Examples of single occupation studies for particular risks have been performed in workers exposed to electromagnetic fields (EMF). The findings obtained by Bortkiewicz et al. indicated that exposure to electromagnetic fields may induce cardiovascular abnormalities: ventricular arrhythmia, elevated arterial blood pressure and impaired day-night BP regulation. These abnormalities correlated with HRV disturbances, mainly with the decrease of parasympathetic activity and with the level of exposure [38–41]. While these studies demonstrate the impact of EMF on cardiovascular deregulation, they could not simultaneously control for potential psychosocial environmental exposures due to the limited psychosocial environmental exposure variance available with just a single occupational group. It was then impossible to test for the main or interactive effects of psychosocial factors and EMF, and thus difficult to generalize the findings with single occupation studies.

There are often numerous unclear distributional implications of disease and prevention costs and benefits. The majority of studies report some individual health status components of the sample, but a comprehensive disease profile description is usually lacking. A few studies restricted their study samples to subjects without the history of CHD based on diverse criteria [29,31,33,34].
The concept of “exhaustion” implies cycles of restoration and depletion — since exhaustion is usually not a permanent condition. However, there are often numerous, unspecified aspects of a subject’s “exhaustion profile”: the status of the individual with response to his/her specific environmental burdens and recovery, with respect to depletion and restoration of many physiological systems. This is needed information to determine whether a subject’s response indicates health or illness. There are likely to be multiple time periodicities of restoration, relating to different physiological systems [42]. For example, for a normal workweek, “healthy response” might be a quick return to normal behavior after one day’s rest. For a glucose load, healthy response might mean return to baseline stable levels within an hour after eating, etc. For a tilt-table test, quick return might be perhaps several seconds, etc. We rarely know whether a subject has (a) just returned from a month’s vacation, or (b) it is a late Friday after a hard week’s work, or (c) they have just come to work in the morning or (d) they are tested during a mid-afternoon “down”. These omissions reflect failure to understand the dynamics of the renewal and depletion complex, multi-level physiological systems. The only available studies that make some distinction between the periodicities of restoration and depletion differentiate between either autonomic dysfunction during work and leisure time [26,29,30] or during wake and sleep time [30,34]. While both reviewers and researchers often understand these differences, the comparisons are made and published nonetheless because at least some of the methods or measures are comparable — and some comparative context is better than none. But the comparability may certainly not be enough to reject the null hypothesis that the studies have consistently proved (or disproved) a specific hypothesis. The major questions above are not definitively answered.

All these micro findings and the resulting chaos of results we actually do observe in the current voluminous literature, make it difficult to interpret the myriad of differences and conflicts between the results. They also complicate attempts to assemble any form of an overall understanding broad enough to be relevant for major public action — for example to reduce chronic disease in aging populations through re-organization of the life-cycle work demands. Consistency may only be visible when a more complete picture is assembled and reviewed.

We are now returning to the primary critique: only fragmentary, unspecified linkages in putative causal physiological chain of integrated physiological/social theory are measured. The requirement to find more consistent answers demands a more comprehensive study design strategy. Nonetheless, what should determine the specification for this “larger kind of study?” — it cannot just be: “include everything, in every way“.

To answer this question we must go back to the putative cause and potential source of an integrated understanding: the models of stress and illness to understand what these “integrative models” should now really compel us to measure.

### SECTION III EVOLUTION OF STRESS THEORIES AND STRESS-DISEQUIilibrium THEORY

**Integrated models of the stress-disease process and physiological function:**

**Homeostasis, allostatics and stress-disequilibrium**

Current stress theories, and Claude Bernard’s mid-19th century homeostasis theory, all present a picture of a disease process that involves an integrated function of many physiological systems to describe when response to daily stressors departs from healthy adaptation to the environment and instead becomes a chronic disease precursor. Homeostasis theory’s early claim was that very stable values on many physiological measures — blood glucose, blood acidity, etc. in the ubiquitous inter-cellular fluids — were necessary for the effective operation of all of the microcellular level processes involved in life sustenance. It has become the basis for modern medicine’s approach to pharmaceutical interventions: where drugs are administered to return a physiological parameter to its “healthy set point” (i.e., the blood pressure).

Sterling and Eyer’s newer Allostasis theory has demonstrated the fallacy of thinking that health status could be assessed by the body’s ability to search for and find...
the stress-disease process. To do this it focuses on the issue of “control” — instead of demands [44]. The requirement of coordination and integrated response in physiological self-regulation — of ordering — of specification of precise physiological response — is the determining “load” for the central control system in information theoretic and general thermodynamic (i.e. Systems Theory) terms. In the SDT the problem is exhausted ordering capacity (control capacity). Therefore, ordering capacity must be periodically restored through rest to maintain healthy response. Job stress and particularly low workplace control could lead to chronic disease risk through de-regulation processes occurring at several linked levels of cardiac and endocrine system mechanisms.

The basic SDT concept is the need for an individual to maintain an “equilibrium of flows” (resources, energy) in order to maintain healthy self-regulatory stability, and — when healthy — from time to time has the possibility to grow. Long-term maintenance of this stable platform involves a short-term cyclic process of creation and then consumption of “ordering capacity” (ordering capacity here refers to a complex organism’s ability to coordinate its own activities so as to take effective action in its environment). This rhythm is of course reflected in the need for balance long noted for physiological systems: catabolism and anabolism in metabolic processes and sympathetic/parasympathetic balance in autonomic function – where the later of the pair, respectively, refer to the regeneration and growth phase of function.

New theory: Stress-Disequilibrium Theory (SDT)
This theory describes how low social control can contribute to the development of chronic diseases through the deregulation of physiological systems — a very general theoretical format. According to SDT [43] a physiological system has a finite capacity to maintain regulatory stability of the physiological system that it has the function to control. This ordering capacity can become exhausted, and must be periodically restored through rest to maintain healthy response. The Stress-Disequilibrium Theory adds the processes of growth and regeneration to the understanding of the stress-disease process. To do this it focuses on the issue of “control” — instead of demands [44]. The requirement of coordination and integrated response in physiological self-regulation — of ordering — of specification of precise physiological response — is the determining “load” for the central control system in information theoretic and general thermodynamic (i.e. Systems Theory) terms. In the SDT the problem is exhausted ordering capacity (control capacity). Therefore, ordering capacity must be periodically restored through rest to maintain healthy response. Job stress and particularly low workplace control could lead to chronic disease risk through de-regulation processes occurring at several linked levels of cardiac and endocrine system mechanisms.

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The Core Idea of the SDT is that ordering capacity is first built up — and then it is used up — which implies cycles (periodicity) of Work. These are based on the 2nd Law of Thermodynamics’ ordering capacity limits for how much Work can be done by a system during a single process. For example: only so much ordered energy can be obtained out of the steam engine piston’s one-dimensional motion for each cycle of disordered steam energy that is input. Many cycles of such Work are usually needed to attain normal system goals. Theoretical biologists are now turning consistently to the thermodynamic principles of the Second Law to explain complex living systems, for
Demands

The “open system” relation between the environment and the system discussed in thermodynamics allows complex organisms to change disordered energy into ordered Work in order to (a) maintain their complex structure, with all its levels of integration and differentiation, and to (b) adapt to the environment (i.e., “be alive”). It is impossible to conceive a living organism (or any complex system) without demands. Absence of demands would imply a situation where there would none of the constant “flows” of energy or nutrients that are constantly transformed into ordered action (work) as needed. Demands come from “just being alive”.

Thus, the special type of equilibrium for “stable living systems (open systems)” actually describes equilibriums of flows — of disordered energy being constantly transformed into ordered energy (Work) rather than a truly non-changing state.

Control

The “open-system” is a simple two-level relationship, in which the system is “the controller” of the way things work, and the environment is “controlled” — only serving to supply undirected energy (albeit unpredictably). Thus, multiple levels of control arise.

In the SDT multiple, nested, multi-level relationships are needed to explain functions in complex organisms. The first SDT addition to standard Systems Theory comes as a three-part structure that provides a more realistic perspective on stress-related processes in human systems. There is a Controller (the central nervous system or management), the System (set of physiological sub-systems, or an organization’s departments) and the Environment. (This perspective is based on two integrated system-environment pairs). The Controller uses its capabilities/skills and its decision autonomy (Decision Latitude) to create the most desirable action strategies for the System as a whole — in its Environment [48]. In this manner, the SDT describes how low social control can add to disease development.

The Stress-Disequilibrium Theory describes multiple, linked-level functioning. High-level Work is ordering capacity that allows high-level controllers to direct the entire organism in coordinated actions in its environment. However, ordering capacity restoration occurs from the lower level, and thereby supports adaptive actions that are controlled from the level above (higher in energy). This basic relationship helps to define the nature of multi-level control processes. These relationships are very similar to Bernard’s “homeostasis” concept.

To make this happen, inside the System there must be a “processing structure” which transforms disordered energy — with many degrees of freedom — into ordered work — at few degrees of freedom: i.e., accurate predictable Work. The Work output from one level (the lower level) provides the constraint structure to restrict the degrees of freedom on the cheap, disordered energy that is available at the higher level above: turning in into High-level Work (Flow 4 in Karasek — “the Neg-Entropy Pump”) [43]. Consequently, the processing structure is “built” using the critical outputs from the lower level systems as components. Thus, the low level contributes to the development of ordering capacity development at the higher level (i.e. the outputs might be enzymes, which at the next higher level are used to process simple input molecules and energy into the complex proteins needed for Work by the organism). The energy in the output Work will be considerably less than the total (albeit disorganized) input energy.

3 Maintaining life requires the maintenance of gradients, namely, constant, improbable deviations from a “true” total equilibrium (which would be a “dead” inert, a “grey” uniform state). which are based on flows of ordered energy. With adaptive environmental activity as a goal, the complex system maintains its structure. This is against the predicted probabilities of the Second Law of Thermodynamics stating that all order decays into disorder — and from time-to-time also grows [43].

4 “As the organism adds levels of functional complexity — in order to achieve the goal of precise regulation — it must add levels of control specificity. To get a high level of complex ordering capacity, one must add a constraint structure at each new level of organization to reduce the enormous range of possible states of all the component parts to the small number that represent the action possibilities of the integrated organism [43].” However, these “constraints” at the lower level are the foundation platform for an organism’s powerful and flexible option actions at a higher level — which give it the needed variety of response to react to the ever-present environmental uncertainties.
This description of growth and regeneration is SDT’s second addition to the standard System Theory. It contributes to our understanding of the disease process by describing how the capacity to handle stress (ordering capacity) is first created and defines the limits to this capacity in our coping activities. This also gives us a theoretical platform for discussion of physiological processes of restoration such as anabolism and parasympathetic response. In addition, the creation of ordering provides an outline of growth processes in complex systems. From time to time the complex system will have the possibility of connecting to new energy sources outside and after appropriate “redistribution of labor” and capabilities, will potentially allow development to a new higher level of functioning — integrating capabilities in a new way into a “meta-capability” to process this energy to the advantage of the organism (these concepts are further explored in the Conductivity Model in Karasek [49,50] in a work organization and political economic context, and in Dollard and Karasek [51] in terms of organizational growth).

Stress and disease
Over the long term, when it becomes impossible for the integrated physiological systems to maintain sufficient ordering capacity to meet the level of environmental challenges undertaken, the development of chronic diseases occurs through the deregulation of physiological systems. Failure of normal restoration of ordering capacity — due to overload of demands, lack of external control, or insufficient restoration periods — can cause shifts: (a) to alternative, slower system response (which eventually becomes chronic disease by definition), or to (b) high-level, acute organism control failures, which are themselves “disease” states. When occurring chronically, exhaustion of some physiological systems can force overall shifts to physiological system equilibriums that result in lower levels of functioning. This description is similar to Selye’s advanced disease process explanations: eventually, the inability to maintain effective control in the face of demands first requires substitution of other systems or costly added resources. Then finally, when demands persist, this ceases to be a viable long-term stable strategy, and at this point a previously integrated set of systems loses its internal coordination — during a potentially unpredictable disruption (chaotic). It must then find a new internal equilibrium relationship between the remaining contributing systems. This is very likely to provide the organism with less adaptive capability than before — chronic disease (thus, the name: Stress-Disequilibrium Theory).

High-level control capacity failure and disease
A unique contribution from the SDT towards understanding the process of disease development is something labeled here as P-OTD: Prevention-Only Treatable Disease, based on high-level control capacity failure [43]. Among stress theories only the SDT has the hypothesis that failure to meet ordering capacity needs at any level can be a sufficient explanation of disease. Thus, high level ordering capacity deficits can explain disease, without the contribution of low-level pathological conditions in this manner: transient vulnerability from high level ordering capacity deficits — through failure of restoration from insufficiency in normal low-level cycle times or of facilitating conditions — can cause deregulation and disease (particularly acute events). Furthermore, high-level failure of ordering capacity is proximal to social environmental causes: the social environmental demands or constraints that “keep coming” and/or “can’t be handled”. Therefore, social organizational changes in control structures or demand levels could have direct health promoting effects by reducing such causes — thus, the label: “P-OTD: Prevention-Only Treatable Disease”. Such a chronic disease is only really treatable by societal-level prevention, because only changes in the external environmental conditions (or high-level functional enhancement) will facilitate recovery. There is nothing to treat at the lower level, because those physiological systems are not “sick”, only in

Footnote: Full discussion is not possible in this paper. However, potential supporting evidence here can be found in acute events involved in two relevant stress-chronic disease areas: (a) sudden cardiac death heart disease (50% of CVD mortalities have no clear lower-level explanations), and (b) in asthma attacks [37], where substantial documentation on preventive biofeedback involving HRV-based parasympathetic control enhancement [53] helps support the hypothesis relating to high-level parasympathetic control system failures).
a transient state of low capacity, soon to recover automatically\textsuperscript{4}.
In summary, the social policy implication of the Stress-Disequilibrium Theory of Chronic Disease Development is that requirements for coordination have been pushed to extremes beyond healthy limits in the context of long-term stressor exposure of humans in their social environments — our global economy for example — with the result of a diminished capacity for physiological coordination, and finally chronic disease development.

SECTION IV: TRANSLATION OF THEORY INTO STUDY DESIGN PARAMETERS
The health implications of SDT “stress” effects are hypothesized to be demonstrable by examining multi-level Controller/Controlled associations to test for both depletion and restoration of ordering capacity in physiological response.
This is a step beyond — but is generally consistent with — predictions from the simple Job Strain hypothesis (low social control in the context of high demands) of the Demand/Control model [44]. Long-term exposure to job strain would change the levels of physiological parameters in a manner associated with chronic disease development: for example: higher blood pressure, adverse levels of psycho-endocrine hormones.
The Stress-Disequilibrium Theory testing further implies the needs to assess:
1. Controller/Controlled relationships between physiological systems at different levels — displaying both depletion and restoration of ordering capacity (See below section: “Definition of exhausted response”).
2. Individual subject’s status in his/her “exhaustion profile”: response effectiveness assessment in relation to a time sequence of differing rhythms of ordering capacity cycles at different levels (See below section: “Methodological issues in measurement of exhaustion”).

Testing the SDT would typically require partitioning of variance in periods of differing exposure to demands — for example differing social periods relating to work, rest days, sleep, high strain work, etc. — to test Controller/Controlled relationships hypothesized to differ between periods (for example, testing the association of HFP and HRV, or HR and BP at work and at rest).
To adequately cover the full sequence of predictions implied in the “Work/Stress/Disease” process, we propose that at least four levels of tests listed below need to be performed — in an integrated manner (Figure 1).
While multiple levels would apparently add complexity to the research challenge, the fact that the same basic Controller/Controlled relationship is tested at all four stages might allow significant simplification of the statistical modeling structure. Thus, the generality of the SDT predictions could make hypothesis testing feasible in models that might otherwise have an overly large number of disparate associations to test.
This study design could simultaneously measure physiological processes associated with physiological restoration and growth such as anabolic response [52] on the metabolic pathway and the recently discussed bio-feedback-based “strengthening” of baroreceptor response along

\textsuperscript{4} Much current medical intervention can be seen from a logically analogous perspective — applied at the dramatically more micro-level of the body’s extra-cellular fluids: Claude Bernard’s “milieu interior” (internal environment). Acute medical interventions, for example, to raise the blood pressure, oxygenate the blood, add blood glucose, etc. here again are justified by the presumption that “only by changing the (cellular) environment” can the acute medical emergency be averted (returning the cell’s environmental parameters to their “normal levels (i.e., “homeostasis in current medical practice). The problem is simply defined on a much lower physiological level.

\textsuperscript{5} Fig. 1. 4-step Controller/Controlled test.
the cardiovascular output control pathway [53]. However, detailed specification of bio-monitoring methods to assess growth and regenerative effects will have to be addressed in a future publication.

Stage 1. Work social structure and central physiological response

The first step is demonstration of the association between social and psychological characteristics of the work (or other institutional) settings and primary physiological control system functions.

The study design should select a physiological system for bio-monitoring known to have significant effects on other physiological systems: for example the autonomic nervous system cardiac control functions or major psycho-endocrine systems.

The effects of the social environment can be assessed in several ways: (a) are the subject’s skills and capabilities suitable to the demands that are presented? (b) is the subject allowed by the social situation to use skills-capabilities in the manner that they select/see as optimal?, and (c) is the subject able to build up capabilities (internal and external) as they should be able to?

Stage 2. Central control exhaustion and physiological dysfunction

This step demonstrates the association between exhaustion of the central “control capacity” and loss of functionality of a major physiological system — i.e., cardiac output regulation, glucose regulation.

1. Short term effects: reduced control variability in the controlled physiological system.

2. Long-term exhaustion of central control capacity (as measured, for example, by reduced HRV or HFP) is associated with the loss of functionality across many social contexts.

Stage 3. Physiological dysfunction and chronic disease development

This step demonstrates that extended depletion of regulatory effectiveness (from stage 2) increases risk for long-term chronic dysfunction, for example: stable hypertension, diabetes II or metabolic syndrome).

This relationship has already been demonstrated in countless other studies, and can potentially be excluded. However, unique to the SDT formulation for this step are: (a) equilibrium shifts which “lock in” the loss of function as demonstrated by correlated changes in a related physiological system function; and (b) detection of the acute high-level loss of control episodes (P-OTD above), observed as part of the overall monitoring process.

Stage 4. Disease prevalence, work functionality deficits and social burden / prevention benefit

This step demonstrates how strongly the functional deficits from the above chronic disease (Stage 3) are associated with public health significance.

1. The “effect sizes” attributable to each preceding stage can be used to understand the potential public health burden associated either with social risks or with a failure to intervene early in a disease development process. These effects also determine the potential benefits of prevention to be assessed for large population groups.

2. There are social adjustments needed for workers who lose sufficient functionality that they (a) can no longer work, requiring disability, (b) can only be reassigned to work in output-limited job positions, or (c) need “redesigned” work — which may involve even further “loss of control” for the worker than the one experienced in Stage 1.

In this way, the four-step sequence above traces the stages of a “vicious-circle” of poor work design, physiological function deficits, and disability.

SECTION V. TOWARD A LARGE NEW STUDY DESIGN FOR CVD

On the basis of the deficiencies noted in the existing literature in Section II, and inputs from the new theory above, we can sketch an outline of requirements for a Large New Study Design in the context of CVD and related metabolic diseases:
Broader population inclusion

1. A full range of variance in working conditions must be assessed: low status and high status workers, multiple industries. This allows understanding the full cost/distributional implications of work conditions and understanding of both prevention benefit and cost issues.

2. In order to justify prevention strategies (for example intervention strategies to create healthy workplaces) we must understand the risk levels in healthy, working populations — where disease risk is developing, but not yet completely debilitating. It is not sufficient to use clinical populations as in some medical research studies of physiology/disease linkage. This implies that funding must come from both labor protection and medical research public sources.

3. In order to understand the full work/economy disease risk burden, it must be measured at all social levels and types of work (including insecure and marginal work which can be highest in overall economy-related stress).

4. Multi-site studies will probably be needed to insure adequate statistical power to assess proposed physiological mechanisms and insure generality of findings. A good example is the Whitehall study, which has a “full range occupational spectrum”, which is indeed the foundation for the study’s best known conclusions (although it is weak on marginal populations and multiple industrial sectors — which should be supplemented). Both Hemingway et al. and Chandola et al. find indications in Whitehall that many steps on the four-stage design above could be successfully tested (workplace social control, HRV monitoring of autonomic response, hypertension and metabolic syndrome/diabetes II development) [32,54]. These two Whitehall studies provide an example of the “context design” — a model of the Large Population Study — which can serve as the platform for the more detailed physiological monitoring strategies that sit at the core of the SDT integrated model. Both micro and macro levels of assessment should be included to assess the four-stage study structure. In Figure 2, we illustrate how a Whitehall-type design can facilitate understanding the social context of causation and the public health implications of physiological monitoring. However, we might not expect to estimate as precisely as in Whitehall the population prevalences of fully developed chronic diseases.

Applying a broader stress-disease model structure for CVD and metabolic syndrome

Detailed new hypotheses would be a linked set of Four Stages of Controller and Controlled Associations — focused on cardio-vascular and metabolic regulation and function — and would test multiple links in the physiological chain of causation in an integrated manner, with clearly structured, multi-level physiological relationships (bio-monitoring of growth and regeneration is not yet specified in the suggestions below).

Stage 1. Work social structure and central physiological response

Low Workplace Control (and Job Strain) reduce the regulatory response effectiveness of the primary CNS mediated cardiovascular output control mechanisms: High Frequency Power (HFP), PNN50, HRV.

Stage 2. Central control exhaustion and physiological dysfunction

Long-term reductions in HFP (and other Stage 1 outcomes above) reduce the regulatory response effectiveness of heart rate variability (HRV) and change the overall sympathetic/parasympathetic balance. This also affects psycho-endocrine response: affecting cortisol response, and affecting glucose/insulin regulation.

Based on Hemingway et al. [32]

Fig. 2. Context of physiological monitoring within the large population study
One possible test strategy here is to select an “exhausted, but still working population” to compare to a “normal working population” (each population with high and low exposure sub-groups). The hypothesized effect of risk exposure leading to regulatory deficits in the exhausted group would be to push subjects over the threshold from temporary regulatory difficulty, to stable physiological dysfunction (a new, low function “equilibrium”, with interlocking physiological contributions).

**Using a broader range of measures and appropriate analytic strategies to assess exhaustion**

“Stress”, the putative major contributor to a variety of chronic diseases, should be measured in its most intense contexts: the workplace — assessing all its complex organizational demands and social organizational constrains and limited control opportunities — also work-family links, and the broader economic security context of jobs. Life-style risk factors, and standard cardiovascular studies background variables must obviously be also included in this study design (see for example listing of often measured variables in Kristensen; Riese; Theorell et al.) [21–23]. However, since many of these measures are well identified in the existing literature, in this paper we will focus discussion on less discussed measurement problems related to detection of “physiological exhaustion”.

This study design makes use of a set of new analytic tools for analysis of HRV data based on long duration bio-monitoring for assessment of exhausted response of HRV in real time that involves very different analytic methodologies than typical clinical usage of EKG data. Assessment of “exhausted response” in multiple-linked levels of physiological regulation — with clear physiological interpretation — poses a major challenge in data reduction, for which strategies are discussed below.

The SDT provides potential insight into the meaning of variability of response in a self-regulatory context (i.e., it represents the variability of system-regulation intervention episodes), which can lead to new data analytic approaches for assessing variability, and even the “variability of the variability” [55].

**Definition: Exhausted response (exhaustion)**

Controller/Controlled relationships can be tested to assess the validity of the SDT. The Controller System has responsibility to determine the response alternatives of the second system — the Controlled System — to insure optimal function of the full organism, in which they may both be components. In exhausted response, the Controller system has depleted capacity to accurately delimit the

**Stage 3. Physiological dysfunction and chronic disease development**

Reductions in HRV reduce the regulatory effectiveness of blood pressure level stability leading to high blood pressures after long exposure in Stage I/II. At the same time, disturbed psycho-endocrine regulation, affecting cortisol response, leads to unstable blood glucose levels (hyperglycemia) and adverse levels of blood lipids (hyper-lipidemia).

Sustained high levels of blood glucose lead to chronic conditions and organ disease (diabetes II) and adverse lipid regulation (metabolic syndrome and obesity).

**Stage 4. Disease prevalence, work functionality deficits and social burden / prevention benefit**

Sustained deregulation of blood pressure (high blood pressure and diabetes II) reduces human behavioral flexibility needed to maintain an active life — due to development of chronic disease conditions, organ damage and cardiac event risk (hypertension, stroke, metabolic syndrome and diabetic diseases). Estimation of effect sizes, at each stage, allow determination of potential prevention benefits.

In addition, the chronic disease conditions now significantly limit the subject’s “workability”. This in turn leads to the requirement to restructure the social organization of work, where the risks began — probably in such a way as to reduce capacities and opportunities in many organizational contexts, and long-term further reductions in healthy behavior (the feedback loop from Stage 4 to Stage 1 in Figure 1).
functions of the Controlled system. This is because of the Second Law of Thermodynamics limitations: there is no longer sufficient ordering capacity remaining for the Controller to do its job (its Neg-entropy available for transfer is depleted).

For example, the variability of the heart rate has been shown to determine the ability of the blood pressure to assume the level most functional for the organism as a whole (allowing it to rise and fall with resting/standing). Low heart rate variability is a marker for orthostatic hypotension (where such adjustments are too slow).

Methodological issues measuring exhausted response (exhaustion)

Multiple contrasts between exposure and restoration

In order to investigate “exhausted response” in healthy, exposed and exhausted subjects and periods, a regulatory effectiveness “spectrum” utilizing multiple contrasts between Work, Waking, Sleep, Rest and high and low Job Stressors (low job control, job strain) exposures — reflecting different time durations — will be assessed using standardized “exhaustion profiles”. A variety of modeling methods might be used in new ways: repeated measures ANOVA, hierarchical modeling, network analyses, etc.

To scale the magnitude of work-related exhaustion, a regulatory effectiveness “spectrum” utilizing multiple contrasts between high and low job stressor (job strain, low control) exposures — reflecting different time durations — needs to be assessed:

- Short period: High job strain task vs. low job strain tasks (via daily dairy).
- Short period: Response to standardized and self/controlled stressors: glucose load tolerance tests.
- Midrange: Awake vs. Sleep (plus other sociological periods differentials: morning at work; post-dinner evening at home, etc. see section below).
- Long period: Work day vs. Rest day.
- Between-subject, Long period: High job strain jobs vs. low job strain jobs.

Sociological period boundaries

Sociological Period Boundaries — based on waking up, sleeping and major meal-times (i.e., at work before lunch, at work after lunch, after work before dinner, etc.) — have been used effectively in our research to define periods in which the variance of physiological response levels and their correlation is to be assessed. There is a presumption that there are different activation levels between categories, and relatively homogenous activation levels within the categories — differentiating across subjects more consistently than absolute times of the day (typical of 24-hour circadian rhythm studies).

Parameters of healthy response

1. Slow response to stressors

Slow responses to stressor can indicate illness: a depleted capacity to respond, due to an exhausted physiological system at some level (this process is described in detail by Selye at the General Adaptation Syndrome, wherein slow, depleted response is the third stage of reaction to chronic stress exposure (a) after initial shock exposure, and (b) long-term stress response with effective reaction.

2. Quick return to baseline

Healthy response also implies a quick return to baseline after dealing with stressor exposure. This “economic response” allows many demands to be encountered. A very delayed return is a mark of exhausted response, but the question of how long is too long must be answered by research on scaling response to known stressors or rest periods. A very long return to baseline is equivalent to chronic disease in the Stress-Disequilibrium perspective.

3. Limited range of control response

Another measure of exhaustion is the inability to maintain the accuracy of response: this is a direct prediction of the SDT use of the Second Law of Thermodynamics, where as response demands deplete ordering capacity, response becomes increasingly less precise. Low strain, non-exhausted subjects have been shown to have significantly greater cardiac vagal control range and variance when compared to high strain and exhausted subjects [54].
SECTION VI. DISCUSSION:
TRADE-OFFS IN STUDY DESIGN

Summary
Our preliminary claim is that a more thorough understanding of the expanding global chronic disease burden for cardiovascular disease (CVD) and related conditions such as diabetes II, metabolic syndrome, and obesity require a new study design structure, related to a new level of stress-related disease theory that goes beyond current single-factor, atheoretic epidemiological study design.

We find consensus that there is social causation involved in this expanding new disease burden, and that while it is likely to be “stress-related” to a significant degree, the pathway of illness causation may involve the individual’s lack of control in social environments, at least as much as the demands of the situations themselves.

We can summarize the reviews of literature by saying that (a) partial models of the disease causation process, (b) partial measures — including insufficient understanding of the time dynamics of exhaustion, and (c) partial populations studies in most research have resulted in fragmented understanding and limited progress in the area.

While stress theory implies integrated physiological processes, our empirical evidence has lagged far behind the challenge of these integrated models.

Further review of the current status of stress theory has illuminated the need for a “low control based” model of the stress-disease development process. Here, the SDT is presented as a candidate theory, based on social situation induced limitations in physiological self-regulatory effectiveness that can lead to disease.

Specifically, the SDT can at least supply more detailed hypotheses to test the “work-stress-disease” process. The SDT provides explanation of how low control could lead to chronic disease through threatened self-regulatory capacity, which can be tested in (a) a hierarchical sequence of multi-level Controlled/Controller relationships, (b) the explanation is based on cycles of build up and exhaustion of regulatory capacity that should also be detectable in bio-monitoring, and (c) SDT provides potential insight into the meaning of the variability of response in a self-regulatory context that can be tested using new data analytic methods. Further along the chain of disease causation, SDT provides two pathways for measurable developmental stages: (d) either control capacity deficits leading to “locked in” coordination of a new physiological equilibrium of low functionality, or (e) transitory high-level control capacity deficits leading to acute high-level regulatory failures. Finally, the generality of SDT hypotheses, and its similarity in simplified form to the well-studied Demand/Control model hypotheses, suggest at the social level (f) which work (or other social) situations could cause risk, and (g) which combinations of preventive social interventions could be proposed — hopefully via a study such as this — and (h) how estimates of the benefits of such actions could be understood.

Translation of the SDT principles into new study design parameters leads us to a description of a study that has:

1. Dual physiological pathways: one through autonomic control of cardiac output, and another through autonomic control of glucose regulation to trace steps from social risks at work, through disease development process stages, back to social consequences of disease on working populations.

2. A four-stage design with four levels of Controller/Controlled relationships to assess health/exhaustion of physiological response to the environment at different stages in the disease development process (Figure 1). Analysis of the transition from exhausted response to physiological dysfunction and disease on the basis of time-related study design contrasts and differential follow-up periods / intake health status.

3. A full-occupation-spectrum healthy working population large enough to assess disease development outcomes, with nested bio-monitoring and reliability studies.

Epidemiological Design Trade-Offs
Design of such a study in practice will involve many trade-offs. The framework will be a large prospective multi-center epidemiological study linking, including preferably industry/factory-based samples or working population-based samples, representative of a large spectrum of work activities. Baseline variables should be investigated, including...
job-strain and metabolic risk factors. Ideally, the enrolled subjects should be re-screened for baseline variables at time intervals (three-four years). The number of people involved should be large enough to generate in a relative short period of time (five-six years) at least 300 incidence events, even if the entire follow-up period should be at ten years. This design allows us to look at the associations between exposures and the coronary heart disease incidence exploring the direct effect of job stress as well as the effect mediated through other risk factors.

Within this wide-spread study, nested studies will be foreseen to explore, on selected sub-samples: (a) in depth clinical examination of subjects in the extreme stress/strain-exposure classes to assess the relationship between chronic job strain and exhaustion from one hand and HRV, cortisol and catecholamine levels, ambulatory blood pressure and glucose and insulin bio-monitoring on the other hand; (b) reliability studies for HR/autonomic control.

**Design Alternatives: Measures**

More Outcomes vs. More detailed Bio-Monitoring

Co-morbidity is not only clearly evident when low status populations are at higher risk for multiple disease conditions [19], but also when current research shows common prevalence of CVD, metabolic syndrome, diabetes II, and obesity — as well as overlapping risk factors for these conditions [32]. Furthermore co-morbidity is almost a logical prerequisite for testing stress theory etiology’s unique form of causality — which involves multiple stressor risks “causing” multiple disease outcomes [44]. This “non-specificity”, originally so prominently identified by Selye, is a marker of the more generalized stress-etiolog- ical “causal” processes, whereas in more conventional epidemiological research such non-specificity is considered to clearly weaken the case for causality (i.e., in occupational cancer epidemiology).

The trade-off is that if Stages 2 to 4 (above in Section III) hypotheses are to be tested, many forms of resource-intensive bio-monitoring must be employed, which may limit the size of the study population. For example, understanding co-morbidity may require CVD autonomic control monitoring (HR monitoring), CVD physiological function monitoring (i.e., blood pressure regulation), long-time duration monitoring to detect exhaustion effects — as well as detection of metabolic disease based on glucose and insulin bio-monitoring, dietary pattern, and metabolic pathological condition data collection.

Alternatively, a large enough sample of subjects could be selected so that clear disease case status prevalence changes could be detected for major outcomes such as chronic hypertension and diabetes II — or potentially even for CHD events and hospitalizations after long durations of follow-up. However, in this case only one disease area could be monitored (no co-morbidity) and perhaps long-term follow-ups could not be afforded, which could detect the transition from exhausted autonomic regulation to stable system dysfunction.

**Long term vs. short term measurements**

Long-term monitoring is far more scientifically useful than short-term monitoring, but also more expensive and potentially burdensome for subjects. How much monitoring shall there be? It was noted above that the physiological interpretation of the 24-hour HRV Holter monitoring differs in interpretation from short-term EKG recording used for clinical assessment of cardiac dysfunction, and that even in the long-term monitoring context, the monitoring epoch length has an effect on possible physiological interpretations that may be made. Furthermore, although 24-hour monitoring can demonstrate association between exposures and the coronary heart disease incidence exploring the direct effect of job stress as well as the effect mediated through other risk factors.

Design alternatives: Populations

Only clinical populations

In order to justify prevention strategies (for example intervention strategies to create healthy workplaces) we must understand risk levels in healthy, working
populations — where disease risk is developing, but not yet completely debilitating. It is not sufficient to use clinical populations, as in some medical research studies of physiology/disease linkage.

The majority of studies of stress-relevant complex cardiovascular physiological response are actually undertaken in clinical populations (but these studies are not discussed in this paper). However, the studies we cite in the literature reviews above include detailed bio-monitoring, but the sample is often a very limited, albeit “healthy”, group of working subjects. Alternatively, the Whitehall study, for example, has a very large and rather diverse population sample and furthermore, has collected significant physiological data. Nevertheless, the physiological data typically involves “one time” measurement (plus one time again at follow up) and would be insufficiently detailed to test our hypotheses. We need real-time bio-monitoring of healthy response compared to exhausted response to stressors, in working (i.e., “healthy”) populations, for the current paper.

This implies that funding might have to be sought from both labor protection and medical research public sources for a study of the type we suggest. Medical research support institutions may fund studies of the physiological evolution of disease, but have less interest in spending large sums to bio-monitor healthy populations. Meanwhile, labor protection ministries may be willing to assess the frequency of problematic work conditions in a representative sample of workers, but can consider physiological monitoring to be either beyond their competence or a potential ethical threat to workers’ personal health status information.

Single occupation studies
While there may sometimes be governmental policy priorities that target single occupations for study because of suspected high risks, this is a problematic approach from this paper’s perspective. Single occupations represent fixed positions in organizational hierarchies, and thus the limitation of the study to a single occupational group substantially limits the variance on a variety of psychosocial workplace risks. This limitation was particularly well illuminated in the Whitehall study, as a full occupational gradient was needed to separate the correlated effects of social status in a generalized meaning from those of job decision latitude. A major message of Whitehall then became the separate effects of low control on CVD.

Single occupation studies lack sufficient psychosocial exposure variance to allow testing of main or interactive effects of psychosocial factors, making it difficult to generalize typical physical exposure-based occupational health findings (above noted EMF studies by Bortkiewicz et al. and Szmigielski et al.) [38–41].

The adverse effect of a limited range of job characteristic variance was also clearly illuminated in the Collins, Karasek, and Costa study [29]. Before using the full-population mean value to determine cut points for the demands and decision latitude scales to define the high risk subjects, which was initially based on the recruited sample’s screening stage risk levels, the “high exposure” group was found to contain only “low exposure” subjects. However, once the full range of population variance was used instead, to determine risk group boundaries, recruitment efforts for “high exposure” could be improved so that the sample had sufficient exposure variance for observing main effect contrasts.

Benefit calculations
Given the important statement made at the paper’s beginning: that there was little disagreement that some social factors were causing the increasing chronic disease burden, then the critical questions are both “what is the cause,” and what level of intervention in such a social cause could yield what level of decreased disease burden. The current costs are enormous but social prevention strategies, particularly those involving work organization and economic structure change, are not yet widespread. How much do we really lose as a society by these “pragmatic” omissions? How much is to be gained by the society if its companies re-organize to create healthier work processes, or in fact how much is to be gained by the companies themselves in reviewing these long-term benefits, instead of more common short-term economic goals?

Since there are no absolute measurement units for psychosocial work organization characteristics, often the benefits to be obtained by social change interventions
have been stated in terms such as these: “a half a population level standard deviation unit increase in job decision latitude would produce a prevalence decrease in CVD of “x”[44; pps, 152–3 and 166–7][56]. However, we need scale variations from full population samples to motivate such claims, and we should be able to check them in a variety of sub-populations as well. For example, it is noted that the healthiest overall population could easily result from a reduction in decision latitude at the very top levels of the occupational spectrum — also hardly a claim that could be made without full population samples to review [44].

Marginal populations
Many occupational epidemiology study protocols exclude marginally employed populations as a component of the study design in order to insure uniformity of exposure to the targeted risks. But here lies a major problem. Often, these are the subjects with “precarious work” — temporary, seasonal jobs, or with recent unemployment risk or experiences — who are the “most stressed”. However by definition their marginality makes them difficult to recruit and retain in studies. Individuals “too stressed” to participate in a complex university hospital bio-monitoring study are precisely the ones who should be most intensively recruited. However, with labor market changes following the prescriptions of the free-market policy orientation that has become more dominant in the last decade, these marginal or “irregularly-linked-to-work” groups are becoming a larger percentage of the population.

The Collins, Karasek and Costas study found that when a normal population, screened for high and low strain jobs was recruited for the study, the first research population had a sample consisting almost entirely of low strain subjects (see also the cut point explanation above) [29]. The study recruitment had to be “redone” to actually recruit the “exposed” population. Recruitment of the high strain population — very often hostile in response and almost always too busy to be interested in participation — was only obtained after major efforts to ease the burdens of the monitoring process were offered (along with large financial incentives). Without the exposed population, the study initially produced only null findings.

How many other studies in medical research have failed to recruit these types of subjects? What do we then learn about either stress response or differential response in stressed vs. non-stressed populations from this research?

Excluded conditions
Perhaps the most recently developing and potentially difficult problem for this paper’s approach is also an increasing problem for many other public health studies assessing social risks. The conventional CVD study protocols exclude subjects on pharmaceutical treatments or with other indications of disease conditions — but these specifications could now cover such a large segment of the populations in some countries that the exhaustion hypotheses may be difficult to test. This is partly the result of the increasing prevalence of medication in countries such as the US. Rather than identifying the primary causal factors in a social chain of disease causation to aide “prevention” goals, pharmaceutical treatments deliver secondary or tertiary care. But these treatments have recently been advocated by medical groups to cover larger and larger populations — for “prevention reasons” seen from their viewpoints (i.e., the prevention of even more serious levels of disease among those already entered in the health care system).

Ironically, this non-primary prevention makes it difficult to gather a sample to demonstrate the efficacy of primary prevention: too many of the borderline subjects are already too drugged to be studied. For example, identifying the exhausted groups (Stage 2B, paragraph 2, in study design, Section 5 above) who are still healthy enough to work for the purpose of demonstrating the transition from exhausted primary regulation to stable dysfunction, could be difficult in a study that excluded any subject with the following typical list of conditions: “[…] diabetes mellitus, tetraplegia, arrhythmias and/or consumption of drugs such as alphalithic drugs, anti-arrhythmic drugs, sartans, ACE-inhibitors, digoxine, antidepressive drugs, benzodiazepines.

Who shall we include and whom shall we exclude in stress-focused field research? Diligent population selection and recruitment methods will be needed to overcome these
last mentioned hurdles, if we are to effectively reap benefits from the “large study design” here presented. Perhaps this further elucidation of the study’s challenges, relating to increasingly medicated and increasingly work-marginalized populations (both potentially putative consequences of failing to address the primary risks here discussed), simply serves to emphasize the increasing costs of failing to understand the social causation of illness process well enough to answer the full set of questions now posed in our field — without further delay.

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