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Stress And The Diabetes Mind: Job Loss Predicts Cognitive Function In The Health And Retirement Study

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Abstract

Introduction

Diabetes is a proposed cause of dementia and age-related cognitive decline. While the effects of hyperglycemia, insulin resistance, and hyperinsulinemia are well-known, scholarship tends to neglect distinct but related pathologies, such as chronic stress. The purpose of this study is to evaluate whether a common proxy- mid-life involuntary job loss- is associated with reduced cognitive function among a cohort of diabetics. A second objective was to determine if age of diabetes onset moderates this relationship.

Methods

This cross-sectional study gathered diabetes data from the 2003 Health and Retirement Study (HRS) Mail Survey on Diabetes, while measures of cognitive function (HRS-Cog) and socio-demographic variables were assessed in the 2002 and 2004 HRS waves. Multivariate regression was used to analyze the impact of job loss on cognitive function between 1992 and 2002 among 153 job losers and keepers with complete data for employment history, the 35-point HRS-Cog, age of diagnosis, and glycemic control (HbA1c).

Results

Job losers scored 1.52 points (-3.28-0.24, $p<0.09$) below keepers in the best fit model, adjusted for age of onset (<=55, >55) HbA1c quartiles, sex, education, hypertension, and retinopathy. Age of onset did not moderate the association between job loss and cognitive function (β = -2.15, CI: -3.89- -0.40; $p=0.016$); sex, however, was solely responsible for the reversed, non-significant association in model two (β = -0.37, CI: -2.17-1.43; $p=0.687$). Adjustment for all covariates eliminated the significance of the job loss differential, as well as the effect of onset. Retinopathy, education, and sex remained significant across all adjustments. Finally, the significance of job loss and onset was independent of each other and their magnitude comparable across most adjustments.

Discussion

The relationship of involuntary mid-life job loss to cognitive function may reflect the myriad effects of chronic stress. Even after controlling for well-established predictors of cognitive decline, the impact of job loss was comparable to the timing of diagnosis. Because the significance of these two variables, as well as retinopathy, remained when modeled simultaneously, the effects of stress may involve unique and systemic pathways. Furthermore, despite strong moderating effects from gender, the magnitude of the coefficient on job loss and the relatively young cohort are evidence for the hypothesis of premature aging. This study demonstrates that appropriate interventions may benefit high-risk groups such as those with type II diabetes and that cortisol could be a viable co-factor related to cognitive function.

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Introduction

A unique set of pathologies links type II diabetes (DM) to dementia and age-related cognitive decline (ARD). Insulin resistance and hyperglycemia, a common cause of vascular disease, share the same molecular basis with the formation of the neurotoxic beta-amyloid protein, and with neurofibrillary tangles, the pathological hallmarks of Alzheimer's disease (AD) (Dore et al., 1997; Luchsinger, 2001). The greater hippocampal and cortical atrophy observed in AD patients with DM compared to non-diabetic age-matched controls, however, was found independent of vascular disease and glycemic status, suggesting the importance of variations in insulin resistance (den Heijer et al., 2003). The pro-survival PI3K-PKB insulin signaling pathway delays neuronal death and, when unresponsive, may accelerate the transport of toxins across the blood-brain barrier (Cole et al., 2006). Among the pathologies that affect this pathway, chronic stress is unique, since glucocorticoids also alter the function of monocytes that inhibit beta-amyloid (Cukierman et al., 2005). The current study, therefore, aims to determine whether stress is a viable candidate to explain the dramatic course of cognitive decline found in DM.

Diabetes and Dementia

A disease of impaired glucose metabolism, DM is estimated to increase risk for cognitive impairment roughly two-fold (Duron & Hanon, 2008). While research supports a generalized cardiovascular complex, including systolic hypertension, high serum cholesterol, and atherosclerosis, diabetes is a global epidemic that entails distinct pathology (Korf et al., 2006). The anticipated "aging of the population" warrants examination of factors such as stress that potentially change the pathogenic relationship between DM and dementia. Estimates, for instance, show that the 65 and older U.S. population will have increased from 18 percent in 2000

to twenty in 2030, and then finally to 1 out of 4 by 2070 (D.R. Williams, 1997). The consequences of these figures to public health and health care in general are evident: the prevalence of DM and dementia will increase sharply through late adulthood (NHANES, 2011). Treatment and care for dementia currently exceeds $600 billion worldwide, or 1 percent of global gross domestic product. DM prevalence in 2010 was approximately 8 percent in the general population but 26.9% among those 65 and older- a 100-fold difference compared to the 0.26 percent of those 20 or younger (ADA, 2011)! Importantly, DM could explain a significant proportion of the expected rise in dementia cases from 40 million today to 115 million by 2050 (ADI, 2010). Therefore, one of the most effective ways to inform national aging policy and public health preventions is to identify specific DM processes and their relation to ARD.

Diabetes, Stress, and Aging

Though hyperglycemia exposes the brain to higher concentrations of AD-related toxins, the latter are still found in the brains of middle-aged diabetics who show no signs of cognitive impairment or neurodegeneration (Li et al., 2005). This limitation is illuminating, since high blood glucose coincides with elevated levels of neurotoxic proteins *and* enhanced permeability within the vasculature itself (Abbott et al., 1990). Moreover, macrovascular (cerebral infarction, peripheral arterial disease) and microvascular (lacunar infarction, arterioscelerosis) lesion pathology is associated with amyloid deposition in vivo, as well as with higher rates of oxidative stress *independently* of hyperglycemia (Whitehead et al., 2005; Oddo et al., 2003). These findings imply that a "second hit" may be necessary to induce neurodegeneration and associated cognitive impairment.

An alternative explanation for glycemic status and vascular disease is insulin resistance proper. While glucocorticoids (primarily cortisol) exacerbate the poor use of insulin, a sizeable number of DM patients may suffer from the withdrawal of cellular signaling that normally protects neurons from a range of insults (Biessels et al., 2006). Equally important is the observation that defects to the insulin-mediated pro-survival pathway overlap with the processing of amyloid-beta and neurofibrillary tangles (Lester-Coll et al., 2006). Though hyperglycemia and hyperinsulinemia facilitate the movement of these toxins across the brain parenchyma, extreme insulin resistance may be more detrimental, as growth factor resistance and plasticity could decline, and protein synthesis accelerate even further (Salkovic-Petrisic, 2006). Within this causal milieu, cortisol can introduce comparable actions; conversely, cortisol could interfere with lymphocyte- and monocyte-mediated detoxification (Whitmer, 2007; Sapolsky, 1999). Finally, it is possible for insulin-mediated growth factor production to remain intact, but for damaged macrophages and Schwann cells to extract insufficient trophic hormone for cellular regeneration (George et al., 1995; Chaudry & Cornblath, 1992). In other words, the cellular regenerative process could remain at least partly functional when insulin-related growth factors do not (Lucas et al., 2001; Stoll & Muller, 1999). Collectively, these outcomes may be more predictive of memory and learning deficits than the similarly diverse effects of hyperglycemia and hyperinsulinemia.

In summary, a significant body of evidence justifies the analysis of stress as a unique and independent etiological agent on the pathway from exposure (DM) to disease (dementia). In addition, observational and psychological studies note lower working memory scores for DM patients and for subjects with a self-reported history of distress (Lupien et al., 1998). Despite the fact that mid-life stress is already a well-established contributor to vascular disease from stroke

to hypertension- conditions already known to affect cognition- few studies have examined whether major adverse events interact with critical markers of chronic disease pathology, such as glycemic control (Hipple, 1999; Turner, 1995; Brenner, 1997; Matoba et al., 2003). As the most common neurodegenerative disorder, AD is indeed often described as a neuroendocrine disorder, as well as a disease of impaired clearance (McDonald et al., 2010; Fontbonne et al., 2001).

Stress and Job Loss

The current study uses middle or late life involuntary job loss as a proxy for chronic stress. This adverse event is a well-established source of chronic psychosocial adversity (Gallo et al., 2004), and often precedes income, health insurance, and pension severance, as well as termination of social support in the workplace and uncertainty of reemployment (Chan & Stevens, 2001; Fallick, 1996). These changes often coincide with lowered perceived behavioral control (Goodman, 2003) and substance abuse (Price et al., 2000). (The former is associated with higher cortisol even when controlling for genetic and environmental factors.) Within the present context, involuntary job loss follows plant, business, or factory closure, and financial or operational downsizing. Iversen (1989), for instance, found shipyard workers were at higher risk for cardiovascular hospital admission after their worksite closed. More recently, Gallo & colleagues (2006) linked late-career job loss with a greater than two-fold increase in both myocardial infarction (HR: 2.48; 95% CI: 1.49-4.14) and stroke (HR: 2.43; 95% CI: 1.18-4.98). As several authors note, both the psychological and physical aspects of involuntary job loss reflect health outcomes associated with chronicity rather than with the buildup of daily hassles or acute challengers (Kirschbaum & Hellhammer, 1994). These results indicate, at the least, a face valid proxy.

The specific objective of this study was to evaluate the association between middle- or late-life involuntary job loss and performance on a telephone-administered test of cognitive function among a nationally representative sample of diabetics. The main hypothesis was that job losers would score significantly lower than keepers. As the most comprehensive population-based longitudinal study on health and aging in the United States, the Health and Retirement Study (HRS) is currently the only dataset that samples sufficient numbers of older diabetics, as well as collects extensive information on employment history, physical health, and cognitive performance.

A second objective was to test the hypothesis that age of onset moderates the relationship between employment status and cognitive performance. Specifically, it was speculated that a variable for the timing of DM diagnosis would capture extreme insulin resistance adequately enough to reduce the job loss coefficient, and that this effect would exist regardless of glycemic control. As previously mentioned, research has shown that severe insulin resistance is sufficient to cause death to a diversity of neurons, and, as importantly, that age of onset may reflect this pathology even when controlling for DM duration (Falkingham & Namazie, 2002). Recent studies have also found timing a more significant predictor of cognitive impairment than a diagnosis alone (Breitling et al., 2012). That is, upon adjustment, differences on COGTEL scores (an instrument similar to HRS-Cog) virtually disappeared between those with and without DM.

Methods

Study Design and Data

This cross-sectional study gathered data for diabetes-related variables from the 2003 HRS Mail Survey on Diabetes, while scores on the 35-point HRS cognitive measure (HRS-cog) were collected in 2002 as part of the HRS Cognition Imputations (1992-2008). The Health and Retirement Study is a nationally representative longitudinal cohort study that samples over 20,000 adults aged 51 years and older biennially. It is administered through the Institute for Social Research at The University of Michigan and funded federally by the National Institute for Aging. The objective of the Mail Survey on Diabetes was to gather self-reported questionnaire data on factors relevant to treatment and self-management, as well as to collect a marker of glycosylated hemoglobin (HbA1c) for measuring blood glucose control. Study instruments were validated at the Michigan Diabetes Research and Training Center, while HbA1c was assayed by Flexisite Diagnostics, Inc. A detailed description of the sampling methodology of both surveys is available elsewhere (HRS, 2003).

The sample criteria for the current study required that participants meet *all* of the following conditions: a self-reported diagnosis of diabetes in the 2002 HRS wave; complete information from the 2003 HRS Mail Survey on Diabetes for age of diagnosis and HbA1c; complete data for employment history from 1992 to 2002; and complete scores on the 2002 cognitive assessment from the HRS Cognition Imputations (1992-2008).

A total of 3,194 respondents reported diabetes in the 2002 wave. From this group 2,385 participants were deemed eligible at the start of the 2003 Diabetes Survey, after which 1,901 mail surveys were returned (79.7 % response rate) and used for analysis. Because the 2003 participants were required first to self-report diabetes in 2002, incident cases between assessments were automatically excluded. This allowed self-reported diabetes to be evaluated as a precedent of cognitive performance in 2002.

Access to the 2003 HRS Mail Survey on Diabetes was approved by the Behavioral Sciences Committee institutional review board at the University of Michigan, while the 2002 HRS wave is available freely to the public. Respondents for both surveys were linked by unique household and personal identifiers that maintain anonymity.

Primary independent variables

All participants who self-reported diabetes in the 2002 HRS Core and returned the 2003 Survey were eligible for analysis. From the 1,901 participants who returned mail surveys, 1,180 had complete data for age of diagnosis, HbA1c, and employment status. The HRS Core has a distinct section for job history, including reasons for leaving and changing employers. As a binary indicator, involuntary job loss was defined as a self-reported plant, factory, or business layoff between the HRS 1992 baseline and the 2002 follow-up. As the calendar year is not recorded for job loss prior to 1992, the exclusion of prevalent events effectively reduced the bias of including those from early and middle adulthood. However, this also resulted in the removal of potential prevalent late life events among older members of the sample. Since the vast majority of elders (65+) were retired at baseline, and thus ineligible for analysis, and because the final sample was limited almost entirely to those who were between 51 and 57 in 1992, this bias is likely insubstantial.

Participants were considered "exposed" and included in the job loss/stress group had they reported employment at baseline, followed by job loss at any of the subsequent five waves. These respondents were also required to have self-reported involuntary job loss at the 2002 HRS wave, thereby assuring they were truly exposed when the dependent measures were obtained. The HRS uses a particular question to assess the cause of unemployment among those who cite

disruption in their work lives: “Did the business close, were you laid off or let go, did you leave to take care of family members, or what?” The present study distinguished those whose sole response was “laid off/let go” from those who attested either to voluntary transition (i.e. on temporary leave, resignation for a better job, retired, etc.) or to departure for medical or personal reasons (i.e. disability or family crisis). The job loss group further excluded the self-employed and the re-employed following loss. However, anyone who began working for a new employer during the 10-year period and who later selected “laid off/let go” was also included.

The comparison group included only respondents employed at baseline and at each subsequent wave up to 2002. (This was considered an effective way to avoid “the healthy worker effect.”) The comparison included job changers and those on temporary leave. Individuals, however, were excluded had they reported retirement, self-employment, or departure on account of illness or disability, regardless of future job gain. Reporting events before 1992 was also grounds for disqualification. Since access to medical care might have differed across employer, insurance status at the time of diagnosis and at the 2002 wave was assessed. An indicator variable was then created comparing those with insurance at both times to those without.

Although the sample was expected to have varying times of diagnoses (both before and after the event), limiting the exposed to a single temporal sequence might have produced insufficient counts. The overwhelming majority (> 90 %), however, reported diagnoses prior to job loss, thus enabling interpretation of how a significant chronic stressor might *alter the vector* of an existing condition of self-reported DM. Because the objective was to evaluate the effects of a stressful event on the diabetic process in general, self-reporting “laid off/let go” before or after diagnosis remained the inclusion criterion. Moreover, to differentiate job loss that reflected

the worsening of chronic disease, participants were excluded if they regarded their illness as a source of occupational challenge.

Glycemic control was measured with an HbA1c Home Test Kit. Of the 1,901 returned surveys, a total of 1,233 valid blood samples were obtained, yielding a response rate of 64.9 percent. Quartiles ($\leq$ 6.3, 6.4-6.9, 7.0-.7.8, > 7.8 mg/dL) were constructed to characterize the sample's measurements, where the highest range was associated with hyperglycemia, and the lowest hypoglycemia.

Model Covariates

Adjustment variables and potential confounders were chosen for their strength of association with cognitive function in the literature, as well as for their bivariate relationship within the sample itself. Socio-demographic data was derived from the 2002 HRS and included age, education, sex, and health insurance. Income was derived from the 2002 Core Income and Wealth Imputations, and comprised all earnings, including labor and investment income, as well as pension accrual. The small number of occupation codes rendered the job class distinction unfeasible. However, prior analysis and imputations with this sample and others show that sex, net earnings, and education are more significant predictors of test scores (Fisher et al., 2012), while blue-collar occupation in the HRS is relatively low (< 30 %) as a whole (Gallo et. al, 2006). Smoking status (never [ref], former, current) was collected in 2002, as well as the self-reported presence of hypertension, high cholesterol, congestive heart failure (CHF), retinopathy, and stroke or transient ischemic attack (TIA). Participants were asked specifically, "Has a doctor ever diagnosed you with [condition]?" Lastly, the Diabetes Survey gathered information on use of insulin and oral hypoglycemic medication.

Primary outcome variable

Cognitive function was evaluated on a 35-point scale (HRS-Cog) modeled after the Telephone Interview for Cognitive Status (TICS), a population-based instrument closely resembling the Mini-Mental Status Examination (MMSE). The HRS-Cog is part of the HRS Cognition Imputations (1992-2008), which consist of immediate and delayed recall tests; a backwards-count from 20 test; a common knowledge test to measure orientation; and a serial-7 subtraction task to measure working memory. Research has shown this test to predict several outcomes, including greater likelihood of nursing home admission (Banaszak-Holl et al., 2004). Because these tests were conducted biennially, a sensitivity analysis was also performed with HRS-Cog data from the 2004 wave. This supplementary analysis was considered appropriate, as some variables (e.g. HbA1c) were gathered after 2002, even though meaningful change is unlikely between successive years (Albright et al., 2001).

Data Analysis

The sample is described by means and standard deviations for continuous variables and frequencies for categorical. Multivariate regression was used to assess the relationship between job loss and cognitive function. The unadjusted model in Table 3 included the independent effects of the three primary study variables, including age of diagnosis and HbA1c quartile. The partially adjusted model 2 was further corrected for age, education, sex, diabetes medication, income, and insurance. Finally, the fully adjusted model comprised smoking and established vascular risks, where factors achieving a specified significance (< 0.20) were initially included but later removed (< 0.15). Variables that altered the coefficient on job loss by greater than 10

percent were retained in the fully adjusted models from both tables. All analyses were conducted in SAS 9.2.

Results

Characteristics of the Sample

A total of 1,180 participants had complete information for employment history, age of onset, and HbA1c levels. Subsequently, forty-one reported work at baseline followed by involuntary loss and 212 stated continuous employment from 1992-2002. The majority of the remaining 927 were retired, but a few were disabled, self-employed, or on temporary leave. The characteristics of the sample are shown in table one. Job losers were slightly older (63.5 v. 61.8, respectively) than their counterparts at the time of assessment, while both groups were significantly younger than the diabetic sample as a whole. The comparison group was more likely to be female (39.7 % v. 23.1 %), to be insured (89.2 % v. 76.3 %), to use oral diabetes medication (72.2 % v. 51.9 %), and to have hypercholesterolemia (69.6% v. 55.0 %). Job losers had significantly higher HbA1c readings (7.7 v. 7.2), an earlier age of onset (50.4 v. 52.9), as well as a higher prevalence of current or former smoking (70.0 % v. 60.7 %). Over half the comparison group had obtained a college degree or more, while job losers were more likely to have a high school degree or less (58.6 % v. 50.0 %), even though a greater percentage lay above the $14,250 median for income (53.7 % v. 36.8 %).

From the 253 participants who met the criteria for inclusion into either the job loss group or the comparison, 153 had complete scores on the HRS-Cog. Five of the 41 job losers and ninety-five of the controls did not complete the cognitive assessment. The 100 excluded were more likely to be younger ($M = 59.9 \pm 8.2$), to have an earlier age of onset ($M = 50.4 \pm 13.9$), and

to have hypertension (74 %). The five excluded job losers were no more likely than the 95 keepers to have a diagnosis above or below the median ($X^2 = 0.251$, p=0.635).

Association with Cognitive Performance

Job losers scored roughly two points below the comparison in the unadjusted analysis (22.8 v. 24.9, p <.017). A similar differential surfaced between those diagnosed before and after age fifty-five (25.5 v. 23.6, p <.014). Neither the scores of the highest HbA1c quartile nor the intermediary quartiles were significantly better than those of the lowest, while a college degree or more conferred a clear advantage, as performance was over five points higher compared to reference (26.2 v. 21.0, p<.001). Higher income (> $14,500) was also beneficial (25.1 v. 23.3, p <.130), and females tended to score higher than males (25.5 v. 24.1, p <0.001). Diabetics who had never smoked (25.6 v. 24.0, p=0.210), and who had hypertension (24.9 v. 23.6, p <.110) or high cholesterol (24.9 v. 23.8, p <0.200) fared superiorly, though these differences did not reach significance.

Table 3 shows that job loss ceased to be significant within the partially adjusted model two. Sex alone accounted for this effect, while education (p<.0001) remained the most significant predictor. The fully adjusted model three recovered this association moderately (-1.18, p = 0.231), where changes to the coefficient were most noticeable upon the inclusion of retinopathy (-3.00, p <0.027). When HbA1c was added, the lowest quartile ($\leq$ 6.3) was clearly associated with the poorest function, whereas the second (6.4-6.9) the highest (1.63, p <0.098).

The best fit models from table 4 indicate that neither onset nor glycemic control moderated the primary study relationship. In fact, the second model demonstrates that job loss became more robust (-2.32, p=0.013). The final model relates this loss to a 1.5 point decrement (-

3.28-0.24, p <0.09), or roughly equivalent to the effect of gender (-1.42, p<0.05). The highest level of education (5.34, p<0.001) and retinopathy (-2.25, p<0.063) were again the most significant. When sex was removed, the magnitude of unemployment peaked (-2.71, p<0.003).

Closer analysis revealed no sex difference among the exposed (23.7 v. 23.6, p = 0.990) but a marginally significant protective effect for females within the comparison (24.5 v. 25.7, p <.095).

Sensitivity Analysis

Repeated analyses were conducted with data from the HRS 2004 Wave of Cognitive Imputations. Though the sample size was smaller, scores were still significantly higher (24.8 v. 22.8, p<.056) among job keepers. Age of onset was also a significant determinant of cognition (24.9 v. 23.1, p<.041), while glycemic control was not (F = 1.13, *3*, p=.343). After adjusting for onset, the association between cognition and job loss declined slightly (-1.62, p=0.136), though sex again had the largest effect on the coefficient (0.41, p=.843). After controlling for retinopathy, hypertension, high cholesterol, and smoking, job loss gained predictive power (-2.46, p<0.036). Age and education were the only other variables to alter the association appreciably.

Discussion

To the extent that abrupt and prolonged unemployment captures psychosocial stress, the current results have several interpretations. A significant stressor was related to poorer cognition independent of age of onset and a clinical marker of glucose control. This association persisted after adjustment for hypertension, high cholesterol, and retinopathy, all vascular processes that overlap with stress. Research often cites delayed recovery from chronic disease, but elevated

cortisol has several effects: upregulation of pro-inflammatory cytokine signaling; increased susceptibility to acute infectious illness; and exacerbation of insulin resistance. While this study is too limited to support a single pathway, the HRS-Cog differential is potentially robust enough to support the simple notion of a diabetes-stress complex. This conclusion, however, obviously depends on whether the relatively small study sample captures the characteristics of the population at-large. If this is the case, the results could reflect what has been described in the literature as "particular combinations of co-factors that activate different mechanisms of brain dysfunction and/or neurodegeneration," as well as "a factor [stress] amplifying the same mechanism as another already present factor [e.g. insulin resistance] (McDonald et al., 2010)." In general, elevated cortisol may be one of several conditions that dramatically affect the pathogenic course of DM.

Compared to diabetes patients stably employed, adult job losers scored roughly two points less on a validated measure of neuropsychological functioning, a gap that was slightly above the difference between those with "early" and "late" onset. Interestingly, a recent cross-sectional analysis of Germans elders arrived at comparable results (Breitling et al., 2012). In this work Germans diagnosed with diabetes before the age of 60 scored 2.76 points (-4.64-0.87, $p<.005$) below their counterparts. This differential was later equated to roughly eight years of excessive aging, and deemed more predictive of cognitive function than a diagnosis alone. The relatively young sample and limited age range makes it difficult to extrapolate within the present study; however, previous research has found HRS-Cog quartiles predictive of several adverse conditions, notably mortality (Mehta et al., 2003). If the job loss differential were influential enough to displace an observation into an adjacent quartile, our understanding of the burden of stress could change appreciably. This is a burden that is, of course, associated with early death

in many studies (Alwin, 2008). Regardless, these results attest strongly to the "premature aging hypothesis," since the differential persisted in the presence of a young cohort and the adjustment for chronic disease.

Models one and two from table 4 imply that age of onset and glucose control might have been insensitive indexes of abnormality and that they failed collectively to mitigate the effects of job loss. Diabetes timing, though, was still associated with reduced performance, and its effect independent of the primary exposure, as well as the demographic factors in model 2 from table three. While onset was likely too broad to capture disease severity accurately, the interaction of job loss with DM may have been significant itself. In support of this conclusion, neither insurance status nor income had discernible impact. Complications arising from inaccessibility to medical care are therefore unlikely to have contributed meaningfully to the observed differences.

Greater oxidative stress is one hypothetical effect of stress-induced job loss. Still, this is an unlikely candidate, since onset and retinopathy were also statistically significant. The significance of retinopathy, a marker for severe oxidation, does confirm recent work with a similar age group (Rosebud, 2008), but because the effect of the primary exposure was still independent of each factor, it is more likely to represent a distinct pathway, such as lowered synaptic plasticity. Though both stress and retinopathy involve changes to the vasculature, the former may also elicit cytokines that impair the removal of toxins. As we have seen, AD is often described as "a disease of impaired clearance."

Within the context of statistical modeling, crude distinctions such as time of onset and self-reported retinopathy (without regard to duration) may be too general to moderate the

systemic and manifold effects of stress. The contributions of cortisol to brain function and memory impairment may also differ by time of onset within the stage of disease. It may, for instance, play an important role in the early stages of ARD, particularly since amyloid accumulation, at its extreme, is unlikely to result from insulin resistance alone (Stewart & Liolitsa, 1999). Future work should integrate descriptive clinical and epidemiological data to determine whether one pathway most strongly modifies the effect of proxies like job loss, leading to what appears here to be "advanced cognitive aging."

In the current analysis, the relationship among stress, diabetes, and cognitive aging depends on how one interprets the role of gender, which single-handedly reversed the primary coefficient. This association effectively vanished, and the hypothesis that time of onset would moderate the relationship between stress and cognition nullified. Interestingly, female sex was associated with higher performance among job keepers but not losers. This finding belies what would otherwise be a tempting interpretation: current research shows that females tend to adapt differently- and more effectively- to adverse major life events (Belle, 1987). Female sex in this sample, however, may reflect occupational variation, differential exposure to complex tasks, or simple biological difference. If being female was related to less work strain, greater job complexity, or more autonomy within the workplace, selection bias could result. (Obviously, bias could have existed differentially between losers and keepers.) Thus the absence of relevant data on occupation and rank is the single most serious flaw that limits the generalizability of these results. On the other hand, research with the same cohort has found sex, rather than job class, a protective influence on the incidence of both cerebrovascular disease and lacunar infarction (Gallo et al., 2004). Future studies should also assess the prevalence and trajectory of

workplace learning and the performance of complex tasks, as well as how they impact each gender.

This is the first epidemiological evaluation of emerging laboratory and clinical evidence for the pathogenic role of chronic stress on diabetes-related cognitive function. Strengths of the analysis include the use of a wide range of physiological measurements, the inclusion of a nationally representative sample of adult diabetics, and a relatively long period of observation (1992-2002). While past studies have assessed the joint effect of blood cortisol levels and chronic disease, the current incorporated detailed data on many of the most relevant markers. In addition, nearly all job losers were diagnosed before the event and excluded had they reported DM to have a negative career effects. The removal of prevalent events at baseline eliminated the bias of including those from middle and early adulthood. Lastly, the diversity of adjustment variables was comparable to past studies (Allen et al., 2004).

Several limitations deserve notice. The aforementioned failure to characterize the nature of both the workplace and the transitional environment was the most critical, even though prior studies differentiated only between blue- and white-collar occupations, and were less likely to incorporate characteristics relevant to the outcome (Gallo et al., 2000). Secondly, recent HRS work has found lower cognitive scores among workers who retire early in life but also acknowledges that poor cognition leads to retirement (Rohwedder & Willis, 2010). The potential for "reverse causality" is considerable, and controlling for this effect is challenging within the HRS. Unlike most studies, however, age was insignificant. This anomaly may reflect the younger sample age (compared to the entire HRS diabetes cohort) and the limited age range, as well as the exclusion of retirees. The small percentage of nona- and octogenarians could have placed a ceiling on the significance of several exposures, notably onset and stroke. Likewise, the

cognitive effects of an adverse midlife event could be insubstantial to older elders compared to the cumulative effects of chronic disease. The prevalence of cerebrovascular disease was also relatively small for an adult sample of diabetics, and the low number of job losers was not representative of a group generally regarded at the very highest risk for ARD. Finally, several variables would likely improve the best fit model from table 4 (adjusted-$R^2 = 0.317$), including the duration and treatment of retinopathy, the nature of post-work social support, and the genotyping of APOE 4, the only known genetic risk factor for late-onset sporadic AD.

The consequences of stress to brain structure and function are not transient. Involuntary job loss shares characteristics with the most harmful stressors, specifically those that are novel, unpredictable, and uncontrollable. Even though most societies have provisions for population change, these measures are undermined by recessions, mass layoffs, and financial hardship. The risk of chronic disease is also greater for the roughly 2 million unemployed Americans over the age of fifty-five, a group that not only requires the longest time to regain employment but that expends greater energy to acquire the same set of skills (Rich, 2010). Even though prevention commonly addresses ARD, few concern the stress response following a major event. Recent research has even shown that high school students diagnosed with the disease are 10 percent less likely to find employment and can expect to lose an average of $160,000 in lifetime earnings (Fletcher & Richards, 2012). It would not be surprising then for a diabetes-stress complex to gain even greater attention in the subsequent years.

List of Tables

Table 1. Description of the Eligible Sample by Involuntary Job Loss (n = 1,180)

Characteristic	All Diabetics N (%)*	Job Loss N (%)*	Non-Job Loss N (%)*
Age (years), mean ± SD	68.6 ± 8.7	63.5 ± 7.8	61.8 ± 6.9
Sex			
Male	330 (28.0)	20 (48.7)	73 (34.4)
Female	289 (24.5)	6 (14.6)	48 (22.6)
Education			
Less than high School	354 (30.0)	10 (24.4)	40 (18.9)
High School	402 (34.1)	14 (34.2)	66 (31.1)
Some college	213 (18.1)	11 (26.8)	44 (20.8)
College or more	211 (17.9)	6 (14.6)	62 (29.3)
Age of onset (years), mean ± SD	57.6 ± 13.5	50.4 ± 13.8	52.9 ± 11.9
HbA1c, mean ± SD	7.2 ± 1.4	7.7 ± 1.4	7.2 ± 1.5
Insurance			
Yes	986 (83.6)	29 (70.7)	181 (85.4)
No	146 (12.4)	9 (21.9)	22 (10.4)
Income			
> 14,250 (US $)	316 (26.8)	22 (53.7)	78 (36.8)
≤ 14,250 (US $)	864 (73.2)	19 (46.3)	134 (63.2)
Insulin use			
Yes	273 (23.1)	9 (22.0)	40 (18.9)
No	879 (74.5)	32 (78.0)	170 (80.2)
Oral diabetes medication use			
Yes	854 (72.4)	31 (51.9)	148 (70.0)
No	291 (24.7)	10 (48.1)	57 (26.9)
Smoking history			
Never	234 (19.8)	9 (22.0)	48 (22.6)
Former	259 (22.0)	12 (29.3)	51 (24.1)
Current	134 (11.4)	9 (22.0)	23 (10.8)
Stroke or transient ischemic attack			
Yes	64 (5.4)	0 (0.0)	5 (2.4)
No	1,073 (90.9)	40 (97.6)	204 (96.2)
Hypertension			
Yes	869 (73.6)	27 (65.9)	145 (68.4)
No	284 (24.1)	14 (34.1)	60 (28.3)
High Cholesterol			
Yes	711 (60.3)	22 (53.7)	142 (67.0)
No	420 (35.6)	18 (43.9)	62 (29.2)
Retinopathy			
Yes	155 (13.1)	5 (12.2)	20 (9.4)
No	964 (81.7)	32 (78.0)	182 (85.8)
Congestive Heart Failure			
Yes	138 (11.7)	3 (7.3)	7 (3.3)
No	999 (84.7)	37(90.2)	202 (95.3)

* Numbers may not sum to 1,180 due to missing data, and percentages may not sum to 100% due to missing data.

Table 2. Mean (95 % confidence intervals) HRS-Cog Scores for Keepers and Losers by Study Characteristic (n = 153)

Characteristic	N*	Total Score	p†
Job Loss			<0.017
Yes	36	22.8 (20.4-25.1)	
No	117	24.9 (24.2-25.6)	
Age of onset (years)			<0.014
≤ 55	84	23.6 (22.4-24.8)	
>55	69	25.5 (24.7-26.3)	
HbA1c (quartiles)			<0.540
≤ 6.3	38	24.0 (22.8-25.1)	
6.4-6.9	44	25.3 (24.0-26.7)	
7.0-7.8	35	24.2 (22.7-25.7)	
> 7.8	36	24.1 (21.9-26.3)	
Age			
51-59	23	23.4 (20.1-26.7)	<0.052
60-69	110	25.0 (24.2-25.8)	
70+	20	22.5 (21.0-24.0)	
Sex			
Male	88	24.1 (23.5-25.3)	0.127
Female	53	25.5 (24.3-26.7)	
Education			<0.001
Less than high School	37	21.0 (19.6-22.4)	
High School	50	24.7 (23.3-26.0)	
Some college	30	26.2 (24.5-27.9)	
College or more	36	26.2 (24.8-27.5)	
Income (US $)			0.021
> 14,250	96	25.1 (24.2-26.0)	
≤ 14,250	57	23.3 (21.9-24.6)	
Insulin use			0.351
Yes	26	25.2 (23.7-26.7)	
No	127	24.3 (23.4-25.1)	
Oral diabetes medication use			<0.650
Yes	115	24.6 (23.6-25.5)	
No	36	24.1 (22.8-25.4)	
Smoking history			0.210
Never	54	25.6 (24.5-26.8)	
Former	61	24.5 (23.6-25.5)	
Current	30	24.0 (21.9-26.1)	
Hypertension			<0.110
Yes	98	24.9 (24.0-25.9)	
No	51	23.6 (22.1-25.1)	
High Cholesterol			
Yes	96	24.9 (23.9-25.8)	<0.200
No	51	23.8 (22.4-25.2)	
Retinopathy			
Yes	13	23.7 (20.7-26.6)	<0.520
No	133	24.6 (23.8-25.4)	

* Numbers may not sum to 153 due to missing data.

† P-value is for pooled equality of variances test (continuous variable).

Table 3. Multiple linear regression models predicting total HRS-Cog scores by 3 primary study variables (n = 153)

	Model 1[a]		Model 2[b]		Model 3[c]	
Predictor	Unadjusted β (95 % Confidence Interval)	**p**	Adjusted β (95 % Confidence Interval)	**p**	Adjusted β (95 % Confidence Interval)	**p**
Involuntary Job Loss						
No	Reference	---	Reference	---	Reference	---
Yes	-2.16 (-3.93- -0.39)	0.017	-0.37 (-2.17-1.43)	0.687	-1.18 (-3.12-0.76)	0.231
Age of onset (years)						
> 55	Reference	---	Reference	---	Reference	---
≤ 55	-1.91 (-3.42-0.40)	0.014	-1.39 (-2.89-0.10)	0.067	-0.88 (-2.51-0.76)	0.290
HbA1c (quartiles)						
≤ 6.3	Reference	---	Reference	---	Reference	---
6.4-6.9	1.34 (0.08-2.29)	0.207	1.23 (-0.62-3.08)	0.191	1.54 (-0.40-3.49)	0.118
7.0-7.8	0.23 (0.05-2.58)	0.841	1.05 (-0.94-3.02)	0.298	1.08 (-0.96-3.11)	0.297
> 7.8	0.08 (-1.98-0.29)	0.942	1.05 (-1.02-3.13)	0.317	1.71 (-0.53-3.96)	0.138

[a] Unadjusted with individual effects of the three predictors.
[b] Adjusted for age, sex, education, income, insurance, insulin, and oral diabetes medication.
[c] Adjusted for age, sex, education, income, insurance, insulin, oral diabetes medication, smoking history (never, former, current), hypertension, high cholesterol, and retinopathy.

Table 4. Best fit multiple linear regression models predicting total HRS-Cog scores by involuntary job loss (n = 153)

	Model 1[a]		Model 2[b]		Model 3[c] R^2 = **0.317**	
Predictor	Adjusted β (95 % Confidence Interval)	**p**	Adjusted β (95 % Confidence Interval)	**p**	Adjusted β (95 % Confidence Interval)	**p**
Involuntary Job Loss						
No	Reference	---	Reference	---	Reference	---
Yes	-2.15 (-3.89- -0.40)	0.016	-2.32 (-4.15- -0.49)	0.013	-1.52 (-3.28- 0. 24)	<0.09

[a] Adjusted for age of onset.
[b] Adjusted for age of onset and HbA1c quartiles.
[c] Best fit model. Adjusted for age of onset, HbA1c quartiles, sex, education, hypertension and retinopathy.

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