Effects of an Intervention to Improve Workplace Flexibility on Employee Biomarkers of Inflammation

Abstract:

Introduction: Studies suggest that inflammation may mediate the relationship between stress and cardiovascular disease. However, no research has examined whether the combined stress of work and family are associated with higher levels of inflammation in the body or if reducing this type of stress results in less inflammation. The current study aims to fill this gap in the literature and examines the effects of a workplace intervention designed to increase flexibility, schedule control and workplace support on employee markers of inflammation as part of a prospective, randomized field experiment.

Methods: Among 949 nursing home employees, treatment status and log transformed biomarkers of inflammation (CRP, IL-6 and IL-1β measured by dried blood spots) served as the primary exposure variable and outcomes, respectively. Data were collected at two time points (baseline and 12 months). We estimated multilevel linear regression models that account for multiple measures per employee as well as the nesting of employees within worksites. We also considered possible subgroup-specific effects in potential changes in employee markers of inflammation by parental status, foreign born status and age.

Results: The workplace intervention did not significantly lead to changes in employee levels of inflammation from baseline to 12 months (β=0.10, p=0.28 for CRP, β=-0.02, p=0.70 for IL-6 and β=-0.11, p=0.36 for IL-1 β). We detected some differences in treatment effects from baseline to 12 months based on foreign-born status in both stratified analyses and models with three-way interaction terms suggesting potentially worse CRP for foreign born employees, improvements in IL-1β for U.S. born employees and benefits in IL-6 for foreign born employees.

Conclusion: This study marks the first randomized field experiment to assess the effects of a workplace program to reduce work and family stressors on employee markers of inflammation over time. We speculate that failure to detect treatment effects may be a result of our healthy study population as well as a somewhat short study period of twelve months.

Introduction:

Demographic shifts in the U.S. prompt American workers to report rising levels of work and family stress [1, 16]. Research suggests that strain from both workplace and home life may contribute to the development of cardiovascular disease (CVD) [2, 16], which is the leading cause of death in our country. The current study seeks to assess the relationship between a novel workplace program designed to address work and family demands and a cardiovascular-related outcome in a racially and ethnically diverse prospective, occupational cohort. Given that CVD often develops over decades but does not manifest until middle or later adulthood, many studies of younger adults consider pre-disease markers to assess likely risk of developing CVD. Prior work has suggested that markers of inflammation serve as sensitive and meaningful indicators of cardiovascular disease risk [69, 70]. This study is the first randomized field experiment that can evaluate the effects of a workplace intervention to improve work and family strain on change in employee levels of inflammation over time.

Work and Family Conflict and Related Policies:

The U.S. labor force has experienced incredible transformations over recent decades. Sixty years ago, less than half of American women participated in the workforce. Today, roughly 70% of women 18 to 64 years of age work outside the home, and a similar proportion of all women with children under the age of 18 years old are employed [71]. In 2008, eighty percent of the workforce lived in dual-earner households, with women contributing nearly half (44%) of the family income despite the persistence of a gender gap in earnings [1]. Roles attributed to men and women at home have evolved substantially as well, with fathers contributing more time today to childcare and household tasks than they did 30 years ago; men spent 2 hours per workday with children in 1977, compared with 3 hours per workday in 2008; women averaged 3.9 hours with children on workdays in both periods [1].

As a result, increasing numbers of women and men may experience competing work and family demands. The incompatibility of home and work life is often referred to as "work/family conflict," a term which Greenhaus and Beutell introduced almost thirty years ago to describe "interrole conflict in which the role pressures from the work and family domains are mutually incompatible in some respect" [10]. Numerous studies suggest a strong link between work/family conflict and worse mental health outcomes such as depression, anxiety, mood and substance disorders [11, 12, 65, 72-75] as well as poorer physical health outcomes as measured by worse ratings of global health, less sleep, obesity, musculoskeletal pain and harmful health behaviors like lower physical activity and unhealthy diet [2, 12, 76, 77].

Surveys of the American workforce indicated that employees report higher levels of work/family conflict in 2008, relative to the late 1970s [1]. Yet, unlike high income countries in Europe, the U.S. is notorious for its weak labor laws and limited family protection policies [78, 79], particularly legislation that protects women of childbearing age [80]. The U.S. remains 1 of

3 countries out of 173 worldwide that does not provide some level of paid parental leave. Aside from the Family and Medical Leave Act (FMLA), which offers up to 12 weeks of unpaid leave to parents who meet certain criteria, federal legislation for parental leave is non-existent. A handful of states expand upon FMLA to provide additional unpaid benefits, but only two states offer some paid entitlements following the birth of a child [81].

In the face of scarce national support, employers have started to acknowledge that effective policies and practices to reduce work and family stressors have the potential to benefit employees, families and organizations. Yet, these benefits remain limited and understudied. In 2000, eighty to ninety percent of employers offered full-time employees paid holiday and vacation leave, and between 20 and 25% of full-time employees receive paid personal leave. However, fewer than 10% receive any form of childcare support, and this proportion drops to l% among full-time employees in small firms [82]. Other forms of institutional support include flexible work arrangements, such as flextime, compressed work weeks, telecommuting and voluntary part-time work including job-sharing [83]. A recent national survey of employers indicates that at least some proportion of employees were allowed to change start and quit times within a range of hours (27%), compress the work week (7%), work from home occasionally (6%) or regularly (2%) and reduce work hours (6%) [84], but the Bureau of Labor Statistics reports that only about one-quarter (27.5%) of the American workforce actually works a so-called flexible schedule [85]. When alternate arrangements exist, they are often uneven, unpredictable and not formalized within organizations and remain largely at the discretion of individual managers, particularly in small and non-unionized organizations [83, 86]. Low-wage workers in particular have less access to supportive work environments and policies and practices that promote employee and family health [87, 88].

Few scientific studies have examined the impacts of existing workplace policies and practices on work/family conflict and employee [86, 89] or employer [90] outcomes. Much of the work regarding policy adoption or implementation concerns what predicts adoption of these workplace programs [91-93], not the outcomes they intend to affect. Limited research has assessed the impact of workplace policies on employee well-being [19, 94-96], and few studies utilize longitudinal data to examine associations between work/family conflict and mental and physical health outcomes [19, 97]. Given their designs, these studies have not sufficiently answered the important question of whether changes to the work environment are *causally* linked to better employee health. We are not aware of any quasi-experimental or experimental studies examining these relationships prior to the research efforts associated with the current study [89].

Work/Family Strain and its Impact on CVD and Inflammatory Markers:

Work and family stressors may be particularly relevant for employee cardiovascular outcomes. One challenge to understanding the social and behavioral predictors of CVD is that the disease takes years, often decades, to emerge, and longitudinal research that anticipates the development of disease with long latency can be costly and logistically demanding. The collection of biomarkers, such as blood pressure, lipids, cortisol, and markers of inflammation, offers a useful alternative in epidemiologic research for a number of reasons. Biomarkers often serve as underlying risk factors for as well as intermediate variables along the pathway to disease, which is particularly useful for conditions that develop slowly over time. They also provide direct information about physiological processes in the body and are thus more reliable than subjective, self-reported measures of health [32]. Research examining the effects of stress on cardiovascular health has started to utilize biomarkers as proxies for and intermediaries of

disease [98] and indicates that markers of inflammation may be altered in response to a variety of stressors [99] and also indicate future CVD risk [70, 100, 101].

The current study focuses specifically on the following markers of inflammation as indicators of CVD risk: C-reactive protein (CRP), interleukin-6 (IL-6) and interleukin-1beta (IL-1 β). The inflammatory response is typically initiated by injury, the entry of bacteria and/or infection in the body. Immune cells including cytokines IL-6 and IL-1β, which are part of the body's natural immune system (and, thus, are not pathogen-specific), are recruited into tissue and prompt the production of proteins in the liver, such as CRP, as well as lymphocytes and neutrophils involved in the immune response. Acute-phase inflammation is understood as adaptive and protective. It involves short-term elevations in inflammatory markers aimed at defending the host against infection and repairing injured tissue. Chronic, low-grade inflammation (characterized by levels of inflammation lower than those involved in acute-phase activity), however, may be maladaptive and implicated in longer-term health problems and disease processes like CVD as well as endocrine, mood and sleep disorders, disability and even mortality [69]. The recurring recruitment of pro-inflammatory cells is believed to result in endothelial injury, which research suggests can lead to the leakage of lipids into the subendothelial space and, ultimately, contribute to the atherosclerotic process. Unstable atherosclerotic plaques are particularly prone to rupture, leading to the formation of clots that may cause stroke, myocardial infarction or other negative cardiovascular outcomes [102]. CRP is also a response to cardiovascular events and thus the causal relationship between the two is controversial [103, 104].

Preliminary evidence suggests that a range of work-related stressors (which we conceptualize broadly to include measures of job strain, burnout, job dissatisfaction, etc.) may be

associated with higher levels of inflammation, though most of this research is cross-sectional in nature and has been conducted with modestly sized samples. A small (n=74) study of working men evaluated the effects of effort–reward imbalance, conceptualized to represent chronic work stress, and found it was significantly associated with higher CRP after administering a laboratory mental stress test, but not at baseline prior to the stress test [105]. A German study of 272 men and 52 women working at an airplane manufacturing plant also indicated that low job control, high job demands and low social support at work were associated with higher circulating CRP [106]. Shirom and colleagues conducted a series of larger cross sectional studies with employed adults in Israel, one of which revealed that job-related burnout was associated with increased CRP among women (n=1563) and another indicated that lower job satisfaction was related to higher CRP among men (n=1539) [107, 108]. However, when they conducted a longitudinal analysis, they found that low perceived control, social support at work and high workload were not associated with changes in CRP levels over a 12 months period in a sample of 1,131 workers [109]. Among a simple random sample of the Whitehall II cohort, low job control and high job demands were not found to be significantly associated with CRP cross-sectionally among 283 men and women [110]. Research involving a variety of work stressors and cytokine outcomes appears more consistent. In samples ranging from 118 to 243 employees with data collected at a single time point (cross-sectional or case control designs), exposures such as low job satisfaction and high job demands were associated with increased levels of pro-inflammatory cytokines IL-4, IL-6 and IL-8 [111-114]. Longitudinal evidence from Italy among 101 nurses similarly suggests that low job satisfaction was associated with increased IL-1β over a 12 month follow-up [115]; however, a smaller study among 38 Korean nurses found that high work stress (objective and subjective) was not associated with this outcome 8 months later [116]. Despite this emerging

work, we are unaware of research that examines both the effects of work and home stressors and related interrole conflict on employee markers of inflammation.

The current study examines whether **a workplace program designed to increase flexibility, schedule control and workplace support affects employee markers of inflammation** as an indicator of cardiovascular health**.** This work is based in the tradition of job strain theory [5, 6], specifically the Demand-Control-Support model which considers the combination of job demands and control that result in job strain and the role of workplace social support that protects against it [7]. Work and family conflict is conceptualized as a stressor or perceived form of stress, and we speculate that the intervention program will benefit all employees randomized to treatment, regardless of their levels of perceived stress at the time of randomization.

Specifically, we seek to address the following aims and hypotheses: **First**, we aim to assess whether a workplace intervention designed to decrease work-family conflict and improve employee well-being and effectiveness in work and family roles leads to reductions in levels of inflammation from baseline to 12 months. We hypothesize that employees randomized to the intervention group will demonstrate reduced levels of inflammation at 12 months post-intervention relative to baseline, compared to employees in the control group. **Second**, we aim to examine whether changes in levels of inflammation from baseline to 12 months are more substantial within certain subgroups. We hypothesize that beneficial effects of the intervention will be more pronounced in the following groups: employed parents who are more likely to report work and family stressors [74]; foreign born employees that comprise a relatively substantial proportion of our sample and may experience more stress and worse health, relative

to U.S. born employees [117-119]; and older employees for whom the effects of stress on immune function may be exacerbated [120].

Methods:

Sample:

This study is part of Phase II of the Work Family Health Network (WFHN) project, a joint research endeavor sponsored by the National Institutes of Health and the Centers for Disease Control and Prevention, among others. This phase involved data collection from employees (as well as their managers, spouses and their children) to assess an employer-supported workplace intervention in a group randomized field experiment. The WFHN identified a New England company with numerous nursing home facilities, which we will refer to as "LEEF" and included thirty worksites that were distributed across Massachusetts, Maine, New Hampshire, Vermont, Connecticut, and Rhode Island and able to support data collection and intervention delivery efforts. Sites were randomly assigned to intervention or control (usual practice) status using a biased coin adaptive randomization technique specifically tailored for group randomization, a flexible approach that offered strong internal validity and less opportunity for contamination across facilities [34], and matched based on number of employees, state and retention rate.

Trained WFHN site managers described the study to managers and employees at each work site and addressed any concerns during data collection. At baseline, each of the 1,723 eligible employees within these 30 worksites (n=15 intervention sites and n=15 control sites) who worked more than 22 hours each week during the day or during the day and night combined (exclusively night workers were not eligible) were invited to complete a computer-assisted

personal interview (CAPI) [34]. A total of 1,524 LEEF employees participated at baseline, resulting in a response rate of over 88%. A total of 1,470 employees provided biosamples at the start of the study, though employees who participated in the CAPI survey and those who provided biosamples were not entirely mutually exclusive. (See Figure 2.1 for study flowchart with details on baseline and 12 month data as well as employees excluded from our analytic sample. We excluded employees with biomarker data below predetermined lower levels of detection and truncated outcomes at the 99^{th} percentile, as described in the Measures section. We also excluded employees who provided only CAPI or biosample data.). We do not have any information on employees who did not consent to participate in the study. The number of assays conducted on markers of inflammation at baseline varied due to laboratory processes (n=1366 for CRP, n=1344 for IL-6 and n=1190 for IL-1β before exclusions to our specific sample were made). The same data collection procedures were used and identical measures were collected at 12 months (n=1201 for CRP, n=949 for IL-6 and n=826 for IL-1β at 12 months before the aforementioned exclusions were made). As discussed further below, dropout from baseline to 12 months in this sample did not vary by treatment status. Employees who provided all data components for the larger WFHN study, including blood samples, received $60 for their participation.

Measures:

Trained field interviewers administered survey instruments and health assessments as described elsewhere [34] which addressed employee demographics, socioeconomic status, family demographics, work environment, physical health, mental health, and family relationships. Identical data was collected at baseline and 12 months, although treatment status

and covariates were not time updated, and only 12 month outcome measures were used in this analysis. After obtaining written consent from all employees, interviews and health assessments lasted approximately 50 and 20 minutes, respectively, and were on occasion collected on different days.

Exposure Variable:

The primary exposure of interest is exposure to the workplace program or intervention status. The workplace program focused on increasing work flexibility, control over how and when work is done as well as increasing the support of supervisors and co-workers for employees' work/family issues in an effort to promote employee health and organizational goals. The field experiment has been described more extensively elsewhere [34, 86, 121-123]. Briefly, over a four-month period, employees and managers in treatment workgroups participated in face-to-face sessions and corresponding exercises during work hours. These activities were geared toward work redesign and the identification of work practices and processes to increase employee control over work time while continuing to meet business needs. Employees and managers were encouraged to work individually and collectively toward the goal of achieving work and family balance for staff. Additionally, managers participated in separate face-to-face training sessions that covered ways to demonstrate support for employees' lives outside of work and performance on the job. Managers also received computer-based training which included tracking exercises to help managers put these lessons learned into practice and to monitor the fidelity of the intervention. Both employee and manager activities were scripted and structured but encouraged participation and interaction. Workgroups randomized to control status continued with "business as usual" policies and practices [124]. The treatment variable, which was

originally double blinded, was later coded yes/no to denote randomization to treatment as part of an intent-to-treat model.

Outcome Variables:

The primary outcomes of interest include three pro-inflammatory markers considered related to CVD risk: CRP and cytokines IL-6 and IL-1β. To obtain assays of these inflammatory biomarkers, employees were asked to provide dried blood spots (DBS) by a finger stick. Interviewers wearing appropriate personal protective equipment disinfected the employee's middle or ring finger with an alcohol swab and proceeded to prick the finger with a sterile, disposable micro-lancet. While venipuncture to draw blood plasma or serum is often employed to collect CRP and other proinflammatory cytokines like those measured here, DBS techniques for examining markers of inflammation are valid and particularly useful in field-based studies when venipuncture with a trained phlebotomist is not feasible or samples are desired from a more generalizable sample (participation rates with DBS are higher than with phlebotomy) [32, 125-128]. As previously described [38], up to five blood spots were collected at once, air-dried, and sealed in a plastic bag for room-temperature shipment by means of a protocol specifically validated for serum to DBS equivalents [39, 126]. For CRP, samples were assayed at the University of Washington laboratory of Dr. Mark Wener. A calibrated punch from the DBS was eluted in a buffer solution and transferred to a well on a microtiter plate coated with an antibody that recognizes a distinct antigenic determinant on the CRP molecule. CRP in the elution solution is bound by the anti-CRP mAb (solid phase immobilization). A conjugate solution containing goat anti-CRP Ab coupled to peroxidase (enzyme-linked antibody) is then added to each well, resulting in CRP molecules being sandwiched between the solid phase and enzyme-

linked antibodies. After incubation, the wells are washed to remove unbound material. A tetramethylbenzidine (TMB) and hydrogen peroxide (H_2O_2) solution is added; H_2O_2, cleaved by the peroxidase, reacts with TMB and causes the solution to develop color**.** The CRP concentration is directly proportional to the absorbance of the solution; absorbance is measured spectrophotometrically. Similarly, for IL-6 and IL-1β microtiter plate wells were also coated with capture antibodies against these cytokines at Northwestern University in the laboratory of Dr. Thomas McDade. Labeled detection antibody binds to the captured cytokine, and an electrochemiluminescent signal was used to quantify the concentration of each cytokine in each sample against a standard curve. The CRP assay lower limit of detection was 0.035mg/L, within-assay imprecision (CV) was 8.1% and between-assay imprecision was 11.0%. Lower levels of detection were 0.3 pg/mL for both IL-6 and IL-1β. For IL-6, within-assay CV ranged between 8.98 and 9.73% and between-assay CV ranged between 3.41 and 8.51%. For IL-1β the within-assay CV ranged between 8.32 and 9.34% and between-assay CV ranged between 6.89 and 15.78%. Because we utilized DBS measures (as opposed to the commonly used plasma concentration), we implemented the following DBS to plasma conversion for CRP: CRP_serum = (CRP_DBS*0.448) - 0.084. To avoid including individuals with acute inflammation due to extreme illness or infection, we excluded all outcomes above the 99th percentile. This criterion removed roughly an equal proportion of employees in the treatment and control groups from our sample (see Figure 2.1). All outcomes were measured continuously and transformed to the logarithmic scale to achieve a normal distribution.

Covariates:

Our final models (see explanation below) adjusted for: occupation (employee's official job title, coded nurse or other), marital status (currently married/permanent romantic partner living with you?), employee gender (male/female), education (high school or less vs. some college or higher) and age in years (measured continuously, as basic scatterplots depicted a fairly linear relationship with the outcomes). Race/ethnicity was coded as Non-Hispanic White, Non-Hispanic Black, Hispanic/Latino or other race. Dummy variables for each racial/ethnic group were generated, and the reference group was assigned to Non-Hispanic White race.

Stratification variables:

For stratified models, we also included foreign-born status (yes/no), number of children living in the household 4 or more days/week and under the age of 19 years (none vs. one or more) and dichotomized the aforementioned age variable (less than or equal to 45 years of age vs. over 45 years).

Analysis:

To examine whether the intervention affected changes in employee markers of inflammation (Aim 1), we used multiple outcomes per employee (with measures taken from employees at baseline and 12 months) and estimated multilevel linear regression models that account for multiple measures per employee and nesting of employees within worksites by modeling random effects for employee and site. Pro-inflammatory markers served as outcomes in separate models and treatment status as the exposure variable as part of an intent-to-treat analysis. We tested time*treatment interactions to examine changes in employee markers of inflammation from baseline to 12 months. We then included a set of sociodemographic covariates hypothesized a priori to predict the outcomes of interest, an approach that improves

the statistical power of our models. The primary treatment effect of interest (the regression coefficients for the time*treatment variable) was similar in models with or without covariates, and we present models with covariate adjustment.[*] Finally, to test our secondary aim, we stratified this final model by parental status (no children vs. 1 or more), foreign born status (yes/no) and age (less than or equal to 45 years of age vs. over 45 years of age). We sought to confirm results from our stratified analyses with models using three-way interaction terms (i.e.: time*treatment*subgroup).

Results:

Sample Characteristics:

At baseline, we included a total of 949 LEEF employees with data available for the main variables of interest. Mean levels of CRP, IL-6 and IL-1β were 1.90 mg/L, 1.78 pg/mL and 53.02 pg/mL, respectively. Roughly half the sample was randomized to treatment (53.1%) and to control (46.9%) status (See Table 2.1 for complete descriptive statistics.). The majority of sociodemographic, health-related and work/family variables included in this study at baseline were not significantly different in the treatment group compared to the control group (including predictors of inflammation like smoking and obesity), although the proportion of females was

[*] $Inflamm_{tij} = \beta_0 + \beta_1 (Treatment_j) + \beta_2 (Time_{tij}) + \beta_3 (Treatment_j)(Time_{tij}) + \beta_4 (Confounders_{tij}) + t_{0tij} + e_{0ij} + u_{0j}$
Where: t= time; i= employee; and j = workgroup
And:
$[e_{0ij}] \sim N(0, \sigma^2_{e0})$
$[u_{0j}] \sim N(0, \sigma^2_{u0})$

Table 2.1: Descriptive Statistics (Baseline)

N= 949	N	Mean(sd) / %
CRP (mg/L)	949	1.90 (2.11)
IL-6 (pg/mL)	949	1.78 (1.71)
IL-1β (pg/mL)	949	53.02 (60.04)
Age	948	38.50 (12.33)
Treatment		
No	504	53.11
Yes	445	46.89
Occupation		
RN/LPN	264	27.88
Other	683	72.12
Sex		
Male	67	7.06
Female	882	92.94
Married/partnered		
Not married/partnered	337	35.51
Married/partnered	612	64.49
Race		
White	615	64.81
Black	116	12.22
Hispanic	138	14.54
Other race	80	8.43
Education		
Grades 1-8	7	0.74
Some High School	43	4.53
High School	326	34.35
Some College	467	49.21
College or more	106	11.17
Foreign Born		
No	711	74.92
Yes	238	25.08
Parent		
No	411	43.35
Yes	537	56.65

significantly higher and age significantly lower in the treatment group compared to the controls. No significant differences in mean outcome levels for CRP, IL-6 or IL-1β between treatment and control groups were present at baseline (see Table 2.2 for complete details).

There were no discernable differences in demographics between our final analytic sample and the overall study sample. However, employees who were excluded from our analytic sample had significantly lower CRP levels and were less obese than those analyzed in the current study (see Appendix 2.1 for descriptive statistics on original sample and Appendix 2.2 for comparisons between those excluded from versus included in the analytic sample). Data for 949 employees were analyzed at baseline and 621 at 12 months. Additionally, in predictive models of dropout from baseline to 12 months, we observed that baseline measures of CRP and IL-1β (but not other covariates) predicted subsequent dropout, although these relationships did not vary by treatment group.[†]

Effects of intervention on changes in employee inflammation:

In multilevel regression models, we found that the workplace intervention was not significantly associated with changes in employee inflammation from baseline to 12 months. Inclusive of aforementioned covariates, there was a 0.10-point greater change in CRP due to treatment from baseline to 12 months (p=0.28) (again, all outcomes log transformed).

[†] Predictors of dropout on log transformed markers of inflammation: $OR_{CRP\ at\ baseline} = 1.22$ (CI = (1.09 - 1.36)); $OR_{IL\text{-}1\beta\ at\ baseline} = 1.18$ (CI = 1.05 - 1.34) (there was no effect of baseline IL6 on subsequent dropout). Predictors of dropout did not appear to depend on treatment status, as there was no significant baseline inflammation*treatment interaction in these models. Though ORs for these interactions were small and NS, the effect of baseline CRP and IL-1β on subsequent dropout was lower for people in the treatment group than control. The association between baseline IL-6 and dropout was higher in the treatment group (although baseline IL6 did not predict dropout on its own).

Table 2.2: Descriptive Statistics by treatment status (Baseline)

	Treatment		Control		
N= 949	**N**	**Mean(sd) / %**	**N**	**Mean(sd) / %**	**p-value***
CRP	445	1.86 (1.96)	504	1.93 (2.23)	0.58
IL-6	445	1.77 (1.97)	504	1.79 (1.46)	0.91
IL-1β	445	51.91 (58.90)	504	54.01 (61.06)	0.59
Age	444	37.63 (12.34)	504	39.26 (12.30)	0.04
Occupation					0.56
RN/LPN	127	28.61	137	27.24	
Other	317	71.39	366	72.76	
Sex					0.001
Male	19	4.27	48	9.52	
Female	426	95.73	456	90.48	
Married/partnered					0.59
Not married/partnered	162	36.40	175	34.72	
Married/partnered	283	63.60	329	65.28	
Race					0.25
White	295	66.29	320	63.49	
Black	58	13.03	58	11.51	
Hispanic	54	12.13	84	16.67	
Other race	38	8.54	42	8.33	
Education					0.70
Grades 1-8	2	0.45	5	0.99	
Some High School	19	4.27	24	4.76	
High School	155	34.83	171	33.93	
Some College	224	50.34	243	48.21	
College or more	34	10.11	61	12.10	
Foreign Born					0.60
No	337	75.73	374	74.21	
Yes	108	24.27	130	25.79	
Parent					0.19
No	203	45.62	208	41.35	
Yes	242	54.38	295	58.65	

*p-values based on chi-square or F tests

The changes in IL-6 and IL-1β due to treatment from baseline to 12 months were also non-significant (IL-6: β=-0.02, p=0.70; IL-1β: β =-0.11, p=0.36) (see Table 2.3a).

Effects of intervention on changes in employee inflammation in subgroups:

Tests of subgroup differences in changes in employee inflammation from baseline to 12 months were conducted with stratified models and models with three-way interaction terms. In stratified models, there were no intervention effects for IL-6 in any strata of parental status, age or foreign born status (see Table 2.3b). For CRP, there was a marginal increase in inflammation due to treatment (a worse treatment effect) from baseline to 12 months for employees born outside the U.S. (β=0.28, p=0.09) but not those born in the U.S. (β=0.04, p=0.73). We also detected a marginal reduction in IL-1β due to treatment (a beneficial treatment effect) from baseline to 12 months for U.S. born employees (β=-0.27, p=0.03) but not those born outside the country (β=0.34, p=0.16).

Models with three-way interaction terms indicated that changes in IL-6 from baseline to 12 months significantly varied by foreign born status (β=-0.26, p=0.009); the effects of treatment did not vary by foreign born status for other markers of inflammation (p-value was 0.34 for CRP and 0.09 for IL-1β). P-values for three-way interaction terms testing variations in treatment effects by parental status were 0.87 for CRP, 0.34 for IL-6 and 0.38 for IL-1β; p-values for three-way interaction terms testing variations in treatment effects by age were 0.41 for CRP, 0.43 for IL-6 and 0.94 IL-1β (results not presented).

Table 2.3a – Main effects of a workplace intervention on employee inflammatory markers from baseline to 12 months

	CRP (log) N= 944 Obs = 1383			IL-6 (log) N= 944 Obs = 1383			IL-1 β (log) N= 944 Obs = 1383		
	Estimate	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value |**
Intercept	-0.69	0.30	0.03	0.16	0.14	0.26	3.38	0.25	<.0001
Treatment vs. Control	0.01	0.11	0.91	-0.05	0.04	0.27	-0.02	0.09	0.84
12 months vs. Baseline	-0.07	0.06	0.24	-0.04	0.03	0.17	0.03	0.08	0.69
Treatment*12 months	0.10	0.09	0.28	-0.02	0.05	0.70	-0.11	0.12	0.36

All models control for race, education, age, sex, occupation and marital status

Table 2.3b – Stratified models indicating subgroup effects of a workplace intervention on employee inflammatory markers from baseline to 12 months

	CRP (log)					
	Estimate	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**
	Without children N= 408 Obs =585			**With children N= 535 Obs =797**		
Intercept	-0.59	0.42	0.17	-0.70	0.45	0.13
Treatment vs. Control	-0.04	0.14	0.78	0.02	0.13	0.91
12 months vs. Baseline	-0.12	0.09	0.20	-0.04	0.08	0.62
Treatment*12 months	0.12	0.14	0.37	0.09	0.13	0.47
	Less than or equal to 45 years N= 652 Obs =956			**Older than 45 years N= 292 Obs =497**		
Intercept	-0.25	0.30	0.43	-0.83	0.58	0.16
Treatment vs. Control	0.03	0.13	0.79	0.09	0.17	0.59
12 months vs. Baseline	0.01	0.09	0.94	-0.13	0.10	0.18
Treatment*12 months	0.05	0.12	0.68	0.22	0.16	0.16
	Not Foreign Born N= 706 Obs =1036			**Foreign Born N= 238 Obs =347**		
Intercept	-0.21	0.39	0.60	-0.67	0.54	0.23
Treatment vs. Control	0.09	0.12	0.44	-0.26	0.17	0.14
12 months vs. Baseline	-0.07	0.07	0.31	-0.06	0.11	0.55
Treatment*12 months	0.04	0.11	0.73	0.28	0.17	0.09

All models control for race, education, age, sex, occupation and marital status

Table 2.3b – Stratified models indicating subgroup effects of a workplace intervention on employee inflammatory markers from baseline to 12 months (continued)

	IL-6 (log)					
	Estimate	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**
	Without children N= 408 Obs =585			**With children N= 535 Obs = 737**		
Intercept	0.28	0.20	0.18	0.19	0.21	0.39
Treatment vs. Control	-0.04	0.06	0.54	-0.06	0.05	0.26
12 months vs. Baseline	-0.03	0.05	0.56	-0.05	0.04	0.17
Treatment*12 months	-0.002	0.08	0.98	-0.03	0.06	0.62
	Less than or equal to 45 years N= 652 Obs =956			**Older than 45 years N= 292 Obs = 427**		
Intercept	0.13	0.15	0.40	0.09	0.30	0.77
Treatment vs. Control	-0.01	0.05	0.84	-0.16	0.08	0.07
12 months vs. Baseline	-0.04	0.04	0.37	-0.06	0.05	0.26
Treatment*12 months	-0.07	0.06	0.26	0.10	0.09	0.25
	Not Foreign Born N= 706 Obs =1036			**Foreign Born N= 238 Obs =347**		
Intercept	0.65	0.19	0.002	0.49	0.26	0.07
Treatment vs. Control	-0.05	0.05	0.34	-0.02	0.08	0.83
12 months vs. Baseline	-0.06	0.04	0.14	-0.02	0.06	0.72
Treatment*12 months	-0.0005	0.06	0.94	-0.07	0.10	0.49

All models control for race, education, age, sex, occupation and marital status

Table 2.3b – Stratified models indicating subgroup effects of a workplace intervention on employee inflammatory markers from baseline to 12 months (continued)

	IL-1β (log)					
	Estimate	**Standard Error**	**p-value**	**Estimate**	**Standard Error**	**p-value**
	Without children N= 408 Obs =585			**With children N= 535 Obs = 797**		
Intercept	3.59	0.36	<.0001	3.14	0.35	<.0001
Treatment vs. Control	0.02	0.14	0.86	-0.03	0.11	0.77
12 months vs. Baseline	0.06	0.12	0.64	0.02	0.10	0.85
Treatment*12 months	-0.05	0.19	0.79	-0.17	0.16	0.28
	Less than or equal to 45 years N= 652 Obs =956			**Older than 45 years N= 292 Obs = 497**		
Intercept	2.99	0.24	<.0001	3.17	0.49	<.0001
Treatment vs. Control	0.03	0.11	0.78	0.05	0.16	0.76
12 months vs. Baseline	-0.12	0.11	0.25	0.19	0.14	0.18
Treatment*12 months	-0.08	0.14	0.55	-0.16	0.23	0.49
	Not Foreign Born N= 706 Obs =1036			**Foreign Born N= 238 Obs =347**		
Intercept	3.66	0.32	<.0001	3.15	0.41	<.0001
Treatment vs. Control	0.01	0.09	0.91	-0.12	0.19	0.54
12 months vs. Baseline	0.05	0.09	0.58	-0.04	0.15	0.80
Treatment*12 months	-0.24	0.14	0.09	0.34	0.24	0.16

All models control for race, education, age, sex, occupation and marital status

Discussion:

This study marks the first randomized field experiment to assess the effects of a workplace program to address work and family stressors on change in employee levels of inflammation over time. Below we will summarize findings and offer possible explanations for the null main effects. Finally, we discuss limitations, strengths and overall conclusions from the study.

Summary of findings and explanations for subgroup differences:

Analyses indicated there was no effect of the WFHN's intervention on three markers of inflammation among employees assessed one year after randomization. Models with three-way interaction terms indicated that changes in IL-6 from baseline to 12 months varied by foreign born status such that the intervention was more beneficial for foreign born employees than those born outside the U.S. Stratified models, however, indicated that there was a borderline, deleterious effect on CRP due to treatment from baseline to 12 months for employees born outside the U.S. and a marginal improvement in IL-1β due to treatment from baseline to 12 months for U.S. born employees. Generally, it does not appear that particularly higher risk groups gained greater benefit from the intervention with regard to improving inflammatory status. Understanding the mechanisms at play in these particular relationships is beyond the scope of this study, and it is also possible that these treatment effects are simply due to chance. We caution the interpretation of our stratified analyses in particular as sample sizes were reduced in these models, and we conducted six subgroup analyses (parents, non-parents, U.S. born, foreign born, older employees and younger employees).

Explanations for null findings:

The translation of observational epidemiological evidence into experimental findings remains one of the fundamental struggles in the social sciences [129]. The epidemiologic literature offers examples of compelling, longitudinal studies reflecting strong links between psychosocial and behavioral exposures and health outcomes, but the randomized control trials (RCTs) aiming to change these conditions have often generated null results. Notably, numerous observational studies have suggested that depression and social support are associated with mortality following a myocardial infarction. Yet, a large RCT, Enhancing Recovery for Coronary Heart Disease Patients (ENRICHD), found no differences in post-MI survival in the treatment and control groups. Similarly, although vast observational evidence suggests that depression is associated with secondary cardiac events following a myocardial infarction, very few psychological interventions have successfully reduced total deaths, risk of revascularization, or non-fatal infarction [130].

Despite predominantly cross-sectional, observational evidence suggesting there may be a link between work strain and employee markers of inflammation (evidence in longitudinal research is less consistent), we did not find support for this hypothesis in the current randomized field experiment. We offer two broad explanations to explain the overall null main effects of the WFHN intervention on changes in employee inflammation: **1)** the WFHN intervention is not causally related to changes in employee markers of inflammation and the pathways by which we assumed the intervention to affect inflammation are not correct; and **2)** the WFHN intervention is causally related to changes in inflammation but did not produce results in the current study context due to incorrect etiologic period and/or issues of selection in our sample. We discuss these possibilities below in more depth.

The intervention does not affect markers of inflammation:

Evidence from other WFHN research suggests that this workplace intervention changed certain health (psychological distress and smoking) and organizational outcomes (organizational citizenship behavior and safety compliance). Still, the WFHN workplace intervention may not influence employee health as measured by changes in levels of inflammation. A lack of effect may be due to the fact that: a**)** the intervention did not change the mediators that it sought to affect along the causal pathway to employee markers of inflammation, namely work-to-family conflict, schedule control and supervisory support; and/or b) changes in these mediators are not causally related to CRP, IL-6 and IL-1 β.

Preliminary evidence from WFHN researchers investigating the effects of an identical intervention at an information technology (IT) company suggests that the workplace program offered statistically significant, albeit modest, improvements in levels of reported work-to-family conflict and other proposed mediators. This study also found that the intervention was most effective among IT employees with high family demands and those with less supportive work environments [124]. A similar study conducted among our sample of extended care workers, however, revealed that the effects of the intervention on organizational outcomes, such as safety compliance and organizational citizenship behavior, did not operate through alterations in work-to-family conflict, schedule control and supervisory support [131]. Thus, it is possible that workplace programs seeking to reduce work and family strain may operate through these pathways in some populations but not in our particular sample, making it challenging to detect overall intervention effects on employee levels of inflammation in this study.

The notion that changes in the proposed mediators relate causally to changes in employee levels of inflammation also warrants further scrutiny. The literature indicates that certain forms

of perceived stress, including interpersonal stress and caregiving responsibilities, correlate with higher levels of pro-inflammatory markers [132]. Research on work stressors and employee markers of inflammation has also started to emerge. While many cross-sectional, observational studies suggest higher work stress is associated with elevated levels of inflammation [105, 106, 111, 115], the limited longitudinal studies in this area have shown mixed results [109, 115, 116]. Like our analysis, these studies have been conducted among relatively healthy employee populations, not individuals presumed to have higher than average levels of stress or inflammation. Thus, it is difficult to know if work stress is simply not associated with employee levels of inflammation or if these effects are diluted by the healthy nature of the individuals in the study. We are also not aware of existing experimental data to support the association between work stress and inflammation nor studies, neither observational nor experimental, to support a link between work and family conflict and levels of employee inflammatory markers specifically.

Given the possibility that this intervention program may not affect the intended mediators and/or that these mediators may not relate to employee markers of inflammation, it is also useful to keep in mind that the overall treatment effect on employee inflammation (c) is equal to the product of the effect of the intervention on the hypothesized mediators (a) and the effect of these mediators on employee markers of inflammation (b) (a*b = c), assuming linear relationships. We can determine rough and comparable estimates for (a), (b) and (c) by consulting the literature and making use of z-transformations. Preliminary WFHN findings from the IT industry suggest significant intervention effects on WTFC from baseline to follow-up [124]. Based on the regression coefficients provided for the treatment*time interaction, we can calculate a predicted effect of treatment on WTFC at follow-up (-0.116). We can also standardize this estimate by the

mean and standard deviation of WTFC in our sample, as the authors did not report this statistic in their publication ((-0.116)/.92= -0.126) for a rough estimate of (a). While there is no research on the effects of work and family stressors on markers of inflammation per se, one study indicates that job burnout is significantly associated with CRP (β=0.30) [108]. When we standardize this estimate by the standard deviation of the exposure in that study, we generate a rough estimate for (b) (0.30/0.78=0.385). These rough estimates suggest that the overall effect of the intervention on CRP may plausibly be -0.049 (a*b= -0.126*0.385).

We are likely underpowered to detect treatment effects of this size given our sample size of 949 employees. In fact, in regression models for CRP, confidence intervals for the effects of treatment from baseline to 12 months (time*treatment) include this estimated effect (-0.049). Of course it is also possible that workplace programs operate through alternate mechanisms. For example, it may be easier to change employee health behaviors relating to markers of inflammation, like BMI, than perceptions of their work environment. We suggest that future research rigorously examine both pathways (that is, a and b referenced above) and explore alternate mechanisms by which workplace interventions may succeed in promoting healthy levels of inflammation.

The intervention does affect markers of inflammation, but these effects were not present in our study:

Assuming that a workplace program designed to improve work-to-family conflict, schedule control and the support of supervisors for work and family issues causally influences markers of inflammation, it may be that the intervention operates through more latent mechanisms than those proposed by the WFHN and this study. To our knowledge, no

psychosocial workplace intervention has attempted to change inflammation levels directly over time. In animal lab studies, experimental surgery, introduction of a virus or wound infliction has resulted in elevated CRP as quickly as 24 hours [133-135]. In humans, laboratory-induced stress has resulted elevated levels of CRP and cytokines such as IL-6 in a little as 10-30 minutes [105, 136-138]. These studies suggest that it is physiologically plausible for our outcomes of interest to change in short periods of time; however, it is not clear whether one year is a sufficient etiologic period for a workplace program to effectively alter work and family stressors and subsequently change markers of inflammation. Interestingly, two related cross sectional studies in Israel suggested that work-related stressors were associated with CRP [107, 108]. However, a subsequent longitudinal study by the same researchers found no association between work stressors and changes in circulating CRP levels over a 12 months period [109], suggesting that even when evidence on work-related exposures and markers of inflammation does exist, the etiologic period to change these outcomes may be longer than one year. We urge future research to investigate the plausibility of these relationships and the time required for psychosocial exposures to effectively change markers of inflammation in a non-laboratory setting.

Last, a causal relationship between the workplace intervention and markers of inflammation may not be detectable given issues of selection in our sample. While plausible, we do not feel that selection sufficiently explains the absence of main effects of our study, however. Employees who were excluded from the analytic sample had significantly lower levels of CRP and obesity at baseline than those who were analyzed, but no other notable differences were present. We also found that baseline levels of employee inflammation may predict dropout of our sample from baseline to 12 months for CRP and IL-1β but that these associations did not vary by treatment status. Thus, “healthier” employees may have been excluded from our original sample,

which would potentially exaggerate results, but we also see that "sicker" individuals left our study over time, which would drive our overall results toward the null. Most importantly, no overwhelming selection trends were detected and, thus, any biases due to exclusion criteria or dropout are likely to be minimal.

Limitations and strengths:

We note some limitations of this research. Our study includes workers only and, in general, employed individuals exhibit better health than those who do not participate in the labor force [139-141], which may make it challenging to detect improvements in markers of health over the course of the study. It is also important to keep in mind that the levels of biomarkers of inflammation studied here do not represent cardiovascular disease risk per se. They serve as correlates of disease [70], though whether they also represent an intermediary along the causal pathway to disease remains debated [98, 142]. Thus, it is difficult to make claims about the intervention effects on overall cardiovascular health from these data. Employees consented to participate and there is also a possibility that either healthier or sicker employees selected into the study, which could bias results in either direction. Finally, the results of this study are only generalizable to employees (predominantly women) in the healthcare industry, and it is not certain whether findings can be extrapolated to other settings.

This research exhibits a number of strengths as well. Most notably, this study represents the first experimental examination of the effects of a workplace program to address work and family strain on changes in employee markers of inflammation over time. Alongside the WFHN, we were able to capitalize on funded research efforts to conduct a randomized field experiment, interview, follow employees longitudinally and collect biomarkers of health, all of which are

extremely time- and financially-intensive endeavors. Cardiovascular disease takes decades to develop, particularly among a relatively young cohort such as the one analyzed here, and markers of inflammation serve as meaningful indicators of cardiovascular disease risk in a short time frame. We were fortunate to access this unique data to rigorously and causally test an unanswered and relevant scientific question. We also make important methodologic contributions to the work/family literature by utilizing data at multiple time points and multilevel modeling techniques to appropriately account for the clustering of multiple measures for each employee as well as the nesting of employees within worksites. This method produces accurate standard errors and confidence intervals. Last, our sample includes racially and ethnically diverse employees, which the job strain (and to some extent work/family) literature greatly lacks.

Conclusion:

In light of major labor force changes in recent decades, the current study examined the effects of a nursing-home based intervention to improve employee work/family conflict, schedule control and support from supervisors on employee markers of inflammation. While we did not detect any significant effects of this particular intervention on the outcomes of interest, we believe this research question warrants continued examination given the prevalence of work-to-family conflict and the burden of heart disease in the U.S. We are optimistic that the WFHN workplace program offers an opportunity to improve employee health, as related research has revealed it does benefit employee mental health and behaviors such as smoking. We recommend future research attempt to replicate or refute this study's findings in a variety of study populations, examine the etiologic period necessary for workplace programs to change markers

of inflammation and investigate pathways by which workplace policies and practices may benefit employee well-being more generally.