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Does inflammation provide a link between psychosocial work characteristics and diabetes?

Analysis of the role of interleukin-6 and C-reactive protein in the Whitehall II cohort study

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ABSTRACT

Objective:

Inflammation may underlie the association between psychological stress and cardiometabolic diseases, but this proposition has not been tested longitudinally. We investigated whether the circulating inflammatory markers interleukin-6 (IL-6) and C-reactive protein (CRP) mediate the relationship between psychosocial work characteristics and diabetes.

Methods:

We used three phases of data at 5 years intervals from the Whitehall II cohort study, originally recruiting 10308 civil service employees aged 35–55 years. The data included repeat self-reports of job demands, control and social support, IL-6 from plasma samples, CRP from serum samples, and diabetes, ascertained through oral glucose tolerance test, medications, and self-reports of doctor-diagnosed diabetes.

Results:

Structural equation models with age, sex and occupational position considering men and women combined, showed that low social support at work, but not high job demands or low job control, was prospectively associated with diabetes (standardized ß=0.05, 95 % confidence interval (CI) 0.01-0.09) and higher levels of IL-6 (ß=0.03, CI 0.00-0.06). The inflammatory markers and diabetes were bidirectionally associated over time. A mediation model including workplace social support, IL-6 and diabetes further showed that 10% of the association between social support and diabetes over the three repeat examinations (total effect ß=0.08, CI 0.01-0.15) was attributable to a weak indirect effect through IL-6 (ß=0.01, CI 0.00-0.02). A similar indirect effect was observed for CRP in men only, while job control was prospectively associated with IL-6 among women.

Conclusions:

This study indicates an association between poor workplace support and diabetes that is partially ascribed to an inflammatory response.

Keywords: social support, occupational stress, psychosocial factors, inflammation, mechanism, pathways, diabetes mellitus

1. INTRODUCTION

Workplace experience may represent an important source of stress, increasing the risk of cardiometabolic disease. For example, a combination of having high job demands and low control (known as job strain), efforts at work exceeding rewards in terms of pay, esteem, or career opportunities (i.e. effort-reward imbalance), and long working hours have been associated with coronary heart disease or stroke.[1] Job strain and long working hours have also been associated with for example diabetes,[2,3] although the findings on diabetes have not been universal.[4] Social support at work and injustice represent other possible risk factors for coronary heart disease[5] and recent work indicate that social stressors, such as bullying and violence, are associated with increased risk of diabetes and cardiovascular disease.[6] While these various links between psychological work characteristics and health endpoints appear to be robust, the mechanisms that explain these effects are not well understood.[1]

Systemic inflammation has been proposed as a plausible mechanism for the association between psychological stress and chronic diseases.[7] Psychosocial factors, including work characteristics, are thought to activate the hypothalamic–pituitary–adrenal and sympathetic adrenal medullary systems, which can increase production of cytokines such as interleukin 6 (IL-6), interferons, and tumor necrosis factors and activate a C-reactive protein (CRP) response.[8] This kind of response to stressors may be beneficial in the short term by a direct activation of the immune system in response to acute threats, but prolonged exposure to stress is assumed to be harmful, contributing to elevated systemic inflammation.[7] These inflammatory markers have also been implicated in the pathogenesis of cardiovascular disease and diabetes,[9] although conclusive evidence is lacking.

A recent large scale study showed a relationship between effort-reward imbalance at work and higher white blood cell count, also a marker of inflammation,[10] and a review focusing on effort-reward imbalance at work found associations with markers of reduced immune competence and increased inflammation.[11] Research on the association between the job demand-control-support model and inflammatory markers has been less conclusive: some studies have found an association between job strain, job demands or job control and CRP[12,13] or IL-6,[14] while no association was observed elsewhere.[15-18] A relationship between social support at work and IL-6[19] or CRP[12] have also been reported but, again, discordant results exist.[16,17]

With most of the evidence regarding work stress and inflammation being derived from cross-sectional studies, concerns about reverse causality are raised. Accordingly, we aimed to investigate whether components of the job-demand-control-support model are longitudinally associated with IL-6 and CRP. Moreover, we investigated whether these inflammatory markers mediate the association of job demands, job control, and workplace support with diabetes, which has not been examined longitudinally. The study was based on repeated measure data, allowing for mediation analyses with proper temporal order between exposure, potential mediator and outcome variables.

2. MATERIAL AND METHODS

2.1 Sample

The study was based on data from the Whitehall II study, in which employees aged 35–55 years were recruited from 20 London-based Civil Service departments.[20] The first data collection took place 1985-1988, when all civil servants were asked to respond to questionnaires, and to visit a research clinic for clinical measurements. In total, 10308 individuals (6895 men and 3413 women) responded, representing 73 % of the invited employees. Since then, study members have been invited to a research clinic at 5-year intervals with questionnaires distributed in the interim. Informed consent was obtained from all participants, and the University College London Medical School Committee on the Ethics of Human Research approved the protocol.

The study sample for the present analyses consisted of study members who participated in three subsequent phases of clinical measurements: phase 3 (1991-1993) when IL-6 and CRP were first measured (our effective 'baseline' in the present analyses), phase 5 (1997-1999), and phase 7 (2003-2004). Of the phase one participants, 85%, 71%, and 68% participated in these phases, respectively. The total number of participants in all three phases included in the different analyses is shown in Supplemental Figure S1. Almost 2000 individuals, still working in phase 7, had complete data on job demands, job control, or workplace support, inflammatory markers and diabetes in all three phases required for the mediation analyses, while up to 4354 individuals provided both questionnaire and clinical data for bivariate analyses.

2.2 Psychosocial work characteristics

Four indicators were investigated in the present study; job demands, job control, social support at work, and job strain (a combination of job demands and control). These indicators were based on the job demand-control-support model.[21,22] Other psychosocial working conditions such as effort-reward imbalance were not available in all three phases. Four questions, based on a modified version of the Job Content Questionnaire, were used to capture job demands (e.g. working very hard/intensively, having enough time) and 15 questions were used to measure job control (e.g., learning new things, high level of skill, a lot of say/what to do). Work social support was ascertained using six items on support from supervisors and colleagues, as well as clarity and consistency of information. The items in each subscale were originally combined into scores ranging between 0-100%, shown to have acceptable internal consistency.[23] We divided the original scales by 10 in order to achieve more equal variances in the models. Finally, we created a measure of job strain by first dichotomizing job demands and job control using median split. In our analyses, we considered people with a combination of high job demands and low control at work as being the group exposed to job strain with the remainder as unexposed.

2.3 Inflammatory markers

Clinical measurements were performed according to standard protocol. Venous blood samples were taken in the morning after over-night fasting, or in the afternoon after no more than a light, fat-free breakfast eaten before 08:00. The blood samples were stored at −80°C. A high-sensitivity immunonephelometric assay was used in a BN ProSpec nephelometer (Dade Behring) to assess CRP from serum samples. Plasma IL-6 levels were measured with a high-sensitivity enzyme-linked immunosorbent assay (R&D Systems). As is standard, values lower than the detection limit [0.154 mg L−1 for CRP (multiplied by 9524 to express the value in mmol L−1) and 0.08 pg mL−1 for IL-6] were assigned a value equal to half the detection

limit. Moreover, values for CRP above 20 mg/L, as may indicate acute infection, were excluded. The original values for CRP and IL-6 were skewed, and were therefore logarithmically transformed for the purposes of our analyses.

2.4 Diabetes

Diabetes was ascertained from both self-reports and clinical measurements including a standard 2-hour 75g oral glucose tolerance test. The self-reports included enquiries about physician-diagnosed diabetes and use of blood glucose-lowering medication. We defined individuals as suffering from diabetes if they had self-reported physician-diagnosed diabetes, used blood glucose-lowering medication, had a fasting glucose of ≥7.0 mmol/L, or had a 2-hour post-load glucose of ≥11.1 mmol/L.[24] This may include both type 1 and type 2 diabetes, although adult onset diabetes generally represent type 2 diabetes.[25]

2.5 Covariates

A number of baseline characteristics measured at phase 3 were also considered as potential confounders including age and sex. Occupational position was categorized into 3 groups: administrative, professional and executive, and clerical and other. Moreover, longstanding illnesses, disability or infirmity other than diabetes and affecting people lives at baseline were considered in additional models. Weight (measured by Soehnle scale to the nearest 0.1 kg) and height (measured to the nearest mm using a stadiometer) were assessed by trained nurses. Body mass index (BMI), calculated as weight divided by height squared, current smoking (yes/no), risky alcohol consumption (drinking more than 21 or 14 units per week for men and women, respectively), low physical activity (less than 1 h of moderate or vigorous physical activity per week), and antihypertensive, CVD or diabetic medication were considered as covariates in supplementary analyses.

2.6 Data analyses

Structural equation modeling was used to perform simultaneous multiple regression analyses. We first assessed associations between each psychosocial work characteristic and each inflammatory marker separately, and between each inflammatory marker and diabetes (bivariate analyses). The models included correlations between variables measured in the same phase, autoregressions between the observed variables in order to account for earlier values of the same measures, and cross-lagged paths in both directions to test bidirectional relationships over time.[26] Estimates of associations were reported as standardized regression coefficients with accompanying 95 % confidence intervals. The corresponding estimates of association across different phases were assumed to be equal to increase precision and reduce model complexity. The models including continuous work characteristics and inflammatory markers only were fitted with Maximum Likelihood (ML) estimation with robust standard errors, while the models of inflammatory markers and diabetes were fitted with Diagonal Weighted Least Squares (DWLS) with robust standard errors to account for the categorical nature of the diabetes estimate.[27] Several different models were fitted, sequentially adjusting for covariates, and multigroup analyses performed to assess if there were any differences between men and women.

If the bivariate analyses showed that work factors were associated with future values of the inflammatory markers and that inflammatory markers were associated with subsequent diabetes, we further fitted models simultaneously including exposure-, putative mediator- and outcome variable. The autoregressive SEM models were specified in accordance with the approach for time-varying exposures and mediators described by VanderWeele and Tchetgen Tchetgen[28] based on a three wave mediation model proposed by MacKinnon.[29] The indirect

effect of a psychosocial work characteristic in phase 3 on diabetes in phase 7 via an inflammatory marker in phase 5 was calculated by the product method and based on standardized regression coefficients. To test whether the results were also robust to possible bias by violations in assumptions about non-linearities and interactions, we also calculated a randomized interventional analogue of the natural indirect effect (NIE^R) based on the counterfactual framework, also referred to as the mediational g-formula.[28] The natural indirect effect essentially compares what would have happened for an exposed if we fixed the mediator to the level it would have been if the person had been unexposed. The NIE^R instead consider what would have happened if the mediator were fixed to a level that is randomly chosen from the distribution of the mediator among all of those unexposed. The NIE^R is based on fewer assumptions and can therefore be identified in settings with time-varying exposures and mediators and when mediator-outcome confounding affected by exposure may be a problem. The three wave model and equations for calculations of indirect effects are presented in Supplemental Figure S2.

Model fit was assessed by the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the root mean square error of approximation (RMSEA) based on recommendations available in the literature.[30] Values of RMSEA less than 0.05 and CFI and TLI close to 1 are assumed to be indicative of a well-fitting model. The analyses were conducted using the lavaan package in R.

3. RESULTS

Table 1 presents the baseline characteristics for the 4638 participants. Compared to excluded individuals, the analytical sample had a higher proportion of men, employees from higher social groups, people with risky alcohol consumption, but a lower prevalence of the current smokers. The mean age was also lower in the analytical sample, as were the levels of IL-6 and CRP, while mean levels of exercise, demands-, control- and support at work were higher.

People with high job demands, low job control and low workplace social support at work had similar distributions of demographic-, lifestyle-, and clinical characteristics as their counterparts.

3.1 Work characteristics and inflammatory markers

The bivariate analyses on work characteristics and inflammatory markers indicated a lagged association between workplace social support and IL-6 (Supplemental Table S1, Figure 1a). Lower workplace social support was associated with higher levels of IL-6 in the subsequent phase (standardized regression coefficient ß=0.03, CI 0.00 to 0.06, p=0.051 after adjusting for sex, age and occupational position). This indicated that a decrement in one standard deviation in support (on a scale from 0-10) increased the level of IL-6 (log scale) by 0.03 standard deviations, meaning an increase with 1.03 on the original scale (0.1-41.3 pg/ml) or by 3%. A correlation was also observed between workplace social support and IL-6 suggesting a contemporaneous association. The results were similar when adjusting for long-term illness and BMI, health behaviors and medication (Supplemental Table S1). However, IL-6 was not determined by job demands or job control in the previous phase (Supplemental Table S2-3, Figure 1b-c), but was, however, associated with lower job demands prospectively (ß =-0.04 95% confidence interval (CI) -0.07 to -0.02, p=0.002), and there was a correlation between

demands and IL-6 measured in the same phase. Neither job demands, job control, job strain, nor workplace support predicted future CRP (Supplemental Table S5-8), but a correlation between contemporary job demands and CRP and between job strain and CRP was found (Supplemental Table S6, S8, Figure 1d). All models above showed acceptable fit to the data according to CFI (0.91-0.95) and/or RMSEA (0.07-0.10).

Figure 1 about here

Multigroup analyses were further performed while adjusting for age and occupational position. Some models stratified for sex showed better to the data according to chi-square difference tests, indicating some difference between men and women. In models regarding job control and IL-6, job control predicted subsequent IL-6 among women but not men and the association between job strain and IL-6 measured at the same phase differed among women (Supplemental Table S9). We also found that a model regarding job strain and CRP stratifying for sex fitted better than a model including both men and women, but there were no major differences in estimates of contemporaneous or lagged effects (Supplemental Table S10).

3.2 Inflammatory markers and diabetes

Next, unadjusted and adjusted analyses confirmed an association between both IL-6 and later diabetes as well as between diabetes and later IL-6 (Figure 2, Supplemental Table S11). A similar pattern was found for CRP (Supplemental Table S12). In models adjusting both for sex, age, occupational position, long-term illness, BMI, health behaviors and medication, even stronger estimates of association were found between diabetes and later inflammatory markers, which were stronger than the estimates of association in the direction from

inflammatory marker to diabetes. The models showed acceptable fit to the data according to CFI (0.92-0.95) and/or RMSEA (0.07).

Figure 2 about here

In multigroup analyses we found that sex-stratified models fitted better to the data. The most obvious difference was a strong relationship between diabetes and subsequent IL-6 among men, while no corresponding statistically significant association was observed among women. These analyses, however, generally confirmed an association between both inflammatory markers and later diabetes as well as between diabetes and later inflammatory markers (Supplementary Table S13).

3.3 Work characteristics, inflammatory markers, and diabetes

Based on the results above we performed subsequent analyses including both workplace social support, IL-6 and diabetes in autoregressive SEM models (n=1794, acceptable model fit (CFI 0.96, TLI 0.88, RMSEA 0.064) when adjusting for sex, age and occupational position). The analyses supported an association between workplace social support and diabetes in the subsequent phase (ß=0.05, CI 0.01-0.09, p=0.03), while job demands and job control were not related to subsequent diabetes. This indicated that a decrement in one standard deviation in support (on a scale from 0-10) increased the risk of later diabetes by 5 %. The analyses also indicated an association between workplace social support and diabetes over the three phases as indicated by increased total effect estimate (assessing the overall relationship through both direct and indirect paths). An adjusted model (Figure 3) showed a total effect of ß=0.08 (CI 0.01 to 0.15, p=0.017) and an indirect effect of ß=0.01 (CI 0.00 to 0.02, p=0.039), indicating that part of the association between workplace social support and

diabetes was explained via an increase in IL-6 in the intermediate phase. This suggested that 10 % of the total effect was mediated through IL-6. The randomized analogue of the indirect effect was similar but not statistically significant in the adjusted model (ß=0.01, CI -0.00 to 0.02, p=0.12). A similar estimate of indirect effect was also found when further adjusting for longstanding illness as well as when additionally accounting for body mass index, although the randomized interventional analogue of the natural indirect effect was not statistically significant in the model adjusting for BMI. An indirect effect was only indicated among men when analyses were performed separately, but the number of women included in the analyses were few (n=443).

Figure 3 about here

A model considering CRP as the potential mediator (n=1804), further indicated a tendency towards an association between workplace social support and subsequent CRP (ß=0.03, CI 0.00-0.05, p=0.05), and a possible indirect effect through CRP over the entire study period (ß=0.01, CI 0.00 to 0.02, p=0.07, 10 % of the total effect mediated), but again the counterfactual based indirect effect estimate was slightly weaker (p=0.17). A statistically significant indirect effect through CRP was, however, evident among men (ß=0.01, CI 0.00 to 0.03, p=0.03, 17 % of the total effect, n=1402) in sex stratified analyses, in which the counterfactual based indirect effect estimate was similar (0.01, CI 0.00 to 0.02, p=0.06). However, no total or indirect effect was observed among women (n=446).

Finally, we also fitted a mediation model looking at job control, IL-6 and diabetes among women, but found no total effect of job control on diabetes over the three phases.

4. DISCUSSION

The main findings of the present study were that poorer social support at work was prospectively associated, although weakly, with diabetes and increased levels of IL-6. This prospective association was partly explained by an indirect effect through IL-6.

4.1 Comparison with previous studies

The finding of an association between workplace social support and diabetes is in contrast to a review and meta-analysis which concluded that there was no relationship between low workplace social support and diabetes, although this meta-analysis relied largely on cross-sectional studies.[31] The present results are also in contrast to a previous study considering job demands, job control and workplace support based on Whitehall II data which did not observe an independent association between work social support and diabetes over 15 years of follow-up.[32] Another study even detected an inverse relationship with diabetes among women.[33] The discrepancy with the previous Whitehall study may be partly due to differences in sample, time frame and single baseline versus repeated measures of support. However, in the Whitehall II study the combination of job strain and low social support at work (iso-strain) appeared to increase the risk of incident diabetes among women. The present study also support a recent study suggestive of an association between social work stress and diabetes.[34] Recent work on negative social interactions also suggest that bullying and violence is a risk factor for diabetes.[6]

Previous evidence on social support at work and inflammatory markers has also been somewhat conflicting, as some studies have observed associations with IL-6 or CRP[19,35] while others have found social support at work to be unrelated to IL-6 or CRP.[16,17] In line with the results of the present study a recent study demonstrated a relationship between positive

interactions with coworkers, a proxy for social support, and IL-6,[35] while no corresponding relationship was observed with CRP. Moreover, Nakata et al. observed an association between supervisor support and IL-6.[19] This is, however, to our knowledge, the first prospective study indicating a longitudinal relationship between social support at work and IL-6. Although this relationship across about 5 years seemed to be weak, these results suggest that poorer work social support may be associated with an inflammatory response. This accords well with a recent meta-analysis on general measures of support and commonly studied inflammatory markers.[36]

The results further supported a link between both IL-6 and CRP, and diabetes as well as between diabetes and IL-6. This was expected as previous research have shown that elevated levels of IL-6 and CRP are associated with increased risk of diabetes[37] and demonstrated that chronically elevated levels of glucose can induce inflammation.[38]

This study further provides novel empirical evidence supportive of IL-6 as an intermediate factor in the association between social support at work and diabetes. The findings for CRP were less clear. Both IL-6 and CRP have been proposed as important indicators of inflammation and stress-related biomarkers, but may relate differently to stress. Studies of acute stress e.g. seem to support stress-related elevation of e.g. IL-6, IL-1ß, TNF-α, IL-2 and IL-10, but not CRP, IL-1RA IFN-γ, supporting that specific inflammatory markers may be affected.[39] It should also be noted that IL-6 and CRP may not be optimal indicators of inflammation as elevated levels may also reflect tissue repair and immune activation without inflammatory process.[40] More research thus seem warranted using more unambiguous inflammatory markers to strengthen the knowledge about inflammation as a pathway.

The results indicated a weak indirect effect, suggesting that around 10 % of the association between work social support and diabetes could be attributed to an increase in IL-6. However, the extent of mediation should be interpreted cautiously. These estimates of mediation may be biased if a number of assumptions are not fulfilled, relating to no confounding and correct specification of models. The no confounding assumptions include: 1) no unmeasured confounding of the exposure-outcome association, 2) no unmeasured confounding of the mediator-outcome association, 3) no unmeasured confounding of the exposure-mediator association, and 4) no mediator-outcome confounder affected by the exposure. These assumptions may be violated if the temporal ordering is not correct, which was considered and modelled explicitly in the present study, increasing the likelihood that exposure preceded the mediator and the mediator preceded the outcome. However, we cannot rule out that previous levels of work stressors and inflammatory markers and unmeasured factors such as personality traits and adverse childhood experiences confound the associations, although some analyses eliminating fixed individual characteristics supported the main findings. Factors such as health behaviors and body mass index may also be confounders affected by the exposure, and hence mediators of the association between psychosocial work characteristics and diabetes. We adjusted for these type of factors at baseline, which did not change the results of this study, but we did not consider time-varying health behaviors that could bias the estimate of indirect effect. The estimates of indirect effect also differed slightly between the product method and the counterfactual based approach. The presence of an indirect effect using the product method may be sufficient for establishing the presence of mediation but suffers from some limitations. The counterfactual based estimate may be more likely to represent a causal estimate because it is interpretable as the indirect effect not attributed to interactions between exposure-mediator and for any type of variables not limited to linear variables, given that the above mentioned assumptions hold. This estimate may

therefore be more informative when it comes to estimating the extent to which an association is mediated.[28]

In line with a number of previous studies, but contrary to some others,[12-18,41] there was a lack of association between job demands/control and inflammatory markers in analyses with men and women combined, indicating no role of IL-6 and CRP as mediators of any association between these work characteristics and diabetes over the time frame of the study, which was relatively long; around 5 years between the subsequent measurements and 10 years in total. We cannot exclude the possibility that job demands and job control are related to inflammation and mediate any relationship over shorter time lags. Moreover, we did not assess accumulated exposure to unfavorable job demands and job control which could give rise to chronic low-grade inflammation even in the absence of a short-term effect.

Job control was, on the other hand, related to subsequent IL-6 among women but not men, although no major sex differences in associations over time was indicated. This partly in line with the previous Whitehall II study that found an association between job strain and diabetes among women but not men.[32] However, no sex differences were found in another meta-analyses, based on multiple cohort studies from Europe on job strain and diabetes[2]. Because the number of women included in the present study was relatively small it is, however, questionable whether the power was sufficient for testing sex differences. Few earlier studies have also examined possible sex differences in the relationship between work characteristics and inflammatory markers. More work thus seems warranted to understand if there are any sex differences in response to stress.[42]

4.2 Strengths and limitations

The findings of the present study should also be interpreted in the light of other strengths and limitations of the study. In our analyses we considered prior values of both exposure, mediator and outcome decreasing the risk of confounding. By also modelling associations in the opposite direction, we reduced the risk of reverse causation. The use of measures from three phases is a major strength since we cannot rule out an influence of inflammatory markers on work characteristics, and there are bidirectional relationships between inflammatory markers and diabetes. If the directionality is uncertain, mediation analyses based on studies not allowing for time to elapse between exposure and mediator as well as mediator and outcome can be severely biased.[43] The potential mediators were also measured in the clinic reducing the risk of misclassification of the mediator, and we used a more accurate assessment of diabetes than simple self-reports, including oral glucose testing. Only the work characteristics exposures were self-reported and hence may suffer from reporting bias, although the risk of common method bias is reduced in our design. We adjusted for several potential confounders in our analyses. Finally, the study was restricted to a relatively small group of people participating repeatedly and still working at the end of follow-up with characteristics generally indicating a healthier profile. It is possible that this type of selection can lead to underestimation of associations.

4.3 Conclusions

This prospective study indicates that poor workplace social support is associated with an increased risk of diabetes and that this is to a small extent mediated through an increase in IL-6. Our results imply that inflammation may be a mechanism that explains the association between social relationships and diabetes.

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Table 1. Characteristics at Phase 3 among participants included in the study

	All n=4638	**Free of diabetes** n=4474	**Diabetes** n=105	**High job demands** n=4282	**Low job control** n=4279	**Low workplace social support** n=7421
	n (%)/mean (SD)	**n (%)/mean (SD)**	**n (%)/mean (SD)**	**n (%)/mean (SD)**	**n (%)/mean (SD)**	**n (%)/mean (SD)**
Female sex	1310 (28%)	1256 (28%)	35 (33%)	712 (25%)	414 (21%)	674 (28%)
Age (39-63)	49.6 (6.0)	49.5 (5.9)	52 (6.2)	49.0 (5.5)	49.3 (5.6)	49.2 (5.7)
Grade						
administrative	1978 (43%)	1926 (43%)	28 (27%)	1480 (51%)	1170 (59%)	1009 (42%)
prof/exec	2084 (45%)	2000 (45%)	55 (53%)	1210 (42%)	737 (37%)	1096 (46%)
clerical/support	563 (12%)	536 (12%)	21 (20%)	191 (7%)	73 (4%)	284 (12%)
Job demands (original scale 0-100 %)	62 (19)	62 (19)	57 (19)			
Job control (original scale 0-100 %)	65 (17)	65 (17)	59 (18)			
Workplace social support (original scale 0-100 %)	76 (17)	76 (17)	72 (18)			
IL-6 (0.1-41.3 pg/ml)	1.8 (1.9)	1.8 (1.9)	2.2 (1.8)	1.8 (2.0)	1.8 (2.0)	1.9 (1.8)
CRP (0.077-71.2 mg/l)	1.7 (3.3)	1.7 (3.3)	2.5 (3.6)	1.7 (3.4)	1.6 (2.8)	1.7 (2.2)
BMI (16.0-45.5)	25.1 (3.5)	25.0 (3.5)	26 (4.0)	25.0 (3.4)	25.1 (3.2)	25.3 (3.6)
Physical activity						
Mild exercise (hours per week)	7.0 (7.0)	7.0 (7.0)	6.3 (5.4)	6.6 (5.8)	6.5 (5.5)	6.6 (6.2)
Moderate exercise (hours per week)	2.7 (3.2)	2.7 (3.2)	2.3 (2.6)	2.6 (2.7)	2.7 (2.7)	2.6 (3.0)
Vigorous exercise (hours per week)	0.8 (1.5)	0.8 (1.5)	0.5 (1.0)	0.8 (1.4)	0.9 (1.7)	0.8 (1.5)
Risky alcohol consumption	747 (16%)	720 (16%)	13 (13%)	502 (17%)	383 (19%)	395 (17%)

Smoking						
No smoking	225 (50%)	2152 (51%)	48 (48%)	1393 (51%)	913 (48%)	1132 (49%)
Former smoking	1699 (39%)	1633 (38%)	42 (42%)	1062 (39%)	773 (41%)	885 (39%)
Current smoking	480 (11%)	464 (11%)	9 (9 %)	288 (11%)	203 (11%)	271 (12%)
Long-term illness (excluding diabetes)	1443 (32%)	1443 (32%)	0 (0%)	927 (33%)	590 (30%)	740 (32%)

Figure legends:

Figure 1. Standardized regression coefficients from the structural equation models considering cross-lagged paths between psychosocial work characteristics and interleukin 6 based on 3 phases of data and adjusting for baseline sex, age and occupational position. 95 % confidence intervals are given within parenthesis.

*=P-value<0.05, **=P-value<0.01, ***=P-value<0.001, P=Whitehall II Phase, DEM=job demands (higher values represents higher demands), CON=job control (higher values represent lower control), WSS=workplace social support (higher values represent lower support), JST= job strain (having job strain compared to no job strain)

Figure 2. Standardized regression coefficients from the structural equation models considering cross-lagged paths between interleukin 6 and Diabetes based on 3 phases of data and adjusting for baseline sex, age and occupational position. 95 % confidence intervals are given within parenthesis.

*=P-value<0.05, **=P-value<0.01, ***=P-value<0.001, P=Whitehall II Phase, IL-6=interleukin 6, DIA=Diabetes

Figure 3. Standardized regression coefficients from the autoregressive mediation model considering cross-lagged paths between workplace social support, interleukin 6, and Diabetes based on 3 phases of data and adjusting for baseline sex, age and occupational position. 95 % confidence intervals are given within parenthesis.

*=P-value<0.05, **=P-value<0.01, ***=P-value<0.001, P=Whitehall II Phase, WSS=workplace social support (higher values represent lower support), IL-6=interleukin 6, DIA=Diabetes

Supplementary Figure S1. Flowchart showing the sample selection for the bivariate analyses on work characteristics and inflammatory markers, bivariate analyses on inflammatory markers and diabetes, as well as mediation analysis considering work characteristics, inflammatory markers and diabetes.

Supplementary Figure S2. An illustration of the three-wave autoregressive mediation model by MacKinnon[1] adapted from Vanderweele and Tchetgen Tchetgen[2], with notations for certain path coefficients in line with Vanderweele and Tchetgen Tchetgen.[2]
A=exposure (job demands, job control or workplace support) M=mediator (Interleukin 6 (IL-6) or C reactive protein (CRP)), Y=outcome (diabetes). The indirect effect according to the product method was calculated using the following equation: $\beta_{11*}\ \theta_{23}$. The randomized interventional analogue of the natural indirect effect was calculated using the following equation: $\{\theta_{23}\beta_{12}+\theta_{25}\theta_{14}\beta_{12}+\beta_{21}\theta_{24}+\beta_{24}\theta_{12}\theta_{24}\}[a(1)-a^*(1)]+\ \beta_{22}\theta_{24}\ [a(2)-a^*(2)]$, in which a refers to an exposure level and a* to the new exposure level following a change in exposure.

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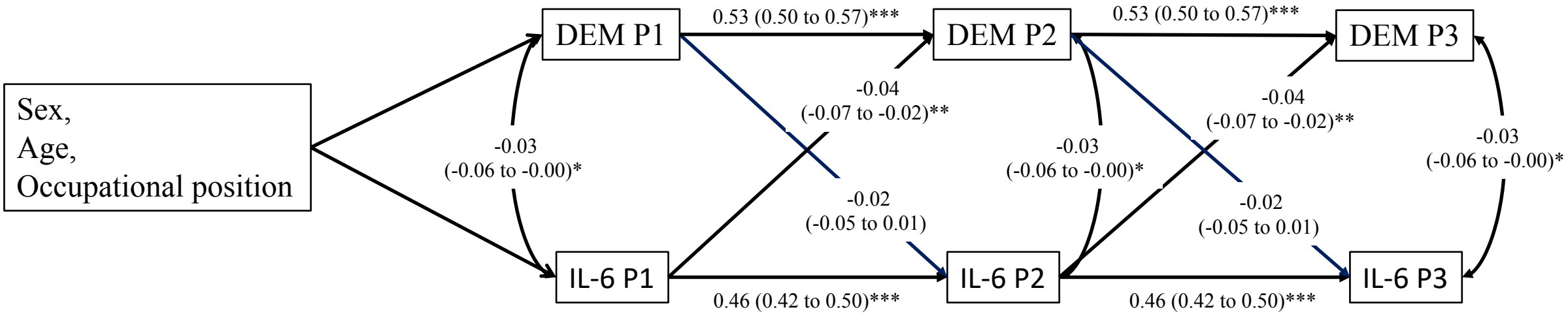
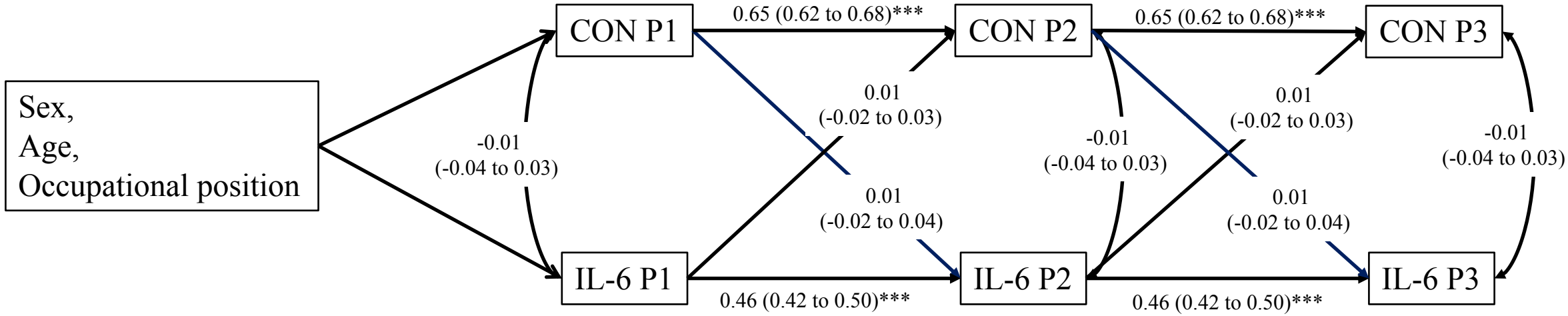
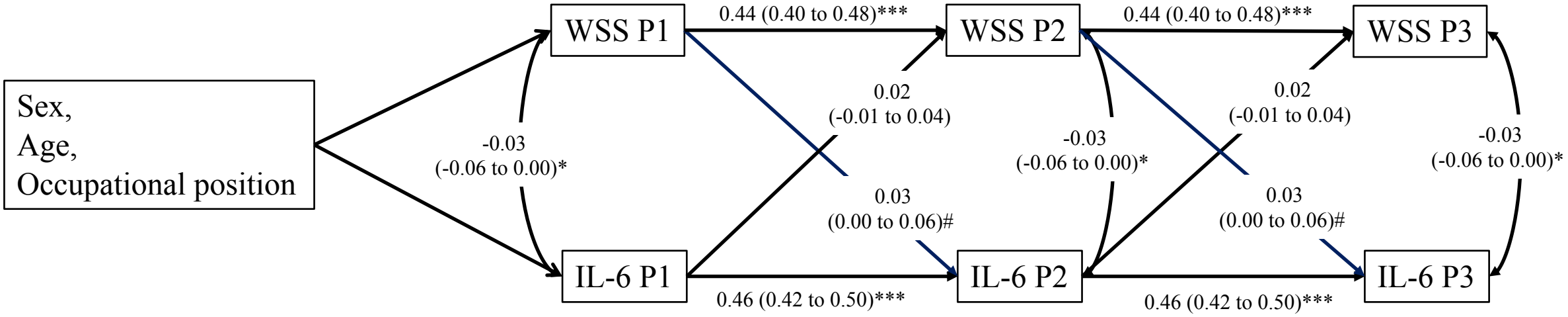
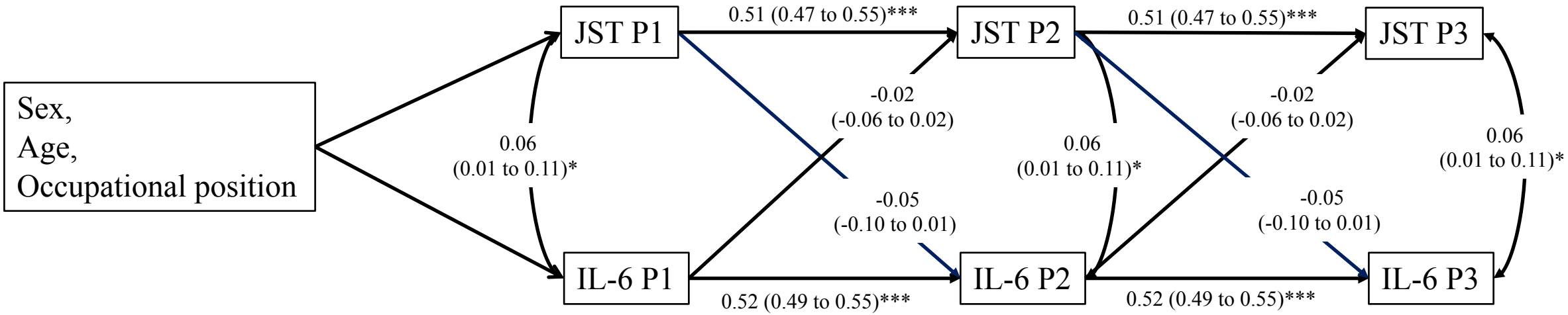
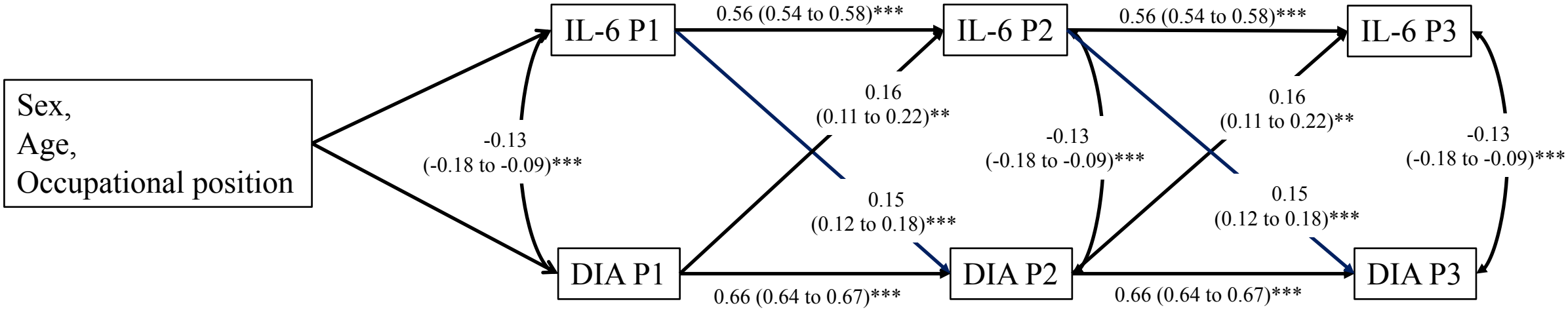
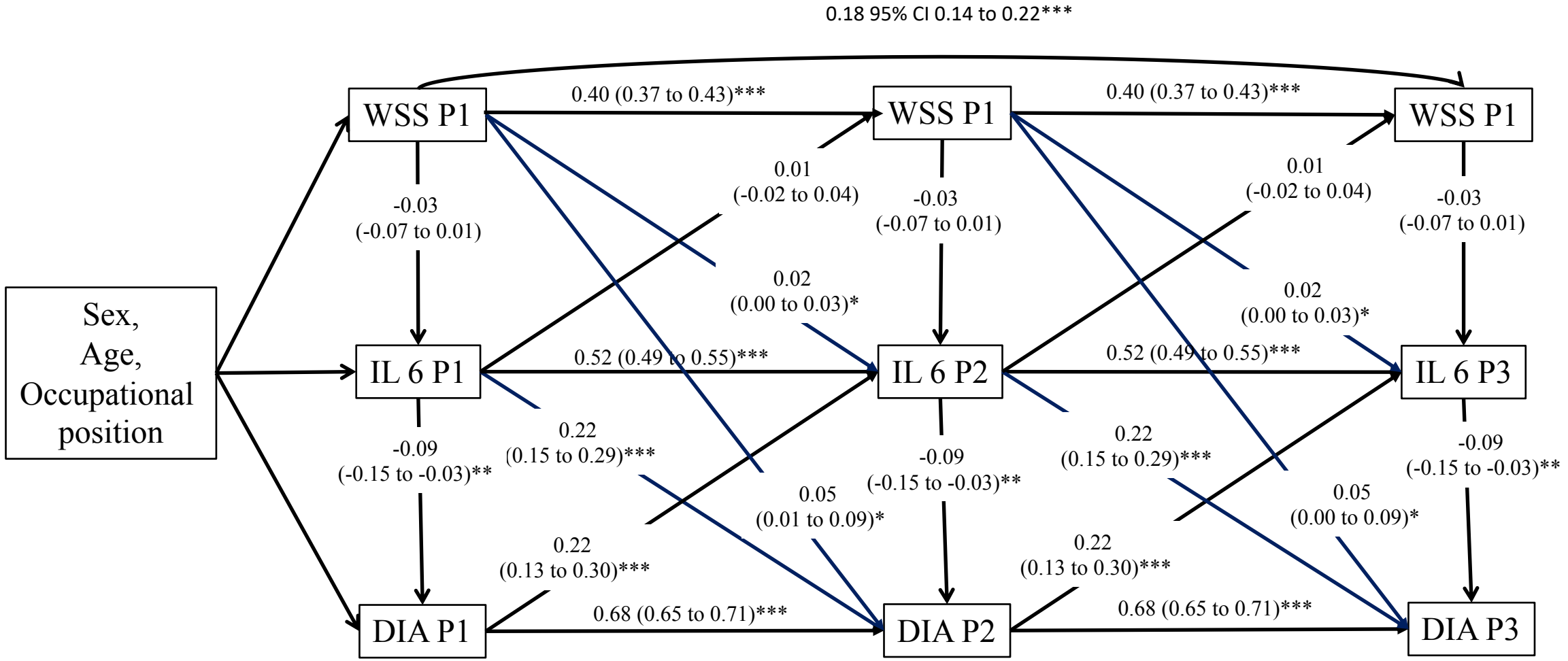

Sex,
Age,
Occupational position
DEM P1
DEM P2
DEM P3
IL-6 P1
IL-6 P2
IL-6 P3
0.53 (0.50 to 0.57)***
0.53 (0.50 to 0.57)***
-0.04
(-0.07 to -0.02)**
-0.04
(-0.07 to -0.02)**
-0.03
(-0.06 to -0.00)*
-0.03
(-0.06 to -0.00)*
-0.03
(-0.06 to -0.00)*
-0.02
(-0.05 to 0.01)
-0.02
(-0.05 to 0.01)
0.46 (0.42 to 0.50)***
0.46 (0.42 to 0.50)***


Sex,
Age,
Occupational position
CON P1
IL-6 P1
CON P2
IL-6 P2
CON P3
IL-6 P3
0.65 (0.62 to 0.68)***
0.65 (0.62 to 0.68)***
0.46 (0.42 to 0.50)***
0.46 (0.42 to 0.50)***
-0.01
(-0.04 to 0.03)
0.01
(-0.02 to 0.03)
0.01
(-0.02 to 0.04)
-0.01
(-0.04 to 0.03)
0.01
(-0.02 to 0.03)
0.01
(-0.02 to 0.04)
-0.01
(-0.04 to 0.03)


Sex,
Age,
Occupational position
WSS P1
WSS P2
WSS P3
IL-6 P1
IL-6 P2
IL-6 P3
0.44 (0.40 to 0.48)***
0.44 (0.40 to 0.48)***
0.02
(-0.01 to 0.04)
0.02
(-0.01 to 0.04)
-0.03
(-0.06 to 0.00)*
-0.03
(-0.06 to 0.00)*
-0.03
(-0.06 to 0.00)*
0.03
(0.00 to 0.06)#
0.03
(0.00 to 0.06)#
0.46 (0.42 to 0.50)***
0.46 (0.42 to 0.50)***


Sex,
Age,
Occupational position
JST P1
JST P2
JST P3
IL-6 P1
IL-6 P2
IL-6 P3
0.51 (0.47 to 0.55)***
0.51 (0.47 to 0.55)***
-0.02
(-0.06 to 0.02)
-0.02
(-0.06 to 0.02)
0.06
(0.01 to 0.11)*
0.06
(0.01 to 0.11)*
0.06
(0.01 to 0.11)*
-0.05
(-0.10 to 0.01)
-0.05
(-0.10 to 0.01)
0.52 (0.49 to 0.55)***
0.52 (0.49 to 0.55)***


Sex,
Age,
Occupational position
IL-6 P1
IL-6 P2
IL-6 P3
DIA P1
DIA P2
DIA P3
0.56 (0.54 to 0.58)***
0.56 (0.54 to 0.58)***
0.16
(0.11 to 0.22)**
0.16
(0.11 to 0.22)**
-0.13
(-0.18 to -0.09)***
-0.13
(-0.18 to -0.09)***
-0.13
(-0.18 to -0.09)***
0.15
(0.12 to 0.18)***
0.15
(0.12 to 0.18)***
0.66 (0.64 to 0.67)***
0.66 (0.64 to 0.67)***


0.18 95% CI 0.14 to 0.22***
Sex, Age, Occupational position
WSS P1
WSS P1
WSS P1
IL 6 P1
IL 6 P2
IL 6 P3
DIA P1
DIA P2
DIA P3
0.40 (0.37 to 0.43)***
0.40 (0.37 to 0.43)***
-0.03 (-0.07 to 0.01)
-0.03 (-0.07 to 0.01)
-0.03 (-0.07 to 0.01)
0.01 (-0.02 to 0.04)
0.01 (-0.02 to 0.04)
0.02 (0.00 to 0.03)*
0.02 (0.00 to 0.03)*
0.52 (0.49 to 0.55)***
0.52 (0.49 to 0.55)***
-0.09 (-0.15 to -0.03)**
-0.09 (-0.15 to -0.03)**
-0.09 (-0.15 to -0.03)**
0.22 (0.15 to 0.29)***
0.22 (0.15 to 0.29)***
0.05 (0.01 to 0.09)*
0.05 (0.00 to 0.09)*
0.22 (0.13 to 0.30)***
0.22 (0.13 to 0.30)***
0.68 (0.65 to 0.71)***
0.68 (0.65 to 0.71)***

Highlights

- Psychological factors at work my influence diabetes risk
- Low social support at work, but not demands or control, was related to diabetes
- IL-6 and CRP (men only) partially mediated the effect for social support at work
- Inflammation may be one factor that underlies the social support–diabetes link