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SCReening Evaluation of the Evolution of New Heart Failure Study (SCREEN-HF): early detection of chronic heart failure in the workplace

Umberto Boffa[1,5] MBBS, GDOHSM, MBA, FAFOEM, FCHSM, Adjunct Senior Research Fellow
Michele McGrady[2] FRACP, MBBS, PhD, Cardiologist
Christopher M. Reid[1] PhD, Professor and Director
Louise Shiel[1] BSc,GradDipAppSci(CompSc),GradDipEd(Sec), Research Manager
Rory Wolfe[1] BSc, PhD, Professor of Biostatistics
Danny Liew[1] MBBS, BMedSc, FRACP, PhD, Chair of Clinical Outcomes Research
Duncan J. Campbell[3] MBBS, BMedSc, PhD, GradDipEpiBiostat, FRACP
Simon Stewart[4] BA, Dip Ed,PhD, RN, Professor of Nursing Research
Henry Krum[1] MBBS, PhD, FRACP, FESC, Director (Deceased)

[1]Department of Epidemiology and Preventive Medicine, Monash University, The Alfred Centre, 99 Commercial Road, Melbourne, Vic. 3004, Australia. Email: C.Reid@monash.edu; louise.shiel@monash.edu; rory.wolfe@monash.edu
[2]Royal Prince Alfred Hospital, Sydney, NSW 2050, Australia. Email: michelle.mcgrdy@centralsydneycardiology.com.au
[3]Department of Molecular Cardiology, St. Vincent's Institute of Medical Research, 41 Victoria Parade, Fitzroy, Vic. 3065, Australia. Email: dcampbell@svi.edu.au
[4]Australian Catholic University, Mary MacKillop Institute for Health Research, Level 5, 215 Spring Street, Melbourne, Vic. 3000, Australia. Email: simon.stewart@acu.edu.au
[5]Corresponding author. Email: dr.umberto.boffa@gmail.com

Abstract

Objective. The aim of the present study was to determine whether asymptomatic heart failure (HF) in the workplace is subject to the health worker effect, making screening using conventional risk factors combined with a cardiac biomarker, namely N-terminal pro B-type natriuretic peptide (NT-proBNP), as useful as in the general population.

Methods. Between June 2007 and December 2009 a 'well' population deemed at high risk for development of HF was identified through health insurance records. Blood was collected from volunteer participants for analysis of urea, electrolytes and creatinine, a full blood count and NT-proBNP. An echocardiogram was performed on selected participants based on high NT-proBNP concentrations.

Results. The mean left ventricular ejection fraction (LVEF) was significantly reduced in participants with the highest compared with the lowest NT-proBNP quintile. In multivariate analysis, log-transformed NT-proBNP was independently associated with impaired LVEF and with moderate to severe diastolic dysfunction after adjustment for age, sex, coronary artery disease, diabetes, hypertension and obesity.

Conclusions. A large burden of asymptomatic left ventricular dysfunction (AVLD) was observed in subjects aged 60 and over with plasma NT-proBNP in the top quintile that was independent of conventional risk factors and work status. HWE does not appear to operate in AVLD. NT-proBNP testing in a population with HF risk factors may cost-effectively identify those at greatest risk of developing HF in a working population and facilitate early diagnosis, treatment and maintenance of work capacity.

What is known about the topic? Chronic heart failure (CHF) has several causes, the most common being hypertension and coronary ischaemia. CHF is a major health problem of increasing prevalence that severely impacts quality of life, shortens lives and reduces worker productivity. It is often not diagnosed early enough to take full advantage of ameliorating medication.

What does this paper add? Population screening for CHF is not currently advocated. This may be because conventional risk factors must be used in combination and there is no useful biomarker available. Yet evidence (SOLVD (Studies of Left Ventricular Dysfunction trials) recommends early diagnosis. We believe the work place is an area of potential screening where there is little supporting evidence. This paper provides evidence that the biomarker NT-proBNP is a useful new tool that improves cost-effectiveness of screening in a selected population. Specifically, the paper recommends CHF screening in the population with the highest potential health gain (i.e. the working population) by the sector with the highest economic gain (i.e. employers).

What are the implications for practitioners? The paper presents important health screening recommendations for medical and health and safety practitioners within a selected population of workers. We feel practitioners should consider screening for incipient heart failure, particularly within Australia's working population, to save lives, provide economic benefit and extend working longevity.

Additional keywords: cardiac biomarkers, echocardiography, ventricular dysfunction.

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Introduction

The aging population has led to a rising prevalence of heart failure (HF).[1] Morbidity, mortality and cost of care remain high, so there is an urgent need for early detection, when early treatment may more favourably affect the course of the disease.[2] Many studies[3–5] have shown the benefit of early diagnosis and treatment. Epidemiological studies have observed that 50% or more of those with left ventricular (LV) dysfunction are asymptomatic, undiagnosed and presumably untreated.[6]

We formulated the hypothesis that 'asymptomatic' LV dysfunction may not be the same as 'undiagnosed' LV dysfunction; furthermore, little work has been undertaken into the quality of life and functional capacity of those with cardiac remodelling that underlies ventricular dysfunction.[4–6]

This makes the early detection and treatment of asymptomatic LV dysfunction (ALVD) important. However, if the healthy worker effect (HWE) operates in ALVD, which is our hypothesis, screening in the workplace would likely not be appropriate. The HWE means workers with high HF risk may have already left the work force.[7,8]

The workplace has been shown to be an important medium of health promotion and screening.[9–14] If the HWE does not operate, screening for HF and ALVD in the workplace may permit earlier treatment, potentially enhancing quality of life and survival, preserving working life and productivity and doing so at containable cost. Screening is important because effective therapy exists for LV systolic dysfunction.[15] Therapy for LV diastolic dysfunction remains empirical.

The SCReening Evaluation of the Evolution of New Heart Failure Study (SCREEN-HF)[16] combined conventional risk factors and the cardiac biomarker N-terminal pro B-type natriuretic peptide (NT-proBNP) to target an asymptomatic population at high risk for subsequent development of HF to investigate whether NT-proBNP would be an effective screening strategy for the detection of ventricular dysfunction in this high-risk population.

NT-proBNP is the 76-amino acid N-terminal inactive protein that is cleaved from its precursor proBNP to release BNP. Both NT-proBNP and BNP are released from the ventricle in response to pressure or stretch.[16]

The present study analysed the working status of participants within the SCREEN-HF[16] population dataset to determine whether workplace screening for ALVD may be a feasible.

Methods

Between June 2007 and December 2009, a Victorian population deemed at high risk for the development of HF was recruited from members of a private health insurer.

Inclusion criteria were age $\geq$60 years and at least one HF risk factor as follows: history of coronary artery disease (myocardial infarction, angina, coronary angioplasty or coronary artery bypass grafts), stroke, valvular heart disease, atrial fibrillation, hypertension or diabetes treated for at least 2 years, or known renal impairment. Exclusion criteria were a pre-existing HF diagnosis or known ventricular dysfunction.

Study subjects responded to a letter of invitation from the insurer by returning a brief HF risk factor questionnaire to the study centre. If inclusion criteria were confirmed by telephone interview with a researcher, the subject was invited to participate by attendance at the study centre.

After informed written consent had been obtained at the baseline visit, participants completed a researcher-administered structured questionnaire.

Past medical and medication history, HF symptoms and activity levels were sought from working and non-working participants. Anthropomorphic and blood pressure measurements were made and blood samples were taken for determination of urea, electrolytes, creatinine, full blood count and NT-proBNP concentrations.

Serum NT-proBNP concentrations were measured by electrochemiluminescence immunoassay using an Elecsys instrument (Roche Diagnostics, Basel, Switzerland). The lower limit of detection of this assay was 0.6 pM.

Following the baseline visit, plasma NT-proBNP concentrations were used to further stratify participants. Those in the top quintile (classified as >31.8 pmol L^{-1}, $n = 710$) and 51 consecutive participants in the bottom quintile ($\leq$5.5 pmol L^{-1}) were invited to attend a second study visit.

At the second visit, participants underwent clinical assessment, including blood pressure measurement, cardiac and lung

auscultation, fluid status and an echocardiogram[17–21] assessment by the study cardiologist (MM).

Statistical analysis

Data analysis was undertaken using Stata SE version 11.0 (StataCorp, College Station TX, USA). Normally distributed variables are summarised as the mean ± s.d. Variables not normally distributed are summarised as the median and interquartile range (IQR). Univariate ordered logistic regression models with NT-proBNP quintile as outcome were used to compare baseline characteristics across the five quintiles (<20th centile $\leq$5.5 pmol L^{-1}, 20–40th centile 5.5–10.1 pmol L^{-1}, 40–60th centile 10.1–16.8 pmol L^{-1}, 60–80th centile 16.8–31.8 pmol L^{-1}, >80th centile >31.8 pmol L^{-1}). Univariate and multivariate logistic regression analysis was used to investigate the relationship between risk factors, NT-proBNP and ventricular structure and function. Because of their skewed distribution, NT-proBNP concentrations were log-transformed for regression analyses. Interobserver reproducibility was investigated and summarised with concordance correlation coefficients.[22]

Ethics

SCREEN-HF was approved by The Alfred Hospital Ethics Committee, the Committee that rules on research done by School of Public Health & Preventive Medicine, Monash University Melbourne, which is on the Alfred Hospital campus (Melbourne, Vic., Australia; Project no. 245/06).

Results

Letters of invitation and questionnaires were sent to 44 000 members of a private health insurance fund who were over 60 years of age and living in Victoria. Just over 25% of questionnaires (n = 11 046) were returned. Consecutive respondents were telephone screened (n = 9256) until 3550 met the inclusion criteria and attended for a baseline visit to enrol in the study after providing informed consent. Of the remaining respondents, 4527 members did not meet inclusion or exclusion criteria and 1179 eligible members who met declined to enrol in the study.

Following further stratification using serum NT-proBNP concentrations measured at the baseline visit, participants in the top NT-proBNP quintile and 51 consecutive participants in the bottom quintile were invited to attend for a second visit at which they were given an echocardiogram.

In all, 3550 participants enrolled and attended the baseline visit. The mean (± s.d.) age of subjects was 70.4 ± 6.7 years (range 65 – 92 years), 55% were male and 14.6% were known to be in work (19.7% of respondents were workers). Seven hundred participants from the top NT-proBNP quintile (45 of these participants (5.9%) later withdrew) and 61 participants from the bottom quintile (10 later withdrew) were invited to attend a second visit and 655 and 51, respectively, completed echocardiography.

Fifteen participants who enrolled in the study were found to meet exclusion criteria (pre-existing HF) and were excluded from analysis.

Primary income source was ascertained for 71% of the cohort, with approximately 30% did not completing income questions (Table 1). Those who did not respond, compared with responders, were older (72.0 ± 7.1 vs 69.6 ± 6.3 years; P < 0.0001) and more likely to report a history of diabetes (odds ratio (OR) 1.2; P = 0.04), but there were no significant differences in gender, history of coronary disease, hypertension or obesity between the two groups. In the top NT-proBNP quintile (>30 pmol/L NT-proBNP; i.e. participants who underwent an echocardiogram), a larger percentage did not complete the income question (36% vs 29% from the overall cohort); again non-responders were older than responders (75.0 ± 7.5 vs 73.4 ± 6.5 years; P = 0.003), but there were no significant differences between the groups in terms of gender, past medical history or LV systolic or diastolic function.

Of the 2487 responders in the study population, only 21% reported that paid work or unemployment benefits were their primary source of income. ‘Workers’ (self-reported full-time, part-time, casual work or unemployment benefits as the primary source of income) compared with ‘retirees’ (self-reported self-funded or pension as the primary source of income) were younger (65.6 ± 5.1 vs 70.7 ± 6.1 years, respectively; P < 0.001; Table 2), more likely to be male (OR 2.0; P < 0.0001) and less likely to have a history of coronary artery disease (OR 0.6; P < 0.0001). However, there were no differences in the history of diabetes, hypertension or obesity between workers and retirees.

Workers in the top NT-proBNP quintile, compared with retirees in that quintile, were younger (68.3 ± 7.1 vs 74.1 ± 6.1 years, respectively; P < 0.0001) but there was no significant difference in mean LV ejection fraction (LVEF) between the two groups (55.8 ± 7.6% vs 56.8 ± 6.8%, respectively; P = 0.3; Table 3). Mean LVEF was tabulated against source of income for respondents (Table 4) to show no significant difference in the burden of moderate to severe

Table 1. Primary source of income for the SCReening Evaluation of the Evolution of New Heart Failure Study (SCREEN-HF) cohort (n = 3550)

Income source	n (%)
Pension	871 (24.54)
Self-funded	870 (24.51)
Self-funded or pension (not stated)	227 (6.39)
Full-time work	203 (5.72)
Part-time work	222 (6.25)
Work (casual)	65 (1.83)
Unemployed	29 (0.82)
No response	1063 (29.94)

Table 2. Median (interquartile range) age by source of income (n = 3550)

Income source	Age (years)
Pension	72 (60–88)
Self-funded	70 (60–89)
Self-funded or pension (not stated)	71 (60–89)
Full-time work	64 (59–90)
Part-time work	66 (60–86)
Work (casual)	67 (60–85)
Unemployed	68 (60–82)
No response	72 (60–92)

diastolic function between workers and retirees (21.9% vs 22% respectively; OR 1.0; $P = 0.9$).

HF risk factors

Comparing across the five NT-proBNP quintiles, mean age increased with high NT-proBNP levels (OR 1.13; 95% confidence interval (CI) 1.12–1.14; $P < 0.001$). Although the presence of an HF risk factor was required for inclusion in the study, those in the higher NT-proBNP quintiles were significantly more likely to have a history of coronary artery disease (OR 2.3; 95% CI 2.0–2.7; $P < 0.001$), stroke (OR 1.7; 95% CI 1.4–2.0; $P < 0.001$), impaired renal function (estimated glomerular filtration rate <60 mL min^{-1} 1.73 m^{-2}; OR 2.7; 95% CI 2.3–3.1; $P < 0.001$) or atrial fibrillation (OR 5.0; 95% CI 4.1–6.2; $P < 0.001$).

Conversely, diabetes (OR 0.8; 95% CI 0.7–0.9; $P = 0.009$), hypertension (OR 0.8; 95% CI 0.7–0.9; $P = 0.007$) and obesity (OR 0.9; 95% CI 0.8–1.0; $P = 0.02$) were more common in the lowest NT-proBNP quintile. Multiple HF risk factors were also more likely to be present in those in the highest NT-proBNP quintile (OR 1.5; 95% CI 1.4–1.6; $P < 0.001$).

Participants who were older, female or had a history of coronary artery disease were significantly less likely to be working. There was no significant correlation between work status and history of atrial fibrillation, diabetes, hypertension, stroke or serum BNP concentrations (Table 5).

Table 3. Top quintile (>80th centile >31.8 pmol L^{-1})
Data are the mean ± s.d. LVEF, left ventricular ejection fraction

	LVEF (%)	*P*-value	Age (years)	*P*-value
Worker	56.8 ± 6.8	0.3	68.3 ± 7.1	<0.0001
Retiree	55.8 ± 7.6		74.1 ± 6.1	

Table 4. Mean left ventricular ejection fraction by primary source of income in subjects in the top N-terminal pro B-type natriuretic peptide (NT-proBNP) quintile undergoing an echocardiogram
Data mean ± standard deviation

Income source	No. subjects	LVEF (%)
Pension	208	56.3 ± 7.0
Self-funded	157	57.6 ± 6.6
Self-funded or pension (not stated)	34	56.3 ± 7.1
Full-time work	25	56.9 ± 7.2
Part-time work	15	54.0 ± 9.8
Work (casual)	9	54.3 ± 5.0
Unemployed	5	58.8 ± 5.5
No response	262	56.9 ± 7.5

LV systolic function

Participants in the upper NT-proBNP quintile who underwent an echocardiogram ($n = 710$), compared with those in the bottom quintile ($n = 51$), were older (74.5 ± 6.8 vs 67.2 ± 4.6 years, respectively; $P < 0.001$) and more were female (OR 1.17; 95% CI 1.12–1.24; $P < 0.001$). Those in the top quintile were less likely to be in work the older they were and if they were female (Table 6).

Forty-four participants (6.6%; 95% CI 4%–8%) had impaired LV systolic function (LVEF ≤45%); these were all in the top NT-proBNP quintile (i.e. elevated NT-proBNP concentrations). The mean LVEF of participants was significantly greater in the lowest compared with the highest NT-proBNP quintile (59.5 ± 5.7% vs 56.5 ± 7.4%, respectively; $P = 0.003$). Male gender, coronary artery disease, hypertension and log NT-proBNP concentration were associated with impaired ejection fraction. In a further multivariate analysis, log NT-proBNP concentration was independently associated with impaired LVEF ($P < 0.001$) after adjustment for age, sex, coronary artery disease, diabetes, hypertension and obesity.

LV diastolic function

Diastolic function was assessed in 553 participants; it was not assessed in 163 participants because of rhythm or valve pathology. Moderate to severe diastolic dysfunction was observed in 131 participants (24%; 95% CI 20%–27%) and was significantly more prevalent in the highest NT-proBNP quintile ($n = 128/503$) than in the lowest quintile ($n = 3/50$; OR 5.4; 95% CI 1.7–17.7; $P = 0.005$). Although diastolic dysfunction worsened with age, this association did not reach statistical significance. Diabetes was associated with moderate to severe diastolic dysfunction after adjustment for age and gender (OR 1.86; 95% CI 1.86–2.98; $P = 0.01$), as was log NT-proBNP concentration (OR 1.67; 95% CI 1.15–2.43; $P = 0.008$). Coronary artery disease,

Table 5. Univariate logistic regression analysis of associations between work and clinical characteristics for the entire cohort ($n = 3350$)
Unless indicated otherwise, data are given as the mean ± s.d. or as *n* (%). Odds ratios (OR) and *P*-values are for log-transformed data. CAD, coronary artery disease; BMI, body mass index; IQR, interquartile range NT-proBNP, N-terminal pro B-type natriuretic peptide

	Workers ($n = 519$)	Retirees ($n = 1968$)	OR	*P*-value
Age (years)	65.6 ± 5.2	70.7 ± 6.1	0.83	<0.0001
Male gender	54 (68%)	1070 (54%)	2.13	<0.0001
CAD	93 (18%)	483 (25%)	0.76	0.06
Atrial fibrillation	51 (10%)	195 (10%)	1.16	0.5
Diabetes	77 (15%)	353 (18%)	0.82	0.2
Hypertension	437 (84%)	1696 (86%)	0.85	0.3
BMI ≥30 kg/m^2	171 (33%)	603 (31%)	0.97	0.8
Median (IQR) NT-proBNP (pM)	8.5 (4.4–15.7)	12.7 (6.7–24.0)	0.94	0.3

Table 6. Univariate logistic regression of associations between work and clinical characteristics for those in the top quintile who answered the work question ($n = 419$)

OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; BP, blood pressure; BNP, B-type natriuretic peptide

Work	OR (95% CI)	$P>\|z\|$
Age	0.85 (0.79–0.91)	0.00
Gender	0.23 (0.09–0.53)	0.00
CAD	0.60 (0.27–1.4)	0.23
Atrial fibrillation	0. 99 (0.43–2.3)	0.99
Diabetes	1.1 (0.46–2.5)	0.87
High BP (>140/90 mmHg)	0.83 (0.36–1.9)	0.67
Stroke	1.5 (0.58–3.8)	0.41
log [NT-proBNP]	0.99 (0.70–1.4)	0.98

hypertension and obesity were not associated with diastolic dysfunction. In a further multivariate analysis, log NT-proBNP concentration was independently associated with moderate to severe diastolic dysfunction ($P = 0.006$) after adjustment for age, sex, coronary artery disease, diabetes, hypertension and obesity.

ALVD in workers

ALVD was observed in more than 20% of participants with elevated NT-proBNP levels (>30 pM). However, there was no difference in LV systolic ($P = 0.08$) or diastolic function ($P = 0.7$) between workers and non-workers (of all types).

Discussion

In the present study, we observed a significant burden of asymptomatic LV systolic and diastolic dysfunction in an undiagnosed population with risk factors for HF and increased concentrations of the biomarker NT-proBNP. Increased NT-proBNP was associated with ALVD independent of established HF risk factors, with no difference in LV systolic ($P = 0.3$) or diastolic function ($P = 0.9$) between workers and non-workers. Hence, HWE does not operate in ALVD and the hypothesis that workers in the population would have a lesser burden of ALVD is disproved.

Elevated biomarkers have been associated with systolic dysfunction in several studies, but these have included pre-existing HF,[23–25] and the use of NT-proBNP at a broader population level has not been demonstrated previously to be cost-effective. In the PROBE-HF study (The Role of N-terminal PRO-Brain Natriuretic Peptide and Echocardiography for Screening Asymptomatic Left Ventricular Dysfunction in a Population at High Risk for Heart Failure), NT-proBNP was useful in excluding ventricular dysfunction, but less effective at predicting the presence of dysfunction.[26] As a sensitive marker of volume overload, myocardial stretch and ventricular dysfunction, our study findings indicate that NT-proBNP may have a role in screening asymptomatic high-risk populations for the detection of ventricular dysfunction or early HF when therapeutic options for prevention and treatment are likely to be more effective.

The prevalence of CHF in the Western world is estimated to be 1.5%–2% of the population, with 26 million people affected worldwide.[27,28] Nearly £1 billion, or 1% of the British National Health Service budget, is devoted to HF with hospitalisation the main cost driver.[28] Importantly, the SOLVD investigators showed that the early treatment of CHF led to fewer patients being hospitalised.[5]

If we conservatively assume that individuals in the middle three quintiles of NT-proBNP concentrations have zero prevalence of ALVD, the overall prevalence of ALVD in the study population can be calculated as 6.6% (prevalence of ALVD in top quintile) $\times$ 0.2 = 1.32%. Thus, the number needed to screen is 1/0.0132 = 75.76. The costs of BNP testing and echocardiography (as per the fees paid by the Australian government in the Medical Benefits Schedule, items 66830 and 55113) are A$58.50 and A$230.60, respectively. Thus, the weighted average cost of screening per high-risk person can be calculated as follows:

$$\text{A\$58.50 (all participants have a NT} - \text{proBNP test)} + 0.2 \times \text{\$230.60 (the top 20\% with BNP >30 pM who undergo an echocardiogram)} = \text{A\$104.62}$$

In comparison, the cost of treatment with an angiotensin-converting enzyme inhibitor for those identified with ALVD is A$15 for 30 days, which adds an annual cost of $183 (calculated on the basis that the Australian Pharmaceutical Benefits Scheme price for 5 mg ramipril is A$12.82 for 30 tablets, whereas for 5 mg perindopril the cost is A$15.10 for 30 tablets, www.pbs.gov.au/; accessed 20 February 2016). Therefore, 75.76 $\times$ A$104.62 = A$7925.76 needs to be spent to detect each case of ALVD. This means that the total cost of detecting and treating a person with ALVD for 5 years is A$7926 + (5 $\times$ A$183) = A$8839.

The Heart Foundation (2013; heartfoundation.org.au/; accessed 20 February 2016) reported that the 2006–07 average cost of a hospital admission in Victoria for simple HF (diagnosis-related group (DRG) 62B) and complex heart failure (DRG 62A) was A$3440 and A$7260, respectively. Thus, break-even requires 2.6 (A$8839/A$3440) simple hospitalisations or 1.2 (A$8839/A$7260) complex hospitalisations to be prevented in 5 years. This cost estimate does not take resultant health gains into account.

The findings of the present study may help better target existing workplace health programs. The present study identified age, male gender and coronary artery disease as important cardiac risk factors in predicting work longevity. However, many current workplace-based health programs concentrate on better management of diabetes and obesity, risk factors the present study was unable to show as predictors of longevity in the workplace.

Limitations

The high-risk population evaluated in the present study was recruited from private health insurance membership, which may affect the generalisation of the study findings to the general working population. Inclusion, however, was defined by HF risk factors (age plus underlying pathology), and these should not differ greatly between the study population and the general working population.

In addition, although only 2487/3550 participants responded to questions regarding income source, but the study's work-related conclusions remain statistically significant.

Conclusion

A large burden of asymptomatic ventricular dysfunction was observed in older subjects with plasma NT-proBNP concentrations in the top quintile and this was independent of conventional risk factors and work status, suggesting that the HWE does not operate in ALVD. This means combining plasma NT-proBNP testing in the older workforce with conventional HF risk factors in the workplace may help identify those with ALVD and thus at greatest risk of developing HF. We have also provided an economic argument for the screening strategy suggested on the basis of the results of the present study[28] and identified important cardiac risk factors in predicting work longevity. These findings may increase the efficiency and cost-effectiveness of future workplace health programs.

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