

Does adding information on job strain improve risk prediction for coronary heart disease beyond the standard Framingham risk score? The Whitehall II study.

Mika Kivimäki, Solja Nyberg, G David Batty, Martin Shipley, Jane Ferrie, Marianna Virtanen, Michael Marmot, Jussi Vahtera, Archana Singh-Manoux, Mark Hamer

► **To cite this version:**

Mika Kivimäki, Solja Nyberg, G David Batty, Martin Shipley, Jane Ferrie, et al.. Does adding information on job strain improve risk prediction for coronary heart disease beyond the standard Framingham risk score? The Whitehall II study.: job strain and CHD risk stratification. *International Journal of Epidemiology*, Oxford University Press (OUP), 2011, 40 (6), pp.1577-84. 10.1093/ije/dyr078 . inserm-00672616

HAL Id: inserm-00672616

<https://www.hal.inserm.fr/inserm-00672616>

Submitted on 21 Feb 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Does adding information on job strain improve risk prediction for coronary heart disease beyond the standard Framingham risk score? The Whitehall II study

Mika Kivimäki,^{1,2*} Solja T Nyberg,² G David Batty,¹ Martin J Shipley,¹ Jane E Ferrie,¹ Marianna Virtanen,^{1,2} Michael G Marmot,¹ Jussi Vahtera,^{2,3} Archana Singh-Manoux⁴ and Mark Hamer¹

¹Department of Epidemiology and Public Health, University College London, London, UK, ²Finnish Institute of Occupational Health, Department of Behavioral Sciences, University of Helsinki, Helsinki, Finland, ³Turku University Hospital, University of Turku, Turku, Finland, ⁴INSERM, U1018, Villejuif, France

*Corresponding author. Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, WC1E 6BT London, UK. E-mail: m.kivimaki@ucl.ac.uk

Accepted 6 April 2011

Background Guidelines for coronary heart disease (CHD) prevention recommend using multifactorial risk prediction algorithms, particularly the Framingham risk score. We sought to examine whether adding information on job strain to the Framingham model improves its predictive power in a low-risk working population.

Methods Our analyses are based on data from the prospective Whitehall II cohort study, UK. Job strain among 5533 adults (mean age 48.9 years, 1666 women) was ascertained in Phases 1 (1985–88), 2 (1989–90) and 3 (1991–93). Variables comprising the Framingham score (blood lipids, blood pressure, diabetes and smoking) were measured at Phase 3. In men and women who were CHD free at baseline, CHD mortality and non-fatal myocardial infarction (MI) were ascertained from 5-yearly screenings and linkage to mortality and hospital records until Phase 7 (2002–04).

Results A total of 160 coronary deaths and non-fatal MIs occurred during the mean follow-up period of 11.3 years. The addition of indicators of job strain to the Framingham score increased the C-statistics from 0.725 [95% confidence intervals (95% CIs): 0.575–0.854] to only 0.726 (0.577–0.855), corresponding to a net reclassification improvement of 0.7% (95% CIs: –4.2 to 5.6%). The findings were similar after inclusion of definite angina in the CHD outcome (352 total cases) and when using alternative operational definitions for job strain.

Conclusion In this middle-aged low-risk working population, job strain was associated with an increased risk of CHD. However, when compared with the Framingham algorithm, adding job strain did not improve the model's predictive performance.

Keywords Coronary heart disease, prevention, primary prevention, public health, risk assessment, risk factors

Introduction

In clinical practice, stratifying people in terms of risk for cardiovascular disease is an important aid in decisions regarding risk factor management.^{1,2} Guidelines recommend using formal risk stratification algorithms—most commonly the Framingham risk score—which incorporates data on routinely measured conventional risk markers, such as blood lipid levels, blood pressure, diabetes mellitus and smoking.^{3,4} Recently, management of emerging social factors, such as stress at work—which is associated with coronary heart disease (CHD)^{5,6}—has also been recommended.^{7,8} The most widely used measure of work stress is job strain (or iso-strain), which is defined as high job demands, low job control and low social support at work.^{9–11}

In principle, job strain could improve prediction of future CHD risk over and above the Framingham score if its association with future risk of developing CHD is not explained by the concurrently measured Framingham risk factors. Job strain might involve mechanisms linked with the key stress axis, including sympathetic nervous system hyper-reactivity and hypothalamic pituitary adrenal axis dysfunction,^{12,13} and be related to greater stress reactivity and poor stress recovery,¹⁴ both risk factors for poor future cardiovascular status.¹⁵ Job strain has also been suggested to be associated with factors that act on subclinical vascular disease.^{12–14} For example, acute work-related stressors triggering myocardial infarction (MI) in susceptible individuals are likely to add to CHD risk prediction beyond the Framingham risk factors.^{12,14}

In this article, for the first time to our knowledge, we examine whether incorporating information on job strain into the Framingham risk score would improve stratification of 10-year absolute risk of CHD in a low-risk working population, the Whitehall II study.

Methods

Population and study design

The Whitehall II study is an ongoing prospective cohort study.¹⁶ On study initiation (1985–88), the target population was all London-based office staff, aged 35–55 years, working in 20 civil service (government) departments. With a response of 73%, the cohort was composed of 10 308 employees (3413 women). All components of the Framingham risk score were assessed for the first time in Phase 3 screening (1991–93), which is the baseline for the analyses reported here. We used responses to questionnaire survey at Phases 1 (1985–88), 2 (1989–90) and at 3 to assess the history of cumulative work stress.

Assessment of Framingham risk factors

The Framingham risk score comprises the following risk factors for men and women: age, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, diabetes mellitus and current smoking. Venous blood was taken in the fasting state or at least 5 h after a light, fat-free breakfast. Serum for lipid analyses was refrigerated at -4°C and assayed within 72 h. Cholesterol was measured with the use of a Cobas Fara centrifugal analyser (Roche Diagnostics System, Nutley, NJ, USA). HDL cholesterol was measured by precipitating non-HDL cholesterol with dextran sulphate–magnesium chloride with the use of a centrifuge and measuring cholesterol in the supernatant fluid. We measured systolic blood pressure twice in the sitting position after a 5-min rest with the Hawksley random-zero sphygmomanometer. The average of the two readings was used in the present analyses. Diabetes was defined by a fasting glucose ≥ 7.0 mmol/l and/or a 2-h post-load glucose ≥ 11.1 mmol/l and/or reported doctor-diagnosed diabetes and/or use of diabetes medication. Anti-hypertensive medication and current smoking were self-reported.

Measurement of job strain

We used the job strain questionnaire^{12,17} to obtain three alternative indicators of job strain used in previous studies. In the main analysis, the following three conditions had to be satisfied for a study member to be defined as experiencing job strain: job demands were high (i.e. above median score); decision latitude (job control) was low (i.e. below the median score); and social support was low (lowest third of work social support).^{12,17} We measured the accumulation of exposure to such strain (also called iso-strain)¹¹ over the three measurement periods (Phases 1–3) by adding together the number of times the participant satisfied these three criteria [range 0–3 (high)]. Participants who were missing job strain data at any of the phases of data collection were excluded from all analyses. This measure of long-term job strain is a strong predictor of CHD risk in the Whitehall II study.^{12,17} In subsidiary analyses, we repeated risk prediction testing with two alternative operational definitions of job strain: (i) a variable in which the demand and control scales at Phase 3 were dichotomized based on their median scores, and participants were assigned to 1 of 4 categories according to scores on each dimension: passive (low demand and low control), active (high demand and high control), low strain (low demand and high control) or high strain (high demand and low control)—this variable corresponds with the original definition of job strain by Karasek;⁹ and (ii) job demands and job control at Phase 3, treated as continuous variables.

Ascertainment of incident CHD

We assessed the occurrence of CHD events between Phases 3 (1991–93) and 7 (2002–04), a mean follow-up of 11.3 [standard deviation (SD) 2.7] years. Prevalent cases at Phase 3, determined by using a procedure similar to that for incident CHD, were excluded from the analysis. Participants were flagged by the British National Health Service (NHS) Central Registry, who notified us of the date and cause of all deaths, classified as CHD if International Classification of Diseases, 9th edition (ICD-9) codes 410–414 or ICD-10 codes I20–I25 were present on the death certificate. Non-fatal CHD included first non-fatal MI or first definite angina. Non-fatal MI was defined following MONICA criteria¹⁸ based on study electrocardiograms (ECGs), hospital acute ECGs and cardiac enzymes. Incident angina was defined on the basis of clinical records and nitrate medication use, excluding cases based solely on self-reported data without clinical verification and participants with definite angina at baseline. Classification was carried out independently by two trained coders, with adjudication by a third party in the event of disagreement, which was rare.

Statistical analysis

Participants were followed until incident CHD, death or the date of clinical examination at Phase 7 in 2002–04, whichever came first. Two composite outcome measures used were: (i) CHD death, non-fatal MI or definite angina and (ii) 'hard endpoints', i.e. coronary death or non-fatal MI excluding definite angina. Complete data on both the Framingham score and job strain were available for 5683 participants. Of them, 150 were excluded due to prevalent CHD at baseline. Thus, the final sample comprised 5533 participants (1666 women) aged 39–61 years at Phase 3. We followed them for CHD until 2004.

We used Weibull regression analysis to examine the association between job strain vs others and incident CHD in a model including the Framingham risk score. We obtained β -coefficients from this model to calculate a 10-year risk prediction score, which included both the Framingham risk score and job strain as components. We used standard methods to compute rate ratios and accompanying 95% CIs for incident CHD by estimated 10-year risk categories (<4.0, 4.0–5.9, 6.0–9.9 and $\geq 10\%$) based on the Framingham risk score and the combination of the Framingham risk score and job strain.

We assessed discrimination of the two models based on C-statistics, although these indices do not appear to be sensitive for detecting differences between models.^{19–21} We examined calibration by calculating the modified Hosmer–Lemeshow chi-square statistic (values below 20 indicate acceptable calibration).²² We determined the extent to which adding the job strain variable reassigned individuals to risk

categories that better reflected their final outcome by using the net reclassification improvement (NRI) measure (this measure was used to assess the extent to which people with and without CHD events are appropriately reclassified into higher or lower risk categories with the addition of a new marker).^{20,21} We repeated this test with the two alternative operationalizations of job strain. In further sensitivity analyses, we examined the NRI separately for men and women and for those <50 vs ≥ 50 years of age at baseline (Phase 3).

All analyses were performed with SAS version 9.2.

Results

In Table 1, we present the characteristics of the 5533 members of the analytic sample. Their mean age at baseline was 48.9 years and 30.1% of them were women. A total of 352 incident CHD events, of which 160 were coronary deaths and non-fatal MIs, occurred during the mean follow-up period of 11.3 years. The total follow-up was 62 425.3 person-years and the crude event rates for all CHD and hard endpoint CHD were 56.4 and 25.1 per 10 000 person-years, respectively. Job strain at 2 or 3 phases, compared with no job strain or job strain at 1 phase, was associated with incident CHD before (hazard ratio 1.58, 95% CI: 1.05–2.38) and after (hazard ratio 1.63, 95% CI: 1.08–2.46) adjustment for the Framingham risk score in addition to age and sex. The corresponding hazard ratios for 'hard' endpoint CHD were 2.04 (95% CI: 1.16–3.57) and 2.08 (95% CI: 1.18–3.65), respectively.

Crude event rate ratios by the Framingham score alone and by incorporating job strain suggest a strong graded association between these risk prediction tools and incident CHD (Supplementary Table S1; available at *IJE* online). However, there was little difference in discrimination and calibration between these two risk algorithms, as indicated by both the C-statistics (0.692, 95% CI: 0.591–0.784 vs 0.692, 95% CI: 0.591–0.785) and Hosmer–Lemeshow chi-square statistics [7.8 (df=8, $P=0.45$) vs 8.5 (df=8, $P=0.38$)]. The corresponding figures for 'hard' endpoint CHD were 0.725 (95% CI: 0.575–0.854) vs 0.726 (95% CI: 0.577–0.855) and 15.5 (df=8, $P=0.05$) vs 14.2 (df=8, $P=0.08$).

Table 2 shows the reclassification of individuals between risk categories after complementing the Framingham risk score with information on job strain. Among the 352 incident CHD cases and 5181 non-cases, the NRI was 1.0% (95% CI: –2.0 to 4.0%), $P=0.27$. For the 160 'hard' endpoint CHD cases and 5373 non-cases, NRI was very similar, 0.7% (95% CI: –4.2 to 5.6%), $P=0.39$. The findings were unchanged when a 3-level job strain variable was used instead of the dichotomous job strain variable [i.e., job strain at 0 ($n=4473$), 1 phase ($n=770$) or 2 or 3 phases ($n=290$)] with the NRI being 0.5% (95% CI: –2.6

Table 1 Characteristics of study participants

Characteristic	<i>n</i>	Statistic ^a
Age (years)	5533	48.9 (5.7)
Sex (%)		
Male	3867	69.9
Female	1666	30.1
Total cholesterol (mmol/l)	5533	6.44 (1.15)
HDL cholesterol (mmol/l)	5533	1.44 (0.41)
Systolic blood pressure (mmHg)	5533	120.1 (13.2)
Treated for hypertension		
No	5190	93.8
Yes	343	6.2
Current smoker		
No	4881	88.2
Yes	652	11.8
Diabetes		
No	5410	97.8
Yes	123	2.2
Long-term job strain		
No	5243	94.8
Yes	290	5.2
Mean follow-up (years)	5533	11.3 (2.7)
Status of incident CHD^b at follow-up		
Non-case	5181	93.6
Case	352	6.4
Status of incident hard endpoint CHD^b at follow-up		
Non-case	5373	97.1
Case	160	2.9

^aStatistics are mean (SD) for continuous variables or percent for categorical variables unless otherwise stated.

^bTotal CHD is defined as CHD death, non-fatal MI or definite angina. Hard endpoint CHD includes the first two, but excludes angina.

to 3.6%), $P=0.38$ for total CHD and -1.2% (95% CI: -6.6 to 4.2% , $P=0.66$) for 'hard' endpoint CHD. Furthermore, reclassification analyses provided largely similar findings for men (NRI = 0.5%, 95% CI: -2.7 to 3.7% , $P=0.38$) and women (NRI = 2.8%, 95% CI: -4.6 to 10.2% , $P=0.23$) (Supplementary Table S2; available at *IJE* online) and age groups <50 years (NRI = 2.9%, 95% CI: -2.6 to 8.4% , $P=0.14$) vs ≥ 50 years (NRI = 0.5%, 95% CI: -3.0 to 4.0% , $P=0.40$) (Supplementary Table S3; available at *IJE* online).

Table 3 shows findings from analyses based on alternative definitions for job strain, i.e. using the original 4-category measure (low strain, passive, active and high strain) and using continuous job demands and job control variables. These results confirm the absence of net reclassification improvement

in analyses based on job strain defined as above median demands and below median job control at Phase 3 [i.e. the original job strain definition by Karasek,⁹ NRI = -0.2% , (95% CI: -2.7 to 2.3%), $P=0.55$ for total CHD and NRI = 2.1% , (95% CI: -3.6 to 7.8%), $P=0.24$ for 'hard' endpoint CHD] as well as based on continuous job demand and job control scores at Phase 3 (NRI = 1.3% , 95% CI: -1.3 to 3.9% , $P=0.16$ for total CHD and NRI = 0.4% , 95% CI: -5.7 to 6.5% , $P=0.45$ for 'hard' endpoint CHD).

Discussion

In this large cohort of apparently CHD-free men and women, we have shown that although job strain was associated with an increased risk of CHD, adding job strain into the Framingham risk score did not improve discriminatory capacity of the new model relative to the existing Framingham algorithm.

General practitioners evaluate a patient's chances of developing CHD by examining standard risk factors, such as blood cholesterol levels, diabetes, high blood pressure, smoking status and age. The Framingham risk algorithm provides a useful mathematical model to summarize this information and is indeed widely used in general practice. However, this model is not perfect; thus, there is a need to test whether adding additional risk markers to the Framingham model would improve the ability to estimate a person's risk of developing CHD in the future. Job strain is potentially an attractive additional risk marker as its ascertainment in a clinical setting is simple, quick and inexpensive. Furthermore, assessment of job strain is not associated with issues of safety or discomfort.

A useful risk stratification algorithm places more people at the extremes rather than in the middle categories of the risk distribution, thus providing clinicians with clear guidance for action. The present evidence suggests that using information on job strain is unlikely to improve identification of individuals at the highest risk of developing CHD. Our findings resemble those of previous studies that have examined the utility of adding other important risk markers for CHD (e.g. socio-economic position, carotid intima-media thickness and C-reactive protein) to the model, but with limited success.^{23,24}

We believe that we have observed a true null finding rather than a type-2 error (false negative). It is increasingly recognized that the C-statistic is little changed even after inclusion of a strong risk factor in the model.¹⁹⁻²¹ However, the null finding was also evident when we examined model performance in terms of net reclassification improvement, a sensitive test to determine the extent to which adding information on new risk markers reassigned participants to risk categories that better reflected their disease outcome. Studies have used various alternative

Table 2 Reclassification of the predicted 10-year risk of incident CHD by using the Framingham risk score vs a risk score based on both the Framingham risk score and long-term job strain

Status at follow-up examination	Predicted 10-year risk (Framingham) (%)	Predicted 10-year risk (Framingham plus job strain)				Reclassified		Net correctly reclassified (%)
		<4%	4–5.9%	6–9.9%	≥10%	Increased risk	Decreased risk	
Total CHD^a								
CHD-case (<i>n</i> = 352)								
	<4	69	5	0	0	15	12	0.9
	4–5.9	5	50	3	0			
	6–9.9	0	2	91	7			
	≥10	0	0	5	115			
Non-case (<i>n</i> = 5181)								
	<4	2527	66	0	0	155	158	0.1
	4–5.9	82	964	56	0			
	6–9.9	0	50	840	33			
	≥10	0	0	26	537			
NRI ^b (95% CI)								1.0 (–2.0 to 4.0)
P-value								0.27
Hard endpoint CHD^a (%)								
	<2	2–3.9	4–5.9	≥6				
CHD-case (<i>n</i> = 160)								
	<2	33	4	0	0	8	8	0.0
	2–3.9	3	34	0	3			
	4–5.9	0	2	33	1			
	≥6	0	0	3	44			
Non-case (<i>n</i> = 5373)								
	<2	3156	87	0	0	156	194	0.7
	2–3.9	120	1147	38	17			
	4–5.9	0	36	371	14			
	≥6	0	0	38	349			
NRI ^b (95% CI)								0.7 (–4.2 to 5.6)
P-value								0.39

^aTotal CHD is defined as coronary death, non-fatal MI or definite angina. Hard endpoint CHD includes the first two, but excludes angina.

^bNet reclassification improvement.

operational definitions of job strain, but our null finding was seen irrespective of which of these definitions were used.

It is important to recognize that the present null findings do not exclude the possibility that job strain can have a role in CHD aetiology, representing, for example, an 'upstream' risk factor in the same pathway that incorporates conventional proximal risk factors included in the Framingham equation.⁵ Thus, despite their inability to improve risk stratification, job strain and other life stresses might still be useful intervention targets,^{7,8} corresponding to risk factors, such as obesity and physical activity, which are not included in the Framingham risk algorithm

although they are highly relevant targets for CHD prevention. However, randomized trials on job strain and CHD are needed to confirm this.

Finally, at least three issues emphasize the need for caution in interpretation of the present findings. First, the Whitehall II study recruited participants from the civil service, which did not include people from the lowest social status groups; generalizations of the present findings to the general working population may therefore be unwise. However, the association between job strain and CHD was comparable with that in previous studies on working populations that included blue-collar workers,^{25,26} thus suggesting that these conclusions may not be substantially different

Table 3 Reclassification of the predicted 10-year risk of incident coronary heart disease by using the Framingham risk score vs a risk score based on both the Framingham risk score and alternative job strain indicators measured at Phase 3

Model	<i>n</i>	Reclassified		Net correctly reclassified (%)
		Increased risk	Decreased risk	
Stress indicator: the original 4-category job strain^a				
Total CHD				
CHD-case	352	9	10	-0.3
Non-case	5181	114	121	0.1
NRI (95% CI)				-0.2 (-2.7 to 2.3)
<i>P</i> -value				0.55
Hard endpoint				
CHD-case	160	12	9	1.9
Non-case	5373	295	304	0.2
NRI (95% CI)				2.1 (-3.6 to 7.8)
<i>P</i> -value				0.24
Stress indicator: continuous job demands and continuous job control				
Total CHD				
CHD-case	352	12	8	1.1
Non-case	5181	154	162	0.2
NRI (95% CI)				1.3 (-1.3 to 3.9)
<i>P</i> -value				0.16
Hard endpoint				
CHD-case	160	12	12	0.0
Non-case	5373	247	269	0.4
NRI (95% CI)				0.4 (-5.7 to 6.5)
<i>P</i> -value				0.45

^aDemand and control scales were dichotomized based on their median scores and participants were assigned to 1 of 4 categories according to scores on each dimension: passive (low demand and low control, *n* = 1470), active (high demand and high control, *n* = 1885), low strain (low demand and high control, *n* = 1285) or high strain (high demand and low control, *n* = 893); this is the original operationalization by Karasek.⁷

in other settings. Second, our study was not well powered for subgroup analyses. Thus, we cannot exclude the possibility that job strain could improve risk stratification in specific groups of the working population, including, for example, those with high >20% absolute 10-year risk of CHD. Third, our analysis was limited to job strain. The present findings are, therefore, not necessarily informative in relation to other work characteristics, such as long working hours, which have been suggested to improve risk prediction.²⁷ Future studies should also examine whether work-related and non-work-related stressors in combination would improve prediction of CHD and whether they improve prediction of other cardiovascular diseases, such as stroke.²⁸

Supplementary Data

Supplementary Data are available at *IJE* online.

Funding

Medical Research Council; British Heart Foundation; Wellcome Trust; Health and Safety Executive; Department of Health; Agency for Health Care Policy Research, UK; John D and Catherine T MacArthur Foundation Research Networks on Successful Midlife Development and Socio-economic Status and Health; National Heart, Lung and Blood Institute and National Institute on Aging, NIH, US; Academy of Finland, Finland; EU New OSH ERA ('New and Emerging Risks in Occupational Safety and Health') Research Programme and European Science Foundation. Academy of Finland (to M.K., S.T.N. and J.V.); EU New OSH ERA Research Programme and the BUPA Foundation, UK (to M.K.); Wellcome Trust Fellow (to G.D.B.); MRC professor (to M.G.M.); British Heart Foundation (to M.J.S. and M.H.); European Science Foundation, 'European Young Investigator Award' (to A.S.-M.); Medical Research Council, UK (to J.E.F.).

Acknowledgements

The authors thank all participating civil service departments and their welfare personnel and establishment officers; the Occupational Health and Safety Agency; the Council of Civil Service Unions; all participating civil servants in the Whitehall II study and all members of the Whitehall II Study Team. The

Whitehall II Study Team comprises research scientists, statisticians, study coordinators, nurses, data managers, administrative assistants and data entry staff, who made the study possible.

Conflict of interest: None declared.

KEY MESSAGES

- To evaluate a patient's risk of developing CHD, clinicians measure standard risk factors, such as adverse lipid levels, high blood pressure, diabetes and smoking habits, and summarize these measurements by using risk algorithms, such as the Framingham risk model.
- Ascertainment of job strain in a clinical setting is easy and several studies have shown an association with CHD. However, it is not known whether adding information on job strain to the Framingham model improves its predictive performance.
- Using the Whitehall II study, we found job strain was associated with an increased risk of developing CHD.
- Importantly, there was no evidence to suggest that adding information on job strain improved risk prediction above the standard Framingham model.

References

- ¹ Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**: 1837–47.
- ² D'Agostino RB Sr, Vasan RS, Pencina MJ *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;**117**:743–53.
- ³ Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143–421.
- ⁴ Grundy SM, Cleeman JI, Merz CN *et al*. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;**110**:227–39.
- ⁵ Kivimaki M, Virtanen M, Elovainio M, Kouvonen A, Vaananen A, Vahtera J. Work stress in the etiology of coronary heart disease—a meta-analysis. *Scand J Work Environ Health* 2006;**32**:431–42.
- ⁶ Eller NH, Netterstrom B, Gyntelberg F *et al*. Work-related psychosocial factors and the development of ischemic heart disease: a systematic review. *Cardiol Rev* 2009;**17**: 83–97.
- ⁷ Graham I, Atar D, Borch-Johnsen K *et al*. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007; **14**(Suppl 2):S1–113.
- ⁸ Yusuf S, Hawken S, Ounpuu S *et al*. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937–52.
- ⁹ Karasek RA. Job demands, job decision latitude and mental strain: implications for job redesign. *Adm Sci Q* 1979;**24**:285–307.
- ¹⁰ Karasek R, Theorell T. *Healthy Work: Stress, Productivity, and the Reconstruction of Working Life*. New York: Basic Books, 1990.
- ¹¹ Johnson JV, Hall EM. Job strain, work place social support, and cardiovascular disease: a cross-sectional study of a random sample of the Swedish working population. *Am J Public Health* 1988;**78**:1336–42.
- ¹² Chandola T, Britton A, Brunner E *et al*. Work stress and coronary heart disease: what are the mechanisms? *Eur Heart J* 2008;**29**:640–48.
- ¹³ Hamer M, Malan L. Psychophysiological risk markers of cardiovascular disease. *Neurosci Biobehav Rev* 2010;**35**: 76–83.
- ¹⁴ Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol* 2005;**45**:637–51.
- ¹⁵ Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. *Hypertension* 2010;**55**:1026–32.
- ¹⁶ Marmot MG, Davey Smith G, Stansfeld S *et al*. Health inequalities among British civil servants: the Whitehall II study. *Lancet* 1991;**337**:1387–93.
- ¹⁷ Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ* 2006;**332**:521–24.
- ¹⁸ Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA

- Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;**90**:583–612.
- ¹⁹ Cook NR. Assessing the incremental role of novel and emerging risk factors. *Curr Cardiovasc Risk Rep* 2010;**4**: 112–19.
- ²⁰ Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;**27**:157–72.
- ²¹ Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;**30**:11–21.
- ²² Hosmer DWJ, Lemeshow S. *Applied Logistic Regression*. New York: J Wiley, 1989.
- ²³ Helfand M, Buckley DI, Freeman M *et al*. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009;**151**: 496–507.
- ²⁴ Woodward M, Brindle P, Tunstall-Pedoe H. SIGN-group-on-risk-estimation. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007;**93**:172–76.
- ²⁵ De Bacquer D, Pelfrene E, Clays E *et al*. Perceived job stress and incidence of coronary events: 3-year follow-up of the Belgian Job Stress Project cohort. *Am J Epidemiol* 2005;**161**:434–41.
- ²⁶ Kivimäki M, Leino-Arjas P, Luukkonen R, Riihimäki H, Vahtera J, Kirjonen J. Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees. *BMJ* 2002;**325**:857–61.
- ²⁷ Kivimäki M, Batty GD, Hamer M *et al*. Using additional information on working hours to predict coronary heart disease: The Whitehall II cohort study. *Ann Intern Med* 2011;**154**:457–63.
- ²⁸ Brisson C, Laflamme N, Moisan J, Milot A, Masse B, Vezina M. Effect of family responsibilities and job strain on ambulatory blood pressure among white collar women. *Psychosom Med* 1999;**61**:205–13.