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Using additional information on working hours to predict coronary heart disease: a cohort study

RUNNING TITLE: Working hours and CHD risk prediction

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Abstract

Background-Long hours are associated with increased risk of coronary heart disease. Adding information on long hours to traditional risk factors could potentially help improve risk prediction.

Objective-To examine whether information on long working hours improves the ability of the Framingham risk model to predict coronary heart disease in a low-risk employed population.

Design-Prospective cohort study; baseline medical examination (1991-1993) and coronary heart disease follow-up to 2004.

Settings-Civil service departments in London (the Whitehall II study).

Participants-7095 adults (2109 women) aged 39 to 62, working full time, and free of coronary heart disease at baseline.

Measurements-Working hours and the Framingham risk score were measured at baseline. Coronary death and non-fatal myocardial infarction were ascertained from three sources: medical screenings every 5 years, hospital data and register linkage.

Results-192 persons had incident coronary heart disease during a median 12.3 year follow-up. After adjustment for the Framingham score, participants working ≥11 hours per day had a 1.67-fold (95% CI: 1.10-2.55) increased risk of coronary heart disease relative to those working 7-8 hours. The addition of working hours to the Framingham score led to a net reclassification improvement of 4.7% (p=0.034), resulting from a better identification of individuals who later developed coronary heart disease (sensitivity gain).

Limitations-The findings may not be generalizable to populations with a larger proportion of high-risk individuals. Furthermore, the predictive utility of working hours was not validated in an independent cohort.

Conclusion-Information on working hours may improve prediction of coronary heart disease risk based on the Framingham risk score in low-risk working populations.

Primary Funding Source-Medical Research Council, British Heart Foundation, BUPA Foundation, UK; National Heart, Lung and Blood Institute and National Institute on Aging, NIH, US.

Key Words: Coronary heart disease ● prevention ● primary prevention ● public health ● risk assessment ● risk factors

INTRODUCTION

In clinical practice, stratifying people in terms of their 10-year risk for coronary heart disease facilitates decisions regarding risk management and treatment (1, 2). Guidelines recommend using formal risk prediction algorithms, most commonly the Framingham risk score, which incorporates data on routinely measured conventional risk factors, such as lipid levels, blood pressure, and smoking (3, 4). Recently, management of emerging psychosocial risk factors, such as stress at work, has also been recommended (5). One such stressor, long working hours, has been shown to be associated with increased risk of coronary heart disease (6-13). In this report from the British Whitehall II study, we examine whether incorporating information on working hours in the Framingham risk score improves prediction of 10-year risk of coronary heart disease in this low risk working population.

METHODS

Population and study design

The Whitehall II study is a prospective cohort study of British civil servants established in 1985 to identify characteristics of the work environment and health-related behaviours that link socioeconomic position to pathophysiological changes and clinical disease (14). As a characteristic of the work environment, the potential of long working hours to improve the prediction of coronary heart disease risk is an extension to this original study question.

Working hours were measured by questionnaire during the Phase 3 screening (August 1991 - May 1993). Being the first time working hours were measured, Phase 3 forms the baseline for the analyses reported here. We excluded participants with prevalent coronary heart disease, part-time employees and those with missing data on working hours at baseline (a flow chart of sample selection is in the **Appendix**, available at www.annals.org). The final sample comprised 7095 participants (4986 men, 2109 women) aged 39 to 62 years, free of prevalent coronary

heart disease. We followed these study members for incident coronary heart disease or death until Phase 7 (October 2002 - September 2004). The University College London ethics committee reviewed and approved the study, and written informed consent was obtained from each participant.

Assessment of Framingham risk factors

We used standard operating protocols to measure the Framingham risk factors at the Phase 3 sreening (August 1991 - May 1993): age, gender, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, and smoking habit (14). Venous blood was taken in the fasting state or at least 5 hours after a light, fat-free breakfast. Serum for lipid analyses was refrigerated at −4°C and assayed within 72 hours. Cholesterol was measured with the use of a Cobas Fara centrifugal analyzer (Roche Diagnostics System, Nutley, NJ). HDL-cholesterol was measured by precipitating non-HDL cholesterol with dextran sulfate-magnesium chloride using a centrifuge and measuring cholesterol in the supernatant. We measured systolic blood pressure twice in the sitting position after 5 minutes rest with a Hawksley random-zero sphygmomanometer (Lynjay Services Ltd., Worthing, UK). The average of the two readings was taken to be the measured systolic blood pressure. Information on antihypertensive medication, lipid-lowering drugs, anti-platelet agents and current smoking was requested at the Phase 3 screening.

Measurement of working hours

We determined working hours at Phase 3 with the following question: "On an average weekday, approximately how many hours do you spend on the following activities (if applicable): Work (daytime and work brought home)?" Response options ranged from 1 to 12 hours. Based on a pre-specified classification (12), we recoded responses for those working full-time using the following categories of daily working hours: 7-8

("normal working hours"), 9 ("1 hour of overtime work a day"), 10 ("2 hours of overtime work") or ≥11 ("3+ hours of overtime work").

Ascertainment of incident coronary heart disease

The outcome used in this study was incident hard endpoint coronary heart disease; first non-fatal myocardial infarction or coronary heart disease death, by Phase 7 (October 2002 - September 2004). Non-fatal myocardial infarction identified at baseline (Phase 3) to exclude prevalent disease and at Phases 5 (April 1997 - January 1999) and 7 to identify incident disease was defined following MONICA criteria (16) and ascertained using data from 5-yearly Whitehall II medical examinations, and hospital records of acute electrocardiograms (ECGs) and cardiac enzymes. To ascertain coronary heart disease death, participants were flagged by the British National Health Service (NHS) Central Registry, who notified us of the date and cause of deaths. These were classified as coronary if either codes 410–414 (ICD-9 (International Classification of Diseases, 9th edition)) or codes I20–I25 (ICD-10) were present on the death certificate. Besides those with a history of myocardial infarction at Phase 3, we excluded participants with a history of angina, identified via questionnaire (17) and corroborated against medical records, by abnormalities in a resting electrocardiogram (ECG), an exercise ECG, or a coronary angiogram. Median incident coronary heart disease follow-up was 12.2 years, close to 10-years recommended in the most recent review of work stress and cardiovascular disease (15). While the number of events this afforded was not large, 192 cases, longer follow-up periods tend to increase within-subject variation in work-related exposures (such as working hours) potentially reducing the precision of the prediction (15).

Statistical analysis

Participants were followed until incident hard endpoint coronary heart disease, last study phase, or death, whichever came first. We used multivariate imputation (18) to

impute values for 396 individuals who had missing data on one or more of the risk factors in the Framingham risk score. We used Weibull regression analysis to examine the association between working hours and incident coronary heart disease. This is a parametric form of the proportional hazards model and takes into account the differing length of follow-up of the study participants. In addition, the model allows the risk of coronary heart disease over a fixed period of time (t) to be calculated as: $r(t) = 1 - \exp(-\exp((\log(t) - X\beta) / \sigma)$ where X is the vector of risk factors, β is the vector of coefficients, and σ the estimated scale parameter. This model has previously been used in the Framingham study to describe risk profiles and the effects of risk factors on coronary outcomes using the Framingham risk score (19).

Based on current recommendations (20-23), we classified participants into three risk categories: 0-<5.0%(low risk), 5.0 to <10% (low-intermediate risk) and ≥10% (intermediate to high risk). Due to small numbers, we were unable to distinguish a high risk category ($\geq$20% risk). We calculated the predicted 10-year risk of coronary heart disease from a Weibull model that included working hours and the Framingham risk score and compared it to the predicted risk from a model which included only the Framingham score.

We tabulated incident coronary heart disease events and person years by risk category for the two models (Framingham risk alone and Framingham risk along with information on working hours) and calculated the incidence rate and the rate ratios. Approximate 95% confidence intervals were calculated by multiplying and dividing the rate ratios by an error factor calculated as $1.96*\exp(\text{sqrt}(1/d_0 + 1/ d_1))$ where d_0 and d_1 are the number of coronary heart disease events in the two groups being compared (24). We examined the discrimination of the two models using C-statistics (25) and Harrell's C-index (26-28), although these indices are not seen to be sensitive for detecting differences between models (29, 30). We used the net reclassification improvement (NRI) measure (31, 32) to assess the extent to which adding information on long working hours reassigned individuals to risk categories that

better reflected their disease outcome. Approximate 95% confidence intervals for the NRI were computed using the same variance terms as used in the test of significance (33). In sensitivity analyses, we examined the NRI separately after excluding non-white participants, diabetic participants and those on antihypertensive, lipid lowering medication or anti-platelet agents.

Goodness of fit and calibration of the two models was assessed by comparing the observed and expected number of coronary events by deciles of predicted risk in a manner similar to the modified Hosmer-Lemeshow chi-square statistic where a value under 20 indicates acceptable calibration (34). We also assessed the risk reclassification calibration (21) by comparing the observed and predicted number of events and their risks in the cross-classification table of predicted risks from the two models, without and with the working hours' variables. The goodness of fit of each model in this cross-classification was assessed using the Hosmer-Lemeshow statistic on cells containing at least twenty individuals (21). The small number of events did not allow us to separate the derivation and the validation cohort. In order to assess the possible bias introduced by this limitation, we also compared results with estimates drawn from 2000 bootstrap simulations (35) as previously described by Cook and Ridker (21) with 95% confidence intervals estimated using the percentile method. All analyses were performed with SAS, version 9.1 for Windows (SAS Institute Inc, Cary, NC, USA)

Role of the Funding Source

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RESULTS

In terms of coronary heart disease incidence, the characteristics of the 7095 participants included in the analysis did not differ from the 1437 participants excluded. However, those included in the analysis were somewhat younger (49.0 vs. 53.6 years), more likely to be men (70.3% vs. 60.1%) and of white ethnicity (91.1% vs. 87.2%). That these differences were statistically significant (all $p<0.001$) is largely due to the high study numbers; absolute differences in characteristics were generally small. (**Appendix** *eTable1*, available at www.annals.org).

In **Table 1** we present the characteristics of the 7095 participants. Mean risk factor levels ranged from low (e.g., systolic blood pressure 120.2 mm Hg, smoking prevalence 13.9%) to moderately elevated (e.g., total cholesterol 6.45 mmol/L). A total of 192 incident hard coronary heart disease events occurred during the median follow-up period of 12.3 (IQR 11.5-12.7) years. 171 participants were censored before the end of follow-up because of death from causes other than coronary heart disease. The total follow-up was 80,411 person-years and the crude event rate for coronary heart disease was 23.9 per 10,000 person-years.

54.0% of the participants worked 7-8 hours per day and 10.4% worked 11 hours or more (table 1). After adjustment for the Framingham risk score, the hazard ratios (95% CIs) for a coronary event among those working 9, 10 and ≥11 hours were 0.90 (0.60 to 1.35), 1.45 (0.99 to 2.12) and 1.67 (1.10 to 2.55) compared to men and women working 7-8 hours.

Crude event rate ratios using the Framingham score alone and by incorporating long working hours suggested a strong graded association between these

two risk prediction tools and incident hard endpoint coronary heart disease, the hazard ratios for an incident coronary event in the high (≥10%) versus low (<5%) risk groups being 3.91 (1.92 to 7.96) and 5.39 (2.92 to 9.96), respectively (**Appendix** *eTable2*, available at www.annals.org). Adjustment for long working hours increased the magnitude of the association of the Framingham risk score with incident coronary heart disease, but only by 2.6%.

The C-statistics for the two risk models (the Framingham score alone and one incorporating working hours) did not change 0.714 (95% CI: 0.650 to 0.777) for both models. The Harrell's C-indices were 0.635 (95% CI: 0.494 to 0.767) and 0.619 (95% CI: 0.477 to 0.752). Adding long working hours to the risk algorithm improved calibration as indicated by Hosmer-Lemeshow chi-square statistics [17.33 (df=8, p=0.027) vs 12.91 (df=8, p=0.119)]. This was also the case when estimates were compared to the median estimate of 2000 bootstrapping simulations [24.71 (df=8, p=0.002) vs 20.99 (df=8, p=0.007)].

Table 2 shows the reclassification of individuals between predicted risk categories after complementing the Framingham risk score with information on long working hours. In 4 cells of the cross-classification the predicted risk was closer to the observed risk using the model including working hours (see "Predicted risk†" in table 2). In 1 cell the two models provide equally accurate prediction and in 2 cells the predicted risk was more accurate for the Framingham score alone. The reclassification calibration statistic indicated a better fit for the model including working hours, χ^2=6.45 (p=0.092), compared to χ^2=10.72 (p=0.013) using the Framingham score alone.

Table 3 shows the reclassification stratified by incident coronary heart disease status at follow-up. The net reclassification improvement (NRI) after adding working hours to the Framingham score was 5.2% among the 192 incident cases and -0.5% in non-cases. Thus, the reclassification improvement was 4.7% (95% CI: 0.3 to 9.1), p=0.034. The mean reclassification improvement did not change when the mean

of 2000 bootstrapped values was calculated. We repeated this analysis after exclusion of non-white and diabetic participants and those treated with antihypertensive therapy, lipid-lowering drugs or anti-platelet agents (**Appendix** *eTable3*, available at www.annals.org). These analyses did not materially change the result.

DISCUSSION

In a cohort of nearly 7100 men and women apparently free of coronary heart disease, we show long working hours to predict incident hard endpoint coronary heart disease and contribute to coronary heart disease risk prediction, over and above the Framingham score. The net reclassification improvement was 4.7%. This was achieved by the more accurate classification of individuals who experienced coronary heart disease to a higher risk group (sensitivity gain) rather than by improving detection of those unlikely to develop the disease. Our findings show the potential predictive utility of long working hours in identifying individuals at increased 10-year risk of coronary heart disease in a low-risk employed population.

We searched the MEDLINE database (accessed November 2010) and identified 5 case-control studies (7-11) and 4 cohort studies (12, 13, 36, 37) that have previously examined the association between long working hours and cardiovascular endpoints. Six studies reported a statistically significant positive association in that a higher risk of acute myocardial infarctions or coronary deaths was observed among those doing overtime in diverse working populations in Sweden, the Netherlands, the United Kingdom and Japan (7-12). Conversely, two Japanese studies provided no firm evidence of an association (36, 37), and a 30-year follow-up of Danish men found employees working long hours to be at increased risk of death from ischemic heart disease, but only if they additionally had poor physical fitness (13). Our study from a British cohort adds to the existing evidence by showing that information on long working hours may have the potential to help clinicians more accurately to determine CHD risk for patients.

In this low-risk working population, a C-statistic of 0.71 for risk prediction based on the Framingham score plus working hours is comparable to those found in other studies attempting to improve risk prediction. Examples are the Women's Health Initiative that added 18 biomarkers to the Framingham score (C=0.73)(38), the Atherosclerosis Risk in Communities (ARIC) study that added ultrasound scans of carotid intima-media thickness and plaques (C=0.76)(22) and the Multi-Ethnic Study of Atherosclerosis that added coronary artery calcium scores (C=0.81)(39) to the Framingham risk score. Overall these statistics indicate moderate discrimination; thus a clinician estimating the 10-year coronary heart disease risk of a given patient may prefer to take into account further information not included in these scores (40, 41).

Cost-effectiveness is an additional aspect of the evaluation of potential new risk markers (20). A potential advantage of working hours as a risk marker is that its ascertainment in a clinical interview is simple, quick and virtually cost-free (20). Furthermore, no safety or acceptability issues are attached to the assessment of working hours.

There are a few caveats to the results reported here. First, our study was not sufficiently powered to allow the partition of data into estimation and validation datasets. Thus, the predictive utility of working hours could not be validated in a dataset independent of the derivation dataset. However, the bootstrapped estimate of the net reclassification index suggests that our estimate is not overoptimistic. Second, we did not account for changes in the risk factors or medications during the follow-up – an approach that is standard in attempts to create or improve risk prediction algorithms. Third, our cohort was comprised primarily of low risk individuals and did not include blue-collar workers. Thus, the findings may not be generalizable to higher-risk groups in the general population.

Given that working long hours are common and have increased in many developed countries in recent years (42, 43), our study potentially has important implications. However, further testing is needed to confirm the added value of

information on long working hours for clinical decision making. First, additional studies need to examine whether the improvement in coronary heart disease prediction is limited to specific populations or is observable across different cohorts, particularly in groups with a risk $\geq$20% risk. Second, future studies should assess whether incorporating information on working hours in the risk prediction algorithm improves the management of patients compared with current standard care. Ideally, this would be undertaken by a clinical trial comparing the two models. Third, it is important to clarify whether long working hours are a marker of coronary heart disease risk or are also a causal risk factor. In the first case, information on working hours could contribute to risk prediction but not preventive treatment. In the second case, clinical benefits avoiding long working hours would need to be shown.

[2944 words]

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Conflict(s) of Interest/Disclosure(s) Statement

The authors have no conflicts of interest to declare.

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