Simplifying cardiovascular risk estimation using resting heart rate

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Aims
Elevated resting heart rate (RHR) is a known, independent cardiovascular (CV) risk factor, but is not included in risk estimation systems, including Systematic COronary Risk Evaluation (SCORE). We aimed to derive risk estimation systems including RHR as an extra variable and assess the value of this addition.

Methods and results
The National FINRISK study (including 14,997 men and 15,861 women) was used to derive two formulas for estimation of 10 year risk of CV disease (CVD) mortality. The first formula contained current SCORE variables—total cholesterol, systolic blood pressure, smoking, age and gender. Inclusion of RHR resulted in only minor improvements in discrimination, based on both area under receiver operating characteristic curve (AUROC, men: 0.840 from 0.838, P = 0.5038; women: 0.87 from 0.865, P = 0.0522) and net reclassification index (NRI). The second, simplified formula contained only, age, smoking, gender, and body mass index. Addition of RHR to this simplified formula resulted in a statistically significant and meaningful improvement in AUROC (men: 0.819 from 0.812, P = 0.037; women: 0.862 from 0.827, P = 0.023) and NRI (0.05). Calibration also improved. A simple chart for estimating 10 year risk of fatal CVD including RHR is presented.

Conclusion
Addition of RHR to formulas already containing lipid and blood pressure measures does not appreciably improve risk estimation. However, inclusion of RHR in simple systems, which can potentially enhance cost-effectiveness and accessibility of risk estimation, is useful.

Keywords
Resting heart rate • Cardiovascular disease • Risk estimation • Primary prevention

Introduction
The development of cardiovascular disease (CVD) is usually caused by multiple risk factors, which interact to produce an individual’s total CVD risk. For this reason, guidelines on the prevention of CVD recommend that preventive measures be based on individuals’ level of total CVD risk so that the most intensive risk factor management can be directed towards those at highest risk.¹ Individuals with established CVD have already declared themselves to be at high risk. Likewise, those with type 2 or type 1 diabetes with microalbuminuria or markedly elevated levels of single risk factors are automatically considered high risk. For other asymptomatic individuals, an assessment of the total risk is required. SCORE (Systematic COronary Risk Evaluation) is the risk estimation system recommended by the European guidelines on CVD prevention.² ³ SCORE estimates 10 year CVD mortality risk based on gender, age, country of origin, total cholesterol, smoking status, and systolic blood pressure.

Many other risk factors are not included in current risk estimation systems. Recently, much attention has focused on attempting to improve risk estimation through the incorporation of these factors. The value of incorporation of extra factors, including high-density lipoprotein (HDL) cholesterol,⁴ C-reactive protein,⁵ and multiple biomarkers⁶ has generally resulted in only minor improvements discrimination of risk formulas.

Observational studies have shown an elevated resting heart rate (RHR) to be associated with future development of CVD.⁷–¹³ Some have shown a greater association with coronary than stroke endpoints,⁷,¹³ and the relationship with sudden death,⁹,¹⁴ and coronary mortality appears particularly strong.⁷ The recent
BEAUTIFUL trial added further evidence for the role of RHR as a CV risk factor by demonstrating a reduction in myocardial infarction in individuals with coronary artery disease and heart rate >70 bpm when randomized to pure heart rate reduction using the I<sub>1</sub> channel blocker, ivabradine. Heart rate reduction has not been proven to result in benefit in the general population.

None of the current risk estimation systems for use in the general population include RHR as a variable, despite the fact that it is simple and inexpensive to measure. The objective of this analysis is to assess the value of incorporating RHR into risk estimation systems, both in addition to variables currently included in risk estimation and in a risk estimation system containing only simple and easily measured variables.

**Study population and methods**

The National FINRISK study, a prospective population-based observational study, was the data set used for the derivation of the risk formulas. Full details of the methodology have been described elsewhere. Only the 1977, 1982, 1987, 1992, and 1997 surveys are included in this report as these have RHR available and sufficient follow-up.

Participants completed a detailed medical questionnaire and examination including the measurement of weight, height, and blood pressure. RHR was measured by palpation of the radial artery pulsation over 30 s, in the sitting position after 5 min rest. All cholesterol determinations were made in the same central laboratory. Follow-up to end of 2003 is available and was collected in accordance with MONICA methodology. The follow-up was based on the mortality register by Statistics Finland, which is linked to the risk factor surveys using social security numbers assigned to every citizen of Finland.

**End point definitions**

The end point definitions used were the same as those used in the SCORE project. CHD mortality was defined as ICD 9 codes 410–414. CVD mortality included, in addition, 401–409, 426–443, 798.1, and 798.2, with exclusion of the following definitely non-atherosclerotic causes of death: 426.7, 429.0, 430.0, 432.1, 437.3, 437.4, 437.5. The corresponding ICD8 and 10 codes were used.

As in the initial SCORE project, those with previous myocardial infarction were excluded. Those with angina and heart failure were also excluded since reduced left ventricular function may cause an elevation in heart rate, which would confound the role of RHR in determining CVD risk. Because of the potential for anti-hypertensives to alter RHR, we also excluded those on anti-hypertensives. Given the young age of the cohort and the exclusions described above, the proportion of the remaining individuals taking heart rate modifying medications would have been negligible.

**Statistical methods**

Formulas for the estimation of 10 year risk of CVD mortality were derived using Cox proportional hazards model. The formulas were derived by combining the baseline survival probability and the beta coefficients for each of the risk factors, as in the SCORE project. Age was included as a risk factor in these formulas as opposed to the time variable in the original SCORE formula. The formulas were derived separately in men and women to assess whether inclusion of RHR resulted in a greater improvement in either gender. Equation 1 (supplementary material) shows how the baseline survival probability and the beta coefficients for the risk factor levels are combined to give the risk estimate. The variables included in the formula were the same as in the original SCORE formula—total cholesterol, systolic blood pressure and current smoking status, plus RHR as a continuous variable. A second formula was also derived, exactly resembling the first except, without including RHR. This was for comparison with the formula including RHR, in order to assess the improvement in risk estimation afforded by the incorporation of RHR. Previous analyses of the effect of RHR have shown that RHR has a stronger effect on CVD mortality in 10 year follow-up when compared with longer observation periods, therefore we have truncated follow-up at 10 years for these analyses.

The performance of the two risk estimation formulas (with and without RHR included) was compared based on the following:

- Discrimination (area under receiver operating characteristic curve (AUROC)).
- Observed to predicted ratios (observed rates calculated as CVD mortality rate per 1000 person years of observation, predicted risk calculated as percent risk of CVD death over 10 years).
- Goodness of fit testing—Hosmer–Lemeshow test. The risk score from the Cox model was divided into deciles and then the estimated event rates were compared with the actual event rates in the deciles.
- Net reclassification index (NRI) —a measure of the net percentage of those who do and do not develop the endpoint within the observation period who are correctly reclassified to a more appropriate risk category (i.e. movement to a higher category is considered more appropriate in an individual who does develop the endpoint and vice versa).

Besides performing an internal validation where the formula was validated using the derivation data set, a simulated external validation was performed, using 10-fold cross validation. The comparison figures and the summary measures of discrimination and calibration in the main paper refer to the cross-validated results. The interval validation results are detailed in the supplementary tables. Using 10-fold cross-validation, the data set is split randomly into 10 equally sized groups. The formula is derived 10 times, each time omitting a different of these groups from the complete data set. Each of the ten risk scores are then validated on the tenth of data which was omitted from their derivation dataset. In this way, the model is tested on each observation but the formula being tested has never been derived from a data set which included that particular observation.

Because only 6-year follow-up is included for the study year 1997, this year is excluded from the data set when testing performance in the internal validation and in the simulated external validation.

Additionally, we assessed the improvement in discrimination after incorporation of RHR as an additional variable in a simpler
formula including only easily measured variables: age, gender, 
smoking status and BMI (analysed as a quadratic variable). Simple 
risk estimation charts containing only these variables were 
created and the discrimination and calibration of the formula was 
assessed as above. The effect of incorporating non-linear effects 
of the variables and interactions was also assessed, but none 
except BMI as a quadratic variable usefully added to the predictive 
ability of the formula.

Statistical analyses were conducted using STATA 9.

Results

Resting heart rate formula (value of 
incorporation of resting heart rate to 
formula containing current SCORE 
variables)

After exclusion of 7588 individuals with previous myocardial infarction (MI), heart failure, angina or on anti-hypertensives and 1394 with missing data for any of the included variables, there were data on 14 997 men and 15 861 women available for this analysis. These were from five of the six National FINRISK study years; no data on RHR was collected in the 1972 survey. Four hundred and forty-six fatal CVD events occurred within the first 10 years of observation, 75% of these were CHD events. The baseline characteristics of those included are shown in Table 1. The median follow-up for the group was 16.8 years.

Table 2 shows beta coefficients for the variables included in the formula. The 10 year survivals centred at age = 40, TC = 6 mmol/L, SBP = 120 mmHg ± RHR = 60 bpm for the formula with and without RHR are also shown in Table 2. The corresponding hazard ratios are given in the see Supplementary material online, Table S1.

Cross-validated AUROCs are shown in Table 3 for the formula with and without RHR. The formula including RHR provided superior discrimination compared with the formula without RHR, but this modest improvement only reached borderline statistical significance in women.

As shown in Table 3, the formulas with and without RHR both demonstrated good calibration, based on predicted-to-observed ratios and goodness of fit testing on cross-validation, but there was no consistent indication of superior calibration when RHR was incorporated. Calibration plots by decile of risk were constructed and confirmed good fit for both models (available on request).

Net reclassification indices indicated no statistically significant improvement in classification using the formula including RHR, for the overall population; with a NRI of 0.003, non-significant.

The results of the internal validation are very similar and are shown in see Supplementary material online, Table S1.

Simple resting heart rate formula (value of 
incorporating resting heart rate into 
formula with only age, gender and body 
mass index)

Risk estimation charts for the simple formula containing RHR are shown in Figure 1. Table 4 shows the beta coefficients and baseline survival probabilities (centred at BMI = 20, non-smoker, RHR = 60) for the simpler risk estimation formula. The corresponding hazard ratios are shown in Supplementary material online.

Table 1 Baseline characteristics of the group included in the analysis

<table>
<thead>
<tr>
<th>n</th>
<th>Age range</th>
<th>Age (median)</th>
<th>RHR (median)</th>
<th>SBP (median)</th>
<th>TC (median)</th>
<th>Smokers (%)</th>
<th>HDL-C (median)</th>
<th>BMI (median)</th>
<th>Diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>14 997</td>
<td>25–74</td>
<td>43</td>
<td>70</td>
<td>140</td>
<td>5.93</td>
<td>42</td>
<td>1.24</td>
<td>25.7</td>
</tr>
<tr>
<td>Women</td>
<td>15 861</td>
<td>25–74</td>
<td>43</td>
<td>72</td>
<td>132</td>
<td>5.68</td>
<td>20</td>
<td>1.52</td>
<td>24.5</td>
</tr>
<tr>
<td>Total</td>
<td>30 858</td>
<td>25–74</td>
<td>43</td>
<td>70</td>
<td>136</td>
<td>5.81</td>
<td>31</td>
<td>1.38</td>
<td>25.2</td>
</tr>
</tbody>
</table>

n, number; RHR, resting heart rate; SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index.

Table 2 Beta coefficients for the variables included in the formula with and without resting heart rate and baseline survival probabilities centred at age = 40, TC = 6 mmol/L, SBP = 120 mmHg ± RHR = 60 bpm

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHR formula</td>
<td>Formula without RHR</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.093</td>
<td>0.092</td>
</tr>
<tr>
<td>TC (per mmol/L)</td>
<td>0.278</td>
<td>0.278</td>
</tr>
<tr>
<td>SBP(per 1 mmHg)</td>
<td>0.018</td>
<td>0.021</td>
</tr>
<tr>
<td>Current smoker vs. non-current smoker</td>
<td>0.709</td>
<td>0.774</td>
</tr>
<tr>
<td>RHR (per 1 bpm)</td>
<td>0.017</td>
<td>—</td>
</tr>
<tr>
<td>Baseline 10 year survival probability</td>
<td>0.9970373</td>
<td>0.9965994</td>
</tr>
</tbody>
</table>
Table 3. Measures of discrimination and calibration in risk formula with and without resting heart rate included (cross-validated formulae)

<table>
<thead>
<tr>
<th></th>
<th>Men Risk formula with RHR</th>
<th>Women Risk formula with RHR</th>
<th>Men Risk formula without RHR</th>
<th>Women Risk formula without RHR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discrimination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUROC for 10 year CVD mortality</td>
<td>0.8396</td>
<td>0.8713</td>
<td>0.8380, P for difference in AUROC = 0.5038</td>
<td>0.8649, P for difference in AUROC = 0.0522</td>
</tr>
<tr>
<td><strong>Calibration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted-to-observed ratios</td>
<td>0.99</td>
<td>1.03</td>
<td>0.98</td>
<td>1.03</td>
</tr>
<tr>
<td>Hosmer–Lemeshow statistic</td>
<td>0.1320</td>
<td>0.8608</td>
<td>0.1487</td>
<td>0.0159</td>
</tr>
</tbody>
</table>

Table S2. BMI was shown to have a J shaped relationship with CVD mortality in women, with a more linear relationship in men. Therefore, the quadratic version of the BMI variable was included for women only.

The simple formula including RHR resulted in good discrimination and calibration, as summarized in Table 5. The AUROC for the simple formula containing RHR was 0.8630, an improvement from 0.8521 for the formula without RHR, \( P = 0.0073 \). Separate AUROCs for men and women are shown in Table 5. Hosmer–Lemeshow goodness of fit testing revealed no lack of fit in either formula. Calibration plots by decile of risk were constructed and are available on request. As shown in Table 5, predicted-to-observed ratios were also superior in the formula, which included RHR.
The addition of RHR to the formula also resulted in an improvement in risk classification, with an NRI of 0.05, using four risk categories: <2%, 2–5%, 5–10%, and >10%, $P = 0.0638$.

### Discussion

**Interpretation of principle results and implications**

RHR has previously been shown to be an important and independent risk factor for the development of CVD in this population, with a two-fold increased risk in men and a three-fold increased risk in women when comparing those with RHRs $>90$ bpm to RHRs $<60$ bpm. Others have also demonstrated this relationship.

In this analysis, we have shown that while the addition of RHR as a continuous variable to the variables currently included in the SCORE risk estimation function improves CVD risk estimation in the healthy population, the difference is not statistically significant and unlikely to be clinically meaningful in the population as a whole. This lack of improvement in AUROC for risk formulas after the addition of an important independent variable has previously been seen for other variables, including multiple biomarkers, HDL cholesterol, and ethnicity. This is probably related to the fact that age and gender alone provide a high AUROC and the potential for improving AUROC beyond this is limited. Additionally, as most of the population will have RHRs close to the mean, the number of individuals whose risk estimate changes substantially in the overall population will be low. Nevertheless, the minority of individuals, who have a high RHR, may be exposed to a considerable increase in risk.

Recently, there has been increasing interest in the use of risk estimation systems, which use only easily measured variables. These systems make risk estimation more accessible and cost-effective. Recently, the Framingham group and the NHANES group have shown little reduction in predictive ability when lipid measures were replaced by BMI. We suggest that RHR would be a particularly useful measure to include in such a system, because it is extremely easily measured and has no associated costs. As shown above, this formula performed well. The AUROC was significantly improved on addition of RHR to this simple formula, particularly in women. However, it did not reach the AUROC of the formula containing RHR in addition to lipid measures and blood pressure. The replacement of the blood pressure variable with RHR means that no medical equipment is required and therefore that the risk score could potentially be self-administered. The choice of BMI as the other factor in the simple score was influenced by the fact that it is a readily available measurement, is modifiable through alterations in lifestyle, and reductions have been shown to favourably affect other risk factors.

Physical activity would be another very useful measure to include in a simple system such as this, the value of this is currently under investigation by the SCORE Investigators.

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**Table 4** Beta-coefficients for risk factors and baseline survival probabilities for the simple scores with and without resting heart rate included (cross-validated formulae)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHR formula</td>
<td>Formula without RHR</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.1011</td>
<td>0.1020</td>
</tr>
<tr>
<td>BMI continuous</td>
<td>0.0640</td>
<td>0.0691</td>
</tr>
<tr>
<td>BMI quadratic term</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Current smoker vs. non-current smoker</td>
<td>0.7763</td>
<td>0.8737</td>
</tr>
<tr>
<td>RHR (per 1 bpm)</td>
<td>0.0229</td>
<td>—</td>
</tr>
<tr>
<td>Baseline 10 year survival probability</td>
<td>0.9969311</td>
<td>0.9961686</td>
</tr>
</tbody>
</table>

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**Table 5** Measures of discrimination and calibration in simple score with and without resting heart rate included (cross-validated formulae)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple score with RHR</td>
<td>Simple score without RHR</td>
</tr>
<tr>
<td>Discrimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUROC for 10 year CVD mortality</td>
<td>0.8193</td>
<td>0.8161, $P = 0.037$</td>
</tr>
<tr>
<td>Calibration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted-to-observed ratios</td>
<td>0.96</td>
<td>0.95</td>
</tr>
<tr>
<td>Hosmer–Lemeshow statistic P-value</td>
<td>0.5199</td>
<td>0.8196</td>
</tr>
</tbody>
</table>
It is possible that part of the reason that inclusion of RHR in the simple risk estimation system results in an appreciable improvement is due to a combination of its independent effect on CVD risk and its association with other risk factors. We have previously shown that those with higher RHRs tend to have higher systolic blood pressure, total cholesterol, triglycerides, waist circumference and lower levels of physical activity and HDL cholesterol. Others have also commented on the association between higher RHRs and components of the metabolic syndrome.14

Strengths and weaknesses of this analysis

Strengths of this analysis include the large numbers of individuals included and the availability of full 10 year follow-up on the majority of those included. Additionally, this data set is very appropriate for assessing the value of including RHR in risk estimation systems because The National FINRISK study forms a large proportion of the data set used for derivation of the SCORE function for use in high-risk countries. One of the limitations of this analysis is that because the variables were measured only once at baseline, we have not been able to adjust for regression dilution bias. Additionally, we have validated the formula by simulated external validation, as well as internally. Validation on an external data set is essential for the evaluation of new risk estimation formulas. However, it is unlikely that the risk formula would perform inferiorly on the population from which it was derived and therefore, our conclusion of the minor improvement in risk estimation on incorporation of RHR is not biased by this.

Heart rate post-exercise and heart rate variability were not included in the analysis. These measures may have had more predictive ability than RHR alone, however, the use of such measures would complicate rather than simplify risk estimation.

It should be remembered that RHR was measured in the sitting position in this study and that RHR may vary depending on the position of the individual at the time of measurement.

Conclusion

RHR is an independent predictor of CVD mortality. Inclusion in risk estimation systems for primary prevention of CVD that already contain blood pressure and lipid measurements does not result in an appreciable improvement in their performance. However, in part due to its association with other risk factors, inclusion in simple risk estimation systems containing only easily measured variables results in useful improvements. As a measure, which is simple and inexpensive to obtain, RHR is particularly suitable for inclusion in this type of risk estimation system. Our presentation of a risk estimation system, including only non-laboratory, non-clinic based measures provides an opportunity for enhancing the cost-effectiveness and accessibility of risk estimation.

Authors’ contribution

All co-authors were involved in the design of the analyses. All co-authors were involved in the revising and finalizing of the manuscript. E.V., T.L., and A.J. were involved in the collection of data and administration of the National FINRISK study. M.T.C. performed all of the statistical analyses and wrote the first draft of the paper.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References


CARDIOVASCULAR FLASHLIGHT

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Cardiac pheochromocytoma

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A 51-year-old man was admitted to Peking Union Medical College Hospital because of hypertension, palpitation, and excessive sweating. Both plasma and urinary catecholamine levels were significantly elevated; however, the computer tomography (CT) scan of bilateral adrenal glands was normal. Subsequently, total body iodine I-131 metaiodobenzylguanidine scintigraphy revealed a tumour in the frontal mediastinum, and cardiac pheochromocytoma (CA) was suspected. The contrast-enhanced CT showed the tumour located at the root of the aorta, between the left atrium and right atrium (Panel A). The coronary angiography showed the majority of the blood supply from the branch of RCA (Panel B) and a minority from the branch of LCX (Panel C). Then the tumour was resected and chromogranin A staining of tumour cell was positive on immunohistochemical staining, and the diagnosis of CA was confirmed. The patient recovered completely after the excision of the tumour.

Cardiac pheochromocytoma is very rare, the incidence is approximately 1–2% of extra-adrenal pheochromocytoma. However, CA is highly vascularized tumour, so the coronary angiography is very important to recognize the blood supplies and help decide the surgical strategy.

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