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CLINICAL RESEARCH
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Ranking of psychosocial and traditional risk factors by importance for coronary heart disease: the Copenhagen City Heart Study

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Aims To rank psychosocial and traditional risk factors by importance for coronary heart disease.

Methods and results The Copenhagen City Heart Study is a prospective cardiovascular population study randomly selected in 1976. The third examination was carried out from 1991 to 1994, and 8882 men and women free of cardiovascular diseases were included in this study. Events were assessed until April 2013. Forward selection, population attributable fraction, and gradient boosting machine were used for determining ranks. The importance of vital exhaustion for risk prediction was investigated by C-statistics and net reclassification improvement. During the follow-up, 1731 non-fatal and fatal coronary events were registered. In men, the highest ranking risk factors for coronary heart disease were vital exhaustion [high vs. low; hazard ratio (HR) 2.36; 95% confidence interval (CI), 1.70–3.26; $P < 0.001$] and systolic blood pressure (≥160 mmHg or blood pressure medication vs. <120 mmHg; HR 2.07; 95% CI, 1.48–2.88; $P < 0.001$). In women, smoking was of highest importance (≥15 g tobacco/day vs. never smoker; HR 1.74; 95% CI, 1.43–2.11; $P < 0.001$), followed by vital exhaustion (high vs. low; HR 2.07; 95% CI, 1.61–2.68; $P < 0.001$). Vital exhaustion ranked first in women and fourth in men by population attributable fraction of 27.7% (95% CI, 18.6–36.7%; $P < 0.001$) and 21.1% (95% CI, 13.0–29.2%; $P < 0.001$), respectively. Finally, vital exhaustion significantly improved risk prediction.

Conclusion Vital exhaustion was one of the most important risk factors for coronary heart disease, our findings emphasize the importance of including psychosocial factors in risk prediction scores.

Keywords Coronary heart disease • Vital exhaustion • Ranking of risk factors

Introduction

Knowledge of prevention of coronary heart disease (CHD) is based on prospective population studies started in the late 1940s, and on intervention trials from early 1970s. In 1961, the term factors of risk in the development of CHD were published for the first time by the Framingham Study, stating that the CHD risk factors were hypertension, hypercholesterolaemia, and the electrocardiographic pattern of left-ventricular hypertrophy.[1] A number of new CHD risk factors have later been added.[2] From the 1970s onwards, psychosocial risk factors have also been linked to CHD.[3–7]

The seminal Interheart study, a case–control study involving 15 152 MI cases from 52 countries, concluded that nine risk factors accounted for ~90% of cases and that psychosocial factors alone were responsible for 32.5%.[8] A direct comparison of the impact of traditional and psychosocial risk factors based on a prospective population study has to our knowledge never been published. The Copenhagen City Heart Study has previously ranked the traditional CHD risk factors by importance for the individual and community.[9] The individual impact of vital exhaustion, social network, and major life events as well as socioeconomic stress on the risks of CHD, stroke, heart failure, and total mortality has also been assessed.[10–16]

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The aim of the present study was to compare traditional and psychosocial risk factors and rank them by importance for incidence of CHD, and further to determine whether psychosocial factors may improve risk prediction in a population free of cardiovascular diseases and diabetes.

Methods

Study population

The Copenhagen City Heart Study is a prospective cardiovascular population study comprising a random sample of 19 329 white men and women aged 20–93 years, when drawn from the Copenhagen Population Register as of 1 January 1976. The first examination was carried out in 1976–78 with 14 223 participants (response rate 74%). Details have been described elsewhere.[17] The present analyses are based on the third examination from 1991 to 1994, with 10 135 participants (response rate 61%). We excluded participants with a history of CHD ($n = 614$), stroke ($n = 362$), and diabetes ($n = 446$), leaving 8882 participants (3714 men and 5168 women) for analyses.

Survey methods

Established procedures and examinations for cardiovascular epidemiology surveys were employed.[18] A self-administered questionnaire including information about smoking, alcohol intake, physical activity in leisure time, diabetes mellitus, family history of cardiovascular disease (parents), education, and psychosocial status was completed. Vital exhaustion was assessed using a 17-item questionnaire, given in *Table 1*, derived from the items used by Appels *et al.*[19] and Prescott *et al.*[15] The number of positive answers (except for the question 'I feel fine' which was reversed) to the 17 items was grouped into four categories: 0, 1–4, 5–9, and 10–17. The social network measure contained a subset of questions drawn from an instrument used in a previous study by Orth-Gomer and Johnson.[5] Participants were asked how frequently they had contact with persons in the following categories: parents, children, other family members, a spouse or partner, colleagues from work, neighbours, friends from youth, other friends, and home help. Response options were daily, weekly, monthly, rarely, or never. The assessment of major life events was based on a shorter and modified version of the Social Readjustment Rating Scale, and it included yes/no questions on (i) major life events in childhood (long-term illness in parents, placed in care outside of the home, serious family conflicts, parents' long-term unemployment, serious economic problems), (ii) major life events in adult life (serious and long-term illness in children, having children with major educational problems, major conflicts with adult children, marital problems, involved in a serious accident or long-term illness, death or long-term illness in a close family member, serious economic problems), and (iii) major life events in work life (not achieving educational goals, job loss, not being promoted, serious conflicts with colleagues, supervisors, or charges).[20] We measured height, weight, blood pressure (London School of Hygiene sphygmomanometer), electrocardiogram, and a comprehensive laboratory blood-sample investigation.[17]

The study was approved by The Committees of Biomedical Research Ethics for the Capital region in Denmark (H-KF-01-144/01). All participants gave written consent.

End points

Participants were followed from the third examination (1991–1994) until April 2013 or death, using the unique personal identification number in the Danish National Central Person Register (all-cause deaths).

Table 1 Vital exhaustion: prevalence (%) of the 17 items for the 3714 men and 5168 women in the Copenhagen City Heart Study

Item	Men	Women
1. Do you often feel tired	35.1	45.5
2. Do you feel altogether weak	4.7	7.7
3. Do you feel you have not accomplished much recently	18.1	25.0
4. Do you, at the moment feel that you do not have what it takes?	24.3	36.4
5. Do you believe you have come to a dead end	6.1	5.7
6. Do you lately feel listless	18.9	24.2
7. Do you feel dejected	13.6	21.1
8. Do you lately have difficulties in concentrating	16.6	19.8
9. Do little things irritate you more than they used to	21.2	22.5
10. Do you feel that you want to give up	5.0	7.1
11. I feel fine	88.1	86.4
12. Do you sometimes feel your body is like a battery running out	16.0	20.8
13. Do you sometimes wish you were dead	5.4	7.6
14. Are you feeling 'not worth a scrap' at present	9.2	17.2
15. Do you have feelings of hopelessness recently	6.8	12.2
16. Do you sometimes just feel like crying	12.7	33.1
17. Do you ever wake up with a feeling of exhaustion	13.7	22.8

Information about morbidity leading to hospitalization was obtained from The National Patient Register until April 2013, and causes of death from The Register of Causes of Death until December 2011. During the observation period, Denmark shifted from the 8th revision of the International Classification of Diseases to the 10th revision, which came into use in January 1994. Coronary heart disease refers to morbidity or death from CHD codes 410–414 until January 1994 and thereafter codes I20–I25. Of the 8882 participants, none were lost to follow-up.

Statistical analysis

Ranking was performed in four ways for both genders separately. (1)–(3) used Cox proportional hazards regression with age as underlying time scale (delayed entry) and (4) used Cox partial likelihood as loss-function and follow-up time as underlying time scale:

(1) Ranking based on forward stepwise selection using the Akaike Information Criterion (AIC).[21]
(2) Ranking based on the final model found in (1) vs. the models with one covariate removed, i.e. one-step backwards elimination using the AIC.
(3) Ranking based on the multivariable adjusted overall Mantel–Haenszel Population Attributable Fraction (PAF) for the covariates in the final model found in (1).[22]
(4) Ranking based on relative influence of the covariates in the final model found in (1) from Gradient Boosting Machine (GBM).[23]

AIC provides a means for model selection as it rewards goodness of fit while penalizing model complexity, hereby minimizing the problem of over-fitting. Model selection is performed as a combination of stepwise forward selection and backward elimination according to AIC. The first

Table 2 Baseline characteristics of the 3714 men and 5168 women in the Copenhagen City Heart Study

Characteristic	Men		Women	
Traditional risk factors				
Age, years	55.6 ± 15.5		58.6 ± 15.5	
Smoking, *n* (%)				
Never	687	(18.7)	1619	(31.6)
Former	1027	(28.0)	1170	(22.8)
1–4 g tobacco per day	77	(2.1)	163	(3.2)
5–14 g tobacco per day	561	(15.3)	943	(18.4)
≥15 g tobacco per day	1314	(35.8)	1227	(24.0)
HDL cholesterol, *n* (%)				
<1.0 mmol/L	402	(11.1)	131	(2.6)
1.0–1.4 mmol/L	1852	(50.9)	1361	(26.9)
≥1.5 mmol/L	1383	(38.0)	3568	(70.5)
Body mass index, *n* (%)				
<18.5 kg/m^2	29	(0.8)	143	(2.9)
18.5–24.9 kg/m^2	1592	(44.1)	2686	(54.0)
25.0–29.9 kg/m^2	1522	(42.2)	1468	(29.5)
≥30 kg/m^2	465	(12.9)	675	(13.6)
Systolic blood pressure, *n* (%)				
<120 mmHg	533	(14.5)	1253	(24.5)
120–139 mmHg	1504	(41.0)	1706	(33.3)
140–159 mmHg	1000	(27.3)	1275	(24.9)
≥160 mmHg or medication	632	(17.2)	889	(17.4)
Total cholesterol, range				
1st quartile	<5.4		<5.4	
2nd quartile	(5.4–6.1)		(5.4–6.1)	
3rd quartile	(6.2–7.0)		(6.2–7.0)	
4th quartile	>7.0		>7.0	
Physical activity in leisure time				
Low	451	(12.3)	619	(12.1)
Moderate	1670	(45.5)	2982	(58.5)
High	1547	(42.2)	1495	(29.3)
Family history of CVD, *n* (%)	145	(4.1)	278	(5.5)
Alcohol intake, *n* (%)				
Never	444	(12.2)	1498	(29.3)
1–21/1–14 drinks/week	2409	(66.0)	3086	(60.3)
≥22/≥15 drinks/week	798	(21.9)	534	(10.4)
Psychosocial risk factors				
Vital exhaustion, *n* (%)				
Score 0	1326	(36.8)	1311	(26.4)
Score 1–4	1646	(45.6)	2218	(44.7)
Score 5–9	459	(12.7)	1002	(20.2)
Score 10–17	177	(4.9)	426	(8.6)
School education, *n* (%)				
<8 years	1141	(31.0)	1723	(33.7)
8–10 years	1401	(38.1)	2013	(39.3)
≥11 years	485	(13.2)	757	(14.8)
University	651	(17.7)	624	(12.2)
Social network, *n* (%)				
0 contacts	119	(3.3)	62	(1.3)
1–2 contacts	1191	(33.4)	1366	(27.9)
3–4 contacts	1735	(48.6)	2722	(55.5)
5–6 contacts	522	(14.6)	752	(15.3)

Continued

Table 2 *Continued*

Characteristic	Men		Women	
Life events during childhood, *n* (%)				
Score 0	1767	(47.6)	2341	(45.3)
Score 1–2	1513	(40.7)	2277	(44.1)
Score 3–4	381	(10.3)	491	(9.5)
Score 5–6	53	(1.4)	59	(1.1)
Work-related life events, *n* (%)				
Score 0	2511	(67.6)	4077	(78.9)
Score 1–2	1099	(29.6)	1018	(19.7)
Score 3–5	104	(2.8)	73	(1.4)
Life events during adolescence, *n* (%)				
Score 0	1492	(40.2)	1559	(30.2)
Score 1–2	1828	(49.2)	2820	(54.6)
Score 3–4	356	(9.6)	690	(13.4)
Score 5–7	38	(1.0)	99	(1.9)

Values are means ± SD for continuous covariates and *n* (%) for categorical covariates except for total cholesterol where the ranges of the quartiles are presented. The body mass index is the weight in kilograms divided by the square of the height in metres. CVD, cardiovascular disease.

step takes a model without any covariates. In each consecutive step, the covariate that improves (according to AIC) the model the most is added. The process is repeated until no covariates improve the model. In each step, covariates included in earlier steps are attempted excluded (backward elimination).

The multivariable adjusted Mantel–Haenszel PAF = p(exposure|event) × (relative risk − 1)/relative risk, where p(exposure|event) is the prevalence of exposure (e.g. low physical activity in leisure time) among events. Relative risk is estimated by the multivariable adjusted hazard ratios. For overall population attributable risk, binary covariates are needed.[22] Hence, for covariates with more than two categories, a single exposed category is formed by combining all exposed categories as one. The bias-corrected population attributable risk and confidence interval was estimated by bootstrap resampling with 10 000 samples.[24] Machine-learned ranking implements ranking based on algorithm-based models that learns from data. Gradient Boosting Machine quantifies the relative influence of each covariate with an overall sum of 100%. Cox partial likelihood for right-censored data was chosen as loss-function and shrinkage was set to 0.001. Follow-up time was chosen as the underlying time scale and all models were adjusted for age. Bias-corrected relative influence and confidence interval was estimated by bootstrap resampling with 10 000 samples. Due to non-normality of the bootstrap statistic for some covariates, the median and percentile confidence interval (2.5th and 97.5th percentile) was reported. Confidence intervals based on normality could potentially include negative values of the relative influence which is meaningless. However, ranking was based on the bias-corrected relative influence.

The possible traditional CHD risk factors tested in the model selection included systolic blood pressure (<120, 120–139, 140–159, ≥160 mmHg or use of blood pressure medication), smoking (never smoker, former smoker, and smoker, expressed in 1–4 g tobacco/day, 5–14 g tobacco/day, ≥15 g tobacco/day; 1 cigarette = 1 g tobacco, 1 cheroot = 3 g, and 1 cigar = 5 g), physical activity in leisure time (low, moderate, high), alcohol intake (never, 1–20 drinks/week for men and 1–14 drinks/week for women, ≥21 drinks/week for men and ≥15 drinks/week for women), body mass index (underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2)), total-cholesterol that was classified in four quartiles (<5.4, 5.4–6.1, 6.2–7.0, >7.0 mmol/L), HDL cholesterol that was classified in three groups (<1.0, 1.0–1.4, ≥1.5 mmol/L), and family history (parental) of cardiovascular diseases. Information on food items was not available.

The psychosocial risk factors considered were years in school (<8, 8–10, ≥11, university), vital exhaustion (number of positive responses to 17 questions: 0, 1–4, 5–9, 10–17), social network (number of contacts: 0, 1–2, 3–4, 5–6), and major life events. The psychosocial factor most strongly associated with CHD was vital exhaustion. The predictive power of the Cox models comparing models without and with vital exhaustion was summarized by Harrell's C-index. To further evaluate the value of vital exhaustion for risk classification, we calculated category-free net reclassification improvement,[24] which is a measure for evaluating the improvement in prediction performance in models with and without vital exhaustion, when including traditional risk factors from the SCORE model.[2,25] Net reclassification improvement measures the expanded models' ability to correctly reclassify individuals with and without events during follow-up into higher or lower risk, respectively. The expected number of events and non-events were used in the estimation of net reclassification improvements to account for censored data and calculated by multiplying the total number of individuals by the Kaplan–Meier estimates at end of follow-up.[26] This approach is optimal in assessing calibration of survival models.[27] The bias-corrected net reclassification improvement and confidence interval was estimated by bootstrap resampling with 10 000 samples.

Results

Study population

Traditional and psychosocial baseline characteristics are presented in *Table 2*. During a median follow-up of 21.5 years there were 1731 coronary events, 1430 non-fatal and 301 fatal.

Table 3 **Risk factors of incident coronary heart disease**

Risk factor	Men hazard ratio (95% CI)	*P*-value	Women hazard ratio (95% CI)	*P*-value
Traditional risk factors				
Smoking				
Never	1.00 (reference)		1.00 (reference)	
Former	1.73 (1.35–2.23)	<0.001	0.97 (0.81–1.16)	0.760
1–4 g tobacco per day	1.51 (0.84–2.72)	0.165	0.94 (0.60–1.47)	0.786
5–14 g tobacco per day	1.65 (1.25–2.19)	<0.001	1.57 (1.31–1.88)	<0.001
≥15 g tobacco per day	1.91 (1.49–2.46)	<0.001	1.84 (1.54–2.21)	<0.001
HDL cholesterol				
<1.0 mmol/L	1.70 (1.35–2.14)	<0.001	1.88 (1.32–2.69)	<0.001
1.0–1.4 mmol/L	1.42 (1.21–1.66)	<0.001	1.61 (1.40–1.84)	<0.001
≥1.5 mmol/L	1.00 (reference)		1.00 (reference)	
Body mass index				
<18.5 kg/m^2	1.48 (0.55–3.98)	0.437	1.24 (0.78–1.96)	0.368
18.5–24.9 kg/m^2	1.00 (reference)		1.00 (reference)	
25.0–29.9 kg/m^2	1.36 (1.15–1.61)	<0.001	1.27 (1.09–1.47)	0.002
≥30 kg/m^2	1.81 (1.47–2.23)	<0.001	1.46 (1.22–1.75)	<0.001
Systolic blood pressure				
<120 mmHg	1.00 (reference)		1.00 (reference)	
120–139 mmHg	1.44 (1.06–1.94)	0.019	1.00 (0.79–1.27)	0.976
140–159 mmHg	1.84 (1.35–2.50)	<0.001	1.27 (1.01–1.61)	0.043
≥160 mmHg or BP medication	2.14 (1.56–2.94)	<0.001	1.42 (1.11–1.81)	0.005
Total cholesterol				
1st quartile	1.00 (reference)		1.00 (reference)	
2nd quartile	1.14 (0.92–1.40)	0.230	1.06 (0.84–1.33)	0.624
3rd quartile	1.25 (1.02–1.54)	0.032	0.97 (0.78–1.22)	0.821
4th quartile	1.88 (1.52–2.32)	<0.001	1.21 (0.98–1.51)	0.079
Physical activity in leisure time				
Low	1.63 (1.31–2.02)	<0.001	1.83 (1.48–2.26)	<0.001
Moderate	1.10 (0.95–1.29)	0.213	1.31 (1.11–1.53)	<0.001
High	1.00 (reference)		1.00 (reference)	
Family history of CVD				
No	1.00 (reference)		1.00 (reference)	
Yes	1.50 (1.06–2.12)	0.021	1.52 (1.19–1.94)	<0.001
Alcohol intake				
Never	1.05 (0.84–1.30)	0.671	1.29 (1.13–1.48)	<0.001
1–21/1–14 drinks/week	1.00 (reference)		1.00 (reference)	
≥22/≥15 drinks/week	0.90 (0.76–1.08)	0.273	1.60 (1.21–2.11)	0.001
Psychosocial risk factors				
Vital exhaustion				
Score 0	1.00 (reference)		1.00 (reference)	
Score 1–4	1.34 (1.14–1.58)	<0.001	1.41 (1.19–1.66)	<0.001
Score 5–9	1.57 (1.24–1.98)	<0.001	1.87 (1.54–2.26)	<0.001
Score 10–17	2.50 (1.85–3.39)	<0.001	2.26 (1.77–2.87)	<0.001
School education				
<8 years	1.76 (1.37–2.27)	<0.001	1.46 (1.07–2.00)	0.017
8–10 years	1.59 (1.24–2.04)	<0.001	1.32 (0.97–1.81)	0.076
≥11 years	1.23 (0.87–1.74)	0.236	0.98 (0.68–1.43)	0.924
University	1.00 (reference)		1.00 (reference)	
Social network				
0 contacts	1.21 (0.78–1.89)	0.392	1.02 (0.58–1.81)	0.942
1–2 contacts	1.27 (0.96–1.68)	0.090	0.99 (0.77–1.28)	0.958

Continued

Table 3 *Continued*

Risk factor	Men hazard ratio (95% CI)	*P*-value	Women hazard ratio (95% CI)	*P*-value
3–4 contacts	1.25 (0.96–1.64)	0.098	0.90 (0.71–1.15)	0.401
5–6 contacts	1.00 (reference)		1.00 (reference)	
Life events during childhood				
Score 0	1.00 (reference)		1.00 (reference)	
Score 1–2	1.11 (0.96–1.30)	0.158	1.10 (0.96–1.26)	0.166
Score 3–4	1.11 (0.87–1.42)	0.394	1.07 (0.84–1.36)	0.583
Score 5–6	0.83 (0.41–1.67)	0.593	1.17 (0.60–2.27)	0.640
Work-related life events				
Score 0	1.00 (reference)		1.00 (reference)	
Score 1–2	0.90 (0.77–1.07)	0.229	1.03 (0.86–1.24)	0.738
Score 3–5	0.61 (0.34–1.08)	0.090	0.81 (0.36–1.81)	0.608
Life events during adolescence				
Score 0	1.00 (reference)		1.00 (reference)	
Score 1–2	1.03 (0.89–1.20)	0.685	1.00 (0.86–1.15)	0.947
Score 3–4	1.18 (0.92–1.52)	0.189	1.22 (0.99–1.50)	0.059
Score 5–7	0.46 (0.17–1.22)	0.118	0.99 (0.58–1.70)	0.982

Univariable Cox proportional hazards regression analyses with age as underlying time scale for the 3714 men and 5168 women in the Copenhagen City Heart Study. CVD, cardiovascular disease.

Univariable analysis

Table 3 gives age-adjusted univariable hazard ratios for incident CHD for each of the traditional and psychosocial risk factors for CHD by gender. Smoking, HDL cholesterol, body mass index, systolic blood pressure, physical activity in leisure time, and family history were statistically significantly related to CHD in both genders, but total cholesterol only in men and alcohol intake only in women.

Of the psychosocial factors examined, vital exhaustion and education were significantly predictive of CHD. For vital exhaustion, the association showed a dose–response relationship reaching a maximum hazard ratio of over two for subjects scoring above 9 on the 17 item-scale (*Table 1*). Social network was not associated with CHD. Life events during childhood, adulthood, or work showed no consistent associations with CHD outcomes and were not considered in further analyses.

Multivariable analyses and ranking of risk factors

In the multivariable analysis (*Figure 1*), vital exhaustion was in men the highest ranking risk factor by importance for CHD, hazard ratio (HR) 2.36 (95% CI, 1.70–3.26; $P < 0.001$), and second in women, HR 2.07 (95% CI, 1.61–2.68; $P < 0.001$) according to AIC.

The risk factors ranked highest by PAF in men were systolic blood pressure (PAF 33.1%; 95% CI, 13.7–52.5%; $P < 0.001$), smoking (PAF 31.5%; 95% CI, 17.2–45.9%; $P < 0.001$), and education (PAF 25.9%; 95% CI, 9.5–42.3%; $P = 0.002$) with vital exhaustion ranking fourth (PAF 21.1%; 95% CI, 13.0–29.2%; $P < 0.001$). In women, the three highest ranking were vital exhaustion (PAF 27.7%; 95% CI, 18.6–36.7%; $P < 0.001$), systolic blood pressure (PAF 18.5%; 95% CI, 1.7–35.4%; $P = 0.031$), and smoking (PAF 16.7%; 95% CI, 8.3–25.1%; $P < 0.001$). Ranking according to one-step backwards elimination of the final model yielded exactly the same ordering of the risk factors as forward stepwise selection shown in *Figure 1*.

The risk factors with the greatest relative influence on CHD according to GBM in men were total cholesterol (21.4%; 95% CI, 12.1–30.8%), systolic blood pressure (20.2%; 95% CI, 9.7–30.6%), and vital exhaustion (16.3%; 95% CI, 7.9–24.8%). For women, vital exhaustion was the second most influential risk factor for CHD (20.2%; 95% CI, 11.4–29.1%) only surpassed by systolic blood pressure (26.7%; 95% CI, 14.8–38.5%). These two risk factors have almost the same relative influence (46.9%) as the remaining five risk factors in the model (53.1%).

When the categorical version of vital exhaustion was substituted with the continuous version (with values given by whole numbers from 0 to 17) the exact same ordering of the covariates was found according to AIC. For men, the continuous version of vital exhaustion was slightly better while the categorical version was better for women.

SCORE risk factors, i.e. age, sex, current smoking, cholesterol, and systolic blood pressure, explained the majority of variation in the CHD outcome as indicated by a Harrell's C-index of 0.800 (95% CI, 0.799–0.802; $P < 0.001$). Inclusion of vital exhaustion in the model increased the prediction significantly but numerically had small impact (improvement in C-index 0.010; 95% CI, 0.009–0.011; $P < 0.001$). However, the net reclassification improvement was 32.0% (95% CI, 24.0–40.0%; $P < 0.001$). For comparison, we estimated the predictive value of systolic blood pressure in a model including age, sex, current smoking, and total cholesterol. Systolic blood pressure was surpassed in performance by vital exhaustion since the increase in C-index for systolic blood pressure was 0.004 (95% CI, 0.003–0.005; $P < 0.001$) and net reclassification improvement 18.2% (95% CI, 14.2–22.3%; $P < 0.001$).

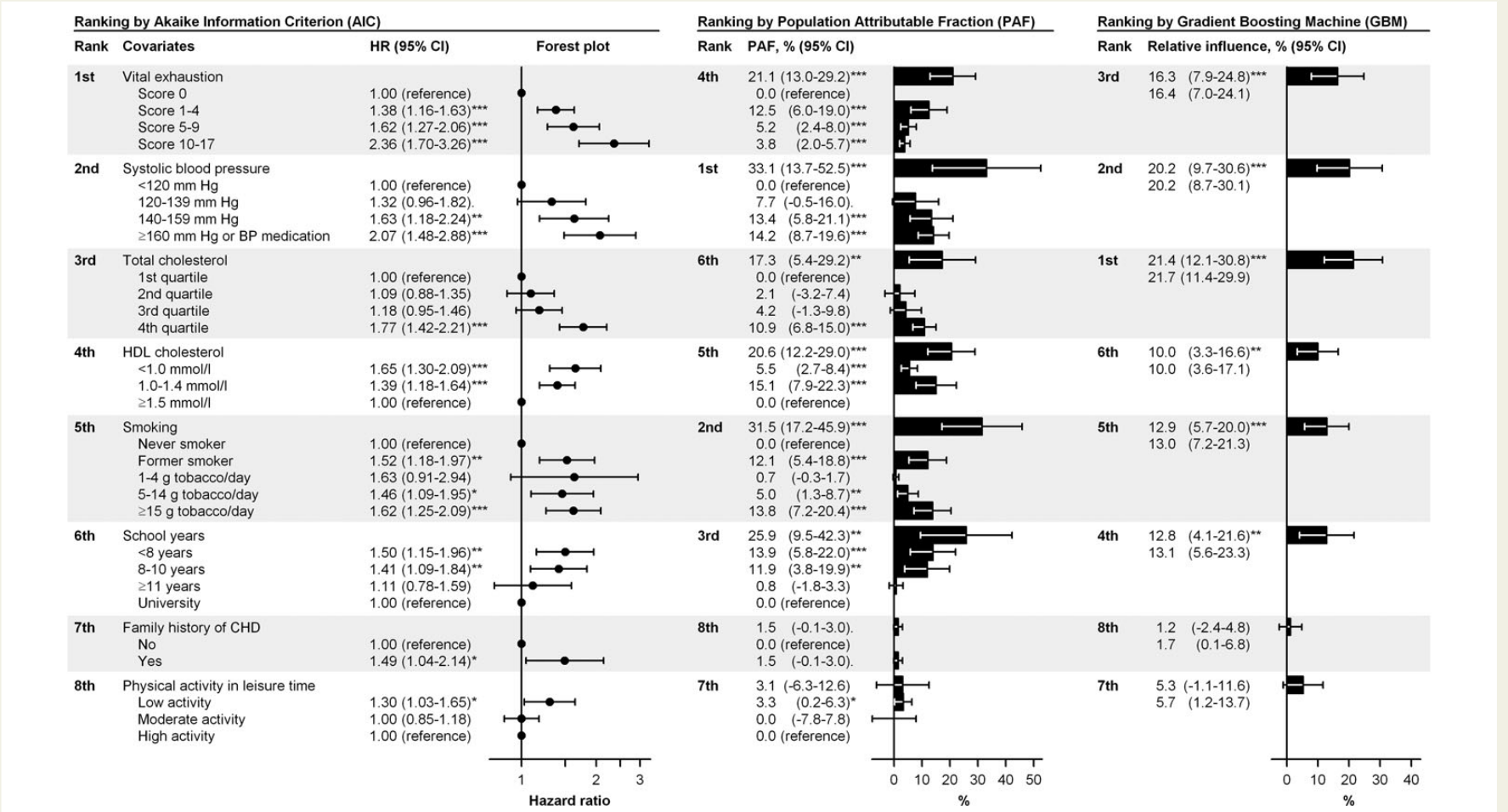

Figure 1 Ranking of risk factors by importance for incident Coronary Heart Disease in 3714 men and 5168 women separately in the Copenhagen City Heart Study. Ranking was based on forward stepwise selection using Akaike Information Criterion (AIC), multivariable adjusted overall Mantel–Haenszel Population Attributable Fraction (PAF) and relative influence according to Gradient Boosting Machine (GBM). Cox regression models with age as underlying time scale were performed for AIC and PAF while Cox partial likelihood with follow-up time as underlying time scale was chosen as loss-function for GBM (including age-adjustment). Bootstrap percentile confidence intervals (2.5th to 97.5th percentile; shown in second line) for the medians were performed in addition to normal confidence intervals (shown in first line) for GBM due to deviations from normality in the bootstrap statistic for some covariates. ‘$P < 0.10$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Figure should be stated that the upper part is men, while the lower part is women.

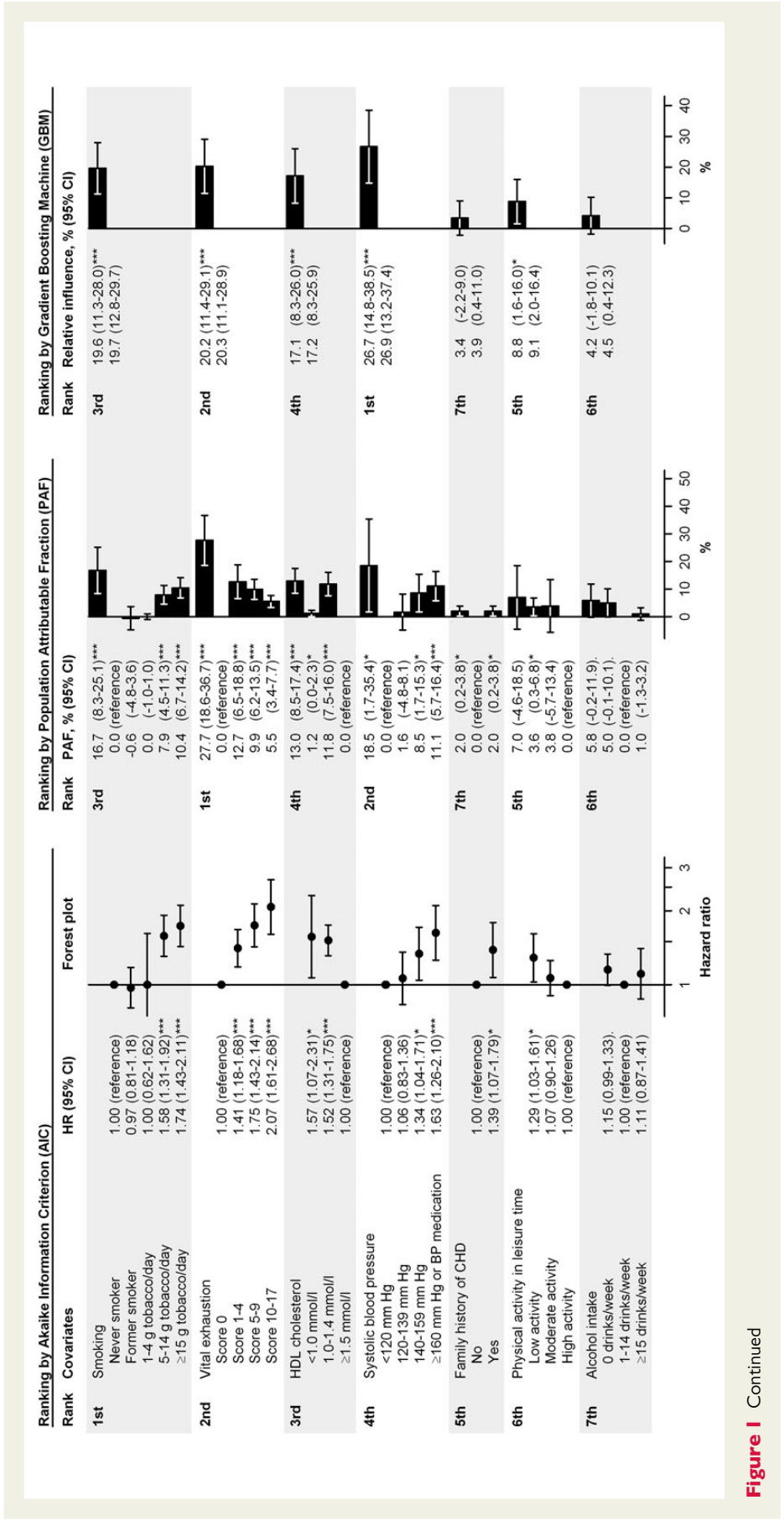

Figure 1 Continued

Discussion

The most important finding in the present study was that vital exhaustion was an independent risk factor for CHD in both men and women and that it ranked first among men and second among women. Furthermore, vital exhaustion significantly improved the risk prediction based on European Society of Cardiology's SCORE-model in this general population.[2]

The vital exhaustion construct was originally developed by Appels in 1987.[19] From the Copenhagen City Heart Study; we have reported a significant association between vital exhaustion and risk of CHD.[14] In the Atherosclerosis Risk In Communities (ARIC) study comprising 12 895 men and women followed for CHD morbidity and mortality, belonging to the highest quartile of vital exhaustion was associated with age- and gender-adjusted hazard ratio of 1.69, which was reduced to 1.46 after multiple adjustment but remained highly significant associated with the outcome ($P = 0.002$).[28]

Vital exhaustion is defined as excessive fatigue, feelings of demoralization, and increased irritability and is often considered a form of adaptation to prolonged distress or burnout. Vital exhaustion is also linked to depression but it is still unclear whether they are conceptually distinct since studies evaluating the overlap between the two concepts have been inconsistent.[29–32] In the most recent study by Vroege *et al.*,[33] vital exhaustion was compared with the Beck Depression Inventory (BDI) in 528 patients hospitalized with MI. Principal component analyses of vital exhaustion yielded only one dimension which had strong overlap with the somatic/affective dimension of the BDI but not with the cognitive/affective dimension. In addition, vital exhaustion and somatic/affective depression were associated with poor cardiovascular outcomes in the patient group while cognitive/affective dimension was not.[33] A recent meta-analysis of 13 prospective studies of depression in heart disease found that the somatic/affective dimension but not the cognitive/affective dimension was associated with mortality and cardiovascular outcomes.[34] We are not aware of similar studies based on healthy population samples, and it is a limitation of our study that a validated depression inventory was not included, however, the data based on patients with CHD indicate that vital exhaustion captures a dimension of depression associated with poor prognosis.

Several hypotheses have been proposed to explain the association between psychosocial distress and the development of CHD, among them enhanced platelet reactivity, lower heart rate variability, increased inflammation, and endothelial dysfunction, but for the present, the pathophysiological links remain unclear.[35] Intervention targeting psychosocial distress to improve cardiovascular risk factors have shown to be effective. A randomized Swedish study comparing cognitive behavioural therapy focusing on stress management with conventional care in 372 patients with CHD found a 41% lower rate of recurrent cardiovascular events ($P = 0.002$).[36]

The most recent European Society of Cardiology guidelines (SCORE) emphasize that psychosocial factors comprising low socioeconomic status, social isolation and lack of social support, stress at work and in family life, depression, anxiety, hostility, anger, and type D personality contribute to the risk of cardiovascular diseases and may be regarded as qualifiers in the recommended SCORE, meaning that the presence of the risk factor can move the person up a class in risk.[2] In the American College of Cardiology and American Heart Association guidelines on the value of novel risk markers in risk prediction and in risk assessment of asymptomatic individuals, psychosocial factors have not yet been considered.[37,38]

In this study, traditional risk factors included in SCORE already gave good prediction as indicated by Harell's C-index of 0.800. This is presumably mainly due to the large age-span in the study and age being the most important predictor of outcome. Thus, any risk factor would need to perform well to improve risk prediction in this setting. However, vital exhaustion improved risk prediction as indicated by significant improvement in Harrell's C-index ($P < 0.001$) and net reclassification improvement ($P < 0.001$) for CHD. Although the nominal increase in C-index was at best modest, the improvement was greater than that seen when adding systolic blood pressure to a SCORE model without systolic blood pressure.

Limitations of the study include that because our study is observational and not a randomized trial, we can demonstrate associations but not casual relationships. However, our cohort was a large random sample from the general population, the response rate was acceptable, 61%, and none were lost to follow-up. It should be mentioned, that several authors have found that observational studies and randomized controlled trials usually produce similar results.[39,40]

In these years, the developed countries see a decline in the incidence of CHD because of improvement in traditional risk factors such as smoking and cholesterol.[41–45] Psychosocial stress on the other hand shows trends towards an increase.[45] The relative importance of psychosocial stress on the risk of CHD is likely to increase and should therefore be considered.

These findings emphasize the importance of including psychosocial factors in public-health priority and implementing cost-effective interventions to reduce its burden on CHD.

Authors' contributions

P.S., E.P., and statistician J.L.M. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design were from P.S., E.P., and J.L.M. Acquisition, analysis, or interpretation of data were done by all authors. P.S., E.P., and J.L.M. involved in drafting of the manuscript. Critical revision of the manuscript for important intellectual content was done by all authors.

J.L.M. performed statistical analysis.

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References

1. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J III. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. *Ann Intern Med* 1961;**55**:33–50.
2. Perk J, De Backer G, Gohlke H, Graham I, Reiner ZVerschuren WMM, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte JM, Reimer O, Vrints C, Wood D, Zamorano JL, Zannad F. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). (Constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635–1701.
3. Jenkins CD. Psychologic and social precursors of coronary disease (first of two parts). *N Engl J Med* 1971;**284**:244–255.

4. Appels A. Psychological prodromata of myocardial infarction and sudden death. *Psychother Psychosom* 1980;**34**:187–195.
5. Orth-Gomer K, Johnson JV. Social network interaction and mortality. A six year follow-up study of random sample of the Swedish population. *J Chronic Dis* 1987; **40**:949–957.
6. Jenkins CD. Psychologic and social precursors of coronary disease. (II). *N Engl J Med* 1971;**284**:307–317.
7. Jenkins CD. Low education: a risk factor for death. *N Engl J Med* 1978;**299**:95–97.
8. Yusuf S, Hawkwn S, Õunpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, on behalf of the INTERHEART Study investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**: 937–952.
9. Schnohr P, Jensen JS, Scharling H, Nordestgaard BG. Coronary heart disease risk factors ranked by importance for the individual and community. A 21 year follow-up of 12 000 men and women from The Copenhagen City Heart Study. *Eur Heart J* 2002; **23**:620–626.
10. Andersen I, Osler M, Petersen L, Gronbaek M, Prescott E. Income and risk of ischaemic heart disease in men and women in a Nordic welfare country. *Int J Epidemiol* 2003; **32**:367–374.
11. Andersen I, Diderichsen F, Kornerup H, Prescott E, Rod NH. Major life events and the risk of ischaemic heart disease: does accumulation increase the risk? *Int J Epidemiol* 2011;**40**:904–913.
12. Barefoot JC, Gronbaek M, Jensen G, Schnohr P, Prescott E. Social network diversity and risks of ischemic heart disease and total mortality: findings from the Copenhagen City Heart Study. *Am J Epidemiol* 2005;**161**:960–967.
13. Kornerup H, Osler M, Boysen G, Barefoot J, Schnohr P, Prescott E. Major life events increase the risk of stroke but not of myocardial infarction: results from the Copenhagen City Heart Study. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:113–118.
14. Kornerup H, Marott JL, Schnohr P, Boysen G, Barefoot J, Prescott E. Vital exhaustion increases the risk of ischemic stroke in women but not in men: results from the Copenhagen City Heart Study. *J Psychosom Res* 2010;**68**:131–137.
15. Prescott E, Holst C, Gronbaek M, Schnohr P, Jensen G, Barefoot J. Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. *Int J Epidemiol* 2003;**32**:990–997.
16. Rod NH, Andersen I, Prescott E. Psychosocial risk factors and heart failure hospitalization: a prospective cohort study. *Am J Epidemiol* 2011;**174**:672–680.
17. Schnohr P, Jensen G, Lange P. The Copenhagen City Heart Study. Tables with data from the third examination 1991–1994. *Eur Heart J* 2011;**3**:H1–H83.
18. Rose GA, Blackburn H. Cardiovascular survey methods. *Monogr Ser World Health Organ* 1968;**56**:1–188.
19. Appels A, Hoppener P, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. *Int J Cardiol* 1987;**17**:15–24.
20. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *J Psychosom Res* 1967; **11**:213–218.
21. Venables WN, Ripley BD. *Modern applied statistics with S*. 4th ed. *Statistics and Computing*. New York, NY, USA: Springer.
22. Benichou J. A review of adjusted estimators of attributable risk. *Stat Methods Med Res* 2001;**10**:195–216.
23. Friedman JH. Greedy Function Approximation: A Gradient Boosting Machine. *Ann Stat* 2001;**29**:1189–1232.
24. 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.
25. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Kell U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, SCORE project group. *Eur Heart J* 2003;**24**:987–1003.
26. Steyerberg EW, Pencina MJ. Reclassification calculations for persons with incomplete follow-up. *Ann Intern Med* 2010;**152**:195–196.
27. Viallon V, Ragusa S, Clavel-Chapelon F, Benichou J. How to evaluate the calibration of a disease risk prediction tool. *Stat Med* 2009;**28**:901–916.
28. Williams JE, Mosley TH Jr., Kop WJ, Couper DJ, Welch VL, Rosamond WD. Vital exhaustion as a risk factor for adverse cardiac events (from the Atherosclerosis Risk In Communities [ARIC] study). *Am J Cardiol* 2010;**105**:1661–1665.
29. Kopp MS, Falger PR, Appels A, Szedmak S. Depressive symptomatology and vital exhaustion are differentially related to behavioral risk factors for coronary artery disease. *Psychosom Med* 1998;**60**:752–758.
30. Kudielka BM, von Känel R, Gander ML, Fischer JE. The interrelationship of psycosocial risk factors for coronary artery disease in a working population: do we measure distinct or overlapping psychological conceps? *Behav Med* 2004;**30**:35–43.
31. van Diest R, Appels A. Vital exhaustion and depression: a conceptual study. *J Psychosom Res* 1991;**35**:535–544.
32. Wojciechowski FL, Strik JJ, Falger P, Lousberg R, Honig A. The relationship between depressive and vital exhaustion symptomatology post-myocardial infarction. *Acta Psychiatr Scand* 2000;**102**:359–365.
33. Vroge EM, Zuidersma M, de Jonge P. Vital exhaustion and somatic depression: the same underlying construct in patients with myocardial infarction? *Psychosom Med* 2012;**74**:446–451.
34. de Miranda Azevedo R, Roest AM, Hoen PW, de Jonge P. Cognitive/affective and somatic/afective symptoms of depression in patients with heart disease and theit association with cardiovascular prognosis: a meta-analysis. *Psychol Med* 2014;**44**: 2689–2703.
35. Melamed S, Shirom A, Toker S. Burnout and risk of cardiovascular disease: Evidence, possible casual paths, and promising research directions. *Psycholog Bull* 2006;**132**: 327–353.
36. Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svardsudd K. Randomized controlled. trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM)1. *Arch Intern Med* 2011;**171**:134–140.
37. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky A, Hodgson J McB, Kushner FG, Lauer MS, Shaw LJ, Smith SC, Taylor AJ, Weintraub WS, Wenger NK. *Circulation* 2010;**122**:e584–e636.
38. Goff DC Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr., Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnel CJ, Robinson J, Schwartz JS, Shero ST, Smith SC Jr., Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**(25 suppl 2):S49–S73.
39. Benson K, Hartz AJ. A comparison of observational studies and randomized controlled trials. *N Eng J Med* 2000;**342**:1878–1886.
40. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;**342**:1887–1892.
41. Young F, Capewell S, Ford ES, Critchley JA. Coronary mortality declines in the U.S. between 1980 and 2000 quantifying the contributions from primary and secondary prevention. *Am J Prev Med* 2010;**39**:228–234.
42. Wijeysundera HC, Machado M, Farahati F, Wang X, Witteman W, Velde G, Tu JV, Lee DS, Goodman SG, Petrella R, O'Flaherty M, Krahn M, Capewell S. Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994–2005. *JAMA* 2010;**303**:1841–1847.
43. Capewell S, Hayes DK, Ford ES, Critchley JA, Croft JB, Greenlund KJ, Labarthe DR. Life-years gained among US adults from modern treatments and changes in the prevalence of 6 coronary heart disease risk factors between 1980 and 2000. *Am J Epidemiol* 2009;**170**:229–236.
44. Unal B, Critchley JA, Capewell S. Modelling the decline in coronary heart disease deaths in England and Wales, 1981–2000: comparing contributions from primary prevention and secondary prevention. *BMJ* 2005;**331**:614.
45. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, Vos T, Whiteford HA. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013;**10**:e1001547.