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# Room for depressed and exhausted mood as a risk predictor for all-cause and cardiovascular mortality beyond the contribution of the classical somatic risk factors in men

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ABSTRACT

*Background and aims:* Depressed mood and exhaustion (DEEX) have gained attention as a risk predictor for cardiovascular disease (CVD). Studies to estimate its ranking in prediction models are sparse.
*Methods:* The study included 3428 men aged 45–74 years who participated in one of three population-based MONICA/KORA Augsburg surveys conducted between 1984 and 1995. Within a follow-up time of 10 years (31,791 person-years), 557 cases of all-cause mortality and 269 fatal CVD events were observed. Adjusted Cox proportional hazards models were used to assess mortality risks for DEEX and five classical cardiovascular risk factors. The predictive ability was evaluated by the area under the receiver-operating characteristic curve, the integrated discrimination improvement statistics and the net classification improvement.
*Results:* The (crude) absolute mortality risk for DEEX was 23.1 cases per 1000 person-years for all-cause and 11.2 for CVD mortality. The adjusted hazard ratios of 1.52 for all-cause and 1.52 for CVD mortality ($p < 0.01$) were higher than those for hypercholesterolemia and obesity, but lower than for hypertension, smoking and diabetes. The improvements in risk prediction from DEEX were comparable to those of hypercholesterolemia and obesity, but substantially lower than those of hypertension, smoking and diabetes. The adjusted population-attributable risk (PAR) for DEEX accounted for about 15% for all-cause and CVD mortality, which gives DEEX a middle ranking amongst the classical risk factors.
*Conclusions:* DEEX is a strong predictor of mortality risk, ranking in a medium position amongst classical somatic risk factors.



## 1. Introduction

Cardiovascular diseases (CVD) continue to rank among the leading causes of premature death in industrialized countries [1,2] underscoring the need of more effective preventive efforts. Particularly, there is still room for improvement in risk prediction in addition to the classical risk factors since risk prediction in individuals with low [3] and intermediate risks remains poor [4]. Among promising new potential CVD risk factors, depressed mood has gained considerable attention: meta-analyses [5–8] have congruently revealed an overall relative CVD risk of 1.60–1.90 for subjects with depressed mood compared to their counterparts. Similar findings have been achieved with studies on excess fatigue and vital exhaustion (VE) [9–11], which may be a clinically more appropriate phenotype to cover the particular clinical picture of negative affectivity in patients with cardiovascular disease [12]. Recently, a high ranking of VE compared to somatic risk factors was shown with data from the Copenhagen City Heart Study [13].

Nevertheless, the potential of depression and exhaustion (DEEX)

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to screen effectively for CVD risk is still rarely acknowledged in clinical practice – most likely because the relative empirical benefit of risk prediction through DEEX in direct comparison to the classical cardiovascular risk factors has not yet been investigated. Therefore, studies to estimate its ranking in prediction models are sparse.

The primary study aim of the present investigation was to achieve a direct comparison of the impact of traditional somatic risk factors and depressed mood (as the most acknowledged psycho-social risk factor so far) on prediction of all-cause mortality and fatal CVD endpoints in an identical source population. To this end, we estimated the absolute, relative and population-attributable risks (PARs) of DEEX adjusted for the five classical somatic risk factors hypertension, hypercholesterolemia, smoking, obesity and diabetes in a prospective population-based study over a ten-year observation period and, to gauge the ranking of DEEX within the context of these risk factors, compared their effect in multiple regression analyses.

The importance of a risk factor to predict CVD mortality may change with the number of risk factors a person has accumulated. Therefore, we assessed the impact of DEEX on all mortality endpoints stratified by somatic risk level as defined by the number of risk factors.

## 2. Materials and methods

### 2.1. Setting

The data were derived from three independent cross-sectional population-based World Health Organization (WHO) *Monitoring trends and determinants on cardiovascular diseases* (MONICA) surveys conducted in the region of Augsburg (Germany) [14] as part of the multinational WHO MONICA project with 13,427 men and women (response rate 77%) aged 25–74 years in 1984/85 (S1), 1989/90 (S2) and 1994/95 (S3). The WHO MONICA Project was initiated in the early 1980s in 26 countries to monitor the risk factors for cardiovascular diseases, such as hypertension, smoking, hypercholesterolemia and obesity in the general population [15]. The vital status was assessed for all participants at the end of 2007 within the framework of the *Cooperative Health Research in the Region of Augsburg* (KORA) [16]. Written informed consent was obtained from each study participant. The study was approved by the local ethics committee and followed the declaration of Helsinki.

Standardized interviews were conducted at baseline examination by trained medical staff to assess information concerning sociodemographic, lifestyle and clinical characteristics. Additionally, participants underwent an extensive standardized medical examination including the collection of non-fasting venous blood samples. All assessment procedures have been described elsewhere in detail [14].

### 2.2. Study population

A psychosocial dataset was available in a subgroup of 12,888 subjects. Based on the assumption of a low probability of adverse coronary heard diseases (CHD) events in men younger than 45 years, the present study was restricted to male study participants (n = 3819) aged 45–74 years. Among them, a total of 381 subjects had missing information on depressive symptoms or any of the somatic risk factors considered at baseline. Furthermore, information on CVD or CHD mortality could not be assessed for 10 subjects leading to a study population of 3428 men aged 45–74 years (mean age 57.5 years) at baseline.

A drop-out analysis revealed that subjects with missing information were older and suffered more often from hypercholesterolemia than subjects with available information ($p < 0.001$ and 0.021).

### 2.3. Assessment of depression and exhaustion (DEEX)

The DEEX subscale from the von Zerssen symptom check list was applied to assess depression and exhaustion. It combines eight items (irritability, fatigue, tiredness, inner tension, loss of energy, difficulty in concentrating, nervousness, anxiety) - each scored 0 to 3, leading to a general score range of 0–24 [17]. Male subjects in the top tertile ($\geq 11$) of the DEEX score distribution were considered as the high DEEX group (index group, n = 1164) compared to a total of 2264 subjects in the low DEEX group (control group).

### 2.4. Assessment of cardiovascular risk factors

Total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) was measured as mg/dl in serum by enzymatic methods (CHOD-PAP, Boehringer Mannheim, Germany) and *hypercholesterolemia* was defined as TC $\geq$ 240 mg/dL for the main analyses. For a sensitivity analysis, *hypercholesterolemia* was defined as TC/HDL-C $\geq$ 5 [18]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and *obesity* was defined as having a BMI $\geq$ 30 kg/m$^2$. Systolic blood and diastolic blood pressure (SBP and DBP) were measured on the right arm in a sitting position using a Hawksley random-zero sphygmomanometer adhering to the WHO MONICA protocol; *hypertension* was defined as a of SBP/DBP $\geq$ 140/90 mmHg [19] or being on anti-hypertensive medication. *Smoking* was defined as currently and regularly smoking at least one cigarette per day. *Diabetes mellitus* was based on self-report of a physician diagnosis or intake of anti-diabetic medication.

### 2.5. Follow-up and mortality endpoints

The cohort of 3428 subjects was followed for 10 years after baseline examination and summed up to a total of 31,791 person-years. During follow-up, a total of 557 male participants had died and 269 experienced a fatal CVD event including 178 fatal CHD events.

Death certificates were obtained from local health departments and coded for the underlying cause of death by a single trained person using the 9th revision of the International Classification of Diseases (ICD-9). In the present study, all-cause mortality, CVD mortality (ICD-9: 390–459) and CHD mortality (ICD-9: 410–414, 798) were used as endpoints.

For mortality analyses, event times were calculated as time to death. Subjects without events or with loss to follow-up were censored at the time point of the last follow-up. The mortality risks were expressed as absolute risks, hazard ratios (HRs) and PARs. The effect estimate PAR was framed to describe the reduction in mortality that would be observed if the population was entirely unexposed, compared with its current exposure pattern.

### 2.6. Statistical methods

Absolute mortality rates for all risk factors were presented per 1000 person-years. Cox proportional hazards models were applied to assess the effects of DEEX and the five classical somatic risk factors on mortality. For each endpoint (all-cause, CVD and CHD mortality) separate Cox models were computed. Multivariate models were adjusted for age, survey and all five classical risk factors (hypercholesterolemia, obesity, hypertension, smoking and diabetes). Proportional hazards could be estimated by fitting models stratified by risk factor categories, and then plotting the

log-log survival curves for each risk factor, which were assessed for parallelism by visual inspection. As no severe deviations from parallelism were observed for DEEX and the five somatic risk factors for each of the three mortality endpoints, proportional hazards were assumed. To assess how the DEEX-mortality associations were affected by the five somatic risk factors, the change-in-estimate (CIE) calculated by the percentage change of the hazard ratio from the model without DEEX to the model with DEEX; a substantial change was assumed by a CIE of >10% as this threshold is commonly used [20]. Potential interactions between two risk factors on mortality were assessed by including interaction terms additionally into the regression equation. Two sensitivity analyses were performed to assess the robustness and potential uncertainties in the findings of the main analyses described above.

PARs for each risk factor and the three endpoints were calculated using the prevalence of the risk factor (prev) and the adjusted HR drawn from the Cox regression (denoted by adjHR) and applying the formula for computing adjusted PAR: adjusted PAR = ((prev * (adjHR −1))/(prev * (adjHR −1) + 1)) * 100 [21]. It should be noted that by using adjHR for RR in this formula, potential confounding in the PAR estimation is addressed in contrast to use of (crude) incidence ratios.

As it is pointed out by Tzoulaki et al. [22], the additive predictive performance of a new risk factor in established risk prediction models is often examined just by a statistical significant association in a multiple regression model. However, the *p* value for this association alone offers usually weak or no information on the predictive ability. Therefore, we investigated the contribution of each risk factor (including DEEX) to risk prediction by calculating the area under the receiver-operating characteristic curve (AUC), the integrated discrimination improvement (IDI) statistics which can be viewed as the difference between improvement in average sensitivity and any potential decrease in average specificity, and (3) the net classification improvement (NRI) to assess the improvement in risk classification by adding a variable into a model compared to a model without that variable [23]. For the risk classification, we chose four classes for mortality risk (<1%, 1 - < 5%, 5 - < 10%, ≥10%), as suggested by the recently published European guideline [24].

For all analyses, a *p* value < 0.05 was considered to be statistically significant. All statistical evaluations were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC). The analysis and the description in this manuscript follow the STROBE guidelines for cohort studies [25].

## 3. Results

### 3.1. Description of prevalence and crude absolute all-cause, CVD and CHD mortality

Overall, in our population of male participants (N = 3428), a proportion of 34% (n = 1164) suffered from DEEX at baseline. The prevalence of the classical somatic risk factors ranged from 6.9% for diabetes to 55.6% for hypertension (Table 1).

The absolute mortality risk (calculated as mortality per 1000 person-years) for DEEX was approximately 23 cases for all-cause, 11 for CVD and 8 for CHD mortality per 1000 person-years. These figures were in a comparable range with all other cardiovascular risk factors in all three mortality endpoints with the exception of diabetes with higher rates and higher than the mortality rates in the total study population (17.5 for all-cause, 8.5 for CVD and 5.6 for CHD mortality).

### 3.2. Relative risk on all-cause, CVD and CHD mortality

Table 2 presents the adjHRs for DEEX and all five classical somatic risk factors for all three mortality endpoints. DEEX was a significant predictor for all-cause (*p* value < 0.001), CVD (*p* value ≤ 0.001) and CHD (*p* value = 0.005) mortality. Regarding the effect estimates, DEEX was comparable to hypercholesterolemia and obesity for CVD and CHD mortality (HRs 1.36–1.55). For all-cause mortality, DEEX had a substantially higher risk than hypercholesterolemia (HRs 1.53 *versus* 1.03), but smoking and diabetes held higher positions for all-cause mortality with HRs close to or higher than two. The correlation with the DEEX-mortality association was rather low indicated by absolute CIE values between 2.5 and 3.8.

### 3.3. PAR for all-cause, CVD and CHD mortality

The public health importance of DEEX on mortality endpoints is further illustrated by the adjusted PARs that were estimated to be 15% for all three mortality endpoints which gives DEEX a concise middle ranking in relation to the classical risk factors. These values were comparable or higher than the PARs for hypercholesterolemia, obesity and smoking for CVD and CHD mortality (ranging from 8.4% to 21.4%), higher than the PARs of diabetes for all mortality endpoints (ranging from 5.5% to 7.8%) and lower than the PARs for hypertension for CVD and CHD mortality (ranging from 29.5% to 34%). Fig. 1 gives an impression about the balanced position of DEEX in terms of relative and population-attributable risks acting in concert with all other risk factors.

### 3.4. Sensitivity analyses

We performed two sensitivity analyses. First, we used TC/HDL-C instead of TC alone with participants having a TC/HDL-C level of ≥5 defined as having hypercholesterolemia (n = 3,421, 49.1%). This analysis revealed almost identical findings as in the main analyses described above. Second, we restricted the observation period for mortality assessment to 5 years and found higher HRs for DEEX for all three mortality endpoints (HRs 1.72 for all-cause, 2.41 for CVD and 2.92 for CHD mortality). For hypertension and diabetes, the

**Table 1**
Distribution of depression and exhaustion (DEEX) and five somatic risk factors with mortality rates in the study population (n = 3,428, men, 45–74 years).

| | N | % | All-cause mortality rate per 1000 PY | CVD mortality rate per 1000 PY | CHD mortality rate per 1000 PY |
|---|---|---|---|---|---|
| DEEX | 1164 | 34.0 | 23.1 | 11.2 | 7.5 |
| Hypercholesterolemia | 1704 | 49.7 | 18.5 | 10.1 | 7.0 |
| Obesity | 777 | 22.7 | 21.9 | 12.0 | 7.9 |
| Hypertension | 1907 | 55.6 | 22.9 | 11.9 | 7.7 |
| Smoking | 794 | 23.2 | 26.8 | 11.6 | 7.4 |
| Diabetes | 236 | 6.9 | 42.6 | 22.6 | 16.0 |
| Overall | 3428 | 100.0 | 17.5 | 8.5 | 5.6 |
| N cases | | | 557 | 269 | 178 |

Hypercholesterolemia: total cholesterol ≥240 mg/dL, obesity: BMI ≥30 kg/m$^2$, hypertension: SBP/DBP ≥140/90 mmHg or being on anti-hypertensive medication.

**Table 2**
Adjusted 10-year risks (hazard ratios, HR) for depression and exhaustion in the context of five somatic risk factors with adjusted population-attributable risks (PARs) (n = 3,428, men, 45–74 years).

| | All-cause mortality | | CVD mortality | | CHD mortality | |
|---|---|---|---|---|---|---|
| | HR (95% CI)<br>*p* value | PAR | HR (95% CI)<br>*p* value | PAR | HR (95% CI)<br>*p* value | PAR |
| DEEX | 1.52 (1.29–1.80)<br><0.001 | 15.1 | 1.53 (1.20–1.94)<br>0.001 | 15.1 | 1.53 (1.13–2.06)<br>0.005 | 15.2 |
| Hypercholesterolemia | 1.03 (0.87–1.22)<br>0.742 | 1.4 | 1.36 (1.06–1.74)<br>0.014 | 15.2 | 1.55 (1.14–2.11)<br>0.005 | 21.4 |
| Obesity | 1.26 (1.04–1.52)<br>0.017 | 5.5 | 1.43 (1.10–1.86)<br>0.007 | 8.9 | 1.41 (1.02–1.94)<br>0.038 | 8.4 |
| Hypertension | 1.55 (1.28–1.87)<br><0.001 | 23.4 | 1.93 (1.44–2.57)<br><0.001 | 34.0 | 1.75 (1.23–2.49)<br>0.002 | 29.5 |
| Smoking | 2.44 (2.04–2.92)<br><0.001 | 25.0 | 2.07 (1.59–2.71)<br><0.001 | 19.9 | 1.91 (1.37–2.66)<br><0.001 | 17.4 |
| Diabetes | 1.85 (1.46–2.35)<br><0.001 | 5.5 | 1.99 (1.44–2.77)<br><0.001 | 6.4 | 2.22 (1.50–3.29)<br><0.001 | 7.8 |
| % Change-in-estimate | −2.6 | | −2.5 | | −3.8 | |

Hypercholesterolemia: total cholesterol ≥ 240 mg/dL, obesity: BMI ≥ 30 kg/m$^2$, hypertension: SBP/DBP ≥ 140/90 mmHg or being on anti-hypertensive medication, % change-in-estimate: change of HRs of DEEX from crude to full model.

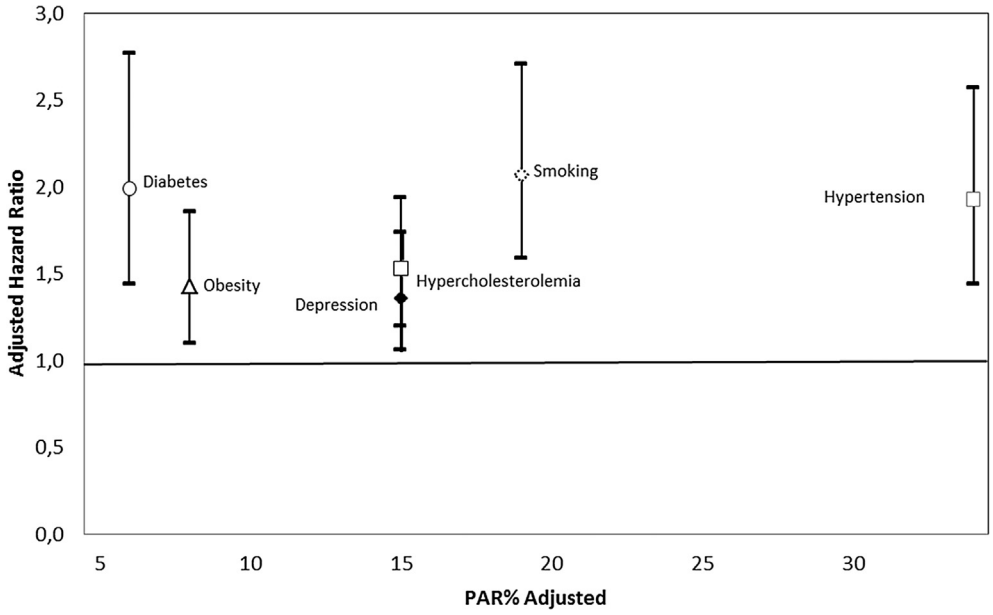


**Fig. 1.** Comparison of DEEX and the "big five" somatic risk factors within the context of adjusted hazard ratios and PARs, presented for CVD mortality.

effect estimates became lower for all three mortality endpoints than in the main analyses. Hypercholesterolemia and smoking had comparable HRs for all-cause and CVD mortality; these estimates became higher (hypercholesterolemia) or lower (smoking) than in a 10-year follow-up period. Obesity lost its significant association for all three mortality endpoints if follow-up was restricted to a five-year period.

### 3.5. Predictive ability

Adding DEEX into a model including somatic risk factors increased the AUC by 0.004 for CVD mortality. As shown in Table 3, comparable non-significant AUC improvements in risk prediction were observed for hypercholesterolemia and obesity. In contrast, high and significant AUC increases (AUC differences ≥ 0.01) were found for smoking and hypertension in the fully-adjusted model. The two other measures of predictive ability (NRI, IDI) gave similar findings for CVD mortality. Regarding the improvement in net reclassification, i.e. in the improvement regarding absolute risk groups, adjustment for risk factors had a strong impact on NRI for all risk factors except for hypertension which remained rather stable whether adjusted only for age and survey (NRI1 = 0.090) or additionally for the other risk factors as well (NRI2 = 0.086). Comparable findings could be observed for all-cause and CHD mortality (see Supplementary Tables 1 and 2).

### 3.6. Association of DEEX and mortality stratified by the number of risk factors

Finally, we estimated the relative risks of DEEX for all-cause, CVD and CHD mortality, stratified for the number of risk factors which ranged from 0 to 4 or 5 (four and five risk factors were combined due to low numbers). The risk estimates revealed a rather U shaped distribution with no association for having none or one as well as four or five risk factors, and a significantly higher HR of around 2 for all three mortality endpoints in subjects suffering

**Table 3**
Contribution of risk factors on the predictive ability of the Cox models assessed by ΔAUC, IDI and NRI for 10-year CVD mortality.

| Risk factor | ΔAUC1[a] | ΔAUC2[b] | IDI1 | IDI2 | NRI1 | NRI2 |
|---|---|---|---|---|---|---|
| DEEX | 0.005 | 0.004 | 0.006** | 0.006* | 0.038 | 0.006 |
| Hypercholesterolemia | 0.005 | 0.002 | 0.005** | 0.004* | 0.031 | 0.004 |
| Obesity | 0.005 | 0.003 | 0.005** | 0.004 | 0.010 | <0.001 |
| Hypertension | 0.016* | 0.012* | 0.012*** | 0.008*** | 0.090** | 0.086** |
| Smoking | 0.015* | 0.013* | 0.009** | 0.008* | 0.109*** | 0.061* |
| Diabetes | 0.012* | 0.006 | 0.011** | 0.008* | 0.031 | 0.013 |

AUC, area under the ROC curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement.
1: adjusted for age and survey, 2: adjusted for all risk factors except risk factor under concern.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] ΔAUC1: Difference in AUC of model with and without respective risk factor, adjusted for age and survey.
[b] ΔAUC2: Difference in AUC of model with all six risk factors and without the respective risk factor under concern, adjusted for age and survey.

from DEEX and having two risk factors as shown Table 4. However, interactions were not significant for three endpoints. The addition of DEEX to the fully-adjusted model resulted in the highest AUC increment in subjects with an intermediate somatic risk level whilst having two risk factors (all-cause: 0.713 *vs*. 0.727, CVD 0.738 *vs*. 0.752, CHD: 0.731 *vs*. 0.751).

## 4. Discussion

### 4.1. Overall findings

The first important finding of the present population based study with >3400 male participants followed over a 10 years-observation period was to show that depressed and exhausted mood is a robust 10-year risk predictor for all-cause, CVD and CHD mortality independent from the "big five" classical somatic risk factors (hypercholesterolemia, obesity, hypertension, smoking and diabetes). Furthermore, the excess mortality risks of all three mortality endpoints could be seen for (crude) absolute mortality rates (presented per 1000 PY) and for adjusted relative risks. Thus, these findings substantiate previous findings from meta-analyses [5–8] indicating a close link of depressed mood and related conditions with cardiovascular mortality. It is of note that the strength of risk prediction for DEEX was most pronounced in subjects who cluster two somatic risk factors and thus are considered as "intermediate risk carriers" [26]. Interestingly, a shorter exposure time of five years increased the risk of DEEX for fatal outcomes which was not the case for hypertension and diabetes. For obesity, a shorter exposure time resulted in an insignificant finding.

Furthermore, DEEX contributes to the clustering of risk factors: when considering DEEX, only a minority of 5.6% in the baseline investigation (of those who later experienced a lethal CVD event) were free of any risk factor. This challenges claims that CVD events commonly occur in persons who have not been exposed to a major risk factor [27].

### 4.2. Ranking position compared to somatic risk factors

The study provides a variety of indicators to estimate the ranking position of DEEX in comparison to the big five risk factors. DEEX reached higher effect sizes than hyper-cholesterolemia and obesity for all mortality endpoints. The mortality risks for DEEX were, however, lower than for hypertension, smoking and diabetes, but had substantially higher PARs than diabetes. The absolute DEEX mortality risks for all endpoints were in the range of obesity and hypercholesterolemia, and were comparable to or lower than those of hypertension and smoking. Only diabetes exceeded all mortality risks of DEEX. The adjusted PAR of DEEX for all three mortality endpoints was lower or comparable than those of hypertension and smoking but exceeded those of obesity and diabetes. In total, these findings show that depressed mood and exhaustion holds a solid middle position within the concert of major cardiovascular risk factors in terms of relative and population-attributable risks for all-cause, CVD and CHD mortality underscoring the need and importance of this condition within the context of public health and prevention.

### 4.3. Inclusion of DEEX in a risk score

Nonetheless, adding DEEX to a risk score based on classical risk factors resulted in only non-significant improvement of mortality risk prediction. Apparently, prediction with the five "big" classical risk factors has reached a ceiling effect, with smoking and hypertension as the most potential predictors. These findings do not come as a surprise since previous studies with new, powerful single risk markers (e.g. C-reactive protein, job strain) have elicited similarly low improvements in risk prediction [28,29]. Accordingly, Tzoulaki et al. [22] stated that "… *a sophisticated new predictor may have good predictive ability on its own but may not improve predictive ability further when simple, easy-to-measure traditional factors are already taken into account*" [22].

The improvement in risk prediction for DEEX is comparable to obesity and hyperchol-esterolemia – the consequence of which may be that, in clinical practice, when case know-ledge on the

**Table 4**
Adjusted 10-year risks (Hazard ratios, HR) for depression and exhaustion by the number of classical cardiovascular risk factors (n = 3,428, men, 45–74 years).

| | All-cause mortality | | CVD mortality | | CHD mortality | |
|---|---|---|---|---|---|---|
| Risk level of classical risk factors | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| 0 (low) | 0.67 (0.31–1.45) | 0.311 | 0.92 (0.23–3.71) | 0.912 | 0.63 (0.13–3.11) | 0.566 |
| 1 (intermediate) | 1.39 (0.99–1.96) | 0.058 | 1.32 (0.80–2.18) | 0.274 | 1.08 (0.55–2.10) | 0.829 |
| 2 (intermediate) | **1.91 (1.46–2.50)** | **<0.001** | **1.99 (1.35–2.94)** | **0.001** | **2.15 (1.32–3.51)** | **0.002** |
| 3 (high) | **1.48 (1.05–2.10)** | **0.027** | 1.38 (0.84–2.28) | 0.203 | 1.70 (0.96–2.99) | 0.066 |
| 4 or 5 (high) | 1.49 (0.75–2.96) | 0.249 | 1.03 (0.47–2.27) | 0.946 | 0.97 (0.35–2.70) | 0.951 |
| *p* for interaction | | 0.116 | | 0.522 | | 0.308 |

Significant associations are in bold.

actual level on hypercholesterolemia is not available, inclusion of depression in the risk score may serve the same purpose. Furthermore, the interchangeable findings in risk prediction may support the physician to decide on his/her own and grounded in evidence based findings which tools he/she may apply to estimate the patient's CHD risks.

### 4.4. Causal pathways

Providing a proof of a causal relation between DEEX and CVD is beyond the scope of the present investigation. Although not a proof of causality, in general, depressed subjects are more likely to cluster self-harming lifestyle behaviors [30] and may be less likely to adhere to prescribed medication [31]. Among underlying biological pathways, promising avenues include imbalances of the autonomic nervous system e.g. impaired heart rate variability [32], endothelial dysfunction [33] and malfunctions of the endocrine system [34]. Furthermore, chronic subclinical inflammation [35], platelet function abnormalities [36] and impaired fibrinolysis [37] predispose depressed patients to clotting diatheses [38].

### 4.5. Therapeutic options

A general screening for depression in primary care settings is controversial [39] mainly because depression screening programs without staff assistance do not show benefits [40]. The PAR findings in the present investigation demonstrate, however, that preventing DEEX would likely result in the reduction of approximately 15% of CVD or CHD mortality which is even higher than the impact of obesity, smoking and diabetes. Generally, CHD risks over 5% in ten years are considered a strong indicator for (pharmacological) interventions [4]. Thus, interventions for depression offer potentially far reaching preventive benefits [41]. Unlike treating risk factors which are clinically unapparent and cause only minor impairments in quality of life, treating depression is likely to have an eminent value for the patient on its own as it is a severe functionally impairing disease condition. Interestingly, treating depression successfully may also improve adherence to cardiac medication regimens [31]. However, treatment of depression in cardiac patients is not an easy task and has yielded disappointing results in the past (overview in [42]:).

Supported by guidelines [43], primary care physicians are accepted as the gatekeepers to detect and consider treatment options for DEEX. Here, serious obstacles still have to be overcome: a British investigation [44] recently revealed that patients with diabetes and CVD who were routinely screened for depression as part of their care, tended to be referred less often to an anti-depressive treatment. Apparently, the practitioners were concerned about possible drug side effects and index patients may have been reluctant to accept treatment particularly as they had been detected by screening rather than by presenting symptoms.

### 4.6. Study strengths and limitations

The major strength of the present investigation is its uniform adjustment and comparative reporting of concurrent risks of major cardiovascular risk factors, indicating its standing in risk prediction [45]. Additionally, the analyses were performed using in a large sample size based on a random sample drawn from the general population, and the availability of a large set of cardio-metabolic risk factors which were scrutinized by standardized and quality-controlled assessments. The choice of an appropriate risk classification in order to assess the improvement in risk prediction when a new risk factor is added to the model varies between studies, mainly depending on study aim and outcome [46]. For appropriate risk classifications, we followed the classifications recently proposed in the 2016 European guideline [24,47].

There are limitations to this study that need to be addressed. The type of depressed and exhausted mood measure may alter the effect size [5]. In the present study, we chose a combined measure of depressed mood and exhaustion which was assessed by the DEEX scale [17]. Despite the highly significant findings presented here, the DEEX scale is not the strongest psychometric option although it has been applied in numerous MONICA/KORA investigations [35,48]. Its strength, however, is to focus on symptoms of reduced vitality, weakness and “vital exhaustion” [9] which have been proven to display mood facets which may particularly account for the depressed mood-mortality effect in population based studies [12,49]. The DEEX inventory includes somatic complaints with symptom overlap between depression and cardiovascular disease (fatigue, tiredness, loss of energy). Therefore, it cannot be fully excluded that a small amount of somatic symptom variance is not necessarily related to depression in post-AMI patients. However, these somatic symptoms are necessary to capture the particular depressed cardiovascular disease phenotype [50]. Additionally, DEEX was measured - as in the vast majority of studies included in meta-analyses [5–8] - at one time point, so that transient depressive mood states could not be distinguished from persistent states.

The present investigation is restricted to men. Particularly in younger age groups, female patients yield risks which are distinct from men [51,52]. Therefore, investigations on CVD risk factors including both sexes are warranted [53]. Due to the complex interaction between exposure, interfering and outcome variables, residual confounding cannot be excluded. The prediction model was not tested in a different sample.

### 4.7. Conclusions

The accurate identification of individuals at risk for CVD remains a challenge [3]. Here, we show that DEEX predicts lower life expectancy and higher CVD mortality risk with an effect size comparable to traditional major risk factors. These findings underline the need for considering depression and exhaustion in a comprehensive screening and treatment strategy to prevent CVD. The present study indicates that a screening for depression and exhaustion is especially worthwhile in subjects with an intermediate status of classical risk factors. Such a screening with sufficient accuracy is inexpensive, easy to obtain and safe.

## Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.12.003.

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