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Sex and gender-stratified risks of psychological factors for adverse clinical outcomes in patients with ischemic heart disease: A systematic review and meta-analysis☆

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ABSTRACT

Background: Psychological factors are associated with adverse prognosis in patients with ischemic heart disease (IHD). However, it is unknown whether these risk factors differ between women and men.
Methods: PubMed, EMBASE, and PsycINFO were searched to identify studies assessing the risk of psychological factors for major adverse cardiovascular events (MACE) in samples with IHD. Psychological factors included anger/hostility, anxiety, depression, psychological distress, social support, Type A behavior pattern, Type D personality, and Posttraumatic Stress Disorder (PTSD).
Results: A total of 44 articles (64 separate reports) including 227,647 women and 321,894 men reporting confounder-adjusted hazard ratios (HRs) or relative risks (RRs) were included in the primary analysis. Results based on random-effects models showed that the association between psychological factors (all combined) and MACE was stronger in men (n = 321,236; 57 reports; HR = 1.37, 95%CI 1.27–1.48) than in women (n = 226,886; 56 reports; HR = 1.21, 95%CI 1.12–1.30; p = .017). A subset of the studies focusing on women showed significant associations between anger/hostility, depression, and distress with MACE. For men, statistically significant associations were found for anxiety, depression, and distress with MACE.
Conclusions: Psychological factors are associated with MACE in samples with IHD in both women and men, with a small, but significant higher risk for men. Because of the limited number of studies on other psychological factors than depression and anxiety and the current major focus on MACE reflecting lesions in the major coronary arteries which is more typical in men than women, more research is needed to better identify sex and gender differences in IHD.

1. Introduction

Cardiovascular disease (CVD) is the most important cause of death globally [1]. Ischemic heart disease (IHD) is the most common clinical presentation of CVD. Patients diagnosed with IHD are at increased risk of experiencing a recurrent acute coronary syndrome (ACS) and have a six times higher annual death rate compared with people without IHD [2]. In the United States, an estimated annual incidence of 580,000 new ACS has been reported in 2017 and 210,000 patients experienced a recurrence [3].

Several psychological factors are common among patients with IHD and are associated with recurrent cardiac events and mortality, including anger/hostility, depression, anxiety, general psychological distress, low social support, Type A behavior, Type D personality, and posttraumatic stress disorder (PTSD) [4,5]. However, little is known about their relative contribution to increased recurrent event risks and whether these risks are equally elevated among men and women.

Psychological factors may affect the prognosis after IHD in women differently than in men, and evidence has suggested potential sex and gender (S&G) differences in these IHD risk factors [5–7]. Vaccarino et al. (2019) mentioned that depression is more severe in women, starting at earlier age compared to men, and is more common in women with IHD than in men with IHD [7]. Several systematic reviews and meta-analyses have investigated the relationship between psychological factors and adverse outcomes in cardiac populations [4,8,9]. Celano et al. (2015) confirmed that anxiety is associated with an increased risk of mortality in both female and male patients with IHD [8]. However, they focused on mortality as outcomes and did not

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include recurrent cardiac events. In addition, no S&G-stratified data were reported. The narrative review of Low et al. (2010) provides a S&G-stratified overview of psychological factors and incident and recurrent IHD [9]. They concluded that both depression and hostility are predictors of recurrent ACS in both women and men, and that general anxiety is a more consistent coronary risk factor for men than for women. The meta-analysis of Doyle et al. (2015) used individual patient data and showed that high levels of depressive symptoms were more common in female post-ACS (36%) than male ACS-patients (29%), but the association between depression and cardiac prognosis was worse for men than women [4]. However, they only investigated depression in post-ACS patients and did not include other common psychological factors in their meta-analysis.

In our current systematic review and meta-analysis, we assess S&G-stratified risks of a broad range of psychological factors for major adverse cardiovascular events (MACE) in patients with established IHD. As a secondary aim, we investigate diversity and confounding factors related to the S&G-stratified risk of psychological factors for adverse outcomes.

2. Methods

The protocol for this meta-analysis has been registered in PROSPERO (#CRD42017067087). The American Heart Association (AHA) standard was used to develop this meta-analysis [10]. The present analyses focus on MACE in patients with IHD; we previously conducted a systematic review and meta-analysis regarding incidence of IHD in S&G-stratified samples [11]. The data, analytic methods, and study materials of the present meta-analysis have been made available [12].

2.1. Search strategy

Four authors (V.S., W.K., A.M., and P.M.) and a medical librarian were involved in the composition of the search terms. Search terms were developed for anger/hostility, anxiety, depression, psychological distress, social isolation/social support/loneliness, Type A behavior pattern, (Type D) personality, and PTSD [5]. Psychological distress was defined as general distress, psychosocial stress, psychological stress, or a combination of similar psychological factors. The literature search was conducted by two authors (V.S. and P.M.) using PubMed, EMBASE, and PsycINFO (Supplemental Table S1). To keep the number of potential articles manageable, (only English) articles published between January 1st 2000 and April 17th 2017 were included. To ensure that all relevant articles would be included in our analyses, a second search was performed on January 17th 2018, updating the previous search. In addition to the electronic search, a manual search in reference lists of relevant reviews was performed by two reviewers (V.S. and P.M.).

2.2. Eligibility criteria

Prospective cohort studies investigating the targeted psychological factors as predictors and MACE as outcome in IHD patients were included in this meta-analysis. MACE included fatal and non-fatal cardiovascular events, and all-cause mortality. Reports regarding incident IHD were excluded ($n = 128$). Psychological factors had to be measured with a self-reported instrument or a clinical interview. For feasibility reasons, we excluded negative psychological constructs such as early life events, and work-related psychological factors. We also excluded other mental disorders, such as schizophrenia, as well as articles with study designs other than prospective cohort studies (e.g. case-control studies, cross-sectional studies, retrospective studies), reviews and meta-analyses, letters to the editors, and dissertation findings.

2.3. Study selection process

The screening process was independently performed by two reviewers (V.S. and P.M.), using Covidence software (covidence.org) based on title/abstract. Eligible articles were screened based on full-text. Risks scores for continuous psychological factors were included when dichotomous factors were not reported. The largest sample size and/or longest follow-up time was chosen in case multiple publications or findings were reported based on the same sample. A third reviewer (A.M. or W.K.) was consulted in case of disagreement.

2.4. Data extraction

Data-extraction was performed by one reviewer (V.S., P.M. or B.v.G.) and verified by a second reviewer (V.S., P.M., or B.v.G.). Data concerning the following categories were extracted [12]: study characteristics, participants, methods, psychological factors, outcomes, and results. Supplemental Table S2 shows the covariates which were adjusted for in the reports.

Both unadjusted and effect sizes adjusted for the most complete set of confounders were extracted. If more than one measure of the same psychological factor was included, we included the measurement most often used in other articles. In case a psychological factor was divided in more than two categories, the most detrimental, often highest score of a factor was used. If more than one outcome was reported, the outcome comprising the most frequent cardiac event was included. Authors were contacted if articles did not report S&G-stratified results or when no effect size estimate was reported and S&G-stratified RRs could not be calculated.

2.5. Statistical analysis

Comprehensive Meta-Analysis version 2.0 was used to perform all statistical analyses. Forest plots were created using MetaXL version 5.3 [13]. In our primary analyses HRs and RRs were pooled, and reported as 'HR'. In addition some studies reported OR's only. However, since we do not want to assume that HR and RR are equivalent effect sizes, we have additionally reported the results of HR, RR, and OR separately as well. When S&G-stratified effect sizes were not reported, but S&G-stratified two-by-two tables were available, RRs and 95% confidence intervals (CIs) were calculated by the authors [14]. Adjusted effect sizes were used in our primary analyses. When only adjusted and minimally adjusted (e.g. for age only) models were reported, the latter were considered as unadjusted.

The following a priori planned subgroup analyses were performed for follow-up duration (<5 years, ≥5 years), global continent of study performance, number of analyzed patients (<1000 or ≥ 1000), percentage of European descent participants (0–50%, 51–75%, 76–100%), mean age at baseline (<60 years, 60–65 years, >65 years), type of measurement (clinical diagnosis, questionnaire), unadjusted raw score vs. minimally adjusted (e.g. age only), adjustment for lifestyle factors (yes vs. no), publication year (2000–2009, 2010–2018), S&G-stratified results reported in article vs. received from authors, and characteristics of IHD samples (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery or ACS, non-obstructive IHD, and combined obstructive and non-obstructive IHD). Additional subgroup analyses included redundant (overlapping but fewer events) reports. When a study included two different outcomes (e.g. a composite of recurrent cardiac events including all-cause mortality, and all-cause mortality only), the report with the composite outcome was included in our primary analyses, and the report on all-cause mortality was included in the subgroup analyses. The cut-offs in the subgroups were calculated by using the rounded median or tertiles of the included reports (e.g. for no. of patients analyzed, and follow-up time). Group differences by gender and within each subgroup (e.g. follow up duration <5 years vs. ≥5 years) were compared using Q-tests based on analysis of variance

[15]. The Bonferroni-Holm procedure was used to correct for multiple testing [16].

We used the Cochran Q statistic [17] and the Higgins I^2-index [17] to assess heterogeneity. Random-effects models were used for the pooled analyses, since we would expect significant heterogeneity among the reports in terms of e.g. sample size, measurement of psychological factors, and follow-up time. Secondary meta-analyses were performed to assess reports using unadjusted data, continuous data, and separately for HRs, RRs, and ORs. Furthermore, psychological factors related to MACE and mortality outcomes were separately analyzed. It has been argued recently that the appropriateness of fixed effects models to estimate overall effects in meta-analyses should not be determined by measures of heterogeneity [18]. Consequently, we additionally fit fixed-effects models to the primary data analyses. Publication bias was investigated using funnel plots, Egger's tests [17], and the Duval and Tweedie Trim and Fill method [17].

3. Results

3.1. Study selection

Title/abstract screening was performed on 12,330 articles of which 668 remained for full-text screening (Supplemental Fig. 1: Flowchart). The most common reasons for exclusion during full-text screening were: overlap with other study ($n = 128$), study design other than prospective cohort study ($n = 94$), and irrelevant outcome ($n = 72$). After full-text screening, 162 articles remained eligible.

In total, 12 (7%) studies reported S&G-stratified results, 8 (5%) reported on women only, and 4 (2%) reported on men only. The remaining 138 articles did not stratify and authors were asked to provide us S&G-stratified results. We received the results of 48 (35%) non-stratified articles, 45 (33%) were unable or unwilling to perform S&G-stratified analyses, 44 (32%) did not respond, and one (1%) could not be reached because of missing contact information. We excluded the 90 articles without S&G-stratified results. In total, 72 articles comprising 138 separate reports were included. For the primary analyses we additionally excluded 28 reports with unadjusted results, 30 reports with overlapping MACE, 11 reports with continuous data, and/or 8 reports reporting ORs only. One report was excluded because no confidence interval could be determined [19]. Exclusion of these reports resulted in 44 articles comprising 64 confounder-adjusted reports. The 64 reports included data from 227,647 women and 321,894 men, with at least 64,492 MACE during follow-up.

3.2. Study characteristics

Supplemental Table S3 shows the baseline characteristics of the 64 reports included in the primary analyses. Of these, 6 (9%) reported results for women only, 3 (5%) for men only, and 55 (86%) reported results stratified for women and men. On average 34% were women (median 28%, range 0–100%). The mean age was 61.6 years (median 62.0, range 54.0–72.0 years).[2] Participants were followed up for an average of 5.5 years (median 4.8, range 1.0–12.1 years). Depression (50%) was the most frequently examined psychological factor, followed by anxiety (27%), and Type D personality (11%). In 83% of the reports, the psychological factor was measured with a questionnaire. On average 23% (median 22%, range 1–62%) of the study participants scored high on a psychological factor, using the questionnaire cutoff or a clinical diagnosis. On average 21% (median 16%, range 6–51%) of the participants scoring high on a psychological factor developed MACE during follow-up, compared to 17% (median 12%, range 4–46%) in the group with low levels. MACE was most commonly measured by (national) registries, medical records, clinical diagnoses, and death certificates. Seventy-three percent of the included reports adjusted for factors related to lifestyle.

3.3. Psychological factors and MACE

Random-effects, adjusted models showed that psychological factors were overall associated with an increased risk of MACE in both women (HR = 1.21, 95%CI 1.12–1.30), and men (HR = 1.37, 95%CI 1.27–1.48) (Figs. 1 and 2). The risk for adverse cardiac events associated with psychological factors (all combined) was higher in men compared to women ($p = .017$). Among women, significantly elevated risks for MACE were found on anger/hostility (HR = 1.54, 95%CI 1.17–2.03), depression (HR = 1.20, 95%CI 1.10–1.32), and distress (HR = 1.40, 95%CI 1.01–1.92). For men, significant results were found on anxiety (HR = 1.38, 95%CI 1.14–1.67), depression (HR = 1.48, 95%CI 1.32–1.65), and distress (HR = 1.30, 95%CI 1.03–1.64). Significantly higher risks were found for men vs. women for anxiety ($p = .012$), and depression ($p = .005$) (Table 1). A moderate degree of heterogeneity was found (men; $Q = 129.7$, $p < .001$, $I^2 = 56.8\%$, women; $Q = 79.8$, $p = .016$, $I^2 = 31.1\%$).

3.4. Subgroup analyses

After Bonferroni-Holm correction, no significant subgroup differences were found for men and women (Table 2). Moderate heterogeneities (range 0–73.8%) were observed in most subgroups.

3.5. Secondary analyses for separate psychological factors

The characteristics of included reports in the secondary analyses are reported in Supplemental Table S4. Unadjusted analyses on psychological factors and MACE including 70 separate reports focusing on women (HR = 1.34, 95%CI 1.24–1.46) and 74 reports on men (HR = 1.39, 95%CI 1.27–1.52), without significant S&G-differences ($p = .573$) (Supplemental Table S5).

In reports on women, significant effects were found for anger/hostility (HR = 1.31, 95%CI 1.02–1.68), depression (HR = 1.41, 95%CI 1.26–1.58), and distress (HR = 1.55, 95%CI 1.18–2.04). With respect to men, significant positive effects were found for each individual psychological factor except Type D personality. The largest unadjusted association for men was found between depression and MACE (HR = 1.63, 95%CI 1.45–1.84). No significant differences between women and men were found on individual psychological factors for the unadjusted analyses. After Bonferroni-Holm correction, no significant subgroup differences on unadjusted analyses were found (Supplemental Table S6).

In addition to the aforementioned random-effects models, we also examined the data using fixed-effects models (Supplemental Table S7). The risk for MACE associated with psychological factors (all combined) was higher in men (HR = 1.20, 95%CI 1.16–1.24) compared to women (HR = 1.10, 95%CI 1.07–1.14) ($p < .001$). Furthermore, significantly higher risks were found for men vs. women for depression ($p = .001$).

Supplemental Table S8 shows both for adjusted and unadjusted effects, separate meta-analyses on studies reporting HR, RR, or OR effect sizes, and separate analyses on studies using a continuous measure of a psychological factor. Regarding adjusted and unadjusted analyses on HR only, statistically significant effects were found on psychological factors and MACE, for both women and men. Analyses on continuous data did not show significant results for women and men.

Supplemental Table S9 shows results of psychological factors and MACE, further divided into recurrent cardiovascular events (MACE-2) and all-cause mortality. Confounder-adjusted data showed significant S&G-differences on anxiety and all-cause mortality ($p = .042$), depression and all-cause mortality ($p < .001$), and all psychological factors combined and all-cause mortality ($p < .001$). These associations were

[2] These statistics are calculated with individual study statistic as unit of analysis. Thus, with respect to for instance age, the reported mean, median, and range are based on the mean age for each study, not on the actual age of each patient. This also applies to the statistics reported on follow-up time.

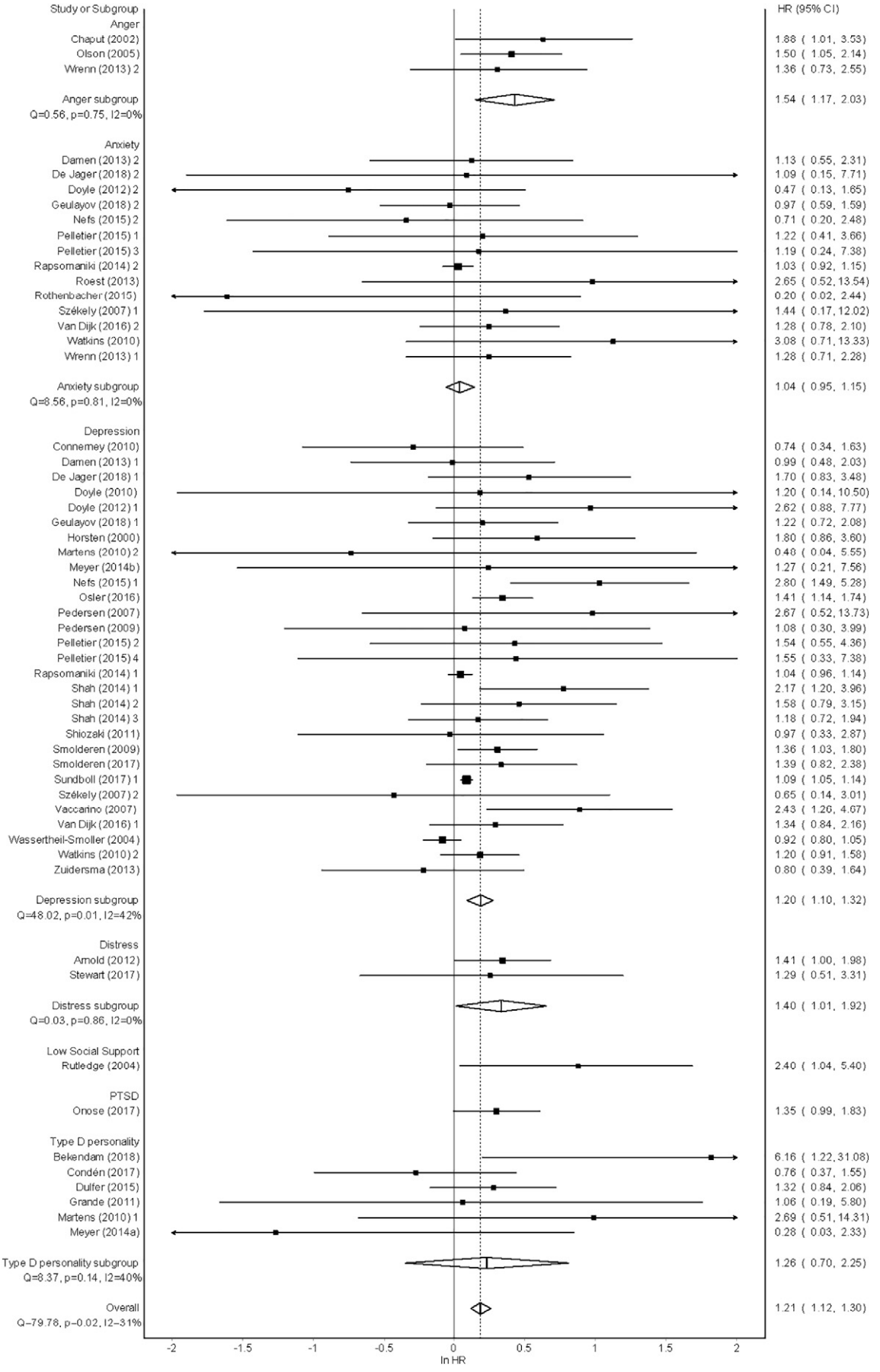

Fig. 1. Forest plot showing individual and overall estimates with 95% confidence intervals of psychological factors and MACE in women: adjusted findings.

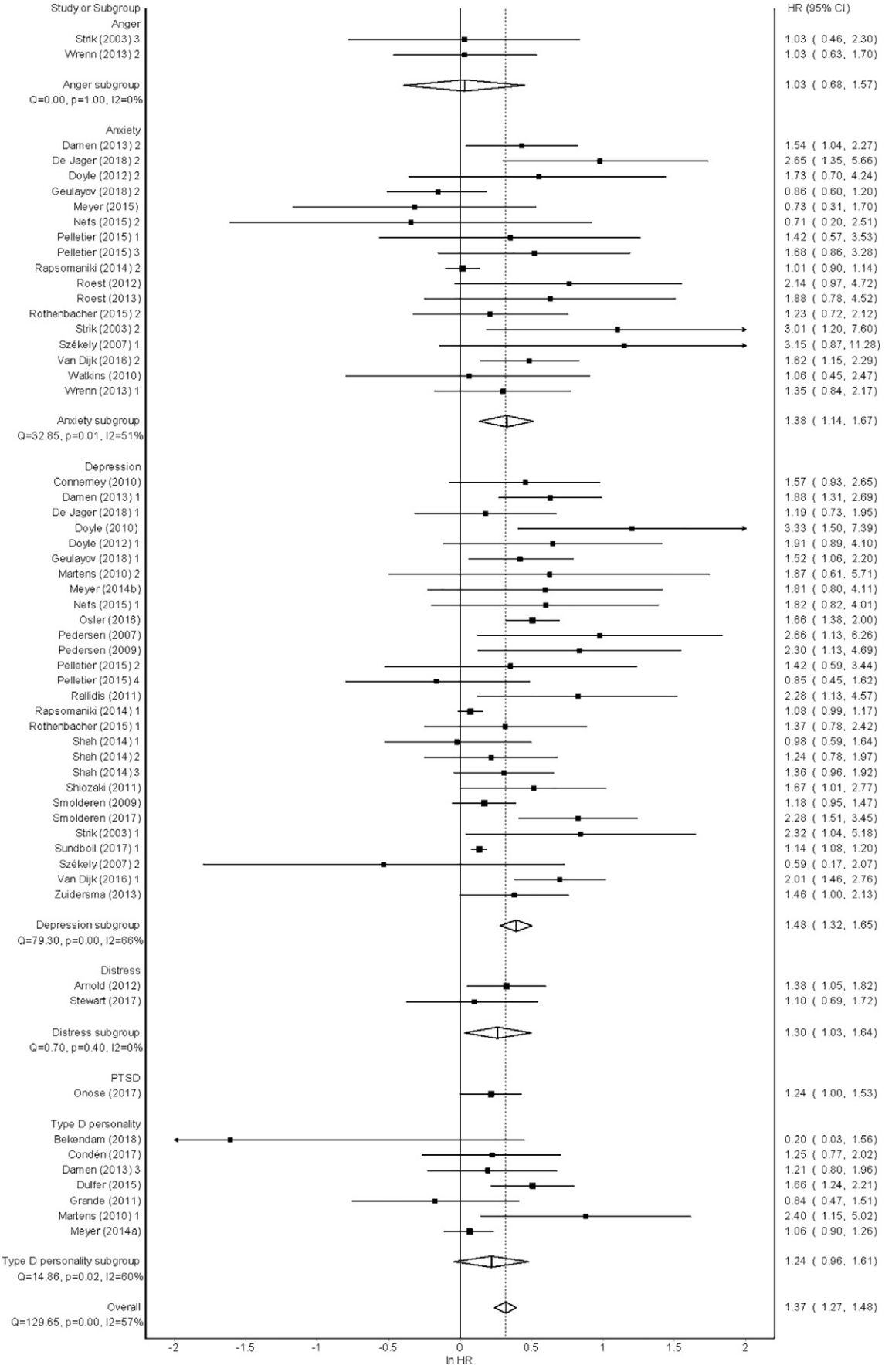

Fig. 2. Forest plot showing individual and overall estimates with 95% confidence intervals of psychological factors and MACE in men: adjusted findings.

Table 1
Adjusted S&G-stratified analyses of HR/RR for MACE associated with psychological factors: adjusted findings using a random effects model.

	Women						Men						
Variable	N	HR (95%CI)	p_{HR}	Q	p_{het}	I^2, %	N	HR (95%CI)	p_{HR}	Q	p_{het}	I^2, %	$p_{between}$
Anger/hostility	3	1.54 (1.17–2.03)	0.002	0.56	0.755	0	2	1.03 (0.68–1.57)	0.891	0	1	0	0.369
Anxiety	14	1.04 (0.95–1.15)	0.389	8.56	0.805	0	17	1.38 (1.14–1.67)	0.001	32.9	0.008	51.3	0.012
Depression	29	1.20 (1.10–1.32)	<0.001	48.0	0.011	41.7	28	1.48 (1.32–1.65)	<0.001	79.3	<0.001	65.9	0.005
Distress	2	1.40 (1.01–1.92)	0.042	0.03	0.861	0	2	1.30 (1.03–1.64)	0.029	0.70	0.404	0	0.725
PTSD	1	–	–	–	–	–	1	–	–	–	–	–	–
Low social support	1	–	–	–	–	–	0	–	–	–	–	–	–
Type A behavior	0	–	–	–	–	–	0	–	–	–	–	–	–
Type D personality	6	1.26 (0.70–2.25)	0.440	8.37	0.137	40.2	7	1.24 (0.96–1.61)	0.102	14.9	0.021	59.6	0.971
Psychological combined	56	1.21 (1.12–1.30)	<0.001	79.8	0.016	31.1	57	1.37 (1.27–1.48)	<0.001	129.7	<0.001	56.8	0.017

N, Number of reports; $p_{between}$, *p*-value between groups (women and men); p_{het}, *p*-value for heterogeneity; p_{HR}, *p*-value Hazard Ratio; Q, Cochran Q Statistic.

stronger in men than in women. With respect to psychological factors and recurrent cardiovascular events, no differences between genders were observed.

3.6. Publication bias

Visual inspection of funnel plots of all included articles in our primary analyses reporting on women (Supplemental Fig. S2) and men (Supplemental Fig. S3) suggests the presence of publication bias since the included articles (white dots) are not distributed symmetrically. Egger's tests suggest evidence of publication bias (women; $p = .002$, men; $p < .001$). Duval and Tweedie's Trim and Fill method estimated that 12 imputed reports for women and 8 for men would be needed to make the funnel plots symmetric. After correcting the effect size based on imputed reports, the effects decreased both for women (HR = 1.15, 95%CI 1.06–1.24), and men (HR = 1.32, 95%CI 1.22–1.42)

Table 2
Adjusted subgroup analyses by S&G of HR/RR for MACE associated with psychological factor.

Variable	Women						Men					
	N	HR (95% CI)	Q	p_{het}	I^2, %	$p_{between}$	N	HR (95% CI)	Q	p_{het}	I^2, %	$p_{between}$
Follow up (years)						0.518						0.516
<5	29	1.21 (1.11-1.32)	53.3	0.003	47.4		27	1.33 (1.19-1.47)	62.5	<0.001	58.4	
≥5	27	1.27 (1.12-1.43)	21.1	0.737	0		30	1.39 (1.25-1.55)	48.1	0.014	39.7	
Global continent						0.219						0.422
Asia	4	1.22 (0.97-1.53)	1.42	0.701	0		4	1.25 (0.97-1.61)	6.80	0.078	55.9	
Europe	31	1.14 (1.05-1.24)	40.2	0.101	23.4		38	1.18 (1.14-1.23)	106.6	<0.001	65.3	
North America	20	1.37 (1.17-1.60)	35.0	0.014	45.7		14	1.31 (1.17-1.41)	13.2	0.430	1.79	
Oceania	1	-	-	-	-		1	-	-	-	-	-
South America	0	-	-	-	-		0	-	-	-	-	-
Africa	0	-	-	-	-	-	0	-	-	-	-	-
No. of patients analyzed						<0.001						0.493
<1,000	33	1.51 (1.27-1.78)	37.1	0.246	13.7		34	1.43 (1.24-1.65)	52.2	0.018	36.8	
≥1,000	23	1.10 (1.04-1.15)	25.4	0.277	13.5		23	1.35 (1.23-1.48)	74.4	<0.001	70.4	
European descent						0.441						0.065
0-50%	-	-	-	-	-		-	-	-	-	-	
51-75%	3	1.38 (1.13-1.69)	0.03	0.987	0		3	1.49 (1.07-2.07)	7.64	0.022	73.8	
76-100%	29	1.26 (1.10-1.44)	40.4	0.002	55.5		14	1.08 (1.02-1.15)	11.2	0.597	0	
Age (years)						0.001						<0.001
<60	17	1.58 (1.33-1.88)	10.7	0.825	0		18	1.53 (1.29-1.83)	21.7	0.198	21.5	
60-65	27	1.24 (1.10-1.40)	18.3	0.865	0		29	1.43 (1.26-1.61)	56.6	0.001	50.5	
>65	9	1.10 (1.01-1.21)	16.8	0.032	52.5		8	1.11 (1.06-1.17)	8.30	0.307	15.7	
Type of measurement						0.001						0.041
Diagnosis by clinical interview	10	1.08 (1.03-1.13)	9.95	0.354	9.56		11	1.22 (1.09-1.37)	29.6	0.001	66.2	
Questionnaire	46	1.34 (1.20-1.49)	62.7	0.041	28.3		46	1.43 (1.30-1.57)	79.8	0.001	42.9	
Adjusted for lifestyle						0.170						0.046
No	13	1.36 (1.11-1.66)	13.4	0.343	10.2		16	1.64 (1.34-2.01)	19.7	0.184	23.9	
Yes	43	1.17 (1.09-1.26)	59.1	0.041	29.0		41	1.32 (1.22-1.42)	88.5	<0.001	54.8	
Publication year						0.100						0.235
2000-2009	11	1.47 (1.12-1.94)	27.1	0.003	63.1		8	1.71 (1.17-2.49)	14.4	0.044	51.5	
2010-2018	45	1.16 (1.09-1.24)	52.7	0.174	16.5		49	1.35 (1.25-1.46)	112.9	<0.001	57.5	
S&G-stratified results in article						0.467						0.160
No	39	1.20 (1.09-1.32)	45.6	0.185	16.7		44	1.42 (1.29-1.57)	107.3	<0.001	59.9	
Yes	17	1.27 (1.12-1.45)	34.0	0.005	53.0		13	1.26 (1.11-1.44)	19.7	0.073	39.2	
IHD sample						0.012						0.158
Non-obstructive*	4	2.39 (1.21-4.73)	4.58	0.206	34.4		3	1.06 (0.45-2.47)	3.43	0.180	41.7	
Combined	22	1.28 (1.12-1.47)	52.0	<0.001	59.6		18	1.25 (1.10-1.42)	40.0	0.001	57.5	
Obstructive	31	1.11 (1.07-1.15)	22.7	0.248	28.3		36	1.46 (1.32-1.62)	82.4	<0.001	57.5	
Outcome stratified†						0.239						0.380
ACM	40	1.17 (1.11-1.24)	49.4	0.123	21.1		40	1.39 (1.29-1.50)	104.9	<0.001	62.8	
MACE	35	1.26 (1.13-1.42)	54.6	0.014	37.7		36	1.31 (1.17-1.46)	60.1	0.005	41.8	

ACM, All-cause mortality; MACE, Major adverse cardiovascular event; N, Number of reports; $p_{between}$, between group *p*-value; p_{het}, *p*-value for heterogeneity; Q, Cochran Q Statistic; S&G, Sex and gender.

* Includes an additional report from the following article: [29]

† Includes additional reports from the following articles: [30-43]

yet remained statistically significant. Lastly, Rosenthal's Fail-safe N estimated that 518 reports for women and 1779 reports for men would be needed in order to bring the *p*-value of the overall effect size estimate in this meta-analysis to $p > .05$ [20]. Although the Funnel plots and Egger's test suggest the presence of publication bias, both the Trim and Fill and Fail-safe N methods support the robustness of the overall effect size estimates in this meta-analysis.

4. Discussion

4.1. General findings

The results of this meta-analysis confirmed that psychological factors are associated with MACE in samples with IHD, in both women and men. Novel findings are that for women, 56 confounder-adjusted reports showed a 21% increase in risk of psychological factors for MACE. For men, 57 adjusted reports pooled together showed a 37% increase in risk. Results were statistically significantly different between women and men, showing that men with psychological factors have a small, but significantly higher risk of MACE than women.

For women, anger/hostility, depression, and distress were separately associated with MACE. For men, a significant effect on MACE was found for anxiety, depression, and distress. Subgroup analyses did not reveal statistically significant S&G-differences.

4.2. Differences between women and men

In men, significantly higher associations were found between depression and MACE, and anxiety and MACE, in comparison with women. This difference might be explained by the fact that our included reports mostly focused on samples with obstructive IHD, which is a classic disease pattern dominated by male patients [21]. Female patients more often have non-obstructive IHD [22] including spasm, Takotsubo cardiomyopathy, and microvascular coronary dysfunction [23]. Although not significant, results from our confounder-adjusted subgroup analyses showed that the risk of MACE associated with psychological factors is more pronounced in women with non-obstructive IHD than in women with obstructive IHD. Including a broader range of IHD, more representative of the female pattern may change the effect between women and men.

Our unadjusted results did not show significant S&G-differences, rather differences were found after covariate adjustment. The differences in risks before and after adjustment may represent gender differences included in the adjustment for covariates. Gender is an important factor related to sociodemographic factors, including education level, employment status, and marital status; women less often receive higher education, having lower income and/or employment, and being divorced or widowed [24]. Furthermore, gender influences lifestyle habits, such as eating behavior, smoking, alcohol use, and physical exercise [24,25]. Therefore, it may be possible that adjustment for these gender-related factors has resulted in increased differences between women and men. However, our subgroup analyses did not reveal significant effects between reports that did and did not adjust for lifestyle factors.

4.3. Comparison with other meta-analyses

Results of our primary analyses showed that the risk between depression and MACE is higher in men than in women. This finding is against our expectations, since previous research suggest that the higher prevalence of depression in women with IHD might lead to a poorer prognosis [26]. However, our results on depression and MACE are similar to the results of the individual patient data meta-analysis of Doyle et al. (2015), who also found a stronger association between depression and a poor cardiac prognosis in men post-ACS [4].

Our results are also similar to the results of the narrative review by Low et al. (2010) [9]. In their review, it is stated that depression and hostility are both associated with an increased risk for recurrent cardiac events or death in women. Furthermore, they conclude that anxiety is a more consistent coronary risk factor for men than women. These results are similar to our findings, which show that depression and anger/hostility are significantly associated with MACE in women, and that men with anxiety have a significantly higher risk of MACE.

Celano et al. (2015) found an anxiety confounder-adjusted OR of 1.20 (95%CI 0.91–1.58) which is higher than the HR we found for women (HR = 1.04, 95%CI 0.95–1.15) and lower than our risk for men (HR = 1.38, 95%CI 1.14–1.67) [8]. However, these differences should be interpreted with care because of the uncertainty in the estimated effects, as illustrated by the overlapping confidence intervals.

4.4. Strengths and limitations

Our search in several databases, additional reference-searches, followed by a screening process and data-extraction performed by at least two reviewers, resulted in a high number of eligible, multivariate-adjusted studies comprising a total sample size of 227,647 women and 321,894 men, which is a strength of the present study. We received S&G-stratified results from 35% of all contacted authors, which increased the number of included reports in our meta-analysis.

The most important limitation of this meta-analysis includes the heterogeneity. Reports differed regarding patient samples, follow-up duration, measurement of psychological factors, covariates in their adjusted analyses, and outcomes. Even when reports used the same (mostly validated) questionnaires to measure a psychological factor, questionnaires could differ in cut-off points, subscales, and versions. We tried to overcome this problem by performing subgroup analyses. However, we did not find significant differences between subgroups.

A second limitation is the possible influence of publication bias, suggestive of smaller associations. However, after importing reports with the Duval and Tweedie's trim-and-fill method, the pooled HR remained significant.

Third, we only included reports with continuous data when no dichotomized data were reported or could not be calculated, lowering the generalizability.

Fourth, a combination of HR and RR can lead to bias and interpretation should be careful [27]. Therefore, we additionally investigated if results based on HR only would differ from results based on HR and RR combined. Results from both analyses did not differ, probably since the major part (91%) used HR as effect size.

4.5. Implications for future research and clinical practice

Several recommendations can be made based on the findings of our meta-analysis. First, since most included reports focused on obstructive IHD samples, more cohort studies focusing on psychological factors in non-obstructive IHD (female) samples should be developed. Moreover, it has been recently shown that feminine gender-roles and personality traits (anxiety) importantly affect outcomes after ACS [28]. In our meta-analysis, we could not distinguish between sex (biological characteristics) and gender (social norms for women and men) [28], since studies did not define these terms as such. Since most studies probably only focused on (biological) sex, (feminine) gender-roles should be studied more often to provide tailored prevention advice to all patients afterwards.

Second, S&G-stratified results should be more reported in IHD research, since S&G-differences are nowadays more recognized by cardiologists. In our meta-analysis, 90 articles (56%) were excluded because no S&G-stratified results were reported or provided by authors.

Third, research should include different types of ethnicity. None of our included studies were conducted in Africa and only a few in South America, Asia, and Oceania, which means Non-western countries and

cultures are underrepresented and our results cannot be generalized to non-Western countries. Only 22 out of 64 reports (34%) reported the number of European descendants ranging from 67% to 99%, which means an underrepresentation of non-European descendants.

Fourth, most of our included studies investigated the association between depression or anxiety and MACE. Since only a few studies focused on anger/hostility, distress, PTSD, low social support, Type A behavior, and Type D personality, these results should be interpreted with caution. More research into these psychological factors is needed to estimate the association between these factors and MACE in women and men.

At last, healthcare professionals should recognize and acknowledge the importance of psychological risk factors in patients with IHD [5,7]. Depressive symptoms in IHD patients are often unrecognized and untreated, although these symptoms are highly prevalent in IHD patients and can affect patient's quality of life and may influence recovery [7]. Psychological interventions including stress management or counseling should be offered to these patients [7].

5. Conclusion

In conclusion, this large meta-analysis of prospective cohort studies confirms that psychological factors are associated with MACE in both women and men. The novelty is that the association between depression, anxiety, and all psychological factors combined with MACE was slightly stronger in men compared to women. However, most articles did not report S&G-stratified findings, studies comprised more male than female participants, and mainly focused on the clinical consequences of obstructive IHD, which is more common in men than women. More data are needed, especially on psychological predictors of IHD patterns that are more prevalent among women, such as non-obstructive IHD and microvascular disease.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.12.014.

References

[1] WHO, Cardiovascular diseases (CVDs), http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds), Accessed date: 14 June 2018.
[2] WHO, Cardiovascular disease, http://www.who.int/cardiovascular_diseases/priorities/secondary_prevention/country/en/index1.html, Accessed date: 10 September 2018.
[3] AHA, Heart disease and stroke statistics 2017 at-a-glance, https://healthmetrics.heart.org/wp-content/uploads/2017/06/Heart-Disease-and-Stroke-Statistics-2017-ucm_491265.pdf 2017, Accessed date: 10 September 2018.
[4] F. Doyle, H. McGee, R. Conroy, H.J. Conradi, A. Meijer, R. Steeds, H. Sato, D.E. Stewart, K. Parakh, R. Carney, K. Freedland, M. Anselmino, R. Pelletier, E.H. Bos, P. de Jonge, Systematic review and individual patient data meta-analysis of sex differences in depression and prognosis in persons with myocardial infarction: a MINDMAPS study, Psychosom. Med. 77 (2015) 419–428.
[5] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, M.T. Cooney, U. Corra, B. Cosyns, C. Deaton, I. Graham, M.S. Hall, F.D.R. Hobbs, M.L. Lochen, H. Lollgen, P. Marques-Vidal, J. Perk, E. Prescott, J. Redon, D.J. Richter, N. Sattar, Y. Smulders, M. Tiberi, H.B. van der Worp, I. van Dis, W.M.M. Verschuren, S. Binno, 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and Other Societies on Cardiovascular Disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts)developed with the special contribution of the European Association for Cardiovascular Prevention & rehabilitation (EACPR), Eur. Heart J. 37 (2016) 2315–2381.
[6] V. Regitz-Zagrosek, Sex and gender differences in health. Science & Society Series on sex and science, EMBO Rep. 13 (2012) 596–603.
[7] V. Vaccarino, L. Badimon, J.D. Bremner, E. Cenko, J. Cubedo, M. Dorobantu, D.J. Duncker, A. Koller, O. Manfrini, D. Milicic, T. Padro, A.R. Pries, A.A. Quyyumi, D. Tousoulis, D. Trifunovic, Z. Vasiljevic, C. de Wit, R. Bugiardini, Depression and coronary heart disease: 2018 ESC position paper of the working group of coronary pathophysiology and microcirculation developed under the auspices of the ESC Committee for practice guidelines, Eur. Heart J. (2019) https://doi.org/10.1093/eurheartj/ehy913 [Epub ahead of print].
[8] C.M. Celano, R.A. Millstein, C.A. Bedoya, B.C. Healy, A.M. Roest, J.C. Huffman, Association between anxiety and mortality in patients with coronary artery disease: a meta-analysis, Am. Heart J. 170 (2015) 1105–1115.
[9] C.A. Low, R.C. Thurston, K.A. Matthews, Psychosocial factors in the development of heart disease in women: current research and future directions, Psychosom. Med. 72 (2010) 842–854.
[10] G. Rao, F. Lopez-Jimenez, J. Boyd, F. D'Amico, N.H. Durant, M.A. Hlatky, G. Howard, K. Kirley, C. Masi, T.M. Powell-Wiley, A.E. Solomonides, C.P. West, J. Wessel, Methodological standards for meta-analyses and qualitative Systematic reviews of cardiac prevention and treatment studies: a scientific statement from the American Heart Association, Circulation. 136 (2017) e172–e194.
[11] V.R. Smaardijk, P. Lodder, W.J. Kop, B. van Gennep, A.H.E.M. Maas, P.M.C. Mommersteeg, Sex and gender-stratified risks of psychological factors for incident ischemic heart disease: a systematic review and meta-analysis, J. Am. Heart Assoc. 8 (e010859) (2019) 1–49, https://doi.org/10.1161/jaha.118.010859.
[12] P.M.C. Mommersteeg, V.R. Smaardijk, P. Lodder, W.J. Kop, B. van Gennep, A.H.E.M. Maas, Replication Data for: Sex and Gender-Stratified Risks of Psychological Factors for Incident Ischemic Heart Disease and Prognosis: A Systematic Review and Meta-Analysis, Dataverse NL, 2018 hdl/10411/7N5GYN.
[13] J.J. Barendregt, S.A. Doi, Y.Y. Lee, R.E. Norman, T. Vos, Meta-analysis of prevalence, J. Epidemiol. Community Health 67 (2013) 974–978.
[14] V. Bewick, L. Cheek, J. Ball, Statistics review 11: assessing risk, Critical Care (London, England). 8 (2004) 287–291.
[15] M. Borenstein, L.V. Hedges, J.P.T. Higgings, H.R. Rothstein, Chapter 19: subgroup analyses *Introduction to Meta-Analysis* Chichester: John Wiley & Sons, Ltd 157 (2009).
[16] M. Giacalone, Z. Agata, P.C. Cozzucoli, A. Alibrandi, Bonferroni-holm and permutation tests to compare health data: methodological and applicative issues, BMC Med. Res. Methodol. 18 (2018) 81.
[17] Cochranecollaboration, Cochrane Handbook for Systematic Reviews of Interventions, www.handbook.cochrane.org 2011, Accessed date: 10 September 2018.
[18] K. Rice, J.P. Higgins, T. Lumley, A re-evaluation of fixed effect(s) meta-analysis, J R Statist Soc A. 181 (2018) 205–227.
[19] K. Šmigelskas, N. Žemaitienė, J. Julkunen, J. Kauhanen, Type a behavior pattern is not a predictor of premature mortality, International Journal of Behavioral Medicine. 22 (2015) 161–169.
[20] R. Rosenthal, The "file drawer problem" and tolerance for null results, Psychol. Bull. 86 (1979) 638–641.
[21] C.N. Merz, The Yentl syndrome is alive and well, Eur. Heart J. 32 (2011) 1313–1315.
[22] V. Regitz-Zagrosek, S. Oertelt-Prigione, E. Prescott, F. Franconi, E. Gerdts, A. Foryst-Ludwig, A.H. Maas, A. Kautzky-Willer, D. Knappe-Wegner, U. Kintscher, K.H. Ladwig, K. Schenck-Gustafsson, V. Stangl, Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes, Eur. Heart J. 37 (2016) 24–34.
[23] V. Vaccarino, L. Badimon, R. Corti, C. de Wit, M. Dorobantu, O. Manfrini, A. Koller, A. Pries, E. Cenko, R. Bugiardini, Presentation, management, and outcomes of ischaemic heart disease in women, Nat. Rev. Cardiol. 10 (2013) 508–518.
[24] P.M. Mommersteeg, L. Arts, W. Zijlstra, J.W. Widdershoven, W. Aarnoudse, J. Denollet, Impaired health status, psychological distress, and personality in women and men with nonobstructive coronary artery Disease: sex and gender differences: the TWIST (Tweesteden mild stenosis) study, Circulation Cardiovascular Quality and Outcomes. 10 (2017), e003387. https://doi.org/10.1161/CIRCOUTCOMES.116.003387.
[25] R. Vari, B. Scazzocchio, A. D'Amore, C. Giovannini, S. Gessani, R. Masella, Gender-related differences in lifestyle may affect health status, Annali dell'Istituto Superiore Di Sanita. 52 (2016) 158–166.
[26] T.Z. Naqvi, S.S. Naqvi, C.N. Merz, Gender differences in the link between depression and cardiovascular disease, Psychosom. Med. 67 (Suppl. 1) (2005) S15–S18.
[27] I. Scott, Interpreting risks and ratios in therapy trials, Austr Prescr. 31 (2008) 12–16.
[28] R. Pelletier, N.A. Khan, J. Cox, S.S. Daskalopoulou, M.J. Eisenberg, S.L. Bacon, K.L. Lavoie, K. Daskupta, D. Rabi, K.H. Humphries, C.M. Norris, G. Thanassoulis, H. Behlouli, L. Pilote, Sex versus gender-related characteristics: which predicts outcome after acute coronary syndrome in the young? J. Am. Coll. Cardiol. 67 (2016) 127–135.
[29] V. Vaccarino, B.D. Johnson, D.S. Sheps, S.E. Reis, S.F. Kelsey, V. Bittner, T. Rutledge, L.J. Shaw, G. Sopko, B.M.C.N. Depression, Inflammation, and incident Cardiovascular Disease in women with suspected coronary ischemia. The National Heart, Lung, and Blood Institute-sponsored WISE study, J. Am. Coll. Cardiol. 50 (2007) 2044–2050.
[30] L.A. Chaput, S.H. Adams, J.A. Simon, R.S. Blumenthal, E. Vittinghoff, F. Lin, E. Loh, K.A. Matthews, Hostility predicts recurrent events among postmenopausal women with coronary heart disease, Am. J. Epidemiol. 156 (2002) 1092–1099.
[31] E. Condén, A. Rosenblad, P. Wagner, J. Leppert, L. Ekselius, C. Åslund, Is type D personality an independent risk factor for recurrent myocardial infarction or all-cause

mortality in post-acute myocardial infarction patients? Eur. J. Prev. Cardiol. 24 (2017) 522–533.
[32] I. Connerney, R.P. Sloan, P.A. Shapiro, E. Bagiella, C. Seckman, Depression is associated with increased mortality 10 years after coronary artery bypass surgery, Psychosom. Med. 72 (2010) 874–881.
[33] T. Meyer, S. Hussein, H.W. Lange, C. Herrmann-Lingen, Anxiety is associated with a reduction in both mortality and major adverse cardiovascular events five years after coronary stenting, Eur. J. Prev. Cardiol. 22 (2015) 75–82.
[34] T. Onose, Y. Sakata, K. Nochioka, M. Miura, T. Yamauchi, K. Tsuji, R. Abe, T. Oikawa, S. Kasahara, M. Sato, T. Shiroto, S. Miyata, J. Takahashi, H. Shimokawa, Sex differences in post-traumatic stress disorder in cardiovascular patients after the great East Japan earthquake: a report from the CHART-2 study, European Heart Journal Quality of Care & Clinical Outcomes. 3 (2017) 224–233.
[35] R. Pelletier, S.L. Bacon, A. Arsenault, J. Dupuis, C. Laurin, L. Blais, K.L. Lavoie, Relative associations between depression and anxiety on adverse cardiovascular events: does a history of coronary artery disease matter? A prospective observational study, BMJ Open. 5 (2015), e006582.
[36] E. Rapsomaniki, A. Shah, P. Perel, S. Denaxas, J. George, O. Nicholas, R. Udumyan, G.S. Feder, A.D. Hingorani, A. Timmis, L. Smeeth, H. Hemingway, Prognostic models for stable coronary artery disease based on electronic health record cohort of 102 023 patients, Eur. Heart J. 35 (2014) 844–852.
[37] A.J. Shah, N. Ghasemzadeh, E. Zaragoza-Macias, R. Patel, D.J. Eapen, I.J. Neeland, P.M. Pimple, A.M. Zafari, A.A. Quyyumi, V. Vaccarino, Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events, J. Am. Heart Assoc. 3 (2014), e000741. https://doi.org/10.1161/JAHA.113.000741.
[38] K.G. Smolderen, J.A. Spertus, K.J. Reid, D.M. Buchanan, H.M. Krumholz, J. Denollet, V. Vaccarino, P.S. Chan, The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction, Circulation: Cardiovascular Quality and Outcomes. 2 (2009) 328–337.
[39] M. Stenman, M.J. Holzmann, U. Sartipy, Relation of major depression to survival after coronary artery bypass grafting, Am. J. Cardiol. 114 (2014) 698–703.
[40] R.A.H. Stewart, D.M. Colquhoun, S.L. Marschner, A.C. Kirby, J. Simes, P.J. Nestel, N. Glozier, A. O'Neil, B. Oldenburg, H.D. White, A.M. Tonkin, Persistent psychological distress and mortality in patients with stable coronary artery disease, Heart 103 (2017) 1860–1866.
[41] S. Wassertheil-Smoller, S. Shumaker, J. Ockene, G.A. Talavera, P. Greenland, B. Cochrane, J. Robbins, A. Aragaki, J. Dunbar-Jacob, Depression and Cardiovascular Sequelae in postmenopausal women: the Women's Health Initiative (WHI), Arch. Intern. Med. 164 (2004) 289–298.
[42] K.C. Wrenn, E. Mostofsky, G.H. Tofler, J.E. Muller, M.A. Mittleman, Anxiety, anger, and mortality risk among survivors of myocardial infarction, Am. J. Med. 126 (2013) 1107–1113.
[43] M. Zuidersma, H.J. Conradi, J.P. Van Melle, J. Ormel, P. De Jonge, Self-reported depressive symptoms, diagnosed clinical depression and cardiac morbidity and mortality after myocardial infarction, Int. J. Cardiol. 167 (2013) 2775–2780.