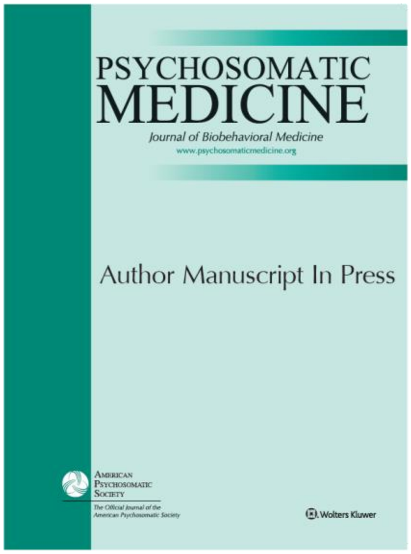

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A network analysis of cardiovascular risk factors in patients with heart disease: the role of socioeconomic status and sex

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ABSTRACT

Objective: Diverse risk factors influence the development and prognosis of coronary heart disease (CHD) independently and mutually. Low socio-economic status (SES) seems to exacerbate these risk factors' influences. Additionally, sex differences have been identified for individual risk factors. Network analysis could provide in-depth insight into the interrelatedness of the risk factors, their predictability, and into the moderating role of sex, to ultimately contribute to more refinement in prevention and cardiac rehabilitation (CR).

Methods: 1682 participants (78% male; M_{age} = 69.2±10.6) with CHD completed questionnaires on psychosocial factors and health behaviors. Cardiometabolic data were retrieved through medical records. An SES index was created based on self-reported occupation and education, and area (i.e., postal code)-based median family income. Using R, we conducted a mixed graphical model network analysis on all risk factors combined with and without the moderating role of sex.

Results: SES belonged to the more influential risk factors with moderate to high levels of expected influence and degree centrality, indicating it plays a considerable role in the risk factor network. When considering the moderating role of sex, relationships between SES and most risk factors were found to be stronger for women (b = 0.06 – 0.48).

Conclusions: The current study provided an insight into an interrelated network of psychosocial and medical risk factors among CHD patients. With SES belonging to the more influential risk factors and female sex influencing the strength of all the SES-risk factor relationships, CR and prevention techniques could be more refined by accounting for both influences.

Keywords: network analysis, socioeconomic status, sex, risk factors, coronary heart disease

Abbreviations

CHD – coronary heart disease

CR – cardiac rehabilitation

CV – cross-validation

ESC – European Society of Cardiology

MGM – mixed graphical model (*mgm* refers to the eponymous R-package)

NA – negative affectivity

NLE – negative life events

PCI – percutaneous coronary intervention

SES – socio-economic status

SI – social inhibition

THORESCI - Tilburg Health Outcomes Registry of Emotional Stress after Coronary Intervention

INTRODUCTION

There is abundant evidence that psychosocial risk factors increase the risk of incident coronary heart disease (CHD), as well as negatively affecting prognosis and mortality rates in case of established CHD (1-7). The European Society of Cardiology (ESC) developed guidelines for the prevention of CHD and summarized multiple psychosocial risk factors such as depression, anxiety, negative affectivity (NA) and social inhibition (SI), stress (e.g., work stress, traumatic stress, family stress), anger, hostility, low socio-economic status (SES), and psychiatric history (1). These psychosocial risk factors are proven to occur both independently as well as conjointly (1, 8), which complicates risk assessment (9).

Psychosocial risk factors often co-occur, which causes an artificial covariance (10). This may arise because of similarity within concepts: e.g., rather than being independent predictors of CHD, anger, anger expression, and hostility often cluster together (i.e., *clustering between variables*) (11). Further, negative affectivity, as experienced in individuals with Type D personality, covaries with depressive and anxiety symptoms (12, 13). Furthermore, previous studies (8, 14) examined psychosocial risk profiles among patients with CHD who received a percutaneous coronary intervention (PCI), and revealed multiple *within-person* psychosocial risk profiles. In addition to psychosocial risk factors co-occurring, there are known relationships between psychosocial risk factors and other types of risk factors. Poor health behaviors (e.g., diet, physical activity and smoking) have been associated with psychosocial factors like depression, anxiety (15), and traumatic stress (16). Cardiometabolic risk factors such as hypertension (17, 18), diabetes (19, 20), and hyperlipidemia (21) similarly have been related to various psychosocial risk factors. Additionally, these cardiometabolic and health behavioral risk factors were also found to be interconnected (e.g., (22)).

In addition to psychosocial, cardiometabolic and health behavioral risk factors, SES may be viewed as both a risk factor and a contextual factor that influences other risk factors. For example, socioeconomic factors have been found to covary with several psychological risk factors (23, 24). A low SES is oftentimes characterized by more financial and employment problems, less control, and eventually more stress (25-31), and has been associated with depression, social isolation and hostility in cardiac patients (32, 33). This could lead to an aggravated risk of cardiac events (23, 34). Moreover, several studies demonstrated that a variety of SES-related characteristics (e.g., education, social class, and income) are associated with health behaviors (e.g., smoking, medication adherence, physical activity, healthy diet; (35-38)), general health (37, 39), and cardiometabolic risk factors such as hypertension (40), cholesterol levels, and diabetes mellitus (41). In cardiac patients, the prevalence of smoking, hypertension, diabetes, as well as the total number of cardiovascular risk factors was higher for those with low SES (42). Overall, SES is believed to be a major influence in the development and worsening of CHD (23), and a strong predictor of cardiovascular health (24, 43) and mortality (44). However, current models oftentimes do not consider the risk that a low SES poses (24), nor does it take the statistical consequences of the interrelatedness of risk factors into account. Even though cardiac care has improved, trends indicate that individuals with a lower SES are still disadvantaged in terms of burden and poorer outcomes which enlarges health disparities between groups (for an overview, see (24)).

Within these multimodal risk factors (i.e., psychosocial, cardiometabolic, health behavioral, SES), sex differences exist. I.e., we previously found sex differences in psychosocial risk profiles, with women generally belonging to profiles characterized by social and emotional distress (8, 14), while the profile that was characterized by higher levels of hostility contained more men (8). When accounting for both sex and gender traits, men generally belonged to the profiles with lower general distress and some hostility and anger (14). Additionally, previous research revealed that the associations between SES and other classical risk factors are stronger for women (45) and that women with low SES are less physically active (46). Furthermore, women's health seems to be disproportionately affected by their vulnerable socioeconomic backgrounds (24), of which income was revealed to be an impactful predictor of MI or cardiovascular death (47). Thus, SES and sex differences seem to be important determinants in the interplay between psychosocial, health behavioral and cardiometabolic risk factors. However, their exact roles in the complex system of risk factors remain largely unknown. Previous research found that low SES (42, 48) and female sex (49, 50) are determinants of less utilization of cardiac rehabilitation (CR) practices, which makes the system of risk factors in association with SES and sex a relevant area of study.

Together, this implies the existence of a complex system of many relevant risk factors and their interdependencies, producing heart disease as a distal outcome. Crucially, the variables within the system not only influence the outcome (i.e., the illness on which we are focusing), but also can have positive or negative effects on each other, have more distal or proximal effects, which can be unidirectional or reciprocal. Networks are fundamental to such complex systems, and network analysis is a powerful methodological approach to investigate the complex pattern of such relationships (51). Networks consist of variables (e.g., risk factors, called *nodes*) and relationships between these variables, called *edges* (52), allowing to gain an in-depth insight into the interrelatedness of these risk factors. Variables are conceptualized by their mutual interaction in a system of connections, rather than being viewed as a function of a latent construct (53, 54). By this, network analysis seems a promising approach to explore complex network systems of interrelated symptoms as compared to other more traditional methods that merely assess the predictive value of variables in multiple regression.

Recently, the use of network analysis as a novel approach to study the interplay between biopsychosocial determinants and how they affect health has increased (51), since network models are deemed as attractive for systems that depend on the interplay of a multitude of variables (55). Especially in clinical psychology (e.g., depression, anxiety (56), and suicide (57)), network approaches have gained popularity in recent years as psychological phenomena are generally seen as dependent (55). For instance, the technique has been predictive of the course of disorders like depression (56, 57), which highlights the benefit for exploratory research in psychosomatic medicine (e.g., preventive cardiology).

Also, in (psychosomatic) medicine, network analysis is receiving increasing attention (58, 59). CHD is influenced by a multitude of risk factors that all differ in magnitude and interconnectedness (e.g., (1, 22, 60)). However, research on cardiac risk often takes a reductionist approach by studying isolated relationships (for example using regression models to examine the relation between depression and a specific outcome such as health behaviors or disease progression) that are part of a larger system of variables. Although important insights may be gained by such research, it is not suited for the study of complex systems of interrelated variables. Network analysis could add more insight into these discrete findings on psychosomatic relationships, by examining cardiac risk factors at the system level, and piecing back the multiple separate research findings into a more complex and complete system (51). This may not only improve the understanding of how these risk factors interact (61), but also reveals the interconnectedness, individual placement, and other structural aspects (e.g., predictability, centrality) of risk factors in the network (61, 62).

Predictability in a network model provides information on whether there are strong interactions between variables (i.e., high predictability) or whether other determinants outside of the network are involved (i.e., low predictability) (55). Predictability may also tell us to what extent a node (i.e., a risk factor) can be predicted by its neighboring nodes, which eventually can be insightful for developing interventions as simultaneously intervening on these neighboring nodes could affect the influence of the node of interest (55). Another structural characteristic of a network is centrality (strength). The strength centrality of a node quantifies the extent to which the node has a more central position in the network (51, 55). A third beneficial feature of network analysis pertains to its powerful visualization tools, which ultimately improves the communication of the findings (61). Finally, a novelty in current network analysis is the inclusion of a moderator (i.e., sex), which may shed light on differentiation of possible interventions within a network and what could possibly work for whom (63), ultimately contributing to personalized medicine (64). Gaining more insight into the moderation effects of sex, and the role of SES in relation to the network of other risk factors could ultimately contribute to more refinement in prevention and CR.

Taken together, the network approach is an insightful methodology that comes with multiple benefits to better understand underlying correlational structures within a complex network of risk factors, rather than studying isolated parts of a larger system in regression analyses and ignoring its organization (65). Additionally, once a network is established, its unique structural features (e.g., predictability, centrality) and visualization tools allow for a clear insight in underlying correlational structures with a broader set of risk factors among patients with CHD, while adding a moderator will show how this differs for men and women. This could aid improvements in both science and clinical practice (51) by providing information on how to tailor and personalize interventions (58).

In the current study, we thus had multiple aims: first, we studied the network of four clusters of risk factors (i.e., biomedical, health behavioral, psychosocial, and SES) in patients with CHD to assess the interrelatedness of these risk factors and the structural characteristics of the system. Additionally, we assessed the moderating role of sex to gain additional insight into this important contextual factor that could explain this interconnectedness among risk factors. Based on previous research outlined above, we hypothesized that SES has a relatively large influence (i.e., more central) in the risk factor network among patients with CHD, and that the relationships between SES and other risk factors would be stronger for women.

METHODS

Procedure and Participants

We included 1682 participants in the current study (77.9% male; M_{age} = 69.2, SD_{age} = 10.6) which is part of the ongoing Tilburg Health Outcomes Registry of Emotional Stress after

Coronary Intervention (THORESCI) study. The THORESCI study is an observational cohort study, in which patients who underwent PCI treatment are followed over a two-year period with multiple time points after the PCI: within five days (T0), the first month (T1), six months (T2), one year (T3) and two years (T4). The study started inclusion in December 2013, and is ongoing. For the current study we used data from T0 and T1. For those whose data were not present at T1 we used the data of T0 instead. Questionnaires on hostile personality were implemented in the study at a later stage (since 2017, at T3 and T4). Eligibility criteria included fluency in Dutch (i.e., verbally and written) and the absence of any cognitive disorders or life-threatening comorbidities. More details regarding the project have been described in full detail previously (66). All participants received additional information on the study, were able to ask questions and provided written informed consent. Both the study protocol and the corresponding amendments were conforming to the Declaration of Helsinki and were previously approved by the Medical Ethical Review Board (METC Brabant, reference number NL46259.028.13).

Materials

We used the total scores of several established, validated questionnaires to cover the psychological risk factors (i.e., depression, anxiety, NA and SI, stress frequency, adverse life events, hostility). Additionally, we included biomedical data as retrieved from the patients' medical records and we collected data on diet, medication adherence, physical activity, and smoking by self-report. SES was constructed by a composite score consisting of self-reported and geographical data.

Psychological risk factors

Depression. Depressive symptoms were assessed with the Patient Health Questionnaire (PHQ-9) (67). The nine items of the PHQ-9 cover the nine DSM-IV criteria required to make a diagnosis for depressive disorder and are rated on a 4-point Likert scale ranging from 0 ('not at all') to 3 ('almost every day'). The items of the PHQ-9 were summed with a total score ranging from 0 to 27 of which a higher score indicated a higher level of depressive symptoms. The internal consistency in the current study was good with levels of .89 (T1) and .85 (T0).

Anxiety. The Generalized Anxiety Disorder (GAD-7) scale was used to measure the symptoms of generalized anxiety with seven items (68). The items were scored on a 4-point Likert scale ranging from 'not at all' (score of 0) to 'almost every day' (score of 3), with a higher score indicating a higher level of anxiety. The internal consistency was excellent ranging from .916 (T0) to .924 (T1).

NA and SI. The Type D scale (DS14) consists of 14 items assessing Type D personality traits (69). There are two subscales of seven items that measure negative affectivity (NA) and social inhibition (SI). The items were rated on a Likert scale ranging from 0 ('false') to 4 ('true') with a higher score indicating higher levels of NA and SI. Cronbach's alphas indicated good (.855 - .901) to excellent (.904 - .912) levels of internal consistency for SI and NA, respectively.

Stress frequency. To assess the level of stress frequency, we used a dedicated item as a general estimator of the past year's level of stress (i.e., to what extent did you experience stress over the past year?) on a Likert scale ranging from 1 ("*almost no stress at all*") to 4 ("*a lot of stress*"). This item has been used in previous research as a separate stress frequency indicator (70), in which it was predictive of physical and mental health. In a previous study, we tested the item to construct an index variable for chronic stress (71), together with other stress indicators, like work stress, and marital stress, life events, and found this item had the largest factor loading (.71) and explained variance (R^2 = 0.51).

Adverse life events. The total number of negative life events was measured by the Life Events Questionnaire (72) which assesses the occurrence of the following negative life events: sexual abuse (self), physical abuse (self), victim of crime (self), violence within home situation, unwanted pregnancy (self or partner), alcohol or drug abuse within home situation, suicide attempt by close relative, divorce (parents/self), long-term severe illness of a close relative, death of close relative. Each item could be scored on a 4-point scale that indicated whether and if so, when the event occurred; a score of zero was assigned when someone answered "*no, in none of those periods*", and a score of one was assigned when someone answered either "*yes, before my 16th year of life*", "*yes, between my 16th year of life and 1 year ago*" or "*yes, in the past year*". A higher score (maximum of 27) indicated a higher level of experienced events.

Hostility. The Williams subscale (73) derived from the MMPI-based Cook and Medley Hostility scale (74) measured the level of hostility. Originally, nine items were empirically identified by only taking those items that were endorsed by a minimum of 20% of participants characterized by high levels of hostility (scoring 11 -15 on the total scale) as compared to those with low hostility (scoring 10 or less). However, this scale was modified by Wong et al. (75) after concerns that two items may be offensive due to their sexual character. Hence, only seven items were used which were rated with either ‘true’ (= 1) or ‘false’ (= 2). The items were reversed in such a way that a higher score indicated a higher level of hostile attribution. This modified subscale has a prognostic performance concerning adverse cardiovascular outcomes (75). As the scale was implemented for T3 and T4 from 2017 onwards, the scale was not assessed in a minority of participants (~37%). Since hostility is a stable personality trait (76), we decided to still include it in the current study. In case T3 was missing, T4 data were used. Internal consistency was average (.65) to acceptable (.70) likely caused by the dichotomous nature of the scale.

Patient characteristics

Health behavioral characteristics were obtained by self-report and included adherence to dietary guidelines (i.e., varied diet, restricting salt and fat) and medication adherence (i.e., forgetting to take medication, taking medication on time, and not taking medication) which were both assessed by three items with scores ranging from 0 ‘never adherent’ to 5 ‘always adherent to the guidelines/medical advice’. The sum score was taken for dietary guidelines and medication adherence separately and could range from 0 to 12. Additionally, we asked patients about whether their level of physical activity was sufficient on a scale from 0 (incorrect) to 4 (correct) which was recoded in a binary variable (yes or no), and whether they smoked (three answer options: yes (1), no (0), quit (0), which we dichotomized). Lastly, patients’ biological sex (at birth) and cardiometabolic characteristics (i.e., hypertension, diabetes mellitus, and hyperlipidemia) were retrieved from their medical records.

Socioeconomic Status (SES)

Previous studies on SES advocate for the use of multiple socioeconomic indicators (77-79), while other studies recommend creating a composite SES-index based on these indicators (80, 81) to capture SES as broadly as possible. Based on these recommendations, we composed an SES-index consisting of three different socioeconomic indicators. We included education and occupational status as reported by the participant. However, instead of merely relying on individual SES characteristics, we also assessed postal code information as a proxy for SES as the socioeconomic environment is similarly found to affect health in multiple ways (82). Postal codes were known for participants to receive mail, and 2016 data for each 4-number postal code was retrieved through the Central Bureau for Statistics (83). This dataset provides information on several socioeconomic indicators per postal code including median family income, which we extracted and used for our index. In line with previous research (81), we divided these socioeconomic indicators into three levels and assigned a value to create low (= 1), medium (=2) and high (= 3) scores based on the combined scoring on below described variables.

Education. Education is commonly associated with health behaviors (84), health, and health outcomes (e.g., (81, 85)), hence its inclusion in our SES index. Information on educational level was acquired at baseline. Participants were asked to indicate their highest attained educational level, including elementary school, high school, middle vocational training, or college/university which were recoded into low (high school or less; 1), medium (2), and high (college or higher; 3) respectively.

Occupational status. We created an automatic SPSS code to divide self-reported occupations into blue, pink, grey and white-collar work. We partially based our grouping decisions on the International Standard Classification of Occupations (ISCO) (86). However, as the ISCO was created in 1990, we took a more modernized approach such that we went beyond classifying occupations in blue-collar and white-collar work. Blue-collar work typically refers to manual labor as performed by the working class (87, 88) such as manufacturing, mechanical and technical work which usually is more physical, while white-collar work refers to jobs that are generally performed by professionals (88) such as high-level managers, doctors, and lawyers that are generally characterized by a white collared suit. Additionally, we made a distinction from the ISCO by adding grey-collar work which refers to those workers that do not fall in either white or blue but do have an accompanying skill set, such as managers, medical assistants and police (88) and pink-collar workers, whose jobs are rather socially interactive (88, 89) such as teachers, entertainers and social workers. We manually recoded when participants listed several job roles (e.g., based on highest role; having an uncommon role). As a large part of our sample is unemployed (i.e., retired, jobless, household duties, declared unfit and voluntary work), we also assigned codes to add more detail in the occupational status codes among those who are not employed, as there may be socioeconomic differences within this group. Like the other coding, we categorized occupations as a lower income than average (= 1; i.e., unemployed, declared unfit, voluntary work, household duties, blue-collar work), average (= 2; i.e., pink-collar work, retired) and above average (= 3; i.e., grey-collar work, white-collar work).

Median Family Income. Income is related to both living and work conditions (84) which substantiates its inclusion in the SES index. The median household income is commonly used to operationalize SES in health research (90, 91). Median family income extracted from the CBS dataset (83) and labeled into seven categories with corresponding descriptions (i.e., ranging from below average, above average, high), which we collapsed into three categories based on the descriptions and the number of participants (e.g., some categories consisted of 3 participants) in a specific category: below average (= 1), average (= 2) and above average – high (= 3).

After that, we summed these three variables, allowing for one missing variable which was in that case was replaced by the mean of the items that were available, and rounded up to create seven distinct categories. The SES-index (M = 7.01 ± 1.66) ranged from 3 to 9 with a higher score indicating a higher SES.

Statistical Analysis

Data were analyzed in SPSS version 24 (92) to conduct the missing value analysis and in RStudio to perform the network analysis. Patient characteristics were analyzed for men and women separately, and additional sex differences were tested by Chi-squared tests for categorical variables and one-way ANOVAs for continuous variables.

Missing data. The amount of missing data ranged from 1.0% (cardiometabolic variables) to 9.0% (education level), except for stress frequency (28.4%), negative life events (21.6%), and hostility (37.5%). To handle the missingness, we used the Impute Missing Data Values option in the Multiple Imputation analysis in SPSS. Each missing value was imputed multiple times (M =

10) to account for any uncertainty in the retrieved imputation, after which we performed the analyses based on the stacking method as recommended by previous research (93-95). In this method, all ten imputed data sets get stacked upon each other, leading to one large dataset with the length *n* (i.e., all participants; 1682) * *M* (i.e., the number of imputed datasets; 10). In our case, our stacked dataset had a length of 16.820 cases.

***Network analyses*.** To import and handle the imputation dataset from SPSS to R, we used the *foreign* (96) and *mice* (97) packages, respectively. The network analysis was conducted with the *mgm* (98) and *bootnet* (99) packages. Additionally, we used the *qgraph* package (100) to visualize the network models. In a network system, the variables (i.e., risk factors) are represented by the *nodes*, and the relationships between the nodes are called *edges* (i.e., the lines in a network). In the current study, we used an undirected (i.e., an edge that indicates a mutual relationship) and unweighted (i.e., edges are existent or nonexistent) network approach (51). Edges do not imply causality, but mere correlations. In addition, as the current data is of cross-sectional nature and contains categorical, dichotomous, and continuous variables, we used a pairwise Mixed Graphical Model (MGM). Through this method, the neighborhood of each node (i.e., the nodes that are connected to it) is estimated, followed by combining all estimated neighborhoods to retrieve the full network. Additional details on MGMs have been described in detail previously (55).

We used the cross-validation (CV) procedure with the OR-rule (i.e., taking the arithmetic mean if both estimates are nonzero). CV specifies the procedure for the tuning parameter selection, which entails splitting the data into several folds (10 by default) while fitting the model by comparing one test-set to the remaining folds. Then, the error of the fold is computed and gets averaged for all folds which results in the CV error, which is then followed by an assigned tuning parameter to minimize this error (101). We used the CV procedure because our network is rather dense (98). As compared to other methods, sensitivity (i.e., the extent of how well a method determines whether a group difference exists or not) is better but the precision (i.e., probability that an estimated parameter is the true parameter (63)) could be less desirable (102). Furthermore, CV with the OR-rule is found to be a bit more liberal (102) which fits the explorative nature of our study.

We first conducted the regular MGM without sex as a moderator. The SES index, stress frequency, and physical activity were entered as categorical variables with multiple categories (up to eight), as well as hypertension, diabetes, and hyperlipidemia with binary categories (i.e., yes or no). All other variables (e.g., psychological questionnaire total scores) were treated as continuous variables. We assessed several characteristics of the network to gain a better insight into the regular MGM. We first calculated the level of predictability, i.e., the extent to which variance of one node (i.e., variable) can be explained by neighboring nodes in the network. In case the predictability of a given node is high, this indicates that a large part of its variance gets predicted by directly connected nodes (103). Using the predictability measures of a node, one can explore to which extent that node can be influenced by intervening on nodes that are connected to it (i.e., neighboring nodes). Centrality of the nodes in the network were examined by retrieving the degree (i.e., number of direct links), closeness (i.e., path length to other nodes) and betweenness (i.e., frequency of the node being between paths) centrality. Centrality measures thus give an insight in the node or nodes that have the most central (i.e., critical) position in the network model (104). Lastly, we examined centrality stability with the *corStability* function in *bootnet*, which in turn assesses the stability of the indices (i.e., degree, betweenness, closeness, expected influence) by bootstrapping the estimates. This eventually will gauge the maximum number of cases that could be dropped to retain a sufficient correlation with the original centrality estimate. (99). Ideally, the level of stability should be higher than .50 (99). We used 500 bootstraps to determine the stability of the strength, expected influence, betweenness and closeness.

For the moderated network model (63, 102), we performed similar analyses of those of the regular MGM with the addition of sex (i.e., male, female) as a moderator. We examined the three-way interactions as an indication of the moderating role of sex for each imputed dataset. As *mgm* only displays nonzero interactions, a nonzero interaction parameter indicates sex moderates the relationship between two risk factors. Since the SES index is of an ordinal nature, there was no sign (i.e., negative or positive) of the relationship disclosed. We used partial correlations as an indication of the direction and strength of relationship, which simultaneously controls for the effects of the other risk factors in the network (51). Additionally, with *qgraph* we also visually inspected group differences.

Because we used a stacked data set, model fit generally provides valid parameter estimates, but the inflated sample size could lead to standard errors that are too small. We corrected these standard errors by assigning a fixed weight to each case in the form of 1/*M* with the weights command in *mgm* (93, 94, 105), and *M* being the number of imputations done.

For sensitivity purposes we carried out the main analyses (i.e., regular MGM, moderated MGM) removing those participants who did not complete the CMHS. We also checked whether there were any differences in patient characteristics by performing Chi-squared tests and one-way ANOVAs.

RESULTS

We included the descriptive statistics of the original data in Table 1 and of the stacked imputations dataset in Table S1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A921, both stratified by sex.

Correlations among all factors in the model (Table S2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A921) were small to moderate. A lower SES was associated with an increased prevalence of classical cardiovascular risk factors, better adherence to medical and dietary guidelines and overall lower psychological risk, except for stress frequency (which is inherent to the fact that we classified pensioners lower than the working population who often report high work stress).

Regular MGM

The network model with the levels of predictability for each node is displayed in Figure 1. SES is among the risk factors with a rather central position in the network meaning it is related to all nodes (i.e., other risk factors), which was also reflected in the levels of predictability and centrality. Negative life events and the experience of stress were among the most central variables of the psychosocial risk factors, while diet, medication adherence, and physical activity were central health behavioral risk factors in the network. Cardiometabolic risk factors were somewhat less influential. See below for more explanation on the network estimation and interpretation.

Predictability. The predictability had a mean explained variance of 0.47 (*SD* = .28). Smoking, hypertension, and hyperlipidemia belonged to the three best predicted nodes (average variance > .70), which indicates the variance of these risk factors is predicted by their neighboring risk factors. Adherence to medication guidelines, hostility and negative life events belonged to the three least predicted nodes in the network (average variance < .11), which suggests that these nodes are largely determined by factors not included in the network and may rather be seen as predictors only. With a variance of .30 and fifth in ranking, SES also showed a relatively low predictability. As SES belongs to the more influential nodes, this may indicate that SES predicts other factors rather than being predicted by factors in the network. The outcomes of the retrieved network, and the node predictabilities in the regular MGM are displayed in Figure 1, with darker donut charts around the nodes indicating higher levels of predictability. Especially for preventive strategies, such as CR, it is of importance to have an insight into which risk factors predict and/or are predicted by other risk factors.

Centrality. Network estimations on degree centrality are displayed in Figure 2. In general, the network was quite dense, with a lot of interconnections, evident in the high level of degree centrality (between 12-14, with a possible range from 0-15). Overall, the SES index is found to be among the most influential and central risk factors, together with stress frequency, hostility, physical activity, negative life events, and adherence to dietary and medication guidelines.

Contrarily, smoking, social inhibition, hyperlipidemia, and diabetes were among the least influential nodes as indicated by their levels of betweenness, closeness and expected influence, albeit a small difference with the influential nodes. The closeness and betweenness were similar to the degree centrality.

Stability. Stability tests demonstrated that the strength, betweenness, closeness and expected influence had correlation stability coefficients of .75, which indicates that these centrality measures are stable across bootstrapped estimations.

Sex moderated MGM

We performed a moderated network analysis for the stacked dataset, which is similar to the regular MGM, but then with sex as a moderator. From this analysis we retrieved the three-way interactions (i.e., risk factor x risk factor x sex). These revealed several important moderation effects. First, sex moderated the relationships between SES and every risk factor in such a way that each relationship in the network was stronger for women (i.e., larger regression weight (106)). Especially in connection to physical activity, diabetes, and anxiety the relationships were found to be much stronger ($b > .38$) for women as compared to men.

Second, a large majority of relationships between risk factors were stronger for women with the most conspicuous differences in the relationships between hypertension and physical activity ($b = .46$; negative)[1], physical activity and stress ($b = .41$; negative), diabetes and stress

[1] Please note that due to the nominal nature of the sex variable, R MGM output does not assign a direction of effect. This is added by gauging the partial correlations in the supplement. Interpretation example: the relationship between hypertension and physical activity was more negative in women than men.

(*b*= .35; negative), smoking and stress (*b* = .39; negative), and diabetes and hyperlipidemia (*b*= .39; positive). For men, the most obvious relationship that was stronger was the relationship between diabetes and hypertension (*b*= .15; positive). Results are displayed in Figure 3, with the edge-width (i.e., line thickness) indicating stronger relationships. Additionally, Figure S1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A921, confirmed these findings through assessing the stability of the pairwise and moderation effects for sex on all relationships in the network by bootstrapping the sampling distributions of all parameters, in addition to showing all pairwise and moderation (three-way interaction) effects. Lastly, partial correlations (controlled for sex) and their interpretations are displayed in supplemental Table S2, http://links.lww.com/PSYMED/A921.

Levels of predictability differed somewhat between men and women. For men, the mean overall predictability of the network (i.e., the extent to which variance of nodes is explained by other, neighboring, nodes) was comparable (Men: .48 (*SD* = .28) vs. Women: .49 (*SD* = .25). Hypertension, hyperlipidemia, and smoking belonged to the three most predicted risk factors for both men and women and medication adherence, negative life events, and hostility to the three least predicted risk factors, which was in accordance with findings in the overall dataset. However, for men anxiety was the third most predicted by neighboring nodes, as compared to hyperlipidemia for women. With regards to SES, results indicated that for men the predictability was somewhat lower (.30; fifth in ranking) as compared to women (.37; sixth in ranking) which indicates its neighboring nodes are more predictive for women than for men. The node predictabilities for men and women separately are displayed in Figure S2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A921. Please note that this figure was constructed based on two separate datasets, one for women, one for men, as the current state of the art in network analysis does not allow for these separate figures in a moderation analysis.

Sensitivity analysis

Descriptive statistics were stratified for participants with completed CMHS questionnaire for hostility as compared to participants who did not fill out the CMHS (Table S3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A921).

The regular MGM demonstrated that the level of predictability largely remained the same (M = .*48*, SD = .28), with some slight changes in variance for the individual risk factors. Medication adherence, negative life events, and hostility remained the three least predicted risk factors (average variance < .11), while hyperlipidemia and smoking had the highest level of predictability (average variance > .82). In the regular analysis, hypertension was the third best predicted node, followed by diabetes while in the sensitivity analysis diabetes and hypertension switched places. With an average variance of .31, SES had a similar level of predictability in both analyses. Taken together, the main conclusions regarding predictability were largely similar (Figure S3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A921).

The levels of centrality differed somewhat in the sensitivity analysis, but this difference was never larger than two levels. SES, stress, adherence to dietary and medication guidelines, and physical activity remained among the most influential risk factors in both models, while hostility and negative life events decreased from most influential in the regular MGM to somewhat less influential (i.e., from 14 to 12). Smoking and social inhibition, on the other hand, became more influential (from 12 to 14).

The sensitivity analysis likewise revealed that all relationships between SES and the other risk factors were stronger for women, in accordance with the findings of the original analysis. Especially the relationships between SES and smoking, physical activity, and anxiety were much stronger (> .41) for women as compared to men. Most of the other risk factors relationships was likewise found to be stronger for women (See Figure S4, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A921).

DISCUSSION

The current study is among the first to combine and explore several clusters of risk factors (i.e., cardiometabolic, health behavioral, psychosocial and SES) among patients with CHD by taking a network approach. Apart from zooming in on the roles of sex and SES, this approach also enabled us to gain a better insight into the interrelatedness between a variety of risk factors. Moreover, the unique features of network analysis allow for strategizing and prioritization to tailor interventions. For example, risk factors that were found to be more central should receive more attention in interventions, and these approaches could differ based on the level of predictability. Our findings were largely consistent with our hypotheses as SES belonged to the more influential risk factors, and the relationships between SES with the other risk factors were stronger for women. The findings also emphasized the importance of health behaviors (e.g., being physically active, and adhering to dietary guidelines) and distress (e.g., stress frequency, negative life events), in the network, as they related to all other risk factors. The network was tightly knit, reflected in high predictability of smoking, hypertension, and hyperlipidemia, with more than 70% of the variance in these variables explained by risk factors (nodes) in the network. NLE, hostility, and medication adherence had low predictability, suggesting the role in the network was that of a predictor only. We gave an overview of the unique features that network analysis offers together with a summary of the current findings (with referencing to the figures) in Figure S5, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A922. The findings generally highlight promising avenues for further discussion and future research.

Network analysis is a relatively new tool to map a wide variety of factors in health research (51, 52). In the current study, we provided insight in the interrelatedness of a network of socioeconomic, psychological, cardiometabolic, and health behavioral risk factors to gain more knowledge on their mutual relationships, influence, and predictability among patients with CHD. We were especially interested in knowing the extent to which SES (as a risk factor by itself) played a role in the risk factor network, as separate previous research studies had demonstrated that socioeconomic factors are a risk factor in both the general population and patients with cardiac disease, but are also known to impact other risk factors (23, 25-33, 35-41, 43) such as smoking, hypertension and diabetes (42). To measure SES, we created an index score combining several socioeconomic factors into one composite score (80, 81, 84, 90, 91). Following our expectations, our results indicated that SES belongs to the most influential risk factors given its centrality and level of expected influence in the network. Additionally, SES as a risk factor functioned as a predictor, rather than a reciprocal risk factor, which demonstrates its importance as a risk factor. For the cardiovascular practice, this implies that SES should be included in risk assessment and treatment choices. The network suggests that through the focus on managing stress in patients with low SES, lifestyle variables and classical risk factors may improve.

Besides SES, the predictability of smoking as a health behavioral risk factor stood out: among both men and women, as well as the group combined, smoking had the highest level of predictability which indicates that smoking is predicted by its neighboring nodes in the network, which is in line with previous studies that revealed relationships between smoking and SES (e.g., stress (107) and depression (108). It also indicates that smoking goes hand in hand with other behavioral and classical cardiovascular risk factors, such as lack of physical activity, and poorer diet, and psychological factors such as stress frequency and negative life events. These risk factors were also central and influential in the risk factor network, suggesting they often cluster together. Of these risk factors, diet was more predictive of neighboring risk factors than being predicted by them, which indicates that changing your diet could be a powerful way to help work on the other risk factors. The results of the current study dictate the importance of considering the multidimensionality and interrelatedness of risk factors, rather than focusing on their single effects.

In addition to the relationships between risk factors, we were also interested in the moderating role of sex on these relationships and the relative importance of the risk factors in the network. Analysis revealed that for all relationships that SES had with other risk factors, the effect was stronger for women which was in accordance with previous research (45). Especially for physical activity, diabetes, and anxiety these relationships were much stronger. Furthermore, when considering the interrelationships between the biomedical, health behavioral, and psychological risk factors, many of the relationships were found to be stronger for women, such as the relationships between stress frequency and respectively physical activity, smoking, and diabetes which indicates that stress frequency could possibly an important risk factor for women. Summarizing, these results highlight the need to consider sex differences in interventions that target risk factors, such as CR.

CR programs focus on a wide range of activities that include health behavioral interventions targeted at healthy eating habits, physical activity and smoking cessation, the management of blood pressure, glucose levels and lipids, and psychological interventions, aiming to lower the associated risk and its negative consequences (109). The current study, by demonstrating that SES plays an influential and predictive role in the risk factor network, provides tangible evidence as a first step for a more tailored CR program. Previous research has highlighted the need for CR in patients with low SES (42, 48). However, at the same time low SES patients are generally under-represented in CR (e.g., (110, 111)), which, in the Netherlands and Europe in general, seems to be related to logistic hurdles and a limited understanding of the benefits (111, 112), rather than a lack of insurance (110). Additionally, multiple studies assessed the importance of promoting CR among underrepresented groups, such as those with a low SES. For example, the screening for these more vulnerable under-represented groups may be facilitated by healthcare providers. Identification and modification of barriers to CR participation could lead to an optimized adherence by intervening based on motivational communication (e.g., by phone calls, home visits) (113, 114). Another study took a social differentiation approach by screening patients and offering patients with a more socially vulnerable background an extended version of CR of which the results suggested higher rates of attendance and adherence (115).

Since smoking was found to be among the risk factors being sensitive to be predicted by other risk factors, the success of smoking cessation could be improved with the findings of the current study. Smoking cessation as provided in CR is proven to be effective in reducing both mortality and morbidity (116), as well as recurrent myocardial infarction (117). Additionally, those who smoke seem to be less likely to enroll to CR and more likely to drop out if they enroll which could be due to less financial resources and limited education (116). The benefits of smoking cessation may not be as obvious to smokers due to a variety of reasons: for example, smokers show less measurable improvements (e.g., HR response) with regards to physical exercise (118) and have a lower likelihood of reaching their fitness goals if they complete CR (119). It is thus suggested that smokers are provided with more attention, information and additional support, by trying several approaches such as medication or smoking cessation programs (116). Furthermore, more emphasis should be put on providing information of the consequences of smoking after a cardiac event and the importance of CR (116). However, besides targeting smoking directly, the current study indicates that the success rate of smoking cessation could be improved when related nodes (i.e., risk factors) are affected: e.g., by reducing stress (107) and negative affectivity (120), and improving physical activity (121), which all could increase the success of smoking cessation. For risk factors with a lower predictability, such as negative life events and SES, more focus could be placed on the consequences that may stem from these risk factors. For example, by teaching coping and emotion regulation strategies for negative life events (122, 123) or offering a social differentiation approach for patients with a more vulnerable social background (115). The negative consequences related to these risk factors and the impact on other risk factors may then be weakened. However, research should study these suggestions more extensively, which eventually may test tailored prevention and improved cardiac rehabilitation strategies.

The moderating role of sex in the relationships between risk factors indicates the need to further study tailored interventions that consider the network of risk factors, including SES and sex differences, with the aim to provide better aid and reduce (the influence of) risk factors. With women having lower adherence and admission rates to CR programs (49, 50), more research should focus on developing a women-focused CR program. Though those programs exist (e.g., (124)), it is unclear to what extent attendance and adherence improve, and how widespread these programs are implemented. As relationships among (SES and) risk factors seem be stronger in women according to the current study, the results of the current study suggest that women with a low SES may therefore be at higher risk. However, it is unclear what their unique barriers are. Therefore, future research may focus on this group which in turn could lead to the development of women-focused CR programs that account for risk factors such as lower SES and stress. To our knowledge such programs does not exist and therefore the current study may serve as a first step towards more specific interventions.

Strengths and limitations

The current study was not without limitations. Firstly, for a few risk factors we had larger amounts of missing data, for which we used ten multiple imputations. To reliably interpret the outcomes of our imputed dataset, we had to account for the imputations by stacking each imputed dataset on top of each other (i.e., the 'stacking' method, see (93, 94)). This method provides valid parameter estimates but could ultimately lead to standard errors that are too small.

We corrected these standard errors by assigning a fixed weight to each case in the form of 1/*M* with the weights command in *mgm*. It is important to note that this ignores the missing information per variable, as all variables get assigned the same weight (93, 94, 105). However, performing a Wald procedure, that is similarly recommended (93, 94, 105), would not be feasible given the lasso estimation in *mgm*. Since hostility had many missing values (~37%) due to the MCHS being administered later in the study, we carried out additional sensitivity analyses to evaluate the possible impact of this missingness. Our main findings largely remained the same. However, we did find some differences in patient characteristics which should not remain ignored. As compared to those who completed the questionnaire, participants who did not fill in the CMHS were overall found to be more often female and a smoker, with higher levels of depressive symptoms, anxiety, and negative affectivity, lower adherence to dietary and physical activity guidelines, and a lower SES. This is largely in accordance with previous findings on drop out characterization (125, 126). Another methodological limitation is that we used the CV method with the OR-rule, which may result in higher levels of sensitivity, but lower levels of precision (102). Deciding which method to take comes with a trade-off between sensitivity and precision. However, generally speaking, a large number of observations is required in each group to recover small differences which was the case in the current study. Additionally, as our study is of an explorative nature we decided to go for a more liberal approach. Though we acknowledge we may run the risk of recovering false positives with this liberal approach, this risk does not outweigh other consequences that missing important risk factor relationships may have if we would take a more conservative approach. The current study also has the limitation that there is a small proportion of women, which is typical for the PCI (CHD) population: women are not only underrepresented in research that focuses on PCI patients (127), but are generally less often revascularized for acute coronary syndrome (128, 129) and stable angina (130). This resulted in larger confidence intervals that already account for the uneven group sizes. Since we still found effects, the level of power should be sufficient. Furthermore, the moderation analysis considers both groups rather than treating them as subgroups. Hence, we can be confident that firm conclusions can be drawn from the effects found. Another limitation concerns the SES index: based on previous recommendations, we captured SES as broadly as possible, using an index score (80, 81). Though we demonstrated that SES is among the most influential risk factors, it does not provide us with the insight into which part of SES plays the largest role. Lastly, another explanation for higher levels of predictability is topical overlap between constructs, in which the predictability seems to reflect alikeness rather than determination: the predictability of anxiety, depression and NA could partly represent their similarity instead of predictability (12, 13). Nevertheless, the current study is to our knowledge among the first to take a novel network approach to gain an insight in the interrelatedness of risk factors while also considering the moderating role of sex.

CONCLUSION

Overall, the current study highlights the importance to consider the multidimensionality of cardiac risk factors as demonstrated by the dense network. We also illustrate that SES plays a key role in the network of risk factors as it is both found to be central, as well as more predictive of other risk factors rather than being predicted. Additionally, we found that the majority of the risk factors relationships and all of the relationships between SES and other risk factors were stronger for women, which indicates risk factors are more pronounced among women (of lower SES). Besides socioeconomic status, the frequency with which stress was experienced was among the risk factors that were also important in the network. The outcomes of the current study lay the foundation for future research with the aim to tailor interventions and CR programs by being more sensitive to one's socioeconomic background and sex, but also should put more emphasis on the interrelatedness of the risk factors and suggest cardiology practice to take a more multidisciplinary approach.

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FIGURE CAPTIONS

Figure 1. *Mixed graphical model (MGM) of psychological, cardiometabolic, and health behavioral risk factors.*

Note: Green and red edges indicate positive and negative relationships respectively between two continuous nodes; grey edges indicate a relationship between at least one categorical variable. Pie charts around each node represent the predictability of the given node in which darker pie charts indicate higher levels of predictability, whereas emptier pie charts imply that the MGM does not contain predictors of that given node. The layout of the MGM is based on Fruchtermann-Rheingold algorithm with a minimum cut-off of 0.1 and a maximum cut-off of 1.0 to control the visibility of each edge. Nodes that are more influential (i.e., with more relationships with other nodes) are more central in the network and nodes that are less influential are in the outside of the network. See supplemental Table S2, http://links.lww.com/PSYMED/A921 for a correlation matrix with all partial correlations (positive and negative).

Figure 2. *Levels of degree centrality*

Note: X-axis shows degree centrality, i.e., a numerical measurement of the importance of a node. It reflects the number of nodes directly connected with a risk factor node (possible range 0-15). The Y-axis shows the three clusters of risk factors, i.e., health behavioral (dark gray), cardiometabolic (white), and psychological risk factors (light gray), and SES.

Figure 3. *Moderated MGM for men (left) and women (right).*

Note: Green and red edges respectively indicate positive and negative relationships between continuous variables. Grey edges indicate relationships in which one of the nodes is categorical. The edge-width is reflective of the proportion of the strength (i.e., size of correlation): a thin line indicates a small partial correlation, while a thicker line indicates a stronger correlation.

Figure 1

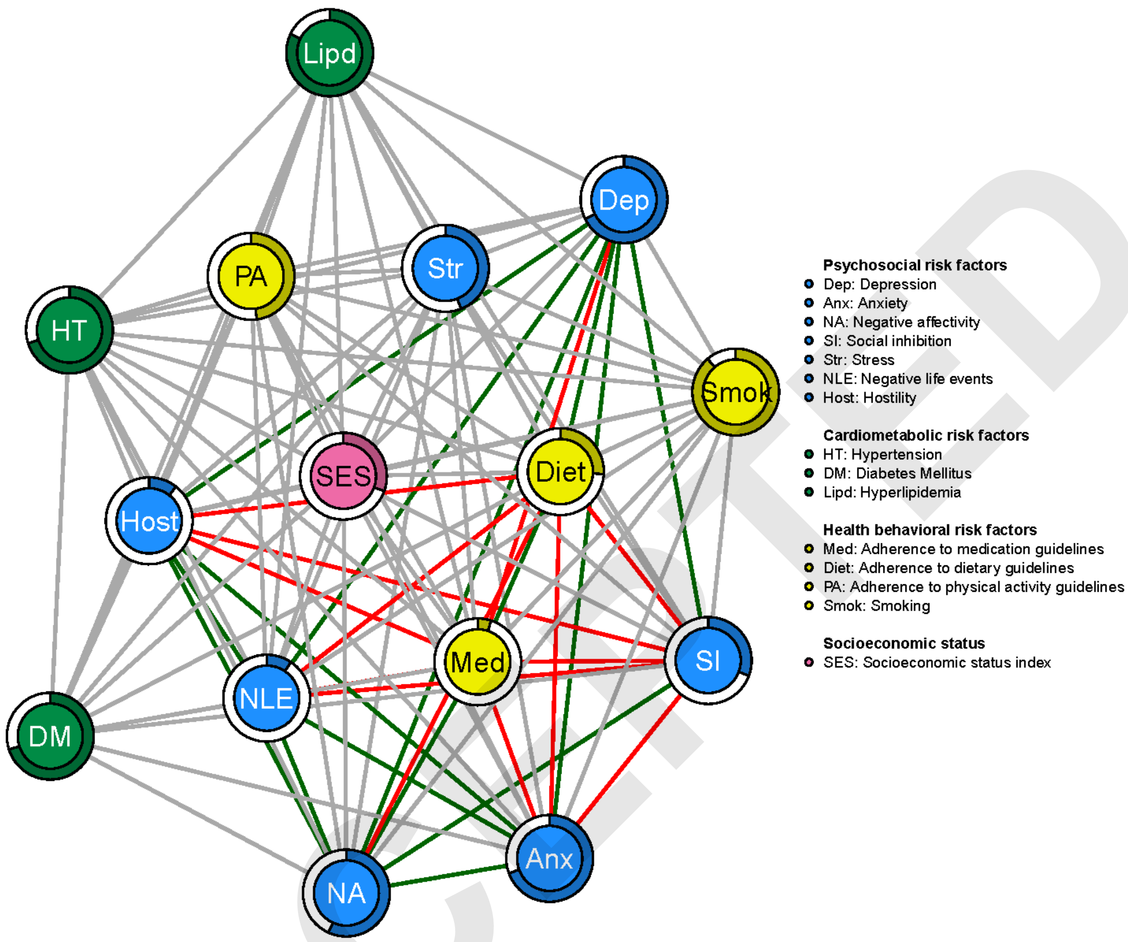

Lipd
Dep
PA
Str
HT
Smok
SES
Diet
Host
Med
SI
NLE
DM
Anx
NA
Psychosocial risk factors
Dep: Depression
Anx: Anxiety
NA: Negative affectivity
SI: Social inhibition
Str: Stress
NLE: Negative life events
Host: Hostility
Cardiometabolic risk factors
HT: Hypertension
DM: Diabetes Mellitus
Lipd: Hyperlipidemia
Health behavioral risk factors
Med: Adherence to medication guidelines
Diet: Adherence to dietary guidelines
PA: Adherence to physical activity guidelines
Smok: Smoking
Socioeconomic status
SES: Socioeconomic status index

Figure 2

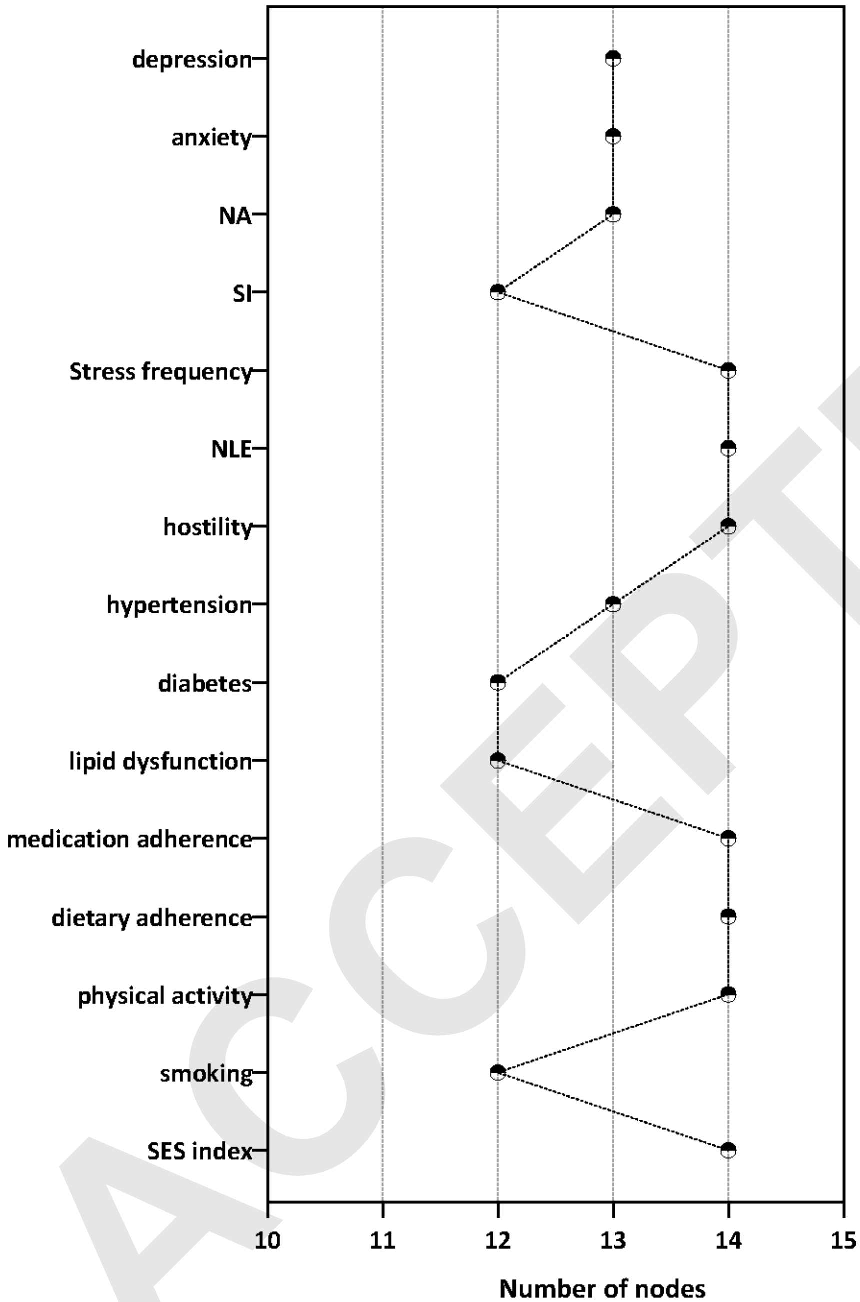
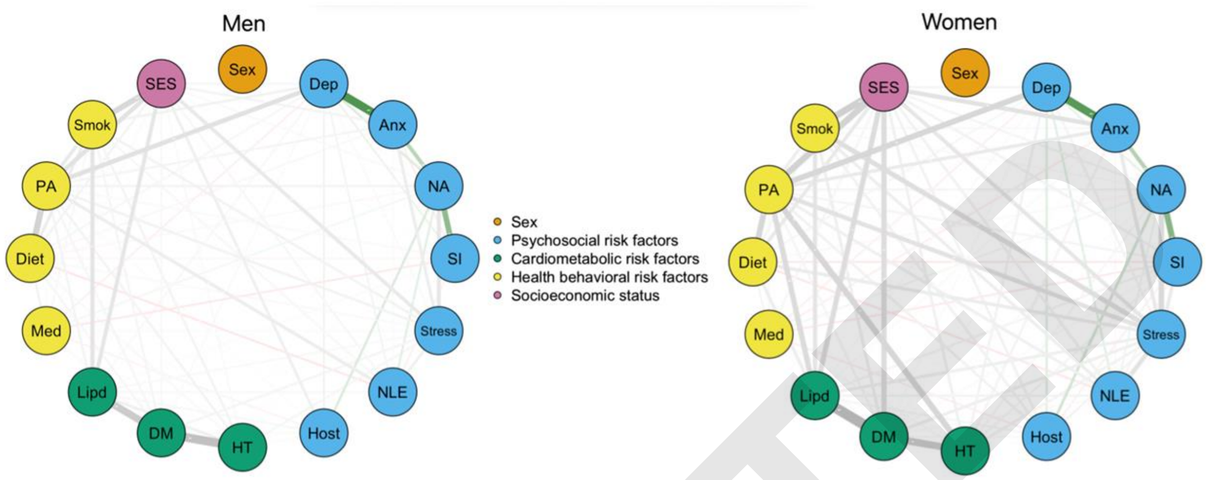

depression
anxiety
NA
SI
Stress frequency
NLE
hostility
hypertension
diabetes
lipid dysfunction
medication adherence
dietary adherence
physical activity
smoking
SES index
10
11
12
13
14
15
Number of nodes

Figure 3



Men
Women
Sex
SES
Dep
Smok
Anx
PA
NA
Diet
SI
Med
Stress
Lipd
NLE
DM
HT
Host
Sex
Psychosocial risk factors
Cardiometabolic risk factors
Health behavioral risk factors
Socioeconomic status

Table 1. Sex-stratified demographics and cardiometabolic, health behavioral, psychosocial, and socioeconomic factors based on the original dataset

	N	Men		Women		Test-value	p-value
		M/N	SD/%	M/N	SD/%		
Demographics							
Age, *M(SD)*	1680	68.91	10.61	70.13	10.50	3.86	**.050**
Employed	1552	525	43%	82	26%	29.83	**< .001**
Cardiometabolic risk factors[a]							
Hypertension [yes]	1671	513	40%	169	56%	4.95	**.026**
Hyperlipidemia [yes]	1670	403	31%	105	29%	0.82	.37
Diabetes mellitus [yes]	1668	229	18%	72	20%	.74	.39
Health behavioral risk factors[a]							
Adherence to dietary guidelines	1629	9.17	2.21	9.65	2.18	13.47	**< .001**
Medication adherence	1609	11.54	1.00	11.55	1.04	0.00	.95
Physically active	1682	2.86	1.10	2.77	1.10	2.15	.14
Smoking [yes]	1629	126	10%	45	13%	1.97	.16
Psychosocial risk factors							
Depressive symptoms (PHQ9)	1580	3.80	4.93	5.86	6.04	45.58	**< .001**
Anxiety (GAD-7)	1583	3.45	4.57	5.05	5.22	31.28	**< .001**
Negative Affectivity (DS14)	1545	7.13	6.54	8.73	6.95	15.32	**< .001**
Social Inhibition (DS14)	1545	8.86	6.90	9.00	6.97	0.11	.74
Stress frequency	1205	2.16	0.97	2.55	0.99	32.64	**< .001**
Negative life events[b]	1319	497	48%	125	44%	.00	.97
Hostility (CMHS)	1052	2.27	1.86	1.65	1.74	18.82	**< .001**
Socioeconomic status[a]							
SES-index score	1644	5.88	1.42	5.54	1.35	21.84	**< .001**
Education level	1521					29.75	**< .001**
Low (1)		351	29%	145	44%		
Medium (2)		526	44%	130	39%		
High (3)		316	27%	53	16%		
Occupation	1551					23.43	**< .001**
Low (1)		386	32%	114	35%		
Medium (2)		628	52%	194	59%		
High (3)		208	17%	21	6%		
Median family income[c]	1666					2.13	.35
Low (1)		304	23%	95	26%		
Medium (2)		650	50%	168	46%		
High (3)		345	27%	104	28%		

Note: Chi-squared tests for categorical variables; one-way ANOVAs for continuous variables; [a]Based on baseline data, [b] One or more negative life event(s) [c] based on postal code CBS data (83); Bold = $p < .05$