MASTERTHESIS

Characteristics of midlife women with coronary microvascular dysfunction, compared with age-matched women with obstructive coronary disease

Name (email): Anneke Lier (t.c.w.lier@student.utwente.nl)

Student number: s1518526

Study: Master Health Psychology,
Faculty of Behavioral, Management and Science
University of Twente

Date: February 26, 2016

First supervisor: Dr. C. Bode

Second supervisor: Dr. M.E. Pieterse

External supervisor: Prof. Dr. A.H.E.M. Maas & Dr. S.E. Elias-Smale,
Radboud University Medical Center

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Objective: This study examined the medical and psychosocial characteristics of women in their middle ages with coronary microvascular dysfunction (CMD), and in what way those women differ from age-related women with coronary artery disease (CAD).
Method: A sample of 64 women in the research (CMD) group and 64 women in the control (CAD) group in the ages of 40 to 65 years, was selected from the cardiology department of the Radboud University Medical Centre. All of the respondents completed an online survey with questions about psychosocial (CAQ, SF-12, HADS, and CIS), personality (Brief COPE and MPS), medical, female reproduction system related, demographical and lifestyle factors. The respondents were age-matched between groups. To compare differences in results on the online survey between the CMD and CAD group student t-tests (Mann Whitney tests in case of non-normal distribution of the data and Pearson's Chi Square tests for nominal data) were performed. To point out the significant covariates for CMD several logistic regression tests were performed.
Results: CMD respondents used more frequently self-distraction as coping style than the CAD respondents. Their low scores on physical wellbeing together with self-distraction, but without controlling for other associated factors, were significant covariates for CMD. The less prevalence of current smoking was shown a significant covariate for CMD, until the addition of the covariate self-distraction to that logistic regression model. Other differences between the CMD and CAD group are: CMD respondents were less frequently former smokers and were higher educated than the CAD respondents. In addition, CMD respondents had higher scores on self-oriented perfectionism, fatigue and cardiac anxiety but a lower score on mental wellbeing than the CAD respondents. Complaints from rheumatism and migraine were also more prevalent in the CMD group than in the CAD group.
Conclusion: Women with CMD in this research form a specific group of patients. A profile of those women could be: highly educated women with high expectations of and demands on themselves. Their preferred coping style for handling difficult situations like stress, possible caused by their complaints of angina, migraine, rheumatism, heart related anxiety, and fatigue, is self-distraction. The limitations in their daily activities burden the CMD respondents most, as measured by a low level of physical wellbeing. Of the traditional Framingham Risk Score factors only current and former smoking were less prevalent among CMD respondents than among CAD respondents; diabetes, hypercholesterolemia and hypertension were equally prevalent among CMD and CAD respondents and their BMI scores were about the same.

Keywords: women, coronary microvascular dysfunction, midlife, medical, psychosocial, lifestyle, demographics.

The improvements in the quality of the present health care in European countries, like The Netherlands, have a disadvantage: the older a person gets, the higher the chance for getting a chronic disease, with at least 4.5 million chronically diseased in 2010 in The Netherlands (Algemene Rekenkamer, 2010). A chronic disease is not only physical challenging for someone, but also a burden for his sense of wellbeing (Centraal Bureau voor de Statistiek, 2011; Hsieh, 2007).

Compared with other chronic diseases coronary heart diseases have a huge mental impact on someone, like causing feelings of anxiety, depression, search for meaning to the changed identity and even 'posttraumatic stress disorder, PTSD' (Doerfler, & Paraskos, 2004; Ogden, 2012). In addition, cardiovascular diseases were the second cause of death in the Netherlands in 2012, with 9720 deaths, most of them caused by an acute myocardial infarction (Blokstra, Poos, & Appelman, 2012; Hartstichting, 2014; Poos, van Dis, Engelfriet & Deckers, 2014). The total prevalence of all coronary heart diseases was 604.500 in January 2011; the incidence for new disease cases that year in The Netherlands was 48.900 (Poos et al., 2014). Coronary heart diseases are besides expensive diseases; according to the Dutch National Institute for Health and Environment they are in the top ten of most expensive diseases (Rijksinstituut voor Volksgezondheid en Milieu, 2011).

Women and heart diseases

Most research has been focused on men with heart diseases, but last decades researchers begin to target their investigations at women too, because of the differences found between men and women having coronary heart diseases. It seems that, in general, women experience problems with heart diseases ten years later than men do (Lerner & Kannel, 1986). Coronary heart diseases, occurring in elderly women, are somehow related to their postmenopausal state (Lerner & Kannel, 1986; Ogden, 2012a). This macrovascular form of ischemic heart diseases (IHD) is mentioned, from now on, 'coronary artery disease (CAD). Only at the age of 75 years, men and women are equally at risk of coronary heart diseases (Lerner & Kannel, 1986).

Macrovascular ischemic heart disease in women (CAD)

CAD is difficult to diagnose in women, as they have other, atypical symptoms and psychosocial factors, than men do (Clarke et al., 2015; Rutledge, Vaccarino, Shaw, & Bairey Merz, 2011). Some general, medical, female reproduction system related and psychosocial factors are known to be associated with CAD in women.

Medical and general risk factors in women with CAD

Some research searched for the general risk factors for coronary heart diseases in women. Examples of these general risk factors are included in the Framingham Risk Score (FRS), like high age, diabetes, smoking, treated and untreated high systolic blood pressure, and total and high density lipoprotein cholesterol (D'Agostino et al., 2008).

Other well-known risk factors, related to CAD in women, are: unhealthy and augmented eating, insufficient physical activity, augmented alcohol usage, low level of education and income, and familiar cardiac history (Carlsson, 2013; Davis-Lameloise et al., 2013; De Carvalho et al., 2014; Eriksson, Jansson, Kaijser, & Sylvén, 1999; Nordahl et al., 2013; Rubinshtein et al., 2010).

Medical risk factors, associated with CAD in women, are: metabolic syndrome, migraine, thyroidal and rheumatic complaints, and an earlier TIA (Transient Ischemic Accident) or CVA (Cerebral Vascular Accident) (Ammann et al., 2000; Bigal et al., 2010; Crowson et al., 2013; Jadhav et al., 2006; Juutilainen, Lehto, Ronnemaa, Pyorala, & Laakso, 2008; Peters, Huxley, & Woodward, 2014; Rockett, Perla, Perry, & Chaves, 2013; Rodondi et al., 2010; Yang et al., 2012).

Female reproduction system related risk factors in women with CAD

Factors related to the female reproduction system, like miscarriages or stillbirths, hypertension or diabetes during pregnancy and ovary or uterus extirpation (especially before the age of 51 years) can increase the risk of cardiovascular diseases later on in life (Bellamy, Casas, Hingorani, & Williams, 2009; Haukkamaa et al., 2004; Hermes et al., 2013; Ingelsson, Lundholm, Johansson, & Altman, 2010; Maas, de Kluiver, & Lagro-Janssen, 2010; Parker et al., 2014; Rademaker et al., 2013; Valdés et al., 2009).

An early menopause (primary ovarian insufficiency), appearing before the age of 40 years, and therefore involved with a shorter period of exposure to endogenous oestrogens, is associated with a higher risk of cardiovascular mortality (De Vos, Devroey, & Fauser, 2010; van der Schouw, van der Graaf, Steyerberg, Eijkemans, & Banga, 1996). The negative effect of an early menopause on the cardiovascular state seems, however, more obvious in artificial early menopause than in early menopause of natural causes (Atsma, Bartelink, Grobbee, & van der Schouw, 2006).

Postmenopausal changes (partly as consequence of the menopause, partly as consequence of the climbing age) are related to a worsening lipid blood ratio and changing insulin release and tolerance (Gaspard, Gottal, & van den Brûle, 1995). Both aspects are related to a higher risk of coronary diseases. A significant association has been found between the risk of CAD and disruption of ovulatory cycling with a lower level of female hormones as result (Bairey Merz et al., 2003; Shaw, Bugiardini, & Bairey Merz, 2009).

Another menopausal risk factor is related to the menopausal complaints women can have, caused by physical changes in the menopause, like hot flashes and night sweats, leg ache, pain in bones, changed sexuality and mental changes, like fatigue and mood swings (Mushtaq, 2011). This kind of complaints are seen secondary related to cardiovascular risk, via higher cholesterol, blood pressure and BMI (body-mass index) (Gast et al., 2008; Gerber, Sievert, Warren, Pickering, & Schwartz, 2007).

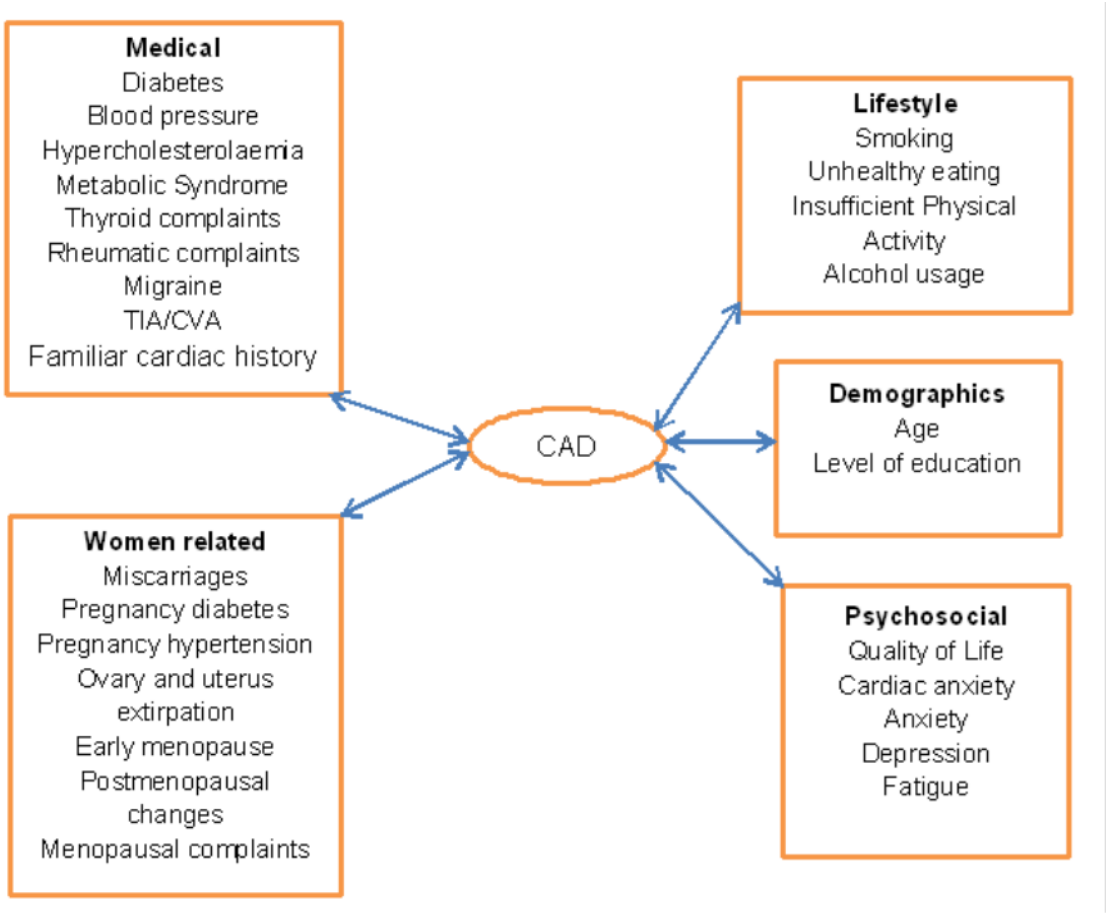
Psychosocial factors in women with CAD

Psychosocial factors, which are associated to CAD, are: physical and emotional wellbeing (as indicators for quality of life), (cardiac) anxiety, depression and fatigue (Gafarov, Panov, Gromova, Gagulin, & Gafarova, 2013; Lier, 2015; McBurney, 2002; Moriel, Roscani, Matsubara, Cerqueira, & Matsubara 2010; Wang et al., 2013; Zikmund, 2003). Especially a combination of depression and anxiety has been found associated to heart diseases, so there might be an interaction effect of those factors on heart diseases (Bhattacharya, Shen, & Sambamoorthi, 2014).

See figure 1 for an overview over the variables, currently known to be associated with CAD in

women. These variables may be either (causal) precursors or consequences of CAD or simply covariates or symptoms of it.

Figure 1 *Variables related to CAD in women*



Microvascular ischemic heart disease in women (CMD)

Another form of ischemic heart diseases, with complaints of angina pectoris, not caused by obstructions in the major but probably in the micro coronary vessels, frequently becomes visible in women at younger ages (Cannon, 2009; Hemmingway, 2006). This form of non-obstructive coronary diseases is nowadays called 'Coronary Microvascular Dysfunction' (CMD), once known as Microvascular Angina, 'MVA' or cardiac syndrome X (Camici & Crea, 2007; Marinescu et al., 2015).

Although no exact numbers of women with CMD in the Netherlands are reported, Dutch hospital data over the year 2012 showed that 40 percent of all female patients, admitted for a day in hospital because of heart complaints, came with angina complaints (Koopman, van Dis, Visseren, Vaartjes, & Bots, 2012). Twenty percent of all patients with angina complaints are expected to have normal coronary arteries and are therefore suspected for CMD (Vermeltfoort et al., 2010). In most

of the cases the diagnosis CMD cannot be confirmed because of the lack of a suitable diagnosis-device (Marinescu, 2015). In addition no optimal treatment has been found, until now, for curing the CMD patients of their disease.

As the diagnosis CMD is often overlooked, many women with CMD are incorrectly soothed and sent home from hospital without treatment (Radico, Cicchiti, Zimarino, & De Caterina, 2014). No control for these patients can lead to a dangerous situation, as they are at higher risk of cardiac events than women with non-obstructive coronary disease but without angina complaints, caused by myocardial ischemia (Kothawade & Bairey Merz, 2011; Petersen & Pepine, 2015). In scientific literature attacks of angina pectoris are mentioned to be the most important complaint of CMD patients; patient information on the Internet however, shows some other possible complaints of CMD like: dyspnea, fatigue, lack of energy and sleeping problems (Heart Information Centre, 2015; Radico et al., 2014).

Factors related to CMD in women

Less research has been done to confirm the existence of the general risk factors for coronary heart diseases for CMD. The Framingham Risk Score seems to be less useful for predicting CMD than for CAD (Rubinshtein et al., 2010; Sayin et al, 2014; Vasheghani-Farahani et al, 2013). Some researchers suggest a lower prevalence of the general factors in CMD patients than in CAD patients, concerning smoking behavior, familiar cardiac history, diabetes mellitus and hyperlipidemia; other researchers suggest a higher correlation of CMD with reduced physical functioning and a lower quality of life, compared with CAD (Johnson et al., 2006; Radico et al., 2014; Vasheghani-Farahani et al, 2013).

In addition, during the period of the middle ages women have, more than age-matched men or older women, an elevated risk of a combination of non-obstructive atherosclerosis with an endothelial dysfunction in the microvascular coronary arteries; a condition comparable with CMD (Maas & Lagro-Janssen, 2011).

Research Objective and questions

As stated above a considerable group of (mostly) women suffers from a cardiac problem (CMD) about which is much uncertainty, especially concerning associated factors to this cardiac disease. Objective of this research is to take a closer look at the medical and psychosocial characteristics of women, suspected for CMD, and see if and in what way they are different from women with CAD. This research wants to present an overview of specific characteristics of women with CMD, which can serve as a foundation for future research. Practical application for this research will be to seek,

beyond the physical complaints of women with CMD, for their specific emotional needs and find a way to provide for their needs.

Research question

To what extent do middle-aged women, suspected for CMD and in treatment at the Radboud University Medical Center, differ in medical and psychosocial variables from age-matched women in treatment at the Radboud University Medical Center for CAD?

Sub questions

1. To what extent do scores, on below mentioned factors, differ in midlife women with CMD from age-matched women with CAD?

Demographical factors

a) Age, BMI, level of education, type of employment, country of origin, marital status

Medical and female reproduction system related factors

b) Medical factors (hypertension, hypercholesterolemia, migraine, earlier cardiac intervention, cardiac infarction, TIA/CVA, angina, dyspnea, rheumatic and thyroid complaints)
c) Female reproduction system related factors (menopause before the age of 40 years, menopausal complaints, miscarriages, hypertension and diabetes during pregnancy, and uterus or ovary extirpation)

Lifestyle factor

d) Alcohol drinking habit

Psychosocial (mental) factors

e) Perfectionism
f) Coping style
g) Cardiac anxiety
h) Fatigue

2. Do the CMD respondents report less (or more in case of depression and anxiety) of the factors below than the CAD respondents?

- less (frequently) familiar cardiac history (coronary or heart diseases in parents, brothers or sisters below 60 years, for male relatives or 65 years, for female relatives),
- less (frequently) diabetes and former and current smoking,
- less Quality of Life (measured as lower scores on physical and mental wellbeing),
- more depression and anxiety.

3. To what extent are the factors, that turn out to be individually associated with CMD, together associated with CMD?

4. Are anxiety and depression together more associated than each factor individually with CMD, controlled for all other factors that turn out to be associated with CMD?

Method

Design

Quantitative research has been used for answering the aforementioned research questions. To determine the relevant factors in midlife women suspected for CMD and to investigate the differences in those factors in an age-matched group of women with CAD, a cross-sectional "case control" study was performed.

Population

Target- and control group

The target group for this research consists of women between 40 and 65 years, in treatment at the cardiology department of Radboud University Medical Centre (UMC) for complaints of stable angina pectoris and suspected for CMD. The control group consists of women between 40 and 65 years, in treatment for CAD at the cardiology department of Radboud UMC. The difference between CAD and CMD is, for this research, defined by the presence of a diameter-narrowing of one or more coronary arteries of at least 50% in CAD and the absence of this kind of narrowing in CMD, as confirmed by angiography (Lee et al., 2015).

Sample size

To measure a clinical relevant difference in psychosocial and medical factors between both groups a medium effect size (Cohen's d) of 0.5 is needed. Such an effect size, pointing at a difference of around one standard deviation between groups, is achievable and relevant (Cohen, 1988). To measure such a difference between groups, based on a significance level of 0.95 ($\alpha = 0.05$) and a desired power of the research of 0.80 ($\beta = 0.20$), a minimum of 64 respondents each group is necessary, as calculated for the two-side student t-Test, logistic regression and Chi Square test, with a statistical power analysis program (Gpower_3.1.9.2) and an online statistics calculator (http://www.danielsoper.com/statcalc/default.aspx). Based on earlier response rates, in similar research with Dutch cardiac patients, and the perceived enthusiasm for research in these groups, a response rate of 83% was expected (Bos et al., 2011; Elias-Smale, Kardys, Oudkerk, Hofman, & Witteman, 2007). Based on this response a minimum of 77 respondents each group was approached for this research.

Samples (research- and control group)

The average age of the total study sample (n=128) was 55.69 years (SD=6.32; range 42-65) and the CMD-CAD-ratio 1:1 (64/64). There were no differences between CMD and CAD respondents concerning age, BMI, type of employment, alcohol usage and marital status: most of them were married, in paid jobs, light alcohol users and have overweight, according to the norm of the World Health Organization (2015).

Differences between groups were found on level of education, country of origin, former and current smoking: CMD respondents in this research are higher educated[1], more often from non-Dutch origin and less frequent former and current smokers. The overall higher level of education of this research sample seems to deny the claim of low level of education as a significant risk factor for CAD and CMD (Nordahl et al., 2013). There was a very low rate of drop-out in this research; only 12 out of the 174 approached women (6.9%) did not want to participate. Reasons for drop out were: being not interested, having no time, staying in a foreign country during the upcoming period and being too emotional to fill in the questionnaire.

See table 1 'Descriptive statistics' below for all characteristics of the respondents in both groups. Results on psychosocial and medical aspects will be explained later on in this report. The columns 't-test/Mann-Whitney U or $\chi 2$' and 'P-value (2-sided) in table 1 are explained in the section 'Results' of this report.

Procedure

A convenience sample was chosen from the database with women in treatment at the cardiology department of Radboud UMC to perform a cross-sectional survey research. Based on the inclusion and exclusion criteria, as mentioned below, 77 women, suspected for CMD, and 77 women, diagnosed with CAD, have been selected and were age-matched. These selected women had received a call (see Appendix 3 for the Dutch version of the phone-scenario) from the researcher to ask for their willingness to take part in this research. If a woman assents to participation, an email had been sent with patient information in writing (see appendix 5 for the Dutch version of that email). Additionally a link for the online survey and unique identification number was sent in that email. In case of no response, at least three weeks after the email was sent, a second telephone call had been made with the respondent to remember her of her research participation. After that phone call the respondents got another two weeks (at least) to fill in the questionnaire.

[1] Higher educated: high general education, high vocational education, scientific education and post-academic educated.

Table 1 *Demographics and other characteristics of both groups*

Factors	CMD (N=64)	CAD (N=64)	Test statistic	P-value (2-side)
Demographics				
Age, mean (SD)	56.08 (6.40)	55.30 (6.26)	1891.50[2]	.46
BMI, mean (SD)	26.33 (5.47)	26.90 (4.85)	1828.30[2]	.30
High Educated[4,7], n (%)	28 (43.8)	12 (18.8)	9.31[3]	.00
Type of employment			1934.50[2]	.54
Paid employment, n (%)	35 (54.7)	33 (51.6)		
Volunteer work, n (%)	6 (9.4)	3 (4.7)		
No job or work, n (%)	23 (35.9)	28 (43.8)		
Marital status			2031.50[2]	.92
Married, n (%)	47 (73.4)	48 (75.0)		
Divorced, n (%)	12 (18.8)	9 (14.1)		
Widow, n (%)	1 (1.6)	3 (4.7)		
Single, n (%)	4 (6.3)	4 (6.3)		
Country of origin (Dutch)[5]				
Respondent, n (%)	59 (92.2)	64 (100)	5.20[3]	.02
Father, n (%)	58 (90.6)	63 (98.4)		
Mother, n (%)	59 (92.2)	59 (92.2)		
Psychosocial (mental)				
Perfectionism, mean (SD)[6]	3.03 (0.28)	2.93 (0.90)	0.671[1]	.50
Self-oriented, mean (SD)	57.60 (19.83)	50.29 (19.73)	2.08[1]	.04
Other-oriented, mean (SD)	38.54 (11.52)	40.68 (12.98)	-0.98[1]	.33
Socialprescrib., mean(SD)	40.42 (14.12)	40.70 (14.87)	-0.11[1]	.91
Totalscore (45-315), mean (SD)	139.49(35.77)	134.82 (41.56)	0.67[1]	.50
Cardiac Anxiety, mean (SD)	2.48 (0.51)	2.28 (0.49)	2.20[1]	.03
Totalscore(0-72), mean (SD)	44.60 (9.16)	41.12 (8.75)	2.20[1]	.03
Distress, mean (SD)	0.86 (051)	0.83 (0.55)	1903.00[2]	.59
Anxiety, mean (SD)	0.96 (0.55)	0.91 (0.57)	1925.00[2]	.66
Depression, mean (SD)	0.77 (0.58)	0.75 (0.61)	1944.00[2]	.62
Totalscore (0-42), mean (SD)	12.11 (7.08)	11.65 (7.67)	1903.00[2]	.59
Fatigue (severity), mean (SD)[6]	43.47 (10.66)	35.43 (12.95)	3.84[1]	.00
Totalscore(20-140), mean (SD)	90.10 (24.56)	77.47 (26.25)	2.81[1]	.01
Wellbeing, mean (SD)	2.81 (0.65)	3.21 (0.62)		
Mental, mean (SD)	3.20 (0.67)	3.46 (0.62)		
Physical, mean (SD)	2.44 (0.76)	3.00 (0.75)		
Physical(scale 0-100), mean (SD)	43.35 (22.72)	59.92 (22.01)	-4.23[1]	.00
Mental(scale 0-100), mean (SD)	51.49 (14.23)	56.35 (14.46)	1516.50[2]	.02
Coping style, mean (SD)	2.30 (0.27)	2.10 (0.36)	3.59[1]	.00
Maladaptive, mean (SD)	1.93 (0.29)	1.78 (0.39)	2.42[1]	.02
Adaptive, mean (SD)	2.59 (0.40)	2.34 (0.46)	1467.00[2]	.01
Self-distract., mean (SD)	2.88 (0.66)	2.32 (0.73)	1135.00[2]	.00
Active coping, mean (SD)	3.04 (0.63)	2.68 (0.69)	1461.00[2]	.00
Denial, mean (SD)	1.51 (0.61)	1.50 (0.55)	2018.50[2]	.88
Substance use, mean (SD)	1.51 (0.61)	1.50 (0.55)	2018.50[2]	.88
Emot.support, mean (SD)	2.41 (0.74)	2.15 (0.69)	1664.00[2]	.06
Lifestyle				
Alcohol a week, mean (SD)	1.14 (0.35)	1.14 (0.63)	1865.50[2]	.13
Current smoker, n (%)[4]	5 (7.8)	15 (23.4)	5.93[3]	.02
Former smoker, n (%)[4]	34 (53.1)	46 (71.9)	4.80[3]	.03

N = 127 – 128 [1]t-test [2]Mann-Whitney U [3]$\chi 2$ [4]yes=1, no=0 [5]Dutch = 0, non-Dutch =1 [6]Recalculated to 7-point score
[7]Higher educated: high general education, high vocational education, scientific education and post-academic educated.

Inclusion criteria:

- **research group:** women, between 40 and 65 years with persistent complaints of angina pectoris for at least three months, but without CAD as confirmed by coronary angiography (CAG) or coronary computed tomography angiography (CCTA) (Bugiardini & Bairey Merz, 2005; Park, Park, & Choi, 2015).
- **control group:** women, between 40 and 65 years, with CAD, with a stenosis of at least 50% of one or more coronary arteries, as confirmed by coronary angiography (CAG) or coronary computed tomography angiography (CCTA).

Exclusion criteria

- Inability to participate in questionnaire research (for instance: language barriers)
- Recent participation in a Mindfulness study in the Radboud UMC
- Oncologic problems during previous five years
- Serious psychiatric problems (psychosis or suicide attempt) during previous five years
- Serious cardiac valve problems

(See for the instruction for inclusion and exclusion of respondents Appendix 1.)

Ethical considerations

Both in the telephone call (to ask for participation) and in the written information (see appendix 4 for the patient information, sent in the invitation mail) participants were informed that they have no obligation to participate in the research and that participation has no consequence at all for their treatment in the hospital. At the same time the confidentiality of their data was explained. If the respondent wanted to fill in the online survey she firstly had to fill out the online informed consent (as part of the survey). This research did not belong to medical research in the context of the law for Medical Research, as confirmed by the committee of Medical Research of the Radboud UMC. The research proposal was approved by the ethical comity of the Faculty of Behavioral, Management and Science (BMS) of the University of Twente.

Measures and Variables

An online survey was built for this research in Qualtrics Software, containing existing scales for perfectionism, coping style, depression and anxiety, fatigue, physical and mental wellbeing and questions concerning other sociodemographic and medical topics.

Perfectionism

The Dutch version of the Multidimensional Perfectionism Scale of Hewitt was used, with permission of Kathleen de Cuyper (via email on 12 May 2015), to test for perfectionism (Hewitt & Flett, 2004; Hewitt & Flett, 1991). Earlier research among psychology students had shown a good internal consistence of the scale, Cronbach's α from 0.76 to 0.91 (de Cuyper, Claes, Hermans, Pieters, & Smits et al., 2014). The calculated reliability for this scale in this research was very good (Cronbach's alpha 0.92).

This questionnaire consists of three parts (Self-oriented perfectionism, Other-oriented perfectionism and Socially prescribed perfectionism), has 45 items in total and is scaled on a 7-points Likert scale (1= disagree, 7 = agree). Examples of statements on this list are 'When I am working on something, I cannot relax until it is perfect' and 'I strive to be the best at everything I do'. Possible scores are between 45 and 315, with a higher score indicating a higher level of perfectionism. To make the scores from this research comparable with scores from other research the measured scores are split up in the earlier mentioned three parts of the scale.

Coping style

For measuring someone's preferred coping style the Brief COPE was used (Carver, 1997). Because of the unavailability of a Dutch version of this questionnaire, it was manually translated (one-way: English to Dutch) for this research. Validity and reliability of this short questionnaire has not been calculated in cardiac patients. Therefore the measured internal consistency (Cronbach's alpha between 0.25 and 0.92) in research for Malaysian breast cancer patients serves as a validity guideline (Yusoff, Low, & Yip, 2010). The calculated reliability for this scale in this research was good (Cronbach's alpha 0.83).

The questionnaire consists of 28 items, scored on a 4-points Likert scale (1 = never, 4 = very much). Examples of statements on this list are 'I've been blaming myself for things that happened' and 'I've been concentrating my effort on doing something about the situation I'm in'. In this questionnaire 14 aspects of coping style (self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioural disengagement, venting, positive reframing, planning, humour, acceptance, religion, and self-blame) were measured, each with two questions. To calculate a general supposed form of maladaptive coping the scores on self-distraction, denial, substance use, behavioural disengagement, venting, and self-blame have been summed in this research (Choi et al., 2015; Kasi et al., 2012; Moore, Biegel & McMahon, 2011).

The five most relevant aspects for these groups were selected by performing a factor analysis with Eigenvalues between 1.08 and 3.83 (Warren-Findlow & Issel, 2010). Those five items deal

with the coping styles: self-distraction (item 1 and 19), active coping (items 2 and 7), denial (items 3 and 8), substance use (item 4 and 11), and the use of emotional support (item 5 and 15). Other factors highly associated with these first five items, are items concerning the coping styles venting, the use of instrumental support, planning and religion. Remarkable high factor loadings were found between instrumental and emotional support (0.74), planning and active coping (0.42), and between self-distraction and active coping (see table 2).

Table 2 *Factor loadings of different coping styles*

Factor	Self-distraction (O1)	Active coping (O2)	Denial (O3)	Substance use (O4)	Emot. support (O5)	Venting (O9)	Instrumental support (O10)	Planning (O14)	Religion (O27)
Self-distraction	1.00	0.37	0.12	0.27	0.15	0.15	0.09	0.18	0.30
Active coping	0.37	1.00	-0.10	0.23	0.27	0.10	0.21	0.42	0.05
Denial	0.12	-0.01	1.00	0.12	0.03	0.30	-0.05	-0.08	0.05
Substance use	0.27	0.23	0.12	1.00	0.20	0.01	0.11	0.16	0.25
Emot. support	0.15	0.27	0.03	0.20	1.00	0.16	0.74	0.20	0.15

Depression and anxiety

In this case of exploratory research it is especially important to make clear to what level women in each group suffer from anxiety or depression. Therefore these characteristics are measured with the Dutch version of the Hospital Anxiety and Depression Scale, HADS (Zigmond & Snaith, 1983). This questionnaire has 14 questions, 7 of them related to depression and 7 related to anxiety. The questionnaire is scored on a 4-point Likert scale. Examples of statements are: 'I can laugh and see the funny side of things' (0 = as much as I always could, 1= not quite so much now, 2= definitely not so much now, 3= not at all) and 'I get sudden feelings of panic' (0= not at all, 1= not very often, 2= quite often, 3= very often indeed). The HADS has been frequently used with cardiac patients and has a good validity with a mean Cronbach's α of 0.83 for anxiety and 0.82 for depression) (Bjelland, Dahl, Haug, & Neckelmann, 2002). The calculated reliability for this scale in this research was good (Cronbach's alpha of respectively 0.85 and 0.82 for the subscales depression and anxiety).

The score on depression was calculated by summing up the items 2, 4, 6, 8, 10, 12 and 14; the

score on anxiety by summing up the items 1, 3, 5, 7, 9, 11 and 13. The scores on depression and anxiety are each between 0 and 21, with a higher score indicating a higher level measured on that aspect. In the end the total HADS-score was calculated by summing up the scores on depression and anxiety with a possible score between 0 and 42.

Cardiac anxiety

Cardiac anxiety was measured with the Cardiac Anxiety Questionnaire (CAQ), as developed by Eifert et al. (2000). The Dutch version of this questionnaire consists of 18 questions on a 5-points Likert scale (0 = never, 4 = always). Examples of statements on this questionnaire are: 'I worry that doctors do not believe my chest pain/discomfort is real' and 'I avoid activities that make my heart beat faster'. The scale has a good internal validity, as measured in heart patients, with a total Cronbach's α of 0.83 (Eifert et al., 2000). The Dutch version of this questionnaire has a good mean internal validity in cardiac patients as measured in research of van Beek et al. (2012b) with a total Cronbach's α of 0.84. The calculated reliability for this scale in this research was a little lower (Cronbach's alpha 0.80). To calculate the total score on cardiac anxiety all sub scores were summed up, with a possible range 0-72, with a higher score indicating a higher level of cardiac anxiety.

Fatigue

To measure fatigue the Checklist Individual Strength (CIS) has been used (Vercoulen, Alberts, & Bleijenberg, 1999). This survey consists of 20 items, scored on a 7-point Likert scale (1 = no, that's not right, 7= yes that's right). Examples of statements on this questionnaire are: ' When I am doing something, I can keep my thoughts on it' and 'Physically I feel exhausted'. The CIS has an excellent reliability with a total Cronbach's α of 0.90, as measured in patients with the chronic fatigue syndrome (Vercoulen et al., 1994). The calculated reliability for this scale in this research was very good (Cronbach's alpha 0.87).

The total score for fatigue was calculated by summing up all items (range 20-140), with a higher score indicating a higher total level of fatigue. To compare scores on fatigue with scores in other research the scores on subjective fatigue (=fatigue severity) by summing up the items 1, 4, 6, 9, 12, 14, 16 and 20 (range from 8 to 56) with a score > 35 indicating severe fatigue.

Physical and mental wellbeing

The physical and mental wellbeing of the respondent was measured with the Short Form 12, SF-12 (Ware, Kosinski, & Keller, 1996). This questionnaire measures two components, known as the physical component (questions W1 to W5 and W8) and mental health (questions W6, W7 and W9

to W12). The raw scores on each dimension were summed up. A higher raw score per component and in common refers to a better health situation. Examples of questions on this questionnaire are: 'How much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?' and 'Have you felt downhearted and depressed?'. This questionnaire is frequently used in cardiac patients with a good reliability and validity (McBurney et al., 2002; Ware, Kosinski, & Keller, 1996). The calculated reliability for this scale in this research was very good with a total Cronbach's alpha of 0.90. To compare the scores of this research with scores in other research the 0-100 scores on physical and mental wellbeing were calculated bases on the measured raw scores (Ware, Kosinki, Turner-Bowker, & Gandek, 2002).

Other variables

Other questions in the online survey concern **demographical factors**: age, length and weight, marital status, type of employment, level of education and country of origin, **lifestyle**: former smoking ('How many years did you smoke?' and 'How many cigarettes, shags, cigars, and pipes did you smoke at mean a day?'), current smoking ('Do you smoke?' If yes: 'How many cigarettes, shags, cigars, and pipes do you smoke at mean a day?'), alcohol usage **(**'How many glasses of alcohol do you drink on an average week?''), **medical state** (questions like ''Do you have rheumatic complaints?' and 'Do you have regular pain, a burdensome, oppressive or heavy feeling on the chest during exertion?'), the **female reproduction system related** factors **(**questions like 'Did you have diabetes during one of your pregnancies?') **and familiar cardiac history** (two questions for cardiovascular problems in female relatives before the age of 65 years or in male relatives before the age of 60 years). See for more information concerning the questionnaire: Appendix 2 Digital Questionnaire).

In this research the distinguishing variable, responsible for assignment of a respondent to the research or control group, was based on the diagnosis that the patient got from her cardiologist: CMD or CAD. This logical variable ('CMD-or-CAD') is also used as dependent variable in the logistic regression tests of this research.

Data-analysis

Corrections to the data file

Missing values in the data file of the online survey were imputed with the Expectation Maximization Method (Dempster, Laird, & Rubin, 1977). Afterward the incorrectly imputed variables (like further questions that cannot be filled in, in case of answering an earlier question negatively), nullified menopausal data and incorrect levelling of some scores, with removal of the highest scores (Brief COPE and HADS scores) were manually corrected. Another correction, done in the data file, concerned the manual changing of incorrect ages in logical ages, for example if a stop age is before the belonging start age. Surveys filled in on paper by the respondents were carefully introduced by the researcher in the computer, with an extra remark with the date of manually entering.

Descriptive analysis

To show the characteristics of the respondents in both groups a few extra calculations has been done. The value of the BMI for each respondent was calculated and an extra variable high-educated (in case of high general education, high vocational education, scientific education and post-academic educated) was added. To distinguish CMD and CAD respondents from each other a new technical variable ‘type-of-problem’ was added with value ‘1’ in case of CMD and else ‘0’. Further in this report this technical variable will be described with the logical distinguishing variable (‘CMD-or-CAD’).

The mean scores for the ratio values were calculated by summing up the scores on that scale and dividing that sum by the number of questions. To compare the scores in this research with scores in other researches the total scores on the scales distress, fatigue and cardiac anxiety were calculated.

Inferential statistical analysis

To determine the 'Normal distribution' for each mean score, the shape of the distribution of a variable was compared with the Normal 'distribution curve' in the statistical program Statistical Package for the Social Sciences (SPSS) 22 of the 'International Business Machines Computer firma' (IBM). To confirm assumptions about Normal distribution a Kolmogorov-Smirnov analysis was performed for each variable.

For the scores, measured on a 5-point Likert scale instead of the original 7-point Likert scale (perfectionism and fatigue), the 7-point score has been recalculated, based on the 5-point score (Colman, Norris, & Preston, 1997). To measure differences in the scale means between both groups

an independent two-sided t-test was performed (Mann Whitney U signed-rank test in case of non-Normal Distribution of the data). For the nominal factors, the differences in frequencies between the groups were calculated with crosstabs (Pearson's Chi Square tests).

The elements of sub question two were tested by performing a one-tailed t-test for Normal distributed data (Mann Whitney Test in case of non-Normal distribution of the data). For the nominal factors, the differences between groups were found in the earlier performed Chi Square tests, as a Chi Square test is in essence a one-sided (or goodness-of-fit) test. The reason for these one-tailed tests was based on the direction of the assumptions in sub question two, supposing the mentioned variable being higher/lower in one group than in the other group. Statistical significance level for all tests was set at $p < .05$.

To test sub question three a binary Logistic Regression was performed for those factors significantly associated to the distinguishing variable ('CMD-or-CAD'). The significantly correlated medical factors angina, cardiac intervention and infarction are left out of scope of the logistic regression tests, as they are actually confounders (connected with the diagnosis CMD or CAD). At first the logistic regression was performed for significantly associated factors which probably would have existed long before the onset of the CMD (or CAD), like demographic, medical and personality factors. Secondly a logistic regression was performed for significantly associated factors of unknown date of origin compared with the onset date of CMD (or CAD), concerning situation-dependent feelings like depression and fatigue. Thirdly the, for this research most optimal model, has been calculated by performing a logistic regression with the significantly correlated factors from the former two logistic regression tests and controlling for the other correlated factors.

Lastly, to test sub question four, and determine a possible reinforcing effect of high scores on both anxiety and depression to the distinguishing variable a logistic regression, including the interaction between anxiety and depression, was performed, controlled for all supposed causal variables.

Linearity of the relationship between each covariate and the logit of the distinguishing variable ('CMD-or-CAD') for all logistic regression tests was checked by the Hosmer & Lemeshow goodness-of-fit test (Hosmer & Lemeshow, 2000). Multicollinearity between the associated factors was low, with a Variance Inflation Factor (VIF) < 1.5.

Results

To answer the research questions firstly the Normal distribution of all characteristic-variables has been inspected. Only the variables perfectionism, cardiac anxiety, fatigue, total and maladaptive coping, and physical wellbeing were normally distributed in this research.

Differences CMD group – CAD group

The first research question for differences between the CMD group and the CAD group can be answered positively: there are significant differences between both groups in this research. Significant differences were found on demographical, medical and psychosocial factors. See for more details, concerning the differences between groups, table 1 (general differences) and table 3 (medical differences).

Demographical and medical differences

CMD respondents were more frequently high-educated and fewer times of Dutch origin than CAD respondents. CMD respondents reported more complaints of angina, rheumatism and migraine, but less cardiac intervention and myocardial infarction than CAD respondents. The differences between the CMD and CAD group are more significant for the factors angina, cardiac intervention, myocardial infarction, and migraine ($p = .00$ to $.01$) than for the factor rheumatic complaints ($p = .04$).

Psychosocial differences

CMD respondents had higher scores on self-oriented perfectionism, coping style (total, maladaptive, adaptive, self-distraction, and active coping), fatigue, and cardiac anxiety. As the mean score on fatigue, in the CMD group, was above 35 (43.47) severe fatigue was indicated.

Table 3 *Medical differences between CMD and CAD respondents*

Factors[1]	CMD	CAD	Test statistic[2]	P-value (2-side)
Hypertension, n (%)	37 (57.8)	35 (54.7)	0.13	.72
Hypercholesterolemia, n (%)	24 (37.5)	35 (54.7)	3.80	.05
Thyroid complaints, n (%)	6 (9.4)	4 (6.3)	0.43	.51
Rheumatic complaints, n (%)	25 (39.1)	14 (21.9)	4.46	.04
Diabetes type 1, n (%)	0 (0.0)	0 (0.0)		
Diabetes type II[4], n (%)	9 (14.1)	10 (15.6)	0.06	.80
Treatment				
Diet, n (%)	5 (7.8)	0 (0.0)		
Medicines, n (%)	2 (3.1)	5 (7.8)		
Injections, n (%)	2 (3.1)	5 (7.8)		
Migraine, n (%)	36 (56.3)	21 (32.8)	7.12	.01
Onset in youth, n (%)	33 (51.6)	20 (31.3)		
Onset in menopause, n (%)	6 (9.4)	4 (6.3)		
Cardiac intervention, n (%)	5 (7.8)	50 (78.1)	64.56	.00
Myocardial infarction, n (%)	2 (3.1)	45 (70.3)	62.17	.00
Angina complaints, n (%)	53 (82.8)	22 (34.4)	30.95	.00
Dyspnea, n (%)	38 (59.4)	27 (42.2)	3.78	.05
TIA/CVA, n (%)	6 (9.4)	6 (9.4)	0.00	1.00
Familiar card. history, n (%)	45 (70.3)	41 (64.1)	0.57	.45
Female reproduction system related				
Start menstruation, mean(SD)	13.13 (2.14)	12.95 (2.24)		
Start menopause, mean (SD)	45.46 (9.83)	46.43 (8.89)		
Menopausal state, n (%)	54 (84.4)	52 (81.3)	0.04	.64
Early menopause, n (%)	11 (17.2)	9 (14.1)	0.20	.65
Menopausal complaints, n (%)	28 (43.8)	26 (40.6)	0.13	.72
Miscarriages, n (%)	19 (29.7)	17 (26.6)	0.39	.53
Pregnancy				
Hypertension, n (%)	23 (35.9)	25 (39.1)	0.13	.72
Diabetes, n (%)	4 (6.3)	5 (7.8)	0.12	.73
Treatment				
Diet, n (%)	3 (4.7)	2 (3.1)		
Medicines, n (%)	0 (0.0)	0 (0.0)		
Injections, n (%)	1 (1.6)	3 (4.7)		
Uterus/ovaria extirpation, n (%)	11 (17.2)	13 (20.3)	0.21	.65
Uterus extirpation, n (%)	8 (12.5)	11 (17.2)	0.56	.46
Ovary extirpation, n (%)	7 (10.9)	7 (10.9)	0.00	1.00

N = 99 - 128 [1]all factors (except start menstruation and menopause): 0 = nee, 1 = ja [2]all factors: $\chi 2$

Factors supposed to appear less (or more in case of anxiety & depression) in the CMD group

To test the assumptions posed in research question two, one-sided statistical tests were performed. These tests showed that the scores on depression and anxiety were not significantly higher in the CMD group, but about the same as in the CAD group. The scores on diabetes and familiar cardiac history also were not significantly lower in the CMD group, but about the same as in the CAD group. The assumptions on former and current smoking and quality of life were confirmed: in the CMD group were less former and current smokers and CMD respondents scored lower on physical and mental wellbeing, compared with the CAD group. See table 4 for more details about the performed one-sided tests for these topics. Most significant are the differences between the CMD and CAD group concerning physical and mental wellbeing (p = .00 to .01); for the dichotomous variables former and current smoking the significance was a little lower (p = .02 to .03).

Table 4 *Factors lower (or higher in case of anxiety and depression) in CMD group*

Factors	CMD	CAD	Test statistic	P-value (1-side)
Depression, mean rank	62.93	66.07	1947.50[2]	0.32
Anxiety, mean rank	63.48	64.51	1983.50[2]	0.44
Physical wellbeing, mean (SD)	2.44 (0.76)	3.00 (0.75)	-4.23[1]	0.00
Mental wellbeing, mean rank	55.96	70.80	1516.50[2]	0.01
Former smoking[4], n (%)	30 (46.9)	46 (71.9)	4.80[3]	0.03
Current smoking[4], n (%)	5 (7.8)	15 (23.4)	5.93[3]	0.02
Familiar history[4], n (%)	45 (70.3)	41 (64.1)	0.57[3]	0.45
Diabetes[4], n (%)	9 (14.1)	10 (15.6)	0.02[3]	0.80

N = 126 - 128 [1] = t-test [2] = Mann-Whitney U [3] = $\chi 2$ [4] yes=1, no=0

Detailed correlations between some factors and CMD or CAD

To create a model with factors correlated to CMD, at first the associated factors were split up in:

1. Relevant factors supposed to exist before the onset of CMD: demographical factors, most of the medical factors, former smoking and stable personality traits like coping style and perfectionism.
2. Other factors (probably arisen during or after onset CMD): current smoking, cardiac anxiety, fatigue, mental and physical wellbeing.

At first a logistic regression was performed for the first set of items: country of origin, high_educated, former smoking, rheumatism, migraine, self-oriented perfectionism, self-distraction, and active coping. Secondly a logistic regression test for the other variables was performed.

The distinguishing variable 'CMD-or-CAD' has been used as dependent variable in the logistic regression tests. In the first performed logistic regression test only the use of self-distraction as coping style appeared to be a significant covariate for CMD in this model (see table 5). This first created model explains 39% of the variance in CMD (Nagelkerke R^2 = .39). The Hosmer and Lemeshow test showed, with D (8) = 5.67, p = .69, a good fit of this logistic regression model with the real data.

Table 5 *Logistic regressions with factors supposed to exist before onset of CMD/CAD*[1]

Included	B (SE)	Odds ratio	P-value
Dutch country of origin[2]	-21.30 (16719.55)	0.00	1.00
High-educated[2, 3]	0.76 (0.49)	2.13	.12
Former smoking[2]	-0.61 (0.46)	0.55	.19
Rheumatism[2]	0.71 (0.48)	2.03	.14
Migraine[2]	0.79 (0.43)	2.20	.07
Self-oriented perfectionism	0.01 (0.01)	1.01	.46
Self-distraction	0.98 (0.33)	2.65	.00
Active coping	0.45 (0.37)	1.57	.22
Constant	16.52 (16719.55)	14995682.94	1.00

R^2 = .39 (Nagelkerke) N = 126 [1] CMD =1, CAD = 0 [2] 0 =no, 1 = yes

[3] High-educated: High general education, high vocational education, scientific education and post-academic educated

Secondly a logistic regression test with the mentioned other associated factors (current smoking, cardiac anxiety, fatigue, mental and physical wellbeing) was performed. These factors explain about a quarter of the variance in CMD (Nagelkerke's R^2 = .24), with only current smoking and physical wellbeing remaining significantly associated with CMD (see table 6). The Hosmer and Lemeshow test showed with D(8) = 4.98, p = .76 a good fit between this model and the real data. Remarkable fact to mention is the change of the association of mental wellbeing with CMD from negative to positive after adding physical wellbeing to the model. The relationship of cardiac anxiety with CMD changed from positive to negative after adding both physical wellbeing and fatigue to the model.

Table 6 *Logistic regression with factors supposed to origin during or after onset of CMD/CAD*[1]

Included	B (SE)	Odds ratio	P-value
Current smoking[2]	-1.34 (0.60)	0.26	.03
Cardiac anxiety	-0.01[3] (0.49)	0.99	.98
Fatigue	0.04 (0.02)	1.04	.08
Mental wellbeing	0.34[4] (0.42)	1.41	.41
Physical wellbeing	-0.83 (0.41)	0.44	.04
Constant	1.10 (2.55)	3.01	.67

R^2 = .24 (Nagelkerke) N = 125 [1] CMD =1, CAD = 0 [2]yes =1, no = 0 [3]negative relationship influenced by physical wellbeing and fatigue [4]positive relationship influenced by physical wellbeing

In the third logistic regression test only those factors were taken which remained significant in the two former logistic regression tests: self-distraction, current smoking and physical wellbeing. The model was controlled for the other factors associated with CMD (high-educated, former smoking, rheumatism, migraine, country of origin, self-oriented perfectionism, active coping, cardiac anxiety, fatigue and mental wellbeing) by adding them in a second block in the logistic regression.

The first part of the test (with only the factors self-distraction, current smoking and physical wellbeing), leading to model 1 in table 7, showed an explained variance for CMD of 35% (Nagelkerke's R^2 = .35). The Hosmer and Lemeshow test showed with D(8) = 3.34, p = .91 a good fit between this first model and the real data. Self-distraction and physical wellbeing were significant covariates ($p < .01$) for CMD in this first model (see table 7, model 1).

The second part of the test, the addition of the other factors (high educated, former smoking, rheumatism, self-oriented perfectionism, active coping, cardiac anxiety, fatigue and mental wellbeing) in a second block to control for them, leading to model 2 of table 7, explained 47% of the variance in CMD (Nagelkerke's R^2 = .47). This second model showed with D(8) = 8.65, p = 0.37 a good fit between this model and the real data. Self-distraction remains the only significant covariates ($p < .05$) for CMD during this whole logistic regression test.

Table 7 *Logistic regression with factors significantly correlated to CMD/CAD[1] in earlier tests, controlled for other significant factors.*

Parameter	Model 1	Odds ratio	Model 2	Odds ratio
Current smoking[2]	-1.31(0.67)	0.27	-1.17 (0.75)	0.31
Self-distraction	1.25** (0.34)	3.49	1.04* (0.37)	2.82
Physical wellbeing	-1.00** (0.31)	0.37	-0.85 (0.50)	0.43
Constant	-0.40 (1.18)	0.67	16.72 (21562.98)	18170193.39
High educated[2]			0.86 (0.54)	2.37
Former smoking[2]			-0.61 (0.51)	0.55
Country of origin			-20.940 (21562.98)	0.00
Rheumatism[2]			0.44 (0.52)	1.56
Migraine			0.59 (0.48)	1.81
Self-oriented Perfectionism			0.01 (0.01)	1.01
Active coping			0.29 (0.41)	1.34
Cardiac anxiety			-0.11[3] (0.59)	0.90
Fatigue			0.02 (0.03)	1.02
Mental wellbeing			0.50[4] (0.50)	1.65
N = 123	R^2 = .35 (Nagelkerke)		R^2 = .47 (Nagelkerke)	

* p < .05 ** p < .01 [1]CMD =1, CAD = 0 [2] 0 = no, 1 =yes [3]negative relationship influenced by physical wellbeing and fatigue [4]positive relationship influenced by physical wellbeing

Interaction effect anxiety & depression on CMD/CAD

As no significant correlation had been found between CMD and anxiety and depression (neither in the tests for measuring differences between groups, nor in the performed correlation tests, (see Appendix 6) anxiety and depression were not added as interaction variables in a logistic regression test, as originally described in the method section of this report.

Discussion

Significant differences between groups

From this research can be concluded that women, suspected for CMD, form a specific group of cardiac patients compared with women with CAD. CMD respondents differ from CAD respondents on medical factors, like migraine and rheumatism. Probably more interesting, with respect to a future determination of their need for care and guidance, are the differences found between both groups on psychosocial and lifestyle factors, like coping, wellbeing, self-oriented perfectionism, fatigue, cardiac anxiety, former and current smoking.

The factor most strongly associated with CMD, remaining significant in all logistic regression tests, is the coping style self-distraction. Physical wellbeing was also a significant covariate (together with self-distraction), until the addition of other associated factors to the model. Current smoking was only a significant covariate for CMD without the addition of the covariate self-distraction. See table 7 for details concerning the covariates of CMD.

The CMD respondents in this research reported more coping in general and especially the use of the coping style self-distraction than the CAD respondents. Self-distraction as coping style is one of the coping style-elements most used in stressful situations, even by healthy people (Sreeramareddy et al., 2007). The strong correlation between CMD and self-distraction probably shows that the CMD respondents cope with difficult situations, like stress (caused by their medical and psychosocial complaints and their uncertain medical future) by the use of self-distraction.

However, the CMD respondents in this research scored twice as low on the coping style self-distraction, than women in other research with breast cancer did, ten weeks after (Yusoff, Low, & Yip, 2010). A possible explanation for the higher use of self-distraction by breast cancer patients than by the CMD respondents in this research could be the higher level of life threatening stress in breast cancer patients than in CMD patients.

CMD respondents in this research scored significantly lower on wellbeing and quality of life, especially on the physical part of it. Questions for physical wellbeing in the online survey of this research concerned mostly the limitations, caused by their cardiac disease, respondents experience in their daily activities. Apparently the CMD respondents experience more physical limitations of their disease than the CAD respondents, probably because of no optimal treatment for CMD and consequently the remaining of their complaints and restrictions caused by the complaints.

The CMD respondents in this research seem to score equally low on physical and mental wellbeing as CAD patients in earlier research, perhaps because of the shorter time of measuring

after discharge from hospital in that research (McBurney et al., 2002). Compared with most other chronically diseased, like former cancer patients and patients with chronic rheumatic diseases, CMD respondents reported a better quality of life (Annunziata et al., 2015; Kreis et al., 2015). Only patients with HIV in The Netherlands and patients with inflammatory bowel disease in other research seem to score a little higher than the CMD respondents in this research (McCombie, Mulder, & Gearry, 2015; Oberjé, Dima, van Hulzen, Prins, & de Bruin, 2014).

Overall the findings in this research support the expectation of a lower Quality of Life in CMD patients than in CAD respondents, but not the expected higher impact on mental wellbeing in CMD compared with other chronic diseases (Radico, 2014; Hsieh, 2007; Johnson, 2006; Vasheghani-Farahni). Apparently the physical aspect of wellbeing and Quality of Life, one of the significant covariates of CMD as found in this research, form the greatest burden for CMD respondents. Probably the higher use of self-distraction as coping style for handling this burden helps them stabilizing their mental aspect of wellbeing.

Other psychosocial differences in CMD respondents compared with CAD respondents were their higher scores on self-oriented perfectionism, severity of fatigue and cardiac anxiety. This research was, as far as we know, the first to investigate the personality trait perfectionism for the differences in scores between women with CMD and women with CAD. No differences were found between the CMD and CAD group on the subscales ‘other oriented’ and ‘socially prescribed’ perfectionism, but the CMD respondents scored significantly higher on self-oriented perfectionism.

Less research has been done for self-oriented perfectionism in chronically disabled. The scores of the CMD respondents in this research seem to be lower than the scores of pain patients in other research, but higher than the scores of under graduated psychology students in another investigation (de Cuyper et al., 2014; Hewitt, Flatt, & Mikail, 1995). Considering perfectionism as a stable personality trait, the differences in scores between students in earlier research and CMD respondents in this research cannot be explained by age-differences between those groups. Future research should search for a possible correlation of pain; pain perception and self-oriented perfectionism. Perhaps CMD patients have lower levels of pain or pain-perception than pain patients and those pain-levels may somehow be associated with higher levels of self-oriented perfectionism.

The higher scores on cardiac anxiety of the CMD respondents in this research, compared with the CAD respondents, correspond with findings in earlier research of patients with cardiac complaints and without coronary artery calcification (van Beek et al., 2012a; Marker, Carmin, & Ownby, 2008). The higher level of fear for heart-related events, sensations, and functioning in

CMD respondents can be explained by the fact they did not receive cardiac interventions for their cardiac complaints, as the CAD respondents and stayed in an insecure medical state, leading to elevated levels of cardiac anxiety (Eifert, Zvolensky, & Lejuez, 2000; Hoyer et al., 2008).

Another significant difference found in this research was the higher score on fatigue in CMD respondents compared with the CAD group. Remarkably, CMD respondents in this research seem to have a lower score on fatigue severity than patients, with chronic Whiplash Associated Disorders 24 hours post exercise, had in other research (Van Oosterwijck, Nijs, Meeus, Van Loo, & Paul, 2012). The scores on fatigue severity for CMD respondents in this research were equal to the scores of patients with amyotrophic lateral sclerosis (ALS) and fatigue, but higher than scores on fatigue of patients in other investigations with incurable cancer, Crohn's disease and Chronic Obstructive Pulmonary Disease (Panitz, Kornhuber & Hanisch, 2015; Peters et al., 2011; Peters, Goedendorp, Verhagen, van der Graaf, & Bleijenberg, 2014; Vogelaar et al., 2013).

Overall the scores on fatigue of the CMD respondents in this research seem higher than or equal to the scores on fatigue in many other chronically diseased in earlier research. No decisive explanation can be found for the higher scores on fatigue in CMD respondents in this research, compared with the fatigue-scores of patients with other types of chronic diseases. Future experimental research is advisable to compare the scores on fatigue in CMD patients with those scores of other chronically diseased under the same conditions.

Medical differences of the CMD respondents compared with the CAD respondents were: the higher prevalence of self-reported rheumatism and migraine in the CMD group. No other medical differences have been found between the CMD and CAD group in this research. Although complaints of migraine and rheumatism were more prevalent in the CMD respondents than in the CAD respondents in this research; this finding can be confounded by an information or conformation bias, as CMD respondents are frequently asked for rheumatism and migraine by their cardiologists. Being asked for some diseases can make the respondents think they should actually have those diseases, leading them to answer questions for those topics in a desirable way.

Regarding demographical differences a significant association exists between on one hand the high level of education and non-Dutch origin and on the other hand CMD. Because of the relatively small samples in this research and the low level of respondents of non-Dutch origin more research for differences between CMD and CAD patients, caused by different countries of origin, must be performed.

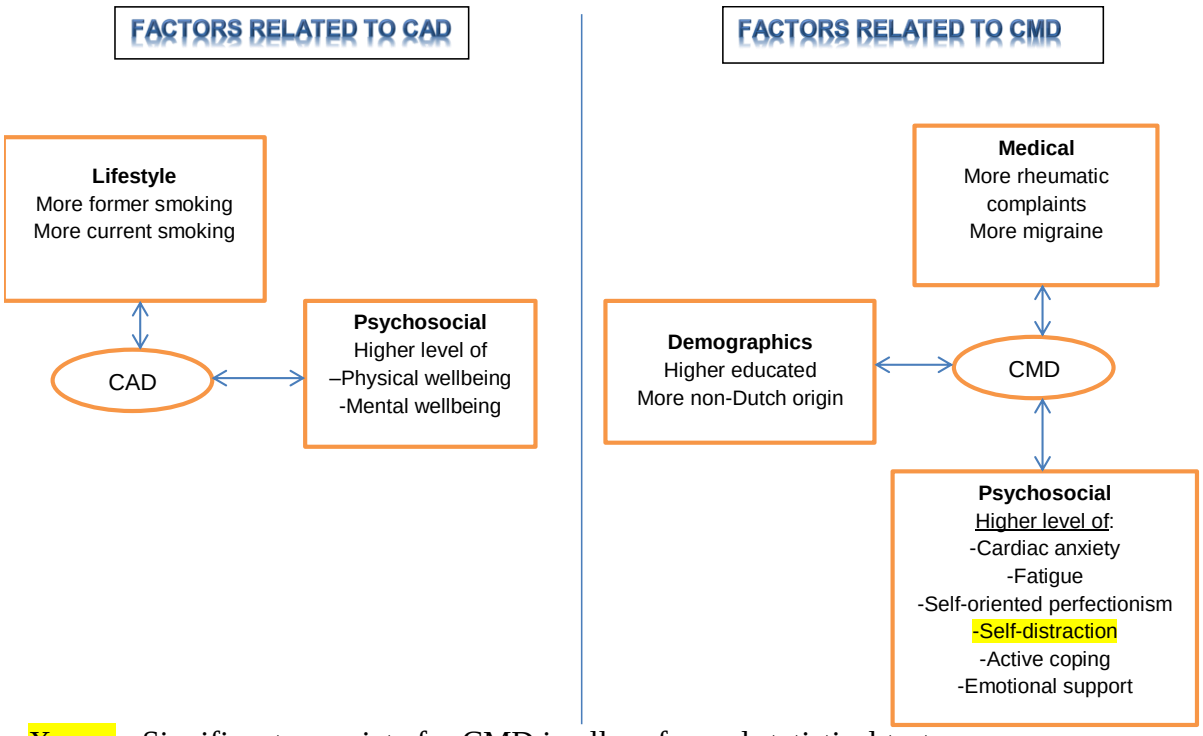
The higher level of education in the CMD group, compared with the CAD group, is relevant.

Even compared with the general Dutch female population between 45 and 65 years, as measured in the period between 2001 and 2012, the CMD respondents of this research are higher educated (Centraal Bureau voor de Statistiek, 2013). To confirm the finding of a higher level of education in women with CMD, compared with women with CAD and healthy women, more detailed research is necessary with a large sample of Dutch women with and without inexplicable complaints of angina.

Last but not least, current smoking was significantly less prevalent in CMD respondents than in CAD respondents. The CMD respondents were also less frequently former smokers than the CAD respondents. In addition, smoking seems less prevalent among the CMD respondents in this research, than among the common Dutch population, as measured in 2014 (Verdurmen, Monshouwer, & van Laar, 2015). Overall this finding may confirm the claim of Rubinshtein et al. (2010) and Vashegahani-Farani et al. (2013) that (current) smoking behaviour is more associated, as risk factor, with CAD than with CMD.

See figure 2 for an overview of the variables associated with CMD or CAD, found in this research.

Figure 2 *Different factors related to CAD-CMD*



Xxxxx - Significant covariate for CMD in all performed statistical tests.

Similarities between groups

Based on current research the elements diabetes, hypertension, hypercholesterolemia and elevated BMI of the Framingham Risk Score (FRS) were equally prevalent among CMD and CAD respondents. The other elements of the FRS (current and former smoking) were less prevalent among CMD than among CAD respondents in this research.

Compared with the general Dutch female population in 2012 only a small percentage of the total sample of this research has overweight (BMI between 25.0 and 29.9), but a larger percentage of this sample is obese (BMI above 30.0), as demonstrated by their BMI-scores (Nationaal Kompas Volksgezondheid, 2012). The high percentage of obese respondents might confirm obesity as a major risk factor for both CMD and CAD (Eckel & Krauss, 1998).

The reporting between CMD and CAD respondents on familiar cardiac history and hypertension are comparable to each other. Earlier research confirms the resemblance of the finding in this research on family history, so the expectation of a lower association of familiar cardiac history in CMD than in CAD patients can neither be confirmed by this research nor by earlier research (Asbury, Creed, & Collins, 2004; Rubinshtein et al., 2010; Vashegahani-Farani et al., 2013). Concerning hypertension the CMD respondents seem to report more frequently hypertension than the total Dutch society in 2012, so perhaps hypertension is as much a potential risk factor for CMD as it is for CAD (Blokstra & van Bakel, 2012; D'Agostino et al., 2008).

No significant differences were measured in this research between the CMD and CAD groups for their scores on depression and anxiety, only on cardiac anxiety. This difference might be explained by the differences in questions of both scales. The HADS scale measures depression, general anxiety and distress and seems to focus on mental feelings (like feeling tense, worried and restless); the CAQ measures heart related anxiety and seems to focus on feelings related to physical experiences (like pain, heartbeat and transpiration).

In addition, according to the cut off scores on the total HADS score (score >= 11) both the CAD and the CMD respondents in this research are suspicious for depression and anxiety (Bjelland, 2002; Zigmond & Snaith, 1983). However CMD respondents in this research seem to score lower than women and patients over the age of 60 years with cardiac problems in earlier research, but a little higher than CAD patients in other research (Ben-Noun, 1999; Cohen, Daniela, Yalonetsky, Gagin, & Lorber, 2010; Emons, Sijtsma, & Pedersen, 2012; Ulvik et al., 2008). The finding in this research seems to contradict the expected significant higher correlation of general anxiety and depression with CMD than with CAD, but not the association of depression and anxiety with both CMD and CAD (Ogden, 2012; Johnson et al, 2006; Doerfler & Paraskos, 2004).

Critical notes, strengths of this research and recommendations

Risk of failures and blurring the results

There are four types of CMD, one of these types could hidden have existed in the CAD respondents in this research and could have blurred the results of this research (Camici & Crea, 2007). Besides, the manual entering of the online survey by the researcher, for all respondents without a personal computer, elevates the chance of failures in this research. In addition, some questions in the survey may have led to misunderstanding by the respondents, especially in questions with negations in them.

Other possible sources of failures were the recalculation of the 5-point scores on perfectionism and fatigue to 7-point scores and the recoding of unexpected automatically assigned codes to answer-items. Also the expectation maximization of the missing values led, in this research, to unwanted outcomes in the data file, like levelling the results on some scales and the 'nullification' of the menopausal complaints.

Risk of bias

A memory bias could have blurred the results in this research, in case of responding on questions about former complaints from a perspective in the past. Another form of bias may exist around the participation and drop out of the research as women, being not interested in or too busy for participation, may have other characteristics than the current respondents. Because of the low dropout rate this form of risk will only be very small.

The self-reporting of all questions may have led to a confirmation bias as respondents may give desirable answers instead of true answers. Validation of the given medical answers with existing medical records should have strengthened this research. Furthermore, this research contains a time intensive questionnaire. Some respondents may have started the questionnaire but are automatically expelled in the end, because they did not end the online survey within the reserved time.

There may be a selection bias in this research caused by the sample of CMD respondents chosen from the database of cardiologists specialized in women-specific cardiology. Probably only the most active part of all CMD patients comes, from all over the country, to consult those cardiologists in the Radboud UMC. Therefore the sample of those CMD respondents in this research may have some characteristics (for example assertiveness or perseverance) they do not share with other CMD patients, who do not seek additional help for their complaints. Last form of sample bias may be originated in the removal of respondents who left many questions of the online survey blank.

Strong points of this research

To our best knowledge is this research the first to compare women in their middle-ages, suspected for CMD, with age-related women diagnosed with CAD. The research was performed by an independent researcher, not in service of the Radboud UMC. This researcher was both online (via email) and by phone available for the participants to answer their questions or note their remarks.

This research contains many topics, so the results give a wide overview of the characteristics of the participants. In addition, this research has been done from both medical and psychological perspective, giving a broad view, compared with research, only medically or psychologically focussed.

Although the questionnaire was very extensive, it could be filled in by the respondents on their own computers (or on a written copy), in their home situations and in their own pace. Respondents were randomly selected from the available medical databases and were age-matched between the groups. This form of sampling did produce an equal spread of participants in both groups concerning their ages.

Future research should be focused on the specific needs for help and care in women with CMD, based on their specific characteristics found in this research.

Future research could be focussed on the topics:

- Migraine and rheumatic complaints: in this research both aspects were more prevalent among CMD respondents than among CAD respondents. Confirmation of the existence of migraine and rheumatism, in an independent way (for example by blood tests), to prevent a bias, is advisable.
- Country of origin: To confirm the effect of country of origin on the individual characteristics of women with CMD, future research with larger samples and more respondents of non-Dutch origin is necessary (Sundaram et al., 2005).
- Level of education: In this research a higher level of education was found in the CMD group, compared with the CAD group. Future research with larger samples of Dutch women with and without unexplainable angina should confirm the higher level of education in CMD patients, compared with CAD patients and healthy women.
- Fatigue scores in CMD patients compared with fatigue scores in other types of chronically diseased: experimental research is advisable to measure scores on fatigue in different types of patients under the same circumstances.
- Correlation between Fatigue and Quality of Life in CMD patients: in this research CMD respondents scored significantly lower on physical and mental wellbeing, implicating a lower Quality of Life, and they had also a higher score on fatigue than the CAD respondents. This finding seems to confirm the correlation between fatigue and quality of life found in earlier research (Casillas et al., 2006). As the search for this correlation was out of scope in this research, further research for this topic is advisable.
- Cardiac anxiety: CMD respondents in this research scored significantly higher on heart

focused anxiety than CAD respondents in this and earlier research. As the scores of the CMD respondents on depression and general anxiety were not significantly different from those scores in CAD respondents, interesting point for future research is to elaborate on the reason of the high scores on cardiac anxiety in CMD patients.

- Self-oriented perfectionism: In this research a significant positive relationship was found between CMD and self-oriented perfectionism. As this research was the first to measure perfectionism in women with CMD this finding needs to be confirmed in future research. Perhaps the self-oriented perfectionism could be a future entrance for health professionals to support women coping with CMD and accepting the disabilities, like cardiac anxiety and fatigue, caused by their disease.
- Correlation between pain (perception) and self-oriented perfectionism in chronically diseased: further research should try to explain the findings in this research of higher levels of self-oriented perfectionism in CMD respondents compared with healthy students but lower levels compared with pain patients.

Conclusion

As there were significant differences displayed in this research between midlife women suspected for CMD and age-matched women with CAD, women with CMD form a specific group of patients with their own characteristics. Although there were some significant medical differences in CMD patients compared with CAD patients, patients in both groups differ especially considering their psychosocial characteristics.

Creating a profile of the psychosocial aspects of midlife women with CMD, based on the findings of this research, shows a group of highly educated women, who seem to pose themselves high demands. Their preferred style of coping with difficult situations is most of all self-distraction. Complaints possible related to their cardiac condition, like angina, rheumatism, migraine, fatigue and cardiac anxiety, accomplished with limitations in daily activities, seem to burden them most, as displayed by a low level of physical and mental wellbeing. In addition, women suspected for CMD seem to be less frequently former and current smokers than women with CAD.

Overall the psychological aspects related to their cardiac disease seem to play a more important role in women with CMD, than in women with CAD. More detailed research is needed to investigate the needs for help and care of midlife women with CMD. Those needs will probably differ from the needs of age-related women with CAD, as consequence of their different psychosocial characteristics.

Used abbreviations

BMI	Body Mass Index
BMS	Behavioral, Management and Science
CAD	Coronary Artery Disease
CAG	Coronary Angiography
CAQ	Cardiac Anxiety Questionnaire
CCTA	Coronary Computed Tomography Angiography
CIS	Checklist Individual Strength
CMD	Coronary Microvascular Dysfunction
CVA	Cerebral Vascular Accident
FRS	Framingham Risk Score
FSS	Functional Somatic Syndrome
HADS	Hospital Anxiety and Depression Scale
ICD	International Classification of Diseases and Related Health Problems
IHD	Ischemic Heart Diseases
MET	Metabolic Equivalent
SES	Social Economical Status
SF-12	Short Form 12 (measuring physical and mental wellbeing)
SPSS	Statistical Package for the Social Sciences
TIA	Transient Ischemic Attack
UMC	University Medical Centre
VIF	Variance Inflation Factor

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Appendix 1: Work instruction for in- and exclusion of respondents

Inclusion CAD-respondents:

-select women between 40 and 65 years with a 50% stenosis of one or more coronary artery as confirmed by CAG or CCTA at maximum one year ago.

-ascertained stenosis may be released by Percutaneous Coronary Intervention (PCI) or **Coronary** Artery Bypass Grafting **(**CABG).

Exclusion CAD-respondents:

- delete respondents with serious cardiac valve problems
- delete respondents with oncological problems between 2010 and 2015
- delete respondents with inflammation rheumatism between 2010 and 2015 (arthritis, polyarthritis or morbus Bechterew).
- delete respondents with serious psychiatric problems (psychosis of suicide attempt) between 2010 and 2015.
- delete respondents known as 'care and cure avoiders' or who are for other reasons not capable in participating in questionnaire research.

Inclusion CMD-respondents:

-select women, between 40 and 65 years, with persistent complaints of angina pectoris during at least three months.

-without a 50% stenosis of one or more coronary artery, as confirmed by CAG or CCTA at maximum one year ago.

Exclusion CMD-respondents:

- delete respondents with serious cardiac valve problems
- delete respondents with oncological problems between 2010 and 2015
- delete respondents with inflammation rheumatism between 2010 and 2015 (arthritis, polyarthritis or morbus Bechterew).
- delete respondents with serious psychiatric problems (psychosis of suicide attempt) between 2010 and 2015.
- delete respondents known as 'care and cure avoiders' or who are for other reasons not capable in participating in questionnaire research.

Appendix 2: Digital Questionnaire

Survey 12-08-2015.pdf

Appendix 3: Protocol Phone call to respondent (in Dutch)

NB bellen alleen op doordeweekse dagen tussen 9 en 20 uur.

Goedemorgen/middag mevrouw…
Komt het gelegen dat ik u even een korte vraag stel?

Zo nee: Zou ik u op een ander moment terug mogen bellen? Wanneer zou het u goed uitkomen als ik bel?

Zo ja:
Ik ben student psychologie en werkzaam als onderzoeker van de afdeling cardiologie van het Radboud UMC. Ik bel om uw medewerking te vragen voor een vragenlijstonderzoek dat u thuis op uw eigen computer kunt doen. Het gaat om een onderzoek naar welke factoren een rol spelen bij hartproblemen bij vrouwen. Zoals u waarschijnlijk weet is er tot voor kort vooral veel onderzoek gedaan naar hartproblemen bij mannen en veel minder bij vrouwen. Toch is het belangrijk, omdat vrouwen nu eenmaal anders in elkaar zitten dan mannen, dat er meer kennis komt over vrouwen in relatie tot hartklachten. Zeker bij vrouwen die problemen met de (grote/kleine) bloedvaten van het hart hebben is meer onderzoek nodig. Daarom zou u ons heel erg helpen als u een uurtje van u tijd zou willen besteden aan het invullen van deze vragenlijst. Deze vragenlijst is speciaal voor dit doel ontwikkeld, in samenspraak met de vrouwencardiologen van het Radboud ziekenhuis, doctor Elias en professor Maas.

Of u al dan niet uw medewerking aan het onderzoek verleent, heeft uiteraard voor u geen consequenties voor uw behandeling op de afdeling cardiologie. Als u mee doet helpt u wel mee aan het in kaart brengen van hartproblemen bij vrouwen. Hoe meer inzicht in belangrijke factoren, hoe meer de zorg en begeleiding uiteindelijk op u en andere vrouwen kan worden afgestemd!

Hebt u zin en tijd om uw medewerking te verlenen aan dit onderzoek?

Zo ja:
Wat is uw email adres waar ik de uitnodiging voor het onderzoek heen kan sturen of
Klopt het emailadres dat ik van u heb nog (<noem bij ons bekend emailadres>) en kan ik u op dat mailadres de uitnodiging voor dit vragenlijstonderzoek sturen

Vandaag ontvangt u van mij een mailtje met daarin een link naar het online onderzoek en nog nadere schriftelijke uitleg over het onderzoek. In dat mailtje staat ook uw persoonlijk identificatienummer, het is belangrijk dat u dat goed invult in de vragenlijst! Mocht u rond het invullen van de vragenlijst of het onderzoek nog vragen hebben kunt u mij altijd bellen of mailen. U vindt mijn gegevens en telefoonnummer in de mail die ik u ga sturen.

Vindt u het goed als ik u eventueel over een week of drie nog een keer bel, mocht u het onverhoopt vergeten de vragenlijst in te vullen?

Hebt u op dit moment nog vragen, mevrouw?
Dan dank ik u heel hartelijk voor uw tijd en toegezegde medewerking.
Dag mevrouw.

Zo nee:
Dat is heel jammer om te horen. Toch wil ik u bedanken voor uw tijd en u een fijne dag toe wensen.
Dag mevrouw.

Appendix 4: Patient information (in Dutch)

Radboud universitair medisch centrum
Afdeling Cardiologie
Postbus 9101, 6500 HB Nijmegen
Huispost 616
Geert Grooteplein Zuid 10
Route 670
T (024) 3614533
Mw. Prof. Dr. A.H.E.M. Maas
Angela.maas@radboudumc.nl
www.radboudumc.nl

Informatiebrief onderzoek:

Verschil in factoren samenhangend met disfunctioneren van de grote versus de kleine bloedvaten van het hart bij vrouwen

Hierbij willen wij u graag informeren over een wetenschappelijk onderzoek naar het verschil in factoren bij vrouwelijke patiënten met hartziekte in de grote vaten versus de kleine bloedvaten van het hart.

In deze studie willen wij onderzoeken of de factoren voor ziekte van de grote kransslagaders van het hart verschillen van de factoren voor ziekte aan de allerkleinste vaatjes die het hart van bloed voorzien. Het onderzoek is gericht op vrouwen omdat disfunctioneren van de kleinste vaatjes vaker bij vrouwen dan bij mannen voorkomt.

Voordat u een beslissing neemt om aan het onderzoek deel te nemen, is het belangrijk om meer te weten over het onderzoek. Deze informatiebrief kan u daarbij helpen.

Hebt u na het lezen van de brief nog vragen, dan kunt u terecht bij één van de onderzoekers of bij een onafhankelijke arts.

Disfunctioneren van de kleinste vaatjes van het hart:

Veel vrouwen op middelbare leeftijd hebben klachten van pijn op de borst vanuit de kleinere haarvaten in de hartspier. Dit heet **micro vasculaire angina pectoris** en wordt veroorzaakt door veroudering in de kleine haarvaatjes van de hartspier. Er zijn dan (nog) geen belangrijke vernauwingen aanwezig in de grotere kransvaten. Meestal ontstaan deze klachten na de overgang, als de vaatverwijdende effecten van de oestrogene hormonen op de kleine haarvaatjes verdwijnen.

Disfunctioneren van de grote vaten van het hart.

Dit wordt meestal veroorzaakt door aderverkalking, ook wel atherosclerose genoemd, wat belangrijke vernauwingen in de grote vaten van het hart geeft. Hierdoor krijgt het hart te weinig zuurstof bij inspanning en ontstaat er pijn op de borst (angina pectoris).

Wat is het doel van het onderzoek?

Over factoren bij afwijkingen van de grote vaten van het hart is al veel bekend. Dit geldt echter niet voor factoren die kunnen samenhangen met afwijkingen aan de kleine vaatjes van het hart. Doel van dit onderzoek is dus duidelijk krijgen welke factoren een rol spelen bij vrouwen met afwijkingen in de kleine vaatjes rond het hart en in hoeverre dit anders is dan bij vrouwen met afwijkingen in de grote vaten van het hart.

Hoe wordt het onderzoek uitgevoerd?

Als u mee wilt doen aan het onderzoek, wordt u op verzoek van uw behandelende cardioloog gevraagd online een aantal vragenlijst in te vullen, wat ongeveer 30 minuten tijd in beslag zal nemen.

Wat zijn mogelijke voor- en nadelen van deelname aan dit onderzoek?

Het invullen van de vragenlijsten zullen tijd en inzet van u vergen. Mogelijk levert het onderzoek resultaten op waardoor we beter inzicht krijgen in de factoren voor met name ziekte van de kleinste vaatjes van het hart, een ziekte waar we momenteel nog weinig van weten. We hopen hiermee vrouwelijke hartpatiënten in de nabije toekomst beter te kunnen helpen

Welke bijwerkingen kunt u verwachten?

Aan dit onderzoek zijn geen directe risico's verbonden
Deelname aan het onderzoek impliceert ***geen verhoogd risico*** voor de deelnemers.

Wat gebeurt er als u niet wenst deel te nemen aan dit onderzoek?

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u besluit niet mee te doen, hoeft u verder niets te doen. U hoeft niets te tekenen. U hoeft ook niet te zeggen waarom u niet wilt meedoen. Als u patiënt bent, krijgt u gewoon de behandeling die u anders ook zou krijgen. Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen. Ook tijdens het onderzoek.

Bent u verzekerd wanneer u aan het onderzoek meedoet?

Omdat aan dit onderzoek geen risico's verbonden zijn, is er een ontheffing verleend van de verzekeringsplicht.

Wat gebeurt er met uw gegevens?

Uw gegevens worden vertrouwelijk behandeld en ze worden alleen gebruikt voor dit onderzoek. Gegevens die wij tijdens het onderzoek over u verzamelen, blijven geheim. Uw gegevens krijgen een code, uw naam wordt weggelaten. Alleen de onderzoekers weten welke code u hebt. Wij zijn wettelijk verplicht uw onderzoeksgegevens 15 jaar te bewaren.

Wordt uw huisarts en/of behandelend specialist geïnformeerd bij deelname?

Uw huisarts en/of behandelend specialist wordt niet door ons geïnformeerd over uw deelname aan het onderzoek. Als u dat op prijs stelt, kan dit in samenspraak met u gebeuren.

Zijn er extra kosten/is er een vergoeding als u besluit aan dit onderzoek mee te doen?

Aan het onderzoek zijn geen kosten verbonden en u krijgt geen vergoeding voor deelname aan het onderzoek.

Welke medisch-ethische toetsingscommissie heeft dit onderzoek goedgekeurd?

De Commissie Mens gebonden Onderzoek Regio Arnhem-Nijmegen heeft ontheffing verleend van goedkeuring van dit onderzoek aangezien het niet onder de wet medisch onderzoek valt.

Wilt u verder nog iets weten?

Als u na het lezen van deze brief nog vragen heeft of meer informatie wilt, dan kunt u contact opnemen met Anneke Lier (gezondheidspsycholoog in opleiding). Wilt u meedoen aan het onderzoek, vult u dan bij de online vragenlijst in dat u akkoord gaat met dit onderzoek (toestemmingsverklaring) . Uw deelname is op vrijwillige basis en het staat u vrij om op elk moment tijdens het onderzoek uw deelname aan het onderzoek in te trekken.

Bij voorbaat dank voor uw medewerking,

Mw. Prof. Dr. Angela Maas, cardioloog
Mw. Dr. Suzette Elias-Smale, cardioloog
Anneke Lier, gezondheidspsycholoog i.o.

Emailadres: vrouwenhart.cardio@radboudumc.nl

Appendix 5: Concept email for respondents (in Dutch)

Beste mevrouw <naam respondent>,

Fijn dat u in ons telefoongesprek aan gaf mee te willen werken aan ons onderzoek.
In de bijlage vindt u, indien gewenst, extra informatie over het onderzoek.

Het digitale onderzoek kunt u benaderen door het aanklikken van deze link:
https://qtrial2014.az1.qualtrics.com/SE/?SID=SV_9X2jpAsIZLo4em9.
Mocht deze link niet werken dan kunt u de tekst ervan ook in de adresregel van uw browser kopiëren.

Uw persoonlijk identificatienummer voor het onderzoek is **<identificatienr>**
Dit nummer kunt u in vullen als in de vragenlijst naar uw persoonlijk identificatienummer gevraagd wordt.
Het is belangrijk dat u dit identificatienummer goed invult in de vragenlijst!

Kleine aanvulling op de vragenlijst: als de vraag gesteld wordt of u last heeft van overgangsklachten (vraag V3) mag u die ook met 'ja' beantwoorden, als u in het verleden overgangsklachten heeft gehad maar daar nu geen last meer van heeft.

Mocht u nog vragen hebben, kunt u ons altijd mailen of bellen.
Ons email adres is vrouwenhart.cardio@radboudumc.nl en telefonisch kunt u ons bereiken op 06-38481282.

Alvast hartelijk bedankt voor uw deelname.

Met vriendelijke groet, mede namens professor Maas en dr. Elias,

Anneke Lier
Onderzoeker cardiologie

Appendix 6: Correlations

Table 9 *Correlations of measured variables with CMD*

Measure	Pearson´s (Spearman's) rho	P-value
Demographics		
Marital State	0.01	.92
Country of origin	0.20	.02
Level of education	0.30	.00
Type of employment	-0.05	.54
Age	0.07	.46
BMI	-0.09	.30
Medical factors		
Fam. cardiac history	0.07	.46
Hypertension	0.03	.72
Hypercholesterolemia	-0.17	.05
Thyroid problems	0.06	.51
Rheumatism	0.19	.04
Diabetes	-0.22	.81
Migraine	0.24	.01
TIA/Stroke	0.00	1.00
Cardiac intervention	-0.71	.00
Infarct	-0.70	.00
Female factors		
Early menopause	0.05	.66
Menopausal complaints	0.03	.72
Miscarriages	0.06	.54
Pregnancy hypertension	-0.03	.72
Pregnancy diabetes	-0.03	.73
Ovaries/uterus extirpation	-0.04	.65
Psychosocial factors		
Former smoker	-0.19	.03
Current smoker	-0.22	.02
Alcohol usage	0.13	.13
Perfectionism	0.06	.50
Coping	0.31	.00
Maladaptive	0.24	.01
Adaptive	0.25	.00
Self-distraction	0.40	.00
Active coping	0.25	.00
Denial	-0.01	.88
Substance use	-0.01	.88
Emotional support	0.17	.06
Distress	0.05	.59
Anxiety	0.04	.66
Depression	0.04	.62
Cardiac anxiety	0.19	.03
Fatigue	0.32	.00
Wellbeing	-0.32	.00
Mental	-0.21	.02
Physical	-0.36	.00

1 = paid job, 2 = volunteer job, 3 = no job