ADHD as a predictor for Coronary Microvascular Dysfunction in women with angina

Author:
M.A. Brinkman
6115888
22-5-2023 till 27-8-2023

Supervisor:
Dr. M.E. Wittekoek
Cardiologist at HeartLife Clinics, Utrecht
Department of Cardiology

UMC Utrecht supervisor:
Dr. T.P. van de Hoef
Cardiologist at UMC Utrecht, Utrecht
Division Heart and Lung
Department of Cardiology

Abbreviations

INOCA	Ischemia with no obstructive coronary artery
CMD	Coronary microvascular dysfunction
ADHD	Attention deficit hyperactivity disorder
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TC	Total cholesterol
LDL	Low-density cholesterol
HDL	High-density cholesterol
TG	Triglyceride
TSH	Thyroid Stimulating Hormone
T4	Free thyroid
CI	Confidence interval
OR	Odd's Ratio

Abstract

Background

There is increasing knowledge regarding differences in cardiovascular health between men and women. In Europe and the Unites States in women with angina, two thirds do not have obstructive coronary artery disease. Attention deficit hyperactivity disorder (ADHD) is underdiagnosed in women and tends to persist during adulthood. This study hypothesized that through the activated state of the nervous system in ADHD patients, this could lead to endothelial dysfunction causing women with ADHD to be prone to develop coronary microvascular dysfunction (CMD).

Methods

In total 635 female patients aged 18 years and older met inclusion criteria. A total of 625 female patients filled out the ultra-short questionnaire for ADHD completely. Patients with stable angina were categorized into functional (CMD), obstructive coronary arteries or a combination of both. A logistical analysis was preformed to determine whether ADHD was a predictor for CMD in female patients with angina.

Results

CMD was diagnosed in 136 of the 625 included patients. ADHD was diagnosed in 40 (29.4%) patients with CMD and 181 (37%) in the control group. At baseline ADHD did not significantly differ between the two groups (p=0.101). In logistical analysis, ADHD was not a significant predictor for CMD both as an individual predictor (p=0.247) and after entering with cardiovascular risk factors (p=0.416).

Conclusion

ADHD was observed not to be a significant predictor of CMD despite the high prevalence of ADHD (29.4%) compared to the general population. This higher prevalence highlights the importance of screening for ADHD in female patients with angina to optimize care and treatment.

Introduction

Angina pectoris is a symptom that should not be ignored, since it is the most common symptom of myocardial ischemia and an acute myocardial infarction. (1) The prevalence of angina is higher in women (6.7 %) compared to men (5.7%). (2) In Europe and the Unites States, patients presenting with symptoms of angina, approximately two thirds of women and one third of men do not have obstructive coronary artery disease (CAD) on coronary angiography. (3–7) These patients are categorized as ANOCA (angina with no obstructive coronary artery), INOCA (ischemia with no obstructive coronary artery) or MINOCA (myocardial infarction with no obstructive coronary artery) when signs/symptoms of a myocardial infarctions are present, which composes two different mechanisms; coronary vasospasm and coronary microvascular dysfunction (CMD). (8,9) It was previously thought that INOCA was a benign condition, nevertheless in women it has been associated with an elevated risk of major cardiac events. (3,4) The Women's Ischemia Syndrome Evaluation study included women with myocardial ischemic symptoms and observed in women diagnosed with INOCA a 12.8% risk of cardiac mortality or myocardial infarction in 10 years compared to 6.7% in women with no coronary artery disease. (10) Additionally, a different study observed a higher hazard ratio for all-cause mortality of 1.52 compared to 1.29 in both women and men with INOCA even after adjusting for traditional cardiac risk factors. (4) INOCA is more often diagnosed in females, of which the majority are postmenopausal women. (11–13) Menopause causes decrease in estrogen levels, therefore estrogen is most likely to play an important role in the development and progression of INOCA (13,14). Furthermore, postmenopausal women are at higher risk of cardiovascular disease due to changes of circulating lipids including triacylglycerol, high- and low-density lipoproteins. (15) In addition, postmenopausal women have higher incidences of diabetes, hypertension and obesity. (16) This all could to some extend explain the higher incidence of coronary artery disease in women aged 60 years and above compared to men. (17)

Under physiological circumstances, exercise increases the cardiac blood flow to meet the increased oxygen demands of the heart. To increase the blood flow, the resistance inside the blood vessel needs to be decreased according to the basic flow equation. As described by Poiseuille, the resistance inside a vessel is inversely proportional by the fourth power of the radius of the vessel. Changes of the vessel diameter are under influence of endothelial factors (e.g. nitric oxide and endothelin, causing respectively vasodilatation and vasoconstriction (13)) and the nervous system. As to the nervous system, the sympathetic nervous system effects the arterial tone of the vascular smooth muscle cells causing vasodilatation through stimulation of the beta-2 receptors. (18)

In CMD the physiological microvascular vasodilatation is reduced resulting in decreased blood flow to the heart, which in turn causes insufficient oxygen delivery to the heart leading to ischemia. (19) The reduced vasodilatation is thought to be caused by endothelial-dependent dysfunction through a disbalance in nitric oxide and endothelin and an endothelial-independent dysfunction through myocyte tones. (13) The disbalance in nitric oxide is assumed to be caused by low grade inflammation as a response to cardiovascular risk factors, causing reduced nitric oxygen secretion. (13) Additionally, due to atherosclerosis the stimulatory effects of the sympathetic nervous system are more towards the alfa-adrenoreceptors resulting in decreased blood flow due to vasoconstriction. (20,21) Even when stimulating with acetylcholine, the parasympathetic hormone, the vasodilation effect is reduced. (22)

As previously mentioned, decreased estrogen levels seems to play a role in both the development and the progression of CMD. With regard to the endothelial-dependent dysfunction, estrogen is observed to improve the production of nitric oxide and induced vasodilatation. (23,24) Due to low levels of estrogen in postmenopausal women, the effect of estrogen is limited which might partly explain the higher incidence of INOCA in postmenopausal women. In respect to the endothelial-independent dysfunction, estrogen appears to decrease basal vasomotor tone of coronary arteries and the arterial stiffness. (25)

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopment disorder affecting around 5.29% of children and 2.5% of adults worldwide. (26,27) It is thought that the a deficit in the neurochemicals norepinephrine- and dopamine are of importance in ADHD, as prescribed medication effecting these system decreases symptoms. (28) According the Diagnostic and Statistical Manual of Disorder, people suffering from ADHD can be divided into three groups; primarily inattention type, primarily hyperactive/impulse type and a combined type. (29)

In childhood boys are 2-2.5 times more often diagnosed with ADHD compared to girls. (30) This disbalance reduces throughout the years to 1.5:1 ratio in adulthood. (31,32) Several explanations regarding the difference between childhood and adulthood are suggested. Firstly, research has shown that women with ADHD are predominantly the aforementioned inattentive type compared to boys, causing less disruptive behavior

leading to lesser diagnosis of ADHD in girls. (30,33,34) In addition, persistence of ADHD symptoms to adulthood is more pronounced in the inattentive type. (35,36) As women are predominately this type, more women will have ADHD in adulthood causing the decreasing ratio. Moreover, there is an increase in severity of symptoms of ADHD is postmenopausal women. (37) The decreasing estrogen levels during menopause causes decreasing dopamine levels thereby leading to increasing ADHD symptoms in menopausal women. (37) This highlights the urgency for ADHD screening in peri-/postmenopausal women suffering from unexplained medical symptoms.

As previously mentioned, under normal physiological circumstances the sympathetic nervous system causes vasodilatation. Due to the activated state of the nervous system in patients with ADHD, this might cause endothelial dysfunction causing women with ADHD to be more prone to develop CMD. This study aimed firstly to investigated whether ADHD is a risk factor for developing CMD in women suffering from ADHD with a symptoms of angina.

Methods

This retrospective research was conducted in patients of the HeartLife Clinics, an outpatient cardiological clinic in Utrecht, The Netherlands, which is specialized in cardiovascular health in women. Consecutive female patients of the HeartLife Clinics visiting between May 2021 and April 2023 aged 18 years were eligible for inclusion. All patients entering the Heartlife Clinics filled out an ultra-short questionnaire for ADHD in advance of their appointment. If any of this questionnaire was incomplete, participants were excluded.

From the electronic health records the following data was subtracted: diagnosis of stable angina, age, menopausal state, smoking status, alcohol consumption, history of diabetes mellitus, drug usage, Body Mass Index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, ultrasound of the carotid, total cholesterol (TC), low-density cholesterol (LDL), high-density cholesterol (HDL), triglyceride (TG), Thyroid Stimulating Hormone (TSH), Free Thyroid (T4) and glucose (both fasting and non-fasting). Menopausal state and history of diabetes were categorized into “yes” and “no”, while smoking status, alcohol consumption and drug usage additionally had “former usage”.

Carotid ultrasound was performed by an experienced cardiologist and findings were categorized into normal, presence of soft or calcified plaque(s) and wall abnormalities/intima media thickening. Based on previous health records and diagnostic testing patients suffering from stable angina were divides into two groups: functional (CMD), obstructive cardiovascular disease or a combination of both. The reference groups consisted of all patients without angina symptoms.

ADHD assessment

As patients referred to the HeartLife clinic had primarily cardiological symptoms, a short screening questionnaire for ADHD was used (appendix I). This questionnaire was initially designed for ADHD detecting in highly suspicion patients, although the questionnaire has not been validated by research it might help to detect ADHD in people in a short and easy manner. The ultra-short questionnaire for ADHD, assessed all three domains of ADHD as described above with symptom duration. A positive answer in one of the three domains and a positive answer in the symptom duration question is indicative for ADHD. A random sample of ten patient were additionally tested by a psychiatrist to confirm the ADHD diagnosis. All patients got a definite ADHD diagnosis.

Statistical analysis

Statistical analysis was performed in SPSS version 29 and significance was determined as a p-value <0.05. Normality of distribution was checked by the Kolmogorov-Smirnov and Shapiro-Wilk test. Normal distributed continuous variables in the baseline table were shown as mean with standard deviation and skewed distributed continuous variables were shown with median and interquartile range. Dichotomous variables are shown with number and percentages within their group. Comparing CMD patients to the reference group at baseline, for normal distributed continuous variables the t-test was used and the Mann-Whitney U-test was used for non-normal distributed variables. The chi-square test was used for the dichotomous variables.

A binary logistical regression was performed to determine whether ADHD is a predictor for CMD. Firstly, only ADHD was entered in the model (Model 1). Secondly, all cardiovascular risk factor, e.g., age, BMI, SBP, DBP, TC, LDL, HDL, TG, menopausal state, diabetes history, smoking status, alcohol consumption and drug usage in addition to ADHD (Model 2). As smoking status, alcohol consumption and drug usage consisted of three categories, e.g., yes, no and former, we dichotomized all three variables through combining “former” and “no” into the same group.

	CMD (N = 136)	Non-CMD (N = 489)	Missing	p-value
Age (years)	58 [52-64]	58 [51-65.5]		0.997
BMI (kg/m2)	25.7 [22.8-29.0]	24.2 [22.2-27.5]		0.002 *
SBP (mmHg)	125.5 [115.3-136.8]	123 [112-136]		0.177
DBP (mmHg)	79.5 [73-88]	80 [73-88]		0.584
Heart rate per minute	74 [65-85.8]	75 [67-84]		0.513
ADHD positive	40 (29.4%)	181 (37%)		0.101
Menopausal state			7 (1.1%)	0.279
Premenopausal	22 (16.2%)	98 (20.3%)		
Peri/postmenopausal	114 (83.8%)	384 (79.7%)		
Diabetes mellitus type 1 or 2	11 (8.2%)	8 (1.7%)	8 (1.3%)	<0.001 *
TC (mmol/L)	5.2 [4.4-6.1]	5.6 [4.9-6.4]	61 (9.8%)	0.005 *
LDL (mmol/L)	3.0 [2.1-3.7]	3.2 [2.6-3.9]	65 (10.4%)	0.005 *
HDL (mmol/L)	1.7 [1.4-2]	1.7 [1.4-2]	65 (10.4%)	0.376
TG (mmol/L)	1.2 [0.9-1.8]	1.2 [0.9-1.7]	75 (12.0%)	0.532
Non-fasting glucose (mmol/L)	5.4 [4.8-5.8]	5.3 [4.8-5.9]	521 (83.4%)	0.912
Fasting glucose (mmol/L)	5.5 [4.9-6.4]	5.1 [4.8-5.6]	526 (84.2%)	0.043 *
TSH (mU/L)	1.2 [1-2]	1.6 [1.1-2.4]	307 (49.1%)	0.013 *
T4 (pmol/L)	13.9 [12.3-15.4]	14.4 [12.9-15.9]	534 (85.4%)	0.636
Echo carotids			52 (8.3%)	0.271
Normal	59 (50.4%)	267 (58.6%)		
Thickened carotid intima media	24 (20.5%)	74 (16.2%)		
Plaque(s)	34 (29.1%)	115 (25.2%)		
Lifestyle				
Smoking			20 (3.2%)	0.452
Current	5 (3.9%)	31 (6.5%)		
Former	46 (36.2%)	183 (38.3%)		
Never	76 (59.8%)	264 (55.2%)		
Alcohol			16 (2.6%)	0.530
Current	85 (65.9%)	325 (67.7%)		
Former	7 (5.4%)	36 (7.5%)		
Never	37 (28.7%)	119 (24.8%)		
Drug usage			63 (10.1%)	0.669
Current	2 (1.8%)	5 (1.1%)		
Former	5 (4.4%)	14 (3.1%)		
Never	106 (93.8%)	430 (95.8%)		

Table 1. Baseline (N = 625). * = significance level <0.05

Note: All continuous variables are described with median and interquartile range. Dichotomized and categorial variables are described with number and percentage in their respective group. BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, ADHD = attention deficit hyperactivity disorder, TC = total cholesterol, LDL = low density lipoprotein, HDL = high density lipoprotein, TG = triglycerides, TSH = thyroid stimulation hormone and T4 = free thyroid.

	Model 1*		Model 2**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
ADHD	0.756 (0.471-1.214)	0.247	0.811 (0.490-1.343)	0.416

Table 2. Logistical regression (N = 480)

Note: ADHD = Attention deficit hyperactivity disorder, OR = Odd's Ratio and 95% CI = 95% Confidence Interval

* Model 1 = unadjusted

** Model 2 = covariates age, body mass index, systolic- and diastolic blood pressure, total cholesterol, low- and high density lipoprotein, triglycerides, menopausal state, presence of diabetes mellitus type 1 or 2, smoking status, alcohol consumption and drug usage.

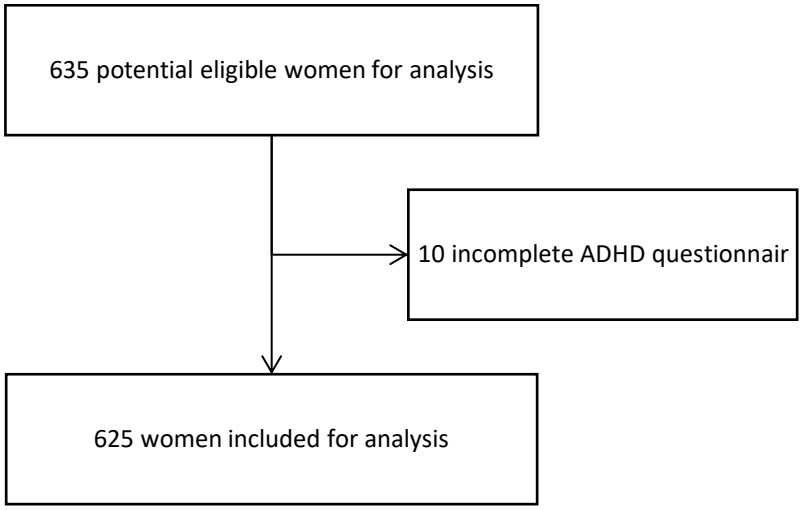

Figure 1. Flowchart inclusion. Note: ADHD = Attention deficit hyperactivity disorder

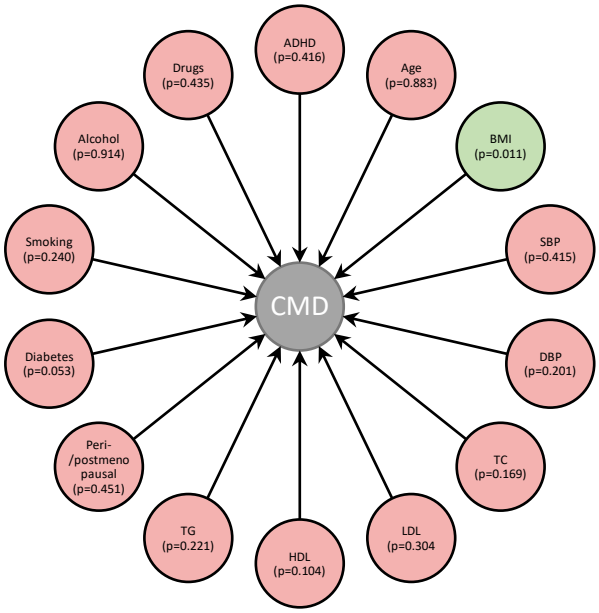

Figure 2. Overview of variables with p-value of Model 2 regression analysis. Note: Green colored variable is significant and red colored variables are not significant. ADHD = attention deficit hyperactivity disorder, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, LDL = low density lipoprotein, HDL = high density lipoprotein, TG = triglycerides.

Results

In total 635 participants were eligible for inclusion, of which 625 participants were included in the analysis (figure 1). CMD was diagnosed in 136 participants (21,8%), of which 40 participants (29,4%) were diagnosed with ADHD through a positive answer on the ultra-short questionnaire. (Table 1) In the control groups 181 participants (37%) were suspected of ADHD, which did not significantly differ from the CMD group (p = 0.101). (Table 1)

All continuous variables were non-normally distributed following the Kolmogorov-Smirnov and Shapiro-Wilk test. The CMD group had a significant higher BMI compared to the control groups of respectively 25.7 and 24.2 kg/m2 (p = 0.002), higher fasting glucose levels of 5.5 mmol/l compared to control group of 5.1 mmol/l (p = 0.043) as well as significant more participants with diabetes (n = 11 (8,1%)) compared to the control group (n = 8 (1,6%)) (p = <0.001). Moreover, the control group compared to the CMD group had significant higher total cholesterol levels (respectively 5.6 mmol/L vs 5.2 mmol/L (p = 0.008)), LDL levels (respectively 3.2 mmol/L vs 3.0 mmol/L (p = 0.005)) and TSH levels (respectively 1.6 mU/L vs 1.6 mU/L (p = 0.013)).

The regression model showed in both analysis; ADHD as an individual predictor of CMD and ADHD with the most common cardiovascular risk factors, that ADHD was not a significant predictor of CMD. (Table 2) In model 2, significant predictor of CMD was BMI (OR 1.074 (95% CI 1.016-1.136) p = 0.011).

Discussion

This retrospective research aimed to determine whether ADHD is a predictor for CMD. We hypothesized that through the activated state of the nervous system in women with ADHD, this might cause endothelial dysfunction causing women with ADHD to be more prone to develop CMD. However, this study did not observe a significant association between ADHD and CMD even after entering the most important cardiovascular risk factors into a binary logistical regression analysis.

However, the prevalence of ADHD in this research was higher in both CMD (29.4%) and control group (37.0%) compared to the general prevalence of 2,5%. (26,27). This high prevalence is consistent with a previous publication (38). Due to the higher prevalence of ADHD in the control group, this might explain why ADHD was not observed to be a significant predictor of CMD despite the high prevalence. Future research should further investigate whether ADHD is a predictor for CMD using a control group in which the prevalence of ADHD is conform the general prevalence.

This study additionally observed significant more women with diabetes mellitus type 1 or 2 in the CMD group compared to the control group. This finding is consistent with the findings of Binak et al. (2006) (39) in which impaired glucose tolerance was observed more often in patients with CMD. Moreover, the higher median fasting glucose levels observed in the CMD group could be explained by the higher prevalence of diabetes mellitus in this group. In addition, diabetes mellitus in a known risk factor for cardiovascular disease, thereby also increasing the risk for developing CMD.

Furthermore, the BMI in the CMD group was higher compared to the control group which is consistent with previous research. (40,41) This higher CMD underlines the pathophysiological mechanism of CMD. Patients with a higher BMI are at risk of developing atherosclerosis, which causes vasoconstriction through more alfa-adrenoreceptor stimulation. (20,21,42) In addition, cardiovascular risk factors causes reduced nitric oxygen secretion. (13) Despite this finding, other cardiovascular risk factors including hypertension, smoking status, alcohol consumption and drug usage did not significantly differ at baseline nor were these variables significant in the regression analysis. This might be for the reason that these risk factors are not only associated with atherosclerosis, but are more general risk factors for many cardiological disease of which the control group is composed of thereby decreasing their association with CMD.

Previous research has shown that a higher TC- and LDL-level are predictors for developing CMD. (40,43,44) Higher TC- and LDL-levels increases the risk of atherosclerosis, thereby increasing the risk of developing CMD. This study however observed in participants with CMD significant lower TC- and LDL-levels compared to the control group. This finding not only contradictory to previous research, but is inconsistent with the pathophysiologic mechanism of CMD. Although the usage of medication was not collected, participants in the CMD might be using more statins due to the higher prevalence of cardiovascular risk factors causing lower TC- and LDL-levels. Moreover, decreased circulating estrogen due to the postmenopausal state in women contributes to the development of CMD. (13) In the absence of lipid deficiency, e.g., higher TC- and LDL-levels, CMD in postmenopausal patients might be a different entity. Nevertheless, this research did not observe a significant difference in postmenopausal state between patients with CMD and no CMD, nor was the menopausal state a significant predictor in the regression analysis.

Regarding the lower TSH-levels in the CMD group, it is noteworthy that the T4-levels additionally are lower in this groups compared to the control group although not significant. Part of the negative endocrine feedback loop, one should expect that the T4 levels should be higher in lower TSH-levels. Impaired thyroid function is associated with patients with type 2 diabetes, as the CMD group has significant more participant with diabetes mellitus this could explain the difference. (45) It must be pointed out, that the median TSH and T4 levels in both groups are still within the normal range.

This is the first research to the knowledge of the authors in which ADHD is investigated as a predictor for CMD. Through a thorough and reliable method, an extensive number of variables including cardiovascular risk factors were gathered. This provided insight in the prevalence of possible ADHD in women diagnosed with CMD and whether ADHD is a risk factor for CMD. This study showed that screening for ADHD in women with cardiac symptoms might be favorable as the prevalence of ADHD is high in this group.

The primarily limitation of this study regards the diagnosis of ADHD, as the ultra-short questionnaire is not a validated questionnaire for detecting ADHD. Therefore, the prevalence of ADHD in this study is most likely an overestimation. Nevertheless, to provide more insight to possible ADHD in participants in the least invasive manner, this was researched through this questionnaire as it consists of only four questions. Additionally, the last question of the ultra-short questionnaire aimed to determine whether the symptoms were present during

childhood which might cause recall bias. Furthermore, the higher prevalence of ADHD in both CMD and control groups might be due to selection bias as all participants were selected from an outpatient cardiac clinic specialized in woman's health. Lastly, all participants of the CMD group were suspected of having CMD. A definitive diagnosis for CMD is through an invasive coronary angiogram with provocation tests. As there are no clinical consequence regarding treatment, the invasive diagnostic test is redundant. Therefore, it is possible that patients were falsely included in the CMD group.

Conclusion

This study observed that ADHD is not a significant predictor of CMD, although this should be interpretated with caution as the prevalence of ADHD in the reference group was considerably higher compared to the general population. Additionally, people diagnosed with CMD have significant higher BMI, more often diabetes and higher fasting glucose levels. Both BMI and diabetes are cardiovascular risk factors, underlining the pathophysiology of CMD. Further research should investigate whether ADHD is a risk factor for CMD through a regression analysis in which the comparison group is good representation of general population mostly regarding the prevalence of ADHD.

References

1. Hermiz C, Sedhai YR. Angina [Internet]. StatPearls. 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557672/
2. Hemingway H, Langenberg C, Damant J, Frost C, Pyörälä K, Barrett-Connor E. Prevalence of angina in women versus men: A systematic review and meta-analysis of international variations across 31 countries. Circulation. 2008;117(12):1526–36.
3. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. Arch Intern Med. 2009 May;169(9):843–50.
4. Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2012 Mar;33(6):734–44.
5. Johnson BD, Shaw LJ, Buchthal SD, Bairey Merz CN, Kim H-W, Scott KN, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation. 2004 Jun;109(24):2993–9.
6. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. JAMA. 2014 Nov;312(17):1754–63.
7. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010 Mar;362(10):886–95.
8. Reynolds HR, Merz CNB, Berry C, Samuel R, Saw J, Smilowitz NR, et al. Coronary Arterial Function and Disease in Women With No Obstructive Coronary Arteries. 2022;529–51.
9. Khan A, Lahmar A, Riasat M, Ehtesham M, Asif H, Khan W, et al. Myocardial Infarction With Non-obstructive Coronary Arteries: An Updated Overview of Pathophysiology, Diagnosis, and Management. Cureus. 2022;14(3).
10. Sharaf B, Wood T, Shaw L, Johnson BD, Kelsey S, Anderson RD, et al. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: Findings from the National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core lab. Am Heart J [Internet]. 2013;166(1):134–41. Available from: https://www.sciencedirect.com/science/article/pii/S0002870313002378
11. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease. JACC Cardiovasc Interv. 2015;8(11):1445–53.
12. Reis SE, Holubkov R, Smith AJC, Kelsey SF, Sharaf BL, Reichek N, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: Results from the NHLBI WISE study. Am Heart J [Internet]. 2001;141(5):735–41. Available from: https://www.sciencedirect.com/science/article/pii/S0002870301653250
13. Tunc E, Eve AA, Madak-Erdogan Z. Coronary Microvascular Dysfunction and Estrogen Receptor Signaling. Trends Endocrinol Metab [Internet]. 2020;31(3):228–38. Available from: https://doi.org/10.1016/j.tem.2019.11.001
14. Hall JE. Endocrinology of the Menopause. Endocrinol Metab Clin North Am. 2015;44(3):485–96.
15. Ko S. Menopause-Associated Lipid Metabolic Disorders and Foods Beneficial for Postmenopausal Women. 2020;
16. Tandon VR, Mahajan A, Sharma S, Sharma A. Prevalence of cardiovascular risk factors in postmenopausal women : A rural study. 2010;1(1):2–5.
17. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association. Circulation [Internet]. 2019 Mar 5;139(10):e56–528. Available from: https://doi.org/10.1161/CIR.0000000000000659
18. Duncker DJ, Koller A, Merkus D, Canty JM. Regulation of Coronary Blood Flow in Health and Ischemic Heart Disease. Prog Cardiovasc Dis [Internet]. 2015;57(5):409–22. Available from: https://www.sciencedirect.com/science/article/pii/S0033062014001765
19. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, et al. Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in Definition on Angiography. Vol. 66, Journal of the American College of Cardiology. 2015. p. 1918–33.
20. Heusch G, Baumgart D, Camici P, Chilian W, Gregorini L, Hess O, et al. α-Adrenergic coronary vasoconstriction and myocardial ischemia in humans. Circulation. 2000;101(6):689–94.

21. Heusch G. The paradox of α-adrenergic coronary vasoconstriction revisited. J Mol Cell Cardiol [Internet]. 2011 Jul 1;51(1):16–23. Available from: https://doi.org/10.1016/j.yjmcc.2011.03.007
22. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries: The ACOVA study (abnormal coronary vasomotion in patients with stable angina and unobstructed coronary arteries. J Am Coll Cardiol. 2012;59(7):655–62.
23. Darkow DJ, Lu L, White RE. Estrogen relaxation of coronary artery smooth muscle is mediated by nitric oxide and cGMP. Am J Physiol. 1997 Jun;272(6 Pt 2):H2765-73.
24. Chen Z, Yuhanna IS, Galcheva-Gargova Z, Karas RH, Mendelsohn ME, Shaul PW. Estrogen receptor alpha mediates the nongenomic activation of endothelial nitric oxide synthase by estrogen. J Clin Invest. 1999 Feb;103(3):401–6.
25. Scuteri A, Lakatta EG, Bos AJ, Fleg JL. Effect of estrogen and progestin replacement on arterial stiffness indices in postmenopausal women. Aging (Milano). 2001 Apr;13(2):122–30.
26. Simon V, Czobor P, Bálint S, Mészáros Á, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry [Internet]. 2018/01/02. 2009;194(3):204–11. Available from: https://www.cambridge.org/core/article/prevalence-and-correlates-of-adult-attentiondeficit-hyperactivity-disorder-metaanalysis/FBBDADEA596D69D26F49318ECAD410C4
27. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis. Am J Psychiatry [Internet]. 2007 Jun 1;164(6):942–8. Available from: https://ajp.psychiatryonline.org/doi/abs/10.1176/ajp.2007.164.6.942
28. Sharma A, Couture J. A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). Ann Pharmacother. 2014 Feb;48(2):209–25.
29. Association AP. ADHD. In: Desk reference to the diagnostic criteria from DSM-5 (R). Arlington, TX: American Psychiatric Association Publishing; 2013.
30. Hinshaw SP, Nguyen PT, O'Grady SM, Rosenthal EA. Annual Research Review: Attention-deficit/hyperactivity disorder in girls and women: underrepresentation, longitudinal processes, and key directions. J Child Psychol Psychiatry Allied Discip. 2022;63(4):484–96.
31. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006 Apr;163(4):716–23.
32. Nussbaum NL. ADHD and female specific concerns: a review of the literature and clinical implications. J Atten Disord. 2012 Feb;16(2):87–100.
33. Biederman J, Mick E, Faraone S V, Braaten E, Doyle A, Spencer T, et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiatry. 2002 Jan;159(1):36–42.
34. Weiss M, Worling D, Wasdell M. A chart review study of the inattentive and combined types of ADHD. J Atten Disord. 2003 Sep;7(1):1–9.
35. Döpfner M, Hautmann C, Görtz-Dorten A, Klasen F, Ravens-Sieberer U. Long-term course of ADHD symptoms from childhood to early adulthood in a community sample. Eur Child Adolesc Psychiatry. 2015 Jun;24(6):665–73.
36. Larsson H, Dilshad R, Lichtenstein P, Barker ED. Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology. J Child Psychol Psychiatry. 2011 Sep;52(9):954–63.
37. Antoniou E, Rigas N, Orovou E, Papatrechas A, Sarella A. ADHD Symptoms in Females of Childhood, Adolescent, Reproductive and Menopause Period. Mater Socio Medica. 2021;33(2):114.
38. Ter Beek L, Wittekoek SMEJ. The association between cardiovascular health and ADHD in Dutch women : a cross-sectional study. Arch Psychiatry. 2023;
39. Binak E, Gunduz H, Sahin M, Kurtoglu N, Dindar I. The relation between impaired glucose tolerance and slow coronary flow. Int J Cardiol. 2006;111(1):142–6.
40. Cui L, Han L, Wang J, Huang P, Tian G, Wang Y, et al. Prevalence and characteristics of coronary microvascular dysfunction in post-percutaneous coronary intervention patients with recurrent chest pain. Cardiovasc Diagn Ther. 2022;12(2):166–76.
41. Bajaj NS, Osborne MT, Gupta A, Tavakkoli A, Bravo PE, Vita T, et al. Coronary Microvascular Dysfunction and Cardiovascular Risk in Obese Patients. J Am Coll Cardiol [Internet]. 2018;72(7):707–17. Available from: https://www.sciencedirect.com/science/article/pii/S0735109718351817
42. Henning RJ. Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity. Am J Cardiovasc Dis [Internet]. 2021;11(4):504–29.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/34548951%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8449192
43. Mayala HA, Yan W, Jing H, Shuang-ye L, Gui-wen Y, Chun-xia Q, et al. Clinical characteristics and biomarkers of coronary microvascular dysfunction and obstructive coronary artery disease. J Int Med Res. 2019;47(12):6149–59.
44. Mangiacapra F, De Bruyne B, Peace AJ, Melikian N, Wijns W, Barbato E. High cholesterol levels are associated with coronary microvascular dysfunction. J Cardiovasc Med. 2012;13(7):439–42.
45. Kalra S, Aggarwal S, Khandelwal D. Thyroid Dysfunction and Type 2 Diabetes Mellitus: Screening Strategies and Implications for Management. Diabetes Ther [Internet]. 2019;10(6):2035–44. Available from: https://doi.org/10.1007/s13300-019-00700-4

Appendix I – ultra-short questionnaire for ADHD

Balance questionnaire

1. Do you usually feel restless? ☐ yes ☐ no
   Example: feeling rushed, difficulty sitting still, fidgeting, exercising a lot or being active

2. Do you usually tend to act first and think later? ☐ yes ☐ no
   Example: blurting things out, overspending or being impatient

3. Do you usually have problems concentrating? ☐ yes ☐ no
   Example: being easily distracted, not finishing things, being easily bored, forgetful or chaotic

4. In case "yes" was answer one or more times to the above questions:

   Have you always had this? ☐ yes ☐ no
   (As long as you can remember, or have you been like this most of your life).