The association between cardiovascular health and ADHD in Dutch women: a cross-sectional study

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List of abbreviations

ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
CIMT	Carotid intima media thickening
CMD	Coronary microvascular dysfunction
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DSM-V	Diagnostic and Statistical Manual of Mental Disorders (fifth edition)
ECG	Electrocardiogram
HDL-c	High density lipoprotein cholesterol
HR	Heart rate
LDL-c	Low density lipoprotein cholesterol
OR	Odds ratio
SBP	Systolic blood pressure
SD	Standard deviation
TC	Total cholesterol
TSH	Thyroid stimulating hormone
T4	Free thyroxine
UKV	Ultra korte vragenlijst voor ADHD

ABSTRACT

Objectives: Evidence suggests that adults with attention deficit hyperactivity disorder (ADHD) are at greater cardiovascular risk. However, past research has produced inconsistent results on the association between ADHD and cardiovascular disease (CVD). The main aim of this study was to investigate the association between ADHD and cardiovascular health in women who attended the cardiac outpatient clinic in Utrecht.

Methods: Data were analyzed from electronic health records of 300 individuals aged 18 years and above who visited the clinic between May 2021 and May 2022. ADHD symptoms were assessed with the self-reported ultra-short questionnaire for ADHD. The primary outcome included the presence of atherosclerosis as measured by carotid ultrasonography.

Results: ADHD in women was not a significant predictor for atherosclerosis. We found significant association between ADHD and alcohol use, but no association was observed between ADHD and obesity, type 2 diabetes, smoking, and drug use. Our hypothesis that women with ADHD are more likely to develop coronary microvascular dysfunction (CMD) was not confirmed.

Conclusions: No significant associations were found between ADHD and CVD (atherosclerosis and CMD) in women. Both ADHD and CVD are underdiagnosed and undertreated in women. This can lead to mental and physical health impairments. To protect women's health, further research is required to better understand the relationship between ADHD, cardiovascular risk and CVD.

1 Introduction

The number of deaths from cardiovascular disease (CVD) in Europe is higher in women than men (2.2 million vs. 1.8 million), accounting for 46% of all deaths in women and 39% of all deaths in men.[1] Despite the fact that CVD is the leading cause of mortality and morbidity worldwide for both men and women, it remains understudied and underdiagnosed in women. Although there is increased awareness that CVD is not solely a 'men's disease', both clinicians and patients are still prone to underestimate the cardiovascular risk in women. Research has shown that women differ from men in clinical presentation, pathophysiology, risk factors, and prognosis of CVD.[2,3] Sex-specific differences in CVD seem to be partly associated with reproductive hormones. Research has suggested that endogenous estrogens have cardioprotective effects through reduction of vascular inflammation and its vasodilatory effects.[2-4] Menopause is associated with a rapid and progressive increase in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c).[3] The loss of estrogen during menopause and the changes in lipid metabolism could partly explain why women develop CVD about a decade later than men.[2]

Women with myocardial infarction are less likely to experience chest pain and more likely to present with atypical symptoms such as pain between the shoulder blades, fatigue, and nausea, than men.[2] Additionally, studies have found that women are more susceptible to develop diffuse atherosclerotic disease, coronary microvascular dysfunction (CMD), and heart failure with preserved ejection fraction while men tend to suffer more from obstructive epicardial stenoses and heart failure with reduced ejection fraction.[2,3,5] CMD can lead to ischemia and myocardial infarction without obstructive coronary artery disease and thus should not be ignored.[3] Several traditional cardiovascular risk factors such as smoking, hypertension, and diabetes mellitus have been associated with greater risk of CVD than in men.[2] Also, risk factors unique to women, including gestational diabetes, polycystic ovarian syndrome, and premature ovarian failure are associated with CVD.[6] Unfortunately, female specific risk factors are currently not included in cardiovascular risk assessment tools. This also applies to psychosocial risk factors such as depression and anxiety disorders, which are both associated with increased risk of CVD.[3,6]

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder which is characterized by a persistent pattern of inattention and/or impulsivity/hyperactivity that has a negative impact on daily functioning.[7,8] The Diagnostic and Statistical Manual of Mental Disorders (fifth edition; DSM-V) describes three presentations of ADHD: predominantly inattentive type, predominantly hyperactive/impulsive type, and combined type.[7] The exact cause of ADHD remains unknown, but it is thought to result from a combination of genetic and environmental risk factors, and their interactions. Several neuroimaging studies have shown small differences in brain development, structure, and function between patients with and without the diagnosis of ADHD.[9] In addition, positive effects of stimulant medication such as amphetamine and methylphenidate suggest that dopaminergic and noradrenergic neurotransmission play a role in ADHD.[7]

Until recently, it was considered that children diagnosed with ADHD would resolve the disorder by adulthood.[10,11] However, various studies have shown that approximately two-thirds of children with ADHD continue to have impairing symptoms as adults.[10] The worldwide prevalence of ADHD is estimated to be around 5.9% in youth and 2.5% in adults.[9] Research has revealed that 80% of adults with ADHD have one or more comorbid psychiatric disorder, including mood disorders and substance use disorders.[12] Although ADHD is one of

the most frequently diagnosed neurodevelopmental disorder in children, it remains misdiagnosed and underdiagnosed in adults.[11] Underrecogniton is likely to be due to the overall lack of awareness of adult ADHD in both healthcare professionals and patients.[10] Recent studies have shed light on the underrepresentation of females in past clinical research on ADHD. Boys are three times more likely to receive an ADHD diagnosis than girls while the ratio of adult males to females approaches 1.5:1. Several studies have highlighted this discrepancy and proposed that this could be due to healthcare professionals being less aware of ADHD in girls. In addition, girls with ADHD have less recognizable symptoms than boys and more often have the inattentive type of ADHD without showing disruptive behavior.[13-15] Research suggest that girls may also develop coping strategies and display socially adaptive behavior to mask their symptoms.[15] This suggests that parents and teachers are less likely to refer girls for ADHD assessment. Undetected girls and women are at higher risk for adverse outcomes, including impairments in mental health and academic underachievement.[15,16] A recent systematic review even showed that women with ADHD were more impaired than men with regard to mood disorders, time perception, social functioning, and stress tackling.[17]

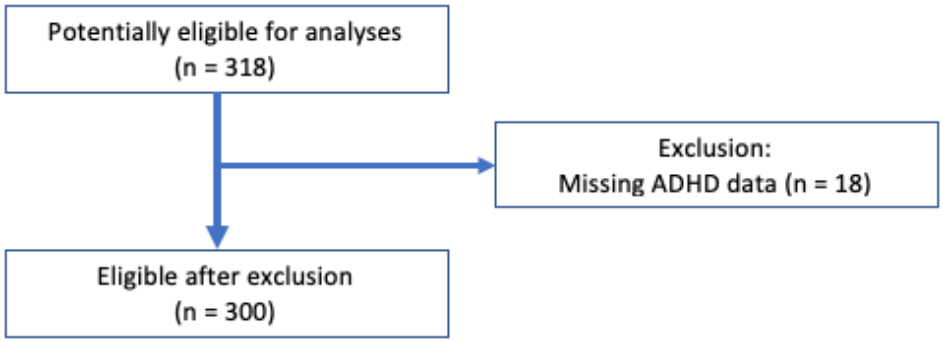
Recent studies have examined the association between adult ADHD and various physical conditions. Significant associations have been found between adult ADHD and obesity and sleep disorders.[9,18,19] A recent study has shown that ADHD is associated with type 2 diabetes but previous research did not find this association.[18,20] In addition, research has revealed that adults with ADHD are more likely to develop an unhealthy lifestyle such as smoking, alcohol, and drug use.[10] The findings mentioned above suggest that adults with ADHD may be at increased risk for CVD. However, past research has focused primarily on the cardiovascular effects of ADHD medications which has shown that use of ADHD medications is associated with an increase in heart rate and blood pressure but not with CVD.[21,22] Previous studies focused on the association between ADHD and CVD have produced inconsistent results, with a tendency to positive correlations between ADHD and CVD.[19,23-31]
There were two main aims for the present study. First, to assess whether ADHD in women is associated with adverse cardiovascular health; and second, to increase awareness of both ADHD and CVD in women.

2 Methods

2.1 Participants

In this retrospective cross-sectional study, clinical data was drawn from electronic health records and the self-reported ultra-short questionnaire for ADHD of patients who applied to HeartLife Clinics between May 2021 and May 2022. HeartLife Clinics, a cardiac outpatient clinic in Utrecht, provides cardiovascular care focusing on both the prevention and treatment of heart disease with specialized expertise on women's heart health. Approximately 1,000 patient visits are made annually. It is estimated that women comprise 85% of the patients with the largest age group between 40 and 60 years.
Female patients aged 18 years and above with and without a history of cardiovascular disease, who were referred to HeartLife Clinics by their general practitioner or specialist were eligible for inclusion. Patients who met the inclusion criteria were asked to complete a baseline questionnaire including the ultra-short questionnaire for ADHD prior to their first appointment. A total of 318 potentially eligible participants were screened. Participants who partially filled in the ultrashort questionnaire for ADHD were excluded (n = 18). A flowchart of participant selection is shown in figure 1. All patients' data were anonymized before analysis.

Figure 1
Flowchart of participant selection.



2.2 Measurements

2.2.1 Assessment of demographics and cardiovascular health indicators

Data collected from electronic health records included demographic information (age and menopausal status), lifestyle related risk factors (smoking status, alcohol consumption, drug usage), medical history (history of diabetes), cardiac symptoms (palpitations, chest pain, dyspnea, and fatigue), physical examination (body mass index, blood pressure, heart rate), laboratory blood measurements (TC, LDL-c, high density lipoprotein cholesterol (HDL-c), triglycerides, non-fasting and fasting glucose, thyroid stimulating hormone (TSH), and free thyroxine (T4)), resting ECG, exercise stress test, carotid ultrasound measurements, and the diagnosis stable angina. Body mass index (BMI) was based on self-reported height and weight. Menopausal status, history of diabetes, and lifestyle-related risk factors were collected by self-reporting. Smoking status, alcohol consumption, and drug usage were categorized as current, former, and never. Resting ECG was categorized as normal and abnormal. All abnormal resting ECG findings are shown in appendix 2. The exercise stress test was categorized into eleven groups: normal (0), hypertensive response (1; systolic blood pressure > 200 mm Hg and/or diastolic blood pressure > 100 mmHg at peak exercise), rhythm/conduction abnormalities on ECG (2), signs of ischemia on ECG (3), other ECG abnormalities (4), combination of 1 and 2, combination of 1 and 4, combination of 2 and 4, combination of 1, 2, and 4, combination of 1-3, combination of 2-4, and combination of 1 and 3. See appendix 3 for a list of other ECG abnormalities with exercise stress test. Examination of the carotid arteries were performed by an experienced cardiologist. The carotid ultrasound measurements were categorized as normal, abnormal carotid intima media thickening (thickened CIMT), and presence of one or more carotid plaques. The diagnosis stable angina was classified into functional (CMD), obstructive, and mixed.

2.2.2 Assessment of ADHD

Participants were screened for ADHD symptoms using the ultra-short questionnaire for ADHD (Ultra Korte Vragenlijst voor ADHD, UKV).[32] UKV is a short screening instrument for ADHD. UKV has not been validated in research but can be helpful in identifying possible ADHD in adults.[33] It covers the main criteria listed in DSM-V for ADHD. The questionnaire was designed to detect patients with high suspicion of ADHD and in need for further diagnostic testing. It contains 4 questions assessing the presence of ADHD symptoms (inattention, impulsivity, and hyperactivity) and the duration of the present symptoms. Each item can be scored as 0 for “no” and 1 for “yes” with a maximum total score of 4. A score of 1 or more on the ADHD symptoms and a score of 1 on the duration (chronicity) is indicative for ADHD. The questionnaire is written in Dutch and presented in appendix 1.

2.3 Statistical analyses

Descriptive analyses were performed for assumptions for analysis of data and to determine incidence for categorical variables (ADHD score, menopausal status, history of diabetes, lifestyle related risk factors, cardiac symptoms, resting ECG, exercise stress test, carotid ultrasound, and stable angina). The normality of data was tested for continuous variables (age, BMI, blood pressure, heart rate, and laboratory measurements) using histograms, boxplots, the Kolmogorov-Smirnov test, and the Shapiro-Wilk test for sample sizes less than 50. Means and standard deviations for continuous data, and frequencies and percentages for categorical data, were reported for both groups (ADHD positive and ADHD negative). Chi-square test and one-way analysis of variance (ANOVA) were used to detect differences in cardiovascular health between the two groups. We created the following dichotomous variables for logistic regression: atherosclerosis (coded 1 = abnormal carotid ultrasound, coded 0 = normal carotid ultrasound) by combining thickened CIMT and presence of plaque, smoking status by combining former smokers and never smokers, alcohol consumption by combining former drinkers and never drinkers, and drug usage by combining former drug users and never users. Binary logistic regression was performed to explore the relationship between ADHD and atherosclerosis (primary outcome) as measured by carotid ultrasonography as being the most concrete outcome variable (model 1), covariates including age (model 2), BMI, menopausal state, blood pressure, total cholesterol, LDL-c, HDL-c, triglycerides, and lifestyle related risk factors (model 3). SPSS (Statistical package for social sciences) statistical package version 28 was used for all the analysis. *P*-values < 0.05 were considered statistically significant.

3 Results

This analysis included 300 female participants (M = 56.90 years; SD = 10.16), 11 (3.7%) had a confirmed clinical diagnosis of ADHD, 4 of whom were receiving ADHD medication. Based on the results of the UKV 195 (65%) participants were classified as ‘ADHD negative’. The Kolmogorov-Smirnov test indicated that the following variables were not normally distributed: age, BMI, diastolic blood pressure, heart rate, LDL-c, HDL-c, triglycerides, non-fasting glucose, TSH, and T4. The Shapiro-Wilk test indicated that fasting glucose was also not normally distributed. However, as ANOVA is considered robust to non-normality, we ran parametric tests.

General characteristics of both groups are listed in table 1. The groups differed significantly in age (55.29 years vs 57.77 years, $p = .043$), with the ADHD positive group being significantly younger. Fasting glucose levels were significantly lower in the ADHD positive group compared with the ADHD negative group, respectively 4.92 and 5.59 ($p = .034$). After adjusting for age, we did not find this ($p = .078$). Patients with a positive ADHD score were less likely to be a never drinker compared to patients with a negative ADHD score (23% vs. 34%, $p = .015$). This association remains after adjusting for age ($p = .265$). None of the other outcomes showed significant group differences.

None of the three regression models showed significant results (table 2). ADHD was not a significant predictor for atherosclerosis ($p = .920$).

Table 1
Characteristics of the study population ($n = 300$).

	ADHD negative	ADHD positive	Total missing values	*p* value*

Age in years, mean (SD)	57.77 (10.50)	55.29 (9.32)		.043
BMI in kg/m^2, mean (SD)	25.76 (4.37)	25.23 (3.91)		.300
SBP in mm Hg, mean (SD)	128.50 (18.17)	125.96 (17.68)		.245
DBP in mm Hg, mean (SD)	82.51 (12.26)	81.57 (11.49)		.517
HR, mean (SD)	76.04 (14.80)	76.21 (12.99)		.920
Menopausal state, *N* (%)			6 (2)	.428
Premenopausal	37 (19)	24 (23)		
Peri/postmenopausal	154 (81)	79 (77)		
Cardiac symptoms, *N* (%)				
Palpitations	86 (44)	51 (49)	1 (.3)	.482
Chest pain	115 (59)	57 (54)	1 (.3)	.404
Dyspnea	62 (32)	28 (27)	1 (.3)	.341
Fatigue	56 (29)	31 (30)	2 (.7)	.865
Diabetes mellitus, *N* (%)	5 (3)	3 (3)		.881
Total cholesterol in mmol/l, mean (SD)	5.68 (1.22)	5.62 (1.26)	41 (13.7)	.712
LDL-c in mmol/l, mean (SD)	3.37 (1.05)	3.33 (1.07)	41 (13.7)	.719
HDL-c in mmol/l, mean (SD)	1.67 (.44)	1.70 (.45)	42 (14)	.586
Triglycerides, mean (SD))	1.51 (.82)	1.37 (.84)	47 (15.7)	.178
TSH in mU/l, mean (SD)	1.76 (1.48)	1.51 (1.13)	169 (56.3)	.327
T4 in pmol/l, mean (SD)	13.76 (1.92)	13.34 (1.41)	248 (82.7)	.489
Non-fasting glucose in mmol/l, mean (SD)	5.56 (1.37)	5.53 (1.17)	247 (82.3)	.927
Fasting glucose in mmol/l, mean (SD	5.59 (1)	4.92 (.24)	257 (85.7)	.034
ECG abnormalities, *N* (%)	85 (44)	35 (33)	1 (.3)	.078
Exercise stress test, *N* (%)	109 (56.2)	70 (66.7)	20 (6.7)	.774
Normal	49 (27)	27 (27)		
1. Hypertensive response	23 (13)	17 (17)		
2. Rhythm/conduction abnormalities	50 (27)	22 (22)		
3. Signs of ischemia	0	0		
4. Other ECG abnormalities	6 (3)	3 (3)		
Combination of 1 and 2	31 (17)	22 (22)		
Combination of 1 and 4	8 (4)	2 (2)		
Combination of 2 and 4	4 (2)	3 (3)		
Combination of 1, 2, and 4	7 (4)	1 (1)		
Combination of 1, 2, and 3	1 (.5)	1 (1)		
Combination of 2, 3, and 4	1 (.5)	0		
Combination of 1 and 3	1 (.5)	1 (1)		
Carotid ultrasound, *N* (%)			22 (7.3)	.153
Normal	105 (58)	62 (64)		
Thickened CIMT	28 (15)	19 (20)		
Presence of plaques	48 (27)	16 (16)		
Lifestyle, *N* (%)				
Smoking status			8 (2.7)	.104
Current smoker	15 (8)	6 (6)		
Former smoker	55 (29)	42 (41)		
Never smoker	120 (63)	54 (53)		
Alcohol consumption			3 (1)	.015
Current drinker	123 (64)	72 (69)		
Former drinker	4 (2)	8 (8)		
Never drinker	66 (34)	24 (23)		
Drug usage			49 (16.3)	.079
Current drug user	1 (.5)	4 (5)		
Former drug user	4 (2)	2 (2)		
Never user	163 (97)	77 (93)		
Stable angina, *N* (%)				.290
Functional	41 (67)	23 (79)		
Obstructive	8 (13)	4 (14)		
Combination of the above	12 (20)	2 (7)		

Note. SD=standard deviation, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate, LDL-c=low density lipoprotein cholesterol, HDL-c=high density lipoprotein

cholesterol, TSH=thyroid stimulating hormone, T4=free thyroxine, ECG=electrocardiogram, CIMT=carotid intima media thickness.
*Based on chi-square test for categorical variables and one-way ANOVA for continuous variables.

Table 2
Logistic regression for presence of atherosclerosis (n = 187).

	Model 1*		Model 2**		Model 3***	
	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
ADHD	.816 [.437, 1.523]	.523	.944 [.473, 1.885]	.871	.962 [.455, 2.034]	.920

Note. OR=odds ratio, 95% CI=95% confidence intervals.
*Model 1: unadjusted.
**Model 2: Model 1 plus adjusted for age.
***Model 3: Model 2 plus adjusted for body mass index, menopausal status, history of diabetes, blood pressure, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, smoking status, alcohol consumption, drug usage.

4 Discussion

One of the main aims of this study was to investigate whether ADHD in women is associated with adverse cardiovascular health. Our results showed that ADHD was not a significant predictor for atherosclerosis. This finding is not in line with recent studies which found a causal effect of ADHD on atherosclerosis.[28,30] This difference highlights the need for additional research. Previous research has found an association between CMD and traditional cardiovascular risk factors and psychological stress.[34] Since adults with ADHD are at increased risk for several cardiovascular risk factors as well as anxiety and depression which induce psychological stress, we hypothesized that ADHD in women may contribute to CMD (functional stable angina). However, we did not find this to be the case. The finding that ADHD is significantly associated with alcohol use is in line with previous research.[10] Surprisingly, the present study found no associations between ADHD, smoking and drug use. One study examining older adults with ADHD found similar results concerning the relationship between ADHD and smoking.[26] A possible explanation could be that the prevalence of smoking and drug use are higher in young adults compared to middle-aged and older adults. The current study found that fasting glucose levels were lower in women with ADHD than women without ADHD. However, after correcting for age, this association did not remain significant. In contrast to our hypothesis, we were not able to confirm the association between ADHD and obesity and type 2 diabetes as previously reported.[9,18,20] Possible confounding variables including sleep disorders and socioeconomic status may explain this difference.[35,36] Importantly, ADHD screening revealed a surprisingly high prevalence of 35% among women at HeartLife Clinics. Previous research suggests that women with ADHD are more likely to experience severe climacteric symptoms than women without ADHD.[37] Perimenopausal women with ADHD may attribute these climacteric symptoms to CVD and decide to consult a cardiologist. Recent research suggests that low estrogen could decrease dopamine levels which in turn may lead to increase in ADHD symptoms in perimenopausal women.[38] Further research is needed to confirm this association.

To the best of our knowledge, this is the first study to examine the association between ADHD in women alone and cardiovascular health. Important strengths of this study include the collection of extensive information on patient cardiovascular health status. Also, most cardiovascular health variables were measured with valid and reliable measurements. Our results suggest a potential value of ADHD screening in women who are referred to

cardiovascular examination.
Our study has some limitations. First, we included patients from one cardiac outpatient clinic with special focus on women's heart health rather than general cardiac care, thus introducing a selection bias. Second, UKV is not a valid screening instrument for ADHD which may have led to an overestimation of the prevalence of ADHD in women. Third, study participants were asked to recall the duration of their ADHD symptoms, which introduce the possibility of a recall bias. Fourth, we were not able to fully correct for comorbidities (psychiatric disorders like depression), family history of CVD, female specific risk factors, and medication use that might influence the association between ADHD and CVD (atherosclerosis and CMD).

5 Conclusion

In conclusion, we found that ADHD is not a significant predictor of atherosclerosis in women. Additional studies are needed to further explore the association between ADHD and CVD in women. Our study revealed that women with ADHD are more likely to start drinking, but are not associated with increased prevalence of obesity, type 2 diabetes, dyslipidemia, hypertension, smoking, drug use, and CMD. Our study showed that women with ADHD may present lower fasting glucose levels, but this association did not remain significant after adjusting for age. Both CVD and ADHD in women are underdiagnosed and undertreated. It is crucial to gain knowledge and increase awareness of CVD and ADHD in women to improve the quality of life and achieve both optimal cardiac and mental healthcare for women. Future studies should be longitudinal with larger sample sizes examining the cardiovascular health in women with ADHD and hormonal fluctuations should be taken into consideration.

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APPENDIX

Appendix figure 1. The ultra-short questionnaire for ADHD.

INTAKEFORMULIER

Balans

1. Voelt u zich doorgaans onrustig? ☐ ja ☐ nee
   Bijv.: gejaagd, moeite met stilzitten, friemelen, veel sporten of beweeglijk zijn?
2. Heeft u doorgaans de neiging eerst te doen en dan pas na te denken? ☐ ja ☐ nee
   Bijvoorbeeld: dingen eruit flappen, teveel geld uitgeven of ongeduldig zijn)
3. Heeft u doorgaans concentratieproblemen? ☐ ja ☐ nee
   Bijvoorbeeld: snel afgeleid zijn, dingen niet afmaken, snel verveeld, vergeetachtig of chaotisch zijn
4. Indien het antwoord op een of meer van bovenstaande vier vragen 'ja' is:

   Heeft u dit altijd gehad? ☐ ja ☐ nee
   (Zolang u zich kunt herinneren, of bent u het grootste deel van uw leven zo geweest).

Appendix 2. Abnormal resting ECG findings.
(run) premature atrial contraction(s), premature ventricular complex(es) in bi(tri)geminy/multiform/doublet, atrial fibrillation, bradycardia, tachycardia, suspicion of left ventricular hypertrophy, sinus arrhythmia, short PQ-interval, pacemaker, CRT-D, signs of anterior myocardial infarction/septal infarction, left axis deviation, prolonged QT interval, QS in V1-V4, right bundle branch block, left bundle branch block, negative T waves in V3 t/m V6 and II, III, aVF and aVR, biphasic P wave V1-V4, QS in V3-V5, RsR in V1 and V2, flat ST-segment V5-V6, situs inversus, first degree AV block, sinus rhythm with third degree AV block, AV junctional escape rhythm, negative T wave in precordial leads, right atrial enlargement.

Appendix 3. Other ECG abnormalities with exercise stress test.
Not significant: negative T waves leads V3-V6, negative T waves leads II and aVR, negative T waves leads II, III, and aVF, bowl-shaped ST-segment leads V4-V6, II, III, and aVF, negative T-waves leads I and aVL, QS complexes leads V1-V4, ST-segment abnormalities leads II, III, and aVF, ST-segment abnormalities leads V5, V6, II, III, and aVF.