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Association between sedentary time, physical activity, biochemical markers in the blood (heart and muscles) and heart failure in adults with congenital heart disease: a study protocol of a cross-sectional cohort study in Sweden (the ACHD trial protocol)

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ABSTRACT

Introduction Adults with congenital heart disease (ACHD) are a heterogeneous group with a large variation in the severity of lesions and symptoms. This population has rapidly grown in recent years due to improved surgical and medical treatments. Sedentary time and physical activity (PA) and health among individuals classified with single lesions, for example, shunt defects such as atrial and ventricular septal defects, and patent foramen ovale (PFO) with stroke are less studied. The present study describes the study protocol and examines associations between sedentary time, PA, circulating biomarkers in the blood (heart and muscles) and heart failure. Results have the potential to supply the healthcare system with information if further action to promote cardiovascular health in ACHD is needed.

Methods and analysis A cross-sectional design will be used with data from the local heart register, Swedish Registry for Congenital Heart Disease in Uppsala, Sweden. Individuals ≥18 years of age with simple congenital heart disease, according to the definition atrial septal defect, ventricle septal defect or PFO as the cause of stroke, will be included.

Outcome measures: Self-reported questionnaire: demographic characteristics, education, the prevalence of diabetes, smoking, ethnicity, self-reported level of sitting time and leisure-time PA/exercise, everyday activities, commuting and degree of symptoms associated with exertion. Blood analyses: blood lipids (total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, apolipoprotein A1 and B), creatinine, cystatin-C (eGFR), creatine kinase, myoglobin, high-sensitivity troponin, brain natriuretic peptide, C-reactive protein and glycated haemoglobin. Quantitative methods will be used for statistical analyses.

Ethics and dissemination The Swedish Ethical Review Authority has approved the study (registration numbers 2022-06525-01 and 2023-02082-02). Results will be disseminated in peer-reviewed journals, research meetings, conferences and possibly patient organisations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study protocol describes sedentary time and physical activity (PA) levels and associations with biomarkers of the heart, muscles, and heart failure, in a population of adults with congenital heart disease (ACHD) with simple heart defects, in all ages and genders.
⇒ Measuring biomarkers in the blood helps explain the health status and the need for possible actions to optimise the treatment.
⇒ Using a questionnaire captures different contexts of sedentary behaviour and PA, for example, commuting, occupational PA, leisure-time PA and everyday activities and includes well-known questions about sedentary time and PA with acceptable reliability and validity.
⇒ The generalisability of our findings will be limited due to a relatively small cohort and only applicable to ACHD with simple shunt lesions.
⇒ Self-report of sedentary time and PA might be a limitation and subject to recall and social desirability bias.

INTRODUCTION

Due to major advances in surgical and medical care, the number of adults living with congenital heart disease (ACHD) has increased rapidly in recent decades.[1] The worldwide prevalence is approximately 9 per 1000 newborns and is the most common birth defect, even though there is variability in geographic locations.[1 2] Persons with ACHD are a heterogeneous group with several

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diagnoses and large variability within the diagnostic group regarding the severity of the lesions and symptoms.[3] Lesions are often classified as simple or complex, which predicts the expected reduction in exercise capacity.[3] A shunt lesion is often classified as a simple lesion, for example, atrial septal defect (ASD) and ventricular septal defect (VSD) being the most common lesions with several anatomical variants. These lesions cause the shunting of oxygenated blood from left to right with volume overloads.[1] Another shunt lesion is patent foramen ovale (PFO), ie, a small opening/connection between the right and left atria of the heart that does not close after birth, allowing blood to bypass the lungs.[4] The opening between the atria remains open for approximately 25% of individuals, usually causing no problems but increasing the risk of stroke.[4] After a PFO-associated stroke, a percutaneous closure reduces the risk of recurrent cryptogenic stroke, especially in younger individuals.[5–7] In Sweden, closure is recommended after stroke for individuals <61–65 years of age if no other cause of stroke is defined or when the stroke is classified as cryptogenic.[5–7] Most ACHD patients have a reduced exercise capacity but to what extent this is caused by the heart defect, sedentary time or level of physical activity (PA) due to restrictions and/or overprotection is less studied.[8]

ACHD with surgically repaired shunt lesions (ASD and VSD) commonly experience chronotropic impairment and achieves 80% to 85% of the predicted maximal heart rate during exercise testing.[9 10]

PA is important for maintaining and promoting health and is extensively described and often used in secondary prevention programmes in patients with acquired cardiovascular disease and chronic heart failure.[2 9 11 12] The definition of PA is any body movement that increases energy expenditure above resting levels and can be performed at work, during transport, in leisure time or as organised exercise or sport.[13 14]

Insufficient PA is defined as less than 150 min of heart rate-raising PA per week at moderate intensity (eg, brisk walking) or less than 75 min per week at a high intensity (eg, running).[14]

Arrhythmias occur in both unrepaired and repaired ACHD patients and can affect the level of PA. PA and exercise capacity are linked to the prognosis. Time spent sitting is also important to consider since excessive sitting and physical inactivity can increase the risk of cardiovascular disease, type 2 diabetes, overweight/obese, different cancer types and all-cause mortality.[9 15] Sedentary behaviour can be defined as sitting or lying activities in the awake state that do not significantly increase energy consumptions beyond that at rest.[14] It is well known that sedentary behaviour and activities such as driving, passive commuting, reading and using a screen can affect overall health.[9 16] In a cohort with simple and complex ACHD, most patients showed an interest and willingness to participate in physical exercise but were uncertain of the safety or benefit.[8] ACHD patients show a range of PA levels between normal and severely limited.[8 12 17] A large-scale international study from Jong *et al*[12] showed that only 30% reported recommended PA levels according to the WHO recommendations.[12] Among the study participants, 27% were classified as having a simple heart defect, including ASD and VSD.[12]

The current guidelines for ACHD promote a physically active lifestyle at an individualised intensity based on haemodynamic and electrophysiological parameters and anticipated effort level.[1 3 10] The recommendation for PA and sports should be based on the underlying congenital heart defect and its potential complications.[11] Furthermore, guidelines highlight that aerobic and muscle-strengthening activities are important to prevent lifestyle-related diseases in this population since a higher risk for cardiovascular diseases is reported.[11 15] Regular PA including exercise is safe for most ACHD, and individuals with an isolated small or repaired ASD or VSD with normal ventricular and valve function usually have no exercise limitations since they have a very low likelihood of adverse responses to exercise.[1 3] No guidelines concerning PFO and PA have been found.[18]

Biomarkers in the blood can help estimate health. Different types of blood biomarkers for muscles, kidneys and heart have been reported to be associated with adverse events in individuals with congenital heart disease (CHD), including markers of myocardial injury (high-sensitivity troponins), low-grade inflammation (high-sensitivity C-reactive protein) and neurohormones like natriuretic peptides (BNP) and N-terminal-pro-BNP (NT-pro-BNP).[1] PA has a positive effect on several of these biomarkers[1 3] although excessive exercise can have a negative impact on renal and heart biomarkers.[19] Organ dysfunction can be present in the ACHD population due to possible constant volume, pressure overloading or ageing.[1] Among neurohormones, N-terminal-pro-BNP is best studied in ACHD patients and can be useful for heart failure monitoring, a potential complication in the ACHD population.[1] In chronic heart failure, PA is indicated and can improve symptoms, exercise endurance and functional capacity.[3 20] Renal impairment (creatinine and cystatin-C) and vascular changes can complicate the management of CHD and are associated with poor outcomes and high healthcare costs.[9] Creatine kinase (CK) and myoglobin indicate muscle damage, and there are some indications of impaired skeletal muscle function in adults with CHD, indicating a need for rehabilitation and muscle strengthening.[21] Dyslipidaemia is poorly described in ACHD, and due to therapeutic advances and ageing, this population is exposed to traditional cardiovascular risk factors for atherosclerotic disease.[22] Measuring blood lipids (HDL- and LDL-cholesterol, total cholesterol and apolipoproteins) is important since hyperlipidemia can exacerbate cardiovascular risk in CHD patients.[23] PA can lead to a more favourable lipid profile.[24] Effects of regular PA are usually observed in HDL-C (increase) and the ratio ApoB/ApoA1 (decrease), since Apo B decreases and ApoA1 increases.[24] An increased apoB/apoA1 ratio is strongly associated with major cardiovascular events,

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in both genders and in all ages.[25] Interestingly, this ratio seems to be a more sensitive marker for sitting time compared with different cholesterol measures.[26] Monitoring glycated haemoglobin (HbA1c) is crucial for detecting and managing diabetes and pre-diabetes and PA can improve glucose control and insulin sensitivity.[27 28] Collectively, certain blood biomarkers and increased knowledge about sedentary time and PA in a cohort of simple CHD can guide further treatment decisions and the need for medications, lifestyle interventions or more intensive monitoring. Biomarkers can also help in prognosis and for early detection of complications. The course of the disease in ACHD is variable and depends on the heart defect, severity and interventions.[1 29] An intervention changes the course but does not rule out later complications. Surgical repair has good long-term outcomes in both ASD and VSD, when performed before adulthood, and can affect the frequency of arrhythmia and heart failure development.[1] The incidence of acute heart failure is expected to rise in ACHD patients due to increasing age, but specific guidelines for ACHD and heart failure are currently missing.[1] In a cohort of 61 adults with congenital heart lesions of different complexity, PA was assessed over 1 week using two accelerometers.[17] When measuring exertion and symptoms of heart failure, individuals classified as New York Heart Association (NYHA) class II or III are less physically active and spend less time at moderate or vigorous PA compared with those classified as NYHA class I.[17] Only a few individuals in NYHA classes I and II reached the PA recommendations, and none did so in NYHA class III, despite a willingness to participate in exercise.[17] ACHD follows the same PA level pattern as the general population, and therefore, there is a need to promote an active lifestyle for ACHD patients and those with impaired NYHA classes.[8] Most ACHDs require lifelong medical and lifestyle follow-up.[1 29] Promoting PA and reducing sedentary time is important since PA and exercise capacity are linked to prognosis.[30] However, there is a lack of studies focusing on ACHD classified with shunt defects, level of sedentary time, PA and different complications.[3 17]

Within this research study, in an ACHD population, the aim is to study associations between sedentary time, PA, heart failure and circulating biomarkers in the blood (heart and muscles). In addition, ACHD with or without arrhythmias and/or other complications, and with or without surgical interventions, will be compared. Study results can help inform future studies and further guide clinical practice.

The following research questions will be addressed in ACHD patients with shunt defects:

1. To what extent are these individuals sedentary or physically active?
2. What muscular/cardiac status and degree of heart failure do these individuals have?
3. Is there any association between sedentary time, the level of PA, muscular/cardiac status and degree of heart failure?
4. Are there any differences between individuals with surgery versus no surgery and those who have or do not have cardiac arrhythmias?
5. Are there any differences in sedentary time, level of PA and muscular/cardiac status in individuals with or without complications?

METHODS

The study design is exploratory, descriptive and cross-sectional using the local medical records heart register, in Uppsala, Sweden, to identify eligible individuals. We will use the STROBE cross-sectional guidelines for reporting this study.[31] A flowchart of the planned study is depicted in figure 1.

Eligibility criteria

Participants are included by meeting the following criteria:

1. Individuals ≥18 years of age classified with simple CHD with a focus on shunt defects, according to the following definition: ASD, VSD or PFO after stroke.
2. Individuals who from January 2017 until July 2023 have been in contact with the Department of Cardiology at Uppsala University Hospital, Sweden, at least once.
3. Participants having sufficient cognition to make decisions about study participation; in other words, they should not have any known cognitive impairments.
4. Individuals providing written informed consent.

Exclusion criteria: complex CHD, Down syndrome.

Individuals with additional complex comorbidities that can affect PA, such as inherited or acquired metabolic conditions or diagnosed pulmonary disease, are not excluded.

Recruitment

The study started in November 2023, and the planned end date for data collection is October 2024 including a reminder of the research request. The Swedish Registry for Congenital Heart Disease and the local heart registry will identify the study cohort and collect information about comorbidity, medications, blood pressure, surgical interventions, arrhythmia and pacemakers. The identified patients will receive an inquiry about study participation, a questionnaire sent home, and an informed consent form.

The questionnaire includes demographic characteristics, questions regarding marital status, diabetes, smoking, ethnicity, education, work situation, commuting, level of sitting time, occupational PA, leisure-time PA, everyday activities and degree of symptoms associated with exertion. A similar questionnaire was previously used in the Västerbotten Intervention Programme and the WHO MONICA study in northern Sweden.[32 33] The overall instructions are '*Please, fill in the questionnaire and mark the options that best suit you. Try to fill in answers to all questions and answer as honestly as you can*'. Individuals in the region of Uppsala can also participate in blood sampling

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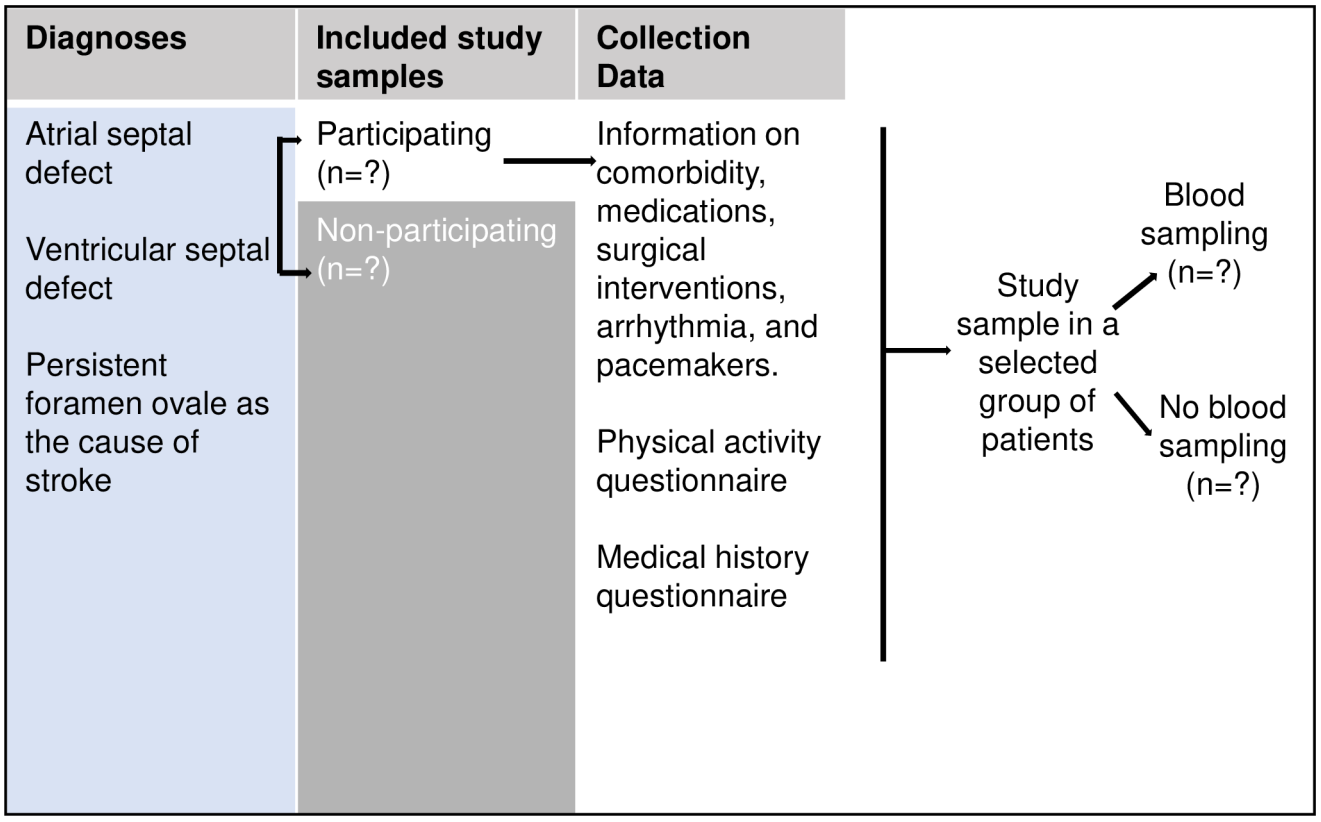

Figure 1 Flowchart describing the inclusion process, data collection and sample strategy. Study sample eligibility (n=340). The anticipated exclusion rate is estimated to be approximately 5%. The local medical heart register, in Uppsala, Sweden, will be used to identify eligible individuals.

to measure heart and muscle health, after giving written informed consent to participate.

Outcomes measures

Marital status is recorded as (i) unmarried/never married, (ii) married/remarried, (iii) separated/divorced, (iv) cohabitant, or (v) widow/widower.

Diabetes, smoking and being a student are recorded with the answer (i) yes or (ii) no.

Ethnicity is recorded with the answer (i) White/Caucasian, (ii) Black African/African-American, (iii) Asian, (iv) Latin American, (v) Middle East/Arab or (vi) other.

Education is recorded as (i) no completed upper secondary education, (ii) completed upper secondary education, (iii) completed bachelor's degree at university/college or (iv) completed a bachelor's degree or higher education.

The current work situation is recorded with the answers (i) full-time work, (ii) part-time work, (iii) housewife/men, (iv) job seekers, (v) unemployed, (vi) early retirement (disability in percentage), (vii) retired or (viii) other.

Questions regarding the level of sedentary behaviour and PA, for example, commuting, occupational PA, leisure-time PA and everyday activities, are included in the survey. The outcomes are assessed at a single time point. The National Board of Health and Welfare in Sweden indicator questions regarding PA and sedentary behaviour will be used.[34] These questions have been tested for validity and reliability and are found to be equivalent to other self-reported questions about PA.[35–37]

Sedentary time

The participants are asked about their daily sitting time, except for sleep. The question is, '*How much time do you sit on a normal day, excluding sleep?*' The following answer options are available: (i) almost all day, (ii) 13–15 hours, (iii) 10–12 hours, (iv) 7–9 hours, (v) 4–6 hours, (vi) 1–3 hours or (vii) never.[34]

Occupational PA

The participants are asked to mark the alternative that best describes their workload. The question is: '*Select the option that best describes your work?*' The following answer options are given: (i) sedentary or standing, (ii) easy but partially mobile, (iii) easy and mobile, (iv) sometimes physically demanding or (v) physically demanding most of the time.

Leisure-time PA

The participants are asked how much time they spend on physical exercise (high intensity) in a typical week, such as running, exercise gymnastics or ball sports. The question is '*How much time do you spend in a typical week doing physical exercises that make you short of breath, such as running, aerobics (calisthenics), or ball sports?*' The following

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answer options are given: (i) 0 minutes no time, (ii) less than 30 min, (iii) 30–60 min (0.5–1 hour), (iv) 60–90 min (1–1.5 hour), (v) 90–120 min (1.5–2 hours) or (vi) more than 120 min (2 hours).[34]

Everyday activities

The participants are asked how much time they spend on everyday activities (moderate intensity) in a typical week, such as gardening, walking, etc. The question is '*How much time do you spend in a typical week on everyday exercise, for example, walking, cycling, or gardening?*' Add up all time. The following answer options are given: (i) 0 minutes no time, (ii) less than 30 min, (iii) 30–60 min (0.5–1 hour), (iv) 60–90 min (1–1.5 hour), (v) 90–150 min 1.5–2.5 hours, (vi) 150–300 min (2.5–5 hour) or (vii) more than 300 min.[34]

The results from these two questions concerning leisure-time physical activity and everyday activities are weighted to a common metric: activity minutes. The middle value of the categories is used for aggregation. The results are weighed together and the time spent in more intensive activity is counted twice; that is 45 min of walking plus 45 min of running equals (45+90 = 135) 135 min.[34]

Active commuting

The participants are asked about commuting habits.[16] Separate answers are given for four seasons. The following answer options are available: car/bus, train, boat/walking/riding a bicycle. They are also asked about the distance to work.

Blood sampling

Circulating biomarkers in the blood are measured. Collection of non-fasting venous blood: (12 mL/person=-total of 2 tubes) for individuals living in or close to the region of Uppsala will be used. Biochemical analyses are performed according to accredited methods of the Department of Clinical Chemistry at the Uppsala University Hospital, Uppsala, Sweden. Blood is analysed directly for circulating levels of biomarkers of heart and muscles, heart failure and inflammation status: blood lipids (total cholesterol, HDL and LDL cholesterol, apolipoprotein A1 and B), creatinine, cystatin-C (eGFR), CK, myoglobin, high-sensitivity troponin, brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP) and $HbA1_C$.

Heart failure

Both NTproBNP and the NYHA classification can be used to grade heart failure and will be used in this study.[3 38] NYHA categorises patients based on their symptoms and limitations during PA into categories. In short, different classes in the NYHA Functional Classification are *Class I*: no limitation of PA and ordinary PA does not cause undue fatigue, palpitation or shortness of breath; *Class II*: slight limitation of PA; comfortable at rest; and ordinary PA results in fatigue, palpitation, shortness of breath or chest pain; *Class III*: marked limitation of PA; comfortable at rest; less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain; and *Class IV*: symptoms of heart failure at rest and any PA causes further discomfort.[3 38] Identified individuals are estimating their limitations in everyday life and during PA.

Patient and public involvement

The study is codesigned in collaboration between ACHD representatives, healthcare professionals and researchers. This study aims to learn more about the health of ACHD patients with congenital shunt defects and if further interventions are needed to increase the level of PA and reduce sedentary time.

Statistics

Approximately 340 patients are eligible for inclusion. Descriptive analyses will be performed according to the type and distribution of variables and presented as means, medians or frequencies. Correlation strength will be calculated using Spearman's rho for non-parametric data or a Pearson correlation for continuous normally distributed variables. ORs and 95% CI or linear regression will be used to analyse how sedentary behaviour and PA co-varies with heart failure and biochemical markers in the blood. PA and sedentary behaviour will be analysed separately. We will adjust for age and sex. To compare characteristics between those with and without arrhythmias and those with and without surgical interventions, we will use the Mann–Whitney U-test or the Student's t-test for ordinal or continuous variables and the X^2 test for categorical variables. To compare characteristics with sedentary time and PA categories, we will use the Kruskal–Wallis independent test for continuous variables and the X^2 test for categorical variables. All calculations will be performed using SPSS 28 (IBM, Armonk, NY).

ETHICS AND DISSEMINATION

Ethical approval was obtained from the Swedish Ethical Review Authority (registration numbers 2022-06525-01 and 2023-02082-02). The study follows the Helsinki Declaration and Good Clinical Practice requirements. Results will be disseminated in peer-reviewed journals, at research meetings, conferences, and possibly to patient organisations.

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Contributors BV is the guarantor of the study. BV and CC contributed substantially to the work's conception and design. BV wrote the study protocol manuscript. CC, CJ and TÅ revised it critically for important intellectual content and approved the final manuscript. All authors agree to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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