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Sympathovagal imbalance decades after atrial septal defect repair: a long-term follow-up study

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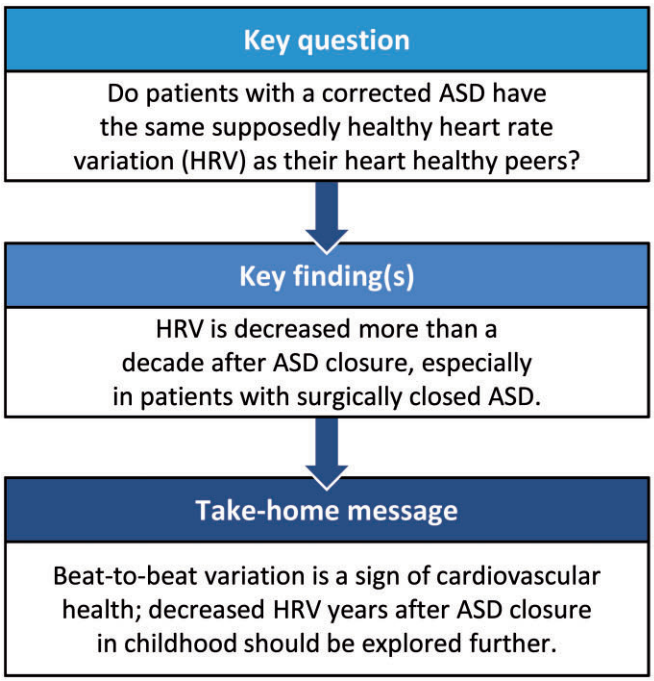

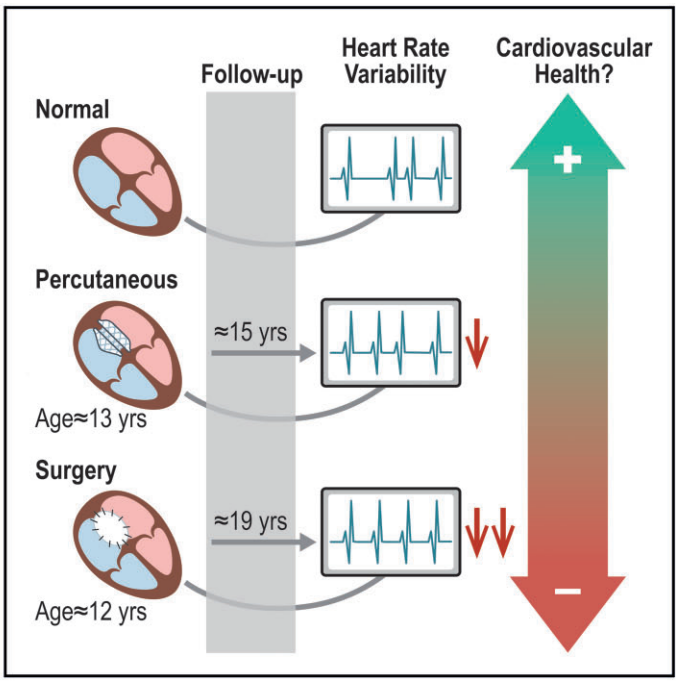

Abstract

OBJECTIVES: Recent evidence suggests that patients with a corrected atrial septal defect (ASD) have higher morbidity and mortality. An abnormal autonomic regulation of the heart may be a part of the explanation for this. Our objective was to study heart rate variability (HRV) in adults with a corrected ASD as a prominent tool to investigate the autonomic regulation of the heart.

METHODS: Autonomic cardiac function was investigated in adults with either a surgically closed or percutaneously closed ASD and healthy control subjects. A 48-h Holter monitor was performed on each participant and HRV was assessed.

†All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

RESULTS: A total of 17 patients with surgically closed ASDs, 18 percutaneously closed ASDs and 18 controls were included. The mean age in the surgical group, percutaneous group and controls was 32 ± 9, 28 ± 7 and 32 ± 10 years, respectively. The mean time since closure was 19 ± 8 years for the surgical group and 15 ± 5 years for the percutaneous group. The surgically closed ASD patients showed decreased HRV in all six parameters studied when compared to the controls. Similarly, the percutaneously closed ASDs showed decreased HRV in three out of six parameters when compared to controls.

CONCLUSIONS: Adults with an ASD, whether closed surgically or percutaneously, have impaired HRV compared to their age- and sex-matched controls, more so in the patients with a surgically closed ASD.

Clinical trial registration number: ClinicalTrials.gov (identifier: NCT03565471).

Keywords: Heart rate variability • Atrial septal defect • Congenital heart disease • Sympathovagal imbalance • Long-term follow-up

ABBREVIATIONS

ASD	Atrial septal defect
HRV	Heart rate variability
NN	Time interval between normal R peaks
pNN50	The percentage of successive NN intervals that differ by more than 50 ms
RA	Right atrium
RBBB	Right bundle branch block
RMSSD	Root mean square of the sum of all differences between successive NN intervals
SD	Standard deviation
SDANN	Standard deviation of the average of the NN intervals for all 5-min periods
SDNN	Standard deviation of all NN intervals
SDNNi	Mean of the standard deviation of all NN intervals for all 5-min periods

INTRODUCTION

Atrial septal defect (ASD) is the third most common congenital heart defect [1]. The majority of ASDs require either surgical or percutaneous closure [2, 3]. The long-term outcome of an ASD is believed to be benign. However, recent evidence documents that ASD patients have increased long-term morbidities such as pneumonia [4], conduction disturbances [5], atrial fibrillation [6, 7], stroke [6], mental health issues [8] and increased mortality [3] compared with the general population.

The causes of increased long-term morbidity in treated ASD patients are far from identified. One explanation may be disrupted activity in the cardiac autonomic nervous system. This has previously been observed in ischaemic heart disease, congestive heart failure and congenital heart diseases and is believed to be a predictor of the prognosis of these diseases [9, 10].

The autonomic nervous system activity can be non-invasively assessed through heart rate variability (HRV) [11] where low variability is strongly correlated with all-cause mortality [12, 13]. Although it improves in the months following surgical or percutaneous closure, HRV has previously been found to be decreased in children with an ASD but improve in the months after ASD closure, whether surgical or percutaneous. Still, the long-term development of HRV into adulthood remains unknown [14–16].

In this long-term follow-up, we investigated adults with either a surgically or percutaneously closed ASD to obtain a better understanding of the development of HRV into adulthood by comparing ASD patients with a group of healthy control subjects.

METHODS

Ethics statement

The Danish Data Protection Agency (chart: 1-16-02-154-18) and The Regional Committee on Health Research Ethics of the Central Denmark Region (chart: 1-10-72-50-18) approved the study. The study is registered on ClinicalTrials.gov (identifier: NCT03565471). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, revised in 2013, and all participants provided written informed consent prior to enrolment. This study meets the STROBE guidelines.

Study design and population

In this long-term observational follow-up study, participants were studied at Aarhus University Hospital, Denmark, in the period between August 2018 and October 2019.

The study population consisted of three study groups: (i) 17 surgically closed ASDs, (ii) 18 percutaneously closed ASDs and (iii) 18 age- and sex-matched control subjects. The inclusion criteria were: an age of ≥2 years at the time of diagnosis and ≥3 years since the time of ASD closure. All patients had an isolated secundum ASD. ASD correction pre-1996 was surgical. From 1996, the decision about surgical or percutaneous closure was made at a multi-disciplinary conference and based upon the defect size, location and morphology. The control participants were included ad hoc via public announcements throughout the study period to match the patients for age and sex. Patients and control participants were investigated in random order.

Patients were excluded if other congenital cardiac defects, lung diseases, ischaemic heart diseases, diabetes, hypertension, valve pathology or associated syndromes, e.g. Trisomy-21, were present. Controls were healthy peers free of medical treatment and with normal blood pressure, electrocardiography and echocardiography.

This study was a part of a study in which the objective was to investigate cardiac performance and haemodynamics during rest and exercise through echocardiography, right heart catheterization, cardiopulmonary exercise testing and Holter monitoring in said population.

Holter monitoring

Participants were equipped with a two-channel Holter monitor (Lifecard CF Digital Holter Recorder, Spacelabs Healthcare, Snoqualmie, WA, USA) for 48 h. The recordings were analysed

using Pathfinder SL software (Spacelabs Healthcare, Snoqualmie, WA, USA). Measurements were expressed as 24-h values.

The Holter recordings were analysed for the presence of arrhythmic events, including a high number of premature ventricular contractions, defined as >200 over 24 h [17], supraventricular and ventricular tachyarrhythmia (defined as ≥1 run of ≥3 beats) and sinus arrest (defined as pauses of ≥2 s).

Atrioventricular block first degree was defined as PQ interval of ≥220 ms. Right bundle branch block (RBBB) was subdivided into complete RBBB defined as an RSr′ or RSR′ configuration in leads V1 or V2 and QRS duration ≥120 ms in leads I, II, III, aVL and aVF or incomplete RBBB (QRS duration <120 ms) [18].

The following HRV time-domain parameters were calculated: standard deviation (SD) of all time intervals between normal R peaks (NN) (SDNN); SD of the average of the NN interval for all 5-min periods (SDANN); mean of the SD of all normal NN interval for all 5-min periods (SDNNi); root mean square of the sum of all differences between successive NN intervals (RMSSD); the percentage of successive NN intervals that differ by >50 ms (pNN50); and integral of the density distribution divided by the maximum of the density distribution, i.e. the total number of NN intervals divided by the number of NN intervals in the modal bin (triangular index).

End points

SDNN was our primary end point. The secondary end points included SDANN, SDNNi, RMSSD, pNN50 and triangular index.

Statistical analyses

Results are reported as mean ± SD for continuous data and as absolute numbers and percentages of participants for binary data. If non-normally distributed variables achieved a Gaussian distribution through log-transformation, this was done before any statistical analyses. Differences between groups were calculated using Student's *t*-test for continuous data with a Gaussian distribution, Mann–Whitney test for continuous data with a non-normal distribution and χ^2 tests for binary data. Results were considered statistically significant when the *P*-values <0.05. Correlation between HRV parameters and size of ASD and HRV parameters and age of ASD closure was evaluated using the Pearson correlation coefficient. Statistical analysis was performed using Stata/SE 15.1 for Mac (StataCorp, College Station, TX, USA).

A power calculation was performed based upon SDNN, the primary end point for this sub-study. In a normal cohort, 11% are expected to have a low SDNN value [17]. We expected the incidence of a low SDNN to be 35% among ASD patients, set alpha to 0.05 and power to 80%, and calculated that 18 participants should to be included in each study group.

Due to poor quality or incomplete Holter recordings, seven additional controls were included to ensure sufficient numbers. Seven controls had no echocardiographic measurements of right ventricular function.

RESULTS

In total, 19 surgically closed patients, 19 percutaneously closed patients and 18 controls were included. One percutaneously closed ASD patient was excluded due to incomplete Holter monitoring. Two surgically closed ASD patients were later excluded because of unusable HRV data. Of these two, one was excluded due to atrial fibrillation and one due to second degree atrioventricular block Mobitz type I and nocturnally advanced second degree atrioventricular block leaving HRV data as an outlier with a deviation of more than two SD in five out of six HRV parameters.

Table 1: Characteristics of participants with surgically or percutaneously closed atrial septal defects and healthy controls including echocardiographic and right heart catheterization parameters

	Surgically closed ASDs (*n* = 17)	Percutaneously closed ASDs (*n* = 18)	Controls (*n* = 18)	*P*-value [a]	*P*-value [b]
Demographics					
Age (years)	32 ± 9	28 ± 7	32 ± 10	0.8814	0.1565
Female gender	12 (71)	11 (61)	10 (56)	0.4887	1.0000
Weight (kg)	80 ± 21	72 ± 16	80 ± 16	0.9950	0.1311
Height (cm)	172 ± 10	172 ± 10	177 ± 9	0.1045	0.1073
Body mass index (kg/m^2)	27 ± 5	24 ± 3	25 ± 5	0.4393	0.3404
Age of ASD closure (years)	12 ± 7	13 ± 9			
Time since closure (years)	19 ± 8	15 ± 5			
ASD size before closure (mm)	22 ± 4	12 ± 4			
Echocardiography					
LV ESV (ml)	42 ± 14	42 ± 14	40 ± 13	0.6282	0.6298
LV EDV (ml)	108 ± 24	103 ± 24	101 ± 23	0.4227	0.7934
LVEF (%)	62 ± 7	60 ± 8	61 ± 6	0.8714	0.4884
RVEF (%)	54 ± 9	54 ± 13	54 ± 8[c]	0.9905	0.9432
RA ESV index)	24 ± 6	18 ± 4	18 ± 4	0.0006	0.6135
RA EDV (ml)	23 ± 6	15 ± 7	17 ± 7	0.0065	0.4208

Data are reported as means ± standard deviations or absolute *n* (%) of participants.

[a] *P*-value between surgically closed ASDs and controls.

[b] *P*-value between percutaneously closed ASDs and controls.

[c] *n* = 11.

ASD: atrial septal defect; EDV: end-diastolic volume; ESV: end-systolic volume; LV: left ventricle; LVEF: left ventricle ejection fraction; RA: right atrium; RVEF: right ventricle ejection fraction.

Table 2: Heart rate variability for participants with surgically or percutaneously closed atrial septal defects and healthy controls

	Surgically closed ASDs (n = 17)	Percutaneously closed ASDs (n = 18)	Controls (n = 15)	P-value	
				[a]	[b]
SDNN (ms)	151 ± 38	159 ± 38	191 ± 44	0.0070	0.0261
SDANN (ms)	136 ± 26	140 ± 37	171 ± 48	0.0135	0.0307
SDNNi (ms)	59 ± 18	66 ± 18	76 ± 19	0.0095	0.0959
RMSSD (ms)	37 ± 13	38 ± 13	48 ± 14	0.0220	0.0428
pNN50 (%)	10 ± 8	13 ± 8	19 ± 10	0.0058	0.0597
Triangular index	41 ± 11	46 ± 13	50 ± 12	0.0232	0.3258

Data are reported as means ± standard deviations.

[a]P-value between surgically closed ASDs and controls.

[b]P-value between percutaneously closed ASDs and controls.

ASD: atrial septal defect; pNN50: the percentage of successive NN intervals that differ by more than 50 ms; RMSSD: root mean square of the sum of all differences between successive NN intervals; SDANN: standard deviation of the average of the NN interval for all 5-min periods; SDNN: standard deviation of all normal sinus intervals; SDNNi: mean of the standard deviation of all normal NN interval for all 5-min periods; triangular index: integral of the density distribution divided by the maximum of the density distribution, i.e. the total number of NN intervals divided by the number of NN intervals in the modal bin.

Table 3: Heart rate variations, events and electrocardiographic data for participants with surgically or percutaneously closed atrial septal defects and healthy controls

	Surgically closed ASD patients (n = 17)	Percutaneously closed ASD patients (n = 18)	Controls (n = 18)
Heart rate variations (beats/min)			
Minimum heart rate	53 ± 7	52 ± 8	49 ± 7
Mean heart rate	76 ± 8	77 ± 8	74 ± 7
Maximum heart rate	141 ± 22	146 ± 21	162 ± 19
Events			
High number of PVCs	0 (0)	1 (6)	1 (6)
Supraventricular tachyarrhythmia	4 (24)	2 (11)	2 (11)
Ventricular tachyarrhythmia	1 (6)	0 (0)	0 (0)
Sinus arrest	1 (6)	3 (17)	0 (0)
Electrocardiography			
Atrioventricular block	0 (0)	0 (0)	0 (0)
Complete RBBB	1 (6)	1 (6)	0 (0)
Incomplete RBBB	6 (35)[a]	5 (28)	1 (6)

Data are reported as means ± standard deviations or absolute n (%) of participants.

[a]P-value <0.05 between study group and controls.

ASD: atrial septal defect; PVCs: premature ventricular contractions; RBBB: right bundle branch block.

A total of 53 Holter recordings were included of which 35 subjects had an ASD, 17 surgically closed, 18 percutaneously closed and 18 controls. Demographic data of the study population are summarized in Table 1. There were no differences between the three groups regarding demographics except for ASD size before closure. Here, surgically closed ASD patients had a larger defect size compared to the percutaneously closed ASD patients (P < 0.0001). Echocardiographic data are also presented in Table 1 showing larger right atrial end-systolic volume index (P = 0.0006) and right atrial end-diastolic volume (P = 0.0065) in surgically closed ASD patients compared to controls.

Table 2 shows time-domain variables for all three groups. Surgically closed ASD patients had lower values in both parasympathetic and sympathetic domains: SDNN (P = 0.0070), SDANN (P = 0.0135), SDNNi (P = 0.0095), RMSSD (P = 0.0220), pNN50 (P = 0.0058) and triangular index (P = 0.0232) compared to controls. The balance between parasympathetic and sympathetic was skewed towards a higher sympathetic activity level and a more depressed vagal tone. Percutaneously closed ASD patients also demonstrated lower levels in SDNN (P = 0.0261), SDANN (P = 0.0307) and RMSSD (P = 0.0428) compared with that of the controls, while the remaining parameters showed a tendency towards lower values without being statistically significant.

Table 3 demonstrates the heart rate characteristics and events in the three groups during the 48-h Holter monitoring as well as electrocardiographic parameters. Both surgically closed and percutaneously closed ASD patients had a lower maximum heart rate compared to the controls (P = 0.0051 and P = 0.0253, respectively).

Surgically closed ASD patients had a higher occurrence of incomplete RBBB compared to the controls (P = 0.0408). The remaining cardiac events were more pronounced in the surgically and percutaneously closed groups, although not different when compared with the controls.

No correlation was found between age at ASD closure and HRV parameters. A negative correlation between ASD size before closure and pNN50 was observed (P = 0.0288) but no correlation was found regarding SDNN (P = 0.7165), SDNNi (P = 0.0631),

SDANN ($P = 0.9310$), RMSSD ($P = 0.1603$) and triangular index ($P = 0.2154$).

DISCUSSION

ASD patients have decreased HRV more than a decade after surgical or percutaneous closure. The HRV impairment is particularly pronounced in the surgical group showing sympathetic dominance and parasympathetic withdrawal.

RMSSD and pNN50 primarily reflect parasympathetic activity in the heart [19]. These parameters were both decreased in the surgically closed ASD patients, whereas only RMSSD was decreased in the percutaneously closed ASD patients. SDNN, SDANN, SDNNi and triangular index, reflecting both sympathetic and parasympathetic activity, were all decreased in surgically closed ASD patients, whereas the percutaneously closed ASD patients only displayed decreased SDNN and SDANN among the combined HRV parameters.

Heart rate varies every moment to accommodate the beat-to-beat variations in our circulation. The heart rate is regulated by the changes in autonomic activity and as such, heart rate functions as a biomarker reflecting the sympathetic and parasympathetic activity in the heart. HRV is lower in congenital heart diseases where the autonomic activity leans towards a sympathoexcitation of the heart reflecting a generally higher physical and/or emotional stress level [10]. In addition, this is associated with an increased risk of fatal arrhythmia [20]. It is believed that an increase in humoral sympathetic mediating molecules and an impairment of the baroreflex control of the autonomic activity is responsible for this finding [21].

In healthy people, sinus arrhythmia is mediated by right atrial tension, when venous blood returns to the right atrium (RA) during inspiration, and the inspiratory inhibition of the carotid sinus reflex. These mechanisms are challenged in patients with an ASD. Compared to an RA within normal dimensions, the communication between the atria through the septum and the dilated RA results in a relatively smaller increase in diastolic volume. As a result, a decrease in HRV can be observed [15].

Horner *et al.* [22] demonstrated this exact mechanism in porcine hearts. An increase in the right atrial pressure stretches the sinoatrial node and reduces the SD of the sinus intervals. This lowering of HRV is believed to be caused by a reduced cyclic variation in the sinoatrial activity as a result of a sustained atrial stretch. Furthermore, the stretching of the RA is a crucial stimulant of the release of natriuretic peptide. A hormone that has numerous regulative functions including vagal influence on cardiopulmonary baroreceptors and a decrease in sympathetic ganglion transmission [23, 24].

Although both the left and right atria may remodel and reduce in size following correction [25, 26], some patients may still have atria affected by the earlier volume-overload. Following correction, ASD patients have been found to have increased biatrial filling pressures indicative of stiffer or more enlarged atria [27]. Similarly, an enlargement of the right atrial end-diastolic and end-systolic volumes was found in the surgical group of our study. These remnants of earlier volume-overload may be part of the explanation for the decreased HRV observed in the ASD patients.

Consequently, HRV has shown to increase in ASD patients in the months following ASD closure with some patients recovering to the HRV level in the controls. The increase in HRV has been observed in both the surgically and percutaneously closed; however, the recovery of HRV seems to have been greater in the percutaneously closed [14–16, 28]. Our literature review on HRV in ASD patients after closure found the longest follow-up time available to be 6 months [14]. In this study, the mean follow-up time of the surgically closed and the percutaneously closed was 19 and 15 years, respectively, enabling us to evaluate the long-term effects of ASD closure on HRV in these patients.

The HRV findings for the percutaneously closed ASD patients did not differ from the controls in as many parameters as the surgically closed ASD patients did. A plausible explanation could be the difference in defect size. A correlation was only detected between defect size and pNN50 indicative of larger defects being associated with reduced parasympathetic tone. In line with this, Massin and von Bernuth [10] found no correlation between HRV parameters and the volume or ratio of the left-to-right shunt. However, a decrease in HRV parameters was found to be related to mean right atrial pressure and right ventricular end-diastolic pressure [10]. We did observe an enlargement of the right atrial end-diastolic and end-systolic volumes in the surgically closed group years after closure but found no correlation between any of the echocardiographic parameters and HRV.

A possible explanation of why the surgically closed ASD patients differed from controls in more HRV parameters could be the difference in closure technique. The autonomic nerve supply to the heart may have been affected during surgery. The autonomic nerves access the heart via the adventitia in the large vessels such as the aorta, the pulmonary artery, the caval veins and the pulmonary veins. During surgery, dissection is made between the aorta and the pulmonary artery for aortic clamp positioning and the caval veins are snared for the establishment of total bypass. The vagal nerves and, in particular, the right vagal nerve innervate the sinoatrial node. This position leaves the vagal activity at particular risk in surgical patients. In support of this, a recent review aimed to describe the chronotropic response to exercise after the closure of ASD or ventricular septal defect. They concluded that surgical closure of the defect lead to permanently impaired peak heart rate [29].

At first glance, the impaired HRV in closed ASD patients, in whom long-term outcome in general is regarded as benign, may be considered a subtle abnormality that does not require much attention. Over a lifetime these changes may, however, carry an increased risk. A recent study by Nyboe *et al.* [3] found the long-term mortality risk to be increased in closed ASD patients with a hazard ratio of 1.4 (1.2–1.7). HRV is known to carry prognostic implications in predicting morbidity and mortality, as impairment of specific parameters, such as SDNN, is deemed a predictor of increased mortality [12, 13]. Hence, our findings could partly explain the increased mortality documented in ASD patients.

Limitations

We found only one statistical difference in events between patient groups and controls, although there was a tendency towards more events in the patient groups. A larger study group and/or a longer Holter monitoring may clarify this. The ASDs were on average closed when the patients were in their teens. Nowadays, ASDs are closed earlier and this cohort predominantly represents the practice from a previous era. ASDs may, however, be detected at all ages, and half of the Danish patients

diagnosed with an ASD during the last 50 years have been diagnosed at an age above 18 years [6, 7] and some patients are still diagnosed with an ASD in adulthood. The problem identified in this study may therefore still be relevant for a vast body of today's patients.

The single-centre nature of this sub-study is another limitation. Therefore, further studies are needed to confirm these data and provide a deeper understanding of the potential impact on morbidity and mortality.

CONCLUSION

Patients who underwent ASD closure a decade or more ago continue to have an impaired HRV compared with their age- and sex-matched controls. Percutaneously closed ASD patients showed a reduction in half of the studied HRV metrics, while surgically closed ASD patients had an overall reduction in all HRV metrics. It remains unclear as to how the reduced variability impacts the patients' physiology over a lifetime as reduced HRV has been associated with increased risk of congestive heart failure and all-cause mortality. These novel findings emphasize the need for continuous surveillance in adult congenital heart clinics and warrant a future focus on late-life complications in patients with a closed ASD.

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Author contributions

Mathias Alstrup: Data curation; Formal analysis; Investigation; Project administration; Visualization; Writing—original draft. **Zarmiga Karunanithi:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Software; Writing—review & editing. **Marie Ø. Maagaard:** Data curation; Formal analysis; Investigation; Writing—review & editing. **Steen H. Poulsen:** Conceptualization; Methodology; Supervision; Writing—review & editing. **Vibeke E. Hjortdal:** Conceptualization; Methodology; Supervision; Writing—review & editing.

Reviewer information

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