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'The sedentary heart': Physical inactivity is associated with cardiac atrophy in adults with an intellectual disability☆

Jeroen C. Vis [a,b], Rianne H. de Bruin-Bon [a], Berto J. Bouma [a], Ad P. Backx [c], Sylvia A. Huisman [d], Luc Imschoot [e], Barbara J. Mulder [a,b,*]

[a] Department of Cardiology, Academic Medical Centre, Amsterdam, The Netherlands
[b] Interuniversity Cardiology Institute of The Netherlands, Utrecht, The Netherlands
[c] Department of Paediatric Cardiology, Academic Medical Centre, Amsterdam, The Netherlands
[d] Prinsenstichting, Residential Centre for People with Intellectual Disabilities, Purmerend, The Netherlands
[e] ASVZ, Residential Centre for People with Intellectual Disabilities, Sliedrecht, The Netherlands

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ABSTRACT

Background: The cardiac muscle is well regulated in response to changes in loading conditions. This cardiac plasticity has been studied intensively and is well known in trained athletes. Conversely, the mechanisms leading to the opposite response are less clear. The aim of this study was to investigate left ventricular (LV) dimensions in a physically inactive population of adults with an intellectual disability.
Methods: Adults with an intellectual disability with and without Down syndrome (DS) and healthy controls were included ($n=182$). Echocardiography was performed in all included subjects and physical activity was measured by means of a questionnaire.
Results: Physical activity was lower in adults with an intellectual disability compared to controls ($p<0.001$). In DS, *i*LVM was significantly lower compared to controls (64 ± 17 g/m^2 vs. 94 ± 17 g/m^2 $p<0.001$). Non-DS adults with an intellectual disability had higher *i*LVM (72 ± 16 g/m^2) compared to subjects with DS, although not significantly different ($p<0.08$). LV volumes were significantly smaller in adults with DS compared to both controls and non-DS adults with an intellectual disability ($p<0.001$). Moderate diastolic dysfunction was found in 57% of the adults with an intellectual disability. In 48 children with DS and 79 controls, mean LV end diastolic diameter was not significantly different during childhood.
Conclusions: LV dimensions are significantly smaller in adults with an intellectual disability compared to controls. These findings appear to be lifestyle related as differences become manifest at adulthood and adults with an intellectual disability generally experience a sedentary lifestyle. Presumably, physical inactivity leads to a condition of cardiac atrophy.

1. Introduction

Quantification of cardiac size, left ventricular (LV) mass and function are among the most clinically important and most frequent requested tasks of echocardiography [1]. These parameters are components of every complete echocardiographic examination and are helpful in the clinical management (treatment and follow-up) of patients with heart failure, valvular disease, hypertension, hypertrophic cardiomyopathy and congenital heart disease [2]. Accurate echocardiographic reference values for LV volumes and mass are of utmost importance [1]. These echocardiographic reference values are missing in patients with a sedentary lifestyle like adults with an intellectual disability and adults with Down syndrome (DS). Cardiac research in DS has been mainly focused on congenital heart disease [3–5]. However, data on cardiac function and dimensions in DS adults with structurally normal hearts are scarce. Since life expectancy of individuals with DS is increasing and most of them now reach adulthood in the developed countries, information about cardiac parameters and dysfunction in this patient group is clinically relevant.

The cardiac muscle is well regulated in response to changes in loading conditions. Increased volume and pressure lead to increase in cardiac muscle mass. This cardiac plasticity has been studied intensively over the past years in pathological conditions, but has also been demonstrated in obesity [6] and exercise training [7–9]. Cardiac dimensions in highly-trained athletes compared with matched control subjects show increases of about 10% for left ventricular end-diastolic dimension, about 15 to 20% for wall thickness and about 45% for calculated left ventricular mass [7].

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* Corresponding author at: Department of Cardiology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 5662193; fax: +31 20 5666809.
E-mail address: b.j.mulder@amc.uva.nl (B.J. Mulder).

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Conversely, the mechanisms leading to the opposite response are less clear. Cardiac atrophy has been described after supine bed rest or short-term spaceflight [10,11]. However, whether prolonged physical inactivity in nonathletic populations causes adaptation of cardiac mass is not clear. Aim of this study was to investigate LV volumes and mass in a physically inactive population of adults with an intellectual disability, including subjects with DS.

2. Material and methods

2.1. Study population

The study population consisted of adults with an intellectual disability (with and without DS) living in residential centres for individuals with an intellectual disability. A control group of healthy non-athletic adult volunteers was randomly sampled from the Academic Medical Centre in Amsterdam (including hospital employees and medical students). All subjects were clinically stable and in normal sinus rhythm. Patients with congenital heart defects, severe valvular regurgitation, severe Alzheimer's disease and prior cardiac surgery were excluded (see Fig. 1). Thyroid function was checked by medical charts according to latest laboratory testing within 1 year. Approval was obtained from ethical boards of all participating institutions and informed consent was acquired from all subjects and/or their legal guardians.

A retrospective study was performed in children with and without DS to investigate LV parameters at childhood. In this manner, we can establish if differences found between adults were already present at young age. Children were recruited from a database of the paediatric cardiology department in the Academic Medical Centre and those with a severe congenital heart defect were excluded.

2.2. Echocardiograms

An echocardiogram was performed in all adults with a portable GE VIVID I (Horten, Norway), by an experienced ultrasound technician and evaluated by a cardiologist. All echocardiographic images were acquired and recorded digitally, and analysed offline. Parasternal views were obtained according to recommendations of the American Society of Echocardiography [12]. The following echocardiographic dimensions were measured: thickness of interventricular septum at end diastole (IVS) and of left ventricular posterior wall at end diastole (LVPW), left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD). End diastole was defined as the onset of the Q-wave on the ECG. End systolic LV-dimension was measured as the smallest LV-dimension during the time interval between the time at peak septal motion and peak anterior movement of the LVPW. LV-mass was calculated using the Devereux formula [13]: LV mass (g) $= 0.8 \times 1.04 \times [(\text{LVEDD} + \text{IVS} + \text{LVPW})^3 - \text{LVEDD}^3] + 0.6$. Height and weight were measured and body surface area (BSA) was calculated based on Mostellers' formula: BSA = SQRT((weight × height)/3600) [14]. LV-mass was indexed by BSA (*i*LVM), $\text{BSA}^{1.5}$ and $\text{height}^{2.7}$ to allow comparisons across individuals of varying body sizes. The LV volumes were calculated using the Teicholz' formula: Volume $= (7 \times \text{LV diameter}^3)/(2.4 + \text{LV diameter})$. The echocardiographic parameters for children were adjusted to weight. Diastolic dysfunction was evaluated by recording mitral inflow at the mitral valve tips to assess early (E) and late (A) diastolic peak velocities and deceleration time. Pulsed DTI was performed to assess lateral annular early diastolic velocity (Ea). LV stiffness was calculated as the ratio of pulmonary wedge pressure: $3.2 + (1.1 \times [\text{E/Ea}])$ to LV EDV.

2.3. Physical activity

To demonstrate a sedentary lifestyle in adults with an intellectual disability, we obtain objective information about patients' lifestyle, by means of a questionnaire. Physical activity was measured by the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) [15]. The SQUASH was developed by the Dutch National Institute of Public Health and the Environment and contains questions on habitual activities with respect to occupation, leisure time, household, transportation means and other daily activities. All adult subjects were requested to fill out the number of days per week, the average time per day and the intensity in which the activity was performed. Based on a patient's self reported effort an individual activity score is calculated by multiplying the intensity of the activity (Ainsworth's compendium of Physical activities) with the number of minutes the activity was performed per week [15,16]. In adults with an intellectual disability, a close caretaker or parent was asked to fill out the questionnaire on behalf of the subject.

2.4. Statistical methods

Descriptive statistics were used to describe baseline characteristics. Differences between two groups were analysed by unpaired Student's *t*-test for continuous variables and Chi-square test for nominal variables. Data are given as mean ± standard deviation (SD) and the level of significance was set at $p<0.05$. Comparison of continuous variables among three or more groups was performed using the ANOVA or Kruskall–Wallis-test and post-hoc tests with a Bonferroni correction. The square root of weight was used to allow comparisons between study groups for the nonlinear association of left ventricular end diastolic diameter and weight. Multivariate linear regression analysis was performed with a stepwise forward regression model, in which each variable with a $p<0.05$ (on basis of univariate analysis) was entered into the model. Statistical analysis was performed with the SPSS software for Windows XP version 15.0.

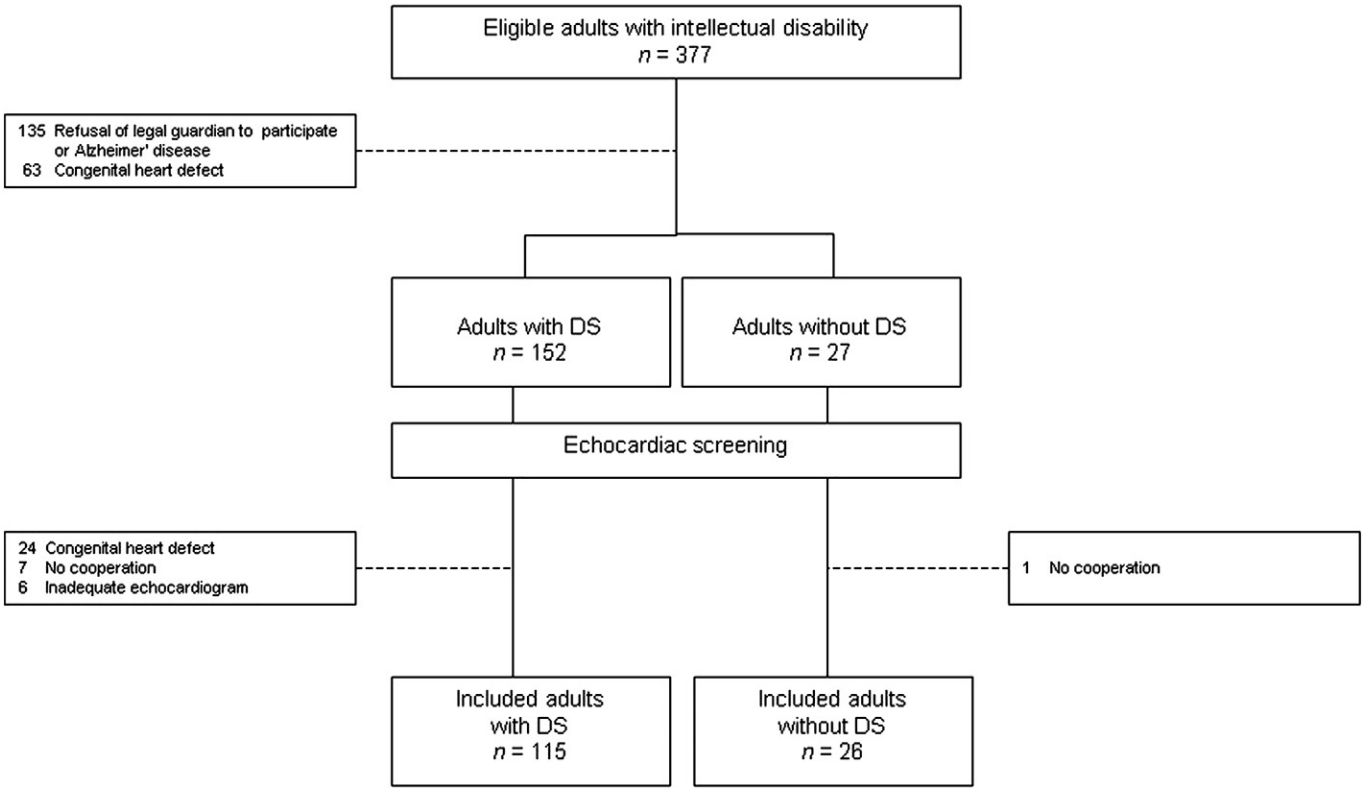

Fig. 1. Flow chart of included subjects. DS, Down syndrome.

3. Results

3.1. Left ventricular mass and volumes in adults

In total 182 adults (mean age 43.6 ± 11.1 years, 45% male) were included in this study; 41 healthy controls, 115 adults with DS and 26 non-DS subjects with an intellectual disability (see Fig. 1). In the non-DS group, 3 adults had cerebral palsy, 1 adults had ring chromosome 18, 1 adult had Fragile X-syndrome, 1 adult had Noonan syndrome and 20 adults had unknown underlying cause of the intellectual disability. In total, 40 patients had hypothyroidism and 5 patients had hyperthyroidism, all regulated under medication. Baseline characteristics are shown in Table 1. In adults with DS, *i*LVM was significantly lower compared to healthy controls (64 ± 17 vs. 94 ± 17 g/m^2; $p<0.001$). Compared to non-DS adults with an intellectual disability, *i*LVM was somewhat lower in adults with DS, although not significantly different ($p<0.08$). LV volumes were significantly smaller in adults with DS compared to both healthy controls and non-DS adults with an intellectual disability ($p<0.001$). Fig. 2 shows cardiac parameters of all included subjects. Aortic root diameter, indexed to BSA was not significantly different between all groups. *i*LVM was inversely correlated with the level of intellectual disability ($r=-0.55$), even when controlled for age or sex by partial correlation. *i*LVM was 94, 72, 66, 64, 59 g/m^2 in adults with no, mild, moderate, severe and profound intellectual disability respectively. Table 2 shows that mild to moderate left ventricular relaxation was found more frequently in adults with an intellectual disability compared to healthy controls ($p<0.01$). Furthermore, LV stiffness was significantly higher in adults with an intellectual disability compared to healthy controls ($p<0.001$) and LV stiffness was inversely correlated with *i*LVM in these subjects ($r=-0.58$; $p<0.001$).

3.2. Physical activity in adults

Physical activity by means of the SQUASH score was nearly twofold higher in healthy controls compared to adults with an intellectual disability ($p<0.001$). No significant difference was found between DS subjects and adults with other causes of intellectual disability. The SQUASH score was positively correlated to *i*LVM ($r=0.41$; $p<0.001$).

3.3. Independent determinants for left ventricular mass and volumes

*i*LVM was correlated with level of intellectual disability. However, A Bonferroni post-hoc analysis showed that *i*LVM was only significantly different between adults with and without an intellectual disability. Therefore in our multivariate linear regression analyses we used the level of intellectual disability as a binary determinant (intellectual disability present or absent). Univariate and multivariate analyses for left ventricular mass and volumes were performed and independent predictors are shown in Table 3. Body surface area, male sex, systolic blood pressure and presence of intellectual disability were all found to be significantly and independently correlated with LVM. SQUASH score was a significant predictor for LV end diastolic volume by multivariate analysis ($r=0.21$; $p<0.001$). Thyroid dysfunction had no influence on cardiac parameters.

3.4. Paediatric study

In total, 127 children (median age 3.0, range 0–18.7 years) were included in this study, 48 children with DS and 79 controls. Baseline characteristics are shown in Table 4. In this retrospective study, DS children with small congenital heart defects but without hemodynamic importance were accepted for inclusion. Of in total 40 children with DS, 5 children had a spontaneously closed ventricular septal defect, 8 children had a small or closed patent arterial duct, 14 children had a small or spontaneously closed atrial septal defect and 10 children had structural normal hearts. In Fig. 3 the mean LV end diastolic diameters are shown by age groups from childhood to adulthood. LV end diastolic diameters were only significantly different in adulthood.

4. Discussion

In this study we demonstrated for the first time that cardiac size was significantly smaller in a large group of adults with an intellectual disability compared to healthy non-athletic controls. These findings were consistent and strongly significant after traditional adjustments for body compositions (height and body surface area) and allometric based criteria (BSA$^{1.5}$ and height$^{2.7}$). LV diameters were not significantly different during childhood, indicating that the smaller cardiac dimensions at adulthood are acquired and lifestyle-related.

In a the prenatal study of Calda et al. in which LV diameters did not differ between DS foetuses and euploid foetuses in the first trimester of gestation [17]. Similarly, in the paediatric study of Russo et al. [18] no significant differences were found in LV volume and *i*LVM between DS children (mean age 3.57 years) and a matched control group. These findings correspond with the hypothesis that differences in cardiac size in our study are lifestyle-related.

Moreover, by comparing cardiac size and volume of DS subjects to non-DS adults with an intellectual disability residing in centres with similar care and day-time activities, we found that LV dimensions were comparable and also significantly smaller compared to healthy controls. Again, these results support the hypothesis that lower LV parameters are lifestyle-related. Most likely, cardiac adaptations

Table 1
Baseline characteristics of adults.

	Total group	Intellectual disability		Control	*P-value*
		DS	Non-DS		
	n = 182	*n = 115*	*n = 26*	*n = 41*	
Male, *n* (%)	82 (45)	48 (42)	15 (58)	19 (46)	0.33
Age, *years*	43.6 ± 11.1	43.4 ± 10.8	50.1 ± 10.6	40.1 ± 11.0	0.001
BSA, m^2	1.73 ± 0.22	1.63 ± 0.2	1.87 ± 0.2	1.87 ± 0.18	<0.001
BMI, kg/m^2	26.1 ± 4.2	27.0 ± 4.2	27.14 ± 4.1	23.3 ± 2.6	<0.001
Height, *cm*	160.3 ± 13.3	153.0 ± 8.0	167.1 ± 13.1	175.3 ± 9.3	<0.001
Weight, *kg*	67.1 ± 12.8	63.2 ± 11.2	75.9 ± 14.7	71.7 ± 11.1	<0.001
Systolic blood pressure, *mm Hg*	116.9 ± 13.3	114.5 ± 12,5	127.7 ± 12.2	114.8 ± 11.0	<0.001
Diastolic blood pressure, *mm Hg*	74.3 ± 9.2	72.3 ± 7.8	81.3 ± 10.5	77.0 ± 10.0	<0.001
Regulated hypothyroidsim, *n* (%)	40 (22)	37 (32)	2 (9)	1 (2)	<0.001
Regulated hyperthyroidsim, *n* (%)	5 (3)	5 (4)	0	0	0.76
Obesity*, *n* (%)	30 (17)	24 (21)	5 (20)	1 (2)	0.03

Continuous values are mean ± SD, BSA; body surface area; BMI, body mass index; DS: Down syndrome.
* Defined as BMI > 30 kg/m^2.

occurred, as adults living in residential centres, experience a sedentary lifestyle. These patients are physically inactive, due to their intellectual and concomitant physical disabilities. The SQUASH score about physical activity was positively correlated with *i*LVM and intellectual disability. Thus, adults with an intellectual disability (with and without DS) living in residential centres are, in general, physically

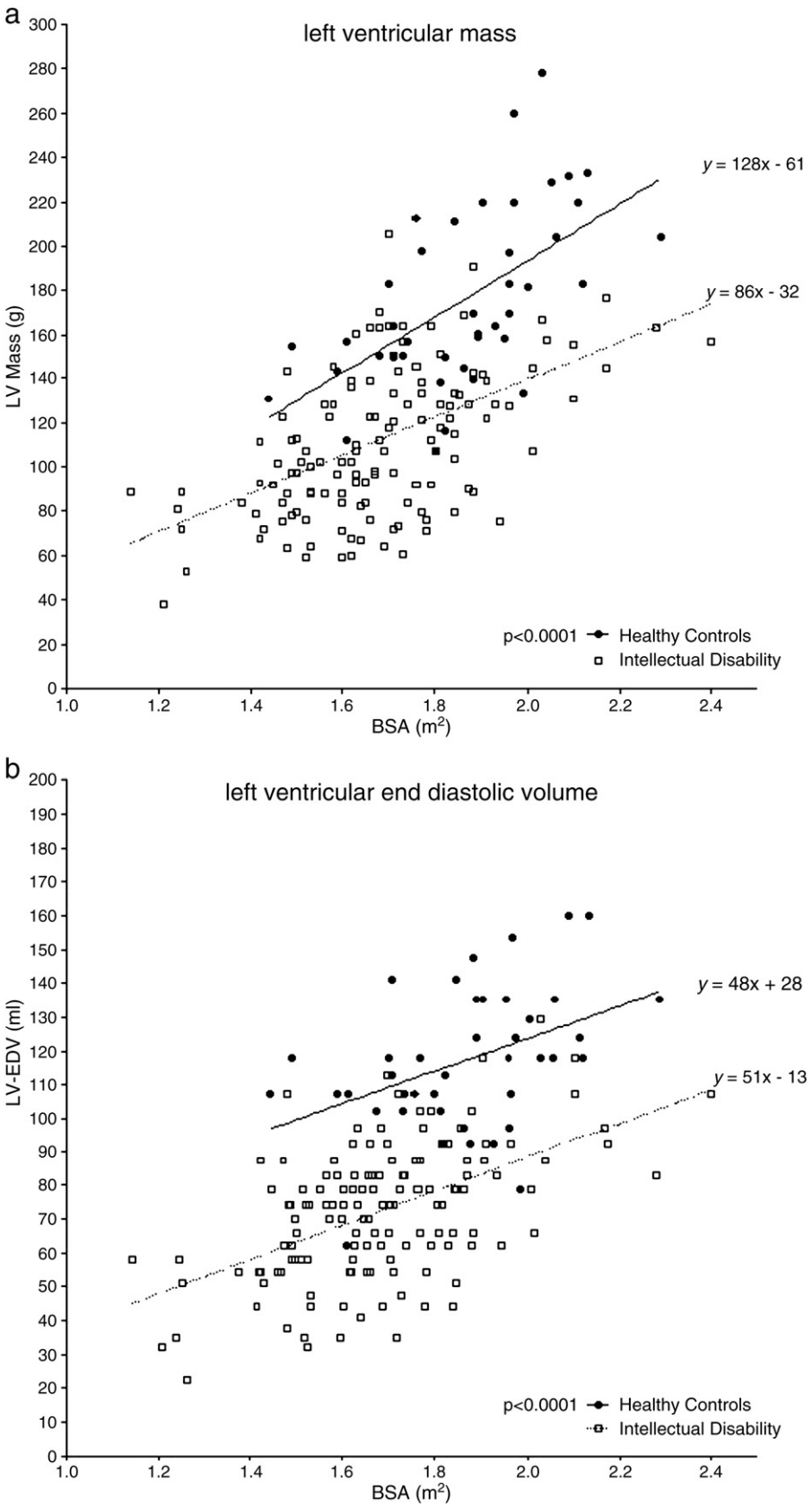

Fig. 2. Echocardiographic parameters of adults. a: left ventricular mass. b: left ventricular end diastolic volume. c: left ventricular end systolic volume. ●, healthy controls. □, adults with an intellectual disability. DS, Down syndrome; LV, left ventricular; BSA, body surface area. LV-EDV, left ventricular end diastolic volume; LV-ESV, left ventricular end systolic volume.

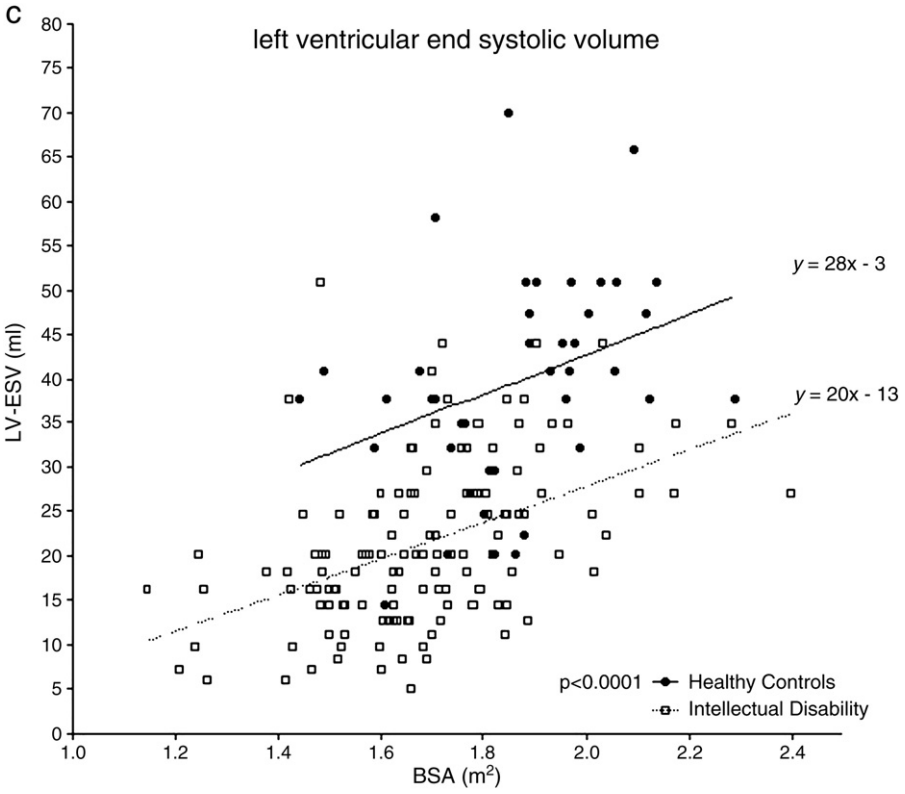

Fig. 2 (*continued*).

Table 2
Results.

	Intellectual disability		Control	*P-value*
	DS	Non-DS		
	n = 115	*n* = 26	*n* = 41	
Cardiac mass and volumes				
LVM, *g*	104 ± 32	134 ± 30	176 ± 40	<0.001
*i*LVM, g/m^2	64 ± 17	72 ± 16	94 ± 17	<0.001
LVM/height2.7, g/m^2	33 ± 9	34 ± 9	39 ± 7	0.005
LVM/BSA1.5, g/m^2	50 ± 13	53 ± 10	69 ± 13	<0.001
*i*LVEDV, ml/m^2	42 ± 11	45 ± 10	63 ± 10	<0.001
*i*LVESV, ml/m^2	12 ± 5	15 ± 5	21 ± 6	<0.001
*i*Aortic root diameter, mm/m^2	18 ± 2	18 ± 3	17 ± 1	0.8
*i*Vena cava inferior diameter, mm/m^2	6.6 ± 1.6	6.4 ± 2.3	10 ± 3	<0.001
*i*Vena cava Inferior diameter collaps, mm/m^2	3.1 ± 1.1	3.0 ± 1.4	5 ± 1.5	<0.001
Relative wall thickness, *mm*	0.4 ± 0.1	0.41 ± 0.1	0.34 ± 0.1	<0.001
LV function				
Fractional shortening, *(%)*	41 ± 6	37 ± 7	37 ± 5	<0.001
Ejection Fraction, *(%)*	72 ± 8	66 ± 10	67 ± 7	<0.001
E, *cm/s*	85 ± 17	73 ± 16	80 ± 17	0.008
A, *cm/s*	62 ± 18	66 ± 18	51 ± 13	0.001
Ea, *cm/s*	9.1 ± 2.6	7.9 ± 2.3	12 ± 2.0	<0.001
DT, *ms*	211 ± 48	210 ± 53	198 ± 35	0.40
E/A ratio, *cm/s*	1.5 ± 0.6	1.2 ± 0.4	1.7 ± 0.5	0.002
E/Ea ratio	9.9 ± 2.6	9.8 ± 3.1	6.8 ± 1.2	<0.001
E/Ea, *n* > 15, *(%)*	5	4	0	0.30
E/Ea, *n* > 10, *(%)*	31	38	0	<0.001
Mild diastolic dysfunction[a], *(%)*	4	8	0	0.2
Moderate diastolic dysfunction[b], *(%)*	53	73	33	0.01
Left ventricular stiffness, *mm Hg/ml*	0.23 ± 0.12	0.18 ± 0.07	0.09 ± 0.02	<0.001
Left ventricular stiffness, *n* > 0.27 *mm Hg/ml (%)*	18	13	0	0.006
SQUASH-score	3639 ± 2556	4163 ± 3013	7837 ± 2832	<0.001

Continuous values are mean ± SD; *i*, indexed to body surface area; LVM, left ventricular mass; DS, Down syndrome; BSA, body surface area; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end diastolic volume; E, peak early filling velocity; A, velocity at atrial contraction; DT, deceleration time; Ea, velocity of mitral annulus early diastolic motion; SQUASH-score, Short Questionnaire to Assess Health-enhancing physical activity score.

[a] E/A ratio < 0.75.

[b] 0.75 < E/A ratio < 1.5 > 140 ms.

Table 3
Multivariate analyses for left ventricular measurements.

	LVM		LVEDV		LVESV	
	Beta	*P-value*	Beta	*P-value*	Beta	*P-value*
Intellectual disability	−0.47	<0.001	−0.46	<0.001	−0.37	<0.001
BSA	0.28	0.003	0.37	<0.001	0.28	0.006
Systolic blood pressure	0.20	0.02		NS		NS
Male sex	0.19	0.03		NS		NS
Down syndrome		NS		NS	−0.25	0.02
SQUASH score		NS	0.21	0.006		NS
Age		NS		NS		NS

All variables entered in this model were significantly correlated by univariate testing; NS, non-significant. LVM, left ventricular mass; LVEDV, left ventricualr end-diastolic volume; LVESV, left ventricular end-systolic volume; BSA, body surface area; SQUASH-score, Short Questionnaire to Assess Health-enhancing physical activity score.

Table 4
Baseline characteristics of children.

	Total group	DS	Control	*P-value*
	n = 127	*n = 48*	*n = 79*	
Male, *n* (%)	70 (55)	27 (56)	43 (54)	0.86
Age, *years*	3.0 (0–18.7)	0.5 (0–16.0)	6.3 (0–18.7)	<0.001
Weight, *kg*	14 (3.0–92)	6.3 (3.0–61)	21 (3.2–92)	<0.001

Values are medians with range; DS, Down syndrome.

inactive compared to healthy controls, resulting in lower cardiac mass and smaller volumes.

A hormonal disturbance could be another possible explanation for reduced cardiac mass in patients with DS. Growth hormone and insulin-like growth factor are known to increase LVM [19]. Adults with DS have several features in common with growth hormone deficient patients like overweight, reduced muscle strength and decreased bone density. Suboptimal growth hormone production has been reported in children with DS [20], although recently published data showed normal growth hormone secretion in young adults with DS [19]. However, whether the effect of growth hormone is altered in DS, leading to a functional growth hormone deficiency, despite an apparently normal growth hormone profile is yet unclear. Almost one third of the patients with DS had hypothyroidism, all regulated under medication. Thereby, thyroid dysfunction had no influence on cardiac dimensions. This finding corresponds to a recent study on 1376 Framingham Heart Study participants which showed that TSH concentration was not related with LV structure [21]. On the other hand, hormonal disturbances in DS do not elucidate the smaller cardiac dimensions in non-DS adults with an intellectual disability.

Previous studies have demonstrated that the cardiac muscle is well regulated in response to changes in loading conditions [22,23]. Increased volume and pressure lead to an increase in cardiac muscle mass. This cardiac plasticity has been studied intensively over the past years and is well known in trained athletes [7,24]. Conversely, the mechanisms leading to the opposite response are less clear. Cardiac atrophy has been described after supine bed rest or short-term spaceflight [10,11]. However, adaptation of the cardiac mass after prolonged physical inactivity in a nonathletic population has never been shown. This study demonstrates that a sedentary lifestyle may lead to cardiac atrophy in adults with an intellectual disability. No differences in aortic root diameter were found, illustrating that basic cardiac morphology is identical between adults with and without an intellectual disability and that the adaptations solely occur in the cardiac muscle.

Another clinically important finding of this study is the high percentage of diastolic dysfunction associated to smaller cardiac mass in adults with an intellectual disability. Abnormal gene regulation and reduced cardiac cell number are found in DS [25]. However, diastolic dysfunction was also demonstrated in subjects without DS, disproving a syndromic feature.

Our study had several limitations. Left ventricular mass and volumes were assessed by echocardiography, which has considerably lower accuracy than magnetic resonance imaging (MRI) for quantitative measurements. However, it was not realistic to perform a MRI in adults with an intellectual disability. Echocardiography could be performed in the familiar surroundings of the residential centre, which made examination of these patients highly successful. Another limitation is that the SQUASH questionnaire is not validated for adults with an intellectual disability. Subjects with moderate to severe intellectual disability were not able to fill in the questionnaire. Therefore, this was done by the daily caretaker or a parent, who was well informed about subjects' daily activities. When no reliable

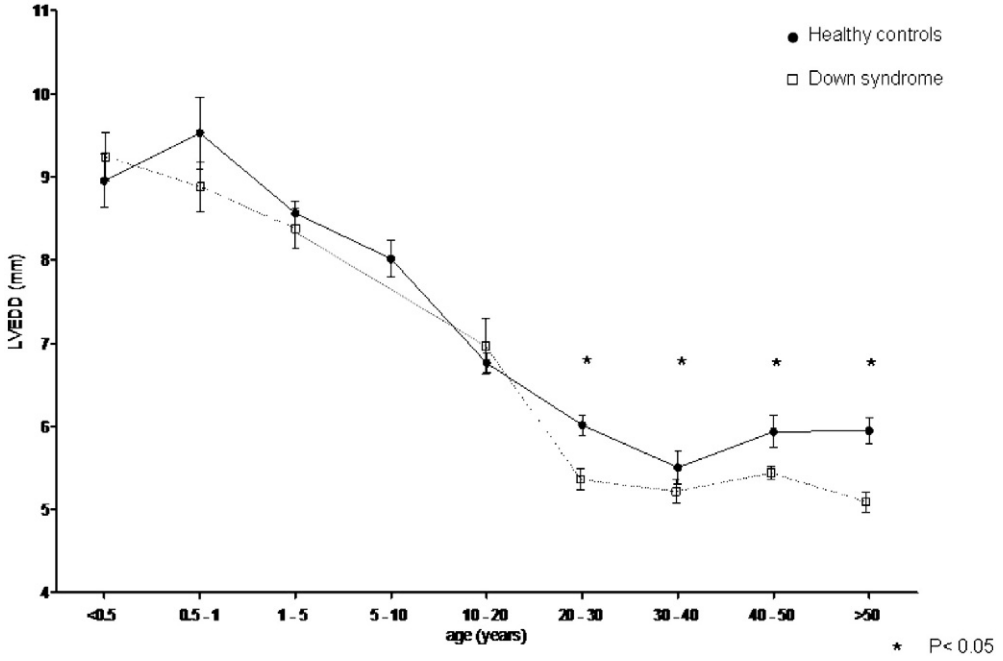

Fig. 3. Left ventricular end diastolic diameter in children and adults. LVEDD: left ventricular end diastolic diameter adjusted to the square root of weight. ●, healthy controls. □, adults with Down syndrome.

information on daily activities could be obtained, we refrained to fill out the questionnaire. Unfortunately data on cardiac function were not available in children.

In conclusion, left ventricular dimensions are significantly smaller in patients with an intellectual disability compared to healthy controls. These findings appear to be lifestyle related as differences become manifest at adulthood and subjects with an intellectual disability generally experience a sedentary lifestyle. Presumably, physical inactivity leads to a condition of cardiac atrophy and seems to be associated to diastolic dysfunction.

Conflict of interest

R.B. reports having received honorarium by Actelion Pharmaceuticals Nederland B.V for performing the echocardiograms.

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