

## **Cardiovascular Physiology and Pathophysiology in Down Syndrome**

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**Short title:** Cardiovascular Physiology in Down Syndrome

## **Abstract**

Down Syndrome (Ds) is the most common chromosomal cause of intellectual disability that results from triplication of chromosome 21 genes. Individuals with Ds demonstrate cognitive deficits in addition to comorbidities including cardiac defects, pulmonary arterial hypertension (PAH), low blood pressure (BP), and differences in autonomic regulation. Many individuals with Ds are born with heart malformations and some can be surgically corrected. Lower BP at rest and in response to exercise and other stressors are a prevalent feature in Ds. These reduced cardiovascular responses may be due to underlying autonomic dysfunction and have been implicated in lower exercise/work capacity in Ds, which is an important correlate of morbidity, mortality and quality of life. Exercise therapy can be beneficial to normalize autonomic function and may help prevent the development of co-morbidities in Ds. We will review cardiovascular physiology and pathophysiology in individuals with Ds, along with exercise therapy and special considerations for these individuals.

**Keywords:** Heart rate, blood pressure, autonomic regulation, Ts65Dn, moyamoya, exercise therapy, intellectual disability.

## **Introduction**

Down Syndrome (Ds) is the most common chromosomal condition, occurring in 1 of every 700 live births [1]. A third copy of chromosome 21 (partial or total) is the cause of Ds, which is also referred to as trisomy 21 [2,3]. Several cardiovascular features, including congestive heart defects (CHD) [4], Moyamoya [5], aberrations in blood pressure (BP) [6] and heart rate (HR) [7], and autonomic dysregulation (as measured by heart rate variability [HRV]) [8] are associated with Ds. Moreover, individuals with Ds undergo premature aging, indicating that they experience certain conditions (e.g., cataracts, gray hairs, hearing loss, osteoarthritis, dementia) in their 40s and 50s that are more prevalent in the elderly in the general population [9]. Nonetheless, they are protected from atherosclerosis. Men with Ds also have reduced risk of myocardial infarction while females with Ds have a similar incident rate of the condition compared to the non-Ds population [10]. These data highlight the complex nature of cardiovascular regulation in Ds. CHDs are perhaps the most characterized cardiovascular complication in Ds, and if not detected early in childhood and surgically corrected, CHDs can deteriorate into the development of more serious conditions such as PAH (i.e., pulmonary arterial pressure > 25mmHg at rest or >30mmHg during exercise).

With improved surgical outcomes, better home care, and de-institutionalization [11], the average life expectancy of individuals with Ds has increased substantially, from 25 years in 1983 [12,13] to 60 years in 2020 [14]. However, there are severe racial disparities as the lifespan of African Americans with Ds (25 years) remains less than half that of Caucasians (60 years) [15]. These racial disparities are an important area of investigation for this population; noting the different experiences resulting in a longer lifespan could inform best practices for overall quality of life in Ds. As Ds individuals across various racial backgrounds are studied, more data about

aging in Ds is being generated. It should be noted that research is still ongoing regarding health and fitness across the lifespan in Ds (for all racial backgrounds), particularly with regards to the cardiovascular system.

Despite the overall increased life expectancy, individuals with Ds have high morbidity and mortality rates compared to the non-Ds population [16]. On average, death from Ds occurs ~20 years earlier than those without Ds. The risk of mortality dramatically increases after 40 years of age [17] compared to other groups. Most individuals with Ds will show some form of Alzheimer's disease after age 40 [18]. Therefore, aging is complex and multifaceted in Ds. Finding ways to increase the quality of life in Ds is important, and exercise therapy may offer an appropriate non-pharmacological intervention that can improve brain and heart health. Proper understanding of the cardiovascular physiology and pathophysiology in the Ds population can be vital to better manage potential secondary diseases and ensure healthy aging.

### **1. Congenital Heart Defects (CHD)**

CHD is a distinct feature of Ds where ~ 40-50% of individuals with the syndrome are born with some type of anatomical heart condition [19]. Atrioventricular septal defect (~45%) accounts for the highest proportion of CHD cases in the Ds population, followed by ventricular septal defect (~35%), atrial septal defect (~8%), persistent ductus arteriosus (~7%), and tetralogy of Fallot (~4%) [4,20]. Sex and race influence the incidence of CHDs in Ds, as females and African Americans are twice as likely to incur CHD than male Hispanics and Caucasians [19], and this topic remains an important area of future investigations. It is possible these higher CHDs may contribute to the earlier mortality observed in African Americans, but CHD does not fully explain the differences in mortality [19], suggesting access of care provided to African

Americans or other aspects of systemic racism could also contribute to lifespan disparities in Ds. Fortunately, most CHDs can be surgically corrected to improve outcomes.

CHDs place this population at a higher risk than the general population for developing PAH (i.e., pulmonary arterial pressure  $> 25\text{mmHg}$  at rest or  $> 30\text{mmHg}$  during exercise) [21], an even more serious and life-threatening condition. The etiology of PAH in Ds is often associated with left-to-right intracardiac shunting as well as chronic upper airway obstruction [22]. Upper airway obstruction can lead to intermittent hypoxia which could exacerbate PAH and cognition deficits. As with many complications in Ds, the causes are multifactorial. Early surgical correction for CHDs is an effective intervention that can improve outcomes in Ds [23,24]. If uncorrected, a substantial proportion of Ds individuals with atrioventricular septal defect and ventricular septal defect, the two most common CHDs in Ds, may also develop life-threatening Eisenmenger syndrome (i.e., an elevation of the pulmonary vascular resistance to a pulmonary-to-systemic resistance ratio  $\geq 1.0$ ) [25], an extreme manifestation of PAH [22,26], further deteriorating the quality of lives of these individuals.

The critical genetic region considered to result in most phenotypes of DS-CHD is located on the 21q22.2 segment of chromosome 21 [27]. Some of the reported candidate genes related to increased risk of CHD in Ds include DSCAM [29], COL6A1 [30], COL6A2 [29,30], and RCAN1 or DSCR1 [31]. The gene DSCAM is responsible for expression of cell adhesion molecules [29]. Increased expression of the DSCAM gene may result in disproportionately high mucoprotein production prior to the development of the endocardial cushion (i.e., precursor structure in the embryo used to create the heart valves) [32]. The excess mucoprotein is hypothesized to prevent endocardial fusion through increased adhesion among myocardial cells, thereby leading to atrioventricular septal defect [33]. COL6A1 and COL6A2 express collagen VI

[30], which is involved in the development of atrioventricular septum. Current data indicates that overexpression of collagen VI is a crucial factor in the formation of atrioventricular septal defect in human fetuses with trisomy 21 [34]. RCAN1 regulates calcineurin [31], which dephosphorylates the nuclear factor of an active T cell only expressed in cardiac endothelial cells [35]. RCAN1 overexpression causes the inhibition of calcineurin and reduces the activity of the nuclear factor of an active T cell in the process of embryonic cardiac development [31]. Ultimately, this process of overexpression via triplication of these genes impairs the proper development of mitral, tricuspid, and septum, leading to CHDs [31].

Micro-RNAs also have roles in CHD associated with Ds. The main role of micro-RNAs is to interact with the three prime untranslated regions of the target messenger RNA (mRNA), leading to the inhibition of mRNA translation [36]. Particularly, researchers showed that microRNA-99a, let-7c, microRNA-125b-2, microRNA-155 and microRNA-802 are overexpressed in cardiac tissue of individuals with Ds [37]. The miR- 99a/let-7c cluster may be involved in the development of CHD in Ds as Coppola et al. [38] showed that the overexpression of this microRNA cluster may inhibit their translation in the fetal cardiac muscle tissue of individuals with the syndrome.

Additionally, signal pathways of vascular endothelial growth factor A [39], the Hedgehog signaling pathway [40], the cross-presentation of particulate exogenous antigens [41], and calcineurin/nuclear factor of an active T cell [31] may also be involved in CHDs related to Ds. Evidence reveals that the vascular endothelial growth factor A pathway consists of a few missense variants that are impaired in Ds individuals with atrioventricular septal defect [39]. Further, Goddeeris et al. [42] observed that failure of Hedgehog signaling reduces the proliferation of dorsal mesocardium protrusion, a crucial structure required for the proper

formation of septum, which in turn leads to atrioventricular septal defect. Although the precise mechanisms are unclear, the cross-presentation of particulate exogenous antigens pathway may be used as an indicator of CHD-Ds as well [41]. Lastly, as previously mentioned, the activity of the nuclear factor of an active T cell is reduced by the RCAN1 overexpression through calcineurin inhibition during embryonic heart development, which in turn interferes with the mitral, tricuspid, and septal development [31]. Of note, these areas have been reviewed in depth quite eloquently elsewhere [43].

Ds individuals diagnosed with CHD in childhood with a history of surgical intervention may still develop further pathology and need additional procedures in later life [44]. Nevertheless, surgical correction of CHD is considered the most common and effective strategy for preventing the deterioration of CHDs. Reports show considerably lower mortality risk after the repair of an atrioventricular septal defect in individuals with Ds compared to other groups [24,45]. Of note, cardiovascular differences across the lifespan in individuals with corrective surgery for CHDs versus those without any CHD are not widely known. It will be important to determine if individuals with CHD (corrected and/or not corrected) within the Ds population need particular medical support or interventions as they age.

## **2. Moyamoya**

Moyamoya is a nonatherosclerotic cerebrovascular disease that occurs due to the stenosis of the internal carotid artery and anterior and middle cerebral artery, increasing the risk of stroke [5,46]. The first discovery and description of the disease came from Takeuchi and Shimizu in Japan. The fragile angiographic pattern led these authors to name the disease “moyamoya” or “puff of smoke” in English. Moyamoya is more prevalent in Ds than in the non-Ds population [5,46]. In fact, the risk of Moyamoya occurrence might be as much as 26-fold higher in Ds

compared to the general population [47], suggesting that Ds may be a risk factor for developing Moyamoya disease, or Moyamoya syndrome as it is referred to in those individuals with a previous underlying condition.

Additionally, a retrospective case control study from Santoro et al. [48] reports that individuals with Ds experience increases in BP for 12 to 18 months prior to Moyamoya diagnosis. Importantly, although higher than baseline values, the BP readings were still within the normal range [48]. This point highlights why characterizing the cardiovascular physiology of Ds across the lifespan has implications for clinical outcomes, as the diagnosis of Moyamoya in Ds usually comes after a stroke occurrence [49]. BP is therefore important for disease prediction and prevention of related sequelae (e.g., stroke). The details of the BP literature in the Ds population are discussed in the following sections (3. Atherosclerosis and 4. Aberrations in Cardiovascular Regulation).

Direct (i.e., anastomosis of superficial temporal artery to a cortical artery) and indirect (i.e., placement of tissue supplied by the external carotid artery in direct contact with the brain) revascularization procedures are recommended for Moyamoya in Ds [50]. Bello et al. [50] state that these procedures result in angiogenesis (i.e., the growth of new blood vessels) in the affected area of the cerebral cortex. Santoro et al. [48] also reported decreases in BP percentiles after revascularization procedures. Hence, increases in BP may be associated with vasculopathy (i.e., a disease affecting blood vessels). We hypothesize the autonomic nervous system is also mediating some of these changes in systemic blood pressure based on the transient BP increase before Moyamoya diagnosis and the return to normal values after intervention. More studies are warranted to investigate these hypotheses.

### **3. Atherosclerosis**



Individuals with Ds have higher prevalence of obesity [51], diabetes [52], sedentary lifestyle [53], and abnormalities in lipid metabolism [54]. Despite the presence of various cardiovascular disease risk factors listed above, these individuals have a lower risk of developing atherosclerosis compared to the general population [55,56]. Murdoch et al. [56] observed no atherosclerosis in five autopsies of individuals with Ds. Head et al. [55] reported a considerably lower number of atherosclerosis and arteriosclerosis in postmortem tissues of individuals with Ds (n = 32), compared to those with sporadic Alzheimer's disease (n = 80) and a healthy control group (n = 37). These findings support the recognition of Ds as an atheroma-free model.

Traditional cardiovascular risk factors do not seem to fully explain the risk for atherosclerosis in Ds as they do in non-Ds populations. Parra et al. [57] showed that surrogate variables of atherosclerosis such as pulse wave velocity and carotid intima thickness were poorly correlated with anthropometric (obesity, body mass index, abdominal obesity, waist circumference, waist-to-hip ratio), hemodynamic (peripheral and aortic systolic BP and diastolic BP), and lipid profiles (low-density and high-density lipoproteins, total cholesterol, triglycerides) in Ds compared to non-Ds group (n=51). Draheim et al. [58] also reported lower carotid intima thickness in Ds, suggestive of lower atherosclerosis. Traditional cardiovascular risk factors (e.g., age, gender, physical activity, insulin, low-density lipoprotein) explained 30% of the variation in carotid intima thickness in the Ds group. The same regression model of cardiovascular disease risk factors accounted for 70% of the carotid intima thickness variation in the non-Ds group matched for sex and age [58]. Overall, these findings reinforce the uniqueness of atherosclerosis development (or lack thereof) in the Ds population, including traditional markers and risk factors for this pathology.

Endothelial cell function may be impaired in Ds individuals despite their protection against atherosclerosis. Bigazzi et al. [59] showed that a Ds group (n=9) had a substantial impairment in endothelial function (as measured by brachial flow velocity) compared to an age-matched euploid group (n=8). Both groups were free of hypertension, dyslipidemia, and diabetes mellitus. Additionally, Perepitchka et al. [60] studied differences in endothelial cells in Ds and euploid induced pluripotent stem cells. Their results demonstrated impairment in endothelial cells as evidenced by the decreased proliferation and reduced migration of induced pluripotent stem cells. Endothelial progenitor cells are involved in the regeneration of endothelial lining of blood vessels and have a key role in the maintenance of endothelial integrity (Reviewed in: Yoder 2012 [61]). Costa et al. [62] revealed that the number of endothelial progenitor cells in plasma samples were reduced in a Ds group (n=50) versus age-matched euploids (n=30). Thus, the impairment in the number of circulating endothelial progenitor cells may also contribute to the complex cardiovascular phenotype in Ds individuals.

Additionally, lower BPs at rest may have protective roles against the development of atherosclerosis in the Ds population. For instance, Rodrigues et al. [6] and Parra et al. [57] reported that reduced peripheral and aortic systolic and diastolic BPs in the Ds group may mitigate the risk of atherosclerosis by reducing arterial stiffening, a risk factor for developing the condition. Several lines of evidence also suggest that reduced HR responses during exercise, cold pressor and tilt tests compared to non-Ds populations may be part of the natural protection against atherogenesis [7,8]. However, the reduced ability to increase HR during times of need could influence the capacity to do work and exercise in Ds. Cardiovascular responses across the lifespan in Ds are still being explored, and perhaps lower BP and HR are protective in one realm (atherosclerosis) but create physiological challenges in response to stressors common in

everyday life. In older individuals without intellectual disability, lower BP is associated with reduced cognitive functioning [63,64]. It is possible the lower BP observed in Ds influences dementia in Ds aging. In fact, a preliminary study observed a strong association with lower cerebral blood flow and Severe Impairment Battery testing in Ds [65]. Since a large majority of individuals with Ds experience dementia after age 40 years [66], understanding how BP is regulated across the lifespan is important for this population as the life expectancy is increased for Ds.

#### **4. Aberrations in Autonomic Regulation**

Lower BP and altered HR in Ds at rest and in response to stressors likely have an autonomic origin [6,8,57]. Physiological stressors in this context include head-up tilt, orthostatic challenge or active standing, isometric handgrip, aerobic exercise, or resistance exercise. The impaired baroreflex control of the sinoatrial node may play a role in the autonomic abnormalities observed in Ds individuals. Iellamo et al. [67] argue that impaired compensatory baroreflex regulation of HR may explain one of the common autonomic phenotypes of Ds- chronotropic incompetence (i.e., lower HR response to exercise). Further, Heffernan et al. [68] demonstrated decreased baroreflex sensitivity (i.e., the reduced ability to respond to a stimulant) at rest and in response to static exercise in the Ds population. Hence, the quantification of the autonomic activity is critical for Ds research.

Autonomic activity is commonly measured invasively via circulating catecholamines, noradrenaline spillover rate, and microneurography; non-invasive techniques include testing of HRV and sudomotor function. HRV is a preferred technique to assess autonomic activity in research settings given its low cost, ease to perform, and the low participant burden related to its non-invasive nature. HRV is defined as the variation in time (ms) among successive heartbeats

(or R waves on an electrocardiogram) and can be analyzed in both the time (e.g., RMSSD) and frequency (e.g., low frequency [LF], high frequency [HF] bands) domains. Time domain measures quantify the amount of variability during the recording [69] where higher variability indicates increased parasympathetic influence on the heart, or vice versa. The frequency domain variables provide information on how the power (i.e., variance of a rhythm) is distributed as a unit of frequency measured in Hertz (Hz) [69]. The discussion over the use and representation of the LF band is still ongoing, but it is generally accepted that the LF band is generated by both the sympathetic and parasympathetic nervous systems [70]. It should be noted that an overwhelming majority of the researchers agree the HF band reflects parasympathetic or vagal modulation.

Low HRV is associated with a reduced ability for an organism to deal with the internal and external causes of stress and counter diseases [69]. The clinical significance of HRV was first highlighted by Hon & Lee in 1965 [71]. They observed that low HRV was the first sign of fetal stress while HR did not change during labor and delivery [71]. Since the initial observation, HRV has gradually advanced as a popular physiological marker 1] to determine the early signs of a pathology, the presence of a chronic disease, or a health condition and its treatment prognosis [72]; and 2] to evaluate the ability to cope with stress and the effectiveness of an intervention (e.g., exercise, medical procedure) [73].

Multiple studies have used HRV to examine autonomic variation or imbalance in Ds. For instance, Baynard et al. [74] investigated HRV at rest and during exercise in Ds (n=16; age: 20.8 yr) and non-Ds (n=15; age: 19.7 yr) groups with intellectual disability. The researchers reported higher time domain measures of standard deviation of normal-to-normal R-R intervals (SDNN) and RMSSD along with increased frequency domain of the HF band in Ds compared to their peers with intellectual disability, implying that autonomic differences in Ds may result from

greater parasympathetic regulation of the heart. Iellamo et al. [67] studied autonomic regulation at rest and during standing in individuals with Ds without CHD (n=10; mean age: 26.3 yr) compared to healthy individuals (n=10; mean age: 26.1 yr). These researchers found reduced LF and HF bands in Ds compared to non-Ds groups, indicating the autonomic difference may be due to the blunted sympathetic and parasympathetic regulation in Ds. Further, Goulopoulou et al. [75] examined the cardiac autonomic modulation only at rest in individuals with Ds without CHD (n=50; mean age: 24.0 yr) compared to healthy individuals (n=24; mean age: 26 yr). The authors demonstrated a significantly lower time domain measure of total variability in Ds than in the control group, suggesting that the autonomic regulation difference in Ds may occur as a result of reduced parasympathetic or increased sympathetic activity. Taken together, these data demonstrate reduced parasympathetic tone in Ds. However, additional studies are presented in Table 1 which suggest more incongruencies across the literature.

The inconsistencies in the literature demonstrate a need for larger cohorts, standardization of methods, and common controls. In terms of the methodology, durations of the HRV recordings, software package for the analysis of HRV, the type of HRV measurement device, and artifact correction methods vastly differ among these studies. These publications are also inconsistent in how they control for HR, intellectual disability, aerobic capacity, medication use, and body weight, all of which could be causes of the discrepancies in the clinical literature on autonomic regulation in Ds. Long-term (e.g., 24 hr) HRV recording is considered better for evaluation as the variables from this recording have higher power in predicting cardiac events and mortality than those of short-term recordings (e.g., 5 min) [76]. All the studies in the clinical literature (Table 1) use short-term HRV recordings (i.e., <15 min), which may be due to the low compliance of using ambulatory HR monitors in Ds individuals. Animal models can, therefore,

offer alternative pre-clinical platforms to study Ds in a more controlled environment with the opportunity to use long-term HRV recordings.

### **5. Mouse Models of Ds to Study Cardiovascular Regulation**

Investigation of Ds has multiple challenges, as large variation exists between individuals with Ds due to the heterogeneity of the condition. A major issue within and across human studies is the ability to recruit appropriate control groups and normalize physiological data. This normalization concern presents important considerations particularly related to examining the cardiovascular components of Ds [77]. Human investigations of Ds have multiple confounding variables to simultaneously control for heart rate, body weight, sex and age differences [78]. Another caveat relates to whether or not controls should have some form of intellectual disability. The use of murine models allows for addressing some of the challenges associated with human research, as appropriate controls can be bred to account for many of the issues listed above. While no mouse model will completely recapitulate the human condition, these experiments can complement human research and add to our understanding of Ds. Importantly, use of animal models allows for more invasive measures and implementation of pharmacological means to stimulate specific physiological challenges.

Several mouse models have been developed to investigate mechanisms of Ds. Orthologs of genes on human chromosome 21 are spread predominantly throughout mouse chromosome 16 (Mmu16), as well as on Mmu17 and Mmu10 [79]. Many of the existing models are segmentally trisomic, resulting in only partial expression of the trisomy associated with human chromosome 21. Previously engineered mouse models completely trisomic for Mmu16 do not normally survive gestation [79]. Of the murine models, the Ts65Dn mouse is the most widely studied and lives to adulthood. This longevity allows for the ability to study Ds across the lifespan. The

Ts65Dn model expresses segmental trisomy of the distal region of Mmu16 attached to the centromeric end of Mmu17, which encompasses ~56% of the genes on human chromosome 21 [81] and the Ds critical region, a segment of 33 genes considered sufficient in producing most Ds phenotypes [82]. Other popular models, including Ts1Cje and Ts1Rhr, contain only 81 and 33 of the genes (respectively) that are trisomic within the Ts65Dn model [83] and are mainly used for investigation of the cognitive and craniofacial complications of Ds [84]. New mouse models are being developed to help re-capitulate a more genetically and phenotypically similar trisomic strain, including TcMAC21, which contains ~93% of the coding genes on human chromosome 21 [85]. This new model is promising, as it displays Ds phenotypes related to heart defects, the craniofacial skeleton, and learning/memory impairments [85]. Nevertheless, the Ts65Dn mouse currently serves as the most cited model for Ds and has been extensively used for proof-of-concept therapeutic studies and pre-clinical trials [86]. The research linking Ts65Dn mice to the Ds clinical phenotype is extensive; this model expresses many Ds-related pathophysiological issues including cognitive and behavioral impairments and craniofacial abnormalities [87]. Cardiac dysfunction and anatomical anomalies displayed by the Ds population are also expressed in the Ts65Dn model [88].

Cardiovascular abnormalities in the form of right aortic arch and intracardiac septal defects have been reported in Ts65Dn neonates [84], similar to that of Ds individuals born with CHD. Moreover, Williams et al. [89] confirmed additional shared cardiac anomalies between Ds patients and the Ts65Dn model. Vascular and intracardiac anatomical defects were found in 17% of Ts65Dn neonates, albeit this incidence rate is lower than that reported (~40%) for the Ds human population [89]. Of note, the TcMAC21 model has been investigated for the presence of CHD and a reported 28.6% of animals had a structural defect of the heart [85], suggesting it

could be of great use for future investigations of Ds and CHD in particular. The ECG abnormalities have also been documented in adult Ts65Dn mice, as evidenced by fragmented waveforms and changes in wave amplitude and suggest conduction defects into adulthood [92].

Deviations in the electrical excitation of cardiac muscle outside of normal parameters has direct implications on cardiovascular function, with the potential to impact variables such as HR and BP down the line [93]. As previously discussed (4. Aberrations in Autonomic Regulation), Ds individuals present with lower BP, reduced HR response, and alterations in HRV response [6,8,57], indicative of potential differences in autonomic regulation. These aberrations have been documented in Ts65Dn mice, suggesting this model serves as a feasible way to study mechanisms of cardiovascular pathophysiology in Ds. Recent work by our group demonstrated lower BP in 6- and 12-month old Ts65Dn mice compared to their wild-type counterparts, as evidenced by lower systolic BP (10 mmHg difference in both age groups) and lower diastolic BP (6-month: 11 mmHg difference, 12-month: 15 mmHg difference), a trend similar to what is observed across the Ds lifespan [7]. Additionally, differences in autonomic regulation elucidated via altered HRV have been noted in the Ts65Dn model. Through heart rate spectral analyses, DeRuisseau et al. [88] reported reduced high frequency power spectra differences in Ts65Dn compared to wild-type (WT) controls, suggestive of reduced parasympathetic tone. Taken altogether, Ts65Dn is a viable and appropriate model to understand mechanisms of altered autonomic function and CV dysregulation in Ds.

Future studies should be aimed at further elucidating autonomic discrepancies within the Ds population, as it is relevant to participation in activities of daily living and could help increase quality of life. The Ts65Dn model serves as a means of investigating autonomic contributions to CV dysfunction across the lifespan and during various activity states (e.g., rest, sleep, exercise,



stress). With a high rate of Moyamoya in Ds individuals, further characterization of peripheral and cerebral BP alterations could shed light on this condition's progression. Additionally, since many individuals with Ds also experience some form of Alzheimer's disease after age 40 [18], fluctuations in blood pressure could be one important piece to the puzzle. Although it should be acknowledged that Alzheimer's disease is multifactorial and likely involves many features associated with triplication of certain genes in Ds. Aging studies using the Ts65Dn model may clarify the contribution of BP responses to future dementia. The similar cardiovascular phenotype displayed by Ts65Dn mice and Ds individuals also warrants exploring the potential for exercise as a non-pharmacological therapeutic agent. This intervention may be particularly crucial to addressing the high rate of Alzheimer's disease within the Ds community. Cardiac dysfunction has important implications for cognitive health in older adults [94] and increasing physical activity could provide a means of alleviating risk, as it has been suggested to do in the general population [95]. Since there are a multitude of safety and experimental design issues specifically related to exercise intervention in the Ds population (discussed in 6. Exercise Therapy), determining the intensity, dose, and mechanism of action may prove to be more feasible through the murine model. Overall, with the Ts65Dn mouse showing many similar cardiovascular traits to Ds, use of this particular model (and other related mouse models) will be crucial to better understanding cardiovascular regulation and ways to increase quality of life in Ds through more mechanistic research questions.

## **6. Exercise Therapy**

As discussed earlier, lifelong reduced BP and HR may contribute to some form of cardio-protection in Ds. However, these individuals may still suffer from acquired cardiovascular diseases (e.g., myocardial infarction, cerebrovascular events) later in life [10], although the risk

is considered lower for atherosclerotic associated pathologies. It should, however, be emphasized that we are still learning about aging in Ds and more studies are needed to identify the prevalence of cardiovascular-related disorders in Ds, and how they influence other comorbidities. Taking into account the increasing lifespan among these individuals, more attention should be given to the prevention and the management of secondary diseases such as Alzheimer's disease, Moyamoya, and dyslipidemia in Ds. Regular exercise therapy can be a valuable non-pharmacological tool for comorbidities common in Ds. Additionally, increased work capacity and physical function as a result of regular exercise can improve quality of life and help maintain independence across the lifespan.

Exercise training is associated with improved body composition, aerobic capacity, and muscular strength, important factors for maintaining an optimum cardiovascular health. A randomized controlled trial from Silva et al. [96] studied the impact of a 2-month exercise intervention with 3x60-min of exercise session a week on the physical fitness of individuals with Ds in comparison with those without Ds (n=12/group). The authors assessed physical fitness using various tests, including speed of limb movement, handgrip strength, running speed, agility, balance, flexibility, standing broad jump, trunk strength, muscular endurance and 6-min walk time. Ds individuals displayed potentiated responses in all tests and thus improved physical fitness compared to those without Ds. This finding of increased physical fitness may contribute to an improved ability to perform daily tasks, an important component of independence.

Regular exercise therapy may also improve and maintain cardiovascular health through improvements in autonomic regulation of the heart. Few studies have examined the impact of exercise therapy on autonomic activity (as measured by HRV) in the Ds population. Mendonca et al. [97] studied the impact of 12-weeks of combined aerobic (3x30min a week at 65-85% of

$VO_{2peak}$ ) and resistance (2x12 reps a week with 9 exercises) exercise training on HRV in individuals with Ds (n=13) and a non-Ds control group (n=13). The authors reported improvements in sympathovagal balance (i.e., increased parasympathetic or decreased sympathetic activity or both) as evidenced by increases in the HF band and decreases in LF/HF ratio in Ds and non-Ds groups. Additionally, Giagkoudaki et al. [98] examined the effects of 6-month exercise training intervention on autonomic activity through HRV in Ds versus non-Ds (n=10/group) individuals. Similar to Mendonca et al. [97], these authors found improvements in vagal modulation and sympathovagal balance following exercise training in both groups. Moreover, these studies showed that the HRV measures of individuals with Ds were similar in value to non-Ds individuals following the exercise training programs [98]. These findings indicate that regular exercise can normalize autonomic modulation in individuals with Ds to the level of those without Ds, identifying potential autonomic benefits of regular exercise in the Ds population.

Practitioners should be cautious when programming exercise prescription for these individuals due to Ds-associated pathological issues (e.g., muscle hypotonia, loose ligaments). Prescreening of these individuals is essential prior to the exercise therapy to determine any health issues that can potentially jeopardize exercise safety. Following medical clearance from their physician, Ds individuals could engage in exercise programs. The focus of exercise prescription in the early stages should be to encourage daily physical activity [99]. The intensity and duration of exercise can be gradually increased as tolerated. Practitioners should refrain from prescribing exercises that include hyperflexion or hyperextension due to high stress imposed on the joints by this type of work [99]. Muscle hypotonia and loose ligaments in Ds can lead to orthopedic problems (e.g., hernias, dislocation of hips) [99]. Therefore, joint stabilizing resistance exercises

should be combined with aerobic exercises to improve the musculoskeletal system and autonomic regulation.

Lack of motivation and attention in individuals with Ds engaging in exercise programs may pose challenges for practitioners. Demonstration of exercises combined with short verbalization (e.g., walk, run, stop) can be helpful to keep individuals with Ds focused on the exercise [99]. Lastly, practitioners should be aware of cardiac medications (e.g., beta-blockers) that individuals with Ds are prescribed when designing an exercise prescription strategy. Cardiac medications can blunt HR responses during exercise [100], leading to inaccurate interpretation of workload perception, which in turn can cause misrepresentation of exercise intensity and thus increase the risk of injury. Therefore, a pictorial Rate of Perceived Exertion Scale may help practitioners to monitor exercise intensity in Ds individuals.

## **Conclusions**

Ds clearly affects the cardiovascular system in anatomical and physiological ways. Surgical correction of CHDs greatly improves cardiovascular outcomes in Ds, but it is unknown how CHD affects cardiovascular physiology across the lifespan. Sex and racial differences regarding CHD in Ds represent an area of exploration that are needed in the clinical literature. More research is also necessary to explore the underlying mechanisms responsible for the low incidence of atherosclerosis in Ds, a finding which could inform therapies for other populations in addition to understanding cardiovascular physiology in Ds. Aberrations in autonomic regulation may similarly have roles in this natural protection against atherosclerosis. However, the direction of the autonomic dysfunction observed in Ds remains unclear due largely to the inconsistent control of various external variables. Use of animal models such as Ts65Dn mice can create a more controlled research environment and allow for examination of the autonomic

differences in Ds. Exercise can be a beneficial non-pharmacological tool to improve overall health of Ds individuals and reduce the risk of some secondary diseases as life expectancy has substantially increased in recent years. Practitioners should be aware of the special considerations for Ds to provide safe and effective exercise therapies.

## Acknowledgments

Funding source: National Institutes of Health: R21HD099573 and 3R21HD099573, DeRuisseau.

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**Table 1.** Aberrations in Autonomic Regulation in Ds Population

Author(s), year	Sample Size		Subject Characteristics		Autonomic Measurements	Considerations	Main Findings	Interpretations
	Ds	Control	Ds	Control				
Ferri et al., 1998 <sup>[28]</sup>	M (7); F (0)	M (6); F (0)	Age (yr):13.9; BMI (kg/m <sup>2</sup> ): 21.4	Age (yr): 12.8; BMI (kg/m <sup>2</sup> ): N/A	ECG (Oxford MPA-II); 10 min during various sleep stages	Did not control for BMI, HR, medication use, aerobic capacity, and ID; HRV analysis was not reported	Higher LF and lower HF bands in Ds than in control during apnea-free periods	Ds individuals have lower vagal modulation during apnea-free stage of sleep
Figueroa et al., 2005 <sup>[90]</sup>	M (8); F (5)	M (6); F (8)	Age (yr):27.8; BMI (kg/m <sup>2</sup> ):32.3; Resting HR(bpm): 76; Handgrip HR (bpm):80; Recovery HR (bpm): 78	Age (yr): 26.4; BMI (kg/m <sup>2</sup> ): 25.9; Resting HR (bpm): 78; Handgrip HR (bpm):90 Recovery HR (bpm): 77	One-lead ECG (BIOPAC); 2 min supine resting; 2 min handgrip; 2 min recovery; Heart Signal software package for HRV analysis	Did not control for ID; peak exercise HR response; aerobic capacity	No difference in HF and LF bands and LF/HF ratio at rest; Higher HF band during handgrip exercise; and Lower HF and higher LF/HF ratio in Ds than in control	Lower HR and BP observed in Ds individuals during handgrip exercise is due to increased parasympathetic or decreased sympathetic modulation
Giagkoudaki et al., 2010 <sup>[98]</sup>	M (4); F (6)	M (5); F (5)	Age (yr): 24.2; BMI (kg/m <sup>2</sup> ): 23.6; pre-training resting HR (bpm): 78.3; post-training HR: N/A	Age (yr): 23.3; BMI (kg/m <sup>2</sup> ): 22.8 Pre-training resting HR: 70.5; post-training HR: N/A	Ambulatory ECG Holter recorder (GBI-3S); long-term HRV measurement before and after 6-month of exercise training (3days/a week);WinTer Holter Analyzer software package for HRV analysis	Did not control for ID; pre- and post-training resting HRs were not reported	Increased HF band following the exercise training in Ds; decreased LF/HF ratio in Ds similar to the ratio in control	The exercise training increased resting vagal tone, and also resulted in an improvement in sympathovagal balance in Ds individuals
Mendonca et al., 2013 <sup>[97]</sup>	M(10); F (3)	M (9); F (3)	Age (yr): 36.5; BMI (kg/m <sup>2</sup> ): 29.3; pre-training resting HR (bpm): 62.7; post-training resting HR: 63.4	Age (yr): 38.7; BMI (kg/m <sup>2</sup> ): 26.6; pre-training resting HR (bpm): 62.6; post-training resting HR: 61.9	Polar R-R Recorder; 10 min of resting supine HRV measurement before and after 12-week of combined aerobic and resistance training; Polar Pro-Trainer software and the	Did not control for ID	Increased resting HFnu and decreased LFnu with a similar magnitude following the exercise training both in Ds and control group	The exercise training led to similar magnitude of increases in parasympathetic activity with a similar magnitude in Ds individuals and their non-Ds peers

					Kubios 2.0 for HRV analysis			
Carvalho et al., 2015 [91]	M (16); F(9)	M (16); F (9)	Age (yr): 8.6; BMI (kg/m <sup>2</sup> ):19.1	Age (yr): 9.1 ; BMI (kg/m <sup>2</sup> ):15.8	Polar RS800 CX monitor; 20 min of resting supine measurement; Polar Precision Performance SW and Kubios software packages for HRV analysis	HR was not reported; did not control for ID	Increased LF band and decreased HF band in Ds individuals at rest compared to their peers in control group	Ds individuals have higher sympathetic or lower parasympathetic activity at rest
Bunsawat and Baynard. 2013 [7]	Handgrip M (6); handgrip F (4) Submaximal M (9); submaximal F (0)	Handgrip M (2); handgrip F (6) Submaximal M (3); submaximal F (6)	Handgrip age (yr): 26; BMI (kg/m <sup>2</sup> ): 39.8; resting HR: 68 Submaximal age (yr):30; BMI: 30.8; resting HR (bpm):73	Handgrip age (yr): 28; BMI (kg/m <sup>2</sup> ): 26; resting HR: 73 Submaximal age (yr):27; BMI: 25.8; resting HR (bpm): 77	5-lead ECG (BIOPAC); 5 min of resting HRV;2 min of handgrip HRV; and 2 min of submaximal HRV; Heart Signal software package for HRV analysis	Did not control for BMI; sex; and ID	Similar time and frequency domain measures at rest, during handgrip, and submaximal cycling compared to their peers in control. BP responses to handgrip and submaximal cycling are similar in both groups	Autonomic and BP responses are not different in Ds individuals
Cunha et al., 2018 [80]	M (sedentary ,15); M (low intensity PA,9); M (vigorous intensity PA level ,12);F (0)	Sedentary M (13); F (0)	Sedentary age (yr):26; low intensity group age (yr):26; high intensity group age (yr):24 Sedentary BMI (kg/m <sup>2</sup> ): 28; low-intensity BMI (kg/m <sup>2</sup> ): 25; high intensity BMI (kg/m <sup>2</sup> ): 23.4	Age (yr): 29;BMI (kg/m <sup>2</sup> ): 27;	ECG; 10 min resting supine and 30 degrees head elevation HRV measurements; Kubios 2.0 software package for HRV analysis	Did not include females; absence of an actual exercise intervention; did not control for ID; sex	Higher LF band and LF/HF ratio and lower total variability and HF band sedentary Ds individuals than in their peers in Ds individuals with low-intensity exercise habit, Ds individuals with high-intensity exercise habit, and control group.	Regular exercise can improve vagal modulation among Ds individuals regardless of exercise intensity

ECG: electrocardiogram; BMI: body mass index; BP: blood pressure; HRV: heart rate variability; HF: high frequency; LF: low frequency; ID: intellectual disability; PA: physical activity