Body Composition, Vascular Health, Cardiorespiratory Fitness, Lung Function, Muscle Architecture, and Physical Activity in People with Young Onset Dementia: A Case-Control Study

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Running head: Health and Fitness in Young Onset Dementia

Abstract

BACKGROUND: Body composition, blood pressure, estimated maximal oxygen uptake (VO_{2max}), lung function, physical activity, muscle architecture, and endothelial function had not previously been examined in people with young onset dementia. Therefore, the study measured these variables in a young onset dementia group, compared them to age-matched controls.

METHODS: Estimated VO_{2max} (via the Astrand-Rhyming test), body composition, blood pressure, lung function (via spirometry), muscle architecture (via ultrasonography) and endothelial function (via flow mediated dilation) were assessed. Physical activity was measured using ActiGraph accelerometers for 7 days.

RESULTS: We recruited 33 participants (16 young onset dementia, 17 controls). The young onset dementia group had shorter fascicle lengths of the vastus lateralis, were sedentary for longer over a seven-day period, and completed less moderate-vigorous physical activity than controls ($p=0.028$, $d=0.81$; large effect, $p=0.029$, $d=0.54$; moderate effect, and $p=0.014$, $d=0.97$; large effect, respectively for pairwise comparisons). Pairwise comparisons suggest no differences at the $p<0.05$ level between young onset dementia and controls for estimated VO_{2max} (despite a moderate effect size [$d=0.66$]), height, body mass, BMI, blood pressure, light physical activity, lung function, muscle thickness, pennation angle, or endothelial function.

CONCLUSION: This study highlights differences between people with young onset dementia and controls, underscoring the need for multicomponent exercise interventions. Future interventions should target muscle architecture, increase moderate-vigorous physical activity, and reduce sedentariness, with the goal of improving quality of life and promoting functional independence.

Key words

Young-onset dementia; neurodegenerative disease; body composition; blood pressure; physical fitness; lung function; physical activity; muscle architecture; endothelial function

Introduction

Dementia is a neurodegenerative condition which leads to partial or complete loss of cognitive function[1]. There are several risk factors associated with dementia such as age, level of education, diet, alcohol use, sleep, smoking, and a range of other factors including chronic comorbidities[2]. In 2015, 50 million people were diagnosed with dementia worldwide[3], which represents ~10% of everyone over 65 years of age[7]. By 2050, this prevalence will mean an incidence of 152 million[4]. This will result in a global cost of dementia of between $1.6 and 2.4 trillion by 2050[5].

Young onset dementia is the onset of dementia before the age of 65 years of age[8] and represents 5% of all dementia cases in the UK, and 3.9 million cases worldwide[9]. A systematic review highlighted an average of 4.4 years between symptom onset and young onset dementia diagnosis, severely impacting upon the support for people with young onset dementia[8]. Possibly in part due to the poor rates of early diagnosis, average life expectancy from young onset dementia diagnosis is 7.9 years, emphasising the aggressiveness of the condition[10.] In young onset dementia, the early age at which symptoms are experienced initiate a cascade of physical and mental decline at a faster rate than late onset dementia[11]. Exercise has been proposed as a non-pharmacological intervention for people with dementia to improve fitness, disease progression, and quality of life[12]. There are several mechanisms by which exercise has been proposed to slow dementia progression[13], including increased serum brain derived neurotrophic factor[14], increased carotid blood flow[15], and reduced cerebral beta amyloid accumulation[16]. However, much mechanistic research excludes those with dementia, and utilises rodent or *in vitro* models[17 18], meaning there is uncertainly whether these mechanisms extend to humans with young onset dementia or late onset dementia. Moreover, whether mechanisms that exist in rodents or *in vitro* correspond to clinically meaningful of even detectable changes at the human level in people with late onset dementia in uncertain, and this lack of data is even more pronounced in young onset dementia.

Dost et al.[21] reported that 53% of 166 people with Alzheimer's disease presented with sarcopenia, highlighting the multi-systems effect of ageing. Cadore et al.[22] attempted to combat this multimorbidity with a lower extremity resistance training, observing improved muscular strength post-intervention, the absence of a control group means these results should be interpreted with caution. With regards to the

'combined training' approach, Bossers et al.[23] found that balance and leg endurance improved in a combined training group more than an aerobic only training group, highlighting benefits of a multi-component exercise approach.

Although exercise is known to exert beneficial effects on several parameters in late onset dementia, there is scant literature concerning young onset dementia is. Concerningly, a recent scoping review revealed not a single study investigated effects of physical exercise on cognition, physical performance, well-being, or quality of life in young onset dementia[25]. Further, there are no cross-sectional studies comparing young onset dementia and healthy controls. Whilst exercise intervention studies in young onset dementia are lacking, implementing such interventions without a pragmatic dependent variable would be impractical. Before targeted support strategies can be developed, we conducted this case-control study to identify physiological differences in young onset dementia compared to age-matched healthy controls. We aimed to compare body composition, blood pressure, physical fitness, lung function, physical activity, muscle architecture, and endothelial function between individuals with young onset dementia and age-matched healthy controls. We hypothesised people with young onset dementia would show poorer values across all variables.

Methods

The study protocol was informed by research involvement activities which included volunteers with young onset dementia viewing demonstration films of the tests to be included. With support of healthcare professionals, the volunteers provided feedback on the acceptability of each test. These involvement activities are discussed fully elsewhere.

Participants

Sample size was based on estimated aerobic capacity using the Astrand-Rhyming cycle ergometer test[26]. To detect a mean difference of 1-metabolic equivalent (MET; 3.5 $mL \cdot kg \cdot min^{-1}$), with a standard deviation of 3.6 $mL \cdot kg \cdot min^{-1}$, a desired power of 0.80, and α of 0.05, we required n=17 per group. We recruited 33 participants (16 young onset dementia, 17 controls), as one young onset dementia participant withdrew due to injury unrelated to the study. Groups were age- and sex-matched. Young onset dementia participants were recruited via NHS partners in Scotland. The South Lanarkshire young

onset dementia team shared details of the study with those diagnosed with young onset dementia during consultations and contact details were passed on. Controls were recruited through social media advertisement, attending a single visit to the Cardiovascular Imaging Laboratory at the University of the West of Scotland between January 2023 and May 2024. The study adhered to Helsinki Declaration principles, with informed consent obtained and ethical approval was given by the NHS London Riverside Ethics Committee. Descriptive statistics for participants are in table 1.

Protocol

Body Composition and Blood Pressure

Stature was measured with a wall-mounted stadiometer (SECA, CE0123, Germany) and recorded in centimetres. Body mass was measured using electronic scales (SECA 876, CE0123, Germany) and recorded in kilograms. Body composition was assessed following ISAK guidelines, and BMI was calculated (BMI = kg/m^2). Resting blood pressure was measured with an automated sphygmomanometer (Omron, the Netherlands). Participants were seated with the BP cuff on the left arm, which was inflated to 200 mmHg, and deflated to 0 mmHg. This was repeated three times with a one-minute rest between repetitions. The mean of the three repetitions was recorded.

Physical Fitness

Aerobic capacity was assessed using the submaximal Astrand-Rhyming test[26] on a cycle ergometer (ProTrainer, Wattbike, England) over six minutes. This test was chosen instead of a maximal test with consideration for participants comfort and clinical condition. Each participant wore a heart rate chest strap (PC.15.11, SIGMA, Germany). Resting HR was recorded, and the target heart rate was 125-175 $b \cdot min^{-1}$, as justified previously[26]. Participants performed a three-minute warm-up without resistance, and then resistance was increased until the target heart rate was achieved. Heart rate and power output (W) were recorded every minute. If heart rate was stable within 5 $b \cdot min^{-1}$ during minutes five and six, the test concluded. If not, adjustments were made, and further minutes were added until the target heart rate was achieved. After the test, participants completed a one-minute cool-down and dismounted the

ergometer. The average heart rate from the final two minutes was used with the Astrand-Rhyming nomogram to predict maximal oxygen uptake (VO_{2max}) in $mL \cdot kg^{-1} \cdot min^{-1}$, with age correction applied.

Lung Function

A plastic peak flow meter (Mini Wright, PEA001, Clement Clarke, New York, USA), was used to assess lung function. The participant sat on a chair/plinth in the laboratory, relaxed, and performed a maximal inhalation before a subsequent maximal exhalation as quickly and forcefully as possible. The participant performed three trials allowing a one-minute rest between trials. The maximum of the three measurements was taken as the final value of peak flow.

Physical Activity

To determine physical activity, each participant wore an wGT3X-BT ActiGraph accelerometer (ActiGraph LLC, Pensacola, FL, USA) on their non-dominant wrist and were instructed to wear the device for 24h across seven days. Further details of the methodological decisions taken when assessing physical activity can be found in supplementary file 1.

To determine physical activity, each participant wore an wGT3X-BT ActiGraph accelerometer (ActiGraph LLC, Pensacola, FL, USA) on their non-dominant wrist. All accelerometer devices were initialized in ActiLife v6.13.4 (ActiGraph, Pensacola, FL, USA) to collect data at 100 Hz, and commence data collection. The "idle sleep mode" in ActiLife v6.13.4 was not enabled. Each participant was instructed to wear the device 24 hours per day for seven days, only removing the device during water-based activities. Once devices were returned, data were downloaded as raw .gt3x files which were processed using the GGIR package version 3.0-5 in R statistical software (R Foundation for Statistical Computing, Vienna, Austria, http://cran.r-project.org/[27]). In GGIR, files were processed to detect abnormally high values, detect nonwear[27], and calibrated using local gravity[28]. Files were excluded from analyses if post calibration error was >0.01 g, or if participants had less than one valid wear day (defined as ≥16 hr per day) or wear data was not present for each 15-min period of the 24-hr cycle[29]. The default non-wear setting was applied during processing within GGIR[30]. Alongside wear time (days), the time spent inactive (<30 mg[31]), in light physical activity (between 30 and 100 mg) and moderate-vigorous

physical activity (>100 mg[32]) was determined. Inactive time is provided exclusive of sleep time after applying the automated Heuristic Algorithm looking at Change of Z-Angle (HDCZA) algorithm within GGIR as previously described[3334]. For participants to be included in analysis, they had to provide a minimum of four days (three weekdays and one weekend day)[35].

Muscle Architecture

Muscle architecture of the vastus lateralis muscle was assessed using ultrasound with a 7-10 MHz, 4.7 cm linear array transducer (Vivid I, GE Healthcare, Horton, Norway). Participants lay supine on a plinth. Scans were taken at the distal third of the vastus lateralis, 35% of the distance between the greater trochanter (100%) and the distal femoral condyle (0%). Femur length was measured with a measuring tape (SECA 201, Germany), and the 35% mark was noted on the leg with a marker pen. The transducer was placed on this mark to capture images. Muscle architecture was analysed using ImageJ software (version 1.42q, National Institute of Health, USA), measuring fascicle length (distance between fascicle insertions at the deep and superficial aponeurosis), muscle thickness (distance between the deep and superficial aponeurosis), and pennation angle (angle between the fascicle and tendon axis). Ultrasound sarcopenia index was calculated by dividing fascicle length and muscle thickness[37 44].

Endothelial Function

Vascular endothelial function was assessed using an ultrasound scan of the brachial artery, focusing on vascular reactivity via flow-mediated dilation, as previously described[38]. Semi-automated edge detection software (Brachial Analyzer, Medical Imaging Applications LLC, Coralville, IA) measured arterial diameter, flow, and shear stress. The software tracked vessel walls and blood velocity, calculating shear stress and arterial diameter over three-second periods. Absolute (mm), relative (%), and shear-normalised flow-mediated dilation (%) were also determined.

Statistical Analysis

All data were assessed for normal distribution and homogeneity of variance and to assess differences, independent samples t-tests were performed. Data were analysed using R Studio (2023.12.0+369). Data are presented without subjective terminology and α levels are reported as exact p values, without

dichotomous interpretation of 'significant' or 'non-significant' as advised by the American Statistical Association[36]. Effect size for paired comparisons was conducted using Cohen's d whereby the difference in means between two samples was divided by the pooled standard deviation (SD). Thresholds of 0.2, 0.5, and 0.8 for small, moderate, and large effects were used for Cohen's d[39]. Figures were generated in R Studio (2023.12.0+369) and displayed as grouped dot plots with mean lines as recommended by Drummond and Vowler[4041].

Results

For physical activity data, all participants met the wear time criteria with a mean of 11 valid hours for both groups and a mean of 6 valid days for both groups. Estimated VO_{2max} (figure 1), lung function (figure 2), physical activity (figure 3), muscular architecture (figure 4), and vascular function (figure 5) are displayed below. Pairwise comparisons suggest no differences between young onset dementia and controls for estimated VO_{2max} (p=0.119, d=0.66; moderate effect). No differences were apparent in the lung function data (p=0.496, d=0.24; small effect). Differences were evident in sedentary time (p=0.029, d=0.54; moderate effect) and moderate-vigorous physical activity (p=0.014, d=0.97; large effect) between the groups. There were no differences observed for light physical activity (p=0.374, d=0.34; small effect). Muscle architecture displayed differences in fascicle length (p=0.028, d=0.81; large effect) and no differences on the remaining parameters (p=0.702, d=0.14; trivial effect). Vascular baseline diameter (p=0.162, d=0.53; moderate effect) and flow-mediated dilation % (p=0.118, d=0.60; moderate effect) was not different between groups. Further to this no differences in handgrip strength were observed between the groups (p=0.284, d=0.39; small effect).

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Discussion

This study addressed the knowledge gap in young onset dementia by examining body composition, blood pressure, estimated VO_{2max}, lung function, physical activity, muscle architecture, and endothelial function. The main findings revealed differences in fascicle length, sedentary time, and moderate-vigorous physical activity between groups. However, no differences were observed in estimated VO_{2max}, vascular function, pennation angle, muscle thickness, ultrasound sarcopenia index, lung function, functional capacity, and light physical activity. Thus, our hypothesis that all parameters would be deficient in people with young onset dementia compared to controls is only partially supported.

Estimated VO_{2max} was 5.3 $mL \cdot kg \cdot min^{-1}$ greater in controls (although not reaching $p<0.05$) with a difference of this magnitude suggesting a greater risk of diabetes and cardiovascular disease[52]. A meta-analysis by Kodama et al.[53] showed that a 1-MET (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) increase in maximal oxygen uptake was associated with a 13% reduction in all-cause mortality. Despite not reaching the $p<0.05$ level in the present study, this area warrants further consideration and aerobic capacity should be considered in support for people with young onset dementia. There is a known association with maximal oxygen uptake and quality of life[55] and longevity[56], although these data are not in people with young onset dementia, so this could be an area of further investigation. Lower aerobic capacity may exist as young onset dementia participants were more sedentary than controls and completed less moderate-vigorous physical activity than controls, which also heightens their risk of obesity and diabetes[49].

Vascular function was similar across both groups, in line with previous studies which measured flow-mediated dilation in those with dementia[57]. However, some previous research has shown a specific link between endothelial dysfunction and Alzheimer's disease due to the reduced availability of nitric oxide which can exacerbate amyloid levels[58]. While our findings do not fall in line with this previous work, it is possible this is due to our smaller sample or due to the fact the young onset dementia group were younger, and so vascular function is likely higher in terms of baseline diameter and reactivity regardless of diagnosis[59].

Fascicle length of the vastus lateralis was shorter in the young onset dementia group compared to controls, with a mean difference of 7.6 mm. A difference in fascicle length of this magnitude may

suggest greater predisposition to frailty in young onset dementia [42]. Moreover, it is possible the shorter fascicle length increases metabolic cost of locomotion[43], which could result in a downward cycle of metabolically costly locomotion resulting in increased perception of effort, resulting in less physical activity, exacerbated by physical inactivity. Considering sarcopenia, while fascicle length is important, frailty and/or sarcopenia is more determined by muscle thickness[44], and whether fascicle length is plastic remains a matter of debate[45-48].

Implications

Our novel findings reported herein can guide future research to support exercise or physical activity interventions. We have highlighted areas of impairment, suggesting physical activity promotion for people with young onset dementia should be explored as less sedentary time may improve muscle architecture and aerobic fitness. A multi-disciplinary, multi-component approach is recommended[9], as these have improved physiological and psychological parameters in late onset dementia[64].

Strengths and Limitations

A key strength of the current study was the target population, focussing on those with young onset dementia addressed an under-represented population, paving the way for further research in the area. By using a case-control design, we isolated effects of young onset dementia on outcome variables. This study is not without limitations, including a modest sample size. To address this, we communicated magnitude-based inferences and precise α values instead of binary 'significance' classifications. This was necessary due to scant normative values in young onset dementia. Secondly, young onset dementia is progressive and therefore data from this study may not be extrapolated to all people with young onset dementia. Future research could stratify participants by young onset dementia stage.

Conclusion

The identified deficits in muscle architecture and physical activity may contribute to disease burden, emphasising the need to recognise and address these issues to improve quality of life. We identified differences between the young onset dementia group and controls in muscle architecture and physical activity. These disparities underscore the need for tailored support interventions incorporating exercise/physical activity.

Authorship contributions according to the CRediT taxonomy

Conceptualisation, L.D.H., N.E.M.S-H., N.F.S., S.M., D.T.; methodology, L.D.H., E.C.J.B., N.E.M.S-H., N.F.S., D.S.B., M.M., D.T.; software, L.D.H., E.C.J.B., N.F.S., D.S.B., M.M.; validation, L.D.H., E.C.J.B., N.E.M.S-H., N.F.S., D.S.B., M.M., S.M., B.C., D.T.; formal analysis, L.D.H., E.C.J.B., N.E.M.S-H., D.S.B., ; investigation, L.D.H., E.C.J.B., N.E.M.S-H., N.F.S., D.S.B., M.M.; resources, L.D.H., N.E.M.S-H., N.F.S., D.S.B., S.M., D.T.; data curation, E.C.J.B.; writing—original draft preparation, L.D.H., E.C.J.B.; writing—review and editing, L.D.H., E.C.J.B., N.E.M.S-H., N.F.S., D.S.B., M.M., S.M., B.C., D.T. ; visualisation, E.C.J.B.; supervision, L.D.H.; project administration, L.D.H., E.C.J.B., S.M., B.C., D.T.; funding acquisition, L.D.H., N.E.M.S-H., N.F.S., D.S.B., S.M., D.T. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest statement

The submitted work was not carried out in the presence of any personal, professional, or financial relationships that could potentially be construed as a conflict of interest.

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Tables and Figures

Table 1: Descriptive data of participants at enrolment.

Variable	Group	Mean ± SD	T-test p value and Cohen's *d*
Age (years)	Young onset dementia (n = 16)	60 ± 7	p=0.577 *d*= 0.20
	Control (n= 17)	58 ± 10	
Stature (cm)	Young onset dementia (n = 16)	167 ± 7	p=0.487 *d*=0.25
	Control (n= 17)	169 ± 7	
Body Mass (kg)	Young onset dementia (n = 16)	79.2 ± 16.5	p=0.501 *d*=0.24
	Control (n= 17)	83.6 ± 20.9	
Body Mass Index (kg/m^2)	Young onset dementia (n = 16)	28.1 ± 4.9	p=0.631 *d*=0.17
	Control (n= 17)	29 ± 6	
Systolic blood pressure (mmHg)	Young onset dementia (n = 16)	150 ± 19	p=0.365 *d*=0.32
	Control (n= 17)	143 ± 24	

Diastolic blood pressure (mmHg)	Young onset dementia (n = 16)	83 ± 9	p=0.465 *d*=0.26
	Control (n= 17)	81 ± 10	
Resting Heart Rate (bpm)	Young onset dementia (n = 16)	76 ± 11	p=0.751 *d*=0.17
	Control (n= 17)	75 ± 15	

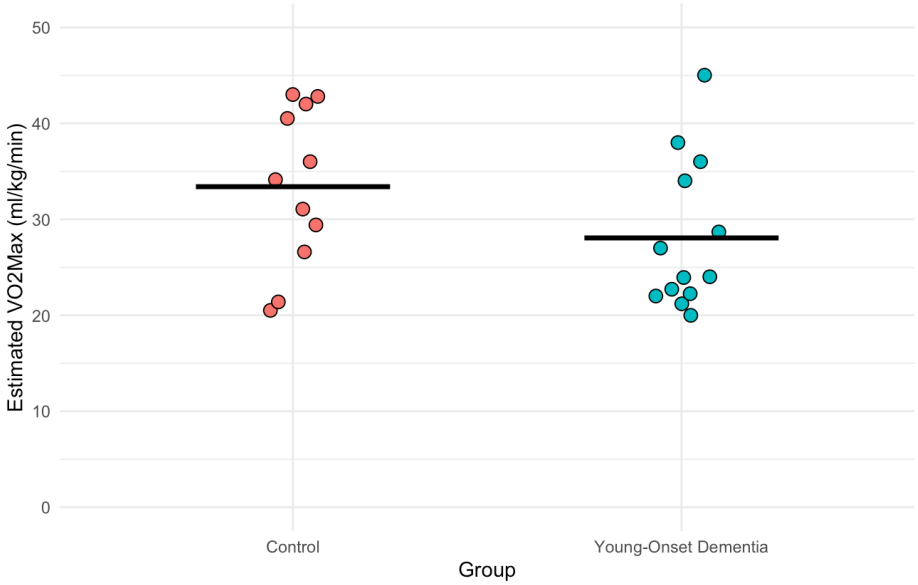

Figure 1. Estimated VO_{2max} data from people with young onset dementia (Young onset dementia; n = 16) and controls (n = 17) from a submaximal Astrand-Rhyming test. Data are presented as individual dot plots with accompanying mean line.

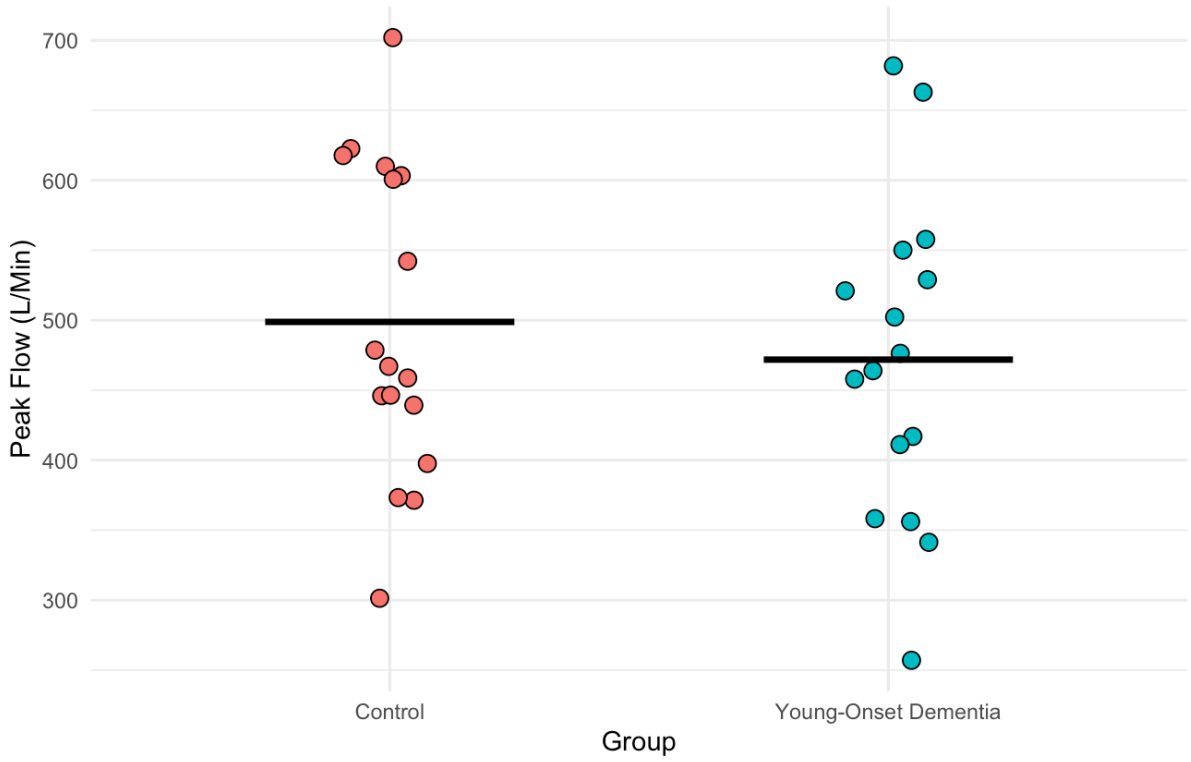

Figure 2. Peak flow data from people with young onset dementia (Young onset dementia; n = 16) and controls (n = 17). Data are presented as individual dot plots with accompanying mean line.

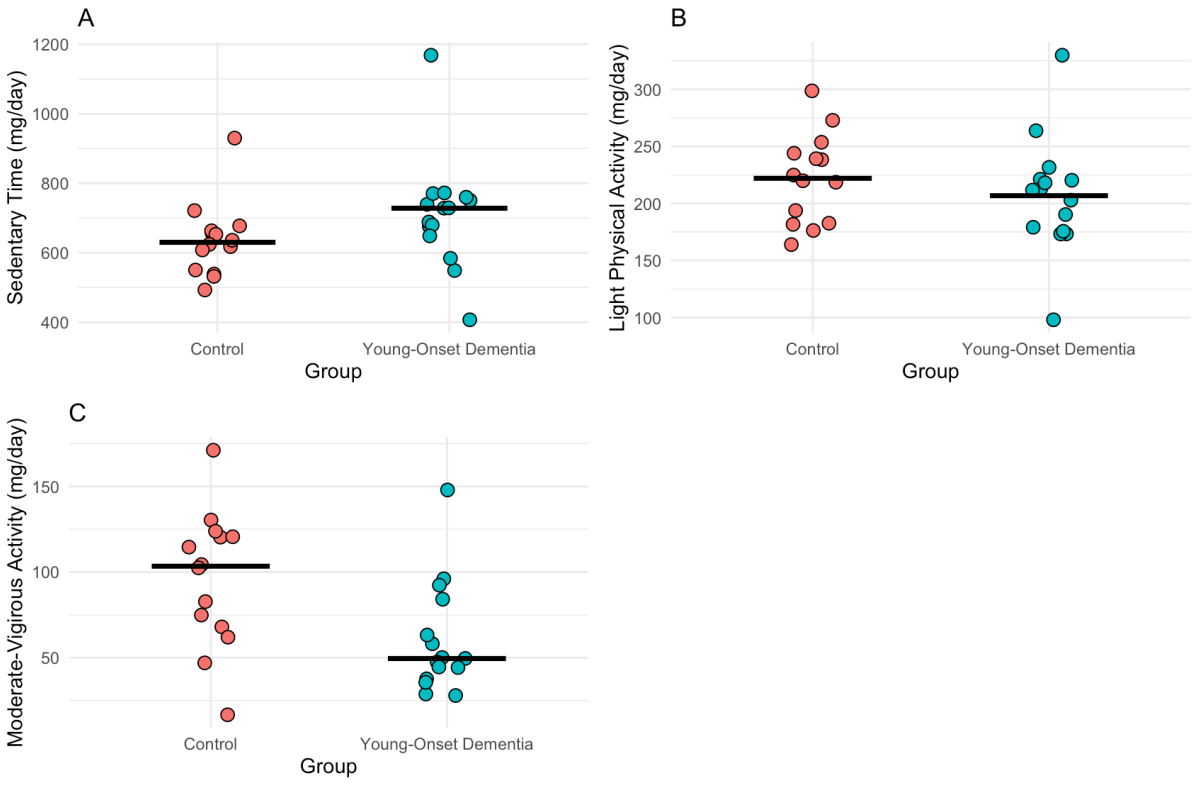

Figure 3. Physical activity parameters from people with young onset dementia (Young onset dementia; n = 16) and controls (n = 17). Data are presented as individual dot plots with accompanying mean line (LPA and MVPA) and median line (sedentary time).

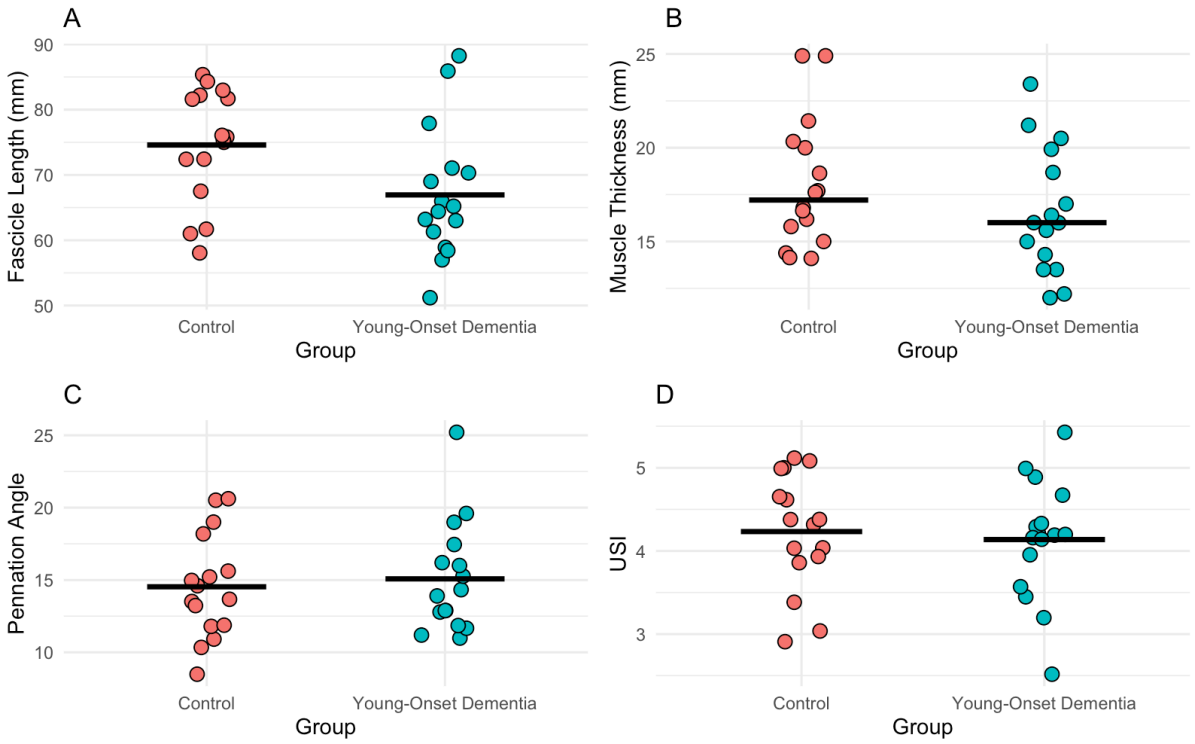

Figure 4. Muscle architecture parameters from people with young onset dementia (Young onset dementia; n = 16) and controls (n = 17). Data are presented as individual dot plots with accompanying mean line (fascicle length, pennation angle and USI) and median line (muscle thickness).

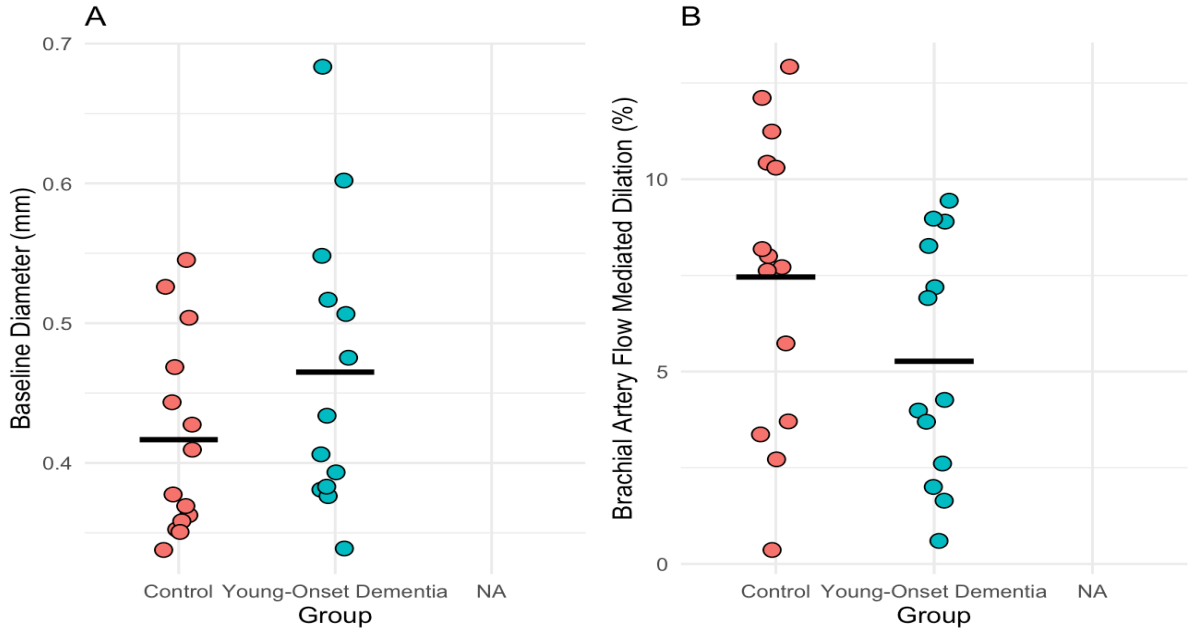

Figure 5. Endothelial function parameters from people with young onset dementia (Young onset dementia; n = 16) and controls (n = 17). Data are presented as individual dot plots with accompanying mean line.

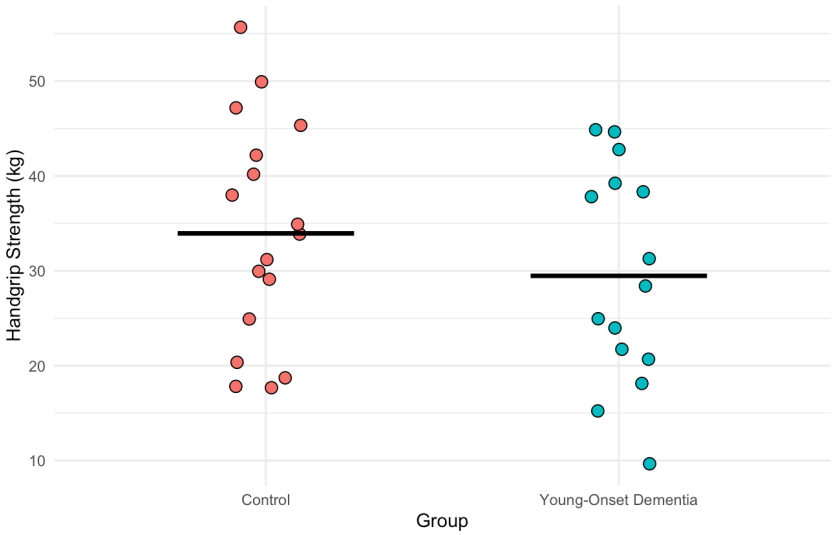

Figure 6. Handgrip strength data from people with young onset dementia (Young onset dementia; n = 16) and controls (n = 17). Data are presented as individual dot plots with accompanying mean line.