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A structured physical activity program in an adolescent population with overweight or obesity: a prospective interventional study

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Running title: Physical exercise in young obesity.

Abstract

Background. Obesity is a significant health problem, with increasing involvement of young population worldwide. The aim of this study was to evaluate the effects of two different types of physical exercise (resistance vs combined aerobic-resistance) on cardiovascular and anthropometric profile of a sample of sedentary adolescents with overweight and obesity.

Methods. After undergoing clinical, cardiovascular and anthropometric-metabolic evaluation (T0), subjects with overweight and obesity were randomized to a 6-months resistance or combined aerobic-resistance training program. Clinical, cardiovascular and anthropometric-metabolic evaluations were repeated after 6 months of training (T1) and after 3 months of detraining (T2).

Results. Thirty adolescents with overweight/obesity were enrolled; 20 subjects completed training program. A significant improvement in body composition was detected after 6 months, with a reduction of BMI (32.1 [30.5-34.4] vs 31.1 [29.6-33.4] kg/m^2, p=0.02) and adipose tissue (45.5 [41.1-49.7] vs 41.6 [37.0-49.2] Kg, p<0.01). A reduction in Diastolic blood pressure (75.5 ± 8.9 vs 68.2 ± 6.4 mmHg, p=0.02) and Pulse Wave Velocity (5.7 [5.1-5.9] vs 5.2 [4.7-5.7] m/s, p=0.04) was also observed. Persistence of the effect on the most important parameters was observed also after detraining period.

Conclusions. Regular physical exercise induces positive metabolic and cardiovascular effects, with persistence also after brief discontinuation.

Novelty bullets.

Physical exercise induces positive effect on cardiovascular risk profile.

Positive effects persist also after brief discontinuation.

Physical exercise reduces early signs of autonomic disfunction.

Keywords. Obesity. Adolescence. Physical exercise.

Introduction

Obesity has become a major health problem, involving not only adults, but also children and adolescents. Its prevalence is dramatically rising worldwide, especially among children, by increasing from 5% to 20.6% in the last three decades (Skinner et al. 2018). In European countries, one third of children and adolescents is overweight or obese (Janssen et al. 2005) and similar prevalence was described in Italy (Istituto Superiore di Sanità 2019).

Cardiovascular diseases represent the first cause of death worldwide, accounting for 31% of all deaths every year. Obesity represents one of the major risk factors for these diseases (Afshin et al. 2017), with an even higher risk profile in subjects being already obese during adolescence than in those developing obesity during adulthood (Must et al. 1992). Furthermore, obesity is frequently associated with other cardiovascular risk factors, as arterial hypertension. Hypertension prevalence in children and adolescent population is about 7%, rising at 15% when considering subjects with overweight and obesity (Song et al. 2019).

Obesity is also associated with insulin resistance and metabolic syndrome, already in young age (Weiss et al. 2004). Additionally, several studies have showed signs of autonomic dysfunction in adolescents with obesity, with a reduced parasympathetic activity on heart rate variability (HRV) (Dangardt et al. 2011), which has been related to all-cause mortality in adults (Dekker et al. 2000).

Furthermore, an early onset of obesity during childhood is frequently associated to persistence and even worsening of fat excess during adulthood (Deshmukh-Taskar et al. 2006).

These findings highlight the importance of prevention and treatment of obesity during childhood and adolescence, as well as of identification of early signs of cardiovascular and metabolic organ damage.

Obesity management should be focused not only on weight reduction, but also on modification of body composition, by increasing the fat-free mass and modifying fat mass distribution (Bosy-

Westphal et al. 2018). In fact, adipose tissue distribution influence overall cardiovascular morbidity and mortality, with higher risk associated with abdominal and intramuscular adiposity (Britton et al. 2013).

Lifestyle interventions represent the main approach available in the young population. In particular, several previous studies had evaluated the role of physical exercise in contrasting young obesity (Kannel et al. 1991; Meyer et al. 2006; Hind and Burrows 2007; Janssen and LeBlanc 2010; Therkelsen et al. 2016). It has been associated to body weight reduction and improvement of body composition (Hind and Burrows 2007); it has positive effects on cardiovascular profile, reducing LDL cholesterol and triglycerides levels, insulin resistance (Meyer et al. 2006) and blood pressure (BP) (Janssen and LeBlanc 2010). Finally, it induces an improvement also in adolescent quality of life, mental health and sleep (Meyer et al. 2006; WHO 2016).

Despite this evidence, lifestyles interventions often reported limited effectiveness, due to poor adherence in young subjects, frequently related to socio-economic factors (Van Stappen et al. 2018). Furthermore, limited experiences are currently available on the choice of a specific type of physical exercise over another, in terms of adherence and cardiovascular and metabolic outcomes.

We conducted a perspective randomised study aiming (i) to assess the effects of physical exercise on autonomic, metabolic and anthropometric profile in a sample of adolescents with overweight or obesity; (ii) to compare the effects of two different kinds of physical training (resistance vs combined aerobic-resistance) on these parameters; (iii) to evaluate effect of a brief period of detraining on these parameters.

Materials and Methods

The study was conducted between June 2017 and December 2018 in Paediatric Endocrinology Unit and Hypertension Centre of the A.O.U. Città della Salute e della Scienza of Turin (Italy). Subjects aged between 14-20 years, with a BMI ≥ 85^{th} percentile for age and sex and a Tanner puberty stage at least III, were enrolled in the study on a voluntary basis. Exclusion criteria were diabetes mellitus or other unbalanced endocrinopathies, secondary hypertension, ongoing antihypertensive treatment, psychiatric conditions, cardiac diseases and/or any pathological condition compromising or contraindicating physical exercise.

All patients underwent a clinical, cardiovascular and anthropometric-metabolic evaluation at baseline (T0). Then, enrolled subjects were randomly allocated to a resistance training program or a combined resistance-aerobic training program.

The randomization was performed using computer-generated balanced blocks, with blocks' size of 4 subjects and 1:1 assignment ratio to each training group. All the investigators were blinded in the randomization process, with exception of personal trainers and other gym staff, who were directly involved in physical training education of subjects.

Both training protocols lasted 6 months and included two sessions per week, 60 minutes each. Minimum significant adherence to physical training program was fixed at ≥ 30% of overall attendance to training program.

Subjects underwent a second and third clinical, cardiovascular and anthropometric-metabolic evaluation after 6 months of physical activity (T1) and, subsequently, after 3 months of detraining (T2). During detraining period, subjects didn't attend any training session; daily-life activity and physical activity of low intensity, as walking outdoor, were allowed. Periodical phone contact was performed to verify on-going physical activity between T1 and T2 evaluation. Study design is summarized in **Figure 1**; summary of evaluated outcomes is reported in **Appendix A**.

Written informed consent was collected from participants or their parents if they were underage. The study was approved by local Ethics Committee (CS2/708).

Physical activity

Subjects underwent a preliminary evaluation of their aerobic and anaerobic capacity. For aerobic exercise, training intensity was based on heart rate (HR) maintenance between 50% and 60% of theorical maximum HR, calculated as 220 – age. For anaerobic exercise, evaluation was based both on a theorical intensity based on Brzycki formula and practical direct assessment with application of increasing load in a progressively decreasing number of repetitions.

In both groups, periodical re-evaluations of subjects were performed, in order to progressively increase exercise intensity and avoid exercise adaptation.

Resistance training sessions consisted of three cycles of eight exercises of weight-lifting, one for each main muscular group. Numbers of repetitions increased from a cycle to another in the first two months, decreased from a cycle to another in the following two months and remained constant in the last two months; load was constant for each two months-period and progressively increased from the first to the third period.

Combined training sessions included both resistance and aerobic exercise. Resistance activity consisted of weight-lifting exercises with the same characteristics of those of resistance group; an increasing number of repetitions with a constant load was applied. Aerobic activity included stationary bicycle or elliptical machine working. In each period, participants practised 30-35 minutes of weight-lifting and 30 minutes of aerobic activity organizes as follow: one resistance exercise followed by 5 minutes of aerobic activity in the first two-months period; two consecutive resistance exercises followed by 10 minutes of aerobic activity in the second one; three consecutive resistance exercises followed by 15 minutes of aerobic activity in the third one.

Clinical evaluation

Clinical evaluation was performed at baseline (T0), after six months of physical training (T1) and after-detraining period (T2) (**Figure 1**).

Data on clinical and family history, including birth weight, family history of obesity and cardiovascular diseases were collected. Participants underwent a complete physical examination, including measurements of weight, height, waist circumference, BP and HR. BMI z-score was calculated on the base of anthropometric curves, according to age and sex (Center for disease Control and Prevention. n.d.; Kavey RW, Simons-Morton DG, de Jesus JM 2011).

Resting BP was measured by a physician on both arms with patient in sitting position, following the European Society of Hypertension (ESH) recommendations (Williams et al. 2018) by using an Microlife BP A150 AFIB oscillometric device (Microlife, Swiss). Measurements were confirmed by auscultatory method. Resting BP values were classified as normal, normal-high or high according to ESH guidelines for hypertension in children and adolescents (Lurbe et al. 2016).

Laboratory tests were performed at T0 and T1 visits and included full blood count, plasma creatinine, electrolytes, fasting plasma glucose, lipid profile, plasma insulin, uric acid levels, urine sample test, thyroid and liver function. Laboratory samples collection was conducted in the morning, in fasting condition for at least 6 hours. Homeostatic model assessment (HOMA) index was calculated according to the following formula: HOMA index = plasma glucose (mmol/L) x plasma insulin (mU/L) / 22.5 (Matthews et al. 1985). Even in the absence of a validated HOMA index cut-off for the definition of insulin-resistance in children and adolescence, a reference value of 2.6 was considered (Andrade et al. 2016).

Cardiovascular and autonomic evaluation

Cardiovascular and autonomic evaluation included: 20-minutes resting electrocardiographic (ECG) monitoring for the calculation of HRV; Pulse Wave Velocity (PWV) measurement and aortic central pressure measurement with Pulse Wave Analysis (PWA). All examinations were repeated at each visit (T0, T1 and T2).

1. Heart rate variability (HRV)

Autonomic function was assessed by HRV: a 20-minutes ECG was recorded at rest and in absence of external stimulations. A Fukuda Denshi FM-180 device and a SCM510W software were used to collect and analyse HRV in time and frequency domain. HRV in time domain was evaluated by standard deviation of NN (R-R) intervals (SDNN), standard deviation of the average NN intervals for 5 minutes interval (SDANN) and root mean square of the successive NN intervals (RMSSD). These parameters reflect parasympathetic regulation of HR, especially in short-term registration. In frequency domain, low frequency (LF), high frequency (HF) and the ratio LF/HF were considered. LF quantifies absolute spectral power in the low frequency band (0.04-0.15 Hz) and represents sympathetic and parasympathetic regulation of HR in response to baroreflex. HF quantifies absolute power of high frequency band (0.15-0.40 Hz) and represents parasympathetic activity related to the respiratory cycle (Shaffer and Ginsberg 2017).

2. Pulse Wave Analysis (PWA) and Pulse Wave Velocity (PWV)

A SphygmoCor SCOR-PVx System (Atcor Medical, Sydney, Australia) was used to assess PWA and PWV. Measurement was performed in supine position and PWV was calculated as the distance from the carotid-to-distal path length divided by the time delay measured between the feet of the two waveforms and reported in meters per second (Laurent et al. 2006). Central BP was estimated by analysing radial waveform (PWA) (Cheng et al. 2013). The average of 3 recordings was considered both for PWV and central BP. Measurements were classified on the base of age and sex related percentiles (Reusz et al. 2010; Elmenhorst et al. 2015).

Bio-impedentiometric evaluation

Body composition was evaluated by a bio-impedentiometric analysis, based on electrical conductive properties of the body, measuring impedance to low-amplitude flow of electrical current at a fixed frequency ("Bioelectrical Impedance Analysis in Body Composition Measurement. Proceedings of a National Institutes of Health Technology Assessment Conference. Bethesda, Maryland, December 12–14, 1994" 1996). A BIA-ACC Device was used (BioTekna Biomedical Technologies, London, UK) and analysis was performed in the morning, in fasting condition for at least 6 hours, with subjects in supine position. This non-invasive cost-effective assessment was previously validated among young population with obesity (Faria et al. 2014). Main parameters of body composition considered were total body water (TBW), fatty mass (FM), free fatty mass (FFM), adipose tissue (AT), abdominal adipose tissue (AAT), intramuscular adipose tissue (IMAT), Bone and Muscle masses.

Statistical analysis

SAS 9.4 Software (SAS Institute Inc., USA) for Windows 10 was used for statistical analysis. Shapiro-Wilk test was used to determine variables distribution. Continue variables were expressed as mean ± standard deviation (SD) or as median [Interquartile Range - IQR], according to their distribution; categorical variables were expressed as absolute number and/or percentage. For independent samples, variables were compared with Student's *t* test and Mann-Whitney test, according to their distribution (normal vs non-normal). For dependent normally distributed variables, ANOVA for dependent sample and Student's *t* test with Bonferroni correction were used. For dependent non-normally distributed variables, Friedman test and Wilcoxon signed-rank test with Bonferroni correction were used. Associations between variables were analysed with Spearman test. A p value < 0.05 was considered as statistically significant. A Beta error of 0.20 was used for study design.

Results

Population characteristics (T0)

Thirty subjects (43% of male) were enrolled in the study and randomised to each group. They had a mean age of 15.6 ± 1.5 years and a median BMI z-score of 2.03 [1.90-2.28]. Eight participants (26.7%) met the criteria for severe obesity and 17 (56.7%) had a familiar history of obesity. Baseline characteristics are summarized in **Table 1**.

Subjects with overweight/obesity had a mean resting BP of 123.3/75.5 ± 9.6/8.9 mmHg. Fifty% of subjects had high-normal BP values and 23% had high BP values.

Median central BP was 101.5/72.5 mmHg [96-113/67-81], with 5 subjects (16.7%) showing a central Systolic Blood Pressure (SBP) higher than 95th percentile for age and sex.

Ten subjects (33.3%) had borderline-low or low plasmatic HDL levels and 4 subjects (13.3%) had borderline-high LDL values. Median HOMA index was 3.36 [1.90-5.73].

According to bio-impedentiometric analysis, body composition was characterized of 42% [39-44] of FM. Median AT was 45.5 Kg [41.1-49.7]; median AAT was 588.4 cm^2 [528.0-676.0] and median IMAT was 2.3% [2.1-2.5] of body mass.

Plasma triglycerides concentration was positively correlated to BMI z-score ($r=0.67$, $p<0.001$) and IMAT ($r=0.63$, $p=0.001$). Among cardiovascular parameters, DBP and PWV showed a positive correlation with adiposity (AT –DBP $r=0.58$, $p=0.001$; PWV - BMI $r=0.59$, $p=0.001$; PWV - BMI z-score $r=0.59$, $p=0.001$).

Clinical, cardiovascular and anthropometric-metabolic evaluation after 6 months of physical training (T1)

After baseline evaluation, cases were randomly allocated to the two different groups (Group A: “Resistance activity program” – n = 15; Group B: “Combined activity program” – n = 15). No significant differences were found between the two groups at baseline (**Supplementary Table S1**).

During the 6 months training program, 8 subjects discontinued the physical activity and 2 subjects did not reach the minimum fixed attendance level (attendance < 30%). Totally, 30% of the enrolled subjects prematurely quitted the study, with an equal distribution in the two training programs (5 subjects for each group).

Cardiovascular and anthropometric parameters of overall residual population (n=20) after 6 months of physical training program are showed in **Table 2**.

A significant reduction of BMI and BMI z-score was observed. Body composition also improved, with a significant reduction of AT, AAT and IMAT and increase of TBW, muscle and bone masses.

A significant reduction of DBP and PWV was observed (T0 vs T1: DBP 75.5 ± 8.9 vs 68.2 ± 6.4mmHg, p=0.022; PWV 5.7 [5.1-5.9] vs 5.2 [4.7-5.6] m/s, p=0.011).

An increasing trend in HDL plasmatic levels was observed, even if not significant (p=0.106). Furthermore, a decrease in HOMA index was observed, more marked in combined training group (T0 Vs T1: 2.50 [1.90-5.73] vs 2.05 [1.39-4.62] p=0.001; **Supplementary Table S1**).

When comparing the two subgroups, combined training program induced a more marked reduction of central SBP values between baseline and follow-up (ΔCentralSBP(A) 0.04 [0.02-0.09] vs ΔCentralSBP(B) -0.03 [-0.13-0], p=0.006). Combined group showed also a higher increase of SDANN and RMSSD after physical exercise when compared to resistance group (ΔSDANN(A) -0.25 [-0.37-0.65] vs ΔSDANN(B) 2.04 [0.67-5.78], p=0.050; ΔRMSSD(A) -0.16 [-0.27-0.11] vs ΔRMSSD(B) 0.22 [-0.19-0.36], p=0.019).

Clinical, cardiovascular and anthropometric-metabolic evaluation after 3 months of detraining (T2)

After 3 months detraining period, BMI and BMI z-score were persistently lower than baseline values in both subgroups. Improvement in body composition observed at T1 was also confirmed at T2, with persistence of FM reduction and TBW increase.

Resting DBP was persistently lower than that measured at baseline (T0 vs T2: 75.5 ± 8.9 vs 66.6 ± 5.4 mmHg, p<0.001). Furthermore, a significant HR reduction was observed (T0 vs T2: 80 [76-90] vs 72 [68-76] bpm, p=0.036).

Finally, a persistence in the increase of RMSSD, SDNN, SDANN and decrease of LF/HF were observed in both training subgroups; on the other hand, persistent reduction in PWV was still observed only in the mixed training group (T0 vs T2: 5.5 [4.9-5.9] vs 5.2 [4.5-5.6] m/s, p=0.016; **Supplementary Table S1**).

Discussion

Our study confirmed that, even in earlier decades of life, obesity is associated to higher prevalence of cardiovascular and metabolic risk factors, known to be related to increased morbidity and all-cause mortality (Cote et al. 2013). In our sample, almost three quarter of enrolled subjects had normal-high or high BP values at baseline. Most of subjects had an altered plasma lipid profile and insulin-resistance. Furthermore, PWV was beyond reference values for age and sex in a significant proportion of the sample. All these characteristics are well known to be associated to an increased morbidity and mortality (Vlachopoulos et al. 2010; WHO 2014).

Physical exercise, even for a short period of time and irrespective of the type (resistance vs combined training), induced not only a BMI reduction, but also a favourable change of body composition. In fact, in our study a reduction of total fat mass was observed, as well as a decrease of abdominal adiposity and intramuscular adipose infiltration. Visceral adiposity is an independent predisposing factor to cardiovascular and metabolic diseases at a given amount of fatty mass (Kannel et al. 1991). Likewise, intramuscular ectopic fat accumulation (IMAT) has been associated to insulin-resistance and metabolic syndrome (Vettor et al. 2009), besides being related to sarcopenia and worse cardiorespiratory fitness (Therkelsen et al. 2016). This evidence strengthens the importance of positive modifications observed in this study, after only 6 months of physical exercise.

Conversely, there was an increase in muscle mass, which is independently related to a longer survival and modulates risk associated to adiposity, by reducing mortality at a given level of BMI and fat mass (Abramowitz et al. 2018). Furthermore, muscle mass is an important contributor of weight loss maintenance by increasing basal metabolic expenditure.

Subjects with overweight and obesity generally present higher absolute muscle mass when compared with normal-weight pairs, but lower muscle mass when related to overall body mass, with a sarcopenic profile of body composition (Tomlinson et al. 2016). Additionally, obesity is associated with lower muscular strength, especially for exercise that involves lifting the body (Ervin et al. 2014). In this study an increase not only in absolute muscle mass was observed, but also of exercise capacity and of relative muscle mass related to overall body weight.

Physical exercise also induced an improvement in cardiovascular and autonomic profile. A significant reduction in DBP was observed; there was a similar trend in SBP, despite not reaching statistical significance. The importance of this finding is supported by previous evidence that even small reductions of BP values (such as - 2 mmHg) reduce the risk of stroke by 14% and the risk of coronary artery disease by 9% in adult population (García-Hermoso et al. 2013).

Obesity leads to autonomic disfunction, characterised by reduced vagal modulation on cardiac activity and increased sympathetic tone; these alterations seem to be more evident in earlier stages of obesity and are mainly mediated by cytokine release from visceral fat adipocytes (DiBona 2013). This autonomic imbalance has important consequences on cardiovascular system and is associated to increase mortality (Dekker et al. 2000). In our study an increase of parasympathetic contribution in autonomic balance was observed after physical training. Therefore, physical exercise demonstrated effective in reversing autonomic alteration, probably at least in part through body composition remodelling (Niemirska et al. 2013).

A significant reduction of resting HR was observed, in line with previous observations of positive relation of HR with adiposity and inverse relation with physical activity (Rabbia et al. 2002). In consideration of the increased mortality associated to higher HR (Zhang et al. 2016), this modification can be considered a further proof of cardiovascular risk profile improvement induced by physical exercise.

Additionally, a reduction of aortic stiffness was observed. PWV is an expression of mechanical wall properties of large vessels and has demonstrated predictive value for future development of hypertension, cardiovascular target organ damage and all cause-mortality (Saladini and Palatini 2018) . Therefore, PWV reduction provides further evidence of the efficacy of physical exercise in improving cardiovascular risk profile.

Interestingly, most of the positive effects on body composition, cardiovascular profile and autonomic balance were persistent even after detraining, suggesting that physical exercise produces a medium-term improvement and that also induces effects on hormonal state and on molecular pathways that are responsible for higher cardiovascular and metabolic risk. Nevertheless, further studies are necessary to clarify specific molecular mechanisms of these effects, duration of persistence over time of these modifications and implications of these observations on long terms morbidity and mortality related to overweight and obesity state.

In the present study, no major differences were found between the two different training programs and between sex in terms of effects on cardiovascular and metabolic profile. In fact, the combined resistance-aerobic program showed more marked increase of RMSSD and SDANN and reduction of central SBP. However, current available evidence is insufficient to guide the choice of a training program over another.

Main limitations of this study are: (I) the limited size of the sample did not allow to further detect possible differences between the two types of physical exercise, because of high beta error and the use of non-parametric test reduce power of statistical analysis; (II) the short term of the training program reduced magnitude of physical exercise effect on cardiovascular and metabolic profile; (III) the short duration of the follow-up did not allow direct observation of effect of physical training on cardiovascular events and mortality; (IV) detraining effect was not further evaluated with fitness tests.

Conclusions

Obesity is related to an increase of metabolic and cardiovascular risk, also in early decades of life. Physical exercise induces significative changes in BP, HR, BMI and body composition. Furthermore, it has demonstrated effective in reducing or reverting early signs of cardiovascular and metabolic alteration, underling its crucial role in the prevention and reduction of cardiovascular mortality. Physical exercise was effective medium-term and irrespective of the type of physical training program proposed. However, neither of the two training programs was demonstrated to be superior to the other, also in motivating subjects and improving the adherence. Future studies are needed to better characterize differences among different type and duration of physical exercise.

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Authors' contribution statement. EF, FR, IR, MG and FV designed the study. EF, FAD, EE, IR, AA and GM collected data. EF analysed data. FV, FR, IR and MP supervised the entire study. EF and FR wrote the original draft. All authors reviewed and edited the final manuscript.

Authors' disclosure statement. The authors have no competing interests to declare.

Supplementary material. Supplementary Table S1 is available online.

References

Abramowitz, M.K., Hall, C.B., Amodu, A., Sharma, D., Androga, L., and Hawkins, M. 2018. Muscle mass, BMI, and mortality among adults in the United States: A population-based cohort study. PLoS One **13**(4): e0194697. Public Library of Science. Available from https://doi.org/10.1371/journal.pone.0194697.

Afshin, A., Forouzanfar, M.H., Reitsma, M.B., Sur, P., Estep, K., Lee, A., Marczak, L., Mokdad, A.H., et al. 2017. Health effects of overweight and obesity in 195 countries over 25 years. N. Engl. J. Med. **377**(1): 13–27. doi:10.1056/NEJMoa1614362.

Andrade, M.I.S. de, Oliveira, J.S., Leal, V.S., Lima, N.M. da S., Costa, E.C., Aquino, N.B. de, and Lira, P.I.C. de. 2016. Identification of cutoff points for Homeostatic Model Assessment for Insulin Resistance index in adolescents: systematic review. Rev. Paul. Pediatr. **34**(2): 234–242. Sociedade de Pediatria de São Paulo. doi:10.1016/j.rpped.2015.08.006.

Bioelectrical Impedance Analysis in Body Composition Measurement. Proceedings of a National Institutes of Health Technology Assessment Conference. Bethesda, Maryland, December 12–14, 1994. 1996. Am. J. Clin. Nutr. **64**(3): 387S-532S. doi:10.1093/ajcn/64.3.387S.

Bosy-Westphal, A., Braun, W., Geisler, C., Norman, K., and Müller, M.J. 2018. Body composition and cardiometabolic health: the need for novel concepts. Eur. J. Clin. Nutr. **72**(5): 638–644. doi:10.1038/s41430-018-0158-2.

Britton, K.A., Massaro, J.M., Murabito, J.M., Kreger, B.E., Hoffmann, U., and Fox, C.S. 2013. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. J. Am. Coll. Cardiol. **62**(10): 921–925. doi:10.1016/j.jacc.2013.06.027.

Center for disease Control and Prevention. (n.d.). CDC Growth Charts. Available from https://www.cdc.gov/growthcharts/cdc_charts.htm [accessed 10 January 2020].

Cheng, H.-M., Lang, D., Tufanaru, C., and Pearson, A. 2013. Measurement accuracy of non-invasively obtained central blood pressure by applanation tonometry: A systematic review and meta-analysis. Int. J. Cardiol. **167**(5): 1867–1876. doi:https://doi.org/10.1016/j.ijcard.2012.04.155.

Cote, A.T., Harris, K.C., Panagiotopoulos, C., Sandor, G.G.S., and Devlin, A.M. 2013. Childhood Obesity and Cardiovascular Dysfunction. J. Am. Coll. Cardiol. **62**(15): 1309–1319. doi:https://doi.org/10.1016/j.jacc.2013.07.042.

Dangardt, F., Volkmann, R., Chen, Y., Osika, W., Mårild, S., and Friberg, P. 2011. Reduced cardiac vagal activity in obese children and adolescents. Clin. Physiol. Funct. Imaging **31**(2): 108–113. John Wiley & Sons, Ltd. doi:https://doi.org/10.1111/j.1475-097X.2010.00985.x.

Dekker, J.M., Crow, R.S., Folsom, A.R., Hannan, P.J., Liao, D., Swenne, C.A., and Schouten, E.G. 2000. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: The ARIC study. Circulation **102**(11): 1239–1244. doi:10.1161/01.CIR.102.11.1239.

Deshmukh-Taskar, P., Nicklas, T.A., Morales, M., Yang, S.-J., Zakeri, I., and Berenson, G.S. 2006. Tracking of overweight status from childhood to young adulthood: the Bogalusa Heart Study. Eur. J. Clin. Nutr. **60**(1): 48–57. doi:10.1038/sj.ejcn.1602266.

DiBona, G.F. 2013. Sympathetic nervous system and hypertension. Hypertension **61**(3): 556–560. American Heart Association. doi:10.1161/HYPERTENSIONAHA.111.00633.

Elmenhorst, J., Hulpke-Wette, M., Barta, C., Dalla Pozza, R., Springer, S., and Oberhoffer, R. 2015. Percentiles for central blood pressure and pulse wave velocity in children and adolescents recorded with an oscillometric device. Atherosclerosis **238**(1): 9–16. doi:10.1016/j.atherosclerosis.2014.11.005.

Ervin, R.B., Fryar, C.D., Wang, C.Y., Miller, I.M., and Ogden, C.L. 2014. Strength and body weight in US children and adolescents. Pediatrics **134**(3): e782–e789. doi:10.1542/peds.2014-0794.

Faria, S.L., Faria, O.P., Cardeal, M.D.A., and Ito, M.K. 2014. Validation Study of Multi-Frequency Bioelectrical Impedance with Dual-Energy X-ray Absorptiometry Among Obese Patients. Obes. Surg. **24**(9): 1476–1480. doi:10.1007/s11695-014-1190-5.

García-Hermoso, A., Saavedra, J.M., and Escalante, Y. 2013. Effects of exercise on resting blood pressure in obese children: a meta-analysis of randomized controlled trials. Obes. Rev. **14**(11): 919–928. John Wiley & Sons, Ltd. doi:10.1111/obr.12054.

Hind, K., and Burrows, M. 2007. Weight-bearing exercise and bone mineral accrual in children and adolescents: A review of controlled trials. Bone **40**(1): 14–27. doi:https://doi.org/10.1016/j.bone.2006.07.006.

Istituto Superiore di Sanità. 2019. OKkio alla salute. Indagine 2019 - Dati nazionali. Available from https://www.epicentro.iss.it/okkioallasalute/indagine-2019-dati.

Janssen, I., Katzmarzyk, P.T., Boyce, W.F., Vereecken, C., Mulvihill, C., Roberts, C., Currie, C., Pickett, W., et al. 2005. Comparison of overweight and obesity prevalence in school-aged youth from 34 countries and their relationships with physical activity and dietary patterns. Obes. Rev. **6**(2): 123–132. doi:10.1111/j.1467-789X.2005.00176.x.

Janssen, I., and LeBlanc, A.G. 2010. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. Int. J. Behav. Nutr. Phys. Act. **7**(1): 40. doi:10.1186/1479-5868-7-40.

Kannel, W.B., Adrienne Cupples, L., Ramaswami, R., Stokes, J., Kreger, B.E., and Higgins, M. 1991. Regional obesity and risk of cardiovascular disease; the Framingham study. J. Clin. Epidemiol. **44**(2): 183–190. doi:https://doi.org/10.1016/0895-4356(91)90265-B.

Kavey RW, Simons-Morton DG, de Jesus JM. 2011. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics **128**: 1–44.

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., et al. 2006. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur. Heart J. **27**(21): 2588–2605. doi:10.1093/eurheartj/ehl254.

Lurbe, E., Agabiti-Rosei, E., Cruickshank, J.K., Dominiczak, A., Erdine, S., Hirth, A., Invitti, C., Litwin, M., et al. 2016. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J. Hypertens. **34**(10): 1887–1920. doi:10.1097/HJH.0000000000001039.

Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., and Turner, R.C. 1985. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia **28**(7): 412–419. doi:10.1007/BF00280883.

Meyer, A.A., Kundt, G., Lenschow, U., Schuff-Werner, P., and Kienast, W. 2006. Improvement of Early Vascular Changes and Cardiovascular Risk Factors in Obese Children After a Six-Month Exercise Program. J. Am. Coll. Cardiol. **48**(9): 1865–1870. doi:https://doi.org/10.1016/j.jacc.2006.07.035.

Must, A., Jacques, P.F., Dallal, G.E., Bajema, C.J., and Dietz, W.H. 1992. Long-Term Morbidity and Mortality of Overweight Adolescents. N. Engl. J. Med. **327**(19): 1350–1355. Massachusetts Medical Society. doi:10.1056/NEJM199211053271904.

Niemirska, A., Litwin, M., Feber, J., and Jurkiewicz, E. 2013. Blood pressure rhythmicity and visceral fat in children with hypertension. Hypertension **62**(4): 782–788. American Heart

Association. doi:10.1161/HYPERTENSIONAHA.113.01292.

Rabbia, F., Grosso, T., Cat Genova, G., Conterno, A., De Vito, B., Mulatero, P., Chiandussi, L., and Veglio, F. 2002. Assessing resting heart rate in adolescents: determinants and correlates. J. Hum. Hypertens. **16**(5): 327–332. doi:10.1038/sj.jhh.1001398.

Reusz, G.S., Cseprekal, O., Temmar, M., Kis, É., Cherif, A.B., Thaleb, A., Fekete, A., Szabó, A.J., et al. 2010. Reference values of pulse wave velocity in healthy children and teenagers. Hypertension **56**(2): 217–224. doi:10.1161/HYPERTENSIONAHA.110.152686.

Saladini, F., and Palatini, P. 2018. Arterial Distensibility, Physical Activity, and the Metabolic Syndrome. Curr. Hypertens. Rep. **20**(5): 39. doi:10.1007/s11906-018-0837-3.

Shaffer, F., and Ginsberg, J.P. 2017. An Overview of Heart Rate Variability Metrics and Norms. Front. Public Heal. **5**(September): 1–17. doi:10.3389/fpubh.2017.00258.

Skinner, A.C., Ravanbakht, S.N., Skelton, J.A., Perrin, E.M., and Armstrong, S.C. 2018. Prevalence of Obesity and Severe Obesity in US Children, 1999–2016. Pediatrics **141**(3): e20173459. doi:10.1542/peds.2017-3459.

Song, P., Zhang, Y., Yu, J., Zha, M., Zhu, Y., Rahimi, K., and Rudan, I. 2019. Global Prevalence of Hypertension in Children: A Systematic Review and Meta-analysis. JAMA Pediatr. **173**(12): 1154–1163. doi:10.1001/jamapediatrics.2019.3310.

Van Stappen, V., Latomme, J., Cardon, G., De Bourdeaudhuij, I., Lateva, M., Chakarova, N., Kivelä, J., Lindström, J., et al. 2018. Barriers from Multiple Perspectives Towards Physical Activity, Sedentary Behaviour, Physical Activity and Dietary Habits When Living in Low Socio-Economic Areas in Europe. The Feel4Diabetes Study. doi:10.3390/ijerph15122840.

Therkelsen, K.E., Pedley, A., Hoffmann, U., Fox, C.S., and Murabito, J.M. 2016. Intramuscular fat and physical performance at the Framingham Heart Study. Age (Omaha). **38**(2): 1–12.

Springer International Publishing. doi:10.1007/s11357-016-9893-2.

Tomlinson, D.J., Erskine, R.M., Morse, C.I., Winwood, K., and Onambélé-Pearson, G. 2016. The impact of obesity on skeletal muscle strength and structure through adolescence to old age. Biogerontology **17**(3): 467–483. doi:10.1007/s10522-015-9626-4.

Vettor, R., Milan, G., Franzin, C., Sanna, M., De Coppi, P., Rizzuto, R., and Federspil, G. 2009. The origin of intermuscular adipose tissue and its pathophysiological implications. Am. J. Physiol. Metab. **297**(5): E987–E998. American Physiological Society. doi:10.1152/ajpendo.00229.2009.

Vlachopoulos, C., Aznaouridis, K., and Stefanadis, C. 2010. Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness: A Systematic Review and Meta-Analysis. J. Am. Coll. Cardiol. **55**(13): 1318–1327. doi:https://doi.org/10.1016/j.jacc.2009.10.061.

Weiss, R., Dziura, J., Burgert, T.S., Tamborlane, W. V, Taksali, S.E., Yeckel, C.W., Allen, K., Lopes, M., et al. 2004. Obesity and the Metabolic Syndrome in Children and Adolescents. N. Engl. J. Med. **350**(23): 2362–2374. Massachusetts Medical Society. doi:10.1056/NEJMoa031049.

WHO. 2014. Global status report on noncommunicable diseases 2014. Available from https://www.who.int/nmh/publications/ncd-status-report-2014/en/ [accessed 10 January 2020].

WHO. 2016. WHO Report of the commission on ending childhood obesity. Available from https://www.who.int/end-childhood-obesity/publications/echo-report/en/ [accessed 10 January 2020].

Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D.L., Coca, A., et al. 2018. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European

Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial . J. Hypertens. **36**(10): 1953–2041. England. doi:10.1097/HJH.0000000000001940.

Zhang, D., Shen, X., and Qi, X. 2016. Resting heart rate and all-cause and cardiovascular mortality in the general population: a meta-analysis. CMAJ **188**(3): E53–E63. 8872147 Canada Inc. doi:10.1503/cmaj.150535.

Figure legends

Figure 1. Study design.

BP = Blood pressure; HR = Heart rate; ECG = Electrocardiographic; PWV = Pulse Wave Velocity; PWA = Pulse Wave Analysis; TBW = Total body water; FFM = Free fatty mass; FM = Fatty mass; AT = Adipose tissue; AAT = Abdominal adipose tissue; IMAT = Intramuscular adipose tissue.

Table 1. Baseline characteristics of study subjects.

	Overall population n = 30	Resistance training group n = 15	Combined training group n = 15	p value§
Age, *years*	15.6 ± 1.5	15.5 ± 1.9	15.7 ± 1.2	0.79
BMI, *kg/m2*	32.1 [30.5-34.4]	32.3 [30.5-33.3]	31.8 [30.5-37.5]	0.67
BMI Z-score	2.03 [1.90-2.28]	2.05 [1.91-2.22]	2.01 [1.77-2.32]	0.97
SBP, *mmHg*	123.3 ± 9.6	122.7 ± 10.8	123.9 ± 8.5	0.56
DBP, *mmHg*	75.5 ± 8.9	75.7 ± 9.8	75.4 ± 8.4	0.93
HR, *bpm*	80 [76-90]	80 [76-87]	85 [76-92]	0.85
TBW, *%*	38 [36-41]	38.5 [37-43]	38 [36-40]	0.57
FM, *%*	42 [39-44]	41.5 [40-44]	43 [38-46]	0.70
AT, *kg*	45.5 [41.1-49.7]	44.3 [39.8-49.6]	45.5 [41.1-51.1]	0.72
AAT, *cm^2*	588.4 [528.0-676.0]	587.6 [508.6-703.8]	624.2 [528.0-642.2]	0.98
IMAT, *%*	2.3 [2.1-2.5]	2.3 [2.1-2.5]	2.2 [2.1-2.5]	0.83
Muscle, *kg*	19.5 [16.8-22.4]	20.4 [16.8-23.5]	19.2 [16.5-22.0]	0.60
Bone, *kg*	3.9 [3.4-4.3]	4.0 [3.4-4.6]	3.9 [3.3-4.3]	0.85

BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HR = Heart rate; TBW = Total body water; FM = Fatty mass; AT = Adipose tissue; AAT = Abdominal adipose tissue; IMAT = Intramuscular adipose tissue.

§p value of comparison between resistance and combined training group for baseline characteristic at randomization time.

Table 2. T0, T1 and T2: characteristics of active participant to training program.

	T0	T1	T2	p value§
BMI, *kg/m2*	31.7 [30.3-34.1]	31.1 [29.6-33.4] **	31.7 [29.4-34.0] **	0.002
BMI z-score	2.01 [1.84-2.27]	1.95 [1.75-2.14] **	1.97 [1.66-2.08] ***	<0.001
SBP, *mmHg*	122.5 ± 7.9	120.0 ± 8.3	119.5 ± 10.5	0.332
DBP, *mmHg*	74.7 ± 8.8	68.2 ± 6.4 **	66.6 ± 5.4 ***	<0.001
HR, *bpm*	80 [76-88]	80 [73-85]	72 [68-76] **	0.015
PVW, *m/s*	5.7 [5.0-5.9]	5.2 [4.7-5.6] **	5.3 [4.8-5.7]	0.052
Central SBP, *mmHg*	100 [95.5-113]	100.5 [96.5-105.5]	100 [97-107.5]	0.571
Central DBP, *mmHg*	71.5 [65.5-80]	67 [64.5-75.5]	70 [65.5-79.5]	0.738
HOMA index	2.50 [1.90-5.73]	2.05 [1.39-4.62] ***		
SDANN, *ms*	6.9 [4.3-21.6]	18.3 [10.4-29.3]	16.4 [6.5-22.8]	0.790
SDNN, *ms*	52.7 [38.9-76.3]	57.1 [45.7-80.3]	71.6 [47.9-85.0]	0.223
RMSSD	33.2 [26.3-63.8]	43.2 [22.3-63.9]	55.9 [30.6-74.9] **	0.066
LF/HF	1.7 [1.4-2.3]	1.6 [1.1-2.6]	1.4 [1.1-2.7]	0.465
TBW, *%*	38 [35.5-40]	40 [38.5-43.5] ***	39 [38-40] **	<0.001
FM, *%*	41 [38.5-44]	40 [37-42.5] ***	41 [38-43] ***	<0.001
AT, *kg*	44.2 [40-49.6]	41.6 [37.0-49.2] ***	43.3 [39.1-52.6]	0.001
AAT, *cm²*	586.6 [511.2-689.9]	557.8 [475.9-667.8] ***	575.1 [499.7-713.8]	<0.001
IMAT, *%*	2.3 [2.1-2.5]	2.2 [2.0-2.5] ***	2.2 [2.0-2.6]	<0.001
Muscle, *kg*	19.5 [16.2-22.2]	20.1 [17.8-22.9] **	18.7 [16.4-23.0]	0.014
Bone, *kg*	3.9 [3.3-4.3]	4.0 [3.7-4.4] ***	3.8 [3.4-4.4]	0.003

In the table ** for $p<0.05$, *** for $p<0.01$ (comparisons referred to T0 evaluation).

BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HR = Heart rate; PWV = Pulse wave velocity; SDANN = Standard deviation of the average of NN intervals; SDNN = Standard deviation of NN intervals; RMSSD = Root mean square of successive RR interval differences; LF = Low frequency band power; HF = High frequency band power; TBW = Total body water; FM = Fatty mass; AT = Adipose tissue; AAT = Abdominal adipose tissue; IMAT = Intramuscular adipose tissue.

§p value of Friedman test for each parameter.


Baseline visit – T0
History and clinic evaluation: resting BP and HR; physical examination (height, weight, waist circumference); laboratory tests.
Cardiovascular evaluation: 20-minutes rest ECG monitoring, PWV, central BP (PWA).
Anthropometric evaluation (BIA-ACC): TBW, FFM, FM, AT, AAT, IMAT, Bone mass, Muscle mass.
Enrollment and randomization (n=30)
Drop off Group A (n=5; 15%)
Group A Resistance training (n=10) 6 months
Group B Combined training (n=10) 6 months
Drop off Group B (n=5; 15%)
Follow up visit – T1
Clinic evaluation: resting BP and HR; physical examination (height, weight, waist circumference); laboratory tests.
Cardiovascular evaluation: 20-minutes rest ECG monitoring, PWV, central BP (PWA).
Anthropometric evaluation (BIA-ACC): TBW, FFM, FM, AT, AAT, IMAT, Bone mass, Muscle mass
Detraining 3 months
Detraining visit – T2
Clinic evaluation: resting BP and HR; physical examination (height, weight, waist circumference); laboratory tests.
Cardiovascular evaluation: 20-minutes rest ECG monitoring, PWV, central BP (PWA).
Anthropometric evaluation (BIA-ACC): TBW, FFM, FM, AT, AAT, IMAT, Bone mass, Muscle mass

Cardiovascular Outcomes

Systolic Blood pressure (SBP)

Diastolic Blood pressure (DBP)

Heart rate (HR)

Pulse Wave Velocity (PWV)

Pulse Wave Analysis (PWA)

Central Blood Pressure (Central BP)

Homeostatic model assessment index (HOMA index)

Heart Rate Variability (HRV) outcomes

Standard deviation of NN intervals (SDNN)

Standard deviation of the average NN intervals for 5 minutes interval (SDANN)

Root mean square of the successive NN intervals (RMSSD)

Low frequency domain (LF)

High frequency domain (HF)

Bioimpdentiometric outcomes

Total body water (TBW)

Fatty mass (FM)

Free fatty mass (FFM)

Adipose tissue (AT)

Abdominal adipose tissue (AAT)

Intramuscular adipose tissue (IMAT)