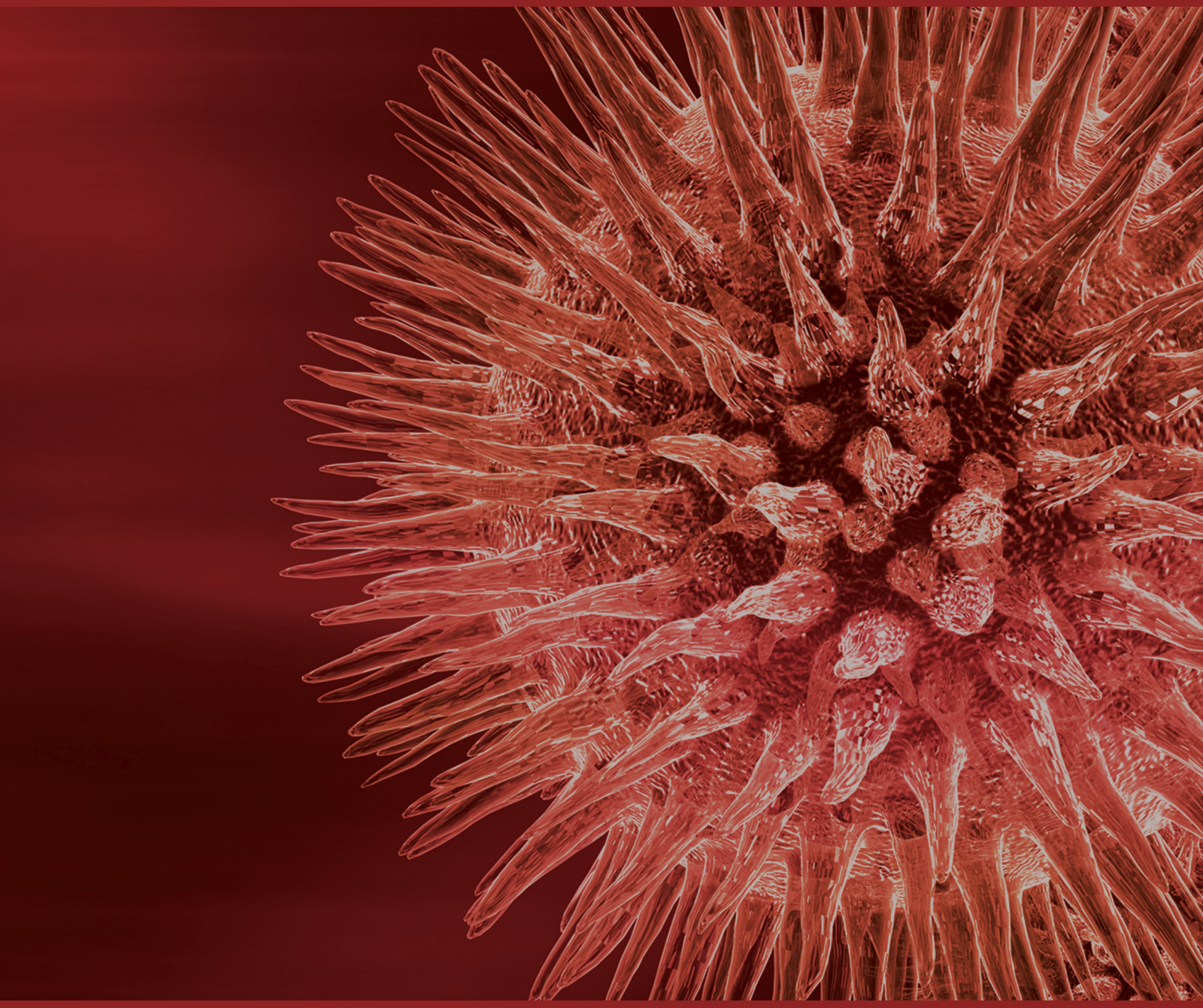
BioMed Research International

Lifestyle Modification Strategies to Counteract the World Epidemic Growth of Obesity and Diabetes

Guest Editors: Pierpaolo De Feo, Jean-Michel Boris, and Claudio Maffeis



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Editorial

Lifestyle Modification Strategies to Counteract the World Epidemic Growth of Obesity and Diabetes

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Obesity and type 2 diabetes are increasing all over the world at an alarming rate due to unhealthy lifestyles. The fight against childhood obesity represents one of the biggest social and health problems all over the world. Diabetes mellitus reduces quality of life and life expectancy and represents a serious economic burden. The correction of unhealthy lifestyles is possible through cost-effective measures and it might prevent about 80% of cases of heart disease, stroke, and type 2 diabetes and 40% of cancers. At present, there is a need to advance in the science of delivering health promotion and reproducible multidisciplinary models for the prevention and treatment of obesity and diabetes using lifestyle change. Particularly alarming is the childhood obesity which represents the most common metabolic disorder in children and adolescents. Three reasons other than the high prevalence justify the urgency of treating and preventing childhood obesity: (i) persistency of childhood obesity into adulthood; (ii) metabolic and nonmetabolic morbidity obesity associated; (iii) higher mortality in adulthood. The American Academy of Pediatrics published guidelines with the targets for prevention and treatment of childhood obesity, based on consistent scientific evidence. Nutrition and physical activity are the main tools of intervention. Recent evidence suggests that prevention should start early, from intrauterine life and infancy, when the sensitivity of the organism to metabolic long-term programming processes is high and the potential impact of the intervention may be considerable. The discouraging results of the impact of available interventions in prevention and treatment of childhood obesity stimulate new emphasis in both clinical and experimental research in the field.

The present special issue has been published to enlarge the knowledge in the field of the battle against childhood and adult obesity and type 2 diabetes.

Four papers address the issue of childhood obesity prevention and treatment. G. Valerio et al. report that perception of task's difficulty level may reflect an actual difficulty in obese children. These findings have practical implications for approaching physical activity in obese children. In order to design exercise programs that allow safe and successful participation it is relevant to explore both the perception of a task's difficulty level and physical performance of obese children. H. Zheng and coworkers originally looked for possible associations between the metabolome and gender, pubertal development, and physical activity in overweight adolescents, which is an important subject group to approach in the prevention of obesity and life-style related diseases. No relations between physical activity and the metabolome could be identified, whereas gender differences in the metabolome are being commenced already in childhood and might be used for identification of individuals susceptible to an early pubertal development. C. Mazzeschi et al. describe the design of the intervention programme EUROBIS (Epode Umbria Region Obesity Intervention Study), an EPODE community-based intervention combined with a clinical

trial, which provides an innovative valuable model to address the childhood obesity prevention and treatment. Finally, A. Verrotti et al. explored a possible relationship between prevalence, frequency, and severity of migraine and obesity in children. Interestingly, data from literature reviewed in this paper suggest that obesity can be linked with migraine prevalence, frequency, and disability in both paediatric and adult subjects, suggesting the importance for the quality of life of children of lifestyle interventions.

Regarding adult obesity, the paper by K. M. J. Azar et al. examined whether baseline BMI may influence behavioural weight-loss treatment effectiveness. The authors show that participants with baseline BMI had greater reductions in mean BMI, body weight, and waist circumference in the coach-led group intervention, compared to usual care and the self-directed individual intervention. These results indicate the importance of taking into account individual's baseline BMI when developing or recommending lifestyle focused treatment strategy. B. Strasser and D. Pesta reviewed the evidence about the role of resistance training in counteracting the metabolic dysfunction in patients with type 2 diabetes. The authors report several beneficial adaptations exerted by resistance training which include increased GLUT4 translocation in skeletal muscle, increased insulin sensitivity, increased energy expenditure, and excess postexercise oxygen consumption. This paper supports the importance of using combined aerobic and resistance exercise as a therapeutic tool for type 2 diabetic patients. A positive message about the beneficial effects of walking in obesity and type 2 diabetes comes out of the paper of C. Mazzeschi et al. who originally report the effects of prolonged exercise (about 400 km walk over 2 weeks) on several health and psychological outcomes. The results of this study demonstrate that long-distance treks are a safe activity for trained overweight/obese people that should be recommended because they improve mood, health status, and the relationship of participants with themselves and with the regular practice of exercise with effects similar to those obtained by healthy normal weight subjects.

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Research Article

Description of the EUROBIS Program: A Combination of an Epode Community-Based and a Clinical Care Intervention to Improve the Lifestyles of Children and Adolescents with Overweight or Obesity

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The present paper describes the Epode Umbria Region Obesity Prevention Study (EUROBIS) and aims to implement the C.U.R.I.A.MO. model through the EPODE methodology. The main goal of the EUROBIS is to change the pendency of slope of the actual trend towards the increase in the yearly rates of childhood overweight and obesity in Umbria and to improve healthy lifestyles of children and their parents. The project is the first EPODE program to be performed in Italy. The aims of the Italian EUROBIS study are: (1) a community-based intervention program (CBP) carrying out activities in all primary schools of the Umbria Region and family settings as first step, to reverse the current obesity trend on a long-term basis, and (2) a clinical care program for childhood and adolescent by C.U.R.I.A.MO. model. C.U.R.I.A.MO. model is a multidisciplinary approach to improve three key aspects of healthy lifestyles: nutrition, exercise, and psychological aspects with the strategy of a family-based approach. The community-based intervention and clinical trial provide an innovative valuable model to address the childhood obesity prevention and treatment in Italy.

1. Introduction

The prevalence of overweight and obesity in children and adolescents is increasing rapidly with dramatic consequences for health [1]. A study of the prevalence and determinants of pediatric overweight and obesity in European countries reveals that the highest values are found in Italy. Italian boys and girls show higher age-specific values of body mass index (BMI), body circumference, waist/hip, and waist/height ratios when compared with other countries [2]. In Italy, pediatric obesity is one of the major public health emergencies: 25% of subjects aged between 0 and 18 years (average) are overweight, with a peak recorded in the 9- to 11-year age group, in which 23% of the population is overweight

and 13% is obese. Specifically, the Umbria Region has a prevalence of overweight (26%) and obesity (9%) above the national mean [3].

Pediatric obesity is a complex phenomenon. Its development and maintenance are influenced by a complex array of factors, genetic predisposition, metabolic and neurobiological factors with lifestyle aspects, eating and physical activity habits, and psychological-psychosocial factors [4–6]. Although genetic and biological risk factors are receiving significant research attention, among psychosocial factors in the last decade there has been an important shift by considering individual factors, to focus on environmental factors, given the evidenced systemic associations between adiposity and familial and parental functioning [7]. Obesity runs in families [8] and a series of familial variables, connected to the multifactorial nature of children overweight, have been identified [9–13]. There are evidences that lifestyle behaviors have their roots early in life and recent studies emphasize the impact of parental and familial variables as risk factors on the development and maintenance of childhood overweight and obesity [14].

The purpose of this paper is to describe the Epode Umbria Region Obesity Prevention Study (EUROBIS), an innovative program based on a community-based approach (EPODE, *Ensemble Prévenons l'Obésité des Enfants*) combined with a clinical intervention in order to prevent and treat overweight and obesity in childhood. EUROBIS is twofold: (1) it is to be intended as a community-based intervention program (CBP) to reduce childhood obesity prevalence carrying out activities in all primary schools of the Umbria Region and family settings as first step, and (2) it has a clinical care program by the mean of C.U.R.I.A.MO. (Centro Universitario Ricerca Interdipartimentale Attività Motoria) model to treat childhood and adolescence overweight and obesity through a family-based approach. The model is based on a multidisciplinary approach, already experimented for adulthood obesity [15–17] and tailored for developmental needs. The present paper describes a strategy that combines a strong prevention approach with a strong management approach. Combining these kinds of interventions into one program is very important and innovative and if successful could mean a breakthrough in combating the obesity epidemic.

2. Study Design: The Combination of Preventive and Curative Action

EUROBIS is one of the EPODE programs. EPODE is a coordinated, capacity-building approach that aims to reduce childhood obesity through a social process in which local environment, childhood settings, and family norms are directed and encouraged to facilitate the adoption of a healthy lifestyle in children [18].

Within the framework of the EPODE methodology, in Italy EUROBIS is based on a combination of preventive and curative strategies. Relying on the preexisting Healthy Lifestyle Institute of the region, EUROBIS aims to overcome the division between prevention and health care.

In accordance with the EPODE philosophy, it is based on multiple components, including a positive approach in tackling obesity, with no cultural or social stigmatization; step-by-step learning; and an experience of healthy lifestyle habits, tailored to the needs of all socioeconomic groups. EPODE target groups are children, families, local stakeholders, and decision makers working in the different sectors of the society involved in environment causes and determinants of childhood obesity. The four EPODE pillars (political commitment, social marketing, mobilization of resources including public-private partnerships, and evidence including a multidisciplinary evaluation) have been subdivided into ten EPODE implementation principles, which describe the EPODE methodology.

(1) Each country (or region) commits to a central coordination support/capacity.

(2) Each local community has a formal political commitment for several years from the outset.

(3) Each local community has a dedicated local project manager with sufficient capacity and cross-sectoral mandate for action.

(4) A multistakeholder approach is integral to the central and local structures and processes.

(5) An approach to action is planned and coordinated using social marketing. This is specifically to define a series of themed messages and actions, informed by evidence, from a wide variety of sources, and in line with official recommendations.

(6) Local stakeholders are involved in the planning processes and are trusted with sufficient flexibility to adapt actions to local context.

(7) The "right message" is defined for the whole community. However, getting the message "right" means tailoring for different stakeholders and audiences.

(8) Messages and actions are solution oriented and designed to motivate positive changes and not to stigmatize any culture or behaviors.

(9) Strategies and support services are designed to be sustainable and backed by policies and environmental changes.

(10) Evaluation and monitoring are implemented at various levels. This is achieved through the collection of information on process, output, and outcome indicators and informs the future development of the program.

An approach to action is planned and coordinated using social marketing. Local stakeholders are involved in the planning processes. Strategies and support services are designed to be sustainable and backed by policies and environmental changes. Evaluation and monitoring are implemented at various levels. EUROBIS, similar to the Epode-like program in the Netherlands (JOGG) (http://www.epode-international-network.com/programes/jogg), has added a fifth pillar to the ones of EPODE methodology, "linking prevention and healthcare," and proposes a structured

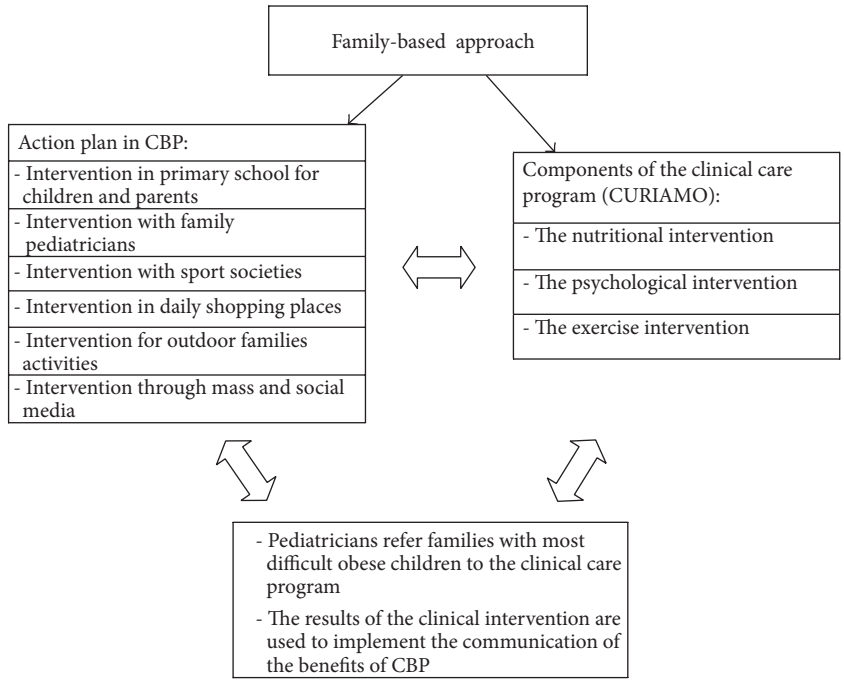

Figure 1: Diagram describing the action plan of the community-based program (CBP) and the clinical care program (C.U.R.I.A.MO.) and the interaction between the preventive and the curative strategies.

combination of preventive and curative actions. In line with the EPODE methodology to mobilize local resources, the added fifth pillar concerning mental health refers to the Healthy Lifestyle Institute of Perugia University. The model is based on a multidisciplinary approach, already experimented for adulthood obesity [15–17, 19], tailored for children and adolescents. The intervention program differs for children and adolescents and it is finalized in improving three key aspects of healthy lifestyle: nutrition, exercise, and psychological wellbeing, using a family-based approach. The C.U.R.I.A.MO. model for pediatric overweight or obesity involves the following health care professionals: pediatricians, endocrinologists, psychologists, dieticians, and exercise physiologists.

As illustrated in Figure 1, the pediatricians have a key role between the two approaches (CBP and C.U.R.I.A.MO.) both facilitating families with overweight or obese children in referring to the clinical care program and communicating the results of the clinical intervention in order to implement the benefits of CBP.

A common perspective of both CBP and C.U.R.I.A.MO. is the family-based approach with an active involvement of the parents in the project of changing. The main aim is to actively involve both the child/adolescent and the two parents (as far as possible) in order to mobilize family resources to improve the efficacy of the program. In this model, the objective is to involve the parents in order to improve their skills and confidence. Working with general and specific parental skills connected to child's care and health, it is possible to teach the parents to recognize the child's needs, manage child's dietary and activity patterns, and promote a healthy lifestyle in the family and consequently in the child. In adolescence it is also necessary to improve parental skills in recognizing the impact of overweight/obesity in the self-esteem of the youth.

The characteristics of CBP and C.U.R.I.A.MO. models will be discussed in detail separately, outlining evaluation and monitoring strategies.

3. The Community-Based Intervention Program (CBP)

In order to mobilize stakeholders at all levels across the public and private sectors through a local steering committee and local networks, the Umbria Region (the President and the vice-President of Umbria Region and the regional assessors of health, welfare, and agriculture and local food), the Director of the Health Prevention Department, the local university, family pediatricians, local private associations, the Regional Olympic Committee, the Regional Federation of Industries, promoters of treks and urban walking activities, the major local companies of food distribution, vending machines, the regional media channel, and web journal all actively collaborate with EUROBIS.

3.1. Action Plan in CBP. According to the Council Recommendations of the European Commission (http://ec.europa.eu/sport/library/documents/c1/com-2013-603-final-council-recommendation-hepa_en.pdf), the plan of action covers different sectors (health, sport, school, and environment) in order to include a series of actions. In order to promote a healthy lifestyle among children and their families, the actions planned include many contexts:

(i) intervention in primary school for children and parents: active transport (pedibus); exercise classes; monthly meetings with parents on healthy nutrition and psychological determinants of obesity (production of media books, web sites, and printed materials);

(ii) intervention with family pediatricians: periodical meetings on effective strategies to prevent childhood obesity;

(iii) intervention with sport societies: promotion of baby and child participation in sports independently of their talent, encouraged through award for excellence to the sport societies, and link of these societies to family pediatricians;

(iv) intervention in daily shopping places: health lifestyle corner and healthy cooking classes in major food shops and distribution of healthy food and beverages in vending machines;

(v) intervention for families: visits to farms and vegetable gardens with tasting on site, mapping of regional healthy trails and promotion of open air activities for families;

(vi) intervention through mass media: global media communication strategy to fight childhood obesity including campaigns to promote healthy nutrition and regular exercise with a family-based approach using a web site (http://www.eurobis.it) and social channels (Facebook, Twitter, YouTube, and Google+).

3.2. Evaluation and Monitoring of CBP. The overall expected outcome for the community-based intervention is to change the pendency of the slope of the actual trend towards the increase in the yearly rates of childhood overweight and obesity in Umbria. Umbria Region has an efficient system of surveillance for the epidemiology of overweight and obesity in children by means of three different approaches: (1) anthropometric measurements performed by family pediatricians every 5 years; (2) a survey "OKKIO alla Salute" (http://www.iss.it/binary/publ/cont/0924.pdf), of a significant number of families from Umbria every 2 years; and (3) a survey Studio PASSI (http://www.iss.it/binary/publ/cont/07-30.1195128446.pdf) of a significant number of families from Umbria every 2 years.

Therefore a historical epidemiology database on overweight and obesity in children from Umbria is available and can be used as a baseline. It is also possible to make comparisons with the closest Regions, which have a lower prevalence of childhood obesity than in Umbria. The process will be monitored and evaluated by measuring in significant subgroups of children body composition, with noninvasive techniques (Bod Pod: air displacement methodology). Continuous monitoring and evaluation practices at a local level will regard input, activities, output, and outcome indicators. The evaluation process will take into account the participation of intervening parties, awareness raised among the political representatives involved in the program, local stakeholders' feeling as part of a common positive action for the community, and participation of the families and children in the program's activities.

A program efficacy indicator will be the number of EUROBIS actions that will be adopted by the 2014–2018 Umbria regional health prevention program. The process of evaluation will be performed by the *Steering and Scientific Committees* examining the data of interviews and questionnaires periodically administered to the target population (children and their parents) of EUROBIS. The monitoring and evaluation also consist in data collection, performed by health professionals, on weight, height (BMI measurements), and waist circumference of children. Other indicators will include physical child performance, energy expenditure (METS/h/week) during leisure time, number of meals consumed in family and quality of the child's life (reported by parents), indicators of well-being both from parents and child perspective, level of healthy attitudes, health status and level of participation of the child in daily life activities (inside and outside families) [20]. Measurements of the interventions impact and publication of the results in international scientific journals, production of media books, web site and printed materials will contribute to the dissemination of the program results.

4. The Clinical Care Program

Study Design. Over three years about 90 children (aged 5–10 years) and 90 adolescents (aged 11–16 years) with overweight or obesity will be enrolled. Inclusion criteria will be as follows: age between 5 and 16 years; BMI higher than 90% percentile. Exclusion criteria will be concomitant diseases contraindicating physical exercise. The enrollment is planned to include 30 subjects every 6 months and to perform the lifestyle intervention described below, in order to reach a total number of about 60 patients/year. The total duration of the study will be 4 years. The medical examination performed by the pediatrician in our institute is finalized to establish the degree of overweight or obesity, the absence of diseases responsible of obesity, and the lack of contraindications to physical exercise.

4.1. The Three Components of the Clinical Care Program

The Nutritional Intervention. The aim is to train children's parents or directly adolescent patients (11–16 years) to be able to regularly choose and eat healthy foods. The intervention is structured in two counseling sessions with a dietician (30 minute of duration at 1 month interval) with children's parents or directly with the adolescent patients and in four educational group sessions. During the two counseling sessions, for promoting weight loss, the dietician does not prescribe a restricted diet but provides nutritional information and uses food log for monitoring dietary habits and their changes. The four nutritional education group sessions are conducted by two dieticians; they last about 120 minutes and are based on interactive learning. Twelve to sixteen parents (both mothers and fathers) of children (5–10 years old) are invited to the four educational sessions or, in the case of

adolescents (11–16 years old), directly 6–8 patients are invited, while their parents are allowed to attend only the first of the four sessions, dedicated to elucidate the general principles of a healthy nutrition. During the educational sessions the dieticians interactively illustrate the strategies to reduce high energy density food consumption in order to cut daily caloric intake of about 300–400 Kcal and daily caloric intake from fat to <30% of total caloric intake (ideal composition of diet: CHO 55%, FAT 30%, and protein 12–15% of total calories) and the strategies to increase the Mediterranean diet score by eating more frequently vegetables, fish, fruit, and food naturally rich in fibers. Every 3 months, in occasion of maintenance nutritional visits, patients' nutrient intake is monitored by food logs reported by children's parents or by adolescent. In order to estimate the changes in nutritional habits the children's parents or the adolescent patients will fill a validated questionnaire to calculate the Mediterranean diet score [21].

The Psychological Intervention. The intervention is primarily characterized by counseling centered on each family's needs, by assessing their characteristics, their strengths, and weaknesses in different domains.

(i) Anamnestic, regarding the child and his parents: there is evidence on the relation between some traumatic life events and obesity [22].

(ii) Personal, regarding each parent separately and the child: this domain refers specifically to anthropometric and psychological risk factors identified as associated with child's obesity. Among them is parents' BMI considered separately, as contributing differently to child's BMI [23], maternal depression, or anxiety [12, 24].

(iii) Familial, considering the family as whole and its functioning in terms of structural factors and emotional climate: family socioeconomic level (SES) has been identified as being correlated with child overweight [10] as well as number of siblings in the family, order of birth, and type of family (in marriage, alone mothers, or alone fathers).

(iv) Parental, from both parents' perspectives (as far as possible): their contribution to the child's care, their parental practice, including modeling [25], their way of caring for the child in terms of style of parenting [10, 26], their alliance in managing the child's development, and the level of distress.

The aim is to create, during the assessment-intervention phase, a tailored psychological program based on each family and parental characteristics along with a shared program followed by the children/adolescent and parents.

The psychological work follows three steps: (1) a first step of psychological assessment; (2) a second step of psychoeducational groups of parents (a) or of adolescents (b); and (3) and (4) two follow-up sessions.

Step 1 (psychological assessment). The program starts with an initial intensive phase (five sessions lasting one month and a half), with the child/adolescent as well as with the parents in order to assess, through the use of psychometric psychological measures, a series of risk factors associated with overweight/obesity in families (anamnestic, personal, parental, and familial) and to assess the presence of eating disorders or other psychological complications according to the guidelines of the Italian Society of Obesity.

Step 2a (psychoeducational group of parents (four sessions)). Both parents are invited to participate in four sessions in small psychoeducational groups (eight to ten people) in order to sustain the child's physical and nutritional program. By using video-recorded material, consisting of scenes derived by a series of movies identified as evocative of specific triggering familial and interactional episodes (POR FSE 2007–2013, Umbria Region Grant 2011/2012), parents (mothers and fathers) participate in a series of psychoeducational sessions. By using video-feedback and self-reflection, parents are trained to allow more insight and empathy, broadening their coping skills toward the use of healthy life habits.

Step 2b (psychoeducational peer group of adolescents (three sessions)). Adolescents are invited to participate in a three-session psychoeducational peer group on the impact of overweight and obesity on self-esteem and on body image. The aim of the group is to share with peers, with the help of a psychologist, the major risk factors of obesity associated with this developmental age.

Steps 3 and 4 (first followup at 6 months and second followup at one year). Clinical interview and psychometric evaluation are conducted for parents and children/adolescents separately, in order to assess program-related changes over the course of treatment and at the end of it. Followup is conducted according to a collaborative approach.

The Exercise Intervention. The exercise protocol intervention is planned with duration of 6 months and a frequency of 2 sessions/week and it is different for children (5–10 years old) and adolescents (11–16 years).

The exercise program for children aims to achieve two outcomes: (a) to improve general physical fitness including spatial coordination, aerobic capacity, flexibility, and muscle strength; (b) to promote the discovery of the feeling of fun with traditional games based on active motion. The activities programmed are performed in the gym for groups of 6–8 kids supervised by exercise physiologist and they consist of four phases: warm-up, exercises for general body fitness, game group, and final stretching for a total of 70–80 minutes per session. During the first and the last of the 52 sessions functional tests are performed to evaluate the aerobic capacity, flexibility, and dynamic muscle strength [27–32].

The training program for adolescents is performed in the gym and supervised by an exercise physiologist with a maximum attendance of 5 patients/group. Each session lasts 90 minutes divided into 60 minutes of aerobic workout and 30 minutes of circuit training for muscular strength and flexibility exercises. The aerobic workout is performed using

ergometers for cardiovascular work (treadmill, cicloergometer, and armergometer) with gradually increasing intensity of work up to 60–70% of heart rate reserve. The workout for muscular strength will use machines and isotonic free loads for training the lower and upper limbs, with gradual increase up to 70–80% of 1 repetition maximum (RM). During the first and the last session aerobic capacity and muscle strength will be measured. Aerobic capacity is estimated using the Rockport Fitness Test [27] on treadmill. The determination of the maximum dynamic force [28, 29] of extensor muscles of the leg and the flexor and extensor muscles of the arms is conducted by the indirect method of extrapolation to one repetition max by using MRI leg press, lat machine, and chest press machine (Technogym, Cesena, Italy).

4.2. Evaluation and Monitoring of Clinical Care Intervention. The aim is to improve the adoption of a healthy lifestyle by children and adolescents. The family-based approach includes the parents as targets of the intervention for nutritional education and the psychological support; in addition for overweight adults there will be the possibility to participate in supervised exercise sessions, during the physical training of their children, using the C.U.R.I.A.MO. model (15). The major outcome of the population intervention will be a reduction of at least 5% in BMI and waist circumference percentiles in children from Umbria and adolescents after 4 years of intervention. The primary outcome is an improvement in lifestyle, using a composite end-point. We postulate that at the end of the study (4 years) more than 70% of children and adolescents enrolled in the C.U.R.I.A.MO. project will improve their lifestyle. Multiple imputations for missing data and intention-to-treat analysis will be used for statistical purpose. A significant improvement in lifestyle (composite major end-point) is defined as an increase of at least 20% of the Mediterranean diet index score combined with an increase of at least 10 $\text{MET/h}^{-1}\cdot\text{week}^{-1}$ of energy expenditure by physical activity and a reduction of at least 5% of the percentiles of BMI and/or waist circumference. Measures of quality of life and psychological well-being will also be included both from parents and children perspectives, aimed at assessing the increased level of healthy attitudes, the level of health status (considered in a broad sense), and the level of child participation in daily life activities (inside and outside families) [33].

5. Discussion

The American Academy of Pediatrics Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity [34] suggested a family-based approach to treat pediatric obesity. According to Kitzman and Beech, family-based interventions are defined as active parent involvement in treatment [35]. There are evidences of clear advantages associated with family-based intervention. Family-based approach is the "gold standard" [36] for pediatric obesity treatment, showing the strongest and longest lasting effects with the inclusion of parents [37, 38]. The approach focused on parents reflects the recognized multifactorial nature of pediatric obesity, engaging both genetics and environmental factors [13] and the fact that lifestyle aspects are consistently shown to be highly predictive and can be more changeable by treatment interventions [5].

Parent self-report measures of adherence outside the treatment setting have been identified as better predictors of child outcome than objective measures: family adherence to the treatment protocol has been identified as a good predictor of treatment success [39]. This conclusion has been reached also by Yackobovitch-Gavan and colleagues devising a major reduction of BMI in those children whose parents completed self-reported measure before and after treatment [24]. Gilles et al. found that increasing parental involvement expands the rate of success [40]. Moreover, parental functioning influences the course of the treatment [41, 42]. In this direction there are studies showing that in pediatric obesity treatment caregiver parental distress is an influential factor compromising successful outcomes and that children's perception of father's acceptance of their treatment is an important factor for a greater weight loss [26, 43, 44]. Zeller and colleagues identified in caregivers of youth treatment seeking for obesity a greater psychological distress, more family conflict, and greater mealtime challenges compared to caregivers of youth of healthy weight [41]. Moreover, in caregivers of school-aged children a high percentage of clinically elevated levels of spousal discord specific to parenting has been detected [12]. Lower maternal sensitivity, measured by direct observation of parent-adolescent interactions, was found to be associated with adolescent obesity [45]. According to Epstein and Wrotniak, there is need to develop new paradigms to treat pediatric obesity by devising programs based on moderators of treatment success to be translated into clinical interventions [39].

Starting from this perspective, the aim of the present study was to illustrate an innovative model trialled by public and private sectors to promote an active and healthy lifestyle in childhood and adolescence overweight and obesity. The model proposed, the Italian EUROBIS study based on an EPODE methodology, is twofold. Both the community-based intervention program and the clinical care program, carried out by the means of the C.U.R.I.A.MO. model, aim to involve parents and their children in the prevention and treatment of overweight and obesity. In order to achieve this aim, the actions planned in the community-based intervention are primarily directed toward involving the whole family. The clinical care program is based on the C.U.R.I.A.MO. model, chosen to entirely counteract the three main factors involved in the current rise of pediatric obesity by enhancing (1) physical activity, (2) healthy nutrition, and (3) motivation for a correct style of life, by working with parents in order to reduce their impact of unhealthy habits on child healthy behaviors and beliefs and, with adolescents, by promoting their skills and empowerment towards a healthy style of life. In our opinion the multidisciplinary approach that characterizes the model and its family-based approach should lead to the future validation of the intervention.

In conclusion, EUROBIS will explore the efficacy of combining clinical care with CBP. We are confident that, on

the basis of the positive results of previous EPODE programs [18], the global strategy adopted in designing EUROBIS intervention will have a significant impact on reducing the burden of childhood and adolescence overweight and obesity in the Region of Umbria.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

The Impact of Strenuous Group Physical Activity on Mood States, Personal Views, Body Composition, and Markers of Myocardial Damage in Overweight/Obese Adults: The "Step-by-Step Italy's Coast to Coast" Trek

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It is clinically relevant to understand whether it is safe to recommend to trained overweight/obese people long-distance treks and whether these experiences could have a negative psychological impact or become even dangerous exposing the trekkers to the risk of clinically silent myocardial damage. To answer these questions we have performed a quantitative/qualitative study comparing the changes in mood profiles, personal views, body composition, and plasma troponin levels of 40 overweight/obese subjects with those of 36 healthy normal weight subjects after the participation in a trek of 388 km from the Adriatic to the Tyrrhenian seas trek: the "Step by step. . .Italy's coast to coast". The results of this study demonstrate that long-distance treks are a safe activity for trained overweight/obese people which should be recommended because they improve mood, health status, and the relationship of participants with themselves and with the regular practice of exercise with effects similar to those obtained by healthy normal weight subjects.

1. Introduction

It is unknown what is the impact of strenuous exercise on overweight or obese people and whether related changes in body weight might influence the mood profiles and the views on physical activity. Potentially, strenuous exercise, like that experienced to perform long-distance treks, might be a stressor agent with a potential negative impact on mood state, views on physical activity [1–3], and the health condition. In this regard, it has been shown that even healthy marathon runners or triathlon athletes during strenuous competitions might experience increments in plasma troponin concentrations suggesting silent myocardial injury [4, 5].

It is clinically relevant to understand whether it is safe to recommend to trained overweight/obese people long-distance treks and if these experiences could have a negative psychological impact or become even dangerous exposing the trekkers to the risk of clinically silent myocardial damage. At present, it is not possible to answer this question because there are no studies reporting the impact of strenuous physical activity on mood states, personal views, and markers of myocardial damage in overweight/obese persons. For these reasons, we have performed a quantitative/qualitative study comparing the changes in mood profiles, personal views, body composition, and plasma troponin levels of 40 overweight/obese subjects with those of 36 healthy normal weight subjects after the participation in a trek of 388 km

from the Adriatic to the Tyrrhenian seas trek: the "Step-by-step. . .Italy's coast to coast."

2. Materials and Methods

2.1. Sample Description. Over the first two weeks of May, 2010 and 2011, 76 subjects participated in the "Step-by-step. . .Italy's coast to coast," a trek across central Italy, between the cities of Ancona (Adriatic Sea) and Talamone (Tyrrhenian sea) for a total of 388 km in 13 days.

The participants were divided into two groups on the basis of their body mass index (BMI, cut off 25 Kg/m^2): normal weight ($n = 36$, BMI 22.1 ± 1.0) and overweight/obese ($n = 40$, BMI 29.3 ± 3.2) subjects. The mean age of the normal weight was 54.2 (SD = 15.3) and that of the overweight was 58.0 (SD = 9.5) with no difference ($t(60) = 4.54$, $P = .185$).

Normal weight participants were habitual long-distance trekkers, in an apparent healthy state with the exception of one subject treated for hypertension; among the 40 overweight/obese, $N = 19$ subjects were treated for hypertension and 13 were affected by uncomplicated type 2 diabetes mellitus.

All the subjects of the overweight/obese group were trained before the trek for at least 10 months following the methodology of the lifestyle intervention trial performed at the Healthy Lifestyle Institute of Perugia University (CURIAMO trial, Australian New Zealand Clinical Trials Registry, ACTRN12611000255987) and approved by the local Ethics Committee (CEAS Umbria Region, HREC number 1/10/1633). The intensive part of the lifestyle intervention program, of three months' duration, was conducted in seven steps that involved different qualified personnel, as described in detail [6]. Briefly, during the intervention, patients underwent (1) an initial medical examination, (2) an assessment by a psychologist, (3) an assessment by a dietician, (4) a physical examination by a specialist in sports medicine, (5) an individualized program consisting of 24 sessions (two per week) of structured indoor exercise, (6) eight sessions of group therapeutic education, and (7) Nordic walking activity combined with walking excursions during weekends. In the maintenance phase of the lifestyle intervention, in order to sustain and improve personal motivation and socialization, we propose to patients the challenge to train for a difficult task such as a long-distance trek.

Organization of the Trek and Meals. The "Step-by-step. . .Italy's coast to coast" is a scenic itinerary of 388 km (GPS measurement) linking the cities of Ancona and Talamone by signposted footpaths. The trek distance has been distributed in 13 days with daily walking distances of about 30 km (28–36 km) in order to allow participants to reach by foot the hotels, after 8–10 hours of daily walk. The daily walking activities were organized in continuous 50–55 minutes of walks followed by 5–10 minutes of resting periods, which were utilized to drink water, to eat some snacks and/or fruit (approximately 20% of daily caloric intake) and, in the case of type 2 DM subjects, to check their capillary blood glucose. Every day, at about half the walking distance, a resting interval of 30–45 minutes was finalized for a picnic lunch to consume approximately 30% of programmed daily caloric intake. The dinner was consumed in the hotels' restaurants, about 1-2 hours after the arrival, and included the remaining 50% of the calculated daily caloric intake. The caloric intake of the diet, monitored by means of daily food diaries, was individualized on the basis of the estimated participants' basal metabolism [7] and energy expenditure to cover daily distances, estimated using the formula: 0,9 Cal × km × kg BW or, in a subgroup of 21 subjects, directly measured by a physical activity monitor (Sense Wear Armband, Body Media Inc., USA). During the trek, a diet with nutrient composition (55–60% of calories CHO, 15% protein, and 25–30% fat) similar in both groups but different in caloric composition was prepared. For normal weight participants the caloric intake of the diet was isocaloric; for overweight/obese participants it was slightly hypocaloric (about 200–300 Cal deficit).

Quantitative Measurements. Height, body weight, body composition by bioimpedenziometry (Tanita SC-330, Japan), waist circumference, and resting blood pressure (average of 2 measurements in the supine position) of all participants were measured on the first and last days of the trek, in the fasting state and after early morning urination. On the first and last days of the trek, 2 mL of blood was withdrawn from a subgroup of 27 participants, immediately refrigerated, and stored for subsequent analysis of cardiac troponin I levels (Troponin I insert 105146B, Beckman Instruments, Inc. Brea, CA). During the trek, blood pressure and heart rate were measured in the sitting position before and after the daily walk. All changes in drug assumption during the trek were recorded.

On the evening of the first and last days of the trek, participants were assessed for mood status using POMS (profile of mood states) [8]. POMS is a rating scale aimed at assessing different mood states, typically consisting of 58 adjectives referring to sensations rated by the subject on a five-point Likert scale (0 = not at all; 4 = very much). The Italian validated version [9] with "at this moment" instructions was used in order to measure the overall mood states of participants before and after participation in the walking trip. The six emotional dimensions of mood were used as indicator of overall distress: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, vigor-activity, confusion-bewilderment, and the total mood disturbance score (TMDS, calculated by subtracting vigor-activity subscale from the sum of the remaining five factors).

Qualitative Data Collection. On the days preceding the start and the end of the trek, participants were invited to narrate, write, and share in group their emotions, difficulties, fears, needs, and limits about key aspects of their strenuous physical activity. The groups were conducted by a doctor of pedagogic sciences, using the focus groups technique: people were stimulated to express and share their experience in different ways, by alternating individual self-reflection via self-writing, with discussions in microgroups and in plenary ones. For all writings, participants were guaranteed

complete anonymity. The narrative approach, by using self-narration and self-writing, enabled participants to acquire an in-depth understanding of their experience and their values and to evaluate their self-esteem and self-perception and the awareness of their condition [10]. At the beginning of the journey, the following topics were proposed for writing and discussion: (1) why am I here and what are my expectations? (2) What are my barriers, fears, needs, and wishes related to this experience? At the end, the proposed topics were as follows: (1) what this experience has meant to me; (2) one word or image to define this walk; (3) a significant memory of the journey; (4) a discovery; (5) a change.

2.2. Statistical and Qualitative Analyses. A t-test for independent sample was performed on quantitative data to test differences among overweight/obese and normal weight participants at baseline and on the changes scores (Delta) between baseline and over the journey values. Levene test has been used to interpret the variance homogeneity. A t-test for matched sample was performed in order to test differences in the two groups before and after the trek. Analysis was conducted using SPSS version 21.0.

Qualitative content analysis was conducted on pre- and postparticipants' writings in order to acquire feedback on personal views of the overall sample about the coast-to-coast experience to better understand the personal view on the experience, to identify the qualitative effect of the experience and the possible mechanisms through which physical activity influences mood [3]. All writings underwent qualitative content analysis by the extraction of semantic units and their grouping into micro- and macrocategories, through a process of understanding and interpretation [11]. Saturation was considered achieved when at least ten narratives reported the same content [10]. The analysis of all the texts was performed at the end of the intervention independently by two experts (N.P., G.R.) and the following aspects were identified as particularly relevant: (1) well-being, new self-perception, self-esteem, and self-empowerment, as benefits of the walk; (2) the relationship with one's own body; (3) the natural environment and being in a group, as facilitators for overcoming the challenge; (4) changes in the perception of oneself; in the relationship with others; in health status; in the motivation for future lifestyle changes.

3. Results

3.1. Quantitative Data. The participants of the normal weight group attended the walking trip for a mean of 9.1 ± 3.1 days and covered a total mean walking distance of 274 ± 92 km. The participants of the overweight/obese group attended the walking trip for a mean of 10.3 ± 2.9 days and covered a total mean walking distance of 308 ± 88 km with no significant difference. One subject of the normal weight group and two subjects of the overweight/obese group did not walk for all the consecutive days but rested for two days because of foot vesicles. Sixteen subjects of the normal weight group and thirteen of the overweight/obese group did not complete the entire distance of trek but walked for a minimum of 7 consecutive days. Their decision to cover half of the distance was taken before the departure, for personal time restrictions.

At baseline the two groups did not differ in mood status (POMS subscales), while the overweight/obese group had greater body weight, waist circumference, fat mass, and systolic and diastolic blood pressure in comparison to normal controls (see Table 1). Descriptive values at the end of the trek for the two groups are reported in Table 2. The subjects of the normal weight group had significant changes (in terms of reduction) in BMI ($t(29) = 2.38$, $P = .028$), body weight ($t(29) = 2.36$, $P = .025$), waist circumference ($t(29) = 5.44$, $P < .001$), and percent fat mass ($t(34) = 6.06$, $P < .001$). Regarding the mood, tension ($t(22) = 4.35$, $P < .001$), depression ($t(22) = 3.03$, $P = .006$), anger ($t(22) = 2.94$, $P = .008$), vigor ($t(22) = 3.37$, $P = .003$), confusion ($t(23) = 4.04$, $P < .001$), and TMDS ($t(22) = 3.66$, $P < .001$) decreased significantly while fatigue ($t(22) = 4.02$, $P < .001$) increased significantly. No differences were found for diastolic ($t(20) = 1.91$, $P = .070$) and systolic blood pressure ($t(34) = .842$, $P = .409$) and for fatigue ($t(23) = -1.73$, $P = .097$). The participants of the overweight/obese group had significant changes (in terms of reduction) in BMI ($t(44) = 5.78$, $P < .001$), body weight ($t(44) = 6.32$, $P < .000$), waist circumference ($t(42) = 6.23$, $P < .001$), percent fat mass, % ($t(44) = 5.76$, $P < .001$), and diastolic blood pressure ($t(43) = 5.27$, $P < .001$). Similarly to the other group, tension ($t(32) = 3.89$, $P < .001$), depression ($t(44) = 3.07$, $P = .004$), anger ($t(35) = 3.51$, $P < .000$), vigor ($t(35) = 3.03$, $P = .005$), confusion ($t(35) = 5.13$, $P < .001$), and TMDS ($t(32) = 4.85$, $P < .001$) decreased while fatigue increased ($t(32) = 3.64$, $P < .001$) significantly. No differences were found for systolic blood pressure ($t(34) = 1.46$, $P = .152$) and for fatigue ($t(35) = -1.89$, $P = .079$).

The comparison of the two groups on the change scores (differences between baseline values and values at the end of the trek) showed that the obese group differed from the normal weight group only for a greater reduction in body weight and BMI (Table 3). Both groups lost fat mass; the overweight/obese group lost body fat mass at a rate of 6.1 grams for every km walked and the normal weight group at a rate of 4.7 grams for every km walked (P = NS).

Plasma troponin I levels, measured on the first and last days of the trek in a subgroup of 27 participants (9 subjects of the normal weight and 18 subjects of the overweight/obese group), were undetectable in all subjects at baseline and at the end of the trek (all values <0.01 ng/mL).

During the trek, in the two DM2 subjects treated with insulin, it was necessary to avoid hypoglycemic episodes to reduce the daily insulin units by 45% and 60%; 14 out of 19 subjects treated for hypertension reduced the antihypertensive drugs (30% less calcium-antagonists and 65% less diuretics) because of the progressive reduction of systolic and diastolic blood pressure.

3.2. Qualitative Data. The set of writings allows defining the "coast-to-coast" experience as entirely positive, having allowed participants to find serenity ("a sense of accomplishment and serenity" and "a sense of general well-being"), harmony and peace with oneself ("I felt in harmony with

Table 1: Baseline characteristics of the two groups of participants to the trek and t-test results. Data are presented as mean ± SD.

	Normal weight ($n = 36$)	Overweight/obese ($n = 40$)	t	P value
BMI (kg/m^2)	22.1 ± 1.0	29.3 ± 3.2	10.98	.000
Body weight (kg)	62.2 ± 9.2	83.3 ± 14.7	4.76	.000
Fat mass (kg)	14.5 ± 3.7	25.2 ± 6.6	4.08	.000
Waist circumference (cm)	82.1 ± 6.8	100.2 ± 9.5	11.12	.000
Systolic BP (mmHg)	118.1 ± 14.6	133.2 ± 14.8	3.15	.003
Diastolic BP (mmHg)	77.7 ± 8.8	83.0 ± 8.3	1.85	.007
Tension	6.76 ± 3.40	7.02 ± 5.81	.207	.837
Depression	4.96 ± 5.72	4.34 ± 5.47	−.13	.897
Anger	3.76 ± 4.02	6.40 ± 9.34	1.4	.167
Fatigue	18.48 ± 5.59	20.28 ± 5.26	1.23	.221
Vigor	4.20 ± 3.03	3.91 ± 4.36	−.087	.931
Confusion	6.64 ± 3.82	5.57 ± 4.35	−.778	.440
TMDS	−1.44 ± 2.94	−.91 ± 4.31	1.015	.314

Table 2: Descriptive statistics for body composition and physiological and mood values at the end of the trek for the two groups. Data are presented as mean ± SD.

	Normal weight	Overweight/obese
BMI (kg/m^2)	21.81 ± 2.36	27.81 ± 2.51
Body weight (kg)	61.81 ± 8.38	80.73 ± 10.63
Waist circumference (cm)	78.14 ± 5.52	96.79 ± 8.39
Fat mass (%)	20.81 ± 4.89	27.76 ± 7.04
Systolic BP (mmHg)	119.29 ± 10.96	127.86 ± 12.04
Diastolic BP (mmHg)	71.43 ± 2.44	75.36 ± 6.92
Tension	2.71 ± 3.4	1.5 ± 1.78
Depression	.85 ± 1.86	1.14 ± 1.65
Anger	.14 ± .37	2.07 ± 3.14
Fatigue	22.57 ± 7.81	23.78 ± 3.88
Vigor	3.28 ± 3.25	2.28 ± 2.26
Confusion	3.00 ± 2.52	3.35 ± 3.18
TMDS	29.73 ± 12.48	30.17 ± 8.09

nature and with myself"), and good mood ("A great joy filled my heart and enriched it"). The walk has stimulated listening to oneself, reflection, and recognizing one's own feelings and discomforts, inducing an "interior reflective change".

Walking for long distances for many consecutive days has induced an interior change and a progressive open-mindedness ("I remember the eyes of my traveling companion, enlightened by something strong and beautiful that he kept closed inside" and "What struck me most in this trip has been my interior change, my starting to be interested in others and in the environment, and not only in myself").

Participants narrate to have found new trust in themselves and to have felt "satisfaction for reaching a difficult target," to be able to walk such a long distance for such a long time ("I discovered to be able to walk for 30 Km! And even for more than that!").

Self-esteem is increased, as well as the awareness that one can attain the most difficult goals: *"I was afraid not to make it, to feel small, awkward, alone. But I am here now, and have accomplished an enterprise that has changed a lot inside me. I reached the independence I was looking for, the awareness that alone I can… I can make, feel, live."*

Determination and will power may let one face the most difficult challenges: *"I got involved to demonstrate myself how much I can still do with so much will power," "Mind and will power lead much further than feet, pain, blisters. One walks anyway and reaches anywhere."* Reaching the goal brings about enthusiasm, happiness, and exaltation: *"I'm enthusiastic I've realized the dream I made that morning with open eyes, knowing that impossible dreams can often become true."*

One of the most significant findings in participants' writings is the relationship with one's own body: "*the discovery of its own pace,*" its capacity of adaptation to fatigue and its potentiality: *"I won my fear of physical pain," "I discovered I could also walk on blisters."* Its limits and reactions are recognized: "*I've learned not to overdo physically, to stop before collapse.*" Participants find again confidence in their own body, "*its extraordinary strength and endurance";* they confront their own age and their own strength: *"It's good listening to my own body, to its needs, its thoughts."*

The body gains strength, faces hardships with more force, and is not afraid of rain, mud, or cold.

(1) Nature represents a privileged environment to walk: 13 days "among fields, woods, and the countryside" enjoying *"the landscape, the colors, the scents," "the times and rhythms of nature,"* a detachment from routine and from everyday life. The immersion into nature becomes the way to *"recognize myself, the others, and our very human nature"* and to think about oneself and about new projects to realize. Nature frees subjects from sad thoughts and worries and gives strong emotions of beauty and astonishment. Nature becomes a resource, and weather problems are easily overcome: *"I discovered I could walk in the rain without any discomfort."*

(2) The group was a key factor for the success of the journey. What cannot be done alone is made in group: *"I discovered that 30 Km are done together, but not alone"* and

Table 3: Means and SD for changes (Delta) of the measured parameter in the two groups after the trek. Comparison between the normal weight and the overweight/obese groups.

Delta	Normal weight		Overweight/obese		F	P
	Mean	SD	Mean	SD		
BMI	.15	.36	.40	.47	6.37	.014
Body weight (kg)	.42	.96	1.06	1.13	6.61	.012
Waist circumference (cm)	1.29	1.27	1.59	1.67	.665	.417
Fat mass (%)	1.78	1.64	2.02	1.64	.237	.629
Systolic BP (mmHg)	2.59	14.34	3.06	12.34	.017	.897
Diastolic BP (mmHg)	3.91	9.36	6.14	6.89	1.05	.309
Tension	4.09	5.94	4.03	5.94	.001	.969
Depression	3.30	5.22	3.00	5.85	.041	.840
Anger	4.55	7.78	1.86	3.04	2.48	.121
Fatigue	−3.75	10.62	−1.75	5.81	.884	.351
Vigor	2.13	3.03	1.88	3.73	.067	.796
Confusion	3.41	4.13	2.69	3.15	.588	.446
TMDS	6.73	8.83	9.81	11.61	1.15	.288

"In good company, nothing is impossible." From an initial feeling of loneliness and discomfort, the group becomes space for meeting, sharing, understanding, acquaintance, and friendship: *"I realized I needed to talk, to share with others, to listen to their stories."* The group gives support: *"The fact that we always helped one-another, with great reciprocal care, made me feel that I will never be alone"* and *"I was particularly supported by some people, who gave me one more stimulus to keep going, by listening to me and understanding me in my life problems."* The group teaches respect and tolerance for the others and their diversity; it is a *"laboratory to fight intolerance."*

(3) The most significant memory of the journey is the strength of the group *"which can always give to those who need without asking anything in exchange" and "the miracle of the individual who becomes community is accomplished."*

The last key aspects which emerged from the writings are related to change in the perception of oneself, in the relationship with others, in health status, and in the motivation to future lifestyle changes.

(4) The journey gave a different, slower pace to the passing of days. Many wish to *"keep going slower in life"* and to *"observe what can be seen and savor every moment, without waiting for the next."* Some tell of having got back to the center of their own life and of their interests, with a *"sense of well-being and of awareness of how life can be lived."*

(5) Reaching the goal has strengthened participants' character, has charged them with *"pure vital energy"*, and has made some feel *"capable of facing any other challenge"* and of *"getting up after falling, never giving up."* The journey becomes a metaphor of life, where *"also more distant horizons become attainable"* and where *"a new way to face life"* is discovered.

(6) The relationship with others has changed; the experience of travelling in group has cured shyness and has made people smile more. The way has helped participants to empty themselves and to reflect on oneself: *"The physical and medical aspect of the walk has not been the most important after all. It has rather been the catalyst of a deeper phenomenon: throwing off the mask, being able to show one's true self, which is almost always better than what we tend to show of ourselves in everyday life."*

(7) Participants feel themselves more open and available for others whom they no longer will value *"on the basis of simple appearance."* For many, being able to relate with others represents an important discovery: *"I feel more open to new acquaintances in group activities."*

(8) From this revitalization with oneself and with others, the purposes of a more structured change *"that continues in life"* are born. Many patients write they want to continue to walk once back at home or they want to start a sport.

(9) The weight reduction and the better control of the disease obtained thanks to the walk represent a strong incentive to change one's lifestyle: *"As a matter of fact I have eliminated night insulin (all insulin). It's a real great change!"*

(10) Eating habits have changed: *"I can eat really less and I don't need alcoholics, at lunch and at dinner as well."* Hunger attacks are controlled more easily, and there is a generalized wish to *"take care of oneself, of one's body,"* and of one's disease whose care is understood as important: *"I was an uninformed patient, who used to minimize and hide his disease. Now, thanks to you, I am a person who knows his diabetes, accepts it, and lives peacefully with it."*

4. Discussion

This is the first study to compare the effects of strenuous physical activity between trained normal weight and overweight/obese trekkers. Our results support the conclusion that walking for long distances and consecutive days is a safe activity which can be recommended to either trained normal weight or overweight/obese persons because it improves body composition, blood pressure, mood status, feelings, and personal views on exercise.

Regular aerobic exercise and, in particular, walking are recommended to healthy subjects and to overweight, obese,

and type 2 diabetic subjects [12]. Several epidemiological and intervention studies demonstrate that beneficial effects of walking become significant over 150 minutes per week with a dose response relationship [13, 14]. For this reason lifestyle interventions for obesity and/or DM2 prevention or care promote regular walking as a major component of the behavioral change [13, 14]. The results of the present study demonstrate that walking for long distances and several consecutive days has a positive impact on the health and mood status and opinion views of trained obese/overweight persons similarly to normal weight individuals. The trained overweight/obese people thanks to the long-distance trek significantly lost body fat mass, at a rate of approximately 6 grams for every km walked, and those on drug therapy reduced the use of antihypertensive and antidiabetic drugs. We also demonstrate that the strenuous physical activity, about 30 km walked every day, does not increase the risk of silent cardiac damage, as assessed by measuring plasma troponin levels.

Regarding the changes in mood status, our findings are in agreement with previous studies showing the positive effects of physical activity on mood [15] and enlarge also the benefits of strenuous exercise also if performed by trained overweight/obese individuals. Engaging in regular physical activity displays better general health outcomes, higher values of health-related quality of life, and better mood states [16]. Specific to mood in the general population, there is a wealth of research which indicates that regular physical activity increases positive mood states (e.g., vigor, friendliness) and decreases negative mood states (e.g., depression, anger, and hostility) [16]. Many cross-sectional studies support the evidence that exercise, physical activity, and physical activity interventions have beneficial effects across different populations with different physical and psychological conditions on well-being [17]. In a review of literature, A. Byrne and D.G. Byrne [18] indicated that 90% of studies demonstrated a decrease in depression and anxiety after participation in physical activity interventions. Obesity is often associated with depression [19, 20]. Depressive mood is considered a cause of the attrition to physical exercise, and a main bulk of the research has been devoted to exploring the association between physical activity and depression or mood disorder in obesity [20–22]. In obesity regular exercise is both a predictor of weight loss and generally associated with improvements in mood profile [23]. Mood profile has been generally investigated by the profile of mood states (POMS) [8], a scale born in the context of counseling or psychotherapy and lately applied in sport and exercise contexts [3]. A review by Berger and Motl [3] has documented the use of POMS in exercise settings, supporting the relationship between exercise and acute mood changes. Our study demonstrates that the improvement of mood, documented by POMS, was similar in the groups of normal weight and overweight/obese, suggesting that when the participants are trained a greater body weight does not preclude the psychological beneficial effects of regular exercise.

Although the mechanisms through which physical activity influences mood are not completely explored [3, 19], the writings of the participants in our study allow identifying some facilitators which influence the mood during a strenuous physical activity. According to the opinion views of our overweight/obese participants, a central facilitator role is played by the opportunity to share their experience of obesity with others like themselves; the group served as a resource and a stimulus, as well as a means of escaping from loneliness and socializing. Another important facilitator is positive thinking, believing in the project with determination, being confident about one's abilities, and accepting the challenge in order to prove to oneself and to others that success can be achieved. The key is found in one's relationship with himself/herself. The participants thanks to the trek acknowledged the positive aspects of physical activity, describing it as an experience of pleasure, fun, and well-being, and asked to repeat it again. The participants report, in agreement with the quantitative data of the POMS, that the trek had positive psychological effects, made them feel free, reduced their stress levels, reinforced their self-confidence, and enhanced the harmony between body and mind.

In conclusion, long-distance treks are a safe activity for trained overweight/obese people which should be recommended because they improve mood, health status, and the relationship of participants with themselves and with the regular practice of exercise with effects similar to those obtained by healthy normal weight subjects. It should be pointed out that the study has concerned a cohort of obese people with no different baseline mood scores than normal weight people, perhaps thanks to the care and training program these people were offered before the trek and/or thanks to a sort of "natural selection" of participants operated by this pretrek program. Results may be different for cohorts of obese people with significantly different mood scores in respect to normal weight people.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Perceived Difficulty with Physical Tasks, Lifestyle, and Physical Performance in Obese Children

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We estimated perceived difficulty with physical tasks, lifestyle, and physical performance in 382 children and adolescents (163 obese, 54 overweight, and 165 normal-weight subjects) and the relationship between perceived physical difficulties and sports participation, sedentary behaviors, or physical performance. Perceived difficulty with physical tasks and lifestyle habits was assessed by interview using a structured questionnaire, while physical performance was assessed through the six-minute walking test (6MWT). Obese children had higher perceived difficulty with several activities of daily living, were less engaged in sports, and had lower physical performance than normal-weight or overweight children; on the contrary, they did not differ with regard to time spent in sedentary behaviors. Perceived difficulty in running and hopping negatively predicted sports participation ($P < 0.05$ and <0.01, resp.), while perceived difficulty in almost all physical activities negatively predicted the 6MWT, independently of BMI ($P < 0.01$). Our results indicate that perception of task's difficulty level may reflect an actual difficulty in obese children. These findings may have practical implications for approaching physical activity in obese children. Exploring both the perception of a task's difficulty level and physical performance may be useful to design exercise programs that allow safe and successful participation.

1. Introduction

Childhood obesity is one of the most serious public health challenges of the 21st century, since it presages adult obesity and is associated with the development of weight-related comorbid conditions and premature mortality. While the cardiovascular and metabolic consequences of pediatric obesity have been extensively studied [1], less attention has been paid to investigating the impact of obesity on physical functioning and disability in children. Physical inactivity in obese children may favor the development of a vicious circle perpetuating obesity, physical inactivity, and health risks [2]. Interrupting this concatenation of events is a central issue for managing weight loss. Most of the expert committees state that increasing physical activity levels and reducing sedentary behaviors, along with intensive dietary and cognitive-behavioral counseling, are the only key challenges and opportunities in the management of childhood obesity [3].

Even in children, obesity has a clear measurable negative impact on self-esteem, perceived athletic competence, physical appearance, and global self-worth [4]. It is important to consider the relationship among perceived difficulty with physical tasks, lifestyle, and physical performance in obese children as this evaluation may have important implications for clinical intervention to improve functioning, weight loss, and quality of life. Therefore, as primary research outcome we assessed perceived difficulty with physical tasks, lifestyle, and physical fitness in a clinical sample of obese children compared to normal-weight and overweight children. As secondary research outcome we explored the relationship between perceived difficulty with physical tasks and sports participation, sedentary behaviors, or physical performance.

2. Materials and Methods

This was a cross-sectional study in which 382 children and adolescents with chronological age range between 7 and

Table 1: Anthropometric data, lifestyle behaviors, and physical fitness of the study population.

	Normal-weight	Overweight	Obese
Number	165	54	163
Male/female	76/89	25/29	79/84
Age (years)	9.8 ± 1.7	9.6 ± 1.8	9.8 ± 2.3
Height (cm)	138.6 ± 10.8	142.2 ± 10.7	143.9 ± 13.1***
Weight (kg)	34.8 ± 8.8	46.3 ± 10.6	62.1 ± 18.3§
BMI-SDS	−0.17 ± 0.94	1.34 ± 0.17	2.28 ± 0.42§
Sports participation *n* (%)	109 (66.1)	34 (63.0)	79 (48.5)**
Sedentary behaviors (h/day)	3.1 ± 2.2	3.0 ± 2.2	3.0 ± 2.1
6MWD (meter)	603.0 ± 67.1	591.2 ± 65.0	532.7 ± 61.1#
Resting HR (bpm)	86.2 ± 17.1	87.6 ± 18.6	90.6 ± 15.1*
Post-6WMT HR (bpm)	140.6 ± 29.9	148.9 ± 28.7	144.6 ± 25.5

*$P = 0.05$ obese versus normal-weight children; **$P = 0.005$ obese versus normal-weight and overweight children; ***$P < 0.001$ obese versus normal-weight children; #$P < 0.001$ obese versus normal-weight and overweight children; §$P < 0.001$ obese versus normal-weight and overweight children; overweight versus normal-weight.

14 years participated. Obese children ($n = 163$) were consecutively recruited from the outpatient clinic of the Department of Translational Medical Science, University of Naples Federico II. The exclusion criterion was the presence of any specific genetic or endocrine pathologic process which may cause obesity. Controls were represented by a community sample of children ($n = 240$) recruited from an elementary school (3 classes) and a middle school (3 classes) in Naples by cluster sampling; from this sample 219 healthy children were considered (165 normal-weight and 54 overweight children), while obese children ($n = 21$) were excluded. The study started in January 2012 and ended in June 2013; it was approved by the review board of the Department. Written informed consent was obtained from all participants and/or their parents or legal guardians in accordance with the revised version of the Helsinki Declaration regarding research involving human subjects.

2.1. Anthropometric Measurements. Height and weight were measured with the children wearing only light clothes and no shoes; the BMI (weight (kg)/height (m^2)) was calculated. Since height and BMI are age- and gender-related, these parameters were transformed into standard deviation score (SDS), based upon the established Italian BMI normative curves [5]. Overweight and obesity were defined according to BMI-SDS ≥1.04 and ≥1.64, which correspond, respectively, to the cut-off of 85th and 95th percentiles. Descriptive data are shown in Table 1.

2.2. Lifestyle. The study included a questionnaire assessment by interview regarding some behavioral issues of children, such as sports participation in the previous 6 months and sedentary habits. A sum of the daily hours spent in television viewing, videogames, and surfing on computer was computed to calculate time spent in sedentary behaviors.

2.3. Perceived Difficulty with Physical Tasks. Perceived difficulty with physical tasks was assessed by interview using a structured questionnaire, which included seven questions regarding physical limitations related to daily movement (walking, running, hopping, bending, stair climbing, feeling clumsy or awkward, and getting up from chairs), taken from the "mobility" domain of the Impact of Weight on Quality-of-Life adapted for adolescents [6]. Examples of questions included "How often do you have trouble with walking?" or "How often do you have trouble with using stairs?" or "How often do you feel clumsy or awkward?" For each mobility subscale, subjects had to select one among five possible responses ranging from "always" to "never." Each answer was then rated on five-point scale ranging from 0 (never), 1 (rarely), 2 (sometimes), 3 (often), and 4 (always); a higher mobility subscale score indicates a greater level of impairment. A perceived global difficulty index was created by summing scores ≥2 for each physical limitation subscale.

2.4. Six-Minute Walking Test (6MWT). The 6MWT was performed indoors along a flat, straight walkway in accordance with the American Thoracic Society guidelines [7]. The walking course length measured 20 m in the two different settings (hospital and school). The length of the corridor was marked every 3 m with a brightly colored tape. Cones were placed at either end of the walking course to indicate the beginning and end points. Additionally, the starting line, which marked the beginning and end of each lap, was marked on the floor using brightly colored tape. Instructions and demonstrations were given to each child. Participants were informed that the purpose of the test was to find out how far they could walk in 6 minutes and were instructed to walk the longest distance possible at their own pace during the allotted time. Hopping, skipping, running, and jumping were not allowed during the test. Only the standardized phrases for encouragement (e.g., "keep going," "you are doing well") and announcement of time remaining were given to the participants. Before and immediately following the test, the participant's hearth rate (HR) was recorded using a finger pulse oximeter (Smiths Medical PM, Inc., Waukesha, WI). Participants were tested individually in the presence of their parents or teacher. The 6MWT was administered by trained testers, who were expert in physical fitness assessment.

Table 2: Perceived difficulty with single physical tasks among normal-weight, overweight, and obese children.

	Normal-weight $n = 165$	Overweight $n = 54$	Obese $n = 163$	normal-weight versus overweight P	normal-weight versus obese P	overweight versus obese P
Walking	0.2 ± 0.7	0.5 ± 1.1	0.9 ± 1.2	0.014	0.000	0.025
Running	0.3 ± 0.7	0.7 ± 1.1	1.3 ± 1.3	0.001	0.000	0.001
Hopping	0.1 ± 0.5	0.3 ± 0.9	0.9 ± 1.3	0.200	0.000	0.001
Bending	0.1 ± 0.3	0.4 ± 0.9	0.6 ± 1.2	0.003	0.000	0.171
Climbing stairs	0.1 ± 0.5	0.5 ± 1.0	1.4 ± 1.4	0.014	0.000	0.000
Feeling clumsy or awkward	0.4 ± 0.7	0.6 ± 1.1	1.1 ± 1.3	0.353	0.000	0.008
Getting up from chairs	0.0 ± 0.3	0.0 ± 0	0.0 ± 0.3	0.410	0.163	0.154

2.5. Statistical Analysis. Statistical analysis was carried out using the Statistical Package of Social Sciences (SPSS, Windows release 21.0; Chicago, IL, USA). Results are presented as mean ± standard deviation, with statistical significance set at $P \leq 0.05$. The Kolmogorov-Smirnov goodness-of-fit test was applied for determining whether sample data likely derive from a normally distributed population. Variables not normally distributed were logarithmically transformed. However, for clarity of interpretation, results are expressed as untransformed values. The independent sample t-test or ANOVA was used to compare the means of continuous variables, while contingency table analyses were used for categorical variables. Pearson correlation coefficients, logistic regression, or linear regression analyses were performed to examine the relationship between perceived difficulty with physical tasks, sports participation, time spent in sedentary behaviors, and measures of 6MWT performance; age, gender, and BMI-SDS were included in the regression models. Clustering of active and/or sedentary behaviors was analyzed according to whether children reported any sports participation and/or ≥3 h/day spent in sedentary behaviors (this value represented the median hours spent in the whole group). Four categories were established, ranging from the most sedentary/least active group (≥3 h/day in sedentary behaviors and no sports participation) to the least sedentary/most active group (<3 h/day in sedentary behaviors and sports participation).

3. Results

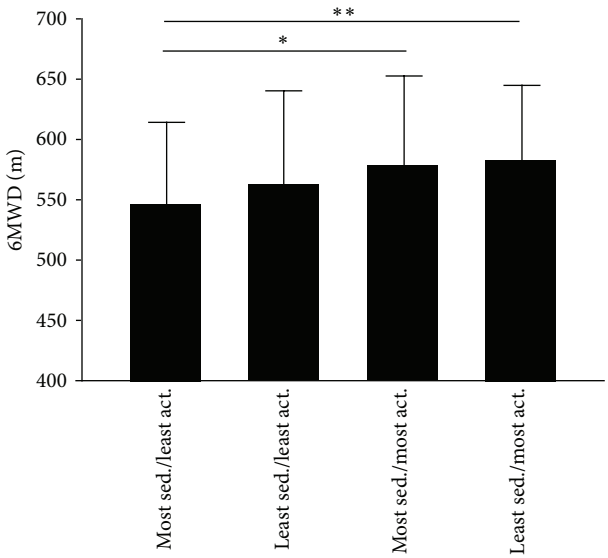
3.1. Perceived Difficulty with Physical Tasks. Perceived difficulty with physical tasks was compared among normal-weight, overweight, and obese children. Perceived difficulty scores progressively increased from normal-weight to obese children (Table 2). Perceived difficulty scores in overweight children were significantly higher than normal-weight children in 4 out 7 tasks (walking, running, bending, and climbing stairs), whereas perceived difficulty scores in obese children were higher than both overweight and normal-weight children in all the explored tasks ($P = 0.0001$), except for bending (not significant versus overweight) or getting up from chairs (not significant versus normal-weight and overweight children, Table 2). Subjects who did not report any perceived difficulty with physical task were 72.1% in normal-weight, 46.3% in overweight, and only 18.4% in the obese group ($P < 0.001$ versus each other).

3.2. Lifestyle. Sports participation significantly differed among groups (obese 48.7%, overweight 63.0%, and normal-weight children 66.1%, $P = 0.005$); slightly more than half of the sample participated in individual sports, independent of the BMI-SDS category (obese 60.5%, overweight 52.9%, and normal-weight children 55.9%, $P = 0.725$). On the contrary, time spent in sedentary behaviors did not differ among groups; the percentage of children spending ≥3 hours/day in sedentary behaviors was 51.5% in obese, 48.1% in overweight, and 55.0% in normal-weight children ($P = 0.647$). Time spent in sedentary behaviors did not differ in children, whether or not they participated in sports activities (3.1 ± 2.2 versus 3.0 ± 2.2 hours, $P = 0.772$).

3.3. 6MWT. The distance achieved in the 6MWT (6MWD) was significantly lower in obese children than that covered by normal-weight and overweight children. Resting HR in obese children was higher than in normal-weight children ($P = 0.05$), while post-6MWT HR did not differ (Table 1).

The 6MWD was compared among four different lifestyle categories, ranging from the most sedentary/least active group to the least sedentary/most active group. Children from the most sedentary/least active group covered the least distance with respect to the other groups (Figure 1). Interestingly, children with the most sedentary/least active lifestyle reported the highest perceived global difficulty index (1.8 ± 1.8) when compared with children of the other three groups (least sedentary/least active 1.5 ± 1.7, most sedentary/most active 1.1 ± 1.4, and least sedentary/most active 0.1 ± 1.4, $P < 0.01$). The percentage of obese children in the most sedentary/least active group was 48.8% versus 32.7% in the least sedentary/most active group ($P = 0.013$).

3.4. Relationships between Perceived Difficulty with Physical Tasks on Sports Participation, Sedentary Behaviors, and 6MWT. In order to analyze which factors may affect sports participation, logistic regression analysis including age, gender, BMI-SDS, and perceived difficulty with single physical tasks was performed in the total sample of children. Sports



Sed.: sedentary; act.: active.
* $P = 0.012$
** $P = 0.003$

Figure 1: Distance achieved in the 6-minute walking test (6MWD) according to categories of children stratified for their lifestyle habits.

participation was negatively predicted by age, BMI-SDS, and perceived difficulty in running or hopping (Table 3).

Interestingly, perceived difficulty with physical tasks did not influence the amount of time spent in sedentary behaviors, except for "getting up from chairs," which was independently correlated with sedentary behaviors, controlling for age, gender, and BMI-SDS (B 0.814, standardized beta 0.1, $P = 0.05$).

The 6MWD negatively correlated with perceived difficulty in physical tasks in the total sample (walking, r—0.330; running, r—0.344; hopping, r—0.282; climbing stairs, r—0.369; feeling clumsy or awkward, r—0.238; all $P < 0.001$; bending, r—0.116, $P < 0.03$). By linear regression analysis the 6MWD was positively associated with sports participation and negatively associated with BMI-SDS, and perceived difficulties in walking, running, hopping, climbing stairs, or feeling clumsy or awkward ($P < 0.01$), controlling for age and gender (Table 4).

4. Discussion

The main results of this study indicate that obese children had higher perceived difficulty with several activities of daily living, were less engaged in sports, and had lower physical performance than normal-weight or overweight children; on the contrary, they did not differ with regard to sedentary behaviors. Perceived difficulties in running and hopping negatively predicted sports participation, while perceived difficulties in almost all physical activities negatively predicted 6MWD, independently of BMI.

Engaging obese children and adolescents in physical activity requires addressing the individual, interpersonal, and

Table 3: Binary logistic regression analyses predicting sports participation in the total sample of children.

	Independent variables	B	ES	P
Model 1	Age	−0.145	0.056	0.009
	Gender	0.015	0.221	0.945
	BMI-SDS	−0.281	0.090	0.002
	Walking	−0.055	0.108	0.612
Model 2	Age	−0.128	0.056	0.023
	Gender	−0.023	0.223	0.919
	BMI-SDS	−0.211	0.094	0.024
	Running	−0.219	0.107	0.041
Model 3	Age	−0.146	0.057	0.010
	Gender	−0.020	0.224	0.928
	BMI-SDS	−0.192	0.091	0.035
	Hopping	−0.363	0.117	0.002
Model 4	Age	−0.144	0.056	0.010
	Gender	0.011	0.221	0.959
	BMI-SDS	−0.272	0.088	0.002
	Bending	−0.128	0.122	0.296
Model 5	Age	−0.142	0.056	0.011
	Gender	0.024	0.221	0.914
	BMI-SDS	−0.265	0.095	0.005
	Climbing stairs	−0.067	0.099	0.496
Model 6	Age	−0.139	0.056	0.013
	Gender	0.025	0.221	0.910
	BMI-SDS	−0.277	0.090	0.002
	Feeling clumsy or awkward	−0.063	0.101	0.532
Model 7	Age	−0.144	0.056	0.010
	Gender	0.016	0.221	0.942
	BMI-SDS	−0.294	0.086	0.001
	Getting up from chairs	−0.182	0.411	0.658

environmental barriers that may deter them from participating in physical activities or sports [8]. Research on youth physical activity participation supports the strong influence of perceived competence and skill level on sports participation, especially in obese children [9, 10]. Among the individual barriers, perceived lack of physical competence is considered to be the most global construct of physical self-efficacy, representing people's overall perceptions of their general physical abilities on physical tasks. A review published by Tsiros et al. [11] indicated that greater weight was associated with lower health-related quality of life. More specifically, there was strong inverse relationship between physical functioning domain and BMI.

Our results demonstrate that perceived difficulty scores progressively increased from normal-weight to obese children and affected obese children in most of the daily physical skills, but at a lesser extent they also concerned overweight children. However, sports participation was significantly reduced only in obese children, and among those engaged in sport, most participated in individual activities. Indeed, being part of a team and having opportunities to demonstrate skills in front of friends and family may be particularly challenging

Table 4: Linear regression analyses predicting 6MWD in the total sample of children.

	R^2	Adjusted R^2	Predictors	Standardized beta coefficients	P
Model 1	0.234	0.223	BMI-SDS	−0.341	0.000
			Sports participation	0.112	0.017
			Walking difficulty	−0.209	0.000
Model 2	0.223	0.212	BMI-SDS	−0.325	0.000
			Sports participation	0.099	0.038
			Running difficulty	−0.191	0.000
Model 3	0.208	0.197	BMI-SDS	−0.360	0.000
			Sports participation	0.097	0.046
			Hopping difficulty	−0.129	0.011
Model 4	0.195	0.184	BMI-SDS	−0.397	0.000
			Sports participation	0.118	0.015
			Bending difficulty	−0.022	0.654
Model 5	0.233	0.222	BMI-SDS	−0.307	0.000
			Sports participation	0.111	0.019
			Stair climbing difficulty	−0.220	0.000
Model 6	0.209	0.199	BMI-SDS	−0.362	0.000
			Sports participation	0.115	0.017
			Feeling clumsy	−0.131	0.009
Model 7	0.194	0.183	BMI-SDS	−0.403	0.000
			Sports participation	0.119	0.014
			Getting up from chairs	0.011	0.818

and thus highly discouraging for obese children. Regarding sedentary habits, no difference was found indeed among obese, normal-weight, or overweight children confirming a previous research [12]. This finding is not surprising, since it has been reported that moderate-vigorous physical activity was independently associated with adiposity indices in children, while sedentary time was not [13]. As it has been suggested, physical activity and sedentary behaviors can coexist in the same individual [14].

To date only few studies have compared the 6MWT in overweight or obese children [15–17]. We found that obese children had lower functional capacity as measured by distance achieved in the 6MWT as compared to both normal-weight and overweight children, while no substantial difference was found between overweight and normal-weight peers, in agreement with other studies [15–17]. The 6MWT is a simple, practical, reliable, and valid measure of submaximal exercise capacity in children [18]. It is also considered as the most relevant walk test that reflects physical activity of daily living as well as cardiopulmonary fitness [19, 20] and its reproducibility has been demonstrated also in obese children and adolescents [15]. Similar to previous reports [16], we found that resting HR was higher in obese children than normal-weight or overweight children. Research has shown an increased sympathetic activity in obese individuals, including children that may thus explain this finding [21].

Perceived lack of physical competence is a subjective view of physical abilities that may or may not coincide with actual ability. Studies which have examined the effect of obesity on perceived physical impairment have failed to investigate whether impairments in body functions really translate into activity/participation restrictions [22]. The finding that perceived difficulties in almost all gait-related physical activities, such as walking, running, hopping, and climbing stairs negatively predicted the performance in the 6MWT may indicate that the estimation of difficulty level is likely to be accurate and may be used to assess the task's real difficulty. Remarkably, difficulties in bending or getting up from chairs had no effect, most likely because these activities are less involved with the gait task explored by the 6MWT. The observed changes in HR (after versus rest 6MWT) were fairly good and did not practically differ among normal-weight (+64%), overweight (+69%), and obese (+59%) children, indicating that motivation and attitude towards the test were the same in obese, normal-weight, or overweight children and that the 6MWT used in the current study was challenging enough to assess exercise capacity. It is interesting to note that perceived difficulty in getting up from chairs, which was the physical impairment less reported by children, significantly predicted time spent in sedentary behaviors, independent of BMI-SDS. Since this finding was unexpected, we did not test whether this perception translated into an actual difficulty. Further studies might explore whether this perceived difficulty is a real determinant or a consequence of sedentary habits.

Exercise performance was negatively affected by a lifestyle habit characterized by no sports participation and more time spent in sedentary habits, which involved more frequently obese children but was present also in normal-weight and overweight children. This result underlines that unhealthy lifestyle habits need to be tackled not only in children with excess weight, but also in normal-weight children, given

the strong relationship between physical activity, physical fitness, and health [23].

A few limitations of our study can be acknowledged. For instance, our results cannot be extended to the whole population of obese children, since we specifically studied a clinical sample of obese children. It may be plausible that obese children who seek treatment may have worse health-related quality of life than obese children or adolescents who do not seek treatment [24]. In addition, overweight children were underrepresented; therefore some results may have been underestimated or undetected because of low statistical power. Lastly, our examination of physical performance was limited to walking test, while other tasks, such as those involving flexibility or strength were not assessed.

In summary, this study provides new data for clinical practice and adds to the recent research field on 6MWT performance in children who are overweight or obese. Based on theories of motivation and behavioral change, the best approach to increasing physical activity participation among obese children is to enhance their self-perception and enjoyment by increasing their actual and perceived motor skill competence. Therefore our findings may have practical implications for approaching physical activity in obese children. Exploring both the perception of a task's difficulty level and physical performance may be useful to discuss with obese children and their families the impact of excess weight on their daily physical activities. This information is essential to allow educators and trainers to design exercise programs that match the child's interests and physical abilities and to allow safe and successful participation in those activities which are less based on lower body loading, at least in the early steps of intervention.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Obesity and Headache/Migraine: The Importance of Weight Reduction through Lifestyle Modifications

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The aim of this study is to determine a possible relationship between prevalence, frequency, and severity of migraine and obesity. All pertinent data from the literature have been critically examined and reviewed in order to assess the possible relationship between obesity and migraine, in particular migraine frequency and disability in children, as well as in adult population studies. Prevalence, frequency, and severity of migraine appear to increase in relation to the body mass index, although this evidence is not supported by all the studies examined. Data from literature suggest that obesity can be linked with migraine prevalence, frequency, and disability both in pediatric and adult subjects. These data have important clinical implications and suggest that clinicians should have a special interest for weight reduction of obese children suffering from migraine, prescribing and supporting intensive lifestyle modifications (dietary, physical activities, and behavioral) for the patient and the entire family.

1. Introduction

Headaches are common during childhood and become more common and more frequent during adolescence. International headache society (IHS) divides headache into primary and secondary headache disorders. Primary headaches comprise migraine, tension-type headache, cluster headache, other autonomic cephalgias, and other primary headache disorders.

Migraine is defined by the IHS as a recurrent headache that occurs with or without aura and lasts 4–72 h. Migraine is best understood as a chronic disorder with episodic manifestations, progressive in some individuals. Consistently, identifying risk factors for progression has emerged as a very important public health priority.

Recent studies suggested a potential role of obesity on migraine outcomes. Obesity occurs with several chronic pain syndromes. Obesity and migraine are both highly prevalent disorders in the general population, and reports in the literature underscore this association. An increasing number of reports suggest that obesity is a risk factor for migraine progression and migraine frequency in adults [1–4] as in children [5–7].

The aim of this review was to summarize and critically appraise evidence from the most recent clinical and population-based studies, evaluating the possible association between obesity and migraine; we also evaluated if the reduction of BMI through modifications of the lifestyle should be a therapeutic approach to reduce frequency and severity of headache/migraine.

Headache and obesity are prevalent and disabling disorders that are influenced by a variety of physiological, psychological, and behavioral mechanisms, many of which are affected by weight loss [8]. It is not unusual for migraineurs patients to be obese. Recently, attention has focused on the potential relation between overweight and frequency and severity of headache attacks [9, 10] and some evidence for this relationship has been demonstrated [11, 12].

One of the largest population studies emphasizes the association between obesity and chronic daily headache

(CDH) although it underlines that this association was relatively specific only for chronic migraine (CM) [13]. The question of the link between obesity and migraine frequency is still matter of debate while the majority of studies have suggested a certain influence of the overweight of the subjects on migraine severity.

2. Epidemiological Relationship between Headache/Migraine and Obesity

A PUBMED search of the English-language studies published between 2000 and 2012 investigating the possible association between migraine and obesity was performed; key terms used alone or in combination included: migraine, obesity, overweight, and body mass index.

Specific review articles and systematic reviews were examined for any further publications, as were the reference sections of all articles identified by literature search. Validation was undertaken by a second review of the search results to ensure that no article had been missed.

The main studies that addressed this relationship are reported in Table 1.

One of the first studies to identify an association between frequent headache and obesity was a study involving 1932 patients, aged 18–65 years, by Scher and colleagues in 2003 [15]. The population studied included 1134 patients who were CDH sufferers and 798 who had episodic headache. The most important result was that the prevalence of CDH was associated with total body obesity (OR 1.34; CI: 1.0–1.8) or overweight (OR 1.26; 1.0–1.7). Moreover, individuals with episodic headache who also had total body obesity at baseline were at increased odds of having CDH at follow-up (OR 5.28; CI: 1.3–21.1).

More in detail, an important percentage (30%) of newly identified cases of CDH showed clearly obesity, while only 13% of patients with episodic headache were obese. The result of this study is that individuals with episodic headache and obesity develop CDH more than 5 times the rate of normal-weight individuals.

Similarly, Ohayon [16] and colleagues found that overweight/obese (BMI > 27) respondents were more likely to report morning headache than were adults with BMI 20–25 and among a sample of ~15,000 Australian women, Brown and colleagues [14] found that obese persons were more likely to report headache (OR = 1.47), confirming again the association between headache and obesity.

In 2005, two small clinic-based studies reported an increased frequency of migraine attacks in those with total body obesity (TBO). In the first study the relationship between migraine and obesity was evaluated and it showed that obese patients were three times as likely as age-matched normal-weight controls to have migraine; in fact Prieto Peres et al. [4] compared 74 patient with TBO (mean age 39 years) who presented obesity surgery clinic to 70 age-matched controls. A total of 75% of those with TBO had life-time headache diagnosis as compared with 42% of the controls, $P < 0.001$. Furthermore, CDH migraine was compared with 18.5% of the nonobese controls, $P < 0.0001$. Similarly, in the second clinic-based study by Horev et al. [23], 63% of 27 patients with TBO reported episodic headache and 48% fulfilled migraine criteria. The results of those studies showed that migraine was the most common diagnosis and was as prevalent in obesity grade III as in overweight and obesity grades I and II.

Bigal et al. [9] showed that obesity was not associated with increased prevalence of migraine but was related to headache attack frequency. In this population-based telephone interview study, the subjects were subdivided into five groups, considering their BMI: 1, underweight (<18.5), 2, normal weight (18.5 to 24.9), 3, overweight (25 to 29.9), 4, obese (30 to 34.9), and 5, severe obese (≥35): the odds ratio for headache frequency increased significantly from group 1 to group 5. There was a robust evidence that groups 3, 4, and 5 migraineurs showed a high risk for having great and frequent headache; in contrast, groups 1 and 2 subjects did not show this risk.

On the other side, another large cross-sectional population research added more evidence about the association between obesity and CDH and demonstrated that obesity is an important determinant for CM but not for chronic tension type headache [13].

The same authors showed that CDH and total body obesity were more significantly associated in transformed migraine than in chronic tension-type headache (CTTH).

The objective of Ford's work [11] was to study the cross-sectional association between body mass index and the prevalence of severe headaches or migraines in a national sample of US adults. They evaluated 7601 participants in the national Health and Nutrition Examination survey (NHEANES), ranging from 20 to 85 years of age. Migraine and severe headache were self-reported, showing that those who were underweight (BMI < 18.5) or obese (BMI > 30) were at higher risk for having severe headaches or migraine compared with those of normal weight.

In the same year Pinhas-Hamiel et al. [7] in a prospective cohort study confirmed these results of Ford and coauthors; in fact this study [7] demonstrated positive correlations between frequency of migraine and obesity.

A total of 21.783 participants were included in the Peterlin's analysis [12] in order to evaluate the prevalence of migraine/severe headaches in those with and without general obesity and abdominal obesity (Abd-O) and the effect of gender and age on this relationship. They found in men and women aged 20–55 years that higher migraine prevalence was associated with both total and abdominal obesity. And, this was the first study which suggested and clearly demonstrated that older individuals or those of postreproductive age who have migraine do not have an association with obesity while those of reproductive age do, which also suggested that both obesity and migraine are modulated by reproductive status. The finding suggests that migraine and obesity are associated in those subjects in reproductive age [12]; this association was also later supported by data from Vo et al. [20] and Robberstad et al. [24]. Vo et al. found a significant association between migraine and obesity and that the odds of migraine increased with increasing obesity status. Robberstad et al.

Table 1: Characteristics and main results of studies concerning obesity and migraine.

Reference	Clinical study design	*N*.	*F*. (%)	Age (average age or range)	Characteristics of migraine or headache prevalence frequency and severity	
Brown et al. [14]	Cohort study	14779	100	18–23	Women in the highest BMI category were more likely to report headaches	Deleterious effects of overweight also for headaches
Scher et al. [15] Pain 2003	Longitudinal study	1932	NA	18–65	Prevalence of CDH was higher in those with TBO > grade II	Obesity and headache frequency were significantly associated with new onset CDH
Ohayon [16]	Observational study	18980	51.3	15 years or older	The prevalence of morning headaches was linked to BMI	A higher prevalence of morning headaches in subjects with BMI less than 20 or >27 than in subjects with normal BMI
Prieto Peres et al. [4] Arq Neuropsiquiatr 2005	Case-control study	74	89	38.4 (14–69)	Increased attacks of severe headache in obese compared with normal weight. Increased prevalence of migraine in obese women than obese men	No correlation between frequency of migraine and obesity. Severity: NA
Bigal et al. [9] Neurology 2006	Observational cohort study	30.125	65	38.7	No correlation between the prevalence of migraine and obesity	Positive correlation between migraine frequency and obesity Severity: NA
Keith et al. [17] Obesity 2006	Cross-sectional analysis	220.370	100	16–94	No correlation between the prevalence of migraine and obesity	NA
Bigal et al. [18] Cephalalgia. 2006	Longitudinal study	176	79.5	44.4	No correlation between the prevalence of migraine and obesity	No correlation between frequency/severity of migraine and obesity
Bigal et al. [10] Arch Intern Med. 2007	Observational cohort study	162.576	NA	≥12	NA	Positive correlation between migraine frequency and obesity Severity: NA
Mattsson et al. [19] Cephalalgia 2007	Cross-sectional analysis	684	100	40–74	No correlation between the prevalence of migraine and obesity	No correlation between frequency/severity of migraine and obesity.
Pinhas-Hamiel et al. [7] Obesity 2008	Prospective cohort study	273	61	13 (9–17)	Increased headaches in overweight girls compared with normal weight	Positive correlation between frequency of migraine and obesity. Severity: NA
Ford et al. [11] Cephalalgia. 2008	Cross-sectional analysis	7.601	48	≥20	Positive correlation between the prevalence of headache and obesity	Increased attacks of severe headache in overweight or obese when compared with normal weight.
Hershey et al. [5] Headache 2009	Large, multicenter, retrospective case	913	59	11.9 (3–18)	Increased attacks of severe headache in overweight or obese compared with normal weight	Positive correlation between frequency/severity of migraine and obesity Severity: NA

Table 1: Continued.

Reference	Clinical study design	*N*.	*F*. (%)	Age (average age or range)	Characteristics of migraine or headache prevalence frequency and severity	
Peterlin et al. [12] Headache 2010	Cross-sectional analysis	21.783	51	≥20	Increased prevalence of migraine in subjects aged <55 with total or abdominal obesity	NA
Kinik et al. [6] Cephalalgia 2010	Cross-sectional analysis	124	62	12.9 (4–17)	Increased attacks of severe headache in overweight or obese compared with normal weight	Positive correlation between frequency/severity of migraine and obesity. No correlation between severity of migraine and obesity.
Vo et al. [20] Headache. 2011	Cross-sectional study	3733	100	18–40	Increased prevalence of migraine in patients with morbid obesity	Positive correlation between migraine severity and obesity
Yu et al. [21] J Headache Pain 2012	Cross-sectional analysis	5041	50	43.6	Increased prevalence of migraine in patients with morbid obesity	No correlation between frequency/severity of migraine and obesity
Winter et al. [22] Cephalalgia 2012	Prospective cohort study	19162	100	50	No correlation between the prevalence of migraine and obesity	No correlation between frequency/severity of migraine and obesity

found that recurrent headache was associated with overweight (odds ratio [OR] = 1.4, 95% CI 1.2–1.6, $P = 0.0001$).

The relationship between obesity and headache/migraine has not been adequately studied with pediatric populations. The first study to examine the prevalence of obesity within a pediatric headache population was the Hershey's work [5] in which were examined 913 patients at 7 pediatric headache centers and the results clearly showed that obesity was significantly correlated with headache frequency and disability in children, and reduction in BMI as associated with greater reduction in headache frequency. Interestingly, the degree of overweight (measured by BMI percentile) correlated with both headache frequency and disability of headache. Of a certain relevance is the fact that the magnitude of weight reduction was related with decreased headachefrequency at 3- and 6-month follow-up visits.

In another pediatric study, Kinik et al. [6] investigated the influence of obesity on the severity of migraine in children. In agreement with previous adult study the authors concluded that obesity seems to occur at greater frequency in children and adolescents with migraine compared with the general population, and obese patients had more frequent migraine attacks than did nonobese patients.

Recently in a retrospective study [25] of 925 children in the Pediatric Headache Clinic, evaluating headache frequency, medication overuse, and BMI compared to population-based healthy subjects, children with headache had a greater percentage of overweight in comparison with the general population. It should be noted that also the patients with chronic tension-type headache showed similar results. On the other hand, there was no increased incidence of overweight in children with medication overuse or chronic migraine. It is important to remember that in adult series [13], a link between chronic migraine and obesity was found but with chronic tension-type headache.

Nevertheless, not all studies found the positive correlation between migraine and obesity. In fact Mattsson [19] failed to detect a significant correlation between obesity and migraine in 684 women aged 40–74 years. Similarly, in the study of Keith et al. [17], migraine prevalence was not related to obesity but obese women (BMI of 30) had increased risk for headache (but not specifically migraine) as compared with those with BMI. Téllez-Zenteno et al. [26] found that there was no association between the disability and severity of migraine and BMI, as well as no correlation between BMI and the frequency and prevalence of migraine was found in the study of Bigal et al. [18] in which 176 subjects (79.5% women, mean of 44.4 years) with normal weight (≤ 24.9), overweight (25–29.9), or obesity (≥30) were observed before and after headache preventive treatment. After treatment, frequency declined in the entire population, but no significant differences were found by BMI group.

Regarding the number of days with severe pain per month, there were also no significant differences at baseline (normal = 6.1, overweight = 6.5, obese = 6.7), and improvement overall ($P = 0.01$). Recently, also Winter et al. [22] in their large prospective study of middle-aged women do not indicate a consistent association between migraine and incident overweight, obesity, or relevant weight gain.

In Yu et al.'s [21] work they had shown that there is an association between morbid obesity and migraine in Asian population, while in the studies of Peterlin et al. [12] and Vo et al. [20] this relation was found in a Caucasian population. In this study it was found that migraine prevalence was significantly raised in the morbidly obese group (but not lesser degrees of obesity), and this was a substantial and statistically significant increase, but they also observed that there was a weak link between being underweight and migraine severity and disability.

3. Obesity-Related Associated Comorbidities: Lifestyle Intervention to Reduce BMI

Childhood obesity and overweight can be related to some adult diseases, in order to be predictive in adult life of obesity and overweight; it is well known that cardiovascular risk factors increase with the rise in BMI. The presence of cardiovascular risk factors during childhood can lead to an enlarged incidence of fatal and nonfatal cardiac events in adulthood.

In pediatric age, diseases associated with obesity are also possible. The pediatric obesity-associated comorbidities already described are type 2 diabetes mellitus (T2DM); dyslipidemia (most commonly a low HDL cholesterol); metabolic syndrome; hyperandrogenemia and hyperinsulinism in pre- to midpubertal girls and consequent polycystic ovary disease (PCOS); systolic blood pressure; proteinuria and focal segmental glomerulosclerosis; obstructive sleep apnea; nonalcoholic fatty liver disease (NAFLD); gallstones; orthopedic pathologies; pseudotumor cerebri; and finally, psychosocial problems [27].

The key determinants of childhood obesity in developing countries are unhealthy nutrition with increased caloric intake, reduced physical activity, urbanization, residence in metropolitan cities, socioeconomic status and sociocultural factors, age, and female gender. Therapeutic lifestyle changes and maintenance of regular physical activity through parental initiative and social support interventions are the most important strategies to challenge childhood obesity [28]. Lifestyle changes should include healthy eating habits (avoiding the consumption of calorie-dense and nutrient-poor foods, eating adequate portion, increasing intake of dietary fiber, fruits, and vegetables, also in school meals, eating timely, particularly breakfast and avoiding constant "gazing" during the day); physical activity (performing 60 minutes of daily moderate to vigorous physical activity, also in schools, walking and cycling to school, decreasing time spent in sedentary activities, such as computer/TV time); parents education (healthy culture patterns related to diet and activity, explaining the caloric needs and essential nutrient requirements of young children) [27].

Childhood obesity is a grave issue that needs to be addressed urgently: the objective of interventions in overweight and obese children and adolescents is the prevention or amelioration of obesity-related comorbidities, for example, glucose intolerance and T2DM, metabolic syndrome, dyslipidemia, and hypertension

[28] and finally also headaches/migraine, because we can consider headache/migraine as another obesity-associated comorbidity.

4. Conclusions

Migraine is a chronic neurological disorder characterized by recurrent attacks of pain that generally impair the quality of life. The real etiology and pathogenetic mechanism(s) of migraine are still unknown. Obesity is another chronic disorder that is very frequent both in adult and in pediatric population. Although a clear comorbidity between these conditions has been recently demonstrated, the real link between them is still matter of debate. Although this comorbidity is now recognized, the basic nature of this association is still unclear; it is possible that migraine and obesity can have some common pathophysiologic mechanisms and share one or more final pathways (e.g., inflammatory mediators). Obesity (and often body mass index of the patients) seems to be related not only to high frequency and to the degree of migraine attacks (especially some types of migraine) but also to the prevalence of the latter. These relations seem to be present in both adult and paediatric subjects. These relations are important for clinical practice and for future research. Given the association between obesity and headache, clinicians should actively consider a child's weight status in the context of treatment for headache. Routine assessment of child weight using BMI percentiles should be undertaken at the initial visit and used in the conceptualization of the presenting problem. For children who are overweight or at risk for overweight at the beginning of treatment, educational intervention may be necessary to improve weight control and subsequent headache treatment outcomes. For some children, referrals for behavioral weight management services may be necessary to facilitate appropriate lifestyle changes (increasing exercise, improving adherence to dietary guidelines) for effective weight control and optimal headache management.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

NMR-Based Metabolomic Profiling of Overweight Adolescents: An Elucidation of the Effects of Inter-/Intraindividual Differences, Gender, and Pubertal Development

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The plasma and urine metabolome of 192 overweight 12–15-year-old adolescents (BMI of $25.4 \pm 2.3\,kg/m^2$) were examined in order to elucidate gender, pubertal development measured as Tanner stage, physical activity measured as number of steps taken daily, and intra-/interindividual differences affecting the metabolome detected by proton NMR spectroscopy. Higher urinary excretion of citrate, creatinine, hippurate, and phenylacetylglutamine and higher plasma level of phosphatidylcholine and unsaturated lipid were found for girls compared with boys. The results suggest that gender differences in the metabolome are being commenced already in childhood. The relationship between Tanner stage and the metabolome showed that pubertal development stage was positively related to urinary creatinine excretion and negatively related to urinary citrate content. No relations between physical activity and the metabolome could be identified. The present study for the first time provides comprehensive information about associations between the metabolome and gender, pubertal development, and physical activity in overweight adolescents, which is an important subject group to approach in the prevention of obesity and life-style related diseases. While this study is preliminary, these results may have the potential to translate into clinical applicability upon further investigations; if biomarkers for Tanner stage can be established, these might be used for identification of individuals susceptible to an early pubertal development.

1. Introduction

Metabolomics is a postgenomic technology that is given great promise for human phenotyping and for assisting in health assessment [1, 2]. Numerous metabolomics studies have investigated the impact of anthropometric factors such as age, gender, and obesity [3–5] in an attempt to understand the human metabolome and interindividual differences. However, these studies have mainly been conducted on either newborns and infants [6, 7] or adults [3–5, 8], whereas studies on children and adolescents are sparse [9–11]. Gu et al. [9] studied the age-related metabolic changes in children of age from newborn to 12 years and by NMR-based metabolomics on urine samples. An age effect on the urinary metabolome was identified as a distinct age-dependent clustering in PCA. Metabolites found to be correlated with age included creatinine, creatine, glycine, betaine/TMAO, citrate, succinate, and acetone. While creatinine increased with age, all the other metabolites decreased [9].

The increase in obesity has been much more pronounced in children and adolescents than other age groups [12], and the prevalence of cardiovascular disease (CVD) among youth is also increasing [13]. In fact, many life-style related diseases are assumed to be commenced already in childhood and during adolescence [14]. Thus, it was recently shown that the level of plasma branched-chain amino acids, which are getting increasing attention because of their potential role in insulin sensitivity and secretion, was elevated already in

obese children aged 8 to 13 years and correlated with insulin resistance determined 18 months later [15]. Tanner stage was first defined by Marshall and Tanner [16, 17] as a scale of physical development based on external primary and secondary sex characteristics. Oldehinkel et al. [18] investigated the relationship between specific mental health problems and pubertal stage in adolescents in a Dutch prospective cohort study and revealed that Tanner stage was positively related to tiredness, irritability, rule-breaking behaviors, and substance use and negatively to fears and somatic complaints. Consequently, Tanner stage seems to be important for health and well-being, and it could be advantageous to obtain a better understanding of the metabolome of adolescents and relation to pubertal development and life-style related factors.

However, to our knowledge, no metabolomics studies on pubertal development have been reported. Pubertal development involves complex physical and psychological processes between childhood and adult life, ultimately resulting in the attainment of adult reproductive capacity [19]. The past decades age at sexual maturation has declined, evident by a gradual younger age at menarche [20, 21] and breast development [22] among girls, and earlier testicular development in boys [23]. The obesity epidemic is thought to affect timing of pubertal development, and the process of pubertal development is a critical period for body composition development [24], but the association between obesity and pubertal development is far from clear [19]. Consequently, taken the increasing obesity epidemics into consideration, this urges us to learn more about of the process of pubertal development and metabolism, and metabolomics may be a useful tool. Therefore, by using nuclear magnetic resonance- (NMR-) based metabolomics, the aim of the present study was to investigate the plasma and urine metabolome of overweight adolescents and elucidate intra- and interindividual differences, the influence of gender, pubertal development measured as Tanner stage, and physical activity.

2. Materials and Methods

2.1. Subjects. The samples used in present study included a subset of samples from a larger intervention study presented in Arnberg et al. [25, 26]. A total of 203 overweight adolescents aged 12–15 years with the BMI ($25.4 \pm 2.3\,kg/m^2$) corresponding to a BMI $> 25\,kg/m^2$ for adults [27] were recruited in the Copenhagen area using extractions from the Civil Registration System. Firstly, a subgroup of 28 subjects was established and a urine sample and a blood sample were collected from each of these at time point 0. These samples served for studies on intra-/interindividual differences. Twelve weeks later, urine and blood samples were collected from all the 203 subjects, and sample sets from 192 subjects were included in the present metabolomics study. All participants were free to consume their usual diet ad libitum and maintain daily physical activity. Samples were frozen and stored at −80°C until analysis.

2.2. NMR Measurements. ^{1}H NMR spectra were measured at 600.13 MHz for proton on a Bruker Avance 600 spectrometer equipped with a 5 mm ^{1}HTXI probe (Bruker BioSpin, Rheinstetten, Germany) at 37°C for blood plasma and 25°C for urine. A standard Bruker "ZGPR" pulse program that applies a presaturation pulse sequence for water suppression was used, and a total of 64 scans were collected into 32 K data points with a relaxation delay of 2 sec. A spectral width of 7288.63 Hz and an acquisition time per scan of 2.25 sec were applied in this study. Prior to analysis, samples were thawed and homogenized using a vortex mixer. Urine samples were centrifuged at 10,000 g for 5 min to remove insoluble material, and 500 μL supernatant was transferred to a 5 mm NMR tube and mixed with 100 μL of a 0.75 M phosphate buffer solution (containing 0.5% sodium trimethylsilyl propionate-d_4 (TSP)) prepared in D_2O. Blood plasma samples were centrifuged at 10,000 g for 10 min and 400 μL supernatant was transferred to a 5 mm NMR tube and then mixed with 200 μL D_2O.

2.3. Physical Activity. Physical activity was measured by means of a short questionnaire daily, wherein participants registered the number of counts measured by using pedometers (Yamax, SW-200) for 7 consecutive days [25, 26].

2.4. Tanner Stage. Tanner stage was determined on a 5-point scale according to an assessment of pubic hair development in boys and breast stage in girls by using self-reported questionnaires [25, 26].

2.5. Data Analysis. All ^{1}H NMR spectra were automatically phased and baseline-corrected using Topspin 3.0 software (Bruker BioSpin, Rheinstetten, Germany). The ^{1}H spectra of blood plasma were referenced to the anomeric signal of α-glucose at 5.23 ppm, while the ^{1}H spectra of urine were referenced to the TSP signal at 0 ppm. Then, all spectra were aligned by using the "icoshift" procedure [28] in MATLAB (version R2012a, The Mathworks Inc., Natick, MA, USA). The spectral region from 0.0 to 10.0 ppm without the residual water resonance region from 4.7 to 5.0 ppm were normalized to the total signal intensities of the NMR spectra, subdivided into 0.01 ppm spectral regions, and integrated to 970 "bin" data for multivariate data analysis.

PCA and OPLS-DA for classification and PLSR for regression were performed on mean-centered and Pareto-scaled data by using the SIMCA 13.0 software (Umetrics, Umeå, Sweden), and a leave-one-out cross validation (LOOCV) method was used to determine the optimal number of latent variables for the models. R^2X and R^2Y are the percentage of the variance in X and Y matrixes explained by the current latent variable of the model, respectively, while Q^2Y is the predictive capability of the model. In addition, the significance test of the model was performed by using CV-ANOVA [29] in the SIMCA software. Outliers in the models were identified as samples located far away from the 95% Hotelling's T_2 confidence limit. For urine, 7 outliers were identified and excluded from the models resulting in a total of 185 samples from 115 girls and 70 boys. For blood, 3 outliers were identified and excluded from the models resulting in a total of 189 samples

from 119 girls and 70 boys. The NMR peaks were assigned based on reported values [30, 31]. To aid spectral assignment, two-dimensional (2D) ^{1}H-^{1}H correlation spectroscopy with double-quantum filter (COSY), 2D ^{1}H-^{1}H total correlation (TOCSY) and 2D ^{13}C-^{1}H heteronuclear single quantum coherence (HSQC), experiments were performed on representative samples of both urine and plasma. For analysis of selected urinary metabolites, integration of the specified ppm area including citrate (CH_2: 2.66–2.71 ppm), creatinine (CH_2: 4.04–4.07 ppm), phenylacetylglutamine (CH: 7.33–7.39 ppm), hippurate (CH_2-2,6: 7.81–7.86 ppm), and urea ($(NH_2)_2$: 5.50–6.10 ppm) in the NMR spectrum was performed by using Topspin 3.0 software, followed by calculation of the relative concentrations according to the known TSP concentration. A linear mixed effects model was performed on the relative concentration by using MIXED procedure in SAS 9.2 (SAS Institute Inc, Cary, NC) to evaluate effect of Tanner stage and gender on these metabolites. The mixed model included the fixed effects of gender, Tanner stage, and their interaction, while the intercept of model and individuals were used as a random effect. The restricted maximum likelihood (REML) approach [32] was used to estimate the variance components of models. The degrees of freedom were determined according to the method of Kenward and Roger [33], and Akaike Information Criterion [34] was performed to evaluate the optimal model. In addition, least square (LS) means procedures were used to calculate means and standard errors and pairwise t-tests for multiple comparisons were estimated by using the Tukey test. In this study, main and interaction effects were considered statistically significant when $P < 0.05$.

3. Results and Discussion

3.1. Inter-/Intrasubject Variations in the Urine and Blood Metabolomes over a 12-Week Period. PCA scores plots (Figure 1) show that, in many cases, the two samples obtained from the same subject are positioned close to each other; however, intrasubject variations of urine and plasma samples are still observed in both genders. A higher intersubject variation is observed for the urine metabolome than for the plasma metabolome (Figure 1), which is in agreement with previous studies [35, 36]. The corresponding loadings from urine (Figure 1(e)) and plasma (Figure 1(f)) samples were examined in order to elucidate the spectral regions most susceptible to inter-/intrasubject variations. The loadings revealed that signals at 3.04 and 4.05 ppm from creatinine and a broad signal from urea at 5.50–6.10 ppm contribute to intrasubject variation in urine metabolome, while minor contribution from hippurate signals at 3.96, 7.54, and 7.82 ppm is also evident (Figure 1(e)). Walsh et al. [36] have also concluded that hippurate and creatinine were the metabolites contributing most to variation in the urinary profiles. Figure 1(f) illustrates that lipids and glucose in plasma mainly contribute to inter-/intrasubject variation, which is in agreement with results from Lenz et al. [35]. Krug et al. [8] reported that the human metabolome is under continuous changes due to anabolic (after meal) and catabolic (during fasting or physical exercise) conditions of metabolism. Thus, the variations in the urine and plasma metabolome can be ascribed to a range of factors including dietary effects, physical exercise, and physiological stress.

3.2. Gender Differences in the Urine and Blood Metabolomes. Gender was found to have a pronounced impact on the urine and plasma metabolomes, and O-PLS models that could discriminate the two gender could be built from the metabolomics data obtained both for urine ($R^2X = 32.8\%$; $R^2Y = 50.4\%$; $Q^2 = 28.3\%$; $P < 0.0001$) (Figure 2(c)), which included samples from 115 girls and 70 boys, and plasma ($R^2X = 73.8\%$; $R^2Y = 46.4\%$; $Q^2 = 26.5\%$; $P < 0.0001$) (Figure 2(d)), which included samples from 119 girls and 70 boys.

Inspection of the corresponding S-line plot from the urine data (Figure 2(e)) revealed that gender differences could be ascribed to differences in the urinary content of citrate (2.53, 2.56, 2.67, and 2.70 ppm), creatinine (3.04 and 4.05 ppm), and urea (5.50–6.10 ppm). Mixed model analysis shows that the concentrations of citrate and creatinine were significantly higher in girls, while urea content was lower in girls compared with boys (Table 1). The results are in agreement with previous studies on adults [3, 4, 37] where higher urinary levels of citrate have been observed in females compared with males. It has been reported that the excretion of urinary citrate is regulated by sex hormones such as estrogen [38] and testosterone [39], which may contribute to the gender differences in urinary citrate. However, the results concerning creatinine are opposing previous studies on adults who all reported that urinary creatinine levels were higher in males than females. A positive association between urinary excretion of creatinine and muscle mass has been reported by Kochhar et al. [3] and Oterdoom et al. [40]. Neu et al. [41] investigated the influence of puberty on muscle development and found that the gender difference in forearm muscle growth decreased until pubertal stage 3 and then increased again. Generally, girls begin and complete each puberty stage earlier than boys, which was also reflected in our study (Table 1). Thus, the contrasting results about urinary creatinine may be related to a higher muscle mass in girls relative to boys. Since urea is the major product of protein catabolism, the higher urinary urea excretion in boys may be caused by a higher protein intake or a higher protein turnover. A higher leucine oxidation in males than in females has been reported, which could cause the gender-specific difference in protein utilization [42, 43]. In addition, females may utilize less protein as an energy source owing to a greater part of exercise energy from fat [44]. In addition, Table 1 shows that girls have a relatively higher urinary excretion of hippurate and phenylacetylglutamine than boys, which is different from results obtained for adults aged 40–59 years [45]. They found a higher hippurate excretion in men compared to women, but no gender difference in phenylacetylglutamine excretion. Consequently, it appears that many of the gender effects observed on the urine metabolome are being commenced already in childhood, while some differences are still evident between adolescents and adults.

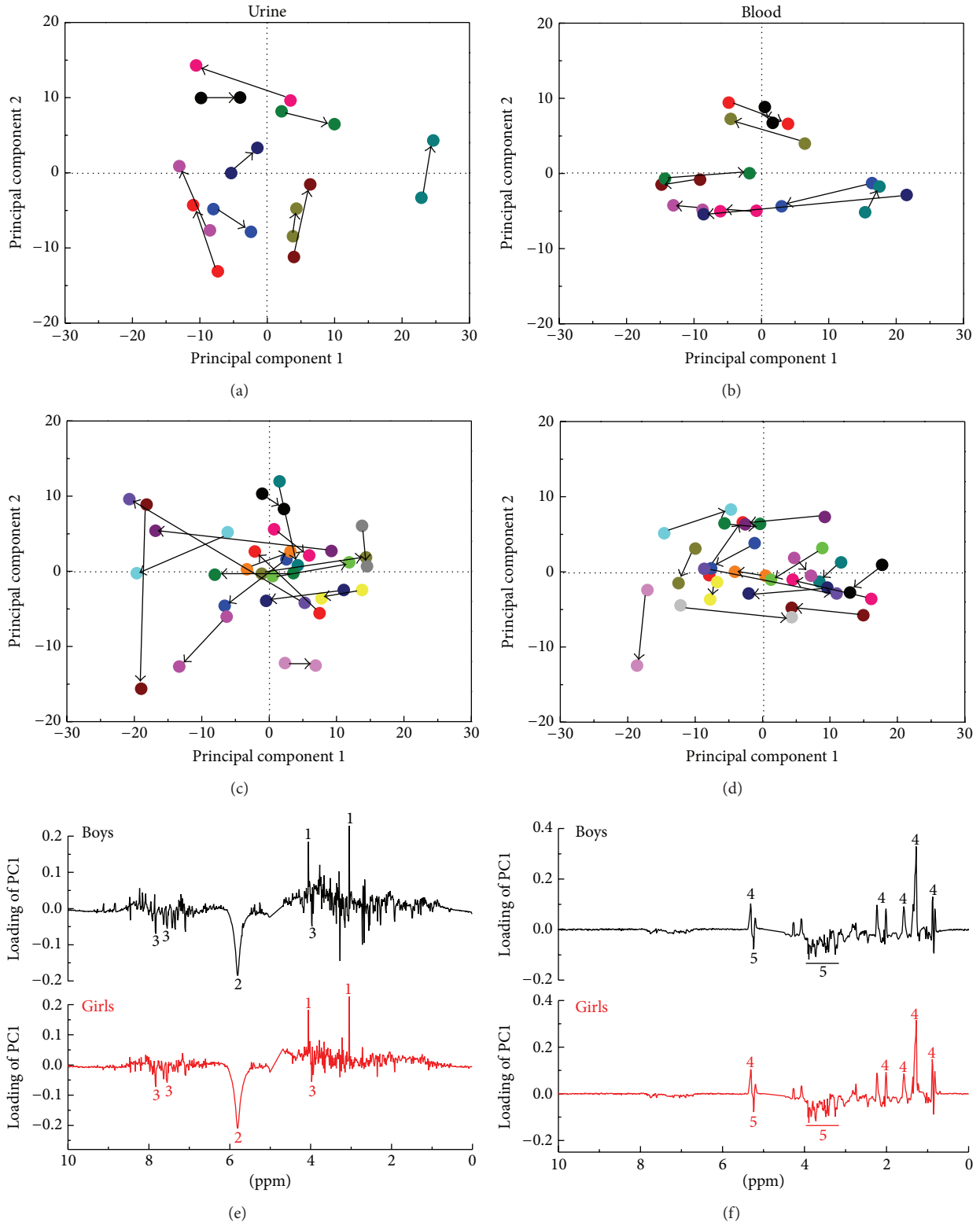

FIGURE 1: Intrasubject variation in the urine and plasma metabolome of adolescents over a 12-week interval: (a) PCA score plot of urine samples from boys (PC1 explains 28.3% and PC2 explains 16.4% of the variation); (b) PCA score plot of plasma samples from boys (PC1 explains 64.3% and PC2 explains 14.4% of the variation); (c) PCA score plot of urine samples from girls (PC1 explains 24.3% of the variation and PC2 explains 10.2% of the variation); (d) PCA score plot of plasma samples from girls (PC1 explains 55.7% and PC2 explains 11.6% of the variation); (e) PC1 loadings of urine samples; (f) PC1 loadings of plasma samples. The same subject is indicated by the same color in PCA score plots and the arrow points from week 0 to week 12. Assignments: 1: creatinine (3.04 and 4.05 ppm); 2: urea (5.50–6.10 ppm); 3: hippurate (3.96, 7.54, and 7.82 ppm); 4: lipids; 5: glucose.

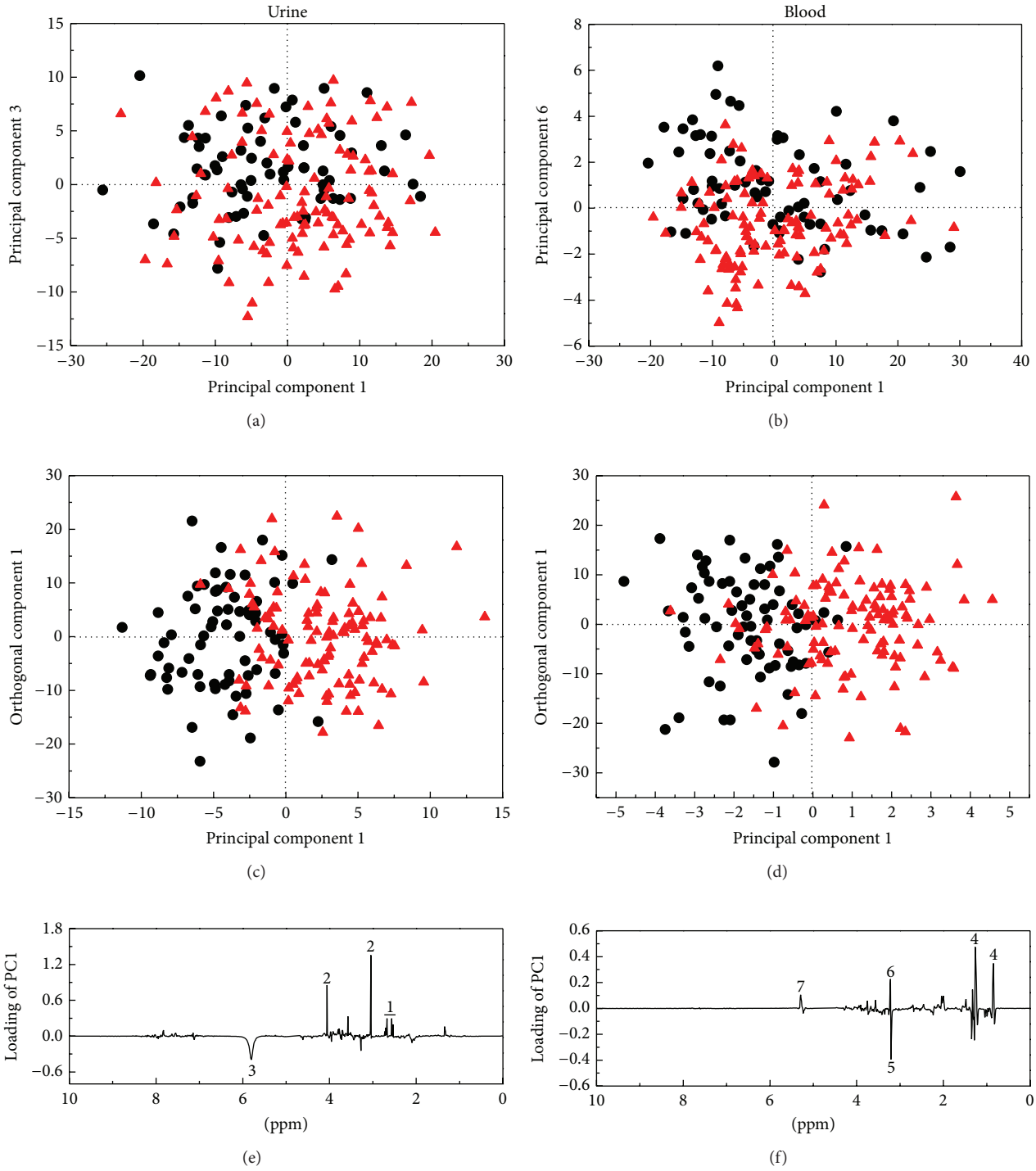

FIGURE 2: Gender difference (●: boys; ▲: girls) in the urine and plasma metabolome of adolescents: (a) PCA score plot of urine samples (PC1 explains 20.3% and PC3 explains 5.4% of the variation); (b) PCA score plot of plasma samples (PC1 explains 59.2% and PC6 explains 2.3% of the variation); (c) OPLS-DA score plot of urine samples (1 predictive and 2 orthogonal components; $R^2X = 32.8\%$; $R^2Y = 50.4\%$; $Q^2 = 28.3\%$; $P < 0.0001$); (d) OPLS-DA score plot of plasma samples (1 predictive and 3 orthogonal components; $R^2X = 73.8\%$; $R^2Y = 46.4\%$; $Q^2 = 26.5\%$; $P < 0.0001$); (e) S-line plot of urine samples; (f) S-line plot of plasma samples. Assignments: 1: citrate (2.53, 2.56, 2.67, and 2.70 ppm); 2: creatinine (3.04 and 4.05 ppm); 3: urea (5.50–6.10 ppm); 4: lipoproteins (0.84 and 1.26 ppm); 5: choline (3.20 ppm); 6: phosphocholine (3.22 ppm); 7: unsaturated lipids (5.29 ppm).

Table 1: Mixed models of Tanner stage and gender effects in overweight adolescents on urinary metabolites[a].

		N[b]	Citrate	Creatinine	Hippurate	Phenylacetylglutamine	Urea
Gender	♂	70	27.1 ± 2.4^{b}	262.9 ± 5.1^{b}	46.6 ± 3.5^{b}	38.9 ± 2.4	1358.2 ± 48.4^{a}
	♀	115	36.4 ± 2.7^{a}	280.0 ± 5.4^{a}	57.1 ± 3.9^{a}	45.4 ± 2.6	1087.3 ± 53.5^{b}
Tanner stage	1	♂: 5; ♀: 2	49.2 ± 6.8^{a}	262.8 ± 12.6^{b}	39.6 ± 9.0	33.7 ± 6.1	1326.5 ± 124.0
	2	♂: 30; ♀: 7	29.7 ± 2.5^{bc}	262.3 ± 6.9^{b}	57.0 ± 5.0	41.2 ± 3.3	1211.8 ± 67.9
	3	♂: 18; ♀: 53	30.8 ± 1.7^{b}	257.7 ± 4.3^{b}	57.4 ± 3.0	47.5 ± 2.2	1256.6 ± 43.1
	4	♂: 13; ♀: 43	25.1 ± 1.9^{c}	270.4 ± 6.6^{b}	56.6 ± 3.8	48.3 ± 2.6	1257.8 ± 54.7
	5	♂: 4; ♀: 10	24.1 ± 4.6^{bc}	303.8 ± 8.9^{a}	48.5 ± 6.4	40.0 ± 4.3	1060.9 ± 87.7
Significant effects (P values)		G[c]	**0.01**	**0.02**	**0.05**	0.07	**0.0002**
		T[d]	**0.005**	**0.0003**	0.30	0.06	0.29
		G ∗ T	0.24	0.81	0.73	**0.009**	**0.03**

[a]Values are the relative concentrations according to a known TSP concentration and expressed mean ± SE; [b]Number of subjects (♂: boys; ♀: girls); [c]Gender; [d]Tanner stages; Different letters indicate significant differences within columns ($P < 0.05$).

Inspection of the S-line plot for blood data shows that the discrimination of the two genders mainly can be ascribed to differences in lipoproteins (0.84 and 1.26 ppm), phosphatidylcholine (3.22 ppm), and unsaturated lipid (5.29 ppm) and lower levels of choline (3.20 ppm) in girls compared with boys (Figure 2(f)). Gender differences in blood lipids have also previously been reported for 17-year-old Scandinavians [5]. According to Brindle et al. [46], the region at 3.22 ppm can be assigned to $-N(CH_3)^{3+}$ groups in molecules, which contain the choline moiety, mostly phosphatidylcholine from HDL. The $-N(CH_3)^{3+}$ groups could also be coupled with a higher level of unsaturated lipids in the blood from girls, implying that the phospholipids are more unsaturated in girls compared to boys [5]. In addition, phosphatidylcholine is a major structural constituent of cell membranes. Thus, our results could possibly reflect that girls have a higher overall plasma membrane turnover compared with boys [5]. A study on mice also found gender differences in phosphatidylcholine [47]. A survey in 2007-2008 estimated mean daily intake of choline in US population and reported that males have a higher choline requirement than females for all age groups above 12 years old [48], which could possibly explain the higher content of choline in the plasma from boys.

3.3. Effect of Pubertal Development Stage on the Urine and Blood Metabolomes. PCA of the NMR urine profiles of 115 girls and 70 boys indicated a tendency for a clustering according to Tanner stage (Figures 3(a) and 3(b)), revealing that Tanner stage is reflected in the urine metabolome. PLS models with Tanner stage as response variable were therefore constructed in order to elucidate the relation between urine metabolite profile and Tanner stage for boys ($R^2X = 27.1\%$; $R^2Y = 51.9\%$; $Q^2 = 25.5\%$; $P < 0.001$) and girls ($R^2X = 37.3\%$; $R^2Y = 69.4\%$; $Q^2 = 24.6\%$; $P < 0.0001$), respectively (Figures 3(c) and 3(d)). The corresponding PLS1 loadings indicate that urinary creatinine excretion is positively correlated with Tanner stage in both boys (Figure 3(e)) and girls (Figure 3(f)), which is supported by results from quantification of creatinine (Table 1). Oterdoom et al. [40] and Wang et al. [49] found a positive association between muscle mass and urinary excretion of creatinine, and increases in muscle mass increases during pubertal development is probably encompassed in the present findings. In addition, a study on creatinine levels surveyed a large US population with ages ranging from 6 to 70 years reported a gradual increase in urinary creatinine concentration up to an age between 20 and 29 years [50].

Intriguingly, a negative correlation is observed between urinary citrate excretion and Tanner stage, which is more evident in boys than in girls (Figures 3(e) and 3(f); Table 1). It has been reported that the flux of citrate through the TCA cycle is regulated by gender hormones such as testosterone [39]. Costello et al. [51] also found that citrate oxidation in rat ventral prostate was stimulated by testosterone. In addition, a strong correlation between estrogen actions and citrate excretion was reported by Dey et al. [38], who found that estrogen replacement increased urinary citrate excretion in postmenopausal women. Therefore, the decrease in the excretion of citrate is most likely attributed to changes in sex hormones during pubertal development.

Loading plots indicate that the aromatic region of ^{1}H NMR spectra (6.80–8.10 ppm) involving mainly hippurate and phenylacetylglutamine to some extent was correlated with Tanner stage, especially for girls (Figure 3(f)). Quantification of hippurate and phenylacetylglutamine by integration of the NMR signals revealed no significant effect of Tanner stage on urinary hippurate, while phenylacetylglutamine tended to be significantly affected by Tanner stage ($P = 0.06$) (Table 1). Gu et al. [9] reported that urinary hippurate excretion may vary less during childhood development, although a relatively large variation in hippurate with age was found for adults by Psihogios et al. [37]. In addition, the data reported by Swann et al. [52] indicated that urinary phenylacetylglutamine concentrations were increased with age in adults. Urinary hippurate and phenylacetylglutamine have often been related to the activity of the gut microflora [53], so our results suggest that the gut microflora may vary with Tanner stage. Thus, further studies including a more detailed description of the gut microflora as function of pubertal development could be of great interest confirming this hypothesis. For blood, a relatively low correlation was obtained between the

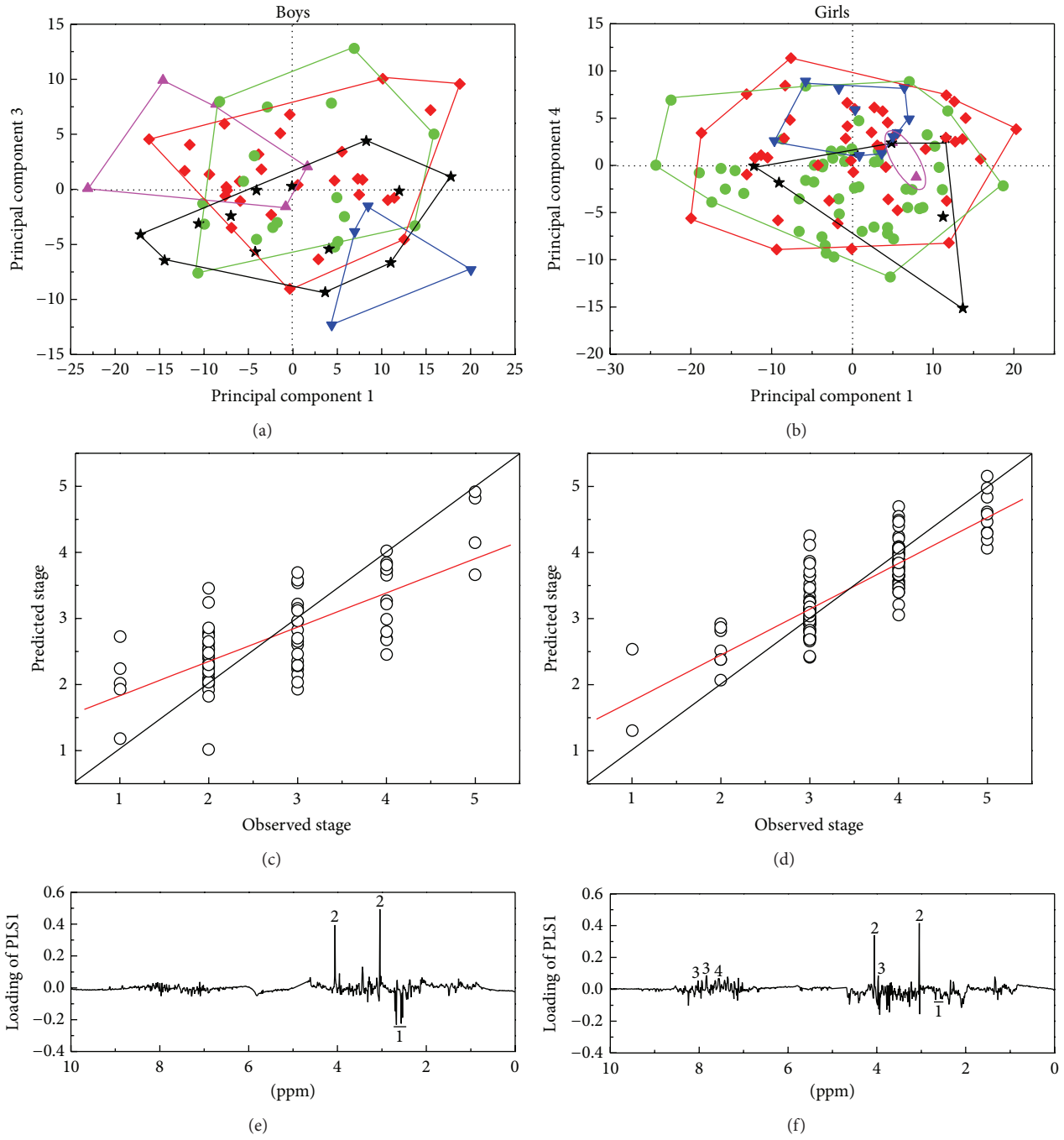

Figure 3: (a) PCA score plot of boys (PC1 explains 21.4% and PC3 explains 6.3% of the variation); (b) PCA score plot of girls (PC1 explains 19.7% and PC4 explains 5.9% of the variation) obtained for the urine metabolome of adolescents and showing Tanner stage (▲: stage 1; ✦: stage 2; ●: stage 3; ★: stage 4; ▼: stage 5). (c) PLSR prediction plot of Tanner stage in boys (the optimal number of PLSs = 2; R^2X = 27.1%; R^2Y = 51.9%; Q^2 = 25.5%; $P < 0.001$); (d) PLSR prediction plot of Tanner stage in girls (the optimal number of PLSs = 4; R^2X = 37.3%; R^2Y = 69.4%; Q^2 = 24.6%; $P < 0.0001$); (e) PLS1 loadings of boys; (f) PLS1 loadings of girls. Assignments: 1: citrate (2.53, 2.56, 2.67, and 2.70 ppm); 2: creatinine (3.04 and 4.05 ppm); 3: hippurate (3.96, 7.54 and 7.82 ppm); 4: phenylacetylglutamine (7.35 ppm).

metabolite profile and Tanner stage (R^2Y = 40.6% and Q^2 = 23.9% for boys; R^2Y = 33.6% and Q^2 = 16.0% for girls) (Figure S1, See the Supplementary Material available online at http://dx.doi.org/10.1155/2014/537157).

3.4. Effect of Physical Activity on the Urine and Blood Metabolomes. Several studies have reported the use of NMR-based metabolomics to study impact of physical exercise on the biofluid metabolome [54–59]. In the present study

the relation between the metabolome and physical activity measured as number of steps taken daily was elucidated. No strong correlation could be identified neither between the blood plasma nor the urine metabolome and daily physical activity (Figure S2, Supplementary Material). Thus, it was not possible to demonstrate a relation between moderate physical activity and the metabolome. Possibly more extreme variations in physical activity would have a more clear effect on the metabolome; however, this remains to be established in future studies.

4. Conclusions

In summary, our findings showed that creatinine, hippurate, and urea in urine and glucose and lipids in plasma are the main metabolites giving rise to inter-/intrasubject variations. We showed that girls have a higher urinary excretion of citrate, creatinine, hippurate, and phenylacetylglutamine and higher plasma level of phosphatidylcholine and unsaturated lipid as compared with boys. In addition, we have identified potential metabolites including creatinine and citrate, which exhibit a relation to pubertal development stage as measured by the Tanner stage. To our knowledge, the present study is the first to elucidate the relation between the metabolome and pubertal development stage.

List of Abbreviations

BMI: Body mass index
COSY: Two-dimensional ^{1}H-^{1}H correlation spectroscopy with double-quantum filter
CVD: Cardiovascular disease
CV-ANOVA: Cross validation-analysis of variance
HDL: High-density lipoprotein
HSQC: Two-dimensional ^{13}C-^{1}H heteronuclear single quantum coherence
LS: Least squares
LOOCV: Leave-one-out cross validation
NMR: Nuclear magnetic resonance
O-PLS: orthogonal-partial least squares
OPLS-DA: Orthogonal partial least squares-discriminant analysis
PCA: Principal component analysis
PLS: Partial least squares
PLSR: Partial least squares regression
Q^2Y: The predictive capability of the model
R^2X: The percentage of the variance in X matrixes explained by the current latent variable of the model
R^2Y: The percentage of the variance in Y matrixes explained by the current latent variable of the model
REML: Restricted maximum likelihood
TMAO: Trimethylamine-N-oxide
TSP: Sodium trimethylsilyl propionate-d_4
TCA: Tricarboxylic acid
TOCSY: Two-dimensional ^{1}H-^{1}H total correlation
wk: Week
ZGPR: Standard Bruker water presaturation sequence.

Conflict of Interests

The authors have no conflict of interests to declare regarding the publication of this paper.

Authors' Contribution

Karina Arnberg, Christian Mølgaard, Kim F. Michaelsen, and Anni Larnkjær designed and conducted the trial; Hong Zheng performed NMR analyses; Hong Zheng, Christian C. Yde, and Hanne C. Bertram analyzed data; Hong Zheng and Hanne C. Bertram wrote the manuscript. All authors contributed to preparation of the final manuscript.

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Review Article

Resistance Training for Diabetes Prevention and Therapy: Experimental Findings and Molecular Mechanisms

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Type 2 diabetes mellitus (T2D) is characterized by insulin resistance, impaired glycogen synthesis, lipid accumulation, and impaired mitochondrial function. Exercise training has received increasing recognition as a cornerstone in the prevention and treatment of T2D. Emerging research suggests that resistance training (RT) has the power to combat metabolic dysfunction in patients with T2D and seems to be an effective measure to improve overall metabolic health and reduce metabolic risk factors in diabetic patients. However, there is limited mechanistic insight into how these adaptations occur. This review provides an overview of the intervention data on the impact of RT on glucose metabolism. In addition, the molecular mechanisms that lead to adaptation in skeletal muscle in response to RT and that are associated with possible beneficial metabolic responses are discussed. Some of the beneficial adaptations exerted by RT include increased GLUT4 translocation in skeletal muscle, increased insulin sensitivity and hence restored metabolic flexibility. Increased energy expenditure and excess postexercise oxygen consumption in response to RT may be other beneficial effects. RT is increasingly establishing itself as an effective measure to improve overall metabolic health and reduce metabolic risk factors in diabetic patients.

1. Introduction

The global epidemic of obesity has contributed to a concomitant increase in the prevalence of type 2 diabetes mellitus (T2D). The number of people with T2D increased from 153 million in 1980 to 347 million in 2008 and is projected to reach 550 million worldwide by the year 2030 [1]; therefore, the disease is a growing public health concern and major socioeconomic burden [2]. Type 2 diabetes mellitus and prediabetic conditions such as impaired glucose tolerance are characterized by varying levels of insulin resistance causing hyperglycemia. Disturbances in glucose and insulin metabolism may not be a normal characteristic of aging but are rather associated with obesity and physical inactivity [3]. Exercise training has received increasing recognition as a cornerstone in the prevention and treatment of T2D. Based on the current position statement from Exercise and Sport Science Australia, it is recommended that patients with T2D or prediabetes accumulate a minimum of 210 min per week of moderate-intensity exercise or 125 min per week of vigorous intensity exercise with two or more resistance training (RT) sessions per week included into the total time [4]. It is well established that endurance exercise brings about numerous beneficial physiological changes such as increased maximal oxygen utilization (VO_{2max}) and cardiopulmonary fitness, as well as peripheral adaptations such as increased fatty acid transport and oxidation, improved capillary density, and mitochondrial capacity [5]. Positive health effects of RT, however, are only relatively recently being recognized and characterized. Before the year 1990, neither the American Heart Association nor the American College of Sports Medicine (ACSM) included guidelines for recommendation of RT for exercise training and rehabilitation. It was in 1990 when the ACSM recognized RT as a contributing factor to a comprehensive fitness program for healthy adults of all ages. The current position statement for exercise and

type 2 diabetes by the ACSM and the American Diabetes Association (ADA) recognizes the beneficial effects of RT and recommends RT at least twice a week in addition to aerobic training for persons with T2D [6]. Evidence from randomized controlled trials has shown that RT improves glycemic control in patients with T2D, increases glucose disposal, and even improves the lipid and cardiovascular disease risk profile of patients with T2D [7, 8]. Furthermore, the Health Professionals Follow-up Study examined the association of RT in the primary prevention of T2D and found a 34% lower risk of T2D in men, independent of aerobic exercise [9]. However, there is limited mechanistic insight into how these adaptations occur. The purpose of this review is to (1) provide an overview of the intervention data on the impact of RT on glucose metabolism, and (2) to hypothesize about the potential role of RT to combat metabolic dysfunction in patients with T2D by describing possible cellular and molecular mechanisms. We included both well-designed randomized and nonrandomized controlled RT trials, but only those non-randomized controlled RT trials were included that were frequently cited by others or had other indicators of good internal controls.

2. Aging, Obesity, and Insulin Resistance

Biological ageing is typically associated with a progressive increase in body fat mass and a loss of lean body mass, particularly skeletal muscle termed sarcopenia [10]. Skeletal muscle mass—the primary site of glucose and triglyceride disposal—declines at a rate of 3 to 8% each decade after the age of 30 [11] which may lead to a rise of risk developing glucose intolerance and T2D [12]. Due to the metabolic consequences of diminished muscle mass with aging, including lowered resting metabolic rate, reduced glucose uptake, and capacity for lipid oxidation, it is understood that normal aging and/or decreased physical activity may lead to a higher prevalence of metabolic disorders. Evidence from epidemiological studies has shown that muscular strength is inversely related to both the metabolic syndrome and all-cause mortality [13, 14]. Visceral fat increases by over 300% between the ages of 25 and 65 years, and this creates an increased risk for the development of T2D and cardiovascular disease (CVD) in adults with normal body mass index [15]. The distribution of excess fat in the abdominal region modifies the health risk profile. In contrast, excess adiposity in the periphery does not appear to increase the risk of developing CVD [16]. Intra-abdominal fat compared to total body fat correlates significantly better with triglycerides, systolic and diastolic blood pressure and is expected to decrease the sensitivity of target tissues to insulin [17, 18]. Intra-abdominal obesity is an important risk factor for low-grade inflammation. The adipokines adiponectin and tumor necrosis factor alpha (TNF-α) play a role in body fat distribution and correlate with aging and insulin resistance [19]. Serum adiponectin levels are negatively associated with fat mass and reduced adiponectin levels play a causal role in the development of insulin resistance. Adiponectin is an insulin-sensitizing protein and hypoadiponectinemia is therefore associated with obesity, insulin resistance, and type 2 diabetes [20]. Adiponectin is believed to activate 5′-AMP-activated protein kinase (AMPK), which activates insulin-independent glucose uptake by the muscle [21]. TNF-α is an inflammatory cytokine secreted by adipose tissue, with high concentrations of TNF-α being linked to obesity and insulin resistance [22].

In obesity and T2D fatty acid metabolism in skeletal muscle is dysregulated, resulting in the accumulation of lipids within the muscle cell [23]. These intramuscular lipid products interfere with insulin signaling within the muscle cell thereby contributing to insulin resistance [24]. Even a single bout of RT increases VLDL-TG plasma clearance rate by 26% as compared with the rest thereby reducing the residence time of VLDL-TG in the circulation of untrained men [25]. This effect may be mediated by increased VLDL-TG catabolism and hydrolysis during recovery by augmentation of lipoprotein lipase (LPL) gene expression and activity in the skeletal muscle [26]. In aging and insulin-resistant conditions the ability of insulin to stimulate GLUT4 translocation decreases, resulting in a reduced GLUT4 content at the plasma membrane [27]. Exercise-induced, contraction-mediated GLUT4 translocation to the muscle membrane is independent of insulin and occurs through calcium/calmodulin-dependent protein kinase IV and, secondarily, through AMPK, which induces expression of PGC-1α, a transcriptional coactivator that is essential for mitochondrial biogenesis [28, 29]. A 40% reduction in mitochondrial function with aging, obesity, and T2D may contribute to declines in glucose uptake and the development of insulin resistance, possibly arising from increases in intracellular lipid stores [30]. Once taken up by the cell, glucose can either be oxidized to carbon dioxide and water or converted to glycogen, the latter being regulated by glycogen synthase. Patients with T2D show significantly lower glycogen synthesis rates compared to healthy controls [31], although obese-diabetic patients tended to have higher muscle glycogen content [32].

Taken together, evidence indicates metabolic dysfunction in skeletal muscle in patients with T2D, characterized by insulin resistance, impaired glycogen synthesis, lipid accumulation, and impaired mitochondrial function. Aging *per se* has an influence on skeletal muscle loss, but the metabolic impairment and functional losses can be largely counteracted by exercise training, especially by RT. Emerging research suggests that RT may influence age-related physiological changes and may impose potent and unique benefits in T2D. An overview of how RT may impact diabetes risk is presented graphically in Figure 1.

3. Implications of Resistance Training

Recent evidence indicates that RT has the power to combat metabolic dysfunction in obese, T2D patients [8, 33–35]. However, only one prospective study has examined the association of RT with risk of T2D. According to the Health Professionals Follow-up Study who observed >32,000 men over a period of 18 years, subjects engaging in RT over >150 min/week showed a 34% reduction in risk of T2D, after adjustment for aerobic activities and body mass index (BMI)

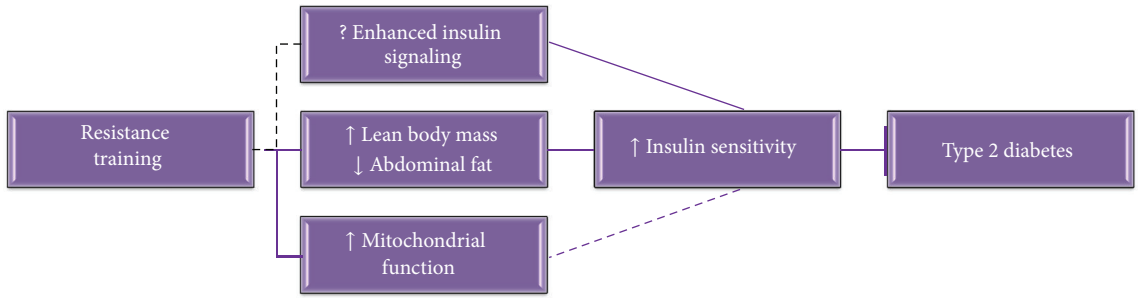

Figure 1: Schematic diagram of future directions to determine mechanisms by which resistance training (RT) increases insulin sensitivity and prevents type 2 diabetes (T2D).

[9]. In addition, those with a BMI ≥ 30 who engaged in RT ≥ 150 minutes per week exhibited an estimated 60% reduction in risk [9]. Thus, part of the beneficial effect of RT was mediated by abdominal adiposity as demonstrated in a previous analysis from the Health Professionals Follow-up Study [36]. Another interesting observation was the 40% reduction is risk in those without a family history of T2D; however, no effect was noted in those with family history. Resistance training may assist prevention and management of T2D by decreasing visceral fat and inflammatory markers [37, 38], increasing the density of GLUT4 [39], and improving insulin sensitivity as noted in a wide range of study groups and discussed in two recent reviews by Hurley et al. [34] and Flack et al. [40]. Acutely performed multiple sets and even single sets of RT increased 24-hour postexercise insulin sensitivity in subjects with impaired fasting glucose [41]. Three months of RT in obese, adolescent boys resulted in a significant reduction of total and visceral fat and intrahepatic lipid as well as increased insulin sensitivity compared with controls [42]. Although a recent systematic review reveals only a slight decrease in visceral fat with RT as the sole intervention in healthy or overweight/obese adults [35], studies have shown that regular RT is effective in reducing abdominal fat among individuals with T2D, even without significant weight loss [43, 44]. Thus, RT is contributing to the decrease of one of the major risk factors for insulin resistance. Resistance training can improve glycemic control and insulin sensitivity [45], likely even more than aerobic endurance training [46, 47]. In subjects with T2D, improvements in insulin sensitivity with RT, compared to sedentary control, have been noted without a change in maximal oxygen uptake ($VO_{2\,max}$), weight loss, or body composition [48]. It is possible that an increase in lean body mass after RT may be an important mediator of the improved glycemic control. An increase in the number of GLUT4 transporters is discussed specifically, because the transporter protein GLUT4 expression at the plasma membrane is related to fibre volume in human skeletal muscle fibres [49]. However, increased muscle mass was not associated with improvement in glycemic control in one of our in-house studies [50]. One possible reason is that improvement in glycemic control is not only dependent on muscle mass change but also on the consequence of intrinsic alterations in the muscle. Holten et al. reported improved insulin action by increased protein content of GLUT4, insulin receptor, protein kinase B-α/β, and glycogen synthase after six weeks of one-leg RT while the untrained leg remained unchanged [39]. Augmented glycemic control thus reduces the amount of insulin necessary to accomplish the clearance of a given amount of glucose. Castaneda et al. found that 16 weeks of RT three times per week increased muscle glycogen by 32% in older adults with T2D, whereas the control group experienced a significant reduction in muscle glycogen [51]. Resistance training can improve glucose transport in both normal and insulin-resistant skeletal muscle by enhancing the activation of the insulin signaling cascade [52]. These training-induced alterations improve the metabolic profile of the skeletal muscle and can occur independently of significant increases in skeletal muscle mass [53]. Dunstan et al. found decreased baseline glucose and insulin values in diabetic patients after 8 weeks of circuit weight training, 3 times a week at 55% 1RM when compared to nonexercising controls [54]. It seems that multiple RT programs are capable of improving insulin sensitivity. However, the effect of RT on insulin action is lost when the training is stopped [55]. Furthermore, because of reduced adherence and training intensity, home-based RT is less effective for maintaining glycemic control than supervised RT [56].

Glycosylated hemoglobin (HbA1c) is the most accepted parameter for assessing long-term glycemic control and is strongly associated with risk of diabetes, CVD, and death [57]. In a recent meta-analysis, aerobic, resistance, and combined exercise training were found to be associated with HbA1c reductions of 0.67% following 12 or more weeks of training [7]. In another meta-analysis of 10 included supervised resistance exercise studies, RT reduced HbA1c by 0.48% [8]. Bacchi et al. recently showed that 4 months of resistance and aerobic training were equally effective in improving hepatic fat content, insulin sensitivity, body fat mass, and HbA1C in adults with type 2 diabetes and NAFLD [58]. Ideally, both aerobic endurance training and RT should be combined in the exercise prescription for T2D and prediabetes. Recent research has identified that combining both forms of exercise of an equal caloric expenditure (12 kcal/kg/week) among combined and separate AET and RT groups may lead to

greater glycemic control benefits (−0.34%) that were not found with either type of training alone [59]. It is recommended that two or more RT sessions per week (2–4 sets of 8–10 repetitions) should be included in the total 210 or 125 min of moderate or vigorous exercise, respectively [4].

Mitochondrial dysfunction and fat accumulation in skeletal muscle (increased intramyocellular lipid content) have been linked to development of T2D [60, 61]. Only very few interventions evaluated the effects of a RT program on muscle lipid content in patients with T2D. Praet et al. reported in individuals with T2D no change in intramyocellular lipid content and muscle oxidative capacity after 10 weeks of RT, three times a week at 60% 1RM, combined with interval training (4–8 cycling bouts of 30 s, at 50–60% of the maximum achieved workload alternated with 60 s of unloaded cycling) [62]. In another study, 44 women with T2D were randomly assigned to three groups for a period of 12 weeks: RT (using elastic bands) at 40–55% of maximal strength five times per week; aerobic endurance training (walking) at moderate intensity five times per week; and control (asked to maintain a sedentary lifestyle) [63]. Changes in subcutaneous, subfascial, and intramuscular adipose tissue were similar among the three groups, but retinol-binding protein-4 which is linked to adipose tissue and insulin sensitivity in diabetics decreased significantly only with RT [63]. Resistance exercise training is an important countermeasure for aging-associated muscle weakness and increases muscle strength and function in older adults, in association with a reduction in markers of oxidative stress and an improvement in mitochondrial function [64]. Pesta and colleagues demonstrated that 10 weeks of RT enhanced mitochondrial respiration to the same extent as aerobic training in skeletal muscle of lean, previously sedentary adults [65]. The objective of a very recent study was to investigate effects of different types of exercise on mitochondrial content and substrate oxidation in individuals with T2D [66]. Patients were randomized to RT, aerobic training, combined training, or nonexercise control. The first significant finding of this investigation was the clear demonstration of an RT-induced increase in mitochondrial content in the skeletal muscle of T2D patients after 9 months of training, and these changes were significantly associated with clinical improvements (i.e., HBA1c, VO_{2max}). Furthermore, combined training improved all measures of lipid and carbohydrate oxidation as well as mitochondrial content and enzyme activity [66]. Thus, available evidence strongly suggests that the lower mitochondrial capacity associated with obesity, T2D, and aging is not an irreversible lesion. Either aerobic or resistance exercise, but not weight loss, has the power to improve mitochondrial content and possibly the function of the individual mitochondrion [67]. However, the link between mitochondrial oxidative capacity and insulin resistance remains inconclusive and requires further research.

Resistance exercise further increases excess postexercise oxygen consumption (EPOC) [68]. This increase in VO_2 after a RT session increases energy expenditure during the recovery period. EPOC after exercise is related to utilization of fat as fuel which is beneficial for weight loss [69]. Resistance training itself and EPOC, which, according to some studies, [70, 71] is higher after RT than after aerobic training, both contribute to an increase in energy expenditure and hence constitute important systemic factors which add to metabolic health.

4. Cellular and Molecular Mechanisms

It is well established that endurance exercise brings about numerous beneficial physiological changes such as increased maximal oxygen uptake (VO_{2max}) and cardiopulmonary fitness, as well as peripheral adaptations such as increased fatty acid transport and oxidation, improved capillary density, and mitochondrial capacity [72]. In this section, the molecular mechanisms that lead to adaptation in skeletal muscle in response to RT and that are associated with possible beneficial metabolic responses will be discussed.

One hallmark of strength and resistance training is an increase in muscle strength and muscle mass, mediated mainly via muscle hypertrophy and neuromuscular remodeling. As already mentioned above, RT can increase insulin sensitivity by qualitative changes independent of a gain in muscle mass. It is well established, however, that body sensitivity to insulin is directly proportional to muscle mass. Gain in muscle mass must therefore remain an important goal in RT for patients. In addition, increase of lean mass leads to an increased resting metabolic rate [73], therefore possibly triggering an upward spiral of metabolic health.

4.1. Mechanisms Responsible for an Increase in Muscle Mass. One of the main pathways responsible for muscle hypertrophy via increased protein synthesis is the IGF-1/PI3K/AKT pathway. Its ligand, insulin-like growth factor 1 (IGF-1), is a well characterized growth promoting factor and plays a crucial role in muscle growth and regeneration. Upon ligand binding to the IGF-1 receptor, several intracellular signaling events finally lead to a phosphorylation of Thr308 residues on AKT to activate AKT [74]. Activated AKT can then act on downstream proteins such as the forkhead box O (FoxO) transcription factor family. FoxO is an important player involved in integrated cellular responses such as protein metabolism [75]. AKT mediates FoxO phosphorylation and repression of this transcription factor which leads to inhibition of protein degradation.

AKT stimulates protein synthesis via mammalian target of rapamycin (mTOR). The mTOR complex consists of two multiprotein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), each of them exhibiting different sensitivities to rapamycin [76]. Activation of mTORC1 leads to phosphorylation of ribosomal protein S6 as well as other factors involved in translation initiation and elongation which results in increased protein synthesis [74].

Next to a change in cross-sectional area and muscle mass, RT also induces a shift in the muscle fiber type distribution from low-oxidative type 2x muscle fibers to moderate-oxidative, more insulin-sensitive type 2a muscle fibers [77].

4.2. Mechanisms Mediating Increased Glucose Clearance. Important for the beneficial metabolic effect of RT is stimulation of glycogen synthesis via inhibition of glycogen synthase kinase 3β (GSK3) by AKT [78]. GSK3β regulates glucose storage in the form of glycogen. AKT can inhibit GSK3 by phosphorylating it at a serine residue (Ser9 in GSK3β). Inhibition of GSK3 promotes activation of glycogen synthase (GS) which contributes to the stimulation of glycogen synthesis. Glycogen synthase is the enzyme responsible for catalyzing the $\alpha(1 \rightarrow 4)$ linkage in the formation of glycogen and is therefore important for nonoxidative glucose disposal. Increased AKT-mediated GS activity is therefore an important adaptation towards glycemic control in response to RT.

It has been observed that AMPK activity is increased as an acute exercise phenotype-specific response to RT [79]. This activation leads to reduced phosphorylation of 4E-BP1 and decreased mTOR signaling. The AMPK-mediated inhibition of mTOR may prevent muscle protein synthesis during resistance exercise. After exercise, inhibition is released and protein synthesis can occur in the muscle [79]. This transient activation of AMPK could possibly lead to phosphorylation of target proteins involved in a number of metabolic pathways which result in an increase of ATP generating pathways such as glucose uptake via increased GLUT4 translocation and fatty-acid oxidation [80]. Hyperinsulinemia decreases beta-oxidation in insulin resistant subjects and therefore reduces the utilization of fatty acids [81]. The insulin-sensitizing effect of RT releases the brake on beta-oxidation and contributes to improved metabolic flexibility and a more balanced utilization of fatty acids as substrates. Increased insulin sensitivity might therefore contribute to increased lipid clearance from the blood. Increased insulin receptor protein expression in response to RT might be another important adaptation responsible for the insulin-sensitizing effect of training [39]. These adaptations might be responsible for restoring metabolic flexibility in T2D in response to RT.

5. Conclusion

There is good evidence that RT improves insulin sensitivity and glucose tolerance and therefore seems to be an effective measure to improve overall metabolic health and reduce metabolic risk factors in diabetic patients. Detailed mechanisms of RT induced adaptations that contribute to an improved metabolic profile remain elusive. It also remains to be determined whether the mechanisms by which RT improves glycemic control are the same as those that affect improvements after endurance training. Increased energy expenditure and excess postexercise oxygen consumption in response to RT may be important systemic factors contributing to metabolic health. The beneficial effects of RT are promising. This is of significant interest as RT can be viewed as a suitable training modality in our time-poor society. In contrast to traditional high-volume endurance training, high-intensity/low-volume RT can be a time-efficient strategy to offer metabolic benefits. Positive effects of RT not only benefit diabetic patients but can also significantly improve quality of life of the elderly who are often suffering from sarcopenia and muscle weakness.

Conflict of Interests

The authors declare no conflict of interests.

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Clinical Study

Baseline Obesity Status Modifies Effectiveness of Adapted Diabetes Prevention Program Lifestyle Interventions for Weight Management in Primary Care

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Objective. To examine whether baseline obesity severity modifies the effects of two different, primary care-based, technology-enhanced lifestyle interventions among overweight or obese adults with prediabetes and/or metabolic syndrome. *Patients and Methods*. We compared mean differences in changes from baseline to 15 months in clinical measures of general and central obesity among participants randomized to usual care alone ($n = 81$) or usual care plus a coach-led group ($n = 79$) or self-directed individual ($n = 81$) intervention, stratified by baseline body mass index (BMI) category. *Results*. Participants with baseline BMI 35+ had greater reductions in mean BMI, body weight (as percentage change), and waist circumference in the coach-led group intervention, compared to usual care and the self-directed individual intervention ($P < 0.05$ for all). In contrast, the self-directed intervention was more effective than usual care only among participants with baseline BMIs between $25 \leq 35$. Mean weight loss exceeded 5% in the coach-led intervention regardless of baseline BMI category, but this was achieved only among self-directed intervention participants with baseline BMIs < 35. *Conclusions*. Baseline BMI may influence behavioral weight-loss treatment effectiveness. Researchers and clinicians should take an individual's baseline BMI into account when developing or recommending lifestyle focused treatment strategy. This trial is registered with ClinicalTrials.gov (NCT00842426).

1. Introduction

Obesity remains a pressing public health problem with adverse medical, psychological, social, and economical consequences. Nearly 70% of US adults are overweight (body mass index [BMI] in kg/m^2 $25 \leq 30$) or obese (BMI ≥ 30), with 36% obese [1]. More alarming still, the 6.3% prevalence of severely obesity (BMI $\geq$ 40) [1] is projected to increase by 130% over the next 2 decades [2]. Although bariatric surgery is the recommended treatment for severely obese individuals and/or moderately obese individuals (BMI $35 \leq$ 40) with comorbidities [3], its implementation is limited by access, cost, recidivism, and complications [4, 5]. Only 1%-2% of obese people eligible for insurance coverage of surgical treatment receive it, compelling an urgent need of alternative treatment strategies for this subpopulation [6]. Weight loss medications have had limited effectiveness, some serious adverse effects, and limited uptake [7].

Emerging data find intensive lifestyle interventions—focusing on calorie-reduced, healthful eating, increased physical activity, and self-management skills training—can lead to clinically significant weight loss in the short [8–10] and long term [10, 11] among individuals with a BMI ≥ 35, who also achieve improvements in cardiovascular disease (CVD) risk factors even despite persistent, albeit reduced, obesity after intervention. Despite a recent and renewed interest in examining the efficacy of intensive behavior therapy for obesity within higher BMI subcategories [12], very few studies have evaluated the comparative effectiveness of evidence-based, empirical lifestyle interventions in real-world settings by baseline obesity status. Implementation of efficacious but resource-intensive, research-based lifestyle

Table 1: E-LITE[a] intervention: key components and features.

	Coach-led intervention	Self-directed intervention
(1) 12-week core curriculum sessions[b]	Clinic-based, small groups	Home-based DVD
(2) Online self-monitoring of weight and physical activity[c]	Preferably daily but at least twice weekly; coach routinely reviewed records	Preferably daily but at least twice weekly; coach did not routinely review records
(3) Personalized lifestyle coaching[d]	Proactive, coach-initiated	As needed, patient-initiated

[a]E-LITE: Evaluation of lifestyle interventions to treat elevated cardiometabolic risk in primary care.

[b]Diabetes Prevention Program (DPP) investigators at the University of Pittsburgh developed the Group Lifestyle Balance (GLB) program following the DPP trial [13]. Its curriculum is publicly available online [14].

[c]Via the American Heart Association's free, secure Heart360 Web portal (http://www.heart360.org/).

[d]Via secure provider-patient online messaging embedded in a fully functional electronic health record system. Coaches could view Heart360 patient self-monitoring records, which they reviewed regularly and used to tailor their ongoing progress feedback via secure messaging for participants in the coach-led intervention.

interventions into real-world settings remains a challenge. Efforts have been made to facilitate this process while retaining essential components of efficacious interventions [13]. However, these same efforts have resulted in wide variation in intervention setting, structure, intensity and form of contact, and resources required—and (unsurprisingly) they have produced mixed results regarding clinical effectiveness. Improved ability to implement targeted interventions for readily defined subgroups of the intended population may result in more efficient and effective use of resources.

The "Evaluation of Lifestyle Interventions to Treat Elevated Cardiometabolic Risk in Primary Care" (E-LITE) study was one of few pragmatic randomized controlled trials that successfully translated the Diabetes Prevention Program (DPP) lifestyle intervention into a primary care setting in the US. Published E-LITE data have demonstrated that two adapted, technology-enhanced DPP interventions (further described in Section 2)—one using a self-directed approach and the other a coach-led approach—were both superior to usual care, whereas the coach-led intervention was superior to the self-directed one, in promoting weight loss among overweight or obese adults with prediabetes and/or metabolic syndrome [15]. The primary aim of the current study was to examine whether changes in clinical measures of general and abdominal obesity differed by baseline BMI category when comparing the two interventions to usual care and to each other. We hypothesized that baseline BMI modified participant response to treatment such that participants with baseline BMI 35+ would benefit from the more structured, coach-led intervention, whereas those with lower starting BMI would respond to either coach-led or self-directed intervention.

2. Materials and Methods

Complete E-LITE trial protocol and methods were published previously [16]. Data collection occurred in 2009–2011. Below we describe methodological details relevant to this study.

2.1. Study Population and Measures. Participants were recruited (July 2009–June 2010) from a single primary care clinic that is part of a large multispecialty group practice in the San Francisco Bay Area. All data collection and intervention visits occurred at the clinic. Inclusion criteria included an age of at least 18 years, a BMI of at least 25, and the presence of prediabetes (defined by impaired fasting plasma glucose level of 100 to 125 mg/dL) or metabolic syndrome. Major exclusion criteria included serious medical or psychiatric conditions (e.g., stroke, psychotic disorder) or special life circumstances (e.g., pregnancy). Eligible and consenting overweight or obese adults with prediabetes and/or metabolic syndrome seen in primary care were randomized to receive usual care alone ($n = 81$) or usual care plus a coach-led ($n = 79$) or self-directed ($n = 81$) behavioral weight-loss intervention. Height was measured at baseline only, and weight and waist circumference were measured at baseline and at 3, 6, and 15 months. Measurements were taken in duplicate per standardized protocols [17, 18]. Body mass index was calculated. Change in BMI from baseline to 15 months was the trial primary outcome [15].

2.2. Intervention. The E-LITE study innovatively integrated the DPP-based Group Lifestyle Balance (GLB) core curriculum [13], which has been recognized by the Centers for Disease Prevention and Control's National Diabetes Prevention Program, with lifestyle coaching and self-management support via high-reach, affordable technologies. Both E-LITE interventions adopted the DPP's weight loss and physical activity goals [19] and delivered the GLB core curriculum for 12 weeks during the intensive treatment phase either through a self-directed, take-home DVD or coach-led, in-clinic small groups. The interventions also provided electronically mediated lifestyle coach contact and online self-monitoring of weight and physical activity goal attainment during a 12-month maintenance phase. Table 1 summarizes the key components and features of the E-LITE self-directed and coach-led interventions.

2.3. Statistical Analyses. Baseline characteristics of each study group by baseline BMI category ($25 \leq 30$, $30 \leq 35$, or 35+) were examined using analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables. Between-group differences by baseline BMI category at 15 months were evaluated by intention-to-treat using all available data and tests of group by baseline BMI category interactions in repeated-measures mixed models. A

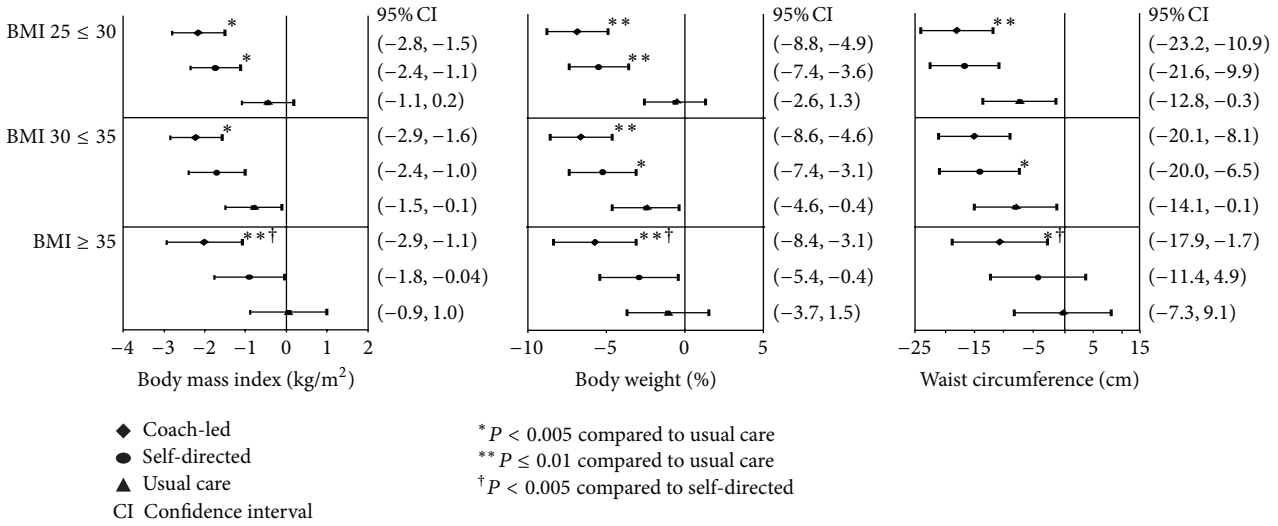

Figure 1: Outcomes by baseline body mass index category and intervention type.

separate model examined change in each of the 3 obesity outcome variables: BMI and percent body weight change for general obesity and waist circumference for abdominal obesity. The group by baseline BMI category interaction terms were significant for all three outcomes ($P < 0.001$). As in the main study [15], these models were adjusted for age, sex, race, and ethnicity, and missing data were handled directly through maximum likelihood estimation via mixed modeling. Model-based least-square mean changes and 95% confidence intervals (CIs) were obtained. All analyses were conducted using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

3. Results and Discussion

3.1. Results. Table 2 shows baseline sample characteristics, stratified by baseline BMI. No significant differences in baseline characteristics were detected between participants in each treatment group. The coach-led intervention resulted in significantly greater mean reductions from baseline to 15 months in BMI (ranging from $-2.0\,kg/m^2$, 95% CI [$-2.9\,kg/m^2$, $-1.1\,kg/m^2$] in the BMI 35+ category to $-2.2\,kg/m^2$, 95% CI [$-2.9\,kg/m^2$, $-1.6\,kg/m^2$] in the BMI 30 ≤ 35 category) and percent body weight change (ranging from −6.8%, 95% CI [−8.8%, −4.9%] in the BMI 25 ≤ 30 category to −5.7%, 95% CI [−8.4%, −3.1%] in the BMI 35+ category) for all three baseline BMI categories, and in waist circumference for the BMI 25 ≤ 30 (−17.1 cm, 95% CI [−23.2 cm, −10.95 cm]) and 35+ (−9.78 cm, 95% CI [−17.9 cm, −1.7 cm]) categories ($P < 0.05$ versus usual care for all; Figure 1). The coach-led group achieved a mean percentage weight loss exceeding 5%, a commonly accepted threshold of clinically significant weight loss, and the upper 95% confidence limit was at least 3% weight loss, across the baseline BMI categories.

The self-directed intervention led to greater improvements in BMI ($P = 0.03$ versus usual care) only for the BMI 25 ≤ 30 category ($-1.7\,kg/m^2$, 95% CI [$-2.4\,kg/m^2$, $-1.1\,kg/m^2$]), in percentage weight loss for the BMI 25 ≤ 30 (−5.5%, 95% CI [−7.4%, −3.6%]; $P < 0.0001$ versus usual care) and 30 ≤ 35 (−5.2%, 95% CI [−7.4%, −3.1%]; $P = 0.02$ versus usual care) categories, and in waist circumference for the BMI 30 ≤ 35 category (−13.2 cm, 95% CI [−20.0 cm, −8.1 cm]; $P = 0.03$). In the self-directed group mean weight loss reached 5% only among those with a baseline BMI of < 35. Moreover, reductions in BMI ($P = 0.01$), weight as percentage change ($P = 0.04$), and waist circumference ($P = 0.04$) were significantly greater in the coach-led versus self-directed intervention within the BMI 35+ category, whereas the two interventions did not differ significantly for any of the three obesity measures in the two lower BMI categories.

3.2. Discussion. Efficacy research has unequivocally shown that intensive, highly structured, individual lifestyle intervention lowers cardiometabolic risk [20]. The unabated obesity epidemic and its associated health problems and rising societal and economical burdens compel the urgency of adapting proven, albeit expensive, interventions into increasingly resource-limited real-world settings while striving to retain the effectiveness of the original treatment. The current findings show that the effects of the successful E-LITE coach-led and self-directed interventions in primary care differed by starting obesity status, suggesting that one size may not fit all when it comes to lifestyle interventions.

Notably participants with moderate or severe obesity (baseline BMI 35+) had greater reductions in all three obesity measures (BMI, percentage weight loss, and waist circumference) in the coach-led intervention, but not in the self-directed intervention, compared with usual care. They also responded more favorably to the coach-led intervention compared to the self-directed intervention. In contrast, overweight participants (baseline BMI 25 ≤ 30) had similar mean BMI and percent body weight reductions in the two active interventions, both of which were more effective than usual care. Similarly, the coach-led intervention had no apparent

Table 2: Baseline characteristics of the study participants[a].

Characteristic	All	Usual care	Coach-led	Self-directed	F/χ^2 (degree of freedom)	P value
Body mass index 25 ≤ 30						
Age, year	53.8 ± 10.5	53.7 ± 10.3	54.7 ± 10.9	53.1 ± 10.6	0.22 (2, 108)	0.80
Female, %	32.4	32.4	33.3	31.6	0.03 (2)	0.99
Race/ethnicity, %					3.29 (6)	0.77
Non-Hispanic white	72.1	75.7	66.7	73.7		
Asian/Pacific Islander	22.5	18.9	27.8	21.1		
Latino/Hispanic	4.5	5.4	5.6	2.6		
College level or above, %	97.2	97.2	94.3	100.0	2.22 (2)	0.33
Income, %					6.62 (6)	0.36
<$75,000	10.3	13.9	8.8	8.1		
$75,000–$124,999	30.8	27.8	41.2	24.3		
$125,000–$149,999	15.9	8.3	20.6	18.9		
$150,000+	43.0	50.0	29.4	48.6		
Weight, kg	83.8 ± 9.9	85.4 ± 9.1	82.6 ± 10.2	83.5 ± 10.6	0.77 (2, 108)	0.46
Waist, cm	98.8 ± 6.4	98.3 ± 6.4	98.0 ± 6.4	100.1 ± 6.4	1.14 (2, 108)	0.32
Fasting plasma glucose, mg/dL	100.3 ± 9.3	99.9 ± 9.5	101.4 ± 9.3	99.6 ± 9.2	0.39 (2, 108)	0.68
Prediabetes, %	56.8	62.2	61.1	47.4	2.08 (2)	0.35
Metabolic syndrome, %	80.2	67.6	88.9	84.2	5.81 (2)	0.06
Prediabetes and metabolic syndrome, %	36.9	29.7	50.0	31.6	3.93 (2)	0.14
Body mass index 30 ≤ 35						
Age, year	54.0 ± 10.8	54.5 ± 11.1	55.3 ± 12.9	52.3 ± 7.9	0.51 (2, 72)	0.60
Female, %	50.7	44.0	50.0	58.3	1.01 (2)	0.60
Race/ethnicity, %					5.25 (6)	0.51
Non-Hispanic white	80.0	80.0	80.8	79.2		
Asian/Pacific Islander	14.7	16.0	7.7	20.8		
Latino/Hispanic	4.0	4.0	7.7	0.0		
College level or above, %	97.3	96.0	96.2	100.0	0.97 (2)	0.62
Income, %					5.16 (6)	0.52
<$75,000	12.5	8.7	15.4	13.0		
$75,000–$124,999	23.6	30.4	23.1	17.4		
$125,000–$149,999	9.7	0.0	15.4	13.0		
$150,000+	54.2	60.9	46.2	56.5		
Weight, kg	94.2 ± 13.8	94.2 ± 12.9	97.2 ± 14.5	91.0 ± 13.8	1.26 (2, 72)	0.29
Waist, cm	106.7 ± 8.1	106.2 ± 8.9	109.2 ± 7.1	104.4 ± 7.9	2.35 (2, 72)	0.10
Fasting plasma glucose, mg/dL	100.3 ± 10.4	98.7 ± 8.6	100.4 ± 10.9	101.8 ± 11.6	0.52 (2, 72)	0.60
Prediabetes, %	50.7	44.0	50.0	58.3	1.01 (2)	0.60
Metabolic syndrome, %	88.0	92.0	80.8	91.7	1.97 (2)	0.37
Prediabetes and metabolic syndrome, %	38.7	36.0	30.8	50.0	2.06 (2)	0.36
Body mass index 35+						
Age, year	49.7 ± 10.1	47.4 ± 10.6	53.4 ± 8.5	48.6 ± 10.4	1.79 (2, 52)	0.18
Female, %	69.1	73.7	76.5	57.9	1.74 (2)	0.42
Race/ethnicity, %					2.58 (4)	0.63
Non-Hispanic white	87.3	78.9	94.1	89.5		
Asian/Pacific Islander	9.1	15.8	5.9	5.3		
Latino/Hispanic	3.6	5.3	0.0	5.3		
College level or above, %	98.2	94.7	100.0	100.0	1.93 (2)	0.38
Income, %					5.15 (6)	0.52
<$75,000	14.8	10.5	23.5	11.1		
$75,000–$124,999	22.2	26.3	29.4	11.1		
$125,000–$149,999	13.0	10.5	5.9	22.2		
$150,000+	50.0	52.6	41.2	55.6		

Table 2: Continued.

Characteristic	All	Usual care	Coach-led	Self-directed	F/χ^2 (degree of freedom)	P value
Weight, kg	113.4 ± 18.2	116.0 ± 20.0	111.6 ± 15.0	112.6 ± 19.4	0.29 (2, 52)	0.75
Waist, cm	120.1 ± 10.9	121.9 ± 11.7	117.3 ± 9.7	120.4 ± 11.4	0.78 (2, 52)	0.46
Fasting plasma glucose, mg/dL	98.7 ± 8.6	98.7 ± 8.7	98.7 ± 9.3	98.8 ± 8.3	0.00 (2, 52)	0.99
Prediabetes, %	54.5	52.6	58.8	52.6	0.18 (2)	0.91
Metabolic syndrome, %	98.2	100.0	94.1	100.0	2.28 (2)	0.32
Prediabetes and metabolic syndrome, %	52.7	52.6	52.9	52.6	0.0005 (2)	0.99

[a]Plus-minus values are means ± SD.

incremental benefit over the self-directed intervention for participants with a baseline BMI of 30 ≤ 35, although they led greater reductions in percentage weight loss and BMI (coach-led) or waist circumference (self-directed) compared with usual care. These results imply that the self-directed intervention can be an effective and efficient alternative to the coach-led intervention for overweight individuals with prediabetes and/or metabolic syndrome but that individuals with the same cardiometabolic risk factors who are moderately or severely obese may only benefit from the latter, more structured approach. These findings add to recent evidence that suggests a structured, intensive—and yet practical—lifestyle intervention is indicated for increased degree of obesity [10, 21], as opposed to a less structured, self-directed approach.

Previously, in the absence of empirical evidence, lifestyle intervention was thought to be ineffective in severely obese individuals [22] but has recently been recognized as a promising approach among this subpopulation [3, 8–12], especially given the risk of postoperative complications, recidivism, and limited reach of surgical options [4, 5, 8]. Modest weight loss for individuals who are overweight or obese (5%–10% reduction in total body weight) has been shown to produce health benefits such as improvement in blood pressure, cholesterol and dysglycemia [19, 23, 24] and was achieved among all participants in the coach-led intervention, including those whose baseline BMI was ≥ 35. A randomized controlled trial by Goodpaster et al. showed that an intensive behavioral weight-loss intervention was effective for severely obese adults and that modest weight reduction, even despite persistent severe obesity, significantly improved cardiovascular risk factors in this population [9]. A secondary analysis of data from the Look AHEAD trial found that nearly 40% of severely obese participants in the intensive, DPP-like lifestyle intervention lost ≥10% of initial weight at 1 year [8], and 26% were able to maintain this weight loss at year 4 [11].

This is the first study, to our knowledge, that suggests the potential effectiveness of a coach-led, technology-enhanced DPP translation intervention in reducing obesity among adults at high risk of Type 2 diabetes and CVD with a BMI of 35 or above. This is a growing segment of the overall population for which surgery is currently recommended; however, surgery cannot be the only solution to an epidemic. It is imperative that alternative strategies are developed that are effective, accessible, and affordable with potential for broad reach and impact. Equally important, our study suggests that the low cost, self-directed intervention can be a viable alternative to the coach-led intervention for high-risk adults with a BMI less than 35. The increased efficiency and reach of the self-directed intervention makes it an appealing public health intervention strategy.

Future studies are needed to explore factors that may modify or mediate the effectiveness of lifestyle interventions among persons with moderate or severe obesity. Potential effect modifiers include sociodemographic characteristics (e.g., sex, race/ethnicity, and education), comorbidity (e.g., severity of coexisting chronic conditions), and community/societal resources (e.g., accessibility of grocery stores or farmers market, neighborhood walkability, and social norms). Possible effect mediators include outcome expectancy, self-efficacy, social support, and self-monitoring, which are theory-based variables that have been shown to predict weight loss in diverse populations [25, 26].

The present findings should be interpreted with consideration of several study limitations. This was a secondary data analysis, and all findings warrant replication in future confirmatory research. The sample size for each BMI-by-treatment subgroup was small, and the trial duration was only 15 months. However, the effect size confidence intervals and data consistency across the three obesity outcome measures suggest that the E-LITE coach-led intervention may have clinically significant benefits beyond usual care for moderately and severely obese adults at high cardiometabolic risk that are worth further investigation in fully-powered, longer-term studies. Also, the generalizability of the current findings may be limited by a rather homogenous study sample in terms of race/ethnicity and socioeconomic status, and participants were recruited from a single primary care clinic. Future research is needed to confirm the generalizability of our findings to more ethnically and socioeconomically diverse populations.

4. Conclusion

In conclusion, baseline obesity status may influence behavioral weight loss treatment effectiveness. Less resource intensive approaches are perhaps adequate for individuals with lower baseline BMI in the overweight and obesity continuum, whereas the incremental benefit of more intensive, structured lifestyle change programs may not be evident except for those with higher BMI indicative of moderate or severe obesity. If confirmed in future definitive study, these findings would suggest that researchers and clinicians should take

an individual's baseline BMI into account when developing or recommending a weight-loss treatment strategy. Understanding how to best allocate healthcare resources in weight-loss treatment may ultimately result in improved quality and affordability of obesity care.

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