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Pediatric Congenital Heart Disease (G Singh, Section Editor)

Childhood Obesity and Insulin Resistance: How Should It Be Managed?

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Opinion statement

Concomitant with the rise in global pediatric obesity in the past decades, there has been a significant increase in the number of children and adolescents with clinical signs of insulin resistance. Given insulin resistance is the important link between obesity and the associated metabolic abnormalities and cardiovascular risk, clinicians should be aware of high risk groups and treatment options. As there is no universally accepted biochemical definition of insulin resistance in children and adolescents, identification and diagnosis of insulin resistance usually relies on clinical features such as acanthosis nigricans, polycystic ovary syndrome, hypertension, dyslipidemia, and non-alcoholic fatty liver disease. Treatment for reducing insulin resistance and other obesity-associated comorbidities should focus on changes in health behaviors to achieve effective weight management. Lifestyle interventions incorporating dietary change, increased physical activity, and decreased sedentary behaviors, with the involvement of family and adoption of a developmentally appropriate approach, should be used as the first line treatment. Current evidence suggests that the primary objective of dietary interventions should be to reduce total energy intake and a combination of aerobic and resistance training should be encouraged. Metformin can be used in conjunction with a lifestyle intervention program in obese adolescents with clinical insulin resistance to achieve weight loss and to improve insulin sensitivity. Ongoing evaluation and research are required to explore optimal protocol and long-term

effectiveness of lifestyle interventions, as well as to determine whether the improvements in insulin sensitivity induced by lifestyle interventions and weight loss will lead to a clinical benefit including reduced cardiovascular morbidity and mortality.

Introduction

Pediatric obesity is a major worldwide health issue. A review of the global trends in obesity in 25 countries for school-age children and in 42 countries for preschool age children, based on studies published from January 1980 to October 2005, shows that the prevalence of childhood overweight has increased in almost all countries [1]. The prevalence of overweight doubled and that of obesity tripled in many countries in most regions, including the Americas (Canada, US, Brazil, and Chile), Europe (Finland, Germany, Greece, Spain, and UK), Australia, and Japan. More than 20 % of children and adolescents in the Americas, Europe, Australia, and the Eastern Mediterranean are overweight and obese. In 2010, it was estimated that, worldwide, 43 million preschool children (35 million in developing countries) were overweight and obese [2]. Concomitant with the rise in pediatric obesity in the last three decades, there has been a significant increase in the number of children and adolescents with clinical signs of insulin resistance (IR). IR is believed to be an important link between obesity and the associated metabolic abnormalities and cardiovascular risk [3, 4]. Therefore, it is essential that children and adolescents with clinical IR are targeted for early intervention. Unmanaged, they are likely to progress to type 2 diabetes (T2DM) and early atherosclerosis [5].

Insulin resistance and type 2 diabetes

IR or reduced insulin sensitivity refers to an impaired function of insulin in mediating glucose uptake, transport, and storage. IR plays a major pathophysiological role in type 2 diabetes (T2DM). In healthy individuals, a balance exists between glucose utilization and glucose production. With the development of IR, the individual progresses to impaired glucose tolerance (pre-diabetes) and finally to T2DM when the pancreatic β-cell reserve diminishes.

Once regarded as a disease of adult populations, T2DM is increasingly prevalent among children and adolescents. The prevalence of pre-diabetes/T2DM in the US adolescents increased from 9 % in 1999–2000 to 23 % in 2007–2008 [6]. Secondary data analysis of 12 years of data (1999–2010) from the US Continuous National Health and Nutrition Examination Survey (NHANES) indicated that T2DM accounted for 43 % of all adolescent diabetes cases in the US, one-third of which were undiagnosed [7•] In some Asian countries, up to 80 % of all new cases of diabetes in children and adolescents are diagnosed as T2DM [8]. In high-risk ethnic groups, such as Australian Aborigines and South East Asians, T2DM appears to be taking over from type 1 diabetes as the predominant cause of diabetes in children and adolescents.

T2DM in adults is associated with significant morbidity, including an increased risk of heart diseases and stroke, hypertension, retinopathy and blindness, end-stage renal disease, and neuropathy leading to amputations [9]. The development of T2DM in young people is of particular concern

because life-long chronic complications are common, and the younger the age of onset, the greater the potential for complications to occur [10, 11••]. There is emerging evidence showing that young-onset T2DM is the more lethal phenotype of diabetes, associated with more unfavorable cardiovascular risk factors, a higher prevalence and earlier occurrence of albuminuria, peripheral neuropathy and macrovascular complications, and a lower quality of life, compared with type 1 diabetes [11••, 12, 13].

Pathogenesis of obesity and insulin resistance-related cardiovascular complications

Obesity and IR promote release of free fatty acids and various adipokines from adipocytes, which lead to acute changes in vascular reactivity and chronic endothelial injury through inflammatory responses and oxidative stress [14]. Furthermore, IR is associated with disruption of endothelial nitric oxide activation [15]. Nitric oxide plays an important role in vasodilatory signaling and detoxification of reactive oxygen species, hence preventing endothelial damage and platelet aggregation. However, in individuals with IR, the insulin-regulated endothelial nitric oxide synthase activity may be disrupted, resulting in impaired vasodilation, impaired thrombolysis, and unchecked reactive oxygen species, all of which impact negatively on endothelial function and structure.

Moreover, both obesity and IR are associated with traditional cardiovascular risk factors such as hypertension and dyslipidemia, leading to the development of atherosclerotic cardiovascular diseases. Data from the landmark Bogalusa Heart Study indicate that overweight children are 12.6, 7.1, and 2.4 times more likely to have elevated fasting insulin concentration, triglyceride level, and diastolic blood pressure, respectively, than their lean peers, and these risks increased with the severity of obesity [16, 17]. Importantly, child and adolescent obesity is strongly associated with a clustering of cardiometabolic risks, and both obesity and obesity-related cardio-metabolic risk factors show a strong tracking effect from childhood into adulthood [17–19]. The US data suggest that obese adolescents have an 80 % to 90 % chance of becoming obese adults, and obese adults who were overweight as adolescents have a higher morbidity and mortality rate from coronary heart disease than those adults who only become obese in adulthood [20, 21].

Measurement of insulin sensitivity in children and adolescents

Various techniques are available for assessing insulin sensitivity, ranging from the more invasive euglycemic hyperinsulinemic clamp, to less invasive methods based on the oral glucose tolerance test, to surrogate measurements calculated from a single fasting blood sample. The euglycemic hyperinsulinemic clamp is regarded as the "gold-standard" for directly measuring whole body insulin sensitivity and β-cell function in humans. However, this method is relatively invasive, labor-intensive, and expensive, and is not practical for epidemiologic studies, screening, or routine assessment. The homeostasis model assessment of insulin resistance (HOMA-IR,

calculated as fasting insulin (μU/mL)*fasting glucose (mmol/L)/22.5), is the most widely used surrogate measure of insulin sensitivity in children and adolescents. However, the whole body insulin sensitivity index or Matsuda index [22], obtained from the oral glucose tolerance test, is noted to better capture improvements in insulin sensitivity in adolescents than fasting measures such as fasting insulin and HOMA-IR, as it includes both fasting measured glucose and insulin and the response to a glucose load [23]. Hence, the Matsuda index is a preferred measure of insulin sensitivity in longitudinal studies. Despite the intense clinical and research interest in IR, no universally accepted definition for IR has been established for children and adolescents [24••].

Clinical features of insulin resistance in children and adolescents

Multiple clinical characteristics related to IR and compensatory hyperinsulinemia can help to identify children and adolescents with IR. These include acanthosis nigricans, polycystic ovary syndrome, hypertension, dyslipidemia, and nonalcoholic fatty liver disease.

Acanthosis nigricans

Acanthosis nigricans is a thickened and pigmented skin lesion in the flexural areas and is associated with high levels of insulin, indicative of IR (Fig. 1), especially in people with pigmented skin. Common sites of involvement include the axillae, posterior region of the neck, elbow, knuckles, and groins. The severity of acanthosis nigricans correlates well with the degree of IR [25].

Polycystic ovary syndrome (PCOS)

PCOS is a common obesity-related comorbidity in adolescent girls. PCOS is characterized by features of ovulatory dysfunction, hyperandrogenism (acne, hirsutism, or alopecia), and polycystic ovarian morphology [26]. IR is present in a majority of obese PCOS cases, with compensatory hyperinsulinemia contributing to hyperandrogenism via stimulation of ovarian androgen secretion and inhibition of hepatic sex hormone-binding globulin production.

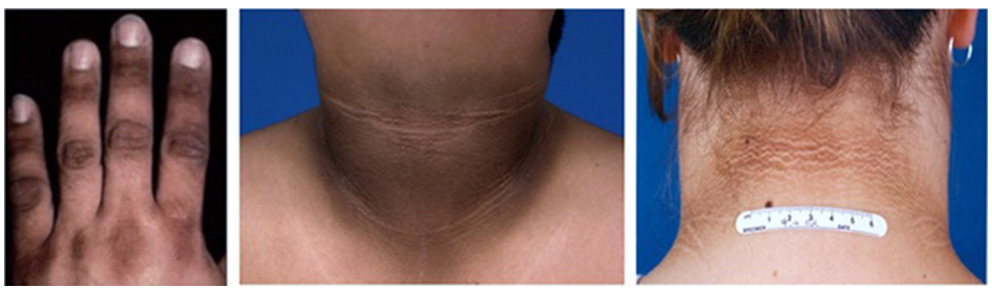

Fig. 1. Acanthosis nigricans is an important clinical sign of insulin resistance.

Nonalcoholic fatty liver disease (NAFLD)

NAFLD is common among obese children and adolescents and is associated with both hepatic and peripheral IR. IR has been proposed as the driving force of lipid deposition in the liver [27]. In a retrospective analysis of 43 children with biopsy-proven NAFLD, 95 % had IR [28]. A recent cross-sectional study showed that the presence of NAFLD determined by magnetic resonance imaging was associated with a 55 % lower insulin sensitivity and a twofold greater prevalence of metabolic syndrome in overweight and obese adolescents aged 13–18 years [29].

Hypertension and dyslipidemia

IR is also related to the development of hypertension and/or an abnormal lipid profile, characterized by elevated triglycerides, low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C) in overweight and obese children and adolescents.

Risk factors for developing insulin resistance

Various risk factors are associated with IR and the development of T2DM in children and adolescents. There is a complex interplay of genetic predisposition and environmental and behavioral factors.

Obesity

Obesity represents the major and most common cause of IR in both adult and pediatric populations [24••]. Analysis of the US NHANES 1999–2000 data indicated that the prevalence of IR was 3 % among healthy weight adolescents aged 12–19 years, but 15 % among those who were overweight and 52 % among those who were obese [30].

Ethnicity

Youth with African-American, Hispanic, Asian, Indian, Middle Eastern, and Arabic origin have a higher risk of IR, pre-diabetes, and T2DM [31, 32]. T2DM, pre-diabetes and IR are also more common in Indigenous Australian and Pacific Islander youth than in the general Australian population [33, 34]. Importantly, T2DM is not just more common in Indigenous Australians; it occurs at a younger age [35] and lower BMI [36] than in non-Indigenous Australians.

Family history

Children with a positive family history of T2DM are more likely to have IR and pre-diabetes than those without a family history of diabetes [37]. Many youth who develop T2DM have at least one parent with diabetes (45 %–80 %) and a first- or second-degree relative (74 %–100 %) with T2DM [32, 38].

Intrauterine and postnatal factors

Fetal and early life nutritional programming might contribute to susceptibility to obesity, IR, β-cell dysfunction, and T2DM in childhood and later

life. Studies have demonstrated a U-shaped relationship between birth weight and the risk of future T2DM, in which children born small for gestational age [39] or large for gestational age [40] are both associated with an increased risk of lower insulin sensitivity and of T2DM than their peers of normal birth weight [41]. Children born prematurely, whatever their birth weight, may also have reduced insulin sensitivity that persists in adulthood [42, 43].

Intrauterine exposure to maternal diabetes, including pre-existing diabetes or gestational diabetes, also increases the risk of obesity, IR, and pre-diabetes in children and adolescents [44, 45]. Apart from maternal diabetes, both maternal obesity and excessive gestational weight gain may also affect the intrauterine environment and place the child at increased risk of obesity and obesity-related metabolic disorders later in life [46–48].

Rapid postnatal weight gain is also associated with an increased risk of obesity and IR in children and adolescents and predicts IR-related outcomes in adults [49, 50], though the timing of rapid weight gain with respect to future IR remains controversial.

Physical inactivity and sedentary behavior

Inactivity is one of the major contributors to overweight and obesity. A sedentary lifestyle is associated with decreased insulin sensitivity in children and adolescents [51, 52]. A Canadian study (n=630, aged 8–10 years) reported that for each additional hour of sedentary behavior per day, insulin sensitivity decreased by approximately 5 % [53]. In contrast, physical activity and increased cardio-respiratory fitness reduce IR and the future risk of developing T2DM. Cross-sectional studies in children and adolescents have shown a positive influence of physical activity and/or fitness on insulin sensitivity, independent of obesity [54–56]. Longitudinal and interventional studies also suggest that increased physical activity improves insulin sensitivity independent of weight change [57, 58].

Dietary factors

Diets high in total fat are related to lower insulin sensitivity in children and adolescents [59]. Although the primary focus regarding obesity and IR has been on total calories ingested, an emerging evidence base suggests that the quality of those calories plays an important role in the pathogenesis of IR. In adults, there is evidence that diets high in polyunsaturated fatty acids and omega-3 fatty acids were beneficial for improving IR [60, 61]. However, there is no consistent evidence linking fat quality and insulin sensitivity in children and adolescents [24••, 62].

There is convincing evidence that higher intakes of sugar, especially from sugar-sweetened beverages, are associated with lower insulin sensitivity and β-cell function in children and adolescents [55, 63–65]. Moreover, a low intake of whole grain carbohydrate or dietary fiber is also associated with lower insulin sensitivity, and a higher fiber intake is associated with higher insulin sensitivity in children and adolescents, with a protective effect against T2DM [66–68]. Studies evaluating the associations between overall dietary

patterns and the risk of IR and metabolic syndrome suggest that a "Western" dietary pattern, high in total fat, saturated fatty acids, refined grains, and added sugars, is associated with a greater risk of obesity and obesity-related metabolic disorders compared with "traditional" patterns, which include high consumption of vegetables, fruits, legumes, fish, and whole grains [69].

Physiological insulin resistance during adolescence

Puberty is associated with rapid changes in various metabolic systems, including hormonal regulation, changes in body fat and fat distribution, as well as insulin sensitivity. During puberty, adolescents develop a transient physiological state of IR. Longitudinal studies have shown that insulin sensitivity declines by approximately 30 % between Tanner pubertal stage 1 and Tanner pubertal stage 3 and returns to pre-pubertal levels when pubertal development is completed [70, 71]. Increased growth hormone secretion in puberty is considered to be responsible for pubertal IR. Because the physiological state of IR can put extra stress on the β-cell, adolescence is a critical period of increased risk for the development of pre-diabetes and T2DM.

Management of obesity and clinical insulin resistance in children and adolescents

Table 1 outlines the key principles of obesity management in children and adolescents. Effective management of obesity-associated comorbidities, including IR, dyslipidemia, hypertension, and nonalcoholic fatty liver disease, is vital for preventing both immediate and long-term complications [72•]. The key for successful treatment of IR and other obesity-associated comorbidities lies in effective weight management. The underlying principle of treatment in children and adolescents is to focus on changes in health behaviors that influence weight [73]. The developmental age of the patient as well as the required levels of parental engagement should be considered when planning a weight management program for children and adolescents [72•].

A consensus statement on the management of IR in children from seven major scientific societies in pediatric endocrinology was published in 2010 [24••]. The consensus statement recommended lifestyle intervention with family involvement as the first line of treatment and advised that metformin therapy should be limited to selected cases [24••].

Lifestyle intervention

Lifestyle interventions are usually comprised of diet and physical activity interventions that involve the use of behavioral modification strategies aimed to decrease caloric intake and increase energy expenditure. Several systematic reviews of childhood obesity have been published, and lifestyle interventions targeting treatment of child and adolescent obesity are reported as efficacious in weight loss at least in the short- to medium-term [74–76]. A 2012 systematic review of randomized controlled trials

Table 1. Principles of obesity management in children and adolescents

- Management of obesity-associated comorbidities
- Family involvement
- A developmentally appropriate approach
- Long-term behavior modification
- Dietary change
- Increased physical activity
- Decreased sedentary behaviors
- Consideration of the use of pharmacotherapy and other forms of nonconventional therapy

Source: Baur, Hazelton and Shrewsbury [72•]

of childhood obesity treatment published between 1975 and 2010 reported that in addition to weight loss, lifestyle interventions also led to significant improvements in insulin sensitivity as well as reduction in low-density lipoprotein cholesterol, triglycerides, and blood pressure up to 1 year from baseline [77••]. Successful lifestyle interventions frequently involve family, particularly in pre-adolescent children. An accompanying review has evaluated whether single component intervention (diet-only interventions) are more effective than a multi-component intervention (diet-plus-exercise interventions) for both weight loss and cardio-metabolic risk reduction in overweight and obese children and adolescents [78•]. The review reported that diet-only and diet-plus-exercise interventions were all able to improve cardio-metabolic profile in overweight and obese children and adolescent. However, the addition of exercise training to dietary intervention led to a greater total body fat loss, greater muscle gain, and greater improvement in insulin sensitivity and HDL-C [78•]. The results support the contention that multicomponent lifestyle interventions are more effective than diet-only programs for cardio-metabolic risk reduction in overweight and obese children and adolescents.

Types of exercise

Evidence from randomized trials has indicated that in the absence of caloric restriction, exercise intervention does not generally cause weight loss [76]. The above-mentioned systematic review showed that diet-plus-resistance-training led to greater fat loss and greater muscle gain than the diet-only intervention [78•]. The same systematic review indicated that diet plus aerobic and resistance training in combination was superior to diet plus either modality alone in improving insulin sensitivity [78•].

Dietary macronutrient content

In the past decades, very low-carbohydrate and high-fat or high-protein diets (eg, the Atkins diet) have received much attention for achieving impressive rapid weight loss and improved cardiovascular risk markers, including fasting glucose, insulin, and triglycerides levels, in adults [79, 80]. A 2013 systematic review comprehensively examined the effectiveness of weight loss interventions (published since 1975), comparing diets with varying macronutrient distributions, on

weight loss and cardio-metabolic risk factors, in overweight or obese children and adolescents [81•]. The review identified seven randomized trials comparing a conventional low fat (≤33 % energy or <40 g/day) to a low carbohydrate diet (<20 % energy or <60 g/day) and six trials comparing increased protein (19 %–30 % energy) to isocaloric standard protein diets (15 %–20 % energy). All included studies reported improvements in weight related outcomes and blood lipids, glucose and insulin homeostasis and blood pressure irrespective of the macronutrient distribution.

An Australian multicentered randomized trial, the RESIST trial, was the first clinical trial to examine the efficacy of a conventional high-carbohydrate, low-fat diet (55 %–60 % of total energy as carbohydrate, 30 % fat, and 15 % protein), and an increased-protein diet, moderate-carbohydrate diet (40 %–45 % carbohydrate, 30 % fat, and 25 %–30 % protein) on insulin sensitivity and weight loss in adolescents (aged 10–17 years) with clinical IR and/or pre-diabetes [82]. The adolescents (n= 111) participated in a 12-month program that comprised an intensive structured dietary intervention (0 to 3 months), a 12-weeek supervised physical activity program (4 to 6 months) and a maintenance phase (7 to 12 months). All participants were treated with metformin (500 mg twice daily). The intervention led to significant improvements in insulin sensitivity, fat loss, and improvement in arterial elasticity from baseline to 12 months [83••, 84, 85••]. However, there were no significant differences in outcomes between the diet groups at any time point.

Very Low Energy Diets

Very Low Energy Diets or meal replacements are hypocaloric diets containing ≤800 kcal/day or less than 12 kcal/kg of ideal body weight per day with an enriched protein content and which provide 100 % of the recommended daily allowance for essential vitamins and minerals [86]. They are designed to create rapid weight loss while preserving lean body mass. There have been no RCTs using Very Low Energy Diets in children or adolescents to date. A meta-analysis of RCTs in adults comparing the effectiveness of Very Low Energy Diets with conventional low calorie diets (providing 800–1800 kcal/day) indicated that Very Low Energy Diets induced significantly greater short-term weight losses than the conventional low calorie diets [87]. However, the long-term weight changes (1–5 years from baseline) were comparable in both diet groups as participants in the Very Low Energy Diets groups showed a greater weight regain [87].

Metformin therapy

Metformin is an approved drug for the treatment of T2DM in adults and adolescents older than 10 years. The key clinical actions of metformin include increasing hepatic glucose uptake, inhibiting gluconeogenesis and reducing hepatic glucose output, as well as decreasing intestinal glucose uptake and increasing both peripheral and liver sensitivity to insulin [88]. In adults, metformin reduces the rate of progression to T2DM with pre-diabetes and reduces the feeling of hunger and food intake [89, 90].

A 2010 systematic review of the treatment of IR or pre-diabetes in children identified five RCTs, all involving metformin therapy [91]. The meta-analysis demonstrated that metformin, whether used alone or in combination with lifestyle interventions, improved insulin sensitivity and reduced body mass index. The largest RCT to date, which was published after the systematic review was undertaken, is the Metformin in Obese Children and Adolescents trial (MOCA trial). The MOCA trial included 151 obese children and adolescents (aged 8–18 years) with hyperinsulinemia and/or pre-diabetes and demonstrated a significant beneficial effect of metformin over placebo for weight loss at 6 months. The metformin group had a mean reduction of 3 % of initial BMI z-score at 6 months compared with a zero mean change in the placebo group [92••]. In the MOCA trial, all participants received general healthy lifestyle advice at the first session. In contrast to other trials that included a structured lifestyle intervention component, the MOCA trial did not show any significant change in the measures of insulin sensitivity in either group after 6 months [92••].

As previously discussed, IR is associated with increased risk of PCOS and NAFLD. The role of metformin in adolescents with PCOS and NAFLD has been previously studied. Metformin is beneficial for adolescent girls with PCOS [93], yet evidence as to its efficacy on NAFLD is not conclusive [94].

The most commonly reported side effects of metformin are mild gastrointestinal upset, including diarrhea, nausea, abdominal pain, and reduced appetite, but the symptoms are generally transient and resolve shortly after initiation of treatment [95••]. Vitamin B12 deficiency has also been reported in metformin-treated adults with T2DM, but no data are available for pediatric populations [96, 97]. The most serious side effect, lactic acidosis, is very rare in adults, and no cases have been documented in children or adolescents [95••].

Surgical treatment

Bariatric surgery is a well-recognized form of therapy for adults with severe obesity if the conventional approach has failed to limit weight gain or to modify comorbidities. Currently, the most commonly performed bariatric procedures in pediatric populations are Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding (LAGB), and vertical sleeve gastrectomy [98].

A recent systematic review, which included 23 studies (1 RCT and 22 non-RCTs) reported that compared with nonsurgical interventions, bariatric surgery in obese children and adolescents is associated with significantly greater short-term (up to 12 months follow-up) body mass index reduction [99•]. To date, there is only one published randomized trial of bariatric surgery in adolescents. That trial included 50 severely obese adolescents (aged 14–18 years, body mass index >35 kg/m^2) who were randomly assigned either to a supervised lifestyle intervention or to undergo LAGB. By 24 months, adolescents in the LAGB group had a mean reduction in BMI of 12.7 kg/m^2 vs 1.3 kg/m^2 in the lifestyle intervention group [100••]. The LAGB group also showed a marked improvement in health, with complete resolution of the metabolic syndrome and IR and enhanced quality of life. However, seven of the 25

adolescents required revisional procedures either for proximal pouch dilatation or tubing injury.

Conclusions

Pediatric obesity is a major worldwide public health issue. Concomitant with the rise in pediatric obesity in the past decades has been a rapid increase in the prevalence of IR in children and adolescents. Youth with obesity, and IR are at increased risk for the development of T2DM and cardiovascular complications. Management of obese children and adolescents with clinical insulin resistance should incorporate family involvement and age-appropriate behavioral modification strategies to achieve effective weight control. Lifestyle interventions with and without metformin therapy are effective in achieving weight loss and improving insulin sensitivity in overweight and obese children and adolescents in the short- to medium-term. Ongoing evaluation and research are required to explore the optimal protocol and long-term effectiveness of lifestyle interventions, as well as to determine whether the improvements in insulin sensitivity induced by lifestyle interventions and weight loss will lead to a clinical benefit, including reduced cardiovascular morbidity and mortality.

Compliance with Ethics Guidelines

Conflict of Interest
All authors declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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