ISSN 2377-8385

Openventio PUBLISHERS

OBESITY RESEARCH

October 2019 | Volume 6 | Issue 1

Open Journal

www.openventio.org

ISSN 2377-8385

OBESITY RESEARCH
Open Journal

Openventio
PUBLISHERS

CONTENTS

ISSN 2377-8385

OBESITY RESEARCH
Open Journal

Openventio
PUBLISHERS

Systematic Review

Importance of Simultaneous Treatment of Obesity and Diabetes Mellitus: A Sequelae to the Understanding of Diabesity-A Review

Kulvinder Kochar Kaur, MD[1*]; Gautam Allahbadia, MD, DNB[2]; Mandeep Singh, MD, DM[3]

[1]*Scientific Director, Centre for Human Reproduction 721, Jalandhar, Punjab-144001, India*
[2]*Scientific Director, Centre for Human Reproduction, Bandra(W), Mumbai-400040, Maharashtra, India*
[3]*Consultant Neurologist, Swami Satyanand Hospital, Jalandhar, Punjab, India*

[*]***Corresponding author***
Kulvinder Kochar Kaur, MD
Scientific Director, Centre for Human Reproduction 721, G.T.B. Nagar, Jalandhar, Punjab-144001, India; Tel. 91-181-9501358180, 91-181-4613422; Fax. 91-181-4613422; E-mail: kulvinder.dr@gmail.com

Article information
Received: February 2nd, 2019; **Revised:** March 13th, 2019; **Accepted:** March 14th, 2019; **Published:** March 22nd, 2019

Cite this article
Kaur KK, Allahbadia G, Singh M. Importance of simultaneous treatment of obesity and diabetes mellitus: A sequelae to the understanding of diabesity-A review. *Obes Res Open J*. 2019; 6(1): 1-10. doi: 10.17140/OROJ-6-136

ABSTRACT

Aim
With the growing epidemic of obesity in children, adolescents and adults globally, obesity has been found to be a risk factor for many non-communicable diseases like type 2 diabetes mellitus (T2DM), hypertension, dyslipidemias and many cancers. So much so that recently a term diabesity (Obesity and diabetes in the same patient, especially when the obesity had a causal influence on the diabetes) got introduced. The aim of this systematic review was to study how we can tackle together so that we can take care of the mortality caused by obesity and T2DM being responsible for more mortalities replacing malnutrition even in developing countries.

Methods
We carried out a PubMed search, along with Excerpta Medica dataBASE (EMBASE)/Cochrane library, web sciences for the Medical Subject Headings (MeSH) Terms "obesity", "diabetes mellitus (DM)", "lifestyle including exercise", "diet therapy for management of diabesity", pharmacotherapy including foods rich in antidiabetics like anthocyanins", "polyphenols", "walnuts", "monoterpenes" for same including "bariatric surgery (BS)".

Results
We found a total of 86,283 articles pertaining to obesity and DM together of which we selected 92 articles for this review after getting articles after searching cross references. No meta-analysis was done.

Conclusion
Till date body mass index (BMI) is used to classify overweight and obesity. With decreased muscle mass being common in these obese patients it is important to measure the body composition. Further, one has to monitor body composition when getting the patient to lose weight. Importantly, the criterion used for labelling obesity also varies in different geographical areas in view of different phenotype of diabetes in South Asia. Weight loss can be achieved using lifestyle interventions like diet, exercise and importance of combining natural products from food in attaining weight loss along with controlling hyperglycemia utilizing pharmacotherapies obesity and T2DM, control. Bariatric Surgery (BS) remains the last resort for morbidly obese although it might have to be resorted in individuals where diabetes is resistant to medical treatment and be needed for those with BMI greater than 35 kg/m^2 or even less in case of resistant diabetics. Role of diets rich in walnuts, anthrocyanins, soyabean, chickpeas, curcumin, polyphenols and other vitamins and micronutrients including vitamin A, also needs to be considered while treating diabesity.

Keywords
Diabesity; Diettherapy; Lifestyle; Body mass index (BMI); Exercise; Metformin; Liraglutide; Bariatric surgery (BS).

Obes Res Open J. 2019; 6(1): 1-10. doi: 10.17140/OROJ-6-136

INTRODUCTION

In the last century obesity has surfaced as the biggest global health problem in view of both, the changes in environment along with changes in society where positive energy balance and thus weight gain has resulted, main changes being consumption of high-calorie foods/high-fat foods, associated with inadequate physical activity, moving towards sedentary lifestyle.[1] As a result obesity prevalence practically doubled since 1980 all over the world, with world health organization (WHO) showing greater than 39% of adults greater than/equal to 18 year were overweight of which 13% were obese.[2] Additionally, a minimum of 41 million children below 5 years were overweight or obese.[2] Importantly severe obesity, a body mass index (BMI) greater than 35 kg/m^2 is becoming a part of this global epidemic, and that has severe bad effects on health, with increase in BMI implying increased mortality risk just like low BMI does.[3-5] However, now overweight or obese have become bigger killers in contrast to malnourished or underweight.[2] As per WHO overweight and obesity are the causative factors for 44% of type 2 diabetes mellitus (T2DM), resulting in 23% of ischemic heart disease patients and roughly 7-41% of some cancers.[4,5] Of these greatest association is of T2DM with obesity, with obesity related T2DM expected to double to 300 millon by the year 2025.[6] Because of which the word diabesity got coined, suggesting that most patients with T2DM are obese.[7,8] The term diabesity highlights the etiogenesis of effect of obesity on T2DM. This term was introduced by Shafir who saw that Israeli sand rats (psammonys obesus) fed high energy diets, became obese and later developed diabetes.[9,10] Thus, in concert they increase mortality risk of the individual by 7 fold.[11] This increasing trend gives an estimation of 60% of total population of the world to be overweight or obese by year 2030.[12,13] As per Zimmet T2DM is proving to be the greatest epidemic of mankind and has beaten all the figures and predictions given by WHO and intermediate distribution frame (IDF), with the numbers increasing to 415 million people and with these diabetics a population of a country can be formed like it is greater than 315 million people of US. Thus need to address diabesity together is there.[14] Since all antidiabetics are not weight neutral and antidiabetics being expensive there is a need to find non-pharmacological answers using diets which have phytocyanins, flavonoids and other pulses, walnuts in the low calorie diets which have inherent insulin resistant effects.

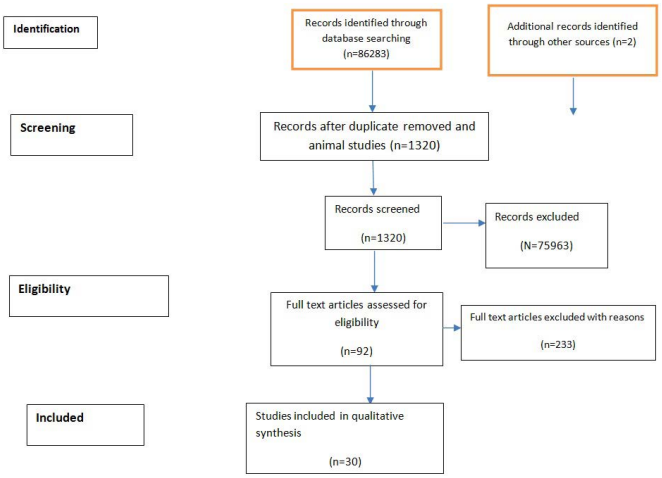
METHODS

We carried out a PubMed search for the Medical Subject Headings (MeSH) terms "obesity", "diabetes mellitus (DM)", "exercise", "dietary therapy" for management of diabesity, "pharmacotherapy", "including natural products" which have antidiabetic properties like "walnuts some vitamins" and "minerals", "anthocyanins", "phenols for same including bariatric surgery (BS)".

RESULTS

We found a total of 86,283 articles pertaining to obesity and DM together of which we selected 92 articles for this review after retrieving articles after searching cross references. No meta-analysis was done (Figure 1).

Figure 1. *Flow Chart for Identificaton and Selection Process*



National and Asian Phenotypes

A sponsored study by Indian Council of Medical Research (ICMR) suggested the widespread, seriousness of diabetes across rural and urban areas with some areas showing prevalence as high as 13%.[15] Now evidence exists, that an "Asian phenotype" exists.[16] The Asian DM patient is characterized by onset at younger age, higher risk even at lower BMI, higher abdominal obesity, higher cardiovascular disease (CVD) in South Asia and stroke in East Asia.[16] Thus these typical characteristics need to influence the way treatment drugs are prescribed based on availability and selected in these geographical areas.[17]

Role of History and Anthropometrics

Before starting the treatment of obesity it is important to consider if the patient has history of any disease for which patient is on any medications. For example if patient is on antidepressants like phenelzine, tranylcypromine mirtazapine, or lithium, drugs known to cause moderate to significant weight gain[18,19] or antipsychotic agents like clozapine, olanzapine, risperidone, quatiapine[20]/or haloperidol again causing moderate to significant weight gain, or some antiepileptics like valproic acid,[21-23] carbamazepine,[22-25] gabapentin,[26,27] causing moderate to severe weight gain by increasing appetite and affecting metabolism, steroid hormones like prednisolone[28,29] or contraceptives like depot medroxyprogesterone acetate (DMPA),[30] some β adrenergic blockers like atenolol, propranolol, atenolol increase weight slowly by inducing fatigue and lower activity.[31] Hence, the importance lies in the physician realizing if one has to select any antidepressants he/she chooses SNRI's like duloloxetine, venlafaxine, milnacipran that don't have weight gaining effects/or even minimal weight-lowering effects, of antipsychotics aripiprazole, ziprasidone having no effect to minimum weight gaining effects, and of antiepileptics choose topiramate or zonisamide in a patient who is slightly overweight or obese.

Openventio PUBLISHERS

Examination includin

Till date, BMI gets used to classify overweight and obesity though this does not take into account the persons body fat mass.[32] Although most people having a BMI>30 kg/m^2 are seen to have a >proportion of body fat it might be observed in roughly 1/3rd of individuals having normal weight also.[33] This incorrect fat-mass distribution occurs secondary to low muscle mass known as sarcopenia. Increased waist circumference (WC) can be used to identify these patients, with WC exceeding 80 cm in women and 94 cm in men of Caucasian origin.[34] In view of differences in ethnicities different cut-offs for different populations have been proposed,[35] like instead of upper limit of BMI of 25 kg/m^2 for normal BMI as per WHO, the suggested cut off for South Asians is 23 kg/m^2, similarly for overweight 23-24.9 kg/m^2 as compared to 25-29.9 kg/m^2 in Caucasians and for obesity as per greater than 30 kg/m^2 for Caucasians, a value of 25 kg/m^2 id recommended in South Asians with a WC 90 cm and 80 cm respectively for men and women in contrast to 102 cm and 88 cm for Caucasians.[35] Independent of BMI, increased visceral fat distribution increases the risk of atherosclerosis along with mortality. This normally needs? for proper measuring a persons body composition say by dual energy X-Ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), BOD-POD, besides measuring WC. Despite drawbacks of these methods, they are important for monitoring the course of weight reduction along with changes in the respective body compartments.[36,37] Besides that what is important is to identify a cheap method to find the early stage of sarcopenia, in view of loss of muscle mass being common. For the elderly a questionnaire called SARC5-that has 5 questions as part, namely strength, assistance in walking, rising from a chair, stair climbing and falls. The global score of this questionnaire varies from 0-10 points, where each part gets a score of 0-2 points. A score of greater than/equal to 4 points predicts sarcopenia and hence warrants more detailed assessment in this aspect.[38] This SARC-F questionnaire is one of best tools regarding screening for sarcopenia, which in routine practice has already proved in late middle-aged and elderly.[39,40] In post BS patients to get detailed information on muscle function, hand-grip tests are used frequently.[41]

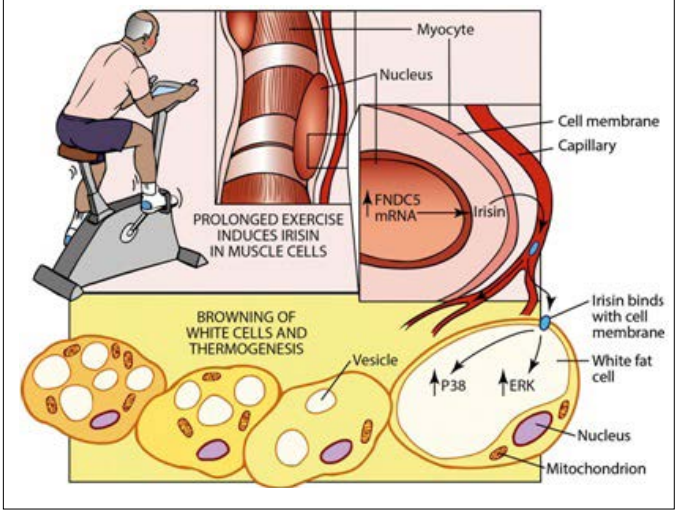
Weight loss Methods in Obese and Overweight People

The main aim is to get weight loss. Various methods used include Life Style interventions which includes diet and exercise, use of antiobesity medications and BS.

Life Style Interventions

Role of Exercise: Exercise is an important part of Life Style interventions. Aerobic exercise remains the best method for getting fat mass reduction. Other advantages an increase in lean mass, reduction in depression by release of endorphins, an improvement in glucose tolerance along with increasing insulin sensitivity, all by increasing irisin, and physical fitness (Figure 2). Because of which all scientific guidelines give a recommendation of at least 150 min/week of moderate aerobic exercise that needs to be combined 3 weekly times of resistance training for increasing muscle strength.[1,42-44] Problem remains that these intensive Life Style interventions are difficult to follow along with maintenance over a long period of time, even if these patients get included in an optimal clinical trial as has been seen in the Look Ahead (Action for health in diabetes) trial.[45] Though exercise remains an integral part of weight loss obtainment, there have been different reports regarding additive weight loss when it gets combined the use of energy restricted diet.

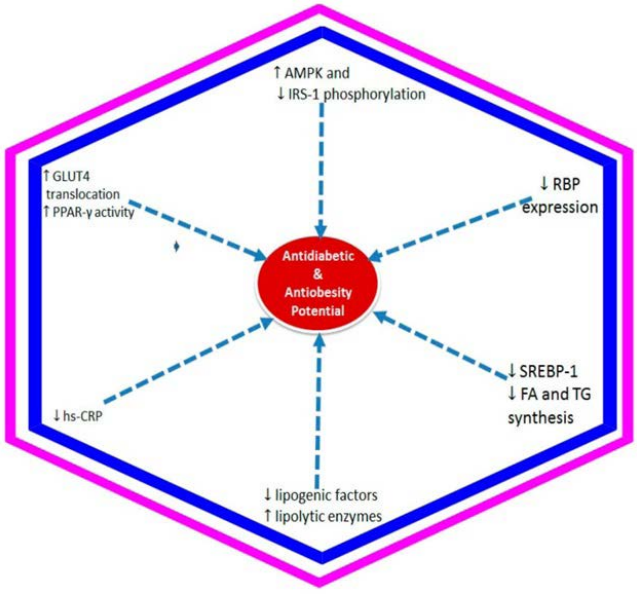
Figure 2. *Recombinant Irisin Regulates the Thermogenic Program in Fat through ERK and p38 Pathways. Recombinant Irisin Produced in Yeast is Glycosylated and Active. It Induces the Thermogenic Gene Program in 3T-L1 Cells and Primary Subcutaneous Adipocytes. In Vitro Treatment of this Recombinant Protein in Mice Show Strong Anti-Obesity Effects and Improve Systematic Glucose Homeostasis*[93]



Role of diet: To get this a low fat, low carbohydrate, or the Mediterranean style diet can get used.[46-48] This Mediterranean style diet has advantages of better metabolic effects along with delaying need for delaying the antihyperglycaemic therapy in patients who had newly diagnosed T2DM.[49] Besides the mediterranean diet that might have these antihyperglycaemic effects, recently natural products have been introduced like anthocyanins which act through multiple mechanisms to increase insulin sensitivity in target organs like i) incresing Galacto-ololigosaccharides that help in increasing glucose transporter 4 (GLUT4) translocation by increasing PPAR γ activity, ii) enhance activation of adenosine monophosphate-activated protein kinase (AMPK), along with downregulating serine phosphorylation pf insulin receptor sbstrate 1(IRS-1) phosphorylation, iii) reduce the retinol binding protein (RBP) Expressionand iv) lowering the highly sensitive C Reactive Protein (hs-CRP). Further weight reduction by anthocyanins is by mechanisms like reduction in sterol regulatory element binding protein-1 (SREBP1) mRNA levels and inhibition of fatty acid and triacylglycerol synthesis enzymes as well as down-regulation of lipogenic factors and upregulation of enzymes (Figure 3). Anthocyanins are present in berries which include blackberries, bilberries, chokeberries, elder berries, cranberries and raspberries that are the richest sources of anthocyanins. Many other highly colored fruits like strawberries, black currant, cherry, grape, coloured cabbage, eggplant and radish also have high levels of anthocyanins, thus it is important to include these in the low-calorie diets plans to improve insulin resistance (IR) along with helping in weight reduction.[50] Similarly importance of adding

soybeans, chickpea to this diet has shown to further improve IR by the bioactive compounds present in these, like anthocyanins, isoflavones, GLUT-4 levels, inhibiting adipogenesis by downregulating peroxisome proliferated–activated receptor-γ (PPAR-γ), reducing adiposity, positively affecting adipokines, and increasing short-chain fatty acid producing beneficial bacteria in gut.[51] A low-fat diet must have adequate carbohydrates with complex carbohydrates instead of mono or disaccharides.[52,53] Although, what counts is maintenance of this diet regularly.[54] Hence in practical life it is to use wide type of diet options which suits the patients good preferences, Life Style along with the medical condition like in an Indian scenario patient using a vegetarian diet might like to consume these soybean, chickpeas and other pulses. Further replacing 1-2 meals/day by dietary supplements (low-calorie diets that have included aloe vera supplements, Habtemariam showed that the marketed supplements had benzoate derivatives along with methanol suggesting they don't meet the international aloe science council certification regulations)[55] might help in consuming very low calorie diet to maintain weight loss.[56] But this type of diet is not suitable for children, adolescents or elderly people.[1] In case of sarcopenia cases, one has to supplement exercise with high protein diet.[57] Time of protein intake and amino acid composition has been controversial.[58] In advanced age, all are important, like acquiring muscle mass, physical fitness along with overall physical activity.[59,60]

Figure 3. *Underlying Mechanism of Anthocyanins Against Insulin Resistance Associated with Diabetes and/or Obesity. The Decrease in Insulin Resistance and Enhancement of Insulin Sensitivity by Anthocyanins in Target Organs have been Shown to be Mediated Through Activation of the adenosine monophosphate-activated protein kinase (AMPK) and Downregulated the Serine Phosphorylation of insulin receptor substrate 1 (IRS-1), Enhanced glucose transporter 4 (GLUT4) Translocation by Increasing the Activity of peroxisome proliferator activated receptor-gamma (PPAR-γ), Lowering the high sensitivity C reactive protein (hs-CRP) Concentration, and reduction of retinol binding 4 (RBP4) Expression. The Reduction of Weight Gain by Anthocyanins is also Reported Through Mechanisms Including Reduction in the sterol regulatory element-binding protein 1 (SREBP-1) mRNA Level and Inhibition of fatty acid (FA) and triglycerol (TG) Synthesis Enzymes as well as Downregulation of Lipogenic Factors and Upregulation of Lipolytic Enzymes*[50]



Use of Weight Loss in Prevention of T2DM and Therapy

The pathogenesis of DM has been demonstrated to be a resistance to insulin action in peripheral tissue insulin is a major regulator of cell metabolism, which in addition, is also a growth factor. Insulin effects in target cells are mediated by the insulin receptor (IR), which is a transmembrane protein with enzymatic (tyrosine kinase) activity. However the IR, is represented by a heterogeneous family of proteins, which include 2 different IR isoforms (Exon 11 minus IR-A and exon 11plus IR-B), along with a hemireceptor of the cognate IGF-1 receptor. These different receptors may bind insulin and its analogs with different affinity and produce different biologic effects. The main physiological role of the IR appears to be the metabolic regulation, whereas other receptor tyrosine kinases are engaged in regulating cell growth and/or differentiation. Receptor tyrosine kinases are allosterically required by their cognate ligands and function as dimers. In all cases but the IR (and 2 closely related receptors), these dimers are noncovalent, but the IRs are covalently maintained as functional dimers by disulfide bonds. It has been known for several years that many cancer cells require insulin for optimal in vitro growth. Recent data show i) that insulin stimulates growth mainly *via* its own receptor and not the IGF-1 receptor ii) in many cancer cells the IR is overexpressed and the A isoform, that has a predominant mitogenic effect, is more represented than the B isoform. These properties give a selective advantage to malignant cells when exposed to insulin. Because of these reasons, all conditions of hyperinsulinemia, both endogenous prediabetes, metabolic syndrome, obesity, type 2 diabetes before pancreatic exhaustion and polycystic ovary syndrome and exogenous (type 1 diabetes) to increase the risk of cancer. The complexity of the diseases associated with hyperinsulinemia and their therapies does not allow an exact evaluation of the cancer promoting effect of hyperinsulinemia, but its detrimental effect on cancer incidence and mortality is well-documented.[61,62]

Insulin resistance (IRe) can be defined as a state in which greater than normal amounts of insulin are required to produce a biological response. Insulin acts by coupling to a cell transmembrane receptor, a tetrameric protein with 2 identical alpha subunits and other 2 beta units. Alpha subunits are extracellular and alter the insulin coupling translate the signal to both intracellular beta subunits which have tyrosine kinase activity and are autophosphorylated with a subsequent increase of their tyrosine kinase catalytic activity. Then endogenous protein substrates are phosphorylated and activate a cascade of intracellular signals which in turn induce migration of glucose transporter (GLUT-4) from intracellular pools to the cellular surface to facilitate glucose entry into the cell. So IR is due to an impairment of one or more of these steps of the process in target tissue which induce compensating hyperinsulinemia to maintain normoglycemia. But as years go by pancreas get exhausted and plasmatic glucose levels start to increase. Once glucose has increased, hyperglycemia has a toxic effect over islet cells (glucotoxicity) and has been demonstrated to impair the kinase function of insulin receptor (downregulation). An important consequence of IR is the increase in free fatty acids, which in turn impairs, even more, the IR (lipotoxicity). Even more IR on hepat-

ic, muscular and adipose tissue is associated with overproduction of proinflammatory cytokines, like interleukin6 (IL6) and tumor necrosis factor (TNF) and relative decrease of anti-inflammatory cytokines like adiponectin. All these factors contribute to chronic inflammatory status.[63]

With most T2DM patients being overweight or obese it is important to achieve weight loss for prevention of T2DM along with managing the disease once it occurs. As reviewed by farr OM and Mantzoros,[64] the Finnish Diabetes Prevention Study showed that an intensive dietary and exercise programme reduced the overall risk of T2DM by 58%.[65] similarly in diabetes prevention program, moderate weight loss with Life Style interventions in an obese population with impaired glucose tolerance test (GTT) could decrease the incidence of T2DM by 58%, though metformin use only reduced it by 31%.[66] Though the data for both strategies was not given in DPP. In another study with each 1 kg weight loss in the 1st year of DM diagnosis in T2DM was associated with 3-4 months increase in survival, with l0 kg loss associated with an increase in life expectancy by 35%.[67] For people having T2DM, it was demonstrated by Williamson DF et al that an intentional Weight loss of 10 kg as was seen in the American Cancer Society's Cancer Prevention study, total mortality got decreased by 25%.[68] Similarly the Look Ahead Study emphasized the improved weight loss that occurred in T2DM patients. As per this study even a 5-10% weight loss improved overall fitness, decreased use of antihyperglycaemic along with antihypertensive and lipid-lowering following 1 year.[69,70] On top of those depressive symptoms and the remission of obstructive sleep apnea or its decrease in severity resulted in secondary to weight loss.[71,72] But what was important was all these good effects needed a minimum of over 5% weight loss. With the need of intensive Life Style interventions, that includes energy restriction along with regular physical activity, getting this much Weight loss can't be the expected primary treatment outcome in real life for all overweight and obese patients. Still, there is need to encourage these patients to reduce energy intake, that might irrespective of their weight loss contribute to improve the glycemic control in them.[73] Consumption of walnuts have been approved for both T2DM prevention and maintenance of glycemic status.[74,75] One proposition is to consider weight loss medications for such cases which are suitable for these patients, giving a tug of war with their weight control.

Figure 4. *Possible Mechanism by which Metformin may be able to Inhibit Cancer Cell Growth. adenosine monophosphate-activated protein kinase (AMPK); endoplasmic reticulum (ER); insulin-like growth factor (IGF); liver kinase B1 (LKB1); mammalian target of rapamycinm (mTOR); thrombospondin (TSP); unfolded protein response (UPR)*[76]

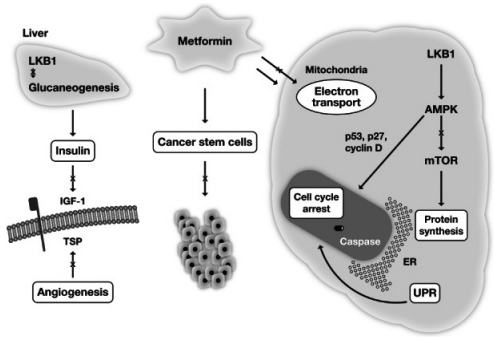
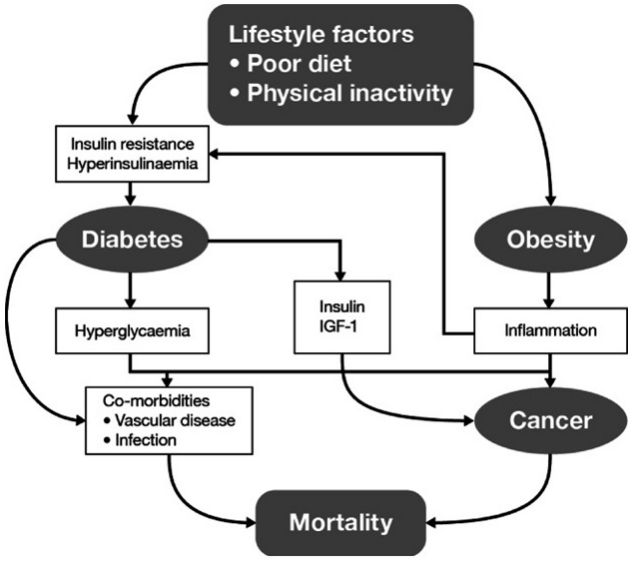


Figure 5. *Interrelationship between Pathological Mechanisms and Modifiable and Non-modifiable Risk Factors Involved in Diabetes, Obesity and Cancer. Insulin-like growth factor (IGF)*[76]



Another important finding has been with diabesity, cancer risk increases, and addition of metformin reduces that risk[76] (Figures 4,5).

Trying Antiobesity and Anti Diabetes Therapy Together

The importance of properly controlling weight, improves body composition along with glycemic control was demonstrated by Olofsson E et al[77] where cardiovascular (CV), stroke along with mortality had a direct relation with weight gain during treatment with antidiabetics. Since many factors might influence these results hence it is difficult to prove a direct correlation of weight gain and morbidity, one can still say that weight gain indicates lesser therapy success and may potentially increase risk of mortality. With studying weight gain during antidiabetic therapies being not ethical still one should aim to use Antidiabetic agents that are weight neutral/help in weight reduction must be the 1st choice after the obligatory metformin therapy like alpha-glucosidase inhibitors, DPP IV inhibitors, SGLT inhibitors.[78]

Various antiobesity pharmacotherapy have been introduced worldwide. Of the new drugs reviewed earlier by us,[79,80] that are available in USA, only 2 of them were licensed for Europe like liraglutide (1.8 mg for T2DM, and 3 mg for treatment of obesity) along with contrave (a combination of naltrexone and bupropion) although not launched in many European countries and similarly not available in most developing countries like India. These drugs have shown to attain weight loss along with improving their Hb A1clevels.[81] Similarly semaglutide has shown improvement in weight control irrespective of BMI in SUSTAIN 1-5 Trials, examining once weekly semaglutide against placebo, sitagliptin, exenatide ER, Insulin glargine as add on to metformin/sulfonoyl ureas, basal insulin trial.[82] Thus need to carry proper studies for finding the effect of antiobesity drugs in patients with T2DM is there.

Role of Bariatric Surgery

BS has been proven to be effective for obese people having a BMI>40 kg/m^2 or those with 35 kg/m^2 in the presence of T2DM or other comorbidities.[83] Of the most prevalent BS's available Roux-en-Y Gastric bypass and biliopancreatic diversions /duodenal switch surgeries are the most common and successful with initial reported excess weight reduction of upto 68-70%, where excess weight is the difference between total pre-operative weight and ideal weight.[84] Notably, improvement of glycaemic control by BS is rapid and often seen even before a clinically relevant weight loss. Despite intense scientific investigation, changes in metabolic rate or intestinal nutrients absorption do not explain the efficacy and sustainability of weight reduction.[85] Changes in food intake are frequently reported which are basically due to changes in food preferences, taste perception and modifications if central reward system.[86,87] In case of BS done in latter case remission was seen along with decrease in CV events in the Swedish Obese subjects study.[88] Currently, these surgeries are done even with lower BMI's. Problem with BS however, remains despite proper pre- and post-operative checkup long-term nutritional and micro nutritional deficiencies need lifelong vitamin and mineral supplementation. Further rapid and massive weight loss of muscle and fat-free mass may greater than equal to malnutrition and osteoporosis. Thus need for follow-up regarding muscle and fat distribution as well as bone health is needed at least 2 years following surgery.[89]

Bariatric Surgery and Drug Therapy Comparison

The surgical treatment and medications potentially eradicate diabetes efficiently 1 trial (STAMPEDE)-this 5 year trial supports the previous findings that BS is superior to intensive medical therapy in terms of glycemic control, weight reduction, decreasing medication use, (all therapies like antidiabetics, antihypertensives and lipid lowering agents) along with improving quality of life. All these effects were also seen in patients having milder obesity (BMI 27-34 kg/m^2. This makes one consider that BS be also considered for these patients with T2DM with milder obesity.[90]

Role of Vitamin A

Further role of vitamin A has been emphasized in both pathogenesis of obesity and diabetes, thus supplementation of vitamin A has been emphasized in both disorders.[91] Vitamin A is delivered by a specific protein called Retinol-binding proteins (RBP 4), which is emerging to have role of insulin resistance, the major cause of diabetes is highly associated with adipose tissue inflammation, and obesity. RBP4 interacts with 2 receptors, the Toll-like receptor 4 (TLR-4) and the plasma membrane protein is stimulated by retinoic acid 6 (STRA6), leading to the activation of c-Jun N terminal protein kinase (JNK) pathways and JAK2/STAT5 cascade respectively. Both mechanisms sustain IR. Hence ablation of STRA6 protects mice from RBP4 induced suppression of IR. Binding of retinol-bound retinol-binding protein to a membrane-binding protein suppresses insulin signaling. All-trans retinoic acid, a derivative of vitamin A, reverses these effects, resulting in increased insulin sensitivity, suppression of the *phosphoenolpyruvate carboxykinase (PEPCK)* gene, and the induction of the glucokinase gene. Glucokinase and PEPCK are also regulated in opposite directions by the vitamin biotin, acting at the transcriptional level. Biotin also regulates the synthesis of insulin by the islet of Langerhans cells of the pancreas. The increase in advanced glycation end products (AGEs) is implicated in the initiation and progression of diabetes-associated microvascular diseases. Not only proteins in vitamin A, shuttle and signaling are emerging in diabesity, recently the discovery of 9 cis retinoic acid (9C RA) with effects on controlling glucose levels have opened a new scenario. Right now only pancreatic β-cells are able to show its synthesis, high-levels of 9C RA correlate with obesity.[92,93]

CONCLUSION

Thus the importance of studying obesity and diabetes together is identifying the populations most specific for these by epidemiological studies as done by Zimmet in various regions of different countries and individualizing the anthropometric data for the geographic area and try to use weight neutral anti-diabetics like liraglutide of available, otherwise preferably SGLT2 inhibitors or DPP IV inhibitors not only improves the quality of life by preventing CVD, renal dysfunction, retinal function and improving life span, but also helps in preventing cancer if metformin is included in the antidiabetic regimen.[76] Further role of vitamin A has been emphasized in both pathogenesis of obesity and diabetes, thus supplementation of vitamin A has been emphasized in diabesity. Importance of using natural plants or fruits available products which have components acting as insulin sensitizers by acting on PPAR Gamma similar to thiazolidinediones, like anthrocyanin, soyabean, chickpeas should be included in diet of dibesity patients along with walnuts. Also besides association of, T2DM, T1DM has also been seen associated with obesity, the incidence of which is increasing and can be taken care of by use of biguanides or GLP-agonists.[94,95]

CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

REFERENCES

1. Yumuk Y, Tsigos C, Fried M, et al. European guidelines for obesity management in adults. *Obes Facts.* 2015; 8: 402-424. doi: 10.1159/000442721

2. World Health Organization (WHO). Obesity and Overweight. Web site. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed September 29, 2017.

3. Prospective Studies Collaboration,Whitlock G, Lewington S, et al. Body-mass index and cause specific mortality in 900 000 adults: Collaborative analysis of 57 prospective studies. *Lancet.* 2009; 373: 1083-1096. doi: 10.1016/S0140-6736(09)60318-4

4. Fried M, Yumuk Y, Oppert JM, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. *Obes Facts.* 2013; 6: 449-468. doi: 10.1159/000355480

5. Fruhbeck G, Toplak H, Woodward E, et al. Obesity: The gateway to ill health-an EASO position statement on a rising public health, clinical and scientific challenge in Europe. *Obes Facts*. 2013; 6: 117-120. doi: 10.1159/000350627

6. Dyson PA.The therapeutics of lifestyle management on obesity. *Diabetes Obes Metabol*. 2010; 12: 941-946. doi: 10.1111/j.1463-1326.2010.01256.x

7. International Diabetes Federation (IDF). IDF Diabetes Atlas-2nd edition. Web site. www.diabetesatlas.org.component/attachments/task=download&id=73. Accessed September 28, 2017.

8. Possain P, Kawar B, El-NahasM. Obesity and diabetes in the developing world-a growing challenge. *N Engl J Med*. 2007; 356: 213-215. doi: 10.1056/NEJMp068177

9. Ziv E, Shafir E. Psammomys obesus (sand rat). [In:] Shafir E (ed) *Nutritionally Induced NIDDM Like Syndrome on a Thrifty Gene Background in Lessons from Animal Diabetes*. London, Smith Gordon: 1995; 5: 285-300.

10. Kalra S. Diabesity. *J Pak Med Asson*. 2013; 63(4): 532-541.

11. Oldridge NB, Stumb TE, Nothwehr FK, Clark DO. Prevalence and outcomes of comorbid metabolic and cardiovascular conditions in middle- and older-age adults. *J Clin Epidemiol*. 2001; 54: 928-934. doi: 10.1016/S0895-4356(01)00350-X

12. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes(Lond)*. 2008; 32: 1431-1437. doi: 10.1038/ijo.2008.102

13. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body mass index since 1980: Systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*. 2011; 377: 557-567. doi: 10.1016/S0140-6736(10)62037-5

14. Zimmet PZ. Diabesity and its drivers: The largest epidemic in human history? *Clinical Diabetes Endocrinol*. 2017; 3: 1. doi: 10.1186/s40842-016-0039-3

15. Anjana RM, Deepa M, Pradeepa R, et al. Prevalence of diabetes and prediabetesin 15 states of India: Results from the ICMR-INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol*. 2017; 5: 585-596. doi: 10.1016/S2213-8587(17)30174-2

16. Ma RC,Chan JC. Type 2 diabetes in East Asians: Similarities and differences with populations in Europe and the United States. *Ann NY Acad Sci*. 2013; 1281: 64-91. doi: 10.1111/nyas.12098

17. Lim LL, Tan AT, Moses K, Rajadhyaksha C, Chan SP. Place of sodium-glucose cotransporter-2 unhibitors in East Asians subjects with type 2 diabetes: Insights into management of Asian phenotypes. *J Diabetes Complications*. 2017; 31: 494-503. doi: 10.1016/j.jdiacomp.2016.10.008

18. Abrahamian H, Kautuky-Willer A, Riesland-Seifert A , et al. Mental disorders and diabetes mellitus. *Wien Klin Wochenschr*. 2016; 128(suppl 2): S170-S178. doi: 10.1007/s00508-015-0939-8

19. Girlin M. Lithium side effects and toxicity: Prevalence and management strategies. *Int J Bipolar Disord*. 2016; 4: 27. doi: 10.1186/s40345-016-0068-y

20. Perez-Iglesias-R, Crespo-Facorro B, Martinez-Garcia O, et al. Weight gain indiced by haloperidol, risperidone and olanzapine after 1 year: Findings of a randomized clinical trial in a drug-naïve population. *Schizophr Res*. 2008; 99: 13-22. doi: 10.1016/j.schres.2007.10.022

21. El-Khatih F, Rauch enzauner M, Lechleitner M, et al. Valproate, weight gain and carbohydrate craving: A gender study. *Seizure*. 2007; 16: 226-232. doi: 10.1016/j.seizure.2006.12.009

22. Gaspari CN, Guerreiro CA. Modification in body weight associated with antiepileptic drugs. *Arq Neuropsiquiatr*. 2010; 68: 277-281. doi: 10.1590/S0004-282X2010000200024

23. Matson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine in the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The department of vetaerans affairs epilepsy cooperative study No. 264 group. *N Engl J Med*. 1992; 327: 765-771. doi: 10.1056/NEJM199209103271104

24. Lampi Y, Eshel Y, Rapaport A, Sarova-Pinhas I. Weight gain , increased appetite and excessive food intake induced by carbamazepine. *Clin Neuropharmacol*. 1991; 14: 251-255.

25. Hamed SA. Antiepileptic drugs influence on body weight in people with epilepsy. *Expert Rev Clin Pharmacol*. 2015; 8: 103-114. doi: 10.1586/17512433.2015.991716

26. De Toledo JC, Toledo I, De Cerce J, Ramsay RE. Changes in body weight with chronic, high dose gabapentin therapy. *Ther Drug Monit*. 1997; 19: 394-396.

27. Baular M, Cavalcanti D, Semah F, Arzimanoglou A, Portal JJ. Gabapentin add on therapy with adaptable dose in 610 patients with partial epilepsy: An open observational study. The French gabapentin collaborative group. *Seizure*. 1998; 7: 55-62.

28. Berthon BS, MacDonald-Wicks LK, Wood LG. A systematic review of the effect of oral glucocorticoids on energy intake, appetite and body weight in humans. *Nutr Res*. 2014; 34: 179-190. doi: 10.1016/j.nutres.2013.12.006

29. Mana boriboon B, Silverman ED, Homsanit M, Chui H, Kaufman M. Weight change associated with corticosteroid therapy in adolescents with systemic lupus erythematosis. *Lupus*. 2013; 22: 164-170. doi: 10.1177/0961203312469260

30. Berenson AB, Rehman M. Changes in weight, total fat,percent

body fat and central to peripheral fat ratio associated with injectable and oral contraceptive use. *Am J Obstet Gynecol.* 2009; 200: e1-329.e8. doi: 10.1016/j.ajog.2008.12.052

31. Sharma AM, Pischon T, Hardt S, Kunz I, Luft EC. Hypothesis: Beta-adrenergic receptor blockers and weight gain: A systematic analysis. *Hypertension.* 2001; 37: 250-254. doi: 10.1161/01.HYP.37.2.250

32. Blundell JE, Dulloo AG, Salvador J, Fruhbeck G. EASO SAB working group on BMI. Beyond BMI-phenotyping the obesities. *Obes Facts.* 2014; 7: 322-328. doi: 10.1159/000368783

33. Gomez-Ambrosi J, Silva C, Galotre JC, et al. Body mass index, classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *Int J Obes(Lond).* 2012; 36: 286-294. doi: 10.1038/ijo.2011.100

34. Cameron AJ, Sicree RA, Zimmett PZ, et al. Cut-points for waist circumference in Europids and South Asians. *Obesity(Silver Spring).* 2010; 18: 2039-2046. doi: 10.1038/oby.2009.455

35. World Health Orginazaion (WHO) Expert Consultation. Appropriate body mass index, for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004; 363: 157-163. doi: 10.1016/S0140-6736(03)15268-3

36. Tsigos C, Hainer V, Basdevant A, et al. Management of obesity in adults: European clinical practice guidelines. *Obes Facts.* 2008; 1: 106-116. doi: 10.1159/000126822

37. Yumuk Y, Fruhbeck G, Oppert JM, Woodward E, Toplak H. An EASO position statement on multidisciplinary obesity management in adults. *Obes Facts.* 2014; 7: 96-101. doi: 10.1159/000362191

38. Beaudart C, McClosekey E, Bruyere O, et al. Sarcopenia in daily practice assessment and management. *BMC Geriatr.* 2016; 16: 170. doi: 10.1186/s12877-016-0349-4

39. Morley JE, Anker SD, Von Haehling S. Prevalence, incidence and clinical impact of sarcopenia: Facts, numbers and epidemiology update 2014. *J Cachexia Sarcopenia Muscle.* 2014; 5: 253-259. doi: 10.1007/s13539-014-0161-y

40. Malmstrom TK, Miller DK, Simonsick EM, Ferucci L, Morley JE. SARC-F: A symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle.* 2016; 7: 28-36. doi: 10.1002/jcsm.12048

41. Otto M, Kautt S, Kremer M, Kienle P, Post S, Hasenberg T. Handgrip strength as a predictor for post bariatric body composition. *Obes Surg.* 2014; 24: 2082-2088. doi: 10.1007/s11695-014-1299-6

42. Portier P, Despres JP. Exercise in weight management of obesity. *Cardiol Clinic.* 2001; 19: 459-470. doi: 10.1016/S0733-8651(05)70229-0

43. Willis LH, Stentz CA, Bateman LA, et al. Effect of aerobic and/or resistance training on body mass and get mass in overweight and obese adults. *J Appl Physiol (1985).* 2012; 113: 1831-1837. doi: 10.1152/japplphysiol.01370.2011

44. Geliebter A, Ochner CN, Dambkowski CL, Hashim SA. Obesity-related hormones and metabolic risk factors: A randomized trial or diet plus either strength or aerobic treaining *versus* diet alone in overweight participants. *J Diabetes Obes.* 2014; 1: 1-7.

45. Look AHEAD Research Group. Eight year weight loss with an intensive lifestyle intervention: The look AHEAD study.*Obesity (Silver Spring).* 2014; 22: 5-13. doi: 10.1002/oby.20662

46. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low carbohydrate, Mediterranean, or low fat diet. *N Engl J Med.* 2008; 359: 229-241. doi: 10.1056/NEJMoa0708681

47. Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of a high protein, low carbohydrate diets in the treatment of type 2 diabetes: A 12 month randomized controlled trial. *Diabetologia.* 2011; 54: 731-740. doi: 10.1007/s00125-010-2027-y

48. Krebs JD, Elley CR, Parry Strong A, et al. The Diabetes Excess Weight loss(DEWL)Trial: A randomized Controlled trial of high protein, *versus* high carbohydratediets over 2 years in type 2 diabetes. *Diabetologia.* 2012; 55: 905-914. doi: 10.1007/s00125-012-2461-0

49. Esposito K, Maiorino MJ, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycaemic druf therapy in newly diagnosed type 2 diabetes: A randomized trial. *Ann Intern Med.* 2009; 151: 306-314.

50. Belwal T, Nabavi SF, Nabavi SM, Habtemariam H. Dietary anthocyanins and insulin resistance: When food becomes a medicine. *Nutrients.* 2017; 9: e1111. doi: 10.3390/nu9101111

51. Clark JL, Taylor CG, Zahradka P. Rebelling against the (insulin)resistance: A review of the proposed insulin-sensitizing actions of soybeans, chickpeas, and their bioactive compounds. *Nutrients.* 2018; 10: e434. doi: 10.3390/nu10040434

52. Low JY, Lacy KE, McBride RL, Keast RS. Carbohydrate taste sensitivity is associated with starch intake and waist circumference in adults. *J Nutr.* 2017; 147: 2235-2242. doi: 10.3945/jn.117.254078

53. Low JY, Lacy KE, McBride RL. The associations between oral complex carbohydrate sensitivity, BMI, liking and consumption of complex carbohydrate based foods. *J Food Sci.* 2018; 83: 2227-2236. doi: 10.1111/1750-3841.14276

54. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the atkins, ornish, weight watchers and zone diets for weight loss and heart disease risk reduction: A randomized trial. *JAMA.* 2005; 293: 43-53. doi: 10.1001/jama.293.1.43

55. Habtemariam H. Could we really use aloe vera food supplements to treat diabetes? Quality control issues. *Evidence Based Complementary and Alternative Medicine.* 2017; 2017: doi: 10.1155/2017/4856412

56. Wadden TA, West DS, Neiberg RH, et al. One year weight losses in the look AHEAD study: Factors associated with success. *Obesity (Silver Spring).* 2009; 17: 713-722. doi: 10.1038/oby.2008.637

57. Wycherley TF, Buckley ID, Noakes M,Clifton PM, Brinkworth GD. Long term effects of a very low carbohydrate weight loss diet on exercise capacity and tole rance in overweight and obese adults. *J Am Coll Nutr.* 2014; 33: 267-273. doi: 10.1080/07315724.2014.911668

58. Kaur KK, Allahbadia GN, Singh M. Weight loss associated with high protein intake in obesity: Interactions of gut microbiota in protein sources influencing this positive effect. *Acta Scientific Nutritional Health.* 2018; 2: 80-89.

59. Cawthon PM, Fox KM, Gandra SR, et al. Do muscle mass, muscle density, strength and physical function similarly influence risk of hospitalization in older adults? *J Am Geriatr Soc.* 2009; 57: 1411-1419. doi: 10.1111/j.1532-5415.2009.02366.x

60. Bellfiore A, Frasca F, Pandini G, Sciacca L,Vigneri R. Insulin receptor isoforms nd insulin receptors/insulin like growth factor receptor hybrids in physiology and disease. *Endocr Rev.* 2009; 30: 586-623. doi: 10.1210/er.2008-0047

61. Signeri R, Goldfine ID, Frittita I. Isulin, insulin receptors and cancer. *Endoc Invest.* 2016; 39: 1365-1376. doi: 10.1007/s40618-016-0508-7

62. Hainer V, Toplak H, Stitch V. Fat or fit: What is more important? *Diabetes Care.* 2003; 26: 3230-3236. doi: 10.2337/dc09-S346

63. Servan PR. Obesity and diabetes. *Nitr Hosp.* 2013; 28 Suppl5: 138-143. doi: 10.3305/nh.2013.28.sup5.6929

64. Farr OM, Mantzoros CS. Treatment options to prevent diabetes in subjects with prediabetes: Efficacy, cost effectiveness and future outlook. *Metabolism.* 2017; 70: 192-195. doi: 10.1016/j.metabol.2016.12.017

65. Lindstrom J, Louheranta A, Mannelin M, et al. The finnish diabetes prevention study (DPS): Lifestyle interventions and 3-year results on diet and physical activity. *Diabetes Care.* 2003; 26: 3230-3236. doi: 10.2337/diacare.26.12.3230

66. Knowler WC, Barrett-Conoor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002; 346: 393-403. doi: 10.1056/NEJMoa012512

67. Leom ME, Powme JK, Anderson AS, Garthwatt PH. Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med.* 1990; 7: 228-233. doi: 10.1111/j.1464-5491.1990.tb01375.x

68. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care.* 2000; 23: 1499-1504. doi: 10.2337/diacare.23.10.1499

69. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care.* 2011; 34: 1481-1486. doi: 10.2337/dc10-2415

70. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle interventions on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four year results of the Look AHEAD trial. *Arch Int Med.* 2010; 176: 1566-1575. doi: 10.1001/archinternmed.2010.334

71. Bristor GD, Borraidale KE, Sanders MH, et al. A randomized study on the effect of weight losson obstructive sleep apnea among obese patients with type 2 diabetes: The sleep AHEAD study. *Arch Int Med.* 2009; 169: 1619-1626. doi: 10.1001/archinternmed.2009.266

72. Rubin RR, Wadden TA, Bahnson JL, et al. Impact of intensive lifestyle interventions on depression and health related quality of life in type 2 diabetes: The Look AHEAD trial. *Diabetes Care.* 2014; 31: 1544-1553. doi: 10.2337/dc13-1928

73. Franz MJ. The role of weight loss in the management of type 2 diabetes. *US Endocrinol.* 2016; 12: 14-15. doi: 10.17925/USE.2016.12.01.14

74. Arab L, Dhaliwal SK, Martin CJ, Larios AD, Jackson NJ, Elashoff D. Association between walnut consumption and diabetes risk in NHANES. *Diabetes Metab Res Rev.* 2018; 34: e3031. doi: 10.1002/dmrr.3031

75. Farr OM, Tuccinardi D, Upadhyay J, Oussada SM, Mantzoros CS. Walnut consumption increasesactivation of the insula to highly desirable food cues: A randomized, double blind placebo-controlled crossover fMRI study. *Diabetes Obes Metab.* 2018; 20: 173-177. doi: 10.1111/dom.13060

76. Garg SK, Maurer H, Reed K, Selagamsetty R. Diabetes and cancer: Two diseases with obesity as a common risk. *Diabetes Obes Metab.* 2014; 16: 97-110. doi: 10.1111/dom.12124

77. Eeg-Oloffson K, Cederholm J, Nilsson PM, et al. Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: An observational study in 13,087 patients. *Diabetologia.* 2009; 52: 65-73. doi: 10.1007/s00125-008-1190-x

78. Toplak H, Hoppichler F, Wascher TC, Schindler K, Ludvuk B. Obesity and type 2 diabetes. *Wien Klin Wochenshr*. 2016; 128(supp2): S196-200. doi: 10.1007/s00508-016-0986-9

79. Kaur KK, Allahbadia GN, Singh M. Current management of obesity in an infertile female-recent advances and future prospec-

tive drugs. *Journal of Pharmacy and Nutrition Sciences.* 2013; 3: 1-13.

80. Kaur KK, Allahbadia GN, Singh M. An update on a etiopathogenesis and management of obesity. *Obesity and Control Therapies:Open Access.* 2016; 3: 1-17. doi: 10.15226/2374-8354/2/2/00123

81. Van Gaal L, Seneen A. Weight management in type 2 diabetes: Current and emergomg approaches to treatment. *Diabetes Care.* 2015; 38: 1161-1172. doi: 10.2337/dc14-1630

82. Ahren B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trial. *Diabetes Obes Metab.* 2018; 20: 2210-2219. doi: 10.1111/dom.13353

83. Kaur KK, Allahbadia GN, Singh M. An update on bariatric surgery with long term efficacy and its utilization for medical therapy development from the different mechanism of action and other short comes to be outcome. *BAOJ Surgery.* 2018; 4: 038.

84. Buchwald H, Avdor Y, Braunwald E, et al. Bariatric surgery: A systematic review and meta-analysis. *JAMA.* 2004; 292: 1724-1737. doi: 10.1001/jama.292.14.1724

85. Bayhan BE, Greenway FL, Bellanger DE, O'Neil CE. Early resolurion of type 2 diabetes seen after Roux-en-Y gastric bypass and sleeve gastrectomy. *Diabetes Technol Ther.* 2012; 14: 30-34. doi: 10.1089/dia.2011.0151

86. Munzberg H, Laque A, Yu S, Rezat-Zadeh K, Berthoud HR. Appetite and body weight regulation after bariatric surgery. *Obes Rev.* 2015; (Suppl 1): 77-90. doi: 10.1111/obr.12258

87. Mathes CM, Spector AC. Food selection and taste changes in humans after Roux-en-Y gastric bypass: A direct measure s approach. *Physiol Behav.* 2012; 107: 476-483. doi: 10.1016/j.physbeh.2012.02.013

88. Sjoholm K, Pejmen P, Karason R, et al. Incidence of remission in type 2 diabetes in relation to degree of obesity at baseline and 2 year weight change: The swedish obese subjects (SOS) study. *Diabetologia.* 2015; 48: 1448-1455. doi: 10.1007/s00125-015-3591-y

89. Thibault R, Huher O, Azagury DE, Pichard C. Twelve key nutritional features in bariatric surgery. *Clin Nutr.* 2016; 35: 12-17. doi: 10.1016/j.clnu.2015.02.012

90. Schauer PR, Bhatt DI, Karwan JP, et al. Bariatric surgery *versus* intensive medical therapy for diabetes -5-year outcomes. *N Engl J Med.* 2017; 376: 641-651. doi: 10.1056/NEJMoa1600869

91. Haner WS. Vitamin A signaling and homeostasis in obesity, diabetes, and metabolic disorders. *Pharmacol Ther.* 2019; S0163-7258: 30012-30019. doi: 10.1016/j.pharmthera.2019.01.006

92. Dakshinamurti K. Vitamins and their derivatives in the prevention and treatment of metabolic syndrome diseases (diabetes). *Can J Physiol Pharmaciol.* 2015; 93: 355-362. doi: 10.1139/cjpp-2014-0479

93. Cione E, Caroleo MC, Cannataro R, Perri M, Pingitore A, Genchi G. Viatamin A and diabesity: New insights for drug discovery. *Mini Review Med Chem.* 2016; 16: 738-742. doi: 10.2174/1389557515666150709112822

94. Holsky S, Ellis SI. Obesity, indulin resistance and type 1 diabetes mellitus. *Curr Opin Diabetes Obes.* 2015; 22: 277-282. doi: 10.1097/MED.0000000000000170

95. Bostrom P, Wu J, Jedrychowski MP, et al. A PGC1-α dependent myokine that drives brown fat like development of white fat thermogenesis. *Nature.* 2012; 481: 463-468. doi: 10.1038/nature10777

ISSN 2377-8385

OBESITY RESEARCH
Open Journal

Openventio
PUBLISHERS

Editorial

Re-evaluating the Optimal Exercise for the Critical Peri and Postmenopausal Years

Ifigeneia Giannopoulou, PhD*

Senior Lecturer in Sport and Exercise Science, School of Sport and Service Management, University of Brighton, Eastbourne, Brighton20 7SR, UK

Corresponding author
Ifigeneia Giannopoulou, PhD
Senior Lecturer in Sport and Exercise Science, School of Sport and Service Management, University of Brighton, Eastbourne, Brighton20 7SR, UK;
Tel. 01273 643731; E-mail: I.Giannopoulou@brighton.ac.uk

Article information
Received: March 7th, 2019; **Accepted:** March 25th, 2019; **Published:** March 28th, 2019

Cite this article
Giannopoulou I. Re-evaluating the optimal exercise for the critical peri and postmenopausal years. *Obes Res Open J.* 2019; 6(1): e1-e4. doi: 10.17140/OROJ-6-e014

Menopause is characterized by marked changes in the circulating estrogen of the female body.[1] As women age, progressively declines in ovarian function lead to a gradual reduction in estrogen secretion that ultimately ceases when menopause is reached. This transitional time is termed the perimenopausal period and it occurs approximately within one year of its commencement.[2] The perimenopausal years are crucial for the future health of females as the observed hormonal alterations can lead to a number of psychophysiological changes that can increase the risk of disease if not prevented early.[2] Specifically, during the perimenopausal years the diminished concentrations of estrogens, reduce their protective role on health and contribute to significant physiological disturbances.[3] Adverse health effects such as reductions in fat-free mass (sarcopenia), accumulation of body fat and intra-abdominal visceral fat and associated adverse cardiovascular and metabolic impairments namely hypertension, atherosclerosis and insulin resistance are observed.[1] Consequently, there is a significantly increased risk in the development of obesity and its comorbidities namely cardiovascular disease and type 2 diabetes, that can reduce the quality of life and dramatically increase the risk of mortality in older women.[3] In conjunction with the aforementioned conditions, significant impairments in cognitive and mood state are observed in the peri and postmenopausal years, further increasing the risk of morbidity and mortality in older women.[4-6] An increased prevalence of anxiety and depression and cognitive declines such as loss of concentration, memory and a high risk of developing dementia and Alzheimer's disease have been noted, recognizing menopause not only as a reproductive but also as a neurological transitional state.[7-9] These effects are exacerbated by the declines in physical activity participation and low exercise compliance observed in older women. The complex and multifaceted pathophysiology of the peri and postmenopausal years, makes the treatment of the aforementioned comorbidities very difficult and challenging and warrants further research on identifying the ideal treatment plan for this population. Particularly, preventive treatment plans during the perimenopausal years are deemed essential in slowing down or delaying the development of chronic mental and non-mental diseases later in life and increasing the well-being and quality of life of older women.

It is well established that exercise is an essential treatment plan for the prevention of chronic diseases in older women.[10] A number of research studies have demonstrated the central role that regular endurance exercise has on the health, well-being, and quality of life of older women by partly attenuating some of the physiological changes occurring with aging.[11,12] In healthy postmenopausal women, participation in moderate intensity continuous exercise training alone has been shown to induce improvements in body fat and abdominal visceral adiposity, insulin resistance, lipid levels and inflammatory markers that can be further accelerated when exercise is combined with a balanced nutrition plan.[13,14] In overweight and obese postmenopausal women, regular moderate-intensity endurance exercise for 3-4 months has been well documented to improve body mass index, body composition and insulin sensitivity.[15] In type 2 diabetic obese postmenopausal women, moderate intensity endurance exercise can induce significant improvements in glycemic control, Hemoglobin A1c and inflammatory markers primarily due to reductions in intra-abdominal visceral adiposity and increases in exercise capacity.[16-18] While, in hypertensive postmenopausal women there is strong evidence to support the important role of endurance exercise on reducing cardiovascular risk factors through significant improvements in blood pressure, autonomic tone, baroreflex sensitivity and oxidative stress.[19,20] Finally, studies on the effects of regular endurance exercise on mood

state in women during the menopausal transition, demonstrate significant improvements in depressive symptoms and reduction in menopause-related anxiety and mood disorders after endurance exercise training.[4,21]

Despite the accumulated evidence on the effects of endurance exercise on the postmenopausal years, there is a scarcity of data on the effects of exercise on the critical time period of the perimenopausal years. The limited studies conducted demonstrate the promising effects of endurance exercise training on the health and exercise capacity of perimenopausal women but also stress the need for more studies to be conducted in this understudied population.[11,22-25] In the few studies that have been conducted, it is evident that moderate-intensity endurance exercise primarily in the form of walking can induce significant improvements in body weight, body fat, aerobic fitness and overall exercise capacity in perimenopausal women.[11,23] Moreover, endurance exercise has been shown to induce significant improvements in independent cardiovascular risk factors such as glucose and lipid levels and overall quality of life in pre and perimenopausal women.[22,24,25] However, no research studies have investigated the effects of exercise on the mood and cognitive state of perimenopausal women, leaving a gap in the literature on a crucial time period for women's mental health. There is an urgent need to conduct more research studies on the perimenopausal years in order to identify optimal lifestyle treatment plans that can prevent the development of mental and non-mental health problems at an early stage.

High-intensity interval exercise (HIIE) has recently emerged as a favourable exercise modality for clinical populations with obesity, type 2 diabetes and cardiovascular disease leading to comparable or even faster improvements in exercise capacity, body composition and cardiometabolic health parameters.[26-29] Specifically, similar or faster improvements in exercise capacity, insulin resistance, blood pressure and cardiac function have been documented in older clinical populations with metabolic syndrome, cardiovascular disease and type 2 diabetes when training with HIIE compared to continuous exercise.[29,30] In older male and female obese populations, HIIE has been documented to have similar effectiveness with moderate intensity continuous exercise across all body composition measures but in a more time-efficient way, by requiring less than 40% training time compared to continuous exercise.[27] Furthermore, HIIE has been reported to lead to similar enjoyment and exercise adherence levels in overweight and obese older males and females with continuous exercise, demonstrating the important role that it might have on exercise compliance in this population.[31] However, limited evidence exists on the effects of HIIE on the exercise capacity and health on the specific high-risk time periods of peri and menopause. In postmenopausal women, 16-weeks of HIIE have been shown to lead to greater weight loss and improvements in body composition compared to continuous moderate intensity exercise in healthy postmenopausal women[32] and greater reductions in intra-abdominal adiposity in obese postmenopausal type 2 diabetic women.[12,33,34] Moreover, Mandrup et al[12] has demonstrated significant improvements in body composition as observed by increases in lean body mass and reductions in fat mass and improvements in cardiometabolic risk factors in postmenopausal women after HIIE training. Finally, Egelund et al[35] studied the effects of HIIE on early postmenopausal women and found marked improvements in cardiac function in terms of systolic and diastolic function after 12 weeks of cycle interval training.

The effects of HIIE on the perimenopausal years is largely understudied. In younger overweight and obese women, HIIE has been shown to be a potentially more effective mode of exercise compared to continuous exercise, in terms of time-efficiency and perception of effort while significantly improving aerobic fitness, blood glucose and lipid levels.[36] In a recent study that our research group conducted investigating the effects of an acute bout of interval exercise on psychophysiological adaptations in overweight perimenopausal women, we found that one acute bout of HIIE alone was effective in inducing significant improvements in the systolic and diastolic blood pressure of this population.[37] Moreover, it led to improvements in mood, exercise enjoyment and exercise tolerance, especially when combined with high carbohydrate *versus* high protein pre-exercise feedings, while no changes were noted in cognitive capacity.[37] Further, in unpublished preliminary data from our research group, we have found that one bout of interval exercise can induce similar fat oxidation rates and exercise enjoyment compared to continuous exercise in a group of overweight perimenopausal women, mimicking the findings of an earlier study in younger women where 7 sessions of HIIE over a two-week period resulted in marked elevations in whole body and skeletal muscle fatty acid oxidation.[38] It is important to note that the improvements seen in our group of perimenopausal women with HIIE were achieved in approximately half the exercise duration compared to continuous exercise, suggesting significant practical training applications for this population, given that "lack of time" is the most commonly cited barrier to regular exercise participation. Research on the effects of long-term HIIE have also shed some light on the potential advantageous effects of this mode of exercise for older women. Seidelin et al[39] recently demonstrated improvements in aerobic capacity in late pre-menopausal women after intermittent exercise training for 12 weeks. Moreover, the group of Mandrup et al[12] reported that a 3-month high-intensity aerobic training intervention induced similar levels of improvements in cardiovascular disease and type 2 diabetes risk factors in pre-menopausal women. Finally, Egelund et al[35] showed that a 12-week HIIE intervention on pre-menopausal women led to significant positive adaptations in cardiac function such as left ventricle mass and left atrial end-diastolic and end-systolic volumes.[40] More evidence is required to further investigate and establish the effectiveness of HIIE on the perimenopausal years, especially in terms of neurological and cognitive health disturbances in this population.[41]

It is evident that additional investigations are needed to assess the effects of exercise on the critical perimenopausal years. Perimenopause offers the unique opportunity for chronic disease risk reduction in women at an early stage, prior to menopause, at which time point the development of chronic diseases is accentuated.[42] More studies need to be conducted on clinical exercise modalities such as high-intensity interval exercise clinical proto-

cols that can optimally counteract the effects of menopause on women's health and reduce the risk of developing mental health-related comorbidities. Re-evaluating the optimal exercise mode for this population could lead to a more effective exercise prescription that could enhance exercise adherence and enjoyment while allowing women to exercise in a more time-efficient manner compared to the traditionally prescribed exercise programs.

REFERENCES

1. Bacon JL. The menopausal transition. *Obstet Gynecol Clin North Am*. 2017; 44(2): 285-296. doi: 10.1016/j.ogc.2017.02.008

2. Hale GE, Robertson DM, Burger HG. The perimenopausal woman: endocrinology and management. *J Steroid Biochem Mol Biol*. 2014; 142: 121-131. doi: 10.1016/j.jsbmb.2013.08.015

3. Van Dijk GM, Kavousi M, Troup J, Franco OH. Health issues for menopausal women: the top 11 conditions have common solutions. *Maturitas*. 2015; 80(1): 24-30. doi: 10.1016/j.maturitas.2014.09.013

4. Bromberger JT, Schott LL, Kravitz HM, et al. Longitudinal change in reproductive hormones and depressive symptoms across the menopausal transition: Results from the Study of Women's Health Across the Nation (SWAN). *Arch Gen Psychiatry*. 2010; 67: 598-607. doi: 10.1001/archgenpsychiatry.2010.55

5. De Kruif M, Spijker AT, Molendijk ML. Depression during the perimenopause: A meta-analysis. *J Affect Disord*. 2016; 206: 174-180. doi: 10.1016/j.jad.2016.07.040

6. Gibbs Z, Lee S, Kulkarni J. Factors associated with depression during the perimenopausal transition. *Womens Health Issues*. 2013; 23(5): e301-e307. doi: 10.1016/j.whi.2013.07.001

7. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nat Rev Endocrinol*. 2015; 11(7): 393-405. doi: 10.1038/nrendo.2015.82

8. Georgakis MK, Kalogirou EI, Diamantaras AA, et al. Age at menopause and duration of reproductive period in association with dementia and cognitive function: A systematic review and meta-analysis. *Psychoneuroendocrinology*. 2016; 73: 224-243. doi: 10.1016/j.psyneuen.2016.08.003

9. Wariso BA, Guerrieri GM, Thompson K, et al. Depression during the menopause transition: Impact on quality of life, social adjustment, and disability. *Arch Womens Ment Health*. 2017; 20(2): 273-282. doi: 10.1007/s00737-016-0701-x

10. Kemmler W, Kohl M, von Stengel S. Long-term effects of exercise in postmenopausalwomen: 16-year results of the erlangen fitness and osteoporosis prevention study (EFOPS). *Menopause*. 2017; 24(1): 45-51. doi: 10.1097/GME.0000000000000720

11. Gao HL, Gao HX, Sun FM, Zhang L. Effects of walking on body composition in perimenopausal and postmenopausal women: a systematic review and meta-analysis. *Menopause*. 2016; 23(8): 928-934. doi: 10.1097/GME.0000000000000627

12. Mandrup CM, Egelund J, Nyberg M. Effects of high-intensity training on cardiovascular risk factors in pre-menopausal and post-menopausal women. *Am J Obstet Gynecol*. 2017; 216(4): 384.e1-384.e11. doi: 10.1016/j.ajog.2016.12.017

13. Mendoza N, De Teresa C, Cano A, et al. Benefits of physical exercise in postmenopausal women. *Maturitas*. 2016; 93: 83-88. doi: 10.1016/j.maturitas.2016.04.017

14. Ross R, Janssen I. Physical activity, total and regional obesity: Dose-response considerations. *Med Sci Sports Exerc*. 2001; 33(6 Suppl): S521-S527. doi: 10.1097/00005768-200106001-00023

15. Bueno-Notivol J, Calvo-Latorre J, Alonso-Ventura V, et al. Effect of programmed exercise on insulin sensitivity in postmenopausal women: A systematic review and meta-analysis of randomized controlled trials. *Menopause*. 2017; 24(12): 1404-1413. doi: 10.1097/GME.0000000000000936

16. Cuff DJ, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD, Frohlich JJ. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. *Diabetes Care*. 2003; 26(11): 2977-2982. doi: 10.2337/diacare.26.11.2977

17. Giannopoulou I, Ploutz-Snyder LL, Carhart R, et al. Exercise is required for visceral fat loss in postmenopausalwomen with type 2 diabetes. *J Clin Endocrinol Metab*. 2005; 90(3): 1511-1518. doi: 10.1210/jc.2004-1782

18. Giannopoulou I, Fernhall B, Carhart R, et al Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. *Metabolism*. 2005; 54(7): 866-875. doi: 10.1016/j.metabol.2005.01.033

19. Jarrete AP, Novais IP, Nunes HA, Puga GM, Delbin MA, Zanesco A. Influence of aerobic exercise training on cardiovascular and endocrine-inflammatory biomarkers in hypertensive postmenopausal women. *J Clin Transl Endocrinol*. 2014; 1: 108-114. doi: 10.1016/j.jcte.2014.07.004

20. Lin YY, Lee SD. Cardiovascular benefits of exercise training in postmenopausal hypertension. *Int J Mol Sci*. 2018; 19(9). pii: E2523. doi: 10.3390/ijms19092523

21. Sternfeld B, Dugan S. Physical activity and health during the menopausal transition. *Obstet Gynecol Clin North Am*. 2011; 38(3): 537-566. doi: 10.1016/j.ogc.2011.05.008

22. Coll-Risco I, Borges-Cosic M, Acosta-Manzano P, Camiletti-Moirón D, Aranda P, Aparicio VA. Effects of concurrent exercise on cardiometabolic status during perimenopause: the

FLAMENCO Project. *Climacteric*. 2018; 21(6): 559-565. doi: 10.1080/13697137.2018.1526892

23. Ring-Dimitriou S, Steinbacher P, von Duvillard SP, Kaessmann H, Müller E, Sänger AM. Exercise modality and physical fitness in perimenopausal women. *Eur J Appl Physiol*. 2009; 105(5): 739-747. doi: 10.1007/s00421-008-0956-7

24. Zhang J, Chen G, Lu W, et al. Effects of physical exercise on health-related quality of life and blood lipids in perimenopausal women: A randomized placebo-controlled trial. *Menopause*. 2014; 21(12): 1269-1276. doi: 10.1097/GME.0000000000000264

25. Wu L, Chen R, Ma D, Zhang S, Walton-Moss B, He Z. Effects of lifestyle intervention improve cardiovascular disease risk factors in community-based menopausal transition and early postmenopausal women in China. *Menopause*. 2014; 21(12): 1263-1268. doi: 10.1097/GME.0000000000000248

26. Hollekim-Strand SM, Bjørgaas MR, Albrektsen G, Tjønna AE, Wisløff U, Ingul CB. High-intensity intervalexercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: A randomized controlled trial. *J Am Coll Cardiol*. 2014; 64(16): 1758-1760. doi: 10.1016/j.jacc.2014.07.971

27. Keating SE, Johnson NA, Mielke GI, Coombes JS. A systematic review and meta-analysis of interval training versus moderate-intensity continuous training on body adiposity. *Obes Rev*. 2017; 18(8): 943-964. doi: 10.1111/obr.12536

28. Su L, Fu J, Sun S, et al. Effects of HIIT and MICT on cardiovascular risk factors in adults with overweight and/or obesity: A meta-analysis. *PLoS One*. 2019; 14(1): e0210644. doi: 10.1371/journal.pone.0210644

29. Wisløff U, Ellingsen O, Kemi OJ. High-intensity interval training to maximize cardiac benefits of exercise training? *Exerc Sport Sci Rev*. 2009; 37(3): 139-146. doi: 10.1097/JES.0b013e3181aa65fc

30. Weston KS, Wisløff U, CoombesJS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med*. 2014; 48(16): 1227-1234. doi: 10.1136/bjsports-2013-092576

31. Vella CA, Taylor K, Drummer D. High-intensity interval and moderate-intensity continuous training elicit similar enjoyment and adherence levels in overweight and obese adults. *Eur J Sport Sci*. 2017; 17(9): 1203-1211. doi: 10.1080/17461391.2017.1359679

32. Grossman JA, Arigo D, Bachman JL. Meaningful weight loss in obese postmenopausal women: a pilot study of high-intensity interval training and wearable technology. *Menopause*. 2018; 25(4): 465-470. doi: 10.1097/GME.0000000000001013

33. Maillard F, Rousset S, Pereira B, et al. High-intensity interval training reduces abdominal fat mass in postmenopausal women with type 2 diabetes. *Diabetes Metab*. 2016; 42(6): 433-441. doi: 10.1016/j.diabet.2016.07.031

34. Maillard F, Pereira B, Boisseau N. Effect of high-intensity interval training on total, abdominal and visceral fat mass: A meta-analysis. *Sports Med*. 2018; 48(2): 269-288. doi: 10.1007/s40279-017-0807-y

35. Egelund J, Jørgensen PG, Mandrup CM, et al. Cardiac adaptations to high-intensity aerobic training in pre-menopausal and recent postmenopausal women: The copenhagen women study. *J Am Heart Assoc*. 2017; 6(8). pii: e005469. doi: 10.1161/JAHA.117.005469

36. Kong Z, Sun S, Liu M, Shi Q. Short-term high-intensity interval training on body composition and blood glucose in overweight and obese young women. *J Diabetes Res*. 2016; 2016: 4073618. doi: 10.1155/2016/4073618

37. Kotopoulea-Nikolaidi M, Watkins E, Giannopoulou I. Effects of high carbohydrate vs. high protein pre-exercise feedings on psychophysiological responses to high intensity interval exercise in overweight perimenopausal women. *Front Nutr*. 2019; 5: 141. doi: 10.3389/fnut.2018.00141

38. Talanian JL, Galloway SD, Heigenhauser GJ, Bonen A, Spriet LL. Two weeks of high-intensity aerobic interval training increases the capacity for fat oxidation during exercise in women. *J Appl Physiol (1985)*. 2007; 102(4): 1439-1447. doi: 10.1152/japplphysiol.01098.2006

39. Seidelin K, Nyberg M, Piil P, Jørgensen NR, Hellsten Y, Bangsbo J. Adaptations with intermittent exercise training in post- and pre-menopausal women. *Med Sci Sports Exerc*. 2017; 49(1): 96-105. doi: 10.1249/MSS.0000000000001071

40. Miszko TA, Cress ME. A lifetime of fitness: Exercise in the perimenopausal and postmenopausal woman. *Clin Sports Med*. 2000; 19(2): 215-232. doi: 10.1016/S0278-5919(05)70200-3

41. Panagiotakos D, Pitsavos C, Chrysohoou C, Skoumas J, Stefanadis C. Status and management of blood lipids in Greek adults and their socio-demographic, life-style and dietary factors: The ATTICA study. Blood lipid distribution in Greece. *Atherosclerosis*. 2004; 173(2): 351-361. doi: 10.1016/j.atherosclerosis.2003.12.03

42. Wisløff U, Støylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: A randomized study. *Circulation*. 2007; 115: 3086-3094. doi: 10.1161/CIRCULATIONAHA.106.675041

ISSN 2377-8385

OBESITY RESEARCH
Open Journal

Openventio
PUBLISHERS

Editorial

Multi-component Lifestyle Interventions for Diabetes and Associated Non-communicable Diseases: Considerations for Future Research

Ahmad Alkhatib, PhD, MSc, RNutr, FRSM*

Professor of Health Nutrition and Sport Science, Institute of Sport Science, University of Taipei, Taipei, Taiwan, Republic of China

Corresponding author
Ahmad Alkhatib, PhD, MSc, RNutr, FRSM
Professor of Health Nutrition and Exercise Science, Institute of Sport Science, University of Taipei, Shilin District, 111, Taipei, Taiwan, Republic of China;
Tel. +886 (0) 934089846; E-mail: drahmadalkhatib@gmail.com

Article information
Received: May 1st, 2019; **Received:** May 16th, 2019; **Accepted:** May 20th, 2019; **Published:** May 23rd, 2019

Cite this article
Alkhatib A. Multi-component lifestyle interventions for diabetes and associated non-communicable diseases: Considerations for future research. *Obes Res Open J.* 2019; 6(1): e5-e6. doi: 10.17140/OROJ-6-e015

Diabetes prevalence is at an alarming level. It is predicted that one in ten adults will have the condition by 2030 compared with one in eleven at present.[1] Despite several global calls for action to reverse such a trend, the number of people with diabetes and associated lifestyle diseases continues to rise leading to significant health burdens, morbidity and premature mortality.[2] Such challenge makes it crucial to adopt immediate preventative policies which embed effective lifestyle diabetes interventions, especially those integrating multi-components interventions.[3]

Adopting a multi-component approach which encompasses changing behavioral and physical aspects is likely to be more effective than a single component diabetes prevention program. Lessons from large lifestyle interventions combining a variety of physical activity patterns with different healthy dietary regimes have unequivocal evidence about their joint long-term effectiveness compared with adopting a single component whether exercise, diet or medication alone.[4,5] For example, the Finish diabetes study was first to show a remarkable 58% reduced rates of diabetes incidence when a longitudinal multi-component intervention (behavioral, exercise and dietary) was followed by individuals with glucose intolerance.[3] Similar longitudinal diabetes risk reduction of 58% was found for those with pre-diabetes in the US diabetes prevention program when exercise and diet approaches were combined, compared with almost half (30% reduction) found when relying on insulin-sensitizing drug Metformin.[5] A fifteen-year follow-up of the latter showed that medication did not elicit better risk-reduction benefits than a multi-component lifestyle intervention.

Adopting healthy behaviors, particularly adopting physical activity and healthy nutrition can have reciprocal favorable outcomes. Observational evidence has reported that amongst older adults (60-80-years-old), those who consumed a healthy diet such as the Mediterranean diet were more likely to be active in their lifestyle than those who consumed a western diet.[6] In such, adopting such a dietary component with an exercise training component provided additional vascular and cardiometabolic protective benefits in high-risk individuals.[7,8] On the other hand, adding an exercise to a multi-nutrient supplementation proved much more effective in preventing age-related decline in high-risk very old frail men and women, than the supplement alone, a single intervention component.[9] The latter study showed that a single component (supplementation only) failed to slow age-related deleterious outcomes compared with favorable outcomes found when strength exercise was combined with the supplementation.[9] In such, interventions should always adopt exercise and nutrition as essential components of a lifestyle intervention strategy. Even at the screening phase, assessing a combined physical activity, cardiorespiratory fitness, nutritional intake alongside diabetes and associated cardiometabolic risk factors, is likely to encourage healthy behavior change in high-risk individuals.[10,11] Therefore, adopting multi-component prevention strategy, both at baseline assessment and throughout the intervention not only augments their benefits but prevents potential hazards.

Addressing as many lifestyle components as feasible is also important. For example, it is now known that sedentary behavior and sleep patterns are associated with the development of diabetes.[12] Recent research evidence has classified sedentary lifestyle behavior, such as TV watching, prolonged sitting hours or driving as an independent risk factor for type-II diabetes.[12,13] Reported as-

sociations include higher type-2 diabetes incidents, cardiovascular disease and all-cause mortality independently of leisure-time physical activity.[13] Since it is difficult to quantify such behaviors in physiological terms, cardiorespiratory fitness remains the gold standard for measuring physical activity or its lack, since that least cardiorespiratory fit individuals suffer from significantly increased chronic disease risks and all cause-mortality risks.[14] Therefore, sedentary behaviors, physical activity, and cardiovascular health can all be assessed through cardiorespiratory fitness as an essential vital sign,[15] and so it should form an integral part of any lifestyle intervention.

The scientific knowledge about the behavioral, lifestyle and biological components is continuously evolving, which enables better targeting of several modifiable disease risk factors for diabetes and associated diseases. This also requires integrating exercise science, nutrition and behavior approaches to personalize future lifestyle interventions. Future studies can take forward previous success stories using multi-component lifestyle interventions based on contemporary knowledge and recent technological advances relevant to the 21st century.

REFERENCES

1. International Diabetes Federation. Diabetes Atlas 7th Edition. 2015. Web site. http://www.diabetesatlas.org/. Accessed April 1, 2019.

2. World Health Organization (WHO). Global Report on Diabetes. 2016. Web site: http://www.who.int/diabetes/global-report/en/. Accessed April 1, 2019.

3. Alkhatib A, Tuomilehto J. Lifestyle diabetes prevention. In: Huhtaniemi I, Martini L, eds. *Encyclopaedia of Endocrine Diseases*, 2nd ed. Amsterdam, Netherlands: Elsevier; 2018.

4. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001; 344(18): 1343-1350. doi: 10.1056/NEJM200105033441801

5. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346(6): 393-403. doi: 10.1056/NEJMoa012512

6. Bibiloni MDM, Julibert A, Argelich E, et al. Western and mediterranean dietary patterns and physical activity and fitness among Spanish older Adults. *Nutrients*. 2017; 9(7): pii: E704. doi: 10.3390/nu9070704

7. Alkhatib A. Effective intervention strategies combining Mediterranean diet and exercise for reducing obesity, metabolic and cardiovascular risks in high-risk populations: Mini review. *Obes Res Open J*. 2015; 1(1): 4-9. doi: 10.17140/OROJ-1-102

8. Alkhatib A, Klonizakis M. Effects of exercise training and Mediterranean diet on vascular risk reduction in post-menopausal women. *Clin Hemorheol Microcirc*. 2014; 57(1): 33-47. doi: 10.3233/CH-131770

9. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994;330(25):1769-75. doi: 10.1056/NEJM199406233302501

10. Alkhatib A. Sedentary risk factors across genders and job roles within a university campus workplace: Preliminary study. *J Occup Health*. 2013; 55: 218-224. doi: 10.1539/joh.12-0158-OA

11. Alkhatib A. High prevalence of sedentary risk factors amongst university employees and potential health benefits of campus workplace exercise intervention. *Work*. 2015; 52(3): 589-595. doi: 10.3233/WOR-152182

12. Alkhatib A. *Sedentary Lifestyle, Predictive Factors, Health Risks and Physiological Implications*. New York, USA: Nova Science Publishers; 2016.

13. Biswas A, Oh PI, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: A systematic review and meta-analysis. *Ann Intern Med*. 2015; 162(2): 123-132. doi: 10.7326/M14-1651

14. Blair SN, Brodney S. Effects of physical inactivity and obesity on morbidity and mortality: Current evidence and research issues. *Med Sci Sports Exerc*. 1999; 31(Suppl): S646-S662. doi: 10.1097/00005768-199911001-00025

15. Despres JP. Physical activity, sedentary behaviours, and cardiovascular health: When will cardiorespiratory fitness become a vital sign? *Can J Cardiol*. 2016; 32(4): 505-513. doi: 10.1016/j.cjca.2015.12.006

ISSN 2377-8385

OBESITY RESEARCH
Open Journal

Openventio PUBLISHERS

Systematic Review

The Role of Genetics in the Pathophysiology of Obesity: A Systematic Review

Renata M. Pinto, MD, MSc[1,2,3,4*]; Lucas S. Steinmetz, [Medical Student][4]; Julio M. G. Barbosa, [Medical Student][4]; Arthur F. C. S. Mendes, [Medical Student][4]; Maria P. Curado, MD, MSc, PhD[1,3]; Aparecido D. da Cruz, MSc, PhD[1,2,5,6]

[1]*Department of Biology, Replicon Research Center, Catholic University of Goiás, Goiânia, GO, Brazil*
[2]*Postgraduate Program in Genetics, Catholic University of Goiás, Goiânia, GO, Brazil*
[3]*Health Sciences PhD Program, Federal University of Goiás, Goiânia, GO, Brazil*
[4]*Department of Pediatrics, Federal University of Goiás, Goiânia, GO, Brazil*
[5]*Laboratory of Human Cytogenetics and Molecular Genetics, Secretary of State for Health of Goiás (LACEN/SESGO), Goiânia, GO, Brazil*
[6]*Biotechnology and Biodiversity Graduate Program, University of Brasília, Brasília, DF, Brazil*

[*]***Corresponding author***
Renata M. Pinto, MD, MSc
Pediatric Endocrinologist, Department of Biology, Replicon Research Center, Catholic University of Goiás, Goiás, Brazil; E-mail: drarenatamachado@gmail.com

Article information
Received: July 7th, 2019; **Revised:** July 30th, 2019; **Accepted:** August 1st, 2019; **Published:** August 14th, 2019

Cite this article
Pinto RM, Steinmetz LDS, Barbosa JMG, Mendes AFCDS, Curado MP, da Cruz AP. The role of genetics in the pathophysiology of obesity: A systematic review. *Obes Res Open J*. 2019; 6(1): 11-17. doi: 10.17140/OROJ-6-137

ABSTRACT

Aim
The obesity epidemic has been largely attributed to changes in lifestyle habits established over the past three decades. These changes are mainly attributed to excessive nutrition and decline in physical activity as well as additional factors such as reduced intestinal microbiota diversity, sleep duration, endocrine disruptors, and reduced variability of the ambient temperature. However, the obesogenic environment is not sufficient to determine the presence of obesity, it is necessary that the lifestyle becomes associated with a personal predisposition for the phenotype to emerge. In this article, we review the main forms of monogenic and syndromic obesity, as well as a historical summary of the search for the genes that add up to confer greater risk for the development of polygenic obesity.

Methods
We carried out a PubMed search, along with ExcerptaMedica database (EMBASE)/Cochrane library, Web Sciences for the Medical Subject Headings (MeSH) terms "obesity" AND "genetics" for the past 5-years.

Results
We found a total of 14057 articles pertaining to obesity and genetics together of which we selected 92 articles for this review after getting articles after searching cross references.

Conclusion
Studies with twins and adopted children show that 55 to 80% of the variation of body mass index (BMI) is attributed to genetic factors. According to the genetic criteria, obesity can be classified as A) Monogenic - when a mutated gene is responsible for the phenotype; B) Syndromic - when a set of specific symptoms are present and a small group of genes is involved; usually the term is used to describe obese patients with cognitive delay, dysmorphic features, organ-specific abnormalities, hyperphagia, and/or other signs of hypothalamic dysfunction; C) Polygenic - also called "common" obesity, present in up to 95% of cases. Many genes add up to give a greater risk to the individual, and if associated with some habits culminates in obesity. In spite of its great relevance, the search for the genes that raise the risk of obesity has not been easy. It is still a challenge for the scientific community to separate the genetic element from the environmental component in the etiology of this disease. Individuals more susceptible to excessive adiposity may carry risk variants in the genes that influence appetite control, the regulation of cellular machinery, lipid metabolism and adipogenesis, the energy expenditure, insulin signaling, and inflammation.

Keywords
Obesity; Genetics; Polygenic; Monogenic; Syndromic; Polymorphism.

INTRODUCTION

Obesity is a serious and growing public health problem. It is a significant risk factor for the leading causes of mortality, including type 2 diabetes, cardiovascular diseases, and certain types of cancer. The number of individuals with weight excess (obesity+overweight) increased from 857 million in 1980 to 2.1 billion in 2013, and it is projected to reach levels of 89% and 85% of men and women, respectively, in 2030.[1,2] Until recently, obesity was considered only as a consequence of an imbalance between intake and energy expenditure; obesity is now seen as a neurobehavioral disease, in which there are alterations in the hypothalamic control of hunger and satiety and energy expenditure.[3,4]

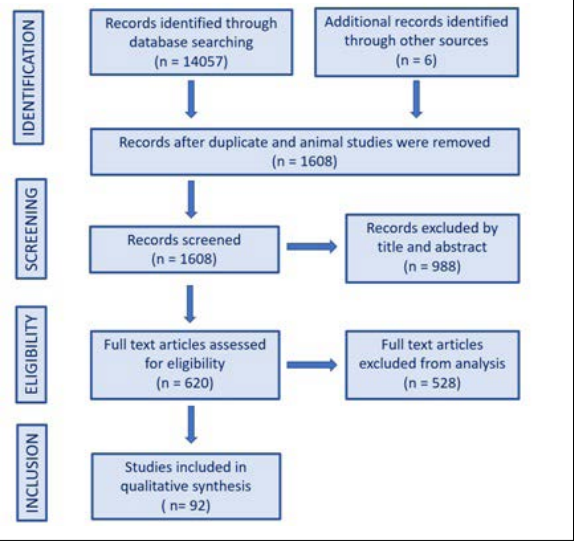
METHODS

We carried out a PubMed search, along with excerpta medica database (EMBASE)/Cochrane library, Web Sciences for the Medical Subject Headings (MeSH) Terms "obesity"AND genetics" for the past 5-years.

RESULTS

We found a total of 14057 articles pertaining to obesity and genetics together, after exclusions and getting articles searching through cross references, 92 articles were selected for qualitative synthesis, and 40 are the basis for this review (Figure 1).

Figure 1. *Article Selection Flowchart*



Obesity Epidemic

The obesity epidemic has been largely attributed to changes in lifestyle habits established over the past three decades. These changes are mainly attributed to excessive nutrition and decline in physical activity,[5,6] as well as additional factors such as reduced intestinal microbiota diversity, sleep duration, endocrine disruptors, and reduced variability of the ambient temperature.[5,7] However, the obesogenic environment is not sufficient to determine the presence of obesity, and it is necessary that the lifestyle becomes associated with a personal predisposition for the phenotype to emerge.[8] Two main evolutionary hypotheses try to explain the current obesity epidemic. They are the "thrifty genotype" and "predator release" hypothesis.

Thrifty Genotype Hypothesis

The "thrifty genotype" hypothesis, described by Neel in 1962,[9] proposes that genetic variations that result in a higher capacity to store energy as fat were positively selected in times of food deprivation. It is believed that over thousands of years this "thrifty genotype" has been perpetuated and was essential in the evolution of humanity. It is postulated that the genes that compose the " thrifty genotype" are responsible for: higher capacity to accumulate energy in the form of fat, ability to save energy in critical periods, ability to "turn off" non-essential metabolic pathways and ability to ingest large amounts of food whenever these are available.[10,11] The same "thrifty genotype" is currently disadvantageous because of easy access to high densely energetic foods and low caloric expenditure.[9]

Predator Release Hypothesis

In 2007, Speakman[12] published the "predator release theory", complementary to the "thrifty genotype" hypothesis.[12] Based on anthropological and epidemiological evidence, genetic tracing and experimental research, the theory postulates that the higher agility characteristic of lean individuals has selected them who are better adapted for food search and escape from predators. That was true until the discovery of fire in the paleolithic period when it is observed a significant increase in body weight over time. The theory attributes this increase in weight not only to the cooking capacity (that leads to better palatability of food and greater absorption of nutrients), but fundamentally to the fact that fire keeps away the main predators (that leads to a reduction on energy expenditure on the run to escape from natural predators). The theory suggests that the initial genetic network responsible for low weight and high body performance characteristics has been suppressed and lost over the millennia.[11]

Genetic Predisposition to Obesity

Several pieces of research show the importance of genetics in the susceptibility to obesity. Studies with twins and adopted children show that 55 to 80% of the variation of body mass index (BMI) is attributed to genetic factors.[13-15] The concordance rate for obesity is higher among monozygotic than dizygotic twins; the weight of adoptive children is closer to that of their biological parents than to their adoptive parents.[13-15]

According to the genetic criteria, obesity is classified as[16]:

A) Monogenic - when a mutated gene is responsible for the phenotype;

B) Syndromic - when a set of specific symptoms are present and

a small group of genes is involved; usually the term is used to describe obese patients with cognitive delay, dysmorphic features, organ-specific abnormalities, hyperphagia, and/or other signs of hypothalamicdys function

C) Polygenic - also called "common" obesity, present in up to 95% of cases. Many genes add up to provide a further risk to the individual, and if associated with some habits culminate in obesity.

Monogenic Obesity

Monogenic obesity disorders are a heterogeneous group of rare conditions that increase food intake and reduce energy expenditure.[16] Many occur from mutations in genes related to the hypothalamic system of energy balance control,[8,11,16,17] as the leptin-melanocortin system. These mutations result in changes in the concentrations and/or activity of hormones, receptors and enzymes, leading to the phenotype of intense hyperphagia with early-onset obesity, sometimes associated with endocrine abnormalities.[8,16-18] The main genes involved in monogenic obesity are summarized in Chart 1.

Chart 1. *Monogenic forms of Obesity*[16]

Gene	Clinical features
LEP (Leptin)	Severe hyperphagia Incapacity of feeling satiety Early-onset obesity within the first year of life Rapid weight gain during childhood and adolescence Hypogonadotropic hypogonadism Hypothalamic hypothyroidism Reduced adult height
LEPR (Leptin receptor)	Severe hyperphagia Incapacity of feeling satiety Early-onset obesity within the first year of life Rapid weight gain during childhood and adolescence Hypogonadotropic hypogonadism Hypothalamic hypothyroidism Reduced adult height
POMC (Proopiomelanocortin)	Neonatal adrenal insufficiency (causing hypoglycemia, liver failure, seizures) Early-onset obesity Hyperphagia Red hair and skin hypopigmentation (Caucasians) Central hypothyroidism (TSH) GH deficiency Hypogonadotropic hypogonadism (FSH and LH)
MC4R (Melanocortin-4 Receptor)	Hyperphagia Early-onset obesity Rapid weight gain during childhood and adolescence Increased linear growth and height Increased bone mass Increased fat and lean mass Subclinical hypothyroidism
PCSK1 (Proprotein convertase subtilisin/kexin type 1)	Intestinal dysfunction Malabsorptive diarrhea Hyperfagia Postprandial hypoglycemia Central hypothyroidism Hypogonadotropic hypogonadism Central Diabetes insipidus

Syndromic Obesity

The term "syndromic obesity" refers to patients with early-onset obesity associated with an intellectual deficit, dysmorphic features, organ-specific abnormalities, extreme hyperphagia, and/or other signs of hypothalamic alteration.[16,19,20] More than 100 syndromes associated with obesity were described; the most common are summarized in chart 2.[17,21]

Chart 2. *Syndromic Obesity*[17,21]

Syndrome	Clinical features and genetic background
Prader–Willi **1:10.000/ 1:15.000 births**	Characteristic facies, small hands and feet, hypopigmentation hypotonia and failure to thrive in newborn Short stature, hyperphagia, obesity, hypogonadism, delayed motor/cognitive development, sleep disturbances, and behavior abnormalities in childhood Lack of the paternal segment 15q11-q13 (microdeletion, maternal disomy, imprinting defect or reciprocal translocation)
Bardet-Biedl **1:125.000/ 1:175.000 births**	Obesity in first year of life, mental retardation, retinal dystrophy or pigmentary retinopathy, dysmorphic extremities, hypogonadism, kidney anomalies Rare recessive, genetically heterogeneous condition 12 genes (BBS1–12) implicated
X fragile **1:2.500 births**	Mental retardation, hyperkinetic behavior, macroorchidism, large ears, prominent jaw X-linked - FMR1 gene (Xq27.3)
Albright's hereditary osteodystrophy **1:20.000/ 1:1.000.000 births**	Short stature, round face, obesity, brachydactyly, subcutaneous calcification, dental and sensorineural abnormalities Generalized hormonal resistance to PTH, TSH, GHRH, and gonadotropins Biochemical functional hypoparathyroidism Autosomal dominant GNAS1 gene (20q13.2)
Cohen Diagnosed in fewer than 1.000 patients worldwide	Retinal dystrophy, prominent central incisors, dysmorphic extremities, microcephaly, cyclic neutropenia Autosomal recessive COH1 gene (chr 8q22-q23)

Polygenic Obesity

Polygenic obesity, also called common obesity, is the most prevalent type of obesity. It is multifactorial and depends not only on genetic factors but also on the existence of a favorable environment, established by an "obesogenic" lifestyle, with overfeeding, sedentary life, stress, among others. The genetic susceptibility comes from the cumulative effect of the contribution of several genes, with each presenting a slight effect on BMI, in a polygenic pattern.[17,22]

Differences between individuals and their predispositions to weight gain indicate that common variations of the genomic DNA sequence may be responsible for weight gain.[19,23] However, in spite of its great relevance, the search for the genes that raise the risk for obesity has not been easy.[24,25] It is still a challenge for the scientific community to separate the genetic element from the environmental component in the etiology of this disease. Individuals more susceptible to excessive adiposity may carry risk variants in the genes that influence appetite control (*NPY*, *POMC*, *MC4R,* etc), the regulation of cellular machinery (*FTO, DRD2,* etc), lipid metabolism and adipogenesis (*PPAR*, *APOE*, *PLIN*, etc.), energy expenditure (*UCP*), insulin signaling (*IRS*, etc) and inflammation (*ADIPOQ*, *IL6*, *RETN*, etc).[18,23,26]

Different approaches have been developed to elucidate the genetic component of polygenic obesity: Candidate gene, genome-wide linkage study (GWLS) and genome-wide association study (GWAS).

Openventio PUBLISHERS

Candidate Gene

Association studies of candidate genes aim to identify the relationship between one or more polymorphisms and a phenotype. During the mid-1990s, studies began to identify common genetic variants (also called SNP - single nucleotide polymorphisms) that contribute to obesity susceptibility.[27]

The genes considered candidates were analyzed because of previous biochemical, physiological and/or clinical research, or even because of their location (in a region of linkage/association) or pharmacological findings, indicating a correlation with BMI variation; being performed in cases of extreme and early-onset obesity or in transgenic animal models.[27,28] The search was then concentrated in those genes that play fundamental roles in the central or peripheral pathways of control of energy consumption and expenditure, influencing the regulation of food intake, energy expenditure, lipid and glucose metabolism, and adipose tissue development.[28] Hundreds of genes have already been investigated as candidates to provide susceptibility to obesity, yet only a few have demonstrated a convincing association,[27] and the replication of the results of most of the work has been inconsistent, so the conclusions of the candidate gene studies remain obscure.[29]

Genome Wide Linkage Study (GWLS)

In the late 1990s, the GWLS emerged. These studies have a generating hypotheses approach of certain chromosomal regions co-segregating with a trace or disease. They screen the entire genome of related individuals, with about 400-600 polymorphic markers, to identify chromosomal regions that segregate with obesity-related traits.[27]

Saunders et al,[30] after conducting a meta-analysis of 37 GWLS studies, concluded that this is not an effective strategy for detecting genetic variants for common obesity since they did not locate any locus with convincing evidence.

Genome Wide Association Study (GWAS)

The GWAS, unlike previous approaches, proved to be quite efficient.[28] In these studies, there is no assumption of the function of the gene being investigated. They are based on the association of several markers, special needs plans (SNP) usually, identifying genomic regions rather than specific genes, and are particularly useful in complex common diseases such as obesity and diabetes.[5,28]

The high success of this type of study stems from three factors: 1) the human genome is screened at a very high resolution with high-density scans, since more than two million genetic variants are tested for association with the characteristic of interest; 2) the sample size is much larger than in the linkage studies because participants do not need to be related, 3) the rigorous level of significance, established by the study design format, in two steps. The first stage identifies the loci for which the associations reach high-levels of significance in the genome scan, and then the second stage tests the loci for association in an independent series of samples. A locus is considered established when the association reaches a significance of $<5\times10^{-8}$ in the subsequent meta-analysis of the results of the first and second stages. Thus, the GWAS studies provide highly credible and robust association results.[22,27,31]

GWAS studies were important to understand the genetics involving obesity. Most studies were performed in white Europeans and addressed various loci in relation to BMI, body fat, waist and hip waist ratio, extreme and early-onset obesity.[5,27] These studies evolved in 4 waves with a progressive increase of the sample.[27]

In the first wave, genetic variations were identified in the fat mass and obesity-associated protein (FTO) intron. The FTO is related, in addition to BMI, to the risk of obesity, abdominal circumference, body fat percentage and with childhood obesity. The second wave corroborated the association of obesity with FTO variations and identified a locus related to the MC4R. Mutations in MC4R are one of the causes of extreme obesity in childhood. The third and fourth waves identified new loci for BMI and, by the end of four waves; GWAS had identified 32 loci unequivocally associated with BMI.[27]

In 2006, Rankinen et al after evaluating 61 GWAS studies, updated the "genetic map of human obesity", which at that time had 253 loci on all chromosomes except Y.[32]

In 2010, the giant-cell tumor medical definition (GIANT) consortium conducted in adults only[33] established[32] susceptibility loci for BMI, several of which were confirmed in French and German children with severe obesity.[34] In 2012, the largest genome-wide association studies (GWAS) meta-analysis study was carried out on children: 5530 cases and 8318 controls were evaluated and the strong genetic influence on the development of childhood obesity was verified.[35]

In 2015, Locke et al[36] published a GWAS study with approximately 340.000 individuals, identifying 97 loci with 2.1 million genetic variations, accounting for 2.7% of the BMI variation.[36] Most of the seloci are expressed in the Central Nervous System (CNS) and carry genes involved in pathways that affect the neuro-circuits of appetite regulation and satiety (*BDNF*, *MC4R* and *NEGR*), as well as insulin secretion and action pathways (TCF7L2, IRS1), adipogenesis and energy and lipid metabolism (*FTO*, *RPTOR*, *MAP2K5*). Some genes also involved in monogenic non-syndromic obesity are associated with polygenic obesity and present common polymorphisms in *PCSK1*, *MC4R*, and *POMC*.[8,36]

In 2019, Khera et al[31] performed a metanalyses of GWAS studies and developed the first conclusive genetic risk score for obesity. After assessing 2.1 million SNPs in more than 300.000 individuals, the authors developed the genomic polygenic score (GPS) that allows the identification of people with high susceptibility to obesity. Each variant is individually associated with minimal differences in birth weight but predicts clear weight differences during early childhood and profound differences in weight trajectory and

risk of developing severe obesity in subsequent years. Therefore, like GPS, other risk scores created from computational algorithms and large data sets are expected to identify a subgroup of the population that is at substantial risk for severe obesity in some cases equivalent to rare monogenic mutations and others that enjoy considerable protection.[22,31] Chart 3 summarizes the phenotypes related to genes involved in the genesis of polygenic obesity.

Chart 3. *Phenotypes and Genes Involved in Polygenic Obesity*[27,32]

Phenotype	Genes
"Thrifty" Involved in energy expenditure	ADRB2 - beta adrenergic receptor 2 ADRB3 - beta adrenergic receptor 3 UCP1 - uncoupling protein 1 UCP2 - uncoupling protein 2 UCP3 - uncoupling protein 3
Adipogenesis	PPAR-gamma - peroxisome proliferator-activated gamma receptor VDR – vitamin D receptor
Sedentary lifestyle	DRD2 – dopamine receptor 2 MC4R – melanocortin receptor 4
Low lipid oxidation	ACE - angiotensin converting enzyme GNB3 – guanine binding protein 3 IL6 – interleucin 6 INS – insulin LDLR – LDL receptor LIPE – hormone sensitive lipase RETN – resistin TNF alpha - tumor necrosis factor
Hyperphagic	DRD2 – dopamine receptor 2 HTR2C - 5-hydrohithritamine receptor LEP – leptin LEPR – leptin receptor MC4R – melanocortin receptor 4 NR3C1 – nuclear receptor subfamily 3 group C member 1
Obesity	FTO - fat mass and obesity associated MAF(near) - proto-oncogene c-Maf MC4R - melanocortin 4 receptor MSRA(near) - mitochondrial peptide methionine sulfoxide reductase NPC1 - Niemann-Pick disease, type C1 PTER (near) - phosphotriesterase related
Body Fat %	FTO - fat mass and obesity associated IRS1(near) - insulin receptor substrate 1 SPRY2 (near) - sprouty homolog 2
BMI Body Mass Index	BCDIN3D -domain containing RNA methyltransferase BDNF region - brain-derived neurotrophic factor ETV5 (near) - ets-related protein ERM FAIM2 - fas apoptotic inhibitory molecule 2 FTO - fat mass and obesity associated GNPDA2 (near) - glucosamine-6-phosphate deaminase 2 KCTD15 - potassium channel tetramerization domain containing 15 MSRA - mitochondrial peptide methionine sulfoxide reductase MTCH2 - mitochondrial carrier homolog 2 NEGR1 - neuronal growth regulator 1 NPC1 - Niemann-Pick disease, type C1 MAF - proto-oncogene c-Maf MC4R - melanocortin 4 receptor NRXN3 - neurexin-3-alpha PRL - prolactin PTER -phosphotriesterase related RASAL2 - ras GTPase-activating protein SEC16B - regucalcin gene promoter region-related protein SDCCAG8 - serologically defined colon cancer antigen 8 SH2B1 region - SH2B Adaptor Protein 1 TFAP2B - transcription factor AP-2 beta TMEM18 - transmembrane protein 18
Waist circumference	FTO - fat mass and obesity associated LYPLAL1 (near)- lysophospholipase-like 1 MC4R - melanocortin 4 receptor MSRA(near) - mitochondrial peptide methionine sulfoxide reductase NRXN3 - neurexin-3-alpha TFAP2B - transcription factor AP-2 beta
Waist-Hip Ratio	CPEB4 - sequence-specific RNA-binding protein DNM3 - dynamin-3 HOXC13 (near) - homeobox protein Hox-C13 LYPLAL1 (near) - lysophospholipase-like 1 NISCH - nischarin TBX15 - T-box transcription factor ZNRF3 - zinc and ring finger 3

Epigenetics and Obesity

Epigenetics refers to changes that occur in deoxyribonucleic acid (DNA) that do not alter the sequence of nitrogenated bases but can control chromatin compaction and interfere with gene expression through the mechanisms of DNA methylation, histone modification, and gene silencing throw non-coding micro ribonucleic acid (mRNA) (small RNA molecules that bind to messenger RNA and there by block protein translation).[37]

The intrauterine environment and nutrient supply during the 1000 days (from conception to the second year of life) modulate the expression of genes involved in appetite regulation, insulin sensitivity, among others and can modify the risk of developing obesity and metabolic diseases.[8,37-39] Exposure to maternal hyperglycemia in utero alters DNA methylation of placental leptin and adiponectin genes in humans, as well as thousands of other genes in umbilical cord tissue and blood that have been implicated in obesity.[38]

A complete review of epigenetic mechanisms in the genesis of obesity is beyond the scope of this article and can be accessed in other reports.[8,40]

CONCLUSION

Genetic predisposition is an essential component in the genesis of obesity. Rare cases of monogenic and syndromic obesity have a well-established genetic background, and this knowledge has contributed to revealing important molecular mechanisms in the pathophysiology of obesity. The diagnosis of these forms of obesity is important because it allows genetic counseling and, in some cases, guides the treatment in a more specific way, as in Prader Willi Syndrome and leptin/melanocortin pathway mutations.

The polygenic nature of common obesity makes the discovery of risk genes and their variants a challenging task. GWAS studies have brought new insights to the understanding of the genesis of obesity. However, the contribution of specific genes to the phenotype of polygenic obesity still accounts for only a small part of BMI variability. Recently the development of GPS has proven to be a valid risk score to identify individuals at higher risk for developing obesity, but still without a place in clinical practice.

It is hoped that in the future, greater knowledge of the contribution of genetic and epigenetic variants to the genesis of obesity will assist physicians in clinical decision making, as early and intense preventive measures for people with a high genetic risk score for the development of obesity, and personalized treatment of the obese based on the genetic background.

CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

REFERENCES

1. Engin A. The definition and prevalence of obesity and metabolic syndrome. In: *Obesity and Lipotoxicity*. New York, USA: Springer; 2017: 1-17.

2. Ng M, Fleming T, Robinson M, et al.. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014; 384(9945): 766-781. doi: 10.1016/S0140-6736(14)60460-8

3. O'Rahilly S, Farooqi IS. Human obesity: A heritable neurobehavioral disorder that is highly sensitive to environmental conditions. *Diabetes*. 2008; 57: 2905-2910. doi: 10.2337/db08-0210

4. Ordovas JM, Corella D. Nutritional genomics. *Annu Rev Genomics Human Genet*. 2004; 5: 71-118. doi: 10.1146/annurev.genom.5.061903.180008

5. Schwartz MW, Randy JS, Lori MZ, et al. Obesity pathogenesis: An endocrinesociety scientific statement. *Endocr Rev*. 2017; 38(4): 267-296. doi: 10.1210/er.2017-00111

6. Pinto RM, Silva JVP, Monteiro GMC, de Resende RC, Clemente RD, de Souza CSB. Physical activity: Benefits for prevention and treatment of childhood obesity. *J Child Obes*. 2018; 3(S2-003:1-5). 1-6. doi: 10.21767/2572-5394.100058

7. Reddon H, Gueant JL, Meyre D. The importance of gene–environment interactions in human obesity. *Clin Sci (Lond)*. 2016; 130(18): 1571-1597. doi: 10.1042/CS20160221

8. Rohde K, Keller M, la Cour Poulsen L, Blüher M, Kovacs P, Böttcher Y. Genetics and epigenetics in obesity. *Metabolism*. 2019; 92: 37-50. doi: 10.1016/j.metabol.2018.10.007

9. Neel JV. Diabetes mellitus: A "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet*. 1962; 14: 353-362.

10. Wang SP, Yang H, Wu JW et al. Metabolism as a tool for understanding human brain evolution: Lipid energy metabolism as an example. *J Hum Evol*. 2014; 77: 41-49. doi: 10.1016/j. jhevol.2014.06.013

11. Pinto RM, Cominetti C, da Cruz AD. Basic and genetic aspects of food intake control and obesity: Role of dopamin receptor D2 TAQIA polymorphism. *Obes Res Open J*. 2016; 2(4): 119-127. doi: 10.17140/OROJ-2-119

12. Speakman JR. A non adaptive scenario explaining the genetic predisposition to obesity: The "predation release" hypothesis. *Cell Metab*. 2007; 6(1): 5-12. doi: 10.1016/j.cmet.2007.06.004

13. Kaprio J, Pulkkinen L, Rose RJ. Genetic and environmental factors in health-related behaviours: Studies on finish twins and twin families. *Twin Res*. 2002; 5: 366-371. doi: 10.1375/136905202320906101

14. Stunkard J, Foch TT, Hrubec Z. A twin study of human obesity. *JAMA*. 1986; 256: 51-54. doi: 10.1001/jama.1986.03380010055024

15. Herskind AM, McGue M, Sorensen TI, Harvald B. Sex and age specific assessment of genetic and environmental influences on body mass index in twins. *Int J Obes Relat Metab Disord*. 1996; 20: 106-113.

16. Pigeyre M, Meyre D. Monogenic obesity. In: Freemark MS, ed. *Pediatric Obesity Etiology, Pathogenesis and Treatment*. 2nd ed. New York, USA: Humana Press; 2018: 135-152. doi: 10.1007/978-3-319-68192-4

17. Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: Clinical approach and current treatments in 2016. *Obes Facts*. 2016; 9: 158-173. doi: 10.1159/000445061

18. Martinez JA. Perspectives on personalizes nutrition for obesity. *J Nutrigenet Nutrigenomics*. 2014; 7: 1-3. doi: 10.1159/000365158

19. Bell CG, Walley AW, Froguel P. The genetics of human obesity. *Nat Rev Genet*. 2005; 6: 221-234. doi: 10.1038/nrg1556

20. Farooqi IS, O'Rahilly S. Monogenic obesity in humans. *Annu Rev Med*. 2005; 56: 443-458. doi: 10.1146/annurev.med.56.062904.144924

21. Irizarry KA, Haqq AM. Syndromic Obesity. In: Freemark MS, ed. *Pediatric Obesity Etiology, Pathogenesis and Treatment*. 2nd ed. New York, USA: Humana Press; 2018: 153-182. doi: 10.1007/978-3-319-68192-4

22. Oussaada SM, van Galen KA, Cooima MI, et al. The pathogenesis of obesity. *Metabolism*. 2019; 92: 26-36. doi: 10.1016/j.metabol.2018.12.012

23. Walley AJ, Asher JE, Froguel P. The genetic contribution to non-syndromic human obesity. *Nat Rev Genet*. 2009; 10(1): 431-442. doi: 10.1038/nrg2594

24. Böettcher Y, Korner A, Kovacs P, et al. Obesity genes: Implication in childhood obesity. *Pediatrics and Child Health*. 2011; 22(1): 31-36. doi: 10.1016/j.paed.2011.08.009

25. Loos RJ. Recent progress in genetics of common obesity. *Br J Clin Pharmacol*. 2009; 68(6): 811-829. doi: 10.1111/j.1365-2125.2009.03523.x

26. Pinto RM, Silva DM, Queiroz FJ, et al. Reward deficiency syndrome in children: obesity and metabolic disorders are associated with the SNP TaqIA C32806T of the DRD2 gene. *Obes Res Open J*. 2015; 2(2): 64-72. doi: 10.17140/OROJ-2-111

27. Loos RJF. Genetic determinants of common obesity and their value in prediction. *Best Pract Res Clin Endocrinol Metab*. 2012; 26: 211-226. doi: 10.1016/j.beem.2011.11.003

28. Hinney A, Giuranna J. Polygenic Obesity. In: Freemark MS, ed. *Pediatric Obesity Etiology, Pathogenesis and Treatment*. 2nd ed. New York, USA: Humana Press; 2018: 183-202. doi: 10.1007/978-3-319-68192-4

29. Shetty B, Shantaram M. Heritability of body weight: An evidence for obesity? *Int. J. Pharm. Med. &Bio*. 2014; 3(1): 15-20.

30. Saunders CL, Chiodini BD, Sham P, et al. Meta-analysis of genome-wide linkage studies in BMI and obesity. *Obesity (Silver Spring)*. 2007; 15: 2263-2275. doi: 10.1038/oby.2007.269

31. Khera AV, Chaffin M, Wade KH, et al. Polygenic prediction of weight and obesity. Trajectories from birth to adulthood. *Cell*. 2019; 177: 587-596.e9. doi: 10.1016/j.cell.2019.03.028

32. Rankinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: The 2005 update. *Obes Res*. 2006; 14: 529-644. doi: 10.1038/oby.2006.71

33. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249.769 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010; 42: 937-948. doi: 10.1038/ng.686

34. Comuzzie AG, Cole AS, Laston SL, et al. Novel genetic loci identified for the pathophysiology of chidhood obesity in the hispanic population. *PLoS One*. 2012; 7(12): e51954. doi: 10.1371/journal.pone.0051954

35. Bradfield JP, Taal HR, Timpson NJ, et al. A genome-wide association meta-analysis identifies new childhood obesity loci. *Nat Genet*. 2012; 44: 526-531. doi: 10.1038/ng.2247

36. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015; 518(7538): 197-206. doi: 10.1038/nature14177

37. Burdge GC, Lillycrop KA. Nutrition, epigenetics and developmental plasticity: Implications for understanding human disease. *Annu Rev Nutr*. 2010; 30: 315-339. doi: 10.1146/annurev.nutr.012809.104751

38. Ma RC, Tutino GE, Lillycrop KA, Hanson MA, Tam WH. Maternal diabetes, gestational diabetes and the role of epigenetics in their long term effects on offspring. *Prog Biophys Mol Biol*. 2015; 118: 55-68. doi: 10.1016/j.pbiomolbio.2015.02.010

39. Parsons TJ, Power C, Manor O. Fetal and early life growth and body mass index from birth to early adulthood in1958 British cohort longitudinal study. *BMJ*. 2001; 323(7325): 1331-1335. doi: 10.1136/bmj.323.7325.1331

40. Herrera BM, Keildsona S, Lindgrena CM. Genetics and epigenetics of obesity. *Maturitas*. 2011; 69: 41-49. doi: 10.1016/j.maturitas.2011.02.018

ISSN 2377-8385

OBESITY RESEARCH
Open Journal

Openventio
PUBLISHERS

Original Research

Relationships between Sleep, Sedentary Behavior, and Physical Activity in Young Adults

Ya-Wen Hsu, MPH, PhD[1,2*]; Chun-Ping Chang, MS[2]; Chia-Chang Liu, MS[2]

[1]*School of Community Health Sciences, University of Nevada, Reno, NV 89557, USA*
[2]*Department of Hospital and Health Care Administration, Chia Nan University of Pharmacy & Science, Tainan, Taiwan*

[*]***Corresponding author***
Ya-Wen Hsu, MPH, PhD
School of Community Health Sciences, University of Nevada, Reno, NV 89557, USA; Tel. 7756829369; E-mail: yawenh@unr.edu

Article information
Received: August 30th, 2019; **Revised:** September 11th, 2019; **Accepted:** September 11th, 2019; **Published:** September 30th, 2019

Cite this article
Hsu Y-W, Chang C-P, Liu C-C. Relationships between sleep, sedentary behavior, and physical activity in young adults. *Obes Res Open J*. 2019; 6(1): 18-24. doi: 10.17140/OROJ-6-138

ABSTRACT

Purpose
While there are some studies on sleep and physical activity, little is known regarding the associations between sleep and sedentary behavior. This study investigated the associations between sleep, sedentary behavior, and physical activity among young adults.

Methods
Cross-sectional data from 124 undergraduate students were included in the analysis (age=21±1 years). Both accelerometer-based and self-report assessments of sleep were included; physical activity and sedentary behavior were assessed by accelerometers. Participants were asked to fill out sleep questionnaires and wear accelerometers for 7 days. Pearson correlations, partial correlations, and analysis of covariance (ANCOVA) analyses were performed to investigate the relationships between sleep, sedentary behavior, and physical activity.

Results
After adjusting for age, gender, percent body fat, educational level, and monthly allowance, prolonged sedentary time was correlated with a shorter sleep onset latency (r=-0.19, p=0.04), shorter time in bed (r=-0.43, p<0.001), and shorter sleep duration (r=-0.38, p<0.001). Moderate-to-vigorous physical activity (MVPA) was positively correlated with sleep onset latency (r=0.43, p<0.001). Sedentary behavior and MVPA were not correlated with sleep quality or daytime sleepiness. After further categorizing sleep duration into three subgroups, individuals with ≤6 hours (p<0.001) of sleep spent more time being sedentary than did those with 6-7 hours (p<0.001) and ≥7 hours (p=0.007) of sleep. Individuals with 6-7 hours of sleep had a higher level of MVPA than did those with ≥7 hours of sleep.

Conclusion
Improving the duration of sleep may be a viable approach to help reduce sedentary behavior among young adults. Future studies with longitudinal designs are needed to further investigate the directionality of these associations and their potential mediators and moderators.

Keywords
Accelerometer; Sleep; Sedentary; Physical activity.

INTRODUCTION

Obesity is a significant public health issue that causes a high economic burden for society, in relation to both direct and indirect costs.[1] In Taiwan, the obesity rate has continually increased over the past two decades. According to nationally representative data from the Nutrition and Health Survey in Taiwan, the prevalence of obesity [body mass index (BMI)≥27 kg/m^2] was 22% in adults aged 19 years and above in 2014.[2] To prevent adverse health outcomes associated with obesity, intervention programs aimed at

improving risk factors of obesity are needed. Three of the important modifiable behavioral factors that influence obesity-related disease risk are sleep, sedentary behavior, and physical activity.[3,4]

There is compelling evidence that physical activity is related to favorable sleep durations and sleep quality.[5] High school students who engaged in more than 3.5 hours of physical activity/week had better sleep quality than those who engaged in 3.5 hours or fewer hours of physical activity/week.[6] Another study showed that daily physical activity for ≥60 minutes is associated with sufficient sleep.[7] While sleep and physical activity have been widely studied, a much smaller amount of data are available regarding the associations between sleep and sedentary behavior. Moreover, findings on the relationships between sleep and sedentary behavior have been less conclusive. One study found that young individuals who watched 3 or more hours of television (TV)/day were at greater risk for sleep problems by early adulthood than those who watched fewer than 3 hours/day.[8] On the other hand, Chen et al[9] found that the number of hours during which Taiwanese adolescents watched TV on weekdays and the number of hours during which they used a computer for purposes other than schoolwork were not associated with insufficient sleep. It has been suggested that more studies are needed to understand how sedentary behavior is linked to different sleep problems, such as sleep onset latency, short sleep durations, and sleep efficiency.[10]

Another gap in the existing literature[8-10] regarding sleep and sedentary behavior is that most studies relied on subjective assessments which may be prone to self-reported bias. Accelerometers can be used to provide objective estimates of sleep, sedentary behavior, and physical activity simultaneously using the same monitors. Hence, the aim of this study is to evaluate the associations between accelerometer measures of sleep, sedentary behavior, and physical activity. To enrich the understanding of how sleep and sedentary behavior are related, subjective measures of sleep quality and daytime sleepiness is also included in the study.

MATERIALS AND METHODS

Participants

A total of 131 college students were recruited from a university in Taiwan. Participants were excluded from the study if they (1) were previously diagnosed with any major illnesses that could affect their physical abilities; or (2) took any medications that may influence body composition and sleep.

Procedures

Flyers were posted on the message boards in the university and interested students could sign up to be contacted. At the health promotion center on campus, trained study team members provided information about the study and obtained written consent from the students who agreed to participate. Eligible participants completed body composition measurements as well as the demographic and questionnaires on sleep quality and daytime sleepiness. Afterwards, participants were instructed to wear an accelerometer for 7 days, except during bathing and aquatic activities. In addition, participants were asked to keep a daily log of the times they wore and took off the activity devices during the 7 day period. During the seven days of data collection, participants were asked to maintain their current levels of physical activity and sleep schedules. The research staff contacted the participants *via* phone calls and text messages to ensure that the accelerometers were worn properly and later retrieved monitors. Institutional Review Board approval was obtained from the Kaohsiung Medical University Chung-Ho Memorial Hospital, Sanmin District, Kaohsiung, Taiwan.

Measurements

Sedentary behavior and physical activity by the accelerometers: The duration of sedentary behavior and physical activity were estimated using the Actigraph GT3X monitors (Actigraph LLC, Pensacola, FL, USA). The accelerometers were programmed to record in 1 minute epochs, and the data were processed using ActiLife® software (version 6.7.2). The periods during which the accelerometers were not worn were defined as 60 minutes of consecutive zero counts and were cross-validated by the participants' self-report logs. The mean minutes per day of sedentary behavior (<100 counts/min) and moderate-to-vigorous physical activity (MVPA; ≥3 metabolic equivalents (METs))[11,12] were calculated by summing the minutes spent daily on these activities and averaging across the 7 days of wear.

Sleep parameters by the accelerometers: The same wrist-worn Actigraph GT3X monitors were used to objectively measure nocturnal sleep and wakefulness. Sleep-wake times from participants' diary logs were entered to calculate summary sleep estimates using ActiLife® software (version 6.7.2). Six sleep parameters of nocturnal sleep were obtained from the accelerometer data, including sleep onset latency (the amount of time it takes to fall asleep), time in bed (the duration of laying in bed from the bedtime to wake-up time),[13] sleep duration (the number of 1 minute epochs in a sleep episode that were scored as 'sleep', excluding any times that were scored as 'wake'),[13] wake after sleep onset (the duration of wake time in a sleep episode after sleep has been initiated),[14] number of awakenings (the total number of awakenings during a sleep episode),[13] and sleep efficiency [(number of hours slept/number of hours spent in bed)×100=habitual sleep efficiency (%)].[15] All sleep variables estimated by accelerometers were computed as the mean of the 7 day accelerometer measurements.

Sleep quality: Sleep quality over the previous month was assessed using the 19-item validated Chinese version of the Pittsburgh sleep quality index (PSQI).[16,17] The PSQI items were categorized into 7 components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction) graded on a score ranging from 0 to 3 points. The global score was calculated by summing the 7 component scores, providing a continuous measure of sleep quality with high scores corresponding to poor sleep quality. A global score higher than 5 indicates a "poor sleeper", whereas a global score lower than 5 represents a "good sleeper".

Daytime sleepiness: The validated Chinese version of the Epworth sleepiness scale[18] was used to evaluate the degree of subjective daytime sleepiness. The scale asked the participants to rate how likely they were to fall asleep in different situations (e.g. sitting and reading, watching TV, in a car, while stopped for a few minutes in the traffic). The scale contained 8 items and each item was rated on a scale of 0 (would never doze) to 3 (high chance of dozing). The sum of all items was used to denote the level of daytime sleepiness; a higher score represented more daytime sleepiness. Participants were dichotomized into <11 (low risk for sleepiness) and ≥11 (high risk for sleepiness) groups based on the sum score.[19]

Body composition: Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a beam medical scale and a wall-mounted stadiometer. The BMI was calculated as kg/m^2. The percent body fat was measured using a bioelectric impedance analyzer (X-SCAN Plus-II, iCare Co., Ltd, Korea). The measurement was performed in a standing position with the participant barefoot and wearing light clothing.

Demographic information: A questionnaire was used to assess demographic information such a sage (in years), sex, parental education level (highest level of mother or father), and average monthly allowance (in new Taiwanese dollars).

Statistical Analysis

Means and frequencies were calculated to describe the study sample. Data were assessed for normality using the Shapiro-Wilk tests. The relationships among sleep variables, sedentary behavior, and MPVA were examined using pearson correlation coefficients and partial correlation coefficients. Analysis of covariance (ANCOVA) with post-hoc analysis least significant difference (LSD) analysis was conducted to compare sedentary behavior and MVPA by sleep duration group (≤6 hours, 6-7 hours, and ≥7 hours), sleep quality (good sleepers and poor sleepers), and daytime sleepiness (low risk for sleepiness and high risk for sleepiness). Covariates included in the partial correlation analysis and ANCOVA models included age, gender, percent body fat, highest parental education level, and monthly allowance. All analyses were conducted using statistical package for the social sciences (SPSS) version 18.0 (IBM Corp., Armonk, NY, USA). The priori significance level was set at $p \leq 0.05$.

RESULTS

Table 1 presents the demographic information of the study sample. Of the 131 college students who completed the screening visit, 7 students was excluded were excluded due to missing data. A total of 124 students (mean age=21.1±1.2 years; females: 78.2%) were included in the current study. The participants' mean BMI was 22.1 kg/m^2; 21% (n=26) was classified as obese (≥27 kg/m^2)/ overweight (≥24 kg/m^2), 64.5% (n=80) was classified as having normal weight, and 14.5% (n=18) was classified as underweight. The mean percent body fat was 18.8% among males and 24.2% among females. On average, participants spent 42.4 minutes in MVPA and 716.4 minutes in sedentary behavior. The mean sleep duration at night was 380.9 minutes and the mean sleep onset latency was 9.5 minutes.

Table 1. *Demographic Characteristics*

	N (%)	Mean	SD
Age (year)		21.12	1.20
Gender			
Female	97(78.2%)		
Male	27(21.8%)		
Percent Fat mass (%)			
Female		24.2	5.3
Male		18.8	7.8
Weight Status			
Underweight (BMI<18.5 kg/m^2)	18(14.5%)		
Normalweight (BMI 18.5-24 kg/m^2)	80(64.5%)		
Overweight (BMI24-27 kg/m^2)	12(9.7%)		
Obese (BMI≥27 kg/m^2)	14(11.3%)		
Parental Education (Highest of mother or father)			
Below high school	33(26.6%)		
High school	68(54.8%)		
College and above	23(18.6%)		
Monthly Allowancea			
≤4,999 NTD	41(33.1%)		
5,000-9,999 NTD	71(57.2%)		
≥10,000-14,999 NTD	12(9.7%)		
Sedentary behavior (minutes/day)		716.4	107.6
MVPA (minutes/day)		42.4	27.3
Sleep Parameters by Accelerometers			
Sleep onset latency (minutes)		9.5	8.5
Time in bed (minutes)		479.8	59.3
Sleep duration (minutes)		380.9	54.9
Wake after sleep onset (minutes)		89.4	38.5
Number of awakenings		4.7	2.1
Sleep efficiency (%)		79.4%	7.4%
Sleep Scales			
Sleep quality scale		7.2	2.4
Daytime sleepiness scale		6.6	3.0

Abbreviations: BMI: Body mass index,SD: Standard deviation, MVPA: Moderate-to-vigorous physical activity, NTD: New Taiwanese dollars. USD 1≈new Taiwanese dollars (NTD)30

Pearson correlations between sleep, sedentary behavior, and MVPA by measurement type are presented in Table 2. Based on the accelerometry data, sleep onset latency was inversely correlated with sedentary behavior (r=-0.19, p=0.03) and positively correlated with MVPA (r=0.45, p<0.001). Less time in bed was correlated with more time spent in sedentary behavior (r=-0.41, p<0.001). Sleep duration was negatively correlated with sedentary behavior (r=-0.34, p<0.001). The aforementioned significant correlations remained significant after adjustment for age, gender, percent body fat, highest parental education level, and monthly allowance. Sedentary behavior and MVPA were not significantly

correlated with sleep quality or daytime sleepiness.

Table 2. *Pearson Correlations/Partial Correlations between Sleep and Physical Activity by Measurement Type*

(a) Sleep and Physical Activity Data by Accelerometers				
	Sedentary Behavior		MVPA	
	Pearson r	**Partial r[a]**	**Pearson r**	**Partial r[a]**
Sleep Parameters				
Sleep Onset Latency	-0.19*	-0.19*	0.45***	0.43***
Time in Bed	-0.41***	-0.43***	-0.12	-0.08
Sleep Duration	-0.34***	-0.38***	-0.18	-0.15
Wake after Sleep Onset	-0.10	-0.10	-0.03	-0.01
Number of Awakenings	0.03	0.03	-0.07	-0.02
Sleep Efficiency (%)	0.05	0.03	-0.12	-0.13
(b) Sleep and Physical Activity Data by Questionnaires				
	Sedentary Behavior		MVPA	
	Pearson r	**Partial r[a]**	**Pearson r**	**Partial r[a]**
Sleep Scales				
Sleep Quality	-0.07	-0.09	0.16	0.17
Daytime Sleepiness	-0.02	0.02	0.08	0.09

Results were based on pearson correlation and partial correlation analyses.
Abbreviations: MVPA: Moderate-to-vigorous physical activity
a. Parameters were adjusted for age, gender, percent body fat, highest parental education level, and monthly allowance.
**p≤0.05; ** p≤0.01; ***p≤0.001*

Table 3 shows the results of the comparisons of sleep variables, sedentary behavior, and MVPA. Daily sleep duration was associated with both sedentary behavior ($p<0.001$) and MVPA ($p=0.03$). When we further categorized sleep duration into three subgroups, adults with fewer than 6 hours of sleep/day spent more time in sedentary behavior than those with 6-7 hours of sleep/day (mean difference: 80.1 minutes/day, $p<0.001$) and those with more than 7 hours of sleep/day (mean difference: 100.1 minutes/day, $p<0.001$). In addition, adults who slept 6-7 hours/day spent 17.9 minutes/day more time in MVPA than those who had more than 7 hours of sleep/day ($p=0.007$). No significant differences were found between sleep quality, daytime sleepiness, sedentary behavior and MVPA.

DISCUSSION

One major study finding is that as an individual's sleep duration increases, he/she spends less time in sedentary behavior. In particular, individuals with fewer than 6 hours of sleep had a higher level of sedentary behavior, after adjusting for age, gender, percent body fat, highest parental education level, and monthly allowance. These results are consistent with those in previous literature. Based on the self-reported questionnaire data, higher amounts of sedentary time were found to be associated with higher odds of short sleep durations in postmenopausal women.[20] One possible explanation for this association is that an increase in sedentary be-

Table 3. *Comparisons of Physical Activityacross Sleep Variables*

(a) Sleep and Physical Activity Data by Accelerometers						
	Sedentary Behavior			MVPA		
	Mean (SD)	***p*-value[a]**	**Post-Hoc Comparisons[b]**	**Mean (SD)**	***p*-value[a]**	**Post-Hoc Comparisons[b]**
Sleep Duration		<0.001	"≤6 hours">"6-7 hours" "≤6 hours">"≥7 hours"		0.03	"6-7 hours">"≥7 hours"
≤6 hours (N=45)	771.03(97.44)			41.35(3.96)		
6-7 hours (N=54)	690.89(99.68)			48.55(3.61)		
≥7 hours (N=25)	670.10(107.98)			30.64(5.45)		
(b) Sleep and Physical Activity Data by Questionnaires						
	Sedentary Behavior			MVPA		
	Mean (SD)	***p*-value[a]**	**Post-Hoc Comparisons[b]**	**Mean (SD)**	***p*-value[a]**	**Post-Hoc Comparisons[b]**
Sleep Quality		0.89			0.99	
Good Sleepers (N=111)	716.41(114.00)			43.39(39.30)		
Poor Sleepers (N=13)	716.12(107.86)			42.32(26.02)		
Daytime Sleepiness		0.26			0.15	
Low Risk for Sleepiness (N=72)	720.31(113.14)			41.39(26.61)		
High Riskof Sleepiness (N=52)	716.15(107.98)			43.89(28.63)		

Results were based on Analysis of covariance (ANCOVA) with post hoc analysis.
Abbreviations: SD: Standard deviation, MVPA: Moderate-to-vigorous physical activity
a. Parameters were adjusted for age, gender, percent body fat, highest parental education level, and monthly allowance.
b. Only significant findings were shown.

havior is linked to an elevated risk of depression,[21,22] which often co-occurs with sleep problems such as insomnia and sleep disturbances.[23,24] In contrast, another study demonstrated that more sedentary time is associated with both short and long sleep durations among adults.[22] There appeared to be an inverse dose-response relationship between sleep duration and sedentary time in our study sample. Particularly, as the sleep duration decreased, more time spent in sedentary activities was recorded. It is alarming that the difference in sedentary time between those who slept fewer than 6 hours and those with 6-7 hours of sleep or more than 7 hours of sleep was approximately 80-100 minutes per day. Considering that sedentary behavior is widely recognized as a risk factor for developing obesity, cardiovascular disease, type 2 diabetes, and metabolic syndrome,[25,26] our findings highlight that improvements in sleep may be an alternative strategy for reducing the amount of time spent in sedentary behavior for young adults.

Sleep onset latency is the elapsed time between being fully awake and the beginning of sleep. The current study is one of the few studies that explored the association between sleep and onset latency. Two studies have shown that longer screen time not sitting time is related to a higher risk of long sleep latency.[27,28] The current study did not measure screen time and sitting time; instead, the total time spent in sedentary activities with small amounts of body movement was recorded by the accelerometers. We found that prolonged sedentary behavior is correlated with a shorter sleep onset latency while more time in MVPA is correlated with a longer sleep onset latency. It has been suggested that individuals with poor sleep spend a longer period of time being sedentary, as they feel a higher degree of fatigue.[29-31] It is likely that adults with more sedentary time feel a higher degree of tiredness and feel less restful during the day; as a result, they fall asleep quickly at night and have a shorter sleep latency. According to a review,[5] the effects of physical activity on sleep, regular exercise training showed beneficial effects on sleep onset latency (i.e., a shorter sleep onset latency). The observed positive correlation between MVPA and sleep onset latency does not necessarily imply that physical activity leads to an unfavorable sleep latency. We would like to note that the average time an individual took to fall asleep was 9 minutes among study participants, which is not considered a long period. Perhaps, when an individual spent more time in MVPA, they felt more energetic and did not fall asleep right away when they laid on the bed. In addition, prior studies did not investigate the roles that intensity, duration, and timing (24 hour clock time of physical activity)[32] of physical activity play in sleep onset latency. Future research is needed to understand whether the influences of physical activity and sleep latency differ by intensity, amount, and timing of physical activity.

Our findings that sedentary behavior was not significantly correlated with perceived daytime sleepiness are congruent with findings of a recent systematic review on sleep and sedentary behavior. Based on the meta-analysis of sixteen studies,[10] it was concluded that daytime sleepiness was not significantly associated with sedentary behavior. In contrast to prior literature in which more time spent performing sedentary activities was found to be related to poor self-reported sleep quality,[33] we did not find a correlation between sedentary behavior and self-reported sleep quality. The inconsistency may reflect the differences in measuring sedentary behavior. Kakinami et al[33] assessed sedentary behavior using the self-reported time spent watching TV and using computers while we estimated the total duration of sedentary behavior based on accelerometers, which captured the time spent in low energy expenditure activities throughout the day. It has been noted that light-emitting diode (LED)-backlit screen exposure can cause sleep disturbances by delaying the biological clock and suppressing the release of the sleep-inducing hormone melatonin.[34] The non-significant relationships between sleep quality and sedentary behavior observed in the present study may be due to the fact that we included a more general estimate of sedentary time. Additional research should examine whether the associations between sleep and sedentary behavior differ by the type of sedentary activity.

STRENGTHS AND LIMITATIONS

The main strength of the study is the inclusion of both subjective and objective measures of sleep. A combination of both approaches would enrich understanding of sleep behaviors. In addition, socioeconomic status factors known to influence sleep and activity levels were assessed and included as covariates to minimize possible confounding effects. This study has some limitations. First, the small sample size and the cross-sectional nature of the study impeded the generalizability of the findings and causal associations. Second, our data did not allow us to study the mechanisms associated with sleep, sedentary behavior, and physical activity. Third, only college students were included in the study and the findings may not be generalizable to other age groups as there may be age-related differences in sleep patterns and activity levels.[35] More studies are needed to identify whether or not the observed associations vary by age groups.

CONCLUSION

In conclusion, the study aids in identifying the cross-sectional relationships between sleep, sedentary behavior, and physical activity. Our findings imply that short sleep durations are associated with higher amounts of sedentary time in young adults. Promoting interventions that aim to reduce sedentary behavior may be an effective approach to enhance sleep for college students in Taiwan. School health education programs on healthy sleep duration are needed to reduce sedentary time for college students. Longitudinal studies with larger sample sizes are needed to clarify the causal inferences on sleep, sedentary behavior, and physical activity. Furthermore, future investigations are warranted to determine the potential moderators or mediators of the relationships between sleep and activity levels.

CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest.

REFERENCES

1. Tremmel M, Gerdtham UG, Nilsson PM, Saha S. Economic burden of obesity: A systematic literature review. *Int J Environ Res Public Health*. 2017; 14(4): pii: E435. doi: 10.3390/ijerph14040435

2. Chang HC, Yang HC, Chang HY, et al. Morbid obesity in Taiwan: Prevalence, trends, associated social demographics, and lifestyle factors. *PLoS One*. 2017; 12(2): e0169577. doi: 10.1371/journal.pone.0169577

3. Chaput JP, Barnes JD, Tremblay MS, et al. Inequality in physical activity, sedentary behaviour, sleep duration and risk of obesity in children: A 12-country study. *Obes Sci Pract*. 2018; 4(3): 229-237. doi: 10.1002/osp4.271

4. Ogilvie RP, Patel SR. The epidemiology of sleep and obesity. *Sleep Health*. 2017; 3(5): 383-388. doi: 10.1016/j.sleh.2017.07.013

5. Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: A meta-analytic review. *J Behav Med*. 2015;38(3):427-449. doi: 10.1007/s10865-015-9617-6

6. Schwartz S, McDowell Anderson W, Cole SR, Cornoni-Huntley J, Hays JC, Blazer D. Insomnia and heart disease: A review of epidemiologic studies. *J Psychosom Res*. 1999; 47(4): 313-333. doi: 10.1016/s0022-3999(99)00029-x

7. Ströhle A. Physical activity, exercise, depression and anxiety disorders. *J Neural Transm*. 2009; 116: 777-784. doi: 10.1007/s00702-008-0092-x

8. Johnson J, Cohen P, Kasen S, First M, Brook J. Association between television viewing and sleep problems during adolescence and early adulthood. *Arch Pediatr Adolesc Med*. 2004; 158(6): 562-568. doi: 10.1001/archpedi.158.6.562

9. Chen M-Y, Wang E, Jeng Y-J. Adequate sleep among adolescents is positively associated with health status and health-related behaviors. *BMC Public Health*. 2006; 6: 59. doi: 10.1186/1471-2458-6-59

10. Yang Y, Shin JC, Li D, An R. Sedentary behavior and sleep problems: A systematic review and meta-analysis. *Int J Behav Med*. 2017; 24(4): 481-492. doi: 10.1007/s12529-016-9609-0

11. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008; 40(1): 181-188. doi: 10.1249/mss.0b013e31815a51b3

12. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: A detailed pooled analysis of the dose-response relationship. *JAMA Intern Med*. 2015; 175(6): 959-967. doi: 10.1001/jamainternmed.2015.0533

13. Korsiak J, Tranmer J, Leung M, Borghese MM, Aronson KJ. Actigraph measures of sleep among female hospital employees working day or alternating day and night shifts. *J Sleep Res*. 2018; 27(4): e12579. doi: 10.1111/jsr.12579

14. Shrivastava D, Jung S, Saadat M, Sirohi R, Crewson K. How to interpret the results of a sleep study. *J Community Hosp Intern Med Perspect*. 2014; 4(5): 24983. doi: 24910.23402/jchimp.v24984.24983

15. Berger I, Obeid J, Timmons BW, DeMatteo C. Exploring accelerometer versus self-report sleep assessment in youth with concussion. *Glob Pediatr Health*. 2017; 4: 2333794x17745973. doi: 10.1177/2333794X17745973

16. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res*. 1989; 28(2): 193-213. doi: 10.1016/0165-1781(89)90047-4

17. Tsai PS, Wang SY, Wang MY, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life Res*. 2005; 14(8): 1943-1952. doi: 10.1007/s11136-005-4346-x

18. Chen NH, Johns MW, Li HY, et al. Validation of a Chinese version of the Epworth sleepiness scale. *Qual Life Res*. 2002; 11(8): 817-821. doi: 10.1023/A:1020818417949

19. Silva GE, Vana KD, Goodwin JL, Sherrill DL, Quan SF. Identification of patients with sleep disordered breathing: Comparing the four-variable screening tool, STOP, STOP-Bang, and Epworth sleepiness scales. *J Clin Sleep Med*. 2011; 7(5): 467-472. doi: 10.5664/JCSM.1308

20. Creasy SA, Crane TE, Garcia DO, et al. Higher amounts of sedentary time are associated with short sleep duration and poor sleep quality in postmenopausal women. *Sleep*. 2019; 42(7): pii: zsz093. doi: 10.1093/sleep/zsz093

21. Teychenne M, Ball K, Salmon J. Sedentary behavior and depression among adults: A review. *Int J Behav Med*. 2010; 17(4): 246-254. doi: 10.1007/s12529-010-9075-z

22. Pengpid S, Peltzer K. Sedentary behaviour and 12 sleep problem indicators among middle-aged and elderly adults in South Africa. *Int J Environ Res Public Health*. 2019;16(8): pii: E1422. doi: 10.3390/ijerph16081422

23. Maglione JE, Ancoli-Israel S, Peters KW, et al. Subjective and objective sleep disturbance and longitudinal risk of depression in a cohort of older women. *Sleep*. 2014; 37(7): 1179-1187. doi: 10.5665/sleep.3834

24. Chen PJ, Huang CL, Weng SF, et al. Relapse insomnia increases greater risk of anxiety and depression: Evidence from a population-based 4-year cohort study. *Sleep Med*. 2017; 38: 122-129. doi: 10.1016/j.sleep.2017.07.016

25. de Rezende LF, Rodrigues Lopes M, Rey-Lopez JP, Matsudo VK, Luiz Odo C. Sedentary behavior and health outcomes: An overview of systematic reviews. *PLoS One*. 2014; 9(8): e105620. doi: 10.1371/journal.pone.0105620

26. Gennuso KP, Gangnon RE, Matthews CE, Thraen-Borowski KM, Colbert LH. Sedentary behavior, physical activity, and markers of health in older adults. *Med Sci Sports Exerc*. 2013; 45(8): 1493-1500. doi: 10.1249/MSS.0b013e318288a1e5

27. Exelmans L, Van den Bulck J. Sleep quality is negatively related to video gaming volume in adults. *J Sleep Res*. 2015; 24(2): 189-196. doi: 10.1111/jsr.12255

28. Buman MP, Kline CE, Youngstedt SD, Phillips B, Tulio de Mello M, Hirshkowitz M. Sitting and television viewing: novel risk factors for sleep disturbance and apnea risk? results from the 2013 National Sleep Foundation Sleep in America Poll. *Chest*. 2015; 147(3): 728-734. doi: 10.1378/chest.14-1187

29. Bromley LE, Booth JN 3rd, Kilkus JM, Imperial JG, Penev PD. Sleep restriction decreases the physical activity of adults at risk for type 2 diabetes. *Sleep*. 2012; 35(7): 977-984. doi: 10.5665/sleep.1964

30. Chasens ER, Umlauf MG, Weaver TE. Sleepiness, physical activity, and functional outcomes in veterans with type 2 diabetes. *Appl Nurs Res*. 2009; 22(3): 176-182. doi: 10.1016/j.apnr.2007.12.001

31. Madden KM, Ashe MC, Lockhart C, Chase JM. Sedentary behavior and sleep efficiency in active community-dwelling older adults. *Sleep Sci*. 2014; 7(2): 82-88. doi: 10.1016/j.slsci.2014.09.009

32. Willis EA, Creasy SA, Honas JJ, Melanson EL, Donnelly JE. The effects of exercise session timing on weight loss and components of energy balance: Midwest exercise trial 2. *Int J Obes (Lond)*. 2019. doi: 10.1038/s41366-019-0409-x

33. Kakinami L, O'Loughlin EK, Brunet J, et al. Associations between physical activity and sedentary behavior with sleep quality and quantity in young adults. *Sleep Health*. 2017; 3(1): 56-61. doi: 10.1016/j.sleh.2016.11.001

34. Zhai L, Zhang Y, Zhang D. Sedentary behaviour and the risk of depression: A meta-analysis. *Br J Sports Med*. 2015; 49(11): 705-709. doi: 10.1136/bjsports-2014-093613

35. Chang VC, Chaput JP, Roberts KC, Jayaraman G, Do MT. Factors associated with sleep duration across life stages: Results from the Canadian Health Measures Survey. *Health Promot Chronic Dis Prev Can*. 2018; 38(11): 404-418. doi: 10.24095/hpcdp.38.11.02