

Women, Biology, Obesity and Health: Implications of the Emerging Bioscience Research

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Abstract

Background: We live in a society where a slim body is seen as the ideal and, particularly over recent years, BMI is equated to health. The response has been a plethora of anti-fat messages, public health interventions and a profitable, thriving weight loss industry. These have been based on the simplistic presumption that excess weight is merely a case of too many kilojoules ingested compared to those expended and that weight loss can be readily achieved by addressing that imbalance and with this stigmatization and frustration for those whose body size exceeds the accepted norm. Many women know well from personal experience that slimness is not simply a matter of diet and will power and easily obtainable by all. The purpose of this paper is to present the accumulating body of current bioscience research that is confirming this.

Methods: A multi-disciplinary literature search was conducted using the Web of Knowledge search engine since it provides a broad-based platform with access to research across the different core sciences including Current Contents Connect, Biological Abstracts, MEDLINE, CAB Abstracts, and ISI proceedings and relevant social sciences.

Results and Conclusions: Inherent biological factors are important determinants in energy metabolism, fat storage and vulnerability to weight gain. These factors include genetics, early development environment, epigenetics and neurohormonal factors that regulate energy metabolism including those specific to women. Emerging research is also re-examining the simplistic link between BMI and health issues such as increased cardiovascular disease risk and fertility. This paper discusses the implications of this emerging bioscience research with a specific focus on women's health.

Introduction

Helen at 59 years of age with a height of 170 cm and a weight of 136 kg has a BMI of 49 kg/m² which classifies her as being seriously obese. She is a health professional and well aware of the health risks associated with her excess weight. She is also a woman living in a society where a slim body is perceived as an essential requirement for feminine beauty and fashion. Over the years Helen has tried most non-fat diets as well as various drugs in her attempts to lose weight. Instead there has been a relentless increase in weight from 82 kg after the birth of her two children when she was 21 years old (a BMI of 28.5 kg/m²) to her current weight and BMI which persists in spite of her healthy diet and not excessive kilojoules intake [1]. Helen is not alone; there are many other women who can testify to similar long term battles against excess weight gain [2,3]. Too often for some, attempts to lose weight leads to frustration, guilt and ultimately failure and a pre-occupation with food and dieting that may for some lead on to eating disorders. Women are not only more vulnerable to these psychological pressures [4], but also their intrinsic physiological make up makes them more prone to weight gain.

Cheap energy dense food in generous portions that is too easily accessible and a sedentary life style in conjunction with socioeconomic factors such as food insecurity and lack of nutritional understanding are certainly important contributing factors to weight gain. But the question remains why, in any community, there are some who find it easier to remain slim, in spite of sharing the same obesogenic environment while others like Helen, a health conscious well informed professional, become increasingly obese. An accumulating body of emerging research in neuroscience and molecular biosciences confirms what many women know well from personal experience – that slimness is not simply a matter of willpower and diet and easily obtainable by all. The objective of this paper is to provide a broad-based literature search on current research in genetics, early development, environmental

factors, gender and physiological pathways that regulate energy turnover and discuss how these may affect body fat storage in the body and biological vulnerability to obesity.

Physiological Aspects of Obesity: Energy Homeostasis

Energy homeostasis involves complex sophisticated neurohormonal pathways that regulate energy balance and ensure adequate energy stores to meet increased demands for growth in children and it is particularly significant for women during pregnancy and lactation. This can be seen in the rapid increase in fat deposition that occurs particularly in critical periods during the human life span: prior to and during pregnancy and in the baby, prior to birth, during the first 6 months of life and prior to weaning [5]. The existence of these energy regulating mechanisms is also seen in the remarkable constancy of human weight, often over many years (and without calorie counting!) for some, and in the resistance to weight change that so often frustrates the attempts for others like Helen when trying to lose weight. The concept of such regulatory mechanisms was postulated over 50 years ago by Kennedy [6] as the 'set point' hypothesis where the body would defend its fat stores as a physiological response to attempts at weight

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Received March 28, 2013; Accepted April 30, 2013; Published June 05, 2013

Citation: Penny SJ, Page RA (2013) Women, Biology, Obesity and Health: Implications of the Emerging Bioscience Research. *Bioenergetics* 2: 106. doi:10.4172/2167-7662.1000106

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reduction by calorie restriction. However, though received with a considerable amount of skepticism at the time, it has been extensively confirmed starting with Coleman's early pioneering experiments with genetically obese mice that led to the identification of leptin and its recognition as a controller of body fat stores, through modulating food intake and energy output [7-9]. Much subsequent research has established the existence of multifaceted neurophysiological energy regulating systems that operates in animal models as well as humans [10,11]. It involves a complex interplay via numerous different neural/hormonal signaling systems that operate between peripheral tissues and key centers in the brain particularly the hypothalamus (Figure 1). In the hypothalamus these different incoming messages and signals are integrated and trigger either an increase in food intake (linked with energy storage and conservation by or exigenic signals such as ghrelin) or a decrease/cessation of food intake (mediated via anorexic/satiety signals such as leptin, insulin and Cholecystokinin (CCK)). These basic energy homeostasis pathways are modulated by physiological factors such as pregnancy and environmental factors such as nutrition [11-14] as well as parts of the brain such as the reward pathways [15-17]. Though less defined at this stage there is also growing evidence that other innate biological differences may occur that make some people more susceptible than others to obesity. These include differences in hypothalamic-pituitary axis (HPA) axis function [18] or in basal energy expenditure for example as a result of mitochondrial function [19] or uncoupling proteins and non-shivering thermogenesis [20-22].

In terms of understanding the implications for human obesity, the relevant point to note is that multiple complex interacting pathways regulate energy stores that have evolved because survival and perpetuation of the human race are absolutely dependant on an energy supply. Also their overall effect is to maintain and defend body energy stores [11].

Specific Aspects of Energy Homeostasis Relevant to Women

Because of their biological role in child-bearing, women are physiologically programmed to store more fat compared to men [5] and in women both total body fat and circulating leptin levels are significantly higher compared to men [23]. Pregnancy and lactation put high demands on energy requirements and leptin (mediating its effect in the hypothalamus via gonadotropin releasing hormone) serves as an important signal that their energy stores are adequate to maintain a pregnancy if they become pregnant [24]. This is the physiological reason behind the well known observation that very low fat stores for example in the highly trained female athlete or extreme thinness may cause absent or irregular menstrual cycles. Leptin is released into the blood stream by fat cells and during pregnancy increasing fat stores

will result in a corresponding increase in plasma leptin levels. However, pregnancy is marked by a state of leptin resistance, as the anorexic effect of leptin is blunted or over-ridden during pregnancy [25,26] predisposing to fat accumulation.

As well, in women, energy homeostasis is markedly modified by fluctuating levels of ovarian hormones, with the onset of menstruation, pregnancy and lactation and post menarche [5,27-29]. The action of progesterone, produced in the second half of the menstrual cycle, and in large amounts during pregnancy is to increase food intake and energy storage [30]. It is a physiological adaptation to ensure there are adequate energy stores to meet the demands of pregnancy and lactation. It is also the likely reason for the weight gain some women experience on progesterone hormonal contraception. Oestradiol has the opposite effect to progesterone, reducing meal size, and increasing leptin sensitivity in the brain [30,31]. During pregnancy the relatively low levels of oestradiol in proportion to levels of progesterone further augments the increase in appetite. Low levels of oestradiol may also be a contributing factor to susceptibility to weight gain in postmenopausal women. Oxytocin has also been implicated in regard to energy homeostasis in women and in the non-pregnant state acts centrally in the brain to reduce food intake [32,33]. During pregnancy, attenuation of oxytocin action on the uterus until term prevents premature labour and functions to maintain the pregnancy. At the same time, inhibition of its action in the hypothalamus is another physiological factor that contributes to increased food intake during pregnancy and vulnerability to weight gain. Prolactin, in women significantly elevated with lactation, has also been linked with increased hyperphagia in a dose dependent manner and involves direct actions of prolactin in the hypothalamus [34]. There is a physiological rationale that a hormone that plays an important role in lactation would also act to ensure adequate energy supplies for the metabolic demands of lactation. What emerges is that energy homeostasis pathways are plastic, and that the 'set point' changes, overall in an upward direction, and that, particularly in women, their inherent hormonal milieu is a powerful determinant for fat accumulation and deposition.

Differences in Energy Homeostasis and Vulnerability to Weight

For many individuals, relatively stable body weight is maintained in spite of the usual day by day variations in food consumption and activity as a result of these energy homeostasis mechanisms [35,36]. However what has become apparent is that the 'set point' or level of defended body energy stored can vary significantly between individuals. Table 1 summarises the biological factors such as genetic, environmental, epigenetic and prenatal/perinatal [37-39] that are relevant to food intake, energy turnover and fat deposition in a woman. For some the outcome is an increased susceptibility to weight gain, advantageous in the past, but which creates strain where modern obesogenic lifestyles are juxtaposed alongside a culture that promotes leanness as the ideal [2,3,40,41].

Genetic Factors

The importance of genetic factors, initially identified from earlier twin and population based studies, has been substantially confirmed in large scale genetic epidemiology studies in animal and human studies [38,42-44]. Though specific genes have been identified, such as the FTO (fat mass and obesity associated gene) [33], (human obesity is predominantly polygenic in nature [44]. Recent research has also provided some evidence that genetics may be an important determinant

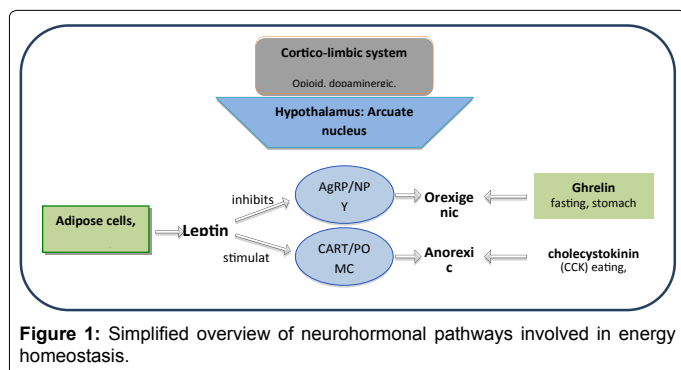


Figure 1: Simplified overview of neurohormonal pathways involved in energy homeostasis.

<p>Genetic factors.</p> <ul style="list-style-type: none"> Genes that influence obesity risk Epigenetic changes that can be carried through to the next generation resulting from prenatal/perinatal environmental factors Early development e.g. under or over nutrition, as risk factors for the metabolic syndrome <p>Genes that affect weight loss and its maintenance</p> <ul style="list-style-type: none"> Other genes e.g. those that affect reward pathways? 	<p>Hypothalamic regulation of food intake.</p> <p>Orexigenic neuropeptides:</p> <ul style="list-style-type: none"> neuropeptide Y (NPY) agouti-related peptide (AgRP) orexin, galanin melanin concentrating hormone (MCH) <p>Anorexic neuropeptides:</p> <ul style="list-style-type: none"> cocaine & amphetamine regulated transcript (CART) pro-opiomelanocortin (POMC) α-melanin stimulating hormone (MSH) corticotrophin releasing hormone (CRH) thyrotrophin releasing hormone (TRH)
<p>Metabolic factors</p> <ul style="list-style-type: none"> Basal metabolic rate (BMR) and body composition ratio of muscle mass to adipose – women lower BMR due lower % muscle mass Thermogenesis Mitochondrial function, uncoupling proteins Insulin resistance, metabolic syndrome, polycystic ovary disease 	<p>Neuroendocrine factors that modulate hypothalamic regulation</p> <ul style="list-style-type: none"> GI tract hormones e.g. cholecystokinin (CCK), ghrelin, glucagon-like peptides Leptin- an adipokine produced by fat cells, satiety signal – leptin resistance women, pregnancy Insulin- central satiety action, but peripheral actions that promote glucose uptake and fat storage (lipogenesis) HPA axis and adrenalcorticosteroid action (possible links with stress response, and circadian clock/sleep) Adrenergic stimulation Thyroid function
<p>Environmental factors</p> <ul style="list-style-type: none"> Perinatal nutrient exposures – kilojoules, fat, protein, folate – both under and over nutrition – epigenetic changes Impacts of highly palatable energy dense processed foods on physiological appetite regulation mechanisms High fat diets – causes leptin resistance Very strict diets and Yo-yo dieting behaviours Physical activity (also serves to maintain muscle mass and so increase BMR) Adverse-effects of medications- e.g. Depo-Provera, tricyclic antidepressants, atypical antipsychotics, development of tolerance and withdrawal from appetite suppressant drugs. 	<p>Neuroendocrine factors that modulate hypothalamic regulation particularly relevant to women.</p> <ul style="list-style-type: none"> progesterone oestrogen oxytocin prolactin Pregnancy/placental hormones including HPL that act as insulin antagonists – gestational diabetes Hormonal changes associated with menarche, pregnancy, lactation, menopause hormonal contraceptives

Table 1: Summary of biological factors that affect food intake, energy turnover and fat relevant to women.

in long-term successful weight loss [45]. The critique that human genes have not changed significantly over recent decades fails to recognize that expression of genes that confer vulnerability such as propensity to weight gain will only become apparent in an obesogenic environment. This critique has also been countered by the rapidly emerging field on the significance of epigenetics in long term gene expression as outlined in the following section.

Developmental Origins of Obesity: Prenatal and Perinatal Factors and Epigenetics

The importance of early environmental factors arose from the initial observations by Barker and Osmond [46,47] that low birth weight in full term babies was linked with an increased risk for obesity and cardiovascular disease as adults. This has been confirmed in much subsequent research in animal models and different human populations, which showed that compromised intrauterine nutrition or low protein, particularly in the first trimester, was linked with an increased risk

for obesity, cardiovascular disease, hypertension and type 2 diabetes mellitus and hypertension in adult life [12,48-51]. This provided a basis for the ‘thrifty phenotype’ hypothesis where the developing foetus in response to early environmental factors, specifically protein or calorie restriction, makes long term adaptations (becomes ‘programmed’) that promote energy conservation and fat storage. At the other end of the spectrum, maternal gestational diabetes and in utero over nutrition increases vulnerability to the development of obesity in later life of the unborn child [39,52-54]. At a cellular level both under-nutrition and over-nutrition have been linked with a resetting of energy homeostasis mechanisms that persist into adulthood and involve epigenetic changes. Epigenetic changes are long term changes in the regulation of gene expression (as distinct from changes in the actual DNA coding in the gene) that occur in response to environmental factors. They are important in determining the phenotype during early development of the child and therefore at the individual level, but also may be passed on to the next generation [13,14].

Obesity-associated Health Risk, the Metabolic Disease and Polycystic Ovary Syndrome

In regard to health, the traditional perception of obesity as the cause for health risks for type 2 diabetes, high blood pressure and cardiovascular disease has also been shown to be more complex due to a growing understanding of the metabolic syndrome. Increasingly the metabolic syndrome is emerging as a multifaceted metabolic disorder where, as well as insulin resistance, hypertension and physiological changes that increase cardiovascular disease risk, there is also an increased susceptibility to weight gain [55]. A common feature is leptin resistance (and hence resistance to its weight reducing effects) and a low-grade chronic inflammatory state [51,56]. An important point that is often overlooked is that it is visceral fat, an “apple shape” pattern of fat distribution that is particularly associated with the classic health risk features of the metabolic syndrome [57,58]. Conversely, hip and thigh fat, a “pear shape” pattern of fat distribution, more typically found in women is not just neutral but may be protective [59].

Problems with conception are commonly blamed on obesity but this is also more complex. Relevant in this context is that polycystic ovary syndrome (PCOS), which is linked with reduced fertility, has also been shown to display all the characteristic manifestations of the metabolic syndrome such as hypertension, blood lipoproteins that increase cardiovascular risks, insulin resistance and type 2 diabetes and abdominal fat [60-63] and as a likely deduction, possible early developmental origins [56,59] with a propensity to gain weight and reduced fertility akin to those well established for the metabolic syndrome. In women with PCOS, the hyperinsulinemia linked with peripheral insulin resistance and altered adipokines are associated with increased ovarian androgen secretion leading to arrest of follicle growth and an ovulation [63] and specifically loss of intra-abdominal fat (as distinct from weight loss per se) was positively correlated with return of ovulation.

Dieting

In spite of a myriad of dietary strategies and a thriving weight loss industry, what has become obvious over two decades of research is that for the majority the dietary based weight loss interventions for obesity fail in achieving long term weight loss [64-68]. It has been estimated that more than 90% of those who lose weight by dieting interventions regain it in 3-5 years. Rather than merely being ineffective long term, dieting and ‘diet’ induced behaviors have been linked with weight

Pre-occupation with body image and weight concerns
Emotional problems, irritability, negative affect and depression
Causal role in aetiology and maintenance of eating disorders- anorexia, bulimia, binge eating
Restrained eating creates vulnerability to emotional eating and problems with eating regulation-restrained eaters eat more after consumption of a high energy preload than after consuming no preload
Pre-occupation with food and eating, food addiction
Weight cycling resulting in negative psychological and physiological effects
Most weight lost by dieting is eventually regained, predisposition to weight gain

*Lowe et al. [65]; Carryer [2]; Garner and Wooley [64]; Cereda et al. 2011.

Table 2: Negative impacts reported in behavioral research associated with dieting and dieting related behaviours*

regain, weight cycling and negative psychological consequences as summarized in Table 2. Behavioral studies that identified associations, but unable to clearly establish cause and effect, have been extended by the emerging understanding of the complex multifaceted neurophysiological mechanisms that determine energy balance, storage and turnover current research in energy homeostasis outlined in previous sections [15,44,70,71]. The impact of calorie restriction on these innate neurohormonal pathways has been extensively studied in animal models. With a decrease in energy intake, especially acute restriction, leptin levels decrease independent of fat stores which generates an inevitable powerful or exigent drive (Figure 1). This provides a biological basis for the weight regain commonly observed. An established feature of energy restriction is a decrease in the Basal Metabolic Rate (BMR). Since for most individuals the BMR contributes 50-60% of total daily energy expenditure this is another factor predisposing to weight regain.

At a basic metabolic biochemical level this decrease in BMR can be partly accounted for calorie-restriction associated loss of muscle mass, especially in the absence of exercise, but, based on animal models, the decrease in leptin may also be a factor in the reduced metabolic rate. Thus an accumulating body of neurohormonal/physiological research serves to confirm the behavioral studies, namely that low energy dietary interventions for obesity may predispose to weight regain, weight cycling and increased weight as a result of an upward cogwheel 'resetting' of the energy homeostasis mechanisms [36]. In terms of obesity linked health concerns, significant energy restriction may promote fat redistribution and increased visceral fat deposition with its related health risks [57,70].

Neuroscience research is also providing some insights into the psychological factors associated with obesity. Penny and Carryer [71] proposed a potential role for leptin in emotional processing based on rat studies that demonstrated leptin to have an antidepressant action and the localization and neuronal activation in response to leptin administration of leptin receptors in limbic structures in the brain particularly the hippocampus. This location is quite distinct from leptin's action on energy homeostasis via neurons located in the hypothalamus. In their experiments standard animal model tests used for determining the action of pharmacological antidepressants, chronic stress was linked with increased cortisol and low leptin levels. In contrast to pharmacological antidepressants whose therapeutic effects generally are not apparent until after 2-3 weeks, leptin had a rapid antidepressant action. A possible deduction from their research is that low leptin levels associated with strict dietary regimes may underlie the dieting related mood changes reported in behavioral studies. Leptin has also been linked with depression with some studies reporting direct correlation between leptin levels on depression while in others there was an inverse relationship [72]. The apparently contradictory results

may reflect methodological issues as suggested by Labad et al. [72] but an alternative explanation may be a blunted response to leptin due to central leptin resistance. Relative leptin resistance has been associated with both the metabolic syndrome (which is linked with type 2 diabetes, abdominal obesity and cardiovascular disease) and women, and in both these groups increased proneness to depression has been reported. Pre-occupation with food at the physiological level, may be an outcome of the sensitization of the brain's reward circuitry and function since this part of the brain is associated with addictive type behaviors [15-17].

Physical Activity

Epidemiological studies, cross sectional and longitudinal, have shown that there is an inverse relationship between physical activity and weight gain in both men and women [73-77]. Energy balance is the most important factor in weight regulation. Excess storage of fat occurs due to greater energy intake than energy expenditure for a period of time. Reduced energy intake (calorie restriction as mentioned in the previous section) can lead to weight loss. Another way to promote weight loss is by increasing energy expenditure e.g. physical activity.

Exercise has become an important intervention for weight loss. Both aerobic and resistance training appear to have different health benefits [13,78-84]. Aerobic exercise seems to improve metabolic activity [85], insulin sensitivity [83] and cardiovascular fitness [3,78] whilst resistance training has been shown to improve body composition [80], lipolysis and muscle mass [85].

Moderate intensity exercise for prolonged period is recommended for treatment of obesity; however more evidence is evolving supporting differences between men and women for loss of weight in response to exercise and amount of physical activity required for maintenance of weight. This means that "one size" or "one exercise" does not suit all. Men do appear to lose more weight in response to exercise [86,87]. A randomized trial comparing the effects of different durations and intensities of exercise on 12 month weight loss in sedentary overweight women found that approximately 10% weight loss occurred with higher amounts of exercise but it was not significantly different to the 8% weight loss with lesser amount of exercise [88]. A randomized control trial [89] comparing effect of 12 weeks of moderate-intensity exercise in young obese men and women, demonstrated significant decreases in body mass and significant increases in resting metabolic rate and VO_2 max for both men and women. Women in the control group (non exercise) had significant increases in body mass which was not observed in the control group for men indicating different biological responses to exercise or lack of exercise between men and women. A recent study [85] investigated the acute impact of moderate-intensity and vigorous-intensity exercise bouts on daily physical activity energy expenditure in postmenopausal women. It was found that women expended more energy on physical activities outside of prescribed exercise on days they did not perform in the center-based exercise, especially if the prescribed exercise was vigorous-intensity. This means that greater weight loss will be achieved if women involved in exercise programs maintain their levels of activity outside of the prescribed exercise session. Women appear to "compensate" i.e. increase energy intake, if they do not maintain their levels of activity which ultimately reduces their ability to lose weight. The Midwest Exercise Trial 1 (MET1), evaluated weight loss to 16 months of exercise (45 min/day, 5 days/week, 75% heart-rate-reserve) in overweight/obese, sedentary men and women without energy restriction [90]. They found that men lost weight and women did not. The gender differences in weight loss were associated with higher energy expenditure in men compared to women,

however they could not conclude that weight loss was due to gender differences. The results from the MET1 study has led to the development of a randomized control trial designated MET2 [91]. MET2 has been designed specifically to examine gender differences in weight response to exercise prescribed at the same level of energy expenditure without diet restriction. This exercise intervention may finally provide results that will clarify if men and women differ in response to exercise and if they do then this will definitely have an impact on how exercise will be prescribed for women wanting to lose weight.

The Implications of the Biology – Body Size, Prejudice or Health and Wellness

Prejudice against women who are perceived as 'fat' or obese can disadvantage them at many levels [92] and weight stigmatization has increased significantly over recent years [93]. This has been fuelled by large numbers of clinical studies where higher BMIs were associated with a greater risk for type 2 diabetes mellitus, cardiovascular disease and other health risks. Parallel to this is the persisting notion that obesity is due to over-eating, laziness and lack of will power. Therefore obese people are not only blamed for their own weight but also held personally responsible for health consequences. The copious amount of scientific evidence, in genetics, epigenetic, neuroscience and metabolic biochemistry that strongly challenge these assumptions has not been so well dispersed. An important reason may be that these different strands of research, particularly in view of their diversity, complexity and evolving nature, are not so readily understood or accessed by those who do not work in these specialist areas. It highlights the need for raising awareness and communicating this more effectively to the non-specialist. Namely, that the simplistic application of an energy balance equation to explain both cause and answer for obesity has been well and truly displaced by the large rapidly expanding body of research in these different bioscience areas. That intrinsic biology is the key determinant of body size rather than personal shortcomings and with it a sense of frustration, personal failure or blame, a common perception all too often re-enforced by health professionals in the name of health promotion [3]. That inherent biological factors, of how energy regulatory mechanism are set, reset or disrupted from a complex interaction of genetic, epigenetic, early development with environmental factors, are powerful determinants of body weight. As a direct result of their gender, in women energy homeostasis mechanisms are further reset promoting fat storage and in response to hormonal changes such as puberty, pregnancy and lactation. It serves to explain why for some women the achievement and maintenance of a lean body is an impossible challenge and why dieting regimes generally do not lead to lasting weight loss and conversely may predispose to weight regain [15,44].

However, the awareness, understanding and acknowledgement of the relevant biology does not contradict the confirmed health benefits that come from healthy well balanced nutrition in conjunction with enjoyable regular physical activity. What it does do is to highlight the need for a clear distinction between health and body size alongside realistic doable goals that emphasize wellbeing and mental and physical health in its widest sense rather than a pre-occupation with BMI. For women in her role as mother it is important that she has awareness that her diet during pregnancy may have long term implications for her child, the need for early intervention for gestational diabetes [94], good nutrition and the well-established benefits of breastfeeding. However just as important, especially for her daughters, is a role model that affirms that it is personality, enjoying life, healthy food, physical activity done for pleasure and not weight loss that determines positive

outcomes in life, not body size and a negative spiral of pre-occupation with food and weight loss regimes. Campaigners in the western world protest at girls being force-fed for marriage in Mauritania where the opposite prevailing cultural norm sees fatness as the ideal in terms of feminine beauty and health [95]. Is this really so significantly different from the pre-occupation with slimness in western cultures and the pressures faced by those whose genetic and biological endowment does not favor a lean body build? What is needed is a positive affirmation and focus on health and wellbeing for everybody, at any body size!

References

1. Penny S (2008) Obesity: More complex than just a case of too much junk food? A case study. *Proceedings of the Nutrition Society of New Zealand* 33: 14-18.
2. Carryer J (2001) Embodied largeness: a significant women's health issue. *Nurs Inq* 8: 90-97.
3. Greener J, Douglas F, van Teijlingen E (2010) More of the same? Conflicting perspectives of obesity causation and intervention amongst overweight people, health professionals and policy makers. *Socio Sci Med* 70: 1042-1049.
4. Ferguson C, Kornblat S, Muldoon A (2009) Not all are created equal differences in obesity attitudes between men and women. *Womens Health Issues* 19: 289-291.
5. Zafon C (2007) Oscillations in total body fat content through life: an evolutionary perspective. *Obes Rev* 8: 525-530.
6. Kennedy GC (1953) The role of depot fat in the hypothalamic control of food intake in the rat. *Proc R Soc Lond B Biol Sci* 140: 578-596.
7. Coleman DL (1973) Effects of parabiosis of obese with diabetes and normal mice. *Diabetologia* 9: 294-298.
8. Ahima RS (2008) Revisiting leptin's role in obesity and weight loss. *J Clin Invest* 118: 2380-2383.
9. Farooqi IS, O'Rahilly S (2009) Leptin: a pivotal regulator of human energy homeostasis. *Am J Clin Nutr* 89: 980S-984S.
10. Valassi E, Scacchi M, Cavagnini F (2008) Neuroendocrine control of food intake. *Nutr Metab Cardiovasc Dis* 18: 158-168.
11. Levin BE (2007) Why some of us get fat and what we can do about it. *J Physiol* 583: 425-430.
12. McMillen IC, Robinson JS (2005) Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev* 85: 571-633.
13. Feil R (2006) Environmental and nutritional effects on the epigenetic regulation of genes. *Mutat Res* 600: 46-57.
14. Waterland RA, Michels KB (2007) Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr* 27: 363-388.
15. Figlewicz DP, Benoit SC (2009) Insulin, leptin, and food reward: update 2008. *Am J Physiol Regul Integr Comp Physiol* 296: R9-R19.
16. Berthoud HR (2006) Homeostatic and non-homeostatic pathways involved in the control of food intake and energy balance. *Obesity (Silver Spring)* 14: 197S-200S.
17. Taylor VH, Curtis CM, Davis C (2010) The obesity epidemic: the role of addiction. *CMAJ* 182: 327-328.
18. Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP (2009) Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. *J Clin Endocrinol Metab* 94: 2692-2701.
19. Bhopal RS, Rafnsson SB (2009) Could mitochondrial efficiency explain the susceptibility to adiposity, metabolic syndrome, diabetes and cardiovascular disease in South Asian populations? *Int J Epidemiol* 38: 1072-1081.
20. Jia JJ, Zhang X, Ge CR, Jois M (2009) The polymorphisms of UCP2 and UCP3 genes associated with fat metabolism, obesity and diabetes. *Obes Rev* 10: 519-526.
21. Jia JJ, Tian YB, Cao ZH, Tao LL, Zhang X, et al. (2010) The polymorphisms of UCP1 genes associated with fat metabolism, obesity and diabetes. *Mol Biol Rep* 37: 1513-1522.

22. van Marken Lichtenbelt WD, Schrauwen P (2011) Implications of nonshivering thermogenesis for energy balance regulation in humans. *Am J Physiol Regul Integr Comp Physiol* 301: R285-296.
23. Woods SC, Gotoh K, Clegg DJ (2003) Gender differences in the control of energy homeostasis. *Exp Biol Med (Maywood)* 228: 1175-1180.
24. Harris RB (2000) Leptin—much more than a satiety signal. *Annu Rev Nutr* 20: 45-75.
25. Grattan DR, Ladyman SR, Augustine RA (2007) Hormonal induction of leptin resistance during pregnancy. *Physiol Behav* 91: 366-374.
26. Ladyman SR, Tups A, Augustine RA, Swahn-Azavedo A, Kokay IC, et al. (2009) Loss of hypothalamic response to leptin during pregnancy associated with development of melanocortin resistance. *J Neuroendocrinol* 21: 449-456.
27. Augustine RA, Ladyman SR, Grattan DR (2008) From feeding one to feeding many: hormone-induced changes in bodyweight homeostasis during pregnancy. *J Physiol* 586: 387-397.
28. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, et al. (2007) Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care* 30: S112-S119.
29. Brunton PJ, Russell JA (2008) The expectant brain: adapting for motherhood. *Nat Rev Neurosci* 9: 11-25.
30. Faas MM, Melgert BN, de Vos P (2010) A Brief Review on How Pregnancy and Sex Hormones Interfere with Taste and Food Intake. *Chemosens Percept* 3: 51-56.
31. Clegg DJ, Brown LM, Zigman JM, Kemp CJ, Strader AD, et al. (2007) Estradiol-dependent decrease in the orexigenic potency of ghrelin in female rats. *Diabetes* 56: 1051-1058.
32. Douglas AJ, Johnstone LE, Leng G (2007) Neuroendocrine mechanisms of change in food intake during pregnancy: a potential role for brain oxytocin. *Physiol Behav* 91: 352-365.
33. Olszewski PK, Klockars A, Schiöth HB, Levine AS (2010) Oxytocin as feeding inhibitor: maintaining homeostasis in consummatory behavior. *Pharmacol Biochem Behav* 97: 47-54.
34. Woodside B (2007) Prolactin and the hyperphagia of lactation. *Physiol Behav* 91: 375-382.
35. Syed Z, Curtis D, Gutttag J, Nesta F, Levine RA (2006) Software enhanced learning of cardiac auscultation. *Conf Proc IEEE Eng Med Biol Soc* 1: 6105-6108.
36. Syed Z, Leeds D, Curtis D, Nesta F, Levine RA, Gutttag J (2007) A framework for the analysis of acoustical cardiac signals. *IEEE Trans Biomed Eng* ;54: 651-662.
37. Prentice AM (2005) Early influences on human energy regulation: thrifty genotypes and thrifty phenotypes. *Physiol Behav* 86: 640-645.
38. Rankinen T, Zuberi A, Chagnon YC, Weisnagel SJ, Argyropoulos G, et al. (2006) The human obesity gene map: the 2005 update. *Obesity (Silver Spring)* 14: 529-644.
39. Thompson NM, Norman AM, Donkin SS, Shankar RR, Vickers MH, et al. (2007) Prenatal and postnatal pathways to obesity: different underlying mechanisms, different metabolic outcomes. *Endocrinology* 148: 2345-2354.
40. Campos P, Saguy A, Ernsberger P, Oliver E, Gaesser G (2006) The epidemiology of overweight and obesity: public health crisis or moral panic? *Int J Epidemiol* 35: 55-60.
41. Saguy AC, Riley KW (2005) Weighing both sides: morality, mortality, and framing contests over obesity. *J Health Polit Policy Law* 30: 869-921.
42. Loos RJ, Bouchard C (2003) Obesity—is it a genetic disorder? *J Intern Med* 254: 401-425.
43. van Vliet-Ostaptchouk JV, Hofker MH, van der Schouw YT, Wijmenga C, Onland-Moret NC (2009) Genetic variation in the hypothalamic pathways and its role on obesity. *Obes Rev* 10: 593-609.
44. Hainer V, Zamrazilová H, Spálová J, Hainerová I, Kunesová M, et al. (2008) Role of hereditary factors in weight loss and its maintenance. *Physiol Res* 57 Suppl 1: S1-15.
45. Goyenechea E, Dolores Parra M, Alfredo Martínez J (2006) Weight regain after slimming induced by an energy-restricted diet depends on interleukin-6 and peroxisome-proliferator-activated-receptor-gamma2 gene polymorphisms. *Br J Nutr* 96: 965-972.
46. Barker DJ, Osmond C (1986) Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1: 1077-1081.
47. Barker DJ (2007) The origins of the developmental origins theory. *J Intern Med* 261: 412-417.
48. Hales CN, Barker DJ (2001) The thrifty phenotype hypothesis. *Br Med Bull* 60: 5-20.
49. Langley-Evans SC (2001) Fetal programming of cardiovascular function through exposure to maternal undernutrition. *Proc Nutr Soc* 60: 505-513.
50. Gluckman PD, Lillycrop KA, Vickers MH, Pleasants AB, Phillips ES, et al. (2007) Metabolic plasticity during mammalian development is directionally dependent on early nutritional status. *Proceedings National Academy of Sciences USA* 104: 12796-12800.
51. Cottrell EC, Ozanne SE (2007) Developmental programming of energy balance and the metabolic syndrome. *Proc Nutr Soc* 66: 198-206.
52. Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD (2000) Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *Am J Physiol Endocrinol Metab* 279: E83-87.
53. Muhlhauser BS, Duffield JA, McMillen IC (2007) Increased maternal nutrition stimulates peroxisome proliferator activated receptor-g, adiponectin and leptin messenger ribonucleic acid expression in adipose tissue before birth. *Endocrinology* 148: 878-885.
54. Remmers F, Delemarre-van de Waal HA (2011) Developmental programming of energy balance and its hypothalamic regulation. *Endocr Rev* 32: 272-311.
55. Kisfali P, Polgár N, Sáfrány E, Sümegi K, Melegh BI (2010) Triglyceride level affecting shared susceptibility genes in metabolic syndrome and coronary artery disease. *Curr Med Chem* 17: 3533-3541.
56. Xita N, Tsatsoulis A (2010) Fetal origins of the metabolic syndrome. *Ann N Y Acad Sci* 1205: 148-155.
57. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, et al. (2008) The metabolic syndrome. *Endocr Rev* 29: 777-822.
58. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI (2009). Harmonizing the metabolic syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society and the International Association for the Study of Obesity. *Circulation* 120: 1640-1645.
59. Lavie CJ, Milani RV, Ventura HO (2009) Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 53: 1925-1932.
60. Baillargeon JP, Carpentier AC (2007) Brothers of women with polycystic ovary syndrome are characterised by impaired glucose tolerance, reduced insulin sensitivity and related metabolic defects. *Diabetologia* 50: 2424-2432.
61. Svendsen PF, Nilas L, Nørgaard K, Jensen JE, Madsbad S (2008) Obesity, body composition and metabolic disturbances in polycystic ovary syndrome. *Hum Reprod* 23: 2113-2121.
62. Hudecova M, Holte J, Olovsson M, Larsson A, Berne C, et al. (2011) Diabetes and impaired glucose tolerance in patients with polycystic ovary syndrome—a long term follow-up. *Hum Reprod* 26: 1462-1468.
63. Kuchenbecker WK, Groen H, van Asselt SJ, Bolster JH, Zwerver J, et al. (2011) In women with polycystic ovary syndrome and obesity, loss of intra-abdominal fat is associated with resumption of ovulation. *Hum Reprod* 26: 2505-2512.
64. Garner DM, Wooley SC (1991) Confronting the failure of behavioral and dietary treatments for obesity. *Clinical Psychology Review* 11: 729-780.
65. Lowe MR, Timko CA (2004) Dieting: really harmful, merely ineffective or actually helpful? *Br J Nutr* 92 Suppl 1: S19-22.
66. Hill AJ (2004) Does dieting make you fat? *British Journal of Nutrition* 92: S15-S18.
67. Mark AL (2008) Dietary therapy for obesity: an emperor with no clothes. *Hypertension* 51: 1426-1434.

68. Bessesen DH (2008) Update on obesity. *J Clin Endocrinol Metab* 93: 2027-2034.
69. Sloboda DM, Hickey M, Hart R (2011) Reproduction in females: the role of the early life environment. *Hum Reprod Update* 17: 210-227.
70. Jackman MR, Steig A, Higgins JA, Johnson GC, Fleming-Elder BK, et al. (2008) Weight regain after sustained weight reduction is accompanied by suppressed oxidation of dietary fat and adipocyte hyperplasia. *Am J Physiol Regul Integr Comp Physiol* 294: R1117-1129.
71. Penny S, Carryer J (2011) Obesity and health--new perspectives from bioscience research suggest directions for clinical practice. *N Z Med J* 124: 73-82.
72. Labad J, Price JF, Strachan MW, Fowkes FG, Deary IJ, et al. (2012) Leptin levels and depressive symptoms in people with type 2 diabetes: the edinburgh type 2 diabetes study. *Psychosom Med* 74: 39-45.
73. Haapanen N, Miilunpalo S, Pasanen M, Oja P, Vuori I (1997) Association between leisure time physical activity and 10-year body mass change among working-aged men and women. *Int J Obes Relat Metab Disord* 21: 288-296.
74. Thune I, Njølstad I, Løchen ML, Førde OH (1998) Physical activity improves the metabolic risk profiles in men and women: the Tromsø Study. *Arch Intern Med* 158: 1633-1640.
75. Wier LT, Ayers GW, Jackson AS, Rossum AC, Poston WS, et al. (2001) Determining the amount of physical activity needed for long-term weight control. *Int J Obes Relat Metab Disord* 25: 613-621.
76. DiPietro L, Kohl HW 3rd, Barlow CE, Blair SN (1998) Improvements in cardiorespiratory fitness attenuate age-related weight gain in healthy men and women: the Aerobics Center Longitudinal Study. *Int J Obes Relat Metab Disord* 22: 55-62.
77. Polak J, Klimcakova E, Moro C, Viguerie N, Berlan M, et al. (2006) Effect of aerobic training on plasma levels and subcutaneous abdominal adipose tissue gene expression of adiponectin, leptin, interleukin 6, and tumor necrosis factor alpha in obese women. *Metabolism* 55: 1375-1381.
78. Wang Y, Simar D, Fiatarone Singh MA (2009) Adaptations to exercise training within skeletal muscle in adults with type 2 diabetes or impaired glucose tolerance: a systematic review. *Diabetes Metab Res Rev* 25: 13-40.
79. Strasser B, Schobersberger W (2011) Evidence for resistance training as a treatment therapy in obesity. *J Obes* 2011.
80. Wang L, Mascher H, Psilander N, Blomstrand E, Sahlin K (2011) Resistance exercise enhances the molecular signaling of mitochondrial biogenesis induced by endurance exercise in human skeletal muscle. *J Appl Physiol* 111: 1335-1344.
81. Wohlgemuth SE, Lees HA, Marzetti E, Manini TM, Aranda JM (2011) An Exploratory Analysis of the Effects of a Weight Loss Plus Exercise Program on Cellular Quality Control Mechanisms in Older Overweight Women. *Rejuvenation Res* 14: 315-324.
82. Strasser B, Arvandi M, Siebert U (2012) Resistance training, visceral obesity and inflammatory response: a review of the evidence. *Obes Rev* 13: 578-591.
83. Urdampilleta A, González-Muniesa P, Portillo MP, Martínez JA (2012) Usefulness of combining intermittent hypoxia and physical exercise in the treatment of obesity. *J Physiol Biochem* 68: 289-304.
84. Wang X, Nicklas BJ (2011) Acute impact of moderate-intensity and vigorous-intensity exercise bouts on daily physical activity energy expenditure in postmenopausal women. *J Obes* 2011.
85. Ballor DL, Keeseey RE (1991) A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. *Int J Obes* 15: 717-726.
86. Donnelly JE, Kirk EP, Jacobsen DJ, Hill JO, Sullivan DK, et al. (2003) Effects of 16 mo of verified, supervised aerobic exercise on macronutrient intake in overweight men and women: the Midwest Exercise Trial. *Am J Clin Nutr* 78: 950-956.
87. Jakicic JM, Marcus BH, Gallagher KI, Napolitano M, Lang W (2003) Effect of exercise duration and intensity on weight loss in overweight, sedentary women: a randomized trial. *JAMA* 290: 1323-1330.
88. Potteiger JA, Kirk EP, Jacobsen DJ, Donnelly JE (2008) Changes in resting metabolic rate and substrate oxidation after 16 months of exercise training in overweight adults. *Int J Sport Nutr Exerc Metab* 18: 79-95.
89. Donnelly JE, Smith BK (2005) Is exercise effective for weight loss with ad libitum diet? Energy balance, compensation, and gender differences. *Exerc Sport Sci Rev* 33: 169-174.
90. Donnelly JE, Washburn RA, Smith BK, Sullivan DK, Gibson C, et al. (2012) A randomized, controlled, supervised, exercise trial in young overweight men and women: the Midwest Exercise Trial II (MET2). *Contemp Clin Trials* 33: 804-810.
91. Swami V, Pietschnig J, Stieger S, Tovée MJ, Voracek M (2010) An investigation of weight bias against women and its associations with individual difference factors. *Body Image* 7: 194-199.
92. Ferguson J (2009) International health issues in adolescents. *Adolesc Med State Art Rev* 20: xiv-xv.
93. Puhl RM, Heuer CA (2010) Obesity stigma: important considerations for public health. *Am J Public Health* 100: 1019-1028.
94. Bristow S, Rowan J, Rush E (2009) Obesity and gestational diabetes mellitus: breaking the cycle. *N Z Med J* 122: 12-19.
95. Smith AD (2009) Girls being force-fed for marriage as fattening farms revived.