

# Lifestyle and Genetics in Obesity and type 2 Diabetes

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## Abstract

Obesity and type 2 diabetes mellitus are multifactorial health threats caused by a complex interplay between genetic predisposition and the environment with dramatically increasing worldwide prevalence. The role of heritability in their etiology is well recognized, however, the numerous attempts made in order certain genetic variants determining individual susceptibility to be identified have had limited success, until recently. At present the advancements in human genetics and the utilization of the genome-wide association approach have led to the identification of over 20 genetic loci associated with, respectively obesity and type 2 diabetes. Most of the genes identified to date, however, have modest effect on disease risk suggesting that both diseases are unlikely to develop without the individual being exposed to obesity- and/or type 2 diabetes-promoting environment. Indeed, unhealthy lifestyle, characterized

by physical inactivity and food overconsumption is an unequivocally established risk factor for obesity and type 2 diabetes. Numerous epidemiological studies and randomized controlled trials, on the other hand, have demonstrated that lifestyle modification is effective in obesity and type 2 diabetes prevention. Furthermore, gene-lifestyle interaction studies suggest that genetic susceptibility to obesity and type 2 diabetes may be partially or totally kept under control by healthy lifestyle or lifestyle modification and that lifestyle determines whether an individual is likely to develop the disease. Inherited factors, however, seem to influence individual response to a lifestyle intervention program and even the motivation for lifestyle change. Personalized interventions according to genotype may be, therefore, considered in the future. By then lifestyle modification targeting dietary change and increased physical activity may be recommended for successful obesity and type 2 diabetes prevention irrespectively of genetic susceptibility.

## Introduction

The prevalence of obesity and type 2 diabetes mellitus (T2DM) is dramatically increasing worldwide. For less than 2 decades the prevalence of obesity has more than doubled to exceed 470 million, representing the most common metabolic disease nowadays (International Obesity Taskforce, 2010). The rise in obesity prevalence is paralleled by a similar rapid increase in the prevalence of T2DM demonstrating the close interrelationship between these metabolic diseases (Wild et al., 2004).

Obesity and T2DM are multifactorial health threats caused by a complex interplay between genetic predisposition and the environment (Neel, 1999). The advancements in human genetics and the utilization of genome-wide association (GWA) approach have recently revealed

valuable insights into the interactions between genetic predisposition and lifestyle factors, namely physical activity (PA) and food consumption. This current progress may have essential contribution to our understanding of the pathophysiology of both diseases, as well as, to the development and implementation of future treatment and prevention strategies. It is, therefore, the aim of the present review to summarize the available literature on the effect of the interactions between lifestyle and genetics on obesity and T2DM.

## Genetics of Obesity and Type 2 Diabetes Mellitus

The role of heritability in the development of obesity and T2DM is well recognized. A good

example in this respect is the existence of severe monogenic forms of both disorders such as the congenital leptin deficiency (Montague et al., 1997), the melanocortin-4 receptor deficiency (Farooqi et al., 2003), and the maturity onset diabetes of the young (MODY) (Vaxillaire and Froguel, 2006). The strong impact of inherited factors on obesity and T2DM has also been confirmed in a large number of family, twin and adoption studies. Studies in twins have demonstrated that 50–70% in the body mass index (BMI) variance may be explained by genetics (Allison et al., 1996), and T2DM concordance was reported ranging from 17–37% in dizygotic to 50–70% in monozygotic twins (Kaprio et al., 1992; Medici et al., 1999; Poulsen et al., 1999). In addition, family and adoption studies have reported heritability ranging from 20–60% for obesity (Rice et al., 1999; Stunkard et al., 1986) and 30–70% for T2DM (Meigs et al., 2000).

During the past 15 years numerous attempts have been made to identify certain genetic variants determining susceptibility to obesity and T2DM. Until recently candidate gene and genome-wide linkage studies have been the main genetic epidemiological approaches. Progress has, however, been slow and success limited with few reproducible results (Vimalaswaran and Loos, 2010). Utilization of the GWA approach and the progress made through the International HapMap project and the Human Genome Project has substantially improved the knowledge about obesity and T2DM genetics (Rankinen et al., 2006). At present, as a result of this technological advancement over 20 loci for respectively obesity and T2DM have been convincingly confirmed in various populations (Herder and Roden, 2010; Vimalaswaran and Loos, 2010).

Extensive description of the genetic variants influencing individual susceptibility to obesity and T2DM is beyond the scope of the current paper (for a detailed review on the topic, please refer to (Herder and Roden, 2010; Vimalaswaran and Loos, 2010)). We are rather aiming at demonstrating the effect of gene-lifestyle interactions on the development of diabetes. Most of the genes identified to date have modest effect on disease risk and both diseases are unlikely to develop without the individual being exposed to obesity- and/or type 2 diabetes-promoting environment. Therefore, in the next section the importance of lifestyle in obesity and T2DM will be discussed.

### Lifestyle in Obesity and Type 2 Diabetes Mellitus

Unhealthy lifestyle, characterized by physical inactivity and food overconsumption is an unequivocally established risk factor for obesity and type 2 diabetes. Increased PA and energy restriction, on the other hand, are associated with lower incidence of obesity and T2DM in numerous epidemiological studies.

#### Lessons from epidemiological studies

Findings from cross-sectional and prospective studies suggest that food overconsumption and a predominantly sedentary lifestyle may cause obesity and T2DM, while adoption of a healthier lifestyle may prevent them. It has been demonstrated that lack of non-sedentary activities, the time spent watching television, and western dietary pattern can substantially increase the odds of becoming obese and of developing T2DM (Ching et al., 1996; Martinez-Gonzalez et al., 1999; Schulze et al., 2006; van Dam et al., 2002). At the same time a healthier lifestyle comprising higher levels of PA and prudent food consumption have been found to significantly reduce the risk (Coakley et al., 1998; Kriska

et al., 2003; Meisinger et al., 2005; Schulze et al., 2006; van Dam et al., 2002). In a recent paper we reported that low levels of leisure time and sport PA, as well as, binge eating behavior are associated with increased BMI and higher T2DM prevalence also among the urban population of Sofia, Bulgaria (Stefanov et al., 2011).

Based on data analyses from the Nurses' Health Study Hu et al. (2003a) concluded that around 30% of the new cases of obesity and 43% of T2DM could be prevented by adoption of a relatively active lifestyle. Indeed, activities of even moderate intensity (e.g., brisk walking) have been found to significantly reduce the risk of obesity and diabetes (Hu et al., 1999; Hu et al., 2003b; Mekary et al., 2009). Remarkably, the effect of PA on diabetes incidence has been observed independently of BMI demonstrating that regular engagement in activities of moderate to high intensity may be beneficial not only for high-risk obese individuals, but also for low-risk lean individuals (Kriska et al., 2003; Meisinger et al., 2005; Schulze et al., 2006). Furthermore, healthier lifestyle has been shown to be associated with decreased incidence of obesity- and T2DM-related complications such as hypertension and cardiovascular disease (Manson et al., 2002; Stampfer et al., 2000).

#### Evidence from randomized controlled trials

The efficacy of lifestyle changes in obesity and T2DM prevention has been established in numerous randomized controlled trials (RCTs). Several of them may, however, be considered of major importance due to their large sample sizes (i.e., 458–3234 individuals) and long-term duration (i.e., 3–6 years). The Chinese Da Qing diabetes prevention study was the first to investigate the effect of 6-year lifestyle change on body weight and diabetes incidence in individuals with impaired glucose tolerance (IGT) (Pan et al., 1997). Pan and co-workers (1997) reported 42% reduction in diabetes incidence, although no significant difference in body weight was present. Similar results were found in the Finnish Diabetes Prevention Study (DPS) and the US Diabetes Prevention Program (DPP). DPS and DPP independently reported reduction in diabetes incidence of 58% accompanied by significant reduction in body weight (5–7%) as a result of the lifestyle modification (Knowler et al., 2002; Tuomilehto et al., 2001). These findings were also confirmed in Japanese and Indian populations, reporting 67.4% and 28.5% reduction in diabetes incidence, respectively (Kosaka et al., 2005; Ramachandran et al., 2006). All the above mentioned findings have been also reproduced in several smaller RCTs (Eriksson and Lindgarde, 1991; Penn et al., 2009; Wing et al., 1998). Remarkably in the Finnish DPS success of achieving study goals was inversely associated with diabetes incidence and none of the subjects who reached 4 of 5 study goals developed T2DM (Tuomilehto et al., 2001). Very recently the interventions that proved efficient in clinical research were successfully translated in a real-world situation (Sanake et al., 2011). Sanake et al. (2011) reported significant reduction in body weight and diabetes incidence at 1, as well as, at 3 years during a lifestyle modification program carried out in a primary healthcare setting among subjects with IGT. All large-scale interventions have been successful in preventing T2DM during the active intervention period. Remarkably when the effectiveness of the lifestyle modification programs was assessed on the long-term after discontinuation of the intervention, diabetes risk still remained substantially reduced. In the Finnish DPS, for instance, at extended follow-up 3 years after the 4-year intervention period a substantial reduction in body weight and T2DM incidence was still present (Lindstrom et al.,

2006). The follow-up period of the Da Qing study was even longer – 14 year. Interestingly diabetes risk at that point was reduced to even greater extent in comparison to the 6-year active intervention (Li et al., 2008). In addition to these observations, 7 years after the intervention was discontinued in the U.S. DPP body weight and T2DM incidence still remained significantly lower in the lifestyle intervention group when compared to the control group (Knowler et al., 2009).

As already pointed out in several of the T2DM prevention studies the reduction in diabetes risk has been paralleled by substantial weight loss and weight reduction has been considered to have major importance for diabetes prevention (Knowler et al., 2002; Kosaka et al., 2005; Lindstrom et al., 2003; Tuomilehto et al., 2001). In some studies although no or just minor weight loss was achieved, diabetes incidence was also reduced (Pan et al., 1997; Ramachandran et al., 2006). In addition, on the long term weight was partially or totally regained in all of the studies (Knowler et al., 2009; Li et al., 2008; Lindstrom et al., 2006; Lindstrom et al., 2003). Despite this regain T2DM risk remained low or decreased further, thus the effect of lifestyle is unlikely to be solely due to body weight reduction. In support of this notion Pan et al. (1997) reported comparable decrease in T2DM incidence in the intervention group of Da Qing among overweight and lean individuals. Furthermore, significant improvement in various metabolic parameters has been observed irrespectively of the degree of weight loss (Eriksson and Lindgarde, 1991; Knowler et al., 2002; Kosaka et al., 2005; Pan et al., 1997; Ramachandran et al., 2006; Tuomilehto et al., 2001; Wing et al., 1998). This reduction remained lower even when weight was partially or totally regained in some of the studies (Pan et al., 1997; Wing et al., 1998). Hence, lifestyle modification seems to have an effect on T2DM not only through reduction in body weight, but also through improvement in insulin sensitivity, blood glucose control and lipid profile.

Whereas there is convincing evidence that lifestyle changes can prevent T2DM in randomized controlled studies, so far little is known whether a lifestyle intervention could also modify cardiovascular morbidity and mortality. The 20-year follow-up results from the Chinese Da Qing diabetes prevention study showed a non-significant 17% reduction in cardiovascular mortality in the combined (diet and/or PA) intervention group vs. controls (Li et al., 2008). Similarly, lifestyle intervention in the Finnish DPS was not found to reduce significantly cardiovascular mortality during the first 10 years of follow-up (Uusitupa et al., 2009). However, this study was not initially designed to examine the effect of lifestyle intervention on total mortality or cardiovascular morbidity, and therefore the statistical power may not have been sufficient to detect small differences in cardiovascular events between the 2 groups. Besides, a longer follow-up period might be needed to answer this question. In the Malmö Preventive trial with a 12-year follow-up of men with IGT total and cardiovascular mortality were lower among participants in the lifestyle intervention group, however, these results should be considered with caution due to the non-randomized design of the study (Eriksson and Lindgarde, 1998). Recent findings of bariatric surgery treatment of very obese subjects showed that weight loss indeed may reduce not only T2DM risk but also total mortality (Sjöström et al., 2007). Further investigations are needed to clarify whether prevention of T2DM by lifestyle modification is associated with cardiovascular disease prevention; until then decisions have to be made on the basis of the best available information.

In conclusion, evidence from epidemiological studies and RCTs demonstrate that lifestyle modification comprising higher levels of PA and prudent food consumption may be effective in obesity and T2DM prevention. The positive effect of lifestyle on body weight seems somewhat transient, whereas the effect on T2DM is sustained for longer periods. Furthermore, lifestyle modification appears to have an effect on diabetes risk independently of body weight and even of weight loss.

### Lifestyle and Genetics in Obesity and Type 2 Diabetes

Recent advancement in human genetics has led to the identification of a relatively big number of obesity- and T2DM-associated loci. Their contribution to disease risk has, however, been shown to be small and their predictive value low, suggesting that lifestyle plays crucial role in obesity and T2DM development (Vimaleswaran and Loos, 2010). Indeed, studies investigating the gene-lifestyle interactions in obesity and T2DM have suggested that the biological effect of genetic predisposition may be partially or totally abolished by healthy lifestyle or lifestyle modification and vice versa.

Epidemiological studies have reported that the negative effect of several obesity- and T2DM-associated genes may be attenuated in individuals with higher PA levels or healthy lifestyle, whereas low PA and western dietary pattern have been found to accentuate it. (Ahmad et al., 2011; Andraesen et al., 2008; Brito et al., 2009; Nelson et al., 2007; Qi et al., 2009; Rampersaud et al., 2008; Ruchat et al., 2010; Ruiz et al., ; Vimaleswaran et al., 2009). In addition, physical activity, dietary and combined lifestyle interventions have been found to induce significant decreases in body weight and other anthropometric traits, thus abolishing obesity risk among carriers of risk alleles in 2 of the genes most strongly associated with obesity – FTO and MC4R (Franks et al., 2008; Haupt et al., 2009a; Haupt et al., 2008; Lappalainen et al., 2009; Mitchell et al., 2010; Razquin et al., 2010). With respect to T2DM results from several large-scale studies have provided strong evidence for amelioration of metabolic traits and attenuation of diabetes risk among TCF7L2 risk allele carriers by diet and exercise (Bo et al., 2009; Florez et al., 2006; Haupt et al., 2010; Wang et al., 2007). The minor allele of PPARgamma gene has also been associated with substantially increased risk for T2DM and atherosclerosis (Deeb et al., 1998; Temelkova-Kurktschiev et al., 2004). Lifestyle modification has, however, been suggested to attenuate its negative effect on metabolic profile, body weight, and diabetes risk (Franks et al., 2007; Kilpelainen et al., 2008; Lindi et al., 2002; Ruchat et al., 2010) (◉ **Table 1**). The notion that lifestyle modification can eliminate the increased risk for development of T2DM in subjects with genetic susceptibility is also supported by findings of Barwell et al. (2008) who reported that women with family history of T2DM experience greater improvement in insulin sensitivity following an exercise intervention than women with no family history.

Although lifestyle modification has been found efficient in obesity and T2DM prevention even among genetically susceptible individuals, considerable heterogeneity in intervention responses has been observed. Genetic influences have been suggested to contribute to this heterogeneity. Risk allele carriers in several obesity- and T2DM-associated genes, for instance, have been found to experience suppressed weight reduction and improvement in various metabolic parameters in response to exercise or combined lifestyle interventions (Franks et al., 2007; Haupt et al.,

**Table 1** Gene-lifestyle interaction studies supporting the protective role of diet, exercise or combined lifestyle interventions in individuals genetically susceptible to obesity and type 2 diabetes.

Study	Population	Intervention	Polymorphism investigated	Findings
Franks et al., 2008	908 individuals with IGT or impaired fasting glucose	Combined lifestyle intervention – 24 weeks of intensive counseling and 3-year follow-up	FTO SNP: rs9939609	Subcutaneous adipose tissue decreased irrespectively of genotype
Lappalainen et al., 2009	502 European individuals with overweight and IGT, aged 40–65 years	Combined lifestyle intervention –1 year of intensive counseling and 3-year follow-up	FTO SNP: rs9939609	No association between the variant and the magnitude of weight reduction
Haupt et al., 2008	204 European individuals with overweight, IGT family history of T2DM or history of gestational diabetes	9-month combined lifestyle intervention	FTO SNP: rs8050136	The FTO variant did not affect reduction in body weight, total fat, subcutaneous fat, visceral, and nonvisceral fat
Mitchell et al., 2010	234 white, overweight postmenopausal women, aged 45–75 years	6-month moderate intensity exercise intervention	FTO SNP: rs8050136	Comparable weight loss occurred among genotypes
Razquin et al., 2010	776 subjects at risk of CVD, aged 55–80 years	3-year dietary intervention	FTO SNP: rs9939609	Risk allele carriers had lower weight gain compared to noncarriers
Haupt et al., 2009a	242 European individuals with overweight, IGT, family history of T2DM or history of gestational diabetes	9-month combined lifestyle intervention	MC4R SNP: rs17782313	The FTO variant did not affect reduction in body weight, total fat, visceral, and nonvisceral fat
Bo et al., 2009	335 nondiabetic, dysmetabolic patients	1-year lifestyle intervention	TCF7L2 SNP: rs7903146	Lifestyle modification improved the metabolic pattern in all genetic subgroups
Florez et al., 2006	3548 individuals with IGT or impaired fasting glucose	Combined lifestyle intervention –24 weeks of intensive counseling and 3-year follow-up	TCF7L2 SNPs: rs12255372 and rs7903146	The effect of the risk alleles in TCF7L2 on the progression to T2DM was abolished by lifestyle
Wang et al., 2007	507 European individuals with overweight and IGT, aged 40–65 years	Combined lifestyle intervention –1 year of intensive counseling and 3-year follow-up	TCF7L2 SNPs: rs12255372 and rs7903146	Genetic susceptibility to T2DM was abolished by lifestyle
Haupt et al., 2010	309 nondiabetic German Caucasian subject at increased risk for T2DM	9-month combined lifestyle intervention	TCF7L2 SNP: rs7903146	“At risk” genotype was not associated with changes in fasting or 120-min glucose, insulin sensitivity or insulin secretion
Lindi et al., 2002	490 European individuals with overweight and IGT, aged 40–65 years	Combined lifestyle intervention –1 year of intensive counseling and 3-year follow-up	PPARGgamma SNP: Pro12Ala	Lifestyle modification was associated with reduced T2DM and decreased body weight irrespectively of genotype
Franks et al., 2007	3234 individuals with IGT or impaired fasting glucose	Combined lifestyle intervention –24 weeks of intensive counseling and 3-year follow-up	PPARGgamma SNP: Pro12Ala	In the lifestyle arm reduction in body weight and subcutaneous adipose tissue occurred irrespectively of genotype
Kilpelainen et al., 2008	479 European individuals with overweight and IGT, aged 40–65 years	Combined lifestyle intervention –1 year of intensive counseling and 3-year follow-up	PPARGgamma SNPs: rs17036314, rs1801282, and rs1152003	Increased PA seems to decrease the negative effect of the risk alleles in rs17036314 and rs1801282, whereas combined lifestyle change abolished rs1152003-associated risk
Ruchat et al., 2010	481 sedentary, non-diabetic white individuals	20-week endurance training program	PPARGgamma SNP: rs1801282	Improvements in metabolic profile occurred across genotypes

SNP, single nucleotide polymorphism

2010; Lindi et al., 2002; Reinehr et al., 2008; Ruchat et al., 2010; Weyrich et al., 2008). Thus, genetic variations in PPARG and PPARGC1A were shown to determine mitochondrial function and change in aerobic physical fitness and insulin sensitivity during lifestyle intervention (Stefan et al., 2007) and individuals carrying the minor alleles of the PPARG SNPs rs1053049, rs6902123, and rs2267668 were found to benefit from exercise and weight loss to a lesser extent (Thamer et al., 2008). Besides, the *NDUFB6* gene polymorphism, known to regulate mitochondrial function, was suggested to contribute to the response of ATP synthesis to exercise training and the A allele carriers of the *NDUFB6* SNP, rs540467,

were reported to show a variation in the response to exercise (Kacerovsky-Bielez et al., 2009).

Furthermore, it has been suggested that genetic factors may be involved in determination of individual PA level and energy intake (Leibel, 2008; Teran-Garcia et al., 2008). With this respect Stubbe et al. (2006) based on analysis from a collaborative study involving 85 198 twins suggested that heritability of exercise participation may range from 48% to 71%. Family studies have also reported heritability of PA ranging from 19% to 46% (Cai et al., 2006; Simonen et al., 2002). In addition obesity-related genetic polymorphisms have been associated with increased energy intake and

preference for foods of high energy density (Haupt et al., 2009b; Speakman et al., 2008; Timpson et al., 2008).

In summary, healthy lifestyle or lifestyle modification may keep genetic predisposition to obesity and T2DM under control. Genetics has, however, been suggested to influence the outcome of a lifestyle intervention or even to determine individual PA level, food intake, and motivation for lifestyle change.

## Conclusions

Obesity and T2DM are clearly the results of a complex interplay between inherited factors and the environment. Recent advancements made through the GWA approach have substantially contributed to our understanding of obesity and T2DM genetics, however, most of the loci identified to date have modest effect on disease risk. Hence, lifestyle factors, namely physical inactivity and food overconsumption seem to have major importance for the development of both diseases.

Healthy lifestyle and lifestyle modification, on the other hand, appear to be the most efficient tools for obesity and T2DM prevention. In addition, gene-lifestyle interaction studies suggest that lifestyle determines whether an individual is likely to develop the disease and that genetic susceptibility may be partially or totally kept under control by lifestyle modification. Since genetics seems to influence individual response to a lifestyle intervention and even the motivation for lifestyle change, personalized interventions according to genotype may be considered in the future. By then lifestyle modification targeting dietary change and increased physical activity may be recommended for successful obesity and T2DM prevention irrespectively of genetic susceptibility.

**Conflict of Interest:** None.

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