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DEDICATION

To God;

To my father, Luiz (*in memoriam*), and to my mother, Leda;

To the memories of Laura Fontes and Cláudio R. Oliveira.

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"If I am not for myself, who will be for me? And, when I am only for myself, what am I? And if not now, when?" Hillel the Elder

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ABSTRACT

Background: Whereas in many countries the smoking prevalence has decreased among men, it has increased among women. One of the reasons for this phenomenon is that smoking is seen by many women as an aid to control their body weight. Although there are studies that show that smokers usually weigh less than non-smokers, there is increasing evidence that smoking is associated with abdominal obesity and other risk factors for the metabolic syndrome, like dyslipidaemia, hyperglycaemia, and hypertension.

Objective: To investigate the association between smoking, abdominal obesity, and some markers of metabolic dysfunction in a sample of healthy Austrian adults.

Participants and methods: A cross sectional study was conducted in 986 Austrian adults (405 men and 581 women), who consented in participating at the time of their annual medical check-up at workplace. Information on body weight, height, body mass index, waist circumference, hip circumference, waist-to-hip ratio, waist-to-height ratio, smoking status, education level, physical activity, diet, and biochemical parameters (fasting blood glucose, serum lipids and lipoproteins, total and differential white blood cell counts) were obtained.

Results: No differences in total body fat and/or body fat distribution were found between the non-smokers, smokers and former smokers; however, among daily smokers, the number of cigarettes smoked per day showed a significant positive association with body weight ($p = 0.001$) and BMI ($p = 0.009$). In smokers, metabolic disturbances were more frequent than in non-smokers and former smokers, and these disturbances were positively associated with both smoking intensity and duration.

Discussion and conclusion: Although in the present study abdominal obesity was not associated with smoking status, among smokers the number of cigarettes smoked per day was positively and significantly associated with both body weight and BMI. The unfavourable metabolic profile observed in smokers suggests a state of low-grade inflammation, which increases the risk of cardiovascular diseases and type 2 diabetes mellitus. Smoking prevention among non-smokers and smoking cessation among smokers should be strongly encouraged.

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LIST OF ABBREVIATIONS

AgRP	Agouti-Related Peptide
AIDS	Acquired Immune Deficiency Syndrome
ARC	Arcuate Nucleus
Apo-AI	Apolipoprotein AI
BAT	Brown Adipose Tissue
AUROC	Area Under the Receiver Operating Characteristic
BBB	Blood-Brain Barrier
BMI	Body Mass Index
BMR	Basal Metabolic Rate
CART	Cocaine- and Amphetamine-Regulated Transcript
CHO	Carbohydrates
CMD	Cardiometabolic Diseases
CNS	Central Nervous System
CO	Carbon Monoxide
CRP	C-Reactive Protein
CT	Computed Tomography
CVD	Cardiovascular Diseases
DI	Deficiency Index
ECS	Endocannabinoid System
EE	Energy Expenditure
EI	Energy Intake
EPIC	European Prospective Investigation into Cancer and Nutrition
EXI	Excess Index
FFA	Free Fatty Acids
FG	Fasting Glucose

GH	Growth Hormone
G/L	Giga per Litre (corresponds to 10^9/L)
GLM	General Linear Model
GLP	Glucagon-Like Peptide
HbA_{1c}	Glycated Haemoglobin or Glycosylated Haemoglobin
HC	Hip Circumference
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HTGW	Hypertriglyceridaemic Waist
IDF	International Diabetes Federation
IL	Interleukin
IPAQ	International Physical Activity Questionnaire
kDa	Kilodalton
LDL-C	Low-Density Lipoprotein Cholesterol
LHA	Lateral Hypothalamic Area
LSD	Least Significance Difference
LR	Leptin Receptors
MCP-1	Monocyte-Chemoattractant Protein-1
MetS	Metabolic Syndrome
MRI	Magnetic Resonance Imaging
α-MSH	Alpha-Melanocyte Stimulating Hormone
NCEP-ATP III	National Cholesterol Education Program – Adult Treatment Panel III
NHI	National Institute of Health
NHLBI	National Heart, Lung, and Blood Institute
NO	Nitric Oxide
NPY	Neuropeptide Y
PA	Physical Activity

PAI-1	Plasminogen Activated inhibitor-1
POMC	Proopiomelanocortin
PVN	Paraventricular Nucleus
PY	Pack-Years
RMR	Resting Metabolic Rate
ROC	Receiver Operating Characteristic
SAT	Subcutaneous Adipose Tissue
SD	Standard Deviation
SHBG	Sex Hormone Binding Globulin
SNS	Sympathetic Nervous System
SPSS	Statistical Package for the Social Sciences
TAG	Triacylglycerol
TC	Total Cholesterol
TC/HDL-C	Ratio of Total Cholesterol to High-Density Lipoprotein Cholesterol
T2DM	Type-2 Diabetes Mellitus
TNF	Tumour Necrosis Factor
TNF-α	Tumour Necrosis Factor-α
TZD	Thiazolidinedione
VAT	Visceral Adipose Tissue
VLDL-C	Very-Low-Density Lipoprotein Cholesterol
WAT	White Adipose Tissue
WBC	White Blood Cells
WC	Waist Circumference
WHR	Wait-to-Hip Ratio
WHO	World Health Organization
WHtR	Waist-to-Height Ratio

1. INTRODUCTION AND OBJECTIVES

Noncommunicable diseases are the leading cause of death worldwide, and most of these deaths can be attributable to diseases associated with smoking, overweight and obesity [WORLD HEALTH ORGANIZATION, 2011].

Tobacco use is considered the single most preventable cause of death in the world today, accounting for more than five million deaths each year—more than tuberculosis, HIV/AIDS and malaria combined [WORLD HEALTH ORGANIZATION, 2008].

It is estimated that in the European Union, with about 100 million daily smokers, the tobacco epidemic is responsible for 25% of all cancer deaths, and 15% of all cause-mortality [BOGDANOVICA et al., 2011].

In Austria, approximately 27% of men and 19% of women aged 15 years and older are daily smokers. Whereas the smoking prevalence has decreased among men, it has increased among women over the last 10 years, and about 90% of smoking beginners are younger than 24 years old [STATISTIK AUSTRIA, 2007]. It is predicted that about 10,000 Austrian citizens die every year from tobacco-related diseases [ÖSTERREICHISCHE KREBSHILFE, 2008].

Obesity and overweight have also become a major public health threat in the European Union, as their prevalence has increased over the last decade, reaching epidemic proportions. The combination of an unbalanced diet and reduced physical activity has been identified as the main risk factor for this increased adiposity [CHOPRA et al., 2002; ELMADFA, 2009]. In Austria, about 38% of men and 22% of women are overweight and about 10% of men and 9% of women are obese in the adult population [ELMADFA, 2009].

The combination of smoking with obesity further increases the mortality, particularly from circulatory diseases [FREEDMAN et al., 2006]. Results from The Framingham Heart Study showed that the life expectancy of women who are obese and smoke was reduced by 13.3 years and in men who are obese and smoke by 13.7 years, compared with non-smokers of normal weight [PEETERS et al., 2003]. Smoking initiation has been

influenced by weight concerns in adolescents, especially among girls, because for many years smoking has been believed to be an effective tool for weight control [HONJO and SIEGEL, 2003; WHITE, 2011].

Similarly, smoking cessation has been associated with weight gain [PERKINS, 1992]. However, weight loss in smokers does not reflect necessarily a decrease in the fat mass, rather it may be caused by a reduction in the lean body mass [CANOY et al., 2005]. In fact, some studies indicate that heavy smokers have higher body weight than light smokers [CHIOLERO et al., 2008]. There is increasing evidence that smoking affects the body fat distribution and is associated with central obesity and insulin resistance [CHIOLERO et al., 2008]. This is of particular importance for the development of the metabolic syndrome (MetS), a well-known risk factor for cardiovascular disease that includes central obesity, dyslipidaemia, hyperglycaemia, and hypertension [CZERNICHOW et al., 2004; WEITZMAN et al., 2005; CHATKIN and CHATKIN, 2007].

In the context of a worldwide obesity epidemic and a high prevalence of smoking, the relations between smoking, obesity and associated metabolic disturbances have major public health relevance.

The aim of this cross-sectional study was to investigate whether cigarette smoking is associated with abdominal obesity and metabolic dysfunction in a sample of Austrian adults. We hope our findings will add new knowledge and deepen existing understanding of such interactions, as well as serve as a basis for a subsequent cohort study.

2. LITERATURE REVIEW

2.1. Obesity, central obesity and cardiometabolic risks

It is now recognized that the clinical importance of obesity is not only a matter of the amount of fat stored, but also how fat is distributed in the body [BAYS, 2011]. The distribution of body fat was found to be an independent factor associated with the MetS in both men and women [GOODPASTER et al., 2005].

Vague [VAGUE, 1956] was the first to use the terms "android-" and "gynoid-obesity" to describe different patterns of body fat distribution in men and women, respectively. He drew attention to the association between the upper body (android) fat distribution and metabolic disturbances. Subsequent studies have demonstrated that individuals with abdominal obesity are at greater risk of developing obese-related disorders [KISSEBAH et al., 1982; KROTKIEWSKI et al., 1983; OHLSON et al., 1985].

The adipose tissue is largely distributed in the body in areas enriched for loose connective tissue. The major adipose tissue depots in mammals are the subcutaneous and intra-abdominal depots. Subcutaneous adipose tissue (SAT) depots are found mainly in the buttocks, thighs, and abdomen [COOK and COWAN, 2009]. The intra-abdominal fat depot consists primarily of omental and mesenteric fat, collectively referred to as visceral fat or visceral adipose tissue (VAT) [WAJCHENBERG, 2000; VOTRUBA and JENSEN, 2007]. **Figure 1** illustrates the major fat depots in mammals. Visceral adipose tissue is thought to be more metabolically active and poses a greater cardiometabolic risk than SAT [TAN et al., 2010; BAYS, 2011; RORIZ et al., 2011], and was found to independently predict the risk of all-cause mortality in men, after adjustment for subcutaneous and liver fat [KUK et al., 2006].

The lipolytic activity in visceral adipocytes is higher than that observed in subcutaneous adipocytes [ARNER, 1998; WAJCHENBERG, 2000] and their lipolysis is more readily stimulated by catecholamines and less readily suppressed by insulin [FRAYN, 2000]. In addition, visceral fat is drained by the portal venous system and has a direct connection with the liver [ARNER, 1998]. Thus, elevated lipolytic rate in the VAT would lead to

increased release of free fatty acids (FFA) and glycerol into the portal vein and into the liver. This causes subsequent stimulation of gluconeogenesis, increased production of very low-density lipoprotein cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) and inhibition of insulin breakdown. The result is hyperglycaemia, dyslipidaemia, and hyperinsulinaemia [ARNER, 1998; KISHIDA et al., 2012].

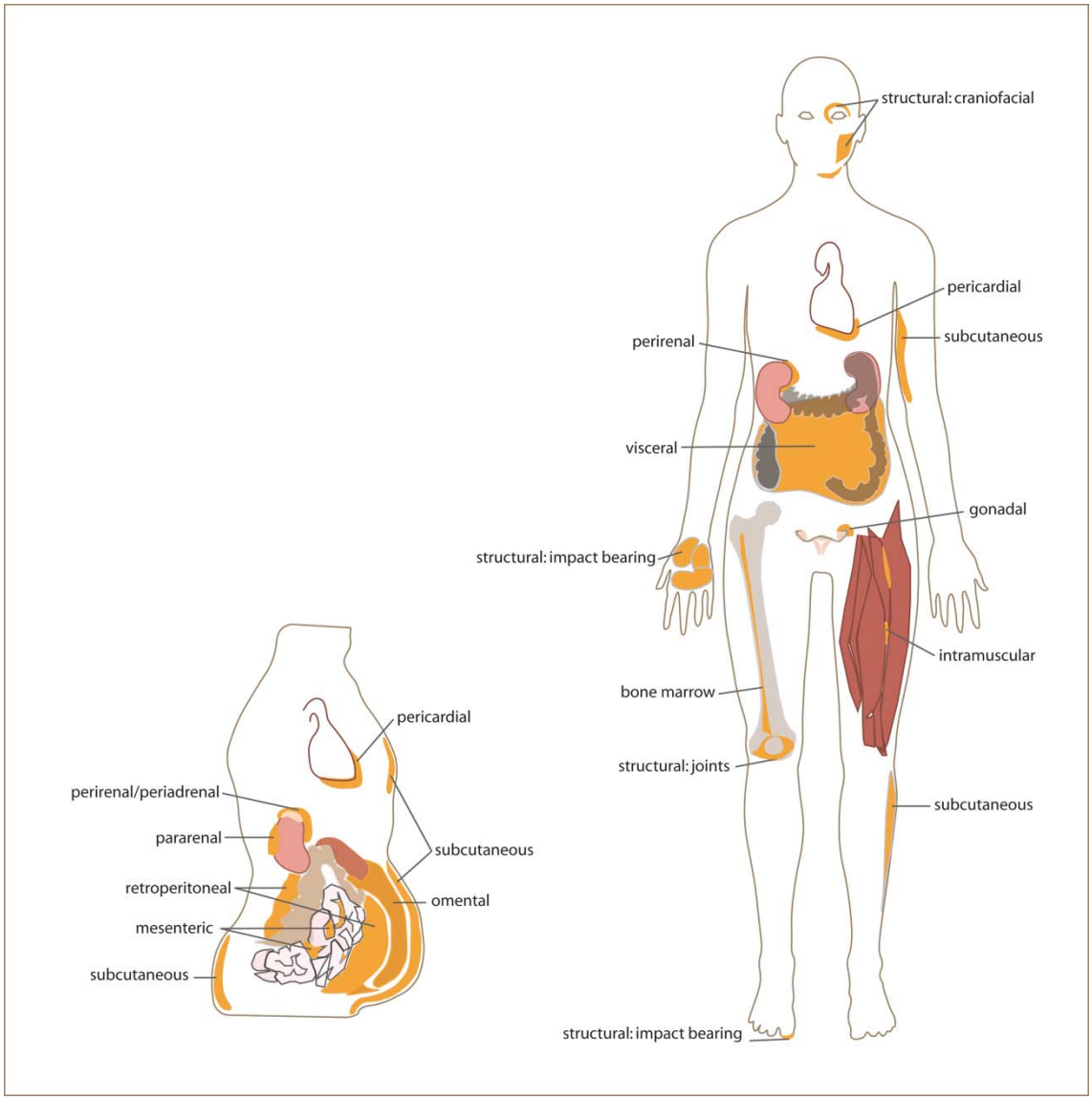

Figure 1: Distribution of the adipose tissue in the body.

The adipose tissue falls under two major classifications: visceral or surrounding organs, and subcutaneous, under the skin. Fat is distributed widely throughout the body and has different functions and growth properties depending on its location. Excessive visceral or gut fat, composed of retroperitoneal fat ("behind the peritoneum"), omental fat (adipose in a sheet of connective tissue hanging as a flap originating at the stomach and draping the intestines), and mesenteric fat (adipose in the sheets of connective tissue holding the intestines in their looping structure), has been shown to be a risk factor for diabetes and cardiovascular diseases [*reproduced from* COOK and COWAN, 2009. http://www.stembook.org/node/561#sec2-1]

Another mechanism by which abdominal obesity would trigger metabolic disorders is the increased production of pro-inflammatory cytokines, especially tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1), commonly associated with the expanded visceral fat depot [ARITA et al., 1999; RASOULI et al., 2007; FONTANA et al., 2007; TSCHONER et al., 2012]. In a prospective study, Lira and co-workers [LIRA et al., 2011] investigated the correlation between circulating cytokines and direct measures of visceral and subcutaneous adiposity in a group of obese adolescents. They found that IL-6 and TNF-α were positively correlated with visceral fat and negatively correlated with adiponectin levels. Other studies showed that the surgical removal of the omental fat significantly improved insulin sensitivity and the metabolic profile both in humans [THÖRNE et al., 2002] and in a mouse model of obesity [XIA et al., 2011]. Such beneficial metabolic effects however were not observed when subcutaneous abdominal fat was removed by liposuction [KLEIN et al., 2004].

2.2. The adipose tissue as an endocrine organ

There are two morphologically and functionally different types of adipose tissue: the brown adipose tissue (BAT) and the white adipose tissue (WAT). Brown adipocytes are mainly involved in the production of heat and lipid oxidation. The thermogenic properties of BAT are mediated by uncoupling protein-1 (UPC-1), a mitochondrial protein specifically expressed in this tissue. In rodents, BAT is detected throughout life span, while in humans it was thought to be present only in infants. However, recent studies have shown that human adults have relevant amounts of metabolically active BAT, which negatively correlate with the body mass index (BMI) and with central obesity [KARASTERGIOU and MOHAMED-ALI, 2010; APOSTOLOPOULOU et al., 2012]. On the other hand, WAT is the most abundant adipose tissue in mammals. It functions as a thermal insulator, an energy storage depot and secretes important metabolically active substances [KARASTERGIOU and MOHAMED-ALI, 2010; HARWOOD, 2011].

For a long time, WAT was considered a passive fat depot for the storage of triacylglycerols (TAG) and the release of fatty acids [ARONNE et al., 2009; DROUET et al., 2012]. Since the identification of leptin in 1994, it has become evident that the

adipose tissue acts as an endocrine organ that communicates with the central nervous system (CNS) [ZHANG et al., 1994; WAJCHENBERG, 2000; HARWOOD, 2011]. Approximately 100 different bioactive substances referred to as "adipokines" or "adipocytokines" have been identified in the adipose tissue, which can act in autocrine, paracrine or endocrine fashion [GNACIŃSKA et al., 2009; GERMAN et al., 2010]. Some of these factors, such as leptin, resistin, TNF-α, IL-6, retinol binding protein-4 (RBP-4), visfatin, monocyte-chemoattractant protein-1 (MCP-1), and PAI-1 have pro-inflammatory properties. Others, like adiponectin, IL-10 and secreted frizzled-related protein-5 (SFRP-5) are anti-inflammatory. An imbalance of these two classes of adipocytokines, caused by an excessive adipose mass, has been thought to trigger metabolic dysfunctions such as insulin resistance, hyperglycaemia, hypertension, and dyslipidaemia, all involved in the MetS [MAURY and BRICHARD, 2010; OUCHI et al., 2011].

2.3. Adipose tissue and inflammation

Obesity has been described as a chronic state of low-grade inflammation, where plasma levels of several biomarkers of oxidative stress and inflammation are increased [HOTAMISLIGIL et al., 1995; VAN GUILDER et al., 2006].

Additionally to adipocytes, adipose tissue is composed of non-adipose cells including pre-adipocytes, lymphocytes, macrophages, fibroblasts and vascular cells [OUCHI et al., 2011]. Macrophage number in the adipose tissue is positively associated with the BMI and the adipocyte size [WEISBERG et al., 2003]. Adipose tissue expansion is accompanied by local hypoxia and adipocyte necrosis, which promotes macrophage differentiation and infiltration into the tissue. The differentiated cells become the main source of TNF-α and other pro-inflammatory cytokines in the adipose tissue, resulting in systemic inflammation and insulin resistance [WEISBERG et al., 2003; KARASTERGIOU and MOHAMED-ALI, 2010; OUCHI et al., 2011].

There are two different subtypes of macrophages in the adipose tissue: The M2 "resident" or "alternatively activated" macrophages and the M1 or "classically activated" macrophages [SAMAAN, 2011; OUCHI et al., 2011]. M2 macrophages are

present under physiological conditions and are involved in maintaining the tissue homeostasis. These cells upregulate the synthesis of anti-inflammatory cytokines and downregulate the production of pro-inflammatory cytokines [SAMAAN, 2011; OUCHI et al., 2011]. On the other hand, the M1 macrophages are bone marrow-derived monocytes that infiltrate the expanded adipose tissue and differentiate into an inflammatory macrophage subtype [SAMAAN, 2011]. Their presence in the adipose tissue was associated with increased expression of TNF-α, MCP-1, inducible nitric oxide synthase (iNOS) and IκB kinase (IKKB) in the stromal-vascular fraction of the adipose tissue, which preceded or coincided with decreased insulin sensitivity [BOURLIER and BOULOUMIE, 2009].

2.4. Some important adipocytokines

2.4.1. Leptin

Leptin (*leptos*, from Greek = thin) is a 16 kDa polypeptide hormone product of the *ob* gene that is mainly produced by adipocytes from WAT. Plasma levels of leptin increase in obesity and decrease during fasting, and correlate positively with the body fat depot and the adipocyte size [KERSHAW and FLIER, 2004; AHIMA, 2006; STOFKOVA, 2009]. Leptin concentrations are higher in SAT than in VAT [KERSHAW and FLIER, 2004], and women have higher leptin levels compared with men, after adjusting for BMI [KELESIDIS et al., 2010]. However, a wide variation in plasma concentrations of leptin has been observed among individuals with similar BMI, fat mass and body fat distribution, suggesting that other factors than fat mass alone influence the regulation of leptin secretion [RESELAND et al., 2005].

Leptin is primarily implicated in the regulation of energy homeostasis, neuroendocrine function, and metabolism [KELESIDIS et al., 2010]. Leptin deficient mice (*ob/ob* mice) show hyperphagia, obesity, hypercortisolemia, insulin resistance and infertility, all of which are reversed by leptin replacement [BULCÃO et al., 2006; OUCHI et al., 2011]. In contrast to the *ob/ob* mice, obese humans have very high leptin levels and are thought to be leptin resistant [GALIC et al., 2010].

Leptin signalling is mediated by specific leptin receptors (LR) in the brain and peripheral tissues. There are several LR isoforms, all produced by a single *lepr* gene and generated by alternative splicing [MÜNZBERG et al., 2005]. They belong to the IL-6 receptor family of class I cytokine receptors. The short leptin receptor isoform (LRa) may play an important role in mediating leptin transport across the blood-brain barrier (BBB). The long isoform (LRb) is crucial for leptin action and is expressed mainly in the brain—more specifically in areas which regulate energy homeostasis and neuroendocrine function, such as the arcuate nucleus (ARC), dorsomedial hypothalamic (DMH), ventromedial hypothalamic (VMH), and premammillary nuclei [MÜNZBERG et al., 2005; KELESIDIS et al., 2010; GALIC et al., 2010]. Leptin binds to LRb in the ARC neurons and stimulates the synthesis of alpha-melanocyte stimulating hormone (α-MSH), derived from the proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), two anorexigenic peptides. Conversely, leptin inhibits the production of the orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP), which are synthesized by another population of ARC neurons. This will result in anorexia, increased thermogenesis, increased insulin sensitivity and fatty acid oxidation [MÜNZBERG et al., 2005; AHIMA, 2006].

Leptin is also thought to act as a pro-inflammatory adipocytokine [OUCHI et al., 2011], and hyperleptinemia has been pointed as an independent risk factor for the development of the MetS [ESTEGHAMATI et al., 2011].

2.4.2. Interleukin-6 (IL-6)

Interleukin-6 is a pro-inflammatory cytokine secreted by numerous cell types. It is estimated that approximately 10% of circulating IL-6 is synthesized by adipocytes [POULOS et al., 2010]. Interleukin-6 is also produced by immune cells, endothelial cells, skeletal muscle, and fibroblasts [BULCÃO et al., 2006]. This cytokine stimulates the production of C-reactive protein (CRP) in the liver, a systemic marker of inflammation [DAS, 2001]. In prospective studies, high levels of IL-6 and CRP at baseline predicted the development of MetS, T2DM, and CVD, independent of other risk factors [LAAKSONEN et al., 2001; PRADHAN et al., 2001; BALLANTYNE and NAMBI, 2005]. In a large Italian study, higher levels of IL-6 and lower levels of adiponectin were

significantly associated with arterial thickness independent of MetS and other cardiovascular risk factors [SCUTERI et al., 2011]. Serum concentrations of IL-6 and CRP were also found to be positively and significantly associated with total and central adiposity, both in male and female adults [VISSER et al., 1999; PARK et al., 2005]. It has been shown that IL-6 stimulates lipolysis in the human adipose tissue, leading to an increase in the circulating levels of FFA. This in turn causes lipid accumulation and insulin resistance in other tissues, such as the skeletal muscle and the liver. These cytokines therefore may constitute a link between local inflammation in the expanded adipose tissue and obesity-related disorders [GOOSSENS, 2008].

2.4.3. Tumour necrosis factor-alpha (TNF-α)

Tumour necrosis factor-alpha is mainly produced by monocytes and macrophages and plays a central role in inflammatory and autoimmune diseases [OUCHI et al., 2011]. It stimulates the production of other cytokines involved in the inflammatory response such as IL-8 and IL-6, both related to obesity and insulin resistance in animals and humans [BULCÃO et al., 2006]. Obese premenopausal women were reported to express 2.5-fold more TNF-α mRNA in subcutaneous abdominal tissue compared with lean controls. Additionally, TNF-α expression in the fat tissue was positively correlated with hyperinsulinaemia and BMI [HOTAMISLIGIL et al., 1995]. A similar study found a 7.5-fold increase in TNF-α expression in the adipose tissue of obese compared with lean individuals, and TNF-α secretion negatively correlated with insulin sensitivity [KERN et al., 2001]. A 5-year follow-up study was carried out to investigate the association between the body fat distribution and changes in the activity of the TNF-α system. It was found that the increase in circulating TNF-α in obesity occurs at an initial stage of abdominal fat accumulation and that plasma TNF-α levels are not influenced by further increases in the fat mass [OLSZANECKA-GLINIANOWICZ et al., 2011].

2.4.4. Adiponectin

Adiponectin—also known as apM1, Acrp30, AdipoQ, and GBP28—is a 30 kDa protein with some structural similarities with collagen, complement component C1q, TNF-α, and the neuropeptide cerebellin [KERSHAW and FLIER, 2004; STOFKOVA, 2009].

Adiponectin circulates in three different forms: low-molecular weight (LMW) trimers, medium-molecular weight (MMW) hexamers and high-molecular weight (HMW) multimers. The latter two are thought to be the most active and clinically relevant [DRIDI and TAOUIS, 2009; LIN and LI, 2002].

The biological effects of adiponectin are primarily mediated through its receptors: AdipoR1, most expressed in skeletal muscle; AdipoR2, most abundant in the liver; and T-cadherin, expressed on vascular endothelial cells and smooth muscle [SUN et al., 2009]. Recently, AdipoR1 and AdipoR2 were found to be expressed in the hypothalamus, particularly in the POMC and NPY neurons in the ARC, suggesting that adiponectin may be also implicated in the central regulation of energy intake (EI) and energy expenditure (EE) [DRIDI and TAOUIS, 2009].

Adiponectin is considered the most abundant adipocytokine, with circulating levels ranging from 3 to 30 μg/dL. Although synthesized almost exclusively by adipocytes, plasma levels of adiponectin are decreased in obesity, for both men and women [OUCHI et al., 2011; ARITA et al., 1999]. Its expression in the adipocyte is downregulated by TNF-α, IL-6, oxidative stress, hypoxia, and sympathetic nervous activity. Conversely, some transcriptional factors, such as peroxisome proliferator-activated receptor-gamma (PPARγ) stimulate adiponectin production [MANGGE et al., 2010; OUCHI et al., 2011].

Plasma levels of adiponectin have also been negatively correlated with waist circumference (WC) [ACKERMANN et al., 2011], smoking [TAKEFUJI et al., 2007], serum TAG and glucose [MILEWICZ et al. 2010], impaired glucose tolerance and T2DM [NAKASHIMA et al., 2008], and oxidized low-density lipoprotein cholesterol (oxLDL-C) [LAUTAMÄKI et al., 2007]. On the other hand, adiponectin levels were found to increase with lifestyle modifications such as weight loss, dietary intervention, cessation of smoking, and regular physical activity [KRIKETOS et al., 2004; EFSTATHIOU et al., 2009; ROLLAND et al., 2011; KIM et al., 2011]. Furthermore, circulating levels of adiponectin appear to predict the course of the MetS [AHONEN et al., 2012].

2.5. The central and peripheral control of food intake and energy balance

Food intake, energy expenditure, and body weight are homeostatically regulated by complex mechanisms involving central and peripheral components. The CNS receives signals from the gastrointestinal tract and the adipose tissue informing on the nutritional status and energy stores. This leads to the synthesis of anorexigenic and orexigenic substances responsible for the energy balance [WILDING, 2003; MURPHY and BLOOM, 2006]. Through this mechanism, most animals and humans maintain a steady body weight for long periods, despite a daily variation in both energy intake and energy expenditure [CHEN et al., 2007]. The main brain regions involved in the regulation of energy balance are the hypothalamus and the brainstem [WILDING, 2003; MURPHY and BLOOM, 2006].

The hypothalamus is subdivided into interconnecting areas and nuclei, including the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventromedial nucleus (VMN), dorsomedial nucleus (DMN), and lateral hypothalamic area (LHA) [SIMPSON et al., 2009]. The ARC comprises two neuronal populations with opposing effects on food intake: neurons which co-express NPY and AgRP stimulate food intake and are anabolic, whereas neurons co-expressing POMC and CART suppress feeding and are catabolic. POMC cleavage produces α-MSH, which binds to melanocortin receptors (MCR3 and MCR4) in the brain leading to reduced food intake and energy stores [ANGELOPOULOS et al., 2005; RICHARD et al., 2009; SUZUKI et al., 2010]. Together, melanocortin receptors α-MSH and AgRP constitute the hypothalamic melanocortin system, which plays a crucial role in translating the signals from the hunger-modulating hormones into changes in the sensation of hunger and satiety [RICHARD et al., 2009; PILLOT et al., 2011]. Neurons from the ARC project to the PVN, which contains neurons that produce oxytocin, thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRH). These peptides decrease food intake and/or increase metabolic rate. Like the PVN, the LHA is also innervated by ARC neurons and is the source of the orexigenic neuropeptides, melanin-concentrating hormone (MCH) and orexin [SCHWARTZ, 2006; AHIMA and ANTWI, 2008].

Two different types of peripheral control are involved in the regulation of appetite and food intake. Food intake is the product of meal size, which reflects the short-term satiety, and the meal number, which reflects the long-term satiety [RAMOS et al., 2005]. The "meal-control signals" or "short-term signals" are signals generated from the gastrointestinal tract in response to a meal. They reach the nucleus tractus solitarius (NTS) in the caudal brainstem, via the vagus nerve and other routes, and are relayed to the hypothalamus [WOODS and SEELEY, 2000; WILDING, 2003; BLEVINS and BASKIN, 2010]. These signals regulate food intake on a meal-to-meal basis, inducing a sense of satiety [VALASSI et al., 2008]. The most important short-term signals are the anorexigenic peptides cholecystokinin (CCK), glucagon-like peptide 1 and 2 (GLP-1 and GLP-2), amylin, peptide tyrosine tyrosine (PYY_{3-36}), pancreatic polypeptide (PP), oxyntomodulin (OXM), and glucagon, in addition to the orexigenic gut hormone ghrelin [VALASSI et al., 2008; SUZUKI et al., 2010]. The "long-term signals" or "adiposity-signals" involved in the regulation of energy homeostasis include the hormones leptin and insulin, whose circulating levels are proportional to the fat mass [SUZUKI et al., 2010]. Circulating insulin levels increase following a meal and insulin crosses the BBB to reach the brain, where insulin receptors are widely distributed. Intracerebroventricular administration of insulin results in a dose-dependent suppression of food intake and body-weight gain in baboons and rodents [SUZUKI et al., 2010]. As already discussed, leptin regulates food intake via NPY/AgRP and POMC/ CART neurons in the ARC. The mechanisms that modulate appetite-control are illustrated in **Figure 2**.

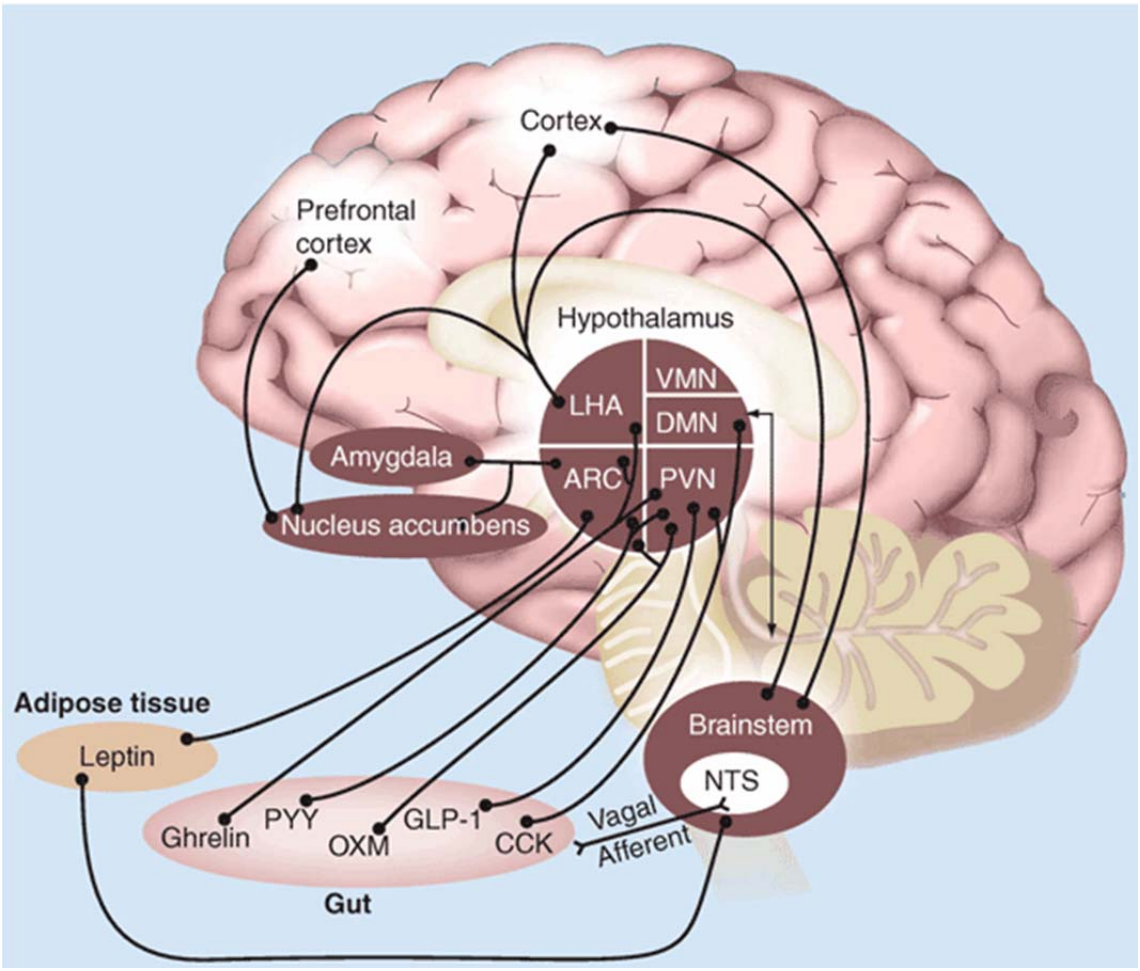

Figure 2: Relationship between the brainstem, hypothalamus, cortical areas and reward circuitry known to modulate appetite control.

Gut hormones acting via vagal afferents act on the NTS in the brainstem, which in turn signals to the hypothalamus. Some gut hormones may also act directly on hypothalamic nuclei via the circulation and across an incomplete blood-brain barrier. There are projections from hypothalamic nuclei to the prefrontal cortex, involved in conditioned taste aversion, as well as reward centres, such as the amygdala and nucleus accumbens. Leptin is also thought to act directly on the NTS as well as hypothalamic nuclei, suggesting that it can modulate appetite through different pathways. ARC: Arcuate nucleus; CCK: Cholecystokinin; DMN: Dorsomedial nucleus; GLP: glucagon-like peptide; LHA: lateral hypothalamic area; NTS: nucleus tractus solitarius; OXM: oxyntomodulin; PYY: peptide tyrosine tyrosine; PVN: paraventricular nucleus; VMN: ventromedial nucleus [*reproduced from* SIMPSON et al., 2008, *with permission of Expert Reviews Ltd.*].

2.5.1. The reward system and the endocannabinoid system

While energy homeostasis is primarily regulated by the hypothalamus and brainstem, reward mechanisms that control appetite and feeding behaviour are thought to be controlled by the corticomesolimbic system [AHIMA and ANTWI, 2008; SIMPSON et al., 2008; SUZUKI et al., 2010]. Endocannabinoid and opioid receptors are largely

distributed within the CNS and play a major role in increased feeding related to reward [SUZUKI et al., 2010]. The most important endocannabinoids produced in the brain are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which together with the cannabinoid 1 and 2 (CB1 and CB2) receptors compose the endocannabinoid system (ECS). An over-activated ECS is associated with obesity and metabolic disorders, by increasing energy intake and reducing energy expenditure, thus promoting fat deposition [LUTZ, 2005; RICHARD et al., 2009]. Interestingly, ECS is also associated with nicotine dependence in smokers. The area of the brain involved in motivation to seek sweet and palatable food is the same area that is involved in nicotine craving in smokers. Hence, endocannabinoids are important for this stimulatory effect of nicotine and for the establishment of tobacco dependence. Indeed, preventing the action of the CBI receptor with rimonabant, a cannabinoid receptor antagonist, was found to alleviate nicotine dependence [LUTZ, 2005].

2.5.2. Monoaminergic neurotransmitters

Monoaminergic neurotransmitters interact with neuropeptides and peripheral hormones in the hypothalamus to control satiety mechanisms and eating behaviour [RAMOS et al., 2005; VALASSI et al., 2008]. Serotonin suppresses food intake and body weight, and this action is mainly mediated by the serotonin 1B receptor. Dopamine regulates hunger and satiety by acting on specific hypothalamic areas, through the D1 and D2 receptors. Noradrenaline activation of α_1- and β_2-adrenoceptors decreases food intake, whereas stimulation of the α_2-adrenoceptor increases food intake [RAMOS et al., 2005].

2.5.3. Smoking and energy balance

It has been reported in several studies that smokers weigh less than non-smokers, and smoking cessation is usually accompanied by weight gain [ALBANES et al., 1987; KLESGES et al., 1989; WILLIAMSON et al., 1991; RÁSKY et al., 1996]. The mechanisms by which cigarette smoking negatively influences body weight are not completely understood and the results of many studies are contradictory [FILOZOF et al., 2004; CHEN et al., 2005; BERLIN, 2009]. Body weight is controlled by food intake and energy expenditure. Energy expenditure, in its turn, is regulated by three principal components:

a) the resting metabolic rate (RMR), which is the energy required to maintain the body functions at rest and which accounts for 60–80% of the total energy expenditure; b) the diet-induced thermogenesis or thermic effect of food, which is the increase of RMR induced by food consumption and represents about 10% of the total energy expenditure, and c) the energy consumed during physical activity [WILDING, 2003; PHAM et al., 2012].

Cigarette smoke is a complex mixture of over 7,000 chemical compounds containing many bioactive substances that undergo complex interactions with human biological systems [NORTHROP-CLEWES and THURNHAM, 2007; NAGAMMA et al., 2011]. Nicotine, a component of the tar phase of tobacco smoke, is the addictive substance [AMBROSE and BARUA, 2004], and is thought to be the primary component responsible for the effects of smoking on body weight [PERKINS et al., 1989]. It is possible that the effects of nicotine on body weigh involve both, increased energy expenditure and reduced energy intake [PERKINS et al., 1990; PERKINS, 1992; CHEN et al., 2005]. It should be noted however that some studies found a positive association between body weight and the number of cigarettes smoked per day, i.e. heavy smokers tend to weigh more than light smokers [BAMIA et al., 2004; JOHN et al., 2005; CHIOLERO et al., 2007]. The reasons for this positive association remain unclear. Possible mechanisms involve differences in some lifestyle factors between light and heavy smokers: the latter are reported to have a higher intake of fat, higher consumption of alcohol and a lower level of physical activity, compared with the former [OH and SEO, 2001; AKBARTABARTOORI et al., 2005; TRAVIER et al., 2009].

2.5.3.1. Effects of nicotine on energy expenditure

Nicotine is a sympathomimetic agent, i.e. it activates the sympathetic nervous system (SNS) and stimulates the release of adrenaline and noradrenaline. Elevated circulating levels of these catecholamines promote lipolysis and increase plasma concentrations of FFA in smokers, contributing therefore to increased thermogenesis [HELLERSTEIN et al., 1994; AUDRAIN-MCGOVERN and BENOWITZ, 2011]. It has been suggested that besides the lipolysis stimulation via catecholamine release, nicotine itself induces lipolysis by

activating nicotinic cholinergic receptors in the adipose tissue [ANDERSSON and ARNER, 2001].

Smoking was found to increase 24-hour energy expenditure by about 10% and this effect seemed to be partially mediated by the SNS [HOFSTETTER et al., 1986]. Perkins and colleagues [PERKINS et al., 1989] conducted a study with 18 male smokers to examine the effects of nicotine on RMR. A moderate (15 μg/kg body weight), low (7.5 μg/kg body weight) or placebo (0 μg/kg body weight) dose of nicotine was administered via nasal-spray solution. Both doses of nicotine increased the RMR by 6% above the baseline and this increase was significantly greater than the 3% increase observed in the RMR following the placebo.

The same authors assessed the effect of nicotine or placebo on the energy expenditure of 20 male smokers during rest and light physical activity. They reported that the nicotine-induced increase in the metabolic rate observed at rest is enhanced during light exercise [PERKINS et al., 1989a].

However, this effect of nicotine on the RMR could be regulated by the mass of body fat, and would vary between individuals within different BMI categories. Compared with overweight smokers, male smokers of normal weight showed a significantly greater increase in plasma nicotine and noradrenaline levels after smoking two high yield cigarettes. These changes in nicotine and noradrenaline levels were also accompanied by a significant increase in the RMR, but only in the normal-weight individuals [WALKER and KANE, 2002].

In contrast with these findings, a recent study, where doubly-labelled water was used to measure the total energy expenditure in adult men and women, found no differences in energy expenditure and BMI between smokers and non-smokers [BRADLEY et al., 2010].

2.5.3.2. Effects of nicotine on food intake

The hypothesis that nicotine suppresses appetite and food intake has been tested in several studies, with conflicting results. Although a transient anorectic effect of nicotine

has been documented in human and animal studies [DANDEKAR et al., 2011], a few studies have reported that smokers actually have a greater caloric consumption than non-smokers [WACK and RODIN, 1982; PERKINS, 1993]. In one study, the chronic administration of nicotine to rats resulted in reduced body weight without significant changes in food intake [SCHECHTER and COOK, 1976]. Bellinger and co-workers [BELLINGER et al., 2003] reported that the intermittent administration of nicotine to adult male rats during 14 days resulted in decreased food intake and body weight, compared with the control group. Food intake was reduced by an immediate reduction in meal size and meal duration. However a significant increase in the meal number was observed at the fifth day of treatment, which was thought to be due to an attempt to normalize food intake. These changes in energy balance were noted for up two weeks after cessation of nicotine administration.

In addition to its effects on meal size and number, nicotine and cigarette smoking are likely to influence the type of food eaten. Administration of nicotine to rodents and cigarette smoking by humans were reported to decrease the intake of sweet-tasting high caloric food, while changes in the consumption of other foods were not observed. The human study, however, was limited to a single meal and did not measure changes in body weight. In the animal study, body weight was reduced as the intake of sweet foods decreased [GRUNBERG, 1982]. Similarly, cessation of smoking led to an increased intake of sweets which was reversed when smoking was resumed [PERKINS et al., 1990a]. When the per capita consumption of cigarettes was compared to the per capita consumption of all major food groups in the United States during a 14-year period, a significant negative correlation between these items was found, i.e. high cigarette consumption was associated with low consumption of sweets and vice-versa. According to the authors of the study [GRUNBERG and MORSE, 1984], these findings indicate that nicotine and cigarette smoking may influence body weight by affecting the consumption of specific foods, particularly sweet foods.

The action of nicotine in suppressing food intake may be influenced by the fat content in the diet, as found in some studies with rodents. Wellman and colleagues [WELLMAN et al., 2005] reported that the impact of nicotine administration on reducing daily caloric intake and body weight was significantly greater in the high-fat chow (58% energy from

fat) group, compared to the standard chow (10.9% energy from fat) group. Nicotine administration reduced meal size in both standard and high-fat chow groups, while cessation of nicotine exposure resulted in transient increases in daily caloric intake in both diet groups. In the study of Hur and colleagues [HUR et al., 2010], male mice receiving a high-fat diet (45% energy from fat) or a normal-fat diet (10% energy from fat) were exposed to nicotine- or saline treatment for 14 days. Nicotine decreased body weight both in the group with high- and normal-fat diet, but the effect was more pronounced in the latter. Weight loss mediated by nicotine-treatment in obese mice resulted from both decreased energy intake and increased energy expenditure. Similar results were reported by Mangubat and co-workers [MANGUBAT et al., 2012]. Male mice consuming a high-fat diet (62% energy from fat) or a standard normal chow diet were treated with nicotine or saline for seven weeks. In the nicotine-treated groups, weight-gain in animals consuming both diets was reduced in a dose-dependent manner. In the normal chow diet, weight loss was mainly attributed to decreased energy intake. In the high-fat diet only 66% of the weight loss was accounted for decreases in energy intake, suggesting that simultaneous increases in energy expenditure took place.

The mechanisms by which nicotine administration reduces food intake are not completely understood. Animal studies suggest that nicotine may influence energy balance by directly acting in the hypothalamus, suppressing NPY expression in the ARC [JANG et al., 2003; CHEN et al., 2005; CHEN et al., 2007]. Recently, Mineur and colleagues [MINEUR et al., 2011]—by using a combination of pharmacological, molecular genetic, electrophysiological, and feeding studies—provided evidence that nicotine diminishes food intake and body weight by stimulating hypothalamic alpha-3 beta-4 nicotinic acetylcholine receptors (α3β4 nAChRs) in the POMC neurons with subsequent activation of the hypothalamic melanocortin system. These findings suggest that drugs acting as α3β4 agonists could be helpful for controlling body-weight gain after cessation of smoking, as well as for treating obesity and related metabolic disorders.

Figure 3 illustrates the possible mechanisms by which cigarette smoking reduces body weight.

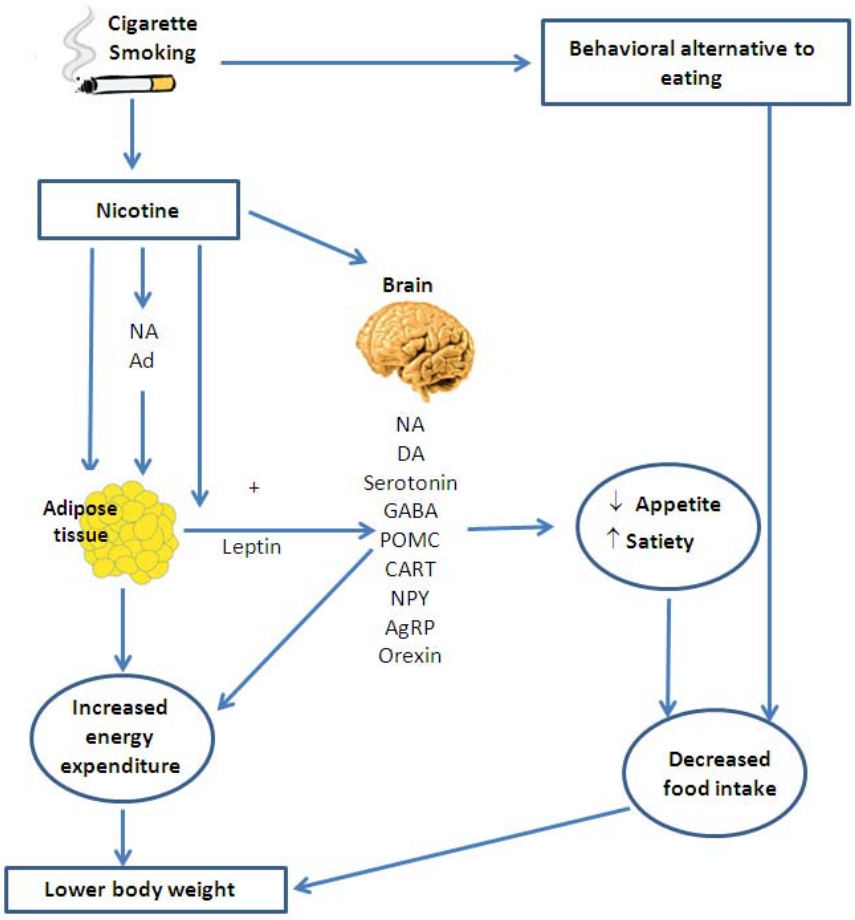

Figure 3: Mechanisms through which cigarette smoking reduces body weight.

Smoking reduces body weight by increasing energy expenditure (EE) and inhibiting the expected compensatory increase in caloric intake. Nicotine increases EE both by direct effects on peripheral tissues, largely mediated by catecholamines, and by effects on central nervous system neuroendocrine circuits. Nicotine's effects on the brain also leads to suppression of appetite, and smoking per se can serve as a behavioural alternative to eating. AgRP: agouti-related peptide; CART: cocaine amphetamine-regulated transcript; DA: dopamine; Ad: adrenaline; GABA: γ-aminobutyric acid; NA: noradrenaline; NPY: neuropeptide Y; POMC: proopiomelanocortin [*adapted from* AUDRAIN-MCGOVERN and BENOWITZ, 2011, *with permission of Nature Publishing Group*].

2.5.3.3. Weight gain following cessation of smoking

Smoking cessation is usually accompanied by weight gain and this has been regarded as a reason why many smokers, especially women, are unwilling to quit [FILOZOF et al., 2004; MUNAFÒ et al., 2009]. Furthermore, weight gain was reported as a reason for relapse among 32% of men and 52% of women who attempted to quit [PISINGER and JORGENSEN, 2007]. The decline in the prevalence of smoking was pointed as a possible cause for the increasing obesity rates in developed countries [CHOU et al., 2004].

However, studies have demonstrated that although a decline in smoking increases body weight, the magnitude of the effect in most quitters is small [FLEGAL et al., 1995; FANG et al., 2009; KASTERIDIS and YEN, 2012]. In addition, it was observed that cigarette smokers who achieve long-term abstinence from smoking revert to a mean BMI roughly equivalent to that of non-smokers [MUNAFÒ et al., 2009; TRAVIER et al., 2009].

The consistency and magnitude of the weight gain following smoking cessation remain controversial and are influenced by several factors [FILOZOF et al., 2004]. Studies demonstrate that most of weight gain occurs within the first year of cessation [KLESGES et al., 1989; O'HARA et al., 1998; BASTERRA-GORTARI et al., 2010].

Williamson and colleagues [WILLIAMSON et al., 1991] observed that the mean weight gain attributable to the cessation of smoking was 2.8 kg in men and 3.8 kg in women over 10-year follow-up. A major weight gain (>13 kg) was observed in 9.8% of the men and 13.4% of the women. For both sexes, the risk factors for this increased weight gain were to be black, younger than 55 years of age, and have smoked 15 cigarettes or more per day.

Lower socio-economic status [SWAN and CARMELLI, 1995], genetic factors [SWAN and CARMELLI, 1995; FREATHY et al., 2011] and being a heavy smoker [MIZOUE et al., 1998; JOHN et al., 2005; CHIOLERO et al., 2007] may increase the risk of a major weight gain after stopping smoking. Similarly, being underweight or overweight on cessation has also been reported as an increased risk factor for excessive weight gain following cessation [LYCETT et al., 2011]. Other authors, however, have found only a modest impact of smoking cessation in overweight and obese individuals [KASTERIDIS and YEN, 2012].

Proposed mechanisms for the postcessation weight gain are increases in caloric intake, and decreases in RMR. However, the results of several studies are inconsistent. While many studies found a sharp increase in eating during the first few weeks of smoking cessation, this effect is less evident after a longer period of abstinence [PERKINS, 1993]. Stamford and co-workers [STAMFORD et al., 1986] reported that the mean energy intake of heavy-smoker women was increased by 227 kcal after cessation, with no changes in the distribution of dietary macronutrients. Another study, however, found that

individuals who stopped smoking and gained weight after cessation did not consume more calories but ate somewhat less protein and significantly more carbohydrate than quitters whose weights did not change [RODIN, 1987]. Accordingly, short-term abstinence from smoking was not found to increase energy intake in a group of 21 women [ALLEN et al., 2000].

Differences in physical activity levels in the postcessation period have not been observed in many studies [HALL et al., 1989; LEISCHOW and STITZER, 1991; ALLEN et al., 2004] and weight gain upon cessation of smoking is not likely to be caused by decreased physical activity levels [PERKINS, 1993].

As stated earlier, the RMR accounts for 60–80% of the adult daily energy expenditure [PHAM et al., 2012], and because of that any effect on the RMR could significantly influence body weight, regardless of changes in caloric intake or physical activity levels [PERKINS, 1993]. In fact, a decreased RMR has been thought to be the most likely cause for weight gain following smoking cessation [DALLOSSO and JAMES, 1984; MOFFATT and OWENS, 1991; PERKINS, 1993; FILOZOF et al., 2004]. Nonetheless, some studies did not find changes in the RMR of quitters [STAMFORD et al., 1986, ALLEN et al., 2000].

Other possible mechanisms implicated in postcessation weight gain are decreased fat oxidation [JENSEN et al., 1995], increased lipoprotein lipase activity—which in turns leads to an increase in adipose tissue metabolism [FERRARA et al., 2001]—and changes in the body weight set-point [CABANAC and FRANKHAM, 2002; CHIOLERO et al., 2008].

2.6. Smoking, body fat distribution and the metabolic syndrome

Adiposity and cigarette smoking are independent however interconnected health risk factors [KOSTER et al., 2008a]. Nearly 5.3% of men and 4.2% of women in the United States are obese and smoke, and this proportion is higher in African-Americans [HEALTON et al., 2006]. Being obese and smoker was found to be significantly associated with all-cause mortality, with very obese smokers showing a 3.5- to 5-fold increased risks, when compared with non-smokers, nonobese individuals [FREEDMAN et al., 2006]. In a 10-year prospective cohort study, Koster and co-workers [KOSTER et al.,

2008a] found that smokers with a BMI of ≥35 kg/m^2 had a mortality risk 6–8 times greater than that of non-smokers of normal weight; when taking into account smoking status and WC measurements, the highest mortality risks were found among current smokers with a large WC.

It has been demonstrated that although smokers weigh less than non-smokers, they tend to accumulate more fat in the abdominal region [JEE et al., 2002; KWOK et al., 2011]. In addition, a dose-dependent association between the smoking burden and abdominal fat has been observed [BARRETT-CONNOR and KHAW, 1989; SHIMOKATA et al., 1989; OH et al., 2005; KOMIYA et al., 2006; CHIOLERO et al., 2008; TRAVIER et al., 2009].

The mechanisms underlying the association between cigarette smoking and abdominal obesity remain to be elucidated, but a cluster of factors may be involved.

Hormonal and endocrine mechanisms are likely to modulate this association. Smoking influences the circulating levels of pituitary, adrenal, and sex steroid hormones [KAPOOR and JONES, 2005; TWEED et al., 2012]. Compared to non-smokers, smokers were found to have higher circulating levels of cortisol [STEPTOE and USSHER, 2006], which increased with the content of nicotine in cigarette smoking [WILKINS et al., 1982]. High levels of cortisol seem to have a key role in the development of visceral adiposity [PASQUALI and VICENNATI, 2000].

Smoking may also have an anti-oestrogenic effect in women [MICHNOVICZ et al., 1986; TANKÓ and CHRISTIANSEN, 2004], probably by inducing changes in hepatic oestrogen metabolism [KAPOOR and JONES, 2005] and increasing catechol oestrogen formation [TZIOMALOS et al., 2004]. Among premenopausal women, chronic cigarette smoking was significantly associated with elevated levels of androgens and suppressed levels of oestradiol and sex hormone binding globulin (SHBG) [DUŠKOVÁ et al., 2012]. This hormone profile was associated with increased waist-to-hip ratio (WHR), hypertrophy of visceral adipocytes, and disturbances in the metabolism of glucose in premenopausal women [EVANS et al., 1993]. In postmenopausal women, cigarette smoking was associated in a dose-dependent fashion with higher levels of androgens, oestrogens, 17-hydroxprogesterone, and SHBG [BRAND et al., 2011]

Among men, an inverse relationship between sex steroid hormones with overall and abdominal obesity has been observed [DERBY et al., 2006; SEIDELL et al., 1990]. The association of smoking with the circulating levels of these hormones however is not well-established. Some studies reported higher levels of testosterone among smokers, compared with non-smokers [ENGLISH et al. 2001; BLANCO-MUÑOZ et al., 2012], while others found no differences between these groups [HALMENSCHLAGER et al 2009; PASQUALOTTO et al., 2006].

Genetic factors have also been implicated in the patterns of body fat distribution [HEID et al., 2010]. It has been suggested that smoking interacts with specific genetic variations associated with central obesity [FIEGENBAUM and HUTZ, 2003; LIU et al., 2012]. In a Brazilian study, an interaction between smoking status and a *Gln360His* polymorphism of apolipoprotein A-IV (APO A-IV) was found to influence WC. Male non-smokers carrying a *360His* allele had a larger WC than homozygotes for the *Gln* allele. Among smokers, the WC of the *360His* carriers did not differ significantly from that of *Gln/Gln* homozygotes [FIEGENBAUM and HUTZ, 2003]. In a recent study, smoking was found to interact with the CYP2A6 genotype. The CYP2A6 gene moderates the activity of the major hepatic metabolic enzyme which metabolizes nicotine into cotinine. After adjustment for possible confounders, an interaction between heavy smoking (≥15 cigarettes per day) and the CYP2A6 genotype was observed, i.e. individuals with CYP2A6 poor metabolizer genotypes were more likely to be centrally obese if they were heavy smokers [LIU et al., 2012].

Finally, dietary factors may also modulate changes in the body fat distribution [ROMAGUERA et al., 2010] and whether cigarette smoking interact with specific macronutrients in the diet to increase visceral fat remains to be explained. Nicotine administration to mice altered the amount of fat in the animals fed with a high-fat diet, but not in the group consuming a normal chow diet. Surprisingly, the amount of visceral fat was reduced in the animals treated with nicotine, but only in those on the high-fat diet. Among the animals on the high-fat diet, decreases in the fat and lean body mass were more pronounced in the group treated with nicotine than in the control group treated with saline [MANGUBAT et al., 2012].

Cross-sectional and longitudinal studies have demonstrated that, compared with non-smokers, smokers are at greater risk of developing MetS and that there is a dose-response relationship between intensity and duration of smoking and the risk of MetS in both smokers and former smokers [GESLAIN-BIQUEZ et al., 2003; ISHIZAKA et al., 2005; NAKANISHI et al., 2005; LEE et al., 2005a; MIYATAKE et al., 2006; WADA et al., 2007].

The risk of MetS in smokers seems to be high even following smoking cessation. In a cross-sectional study with 5,697 Japanese men, Matsushita and colleagues [MATSUSHITA et al., 2011] found that the VAT area, the SAT area, and the prevalence of MetS were higher among former smokers (<15 years of cessation) than among non-smokers and current smokers. Using non-smokers as the reference group, the odds ratio of having Mets for smokers and former smokers with ≤4, 5–9, 10–14, and ≥15 years of cessation were 1.02, 1.33, 1.36, 1.40, and 1.09, respectively. Among former smokers, after adjusting for the VAT area, the odds ratio of having MetS were 51.5%, 55.6%, and 35% lower for those with ≤4, 5–9, and 10–14-years of cessation, respectively. In some cases, the risk of MetS was found to remain over 20 years after quitting [WADA et al., 2007**].**

2.6.1. Smoking and insulin resistance

It has been demonstrated that smoking is associated with an increased risk of developing T2DM [RIMM et al., 1995; KAWAKAMI et al., 1997; WILSON et al., 1999; SARGEANT et al., 2001; MAKI et al., 2010; TERATANI et al., 2012] and insulin resistance, as evidenced both by euglycaemic insulin clamp studies and by studies of glucose/insulin response to glucose loading [TARGHER et al., 1997; BENOWITZ, 2003; BERLIN, 2009].

How cigarette smoking triggers these metabolic disturbances is not fully understood but it may involve hormonal regulation, altered inflammatory response and oxidative stress. Nicotine increases the plasma levels of catecholamines and other neurotransmitters, which act centrally and peripherally. Catecholamines are powerful antagonists of insulin action and leads to increased lipolysis [HELLERSTEIN et al., 1994; ELIASSON et al., 1994; BENOWITZ, 2003; RESELAND et al., 2005; BULLEN, 2008]. Elevated FFA and glycerol concentrations in the blood as a consequence of lipolysis also decreases the levels of

circulating adiponectin, inducing insulin resistance and endothelial dysfunction [VAN GAAL et al., 2006; GOOSSENS, 2008]. Nicotine is also thought to promote increased release of corticosteroids and growth hormone, also contributing to insulin resistance [BENOWITZ, 2003; TZIOMALOS and CHARSOULIS, 2004]. Bergman and co-workers [BERGMAN et al., 2009] reported increased saturation of intramuscular TAG and diacylglycerols (DAG), together with increased insulin receptor substrate-1 Ser^{636} phosphorylation in smokers, compared with non-smokers. Smokers were also less insulin sensitive and, according to the authors, these metabolic differences could explain the decreased insulin action in smokers because of basal inhibition of insulin.

Cigarette smoking increases circulating levels of the inflammatory markers TNF-α, IL-6, and CRP. It also causes a dose-dependent increase in plasma intercellular adhesion molecule-1 (ICAM-1) [FERNANDEZ-REAL et al., 2003; VAN GAAL et al., 2006; BERGMANN and SIEKMEIER, 2009], thereby decreasing adiponectin levels and inducing insulin resistance [VAN GAAL et al., 2006].

Figure 4 summarizes the mechanisms by which smoking and obesity trigger metabolic disturbances.

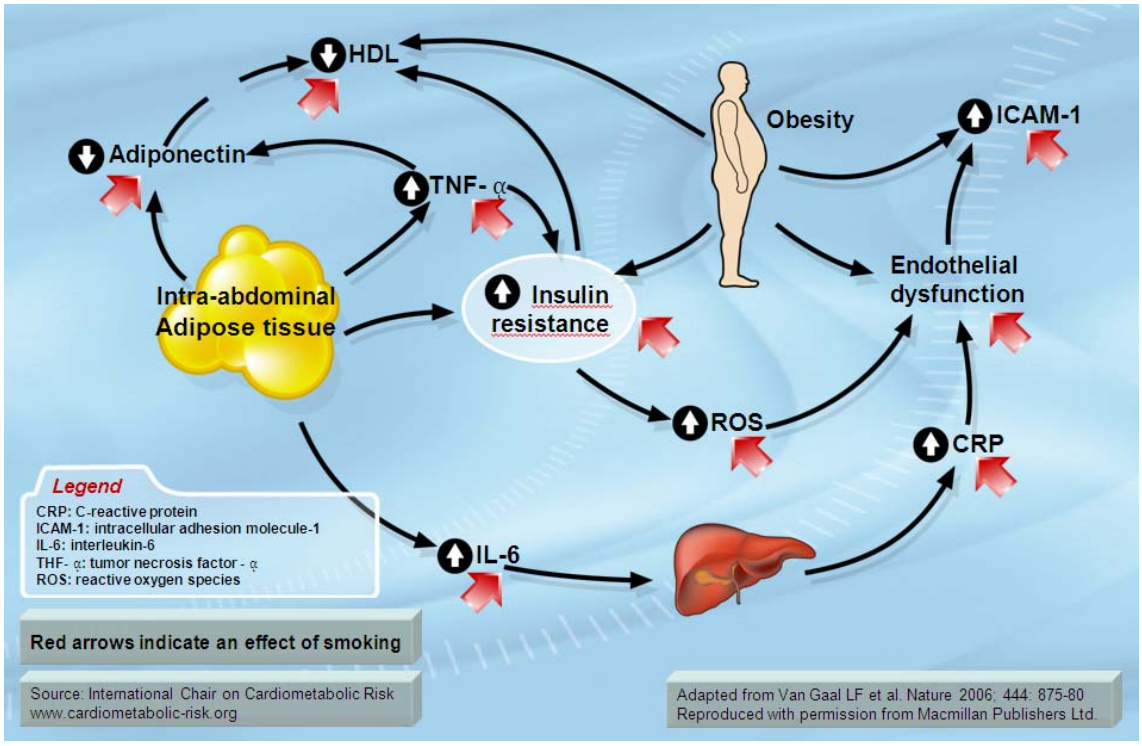

Figure 4: Schematic representation of how smoking might add several mechanisms linking obesity to cardiovascular disease.

CRP: C-reactive protein; ICAM-1: intracellular adhesion molecule-1; IL-6: interleukin-6; TNF-α: tumour necrosis factor-alpha; ROS: reactive oxygen species [*reproduced from* International Chair on Cardiometabolic Risk. www.myhealthywaist.org, *with permission*].

In a retrospective Austrian study with 3,804 non-diabetic men, smoking was associated with high fasting glucose and dyslipidaemia, indicating a higher degree of insulin resistance. This unfavourable metabolic profile was most evidenced in smokers with CVD, although also present in those without clinically manifest CVD. According to the authors, insulin resistance may represent an important link between smoking and CVD [DZIEN et al., 2004].

In a prospective study, Morimoto and colleagues [MORIMOTO et al., 2012] found that the risk of developing T2DM persisted at five years after smoking cessation among overweight individuals. A higher risk was found among former smokers with more than nine years of quitting, in both normal and overweight groups.

2.6.2. Smoking and cardiovascular diseases

Cardiovascular diseases are the leading cause of premature death related to smoking [MICHAEL PITTILO, 2000; ERHARDT, 2009]. Smoking is a well-established risk factor for CVD [FREUND et al., 1993; GEPNER et al., 2011; DE GRANDA-ORIVE et al., 2012]. Women who smoke are at a greater risk of developing CVD than men who smoke, even after adjusting for other cardiovascular risk factors [HUXLEY and WOODWARD, 2011]. **Table 1** shows the main CVD associated with smoking.

Table 1: Main cardiovascular diseases associated with cigarette smoking.

Coronary artery disease
Stroke and cerebrovascular disease
Peripheral artery disease
Aortic aneurysm
Hypertension
Heart failure
Arrhythmias
Endothelial dysfunction
Atherosclerosis

Source: LEONE, 2011.

Cigarette smoke contains large amounts of substances hazardous to health, with potential carcinogenic, cardiovascular and respiratory effects [TALHOUT et al., 2011]. The thousands of chemicals in cigarette smoke are conventionally divided into a tar (particulate) phase and a gas phase. Nicotine, polycyclic aromatic hydrocarbons (PAHs), carboxylic acids, phenols, water, humectants, tobacco-specific nitrosamines (TSNAs), and catechols are among the constituents of the tar phase; nitrogen (N_2), oxygen (O_2), carbon dioxide (CO_2), carbon monoxide (CO), hydrogen cyanide (HCN), acetaldehyde, nitric acid, acetone, acrolein and ammonia are found in the gas phase [AMBROSE and BARUA, 2004; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, 2010].

One puff of cigarette smoke contains 10^{14}–10^{16} free radicals that cause lipid peroxidation and increase oxidative stress [KODE et al., 2006; BRUNO and TRABER,

2006; CAMPBELL et al., 2008]. This can be evidenced by the higher plasma thiobarbituric acid reactive substances (TBARS) concentration in smokers compared with non-smokers [NAGAMMA et al., 2011].

Nicotine, CO, and oxidant gases are all contributors to cigarette-smoking induced CVD, although CO is suspected to play a major role in the disease [ZEVIN et al., 2001; TONSTAD and ANDREW JOHNSTON, 2006].

One of the main mechanism by which CO causes heart disease is provoking hypoxia [ZEVIN et al., 2001]. Haemoglobin has a very strong affinity for CO, so the exposure to cigarette smoke increases the carboxyhemoglobin levels and reduces the amount of haemoglobin available to carry oxygen to the tissues [BENOWITZ, 2003; TONSTAD and ANDREW JOHNSTON, 2006]. These effects are more profound in the myocardium than in the peripheral tissues because of the very high oxygen extraction by the myocardium at rest [ZEVIN et al., 2001].

Both active and passive smoking are associated with endothelium damage and dysfunction, mainly caused by a decrease in endothelial nitric oxide (NO), a free radical primarily responsible for the endothelium-dependent vasodilation in response to hemodynamic changes [AMBROSE and BARUA, 2004; TONSTAD and ANDREW JOHNSTON, 2006; ERHARDT, 2009]. Nitric oxide also helps to regulate inflammation, leukocyte adhesion, platelet activation and thrombosis; a decrease in NO bioavailability due to oxidants in cigarette smoke may contribute to the increased vessel contraction, and the pro-thrombotic and pro-inflammatory states seen in smokers [TONSTAD and ANDREW JOHNSTON, 2006; ERHARDT, 2009; GASTALDELLI et al., 2010]. This leads to formation, progression, and destabilization of atherosclerotic plaques which may result in myocardial infarction, stroke and cardiovascular death [GRASSI et al., 2010]. Young smokers who refrained from smoking showed significant improvement in impaired coronary endothelial vasomotor dysfunction within one month of cessation, indicating that coronary endothelial dysfunction may be reversible with smoking cessation [MORITA et al., 2006].

In addition, cigarette smoking was associated in a dose-dependent manner with increased levels of CRP, fibrinogen, and homocysteine, which are novel risk factors for the development of atherosclerotic diseases [BAZZANO et al., 2003].

Cigarette smoking is also associated with an atherogenic lipid profile. It has been shown that smokers have higher levels of total cholesterol (TC), LDL-C, VLDL-C, and TAG, and lower levels of HDL-C and apolipoprotein AI (apo-AI) [CRAIG et al., 1989; VENKATESAN et al., 2006; YUVRAJSING, 2008; MEENAKSHISUNDARAM et al., 2010; BEAUCHAMP et al., 2010]. Similarly, cessation of smoking was shown to increase the levels of HDL-C and apo-AI, contributing to a reduced risk of CVD in former smokers [STAMFORD et al., 1986; RICHARD et al., 1997; MAEDA et al., 2003; GEPNER et al., 2011].

The mechanisms behind the unfavourable lipid profile in smokers are not completely clarified. Hellerstein and colleagues [HELLERSTEIN et al., 1994] reported that acute cigarette smoking in heavy smokers increased the flux of FFA and glycerol into the circulation by 77% and 82%, respectively. According to the authors, this effect was possibly mediated by catechols. Concurrently, serum FFA concentrations were elevated by 73%, and hepatic reesterification of FFA was enhanced by more than threefold. These metabolic processes were thought to increase hepatic VLDL-C production and lead to atherogenesis.

Likewise, the oxidant-antioxidant imbalance triggered by smoking results in a chronic state of low-grade inflammation, which also contributes to perturbations in the lipid metabolism, especially increased serum TAG and decreased HDL-C [ESTEVE et al., 2005; CHOURAKI et al., 2008]. In addition, nicotine and oxidants in cigarette smoke may enhance LDL-C oxidation, increasing its atherogenic potential [HEITZER et al., 1996; STEINBERG and CHAIT, 1998; KASSI et al., 2009].

Another explanation for the dyslipidaemic profile in smokers is that these metabolic abnormalities would be secondary to insulin resistance. Farin and colleagues [FARIN et al., 2007] compared two groups of smokers, with similar age and BMI, differing only in their insulin sensitivity state. Serum levels of TAG and VLDL-C were significantly elevated in the insulin-resistant smokers, compared with the insulin-sensitive smokers.

No significant differences in the levels of TC, LDL-C and HDL-C were found between the groups. In addition, smokers were found to show impaired postprandial TAG elimination, associated with higher levels of small dense LDL-C-particles, in the presence of an insulin-resistant state [ELIASSON et al., 1997]. However, other researchers failed to demonstrate that insulin resistance is a base condition for the impaired lipid metabolism commonly observed in smokers [KABAGAMBE et al., 2009].

2.7. Assessment of obesity and body fat distribution

There is a large variety of clinical tools that can be used for the assessment of total adiposity and body fat distribution in humans [INTERNATIONAL CHAIR ON CARDIOMETABOLIC RISK, 2012]. Accurate and reliable methods for assessing total body fat, which also allow to distinguish between fat mass and lean mass are underwater weighing (UWW), dilution techniques, computed tomography (CT), magnetic resonance imaging (MRI), dual energy X-ray absorptiometry (DXA), bioimpedance, and air displacement plethysmography (ADP) [MCCRORY et al., 1998; ELLIS, 2000]. However, because they are expensive and time-consuming, such methods are preferentially used in clinical studies [HAN et al., 2006; SNIJDER et al., 2006]. In epidemiological studies, BMI and skinfold-thickness are commonly used for the assessment of total and regional adiposity [SNIJDER et al., 2006; INTERNATIONAL CHAIR ON CARDIOMETABOLIC RISK, 2012]. Although they offer advantages, such as low cost and practicality, they also have limitations: BMI does not differentiate between fat mass and lean mass [SNIJDER et al., 2006]; the skinfold-thicknesses are useful for estimating total adiposity, but are unable to measure intra-abdominal fat directly [INTERNATIONAL CHAIR ON CARDIOMETABOLIC RISK, 2012a]. In addition, measuring the skinfold-thicknesses requires highly skilled personnel in order to produce reliable values [MINEMATSU et al., 2011; INTERNATIONAL CHAIR ON CARDIOMETABOLIC RISK, 2012a].

Visceral adiposity can be accurately measured by imaging techniques, such as CT, MRI and DXA. Nevertheless, as stated earlier, they are expensive and not suitable for epidemiological studies [KAMEL et al., 1999; LEE et al., 2005]. For epidemiological studies and for routine clinical use, cheaper and also reliable alternatives for abdominal adiposity assessment are sagittal diameter (SAD), conicity index (COI), WC, WHR and

waist-to-height ratio (WHtR) [VALDEZ et al., 1993; VAN DER KOOY et al., 1993; SNIJDER et al., 2006; SAMPAIO et al., 2007; BROWNING et al., 2010].

This review has been focused on the anthropometric methods that were employed in the current study.

2.7.1. Body mass index (BMI)

Body mass index has long and successfully been used to assess thinness and fatness and it is obtained by dividing the weight (in kilograms) by the square of the height (in meters). The international BMI cut-off points suggested by World Health Organization (WHO) [WHO EXPERT CONSULTATION, 2004] allow to classify the individuals as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese class I (30–34.9 kg/m^2), obese class II (35–39.9 kg/m^2), and obese class III (≥40 kg/m^2). This classification is intended to identify individuals with higher risk of cardiometabolic diseases (CMD). However, because of ethnic differences in the patterns of body fat distribution, especially reported in the Asian populations, WHO recommends that additional cut-offs points of 23, 27.5, 32.5, and 37.5 should also be used for public health actions, as illustrated in **Figure 5.** [WHO EXPERT CONSULTATION, 2004].

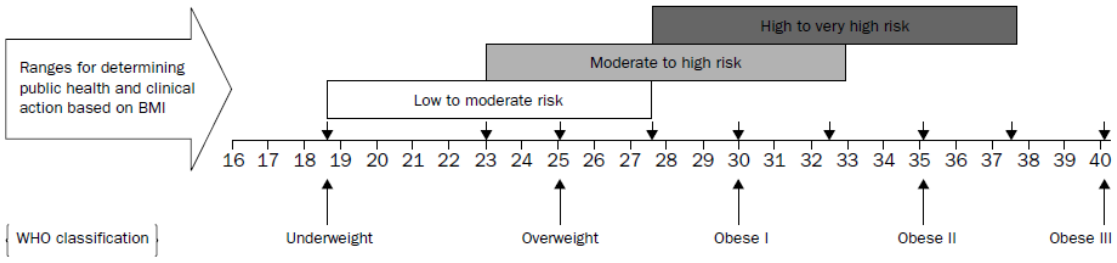

Figure 5: WHO proposed BMI cut-off points for public health action

WHO: World Health Organization; BMI: body mass index. R*eproduced from* WHO EXPERT CONSULTATION, 2004, *with permission of Elsevier*.

Increased health risks and death rates have been observed among individuals with elevated BMI [HAN et al., 2006; WHO EXPERT CONSULTATION, 2004]. Recently, a large prospective study investigated the association of BMI and mortality, analysing individual data from almost 900,000 participants. For both sexes and at all ages, mortality was lowest at BMI between 22.5 and 25 kg/m^2. Above this range, each 5 kg/m^2 increment of BMI was associated with an increase of 30% in all-cause mortality. Below the range 22.5–25 kg/m^2, an inverse association between BMI with overall mortality was observed, mainly due to the strong inverse association with smoking-related diseases [PROSPECTIVE STUDIES COLLABORATION, 2009]. Results from a cohort study in Austria showed a U-shaped association between BMI and all-cause mortality in both men and women. High risks were found both in the highest and the lowest category of BMI. However, the association with the latter was less pronounced in non-smokers than in ever-smokers [KLENK et al., 2009].

Although accepted as a relatively good measure of general adiposity, BMI provides no information about the fat mass distribution and does not differentiate between lean and fat body mass. Hence it can underestimate metabolic risks in individuals with a high mass of body fat despite of a normal BMI [ROMERO-CORRAL et al., 2008; DE LORENZO et al., 2011]. Therefore, the use of anthropometric measures of regional adiposity, such as WC and WHR, has been recommended by the scientific community as a better tool than BMI to predict health risks and mortality [JANSSEN et al., 2002; JANSSEN et al., 2004; YUSUF et al., 2005; LEE et al., 2008; KOSTER et al., 2008].

2.7.2. Measurements of abdominal obesity

2.7.2.1. Waist circumference (WC)

Waist circumference has been shown to be strongly correlated with visceral fat [POULIOT et al., 1994; KAMEL et al., 1999; RORIZ et al., 2011]. It is similarly highly correlated with BMI, abdominal subcutaneous fat, total abdominal fat, and total body fat [MOLARIUS and SEIDELL, 1998]. It has been demonstrated that WC values are strong predictors of cardiometabolic risk factors [POULIOT et al., 1994; ZHU et al., 2002].

A meta-analysis of prospective studies showed that each 1 cm increase in WC is associated with an increase of 2% in the risk of future CVD [DE KONING et al., 2007]. Furthermore, results from the European Prospective Investigation into Cancer and Nutrition (EPIC) suggested that reducing WC by 5 cm would decrease the risk of CVD by 11% in men and 15% in women [CANOY et al., 2007].

Results from the European InterAct Study showed that both BMI and WC are independently and significantly associated with T2DM. A high WC was a stronger risk factor in women, compared with men. In terms of absolute risk, 7% of men and 4.4% of women who were overweight and had a large WC at baseline developed T2DM over a 10-year period, placing them at an absolute risk equivalent or higher than that of obese participants [THE INTERACT CONSORTIUM, 2012].

The literature has proposed different cut-off points for the definition of a high WC. The National Institute of Health (NIH) suggested sex-specific cut-off points for WC based on the development of obesity-associated risk factors in most adults with a BMI between 25–34.9 kg/m^2 [NATIONAL INSTITUTE OF HEALTH, 1998]. The proposed cut-off points of 102 cm for men and 88 cm for women were based on WC values corresponding to a BMI of 30 kg/m^2 in Caucasian populations [INTERNATIONAL CHAIR ON CARDIOMETABOLIC RISK, 2012b; NATIONAL INSTITUTE OF HEALTH, 1998]. In individuals with a BMI greater than 35 kg/m^2, they would lose their incremental predictive power, because the established cut-off points would be exceeded [NATIONAL INSTITUTE OF HEALTH, 1998]. Lean and co-workers [LEAN et al., 1995] proposed two action levels for WC, which should be used for the identification of individuals at health risks. Men with WC ≥94 cm and women with WC ≥80 cm should gain no further weight (action I). Men with WC ≥102 cm and women with WC ≥88 cm should reduce their weight (action II). These two action levels were based on both BMI (cut-offs of 25 kg/m^2 for action I and 30 kg/m^2 for action II, for both men and women) and WHR (0.95 for men and 0.80 for women, for both action levels). According to the authors, the cut-offs of BMI and WHR used in the study showed high specificity and sensitivity for WC as an indicator of need for weight management. In addition, the proposed action levels led to misclassification of only 1.5% of the overweight men and women.

The same criteria suggested by Lean and colleagues [LEAN et al., 1995] are recommended by WHO, with the terms "increased risk" and "substantially increased risk" being used instead of "action I" and "action II", respectively [WORLD HEALTH ORGANIZATION, 2008a].

However, these cut-off points were derived for Caucasian individuals and might not be applicable for other ethnic groups [MISRA et al., 2005]. As seen in **Table 2**, the International Diabetes Federation (IDF) proposed WC cut-offs that take into account sex, ethnicity and geography [ALBERTI et al., 2006].

Other authors also suggested different cut-off points for WC taking into accounting ethnicity and specific health risks [NARISAWA et al., 2008; AL-LAWATI and JOUSILAHTI, 2008; KIM et al., 2009; WANG et al., 2010; BERBER et al., 2001; ZADEH-VAKILI et al., 2011].

There is no universally accepted method for measuring WC, and values of WC can be obtained at four different anatomic sites: a) immediately below the lowest rib; b) at the narrowest part of the waist; c) the midpoint between the lowest rib and the iliac crest; and d) immediately above the iliac crest. Measures of WC taken at all 4 sites were significantly correlated with total body fat mass in both sexes, but this correlation was higher when WC was measured immediately above the iliac crest [WANG et al., 2003].

Table 2: IDF cut-off points for WC, according to sex, country and ethnicity.

Country/ethnic group		WC (cm)
Europids (Caucasians)	Men Women	≥94 ≥80
South Asians	Men Women	≥90 ≥80
Chinese	Men Women	≥90 ≥80
Japanese	Men Women	≥85 ≥90
Ethnic South and Central Americans		Use South Asian recommendations until more specific data are available
Sub-Saharan Africans		Use European data until more specific data are available
Eastern Mediterranean and Middle East		Use European data until more specific data are available (Arab) populations

IDF: International Diabetes Federation; WC: waist circumference. According to IDF, WC should be measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest [*adapted from* ALBERTI et al., 2006].

The concept of a *hypertriglyceridaemic waist* (HTGW), defined as the co-occurrence of a high WC and high levels of TAG, was first introduced by Lemieux and colleagues [LEMIEUX et al., 2000] as a tool to identify individuals at increased risk of CAD. Earlier, a prospective Canadian study [LAMARCHE et al., 1998] showed that the high levels of TAG in the study population would reflect additional metabolic disorders—such as elevated levels of fasting glucose, apolipoprotein B, and small dense, LDL-C particles—which substantially increased the risk of ischemic heart disease. Subsequent studies confirmed the HTGW as a reliable method for the early screening of individuals at risk of future CAD [LAMONTE et al., 2003; ROGOWSKI et al., 2009; BLACKBURN et al., 2012].

2.7.2.2. Waist-to-hip ratio (WHR)

Two important studies in the early 1980s stressed the association of WHR with an altered lipid profile and cardiovascular risks [KROTKIEWSKI et al., 1983; HARTZ et al., 1984]. In a 20-year prospective study with Swedish women, Bengtsson and colleagues [BENGTSSON et al., 1993] found that WHR was significantly associated with total mortality and death from myocardial infarction. Body fat distribution was more

important than obesity as a risk factor in women. WHR was found to be the best measure of obesity to predict all-cause mortality and CVD mortality in an Australian follow-up study [WELBORN and DHALIWAL, 2007]. Likewise, in high-functioning older adults, all cause-mortality increased with WHR, but was not associated with BMI or WC [SRIKANTHAN et al., 2009]. On the other hand, Visscher and co-workers [VISSCHER et al., 2001] reported that differently from high quintiles of WC, high quintiles of WHR did not predict an increased risk of all-cause mortality among non-smoker men.

Waist-to-hip ratio was also highly correlated with intra-abdominal adiposity assessed by CT, even after adjusting for the effects of age and degree of overweight [KISSEBAH, 1996]. However, these findings were not confirmed by other authors [HAN et al., 1997]. Ross and colleagues [ROSS et al., 1992] used MRI to measure the distribution of total and regional adipose tissue in a group of men, and the results were compared with anthropometric measures of adiposity. Although WHR was strongly correlated with the volume of VAT, after controlling for age and adiposity WHR explained only 12% of the variation in the absolute VAT and less than 1% of the variation in the ratio of visceral fat-to-subcutaneous fat. When WC was used as a criterion for adiposity in an Australian sample, 57.4% of the individuals fell into the "action I" category (established as WC ≥95 cm for men and WC ≥80 cm for women), and 36.7% fell into the "action II" (WC ≥100 cm for men and WC ≥80 cm for women). However, only 16.7% of the sample was categorised as obese when WHR (cut-offs of 1.0 for men and 0.85 for women) was used as the anthropometric criterion for obesity [GILL et al., 2003]. These results show the limitations of WHR as an index of central obesity. Ratios are usually difficult to interpret biologically and a change in body fat distribution may produce little or no changes in the ratios. Weight reduction is normally accompanied by a reduction in both WC and hip circumference (HC), and this will not lead necessarily to a reduction in WHR [MOLARIUS and SEIDELL, 1998]. Variation in WC is likely to reflect variation in subcutaneous and visceral fat, whereas variation in HC may be due to variation in bone structure (pelvic width), gluteal muscle, and subcutaneous gluteal fat [SEIDELL et al., 2001]. Hence, a high WHR may reflect an increase of visceral and subcutaneous fat affecting WC (numerator), or a decrease in the gluteofemoral muscle affecting HC (denominator) alone [JEE et al., 2002a; INTERNATIONAL CHAIR ON CARDIOMETABOLIC RISK, 2012c]. Unlike WC, changes in WHR do not consistently lead to changes in intra-

abdominal fat, especially in women [INTERNATIONAL CHAIR ON CARDIOMETABOLIC RISK, 2012c].

Different cut-off points for WHR have been proposed in the literature. Most used cut-offs are 1.0 for men and 0.85 for women [ELMADFA, 2004; PISCHON et al., 2008; GILL et al., 2003]. Lean and colleagues [LEAN et al., 1995] suggested the values 0.95 and 0.80 for Caucasian men and women, respectively, while WHO [WORLD HEALTH ORGANIZATION, 2008a] recommends the cut-off points of 0.90 for men and 0.85 for women. As observed with WC, these cut-offs may vary according to ethnicity. The cut-off point that best identified individuals with high risk of CVD among Omani Arabs was 0.91 for both men and women [AL-LAWATI and JOUSILAHTI, 2008]. Proposed cut-offs for predicting the likelihood of T2DM, hypertension and dyslipidaemia in a Mexican population are 0.90 for men and 0.85 for women [BERBER et al., 2001].

2.7.2.3. Waist-to-height ratio (WHtR)

During the 1990s, some researchers suggested that WHtR—defined as WC (cm) divided by height (cm)—would be a better predictor of CMD [HSIEH and YOSHINAGA, 1995], intra-abdominal fat [ASHWELL et al., 1996], overweight/obesity [ASHWELL et al., 1996a] and mortality [COX and WHICHELOW, 1996] than WC or BMI.

Later, Ashwell and Hsieh [ASHWELL and HSIEH, 2005] listed some reasons for the superiority of WHtR compared to BMI as a screening tool in public health: "WHtR is more sensitive than BMI as an early warning of health risks; it is cheaper and easier to measure and calculate than BMI; a boundary value of 0.5 can be used as an indicator or increased risk irrespective of gender, age and ethnicity; WHtR boundary values can be converted into a consumer-friendly chart". Finally, they argued that a simple and global public health message could be derived from this anthropometric index: "*keep your waist circumference to less than half your height*" [ASHWELL and HSIEH, 2005].

Subsequent studies have confirmed WHtR as a better predictor of CMD [HSIEH and MUTO, 2005; SIAVASH et al., 2008; GELBER et al., 2008; AL-ODAT et al., 2012], MetS [SOTO-GONZÁLEZ et al., 2007], T2DM [HADAEGH et al., 2006] and insulin resistance [MATOS et al., 2011].

Browning and colleagues [BROWNING et al., 2010] systematically reviewed 78 studies of adults and children, which used WHtR and WC or BMI as predictors of T2DM and CVD. Waist-to-height ratio and WC were found to be similar predictors of these diseases, both being stronger than and independent of BMI. Specificity and sensitivity were determined from receiver operator characteristic (ROC) analysis, which demonstrated that WHtR presented higher mean area under ROC (AUROC) values for all the outcome measures related to diabetes and CVD, with a weighted mean boundary value of 0.5. According to the authors, the findings suggest that WHtR would be a good screening tool, probably better than WC.

Results from other studies also corroborated the proposed cut-off point of 0.5 as an indicator of increased metabolic risk for men and women of different ethnic groups [He et al., 2009; PARK et al., 2009; TAYLOR et al., 2010], as well as for children and adolescents [HARA et al., 2002; GARNETT et al., 2008]. Among a large population of adolescents and young adults in mainland China, a WHtR ≥0.5 was reported to be a better predictive of MetS and elevated serum alanine aminotransferase—a surrogate marker of abnormal liver function—than WC and WHR [WU et al., 2012].

Certain studies however have not confirmed WHtR as a superior anthropometric indicator for identifying individuals at higher risk of CMD [MUKUDDEM-PETERSEN et al., 2006; LÓPEZ DE LA TORRE et al., 2010; GWYNN et al., 2011]. At least one study reported that a high WHtR was not able to predict new cases of T2DM among older adults [KUO et al., 2011].

Likewise, some studies have reported disparities in the optimal cut-off points between people from different ethnic groups [LIN et al., 2002; CAN et al., 2010; AL-ODAT et al., 2012; VAN VALKENGOED et al., 2012].

In addition, according to some authors, because WC is only weakly correlated with height, there would be a minimal need to adjust waist for height [MOLARIUS and SEIDELL, 1998].

3. PARTICIPANTS AND METHODS

3.1. Participants

Participants were recruited among employees in a financial institution based in Vienna. Once a year the employees undergo a health screening at the company. After information on the purpose of the study and its procedures, they were invited to participate. Two days before the medical examination they received a self-administered questionnaire, which was collected on the examination day. The questionnaires included questions about smoking habits, dietary patterns, physical activity, education and health status (see **Appendix**).

Questions about drinking patterns, date of birth, income and marital status were considered very personal by the employers and not appropriate for an annual health examination. Therefore, these questions were excluded from the questionnaire. All participants signed an informed consent and the study protocol was in accordance with the Declaration of Helsinki.

The health examinations were carried out from September 2009 to July 2010. A total of 1,247 employees filled in the questionnaires. From- this total, 261 individuals were subsequently excluded: those who reported a history of cancer (20) or thyroid dysfunction (37), those who provided no information on gender (3), age (1), body weight (1), smoking status (80) and health status (24); pregnant women (3); individuals under nicotine replacement therapy at the time of the study (4); those with a BMI lower than 18.5 kg/m^2 or greater than 40 kg/m^2 (20); those whose WC could not be measured (65) or with a WC lower than 60 cm (3). Data of 986 individuals (405 men and 581 women) aged 19–65 years were included in the final analyses.

Included and excluded subjects did not differ significantly regarding age and anthropometric variables (**Table 3**).

Table 3: Age and anthropometric characteristics of excluded and included participants.

	Excluded cases (*n*=259)	**Included Cases** (*n*=986)	***p*-value**
Age, years	41.2 ± 10.4	40.9 ± 9.7	0.737
Height, cm	171.2 ± 8.1	172.0 ± 8.6	0.168
Body Weight, kg	71.8 ± 15.3	72.6 ± 13.7	0.452
BMI, kg/m^2	24.5 ± 4.9	24.4 ± 3.7	0.889

Values are shown as mean ± SD.

The number of participants available for each parameter analysed in this study is displayed in **Table 4**.

Table 4: Number of participants available for specific parameters analysed in the study.

	Men (n = 405)		**Women (n = 581)**	
	n	%	n	%
Sample size for specific parameters				
Age	405	100	581	100
Body weight	405	100	581	100
Height	405	100	581	100
Body mass index (BMI)	405	100	581	100
Waist circumference (WC)	405	100	581	100
Hip circumference (HC)	405	100	581	100
Waist-to-hip ratio (WHR)	405	100	581	100
Waist-to-height ratio (WHtR)	405	100	581	100
Fasting glucose (FG)	355	87.7	530	91.2
Total cholesterol (TC)	355	87.7	530	91.2
High-density lipoprotein cholesterol (HDL-C)	355	87.7	530	91.2
Low-density lipoprotein cholesterol (LDL-C)	350	86.4	523	90
Triacylglycerols (TAG)	355	87.7	530	91.2
Total white blood cells count (WBC)	347	85.7	505	86.9
Education level	405	100	578	99.5
Energy intake (EI)	237	58.5	420	72.3
Physical activity (PA)	335	82.7	447	76.9

3.2. Anthropometric measurements

3.2.1. Body weight and height

Participants reported their height in centimetres and weight in kilograms.

3.2.2. Waist circumference (WC) and hip circumference (HC)

Waist and hip circumferences were measured with participants in light clothing without shoes. Measurements were made to the nearest 0.1 cm, using a non-elastic flexible tape.

Waist circumference was measured at the top of the right iliac crest, at the end of a normal expiration according to the NHLBI guidelines [NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, 2000]. The cut-off points proposed by WHO [WORLD HEALTH ORGANIZATION, 2008a] were used (increased risk: ≥94 cm for men and ≥80 cm for women; substantially increased risk: ≥102 cm for men and ≥88 cm for women).

Hip circumference was measured at the largest posterior extension of the buttocks.

3.2.3. Waist-to-hip ratio (WHR)

Waist-to-hip ratio was calculated as WC divided by HC, both in centimetres. We used the cut-off points of 1.0 for men and 0.85 for women [NATIONAL INSTITUTE OF HEALTH, 1998].

3.2.4. Waist-to-height ratio (WHtR)

Waist-to-height ratio was calculated as WC divided by height, both in centimetres. For both men and women, the cut-off point of 0.5 was used [ASHWELL and HSIEH, 2005].

3.2.5. Body mass index (BMI)

Body mass index was calculated as the ratio of weight in kilograms divided by the square of the height in meters (kg/m^2). The cut-off points for normal weight (BMI of

18.5–24.9 kg/m^2), overweight (BMI of 25–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) were defined according to WHO [WHO EXPERT CONSULTATION, 2004].

3.3. Smoking status

Smoking status was assessed in one section of the self-administered questionnaire. Participants who answered "no" to the following questions: "Have you ever smoked daily?", "Have you smoked at least 100 cigarettes, cigar, pipes or other tobacco products in your entire life?", "Do you smoke now?" were categorised as non-smokers [ALBANES et al., 1987; WAGENKNECHT et al., 1992; POMERLEAU and SAULES, 2007]. Individuals who reported smoking at the time of the enrolment or quitted less than one year before, where classified as smokers [PITSAVOS et al., 2003]. Smokers included both occasional (<1 cigarette per day) and daily smokers (≥1 cigarette per day).

Former smokers were defined as individuals who used to smoke and quitted at least one year prior to their recruitment [PITSAVOS et al., 2003]. The reason for this definition is the very high rates of relapse smoking observed in the first months of smoking cessation [VOGIATZIS et al., 2010]. Without treatment, only 5% of smokers who try to quit maintain the abstinence in the first six months, and as little as 4% are abstinent after 12 months [HUGHES et al., 2004]. Abstinences rates of as high as 35.5% after one year of cessation were reached when a combination of nicotine and bupropion was used [JORENBY et al., 1999].

Daily smokers were further subgrouped into three groups, according to the number of cigarettes smoked per day: light smokers (1–10 cigarettes per day), moderate smokers (11–20 cigarettes per day), and heavy smokers (>20 cigarettes per day) [KOLAPPAN and GOPI, 2002; CLAIR et al., 2011; LIU et al., 2011; TERATANI et al., 2012].

Similarly, cumulative smoking exposure in daily smokers was assessed by pack-years (PY). Pack-years were calculated as the number of cigarettes smoked per day divided by 20 (one pack has 20 cigarettes) and multiplied by the number of years smoked [CLEMENS et al., 2003]. Three PY-categories were then created (**Table 5)**.

Table 5: Pack-year categories.

PY-Categories	Number of PY
First	0 < PY ≤ 5
Second	5 < PY ≤ 15
Third	PY >15

3.4. Blood sampling

Blood samples were taken by venipuncture after an overnight fast and collected into heparinized tubes. Complete blood count was performed automatically (Sysmex XT 2000i); fasting glucose (FG), TC, HDL-C and TAG were also analysed by automated methods (Roche Modular, Roche Diagnostics, Vienna, Austria). Plasma LDL-C was calculated using the Friedewald formula, (LDL-C = TC - HDL-C - TAG/5) and was only available for TAG levels lower than 400 mg/dL [FRIEDEWALD et al., 1972].

Blood analyses were available for the majority of the participants (approximately 88% of men and 91% of women).

Results were interpreted according to the guidelines of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) [NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002]. Total cholesterol was classified as desirable (<200 mg/dL), borderline high (200–239 mg/dL), and high (>240 mg/dL). LDL-C was classified as optimal (<100 mg/dL), near optimal (100–129 mg/dL), borderline high (130–159 mg/dL), high (160–189 mg/dL), and very high (≥190 mg/dL). Plasma levels of TAG ≥150 mg/dL and fasting glucose ≥100 mg/dL were considered elevated, and levels of HDL-C <40 mg/dL for men and <50 mg/dL for women were considered low [NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002].

The cut-off points for the ratio of total cholesterol to HDL-C were defined as ≥5 for both men and women [WANG et al., 2001].

3.5. Hypertriglyceridaemic waist (HTGW)

Hypertriglyceridaemic waist was defined as a simultaneous occurrence of high WC and elevated TAG levels and was calculated as an index of atherogenic risk [LEMIEUX et al., 2000]. For the purpose of this study, high WC was defined as ≥94 cm in men and ≥80 cm in women [WORLD HEALTH ORGANIZATION, 2008a] and elevated TAG as ≥150 mg/dL in men and women or in drug treatment for elevated TAG [NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002].

3.6. Physical activity (PA)

Information on PA was obtained using a questionnaire derived from the short form of the International Physical Activity Questionnaire - IPAQ [CRAIG et al., 2003]. MET-minutes/week were then calculated according to the IPAQ scoring protocol, and participants were categorised into three PA levels: low, moderate, and high [SJÖSTRÖM et al., 2005].

3.7. Dietary assessment

3.7.1. Energy intake (EI) and diet quality

Dietary intake was obtained by means of self-administered 24-hour recalls. Participants were asked to write down in detail their intake of food and beverages during the last 24 hours. Instructions on how to fill in the questionnaire, as well as a validated photographic manual [SLIMANI and VALSTA, 2002; HIMMERICH et al., 2004] describing portion sizes, were also attached to the questionnaires. All records were analysed using the nutritional software nut.s [dato Denkwerkzeuge, Software: nut.s science, v1.31.30; Wien, 2010].

Diet quality was assessed according to an adapted version of the method developed by Thiele and colleagues [THIELE et al., 2004]. They proposed two indices to assess diet quality: the *deficiency index* and the *excess index*.

The deficiency index (DI) combines 13 vitamins (A, D, E, K, B_1, B_2, niacin, B_6, folate, pantothenic acid, biotin, B_{12} and vitamin C), 12 minerals (sodium, chloride, potassium, calcium, phosphorus, magnesium, iron, iodine, fluoride, zinc, copper and manganese), proteins, carbohydrates, two essential fatty acids (linolenic and linoleic acid) and dietary fibre. This index (ranging from 0 to 3,000) provides information on the extent of under-consumption of these nutrients.

In our study, the DI did not include vitamin K and fluoride. Vitamin K was not included because the food content data on this vitamin provided by the German Food and Nutrition Database (BLS 2.3) was insufficient, since the data sources were not exclusively based on HPLC-measurements [NIMPTSCH et al., 2008]. Fluoride was not included because the intake of this mineral depends very much on its content within the water, which is not the same in different regions. Therefore, it cannot entirely be covered by the values in the BLS 2.3 [NELL and SPERR, 1994; WARREN et al., 2009]. We included the sum of the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in this index, because these fatty acids are important dietary factors in the protection against CMD [BAIK et al., 2010; DE CATERINA, 2011]. Therefore, the scores for DI in our study ranged from 0 to 2,900.

The excess index (EXI) includes fat, cholesterol, ratio of saturated to unsaturated fatty acids, sugar, alcohol and sodium, and assesses their over-consumption in the diet, with a score ranging from 0 to 600 [THIELE et al., 2004].

The adequacy of the nutrients was calculated according to the DACH-Reference, which are reference values for nutrient intake in Germany, Austria and Switzerland [DEUTSCHE GESELLSCHAFT FÜR ERNÄHRUNG et al., 2008], and the Food and Agriculture Organization of the United Nations (FAO) [JOINT FAO/WHO EXPERT CONSULTATION ON FATS AND FATTY ACIDS IN HUMAN NUTRITION, 2008].

3.7.2. Under- and over-reporting calculation

Basal metabolic rates (BMR) were estimated according to the Schofield equations [SCHOFIELD, 1985]. Misreporting of energy intake was calculated according to the methods proposed by Goldberg and colleagues [GOLDBERG et al., 1991] and Black [BLACK, 2000]. From these calculations, under-reporting was detected if the ratio of

energy intake-to-BMR (EI:BMI) was lower than 0.87, and over-reporting if this ratio was greater than 2.75.

3.8. Statistical analyses

Metric scaled variables are expressed as mean ± standard deviation (SD). Frequencies are given in absolute (counts) or relative values (%).

T-test was used to compare differences in metrical variables between two groups. Chi-square tests were used to compare frequency distributions of categorical variables. Pearson's correlation coefficients were used to characterize relationships between BMI and WC.

For the univariate analyses, factor levels were compared using the Least Significant Difference (LSD) post-hoc procedure.

Multivariate analyses of variances (MANOVA) were performed to evaluate the impact of smoking status, pack-years or number of cigarettes on the anthropometric and biochemical parameters.

Since men and women differed significantly concerning the anthropometric and biochemical parameters, comparisons between non-smokers, smokers and former smokers were performed separately for men and women. Smoking status and level of education were used as fixed factors.

In the models where pack-years or number of cigarettes per day were used, gender was added as a fixed factor.

Several general linear models (GLM) were used to evaluate the influence of possible confounders in the results. The level of complexity was increased stepwise by adding specific variables such as age, physical activity level, total energy intake, and the two indices of diet quality as covariates to the model. The results of the simplest model will be presented, when *p*-values remained unchanged after correcting for the different covariates.

For all analyses a two-tailed *p*-value less than 5% ($p < 0.05$) was considered statistically significant. All statistical analyses were performed using the IBM SPSS version 20 (SPSS Inc., Chicago, IL, USA).

4. RESULTS

4.1. Overall results for male and female participants

Baseline characteristics of the participants, according to gender, are presented in **Table 6**. The average age of women was 40 ± 9.3 years, while men were significantly older (42.3 ± 10; $p < 0.001$).

Body weight (mean ± SD) was 82 ± 11.3 kg in men and 66 ± 11.2 kg in women. Body mass index was 25.4 ± 3.2 kg/m^2 and 23.7 ± 3.8 kg/m^2 in men and women, respectively. These values differed significantly between the two groups ($p < 0.001$).

Overweight (BMI of 25–29.9 kg/m^2) was observed in 38.5% of men and 21.7% of women, whereas 9.4% of men and 7.6% of women were obese (BMI ≥30 kg/m^2) (**Figure 6**).

Waist circumference at increased risk level (94–101.9 cm in men and 80–87.9 cm in women) was observed in 27.4% of men and 31% of women. Levels of abdominal obesity which represent a substantially increased risk (WC ≥102 cm in men and ≥88 cm in women) were found in 17.5% of men and 31% of women (**Figure 7**).

Table 6: Baseline characteristics of the participants, by gender.

	Men (*n* = 405)	**Women** (*n* = 581)	***p*-value**
Age, years	42.3 ± 10.0	40.0 ± 9.3	<0.001
Height, cm	179.5 ± 6.1	166.8 ± 5.8	<0.001
Body weight, kg	82.0 ± 11.3	66.0 ± 11.2	<0.001
Body mass index (BMI), kg/m^2	25.4 ± 3.2	23.7 ± 3.8	<0.001
Waist circumference (WC), cm	92.8 ± 9.7	83.8 ± 10.7	<0.001
Hip circumference (HC), cm	99.1 ± 7.4	97.2 ± 9.7	0.001
Waist-to-hip ratio (WHR)	0.937 ± 0.07	0.862 ± 0.06	<0.001
Waist-to-height ratio (WHtR)	0.525 ± 0.06	0.498 ± 0.07	<0.001
Fasting glucose (FG), mg/dL	82.1 ± 13.1	78.3 ± 14.3	<0.001
Total cholesterol (TC), mg/dL	216 ± 39	210 ± 38	0.027
HDL-C, mg/dL	54.2 ± 13.3	68.0 ± 15.8	<0.001
LDL-C, mg/dL	138 ± 34	124 ± 35	<0.001
TC to HDL-C ratio	4.2 ± 1.2	3.2 ± 0.9	<0.001
Triacylglycerol (TAG), mg/dL	120 ± 76	90.3 ± 43.2	<0.001
Total WBC, G/L	6.5 ± 1.6	6.8 ± 1.8	0.013
Granulocytes, G/L	4.0 ± 1.3	4.4 ± 3.2	0.042
Monocytes, G/L	0.325 ± 0.10	0.295 ± 0.10	<0.001
Lymphocytes, G/L	2.2 ± 0.5	2.2 ± 0.6	0.013

HDL-C: high density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; WBC: white blood cells; G/L: 1x10^9 cells/L. Values are shown as mean ± SD.

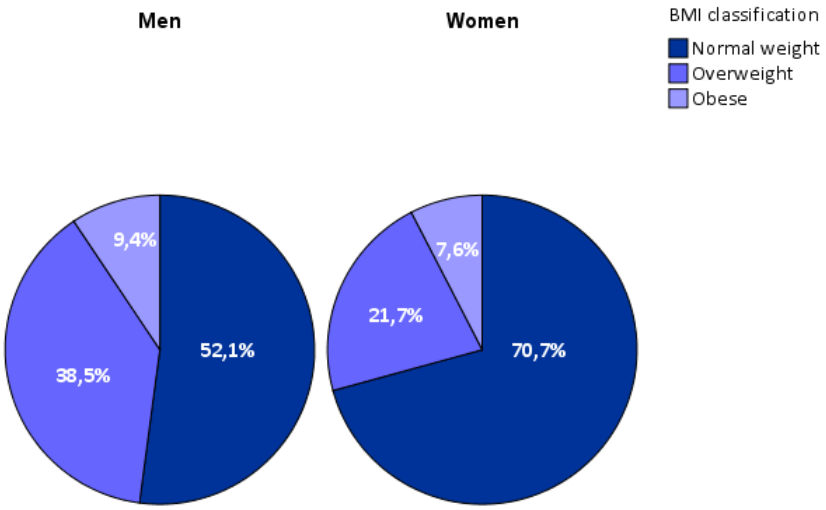

Figure 6: Frequency (%) of normal-weight, overweight and obesity, by gender.

Normal weight: BMI of 18.5–24.9 kg/m^2; overweight: BMI of 25–29.9 kg/m^2; obese: BMI ≥30 kg/m^2 [WHO EXPERT CONSULTATION, 2004].

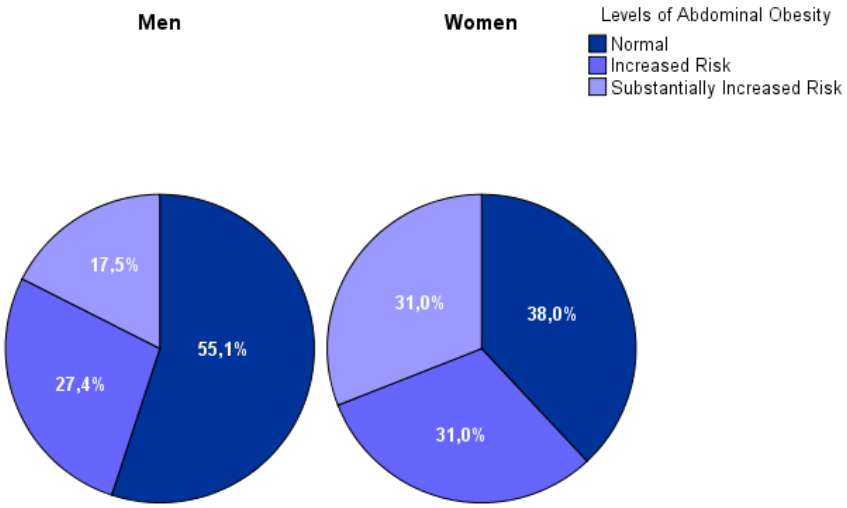

Figure 7: Frequency (%) of different levels of abdominal obesity, by gender.

Normal: WC <94 cm in men and <80 cm in women; increased risk: WC of 94–101.9 cm in men and 80–87.9 cm in women; substantially increased risk: WC ≥102 cm in men and ≥88 cm in women [WORLD HEALTH ORGANIZATION, 2008a].

The frequencies of overweight and obesity (BMI ≥25 kg/m^2) and of abdominal obesity—assessed by high WC (≥94 cm in men and ≥80 cm in women), high WHR (≥1.0 in men and ≥0.85 in women), or high WHtR (≥0.5 in both men and women)—are presented in **Table 7**, for both men and women. The observed frequencies of overweight and obesity were higher among men (47.9%), compared with women (29.3%) and the differences were statistically significant ($\chi^2 = 35.6$, $p < 0.001$). High WC and high WHR were significantly more frequent in women than in men (WC: $\chi^2 = 27.9$, $p < 0.001$; WHR: $\chi^2 = 186$, $p < 0.001$). Among men, the cut-offs used to define a high WHR identified 14.6% of individuals as having abdominal obesity. When WHtR was used as the diagnostic criterion, the frequency of abdominal obesity was as high as 62.7%. The frequency of high WHtR was significantly increased in men, compared with women ($\chi^2 = 28.6$, $p < 0.001$).

Table 7: Frequencies of overweight and abdominal obesity among men and women.

	Men (*n* = 405)		Women (*n* = 581)		Chi-square	*p*-value
	n	%	n	%		
Overweight and obesity[(1)]	194	47.9	170	29.3	35.6	<0.001
Abdominal obesity						
High WC[(2)]	182	44.9	360	62.0	27.9	<0.001
High WHR[(3)]	59	14.6	336	57.8	186.0	<0.001
High WHtR[(4)]	254	62.7	264	45.4	28.6	<0.001

(1) BMI ≥25 kg/m^2 in men and women [WHO EXPERT CONSULTATION, 2004]; (2) waist circumference (WC) ≥94 cm in men and ≥80 cm in women; (3) waist-to-hip ratio (WHR) ≥1.0 in men and ≥0.85 in women [PISCHON et al., 2008]; waist-to-height ratio (WHtR) ≥0.5 in men and women [ASHWELL and HSIEH, 2005].

In both men and women, BMI and WC were highly correlated, as illustrated in **Figures 8 and 9**. Among men, 67.4% of the variance in BMI was explained by WC ($r = 0.82$, $p < 0.001$). Among women, 68.7% of the variance in BMI was accounted for WC ($r = 0.83$, $p < 0.001$).

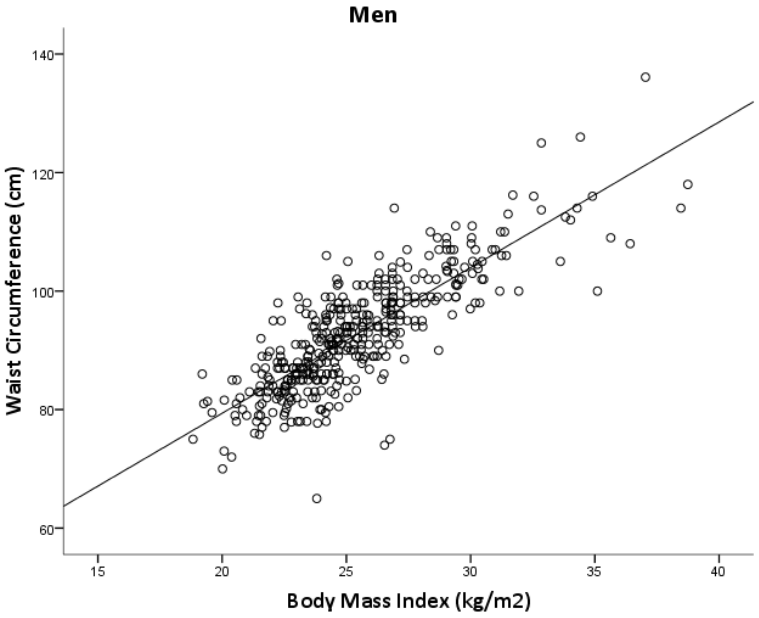

Figure 8: Correlation between WC and BMI in male participants.

WC: waist circumference (in centimetres); BMI: body mass index (in kg/m^2); $r = 0.82$ ($p < 0.001$).

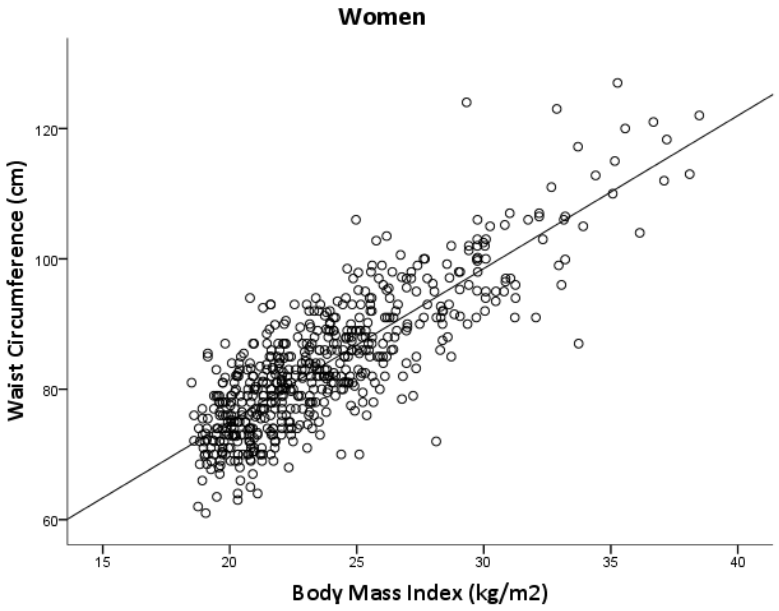

Figure 9: Correlation between WC and body mass index BMI in female participants.

WC: waist circumference (in centimetres); BMI: body mass index (in kg/m^2); $r = 0.83$ ($p < 0.001$).

In the whole sample (male and female participants), the Pearson's correlation between WHR and BMI was $r = 0.46$, between WHtR and BMI was $r = 0.82$, between WHR and body weight was $r = 0.54$, and between WHtR and body weight was $r = 0.71$ ($p < 0.001$ for all correlations).

Table 8 shows the frequencies of diabetes, elevated fasting glucose (≥100 mg/dL or on drug treatment for elevated blood glucose) and dyslipidaemia among men and women. Diabetes was self-reported by 1.1% of the participants (men: 1.2%; women: 1.0%) and 63.6% of all cases of diabetes were non-insulin dependent. Elevated fasting blood glucose was observed in 5.3% of men and 3% of women, and the differences were not statistically significant. Elevated levels of TAG (≥150 mg/dL or on drug treatment for elevated TAG) were observed in 22.1% of men and 8.5% of women ($\chi^2 = 32.9$, $p < 0.001$).

Elevated total cholesterol (≥240 mg/dL or on drug treatment for elevated cholesterol levels) was present in 28.9% of men and 20% of women, and the differences were statistically significant between the two groups ($\chi^2 = 9.4$, $p = 0.002$).

The frequencies of reduced HDL-C (<40 mg/dL in men and <50 mg/dL in women or on drug treatment for reduced HDL-C) were 14.9% among men and 10.4% among women and the differences between the two groups were statistically significant ($\chi^2 = 4.0$, $p = 0.045$).

The frequency of HTGW, defined as the co-occurrence of a high WC (≥94 cm in men and ≥80 cm in women) and elevated levels of TAG (≥150 mg/dL or on drug treatment for elevated TAG levels) was increased among men, compared with women ($\chi^2 = 11.8$, $p = 0.001$).

Table 8: Frequencies of self-reported type I and II diabetes, elevated fasting glucose, dyslipidaemia, and HTGW in men and women.

	Men		Women		Chi-square	*p*-value
	n	%	n	%		
Self-reported diabetes	5	1.2	6	1.0	0.09	0.769
Elevated FG[(1)]	19	5.3	16	3.0	2.99	0.084
Elevated TAG[(2)]	79	22.1	45	8.5	32.9	<0.001
Elevated TC[(3)]	104	28.9	106	20.0	9.4	0.002
Reduced HDL-C[(4)]	53	14.9	55	10.4	4.0	0.045
HTGW[(5)]	49	13.7	36	6.8	11.8	0.001

[(1)] Fasting glucose (FG) ≥100 mg/dL or on drug treatment for elevated blood glucose; [(2)]Triacylglycerol (TAG) ≥150 mg/dL or on drug treatment for high TAG; [(3)]Total cholesterol (TC) ≥240 mg/dL or on drug treatment for elevated cholesterol levels; [(4)]High-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women or on drug treatment for reduced HDL-C [NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002]; [(5)]Hypertriglyceridaemic waist (HTGW): co-occurrence of (2) and high waist circumference (≥94 cm in men and ≥80 cm in women) [LEMIEUX et al., 2000; NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002; WORLD HEALTH ORGANIZATION, 2008a].

Figure 10 illustrates the frequencies of different levels of LDL-C in men and women, according to the NCEP-ATP III cut-off points [NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002]. Approximately 25.7% of men and 13.6% of women were found to have either high (≥160 mg/dL) or very high (≥190 mg/dL) levels of LDL-C ($\chi^2 = 19.8$; $p < 0.001$).

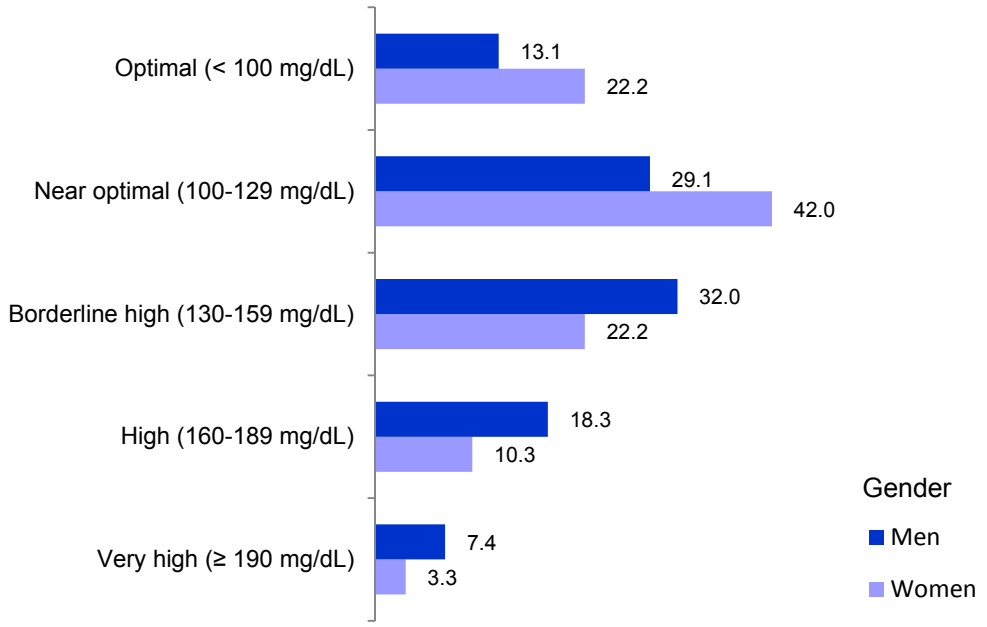

Figure 10: Frequency (%) of different levels of LDL-C in men and women.

LDL-C: low-density lipoprotein cholesterol; cut-off points defined according to the NCEP-ATP III [NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002].

4.2. Characteristics of the participants, according to the smoking status.

The frequencies of non-smokers, smokers and former smokers among men were 44.4%, 30.1% and 25.5%, respectively. Among women, 47.5%, 31.2% and 21.3% were non-smokers, smokers and former smokers, respectively. These frequencies did not differ significantly between the sexes.

Among smokers and former smokers, 82% of men and 78% of women started smoking before the age of 20 years. The average age for starting smoking was 18 years, for both men and women.

The majority of the smokers (94.6%) reported to smoke cigarettes from the box and, from this amount, 4.2% uses to smoke also a second type of cigarette (either hand-rolled cigarettes, cigar/cigarillos or other tobacco products). Among male smokers, the average number of cigarettes smoked per day was 11.1 ± 7.8; the average number of pack-years was 12.4 ± 11.4. Women smoked 11.4 ± 7.6 cigarettes per day and had on average

12.7 ± 11.0 pack-years. No statistically significant differences between men and women were observed for number of cigarettes per day or pack-years.

Smokers of both sexes were younger than non-smokers and former smokers. Among men, the average ages of non-smokers, smokers and former smokers were 43 ± 9.5, 38.3 ± 10.8, and 45.9 ± 8.2 years, respectively. Differences between the three groups were statistically significant (non-smokers *versus* smokers: $p < 0.001$; non-smokers *versus* former smokers: $p = 0.016$; smokers *versus* former smokers: $p < 0.001$). Among women, non-smokers, smokers and former smokers aged on average 40.5 ± 8.7, 37.6 ± 10.1, and 42.4 ± 8.5 years, respectively. Smokers differed significantly from non-smokers ($p = 0.001$) and former smokers ($p < 0.001$).

The baseline characteristic of the participants, according to gender and smoking status are presented in **Table 9** (anthropometric indices) **and Table 10** (blood parameters).

Table 9: Anthropometric characteristics of the participants according to the smoking status.

	Non-Smokers	Smokers	Former Smokers	*p*-value
Men				
Sample size, n (%)	180 (44.4)	122 (30.1)	103 (25.4)	
Height, cm	179.8 ± 5.9	179 ± 5.7	179 ± 7.1	0.560
Body weight, kg	81.3 ± 10.9	81.5 ± 11.9	83.7 ± 11.2	0.777
BMI, kg/m^2	25.1 ± 3.0	25.3 ± 3.3	26.1 ± 3.5	0.634
WC, cm	92.2 ± 9.5	92.1 ± 10.1	94.6 ± 9.4	0.911
HC, cm	99.0 ± 7.4	98.6 ± 7.2	99.7 ± 7.6	0.895
WHR	0.931 ± 0.07	0.932 ± 0.06	0.950 ± 0.08	0.466
WHtR	0.524 ± 0.06	0.520 ± 0.06	0.540 ± 0.06	0.827
Overall				0.592
Women				
Sample size, n (%)	276 (47.5)	181 (31.2)	124 (21.3)	
Height, cm	166.8 ± 5.7	166.3 ± 6.0	167.6 ± 5.7	0.246
Body weight, kg	65.6 ± 11.0	65.3 ± 10.4	68.1 ± 12.7	0.610
BMI, kg/m^2	23.6 ± 3.8	23.6 ± 3.4	24.2 ± 4.2	0.637
WC, cm	83.4 ± 10.2	83.4 ± 9.9	85.2 ± 12.7	0.467
HC, cm	97.2 ± 9.5	96.6 ± 8.6	98.1 ± 11.4	0.857
WHR	0.858 ± 0.06	0.863 ± 0.06	0.867 ± 0.06	0.332
WHtR	0.494 ± 0.06	0.499 ± 0.06	0.505 ± 0.08	0.374
Overall				0.815

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio. Values are shown as mean ± SD; *p*-value determined by multivariate ANOVA and adjusted for age, physical activity, education level and energy intake.

Among both men and women, no statistically significant differences were found between the three groups regarding the anthropometric indices. The results did not change after excluding occasional smokers (<1 cigarette per day) from the group of smokers (data not shown).

Among both men and women, fasting glucose, total cholesterol, LDL-C, ratio of total cholesterol to HDL-C, and LDL-C, did not differ significantly between non-smokers, smokers and former smokers, after controlling for age, physical activity and energy intake.

Table 10: Blood parameters of the participants according to the smoking status.

	Non-Smokers	Smokers	Former Smokers	*p*-value
Men				
FG, mg/dL	82.6 ± 10.4	81.1 ± 18.6	82.5 ± 9.1	0.217
TC, mg/dL	217 ± 39	212 ± 42	218 ± 34	0.683
HDL-C, mg/dL	54.1 ± 12.7	52.7 ± 14.3	56.2 ± 12.9	0.025
LDL-C, mg/dL	140 ± 35	134 ± 36	138 ± 32	0.990
TAG, mg/dL	113 ± 59	130 ± 85	122 ± 90	0.006
TC to HDL-C ratio	4.2 ± 1.2	4.3 ± 1.3	4.1 ± 1.2	0.098
Total WBC, G/L[(a,b)]	6.2 ± 1.4	7.1 ± 1.9	6.3 ± 1.2	0.009
Granulocytes, G/L	3.9 ± 1.2	4.4 ± 1.7	3.8 ± 0.9	0.060
Monocytes, G/L[(a,b)]	0.307 ± 0.09	0.359 ± 0.11	0.315 ± 0.09	0.004
Lymphocytes, G/L[(a,b)]	2.1 ± 0.5	2.3 ± 0.5	2.1 ± 0.5	0.020
Overall				0.006
Women				
FG, mg/dL	78.5 ± 15.6	77.0 ± 12.9	79.6 ± 13.0	0.097
TC, mg/dL	212 ± 39	209 ± 38	207 ± 34	0.318
HDL-C, mg/dL	70.5 ± 15.9	63.9 ± 15.5	68.1 ± 14.5	0.177
LDL-C, mg/dL	124 ± 35	126 ± 36	122 ± 32	0.510
TAG, mg/dL	87.3 ± 39.1	96.9 ± 51.1	87.5 ± 38.9	0.448
TC to HDL-C ratio	3.1 ± 0.8	3.5 ± 1.1	3.2 ± 0.8	0.083
Total WBC, G/L[(a,b)]	6.4 ± 1.5	7.7 ± 2.1	6.3 ± 1.8	<0.001
Granulocytes, G/L[(a,b)]	4.0 ± 1.2	5.4 ± 5.4	3.9 ± 1.6	<0.001
Monocytes, G/L	0.276 ± 0.09	0.328 ± 0.11	0.291 ± 0.08	0.152
Lymphocytes, G/L[(a,b)]	2.2 ± 0.6	2.4 ± 0.6	2.1 ± 0.5	0.005
Overall				<0.001

FG: fasting glucose; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TAG: triacylglycerols; WBC: white blood cells; G/L: $1x10^9$ cells/L. Values are shown as mean ± SD; *p*-value determined by multivariate ANOVA and adjusted for age, physical activity, and energy intake; LSD was the post-hoc procedure. (a): statistically significant differences between non-smokers and smokers; (b): statistically significant differences between smokers and former smokers.

In the uncorrected model, the levels of HDL-C and TAG did not differ significantly between the groups, both in men and women. However, among men, the differences

became significant between the three groups, after controlling for age, physical activity, and energy intake (HDL-C: $p = 0.025$; TAG: $p = 0.006$). The distribution of TAG for men and women are illustrated in **Figure 11**.

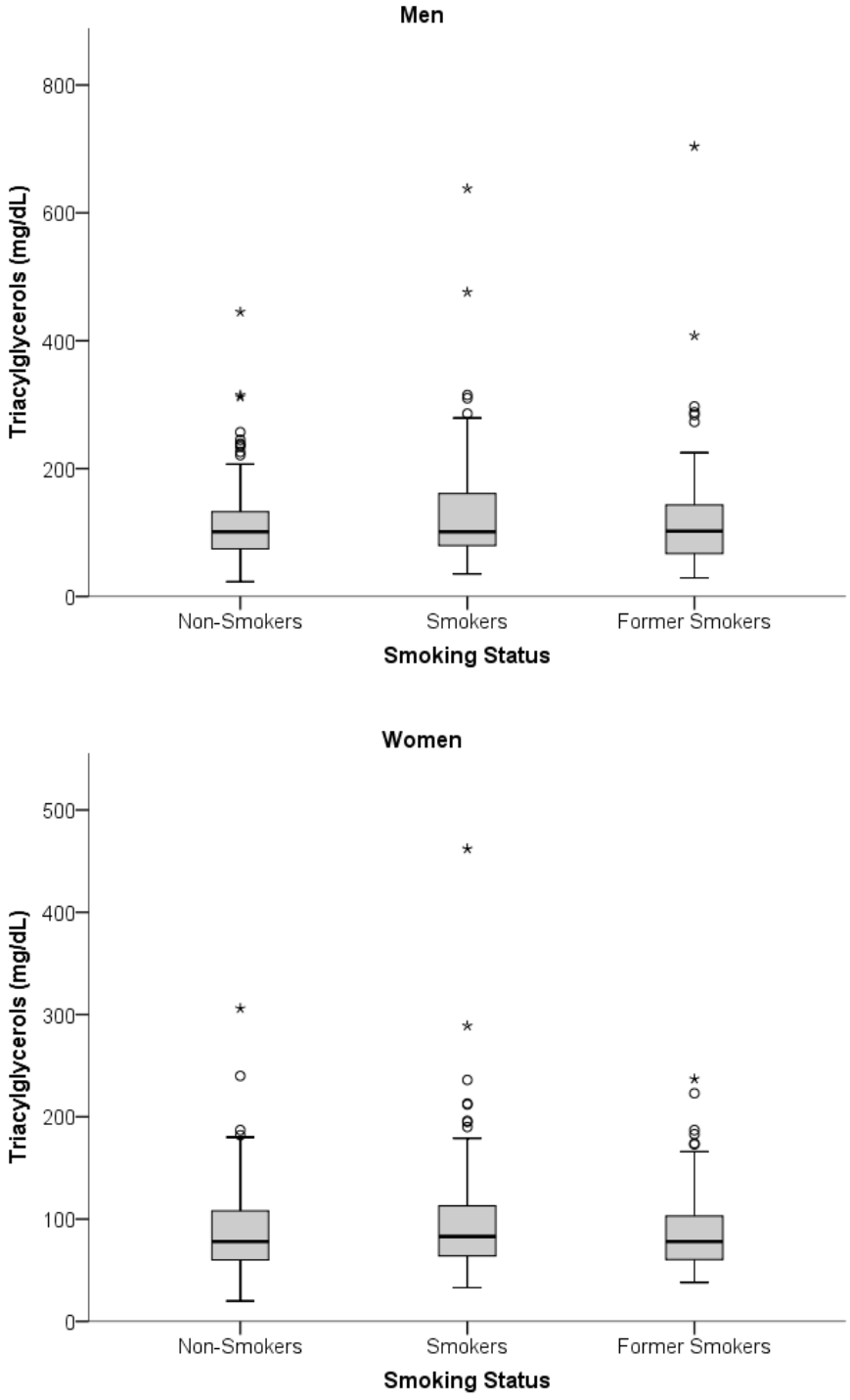

Figure 11: Distribution of TAG levels in men and women, according to the smoking status.
TAG: triacylglycerol

There were no significant differences in the observed frequencies of HTGW among smokers, non-smokers and former smokers.

Among men, total WBC counts were significantly elevated in smokers, compared with non-smokers ($p < 0.001$) and former smokers ($p < 0.001$). The same was observed for monocytes (non-smokers *versus* smokers: $p = 0.001$; smokers *versus* former smokers: $p = 0.003$) and lymphocytes (non-smokers *versus* smokers: $p < 0.001$; smokers *versus* former smokers: $p = 0.009$). The differences between the groups remained statistically significant after controlling for age, physical activity and energy intake. In the uncorrected model, the granulocyte counts differed significantly between the groups (non-smokers *versus* smokers: $p = 0.001$; smokers *versus* former smokers: $p = 0.003$), but the significance disappeared after controlling for confounders (**Table 10**).

Among women, the total WBC, granulocytes and lymphocyte counts were significantly higher in smokers, compared with both, non-smokers ($p < 0.001$) and former smokers ($p < 0.001$), and the differences remained significant after controlling for confounders. No differences in the total or differential WBC counts were found between female non-smokers and female former smokers.

When asked to describe their overall health, 44% of smokers rated it as very good, compared with 49.1% of non-smokers and 51.3% of former smokers (**Figure 12**).

When asked to compare their overall health at the moment of the study with the previous year, 69.7% of non-smokers, 71.1% of smokers and 73.6% of former smokers described their overall health as similar (**Figure 13**).

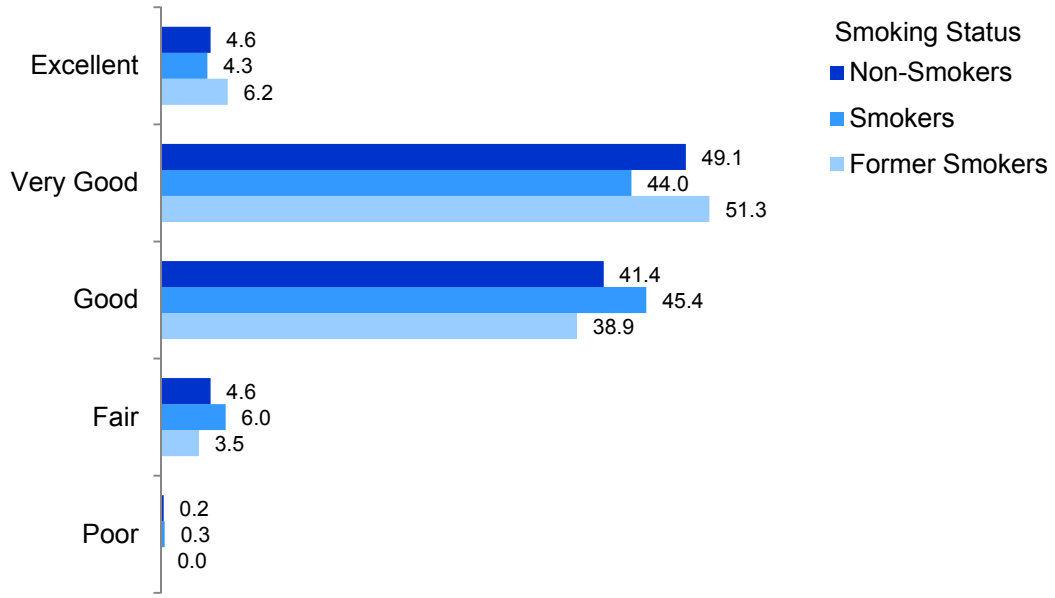

Figure 12: Self-rated overall health, according to the smoking status.

Values are expressed as percentage (%).

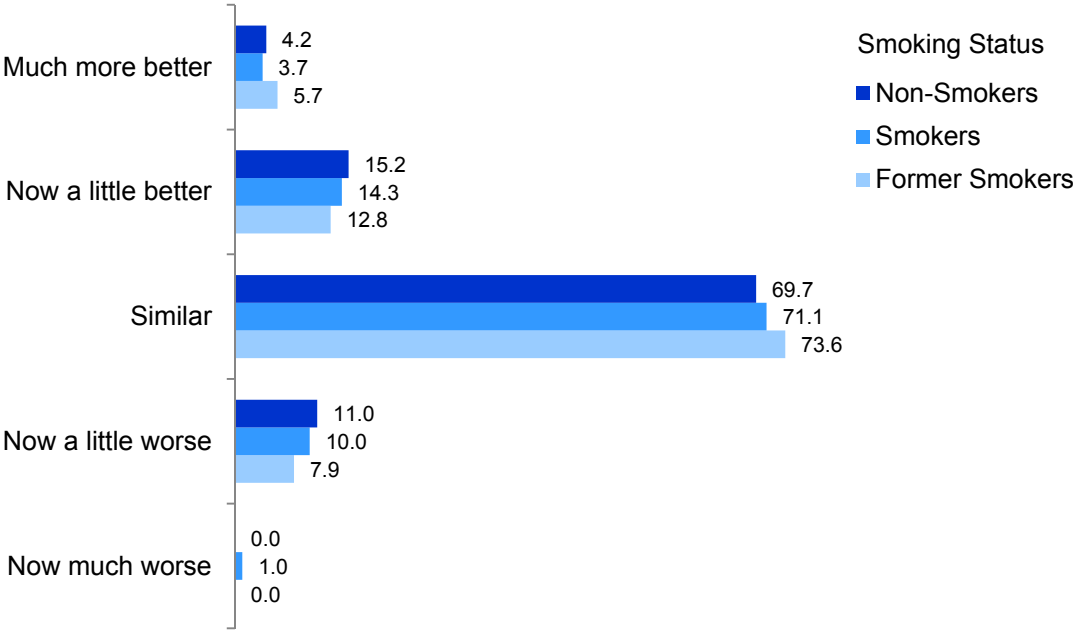

Figure 13: Self-rated overall health, compared to the year prior to the recruitment in the study, according to the smoking status.

Values are expressed as percentage (%).

Education level is presented separately for men and women in **Table 11**. There were only few participants (five men and nine women) with a low level of education, therefore the low and medium levels were combined. Subsequently, differences concerning the levels of education according to the smoking status were calculated.

Table 11: Education levels of the participants based on the ISCED, according to the smoking status.

Education Levels	Non-Smokers		Smokers		Former Smokers	
	n	%	n	%	n	%
Men						
Medium[a,b]	103	57.2	94	77.0	77	74.8
High[a,b]	77	42.8	28	23.0	26	25.2
Total	180	100	122	100	103	100
Women						
Medium[a,c]	207	75.3	162	90	101	82.1
High[a,c]	68	24.7	18	10	22	17.9
Total	275	100	180	100	123	100

Low and medium education levels were combined due to the small number of participants (five men and nine women) with low level of education. Frequencies are expressed as absolute (n) and relative (%) values; a: statistically significant differences between non-smokers and smokers; b: statistically significant differences between non-smokers and former smokers; c: statistically significant differences between smokers and former smokers (Chi-square test).

Among men, non-smokers differed significantly from both, smokers ($\chi^2 = 12.6$, $p < 0.001$) and former smokers ($\chi^2 = 8.7$, $p = 0.003$), with a higher proportion of individuals with high levels of education in the non-smoking group. No significant differences were found between smokers and former smokers. Among women, significant differences were found between non-smokers and smokers ($\chi^2 = 15.4$, $p < 0.001$) and between smokers and former smokers ($\chi^2 = 4.0$, $p = 0.046$) with respect to the frequencies of individuals with high levels of education. No differences were found between female non-smokers and female former smokers. Comparing men and women, independent of the smoking status, high levels of education were observed in 32.3% of men and 18.7% of women ($\chi^2 = 24.15$, $p < 0.001$).

Table 12 presents the results for physical activity levels according to the smoking status for men and women. Among men, there were no significant differences between non-smokers, smokers and former smokers. Among women, non-smokers and smokers differed significantly in the proportion of individuals in the low and medium ($\chi^2 = 4.8$;

$p = 0.028$) and in the medium and high ($\chi^2 = 8.2$; $p = 0.004$) physical activity levels. Female former smokers did not differ significantly from either female smokers or non-smokers concerning the frequencies of individuals in the low, medium or high physical activity levels.

Table 12: Physical activity (PA) levels of the participants, according to the smoking status.

PA Levels	Non-Smokers		Smokers		Former Smokers	
	n	%	n	%	n	%
Men						
Low	52	33.5	31	33.0	25	29.1
Medium	72	46.5	46	48.9	41	47.7
High	31	20.0	17	18.1	20	23.3
Total	155	100	94	100	86	100
Women						
Low	72	33.3	36	26.5	23	24.2
Medium[(a)]	94	43.5	82	60.3	50	52.6
High[(a)]	50	23.1	18	13.2	22	23.2
Total	216	100	136	100	95	100

Frequencies are expressed as absolute (n) and relative (%) values; (a): statistically significant differences between non-smokers and smokers (Chi-square test).

Regarding the dietary patterns (**Table 13**), among men no significant differences were found in total energy intake and indices of diet quality between the three groups, after adjusting for age. However, in non-smokers the average percentage of energy provided by protein (15.3 ± 3.6) was significantly lower compared with both, smokers (17.0 ± 4.5; $p = 0.014$) and former smokers (16.7 ± 5.3; $p = 0.036$). Likewise, the average amount of energy from carbohydrates in non-smokers (46.5 ± 8.9) was significantly higher, compared with both, smokers (41.8 ± 9.0; $p = 0.002$) and former smokers (43.5 ± 9.0; $p = 0.036$). The amount of energy provided by fats was not significantly different between the groups.

Among women, smokers consumed significantly less calories than non-smokers ($p = 0.002$) and had a worse score for the deficiency index than non-smokers ($p < 0.001$) and former smokers ($p < 0.001$). However, they presented a better score for the excess index, compared with non-smokers ($p = 0.003$). No significant differences in the amount of energy provided by proteins, carbohydrates or fats were observed between the three groups.

Table 13: Dietary intake of male and female participants, according to the smoking status.

	Non-Smokers	Smokers	Former Smokers	*p*-value
Men	(*n*=123)	(*n*=55)	(*n*=59)	
EI, kcal	2 221 ± 557	2 244 ± 445	2 246 ± 562	0.941
% EI from protein[a,b]	15.3 ± 3.6	17.0 ± 4.5	16.7 ± 5.3	0.019
% EI from CHO[a,b]	46.5 ± 8.9	41.8 ± 9.0	43.5 ± 9.0	0.004
% EI from fat	35.0 ± 7.9	36.6 ± 7.5	34.8 ± 7.3	0.342
DI, points	2 421 ± 220	2 423 ± 195	2 446 ± 212	0.755
EXI, points[a]	388 ± 72	363 ± 71	389 ± 73	0.072
Overall				<0.001
Women	(*n*=213)	(*n*=114)	(*n*=93)	
EI, kcal[a]	1 825 ± 424	1 668 ± 431	1 762 ± 477	0.008
% EI from protein	16.0 ± 6.6	16.4 ± 4.4	15.7 ± 4.3	0.686
% EI from CHO	45.5 ± 8.2	44.9 ± 10.0	46.1 ± 9.2	0.617
% EI from fat	35.9 ± 7.2	36.0 ± 8.4	35.1 ± 8.3	0.605
DI, points[a,c]	2 410 ± 238	2 270 ± 272	2 394 ± 216	<0.001
EXI, points[a]	385 ± 76	412 ± 69	397 ± 90	0.011
Overall				<0.001

EI: total energy intake; CHO: carbohydrates; DI: deficiency index; EXI: excess index. Values are shown as mean ± SD: *p*-value determined by multivariate ANOVA and adjusted for age; LSD was the post-hoc procedure. (a): statistically significant differences between non-smokers and smokers; (b): statistically significant differences between non-smokers and former smokers; (c): statistically significant differences between smokers and former smokers.

4.2.1. Characteristics of daily smokers, according to the number of pack-years

In daily smokers, the number of pack-years (PY) was calculated and they were categorised into three different PY-categories: first ($0 < PY \leq 5$), second ($5 < PY \leq 5$) and third ($PY > 15$).

Mean ± SD age of non-smokers and smokers from the first, second, and third PY-categories were respectively 41.5 ± 9.1, 30.5 ± 10, 38.1 ± 9.1, and 45.6 ± 5.9 years, and these values differed significantly between the four groups ($p < 0.001$).

Table 14 shows the anthropometric characteristics of non-smokers and smokers from different PY-categories. The results for blood analyses are presented in **Table 15.**

Table 14: Anthropometric characteristics of non-smokers and daily smokers from different pack-year (PY) categories.

	Non-Smokers	Pack-Year Categories			*p*-value
		First (0 < PY ≤ 5)	Second (5 < PY ≤ 15)	Third (PY >15)	
	n = 456	*n* = 81	*n* = 81	*n* = 89	
Height, cm	171.9 ± 8.6	171.9 ± 9.4	171.0 ± 8.3	170.7 ± 8.2	0.230
Body weight, kg	71.8 ± 13.4	70.7 ± 14.9	71.0 ± 12.1	73.0 ± 13.9	0.844
BMI, kg/m^2	24.2 ± 3.6	23.8 ± 3.6	24.2 ± 3.1	24.9 ± 3.7	0.501
WC, cm	86.9 ± 10.8	85.4 ± 12.1	85.8 ± 9.6	88.8 ± 11.1	0.607
HC, cm	97.9 ± 8.7	96.0 ± 9.4	97.3 ± 7.1	98.6 ± 8.6	1.000
WHR	0.887 ± 0.07	0.889 ± 0.08	0.882 ± 0.07	0.900 ± 0.07	0.204
WHtR	0.506 ± 0.06	0.498 ± 0.06	0.502 ± 0.05	0.518 ± 0.07	0.589
Overall					0.894

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio. Values are shown as mean ± SD; *p*-value determined by multivariate ANOVA and adjusted for age.

Table 15: Blood parameters of non-smokers and daily smokers from different pack-year (PY) categories.

	Non-Smokers	Pack-Year Categories			*p*-value
		First (0 < PY ≤ 5)	Second (5 < PY ≤ 15)	Third (PY >15)	
	n = 411	*n* = 70	*n* = 76	*n* = 78	
FG, mg/dL	80.1 ± 14.0	75.8 ± 11.9	78.0 ± 11.4	83.1 ± 21.7	0.408
TC, mg/dL	214 ± 39	198 ± 44	209 ± 40	220 ± 36	0.974
HDL-C, mg/dL$^{(b,c,e)}$	64.4 ± 16.8	62.4 ± 17.0	58.6 ± 14.9	54.9 ± 15.4	<0.001
LDL-C, mg/dL	130 ± 35	117 ± 42	129 ± 35	140 ± 32	0.535
TC to HDL-C ratio$^{(c,d,e,f)}$	3.5 ± 1.1	3.4 ± 1.2	3.8 ± 1.2	4.3 ± 1.4	<0.001
TAG, mg/dL$^{(c,e,f)}$	96.9 ± 49.3	97.2 ± 46.6	100 ± 59	134 ± 94	0.009
WBC, G/L$^{(b,c,d,e,f)}$	6.4 ± 1.4	6.6 ± 1.6	7.3 ± 1.8	8.5 ± 2.3	<0.001
Granulocytes, G/L$^{(b,c,d,e)}$	4.0 ± 1.2	3.9 ± 1.2	5.6 ± 7.6	5.7 ± 2.1	<0.001
Monocytes, G/L$^{(b,c,d,e)}$	0.288 ± 0.09	0.304 ± 0.10	0.366 ± 0.11	0.367 ± 0.12	<0.001
Lymphocytes, G/L $^{(a,b,c,)}$	2.1 ± 0.5	2.4 ± 0.6	2.4 ± 0.6	2.4 ± 0.6	<0.001
Overall					<0.001

FG: fasting glucose; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TAG: triacylglycerols; WBC: white blood cells; G/L: 1x10^9 cells/L. Values are shown as mean ± SD; *p*-value determined by multivariate ANOVA and adjusted for age, BMI and WC; LSD was the post-hoc procedure. (a): statistically significant differences between non-smokers and first PY-category; (b): statistically significant differences between non-smokers and second PY-category; (c): statistically significant differences between non-smokes and third PY-category; (d) statistically significant differences between first and second PY-categories; (e) statistically significant differences between first and third PY-categories; (f) statistically significant differences between second and third PY-categories.

No significant differences in the anthropometric indices were found between non-smokers and smokers from any of the three PY-categories, after controlling for age. Similarly, no differences in the levels of fasting glucose, total cholesterol and LDL-C were found between the groups, after controlling for age, BMI and WC.

In the uncorrected model, the levels of HDL-C were significantly higher in non-smokers, compared with smokers from the second ($p = 0.005$) and third ($p < 0.001$) PY-categories. Significant higher levels were also observed in smokers in the first, PY-category, compared with those in the third PY-category ($p = 0.006$). The significances remained after controlling for age, BMI, and WC ($p < 0.001$).

The distribution of HDL-C according to the smoking categories is illustrated in **Figure 14**.

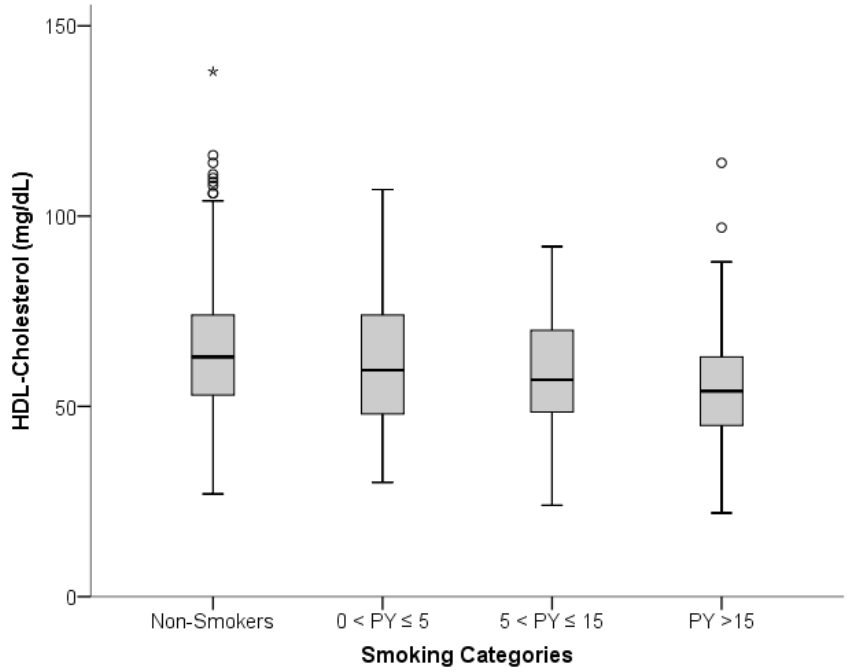

Figure 14: Distribution of HDL-C levels in non-smokers and in smokers from different pack-year (PY) categories.

HDL-C: high-density lipoprotein cholesterol; 0 < PY ≤ 5: first PY-category; 5 < PY ≤ 15: second PY-category; PY >15: third PY-category.

The frequencies of reduced levels of HDL-C were lower among non-smokers compared with smokers from the second ($\chi^2 = 4.9$; $p = 0.026$) and the third ($\chi^2 = 23.7$; $p < 0.001$) PY-categories (**Figure 15**). No differences in the frequencies of reduced HDL-C were observed between the PY-categories.

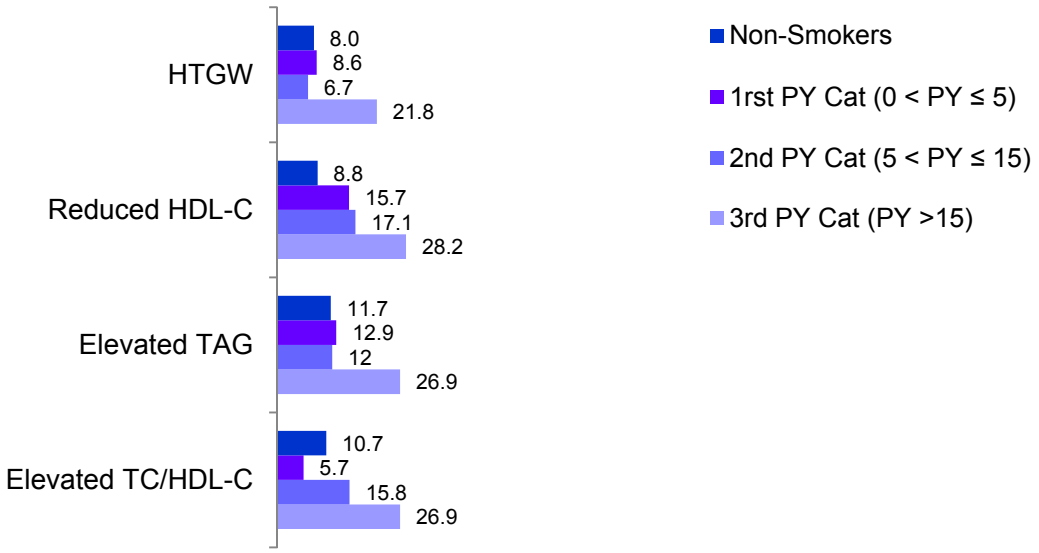

Figure 15: Frequencies of HTGW, reduced HDL-C, elevated TAG, and elevated TC/HDL-C in non-smokers and smokers from different pack-year (PY) categories.

Values are expressed as percentage (%); HTGW (hypertriglyceridaemic waist): co-occurrence of high waist circumference (WC ≥94 cm in men and ≥80 cm in women) and elevated triacylglycerols (TAG) levels (≥150 mg/dL in men and women or on drug treatment for elevated TAG) [LEMIEUX et al., 2000; WORLD HEALTH ORGANIZATION, 2008a; NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002]; reduced HDL-C (high-density lipoprotein cholesterol): ≤40 mg/dL in men and ≤50 mg/dL in women [NATIONAL CHOLESTEROL EDUCATION PROGRAM, 2002]; Elevated TC/HDL-C (ratio of total cholesterol to HDL-C): ≥5.0 in men and women [WANG et al., 2001].

The ratios of total cholesterol to HDL-C were significantly higher in smokers from the third PY-category, compared with non-smokers ($p < 0.001$). Among smokers, this ratio increased with the number of pack-years, and the differences were significant (first *versus* second PY-category: $p = 0.032$; first *versus* third PY-category: $p < 0.001$; second *versus* third PY-category: $p = 0.005$). The differences remained significant even after controlling for age, BMI and WC ($p < 0.001$).

Accordingly, the frequencies of individuals with elevated ratio (≥5) of total cholesterol to HDL-C (**Figure 15**) differed significantly between non-smokers and smokers from the third PY-category ($\chi^2 = 14.96$, $p < 0.001$).

In the uncorrected model, the levels of TAG differed significantly between non-smokers and smokers from the third PY-category ($p < 0.001$). Significant differences were also found between the first and third PY-categories ($p < 0.001$) and between the second and third PY-categories ($p < 0.001$). The significance remained after controlling for confounders ($p = 0.009$).

As illustrated in **Figure 15**, elevated levels of TAG were less frequently observed among non-smokers (11.7%) than among smokers from the third PY-category (26.9%), and the differences were statistically significant ($\chi^2 = 12.6$; $p < 0.001$). Similarly, the frequencies of elevated TAG in smokers from the first and third PY-categories differed significantly ($\chi^2 = 4.5$; $p = 0.034$), as well as between smokers from the second and the third PY-categories ($\chi^2 = 5.4$; $p = 0.020$).

The frequency of HTGW was significantly higher in smokers from the third PY-category, compared with non-smokers ($\chi^2 = 13.6$; $p < 0.001$) and compared with smokers from the second ($\chi^2 = 7.1$; $p = 0.008$) and third ($\chi^2 = 4.9$; $p = 0.027$) PY-categories.

The total and differential WBC counts also differed significantly between most of the groups (**Table 15**). Statistically significant differences in the total WBC counts were found between non-smokers and smokers from both the second and third PY-categories ($p < 0.001$). Among smokers, significant differences were also found between the PY-categories (first *versus* second: $p = 0.005$; first *versus* third: $p < 0.001$; second *versus* third: $p < 0.001$), with values increasing as the intensity and duration of smoking increased. The significance persisted after controlling for age, BMI, and WC ($p < 0.001$). The distributions of total WBC according to the smoking categories are illustrated in **Figure 16**.

Differences in the granulocyte counts were also significant between non-smokers and smokers from both the second and third PY-categories ($p < 0.001$), but non-smokers did not differ significantly from the first PY-category. Across the PY-categories, significant differences in the granulocyte counts were also observed between smokers from the first and second PY-categories ($p < 0.001$) and between the first and third PY-categories ($p < 0.001$). Controlling for confounders did not change the significance. No differences in the granulocyte counts were found between the second and third PY-categories.

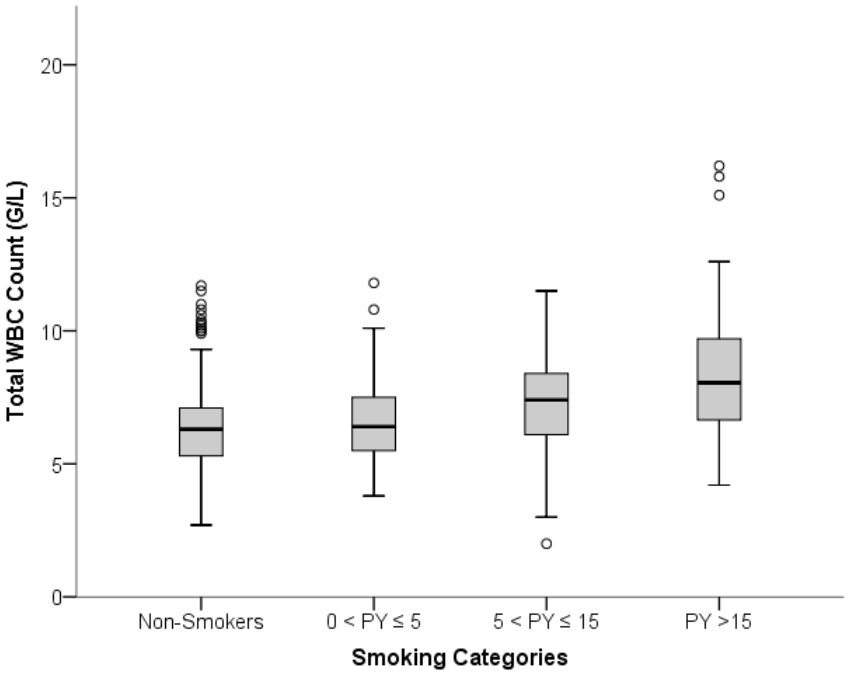

Figure 16: Distribution of total WBC count in non-smokers and smokers from different PY-categories.

WBC: total white blood cell; PY: pack-years (0 < PY ≤ 5: first PY-category; 5 < PY ≤ 15: second PY-category; PY >15: third PY-category.

Monocyte counts differed significantly between non-smokers and smokers from the second ($p < 0.001$) and third ($p < 0.001$) PY-categories. Significant differences were also found between the first and second PY-categories ($p < 0.001$) and between the first and third PY-categories ($p < 0.001$). The significance persisted in the corrected model ($p < 0.001$).

Lymphocyte counts differed significantly between non-smokers and all the three PY-categories (non-smokers versus first PY-category: $p = 0.002$; non-smokers versus second PY-category: $p = 0.001$; non-smokers versus third PY-category: $p < 0.001$). The differences remained significant for all these parameters after controlling for age, BMI, and WC ($p < 0.001$). No statistically significant differences in the lymphocyte counts were found across the PY-categories.

4.2.2. Characteristics of daily smokers, according to the number of cigarettes smoked per day

Smokers were further categorised according to the number of cigarettes consumed per day into light smokers (1–10 cigarettes per day), moderate smokers (11–20 cigarettes per day) or heavy smokers (>20 cigarettes per day) and differences in the anthropometric and blood parameters between these three groups were analysed. The mean ± SD number of cigarettes per day was 6.3 ± 3.3 for light smokers, 17.3 ± 2.8 for moderate smokers, and 28.8 ± 5.5 for heavy smokers.

Mean ± SD age of light smokers, moderate smokers, and heavy smokers were 37 ± 10.7, 39.3 ± 10.2, and 43.8 ± 7.4, respectively. Heavy smokers were significantly older than light smokers ($p = 0.023$). No significant differences in the average age at which participants started smoking were observed between the groups. However, they differed significantly ($p = 0.020$) regarding the years of smoking (light smokers: 18.9 ± 9.8 years; moderate smokers: 21.8 ± 9.9 years; heavy smokers: 24.7 ± 7.3 years).

The anthropometric characteristics of smokers, according to the number of cigarettes smoked per day, are shown in **Table 16**.

Table 16: Anthropometric characteristics of daily smokers, according to the smoking intensity.

	Smoking Intensity			
	Light Smokers (*n* = 135)	**Moderate Smokers** (*n* = 106)	**Heavy Smokers** (*n* = 13)	***p*-value**
Body weight, kg[b,c]	71.3 ± 13.6	70.8 ± 12.8	81.3 ± 18.0	0.009
BMI, kg/m^2[b,c]	24.2 ± 3.5	24.1 ± 3.5	27.5 ± 3.4	0.023
WC, cm	86.0 ± 11.4	86.9 ± 10.2	94.3 ± 11.7	0.059
HC, cm	96.5 ± 8.6	97.7 ± 8.0	102.6 ± 8.5	0.163
WHR	0.890 ± 0.08	0.890 ± 0.07	0.920 ± 0.07	0.280
WHtR	0.502 ± 0.06	0.508 ± 0.06	0.545 ± 0.05	0.266
Overall				0.108

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio. Values are shown as mean ± SD; *p*-value determined by multivariate ANOVA and adjusted for age, physical activity and energy intake; LSD was the post-hoc procedure; (a): statistically significant differences between light and moderate smokers; (b): statistically significant differences between light and heavy smokers; (c): statistically significant differences between moderate and heavy smokers. Light smokers: 1–10 cigarettes per day; moderate smokers: 11–20 cigarettes per day; heavy smokers: >20 cigarettes per day.

In the unadjusted model, heavy smokers had significantly greater values of body weight ($p = 0.030$), BMI ($p = 0.003$), WC ($p = 0.032$), and HC ($p = 0.036$) than light and moderate smokers. After controlling for age, physical activity and energy intake, the significance remained only for body weight ($p = 0.009$) and BMI ($p = 0.023$).

Overweight and obesity were observed in 84.6% of heavy smokers, compared with 35.6% of light smokers and 33% of moderate smokers ($\chi^2 = 13.5$, $p = 0.001$).

The distributions of body weight according to the number of cigarettes smoked per day are illustrated in **Figures 17 and 18**, respectively.

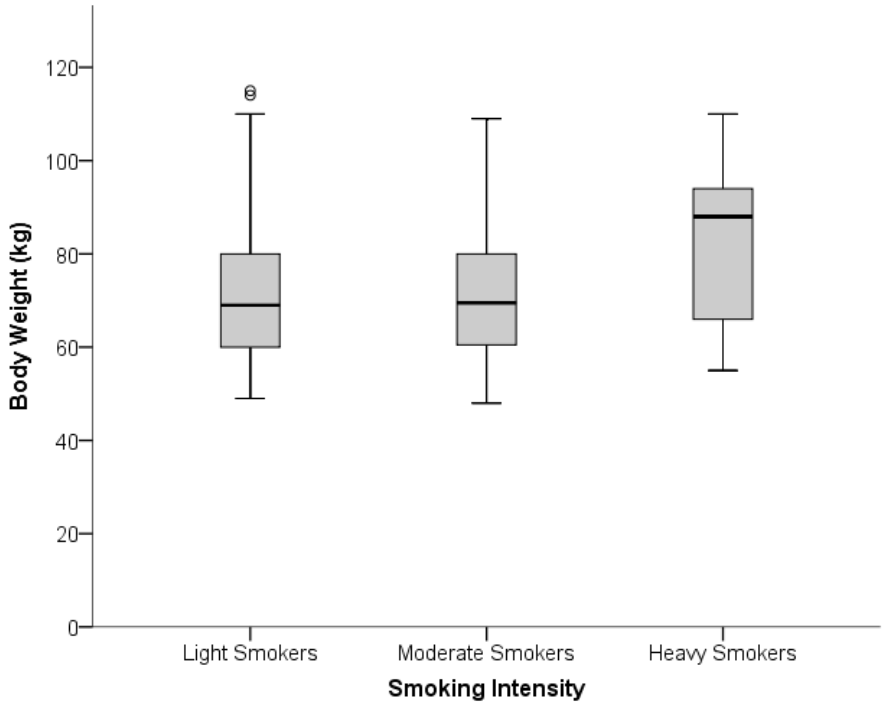

Figure 17: Distribution of body weight (kg) in daily smokers, according to the smoking intensity.

Light smokers: 1–10 cigarettes per day; moderate smokers: 11–20 cigarettes per day; heavy smokers: >20 cigarettes per day.

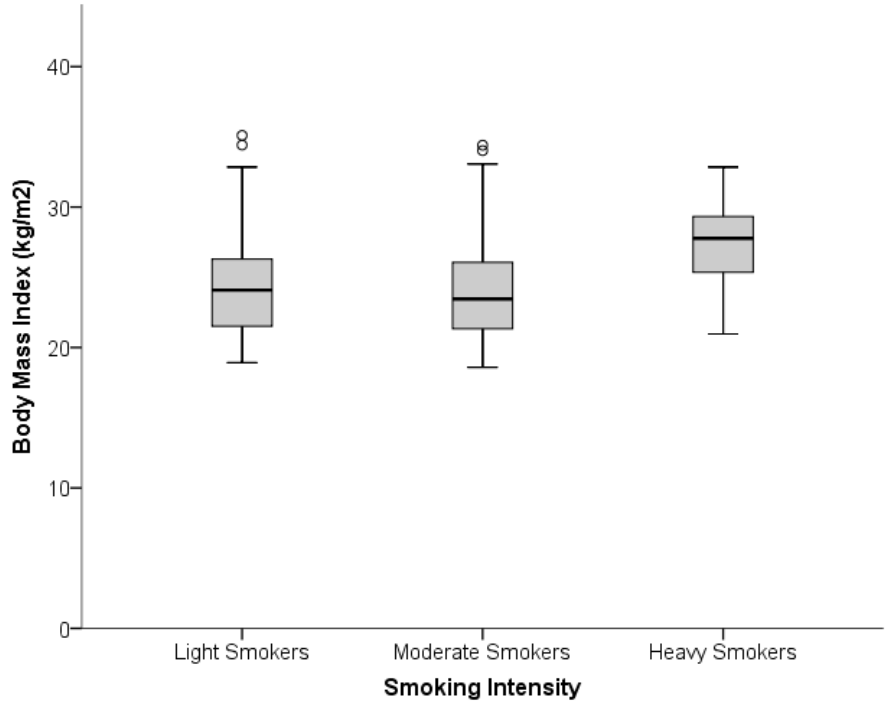

Figure 18: Distribution of body mass index (kg/m^2) in daily smokers, according to the smoking intensity.

Light smokers: 1–10 cigarettes per day; moderate smokers: 11–20 cigarettes per day; heavy smokers: >20 cigarettes per day.

Table 17 presents the mean ± SD of the blood parameters according to the number of cigarettes smoked per day.

In the unadjusted model, significantly higher levels of fasting glucose (p = 0.002), ratio of total cholesterol to HDL-C (p < 0.001), TAG (p = 0.001), and total WBC counts (p = 0.001), and reduced levels of HDL-C (p = 0.004) were found in heavy smokers, compared with moderate and light smokers. After controlling for age, physical activity and energy intake, the differences remained statistically significant for fasting glucose (p = 0.010), ratio of total cholesterol to HDL-C (p = 0.033), TAG (p = 0.006), and total WBC counts (p = 0.035).

Table 17: Blood parameters of daily smokers, according to the smoking intensity.

	Smoking Intensity			
	Light Smokers (*n* = 113)	**Moderate Smokers** (*n* = 94)	**Heavy Smokers** (*n* = 9)	***p*-value**
FG, mg/dL[(b,c)]	77.6 ± 1.4	79.1 ± 14.5	95.0 ± 46.9	0.010
TC, mg/dL	209 ± 44	209 ± 38	215 ± 28	0.399
HDL-C, mg/dL	60.7 ± 15.2	58.0 ± 16.5	42.1 ± 11.9	0.057
LDL-C, mg/dL	128 ± 41	129 ± 34	140 ± 24	0.515
TC to HDL-C ratio[(b,c)]	3.6 ± 1.2	3.9 ± 1.2	5.5 ± 1.8	0.033
TAG, mg/dL[(b,c)]	101 ± 56	111 ± 65	218 ± 170	0.006
Total WBC, G/L[(a)]	7.0 ± 1.8	8.0 ± 2.3	8.0 ± 2.2	0.035
Granulocytes, G/L	4.9 ± 6.1	5.2 ± 2.1	5.3 ± 1.9	0.056
Monocytes, G/L	0.331 ± 0.11	0.363 ± 0.12	0.367 ± 0.14	0.226
Lymphocytes, G/L	2.3 ± 0.6	2.5 ± 0.6	2.3 ± 0.6	0.211
Overall				0.003

FG: fasting glucose; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TAG: triacylglycerols; WBC: white blood cells; G/L: 1 x10^9 cells/L. Values are shown as mean ± SD; *p*-value determined by multivariate ANOVA and adjusted for age, physical activity and energy intake; LSD was the post-hoc procedure. (a): statistically significant differences between light and moderate smokers; (b): statistically significant differences between light and heavy smokers; (c): statistically significant differences between moderate and heavy smokers. Light smokers: 1–10 cigarettes per day; moderate smokers: 11–20 cigarettes per day; heavy smokers: >20 cigarettes per day.

Elevated fasting glucose was found in 1.7% of light smokers, 6.2% of moderate smokers and 10% of heavy smokers and the differences between the groups were not statistically significant.

The frequencies of elevated TAG were 14.5%, 17.7%, and 50% in light, moderate and heavy smokers, respectively. Differences were statistically significant between heavy and light smokers ($\chi^2 = 8.3$, $p = 0.004$) and between heavy and moderate smokers ($\chi^2 = 5.7$, $p = 0.017$), but did not differ between light and moderate smokers.

The distribution of TAG in light, moderate and heavy smokers is illustrated in **Figure 18.**

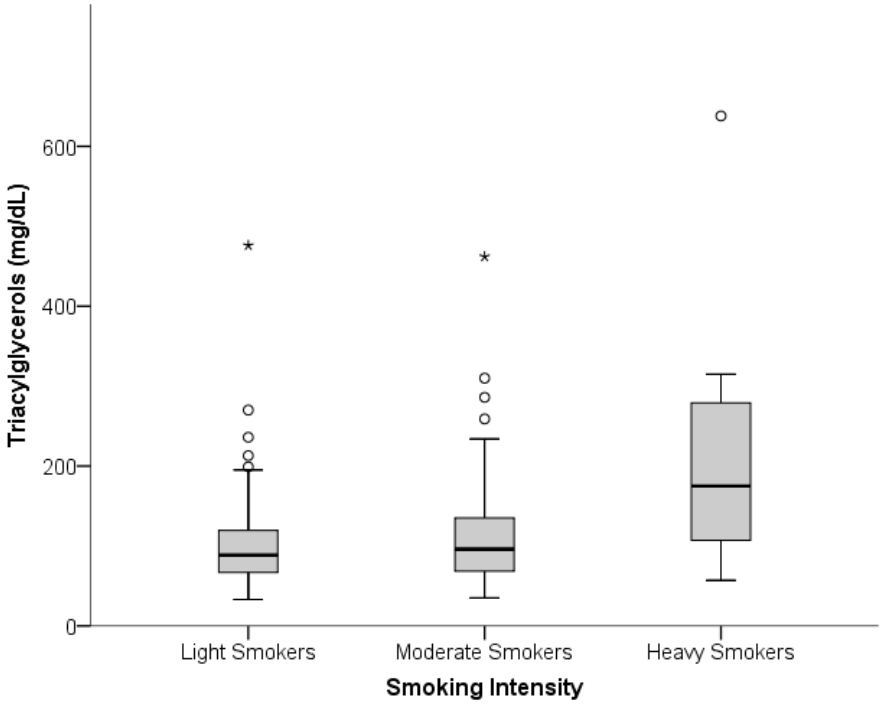

Figure 19: Distribution of TAG in daily smokers, according to the smoking intensity.

TAG: triacylglycerols (mg/dL); Light smokers: 1–10 cigarettes per day; moderate smokers: 11–20 cigarettes per day; heavy smokers: >20 cigarettes per day.

Observed frequencies of high ratios (≥5) of total cholesterol to HDL-C were also higher among heavy smokers, compared with light smokers ($\chi^2 = 13.0$; $p < 0.001$) and moderate smokers ($\chi^2 = 4.3$; $p = 0.039$).

Hypertriglyceridaemic waist was found in 9.2% of light smokers, 12.5% of moderate smokers, and 50% of heavy smokers. Differences were statistically significant between light and heavy smokers ($\chi^2 = 14.1$, $p < 0.001$) and between moderate and heavy smokers ($\chi^2 = 9.5$, $p = 0.002$).

The distribution of the total WBC count according to the smoking intensity is illustrated in **Figure 19**.

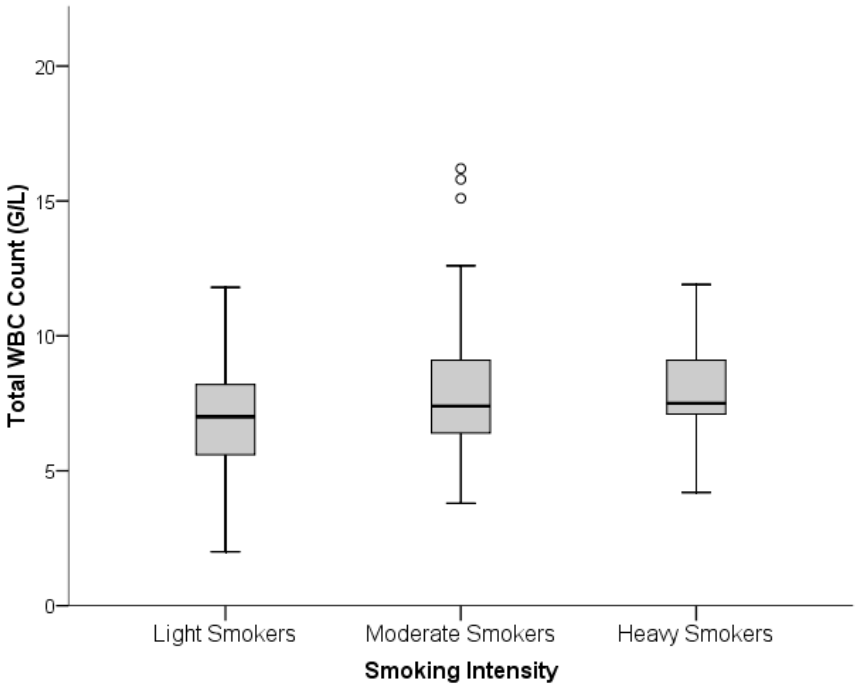

Figure 20: Distribution of total WBC count in daily smokers, according to smoking intensity.

WBC: white blood cell; Light smokers: 1–10 cigarettes per day; moderate smokers: 11–20 cigarettes per day; heavy smokers: >20 cigarettes per day.

5. DISCUSSION

5.1. Differences between male and female participants

In this study, men were on average slightly older than women and the observed frequencies of overweight and obesity were significantly higher in men than in women. Both in men and women, the mean values of BMI are in agreement with those recently reported for the Austrian population. The latest Austrian Nutrition Report—a population study which included 1,002 participants aged 7 to 80 years—found that the BMI of adults (18–64 years old) was on average 25.9 kg/m^2 among men, and 24 kg/m^2 among women [ELMADFA et al., 2012].

Although overweight and obesity were more frequent among men than among women, the observed frequencies of abdominal obesity were higher among women when a high WC or a high WHR were the diagnostic criteria. However, when abdominal obesity was diagnosed on the basis of a high WHtR, its observed frequencies were higher in men than in women.

The selected cut-off points for these anthropometric indices can partially explain the differences in the results. While most authors have used or suggested the boundary value of 0.85 for WHR in women [POULIOT et al., 1994; BERBER et al., 2001; GILL et al., 2003; ELMADFA, 2004; WORLD HEALTH ORGANIZATION, 2008a; PISCHON et al., 2008], the proposed cut-off points for men differ among authors: ≥0.95 [POULIOT et al., 1994]; ≥0.90 [BERBER et al., 2001; WORLD HEALTH ORGANIZATION, 2008a]; and ≥1.0 [BJÖRNTORP, 1985; GILL et al., 2003; ELMADFA, 2004; PISCHON et al., 2008]. In the present study, only 59 out of 405 men were found to have a high WHR (≥1.0), while among women 336 out of 581 showed a high WHR (≥0.85). When a high WHtR (≥0.5) was used to identify abdominal obesity, 254 out of 405 men were found to be centrally obese, compared with 264 out of 581 women.

Gender and ethnicity may also influence the correlation of some of these anthropometric indices with visceral adiposity [MISRA et al., 2005]. In one study [RANKINEN et al., 1999], WHR was found to be a poor surrogate for the visceral fat assessment in women.

Other authors [WEINSIER et al., 2001] suggested that neither WC nor WHR were correlated with changes in visceral adiposity in black women.

In Caucasian men, WC was found to be superior to WHR or BMI in predicting both visceral and subcutaneous adiposity [CHAN et al., 2003], whereas, in Chinese men, WHtR showed the best correlation with these fat depots, compared with WC, WHR or BMI [WU et al., 2009].

In the present study, both in men and women, WC and WHtR showed a stronger positive correlation with both body weight and BMI, compared with WHR. This is in agreement with previous studies [SKRZYPCZAK et al., 2008]. However, it cannot be inferred, based on these findings, that WC or WHtR are superior markers of abdominal obesity, compared with WHR.

What is evidenced by the results is that different anthropometric indices and cut-off points produce different results that can lead to misclassification of individuals according to the levels of abdominal obesity. Further studies are warranted to clarify which anthropometric measure best predicts the amount of visceral fat, taking into account gender, age and ethnicity.

Metabolic disturbances were also more frequent among men. Significantly higher frequencies of elevated levels of TAG, total cholesterol, and LDL-C, along with reduced levels of HDL-C were observed in men, compared with women. Likewise, HTGW was more frequent among men than among women.

The observed frequencies of male and female smokers were similar (31%). Likewise, both the average number of cigarettes smoked per day and the number of pack-years did not differ significantly between men and women. The high frequency of female smokers contrasts with that reported for the Austrian population. According to an Austrian survey [STATISTIK AUSTRIA, 2007], approximately 27% of men and 19% of women are smokers in Austria. One possible explanation for the differences in the frequencies of female smokers is that in the Austrian survey only daily smokers (≥1 cigarette per day) were classified as smokers.

The reported average number of cigarettes smoked per day in the Austrian population was somewhat greater (17 cigarettes per day) [STATISTIK AUSTRIA, 2007], compared with the participants of the present study (11 cigarettes per day). Likewise, the difference can be attributed to the fact that the definition of smokers in this study included also occasional smokers (<1 cigarette per day).

Another factor known to influence smoking habits is the education level [HUISMAN et al., 2005]. In the present study, 35.3% of men and 18.7% of women were found to have a high level of education and the differences were statistically significant. These findings contrast with the Austrian population, where 13.9% of men and 15.4% of women were shown to have a tertiary education [STATISTIK AUSTRIA, 2012]. Since individuals with more years of education are less likely to be smokers [CAVELAARS et al., 2000], this can partially explain the greater frequency of female smokers in the present study.

5.2. Differences between participants according to the smoking habits

5.2.1. Education, diet, total body fat and abdominal obesity

Non-smokers of both sexes had more years of education than their smoking counterparts. As stated above, these findings are in agreement with several other studies which reported non-smokers to have a higher level of education than smokers [FROOM et al., 1999; CAVELAARS et al., 2000; HUISMAN et al., 2005; PEPINO et al., 2007].

Smokers have been reported to consume a less healthy diet and to have a higher intake of alcohol than non-smokers, which along with the harmful effects of cigarette smoking aggravates the risk of chronic diseases [ENGLISH et al., 1997; PALANIAPPAN et al., 2001; DYER et al., 2003]. In the present study, no statistical differences in total energy intake or in the indices of diet quality were found between men with different smoking status. However, the percentage of energy provided by protein was significantly higher, while energy provided by carbohydrates was significantly lower in male smokers, compared with non-smokers and former smokers. Less energy derived from carbohydrates was

previously reported in male smokers, compared with both non-smokers and former smokers [TROISI et al., 1991]. The energy intake of female smokers was significantly lower compared with female non-smokers. They also had a lower score for the deficiency index (i.e. a poorer diet quality) than their non-smoking counterparts. The lower energy intake in female smokers may be a result of the appetite-suppressant effect of nicotine on the brain [MINEUR et al., 2011; HUANG et al., 2011] or could reveal a greater weight concern in female smokers [BOLES and JOHNSON, 2001].

In the present study, no statistical differences in the mean values of body weight and BMI were found between non-smokers, smokers and former smokers. Likewise, no statistically significant differences in the patterns of abdominal obesity—assessed by WC, WHR, or WHtR—were found between the three groups.

Several studies have found that smokers have lower body weight and BMI than non-smokers and former smokers [ALBANES et al., 1987; KLESGES et al., 1989; WILLIAMSON et al., 1991; RÁSKY et al., 1996; MOLARIUS et al., 1997; AKBARTABARTOORI et al., 2005]. However, the results in the literature are conflictive. Other studies found no significant differences between smokers and non-smokers regarding those anthropometric indices [KARAKAŞ and BOZKIR, 2012; RIMM et al., 1995; BRADLEY et al., 2010].

Previous studies suggested that smokers tend to accumulate more abdominal fat than non-smokers [BARRETT-CONNOR and KHAW, 1989, SHIMOKATA et al., 1989]. However, these findings were not confirmed by others. A cross-sectional study in Switzerland [CLAIR et al., 2011] and a prospective study in Finland [NISKANEN et al., 2004] found the highest values of WC among former smokers.

A cross-sectional study in Slovenia, with 1,343 men and women, found that, among men in the age groups 35–44 and 45–54 years, smokers had significantly lower values of WC compared with non-smokers and former smokers. In the age group 45–54 years, WHR was also significant lower among smokers, compared with their counterparts. Among women in all age categories, no differences were found in the values of WC and WHR between the groups [CAKS and KOS, 2009].

Earlier studies of former smokers have reported that smoking cessation is often accompanied by weight gain, especially among heavy smokers [WILLIAMSON et al., 1991; FILOZOF et al., 2004]. In the present study, former smokers were not found to have significantly higher body weight or BMI than non-smokers or smokers. Because most of the weight gain in former smokers is reported to occur in the first year following cessation [KLESGES et al., 1989; O'HARA et al., 1998; BASTERRA-GORTARI et al., 2010], former smokers in the present study were further categorised according to years of cessation. Four categories of years of cessation were created: 1–5; 6–10; 11–20; and >20. Individuals from these categories were then compared with both, non-smokers and smokers. After adjusting for age, no significant differences in any of the anthropometric parameters were found within the categories. Likewise, former smokers from any of these categories did not differ significantly from either smokers or non-smokers (**Tables 18 and 19, Appendix**).

In order to investigate the effect of the degree of smoking exposure in the anthropometric variables, non-smokers were further compared with daily smokers stratified according to the number of pack-years. No significant differences in the anthropometric indices were found either between non-smokers and smokers from any of the three pack-year categories, or across the pack-year categories. However, the mean values of almost all anthropometric indices increased with the number of pack-years. Although the association was not statistically significant, the trend was consistent and should not be ignored.

Similarly, heavy smokers (>20 cigarettes per day) had significantly higher values of both body weight and BMI, compared with light (1–10 cigarettes per day) and moderate (11–20 cigarettes per day) smokers. The significance remained even after controlling for age, physical activity, and energy intake. Likewise, the observed frequencies of overweight and obesity were significantly higher in heavy smokers, compared with both light and moderate smokers.

The mean values of WC, HC and WHtR increased gradually with the number of cigarettes, suggesting a dose-dependent association; however the differences between the means were not significant after controlling for confounders.

Many authors have reported a U-shaped relationship between the number of cigarettes smoked per day and the body weight or BMI of smokers. Moderate smokers were reported to be the leanest [JACOBS and GOTTENBORG, 1981; ALBANES et al., 1987; CHIOLERO et al., 2007; SNEVE and JORDE, 2008]. Equally, a positive dose-dependent association between cigarette smoking and abdominal obesity has been suggested in the literature [BARRETT-CONNOR and KHAW, 1989; SHIMOKATA et al., 1989; BAMIA et al, 2004; CHIOLERO et al., 2007; TRAVIER et al., 2009; CLAIR et al., 2011], although not observed in other studies [NISKANEN et al., 2004; XU et al., 2007; CAKS and KOS, 2009].

Heavy smokers were suggested to differ from light smokers in personality [KILLEN et al., 1988] and some lifestyle characteristics [BAUMERT et al., 2010] that may increase their risk of becoming overweight and obese [CHIOLERO et al., 2007]. They were reported to consume more alcohol, be less active and have a poorer diet, compared with light and moderate smokers [CHIOLERO et al., 2006]. It is possible that the higher consumption of alcohol among heavy smokers leads to a weight gain which is not observed in light and moderate smokers [OH and SEO, 2001]. Finally, it was suggested that overweight and obese individuals (especially women), start smoking and become heavy smokers in an attempt to lose weight, with smoking being a consequence, rather than the cause of an increased adiposity [JACOBS and GOTTENBORG, 1981].

The number of cigarettes smoked per day is a measure of smoking intensity, whilst for the calculation of pack-years both smoking intensity and duration (years of smoking) are considered. Therefore, it would also be pertinent to investigate the association of years of smoking with the markers of total and central obesity. In a Finnish study, the duration of smoking in current smokers was significantly and inversely associated with body weight, after controlling for age and number of cigarettes [MARTI et al., 1989]. Albanes and colleagues [ALBANES et al., 1987] also found that the BMI of smokers decreased with duration of smoking, except for those with 1–10 years of smoking, who showed a slightly lower BMI, compared with individuals with a smoking history of 11–20 years. Controlling for smoking intensity (number of cigarettes) did not change the results.

In the present study, the association between smoking duration and the anthropometric indices was also investigated. Differences in the mean values of body weight, BMI, WC, HC, WHR and WHtR across four different categories of years of smoking (1–10, 11–20; 21–30; and ≥31) were investigated (**Table 20**, **Appendix**). The analyses were controlled for age and number of cigarettes. The mean values of those anthropometric indices increased with the years of smoking, similarly to what was observed across the pack-year categories. However the differences were not significant after controlling for age and number of cigarettes. The results of this study suggest that cigarette smoking may have an acute effect on body weight and other anthropometric measures, rather than influence them in a chronic manner.

The findings of this study are important to demystify the effectiveness of cigarette smoking as a tool for losing or controlling body weight. For many years the tobacco industry used the fear of weight gain as a strategy to promote their products. *"Light a Lucky and you will never miss sweets that make you fat"* was a successful vintage ad targeting female consumers [BRANDT, 2007]. Especially among young women, smoking initiation has been motivated by the wish of achieving a slim figure [BOLES and JOHNSON, 2001; HONJO and SIEGEL, 2003]. However, a prospective study with 4,296 twins in Finland showed that smoking 10 or more cigarettes per day during adolescence increased significantly the risk of abdominal obesity in both sexes, and of overweight in women [SAARNI et al., 2009]. Likewise, in the Austrian Nutrition Report, the prevalence of overweight and obesity among smokers of both sexes was 53%, whilst among non-smokers and former smokers it was 33% and 11%, respectively [ELMADFA et al., 2012].

The results in the literature are conflictive and the mechanisms by which smoking influences body weight remains to be elucidated. Recently, genetic variations have been suggested to play an important role in these mechanisms. An interaction between cigarette smoking with a genetic variation in the CHRNA5-CHRNA3-CHRNB4 gene region (chromosome 15q25) was reported to strongly influence the BMI of smokers [FREATHY et al., 2011]. Further investigations of the matter are still required.

5.2.2. Biochemical parameters according to the smoking habits

Regarding the laboratory analyses, differences in the lipid profile, according to the smoking status, were found only in men, after controlling for age, physical activity and energy intake. In women, although the analyses were not controlled for menstrual cycle, controlling for the use of hormonal contraceptive or hormonal replacement therapy did not change the results (data not shown). Male smokers presented higher levels of TAG and lower levels of HDL-C. Stratifying smokers by pack-years resulted in statistically significant differences in the levels of TAG, ratio of TC to HDL-C, and HDL-C between non-smokers and some of the pack-year categories, as well as between smokers from different pack-year categories. Similar results were observed among smokers stratified by the number of cigarettes smoked per day, except for HDL-C, which did not differ between heavy, moderate and light smokers, after controlling for confounders. In addition, the levels of fasting glucose increased significantly with the number of cigarettes smoked per day, and the significance remained after controlling for age, physical activity and energy intake.

Overall, neither smoking status nor smoking intensity and/or duration were positively associated with the levels of total cholesterol or LDL-C. These serum lipid parameters seem to be little influenced by smoking, according to some studies [YASUE et al., 2006; WIETLISBACH et al., 2011]. However, other authors found a clear association of cigarette smoking with low levels of total cholesterol and LDL-C [CRAIG et al., 1989; ELIASSON et al., 1994].

In the present study, lower levels of HDL-C were associated with smoking status in men, and with the number of pack-years in the whole study population, after controlling for several confounders.

The levels of HDL-C have been considered as strong independent predictors of CVD [GORDON et al., 1989]. Biological mechanisms by which HDL-C protects against CVD include the enhancement of reverse cholesterol transport, i.e. excess cholesterol is removed from peripheral tissues and returned to the liver in order to be catabolised or secreted into bile. HDL-C has also anti-inflammatory, anti-thrombotic, and antioxidative effects [DAVIDSON and ROSENSON, 2009]. Barter and colleagues [BARTER et al., 2007],

reported that each increase in concentration of 1 mg/dL in HDL-C was associated with a decrease of 1.1% in the risk of major cardiovascular events ($p = 0.003$). Even in normolipidaemic individuals, smoking may prevent the intravascular remodelling of HDL-C, leading to severe impairment of many steps of the reverse cholesterol transport. These abnormalities in the HDL-C metabolism predispose smokers to atherogenesis and CVD [ZARATIN et al., 2004].

The ratios of total cholesterol to HDL-C were significantly higher in smokers from the highest pack-year category, compared with non-smokers. Among smokers it increased with the number of pack-years and with the number of cigarettes smoked per day. Accordingly, the observed frequencies of high ratio of total cholesterol to HDL-C (≥5) were significantly higher among smokers from the highest pack-year category, compared with non-smokers. Likewise, high ratios of total cholesterol to HDL-C were significantly more frequent among heavy smokers, compared with both light and moderate smokers.

The ratio of total cholesterol to HDL-C was reported to be a reliable predictor of ischaemic heart disease in men, probably because this ratio is associated with other metabolic dysfunctions found in individuals with high levels of TAG and low levels of HDL-C [LEMIEUX et al., 2001]. Accordingly, plasma levels of VLDL in individuals with a high ratio of total cholesterol to HDL-C were found to be four times higher than that observed in individuals with a low ratio of total cholesterol to HDL-C [JEPPESEN et al., 1998]. In addition, individuals with high total cholesterol to HDL-C ratio showed higher levels of plasma total cholesterol and LDL-C, and lower levels of plasma HDL-C. They also had higher blood pressure, increased TAG levels and were significantly more insulin resistant and glucose intolerant than individuals with a low ratio of total cholesterol to HDL-C [JEPPESEN et al., 1998]. Finally, this ratio was found to be an independent determinant of early stage atherosclerosis in individuals with T2DM [KATAKAMI et al., 2011].

With respect to the levels of fasting glucose, no differences were observed between smokers, non-smokers and former smokers. In a similar way, no differences were found among smokers from different pack-year categories. However, heavy smokers (>20 cigarettes per day) showed significantly higher levels of fasting glucose compared

with both light and moderate smokers. The significance persisted after controlling for age, physical activity and energy intake. The absolute mean values of fasting glucose increased in a graded manner according to the smoking intensity.

The increase in the levels of fasting glucose according to the smoking exposure suggests both an acute and long-term effect of smoking on this blood parameter. In a cross-sectional study with 2,704 men and 3,385 women, smoking was found to raise blood glucose as measured by glycated haemoglobin (HbA_{1c})—a marker of long-term glucose homeostasis—in a dose-dependent manner. The mean HbA_{1c} was highest in smokers, intermediate in former smokers and lowest in never-smokers. Both number of cigarettes smoked per day and number of pack-years were positively and significantly associated with the levels of HbA1c, suggesting a dose–response association [SARGEANT et al., 2001]. Transient effects of cigarette smoking on fasting glucose have also been reported in the literature [SANDBERG et al., 1973; BORNEMISZA and SUCIU, 1980], although not supported by others [RHEDER and ROTH, 1959; WALSH et al., 1977].

The findings of the present study are of particular relevance, because in a large number of prospective studies cigarette smoking has been associated with a higher risk of T2DM [WILLI et al., 2007]. The risk was found to be higher in heavy smokers, compared with light smokers [RIMM et al., 1995]. In another prospective study, the risk of T2DM was increased in heavy smokers who were obese compared with never-smokers (HR [95% CI]: 1.37 [1.05–1.80]), but, curiously, was reduced in heavy smokers (HR [95% CI]: 0.74 [0.41–1.33]) and light smokers (HR [95% CI]: 0.45 [0.23–0.88]) at the lowest BMI quartile [NAGAYA et al., 2008]. Other studies found that the risk increased in a dose–response fashion with the number of cigarettes smoked per day [WILL et al., 2001; TERATANI et al., 2012], the number of pack-years [RAFALSON ET AL., 2009], or both [MANSON et al., 2000].

In former smokers, the risk of incident T2DM was found not to be reduced [BEZIAUD et al., 2004], not to be increased [SAIRENCHI et al., 2004; MEISINGER et al., 2005], or to decrease with the time since quitting [WILL et al., 2001; YEH et al., 2010], compared with non-smokers.

There are many proposed mechanisms by which cigarette smoking can lead to impaired fasting glucose levels, insulin resistance and T2DM. Smoking increases the levels of hyperglycaemic hormones, especially catecholamines, corticosteroids and growth hormone [BENOWITZ, 2003; TZIOMALOS and CHARSOULIS, 2004; RESELAND et al., 2005]. The increase in the circulating levels of these neuroendocrine substances is accompanied by increased lipolysis and circulating levels of FFA, resulting in insulin resistance [ARNER, 2002; VAN GAAL et al., 2006]. Smoking also causes oxidative stress and leads to a state of low-grade inflammation [CSISZAR et al., 2009; CAMPBELL et al., 2008], which contributes to the development of T2DM [BASTARD et al., 2006; CALLE and FERNANDEZ, 2012]. An android fat distribution—frequently observed in smokers—is also involved in the aetiology of insulin resistance and T2DM [KISSEBAH, 1996; VAN GAAL et al., 2006].

Finally, genetic factors may equally play an important role in this association. An interaction between smoking and the CYP2A6 genotype has been suggested as a possible mechanism for the development of T2DM in smokers [LIU et al., 2011]. Compared with light smokers, heavy smokers showed a significantly higher risk of developing T2DM (adjusted OR [95% CI]: 1.75 [1.01–3.05]). The association of smoking with T2DM was moderated by the CYP2A6 genotype in such manner that heavy smokers with either slow or poor metabolizer genotypes were more likely to have T2DM than normal metabolizers. Likewise, the relationship between smoking intensity and the risk of T2DM was mediated by serum cotinine, abdominal obesity, insulin resistance and insulin secretion [LIU et al., 2011].

The observed frequencies of HTGW—another marker of metabolic dysfunction—differed significantly between non-smokers and smokers from the highest pack-year category. Among smokers, the occurrence of HTGW also increased significantly with the number of pack-years. Likewise, the number of cigarettes smoked per day was positively and significantly associated with the frequencies of HTGW, as well with the levels of TAG.

The HTGW has been claimed as a useful clinical tool for the identification of individuals at high risk of CAD and CHD, even in the absence of classical risk factors, like hyperglycaemia, reduced HDL-C or hypertension [LEMIEUX et al., 2007;

CZERNICHOW et al., 2007]. This is because individuals with the HTGW phenotype were found to have a high prevalence of the atherogenic metabolic triad, described as elevated plasma insulin, apolipoprotein B, and small dense LDL-C particles [LEMIEUX et al., 2000; LAMONTE, 2003; GAZI et al., 2006].

The increase in the frequencies of HTGW according to the number of pack-years and cigarettes smoked per day suggests that smokers with a higher smoking exposure are at greater risk of developing MetS, T2DM and CVD. This risk may be enhanced by the presence of a high WBC count, as discussed below.

The crude and adjusted mean values of total and differential WBC counts were significantly higher in male and female smokers, compared with their non-smoking and former smoking counterparts. Exceptions were granulocytes in men and monocytes in women, which did not differ significantly between the groups. No differences were observed between non-smokers and former smokers, indicating a decrease in the WBC count after smoking cessation, close to the levels found in never-smokers.

Among smokers, both total and differential WBC count increased significantly across the pack-year categories, in a dose-dependent association. When smokers were categorised according to the number of cigarettes smoked per day, statistically significant differences in the total WBC counts were found between light and moderate smokers, after controlling for confounders. Although no significant differences were found between light and heavy smokers, it is important to observe that the absolute differences between the means of the WBC counts in light and moderate smokers were the same of that between light and heavy smokers. The latter has not achieved statistical significance probably due to the small number or heavy smokers in the sample, in comparison to light and moderate smokers.

No significant differences were found for granulocytes, monocytes, and lymphocytes between light, moderate or heavy smokers.

Cigarette smoking is a well-known risk factor for atherosclerosis and CVD, as discussed before, and it has been recognized as the single most important factor known to influence the WBC count [SMITH et al., 2003]. A positive association between smoking

and WBC counts has long been established both in cross-sectional and prospective studies [CORRE et al., 1971; TAYLOR et al., 1985; SUNYER et al., 1996; OGAWA et al., 1998; JENSEN et al., 1998; FERNÁNDEZ et al., 2012]. Flouris and colleagues [FLOURIS et al., 2012] reported an acute effect of cigarette smoking on the total and differential WBC counts. They found that both active and passive smoking increased WBC, lymphocyte, and granulocyte counts for at least one hour ($p < 0.05$). Likewise, Van Tiel and colleagues [VAN TIEL et al., 2002] found that in smokers who refrained to smoke within 24 hours preceding the blood collection, the counts of total and differential WBC were closer to that observed in non-smokers.

The WBC count has been long correlated with CHD and is considered a biomarker of inflammatory processes that contribute to endothelial dysfunction and atherosclerosis progression [RUGGIERO et al., 2007; MADJID et al., 2004]. It was observed that a decrease in the WBC count of 1,000 cells/mm^3 (1.0 x 10^9 cells/L) corresponded to a decrease of 14% in the risk of CHD, after controlling for possible confounders, including smoking [GRIMM et al., 1985].

Among the WBC subpopulations, granulocytes and monocytes are thought to be more strongly involved in the pathogenesis of CHD and atherosclerosis [LEE et al., 2001]. A high monocyte count was found to be strongly associated with the risk of CHD in the Paris Prospective Study II [OLIVARES et al., 1993]. After adjustment for other classical risk factors, each increase in the monocytes of 100 cells/mm^3 was associated with an increase of about 15% (1.15 times) in the risk of CHD.

Mechanisms by which the WBC count contributes to the progression of these diseases include proteolytic and oxidative damage to coronary arteries, impaired blood flow through the cardiac microvasculature, and abnormal leukocyte aggregation [MADJID et al., 2004]. In addition, an increased WBC count has been positively associated with other markers of the MetS, such as elevated levels of insulin, TAG, and fasting glucose, elevated systolic and diastolic blood pressure, and lower levels of HDL-C [MADJID et al., 2004; LEE et al., 2001; ISHIZAKA et al, 2007]. Higher counts of WBC in smokers are also generally associated with increased levels of C-reactive protein, fibrinogen, IL-6 and TNF-α, perpetuating a state of low-grade inflammation [FRÖHLICH et al., 2003; MADJID et al., 2004; WATANABE et al., 2011].

The results of this study are in accordance with previous studies that found a strong relationship between cigarette smoking and the total and differential WBC count. Since the participants were screened during a preventive health check-up at their workplace, it is assumed they were free of any acute health problem known to influence the WBC counts and other blood parameters.

5.2.3. Strengths and limitations of the study

This study has strengths and limitations. The strengths are the large sample size with a wide age range (19–65 years), and the use of validated questionnaires for the assessment of smoking status and lifestyle—including diet, education level, and physical activity. Therefore adjustment for important confounders could be performed.

The limitations were the cross-sectional design of the study—which does not allow one to infer about cause and effect—and the use of self-reported weight and height, which could introduce bias to the study. However, several studies have demonstrated the validity and reliability of self-reported height and weight in different study populations [BOLTON-SMITH et al., 2000; SPENCER et al., 2002; WADA et al., 2005; BASTERRA-GORTARI et al., 2007; DEKKERS et al., 2008; STOMMEL and SCHOENBORN, 2009]. Moreover, self-reported BMI and measured WC were highly correlated in the present study, which suggests good quality of the present data.

Similarly, cigarette smoking was also self-reported, which could lead to some misclassification of smoking status. Several studies have confirmed that self-reported smoking is as a reliable tool for the assessment of smoking status [PATRICK et al., 1994; MCDONALD et al., 2005; WONG et al., 2012; KVALVIK et al., 2012]. However, the measurements of plasma, salivary, or urinary cotinine—the major metabolite of nicotine [PETERSEN et al., 2010]—would contribute to validate the self-reported smoking status and to measure the exposure to second-hand smoke in non-smokers.

Regrettably, the average daily number of cigarettes smoked by former smokers before they quitted was not available. This should be included in future studies to estimate the number of pack-years also in former smokers.

Unfortunately, information on alcohol consumption—usually higher in smokers and known to increase the risk of abdominal obesity and metabolic disturbances [ENGLISH et al., 1997; CHEN et al., 2012]—could not be assessed because such approaches were considered inappropriate as part of a health check-up at workplace.

For the same reasons, the monthly income of the employees could not be assessed. Income is a factor known to be independently associated with smoking [HUISMAN et al., 2005] and to influence food choices and lifestyle of individuals [WAGSTAFF, 1986; CHOU et al., 2004; LALLUKKA et al., 2007]. However, considering that the employees of the company in this study have medium or high levels of education, their income may follow their higher qualification and it is not likely that a wide gap exists between them.

5.3. Conclusion

In this sample of healthy employees in Vienna, smoking status was not associated with total adiposity (body weight and BMI) or with patterns of central body fat distribution. However, the number of cigarettes smoked per day showed a positive association with total adiposity. A positive and significant association of smoking (current smoking status, pack-years of cigarettes and number of cigarettes smoked per day) with dyslipidaemia, and higher counts of total WBC was observed. The levels of fasting glucose also increased significantly with the number of cigarettes smoked per day. This altered metabolic profile in smokers can lead to several diseases, including T2DM, CHD, and cancer.

Given the well-established harms of active and passive cigarette smoking and the high prevalence of smoking in Austria, it is urgent—from a public health perspective—to implement health policies for tobacco use prevention and control, in addition to provide strong support for smoking cessation. This is in agreement with the guidelines proposed by the World Health Organization Framework Convention on Tobacco Control (WHO FCTC), ratified by Austria in 2005 [WHO FRAMEWORK CONVENTION ON TOBACCO CONTROL, 2012].

6. ZUSAMMENFASSUNG

Hintergrund: Während in vielen Ländern die Prävalenz des Rauchens bei Männern abnimmt, steigt sie bei Frauen an. Einer der Gründe für dieses Phänomen ist, dass das Rauchen von vielen Frauen als Unterstützung zur Gewichtskontrolle gesehen wird. Obwohl es Studien gibt, die zeigen, dass Raucher in der Regel ein geringeres Körpergewicht haben als Nichtraucher, gibt es auch zunehmend Hinweise, dass das Rauchen mit abdominaler Fettleibigkeit und weiteren Risikofaktoren des metabolischen Syndroms, wie Dyslipidämie, Hyperglykämie und Bluthochdruck, assoziiert ist.

Ziel: Den Zusammenhang zwischen Rauchen, abdominaler Adipositas und weiteren Markern einer metabolischen Dysfunktion in einer Stichprobe von gesunden österreichischen Erwachsenen zu untersuchen.

Teilnehmer und Methoden: Es wurde eine Querschnittsstudie mit 986 österreichischen Erwachsenen (405 Männer und 581 Frauen) durchgeführt, die zustimmten, im Rahmen ihrer jährlichen Gesundenuntersuchung am Arbeitsplatz an dieser Studie teilzunehmen. Es wurden Informationen über Körpergewicht, Größe, Body-Mass-Index (BMI), Taillenumfang, Hüftumfang, Taille-Hüft-Verhältnis, Taille-zu-Körpergröße-Verhältnis, Rauchen, Bildungsniveau, körperliche Aktivität, Ernährung und biochemische Parameter (Nüchternblutglucose, Serumlipide und Lipoproteine, Gesamt-und Differentialblutbild der weißen Blutkörperchen) erhoben.

Ergebnisse: Es wurden keine Unterschiede beim Gesamtkörperfett und /oder der Körperfetterteilung zwischen den Nichtrauchern, Rauchern und Ex-Rauchern gefunden, aber bei den Personen die täglich rauchten zeigte die Anzahl der gerauchten Zigaretten pro Tag einen signifikanten positiven Zusammenhang mit dem Körpergewicht (p = 0,001) und BMI (p = 0,009). Raucher hatten häufiger Stoffwechselstörungen als Nichtraucher und ehemalige Raucher, und diese Störungen korrelierten positiv mit der Intensität und Dauer des Rauchens.

Diskussion und Schlussfolgerung: Obwohl in der vorliegenden Studie abdominale Adipositas nicht mit dem Raucherstatus assoziiert war, war bei Rauchern die Anzahl der gerauchten Zigaretten pro Tag positiv und signifikant mit Körpergewicht und BMI assoziiert. Das ungünstige metabolische Profil, welches bei Rauchern beobachtet wurde,

lässt auf einen Entzündungszustand schließen, der das Risiko von Herz-Kreislauf-Erkrankungen und Typ-2-Diabetes mellitus erhöht. Die Prävention des Rauchens bei Nichtrauchern und Raucherentwöhnung bei Rauchern sollten stark gefördert werden.

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8. APPENDIX

8.1. Self-administered questionnaire used in the study.

1 – QUESTIONS TO YOUR PERSON

Age: _____ years

Height: _____ cm

Body weight: _____ kg

Gender: ❑ Female ❑ Male

How many persons live in your household (you included)? _____ persons.

What is your highest complete education?

- ❑ Elementary school
- ❑ Primary school/lower level AHS
- ❑ Vocational school (Teaching)/Intermediate technical and vocational school (no Secondary School degree)
- ❑ Vocational high school/academic upper secondary (with Secondary School degree)
- ❑ University/College
- ❑ Other (please, specify): _____

2 – BODY/ HEALTH

2.1. Are you taking at the moment:

2.1.1. Lipid-lowering medications? (e.g. Statins etc.)

- ❑ Yes
- ❑ No
- ➢ <u>If YES</u>,

Which one(s) (medication's name): _____

Since when: _____

2.1.2. Glucose-lowering medications? (e.g. insulin, sulfonylurea, metformin, etc.)

- ❑ Yes
- ❑ No
- ➢ <u>If YES</u>,

Which one(s) (medication's name): _____

Since when: _____

2.1.3. Medications for high blood pressure?

- ❑ Yes
- ❑ No
- ➢ If YES,

Which one(s) (medication's name): _____

Since when: _____

2.1.4. Other medications?

- ❑ Yes
- ❑ No
- ➢ If YES,

Which one(s)/how often? _____

2.1.5. Are you currently taking nicotine replacement products?

- ❑ Yes
- ❑ No
- ➢ If YES,

Which one(s)?

❑ Nicotin Patch ❑ Nicotin gum ❑ Nicotine inhaler ❑ Nicotin nasal spray

Since when: _____ How often? _____

2.2. Are you currently taking vitamin and/or mineral supplements? (e.g. Centrum®, Supradyn®, Multibionta®; Magnosolv®) or red clover extracts, flavonoids, aloe vera gel?

- ❑ Yes
- ❑ No
- ➢ If YES,

Which one(s)/how often? _____

2.3. Questions for women (Men: go to 2.4)

2.3.1. Are you currently taking hormonal contraceptives?

- ❑ Yes
- ❑ No

2.3.2. Are you pregnant?

- ❑ Yes
- ❑ No

2.3.3. Are you currently undergoing hormonal therapy?

- ❑ Yes
- ❑ No

2.3.4. Do you have biological children?

- ❑ Yes
- ❑ No
- ➢ If YES,

How many?_____ children

2.4. How would you describe your overall health?

	Excellent	Very good	Good	Moderate	Poor
	❑	❑	❑	❑	❑

2.5. How would you describe your current overall health compared to the last year?

	Much better	Now a little better	Similar	Now a little worse	Now much worse
	❑	❑	❑	❑	❑

2.6. How right or wrong are the following statements for you?

	Absolutely right	Mostly right	Do not know	Mostly wrong	Absolutely wrong
I get sick more easily than other people	❑	❑	❑	❑	❑
I am as healthy as everyone else	❑	❑	❑	❑	❑
I expect that my health will deteriorate	❑	❑	❑	❑	❑
My health is excellent	❑	❑	❑	❑	❑

2.7. Have you suffered in recent times from any of the following problems?

	YES	NO
Diabetes	❑	❑
➢ If YES: insulin-dependent diabetes?	❑	❑
Cardiovascular diseases (“angina pectoris”, heart attack, stroke, poor circulation in the legs, atherosclerosis, etc.)	❑	❑
Cancer	❑	❑
Elevated blood lipids or cholesterol	❑	❑
Gout, elevated uric acid	❑	❑
High blood pressure (even if on medication)	❑	❑
Constipation	❑	❑
Gastro-intestinal diseases (gastritis, enteritis, etc.)	❑	❑

Osteoporosis (bone loss)	❑	❑
Joint diseases (arthritis, osteoarthritis, rheumatism, etc.)	❑	❑
Respiratory diseases	❑	❑
➢ If YES: ❑ asthma ❑ bronchitis ❑ COPD ❑ emphysema	❑	❑
Liver or biliary diseases (liver cirrhosis, fatty liver, hepatitis, etc.)	❑	❑
Kidney disease	❑	❑
Other (please specify):_____	❑	❑
Operations	❑	❑
➢ If YES: please specify:_____	❑	❑

3 – SMOKING

3.1. Have you ever smoked daily?

- ❑ Yes
- ❑ No

3.2. Have you smoked at least 100 cigarettes in your entire life?

- ❑ Yes
- ❑ No

3.3. How old were you when you first started to smoke cigarettes fairly regularly?
_____ years old.

When more than one smoke episode, age of the first episode.

3.4. Do you smoke now?

- ❑ Yes, daily * Go to 3.7
- ❑ Yes, occasionally
- ❑ No

3.5. How long has it been since you quit smoking?

- ❑ Less than a month ago
- ❑ A month ago to less than one year
- ❑ If more than one year, please indicate the years: _____years

3.6. Did you apply for help to stop smoking?

- ❑ No help
- ❑ Help of a doctor or therapist
- ❑ Help of a drug (including nicotine patches, gum, inhaler)
- ❑ Other

3.7. On average, how many cigarettes, cigars, pipes or other tobacco products do you smoke per day?

_____/day

In a cigarette box there are 20 cigarettes included

3.8 Which of the following products do you smoke often?

A – Cigarette from the box	❑ Yes	❑ No
B – Hand-rolled cigarettes	❑ Yes	❑ No
C – Whistle	❑ Yes	❑ No
D – Cigars/ cigarillos	❑ Yes	❑ No
E – Other products	❑ Yes	❑ No

3.9. Has a physician or other health care professional advised you to quit smoking during the last year?

❑ Yes

❑ No

3.10. How soon after you wake up do you smoke?

❑ Within 5 minutes
❑ From 6 to 30 minutes
❑ From more than 30 min to 1 hour

3.11. Which cigarette would you hate most to give up?

❑ The first in the morning
❑ Any other

3.12. Do you smoke more frequently during the first hours after waking up than during the rest of the day?

❑ Yes

❑ No

4 – PHYSICAL ACTIVITY

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

4.1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ days per week

☐ No vigorous physical activities → ***Skip to question 3***

4.2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

4.3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ days per week

☐ No moderate physical activities → ***Skip to question 5***

4.4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

4.5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ days per week

☐ No walking → ***Skip to question 4.7***

4.6. How much time did you usually spend walking on one of those days?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

4.7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

5 – 24-h-RECALL

Meal	What did you eat and drink yesterday?	Exact amount
Breakfast	*Did you think about the beverages?* Where? ❑ at home ❑ elsewhere	
Morning snack	Where? ❑ at home ❑ elsewhere	
Lunch	*Did you think about the beverages?* Where? ❑ at home ❑ elsewhere	
Afternoon snack	Where? ❑ at home ❑ elsewhere	
Dinner	*Did you think about the beverages?* Where? ❑ at home ❑ elsewhere	
Late meal	Where? ❑ at home ❑ elsewhere	

My meals were today (please, check one)

❑ As always ❑ differently than usual

How do I fill out a 24-h recall?

Please write down **EVERYTHING** you have **EATEN** and **DRUNK** in the previous day!

And so it is done:

1. **Describe** all the food or beverage as accurately as possible. For example:

   Yogurt 1%, Wholemeal bread with sesame seeds, peeled apple, Hot Dog with Ketchup, Banana milk with sugar, tee with lemon, etc.
   If you wish, you can also inform the name and brand, e.g., *Iglo* Fisch fingers, *Milka* chocolate, *Nöm* cocoa, *Manner Schnitten*.

2. Estimate the **portion size** so accurately as possible:

The accompanying photos can help you to better estimate the portion size. The portion size “small”, “medium” and “large” can be found in the pictures.

Of course you can also specify the amounts consumed by using household measures, such as:

- Tee spoon, tablespoon
- Slice of bread, piece (of apple, for instance)
- Cup, glass, bowl, plate => see photos.
- If you know the exactly amount, you can of course specify the serving size in grams (g) or mililiter (mL), and so on.

8.2. Other results

Table 18: Anthropometric characteristics of non-smokers and former smokers stratified by years of cessation.

		Former smokers stratified by years since cessation				*p*-value
	Non-Smokers	1–5	6–10	11–20	>20	
	n = 456	*n* = 75	*n* = 52	*n* = 60	*n* = 39	
Height, cm	171.9 ± 8.6	173.3 ± 8.1	172.3 ± 9.7	172.7 ± 8.8	172.5 ± 7.8	0.476
Body weight, kg	71.8 ± 13.4	73.4 ± 13.5	73.8 ± 14.6	76.7 ± 15.6	77.3 ± 12.5	0.916
BMI, kg/m^2	24.2 ± 3.6	24.3 ± 3.5	24.8 ± 4.4	25.6 ± 4.3	25.9 ± 3.5	0.728
WC, cm	86.9 ± 10.9	87.5 ± 11.4	88.9 ± 12.3	90.1 ± 13.3	92.0 ± 10.9	0.736
HC, cm	97.9 ± 8.7	97.1 ± 9.0	98 ± 10.2	100.6 ± 10.4	100.0 ± 8.9	0.908
WHR	0.887 ± 0.07	0.903 ± 0.10	0.907 ± 0.07	0.896 ± 0.07	0.920 ± 0.07	0.299
WHtR	0.506 ± 0.06	0.507 ± 0.06	0.519 ± 0.08	0.520 ± 0.07	0.533 ± 0.07	0.552
Overall						0.145

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio. Values are shown as mean ± SD; *p*-value determined by multivariate ANOVA and adjusted for age.

Table 19: Anthropometric characteristics of smokers and former smokers stratified by years of cessation.

		Former smokers stratified by years of cessation				
	Smokers	1–5	6–10	11–20	>20	***p*-value**
	n = 303	*n* = 75	*n* = 52	*n* = 60	*n* = 39	
Height, cm	171.5 ± 8.7	173.3 ± 8.1	172.3 ± 9.7	172.7 ± 8.8	172.5 ± 7.8	0.670
Body weight, kg	71.8 ± 13.6	73.4 ± 13.5	73.8 ± 14.6	76.7 ± 15.6	77.3 ± 12.5	0.756
BMI, kg/m^2	24.3 ± 3.5	24.3 ± 3.5	24.8 ± 4.4	25.6 ± 4.3	25.9 ± 3.5	0.424
WC, cm	86.9 ± 10.8	87.5 ± 11.4	88.9 ± 12.3	90.1 ± 13.3	92.0 ± 10.9	0.341
HC, cm	97.4 ± 8.1	97.1 ± 9.0	98 ± 10.2	100.6 ± 10.4	100.0 ± 8.9	0.924
WHR	0.891 ± 0.07	0.903 ± 0.10	0.907 ± 0.07	0.896 ± 0.07	0.920 ± 0.07	0.060
WHtR	0.507 ± 0.06	0.507 ± 0.06	0.519 ± 0.08	0.520 ± 0.07	0.533 ± 0.07	0.168
Overall						0.077

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio. Values are shown as mean ± SD; *p*-value determined by multivariate ANOVA and adjusted for age.

Table 20: Anthropometric characteristics of the daily smokers by years of smoking.

	Years of Smoking				
	1–10 (n = 58)	11–20 (n = 61)	21–30 (n = 83)	≥31 (n = 49)	*p*-value
Body weight, kg	69.1 ± 13.4	72.0 ± 12.7	72.3 ± 14.6	72.9 ± 13.6	0.838
BMI, kg/m	23.3 ± 3.3	24.1 ± 3.2	24.6 ± 3.7	25.2 ± 3.5	0.949
WC, cm	83.2 ± 9.4	87.1 ± 9.7	87.2 ± 12.1	89.7 ± 11.8	0.546
HC, cm	94.9 ± 8.8	97.8 ± 6.4	97.9 ± 9.4	98.6 ± 8.2	0.788
WHR	0.878 ± 0.07	0.890 ± 0.07	0.889 ± 0.07	0.908 ± 0.08	0.255
WHtR	0.485 ± 0.05	0.509 ± 0.06	0.509 ± 0.07	0.525 ± 0.07	0.528
Overall					0.957

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio. GLM adjusted for age and number of cigarettes smoked per day. Values are shown as mean ± SD.

9. CURRICULUM VITAE

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Education	
Since 2007	Doctoral Student: Nutritional Sciences
2001	Updating in Nutrition, Dietetic and Diet therapy Federal University of Viçosa (Brazil) and University of Navarra (Spain)
1996	Master in Food Science and Technology - Federal University of Viçosa (Brazil) Title of the Thesis: "*Development of a dietary supplement for athletes*" Supervisor: Prof. Dr. José Carlos Gomes
1991	Nutritionist Federal University of Viçosa (Brazil)

Publications

1. FONTES, LO; MONTEIRO, JBR. Sport nutrition: a review. Revista Mineira de Educação Física 1997;.5(2):22-30

FONTES, LO, MONTEIRO, JBR; COSTA, NMB. Nutritional aspects related to the premenstrual syndrome: a reflexion. Cadernos de Nutrição 1996; 12:31–42.

Post Presentations

FONTES, LO; GOMES, JC; MONTEIRO, JBR; COELHO, DT. Development of a dietary supplement for athletes. In: Congresso Brasileiro de Ciência e Tecnologia de Alimentos (SBCTA), 1996, Poços de Caldas, Minas Gerais. Resumo do Congresso Brasileiro de Ciência e Tecnologia de Alimentos XV SBCTA, 1996. p.40–40

FONTES LO, ELMADFA I, MOSHAMMER H. Smoking and metabolic syndrome. In: European Respiratory Society (ERS) Annual Conference. 2012, Vienna. P1982

Work Experience	
1998–2005	Consultant in Social Welfare II Company of Technical Assistance and Rural Extension of the State of Minas Gerais (EMATER-MG) Technical assistance provided in rural communities to farming organizations and small farmers and their families in agricultural activities, home food industry, handcraft, food and nutrition, basic hygiene (sanitation) and environment preservation.
2004–2005	Visiting Professor Centro Universitário de Belo Horizonte- UNIBH -Belo Horizonte, MG - Brazil Supervision of university students during training in public health in a rural area.
1999–2005	Clinical Nutritionist at Private Practice– Viçosa-MG, Ipanema-MG Diet planning and nutritional advise.
1992–1993	Administrative nutritionist at Caipa Comercial Agrícola Ltda. Ipatinga-MG, Brazil Menu planning, monitoring the food preparation, estimation and purchase of food supplies and equipment receiving, checking and taking inventories of provisions.

Memberships

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