HAROKOPIO UNIVERSITY

School of Health Science and Education

Department of Nutrition and Dietetics

Postgraduate Program (P.P.) in Applied Nutrition and Dietetics

Discipline of Clinical Nutrition

Diet and physical activity indices in relation to insulin levels in families at high risk for type 2 diabetes in Europe

Master Thesis

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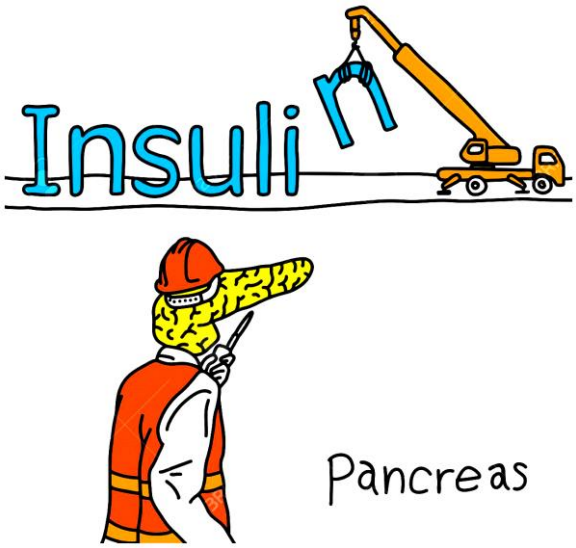

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ΧΑΡΟΚΟΠΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ

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ABSTRACT

Type 2 diabetes (T2D) is one of the most common metabolic diseases worldwide and its prevalence is estimated to be 8.8%. Previous lifestyle intervention programs have been reported to prevent or delay the onset of diabetes among high-risk populations, such as those with impaired glucose tolerance. The effect of lifestyle factors either combined or separately on glucose metabolism and insulin resistance have been studied both in healthy and T2DM individuals. Aim of this study is to investigate the most dominant behaviors associated with glucose and insulin levels and insulin resistance in adults at high risk for developing T2DM from families in a large sample from 6 European countries

Logistic and linear regression models were used to test the associations of lifestyle factors (diet, physical activity) with glucose and insulin levels, insulin resistance calculated by HOMA-IR, at the baseline, in total sample and according to region (Central North and southeast Europe), SES (0-14 years and >15 years of education) and age (<45 and >45 years). All regression models were adjusted for sex and smoking and were stratified by low and high risk group based on the FINDRISC score >12. BMI was also added to the analysis to detect those factors predominantly associated with the dependent variables independently from all variables tested and from BMI.

In the high risk group, BMI was the predominant independent factor positively associated with glucose, insulin and insulin resistance in the total sample. Regarding glucose levels, high consumption of juices with sugar (β=0.15, 95% CI 0.06-1.27) was positively associated with glucose in the total sample, in southeast Europe, in low SES and in participants< 45years. Regarding insulin resistance, increased consumption of refined cereal (OR= 5.69, 95% CI 1.73-18.77) was positively associated with insulin resistance in the total sample and in the low SES group. In addition to refined cereals, juices with sugar, high BMI values and low intake of fruits and juices without sugar were factors positively associated with increased risk for insulin resistance in the age group <45 years of high risk individuals.

Among all the behaviors examined, BMI, high consumption of juices with sugar and refined cereals seem to be the predominant risk factors positively associated with glucose levels and insulin resistance in adults at high risk for diabetes. Therefore, future prevention programs should aim to early identify these behaviors and efficiently tackle risk for T2DM.

ΠΕΡΙΛΗΨΗ

Ο σακχαρώδης διαβήτης τύπου 2 (ΣΔ2) αποτελει μία από τις πιο κοινές μεταβολικές ασθένειες παγκοσμίως με επιπολασμός 8,8%. Τα τελευταία χρόνια προγράμματα παρέμβασης στον τρόπο ζωής πέτυχαν την πρόληψη ή την καθυστέρηση της εμφάνισης του διαβήτη σε πληθυσμούς υψηλού κινδύνου όπως εκείνοι με διαταραγμένη ανοχή στη γλυκόζη. Οι επιδράσεις των παραγόντων του τρόπου ζωής είτε συνδυαστικά είτε μεμονομένα στον μεταβολισμό της γλυκόζης και στην αντίσταση στην ινσουλίνη έχουν μελετηθεί τόσο σε υγιή όσο και σε άτομα με διαβήτη. Σκοπός της παρούσας μελέτης είναι η διερεύνηση των κυριότερων συμπεριφορών που σχετίζονται με τα επίπεδα γλυκόζης και ινσουλίνης και την αντίσταση στην ινσουλίνη σε φαινομενικά υγιείς ενήλικες, οι οποίοι όμως έχουν υψηλό κίνδυνο ανάπτυξης διαβήτη από οικογένειες σε μεγάλο δείγμα από 6 ευρωπαϊκές χώρες.

Πολυπαραγοντικά μοντέλα λογιστικής και γραμμικής παλινδρόμησης χρησιμοποιήθηκαν για τον έλεγχο της συσχέτισης σημαντικών συμπεριφορών (διατροφή και άσκηση) με τα επίπεδα γλυκόζης, ινσουλίνης και της αντίστασης στην ινσουλίνη που βασίστηκε στον υπολογισμό του HOMA-IR, στη συγχρονική φάση της παρέμβασης Feel4Diabetes, στο συνολικό δείγμα και σε επιμέρους κατηγορίες όπως ανά περιοχή (Κεντρική Βόρεια και Νοτιοανατολική Ευρώπη), κοινωνικοοικονομικό επίπεδο (ως έτη εκπαίδευσης: 0-14 ετών και> 15) και ηλικία (<45 και> 45 ετών). Όλα τα μοντέλα παλινδρόμησης διορθώθηκαν ως προς το φύλο και το κάπνισμα και αναλύθηκαν σε 2 ομάδες: χαμηλού και υψηλού κινδύνου με κατώφλι στο FINDRISC σκορ το 12. Επίσης, προστέθηκε στην ανάλυση ο δείκτης μάζας σώματος (ΔΜΣ) για να ανιχνεύσει τους επικρατέστερους παράγοντες που συνδέονται κυρίαρχα με τη γλυκόζη και την αντίσταση στην ινσουλίνη ανεξάρτητα από όλες τις υπό έλεγχο μεταβλητές και το ΔΜΣ.

Όσον αφορά την ομάδα υψηλού κινδύνου, ο ΔΜΣ ήταν ένας από τους ισχυρότερους ανεξάρτητους παράγοντες που συσχετίστηκε θετικά με τα επίπεδα γλυκόζης και ινσουλίνης και την ινσουλινοαντίσταση στο συνολικό δείγμα. Σε ότι αφορά τη γλυκόζη, η υψηλή κατανάλωση χυμών με ζάχαρη (β= 0,15, 95% CI 0,06-1,27) συσχετίστηκε θετικά με τα επίπεδα γλυκόζης στο συνολικό δείγμα, στη νοτιοανατολική Ευρώπη, στο χαμηλό κοινωνικοοικονομικό επίπεδο και σε συμμετέχοντες <45 ετών. Σε ότι αφορά την αντίσταση στην ινσουλίνη, η αυξημένη κατανάλωση επεξεργασμένων δημητριακών (OR= 5,69, 95% CI 1,73-18,77) συσχετίστηκε θετικά με το HOMA-IR στο συνολικό δείγμα και στην ομάδα με χαμηλό

κοινωνικοοικονομικό επίπεδο. Εκτός από τα επεξεργασμένα δημητριακά, οι χυμοί με ζάχαρη, οι υψηλές τιμές ΔΜΣ και η χαμηλή πρόσληψη φρούτων και χυμών χωρίς ζάχαρη ήταν παράγοντες που συσχετίστηκαν επίσης θετικά με αυξημένο κίνδυνο για ινσουλινοαντίσταση σε <45 ετών ατόμων υψηλού κινδύνου.

Μεταξύ όλων των συμπεριφορών που εξετάστηκαν, ο ΔΜΣ, η υψηλή κατανάλωση χυμών με ζάχαρη και επεξεργασμένων δημητριακών αποτελούν τους κυρίαρχους παράγοντες κινδύνου που σχετίζονται με τα επίπεδα γλυκόζης και την ινσουλινοαντίσταση σε ενήλικες με αυξημένο κίνδυνο για διαβήτη. Συνεπώς, τα μελλοντικά προγράμματα πρόληψης του ΣΔ2 θα πρέπει να ανιχνεύουν αυτούς τους παράγοντες προκειμένου να δράσουν με αποτελεσματικότητα στη μείωση του κινδύνου για εμφάνιση ΣΔ2.

TABLE LIST

ABBREVIATIONS

T2DM	Type 2 Diabetes Mellitus
GDM	Gestational Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
BMI	Body Mass Index
TV	Television
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
HbA1c	Hemoglobin A1c
CVD	Cardiovascular Disease
FPG	Fasting plasma glucose
GI	Glycemic Index
GL	Glycemic Load
ADA	American Diabetes Association
DM	Diabetes Mellitus
BMI	Body Mass Index
MUFA	Monounsaturated fatty acids
PUFA	Polyunsaturated fatty acids
HOMA-IR	Homeostasis model assessment for insulin resistance
SFA	Saturated fatty acids
SSBs	Sugar-sweetened Beverages
GLP-1	glucagon-like peptide-1
GI	glycemic index
GL	glycemic load
ADF	Alternate day fasting
CR	Calorie restriction
IF	Intermittent fasting
AHEI	Alternative Healthy Eating Index
AE	Aerobic Exercise
RT	Resistance Training
PA	Physical Activity
EBRBs	energy balance related behaviors
2hPG	2-hour plasma glucose

1. INTRODUCTION

1.1 THE BASIC BACKGROUND IN DIABETES

1.1.1 DEFINITION AND TYPES

Diabetes Mellitus is a metabolic condition comprised of heterogeneous types and characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. Hyperglycemia over the long term can cause damage, dysfunction and failure to various body organs, leading to disabling and life-threatening health complications such as cardiovascular disease, neuropathy, nephropathy, retinopathy and blindness [2].

There are three main types of diabetes, type 1, type 2 and gestational diabetes (GDM). However, it can be further categorized to other types due to other causes [3]. Type 2 Diabetes (T2D) (90% of all cases) is manifested with hyperglycemia, derived from the disorders of insulin action and insulin secretion. The inability of the body to respond fully to insulin is defined as insulin resistance. During insulin resistance, insulin is ineffective and therefore initially induces an increase in insulin production to reduce rising glucose levels but over time a relative inadequate production of insulin can develop [2]. T2D is most commonly seen in older adults, but it becomes increasingly common in youth due to the epidemic of obesity, the rising rates of physical inactivity and poor diet. The symptoms may include increased thirst, frequent urination, tiredness, slow-healing wounds, recurrent infections and tingling or numbness in hands and feet [2].

1.1.2 PREVALENCE

Worldwide, some 451 million adults aged 18-99 years, mostly in low to middle income areas, are suffering from diabetes and 7.7% of adults aged 20-79 years have impaired glucose tolerance (IGT) [2]. In Europe in 2017, the prevalence of T2D was estimated at 8.8% and the prevalence of impaired glucose tolerance (IGT) was 5.5% [2]. Particularly in Greece, the

prevalence is 7.0%, possibly due to the rising rates of obesity and the induction of economic crisis [4].

1.1.3 RISK FACTORS

Type 2 Diabetes Mellitus (T2DM) is considered to be an outcome of the interaction of environmental, genetic, lifestyle and metabolic risk factors. Some of those factors can be modified while others cannot. Among the non-modifiable factors are ethnicity, family history of T2DM, puberty, low birth weight, previous gestational diabetes and older age. On the other hand, modifiable risk factors like overweight and obesity, unhealthy diet, low physical activity, sedentary lifestyle and smoking should be the main targets of prevention programs in order to tackle T2DM [5, 6]. The strongest risk factor for T2DM is excess body fat, an indicator of dietary habits and physical activity. Higher waist circumference and body mass index (BMI) are associated with increased risk of T2DM, with a variation among different populations. Populations in South-East Asia, for example, develop T2DM at a lower level of BMI than those in European origin [6]. High levels of physical activity decrease the relative diabetes risk, due to involvement in energy balance and weight management. While a sedentary lifestyle, indicated by prolonged TV(television) watching , is an important risk factor of T2DM, due to its direct relation with obesity and weight gain through lower energy expenditure and higher caloric intake [6-8]. In addition, higher consumption of coffee, whole grains, fruits, and nuts is associated with lower risk of diabetes, whereas regular consumption of refined grains, red and processed meats, and sugar-sweetened beverages including fruits juices is associated with increased diabetes risk [9, 10]. Moreover, smoking correlated with central obesity, increased oxidative stress and inflammation leads to insulin resistance and hyperglycemia, with the highest impact on heavy smokers. After its cessation, the risk remains elevated for about 10 years [6].

1.1.4 THE ROLE OF PREDIABETES IN THE EVOLUTION OF T2DM

Prediabetes is the intermediate metabolic phase of abnormal glucose regulation. It includes individuals with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both and Hemoglobin A1c (HbA1c) in the high normal range [11, 12]. IFG is associated with reduced

hepatic insulin sensitivity and first-phase insulin response, while IGT is associated with reduced peripheral insulin sensitivity, increased endogenous glucose production and first and second-phase insulin response [13]. Although individuals can spend years in a prediabetes stage, an expert American Diabetes Association (ADA) panel estimated that up to 70% of individuals with prediabetes will eventually progress to type 2 diabetes [14]. A meta-analysis of prospective cohort studies showed that the annual incidence of diabetes in people with IGT, IFG, or both was 6.1%, 7.0%, and 14.0%, respectively[15]. However, predictor risk factors for the transition from pre-diabetes to diabetes remained uncertain. A longitudinal study among American-Indians without diabetes, which proved that pre-diabetes at baseline is an independent predictor of transition to T2DM, showed that measures of baseline obesity, HbA1c, fasting blood glucose, 2-hour fasting plasma glucose, fasting insulin, albuminuria and insulin resistance can help to predict the transition [16]. Moreover, a nested cohort study among Mexican-Americans with pre-diabetes showed that deteriorating metabolic health and/or increasing BMI significantly raises the risk of transitioning from pre-diabetes to diabetes and vice versa, underlying the importance of lifestyle management to prevent the T2DM development [17].

2. THE IMPACT OF LIFESTYLE PARAMETERS IN HIGH-RISK ADULTS IN EUROPE FOR THE PREVENTION OF DIABETES

2.1 ENERGY, MACRONUTRIENTS AND MICRONUTRIENTS

Nutrient composition and a diet-induced modest weight loss or a healthy body weight maintenance can affect positively insulin sensitivity and β-cell function [18, 19] through controlled glycaemia, blood pressure, and lipids [20, 21]. Recent in vivo and in vitro studies in early T2DM report that low calorie diets may reduce ectopic fat and glucotoxitciy allowing the β-cell to rest and regenerate [22, 23]. According to prospective observational studies in non-diabetic individuals, the total carbohydrate intake in a diet does not appreciably influence diabetes risk. High fiber intake has been associated with a lower BMI and higher insulin sensitivity [24], with stronger evidence for insoluble fiber found in cereals [25, 26]. In interventions in high risk for T2DM groups, fiber may increase glucagon-like peptide-1 (GLP-1) or improve β-cell function through the colonic production of short-chain fatty acids [27]. In a meta-analyses of prospective studies in free of diabetes people at baseline, low GI (Glycemic

Index) and GL (Glycemic Load) diets lowered the risk for diabetes compared with diets with higher GI and GL [21]. Evidence from cohort studies reports that total and animal protein consumption are risk factors for T2DM, while plant protein protects only women against T2DM. Various high-protein foods have also a different effect on T2DM risk. [28]. According to ADA a usual protein intake should be 15 - 20% of total daily energy. A slightly higher intake (20–30% of total energy) of total protein have been reported to be beneficial for older adults, glucose control and weight loss in both diabetes and prediabetes [29, 30]. The amount and quality of dietary fat may also modify glucose tolerance and insulin sensitivity. Specifically, in different subtypes of pre-diabetes , higher intake of dietary SFA (saturated fatty acids) is linked to higher fasting and 2hPG (2 hour plasma glucose) concentration [31], while higher intake of MUFA (monounsaturated fatty acids) and PUFA (polyunsaturated fatty acids) with increased insulin sensitivity [32]. Further, controlled intervention studies report improvements in insulin sensitivity when SFA and TFA (trans-fatty acids) are replaced with MUFA or PUFA (especially linoleic acid) in healthy subjects. On the contrary, in subjects with IGT or T2DM outcomes in similar studies showed no significant differences in insulin sensitivity despite significant changes in plasma FA composition [33].

2.2 INDIVIDUAL FOODS AND FOOD GROUPS

Epidemiological studies, dietary interventions and metabolic studies support that the consumption of unrefined whole grain foods and legumes can protect healthy and high-risk for T2DM individuals against T2DM development and improve glycemic control in T2D cases. The diabetes risk reduction is evident even when foods containing as little as 25% whole grain are consumed [34]. The beneficial effects of whole grain foods lie in its insoluble fiber co-ingested with other nutrients and their low glycemic index [26, 35, 36]. On the other hand, legumes have small fat content, high content of vegetable protein, micronutrients, high dietary fiber content (90g or ½ cup boiled supplies 2-4g of mixture of soluble and insoluble) and low glycemic index [26]. According to large prospective studies in healthy participants, people consuming about three servings per day of whole grain foods are less likely to develop T2DM than those consuming less portions [34]. Additional prospective cohort studies in healthy populations conclude that the consumption of cereal fiber or mixtures of whole grains and bran is proved to reduce diabetes risk by 18% to 40% [36]. In two meta-analysis with many cohort studies in

common in healthy subjects, total intake of fruits and vegetables was also weakly associated with diabetes risk, but green leafy and root vegetable intake was associated with a significant lower risk [37, 38]. Moreover, data from three prospective cohort studies in US adults show that the consumption of specific whole fruits such as blueberries, grapes, and apples may improve the glucose metabolism and reduce significantly the diabetes risk [39]. Other Additional finding of the above studies was that frequent consumption of red meats, especially processed red meats due to their sodium content (nitrates, nitrites, nitrosamines) was strongly associated with higher diabetes risk. However, a meta-analysis of 6 prospective studies along with the above three showed that even a 100-g/d unprocessed red meat increase was associated with a 19% (95% CI: 4%, 37%) increased incidence of T2DM. Mechanisms responsible for that adverse effect involve the prooxidant effect of heme-iron [40].

A meta-analysis of cohort studies, three prospective cohorts of US men and women and an European large prospective case-cohort study in healthy participants all agreed that higher consumption of dairy products may marginally affect prevention of T2DM, with more consistent evidence for the benefits of fermented dairy products, such as yogurt [41, 42]. This stable effect is due to their probiotic properties on the antioxidant status and lipid profile [42]. Apart from calcium and vitamin D, experimental studies in both healthy and T2DM individuals have showed that milk proteins, such as whey proteins may enhance satiety and reduce the risk of overweight, high blood pressure and obesity [43]**.** A prospective study in men reported also that yogurt due to its insulinotropic properties and the relatively low GL may improve glucose tolerance and insulin sensitivity [44]**.** Moreover, in a prospective cohort study among older adults, circulating trans-palmitoleate concentrations in dairy products have been inversely associated with insulin resistance, atherogenic dyslipidemia and diabetes incident [45].

In a meta-analysis of 13 prospective studies across the world (US, Asia, Australia and Europe) in free of diabetes subjects, fish intake presents different associations with the risk of developing T2D, with no association among European studies [46]. It's basic bioactive compound, long-chain n-3 fatty acids may inhibit inflammatory pathways and suppress expression of genes related to lipid metabolism leading to reduced insulin resistance, according to intervention and epidemiological studies in healthy and overweight or obese participants. Fish is also great source of selenium and vitamin D, which are linked to diabetes risk [46, 47]. A meta-analysis of

prospective cohort studies in healthy adults show that frequent nut consumption, especially walnuts and peanuts [48, 49], can reduce the diabetes risk through glycemic control and weight management, mechanisms also observed from two meta-analysis of randomized trials in normal and high diabetes risk groups [50]. Nuts owe their effects to their bioactive nutrient composition. In a meta-analysis of randomized trials in high diabetes risk groups, the substitution of both carbohydrates and saturated fat with unsaturated fatty acids appeared to significantly decrease HbA1c, 2-h postprandial insulin, fasting insulin and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) [51]. In addition, it has been found in two intervention studies in subjects with normal and high fasting triglycerides that β-cells behave differently depending on the type – and possibly the amount – of dietary fatty acids, with SFAs inducing more insulin synthesis and secretion than MUFAs [52-54]**.**

In a meta-analysis of cohort studies in healthy and T2DM individuals and in a prospective European study, high consumption of sugar-sweetened beverages (SSBs) increases statistically significant the risk for T2D even after adjustment for BMI, total energy, and incident type 2 diabetes. They create a high GL leading to glucose intolerance, insulin resistance, β-cell dysfunction and inflammation. The advanced glycation end products, produced during the caramelization in cola-type beverages may also affect the pathophysiological pathways of T2D [55, 56]. A meta-analysis in healthy, pre-diabetic and diabetic participants found that isoenergetic fructose substitution resulted in a significantly slight reduction in fasting glucose, HbA1c, body weight, and triglycerides without adverse effects on blood lipids. [57, 58]. Two other meta-analysis of cohort studies in normal and T2DM cases showed that both caffeinated and decaffeinated coffee consumption has been consistently associated with a lower risk of diabetes in a dose-response manner [59, 60]. In short-term trials in healthy human subjects [61], the hyperglycemic effects of caffeine dominate over the possible beneficial effects of other components, while in long-term studies, its antioxidant and anti-inflammatory effects expressed improve glucose metabolism [59]. Apart from caffeine, other bioactive compounds also assist glucose metabolism [60]. In a population-based cohort study in healthy participants, the habitual coffee consumption improves consistently the insulin sensitivity through its effects on post-load rather than fasting glucose metabolism [62]. Moderate alcohol consumption, in a meta-analysis of epidemiological studies, decrease by 30% the diabetes risk possibly due to a U- or J-shaped relationship with either insulin sensitivity or plasma insulin concentrations [63, 64].

However, its chronic consumption may trigger the progression or development of T2D through impaired glucose metabolism, pancreatic β-cell dysfunction and apoptosis, as it is reported in a review of experimental studies in humans and animal models [65]. Additionally, a cross sectional study in Korean adults shows that its consumption is associated with diminished β-cell function, and correlate its high intake with an increased risk of hypertriglyceridemia in subjects with isolated decreased insulin sensitivity or decreased β-cell function [66].

2.3 DIETARY PATTERNS

Evidence from epidemiological studies revealed that dietary patterns high in fiber-rich plus white meat sources could protect against insulin resistance phenotypes. Opposite results display dietary plans rich in processed and red meat, refined cereals, and SFAs [20]. Mediterranean-style diets have been associated with lower incident of T2DM in prospective cohort studies in healthy or high cardiovascular risk subjects [67-70]. In the PREDIMED trial after a 4.1-year follow-up, participants with high cardiovascular risk assigned to a Mediterranean diet without calorie-restriction had a significant 40% diabetes risk reduction with extra-virgin olive oil supplementation and a non-significant 18% risk reduction with mixed nut supplementation compared to a low-fat control diet [68]. Adherence to the Dietary Approaches to Stop Hypertension (DASH) diet was also associated with lower diabetes risk in normal, impaired and diabetic populations [71, 72]. Further, a high quality diet assessed by the Alternative Healthy Eating Index (AHEI) was strongly associated with lower diabetes risk in healthy individuals from two cohort studies [73]. The effects of IF (Intermittent fasting) in high risk for T2DM groups on insulin sensitivity is unclear, with some trials showing benefit and others an adverse effect [74, 75]. However, a recent small trial concluded that restricting energy intake from 6:00 a.m. to 2:00 p.m. for 5 weeks in obese males with prediabetes improved insulin sensitivity and increased fat oxidation compared to usual energy intake [76]. Vegetarian diets (vegan, lacto ovo, semi-) were demonstrated to reduce diabetes risk in cohort studies with free of diabetes participants [77, 78].

2.4 EXERCISE AND SEDENTARY TIME

Insulin sensitivity may be improved from both short and long periods of physical activity in normal, high risk for T2DM and diabetic individuals. An acute bout of exercise has been shown to improve insulin sensitivity in both diabetic [79] and healthy cohorts [79-81], but this effect is transient and may be lost after 48 to 72 hours [79]. On the contrary, regular exercise enhances insulin sensitivity in individuals with T2DM due to adaptations in muscle insulin signaling and its magnitude may persist beyond 72 hours after the last exercise session. [82]. In addition to the favorable metabolic effects associated with regular exercise, epidemiological data from large prospective cohort studies in T2DM individuals indicate that moderate exercise, such as walking, and more vigorous activities, protects against T2DM development [83-85]. A clinical trial in healthy previously sedentary adults, showed also a positive dose-response relationship between the exercise performed (a combination of intensity, duration, and frequency) and the improvements in insulin sensitivity [86]. A review of exercise interventions in T2DM participants revealed that even if all the different types of exercise may improve insulin sensitivity at a variety of intensities and degrees, the most efficient training strategy is the combination AE (aerobic exercise) and RT (resistance training) [87]. On the contrary, one meta-analysis examined 10 studies (6 prospective) in healthy participants found that high amounts of sedentary time (TV) increase T2DM risk, independent of physical activity [88, 89]**.** Possible mediator of this result may be the strong association between sedentary behavior and unhealthy dietary habits, high BMI and even altered states of muscle contractile activity in healthy and high risk for T2DM groups [89, 90]**.**

Aim of this thesis: This work has been carried out with data collected within the Feel4Diabetes intervention. The aim of the EU-funded Feel4Diabetes-study was to develop, implement and evaluate a school- and community-based intervention promoting healthy eating and active lifestyle through the provision of a more supportive social and physical environment at home, school and municipality level as well as lifestyle counseling to the parents with increased T2DM risk. The observed benefits for the glucose homeostasis and insulin for the prevention of T2D in people at high risk rely on results from long term cohort studies and randomized controlled trials in general populations and people with T2DM and on diabetes prevention trials in high for T2DM risk individuals. They all converge on promoting patterns of food intake high in vegetables, fruit, whole grains, legumes, nuts, and dairy products such as yogurt, moderate in alcohol consumption, and lower in refined grains, red/processed meats, and sugar-sweetened

beverages. They also encourage the adoption of certain healthful dietary patterns such as the Mediterranean diet and highlight the importance of the quality of dietary fats and carbohydrates in comparison with their quantity. Despite much research on nutritional components and patterns in relation to the glucose metabolism and insulin, the relevant evidence for several individual food groups is not entirely clear yet. With regard to exercise, its beneficial effect at a variety of intensities and degrees in insulin sensitivity is definite among healthy and T2DM individuals in both short and long periods. On the contrary, prolonged sedentary lifestyle increases the risk for T2DM in the above groups and diminishes insulin function. However, both behaviors (diet and physical activity) need to be further examined for their efficacy in relation to glucose metabolism and insulin resistance in high risk people for developing T2DM, which are far less investigated with less evidenced conclusions. Therefore, the aim of this master dissertation is to investigate possible associations between lifestyle behaviors (diet, physical activity) with insulin, glucose levels and insulin resistance in adults at high risk for developing T2DM in a large sample from 6 European countries.

3. METHODOLOGY

3.1 Recruitment

The intervention was implemented within the academic years 2016-2017 and 2017-2018.The sample of the intervention was consisted of families (children, parents and grandparents) from "vulnerable" social groups from 6 European countries. As "Vulnerable" groups were defined people from low / middle income countries (Bulgaria, Hungary), from low socioeconomic regions to high income countries (Belgium, Finland) and from countries in economic crisis (Greece / Spain). In all countries, after taking the necessary approval(s) from local authorities (Ethical Committees, Ministries, Municipalities, etc.) lists of all primary schools clustered within the randomly selected “vulnerable” areas were created and primary schools were randomly selected from each area until the recruitment goal was met. Children attending the first three grades of compulsory education and their families (i.e. “all families”) were recruited to the study from these primary schools. The identification of the high-risk families was based on T2DM risk estimation using the Finnish Diabetes Risk Score (FINDRISC). To be regarded as a

“high-risk family”, at least one parent in the family had to fulfil the country-specific cut-off point.

3.2 The questionnaires and diagnostic tool FINDRISK

At the first phase of recruitment, a questionnaire including the FINDRISK tool was given to the parents and grandparents. The FINDRISK tool was completed by the parents (biological or adoptive) of the child who participated in the program and included six questions about a) age; b) weight; c) height; d) waist circumference; e) the existence of at least 30 minutes of physical activity daily f) daily consumption of fruits and vegetables. In addition to the FINDRISK tool, the questionnaire included questions about demographic (education, employment) and family status (the number and age of family members and the financial situation). Moreover, parents filled out both for themselves and for their child, a short Food Frequency Questionnaire (FFQ), questions about the frequency and quality of breakfast, and their physical activity. Finally, the questionnaire included questions about the availability of food at home, eating habits, the parent's psychological condition and the existence of electronic devices in the child's room. In Greece, to be regarded as a “high-risk family”, at least one parent in the family had to have a score of FINDRISC ≥9. The high risk families received additional questionnaires (one for parents and one for the children) about dietary habits and physical activity / sedentary life. The parents' questionnaire included also questions about demographic characteristics, educational level, smoking, sleeping hours, history of diabetes, history of hypertension, and history of cholesterol.

3.3 Final Sample

The FINDRISK tool divided the intervention into two levels. The first level referred to all families, regardless of the risk of developing T2D and included improvements to the social and physical environment of the school and home, municipal initiatives and a session with general guidelines for a healthy and active lifestyle. The second level aimed only at the high-risk families and consisted of seven counseling sessions out of the school environment and text messaging.

A minimum sample of 1,200 “all families” and 300 “high-risk families” per country, resulting in a total sample of 7,200 “all families” and 1,440 “high-risk families”, was initially targeted. However, to account for an estimated dropout rate of about 20%, a minimum total number of about 9,000 “all families” and 2,160 “high-risk families” were aimed to be recruited in the six participating countries. Finally, the study sample at baseline comprised of 11,511 “all-families” and 2,230 “high-risk families”.

3.4 Measurements

One parent from each high risk family was invited, apart from filling in a second questionnaire for him/herself and the child, to undergo anthropometric measurements (weight, height, and waist circumference), blood pressure measurement, and blood tests. They were also given pedometers or accelerometers to measure physical activity. In addition, the date of the assessments and any possible conditions during the measurements were recorded.

Physical activity (PA)

Step counts were assessed using pedometers (OMRON model HJ-720IT-E2 Walking style Pro and Omron HJ-322U-E Walking Style Pro 2.0 3D USB Accelerator Sensor Step Counter) or the step count function of accelerometers (GT1M ActiGraph, GT3X ActiGraph, GT3X+ ActiGraph, Traxmeet). Before the PA-monitors were handed out, they had to be reset and checked for proper fit and function. Regarding accelerometers, the 15-second epoch length needed to be selected. The volunteer had to be clipped with the main unit to the band or belt of the skirt, shorts or trousers and strap to the shorts or trousers. The PA-monitor had to positioned on the right hip, in line with the midpoint of the knee of the volunteer and be used for 6 days during walking hours. The first day (e.g. on Wednesday), the researchers had to fit and prepare the PA-monitor and thereafter, the device was worn for the next four consecutive days (e.g. on Thursday, Friday, Saturday and Sunday) (2 weekdays and 2 weekend days) and returned on the sixth day (e.g. on Monday). An activity diary had been handed over to the parents and measurements had to be obtained for both weekdays and weekend days. In case the device needed to be taken off, the reason and time had to be noted in the diary.

Height

Height measurement was carried out with a SECA 214, SECA 217, SECA 213, SECA 225 telescopic height measuring instrument. The volunteer, without shoes or any accessories, had to stand firmly in a natural position on the stadiometer, with the back facing it, the legs parallel touching each other and the heels slightly distant touching its back part and the back of the head, the shoulders, the buttocks and the heels touching or aligned with it. The head had to be focused on a fixed point in the straight line of the eyes and be in such a position that the Frankfort Plane line is parallel to the floor. The Frankfort Plane line is an imaginary straight line that connects the ear canal with the bottom of the eye socket. After a deep breath, the measurement was taken. If after the exhalation, the head was not in the correct position, the above procedure was repeated. The measurement was performed twice, and if the previous measurements differ > 1cm, a third measurement was conducted.

Weight

The weight was measured with an SECA 813, SECA 877 accredited electronic scale. Once the indication was 0, the volunteer had to stand without shoes or heavy objects, in the center of the platform with the back to the monitor, loose shoulders and remain still until the measurement is complete. The measurement was recorded at the value closest to the tenth of a kilogram (0,1Kg) and was performed twice. If the previous measurements differ >100g, a third measurement was conducted. In data analysis, the volunteers were categorized according to their Body Mass Index (BMI). BMI is calculated as the ratio of weight to square of height: BMI = weight (Kg) / (height) 2 (m2). The classification was based on the World Health Organization Criteria)[91]

Waist Circumstance

The waist circumference is an indicator of visceral fat and is related to fat-free mass. Waist is defined as the point midway between the iliac crest and the costal margin (lower rib). For the measurement, a non-elastic insertion tape calibrated in mm type SECA 201 was used. In order to locate those levels, the investigator used the fingers of the right hand held straight and pointing in front of the participant to slide upward over the iliac crest. Men's waists usually are above the top of their trousers whereas women's waists tend to be under the waistband of their trousers or skirts. Before the measurement, the volunteer was asked to empty his/her bladder, if possible, and was instructed to remove heavy objects and clothes to reveal the waist. If the volunteer did not feel comfortable, the measurement could be done with light

clothing and this information was recorded. The volunteer had to stand in a relaxed position with hands hanging loosely on the side of the body and the weight evenly distributed on both legs and breathe normally. With palpation, the correct measuring point was located and the tape was placed around the body in the same straight line along its length and loose enough enabling a finger to slip inside the tape. The investigator asked the volunteer to breathe out normally and the measurement was recorded at the end of a normal exhalation. The recording was to the nearest tenth of centimeter (i.e. 0.1 cm). The measurement was performed twice by the same researcher, and if the previous measurements differ> 1cm, a third measurement was conducted. Volunteers were categorized according to their waist circumference. The limits used are: <80cm or <94cm, 80-88cm or 94-102cm,> 88cm or> 102cm for women and men respectively [91].

Blood tests

Blood was collected from the volunteers to determine fasting glucose, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride (TAG) levels. Blood tests were performed on all volunteers in the morning (08:30-10:30 am) after twelve hours overnight fasting. A day before the blood tests, one investigator had to communicate with the parents to ensure the overnight fasting. The collection of blood samples (up to 16 mL of blood) was performed with venipuncture by professional staff. Some of the samples were left to coagulate for 30 to 120 minutes without the use of an anticoagulant to separate the serum. This blood was centrifuged at 3000 rpm for 10 minutes and the serum was divided into fractions and stored at -80 ° C. All serum samples were transferred to dry ice in the Dietetic and Clinical Dietetics Laboratory of Harokopio University of Athens where they were stored at -80oC.

Glucose was determined by the GOD-PAP enzymatic reaction (hexokinase method). For the diagnosis of pre-diabetes, dysglycemia and diabetes, the criteria of the World Health Organization [92] were used. Blood lipids were determined by an automatic analyzer (Roche / Hitachi Modular) twice, using the Enzymatic Colorimetric Analysis (Roche Diagnostics SA, Vasilia, Switzerland). HOMA-IR for estimating insulin resistance was calculated according to the formula: fasting insulin (microU/L) x fasting glucose (mmol/L)/22.5 [93]. HOMA-IR values > 2.05 define insulin resistance in high risk adults for DM. . This threshold is slightly lower than others in European healthy adult populations, with no metabolic risks taken into account [94, 95] and higher than values in non-European populations with metabolic risks[96]. It is also close to the

value (HOMA-IR ≥2.00) proposed by EGIR (the European Group for the Study of Insulin Resistance) from RISC study, yet proposed for healthy people with no signs or symptoms of disease [97]. However, after the completion of RISC study new data and research have emerged with new thresholds of HOMA-IR in various populations and by different methods. The threshold 2.05 of HOMA-IR was chosen based on a cross sectional study in a large and well characterized population based sample of non-diabetic Spanish adults with multiple metabolic risk factors, which best matched with the profile of the high risk group of this study [98, 99]. For those reasons the value 2.05 of HOMA-IR was estimated to be more suitable for the purpose of this study.

Blood Pressure

Accredited automated Omron M6 AC or Omron M6 devices, which recorded systolic and diastolic pressure and pulses / minute, were used to measure blood pressure. Each device was accompanied by 3 cuffs of a different size (the width and length of the armband should be at least 40% and 80% respectively of the arm circumference). The equipment was checked daily for any problems. Prior to the measurement, the investigator asked the volunteer whether he had consumed anything except water if he had smoked and if he had been physically active or diagnosed with atrial fibrillation. If the answer was positive to one of the above, it was recorded along with the measurement. The measurement was performed on the right hand, which was resting on a desk, so that the upper arm is at the level of the heart. The volunteer was sitting on a chair so the back rests and the legs form a right angle, without talking. The volunteer had to remain still and rest for 5 minutes, while at the same time the investigator explained the process to him and applied the appropriate cuff to his/her hand. The position of the cuff should be such that it is just above the elbow joint and based on the device's instructions. At the end of 5 minutes the investigator pressed the START button on the device and waited for the measurement to appear on the screen to record it. With the volunteer remaining in the same position, two more measurements were conducted with one minute between them.

3.5 Statistic Analysis

For the statistical analysis of the study data, SPSS 21.0 (SPSS: Statistical package for social sciences, SPSS Inc., Chicago, IL, USA) was used and the statistical significance level was set at $p \leq 0.05$. The categorical variables are presented as relative frequencies (%), while the

continuous variables as mean ± standard deviation (SD). The normality of distribution of variables was determined by the Kolmogorov – Smirnov test. To assess the possible independent associations of the dietary and physical activity variables with either fasting glucose or fasting Insulin levels, multivariate linear regression analysis was performed. The independent associations of the above mentioned factors with the existence of insulin resistance (calculated by HOMA-IR) was also tested by multiple logistic regression analysis. All the analyses were performed in the total sample as well as according to region, age and SES categories for both high and low risk for T2DM adults. Both of the above mentioned statistical analyses were simultaneously adjusted for smoking and sex in order to identify the most dominant behaviors independently associated with glucose, insulin and insulin resistance. BMI was added in both linear and logistic multivariate models in order to detect those factors independently associated with glucose, insulin or existence of insulin resistance from all the factors tested and BMI as well.

4. RESULTS

The following results were extracted from the sample of individuals who had completed all the necessary data.

4.1 Descriptive characteristics

The study sample consisted of 2500 adults with mean BMI 28.53 (±5.44) kg/m^2, mean glucose levels at 94.7 (± 14.11) mg/dL and mean insulin levels at 69.12 (± 62.41) pmol/L. In addition, the 41.9% of them had insulin resistance (HOMA-IR > 2.05). Also, 1550 adults were defined as low risk (FINDRISC<12) and 890 as high risk (FINDRISC>12). The high risk adults had higher values of BMI, waist circumference, glucose and insulin levels and insulin resistance compared to the low risk individuals. In Table 3a, baseline characteristics of the study population are presented.

Table 3a: The descriptive characteristics of the study sample.

Variables	**Total** (N=2500)	**FINDRISK<12** (N=1550)	**FINDRISK>12** (N= 890)
	Mean ±SD or relative frequencies (%)		
Age			
<45	76.1%	81.7%	66.4%
>45	23.9%	18.3%	33.6%
Gender			

Female	66.3%	66.7%	66.9%
Male	33.7%	33.3%	33.1%
Region			
Central, North Europe	28.5%	28.1%	29.2%
Southeast Europe	71.5%	71.9%	70.8%
SES (years of education)			
0-14	40.6%	38.7%	42.5%
>15	59.4%	61.3%	57.5%
Weight status			
<18.5 kg/m^2	0.6%	0.8%	0.2%
18.5-25 kg/m^2	27.4%	36.7%	11.1%
25-30 kg/m^2	35.5%	37.1%	32.3%
>30 kg/m^2	36.5%	25.4%	56.4%
BMI (kg/m^2)	28.53 (±5.44)	27.11 (±4.90)	31.03 (±5.38)
Waist circumference (cm)	94.68 (±14.30)	91.20 (±13.49)	100.88 (±13.62)
Tchol (mg/dL)	194.39 (±37.65)	192.33 (±36.79)	198.23 (±38.67)
LDL (mg/dL)	120.58 (±32.88)	118.21 (±32.36)	124.54 (±33.25)
HDL (mg/dL)	53.12 (±13.95)	54.56 (±14.46)	50.94 (±12.70)
TG (mg/dL)	109.17 (±85.07)	101.71 (±72.12)	122.82 (±104.39)
Glucose (mg/dL)	94.7 (± 14.11)	93.06 (±11.95)	97.78(±16.86)
Insulin (pmol/L)	69.12 (± 62.41)	60.91 (±45.08)	84.70 (± 78.05)
HOMA-IR			
<2.05	58.1%	65.5%	42.3%
>2.05	41.9%	34.5%	57.7%
SBP (mmHg)	117.77 (±16.66)	116.06 (±16.36)	120.93 (±16.98)
DBP (mmHg)	78.29 (±11.42)	77.08 (±11.13)	80.57 (±11.64)
Findrisc	10.27 (±4.06)	7.98 (±2.96)	14.23 (±2.25)
Low fat dairy (240mL/day)	0.82 (±1.19)	0.79 (±1,17)	0.90 (±1.25)
Full fat dairy (240mL/day)	0.43 (±0.76)	0.45 (±0,78)	0.42 (±0.4)
Vegetables (cups/day)	0.58 (±0.55)	0.60 (±0.56)	0.56 (±0.54)
Fruits and berries (cups/day)	0.52 (±0.51)	0.53 (±0.50)	0.50 (±0.52)
Refined cereals (30g)	0.16 (±0.59)	0.16 (±0,54)	0.15 (±0.69)
Whole grain cereals	0.47 (±0.89)	0.48 (±0,89)	0.45 (±0.85)
Legumes (cups/day)	0.28 (±0.25)	0.29 (±0,26)	0.28 (±0.24)
Red meat (g/day)	73.43 (±55,70)	70.40 (±50,69)	78.26 (±62.71)
White meat (g/day)	55.95 (±42,87)	54.69 (±41,04)	59.50 (±45.65)
Fish (g/day)	33.92 (±28.10)	33.81 (±27,83)	35.00 (±28.67)
Salty snacks (portions/day)	0.24 (±0.31)	0.23 (±0.28)	0.25 (±0.33)
Sweet snacks (40g/day)	0.57 (±0.73)	0.56 (±0.69)	0.58 (±0.74)
Nuts and seeds (30g/day)	0.31 (±0.49)	0.32 (±0.52)	0.28 (±0.42)
Coffee (250mL/day)	1.48 (±1.29)	1.47 (±1.22)	1.50 (±1.38)
Soft drinks with sugar (250mL/day)	0.20 (±0.48)	0.19 (±0.47)	0.21 (±0.49)
Soft drinks without sugar (250mL/day)	0.24 (±0.59)	0.22 (±0.58)	0.27 (±0.61)
Juice without sugar (250mL/day)	0.24 (±0.38)	0.25 (±0.36)	0.24 (±0.43)
Juice with sugar (250mL/day)	0.10 (±0.27)	0.09 (±0.27)	0.10 (±0.26)
Beer and cider (330mL/day)	0.26 (±0.58)	0.25 (±0.46)	0.26 (±0.52)
Wine (125mL/day)	0.18 (±0.35)	0.18 (±0,33)	0.17 (±0.39)
Spirits (40mL/day)	0.10 (±0.29)	0.09 (±0,25)	0.10 (±0.33)
MPA (min/day)	40.52 (±62.16)	40.16 (±61.61)	39.99 (±62.32)
VPA (min/day)	44.46 (±87.52)	44.27 (±86.31)	43.75 (±85.89)
Walking (min/day)	64.96 (±105.91)	66.22 (±105.55)	64.68 (±109.28)
Sitting (hours/day)	5.35 (±3.35)	5.26 (±3.34)	5.52 (±3.37)
Smoking status			
Never smoked	45.9%	48.2%	41.8%
Former smoker	28.3%	26.5%	31.8%
Current smoker	25.9%	25.3%	26.4%

Tchol (Total cholesterol), LDL (Low-density lipoprotein), HDL (High-density lipoprotein), SBP (systolic blood pressure), DBP (diastolic blood pressure), TG (triacylglycerols), MPA (moderate physical activity), VPA (vigorous physical activity), SES (Socioeconomic status).

4.2 Associations between dietary and physical activity factors, smoking and BMI with glucose, insulin and insulin resistance in the total sample in both low and high risk for T2DM adult groups.

BMI is positively and statistically significant associated with all the dependent variables tested (glucose, insulin and HOMA-IR) in both low and high risk group. In the high risk group, higher consumption of juices with sugar is positively associated with fasting glucose levels and consumption of refined cereal grains increases 5- 6 times the risk for developing insulin resistance, which remain significant even after adjustment with BMI. Also, higher consumption of refined cereals and higher BMI were the predominant risk factors positively associated with insulin levels independently from all the other variables tested and from gender. On the contrary, in the low risk groups BMI is the predominant factor positively and independently associated with insulin resistance (Table 3b).

Table 3b: Associations between dietary and physical activity factors, smoking and BMI with glucose, insulin and HOMA-IR is presented in the total sample of the study.

Variables (Total)	TOTAL					
	FINDRISK<12			FINDRISK>12		
	Glucose (mmol/L) (n=595)	**Insulin (mU/L)** (n=429)	**HOMA-IR**** (n=481)	**Glucose (mmol/L)** (n=275)	**Insulin (mU/L or µIU/mL)** (n=187)	**HOMA-IR** (n=209)
	Beta coefficients 95% CI		**Exp(B) 95% CI**	**Beta coefficients 95% CI**		**Exp(B) 95% CI**
Low fat dairy (cups/day, 240mL)	0.02 (-0.05-0.08)	0.01 (-0.60-0.75)	1.16 (0.88-1.52)	-0.03 (-0.17-0.10)	0.00 (-2.04-2.12)	1.13 (0.76-1.70)
Full fat dairy (cups/day, 240mL)	0.04 (-0.04-0.11)	-0.01 (-0.79-0.66)	0.90 (0.65-1.25)	0.03 (-0.18-0.30)	-0.03 (-3.56-2.42)	0.75 (0.40-1.40)
Vegetables (cups/day)	-0.05 (-0.15-0.04)	0.05 (-0.43-1.30)	1.16 (0.82-1.64)	-0.02 (-0.33-0.23)	0.02 (-2.66-3.54)	1.65† (0.83-3.27)
Fruits and berries (cups/day)	-0.07 (-0.23-0.03)	-0.07 (-1.93-0.45)	0.63 (0.37-1.07)	-0.07 (-0.51-0.16)	-0.07 (-4.87-2.25)	0.54 (0.25-1.17)
Refined cereals (30g)	0.02 (-0.10-0.15)	0.08 (-0.26-1.95)	1.15 (0.74-1.79)	0.06 (-0.16-0.42)	**0.23† (1.13-7.02)**	**5.69† (1.73-18.77)**
Whole grain cereals	0.00 (-0.06-0.07)	-0.04 (-0.78-0.36)	0.80 (0.61-1.05)	-0.02 (-0.17-0.13)	-0.04 (-2.31-1.49)	0.95 (0.66-1.38)
Legumes (cups/day)	-0.06 (-0.40-0.05)	-0.04 (-2.94-1.19)	0.58 (0.24-1.38)	-0.01 (-0.68-0.55)	-0.01 (-6.57-6.19)	0.31 (0.08-1.20)
Red meat (g/day)	-0.06 (-0.00-0.00)	0.08 (-0.00-0.02)	1.00 (0.99-1.01)	-0.09 (-0.00-0.00)	0.06 (-0.02-0.04)	1.00 (0.99-1.01)
White meat (g/day)	-0.02 (-0.00-0.00)	0.03 (-0.01-0.02)	1.00 (0.99-1.01)	0.07 (-0.00-0.01)	0.03 (-0.04-0.05)	1.00 (0.99-1.01)
Fish (g/day)	**0.10† (0.00-0.01)**	-0.04 (-0.04-0.02)	1.00 (0.98-1.01)	0.08 (-0.00-0.01)	-0.00 (-0.08-0.08)	1.01 (0.99-1.03)
Salty snacks (portions/day)	-0.03 (-0.21-0.10)	0.02 (-1.22-1.79)	0.99 (0.54-1.01)	-0.06 (-0.62-0.26)	0.01 (-4.08-4.75)	1.51 (0.57-4.01)
Sweet snacks (40g/day)	-0.04 (-0.12-0.05)	-0.02 (-0.90-0.57)	1.00 (0.75-1.34)	0.00 (-0.25-0.27)	0.06 (-1.97-3.64)	0.93 (0.54-1.59)
Nuts and seeds (30g/day)	0.04 (-0.05-0.15)	0.04 (-0.61-1.34)	1.26 (0.85-1.88)	0.03 (-0.20-0.32)	-0.06 (-3.75-1.76)	0.74 (0.42-1.30)
Coffee (250mL/day)	0.05 (-0.02-0.07)	-0.07 (-0.83-0.18)	0.88 (0.72-1.07)	0.01 (-0.11-0.12)	-0.06 (-2.14-1.05)	0.80 (0.57-1.12)
Soft drinks with sugar (250mL/day)	-0.03† (-0.19-0.10)	0.03† (-1.03-1.94)	0.90 (0.51-1.58)	0.04 (-0.32-0.57)	-0.02 (-5.96-4.67)	0.94 (0.32-2.78)
Soft drinks without sugar	0.02	0.09	1.06	0.01	-0.05	0.86

(250mL/day)	(-0.08-0.13)	(-0.09-1.82)	(0.73-1.53)	(-0.22-0.24)	(-3.25-1.68)	(0.53-1.40)
Juice without sugar (250mL/day)	0.02 (-0.13-0.21)	0.02 (-1.42-1.97)	0.99 (0.49-2.00)	0.11 (-0.07-0.91)	-0.06 (-9.00-3.95)	0.27 (0.07-1.07)
Juice with sugar (250mL/day)	0.04 (-0.11-0.29)	0.04 (-1.35-3.39)	0.82 (0.30-2.26)	**0.15† (0.06-1.27)**	0.00 (-8.77-8.77)	3.11† (0.43-22.68)
Beer and cider (330mL/day)	0.06 (-0.04-0.21)	-0.06 (-1.89-0.58)	0.81 (0.49-1.33)	0.08 (-0.17-0.59)	0.13 (-2.44-9.88)	2.38 (0.53-10.69)
Wine (125mL/day)	-0.06 (-0.32-0.06)	0.02 (-1.45-2.02)	0.99 (0.48-2.03)	-0.10 (-0.97-0.16)	-0.13 (-10.92-2.20)	0.28 (0.07-1.21)
Spirits (40mL/day)	0.01 (-0.22-0.27)	0.05 (-1.50-4.24)	1.62 (0.50-5.29)	-0.00 (-0.44-0.43)	-0.05 (-7.34-4.44)	1.70 (0.41-7.00)
MPA (min/day)	-0.06 (-0.00-0.00)	-0.04 (-0.01-0.01)	1.00 (0.99-1.00)	0.07 (-0.00-0.00)	-0.07 (-0.04-0.02)	1.00 (0.99-1.01)
VPA (min/day)	0.02 (-0.00-0.00)	-0.04 (-0.01-0.00)	1.00 (0.99-1.00)	-0.03 (-0.00-0.00)	-0.03 (-0.03-0.02)	1.00 (0.99-1.01)
Walking (min/day)	0.07 (-0.00-0.00)	0.05 (-0.00-0.01)	1.00 (0.99-1.00)	-0.08 (-0.00-0.00)	0.07 (-0.01-0.02)	1.00 (0,99-1.00)
Sitting (hours/day)	0.04 (-0.01-0.03)	-0.03 (-0.21-0.11)	0.95 (0.89-1.01)	0.03 (-0.03-0.05)	0.01 (-0.50-0.55)	0.98 (0.88-1.10)

In bold letters, are the statistically significant findings before the correction of the analysis with BMI.

*** statistically significant associations after correction for BMI.**

† statistically significant associations when also BMI has a significant association with the dependent variable.

**** BMI is the only variable with a statistical significant association with the dependent variable.**

4.3 Associations between dietary and physical activity factors, smoking and BMI with glucose, insulin and insulin resistance according to region, SES and age categories in both low and high risk for T2DM adult groups.

With regard to glucose levels, in the high risk group increased consumption of juice with sugar has a positive association in southeast Europe, in low SES groups and in participants <45years. In this later group (<45 years) BMI was also positively and independently associated with glucose levels, while these associations were not observed in the low risk group. Regarding insulin levels, in the high risk group increased BMI and high consumption of refined cereals were the most dominant variables independently associated with elevated insulin levels in southeast Europe and in high SES, while in the low risk group reduced BMI and increased coffee consumption were independently associated with reduced insulin levels in Southeast Europe, in high SES and in participants <45years of age. Also, increased BMI was the predominant factor for increased HOMA-IR values in the both Southeast and central North Europe in both low and high risk groups. Increased consumption of refined cereals together with increased BMI was strongly associated with insulin resistance in high risk, low SES groups. Also increased consumption of refined grains and juices with sugar and decreased consumption of fruits and juices without sugar together with increased BMI were positively associated with insulin resistance in high risk participants under 45 years of age.

Tables 3 c-e: Associations between dietary and physical factors, smoking and BMI with glucose (3c), insulin (3d) and HOMA-IR (3e) are presented according to region, SES and age in both low and high risk groups.

Variables	Fasting glucose (mmol/L)											
	FINDRISK <12						FINDRISK>12					
	Beta coefficients 95% CI											
	Central North Europe (n=187)	**Southeast Europe** (n=408)	**0-14** (n=251)	**>15** (n=344)	**<45** (n=500)	**>45** (n=95)	**Central North Europe** (n=101)	**Southeast Europe** (n=174)	**0-14** (n=132)	**>15** (n=143)	**<45** (n=193)	**>45** (n=82)
Low fat dairy (cups/day, 240mL)	0.03 (-0.12-0.18)	0.01 (-0.06-0.08)	0.07 (-0.05-0.14)	0.04 (-0.07-0.13)	0.06 (-0.02-0.09)	-0.06 (-0.53-0.54)	0.15 (-0.03-0.19)	-0.13 (-0.62-0.10)	-0.00 (-0.28-0.27)	0.01 (-0.13-0.14)	-0.02 (-0.20-0.15)	0.08 (-0.20-0.34)
Full fat dairy (cups/day, 240mL)	0.10 (-0.08-0.33)	0.01 (-0.06-0.08)	-0.04 (-0.11-0.06)	0.08 (-0.03-0.21)	0.08 (-0.00-0.13)	0.00 (-0.35-0.36)	0.12 (-0.08-0.41)	-0.07 (-0.52-0.21)	0.05 (-0.38-0.66)	0.03 (-0.21-0.28)	0.04 (-0.26-0.42)	0.05 (-0.28-0.42)
Fruits and berries (cups/day)	-0.14 (-0.65-0.09)	-0.01 (-0.12-0.11)	-0.07 (-0.23-0.08)	-0.06 (-0.30-0.09)	-0.07 (-0.18-0.03)	-0.17 (-1.53-0.49)	-0.08 (-0.53-0.25)	-0.06 (-0.62-0.31)	-0.05 (-0.84-0.55)	-0.11 (-0.53-0.14)	-0.05 (-0.59-0.30)	-0.16 (-0.71-0.18)
Refined cereals (30g)	-0.06 (-0.61-0.28)	0.07 (-0.03-0.18)	0.02 (-0.12-0.18)	0.02 (-0.16-0.24)	0.02 (-0.08-0.12)	0.04 (-1.41-1.88)	-0.12 (-0.73-0.19)	0.15 (-0.07-0.74)	0.14 (-0.19-1.15)	-0.05 (-0.35-0.20)	0.13 (-0.07-0.83)	-0.12 (-0.57-0.25)
Whole grain cereals	0.05 (-0.11-0.21)	-0.00 (-0.06-0.06)	-0.04 (-0.10-0.05)	0.00 (-0.10-0.10)	0.03 (-0.04-0.08)	-0.04 (-0.33-0.24)	-0.03 (-0.15-0.11)	0.00 (-0.29-0.30)	-0.10 (-0.51-0.15)	-0.04 (-0.19-0.13)	-0.03 (-0.24-0.16)	0.03 (-0.21-0.26)
Legumes (cups/day)	-0.09 (-1.37-0.37)	-0.07 (-0.34-0.06)	0.04 (-0.19-0.36)	-0.08 (-0.60-0.09)	-0.07 (-0.35-0.04)	-0.07 (-1.85-1.20)	0.01 (-1.88-2.07)	-0.13 (-1.46-0.17)	0.01 (-1.04-1.11)	0.06 (-0.55-0.95)	0.00 (-0.91-0.94)	-0.01 (-0.78-0.75)
Red meat (g/day)	**-0.19† (-0.01--0.00)**	0.08 (-0.00-0.00)	0.02 (-0.00-0.00)	-0.09 (-0.00-0.00)	-0.03 (-0.00-0.00)	-0.14 (-0.01-0.00)	-0.14 (-0.01-0.00)	-0.11 (-0.01-0.00)	-0.09 (-0.01-0.00)	0.03 (-0.00-0.00)	-0.18† (-0.01--0.00)	0.20 (-0.00-0.01)
White meat (g/day)	-0.08 (-0.01-0.00)	-0.07 (-0.00-0.00)	-0.12 (-0.00-0.00)	0.01 (-0.00-0.00)	-0.02 (-0.00-0.00)	-0.04 (-0.01-0.01)	-0.01 (-0.01-0.01)	0.10 (-0.00-0.01)	0.12 (-0.00-0.01)	-0.03 (-0.00-0.00)	0.09 (-0.00-0.01)	0.08 (-0.01-0.01)
Fish (g/day)	**0.21† (0.00-0.03)**	0.02 (-0.00-0.00)	0.01 (-0.00-0.00)	**0.16* (0.00-0.01)**	**0.12† (0.00-0.06)**	0.07 (-0.01-0.02)	0.15 (-0.00-0.01)	0.04 (-0.01-0.01)	-0.04 (-0.01-0.01)	**0.20 (0.00-0.02)**	0.18 (-0.00-0.02)	-0.15 (-0.02-0.00)
Salty snacks (portions/day)	-0.03 (-0.49-0.33)	-0.01 (-0.16-0.13)	0.06 (-0.10-0.23)	-0.09 (-0.55-0.05)	**-0.09 (-0.35--0.01)**	-0.03 (-0.60-0.50)	-0.09 (-1.16-0.57)	-0.07 (-0.76-0.37)	-0.08 (-1.82-0.88)	-0.00 (-0.39-0.38)	-0.03 (-0.64-0.45)	-0.24 (-1.91-0.12)
Sweet snacks (40g/day)	-0.02 (-0.19-0.14)	**-0.11 (-0.20--0.01)**	0.02 (-0.09-0.12)	-0.05 (-0.17-0.07)	-0.05 (-0.11-0.03)	-0.02 (-0.42-0.34)	0.00 (-0.35-0.36)	-0.01 (-0.38-0.34)	-0.08 (-0.81-0.39)	-0.03 (-0.28-0.21)	-0.02 (-0.38-0.32)	0.12 (-0.23-0.64)
Nuts and seeds (30g/day)	0.05 (-0.16-0.27)	-0.01 (-0.12-0.09)	0.01 (-0.10-0.11)	0.04 (-0.11-0.23)	0.05 (-0.04-0.13)	-0.01 (-0.63-0.59)	0.00 (-0.39-0.39)	0.03 (-0.29-0.42)	0.13 (-0.18-0.71)	-0.06 (-0.43-0.22)	-0.05 (-0.51-0.25)	0.16 (-0.12-0.55)
Coffee (250mL/day)	-0.02 (-0.11-0.08)	0.03 (-0.04-0.08)	0.09 (-0.02-0.10)	0.04 (-0.04-0.09)	0.05 (-0.02-0.06)	0.04 (-0.21-0.29)	-0.03 (-0.10-0.07)	0.05 (-0.17-0.30)	0.08 (-0.14-0.28)	-0.01 (-0.13-0.11)	0.02 (-0.12-0.16)	0.11 (-0.13-0.29)
Soft drinks with sugar (250mL/day)	-0.07 (-0.46-0.19)	0.08 (-0.03-0.26)	-0.04 (-0.25-0.13)	-0.01* (-0.23-0.18)	0.00 (-0.12-0.13)	-0.03 (-1.10-0.86)	-0.09 (-0.56-0.23)	0.11* (-0.32-1.24)	0.09 (-0.57-1.19)	-0.04 (-0.64-0.41)	0.05 (-0.45-0.79)	0.17 (-0.32-1.12)
Soft drinks without sugar (250mL/day)	0.04 (-0.13-0.23)	0.07 (-0.05-0.30)	**-0.16† (-0.34--0.04)**	0.10 (-0.01-0.26)	0.01 (-0.08-0.10)	0.04 (-0.39-0.52)	-0.12 (-0.27-0.07)	**0.17 (0.04-1.22)**	-0.02 (-0.39-0.31)	0.06 (-0.22-0.43)	0.04 (-0.21-0.35)	0.15 (-0.21-0.78)
Juice without sugar (250mL/day)	0.07 (-0.25-0.72)	-0.00 (-0.16-0.14)	0.08 (-0.07-0.33)	-0.02 (-0.33-0.22)	0.04 (-0.07-0.21)	-0.08 (-1.39-0.69)	0.17 (-0.06-0.87)	0.11 (-0.29-1.26)	0.12 (-0.35-1.46)	0.13 (-0.14-0.87)	0.09 (-0.26-1.00)	0.08 (-0.50-0.97)
Juice with sugar (250mL/day)	0.12 (-0.12-0.96)	-0.06 (-0.30-0.06)	-0.01 (-0.34-0.29)	0.06 (-0.13-0.41)	-0.05 (-0.31-0.07)	0.24 (-0.04-1.64)	0.08 (-0.36-0.80)	**0.23* (0.23-2.18)**	**0.31* (0.48-2.70)**	-0.16 (-1.23-0.15)	**0.22† (0.24-1.90)**	-0.10 (-1.17-0.51)
Beer and cider (330mL/day)	**0.24† (0.09-**	-0.01 (-0.12-	-0.04 (-0.21-	**0.12* (0.00-**	0.01 (-0.10-	0.21 (-0.15-	**0.29* (0.03-**	0.06 (-0.51-	-0.03 (-1.02-	0.15 (-0.10-	0.01 (-0.50-	0.23 (-0.11-

	0.78)	0.10)	0.12)	**0.35)**	0.12)	1.14)	**0.76)**	0.94)	0.80)	0.62)	0.58)	0.96)
Wine (125mL/day)	-0.17 (-1.15-0.01)	-0.03 (-0.21-0.12)	0.03 (-0.21-0.32)	-0.09 (-0.49-0.05)	-0.07 (-0.28-0.04)	-0.01 (-1.17-1.07)	-0.17 (-1.24-0.12)	-0.03 (-0.97-0.73)	0.06 (-0.82-1.40)	-0.17 (-1.22-0.08)	-0.02 (-0.86-0.71)	**-0.26 (-1.57--0.04)**
Spirits (40mL/day)	0.04 (-0.75-1.21)	-0.03 (-0.27-0.14)	-0.03 (-0.48-0.31)	0.03 (-0.23-0.43)	0.03 (-0.13-0.29)	-0.12 (-2.18-0.81)	0.11 (-0.17-0.53)	-0.06 (-1.34-0.70)	-0.03 (-1.02-0.75)	0.01 (-0.45-0.48)	0.05 (-0.52-0.91)	0.01 (-0.55-0.59)
MPA (min/day)	-0.10 (-0.00-0.00)	-0.05 (-0.00-0.00)	-0.07 (-0.00-0.00)	-0.06 (-0.00-0.00)	-0.06 (-0.00-0.00)	-0.01 (-0.01-0.01)	-0.03 (-0.00-0.00)	0.13 (-0.00-0.01)	0.10 (-0.00-0.01)	-0.05 (-0.00-0.00)	0.12 (-0.00-0.01)	0.02 (-0.00-0.00)
VPA (min/day)	-0.00 (-0.00-0.00)	0.02 (-0.00-0.00)	0.07 (-0.00-0.00)	-0.01 (-0.00-0.00)	0.04 (-0.00-0.00)	-0.07 (-0.01-0.00)	0.10 (-0.00-0.00)	-0.13 (-0.01-0.00)	0.02 (-0.00-0.00)	0.07 (-0.00-0.00)	-0.03 (-0.00-0.00)	-0.03 (-0.00-0.00)
Sitting (hours/day)	0.08 (-0.03-0.07)	0.06 (-0.01-0.03)	0.13† (-0.00-0.04)	0.00 (-0.03-0.03)	0.02 (-0.01-0.02)	0.13 (-0.05-0.14)	0.12 (-0.02-0.07)	0.02 (-0.06-0.07)	-0.02 (-0.10-0.08)	0.11 (-0.02-0.08)	-0.01 (-0.06-0.05)	0.09 (-0.06-0.10)

In bold letters, are the statistically significant findings before the correction of the analysis with BMI.

*** statistically significant associations after correction for BMI.**

† statistically significant associations when also BMI has a significant association with the dependent variable.

**** BMI is the only variable with a statistical significant association with the dependent variable.**

Variables	**Fasting Insulin (mU/L)**											
	FINDRISK <12						**FINDRISK>12**					
	Beta coefficients 95% CI											
	Central North Europe (n=95)	**Southeast Europe** (n=334)	**0-14** (n=206)	**>15** (n=223)	**<45** (n=358)	**>45** (n=71)	**Central North Europe** (n=36)	**Southeast Europe** (n=151)	**0-14** (n=105)	**>15** (n=82)	**<45** (n=124)	**>45** (n=63)
Low fat dairy (cups/day, 240mL)	0.07 (-1.73-2.77)	0.03 (-0.57-0.85)	0.11 (-0.36-1.83)	-0,01 (-1.05-0.87)	0.01 (-0.64-0.81)	0.12 (-1.51-3.29)	0.04 (-1.98-2.23)	-0.06 (-5.01-2.94)	-0.03 (-3.82-3.10)	-0.02 (-3.55-3.01)	0.02 (-2.44-2.93)	-0.30 (-9.61-2.16)
Full fat dairy (cups/day, 240mL)	0.10 (-1.87-3.68)	-0.07 (-1.21-0.27)	-0.11 (-1.80-0.25)	0.05 (-0.67-1.46)	-0.02 (-1.07-0.72)	0.16 (-0.57-2.04)	0.11 (-6.94-9.70)	-0.04 (-4.44-2.80)	-0.07 (-6.80-3.75)	-0.04 (-4.89-3.86)	-0.07 (-6.02-3.18)	-0.09 (-6.00-3.51)
Fruits and berries (cups/day)	-0.30 (-9.13-0.81)	-0.06 (-1.71-0.61)	-0.02 (-1.88-1.43)	-0.10 (-3.00-0.61)	-0.06 (-1.98-0.62)	-0.33 (-7.41-0.61)	0.07 (-7.17-8.45)	-0.08 (-6.12-2.71)	-0.07 (-7.97-5.06)	-0.14 (-7.41-2.54)	-0.12 (-7.28-2.37)	-0.02 (-6.77-5.90)
Refined cereals (30g)	0.08 (-3.69-6.25)	0.05 (-0.66-1.47)	0.08 (-0.70-2.53)	0.07 (-0.92-2.39)	0.08 (-0.36-1.98)	-0.02 (-7.58-6.41)	0.44 (-1.56-9.49)	**0.27† (1.13-8.91)**	0.14 (-2.97-10.08)	**0.35† (0.86-7.98)**	0.13 (-1.75-7.29)	**0.50† (0.82-12.62)**
Whole grain cereals	0.05 (-1.25-2.25)	-0.08 (-1.06-0.19)	-0.03 (-0.96-0.65)	-0.09 (-1.39-0.37)	-0.01 (-0.77-0.61)	-0.21 (-1.96-0.52)	-0.04 (-2.10-1.79)	-0.01 (-3.11-2.76)	-0.06 (-5.20-3.21)	0.03 (-2.01-2.46)	-0.10 (-3.39-1.26)	0.05 (-4.00-5.26)
Legumes (cups/day)	-0.00 (-8.09-8.03)	-0.03 (-2.74-1.56)	-0.06 (-4.16-1.90)	0.02 (-2.71-3.36)	-0.02 (-2.67-1.99)	-0.18 (-8.95-2.68)	-0.37 (-75.93-33.59)	-0.01 (-8.36-7.54)	0.01 (-9.94-10.57)	-0.05 (-11.67-8.38)	0.03 (-9.01-11.18)	-0.05 (-11.82-8.53)
Red meat (g/day)	-0.06 (-0.05-0.03)	**0.15 (0.00-0.03)**	**0.22† (0.01-0.04)**	-0.00 (-0.02-0.02)	0.09 (-0.00-0.03)	-0.12 (-0.04-0.02)	0.21 (-0.07-0.11)	0.10 (-0.02-0.05)	0.08 (-0.04-0.06)	0.07 (-0.03-0.05)	-0.13 (-0.06-0.02)	0.35 (-0.00-0.12)
White meat (g/day)	-0.06 (-0.06-0.04)	0.02 (-0.01-0.02)	-0.14 (-0.04-0.01)	0.15 (-0.00-0.05)	-0.01 (-0.02-0.02)	0.19 (-0.02-0.07)	-0.05 (-0.06-0.05)	0.04 (-0.05-0.07)	0.09 (-0.06-0.11)	-0.08 (-0.07-0.04)	0.11 (-0.04-0.08)	0.04 (-0.10-0.13)
Fish (g/day)	-0.03 (-0.16-0.13)	-0.03 (-0.03-0.02)	-0.02 (-0.05-0.04)	-0.06 (-0.06-0.03)	-0.03 (-0.04-0.03)	-0.15 (-0.09-0.03)	-0.08 (-0.16-0.14)	-0.04 (-0.13-0.10)	-0.05 (-0.14-0.10)	-0.02 (-0.16-0.15)	0.07 (-0.09-0.16)	-0.16 (-0.21-0.07)
Salty snacks (portions/day)	-0.24 (-13.75-1.73)	0.09 (-0.33-2.52)	0.10 (-0.70-2.76)	-0.07 (-5.18-1.90)	-0.08 (-4.25-0.70)	0.14 (-1.47-3.15)	-0.30 (-21.54-12.10)	0.03 (-4.80-5.96)	-0.14 (-19.20-6.46)	0.10 (-3.33-6.22)	-0.08 (-7.13-3.83)	-0.30 (-25.97-

												2.40)
Sweet snacks (40g/day)	0.01 (-1.64-1.76)	-0.10 (-1.76-0.17)	0.02 (-1.03-1.39)	-0.03 (-1.21-0.80)	-0.01 (-0.93-0.81)	-0.15 (-2.14-0.63)	0.40 (-3.31-9.03)	0.05 (-2.72-4.32)	0.09 (-4.28-8.50)	0.08 (-2.28-3.96)	0.21 (-0.93-6.63)	-0.15 (-8.91-3.55)
Nuts and seeds (30g/day)	0.28 (-0.86-5.50)	0.02 (-0.95-1.28)	-0.06 (-1.58-0.74)	0.09 (-0.78-3.08)	0.04 (-0.67-1.44)	-0.02 (-4.05-3.64)	-0.12 (-9.49-6.85)	-0.04 (-3.97-2.68)	-0.06 (-4.98-3.12)	-0.10 (-6.78-3.01)	-0.12 (-6.20-2.04)	0.02 (-4.46-4.94)
Tea (250mL/day)	-0.26 (-3.78-0.28)	-0.08 (-1.58-0.31)	0.00 (-0.95-0.99)	**-0.18† (-3.10- -0.34)**	-0.05 (-1.25-0.51)	-0.10 (-2.19-1.09)	-0.33 (-10.36-6.48)	-0.07 (-5.94-2.71)	-0.08 (-7.40-4.10)	0.08 (-2.91-5.02)	-0.02 (-5.09-4.18)	-0.11 (-6.86-3.35)
Coffee (250mL/day)	-0.09 (-1.63-0.82)	-0.04† (-0.77-0.39)	-0.12† (-1.35-0.16)	-0.03 (-0.85-0.61)	-0.09† (-1.04-0.09)	0.25† (-0.20-2.26)	0.32 (-3.00-4.90)	-0.05 (-2.91-1.75)	-0.09 (-4.09-2.09)	0.02 (1.90-2.24)	-0.15 (-3.62-0.58)	0.08 (-2.63-4.15)
Soft drinks with sugar (250mL/day)	0.10 (-2.37-4.67)	-0.04 (-2.58-1.31)	0.03 (-1.73-2.43)	0.05 (-1.59-2.99)	0.07† (-0.71-2.64)	-0.04 (-4.18-3.21)	0.10 (-4.99-6.66)	-0.07 (-11.32-5.63)	-0.09 (-12.50-7.24)	0.16 (-3.18-12.13)	-0.15 (-11.58-2.49)	**0.51† (1.12-25.93)**
Soft drinks without sugar (250mL/day)	0.07 (-1.55-2.54)	0.09 (-0.40-3.19)	0.09 (-0.74-2.74)	**0.15 (0.02-2.54)**	**0.13 (0.21-2.46)**	-0.22 (-3.45-0.38)	-0.11 (-2.63-1.86)	0.00 (-5.63-5.84)	-0.08 (-4.40-2.33)	0.00 (-6.17-6.36)	-0.06 (-3.76-2.26)	0.13 (-5.05-11.59)
Juice without sugar (250mL/day)	-0.01 (-6.03-5.81)	0.07 (-0.73-2.73)	0.14 (-0.20-4.36)	-0.05 (-3.75-1.78)	0.01 (-1.78-2.04)	-0.01 (-4.38-3.99)	-0.03 (-12.37-11.31)	-0.05 (-10.28-6.02)	-0.22 (-19.43-1.12)	0.15 (-4.53-15.46)	-0.17 (-15.22-1.93)	0.12 (-7.56-16.76)
Juice with sugar (250mL/day)	-0.06 (-9.88-6.16)	0.09 (-0.47-4.33)	0.02 (-3.78-4.83)	0.05 (-2.07-4.28)	0.02 (-2.23-3.10)	**0.41 (1.20-14.51)**	0.49 (-1.93-18.47)	-0.03 (-13.72-10.55)	0.09 (-10.12-19.65)	-0.14 (-18.49-6.43)	0.17 (-4.33-21.26)	**-0.39† (-36.34--1.46)**
Beercider (330mL/day)	0.09 (-3.39-5.44)	-0.08 (-2.16-0.41)	-0.13 (-3.97-0.71)	-0.00 (-1.64-1.55)	-0.06 (-1.99-0.75)	0.02 (-3.21-3.51)	0.62 (-6.92-22.95)	0.20 (-2.07-14.46)	0.04 (-9.22-11.57)	0.22 (-2.79-15.44)	-0.03 (-9.68-8.23)	0.14 (-7.15-15.31)
Wine (125mL/day)	-0.15 (-10.39-4.62)	0.02 (-1.40-2.06)	0.12 (-1.19-5.37)	-0.01 (-2.46-2.15)	0.02 (-1.55-2.33)	-0.16 (-6.84-2.95)	-0.27 (-15.43-8.23)	-0.13 (-13.46-3.84)	-0.07 (-13.57-9.28)	**-0.31† (-21.01--0.97)**	-0.03 (-10.35-8.25)	-0.15 (-16.11-6.61)
Spirits (40mL/day)	0.14 (-6.36-17.21)	0.03 (-2.31-3.43)	-0.05 (-5.96-3.03)	0.10 (-1.51-6.60)	0.04 (-2.16-4.38)	0.01 (-6.80-7.26)	-0.06 (-8.84-7.76)	-0.11 (-14.70-5.14)	0.03 (-7.56-9.19)	**-0.29 (-24.17--0.73)**	0.10 (-4.41-10.18)	-0.35 (-31.25-2.31)
MPA (min/day)	-0.11 (-0.04-0.02)	-0.01 (-0.01-0.01)	-0.03 (-0.01-0.01)	-0.08 (-0.02-0.01)	-0.03 (-0.01-0.01)	-0.10 (-0.03-0.02)	-0.25 (-0.07-0.04)	-0.07 (-0.05-0.02)	-0.00 (-0.05-0.05)	-0.11 (-0.06-0.03)	-0.07 (-0..05-0.03)	0.10 (-0.04-0.07)
VPA (min/day)	0.09 (-0.03-0.05)	-0.07 (-0.01-0.00)	-0.04 (-0.01-0.01)	0.04 (-0.01-0.02)	-0.04 (-0.01-0.01)	-0.20 (-0.03-0.01)	0.37 (-0.09-0.18)	-0.07 (-0.04-0.02)	-0.04 (-0.04-0.03)	0.11 (-0.03-0.07)	0.02 (-0.03-0.04)	-0.31 (-0.10-0.03)
Sitting (hours/day)	0.18 (-0.33-1.12)	-0.05 (-0.23-0.09)	-0.07 (-0.32-0.13)	-0.01 (-0.30-0.25)	-0.04 (-0.24-0.13)	-0.18 (-0.62-0.17)	-0.21 (-1.48-0.95)	-0.00 (-0.68-0.67)	0.02 (-0.89-1.00)	0.07 (-0.63-1.02)	-0.03 (-0.86-0.68)	-0.00 (-1.07-1.06)
Smoking status	0.03 (-2.50-2.98)	-0.08 (-1.06-0.23)	0.04 (-0.70-1.15)	-0.14 (-1.99-0.08)	-0.07 (-1.16-0.33)	-0.13 (-2.08-0.77)	0.16 (-3.05-5.34)	-0.14 (-4.19-0.60)	-0.12 (-4.83-1.55)	0.01 (-2.75-2.90)	-0.11 (-4.00-1.21)	-0.21 (-7.46-2.18)

After the classification into the different categories (region, SES, age), in age group >45 years old in both low and high risk groups and in region group Central/North Europe in high risk adults, the sample emerged was small.

In bold letters, are the statistically significant findings before the correction of the analysis with BMI.

*** statistically significant associations after correction for BMI.**

† statistically significant associations when also BMI has a significant association with the dependent variable.

**** BMI is the only variable with a statistical significant association with the dependent variable.**

Variables	HOMA-IR											
	FINDRISK <12						FINDRISK>12					
	Exp(B) 95% CI											
	Central North Europe** (n=109)	**Southeast Europe**** (n=372)	**0-14** (n=229)	**>15** (n=252)	**<45** (n=404)	**>45** (n=77)	**Central North Europe** (n=46)	**Southeast Europe**** (n=163)	**0-14** (n=117)	**>15** (n=92)	**<45** (n=138)	**>45** (n=71)
Low fat dairy (cups/day, 240mL)	1.61 (0.72-3.60)	1.27 (0.91-1.78)	1.44 (0.87-2.38)	1.18 (0.80-1.75)	1.15 (0.85-1.55)	3.48 (25-48.75)		0.76 (0.37-1.55)	1.11 (0.61-2.05)	1.37 (0.44-4.30)	1.52 (0.84-2.77)	0.04 (0.00-1.37)
Full fat dairy (cups/day, 240mL)	0.54 (0.18-1.60)	0.95 (0.66-1.39)	0.64 (0.38-1.10)	0.99 (0.60-1.63)	0.74 (0.49-1.12)	5.00 (0.81-30.80)		0.66 (0.34-1.31)	0.65 (0.23-1.84)	0.54 (0.12-2.42)	0.54 (0.20-1.49)	0.60 (0.07-4.76)
Fruits and berries (cups/day)	**0.10 (0.01-0.82)**	0.65 (0.36-1.17)	0.69 (0.32-1.50)	0.64 (0.28-1.45)	0.71 (0.41-1.23)	0.00 (0.00-1.24)		0.59 (0.25-1.38)	**0.24 (0.06-0.97)**	2.28 (0.36-14.47)	**0.17† (0.04-0.69)**	1,98 (0.31-12.54)
Refined cereals (30g)	1.60 (0.36-7.07)	1.14 (0.69-1.88)	1.32 (0.66-2.63)	1.01 (0.53-1.95)	1.13 (0.71-1.81)	5.38 (0.00-7.18)		**8.58 (1.75-42.02)**	**7.43† (1.20-45.89)**	8.80 (0.23-7.88)	**6.79† (1.69-27.39)**	1.40 (0.00-0.00)
Whole grain cereals	1.53 (0.66-3.53)	0.78 (0.56-1.08)	0.96 (0.67-1.38)	**0.53† (0.32-0.88)**	0.90 (0.66-.122)	**0.01 (0.00-0.67)**		1,18 (0.70-1.99)	1.19 (0.50-2.85)	2.14 (0.93-44.94)	0.72 (0.43-1.18)	3.48 (0.80-15.10)
Legumes (cups/day)	0.32 (0.01-21.78)	0.62 (0.52-1.76)	0.91 (0.23-3.69)	0.54 (0.14-2.16)	0.86 (0.33-2.23)	0.21 (0.00-8.48)		0.40 (0.09-1.72)	0.17 (0.02-1.23)	0.66 (0.03-15.90)	0.79 (0.08-7.65)	**0.01 (0.00-0.58)**
Red meat (g/day)	1.00 (0.99-1.02)	**1.01 (1.00-1.01)**	**1.01† (1.00-1.02)**	1.00 (0.99-1.01)	1.01 (0.99-1.01)	1.00 (0.96-1.04)		1.00 (0.99-1.01)	1.01 (0.99-1.02)	1.00 (0.99-1.02)	1.00 (0.99-1.01)	1.03 (0.99-1.08)
White meat (g/day)	0.99 (0.97-1.01)	1.00 (0.99-1.01)	0.99 (0.98-1.00)	**1.01 (1.00-1.02)**	1.00 (0.99-1.01)	1.03 (0.97-1.11)		1.00 (0.99-1.01)	0.99† (0.97-1.01)	1.00 (0.98-1.02)	1.00 (0.99-1.02)	0.99 (0.95-1.03)
Fish (g/day)	1.00 (0.95-1.05)	1.00 (0.98-1.01)	1.00 (0.98-1.02)	0.99 (0.97-1.01)	0.99 (0.98-1.01)	0.96 (0.86-1.07)		1.00 (0.98-1.02)	1.02 0.99-1.04)	0.98 (0.93-1.03)	1.02 (0.99-1.05)	0.99 (0.93-1.06)
Salty snacks (portions/day)	0.18 (0.01-3.12)	1.28 (0.67-2.48)	1.16 (0.55-2.43)	0.66 (0.15-2.96)	0.41 (0.15-1.15)	0.35 (0.02-6.13)		1.40 (0.49-4.05)	0.18 (0.02-2.11)	1.47 (0.19-11.38)	1.21 (0.36-4.06)	0.01 (0.00-4.16)
Sweet snacks (40g/day)	**2.39 (1.16-4.94)**	**0.51 (0.31-0.86)**	1.55† (0.87-2.73)	0.98 (0.63-1.51)	1.15 (0.83-1.59)	0.00 (0.00-0.87)		0.94 (0.51-1.75)	1.71 (0.49-5.91)	1.32 (0.55-3.18)	1.12 (0.53-2.63)	1.15 (0.09-15.49)
Nuts and seeds (30g/day)	3.16 (0.61-16.34)	1.19 (0.68-2.06)	0.67 (0.33-1.36)	**3.37† (1.41-8.03)**	1.28 (0.86-1.93)	1.33 (0.00-9.89)		0.90 (0.49-1.65)	1.03 (0.51-2.10)	**0.03† (0.00-0.47)**	0.64 (0.28-1.47)	1.23 (0.29-5.14)
Coffee (250mL/day)	0.68 (0.44-1.06)	1.01 (0.77-1.31)	0.95 (0.67-1.34)	0.86 (0.63-1.16)	0.81† (0.65-1.02)	8.97 (0.94-85.16)		0.85 (0.56-1.31)	0.74 (0.38-1.44)	0.62 (0.28-1.40)	0.68 (0.42-1.10)	0.76 (0.15-3.85)
Soft drinks with sugar (250mL/day)	2.57 (0.77-8.54)	0.70 (0.26-1.84)	0.97 (0.38-2.44)	1.05 (0.42-2.60)	1.03 (0.54-1.94)	1.29 (0.03-51.25)		0.86 (0.17-4.46)	0.92 (0.13-6.36)	1.33 (0.17-10.53)	0.39 (0.09-1.65)	2.70 (0.50-2.45)
Soft drinks without sugar (250mL/day)	1.06 (0.51-2.20)	1.54 (0.65-3.67)	0.72 (0.30-1.75)	1.31 (0.78-2.21)	1.15 (0.76-1.75)	0.25 (0.05-1.36)		1.92 (0.65-5.67)	0.68 (0.36-1.29)	7.90 (0.97-64.72)	0.77 (0.42-1.41)	7.39 (0.32-169.02)
Juice without sugar (250mL/day)	0.45 (0.06-3.47)	1,15 (0.50-2.64)	1.86 (0.68-5.08)	0.55 (0.16-1.93)	1.07 (0.49-2.33)	0.04 (0.00-6.93)		0.38 (0.08-1.87)	**0.05 (0.01-0.39)**	1.73 (0.09-33.41)	**0.08† (0.01-0.57)**	4.05 (0.04-376.96)
Juice with sugar (250mL/day)	0.22 (0.01-4.28)	1.28 (0.41-3.99)	0.65 (0.10-4.30)	0.79 (0.14-4.36)	0.65 (0.19-2.19)	**2.17 (1.03-3.69)**		0.99 (0.09-11.61)	1.70 (0.07-40.89)	4.58 (0.03-676.89)	20.49† (0.55-761.19)	0.00 (0.00-32.22)
Beer and cider (330mL/day)	4.84 (0.87-	0.59 (0.31-	0.72 (0.24-	0.94 (0.50-	0.88 (0.51-	2.87 (0.04-		3.57 (0.67-	1.11 (0.13-	8.95 (0.85-	0.21 (0.03-	0.47 (0.30-

	26.84)	1.12)	2.20)	1.76)	1.52)	237.66)		18.99)	9.32)	3,26)	1.76)	2,16)
Wine (125mL/day)	0.08 (0.00-1.53)	0.98 (0.42-2.26)	1.82 (0.42-7.95)	0.65 (0.24-1.78)	1.10 (0.49-2.45)	0.30 (0.00-83.95)		0.22 (0.04-1.22)	0.22 (0.02-2.13)	0.05 (0.00-1.51)	1.14 (0.11-11.25)	0.01 (0.00-4.11)
Spirits (40mL/day)	0.62 (0.00-85.96)	2.13 (0.54-8.48)	0.32 (0.03-3.40)	5.00 (0.72-34.67)	1.64 (0.44-6.11)	0.08 (0.00-61.99)		1.29 (0.19-8.96)	4.73 (0.31-72.58)	0.26 (0.01-9.14)	5.94 (0.81-43.84)	0.00 (0.00-1.61)
MPA (min/day)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	0.98 (0.96-1.01)		1.00 (0.99-1.01)	1.00 (0.99-1.01)	**1.02† (1.00-1.05)**	1.00 (0.99-1.01)	1.01 (0.99-1.03)
VPA (min/day)	1.00 (0.98-1.01)	1.00 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (0.99-1.01)	1.00 (0.99-1.00)	0.98 (0.96-1.01)		1.00 (0.99-1.00)	1.00 (0.99-1.01)	0.99 (0.98-1.01)	1.00 (0.99-1.01)	0.99 (0.96-1.01)
Sitting (hours/day)	1.11 (0.86-1.44)	0.94 (0.87-1.02)	0.93 (0.84-1.05)	0.94 (0.84-1.05)	0.95 (0.88-1.02)	**0.40 (0.18-0.88)**		0.97 (0.86-1.10)	1.03 (0.86-1.22)	1.07 (0.83-1.39)	0.97 (0.82-1.13)	1.18 (0.83-1.69)

The data from the region group Central/North Europe in high risk adults are missing due to the uneven distribution of the sample within the two categories of HOMA-IR variable.

In bold letters, are the statistically significant findings before the correction of the analysis with BMI.

*** statistically significant associations after correction for BMI.**

† statistically significant associations when also BMI has a significant association with the dependent variable.

**** BMI is the only variable with a statistical significant association with the dependent variable.**

5. Discussion

The present study showed that BMI was the predominant risk factor positively and independently associated with glucose, insulin and insulin resistance in both low and high risk group. In the high risk group, increased consumption of juices with sugar was positively associated with glucose levels, which was evident in the total sample as well as in southeast Europe, low SES adults and in participants< 45years. Also, high consumption of refined cereals was positively associated with insulin (in the total sample, in southeast Europe and in high SES groups) and with insulin resistance. High intake of refined cereals, juices with sugar, low intake of fruits and juices without sugar were positively associated with increased risk for insulin resistance in the age group <45 years. In the low risk group, regarding glucose and insulin levels these findings were not observed. However, BMI was the dominant factor independently positively associated with HOMA-IR as well. Also, high coffee intake was negatively and independently associated in southeast Europe, high SES and participants <45 years.

Current literature focus mainly on associations of single or combined food groups with glucose status and insulin resistance in healthy and/or T2DM individuals, with very few studies conducted in adults with high risk for T2DM. In line with the present findings, a prospective

cohort study in middle-aged adults, it was shown that higher intake of sugar contained in sweetened beverages (as juice with sugar) was modestly associated with a higher incidence of prediabetes and increased insulin resistance, after adjustment for multiple confounders, including BMI [100]. Also, in a meta-analysis of cohort studies in healthy and T2DM individuals, high consumption of SSBs increased statistically significant the risk for T2D, even after adjustment for BMI [55]. Further, the prospective European study, EPIC-InterAct conducted in healthy adults showed that Juice and nectar consumption was not associated with diabetes incidence. However, the definition of juices and nectars used in the present analysis included beverages with and without added sugars [56]. Moreover, the KORA FF4 cross sectional study, which examined the associations between multiple food groups and different glucose status in a large sample, also demonstrated that SSBs were positively associated with undetected DM and self-reported diabetes, after adjusting for major covariates (BMI, smoking, education etc.) [101] Partly, in line with the observed association of refined cereals with insulin levels, the cross-sectional Baltimore Longitudinal Study of Aging showed in a subgroup analyses that refined grains were positively associated with fasting insulin, only among women (P for trend = 0.002) [102]. Regarding coffee consumption, a review of epidemiological studies in healthy subjects indicated that chronic coffee consumption can prevent the onset and may limit the progression of T2DM [103], while randomized controlled trials conducted in healthy volunteers showed that high coffee consumption for 4 weeks was positively associated with fasting insulin concentrations [104]. Also, in a cross-sectional analysis of subjects aged 45-64 years from the population-based FINRISK study, it was found that coffee consumption was significantly and inversely associated with fasting insulin in both men and women, after adjusting for confounding factors (smoking, BMI, physical activity etc.), which is partly in agreement with the results of the present study [105].

In general, the literature is limited with regard to the study of combined behavioral risk factors and both prediabetes and insulin resistance. In that direction, a Community-Based Epidemiologic Survey in Boston healthy population showed that there was no association between diet, physical activity, smoking and the presence of multiple risk factors and prediabetes or IR, after adjusting for SES indicators (education and income), while BMI was independently from SES and positively associated with insulin resistance and presented to offer higher odds for pre-diabetes [106]. However, there are not sufficient number of studies, with a similar design and population profile (high risk individuals) to support our data. From a broaden

perspective, the results of the present study are in accordance with the guidelines for pre-diabetic and diabetic individuals, which discourage high consumption of sweetened beverages (included juices with added sugars), refined cereals and encourage the increased fruit, whole grain cereals and coffee intake [107].

The Feel4Diabetes-intervention has certain strengths and limitations. The large study sample, the standardized protocols and procedures followed across all centers and the objectively collected data (i.e. blood and anthropometric indices, blood pressure safeguard the more objective and reliable assessment and increase the generalizability of findings. On the other hand, part of the collected data is self-reported thus prone to recall bias and social desirability. Also regarding the results of the present analysis, the insufficient amount of participant's data regarding insulin and consequently HOMA-IR in some categories such as region (Central/North Europe), age (<45 and >45) used in the analysis, may lead to results requiring attention at their interpretation when generalizing them to the high risk population groups.

6. Conclusion

BMI was the consistent predominant independent factor positively associated with glucose, insulin and insulin resistance in both low and high risk group. Also, in the high risk group, high consumption of juices with sugar was positively associated with glucose levels and increased consumption of refined cereals with insulin resistance and insulin levels, while in the low risk group no such association was observed. These behaviors should be identified in future prevention programs in order to be more efficient in reducing risk of T2DM.

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