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Lifestyle factors modulate postprandial hypertriglyceridemia: From the CORDIOPREV study

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HIGHLIGHTS

- We studied the influence of regular alcohol intake, physical activity and smoking habit modulating PPT in the CORDIOPREV study.
- PPT and the prevalence of undesirable response was evaluate in each subgroups. We assessed the main determinants risk factors in the presence of undesirable response.
- Smoking is an independent risk factor modulating the magnitude of PPT.
- After tobacco cessation, in long-term ex-smokers, PPT progressively decreases to similar magnitude to never smokers.
- No differences observed in the magnitude of PPT according to regular physical activity or alcohol intake habits.

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ABSTRACT

Background and aims: Recent evidence suggests that postprandial hypertriglyceridemia (PPT) is associated with the incidence of CVD. Several non-modifiable factors (genetics, age, gender) and lifestyle factors (physical activity, smoking, regular alcohol) have shown their ability to modulate PPT. We evaluate the influence of regular alcohol intake, physical activity and smoking habit modulating PPT in the CORDIOPREV study (NCT00924937).
Methods: 1002 patients were subject to an oral fat load test meal and serial blood samples were drawn at 0, 1, 2, 3 and 4 h during postprandial state. A PPT concentration above 2.5 mmol/L (220 mg/dL) at any time point has been established as a detrimental response. Alcohol consumption was defined as non-drinkers, moderate and severe intake; regular physical activity exceeding than or lower than 1000 MET/week; smoking habit was classified in current, never, recent ex-smokers and long-term ex-smokers.
Results: The prevalence of undesirable PPT response was 68% in current, 58% in recent ex-smokers, 49% in long-term ex-smokers and 48% in never smokers ($p < 0.001$). Current and recent ex-smokers displayed higher PPT response as well as a greater area under the curve (AUC) and higher incremental (iAUC) of triglycerides (TG) compared with long-term ex-smokers and never smokers ($p < 0.05$), without differences among these subgroups. No differences were observed in the magnitude of PPT according to regular physical activity or alcohol intake habits.

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Conclusions: Smoking is an independent risk factor modulating the magnitude of PPT. However, after tobacco cessation, ex-smokers show a progressive decrease on their PPT to reach levels similar to those of never smokers.

1. Introduction

A worldwide epidemic of cardiovascular diseases is evolving, out of which atherosclerosis appears to be the most frequent underlying cause [1]. Postprandial hyperlipidemia is a condition in which plasma triglycerides (TG) and TG-rich chylomicron remnants are increased during the postprandial period, and hypertriglyceridemia is protracted. The current evidence supports that non-fasting TG levels predict the incidence of CVD [2–4]. Several non-modifiable factors (genetic background, age, gender) and lifestyle factors (physical activity, smoking, alcohol intake) have shown their ability to modulate postprandial hypertriglyceridemia (PPT) [5]. Regular aerobic exercise might reduce PPT [6], whereas the association with alcohol drinking is more complex, showing a J-shaped effect, and possible transient effects [7].

Smoking has been associated with increased PPT as well as higher total cholesterol (TC), TG, very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C) and lower levels of high-density lipoprotein cholesterol (HDL-C) as compared with non-smoking, and these lipids abnormalities are considered a significant risk factor for developing atherosclerosis [8]. Nevertheless, studies are needed to investigate the interactions of these lifestyle risk factors and their role in the modulation of PPT in large cohorts, as well as the effect of smoking cessation in PPT. This study aimed to evaluate the influence of regular alcohol consumption, physical activity, smoking and smoking cessation on PPT in a large cohort of patients with established cardiovascular disease from the CORDIOPREV clinical trial (NCT00924937).

2. Materials and methods

2.1. Population

The current work was conducted within the framework of the CORDIOPREV study. The CORDIOPREV study is an ongoing prospective, randomized, opened, controlled trial including 1002 patients with coronary heart disease (CHD), which had their last coronary event more than six months before enrollment in two different dietary models (Mediterranean and low-fat), over a period of five years in addition to conventional treatment for coronary heart disease. Patients were recruited from November 2009 to February 2012, mostly at the Reina Sofia University Hospital (Cordoba, Spain), but other centers from the Cordoba and Jaen provinces were also included. Inclusion and exclusion criteria have been previously published [9]. In summary, patients were eligible if they were older than 20 years, but younger than 75, had established CHD without clinical events in the last six months, were thought to follow a long-term dietary intervention and did not have severe diseases or expected life expectancy lower than five years.

We have selected a total of 1002 patients of CORDIOPREV study, which were categorized according to their baseline smoking status: never smokers (those who never smoke or have smoke < 100 cigarettes in their life), active smokers and past smokers (is considered at least 12 months of abstinence). In addition, past smokers were classified in recent ex-smokers, those who have given up smoking less than 5 years ago, and long-term ex-smokers, those who have given up smoking 5 or more years ago [10,11]. Regular physical activity was defined by MET/weeks. MET refers to the Metabolic Equivalent Task, and 1 MET is the rate of energy expenditure while sitting at rest. It is taken by convention to be an oxygen uptake of 3.5 ml per kilogram of body weight per minute. Physical activities frequently are classified by their intensity, using the MET as a reference. We have considered an adequate regular physical activity in patients with > 1000 METs/week, and insufficient physical activity with values ≤ 1000 METs/week [12,13]. Alcohol consumption intake was categorized by standard drinks units. Although the definition of a moderate dose somewhat differs among authors, one drink a day (10–15 g of alcohol) for women and 2 drinks a day (20–30 g of alcohol) for men may be generally considered a moderate level of ethanol consumption. In this sense, we categorized in non-drinkers, moderate consumption and severe range drinkers (> 1 standard drink a day for women; > 2 drinks a day for men) [14].

All patients gave written informed consent to participate in the study. The trial protocol and all amendments were approved by the local ethics committees, following the Helsinki declaration and the good clinical practices.

2.2. The methodology of the oral fat tolerance test

An oral fat tolerance test was performed in all participants. Previously to the initiation of the test, the patients had been fasting for 12 h and were asked to refrain from smoking during the fasting period and from alcohol intake during the preceding 7 days. They were also asked to avoid strenuous physical activity the day before the test was given. At 8:00 a.m., patients registered in the study clinic, completed anthropometric (weight, height, waist circumference, body mass index (BMI)) and biochemical measurements, donated a fasting blood sample and, under supervision, ingested the fatty food meal. The breakfast was eaten in 20 min. After the meal, volunteers were resting and consumed no food for 5 h, but were allowed to drink water [15]. Blood samples for biochemical testing were collected before the meal and every hour during the next 4 h, following recommendations for an oral fat tolerance test proposed by Mihas et al. [16]. Postprandial TG concentration > 2.5 mmol/L (220 mg/dl) at any point during the test was considered a detrimental response.

2.3. Laboratory test

Venous blood was sampled from the antecubital vein and collected into Vacutainer tubes with no anticoagulant and into tubes containing EDTA, and immediately transferred to 4 °C. To minimize proteolytic degradation, plasma was supplemented with protease inhibitor cocktail (Roche Diagnostic, Germany) 40 μL per mL of plasma. Plasma and serum samples were frozen at −80 °C for further biochemical analysis. Serum parameters were measured in Architect c-16000 analyzers (Abbott®, Chicago, Illinois, USA) by spectrophotometric techniques (enzymatic colorimetric methods): hexokinase method for glucose, and oxidation-peroxidation for total cholesterol (TC), high-density cholesterol (HDL-c), low-density cholesterol (LDL-c) and TG. hs-CRP were determined by high-sensitivity ELISA (BioCheck, Inc., Foster City, CA, USA).

2.4. Statistical analysis

All statistical analyses were made with PASW Statistics software; version 25.0.0 Continuous variables were compared using the analysis of variance (ANOVA). Data are presented as means ± standard deviation (SD) for continuous variables and as frequencies or percentages for categorical variables. Qualitative variables were compared using Chi-Square test. To determine the influence of smoking in the postprandial metabolism, we used a general linear model of repeated measures of each postprandial parameter, with the different groups (smokers, never smokers, recent ex-smokers and long-term ex-smokers), (blood drawn time as within-subject variable and gender, age, BMI and

lipid-lowering drugs as covariates). Equally, the effect of regular physical activity and alcohol consumption was evaluated with a general linear model for each postprandial parameter. We used the total area under the curve (AUC) and incremental of AUC (iAUC) using the trapezoid rule to assess the magnitude of change during the postprandial state, as in previous works of our group. Bonferroni's test was used in the post-hoc analysis. All analyses were adjusted for potential confounders and $p < 0.05$ was considered to be significant.

Furthermore, interaction terms for lifestyle factors were added to this model to predict health outcomes. Multiple logistic regression model with the "Enter" method comprised dependent variable (presence of deleterious response/lack of deleterious response) and independent variables including smoking status, regular alcohol consumption, physical activity, hs-CRP, waist circumference, fasting-TG and low HDL-c (defined by metabolic syndrome criteria) and interaction terms for lifestyle. Data were presented with odds ratio (OR) and 95% confidence interval for OR (95% CIs).

3. Results

Baseline demographic and metabolic characteristics according to smoking status are presented in Table 1. We examined PPT response according to smoking status at baseline. A total of 1002 patients were classified in four subgroups: 265 never smokers, 100 active smokers, 321 recent ex-smokers (those who have given up smoking less than 5 years ago) and 316 long-term ex-smokers (those who have given up smoking 5 or more years ago).

Active smoker patients displayed higher PPT compared with never smoker patients ($p < 0.001$). Moreover, recent ex-smokers presented higher PPT levels compared with long-term ex-smokers ($p < 0.001$). However, no differences in the postprandial response TG were observed among long-term ex-smokers and never smoker patients, and equally, no differences were observed between current smokers and recent ex-smokers ($p > 0.05$) (Fig. 1A).

Consistently, the area under the curve (AUC) of TG and the iAUC-TG was greater among current smokers compared with past smokers and never smokers ($p = 0.002$). Specifically, in past smokers, the magnitude of PPT was greater in recent ex-smokers than in long-term ex-smokers ($p < 0.001$) (Fig. 1A). However, no differences in the AUC-TG were shown according to long-term ex-smokers and never smokers as well as between active smokers and recent ex-smokers ($p > 0.05$) (Table 2).

The prevalence of undesirable PPT response was 68% in current, 58% in recent ex-smokers, 49% in long-term ex-smokers and 48% in never smokers ($p < 0.001$) (Supplementary Fig. 1A).

No differences in the PTT or prevalence of deleterious response were observed according to subgroups of physical activity or regular alcohol consumption ($p > 0.05$) (Fig. 1B and C and Supplementary Figs. 1B and C).

To evaluate the lifestyle risk and other cardiometabolic parameters as determinants of deleterious lipemic response, we carried out multiple logistic regression analysis. Active smoking was an independent risk factor for the presence of deleterious PPT response. Current smokers increased the risk of deleterious response (OR 3.02 (95% IC: 1.52–6) compared with past and never smokers. In addition, the presence of fasting TG > 150 mg/dl (OR 16.18 (95% IC: 9.9–26.3)) and abdominal obesity (OR 1.53 (95% IC: 1.04–2.24)) increased the risk of deleterious response. Nonetheless, a moderate alcohol intake, no increased the risk of deleterious response (OR 0.53 (95% IC: 0.28–0.99). However, no consistent differences were observed in hs-CRP levels, HOMA-IR, and regular physical activity. In multiple logistic regression analysis, we used the comparison of the presence or absence of a deleterious response as the dependent variable, and the following as independent variables: smoking status, exercise behavior, regular alcohol consumption, abdominal obesity, fasting TG levels, low HDL-c and CRP (Table 3).

4. Discussion

Our findings showed that active smokers displayed higher PPT compared with past smokers and never smokers. Specifically, recent ex-smokers presented higher PPT levels compared with long-term ex-smokers. Interestingly, after tobacco cessation, the PPT levels decreased progressively over time, to be similar to never smokers. In our population, no differences in the magnitude of PPT or of an abnormal response have been shown according to physical activity or alcohol consumption habits. In this large cohort, we confirmed previous data indicating that smoking habit is associated with abnormal postprandial lipoprotein metabolism [17]. Thus, the frequency of deleterious response increased progressively according to never smokers (48%), long-term ex-smokers (49%), recent ex-smokers (58%) and active smokers

Table 1
Baseline characteristics according to smoking status.

	Smokers n = 100	Recent ex-smokers n = 321	Long-term ex-smokers n = 316	Never smokers n = 265	*p* value
Age (years)	56 ± 8.6[a]	56.04 ± 8.4[b]	61 ± 8.5[ab]	63 ± 8.4[ab]	0.001
Male/Female	89/11	289/32	298/18	161/104	< 0.001
BMI (Kg/m^2)	30.3 ± 4.3	31.2 ± 4.4	31.2 ± 4.2	31 ± 4.9	0.311
Waist circumference (cm)	104 ± 11.3	105.5 ± 11.9	107 ± 10.6[a]	103 ± 12.1[a]	0.001
Fasting TG (mg/dl)	147.3 ± 69.8[ab]	143 ± 69.8[ab]	124.76 ± 58.5[b]	124.7 ± 60.7[a]	0.001
TC (mg/dl)	167.5 ± 34.2[c]	159.5 ± 28.7[b]	152.9 ± 30.3[abc]	162.3 ± 32.4[a]	0.001
LDL-c (mg/dl)	92 ± 27.9	88.8 ± 24.7	84.9 ± 25.3[a]	91.2 ± 26.2[a]	0.013
HDL-c (mg/dl)	40.3 ± 10.8[ab]	41.4 ± 10.2[b]	41.2 ± 8.8[a]	44.9 ± 10.7[ab]	0.04
HbA1c (%)	6.7 ± 1.3	6.5 ± 1.0	6.6 ± 1.1	6.7 ± 1.2	0.119
hs-CRP (mg/dl)	3.2 ± 2.3[abc]	2.4 ± 2.1[b]	2.1 ± 1.7[c]	2.4 ± 2.0[a]	0.001
HOMA-IR	3.3 ± 0.5	4.7 ± 0.3	3.4 ± 0.2	4.1 ± 0.83	0.692
Insulin (mU/L)	10.6 ± 1	11.3 ± 0.6	11 ± 0.5	10.6 ± 0.8	0.874
Undesirable response (%)	68	58	49	48	0.001
Lipid-lowering drugs					
Statins (%)	86	85.6	85.7	85	0.789
Fibrates (%)	2	1.8	2.2	0.3	0.312
Other[1]	6	5.9	3.8	4	0.532

Values are mean ± SD. One-way ANOVA.
BMI: body mass index; TG: triglycerides levels; TC: total cholesterol; LDL-c: low density lipoprotein cholesterol; HDL-c: high density lipoprotein-cholesterol; HbA1c: glycated hemoglobin; hsPCR: high sensitivity C-reactive protein; HOMA-IR: homeostatic model assessment; Undesirable response: postprandial TG levels at any point > 2.5 mmol/L (220 mg/dL).
[abc]$p < 0.05$ *post-hoc* Bonferroni analysis according to four subgroups. Superscript characters indicate differences between groups (a,b,c) within the same row.
[1]Other lipid-lowering drugs: ezetimibe and nicotinic acid.

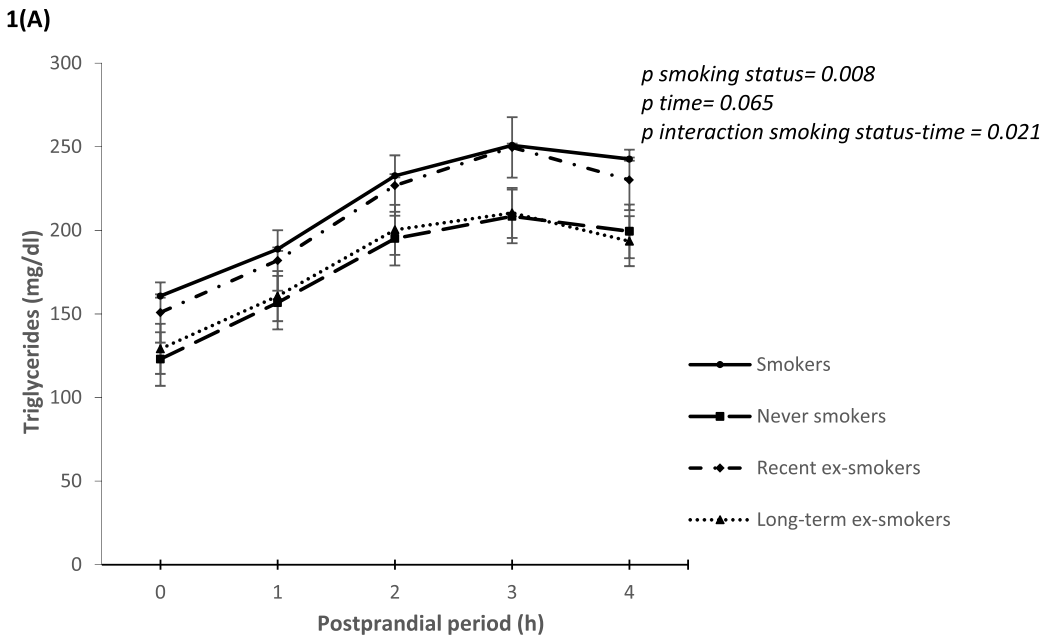

Fig. 1(A). Evolution of triglycerides (TG) after the oral fat tolerance test, according to smoking status: never smokers, current smokers, recent ex-smoker and long-term ex-smoker patients. Results as plotted as mean ± SD. Variables were compared using repeated measure ANOVA, with age, BMI, gender and lipid-lowering drugs (statins, fibrates, ezetimibe and nicotinid acid) as covariates.

(68%).

Smoking is a well-established CV risk factor for atherosclerotic CVD, coronary heart disease, cerebrovascular disease, heart failure, diabetes, and all-cause mortality, with an apparent dose-dependent relationship [18,19]. Active smoking has been associated with endothelial dysfunction [20,21], adverse effect on blood coagulability, including increased fibrinogen levels and platelet aggregation [22,23], and also modifies the lipid profile itself increasing plasma levels of TC, fasting TG, VLDL-C, LDL-C, and decreasing level of HDL-C compared which non-smokers subjects [24]. The increased risk of cardiovascular disease smoking risk was reflected by a higher inflammatory state (as indicated by hs-CRP levels) and altered lipid profile, with high levels of TG and decreased c-HDL levels being the most pronounced changes. In our large cohort, we have corroborated these findings, smokers showed higher levels of TC, fasting TG, LDL-c and low-HDL-c levels compared with ex-smokers and never smokers patients. This altered lipoprotein metabolism accelerates atherosclerosis process and in consequence, increases the risk of ischemic heart disease and stroke [25–27]. In recent ex-smokers and long-term ex-smokers, hs-CRP levels and the magnitude of PPT progressively decrease with years from smoking cessation. In addition, no consistent differences were shown in BMI and other insulin resistance biomarkers levels between these subgroups. Attard et al. evaluated the influence of passive smoking, active smoking and smoking cessation on lipid profile and the risk of myocardial infarction (MI). The risk of MI increased with smoking intensity and decreased after 5 years from smoking cessation. This increased risk of MI was related with a higher inflammatory state (as indicated by hs-CRP levels) and altered lipid profile with an elevation of TG levels and decrease HDL-c levels being the most pronounced changes [11].

While smoking has been widely studied as an isolated CV risk factor and fasting dyslipidemia, it has been poorly evaluated as a factor that potentially alters PPT. Smokers have been shown to have a longer and more pronounced postprandial TG response in plasma than non-smokers, due to defective clearance of chylomicrons (ChM) and ChM remnants [28]. Responses of intestinally derived lipoproteins are substantially increased in current smokers. Previous studies showed that smokers had a significantly increased postprandial response in TG, ChM, VLDL1, VLDL2, and IDL. Moreover, smoking raised retinyl esters (RE) responses of all TRL fractions and apoB-48 in QM compared with non-smokers [29–31]. Besides, smokers exhibit an excess of small dense LDL, have altered postprandial HDL-c, apolipoprotein composition, and lipid transfer protein activities. Postprandially esterification rates increased, but CETP and LPL activities decreased in smokers. The shift of cholesterol and apoE from HDL to the TRL fraction, together with decreased plasma apoA-I and LpA-I concentrations may indicate impaired reverse cholesterol transport [30]. Therefore, the smoking-related effects on plasma lipoproteins may be attributed, at least in part, to decreased post-heparin lipoprotein lipase (LPL) activity, the postprandial increase in TRL and the lowering of HDL, that may promote atherogenesis in smokers.

To our knowledge, there are no previous studies that assessed this relation in past smokers according to the time since giving up smoking.

Table 2
Postprandial area under the curve (AUC) an incremental (iAUC) of TG and TRLs-TG according to the smoking status.

	Smokers n = 100	Recent ex-smokers n = 321	Long-term ex-smokers n = 316	Never smokers n = 265	*p* value
AUC-TG	49,370.4 ± 19,755^{acd}	49,898.9 ± 22,275^{bcd}	42,344.4 ± 17,499^{abc}	42,726.1 ± 20,419^{abd}	0.001
iAUC-TG	14,211.0 ± 9352	15,403.5 ± 10211^{a}	13,268.7 ± 9532^{a}	13,501.6 ± 9564	0.045
AUC-TRLs-TG	22,118.8 ± 16231^{acd}	20,506.5 ± 17324^{bcd}	16,745.3 ± 1013^{abc}	13,757.6 ± 919^{abd}	0.002

Values are mean ± SD. One-way ANOVA.
AUC-TG: area under the curve of triglycerides; iAUC-TG: incremental of the area under the curve of triglycerides; AUC of the large triacylglycerol-rich lipoproteins (TRLs)-TG.
Superscript indicate differences between groups (a,b,c,d) within the same row.

1(B)

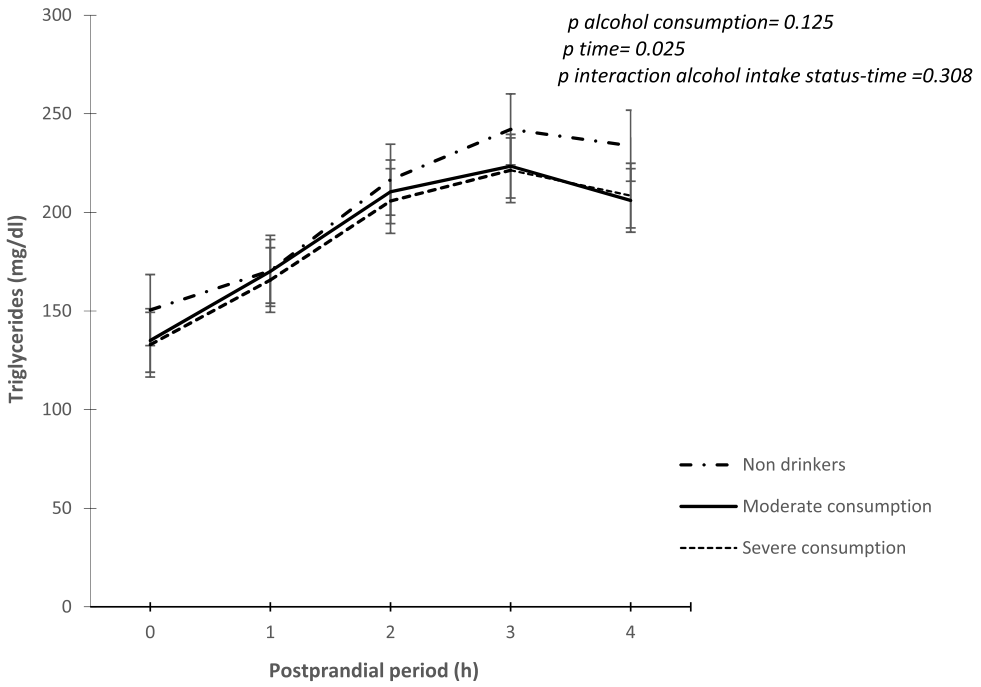

Fig. 1(B). Evolution of triglycerides (TG) after the oral fat tolerance test, according to the regular alcohol consumption subgroups: non-drinkers, moderate and severe consumption. Results as plotted as mean ± SD. Variables were compared using repeated measure ANOVA, with age, BMI, gender and lipid-lowering drugs (statins, fibrates, ezetimibe and nicotinid acid) as covariates.

1(C)

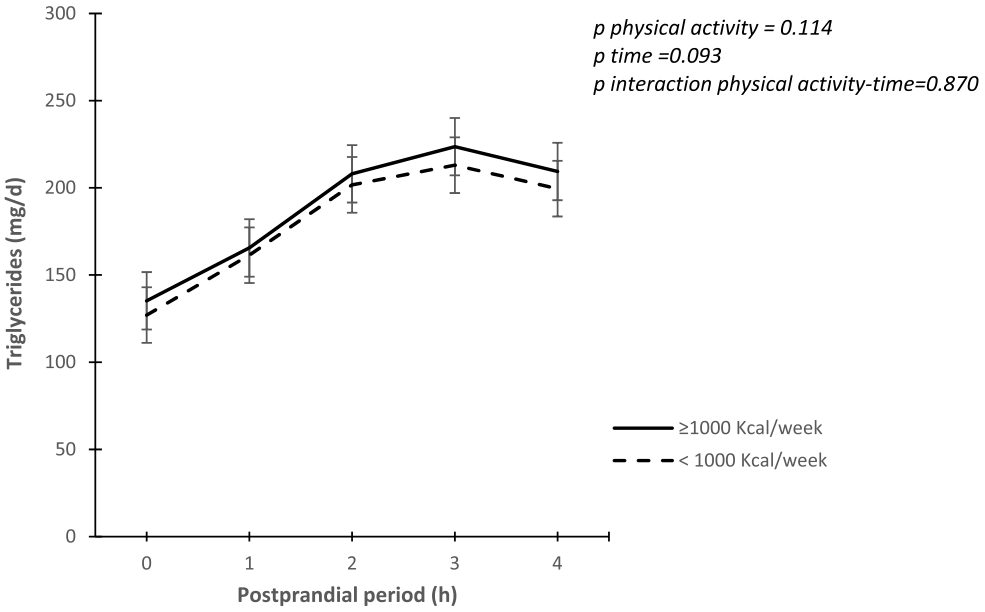

Fig. 1(C). Evolution of triglycerides (TG) after the oral fat tolerance test, according to the regular physical activity subgroups: ≥1000 kcal/week and < 1000 kcal/week. Results as plotted as mean ± SD. Variables were compared using repeated measured (ANOVA), with age, BMI, gender and lipid-lowering drugs (statins, fibrates, ezetimibe, and nicotinid acid) as covariates.

Previous studies indicate a reasonable cut-off period established at 5 years after smoking cessation to define past smokers [32,33]. Our results indicate that the magnitude of PPT is consistently higher in current smokers and recent ex-smokers compared with long-term ex-smokers and never smokers, without no differences in the magnitude of PPT levels between current and recent past smokers, as well as in long-term ex-smokers compared with never smokers. Therefore, the PPT levels decrease progressively after 5 years from smoking cessation, reaching a similar lipid profile to never smokers. Our results show a significant contribution of fasting TG levels on AUC-TG. Nonetheless, even after

Table 3
Results of multiple logistic regression analysis. Variables associated with the presence of an undesirable response.

	p value	OR	IC (95%)
Smoking status			
Long-term ex-smokers	0.182	1.38	(0.85–2.23)
Recent ex-smokers	0.208	1.37	(0.84–2.23)
Active smokers	**0.002**	3.02	(1.52–6.00)
Non-smokers	*reference*		
Alcohol intake			
Moderate intake	**0.048**	0.53	(0.28–0.99)
Severe intake	0.813	0.93	(0.51–1.67)
Non drinker	*reference*		
Physical activity			
Physical activity (< 1000 kcal/week)	0.394	0.85	(0.59–1.22)
Physical activity (> 1000 kcal/week)	*reference*		
Abdominal obesity			
Waist circumference > 88 cm in women, > 102 cm in men	**0.003**	1.53	(1.04–2.24)
Waist circumference ≤88 cm in women, ≤102 102 cm in men	*reference*		
Fasting TG (> 150 mg/dl)	**0.001**	16.18	(9.92–26.37)
Fasting TG (≤150 mg/dl)	*reference*		
Low HDL-c (< 50 mg/dl in men; < 40 mg/dl in women)	0.093	1.36	(0.94–1.97)
HDL-c (≥50 mg/dl in men; ≥40 mg/dl in women)	*reference*		
hs-CRP (mg/dl)	0.912	1.02	(0.69–1.49)

ORs for each variable within the model according to smoking status, alcohol intake, physical activity, abdominal obesity, fasting hypertriglyceridemia, low-HDL-c and hs-CRP levels.
CI: confidence interval of 95%. OR: odds ratio.
Abdominal obesity: waist circumference > 88 cm in women, > 102 cm in men; Fasting TG: fasting triglycerides levels > 150 mg/dl; HDL-c: low density lipoprotein-cholesterol (< 50 mg/dl in men; < 40 mg/dl in women); hs-CRP: high sensitivity C-reactive protein; (g/d): grams/day; Kcal/week: Kilocalories/week; undesirable response: TG concentration > 2.5 mmol/L (220 mg/dL) at any time after an OFTT meal.

correcting by fasting TG levels, active smoking status was independently associated with an elevated PPL response.

Aldaham et al. explored the influence of smoking status on inflammatory markers in a randomized trial of current and former heavy smokers. No differences in hs-CRP levels were objectified between smokers and former smokers, but instead, the serum levels of IL-6 were significantly higher among male smokers compared to former smokers [34–38]. Concordant with these findings, in our population, we have shown a strong relationship between an abnormal lipemic response and the presence of abdominal obesity and fasting hypertriglyceridemia, but not association have been established with hs-CRP levels or low HDL-c. These results may suggest an insulin resistance state underlying as a potential mechanism by which smoking contributes to an increase in their high residual risk [39]. Further studies are needs to elucidate the main pathophysiological mechanisms of smoke-induced atherosclerosis.

Nevertheless, many non-modifiable risk factors as ageing and gender may modulate PPT. Based on that, we have evaluated the effect in our population with a significant percentage of men and in basis of body fat distribution according gender. PPT has been shown to vary according to different age stages, and it was higher in older compared to younger. In addition, the link between aging, PPT and atherosclerosis has also been demonstrated although the mechanism behind this effect is uncertain. The reduction in the rate of gastric emptying, rather than intestinal motility, has been proposed to be responsible for exaggerated lipemia with increasing age. Since older individuals have a longer gastric emptying time, the absorption of fat can be expected to be slower, explaining the later increase in TG levels. However, other studies have been contradictory. Therefore, further investigation of the postprandial mechanism is needed. Nonetheless, the association of aging with PPT may partly explain the influence of age on atherosclerosis [28].

Moreover, it has been demonstrated that the magnitude of PPT and postprandial free fatty acid levels (FFA) are greater in men compared with female subjects. However, when the data were adjusted for visceral adipose tissue mass, the gender difference in postprandial response was eliminated, suggesting that the gender difference in body fat distribution is also an important contributing factor (men in the abdominal region and women preferentially in the subcutaneous areas (buttocks and thighs)). The volume of abdominal fat has been inversely associated with suppression of FFA release from adipocytes, so that is important for the assembly of VLDL. Consequently, women have a more rapid clearance of fat, resulting in lower PPT compared to men.

On the other hand, recent evidence suggests that alcohol consumption in a low dose can decrease triglyceridemia compared to abstainers, resulting in a J-shape curve; but this effect may be transient [40]. These effects can be at least partially explained by the combination of long-term and acute effects of ethanol consumption on LPL activity [28]. In relation to PPT, we have not observed differences in the magnitude of PPL among regular moderate intake with the other range's consumption subgroups. However, we observed a marginal influence ($p = 0.048$) of moderate alcohol consumption as a lower presence of deleterious response. Nonetheless, due to the risk associated with the development of addiction to alcohol, it does not seem wise to recommend abstainers to start drinking alcohol to prevent CVD.

Physical Activity Guidelines for Americans include a recommendation of 500–1000 MET-minutes per week for significant health benefits [12]. Evidence indicates that vigorous exercise training can significantly reduce PPT, but this effect is transient, and it depends on energy. Moreover, PPL increases after training cessation, so that, a continuous moderate-intensity aerobic exercise is recommended in order to reduce PPL, instead of vigorous exercise performed only occasionally, specifically in patients con CVD [41,42]. Based on our results, no differences have been shown according to different ranges of regular physical activity in the modulation of PPT, nor as an independent modulator postprandial lipemic response.

Despite the strengths of our study (large population size, dynamic fat tolerance test, standardized methodology, etc.) there were some limitations. In this sense, because of the complexity, it is difficult to evaluate the effect in possible PPL modulation by specific types of alcoholic beverages and/or tobacco, as well as the cumulative dose in smokers.

In summary, our study shows the deleterious effect of smoking in postprandial metabolism and the influence as a determinant risk factor of undesirable response in patients with coronary heart disease. After tobacco cessation, PPL decreased progressively to a similar magnitude than never smokers. Smoking, fasting triglycerides and abdominal obesity are the major contributors to the PPL levels. Our findings imply the need for advice cessation in smokers, to decrease their cardiovascular risk.

Declaration of Competing Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.09.025.

References

[1] Collaborators GBDCoD, Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet 392 (10159) (2018)

1736–1788.
[2] A.R. Sharrett, G. Heiss, L.E. Chambless, E. Boerwinkle, S.A. Coady, A.R. Folsom, et al., Metabolic and lifestyle determinants of postprandial lipemia differ from those of fasting triglycerides: the Atherosclerosis Risk in Communities (ARIC) study, Arterioscler. Thromb. Vasc. Biol. 21 (2) (2001) 275–281.
[3] G. Steiner, Triglyceride-rich lipoproteins and atherosclerosis, from fast to feast, Ann. Med. 25 (5) (1993) 431–435.
[4] S. Bansal, J.E. Buring, N. Rifai, S. Mora, F.M. Sacks, P.M. Ridker, Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women, Jama 298 (3) (2007) 309–316.
[5] J. Lopez-Miranda, C. Williams, D. Lairon, Dietary, physiological, genetic and pathological influences on postprandial lipid metabolism, Br. J. Nutr. 98 (3) (2007) 458–473.
[6] E. Zotou, F. Magkos, C. Koutsari, E. Fragopoulou, T. Nomikos, L.S. Sidossis, et al., Acute resistance exercise attenuates fasting and postprandial triglyceridemia in women by reducing triglyceride concentrations in triglyceride-rich lipoproteins, Eur. J. Appl. Physiol. 110 (4) (2010) 869–874.
[7] S. Andreasson, Alcohol and J-shaped curves, Alcohol Clin. Exp. Res. 22 (7 Suppl) (1998) 359S-64S.
[8] Ch S. Rao, Y.E. Subash, The effect of chronic tobacco smoking and chewing on the lipid profile, J. Clin. Diagn. Res. J. Clin. Diagn. Res. 7 (1) (2013) 31–34.
[9] J. Delgado-Lista, P. Perez-Martinez, A. Garcia-Rios, J.F. Alcala-Diaz, A.I. Perez-Caballero, F. Gomez-Delgado, et al., CORonary Diet Intervention with Olive oil and cardiovascular PREVention study (the CORDIOPREV study): rationale, methods, and baseline characteristics: a clinical trial comparing the efficacy of a Mediterranean diet rich in olive oil versus a low-fat diet on cardiovascular disease in coronary patients, Am. Heart J. 177 (2016) 42–50.
[10] WHO Report on the Global Tobacco Epidemic, 2017: Monitoring Tobacco Use and Prevention Policies, World Health Organization, Geneva, 2017 Licence: CC BY-NC-SA 30 IGO. 2017.
[11] R. Attard, P. Dingli, C.J.M. Doggen, K. Cassar, R. Farrugia, S.B. Wettinger, The impact of passive and active smoking on inflammation, lipid profile and the risk of myocardial infarction, Open Heart 4 (2) (2017) e000620.
[12] K.L. Piercy, R.P. Troiano, R.M. Ballard, S.A. Carlson, J.E. Fulton, D.A. Galuska, et al., The physical activity Guidelines for Americans, Jama 320 (19) (2018) 2020–2028.
[13] G. O'Donovan, A.J. Blazevich, C. Boreham, A.R. Cooper, H. Crank, U. Ekelund, et al., The ABC of physical activity for health: a consensus statement from the British association of sport and exercise sciences, J. Sport. Sci. 28 (6) (2010) 573–591.
[14] V.A. Moyer, F. Preventive Services Task, Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: U.S. preventive services task force recommendation statement, Ann. Intern. Med. 159 (3) (2013) 210–218.
[15] B. Gomez-Marin, F. Gomez-Delgado, J. Lopez-Moreno, J.F. Alcala-Diaz, R. Jimenez-Lucena, J.D. Torres-Pena, et al., Long-term consumption of a Mediterranean diet improves postprandial lipemia in patients with type 2 diabetes: the Cordioprev randomized trial, Am. J. Clin. Nutr. 108 (5) (2018) 963–970.
[16] C. Mihas, G.D. Kolovou, D.P. Mikhailidis, J. Kovar, D. Lairon, B.G. Nordestgaard, et al., Diagnostic value of postprandial triglyceride testing in healthy subjects: a meta-analysis, Curr. Vasc. Pharmacol. 9 (3) (2011) 271–280.
[17] E.K. Kabagambe, J.M. Ordovas, M.Y. Tsai, I.B. Borecki, P.N. Hopkins, S.P. Glasser, et al., Smoking, inflammatory patterns and postprandial hypertriglyceridemia, Atherosclerosis 203 (2) (2009) 633–639.
[18] D.M. Burns, Epidemiology of smoking-induced cardiovascular disease, Prog. Cardiovasc. Dis. 46 (1) (2003) 11–29.
[19] J.H. Lubin, D. Couper, P.L. Lutsey, M. Woodward, H. Yatsuya, R.R. Huxley, Risk of cardiovascular disease from cumulative cigarette use and the impact of smoking intensity, Epidemiology 27 (3) (2016) 395–404.
[20] A. Jagla, J. Schrezenmeir, Postprandial triglycerides and endothelial function, Exp. Clin. Endocrinol. Diabetes 109 (4) (2001) S533–S547 official journal, German Society of Endocrinology [and] German Diabetes Association.
[21] R. Michael Pittilo, Cigarette smoking, endothelial injury and cardiovascular disease, Int. J. Exp. Pathol. 81 (4) (2000) 219–230.
[22] W.B. Kannel, R.B. D'Agostino, A.J. Belanger, Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham Study, Am. Heart J. 113 (4) (1987) 1006–1010.
[23] C. Napoli, L.J. Ignarro, Nitric oxide and atherosclerosis, Nitric Oxide Biol. Chem. 5 (2) (2001) 88–97.
[24] L.K. Gossett, H.M. Johnson, M.E. Piper, M.C. Fiore, T.B. Baker, J.H. Stein, Smoking intensity and lipoprotein abnormalities in active smokers, J. Clin. Lipidol. 3 (6) (2009) 372–378.
[25] Y. Liu, T. Han, M. Gao, J. Wang, F. Liu, S. Zhou, et al., Clinical characteristics and prognosis of acute myocardial infarction in young smokers and non-smokers (< /= 45 years): a systematic review and meta-analysis, Oncotarget 8 (46) (2017) 81195–81203.
[26] K.A. Epstein, C.M. Viscoli, J.D. Spence, L.H. Young, S.E. Inzucchi, M. Gorman, et al., Smoking cessation and outcome after ischemic stroke or TIA, Neurology 89 (16) (2017) 1723–1729.
[27] J.F. Meschia, T. Brott, Ischaemic stroke, Eur. J. Neurol. 25 (1) (2018) 35–40.
[28] C.B. Dias, P.J. Moughan, L.G. Wood, H. Singh, M.L. Garg, Postprandial lipemia: factoring in lipemic response for ranking foods for their healthiness, Lipids Health Dis. 16 (1) (2017) 178.
[29] N. Mero, M. Syvanne, B. Eliasson, U. Smith, M.R. Taskinen, Postprandial elevation of ApoB-48-containing triglyceride-rich particles and retinyl esters in normolipemic males who smoke, Arterioscler. Thromb. Vasc. Biol. 17 (10) (1997) 2096–2102.
[30] B. Eliasson, N. Mero, M.R. Taskinen, U. Smith, The insulin resistance syndrome and postprandial lipid intolerance in smokers, Atherosclerosis 129 (1) (1997) 79–88.
[31] J.S.H. Muntwyler, H. Drexel, D.J. Vonderschmitt, J.R. Patsch, F.W. Amann, Regression of postprandial lipemia after smoking cessation, J. Am. Coll. Cardiol. 27 (412) (1996).
[32] O. Uzuner, Second i2b2 workshop on natural language processing challenges for clinical records, Proc. Annu. Symp. AMIA (2008) 1252–1253.
[33] O. Uzuner, I. Goldstein, Y. Luo, I. Kohane, Identifying patient smoking status from medical discharge records, J. Am. Med. Inform. Assoc. : JAMIA 15 (1) (2008) 14–24.
[34] S. Aldaham, J.A. Foote, H.H. Chow, I.A. Hakim, Smoking status effect on inflammatory markers in a randomized trial of current and former heavy smokers, Int. J. Inflamm. 2015 (2015) 439396.
[35] S. Cheng, A. Lyass, J.M. Massaro, G.T. O'Connor, J.F. Keaney Jr., R.S. Vasan, Exhaled carbon monoxide and risk of metabolic syndrome and cardiovascular disease in the community, Circulation 122 (15) (2010) 1470–1477.
[36] A. Festa, R. D'Agostino Jr., G. Howard, L. Mykkanen, R.P. Tracy, S.M. Haffner, Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS), Circulation 102 (1) (2000) 42–47.
[37] P.M. Ridker, C.H. Hennekens, J.E. Buring, N. Rifai, C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women, N. Engl. J. Med. 342 (12) (2000) 836–843.
[38] A. Asthana, H.M. Johnson, M.E. Piper, M.C. Fiore, T.B. Baker, J.H. Stein, Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers, Am. Heart J. 160 (3) (2010) 458–463.
[39] P. Perez-Martinez, D.P. Mikhailidis, V.G. Athyros, M. Bullo, P. Couture, M.I. Covas, et al., Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation, Nutr. Rev. 75 (5) (2017) 307–326.
[40] J. Kovar, K. Zemankova, Moderate alcohol consumption and triglyceridemia, Physiol. Res. 64 (Suppl 3) (2015) S371–S375.
[41] Y. Wang, D. Xu, Effects of aerobic exercise on lipids and lipoproteins, Lipids Health Dis. 16 (1) (2017) 132.
[42] C.S. Teeman, S.P. Kurti, B.J. Cull, S.R. Emerson, M.D. Haub, S.K. Rosenkranz, Postprandial lipemic and inflammatory responses to high-fat meals: a review of the roles of acute and chronic exercise, Nutr. Metab. 13 (2016) 80.