

Postprandial lipemia and the risk of coronary heart disease and stroke: the Atherosclerosis Risk in Communities (ARIC) Study

Dmitry Kats,¹ A Richey Sharrett,² Henry N Ginsberg,³ Vijay Nambi,^{4,5,6} Christie M Ballantyne,^{5,6} Ron C Hoogeveen,^{5,6} Gerardo Heiss¹

To cite: Kats D, Sharrett AR, Ginsberg HN, *et al*. Postprandial lipemia and the risk of coronary heart disease and stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *BMJ Open Diabetes Research and Care* 2017;**5**:e000335. doi:10.1136/bmjdr-2016-000335

Received 29 September 2016
Revised 1 December 2016
Accepted 11 December 2016

ABSTRACT

Objective: Excessive levels of triglyceride-rich lipoproteins during postprandial lipemia (PPL) have been reported to be atherogenic. However, it is unclear whether the degree of PPL independently predicts cardiovascular disease (CVD) given the scarcity of longitudinal data with standardised measures of postprandial change. We reexamined associations of PPL with incident CVD events in a population-based cohort using detailed measures of postprandial change from a standardised fat challenge.

Research design and methods: Postprandial triglycerides, TG-rich lipoprotein triglycerides, retinyl palmitate and apolipoprotein B48 to B100 ratio were measured before (following a 12-hour fasting period) and after a fat-tolerance test meal in a middle-aged, biracial subcohort without CVD (coronary heart disease (CHD) or stroke) from the community-based Atherosclerosis Risk in Communities (ARIC) Study in 1990–1993. Using these measures, we estimated associations of postprandial change with incident CVD (CHD, stroke) through 2012. Stratified analyses by race, obesity and carotid atherosclerotic severity were also conducted.

Results: Of 559 participants, 127 (23%) developed CHD and 27 (5%) experienced a stroke over more than 20 years of follow-up. None of the measures of postprandial change were associated with incident CVD events in the overall sample, or by subgroups of race, obesity or carotid atherosclerotic severity (all $p>0.3$).

Conclusions: The degree of PPL was not shown to predict excess CVD risk in extended follow-up of a population-based sample. While our study is the largest to examine the association between PPL and incident CVD using standardised postfat challenge measures, prospective investigation with similar assessment of PPL in more powered samples is warranted.

INTRODUCTION

Postprandial lipemia (PPL) refers to the metabolic state in which there is an increase of triglyceride-rich lipoproteins in circulation following fatty food consumption. While

Significance of this study

What is already known about this subject?

The longitudinal association of postprandial lipemia with cardiovascular disease risk is not clear, stemming from limitations in how postprandial variables have been assessed in prospective studies.

What are the new findings?

There were no statistically significant associations between any of the multiple measures of postprandial change used in this study and incident cardiovascular outcomes.

How might these results change the focus of research or clinical practice?

More powered prospective studies using detailed, standardised measures of postprandial change are needed to elucidate the association of postprandial lipemia with the development of cardiovascular disease.

exaggerated levels of such triglycerides during PPL have been linked to prevalent atherosclerosis and cardiovascular disease (CVD) in case-control studies,^{1 2} understanding of the association between PPL and incident atherothrombotic events is hampered by limitations in how PPL was assessed in previous longitudinal investigations.^{3–8} These studies, while extremely large in scale, used fasting or non-fasting postprandial triglycerides measured by a non-standardised protocol and at only one point in time.

Reliance on non-fasting triglycerides is flawed due to the high variability in their concentrations depending on the timing and contents of the last meal. Reported associations between fasting triglycerides and incident CVD events have been noticeably attenuated on adjustment for high-density lipoprotein cholesterol (HDL-C), ensuing debate in terms of whether excessive PPL confers any residual risk on the development of CVD beyond its relationship with HDL-C.⁷



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For numbered affiliations see end of article.

Correspondence to

Dr Dmitry Kats;
dkats@email.unc.edu

Furthermore, concentrations of triglycerides taken at a single time point are not necessarily accurate indicators of postprandial change.⁹ Valid assessment of postprandial change is achieved instead through the synthesis of repeat measurements of postprandial moieties obtained over the course of a fat-tolerance test.⁹ Given the lack of prospective investigations with such detailed, standardised measures of postprandial change, the role PPL plays in CVD development is unclear.

Our study reassessed the longitudinal relationship between PPL and CVD using standardised fat challenge measures of postprandial change in a subsample from the population-based Atherosclerosis Risk in Communities (ARIC) Study. Associations of postprandial change with incident CVD events over ~20 years were estimated in white and African-American men and women. We further examined associations between these PPL measures and CVD risk by subgroups of race, body mass index (BMI) and baseline carotid intima media thickness (IMT), a measure of atherosclerosis severity.

RESEARCH DESIGN AND METHODS

Study population

The ARIC Study is an ongoing community-based cohort of 15 792 men and women (mostly whites and African-Americans) aged 45–64 years at baseline (1987–1989) who were probabilistically selected from four US communities (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota and Washington County).¹⁰ Our study sample originated from 1114 ARIC participants invited into a nested case–control study during ARIC visit 2, which occurred from 1990 to 1993.^{1 11} This substudy, composed of cases with subclinical carotid atherosclerosis and controls with minimal or no carotid artery atherosclerosis, was designed to examine the relationship between PPL and subclinical atherosclerosis, among participants without prevalent CVD.^{1 11}

Fat-tolerance test

After a 12-hour period of fasting and avoidance of exercise, fasting blood specimens were collected. A liquid test meal was then administered, which consisted of heavy whipping cream, ice cream, safflower oil, chocolate syrup and powdered protein (Promod, Ross Laboratories) and contained 1265 kcal, 32 g protein, 48 g carbohydrate, 105 g fat (52 g saturated) and 300 mg cholesterol, in addition to 100 000 IU vitamin A (Aquasol, Armour Pharmaceutical Co.) for each 2 m² of body surface area. As a safeguard against potential lactose intolerance, Lactaid was added to the meal. Participants were allotted 15 min to consume the test meal and instructed to ingest only water, unsweetened coffee or tea or sugarless soft drinks for 8 hours thereafter. Blood specimens were drawn 3.5 and 8 hours following test meal consumption. The number of

postprandial blood collections (ie, the difference between two and four measurements) has shown minimal influence on the classification of postprandial response.² Hence, measurements of PPL variables taken post-fasting and then 3.5 and 8 hours after consumption of the test meal should be suitable to assess postprandial response to a fatty meal over an 8-hour time period.

Blood specimens were centrifuged for 20 min (1500 g, at 4°C) to separate plasma. Plasma samples were shipped on dry ice and stored in liquid nitrogen at the central laboratory until analysis within a few days. Details of this procedure have been described elsewhere.^{1 11}

PPL assays

Variation in CVD risk by subclasses of PPL-related variables was considered by using four separate measures of postprandial markers (each assessed at visit 2): postprandial triglycerides (TG), TG-rich lipoprotein triglycerides (TRL-TG), retinyl palmitate (RP) and apolipoprotein B48 to apolipoprotein B100 ratio (apoBR). TG and TRL-TG appear in the ‘top fraction’ and are markers of very low-density lipoproteins, whereas measures of RP and apoBR are surrogates for chylomicrons. In this study, TG levels were measured enzymatically, TRL-TG samples were isolated by ultracentrifugation,¹² plasma RP levels were determined using high-pressure liquid chromatography¹³ and apoBR values were ascertained by sodium dodecyl sulfate electrophoresis.¹⁴

To yield a measure of postprandial change, the incremental area under the curve (iAUC) defined by each PPL parameter across the available time points (0, 3.5 and 8 hours after the test meal) was calculated, with negative results set to 0.¹ For the purposes of this study, the iAUC can be interpreted as the two-dimensional postprandial response over 8 hours. The iAUC measures were transformed into weighted SD units to reflect the sampling weights of the overall ARIC sample from which case–control participants were drawn. Weighted SD units can be interpreted in the same manner as conventional SD units.

Other covariates

HDL-C and low-density lipoprotein cholesterol (LDL-C) were measured at visit 2.^{15 16} Trained ARIC personnel used a standardised protocol to measure height, weight, former as well as current cigarette smoking status and diastolic and systolic blood pressure at visit 2.¹⁷ Prevalent hypertension was indicated by a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg and/or self-reported use of antihypertensive medication. The use of lipid-lowering medications was self-reported by the patient and verified by ARIC personnel (checking of medications brought by the patient) at visit 2. Fasting blood glucose measures were also taken at visit 2.

Severity of atherosclerosis was assessed using B-mode ultrasound as in the aforementioned nested case–control study during visit 2.^{1 11} In that study, white participants with IMT values above the 95th centile of

the ARIC distribution were sampled as cases, while the 90th centile was applied to obtain a sufficient number of cases among black participants. Controls in race/ethnicity groups were below the 75th centile of IMT in all artery segments evaluated, as IMT values greater than the 75th centile are considered abnormal and indicative of increased CVD risk.¹⁸ Cases from that study were classified as having a high severity of atherosclerosis in this study, and controls as having a low severity of atherosclerosis.

Ascertainment of CVD

Incident CHD events included definite or probable myocardial infarction (MI), 'silent' MI per centrally interpreted ECG, definite CHD death or coronary revascularisation. This information was obtained through annual contact of participants, yearly discharge lists from local hospitals and ongoing survey of death certificates.¹⁷ Incident (ischaemic) stroke was identified through hospital discharge codes and deaths attributed to stroke.¹⁹ Physician reviewers adjudicated all possible CHD and stroke events and classified them as definite, probable or non-events based on information abstracted from medical records.¹⁹ Cohort follow-up of incident CHD and stroke events through 31 December 2012 was included in these analyses.

Statistical analyses

Plots of residuals depicted a relatively linear relationship between each PPL parameter (as the iAUC-transformed weighted SD measure) and incident CVD (CHD or stroke). For each PPL parameter, we therefore estimated crude, age-sex adjusted and fully adjusted associations between an increase of 1-unit in the iAUC-transformed weighted SD measure and incident CVD events (CHD individually, stroke individually, and CHD or stroke as a merged outcome). Cox proportional hazard models²⁰ were used to quantify estimates of associations on the relative scale via HRs, and incident rate differences (IRDs) from Poisson models²¹ were used as estimates on the absolute scale.

Since knowledge of the biological mechanism involved in postprandial change and CVD development is not clear, we applied stepwise selection ($p < 0.15$ for inclusion and exclusion)—as opposed to a priori adjustment—to guide in the choice of covariates for fully adjusted models. The following variables, each at visit 2, were considered in such models: age, sex, race (white or African-American), study center location, BMI (≥ 30 kg/m² or < 30 kg/m²), atherosclerosis severity (high or low), HDL-C, LDL-C, fasting blood glucose, current cigarette smoking, former cigarette smoking, prevalent hypertension and use of lipid-lowering medications.

As per findings from the ARIC case-control study of PPL and atherosclerosis,¹ we also estimated associations of our PPL measures with incident CVD by dichotomies of race, BMI and atherosclerosis severity. Comparison of effect measures across these subgroups of low versus

high cardiometabolic risk may provide insights into the temporality and etiology of potential mechanisms. For instance, evidence of an independent association between excessive PPL and incident CVD in participants with low but not high IMT would suggest that PPL exerts its role in the pathophysiology of CVD prior to or during the earlier stages of atherosclerosis. In this study, all statistical analyses were performed using SAS V.9.3 (SAS Corp, Cary, North Carolina, USA).

RESULTS

Of 1114 participants invited into the original ARIC case-control study, 555 individuals were excluded from this study (84 declined participation, 195 had prevalent CVD, 179 had other medical exclusions and 97 had test meal intolerance). Our final analytic sample consisted of 559 participants—228 (41%) women and 148 (26%) African-Americans distributed similarly across the four study sites. Baseline characteristics of participants are presented in [table 1](#).

The mean values of the iAUC-transformed weighted SD measures of PPL at visit 2 were 1.7 for TG, 1.4 for TRL-TG, 1.9 for RP and 1.4 for apoBR. The means of the iAUC PPL measures prior to weighted SD transformation were 708 mg/dL×hour (SD=473) for TG, 536 mg/dL×hour (SD=432) for TRL-TG, 5781 µg/L×hr (SD=3051) for RP and 15 hour (SD=12) for apoBR. Before iAUC calculations were performed, the mean values of the PPL parameters were 121 mg/dL (SD=60) for TG, 71 mg/dL (SD=54) for TRL-TG, 19 µg/L (SD=36) for RP and 3.0 (SD=1.8) for apoBR.

A total of 127 (23%) incident cases of CHD and 27 (5%) incident cases of stroke accrued in the study sample by the end of 2012 (median follow-up=20.5 years). The study was sufficiently powered (at 80%) to detect an HR=1.3 in the overall sample. However, analyses in the overall sample did not reveal any significant associations between the PPL measures and incident CHD or stroke ([table 2](#)). Point estimates of effect sizes (HRs and IRDs) were generally null, even in crude models. As interpreted using the 95% CIs of fully adjusted HRs, estimates of the excess CVD risk (attributed to each 1-unit increase in the iAUC-transformed weighted SD of RP, in this case) are not expected to surpass 28% in 95% of study repetitions.

In stratified analyses, the smallest effect size capable of being detected with sufficient power was an HR=1.6 (in the subgroup of white participants). Similar to as in the overall sample, no significant associations between the PPL measures and incident CVD events were observed by race, BMI category or atherosclerosis severity (all $p > 0.4$). Point estimates of the associations between our PPL measures and CVD from each of these subgroup models were centered around the null value in a similar fashion as in the overall sample. Given the relatively smaller sample size of each subgroup compared to the overall sample, as expected, estimates were also less

Table 1 Characteristics of study participants (N=559) from the ARIC nested case-control study of PPL and atherosclerosis during 1990–1993 by tertiles of the AUC-transformed weighted SD measure of postprandial triglycerides (TG)

Covariates	TG tertile		
	1	2	3
Age mean (SD), years	57.9 (5.6)	58.6 (5.3)	58.1 (5.4)
Sex			
Female, n (%)	103 (56)	69 (37)	54 (29)
Male, n (%)	82 (44)	116 (63)	131 (71)
Race			
African-American, n (%)	47 (25)	48 (26)	50 (27)
White, n (%)	138 (75)	137 (74)	135 (73)
Study centre			
Forsyth, NC, n (%)	34 (18)	47 (25)	59 (32)
Jackson, MS, n (%)	46 (25)	46 (25)	48 (26)
Minneapolis, MN, n (%)	63 (34)	43 (23)	44 (24)
Washington County, MD, n (%)	42 (23)	49 (27)	34 (18)
BMI			
≥ 30 kg/m ² , n (%)	29 (16)	42 (23)	42 (23)
< 30 kg/m ² , n (%)	156 (84)	143 (77)	143 (77)
Carotid IMT level			
High, n (%)	52 (28)	70 (38)	80 (43)
Low, n (%)	133 (72)	115 (62)	105 (57)
HDL-C mean (SD), mg/dL	14.2 (8.5)	10.3 (6.4)	8.2 (4.8)
LDL-C mean (SD), mg/dL	124 (32)	131 (36)	139 (31)
Fasting blood glucose mean (SD), mg/dL	108 (36)	111 (38)	108 (30)
Current cigarette smoking			
Smoker, n (%)	40 (22)	48 (26)	50 (27)
Non-smoker, n (%)	145 (78)	136 (74)	135 (73)
Former cigarette smoking			
Smoker, n (%)	67 (36)	71 (39)	81 (44)
Non-smoker, n (%)	118 (64)	113 (61)	104 (56)
Prevalent hypertension			
Present, n (%)	52 (28)	48 (26)	49 (27)
Absent, n (%)	133 (72)	136 (74)	135 (73)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

precise in stratified analyses. For brevity, quantitative results from stratified analyses are not depicted.

CONCLUSIONS

Extended follow-up of a well-characterised biracial sample of men and women did not reveal evidence of a relationship between exaggerated PPL response and increased incidence of CVD events. Further, no associations between the extent of PPL and incident CVD were observed by obesity status or level of carotid atherosclerosis.

Given the lack of statistically significant associations between our comprehensive measures of PPL and CVD risk, together with the consistently null-sized estimates of these associations, the results of this study suggest that PPL does not influence the risk of atherothrombotic events in a discernible way. Our negative findings mimic those from case-control studies that used a similar lipid load and postchallenge PPL measures,^{2 22} but they are not consistent with the significant (albeit modest) associations reported in considerably more powered

prospective investigations.^{3–8} However, these large-scale prospective studies were limited to non-standardised measures of fasting or non-fasting triglycerides assessed at only one time point. Our investigation was able to assess lipemic response over time using diverse lipoprotein and apolipoprotein measurements from a standardised fat challenge.

Equally important to acknowledge is the low statistical power of this study. Notwithstanding this limitation, until now, this is the largest and most extensive population-based study to examine the longitudinal association between PPL and CVD using standardised postchallenge lipid moieties as measures of PPL. Our findings ultimately point to excessive PPL not being as strong an independent predictor of CVD risk as previously indicated. Nevertheless, on the population level, PPL may be an important overall risk determinant and therapeutic target which influences other CVD risk factors such as HDL-C. Better powered prospective studies with detailed, standardised measures of postprandial change are needed to clarify the role (if any) of excessive PPL in CVD pathophysiology.

Table 2 HR and IRD estimates (with 95% CIs and p values) for associations between an increase of 1-unit in the iAUC-transformed weighted SD measure of each PPL parameter and incident CHD or stroke

PPL parameter	Model	N	Events	HR (95% CI)	p Value	IRD* (95% CI)	p Value
TG	Crude	534	123	0.94 (0.80 to 1.11)	0.459	-4.1 (-12.4 to 5.0)	0.382
	Age and sex	534	123	0.93 (0.80 to 1.10)	0.414	-3.3 (-14.2 to 3.9)	0.386
	Fully adjusted†	519	117	0.95 (0.80 to 1.13)	0.557	-3.8 (-15.3 to 4.2)	0.541
TRL-TG	Crude	495	112	0.97 (0.82 to 1.15)	0.710	-2.2 (-10.1 to 6.5)	0.617
	Age and sex	495	112	0.96 (0.81 to 1.15)	0.662	-2.0 (-11.3 to 6.4)	0.588
	Fully adjusted†	480	106	0.98 (0.81 to 1.18)	0.828	-1.4 (-11.6 to 7.1)	0.674
RP	Crude	534	122	1.06 (0.89 to 1.25)	0.532	2.3 (-5.7 to 10.6)	0.558
	Age and sex	534	122	1.05 (0.89 to 1.25)	0.565	1.1 (-4.5 to 9.2)	0.552
	Fully adjusted†	519	116	1.07 (0.90 to 1.28)	0.437	1.3 (-5.2 to 9.4)	0.517
apoBR	Crude	485	112	0.91 (0.76 to 1.10)	0.340	-1.2 (-9.8 to 7.5)	0.679
	Age and sex	485	112	0.91 (0.76 to 1.10)	0.344	-1.3 (-11.0 to 7.3)	0.698
	Fully adjusted‡	470	106	0.93 (0.77 to 1.13)	0.460	-1.5 (-12.3 to 6.7)	0.706

*Estimate of IRD per 1000 person-years.

†Adjusted for age, sex, race and fasting blood glucose, following stepwise selection.

‡Adjusted for age, sex, race, fasting blood glucose and current smoking status, following stepwise selection.

apoBR, apolipoprotein B100 ratio; IRD, incident rate difference; PPL, postprandial lipemia; RP, retinyl palmitate; TG, postprandial triglycerides; TRL-TG, TG-rich lipoprotein triglycerides.

Author affiliations

¹Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

³Irving Institute for Clinical and Translational Research, Columbia College of Physicians and Surgeons, New York, New York, USA

⁴Michael E DeBakey Veterans Affairs Hospital, Houston, Texas, USA

⁵Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA

⁶Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas, USA

Acknowledgements The authors thank the staff and participants of the ARIC Study for their important contributions.

Contributors DK performed the statistical evaluation of the data and wrote the manuscript. ARS designed the original study protocol, directed the study and provided input throughout the manuscript preparation. HNG, VN, CMB and RCH provided expert input and critical review throughout the manuscript preparation. GH coordinated the study, provided input during manuscript preparation and provided funding. All authors approved the final manuscript.

Funding This work was supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C and HHSN268201100012C).

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Competing interests HNG reports grants from National Institutes of Health USA, during the conduct of the study. VN reports personal fees from Siemens Laboratory, other from Roche, outside the submitted work; and Coinvestigator on a provisional patent filed along with Baylor College of Medicine and Roche for 'Biomarkers to improve prediction of heart failure.' CMB reports personal fees from AstraZeneca, grants and personal fees from Amarin, grants and personal fees from Amgen, grants and personal fees from Eli Lilly, grants and personal fees from Esperion, personal fees from Matinas BioPharma, personal fees from Merck, grants and personal fees from Novartis, grants and personal fees from Pfizer, grants and personal fees from Regeneron, grants and personal fees from Sanofi-Synthelabo, grants from National Institutes of Health, grants from American Heart Association, grants from American Diabetes Association, grants and personal fees from Ionis, outside the submitted work. RCH reports grants from Denka Seiken Co, outside the submitted work; In addition, RCH has a patent 'Biomarkers to Improve Prediction of Heart Failure Risk' (patent no. 61721475) pending.

Ethics approval Institutional Review Boards from all participating institutions approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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