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Original Research Article

Circulating palmitoleic acid is associated with cerebral glucose metabolism in healthy middle-aged individuals: results from the Progression of Early Subclinical Atherosclerosis prospective cohort study

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A B S T R A C T

Background: Excess energy intake upregulates de novo lipogenesis (DNL). Circulating palmitoleic acid (POA) is an objective DNL biomarker associated with higher cardiovascular risk, which has been linked to cerebral hypometabolism. Whether POA also relates to altered cerebral glucose metabolism in midlife remains unknown.

Objectives: This study aimed to examine cross-sectional and longitudinal associations between circulating POA (predictor) and cerebral glucose hypometabolism (outcome), a neuroimaging marker linked to increased risk of subsequent cognitive decline.

Methods: We studied 461 middle-aged [median age, 51 (47–54) y] individuals with subclinical atherosclerosis from the Progression of Early Subclinical Atherosclerosis (PESA) study, a longitudinal observational cohort of asymptomatic individuals (NCT01410318). Red blood cell (RBC) POA was quantified by gas chromatography in blood samples collected at 2 visits of PESA participants who had undergone longitudinal cerebral ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (4.9 y of follow-up time). Dietary data were derived from a validated food-frequency questionnaire. Associations were assessed using region-of-interest and voxelwise multiple regression models as well as mediation analysis.

Results: Cross-sectionally, higher RBC POA was associated with widespread lower FDG uptake across the brain [$\beta = -0.119$ (95% confidence interval: -0.206, -0.032), $P = 0.007$], even after adjusting for cardiovascular risk. Longitudinally, participants with sustained high RBC POA exhibited a 65% greater decline in cerebral FDG uptake compared with those with sustained low POA [$\beta = -0.403$ (-0.744, -0.063), $P = 0.021$], particularly in frontal and parietal regions. RBC POA proportions were higher among individuals adhering to the predefined "Social-Business" dietary pattern and were significantly associated with increased alcohol intake. Furthermore, the association between alcohol intake and subsequent precuneus hypometabolism was partially mediated by RBC POA proportions.

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; DNL, de novo lipogenesis; FDG-PET, fluorodeoxyglucose positron emission tomography; FDR, false discovery rate; PESA, Progression of Early Subclinical Atherosclerosis; POA, palmitoleic acid; RBC, red blood cell; ROI, region-of-interest; SCORE2, Systematic Coronary Risk Evaluation 2; SUVR, standardized uptake value ratio.

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Conclusions: RBC POA, a marker of DNL, is associated with cerebral glucose hypometabolism, supporting that healthy dietary habits in midlife are key to preserving brain health.
This trial was registered at clinicaltrials.gov as NCT01410318.

Keywords: diet, brain health, neuroimaging, energy metabolism, biomarkers

Introduction

Increased energy intake, fueled by overconsumption of modern, cheap, highly palatable, energy-dense processed foods, is at the core of the obesogenic environment [1]. Energy surplus leads to increased acetyl-CoA bioavailability [2]. In a fasting state, acetyl-CoA is metabolized through the tricarboxylic acid cycle in the mitochondria to obtain energy. Under a fed state, acetyl-CoA is redirected from mitochondria to cytosol for synthesis of fatty acids [3], a process known as de novo lipogenesis (DNL), which primarily occurs in the liver and adipose tissue [4]. Although DNL is a metabolic safety valve to avoid the harms of energy surplus, its sustained upregulation leads to the accumulation of visceral and ectopic fat and increased cardiovascular risk [5].

This has spurred interest in DNL assessment in clinical settings [6]. The use of isotopically labeled tracers remains the gold-standard to measure DNL activity [7]; however, these methods are expensive and do not capture the long-term exposure to energy surplus [6]. Lipidomics is now recognized as a low-cost, straightforward, and widely accessible alternative. Because it does not require preadministration of isotope-labeled tracers, lipidomics can leverage stored samples from observational studies to generate clinical evidence on DNL. Lipidomic assessment of DNL relies on the profiling of de novo fatty acids. Palmitic, stearic, and oleic acids are end-products of DNL; however, they can also derive from exogenous (dietary) origin, making it challenging to disentangle the exact contribution of DNL to their blood concentrations. In contrast, cis-palmitoleic acid (C16:1n-7, POA) is also an end-product of DNL but is rarely present in food and its circulating concentrations primarily reflect endogenous synthesis [8]. Therefore, circulating POA emerged as a widely accepted biomarker of DNL in observational studies, showing consistent associations with cardiovascular risk factors such as fatty liver disease [9], hypertriglyceridemia and insulin resistance [10], glycemia worsening [11], and incident type 2 diabetes [12]. The implications of sustained upregulated DNL might extend to the central nervous system, because energy intake is increasingly perceived as a determinant of brain health [13].

Cerebral glucose hypometabolism, as measured by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), is a sensitive biomarker for brain health and is associated with increased cardiovascular risk [14,15] and risk of subsequent cognitive decline, even in cognitively unimpaired individuals [16–18]. Because the link between sustained upregulated DNL and brain health in midlife remains unknown, our primary analyses examined cross-sectional and longitudinal associations between circulating POA and cerebral glucose metabolism in middle-aged asymptomatic participants from the Progression of Early Subclinical Atherosclerosis (PESA) cohort [19]. Our secondary analyses examined the interplay between diet, cardiovascular risk, and brain health. This could offer a novel insight into whether a mechanism activated upon sustained overfeeding, besides increasing cardiovascular risk, leads to early brain health deterioration.

Methods

Study population

The PESA study (NCT01410318) is an observational, prospective, and longitudinal cohort study that recruited 4184 asymptomatic individuals aged 40 to 54 y to examine the prevalence and progression of subclinical atherosclerosis and its risk factors in midlife [19]. All male and female Santander Bank employees based in Madrid (Spain) aged 40 to 55 y at recruitment were invited to participate on a volunteer basis. Exclusion criteria included cardiovascular disease, cancer, or any disease expected to shorten lifespan or influence protocol adherence. Further details of the rationale and design of the PESA study can be found in the original study protocol [19].

All 3 study visits included extensive vascular imaging, medical assessments, lifestyle questionnaires, and blood collection at baseline (Visit 1, from June 2010 to March 2014), 3-y (Visit 2, from June 2013 to March 2017) and 6-y (Visit 3, from July 2016 to January 2020) follow-up visits. Participants with high burden of subclinical atherosclerosis at baseline, defined as being in the highest plaque thickness tertile or having a coronary artery calcification score $\geq$1, additionally underwent 2 full-body FDG-PET scans at baseline (from February 2013 to February 2015, between visits 1 and 2) and follow-up (from November 2017 to August 2019, in Visit 3) [20]. In this study, we included PESA participants with available data on measurements of circulating POA [baseline = Visit 2; follow-up = Visit 3; follow-up time, 3.1 (2.8–3.5) y] and 2 brain FDG-PET scans [follow-up time, 4.9 (4.4–5.3) y]. The PESA study was approved by the ethics committee of the Instituto de Salud Carlos III, Madrid, Spain, and all participants provided informed consent for all clinical evaluations before enrolment.

Sample collection and fatty-acid analysis

Fatty-acid analysis was performed at the Hospital del Mar Research Institute (Barcelona, Spain) in fasting blood samples obtained and stored at −80°C. In short, we isolated red blood cell (RBC) membranes by centrifugation, extracted lipids, and obtained the fatty-acid methyl esters by treatment with boron trifluoride–methanol. Fatty-acid methyl esters were quantified using gas chromatography/electron ionization mass spectrometry. Further details on chromatographic conditions can be found in a previous study, involving determination of 24 different fatty acids [21]. Measurement of 2 new species was recently incorporated in the platform, so RBC POA is expressed as a percentage of the total amount of 26 determined fatty acids. The upper and lower limits of quantification of RBC POA were 8.0 and 0.5 μg/mL, respectively. To ensure the between-batch reproducibility of the measurements, quality control samples were analyzed in every batch. The interassay coefficient of variation for POA was 5.1%. Follow-up and baseline RBC POA values were subtracted and divided by baseline proportions to obtain % change of RBC POA.

FDG-PET image acquisition and processing

The acquisition protocol has been previously described [14,15]. Briefly, upper-body craniocaudal PET scans were acquired in 5 bed

positions (3 min/bed) on a hybrid PET/MR Philips Ingenuity system (Philips Healthcare) at 120 min after radiotracer intravenous injection. Fasting participants received a mean target FDG dose of 294 (270–300) MBq. Data were reconstructed in 3D mode using a blob-based, list-mode iterative algorithm with time-of-flight information and corrected with MR attenuation maps. Reconstructed images had a transverse field of view of 576 mm and a voxel size of $4 \times 4 \times 4$ mm^3. All images were reviewed by expert technicians, radiologists, or nuclear medicine specialists.

All FDG-PET scans were aligned and cropped to retain the brain in the field of view. For longitudinal analysis, an extra processing step included coregistration to achieve a robust intrasubject alignment between timepoints. All scans were then spatially normalized to a sample-specific template in the Montreal Neurological Institute (MNI) standard space [22] and FDG uptake was normalized to a reference region derived from a data-driven approach [23], yielding standardized uptake value ratio (SUVR) images that were finally smoothed with a Gaussian filter. For longitudinal analysis, resulting baseline and follow-up SUVR images were subtracted and divided by baseline SUVR to obtain SUVR % change maps. All processing steps were carried out using SPM12 [14,15]. In addition to parametric maps for voxelwise analysis, volume-weighted mean SUVR at baseline and follow-up were calculated in the whole cortex and other post hoc regions of interest (ROIs) for ROI-based analysis.

Cardiovascular risk, subclinical atherosclerosis, and dietary assessment

Cardiovascular risk factors were determined from medical interviews, body measurements, and blood samples at all visits [20]. Cardiovascular risk was assessed with the Systematic Coronary Risk Evaluation 2 (SCORE2), a risk scale calibrated to a middle-aged European population based on the following risk factors: age, sex, total and HDL cholesterol, systolic blood pressure, smoking status, and diabetes [24]. Subclinical atherosclerosis was assessed using 3D vascular ultrasound with standardized 6-cm acquisition in the carotid and femoral arteries [25]. Total atheroma plaque volume was calculated as the sum of plaque volumes in the left and right arteries of carotid and femoral territories and was transformed into data-driven quartiles.

Moreover, habitual food intake was assessed by the computerized Dietary History-Enrica 1-h questionnaire developed and validated for the Spanish population [26]. Participants reported all the foods usually consumed in the previous year, defined as food consumed at least once every 15 d. This questionnaire collects standardized information on 861 foods, additionally including 184 recipes for traditional or commonly consumed dishes in Spain, and it automatically converts the foods to nutrients using food composition tables from Spain. In a previous study, foods were classified into 21 groups according to nutrient content and submitted to factor analysis to identify dietary patterns in the PESA study [27]. Three clusters were identified, namely Mediterranean, Western, and Social-Business diets [27]. In this study, we used information from Visit 1 on dietary clusters. In addition, because acetyl-CoA (the precursor of POA) serves as a central metabolic intermediate integrating the catabolism of fat, carbohydrates, proteins, and alcohol, we also used information from Visit 1 on these dietary items.

Statistical analysis

Summary descriptions of measurements were presented as median (IQR) for continuous variables and *n* (%) for categorical variables. We used multiple linear regression models to examine cross-sectional associations between RBC POA (exposure) and cortical FDG uptake (outcome) at both baseline and follow-up visits, adjusting for age at baseline, sex, APOE4 carriership, education level, and blood glucose concentration at the time of the FDG-PET scans (Model 1). Covariates are specified in **Supplementary Methods**. These models were further adjusted for SCORE2 to study whether the association between RBC POA and cerebral glucose metabolism was independent of cardiovascular risk (Model 2). Secondary analyses assessed the effect of RBC POA (exposure) on SCORE2 and total plaque burden (outcomes), adjusting for age at baseline, sex, and *APOE4* carriership.

For longitudinal analysis, we tested the association between the % change in RBC POA (exposure) and % change in cortical FDG uptake (outcome) using a multiple linear regression model, adjusting for the same covariates listed in cross-sectional analyses. Given the expected small effect sizes from longitudinal models involving RBC POA as exposure [28], we also categorized our sample into "low" and "high" RBC POA proportions as defined by the first and third tertiles at each

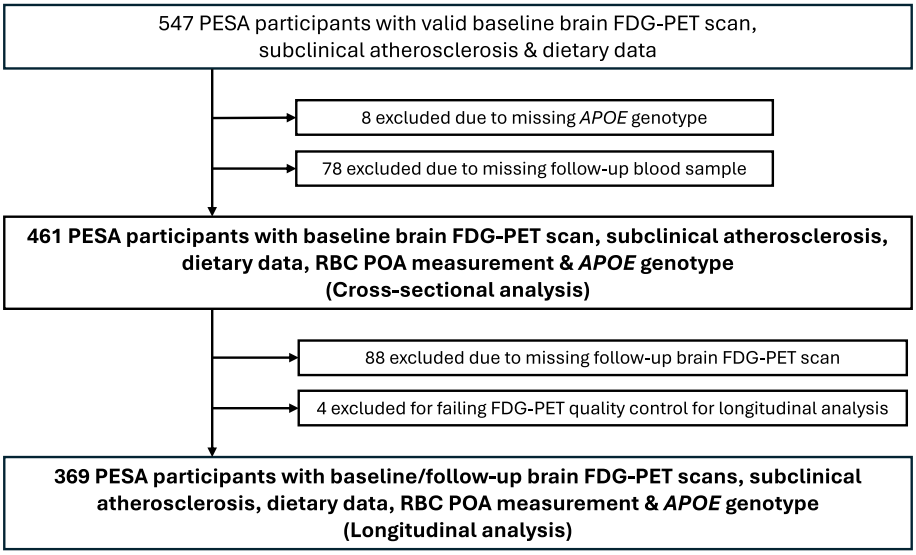


FIGURE 1. Participant flowchart.

visit. Longitudinal groups were then defined as participants who had sustained "low" and "high" RBC POA proportions over time, and those who changed from one group to another. Differences in cortical glucose metabolism % change over time across groups were assessed with analysis of variance (ANOVA) and post hoc Bonferroni-corrected comparisons. In addition, interaction effects of RBC POA and RBC POA % change with age, sex, and *APOE4* carriership were included in the main cross-sectional and longitudinal regression models, respectively. For visualization, age was categorized into groups of 40 to 44, 45 to 49, and 50 to 54 y. Similar models compared SCORE2 % change and total plaque volume change between RBC POA change groups.

With respect to diet, we evaluated the differences in baseline RBC POA and FDG uptake across the diet clusters previously identified in the PESA cohort (Mediterranean, Western, and Social-Business) [27] using ANOVA and post hoc Bonferroni-corrected comparisons. We also examined the association between intake of fat, carbohydrates, proteins, and alcohol at Visit 1 with RBC POA measured at later visits. Taking advantage of the longitudinal nature of the PESA study, we evaluated whether the association between the intake of dietary items (Visit 1, exposure) and FDG uptake (Visit 3, outcome) was mediated by RBC POA (Visit 2, mediator). We computed the mediation model using the *mediate* package in R (R Core Team) with 1000 bootstrap simulations to estimate the direct and indirect effects, which represent the extent to which a dietary item intake affects cerebral glucose metabolism via RBC POA proportions.

To complement cross-sectional and longitudinal ROI-based analyses, identical voxelwise models were computed, using the threshold-free cluster enhancement method [29] and false discovery rate (FDR) correction for multiple comparisons in SPM12.

In all cases, outcome variables were centered for improved visualization and the residuals from adjusted models were plotted. Variables with non-normal distributions, including RBC POA and POA % change, were log-transformed. Cases with missing data were excluded from the respective analyses and final sample sizes were reported in all figure/table captions. Standardized β and 95% confidence intervals (CIs) were reported for linear regression models and F-statistics, partial effect sizes ηp^2 and 95% CIs were reported for ANOVAs. Statistical significance was set at $\alpha = 0.05$. R 4.4.1 was used for statistical analysis.

Given the limited availability of prior literature on the association between RBC POA proportions and neuroimaging outcomes, and considering that this work was originally designed as an exploratory substudy within participants of the PESA study with available data, an a priori power calculation was not feasible. Nevertheless, a post hoc power analysis was performed to determine the statistical power attainable with our sample size (Supplementary Methods).

Results

Sample characteristics

In this study, we measured RBC POA longitudinally in 461 PESA participants, selected from 547 participants with baseline FDG-PET scans [14] (Figure 1). A total of 78 (17%) participants were female and 73 (16%) were *APOE4* carriers, and the median (IQR) age of the participants was 51.3 (47.2–53.9) y (Table 1). A total of 369 participants also had follow-up brain FDG-PET data and were included in the longitudinal analyses (Figure 1). The median (IQR) RBC POA increased from 0.19% (0.15%–0.25%) at baseline to 0.32% (0.25%–0.42%) at follow-up.

TABLE 1
Characteristics of the study sample[1]

Demographics	Baseline ($n = 461$)	Follow-up ($n = 369$)
Age at FDG-PET (y)	51.3 [47.2–53.9]	55.7 [52.0–58.6]
Sex, *n* (%)		
Female	78 (17%)	58 (16%)
Male	383 (83%)	311 (84%)
APOE4 carriership, *n* (%)		
No	388 (84%)	303 (82%)
Yes	73 (16%)	66 (18%)
Total cholesterol (mg/dL)	209 [187–230]	203 [176–227]
HDL cholesterol (mg/dL)	44 [38–51]	49 [42–57]
Systolic blood pressure (mm Hg)	120 [113–129]	121 [113–132]
Diabetes, *n* (%)		
No	442 (96%)	348 (94%)
Yes	19 (4%)	21 (6%)
Smoking, *n* (%)		
No	346 (75%)	300 (81%)
Yes	115 (25%)	69 (19%)
Hypertension[2], *n* (%)		
No	374 (81%)	257 (70%)
Yes	87 (19%)	112 (30%)
RBC POA (%)	0.19 [0.15–0.25]	0.32 [0.25–0.42]
RBC POA change groups, *n* (%)		
Sustained-low	63 (17%)	
Sustained-high	66 (18%)	
SCORE2 risk score[3] (%)	3.15 [2.27–4.28]	4.01 [2.83–5.07]
Total plaque volume[4] (mm^3)	80.3 [14.3–188.5]	117.2 [31.5–247.8]
Estimated intake of protein (g/d)	99.6 [89.3–111.6]	97.6 [84.7–111.3]
Estimated intake of fat (g/d)	105.5 [92.6–121.9]	102.6 [85.6–120.1]
Estimated intake of carbohydrates (g/d)	212.7 [176.3–251.0]	207.9 [163.2–250.0]
Estimated intake of alcohol (g/d)	9.8 [3.3–19.0]	9.8 [3.6–18.6]
Dietary clusters[5], *n* (%)		
Mediterranean	149 (33%)	—
Western	189 (42%)	—
Social-Business	120 (26%)	—

Abbreviations: FDG-PET, fluorodeoxyglucose – positron emission tomography; POA, palmitoleic acid; RBC, red blood cell; SCORE2, Systematic Coronary Risk Evaluation 2.

[1] Data are median [IQR] for continuous variables and *n* (%) for categorical variables.

[2] $n = 368$ at follow-up.

[3] $n = 429$ at baseline, $n = 332$ at follow-up.

[4] $n = 426$ at baseline; $n = 367$ at follow-up.

[5] $n = 458$.

Cross-sectional associations between RBC POA and cerebral glucose metabolism

First, we assessed the cross-sectional linear associations between RBC POA and cerebral glucose metabolism. At baseline, higher RBC POA was significantly associated with lower cortical FDG uptake [Model 1, $\beta = -0.119$ (95% CI: −0.206, −0.032), $P = 0.007$; Figure 2A]. FDR-corrected voxelwise analysis further revealed that this negative association was widespread across the brain (Figure 2B). Given that higher RBC POA was associated with higher SCORE2 (Supplementary Figure 1A) and that cardiovascular risk has been shown to impact cerebral glucose metabolism in middle-aged PESA participants [14,15], we additionally adjusted the previous model for SCORE2. Although the effect size decreased when adjusted for SCORE2 at the cortical level [Model 2, $\beta = -0.090$ (95% CI: −0.184, 0.004) $P = 0.061$; Figure 2C], the negative association between RBC POA and FDG uptake was partially independent of cardiovascular risk across the brain at the voxelwise level (Figure 2D). Interestingly,

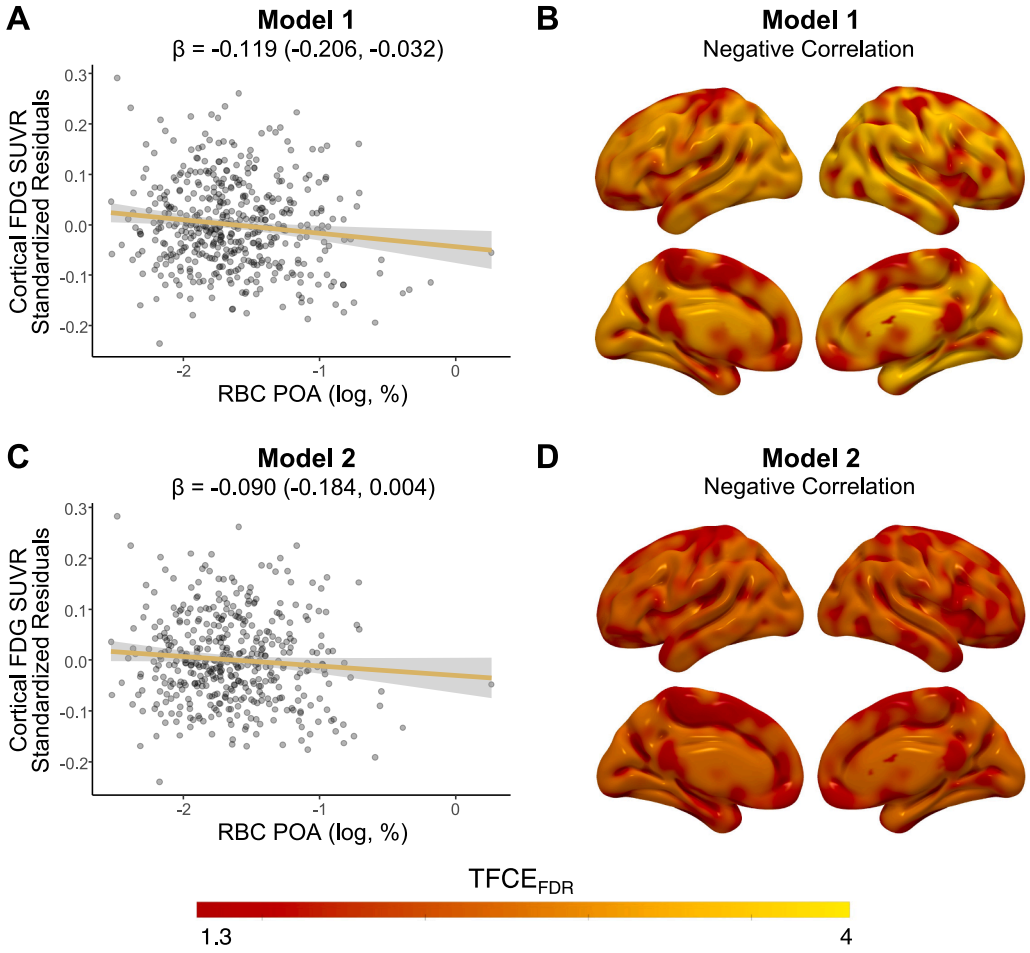


FIGURE 2. Cross-sectional associations between RBC POA and cortical FDG uptake at baseline. Scatterplot showing the baseline association between RBC POA and cortical FDG uptake (A) and corresponding FDR-corrected voxelwise clusters showing the negative correlation between RBC POA and FDG uptake (B) for model 1 and for model 2 (C, D), using multiple linear regression. Model 1 was adjusted for age, sex, *APOE4* carriership, education levels, and blood glucose proportions at the time of scan (n = 461). Model 2 was further adjusted for Systematic Coronary Risk Evaluation 2 (SCORE2) (n = 429). In scatterplots, color lines show estimated regression slopes and gray shadows represent 95% CI, y-axes represent the adjusted residuals, and β represent standardized regression coefficients (95% CI) of the associations. CI, confidence interval; FDG, fluorodeoxyglucose; FDR, false discovery rate; POA, palmitoleic acid; RBC, red blood cell.

higher RBC POA was also significantly associated with greater burden of total plaque volume, both at baseline and follow-up (Supplementary Figure 1B).

Additionally, we assessed the interactions between baseline RBC POA and age, sex, and *APOE4* carriership to explain baseline cortical glucose metabolism. We found a significant interaction between RBC POA and age [β = 0.120 (95% CI: 0.026, 0.213), P = 0.012; Supplementary Figure 2A], with a weaker negative correlation between RBC POA and cortical FDG uptake in older individuals. No interactions were observed with sex or *APOE4* carriership (Supplementary Figure 2B, C).

Of note, our baseline results were consistently replicated at the follow-up visit (Supplementary Figure 3). RBC POA was negatively associated with cortical FDG uptake before [Model 1, β = −0.133 (95% CI: −0.229, −0.036), P = 0.007] and after adjusting for SCORE2 [Model 2, β = −0.141 (95% CI: −0.246, −0.036), P = 0.009]. Moreover, voxelwise maps revealed that RBC POA had an effect on glucose metabolism in superior and frontal areas of the brain.

Longitudinal association between RBC POA and cerebral glucose metabolism

Next, longitudinal changes in RBC POA were assessed in relation to changes in cerebral glucose metabolism. RBC POA % change was not linearly associated with cortical FDG uptake % change [β = −0.041 (95% CI: −0.146, 0.064), P = 0.446; Figure 3A]. There were no interactions between RBC POA % change and age, sex, or *APOE4* carriership (Supplementary Figure 4).

We then classified participants into longitudinal RBC POA change groups using data-driven tertiles thresholds (sustained low and high RBC POA over time and change from low to high or high to low RBC POA). However, because of the small sample sizes of the RBC POA

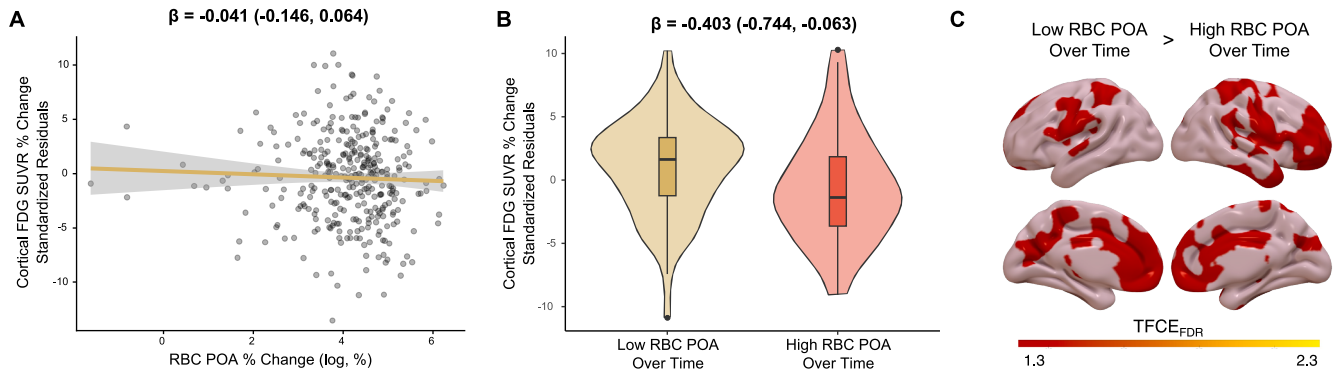


FIGURE 3. Longitudinal associations between RBC POA and cortical FDG uptake. Scatterplot showing the association between RBC POA % change and cortical FDG uptake % change (A), using multiple linear regression ($n = 369$). Color line shows estimated regression slope and gray shadow represents 95% CI. Violin plots showing the differences in cortical FDG uptake % change between groups of sustained low ($n = 63$) and high ($n = 66$) RBC POA proportions over time (B) and corresponding FDR-corrected voxelwise clusters showing differences in FDG uptake between the 2 groups (C), using ANOVA. Boxplots indicate median (bold line), first and third quartiles (box limits), and interquartile range (whiskers). All models were adjusted for age, sex, *APOE4* carriership, education levels, and blood glucose proportions at the time of both scans. In all plots, y-axes represent the adjusted residuals. β represent standardized regression coefficients (95% CI) of the associations. ANOVA, analysis of variance; CI, confidence interval; FDG, fluorodeoxyglucose; FDR, false discovery rate; POA, palmitoleic acid; RBC, red blood cell.

change groups, we focused on sustained-high ($n = 66$) and sustained-low ($n = 63$) RBC POA categories. We found a significant difference in cortical FDG uptake % change between sustained high and low RBC POA groups [$\beta = -0.403$ (95% CI: −0.744, −0.063), $P = 0.021$; Figure 3B]. Participants with sustained high RBC POA showed a 65% greater decrease in cortical glucose metabolism (3.53% ± 4.48%, 0.72% decline/y) compared with those with sustained low RBC POA (2.14% ± 3.60%, 0.43% decline/y). Voxelwise analyses revealed modest effects, most pronounced in frontal and parietal regions (Figure 3C). Across the main 4 RBC POA change groups, we observed a significant difference in cortical glucose metabolism (Supplementary Figure 5). There were no significant differences in SCORE2 % change between sustained-high and sustained-low RBC POA (Supplementary Figure 6A), but participants in the sustained-high RBC POA group exhibited greater increases in total atheroma plaque volume than the sustained-low group [$\beta = 0.558$ (95% CI: −0.205, −0.912), $P < 0.001$; Supplementary Figure 6B].

Dietary intake, RBC POA, and cerebral glucose metabolism

Finally, we assessed the interplay between dietary items, RBC POA, and cerebral glucose metabolism. At baseline, we observed a significant difference in RBC POA among the dietary clusters previously identified in the PESA study [27] [$F = 1.948$, $\eta p^2 = 0.018$ (95% CI: 0.001, 0.046), $P = 0.008$], with individuals following the Social-Business pattern having the highest RBC POA [Mediterranean compared with Western: $\beta = 0.038$ (95% CI: −0.052, 0.128), $P = 0.409$, $P_{adj} = 1.000$; Mediterranean compared with Social-Business: $\beta = 0.139$ (95% CI: 0.037, 0.240), $P = 0.008$, $P_{adj} = 0.023$; Western compared with Social-Business: $\beta = 0.101$ (95% CI: 0.006, 0.195), $P = 0.037$, $P_{adj} = 0.110$; Figure 4A]. The main contributor to the Social-Business dietary pattern is alcohol intake, as we previously identified [27] (Figure 4B). No differences in cortical FDG uptake were found across dietary clusters [$F = 8.202$, $\eta p^2 = 0.008$ (95% CI: 0.000, 0.030) $P = 0.442$; Supplementary Figure 4C]. However, FDR-corrected voxelwise analysis identified a cluster in the precuneus where glucose metabolism was significantly lower in individuals following the Social-Business dietary pattern compared with those following the Mediterranean diet (Figure 4D). Regarding the dietary contributors to the pool of acetyl-CoA (i.e., total protein, total fat, total carbohydrates, and alcohol intake), alcohol was the only factor significantly associated with higher RBC POA at both visits [$\beta = 0.173$ (95% CI: 0.078, 0.267), $P < 0.001$ at Visit 2; $\beta = 0.230$ (95% CI: 0.124, 0.336), $P < 0.001$ at Visit 3; Supplementary Table 1]. Leveraging the availability of measurements at different timepoints, we tested whether alcohol intake (Visit 1) was associated with subsequent precuneus glucose hypometabolism (Visit 3) and whether this association was mediated by RBC POA (Visit 2). We observed that higher baseline alcohol intake was associated with subsequent 6-y lower glucose metabolism in the precuneus [total effect: $\beta = -0.183$ (95% CI: −0.286, −0.080), $P = 0.001$; Figure 4E]. The mediation analysis revealed that this association was partially (17%) mediated by RBC POA proportions [indirect effect: $\beta = -0.032$ (95% CI: −0.062, −0.007), $P = 0.010$; direct effect: $\beta = -0.154$ (95% CI: −0.260, −0.050), $P = 0.008$; Figure 4F].

Discussion

In this longitudinal study of asymptomatic, middle-aged participants from the PESA study, we examined the interplay between RBC POA, an objective biomarker of DNL, cerebral glucose metabolism, and diet. Higher RBC POA proportions were associated with lower cortical FDG uptake, a sensitive marker of brain health and increased vulnerability to subsequent cognitive decline. Participants with sustained high RBC POA over time (i.e., high rates of DNL) exhibited a greater decline in cortical FDG uptake, particularly in frontal regions, than those with sustained low levels. In addition, RBC POA was higher among individuals adhering to the "Social-Business" dietary pattern, and partially mediated the association between higher self-reported alcohol intake (a key feature of this dietary pattern) and reduced precuneus FDG uptake 6 y later. Together, these findings strengthen the link between diet-related energy surplus, cardiovascular risk, and early brain health deterioration.

Three aspects of this study should be emphasized. First, the clinical relevance of the main finding. Although the link between DNL and adverse cardiometabolic health is well established, to our knowledge, no prior work has investigated whether DNL relates to brain health in midlife. In this study, we show that higher RBC POA proportions are

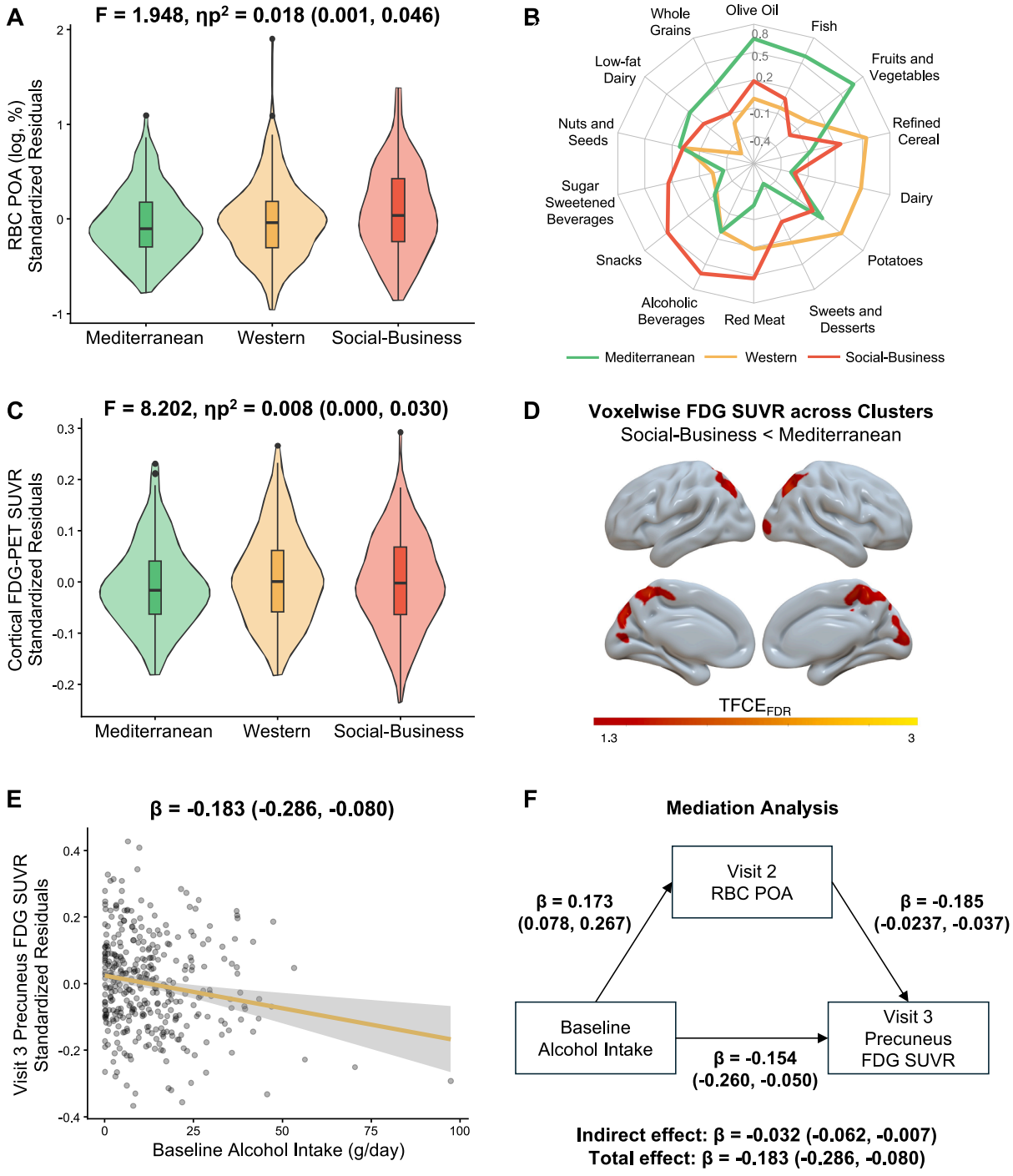


FIGURE 4. Interplay between diet, RBC POA and cerebral glucose metabolism. Violin plots showing the differences in baseline RBC POA across the dietary patterns identified previously in the PESA study—Mediterranean, Western, and Social-Business diets [27] using ANOVA (n = 458) (A). Radarplot from Peñalvo et al. [27] showing the weight of each food group on dietary patterns in a previous study in the PESA cohort after component analysis (B). Violin plots showing the differences in baseline FDG uptake across those dietary patterns using ANOVA (n = 458). (C). FDR-corrected voxelwise clusters showing brain regions where FDG uptake was lower in the Social-Business group compared with the Mediterranean group (D), using ANOVA. Boxplots indicate median (bold line), first and third quartiles (box limits), and interquartile range (whiskers). ANOVA results are represented as F-statistics and partial effect sizes ηp^2 (95% CI). Scatterplot showing the association between baseline alcohol intake and 6-y follow-up (Visit 3) FDG uptake in the precuneus (E), using multiple linear regression (n = 369). Color line shows estimated regression slope and gray shadow represents 95% CI. Mediation analysis showing the mediator role of RBC POA (Visit 2) on the association between alcohol intake at baseline (predictor) and Visit 3 precuneus FDG uptake (outcome) (n = 369) (E). All models were adjusted for age, sex, and *APOE4* carriership, and additionally for education levels and blood glucose proportions at the time of scan in the case of using FDG uptake as outcome. In all plots, y-axes represent the adjusted residuals. β (95% CI) are standardized regression coefficients and respective CI. ANOVA, analysis of variance; CI, confidence interval; FDG, fluorodeoxyglucose; FDR, false discovery rate; PESA, Progression of Early Subclinical Atherosclerosis; POA, palmitoleic acid; RBC, red blood cell.

associated with widespread lower glucose metabolism in the cortex, consistent across timepoints, in line with increased susceptibility to later cognitive decline. Moreover, individuals with sustained high RBC POA proportions over time exhibited a 65% greater decline in cortical metabolism than those with sustained low levels. Relative to the sustained-low group's annual decline of 0.43%, the sustained-high group's annual decline of 0.72% represents a 1.67-fold acceleration in metabolic aging. This means that over a 10-y period, the brain metabolism of individuals with sustained high RBC POA proportions will have aged 16.7 y. Notably, greater metabolism decline in the sustained-high RBC POA group was most prominent in frontal regions, where glucose metabolism has been implicated in brain resilience processes [30]. This suggests that sustained high RBC POA over time may relate to reduced metabolic resilience, potentially lowering the brain's capacity to buffer age- and disease-related cognitive deterioration.

In addition, we previously reported in this cohort that cortical hypometabolism is associated with high cardiovascular risk both cross-sectionally and longitudinally [14,15]. Notably, the link between RBC POA and cerebral glucose uptake was minimally attenuated after adjustment for SCORE2, suggesting an effect that extends beyond classic cardiovascular risk. Future studies should determine whether DNL biomarkers such as RBC POA provide additional value over standard risk scores for identifying individuals at risk of early brain metabolic decline. These observations support potential cognitive benefits of limiting energy surplus, plausibly mediated through effects on neuronal plasticity and altered cerebrovascular regulation (e.g., impaired neurovascular coupling, microvascular reactivity or glucose transport), among other mechanisms [31].

The second aspect relates to dietary determinants of circulating POA, because no studies to date have examined DNL in relation to dietary patterns, which capture the complex relationships among dietary items in real life. We leveraged previous PESA findings [27], showing that adherence to the "Social-Business" eating pattern, characterized by frequent snacking, eating out, and increased alcohol intake, was linked to a higher burden of subclinical atherosclerosis and greater cardiovascular risk than Mediterranean or Western patterns. In this study, RBC POA proportions were significantly higher in the "Social-Business" pattern than among those adhering to the other patterns, underscoring the potential of RBC POA to identify individuals following harmful dietary patterns. Notably, high alcohol consumption, a salient feature of this pattern [27], was also associated with increased RBC POA. This is mechanistically linked to the ability of alcohol to stimulate hepatic DNL through multiple pathways [32]. In line with this, higher alcohol intake was associated with lower precuneus glucose uptake 6 y later, an association partially mediated by RBC POA proportions. This is consistent with findings of cerebral glucose hypometabolism in the orbitofrontal gyrus and superior parietal cortex in individuals with alcohol use disorder [33], with heavy alcohol consumption being hypothesized to facilitate alternative brain energy substrates [34]. Moreover, alcohol consumption in midlife has been linked to structural brain changes in frontal and parietal cortices [35]. Although our findings should be interpreted with caution because of the small mediation effect, they are particularly relevant because the precuneus is among the most metabolically active regions at rest and supports higher-order cognitive functions [36]. Importantly, metabolic decline in the precuneus has been linked to accelerated brain aging and cognitive impairment [37–39]. By uncovering the interplay between dietary alcohol—high RBC POA—reduced brain glucose metabolism, our findings strengthen the inference that diet at midlife may play a protective role in brain function. If causality is confirmed by randomized controlled trials, limiting energy surplus (i.e., by limiting alcohol intake) could serve as a safe, accessible population-level strategy to promote cognitive health.

Third, we highlight the methodological approach of our study. Fatty acids biomarkers can be measured in different blood pools; however, because plasma sample collection is routine, most observational studies of POA have relied on total plasma or plasma fractions, whereas RBC POA has been largely overlooked [12]. Yet, blood pools are not interchangeable. First, POA undergoes partitioning, being enriched in plasma triglycerides [40]. Thus, measurements on total plasma or the triglyceride fraction may overestimate POA in hypertriglyceridemia, complicating comparisons across groups with different fasting triglyceride proportions [41]. Using RBCs mitigates this limitation, as their fatty-acid composition is unaffected by the presence of hypertriglyceridemia. Second, lipid pools differ in fatty-acid turnover and therefore represent distinct exposure windows: fasting plasma reflects the past few hours (triglycerides) to days (cholesteryl esters), whereas RBC fatty-acid profile is less labile because of the ~120-d RBC lifespan indexing the nutritional/metabolic milieu over the preceding 2 to 3 mo [42], thus being a reliable indicator of the long-term exposure to environment.

Our study has several limitations. The observational PESA study precludes causal inferences and residual confounding from unmeasured environmental or genetic factors cannot be ruled out. Future studies are needed to account for additional confounders within the associations among alcohol intake, RBC POA proportions, and cerebral glucose metabolism. In addition, all PESA participants were employees of one of the largest banks in Spain with a middle-to-high socioeconomic status and specific lifestyle habits, and only 17% were female, which limits the generalizability of our findings. Also, the absence of cognitive outcome data limits the clinical interpretation of our findings, as we cannot assess whether the associations among RBC POA, alcohol intake, and cerebral hypometabolism are accompanied by cognitive deterioration. Although substantial cognitive decline is not expected in PESA participants given their relatively young age, ongoing and future follow-up of the cohort, including cognitive assessments, will be essential to determine whether these metabolic changes translate into cognitive trajectories [43]. Additionally, food consumption was self-reported, introducing potential response bias. Finally, the 3-y gap between dietary assessment (Visit 1) and RBC POA measurement (Visit 2) is a limitation, although it also strengthens temporal ordering for mediation analyses, which are generally ill advised in purely cross-sectional data.

Key strengths of this study include the large number of longitudinal FDG-PET scans in middle-aged asymptomatic individuals (an ideal prevention target), comprehensive clinical phenotyping, sequential measurements of DNL biomarkers, and the careful choice of the blood pool for fatty-acid determination.

In conclusion, our results uncover a modifiable lifestyle/dietary factor linking cardiovascular risk and brain health. Future research should focus on whether targeting blood POA (i.e., by avoiding energy surplus during midlife, mostly by limiting alcohol intake) may be a cost-effective strategy not only to protect cardiovascular health but also to preserve cognitive performance at later stages.

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Author contributions

The authors' responsibilities were as follows – AS-V, CT-P, JDG, BI, VF, MC-C: conceptualization; AS-V, CT-P, AF-P, JM-S, IG-L, AG-A, JDG, MC-C: data curation; AS-V, BI, VF, MC-C: funding acquisition; AS-V, CT-P, IL, IG-L, MAM, AG-A, JD-G, BI, VF, MC-C: investigation; CT-P, MS, JS-G, JDG, MC-C: formal analysis; AS-V, CT-P, AF-P, JM-S, JS-G, JDG, MC-C: methodology; CP-H, BI, MC-C: project administration; MAM, VF, MC-C: resources; JDG, BI, VF, MC-C: supervision; JDG, MC-C: validation; AS-V, CT-P, MC-C: writing – original draft; AS-V, CT-P, IL, MS, AF-P, JM-S, IG-L, CP-H, MAM, AG-A, JS-G, JDG, BI, VF, MC-C: writing – review and editing; and all authors: have read and approved the final manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that no generative AI or AI-assisted technologies were used in the writing of this manuscript.

Conflict of interest

JS-G is a Philips employee. JDG is currently an AstraZeneca employee and has received research support from GE healthcare, Roche Diagnostics, and Hoffmann-La Roche, has given lectures in symposia sponsored by General Electric, Philips, Life Molecular Imaging, and Biogen, has served at scientific advisory boards and/or as a consultant for Prothena and Roche Diagnostics, and is the inventor, founder, and co-owner of BetaScreen. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data described in the manuscript, code book and analytic code will be made available upon request to the corresponding authors and approval by the Progression of Early Subclinical Atherosclerosis Scientific Committee. For additional information, please see our website at http://www.pesastudy.org/.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2026.101392.

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