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Pelargonidin and Berry Intake Association with Alzheimer's Disease Neuropathology: A Community-Based Study

Puja Agarwal[a,b,c,*], **Thomas M. Holland**[b,d], **Bryan D. James**[a,b], **Laurel J. Cherian**[e], **Neelum T. Aggarwal**[a,e], **Sue E. Leurgans**[a,e], **David A. Bennett**[a,e], **Julie A. Schneider**[a,e,f]

[a]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA

[b]Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA

[c]Department of Clinical Nutrition, Rush University Medical Center, Chicago, IL, USA

[d]Rush Institute of Healthy Aging, Rush University Medical Center, Chicago, IL, USA

[e]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

[f]Department of Pathology, Rush University Medical Center, Chicago, IL, USA

Abstract

Background: An anthocyanidin, pelargonidin, primarily found in berries, has antioxidant and anti-inflammatory properties, and is associated with better cognition and reduced Alzheimer's dementia risk.

Objective: This study investigated if pelargonidin or berry intake is associated with Alzheimer's disease (AD) neuropathology in human brains.

Methods: The study was conducted among 575 deceased participants (age at death = 91.3 ± 6.1 years; 70% females) of the Rush Memory and Aging Project, with dietary data (assessed using a food frequency questionnaire) and neuropathological evaluations. Calorie-adjusted pelargonidin intake was modeled in quartiles and berry intake as continuous (servings/week). Mean amyloid-beta load and phosphorylated tau neuronal neurofibrillary tangle density across multiple cortical regions were assessed using immunohistochemistry. Global AD pathology burden, a quantitative summary score of neurofibrillary tangles, and diffuse and neuritic plaques using Bielschowsky silver stains in multiple brain regions, was also assessed.

Results: In a linear regression model adjusted for age at death, sex, education, *APOE ε*4 status, vitamin E, and vitamin C, participants in the highest quartile of pelargonidin intake when compared to those in the lowest quartile, had less amyloid-β load (β (SE) = −0.293 (0.14), $p = 0.038$), and fewer phosphorylated tau tangles (β (SE) = −0.310, $p = 0.051$). Among *APOE ε*4 non-carriers, higher strawberry (β (SE) = −0.227 (0.11), $p = 0.037$) and pelargonidin (Q4 versus Q1: β (SE) = −0.401 (0.16), $p = 0.011$; p trend = 0.010) intake was associated with

*Correspondence to: Puja Agarwal, Rush University Medical Center, 1750 W Harrison st, ST 1000, Chicago, IL 60612, USA. Tel.: 312-947-7232; puja_agarwal@rush.edu.

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SUPPLEMENTARY MATERIAL

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less phosphorylated tau tangles, no association was observed in *APOE ε*4 carriers. Berry intake was not associated with AD pathology. However, excluding participants with dementia or mild cognitive impairment at baseline, strawberry ($p = 0.004$) and pelargonidin (ptrend = 0.007) intake were associated with fewer phosphorylated tau tangles.

Conclusion: Higher intake of pelargonidin, a bioactive present in strawberries, is associated with less AD neuropathology, primarily phosphorylated tau tangles.

Keywords

Alzheimer's disease pathology; anthocyanidin; berries; pelargonidin

INTRODUCTION

Alzheimer's disease (AD), the most common neurodegenerative disorder among older adults, is associated with disabilities, cognitive and motor decline, and overall loss of well-being [1–3]. There are few treatment options available for AD, and it is vital to investigate further the roles of non-pharmacological and modifiable factors such as diet in the disease. The presence of plaques and tangles in the brain is the hallmark of AD. Increased oxidative stress and inflammation are considered a potential mechanistic link in the disease process [4–6]. A diet rich in antioxidants including vitamin E, vitamin C, total carotenoids, total flavonoids, and its subclasses anthocyanidins and flavanols has been associated with a reduced risk of AD dementia in prospective cohort analyses [7–12]. Foods rich in these nutrients, i.e., berries [13], leafy greens [14], and other vegetables [15] are also associated with slower cognitive decline in older adults.

We recently reported that strawberries and pelargonidin, one of the anthocyanidins (primarily found in strawberries), have a robust association with AD dementia risk [12]. Strawberries and other berries have been shown to improve neuronal signal transduction, cognitive and motor performance, and increased brain neurons in animal models [16–19]. The randomized controlled trials also found the beneficial effect of berries on working memory, episodic memory, visual-spatial and semantic memory [20–22], metabolic function [23], and neural response during working memory challenge [24]. The proposed mechanism is that bioactive in berries may reduce oxidative stress, neuroinflammation, and neurodegeneration [25]. Various animal studies also reported that pelargonidin can cross the blood-brain barrier [26] and describe how pelargonidin reduces oxidative stress, improves memory deficits [27, 28], and is neuroprotective [29]. However, to our knowledge, no study has investigated the relation between berry intake or dietary intake of pelargonidin and AD neuropathology in the human brain. Here we investigate the association of berry consumption and dietary intake of pelargonidin with AD neuropathology among autopsied participants of a community-based neuropathologic study.

METHODS

The study was conducted among the autopsied participants of the Rush Memory and Aging Project (MAP), an ongoing longitudinal clinical-neuropathologic cohort of older adults residing in retirement communities, subsidized housing as well as individual homes in

Chicagoland. At enrollment, persons without known dementia sign informed consent for annual assessments during follow-up and sign an Anatomic Gift Act for brain donation at the time of death. MAP was initiated in 1997, and dietary assessments started in 2004. As of April 2021, out of all deceased participants (n = 1158), autopsies were done on 950 and 916 had a complete and approved neuropathological examinations at the time of analyses. Excluding participants who refused to fill the FFQ (n = 7) or have incomplete dietary data (i.e., the nutrient processing underway, n = 334) during the years of follow-up prior to death, the final analytical sample for this study was 575. The institutional review board of Rush University approved the study.

Dietary assessments

Prior to death, during the years of follow-up, the study participants underwent annual dietary assessments using a 144-item food frequency questionnaire (FFQ) that was previously validated in older adults [30, 31]. For each food in the FFQ, total calories and nutrient levels (including pelargonidin) in one portion size were multiplied by the frequency of intake reported, and these levels from all the foods were summed together to obtain the 'participant's daily intake for each nutrient. The portion sizes were described as either natural portion size (e.g., one banana) or mean portion sizes reported by the oldest men and women in national survey data collected by 24-h dietary recalls. Total calories and nutrient intakes were based on United States Department of Agricultural (USDA) National Nutrient Database [32]. Food levels of pelargonidin as per milligrams/serving size for each food in the FFQ were based on the Nutrition Coordinating Center Flavonoid and Proanthocyanidin Provisional Table from the University of Minnesota [33], which draws heavily on the USDA Database for the Flavonoid Content of Selected Foods, Release 3.3 (March 2018) and The USDA Database for the Proanthocyanidin Content of Selected Foods, Release 2.1 (March 2018), with additional data from study publications. Following foods in the FFQ contributed to the pelargonidin intake in our study population: strawberry (24.9 mg/100 grams); peas and beans (0.02 mg/100 grams); raisins and grapes (0.01 mg/100 grams). For this study, we used the mean dietary intake for pelargonidin, and berries obtained from the FFQ administered over the years of follow-up prior to death. The FFQ has a question on strawberry consumption with the following response options: never or less than once per month, 1–3 times per month, once per week, and 2–4 times per week. Any other berry consumption (blueberry, raspberry) is captured in the open-ended question at the end, which asks participants to list any foods they usually eat at least once a week or more otherwise not captured in the questionnaire. Overall berry consumption was based on combining strawberry and any other berry reported in the open-ended question. There was no variation in the reporting of strawberry intake by season or by the month of FFQ administration.

Brain neuropathology

The brain autopsy methods and pathological evaluations were described in detail previously [34]. AD neuropathology was assessed on tissue samples from different brain regions. The contralateral hemisphere fixed in 4% paraformaldehyde was used to dissect slabs from different brain regions, which were embedded in paraffin blocks, cut into 6-micron sections, and mounted onto slides. Molecularly specific immunohistochemistry was used to identify amyloid-β protein (using one of 3 antibodies as described earlier) and neuronal

neurofibrillary phosphorylated tau tangles (using antibodies to abnormally phosphorylated tau protein, AT8) in eight brain regions, which was quantified by image analysis, and mean score from all the regions were considered [35]. Additionally, global AD neuropathology, including diffuse and neuritic amyloid plaques and neurofibrillary tangles, were identified using modified Bielschowsky silver-stained 6-micron sections in multiple cortical regions. Each count was scaled in each region and then averaged across all the regions to obtain a summary Global AD pathology burden. Presence of AD was based on the pathological diagnosis using the National Institute on Aging (NIA)-Reagan criteria with intermediate and high likelihood cases [34]. A board-certified neuropathologist blinded to participant ages and clinical data determined the neuropathology diagnoses.

Other covariates

Age at death in years is computed from the dates of birth and death. Sex and education (in years) were self-reported at the time of enrollment into the study. Apolipoprotein (*APOE ε*) genotyping was performed by Polymorphic DNA Technologies [36]. Clinical AD dementia diagnosis was based on the criteria of the joint working group of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) [37]. Other dietary factors (vitamin E, vitamin C, fish, and leafy green intake) were also assessed using the FFQ data as described previously [14, 38, 39].

Statistical analysis

All the analyses were programmed in SAS version 9.4 (SAS Institute, Cary, NC). We assessed the correlation between strawberry and pelargonidin intake using Spearman's rank correlation coefficient. The association between pelargonidin and strawberry consumption with AD pathology was tested using linear regression models. Pelargonidin was energy-adjusted using the residual regression method [40] and modeled in quartiles with the lowest quartile as the referent category. Frequency of berry consumption was modeled as a continuous variable with ordinal values given such as 0 (never or less than once a month); 0.5 (1–3 times/month); 1.0 (once - per week), and 2 (2 or more times/week). Global AD pathology, amyloid-β load, and tangle density as outcomes were square root transformed and linear regression models were used.

The models to assess the association of berry with AD neuropathology were adjusted for age at death, sex, education, and total calorie intake. These models were further adjusted for *APOE ε*4 status, and additionally for other food groups that are known to be related to AD dementia/AD pathology (leafy greens [14] and seafood intake [39, 41]). The association of pelargonidin with AD pathology was assessed using regression models adjusted for age at death, sex, education, *APOE ε*4 status and other nutrients with antioxidant properties including total vitamin E (known to be related with AD outcomes) [42] and vitamin C (nutrient content high in strawberries) intake. It was further controlled for other flavonoids intake (sum of other flavonoids subclasses and constituents excluding pelargonidin). A test of linear trend of the association was assessed for each model by assigning the median quartile intake level to all those in each quartile and modeling the dietary intake as a single continuous variable. For sensitivity analysis, we excluded people diagnosed with

clinical dementia and mild cognitive impairment (MCI) at baseline FFQ assessment and reanalyzed these associations. Tests for potential effect modification by age at death (> 90 years/≤90 years), sex, education (> 15 years/15≤ years), and *APOE ε*4 status were conducted by including a multiplicative term between the dietary exposure variable and the effect modifier of interest. For significant interaction terms ($p \leq 0.05$), we further conducted stratified analysis for basic models.

RESULTS

The analytical sample was 91.3 (±6.1) years old at the time of death, and primarily female (Table 1). The characteristics were comparable to entire group of deceased participants from MAP (n = 1,158, age at death = 89.9 (6.4) years; female = 69%; education = 14.6 (3.1 years; *APOE ε*4 allele (21%)). The mean (SD) postmortem time interval was 9.5 (±8.9) h. The mean follow-up time from the first dietary assessment until death was 7.0 (±3.8) years. Based on the consensus clinical judgement proximal to death, overall, 40% of participants (n = 230) had the diagnosis of clinical dementia. 377 (65%) participants had a pathologic diagnosis of AD (NIA Reagan diagnosis of AD) at the time of death. The characteristics of the study participants were similar across quartile of pelargonidin intake, except that there were more females in the highest quartile (Table 1). Over the years of follow-up, 30% of participants completed one FFQ, 18% completed two, and 52% completed three or more. The berry intake at the study baseline (mean: 0.60 ± 0.5 servings/week) and the last visit (mean: 0.62 ± 0.5 servings/week) before death were highly correlated (spearman rank-order correlation coefficient = 0.61, $p \leq 0.0001$). The component of variance due to participant was around 40% and we have used average intake to average out fluctuations over the follow-up visits. Strawberries contain 18.9 mg pelargonidin in half cup serving and contributed mostly to the mean pelargonidin intake of the study population, and the two measures were highly correlated (ρ = 0.82, p 0.0001). Other foods in the FFQ contributing to pelargonidin intake include peas (0.016 mg/serving), beans (0.010 mg/serving), grapes (0.007 mg/serving), and raisins (0.003 mg/serving).

Berry intake and AD neuropathology

The mean berry intake over the years of follow-up for the analytical sample was 0.61 ± 0.52 servings/week. Overall berry intake was not associated with amyloid-β load (β (SE) = −0.137 (0.10), p = 0.16), phosphorylated tau tangles (β (SE) = −0.102 (0.11), p = 0.36) or global AD pathology (β (SE) = −0.038 (0.03), p = 0.21) when adjusted for age at death, sex, education, and total calorie intake. When further adjusting for *APOE ε*4 status, the results were essentially unchanged (Table 2). Additionally, further adjustment with leafy green vegetables and seafood intake resulted in no material difference in the effect estimates (Table 2). In the sensitivity analysis, i.e., excluding participants with dementia or MCI at the analytical baseline. i.e., first FFQ assessment, berry intake was associated with fewer phosphorylated tau tangles (β (SE) = −0.254 (0.12), p = 0.04) but not with global AD pathology or amyloid load ($p > 0.05$, Supplementary Table 1).

The interaction terms with age at death, sex, and education was not significant. Berry intake interacted with *APOE ε*4 status for its relationship with phosphorylated tau tangles (p for

interaction < 0.05). In stratified analysis, among those without *APOE ε*4 allele (N = 452), berry intake was significantly associated with fewer phosphorylated tau tangles, but not with amyloid load or global AD pathology (Table 3). Whereas, among *APOE ε*4 allele carriers (*n* = 120) none of the associations were significant (Table 3).

Pelargonidin intake and AD neuropathology

Those in the highest quartile of dietary pelargonidin intake had lower amyloid-β load, and fewer phosphorylated tau tangles, and overall, less global AD pathology burden than those in the lowest quartile (models controlled for age at death, sex, education, *APOE ε*4 status, vitamin E, and vitamin C; Table 2). When further adjusted for other flavonoids, the association of pelargonidin with phosphorylated tau tangles was retained while the association with amyloid-load and global AD pathology was no longer significant (Table 2). In sensitivity analysis after removing participants with dementia and MCI at the time of FFQ administration, for those in the highest quartile of pelargonidin intake when compared to those in the lowest quartile we found similar associations for global AD pathology (Q4 versus Q1: β (SE) = −0.123 (0.06), $p = 0.040$) and more robust with higher effect estimates for phosphorylated tau tangles Q4 versus Q1: overall analysis, β (p) = −0.309 (0.05) and sensitivity analysis β (p) = −0.616 (0.001) (Supplementary Table 1).

We previously reported that pelargonidin intake is associated with reduced clinical AD dementia risk in the MAP cohort [12]. For this analytical subsample with neuropathology data, we found those in the highest quartile of pelargonidin intake had lower odds of dementia diagnosis proximate to death (OR = 0.57 (0.34, 0.94) $p = 0.028$; the model controlled for age at death, education, sex, *APOE ε*4 status, vitamin E and vitamin C intake). To investigate if this association is mediated by global AD neuropathology, we further added its term to the model above and the attenuation in effect estimates may indicate some degree of mediation (OR = 0.63 (0.37, 1.06) $p = 0.083$) because the entire confidence interval is slightly closer to 1, with the value 1 being in the upper part of this interval. Similar confidence intervals were observed when amyloid load (OR = 0.63 (0.37, 1.07) $p = 0.084$) or phosphorylated tau tangles (OR = 0.65 (0.38, 1.14) $p = 0.133$) was added to the model separately. This supports a potential pathway for pelargonidin reducing AD dementia risk through AD pathology.

We also investigated potential modification of the observed associations between pelargonidin intake and AD neuropathology by age at death, sex, education and *APOE ε*4 status. There were no interactions found. Because of the interaction of *APOE* and strawberry intake, we further explored association of pelargonidin with AD pathology stratified by *APOEε*4 status. Among *APOEε*4 non-carriers higher pelargonidin was associated with less global AD pathology and phosphorylated tau tangles but not among *APOE ε*4 carriers (Table 2).

DISCUSSION

In this study among autopsied MAP participants, higher dietary intake of pelargonidin over the years of follow-up before death was inversely associated with amyloid-β load, and phosphorylated tau tangles density independent of demographic factors, *APOE*, and other

antioxidant nutrients. Pelargonidin intake was highly correlated with berry intake, and we found an inverse association between berry intake and phosphorylated tau tangles among those without *APOE* ε4 allele and among those without dementia or MCI at analytical baseline. Among berries, strawberries are the most abundant source of pelargonidin (25 mg/100 grams), their role in maintaining brain health in older adults should be assessed further. These findings indicating an association of pelargonidin with lessened AD neuropathology further highlight this anthocyanidin's potential neuroprotective role in the human brain.

Large population-based studies have previously reported the beneficial relation of various bioactive compounds (flavonoids and its subclasses) present in fruits, vegetables, and other plant-based sources with AD dementia risk and cognitive decline [10, 13]. To our knowledge, this is the first study reporting the association between mean pelargonidin intakes over several years of follow-up and AD neuropathology in postmortem brains from a community-based sample of older adults. We do not see similar strong association of the berry intake with AD pathology overall, this may be due to limited potential effect of single food/food group rather than combination of foods, or overall effect of nutrient/bioactive coming from different food sources. The interaction for pelargonidin intake with *APOE* ε4 status for its association with AD pathology was non-significant, but berry intake interacted with *APOE* ε4 only for its relationship with phosphorylated tau tangles. When further explored with the stratified analysis we found higher berry and pelargonidin intake associated with less phosphorylated tau tangles only among *APOE* ε4 non-carriers and not in *APOE* ε4 carriers. This can possibly be due to a smaller group with the *APOE* ε4 allele, or because the genetic factors might be masking the effect of dietary factors. Another potential explanation can be the role of *APOE* ε4 in nutritional metabolomics which needs further exploration. Thus, future studies with more *APOE* ε4 carriers are needed to further establish the role of precision nutrition in AD. The current neuropathologic study results are supported by various other epidemiological study findings on strawberries and/or pelargonidin association with cognitive decline [13], AD dementia [12] and by randomized placebo-controlled trial that reports the beneficial effect of mixed berry beverage on working memory [43] and strawberry intake on virtual spatial and verbal learning memory tests performance among older adults [20]. These findings reinforce the possible role of bioactive compounds from various food sources in brain health.

From animal studies, we know that pelargonidin crosses the blood-brain barrier [26] and has a neuroprotective effect [29]. A study in rat amyloid-$\beta_{25–35}$ model of AD depicted the improvement in amyloid-β induced memory dysfunction in pelargonidin treated rats via inhibition of glial activation, cholinesterase, and oxidative stress and was independent of estrogen receptor pathway [27, 28]. It is shown that pelargonidin restores hippocampal antioxidant capacity in male rats [44] and its neuroprotective effect was associated with overexpression of the Nuclear factor-E2-related factor 2 (Nrf2) and heme oxygenase 1 pathways in the rat model of focal cerebral Ischemic/Reperfusion injury [45]. Our study shows pelargonidin strongly associated with phosphorylated tau tangles rather than amyloid load. We speculate that the anti-inflammatory properties of pelargonidin may downregulate overall neuroinflammation and prolonged activation of microglia, which in turn may reduce cytokine production and thus may decrease phosphorylation of tau and its misfolding [46,

47]. This suggests that the pelargonidin may independently or synergistically with other factors may protect the aging brain from developing AD neuropathology.

These findings have several important strengths, including the study design where the community-based sample of dementia-free older adults are observed until death, thus minimizing selection bias due to loss to follow-up. Other strengths include large sample size, annual dietary assessments using a comprehensive and validated tool for older adults, structured assessments, and standardized neuropathological measures, thus minimizing measurement error. However, there are also some limitations. This is an observational study in which we examine associations with pathology observed once at autopsy; we cannot establish any causal relationships. Further there is likely unaddressed confounding by other nutrients and compounds that are common in foods high in pelargonidin. Additionally, our dietary assessment tool had one berry question which considered intake of strawberries and other berries were captured in the open-ended question if consumed once per week or more. Thus, there is a possibility of underreporting or misreporting by those consuming other berries (blueberry, raspberries, blackberries, or cranberries) which were otherwise captured in the open-ended question on other frequently consumed foods. The study participants at the time of enrollment are older than 65 years without any known dementia symptoms and had higher mean age of death than the national average age of death. This may indicate selection bias of healthier individuals or survival bias. Additionally, participants were mostly non-Hispanic white individuals. Thus, the results may not generalize to younger adults or to non-white or Hispanic populations.

In these analyses among older adults, we found mean dietary intake of pelargonidin (an anthocyanidin primarily found in strawberries) over the years of follow-up associated with less AD neuropathology at the time of death, primarily with less phosphorylated tau tangles. The association was robust among those without dementia or MCI at analytical baseline and among *APOE ε*4 non-carriers. Strawberry and pelargonidin intake should be further assessed for their role in maintaining brain health in older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics by quartile of pelargonidin intake, 575 deceased MAP participants

Variables,	Overall	Pelargonidin Intake			
		Q 1	Q 2	Q 3	Q 4
N	575	143	144	144	144
Pelargonidin intake mg/wk median (IQR)	8.75 (3.99, 15.12)	0.07 (0, 2.17)	6.44 (4.90, 7.63)	11.06 (9.73, 12.74)	22.40 (17.92, 32.2)
Age at death, y; mean ± SD	91.3 ± 6.1	91.3 ± 6.2	91.2 ± 5.5	91.3 ± 6.1	91.3 ± 6.8
Female, %	70 %	69%	69 %	70 %	80%
Education, y; mean ± SD	14.8 ± 2.8	14.6 ± 2.9	14.7 ± 2.9	15.2 ± 2.5	14.5 ± 2.6
APOE ε4, %	21 %	21 %	17 %	31 %	18 %
Mean Strawberry intake servings/wk; mean ± SD	0.61 ± 0.52	0.10 ± 0.17	0.48 ± 0.25	0.67 ± 0.32	1.19 ± 0.53
Total calories/day; mean ± SD	1810 ± 531	1916 ± 651	1994 ± 493	1785 ± 392	1545 ± 443
Vitamin E intake (mg/day); mean ± SD	58.5 ± 84.4	45.8 ± 67.3	54.8 ± 69.7	58.8 ± 70.0	74.4 ± 118.1
Vitamin C intake (mg/day); mean ± SD	330.7 ± 330	276.1 ± 291.3	278.7 ± 228.4	351.1 ± 309.5	416.6 ± 437.4
Fish Intake (servings/wk); mean ± SD	1.7 ± 1.1	1.6 ± 1.0	1.7 ± 1.2	1.8 ± 1.2	1.8 ± 1.2
Leafy green Intake (servings/wk); mean ± SD	4.2 ± 2.7	3.9 ± 2.5	4.1 ± 2.7	4.4 ± 2.7	4.9 ± 2.8

IQR, intraquartile range; wk, week; mg/wk, milligrams/week; mg/day, milligram/day.

Table 2

Association of strawberry and pelargonidin intake with global AD pathology, amyloid-β load, and phosphorylated tau tangles, among deceased participants of the Rush Memory and Aging Project

	Global AD pathology burden	Amyloid-β Load	Phosphorylated tau tangles
N	572	538	560
A. Berry Intake (Continuous (SE,*p*))			
Model 1A	−0.042(0.03, 0.144)	−0.144(0.09, 0.131)	−0.114 (0.10, 0.285)
Model 2A	−0.012 (0.06, 0.390)	−0.091(0.09, 0.351)	−0.159 (0.11, 0.150)
B. Pelargonidin Intake *			
Model 1B			
Quartile 1	Ref	Ref	Ref
Quartile 2 β (SE, *p*)	−0.003 (0.04, 0.938)	−0.073 (0.14, 0.596)	−0.210 (0.15, 0.176)
Quartile 3 β (SE, *p*)	−0.057 (0.04, 0.180)	−0.276 (0.14, 0.047)	−0.320 (0.16, 0.041)
Quartile 4 β (SE, *p*)	−0.083 (0.04, 0.056)	−0.293 (0.14, 0.038)	−0.309 (0.16, 0.051)
p for trend	0.031	0.024	0.060
Model 2B			
Quartile 1	Ref	Ref	Ref
Quartile 2 β (SE, *p*)	−0.003 (0.04, 0.948)	−0.068 (0.14, 0.619)	−0.212 (0.15, 0.170)
Quartile 3 β (SE, *p*)	−0.056 (0.04, 0.194)	−0.255 (0.14, 0.067)	−0.329 (0.16, 0.036)
Quartile 4 β (SE, *p*)	−0.081 (0.04, 0.063)	−0.265 (0.14, 0.062)	−0.321 (0.16, 0.044)
p for trend	0.037	0.043	0.052

Linear regression models: Model 1A: adjusted for age at death, sex, education, total calories, and *APOE ε*4 status; Model 2A: adjusted for age at death, sex, education, total calories, *APOE ε*4 status, leafy green vegetables, and seafood.

*Calorie-adjusted pelargonidin intake; Model 1B: adjusted for age at death, sex, education, *APOE ε*4 status, vitamin E and vitamin C; Model 2B: adjusted for age at death, sex, education, *APOE ε*4 status, vitamin E and vitamin C intake, and other flavonoids intake.

Table 3

Association of strawberry and pelargonidin intake with AD pathology among deceased participants of the Rush Memory and Aging Project Stratified by their *APOE ε4* status

Stratified analysis	Global AD pathology burden	Amyloid-β Load	Phosphorylated tau tangles
Strawberry Intake (Model A) β (SE, *p*);			
APOE ε4 non-carriers (*n* = 452)	−0.058 (0.03, 0.076)	−0.150 (0.11, 0.172)	−0.227 (0.11, 0.037)
APOE ε4 carriers (*n* = 120)	0.019 (0.06, 0.761)	−0.139 (0.19, 0.476)	0.292 (0.11, 0.292)
Pelargonidin Intake * (Model B)			
APOE ε4 non-carriers (*n* = 452)			
Quartile 1; *n* = 115	Ref	Ref	Ref
Quartile 2 β (SE, *p*); *n* = 116	0.011 (0.05, 0.804)	−0.061 (0.16, 0.696)	−0.166 (0.15, 0.283)
Quartile 3 β (SE, *p*); *n* = 105	−0.073 (0.05, 0.131)	−0.329 (0.16, 0.042)	−0.301 (0.16, 0.060)
Quartile 4 β (SE, *p*); *n* = 117	−0.101 (0.05, 0.033)	−0.291 (0.16, 0.067)	−0.401 (0.16, 0.011)
p for trend	0.013	0.043	0.010
APOE ε4 carriers (*n* = 120)			
Quartile 1; *n* = 28	Ref	Ref	Ref
Quartile 2 β (SE, *p*); *n* = 28	−0.039 (0.10, 0.69)	−0.087 (0.30, 0.770)	−0.225 (0.46, 0.626)
Quartile 3 β (SE, *p*); *n* = 39	0.038 (0.09, 0.69)	−0.082 (0.29, 0.774)	−0.136 (0.44, 0.757)
Quartile 4 β (SE, *p*); *n* = 25	0.047 (0.11, 0.66)	−0.243 (0.33, 0.460)	0.315 (0.49, 0.525)
p for trend	0.53	0.463	0.430

Linear regression models: Model A: adjusted for age at death, sex, education, and total calories.

* Calorie-adjusted pelargonidin intake; Model B: adjusted for age at death, sex, education, vitamin E, and vitamin C.

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