Adiponectin and leptin levels in migraineurs in the Atherosclerosis Risk in Communities Study

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ABSTRACT

Objective: To evaluate adiponectin and leptin levels in older men and women with migraine.

Methods: Fasting total and high molecular weight (HMW) adiponectin and leptin levels were evaluated in a case–cohort study of nondiabetic older migraine and nonmigraine control participants from the ongoing, longitudinal, general population, Atherosclerosis Risk in Communities Study at visit 1 (1987–1989). A standardized headache questionnaire was completed at visit 3 (1993–1995). Logistic regression models adjusted for age, sex, race, center, body mass index, and fasting glucose were used to evaluate the association of each adipocytokine with migraine.

Results: Of the 981 participants, the mean age at baseline was 52.8 years (SE 0.3); 131 fulfilled migraine criteria. Crude, mean total adiponectin levels were greater in men and women with migraine (8.1 μg/mL, SE 0.5) as compared to those without migraine (7.0 μg/mL, SE 0.2) (p = 0.031). After adjustments, the odds of migraine were increased by 88% with each SD increase in total adiponectin in men (odds ratio [OR] 1.86; 95% confidence interval [CI] 1.15, 3.01; p = 0.011), but not in women (OR 1.05; 95% CI 0.80, 1.37; p = 0.728; p interaction = 0.029). Similar results were demonstrated for HMW adiponectin. Crude and adjusted leptin levels were not associated with migraine.

Conclusions: Although crude, total adiponectin levels were higher in older men and women with migraine than controls, after adjustments, the prevalence of migraine was significantly associated with total adiponectin only in older men, suggesting the association may be confounded or absent in older women. Leptin was not associated with migraine in older men or women.
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GLOSSARY

all-Mig = combined group of participants with migraine and probable migraine; **ARIC** = Atherosclerosis Risk in Communities Study; **BMI** = body mass index; **CI** = confidence interval; **HMW** = high molecular weight; **ICHD** = International Classification of Headache Disorders; **IL-6** = interleukin-6; **LMW** = low molecular weight; **MMW** = middle molecular weight; **NFκβ** = nuclear factor κβ; **OR** = odds ratio; **prob-Mig** = probable migraine.

Migraine is a neurologic disorder associated with obesity,[1] hyperlipidemia,[2] and insulin resistance.[3] Current theories suggest that the neurogenic inflammation[4] of migraine involves neurotransmitters and proteins that participate in energy regulation and metabolism (e.g., serotonin).[5,6] More recently, adipocytokines (cytokines predominantly secreted from fat cells, such as adiponectin and leptin) have been suggested to contribute as inflammatory mediators of migraine.[7,8]

While the high molecular weight (HMW) oligomer of adiponectin is largely proinflammatory, the low molecular weight (LMW) oligomer is anti-inflammatory. HMW adiponectin has been shown to activate nuclear factor κβ (NFκβ) and to induce interleukin-6 (IL-6).[9,10] In contrast, LMW adiponectin has been shown to reduce IL-6 secretion.[11]

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Supplemental data at Neurology.org

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Although adiponectin levels are decreased in obesity states,[12,13] recent studies reported increases of adiponectin levels in migraineurs. Specifically, these studies reported that baseline total adiponectin levels were elevated in reproductive-aged women with chronic migraine[7] and that levels decline in episodic migraineurs in pain following successful treatment.[8] In contrast to adiponectin, plasma levels of the adipocytokine leptin are increased in patients with obesity[14]; however, no changes in leptin levels have been reported in migraineurs after adjusting for body mass index (BMI).[15,16]

Recent epidemiologic research supports that obesity in migraineurs exhibits a differential effect by age and sex, with the greatest association in younger women (<50).[17] Given previous data demonstrating age- and sex-specific differences in adiponectin and leptin in healthy individuals,[18,19] our aim was to evaluate these levels in older migraineurs. We hypothesized that adiponectin, and not leptin, would be elevated in older migraineurs.

METHODS

Study design. The Atherosclerosis Risk in Communities Study (ARIC) is a longitudinal community-based study conducted at 4 sites (Jackson, MS; Forsyth County, NC; Washington County, MD; suburban Minneapolis, MN). The initial recruitment and study participation has been previously described.[20] In brief, ARIC includes a predominantly biracial population of 15,792 adults, who upon initial recruitment were between 45 and 64 years of age.[20] The first visit occurred during 1987–1989, with visits 2 (1990–1992), 3 (1993–1995), and 4 (1996–1998) occurring approximately 3 years apart. Visit 5 occurred during 2011–2013 among surviving participants.

The current study used data from a prospective case–cohort within ARIC, which was originally designed to investigate the role of plasma biomarkers collected at visit 1 (1987–1989) in the development of diabetes.[21] The study also used headache questionnaires collected approximately 6 years later at visit 3 (1993–1995). Of the 15,792 participants who attended visit 1, the case–cohort study excluded those with prevalent diabetes (n = 2,018), 95 with race other than black or white, the few black subjects from the Minnesota and Washington County sites, 853 not returning to any follow-up visit, 26 with no diabetes determination at follow-up, and 6 with restrictions on plasma use. Additionally, 12 were excluded for missing baseline anthropometrics, 2,514 participants in a previous ARIC case–control and case–cohort study using stored plasma, 212 for incomplete fasting, and 315 with missing information for key covariates.[22] From this population, a random cohort (n = 591) and incident diabetes case sample (n = 599) were sampled by race strata. Additionally, participants who were missing adiponectin levels (n = 106) (none were missing leptin levels) and headache questionnaires (n = 103) were excluded, leaving a total of 981 participants (figure e-1 on the *Neurology*® Web site at www.neurology.org).

Ascertainment of headache status. At visit 3, trained interviewers administered a headache questionnaire to all participants.[23,24] Participants were queried as to whether they ever experienced headaches lasting 4 or more hours. Those reporting never experiencing headaches lasting ≥4 hours were categorized as nonmigraine controls, herein referred to as controls. Participants responding affirmatively were asked more detailed questions regarding location, quality, duration, and accompanying symptoms including nausea or vomiting, photophobia, phonophobia, and if they felt like lying down in a dark room during headaches. Additionally, participants were asked if they experienced a visual aura (spots, jagged lines, or heat waves) in association with their headaches.

Based on the responses to a headache questionnaire administered at visit 3, migraine was characterized for these analyses using modified International Classification of Headache Disorders (ICHD), 2nd edition, criteria. Participants were categorized as having migraine who fulfilled the following 4 criteria: (1) headache lasting ≥4 hours; (2) headache with at least 2 out of the following 3 features: (a) throbbing, pulsing, or pounding quality, (b) unilateral location, (c) desire to go to a dark room and lie down; (3) nausea or vomiting or both photophobia and phonophobia; and (4) ≥1 year history of headaches (at any point in their life). Those participants with a history of headache lasting ≥4 hours and satisfying 2 out of 3 of criteria of the second criteria were categorized as probable migraine (prob-Mig). Those not fulfilling migraine or prob-Mig criteria were categorized as controls. Additional analyses were conducted for the combined group of participants with migraine and prob-Mig (all-Mig). Finally, subgroup analyses were conducted for migraine groups based on the presence or absence of visual aura, with those responding affirmatively to experiencing a visual aura categorized as with aura and those responding negatively as without aura.

Covariates. All covariates used in the regression models were assessed at visit 1.[20] Covariates included age (years), sex, race/center (Maryland whites; Minnesota whites; North Carolina whites; North Carolina blacks; Mississippi blacks), BMI (kg/m^2), and fasting blood glucose (mg/dL). A combined race/center variable was created to adjust for confounding between these 2 variables. BMI was calculated as weight in kilograms/height in meters.[2]

Laboratory methods. Fasting plasma blood samples collected at visit 1 (1987–1989) were centrifuged, aliquoted, and stored at −70°C for approximately 20 years, until thawed and maintained at 4°C until measured (no longer than 24 hours later).[22] Total and HMW adiponectin were assessed with sandwich ELISA (American Laboratory Products Company, Salem, NH) with a minimum assay sensitivity of 0.04 ng/mL. Pretreatment with proteinase K, which digests all isoforms except for HMW adiponectin, allowed for HMW adiponectin to be measured at the same time as total adiponectin. Reliability coefficients for total, HMW, and HMW:total adiponectin ratio were 0.93, 0.98, and 0.70, respectively.[22] Leptin was measured in duplicate using a sandwich ELISA (Linco Research, St. Charles, MI) with a reliability coefficient of 0.94 and a minimum assay sensitivity of 0.5 ng/mL.[25] Fasting glucose and cholesterol were measured using standard laboratory techniques.[26]

Statistical analysis. All statistical analyses were weighted to account for the case–cohort study design using the svy command and pweights in Stata version 13 (StataCorp LP, College Station, TX). This method involves inverse weighting of the observations according to the sampling design, to permit statistical estimation and inference relevant to the entire cohort, which adjusts for the oversampling of incident diabetes. All standard errors were estimated using the Taylor series linearization method. p Values were calculated using linear regression and χ^2 test statistics.

Means (SE) and proportions (SE) of baseline characteristics of study participants were reported overall and by migraine category. We examined the association of total, HMW, and the ratio of HMW to total adiponectin and leptin with migraine using logistic regression models. Odds ratios (ORs) from the logistic regression models were calculated per 1 SD increase in adipocytokine level, where the SD was based on the random cohort sample. Model 1 was adjusted for age, sex, race/center, and BMI. Given the association of migraine with impaired insulin sensitivity[27] as well as the association of adiponectin with diabetes,[22] model 2 was adjusted for variables in model 1 plus fasting glucose. We formally tested for multiplicative interaction by age, sex, and BMI and present stratified results when interaction was present with a p value <0.05. Our primary outcome was all-Mig; additionally, a sensitivity analysis using migraine as the outcome was conducted.

Standard protocol approvals, registrations, and patient consents. The institutional review boards of all participating institutions approved the study, and all participants provided written informed consent.

RESULTS

Participants. Demographic, socioeconomic, and laboratory characteristics of the 981 participants (360 men and 621 women) are presented in table 1. The mean age of participants was 52.8 years (SE 0.3) (range 45–64). A total of 13.4% (131/981) of participants met criteria for all-Mig (72 migraine, 59 prob-Mig). Participants with all-Mig were more likely to be female ($p = 0.055$) and younger ($p < 0.001$) and have lower fasting glucose ($p = 0.033$) than controls. A total

Table 1 Demographic and laboratory characteristics

	Overall (n = 981)	Controls (n = 850)	Migraine (n = 72)	p Value[a]	Prob-Mig (n = 59)	p Value[b]	All-Mig (n = 131)	p Value[c]
Age, y, mean (SE)	52.8 (0.3)	53.2 (0.3)	50.8 (0.7)	0.001	50.6 (0.3)	0.004	50.7 (0.5)	<0.001
Sex								
Male	36.7 (2.2)	38.6 (2.4)	25.0 (6.6)	0.080	29.6 (8.6)	0.342	26.7 (5.2)	0.055
Female	63.3 (2.2)	61.4 (2.4)	75.0 (6.6)		70.4 (8.6)		73.3 (5.2)	
Race/field center								
Washington County, MD, whites	31.2 (2.1)	30.1 (2.3)	40.3 (7.5)	0.066	31.4 (8.9)	0.873	37.0 (5.7)	0.200
Minneapolis, MN, whites	27.3 (2.1)	26.4 (2.3)	34.7 (7.3)		27.7 (8.6)		32.1 (5.6)	
Forsyth County, NC, whites	23.0 (2.0)	23.9 (2.2)	18.5 (6.0)		17.9 (7.5)		18.2 (4.7)	
Forsyth County, NC, blacks	2.0 (0.4)	2.3 (0.4)	0.0 (0.0)		1.3 (1.3)		0.5 (0.5)	
Jackson, MS, blacks	16.5 (0.7)	17.4 (1.3)	6.6 (2.1)		21.6 (5.3)		12.2 (2.4)	
Education								
<HS	16.3 (1.5)	16.8 (1.7)	17.5 (5.7)	0.991	6.6 (2.8)	0.085	13.4 (3.8)	0.562
HS or equivalent	45.2 (2.2)	45.6 (2.4)	44.7 (7.5)		40.4 (9.0)		43.1 (5.8)	
>HS	38.5 (2.2)	37.5 (2.4)	37.8 (7.3)		53.0 (9.1)		43.5 (5.8)	
Family income								
<$35,000	46.9 (2.2)	47.6 (2.4)	40.8 (7.4)	0.281	46.1 (9.0)	0.307	42.8 (5.7)	0.153
≥$35,000	48.0 (2.20	46.7 (2.4)	56.2 (7.4)		52.7 (9.1)		54.9 (5.8)	
Not reported	5.1 (0.9)	5.7 (1.1)	3.0 (1.4)		1.2 (0.7)		2.3 (0.9)	
Smoking status								
Current	18.8 (1.7)	19.6 (1.9)	12.8 (4.9)	0.382	17.7 (7.0)	0.910	14.6 (4.0)	0.418
Former	32.5 (2.1)	32.9 (2.3)	29.8 (7.0)		30.7 (8.6)		30.1 (5.4)	
Never	48.8 (2.2)	47.5	57.4 (7.5)		51.6 (9.1)		55.2 (5.8)	
Aura	NA	NA	23.0 (6.0)		12.0 (6.0)	0.044	18.7 (4.4)	
BMI, kg/m^2, mean (SE)	27.1 (0.2)	27.3 (0.2)	27.0 (0.7)	0.776	25.9 (0.6)	0.954	26.6 (0.5)	0.243
Hypertension	26.3 (1.8)	26.7 (2.0)	21.9 (6.1)	0.477	27.2 (7.5)		23.9 (4.7)	0.589
Standard laboratories, mean (SE)							0.317	
Fasting glucose, mg/dL	99.9 (0.4)	100.3 (0.4)	97.6 (1.3)	0.047	98.9 (1.3)	0.712	98.1 (0.9)	0.033
Total cholesterol, mg/dL	210.0 (1.7)	210.4 (1.8)	208.5 (5.9)	0.755	206.5 (10.4)		207.8 (5.4)	0.638

Abbreviations: All-Mig = probable migraine + migraine; BMI = body mass index; HMW = high molecular weight; HS = high school; NA = not applicable; prob-Mig = probable migraine.
Data are presented as % (SE) except where noted as mean (SE).
[a] Comparisons of migraine to controls.
[b] Comparisons of prob-Mig to controls.
[c] Comparisons of the combined all-Mig group to controls.

of 18.7% of participants (SE 4.4) with all-Mig had a history of aura (table 1).

Adipocytokines. ***Adiponectin.*** As previously described in the literature,[18,28] total and HMW adiponectin levels in our sample were higher in women (total 8.15, SE 0.23 μg/mL, HMW 3.80, SE 0.15 μg/mL) than men (total 5.41, SE 0.21 μg/mL, $p < 0.001$; HMW 2.1, SE 0.11 μg/mL, $p < 0.001$; table e-1). As compared to controls, crude total adiponectin levels were increased in those with all-Mig as well as those with migraine alone but were not significantly different in those with prob-Mig (table 2 and figure 1). HMW adiponectin levels were nominally higher in those with all-Mig and migraine alone, as compared to controls, but did not reach statistical significance (table 2, figure 1). The HMW:total adiponectin ratio was not different across groups (table 2). Mean crude total, HMW, and HMW:total adiponectin levels were not different between all-Mig participants with and without aura (table e-2).

Although there was no difference in crude, sex-stratified adiponectin levels across migraine groups compared to controls (table e-1), after adjustments, the odds of all-Mig were increased by 86% in men (OR 1.86, 95% confidence interval [CI] 1.15–3.01) for each 1-SD increase in total adiponectin (table 3). Similarly, after adjustment, the odds of all-Mig was almost twofold greater in men for each SD increase in HMW adiponectin (OR 1.96; 95% CI 1.11, 3.48). The HMW:total ratio was not associated with increased odds of all-Mig in men. In contrast, the odds of all-Mig and migraine did not increase with increasing total, HMW, or HMW:total adiponectin levels in women (table 3, p value, sex interaction: total $p = 0.029$, HMW $p = 0.036$, HMW:total $p = 0.537$). Due to the small number of male participants with aura (n = 6), reliable interpretation of adiponectin levels stratified by sex with and without aura was not possible.

Leptin. As previously described in the literature,[28,29] crude leptin levels were lower in men than in women, independent of migraine status (mean leptin: women 24.6, SE 1.2 ng/mL; men 6.0, SE 0.4 ng/mL, $p < 0.001$). However, crude and adjusted leptin levels were not significantly different in any of the migraine groups compared to controls (tables 2 and 3), and there was no sex-specific interaction for leptin ($p = 0.293$). Additionally, leptin levels did not vary in all-Mig participants by aura status (table e-2).

DISCUSSION We conducted an analysis in the first large general population study to investigate the association between migraine and adipocytokines and present 3 main findings. First, crude total adiponectin levels were higher in those with migraine as compared to those without migraine. Second, there was an interaction by sex such that increasing total adiponectin was associated with increased odds of migraine in older men, but not women. Finally, leptin did not significantly differ in migraineurs as compared to nonmigraine controls. Supporting our findings that adiponectin differs by migraine status is a prior clinical trial of 37 reproductive-aged women that demonstrated higher total adiponectin levels in women with chronic migraine[7]; however, no studies have interpreted the sex-specific effect.

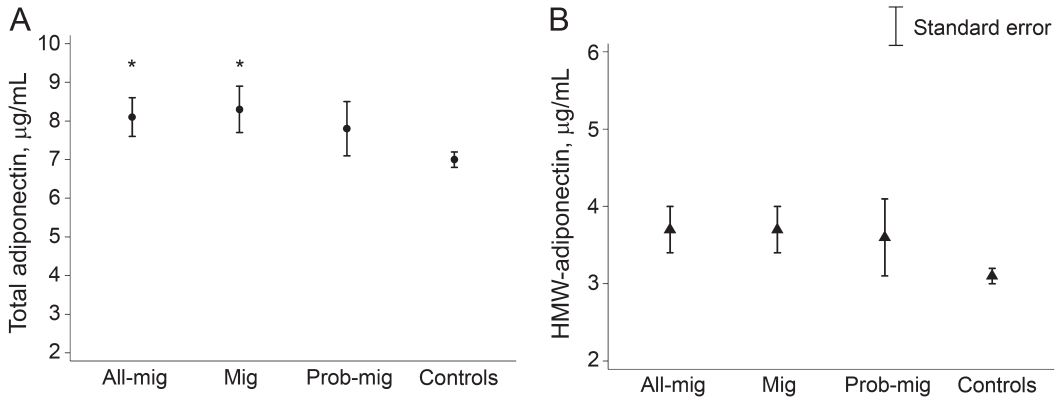
There are several potential explanations for the sex interaction with adiponectin and migraine. First, it is possible that the sex differences in the expression of circulating total and multimeric adiponectin contribute partially to the increased risk of migraine in older men but not women. Younger women of reproductive age have been shown to have higher total adiponectin and HMW adiponectin, but comparable LMW adiponectin levels, in comparison with younger men.[18,28,30] The lower adiponectin levels in younger men may be, at least in part, due to the effects of testosterone.[31] Castrated mice have high levels of

Table 2 Crude adipocytokines levels in migraine and nonmigraine control participants in the Atherosclerosis Risk in Communities Study

	Overall (n = 981)	Controls (n = 850)	Migraine (n = 72)	p Value[a]	Prob-Mig (n = 59)	p Value[b]	All-Mig (n = 131)	p Value[c]
Adiponectin								
Total ADP, μg/mL	7.1 (0.2)	7.0 (0.2)	8.3 (0.6)	0.050	7.8 (0.7)	0.278	8.1 (0.5)	0.031
HMW ADP, μg/mL	3.2 (0.1)	3.1 (0.1)	3.7 (0.3)	0.080	3.6 (0.5)	0.320	3.7 (0.3)	0.057
HMW:total ADP	0.41 (0.01)	0.41 (0.01)	0.43 (0.01)	0.108	0.42 (0.02)	0.498	0.43 (0.01)	0.126
Leptin, ng/mL	17.8 (0.8)	17.7 (0.9)	20.6 (3.1)	0.371	14.7 (2.0)	0.194	18.4 (2.1)	0.755

Abbreviations: ADP = adiponectin; all-Mig = probable migraine + migraine; HMW = high molecular weight; prob-Mig = probable migraine.
Data are presented as mean (SE).
[a] p Values are for comparisons of migraine to controls.
[b] p Values are for comparisons of prob-Mig to controls.
[c] p Values are for comparisons of the combined all-Mig group to controls.

Figure 1 Crude mean total and high molecular weight adiponectin levels in migraine and control participants in the Atherosclerosis Risk in Communities Study



(A) Crude mean total and (B) high molecular weight (HMW) adiponectin levels. *$p < 0.05$ Compared to controls. All-Mig = both probable migraine and migraine; Mig = migraine; prob-Mig = probable migraine.

plasma adiponectin and testosterone treatment reduced plasma adiponectin.[32] Further, in rat adipocytes, testosterone selectively impeded HMW adiponectin but not middle molecular weight (MMW) or LMW adiponectin.[33] As such, it may be that the multimers MMW or LMW are more important for migraine, and these levels are differentially expressed between sexes.

It is also possible that by looking only at older migraineurs, we are missing a differential sex effect by age, in which adiponectin levels are increased in young but not older women with migraine. Adiponectin levels were shown to increase with age, particularly in men.[19,34] Whereas men over 65–70 years of age have significantly higher plasma adiponectin levels than young men, women may have less of an increase in total adiponectin with age. Thus with age (and declining testosterone), men have a greater increase in total adiponectin and specifically more HMW adiponectin than older women, potentially placing men with higher adiponectin at greater risk of migraine in the age group studied.

We were not able to evaluate the LMW and MMW adiponectin oligomers. It is possible that the extent of the increase in the ratio of the proinflammatory (HMW) to anti-inflammatory (LMW) oligomers

Table 3 Adjusted odds ratio of migraine with 95% confidence intervals in relationship to 1 SD increase in adipocytokine level

	Model 1			Model 2		
	Odds ratio	95% CI	*p* Value	Odds ratio	95% CI	*p* Value
Women						
Adiponectin (per 1 SD)						
Total ADP	1.08	0.83, 1.39	0.570	1.05	0.80, 1.37	0.728
HMW ADP	1.04	0.82, 1.33	0.718	1.02	0.80, 1.31	0.875
HMW:total ADP	1.01	0.74, 1.39	0.941	1.00	0.72, 1.37	0.981
Leptin (per 1 SD)	1.08	0.72, 1.62	0.703	1.10	0.74, 1.63	0.651
Men						
Adiponectin (per 1 SD)						
Total ADP	1.88	1.18, 3.00	0.008	1.86	1.15, 3.01	0.011
HMW ADP	1.99	1.14, 3.48	0.015	1.96	1.11, 3.48	0.021
HMW:total ADP	1.16	0.73, 1.83	0.535	1.14	0.72, 1.81	0.566
Leptin (per 1 SD)	3.98	0.31, 50.71	0.286	3.96	0.28, 56.3	0.308

Abbreviations: ADP = adiponectin; CI = confidence interval; HMW = high molecular weight.
Model 1 adjusted for age, race/center, body mass index; model 2 adjusted for variables in model 1 plus glucose; 1 SD of cohort: total adiponectin: 3.71 μg/mL; HMW adiponectin: 2.25 μg/mL; HMW:total adiponectin: 0.12; leptin: 22.36 ng/mL; *p* value for sex interaction, model 1: total $p = 0.029$, HMW $p = 0.036$, HMW:total $p = 0.537$, leptin $p = 0.293$.

contributes to migraine risk. Thus, as older men have a larger increase in total and HMW adiponectin than women, they may also have larger increases in the HMW:LMW ratio and thus greater vulnerability to inflammation and migraine as compared to older women. As LMW adiponectin was not evaluated, we were not able to test this hypothesis.

It is also possible that total and HMW adiponectin may be only increased ictally in women with active migraine pain, and not interictally when migraineurs are pain-free.[7] Previous studies have shown that total and HMW adiponectin were elevated in chronic migraineurs with active pain as compared to both episodic migraineurs when interictal and controls without pain.[7] In addition, a second study demonstrated that total, HMW adiponectin, and HMW:LMW ratio were increased during acute moderate to severe pain in episodic migraineurs as compared to levels after successful treatment with mild or no pain.[8] As we were unable to assess the level of migraine pain at the time of the blood draws, it is possible that pain severity is an unmeasured confounder in sex interaction in migraineurs resulting in a missed association of adiponectin and migraine in older women.

Leptin has been studied in relationship to migraine in prior clinic-based studies. One study measured leptin levels in 84 women[16] and found that although crude leptin levels were lower in migraineurs than controls, this difference was attenuated after adjusting for fat mass.[15] Our results show no association with migraine and leptin, and taken together this suggests that while leptin may participate in energy homeostasis and modulation of inflammatory process (e.g., modulation of NFκβ), it may have less or no direct role in the modulation of inflammation and pain related to migraine.

Our study has several strengths. It permitted assessment of the association between migraine and adiponectin levels in a large biracial population-based sample, not impacted by the limited generalizability inherent in clinical samples. Participants in a community-based sample of older individuals allowed investigation into associations with migraine, independent of BMI and other rigorously measured confounders. Our ascertainment of migraine is in close alignment with standardized criteria.

There are several limitations of our study. First, migraine assessments and blood draws were done approximately 6 years apart, thus we were not able to determine the presence or absence of active migraine pain at the time of the blood draw. As a result, while we can say that in older men the risk of migraine is increased with increasing total adiponectin, because pain is unmeasured, it is not clear that there is an absence of an association in older women between total adiponectin and migraine. The nonconcurrent cross-sectional design permits the possibility that some participants classified as nonmigraine controls developed migraine between visits 1 and 3, and thus the adiponectin values would have been drawn prior to development of migraine. It is likely that this only occurred in a small number of participants, as migraine has the highest incidence in the second decade of life, with a very low incidence after age 50 years.[35,36] Another consideration is that adiponectin levels increase with age,[17] and are likely lower at visit 1 than would be projected 6 years later at visit 3; however, this should occur nondifferentially across all participants included in the current analysis (i.e., irrespective of presence or absence of migraine).

Second, adiponectin is a complex hormone with respect to its role in inflammation, with both proinflammatory and anti-inflammatory properties, depending on the oligomers and ratio of the HMW:LMW units of adiponectin. As LMW adiponectin was not evaluated, a potentially important piece of the inflammatory role adiponectin plays in older migraineurs may be missing from the current study. It is possible that the LMW or HMW:LMW ratio may be more sensitive of a marker of migraine in both women and men.

Finally, migraine ascertainment is subject to recall bias, and we were not able to exclude remitted migraineurs or nonmigraine headaches (e.g., tension-type headache) from our control group, which may have biased our findings toward a null effect.[37] While it is possible that some migraineurs may have been part of the nonmigraine control group, the migraine groups more accurately reflect those with actual migraine, therefore any associations observed are conservative estimates. This potential misclassification could lead to attenuation of the results described, especially in women.[38] Unlike a clinic-based population, expanding the modified ICHD criteria to the ARIC cohort study has an unknown sensitivity for detecting migraine, and has not been validated with physician adjudication. Although aura was not a main outcome, it was classified based on one question, which can lead to misclassification of aura status. Most importantly, participants were only asked about visual symptoms, and aura can take many other forms.

Despite these limitations, the present study demonstrates that in older individuals, total adiponectin is increased in migraineurs and that the risk of migraine demonstrates a sex-specific effect such that higher total adiponectin levels are associated with a greater prevalence of migraine in older men, but not older women. Additionally, leptin is not associated with migraine in older men or women. Further research examining the association

between migraine and adiponectin, and particularly LMW adiponectin and the HMW:LMW ratio in older men and women inside and outside acute pain states, is warranted.

AUTHOR CONTRIBUTIONS

Jennifer Dearborn: primary authorship of manuscript, data interpretation, approval of final manuscript. Andrea L.C. Schneider: primary statistical analyst, manuscript revision, approval of final manuscript. Rebecca F. Gottesman: statistical assistance, data interpretation, manuscript revision, approval of final manuscript. Tobias Kurth: study design, data interpretation, manuscript revision, approval of final manuscript. James S. Pankow: acquisition of data, data interpretation, manuscript revision, approval of final manuscript. David Couper: statistical assistance, data interpretation, manuscript revision, approval of final manuscript. Kathryn M. Rose: data interpretation, manuscript revision, approval of final manuscript. Michelle Williams: study design, data interpretation, manuscript revision, approval of final manuscript. B. Lee Peterlin: study conception and design, data interpretation, manuscript revision, approval of final manuscript.

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