THE WOMEN'S HEALTH INITIATIVE

Plenary 1: Migraine and Stroke Risk in Postmenopausal Women: The Role of WHI in Advancing Knowledge of Epidemiology, Mechanisms and Preventive Strategies

Chair: Tracy Madsen, University of Vermont

Migraine and Stroke: An Opportunity for Improved Stroke Prevention in Women

Brian Silver, MD

May 1, 2025

UMass Chan
MEDICAL SCHOOL

Epidemiology of migraine

- Prevalence of ~ 12% of people globally
- Migraine is significantly more common in women than men, with prevalence rates of around 17.1% in women and 5.6% in men.
- The highest 1-year prevalence of migraine is between ages of 25 and 55 years, and it is estimated that 22%–37% of women will experience migraine during their reproductive years.

Øie LR, Kurth T, Gulati S, *et al.* Migraine and risk of stroke. *Journal of Neurology, Neurosurgery & Psychiatry* 2020;**91:**593-604.

Migraine definitions

Migraine without aura

Diagnostic criteria:

1. At least five attacks fulfilling criteria B-D
2. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
3. Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
4. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia

5. Not better accounted for by another ICHD-3 diagnosis.

https://ichd-3.org/

Migraine definitions

1.2 Migraine with aura

Description:

Recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

Visual, sensory, speech and/or language, motor, brainstem, retinal

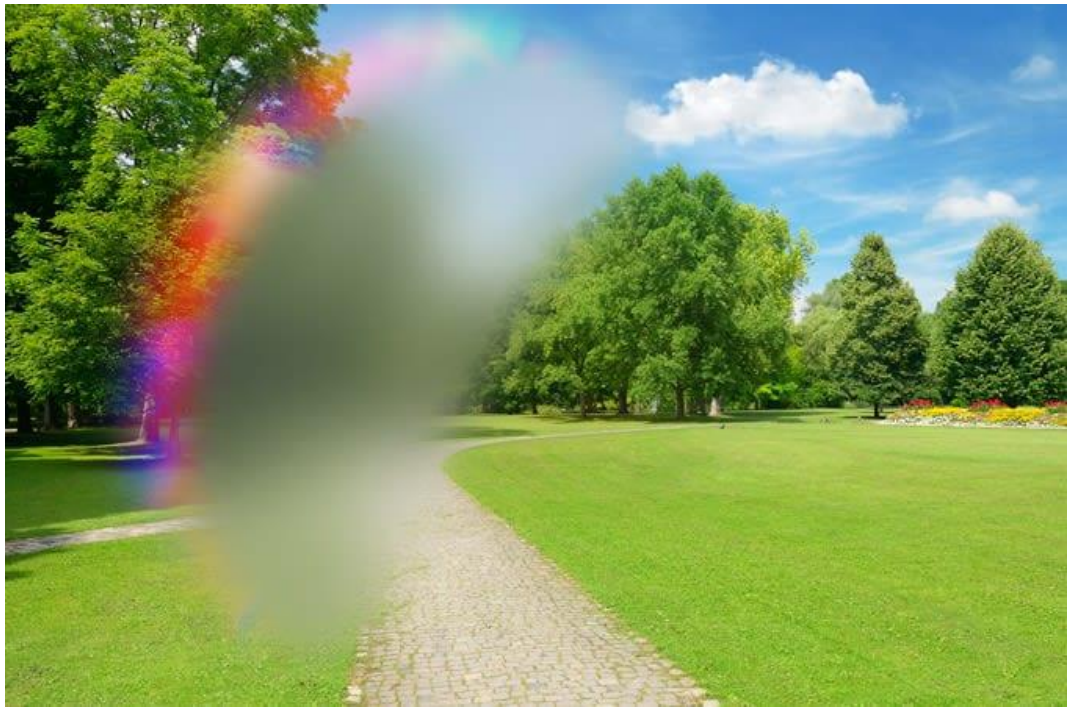
C. At least three of the following six characteristics:

1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5-60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache

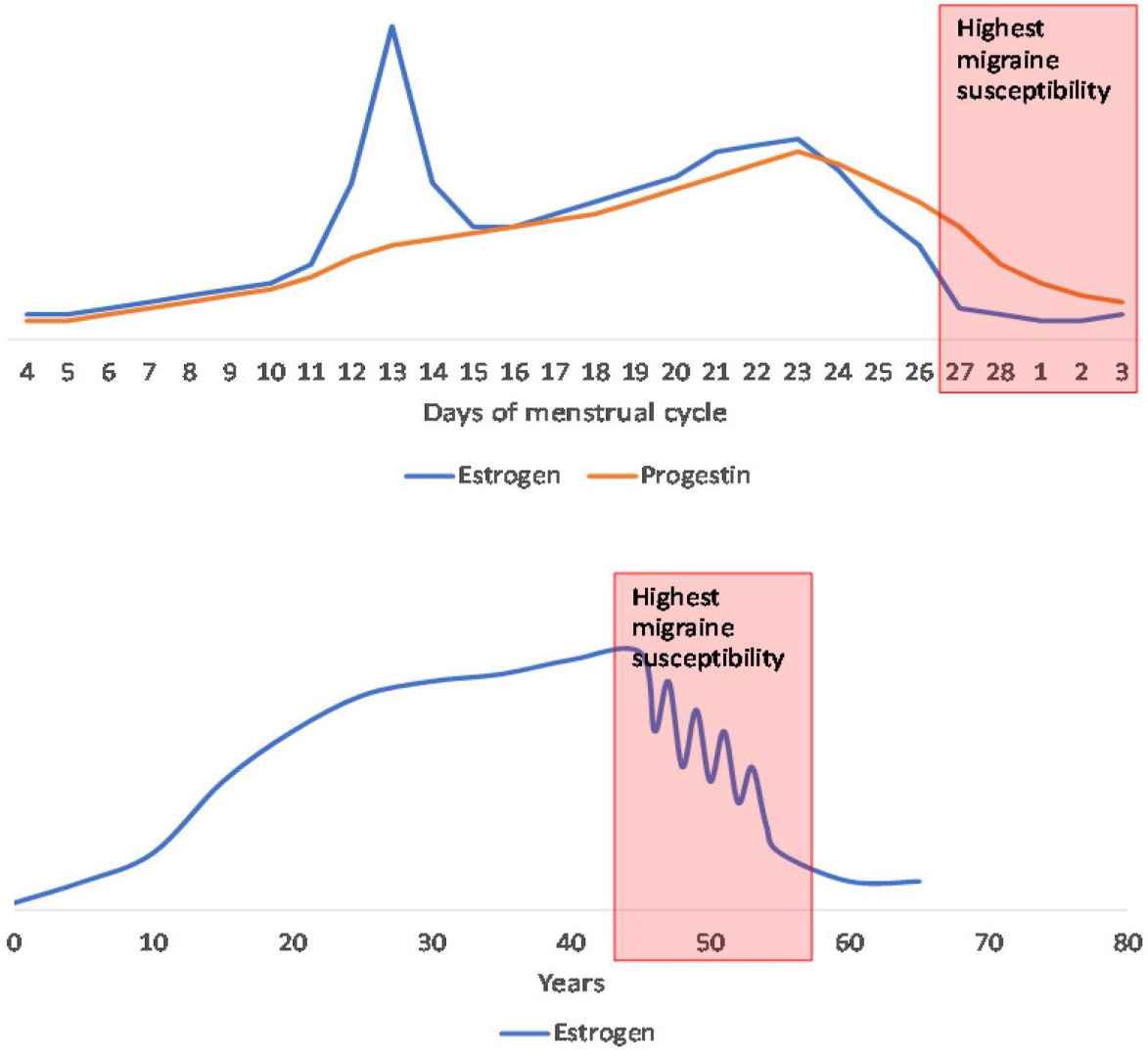
D. Not better accounted for by another ICHD-3 diagnosis.

https://ichd-3.org/

Migraine with aura



Hormonal influences in migraine



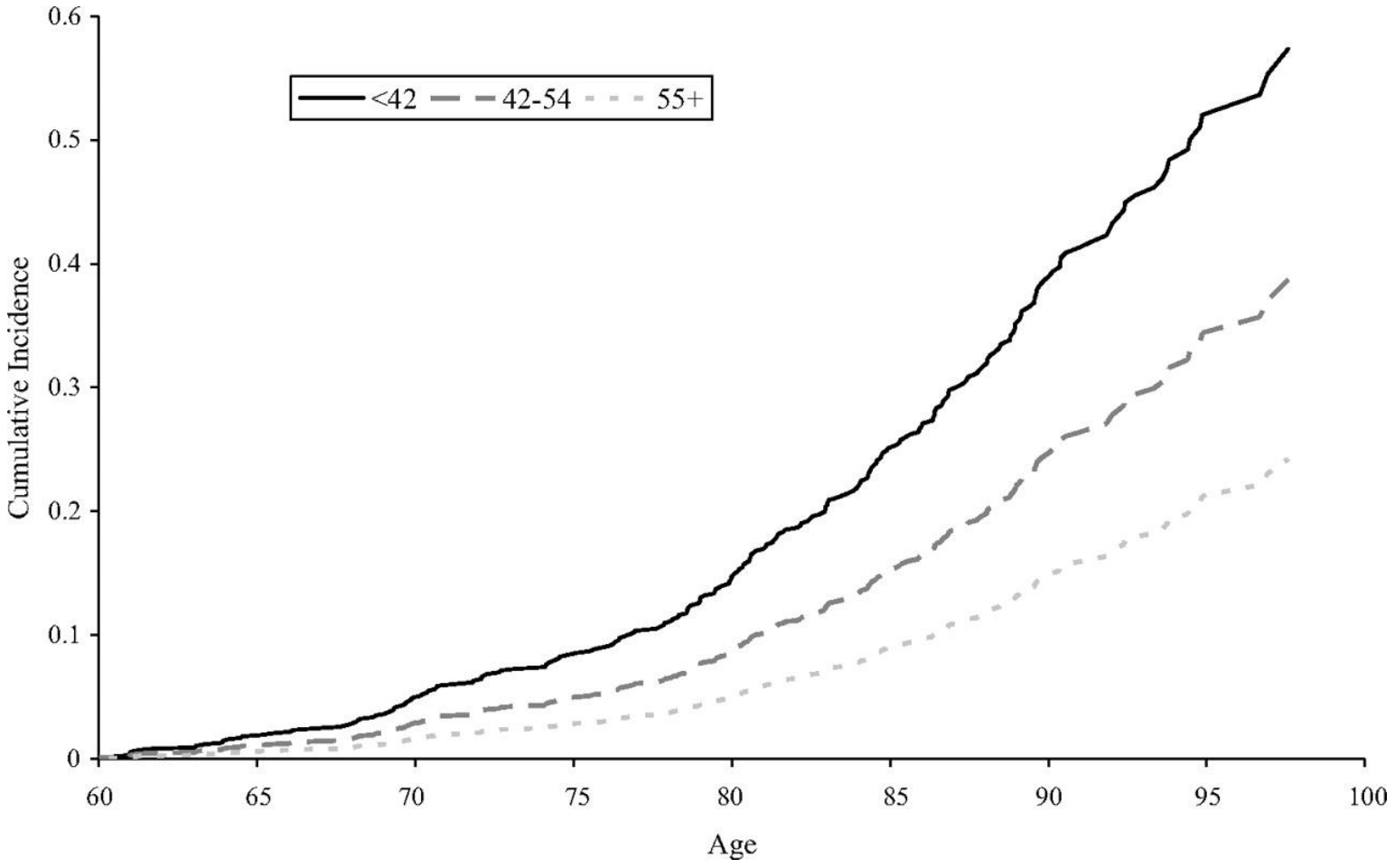
Ornello, R.; De Matteis, E.; Di Felice, C.; Caponnetto, V.; Pistoia, F.; Sacco, S. Acute and Preventive Management of Migraine during Menstruation and Menopause. *J. Clin. Med.* **2021**, *10*, 2263.

Migraine in midlife

- The recognition of a 5-day window of migraine occurrence around the start of menses is predominantly based on women's frequent reports that menstruation triggers their migraines.
- Faster decline in urinary estradiol in the 2-day postluteal peak in women with migraine compared with controls, independent of headache occurrence in the cycle, suggesting that faster estrogen decline is an inherent trait of women with migraine
- Women's Health Initiative study evaluating the risk of CVD in postmenopausal women did not detect significant risk associated with history of migraine if hormone therapy was used

Pavlović JM. Evaluation and management of migraine in midlife women. Menopause. 2018 Aug;25(8):927-929.

Stroke and menopause



Cumulative incidence of ischemic stroke by age and age at natural menopause among women in the Framingham Heart Study (n=1430).

Welten SJGC, Onland-Moret NC, Boer JMA, Verschuren WMM, van der Schouw YT. Age at Menopause and Risk of Ischemic and Hemorrhagic Stroke. Stroke. 2021 Aug;52(8):2583-2591.

Migraine and stroke risk

	Etminan *et al*	Schurks *et al*	Spector *et al*	Hu *et al*	Mahmoud *et al*
Number of studies (total)	14	25	21	11	16
Number of participants	—	—	622 381	2 221 888	1 152 407
Outcome	Migraine and risk of ischaemic stroke	Migraine and risk of cardiovascular disease	Migraine and risk of ischaemic stroke	Migraine and risk of stroke	Migraine and risk of cardiovascular and cerebrovascular events
Overall migraine					
All studies	2.16 (1.89–2.48)	1.73 (1.31–2.29)	2.04 (1.72–2.43)		
Case–control studies	2.18 (1.86–2.56)	1.96 (1.39–2.76)	—		
Cohort studies	2.10 (1.61–2.75)	1.47 (0.95–2.27)	—	1.64 (1.22–2.20)	1.32 (1.03–1.68)
Women	—	2.08 (1.13–3.84)	—	—	—
Men	—	1.37 (0.89–2.11)	—	—	—
Women and men <45 years	2.36 (1.92–2.90)	2.65 (1.41–4.97)	—	—	—
Women <45 years	2.76 (2.17–3.52)	3.65 (2.21–6.04)	—	—	—
Oral contraceptive use	8.72 (5.05–15.05)	7.02 (1.51–32.68)	—	—	—
Smoking	—	9.03 (4.22–19.34)	—	—	—
Migraine with aura	2.27 (1.61–3.19)	2.16 (1.53–3.03)	2.41 (1.81–3.43)	2.14 (1.33–3.43)	1.56 (1.30–1.87)†
Smoking	—	1.5 (1.1–2.3)	—	—	—
Women currently using oral contraceptives and smoking	—	10.0 (1.4–73.7)	—	—	—
Migraine without aura	1.83 (1.06–3.15)	1.23 (0.90–1.69)	1.52 (0.99–2.35)	1.02 (0.68–1.51)	1.11 (0.94–1.31)

Øie LR, Kurth T, Gulati S, *et al.* Migraine and risk of stroke. *Journal of Neurology, Neurosurgery & Psychiatry* 2020;**91:**593-604.

Migraine and stroke risk

- The association between migraine and ischemic stroke is particularly strong in women with migraine with aura under the age of 45
- Smoking and oral contraceptive use are also associated with a significantly elevated risk.

Øie LR, Kurth T, Gulati S, *et al.* Migraine and risk of stroke. *Journal of Neurology, Neurosurgery & Psychiatry* 2020;**91:**593-604.

- But what about post-menopausal women with migraine?

Migraine as a Risk Factor for Stroke across the Lifespan and Modification of Risk after Menopause

Tracy Madsen, MD, PhD, FAHA*

Women's Health Initiative Investigator's Meeting

May 1, 2025

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Disclosures

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- The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, 75N92021D00005.
- NHLBI, NIGMS (R01HL164485)

- Consultant for Fred Hutchinson Cancer Center / WHI Coordinating Center

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Objectives

1) To evaluate the association between history of migraine and stroke (overall, by IS/hemorrhagic subtype, and by TOAST mechanism) in postmenopausal women

2) To investigate the potential for effect modification by age

3) To investigate the role of modifiable factors, specifically medication use, in stroke risk among women with migraine histories

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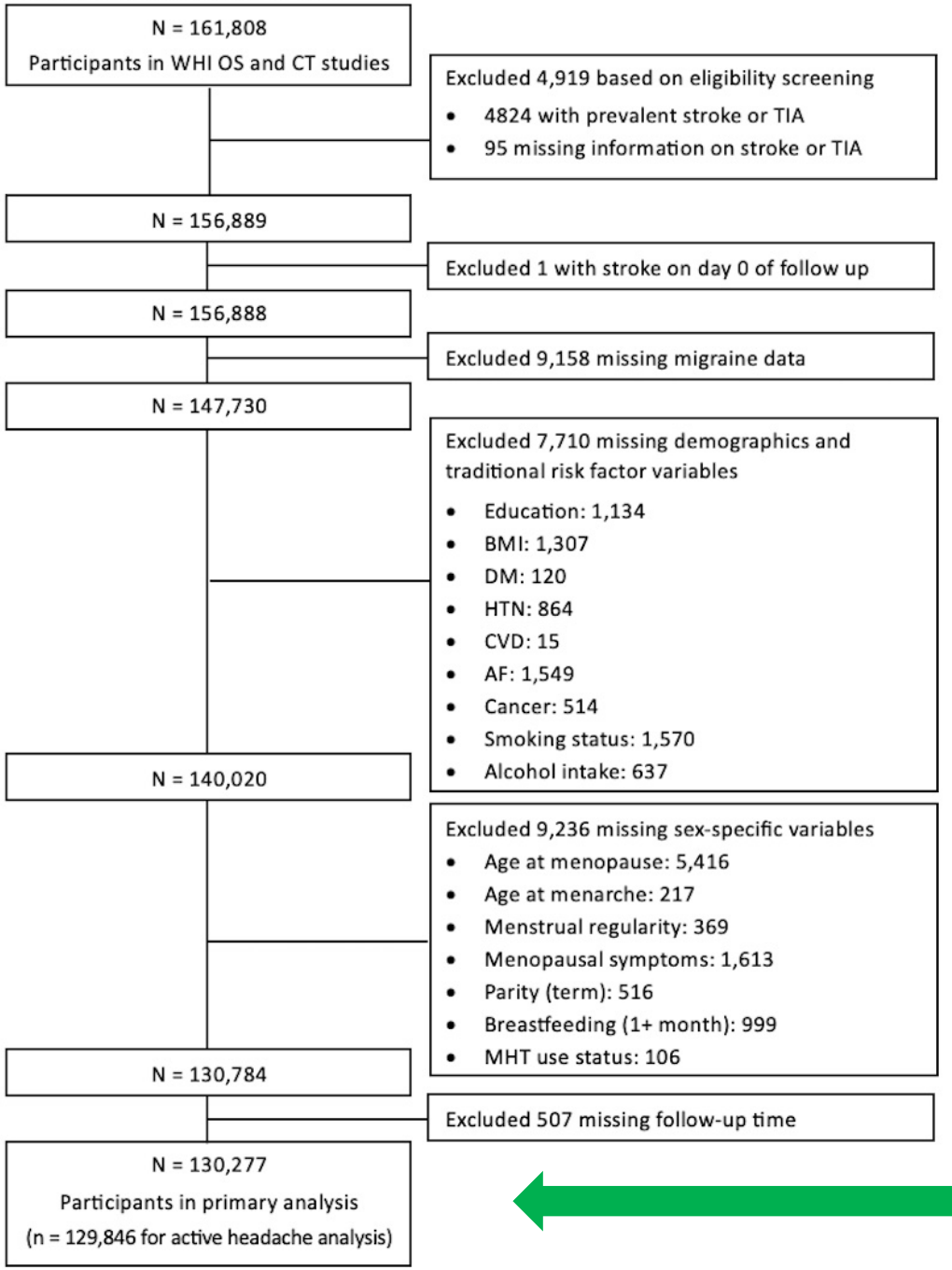
Migraine Variables in WHI (Baseline)

Form 30: MIGRAINE: Has a doctor told you that you have any of the following conditions (Migraine)?

Form 37: Headaches or migraines: Below is a list of symptoms people sometimes have. For each item, mark the one oval that best describes how bothersome the symptom was during the past 4 weeks for you.
(Did not occur/ mild/ moderate/ severe)

Study Sample, Objective 1

Figure 1: Participant Flow Diagram



PREVALENT STROKE

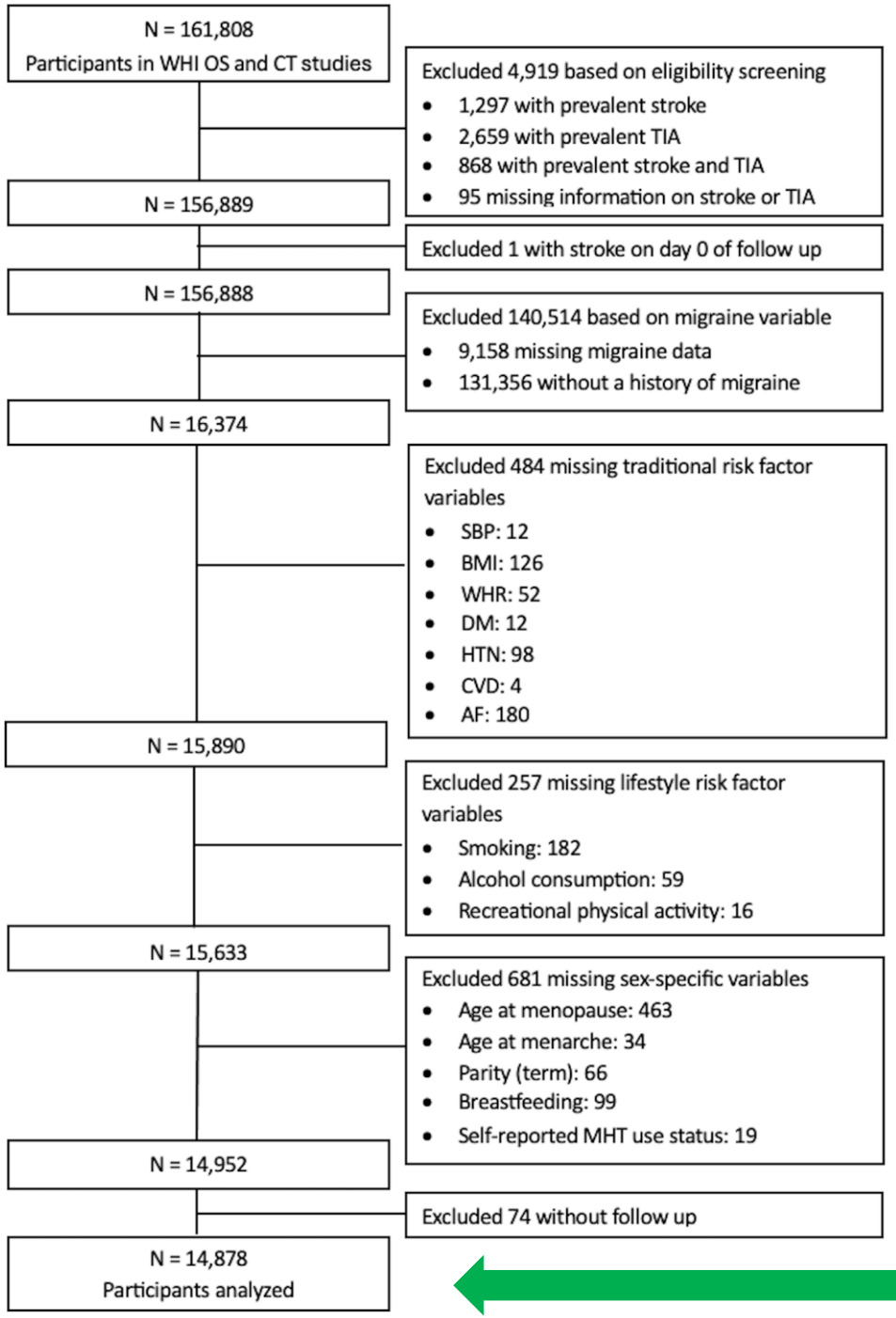
MISSING DATA

N= 130,277

Statistical Analysis, Objectives 1-2

- Cox proportional hazards models were used to model stroke (total, ischemic, hemorrhagic, and by TOAST subtype)
- Cox stratification procedure was used to account for possible non-proportionality (by participation in CT vs. OS, treatment arm within HT trial, 5-year age groups at baseline)
- Sequential models were adjusted for age, traditional stroke risk factors, and sex-specific stroke risk factors
- Overall and and age-specific effects estimates were reported

Study Sample, Objective 3



PREVALENT STROKE

MISSING MIGRAINE/ NO MIGRAINE

MISSING OTHER DATA

N= 14,878 women with migraine

Statistical Analysis, Objective 3

- Cox proportional hazards models were used to model total stroke
- Sequential models were adjusted for age, traditional stroke risk factors, and sex-specific stroke risk factors
- Primary exposure of interest was medication use as taken from WHI medication inventory (Form 44- Current medications)
- Categorization of medications using therapeutic classes and search of generic names to verify groups
- Time varying medication use incorporated when available
- HT use at baseline only (for now)

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Table 1: Baseline Characteristics	Migraine History 11.2% (n=14,630)	No Migraine History 88.8% (n=115,647)
Age (median)	61 (56-67)	63 (57-69)
Race/ Ethnicity	87.1% White 7.8% Black 4.2 % Hispanic 1.5% Asian	83.3% White 8.2% Black 4.0% Hispanic 2.8% Asian
Current treatment for HTN	20.1%	15.1%
Current treatment for diabetes	3.4%	4.1%
Moderate/Severe active HA	4.3%	6.6%
Age at menopause	49 (43-52)	50 (45-52)
Presence of vasomotor symptoms	79.5%	71.7%
Hormone therapy Use	50.9%	41.6%

Table 2: Multivariable Cox proportional hazards regression for total stroke and subtypes associated with history of migraine in the Women's Health Initiative

	Number of events		Cause-specific HR (95% CI) Migraine vs. No Migraine		
Stroke outcome	Migraine history (n=14,630)	No migraine history (n=115,647)	+Age-adjusted	+Traditional factors	+Sex-specific factors
Total	612	5,131	1.10 (1.01-1.19)	1.08 (0.99-1.17)	1.07 (0.99-1.17)
Ischemic	471	3,765	1.15 (1.04-1.26)	1.12 (1.02-1.24)	1.12 (1.02-1.23)
Hemorrhagic	72	733	0.87 (0.68-1.11)	0.85 (0.67-1.09)	0.85 (0.67-1.09)
By Trial of Org 10172 in Acute Stroke Treatment (TOAST) Subtype					
Large artery atherosclerosis	26	262	0.91 (0.61-1.36)	0.86 (0.57-1.29)	0.87 (0.58-1.31)
Cardio-embolism	146	1,139	1.23 (1.03-1.46)	1.16 (0.97-1.38)	1.17 (0.98-1.39)
Small vessel occlusion	90	704	1.12 (0.90-1.40)	1.14 (0.91-1.42)	1.13 (0.90-1.41)
Undetermined	191	1,500	1.16 (0.999-1.35)	1.16 (0.99-1.35)	1.14 (0.98-1.33)

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Cox proportional hazards models were stratified by participation in the WHI observational study, hormone therapy trial (no participation, control, intervention), and age at baseline in 5-year groups. Models were sequentially adjusted for age, traditional risk factors (BMI, race and ethnicity, education, treated diabetes, treated hypercholesterolemia, treated hypertension, cardiovascular disease (CVD), atrial fibrillation, cancer, smoking status, alcohol consumption), and sex-specific risk factors (age at menopause, age at menarche, menstrual irregularity, presence of vasomotor symptoms, parity, breastfeeding, use of menopausal hormone therapy).

Figure: Adjusted hazard ratios of total stroke by history of migraine among postmenopausal women in the Women's Health Initiative Study, stratified by age at baseline

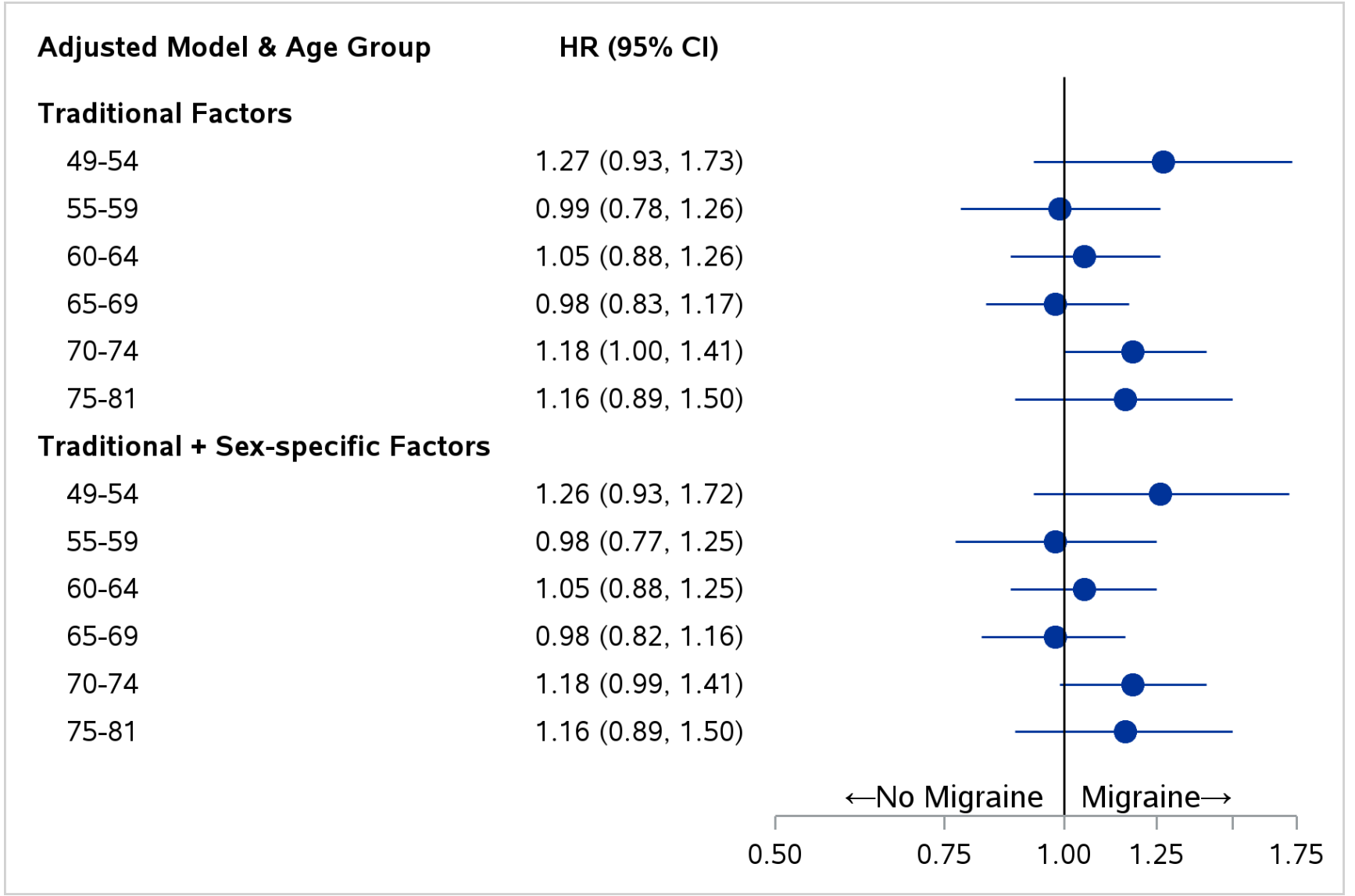


Figure: Baseline Medication Use Among Women with Migraine in the WHI (n = 14,878)

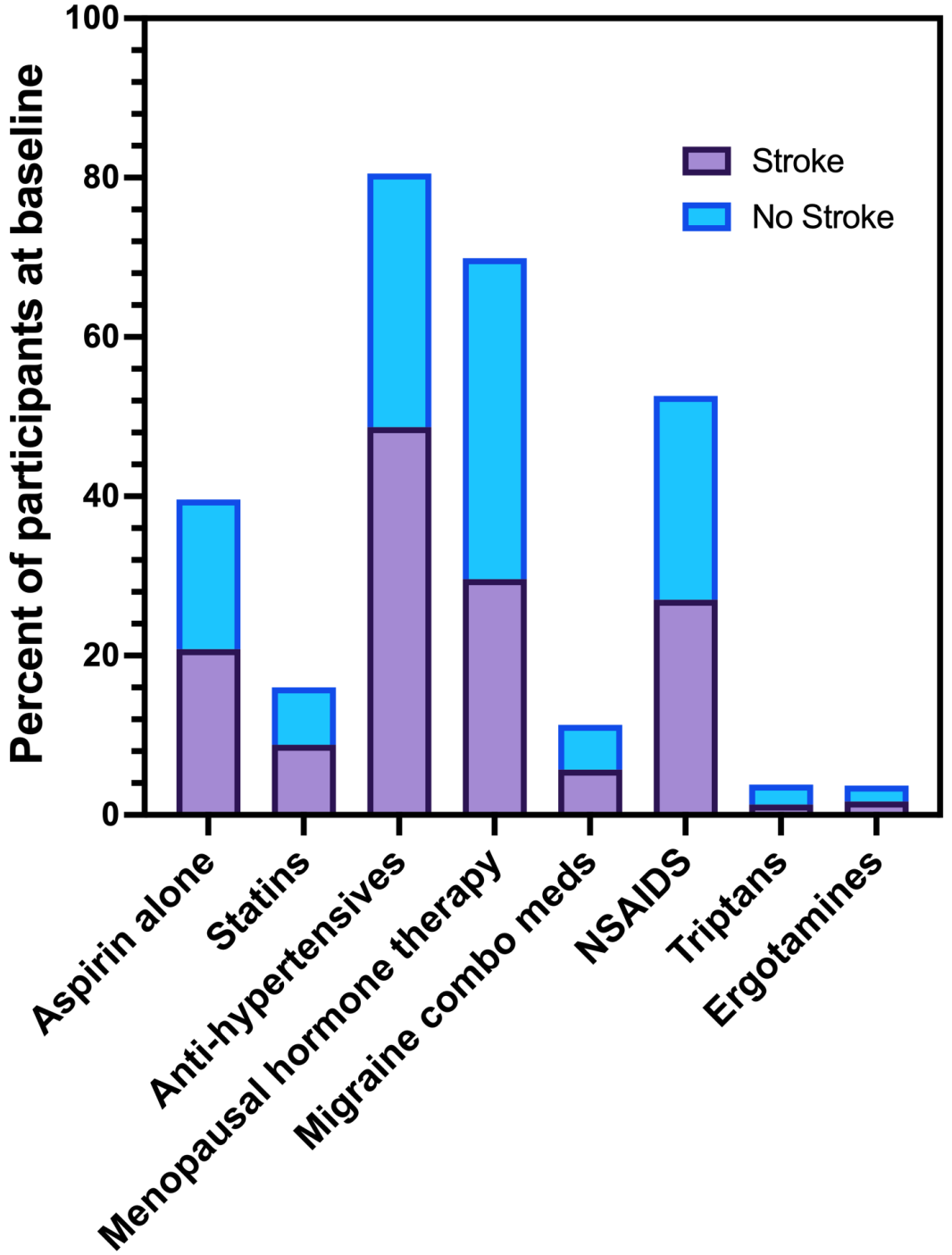
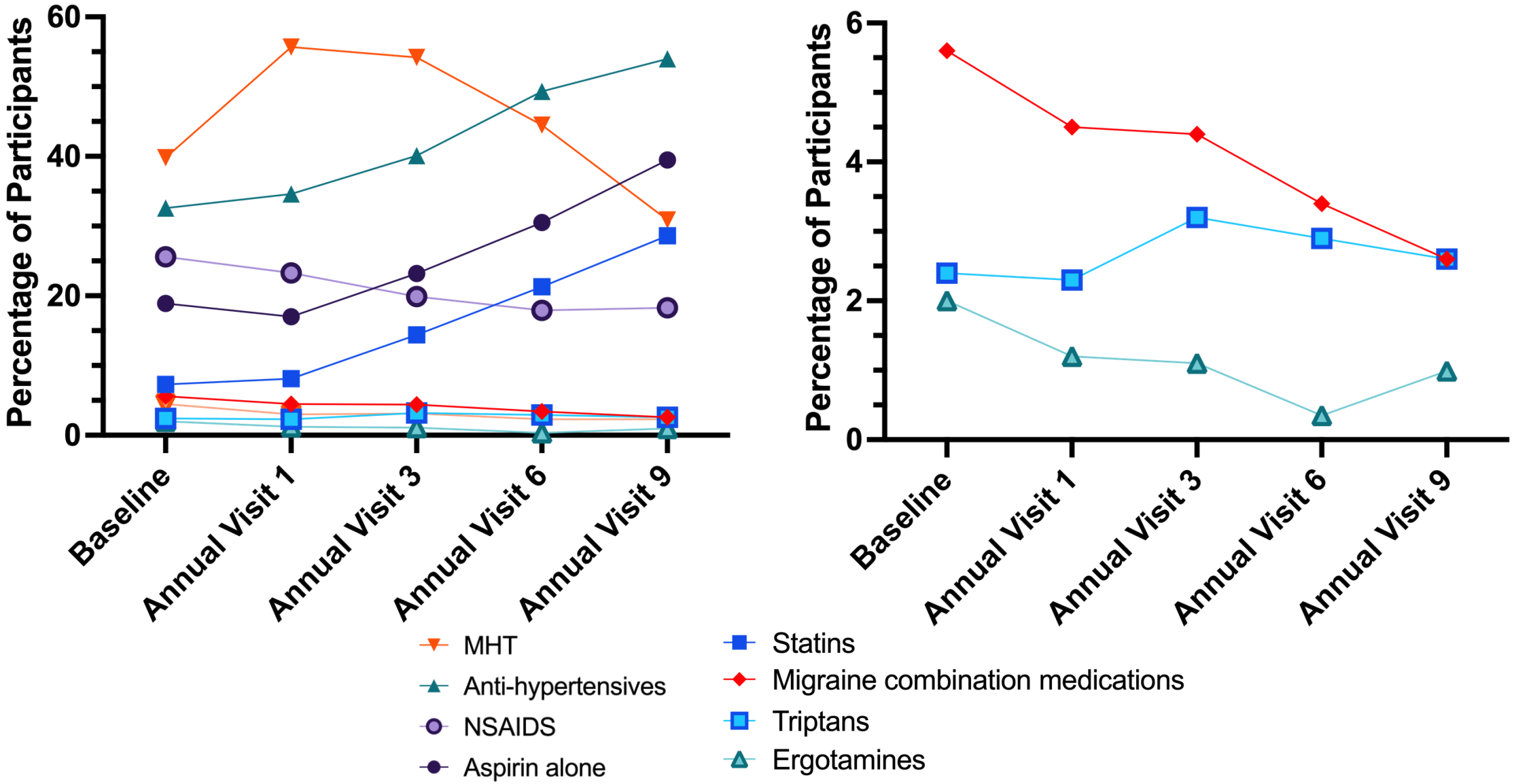


Figure: Medication Use Over Time in Women with Migraine History in the WHI



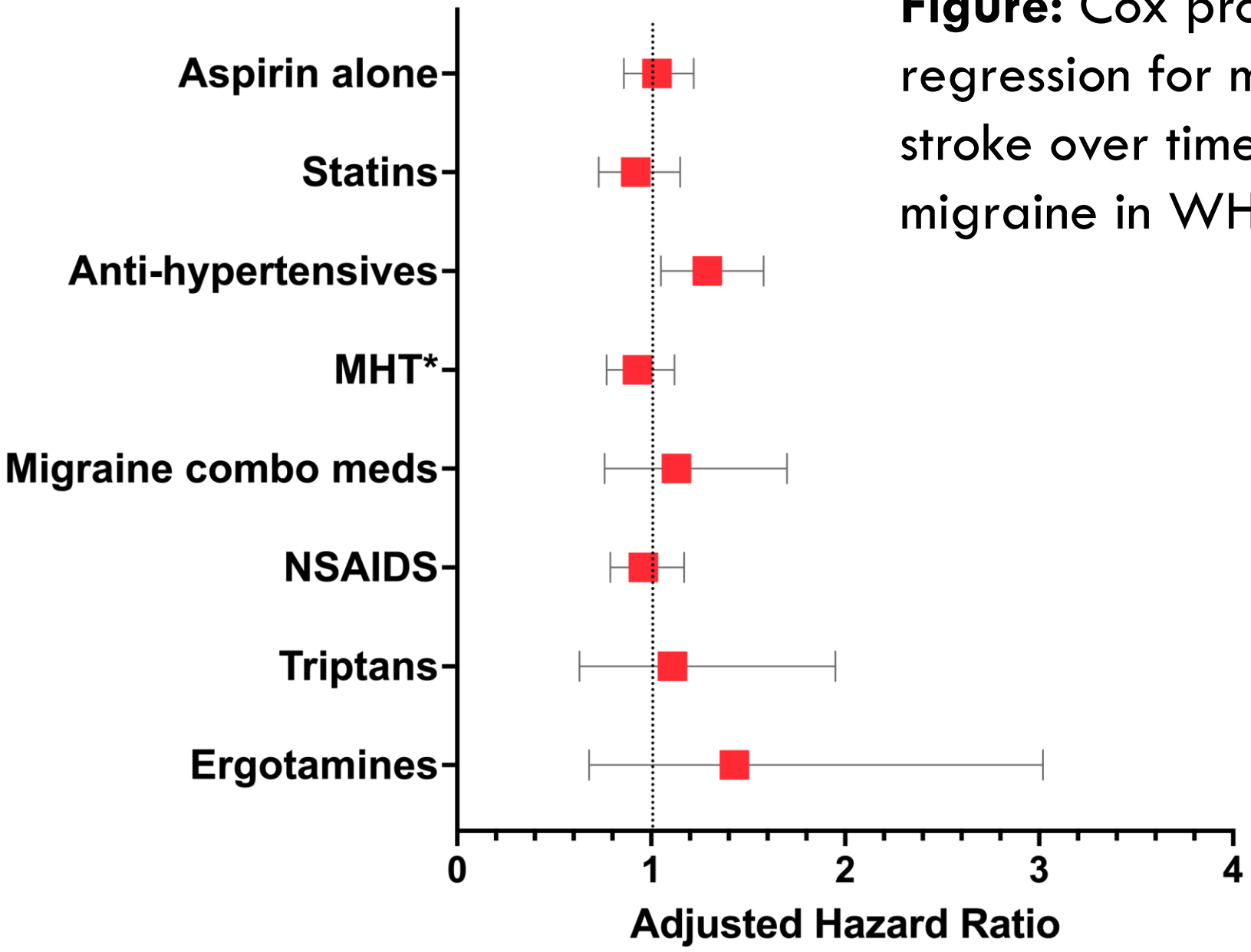


Figure: Cox proportional hazards regression for medication use and total stroke over time, among women with migraine in WHI

Models were stratified by participation in the WHI observational study, HT trial. Models were sequentially adjusted for age, traditional risk factors (age, treated HTN, systolic BP, DM, atrial fibrillation, CVD, treated cholesterol, WHR, smoking status, alcohol intake, physical activity), and sex-specific risk factors (age at menopause, age at menarche, menstrual irregularity, presence of vasomotor symptoms, parity, breastfeeding, use of menopausal HT as appropriate). *At baseline, HT retained as yes/ no without specific study arm.

Discussion

- Postmenopausal women had a modest increase (12%) in risk of ischemic stroke after adjusting for traditional and female-specific risk factors
- Effect estimates were attenuated compared to other cohort studies
- No association was found with hemorrhagic strokes
- Among women with migraine, no significant association between HT use at baseline and stroke risk
- Significant association with anti-hypertensives but not other medication groups

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Limitations / Future Directions

- Lack of data on migraine with aura
- Lack of repeat data on development of migraine headache or active headache symptoms over time
- Future work ongoing with respect to role of other modifiable risk factors
- Screening of women for risk factors (including migraine) is critical
- Future work needed to confirm medication safety among women with migraine histories

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Acknowledgements

- Christina Raker, Brian Silver, Jelena Pavlovich, Zailing Xing, all other co-authors
- WHI Investigators: The authors thank the WHI participants, clinical sites, investigators, and staff for their dedicated efforts. For a list of all the investigators who have contributed to WHI science, please visit: https://www-whi-org.s3.us-west-2.amazonaws.com/wp-content/uploads/WHI-Investigator-Long-List.pdf

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Migraine and Mechanism: The Role of Inflammatory Biomarkers in the Link between Migraine and Stroke

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Postdoctoral Associate
Department of Emergency Medicine
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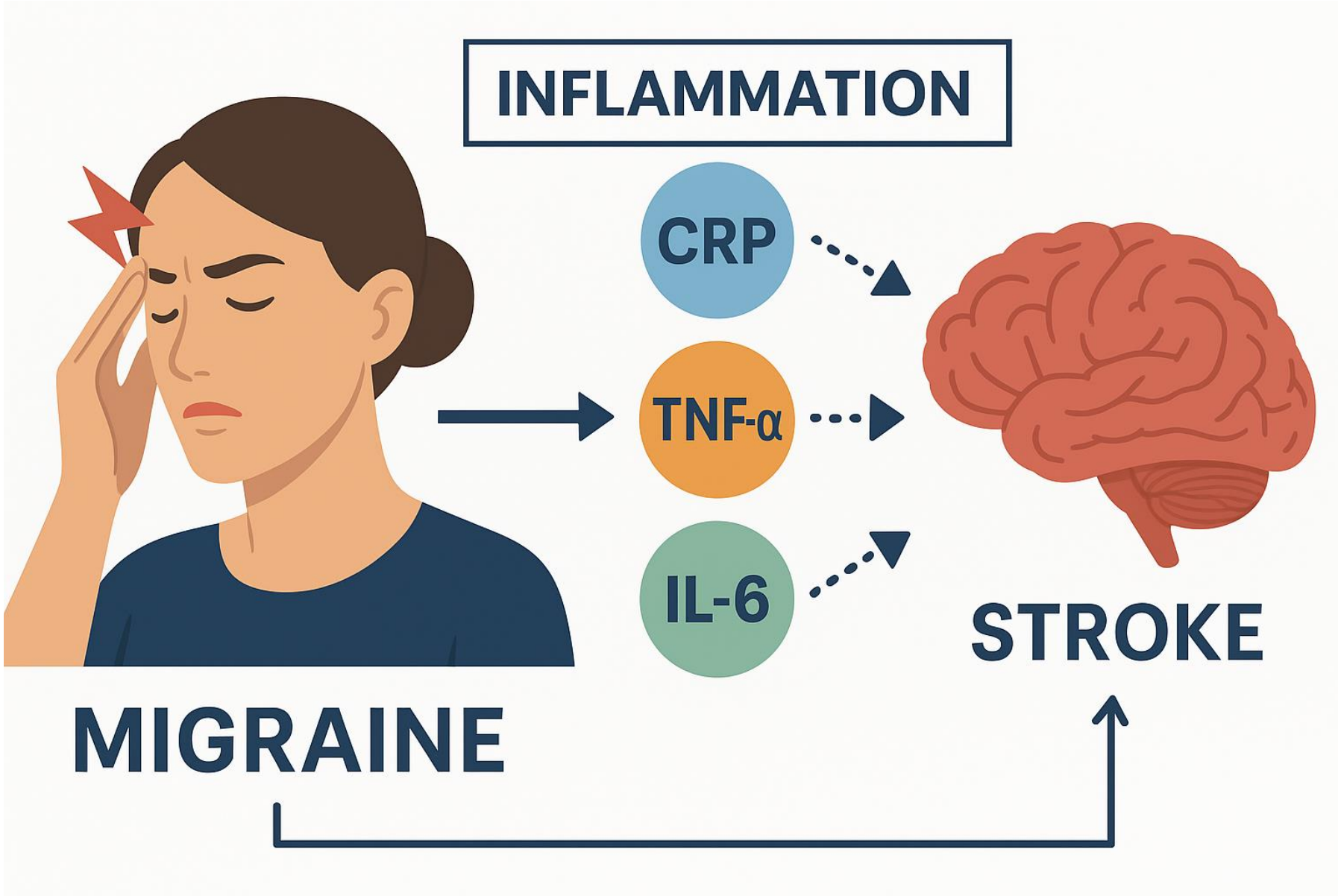
Background

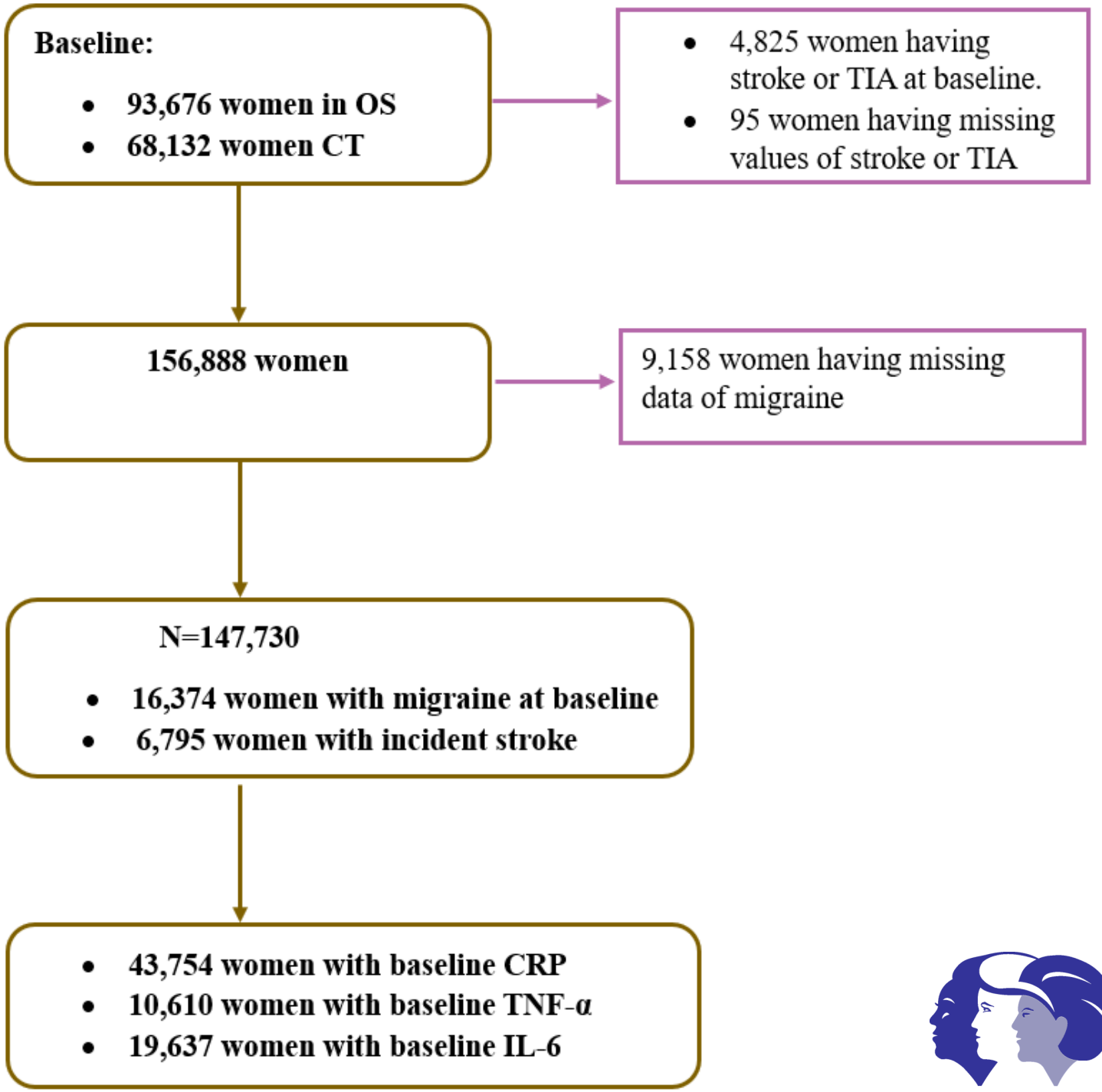


Objective

To examine the potential mediating effect of baseline inflammatory biomarkers (CRP, TNF-α, and IL-6) on the association between baseline migraine history and incident stroke among postmenopausal women.

Study population

- Postmenopausal women in the full WHI cohort.
- Exclude participants with prevalent stroke at baseline, and individuals lacking data on exposure and outcome.



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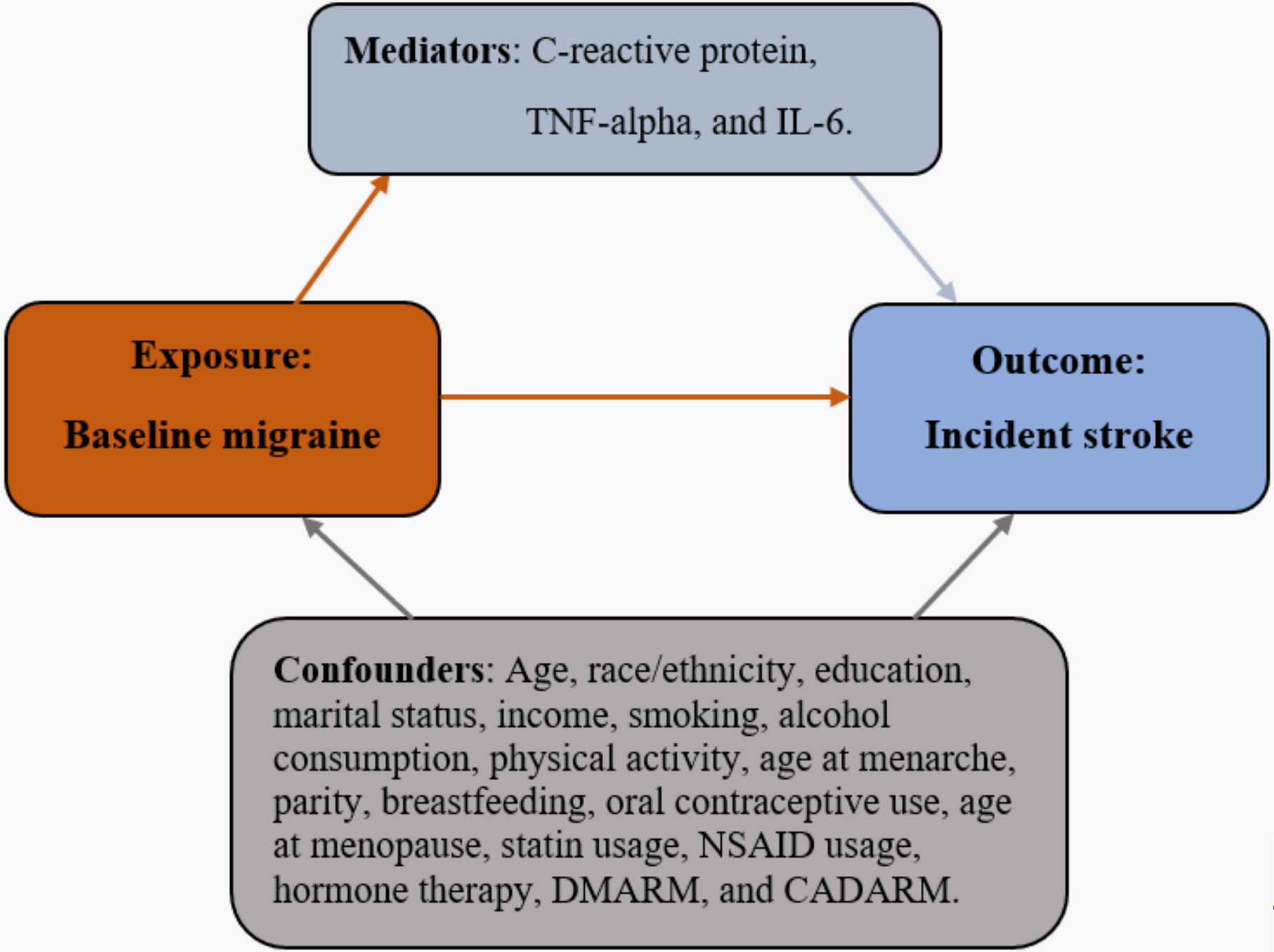

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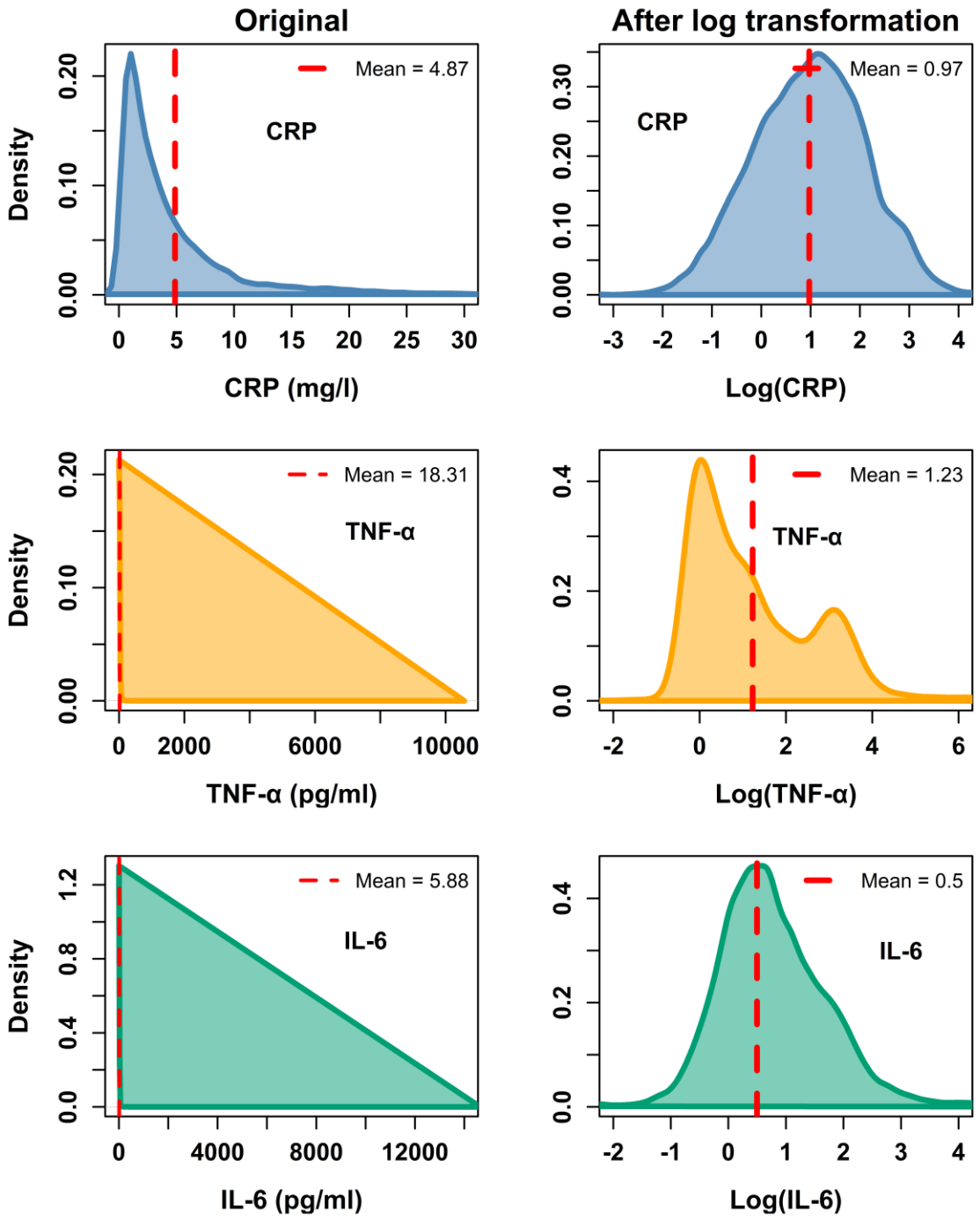
Statistical analysis

- Exposure → Mediators: Generalized linear regression models to estimate the adjusted association between migraine history and the levels of each biomarker.
- Exposure → Outcome: Cox proportional hazards models for the association between migraine and incident stroke.
- Mediators → Outcome: Cox proportional hazards models for the association between biomarkers and incident stroke.
  - Quantile-categorized biomarkers
  - Restricted cubic splines for continuous biomarkers
- Causal mediation analysis to estimate the total, direct, and indirect effects of migraine on incident stroke.

Results

Distribution of baseline CRP, TNF-α, and IL-6 before and after log transformation.



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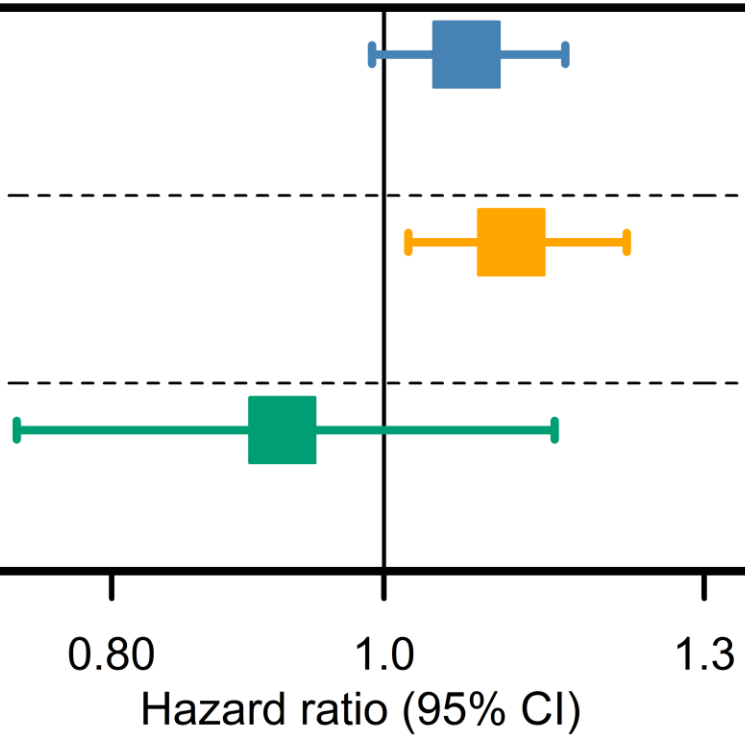
Adjusted association between migraine history and incident stroke

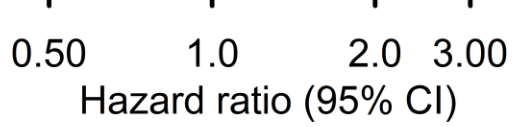
Stroke type	Migraine history	N(events)	HR (95% CI)
Total	Yes	16,374(707)	1.07(0.99-1.16)
	No	131,356(6,088)	1.00
Ischemic	Yes	16,374(539)	1.11(1.02-1.22)
	No	131,356(4,440)	1.00
Hemorrhagic	Yes	16,374(90)	0.92(0.74-1.15)
	No	131,356(862)	1.00



Note: Adjusting for age, race, education, marital status, income, smoking, alcohol consumption, age at menarche, oral contraceptive usage, parity, breastfeeding, age at menopause, physical activity, statin usage, NSAID usage, hormone therapy, DMARM, and CADARM.

Adjusted association between quantile-categorized biomarkers and total stroke

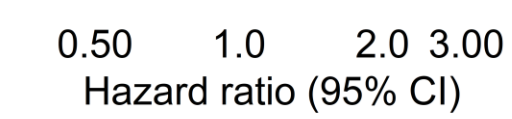
Biomarkers	Quantiles	N(events)	HR (95% CI)
Log(CRP)	Q1	11,017(898)	1.00
Log(CRP)	Q2	10,901(1,005)	1.15(1.05-1.26)
Log(CRP)	Q3	10,942(1,014)	1.22(1.11-1.33)
Log(CRP)	Q4	10,894(1,143)	1.53(1.40-1.68)
Log(TNF-α)	Q1	2,652(281)	1.00
Log(TNF-α)	Q2	2,637(528)	1.78(1.54-2.06)
Log(TNF-α)	Q3	2,668(208)	0.67(0.56-0.80)
Log(TNF-α)	Q4	2,653(175)	0.57(0.46-0.70)
Log(IL-6)	Q1	4,897(201)	1.00
Log(IL-6)	Q2	4,927(471)	2.33(1.98-2.75)
Log(IL-6)	Q3	4,902(604)	2.97(2.53-3.50)
Log(IL-6)	Q4	4,911(517)	2.62(2.22-3.10)



Note: Adjusting for age, race, education, marital status, income, smoking, alcohol consumption, age at menarche, oral contraceptive usage, parity, breastfeeding, age at menopause, physical activity, statin usage, NSAID usage, hormone therapy, DMARM, and CADARM..

Adjusted association between quantile-categorized biomarkers and ischemic stroke

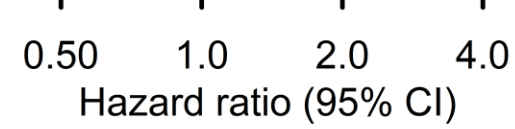
Biomarkers	Quantiles	N(events)	HR (95% CI)
Log(CRP)	Q1	11,017(620)	1.00
Log(CRP)	Q2	10,901(727)	1.20(1.08-1.33)
Log(CRP)	Q3	10,942(785)	1.36(1.22-1.51)
Log(CRP)	Q4	10,894(866)	1.66(1.49-1.84)
Log(TNF-α)	Q1	2,652(259)	1.00
Log(TNF-α)	Q2	2,637(510)	1.86(1.60-2.16)
Log(TNF-α)	Q3	2,668(177)	0.61(0.50-0.74)
Log(TNF-α)	Q4	2,653(125)	0.43(0.34-0.55)
Log(IL-6)	Q1	4,897(157)	1.00
Log(IL-6)	Q2	4,927(410)	2.62(2.18-3.15)
Log(IL-6)	Q3	4,902(528)	3.38(2.82-4.04)
Log(IL-6)	Q4	4,911(428)	2.83(2.35-3.42)



Note: Adjusting for age, race, education, marital status, income, smoking, alcohol consumption, age at menarche, oral contraceptive usage, parity, breastfeeding, age at menopause, physical activity, statin usage, NSAID usage, hormone therapy, DMARM, and CADARM..

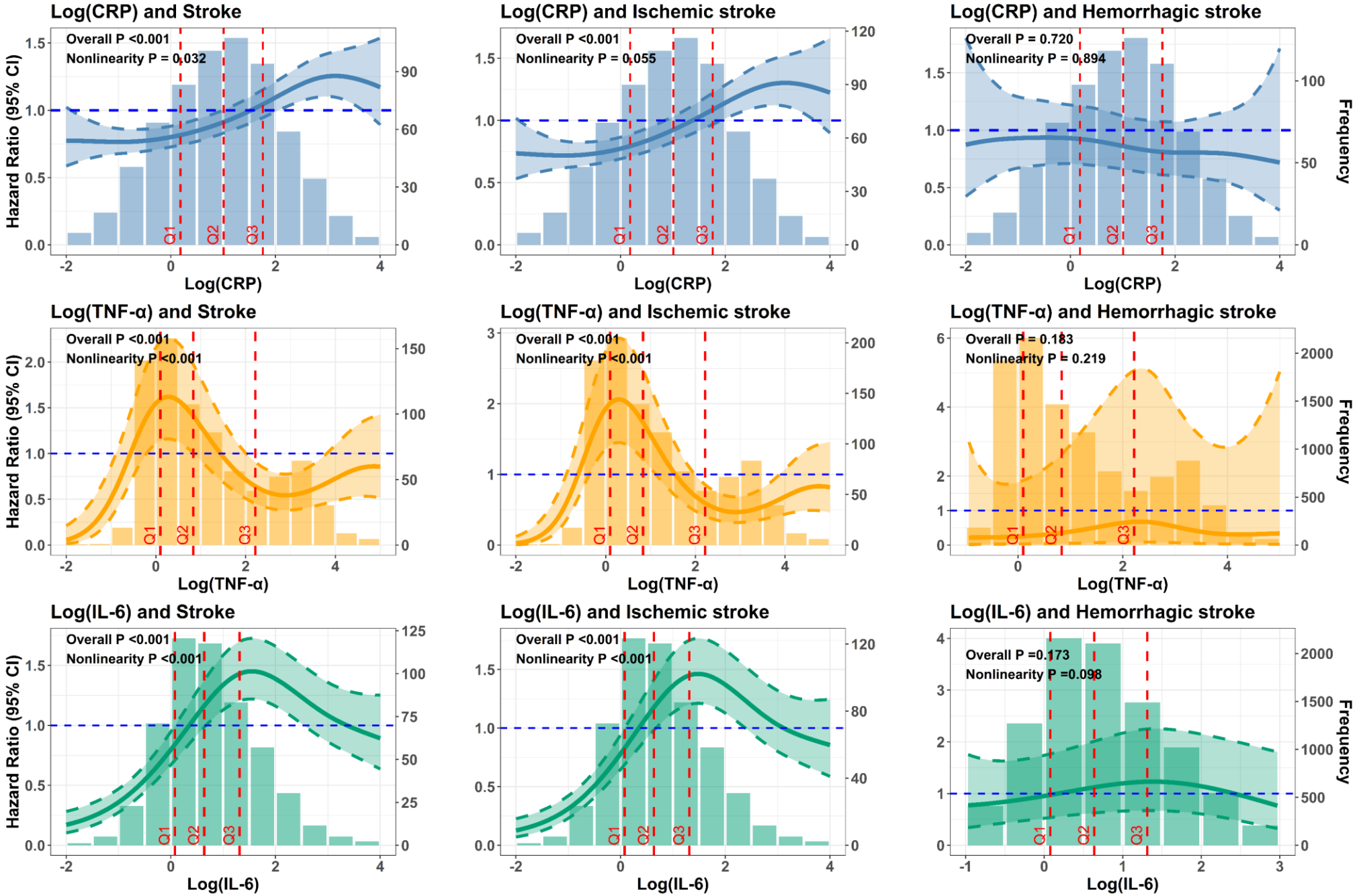
Adjusted association between quantile-categorized biomarkers and hemorrhagic stroke

Biomarkers	Quantiles	N(events)	HR (95% CI)
Log(CRP)	Q1	11,017(144)	1.00
Log(CRP)	Q2	10,901(139)	1.01(0.80-1.28)
Log(CRP)	Q3	10,942(108)	0.82(0.63-1.05)
Log(CRP)	Q4	10,894(116)	0.96(0.74-1.23)
Log(TNF-α)	Q1	2,652(9)	1.00
Log(TNF-α)	Q2	2,637(9)	0.99(0.39-2.51)
Log(TNF-α)	Q3	2,668(15)	1.75(0.75-4.06)
Log(TNF-α)	Q4	2,653(18)	2.01(0.82-4.90)
Log(IL-6)	Q1	4,897(28)	1.00
Log(IL-6)	Q2	4,927(37)	1.20(0.73-1.97)
Log(IL-6)	Q3	4,902(36)	1.11(0.67-1.84)
Log(IL-6)	Q4	4,911(43)	1.26(0.76-2.09)

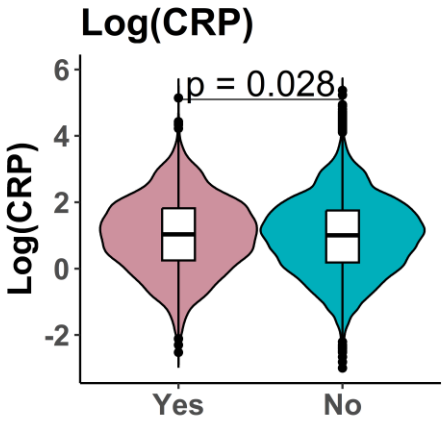


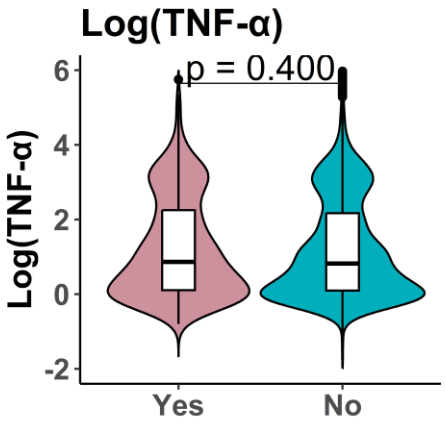
Note: Adjusting for age, race, education, marital status, income, smoking, alcohol consumption, age at menarche, oral contraceptive usage, parity, breastfeeding, age at menopause, physical activity, statin usage, NSAID usage, hormone therapy, DMARM, and CADARM.

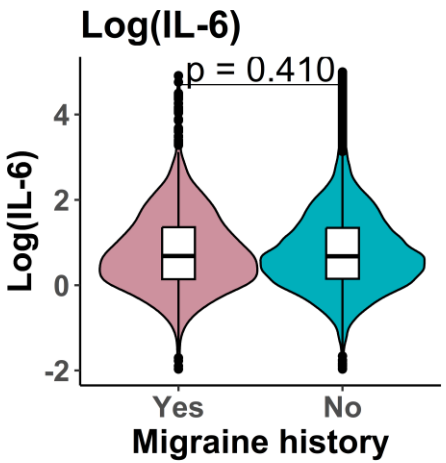
Adjusted association between continuous inflammatory biomarkers and incident stroke

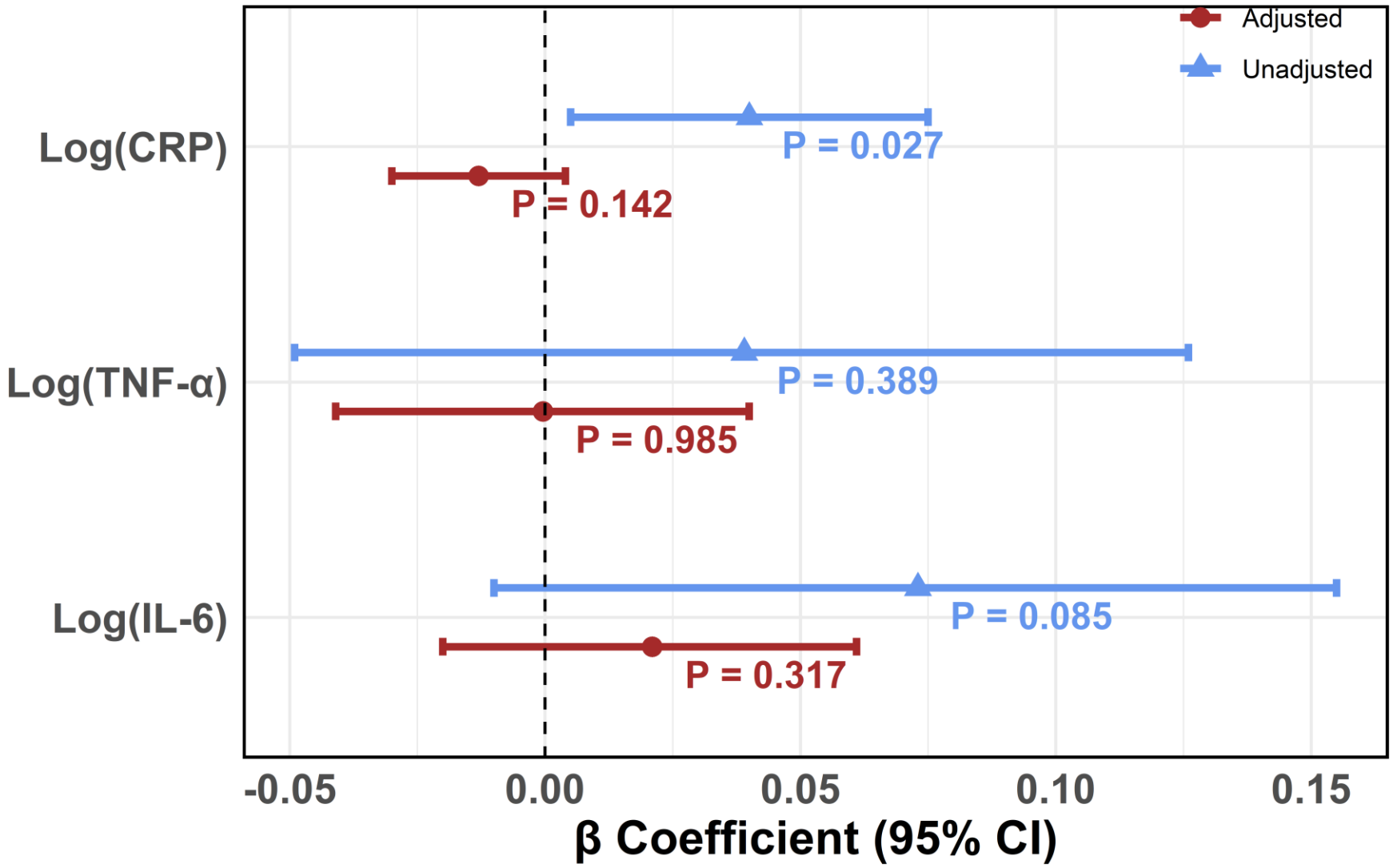


Association between migraine and inflammatory biomarkers









Conclusion

- CRP, TNF-α, and IL-6 were significantly associated with both incident total stroke and ischemic stroke, with non-linear associations observed for TNF-α and IL-6, but not for CRP.
- The adjusted association between migraine and the three biomarkers was not statistically significant.
- This suggests that these biomarkers may not directly mediate the relationship between migraine and stroke in this study population, potentially limiting the understanding of the mechanistic pathway.

Limitations

- The WHI cohort includes only postmenopausal women, limiting generalizability to younger populations.
- Migraine and stroke mechanisms may differ across age groups.
- Baseline biomarkers do not capture time-varying inflammation.
- Key migraine characteristics (e.g., aura status, age at onset, duration) were not collected.
- Some baseline covariates may reflect post-exposure factors, complicating causal inference.
- Biomarkers were obtained from ancillary studies, introducing potential selection bias.

Future directions

- Apply inverse probability weighting to further analyze the biomarker sample.
- Investigate the association between migraine and additional biomarkers, including MCP-1, fibrinogen, IL-1β, PAI-1, E-selectin, and VCAM-1, to identify alternative inflammatory pathways.
- Examine the relationship between migraine and longitudinal trajectories of inflammatory biomarkers to capture dynamic patterns over time.
- Validate findings in external cohorts or databases to assess the reproducibility and generalizability of the observed associations.
- Apply genetic variants (e.g., SNPs) as instrumental variables to infer the potential causal effect of migraine on inflammatory biomarker levels.

Acknowledgement

- Drs. Tracy Madsen, Christina Raker, Brian Silver, and Jelena Pavlovic.
- All professionals and participants of the WHI study
- American Heart association

University of Vermont

Thank you!

The Future of Migraine Research in Postmenopausal Women

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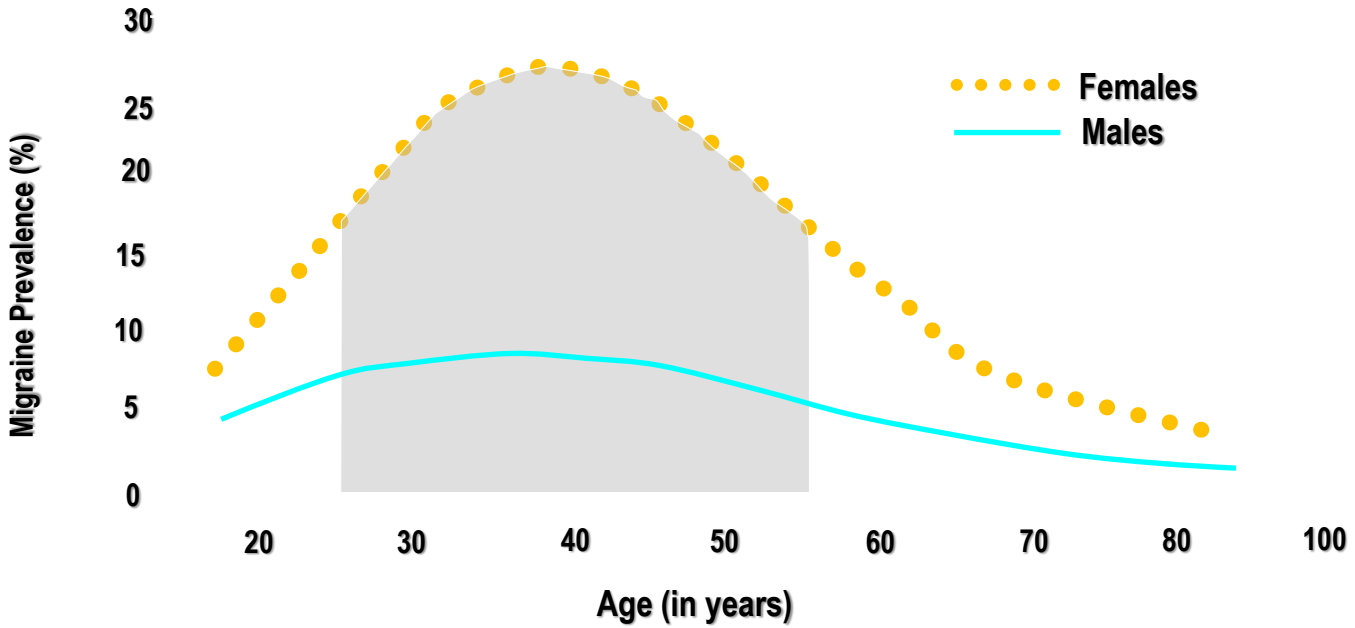
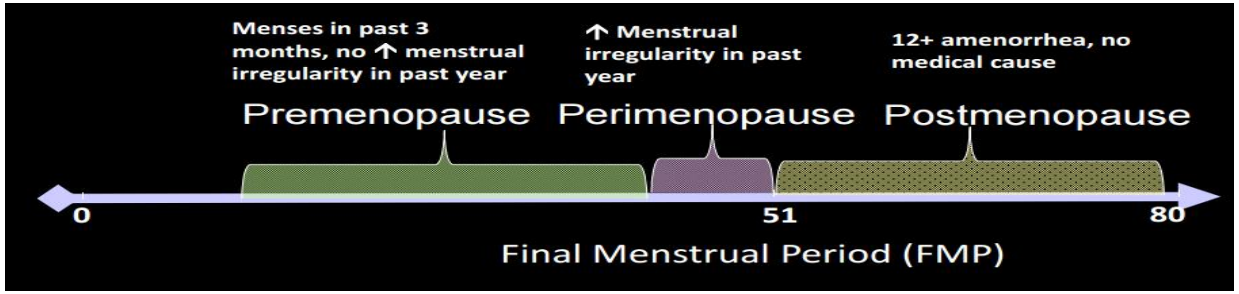
Migraine in Women: Complex Long-Term Relationship

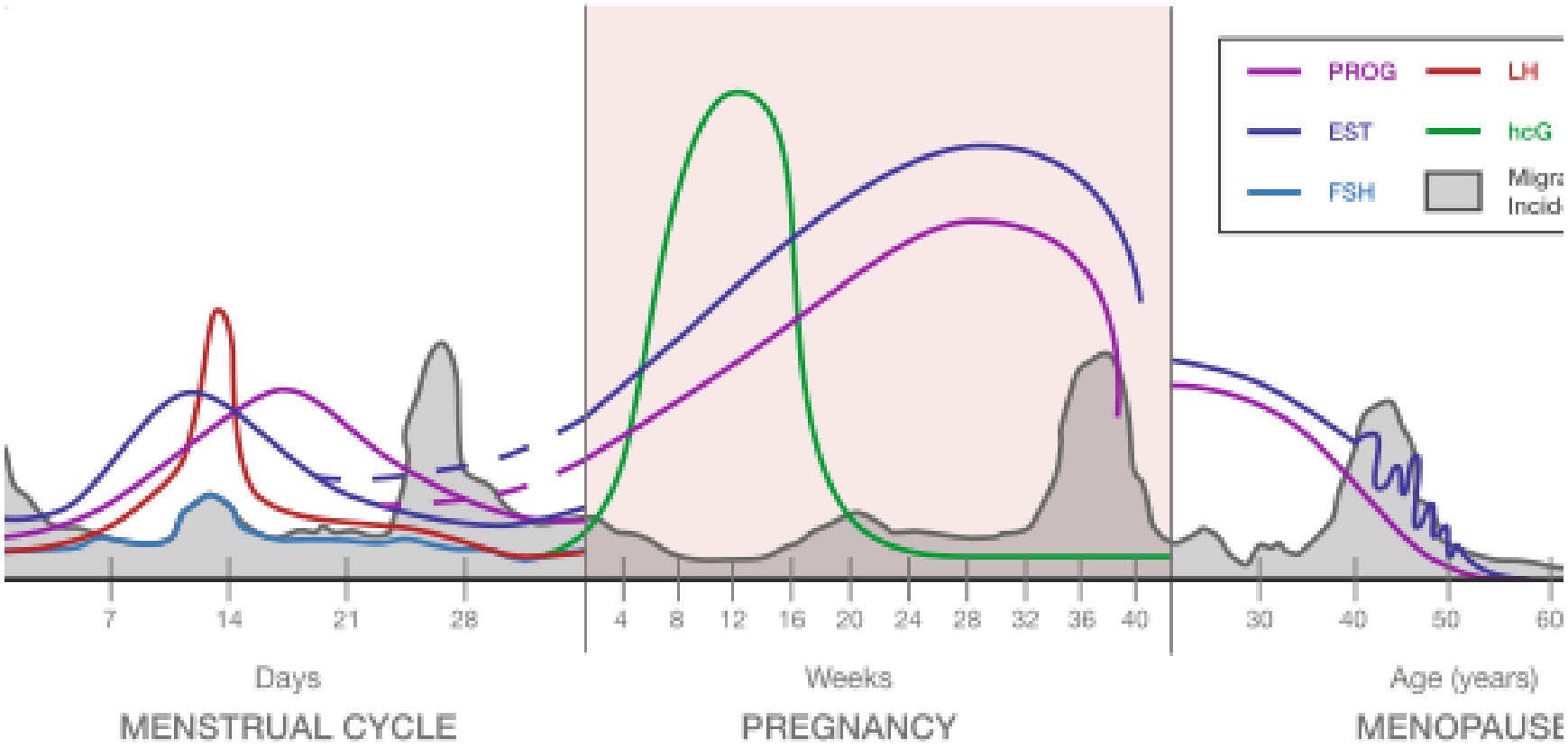




- Field has focused on migraine in women of reproductive age
- Numerous knowledge gaps in understanding of migraine epidemiology; symptom and disease co-morbidities in postmenopausal women
- Hx of migraine vs active migraine as a risk factor in aging (CVD, cognitive health, etc)
- Lack of evidence from longitudinal studies regarding use of HT in women with migraine (hx and current)

Lipton et al. Neurology 2007;68:343-349

Migraine occurrence in women through the lifespan – female life events



Sacco S et al. J Headache Pain. 2012 Apr;13(3):177-89.

Consensus Guidelines for Exogenous Estrogen Use in Migraine

	WHO	ACOG	IHS
Migraine w/o aura < 35 yo	**Yes**	**Yes if nonsmoker**	**Yes**
Migraine w/o aura >35 yo	generally should not use	generally should not use	**Yes**
Migraine w aura Any age	**No**	**No**	**+/- case-by-case**

- World Health Organization, Reproductive Health and Research 2004
- American College of Obstetrics and Gynecology. Obstet Gynecol. 2006;107:1453-7
- International Headache Society Task on Combined Oral Contraceptives & Hormone Replacement Therapy. Cephalalgia. 2000;20(3):145-7

Migraine, CVD and Exogenous Hormones Summary

- Conflicting studies depending on aura status, age of population and CVD outcomes examined

- Risk consistently associated with AURA, female gender, younger age, and smoking

- Clinically challenging, as exogenous hormones often needed to treat migraine

- Outside of WHI, the effect of HT on women with migraine has not been examined in longitudinal studies

Migraine, CVD and Exogenous Hormones in Menopausal Transition and Postmenopause: Clinical Dilemma

- No formal guidelines exist for use of HT in migraine, there are no known contraindications

- Strict guidelines regarding OCP/COC use in migraine

- These may bias against HT use in women with migraine:
    - treatment of migraine
    - treatment of menopausal symptoms
    - other potential benefits

Migraine and Menopause: Presence of Other Symptoms?

	OS Cohort Migraine		HT Cohort Migraine	
	No	Yes	No	Yes
n	59907	7322	15631	1482
Bilateral oophorectomy = Yes (%)	11151 (19.0)	1722 (23.9) *	2172 (14.3)	229 (15.9)
Hyperlipidemia = Yes (%)	7282 (12.2)	979 (13.4)	1677 (10.7)	195 (13.2) *
Hypertension= Yes (%)	16942 (28.4)	2172 (29.8)	4436 (28.5)	472 (32.0) *
Night sweat (%)				
Symptom did not occur	45910 (77.2)	5203 (71.8)	10431 (67.4)	922 (63.0)
Symptom was mild	10114 (17.0)	1436 (19.8)	3428 (22.1)	335 (22.9)
Symptom was moderate	2798 (4.7)	483 (6.7)	1339 (8.6)	167 (11.4)
Symptom was severe	629 (1.1)	129 (1.8)	288 (1.9)	39 (2.7)
Hot Flash (%) *				
Symptom did not occur	46489 (78.1)	5219 (71.7)	10525 (67.8)	914 (62.3)
Symptom was mild	9675 (16.2)	1402 (19.3)	3353 (21.6)	345 (23.5)
Symptom was moderate	2700 (4.5)	503 (6.9)	1316 (8.5)	164 (11.2)
Symptom was severe	679 (1.1)	154 (2.1)	324 (2.1)	45 (3.1)

* SMD >0.05

Pavlovic et al. In preparation

Limitations/Caveats of the WHI cohort in studying Migraine

1. Migraine history was based on self-report
2. Information on aura status not available
3. Migraine status at baseline and on follow up either unknown or challenging to determine – active vs. inactive migraine

4. ? frequency of attacks, associated symptoms, specific treatment(s) used for migraine vs. other reasons

5. Survivorship bias

Future directions of Migraine studies in WHI and postmenopausal women at large

1. **Age-Specific Migraine Assessment Tools**
    - Use screening instruments specifically designed for older women
    - Evaluate for history of aura that may have resolved with age vs present aura vs evolving symptoms which may resemble aura
    - Incorporate assessment of changing migraine presentations in postmenopausal women
    - Implement more detailed migraine phenotyping with standardized questionnaires
    - Collect prospective data on current headache patterns and treatment(s)
    - Address potential recall challenges

Future directions of Migraine studies in WHI and postmenopausal women at large

2. Evaluate Cardiovascular outcomes in relation to migraine with improved phenotyping

- MIMS (Myocardial Ischemia and Migraine Study (OC) – PI Dr. Smoller) **study provides an important opportunity in WHI - n=3369 participants completed** Migraine Status Questionnaire (14 item self-report including AURA)

- Active migraine status vs. inactive and CVD-related outcomes
- Examine if aura status changes CVD risk stratification in the WHI OC cohort (MIMS)

3. Hormone Therapy Effects on Migraine Frequency and Severity

- Effects of HT on migraine presentation and treatment
- Dose-dependent effects on migraine characteristics
- Risk of HT on CVD outcomes in Migraine (active vs. inactive; +/- aura)

Future directions of Migraine studies in WHI and postmenopausal women at large

Address critical knowledge gaps in understanding migraine in older women by leveraging WHI's comprehensive datasets

5. Biomarker Analysis

- Utilize WHI's extensive biorepository to identify markers associated with migraine beyond inflammatory markers

- Explore markers that may be related to migraine persistence into postmenopausal age

- Investigate potential new biomarkers specific to late-life migraine

6. Cognitive Function and Migraine History

- WHIMS (WHI Memory Study) data in relation to migraine history

- Investigate if migraine serves as an independent risk factor for cognitive decline

7. Impact of Migraine on Physical activity, Psychosocial Health and QoL, Diet, Bone Health, etc