

April 23, 2024 - EPA Tri-Regional Radon Stakeholders Meeting

WHI Risk It?
The Women's Health
Initiative Radon Risk
Investigation

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Lung Cancer

Lung Cancer

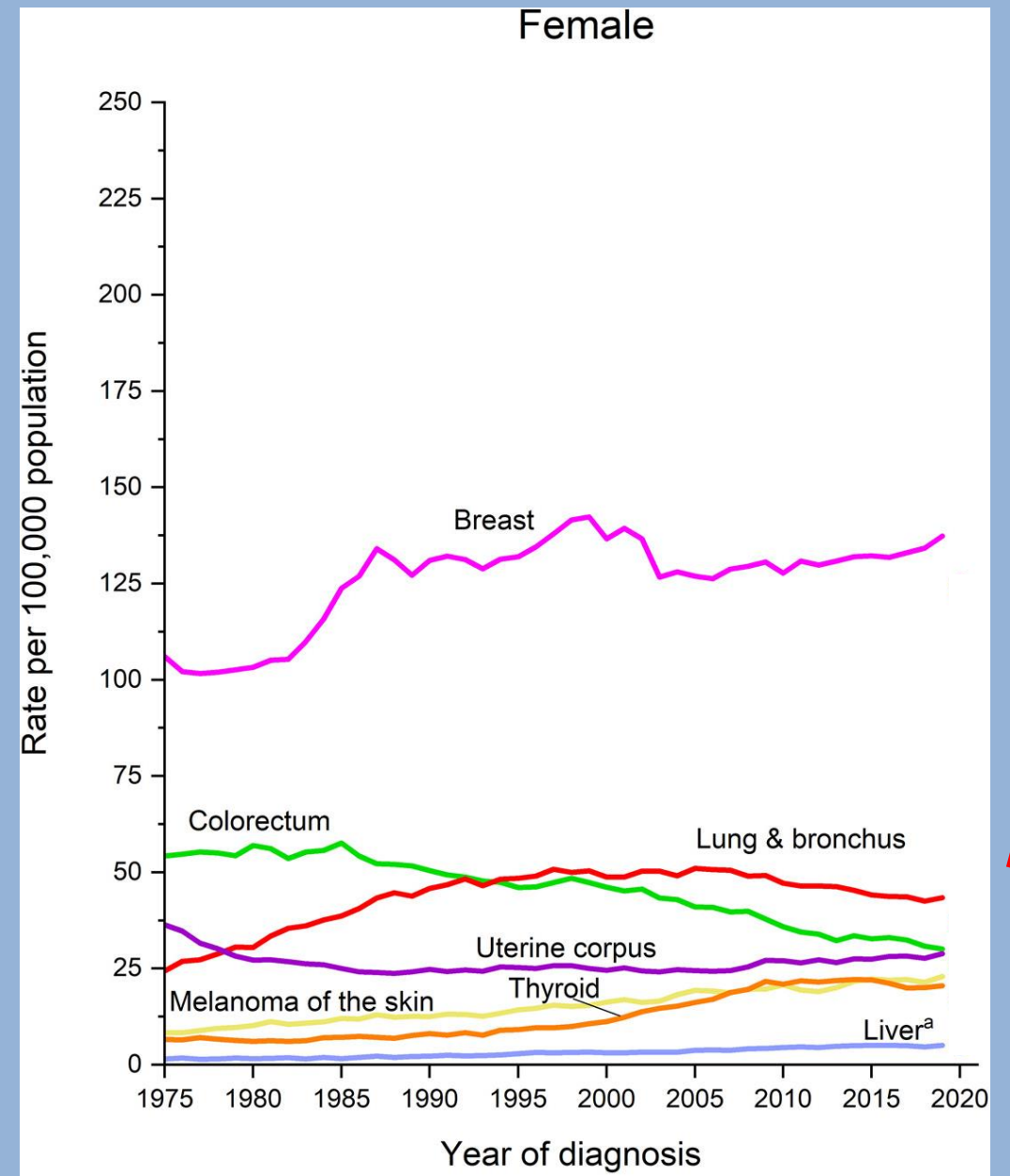
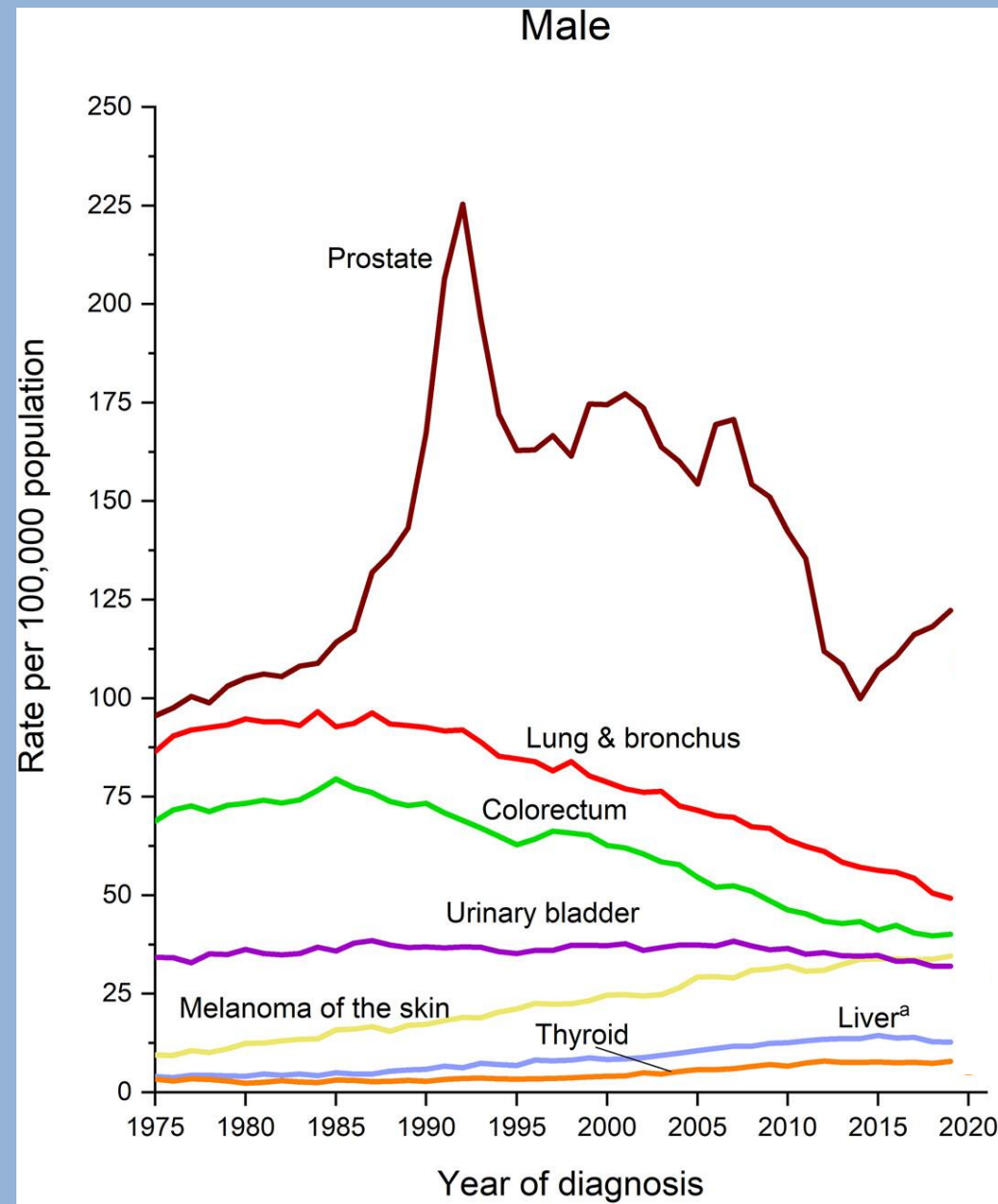
- ↓ incidence
- ↓ mortality
- common
- societally burdensome



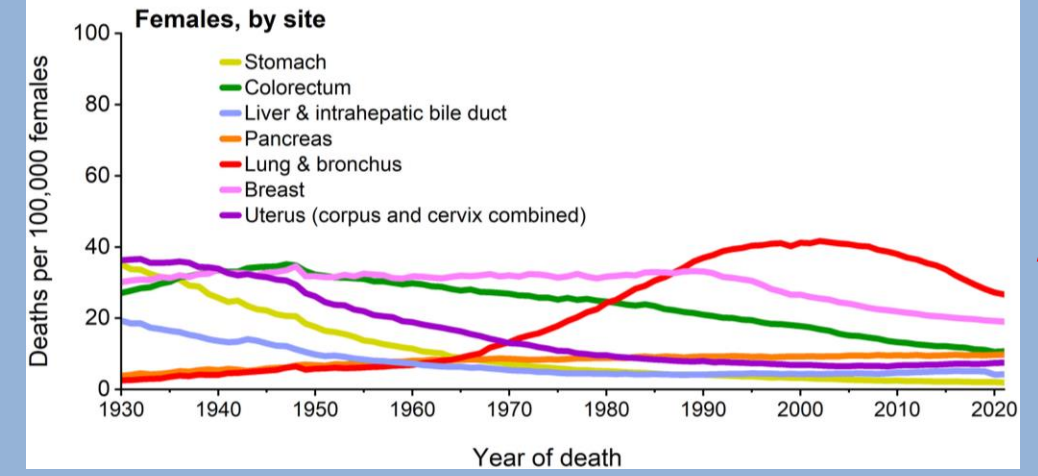
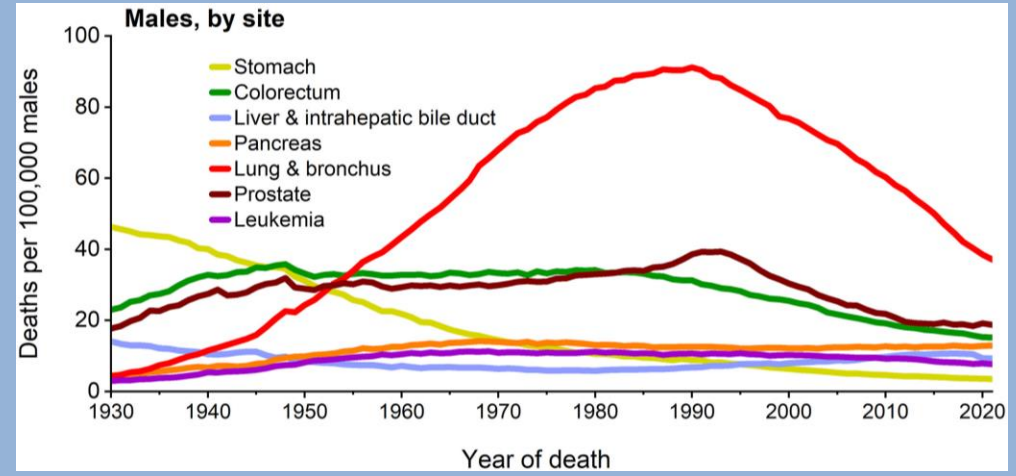


U.S. Lung Cancer Statistics

Incidence



Mortality





U.S. Lung Cancer Statistics

Lung Cancer Statistics

<u>Estimate</u>	<u>Lung Cancer*</u>
Lifetime Risk	6.1%
New Cases	234,580
Deaths, total	125,070
Deaths/day	340
<u>Deaths/10⁵ persons[†]</u>	<u>35.0</u>

*In 2023 except lifetime risk (2017-2019) and deaths/10⁵ persons (2016-2020). †Age-adjusted.





U.S. Lung Cancer & Stroke Statistics

Lung Cancer & Stroke Statistics

<u>Estimate</u>	<u>Lung Cancer*</u>	<u>Stroke†</u>
Lifetime Risk	6.1% <	18.0%
New Cases	234,580 <	610,000
Deaths, total	125,070 <	162,890
Deaths/day	340 <	445
<u>Deaths/10⁵ persons‡</u>	<u>35.0 <</u>	<u>41.1</u>

*In 2024 except lifetime risk (2017-2019) and deaths/10⁵ persons (2016-2020). †In 2021 except new cases (1999). ‡Age-adjusted.





U.S. Stroke Disparities

Stroke Disparities

<u>Disparity</u>	<u>Women</u>		<u>Men</u>
Lifetime risk	20.0%	>	16.0%
Prevalence [*]	3.6%	>	2.9%
Incidence [†]	53.5%	>	46.5%
Deaths [‡]	57.0%	>	43.0%
<u>Mortality[§]</u>	<u>56.5%</u>	<u>></u>	<u>43.5%</u>

^{*}Ages ≥ 20 years (2017-2020). [†]The proportion of total incidence, all ages (1999). [‡]The proportion of total deaths (2019). [§]The proportion of total mortality, all ages (2021).





U.S. Stroke Disparities

Potential Reasons Why?

- Lifespan:
 - NVSS: 79.3 (♀) - 73.5 (♂) = 5.8 years
- Time indoors @ home:
 - NHAPS: 17.5 (♀) – 15.8 (♂) = 1.7 hour/day
- Indoor radon-related stroke risk
 - KNHANES: ↑ 20% @ pCi/L > 2.7
 - REGARDS: ↑ 39% @ pCi/L > 2.0 } non-smokers



NVSS = National Vital Statistics System. Arias E, et al. National Vital Statistics Reports 2023;72(12).
NHAPS = National Human Activity Pattern Survey. †NERL. Report No.: EPA/600/R-96/148. 1996.
KNHANES = Korean National Health and Nutrition Examination Survey. *Kim SH, et al. Medicine 2020;99(4):e18859.
REGARDS = REasons for Geographic and Racial Differences in Stroke. Zhang Y, et al. Stroke 2023;54(11):2737-2744.



U.S. Stroke Disparities

Limitations

- KNHANES
 - design = cross-sectional
 - outcome = self-reported
- KNHANES & REGARDS
 - population = men & women
 - exposure = ecologic, categorical
 - results = inconsistent
 - mechanism = unexplained



WHI Risk It?

The Women's Health Initiative Radon Risk Investigation



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The Epidemiology and Somatic Genomic Pathogenesis of Radon-Related Stroke (R01ES034050).

<https://reporter.nih.gov/search/BmeyGQHPhkC1GCNuktQFIQ/project-details/10580385>.



Women's Health Initiative

Women's Health Initiative (WHI)

- Design: cohort
- Postmenopausal women: 161,808
- Baseline: 1993-1998
- Three trials: HT, CaD & DM
- An observational study: OS
- U.S. clinical centers: 40



HT = Hormone Therapy.
CaD = Calcium / Vitamin D.
DM = Dietary Modification.

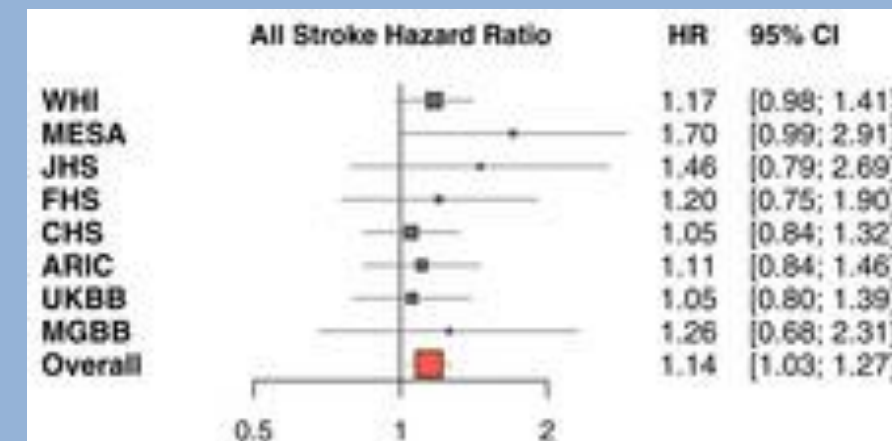
LaMonte MJ, et al. J Am Coll Cardiol 2022;80(3):256-275.



WHI Risk It? Aims

To estimate among US women the association between home radon concentrations and

- 1) incident, physician-adjudicated stroke
- 2) acquired mutations* predictive of stroke

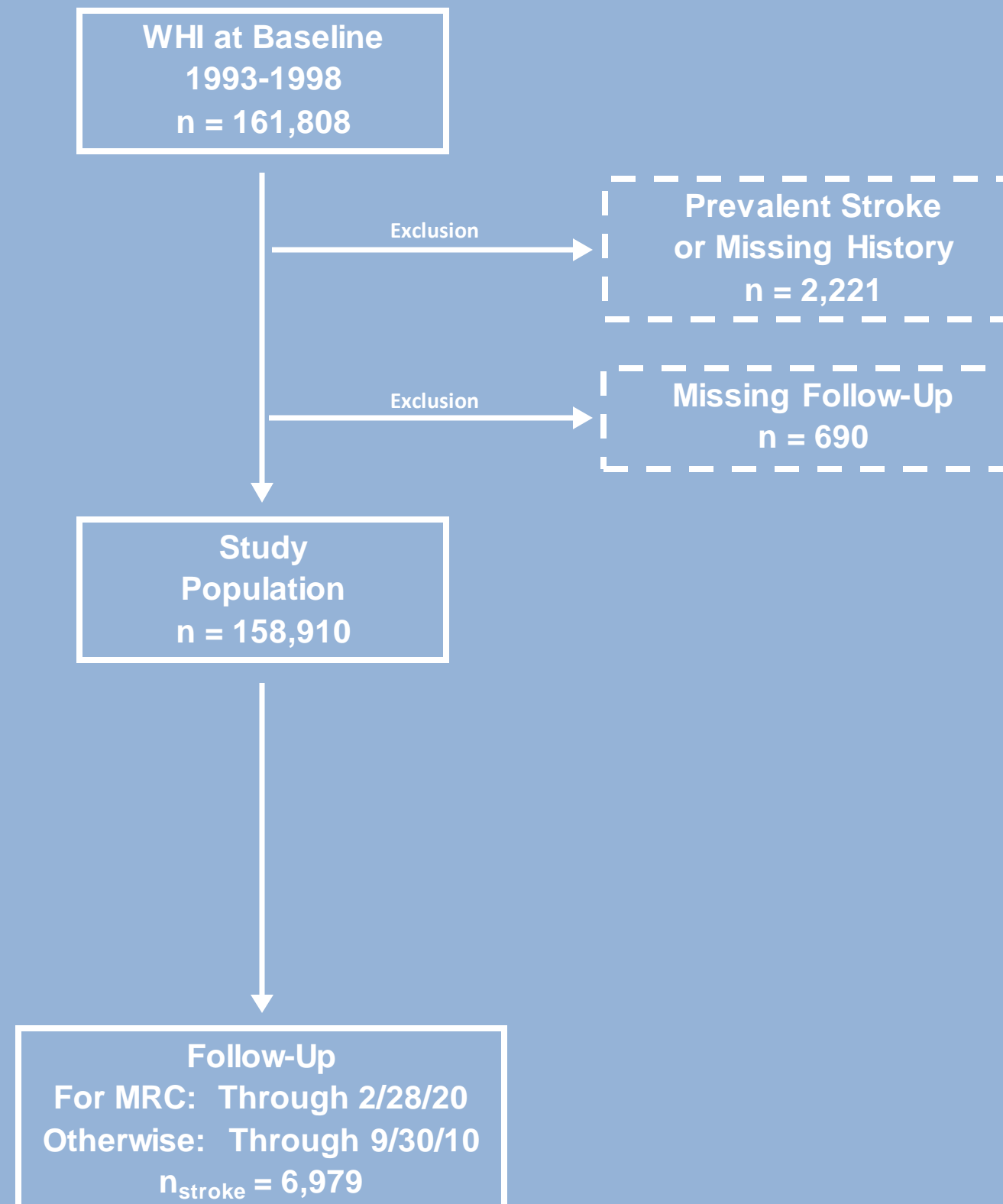


*Clonal hematopoiesis of indeterminate potential (CHIP)-defining
Bhattacharya R, et al. Stroke 2022;53(3):788-797.



Aim 1: Eligibility, Exclusion & Follow-up

1) incident, physician-adjudicated stroke



MRC = Medical Records Cohort

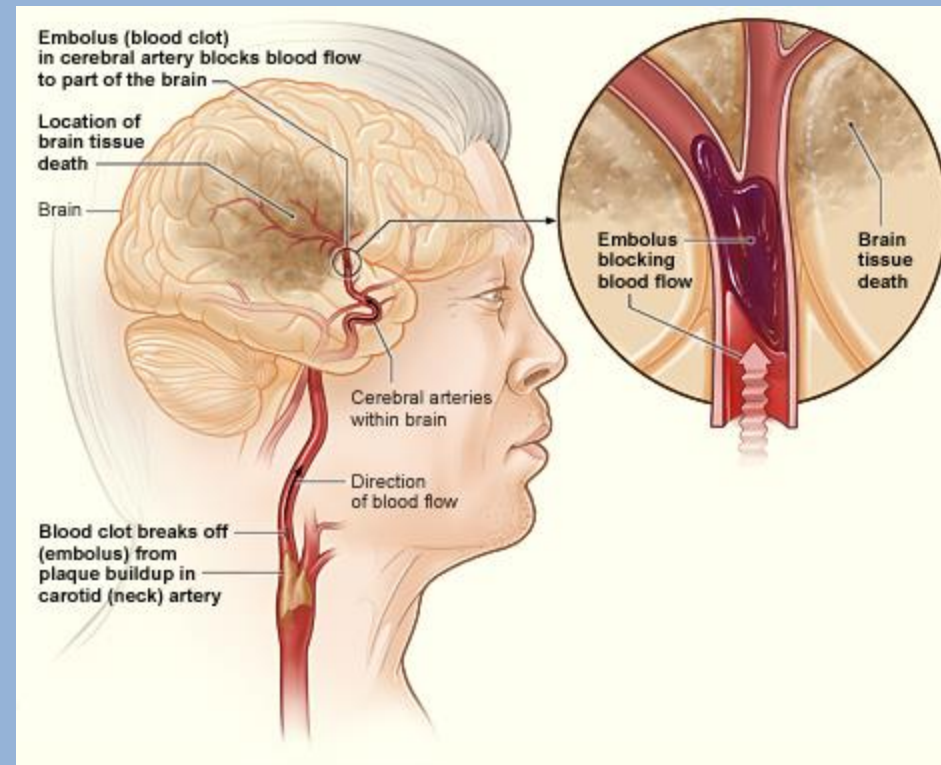




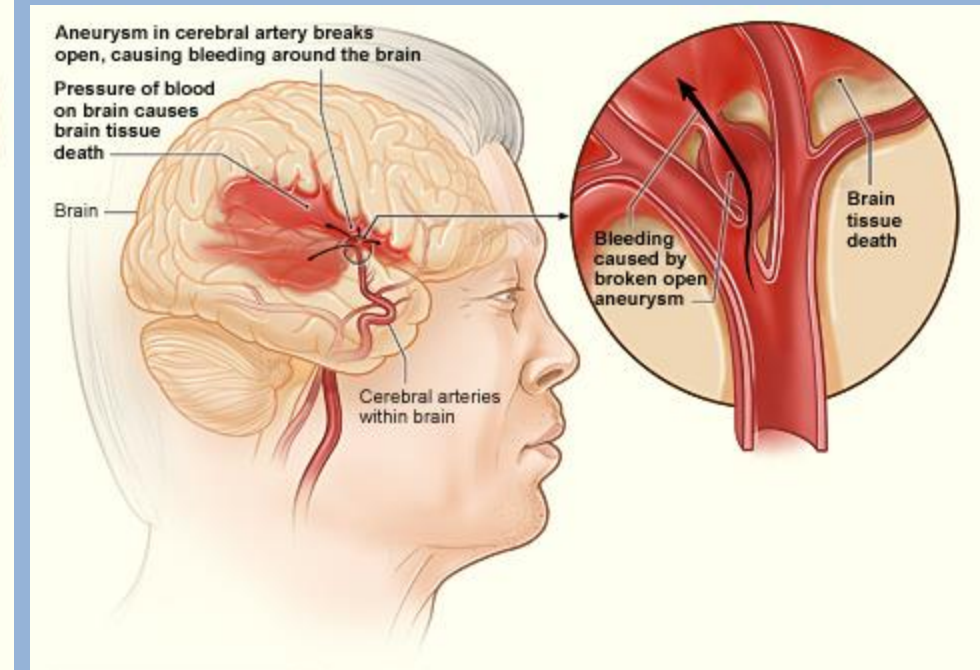
Stroke Outcomes

Incident Stroke

- Blocked or ruptured artery supplying brain



Ischemic Stroke



Hemorrhagic Stroke

- Reduced oxygen & nutrient delivery
- Injury & death of brain tissue
- Rapid onset of symptoms
 - numbness or weakness face, arm, or leg
 - confusion or difficulty speaking or understanding
 - difficulty seeing, walking or balancing





Stroke Outcomes

Incident Stroke

- Participant self-reported
- Medical record-based
- Physician-adjudicated
 - rapid onset of neurological symptoms
 - brain arterial obstruction / rupture
- Brain MRI / CT-typed
 - + hemorrhage = hemorrhagic
 - - hemorrhage = ischemic
- TOAST-subtyped



MRI = magnetic resonance imaging

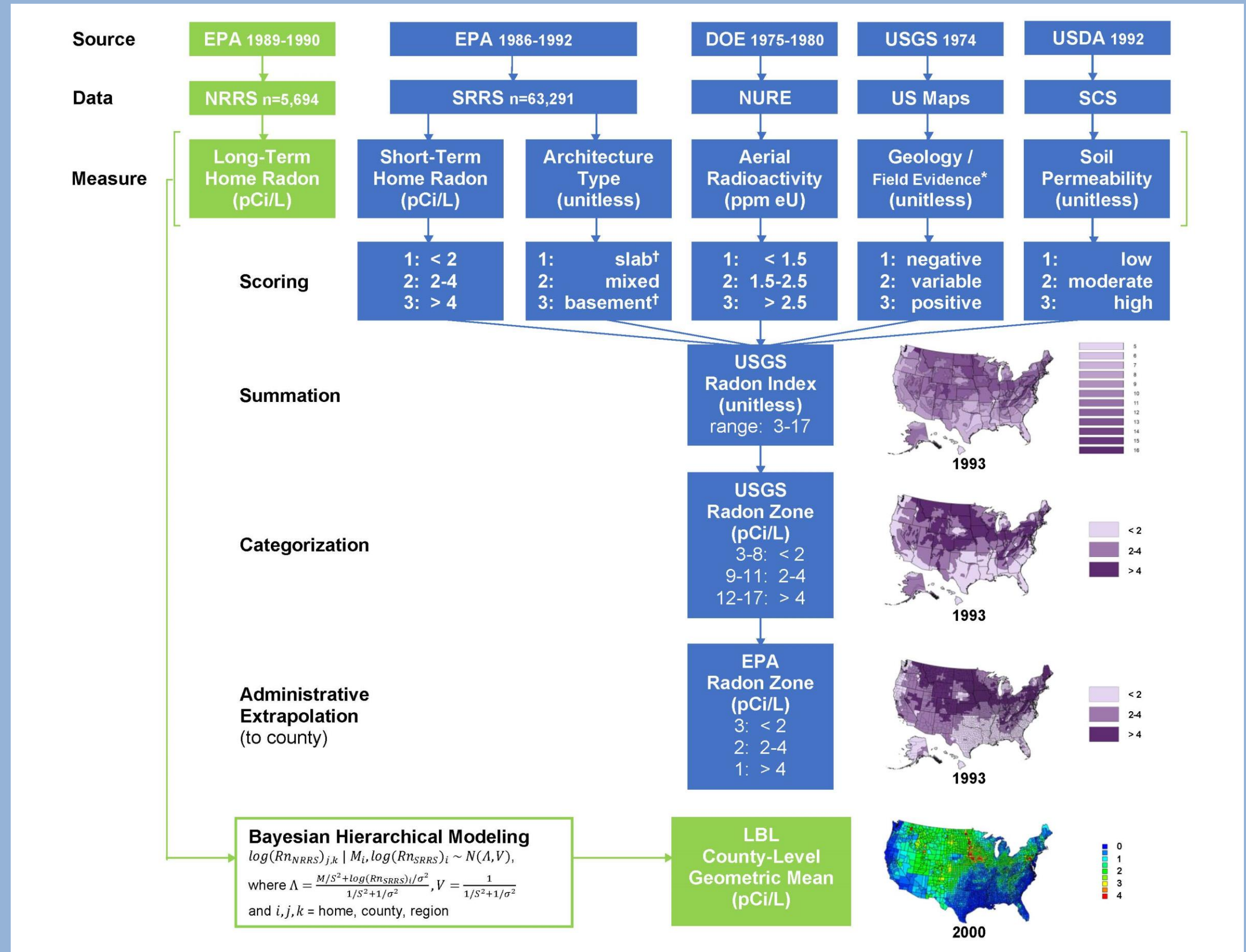
CT = computed tomography

TOAST = Trial of ORG 10172 in Acute Stroke Treatment criteria

Adams HP, et al. Stroke 1993;24(1):35-41.



Radon Exposures

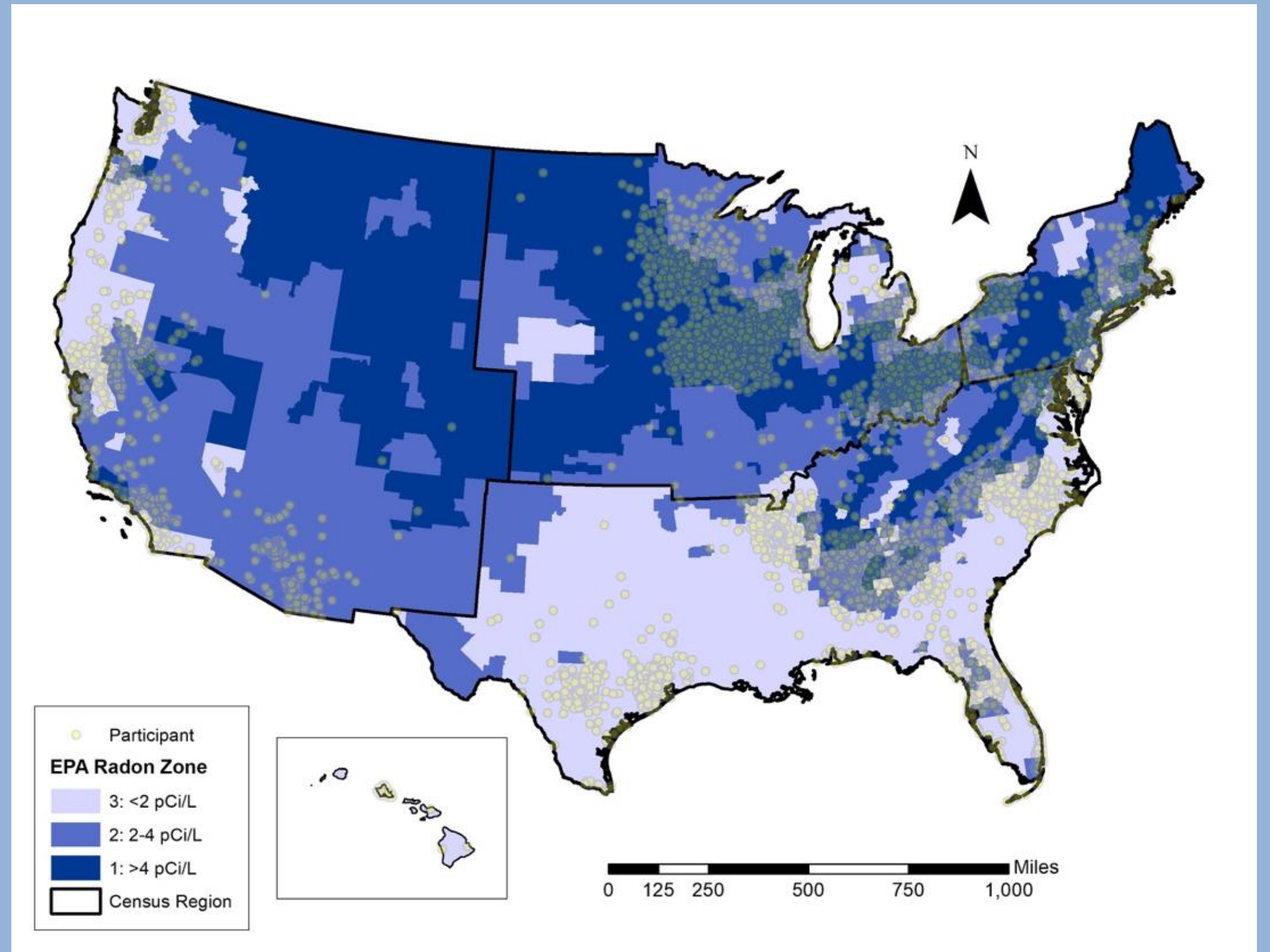


Geographically linked to participant addresses @ baseline geocoded as described in
 Whitsel EA, et al. Epidemiol Perspect Innov 2006;3:8.
 Buchheit SF, et al. Neurology 2024;102(4):e209143.





Radon Exposures



Radon Zone	pCi/L	Women at Risk n	(%)
3	< 2	52,712	(33%)
2	2-4	62,029	(39%)
1	> 4	44,165	(28%)
All*	Any	158,906	(100%)

*Missing zone (n=4).





Baseline Characteristics

Baseline Characteristics

- **design**

- Clinical trial
- Hormone therapy arm
- Medical records cohort

- **demographic**

- Age (years)
- Race/ethnicity
- US Census region

- **social**

- Education
- Occupation
- Neighborhood SES (z score)

- **behavioral**

- Smoker ever
- Drinker ever
- 2005 healthy eating index
- Physical activity* (MET-hr/wk)
- Sodium intake (g/day)

- **clinical**

- Body mass index (kg/m²)
- Systolic blood pressure (mmHg)
- Hypercholesterolemia
- Diabetes mellitus
- Atrial fibrillation
- Deep vein thrombosis
- Pulmonary embolism

SES = socioeconomic status

MET = metabolic equivalent

*Total energy expenditure in recreational physical activity





Baseline Characteristics

Table 1. Characteristics of 158,910 Participants at the Baseline Visit (Women's Health Initiative, 1993-1998)

Characteristic		Mean (SD) or n (%)
Design	Clinical Trials Participant	67,165 (42.3%)
	Hormone Trial Arm	
	Estrogen	5,212 (3.3%)
	Estrogen Control	5,316 (3.3%)
	Estrogen+Progestin	8,419 (5.3%)
	Estrogen+Progestin Control	8,005 (5.0%)
	Not Randomized	131,958 (83.0%)
Demographic	Medical Records Cohort Participant†	22,098 (13.9%)
	Age (years)	63.2 (7.2)
	Race/Ethnicity	
	White	131,574 (82.8%)
	Black/African American	14,120 (8.9%)
	Hispanic/Latina	6,241 (3.9%)
	Other	6,588 (4.1%)
	US Census Region	
	Northeast	36,397 (22.9%)
	South	41,050 (25.8%)
Social	Midwest	34,920 (22.0%)
	West	46,543 (29.3%)
	Education < College	35,344 (22.2%)
	Occupation = Homemaker	37,933 (23.9%)
Behavioral	Neighborhood SES (z score)	-0.03 (5.4)
	Ever Smoker‡	76,763 (48.3%)
	Ever Drinker	111,274 (70.0%)
	Healthy Eating Index	67.3 (10.7)
	Physical Activity§ (MET-hr/wk)	12.5 (13.8)
Clinical	Sodium Intake (g/day)	2,723 (1286)
	Body Mass Index (kg/m ²)	28.0 (5.9)
	Systolic Pressure (mmHg)¶	127 (18)
	Hypercholesterolemia	20,843 (13.1%)
	Diabetes	9,166 (5.8%)
	Atrial Fibrillation	6,757 (4.3%)
	Deep Vein Thrombosis	5,269 (3.3%)
	Pulmonary Embolism	1,341 (0.8%)

†Hormone therapy trial, Black/African-American, or Hispanic/Latina participant in Extension 2.
‡Includes 10838 (8.8%) current and 65927 (41.5%) former smokers. §Total energy expenditure in recreational physical activity. ¶Measured among 47459 (29.9%) participants with and 111451 (70.1%) without medication-treated hypertension. MET = metabolic equivalent of task. n = sample size. SD = standard deviation. SES = socioeconomic status.





Missingness of Covariates

Table S2. Missing Participant Characteristics at Baseline (Women's Health Initiative, 1993-1998)*

Characteristic [†]		n (%) [‡]
Exposure	US EPA Radon Zone	4 (0.0%)
	USGS Radon Zone	4 (0.0%)
	USGS Radon Index	4 (0.0%)
	LBL Geometric Mean	3,464 (2.2%)
Demographic	Age (years)	0 (0.0%)
	Race/Ethnicity	387 (0.2%)
	US Census Region	0 (0.0%)
Social	Education < College	1,190 (0.7%)
	Occupation = Homemaker	12,837 (8.1%)
	Neighborhood SES (z score)	194 (0.1%)
Behavioral	Ever Smoker	2,043 (1.3%)
	Ever Drinker	1,191 (0.7%)
	Healthy Eating Index	83 (0.1%)
	Physical Activity [§] (MET-hr/wk)	7,361 (4.6%)
	Sodium Intake (g/d)	295 (0.2%)
Clinical	Body Mass Index (kg/m ²)	1,383 (0.9%)
	Systolic Pressure (mmHg)	125 (0.1%)
	Hypercholesterolemia	9,236 (5.8%)
	Diabetes	92 (0.1%)
	Atrial Fibrillation	2,647 (1.7%)
	Deep Vein Thrombosis	80 (0.1%)
	Pulmonary Embolism	39 (0.0%)

*Before multiple imputation. [†]No design characteristics were missing. [‡]Of n = 158,910, rounded to the nearest tenth percent. [§]Total energy expenditure in recreational physical activity. EPA = US Environmental Protection Agency. LBL = E.O. Lawrence Berkeley National Laboratory. MET = metabolic equivalent of task. n = sample size. SD = standard deviation. SES = socioeconomic status. USGS = US Geological Survey.





Stroke Outcomes

Table S1. Stroke Type / Subtypes (Women's Health Initiative, 1993-2020)

Stroke Type	Subtype	n (%)
Hemorrhagic	Subarachnoid Hemorrhage	229 (3.3%)
	Intraparenchymal Hemorrhage	762 (10.9%)
	Other [*]	23 (0.3%)
Ischemic [†]	Cardioembolism	1,560 (22.4%)
	Small Vessel Occlusion	1,002 (14.4%)
	Large Artery Atherosclerosis	360 (5.2%)
	Other [‡]	2,281 (32.7%)
Unclassified [§]		762 (10.9%)
All		6,979 (100.0%)

^{*}Not analyzed separately given low sample size or lack of specificity. [†]Classified by Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. [‡]Other determined etiology, ≥ 2 causes, negative or undetermined evaluation, or missing TOAST classification data. [§]Cause of death = stroke, without typing / subtyping.





Risk Estimation

Absolute Risk

- incidence proportion (strokes per 10^3 women @ risk)
- incidence rate (strokes per 10^5 woman-years)

Relative Risk

- Cox proportional hazards regression
 - to estimate HRs (95% CIs)
 - on attained age scale
 - \pm sequential covariate adjustment



Absolute Risk

Table 2. Absolute Risk of Stroke by EPA Radon Zone (Women's Health Initiative, 1993-2020)

Radon Zone	pCi/L	Women at Risk n (%)	Follow-Up (years) [†]	Strokes n (%)	Incidence Proportion [‡]	Rate [§]
3	< 2	52,712 (33%)	13.4	2,190 (31%)	42	333
2	2-4	62,029 (39%)	12.8	2,730 (39%)	44	343
1	> 4	44,165 (28%)	12.5	2,059 (30%)	47	349
All*	Any	158,906 (100%)	13.4	6,979 (100%)	44	341

*Missing zone (n=4). [†]Mean. [‡]Strokes per 10³ women at risk. [§]Strokes per 10⁵ woman-years. EPA = US Environmental Protection Agency. n = sample size. pCi/L = picocuries per liter.





Relative Risk

Table 3. Relative Risk of Stroke by EPA Radon Zone and Model Adjustment (Women's Health Initiative, 1993-2020)

Cumulative Adjustment*	Hazard Ratio (95% Confidence Limit)		
	Zone 3 < 2 pCi/L	Zone 2 2-4 pCi/L	Zone 1 > 4 pCi/L
None	1.00	1.01 (0.96-1.07)	1.05 (0.99-1.12)
+ Design	1.00	1.01 (0.96-1.07)	1.03 (0.97-1.10)
+ Demographic	1.00	1.04 (0.98-1.11)	1.10 (1.03-1.18)
+ Social	1.00	1.06 (1.00-1.13)	1.13 (1.05-1.22)
+ Behavioral	1.00	1.06 (0.99-1.13)	1.13 (1.05-1.22)
+ Clinical	1.00	1.06 (0.99-1.13)	1.14 (1.05-1.22)

*For the additional design + demographic + social + behavioral + clinical characteristics in Table 1. EPA = US Environmental Protection Agency. pCi/L = picocuries per liter





Sensitivity Analysis

Examined sensitivity to...

- Adjusting for other covariates
- Multiply imputing missing data
- Adding a smoking x radon interaction
- Substituting other stroke outcomes
- Substituting other radon exposures
 - USGS radon zone* (< 2; 2-4; > 4 pCi/L)
 - USGS radon index* (unitless range: 5-16)
 - LBL geometric mean† (pCi/L)
- Non-linear modeling of USGS radon index*
- Substituting lung cancer for stroke



USGS = United States Geologic Survey

LBL = E. O. Lawrence Berkeley National Laboratory

*Based on short-term (2-day), lowest living level, charcoal canister screening

†Based on long-term (365-day), pan-living area, alpha-track detection



Sensitivity Analysis

Table 4. Sensitivity of the Fully Adjusted Radon-Stroke Association (Women's Health Initiative, 1993-2020)

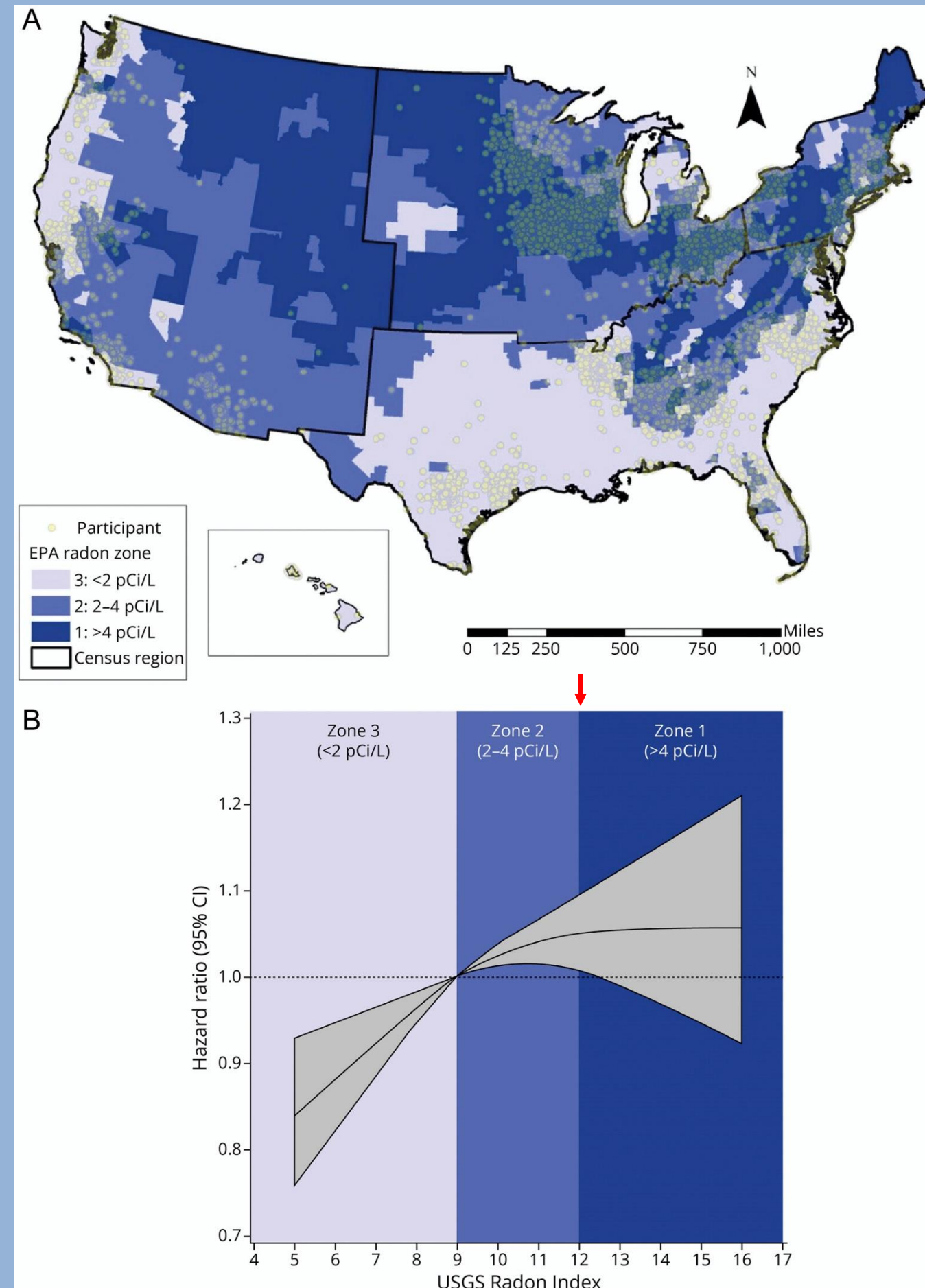
Sensitivity to:	Hazard Ratio (95% Confidence Limit)		
	Zone 3 < 2 pCi/L	Zone 2 2-4 pCi/L	Zone 1 > 4 pCi/L
Referent*	1.00	1.06 (0.99-1.13)	1.14 (1.05-1.22)
Adjustment for			
Clinical Center	1.00	1.06 (0.97-1.15)	1.11 (1.00-1.22)
Medication-Treated Hypertension	1.00	1.06 (1.00-1.13)	1.13 (1.05-1.22)
Redefined Smoking [†]	1.00	1.06 (1.00-1.13)	1.14 (1.05-1.22)
Multiple Imputation	1.00	1.06 (1.00-1.12)	1.12 (1.04-1.20)
Smoking-Radon Interaction ^{‡§}			
Never Smokers	1.00	1.04 (0.98-1.12)	1.09 (0.99-1.19)
Ever Smokers	1.00	1.07 (1.00-1.14)	1.14 (1.04-1.25)
Stroke Outcome Substitution [‡]			
Hemorrhagic	1.00	1.02 (0.88-1.19)	1.08 (0.90-1.30)
Subarachnoid Hemorrhage	1.00	0.97 (0.87-1.07)	1.07 (0.95-1.21)
Intraparenchymal Hemorrhage	1.00	1.05 (0.99-1.11)	1.10 (1.02-1.17)
Ischemic [¶]	1.00	1.07 (1.00-1.14)	1.15 (1.06-1.25)
Cardioembolism	1.00	1.14 (1.10-1.19)	1.16 (1.10-1.21)
Small Vessel Occlusion	1.00	1.15 (1.10-1.21)	1.38 (1.30-1.46)
Large Artery Atherosclerosis	1.00	1.13 (1.04-1.24)	1.24 (1.12-1.37)
Other [¶]	1.00	1.00 (0.97-1.03)	1.07 (1.03-1.10)
Unclassified ^{**}	1.00	0.93 (0.75-1.15)	1.01 (0.85-1.20)
Mortality ^{††}	1.00	1.05 (0.99-1.11)	1.11 (1.03-1.19)
Radon Exposure Substitution [‡]			
USGS Radon Zone	1.00	1.12 (1.06-1.18)	1.16 (1.07-1.25)
USGS Radon Index		1.03 (1.01-1.04) ^{‡‡}	
LBL Geometric Mean		1.04 (0.98-1.09) ^{§§}	

*Fully adjusted model of the EPA Radon Zone-stroke association from Table 3. [†]As (current; former; never). [‡]And multiple imputation. [§] $P_{interaction} = 0.4697$. [¶]Classified by Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. ^{¶¶}Other determined etiology, ≥ 2 causes, negative or undetermined evaluation, or missing TOAST classification data. ^{**}Cause of death = stroke, without typing / subtyping. ^{††}Cause of death = stroke, with or without typing / subtyping. ^{‡‡}Expressed per 1-unit increase. ^{§§}Expressed per 1 pCi/L increase. EPA = US Environmental Protection Agency. LBL = E. O. Lawrence Berkeley National Laboratory. pCi/L = picocuries per liter. USGS = US Geological Survey.





Sensitivity Analysis



Spline of the USGS Radon Index, centered at its median value.

$P_{\text{non-linear association}} = 0.0004$. \downarrow = EPA Radon Action Level.
 Buchheit SF, et al. Neurology 2024;102(4):e209143.



Sensitivity Analysis

Table S4. Relative Risk of Stroke and Lung Cancer (Women's Health Initiative, 1993-2020)

Risk Factor	Category [†]	%‡	Hazard Ratio (95% Confidence Interval) [*]	
			Stroke [§]	Lung Cancer [§]
Diabetes	Yes	6%	1.69 (1.56-1.83)	NA
Atrial Fibrillation	Yes	4%	1.63 (1.50-1.78)	NA
Systolic Pressure	> 140 mmHg	21%	1.57 (1.49-1.65)	NA
Race	Black	9%	1.49 (1.37-1.62)	1.33 (1.16-1.52)
Pulmonary Embolism	Yes	1%	1.27 (1.01-1.60)	NA
Deep Vein Thrombosis	Yes	3%	1.20 (1.06-1.35)	NA
Ever Smoker	Current/Former	48%	1.17 (1.12-1.23)	5.23 (4.82-5.67)
Healthy Eating Index	< p25	25%	1.17 (1.11-1.24)	1.40 (1.31-1.50)
Energy Expenditure [¶] (MET-hr/wk)	< p25	28%	1.13 (1.07-1.20)	1.24 (1.16-1.34)
EPA Radon Zone 1	> 4 pCi/L	28%	1.10 (1.03-1.18)	0.98 (0.90-1.08)
EPA Radon Zone 2	2-4 pCi/L	39%	1.05 (0.99-1.11)	1.01 (0.93-1.08)
Ethnicity	Hispanic	4%	1.10 (0.96-1.27)	0.86 (0.67-1.11)
Neighborhood SES (z score)	< p25	25%	1.06 (1.00-1.14)	1.13 (1.04-1.23)
Body Mass Index	> 30 kg/m ²	30%	1.06 (1.00-1.11)	0.84 (0.78-0.90)
Hypercholesterolemia	Yes	13%	1.05 (0.99-1.12)	NA
Homemaker	Yes	24%	1.01 (0.96-1.07)	0.95 (0.89-1.03)
Sodium Intake (g/day)	> p75	25%	1.00 (0.95-1.06)	NA
Education	< College	22%	0.96 (0.91-1.02)	1.10 (1.02-1.18)
Ever Drinker	Current/Former	70%	0.90 (0.86-0.95)	0.92 (0.85-0.99)

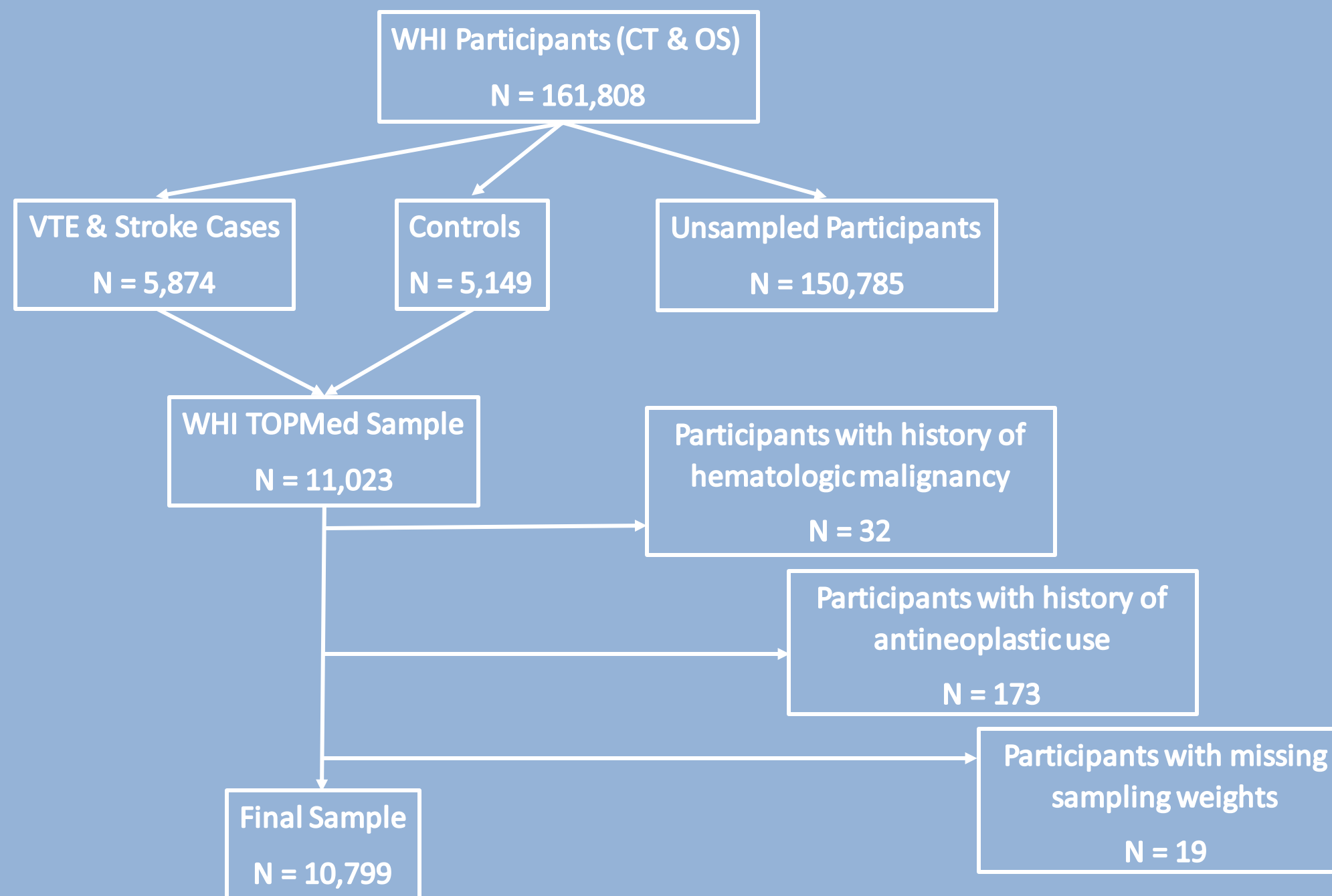
^{*}Estimated in Cox proportional hazards models simultaneously adjusting for all Table 1 design characteristics and risk factors, tabulated from high to low risk of stroke. [†]Dichotomized to aid comparison among ordered risk factors and outcomes. [‡]Percent with the risk factor. [§]Based on analysis of 6,979 incident strokes (4,167 incident lung cancers) among 158,910 (159,234) women at risk followed for a mean of 13.4 (16.3) years. [¶]Total energy expenditure in recreational physical activity. ^{||}Differs from 25% given tied percentiles. EPA = US Environmental Protection Agency. MET = metabolic equivalent of task. NA = not applicable, so not modeled. pCi/L = picocuries per liter. p25 & p75 = 25th and 75th percentiles. SES = socioeconomic status.





Aim 2: Eligibility, Sampling & Exclusion

2) acquired mutations* predictive of stroke



VTE = venous thromboembolism

*Clonal hematopoiesis of indeterminate potential (CHIP)-defining
Bhattacharya R, et al. Stroke 2022;53(3):788-797.





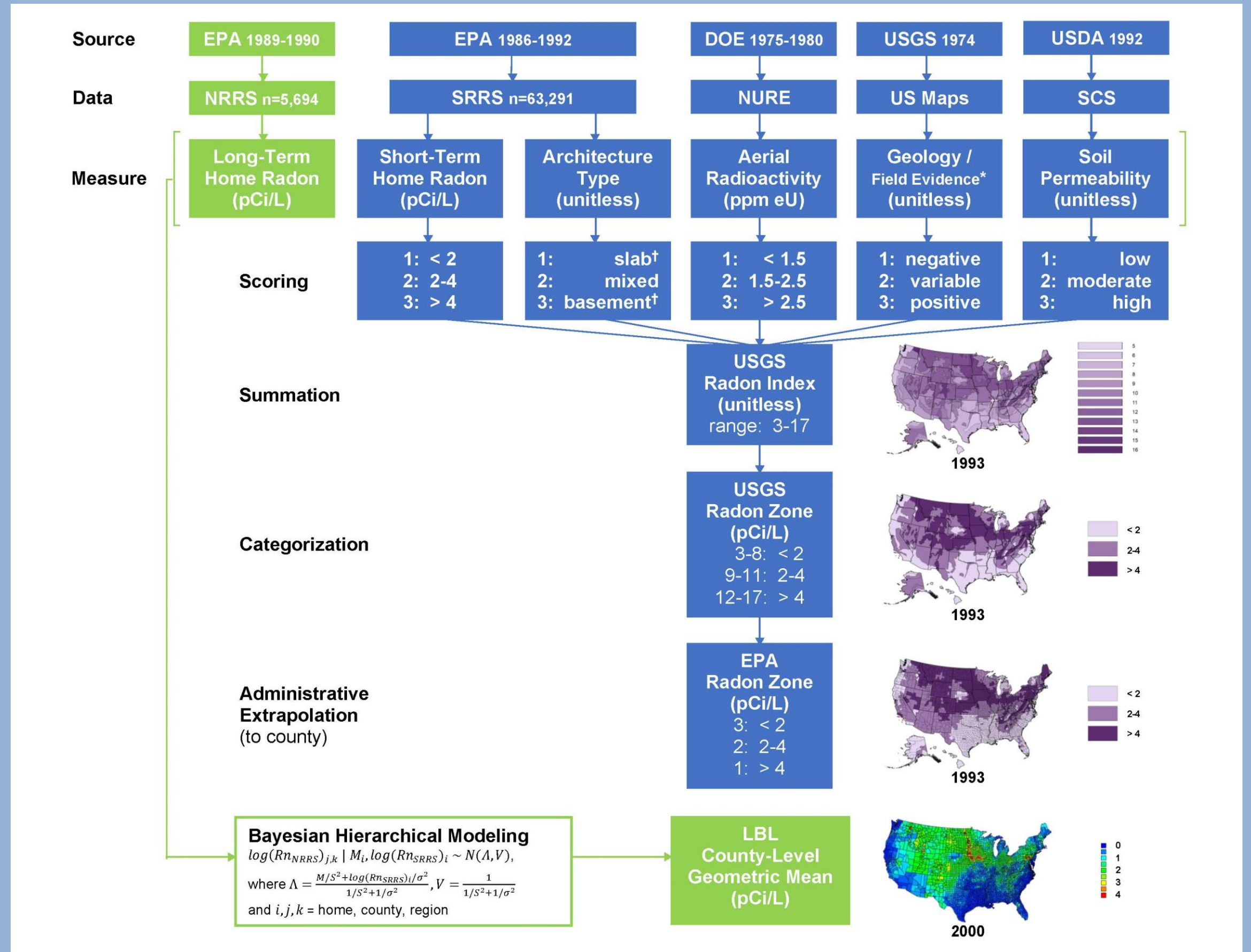
CHIP Outcome

CHIP Identification

- Phlebotomy @
 - SV (31%) AV1 (27%)
 - AV3 (35%) AV6 (5%)
 - AV9 (1%)
- Centrifugation → buffy coat
- Extraction of leukocyte DNA
- Whole genome sequencing
- Interrogation of 74 CHIP driver mutations
- CHIP = variant allele fraction > 0.02 in $\geq 1/74$



Radon Exposures

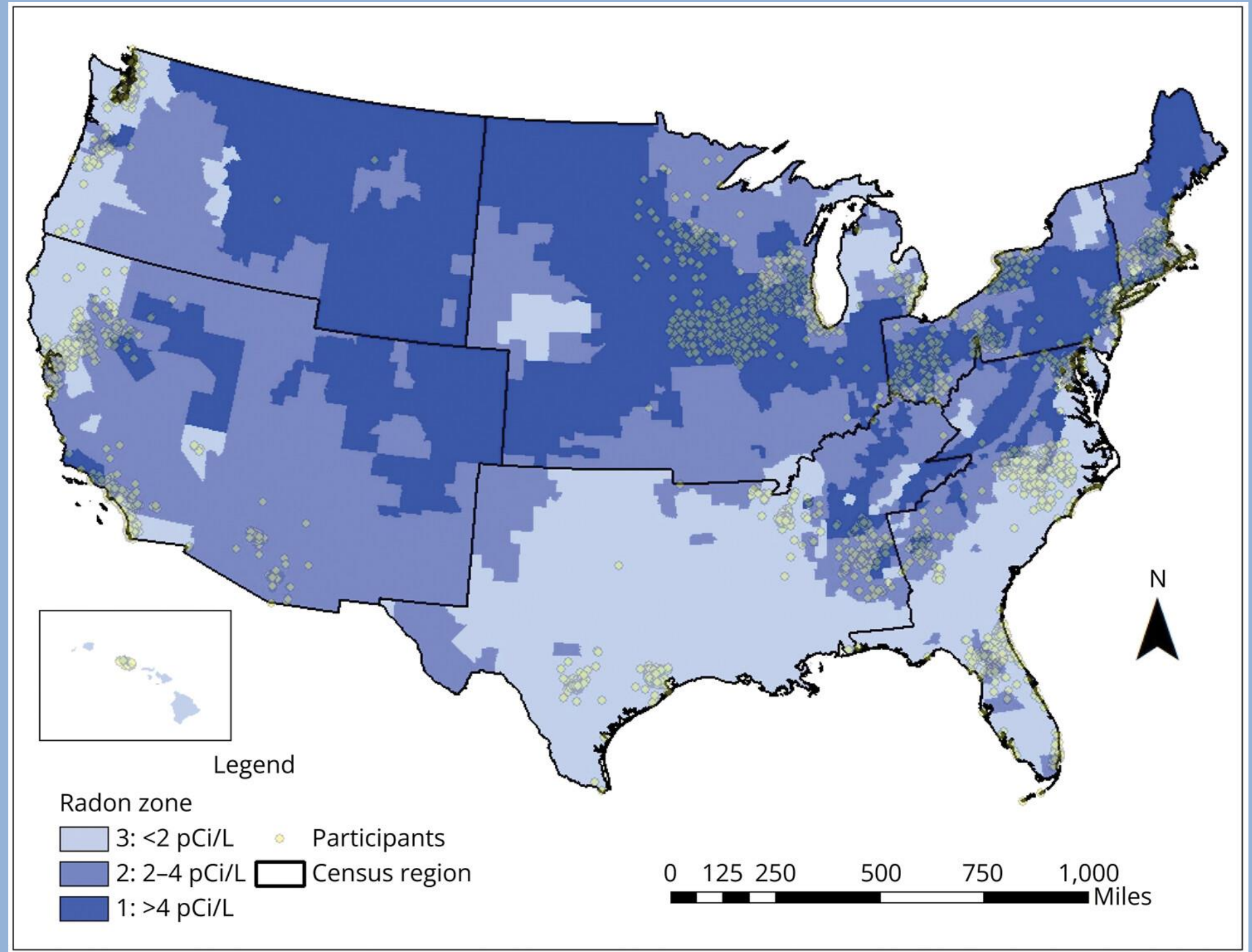


Geographically linked to participant addresses @ baseline geocoded as described in Whitsel EA, et al. Epidemiol Perspect Innov 2006;3:8.





Radon Exposures



Radon (pCi/L)	CHIP present n (%)	CHIP absent n (%)
<2	248 (7.7)	2,967 (92.3)
2-4	356 (8.4)	3,862 (91.6)
>4	303 (9.0)	3,063 (91.0)





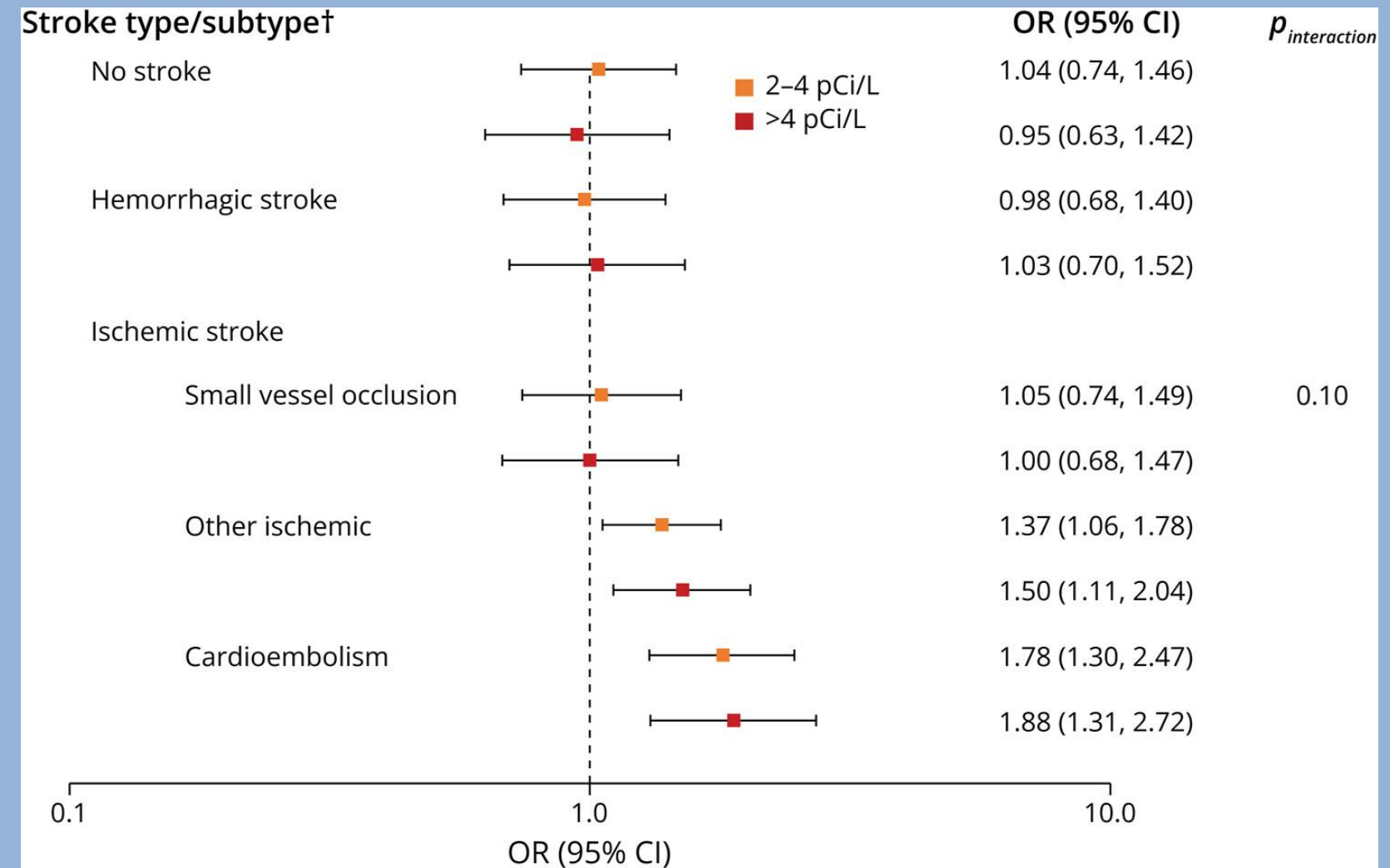
Risk Estimation

Logistic regression

- to estimate ORs (95% CIs)
- multiple imputation
- stratification by stroke type / subtype
- weighting for inverse probability of sampling
- covariate adjustment



Odds Ratios



Regression models were adjusted for self-reported age, race/ethnicity, education, homemaker status, Census region, neighborhood socioeconomic status summary z score, smoking, body mass index, physical activity, clinical trial intervention (hormone therapy, calcium/vitamin D, and dietary modification), and stroke type/subtype. Regression models also were weighted for the inverse probability of sampling. Ischemic stroke subtyped using Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria including cardioembolism, small vessel occlusion, and "other ischemic", i.e., large artery atherosclerosis, other determined etiology, two or more causes, negative evaluation, or incomplete/missing evaluation. †Among participants with reviewed, classified, and adjudicated stroke.





Sensitivity Analysis

Examined sensitivity to...

- Weighting for attrition
- Adjusting for ancestry
- Excluding prevalent stroke
- Restricting to common mutations
- Substituting other radon exposures
 - USGS radon zone* (< 2; 2-4; > 4 pCi/L)
 - USGS radon index* (unitless range: 5-16)
 - LBL geometric mean† (pCi/L)



USGS = United States Geologic Survey

LBL = E. O. Lawrence Berkeley National Laboratory

*Based on short-term (2-day), lowest living level, charcoal canister screening

†Based on long-term (365-day), pan-living area, alpha-track detection



Sensitivity Analysis

Sensitivity of Radon-Related Risk of CHIP*, by Stroke Type / Subtype† (WHI TOPMed)

Sensitivity to:	Cardioembolism	
	2-4 pCi/L	>4 pCi/L
Referent (no change)	1.78 (1.30, 2.47)	1.88 (1.31, 2.72)
Attrition Weighting	1.83 (1.32, 2.55)	2.12 (1.46, 3.08)
Ancestry Adjustment		
3 PCAs	1.75 (1.27, 2.43)	1.84 (1.27, 2.68)
10 PCAs	1.73 (1.24, 2.41)	1.92 (1.31, 2.79)
Prevalent Stroke Exclusion	1.76 (1.26, 2.45)	1.88 (1.29, 2.74)
CHIP driver mutation:		
<i>DNMT3A</i>	1.96 (1.32, 2.92)	2.26 (1.45, 3.52)
<i>TET2</i>	1.03 (0.58, 1.82)	0.59 (0.29, 1.20)
EPA Zone Substitution		
USGS Radon Zone	1.26 (0.94, 1.68)	1.44 (1.00, 2.09)
USGS Radon Index‡	1.03 (0.97, 1.10)	
LBL Geometric Mean§	1.14 (0.91, 1.42)	

Regression models were adjusted for self-reported age, race/ethnicity, education, homemaker status, US Census region, neighborhood socioeconomic status z score, smoking, body mass index, physical activity, and clinical trial intervention (hormone therapy, calcium/vitamin D, and dietary modification). Regression models also were weighted for the inverse probability of sampling. *Odds ratio (95% confidence intervals). †Among participants with reviewed, classified, and adjudicated stroke. ‡Expressed per 1-unit increase. §Expressed per 1 pCi/L increase. LBL: E. O. Lawrence Berkeley National Laboratory; pCi/L: picocuries/liter; PCA: principal components of ancestry; USGS: United States Geological Survey.





Summary

In this cohort of postmenopausal women, radon is associated with...

- incident, adjudicated stroke
- acquired mutations* predictive of stroke

The graded associations are...

- robust
- significant at < 4 pCi/L
- stronger for ischemic v. hemorrhagic stroke
- similar to those in KNHANES & REGARDS



*Clonal hematopoiesis of indeterminate potential (CHIP)-defining
Bhattacharya R, et al. Stroke 2022;53(3):788-797.



Limitations

To date, we have not examined...

- individual-level radon exposures
- time-varying covariates
- replicability

Unknown generalizability to...

- underrepresented racial/ethnic groups
- premenopausal women
- women aged < 50 years
- men



Strengths

Population

- large
- diverse

Outcomes

- adjudicated

Analyses

- longitudinal
- well-powered

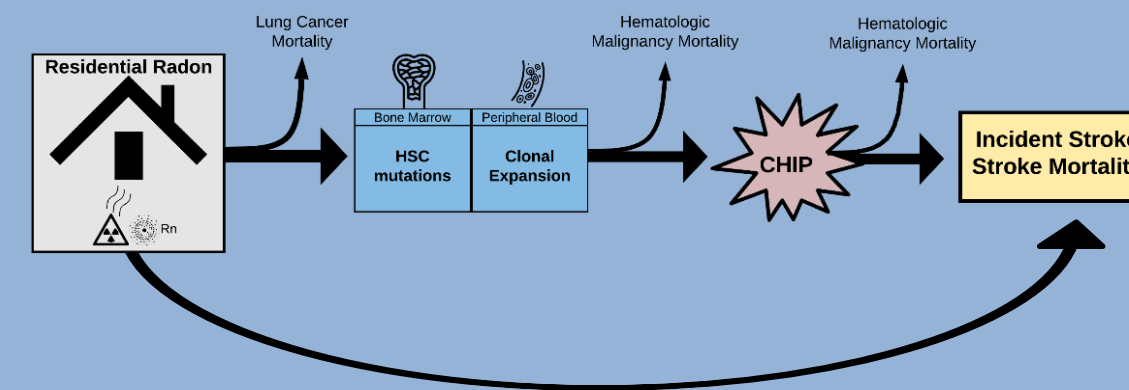
Results

- robust

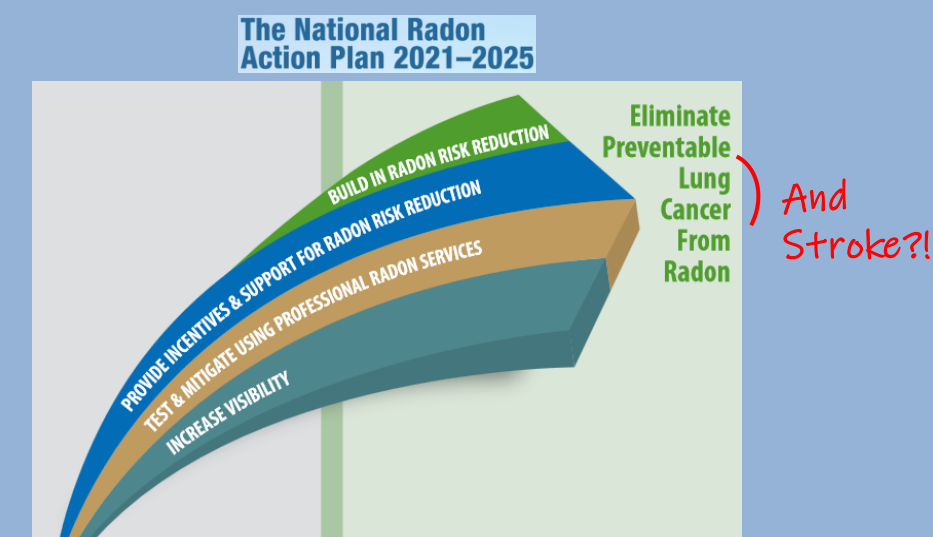


In Conclusion

- Radon may be a risk factor for stroke
- Radon may be acting partly through CHIP



- Individual-level radon exposure, cross-cohort replication & mediation analyses are needed
- *WHI Risk It?*



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