THE WOMEN'S HEALTH INITIATIVE

Plenary 5: Evaluating the Cardiovascular-Kidney-Metabolic Syndrome in the WHI DEXA Cohort

Chair: Deepika Laddu, Northwestern University

Evaluating the Cardiovascular-Kidney-Metabolic Syndrome in the WHI DEXA Cohort

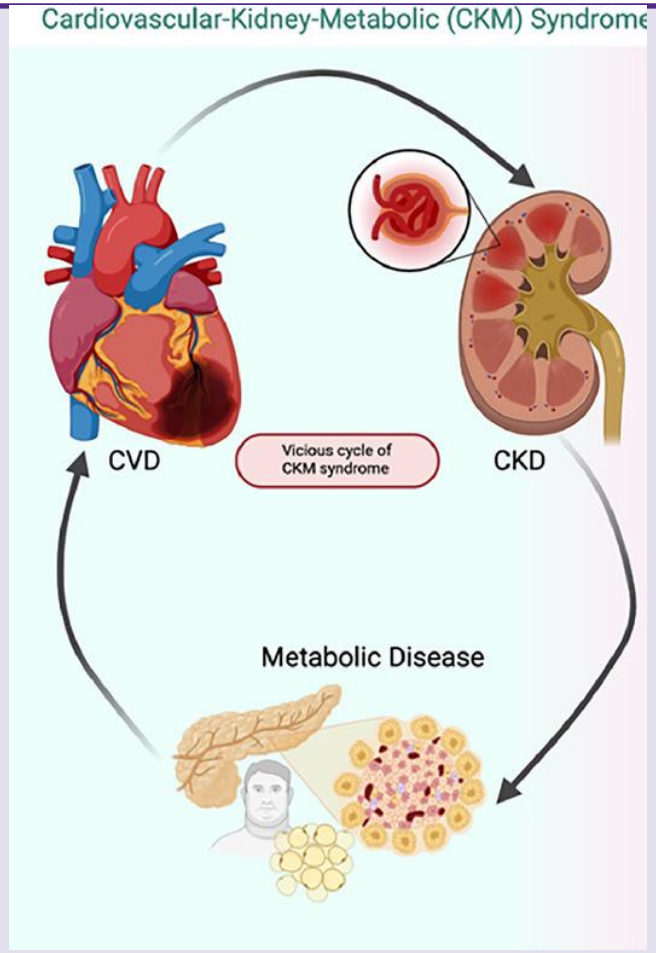
Session Chair: Deepika Laddu & Marcia Stefanick

Speakers: Andrew Odegaard, Jen Bea, Michael Lamonte

Defining the Cardiovascular-kidney-metabolic (CKM) syndrome

What is CKM Syndrome:

- A new integrated framework that recognizes the interconnected risk and progression between cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic conditions



Key Characteristics:

- **Shared pathology:** Inflammation, insulin resistance, endothelial dysfunction

- **Bidirectional risk:** Disease in one system increases risk in others

CKM syndrome includes those <u>at risk for</u> and those <u>with</u> CVD

Circulation. 2023;148:1606–1635

Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association

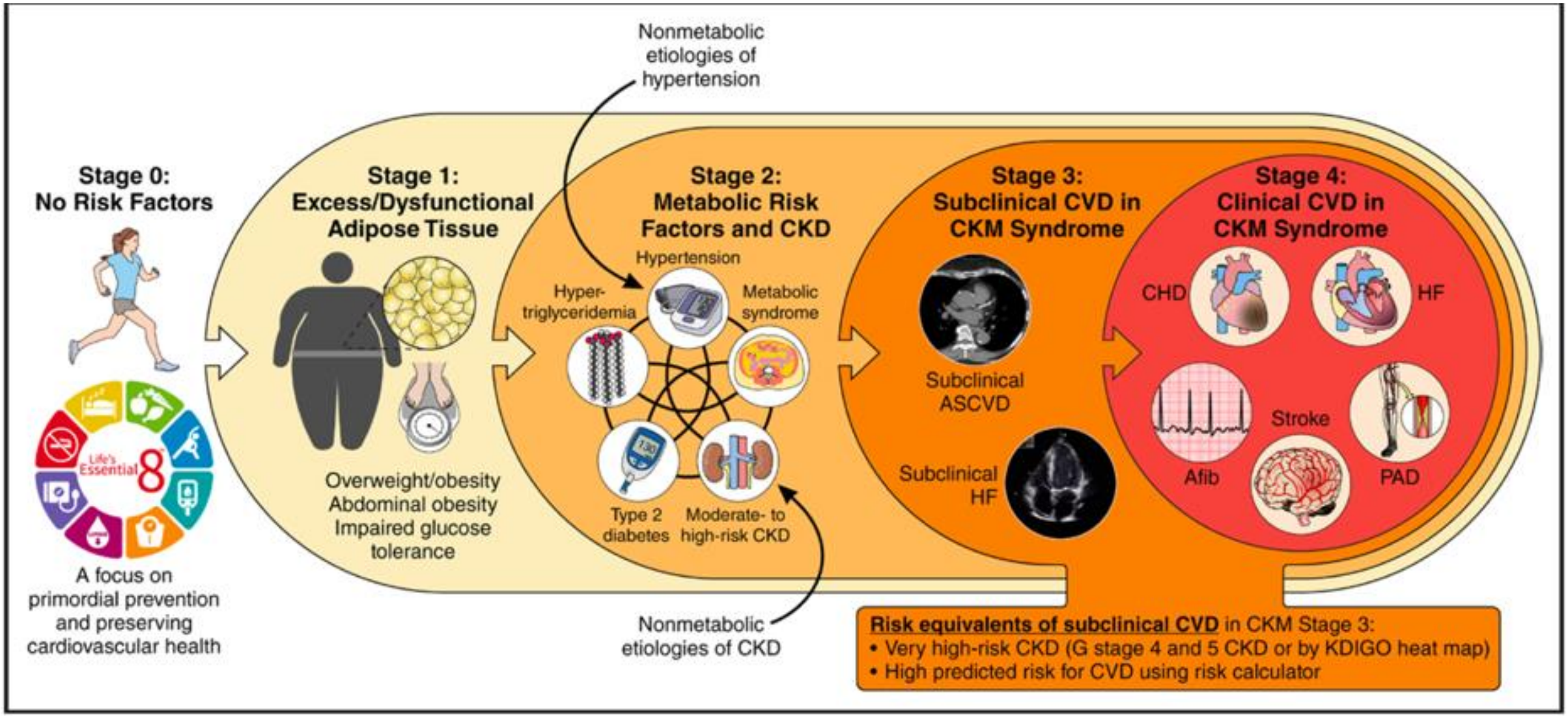


Figure 1. Stages of CKM syndrome.

Pathological Driver:

Excess adipose tissue and/or
Dysfunctional adipose tissue

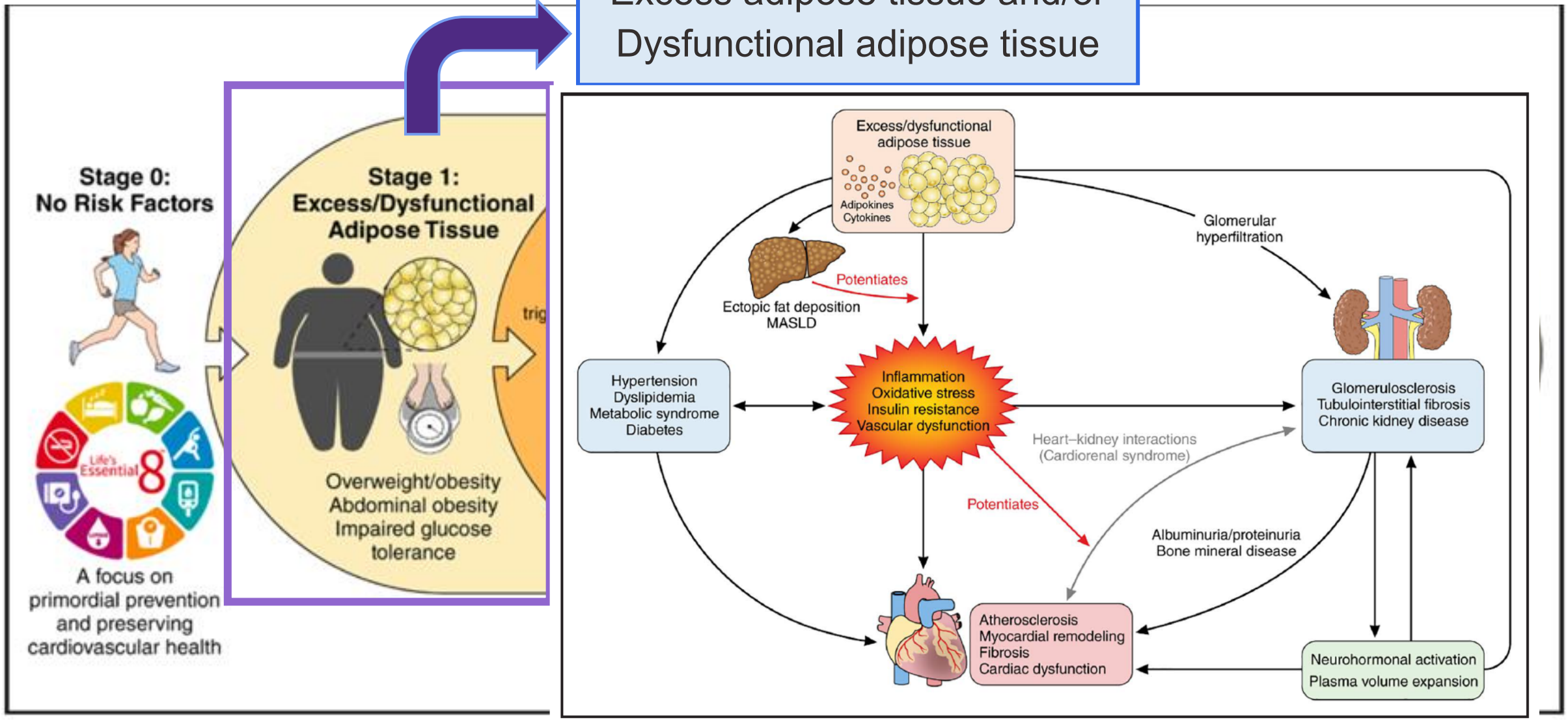
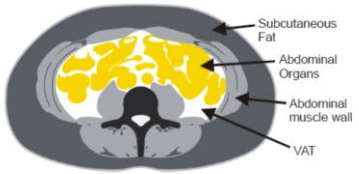
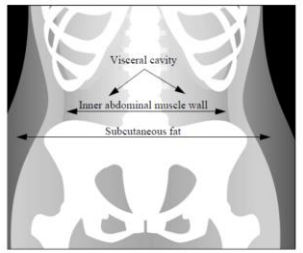


Figure 1. Stages of CKM syndrome.

Circulation. 2023;148:1636–1664.

Leveraging the WHI DXA Cohort





Jennifer Bea, PhD

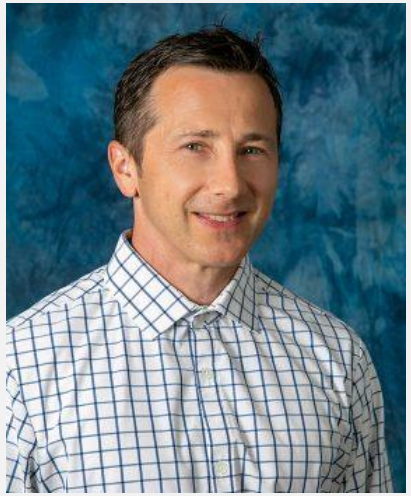
Univ. of Arizona

CKM Stage 1 & 2

Metabolic Risk factors

Andrew Odegaard, PhD, MPH

UC Irvine



CKM Stage 3 &4

ASCVD

Michael LaMonte, PhD

Univ. of Buffalo

CKM Stage 3 &4

Heart Failure

WHI DXA Cohort
Stage 1 & 2 CKM: What WHI can contribute

Jennifer W. Bea, PhD

Health Promotion Sciences, University of Arizona

WHI Annual Meeting

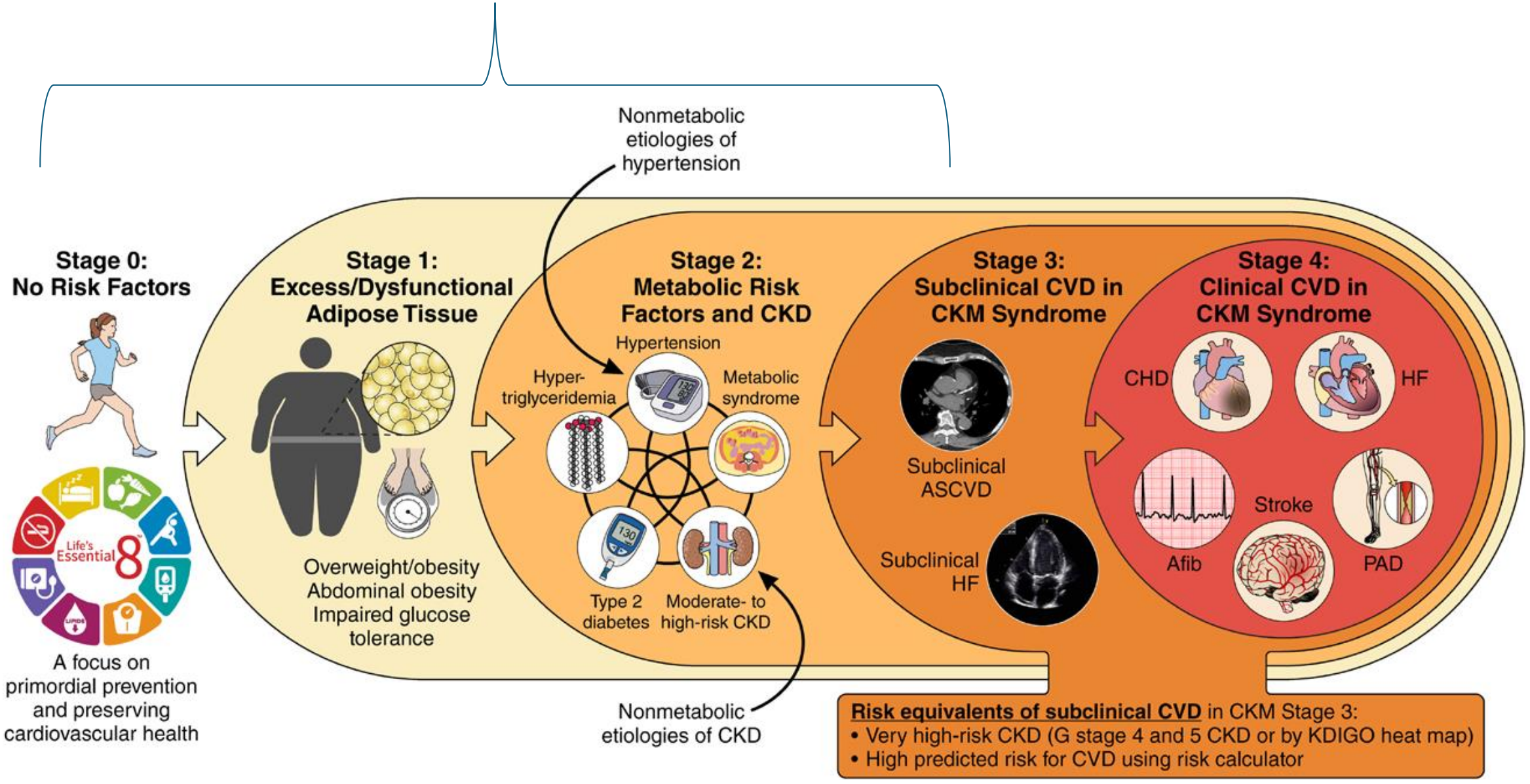
Seattle, WA

May 2, 2025

THE UNIVERSITY OF ARIZONA Cancer Center

WOMEN'S HEALTH INITIATIVE

Risk Factors: Setting the Stage



Stage 0: Life's Essential 8

Essential 8	Baseline N	WHI FORM #	Years Available
1. Diet	1. 161,509 (self-report)	60	All: 0 OS: 3 DM: 1 | %DM: 2, 3, 4, 5, 6, 7, 8, 9
2. Physical Activity (METs) 3. Tobacco (cessation)	2. 154,337 (self-report) 3. 160,480 (self-report)	34	All: 0 CT: 1, 3, 6, 9
4. Sleep	4. 160,344 (self-report)	37	All: 0 CT: 10
5. Weight (BMI)	5. 160,381 (measured)	80 (measured) 144, 145, 146, 147, 148 (self-report)	All: 0, 3 CT: Every year OS: 4-8
6. Cholesterol 7. Blood Sugar (Glucose)	6. 5,479 (measured) 7. 5,467 (measured)	Core Analyte Results (100)	All: 0 CT: 3 | %CT: 1, 6, 9 %OS: 3
8. Blood Pressure (Measured)	8. 161,681 (measured)	80 (measured) 30, 31 (self-report)	All: 0, 3 CT: Every year

Stage 0: normal weight, glucose, BP, lipids, and kidney function; no evidence of subclinical or clinical CVD

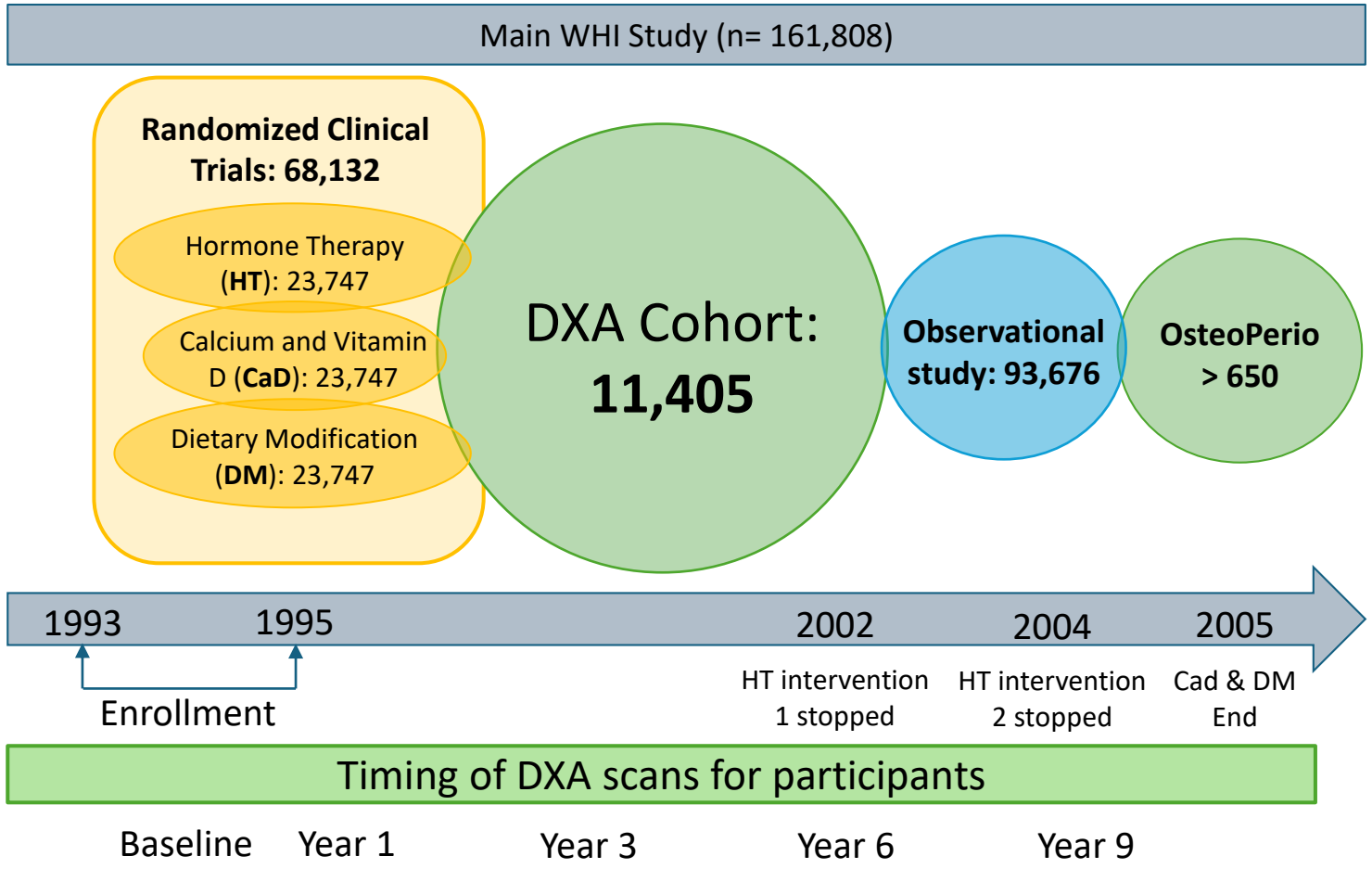
Stage 1: Excess/Dysfunctional Adipose Tissue

	Baseline (n %)	Mean (SD)	Year 3 (n %)	Mean (SD)
Overweight (BMI)	55,680 (34.4%)	27.3 (±1.4)	47,893 (29.6%)	27.3 (±1.4)
Obese (BMI)	48,366 (30.0%)	35.1 (±5.0)	42,133 (26.0%)	35.0 (±4.9)
Abdominal obesity (WC ≥88cm)	66,683 (41.2%)	99.7 (±10.3)	41,983 (25.9%)	99.5 (±10.2)
Glucose (mg/dl)	5,467 (3.4%)	101.6 (±30.3)	3,595 (2.2%)	101.3 (±29.3)
Insulin (uIU/ml)	5,312 (3.3%)	11.9 (±9.6)	3,403 (2.1%)	13.2 (±10.8)

For more directly measured adipose tissue levels, we utilized the DXA cohort

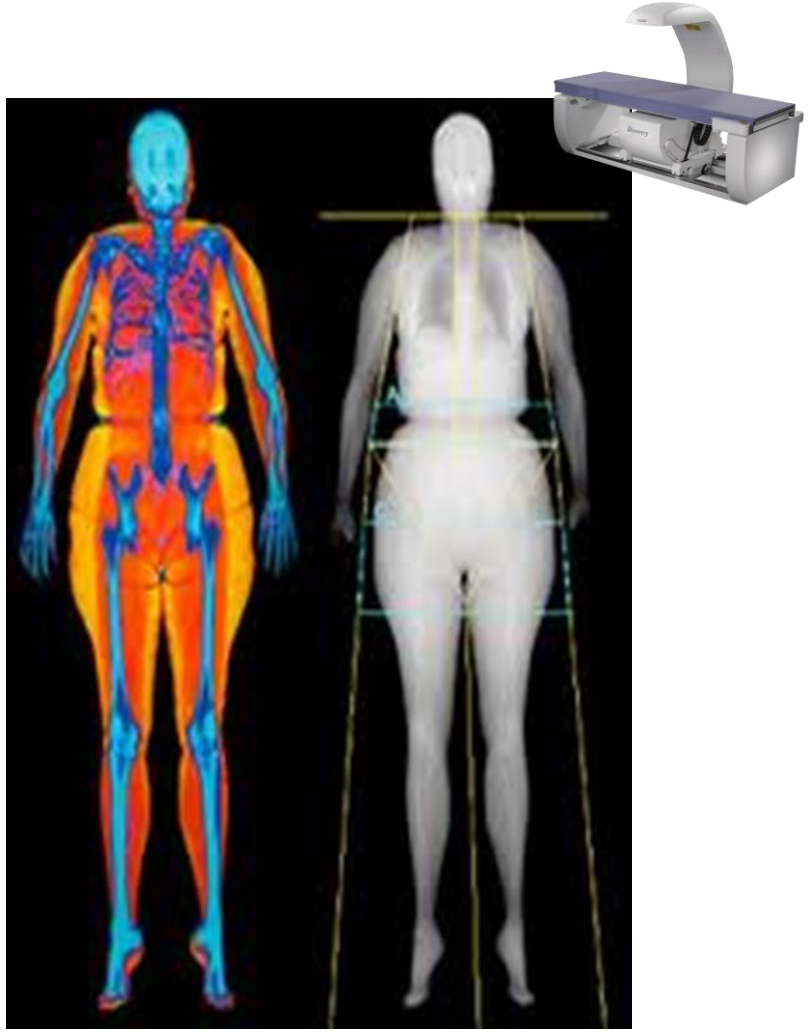
Dual-energy X-ray absorptiometry (DXA) Cohort

- 11,405 participants
- Aged 50-79 at enrollment
- 42% RCT/58% OS
- Recruited from Arizona, Pennsylvania, and Alabama clinical sites
- Adjudicated outcomes up to 30 yrs (2024)
- Additional DXA scans in the Buffalo OsteoPerio study
  - Only OS members
  - Scans at years 3, 8, 20



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

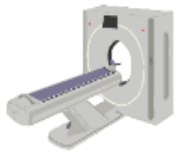
Historic DXA Scans



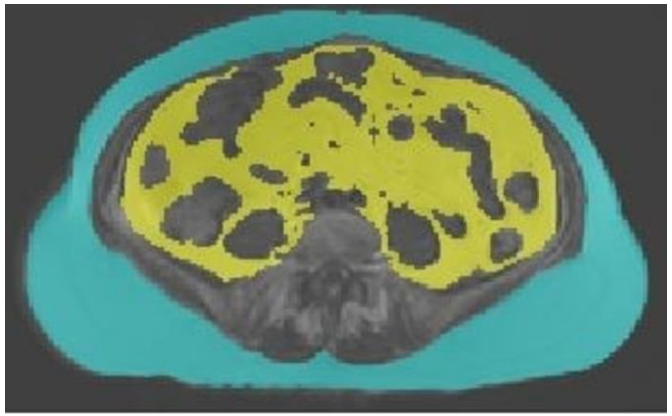
- Whole-body Hologic DEXA scans (model QDR2000, 2000+, or 4500W)
- 39,788 scans in Main WHI DXA Cohort
- Examples:
  - Trunk Fat
  - Whole body fat mass
  - Whole body percent fat
  - Whole body lean soft tissue mass
  - Appendicular lean soft tissue mass
  - Total and regional BMD

Images from: https://www.itnonline.com/content/hologic-discovery-dxa-offers-advanced-body-composition-assessment

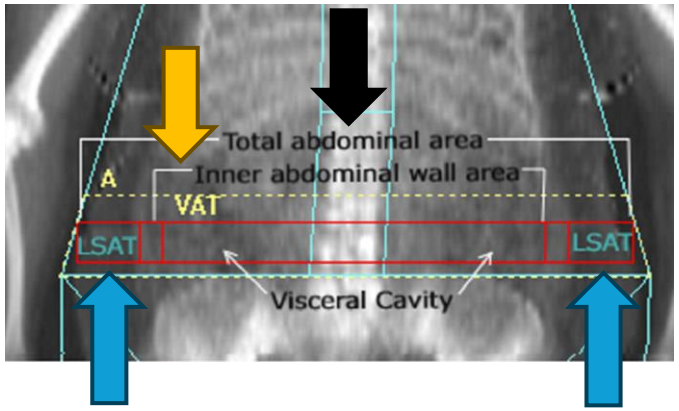
Abdominal Adipose Added to the WHI Resource



MRI scan



DEXA scan



- DXA APEX 4.0 abdominal adipose validated against MRI
- Quantified adipose tissue abdominal (cm^2, g)
  - visceral adipose tissue (**VAT**)
  - subcutaneous adipose tissue (**SAT**)
  - total adipose tissue (**TAT**)
- 5cm high section across the abdomen, above the iliac crest; approximately the 4^{th} lumbar vertebrae
- Abdominal ROI illustrated by the red box
- Visible lateral subcutaneous adipose tissue (**LSAT**) used to estimate total A/P **SAT**.

VAT = TAT - SAT

Images from: Bea, JW, et al. J. Clin. Densitom. 2022;25(2):189-187

Number of available participants per year by file type

- Not all scans available for reanalysis due to missing or corrupted scans
- Some scans are incomplete across body composition variables

Year	Historic file	New VAT file	Missingness
Missing	221		221
0	**11,393**	**10,832**	**561**
1	4,525	4,315	210
2	40	35	5
3	**9,399**	**8,379**	**1,020**
4	34	32	2
5	9	9	0
6	**8,314**	**7,170**	**1,144**
7	186	183	3
8	651	557	94
9	4,595	4,352	243
10	261	215	46
11	160	114	46
Total	39,788	36,193	3,595

Number of available participants per year for various body composition variables

Corrected Body Composition Variables	Baseline	Year 1	Year 3	Year 6	Year 9
Historic WHI file					
Total body fat (TBF)	11,285	4,512	9,351	8,174	4,565
Total body fat percent (%TBF)	11,285	4,512	9,351	8,174	4,565
Total body fat-free mass (FFM)	11,285	4,512	9,351	8,174	4,565
Whole body lean soft tissue mass	11,285	4,512	9,351	8,174	4,565
New Reanalyzed file					
Trunk fat*	10,786	4,308	8,332	7,138	4,338
Android fat	10,832	4,315	8,397	7,170	4,352
Gynoid fat	10,832	4,315	8,397	7,170	4,352
Abdominal visceral adipose tissue (VAT)	10,832	4,315	8,378	7,167	4,342
Abdominal subcutaneous adipose tissue (SAT)	10,832	4,315	8,378	7,167	4,342
Abdominal total adipose tissue (TAT)	10,832	4,315	8,378	7,167	4,342

* Trunk fat is available in historical scans, but trunk fat corrected for DXA machine model is only available in reanalyzed slides

Stage 2: Metabolic Risk Factors and CKD

	Define	Baseline (N)
Metabolic Syndrome		
Hypertriglyceridemia	≥150 mg/dL	2,110
Hypertension (Systolic | Diastolic)	≥130 | ≥80	38,067
Stage 1	130-139 | 80-89	29,930
Stage 2	≥140 | ≥90	8,137
Hypertensive Crisis	≥180 | ≥120	2
High Glucose	≥100 mg/dL	1,774
Lower HDL Cholesterol	≤40 mg/dL	520
Abdominal obesity (waist circumference)	≥88 cm	66,683
Type 2 Diabetes	Self-reported	9,618
Kidney Function*		
Creatinine (serum)	mg/dL	28,021
Creatinine (EDTA)	mg/dL	5,354
Creatinine (urine)	mg/dL	4,596
Cystatin-C (serum)	mg/L	3,220
Albumin (serum)	G/dL	300
Albumin (EDTA)	G/dL	4,850

*CKD is not adjudicated or measured

eGFR Calculator | National Kidney Foundation

EXAMPLES

Stage 0: Dietary Factor

Higher Calibrated Protein Intake Not Associated w/ Impaired Renal Function

TABLE 3. Adjusted weighted OR of estimated glomerular filtration rate (e-GFR) , 60 in women by quartile of calibrated protein intake[1]

	Daily calibrated protein intake OR (95% CI)		
	Absolute (g)	Relative to energy intake (% energy)	Relative to body weight [g/(kg body weightd)]
Quartile 2	0.96 (0.39–2.96)	1.06 (0.47–2.03)	0.93 (0.34–2.06)
Quartile 3	0.90 (0.24–3.04)	1.06 (0.44–2.47)	0.61 (0.22–1.63)
Quartile 4	1.22 (0.16–4.66)	0.44 (0.19–1.66)	0.48 (0.10–1.69)

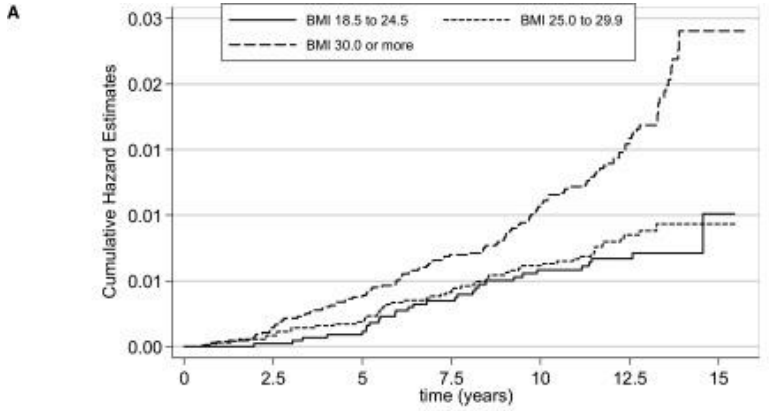
1

Weighted logistic regression model estimates (95% CI) comparing protein intake to the lowest quartile, accounting for factors associated with selection into original case-control studies (age, race/ethnicity, year of blood draw, region, and history of fracture). Covariates were age, race/ethnicity, BMI, calibrated energy, vegetable and fruit intake, percentage of energy from fat, education, income, smoking, physical activity, alcohol intake, general health status, and previous medical conditions (cardiovascular disease, myocardial infarction, stroke, congestive heart failure, hypertension, and treated diabetes).

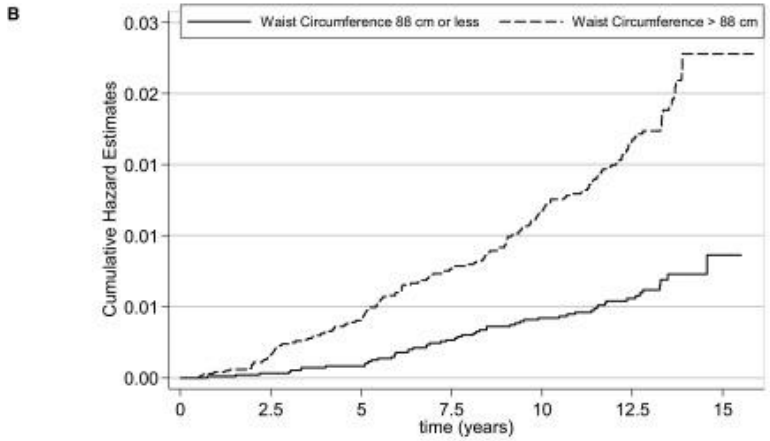
- 2 nested case-control studies in the OS (n= 2419)
- Calibrated protein intake 1.1 ± 0.2 g/kg body wt
- eGFR <60 mL/(min1.73m^2) = impaired renal fxn
- 12% impaired renal function
- Odds of impaired renal function not associated with calibrated protein intake
- Protein g/kg body wt was associated with higher eGFR, but not absolute g or % of kcals
- No effect modification by age, BMI or health status
- Among PM women without CKD, higher protein intake not associated with impaired renal function

Beasley et al 2011 https://doi.org/10.3945/jn.110.135814

Stage 1: Excess Adiposity



No. at Risk	0.0	2.5	5.0	7.5	10.0	12.5	15.0 years
BMI 18.5-24.5	4566	4481	4340	3992	3614	2462	48
BMI 25.0-29.9	7097	6967	6743	6261	5646	3852	114
BMI 30 or more	8454	8282	7977	7358	6634	4435	119



No. at Risk	0.0	2.5	5.0	7.5	10.0	12.5	15.0 years
Waist ≤88 cm	9869	9713	9451	8810	8005	5443	128
Waist >88 cm	10248	10016	9611	8798	7889	5307	145

BMI associated with ESRD

- Potentially mediated through HTN and T2DM

Waist circumference associated with increased risk of ESRD

- Incl. among women with normal BMI
- not among women with reduced baseline kidney function

Franceschini et al; **Adiposity Patterns and the Risk for ESRD in Postmenopausal Women.** 2014 Dec 1;10(2):241–250. doi: 10.2215/CJN.02860314

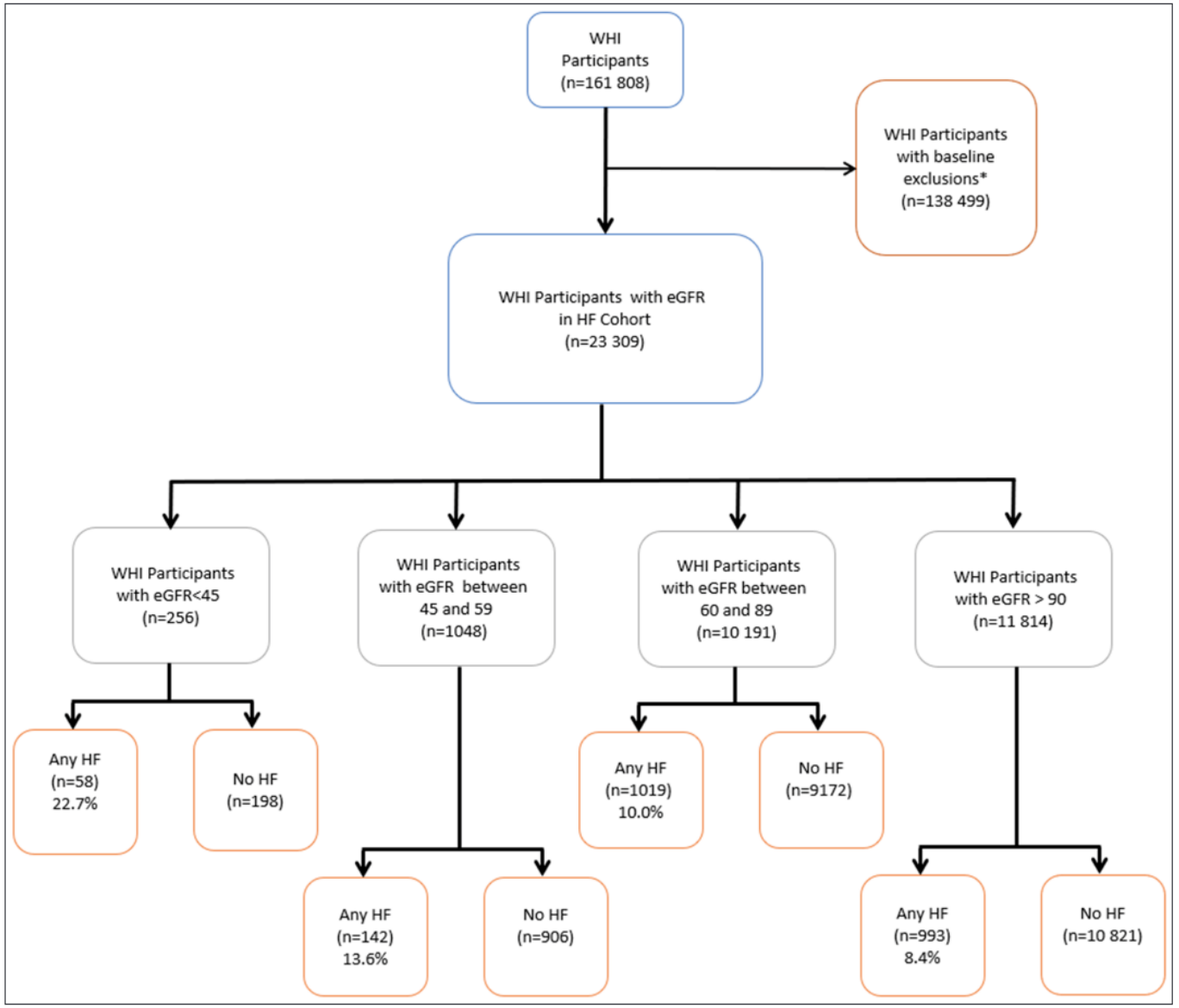
Stage 4: HF

Association of Kidney Function With Incident Heart Failure: An Analysis of the Women's Health Initiative

Cheng et al; 2025 Mar 4;14(5):e037051.

doi: 10.1161/JAHA.124.037051.

Epub 2025 Feb 25



Stage 0-4: Genetic Resources
WHI & the COGENT-Kidney Consortium

Supplementary Table 12. Sample characteristics of GWAS contributing to the COGENT-Kidney Consortium.

Study (acronym)	Ethnicity (Country of origin)	Sex	Sample size	Age (years) mean (SD)	Serum Creatinine (mg/dL) mean (SD)	eGFR mean (SD)
Women's Health Initiative Genome-wide Association Research Network into Effects of Treatment (WHI-GARNET)	European (USA)	Males	0	N/A	N/A	N/A
		Females	4,116	65.6 (6.9)	0.74 (0.15)	88.1 (19.3)
Women's Health Initiative Memory Study (WHIMS+)	European (USA)	Males	0	N/A	N/A	N/A
		Females	5,655	68.1 (5.9)	0.75 (0.15)	85.6 (17.8)
Women's Health Initiative SNP Health Association Resource: African Americans (WHI-SHARe-A)	African American (USA)	Males	0	N/A	N/A	N/A
		Females	8,224	61.6 (7.0)	0.82 (0.22)	80.1 (19.4)
Women's Health Initiative SNP Health Association Resource: Hispanic Americans (WHI-SHARe-H)	Hispanic/Latino (USA)	Males	0	N/A	N/A	N/A
		Females	3,549	60.3 (6.7)	0.71 (0.19)	94.7 (21.9)

Senior Author: WHI's Nora Franceschini
https://pubmed.ncbi.nlm.nih.gov/30604766/

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Evaluating the Cardiovascular-Kidney-Metabolic Syndrome in the WHI DEXA Cohort

Session Chair: Deepika Laddu & Marcia Stefanick

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CKM Stage 3 & 4 : Adipose tissue depots and ASCVD in the WHI

- Andrew Odegaard
- Associate Professor
- University of California, Irvine
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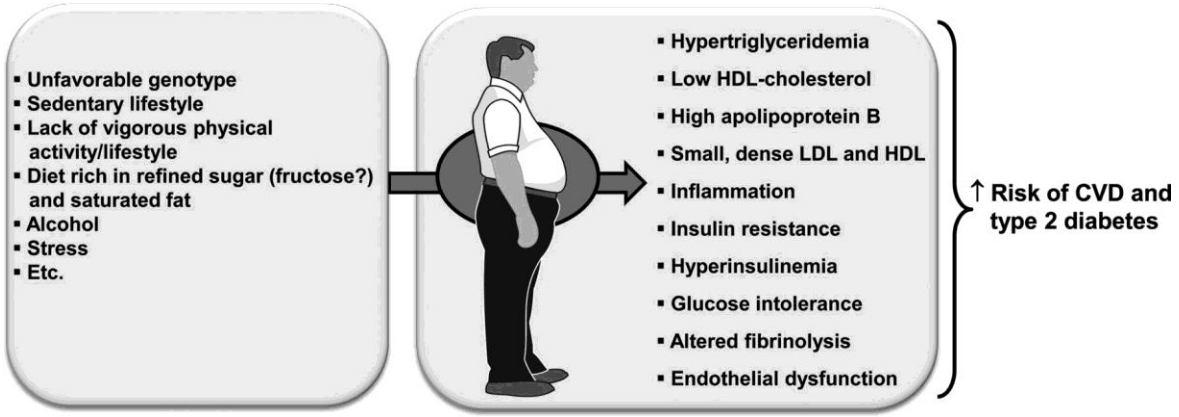
Outline

- Context and Definitions
- Some data
- Summary
- Discussion

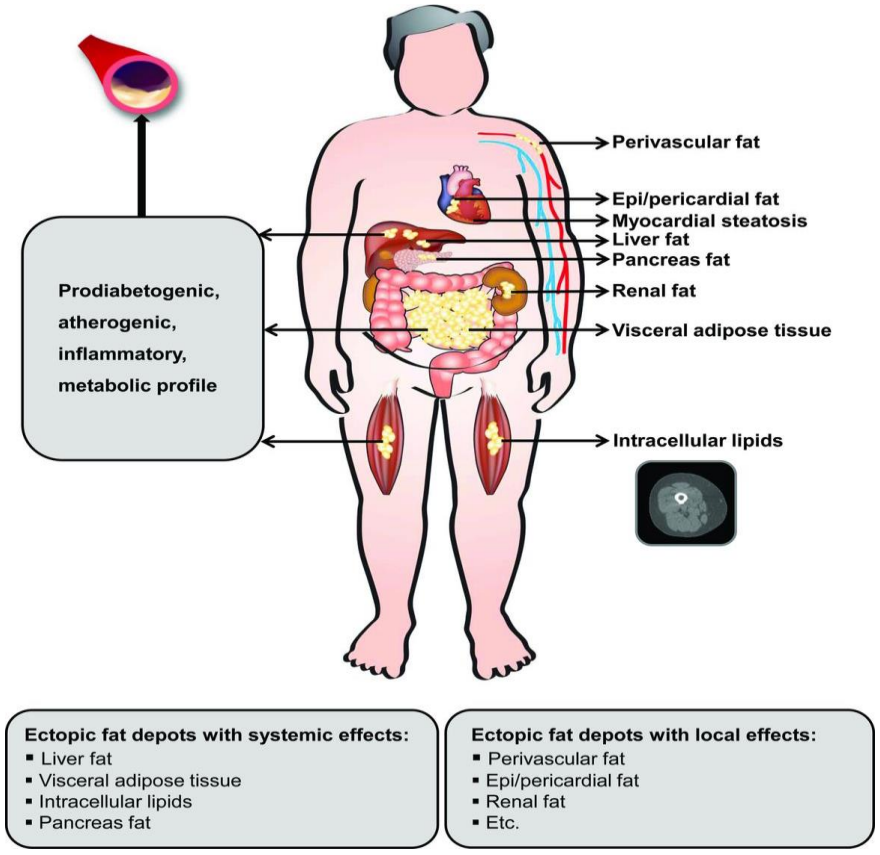
Adiposity and overall body composition – an essential component of CKM staging

Ectopic fat depots and various regional measures of

Subcutaneous adipose tissue (plus other body comp measures)



SYNDROME X (REAVEN'S SYNDROME)?
INSULIN RESISTANCE SYNDROME?
METABOLIC SYNDROME?
EXCESS VISCERAL/ECTOPIC FAT?



Body Fat Distribution and Risk of Cardiovascular Disease, Volume: 126, Issue: 10, Pages: 1301-1313, DOI: (10.1161/CIRCULATIONAHA.111.067264)

Context and definitions

- ***Forthcoming paper***: etiological prediction of Atherosclerotic Cardiovascular Disease (**ASCVD**) from DXA abdominal adipose tissue depots, plus other phenotypic body composition measures (android/gynoid adipose tissue, appendicular (leg), lean mass)

- **ASCVD**: CHD, ischemic stroke, peripheral arterial disease, carotid artery disease, and death from cardiovascular disease (due to definite coronary heart disease, cerebrovascular disease, pulmonary embolism, or other or unknown cardiovascular causes)

Model summary (for following slides)

- **Model 1**: Adjusted for age, race/ethnicity, education, income, age menarche, parity, (observational v.-controlled trial status).
- **Model 2**: Model 1 + smoking, alcohol, diet pattern score and energy intake, physical activity, sleep
- **Model 3**: Model 2 + baseline abdominal SAT levels
- **Model 4:** Model 2 + baseline gynoid fat
- **Model 5:** Model 2 + baseline lower leg fat (appendicular fat)
- **Model 6:** Model 2 + total body fat

Visceral Adipose Tissue (VAT)

Prediction of ASCVD from CKM stage 1*

Hazard ratios (95% CI) of incident ASCVD according to baseline VAT

VAT	Q1 (n=1881)	Q2 (n=1833)	Q3 (n=1786)	Q4 (n=1742)	Q5 (n=1711)
Cases / 10,000 PY	**46**	**53**	**64**	**68**	**86**
Model 1	1.0	1.10 (0.90, 1.35)	1.23 (1.01, 1.51)	1.21 (0.99, 1.48)	1.40 (1.15, 1.71)
Model 2	1.0	1.05 (0.85, 1.28)	1.13 (0.93, 1.38)	1.12 (0.92, 1.37)	1.33 (1.09, 1.63)
Model 3	1.0	1.10 (0.89, 1.37)	1.24 (0.99, 1.56)	1.26 (0.98, 1.63)	1.56 (1.17, 2.08)
Model 4	1.0	1.09 (0.88, 1.34)	1.21 (0.98, 1.49)	1.23 (0.99, 1.53)	1.54 (1.21, 1.95)
Model 5	1.0	1.08 (0.88, 1.33)	1.19 (0.97, 1.47)	1.22 (0.99, 1.51)	1.51 (1.21, 1.89)
Model 6	1.0	1.15 (0.92, 1.43)	1.30 (1.03, 1.64)	1.33 (1.04, 1.71)	1.66 (1.26, 2.19)

Subcutaneous Adipose Tissue (SAT)

Prediction of ASCVD from CKM stage 1*

Hazard ratios (95% CI) of incident ASCVD according to baseline SAT

Abdominal SAT	Q1 (n=1838)	Q2 (n=1787)	Q3 (n=1809)	Q4 (n=1757)	Q5 (n=1762)
Cases / 10,000 PY	57	59	57	69	70
Model 1	1.0	1.02 (0.84, 1.24)	0.92 (0.76, 1.12)	1.05 (0.87, 1.27)	0.97 (0.80, 1.19)
Model 2	1.0	1.02 (0.84, 1.24)	0.91 (0.75, 1.11)	1.09 (0.90, 1.32)	1.13 (0.92, 1.38)
Model 3	1.0	0.90 (0.74, 1.11)	0.74 (0.59, 0.92)	0.80 (0.62, 1.04)	0.77 (0.58, 1.03)

Model 1: Adjusted for age, race/ethnicity, education, income, age menarche, parity, (observational v.-controlled trial status).

Model 2: Model 1 + smoking, alcohol, diet pattern score and energy intake, physical activity, sleep

Model 3: Model 2 + baseline abdominal VAT levels

What about BMI (kg/m^2) and Waist?

BMI (kg/m^2) and Waist (cm)

Prediction of ASCVD from CKM stage 1*

Hazard ratios (95% CI) of incident ASCVD according to baseline

	Q1	Q2	Q3	Q4	Q5
BMI: Model 2	1.0	0.92 (0.78, 1.08)	0.93 (0.79, 1.09)	1.01 (0.86, 1.18)	1.03 (0.87, 1.22)
WC: Model 2	1.0	1.05 (0.89, 1.23)	1.14 (0.97, 1.34)	1.22 (1.04, 1.44)	1.27 (1.07, 1.51)

Model 1: Adjusted for age, race/ethnicity, education, income, age menarche, parity, (observational v.-controlled trial status).

Model 2: Model 1 + smoking, alcohol, diet pattern score and energy intake, physical activity, sleep

Major ASCVD sub-group findings (qualitative)

CHD	Stroke	PAD
VAT strongly predicts; SAT no association	No association of any adiposity, body composition or anthropometric	No association of any adiposity, body composition or anthropometric

ASCVD summary

- Strong, graded relation between VAT and overall ASCVD, and CHD
- No association adipose with stroke or PAD
- BMI no association ASCVD, WC + association

Ideas for leveraging WHI to inform CKM

- Different analytic approach
- Isolate by staging
- Simplified predictive modeling

Questions and discussion

CKM

Heart Failure and Adiposity

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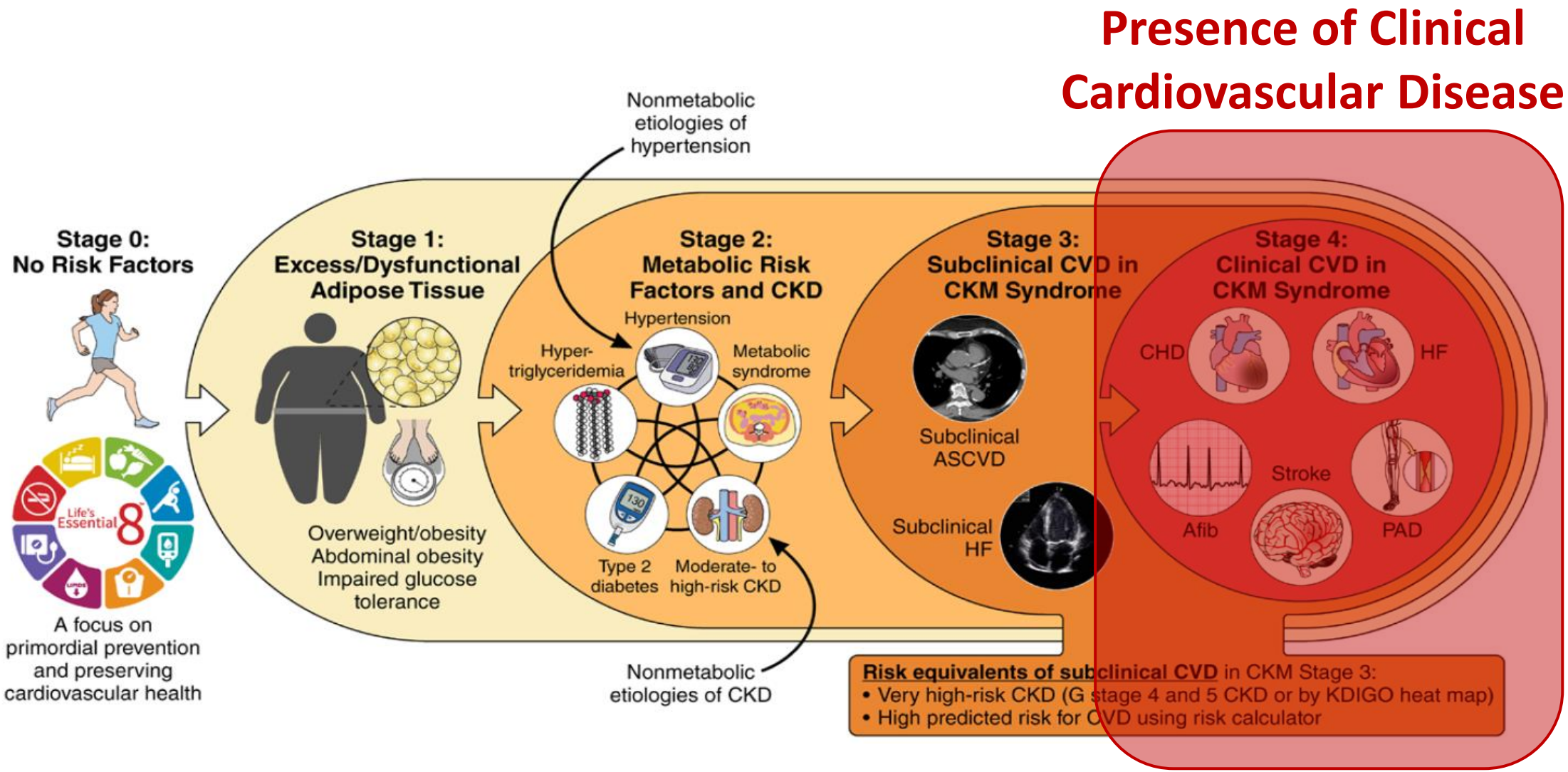
WHI Investigator Meeting, May 2025

University at Buffalo
The State University of New York

CKM Stages



Ndumele CE. Circulation 2003;148:1606

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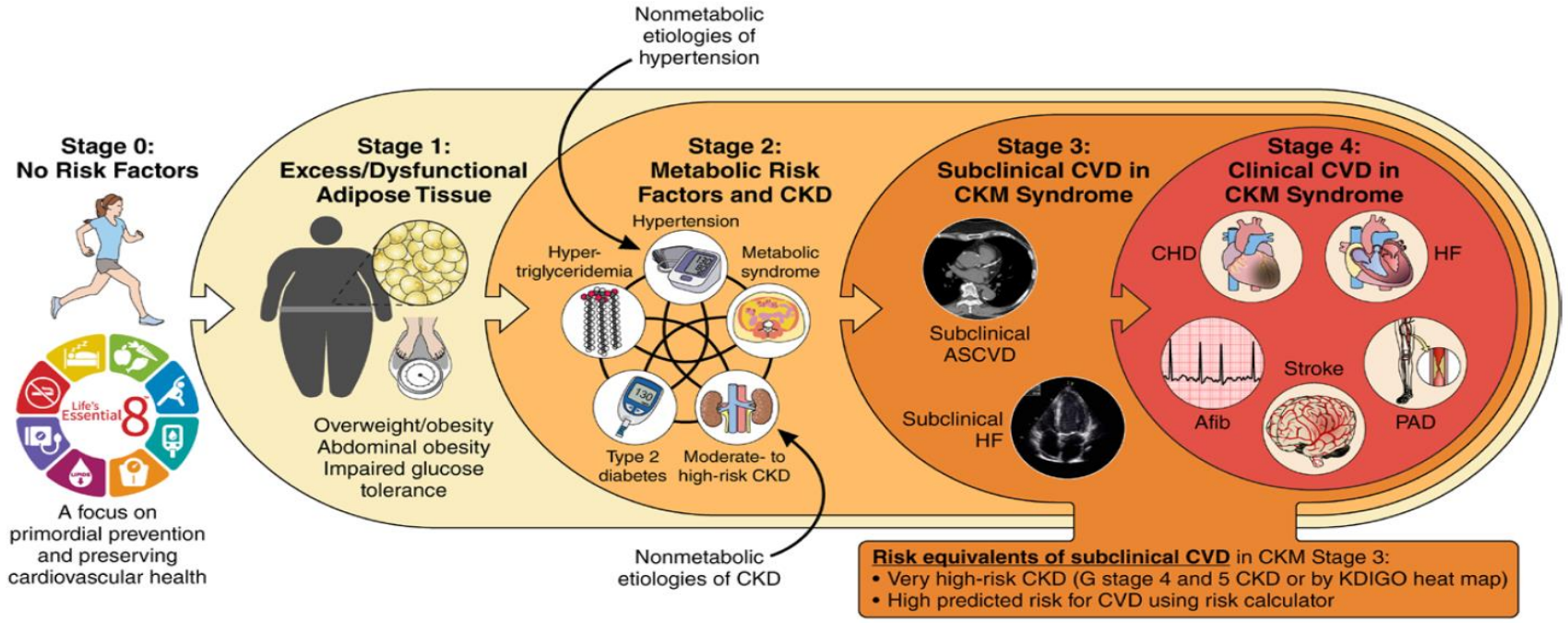
CKM Stages

Ndumele CE. Circulation 2003;148:1606



HF Stages

Hunt SA. Circulation 2001;104:2996

Stage A "At Risk"	Stage B "Pre-HF"	Stage C "HF"	Stage D "Advanced HF"
• HF risk factors • No HF signs/Sx • No structural • No biomarker	• HF signs/Sx • At least 1: ✓ Structural ✓ Function ✓ BNP or cTnT	• HF signs/Sx ↑ • Structural • Functional	• Severe Sx at rest • Recurrent hospital • Circulatory support • Transplant • Palliative care

CKM Stage 4

Clinical CVD … Heart Failure

Association of Kidney Function with Incident Heart Failure: The WHI

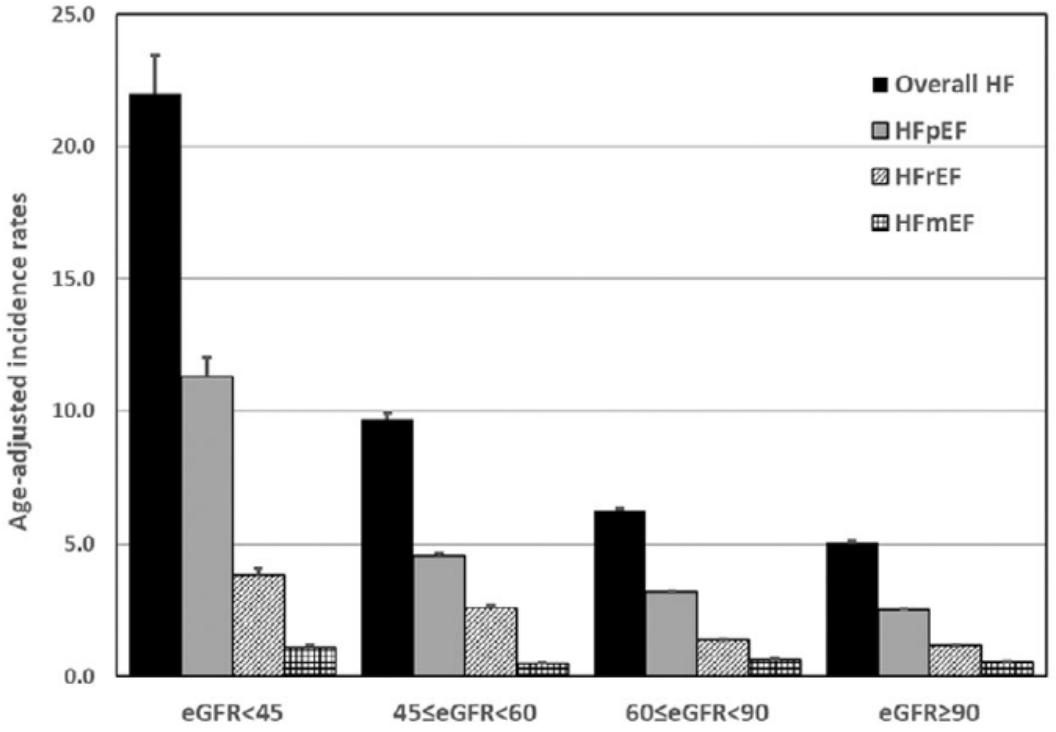
Chang RK et al. J Am Heart Assoc. 2025;14:e037051

- 23,309 women, ages 50-79 years, in HAH (UNC) Subcohort
- Available serum creatinine; without prior HF diagnosis
- Followed 18 years (median)
- **eGFR** (CKD-EPI, 2021) **Incident HF cases:**
  - ✓ **<45** (n=256) 58 (22.7%)
  - ✓ **45-59** (n=1,048) 142 (13.6%)
  - ✓ **60-89** (n=10,191) 1,019 (10%)
  - ✓ **≥90** (n=11,814) 993 (8.4%)

Association of Kidney Function with Incident Heart Failure: The WHI

Chang RK et al. J Am Heart Assoc. 2025;14:e037051

Age-adjusted Incidence



Multivariable HR (95% CI)

	eGFR			
	≥90	60-89	45-59	<45
HF	1.00	**1.02** (0.99-1.06)	**1.36** (1.26-1.47)	**2.46** (2.18-2.78)
HFpEF	1.00	**1.07** (1.01-1.12)	**1.51** (1.36-1.69)	**2.80** (2.36-3.32)
HFrEF	1.00	**1.06** (0.99-1.14)	**1.51** (1.29-1.76)	**2.18** (1.66-2.87)

Trend, P<.001 all.

Adjusted for age, race, ethnicity, diabetes, hypertension, SBP, DBP, A-fib, hysterectomy, CHD, **BMI**, physical activity, smoking, diet quality, alcohol, ability to walk 1 block.

CKM Stage 4

Clinical CVD … Heart Failure

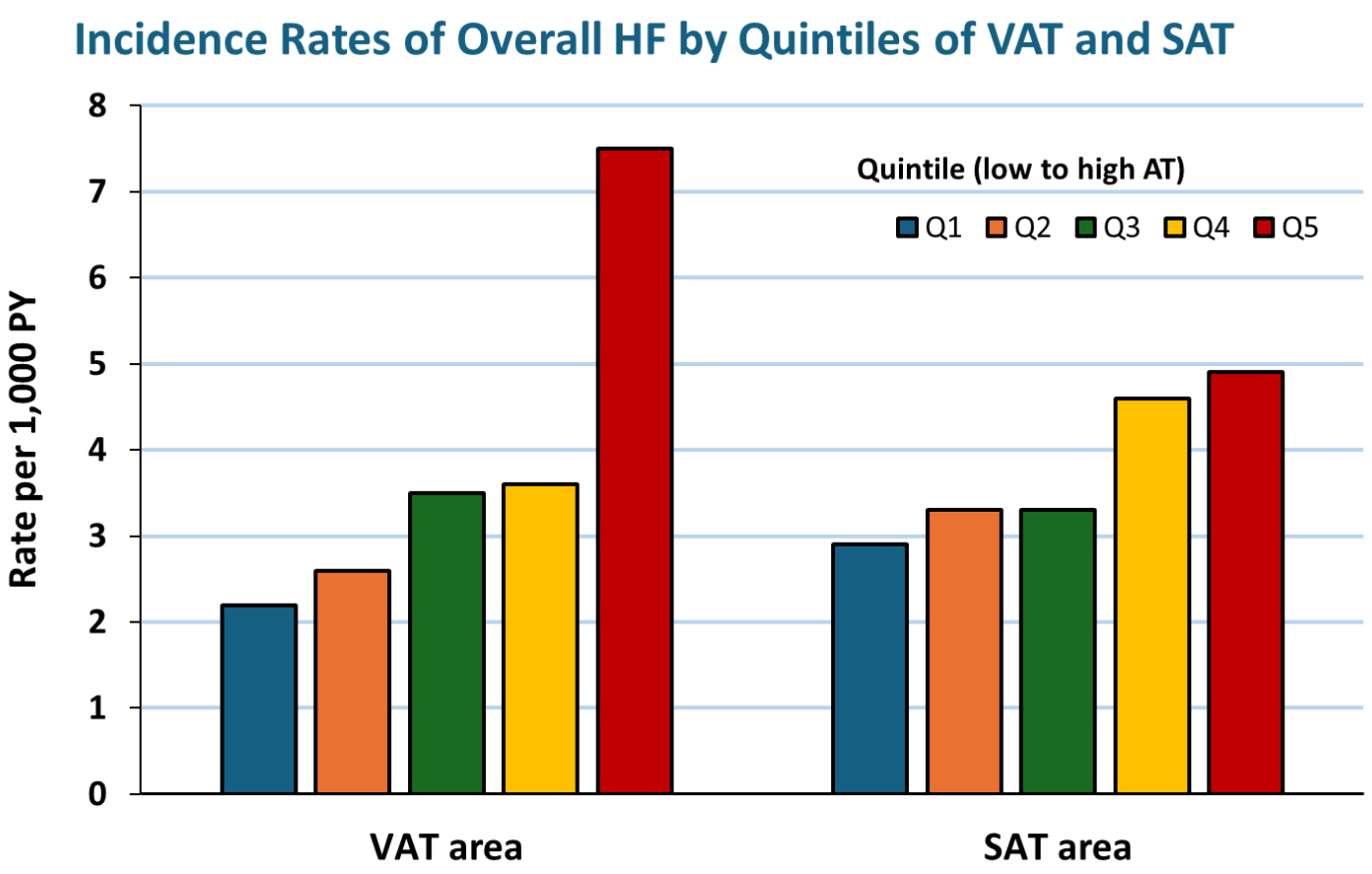
Association of Body Composition with Incident Heart Failure: The WHI

LaMonte MJ et al. In journal review.

- 10,521 women, ages 50-79 years in DXA Subcohort
  - ➢ 3,528 women in HAH (UNC) Subcohort
- Without prior HF diagnosis
- Followed 16 years (mean)
- **Incident HF cases:**
  - 852 HF
  - 116 HFpEF
  - 107 HFrEF

Association of Body Composition with Incident Heart Failure: The WHI

LaMonte MJ et al. In journal review.



	HR (95% CI) per 1-SD
HF	
VAT	**1.10** (1.02 – 1.18)
SAT	1.05 (0.98 – 1.14)
HFpEF	
VAT	**1.34** (1.09 – 1.66)
SAT	1.16 (0.94 – 1.43)
HFrEF	
VAT	0.90 (0.71 – 1.13)
SAT	0.79 (0.63 – 1.01)

Adjusted for WHI component, CT randomization, age, race, ethnicity, education, income, smoking, diet quality, total energy, alcohol, physical activity, sleep duration, age at menarche, parity, hypertension, diabetes, hyperlipidemia, atrial fibrillation, stroke, time-varying CHD, cancer, physical function score, statin use, aspiring use, antihypertensive use.

CKM Stage 4

Clinical CVD … Heart Failure

Association of APOL1 with Heart Failure in African American Women: The WHI

Franceschini N et al. JAMA Cardiol 2018;3:712.

- 11,137 African American women, ages 50-79 years, without HF
- **APOL1 high risk** (G1 and G2 genotypes) → 13% African Americans
- Increased risks of CVD and **ESRD** … *HF understudied*
- WHI APOL1 variant
  - high risk (n=1,370; 12.3%)
  - low risk (n=9,767; 87%)
- Followed 11 years (mean)

Association of APOL1 with Heart Failure in African American Women: The WHI

Franceschini N et al. JAMA Cardiol 2018;3:712.

	APOL1 variant		
Incident disease (cases)	**Low risk**	**High risk***	**Further adjusted for *baseline eGFR***
HF (342)	1.00	1.18 (0.89-1.58)	1.13 (0.84-1.50)
HFpEF (128)	1.00	**1.58** (1.03-2.41)	1.50 (0.98-2.30)
HFrEF (126)	1.00	1.05 (0.64-1.71)	1.00 (0.61-1.65)
ESRD (199)	1.00	**1.43** (1.01-2.02)	1.02 (0.72-1.45)
CHD/stroke (710)	1.00	1.01 (0.84-1.22)	1.00 (0.83-1.20)

*Adjusted for WHI component, age, education, income, region, waist, smoking, SBP, DBP, treated hypertension, diabetes, hyperlipidemia.

CKM Stage 4

Clinical CVD … Heart Failure

Metabolically Healthy/Unhealthy Obesity and Incident Heart Failure: The WHI

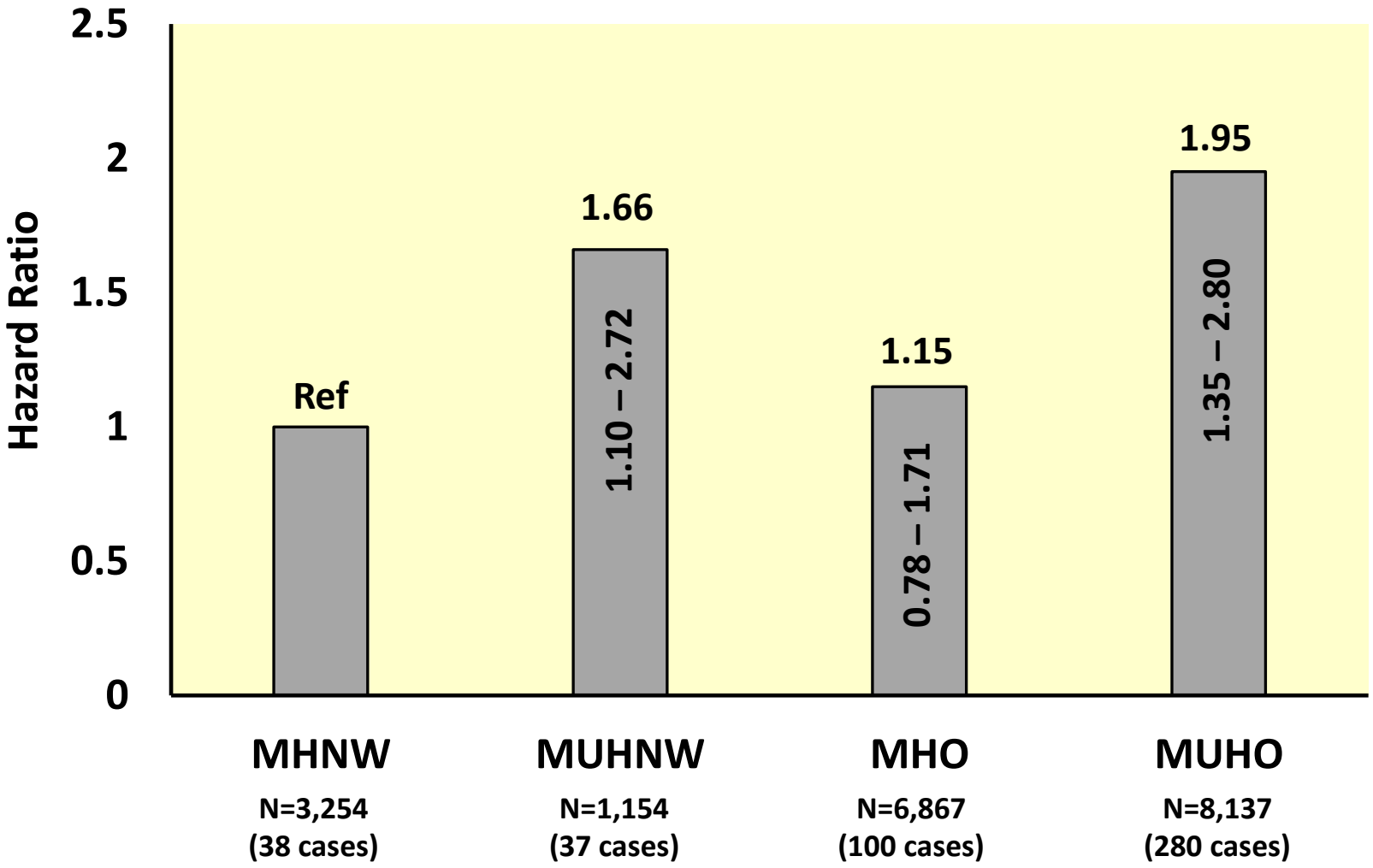
Cordola-Hsu AR et al. Circulation Heart Failure 2021;14:e007297.

- 19,412 women, ages 50-79 years, without CVD or HF
- **Normal weight** = BMI 18.5-24.9 kg/m^2 **AND** waist <88 cm
- **Overweight/Obese** = BMI ≥25 kg/m^2 **OR** waist ≥88 cm
- Metabolically unhealthy, ≥2 cardiometabolic factors:
  - ✓ **Triglyceride** ≥150 mg/dL; **HDL-C** <50 mg/dL; **glucose** ≥100 mg/dL or meds; **SBP** ≥ 130 mmHg or **DBP** ≥85 mmHg or meds.
- Followed 11 years (mean); 455 HF cases

NOTE: eGFR or history of renal disease was not included in the metabolic constellation

Metabolically Healthy/Unhealthy Obesity and Incident Heart Failure: The WHI

Cordola-Hsu AR et al. Circulation Heart Failure 2021;14:e007297.



MHNW, metabolically health normal weight.

MUHNW, metabolically unhealthy normal weight.

MHO, metabolically healthy, ovrwt/obese.

MUHO, metabolically unhealthy ovrwt/obese.

Adjusted for age, race, ethnicity, income, smoking, treated diabetes, diet quality, physical activity, total cholesterol.

University at Buffalo
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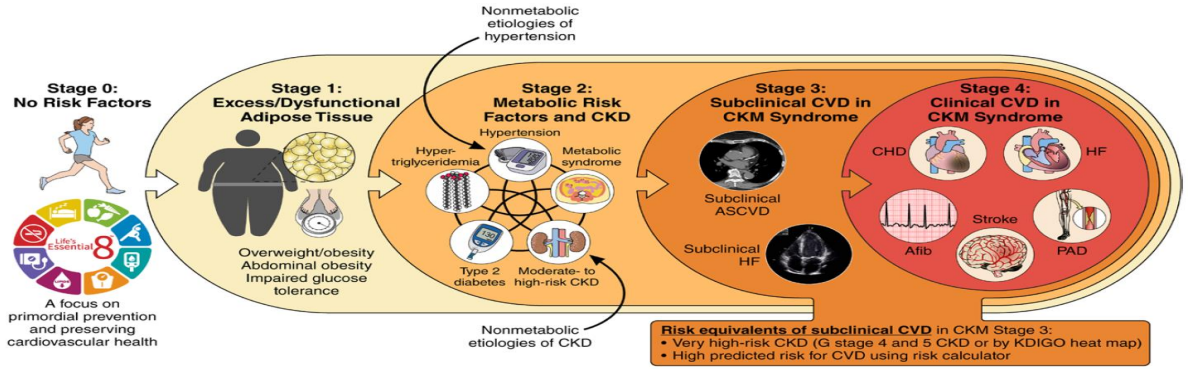
CKM and Heart Failure



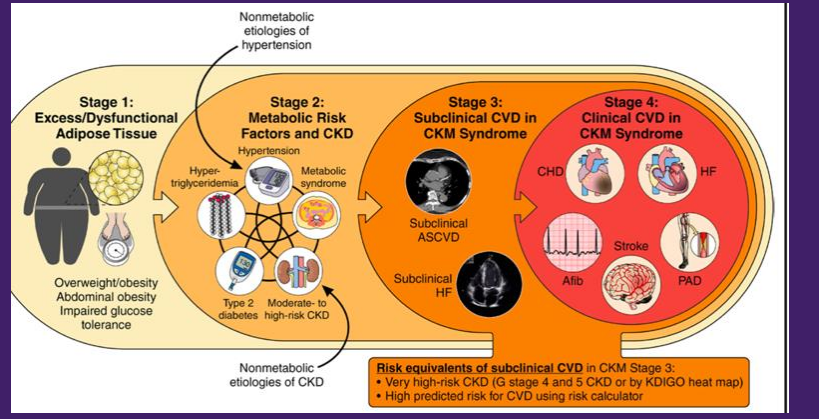
Conclusion …

Next Steps for WHI to make a major contribution to CKM syndrome work

CKM Syndrome vs. Standard Screening Models

Aspect	Standard Screening	CKM Syndrome Framework
Purpose	*Detect* individual diseases	**Screening + risk prediction** for multi-system disease
Focus	Single disease (e.g., CVD, diabetes, CKD)	**Interconnected systems**: heart, kidneys, metabolism
Approach	Disease-specific thresholds (e.g., LDL > 130)	**Staged risk model** across systems incorporating disease specific thresholds
Screening Tools	A1c, BP, LDL, GFR individually	Combined risk markers (e.g., **UACR , BP, A1c/fasting glucose, lipids**)
Intervention Timing	Often reactive (after disease onset)	**Proactive** and **preventative**, even in Stage 1
Care Model	Siloed specialties	**Team-based, integrated, holistic care approach**

Using WHI data to move CKM syndrome forward



Prevention Focus:

Focus on detecting individuals in the preclinical phase, with the goal of delaying or averting the onset of clinical CVD and kidney failure

WHI provides valuable data and opportunities

- Characterize LE8 metrics (**Stage 0**)
- Dysfunctional adiposity: visceral and subcutaneous fat (**Stage 1**)
- Clinically available data on metabolic risk factors, CV biomarkers pertinent to CKMS – **Stage 2**)
- Adjudicated and self-reported outcomes (**Stage 2-4**)

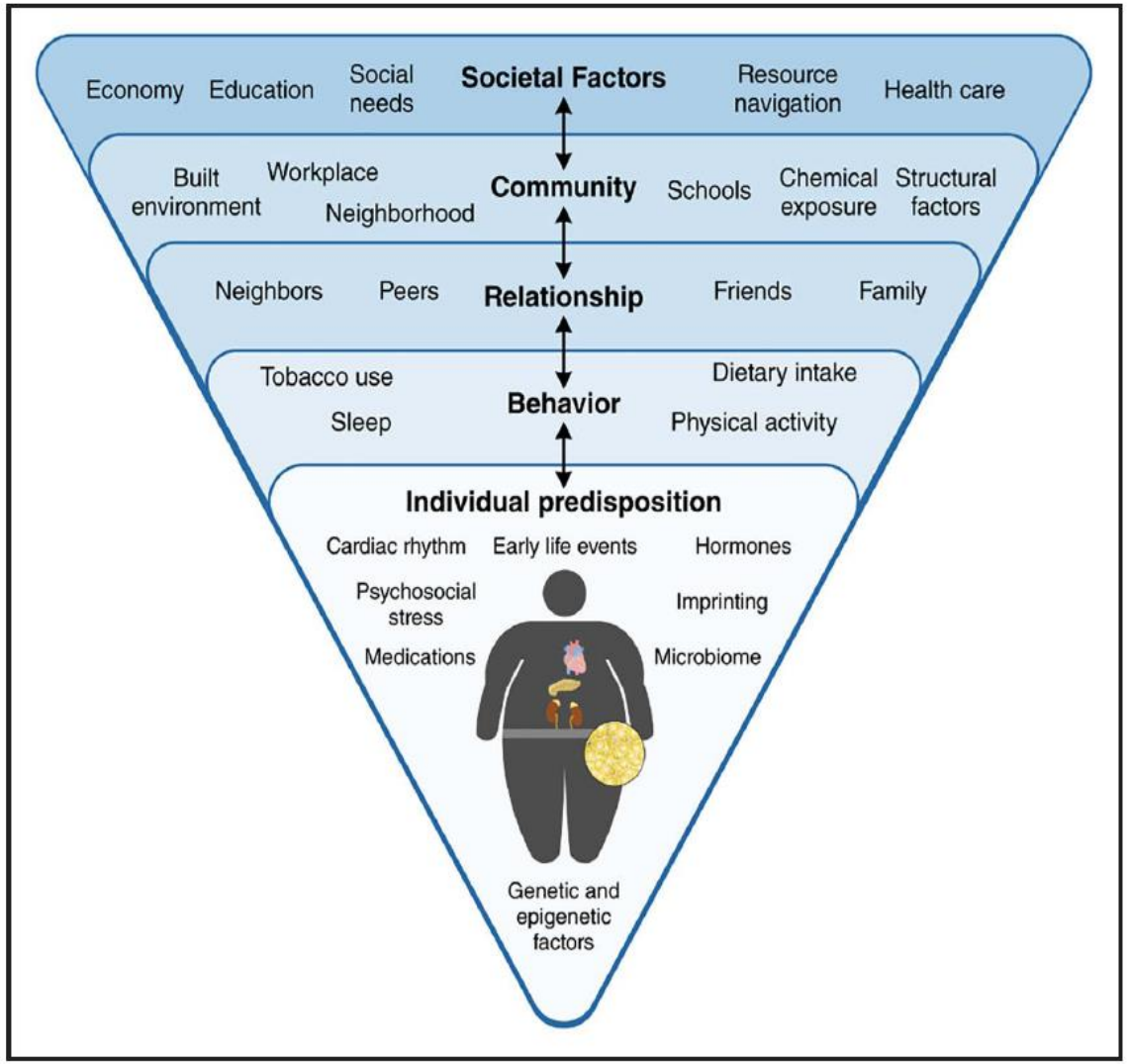
Circulation. 2023;148:1606–1635

CKM Syndrome Screening Categories

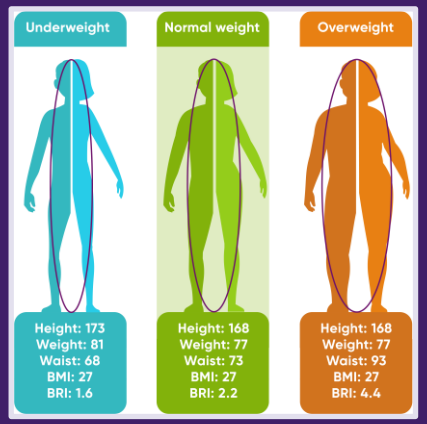
Biological factors

CKM syndrome stages	Definition
Stage 0: No CKM risk factors	Individuals with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD
Stage 1: Excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD BMI ≥25 kg/m^2 (or ≥23 kg/m^2 if Asian ancestry), Waist circumference ≥88/102 cm in women/men (or if Asian ancestry ≥80/90 cm in women/men), or Fasting blood glucose ≥100–124 mg/dL or HbA1c between 5.7% and 6.4%*
Stage 2: Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension, MetS,† diabetes), or CKD
Stage 3: Subclinical CVD in CKM	Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-troponin T ≥14 ng/L for women and ≥22 ng/L for men, hs-troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with a combination of the 2 indicating highest HF risk. Risk equivalents of subclinical CVD Very high-risk CKD (stage G4 or G5 CKD or very high risk per KDIGO classification) High predicted 10-y CVD risk
Stage 4: Clinical CVD in CKM	Clinical CVD (coronary heart disease, HF, stroke, peripheral artery disease, atrial fibrillation) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present

Social Determinants of Health factors



Relevant questions and Opportunities



What is the comparative utility of VAT vs. anthropometric measures or body roundness index with respect to CKM syndrome?

What does kidney health data add in terms of cardiometabolic risk and CVD outcomes?

How do we integrate SDOH for CKM syndrome screening and prevention in older women?