CARDIOVASCULAR CARE IN WOMEN VETERANS

A Call to Action

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VA Greater Los Angeles Healthcare System

UCLA Health

Circulation

FRAME OF REFERENCE

ORIGINAL RESEARCH ARTICLES

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STATE OF THE ART

Circulation

American Heart Association. Go Red for women.

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PRIMER

Cardiovascular Care in Women Veterans

A Call to Action

ABSTRACT: Cardiovascular disease is the number one cause of death for women in the United States. Of the 1.3 million active duty service members, 16.3% are currently women, and the number of women veterans is expected to increase. Women veterans have higher rates of cardiovascular disease than civilian women and present a unique population. We focus on 5 key areas regarding cardiovascular disease care for women veterans: (1) the rapidly changing demographic; (2) prevalence of traditional risk factors; (3) prevalence of less traditional risk factors (eg, homelessness, military sexual trauma, and mental health disorders); (4) treatment and outcomes of cardiovascular disease; and (5) the current state and future directions of research in this area. This review is a call to action for continued improvements in the cardiovascular care and research for this rapidly growing, at-risk, and under-represented population.

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Call to Action:

Cardiovascular care in women veterans

#1 There will be over 2 million women veterans by the year 2025

Women veterans are more ethnically diverse than male veterans & civilian women

Women veterans experience more healthcare delays and less aggressive CVD care than male veterans

Women veterans are less well-informed about CVD

#2 Women veterans have a high prevalence of traditional CVD risk factors

40% have hypertension

44% are obese

27% have hyperlipidemia

#3 Women veterans have a high prevalence of non-traditional CVD risk factors

40% have suffered military sexual trauma

32% Have depression or PTSD

#4 More research is needed regarding CVD in women veterans

3 On-going studies:

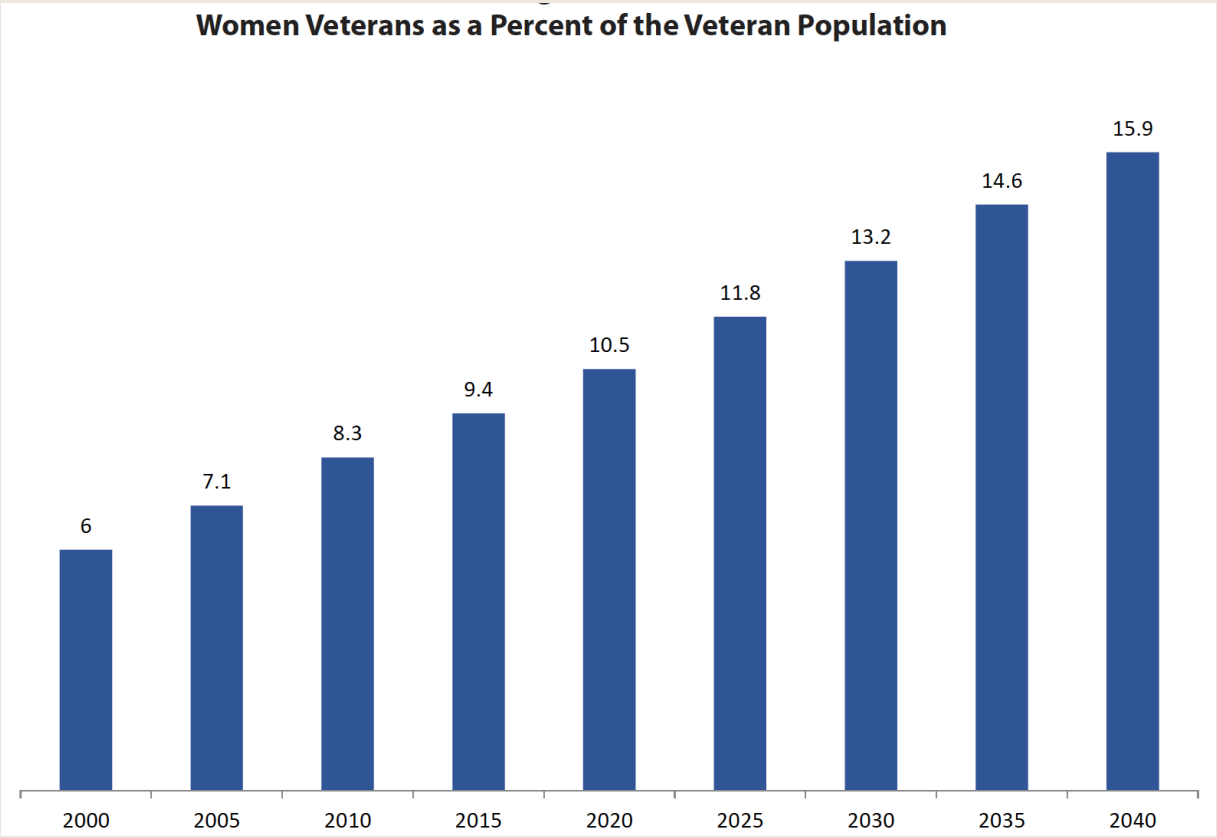
1. EMPOWER Trial CVD arm
2. WARRIOR Trial
3. PTSD and CVD in women veterans

ABOUT FACE:

Background & Women Veterans' Changing Sociodemographics

Background

- Women have served in the US military since its inception, with the first formal action when the Army Nurses' Corps was formed (1901).
- 1.3 million active duty women, 16.3% of military, all branches
- 19.6 million living veterans is projected to decline over time
- Number of women veterans (WVs) is projected to ***increase*** from 1.9 million to over 2.2 million over the next 25 years

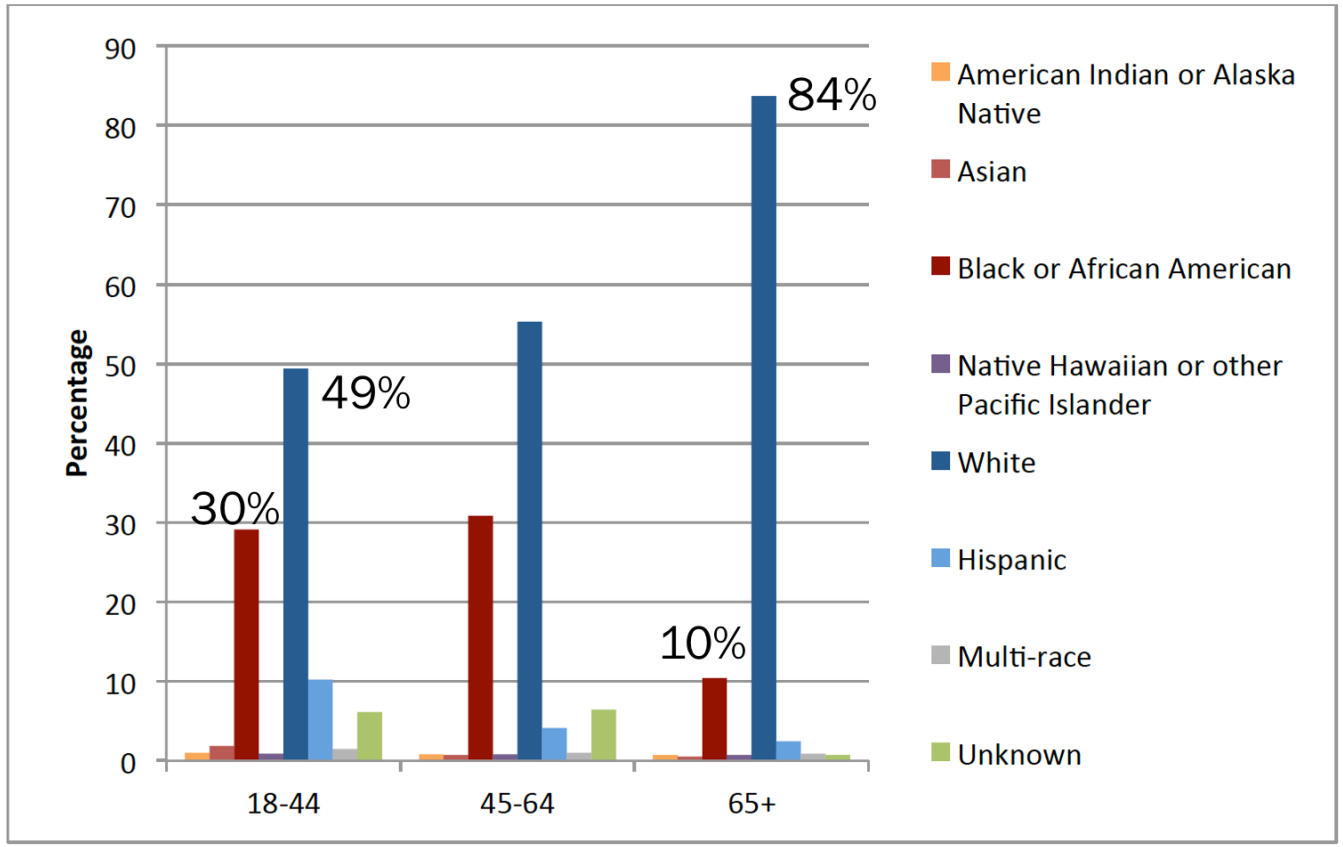


National Center for Veterans Analysis and Statistics. Veteran Population. Population Tables. Age/Gender. https://www.va.gov/vetdata/veteran_population.asp.
National Center for Veterans Analysis and Statistics, Department of Veterans Affairs. Women Veterans Report: The Past, Present, and Future of Women Veterans. Washington, DC; February 2017.

Sociodemographics

- Largest group: 44 to 65
- Second group: 20s-30s (Iraq and Afghanistan conflicts)
- Younger WV patients are more ethnically diverse: ~30% are Black, 10% are Hispanic
- Quality of care has improved within the VA system
- Racial disparities persist, esp for measures that impact CVD: diabetes mellitus, hypertension, and lipid control
- Younger minority WVs found to have a high rates of delayed care or unmet medical needs

Figure 2. Racial/ethnic distribution of women Veteran VHA patients by age, FY14



National Center for Veterans Analysis and Statistics, Department of Veterans Affairs. Women Veterans Report: The Past, Present, and Future of Women Veterans. Washington, DC; February 2017.
Maher NH, et al. State of Cardiovascular Health in Women Veterans. Volume 2: Risk Factors, Diagnoses, and Procedures in Fiscal Year (FY) 2014. Vol 2. 2017.

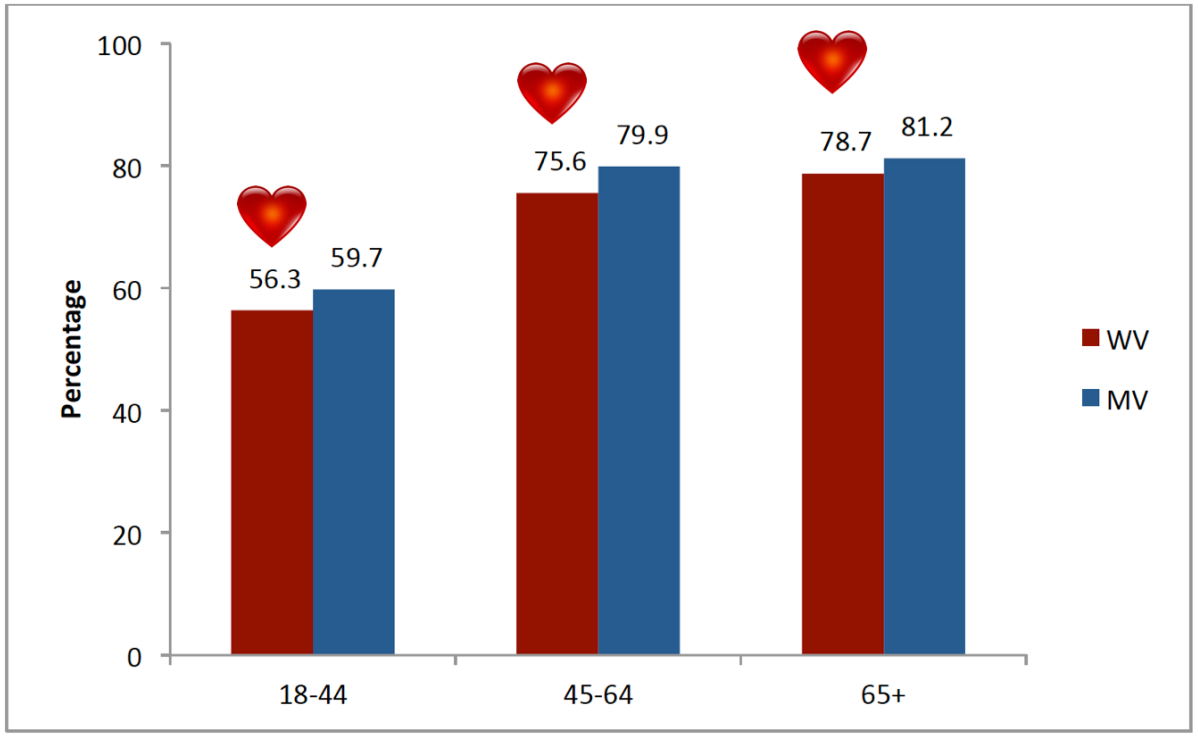
GATHERING INTELLIGENCE:

Traditional Cardiovascular Risk Factors in Women Veterans

Scope of the Problem

- For the past 70 years, CVD has remained the number one killer of women in the United States, affecting 36% of the female population
- One women dies from CVD every 1 minute and 19 seconds.
- Overall, 11% of WVs have been diagnosed with CVD; over the age of 65, 32% are affected
- 60% of younger WVs have at least 1 major CVD risk factor
- 75% in 44 to 65 age group
- 80% in > 65 age group.9

Figure 3. Proportion of Veterans with any major CVD risk factor by gender and age, FY14



Benjamin EJ, et al. Heart disease and stroke statistics-2018 update: a report from the AHA. Circulation. 2018.
Maher NH, et al. State of Cardiovascular Health in Women Veterans. Volume 2: Risk Factors, Diagnoses, and Procedures in Fiscal Year (FY) 2014. Vol 2. 2017

Obesity prevalence

- Veterans have higher rates of obesity than the general population: 78% of veterans are either overweight or obese, compared to 68% in the overall US population
- More WVs (44%) than MV (41%) meet criteria for obesity
- Black WVs (51%) have higher obesity rates than black MVs (43%) and are twice as likely to be obese as white WVs
- WVs with mental health disorders are often more likely to be obese than MVs with the same mental health disorders.

Overweight and Obesity Classification by BMI and Associated Disease Risk			
Classification	**BMI (kg/m^2)**	**Disease Risk with Normal Waist Circumference***	**Disease Risk with Excessive Waist Circumference***
Underweight	< 18.5	–	–
Normal	18.5 – 24.9	–	–
Overweight	25.0 – 29.9	Increased	Moderate
Obese I	30.0 – 34.9	Moderate	Severe
Obese II	35.0 – 39.9	Severe	Very Severe
Obese III	≥ 40.0	Very Severe	Very Severe

Table 1. (continued)

	Row N	Obesity prevalence		
	Total sample	**Total sample**	**Women***	**Men***
		N = 4,914,208	**N = 347,112**	**N = 4,567,096**
Bipolar disorder	123,252	**47%**	**49%**	**46%**
PTSD	675,921	**47%**	**46%**	**47%**
Anxiety disorder	528,765	42%	42%	42%
Schizophrenia	77,747	42%	**56%**	41%
Drug use disorder	232,876	33%	36%	33%
Alcohol use disorder	377,873	34%	35%	34%
3+ Conditions‡	2,348,005	**50%**	**54%**	**49%**

The Management of Overweight and Obesity Working Group. VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity. 2014.
Breland et al. J Gen Intern Med. 2017;32(Suppl 1):11–17.
Rose et al. J Gen Intern Med. 2013;28 Suppl 2:S524–S528.

Diabetes mellitus prevalence

- 9.1% of the general population have DM
- Between 2005 to 2014, the prevalence of diabetes mellitus (DM) in veterans increased from **15.5% → 20.5%**
- **More WV than civilian women have DM**: 11% vs 9%.
- **WVs outpace the general population** for DM prevalence in every age category:
  - *Increases to* ***~ 25% in >65 y.o.***
  - *In one study of 900 Vietnam-era WVs who used both VA and non-VA care,* ***DM prevalence was 30%***
- **Hispanic and black WVs** have > 4-fold and 2.5-fold higher risk when compared with white WVs.
- ~25% of WVs with DM have a HbA1c level greater than 9%.

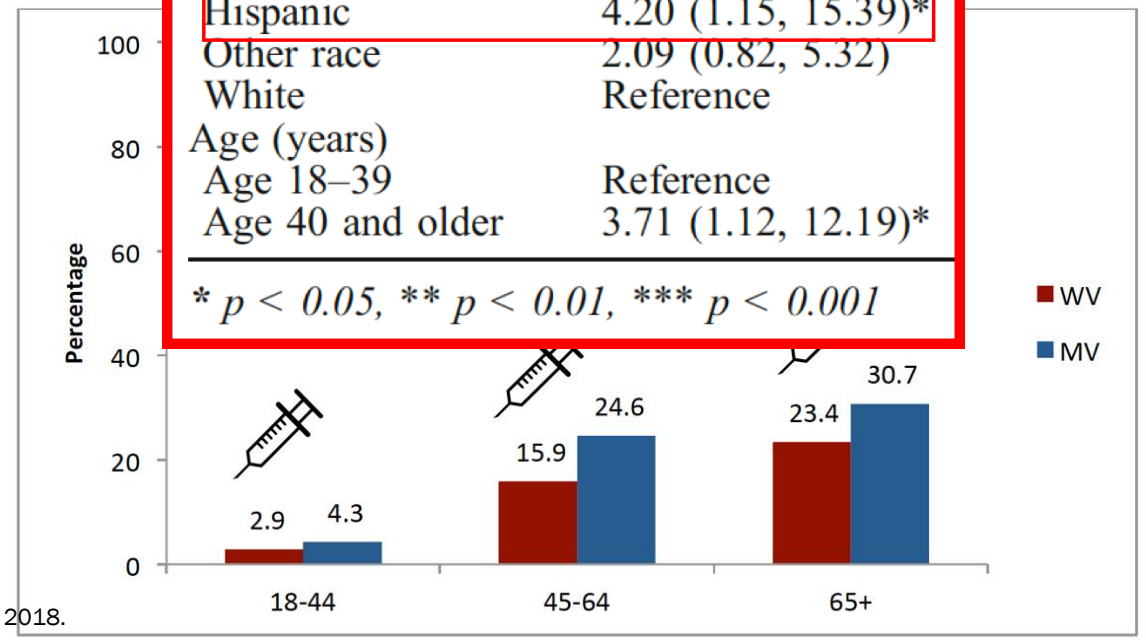
AHA Heart disease and Stroke statistics 2019

Population Group	Prevalence of Physician-Diagnosed DM, 2011–2014: Age ≥20 y
Both sexes	23 400 000 (9.1%)

	Diabetes OR (95 % CI)
Race/Ethnicity	
Black	2.58 (1.07, 6.21)*
Hispanic	4.20 (1.15, 15.39)*
Other race	2.09 (0.82, 5.32)
White	Reference
Age (years)	
Age 18–39	Reference
Age 40 and older	3.71 (1.12, 12.19)*

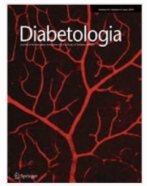
** $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$*

Figure 7. Pro … d age, FY14



Benjamin EJ, et al. Heart disease and stroke statistics-2018 update: a report from the AHA. Circulation. 2018.
Maher NH, et al. State of Cardiovascular Health in Women Veterans. Volume 2: Risk Factors, Diagnoses, and Procedures in Fiscal Year (FY) 2014. Vol 2. 2017
Klibourne AM, et al. J Women's Health. 2017. 26:1244-1251.
Rose et al. J Gen Intern Med. 2013;28 Suppl 2:S524–S528.

Gestational diabetes



Diabetologia
June 2019, Volume 62, Issue 6, pp 905–914 | Cite as

Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis

Authors | Authors and affiliations

Caroline K. Kramer, Sara Campbell, Ravi Retnakaran

(5,390,591 women)

The diagnosis of GDM identifies young women who have a twofold higher risk of cardiovascular events postpartum compared with their peers. This risk is not dependent upon intercurrent type 2 diabetes and is apparent within the first decade after pregnancy. Thus, even without progressing to type 2 diabetes, women with GDM comprise an at-risk population for CVD and hence a potential opportunity for early risk factor surveillance and risk modification.

Acta Diabetologica
April 2018, Volume 55, Issue 4, pp 315–322 | Cite as

Gestational diabetes and risk of cardiovascular disease up to 25 years after pregnancy: a retrospective cohort study

Authors | Authors and affiliations

Safyer McKenzie-Sampson, Gilles Paradis, Jessica Healy-Profitós, Frédérique St-Pierre, Nat

(1,070,667 women, 67,356 with GDM)

Women with gestational diabetes had a higher cumulative incidence of hospitalization for cardiovascular disease 25 years after delivery (190.8 per 1000 women) compared with no gestational diabetes (117.8 per 1000 women). Gestational diabetes was associated with a higher risk of ischemic heart disease (HR 1.23, 95% CI 1.12–1.36), myocardial infarction (HR 2.14, 95% CI 1.15–2.47), coronary angioplasty (HR 2.23, 95% CI 1.87–2.65), and coronary artery bypass graft (HR 3.16, 95% CI 2.24–4.47).

JAMA Internal Medicine | Original Investigation

Association of History of Gestational Diabetes With Long-term Cardiovascular Disease Risk in a Large Prospective Cohort of US Women

Deirdre K. Tobias, ScD; Jennifer J. Stuart, MSc; Shanshan Li, ScD; Jorge Chavarro, MD, ScD; Eric B. Rimm, ScD; Janet Rich-Edwards, ScD; Frank B. Hu, MD, PhD; JoAnn E. Manson, MD, DrPH; Cuilin Zhang, MD, PhD, MPH

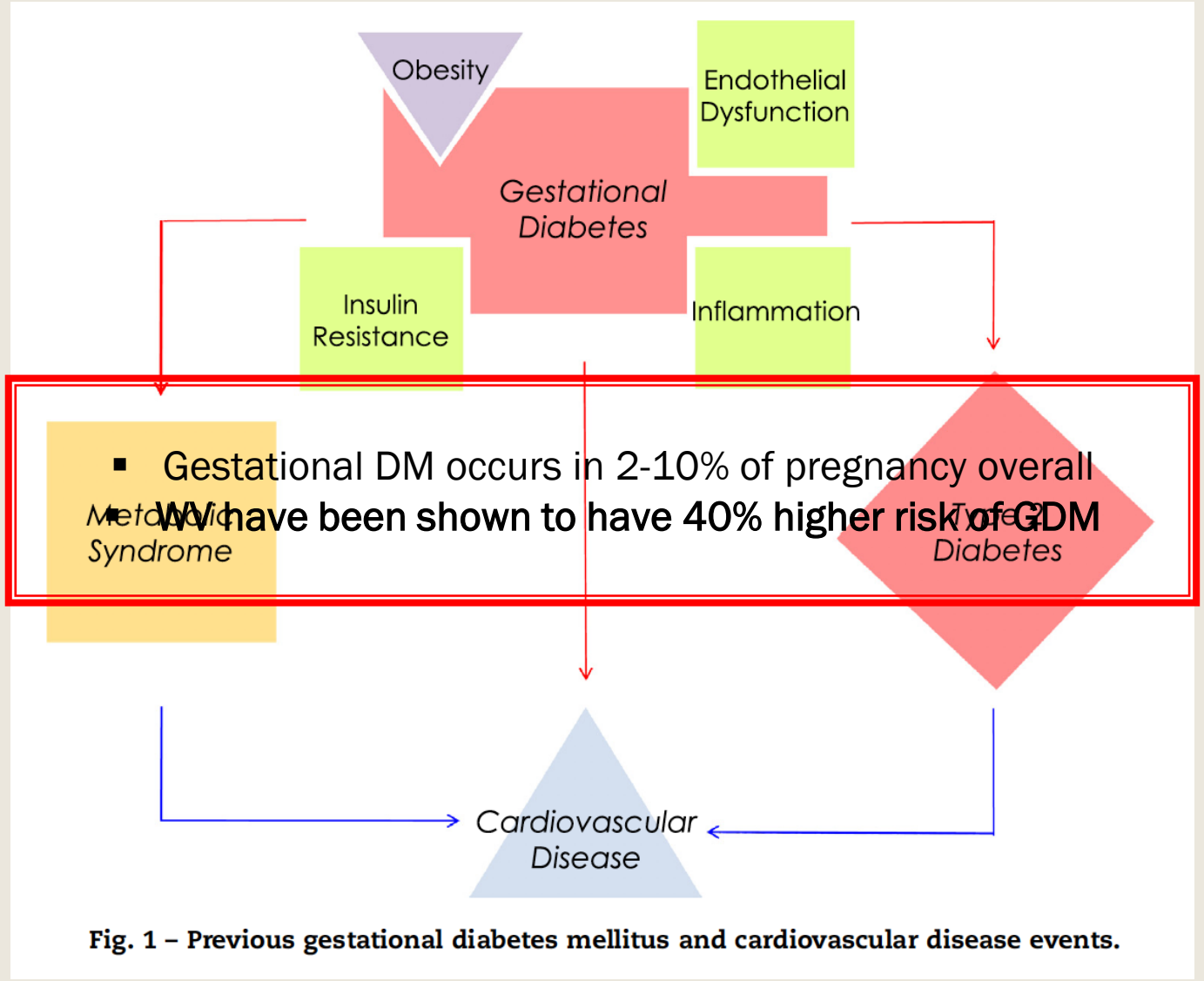
(89,479 women, 5292 with GDM)

Table 2. History of GD and Long-term Risk of Cardiovascular Disease Among 89 479 Parous US Women in the Nurses' Health Study II Cohort, 1989-2015

Characteristic	HR (95% CI)		P Value
	No History of GD	History of GD	
Total CVD			
Events, No.	1079	82	
Person-years, No.	976 307	60 050	
Incidence rate, per 1000 person-years	1.10	1.37	
Age-adjusted	1 [Reference]	1.60 (1.26-2.04)	<.001
Multivariable model[a]	1 [Reference]	1.43 (1.12-1.81)	.004
Multivariable model + current lifestyle factors[b]	1 [Reference]	1.29 (1.01-1.65)	.04

Gestational Diabetes:

- Combination of factors
  - *Obesity*
  - *Endothelial Dysfxn*
    - Impaired endothelium-dependent vasodilation
    - Impaired coronary flow reserve (microvascular dyfxn)
    - Increased CIMT
  - *Insulin resistance*
  - *Inflammation*
    - Higher hsCRP
- Subsequent weight gain
- Lack of healthy lifestyle



- Gestational DM occurs in 2-10% of pregnancy overall
- W/ have been shown to have 40% higher risk of GDM

Fig. 1 – Previous gestational diabetes mellitus and cardiovascular disease events.

Di Cianni G. Diabetes Research & Clinical Practice. 2108. 145: 184-192.
Katon J et al. J of Womens Health. 2013:23 (10): 792-800

Hypertension prevalence

- Nearly **40% of WVs between the ages of 45 to 65 have hypertension.**
  - *After age 85, more WVs than MVs have hypertension*
- Like black civilian women (46.3%), **black WVs have the highest prevalence** compared with all veterans of any race or age
  - *Except black MVs have the highest prevalence overall*
- Black WVs were found to have **2.3 times higher odds of having hypertension** than white WVs
- Hypertension control in WVs has also been found to be significantly worse

	Hypertension OR (95 % CI)
Race/Ethnicity	
Black	2.31 (1.10, 4.83)*
Hispanic	0.21 (0.07, 0.64)**
Other race	1.44 (0.68, 3.05)
White	Reference
Age (years)	
Age 18–39	Reference
Age 40 and older	6.51 (3.08, 13.78)***

** $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$*

Benjamin EJ, et al. Heart disease and stroke statistics-2018 update: a report from the AHA. Circulation. 2018.
Maher NH, et al. State of Cardiovascular Health in Women Veterans. Volume 2: Risk Factors, Diagnoses, and Procedures in Fiscal Year (FY) 2014. Vol 2. 2017
Rose et al. J Gen Intern Med. 2013;28 Suppl 2:S524–S528.

Hypertensive disorders of pregnancy

- Hypertensive disorders of pregnancy have been shown to be a women specific CVD risk factor
  - *Gestational HTN*
  - *Preeclampsia*
  - *Chronic HTN*
  - *Chronic HTN + preeclampsia*
- Associated with a 2 – 8 fold risk for development of future CVD

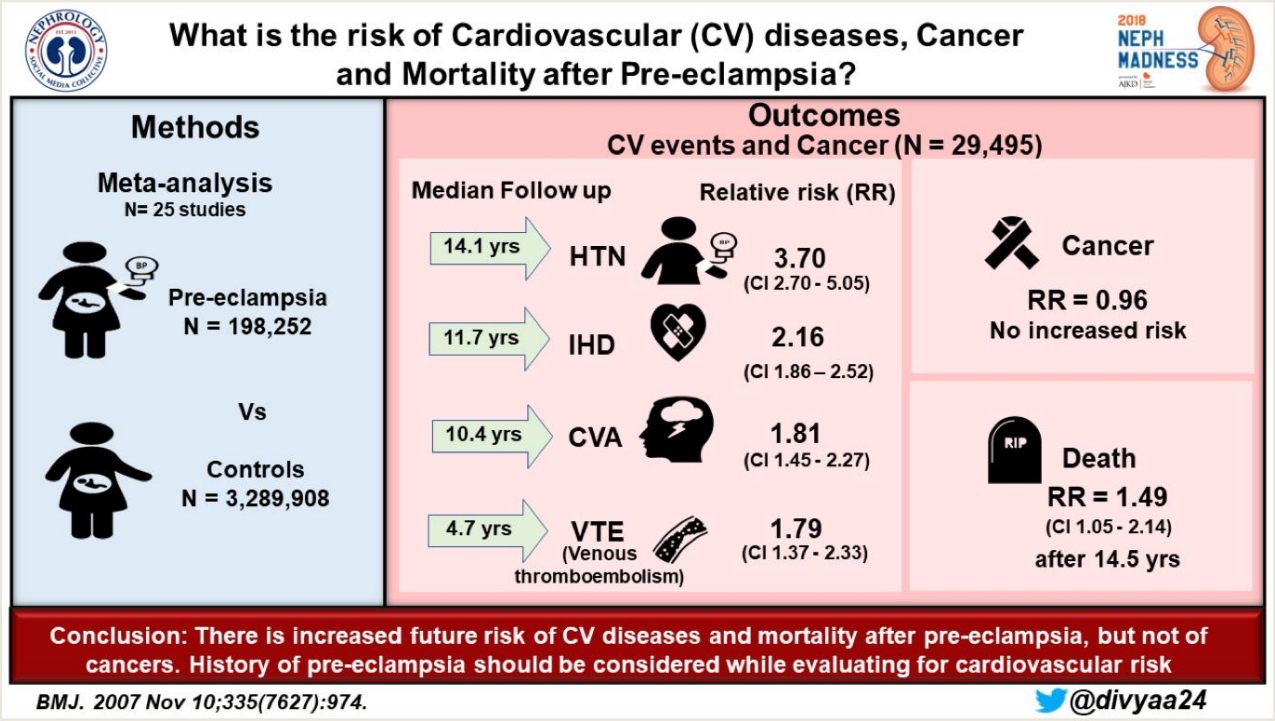
All Hypertensive Disorders of Pregnancy Increase the Risk of Future Cardiovascular Disease

Jane Tooher ✉, Charlene Thornton, Angela Makris, Robert Ogle, Andrew Korda, and Annemarie Hennessy

Originally published 11 Sep 2017 | https://doi.org/10.1161/HYPERTENSIONAHA.117.09246 | Hypertension. 2017;70:798–803

Table 1. The Adjusted OR of Admissions for Future Disease for Women With Preeclampsia, Gestational Hypertension, and All Women With HDP Compared With Women Who Remained Normotensive

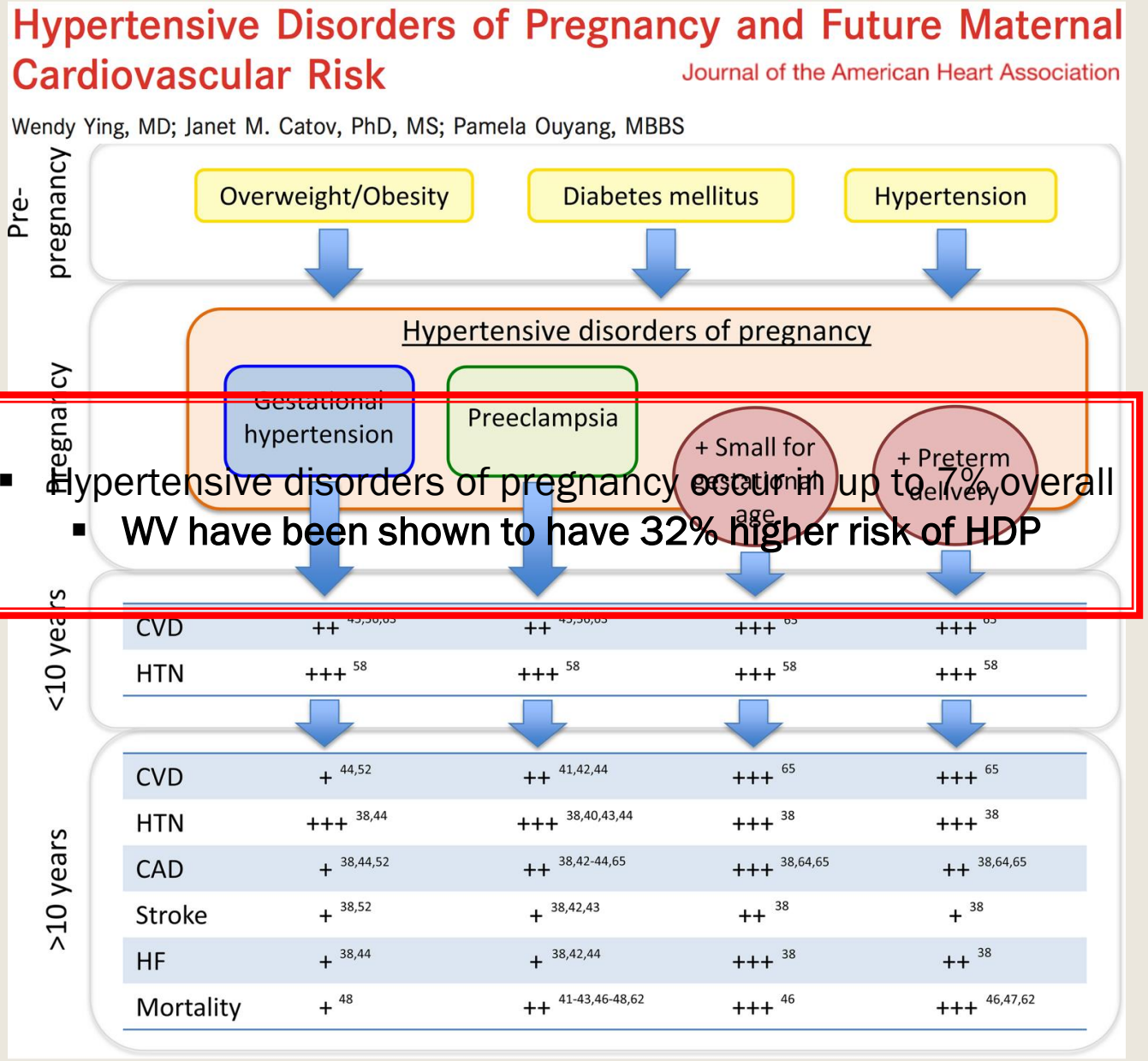
Future Disease	Preeclampsia, OR (95% CI)*	Gestational Hypertension, OR (95% CI)*	All HDP, OR (95% CI)†
Future hypertension	3.06(2.18–4.29)	4.08 (3.23–5.10)	2.78 (2.47–3.13)
Ischemic heart disease	2.67 (1.49–4.81)	3.19 (2.11–4.83)	2.16 (1.98–3.84)
Stroke	2.03 (0.75–5.49)	0.57 (0.14–2.31)	1.94 (1.39–2.69)
Renal disease	4.74 (2.19–10.20)	3.45 (1.74–6.85)	2.76 (1.98–3.84)



Ying W, et al. J Am Heart Assoc. 2018;7:e009382
Tooher J, et al. Hypertension. 2017;70:798-803
Hypertension in Pregnancy. ACOG. 2013: 122 (5): 122-131.
Katon J et al. J of Womens Health. 2013:23 (10): 792-800

Hypertensive disorders of pregnancy

- **Pre-pregnancy risk factors**
  - *50% of the association between HDP and later life BP, BMI, lipid levels*
- **Inflammation & lipid-laden macrophages** in preeclamptic vascular insufficient placentas ~ early stage atherosclerotic plaques.
  - *?early expression of susceptibility to vascular impairments later in life*
- ?? **Persistent endothelial dysfunction**??
  - *elevated markers of endothelial dysfunction, arterial stiffness, & systemic inflammation up to 8 years after preeclampsia*



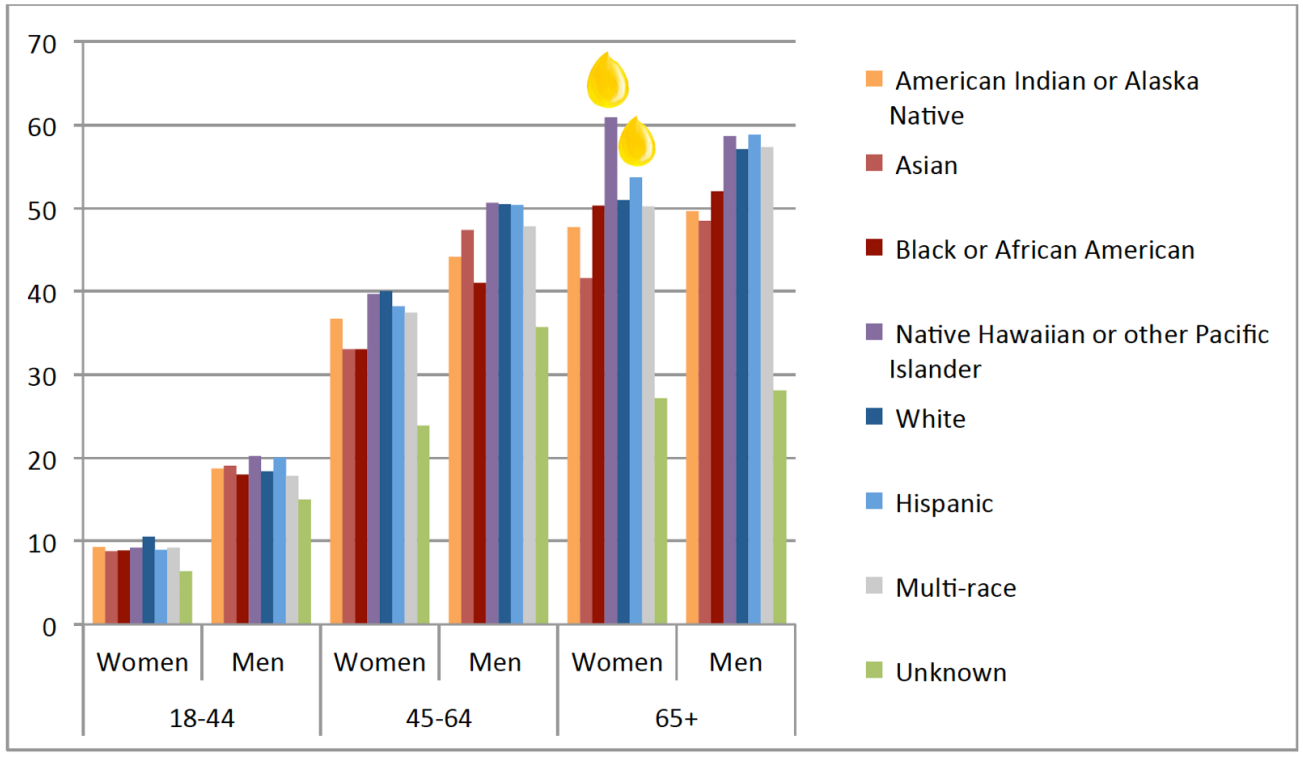
- Hypertensive disorders of pregnancy occur in up to 7% overall
  - WV have been shown to have 32% higher risk of HDP

Ying W, et al. J Am Heart Assoc. 2018;7:e009382
Katon J et al. J of Women's Health. 2013:23 (10): 792-800

Dyslipidemia prevalence

- ~50% of all veterans have a diagnosis of dyslipidemia
- WVs have lower prevalence of dyslipidemia than MVs: 27% vs 47%
- **Even /worse after age 65:**
  - *51% of WVs are affected vs 56% of MVs*
  - *Hispanic and Pacific Islander WVs > 65 years old have a prevalence of > 50 & 60%.*
- **Higher in those with mental illness / substance use**
  - *40% of those with depression*
  - *45% of those in tobacco cessation treatment*
- **WV have poorer control of lipids than MV**

Figure 6. Proportion of Veterans with a diagnosis of dyslipidemia by gender, age, and race/ethnicity, FY14



Maher NH, et al. State of Cardiovascular Health in Women Veterans. Volume 2: Risk Factors, Diagnoses, and Procedures in Fiscal Year (FY) 2014. Vol 2. 2017
Goldstein KM, et al. Women's Health Issues. 2014:24-5: 477–483

Tobacco use:

- Veterans have higher rates of tobacco use than the general population (29.2% vs 15.5%)
- **More WVs smoke cigarettes than MVs** (28.9% vs 21.1%)
- **More WVs use tobacco compared with civilian women** (29.7% vs 13.5%)
- Hispanic WVs use tobacco nearly 3.5 times more than white WVs
- WVs are less likely to be successful at quitting smoking than MVs

Characteristic	Cigarettes % (95% CI)	Any tobacco product¶ % (95% CI)
Overall (n = 13,140)	**21.6 (20.7–22.6)**	**29.2 (28.1–30.2)**
Sex		
Male	21.1 (20.1–22.1)†	29.1 (28.0–30.2)
Female	28.9 (25.3–32.5)†	29.7 (26.1–33.3)
Veterans (n = 13,140)		
18–25 (male)	50.2 (45.8–54.5)†	61.7 (57.4–66.0)†
18–25 (female)	36.4 (28.8–44.0)†	37.9 (30.2–45.5)†
26–34 (male)	45.5 (41.6–49.5)†	55.9 (51.9–59.8)†
26–34 (female)	35.2 (28.2–42.3)†	37.4 (30.3–44.5)†
35–49 (male)	31.5 (29.2–33.7)†	44.8 (42.3–47.2)†
35–49 (female)	31.5 (26.3–36.7)†	32.7 (27.5–38.0)†
≥50 (male)	17.0 (15.8–18.1)	23.7 (22.5–25.0)
≥50 (female)	24.8 (18.8–30.8)†	24.9 (10.9–30.9)†
Nonveterans (n = 224,648)		
18–25 (male)	35.3 (34.7–35.9)†	45.3 (44.7–45.9)†
18–25 (female)	26.0 (25.5–26.5)†	28.8 (28.3–29.3)†
26–34 (male)	36.3 (35.3–37.3)†	45.2 (44.2–46.3)†
26–34 (female)	26.7 (25.9–27.5)†	28.3 (27.5–29.1)†
35–49 (male)	26.3 (25.5–27.1)†	35.6 (34.7–36.4)†
35–49 (female)	23.0 (22.3–23.6)†	23.8 (23.2–24.4)†
≥50 (male)	18.1 (17.2–18.9)	25.1 (24.2–26.1)
≥50 (female)	14.8 (14.2–15.3)†	15.4 (14.8–16.0)†

Odani S, et al. Tobacco productuse among military veterans - United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2018;67:7–12.
Jamal A, et al. Currentcigarette smoking among adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67:53–59. doi: 10.15585/mmwr.mm6702a1

Why ↑ CVD risk factors?

Not fully understood & likely multifactorial!

WV have been found to have suboptimal health literacy

WVs do not exercise regularly

- Even when enrolled in weight management programs, WVs lose less weight than MVs

- Due to ↑ rates of military sexual trauma, less willing to join male-dominated VA weight-loss programs

↓ enrollment rates into smoking cessation programs (despite tailoring programs to WVs needs - providing multiple choices of programs, tools, & support based on WVs' input)

Compared to MV, WV are:

- less willing to take lipid-lowering medications
- 12% & 20% less likely to receive *any* statin therapy / be on a high-intensity statin for 1* prevention
- Rx'd significantly less high-intensity statins for 2* prevention (28.7% vs 35%)

Compared to MV, WV:

- less social support to help track medications
- less likely to have someone accompany them to medical visits
- more likely to be homeless

↑ rates of mental health disorders (anxiety, depression, PTSD) may also play a role

WV may be less willing to seek care at VA in general due to sexual harassment from MVs

International Journal of Preventive Medicine
Wolters Kluwer -- Medknow Publications

Veterans and Risk of Heart Disease in the United States: A Cohort with 20 Years of Follow Up

Shervin Assari

- 8375 pts >50
- Followed Q2y x 20y
- Veteran status = independent RF for CVD (RR 1.5-2.0)

	RR	95% CI	P
Model I			
Veteran status	1.996	1.694-2.351	<0.001
Model II			
Veteran status	1.481	1.194-1.837	<0.001
Black	0.881	0.654-1.185	0.402
Female gender	0.581	0.469-0.720	<0.001
Age	1.03	1.015-1.046	<0.001
Education years	0.988	0.963-1.015	0.379
Marital status			0.002
Never married	4.357	1.002-18.945	0.05
Divorced	2.204	1.294-3.752	0.004
Model III			
Veteran status	1	1.207-1.865	<0.001
Black		5.073	0.133
Female gender			<0.001
Age			
Education years			
Marital status			
Never married	4.914		
Divorced	2.306	1.347-	
Diabetes	1.490	1.086-2.046	
Hypertension	1.729	1.461-2.045	<0.001
Model IV			
Veteran status	1.505	1.210-1.872	<0.001
Black	0.785	0.581-1.060	0.115
Female gender	0.61	0.490-0.759	<0.001
Age	1.029	1.013-1.045	<0.001
Education years	1.000	0.972-1.028	0.976
Marital status			0.001
Never married	5.043	1.165-21.832	0.03
Divorced	2.272	1.326-3.894	0.003
Diabetes	1.502	1.091-2.067	0.013
Hypertension	1.743	1.472-2.064	<0.001
Smoking	1.289	1.050-1.582	0.015
Drinking	0.963	0.807-1.149	0.677
Exercise	1.095	1.024-1.171	0.008

RR=Relative risk, CI=Confidence interval

	RR	95% CI	P
Model V			
Veteran status	1.504	1.209-1.871	<0.001
Black	0.744	0.550-1.007	0.056
Female gender	0.623	0.500-0.775	<0.001
Age	1.03	1.014-1.046	<0.001
Education years	1.003	0.976-1.031	0.818
Marital status			0.001
Never married	5.51	1.268-23.949	0.023
Divorced	2.301	1.341-3.947	0.002
Diabetes	1.422	1.031-1.962	0.032
Hypertension	1.645	1.384-1.954	<0.001
Smoking	1.339	1.090-1.647	0.006
Drinking	0.973	0.815-1.161	0.758
Exercise	1.077	1.006-1.152	0.032
	1.032	1.013-1.051	0.001
		1.176-1.871	0.001
		525-0.995	0.047
		.465-0.740	<0.001
		1.019-1.052	<0.001
Education		0.980-1.040	0.517
Marital status			0.001
Never married	5.982	1.369-26.136	0.017
Divorced	2.429	1.364-4.325	0.003
Diabetes	1.451	1.042-2.021	0.028
Hypertension	1.599	1.335-1.915	<0.001
Smoking	1.461	1.177-1.814	0.001
Drinking	1	0.831-1.205	0.996
Exercise	1.059	0.986-1.138	0.118
BMI	1.034	1.014-1.054	0.001
Depression	1.084	1.027-1.143	0.003

RR=Relative risk, BMI=Body mass index, CI=Confidence interval

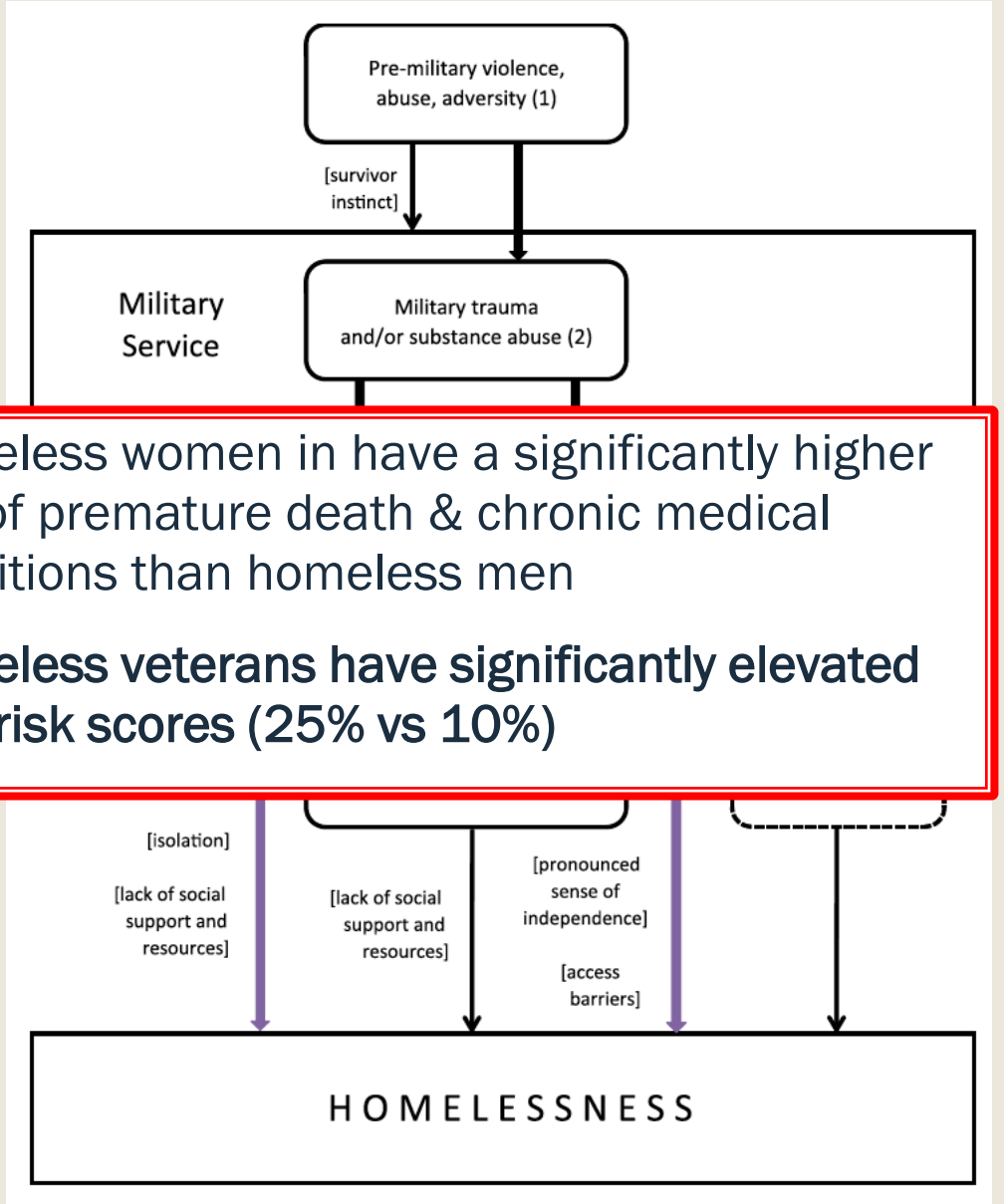
Veteran status – per se– may be a risk factor for CVD

STEALTHY ASSASSINS:

Non-Traditional Cardiovascular Risk Factors in Women Veterans

Homelessness

- WVs have a 4-fold increased risk of homelessness vs civilian women
- **Web of Vulnerability**
  - *abuse or violence prior to, during, or after military service*
  - *postmilitary physical or mental illness /substance abuse*
  - *unemployment*
  - *criminal justice involvement*
  - *MST*
- → sense of isolation / lack of support → poor overall health outcomes
- 30% of homeless WVs live >40 miles from a VA medical center
  - *Rural homeless WVs ~ 107 miles from a VA specialty center, further increasing their barrier to subspecialty care*

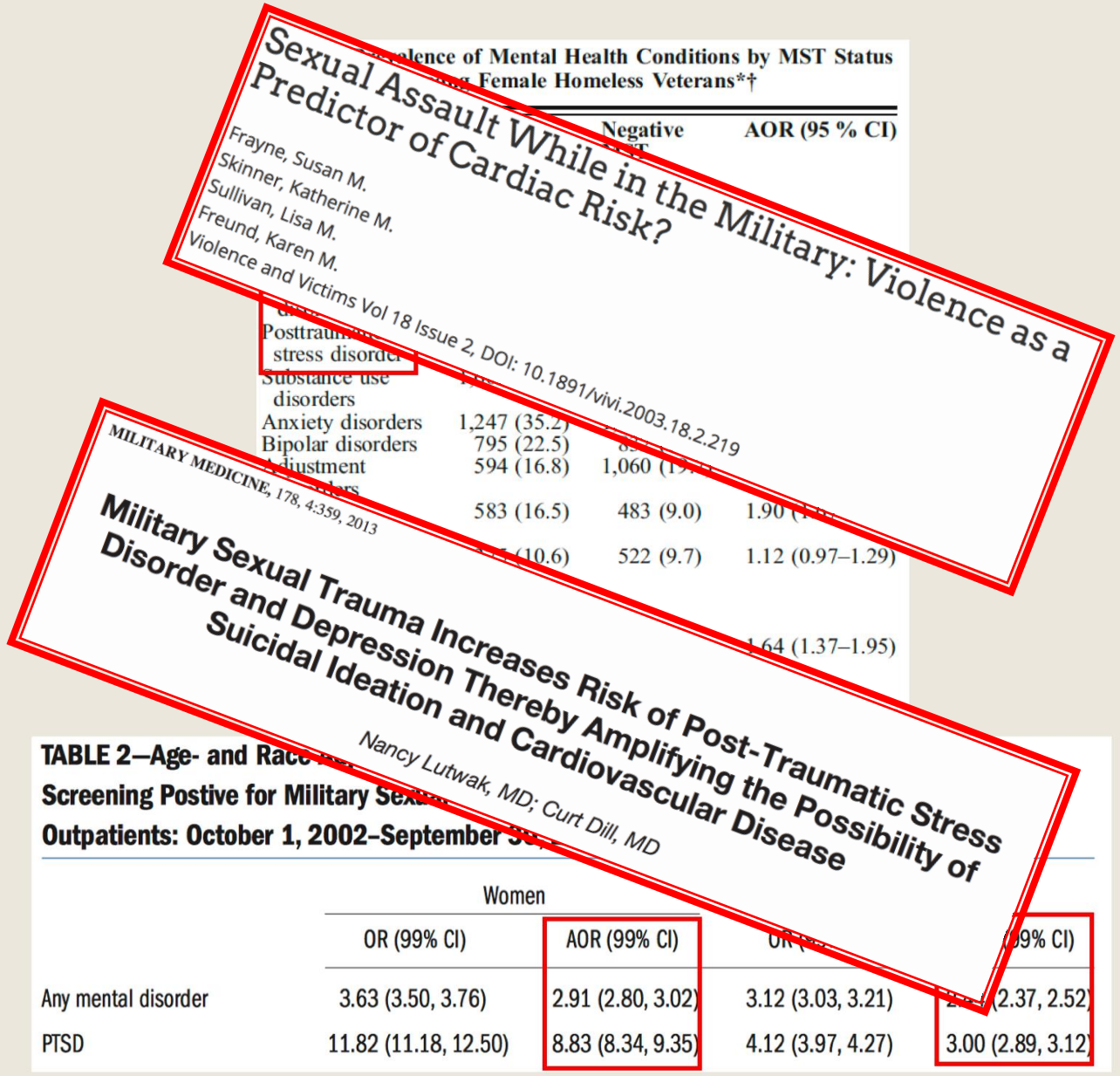


- Homeless women in have a significantly higher risk of premature death & chronic medical conditions than homeless men
- **Homeless veterans have significantly elevated CVD risk scores (25% vs 10%)**

Hamilton AB et al. Women's Health Issues. 2011: 21-4S: S203–S209
Montgomery AE et al. Womens Health Issues. 2017;27:256–263.
Gozdzik A et al. BMC Public Health. 2015;15:1

Military sexual trauma

- **WVs experience more sexual assault than civilian women.**
  - *30-40% (range 20-68%) of WVs report having been sexually assaulted while in the military*
  - *17% of civilian women*
- **Homeless WVs have a higher rate of MST than housed WV** (40 - 53.3% vs 26.8%)
- **25% of WVs experience stranger harassment in VHA** care environments
  - *3x ↑er rate in WV with a history of MST, increasing their risk for delayed or missed healthcare*
- WVs with MST have:
  - *↑ risk of DM, HTN, & obesity*
  - *↑ heart rates, ↑ heart rate variability*
  - *2-fold greater risk of depression*
  - *6 to 9-fold increased risk of PTSD*



Wolff K, et al. Military Medicine. 2016; 181(8):840
Kimmerling et al. *Am J Public Health.* 2007;97:2160–2166
Pavao et al. J Gen Intern Med 28(Suppl 2):S536–41

Depression & PTSD

- Overall, Veterans have higher rates of mental illnesses, particularly depression and PTSD, than the general US population.
  - *In Vietnam-era veterans, the estimated lifetime prevalence of PTSD was approximately 30%*
  - *In 2015, post-9/11 veterans evaluated at a VA facility:*
    - 45% had depression
    - 56% had PTSD
- WVs are more likely than MV to have a diagnosis of **depression or PTSD** (31.6% vs 11.8%)
- **More WVs have depression** than civilian women (8.5%)
- **More WVs (17.0%) have PTSD** than MVs (12.3%) and civilian women (5.2%)
- Notably, PTSD and depression in WVs stems not only from experiencing violence in combat but also significant MST exposure

Figure 11. Proportion of Veterans with a diagnosis of depression by gender and age, FY14

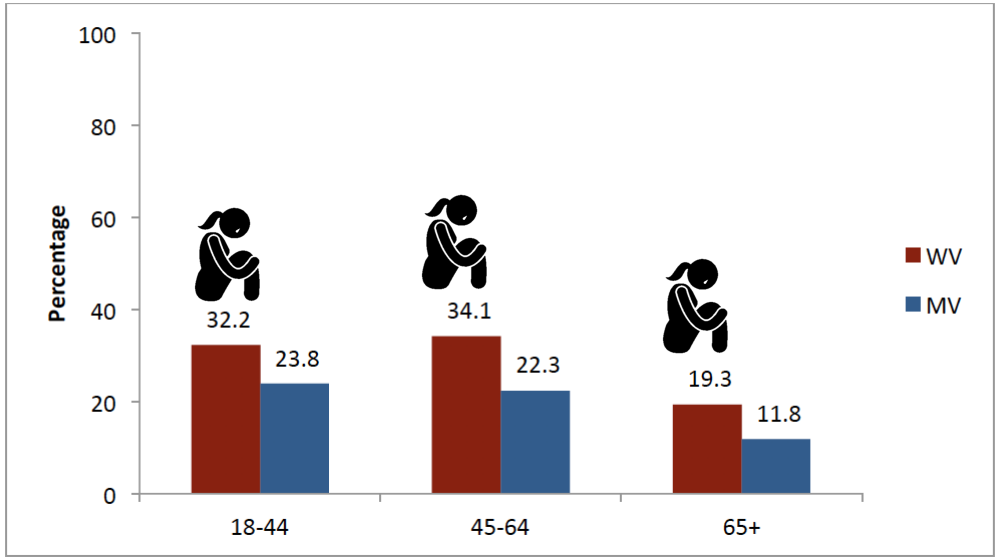
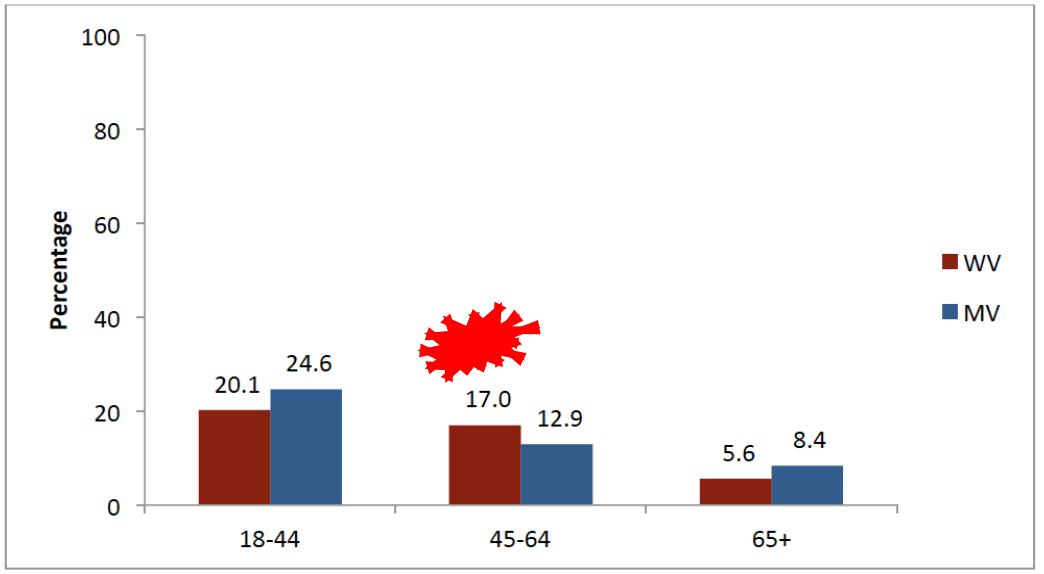


Figure 13. Proportion of Veterans with a diagnosis of PTSD by gender and age, FY14



Kulka R, et al. Trauma and the Vietnam War Generation: Report of Findings from the Vietnam Readjustment Study. Brunner Mazel Publishers: New York, New York; 1990.
Maher NH, et al. State of Cardiovascular Health in Women Veterans. Volume 2: 2017
National Institutes of Mental Health. Statistics. www.nimh.nih.gov/statistics/index.shtml.

Depression, PTSD, MST & CVD

- Young women with depression, have been shown to have significantly ↑ risk of CAD, death, / major adverse cardiovascular events (MACE)
- Study of 157 195 WVs showed that those with depression had a 60% increased CAD risk, similar to that of smoking
- The odds of having of CAD increased by another 44% with every additional mental health diagnosis
- Associations between trauma/PTSD are also starting to be seen

Table 3. Adjusted Hazard Ratios (95% Confidence Intervals) for the Association of Trauma Exposure and PTSD Symptoms With Risk of Incident MI and Stroke, 1989 to 2009

	MI(n=277)	Stroke(n=271)
No trauma exposure	1.00	1.00
Trauma/no symptoms	1.96* (1.38–2.78)	1.09 (0.80–1.50)
Trauma/1–3 symptoms	1.11 (0.68–1.81)	0.93 (0.59–1.44)
Trauma/4+ symptoms	1.58 (1.02–2.46)	1.64 (1.12–2.39)

MI indicates myocardial infarction; and PTSD, posttraumatic stress disorder.

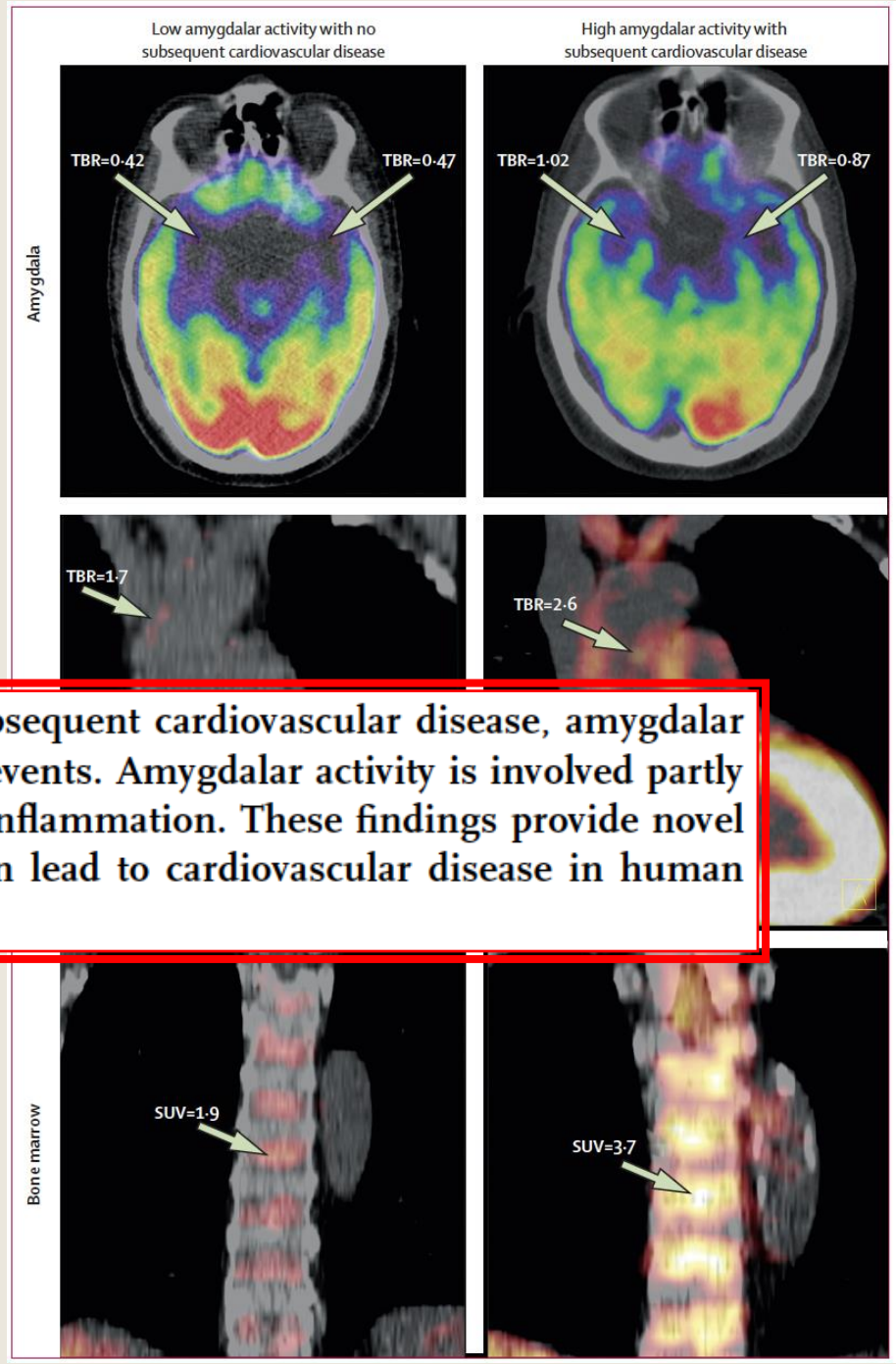
*Adjusted for age, race/ethnicity, parental education, maternal and paternal history of MI or stroke, and age 5 somatotype.

Shah A. J Am Heart Assoc. 2014;3:e000741
Sumner JA, et al. Circulation. 2015;132:251–259

Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study

Ahmed Tawakol, Amorina Ishai*, Richard AP Takx, Amparo L Figueroa, Abdelrahman Ali, Yannick Kaiser, Quynh A Truong, Chloe JE Solomon, Claudia Calcagno, Venkatesh Mani, Cheuk Y Tang, Willem JM Mulder, James W Murrough, Udo Hoffmann, Matthias Nahrendorf, Lisa M Shin, Zahi A Fayad†, Roger K Pitman†*

Amygdalar activity is upregulated in conditions marked by stress, such as PTSD, & depression



- 293 patients
- [illegible]
- [illegible]
- [illegible]
- [illegible]
  - ↑ *bone-marrow activity (p<0.0001)*
  - ↑ *arterial inflammation (p<0.0001)*
  - ↑ *risk of cardiovascular disease events (p<0.0001)*

Interpretation In this first study to link regional brain activity to subsequent cardiovascular disease, amygdalar activity independently and robustly predicted cardiovascular disease events. Amygdalar activity is involved partly via a path that includes increased bone-marrow activity and arterial inflammation. These findings provide novel insights into the mechanism through which emotional stressors can lead to cardiovascular disease in human beings.

Tawakol, A. et al. Lancet 2017; 389: 834–45

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 25, 2019

PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

Stress-Associated Neurobiological Pathway Linking Socioeconomic Disparities to Cardiovascular Disease

Ahmed Tawakol, MD,[a,b] Michael T. Osborne, MD,[a,b] Ying Wang, MD, PhD,[b,c] Basma Hammed, MD,[b] Brian Tung, MS,[b] Tomas Patrich, BA,[b] Blake Oberfeld, BS,[b] Amorina Ishai, MD,[b] Lisa M. Shin, PhD,[d] Matthias Nahrendorf, MD,[e] Erica T. Warner, ScD,[f] Jason Wasfy, MD,[a] Zahi A. Fayad, PhD,[g] Karestan Koenen, PhD,[h] Paul M Ridker, MD,[i] Roger K. Pitman, MD,[j] Katrina A. Armstrong, MD[k]

ABSTRACT

BACKGROUND Lower socioeconomic status (SES) associates with a higher risk of major adverse cardiac events (MACE) via mechanisms that are not well understood.

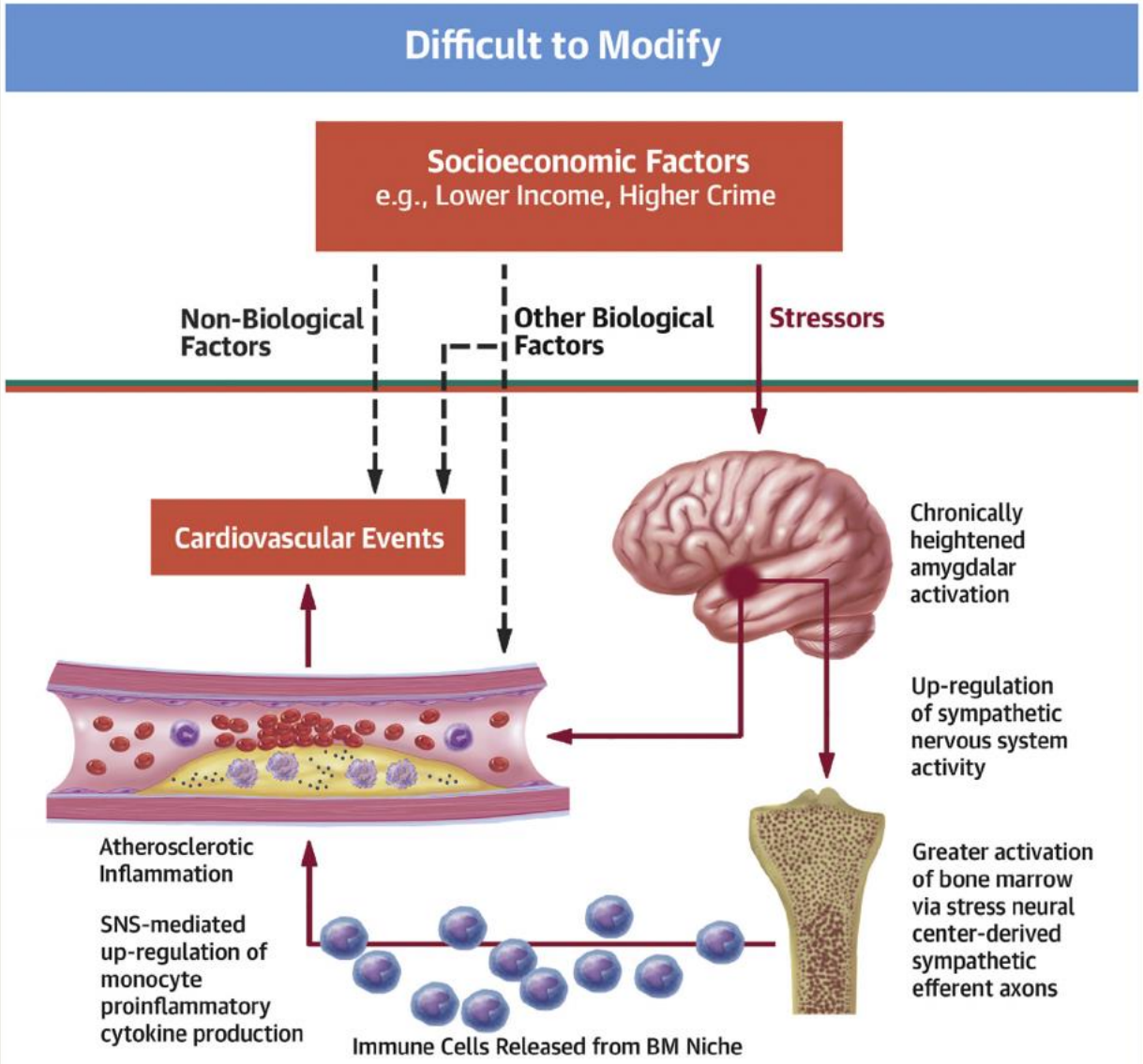
OBJECTIVES Because psychosocial stress is more prevalent among those with low SES, this study tested the hypothesis that stress-associated neurobiological pathways involving up-regulated inflammation in part mediate the link between lower SES and MACE.

METHODS A total of 509 individuals, median age 55 years (interquartile range: 45 to 66 years), underwent clinically indicated whole-body ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography imaging and met pre-defined inclusion criteria, including absence of known cardiovascular disease or active cancer. Baseline hematopoietic tissue activity, arterial inflammation, and in a subset of 289, resting amygdalar metabolism (a measure of stress-associated neural activity) were quantified using validated ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography methods. SES was captured by neighborhood SES factors (e.g., median household income and crime). MACE within 5 years of imaging was adjudicated.

RESULTS Over a median 4.0 years, 40 individuals experienced MACE. Baseline income inversely associated with amygdalar activity (standardized β: −0.157 [95% confidence interval (CI): −0.266 to −0.041]; $p = 0.007$) and arterial inflammation (β: −0.10 [95% CI: −0.18 to −0.14]; $p = 0.022$). Further, income associated with subsequent MACE (standardized hazard ratio: 0.67 [95% CI: 0.47 to 0.96]; $p = 0.029$) after multivariable adjustments. Mediation analysis demonstrated that the path of: ↓ neighborhood income to ↑ amygdalar activity to ↑ bone marrow activity to ↑ arterial inflammation to ↑ MACE was significant (β: −0.01 [95% CI: −0.06 to −0.001]; $p < 0.05$).

CONCLUSIONS Lower SES: 1) associates with higher amygdalar activity; and 2) independently predicts MACE via a serial pathway that includes higher amygdalar activity, bone marrow activity, and arterial inflammation. These findings illuminate a stress-associated neurobiological mechanism by which SES disparities may potentiate adverse health outcomes. (J Am Coll Cardiol 2019;73:3243-55) © 2019 by the American College of Cardiology Foundation.

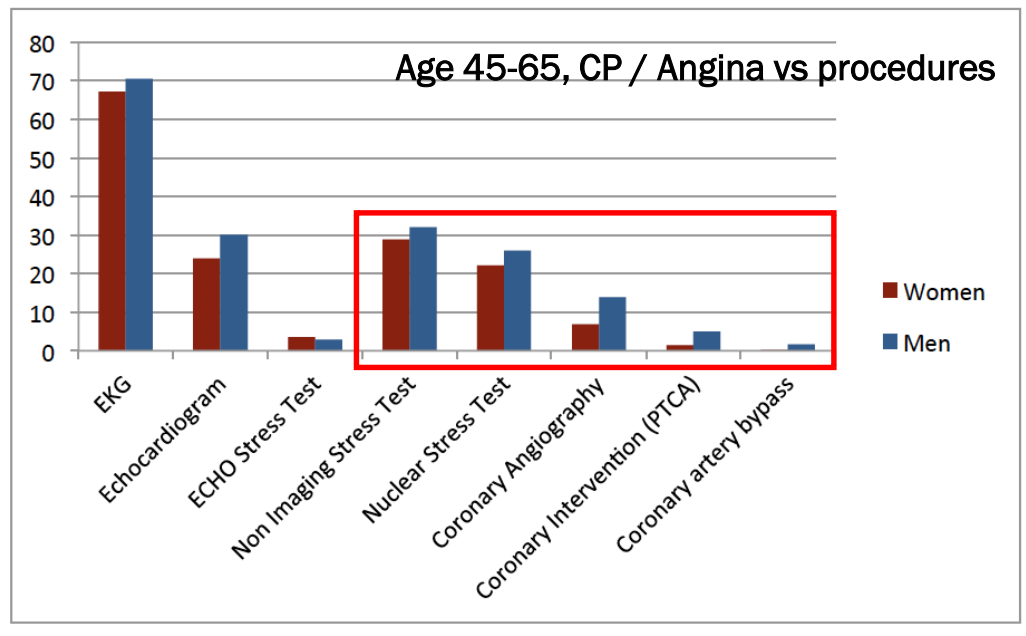
CENTRAL ILLUSTRATION A Model of Lower Socioeconomic Status Leading to Major Adverse Coronary Events

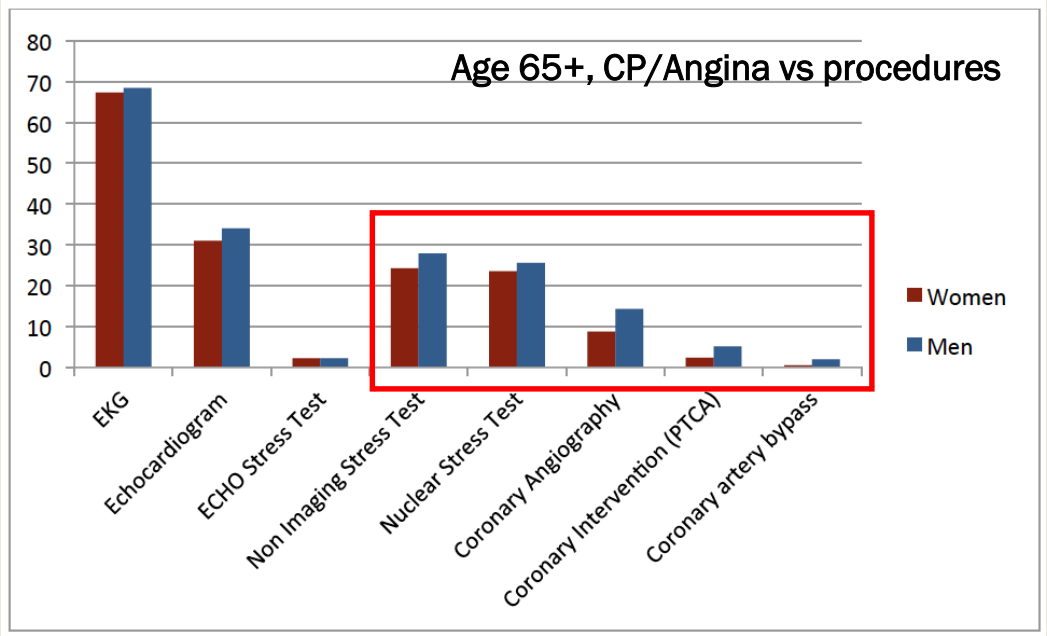


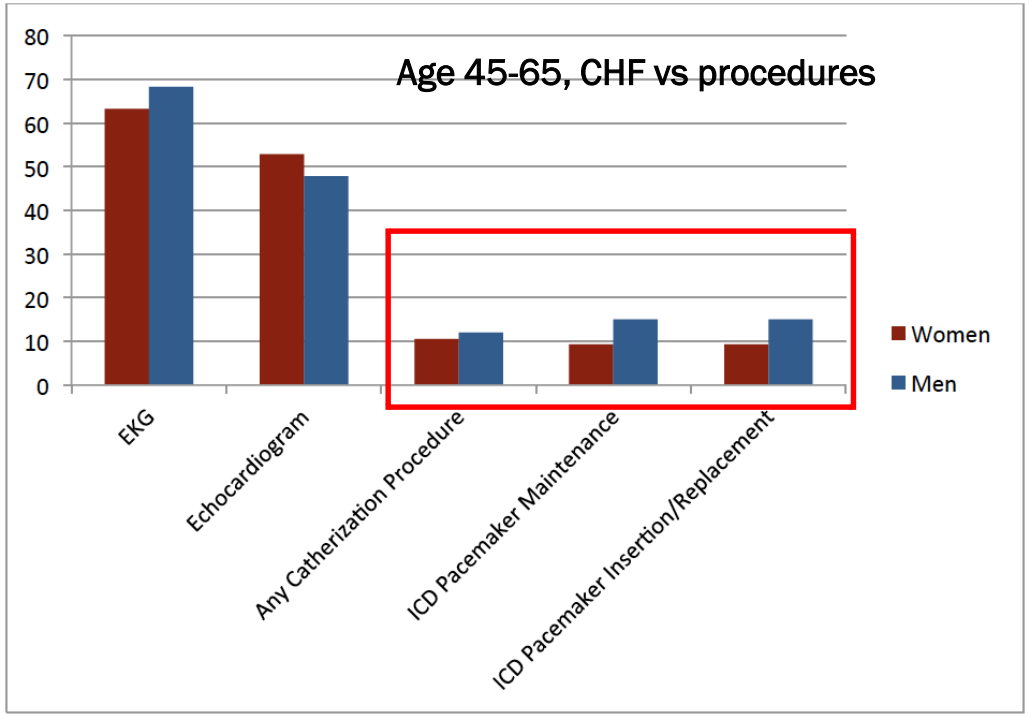
Tawakol, A. et al. J Am Coll Cardiol. 2019;73(25):3243-55.

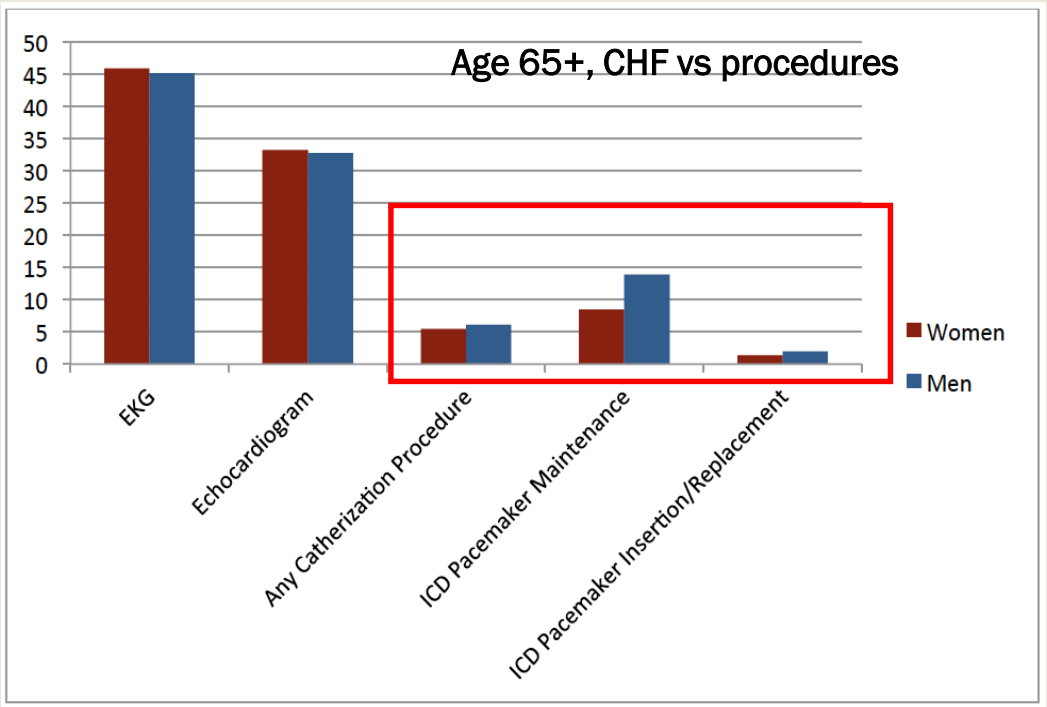
INTO THE BREACH:

Treatment of Cardiovascular Disease in Women Veterans









Maher NH, et al. State of Cardiovascular Health in Women Veterans. Volume 2: (FY) 2014. 2017

Characteristics and Outcomes of Women Veterans Undergoing Cardiac Catheterization in the Veterans Affairs Healthcare System

Insights from the VA CART Program

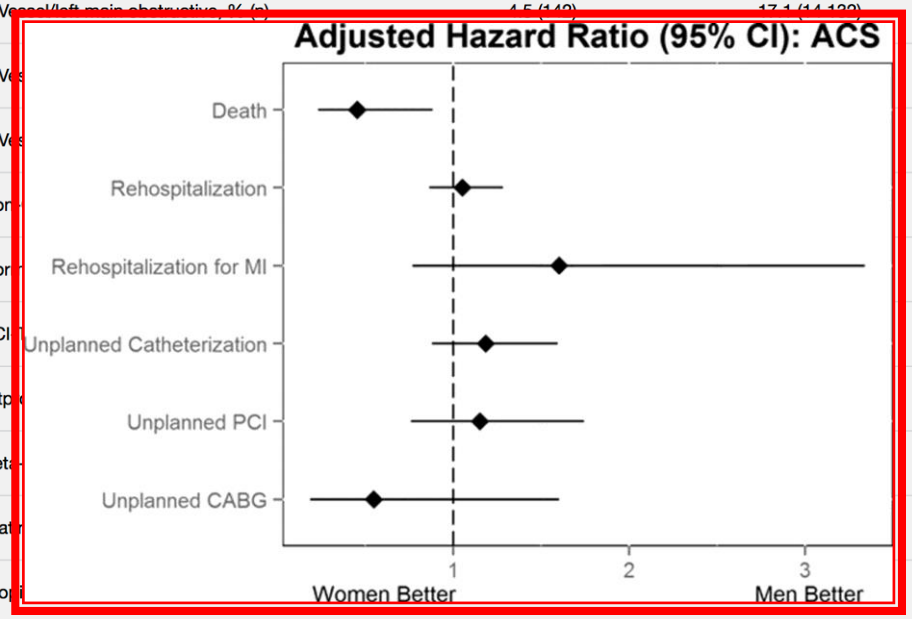
Circulation:
Cardiovascular Quality and Outcomes

Melinda B. Davis, Thomas M. Maddox, Paula Langner, Mary E. Plomondon, John S. Rumsfeld, and Claire S. Duvernoy

Originally published 24 Feb 2015 | https://doi.org/10.1161/CIRCOUTCOMES.114.001613 | Circulation: Cardiovascular Quality and Outcomes. 2015;8:S39–S47

Table 3. Coronary Anatomy, Postprocedural Medications, and Unadjusted Outcomes

	Women (N=3181)	Men (N=82 755)	*P* Value
Coronary anatomy and treatment			
3-V[illegible]	4.5 (143)	17.1 (14 139)	<0.0001
2-V[illegible]			<0.0001
1-V[illegible]			<0.0001
Non[illegible]			0.0563
Non[illegible]			<0.0001
PCI[illegible]			<0.0001
Postp[illegible]			
Bet[illegible]			<0.0001
Stat[illegible]			<0.0001
Clop[illegible]			<0.0001
Long-acting Nitrate, % (n)	24.1 (768)	31.3 (25 902)	<0.0001
Calcium channel blocker, % (n)	23 (733)	22.9 (18 974)	0.8795

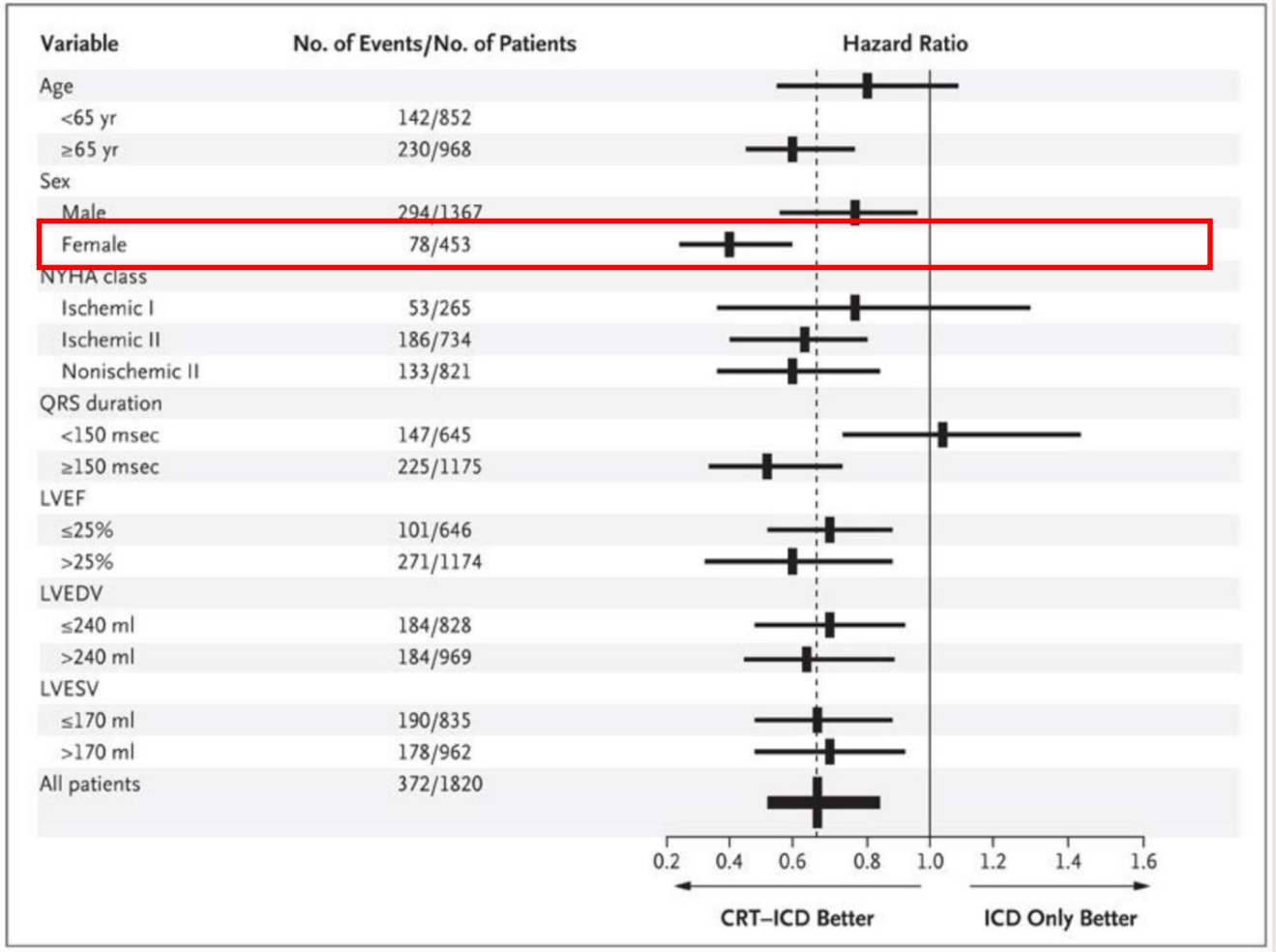


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events

Arthur J. Moss, M.D., W. Jackson Hall, Ph.D., David S. Cannom, M.D., Helmut Klein, M.D., Mary W. Brown, M.S., James P. Daubert, M.D., N.A. Mark Estes, III, M.D., Elyse Foster, M.D., Henry Greenberg, M.D., Steven L. Higgins, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., et al., for the MADIT-CRT Trial Investigators*



FORGING AHEAD:

A Multipronged Attack

So, what have we learned?

- WVs are a unique population in the CVD world.
- ↑ Traditional CVD risk factors that are more poorly controlled than the general population of women.
- ↑ Non-traditional CVD risk factors of MST, PTSD, and depression at a higher rate than their MV colleagues.
- *These issues may place WVs at higher risk for CVD-related morbidity and mortality.*

Where do we go from here?

Education & outreach

Suboptimal health literacy re: CVD, CVD RF & consequences

For Women Veterans:

- Emphasis on:
  - Improving WV's awareness of CVD
  - Educating WVs about the importance of CVD
  - Encouraging WVs to take ownership of their CV health
- Partnership with **AHA's "Go Red for Women"** campaign
  - raise WVs awareness of CVD
  - online resources for education, nutrition/fitness programs
  - connection with other women w CVD

For VA providers:

- Emphasis on:
  - Improving provider awareness & education re: women, CVD and gender disparities
  - Providing gender-tailored CVD risk screening & treatment to reduce disparities

Yano EM, et al. Womens Health Issues. 2006;16:226–235.
Canter DL et al. J Surg Res. 2009;157:175–180.
VA, American Heart Association's "Go Red For Women" Fight Heart Disease in Women Veterans. www.va.gov/opa/pressrel/pressrelease.cfm?id=2319. Published 2012

Research: Current status

- Studies regarding veterans' CVD & CVD risk factors
  - *have included very few WVs*
  - *included MVs only*
  - *did not stratify results by gender*

- 2004: VA pursued a formal women's health research agenda
  - 2006: 1st systematic review of WVs' research
    - 182 research articles studied WVs
    - *None on CVD*

- VA Women's Health Research Network formed
  - 2011: more WV studies published than the previous 25 years combined
  - 2017 systematic review:
    - 2x research articles since the original review (>440 articles)
    - *Only 11 were specifically about WVs and CVD*

Increase provider / researcher awareness of Women's Health Research WHRN's **Practice Based Research Network:**

- facilitate investigator access to sites needed to help oversample WV / recruit WVs into multisite studies
- enlist local managers, providers and researchers
- provide infrastructure support

Goldzweig CL, et al. J Gen Intern Med. 2006;21 Suppl 3:S82–S92.
Bean-Mayberry B et al. Womens Health Issues. 2011;21(4Suppl):S84–S97
Danan ER et al.J Gen Intern Med. 2017;32:1359–137
Frayne SM et al. J Gen Intern Med. 2013;28 Suppl 2:S504–S509

Research: Future

Research in WVs' CVD must continue to be actively conducted to:

- better understand multilevel determinants of gender disparities in CVD, screening, treatment, & outcomes
- use that information to design
  - more prospective, randomized clinical trials of interventions for WVs' CVD
  - data-driven strategies capable of system improvements
- ensure the best possible CVD-related outcomes for those that rely on the VA

Trials must also focus on understanding, improving, and implementing CVD prevention in the rapidly growing younger WVs population

Doing this will benefit not only WVs but the female population as a whole!

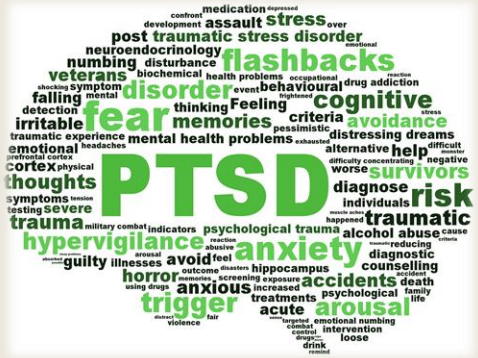
Research: On-Going

Facilitating Cardiovascular Risk Screening & Risk Arm

- Nonrandomized stepped-wedge trial
- Goal: to evaluate the implementation of a gender-tailored CVD prevention toolkit to help providers identify CVD risks in WVs
- Primary outcome: referrals to health promotion & disease prevention services
- Currently recruiting

The WARRIOR trial (Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD)

- Funded by Department of Defense
- Multicenter, prospective, randomized, blinded outcomes trial
- Intensive medical therapy vs usual care in nonobstructive coronary disease
- Veteran & active duty women
- Primary outcome: major adverse cardiovascular events
- Currently recruiting



- Newly-funded Department of Defense project
- Goal: examine the intersection of PTSD & CVD in WVs

URL: http://www.clinicaltrials.gov; Unique identifier: NCT02991534
URL: http://www.clinicaltrials.gov; Unique identifier: NCT03417388
CDMRP award number W81XWH-18-1-0725

Significant advancements have been made over the past decade in better characterizing CVD in WVs, but there remains a large gender gap and paucity of prospective, randomized, interventional clinical trials.

The time is now to continue to push to the forefront the cardiovascular care of WVs—to help save the hearts and lives of the women who have bravely served our country.

THANK YOU!

With special thanks to co-authors:
Elizabeth Yano, PhD, MSPH
Karol Watson, MD, PhD
Ramin Ebrahimi, MD

VA | U.S. Department of Veterans Affairs
VA Greater Los Angeles Healthcare System

UCLA Health

Stress and Cardiovascular Disorders; Focus on PTSD

Ramin Ebrahimi

Stress

- Organism's reaction to a change that requires a physical, mental or emotional adjustment or response

- Anxiety is a negative affective state resulting from an individual's perception of threat and characterized by a perceived inability to predict, control or gain the preferred results in given situations

Types of Stress

- Acute: earthquake, physical altercation, motor vehicle accident
- Chronic: job, marital, discrimination, poverty
- Not always is it an unpleasant circumstance (birth of a new child, promotion, relocation)

1994 Northridge Earthquake

- Review of the record of the department of coroner for the week before the earthquake, the day of earthquake, and the following six days compared to the corresponding control periods in 1991, 1992, 1993.
- On the day of the earthquake there was a sudden increase in number of sudden deaths from cardiac causes related to atherosclerotic disease from average daily baseline of 4.6±2.1 per day in the preceding week to 24 on the day of earthquake ($p<0.0001$)
- Only 3 sudden deaths might have been related to unusual physical activity.
- During the following 6 days, the number of sudden death decreased to below the baseline level, to 2.7±1.2 per day.

- Leor et al NEJM 1996;334:413-19

Northridge earthquake

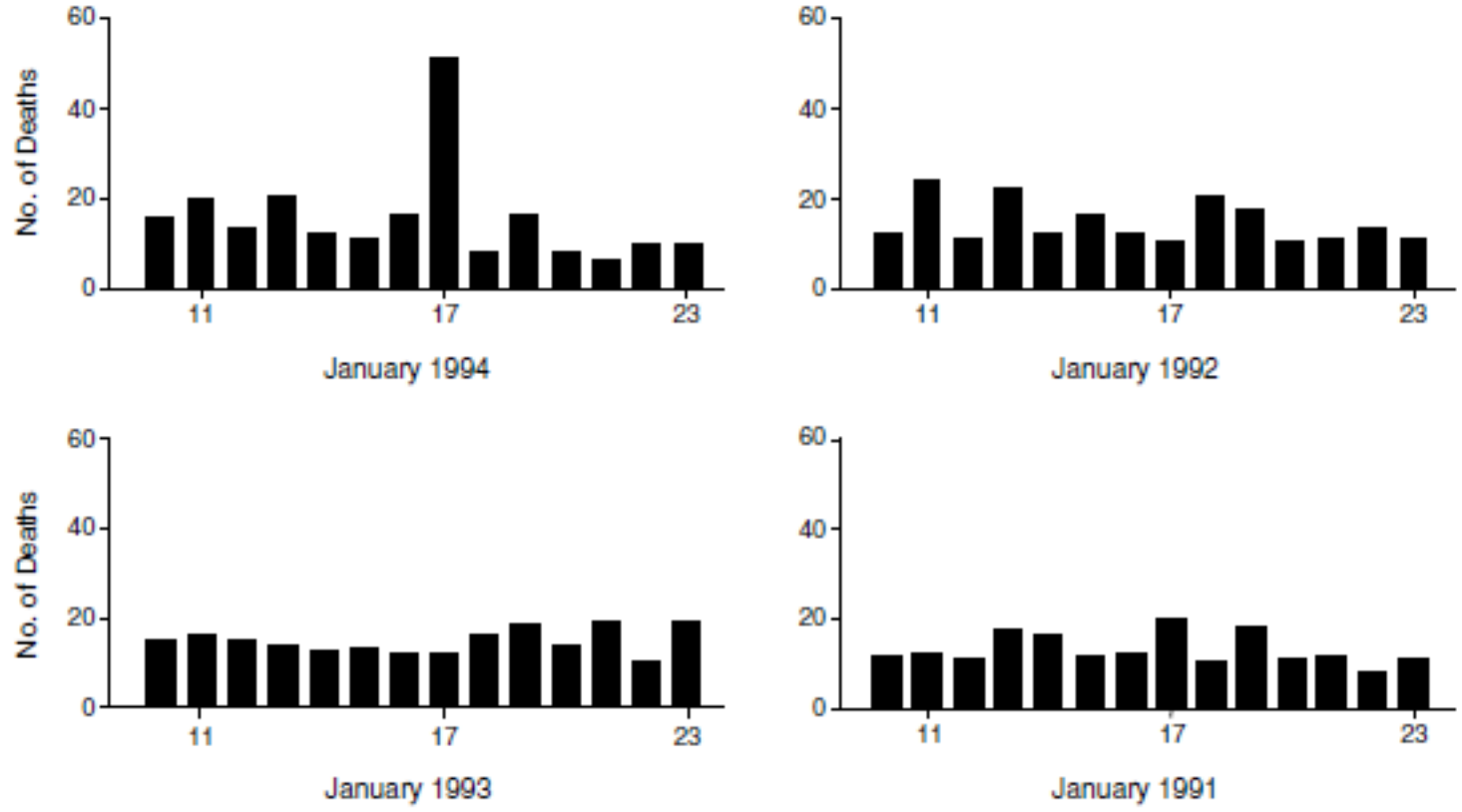


Figure 2. Daily Numbers of Deaths Found to Be Related to Atherosclerotic Cardiovascular Disease from January 10 through 23, 1991, 1992, 1993, and 1994.

On the day of the earthquake (January 17, 1994), there was a sharp rise in the number of deaths related to atherosclerotic cardiovascular disease (n = 51; relative risk, 2.6; 95 percent confidence interval, 1.8 to 3.7). The daily number of deaths related to atherosclerotic cardiovascular disease declined in the six days after the earthquake (z = 3.15, P = 0.002).

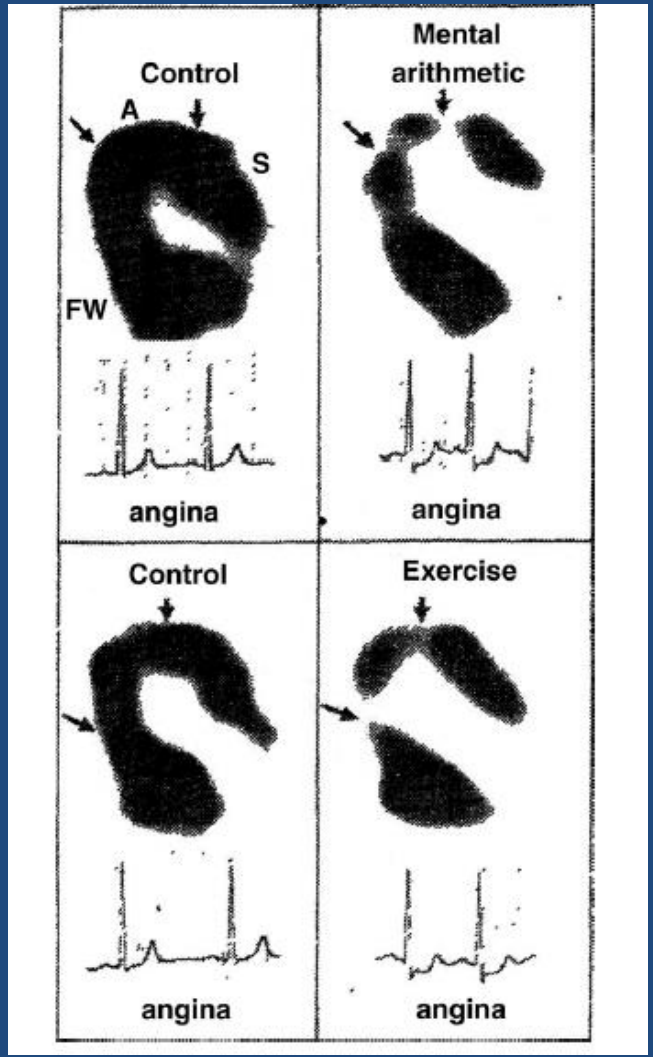
Mental Stress and Ischemia

- 16 subjects with stable angina underwent physical exercise and 2-minute serial 7 subtraction as means of mental stress to assess ischemia and angina using electrocardiogram as well as positron emission tomography using rubidium-32 to assess regional perfusion.

- After mental stress 12 (75%) had abnormalities of regional perfusion, accompanied in only 6 by ST-segment depression and in 4 of these 6 by angina.

- After physical exercise, all subjects showed abnormal regional perfusion and ST-depression and 15 had angina.

- Deanfiled J, et al Lancet 1984 Nov 3;2 (8410):1001 5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Mental Stress & CV Risk Factors

Rozanski Circ 1999

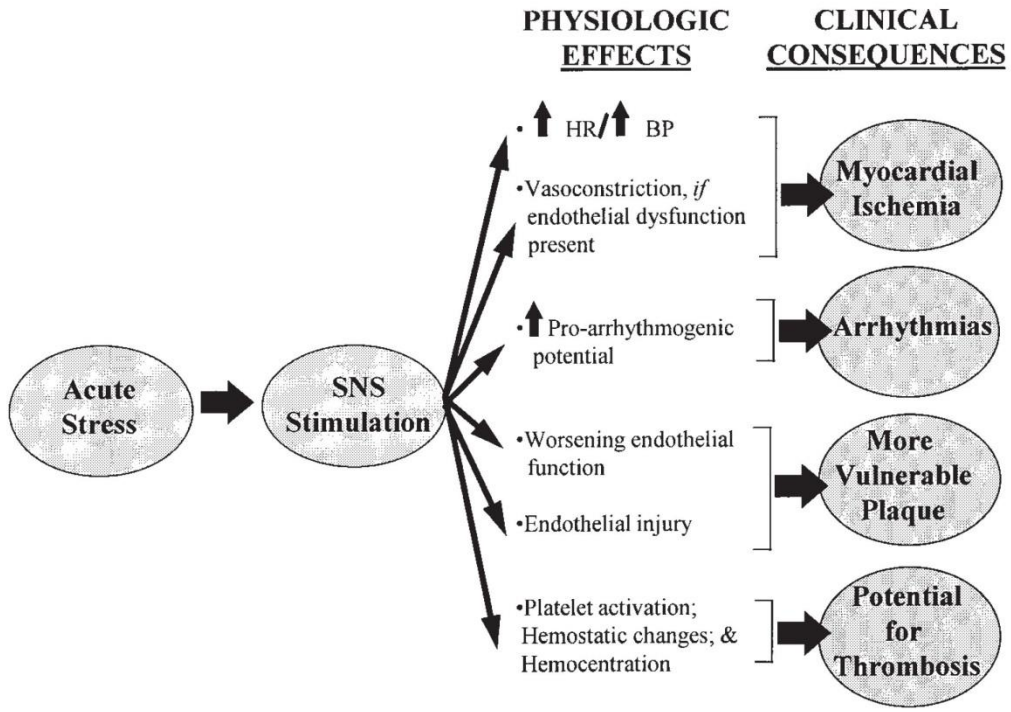


Figure 3. Schematic of pathophysiological effects of acute psychosocial stress. Sympathetic nervous system (SNS) stimulation emanating from acute stress leads to a variety of effects, ranging from heart rate and blood pressure stimulation to direct effects on coronary vascular endothelium. Clinical consequences of these effects include development of myocardial ischemia, cardiac arrhythmias, and fostering of more vulnerable coronary plaques and hemostatic changes. These changes form substrate for development of acute myocardial infarction and sudden cardiac death.

Chronic Stressors

- Examples include job, marital, discrimination, care giving
- Studies to evaluate effect on cardiovascular system are usually epidemiologic as opposed to physiologic.
- Chronic stressors may have confounding effects on risk/protective factors such as diet, exercise and smoking

INTERHEART: Focus on 9 risk or protective factors

Design	Large international case-control study
Participants	12,461 cases; 14,637 controls; 52 countries
Objective	To determine association of first MI with: Smoking, Lipids, Hypertension Diabetes, Obesity, Diet Physical activity, Alcohol consumption, Psychosocial factors*
Follow-up	4 years, February 1999–March 2003

*eg, stress, depression

Yusuf S et al. *Lancet*. 2004;364:937 52.

INTERHEAT Study

Variable	Odds Ratio	p-value	Population attributable risk %
Smoking	2.87	0.0001	35.7
History of HTN	1.91	0.0001	17.1
Diabetes	2.37	0.0001	9.9
Abdominal Obesity	1.12	0.0001	20.1
Psychological factors	2.67	0.0001	32.5
Alcohol use	0.91	0.0001	6.7
Physical activity	0.86	0.0001	12.2

Anxiety and CAD

Rozanski Circ 1999

Investigator	No. of Subjects	F/U, y	Condition Studied	Scale	End Points	RRs
Healthy subjects						
Phobic anxiety						
Haines et al, 1987	1457	6	Phobic anxiety	Crowne-Crisp	CD	3.8 (1.6–8.6)
					MI	1.3 (0.6–2.5)
Kawachi et al, 1994	33 999	2	Phobic anxiety	Crowne-Crisp	CD	2.5 (1.0–6.0)*
					MI	0.9 (0.5–1.8)
Kawachi et al, 1994	2271	32	Anxiety	Anxiety SS of the Cornell Medical Index	CD	1.9 (0.7–5.4)†
					MI	1.0 (0.3–3.6)
Other syndromes						
Weissman, 1990	60 with panic;	NR	Panic disorder	DIS	CD	NR
	3778 healthy				MI	4.5 (1.7–12.3)
Kubzansky et al, 1997	1759	20	Worry	Worries Scale	CD	0.8 (0.5–1.4)‡
					MI	2.4 (1.4–4.1)‡
CAD patients						
Frasure-Smith et al, 1995	222 pts, s/p MI	1	Anxiety	State Trait Anxiety Inventory	Combined 1	2.5 (1.6–5.6)
Moser et al, 1996	86 pts, s/p MI	IHS	Anxiety	Brief Symptom Inventory	Combined 2	4.9 (2.1–12.2)
Denollet et al, 1998	87 pts, s/p MI	7.9	Anxiety	State Anxiety Scale	Combined 3	3.9 (1.2–9.6)§
Herrman et al, 1998	454 pts; 273 with cardiopulmonary disease‖	1.9	Anxiety	HADS	ACM	2.5 (1.4–4.4)

NR indicates not reported: IHS, in-hospital study of cardiac events; 1, events include CD, MI and unstable angina. 2, events include CD, MI, acute ischemia; sustained VT or VF. 3, CD; MI; unstable angina; cardiac arrest survival. Other abbreviations as in Table 1.

*RR for sudden CD=6.1 (2.4–15.7); RR compares highest- vs lowest-risk quartiles.

†RR for sudden CD=4.7 (0.9–21.6).

‡RR for highest vs lowest terciles.

§Crude RR. Adjusted RR not reported.

‖Other patients had other medical conditions.

Anxiety & Coronary heart Disease

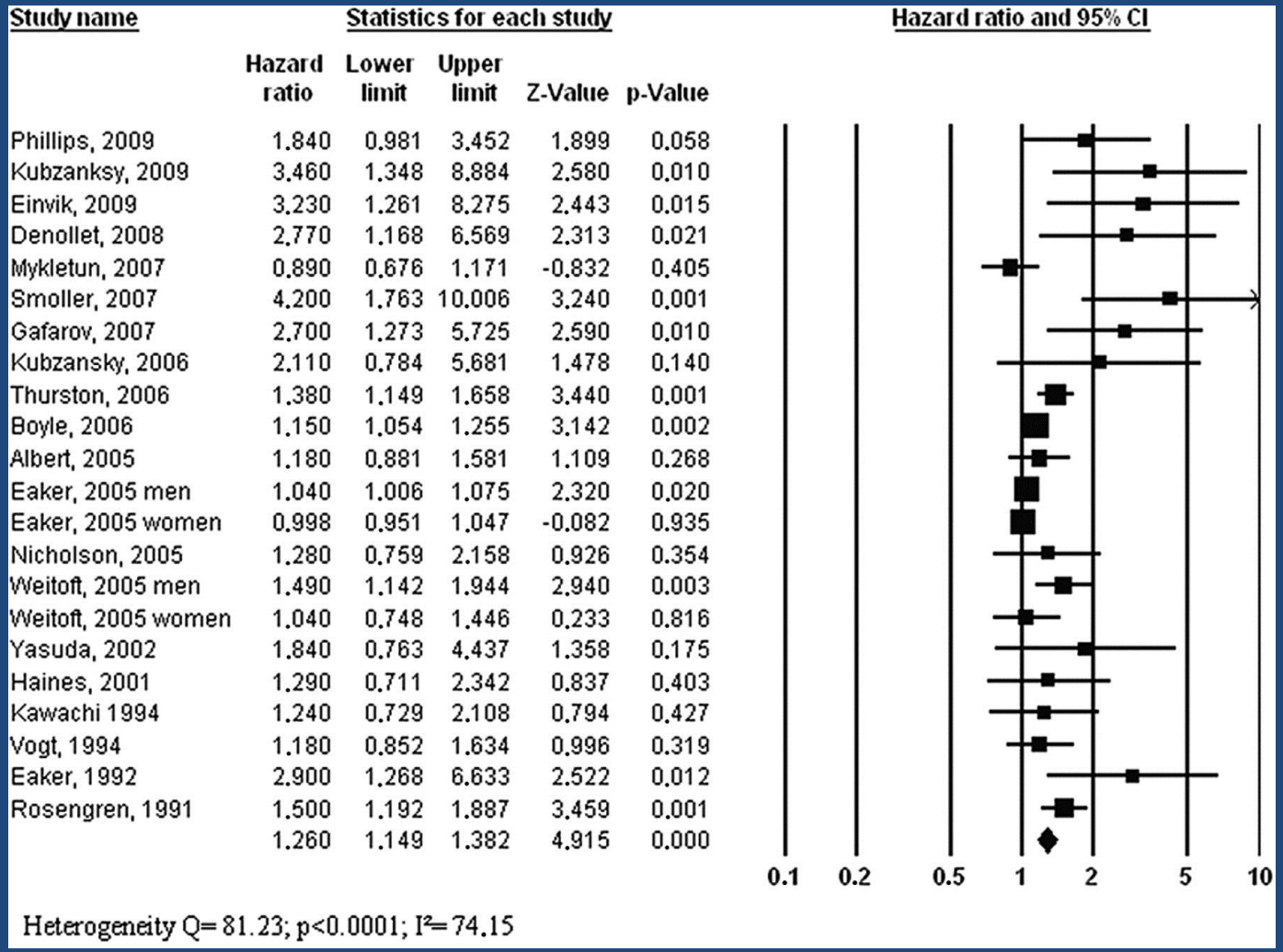
Meat-analysis of studies from 1980-2009 without language restriction.

Prospective studies of non-psychiatric cohorts of initially healthy persons with anxiety assessed at baseline

Endpoint were cardiac death, myocardial infarction, other cardiac events

Roest, A. M. et al. J Am Coll Cardiol 2010;56:38 46

Anxiety and Risk of Incident CHD



Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Phillips, 2009	1.840	0.981	3.452	1.899	0.058
Kubzanksy, 2009	3.460	1.348	8.884	2.580	0.010
Einvik, 2009	3.230	1.261	8.275	2.443	0.015
Denollet, 2008	2.770	1.168	6.569	2.313	0.021
Mykletun, 2007	0.890	0.676	1.171	-0.832	0.405
Smoller, 2007	4.200	1.763	10.006	3.240	0.001
Gafarov, 2007	2.700	1.273	5.725	2.590	0.010
Kubzansky, 2006	2.110	0.784	5.681	1.478	0.140
Thurston, 2006	1.380	1.149	1.658	3.440	0.001
Boyle, 2006	1.150	1.054	1.255	3.142	0.002
Albert, 2005	1.180	0.881	1.581	1.109	0.268
Eaker, 2005 men	1.040	1.006	1.075	2.320	0.020
Eaker, 2005 women	0.998	0.951	1.047	-0.082	0.935
Nicholson, 2005	1.280	0.759	2.158	0.926	0.354
Weitoft, 2005 men	1.490	1.142	1.944	2.940	0.003
Weitoft, 2005 women	1.040	0.748	1.446	0.233	0.816
Yasuda, 2002	1.840	0.763	4.437	1.358	0.175
Haines, 2001	1.290	0.711	2.342	0.837	0.403
Kawachi 1994	1.240	0.729	2.108	0.794	0.427
Vogt, 1994	1.180	0.852	1.634	0.996	0.319
Eaker, 1992	2.900	1.268	6.633	2.522	0.012
Rosengren, 1991	1.500	1.192	1.887	3.459	0.001
	1.260	1.149	1.382	4.915	0.000

Roest, A. M. et al. J Am Coll Cardiol 2010;56:38-46

Depression and CAD

Rozanski Circ 1999

Study	No. of Subjects	F/U, y	Scales	End Points	RR (95% CI) or Other Statistical Results
Healthy subjects					
Anda et al, 1993	2832	12.4	SS of generalized well-being schedule	CD, non-fatal IHD	RR for depressive sx=1.5 (1.0–2.3)
					RR for severe hopelessness=2.1 (1.1–3.9)
Arooma et al, 1994	5355	6.6	SS of GHQ	MI	RR for depressive sx=3.5 (1.8–6.8)
			SS of PSE	MI, CHF, CVA,	
Vogt et al, 1994	2573	15	Investigator-tailored scale	ACM	*P*=NS for depressive sx
Everson et al, 1996	2428	6	SS of MMPI	CD; ACM	RR for severe hopelessness=2.3 (1.1–3.9)
			Hopelessness scale		RR for moderate hopelessness=1.6 (1.0–2.5)
Wasserthal-Smoller et al, 1996	4736	4.5	CES-D scale	ACM, CD, MI; CVA	*P*=NS for baseline depressive sx
					RR for increasing depressive sx=1.3 (1.2–1.4)
Pratt et al, 1996	1551	13	DIS	MI	RR for MDE=4.5 (1.7–12.4)
					RR for dysphoria=2.1 (1.2–3.7)
Barefoot et al, 1996	730		OBD SS of MMPI	CD; MI	RR for depressive sx=1.7 (1.2–2.3) (for MI)*
Ford et al, 1998	1190	37	Tailored scale	MI	RR for depressive sx=2.1 (1.2–4.1)
Known disease					
Kennedy et al, 1987	88 pts; syncope or arrhythmia	1.5	Tailored scale	CD	*P*=0.01 for depressive sx
Carney et al, 1988	52; CAD on cath	1.0	DIS	CD, MI, PTCA; CABG	RR for MDE=2.5, *P*<0.02†
Ahern et al, 1990	502, s/p MI and arrhythmia	1.0	BDI	ACM; CD	*P*<0.05 for depressive sx
Frasure-Smith et al, 1995	222, s/p MI	1.5	DIS; BDI	CD	RR for MDE=3.6 (1.3–10.1)
					RR for depressive sx=7.8 (2.4–25.3)
Barefoot et al, 1996	1250; s/p MI	15.2	Zung Self-Rating Depression scale	CD	*P*=0.002 for depressive sx
Denollet et al, 1998	87; s/p MI & EF<50%	7.9	Million Behavioral Health Inventory and BDI	CD; MI	RR for depressive sx=4.3 (1.4–13.3)
Hermann et al, 1998	273, cardiopulmonary	1.9	HADS	ACM	RR for depressive sx=2.6 (1.1–6.3)
Frasure-Smith et al, 1999	896, s/p MI	1.0	BDI	CD	RR for depressive sx=3.2 (1.7–6.3)

F/U indicates follow-up; RR, risk ratio; pts, patients; cath, catheterization; s/p, status post; MI, myocardial infarction; EF, ejection fraction; SS, subscale; GHQ, General Health Questionnaire; PSE, Present State Examination; MMPI=Minnesota Multiphasic Personality Inventory; CES-D, Center for Epidemiological Studies–Depression; DIS, Mental Health Diagnostic Interview Schedule (DSM-III diagnosis of depression); OBD, obvious depression; BDI, Beck Diagnostic Interview (measures depressive symptoms); HADS, Hospital Anxiety and Depression Scale; CD, cardiac death; IHD, ischemic heart disease; CHF, congestive heart failure; CVA, cerebrovascular accident; ACM, all-cause mortality; Sx, symptom; and MDE, major depression episode.

*RR for cardiac death=1.62, *P*<0.03; †no CI reported.

Post-Traumatic Stress Disorder

Diagnosis of PTSD requires:

1) Exposure to extreme stressor or traumatic event that invokes fear, helplessness, or horror
2) Re-experiencing the event (images, nightmares, or flashbacks)
3) Avoidance (attempts to avoid reminders of the event)
4) Hyperarousal (Insomnia, irritability, impaired concentration, hypervigilance, increased startle reactions)

DSM

PTSD Prevalence

- Lifetime prevalence of PTSD in combat veterans is 5% to 20% in United States (1,2) and is even more prevalent in military personnel serving in Iraq and Afghanistan.(2)

- The lifetime prevalence of PTSD is twice as common in women (10%) compared to men (5%). (3)

1. Cohen et al. *JAMA* 2009;302:489–492.
2. Richardson et al. *Aust N Z J Psychiatry* 2010;44:4 –19.
3. Kessler Arcg Gen Psychiatry 1995

Types of PTSD

- Acute PTSD - symptoms less than three months
- Chronic PTSD - symptoms more than three months
- Although symptoms usually begin within 3 months of exposure, a delayed onset is possible months or even years after the event has occurred.

[Can J Psychiatry, Vol 51, Suppl 2, July 2006

PTSD and Health measures

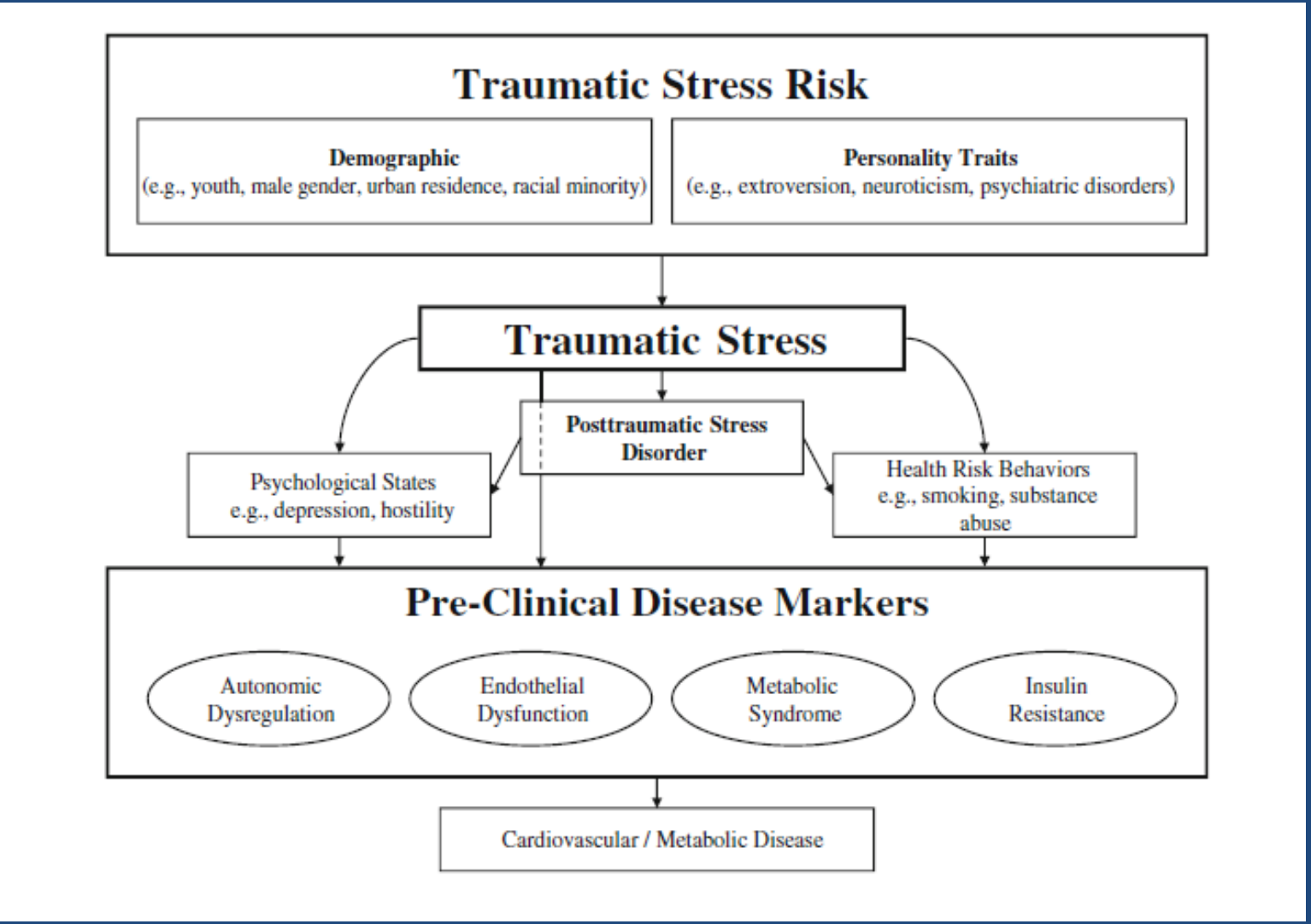
- Individuals with PTSD:

1) Report more health complaints
2) Have more medical illnesses diagnosed
3) Have a higher healthcare utilization

Beckham Am J Psychiatry 1998
Boscarino Psychosom Med 1997

Mechanistic Model for Development of Cardiovascular and Metabolic Disorders in PTSD

Schnurr PP Semin Clin Neuropsychiatry 1999



Heart Rate

PTSD is associated with higher resting heart rate (1,2)

There does appear to be a more pronounced increase in heart rate in response to trauma cues in those with PTSD (5,6)

There does not appear to be an association between trauma cues and heart rate in those with trauma and PTSD compared to those with tranuma and without PTSD (3,4)

- 1) Buckley J Trauma Surg 2004
- 2) Beckham J Trauma Stress 2003
- 3) Newton Biol Psychol 2005
- 4) Jones Alexander Appl Psychophysiol Biofeedback 2005
- 5) Rabe Appl Psychphysiol Biofeedback 2006
- 6) Orr Psychiatr Clin North Am 2002

Blood Pressure

Meta-analysis reveals a trend towards higher BP in individuals with PTSD (1)

Traumatized individuals with PTSD have exaggerated increase in BP compared to traumatized individuals without PTSD in response to trauma scripts (2,3)

- 1) Buckley Psychosom Med 2001
- 2) Lindauer Psychol Med 2007
- 3) Buckley J Trauma Stress 2004

Lipids

PTSD is associated with:

1) Elevated cholestrol
2) Elevated LDL
3) Elevated TG

- 1) Solter Croat Med J 2002
- 2) Triefd J Behav Med 2006
- 3) Karlovic J Korean Med Sci 2004
- 4) Karlovic Acta Med Okayama 2004
- 5) Maia J Affect Disord 2008

Endothelial dysfunction in PTSD

Besides flow mediated dilation endothelial dysfunction may be measured by presence of circulating proteins that promote blood coagulation.

In a study of 14 PTSD patients and 14 matched patients,levels of Soluble Tissue Factor (sTF), and Von Willebrand Factor (VWF) was increased in PTSD patients compared to controls.

However levels of Soluble Intracellular Adhesion Molecule (SICAM) was similar between groups.

Kanel, et al Psychiatry Research 158 (2008) 363 373

Allostasis hypothesis/model

The process of adaptation to stressors to achieve stability through change

Exposure to new stressors frequently, or failure to shut off physiologic responses after stressor is over, or failure to adopt to the stressor may be harmful and manifest as dyslipidemia, HTN, inflammatory states.

1) Friedman Trauma and Health 2004
2) McEwen NEJM 1998

Hypothalamic-Pituitary-Adrenal Pathway

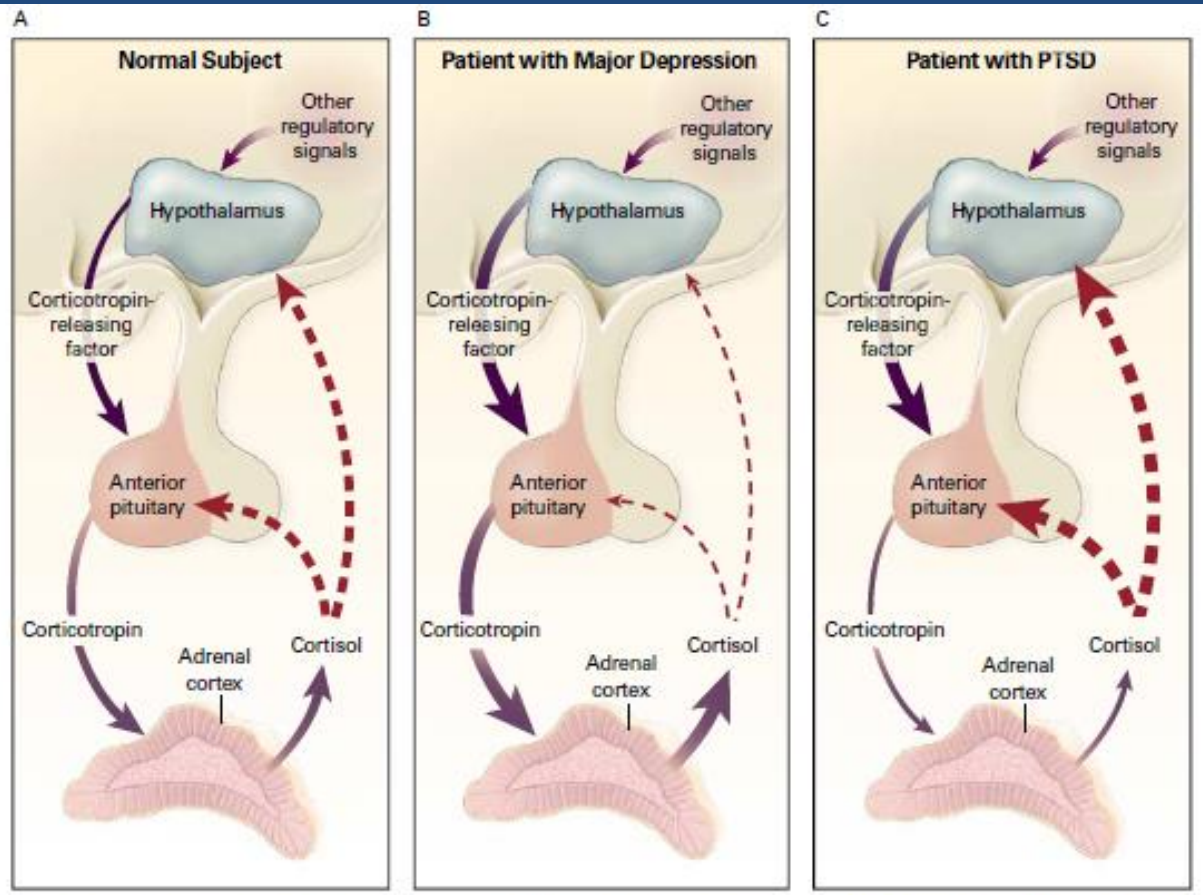


Figure 1. Response to Stress in a Normal Subject (Panel A), a Patient with Major Depressive Disorder (Panel B), and a Patient with PTSD (Panel C).

In normal subjects (Panel A) and in patients with major depression (Panel B), brief or sustained periods of stress are typically associated with increased levels of both cortisol and corticotropin-releasing factor. In each panel the thickness of the interconnecting arrows denotes the magnitude of the biologic response. Corticotropin-releasing factor stimulates the production of corticotropin, which in turn stimulates the production of cortisol. Cortisol inhibits the release of corticotropin from the pituitary and the release of corticotropin-releasing factor from the hypothalamus. It is also responsible for the containment of many stress-activated biologic reactions. In patients with PTSD (Panel C), levels of cortisol are low and levels of corticotropin-releasing factor are high. In addition, the sensitivity of the negative-feedback system of the hypothalamic–pituitary–adrenal axis is increased in patients with PTSD rather than decreased, as often occurs in patients with major depression.[31]

Risk Factor Comparison of Veterans Based on Mental Health Diagnoses

Table 2. Prevalence and Adjusted Odds of Cardiovascular Disease Risk Factors in 35 912 Female OEF/OIF Veterans by Mental Health Status[a]

	Mental Health Diagnoses		
	None (n = 21 634)	Mental Health Diagnoses Excluding PTSD (n = 7314)[b]	PTSD With or Without Other Mental Health Diagnoses (n = 6964)[b]
Cardiovascular risk factors			
Tobacco use			
Prevalence, %	7.0	19.2	21.7
Model 1 OR (95% CI)[c]	1 [Reference]	2.97 (2.74-3.22)	3.58 (3.30-3.88)
Model 2 OR (95% CI)[d]	1 [Reference]	2.17 (1.95-2.40)	2.29 (2.06-2.54)
Hypertension			
Prevalence, %	4.3	8.1	10.4
Model 1 OR (95% CI)[c]	1 [Reference]	2.31 (2.06-2.59)	2.99 (2.67-3.33)
Model 2 OR (95% CI)[d]	1 [Reference]	1.48 (1.28-1.70)	1.59 (1.38-1.82)
Dyslipidemia			
Prevalence, %	5.9	11.2	13.9
Model 1 OR (95% CI)[c]	1 [Reference]	2.12 (1.92-2.33)	2.68 (2.44-2.95)
Model 2 OR (95% CI)[d]	1 [Reference]	1.26 (1.22-1.42)	1.37 (1.22-1.54)
Obesity			
Prevalence, %	6.5	15.1	16.9
Model 1 OR (95% CI)[c]	1 [Reference]	2.59 (2.37-2.82)	3.01 (2.76-3.28)
Model 2 OR (95% CI)[d]	1 [Reference]	1.72 (1.55-1.91)	1.69 (1.52-1.89)
Diabetes			
Prevalence, %	0.7	1.3	1.7
Model 1 OR (95% CI)[c]	1 [Reference]	2.17 (1.66-2.83)	2.86 (2.21-3.71)
Model 2 OR (95% CI)[d]	1 [Reference]	1.23 (0.91-1.66)	1.43 (1.07-1.92)
Medical visits, mean (SD), No.			
Primary care visits	2.6 (3.9)	6.0 (6.1)	7.5 (7.3)
Medical subspecialty visits	3.4 (4.1)	5.2 (6.9)	6.5 (8.6)

Abbreviations: CI, confidence interval; *ICD-9*, *International Classification of Diseases, Ninth Revision*; OEF/OIF, Operation Enduring Freedom/Operation Iraqi Freedom; OR, odds ratio; PTSD, posttraumatic stress disorder.

[a] *ICD-9* codes for mental health diagnoses are listed in Table 1. The most common diagnoses in the non-PTSD group included depression, 61%; anxiety, 34%; adjustment disorders, 33%; alcohol use disorder, 7%; and substance use disorder, 3%.

[b] All comparisons in models 1 and 2 to reference group of no mental health diagnoses were significant at $P < .001$ (except in model 2) except $P = .18$ for diabetes in mental health diagnoses excluding PTSD and $P = .02$ for diabetes in PTSD with or without other mental health diagnoses.

[c] Model 1 was adjusted for age, race (defined by self-report as white, black, Hispanic, or other), component type, rank, branch, and multiple deployments.

[d] Model 2 included all covariates in model 1 plus number of primary care visits and number of medical subspecialty visits.

PTSD and CVD

- Vietnam veterans with PTSD had increased CVD (1)
- Trauma exposure increased CVD (2)
- PTSD increased self reported CVD (3)
- Increasd CVD in WWII POW with PTSD (4)
- Increased mortality and CVD in US Army veterans 30 years after military service (5)

1) Boscarino Ann Behav Med 1999
2) Sibai Am J Epiddemiol 2001
3) Lauterbach Psychosom Med 2005
4) Kang Ann Epidemiol 2006
5) Bodcarino Ann Epidemiol 2006

Limitations of Literature on PTSD and CAD

- Most studies are retrospective
- Diagnosis of CAD is self reported
- Studies do not assess directly atherosclerosis as a hard endpoint for diagnosis of CAD (myocardial infarction can be caused by mechanisms other than atherosclerosis (spasm, demand ischemia, embolic events)
- Most studies do not adjust for depression and anxiety
- Most studies are in male subjects
- Most studies are in veterans
- Genetic factors

PTSD and CHD in Women

Prospective study using data from women in the Baltimore cohort of the Epidemiologic Cathment Area study (n=1059)

Women with five or more symptoms of PTSD had significantly increased risk of CHD age-adjusted OR =3.21, 95% CI 1.29-7.98). DSM IV requires 5 symptoms for dx of PTSD

Women with 1-4 symptoms did not have elevated risk of CHD (age adjusted OR = 1.22 95% CI 0.46-3.24 p=0.69)

Kubzansky Health Psychol 2009

PTSD and CVD in Women

Examined trauma exposure and PTSD symptoms in relation to CVD over 20 years in the Nurses' Health Study II

PTSD symptoms was associated with increased CVD (HR 1.6, 95% CI 1.2-2.13)

Data on trauma was more conflicting :

- Being trauma exposed and having no PTSD was also associated with increased CVD (HR 1.45, 95% CI 1.15-1.83)
- Although being trauma exposed and having less severe symptoms of PTSD was not associated wit increased CVD

Sumner et. al. Circulation 2015

Combat, PTSD and CHD

Prospective cohort study from the Millenium Cohort Study 2001-2008 (n=60025)

Combat experience was associated with increased self reported CHD (Adjusted OR 1.93 95% CI 1.31-2.84)

Screening for PTSD was associated with significantly increased newly self reported CHD (OR 2.25, 95% CI 1.49-3.39).

In PTSD subjects:

Adjusted OR but not for anxiety and depression (OR 1.66, 95%CI 1.10-2.50)

Adjusted OR for anxiety and depression (OR 1.27 95%CI 0.76-2.12)

Crum Cianflone Circ 2014

Combat , PTSD and CHD

Table 2. Adjusted Odds of Newly Self-Reported Coronary Heart Disease in the Millennium Cohort Study (2001–2008): Deployment Status and PTSD

Characteristic	Age, Sex, and Race Adjusted	All Covariates Except Anxiety and Depression*	All Covariates†
Deployment experiences			
Deployed, no combat	1.00	1.00	1.00
Nondeployed	1.06 (0.68–1.66)	1.01 (0.64–1.58)	1.01 (0.64–1.58)
Deployed, combat	1.81 (1.25–2.64)	1.64 (1.11–2.41)	1.63 (1.11–2.40)
PTSD, specific criteria	2.25 (1.49–3.39)	1.66 (1.10–2.50)	1.27 (0.76–2.12)

Table 3. Adjusted Odds of New Diagnostic Code for Coronary Heart Disease in the Millennium Cohort Study (2001–2008): Deployment Status and PTSD

Characteristic	Age, Sex, and Race Adjusted	All Covariates Except Anxiety and Depression*	All Covariates†
Deployment experiences			
Deployed, no combat	1.00	1.00	1.00
Nondeployed	1.29 (0.82–2.03)	1.30 (0.82–2.07)	1.30 (0.81–2.07)
Deployed, combat	2.03 (1.38–2.98)	1.93 (1.31–2.85)	1.93 (1.31–2.84)
PTSD, specific criteria	0.78 (0.29–2.15)	0.62 (0.22–1.72)	0.49 (0.16–1.53)

Twins Study

Prospective study of 562 twins from the Vietnam Era Twin Registry without self reported CHD at baseline. Subjects had clinic follow up at ~ 13 years.

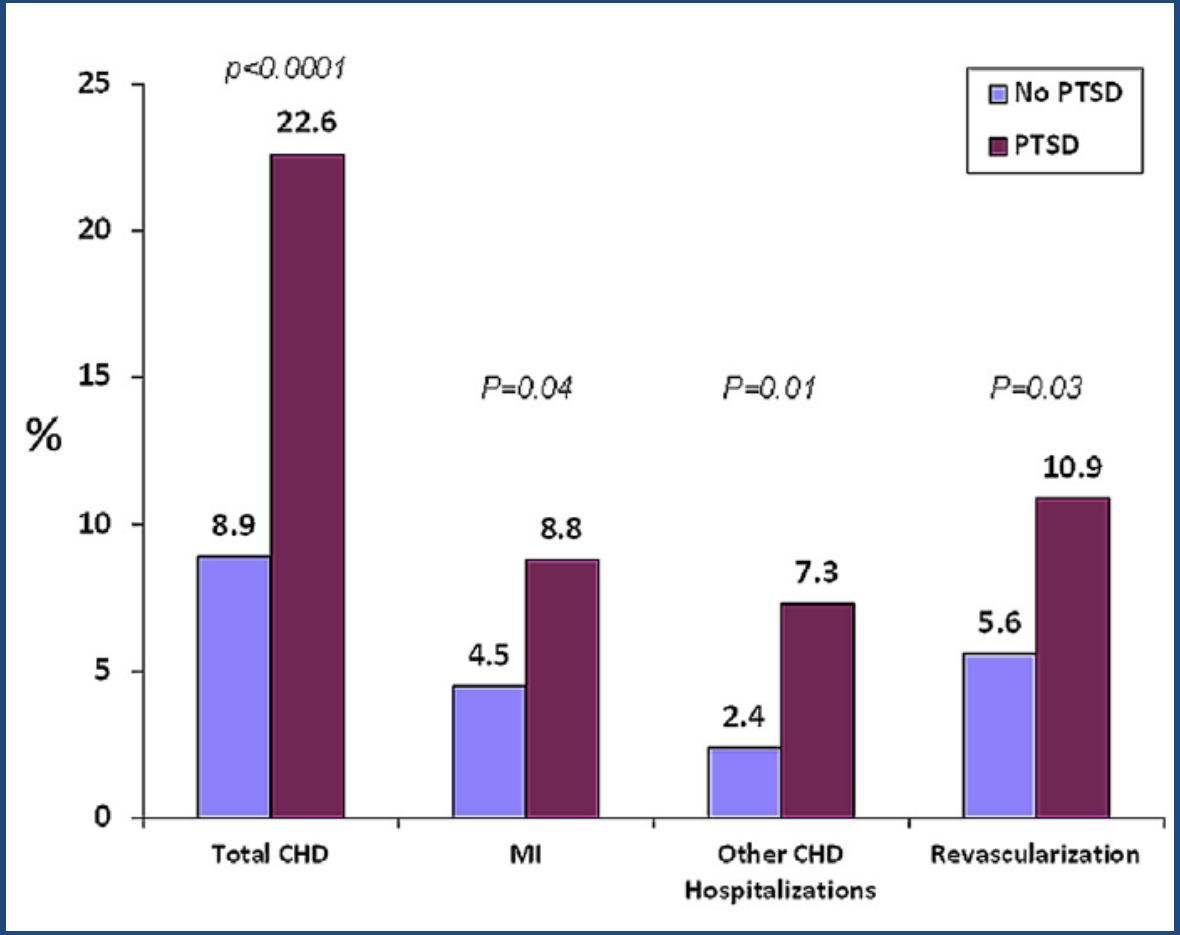
Incidence of CHD was significantly higher in PTSD patients (22.6% vs 8.9% $p<0.001$). Adjusted OR remained significant (OR 2.2 95% CI 1.2-4.1) even after adjustment for depression

Reported CVA was 5.1% in PTSD and 2.5% in non-PTSD subjects (p=0.14)

Within-pair analysis revealed increased incidence of CHD in brothers with PTSD (22.2% vs 12.8% p=0.04), (OR 1.9 95% CI 1.0-3.6)

Vaccarino JACC 2013

Twins Study


p<0.0001
22.6
8.9
P=0.04
8.8
4.5
P=0.01
7.3
2.4
P=0.03
10.9
5.6
No PTSD
PTSD
%
25
20
15
10
5
0
Total CHD
MI
Other CHD Hospitalizations
Revascularization

Twins Study

Model	Odds Ratio (PTSD vs. No PTSD)	95% Confidence Interval	p Value
Unadjusted	3.0	1.7–5.1	<0.001
Adjusted for sociodemographic factors*	2.5	1.5–4.4	<0.001
Service in Southeast Asia	2.8	1.6–4.8	<0.001
Lifestyle and CHD risk factors†	2.3	1.3–4.2	0.006
Major depression	2.2	1.2–4.1	0.01
Other psychiatric diagnoses‡	2.1	1.1–3.9	0.02

PTSD and Coronary Atherosclerosis

Incidence Density Sampling and Nested Case Control Analysis

637 veterans without known CAD undergoing Coronary Artery Calcium scanning (CAC)

Electronic Medical Records were utilized to assess conventional cardiovascular risk factors, PTSD, and atherosclerosis

Patients with known CAD and major psychiatric disorders were excluded

- Ahmadi et al Am J Cardiol. 2011 Jul 1;108(1):29 33.

PTSD Diagnosis

- The PTSD Checklist–Military and Clinician Administered PTSD Scale were administered.
- The PTSD Checklist–Military is a 17-item questionnaire adapted from PTSD criteria B to D from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, which inquires about the 3 symptom clusters of PTSD: 5 re-experiencing symptoms, 7 numbing/avoidance symptoms, and 5 hyperarousal symptoms.
- The Clinician Administered PTSD Scale assesses the frequency and intensity of PTSD symptoms during the previous month.
- Those patients with positive Clinician Administered PTSD Scale and PTSD Checklist–Military scores were classified as having PTSD.

Ahmadi et al Am J Cardiol. 2011 Jul 1;108(1):29-33.

Baseline Characteristics and Results

Variable	No PTSD (n = 549)	PTSD (n = 88)	p Value
Age (years)	58 ± 10	59 ± 9	0.3
Men	84%	98%	0.001
Hypertension*	54%	63%	0.1
Hypercholesterolemia†	47%	63%	0.006
Diabetes mellitus‡	25%	29%	0.4
Current smoker	30%	42%	0.03
Body mass index (kg/m^2)	29.3 ± 6.2	31.0 ± 5.9	0.02
Creatinine (mg/dl)	1.03 ± 0.22	1.05 ± 0.24	0.3
Systolic blood pressure (mm Hg)	128 ± 14	127 ± 14	0.7
Diastolic blood pressure (mm Hg)	77 ± 8	77 ± 9	0.9
Total cholesterol (mg/dl)	174 ± 46	163 ± 45	0.04
Low-density lipoprotein (mg/dl)	104 ± 34	100 ± 37	0.3
High-density lipoprotein (mg/dl)	44 ± 17	38 ± 13	0.005
Triglyceride (mg/dl)	133 ± 69	141 ± 76	0.3
Framingham Risk Score	12.1 ± 8.1	14.1 ± 6.7	0.02
Coronary artery calcium score	332 ± 336	448 ± 472	0.0001
Follow-up (months)	43 ± 12	39 ± 15	0.04
Mortality	10.4%	17.1%	0.003

Values presented as mean ± SD or percentage of patients.

* Self-reported diagnosis of hypertension, prescribed medication for hypertension, or current systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg diastolic (>130/80 mm Hg if diabetic).

† Self-reported diagnosis of high cholesterol, prescribed medication for high cholesterol, or current total cholesterol level >200 mg/dl.

‡ Self-reported diagnosis of diabetes (type 1 or 2) or prescribed medication for diabetes.

Relative Risk of Death Based on CAC & PTSD

CAC	No PTSD	PTSD	p Value
0	1.0 (reference)	1.04 (0.67–6.82)	0.4
1–100	1.0 (reference)	1.23 (1.04–6.55)	0.03
101–400	1.0 (reference)	1.51 (1.16–4.86)	0.01
≥400	1.0 (reference)	1.81 (1.16–3.74)	0.001

Cox regression survival analysis; adjusted for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary heart disease, and smoking status.

Prevalence ratio of PTSD Based on CAC

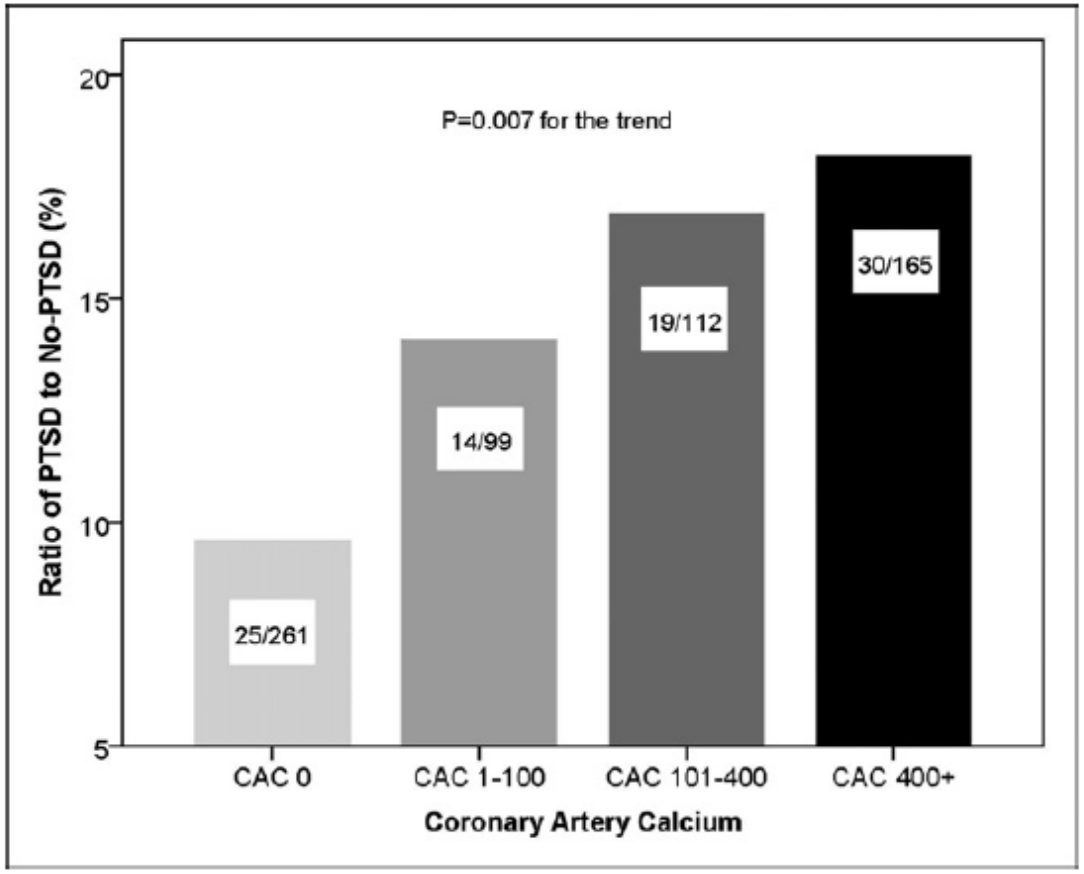


Figure 1. Prevalence ratio of post-traumatic stress disorder to increasing severity of coronary artery calcium.

Association of FRS to CAC Score Based on PTSD Diagnosis

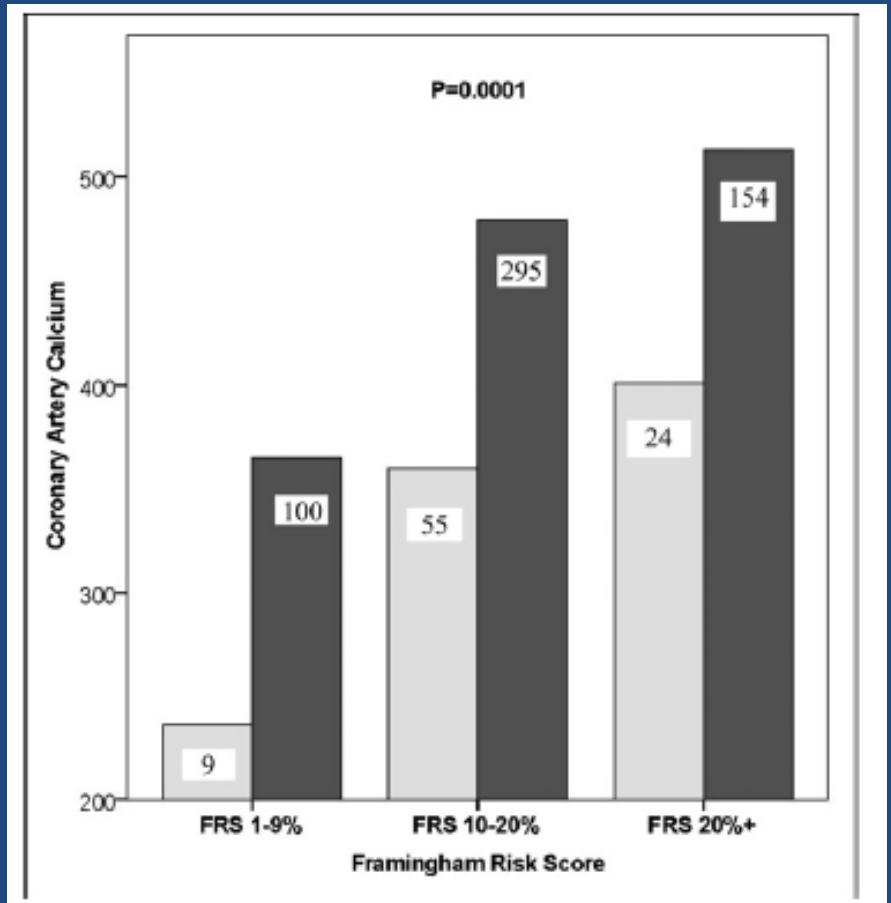
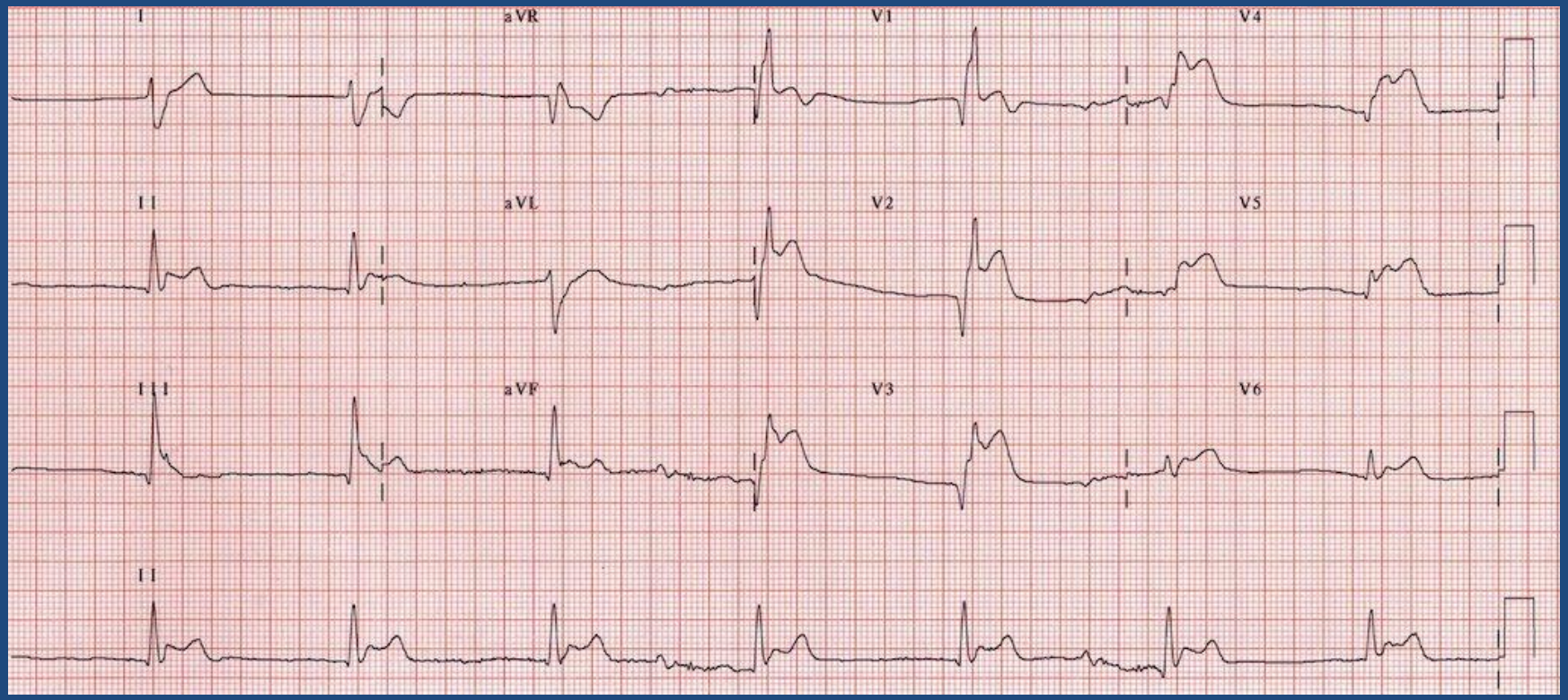


Figure 2. Association of increasing Framingham Risk Score (FRS) and coronary artery calcium in patients with *(black bars)* and without *(gray bars)* post-traumatic stress disorder.

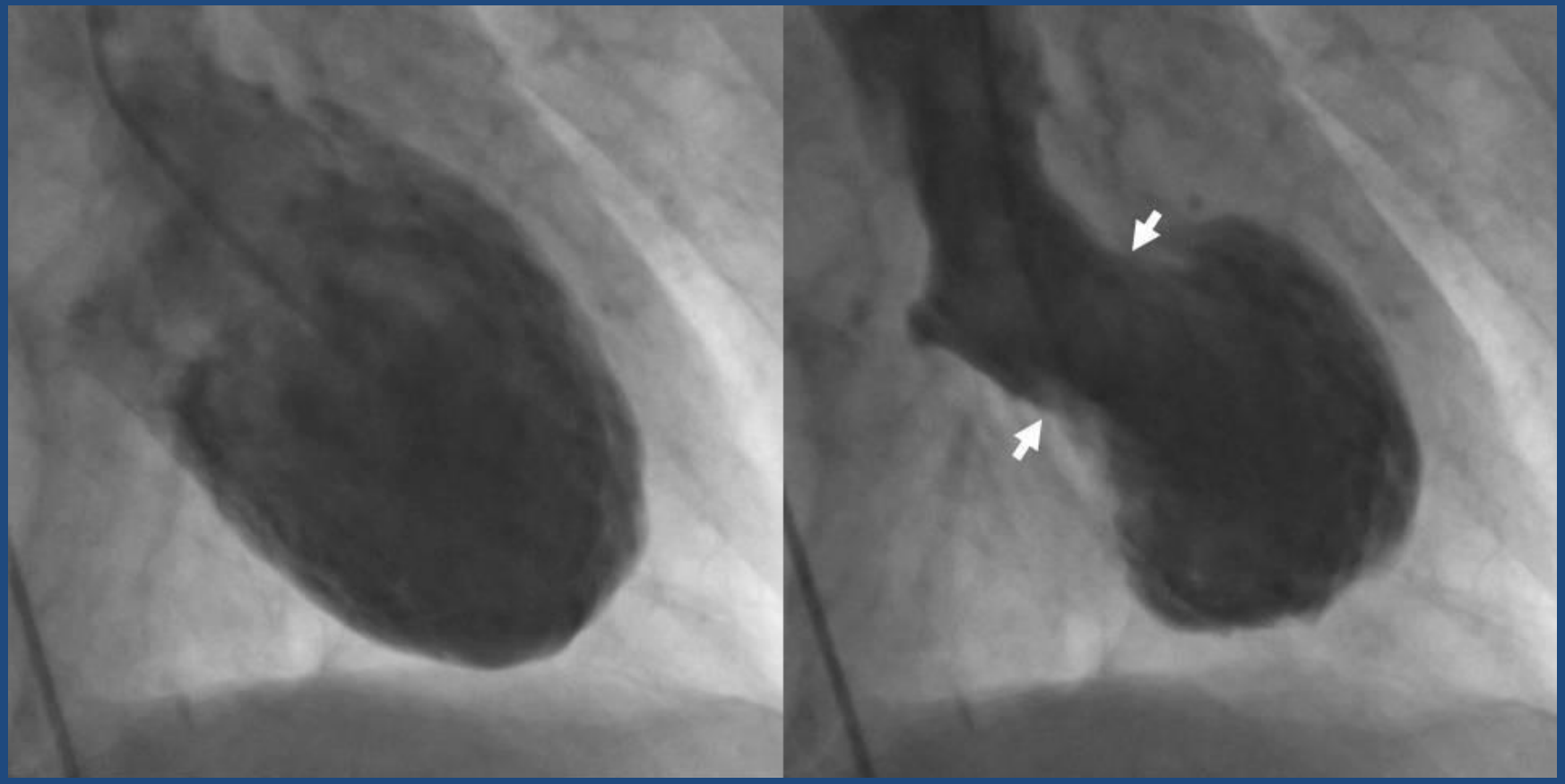
Does Stress Cause Cardiovascular Disorders?

- Yes
- No
- Maybe

54 year old female presents to ER with chest pain after learning about the death of her brother



Takotsubo Cardiomyopathy



What we Know

PTSD is associated with increased CVD

PTSD is associated with increased CVD risk factors

PTSD is associated with increased depression and Anxiety

Anxiety and depression are associated with increased CVD

Some of the unknowns

Is PTSD a true risk factor or a risk modulator (does it matter)?

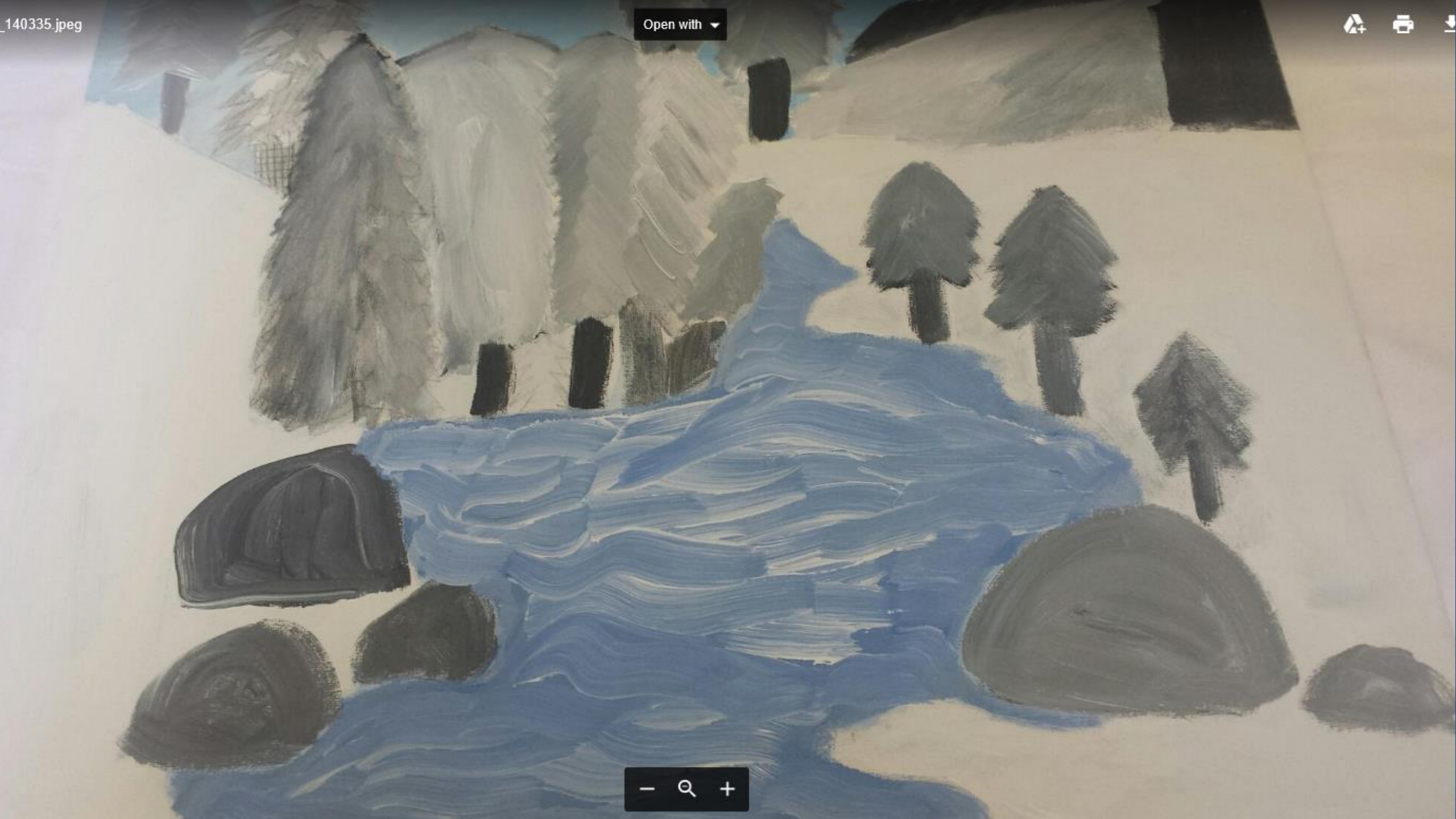
Are all PTSDs the same (e.g. combat PTSD, MST-PTSD, dog bite PTSD, …)?

Does PTSD increase risk of non-atherosclerotic heart disease

What are the effects of psychiatric medications on cardiovascular system in PTSD ?

Is response to therapy different in PTSD and non-PTSD patients?

What are the genetic markers, if any in PTSD?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