Considering depression as a risk marker for incident coronary disease

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Coronary Disease in women

- CVD Number 1 killer of women in Australia
  - United States
  - United Kingdom
  - South Africa
  - Brazil
  - Globally[1]

- Kills more women than all cancers, tuberculosis, HIV/AIDS, malaria combined[1]

- No longer viewed as “male” disease

[1] World Heart Federation

Depression in Australian women

Almost half of Australian adults 45% (7.3 million people) will have a mental disorder in their lifetime

Depression more common in women: 1 in 5 (compared with 1 in 8 men) will experience depression at some stage of their lives.

National Survey of Mental Health and Wellbeing (NSMHWB)

Relationship between depression & CHD

- Depression & CHD highly comorbid
- 15-20% of myocardial infarct (MI) patients report major depression; ~20% mild-moderate symptoms
- Post MI, depression increases risk of:
  - morbidity
  - mortality
  - more frequent angina
  - poor health service utilisation
  - poor medication adherence

- May be reactionary to MI, but it is more complicated than that…

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Does depression precede heart disease?

ORIGINAL INVESTIGATION

Depression Is a Risk Factor for Coronary Artery Disease in Men

The Precursors Study

Daniel E. Ford, MD, MPH; Lucy A. Mead, ScM; Patricia P. Chang, MD; Lisa Cooper-Patrick, MD, MPH; Nae-Yuh Wang, MS; Michael J. Klag, MD, MPH

Background: Several studies have found that depression is an independent predictor of poor outcome after the onset of clinical coronary artery disease. There are few data concerning depression as a risk factor for the development of coronary artery disease.

Objective: To determine if clinical depression is an independent risk factor for incident coronary artery disease.

Patients and Methods: The Johns Hopkins Precursors Study is a prospective, observational study of 1190 male medical students who were enrolled between 1948 and 1964 and who continued to be followed up. In medical school and through the follow-up period, information was collected on family history, health behaviors, and clinical depression. Cardiovascular disease end points have been assessed with reviews of annual questionnaires, National Death Index searches, medical records, death certificates, and autopsy reports.

Results: The cumulative incidence of clinical depression in the medical students at 40 years of follow-up was 12%. Men who developed clinical depression drank more coffee than those who did not but did not differ in terms of baseline blood pressure, serum cholesterol levels, smoking status, physical activity, obesity, or family history of coronary artery disease. In multivariate analysis, the men who reported clinical depression were at significantly greater risk for subsequent coronary heart disease (relative risk [RR], 2.12; 95% confidence interval [CI], 1.24-3.63) and myocardial infarction (RR, 2.12; 95% CI, 1.11-4.06). The increased risk associated with clinical depression was present even for myocardial infarction occurring 10 years after the onset of the first depressive episode (RR, 2.1; 95% CI, 1.1-4.0).

Conclusion: Clinical depression appears to be a independent risk factor for incident coronary artery disease for several decades after the onset of the clinical depression.

Arch Intern Med. 1998;158:1422-1426

Soc Psychiatry Psychiat Epidemiol (2012) 47:1145–1151
DOI 10.1007/s00127-011-0421-5

ORIGINAL PAPER

Co-morbid cardiovascular disease and depression: sequence of disease onset is linked to mental but not physical self-rated health. Results from a cross-sectional, population-based study

Adrienne O'Neil · Emily D. Williams · Christopher E. Stevenson · Brian Oldenburg · Michael Berk · Kristy Sanderson

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Abstract
Purpose Self-rated health has been linked to important health and survival outcomes in individuals with co-morbid depression and cardiovascular disease (CVD). It is not clear

self-rated mental and physical health for those reporting pre-cardiac and post-cardiac depression.
Results The proportion of individuals in whom MDD preceded CVD was 80.36% (CI: 72.57–88.15). One-fifth

Depression as a Risk Factor for Coronary Artery Disease: Evidence, Mechanisms, and Treatment

Heather S. Lett, MA, James A. Blumenthal, PhD, Michael A. Babyak, PhD, Andrew Sherwood, PhD, Timothy Strauman, PhD, Clive Robins, PhD, and Mark F. Newman, MD

Objective: The present paper reviews the evidence that depression is a risk factor for the development and progression of coronary artery disease (CAD). **Methods:** MEDLINE searches and reviews of bibliographies were used to identify relevant articles. Articles were clustered by theme: depression as a risk factor, biobehavioral mechanisms, and treatment outcome studies. **Results:** Depression confers a relative risk between 1.5 and 2.0 for the onset of CAD in healthy individuals, whereas depression in patients with existing CAD confers a relative risk between 1.5 and 2.5 for cardiac morbidity and mortality. A number of plausible biobehavioral mechanisms linking depression and CAD have been identified, including treatment adherence, lifestyle factors, traditional risk factors, alterations in autonomic nervous system (ANS) and hypothalamic pituitary adrenal (HPA) axis functioning, platelet activation, and inflammation. **Conclusion:** There is substantial evidence for a relationship between depression and adverse clinical outcomes. However, despite the availability of effective therapies for depression, there is a paucity of data to support the efficacy of these interventions to improve clinical outcomes for depressed CAD patients. Randomized clinical trials are needed to further evaluate the value of treating depression in CAD patients to improve survival and reduce morbidity. **Key words:** depression, coronary artery disease, physiological mechanisms, behavioral mechanisms, randomized clinical trials.

Depression as a Risk Factor for Mortality in Patients With Coronary Heart Disease: A Meta-analysis

Jürgen Barth, PhD, Martina Schumacher, MA, and Christoph Herrmann-Lingen, MD

Background: Prospective studies on physically healthy subjects have shown an association between depression and the subsequent development of coronary heart disease (CHD). The relative risk in meta-analytic aggregation is 1.64 (confidence interval [CI], 1.29–2.08) for any CHD event. However, the adverse impact of depression on CHD patients has not yet been the subject of a meta-analysis. **Objective:** To quantify the impact of depressive symptoms (eg, BDI, HADS) or depressive disorders (major depression) on cardiac or all-cause mortality. We analyzed the strength of the relationship, the time dependency, and the differences in studies using depressive symptoms or a clinical diagnosis as predictors of mortality. **Method:** English and German language databases (Medline, PsycInfo, PSYNDEX) from 1980 to 2003 were searched for prospective cohort studies. Sixty-two publications were identified. The inclusion criteria were met by 29 publications reporting on 20 studies. A random model was used to estimate the combined overall effect as crude odds ratios (OR) or adjusted hazard ratios (HR [adj]). **Results:** Depressive symptoms increase the risk of mortality in CHD patients. The risk of depressed patients dying in the 2 years after the initial assessment is two times higher than that of nondepressed patients (OR, 2.24; 1.37–3.60). This negative prognostic effect also remains in the long-term (OR, 1.78; 1.12–2.83) and after adjustment for other risk factors (HR [adj], 1.76; 1.27–2.43). The unfavorable impact of depressive disorders was reported for the most part in the form of crude odds ratios. Within the first 6 months, depressive disorders were found to have no significant effect on mortality (OR, 2.07; CI, 0.82–5.26). However, after 2 years, the risk is more than two times higher for CHD patients with clinical depression (OR, 2.61; 1.53–4.47). Only three studies reported adjusted hazard ratios for clinical depression and supported the results of the bivariate models. **Conclusions:** Depressive symptoms and clinical depression have an unfavorable impact on mortality in CHD patients. The results are limited by heterogeneity of the results in the primary studies. There is no clear evidence whether self-report or clinical interview is the more precise predictor. Nevertheless, depression has to be considered a relevant risk factor in patients with CHD. **Key words:** depression, coronary heart disease, mortality, meta-analysis, depressive symptoms, risk factor.

What do the experts say?

AHA Scientific Statement

Depression as a Risk Factor for Poor Prognosis Among Patients With Acute Coronary Syndrome: Systematic Review and Recommendations

A Scientific Statement From the American Heart Association

Judith H. Lichtman, PhD, MPH, Co-Chair; Erika S. Froelicher, RN, MA, MPH, PhD, FAHA, Co-Chair; James A. Blumenthal, PhD, ABPP; Robert M. Carney, PhD; Lynn V. Doering, RN, DNSc, FAHA; Nancy Frasure-Smith, PhD; Kenneth E. Freedland, PhD; Allan S. Jaffe, MD; Erica C. Leifheit-Limson, PhD; David S. Sheps, MD, MSPH, FAHA; Viola Vaccarino, MD, PhD, FAHA; Lawson Wulsin, MD; on behalf of the American Heart Association Statistics Committee of the Council on Epidemiology and Prevention and the C

Background—Although prospective studies, systematic revie depression and increased morbidity and mortality in a v formal recognition as a risk factor for poor prognosis in Association and other health organizations. The purpose recommend whether depression should be elevated to the

Methods and Results—Writing group members were appro and Manuscript Oversight Committees. A systematic liter acute coronary syndrome was conducted that included a for mortality and nonfatal events. The review assessed th the published studies. A total of 53 individual studies (32 mortality, and 22 on composite outcomes) and 4 meta-a studies in terms of the demographic composition of study follow-up, and covariates included in the multivariable m identified generally consistent associations between depr

Conclusions—Despite the heterogeneity of published stu supports the recommendation that the American Heart As for adverse medical outcomes in patients with acute coro

Key Words: AHA Scientific Statements ■ acute co ■ risk

- Depression should be elevated as risk factor for poor prognosis after MI but…..
- Need to clarify the role of depression as a potential risk factor for incident CHD

Recommendations….

The role of depression in the primary prevention of cardiovascular disease

TO THE EDITOR: The latest guidelines for the management of absolute cardiovascular disease (CVD) risk released by the National Vascular Disease Prevention Alliance[1] question the utility of conventional risk assessment methods to accurately estimate cardiovascular risk of individuals with depression. Subsequently, these guidelines advocate that individuals assessed for CVD risk be assessed for depression and other psychosocial factors. This appears to be a promising advance, as the current scope of CVD prevention and management activities in medical and public health spheres remains somewhat limited to more traditional risk factors.

Indeed, the World Health Organization identifies tobacco, alcohol use, physical inactivity and poor diet as the key risk factors for CVD.[2] Notwithstanding the importance of these factors and their contribution to conditions that accelerate the onset of CVD (eg, hypertension, hypercholesterolaemia, obesity), it is now clear that depression is also an important risk factor for CVD. For individuals with both conditions, depression commonly begins decades before clinical manifestation of CVD.[3] Such evidence not only provides important insights into the pathogenesis of CVD, but also highlights a unique opportunity for CVD prevention through early intervention in depressed populations.

The de-emphasis on depression in primary CVD prevention to date is likely for two reasons: first, the remaining gaps in our understanding of the relationship between depression and CVD, and particularly, of the key mediators underpinning this association; and second, the lack of a sound evidence base for suitable interventions. It has been argued that "we urgently need randomized studies … to establish which treatment is most effective in reducing the risk for CVD".[4] We can help close this research gap by improving our understanding of the role of depression in the pathogenesis of CVD, and developing interventions that target depressed individuals for reduction of CVD risk.

As the contribution of CVD and mental disorders to Australia's disease burden remains substantial,[5] with each a National Health Priority Area, there is an urgent need to expand on existing primary prevention strategies to reduce the CVD-related burden in this country. We need a greater emphasis on promoting CVD risk reduction in populations with poor mental health, which are particularly susceptible to the onset of CVD. The acknowledgement and inclusion of mental health assessment in these latest guidelines appears an important step in expanding on putative risk factors.

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This approach may lead to:
"undue worry about the risk of CHD by individuals diagnosed with depression" or "over-diagnosis & over-treatment of depression"

"In light of identified methodological shortcomings and the inconsistent findings reported we suggest that there is as yet no convincing evidence that depression is an independent causal risk factor for CHD".

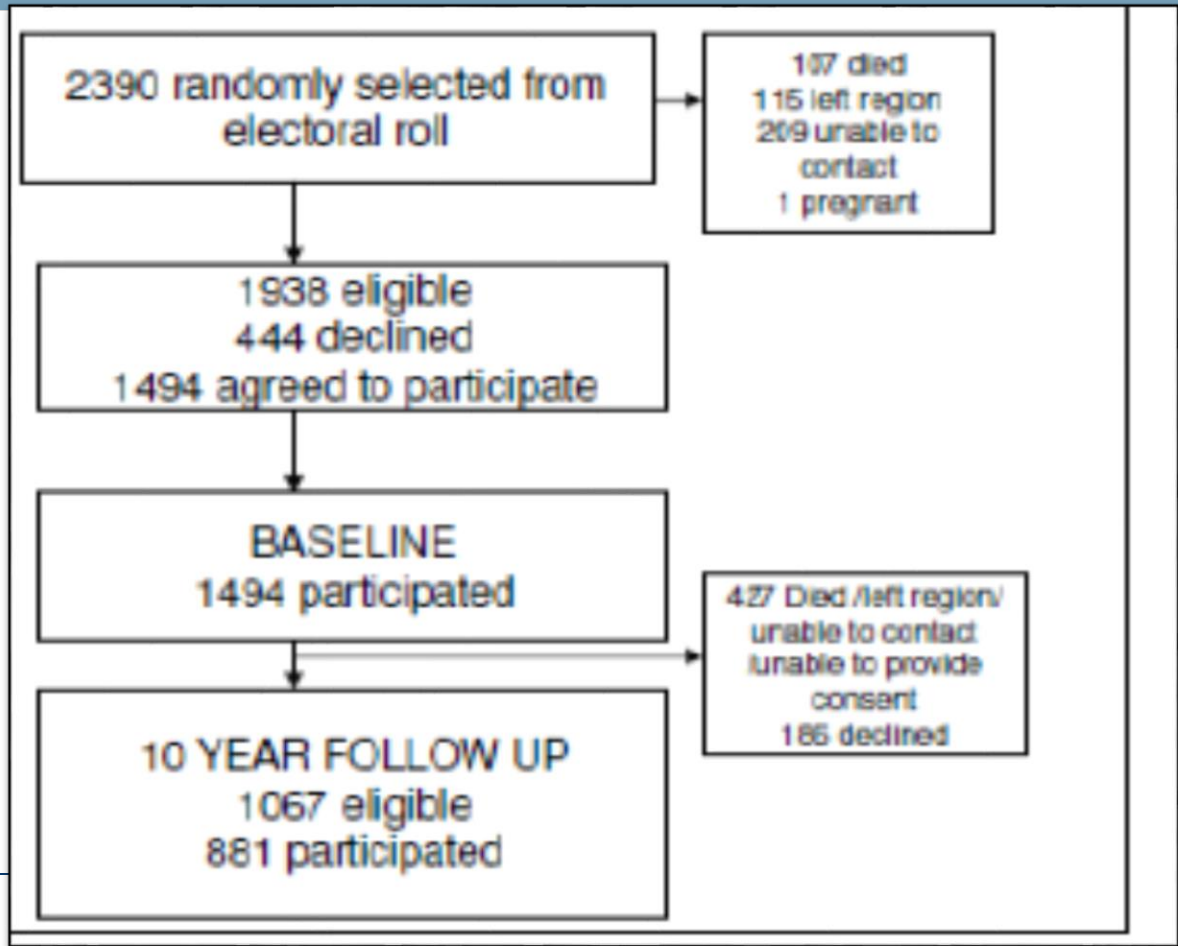
Stampfer HG, Hince DA, Dimmitt SB. Depression as a risk factor for coronary heart disease – how strong is the evidence? *O J Psych* 2012; 2: 284-291

Study setting

- Total & female population of 259,013 & 132,124, respectively.
- Geelong (45 mins west of Melbourne) in South East Australia
- Well suited to epidemiological research
- Populations from a range of social, cultural and geographical settings

Study Design

Does any depressive disorder identified at baseline independently predict CHD in women?



Study Measurements

Exposure: Primary/secondary diagnosis of depressive disorder

Data extracted from Geelong hospitals between 1993 and 2011 on:

Primary outcome:

- Cardiac death
- Non-fatal Myocardial Infarction
- Coronary intervention.

Secondary outcome

Any cardiac event (un/stable angina, cardiac event not otherwise defined)

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Results: Regression analyses

n=860	adj. OR	95% CI
Baseline Depression (unadjusted)	2.39	(1.19, 4.82)*
Baseline Depression (adjusted Model 1) ^	3.22	(1.45, 6.93)*
Baseline Depression (adjusted Model 2)&	3.28	(1.36, 7.90)*

^typical risk factors; & (a)typical risk factors

- Results slightly weaker when expanding outcome to include Depression did not predict ***number*** of CHD events

O'Neil et al. (2016) Journal of Affective Disorders. http://dx.doi.org/10.1016/j.jad.2016.02.029

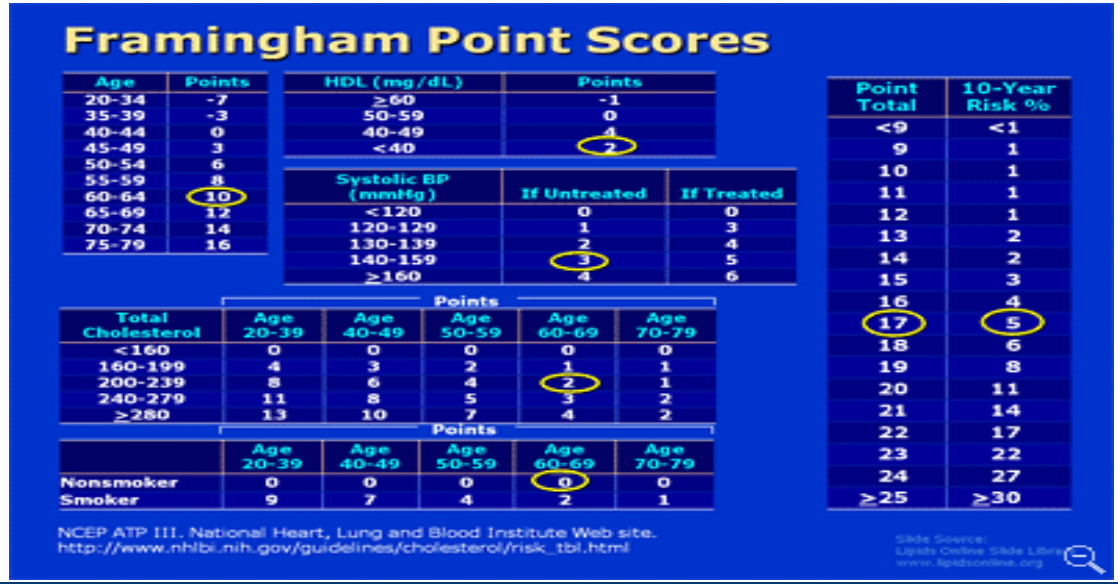
Conclusions

- Validate the host of other studies in this area indicating depression is a risk factor for incident CHD
- Adds to the evidence base for AHA consideration
- What does this mean for identification, prevention & treatment?

Example: Risk Assessment

- Framingham Risk Equation
- Incorporates 6 variables to assess patients' % CHD risk over 10 years:

✓ Age
✓ HDL cholesterol
✓ Total cholesterol
✓ Systolic BP
✓ Smoking status
✓ Taking BP medication



Framingham Point Scores

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Points

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

Points

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

Point Total	10-Year Risk %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

NCEP ATP III. National Heart, Lung and Blood Institute Web site.
http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.html

Slide Source:
Lipids Online Slide Library
www.lipidsonline.org

Framingham Heart Study

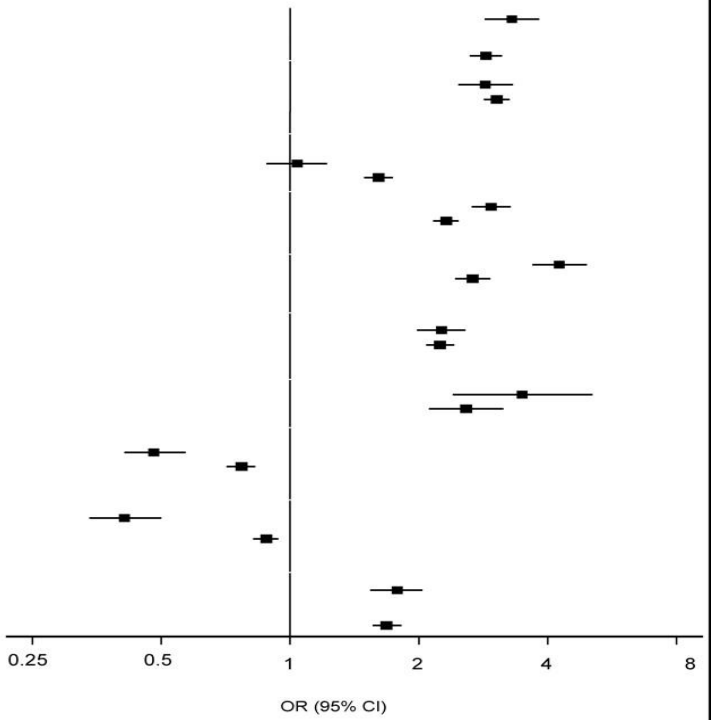
Limitations:

- Underestimates risk of subclinical CHD among asymptomatic women
- Considers only traditional risk factors
- Omitting less conventional risk factors, like depression is a serious deficiency affecting accuracy

Risk factors for “heart attack”

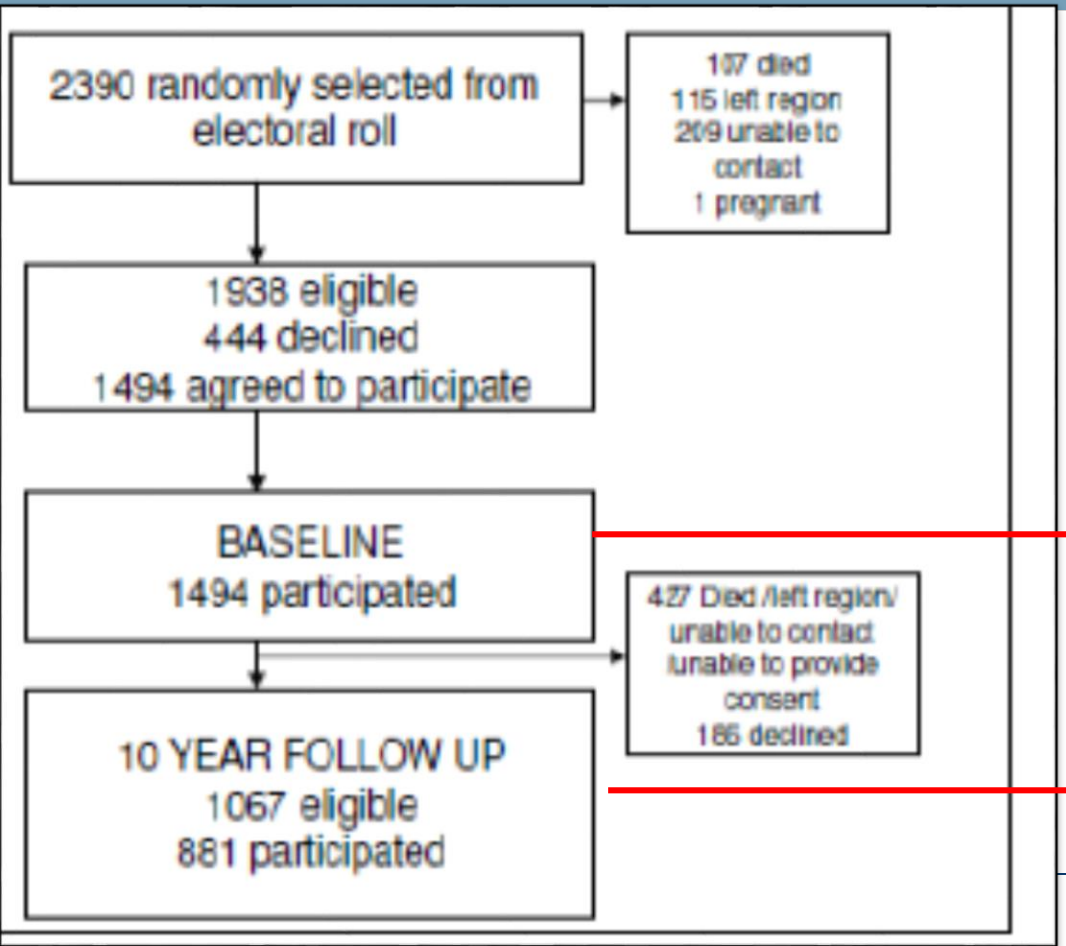
- Social isolation
- Stress
- Common Mental Disorders: anxiety, depression

Risk factor		Control prevalence	Odds ratio (95% CI)	*P*-value for interaction
ApoB/ApoA-1 ratio	♀	24.3	3.30 (2.85,3.82)	0.20
	♂	36.2	2.87 (2.63,3.13)	
Current smoking	♀	9.2	2.86 (2.47,3.32)	0.06
	♂	33.0	3.04 (2.84,3.26)	
Former smoking	♀	11.6	1.04 (0.88,1.22)	<0.0001
	♂	24.7	1.61 (1.49,1.74)	
Hypertension	♀	28.3	2.95 (2.66,3.28)	0.0001
	♂	19.7	2.32 (2.16,2.48)	
Diabetes	♀	7.97	4.26 (3.68,4.94)	<0.0001
	♂	7.40	2.67 (2.43,2.94)	
Abdominal obesity	♀	33.3	2.26 (1.98,2.57)	0.03
	♂	33.3	2.24 (2.08,2.42)	
Psychosocial	♀	88.6	3.49 (2.40,5.09)	0.02
	♂	88.8	2.58 (2.11,3.15)	
Physical activity	♀	16.5	0.48 (0.41,0.57)	<0.0001
	♂	20.3	0.77 (0.71,0.83)	
Alcohol	♀	11.2	0.41 (0.34,0.50)	<0.0001
	♂	29.01	0.88 (0.82,0.94)	
High risk diet	♀	17.9	1.78 (1.54,2.04)	0.20
	♂	23.3	1.68 (1.56,1.82)	



Yusuf S et al. INTERHEART: case-control study. Lancet. 2004;364:937-52.

Geelong Osteoporosis Study



Aim: to determine accuracy of augmented FRE that includes depression as a predictor

- Barwon residents randomly selected from electoral rolls
- Women (20-94 years)

BASELINE: Smoking, SBP, Total, HDL lipids, medication for BP

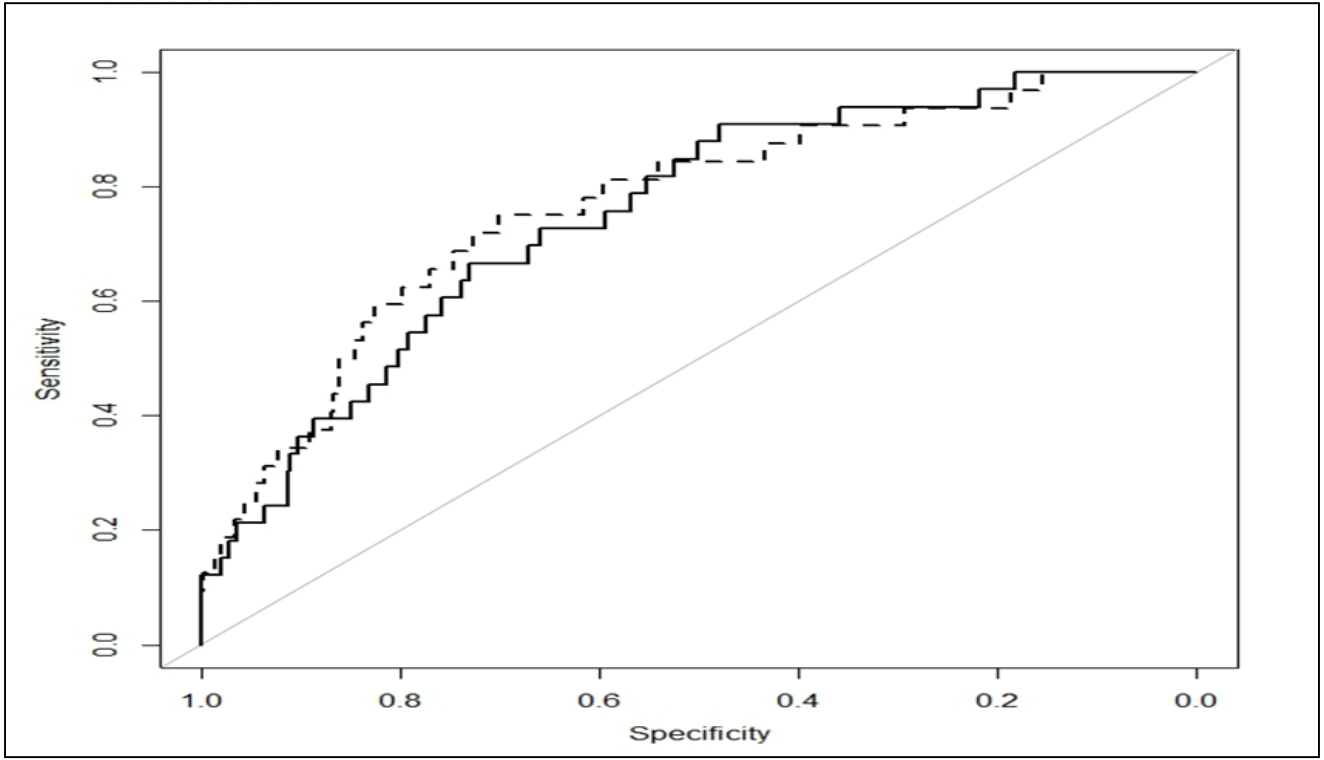
10 years: Psychiatric interview (age of onset) Retrospective data linkage with hospital records (CHD events by adjudication panel; BL to 10 years)

Results

FRE variables plus depression	*OR*	*95% CIs*	*p value*
Age	**1.05**	**1.02, 1.08**	**0.003**
Smoker	2.26	0.95, 5.38	0.07
HDL (mmol/L)	0.44	0.17, 1.15	0.09
Total Cholesterol (mmol/L)	1.23	0.90, 1.68	0.18
Systolic Blood Pressure (mm Hg)	1.00	0.98, 1.02	0.95
Blood Pressure Medication	**2.34**	**1.07, 5.14**	**0.03**
Baseline Depression Status	**2.62**	**1.22, 5.60**	**0.01**

Age, BP Medication and depression at baseline significant predictors

New Risk Equation for Women



Better overall accuracy

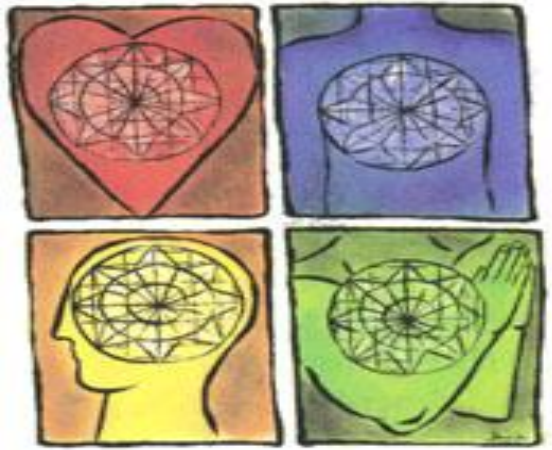
↑ true positives, at small increase in false positive rate.

Original Framingham Risk Equation (solid line), Augmented to include depression (dashed) over 10-year

O'Neil, et al (Preventive Medicine, In Press)

Conclusions

- Depression appears a independent risk **factor** for CHD in women
- Accuracy of risk assessment models could be improved with inclusion of mental health parameters
- But what is the effort – reward?
- May assist in setting accurate threshold targets for determining allocation of resources
- Requires validation in: larger samples, men, using proxy markers/self-reported measures



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Implications

COMMENTARY Open Access

A shared framework for the common mental disorders and Non-Communicable Disease: key considerations for disease prevention and control

Adrienne O'Neil[1,2,3*], Felice N Jacka[4,5,6], Shae E Quirk[1], Fiona Cocker[7], C Barr Taylor[3], Brian Oldenburg[7] and Michael Berk[1,8,9]

Abstract

Background: Historically, the focus of Non Communicable Disease (NCD) prevention and control has been cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), cancer and chronic respiratory diseases. Collectively, these account for more deaths than any other NCDs. Despite recent calls to include the common mental disorders (CMDs) of depression and anxiety under the NCD umbrella, prevention and control of these CMDs remain largely separate and independent.

Discussion: In order to address this gap, we apply a framework recently proposed by the Centers for Disease Control with three overarching objectives: (1) to obtain better scientific information through surveillance, epidemiology, and prevention research; (2) to disseminate this information to appropriate audiences through communication and education; and (3) to translate this information into action through programs, policies, and systems. We conclude that a shared framework of this type is warranted, but also identify opportunities within each objective to advance this agenda and consider the potential benefits of this approach that may exist beyond the health care system.

Keywords: Non-Communicable Disease, Common mental disorders, Prevention, Depression, Anxiety, Cardiovascular disease, Type 2 diabetes mellitus, Co-morbidity

- Greatest victories in cardiology occurred through prevention targeting putative risk factors
  - ✓ Smoking
  - ✓ Blood pressure
  - ✓ Advances in pharmacotherapy
  - ? Mental health
- Composite approaches to prevention & treatment are warranted

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