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Clinical prediction of incident heart failure risk: a systematic review and meta-analysis

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ABSTRACT

Background: Early treatment may alter progression to overt heart failure (HF) in asymptomatic individuals with stage B HF (SBHF). However, the identification of patients with SBHF is difficult. This systematic review sought to examine the strength of association of clinical factors with incident HF, with the intention of facilitating selection for HF screening.

Methods: Electronic databases were systematically searched for studies reporting risk factors for incident HF. Effect sizes, typically HRs, of each risk variable were extracted. Pooled crude and adjusted HRs with 95% CIs were computed for each risk variable using a random-effects model weighted by inverse variance.

Results: Twenty-seven clinical factors were identified to be associated with risk of incident HF in 15 observational studies in unselected community populations which followed 456 850 participants over 4–29 years. The strongest independent associations for incident HF were coronary artery disease (HR=2.94; 95% CI 1.36 to 6.33), diabetes mellitus (HR=2.00; 95% CI 1.68 to 2.38), age (HR (per 10 years)=1.80; 95% CI 1.13 to 2.87) followed by hypertension (HR=1.61; 95% CI 1.33 to 1.96), smoking (HR=1.60; 95% CI 1.45 to 1.77), male gender (HR=1.52; 95% CI 1.24 to 1.87) and body mass index (HR (per 5 kg/m^2)=1.15; 95% CI 1.06 to 1.25). Atrial fibrillation (HR=1.88; 95% CI 1.60 to 2.21), left ventricular hypertrophy (HR=2.46; 95% CI 1.71 to 3.53) and valvular heart disease (HR=1.74; 95% CI 1.07 to 2.84) were also strongly associated with incident HF but were not examined in sufficient papers to provide pooled hazard estimates.

Conclusions: Prediction of incident HF can be calculated from seven common clinical variables. The risk associated with these may guide strategies for the identification of high-risk people who may benefit from further evaluation and intervention.

KEY MESSAGES

What is already known about this subject?

- A variety of risk factors are known to be associated with heart failure (HF)—ranging from social determinants of health to lifestyle characteristics (smoking, physical inactivity, increased salt intake) and common comorbidities (hypertension (HTN), type 2 diabetes mellitus, coronary artery disease (CAD), obesity and metabolic syndrome and precursors of myocardial disease including a history of chemotherapy or a family history of cardiomyopathy.

What does this study add?

- The relative magnitude of these risk factors, and their combined effects, are not well known. This systematic review sought to examine the strength of association of clinical factors with incident HF, with the intention of creating a practical clinical score to facilitate selection for HF screening. The strongest associations for incident HF (adjusted HR ≥2) were CAD (HR=2.94; 95% CI 1.36 to 6.33) and diabetes mellitus (HR=2.00; 95% CI 1.68 to 2.38). Adjusted HRs ≥1 were age (HR (per 10 years)=1.80; 95% CI 1.13 to 2.87), HTN (HR=1.61; 95% CI 1.33 to 1.96), smoking (HR=1.60; 95% CI 1.45 to 1.77), male gender (HR=1.52; 95% CI 1.27 to 1.59) and body mass index (HR (per 5 kg/m^2) =1.15; 95% CI 1.06 to 1.25).

How might this impact on clinical practice?

- The early detection of asymptomatic patients with left ventricular dysfunction is now possible with a variety of sensitive biochemical and imaging techniques, and should lead to the use of cardioprotective strategies to prevent progression of disease. The estimation of HF risk is a critical step in appropriate selection of patients for imaging.

The incidence and prevalence of heart failure (HF) are growing and assuming epidemic proportions, affecting an estimated 23 million people worldwide.[1] In the USA, 5 million people suffer from HF with a rate of 550 000 new cases diagnosed each year.[2] HF is predominantly a problem of old age, the most frequent cause of hospitalisation in the elderly and a major burden on the community due to the cost of care and poor quality of life. The total direct and indirect cost of HF in the USA exceeds $30 billion,[3] where it accounts for 12–15 million office visits and 6.5 million hospital days each year.[2]

The morbidity and cost of late-stage HF may be delayed or even prevented by pharmacological interventions, once evidence of structural heart disease (stage B HF, SBHF) has been defined.[4–9] Subclinical cardiac impairment is most readily identifiable in patients with prior myocardial infarction. Identification of SBHF in approximately 50% of patients with HF who are non-ischaemic might be possible with echocardiographic or biochemical screening,[10] but this would be most feasible if there was a means of identifying risk on clinical grounds. Various risk factors have been associated with HF, ranging from lifestyle characteristics such as smoking, physical inactivity, increased salt intake and lower socioeconomic status to common comorbidities including hypertension (HTN), type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), obesity and metabolic syndrome (MS). Risk factors also include a history of chemotherapy or a family history of cardiomyopathy.[11 12] We undertook a systematic review and meta-analysis of studies reporting risk factors relating to incident HF in unselected community-based populations. The goal of this was to identify a series of clinical markers which could be used to identify participants from a community-based population in whom further evaluation and intervention might be warranted.

METHODS

Search strategy

The research strategy, study selection and analysis method used in the study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).[13] Electronic databases (MEDLINE, EMBASE) were systematically searched for published studies reporting risk factors related to incident HF. Search key terms were: 'incident heart failure' and 'risk factors', 'risk assessment', 'risk impact', 'risk prediction', 'risk score', 'risk prevention'. To ensure the identification of all relevant articles and publications, the reference lists of these articles were also reviewed to identify additional studies. The last search was performed on 7 October 2013.

Study inclusion

From these lists, studies were included if they met each of the following criteria: (1) studies of a full-length publication in a peer-reviewed English language journal; (2) studies carried out on human adults >18 years of age; (3) studies carried out on an unselected community population; (4) studies reporting risk factors relating to incident HF; (5) studies using Cox proportional hazard models reporting risk effect sizes in HR with 95% CIs and/or associated p value. This review incorporated mainly observational cohort studies.

Outcomes

The primary outcome of interest was incident HF. The criteria for identification of incident HF were described as one or more of the following: (1) medical diagnosis from physician's records; (2) evidence of treatment for HF (ie, diuretics and either digitalis or a vasodilator); (3) hospital or nursing home stays in which the participant had a discharge diagnosis with a code of International Statistical Classification of Diseases and related health problems (ICD-9 code of 428.0 to 428.9); (4) death certificate report in which the underlying cause of death was recorded using an ICD-9 code of 428.0 to 428.9.

Data extraction

Data were extracted independently by reviewers (HY, KN and PO). All discrepancies were reviewed and resolved by consensus. For the systematic review, the following data concerning the individual study populations were extracted: demographic and clinical characteristics and associated risk prevalence at baseline; study design; years of follow-up; statistical models; statistic models; risk effect sizes and their associated 95% CIs with p values; covariates included in the risk assessment models in relation to outcome. In situations in which multiple articles were published from a single cohort, data were included only if different risk variables were analysed and reported.

Statistical analysis

Reported risk effect sizes and the statistical models used in each study were reviewed. Crude measures of effect with 95% CIs were extracted for each risk variable. Multiple within-study effects stratified in subgroups were combined by weighting each group by its number of participants. Study risk estimates reported per categorical change were recalculated as continuous variables for body mass index (BMI).[14] Risk estimates from the majority of studies were estimated using Cox proportional hazard models and pooled as HRs (although some incorrectly labelled these as relative risk/rate).[15 16] Risk estimates reported as 'Relative Risk' using the Mantel-Haenszel[17] or linear regression model[18] or OR using the logistic regression model[19] were excluded for further analysis. Consequently, pooled risk estimates were all from studies using Cox proportional hazard models and were suitable for providing summary risk estimates. Both unadjusted and maximally adjusted risk effects were pooled using random-effects models weighted by inverse variance.[20] Further, a subset of studies reporting seven mutually adjusted risk effects (age, male gender, BMI, smoking, HTN, diabetes mellitus (DM) and CAD) were also pooled. When CIs were not reported, their associated p values were used to estimate variance of the risk estimate.[21]

The Cochrane Q statistic and I^2 values index were used to assess the degree of heterogeneity across studies. Funnel plots were constructed and Egger's test was used to assess potential publication bias. Duval and Tweedie's trim and fill method was used to assess the potential effects of publication bias on risk estimates. Meta-

regression was also performed for each risk factor to examine possible study factors associated with heterogeneity. The assessment of study quality was performed using the Newcastle-Ottawa Scale (NOS) for non-randomised studies in meta-analyses.[22] Statistical analysis was performed using statistics package R V.3.1.1.

RESULTS

Study selection

The process of article selection based on PRISMA guidelines is presented in figure 1. After exclusion of duplicates, the initial search revealed a total of 1974 original articles published from 1967 to 2013. After exclusion of inappropriate papers, or studies without relevant risk analysis, there were 15 studies eligible for inclusion, from which 4 had more than one eligible article either from the same data set or from a pilot study set. Therefore, a total of 20 articles were systematically reviewed and eligible for quantitative synthesis (figure 1).[15–17 21 23–38] Risk estimates from two articles[23 24] were not included in the meta-analysis since they duplicated estimates from the same cohort, and estimates from Gottdiener *et al*[16] and Mujib *et al*[21] were only included where they were absent from the corresponding articles on the same cohorts; a similar approach was applied to risk estimates from Butler *et al*[26] and Kalogeroupoulos *et al*,[17] respectively. The included articles were published between 1993 and 2013.

Baseline characteristics

The baseline demographic characteristics of included studies (15 prospective cohort studies) are summarised in table 1. The geographic distribution of the studies was predominantly in North America and Europe (11 studies in the USA, 4 in Europe). There were a total of 456 850 participants—the reported mean age of participants was 24–81 years (weighted mean 42±13 years), the proportion of male participants ranged from 32% to 100% (weighted mean 49±9%), and the majority of participants were Caucasian 39–100% (weighted mean 64±6%). Over an average follow-up time of 4–29 years, there were 11 467 incident HF cases, giving an average cumulative incident HF rate of 0.97±0.11% (table 1).

The detailed baseline prevalence of cardiovascular and non-cardiovascular comorbidities is summarised in online supplementary appendices A1 and A2. The BMI was 25–28 kg/m^2 (weighted mean 26±3 kg/m^2). The prevalence of DM varied from 2% to 25% (weighted mean 4±1%), CAD varied from 0.3% to 44% (weighted mean 2.2±0.2%), HTN 3–58% (weighted mean 16±2%) and left ventricular hypertrophy (LVH) 1.5–31% (weighted mean 6±1%). In the study populations, 22–78% were either current or past smokers.

Clinical factors associated with incident HF

Twenty-seven variables were reported to be associated with incident HF, including 20 clinical variables, 6 biomarkers and 1 echocardiographic marker. These variables were age, male gender, black race, family history of cardiac disease, excessive use of alcohol, smoking, physically inactive, obesity, education level, DM, CAD, LVH by ECG, HTN, chronic obstructive pulmonary disease, valvular heart disease (VHD), chronic kidney disease, stroke, resting heart rate, atrial fibrillation (AF), abnormal ECG which includes bundle branch block, ST-T and QRS changes, and echocardiographic left ventricular ejection fraction (EF). Biomarkers were fasting glucose, C reactive protein, creatinine, albumin, dyslipidaemia and N-terminal-pro-brain natriuretic peptide (NT-proBNP).

Crude and adjusted risk ratios were extracted. The reporting details of each risk variable and overall reporting frequency are summarised in appendix B. We selected variables only if they were reported in four or more of the included studies for quantitative synthesis. Thirteen variables met this requirement. We excluded abnormal ECG due to heterogeneous criteria based on the presence of QRS changes,[27] ST-T changes[16] and bundle branch block.[25] We also excluded dyslipidaemia and fasting glucose, due to inconsistency in categorical[15 30 34 38] as well as continuous cut-offs of these two biomarkers[25–27 33] in risk calculation between studies. Therefore, a total of 11 risk variables (age, male gender, black race, obesity, smoking, DM, CAD, HTN, LVH, VHD and AF) were selected for further synthesis. Pooled unadjusted and adjusted HRs with 95% CIs are listed in table 2.

The details of other factors used in multivariate models of included studies are summarised in appendix C.

Strength of independent association with incident HF

Further subset meta-analyses were conducted from six studies,[15 16 25 33 36 38] where each of seven risk variables was mutually adjusted in models within each study. The strength of independent association for incident HF was highest for CAD (2.94 (1.36 to 6.33)) followed by DM (2.00 (1.68 to 2.38)) and age (per 10 years increase; 1.8 (1.13 to 2.87); table 3).

Publication bias, sensitivity and study quality

Egger's test for pooled adjusted risk indicated significant bias for the estimates of BMI, male gender and AF (table 2B), and BMI for mutually adjusted risk estimates (table 3). No publication bias was detected for crude estimates (table 2A). Duval and Tweedie's trim and fill results are presented for all risk estimates where at least three studies were pooled. The NOS[22] for cohort studies is summarised in appendix D; most studies were of high quality.

Exploration of study heterogeneity

Metaregression was performed for each of the seven risk factors in the mutually adjusted models; the following study factors were examined: follow-up time, cumulative incidence, mean age, male proportion, smoking

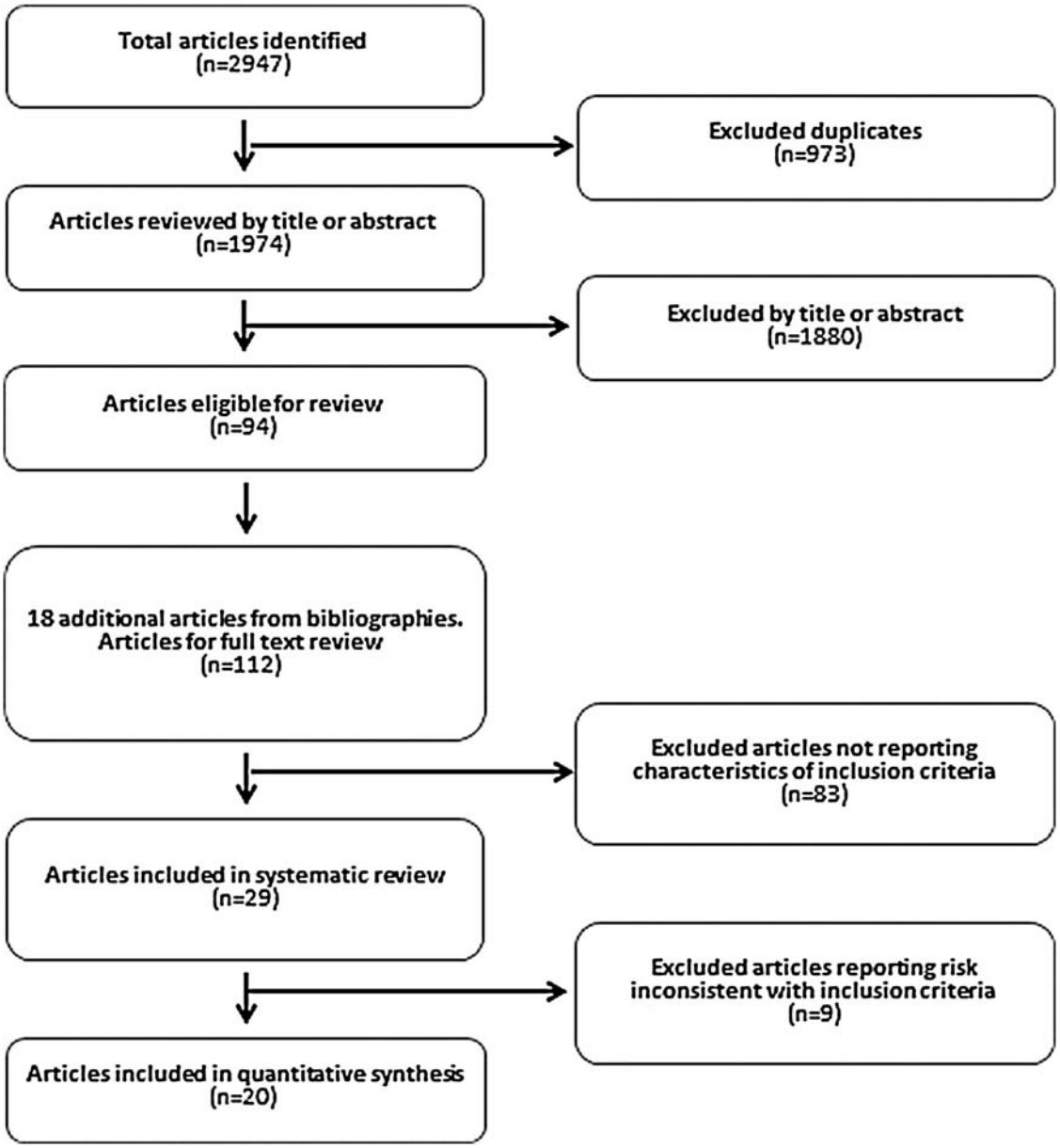

Figure 1 Process of article selection based on PRISMA.

proportion, mean BMI, DM proportion, HTN proportion, VHD proportion, CAD proportion and study quality. Even though the estimates from these seven studies were adjusted for smoking, the pooled risk effect of DM increases by approximately 10% for each 10% increase in the proportion of smokers in a study, implying some interaction between these risks. Likewise, the pooled risk effect of male sex increases by 38% for each 10% increase in the proportion of participants with diabetes in a study.

DISCUSSION

The findings of this systematic review demonstrated 11 common cardiovascular and non-cardiovascular risks associated with incident HF. Results from meta-analysis revealed the independent risk associated with the seven most common comorbidities. Knowledge of the relative effect sizes may facilitate the process of risk assessment in a community-based population. The factors most strongly independently associated with incident HF were CAD (2.94 (1.36 to 6.33)) followed by DM (2.00 (1.68 to 2.38)).

Calculation of HF risk

Although the role of HF risk factors has been documented in numerous previous publications, the reported level of risk has been heterogeneous, so the relative contribution of each factor to the development of HF remains controversial. To date, three population-based studies have sought to integrate risk factors into a single estimate of HF risk.[24 26 27] Of these, the Atherosclerosis Risk in Communities (ARIC) HF risk score is a well-validated parsimonious score, whereas concern has been

Table 1 Baseline population demographic characteristics and risk prevalence

	Author(s)	Publish (year)	Trial (study name)	Total (n)	Follow-up (year)	Incident HF (n)	Cumu incidence (%)	Age (years)	Male (%)	Risk ratio	Stats model used	Smoke (%)	BMI	DM (%)	CAD (%)	LVH (%)	HTN (%)	VHD (%)
1	Ho *et al*[23]	1993	Framingham	9405*	40*	652*				RR	CPH							
	Kannel *et al*[24]	1999	and offspring	15 267 pe*	38*	486*				OR	PLR							
	Ho *et al*[25]	2013	(USA)	6340	8	512	8.1	60±12	46	HR	CPH	22	27±4	7	8	8	46	1
2	Butler *et al*[26]	2008	Health ABC	2934	7	258	8.8	74±2.9	48	HR	CPH	56	27.3±4.8	15	17	12	43	
	Kalogeropoulos *et al*[17]	2009	study (USA)							RR	MH							
3	He *et al*[15]	2001	NHANES (USA)	13 643	19	1382	10.1	50±15	41	Risk ratio	CPH	35	25.6±5	4	5		28	5
4	Agarwal *et al*[27]	2012	ARIC (USA)	13 555	16	1487	11.0	54±5.8	45	HR	CPH	25	27.6±5.2	10	4	2		1
5	Goyal *et al*[28]	2010	Million P-Yr (USA)	359 947	5	4001	1.1	38±14	47	HR	CPH			3	1		12	1
6	Bahrami *et al*[29]	2008	MESA (USA)	6814	4	79	1.2	65±0.7	47	HR	CPH	49	28.4±0.1	14		10	48	
	Bahrami *et al*[30]	2008																
7	Gottdiener *et al*[16]	2000	Cardio	5625	12	597	10.6	73±4.5	42	RR	CPH	54		17			58	
	Mujib *et al*[21]	2010	Vascular Health (USA)							HR	CPH							
8	Chen *et al*[31]	1999	EPESE (USA)	1749	8	173	9.9	74±6.8	41	HR	CPH	78		11			54	
9	Bibbins-Domingo *et al*[32]	2009	CARDIA (USA)	5115	20	27	0.5	24±3.5	45	HR	CPH	31	24.5±4.8	2		6	3	
10	Ingelsson *et al*[33]	2005	ULSAM (Sweden)	2321	29	259	11.2	50±0.0	100	HR	CPH	51	25±3.2	6	0	2	43	
11	Wang *et al*[34]	2010	Kuopio (Finland)	1032	21	303	29.4	69±2.8	38	HR	CPH	29	27.2±4.0	17	7	31	26	
12	Aronow *et al*[35]	1999	Mt Sinai (USA)	2902	4	794	27.4	81±8.0	32	HR	CPH			25	44		46	
13	Smith *et al*[36]	2010	MDCS (Sweden)	5187	14	112	2.2	58±5.9	41	HR	CPH	27	25.7±3.9	8	2		17	
14	Kenchaiah *et al*[37]	2009	Physician's heart (USA)	21 094	21	1109	5.3	53±9.4	100	HR	CPH	48	24.8±1.4	3	9		24	
15	Brouwers *et al*[38]	2013	Prevend (the Netherlands)	8592	12	374	4.4	49±12	50	HR	CPH	38	26±4.0	4	6		32	
	Sum	1993–2013	15 studies	456 850	198	11 467												
	Mean (weighted)			30 457	7	3323	0.97	42	49			39	26	4	2.23	6	16	1
	SD (weighted)				1.0	811	0.11	12.6	9			2.70	3	1	0.23	1	3	0.2
	Maximum			359 947	29	4001	29.36	81	100			78	28	25	44	31	58	5
	Minimum			1032	4	27	0.53	24	32			22	25	2	0.3	1.5	3.0	0.5

*Duplicated counts from a single study, not included in total and cumulated incidence.
ARIC, the Atherosclerosis Risk in Communities; BMI, body mass index; CAD, coronary artery disease; CARDIA, Coronary Artery Risk Development in Young Adults; CPH, Cox proportional hazard; Cumu incidence, cumulative incident rate; CVH, Cardio Vascular Health study; DM, diabetes mellitus; EPESE, Established Population for Epidemiologic Studies of the Elderly programme; FHS, Framingham Heart Study; HABC, Health Aging and Body Composite Study; HF, heart failure; HTN, hypertension; Kuopio, Kuopio Finland study; LVH, left ventricular hypertrophy; MDCS, the Malmo Diet and Cancer Study in Swedish people; MESA, Multi-Ethnic Study of Atherosclerosis; MH, Mantel-Haenszel; Million P-Yr, One Million Person-Year study; Mt Sinai, Study at Mt Sinai; NHANES, National Health Nutrition Examination Survey; pe, person examination; Physician Heart, the Physician heart study; PLR, pooled logistic regression; Prevend, Prevention of Renal and Vascular End-stage Disease; P-Yr, person year; RR, relative risk; ULSAM, Uppsala Longitudinal Study of Adult men; VHD, valvular heart disease.

Table 2 Pooled risk estimates for common risk variables, unadjusted and adjusted for various confounders

	Pooled HR	95% CI	I^2	Study (n)	Q-χ^2	Q-p value	Egger's test	Trim-fill HR (95%CI)
(A) Unadjusted								
BMI (5 kg/m^2)	**1.54**	**1.21 to 1.95**	96.5	4	86.2	<0.001	0.553	1.28 (1.03 to 1.59)
Gender (male)	**1.51**	**1.07 to 2.12**	52.5	3	4.2	0.122	0.916	1.51 (1.07 to 2.12)
Smoker (yes)	**1.82**	**1.49 to 2.23**	48.0	4	5.8	0.123	0.505	2.03 (1.65 to 2.49)
Race (black)	**1.78**	**1.60 to 1.98**		1				
Age (10 years)	**2.29**	**2.09 to 2.51**	57.2	4	7.0	0.072	0.842	2.29 (2.09 to 2.51)
HTN (yes)	**3.49**	**1.25 to 9.74**	98.5	4	195.9	<0.001	0.111	8.35 (3.16 to 22.09)
Diabetes (yes)	**3.27**	**2.27 to 4.72**	93.3	6	74.6	<0.001	0.278	4.49 (3.15 to 6.39)
VHD (yes)	**3.92**	**1.85 to 8.31**	96.2	2	26.2	<0.001	*	
CAD (yes)	**5.07**	**2.47 to 10.40**	97.5	4	120.5	<0.001	0.496	9.63 (4.64 to 20.00)
LVH (yes)	**4.4**	**2.25 to 8.58**	87.2	5	31.3	<0.001	0.527	3.29 (1.63 to 6.64)
AF (yes)	**13.77**	**11.79 to 16.08**		1				
(B) Adjusted								
BMI (5 kg/m^2)	**1.21**	**1.10 to 1.33**	94.1	9	134.8	<0.001	0.062	1.05 (0.96 to 1.16)
Gender (male)	**1.51**	**1.32 to 1.72**	58.1	8	16.7	0.019	0.020	1.32 (1.14 to 1.53)
Smoker (yes)	**1.65**	**1.45 to 1.88**	43.3	8	12.3	0.090	0.201	1.56 (1.34 to 1.82)
Race (black)	**0.96**	**0.75 to 1.23**	73.3	4	11.3	0.010	0.825	0.91 (0.72 to 1.16)
Age (10 years)	**1.70**	**1.33 to 2.16**	99.1	9	848.2	<0.001	0.949	1.70 (1.33 to 2.16)
HTN (yes)	**1.79**	**1.41 to 2.27**	91.9	11	123.7	<0.001	0.533	2.55 (1.92 to 3.37)
Diabetes (yes)	**1.94**	**1.71 to 2.19**	56.4	11	23.0	0.011	0.400	1.94 (1.71 to 2.19)
VHD (yes)	**1.74**	**1.07 to 2.84**	92.9	3	28.0	<0.001	0.150	1.74 (1.07 to 2.84)
CAD (yes)	**2.90**	**1.85 to 4.54**	97.2	9	285.5	<0.001	0.987	2.90 (1.85 to 4.54)
LVH (yes)	**2.46**	**1.71 to 3.53**	74.1	6	19.3	0.002	0.431	2.17 (1.47 to 3.19)
AF (yes)	**1.88**	**1.60 to 2.21**	16.2	4	3.6	0.310	0.020	1.99 (1.66 to 2.39)

*Egger's test was used only if the number of studies was three or greater.
AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; HTN, hypertension; LVH, left ventricular hypertrophy; VHD, valvular heart disease.
Columns in bold correspond to pooled HR (95%CI) to differentiate from the Trim-fill HR (95%CI) in the same table. The latter is obtained from Duval and Tweedie's method to check for publication bias.

expressed regarding the selection of patients into the Framingham Heart Failure Risk Score (which is much influenced by ischaemic aetiology), and the Health ABC Heart Failure Score requires blood testing that may not be accessible at community screening.

It is paradoxical that while the performance of an echocardiogram is considered appropriate in patients with symptomatic HF, its use in the preclinical stage is considered inappropriate.[39] Perhaps this is the reason that screening for HF has not been widely applied, even in at-risk patients such as those with DM, HTN and CAD, despite the wide availability of echocardiographic assessment of systolic and diastolic dysfunction. Moreover, left ventricular (LV) assessment using two-dimensional imaging may be hard to reproduce, and although there have been initial reports of both in community studies,[40] the place of both in community screening is undefined. In any case, some clinical definition of risk would still be required.

HF screening

SBHF lies between overt HF (stages C and D) and patients with HF risk factors (stage A). These asymptomatic patients have evidence of LV damage, which may be

Table 3 Pooled HR estimates for mutually adjusted risk variables

	Pooled HR	95% CI	I^2	Study (n)*	Q-χ^2	Q-p value	Egger's test	Trim-fill HR (95%CI)
BMI (5 kg/m^2)	**1.15**	**1.06 to 1.25**	89.8	5	39.34	<0.001	0.039	1.06 (0.96 to 1.16)
Gender (male)	**1.52**	**1.24 to 1.87**	71.5	5	14.05	0.007	0.107	1.27 (1.03 to 1.56)
Smoker (yes)	**1.60**	**1.45 to 1.77**	0.0	5	2.69	0.611	0.783	1.60 (1.45 to 1.77)
HTN (yes)	**1.61**	**1.33 to 1.96**	64.1	5	11.14	0.025	0.358	1.41 (1.15 to 1.73)
Age (10 years)	**1.80**	**1.13 to 2.87**	99.1	4	331.4	<0.001	0.64	2.41 (1.49 to 3.91)
DM (yes)	**2.00**	**1.68 to 2.38**	50.6	6	10.12	0.072	0.841	2.00 (1.68 to 2.38)
CAD (yes)	**2.94**	**1.36 to 6.33**	97.7	6	212.6	<0.001	0.583	6.71 (2.69 to 16.74)

*Number of studies included in estimates for each listed risk factor.
BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension.
Columns in bold correspond to pooled HR (95%CI) to differentiate from the Trim-fill HR (95%CI) in the same table. The latter is obtained from Duval and Tweedie's method to check for publication bias.

detected as disturbances of LV structure or function, which predispose towards the development of HF.[41] SBHF is relatively easy to identify in patients with previous myocardial infarction and regional dysfunction, or with reduced ejection fraction. However, nearly 50% of HF is of non-ischaemic origin,[10] and in this circumstance, the identification of SBHF may be difficult in the absence of LVH.

Although HF may be prevented by control of HF risk factors, early detection of LV dysfunction may permit the institution of measures that prevent progression of the problem.[4 42 43] Screening for SBHF is supported by previous studies of subclinical LV systolic and diastolic dysfunction. The prevalence of asymptomatic EF <50% is 7.2% in those aged 60–69 years and doubles to 14.3% in those aged >80 years.[44] The prevalence of diastolic dysfunction varies with grade among patients with different risk groups. In older (>65 years) patients with a diagnosis of HTN or coronary disease, the prevalence of mild diastolic dysfunction is 36%, whereas that of moderate or severe diastolic dysfunction is 16%.[45] Abnormal myocardial function can be documented in 20–30% of patients with obesity and diabetes.[46 47]

The application of any screening test is most effective when the condition is of at least moderate prevalence in the population under study. For example, focusing the screening effort on those with non-ischaemic risk factors for HF (diabetes, HTN, overweight, MS, cardiotoxic chemotherapy, familial cardiomyopathy) would permit restriction of screening tests to the group most likely to have a problem. Nonetheless, these HF risks are highly prevalent in the general population and their relative and additive importance is not well known.

The consistency of association of various risk factors with HF supports the concept that HF is predictable in many patients. The development of this simple risk calculation strategy derived from this study could be used to focus resources (eg, open access echocardiography) on at-risk patients without ischaemia. However, the predictive value of the risk calculation, the benefit of imaging surveillance and the cost-effectiveness of screening of stage A HF in the community will need to be validated prospectively. We are undertaking this at present in a population-based study (http://www.anzctr.org.au/; ACTRN12614000080628).

Limitations

Like all meta-analyses, this work is limited by variations in the original studies, although all involved at-risk individuals. Likewise, the constituent observational studies may be limited by biases in the recruitment process. The high levels of I^2 attest to substantial heterogeneity between studies. The original intention of the analysis was to develop a risk score using the available clinical variables. This was limited by the heterogeneity in the studies, particularly in the various cohorts used in each study and in the variables used for adjustment. Without access to individual-level data, we can only propose that the combined risk measures derived from this study be used as a marker of the magnitude rather than as exact risk estimates. Furthermore, our primary interest was to identify and quantify the potential HF risks in non-ischaemic HF. While CAD is ubiquitous in these, the proportion with CAD is low (weighted average 2.2%, table 1). Moreover, the benefit of a meta-regression is that we were able to address the role of other factors independent of CAD. Finally, this systematic review was not registered prospectively.

CONCLUSION

This systematic review and meta-analysis of 456 850 participants shows that CAD, diabetes, age, HTN, smoking, male gender and increased BMI are consistently and independently associated with a higher risk of incident HF. AF, LVH and valve heart disease are also strongly associated with incident HF. The estimation of HF risk may become useful in selection of asymptomatic patients for imaging as sensitive, new imaging and biochemical techniques for identification of LV dysfunction become more widely available.

Contributors HY was involved in reviewing, synthesis, analysis and drafting. KN was involved in reviewing and drafting. PO was involved in analysis and drafting. THM was involved in design, synthesis, analysis and drafting.

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Competing interests None.

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Appendix A1 - Baseline characteristics of included studies - demographic characteristics

	Study	Publish (year)	Trial (study name)	Data Collection (year)	Total (n)	Follow-Up (year)	HF develop (n)	Incident Rate (1000 p-yr*)	Cumulative Incident rate (%)	Age (±SD)	Gender (%male)
	Ho KK et al [23]	1993		1948-1988	9405 ǂ	40ǂ	652ǂ	1.85			
1	Kannel et al[24]	1999	Framingham and offspring (US)		15267 pe*ǂ	38ǂ	486ǂ				
	Ho J et al[25]	2013		1981-2008	6340	8	512	5	8.1%	60±12	46%
2	Butler et al[26] Kalogeropoulos et al[17]	2008 2009	Health ABC study (US)	1997-2004	2934	7	258	13.6	8.8%	74±2.9	48%
3	He et al[15]	2001	NHANES (US)	1971-1992	13643	19	1382		10.1%	50±15	41%
4	Agarwal et al[27]	2012	ARIC (US)	1987-2005	13555	16	1487		11.0%	54±5.8	45%
5	Goyal et al[28]	2010	Million P-Yr *(US)	2000-2005	359947	5	4001	3.96	1.1%	38±14	47%
6	Bahrami et al[29] Bahrami et al[30]	2008 2008	MESA (US)	2000-2006	6814	4	79	3.1	1.2%	65±0.7	47%
7	Gottdiener et al[16] Mujib et al [21]	2000 2010	Cardio Vascular Health (US)	1989-1996	5625	12	597	19.3	10.6%	73±4.5	42%
8	Chen et al[31]	1999	EPESE (US)	1982-1992	1749	8	173	12.5	9.9%	74±6.8	41%
9	Bibbins-Domingo et al[32]	2009	CARDIA (US)	1985-2006	5115	20	27		0.5%	24±3.5	45%
10	Ingelsson et al[33]	2005	ULSAM (Sweden)	1970-2001	2321	29	259	4.5	11.2%	50±0.0	100%
11	Wang et al[34]	2010	Kuopio (Finland)	1986-2006	1032	21	303		29.4%	69±2.8	38%
12	Aronow et al[35]	1999	Mt Sinai (US)	N/A	2902	4	794		27.4%	81±8.0	32%
13	Smith et al[36]	2010	MDCS (Sweden)	1991-	5187	14	112		2.2%	58±5.9	41%
14	Kenchaiah et al[37]	2009	Physician's heart (US)	1982-2007	21094	21	1109	2.57	5.3%	53±9.4	100%
15	Brouwers et al[38]	2013	Prevend (Netherlands)	1997-2010	8592	12	374		4.4%	49±12	50%
	Sum	1993-2013	15 studies	1967-2007	456850	198	11467				
	Mean (Weighted)				30457	7	3323	3.75	0.97%	42	49%
	SD (Weighted)					1.0	811	1.07	0.11%	12.6	9%
	Maximum				359947	29	4001	19.3	29.36%	81	100%
	Minimum				1032	4	27	2.57	0.53%	24	32%

*pe (person exam); p-yr (person year); ǂ duplicated counts from a single study, not included in counts for total and cumulated incidence.

FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (Study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician Heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease)

Appendix A2 - Baseline characteristics of included studies - Risk prevalence

Author(s)	% White	% >Hi/Sc*	% F/Hx*	% Smoke	% Alcohol	BMI (mean)	SBP (mean)	DBP (mean)	% Inactive	% DM	% CAD	% LVH	% HTN	% VHD	% Stroke or TIA	% Abn ECG	Heart rate (mean)	% COPD	% AF	% CKD	Total CHOL
Ho KK et al ; [23]																					
Kannel et al;[24]																					
Ho J et al[25]	100%			22%		27±4	132	77±11		7%	8%	8%	46%	1%	3%	3%	65		2%		213
Butler et al; [26] Kalogeropoulos et al[17]	59%	89%		56%		27±5	136	71±12		15%	17%	12%	43%		7%		65				203
He et al[15]	85%	56%		35%	25%	26±5	134		44%	4%	5%		28%	5%							222
Agarwal et [27]al[27]	74%			25%		28±5	120			10%	4%	2%		1%		3%	67	8%			
Goyal et al[28]										3%	1%		12%	1%					0%		
Bahrami et al[29] Bahrami et al[30]	39%			49%		28±0.0	127	72±0.2		14%		10%	48%								194
Gottdiener et al[16] Mujib et al [21]	85%	71%		54%			136	71±11		17%			58%		5%	15%		25%	2%		211.9
Chen et al[31]	80%	48%		78%						11%			54%		4%						
Bibbins-D et al[32]	48%	60%	12%	31%	12%	25±5	110	69±9		2%		6%	3%							4%	
Ingelsson et al[33]				51%		25±3				6%	0%	2%	43%								
Wang et al[34]				29%	30%	27±4	157	82±14	25%	17%	7%	31%	26%								254
Aronow et al[35]	67%									25%	44%		46%								
Smith et al[36]				27%		26±4	141	87±9		8%	2%		17%						1%		
Kenchaiah et al et al[37]				48%	25%	25±1	126	79±7	14%	3%	9%		24%								
Brouwers et al[38]	95%			38%		26±4	128	74±10		4%	6%		32%				69		1%	6%	199
Sum																					
Mean (Weighted)	64%			39%		26	128	76	25.5	4%	2.23%	6%	16%	1%	5%	5.8%	67	13.1%	0.4%	5.2%	210
SD (Weighted)	5.8%			2.70%		3	16	8	8.1%	1%	0.23%	1%	3%	0.2%	0.6%	1.4%	10	0.9%	0.1%	1.9%	20
Maximum	100%	89%	12%	78%	30%	28	157	87	44%	25%	44%	31%	58%	5%	7%	15%	69	25%	2%	6%	254
Minimum	39%	48%	12%	22%	12%	25	110	69	14%	2%	0.3%	1.5%	3.0%	0.5%	2.7%	2.7%	65	8.4%	0.3%	3.5%	194

*Hi/Sc (high school); F/Hx (family history of cardiac disease); BMI (Body Mass Index); DM (Diabetes Mellitus); CAD (Coronary Artery Disease); LVH (Left Ventricular Hypertrophy); HTN (Hypertension); VHD (Valvular Heart Disease); TIA (Transient Ischaemic Attack); COPD (Chronic Obstructive Pulmonary Disease); AF (Atrial Fibrillation); CKD (Chronic Kidney Disease); CHOL (cholesterol)

Appendix B - Heterogeneity of risk variables reported in studies

Variables	Frequency (n)	(%)	FHS	Health ABC	NHANES	ARIC	Million P-Y	MESA	CVH	EPESE	CARDIA	ULSAM	Kuopio	Mt Sinai	MDCS	Physician Heart	PREVEND
Hypertension	14	93%	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Diabetes	13	87%	+	+	+	+	+	+	+	+	+	+		+	+		+
Age	11	73%	+	+		+	+	+	+	+	+			+	+		+
Male Gender	11	73%	+		+	+	+	+	+	+	+			+	+		+
Obesity	10	67%	+		+	+				+	+	+	+		+	+	+
Smoking	10	67%	+	+	+	+		+	+		+	+			+		+
CAD	10	67%	+	+	+	+	+		+			+		+	+		+
Dyslipidemia	8	53%	+		+	+		+			+	+	+				+
LVH	7	47%	+	+		+		+	+		+	+					
Black Race	6	40%			+	+		+	+		+			+			
Fasting Glucose	5	33%		+		+			+				+				+
Valvular Disease	4	27%	+		+	+	+										
Atrial Fibrillation	4	27%	+				+		+								+
Abnormal ECG	3	20%	+			+			+								
Heart Rate	3	20%	+	+		+											
Excessive Alcohol	3	20%			+						+						
CKD	3	20%		+							+						+
NT-proBNP	3	20%				+									+		+
C-Reactive Protein	3	20%				+			+								+
Albumin	3	20%		+		+			+								
Creatinine	3	20%		+		+			+								
Stroke	2	13%							+						+		
Family History	2	13%									+						
Education	2	13%			+						+						
COPD	2	13%				+			+								
LVEF (echo)	2	13%							+		+						
Physical Inactive	1	7%			+												

CAD (Coronary Artery Disease); LVH (Left Ventricular Hypertrophy); AF (Atrial Fibrillation); VHD (Valvular Heart Disease); COPD (Chronic Obstructive Pulmonary Disease); CKD (Chronic Kidney Disease)
FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (Study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician Heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease)

Appendix C - Heterogeneity of risk variables used for adjusted analysis

	Author	Study (Trial)	Risk ratio	Stats Model used	Age¶	Gender¶	Smoking¶	BMI ¶	DM ¶	CAD ¶	LV H	HTN ¶	VH D	H R	A F	
	Ho KK[23]	FHS	RR	CPH	+											
1	Kannel[24]	FHS	OR	PLR	+	+	+	+	+	+	+	+	+	+		
	Ho J #[25]	FHS	HR	CPH	+	+	+	+	+	+	+	+	+	+	+	LBBB; HDL; MI
2	Butler[26]	Health ABC	HR	CPH	+		+		+	+	+	+		+		creatinine
	Kalogeropoulos[17]	Health ABC	RR	MH			+		+	+	+	+		+		race
3	He#[15]	NHANES	RR	CPH	+		+	+	+	+		+	+			education, alcohol, low physical activity, cholesterol,
4	Agarwal[27]	ARIC	HR	CPH	+	+										
5	Goyal[28]	Million P-Y	HR	CPH	+	+			+	+		+	+		+	
6	Bahrami[29]	MESA	HR	CPH	+	+	+	+	+		+	+				
7	Gottdiener#[16]	CVH	RR	CPH	+	+		+	+	+	+	+				
	Mujib[21]	CVH	HR	CPH	+	+	+		+	+	+	+			+	race, stroke, COPD and peripheral arterial disease,
8	Chen YT[31]	EPESE	HR	CPH	+	+		+	+	+		+				
9	Bibbins-D[32]	CARDIA	HR	CPH				+				+				Cholesterol, CKD
10	Ingelsson#[33]	ULSAM	HR	CPH			+	+	+	+	+	+				cholesterol
11	Wang J[34]	Kuopio	HR	CPH	+	+	+		+			+				low physical activity, alcohol cholesterol
12	Aronow[35]	Mt Sinai	HR	CPH	+	+			+	+		+				
13	Smith JG#[36]	MDCS	HR	CPH	+	+	+	+	+	+		+				cholesterol, BNP, CRP
14	Kenchaiah[37]	Physician Heart	HR	CPH	+		+			+						Alcohol, FHx and medication
15	Brouwers#[38]	Prevend	HR	CPH	+	+	+	+	+	+		+			+	Cystatine, UAE, CRP, NT-proBNP, hs-TnT

¶ Variables used for mutually adjusted risk calculation; # Studies included for mutually adjusted risk calculation.

RF (Risk Factor); HR (Hazard Ratio); OR (Odds Ratio); RR (Relative Risk); FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (Study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician Heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease)

LBBB (left bundle branch block); HDL (high density lipoprotein); MI (myocardial infarction); CKD (chronic kidney disease); BNP (brain natriuretic peptide); CRP (c-reactive protein); FHx (family history); UAE (urinary albumin excretion); hs-TnT (highly sensitive troponin T.

Appendix D- Newcastle–Ottawa scale for included studies

	Author	Study (Trial)	#1_Selection_Representativeness of exposed	#2_Sellection_of Non-exposed	#3_Selection_Ascertainment of exposure	#4_Outcome demonstration at start (★=yes)	#5_Comparability	#6_Assessment of Outcome	#7_Follow-up Long enough for outcome to occur	#8_Follow-up adequacy	Total ★
1	Ho KK[23] Kannel[24] Ho J[25]	Framingham study	□	□	□	□	□	□	□	□	8
2	Butler[26] Kalogeropoulos[17]	Health ABC study	□	□	□	□	□	□		□	7
3	He[15]	NHANES	□	□	□	□	□	□	□	□	8
4	Agarwal[27]	ARIC	□	□	□	□	□	□	□	□	8
5	Goyal[28]	Million P-Y	□	□	□	□	□	□		□	7
6	Bahrami[29] Bahrami[30]	MESA	□	□	□	□	□□	□		□	8
7	Gottdiener[16] Mujib[21]	Cardio Vascular Health		□	□	□	□□	□	□	□	8
8	Chen YT[31]	EPESE		□	□	□	□□	□		□	7
9	Bibbins-D[32]	CARDIA		□	□	□	□	□	□	□	7
10	Ingelsson[33]	ULSAM		□	□	□	□	□	□	□	7
11	Wang J[34]	Kuopio		□	□	□	□□	□	□	□	8
12	Aronow[35]	Mt Sinai		□	□	□	□	□		□	6
13	Smith JG[36]	MDCS	□	□	□	□	□□	□	□	□	9
14	Kenchaiah[37]	Physician's heart		□	□	□	□	□	□	□	8
15	Brouwers[3838]	Prevend	□	□	□	□	□	□	□	□	8

Selection: No ★is given to cohort with men or women only, or with an age selection range;
Comparability: ★if risk adjusted for confounders, or with subgroup analysis of age or gender; ☆☆ if adjusted for interim myocardial infarction
Follow-up length ★only if ⩾ 5 years
FHS (Framingham Heart Study); HABC (Health Aging and Body Composite Study); NHANES (National Health Nutrition Examination Survey); ARIC (The Atherosclerosis Risk in Communities); Million P-Y (One Million Person-Year study); MESA (Multi-Ethnic Study of Atherosclerosis); CVH (Cardio Vascular Health study); EPESE (Established Population for Epidemiologic Studies of the Elderly program); CARDIA (Coronary Artery Risk Development in Young Adults); ULSAM (Uppsala Longitudinal Study of Adult men); Kuopio (Kuopio Finland study); Mt Sinai (study at Mt Sinai); MDCS (the Malmo diet and Cancer Study in Swedish people); Physician's heart (the Physician heart study); Prevend (Prevention of Renal and Vascular End-stage Disease)

Appendix E Reasons for excluded Studies

	Reasons for excluded Studies after full text review (n=83+9=92)	
	Author, year	**Reasons for exclusion**
1	Eriksson, 1989 (Eur Heart J)	Risk estimates not meeting inclusion criteria
2	Wilhelmsen, 2001 (J Intern Med)	Risk estimates not meeting inclusion criteria
3	Ansari,2003 (Am Heart J)	risk for CV hospitolization
4	Kardys, 2006 (Am Heart J)	Risk estimates not meeting inclusion criteria
5	Gurwitz, 2013 (Am J Med)	Risk estimates for HFpEF
6	Wannamethee, 2011 (J Am Coll)	Risk estimate not meeting inclusion criteria
7	Baena-Diez, 2010 (Clinical Cardiology)	Risk estimates not meeting inclusion criteria
8	Britton, 2009 (Eur J Heart Fail)	Risk estimates not meeting inclusion criteria
9	Dunlay,2009 (Am J Med)	case matched study
10	Gupta, 2010 (Am Heart J)	No risk effect estimates
11	Kenchaiah, 2002 (N Engl J Med)	Duplication of study population (FHS)
12	Ebong, 2013 (Obesity)	Duplication of study population (MESA)
13	Vasan, 2003 (Circulation)	Duplication of study population (FHS)
14	Cesari, 2003 (Circulation)	Duplication of study population (HABC)
15	Ingelsson, 2006	Duplication of study population (ULSAM)
16	Bibbins, 2004 (Circulation)	Not an unselected population
17	Azad, 2011 (Journal of geriatric cardiology)	review article
18	Carr, 2005 (Am J Cardiol)	Not an unselected population
19	De Simone, 2013 (Nutr Metab Cardiovasc Dis)	Not an unselected population
20	Senni, 1999 (Arch Intern Med)	risk for mortality
21	Owan, 2006 (N Engl J Med	risk for mortality
22	Adlam 2005 (European Heart Journal)	Not reporting characteristics of inclusion
23	Arnlov, 2004 (European heart Journal)	Not reporting characteristics of inclusion
24	Arnold, 2005 (J Am Geriatr Soc)	Not reporting characteristics of inclusion
25	Aurigemma, 2001 (JACC)	Not reporting characteristics of inclusion
26	Babb, 2009 (AORN J)	review article
27	Barnard, 2005 (Current Cardiology reports)	review article
28	Belin, 2011 (Am J Clin Nutr)	Not reporting characteristics of inclusion
29	Bertoni, 2004 (Diabetes care)	Diabetic population
30	Bibbins, 2009 (N Engl J Med)	Not reporting characteristics of inclusion
31	Bleumink, 2004 (European Heart J)	No risk effect estimates
32	Brenyo, 2011 (Cardiol J)	Not reporting characteristics of inclusion
33	Bruch, 2006 (J Am Soc Echo)	echo and bnp for CV events
34	Bui, 2011 (Nature reviews)	review article
35	Cabrera, 2012 (Clin Interv Aging)	CV events
36	Campbell, 2003 (MJA)	review article
37	Castagno, 2012 (JACC)	Population not meeting inclusion
38	Chae,2003 (The Am J of Cardiology)	Risk estimat not meeting inclusion
39	Cowie, 1997 (European Heart Journal)	review article
40	Cowie, 1999 (European Heart Journal)	No risk effect estimates
41	Curtis, 2008 (Archives of internal Med)	No risk effect estimates
42	De Simone, 2007 (Diabetes care)	Population not meeting inclusion
43	Desimone, 2010 (Journal of Hypertension)	Population not meeting inclusion
44	Deswal, 2011 (JACC)	review article
45	Dhingra, 2010 (Arterioscler Throm Vasc Biol)	Not reporting characteristics of inclusion
46	Ekundayo, 2009 (Hypertension)	Not reporting characteristics of inclusion
47	Filippatos, 2011 (Eur J of HF)	Not reporting characteristics of inclusion
48	Folsom, 2009 (Circulation, heart failure)	Not reporting characteristics of inclusion
49	Giamouzies, 2011 (J Cardiac Fail)	review article
50	Haass, 2011 (Circulation, heart failure)	Not reporting characteristics of inclusion
51	Hagege, 2010 (Archives of Cardiovascular Dis)	Population not meeting inclusion
52	Hoffman, 1994 (Arch Intern med)	Population not meeting inclusion
53	Horne, 2010 (European Journal of heart failure)	Risk estimate not meeting inclusion criteria
54	Hsich, 2011 (JACC)	Edtorial comment
55	Jain, 2011 (Circ cardiovasc Imaging)	Risk estimate for CV disease
56	Kaczorowski, 2011 (BMJ)	Not reporting characteristics of inclusion

57	Kalogeropoulos, 2010 (Circ Heart Fail)	Not reporting characteristics of inclusion
58	Kannel, 2000 (Heart Failure Reviews)	review article
59	Kawut, 2012 (Circulation)	risk estimates for HF or death
60	Ketchum, 2011 (Congestive heart failure)	review article
61	Khatibzadeh, 2012 (International journal of cardiology)	review article
62	Krishnan, 2009 (Circ Heart Fail)	Not reporting characteristics of inclusion
63	Lam, 2011 (Circulation)	duplication of population (FHS)
64	Laugsand, 2013 (European Heart journal)	Not reporting characteristics of inclusion
65	Leung, 2009 (Journal of cardiac failure)	Diabetic population
66	Liszka, 2005 (Ann Fam Med)	Duplication of study population (NHANESI)
67	Lloyd-Jones, 2002 (Circulation)	Not reporting characteristics of inclusion
68	Loehr, 2008 (Am J Cardiol)	Duplication of study population (ARIC)
69	Luepker, 1990 (American J of Epidemiology)	Not reporting characteristics of inclusion
70	Marwick, 2006 (JACC)	review article
71	Mostofsky, 2012 (Circulation. Heart failure)	review article
72	Mujib,2012 (Ann Med)	Not reporting characteristics of inclusion
73	Okin, 2011 (Circ Cardiovasc Qual Outcomes)	Population not meeting inclusion
74	Okin, 2012 (Am J Cardiol)	Risk estimate not meeting inclusion criteria
75	Palazzuoli, 2011 (Intern Emerg Med)	review article
76	Pfister, 2012 (European Heart Journal)	Not reporting characteristics of inclusion
77	Redfield, 2012 (Heart failure clinics)	review article
78	Rod, 2011 (Am J epidemiol)	Risk estimate not meeting inclusion criteria
79	Roger, 2004 (JAMA)	Risk estimate not meeting inclusion criteria
80	Roy, 2011 (Am J Cardiol)	Propensity matched study in diabetes
81	Sanderson, 1995 (International Journal of Cardiology)	Risk estimates not meeting inclusion criteria
82	Schnabel, 2013 (European Journal of Heart Failure)	Population not meeting inclusion
83	Senni, 1998 (Circulation)	Risk estimates not meeting inclusion criteria
84	shah, 2011 (J Am Coll Cardiol)	Risk estimates not meeting inclusion criteria
85	Silver, 2003 (Congestive heart Failure)	Not reporting characteristics of inclusion
86	Sprafka, 1990 (Am J Epidemiol)	Risk estimates not meeting inclusion criteria
87	Suzuki, 2008 (Circulation. Heart Failure)	duplication of population (CVH)
88	Varadarajan, 2006 (J Am Soc Echocardiogr)	Population not meeting inclusion
89	Victor, 2004 (Am J Cardiol)	Risk estimates not meeting inclusion criteria
90	Wang, 2011 (Am J Epidemiol)	Not reporting characteristics of inclusion
91	Wang, 2012 (Circulation)	duplication of study population (FHS)
92	Yan, 2011 (JACC)	Risk estimates not meeting inclusion criteria