Estimates of Mortality Benefit From Ideal Cardiovascular Health Metrics: A Dose Response Meta-Analysis

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Background—Several studies have shown an inverse relationship between ideal cardiovascular health (CVH) and mortality. However, there are no studies that pool these data to show the shape of the relationship and quantify the mortality benefit from ideal CVH.

Methods and Results—We conducted a systematic internet literature search of multiple databases including MEDLINE, Web of Science, Embase, CINAHL, and Scopus for longitudinal studies assessing the relationship between ideal CVH and mortality in adults, published between January 1, 2010, and May 31, 2017. We included studies that assessed the relationship between ideal CVH and mortality in populations that were initially free of cardiovascular disease. We conducted a dose-response meta-analysis generating both study-specific and pooled trends from the correlated log hazard ratio estimates of mortality across categories of ideal CVH metrics. A total of 6 studies were included in the meta-analysis. All of the studies indicated a linear decrease in (cardiovascular disease and all-cause) mortality with increasing ideal CVH metrics. Overall, each unit increase in CVH metrics was associated with a pooled hazard ratio for cardiovascular disease mortality of 0.81 (95% confidence interval, 0.75–0.87), while each unit increase in ideal CVH metrics was associated with a pooled hazard ratio of 0.89 (95% confidence interval, 0.86–0.93) for all-cause mortality.

Conclusions—Our meta-analysis showed a strong inverse linear dose-response relationship between ideal CVH metrics and both all-cause and cardiovascular disease–related mortality. This study suggests that even modest improvements in CVH is associated with substantial mortality benefit, thus providing a strong public health message advocating for even the smallest improvements in lifestyle. (*J Am Heart Assoc*. 2017;6:e006904. DOI: 10.1161/JAHA.117.006904.)

Key Words: cardiovascular disease prevention • cardiovascular disease risk factors • mortality

Cardiovascular health (CVH), as defined in the 2010 American Heart Association's national goal,[1] describes a construct of 7 health metrics, each of which is classified into levels as poor, intermediate, and ideal. Researchers have often represented these metrics as numeric scores in order to categorize CVH based on the number of ideal CVH metrics achieved. Many studies have defined ideal CVH as the presence of as few as 5 and as many as 7 ideal CVH metrics.[2,3]

There is increasing evidence of the benefits of achieving ideal CVH in the primary prevention of cardiovascular disease (CVD), mortality, and non-CVD outcomes such as cancer and depression.[4] However, the prevalence of ideal CVH in US and non-US populations is low, ranging from 0.5% to 12%.[4]

Studies on ideal CVH have shown a fairly consistent inverse association with CVD and all-cause mortality.[2,3,5–8] However, the shape and the pooled strength of the association remains unknown. A previous meta-analysis compared

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Clinical Perspective

What Is New?

- Employing a dose-response meta-analytic approach, the risk of mortality was quantified for each unit change in ideal cardiovascular health metrics.
- A linear inverse relationship exists between increasing number of ideal cardiovascular health and both cardiovascular disease and all-cause mortality.

What Are the Clinical Implications?

- The study findings suggest that there is life-saving benefit associated with improving cardiovascular health by as little as one ideal cardiovascular health metric.
- This information is clinically relevant and useful for conversations with patients on the benefits of cardiovascular health.

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high versus low numeric CVH scores and showed an inverse relationship between higher numbers of ideal CVH metrics and mortality.[9] The limitation of this approach is that such an analysis ignores the shape (linear or otherwise) of the association and does not estimate mortality benefit associated with per-unit increases in ideal CVH metrics. Therefore, we conducted a dose-response meta-analysis to quantify and examine the shape of the association between an increasing number of ideal CVH metrics and mortality.

Methods

We conducted an internet literature search of multiple databases—MEDLINE database using PubMed and OvidSP interfaces, Web of Science, Embase, CINAHL and Scopus—for studies on the association of ideal CVH and mortality. We combined search words such as "ideal cardiovascular health," "cardiovascular health metrics," and "life's simple seven" with "mortality," "cardiovascular mortality," and "cardiovascular death." We included studies published from January 1, 2010, to March 31, 2017.

To be included in the meta-analysis, studies had to be longitudinal, have assessed the relationship between ideal CVH (using the American Heart Association definition) and mortality in a population aged 18 years and older that was initially free of CVD, and be published in English.

Data were manually extracted from the articles to an Excel spreadsheet. Information extracted included first author name, publication date, study date, follow-up period, age range, sex distribution, comparison groups, total population at baseline, total mortality and mortality in each comparison group at baseline, hazard ratios (HRs) and confidence intervals for exposure group, and covariates that were

Table. Description of Studies Included in the Meta-Analysis

Study	Patients, No.	Country/Cohort	Date of Study	Mean Age or Age Range, y	Women, %	Adjustments	Comparison Groups	Referent CVH Metric Categories
Yang, 2012[2]	15 305	United States/NHANES	1988–2010	20–80+	51.8	Age, sex, and race-ethnicity	6	0 to 1
Artero, 2012[3]	11 993	United States/ACLS	1987–1999	20–88	24.3	Age, sex, examination year, alcohol, and family history of CVD	3	0 to 2
Ford, 2012[5]	7622	United States/NHANES	1999–2002	Mean, 43	52	Age, sex, race-ethnicity, education, self-reported health status, health insurance, alcohol, and cancer history	6	0
Liu, 2014[6]	91 698	China/KaiLuan Study	2006–2007	18–98	21	Age, sex, income, education, alcohol, previous MI, stroke, and cancer	5	0 to 1
Kim, 2012[7]	12 538	Korea/Seoul Male Cohort Study	1993	40–59	0	Age, education, alcohol, and family history of CVD	5	0 to 2
Dong, 2012[8]	2981	United States/NOMAS	1993–2001	Mean, 69	63.7	Age, sex, and race-ethnicity	5	0 to 1

ACLS indicates Aerobics Center Longitudinal Study; CVD, cardiovascular disease; CVH, cardiovascular health; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; NOMAS, Northern Manhattan Study.
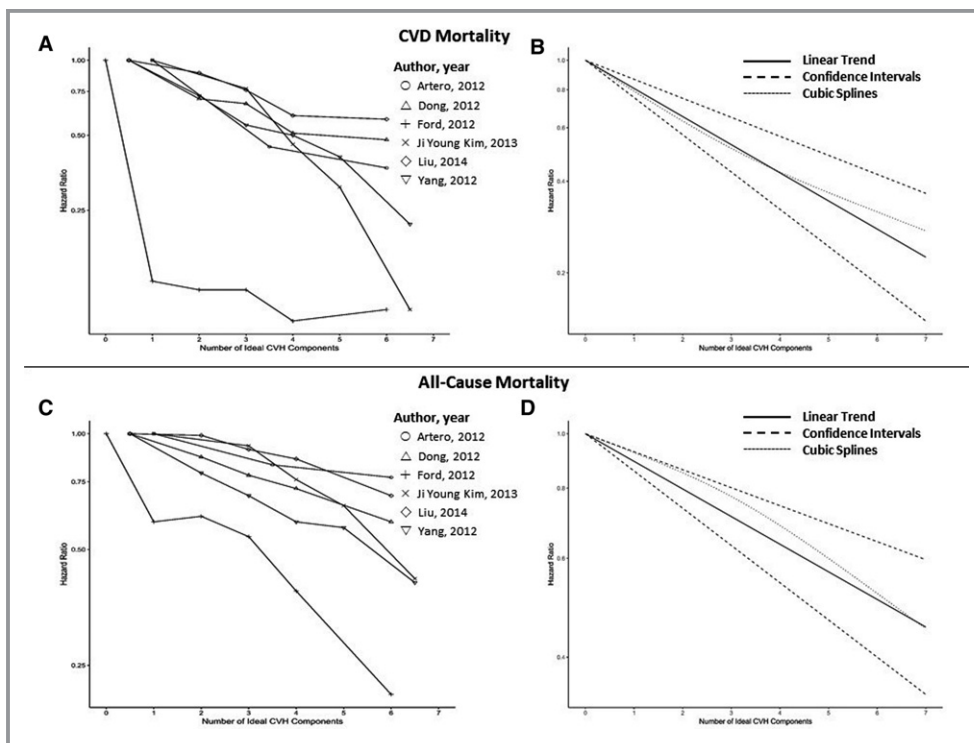
Figure 1. A and C, Spaghetti plot showing the association of ideal cardiovascular health (CVH) with (A) cardiovascular disease (CVD) and (C) all-cause mortality in the included studies. B and D, Estimated linear trends of showing association of ideal CVH with (B) CVD mortality and (D) all-cause mortality in the included studies. Solid lines represent linear trend, dashes represent confidence intervals, and dotted lines represent cubine splines.

adjusted for in regression models. For each study, CVH categories were assigned to their corresponding HR estimate. Where categories were greater than a single CVH metric, the midpoint between the upper and lower boundary for that category was used.

Using methods described by Greenland and Longnecker[10] and Orsini et al,[11] we estimated the trend from the correlated log HR estimates of mortality across categories of ideal CVH metrics. We investigated a potential nonlinear relationship using restricted cubic splines with 3 knots located at the 10th, 50th, and 90th percentiles of the exposure distribution. These cubic spline knots correspond to values 0.5, 3, and 6 in the 7-point ideal CVH score scale. We assumed that the curves were linear below the first and above the last knot.

A random-effects meta-analysis was used to account for the heterogeneity across studies. Statistical heterogeneity between studies was further evaluated using I^2 statistics.[12] Publication bias was evaluated with the use of the Egger regression asymmetry test.[13] $P<0.05$ was considered statistically significant. All statistical analyses were performed in R statistical software[14] using the *dosresmeta* package.[15]

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure S1) details the search results. In total, 6 studies with a combined population of 142 137 participants met the study's inclusion criteria.[2,3,5–8] Details of the individual studies are shown in the Table and Table S1.

The spaghetti plots shown in Figure 1A and 1C show the study-specific HRs as a function of the ideal CVH metrics for CVD and all-cause mortality. The general appearance of these plots shows that the HRs decreased as the number of ideal CVH components increased. However, the study by Ford et al[5] appeared visually distinct from the others in that it had a rapid decline in the risk of mortality and thereafter plateaued. This was more prominent in the CVD mortality plot.

The test of nonlinearity was not statistically significant for both CVD mortality ($P=0.26$) and for all-cause mortality ($P=0.64$), suggesting that the difference in the shape of the curves (between Ford et al and the other 5 studies) may have been caused by chance. As such, a linear model was adopted for both analyses. The estimated linear trends for the individual studies and the pooled estimates are shown in
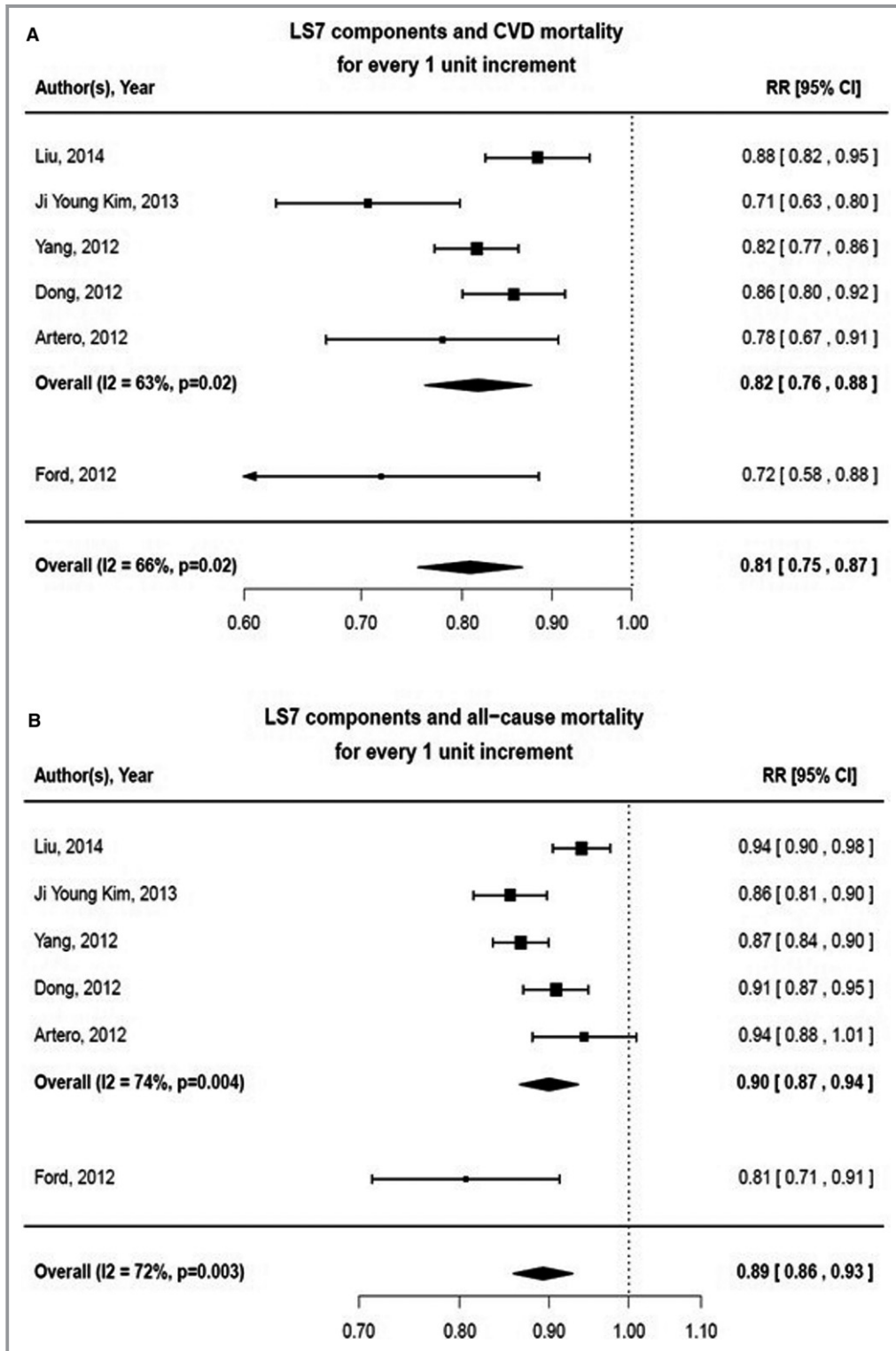
Figure 2. Forest plot showing results of meta-analysis of studies on the relationship between ideal cardiovascular health (CVH) and (A) cardiovascular disease (CVD) and (B) all-cause mortality.

Figures 1B and 1D and 2 for CVD and all-cause mortality, respectively.

Overall, each unit increase in CVH metrics was associated with a pooled HR for CVD mortality of 0.81 (95% confidence interval, 0.75–0.87) with moderate heterogeneity (I^2=66%, P=0.02; Figure 2A). For all-cause mortality, each unit increase in ideal CVH metrics was associated with a pooled HR of 0.89 (95% confidence interval, 0.86–0.93) with moderate

heterogeneity (I^2=72%, *P*=0.003; Figure 2B). There was no evidence of publication bias (Egger test, *P*=0.17 for CVD mortality and 0.63 for all-cause mortality).

In the sensitivity analyses excluding the results from Ford et al, there was no substantial difference in the pooled HRs (Figure 2).

Discussion

In this dose-response meta-analysis of 6 studies with over 140 000 participants, we observed an inverse linear relationship between ideal CVH metrics and mortality. For each additional ideal CVH metric a person has, we estimated a 19% reduction in mortality from CVD and 11% decline in the risk of all-cause mortality.

In addition to confirming the findings of previous individual longitudinal studies that showed a net mortality benefit from ideal CVH, the present meta-analysis also shows that even small improvements in CVH, such as achieving only one additional ideal CVH metric, is associated with significant reduction in death. Furthermore, findings from this meta-analysis suggest a linear dose-response relationship between ideal CVH and mortality reduction, supporting a possible causal link between the 2 entities.

The dose-response methodology employed in this meta-analysis has the advantage of quantifying per-unit risk. This technique also takes into account the individual HRs from studies thus preserving the control for confounders conducted in the individual studies. It also circumvents the difficulties in conducting a conventional meta-analysis at instances in which there are multiple levels of exposure. The use of restricted cubic spline analysis allows for observing the mortality decline with each unit increase in ideal CVH metric. Interestingly, as shown in Figure 1, there was minimal difference between the cubic spline and linear trend graphs. This is the first study to show a dose-response relationship between ideal CVH metrics and mortality reduction.

Study Limitations

Our study is limited by significant heterogeneity between the studies. The source of this heterogeneity is unclear; however, the results of our sensitivity analysis that excluded the work of Ford et al showed no substantial change in our findings. Because of the small number of studies, we were limited in our ability to conduct stratified analysis, and we were also unable to conduct a meta-regression analysis. There is some variability in the levels of CVH metrics that were considered in the different studies; however, the range of exposures is similar across studies with the minimum of 0 to 1 and a maximum of 6 to 6.5. Thus, all studies

contributed in determining the pooled association at the extremes of CVH metrics (≤1 and ≥6). None of the studies included in this meta-analysis assessed the impact of intermediate ideal CVH metrics on mortality and as such we were limited in our ability to assess intermediate levels of CVH and mortality on an aggregate basis. We were also limited by the shortcomings of the individual studies such as their lack of repeated exposure assessment and the varying follow-up periods.

While unable to predict the effort required by individuals at various levels of CVH to effect improvements in their CVH status, the findings of this study suggest that there is life-saving benefit associated with improving CVH by as little as one ideal CVH metric. More is needed to better understand which individual metrics have the greatest impact on mortality in the setting of CVH.

Conclusions

Our meta-analysis of 6 individual longitudinal studies shows a strong inverse linear dose-response relationship of ideal CVH with mortality. This study's findings suggest that even modest improvements in CVH is associated with substantial mortality benefit, thus providing a strong public health message emphasizing the benefits of incremental improvements in lifestyle.

Disclosures

None.

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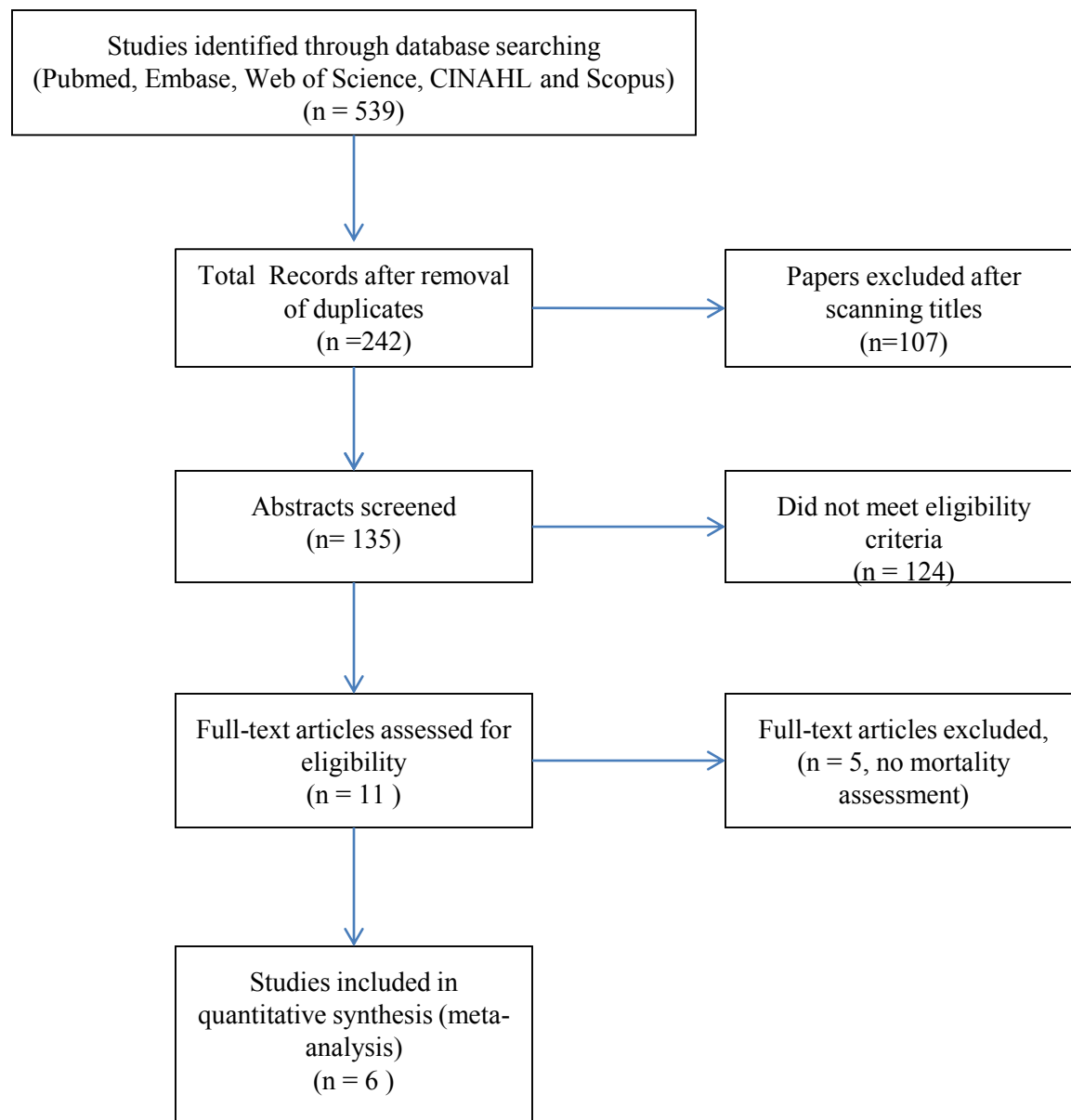15. Crippa A, Orsini N. Multivariate dose-response meta-analysis: the dosresmeta R package. *J Stat Softw*. 2016;72.

SUPPLEMENTAL MATERIAL

Table S1. Additional description of studies included in the meta-analysis.

First Author, Year	Number of Ideal CVH Metrics	Exposure Level[*]	CVD Mortality		All-Cause Mortality	
			Cases	N	Cases	N
Yang, 2012[1]	0 – 1	0.5	183	1236	405	1236
	2	2	303	2608	723	2608
	3	3	300	3370	760	3370
	4	4	201	3081	490	3081
	5	5	77	2060	226	2060
	6 – 7	6.5	21	957	69	957
Artero, 2012[2]	0 – 2	1	45	4675	145	4675
	3 – 4	3.5	20	5116	123	5116
	5 – 7	6	5	2202	37	2202
Ford, 2012[3]	0	0	7	111	10	111
	1	1	13	675	57	675
	2	2	26	1468	104	1468
	3	3	27	1900	104	1900
	4	4	13	1497	49	1497
	5 – 7	6	4	1204	15	1204
Liu, 2014[4]	0 – 1	0.5	75	12882	223	12882
	2	2	133	22776	430	22776
	3	3	142	28003	492	28003
	4	4	83	19684	328	19684
	5 – 7	6	25	8353	91	8353
Ji Young Kim, 2013[5]	0 – 2	1	21	695	87	695
	3	3	50	2229	246	2229
	4	4	60	4231	371	4231
	5	5	36	3932	284	3932
	6 – 7	6.5	4	1451	66	1451
Dong, 2012[6]	0 – 1	0.5	95	566	211	566
	2	2	127	953	344	953
	3	3	136	906	342	906
	4	4	59	426	178	426
	5 – 7	6	18	131	48	131

[*]Exposure level corresponds to number of ideal CVH metrics or the median when it is a range of metrics.
CVH Cardiovascular Health; CVD Cardiovascular Disease

Figure S1. PRISMA flow chart

Studies identified through database searching
(Pubmed, Embase, Web of Science, CINAHL and Scopus)
(n = 539)

Total Records after removal of duplicates
(n =242)

Papers excluded after scanning titles
(n=107)

Abstracts screened
(n= 135)

Did not meet eligibility criteria
(n = 124)

Full-text articles assessed for eligibility
(n = 11)

Full-text articles excluded,
(n = 5, no mortality assessment)

Studies included in quantitative synthesis (meta-analysis)
(n = 6)

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