

Ramírez-Vélez, R., Saavedra, J. M., Lobelo, F., Celis-Morales, C. A., Pozo-Cruz, B. d. and García-Hermoso, A. (2018) Ideal cardiovascular health and incident cardiovascular disease among adults: a systematic review and meta-analysis. *Mayo Clinic Proceedings*, 93(11), pp. 1589-1599. (doi:10.1016/j.mayocp.2018.05.035)

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

http://eprints.gla.ac.uk/171308/

Deposited on: 12 October 2018

Enlighten – Research publications by members of the University of Glasgow <a href="http://eprints.gla.ac.uk">http://eprints.gla.ac.uk</a>

Ideal cardiovascular health and incident cardiovascular disease among adults: a systematic review and meta-analysis

Robinson Ramírez-Vélez<sup>1</sup>, José M. Saavedra<sup>2</sup>, Felipe Lobelo<sup>3</sup>, Carlos A. Celis-Morales<sup>4,5</sup>, Antonio García-Hermoso<sup>6</sup>

- <sup>1</sup> Centro de Estudios en Medición de la Actividad Física (CEMA), Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, D.C, Colombia
- <sup>2</sup> Physical Activity, Physical Education, Sport and Health Research Centre, Sports Science Department, School of Science and Engineering, Reykjavik University, Reykjavik, Iceland
- <sup>3</sup> Hubert Department of Global Health, Rollins School of Public Health and Exercise is Medicine Global Research and Collaboration Center, Emory University, Atlanta, GA, USA
- <sup>4</sup> BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK, G12 8TA.
- <sup>5</sup> Centro de Fisiología y Biomecánica, Universidad Mayor, Santiago, Chile.
- <sup>6</sup> Laboratorio de Ciencias de la Actividad Física, el Deporte y la Salud, Facultad de Ciencias Médicas, Universidad de Santiago de Chile, USACH, Santiago, Chile

Corresponding author information: Antonio García-Hermoso. Laboratorio de Ciencias de la Actividad Física, el Deporte y la Salud, Universidad de Santiago de Chile, USACH, Chile. Avenida Libertador Bernardo O'Higgins nº 3363. Estación Central. Santiago. Chile; Telephone: (+562) 2 718 00 00. E-mail: antonio.garcia.h@usach.cl

# Take home points

- The number of ideal cardiovascular health metrics is a strong predictor of CVD incidence
- Meeting 5-7 ideal metrics is associated with the lowest rate of CVD incidence
- Meeting less than 5 ideal metrics also protects against CVD incidence
- Older individuals having a higher number of ideal CVH metrics was related with weaker protection of CVD events

### Abstract

In 2010 the American Heart Association proposed a definition of ideal cardiovascular health (CVH) including seven behaviours and health factors that they called "Life's Simple 7". The aim of the study was to investigate the association between ideal CVH metrics and incident CVD by conducting a systematic review and meta-analysis of prospective cohort studies. We searched the MEDLINE, EMBASE, and CINAHL databases for studies that met the following criteria: i) prospective studies conducted in adults, ii) with outcome data on CVD incidence, and iii) a measure of ideal cardiovascular health metrics. Eight studies (219,050 adults) were included in this analysis. Compared to those adults who met 0-2 of the ideal CVH metrics (high risk individuals), a significantly lower hazard for incidence CVD was observed on those who had 3-4 points for the ICH metrics (Hazard Ratio [HR]=0.54, 95% CI 0.48-0.59) and 5-7 points (HR: 0.28, 95% CI 0.23-0.33). Weaker associations were observed in studies with older individuals, therefore suggesting there is a positive relationship between age and HR. Although meeting 5-7 metrics is associated with the lowest hazard for CVD incidence, meeting 3-4 metrics still offer an important protective effect for CVD. Therefore, a realistic goal in general population in the short term could be to promote at least an intermediate ideal CVH profile (3-4 metrics).

**Key words.** Risk factors; Health behaviors; Life's Simple 7; Stroke; Cardiac Prevention.

### Introduction

Cardiovascular disease (CVD) is responsible for the largest proportion of global premature non-communicable chronic disease (NCD) mortality <sup>1</sup>; Increasing evidence suggests that shared lifestyle and biologic risk factors, including unhealthy diet, physical inactivity, hypertension, obesity, and dyslipidemia increase the risk of incident CVD <sup>2, 3</sup>. The World Health Organization have given special emphasis on reducing these shared risk factors as a strategy for reducing CVD risk <sup>4</sup> and overall premature NCD mortality.

In this context, The American Heart Association (AHA) proposed a definition of ideal cardiovascular health (CVH) metrics, also known as Life's Simple-7, which include four favourable health behaviours (never smoker or quit, ideal body mass index, meeting physical activity guidelines and consumption of a diet that promotes cardiovascular health) and three health factors (untreated total cholesterol <200 mg/dl, untreated blood pressure <120/80 mm/Hg, and absence of diabetes mellitus), in addition to the absence of established clinical CVD diagnosis; based on these an ideal CVH score was derived and individuals were categorized as: poor, intermediate and ideal CVH with only 0.5% to 15% of the U.S adult population meeting the ideal CVH criteria <sup>6</sup>.

A recent meta-analysis suggested a reduction in the risk of mortality in a dose-response fashion, indicating that even minor improvements in cardiovascular health are associated with significant CVD death risk reductions <sup>6</sup>. These results are of major public health importance because an ideal CVH profile (i.e. meeting 5-7 metrics) is associated with 25% lower CVD health care costs, compared against those with a lower ideal CVH score. <sup>7</sup> Another recent meta-analysis by Fang et al, concluded that individuals meeting more ideal CVH metrics at baseline have a significantly lower CVD or all-cause mortality than those with a less ideal CVH profile <sup>8</sup>. However, Fang and colleagues did not include several large prospective studies <sup>9-12</sup>. In addition, the authors did not analyze the association between individual ideal CVH metrics and mortality and the impact of achieving 3-4 metrics (intermediate ideal CVH profile), something that could probably be considered a more realistic goal for the population at large and a marker for successful patient

engagement in CVD risk reduction interventions. Therefore, the aim of the study was to investigate the associations between meeting individual and combined ideal CVH metrics and incident CVD by conducting a systematic review and meta-analysis of prospective cohort studies.

#### **Materials and Methods**

A systematic review and meta-analysis was conducted following the guidelines of the Cochrane Collaboration <sup>13</sup> and the most recent AHA Scientific Statement on Methodological Standards for Meta-Analyses <sup>14</sup>. Findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) <sup>15</sup>. The review was registered in PROSPERO (registration number: CRD42017073875).

### Data Sources and Searches

An electronic search in three databases was performed: MEDLINE (PubMed and OvidSP) (January 2010- 09 July 2017), EMBASE (January 2010- 09 July 2017), and CINAHL (January 2010- 09 July 2017). The search strategies for all databases queried can be found in the Supplementary Materials appendix. In PubMed, comprehensive free text and MeSH synonyms for "American Heart Association 2020", "Cardiovascular Health", "Life's Simple 7", "ideal cardiovascular health", "AHA 2020" and "Cardiovascular Disease" were used. Only English articles were included. In addition, the reference lists and related links of retrieved articles were examined to detect studies potentially eligible for inclusion.

### Study selection

The a *priori* inclusion criteria for this meta-analysis were as follows: i) participants: adult (e.g. ≥ 18 years of age) population without history of myocardial infarction or stroke; ii) type of the study: observational studies analyzing ideal CVH, as defined by the AHA, and termed as: "Cardiovascular Health" or "Ideal Cardiovascular Health"; and iii) main outcomes: incident CVD. Two authors (AG-H & RR-V) independently assessed the electronic search results. When an article title seemed relevant, the abstract was reviewed for eligibility. When more information was

required, the full text of the article was retrieved and appraised for possible inclusion. Any differences between the two authors were discussed and, if necessary, a third author was referred to for arbitration (JMS). Reasons for exclusion of identified articles were recorded in all cases.

### Data extraction and risk of bias

Data were extracted from all articles that met selection criteria and deemed appropriate for detailed review by two authors. Details of individual studies were collected and characterized on the basis of study design, participants, region of study of each study and hazard ratios (HR) (and their associated 95% CIs).

Two authors independently (AG-H & RRV) assessed the quality of included articles according to the Newcastle-Ottawa quality scale (NOS) <sup>16</sup>. This scale contains 8 items categorized into 3 domains (selection, comparability, and exposure). A star system is used to enable semi-quantitative assessment of study quality; such that the highest-quality studies are awarded a maximum of 1 star per item with the exception of the comparability domain, which allows allocating 2 stars. Thus, the score ranges from 0 to 9 stars.

## Patient involvement

Due to the nature of the study, no participants were involved in the systematic review and meta-analysis. No patients were involved in the development of the research question or outcome measures, nor were they involved in the design, implementation, recruitment, or conduct of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants.

#### Data Synthesis and Analysis

The a *priori* plan was to conduct a one-step individual participant data meta-analysis. All analyses were carried out using STATA (version 14.0, STATA Corporation, College Station, Tex). Hazard Ratios (HR) with associated 95% CIs were extracted from studies for each outcome of interest (used to estimate the risk for CVD incidence for individual and number of health metrics) and pooled HR was then calculated using random effect (DerSimonian and Laird) models. The

likelihood approach with random effects was used to better account for the imprecision in the estimate of between-study variance <sup>17</sup>. When studies presented several statistical risk-adjustment models, we only considered HR associated with the statistical models that contained the fewest number of additional covariates to improve comparability across studies.

The percentage of total variations across the studies due to heterogeneity (Cochran's Q-statistic)  $^{18}$  was estimated using  $I^2$ , considering  $I^2$  values of <25%, 25–50%, and >50% as small, medium, and large amounts of heterogeneity respectively  $^{19}$ .

Small-study effects biases were assessed using the extended Egger's test <sup>20</sup> and presence of publication bias was investigated graphically by funnel plots.

Sensitivity analysis was conducted to assess the robustness of the summary estimates in order to determine whether or not a particular study accounted for the heterogeneity. Thus, in order to examine the effects of each result from each study on the overall findings, results were analyzed with each study deleted from the model once.

Finally, random-effects meta-regression analyses were used to separately evaluate whether results were different by mean age of participants at baseline <sup>21</sup>.

#### Results

### Literature Search

The electronic search strategy retrieved 812 articles. After removing duplicate references and based on title and abstract, 22 articles were read in full. The reasons for exclusion based on full text were (n=10): (i) inappropriate study design (4 articles); (ii) inappropriate outcome (1 article); (iii) inappropriate exposure measurement (2 articles); (iv) duplicate data (2 articles); and (v) study population (1 article). Finally, twelve studies <sup>9-12, 22-29</sup> met our inclusion criteria and were included in the systematic review and eleven in the meta-analysis (Figure 1). One study was not included in the analysis due to lack of data availability based on the ideal CVH categorization <sup>28</sup>.

## \*\*\*Figure 1 about here\*\*\*

### Study Characteristics

Table 1 summarizes the characteristics of the twelve included studies. All of them were prospective observational studies, and were published from 2011 to 2017. The studies included 219,050 participants. Sample sizes ranged from 2,392 <sup>11</sup> to 91,598 participants <sup>26</sup>. Participants were mostly women (55.1%, 120,697 women) and the average age of the participants was 59.4 years old. Studies were conducted in the USA <sup>10-12, 22-24, 27-29</sup>, China <sup>26</sup>, France <sup>9</sup>, and Europe <sup>25</sup>.

The percentage of the total sample having an ideal CVH profile ( $\geq 5$  metrics or >10 points) was low (13.2 ± 15.1 %; n= 28,914). Those with an intermediate ideal CVH profile (3-4 metrics or 5-9 points) represented 49.6 ± 17.1 % of the total sample (n= 108,648). The percentage of participants having a poor ideal CVH profile (1-2 metrics or <5 points) was 37.2 ± 26.8% (n= 81,487). The prevalence of ideal levels for each of the 7 individual ideal CVH metrics at baseline is shown in the Supplementary Material section (Figure S1).

#### Primary outcome

The CVD spectrum of outcomes included stroke <sup>9, 10, 22, 24-26, 28</sup>, myocardial infarction <sup>22, 26</sup>, incident heart failure <sup>11, 12, 23</sup>, venous thromboembolism <sup>24, 27</sup>, coronary heart disease <sup>9, 25</sup>, and a composite variable of CVD events <sup>22, 24-26</sup>.

## Baseline examination (metrics)

Assessment of smoking habits, body mass index, biochemical parameters (total cholesterol and fasting glucose or glycated hemoglobin <sup>25</sup>) and blood pressure were carried out using standarized protocols, and physical activity used questionnaire-based measures. The instruments used to evaluate the diet were as follows: Dong et al. <sup>22</sup> used a structured in-person interview with questions adapted from the National Cancer Institute Food Frequency questionnaire; Folsom's studies <sup>23, 24, 29</sup> assessed dietary intake by a slightly modified 66-item Harvard food frequency

questionnaire; Gaye et al.  $^9$  used a brief food frequency questionnaire without information about fiber and sodium intake; Kulshreshtha et al.  $^{10}$  and Olson et al.  $^{27}$  applied a food frequency questionnaire adapted for the REGARDS study; Lachman et al.  $^{25}$  used dietary information obtained from a 130-item food frequency questionnaire; Miao et al.  $^{26}$  used salt intake as a proxy for dietary behaviour; Nayor et al.  $^{11}$  assessed dietary intake using a food frequency questionnaire ( $\geq 4.5$  cups/day fruits and vegetables,  $\geq 2x3.5$  oz servings/week of fish,  $\geq 3x1$  oz servings/day of fiber-rich whole grains, < 1500 mg/d of sodium, and < 36 oz/week of sugar sweet beverages); Ogunmoroti et al.  $^{12}$  used a validated 120-item food frequency questionnaire; finally, Ommerborn et al.  $^{28}$  applied a validated food frequency questionnaire adapted for adults living in the Mississippi Delta Region. *Risk of bias* 

All twelve studies met at least seven NOS criteria and were considered to have adequate methodological quality. The average total score was 7.7 with a range from 7 to 8 (Table 1).

Association between ideal CVH metrics and incident CVD

Overall, compared to individuals with a poor ideal CVH profile (meeting only 1-2 metrics), incident CVD was lower in those who had an ideal CVH profile (meeting 5-7 metrics) (HR=0.28, 0.23-0.33, P<.001;  $I^2 = 70.5\%$ ) and in those with an intermediate ideal CVH profile (3-5 metrics) (HR=0.53, 0.47-0.59, P<.001;  $I^2 = 71.2\%$ ).

Analyzing each incident CVD outcome, individuals who have an ideal or intermediate ideal CVH profile have fewer odds of having myocardial infarction (Ideal, HR=0.24, 0.15-0.34, P<.001;  $I^2 = 0\%$ ; Intermediate, HR=0.54, 0.46-0.62, P<.001;  $I^2 = 0\%$ ), stroke (Ideal, HR=0.33, 0.21-0.45, P<.001;  $I^2 = 52.5\%$ ; Intermediate, HR=0.58, 0.44-0.72, P<.001;  $I^2 = 76.8\%$ ), incident heart failure (Ideal, HR=0.26, 0.15-0.37, P<.001;  $I^2 = 67.1\%$ ; Intermediate, HR=0.49, 0.41-0.56, P<.001;  $I^2 = 26.5\%$ ), venous thromboembolism (Ideal, HR=0.48, 0.35-0.61, P<.001;  $I^2 = 0\%$ ; Intermediate, HR=0.69, 0.52-0.86, P<.001;  $I^2 = 0\%$ ), coronary heart disease (Ideal, HR=0.21, 0.05-0.36, P<.001;  $I^2 = 0\%$ ; Intermediate, HR=0.56, 0.36-0.75, P<.001;  $I^2 = 50.9\%$ ), and a composite variable of CVD events (Ideal, HR=0.23, 0.13-0.34, P<.001;  $I^2 = 82.0\%$ ; Intermediate, HR=0.45, 0.31-0.58, P<.001;

 $I^2 = 85.5\%$ ) compared to those with a poor ideal CVH profile (Figure 2 and 3).

\*\*\*Figure 2 about here\*\*\*

\*\*\*Figure 3 about here\*\*\*

Meta-regression analyses plotting mean age shows that there were significant age effects on the HR estimates for overall incident CVD (beta= 0.026; P= .016 and beta= 0.012; P= .042) in the ideal and intermediate ideal CVH profile groups, respectively) (Figure 4).

\*\*\*Figure 4 about here\*\*\*

Publication bias and sensitivity analysis

When the impact of individual studies was examined by removing studies from the analysis one at a time, we observed that the pooled HR estimate remained constant. Evidence suggesting publication bias was apparent, according to the Egger test results (P=.562 and P=.836 in ideal and intermediate ideal CVH profile groups, respectively). The observed asymmetry in the funnel plots indicates the pooled HRs may have been overestimated due to reporting bias. Also, the funnel plots for the relationships of ideal CVH metrics and incident CVD were asymmetric (Supplementary Material Figure S2).

#### Discussion

Our findings suggest a strong inverse association between the number of ideal cardiovascular health metrics and incident CVD events. For individuals with an ideal CVH profile (meeting 5-7 metrics) an average reduction of 52% to 76% was found for incident CVD. Furthermore, an intermediate ideal CVH profile (meeting 3-4 ideal CVH metrics) was also associated with a significant average reduction in incident CVD of 31% to 56%. Therefore, for purposes of primary and secondary prevention risk, communication could be the promotion of at least achieving an intermediate ideal CVH profile.

Our meta-regression analysis showed that the CVD protection associated with attaining more ideal CVH metrics was lower among older populations. This finding is of special importance due to the exponential relationship of age with mortality and CVD events <sup>30</sup>. The only study included in this meta-analysis addressing elderly individuals reported that attaining more ideal CVH metrics is highly beneficial regarding incident CVD risks; this risk reduction was consistent across age groups, except for individuals older than 76 years old <sup>9</sup>. Therefore, the promotion of ideal CVH metrics should occur across population groups and especially in elderly subjects.

The results of the present meta-analysis showed that achieving a higher number of ideal CVH metrics is related to a lower incidence of CVD. An ideal CVH profile was associated with reduced odds of 77% for a composite variable of CVD events, 79% for coronary heart disease, 76% for myocardial infarction, 74% for incident heart failure, 67% for stroke and 52% for venous thromboembolism. Similarly, an intermediate profile was associated with reduced odds of 55% for the CVD event composite variable, 64% for coronary heart disease, 46% for myocardial infarction, 43% for incident heart failure, 42% for stroke and 31% for venous thromboembolism. The pathogenesis of these various CVD events and the role of traditional cardiovascular risk factors and lifestyle behaviors has some commonalities but also some differences. For example, according to the INTERHEART Study <sup>31</sup>, myocardial infarction is strongly associated with the presence of smoking, hypertension, diabetes, and dyslipidemia. Along the same line, the INTERSTROKE Study <sup>32</sup> showed that hypertension had a greater association with intracerebral hemorrhage stroke, whereas current smoking and diabetes were more associated with ischemic stroke. Also, the Framingham Heart Study reported that hypertension can be considered as one of the frequent causes of heart failure <sup>33</sup>. Regarding venous thromboembolism, obesity is the lifestyle risk factor most consistently associated with its incidence <sup>34</sup>. Finally, the most common risk factor associated with coronary heart disease is smoking, but diabetes, hypertension, smoking, dyslipidemia and obesity account for about 85% to 90% of premature coronary heart disease patients <sup>35</sup>.

The information summarized in this study suggests that a substantial reduction in incident CVD can be expected if at least 3-5 ideal CVH behavioural and/or biological metrics are achieved, with even larger reductions in CVD incidence associated with meeting more ideal CVH metrics. In terms of preventive cardiology practice, achieving an intermediate profile could be a more realistic goal for many patients, especially because of the low prevalence of ideal blood pressure (21.1%) and diet (4.1%) reported in included studies. A large number of studies have shown that moderate physical activity, smoking cessation, and a healthy diet are beneficial for prevention of CVD events <sup>36</sup>. In our review, the mean prevalence of meeting the ideal smoking metric was relatively high (68.7%), but in contrast ideal physical activity and diet were low (≈32%). These findings suggest that particular efforts in clinical practice should be made in the counselling and promotion of physical activity and healthy dietary behaviors <sup>37</sup>, aided by linkage to community-based lifestyle intervention efforts. If successful, this would have an impact on blood pressure <sup>38</sup>, glucose homeostasis <sup>39</sup>, and dyslipidemia and therefore in CVD events incidence <sup>40</sup>. The U.S. Preventive Services Task Force recommends medium- or high-intensity behavioral interventions to promote a healthful diet and physical activity and suggests that these interventions may be provided to individual patients in primary care settings or in other sectors of the health care system after referral from a primary care clinician 41. Previous studies also support the potential of using populationbased strategies targeting multiple risk factors simultaneously to achieve reductions in CVD rates in communities <sup>42</sup>.

# Strength and limitations

Strengths of this meta-analysis include the relatively large number of participants (n=219,050) and the various CVD outcomes studied. However, several limitations must be considered when interpreting these findings. First, some of these incident CVD outcomes have a somewhat different aetiology, particularly venous thromboembolism. However, the behavioural and biologic risk factors included in the AHA ideal CVH profile contribute to increased CVD risk

through various shared mechanisms such as inflammation, atherosclerosis and hypercoagulability <sup>6</sup>. Second, the follow-up of several studies were of limited duration. Third, different studies included different sets of covariates and hazards models that could have an impact on CVD incidence. Fourth, measurements of diet and physical activity were sometimes not standardized (did not report the use of a valid and reliable measure). Fifth, the study included a relatively healthy population with lower incident CVD risk. Finally, the composite variable of CVD events varied in the included studies and therefore its ethiology and related factors may differ.

In conclusion, our findings suggested an inverse association between the number of ideal CVH metrics (attainment of at least three metrics) and incident CVD. Also, in older individuals having a higher number of ideal CVH metrics was related with weaker protection of CVD events. This meta-analysis supports the use of the American Heart Association ideal CVH metrics and highlights the importance of improving individual health-related behaviours in order to reduce adult incident CVD.

## References

- 1. MEMBERS WG, Go AS, Mozaffarian D, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129:e28.
- 2. Bodenant M, Kuulasmaa K, Wagner A, et al. Measures of abdominal adiposity and the risk of stroke. Stroke. 2011:STROKEAHA. 111.614099.
- 3. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath Jr CW. Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med. 1999;341:1097-1105.
- 4. Sacco RL. Achieving ideal cardiovascular and brain health: opportunity amid crisis. Circulation. 2011;123:2653-2657.
- 5. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction the American Heart Association's Strategic Impact Goal through 2020 and beyond. Circulation. 2010;121:586-613.

- 6. Younus A, Aneni EC, Spatz ES, et al. A systematic review of the prevalence and outcomes of ideal cardiovascular health in US and non-US populations. Mayo Clin Proc. 2016;91(5):649-670.
- 7. Willis BL, DeFina LF, Bachmann JM, et al. Association of ideal cardiovascular health and long-term healthcare costs. Am J Prev Med. 2015;49:678-685.
- 8. Fang N, Jiang M, Fan Y. Ideal cardiovascular health metrics and risk of cardiovascular disease or mortality: A meta-analysis. Int J Cardiol. 2016;214:279-283.
- 9. Gaye B, Canonico M, Perier M-C, et al. Ideal Cardiovascular Health, Mortality, and Vascular Events in Elderly Subjects: The Three-City Study. J Am Coll Cardiol. 2017;69:3015-3026.
- 10. Kulshreshtha A, Vaccarino V, Judd SE, et al. Life's Simple 7 and risk of incident stroke. Stroke. 2013;44:1909-1914.
- 11. Nayor M, Enserro DM, Vasan RS, Xanthakis V. Cardiovascular health status and incidence of heart failure in the Framingham Offspring Study. Circulation: Heart Failure. 2016;9:e002416.
- Ogunmoroti O, Oni E, Michos ED, et al. Life9s Simple 7 and Incident Heart Failure: The
  Multi Ethnic Study of Atherosclerosis. J Am Heart Assoc. 2017;6:e005180.
- 13. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.
- 14. Goutham Rao, Francisco Lopez-Jimenez, Jack Boyd, et al. Methodological Standards for Meta-Analyses and Qualitative Systematic Reviews of Cardiac Prevention and Treatment Studies. Circulation. 2017.
- 15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151:W-65-W-94.
- 16. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2000.

- 17. HARDY RJ, THOMPSON SG. A likelihood approach to meta analysis with random effects. Stat Med. 1996;15:619-629.
- 18. Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-560.
- 19. Higgins J, Thompson SG. Quantifying heterogeneity in a meta analysis. Stat Med. 2002;21:1539-1558.
- 20. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-634.
- 21. Thompson SG, Sharp SJ. Explaining heterogeneity in meta analysis: a comparison of methods. Stat Med. 1999;18:2693-2708.
- 22. Dong C, Rundek T, Wright CB, Anwar Z, Elkind MS, Sacco RL. Ideal cardiovascular health predicts lower risks of myocardial infarction, stroke, and vascular death across whites, blacks and Hispanics: the northern Manhattan study. Circulation. 2012:CIRCULATIONAHA. 111.081083.
- 23. Folsom AR, Shah AM, Lutsey PL, et al. American Heart Association's Life's Simple 7: avoiding heart failure and preserving cardiac structure and function. Am J Med. 2015;128:970-976. e972.
- 24. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol. 2011;57:1690-1696.
- 25. Lachman S, Peters RJ, Lentjes MA, et al. Ideal cardiovascular health and risk of cardiovascular events in the EPIC-Norfolk prospective population study. Eur J Prev Cardiol. 2016;23:986-994.
- 26. Miao C, Bao M, Xing A, et al. Cardiovascular health score and the risk of cardiovascular diseases. PloS One. 2015;10:e0131537.

- 27. Olson NC, Cushman M, Judd SE, et al. American Heart Association9s Life9s Simple 7 and Risk of Venous Thromboembolism: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. J Am Heart Assoc. 2015;4:e001494.
- 28. Ommerborn MJ, Blackshear CT, Hickson DA, et al. Ideal Cardiovascular Health and Incident Cardiovascular Events: The Jackson Heart Study. Am J Prev Med. 2016;51:502-506.
- 29. Folsom AR, Olson NC, Lutsey PL, Roetker NS, Cushman M. American Heart Association's Life's Simple 7 and incidence of venous thromboembolism. Am J Hematol. 2015;90.
- 30. Laslett LJ, Alagona P, Clark BA, et al. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. J Am Coll Cardiol. 2012;60:S1-S49.
- 31. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-952.
- 32. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388:761-775.
- 33. Mahmood SS, Wang TJ. The epidemiology of congestive heart failure: Contributions from the Framingham Heart Study. Glob heart. 2013;8:77-82.
- 34. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism. Circulation. 2008;117:93-102.
- 35. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003;290:898-904.
- 36. Bull ER, Dombrowski SU, McCleary N, Johnston M. Are interventions for low-income groups effective in changing healthy eating, physical activity and smoking behaviours? A systematic review and meta-analysis. BMJ Open. 2014;4:e006046.

- 37. Berra K, Rippe J, Manson JE. Making physical activity counseling a priority in clinical practice: the time for action is now. JAMA. 2015;314:2617-2618.
- 38. Stewart J, Manmathan G, Wilkinson P. Primary prevention of cardiovascular disease: A review of contemporary guidance and literature. JRSM Cardiovasc Dis. 2017;6:2048004016687211.
- 39. Zhang X, Devlin HM, Smith B, et al. Effect of lifestyle interventions on cardiovascular risk factors among adults without impaired glucose tolerance or diabetes: A systematic review and meta-analysis. PloS One. 2017;12:e0176436.
- 40. Hozawa A, Folsom AR, Sharrett AR, Chambless LE. Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors: comparison of African American with white subjects—Atherosclerosis Risk in Communities Study. Arch Intern Med. 2007;167:573-579.
- 41. Lin JS, O'connor E, Whitlock EP, Beil TL. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the US Preventive Services Task Force. Ann Intern Med. 2010;153:736-750.
- 42. Stamler J, Stamler R, Neaton JD, et al. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. JAMA. 1999;282:2012-2018.

## Figure legend

- Figure 1. Flow chart for identification of trials for inclusion in the meta-analysis.
- Figure 2. Hazard Ratios (95% Confidence Interval) for cardiovascular events for ideal versus poor profile.
- Figure 3. Hazard Ratios (95% Confidence Interval) for cardiovascular events for intermediate versus poor profile.

Figure 4. Association between log hazard ratios of CVD events and age mean at baseline (years). A, ideal versus poor profile. B, intermediate versus poor profile. Solid line indicates a linear relationship. Size of each data point is proportional to its statistical weight.

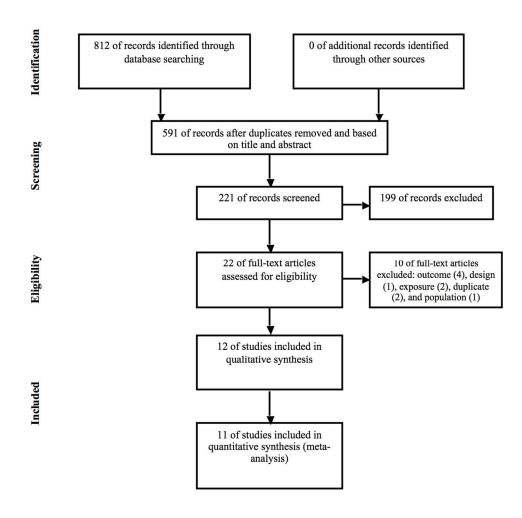


Figure 1. Flow chart for identification of trials for inclusion in the meta-analysis.

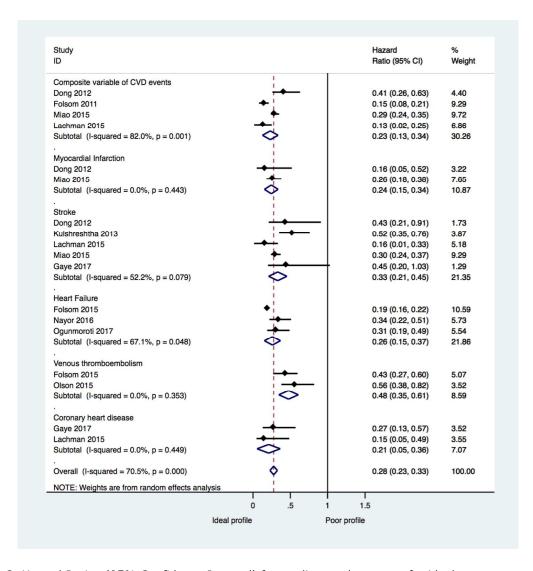


Figure 2. Hazard Ratios (95% Confidence Interval) for cardiovascular events for ideal versus poor profile.  $206 \times 218 \text{mm} \ (144 \times 144 \ \text{DPI})$ 

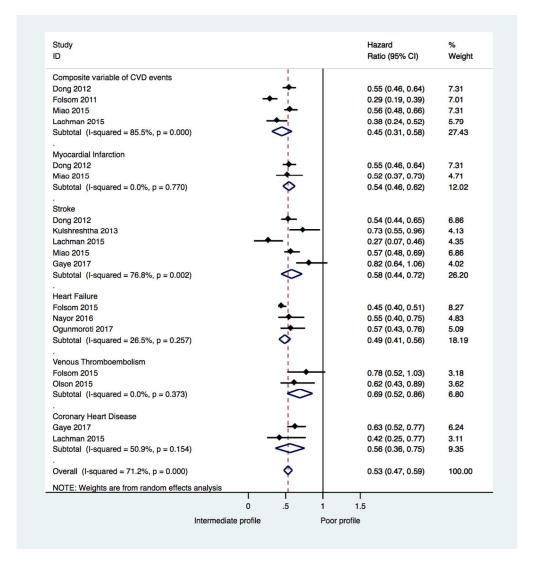


Figure 3. Hazard Ratios (95% Confidence Interval) for cardiovascular events for intermediate versus poor profile.

204x218mm (144 x 144 DPI)

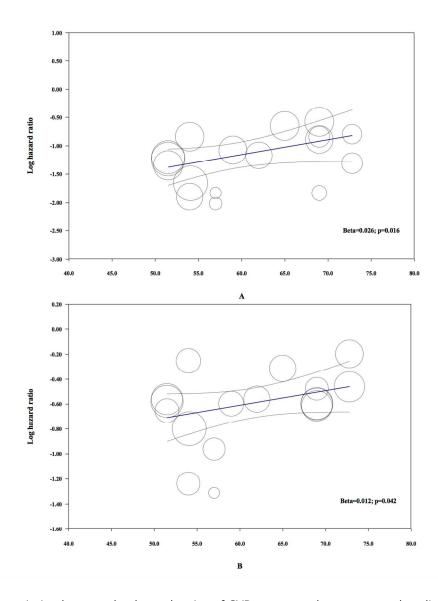


Figure 4. Association between log hazard ratios of CVD events and age mean at baseline (years). A, ideal versus poor profile. B, intermediate versus poor profile. Solid line indicates a linear relationship. Size of each data point is proportional to its statistical weight.

Table 1. Characteristics of included studies.

Study, year (reference)	Country	Sample size	Mean Age, y	Men, %	Study name	Mean follow-up, y	Main outcome measure	Adjusted for
Dong et al. 2012	USA	2,981	69.0	36.3	NOMAS study	8.0	Composite variable of CVD events, myocardial infarction and stroke	Age, sex, and ethnicity
Folsom et al. 2011	USA	12,744	54.0	46.4	ARIC study	18.7	Composite variable of CVD events and stroke	Age, sex, and race
Folsom et al. 2015	USA	4,855	54.1	46.4	ARIC study	22.5	Heart failure	Age, sex, and race
Folsom et al. 2015	USA	14,098	54.0	46.4	ARIC study	22.5	Venous thromboembolism	Age, sex, and race
Gaye et al. 2017	France	7,371	72.8	36.7	The Three-City Study	9.0	Coronary heart disease and stroke	Age, sex, study site, education level, and living alone at baseline
Kulshreshtha et al. 2013	USA	22,914	65.0	42.0	REGARDS study	4.9	Stroke	Age, race, sex, income, alcohol use, education, an geographic region
Lachman et al. 2015	Europe	10,043	57.0	44.1	EPIC-Norfolk Study	10.0	Composite variable of CVD events, coronary heart disease, and stroke	Age and sex
Miao et al. 2015	China	91,598	51.5	79.5	Kailuan Study	6.8	Composite variable of CVD events, myocardial infarction, and stroke	Age, sex, alcohol consumption, income, education and history of cardiovascular disease, he rate, uric acid, and high- sensitivity CRP

Nayor et al. 2016	USA	2,392	59.0	44.0	Framingham Offspring Study	12.3	Heart failure	Age and sex
Ogunmoroti et al. 2017	USA	6,506	62.0	47.0	Multi-Ethnic Study of Atherosclerosis	12.2	Heart failure	Age, sex, race/ethnicity, education, income, and health insurance
Olson et al. 2015	USA	30,239	69.0	45.0	REGARDS study	5	Venous thromboembolism	Age, sex, income, education, race, region, and race x region interaction
Ommerborn et al. 2016	USA	4,702	54.5	35.0	Jackson Heart Study	8.3	Composite variable of CVD events	Age, sex, income, and education



# MEDLINE (2010- July 2017)

WEBEN	VL (2010- July 2017)
	Key words
1	American heart association[MeSH Terms]
2	american heart association
3	#1 or #2
4	"cardiovascular health"
5	"ideal cardiovascular health"
6	"life's simple 7"
7	ideal health metrics
8	ideal cardiovascular health metrics
9	#4 or #5 or #6 or #7 or #8
10	#3 and #9
11	blood pressure[MeSH Terms]
12	Pressure, Blood
13	blood pressure
14	Systolic Pressure
15	Pressure, Systolic
16	Pressures, Systolic
17	Diastolic Pressure
18	Pressure, Diastolic
19	Pulse Pressure
20	Pressure, Pulse
21	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
22	Blood glucose[MeSH Terms]
23	Blood glucose
24	Blood Sugar
25	Sugar, Blood
-	

26	Glucose, Blood
27	#22 or #23 or #24 or #25 or #26
28	Cholesterol[MeSH Terms]
29	Cholesterol
30	epicholesterol
31	#28 or #29 or #30
32	exercise[MeSH Terms]
33	exercise
34	physical fitness[MeSH Terms]
35	physical fitness
36	Exercise, Physical
37	Exercises, Physical
38	Physical Exercise
39	#32 or #33 or #34 or #35 or #36 or #37 or #38
40	diet[MeSH Terms]
41	diet
42	diets
43	#40 or #41 or #42
44	smoking[MeSH Terms]
45	smoking
46	Smokings, Tobacco
47	Tobacco Smokings
48	Smoking, Tobacco
49	#44 or #45 or #46 or #47 or #48
50	body mass index[MeSH Terms]
51	body mass index
52	Index, Body Mass
53	Quetelet Index

54	Index, Quetelet
55	Quetelet's Index
56	Quetelets Index
57	#50 or #51 or #52 or #53 or #54 or #55 or #56
58	#21 and #27 and #31 and #39 and #43 and #49 and #57
59	cardiovascular disease [MeSH Terms]
60	event
61	myocardial infarction [MeSH Terms]
62	infarction
63	myocardial
64	stroke [MeSH Terms]
65	heart failure [MeSH Terms]
66	heart
67	failure
68	venous thromboembolism [MeSH Terms]
69	venous
70	thromboembolism
71	coronary disease [MeSH Terms]
72	coronary
73	peripheral artery disease [MeSH Terms]
74	peripheral
75	#59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74
78	#75 Filters: Publication date from 2010/01/01

# EMBASE (2010- July 2017)

	Key words
1	
1	'blood pressure'/exp
2	blood pressure'
3	cholesterol'/exp
4	cholesterol
5	epicholesterol
6	glucose blood level'/exp
7	'blood glucose'
8	'exercise'/exp
9	exercise
10	fitness
11	'diet'/exp
12	diet
13	diets
14	'body mass'/exp
15	'body mass index'
16	'quetelet index'
17	'somking'/exp
18	smoking
19	tobacco
20	'behavior, smoking'
21	'smoking behavior'
22	#1 or #2
23	#3 or #4 or #5
24	#6 or #7
25	#8 or #9 or #10
26	#11 or #12 or #13

27	#14 or #15 or #16
28	#17 or #18 or #19 or #20 or #21
29	#22 and #23 and #24 and #25 and #26 and #27 and #28
30	'American Heart association'
31	'Cardiovascular Health'
32	'Ideal Cardiovascular Health'
33	'Lifes simple 7'
34	'Life simple 7'
35	'Ideal Health Metrics'
36	'Ideal Cardiovascular Health Metrics'
37	#31 or #32 or #33 or #34 or #35 or #36
38	#30 and #37
39	'cardiovascular disease'
40	'myocardial infarction'
41	'stroke'
42	'heart failure'
43	'venous thromboembolism'
44	'coronary disease'
45	'peripheral artery disease'
46	#39 or #40 or #41 or #42 or #43 or #44 or #45
47	#29 or #38
48	#46 and #47
49	#46 and #57 and [2010-2017]/py
·	

# CINAHL (2010- July 2017)

	2 (2010- July 2017)
	Key words
1	MeSH descriptor: [American Heart Association] explode all trees
2	"American heart association"
3	#1 or #2
4	Cardiovascular Health
5	ideal cardiovascular health
6	Life's simple 7
7	ideal health metrics
8	ideal cardiovascular health metrics
9	#4 or #5 or #6 or #7 or #8
10	#9 and #3
11	MeSH descriptor: [Blood Pressure] explode all trees
12	blood pressure
13	Pressure, Blood
14	Systolic Pressure
15	Pressure, Systolic
16	Pressures, Systolic
17	Diastolic Pressure
18	Pressure, Diastolic
19	Pulse Pressure
20	Pressure, Pulse
21	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
22	MeSH descriptor: [Blood Glucose] explode all trees
23	blood glucose
24	Blood Sugar

	T
25	Sugar, Blood
26	Glucose, Blood
27	#22 or #23 or #24 or #25 or #26
28	MeSH descriptor: [Cholesterol] explode all trees
29	Cholesterol
30	Epicholesterol
31	#28 or #29 or #30
32	MeSH descriptor: [Exercise] explode all trees
33	exercise
34	MeSH descriptor: [Physical Fitness] explode all trees
35	physical fitness
36	Exercise, Physical
37	Exercises, Physical
38	Physical Exercise
39	#32 or #33 or #34 or #35 or #36 or #37 or #38
40	MeSH descriptor: [Diet] explode all trees
41	diet
42	diets
43	#40 or #41 or #42
44	MeSH descriptor: [Body Mass Index] explode all trees
45	body mass index
46	Index, Body Mass
47	Quetelet Index
48	Index, Quetelet
49	Quetelet's Index
50	Quetelets Index
51	#44 or #45 or #46 or #47 or #48 or #49
	<del></del>

Figure S1. Prevalence of ideal levels for each of the 7 metrics of cardiovascular health at baseline. Favorable health behaviors: smoking abstention in the last year, ideal body mass index, physical activity and consumption of a diet that promotes cardiovascular health; and health factors: untreated total cholesterol< 200 mg/dl, untreated blood pressure <120/80 mm/Hg, and absence of diabetes mellitus. BMI, body mass index; BP, blood pressure; PA, physical activity; TC, total cholesterol.

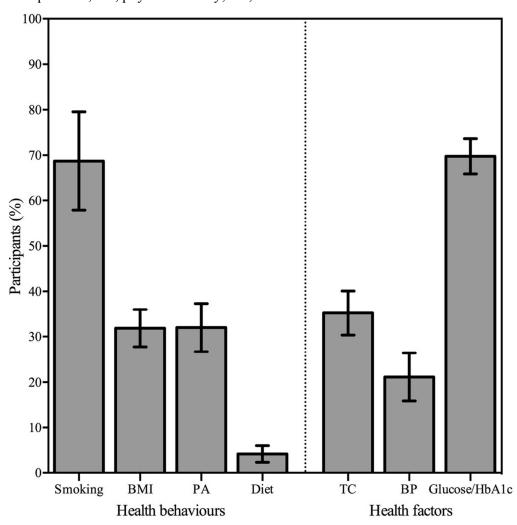


Figure S2. Funnel plots for log hazard ratios of CVD events for ideal (A) and intermediate profile (B).

