Original Article

Ideal Cardiovascular Health and Risk of Frailty in Older Adults

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***Background*—**The major cardiovascular risk factors and existing cardiovascular disease have been linked to increased risk of the frailty syndrome. However, the association between ideal cardiovascular health and the risk of frailty in older adults is uncertain.

***Methods and Results*—**Prospective cohort study of 1745 individuals (≥60 years and free of cardiovascular disease) recruited during 2008 to 2010. Cardiovascular health was defined as having 7 ideal metrics: never smoking, physically active, healthy diet, body mass index <25 kg/m^2, untreated serum cholesterol <200 mg/dL, untreated blood pressure <140/90 mm Hg, and untreated fasting serum glucose <100 mg/dL. Participants were followed-up through 2012 to assess incident frailty, defined as ≥3 of the 5 Fried criteria. Statistical analyses were performed with Cox regression and adjusted for main confounders. During a mean follow-up of 3.5 years, 117 cases of incident frailty were identified. Compared with meeting 0 to 1 ideal metrics, the hazard ratio (95% confidence interval) of frailty was 0.51 (0.30–0.84) for 2 metrics and 0.630 (0.39–0.99) for ≥3 metrics. Results were similar after excluding incident cases of cardiovascular disease. The number of ideal metrics showed a tendency to a reduced risk of all frailty criteria. The cardiovascular metrics associated with the greatest reduction of frailty risk were being physically active and ideal body mass index.

***Conclusions*—**Reaching old age in ideal cardiovascular health is associated with a reduced risk of frailty. This highlights the importance of a life-course approach for frailty prevention. **(*Circ Cardiovasc Qual Outcomes*. 2016;9:00-00. DOI: 10.1161/CIRCOUTCOMES.115.002294.)**

Key Words: cardiovascular diseases ■ epidemiology ■ frail elderly ■ lifestyle ■ risk factors ■ Spain

Frailty is a geriatric syndrome characterized by increased vulnerability to even minor stressors, which leads to higher risk of hospitalization, disability, institutionalization, and death.[1–3] Frailty has a complex pathogenesis, but it seems to result from a decline across multiple biological systems because of age-associated physiological impairment or existing disease[1–3]

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There is evidence of a strong link between cardiovascular disease (CVD) and frailty in older adults. Specifically, lifestyle-related cardiovascular risk factors, including smoking,[4] poor diet,[5] physical inactivity,[6] or obesity[7] increase the risk of frailty. Biological risk factors, such as hypertension,[8] dyslipidemia,[8] or diabetes mellitus[9] are also associated with higher frequency of frailty. Moreover, a higher score on the Framingham or SCORE risk equations has been shown to identify future frailty.[10,11] Finally, frailty is more frequent among individuals with endothelial dysfunction or existing CVD.[12,13]

CVD and its risk factors often develop early in life. Moreover, once adverse levels of risk factors are present (eg, obesity, hypertension), they are difficult to reverse, and substantial elevations in long-term and lifetime risks for CVD are largely unavoidable.[14] Therefore, effective CVD prevention should adopt a life-course approach by avoiding the development of cardiovascular risk factors in the first place (primordial prevention).[15] The American Heart Association (AHA) has charted a new strategy for CVD prevention by focusing on improving cardiovascular health through primordial prevention during the life-course.[14] According to the AHA, cardiovascular health comprises 7 metrics: 4 ideal health behaviors (nonsmoking, being physically active, eating a healthy diet, and normal body mass index [BMI]) together with 3 ideal health factors (untreated normal total cholesterol, blood pressure [BP], and fasting blood glucose).[14] Recent studies have shown that meeting a higher number of ideal cardiovascular health metrics predicts a lower risk of death from all causes and from diseases of the circulatory system.[16–18]

To our knowledge, this is the first study to examine the association between ideal cardiovascular health and the risk of frailty in older adults. The progressive ageing of the world population will probably increase the frequency of frailty and

Received October 22, 2015; accepted March 8, 2016.

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The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.115.002294/-/DC1.

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WHAT IS KNOWN

- Ideal cardiovascular health predicts a lower risk of death from all causes and from diseases of the circulatory system.
- In older adults, the major cardiovascular risk factors and existing cardiovascular disease have also been linked to a higher risk of developing frailty, but the association between ideal cardiovascular health and frailty is unknown.

WHAT THE STUDY ADDS

- Among older adults who were followed for a duration of 3.5 years, the number of ideal cardiovascular health metrics was inversely associated with the risk of incident frailty. The metrics associated with the greatest reduction of frailty risk were being physically active and ideal body mass index.
- Reaching old age in ideal cardiovascular health is associated with a reduced risk of frailty, supporting further investigation to determine if strategies that maintain cardiovascular health over the life course prevent frailty.

its severe complications; thus, this work is important because it might serve to establish whether primordial CVD prevention could not only reduce CVD incidence and mortality, but also palliate some of the undesired consequences of ageing.

Methods

Study Design and Participants

Data were taken from a cohort of 2614 community-dwelling individuals aged ≥60 years, whose methods have been reported elsewhere.[5,19] The study participants were selected by stratified cluster sampling of the noninstitutionalized adult population of Spain. The sample was first stratified by province and size of municipality, then clusters were selected randomly in 2 stages (municipalities and census sections), and finally, the households within each section were selected by random telephone dialing. Subjects in the households were selected proportionally to the age and sex distribution of the population of Spain. Baseline information was obtained during 2008 to 2010 and included data on cardiovascular health, frailty, and potential confounders. Participants were followed-up to 2012. We excluded 145 subjects who were frail at baseline, 95 subjects who died during follow-up, and 289 subjects without complete data on frailty in 2012. When comparing the baseline characteristics between the 2614 individuals comprising the entire cohort and the remaining 2085 subjects, the latter had slightly less morbidity.

Study participants provided informed written consent. The study was approved by the Clinical Research Ethics Committee of the La Paz University Hospital in Madrid.

Study Variables

Data were collected by personnels trained and certified in the study procedures. At baseline and at follow-up, they conducted a phone interview to collect data on health status, lifestyle, and morbidity, as well as a home visit to obtain biological samples, to perform a physical examination and to record habitual diet.[19]

At baseline, study participants reported their age, sex, level of education, and smoking status. To assess physical activity, we applied the Spanish-validated questionnaire used in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort study, which combines physical activity at work and during leisure time into 4 levels (very active, moderately active, moderately inactive, and inactive).[20] Food and beverage consumption was recorded with a validated computerized diet history, also developed from the one used in the EPIC cohort.[21,22] In addition, individuals reported if they had any of the following physician-diagnosed diseases: CVD (coronary heart disease, heart failure, stroke), osteomuscular disease (osteoarthritis, arthritis, hip fracture), cancer at any site, chronic obstructive lung disease, and depression requiring treatment. Limitations in instrumental activities of daily living (IADL) were assessed with the Lawton–Brody test.[23] Weight and height were measured twice in each subject under standardized conditions, using electronic scales (model Seca 841, precision to 0.1 kg) and portable extendable stadiometers (model Ka We 44 444 Seca).[19] BMI was calculated as weight in kilogram divided by squared height in meters. BP was measured ≤6×, using standardized procedures with validated automatic devices (model Omron M6) and cuffs of 3 sizes according to arm circumference.[19] In the analyses, BP was calculated as the mean of at least 3 of the last 5 readings, excluding the first one to reduce the alerting reaction. Individuals also underwent a physical examination, including grip strength and gait speed.[5] Finally, study participants reported their current use of medication, which was checked against drug packages by the study personnel at the participants' homes.

At baseline, each study participant provided 12-hour fasting blood samples. Total cholesterol and glucose were measured by standard methods on the ADVIA 2400 Chemistry System, Siemens.

Cardiovascular Health

In accordance with the AHA, cardiovascular health was defined based on 7 ideal health metrics: never smoking, being physically active, eating a healthy diet, BMI <25 kg/m^2, untreated serum cholesterol <200 mg/dL, untreated systolic/diastolic BP <140/90 mm Hg, and untreated fasting serum glucose <100 mg/dL.[14,24]

The AHA definition of ideal smoking status includes former smokers who have not smoked for 12 months or longer. Because time since smoking cessation was not assessed in our study, we used only never smoking as the ideal category for smoking status.[24] Ideal physical activity was defined as being very active or moderately active. A healthy diet was defined as meeting at least 4 of the following 5 goals: ≥4.5 cups/d of fruits and vegetables; ≥2 (3.5 oz) servings/week of fish; ≥1.1 g of fiber per 10 g of carbohydrate/d; <1500 mg/d of sodium; and ≤450 kcal (36 oz) per week of sugar-sweetened beverages. Finally, although the AHA considers ideal BP to be <120/80 mm Hg, this category is infrequent in older adults from Western countries because systolic BP usually increases with age; thus, for the purpose of this work, the ideal category was defined as untreated BP <140/90 mm Hg.

In some analyses, we also considered intermediate and poor health metrics. For smoking, they were, respectively, former smoking and current smoking. The corresponding metrics for BMI were 25 to 29.9 and ≥30 kg/m^2, whereas for physical activity, they were moderately inactive and inactive. Intermediate and poor diets were defined as meeting 2 to 3 and 0 to 1 of the above dietary goals, respectively. As regards biological factors, the intermediate and poor metrics for total cholesterol were, respectively, 200 to 239 mg/dL or treated and ≥240 mg/dL. The corresponding values for BP were treated <140/90 and ≥140/90 mm Hg, whereas for fasting serum glucose, they were 100 to 125 mg/dL or treated and ≥126 mg/dL.

Frailty

We used the operational definition of frailty developed by Fried et al in the Cardiovascular Health Study.[25] Specifically, frailty was defined as having at least 3 of the following 5 criteria: (1) exhaustion, based on a response of ≥3 to 4 days a week to any of the following questions from the Center for Epidemiological Studies Depression Scale: "I felt that anything I did was a big effort" or " I felt that I could not keep on doing things"; (2) low physical activity, defined as walking ≤2.5 h/week in men and ≤2 h/week in women; (3) slow walking speed, defined as the lowest quintile in our study sample for the 3-m walking speed test, adjusted for sex and height; (4) weight loss, defined as involuntary loss of ≥4.5 kg in the preceding year; and (5) weakness, defined as the lowest quintile in the Cardiovascular Health Study of maximum strength on the dominant hand adjusted for sex and BMI. Strength was measured with a Jamar dynamometer, and we selected the highest value in 2 consecutive measures.

Statistical Analysis

Among the 2085 study participants with information on frailty in 2012, we excluded 96 with reported history of myocardial infarction, stroke, or congestive heart failure at baseline and 244 who lacked data either on cardiovascular health metrics or on other study variables. Therefore, the analyses were conducted on 1745 individuals.

The association between cardiovascular health at baseline and subsequent risk of frailty was summarized with hazard ratios (HR) and their 95% confidence interval (CI), obtained from Cox regression with age as the time scale and individual follow-up starting times (age at baseline examination) treated as staggered entries. Because of limitations in the number of frailty cases observed, cardiovascular health was classified into 3 categories: 0 to 1 ideal metrics (reference), 2 metrics, and ≥3 metrics. Cox models were adjusted for sex, age, and education (model 1) or additionally for alcohol intake, morbidity, limitation in IADL, and the number of frailty criteria at baseline (model 2). In addition, to better characterize the dose–response association between cardiovascular health and frailty, we also built a cardiovascular metric score, where we assigned 0 to a poor metric, 1 to an intermediate metric, and 2 to an ideal metric. The score was calculated by summing values for each of the 7 metrics (possible range 0–14). To obtain a fairly homogeneous distribution of frailty, we defined the following categories of this score: 0 to 5, 6, 7, 8, and >8.

Several sensitivity analyses were performed to check that the main results were robust. First, because frailty may overlap with disability, the analyses were replicated after excluding the 182 individuals with baseline limitations in IADL. Second, given that optimum cardiovascular health has been associated with lower risk of depression, which in turn is a risk factor for frailty, the analyses were repeated after excluding 122 subjects diagnosed at baseline with depression requiring drug treatment. Third, given that apparent optimum weight at baseline may result from weight loss derived from subclinical disease, the analyses were rerun with frailty defined as having 2 out of the 4 remaining Fried criteria, excluding the weight loss criterion. Fourth, to rule out that the study association was driven by low physical activity (which is both a CVD metric and a frailty criterion), we conducted 2 analysis: one with frailty defined as having 2 out of 4 Fried criteria excluding the physical activity criterion, and another analysis with exclusion of the 96 subjects having the low activity criterion at baseline. Finally, to assess if the association between cardiovascular health and frailty risk was mediated by incident CVD, the analyses were repeated after excluding 111 individuals diagnosed with CVD or atrial fibrillation during follow-up.

Similar analyses were conducted to assess the association of optimum cardiovascular health with risk of each frailty criterion. We also investigated the link between each ideal cardiovascular metric and the risk of frailty; this analysis was further adjusted for all cardiovascular metrics

To test if the association between cardiovascular health and risk of frailty varied with sex, we ran analyses with interaction terms defined as the product of cardiovascular health categories by sex. Models with and without interaction terms were then compared with likelihood ratio tests based on the partial likelihood. Because no significant sex interactions were found, results are presented for the total study sample.

We assessed the assumption of proportionality of hazards both graphically and by testing the significance of interaction terms for the cardiovascular metrics and the time variable. No evidence was found of departure from the proportional hazards assumption (P>0.1).

Table 1. Characteristics of Study Participants According to the Number of Ideal Cardiovascular Health Metrics at Baseline

		Number of Ideal Cardiovascular Health Metrics			
	Total, N=1745	0–1 (n=437)	2 (n=512)	≥3 (n=796)	*P* Value for Trend
Women, %	51.5	29.5	49.6	64.7	<0.001
Age, y (mean±SD)	68.5±6.3	68.9±6.3	68.5±6.7	68.2±6.0	0.164
Primary or less education, %	52.8	51.9	54.7	52.1	0.921
Alcohol intake, g/d, mean±SD	10.8±18.0	17.2±23.4	11.5±19.4	6.8±11.6	<0.001
Morbidity					
Cancer at any site, %	1.7	1.6	1.6	1.8	0.812
Chronic obstructive lung disease, %	7.2	6.2	9.2	6.5	0.917
Osteomuscular disease,* %	46.4	40.0	47.5	49.1	0.004
Depression needing treatment, %	7.0	3.4	7.2	8.8	0.001
Limitation in IADL, %	9.0	8.6	10.3	8.4	0.755
Ideal cardiovascular health metrics					
Smoking (never), %	57.9	25.4	53.1	78.8	<0.001
BMI (<25 kg/m^2), %	19.4	2.1	11.1	34.3	<0.001
Physical activity (at goal), %	22.5	4.8	13.1	38.2	<0.001
Healthy diet, %	21.4	4.6	13.9	35.6	<0.001
Total cholesterol (<200 mg/dL, untreated), %	29.5	12.8	25.2	41.3	<0.001
Blood pressure (<140/90 mm Hg, untreated), %	35.2	8.7	25.0	56.4	<0.001
Serum glucose, (<100 mg/dL, untreated), %	59.2	20.1	58.6	81.0	<0.001

BMI indicates body mass index; IADL, instrumental activities of daily living; and SD, standard deviation.
*Osteoarthritis, arthritis, hip fracture.

Table 2. Association Between the Number of Ideal Cardiovascular Health Metrics or the Cardiovascular Metric Score and the Risk of Frailty

	No. of Frailty Cases	Hazard Ratio (95% CI)	
		Model 1	Model 2
Number of ideal health metrics			
0–1 ideal metrics	40	Ref	Ref.
2 ideal metrics	31	0.54 (0.33–0.88)*	0.51 (0.30–0.84)*
≥3 ideal metrics	46	0.55 (0.39–0.99)†	0.63 (0.39–0.99)*
Cardiovascular metric score‡			
0–5	26	Ref.	Ref.
6	27	0.99 (0.57–1.71)	1.00 (0.57–1.78)
7	23	0.74 (0.41–1.31)	0.82 (0.45–1.50)
8	22	0.57 (0.32–1.00)	0.75 (0.41–1.36)
>8	19	0.36 (0.29–0.66)†	0.42 (0.22–0.80)†

CI indicates confidence interval; and IADL, instrumental activities of daily living. Model 1, adjusted for sex, age (years), and education (primary school or lower/secondary or high school/university). Model 2, adjusted as in model 1 and additionally for alcohol intake (g/d), cancer (no/yes), obstructive lung disease (no/yes), osteomuscular disease (no/yes), depression requiring treatment (no/yes), IADL limitation (no/yes), and number of frailty criteria (0/1/2) at baseline.

*$P<0.05$.

†$P<0.01$.

‡Cardiovascular metric score, where we assigned 0 to a poor metric, 1 to an intermediate metric, and 2 to an ideal metric. The score was calculated by summing values for each of the 7 metrics (possible range 0 to 14). To obtain a fairly homogeneous distribution of frailty, we defined the following categories of this score: 0–5, 6, 7, 8, and >8.

Analyses were performed with the SPSS version 21 software (IBM, Armonik, NY).

Results

At baseline, 437 (25%) study participants had 0 to 1 ideal cardiovascular metrics, 512 (29%) had 2 metrics, and 796 (46%) had ≥3 metrics. Compared with individuals with 0 to 1 ideal metrics, those with a higher number of metrics were more frequently women, had lower alcohol intake, and more frequently had osteoarticular disease and depression (Table 1).

During a mean follow-up of 3.5 years, 117 (6.7%) subjects developed incident frailty. After full adjustment for potential confounders, optimum cardiovascular health was associated with lower risk of frailty; specifically, compared with meeting 0 to 1 ideal metrics, the HR (95% CI) of frailty was 0.51 (0.30–0.84) for 2 metrics and 0.63 (0.39–0.99) for ≥3 metrics. When we used the cardiovascular metric score, we observed a clear inverse dose–response for the study association; compared with those with a score 0 to 5, the HR (95% CI) of frailty among those with a score 6, 7, 8, and >8 was, respectively, 1.00 (0.57–1.78), 0.82 (0.45–1.50), 0.75 (0.41–1.36), and 0.42 (0.22–0.80) (Table 2). Results were similar when the analyses were repeated among individuals free of IADL limitation or without depression at baseline, when the weight loss or the low physical criterion was excluded from the definition of frailty, when subjects with low physical activity at baseline were removed, and after excluding those subjects diagnosed with CVD or atrial fibrillation during follow-up (Table in the Data Supplement).

Table 3 shows the association between the number of ideal cardiovascular metrics and the risk of each frailty criterion. Better cardiovascular health tended to be associated with a reduced risk of all frailty criteria, achieving statistical significance for low physical activity. Compared with having 0 to 1 ideal metrics, the HR (95% CI) of physical activity was 0.93 (0.67–1.29) for 2 metrics and 0.73 (0.53–0.99) for ≥3 metrics.

Finally, being physically active, having a BMI <25 kg/m^2, and having untreated serum glucose <100 mg/dL were associated with lower risk of frailty in the analyses adjusted for age, sex, and educational level. After full adjustment, only physical activity and ideal BMI remained significantly associated with frailty risk. Specifically, the HR (95% CI) of frailty was 0.49 (0.24–0.97) for being active versus inactive and 0.43 (0.22–0.85) for having an ideal weight versus obesity (Table 4).

Table 3. Association Between the Number of Ideal Cardiovascular Health Metrics and the Risk of Each Frailty Criterion

	No. of Frailty Cases	Hazard Ratio (95% CI)	
		Model 1	Model 2
Exhaustion			
0–1 ideal metrics	58	Ref.	Ref.
2 ideal metrics	66	0.82 (0.57–1.17)	0.82 (0.57–1.20)
≥3 ideal metrics	91	0.69 (0.49–0.97)*	0.75 (0.53–1.07)
Low physical activity			
0–1 ideal metrics	75	Ref.	Ref.
2 ideal metrics	85	0.95 (0.69–1.30)	0.93 (0.67–1.29)
≥3 ideal metrics	104	0.71 (0.52–0.96)*	0.73 (0.53–0.99)*
Slow walk			
0–1 ideal metrics	78	Ref.	Ref.
2 ideal metrics	70	0.86 (0.62–1.19)	0.92 (0.66–1.28)
≥3 ideal metrics	110	0.91 (0.67–1.23)	0.96 (0.70–1.31)
Weight loss			
0–1 ideal metrics	37	Ref.	Ref.
2 ideal metrics	43	0.90 (0.57–1.41)	0.99 (0.62–1.58)
≥3 ideal metrics	56	0.72 (0.47–1.11)	0.78 (0.49–1.24)
Weakness			
0–1 ideal metrics	152	Ref.	Ref.
2 ideal metrics	186	1.05 (0.84–1.31)	1.07 (0.85–1.33)
≥3 ideal metrics	246	0.91 (0.74–1.12)	0.93 (0.75–1.15)

CI indicates confidence interval; and IADL, instrumental activities of daily living. Model 1, adjusted for sex, age (years), and education (primary school or lower/secondary or high school/university). Model 2, adjusted as in model 1 and additionally for alcohol intake (g/d), cancer (no/yes), obstructive lung disease (no/yes), osteomuscular disease (no/yes), depression requiring treatment (no/yes), IADL limitation (no/yes), and number of frailty criteria (0/1/2) at baseline.

*$P<0.05$.

Table 4. Association Between Each Cardiovascular Health Metric Categories and the Risk of Frailty

	No. of Frailty Cases	Hazard Ratio (95% CI)	
		Model 1	Model 2
Smoking			
Poor (current)	6	Ref.	Ref.
Intermediate (former)	30	1.46 (0.60–3.56)	1.04 (0.41–2.63)
Ideal (never)	81	1.00 (0.42–2.41)	0.96 (0.39–2.35)
Physical activity			
Poor (inactive)	80	Ref.	Ref.
Intermediate (moderately inactive)	26	0.49 (0.31–0.77)*	0.60 (0.37–0.97)†
Ideal (active)	11	0.40 (0.21–0.76)*	0.49 (0.24–0.97)†
Healthy diet score			
Poor (0–1 components)	26	Ref.	Ref.
Intermediate (2–3 components)	67	0.62 (0.39–0.98)†	0.72 (0.44–1.17)
Ideal (4–5 components)	24	0.71 (0.40–1.24)	0.88 (0.49–1.61)
Body mass index			
Poor (≥30 kg/m^2)	59	Ref.	Ref.
Intermediate (25–29.9 kg/m^2)	46	0.46 (0.31–0.68)*	0.58 (0.38–0.89)†
Ideal (<25 kg/m^2)	12	0.32 (0.17–0.61)*	0.43 (0.22–0.85)†
Serum total cholesterol			
Poor (≥240 mg/dL)	12	Ref.	Ref.
Intermediate (200–239 mg/dL or treated)	68	1.62 (0.87–3.01)	1.52 (0.81–2.87)
Ideal (<200 mg/dL, untreated)	37	1.80 (0.93–3.50)	1.33 (0.66–2.66)
Blood pressure			
Poor (≥140/90 mm Hg)	61	Ref.	Ref.
Intermediate (≥140/90 mm Hg, treated)	22	1.23 (0.75–2.04)	0.99 (0.58–1.70)
Ideal (<140/90 mm Hg, untreated)	34	1.19 (0.77–1.85)	1.48 (0.92–2.36)
Serum glucose			
Poor (≥126 mg/dL)	21	Ref.	Ref.
Intermediate (100–125 mg/dL or treated)	43	0.74 (0.44–1.26)	0.87 (0.50–1.54)
Ideal (<100 mg/dL, untreated)	53	0.48 (0.29–0.81)*	0.69 (0.40–1.20)

CI indicates confidence interval; and IADL, instrumental activities of daily living. Model 1, adjusted for sex, age (years), and education (primary school or lower/secondary or high school/university). Model 2, adjusted as in model 1 and additionally for alcohol intake (g/d), cancer (no/yes), obstructive lung disease (no/yes), osteomuscular disease (no/yes), depression requiring treatment (no/yes), IADL limitation (no/yes), number of frailty criteria (0/1/2) at baseline, and for the rest of the metrics: smoking status (never smoker/former smoker/current smoker), physical activity (MET h/week), healthy diet score (0–5), body mass index (kg/m^2), total cholesterol (mg/dL), blood pressure (mm Hg), fasting glucose (mg/dL), as appropriate.

*P<0.01.

†P<0.05.

Discussion

Our results show that reaching old age in optimum cardiovascular health, as represented by a higher number of ideal cardiovascular metrics, is associated with lower risk of frailty and that the main contributors to this association are physical activity and ideal weight.

There are 2 main reasons why the association between cardiovascular health and reduced risk of frailty was to be expected. First, there is substantial evidence that frailty is more frequent among older adults with existing CVD than in those without.[13] And second, several individual CVD risk factors or higher scores in CVD risk equations (eg, Framingham and SCORE) in middle- and old-age have been associated with higher risk of frailty.[4–11] Our study extends the knowledge in this field by showing that older adults with ideal cardiovascular health metrics are less likely to develop frailty. We did not obtain information on the potential mechanisms of the study association; however, they could be both clinical (eg, chronic diseases resulting cardiovascular risk factors) and subclinical, such as delayed vascular aging (arterial stiffness, thickness of the carotid intima-media, and reduced blood flow to peripheral tissues) and less frequent subclinical cardiac disease and brain infarcts.[10,11] In fact, previous studies have found a cross-sectional association between subclinical CVD and frailty.[12,26,27]

In our study, a higher number of ideal cardiovascular metrics was associated with a tendency to a lower risk of several frailty criteria, although statistical significance was achieved only for low physical activity. It is noteworthy that low physical activity leads to exhaustion, muscle weakness (sarcopenia), and the other components of the frailty cycle, which in turn further reduce physical activity. Moreover, this finding was consistent with the fact that being physically active as well as keeping a normal weight were the 2 ideal metrics with the strongest relationship with frailty because both of them are good predictors of exhaustion and low physical activity. Also, clinical trials with physical exercise have shown benefits in frailty, physical function, and cardiovascular risk in older adults.[28,29]

We observed no association between ideal values of biological CVD risk factors and frailty. This is consistent with previous studies using the Framingham and SCORE risk equations, neither of which found that BP, serum cholesterol, or serum glucose were single drivers of the association between CVD risk and incident frailty.[10,11] However, the results for serum glucose require additional confirmation in future research. First, because diabetes mellitus is a well-stablished risk factor for frailty,[9] and second, because it is possible that the association of serum glucose with frailty was partly obscured by the effect of physical activity and BMI on serum glucose. In fact, in our study, ideal serum glucose did show an association with lower frailty risk in relatively crude analyses, but it was substantially weakened and lost statistical significance after adjusting for morbidity, IADL limitation, and the rest of the cardiovascular metrics. Moreover, in a recent analysis of the Northern Manhattan Study cohort, ideal cardiovascular health was linked to lower risk of disability in basic activities of daily living, and this association was partly because of ideal serum glucose, but not to other biological risk factors.[30]

Strengths and Limitations

Among the strengths of this study is the prospective study design and the fact that the main study variables were appropriately measured; specifically, physical activity and food consumption were assessed with validated instruments; BMI and BP were measured by trained personnel under standardized conditions; and serum cholesterol and glucose were determined in a central laboratory. Finally, the analyses were adjusted for many potential confounders, and the main results were robust in several sensitivity analyses.

This study also has several limitations. First, the analytic sample was somewhat heathier than the entire cohort; although results were robust in sensitivity analyses across subgroups with different health status, we cannot rule out some attrition bias whose effect on study results would be unknown. Second, this was a cohort of relatively young and noninstitutionalized older adults. Several studies on cardiovascular risk and frailty have been conducted with individuals of the same age or younger than ours,[10,11,30] possibly because the relative (though not the absolute) effect of cardiovascular risk factors on health outcomes decreases with age, and it is easier to observe in younger subjects. Notwithstanding this, our results might not apply to the oldest old or in other settings. Third, the duration of follow-up was only 3.5 years, which could not allow for observing the full impact of ideal cardiovascular health on frailty. However, several classic studies on frailty also have a short follow-up[4,11] because frailty is a rather frequent outcome, and the relatively short life expectancy of older adults makes of particular interest to reveal short-term effects of both risk factors and preventive interventions. Fourth, frailty can be assessed with 2 main approaches (the phenotypic one based on the Fried criteria and the deficit accumulation approach), as well as with many modifications of their original versions.[1–3] It is also known that the different approaches could make a substantial impact on study results.[31] Thus, despite we ascertained frailty with the Fried criteria, which are widely used in the literature, our results should be confirmed using other definitions. Fifth, ideal cardiovascular metrics were assessed only once at baseline; thus, we cannot be sure that they represent long-term values, particularly for physical activity, diet, and BMI. However, physical activity usually decreases over the life course,[29] while BMI tends to increase up to the age of 70,[32] and so it is likely that most individuals with ideal metrics for these variables have presented them for a long time. Moreover, the main driver of changes in health behaviors is the diagnosis of a health disorder. Given that our analyses were based on individuals free of CVD at baseline and that ideal metrics for BP, serum cholesterol, and glucose were based on untreated values, it is unlikely that ideal metrics for physical activity, diet, or BMI in old age could have resulted from the diagnosis of CVD or any of its biological risk factors. And sixth, given that this was an observational study, and despite the analyses accounted for many variables related to both cardiovascular health and frailty, a certain residual confounding cannot be ruled out.

Conclusions

Our results showing a lower frailty risk in older adults with ideal cardiovascular health are of public health relevance for several reasons. First, they suggest that population-wide primordial prevention is a key strategy for preventing frailty and reducing the undesired consequences of population aging. By contrast to primary CVD prevention (control of established CVD risk factors), which requires continuous health care, primordial intervention through appropriate social changes could definitively minimize CVD burden without extensive provision of health services. Second, our results point to the predominant role of behavioral over biological CVD risk factors in frailty prevention. Maintaining an active life and a normal BMI entails keeping anthropological normality throughout adult life because most infants and children are physically active and have a healthy weight. This also seems to be a rational approach for preventing the onset of biological risk factors (eg, high BP) and achieving longevity without CVD and frailty.

Sources of Funding

Funding specific for this works was obtained from the Spanish Government FIS grants 12/1166, 13/00288, and 13/02321 (Instituto de Salud Carlos III and FEDER/FSE), the FRAILOMIC Initiative (EU FP7-HEALTH-2012-Proposal no. 305483-2), and the ATHLOS project (EU H2020-Project ID: 635316). Funders had no role in data analyses, in the preparation of the article, or in the decision to submit it for publication.

Disclosures

None.

References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381:752–762. doi: 10.1016/S0140-6736(12)62167-9.
2. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, Gonzalez-Colaço Harmand M, Bergman H, Carcaillon L, Nicholson C, Scuteri A, Sinclair A, Pelaez M, Van der Cammen T, Beland F, Bickenbach J, Delamarche P, Ferrucci L, Fried LP, Gutiérrez-Robledo LM, Rockwood K, Rodríguez Artalejo F, Serviddio G, Vega E; FOD-CC group (Appendix 1). Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci*. 2013;68:62–67. doi: 10.1093/gerona/gls119.
3. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, Cesari M, Chumlea WC, Doehner W, Evans J, Fried LP, Guralnik JM, Katz PR, Malmstrom TK, McCarter RJ, Gutierrez Robledo LM, Rockwood K, von Haehling S, Vandewoude MF, Walston J. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14:392–397. doi: 10.1016/j.jamda.2013.03.022.
4. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, Masaki K, Murray A, Newman AB; Women's Health Initiative. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc*. 2005;53:1321–1330. doi: 10.1111/j.1532-5415.2005.53405.x.
5. León-Muñoz LM, García-Esquinas E, López-García E, Banegas JR, Rodríguez-Artalejo F. Major dietary patterns and risk of frailty in older adults: a prospective cohort study. *BMC Med*. 2015;13:11. doi: 10.1186/s12916-014-0255-6.
6. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. The association between sedentary behaviour, moderate-vigorous physical activity and frailty in NHANES cohorts. *Maturitas*. 2015;80:187–191. doi: 10.1016/j.maturitas.2014.11.010.
7. García-Esquinas E, José García-García F, León-Muñoz LM, Carnicero JA, Guallar-Castillón P, Gonzalez-Colaço Harmand M, López-García E, Alonso-Bouzón C, Rodríguez-Mañas L, Rodríguez-Artalejo F. Obesity, fat distribution, and risk of frailty in two population-based cohorts of older adults in Spain. *Obesity (Silver Spring)*. 2015;23:847–855. doi: 10.1002/oby.21013.
8. Ramsay SE, Arianayagam DS, Whincup PH, Lennon LT, Cryer J, Papacosta AO, Iliffe S, Wannamethee SG. Cardiovascular risk profile and frailty in

a population-based study of older British men. *Heart*. 2015;101:616–622. doi: 10.1136/heartjnl-2014-306472.
9. Morley JE, Malmstrom TK, Rodriguez-Mañas L, Sinclair AJ. Frailty, sarcopenia and diabetes. *J Am Med Dir Assoc*. 2014;15:853–859. doi: 10.1016/j.jamda.2014.10.001.
10. Bouillon K, Batty GD, Hamer M, Sabia S, Shipley MJ, Britton A, Singh-Manoux A, Kivimäki M. Cardiovascular disease risk scores in identifying future frailty: the Whitehall II prospective cohort study. *Heart*. 2013;99:737–742. doi: 10.1136/heartjnl-2012-302922.
11. Gale CR, Cooper C, Sayer AA. Framingham cardiovascular disease risk scores and incident frailty: the English longitudinal study of ageing. *Age (Dordr)*. 2014;36:9692. doi: 10.1007/s11357-014-9692-6.
12. Alonso-Bouzón C, Carcaillon L, García-García FJ, Amor-Andrés MS, El Assar M, Rodríguez-Mañas L. Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging. *Age (Dordr)*. 2014;36:495–505. doi: 10.1007/s11357-013-9576-1.
13. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, Popma JJ, Ferrucci L, Forman DE. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol*. 2014;63:747–762. doi: 10.1016/j.jacc.2013.09.070.
14. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; American Heart Association Strategic Planning Task Force and Statistics Committee. 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. doi: 10.1161/CIRCULATIONAHA.109.192703.
15. Strasser T. Reflections on cardiovascular diseases. *Interdiscip Sci Rev*. 1978;3:225–230.
16. Liu K, Daviglus ML, Loria CM, Colangelo LA, Spring B, Moller AC, Lloyd-Jones DM. Healthy lifestyle through young adulthood and the presence of low cardiovascular disease risk profile in middle age: the Coronary Artery Risk Development in (Young) Adults (CARDIA) study. *Circulation*. 2012;125:996–1004. doi: 10.1161/CIRCULATIONAHA.111.060681.
17. Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. *Circulation*. 2012;125:987–995. doi: 10.1161/CIRCULATIONAHA.111.049122.
18. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, Gillespie C, Merritt R, Hu FB. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. 2012;307:1273–1283. doi: 10.1001/jama.2012.339.
19. Rodríguez-Artalejo F, Graciani A, Guallar-Castillón P, León-Muñoz LM, Zuluaga MC, López-García E, Gutiérrez-Fisac JL, Taboada JM, Aguilera MT, Regidor E, Villar-Álvarez F, Banegas JR. [Rationale and methods of the study on nutrition and cardiovascular risk in Spain (ENRICA)]. *Rev Esp Cardiol*. 2011;64:876–882. doi: 10.1016/j.recesp.2011.05.019.
20. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr*. 2003;6:407–413. doi: 10.1079/PHN2002439.
21. Relative validity and reproducibility of a diet history questionnaire in Spain. I. Foods. EPIC Group of Spain. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol*. 1997;26(suppl 1):S91–S99.
22. Guallar-Castillón P, Sagardui-Villamor J, Balboa-Castillo T, Sala-Vila A, Ariza Astolfi MJ, Sarrión Pelous MD, León-Muñoz LM, Graciani A, Laclaustra M, Benito C, Banegas JR, Artalejo FR. Validity and reproducibility of a Spanish dietary history. *PLoS One*. 2014;9:e86074. doi: 10.1371/journal.pone.0086074.
23. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179–186.
24. Graciani A, León-Muñoz LM, Guallar-Castillón P, Rodríguez-Artalejo F, Banegas JR. Cardiovascular health in a southern Mediterranean European country: a nationwide population-based study. *Circ Cardiovasc Qual Outcomes*. 2013;6:90–98. doi: 10.1161/CIRCOUTCOMES.112.967893.
25. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156.
26. Elbaz A, Ripert M, Tavernier B, Février B, Zureik M, Gariépy J, Alpérovitch A, Tzourio C. Common carotid artery intima-media thickness, carotid plaques, and walking speed. *Stroke*. 2005;36:2198–2202. doi: 10.1161/01.STR.0000181752.16915.5c.
27. Buchman AS, Yu L, Wilson RS, Schneider JA, Bennett DA. Association of brain pathology with the progression of frailty in older adults. *Neurology*. 2013;80:2055–2061. doi: 10.1212/WNL.0b013e318294b462.
28. Giné-Garriga M, Roqué-Fíguls M, Coll-Planas L, Sitjà-Rabert M, Salvà A. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2014;95:753–769.e3. doi: 10.1016/j.apmr.2013.11.007.
29. American College of Sports Medicine, Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, Skinner JS. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc*. 2009;41:1510–1530. doi: 10.1249/MSS.0b013e3181a0c95c.
30. Dhamoon MS, Dong C, Elkind MS, Sacco RL. Ideal cardiovascular health predicts functional status independently of vascular events: the Northern Manhattan Study. *J Am Heart Assoc*. 2015;4:. doi: 10.1161/JAHA.114.001322.
31. Theou O, Cann L, Blodgett J, Wallace LM, Brothers TD, Rockwood K. Modifications to the frailty phenotype criteria: Systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. *Ageing Res Rev*. 2015;21:78–94. doi: 10.1016/j.arr.2015.04.001.
32. Villareal DT, Apovian CM, Kushner RF, Klein S; American Society for Nutrition; NAASO, The Obesity Society. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *Obes Res*. 2005;13:1849–1863. doi: 10.1038/oby.2005.228.